A Knowledge Perspective of Strategic Alliances and Management of Biopharmaceutical Innovation: Evolving Research Paradigms

by

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Information from the Human Genome Project is being integrated into the drug discovery and development process to permit novel drug targets to be identified, clinical trial testing to be made more efficient, and efficacious therapeutics to be approved and made widely available. Knowledge of the genome will allow for the description and quantification of disease and susceptibility to disease as informational errors or deficits.

The creation and application of knowledge occur through cooperative or competitive interactions, often reflecting the perceived value of the knowledge. The public or private value of the knowledge, both for itself and for potential applications, can be determined through an understanding of the classification and characterization of this knowledge, as well as the position of the knowledge within the drug discovery and development pipeline.

The transformation of knowledge from a purely public good to a quasi-private good has highlighted the need for balance between incentives for the market provision of scientific and technological knowledge by an innovator and incentives for the market provision of incremental knowledge by a follow-on developer. It has been suggested that a patent system developed for a discrete model of innovation may no longer be optimal for an information-based, cumulative model of innovation. Consequently, it is necessary to reanalyze models of intellectual property protection and strategies of knowledge sharing in biopharmaceutical discovery research.

Under certain conditions, the biotech commons is an efficient institution that can preserve downstream opportunities for multiple researchers fairly and efficiently. A framework for classifying and characterizing discovery knowledge is developed in this research and the role of research consortia in preserving the biotech commons is analyzed. This study also addresses the value of pooling versus unilaterally holding knowledge, the benefits associated with appropriating from the commons, the role of knowledge characteristics in bargaining between licensor and licensee, and the overall management of the biotech commons.

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Chapter 1: Introduction

1.1 Medicine in the Post-Human Genome Era

It is anticipated that the genomic information revealed from the Human Genome Project will revolutionize the diagnosis and treatment of countless diseases. Individuals will be diagnosed and treated based on their genotype, not simply on their clinical symptoms. Currently, information from the Human Genome Project is being integrated into the drug discovery and development process to permit novel drug targets to be identified, clinical trial testing to be made more efficient, and efficacious therapeutics to be approved and made widely available.

The Human Genome Project has advanced the view that biology is an information science. Biological knowledge operates on multiple hierarchical levels and is processed in complex networks [Ideker et al., 2001]. Information storage, information processing, and the execution of various cellular programs occurs at the level of the cell's genome (the complete set of genetic information for an organism), transcriptome (the complete set of gene expression profiles for an organism), proteome (the complete set of proteins encoded by the genome for an organism), and metabolome (the set of all small molecular weight metabolites inside a cell). These building blocks organize themselves into recurrent patterns call pathways. Genes and proteins are interconnected along these informational pathways [Oltvai and Barabási, 2002]. These pathways form functional modules or groups of nodes that are responsible for cellular function. The modules are themselves nested in a hierarchical fashion to define the cell's large scale functional organization including tissue networks and organ structure [Oltvai and Barabási, 2002].

Pharmacogenomics is the study of the genetic variations or single nucleotide polymorphisms (SNP) between individuals that are associated with common diseases and linked to drug responses [Akhtar, 2002]. Pharmacogenomics will identify candidate genes and polymorphisms, predict drug responses and clinical outcomes with the objectives to reduce adverse reaction events and enable for dosing of therapeutic drugs on the basis of a patient's genotype [Akhtar, 2002]. Pharmacogenomics will change the

current drug discovery and development process as customized drugs are developed for defined sub-populations of patients and perhaps even tailored for specific individuals. Clinical trials will target specific genetic population groups. Advanced screening for disease susceptibility based on a patient's genotype will also become possible [Akhtar, 2002]. With the accumulation of genomic data, proteomic data, transcriptome data, pathway information, and a variety of other biological data, the task now is to integrate and analyze these data for the purpose of biological and pharmacological discoveries.

The creation and application of discovery and development knowledge occur through cooperative or competitive interactions, often reflecting the perceived value of the knowledge. The public or private value of the knowledge both for itself and for potential applications can be determined through an understanding of the classification and characterization of this knowledge as well as the position of the knowledge within the drug discovery and development pipeline. The biopharmaceutical industry must differentiate knowledge as it progresses from the gene sequence, to gene products and modification of gene products, to the development of therapeutics and diagnostics, as knowledge that is discovered versus knowledge that is created and applied through an invention. It is this distinction that will enable biopharmaceutical industry participants to interact fairly and efficiently with other players in the industry.

1.2 The Scale of Research and Strategic Alliances

Given the broad scope of the current systems biology paradigm, collective effort is required from multiple research arenas including: molecular biology, cell biology, physiology, mathematics, physics and chemistry, computer science, electrical, mechanical, and biological engineering. Life sciences research has long been dominated by a culture of independent laboratories organized around single principal investigators. However, the need in systems biology for diverse skills and the complexity of the experimental technologies require the formation of interdisciplinary research teams [Kitano, 2001]. Teams of biologists, engineers, and computational scientists from the

public and private sectors, will increasingly collaborate to handle the iterative and multi-dimensional aspects of systems biology [Ideker al el., 2001].

Although strategic alliances such as joint ventures and mergers and acquisitions are used to gain access to both tacit and codified molecular knowledge, these alliances tend to be associated with downstream knowledge—knowledge that is used for the purpose of medical application development [Greis et al., 1995; Das and Teng, 2000]. Upstream knowledge that is far removed from commercial application is typically developed through research-based partnerships between universities, biotechnology, and pharmaceutical companies [Arora and Gambardella, 1990; Blumenthal, 1992; Senker and Sharp, 1997]. Furthermore, the era of the Human Genome has highlighted the need for partnerships that are broad and not only cross institutional boundaries, but also cross regional boundaries. The breadth of upstream research to be conducted to ensure successful downstream drug development, particularly in a decade marked by shrinking pipelines and blockbuster drug patent expirations, has reinforced the need for knowledge-based networks.

Networks of collaboration allow multiple institutions and systems biology researchers to collaborate despite their geographic distance [Foray, 2004]. The creation of a virtual knowledge environment will enable scientists to make new connections between information from diverse sources, and to support educational, collaborative, and community-building efforts. Knowledge production and dissemination in this paradigm will require the development of common data standards for representing complex biological information, and the establishment of efficient communication and knowledge sharing mechanisms across disciplines and geographies [Foray, 2004]. The ability to generate new wealth depends on the capacity of researchers to learn from other researchers in a knowledge network or alliance. The structure of the network mechanisms used to enable knowledge transfer and transparency with respect to knowledge production and dissemination, are critical to ensure that collective learning occurs [Larsson et al., 1998].

1.3 Complex Intellectual Property Issues

Existing patent law allows a researcher who has discovered a new, nonobvious, and useful process, machine, article of manufacture, or composition of matter to receive a patent [Kieff, 2003; Foray 2004; USPTO, 2007]. Consider the example of Tagamet, a breakthrough drug in antiulcer therapies that was introduced in 1977. Tagamet was the first drug to relieve ulcers by blocking the histamine 2 (H2) receptors in the lining of the stomach from stimulating acid production by the parietal cells [Berndt et al., 1994]. Six years after Tagamet became available, a second H2 antagonist, Zantac, was approved; it eventually became the largest-selling drug in both the United States and the world [Berndt et al., 1994]. By 1989, two additional H2 antagonists, Pepcid and Axid, were available. Thus, four slightly different drugs using the same therapeutic mechanism (blocking the H2 receptor) were all patentable, with the breakthrough drug having only six years of market exclusivity before being challenged by a competitor compound [Berndt et al., 1994].

Currently, under existing patent law, biological information is considered a new article of manufacture or composition of matter. However, patent examiners are increasingly finding it difficult to apply the chemical patent law doctrines to biological information [Drew, 1998]. The consequence of this has been the granting of and enforcement of broad patents on biotechnological entities that perhaps should not be enclosed with serious negative consequences for subsequent research and development activities.

For example, the OncoMouse or Harvard mouse is a type of laboratory mouse that has been genetically modified by researchers at Harvard University and DuPont to carry an activated oncogene. The activated oncogene significantly increases the mouse's susceptibility to cancer, and thus makes the mouse suitable for cancer research [WIPO Magazine, 2006; Wikipedia, 2007].

Patent applications on this upstream research tool were filed in the mid-1980s in numerous countries including the United States, Canada, Europe, and Japan. Two separate patents were issued to Harvard College covering methods for providing a cell

culture from a transgenic non-human animal (U.S. 5,087,571) and testing methods using transgenic mice expressing an oncogene (U.S. 5,925,803) [Wikipedia, 2007].

In 2002, the Canadian Supreme Court rejected the patent in Harvard College v. Canada (Commissioner of Patents), overturning a Federal Court of Appeal verdict which ruled in favour of the patent by overturning a lower court's rejection. However, on October 7th 2003, Canadian patent 1,341,442 CA was granted to Harvard College. The patent was amended to omit the "composition of matter" claims on the transgenic mice. The Supreme Court had rejected the entire patent application on the basis of these claims, but Canadian patent law allowed the amended claims to grant under pre-GATT rules [WIPO Magazine, 2006; Wikipedia, 2007]. This notion of biological entities as being composition of matter from the chemistry perspective tends to support the view that extending patent protection to biotechnological inventions is nothing new but simply a matter of expanding an existing logical patent category.

In the systems biology paradigm, the focus of intellectual property rights should gradually shift to the patenting of information. This information perspective must incorporate an understanding of the impact of enclosing hierarchical and complementary, basic biological knowledge, on the technological opportunities available for the development of novel medical products [Hood, 2000]. Systems biology does not focus on individual genes and proteins one at a time, but focuses on the behaviour and relationships of all elements in a particular biological system from a functional perspective [Ideker et al., 2001]. Targets that function across diseases, playing a central role in these diseases, will be chosen to develop drugs that either augment or suppress the associated biological systems, enabling for better disease intervention, and blockbuster status on the market. Blockbuster drugs will not simply target one system, but will eventually target multiple systems at a common intervention point.

As an example of the complexities associated with systems biology patents, is U.S. Patent No. 6,410,516 filed on the NF-κB cell signaling system. This patent was assigned to Harvard College (Cambridge, MA), the Massachusetts Institute of Technology

(Cambridge, MA), and the Whitehead Institute for Biomedical Research (Cambridge, MA). The patent claims cover methods of treating human disease by regulating NF-κB activity, methods of treating disease by inhibiting NF-κB, and methods useful for treating various disease conditions through modulation of NF-κB activity. The associated patent on the upstream system itself was awarded in 2002, with claims that may cover almost every putative downstream application of this fundamental signaling pathway. Licensed to Ariad Pharmaceuticals in 2002, Ariad sued Eli Lilly, arguing that Lilly's Evista and Xigris products for osteoporosis and sepsis, approved in 1997 and 2001 respectively, infringe upon their patent since the drugs work via the NF-κB pathway [Rai and Eisenberg, 2003].

The current patent system is thought to fit a model of research and development where knowledge is discrete and the result of a linear research process. In contrast, for many industries, concern has been expressed where the research process is primarily knowledge based, the process of invention may be cumulative and iterative, with downstream knowledge dependent on upstream knowledge. Therefore, a patent system that was developed for a discrete model of innovation may no longer be optimal for an information-based, cumulative model of innovation [Dalrymple, 2003]. With the reforms outlined in the U.S. Patent Reform Act of 2007, it is hoped that the U.S. system will incorporate some of the processes that have worked well in other patent systems including a post-grant review process to challenge and resolve patent issues immediately after the granting of a patent application; the involvement of the public sector to assist with the search for prior art with respect to patent applications; and raising the obviousness standard associated with derivative innovation.

It is worthwhile to note that, in this thesis, the majority of the issues discussed revolve around the U.S. patent system. While innovators seeking protection for their inventions in Canada, the U.S., Europe, and Japan must file for a patent in each place, most companies are likely to first patent inventions in the much larger U.S. market. It is also assumed that policy changes with respect to encouraging innovation and protecting intellectual property rights initiated in the U.S., such as the 1980 Bayh-Dole Act, are likely to be

emulated in some form in other markets. Hence, we focus our attention on patent and policy issues stemming from the U.S. market.

The complexities associated with intellectual property will be further exacerbated as multiple disciplines increasingly work together in the systems biology paradigm. Each discipline will have its own priorities and conventions regarding knowledge dissemination and knowledge appropriation. One discipline may signal its success during knowledge generation through enclosure and the sale of disembodied knowledge. Another discipline may measure its success exclusively by the embodiment of knowledge in medical products. As collaborations cross institutional boundaries, the parceling out of intellectual property rights may be too difficult a task. With the assignment of property rights, the role of the patent holder in providing broad versus narrow access to the knowledge will then depend on the original incentives for producing the knowledge. We contend therefore, that it is necessary to reanalyze models of intellectual property protection and strategies of knowledge sharing in biopharmaceutical discovery research.

In this thesis, the role of the biotech commons (the public domain for biotechnology knowledge) is investigated as an efficient institution for preserving downstream development opportunities for multiple researchers. Identifying the boundary ("the transition point") between the commons and the private realm is important during this investigation. The transition point can be defined as the moment in discovery research when the characteristics associated with knowledge change so that privatization of the knowledge is critical for downstream research and the development of medical products. In this thesis, we assume that patents protect the future right to pursue downstream development in a technological arena. The complexities of knowledge discussed in this thesis tend to be associated with upstream research; hence we assume that should patents be filed, the intent is to protect the right to downstream research and/or product development—in some cases through internal development and in other cases (including jointly) through licensing agreements. As products are developed, patents can protect against future loss of profit through imitation and can be used to prevent competitors from entering the market.

1.4 Understanding the Structure of and Management of Knowledge Assets

It is important to determine during the drug discovery and development process whether knowledge should be deposited into the biotech commons or should be privatized and assigned property rights. Cooperative interactions during discovery research can ensure that knowledge is generated for the purpose of disclosure and deposit into the biotech commons. Alternatively, the ability to appropriate knowledge will preserve the incentive to progress further downstream into development work—work that is very costly and risky in the biopharmaceutical industry. Knowledge that belongs in the public domain is unique and can be distinguished from knowledge that is privatized to appropriate its full value. A framework for classifying and characterizing discovery knowledge is developed in this thesis (Chapters 3, 4, 5) and the role of pre-competitive research consortia (Chapter 6) in preserving the biotech commons is analyzed. Researchers will face many decisions in the biotech commons including the decision to participate in the biotech commons by pooling resources or knowledge, the decision to pursue a cooperative versus competitive strategy within the commons, the decision to bargain for and license privatized knowledge, and the decision to develop rules to ensure cooperation and maintain the commons.

We first conduct a patent analysis on key biological systems to determine if and where problems will potentially occur in the current systems paradigm (Chapter 4) and use a historical analysis of upstream research-based alliances across drug discovery paradigms (Chapter 5) to understand the objective of such alliances and the focus of (including evolution of) intellectual property strategies. By then studying various pre-competitive research consortia (Chapter 6), established primarily after the completion of the Human Genome Project, we determine how this *specific* alliance model has enabled for the management of complex knowledge assets including knowledge production, knowledge appropriation, and knowledge dissemination. Based on this understanding, we develop game models to determine the impact of knowledge characteristics on the decision to participate in pre-competitive research consortia (Chapter 7), the decision to appropriate knowledge developed within such consortia (Chapter 8), and the impact of knowledge

characteristics on strategies used during the bargaining process involving a licensor and licensee (Chapter 9).

1.5 The Game Models

Game models are mathematical models of interactive decision problems. In these models, two or more players or decision makers make choices that determine an outcome. Player's choices are assumed to reflect their preferences and their understanding of how their choices are converted into outcomes [Kilgour, 2006]. Each player is assumed to act in his or her own best interest. The Nash equilibrium is a solution concept of a game involving two or more players, in which no player has anything to gain by unilaterally changing only his or her own strategy. If each player has chosen a strategy and no player can benefit by unilaterally changing his or her strategy, then the current set of strategy choices and the corresponding payoffs constitute a Nash equilibrium and a solution to the game [Kilgour, 2006]. A game can have more than one pure Nash equilibrium. Pure strategy Nash equilibria are Nash equilibria where all players are playing single strategies with probability one [Kilgour, 2006]. Alternatively, a mixed strategy is a probability distribution over strategies [Kilgour, 2006]. Strategies can also be dominated by other strategies. Dominance occurs when one strategy is better than another strategy for one player, no matter what the other player chooses. A strategy can be strictly dominated if and only if it always dominates other strategies i.e., always give a better outcome no matter what the other player chooses. Once a strictly dominated strategy is found, it is this strategy that will always be chosen by a player [Kilgour, 2006]. In game models, is it assumed that the players are "rational," which means that they always make choices that maximize their own interests. For example, a rational player will always select a dominant strategy (if one exists).

In this thesis, we use game models to represent and analyze interactions between partners in collaborative alliances. Our contention is that a researcher's "freedom to operate" downstream is determined by cooperate-versus-defect decisions upstream, as discovery knowledge is being produced and subsequently disseminated. These decisions therefore

determine whether researchers can equitably pursue downstream opportunities for medical application development.

In a basic model, two researchers can either cooperate (C) in knowledge production or dissemination, or defect (D) by generating knowledge privately and/or making their knowledge private. The outcomes are the four cells shown Table 1.1. Preferences over outcomes are given ordinally; each player's most preferred outcome is assigned payoff ("utility") 4, the next most preferred outcome is assigned 3, and so on down to 1 for the least preferred outcome. In this simple game, communication is not permitted.

	$\mathbf{C_2}$	$\mathbf{D_2}$
$\mathbf{C_1}$	3, 3	1, 4
$\mathbf{D_1}$	4, 1	2, 2

Table 1.1: Game Model of Discovery Research Interaction

Researcher 1 chooses C_1 or D_1; the first number in each cell is Researcher 1's ordinal payoff.
Researcher 2 chooses C_2 or D_2; the second number in each cell is Researcher 2's ordinal payoff.
C=Cooperate; D=Defect

In the model of Table 1.1, mutual cooperation (C_1, C_2) is the next-best outcome for both players, reflecting that cooperation during knowledge production will increase the probability of success, bring success more quickly, and help contain costs. A player who chooses D rather than C is choosing unilateral research, under which any discovery is private. Despite the higher costs of unilateral action and the greater risk of failure, the benefits from unilateral defection are often very high, especially if the defector can establish ownership of knowledge. The mutual defection outcome, (D_1, D_2), represents a race for discovery. Because discovery research in the systems biology paradigm is extremely complex, players who choose to race will likely face higher costs and greater risks of failure, making this outcome inferior to the mutual cooperation outcome, in the sense that both players are worse off. This game is commonly known as Prisoners' Dilemma (PD) [Rapoport and Chammah, 1965].

We see from the above example that Prisoner's Dilemma has several applications beyond being used as a parlor game played for money. The monetary gains and losses can be replaced by other kinds of rewards and punishments and interpretations. The two players for example can be asked to imagine that they are two firms in competition. Each firm has a choice of selling a product at one of two price levels. If one firm sells at a high level while the other sells at a low level, the second firm will attain the profits by capturing the market. If both sell at a high level, both profit, but not as much as when competition does not exist. If both firms sell at the low level, both will lose money. In another scenario, the players can imagine that they are rival power blocs who have made a disarmament agreement. The cooperative choice is keeping the agreement; the defecting choice is to break the agreement. There may also be some advantage accruing to the bloc that breaks the agreement unilaterally. Therefore, by using the Prisoner's Dilemma as a framework, various games (experimental or real) can test the ethical convictions of players or their cognitive sets on various matters.

A crucial feature of PD is that the players' incentives drive them toward mutual defection. As is easy to verify in Table 1.1, either player achieves a preferred outcome by defecting, no matter what choice the opponent makes. In game-theoretic terms, defection (D) strictly dominates cooperation (C); any rational player who recognizes the situation will defect immediately. The reason that PD has attracted so much interest is that mutual defection, (D_1, D_2), is the only possible outcome according to a very convincing criterion of individual rationality, and at the same time it is "collectively irrational" in that both players are better off at mutual cooperation, (C_1, C_2).

In the discovery research context, the incentive to defect may be strong if a researcher fears being left behind, spending time and money on research but receiving no benefits or accolades. (In Table 1.1, for example, if Researcher 1 is the sole cooperator, the outcome is (C_1, D_2), which is Researcher 1's least preferred outcome.) In fact, it is the characteristics of the players that determine the appeal of defection. Players from the private sector are generally motivated to obtain patents, and are therefore more likely to engage in unilateralism, secrecy, and competition. The same phenomenon is likely if only

one researcher is from the private sector; the players could quickly become direct competitors, as scientists in public institutions are increasingly business-oriented, targeting their research toward applications and patents. There are even incentives for public-sector researchers to defect—they seek credit, priority in discovery, and patent priority, reflecting that the line between basic and applied research is often blurred in biotechnology [Blumenthal, 1992; Atkinson et al., 1998].

Using the above game model as a framework including game concepts and perceptions associated with the Prisoner's Dilemma game, we develop our game models as outlined in section 1.4. The objective of these models is to understand under what circumstances cooperation dominates unilateral and mutual defection. If however, the decision is made to defect and unilaterally produce and hold knowledge, we analyze the various licensing scenarios available to the defector or licensor (with defection occurring through the appropriation of knowledge via the filing of patents).

1.6 Implications of Research

The transformation of knowledge from a purely public good to a quasi-private good has highlighted the need for balance between incentives for the market provision of scientific and technological knowledge by an innovator and incentives for the market provision of incremental knowledge by a follow-on developer. Without this balance in incentives for the upstream innovator and downstream developer, tragedies are possible.

The tragedy of the biotech commons is a result of free riding by other users and the inability of the original inventor to appropriate knowledge. Property rights can ensure that knowledge is indeed produced and diffused for others to use, avoiding the tragedy where innovative knowledge is not generated [Hardin, 1968].

On the other hand, a tragedy of the anticommons can occur in which follow-on developers underuse a scarce resource because too many owners can block these innovators and no one has effective privilege of use. The possibility exists then that

critical technological opportunities will not be exploited in downstream development activities.

Both of these tragedies, where knowledge is not discovered or created and then exploited in the development of therapeutics and diagnostics, are problems for the corresponding innovators as the potential to enjoy profits in the resulting markets may be diminished. However, the ultimate tragedy occurs when the patient is not provided with the choice of new or improved medical treatment options. Therefore, the role of the proposed biotech commons is to encourage drug discovery research and development with private benefits for multiple innovators and social benefits for the consumer.

Chapter 2: Theoretical Perspectives of the Economics of Knowledge and Strategic Alliances

2.1 Characterizing Knowledge: Public Good vs. Quasi-Private Good

Kenneth Arrow and Richard Nelson have long shaped the discussion about knowledge and its supply [Nelson, 1959; Arrow, 1962]. Technological knowledge has traditionally been classified as a public good associated with the properties of non-rivalry, non-excludability hence non-appropriability, and indivisibility [Antonelli, 2003]. (Table 2.1)

Non-rivalry implies that there is a zero marginal cost from an additional individual using the knowledge [Foray, 2004]. Even if one could exclude another user from using the knowledge, it would be undesirable to do so because there are no marginal costs to sharing the benefits associated with the knowledge. Non-subtractability also used in the literature, means that usage by one firm or individual does not reduce the availability of that information for use by others [Foray, 2004]. Knowledge is not destroyed or altered by use. Often, increased usage of the knowledge can enhance its value and applicability, thereby exhibiting positive externalities [Antonelli, 2003].

Free-rider problems are traditionally associated with the provision of public goods—as the producer of knowledge cannot easily exclude others from using the knowledge. Free-riders do not need to reveal their preferences concerning which public goods should be provided. These individuals will understate their true preferences in the hope that others will bear the burden of the cost of producing the good. However, with individuals acting in their own self-interest, resources may be under-allocated to the provision of such goods [Nicholson, 1985].

Knowledge is also indivisible as the utility of this good cannot be parceled out among different individuals. Instead, value may be created through the collective use of the knowledge with individuals jointly benefiting from the knowledge [Antonelli, 2003].

In the Arrowian tradition of classifying knowledge as a public good, markets are not able to provide appropriate levels of knowledge because of the lack of incentives associated with non-excludability and non-appropriability. The public provision of scientific knowledge became a long regarded basic remedy to the problem of under-provision of knowledge and under-allocation of resources to knowledge production. Accelerating the introduction of new technology stemming from scientific discoveries became the domain of large corporations that could fund new technical knowledge production. Ex-ante monopolistic market power based on barriers to entry in existing product markets would provide the financial resources to fund new knowledge production [Antonelli, 2003]. Appropriability would then be ensured by barriers to entry based on cost rather than barriers to entry based on imitation [Antonelli, 2003]. With the creation of intellectual property rights and the ability to trade knowledge, incentives to produce both scientific and technological knowledge could be ensured by the market.

The transformation of knowledge from a purely public good to a "quasi-private good" has highlighted the need for balance between incentives for the market provision of scientific and technological knowledge by a first innovator and incentives for the market provision of incremental knowledge by a follow-on developer [Scotchmer, 1991; 2004]. The possibilities for holdouts and high transaction costs associated with gaining the right to use knowledge in downstream activities, increase as a function of the complementarity, non-substitutability, and applicability of the knowledge. Holdouts occur when buyers need to acquire complementary assets from sellers and sellers raise their prices to capture some of the value the buyer attributes to collectively holding the assets [Merges, 1994]. Holdouts can also occur when owners control blocking patents, requiring the follow-on developer to license the knowledge for downstream research or to sell a product that embodies the knowledge. In this case, the first innovator will try to garner as much of the value of improvements or of the downstream product as possible [Merges, 1994]. Licensing can involve fixed-fees, royalties, and reach-through claims on future knowledge [Burk and Lemley, 2003]. Hence, bargaining failures occur when the first innovator and follow-on developer are unable to reach an agreement regarding the license to knowledge and the rights to future developments.

Upstream complementarity occurs among research inputs during the generation of new knowledge while downstream complementarity occurs in the development phase during the application of new knowledge [Antonelli, 2003]. Complementary knowledge can be used to generate new knowledge in the same specific context or in other adjacent ones. Knowledge will be pooled from the public domain or from owners of the knowledge willing to trade at a reasonable cost. Knowledge may also be lacking in direct substitutes. Others may not be able to substitute for or "invent around" the knowledge and may require varying degrees of access for new knowledge creation. Without the availability of substitute knowledge, the owner can extract high rents from potential users. Finally, knowledge can be applied to a variety of new products and processes. Both the owner and downstream user of knowledge will treat knowledge that applies to a narrow and specific range of activities differently than knowledge that has important applications to a great array of downstream activities.

Knowledge Property	Definition
Non-rival	Zero marginal cost from an additional individual using the knowledge.
Non-subtractable	Use of knowledge does not reduce the availability of that knowledge for use by others.
Non-excludable	One cannot easily exclude others from using the knowledge; Free riding occurs.
Indivisible	Utility of knowledge cannot be parceled out among different individuals; Value created through the collective use of knowledge.
Complementarity	New knowledge production is conditional on the identification and integration of diverse and dispersed units acting as inputs.
Non-substitutable	Knowledge may be lacking in direct substitutes; One may not be able to "invent around" the knowledge.
Applicability	Knowledge can vary in terms of applicability in downstream use—from narrow to wide-ranging application.
Embodiment	Knowledge may serve as inputs into downstream use or as part of final embodiment.

Table 2.1: The Properties of Knowledge

Knowledge first begins as an idea or concept. Knowledge may therefore, serve as an input into further development and the creation of new knowledge or serve as components of the final embodiment of research and development activities. (Figure 2.1) From purely public knowledge, to quasi-private knowledge, to private knowledge

embodied in products or processes, knowledge moves into the market with varying degrees of power provided to the owner [Dalrymple, 2003]. Figure 2.1 graphically demonstrates the links between upstream and downstream biological knowledge.

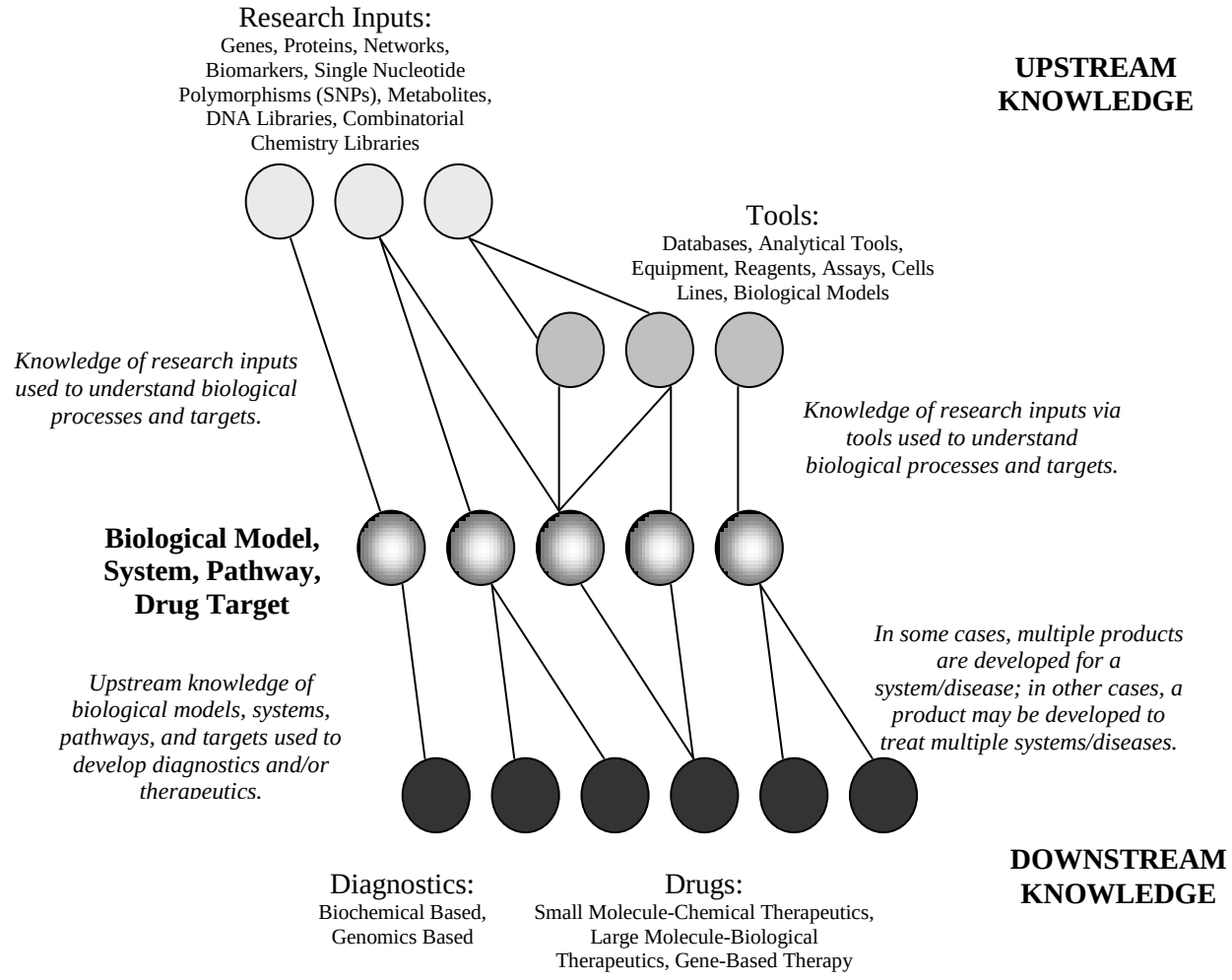


Figure 2.1: The Links between Upstream and Downstream Knowledge
Adopted from Chuck Eesly: "Hear No Evil Patents, See No Evil Patents, Speak of No Evil Patents: Research Tool Patents From the Scientist's Perspective", Economics of Innovation PhD seminar paper, April 2004.

2.2 A Knowledge Perspective of the Drug Discovery and Development Cycle

The upstream (discovery or research) phase involves discovering human drug targets, screening targets, screening new chemical entities (NCE) or new biological entities (NBE) against a target for therapeutic activity, and optimizing chemical or biological entities. Preclinical testing involves the testing of NCEs/NBEs *in vitro* (within the glass)

and *in vivo* (inside) in animal models. Upstream research inputs include: genes and their associated regulatory components, single nucleotide polymorphisms (SNPs), gene transcripts, proteins and their associated networks, drug targets, and metabolites. Tools that aid discovery activities include: analytical tools, assays, reagents, biological materials such as cells, tissue samples and model organisms, databases, algorithms, techniques including the use of combinatorial chemistry to rapidly generate drug leads, other protocols, and equipment.

As we move downstream (into product development), chemical based libraries (relying on traditional chemical processes) from which drugs are sought, or biological therapeutics (developed through the use of biological processes) such as recombinant proteins, monoclonal antibodies, and even gene delivery, are developed to correct malfunctioning processes, the informational errors, or deficits in a system. Alternatively, diagnostics use research inputs such as genes, proteins, biomarkers, and SNPs to detect disease susceptibility, disease progression, and predict therapeutic response. (Figure 2.2)

Phase I Trials include initial studies to determine the metabolic and pharmacological action of the drug in humans, the side effects associated with increasing doses, and the effectiveness of the drug [PhRMA, 2007]. These trials may include healthy participants and patients. Phase II Trials include controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication in patients with the disease or condition under study [PhRMA, 2007]. Phase II Trials are also conducted to determine the common short-term side effects and risks associated with the drug [PhRMA, 2007]. Phase III Trials include expanded, long-term, controlled, and uncontrolled trials. These trials are conducted to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for labeling [PhRMA, 2007]. Once clinical trials are completed and FDA approval is received, manufacturing can commence. The drug is then introduced to the market and adverse reaction events in consumers (Phase IV trials) are monitored. Additionally, approval and marketing can be further expanded to meet global market needs [PhRMA, 2007].

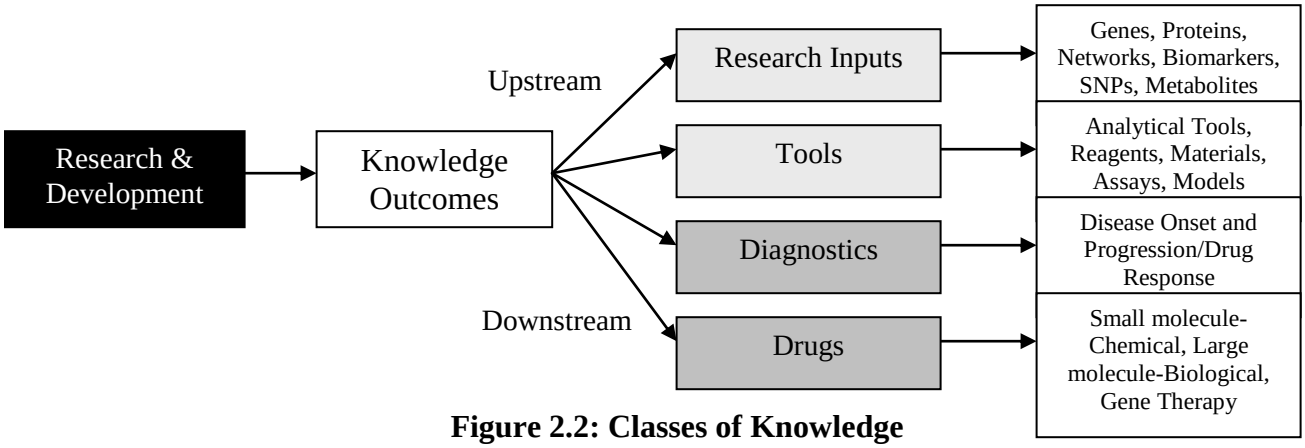


Figure 2.2: Classes of Knowledge

Complementary types of data are clustered to provide for the basis of understanding biological systems under normal conditions and diseased states. Platform technologies that take advantage of central intervention nodes or pathways, found in multiple systems, are being developed as part of the blockbuster strategy. These technologies are based on an understanding of the organizational levels of biological knowledge [Oltvai and Barabási, 2002]. Genes can be categorized by location, structure, and function. Proteins can also be clustered into families based on structural and functional characteristics. Proteins interact with one another in various pathways and biochemical networks and as such, can be classified by these pathways and networks [Oltvai and Barabási, 2002]. From these proteins, the search for targets or points of drug intervention is conducted. Target families are clustered into families that function across biological systems. With the availability of target proteins, new medicinal entities are designed to interact with these targets and their associated pathways [Oltvai and Barabási, 2002]. These entities can also be grouped on the basis of their structural properties and mechanisms of action.

The clustering of data for biological analysis can have a profound technological impact when property rights are sought. Specifically, intellectual property rights are increasingly sought for gene families, target families, and biological pathways. By staking out claims to such families and pathways, if the claims in a patent cover more than the territory of innovation of a first innovator, subsequent innovations by other innovators, based on the first innovation, can be blocked [Scherer, 2000]. If the first innovator cannot or chooses not to fully exploit all technological opportunities presented by the patent, high private

costs exist for those follow-on innovators who cannot "get around" such patents [Scotchmer, 1991; Merges, 1994].

In Figure 2.3, we show two different knowledge units with varied characteristics and the impact on downstream product development. Knowledge unit A is high in complementarity, high in applicability, but also high in substitutability. The products developed from knowledge unit A are represented by the inner circle. The outer circle encloses substitute products that are supplied by competitors (targeting the same market) with noninfringing knowledge, thereby constraining the profits earned by the owner of knowledge unit A. Knowledge unit B is high in complementarity, high in applicability, but low in substitutability. The products developed from knowledge unit B are represented by the inner circle. In this case, a patent on knowledge unit B is a blocking patent. Other firms will have to acquire a license from the owner of knowledge unit B in order to develop products that embody this knowledge; these infringing products are represented by the outer circle. It is possible that firms may develop products that will target the same market. The decision therefore to license knowledge unit B will have to consider the increase in revenue from licensing versus the loss in revenue from competitor products.

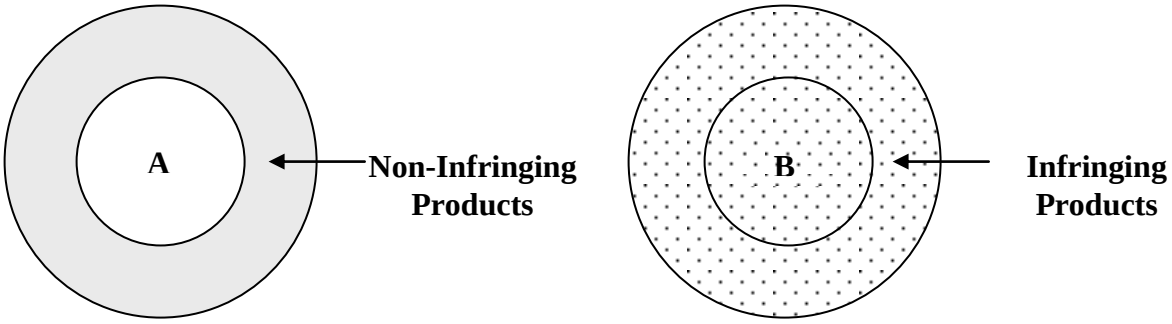


Figure 2.3: Comparing Knowledge Characteristics and the Impact on Downstream Development

As the degree of complementarity, non-substitutability, and applicability of upstream knowledge increases, excessive privatization will increase the transactions costs associated with procuring licenses to the required knowledge and the possibility of bargaining failures [Merges 1994; Antonelli, 2003]. Differences in the ability to tolerate

these transaction costs will complicate the bargaining process. Large corporations with substantial resources will be in a better position to negotiate licenses on a case-by-case basis than public sector institutions or small startup firms. This asymmetry may make it difficult to develop mutually advantageous licensing agreements [Heller and Eisenberg, 1998].

2.3 Changing Paradigms and Knowledge Structures

The pharmaceutical industry arose as a result of the aniline dye industry (a byproduct of gas derived from the carbonization of coal for commercial and residential use) and the institution known as the apothecary used to fill prescriptions written by physicians [Drews, 1998]. Dyes became the basis for the manufacture of medicines containing ring and chain carbon compounds that could serve as starting material for synthetic chemistry. As other sources for medicine were discovered, the need to make these substances available in larger quantities required large-scale, quality-controlled production. Consequently, several apothecaries evolved into industrial apothecaries or pharmaceutical companies [Drews, 1998].

Chemical compounds were isolated from living organisms or could be synthesized. In addition to methodologically assured means of production, compounds that were isolated or synthesized needed to be tested for effectiveness. The measurement and classification of the effectiveness of drugs became part of the domain of pharmacology. Pharmacology evolved from a focus on physiology and an understanding of normal body functions into the correction of malfunctioning processes through the use of pharmaceuticals. Animal models exhibiting disease symptoms were used to test the effectiveness and safety of new compounds [Drews, 1998; Dutfield, 2003]. Hence, medicine oriented itself toward experimentation and observation, paying less attention to abstract theories and speculation [Drews, 1998; Dutfield, 2003]. From the notion of treating diseases evolved the desire to quantify the dosage and bodily effects of new compounds as well as the need to characterize the toxicity of drugs. This research into drug metabolism is thought to have aligned pharmacology more closely to biochemistry.

Dyes that preferentially stained tissues led to the birth of chemotherapy [Drews, 1998; Dutfield, 2003]. Chemical affinities between dyes and tissues—cells or cellular components, led to the exploration of the binding properties of biological structures and chemical compounds in living organisms [Drews, 1998; Dutfield, 2003]. Researchers postulated that cells carry on their surfaces and then eventually in their interior, receptors that preferentially bind to certain chemical compounds. The challenge for chemotherapy would be to find chemical compounds that would only bind to cells that a therapist would hope to eliminate from the body of a diseased patient [Drews, 1998; Dutfield, 2003].

From the perspective of pharmacology, receptors are viewed as signal receivers. These targets interact selectively with a signal and transmit the signal information to intracellular effector organelles—a process known as signal transduction [Drews, 1998; Dutfield, 2003; PhRMA, 2007]. It is this biochemical understanding of receptors, enzymes, and even ion channels (all targets for intervention by pharmaceuticals) that was responsible for the drug revolution in the 1950s and 1960s, resulting in the production of numerous medicines [Drews, 1998; Dutfield, 2003].

Dye chemistry, synthetic chemistry, pharmacology, and biochemistry have therefore, collectively influenced the development of the pharmaceutical industry. In this chemical paradigm for drug discovery and development, vital body processes are described in chemical terms and diseases are described as measurable deviations from normal chemical processes. From this perspective, drug intervention is merely an attempt to normalize this dynamic equilibrium through the use of chemical substances [Drews, 1998; Dutfield, 2003; PhRMA 2007].

Alongside the emergence of the pharmaceutical industry and chemical paradigm for drug discovery and development, the discovery of the Double Helix by Francis Crick and James Watson has been one of the major scientific events of the last century [Watson, 1968; Crick, 1988]. The pathway from the discovery of the double helix to the completion of the Human Genome project (HGP) has been marked by an explosion of

research in a number of areas in molecular biology. Molecular biology is the study of biology at a molecular level. The field overlaps with other areas of biology and chemistry, including genetics and biochemistry [Drews, 1998]. Molecular biology has as its objective the understanding of the interactions between the various components of a cell, including the interrelationship of and regulation of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein synthesis [Drews, 1998; BIO.org, 2007].

By the turn of the century, it was known that nucleic acids were present in all cells. Also established were the three essential features of nucleic acids: a sugar, a phosphate, and the various bases (made for the most part from nitrogen and carbon). By the early 1920's, it had also been proven that there were actually two nucleic acids—RNA and DNA [Watson, 1968]. Then in 1944, Oswald Avery showed that purified DNA was the primary carrier of genetic information [Watson, 1968]. As such, the stage was set for Watson and Crick to investigate the role of DNA in the gene. The specific role of DNA would only be elucidated once the structure of the DNA molecule was solved in 1953 [Watson, 1968].

Once the structural simplicity of the DNA molecule was indeed grasped, and the pairing of bases understood, the mechanism of heredity via the molecular replication of DNA became apparent i.e., the passage of information from generation to generation [Watson, 1968; Crick, 1988]. Each of the two strands of the double helix, upon separation, could serve as a template for the synthesis of a new complementary strand to create two new strands, each a replica of an original, to be separated into two daughter cells [Watson, 1968; Crick, 1988].

Molecular biology has introduced a new paradigm [Schadt et al., 2003]. The genome consists of all the directions for the development and function for an organism via RNA and protein synthesis. Genetic changes lead to functional loss or alteration of these instructions. Disease results from such genetic changes. Knowledge of the genome will allow for the description and quantification of disease and susceptibility to disease as informational deficits or errors [Drew, 1998]. The treatment of disease from this

perspective involves the replacement of information that has been lost or the correction of information that is erroneous in the form of DNA, RNA, or protein.

The biotechnology industry originated in the 1970s, based largely on new recombinant DNA techniques developed by Stanley Cohen of Stanford University and Herbert Boyer of the University of California, San Francisco [BIO.org, 2007]. Recombinant DNA is a method of making proteins in cultured cells under controlled manufacturing conditions [BIO.org, 2007]. The understanding of disease from a molecular perspective and the use of molecular techniques to create recombinant DNA has produced a vast number of drugs such as vaccines, monoclonal antibodies, recombinant products, and gene-based drugs [BIO.org, 2007].

With the completion of the Human Genome Project, discovery research no longer simply focuses on individual units of knowledge, but considers the behaviour and relationships of all units of knowledge in a particular biological system from a functional perspective [Kitano, 2001; 2002]. Genomes are now being described as consisting of complex, intersecting systems rather than unitary collections of separately functioning structures [Hood, 2000; Dutfield, 2003]. The assumption that these structures have independent functions has proven to be too simplistic in the post Human Genome era. In light of this new information paradigm, many biopharmaceutical companies are reconsidering their competitive strategies with respect to upstream genomic discovery research [Eisenberg, 2000; Cassier, 2002]. (See Chapter 4 for an in-depth analysis of the systems biology paradigm.)

2.4 Evolving Models of Innovation

It is anticipated that the genomic information revealed from the Human Genome Project will revolutionize the diagnosis and treatment of countless diseases. Individuals will be diagnosed and treated based on their genotype, not simply their clinical symptoms. By sequencing an individual's genome, analysis of disease risks, life expectancy, and the ability to customize drug treatment based on individual's unique genetic profile will

become possible [Akhtar, 2002]. The successful forward integration of genomics-based information into the drug discovery paradigm is central to the identification of novel drug targets, the development of therapeutics, and for the development of diagnostics.

New knowledge components of a changing genomics driven drug discovery paradigm include the genome—the study of the complete set of genetic information contained within a cell or an organism including the assignment of function to the genes within this set; genome maps that allow for a more rapid identification of genes of interest based on physical location and relative position of genes on a chromosome; the proteome—the study of proteins encoded by the genome including the assignment of function to such proteins and the understanding of protein-protein interactions within biological pathways; gene expression information including patterns of gene expression as a function of cell type, disease state, therapeutic intervention; single nucleotide polymorphism—single base pair changes in DNA located either outside the coding region of the gene or located within the coding region of the gene, often having a functional significance in terms of disease susceptibility and/or drug response; pharmacogenomics—the use of genetic variations to design drugs keeping in mind the influence of an individual's genetic makeup on variability of therapeutic response; biomarkers—factors that are objectively measured and evaluated as indicators of normal biological processes or pathogenic processes and/or as indicators or pharmacological responses to therapeutic intervention [BIO.org, 2007; Akhtar, 2002; Colburn, 2003; PhRMA, 2007].

Target identification will link genes to diseases and will seek out targets for therapeutic intervention based on an understanding of gene transcripts (mRNA) or proteins encoded by the genome [PhRMA, 2007]. Target validation will verify that the gene of interest and/or its products are an appropriate therapeutic target, lying within a control point of a disease pathway and that a therapeutic will interact with the target in a beneficial manner. During lead generation, drug targets are then screened against large numbers of small or large molecule compounds to identify those that indeed interact with the target and result in the desired outcome [PhRMA, 2007]. Expression profiling can be used to assess the response of a gene to exposure to a drug [PhRMA, 2007]. Through the identification of

genes involved in drug metabolism and drug efficacy, companies will be able to screen compounds at the preclinical stages of development for efficacy, toxicity, and/or likely adverse reactions [PhRMA, 2007]. Pharmacogenomics technology can be used to correlate drug response to individual genotypes and the variations found in genes known to contribute to either mechanism of action or metabolism of a drug [Akhtar, 2002].

Drug discovery and development has traditionally been a linear process with little feedback from the later stages of drug development. However, the adoption of a personalized medicine strategy that includes an understanding of SNPs, disease susceptibility variations, and drug response variations, has transformed the linear process of discovery and development, involving little feedback, to one that involves a series of research feedback loops [Ideker et al., 2001; Kitano, 2002]. In this feedback-based paradigm, the early stages of discovery, including the selection and validation of drug targets, small-molecule screening and chemistry or biologics development, as well as the preclinical assessment of such compounds in animal models, will be linked with the later stages of clinical development [Ideker et al., 2001; Kitano, 2002].

As the industry evolves to incorporate the systems paradigm, it is anticipated that the drug discovery and development feedback cycle will incorporate novel technologies and disciplines. Global observations made during discovery research are matched to model predictions or hypotheses in an iterative manner, leading to new patient models, predictions, and methods of patient experimentation [Ideker et al., 2001]. Computational experiments will identify and virtually screen lead compounds. Successful leads will be synthesized and then tested via *in vitro* and *in vivo* experiments as well as clinical studies [Kitano, 2002]. The systems biology research cycle and drug discovery and development cycle will be linked to each other through feedback processes that update biological, physiological, system, and patient model information. *In silico* (computer simulation) experiments of drug systems and the screening of lead candidates will play a central role in upstream biopharmaceutical research, with the joint objectives of reducing costs and increasing the success of a drug during human clinical trial testing. (Figure 2.4)

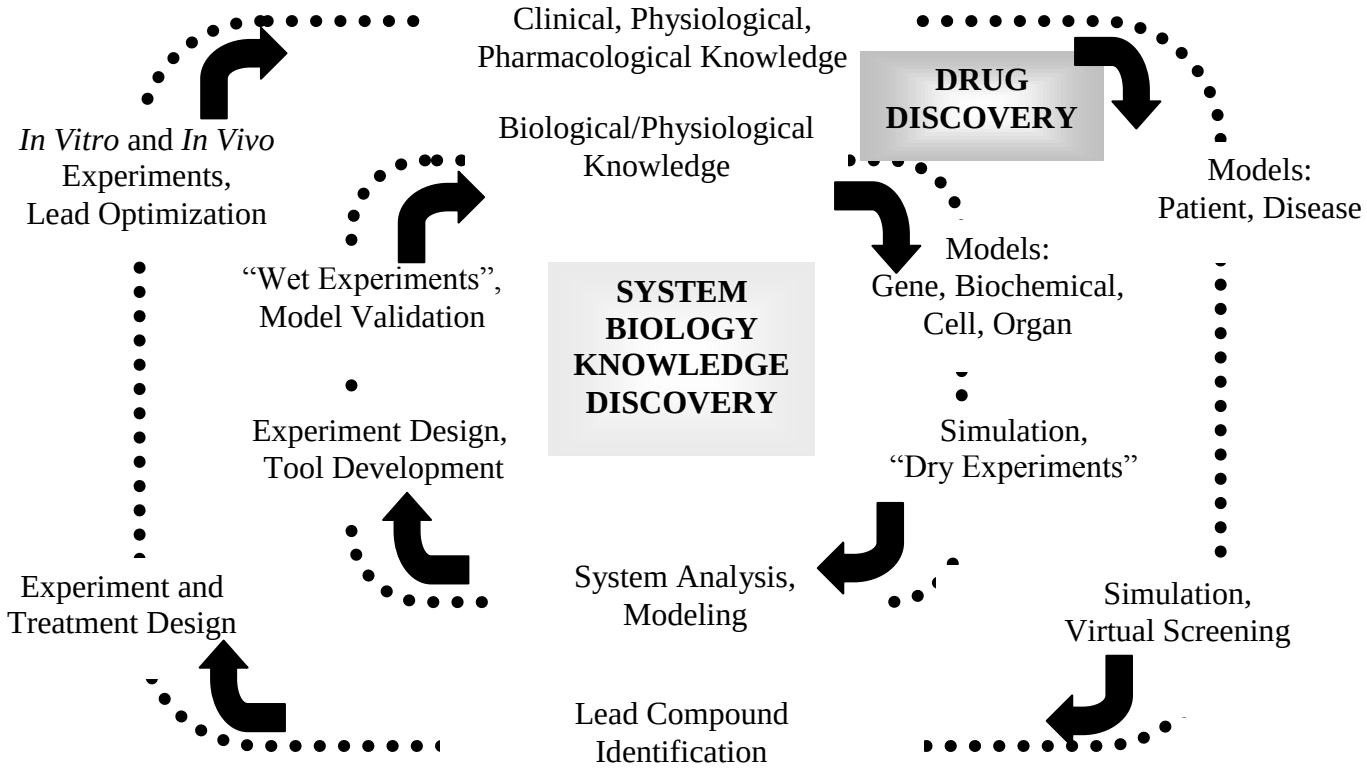


Figure 2.4: Linking Systems Biology Research with Drug Discovery Research
Adopted from Kitano, H.: "Computational systems biology", Nature 420(6912), 207, 2002.

2.5 Changing Incentives for Research

The tradition of open science and basic research with a quest for fundamental knowledge, often associated with public institutions, has increasingly evolved into secrecy and a quest for intellectual property. Furthermore, the gap between fundamental research and commercial application has become narrower in the biomedical arena [Rai and Eisenberg, 2003].

Traditionally, priority and the claim to be the first discoverer to gain recognition by peers, in the form of paper citations and even prizes, were norms associated with the public sector [Merton and Lewis, 1971]. Merton has discussed the idea that the annals of science are lined with cases of scientists who were spurred on to more intense effort by the knowledge that other scientists were on the very same discovery track. In such

circumstances, scientists engaged in a race, with quick publications used to ensure priority, sometimes at the expense of other scientists wanting to do a more thorough job before publishing their findings [Merton and Lewis, 1971]. As early as the discovery of the double helix, "aggressive, prize-seeking and competitive behaviour" is evident. However, once a scientist makes his/her contribution, the scientist no longer has exclusive rights of access to it. In this sense, the tradition of open science could be preserved.

Biotechnology is an area that has often been termed a "hot field" dealing with "hot subjects" [Merton and Lewis, 1971; Allarakhia, 2001]. Merton also explains that the decisive characteristic of a hot field seems to be the high rate of significant discoveries, with a lower ratio of routine to highly consequential ideas and findings [Merton and Lewis, 1971]. Hot fields are not only more active than cold ones, but their results also have implications beyond the borders of the specialty. Rivalry and the race for priority are all associated with such fields and can be noted for example, by the number of articles published in the field over a period of time [Merton and Lewis, 1971].

With the blurring of the line between basic research and applied research in the biomedical arena, new norms have become central to the scientist and his/her claim for priority. These norms revolve around the priority for intellectual property—enabling a researcher to secure royalties on an invention and funding from a possible private sector collaborator for future work. Powell and Owen-Smith (1998) argue that the separation of the scientist in the academic world and the technologist in the private arena no longer holds in the life sciences. Universities have become much more oriented to the commercialization of research [Powell and Owen-Smith, 1998]. The shift is argued to be a result of changing incentives favouring the commercialization of research. With the 1980 Patent and Trademark Law Amendments Act, also known as the Bayh-Dole Act, universities were given the right to retain property rights to inventions derived from federally funded research [Powell and Owen-Smith, 1998]. The intent of Congress was to promote collaboration between commercial enterprise and academic institutions. In 1984, the rights of universities were more broadly expanded to permit universities to assign

their property rights to others [Powell and Owen-Smith, 1998]. Powell and Owen-Smith (1998) explain that many of the legislative changes of the 1980s and 1990s sparked a considerable upsurge in licensing, as well as the growth in the number of university-industry research centres, consortia, and agreements. Universities are now in the position to grant licenses including exclusive licenses to their inventions to private firms. It was anticipated that such licenses were necessary to provide private firms the incentive to invest in the downstream development of commercial products [Rai and Eisenberg, 2003]. However, no distinction has been made between downstream knowledge that leads directly to commercial products and fundamental knowledge that serves as an input into downstream research that is far removed from commercial product development. Universities have therefore, filed applications on knowledge such as DNA sequences, protein structures, and protein pathways. Even when universities do not file patents, restrictions are placed on the dissemination of biomedical research materials and reagents that might have future commercial value. Secrecy, restrictions, and patents are therefore, enclosing the scientific commons [Merges, 1996].

Adding to this situation, the explosion of new scientific insights and ideas generated by the Human Genome Project is largely occurring outside the walls of major drug companies. Consequently, companies are increasingly entering into mission-driven partnerships with biotechnology companies and academic institutions [Bower and Whittaker, 1992; Powell et al., 1996; Blumenthal et al., 1997]. By collaborating with institutions on the cutting edge of this research, pharmaceutical companies can access knowledge that can be the basis for successful discovery and development projects. In return, these partnerships provide for alternative funding mechanisms for small biotechnology companies and academic institutions [Bower and Whittaker, 1992; Powell et al., 1996; Blumenthal et al., 1997]. Problems however arise when intellectual property rights and exclusive licenses are assigned to partner companies, as fewer technological opportunities remain open for other industry participants. Secrecy, the inability to share biological materials resulting from the partnership, and exclusivity with respect to downstream research, are transforming not only the size of the public domain of

knowledge, but also the interactions that are typically associated with participation in the public commons [Maurer, 2003].

2.6 Appropriating Research

Patents confer upon an inventor the ownership right to a product or process for a designated number of years and thereby permit collection of a reward for invention [Kamien and Schwartz, 1974]. Justification for patents is often based on the fact that the cost of the discovery or downstream development is high relative to the cost of imitation. If the discovery can quickly be imitated, the economic gains to the inventor will be reduced, as will be the incentive to invest in inventive activity. Patents are therefore, thought to enable the inventor to appropriate the monetary benefits of his/her contribution over a limited period of time, thereby counteracting the tendency toward underinvestment [Kamien and Schwartz, 1974].

In the winner take all situation, the incentive to race to achieve patent priority is strong [Kamien and Schwartz, 1974; Lerner, 1995]. Two firms would be better off by cooperating in their research and development activities—keeping costs low and increasing the likelihood of success, but the incentive to defect and race is too strong, particularly in the first-to-invent patent granting scenario. If one researcher defects and is first to reduce the invention to practice, the patent payoff can grant the defector a monopoly over the invention for several years. The payoff for being left behind, by being the second-in-time, is lost investment in research and development. If the patent is granted to the defector, this may also present an effective obstacle for future development for the laggard firm [Scotchmer, 1991; Merges, 1994].

Although patents are thought to encourage disclosure, the granting of rights to exclude others from using the patented inventions can threaten downstream research. Property rights have become the means to generate the resources required to finance research and development activities. Small biotechnology companies, including those that are spin-offs from academic institutions, use their patent portfolios as a signal of their value for

the purpose of attracting investment. The system is however thought to fit a model of research and development where patented knowledge is discrete and the result of a linear research process. In contrast, for many industries, concern has been expressed where the research process is primarily knowledge based, the process of invention may be cumulative and iterative, with downstream knowledge dependent on upstream knowledge [Scotchmer, 2001; Foray, 2002; Antonelli, 2003; Dalrymple, 2003; Scotchmer, 2004]. A patent system that was developed for a discrete model of innovation may no longer be optimal for an information-based, cumulative model of innovation [Dalrymple, 2003]. Consequently, it is necessary to reanalyze models of intellectual property protection and strategies of knowledge sharing in biopharmaceutical discovery research.

In the sections that follow, we provide an overview of both ex-post and ex-ante perspectives including new models of intellectual property.

2.6.1 The Ex-Post View

Roberto and Nelson discuss four different broad theories about the principal objectives of patents. These theories include providing motivation for innovation called the "invention motivation" theory; providing an incentive to disclose inventions (instead of relying on secrecy) thereby enabling the dissemination of knowledge about inventions, known as the "invention dissemination" theory; enabling innovators to secure the needed investments to develop and commercialize these inventions, known as the "induce commercialization" theory; and enabling the orderly exploration of broad prospects, i.e., opening up a whole range of follow-on developments or inventions based on a broad patent, known as the "exploration control" theory [Roberto and Nelson, 1998].

Invention Motivation Theory: The invention motivation theory assumes that the social benefits of patent protection stem from the additional invention induced by the prospect of a patent. Roberto and Nelson discuss that this theory should naturally lead to the analysis of the optimal patent strength i.e., from the perspective of duration [Nordhaus 1969, Scherer et al., 1990] or breadth [Klemperer, 1990], and in terms of a tradeoff between the increased invention induced by greater patent strength and the increased cost

to society associated with the stronger monopoly position of the patent holder [Gilbert and Shapiro, 1990]. The notion of inventive races also needs to be considered when multiple firms end up focusing on a common research strategy or inventive goal [Dasgupta and Stiglitz, 1980a]. When competitive R&D is allowed, duplication of research may occur i.e., more inventing does not imply more useful inventing. If the common focus is on a broader but still limited pool of invention possibilities, one might consider instead overfishing models [Dasgupta and Stiglitz, 1980b]. In this case, although patents could strengthen the incentive to invent to receive a patent, with the anticipation that a patent will be awarded to the inventor that gets there first, the problem of racing could worsen with the awarding of a broad patent covering many claims, research arenas, and downstream product markets [Roberto and Nelson, 1998]. If an inventor perceives that other inventors are in the race, the inventor may see that the returns are dependent not simply on whether the inventor achieves an invention, but on whether the inventor achieves it first. Dasgupta and Stiglitz (1980a) argue that in this case, patent protection will result in a competitive R&D market where firms invest their resources at a faster rate and too many firms race toward the same invention goal. The tradeoff between the benefits and costs of patenting may then favour the latter. Roberto and Nelson state that perhaps society should opt for stronger patents in fields where stronger intellectual property protection yields a larger flow of valuable inventions, than in fields where stronger patents lead largely to more inventions, that is "barking up the same tree" [Dasgupta and Stiglitz, 1980a].

With respect to the granting of broad patents, Joshua Lerner found that the awarding of broad patents to one party inventing in a field, could cause other inventors to stop or divert their efforts, even if the inventions would have been somewhat different. Lerner found that in biotechnology, the holding of patents by large firms tended to deter small firms from trying to invent in these same areas [Lerner, 1995]. Roberto and Nelson (1998) discuss further that the issue of greater patent length or scope can have tremendous consequences if today's invention not only have direct use, but also form the basis for subsequent invention. This seems to be case with gene patents, where genes not only have value as part of today's diagnostics, but also as part of tomorrow's medical

therapies. The long-term effect of granting a broad, strong patent on the initial sequence of a gene will depend on how the gene patent will affect subsequent medical therapy development [Roberto and Nelson, 1998].

Invention Disclosure Theory: The invention disclosure theory proposes that patents encourage disclosure and provide a vehicle for the quick and wide diffusion of the technical information underlying new inventions. One can argue that this theory turns the invention motivation theory on its head at first glance. Roberto and Nelson (1998) argue that this may not be as simple as it appears, since in most specific cases, the possibility to make more profit through wider disclosure for example, through licensing the invention, enhances the incentives for invention in the first place. However, the invention disclosure theory does not cause the reduction in use of an invention that it does in the canonical version of the invention motivation theory [Roberto and Nelson, 1998]. Instead, the focus is on incentives for disclosure, particularly important when an inventor cannot exploit all the possible uses of the invention [Roberto and Nelson, 1998]. As an example, gene patents can facilitate licensing, thereby not only increasing the monetary rewards to the inventor, but also facilitating wider use of the gene in areas of therapy that the original inventor cannot or wishes to not pursue. Various studies have also shown that in certain industries, firms regularly engage in cross-licensing of technology—sharing of technology that would likely be more difficult if patents were not available on the technology [Roberto and Nelson, 1998]. However, the wide dissemination and use of a patented technology does depend on whether an exclusive or nonexclusive licensing strategy is pursued [Eisenberg, 1996]. Exclusive licensing can give a particular company the ‘right of first refusal’ to develop a technology, placing one company in a strategically advantageous position [Eisenberg, 1996]. Non-exclusive licensing on the other hand can allow many firms to have access to the technology, with licenses sold at a cheaper price [Eisenberg, 1996].

Commercialization Theory: The induce commercialization theory is discussed as a possible variant of the invention motivation theory—with patenting occurring early in the process of inventing and with a lot of follow on work to be conducted before the crude

invention, e.g., a gene is ready for use in a medical therapy. A patent at the early stage is seen as providing assurances that if the development of the technology is successful, its economic rewards can be appropriated, thus inducing a further positive development decision. Eisenberg has added to this argument by stating that the patent enables the patent holder to approach capital markets for financing [Eisenberg, 1997]. This capability might be crucial for a small firm facing large development costs, as in the biotechnology and pharmaceutical industries, for clinical testing and development of a medical therapy—costs that are assumed even before the invention reaches the market. Therefore, the induce commercialization theory becomes distinctively different than the invention motivation theory in circumstances where one organization does the early inventing work, e.g., a firm conducts research to find a gene, but is not in a position to complete the development work required to test the gene and develop it in the context of a medical therapy [Roberto and Nelson, 1998]. Under this circumstance, the possession of a patent by the original inventor facilitates handing off the task, via licensing of protected technology, to an organization better suited for development and commercialization. If a first-stage inventor is in the game for profits and knows that profiting will require handing-off the invention to another organization for development, then expectation of a patent may be necessary to induce the initial invention [Roberto and Nelson, 1998]. In context, the Bayh-Dole Act of 1980 gave universities patent rights on inventions that resulted from their government-funded research projects [Powell and Owen-Smith, 1998]. Companies were likely to undertake such development, but would only do so if they possessed the patent rights to the invention it licensed from the university. This placed universities in a strong position to sell such licenses [Powell and Owen-Smith, 1998].

The contrary argument is that the presence of a patent and the requirement to acquire a license to conduct further work on the original idea, could restrict the number of parties who could indeed complete the development work. In the case of gene patents, possibly granted with a limited understanding of its future utility, if potential developers are diverse in their approach to using the gene for medical therapies, and if licensing arrangements of the preliminary gene sequence, whose commercial value is unclear, are

not easy to work out, companies may opt to work on other easily accessible technologies or research arenas [Roberto and Nelson, 1998; Walsh et al. 2003]. Furthermore, if a developer needs to license different parts of a technological puzzle in order to advance a given project, the royalties that need to be paid out could reduce the eventual product's monetary attractiveness. The notion of companies "stacking royalties" is of concern to developers such as the larger pharmaceutical companies. When companies actually sue these pharmaceutical developers to enforce payments for milestones and royalties, or if a pharmaceutical company licenses a lead from a biotechnology firm and that compound is later blocked by another party's patent, the costs (with possible royalty stacking) become even higher [Signals, 1998].

Exploration Control Theory: The exploration control theory assumes that from an initial discovery or invention, a whole range of follow-on developments or inventions are possible. Under this theory, Roberto and Nelson argue that unless there is a controlling, broad patent, a lot of inventors would see the same opportunity and know that their competitors also see them, with the consequence being a race for specific targets of opportunity and a general overfishing in the prospect "pond". Thus, a broad patent on the initial invention may be necessary if the "wasteful mining of the prospect" or the "overfishing of the pool" is to be avoided [Roberto and Nelson, 1998]. However, if one assumes that different inventors see very different opportunities from a prospect, there might be very high social costs to granting a broad patent that gives monopoly rights on the exploration of the prospect. This would essentially cut down the number of diverse inventors who would be induced to work on the prospect in anticipation of a profitable invention down the road, since their ability to work on the invention would be limited by their ability to negotiate a license with the holder of the original prospect-defining patent. In biotechnology, where litigations are high and the transaction costs of negotiating a license high, one needs to seriously consider the impact of granting a large prospect-controlling patent [Roberto and Nelson, 1998]. For example, the role of particular receptors in a disease pathway may not be clear when identified at the outset, but their probable importance as drug targets implies that firms will patent them regardless. Metabolic pathways involved in many common diseases will be complex, so it may be

better for the firm to patent and allow the patent to lapse if in due course, a particular receptor or enzyme (and hence the gene associated with the receptor or enzyme) proves not to be relevant in the proposed medical therapy. Because the scale of genetic information production today is so large and many thousands of genes can be sequenced in a particular set of disease tissues, owning the rights to these molecules becomes critical; however the problem arises with over-patenting and firms pursuing the same information for the same diseases [Thomas, 1999].

Implications from the Roberto and Nelson paper are particularly applicable to science-based industries such as biotechnology. Roberto and Nelson discuss that patent races are more common to such science-based industries. Multiple players are often attracted to the same opportunity i.e., see the same broad unmet needs and particular avenues to follow. Science-based industries are the arena where the need for "technology transfer" between university and industry researchers is most salient. Strong patents are needed to induce companies to develop these university inventions and in a number of instances, university researchers in control of patents have been directly instrumental in setting up new ventures. Science-based technologies tend to require a lot of work to be brought to practice, and there may be significant uncertainty as to how to accomplish this. An early patent on such findings can narrow down the number of parties who have the incentive to do the follow-on work.

Patent Structures and Firm Behaviour: Several other studies have been conducted on patent issues such as: the optimal duration and scope of patent life [Nordhaus 1969, Scherer and Ross, 1990]; level of research activity required, the cost reduction achieved and the relationship of the magnitude of the invention sought versus patent life [Nordhaus, 1969]; the consequence of rivalry among potential inventors prior to granting of the patent; the development time frame chosen for research and development and how appropriability and rivalry enter a firm's determination of the introduction date of an innovation [Scherer and Ross, 1990]. For example, the earlier an innovation is introduced, the sooner the benefits become available [Scherer and Ross, 1990]. But more rapid development usually occurs at a higher cost. Incomplete appropriability of profits

by the inventor may prolong the development period, while on the other hand, the benefits of being first can accelerate development [Kamien and Schwartz, 1974].

What is most interesting is the impact of rivals prior to and after the granting of a patent to an inventor. Kamien and Schwartz (1974) develop a model to demonstrate the impact of several variables on development and expenditures on a particular invention. Variables in this model include magnitude of inventive effort, introduction date and development period, the discount rate of expenditures, the level of rivalry and entry of rivals, the reward stream possible from a patent, and the patent duration.

Their model determined that the present value of expected expenditure on development increased as the development period contracted and as the amount of effort required for the invention increased [Kamien and Schwartz, 1974]. It also increased as the discount rate fell—since future expenditures would be less heavily discounted. The present value of expenditures also rose as the instantaneous probability of rival entry fell or as the expected rival entry date became more distant i.e., the later a rival project is completed, the more development a firm will have been able to conduct [Kamien and Schwartz, 1974]. Development expenditures were only made once the patent issued and rewards are collected by the firm only if it is the recipient of the patent; a firm will lose whatever investment it has already made and does not get anything if a rival completes the R&D first and receives the patent. Hence, this represents a winner take all situation [Kamien and Schwartz, 1974].

Kamien and Schwartz further demonstrate for a single potential invention of given size, that development will occur only if the reward stream is large, the patent duration sufficiently long, and the required R&D effort to get the patent and discount rate are somewhat low [Kamien and Schwartz, 1974]. Rivalry must also not be too intense or the expected time of rival claims to the patent, distant. As far as the speed of development or timing of innovation, the planned development period will be longer in this model, the smaller the value of the reward stream from the new product or process, the greater the effort required to obtain the innovation and patent, and the higher the discount rate

[Kamien and Schwartz, 1974]. These factors can be used to determine if a multi-participant race for a patent will ensue initially and then a race to get a medical therapy/diagnostic out onto the market with respect to biotechnology [Kamien and Schwartz, 1974].

Lippman and McCardle (1987) have studied what conditions caused a firm after having invested in R&D to drop out of a competitive race. Lippman and McCardle refer to Kamien and Schwartz, indicating that their model did not take into account how a firm's decision would affect the R&D efforts of unknown rivals and their model is static—never the case that a firm enters the race and then drops outs, instead that the firm does not pursue research if rivalry is sufficiently intense [Lippman and McCardle, 1987]. Lippman and McCardle also discuss that many papers assume that a race is symmetric and no one firm takes the lead, with competition ensuing until the invention is discovered. None of these models entailed a dropout by any firm. In contrast, the authors discuss the possibility of a firm having invested in R&D, dropping out of the race, due to its own misfortune or the good fortune of a competitor [Lippman and McCardle 1987]. The Lippman and McCardle model demonstrates that in the case of identical firms, it may be optimal for a firm to dropout out of a race if a rival firm attains a large lead. By moving ahead a stage in the race, a firm is thought to increase its experience level, thereby increasing its probability of beating the other firm [Lippman and McCardle 1987]. A follower firm in this case may begin the race, and upon falling behind drop out, particularly since it is assumed that increments to experience arrive exponentially [Lippman and McCardle 1987].

If the firms do not share the same value for the technology being sought, costs of doing research, and/or efficiencies i.e., the arrival rates to the end of each stage of the race, with an increase in value assessment or efficiency and a decrease in cost of research for one firm, this can increase the chance that a rival firm will drop out [Lippman and McCardle 1987]. Even the firm in the lead may drop out in this case if these parameters clearly favour another firm. For instance, a small firm may regard the invention as providing an opportunity for it to survive, whereas a larger firm may regard the invention as just

another product. One firm may be better able to also exploit the invention. These differences can cause even a leader to find it optimal to drop out of a race [Lippman and McCardle 1987].

Other studies have shown the impact of novelty requirements on the incentive to conduct research, the value of the patent, and how much technical information is shared among firms through patenting [Scotchmer and Green, 1990]. Scotchmer and Green discuss that the social goal of protecting an inventor's profit and the incentive to conduct research is served by a strong novelty requirement i.e., that small derivative improvements to an invention will clearly infringe on a prior patent. Therefore, the patent is likely to have a long effective life before a sufficiently different technology replaces it [Scotchmer and Green, 1990]. Patents are also issued to accelerate future innovation through disclosure of inventions. If each technological advance is disclosed, as would be promoted by a weak novelty requirement, the shared technical knowledge could help other innovators in their research, reduce redundancy, and quicken the time for subsequent innovation. Therefore, Scotchmer and Green (1990) argue that in contrast, the social goal of disclosure is served by a weak novelty requirement.

These authors discuss the decisions that have to be made by firms as an R&D race unfolds. The initial decision may be to enter the race, which depends on whether R&D is expected to be profitable [Scotchmer and Green, 1990]. Second, if the novelty requirement is weak so that a small technical advance does not infringe on a previous patent, the inventor of the small advance must decide whether to disclose it by marketing it or patenting it [Scotchmer and Green, 1990]. There is a tradeoff between the profit attained from marketing it and the value of maintaining one's competitive advantage in technical know-how (by not disclosing) for later stages of the race. The third decision may be whether or not the lagging firm should drop out of the race when the first innovator has not disclosed its technical advance, since it is unlikely that the lagging firm will catch up [Scotchmer and Green, 1990]. An important reason why an early innovator might not patent a first advance is that it might be able to force a shakeout by sending a signal that it has innovated, but not patented, thereby not revealing its technical know-

how immediately and losing ex-ante profits that might occur under a weak novelty requirement [Scotchmer and Green, 1990]. Under the weak novelty requirement, disclosure can reduce the probability that the first innovator will achieve the final patent [Scotchmer and Green, 1990]. Since a final patent is likely to have a longer effective life than an interim patent, the innovator may opt not to earn the interim profits, and instead make the patent stronger by continuing onto the next stage of innovation. In this case, there is no difference between weak and strong novelty requirements as both do not result in disclosure. As well, with strong novelty requirements, competition occurs between a base technology and more advanced technology, rather than a close substitute, and therefore, the innovator will be assured a higher profit stream [Scotchmer and Green, 1990]. Consequently, the strong novelty requirement may be socially better than the weak requirement, as it might induce entry into an R&D race when the weak requirement would not [Scotchmer and Green, 1990].

The decision to disclose or suppress an innovation and whether to continue in a race also depends on the legal conditions of priority under which a patent can be granted—first-to-file or first-to-invent. The first-to-invent rule will discourage disclosure relative to the first-to-file rule. With first-to-invent, a first innovator does not need to patent in order to keep a claim alive [Scotchmer and Green, 1990]. If a competitor catches up in this case and attempts to patent the invention, the first innovator can successfully counterpatent to receive the patent, in contrast to the first-to-file system where the counterpatent would be unsuccessful [Scotchmer and Green, 1990]. There may be an advantage in not patenting initially since information that could enable a competitor to catch up is not disclosed. In the first-to-file system, besides more disclosures, the incentives for firms to stay in the race are also strong [Scotchmer and Green, 1990]. However, the incentives to remain in the race under the first-to-invent regime are weaker than those under file-to-file. First-to-invent can encourage firms to drop out of the race when it is socially efficient, whereas first-to-file can induce them to stay in [Scotchmer and Green, 1990].

Licensing Strategies: Knowledge governance strategies include openly disclosing knowledge, depositing knowledge into the existing pool of knowledge, restricting usage

if the knowledge is developed by a collective group, licensing knowledge exclusively to one party for further downstream development, licensing knowledge to multiple parties through a non-exclusive licensing strategy, or using the knowledge internally as an input in downstream development activities.

Transaction costs will impact the choice of governance strategy. Antonelli (2003) distinguishes between demand-side knowledge transaction costs and supply-side knowledge transaction costs. Demand-side knowledge transaction costs include all the costs associated with searching, screening, processing, and contracting for knowledge. Supply-side knowledge transaction costs include all the costs associated with preventing unintentional disclosure, marketing the knowledge, identifying potential buyers, and creating the appropriate contracts with such buyers. (Table 2.2)

Governance Mechanism	Possible Organizational Structure	Major Transaction Costs
Open Access	Individual/ Informal groups	Knowledge coordination/ Knowledge diffusion
Common Pool	Formal groups, Joint ventures, Private pools	Knowledge diffusion
Disembodied Market Transaction: Non-Exclusive Licensing	Public and/or Private collaborations	Search costs, Bargaining costs, Contract costs
Disembodied Market Transaction: Exclusive Licensing	Public and/or Private collaborations/Co-development	Search costs, Bargaining costs, Contract costs
Embodied Transaction/ Integration: Product Market	Private Firm-Consumer interaction	Costs associated with purchase

Table 2.2: Governance Mechanisms, Organizational Structures, and Transaction Costs

The decision to sell disembodied knowledge in the form of patents and licenses can complement or substitute for the sale of embodied knowledge. Substitution occurs when the profits from the sale of disembodied knowledge are greater than those from the sale of embodied knowledge [Antonelli, 2003; Arora and Fosfuri, 2003]. For example, when the costs of internal coordination of the knowledge are larger than the transaction costs associated with the market for technical knowledge, or when special assets are required to

progress further downstream, the patent holder may chose to maximize revenue through a licensing strategy, specifically an exclusive licensing strategy [Teece, 1986; Antonelli, 2003]. Complementarity between the sale of disembodied knowledge and internal embodiment occurs when knowledge possesses high applicability and it is possible to operate in different markets from other licensees of the knowledge [Teece, 1986; Arora and Fosfuri, 2003, Foray, 2004]. In this case, a non-exclusive licensing strategy can ensure that multiple participants can pursue multiple streams of research. Furthermore, cross-licensing is a useful governance mechanism when knowledge exhibits high levels of complementarity [Shapiro, 2001]. With downstream activities dependent on the recombination of a variety of knowledge, the cost of the coordination including accumulation of the full range of required knowledge may be too high for one researcher [Antonelli, 2003; Burk and Lemley, 2003]. Specifically, the capabilities of the one researcher may only cover a portion of the research domain. Consequently, researchers may find it profitable to engage in cross-licensing for knowledge. However, the ability for each researcher to access knowledge depends of the amount and type of proprietary knowledge each one is able to contribute in any bargaining event [Antonelli, 2003].

Licensing imposes a negative pecuniary externality upon other firms in the product market. Although licensing reduces profits from the product market because of increased competition from multiple users of the knowledge, this strategy can increase a licensor's share of such profits. Arora and Fosfuri (2003) propose that there are two main effects that licensing generates on the profits of the licensor—the revenue effect and rent dissipation effect. The revenue effect occurs when rent accrues to the patent holder in the form of licensing payments. The rent dissipation effect occurs through the erosion of profits of the licensor in the product market as a result of increased competition [Arora and Fosfuri, 2003]. The corresponding market power conferred to the licensor through the assignment of property rights will be a major factor in the decision to license technology to enjoy the revenue effect versus the decision to remain a monopolist on the product market to avoid the rent dissipation effect [Arora and Fosfuri, 2003].

Chokshi, Parker, and Kwiatkowski (2006) discuss the usage of geographic exclusivity or co-exclusivity by the National Institutes of Health (NIH) Office of Technology Transfer as an incentive for a licensee to develop a product for particular regional markets. Depending on the needs of the regional market, a license is therefore, non-exclusive, co-exclusive, or exclusive [Chokshi, Parker, and Kwiatkowski, 2006].

Under the compulsory license mechanism, the government or a court can compel a patent holder to license his rights. In general, compulsory licenses are provided in cases of dependency of a downstream patent on an upstream patent, and in cases in which the invention is not (or insufficiently) exploited [Overwalle et al., 2006]. Recently, it has been suggested that the compulsory licensing mechanism can be invoked to address the problems of innovation that affect public health care [WTO, 2002]. Such an approach was formally recognized during the WTO Ministerial Conference in Doha, Qatar, confirming that the Agreement on Trade Related Aspects of Intellectual Property Rights and the compulsory licensing regime are part of a wider national and international strategy to address public-health problems [WTO, 2001; 2002].

Research Exemptions: In Europe, the research exemption is part of patent law. The original provision, which was laid down in the Community Patent Convention, states that the rights that are conferred by a patent shall not extend to "acts done for experimental purposes relating to the subject-matter of the patented invention". The equivalent provisions in the European member-states mirror but sometimes also deviate from this wording. Because different national legislations and court rulings exist, the exact scope of the exemption differs from country to country [Overwalle et al., 2006].

In the U.S., the research exemption is not part of the patent act but exists as a theory. The theory has a very narrow scope of application. In the landmark case *Madey v. Duke University*, it was recalled that:

> Regardless of whether a particular institution or entity is engaged in an endeavour for commercial gain, so long as the act is in furtherance of the alleged infringer's

> legitimate business and is not solely for amusement, to satisfy idle curiosity, or for strict philosophical inquiry, the act does not qualify for the very narrow and strictly limited experimental use defense [Madey v. Duke University, Fed. Cir. 2002].

Therefore, research projects that are financed by major research universities, but that have no prospect of commercialization, still further the institution's legitimate business objectives, including "educating and enlightening students and faculty participating in these projects", and "serve to increase the status of the institution and lure lucrative research grants, students and faculty" [Madey v. Duke University, Fed. Cir. 2002]. As a result of the *Madey v. Duke University* case, universities can no longer invoke experimental use in their defense. In practice however, the research exemption is administered more flexibly as companies would prefer not to sue universities [Walsh et al., 2001].

Patent Pools: Shapiro (2001) discusses that when two or more companies control patents necessary to make a given product, a patent pool or a package license may be an effective solution. Under a patent pool, an entire group of patents is licensed in a package, either by one of the patent holders or by a new entity established for this purpose, usually to anyone willing to pay the associated royalties [Shapiro, 2001]. Under a package license, two or more patent holders agree to the terms on which they will jointly license their complementary patents and divide up the proceeds [Shapiro, 2001].

In 1995, U.S. Justice Department and the FTC issued the Antitrust Guidelines for the Licensing of Intellectual Property ("IP Guidelines"), which sets forth their enforcement policies in this area [IP Guidelines, 1995]. The IP Guidelines specifically address pooling arrangements involving intellectual property owners and their rights [IP Guidelines, 1995].

In particular, the IP Guidelines state that intellectual property pooling is procompetitive when it:

(1) integrates complementary technologies,

(2) reduces transaction costs,
(3) clears blocking positions,
(4) avoids costly infringement litigation, and
(5) promotes the dissemination of technology [IP Guidelines, 1995].

The IP Guidelines also discuss that excluding firms from an intellectual property pool may be anticompetitive if:
(1) the excluded firms cannot effectively compete in the relevant market for the good incorporating the licensed technologies,
(2) the pool participants collectively possess market power in the relevant market, and
(3) the limitations on participation are not reasonably related to the efficient development and exploitation of the pooled technologies [IP Guidelines, 1995].

Currently, the guidelines have been "collapsed" into the following two overarching questions:
(1) "whether the proposed licensing program is likely to integrate complementary patent rights," and (2) "if so, whether the resulting competitive benefits are likely to be outweighed by competitive harm posed by other aspects of the program." [Clark et al., 2000].

As an example, it is anticipated that the Knockout Mouse Project (see Chapter 6) will require the resolution of several intellectual property claims involving both the production and use of knockout mice. To effectively deal with existing intellectual property covering knockout technology, the researchers in the Knockout Mouse Project advocate the use of a patent pool. Austin et al. (2004) indicate that several researchers from various organizations/institutions controlling such patents have agreed to the formation of a patent pool of mouse knockout technologies.

2.6.2 The Ex-Ante View

The ex-post view analyzes strategies for enabling intellectual property assignment and transfer as a means of providing access to and then enabling downstream knowledge use

in product development. In contrast, the ex-ante view analyzes other mechanisms available, either prior to patent assignment or during patent assignment, to ensure access to and use of knowledge for product development.

Open Source Initiatives: The open source model has provided a valuable framework for collective knowledge production and dissemination beyond the software community. Mirroring the efforts of the open source community that developed Linux, open knowledge networks and other cooperative strategies (classified as open source discovery initiatives) are enabling biopharmaceutical companies to access disembodied knowledge-based resources critical to downstream drug development. The objective of these cooperative strategic alliances is to preserve the downstream technological opportunities for multiple firms. When upstream discovery research cannot yield commercial products and when the costs associated with excessive upstream competition are too high, companies jointly benefit from cooperative knowledge production and open knowledge dissemination [Nelson, 1959; Reichman, 2003].

The Human Genome era has emphasized the notion that biological knowledge is complex. Discovery research no longer simply focuses on individual units of knowledge, but considers the behaviour and relationships of all units of knowledge in a particular biological system from a functional perspective. Genomes are now being described as consisting of complex, intersecting systems rather than unitary collections of separately functioning structures [Hood, 2000; Dutfield, 2003]. In this sense, we can observe many similarities to software development. Software is a complex system, developed from many intersecting components (lines of code). Thousands of developers may be required to develop these intersecting lines of code to enable the processes associated with this code to emerge and function. Demarking the lines of ownership in this case can be an onerous task—both in terms of inventor and in terms of invention.

The International Human Genome Project catalyzed the open-source movement in genomics-based research. Globally dispersed laboratories jointly collaborated to map and sequence the Human Genome. The resulting data were rapidly deposited into the public

domain to ensure an open and level playing field for all researchers. Open source has also flourished in bioinformatics, where software code and databases are traded and pooled on a mutual sharing basis.

Efforts in the public sector to enable large-scale genomics research through open knowledge networks or open source initiatives have encouraged the private sector to promote and participate in open source initiatives. The Single Nucleotide Polymorphisms (SNP) Consortium brought together ten of the world's largest pharmaceutical firms. Consortium members recognized the SNP map as a pre-competitive, research tool. The competitive members viewed the map as a tool to be jointly developed and shared, with open access to the Consortium's data guaranteed for the public at large. Firms relinquished any property rights to the knowledge generated within the Consortium [Davies 2001].

Open Review System/Peer Review with Monitoring: Certain national legal systems provide for the ability to oppose patents after they are granted. The U.S. Patent Reform Act of 2007 hopes to create such a post-grant review to challenge issued patents. Other systems provide for the possibility of opposing applications before patent rights are granted. Foray discusses that the pre-grant opposition is only possible if information concerning the patent application is published early in the process i.e., within 18 months of the application [Foray, 2000].

On June 15th 2007, the United States Patent and Trademark Office (USPTO) opened the patent examination process for online public participation. With the consent of the inventor, the Peer-to-Patent: Community Patent Review pilot, developed by the New York Law School Institute for Information Law and Policy in cooperation with the USPTO, enables the public to submit prior art and commentary relevant to the claims of 250 pending patent applications in Computer Architecture, Software, and Information Security [USPTO, 2007].

Peer-to-Patent involves 1) reviewing and discussing posted patent applications, 2) locating prior art references 3) uploading prior art references relevant to the claims, 4) annotating and evaluating submitted prior art, and 5) submitting the top ten references, along with a commentary to the USPTO. The goal of this pilot is to determine if organized public participation can improve the quality of issued patents [USPTO, 2007].

New Category of Goods: Foray suggests that a new category of intellectual property such as "common goods" may be required to deal with the uncertainties associated with new forms of knowledge. He suggests that with new, complex objects such as genes that do not ideally fit into the usual categories of private-public goods, that the new category of common goods might prove useful. Under this regime, an organization or institution that is in possession of a good useful in product development, would not serve as the owner, but simply the manager of the good [Foray, 2000].

Overwalle et al. (2006) allude to this management of goods via clearinghouses—by which providers and users of goods are matched. For example, the Science Commons encourages technology transfer and intellectual property licensing via the adoption of standardized licenses to create transparency in the use of patented technology in science. Similarly, the Creative Commons enables the transferring and licensing of copyrighted material [Overwalle et al., 2006].

Biological Innovation for Open Society (BiOS) is an initiative of the Centre for Applications of Molecular Biology in Agriculture (CAMBIA) with the objective to develop new means for cooperative invention, improvement, and delivery of technologies for life sciences. Research tools that have resulted from the BiOS initiative are made available on the basis of a BiOS license [Overwalle et al., 2006]. Instead of royalties or other conditions that disfavour creation of products, under a BiOS-compliant agreement, the user must agree to conditions that encourage cooperation and development of the technology in order to obtain the right to use the technology [Sulston, 2006].

These conditions include a provision that licensees cannot exclusively appropriate the fundamental essence of the technology and/or improvements. The base technology remains the property of the entity that developed it, but improvements can be shared with others that support the development of a protected commons around the technology; those participants who agree to the same terms of sharing obtain access to improvements, and other information such as regulatory and biosafety data [www.bios.net, 2007].
To maintain legal access to the technology, users must agree not to prevent others who have agreed to the same terms from using the technology and any improvements in the development of varied products.

The Commons: In this regime, all researchers have the privilege of using knowledge and resources. In the commons, researchers have one guaranteed right—that of not being excluded from exploiting knowledge or resources. Concerns about the enclosure of genomic resources have led to movements within the industry to preserve the existing "biotech commons" and to reclaim knowledge that has already been privatized.

Under certain conditions, the biotech commons is an efficient institution that can preserve downstream opportunities for multiple researchers fairly and efficiently. Cooperative interactions during discovery research can ensure that knowledge is generated for the purpose of disclosure and deposit into the biotech commons. Foray (2004) proposes five classes of incentives to participate in the commons and freely reveal knowledge:

1) Voluntary spillovers are likely to occur when reward systems specifically encourage knowledge diffusion e.g., collegial reputation as a reward for working in open science.
2) Voluntary spillovers are likely to occur when researchers or organizations need to create "general reciprocity obligations" in order to access external knowledge from others working in a similar arena.
3) Voluntary spillovers are likely to occur when an organization freely reveals an innovation in order to benefit from its increased diffusion e.g., to influence adoption of a technology or technology standard.

4) Voluntary spillovers are likely to occur when firms are interested in improvements of the average aggregate performance of an industry e.g., to increase safety and regulation associated within an industry.
5) Voluntary spillovers are likely to occur when an organization is attempting to pre-empt rivals from pursuing a particular technological pathway or enclosing a technological arena e.g. SNP Consortium.

2.7 Strategic Alliances: Knowledge Acquisition versus Knowledge Access

Knowledge Acquisition: Alliances between biotechnology and pharmaceutical companies provide access to complementary assets [Teece, 1986; 1992]. In resource-based alliances, parties are assumed to be mutually dependent upon the resources controlled by other parties and common benefits are associated with pooling resources [Powell, 1990; Das and Teng, 2000]. The exchange and accumulation of resources becomes necessary when resources are mingled with other resources or embedded in organizations [Das and Teng, 2000]. Mergers, acquisitions, and strategic alliances are alternatively employed to access these resources [Child and Faulkner, 1998; Kogut, 1998; Das and Teng, 2000].

For example, academic institutions and biotechnology companies can supply new insight and ideas for drug pipelines, validate drug targets, and develop compounds, therapies, and technologies. Large traditional pharmaceutical manufacturers possess complementary research capabilities such as large research assets not available in smaller biotechnology companies and resources for large-scale development and marketing. Hence, clinical testing, manufacturing, and marketing know-how, have encouraged smaller biotechnology companies to form alliances with pharmaceutical companies possessing these intangible resources [Arora and Gambardella, 1990; Greis et al., 1995; Powell et al., 1996]. This division of labor allows small biotechnology firms to focus on upstream research and large pharmaceutical companies to gain access to newer technologies by exploiting their large-scale development advantages. Small biotechnology firms may

invest in research despite not being able to develop and commercialize their inventions. Instead, these small firms rely on licensing scientific knowledge and technology to larger pharmaceutical firms. Consequently, genes, proteins, biological systems and their associated patents have become strategic knowledge-based assets [Blumenthal, 1992; Powell and Owen-Smith, 1998; Arora and Fosfuri, 2003; Jackson, 2003].

Concerns about protecting knowledge-based resources in strategic alliances will impact the decision to form an alliance and the structural choice for the alliance. From the resource-based perspective, firms are not only interested in acquiring complementary assets, but are also interested in protecting their own resources and knowledge in an alliance. Studies indicate that firms will choose a more hierarchical structure when partnering with other firms in environments with weak intellectual property protection [Oxley, 1999]. A hierarchical structure, including equity based alliances, are used to monitor the behaviour of alliance partners, limit a partner's use of technology, and encourage adherence to the spirit of any agreement between the parties [Pisano et al., 1989; Oxley, 1999]. However, hierarchies do have their costs as technological opportunities may not be optimally or completely exploited within these alliances.

In alliances such as joint R&D, joint production, and joint marketing, bilateral contract-based alliances provide more opportunities for learning than unilateral contract-based alliances such as licensing and subcontracting [Das and Teng, 2000]. Of import in such alliances, is that scholars suggest that once learning has been accomplished, alliances will be terminated, with each firm progressing unilaterally thereafter [Khanna et al., 1998].

Unilateral contract-based alliances are preferred when partners are contributing property-based resources to the alliance. These alliances can include licensing, subcontracting, and distribution agreements. In such alliances, there is essentially an exchange of property rights e.g., intellectual property rights for licensing fees, royalties, or the future right to licenses on downstream applications of the original intellectual property [Eisenberg, 1996; Das and Teng, 2000; Kieff, 2003]. Table 2.3 outlines the above alliance structures

and the incentive to participate in such alliances from a knowledge acquisition perspective.

Alliance Structure	Knowledge Acquisition Incentive
Mergers and Acquisitions- Equity Based Alliances	"A firm will favour acquisitions over joint ventures when the assets it needs are not commingled with other unneeded assets within the firm that holds them, and hence can be acquired by buying the firm or a part of it." [Hennart and Reddy, 1997]. "If the market is munificent or the firm is pursuing a strategy for which it has extensive resource capabilities, there is much less incentive to cooperate. Firms are more likely to continue alone." [Eisenhardt & Schoonhoven, 1996].
Strategic Alliances- Joint R&D, Joint Marketing, Bilateral Contract-Based Alliances	Alliances are preferred "when the critical inputs required to pursue the opportunity are owned by different parties and when these inputs are inseparable from the other assets of the owner firms." [Ramanathan et al., 1997]. "Collaborations are a useful vehicle for enhancing knowledge in critical areas of functioning where the requisite level of knowledge is lacking and cannot be developed within an acceptable timeframe or cost." [Madhok, 1997].
Market-Based Transactions- Licensing, Subcontracting	When "the purchase of the resource…from the firm that possesses it" [Chi, 1994] can be efficiently conducted through the market.

Table 2.3: Theories of Knowledge Acquisition

Knowledge Access: Grant and Baden-Fuller (2004) contend that the primary basis for knowledge-based alliances is knowledge access rather than knowledge acquisition [Mody, 1993; Mowery et al., 1996; Larsson et al., 1998; Mowery et al., 1998; Das and Teng, 2000; Kale et al., 2000; Grant and Baden-Fuller, 2004]. Such alliances contribute to the efficient utilization of knowledge and the efficient integration of knowledge into the development of products. These efficiencies are critical when there is uncertainty as to the role of future knowledge requirements for new product development and where there are early-mover advantages associated with rapid knowledge access and product

development [Greis et al., 1995; Grant and Baden-Fuller, 2004]. Where products require a broad range of different types of knowledge, efficiency of integration is maximized through separate firms specializing in different knowledge areas that are linked by strategic alliances [Liebeskind et al., 1996; Grant and Baden-Fuller, 2004]. As the breadth of knowledge required to generate new products increases, the propensity to form alliances with other firms who have specialized in the requisite knowledge, also increases [Grant and Baden-Fuller, 2004].

2.8 Using Game Models to Understand Firm Behaviour

A game of strategy is conceived in game theory as "as a situation in which two or more players make choices among available alternatives" [Rapoport and Chammah, 1965]. The totality of choices determines the outcome of the game and the rank order of preferences of outcomes is assumed to vary for different players. Thus the "interests" of the players could be in conflict. Rapoport and Chammah state that psychologically the most interesting situations arise when the interests of the players are only partly opposed and/or partly coincident, because of the possibility of conflicts not only among the players, but also inner conflicts "within" players [Rapoport and Chammah, 1965]. Mixed motive games with conflicting parties and conflicting motives within participants are formalized in game theory as "nonzero-sum games".

By definition, in nonzero sum games, some outcomes of these games are jointly better for both players than other outcomes. This is in contrast to two-person zero-sum games in which the preferences of the two players must always be opposite [Rapoport and Chammah, 1965]. Prisoner's Dilemma is an example of a nonzero-sum game, with a mixture of interpersonal and intrapersonal conflicts.

Prisoner's Dilemma has been commented upon but forgotten many times in literature, usually without the realization that it is a universal problem. Political scientist Robert Axelrod told Poundstone that "…with Prisoner's Dilemma, you can say there's a conflict

between individual and group interests, but you can't really get very far without the framework of game theory" [Poundstone, 1992].

Prisoner's Dilemma, derives from the following anecdote used to illustrate the game:

> Two prisoners, held incommunicado, are charged with the same crime. They can be convicted only if either confesses. The payoff associated with conviction on the basis of confession is –1 and the payoff associated with acquittal is +1. Further, if one prisoner confesses, he is set free for having turned state's evidence and is given a reward with the payoff of +2. The prisoner who has held out is convicted on the basis of the previous prisoner's testimony and is given a more severe sentence than if he had also confessed with a payoff of –2 [Rapoport and Chammah, 1965].

The most common type of Prisoner's Dilemma in everyday life is the "free-rider dilemma". This is a dilemma with many, rather than just two players. The name of this dilemma refers to the problem confronting public transit riders. Simply: It's late at night, and there's no one in the subway station. Why not just hop over the turnstiles and save yourself the fare. But if everyone hopped the turnstiles, the subway system might not be able to maintain itself to the detriment of all of its users. There can be no doubt that many people will defect and hop the turnstiles. Since there will always be people who "get away with" not paying, the others are suckers who pay full fare [Poundstone, 1992].

In New Zealand, newspaper boxes operate on an honour system. Readers are supposed to drop a coin into the payment box, but nothing physically prevents someone from taking a newspaper without paying. However, few readers evidently steal, recognizing the consequences of mass defection [Poundstone, 1992].

The free-rider dilemma can be even more hopeless than the two-person Prisoner's Dilemma as defectors can hide in the crowd. Taxes are one way governments avoid free-rider dilemmas. It would be nice if people voluntarily contributed money for maintaining roads, running schools, and other such public works. But few people would do so

knowing that many others would pay nothing. Most people can be convinced that taxes for public works are desirable, provided that everyone pays. Thus, the government enforces the payment of taxes [Poundstone, 1992]. In the government however, Poundstone distinguishes between the liberal cooperators and the conservative defectors. A liberal is described as a "cooperator"—someone willing to put himself at risk for exploitation in order to increase the common good. Liberals favour paying taxes that go to help the homeless in the expectation that the homeless will not fritter way such aid, but will use it to get on their feet. Conservators are "defectors" in that they seek to guarantee themselves the best outcome possible on their efforts alone. Taxes may be squandered, so the best course it to let people keep as much of their income (i.e. via lower taxes) as possible and decide individually how best to spend it [Poundstone, 1992].

The Tragedy of the Commons: A common view is that a multi-player Prisoner's Dilemma can be reflected in what Garret Hardin popularized as "the tragedy of the commons" [Hardin, 1968]. Hardin's tragedy of the commons develops in the following way: Each member of a group of neighboring farmers prefers to allow his cow to graze on the commons (common land), rather than keeping it on his own inadequate land. But the commons will be rendered unsuitable for grazing if more than some threshold number of farmers uses it [Hardin, 1968].

As the human population increased, the idea of the commons had to be abandoned in one aspect after the other. The overgrazing problem was solved with the institution of private property or the allocation of the right to enter the commons area. Restrictions have been placed on the disposal of domestic sewage, with an ongoing attempt to close the commons to pollution by automobiles, factories, insecticide sprayers, fertilizing operations, and atomic energy installations. Taxes can be used to induce people to be temperate in their use of the commons i.e., not forbidding a person from using the commons, merely making it expensive to do so. Hardin also believed that while abandoning of the commons in breeding is difficult, it needed to be dealt with [Hardin, 1968]. The figure that follows (Figure 2.5) graphically shows the transition from the commons to private property with the parceling of the commons into distinct sections of

privately owned property—denoted as A, B, and C, owned by three individuals—denoted as 1, 2, and 3. In this regime, individuals 1, 2, and 3 are able to exploit their property (or resource) in their entirety.

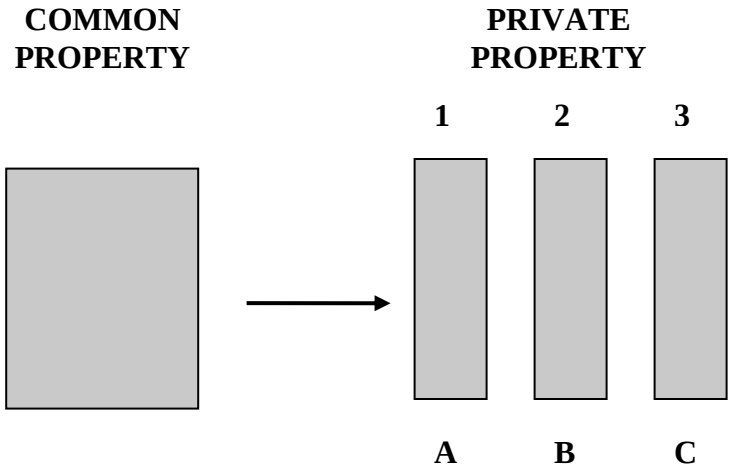


Figure 2.5: The Transition from a Commons to Private Property

Tragedies in Biotechnology Research: Merges (1996) discusses that cooperating is very attractive if it is mutual, but defecting is proof against being a "sucker" (ending up at one's worst outcome), which explains why players may defect unless the opponent's cooperation is assured [Axelrod, 1984; Gulati et al., 1994; Kollock, 1998]. Each researcher will find defection in his or her own interest, and will therefore expect the partner to similarly defect [Merges, 1996].

The tragedy of the biotech commons is a result of free riding by other users and the inability of the original inventor to appropriate knowledge. The properties of non-rivalry and non-excludability will enable non-authorized users to benefit from use of the knowledge at little or no cost. Therefore, patents provide a temporary monopoly to the original innovator to use or assign rights for usage of knowledge for appropriation. Specifically, the owner will have control over the rights to use, returns from any activity that will use the knowledge, and any transfer of usage. The first innovator's incentive to invest will be ensured if he/she can receive a private return on first-generation knowledge and possibly on second-generation knowledge produced either internally or externally by

others. The tragedy where innovative knowledge is not generated and diffused for others to use can be avoided through the assignment of property rights [Hardin, 1968; Foray 2004].

In contrast, Heller and Eisenberg propose that with the proliferation of property rights in biomedical research—a tragedy of the anticommons, can occur in which follow-on innovators underuse a scarce resource because too many owners can block these innovators and no one has effective privilege of use [Heller and Eisenberg, 1998]. This tragedy occurs in the course of downstream research and product development based on a proliferation of upstream property rights. In Figure 2.6, the anticommons results from the fact that private ownership rights fragment goods. Tragedy occurs as a result of multiple owners of fragments of A, B, and C. The owners 1, 2 and 3 can exclude others from using their fragments, however, nobody can exploit these good in their entirety [Foray, 2004]. Overcoming the tragedy involves managing transaction costs, dealing with problems associated with bargaining for rights to use of knowledge, and preventing holdouts. Similarly, excess privatization can occur when initial patents are too broad and reward early innovators too generously, thereby blocking the possibility for incremental innovation and the exploitation of technological opportunities not captured by the early innovator [Foray, 2004]. Although the tragedy of the anticommons is associated with excessive fragmentation of the knowledge base, both scenarios of excessive privatization pose a problem for downstream innovators.

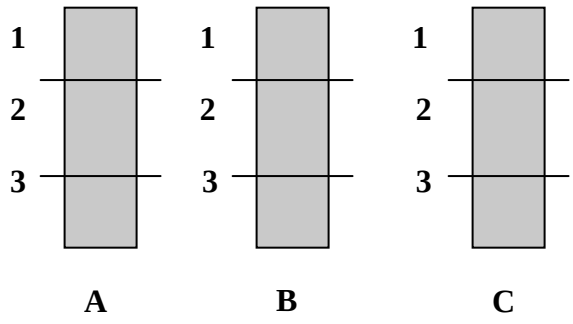


Figure 2.6: The Anti-Commons

In the winner take all situation, the incentive to race is strong. In the two-player game, if one firm defects and is first to reduce the invention to practice, the payoff is a patent that

grants the defector a monopoly over several years for the invention. The patent can become a crucial bargaining tool for the defector. The payoff for being left behind, either by being the lone cooperator or being the second-in-time, is lost investment in research and development. Therefore, it makes rational sense to defect no matter what the other company does, with the possibility of being first-to-invent or even the first-to-file and receive the patent on one's invention. With a responsibility of the firm to its shareholders, a company is obligated to protect its R&D and its monetary investments. It is therefore likely that both companies will defect, exacerbating the race, with high costs before and after the patent is granted (i.e. via litigation to defend patent rights). A possible game matrix of these payoffs is shown in Table 2.4.

Player 1/Player 2	**C_2 Cooperates**	**D_2 Defects and Races**
C_1 **Cooperates**	R=Faster discovery or increased probability of discovery and profits; Cost containment	S=Sunk Costs/No patent; T=Patent granted/Monopoly over invention
D_1 **Defects and Races**	T=Patent granted/Monopoly over invention; S=Sunk costs/No patent	P=Exorbitant costs with no guarantee on the patent situation

Table 2.4: The Patent Race

"R" stands for reward and refers to the payoff each player receives as reward for cooperating; the "S" stands for the sucker's payoff and is the payoff received by the player who cooperated while the other player defected; the "T" stands for temptation—the payoff that a player may hope to get if he can defect and get away with it; and the "P" stands for punishment, given out to both players when both have defected [Rapoport and Chammah, 1965].

To avoid an anti-commons situation, cooperation should be encouraged via joint licensing, including cross-licensing of intellectual property between companies for further research and development activities. (Table 2.5) Companies can use their patent positions to trade with other companies for access to other research tools. Defection occurs when companies engage in the use of submarine patents, large and complex agreements including reach through licensing agreements (RTLAs) to profit from a licensee's downstream product development, charge high royalties fees, or license patents on an exclusive basis [Kieff, 2003].

	C_2 Cooperates	**D_2 Defects**
C_1 **Cooperates**	R=Faster discovery or increased probability of discovery and profits; Cost containment	S=Cost of licensing, royalty payments, or 0 if no license is granted; T=Large royalty streams, even RTLAs
D_1 **Defects**	T=RTLAs, large royalty stream; S=0 or Cost of licensing and royalty payments	P=Exorbitant costs to both; Royalty stacking; Project/Product withdrawals

Table 2.5: Avoiding the Anti-commons

Both companies are better off engaging in cooperative behaviour to remove any downstream obstacles. However, submarine patents, exclusive licensing, and large royalty payments provide a strong incentive to defect as a result of the large payments that can be extracted from a downstream developer. If a company engages in defective behaviour it can secure a large future royalty stream—even negotiate a RTLA on future products, and not be the "sucker" who cooperates. Double defection can be seen as a "TIT for TAT" move—a punishment for other companies defecting, with the end result becoming a "tragedy of the anticommons". Even Eisenberg does not expect the biotechnology industry to come together cooperatively to widely cross-license patents to ease product development. "I haven't seen any signs of that. I mean, every biotechnology product that has come to market has been accompanied by litigation—to the death", states Eisenberg [Garber, 2000]. She further states that the biggest losers could be the small biotechnology firm that lacks the "trading currency" for equitable cross-licensing [Garber, 2000].

In the sections that follow below as well as in Chapter 6, we analyze how new models of operation are in fact enabling for cooperative knowledge production and dissemination to alleviate problems associated with the anti-commons.

2.9 Models of Cooperation

Open Innovation: Chesbrough explains that innovation has become increasingly open through a division of labour. In many industries, the vertically integrated organizational structure where innovation is solely an internal activity is gradually transforming into a more fluid structure tapping into both internal and external sources of innovation. For example, companies are finding value through the licensing of intellectual property, the development of joint R&D ventures, or other arrangements to exploit technology outside the boundaries of the firm [Chesbrough, 2003; 2007]. In the pharmaceutical industry, giants such as Merck and Pfizer have watched as biotechnology upstarts such as Genentech, Amgen, and Genzyme have exploited external discoveries to become major players in this industry. These companies have used an open business model in which ideas move from discovery to commercialization through at least two different organizations—with different parties involved in the innovation process [Chesbrough 2003].

Rising costs, technological complexities, and shorter life cycles have put pressure on companies and their internal innovation processes. The pharmaceutical industry is facing patent expirations, empty pipelines, increased regulatory complexities, and a shorter life cycle created by brand competitors and generic competitors that quickly enter the market. Chesbrough (2003) discusses that open business models can enable pharmaceutical companies to leverage external resources and human capital to save time and money during the innovation process. The open business model further enables companies to generate revenue through the licensing of technologies that cannot be fully exploited within an organization and through the in-licensing of technologies that are discovered outside the boundaries of the organization [Chesbrough 2003].

From a knowledge perspective, in the closed model, human capital is employed within the boundaries of the organization. Knowledge is generated within and belongs to the originating firm. The organization's profit model revolves around the notion that knowledge is discovered, developed, and then embodied within firm-only products

[Chesbrough 2003]. Appropriated knowledge is controlled by the originating firm. In the open model, human capital and knowledge are accessed both inside and outside the boundaries of the organization. External knowledge can create significant value for a firm; internal innovation processes are therefore also needed to evaluate and exploit this knowledge. Firms can profit from the embodiment of knowledge within internally developed products as well the embodiment of knowledge in products developed by other firms [Chesbrough, 2003].

Knowledge-Based Networks: Knowledge-based networks are communities of individuals with the objectives of producing and disseminating knowledge. Norms or rules for knowledge sharing and knowledge appropriation are necessary in networks with varied types of researchers [Ostrom et al., 1994; Liebeskind et al., 1996]. Knowledge networks enable multiple researchers to pool assets, know-how, and expertise for the purpose of knowledge generation, knowledge validation, and new wealth creation [Powell et al., 1996; Reid et al., 2001].

Open network structures exists to undertake research and to generate new knowledge in a specific scientific or technological domain [Hacklin et al., 2004]. These alliances are only concerned with the generation of new, disembodied knowledge. They are not concerned with the possible application and embodiment of knowledge [Liebeskind et al., 1996; Stokes, 1997]. A formal organizational structure, rules for participation (by invitation or match of qualifications to the theme of the network) as well as norms regarding knowledge dissemination are typical of these types of network structure [Liebeskind et al., 1996]. In this type of alliance, members provide a function or resource that is complementary to and synergistic with the contributions of other members of the alliance [Child and Faulkner 1998; Reid et al., 2001]. Firms are able to benefit not only from their own knowledge, but also through the recombination of knowledge from other firms [Kogut, 1998]. (Figure 2.7)

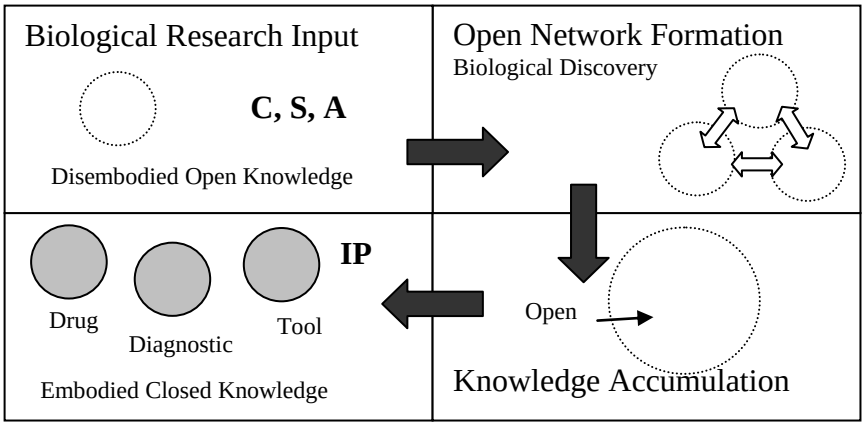


Figure 2.7: Upstream Knowledge Creation through Strategic Alliances
C=Complementarity, S=Substitutability, A=Applicability, IP=Intellectual Property Rights Sought; Dotted, clear circle=Disembodied, open knowledge; Solid, filled circle=Embodied, closed knowledge

In contrast, development networks exist to create new knowledge and to accelerate the application of the knowledge [Stokes, 1997]. A variety of formalized projects may be undertaken in this type of network. Participants are carefully chosen based on reputation and capabilities. These networks are marked by tight forms of governance and hierarchy [Reid et al., 2001]. Given the application orientation of these networks, issues relating to the ownership of intellectual property can become important [Oxley, 1999; Das and Teng, 2000]. (Figure 2.8)

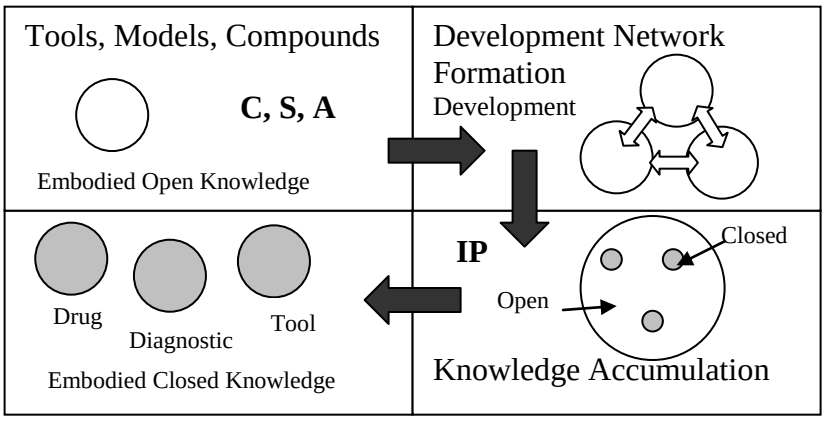


Figure 2.8: Downstream Knowledge Creation through Strategic Alliances
C=Complementarity, S=Substitutability, A=Applicability, IP=Intellectual Property Rights Sought; Solid, clear circle=Embodied, open knowledge; Solid, filled circle=Embodied, closed knowledge

Relevant Models from the Information Technology Sector: Models of cooperation associated with open standard development and open source software development provide us with valuable insight for cooperative biotechnology development.

Open standard development reflects collaborative technology production between multiple organizations. Open source software development entails both collaborative production as well as implementation of a technology.

Open standards are essentially a set of rules for the design of new products. These rules enable coordination between products and components by establishing a common interface to manage their cross-interaction [Chesbrough et al., 2006]. Voluntary non-market Standard Setting Organizations that operate in industries such as software development, where coordination is large, can have a considerable impact on the rate and direction of technological change i.e., via the adoption of a particular technology as an industry standard [Chesbrough et al., 2006].

Open standards create value for consumers by promoting competition between implementations. Firms selling products that implement a standard enjoy less uncertainty associated with the coordination of products [Chesbrough et al., 2006]. It is anticipated that firms that produce technologies used to implement a standard, participate in open standard groups to capture the value associated with the development of a new compatibility standard e.g., absorptive capacity, early access to technology [Cohen and Levinthal, 1990; Chesbrough et al. 2006].

In the management of standard creation, standard setting organizations establish a set of rules and obligations for members as outlined in the charter and bylaws of the organization [Lemley, 2002]. Intellectual property rights (IPRs) in open standard development are governed by these rules and address searching for IPRs within member files and or the broader literature, disclosing information within the organization, and licensing of IPR. These rules are essentially designed to prevent members from adopting a standard that entails ex-post hold-ups by patent owners offering a licensing that likely would not have been accepted ex-ante. Table 2.6 outlines the intellectual property strategies used in the creation of standards [Chesbrough et al., 2006].

Strategy	Description	Examples
Contributing IPRs	Royalty-free licensing to promote implementation of standard.	Ethernet
Defensive Patent Pools	Aggregating patents in the public domain.	Cable Labs
Open-source Licensing	Freely licensing any follow-on innovations.	Linux, Apache
Participatory Licensing	Disclosing of patents during standard setting and licensing to implementers.	RSA cryptography patents
Ex-post Licensing	Conducting a search for standard related IPR and approaching implementers about licensing.	Eolas vs. Microsoft BT hyperlink suit
Active Hold-up	Participating without disclosure and then pursuing ex-post licensing.	Rambus
Cross-Licensing Alliances	Cross-licensing that replicates the patent pool.	GSM Semi-conductors
Royalty-generating Patent Pool	Pooling of patents within a centrally administered licensing authority.	MPEG-LA

Table 2.6: Intellectual Property Strategies Used in Standard Creation

Open source software development reflects both collaborative production and shared implementation of a technology [Chesbrough et al., 2006]. Open source software is considered to be a reaction to the proprietary software model, differing from this latter model in terms of intellectual property rights and its production. Namely, open source software involves collaborative production and requires free distribution of software source code and the right for others to modify the code.

Lakhani and von Hippel (2003) discovered in their research three types of incentives driving firm participation in open source software development including: direct utility to the organization from collaborative, open software development e.g., absorptive capacity development and early access to technology; intrinsic benefit from participating in the development of this software e.g., learning a new skill; and signaling one's abilities in a technological arena to one's peers or firms. Two highly visible open source projects are the Linux operating system through the Open Source Development Labs (OSDL) and the

Mozilla web browser project. In both cases, firms donate their research to the open source project while exploiting the pooled R&D of the project to enable the sale of related products [Chesbrough et al., 2006].

Open source software and related free software are essentially about intellectual property rights. Both models require the public disclosure of source code and ensure that all users have the right to modify the source code. However, there are key differences between the two models that should be noted [West and Dedrick, 2001]. (Table 2.7) Open source licenses impose fewer restrictions and are attractive to firms to use as components of their own systems. Free software licenses are much more restrictive. Licenses such as the General Public License (GPL) require modifications to GPL-licensed technology to be publicly disclosed as a means of preventing firms from developing proprietary derivative works to supplant the free version [West, 2003]. Valimaki (2003) discusses that firms use the restrictions of the GPL to their advantage—releasing the details of a technology to make it less attractive for use by direct competitors.

License	Terms	Strategic Advantage
Open Source	Source code should be disclosed; Modifications possible by any user.	Free access to technology that can serve as a platform for internal innovation and technology development that can supplant open source technology.
Free Software	Source code should be disclosed; Modifications possible by any user; Modifications should also be disclosed.	Shared innovations remain shared; Limiting the incentives for competitors to develop proprietary technology to supplant shared version.

Table 2.7: Comparing Open Source and Free Software Licenses

We use the above theoretical concepts and models (including strategies employed by the information technology sector) to provide a foundation for our discussion of the biotech commons as outlined below.

In Chapters 4 and 5, we begin the discussion by describing the simultaneous evolution of research paradigms and knowledge structures supporting such paradigms. As the current systems biology paradigm emerges, we discuss knowledge appropriation and the impact on downstream development if the current strategies are used to award intellectual property rights. To determine if problems may exist on the horizon, we analyze seven biological systems and the patents filed on these systems; we specifically analyze the focus of each patent in terms of paradigm, stage of development, and institutional ownership. In Chapter 5, we open the discussion further and analyze the impact of knowledge structures generally on the formation of upstream research-based alliances. We discuss (using data acquired for the period 1980 to 2005) how upstream research-based alliances (including targets for knowledge appropriation) in the public and private sectors have evolved with drug discovery and development paradigms. In Chapter 6, we then specifically analyze one type of strategic alliance—the research consortia and its role in preserving the biotech commons. In this chapter, we analyze 39 consortia formed since the Human Genome Project including the structure of these consortia, the underlying knowledge production processes, and knowledge appropriation strategies used to ensure broad dissemination and exploitation of consortium knowledge. Based on this understanding, we develop three game models to understand (1) the incentive to participate in such research consortia (Chapter 7), (2) the incentive to keep knowledge in the biotech commons rather than appropriate knowledge through the filing of patents (Chapter 8), and (3) the bargaining process once patents are filed and the impact of knowledge structures on the interactions between licensor and licensee (Chapter 9).

We anticipate that our ex-ante perspective on knowledge structures will enable industry stakeholders to better understand how knowledge production, dissemination, and appropriation strategies need to evolve as our understanding of disease and medical intervention deepens. The decisions made by these industry stakeholders with respect to alliance formation, knowledge management within such alliances, and unilateral versus cooperative product development should therefore, take account into the changing value of knowledge. This notion of "changing value of knowledge" is our novel contribution to the current literature on intellectual property rights; our game models also provide a

nuanced framework for understanding the decisions made on the basis of knowledge valuation.

Chapter 3: Methodology

3.1 Purpose of Models

Drug discovery research and development has become increasingly complex and costly. As paradigms change—from the chemical paradigm, to the molecular biology paradigm, and now the systems (information) paradigm—new models of innovation are emerging. What was once a simple linear race to the market by pharmaceutical companies has become an integrated system of alliances with multiple feedback links between pharmaceutical companies, biotechnology companies, and academic institutions. This system of alliances and links is enabling traditional pharmaceutical companies to access new discoveries and technologies, and biotechnology companies as well as academic institutions to access capital needed to progress into drug development. The objective of this new model of innovation is to better manage the time and cost to market.

Adding to the complexities associated with drug discovery and development, is the need to design new intellectual property strategies. From the notion that any new composition of matter or article of manufacture can be patented, has evolved the notion that biological organisms and material including genomic material can be patented, and now the notion that entire biological systems can be appropriated. With limited insight into the role that genomic material and biological systems play in future drug discovery and development efforts, industry stakeholders are forming alliances to efficiently handle upstream and downstream knowledge management issues. Open source initiatives have as their objective the open dissemination of knowledge for members and the public at large. With competition best reserved for product development, members of these open source initiatives are hoping to level the playing field.

In this thesis, we analyze the patenting strategies of both public institutions and private organizations across paradigms—with an in-depth analysis of current patenting strategies across several biological systems. The goal of this analysis is to determine if problems lie on the horizon as the biopharmaceutical industry increasingly adapts to the systems biology paradigm. We then broaden our analysis of patenting and licensing strategies by

analyzing early research-based alliances in the public and private sectors. The goal of this analysis is to understand the evolution and focus of alliances as drug discovery paradigms evolve (as described in section 3.3) as well as the focus of licensing across paradigms. As part of the solution to potential knowledge production and management problems, we then analyze how both open innovation and open source initiatives are currently managing the collective production and dissemination of biological knowledge. Using a game framework, we model the decision to cooperate versus compete in knowledge production and dissemination—with the goal of providing stakeholders a novel mechanism to analyze knowledge management strategies employed as knowledge structures change.

While we contend that valuing knowledge is a complex process, the game models we develop provide a simple framework to strategically analyze the interactions occurring during drug discovery and development. Using subjective values for knowledge, ascertained through an understanding of the characteristics of the knowledge itself, firms can hopefully determine when cooperation (within strategic alliances) will enable for cost-effective and timely product development. Furthermore, it is anticipated that firms should be able to better understand competitor strategies given the characteristics associated with knowledge and the game models developed in this thesis.

3.2 Methods of Inquiry

We use a variety of methods in this thesis including patent analysis using the United States Patent and Trademark Office (USPTO) public database, analysis of the Recombinant Capital Alliances Database, literature analysis and survey of selected open innovation and open source directors, and case analysis for the purpose of game model development.

For the patent analysis, we used title based searches to isolate those patents that focus on the selected biological systems. We use a title based search as a means of isolating those patents that centrally discuss and claim the selected biological systems from those patents

that may only peripherally discuss the biological systems. From this collection of patents, we then analyzed patent abstracts and patent claims to complete our data analysis. While innovators seeking protection for their inventions in Canada, the U.S., Europe, and Japan must file for a patent in each place, most companies are likely to first patent inventions in the much larger U.S. market; hence, we limit our analysis to the USPTO database with this assumption [Gold, 2006].

For the strategic alliances analysis, we used the Recombinant Capital Alliances database. Recombinant Capital has earned its reputation in the biotech industry by building some of the largest and most detailed biotech business intelligence databases in the world. Using the Alliances database we isolated upstream research-based alliances namely collaborative, research, and licensed based alliances. Based on an analysis of the Recombinant Capital database we were able to determine that the above three categories represented early upstream focused alliances. Furthermore, by using literature references, we determined that the strongest early mover advantages exist in the upstream research-based phases. From this collection of alliances, we then analyzed alliance formation across periods and paradigms, as well as licenses issued across alliances and paradigms.

For the open innovation and open source initiative (consortia) analysis, we isolated 39 post-Human Genome initiatives. We focus on large-scale alliances, namely the consortium model, as literature review seems to suggest that this is becoming a dominant model for the management of upstream-based research in the post-genome paradigm. Using literature analysis we were able to determine that these consortia are visible and significant in their achievements, thereby enabling us to retrieve adequate literature sources for usage in our study. We analyzed the type of participants in each consortia, the structure of the knowledge generated within each consortia, and the subsequent knowledge management strategies adopted.

Based on the above consortia case studies, we then model the decision to participate in research-based consortia as well as the decision to appropriate knowledge. Using game models we hope to demonstrate the decisions and outcomes available as knowledge

structures (represented as the common and private value of knowledge) change. The game models serve as a simple framework to understand the current interactions between industry stakeholders and to highlight key issues at hand from a knowledge perspective.

3.3 Knowledge Framework Development

Underlying our empirical analysis and game model development is a knowledge framework that we develop to provide a nuanced understanding of strategic alliances and intellectual property strategies. As research and development paradigms evolve, we contend that knowledge structures change. From the chemical paradigm to the molecular biology paradigm, and now the systems or information paradigm, we see the target of knowledge appropriation activities also evolve—from chemical substances, to genomic-based information and biological organisms, to biological systems and their underlying components. Furthermore, the focus of strategic alliances including the open source initiatives analyzed in this thesis changes from the simple objective of knowledge acquisition to knowledge access in an increasingly complex drug discovery and development paradigm. Refer to Chapter 2—sections 2.1 to 2.3, Chapter 4—sections 4.1 to 4.4 and Chapter 5—section 5.3 for the knowledge framework.

By understanding intellectual property and strategic alliance formation strategies from the perspectives of phase of knowledge—upstream or downstream, paradigm—chemical, biological, or information, knowledge structure—complementarity, substitutability, applicability, and subject matter—general upstream research, broad drug discovery research, tool development, process development, or targeted therapeutic development, we make a novel contribution to the existing intellectual property and strategic alliance literature.

3.4 Patent Analysis

Existing patent law allows a researcher who has discovered a new, nonobvious, and useful process, machine, article of manufacture, or composition of matter to receive a

patent. However, the notion of biological entities as being composition of matter from the chemistry perspective tends to support the view that patent protection of biotechnological inventions is simply an expansion of an existing logical patent category. Given the complexities associated with systems biological, an information perspective to intellectual property should be adopted and should include an understanding of the impact of enclosing hierarchical and complementary, basic biological knowledge, on the technological opportunities available for the development of novel medical products [Hood, 2000].

We propose the following based on the above:

Analysis 4.1*: A closer examination of patents filed on key biological systems will reveal the paradigm focus and subsequent intellectual property focus for the selected systems.

Analysis 4.2: A closer examination of patents filed on key biological systems will reveal the breadth of claims and possible impact on downstream product development.

*Note: The first number refers to the chapter where the analysis is discussed; the second number refers to the sequence of analysis.

Case Selection: In order to understand the current paradigm and the state of patenting in the current paradigm, we selected seven biological systems based on their biological significance i.e., in terms of biological function and role in disease development, as determined from literature analysis, including: the Akt (Protein Kinase B), BCR-ABL, GPCR (G-Protein-Coupled Receptor), JAK/STAT (Janus Kinase/Signal Transducers and Activators of Transcription), MAP Kinase, NF-κB (Nuclear Factor Kappa B), and the Phospholipase C signaling pathway. In order to assess the biological significance of these systems we first analyzed the number of articles published over the approximate period of patent approvals using PubMed. In almost all cases, over 1000 articles had been published over the equivalent period. Next, we generally searched through company press releases to understand the focus of product development with respect to cell signaling systems—the goal was to verify the significance of the chosen systems to companies in terms of product development. Finally, we researched the specific biological significance

of each system in terms of involvement in biological and disease processes using the BioCarta cell signaling database [www.biocarta.com, 2007].

Data Collection: We searched the public United States Patent and Trademark Office (USPTO) database specifically for patents with these cell signaling systems mentioned in their titles.

Patent Analysis: Patents were first categorized by target area: structural patents with reference to the 2-dimensional (sequence) and 3-dimensional (folded) structure of the key system component(s) as well as localization of the key system component(s); method or assay patents targeting the cell signaling systems; activator, modulator, or inhibitor patents with reference to the cell signaling systems; and usage patents that specifically refer to pharmaceutical compositions, disease intervention, or process/production patents with respect to the cell signaling systems. The title and abstract were analyzed to categorize by target area.

From this first categorization we then associated each patent with paradigm—chemical, biological, or information. As well, we categorized the research by phase as being upstream—focusing on disembodied knowledge generation, or downstream—focusing on applications including tools, drugs, and diagnostics. The title of the patent, abstract, and claims were closely analyzed to categorize both by paradigm and phase of research. The definitions used for the paradigm and phase categorization are provided in Table 3.1. By strictly adhering to the definitions provided in Table 3.1 we attempt to remove any bias during the categorization process. These definitions are based on well-known industry terms used to describe R&D paradigms and phases [BIO.org, 2007; PhRMA.org, 2007].

The final component of our analysis involved determining patent ownership details. We have collectively analyzed the number of patents owned by public organizations and/or private organizations for each biological system. As well, we have analyzed the major patent holders (from this collective analysis), for each biological system, using the criteria of three or more patents owned by the same public or private institution.

Categorization	Definition
Chemical Paradigm	Focus of alliance activities on chemical knowledge, and on the traditional aspects of drug discovery including small molecule pharmaceuticals e.g. medicinal chemistry, bioorganic chemicals.
Biological Paradigm	Focus of alliance activities on biological knowledge, including physiology and molecular biology as well as large molecule biologics e.g. vaccines, antibodies, gene therapy, stem cells.
Information Paradigm	Focus of alliance activities on genomics-based or systems-based information development or tool development e.g. genomic and proteomic information, bioinformatic tools.
Upstream Research	Focus on disembodied, early knowledge and/or early phase knowledge e.g. discovery research, structural information.
Downstream Research	Focus on embodied knowledge; clearly focused on the later stages of development e.g. small molecule or large molecule development, diagnostic, or tool development.

Table 3.1: Patent Analysis Parameters

The results of our patent analysis are presented in Chapter 4—tables 4.1 through to tables 4.8. We also include the original patent data and analysis in the appendix (Appendix tables 1 to 7).

Analysis Limitations: While we limit our analysis of biological systems to seven significant systems, there may be value in extending our analysis to other biological systems. Analyzing patent usage patterns i.e., internal usage or external usage through licensing, may also enable us to determine potential downstream product development issues including blocks for other researchers who need to acquire the right to use the knowledge contained within key biological system patents. It may also be worthwhile to extend our patent analysis to other databases including the Canadian and World Intellectual Property Organization (WIPO) databases.

3.5 Historical Analysis of Alliances

As the pharmaceutical industry transitions into the systems biology paradigm, the nature of biological knowledge, namely the complementary nature of upstream biological knowledge, its complexity in terms of function, and its breadth of application, will

encourage the formation of strategic alliances to ensure equitable access to knowledge for future product development. Strong early-mover advantages in drug development rest on the ability to rapidly identify, access, and integrate new combinations of knowledge [Antonelli, 2003; Grant and Baden-Fuller, 2004].

Where products require a broad range of different types of knowledge, efficiency of integration is maximized through separate firms specializing in different knowledge areas that are linked by strategic alliances [Grant and Baden-Fuller, 2004]. As the breadth of knowledge required to generate new products increases, the propensity to form alliances with other firms who have specialized in the requisite knowledge, also increases.

Based on this understanding, we propose the following:

Analysis 5.1*: An examination of strategic alliances from a paradigm perspective will reveal the formation of alliances as paradigms evolve i.e., trends across time periods and paradigms.
Analysis 5.2: An examination of strategic alliances from a subject matter perspective will further reveal the knowledge focus—upstream vs. downstream activities; a correlation across paradigms should also prove useful.
Analysis 5.3: An examination of strategic alliances and licenses issued within these alliances will reveal the knowledge focus of licenses across paradigms.

*Note: The first number refers to the chapter where the analysis is discussed; the second number refers to the sequence of analysis.

Data Collection: To better understand how strategic alliances have evolved over time and since the development of recombinant technology (a milestone attributed to the development of the biotechnology industry), we acquired access to the Recombinant Capital Alliances Database. Using the Recombinant Capital Alliances Database we analyzed biopharmaceutical alliances that were formed between 1980 and 2005 [www.recap.com, 2006].

Data Selection: Collaborative alliances, research-based alliances, and license-only alliances were chosen in order to concentrate our analysis on the earlier phases of (i.e. where strong early mover advantages exist) the drug discovery and development paradigm as assessed through the categorizations used in the database and then verified through a more detailed analysis of the alliances themselves. We analyzed both public-private and private alliances between academic institutions, nonprofit research-based institutions, and biotechnology or pharmaceutical firms.

Data Analysis: Initially, each alliance was associated with a knowledge paradigm—chemical, biological, information. (Table 3.1) We associated each alliance with a paradigm based on the primary research activity. From the perspective of knowledge production, our analysis specifically investigates the evolutionary path of alliance focus over the period 1980 to 2005. We also investigate how the relative frequency of alliances changes as the underlying knowledge paradigm changes. We segregate data into 5-year periods to better observe/note any trends.

From the perspective of knowledge access, we determined if and when privatization (or enclosure) of knowledge occurred within each alliance (denoted by the granting of a license; we assume that patenting precedes licensing). It is important to note that licenses were issued in license-only alliances as well as in collaborative or research-based alliances. Licenses were analyzed across knowledge paradigms. By further analyzing the scope of the licenses, we determined the focus of privatization i.e., upstream or downstream knowledge. (Table 3.1) By strictly adhering to the definitions provided in Table 3.1 we attempt to remove any bias during the categorization process. These definitions are based on well-known industry terms used to describe R&D paradigms and phases. As well, the categorization process was completed at one sitting to ensure consistency during the categorization process. Only a limited number of entries posed difficulties for categorization at the first sitting; however, by referring to the first-round of categorizations we were able to complete these remaining categorizations.

The final component of our analysis involved categorization by subject matter. We closely analyzed each alliance from the perspective of subject matter focus namely prediscovery research, general drug discovery, tool development, targeted therapeutic development, combinatorial chemistry and/or screening, and other process development. The goal of this analysis was to determine the subject matter focus as paradigms evolve.

Analysis Limitations: While we do attain some interesting results from this analysis, we do assert that the study should be extended into the next five year period i.e., from 2006 to 2010 to determine if key trends (particularly with respect to the current paradigm) continue.

We also contend that our results depend on the accuracy of data collection by the creators and managers of the Recombinant Capital Alliances Database. While the database contains alliance information from the U.S., several European countries, and countries from Asia such as Singapore and Japan, Canadian information is not as well represented; this may be the result of reporting or information acquisition issues from Canadian institutions and/or companies Therefore, it may be worthwhile to augment our current data with Canadian alliance and licensing information such as from the Association of University Technology Managers' database.

In terms of model replicability, it would be worthwhile to have an outside expert analyze our categorizations. Strictly using the definitions outlined in Table 3.1, such an expert should be provided the opportunity to analyze the public-private and private alliances in our model. Should the categorizations match, we would be able to state with greater confidence that our model is accurate and our process replicable. The model should also be tested for falsifiability. A model is falsifiable if and only if there is some possible observation which could show that it is false i.e. if an outside expert can provide counterexamples that our categorizations are incorrect or can provide an alternative set of industry accepted categories for the model analysis.

The results of our analysis are presented in Chapter 5—tables 5.3 through to tables 5.6 as well as Figures 5.3 and 5.4. We include the condensed version of Recombinant Capital data in the appendix to demonstrate the paradigm, phase, and then subject matter categorization for selected alliances. (Appendix tables 8 and 9)

3.6 Consortium Analysis

It has become apparent that the premature appropriation of upstream knowledge poses great risks for downstream development. Ensuring that these downstream opportunities are available for multiple firms has become the objective of open source initiatives (consortia) catalyzed by the public and private sectors.

The ability to join an open initiative will be tempered by the existence of informal versus formal rules of participation. With formality, entrance costs may be used to enable research and development activities as well as to signal cooperation and commitment to the consortium. Furthermore, rules may be used to determine the dissemination and/or appropriation (including licensing terms) of knowledge produced within the consortium.

An analysis of 39 consortia provides us with information on: the likely participants in such open source initiatives, the focus of knowledge production activities, the characteristics of the knowledge generated, and the management of joint knowledge assets. The objective of the consortium analysis is to determine the impact of knowledge structures on alliance formation and the dissemination of knowledge assets generated within each consortium. Based on this, we propose the following:

Analysis 6.1*: An analysis of the selected consortia will reveal the structure of each consortium including type of participants and their geographic dispersion.
Analysis 6.2: Furthermore, a closer examination of the rules established by consortia members will reveal the requirements if any, for participation within the selected consortia.

Analysis 6.3: A closer examination of the knowledge generated by consortia members including focus and structure will reveal the purpose of each consortium and if any rules are required to enable knowledge dissemination.
Analysis 6.4: An analysis of the rules established with respect to patenting will enable for an understanding of common and contrasting licensing strategies used to manage knowledge dissemination (including as a function of knowledge structure).

*Note: The first number refers to the chapter where the analysis is discussed; the second number refers to the sequence of analysis.

Data Collection and Selection: The International Human Genome Project catalyzed the open-source movement in genomics-based research. The achievements and failures of the Human Genome Project, which involved the cooperation of globally dispersed labs, prompted us to analyze other such consortia focused on genomic and post-genomic research. Through extensive literature search we were able to isolate several post Human Genome consortia that would warrant inclusion in our study. Using the Science of Collaboratories project and PubMed literature database as a starting basis for our data collection, we isolated approximately 50 consortia that focused on genomic, proteomic, and systems-based research. The goal was to analyze mechanisms of cooperative knowledge production and dissemination in the current information paradigm.

We then selected 39 such consortia for further analysis. These consortia are visible and significant in their achievements, thereby enabling us to 1) accurately analyze interactions over a reasonable period of time, 2) analyze the policies established with respect to knowledge production and dissemination, and 3) retrieve adequate literature sources for usage in our study. Therefore, in cases where consortia are premature and still developing so that the period of study would be relatively too short, policies would not have been established to address knowledge production and/or dissemination, and where additional material beyond consortia websites was not available, we eliminated these from our original list—hence leaving us with 39 consortia.

Literature sources analyzed included: peer-reviewed journal articles by consortium members or third-party researchers, press-releases, consortia websites, publications,

and/or presentations. We also were able to substantiate the data through a survey of directors of such consortia. (See Appendices 5 and 6) These directors were asked to verify the focus of research, the types of participants including private sector participants and communication strategies used, the sources of funding, and the existence of rules regarding participation, knowledge generation, knowledge dissemination, and/or knowledge appropriation. The appendix lists the sources of data used in each case. (Appendix Table 10)

Data Analysis: In terms of participation, we analyzed the type of participants—namely from the public sector including academia, government, the non-profit, and/or private sector. It was important to also determine the geographic location of participants i.e., to determine the scale of participation. We further determined if rules existed to address participation i.e., who can participate and how participation is signaled as a function of alliance structure used.

We then analyzed the research activities of each consortium. The aim was to determine the focus of research activities and the structure of knowledge being generated in each consortium. We strictly adhere to the knowledge framework and definitions outlined in section 3.3 (see also Table 2.1 for knowledge characteristics).

Based on this knowledge analysis, we determined whether not rules exist to manage the dissemination of knowledge generated within each consortium. We comparatively analyze the rules established for the dissemination of disembodied knowledge such as raw data and the dissemination of embodied knowledge such as tools, reagents, and biomaterials.

Finally, we determine the licensing arrangements used, if any, to enable the sharing of data, tools, reagents, and biomaterials. If appropriation occurs, a close analysis of the rules surrounding the patenting of knowledge assets reveals the type of participant that is permitted to pursue appropriation activities.

Analysis Limitations: An extension of our consortium analysis during the chemical and biological paradigms should yield interesting results regarding participation within such alliances, the knowledge assets generated, and the management of such knowledge assets across paradigms. Therefore, a comparative analysis across paradigms may provide more robust results regarding consortium alliance formation as a function of knowledge structures.

3.7 Game Model Development

Based on the consortium analysis we then develop game models to better understand the decision to participate in strategic alliances such as the consortium, the decision to appropriate knowledge from a consortium, and then the bargaining problem between a licensor and licensee.

The decision to participate in a consortium is affected by the degree of accessibility of the associated knowledge. Open access ensures that knowledge will be available to all participants in future downstream research regardless of participation. In this case, the possibility exists that other participants will free-ride by enjoying knowledge disclosed at little or no cost, and without contributing knowledge to the alliance. Closed access, in contrast, ensures that knowledge is available only to contributing members of the alliance or consortium; therefore, a researcher outside the alliance may be unable to pool internal knowledge with that of the alliance or may do so only at a cost that varies according to the market power of the closed group. Therefore, we model the decision to participate in a consortium when knowledge is accessible by the public at large (public access setting) and when knowledge is accessible only to consortium members (restricted access setting). We also consider the scenario where only two players exist to form a new consortium and alternatively, where two players exist and can decide to join an existing consortium.

Analysis 7.1: The objective of the participation model is to understand under what circumstances players choose to cooperate and join a consortium i.e., to jointly produce and disseminate knowledge.

Once a commitment is made to participate in a consortium, researchers will face the decision on when to privately (and if indeed to) appropriate knowledge. In the case of biotechnology, appropriation most often occurs through the filing of patents. The common benefits from contributing to versus the private benefits associated with appropriating knowledge will determine when a participant will choose to signal his/her departure from the consortium. For example, when the private benefits from filing patents are higher than the common benefits from open knowledge dissemination, researchers will choose to defect and likely depart from the alliance [Khanna et al., 1998]. The probability of receiving a patent will depend on whether the knowledge is nonobvious, novel, and has utility and can be affected by a rival firm's disclosure through the creation of patent defeating prior art [Parchomovsky, 2000]. From a knowledge perspective, common benefits will derive from the characteristics associated with the knowledge and the value from collectively holding together the knowledge in the public domain. Equivalently, private benefits derive from the characteristics associated with the knowledge—namely the level of substitutability, complementarity, and applicability. Consequently, we model the decision to appropriate knowledge as knowledge characteristics change.

Analysis 8.1: The objective of the appropriation model is to similarly understand when consortium participants voluntarily choose to cooperate and keep knowledge in the "commons" and/or when participants pre-emptively disclose knowledge to ensure its availability for downstream product development.

Our third model analyzes the licensing environment where two players exist—the licensor and licensee. The terms of the license will be the outcome of bargaining, which will depend on the threat points for each player and bargaining surplus. The threat point—each player's BATNA (Best Alternative to Negotiated Agreement)—is the

expected profit he/she can guarantee itself if he/she leaves the bargaining table. The bargaining surplus is the total amount by which the players will be richer if bargaining is successful. In our model, we specifically explore the impact of knowledge characteristics on the licensing process.

Analysis 9.1: The objective of the bargaining model is to understand whether or not a license is issued, when it is issued, and the type of license issued as knowledge characteristics change.

Game Model Validation: We use various case studies as presented in our consortium analysis to demonstrate the utility of our participation and appropriation models. The game models are simple representations of firm behaviour during upstream research and downstream development activities. By using the case studies to validate our models, we are able to demonstrate their usefulness in the "real world". We also use case analysis to model various bargaining (licensing) settings. For example, we use various knowledge settings by changing the characteristics of knowledge and using examples to better understand the decisions made by the licensor and licensee. Through the use of case studies we search for dominant strategies favouring cooperation or failing that, Nash equilibria. Future research should evaluate the stability of these equilibria regardless of case example.

Game Model Limitations: The value of knowledge cannot be accurately measured. As such, we assign subjective values for knowledge and hence game payoffs only as a simple means to understand firm behaviour in our participation, appropriation, and bargaining models. Future research might include assigning values to these payoffs. However, we contend that these payoffs will vary according to phase of research. If upstream knowledge is at stake (particularly upstream knowledge that does not have commercial value on its own, but needs to be embodied in a downstream product), the private payoffs associated with unilateral knowledge production and/or appropriation might derive from licensing revenue. If downstream knowledge is at stake, the private

payoffs will likely stem not only from licensing revenues, but also profits from internal product development.

Although, for simplicity, we chose to evaluate simultaneous decisions in our participation and appropriation game models, it is worthwhile to consider the impact of sequential decisions on 1) the decision to join an alliance and engage in cooperative knowledge production and 2) the decision to continue cooperation during the knowledge dissemination phase. Signals of cooperation are visible and (binding) cooperative agreements are possible in games involving sequential decisions. We do however consider sequential decisions in the bargaining game (Chapter 9).

3.8 Definitions

Chemical paradigm: Focus of alliance activities on chemical knowledge, and on the traditional aspects of drug discovery including small molecule pharmaceuticals.

Biological paradigm: Focus of alliance activities on biological knowledge, including physiology and molecular biology as well as large molecule biologics.

Information paradigm: Focus of alliance activities on upstream genomics-based, systems-based (or other upstream) information development including information-based tool development.

Upstream: Focus on early knowledge and/or early phase knowledge e.g. drug discovery.

Downstream: Focus on the later stages of development e.g., small molecule or large molecule development, diagnostic, or tool development.

Complementarity: New knowledge production is conditional on the identification and integration of diverse and dispersed units acting as inputs.

Non-substitutability: Knowledge may be lacking in direct substitutes; a researcher may not be able to "invent around" the knowledge.

Applicability: Knowledge can vary in terms of applicability in downstream use—from narrow to wide-ranging application.

Disembodied knowledge: Pure knowledge; Can be sold in the market for technological knowledge in the form of patents and licenses.

Embodied knowledge: Knowledge that is applied in products and processes; Can be sold in the product marketplace in the form of tools, diagnostics, and drugs.

Pre-discovery: Disease related research or genomics-based research.

General drug discovery: Broad drug discovery research of drug targets and leads.

Tool development: Upstream or downstream tool development including the development of analytical tools, assays, reagents, biological materials such as cells, tissue samples and model organisms, databases, algorithms, techniques, protocols and equipment.

Targeted therapeutic development: Chemical-based or biologics-based drug development targeting a specific disease and/or system.

Combinatorial chemistry and/or screening: The rapid synthesis and screening of a large number of different but structurally related molecules.

Process development: Small or large-scale drug process development e.g., antibody production, gene vector production.

Open network: Knowledge network focused on upstream research; intellectual property rights are not important in this network.

Development network: Knowledge network focused on the application of knowledge; intellectual property rights are important in this network as products are developed.

Chapter 4: A Knowledge Perspective of System-Based Research and Development

4.1 Introduction

In this chapter, we develop our knowledge framework to better understand the research and development activities associated with the *current systems biology paradigm*. Using this knowledge framework, we then analyze the appropriation activities of the public and private sector in this paradigm. By analyzing patenting trends across seven biological systems, we uncover the focus (Analysis 4.1) of and breadth of these patents (Analysis 4.2) as well as possible downstream problems associated with the claims filed.

With the completion of the Human Genome Project, systems biology or the information paradigm has emerged. The Human Genome Project has advanced the view that biological information operates on multiple hierarchical levels and is processed in complex networks. A new hierarchical framework for biological knowledge is being constructed to understand the relationships between the various levels of biological information.

Systems biology does not focus on individual genes and proteins one at a time, but focuses on the behaviour and relationships of all components, in a particular biological system, from a functional perspective [Kitano, 2001; 2002]. Biological systems are fundamentally composed of information: genes, their encoded products, and the regulatory components controlling the expression of these genes [Ideker et al., 2001]. Targets that function across diseases will be selected to develop drugs that either augment or suppress the associated biological systems, thereby enabling for disease intervention. It is anticipated that blockbuster drugs will eventually target multiple systems at a common intervention point.

In the systems biology paradigm, the focus of intellectual property rights will also gradually shift to the patenting of information [Hood, 2000]. This information perspective must incorporate an understanding of the impact of enclosing hierarchical and

complementary, basic biological knowledge, on the technological opportunities available for the development of novel medical products.

4.2 Characterizing Systems Knowledge

As an understanding of the interconnections between structures across systems and the interconnections between systems is still forming, actions that result in the enclosing of large research terrains are likely to have significant impact on the technological opportunities available for follow-on developers should patent holders not provide fair access to complementary knowledge. Furthermore, research is being conducted to better understand biological systems, the associated pathways, and the central nodes functioning across systems. The greater the applicability, the higher is the likelihood that multiple systems, domains, and disease models will share the same pool of knowledge. The single structure-single function, system, or disease view is problematic as it lacks the biological insight that is required to correctly intervene in a system or disease [Scherer, 2000]. This view also distorts the incentives for both a first innovator and follow-on innovator to conduct further research if patent rights are granted on the basis of a single function [Scherer, 2000].

Organizational Hierarchy of Biological Information: The Human Genome Project has advanced the view that biological information operates on multiple hierarchical levels [Ideker et al., 2001]. From this perspective, it is no longer sufficient to develop a model and perform analysis at only one or two levels of biological information. Information storage, information processing, and the execution of the various cellular programs occur at the level of cell's genome, transcriptome, proteome, and metabolome. These building blocks organize themselves into recurrent patterns called pathways in genetic-regulatory networks [Oltvai and Barabási, 2002]. These pathways and motifs form functional modules or groups of nodes that are then responsible for cellular function [Oltvai and Barabási, 2002]. (Figure 4.1)

Modular Framework for Biological Knowledge: Scientists have accumulated vast amounts of genomic data, proteomic data, expression profile data, and molecular interaction data along the biological hierarchy. The central task is to now integrate and analyze these data for the purpose of biological and pharmacological discoveries. Clustering of data based on structure, function, patterns of expression, interactions, and association with biological system has become a key feature of systems biology. The attempt to capture systems-level laws governing cells is in fact a search for the common patterns that apply to complex systems and networks in general. A modular framework for biology will organize systems into classes that share a common set of characteristics performing a common function.

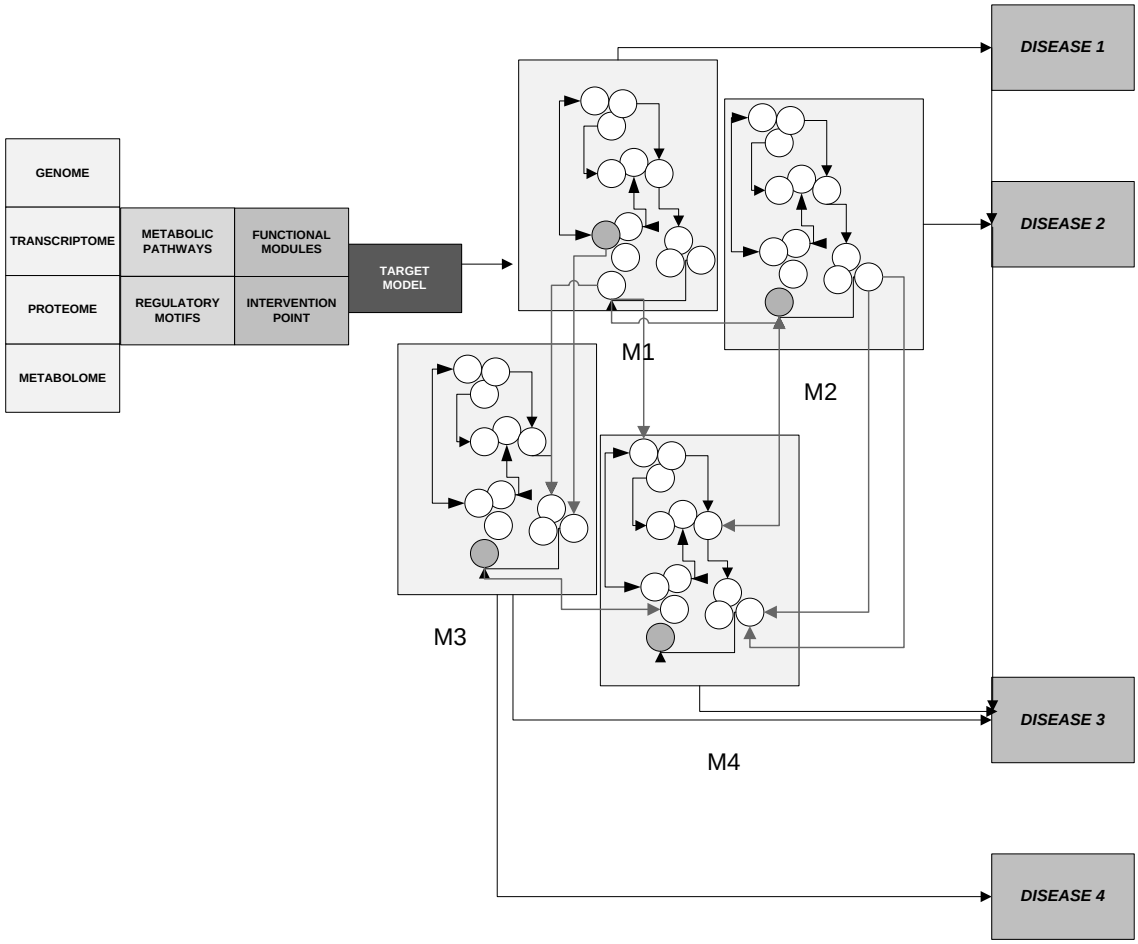


Figure 4.1: A Knowledge Perspective of Systems Biology

M=Modules; Module Black Arrow=Internal System Relationship; Module Grey Arrow=External System Relationship; Grey Circle=Putative Intervention Point

4.3 Knowledge Production in the Systems Paradigm

Systems biology is an integrated process of computational modeling or "dry experiments", system analysis, technology development for experiments, and quantitative "wet" experiments [Ideker et al., 2001; Kitano, 2001; 2002]. Computational biology involves knowledge discovery, data mining to uncover the patterns from experimental data, and simulation-based analyses that will test hypotheses with *in silico* experiments.

Biological and physiological knowledge enables for the development of virtual models of gene networks, biochemical networks, cells, and organs. Computational "dry" experiments test system models and related hypotheses. Data are integrated and displayed graphically and system responses are modeled mathematically to predict the structure and behaviour of informational pathways in systems. Experimental techniques are developed and "wet" experiments are used to verify or reject hypotheses from computational experiments. Once sufficient information has been gained about a system, this experimental cycle can be applied to drug discovery research targeting the system [Kitano, 2001; 2002].

Given the broad scope of systems biology, collective effort is required from multiple research arenas including: molecular biology, cell biology, physiology, mathematics, physics and chemistry, computer science, electrical, mechanical, and biological engineering. Life sciences research has long been dominated by a culture of independent laboratories organized around single principal investigators. However, the need in systems biology for diverse skills and the complexity of the experimental technologies require the formation of interdisciplinary research teams [Kitano, 2002]. Teams of biologists, engineers, and computational scientists from the public and private sectors, will increasingly collaborate to handle the iterative and multi-dimensional aspects of systems biology [Ideker et al., 2001].

4.4 Knowledge Appropriation in the Systems Paradigm

In a systems biology network, each scientific or technical field has its own conventions regarding knowledge dissemination and appropriation. These conventions may not be identical or stable; it cannot be assumed that the conventions of all members will converge simply through the creation of a cross-disciplinary organizational structure [Hilgartner, 1996]. Knowledge can be valued as a good itself and sold in disembodied form as intellectual property in the market for technological knowledge. Transactions for embodied knowledge occur through the sale of tools, drugs, and other medical products. Intellectual property concerns will likely be mediated by the value placed on disembodied versus embodied knowledge by the participating disciplines. Measures and signals of success in knowledge generation activities will determine the value placed on this knowledge by the various disciplines. Through the development of rules to manage the knowledge collectively generated by these participants, the downstream opportunities for multiple researchers can be preserved [Hilgartner, 1996; Dalrymple, 2003].

The Transition Point: Studies indicate that scientists' collaborative relationships change according to the stage of research [Atkinson et al., 1998]. The continuum of scientific interactions ranges from full cooperation among all participants, to fully cooperative subcollaborations, to secrecy, and finally to outright competition [Atkinson et al., 1998]. The gene races of the past decade followed a trajectory from cooperation to competition. Collaboration is certainly the norm in the early phases of research. But as projects progress, for example as the discovery of a gene becomes imminent, the private gains associated with achieving priority (first to discover or first to patent) are often seen to exceed the common benefits of joint discovery [Davies, 2001]. While competition may hasten discovery, the outcome may be less than optimal, as premature enclosure of knowledge may prevent downstream researchers from applying it to develop diagnostics and therapeutics.

Therefore, we define the *transition point* in discovery research to be the moment when researchers come to believe that private gains from unilateral knowledge are greater than shared gains from joint knowledge. The key is to find this transition point. If it occurs too

far upstream, holdouts and bargaining failures may make knowledge inaccessible for development downstream. A researcher who takes a strong ownership position with respect to knowledge being sought (by capturing a patent, for example), may be giving too little priority to the shadow of the future (the likelihood of future interactions with individuals whose past behaviour is known) and therefore less likely to succeed in bargaining for future knowledge held by erstwhile collaborators.

Data Hierarchies in Systems-Based Intellectual Property: From the perspective of intellectual property, the challenge is to determine whether or not systems as a whole are patentable. In any system, there are two-dimensional and three-dimensional structures e.g., gene sequences and the corresponding folded protein structures respectively, as well as their time variant interconnections. These elements themselves are individually patentable. If prior patents on such structures or subsystems exist, what is then the impact on the patent filed to cover the entire system? Given the fact that the individual structures and subsystems in isolation do not provide information about a system as a whole, its properties, and role in disease, by mapping a system in entirety, new, possibly patentable, knowledge is created.

Complicating the matter is the hierarchical nature of biological information in a system. At any level in this hierarchy, patents may exist. Depending on the breadth of patents filed at a particular level, these patents can dominate over other hierarchical levels of biological information [Hood, 2000]. Dominance of patents filed earlier in time, at the lowest levels of the biological information hierarchy, can hinder the incentive to progress into the higher levels of the hierarchy where appropriation may not be possible. Furthermore, if multiple researchers own patents over the structures or subsystems comprising a system, the system may become so fragmented that other researchers may no longer be able to exploit the system in its entirety [Heller and Eisenberg, 1998; Foray, 2004]. The transaction costs associated with recombining the elements that comprise the system, for downstream exploitation, may be too high for a downstream developer [Heller and Eisenberg, 1998; Foray, 2004].

4.5 Analyzing Patents on Critical Cell Signaling Systems

We selected seven systems based on their biological significance i.e., in terms of biological function and role in disease development, as determined from literature analysis, including: the Akt (Protein Kinase B), BCR-ABL, GPCR (G-Protein-Coupled Receptor), JAK/STAT (Janus Kinase/Signal Transducers and Activators of Transcription), MAP Kinase, NF-κB (Nuclear Factor Kappa B), and Phospholipase C signaling pathway, for our patent analysis. We searched the public United States Patent and Trademark Office (USPTO) database specifically for patents with these cell signaling systems mentioned in their titles. Patents have been categorized by target area: structural patents with reference to the 2-dimensional and 3-dimensional structure of the key system component(s) as well as localization of the key system component(s); method or assay patents targeting the cell signaling systems; activator, modulator, or inhibitor patents with reference to the cell signaling systems; and usage patents that specifically refer to pharmaceutical compositions, disease intervention, or process/production patents with respect to the cell signaling systems. A closer scrutiny of these patents reveals in which target area the greatest number of patents have been filed—an indication of the research trajectory as well as ownership patterns. Table 4.1 provides a collective summary of our analysis across these cell signaling systems.

In some cases, there appears to be a primary area of focus for research. For example, in the case of the GPCR signaling pathway, the focus of research is on upstream information discovery i.e., structural components of the signaling pathway and/or the receptor itself followed by methods or assays associated with the signaling pathway and uses including the treatment of disease. Almost half of the patents filed on the Phospholipase C cell signaling pathway are focused on downstream applications and the other half on upstream discovery. In the case of the Akt, BCR, JAK, Map Kinase, and NF- κB signaling pathways, the emphasis appears to be on downstream application i.e., techniques/technologies that activate, modulate, or inhibit the associated pathway.

In terms of patent assignee, the private sector is the primary location of research concerning the Akt, GPCR, Map Kinase, and Phospholipase C cell signaling pathways.

However, the public sector dominates in terms of research on the BCR and JAK pathways. Interestingly, the private and public sectors have their attention equally focused on the NF- κB pathway.

Cell Signaling System	USPTO Patents	Publication Dates	S	MA	AMI	U	PR	PUB	IND
Akt	10	1999-2006	1	0	7	2	10	0	0
BCR	5	1994-2003	0	1	2	2	1	5	0
GPCR	133	1993-2006	71	26	10	26	92	43	5
JAK	14	1998-2006	0	1	13	0	1	13	0
MAP Kinase	27	1997-2006	8	3	14	2	21	6	0
NF-κB	13	1998-2006	2	1	9	1	6	7	0
Phospholipase C	14	1994-2006	6	2	6	0	12	2	0

Table 4.1: Patent Statistics for Cell Signaling Systems

Categorization of Patents: S=Structural, MA=Method or Assay, AMI=Activator, Modulator, Inhibitor, U=Use; Patent Assignee: PR=Private Entity, PUB=Public Entity, IND=Individual; Totals may not add correctly due to multiple category placement of patents.

We further analyzed each patent filed on and the associated claims for the seven cell signaling systems to determine the focus of research in terms of phase of activities—upstream versus downstream, paradigm followed—chemical (with a focus on chemical forms of medical intervention), biological (with a focus on the use of biological processes and biological forms of medical intervention, namely genomic, proteomic, cellular), or information (with a focus on disembodied knowledge about the system, namely structural aspects of the systems), as well the major patent holders—public or private. Interestingly, our analysis revealed key institutions as owners of the majority of the patents with respect to each biological system. (See Appendix Tables 1 to 7 for Expanded Patent Lists and Associated Analysis by Phase, Paradigm, and Patent Holder.)

Akt (Protein Kinase B): Akt signaling regulates cell proliferation and survival, cell growth (size), glucose metabolism, cell motility, and angiogenesis. Aberrant regulation of these processes result in cellular perturbations considered hallmarks of cancer, and

numerous studies testify to the frequent hyperactivation of Akt signaling in many human cancers [Dudek et al., 1997; Frane et al., 1997; Hemmings et al., 1997; Kauffmann-Zeh et al., 1997; Kulik et al., 1997; Altomare and Testa, 2005].

Phase		Paradigm			Major Patent Holder	
U	**D**	**C**	**B**	**I**	**P**	**PR**
1	9	4	5	1		Merck & Co., Inc. (Rahway, NJ); Isis Pharmaceuticals, Inc. (Carlsbad, CA)

Table 4.2: Patents Held on the Akt Cell Signaling System
U=Upstream Focus; D=Downstream Focus; C=Chemical Paradigm; B=Biological Paradigm; I=Information Paradigm; P=Public Institution; PR=Private Organization

From our analysis it appears that the focus of U.S. patents is on downstream applications associated with the Akt signaling pathway. Interestingly, both the chemical and biological paradigms are used for downstream technology development. Merck and Co. and Isis Pharmaceuticals each own 4 and 3 of the 10 patents respectively.

BCR-ABL: Activation of the oncogenic (cancer) potential of normal cellular proteins such as protein tyrosine kinases may occur by alteration of the proteins' corresponding enzymatic activities, their inappropriate binding to other cellular components, or both.

For example, the BCR-ABL protein tyrosine kinase oncoprotein may transform cells via changes in enzyme activity and/or altering of noncovalent protein-protein interactions. The gene encoding the BCR-ABL oncoprotein is a chimeric oncogene generated by the translocation of sequences from the ABL protein tyrosine kinase on chromosome 9 into BCR sequences on chromosome 22 [Kurzrock et al., 1998; Rosenberg and Witte, 1998]. The BCR-ABL oncogene has been implicated in the patheogenesis of Philadelphia chromosome (Ph.sup.1) positive human leukemias. Specifically, the kinase activity of ABL in the abnormal BCR-ABL protein becomes activated and unregulated, thereby driving uncontrolled cell growth [Sattler and Griffin, 2001].

There are a variety of cellular substrates of the BCR-ABL kinase that may be involved in cellular transformation. BCR-ABL is associated with the cytoplasm as part of a large signaling complex.

Phase		Paradigm			Major Patent Holder	
U	D	C	B	I	P	PR
0	5	0	5	0	The University of Texas Systems (Austin, TX)	

Table 4.3: Patents Held on the BCR-ABL Cell Signaling System
U=Upstream Focus; D=Downstream Focus; C=Chemical Paradigm; B=Biological Paradigm; I=Information Paradigm; P=Public Institution; PR=Private Organization

In this case, all five patents are downstream applications associated with BCR-ABL cell signaling system and all five ascribe to the biological paradigm. The University of Texas Systems owns 3 of the 5 patents.

GPCR (G-Protein-Coupled-Receptor): G-protein-coupled receptors (GPCRs) constitute a major class of proteins responsible for transducing a signal within a cell and are a major target for drug action and development [Beaumont and Negulescu, 1999]. Upon binding of a ligand to an extracellular portion of a GPCR, a signal is transduced within the cell that results in a change in a biological or physiological property of the cell [Beaumont and Negulescu, 1999].

Phase		Paradigm			Major Patent Holder	
U	D	C	B	I	P	PR
71	62	7	55	71	Duke University (Durham, NC); The Regents of The University of California (Oakland, CA)	Arena Pharmaceuticals, Inc. (San Diego, CA); Human Genome Sciences, Inc. (Rockville, MD); Millennium Pharmaceuticals, Inc. (Cambridge, MA); SmithKline Beecham Corporation (Philadelphia, PA); Takeda Chemical Industries, Ltd. (Osaka, JP); ZymoGenetics, Inc. (Seattle, WA)

Table 4.4: Patents Held on the GPCR Cell Signaling System
U=Upstream Focus; D=Downstream Focus; C=Chemical Paradigm; B=Biological Paradigm; I=Information Paradigm; P=Public Institution; PR=Private Organization

Alarmingly, more than half of the patents on the GPCR cell signaling systems are upstream-based, and discovery oriented applications; hence the dominance of the information paradigm. Interestingly, of the 62 downstream application based patents, 55

ascribe to the biological paradigm. Of further concern, is the fact that almost half of the patents on these systems are owned by a concentrated number of private organizations and public institutions. For example, on the private side, SmithKline Beecham owns 14 patents and on the public side, University of California owns 10 patents.

JAK/STAT (Janus Kinase/Signal Transducers and Activators of Transcription):
In mammals, the JAK/STAT pathway is the principal signaling mechanism for a wide array of cytokines and growth factors. JAK activation stimulates cell proliferation, differentiation, cell migration, and apoptosis [Igaz et al., 2001; O'Shea, 2002]. These cellular events are critical to hematopoiesis, immune development, mammary gland development and lactation, adipogenesis, sexually dimorphic growth, and other processes. Mutations that reduce JAK/STAT pathway activity affect these processes [Igaz et al., 2001; O'Shea, 2002]. Conversely, mutations that constitutively activate or fail to regulate JAK signaling properly cause inflammatory disease, erythrocytosis, gigantism, and an array of leukemias [Igaz et al., 2001; O'Shea, 2002].

Phase		Paradigm			Major Patent Holder	
U	**D**	**C**	**B**	**I**	**P**	**PR**
0	14	9	5	0	St. Jude Children's Research Hospital (Memphis, TN); Parker Hughes Institute (Roseville, MN)	

Table 4.5: Patents Held on the JAK/STAT Cell Signaling System
U=Upstream Focus; D=Downstream Focus; C=Chemical Paradigm; B=Biological Paradigm; I=Information Paradigm; P=Public Institution; PR=Private Organization

All 14 patents are downstream applications with the majority ascribing to the chemical paradigm. Interestingly, two public institutions—the St. Jude Children's Research Hospital and the Parker Hughes Institute own 4 and 8 out of the 14 patents, respectively.

MAP KINASE (MAPK): The mitogen-activated protein kinase (MAP kinase) pathways consist of four major groupings and numerous related proteins which constitute interrelated signal transduction cascades activated by stimuli such as growth factors, stress, cytokines, and inflammation. The four major groupings are the ERK, JNK or SAPK, p38, and the Big MAPK or ERK5 cascades [Chang and Karin, 2001].

MAPK activity is regulated through three-tiered cascades composed of a MAPK, MAPK kinase (MAPKK, MKK or MEK), and a MAPKK kinase or MEK kinase (MAPKKKor MEKK) [Chang and Karin, 2001]. MAPKs are evolutionary conserved enzymes connecting cell-surface receptors to critical regulatory targets within cells [Chang and Karin, 2001]. For example, signals from cell surface receptors such as GPCRs and growth factor receptors are transduced, directly or via small G proteins such as ras and rac, to tiers of protein kinases that amplify these signals and/or regulate each other. The endpoints of these cascades include the MAPK activated protein kinases (MAPKAPK) and some of the numerous transcription factors that regulate genes involved in apoptosis, inflammation, cell growth, and differentiation [Chang and Karin, 2001; Wheeler-Jones, 2005].

Phase		Paradigm			Major Patent Holder	
U	D	C	B	I	P	PR
8	19	13	6	8		Syntex (U.S.A.) LLC (Palo Alto, CA); Incyte, Inc. (Palo Alto, CA)

Table 4.6: Patents Held on the MAP KINASE (MAPK) Cell Signaling System
U=Upstream Focus; D=Downstream Focus; C=Chemical Paradigm; B=Biological Paradigm; I=Information Paradigm; P=Public Institution; PR=Private Organization

In this case, 19 out of the 27 patents focus on downstream applications of the cell signaling system. Although the majority use the chemical paradigm for technology development, 8 are upstream, discovery-based patents focused on the structural (informational) aspects of this cell signaling systems; 7 of these 8 upstream patents are owned by private organizations.

NF-κB (Nuclear Factor Kappa B): The Nuclear Factor -κB (NF-κB) cell signaling pathway is a key biological component described in more than 5,000 scholarly papers and a convergent pathway for a number of stimuli that impact cells. There is a great deal of interest in this signal transduction pathway in the biopharmaceutical industry. Given the central effector role that this pathway occupies for a number of cell-surface receptors, it is

an important drug target as well as proxy for other effector molecules located on the pathway [Ashok et al., 2004; Coutois and Gilmore, 2006].

The Nuclear Factor -κB is a nuclear transcription factor that regulates the expression of a large number of genes that are critical for the regulation of cell death, viral replication, tumorigenesis, inflammation, and various autoimmune diseases [Ashok et al., 2004; Coutois and Gilmore, 2006]. Companies are researching how to prevent the activation of NF-κB and the subsequent expression of select disease-associated genes responsible for the onset and progression of cancer, autoimmune, inflammatory, neurological, and cardiovascular diseases [Ashok et al., 2004; Coutois et al., 2006]. Various small molecule inhibitors are being sought to modulate or inhibit targets within this signal transduction pathway.

Phase		Paradigm			Major Patent Holder	
U	D	C	B	I	P	PR
2	11	7	6	2	7	7

Table 4.7: Patents Held on the NF-κB (Nuclear Factor Kappa B) Cell Signaling System

U=Upstream Focus; D=Downstream Focus; C=Chemical Paradigm; B=Biological Paradigm; I=Information Paradigm; P=Public Institution; PR=Private Organization

While our patent analysis reveals that the majority of patents filed on this cell signaling system are downstream applications, adhering to both the chemical and biological paradigms, this system is an interesting case by virtue of one patent filed and exclusively licensed by three public institutions. From this one patent case we learn that it may not simply be a matter of several patents filed on a cell signaling system, but the case of one patent with broad claims covering the system including intervention mechanisms, that can be the source of downstream conflict.

U.S. Patent No. 6,410,516 on the NF-κB cell signaling system is assigned to Harvard College (Cambridge, MA), the Massachusetts Institute of Technology (Cambridge, MA), and the Whitehead Institute for Biomedical Research (Cambridge, MA). The patent claims cover methods of treating human disease by regulating NF-κB activity, methods of treating disease by inhibiting NF-κB, and methods useful for treating various disease

conditions through modulation of NF-κB activity. The associated patent on the upstream system itself was awarded in 2002, with claims that may cover almost every putative downstream application of this fundamental signaling pathway. Licensed to Ariad Pharmaceuticals in 2002, Ariad sued Eli Lilly, arguing that Lilly's Evista and Xigris products for osteoporosis and sepsis, approved in 1997 and 2001 respectively, infringe upon their patent since the drugs work via the NF-κB pathway [Rai and Eisenberg, 2003]. A federal jury ruled on May 4th 2006 that Eli Lilly & Company had infringed the NF-κB patent covering drugs that work on this basic biological pathway, and ordered Lilly to pay $65.2 million in back royalties to Ariad Pharmaceuticals [Mack, 2006]. A separate trial, or bench trial, however, commenced before the judge on August 7th 2006 on certain defenses asserted by Lilly relating to the validity and enforceability of the claims of the patent; these defenses must be addressed before the court enters a final judgment in this lawsuit [Civil Action No. 02 CV 11280 RWZ, 2006]. Interestingly in June 2005, the U.S. Patent and Trademark Office (USPTO) also commenced a reexamination of the U.S. patent. In the reexamination, the USPTO has asserted that there exists a substantial new question of patentability for certain claims of the patent [Re-examination C.N. 90/007,503].

Describing a system and its informational pathways are critical for treating a disease, but legal scholars are unsure whether the value of this information is equivalent to discovering and developing a drug that acts on the biological pathway to effectively treat the disease. Legal scholars are divided on whether the discovery of a biological pathway is sufficient in itself to merit the granting of a broad patent that lays claim to any treatment acting on the pathway. The case of the Nuclear Factor-κB (NF-κB) cell signaling pathway relates directly to these questions. Lawyers contend that the breadth and assertiveness of the patent filed by the Massachusetts Institute of Technology (MIT), the Whitehead Institute of Biomedical Research, and Harvard University and then exclusively licensed to Ariad Pharmaceuticals, could signal a paradigm shift among academic research institutions that have historically collaborated with other researchers [Rai and Eisenberg, 2003]. Such institutions could collect patents and use such patents against other researchers, blocking off research pathways in the hopes of

commercializing their discoveries [Rai and Eisenberg, 2003]. If it is not possible to circumvent the enclosed pathway, then the market power conferred to the owner of such a broad patent will be very strong, leaving follow-on innovators who cannot license the knowledge in a weak position with regard to downstream activities.

PHOSPHOLIPASE C: Phospholipase C (PLC) belongs to a family of enzymes, also known as disulfide isomerases, which play an important role in mediating signal transduction pathways. Many extracellular signaling molecules including hormones, growth factors, neurotransmitters, and immunoglobulin bind to their respective cell surface receptors and activate PLCs [Nishizuka, 1992; Nishizuka, 1995]. Its main function is to hydrolyze phosphatidylinositoldiphosphate into diacylglycerol (DG) and inositoltriphosphate (IP3). DG is necessary for further activation of Protein Kinase C (PKC) while IP3 leads to the release of intracellular calcium. PKC activation is known to be involved in diverse array of cellular responses in the endocrine, exocrine, nervous, muscular, inflammatory, and immune systems [Nishizuka, 1992; Nishizuka, 1995].

Phase		Paradigm			Major Patent Holder	
U	**D**	**C**	**B**	**I**	**P**	**PR**
6	8	3	5	6		Merck & Co., Inc.; Kyowa Hakko Kogyo Co., Ltd. (Tokyo, JP)

Table 4.8: Patents Held on the Phospholipase C Cell Signaling System
U=Upstream Focus; D=Downstream Focus; C=Chemical Paradigm; B=Biological Paradigm; I=Information Paradigm; P=Public Institution; PR=Private Organization

In this case, almost half of the patents are focused on downstream applications and the other half on upstream, discoveries; the majority of patents ascribe to the biological or information paradigm. Once again, problems may exist on the horizon due to the number of upstream, information-based patents owned by private organizations.

4.6 Discussion

Systems biology attempts to understand the interactions and informational flow between structures in the cell. Data from various hierarchical levels of biological information will be incorporated into the modeling of systems. Each level of information builds on

information found at lower levels in this hierarchy. Consequently, system biology uses cumulative knowledge to build models, providing positive externalities to researchers who can use this knowledge to generate and embody the knowledge in new products. Given the uncertainty associated with the function of the structures that comprise a system and the role of a system in disease, the incentives to find the full breadth of a system's properties and functions should be preserved for multiple researchers. Blocks, holdouts, and bargaining failures are all possible if a first innovator is granted an excessively broad patent, conferring strong market power over downstream research. Blocking critical pathways whose functions are yet to be discovered can reduce the opportunity to develop novel and more effective medical products. Despite the fact that existing patent law allows a researcher who has discovered a new, nonobvious, and useful process, machine, article of manufacture, or composition of matter to receive a patent, is the discovery of a system and putative function enough to enclose not only the system but also all possible medical developments that arise from the system?

These complexities will be exacerbated as multiple disciplines increasingly work together in the systems biology paradigm. Each discipline will have its own priorities and conventions regarding knowledge dissemination and knowledge appropriation. One discipline may signal its success during knowledge generation through enclosure and the sale of disembodied knowledge. Another discipline may measure its success exclusively by the embodiment of knowledge. As collaborations cross institutional boundaries, the parceling out of intellectual property rights may be too difficult a task. With the assignment of property rights, the role of the patent holder in providing broad versus narrow access to the knowledge will then depend on the original incentives for producing the knowledge.

Table 4.9 describes these problems and offers solutions to the challenges presented in systems biology. With the transition to a systems biology paradigm, the research challenges are greater with far reaching consequences for the industry and its consumers.

In Chapter 5 we broaden our framework to generally understand the evolution of biological knowledge structures across paradigms including the systems (information) paradigm and the impact of knowledge structures generally on the formation of upstream research-based alliances. We further analyze how upstream research-based alliances (including appropriation targets within alliances) in the public and private sectors have evolved with drug discovery and development paradigms.

Research/Technological Challenge	Problem	Possible Solution
Cross-Disciplinary Research	Differing conventions by scientists vs. engineers regarding knowledge dissemination & appropriation.	Early establishment of rules to manage knowledge activities.
Complexity of Research	Need for access to complementary expertise & information	Networks of collaboration; Cross-licensing.
Composition of Matter Patents for Biological Information	Upstream, basic patents assigned.	Better understanding of the patenting of disembodied knowledge i.e. informational view to patenting.
Interconnectivity between Biological Information	Unknown function and interconnections in system when patenting.	Protection for narrower patent claims; Non-exclusive licensing.
New Organizational Hierarchy of Biological Information	Dominance of patents filed on genes and proteins (lower level of hierarchy) over biological systems (higher level of hierarchy).	Protection for narrower patent claims; Non-exclusive licensing.
Technological Opportunities Across Diseases	Unknown role of system and its structures across diseases.	Protection for narrower patent claims; Avoid reach through to medical products.

Table 4.9: Policy Implications of the Current System Biology Paradigm

Chapter 5: A Knowledge Perspective of Strategic Alliances

5.1 Introduction

A rapidly evolving drug discovery and development paradigm, as evidenced through the scientific and technical knowledge requirements for the successful development of new medical entities, is encouraging companies to form alliances to fill gaps in their upstream knowledge and/or downstream capabilities [Gambardella, 1995; Greis et al., 1995]. Alliances between academic institutions, biotechnology companies, and pharmaceutical companies provide access to complementary assets [Teece, 1986; 1992]. In resource-based alliances, parties are assumed to be mutually dependent upon the resources controlled by other parties and common benefits are associated with pooling resources [Powell, 1990; Das and Teng, 2000]. Mergers, acquisitions, and strategic alliances such as joint ventures, represent alternative strategies that may be used to acquire or access these resources [Child and Faulkner, 1998; Kogut, 1998; Das and Teng, 2000]. It is our contention however, that a framework that is centrally focused on knowledge will provide a nuanced view of pharmaceutical alliances in the post Human Genome era. [Hall, 1992; Liebeskind et al., 1996; Mowery et al., 1996; Reid et al., 2001; Foray, 2004].

As the pharmaceutical industry transitions into the systems biology paradigm, the nature of biological knowledge, namely the complementary nature of upstream biological knowledge, its complexity in terms of function, and its breadth of application, will encourage the formation of strategic alliances to ensure equitable access to knowledge for future product development. Strong early-mover advantages in drug development rest on the ability to rapidly identify, access, and integrate new combinations of knowledge [Antonelli, 2003; Grant and Baden-Fuller, 2004]. Where products require a broad range of different types of knowledge, efficiency of integration is maximized through separate firms specializing in different knowledge areas that are linked by strategic alliances [Grant and Baden-Fuller, 2004]. Consequently, many pharmaceutical companies are reconsidering their strategies with respect to upstream, pre-competitive, discovery research [Eisenberg, 2000; Cassier, 2002].

We use our knowledge framework in this chapter to specifically analyze the role of knowledge characteristics on biopharmaceutical alliance formation, the role of knowledge form on the choice of alliance structure, as well as the impact of knowledge valuation as a function of knowledge form, on alliance performance. Our proposed knowledge view of biopharmaceutical alliances, not only advances the notion of knowledge access as a strong motivator for interfirm alliances, but also closely analyzes the nature of knowledge structures and the process of knowledge generation in the biopharmaceutical industry as impacting the need for knowledge access. We begin with a discussion of the resource-based view of strategic alliances and role of resource characteristics and types on alliance formation [Das and Teng, 2000]. We then outline the traditional view of complementary assets as encouraging biopharmaceutical alliances and discuss how, in the information paradigm of drug discovery and development, the need exists to view these alliances specifically from a knowledge perspective.

Then using the Recombinant Capital Alliances Database, a private, searchable database of almost 13,000 strategic alliances, we analyze discovery-based/early research-based biopharmaceutical alliances covering the period from 1980 to 2005 [www.recap.com, 2006]. Through our preliminary analysis, we discover that the focus of research in public-private alliances favours the biological paradigm across time periods. With respect to private alliances, of interest is the continued focus on the chemical paradigm in the later periods of our analysis. Appropriation activities across the chemical and biological paradigms tend to focus on downstream, application oriented discoveries. However, the relative frequency of licenses on upstream oriented knowledge and discoveries when the focus of research is information-based warrants closer scrutiny to determine if problems exist on the horizon for downstream development of products based on these patents.

5.2 A Resource-Based View of Strategic Alliances

A resource-based view of strategic alliances considers resource characteristics and the impact of value maximization through the pooling of such resources as encouraging the formation of alliances. Imperfect mobility, imperfect imitability, and imperfect

substitutability of required resources are instrumental in the decision to form an alliance with firms that own these resources [Barney, 1991; Das and Teng, 2000]. Strategic alliances become critical institutional mechanisms to facilitate the pooling of, sharing of, and exchanging of valuable resources with other firms when these resources cannot be acquired efficiently through market transactions or mergers and acquisitions [Gulati, 1995; Ramanathan et al., 1997; Das and Teng, 2000].

Barney (1991) describes firm resources as "all assets, capabilities, organizational processes, firm attributes, information, and knowledge controlled by a firm that enable the firm to conceive of and implement strategies that improve its efficiency and effectiveness". Imperfectly mobile and imitable resources provide firms with competitive advantage through the provision of sustainable economic rents, assuming that the resources have no substitutes or strategic equivalents [Barney, 1991; Chi, 1994]. Kogut's (1998) organizational learning model further suggests that alliance formation is intended to either acquire another firm's "know-how" or to augment one's know-how by benefiting from the other firm's knowledge or technology. Kogut also argues that opportunities for interfirm transfer of knowledge or technology will influence the choice of strategic alliance structure used.

For example, a firm will favour acquisitions over joint ventures when the resources required are not commingled with other unneeded resources within the firm that possesses them [Hennert and Reddy, 1997]. Hennert and Reddy refer to such resources as "digestible". In contrast, strategic alliances such as joint ventures are used when required resources are owned by different firms and when these resources are inseparable from other resources owned by a firm [Ramanathan et al., 1997]. It has also been suggested that appropriability problems will impact the decision to choose a more hierarchical alliance structure. Indeed, where appropriability problems are sufficiently high, vertical integration will be preferred to collaborative innovation [Teece, 1986; Pisano et al., 1998; Oxley, 1999]. Firms may be hesitant to share their knowledge or technology through collaborative alliances when legal protection of these resources is uncertain, unless this cost is outweighed by other benefits [Greis et al., 1995].

Characteristics of Resources: The resource-based view suggests that firm resource heterogeneity can be a source of sustained competitive advantage [Barney, 1991]. Resource characteristics that prevent firms from achieving resource homogeneity include: imperfect mobility, imperfect imitability, and imperfect substitutability [Barney, 1991; Chi, 1994; Das and Teng, 2000]. Imperfect mobility refers to the difficulty associated with transferring resources from one firm to another. Peteraf (1993) describes this as specificity—the condition that a resource is so specialized to one firm that it is either not tradable at all or is imperfectly tradable. For example, tacit knowledge can lose its value if transferred from one organizational context to another. Imperfect imitability is associated with the notion of causal ambiguity—where the precise nature of the causal connection between a resource and the competitive advantage it confers is not visible to outside firms [Barney, 1991; Chi, 1994; Das and Teng, 2000]. Competitive advantage is sustained when the firm that possesses the resource has better knowledge of these causal connections [Chi, 1994]. Firms also enjoy sustainable competitive advantage when resources have no strategic equivalents and are themselves rare and imperfectly imitable [Barney, 1991]. In the pharmaceutical industry, small biotechnology firms collaborate with large pharmaceutical companies to gain access to resources such as clinical trial networks, marketing and distribution channels, and regulatory know-how, which represent resources that are immobile, imperfectly imitable, and non-substitutable [Arora and Gambardella, 1990; Greis et al., 1995; Powell et al., 1996; Das and Teng, 2000].

Types of Resources: Barney (1991) classifies firm resources into physical capital resources, human capital resources, and organizational capital resources. However, for our purposes, we consider the Miller and Shamsie classification (1996) most appropriate. Miller and Shamsie classify resources into two broad categories: property-based resources and knowledge-based resources. Property-based resources are legal properties owned by a firm including financial capital, physical resources, and human resources. Owners enjoy clear property rights relating to these resources or rights to use these resources. Knowledge-based resources typically refer to a firm's intangible know-how and skills. Tacit knowledge and technological resources fall into this category [Hall,

1992]. The central difference between property-based resources and knowledge-based resources is that protection of knowledge is not perfect. Knowledge-based resources are vulnerable to unintended transfers and as a result, appropriation problems [Arrow, 1962]. The protection of such knowledge-based resources has traditionally been a critical concern when forming alliances [Hamel, 1991; Mowery et al., 1996]. In contrast, property-based resources enjoy near-perfect legal protection.

Alliance Structures: Concerns about protecting knowledge-based resources in strategic alliances will impact both the decision as to whether to form an alliance and the structural choice for the alliance. From the resource-based perspective, firms are not only interested in accessing or acquiring complementary assets, but are also interested in protecting their own resources and knowledge in an alliance [Hamel, 1991; Mowery et al., 1996]. Hierarchical structures, including equity based alliances, may be used to monitor the behaviour of alliance partners, limit a partner firm's use of knowledge or technology, enable learning across firms, and encourage adherence to the spirit of any agreement between firms [Pisano et al., 1989; Oxley, 1999].

In strategic alliances such as joint R&D, joint production and joint marketing, and bilateral contract-based alliances, more opportunities exist for learning and interfirm knowledge transfer than in unilateral contract-based alliances such as licensing and subcontracting [Das and Teng, 2000]. In such alliances, partner firms work closely together, pooling resources, and sharing knowledge. Property-based or knowledge-based resources can be contributed by member firms to the alliance. However, it has been suggested that once learning and interfirm knowledge transfer has been accomplished, alliances are terminated, with each firm progressing unilaterally thereafter [Khanna et al., 1998]. Firms engaged in a knowledge transfer alliance must therefore take care to avoid a premature learning or development race [Hamel, 1991; Larsson et al., 1998].

Unilateral contract-based alliances are preferred when partners are contributing property-based resources to the alliance. These alliances can include licensing, subcontracting, and distribution agreements. In such alliances, there is essentially an exchange of property

rights e.g., intellectual property rights for licensing fees, royalties, or the future right to licenses on downstream applications of the original intellectual property [Eisenberg, 1996; Das and Teng, 2000; Kieff, 2003]. Unilateral alliances create fewer opportunities for knowledge transfer as firms are expected to perform independently without much coordination or collaboration [Mowery et al., 1996, Das and Teng 2000].

The Performance of Alliances: The resource-based view suggests that competitive advantage is derived from the effective integration of partner firms' resources. The manner in which resources are aggregated will significantly impact the performance of the alliance [Hagedoorn, 1993]. Researchers have discussed the role of complementary or supplementary resources in alliance performance and the degree to which contributed resources are utilized for achieving alliance goals. Resource alignment between partners is supplementary when firms contribute similar resources, thereby creating greater value from the collective pooling of resources. Complementary alignment occurs when partners bring distinctive complementary assets to the alliance and synergy is created through a recombination of resources. Both supplementary and complementary alignments have a positive effect on alliance performance. The capacity to take advantage of these positive externalities will in turn determine if alliance goals are achieved [Das and Teng, 2000].

However, the incentive to invest resources will differ as the alliance evolves. Common benefits are those that will accrue to each partner firm in an alliance from the collective pooling of resources and collective learning that partners experience. Private benefits are those that a firm can earn unilaterally by learning from another firm. By pooling a partner firm's resources and knowledge with internal firm resources and knowledge, a firm can gain a competitive advantage to progress unilaterally in downstream activities. Once a firm has learned enough from a partner it has no incentive to continue participating in the alliance and as such, it will choose to terminate the alliance. However, studies do indicate that if there is no incentive for a leading firm to quit or exit an alliance once it achieves private benefits, the laggard firm may not be locked out from the alliance or denied access to the full set of resources and knowledge [Khanna et al., 1998]. The situation can arise when there is an expectation of future common benefits and future interactions

between firms [Khanna et al., 1998]. Therefore, the structure of mechanisms for knowledge transfer and the transparency of motives during knowledge production are crucial to the sharing of knowledge [Larsson et al., 1998].

5.3 A Nuanced View of Strategic Alliances

Alliances between biotechnology and pharmaceutical companies are often viewed from the perspective of complementary assets. When firms possess what Teece called complementary assets and where these assets are bound up in tacit or firm-specific knowledge, firms seek collaborations [Teece, 1986]. Academic institutions and biotechnology companies supply new insight and ideas for drug pipelines, validate drug targets, and develop compounds, therapies, and technologies. Large traditional pharmaceutical manufacturers possess complementary research capabilities such as large research assets not available in smaller biotech companies [Starpoli, 1998]. This division of labour allows small biotechnology firms to focus on upstream research and large pharmaceutical companies to gain access to novel technologies by exploiting their large-scale development advantages.

In the pharmaceutical industry, the development of many new drugs hinges upon advances in molecular biology and genetic engineering. As a result, research activity that adheres to the molecular biology paradigm (and now the information paradigm) often requires network-like alliances between academic institutions, biotechnology companies, and traditional drug manufacturers [Bower and Whittaker, 1992; Powell et al., 1996; Blumenthal et al., 1997]. The genomics era has further highlighted the need for partnerships that are broad and cross institutional boundaries. For example, genomics-based research is producing new drug targets that are unmanageable by even the largest of pharmaceutical companies [Roses, 2002]. Therefore, the breadth of upstream research to be conducted to ensure successful downstream drug development, particularly in a decade marked by shrinking pipelines and blockbuster drug patent expirations, has reinforced the need for knowledge-based networks [Reid et al., 2001].

Genes, proteins, biological systems, and their associated patents are strategic knowledge-based assets [Blumenthal, 1992; Powell et al., 1998; Arora and Fosfuri, 2003; Jackson, 2003]. The importance of these knowledge-based assets, combined with the increased complexity of molecular and systems-based knowledge, is encouraging the view that alliances between firms in this industry should be viewed centrally from a knowledge-based perspective [Hood, 2000; Reid et al., 2001]. Our knowledge framework provides a nuanced understanding of the cooperation between academic institutions, biotechnology companies, and pharmaceutical companies during the drug discovery research and development process. Although the extent to which critical knowledge assets are protected governs the decision to engage in these alliances, it is interesting to observe, that many biotechnology and pharmaceutical companies also promote and engage in alliances that are committed to open source drug discovery—through which discoveries are made freely available to researchers. We anticipate that the decision to engage in open source drug discovery is a function of the structure of the associated knowledge in addition to the nature of the intellectual property rights associated with the knowledge in question. Specifically, biological knowledge characteristics are thought to impact the decision to participate in an alliance; the form of biological knowledge to be produced will impact the type of alliance structure; and the value placed on the knowledge by participating firms in an alliance will impact the performance of the alliance. It is important to note that the nature, strength, and perceived value of biological knowledge are likely to be dynamically determined by the existing state of knowledge.

5.3.1 Knowledge Characteristics and Alliance Formation

The transformation of knowledge from a purely public good to a quasi-private good has highlighted the need for balance between incentives for the market provision of scientific and technological knowledge by a first innovator and incentives for the market provision of incremental knowledge by a follow-on developer [Scotchmer, 1991; Caskey, 1996; Heller and Eisenberg, 1998; Scherer, 2000]. The possibilities for holdouts and the likelihood of high transaction costs associated with gaining the right to use knowledge in downstream activities, increase as a function of the complementarity, non-substitutability, and applicability of upstream knowledge [Merges, 1994; 1996]. Holdouts occur when

buyers need to acquire complementary assets from sellers and sellers raise their prices to capture some of the value buyers attribute to collectively holding the assets [Merges, 1994]. Bargaining failures occur when the first innovator and follow-on developer are unable to reach an agreement regarding access to knowledge and the rights to future developments [Merges, 1994].

Complementarity: Drug discovery research has become associated with a high level of knowledge complexity as the sources of knowledge are diverse and derive from a wide variety of scientific fields and technological competencies. The chance of generating new knowledge and embodying knowledge in products or processes may be conditional on the ability to access and then piece together a significant variety of complementary research inputs [Scotchmer, 1991; Foray, 2004]. Upstream complementarity occurs among research inputs during the generation of new knowledge while downstream complementarity occurs in the development phase during the application of new knowledge [Antonelli, 2003]. Complementary knowledge can be used to generate new knowledge in the same context or in other adjacent ones. Knowledge will be pooled from the public domain or from owners of the knowledge willing to trade at a reasonable cost.

Non-substitutability: Non-substitutability occurs when knowledge is discovered rather than invented. The ability to invent around knowledge will determine whether or not new knowledge can be generated and then embodied by follow-on researchers that do not directly own the knowledge. The discovery of facts from nature, as is associated with many of the informational, upstream, research inputs in genomics, cannot be substituted. These research inputs can be discovered and then used to generate new knowledge. As the centrality of this type knowledge to the research domain, biological system, or disease increases, the ability to substitute for or access knowledge will be critical for continued medical progress. When follow-on innovators cannot develop or obtain substitute knowledge, first innovators can potentially extract high rents for rights to access and use their knowledge. If the anticipated rent is higher than the value placed on the non-substitutable knowledge by the follow-on researcher, bargaining failures are possible.

Consequently, excess appropriability can slow down if not impede downstream knowledge access and generation.

Applicability: Research activities are characterized by high levels of risk and uncertainty in terms of both generating knowledge and then in terms of applying knowledge in downstream activities. In the genomics arena, a great deal of uncertainty exists with respect to the role of genes in disease susceptibility and progression, the hierarchy of proteins in any system, and the function of such genes and proteins during drug intervention. The simple discovery of a gene and its sequence do not necessarily provide this information. In one scenario, this knowledge may have a limited, specific role in one disease or system and in another scenario, the gene and its encoding products may have a central role across multiple diseases or drug intervention pathways. Given the functional uncertainty of this upstream knowledge, it can be difficult to assess ex-ante the economic value stemming from the putative application of biological knowledge in downstream activities [Dutfield, 2003]. As patent holders may not be aware ex-ante what knowledge will be key in disease development or drug intervention, patent holders should be willing to provide access to this biological knowledge at a fair price.

From the perspective of knowledge access, in an increasingly complex drug discovery and development paradigm, firms will form strategic alliances to ensure equitable access to upstream biological knowledge. Studies indicate that cooperation levels are greatest when alliance members are asked to contribute to a public good that is indivisible. Generating a public good such as knowledge that is indivisible and in the case of biological knowledge, possibly non-substitutable, will likely reinforce a sense of group identity and interdependency among alliance members [Kollock, 1998]. If the value of the knowledge increases with joint production, cooperative behaviour is optimal. The shadow of the future in terms of knowledge access and transaction costs to invent, should knowledge be fragmented, will also moderate the temptation to defect and encourage cooperation in knowledge dissemination [Kollock, 1998].

From the two-dimensional information of the gene, to the three-dimensional information of proteins, biological research has moved into the fourth dimension of observing and mapping the time variant information present in biological systems [Hood, 2000]. Of particular importance will be the ability to follow the flow of information along the pathways that comprise such systems. To map this flow of information, complex systems will be divided into subsystems whose properties and interactions are observable. From each subsystem, the structures within each subsystem will be identified along with their interconnections with other structures. Ultimately, the flow of information from subsystem to subsystem will be mapped and modeled, thereby enabling researchers to decipher the structure of the informational pathway and the resulting system properties.

In Figure 5.1, we use a graphical example to demonstrate the possible connections between knowledge units across five hypothetical projects/systems. Across these five projects/systems (1-5) knowledge units (A-E) have varied applicability. In this case, knowledge units A and E are substitutable with each other. Where knowledge unit A or E (e.g. isoforms of a proteomic sequence) applies to a project, knowledge unit B (e.g. corresponding genomic sequence) is also applicable to the same project as it is complementary to knowledge units A or E. Knowledge unit D (e.g. a regulatory component) has applicability across all projects. Whereas, knowledge unit C is centrally important only across projects 1, 3, and 5—serving as the point of medical intervention (e.g. drug target).

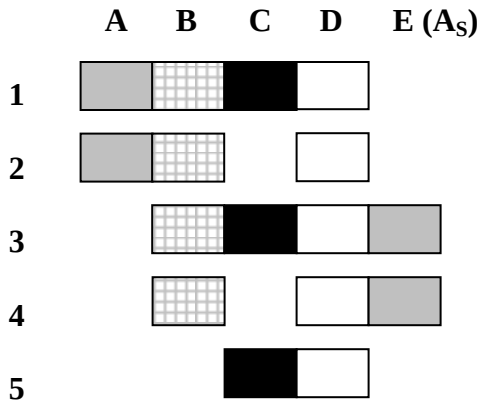


Figure 5.1: Linking Knowledge Structures

Letters=Knowledge Units; Numbers=Projects; E(A_s)=Substitutable Version of Knowledge Unit A; Solid Grey Box (Knowledge Units A and E)=Substitutable Knowledge Units; Patterned Grey Box (Knowledge Unit B)=Complementary Knowledge Box (A or E Complementary to B); Black Box=Medical Intervention Point

5.3.2 Knowledge Form and the Choice of Alliance Structure

Knowledge may serve as an input into further development and the creation of new knowledge or serve as a component of the final embodiment of research and development activities. As knowledge evolves from the idea stage, through the research process, disembodied knowledge or pure knowledge is generated. Knowledge that is applied can be embodied in products and processes. Biological inputs such as genes, proteins, and drug targets as well as tools such as biological materials, databases, and analytical tools feed into the drug discovery and development process [Walsh et al., 2003]. Medical diagnostics embody knowledge of research inputs such as genes and proteins, to detect disease susceptibility and disease progression, as well as to predict therapeutic response. As research progresses further downstream, chemical based libraries are created from which drugs are sought, or biological therapeutics such as recombinant proteins, monoclonal antibodies, and even gene delivery are developed to correct malfunctioning processes. These therapeutic products are also embodiments of upstream discovery knowledge.

Mergers, acquisitions, and strategic alliances are used to gain access to both tacit and codified molecular knowledge, and tend to be associated with downstream knowledge-knowledge that is used for the purpose of medical application development [Greis et al., 1995; Das and Teng, 2000]. Upstream knowledge that is far removed from commercial

application is typically developed through research-based partnerships between universities, biotechnology companies, and pharmaceutical companies [Arora and Gambardella, 1990; Blumenthal, 1992; Senker and Sharp, 1997].

Knowledge-based networks are communities of individuals with the objectives of producing and disseminating knowledge. Norms or rules for knowledge sharing and knowledge appropriation are necessary in networks with varied types of researchers [Ostrom et al., 1994; Liebeskind et al., 1996]. Knowledge networks enable multiple researchers to pool assets, know-how, and expertise for the purpose of knowledge generation, knowledge validation, and new wealth creation [Powell et al., 1996; Reid et al., 2001]. The ability to generate new wealth depends on the capacity of researchers to learn from other researchers in a knowledge network or alliance. Asymmetric learning can lead to disappointing performance in a network or alliance [Larsson et al., 1998]. The formation of trust, through repeated interactions and communication between the researchers, will facilitate knowledge exchange and adherence to network norms [Merton, 1957; Axelrod, 1985; Merges, 1996].

5.3.3 The Valuation of Knowledge, Knowledge Appropriation and Performance of Alliances

Once a commitment is made to participate in a strategic alliance, firms will face the decision as to when (or indeed if) to privately appropriate knowledge. Appropriation most often occurs through the decision to formally patent knowledge. The common benefits from contributing knowledge to an alliance versus the private benefits associated with unilaterally appropriating knowledge from an alliance will impact the performance of the alliance and will determine when a firm will choose to signal its exit [Axelrod, 1985; Gulati et al., 1994; Gulati, 1995]. A higher ratio of private to common benefits is likely to lead to departures from cooperation in favour of defection or competitive behaviour, despite the original agreement to adhere to the norms associated with an alliance [Ostrom et al., 1994; Lerner, 1995; Atkinson et al., 1998; Khanna et al., 1998]. However, depending on the characteristics associated with the knowledge, accessibility may be required for multiple researchers to progress further downstream in the development of diagnostics and therapeutics. The key is then to find the transition point. The occurrence

of the transition point too far upstream may lead to holdouts and bargaining failures for access to and use of knowledge in downstream research.

The decision to sell disembodied knowledge in the form of patents and licenses can complement or substitute for the sale of embodied knowledge. Substitution occurs when the profits from the sale of disembodied knowledge are greater than those from the sale of embodied knowledge [Antonelli, 2003; Arora and Fosfuri, 2003]. For example, when the costs of internal coordination of the knowledge are larger than the transaction costs associated with the market for technical knowledge, or when special assets are required to progress further downstream, the patent holder may chose to maximize revenue through a licensing strategy, specifically an exclusive licensing strategy [Teece, 1986; Antonelli, 2003]. Complementarity between the sale of disembodied knowledge and internal embodiment occurs when knowledge possesses high applicability and it is possible to operate in different markets from other licensees of the knowledge [Teece, 1986; Arora and Fosfuri, 2003, Foray, 2004]. In this case, a non-exclusive licensing strategy can ensure that multiple participants can pursue multiple streams of research. Furthermore, cross-licensing is a useful governance mechanism when knowledge exhibits high levels of complementarity [Shapiro, 2001]. With downstream activities dependent on the recombination of a variety of knowledge, the cost of the coordination including accumulation of the full range of required knowledge may be too high for one researcher [Antonelli, 2003; Burk and Lemley, 2003]. Specifically, the capabilities of the one researcher may only cover a portion of the research domain. Consequently, researchers may find it profitable to engage in cross-licensing for knowledge. However, the ability for each researcher to access knowledge depends on the amount and type of proprietary knowledge each one is able to contribute in any bargaining event [Antonelli, 2003].

Bargaining stalemates are especially likely when the first innovator has been awarded a broad patent covering follow-on development [Roberto and Nelson, 1998]. This broad protection can lead to deficient incentives to develop second-generation knowledge or products. The second innovator who cannot progress downstream without a license is in a very weak bargaining position. The situation is troublesome particularly when first

generation knowledge does not have commercial value by itself, but needs to be recombined with other knowledge [Merges 1994; Antonelli, 2003]. The second innovator, who plans to invest substantial sums in downstream activities including testing, gaining regulatory approval, and marketing, will demand that he/she receive the lion's share of the revenue from these activities [Scherer, 2002]. In contrast, the first innovator with the ability to completely block development will demand an incompatibly large share [Scherer, 2002].

In Figure 5.2, we extend our previous example to demonstrate the impact of knowledge appropriation. In this hypothetical example, the projects are assigned to five researchers (R_i; see Figure 5.1 for corresponding project numbers); however, only three researchers have each appropriated various knowledge units. Researcher 1 has appropriated (through filing a patent) knowledge unit C. Researcher 2 has appropriated knowledge units A and B. And researcher 3 has appropriated knowledge units D and E. Since knowledge units A and E are substitutable with each other the researchers 2 and 3 do not have a strong bargaining position with respect to these knowledge units as researchers can approach either patent holder. However, researcher 2 is definitely in a strong bargaining position for projects 1 and 3 by having patented complementary knowledge units A and B and for project 4 having patented knowledge unit B. Similarly, given that knowledge unit C is centrally important across projects 1, 3, and 5 serving as the point of medical intervention (e.g. drug target), researcher 1 is in a strong bargaining position for projects 3 and 5. However, it is researcher 3 that is in the strongest position having patented knowledge unit D. This knowledge unit has applicability across all projects. Cross-licensing knowledge unit B with researcher 3 for knowledge unit D is a possibility for researcher 2 who only needs this one knowledge unit to pursue his/her project. In contrast, researcher 1 will have to bargain with both researchers 2 and 3 to access knowledge units A-B and D respectively. While cross-licensing with researcher 3 is an option to access knowledge unit D for researcher 1 and knowledge unit C for researcher 3, researcher 2 does not require any units from researcher 1. As such, researcher 2 is a very strong position with researcher 1 for knowledge units A-B. Similarly, researchers 4 and 5 have nothing to offer in the bargaining setting (not having patented any knowledge units); hence both are

in a weak position with respect to bargaining for knowledge units. Depending on the terms offered, these researchers may not be able to pursue their respective projects.

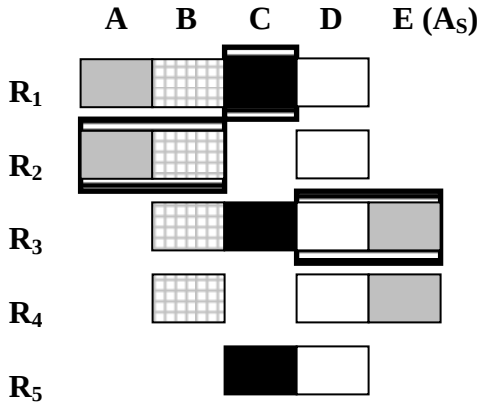


Figure 5.2: Appropriating Knowledge
Letters=Knowledge Units; R=Researcher—Researchers are assigned to a Project; Dark Patterned Boxes around Knowledge Units C, A-B and D-E=Patented Knowledge Units by Respective Researchers 1-3.

5.4 Analyzing Paradigms and Alliances

Using the Recombinant Capital Alliances Database, we analyzed biopharmaceutical alliances that were formed between 1980 and 2005. Collaborative alliances, research-based alliances, and license-only alliances were chosen in order to concentrate our analysis on the earlier phases of the drug discovery and development paradigm as assessed through the categorizations used in the database and then verified through a more detailed analysis of the alliances themselves. We analyzed both public-private and private alliances between academic institutions, nonprofit research-based institutions, and biotechnology or pharmaceutical firms.

Initially, each alliance was associated with a knowledge paradigm—chemical, biological, or information paradigm. (Table 5.1) We associated each alliance with a paradigm based on the primary research activity. From the perspective of knowledge production, our analysis specifically investigates the evolutionary path of alliance focus over the period 1980 to 2005. We also investigate how the relative frequency of alliances changes as the underlying knowledge paradigm changes. (Analysis 5.1) We segregate data into 5-year periods to better observe/note any trends.

From the perspective of knowledge access, we determined if and when privatization (or enclosure) of knowledge occurred within each alliance (denoted by the granting of a license; we assume that patenting precedes licensing). It is important to note that licenses were issued in license-only alliances as well as in collaborative or research-based alliances. Licenses were analyzed across knowledge paradigms. (Analysis 5.2) By further analyzing the scope of the licenses, we determined the phase of research i.e., upstream or downstream.

We include the condensed version of Recombinant Capital data in the Appendix to demonstrate the paradigm, phase, and then subject matter categorization for each alliance. (See Appendix Tables 8 and 9) The following examples provide a preliminary indication of the categorization process used.

Alliance Focus	Phase	Paradigm	Subject Matter
Alzheimer's research	Upstream Research	Biological	Disease Research
Identification of bacterial virulence genes	Upstream Discovery	Information	Biological Information
Drug discovery for pain & urinary tract disorders	Upstream Discovery	Chemical	Drug Discovery
GeneChip(R) tech. to analyze genomic information	Downstream Application	Information	Tool
Access to ChemDiv compound libraries	Downstream	Chemical	Tool
Fibroblast retroviral gene transfer	Downstream Application	Biological	Therapeutic
Lipid vectors in cancer gene therapy	Downstream Application	Biological	Tool
Antibody production	Downstream	Biological	Process
Nitric oxide donating drugs	Downstream	Chemical	Therapeutic
Library screening for cancer	Downstream	Chemical	Screening

Table 5.1: Analyzing the Recombinant Capital Database

Disease research is categorized as following the biological paradigm; however, we categorized genomic research as specifically adhering to the information paradigm. Both disease research and genomic related research are then categorized as pre-discovery research from a subject matter perspective in Figures 5.3 and 5.4. (Analysis 5.3) Several

examples also exist in the database of general drug discovery collaborations following the biological or chemical paradigms.

Assay development, chip development, and database development are categorized as tools enabling discovery research or drug development; in Table 5.1 we have tool development adhering to all three paradigms.

While gene transfer is categorized as focusing on therapeutic development, the development of vectors for use in gene therapy is categorized as tool development. Similarly, while monoclonal antibodies serve as biological therapeutics, we categorized the production of such antibodies as process development. We also differentiate between drug development and screening in Table 5.1, thereby maintaining the same consistency in the chemical paradigm as done for the biological paradigm. As shown in Figures 5.3 and 5.4, for simplicity, alliances that focus on combinatorial chemistry and screening form one subject-matter category.

Finally, in Table 5.1, general disease research, gene discovery research, and drug discovery are all examples of upstream research; in contrast, biological or chemical drug development, supporting tool development, antibody production, and drug screening are all categorized as downstream development work.

Public-Private Alliances: Based on our preliminary analysis of 667 public-private alliances, the frequency of alliance formation between academic or nonprofit organizations and biotechnology or pharmaceutical firms generally appears to increase, with a substantial increase over the 2001-2005 period. The focus of public-private alliances favours the biological paradigm over the traditional chemical paradigm across time periods. (Table 5.2) However, we also note a gradual increase in alliances focusing on the information-based paradigm over the 2001-2005 period; the analysis should be continued through the next five-year period to ascertain whether this trend will continue.

Paradigm Date	Chemical Paradigm	Biological Paradigm	Information Paradigm
1980-1985	3	16	4
1986-1990	12	22	11
1991-1995	46	77	32
1996-2000	43	60	34
2001-2005	93	112	102
Subtotals	**197**	**287**	**183**

Table 5.2: Analyzing Discovery and Early Phase Public-Private Alliances across Knowledge Paradigms

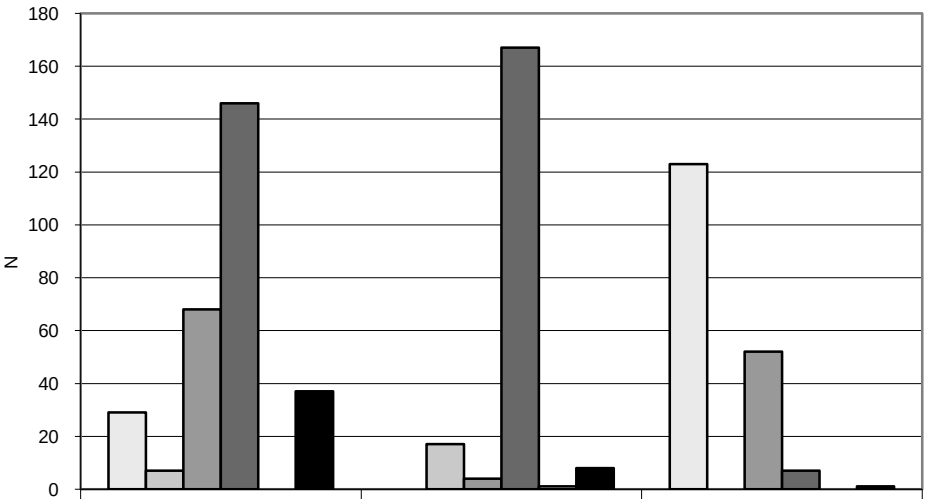
In terms of licenses (from 667 discovery/early research alliances, 548 licenses were issued within these alliances), our analysis indicates that across the chemical and biological paradigms, the majority of licenses focus on downstream, clearly application oriented discoveries. (Table 5.3) Of concern however, is the significant number of licenses on upstream oriented knowledge and discoveries when the focus of research is information-based. Further study is necessary over the next five-year period to determine if this trend will continue.

Paradigm	Chemical Paradigm		Biological Paradigm		Information Paradigm	
Type of License	U	D	U	D	U	D
Subtotals	17	150	38	200	96	47

Table 5.3: Analyzing Licenses across Knowledge Paradigms from Public-Private Alliances

U=Upstream; D=Downstream

A closer examination of the specific subject matter of each alliance is also of interest. When we categorize subject matter as being pre-discovery, general drug discovery research, tool development both pre-discovery and discovery-based, or targeted therapeutic research (drug or biologic), and compare subject matter for public-private alliances across paradigms, we notice that in the biological and chemical paradigms, targeted therapeutic research (drug or biologic) dominates other categories. In contrast, an analysis of the information paradigm reveals that pre-discovery research dominates all other subject matter categories. (Figure 5.3)



	BP	CP	IP
Pre-Discovery Research (Genomic, Disease Related)	29	0	123
General Drug Discovery Research	7	17	0
Tools Development (Pre-Discovery and Discovery)	68	4	52
Targeted Drug, Biologic Research	146	167	7
Combinatorial Chemistry/Screening	0	1	0
Other	37	8	1

Figure 5.3: Analyzing the Subject Matter of Public-Private Alliances across Paradigms

CP=Chemical Paradigm; BP=Biological Paradigm; IP=Information Paradigm; Pre-Discovery=Broad genomics, disease related research; General Drug Discovery Research=Broad research into the discovery of new drug/biologic therapeutics; Tool Development=Broad research-based tools or drug discovery-based tools; Targeted Drug/Biologic Research=Specific research into a drug/biologic therapeutic; Combinatorial Chemistry/Screening=Combinatorial methods used for and High-throughput screening of drug leads; Other=Process related or Other unknown research.

Private Alliances: Based on our preliminary analysis of 680 private biotechnology and/or pharmaceutical alliances, the frequency of alliance formation between biotechnology and/or pharmaceutical firms appears to increase, with a substantial increase over the 2001-2005 period. The focus of the alliances only slightly favours the biological paradigm over the traditional chemical paradigm. Although we note a gradual increase in alliances focusing on the information-based paradigm over the 2001-2005 period, among

private firms, the chemical paradigm is still a significant focus for alliances over this later period. (Table 5.4)

Paradigm Date	Chemical Paradigm	Biological Paradigm	Information Paradigm
1980-1985	1	5	0
1986-1990	4	3	0
1991-1995	11	12	4
1996-2000	58	51	78
2001-2005	157	177	119
Subtotals	**231**	**248**	**201**

Table 5.4: Analyzing Discovery and Early Phase Private Alliances across Knowledge Paradigms

The continued focus of alliances on the chemical paradigm may be a reflection of the need to share the risk and cost associated with drug discovery and development in a technologically complex traditional paradigm. Furthermore, the prevalence of high-throughput screening and combinatorial chemistry technologies post 2000, within the private sector, may be encouraging traditional biopharmaceutical companies to form collaborative alliances even when adhering to the traditional chemical paradigm [Beeley et al., 2000].

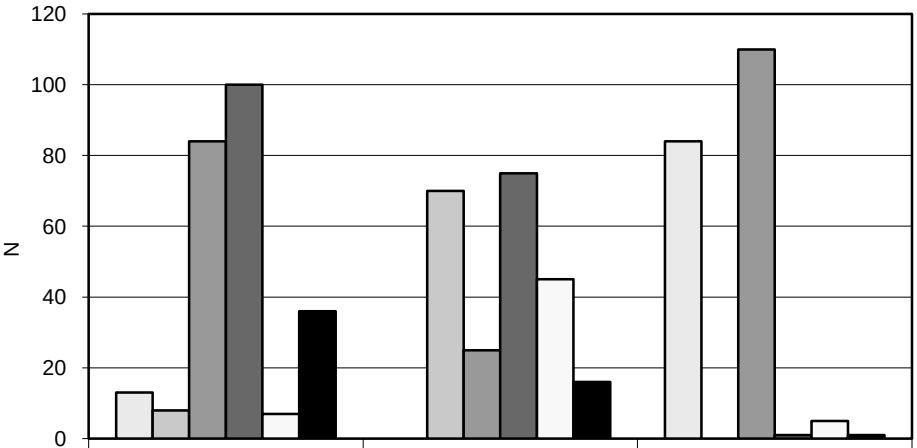
With respect to the nature of licenses (from 680 discovery/early research alliances, 555 licenses were issued from these alliances), our analysis indicates that across the chemical and biological paradigms, the majority of licenses are focused on downstream, clearly application oriented discoveries. (Table 5.5) When the focus of research is information-based, interestingly an equivalent number of upstream and downstream licenses are issued. Further study is necessary over the next five-year period to determine if this trend will continue or change in either direction.

Paradigm	Chemical Paradigm		Biological Paradigm		Information Paradigm	
Type of License	U	D	U	D	U	D
Subtotals	40	141	36	176	81	81

Table 5.5: Analyzing Licenses across Knowledge Paradigms from Private Alliances

U=Upstream; D=Downstream

A closer examination of the specific subject matter of each private alliance similarly provides interesting results. Although targeted therapeutic research dominates as subject matter for the biological paradigm, tool development closely follows. Similarly, targeted therapeutic research (drug or biologic) only slightly dominates as subject matter for the chemical paradigm, with general drug discovery following closely behind. When adhering to the chemical paradigm, combinatorial chemistry and screening are also notable subject matters for private-based alliances. Finally, although pre-discovery is a notable subject matter, tool development dominates within the information paradigm. Interestingly, within private alliances (as is the case for public-private alliances), the majority of pre-discovery research is following the information paradigm. (Figure 5.4)



	BP	CP	IP
Pre-Discovery Research (Genomic, Disease Related)	13	0	84
General Drug Discovery Research	8	70	0
Tools Development (Pre-Discovery and Discovery)	84	25	110
Targeted Drug, Biologic Research	100	75	1
Combinatorial Chemistry/Screening	7	45	5
Other	36	16	1

Paradigm

Figure 5.4: Analyzing the Subject Matter of Private Alliances across Paradigms

CP=Chemical Paradigm; BP=Biological Paradigm; IP=Information Paradigm; Pre-Discovery=Broad genomics, disease related research; General Drug Discovery Research=Broad research into the discovery of new drug/biologic therapeutics; Tool Development=Broad research-based tools or drug discovery-based tools; Targeted Drug/Biologic Research=Specific research into a drug/biologic therapeutic; Combinatorial Chemistry/Screening=Combinatorial methods used for and High-throughput screening of drug leads; Other=Process related or Other unknown research.

5.5 Discussion

Through our analysis of public-private and private alliances formed from 1980 to 2005, we were able to determine the paradigms followed, phase of research and development activities, as well as central focus of these alliances. An analysis of 667 public-private alliances indicates that the frequency of alliance formation between academic or nonprofit organizations and biotechnology or pharmaceutical firms generally appears to increase, with a substantial increase over the 2001-2005 period. Similarly, our analysis of 680 private biotechnology and/or pharmaceutical alliances reveals the same trends.

The focus of public-private alliances favours the biological paradigm over the traditional chemical paradigm across time periods. However, we also note a gradual increase in public-private alliances focusing on the information-based paradigm over the 2001-2005 period. In contrast, the focus of private alliances only slightly favours the biological paradigm over the traditional chemical paradigm. Although we note a gradual increase in alliances focusing on the information-based paradigm over the 2001-2005 period, among private firms, the chemical paradigm is still a significant focus for alliances over this later period.

When we categorize subject matter as being pre-discovery, general drug discovery research, tool development both pre-discovery and discovery-based, or targeted therapeutic research (drug or biologic), and compare subject matter for public-private alliances across paradigms, we notice that in the biological and chemical paradigms, targeted therapeutic research (drug or biologic) dominates other categories. In contrast, an analysis of public-private alliances following the information paradigm reveals that that pre-discovery research dominates all other subject matter categories. Comparatively, although targeted therapeutic research also dominates as subject matter for the biological paradigm among private only alliances, tool development closely follows. Similarly, targeted therapeutic research (drug or biologic) only slightly dominates as subject matter for the chemical paradigm, with general drug discovery following closely behind for these private alliances. In addition, when adhering to the chemical paradigm, combinatorial chemistry and screening are also notable subject matters for private-based alliances. Finally, although pre-discovery is a notable subject matter for these alliances, tool development dominates within the information paradigm. Interestingly, within both types of alliances, the majority of pre-discovery research is following the information paradigm. Given the significant paradigm change since the completion of the Human Genome Project, it is understandable that pre-discovery research would focus on the search for genomic, proteomic, systems information to enable an understanding of viable drug targets for downstream product development.

In terms of licenses issued within public-private and private alliances, our analysis indicates that across the chemical and biological paradigm, the majority of licenses focus on downstream, clearly application oriented discoveries. Interestingly, a significant number of licenses have also been issued on upstream oriented knowledge and discoveries when the focus of research is information-based within these public-private alliances. In contrast, when the focus of research is information-based within private alliances, an equivalent number of upstream and downstream licenses were issued.

Drug discovery research has become associated with a high level of knowledge complexity as the sources of knowledge are increasingly diverse and derive from a wide variety of scientific fields and technological competencies. As a result, the chance of generating new knowledge and embodying knowledge in new products or processes is likely to be conditional on the ability to access and then piece together a significant variety of complementary research inputs [Scotchmer, 1991; Foray, 2004]. In the genomics arena, a great deal of uncertainty exists with respect to the role of genes in disease susceptibility and progression, the hierarchy of proteins in any system, and the function of such genes and proteins during drug intervention [Reid et al., 2001; Roses, 2002]. Hence, pharmaceutical companies and even the larger biotechnology companies adapting to the information paradigm, are forming alliances with academic institutions and the smaller biotechnology companies that are often significantly further down the molecular biology and genomics learning curves, accessing both disembodied knowledge and embodied knowledge in the form of therapeutics or supportive tools [Bower and Whittaker, 1992; Liebeskind et al., 1996; Powell et al., 1996; Blumenthal et al., 1997].

To complete the sequence map of the Human Genome required breakthroughs in computational sciences, measurement technologies, statistics, and data management [Kitano, 2001]. Tools enabling high-through quantitative measurements of biological information were developed from this collective understanding. Today, such tools have become an integral component of drug discovery research. Therefore, it is interesting to note that tool development is a significant focus within private alliances following the biological and information paradigms.

With the prevalence of high-throughput screening and combinatorial chemistry technologies in drug discovery and development, pharmaceutical firms may need to form strategic alliances with their traditional chemical counterparts to similarly manage the complexities associated with the chemical paradigm. Based on our analysis, these firms are also not only accessing therapeutics, but also expertise in drug discovery.

Once a commitment is made to participate in a strategic alliance, individuals or firms will face the decision as to when (or indeed if) to privately appropriate knowledge. Appropriation most often occurs through the decision to formally enclose knowledge by filing a patent. In the information-based paradigm, of concern is that as the degree of complementarity, applicability, and functional uncertainty of biological knowledge increases, excessive privatization will increase the transactions costs associated with procuring licenses for access to the required knowledge should intellectual property rights be assigned to upstream knowledge.

It is interesting to observe that in the case of the information paradigm, cooperative strategies including open discovery initiatives are enabling companies to access disembodied, upstream knowledge-based resources critical to downstream drug development and provide further evidence of our assertions [Eisenberg, 2000; Cassier, 2002]. One of the principal objectives of these cooperative strategic alliances is to preserve downstream technological opportunities for multiple firms. These initiatives, analyzed in Chapter 6, are essentially seeking to reverse the trend we observe with respect to upstream, information-based patents. When upstream discovery research cannot yield commercial products and when the costs associated with excessive upstream competition are high, then companies jointly benefit from cooperative knowledge production and open knowledge dissemination [Nelson, 1959; Reichman, 2003]. Norms or rules for knowledge sharing and knowledge appropriation are often established within such alliances to ensure equal opportunities for learning for all participants [Ostrom et al., 1994; Liebeskind et al., 1996].

Chapter 6: Open Innovation-Managing the Complexities of the Information Paradigm through the Consortium Model

6.1 Introduction

In October of 2004, Novartis, the Broad Institute of MIT, and Harvard announced a joint project to decipher the genetic causes of type 2 diabetes. The collaboration reflects the mission of the Broad Institute to bring together researchers to solve complex problems that require multi-disciplinary teams and that are difficult to solve in the traditional (isolated) laboratory setting [Lawler, 2004].

Companies typically demand that data created in cooperative ventures be kept away from competitors. However, Novartis argues that the benefits of openness will outweigh those of secrecy, and the company intends to put the genetic variation data it collects on a public web site. While the team will not file patents on the database, it will allow others to patent new therapies or diagnostic tests based on the public information (delaying appropriation to downstream activities) [Lawler, 2004]. Novartis' decision is a signal of an emerging change in attitude toward the appropriation of all forms of biological knowledge— an industry correction that is increasingly common in the initiatives analyzed in our study.

6.2 The Drive toward the Consortium Model

Biology knowledge is complex and derives from a variety of scientific and technical disciplines. The molecular level of analysis, the computational nature of discovery research, and the global scale of research, all provide evidence that the drug discovery and development paradigm has changed dramatically. From a knowledge perspective, biopharmaceutical knowledge production processes, knowledge dissemination processes, and even knowledge appropriation mechanisms are rapidly evolving. Networks of collaboration that are supported by information and communication technologies are enabling researchers from a variety of disciplines and laboratories to generate and validate biological and even chemical knowledge. The structure and rules associated with

knowledge-based networks further support the global production and dissemination of knowledge.

6.3 Analyzing Biopharmaceutical Consortia

The International Human Genome Project catalyzed the open-source movement in genomics-based research. The achievements and failures of the Human Genome Project, which involved the cooperation of globally dispersed labs, prompted us to analyze other such consortia focused on genomic and post-genomic research. Through extensive literature search we were able to isolate several post Human Genome consortia that would warrant inclusion in our study.

We then selected 39 such consortia for further analysis; these consortia are visible and significant in their achievements, thereby enabling us to retrieve adequate literature for our study. Literature sources analyzed included: peer-reviewed journal articles by consortium members or third-party researchers, press-releases, consortia websites, publications, and/or presentations. We also were able to substantiate the data through a survey of directors of such consortia. (See Appendices 5 and 6) These directors were asked to verify the focus of research, the types of participants including private sector participants (Analysis 6.1) and communication strategies used, the sources of funding, and the existence of rules regarding participation (Analysis 6.2), knowledge generation, knowledge dissemination (Analysis 6.3), and/or knowledge appropriation (Analysis 6.4). The appendix lists the sources of data used in each case. (See Appendix Table 10)

6.4 Participating in a Consortium

The ability to join a consortium is tempered by informal and formal rules of participation. With formality, entrance costs may be used to facilitate research and development activities as well as to signal cooperation and commitment to the consortium [Kollock, 1998; Gintis et al., 2001]. The role of such entrance costs or rules for participation is to create trust through a visible signal. For example, committing resources in advance

including monetary fees, makes other participants in the consortium, and future researchers who are considering participation, aware of a researcher's cooperative intentions [Gulati et al., 1994].

The decision to participate in a consortium is also affected by the degree of accessibility to the associated knowledge. Open access ensures that knowledge will be available to all participants in future downstream research regardless of participation. In this case, the possibility of free-riding exists by outside firms who can enjoy the disclosed knowledge at little or no cost [Gintis et al., 2001]. Closed access in contrast, ensures that knowledge is available only to contributing members within the alliance; therefore, a researcher outside the alliance may be unable to pool internal knowledge with that from the closed group, or may face a cost that will vary with the market power of the closed group.

Type of Participant: Researchers from academia are present in all 39 consortia; similarly researchers from non-profit research organizations are present in the majority of the cases. In 17 cases, there are government researchers and/or government participation via consortium catalyzation or monetary support. In terms of the private sector, 22 cases exist where there is significant participation by private firms. Interestingly, in 6 of these cases, private sector participants are directly or significantly responsible for the catalyzation of the initiative-namely, the SNP Consortium, the Novartis-Broad Initiative, the Accelrys Combinatorial Chemistry Consortium, the Accelrys Functional Proteomics Consortium, the Accelrys Nanotechnology Consortium, and the Agilent-Industry Open Microarray Design Program [Davies, 2001; Cassier, 2002; Lawler, 2004; www.agilent.com, 2007; www.accelrys.com, 2007]. (Table 6.1)

In terms of geographical representation, 31 of the 39 consortia include researchers and/or firms from two or more continents. The remaining 8 consortia either have only U.S. or European members.

Interestingly, although 32 out of the 39 consortia are funded by public sources (primarily via government grants), 15 consortia are also jointly funded and/or sponsored by private

organizations; 4 consortia, namely the Accelrys consortia and the Cancer Vaccine Consortia are funded primarily by the associated private sector participants. (Table 6.2)

Out of 39 consortia, 15 have established external partnerships i.e., beyond consortium membership, with academic researchers, institutions, and/or private sector organizations for the provision of research-based resources such as human capital, tools, and facilities, financial-based resources to support consortia activities, or as part of their data management strategy. Based on our analysis, there is no evidence of influence from these external partners on the activities or organizational processes associated with the consortia. (Table 6.2)

Alliance Structures: Based on the definitions provided in Chapter 3, all but 3 of the consortia use an open access alliance structure. The Accelrys Combinatorial Chemistry Consortium, the Accelrys Functional Proteomics Consortium, and the Accelrys Nanotechnology Consortium are all closed access consortia—ensuring that knowledge is only available to those contributing members within the consortium [www.accelrys.com, 2007].

Focus of Alliances: In our analysis, almost half of the 39 consortia have as their focus genomic or proteomic research; an additional 7 consortia are focusing on systems-based research. Interestingly, some of the consortia are progressing further downstream and are developing tools to support molecular biology-based drug discovery or chemistry-based drug discovery; in some cases, consortia are enabling pre-clinical and clinical research. Only two initiatives, the Biological Innovation for Open Society (BIOS) and the Cancer Vaccine Consortium are focused on downstream biological product development [Sulston, 2006; www.sabin.org, 2007]. (Table 6.3) From the perspective of knowledge structures, the knowledge being generated in the majority of cases is high in complementarity, non-substitutable, and high in applicability. Highly complementary knowledge involves the identification and integration of diverse and dispersed units acting as inputs into downstream product development—including genomic, proteomic, or systems-based biological information. Non-substitutable knowledge is knowledge that

cannot be replicated through human processes with complete preservation of biological form or biological function. While genes or proteins can be expressed outside the body, their complete biological form including association with other biological entities cannot be maintained outside the body. In contrast, some of the tools supporting drug discovery and development developed by the consortia are indeed substitutable—through duplication or work-around solutions. High applicability of knowledge occurs when the target of knowledge is more than one biological intervention pathway or domain; generally knowledge that is high in applicability can be targeted toward multiple products or markets. (See Table 2.1 for definitions used to determine knowledge structures.)

Tool development across 11 consortia includes the generation of embodied knowledge that is high in complementarity in terms of downstream development and high in terms of applicability. Mouse models, microarrays, software, databases, and/or reagents however, are in most cases, tools that are reproducible by other firms or substitutable by other technologies. It is likely then that the complexities associated with tool development are driving the formation of strategic alliances e.g., the Combinatorial Chemistry Consortium, where simulation software is the focus of development, and the Collaborative Cross initiative, where multiple animal models are being developed [Churchill et al., 2004; www.accelrys.com, 2007].

In the case of the Biological Innovation for Open Society where materials and methods are shared for the purpose of downstream development under an open-source agreement and the Cancer Vaccine Consortium with the goal of accelerating the process of bringing cancer vaccines from the development stage to the clinic, embodied knowledge is being generated that is high in complementarity, high in applicability, and likely substitutable. In both cases, knowledge that is complex from a structural perspective (multiple components) or from a production perspective (multiple clinical trials and global regulatory approval), provides the incentive to form such downstream-based alliances [Sulston, 2006; www.sabin.org, 2007].

Rules for Participation: In terms of participation, 18 consortia have established rules regarding membership. Offering monetary commitments, making formal commitments to the mandate and policies of the initiative, or licensing products used within the initiative, are signals of cooperation used when joining consortia. (Table 6.4)

While the majority of consortia allow members with the requisite research experience to join voluntarily, 7 of these 18 initiatives use formal invitations or applications, steering or executive committees, or by-laws to determine membership. Where formal commitments are made, as in the case of the International Regulome Consortium, participation by-laws and agreements tend to address admission policies, exit policies, as well as the objectives and rules of participation of the consortium.

Ten consortia require a monetary commitment as part of membership—out of this group, 2 require the maintenance of grants and 8 require up-front membership fees. In open access initiatives such as the SNP Consortium, large upfront payments are made to support research [Davies, 2001]; in other instances, such as the International Structural Biology Consortium, membership fees are paid, as verified by the director in our survey. These membership fees entitle a member to access beta-version software, experimental instruments, and technology developed by associated research labs and institutions.
In the case of the Accelrys closed consortia, both monetary fees and licenses of pre-requisite software are required to join these consortia. As Accelrys software forms the basis of the Consortium project, in order to take part in and obtain the benefits of the project work, members are required to maintain licenses to a number of products which form the core of Consortium technology [www.accelrys.com, 2007].

6.5 Appropriation of Knowledge from a Consortium

Ostrom argues that private property rights do not emerge spontaneously from a common property system. Private property rights depend on the existence and enforcement of rules that define who has a right to pursue which activities involving a resource and how the

returns from that activity will be allocated [Ostrom, 1989]. For example, the use of binding agreements can ensure cooperation during knowledge dissemination.

Rules for Knowledge Dissemination: In terms of knowledge dissemination, 32 consortia have explicit rules and/or procedures described on consortia websites and/or policy statements to ensure knowledge dissemination including the dissemination of data and the sharing of tools, biomaterials, and reagents created by consortium members. In the case of the Agilent-Industry Open Microarray Design Program, the rules for knowledge dissemination are determined by the participating researchers and/or consortia. We also note that 5 other consortia have plans in development to disseminate knowledge. (Tables 6.5 and 6.6)

Rules for Open Dissemination of Data-Non-substitutable Knowledge: In most cases data is released almost immediately with complete access provided to members and the public at large. Data are maintained within large data repositories with the objectives of standardizing data and enabling linkages between repositories developed within the consortium and between external repositories. For example, 30 consortia use or plan to use databases to provide access to upstream genomic, proteomic, systems, biochemical, or cell biology information. These consortia address the open dissemination of data as part of their rules for sharing of information with members and the public at large. In addition, 22 consortia use peer-reviewed publications to provide validated information to the public. (Table 6.6)

Rules for Open Licensing of Tools, Biomaterials, and Reagents-Substitutable Knowledge: We were able to determine that in the case of 16 consortia where tools, biomaterials, or reagents are a either a direct outcome or byproduct of consortia member research, rules exist that address the sharing of these items with members or the public at large. These rules advocate sharing of materials for consortium research, ensuring access to open repositories where animal models are housed, or providing for the wide dissemination of materials for the public at large; only in a few cases is restricted access to tools ensured for members only. (Table 6.6)

Although tools, biomaterials, and reagents supporting drug discovery and development may be highly dependent on complementary upstream knowledge such as gene sequences or SNPs, these downstream products can often be substituted for competitive products. In each of these cases, we assume that the target of knowledge appropriation is downstream products (tools and uses) rather than the upstream knowledge embodied in the tool. In the majority of these cases, consortia have developed rules regarding appropriation strategies including royalty free licensing or open licensing strategies, patent pooling, open dissemination, limited use licensing, or closed licensing.

In the case of the RNAi consortium, reagents are distributed by Sigma-Aldrich and by Open Biosystems. Open Biosystems enables the life science community to access technologies through the Open Access Program and the Open Labs Program [www.broad.mit.edu, 2007; www.openbiosystems.com, 2007]. Open Access enables researchers to access leading-edge technologies available through existing core facilities, while Open Labs builds relationships with leading labs from around the world to provide access to novel tools and genomic content [www.openbiosystems.com, 2007].

In the case of closed access consortia such as the Accelrys consortia, access to data and supporting tools are benefits reserved for members only. The aim of such consortia is to provide early and competitive access to drug discovery and development technology—enabling members to pre-empt outside rivals during product development [www.accelrys.com, 2007].

6.6 Bargaining for Appropriated Knowledge

Once the decision has been made to privatize knowledge (as governed by the rules of a cooperative alliance), a patent holder may unilaterally choose one of three strategies:

- to issue a non-exclusive license to facilitate rapid diffusion, thereby benefiting from the rent of several licensees, particularly when knowledge is substitutable;

- to maximize revenue through the granting of an exclusive license to one licensee willing to pay the highest price for the knowledge;
- or not to issue a license when the value from internal exploitation (given the resources the patent holder has to internally exploit the knowledge) is greater than the additional value received from renting the knowledge [Arora and Fosfuri, 2003].

Similarly, during bargaining, the licensee will be faced with the choices of a non-exclusive license or an exclusive license. In the event that the parties cannot agree on the valuation of the knowledge and amount of shared surplus from downstream research, or in the event that a license is denied altogether, the buyer will have to determine if he/she can substitute for the knowledge through an internal duplication strategy that will not infringe on the licensor's patent. If the licensee can substitute for the knowledge, his/her bargaining position changes. The probability of duplication and the value from this knowledge, taking into account the costs associated with duplication, must be considered by the licensee before pursuing this strategy. Walsh, Arora, and Cohen (2003) provide evidence of work-around solutions that researchers may attempt should they be unable to agree on the licensing terms for an upstream blocking patent including: inventing-around technology, ignoring patents (sometimes invoking an informal research exemption), going offshore, creating public databases, and challenging patents in court.

From the consortium analysis, we were able to identify the various licensing agreements employed to disseminate embodied knowledge in the form of tools, biomaterials, and reagents, as well as copyrighted material. (Table 6.7)

Non-exclusive license: Many instances can be found from our analysis of Non-Exclusive, Royalty-Free Licenses used to disseminate knowledge generated by consortium members.

A Limited Use License is associated with products purchased from Open Biosystems. This license conveys to the researcher a limited, non-exclusive, non-transferable right to

the product (with no right to resell, repackage, or further sublicense). For example, the purchase of products distributed through Open Biosystems does not include nor carry any right or license to use, develop, or otherwise exploit products commercially [www.openbiosystems.com, 2007].

MIT license: DopaNet's Molecular Pages is a collection of annotated quantitative data. DopaNet Molecular Pages are available under the terms derived from the MIT License [Novere and Donizelli, 2004]. The MIT License, also called the X License or the X11 License, originated at the Massachusetts Institute of Technology, and is a license for the use of certain types of computer software; essentially, a non-copyleft (licenses that use copyright law to give permission instead of forbid, usually permission to copy, use, modify, and share) free software license. The license allows a user to deal with the software without restriction, including without limitation the rights to use, copy, modify, merge, publish, distribute, sublicense, and/or sell copies of the software [www.opensource.org, 2007].

Creative Commons license: The International Molecular Exchange Consortium applies the Creative Commons Attribution License. The Creative Commons offers licenses that enable researchers to keep their copyright but allow others to copy and distribute the work provided that credit is assigned and only in accordance with specified pre-conditions including attribution plus non-commercial use only, attribution and non-derivative use, or attribution and sharing with others that follow the same conditions set by the original researcher [imex.sourceforge.net, 2007; creativecommons.org, 2007].

Biological Open Source license: Of particular interest is the Biological Innovation for Open Society (BIOS) Initiative License. Under a BiOS-compliant agreement, the user must agree to conditions that encourage cooperation and development of the technology in order to obtain the right to use the technology, instead of royalties or other conditions that discourage creation of products [Sulston, 2006].

The conditions include a provision that licensees cannot exclusively appropriate the "fundamental essence of the technology or improvements" [www.bios.net, 2007]. The base technology remains the property of the entity that developed it, but improvements can be shared with others that support the development of a protected commons around the technology; participants who agree to the same terms of sharing obtain access to improvements and other information, such as regulatory and biosafety data [www.bios.net, 2007]. To maintain legal access to the technology, users must agree not to prevent others who have agreed to the same terms from using the technology and any improvements in the development of varied products.

Click-wrap license: From the outset, the International HapMap Project followed the example of the Human Genome Project and made most of its data quickly and freely available through public databases on the Internet. However, there were concerns that outside groups might combine some HapMap data with their own knowledge to generate patentable inventions. To prevent this, the HapMap consortium required users to sign, using a simple mouse click from their computers, a free, non-exclusive, non-royalty-bearing licensing agreement to obtain access to certain types of data the project had collected on individuals' DNA sequences—namely, genotypic information. Under terms of that license, users agreed not to prevent others from using the individual genotype data and to share data only with those who had also agreed to this condition [www.hapmap.org, 2007].

As of December 10th 2004, the HapMap Project dropped the click-wrap license. As a result, all of the consortium's data are now completely available to the public [NIH News Release, 12/10/2004].

Patent pool: It is anticipated that the Knockout Mouse Project will require the resolution of several intellectual property claims involving both the production and use of knockout mice. To gain access to existing intellectual property covering knockout technology, the researchers in the Knockout Mouse Project advocate the use of a patent pool. Researchers

from various organizations and institutions controlling such patents have agreed to the formation of a patent pool of mouse knockout technologies [Austin et al., 2004].

Geographic-based licensing: The Grand Challenges in Global Health, which funds MalariaGEN, has developed the Global Access Strategy. This system requires grantees to prepare both a strategy for commercialization of research and an intellectual property management policy. Key provisions of the Global Access Strategy include a requirement that the principles of the Strategy apply to licenses and contracts that use intellectual property of the consortium; that downstream licensees of the consortium's intellectual property not apply for secondary patents in the developing world that would prevent access to affordable health care solutions; and a stipulation that prohibits exclusive licensing of consortium's intellectual property except in cases where it is necessary to provide a marketing incentive. Chokshi, Parker, and Kwiatkowski (2006) further discuss the usage of geographic exclusivity or co-exclusivity by the NIH Office of Technology Transfer as an incentive for a licensee to develop a product for particular regional markets. Depending on the needs of the regional market, a license is therefore, non-exclusive, co-exclusive, or exclusive [Chokshi et al., 2006].

6.7 Discussion

To manage the uncertainties of drug discovery in the systems paradigm, a new model of cooperation is emerging— the public-private consortium. The need for diverse skills in systems biology and the complexity of the experimental technologies require the formation of large-scale teams or consortia [Kitano, 2001; Chokshi et al., 2006]. In these consortia, the issues of data-sharing and intellectual property are closely related. As Chokshi, Parker, and Kwiatkowski discuss, consortia must decide in advance what data should be released to the public to ensure equitable downstream access to the data and open opportunities for the development of products; alternatively, in some cases, in may also be necessary to ensure, through the appropriation of data, that downstream incentives for product development are maintained for consortium members. Rules and policies will determine which option should take precedence in a project, consortium, and/or situation.

In our analysis, consortia differentiate between disembodied knowledge in the form of raw data and embodied knowledge created by consortium members in the form of tools, biomaterials, and reagents. Although data is mandated in most cases for almost immediate release, tools, biomaterials, and reagents may be appropriated and licensed to consortium members and the public at large. Interestingly, this appropriation is also regulated in most cases by the provision of rules regarding licensing terms. Supporting data and materials sharing policies provided by the NIH, the Wellcome Trust, the Creative Commons, the Biological Innovation for Open Society, and even private sector firms such as Open Biosystems enable for relatively easy access to disembodied and embodied knowledge created within consortia.

Chapters 7 and 8 outline game models that study the incentive to participate in such strategic alliances, and the strategies used when appropriating knowledge jointly developed within strategic alliances respectively. Chapter 9 then outlines the development of a game model to address the strategic environment of licensing once knowledge has been appropriated. The aim of these systems is to ensure that a first innovator and a follow-on innovator are rewarded for their research contributions. It is critical to ensure that investments are made to develop first inventions permitting second generation products to be developed and profitable through the fair sharing of the bargaining surplus—the amount by which each innovator will be richer in total if licensing (the bargaining process) is successful.

We anticipate that our analysis should provide a preliminary framework of knowledge management for emerging consortia. In the management of consortia, the research outcomes to be disseminated, the format for dissemination, and the knowledge to privatize for appropriation, should be clearly understood by all the participants. Internal rules or mechanisms used to promote cooperative behaviour can include: formalizing the requirements to join the knowledge network, ensuring frequent interactions, encouraging communication between participants, punishing defection, and setting the boundary for access to resources. An authority that regulates access to knowledge can ensure that a fair

and efficient knowledge governance strategy is used. The final outcome of these initiatives should be the rapid and cost-effective development of a knowledge domain or product marketplace.

Consortium	Alliance Structure	Significant Participants	Geographic Location
Affymetrix-National Alliance for Autism Research; Est. 1994	Open	A,N,G,P	I
Agilent-Industry Open Microarray Design Program; Est. 2005	Open	A,N,G	I
Alliance for Cellular Signaling (AfCS); Est. 2002	Open	A,N	I
Beta Cell Biology Consortium (BCBC); Est. 2001	Open	A,N,G	I
Biological Innovation for Open Society (BIOS); Est. 2004	Open	A,N,P	I
Cancer Vaccine Consortium; Est. 2002	Open	A,N,G,P	I
Cell Migration Consortium; Est. 2001	Open	A,N	I
Collaborative Cross; Est. 2005	Open	A,N,G	U.S.
Combinatorial Chemistry Consortium; Est. 1996	Closed	A,P	I
Consortium for Functional Glycomics (CFG); Est. 2001	Open	A,N,G	I
DopaNet; Est. 2002	Open	A,N,G	Europe
Functional Proteomics Consortium; Est. 2000	Closed	A,P	I
HepatoSys; Est. 2004	Open	A,N,P	Germany
Human Epigenome Consortium; Est. 2003	Open	A,N,P	I
Human Genome Consortium; Est. 1990	Open	A,N,P	I
International Genomics Consortium; Est. 2004	Open	A,N,P	I
International HapMap Project; Est. 2002	Open	A,N,P	I
International Molecular Exchange Consortium; Est. 2005	Open	A,N	I
International Regulome Consortium; Est. 2004	Open	A,N,G,P	I
International Rice Functional Genomics Consortium; Est. 2003	Open	A,N	I
International Rice Genome Sequencing Project; Est. 1997	Open	A,N	I
International Sequencing Consortium; Est. 2002	Open	A,N,G	I
Knockout Mouse Project; Est. 2006	Open	A,N	I

Consortium	Alliance Structure	Significant Participants	Geographic Location
MalariaGEN; Est. 2005	Open	A,N,G	I
MitoCheck Consortium; Est. 2004	Open	A,N,G,P	Europe
Mouse Genome Sequencing Consortium (MGSC); Est. 2000	Open	A,N,G,P	I
Mouse Models of Human Cancers Consortium (MMHCC); Est. 1999	Open	A,N,G,P	I
Nanotechnology Consortium; Est. 2004	Closed	A,P	I
Novartis Institutes for Biomedical Research-Broad Institute Alliance; Est. 2004	Open	A,P	I
Osteoarthritis Initiative; Est. 2001	Open	A,N,G,P	I
Public Population Project in Genomics; Est. 2004	Open	A,N,G	I
Receptor Tyrosine Kinase (RTK) Networks Consortium; Est. 2005	Open	A,N,G	I
Research Collaboratory for Structural BioInformatics (RCSB); Est. 1998	Open	A	U.S.
RNAi Consortium (TRC); Est. 2005	Open	A,N,P	U.S.
SNP Consortium; Est. 1999	Open	A,N,P	I
Structural Genomics Consortium; Est. 2003	Open	A, N, P	I
SYMBIONIC; Est. 2004	Open	A,N,P	Europe
TB Structural Genomics Consortium; Est. 2000	Open	A,N	I
The Lipid MAPS Consortium; Est. 2003	Open	A,N,G,P	U.S.

Table 6.1: Analyzing Participant Type and Geographic Location

A=Academic; N=Non-Profit Research Institutes; G=Government (including Government Funding Agencies and Government Laboratories); P=Private Organization; I=International Location

Consortium	Funding Sources	External Partnerships i.e. Beyond Membership	Special External Partner Role
Affymetrix-National Alliance for Autism Research; Est. 1994	PB	N	
Agilent-Industry Open Microarray Design Program; Est. 2005	PR/PB	N	
Alliance for Cellular Signaling (AfCS); Est. 2002	PB	Y	Data Management
Beta Cell Biology Consortium (BCBC); Est. 2001	PB	N	
Biological Innovation for Open Society (BIOS); Est. 2004	-	N	
Cancer Vaccine Consortium; Est. 2002	PR	Y	Research-Based Resources
Cell Migration Consortium; Est. 2001	PB	N	
Collaborative Cross; Est. 2005	PB	N	
Combinatorial Chemistry Consortium; Est. 1996	PR	N	
Consortium for Functional Glycomics (CFG); Est. 2001	PB	Y	Data Management
DopaNet; Est. 2002	PB	N	
Functional Proteomics Consortium; Est. 2000	PR	N	
HepatoSys; Est. 2004	PB	Y	Research-Based Resources; Data Management
Human Epigenome Consortium; Est. 2003	-	N	
Human Genome Consortium; Est. 1990	PB	N	
International Genomics Consortium; Est. 2004	PB/PR	Y	Financial Capital; Research-Based Resources
International HapMap Project; Est. 2002	PB	Y	Research-Based Resources
International Molecular Exchange Consortium; Est. 2005	-	N	
International Regulome Consortium; Est. 2004	PB/PR	N	
International Rice Functional Genomics Consortium; Est. 2003	PB	N	
International Rice Genome Sequencing Project; Est.	PB	N	

Consortium	Funding Sources	External Partnerships i.e. Beyond Membership	Special External Partner Role
1997			
International Sequencing Consortium; Est. 2002	PB	N	
Knockout Mouse Project; Est. 2006	PB	Y	Research-Based Resources
MalariaGEN; Est. 2005	PB	Y	Financial Capital
MitoCheck Consortium; Est. 2004	PB	N	
Mouse Genome Sequencing Consortium (MGSC); Est. 2000	PB/PR	N	
Mouse Models of Human Cancers Consortium (MMHCC); Est. 1999	PB/PR	Y	Research-Based Resources
Nanotechnology Consortium; Est. 2004	PR	N	
Novartis Institutes for Biomedical Research-Broad Institute Alliance; Est. 2004	PB/PR	N	
Osteoarthritis Initiative; Est. 2001	PB/PR	Y	Financial Capital; Research-Based Resources
Public Population Project in Genomics; Est. 2004	PB/PR	N	
Receptor Tyrosine Kinase (RTK) Networks Consortium; Est. 2005	PB	Y	Research-Based Resources
Research Collaboratory for Structural BioInformatics (RCSB); Est. 1998	PB	N	
RNAi Consortium (TRC); Est. 2005	PB/PR	Y	Research-Based Resources
SNP Consortium; Est. 1999	PB/PR	N	
Structural Genomics Consortium; Est. 2003	PB/PR	Y	Financial Capital; Research-Based Resources
SYMBIONIC; Est. 2004	PB	Y	Research-Based Resources
TB Structural Genomics Consortium; Est. 2000	PB	N	
The Lipid MAPS Consortium; Est. 2003	PB	Y	Research-Based Resources

Table 6.2: Analyzing Sources of Funding and External Partnerships

PB=Public Funding; PR=Private Funding; Y=Yes; N=No

Consortium	Alliance Structure	Knowledge Type	Paradigm	Knowledge Characteristics
Affymetrix-National Alliance for Autism Research; Est. 1994	Open	Genomic	Biological	HC, NS, HA
Agilent-Industry Open Microarray Design Program; Est. 2005	Open	Tool Development	Biological	HC, S, HA
Alliance for Cellular Signaling (AfCS); Est. 2002	Open	Systems	Biological	HC, NS, HA
Beta Cell Biology Consortium (BCBC); Est. 2001	Open	Cell Biology	Biological	HC, NS, HA
Biological Innovation for Open Society (BIOS); Est. 2004	Open	Downstream Development	Biological	HC, S, HA
Cancer Vaccine Consortium; Est. 2002	Open	Downstream Development	Biological	HC, S, HA
Cell Migration Consortium; Est. 2001	Open	Systems	Biological	HC, NS, HA
Collaborative Cross; Est. 2005	Open	Tool Development	Biological	HC, S, HA
Combinatorial Chemistry Consortium; Est. 1996	Closed	Tool Development	Chemical	HC, S, HA
Consortium for Functional Glycomics (CFG); Est. 2001	Open	Systems	Biological	HC, NS, HA
DopaNet; Est. 2002	Open	Systems	Biological	HC, NS, HA
Functional Proteomics Consortium; Est. 2000	Closed	Proteomic	Biological	HC, NS, HA
HepatoSys; Est. 2004	Open	Systems/Tool Development	Biological	HC, NS, HA
Human Epigenome Consortium; Est. 2003	Open	Genomic	Biological	HC, NS, HA
Human Genome Consortium; Est. 1990	Open	Genomic	Biological	HC, NS, HA
International Genomics Consortium; Est. 2004	Open	Genomic/Pre-Clinical	Biological	HC, NS, HA
International HapMap Project; Est. 2002	Open	Genomic	Biological	HC, NS, HA
International Molecular Exchange Consortium; Est. 2005	Open	Tool Development	Biological	HC, S, HA
International Regulome Consortium; Est. 2004	Open	Genomic	Biological	HC, NS, HA
International Rice Functional Genomics Consortium; Est. 2003	Open	Genomic/Tool Development	Biological	HC, NS, HA
International Rice Genome Sequencing Project; Est. 1997	Open	Genomic	Biological	HC, NS, HA

Consortium	Alliance Structure	Knowledge Type	Paradigm	Knowledge Characteristics
International Sequencing Consortium; Est. 2002	Open	Genomic	Biological	HC, NS, HA
Knockout Mouse Project; Est. 2006	Open	Tool Development	Biological	HC, S, HA
MalariaGEN; Est. 2005	Open	Genomic	Biological	HC, NS, HA
MitoCheck Consortium; Est. 2004	Open	Cell Biology	Biological	HC, NS, HA
Mouse Genome Sequencing Consortium (MGSC); Est. 2000	Open	Genomic	Biological	HC, NS, HA
Mouse Models of Human Cancers Consortium (MMHCC); Est. 1999	Open	Tool Development	Biological	HC, S, HA
Nanotechnology Consortium; Est. 2004	Closed	Tool Development	Other	HC, S, HA
Novartis Institutes for Biomedical Research-Broad Institute Alliance; Est. 2004	Open	Genomic	Biological	HC, NS, HA
Osteoarthritis Initiative; Est. 2001	Open	Biochemical/Clinical	Biological	HC, NS, HA
Public Population Project in Genomics; Est. 2004	Open	Tool Development	Biological	HC, S, HA
Receptor Tyrosine Kinase (RTK) Networks Consortium; Est. 2005	Open	Systems	Biological	HC, NS, HA
Research Collaboratory for Structural BioInformatics (RCSB); Est. 1998	Open	Proteomic	Biological	HC, NS, HA
RNAi Consortium (TRC); Est. 2005	Open	Tool Development	Biological	HC, S, HA
SNP Consortium; Est. 1999	Open	Genomic	Biological	HC, NS, HA
Structural Genomics Consortium; Est. 2003	Open	Proteomic	Biological	HC, NS, HA
SYMBIONIC; Est. 2004	Open	Systems	Biological	HC, NS, HA
TB Structural Genomics Consortium; Est. 2000	Open	Proteomic	Biological	HC, NS, HA
The Lipid MAPS Consortium; Est. 2003	Open	Biochemical	Biological	HC, NS, HA

Table 6.3: Analyzing Consortium Structures and Knowledge Types

C=Complementarity (H=High); S=Substitutable; NS=Non-substitutable; A=Applicability (H=High);
Biological= Focus of alliance activities on biological knowledge; Chemical= Focus of alliance activities on chemical knowledge;
Other=Focus of alliance activities on other knowledge

Consortium	Alliance Structure	Knowledge Characteristics	Rules for Participation
Affymetrix-National Alliance for Autism Research	Open	HC, NS, HA	MC (Grants), Selection
Agilent-Industry Open Microarray Design Program	Open	HC, S, HA	Based on Consortium
Cancer Vaccine Consortium	Open	HC, S, HA	EC
Cell Migration Consortium	Open	HC, NS, HA	SC
Combinatorial Chemistry Consortium	Closed	HC, S, HA	MC, License
Consortium for Functional Glycomics (CFG)	Open	HC, NS, HA	Application
Functional Proteomics Consortium	Closed	HC, NS, HA	MC, License
HepatoSys	Open	HC, NS, HA	Invitation
International Regulome Consortium	Open	HC, NS, HA	By-laws
Mouse Genome Sequencing Consortium (MGSC)	Open	HC, NS, HA	MC
Mouse Models of Human Cancers Consortium (MMHCC)	Open	HC, S, HA	MC (Grants)
Nanotechnology Consortium	Closed	HC, S, HA	MC, License
Public Population Project in Genomics	Open	HC, S, HA	MC
Receptor Tyrosine Kinase (RTK) Networks Consortium	Open	HC, NS, HA	EC
RNAi Consortium (TRC)	Open	HC, S, HA	MC
SNP Consortium	Open	HC, NS, HA	MC
Structural Genomics Consortium	Open	HC, NS, HA	MC
TB Structural Genomics Consortium	Open	HC, NS, HA	Application

Table 6.4: Analyzing Consortium Structures and Rules for Participation

C=Complementarity (H=High); S=Substitutable; NS=Non-substitutable; A=Applicability (H=High);
MC=monetary commitment (upfront fees, membership fees, maintenance of grants); EC=Executive Committee; SC=Steering Committee

Consortium	Alliance Structure	Knowledge Characteristics	Explicit Rules Used for Knowledge Dissemination
Agilent-Industry Open Microarray Design Program	Open	HC, S, HA	Based on Consortium
Alliance for Cellular Signaling (AfCS)	Open	HC, NS, HA	Yes
Beta Cell Biology Consortium (BCBC)	Open	HC, NS, HA	Yes
Biological Innovation for Open Society (BIOS)	Open	HC, S, HA	Yes
Cancer Vaccine Consortium	Open	HC, S, HA	Yes
Cell Migration Consortium	Open	HC, NS, HA	Yes
Combinatorial Chemistry Consortium	Closed	HC, S, HA	Yes
Consortium for Functional Glycomics (CFG)	Open	HC, NS, HA	Yes
DopaNet	Open	HC, NS, HA	Yes
Functional Proteomics Consortium	Closed	HC, NS, HA	Yes
Human Epigenome Consortium	Open	HC, NS, HA	Yes
Human Genome Consortium	Open	HC, NS, HA	Yes
International Genomics Consortium	Open	HC, NS, HA	Yes
International HapMap Project	Open	HC, NS, HA	Yes
International Molecular Exchange Consortium	Open	HC, S, HA	Yes
International Regulome Consortium	Open	HC, NS, HA	Yes
International Rice Functional Genomics Consortium	Open	HC, NS, HA	Yes
International Rice Genome Sequencing Project	Open	HC, NS, HA	Yes
International Sequencing Consortium	Open	HC, NS, HA	Yes
MalariaGEN	Open	HC, NS, HA	Yes
Mouse Genome Sequencing Consortium (MGSC)	Open	HC, NS, HA	Yes
Mouse Models of Human Cancers Consortium (MMHCC)	Open	HC, S, HA	Yes
Nanotechnology Consortium	Closed	HC, S, HA	Yes
Novartis Institutes for Biomedical Research-Broad Institute Alliance	Open	HC, NS, HA	Yes
Osteoarthritis Initiative	Open	HC, NS, HA	Yes
Public Population Project in Genomics	Open	HC, S, HA	Yes
Receptor Tyrosine Kinase (RTK) Networks Consortium	Open	HC, NS, HA	Yes

Consortium	Alliance Structure	Knowledge Characteristics	Explicit Rules Used for Knowledge Dissemination
Research Collaboratory for Structural BioInformatics (RCSB)	Open	HC, NS, HA	Yes
RNAi Consortium (TRC)	Open	HC, S, HA	Yes
SNP Consortium	Open	HC, NS, HA	Yes
Structural Genomics Consortium	Open	HC, NS, HA	Yes
TB Structural Genomics Consortium	Open	HC, NS, HA	Yes
The Lipid MAPS Consortium	Open	HC, NS, HA	Yes

Table 6.5: Analyzing Consortium Structures and Explicit Rules for Knowledge Dissemination

C=Complementarity (H=High); S=Substitutable; NS=Non-substitutable; A=Applicability (H=High)

Consortium	Knowledge Characteristics	Rules or Mechanisms used to Disseminate Data	Rules Regarding Sharing of Tools, Biomaterials, and Reagents
Agilent-Industry Open Microarray Design Program	HC, S, HA	Based on Consortium Rules	Based on Consortium Rules
Alliance for Cellular Signaling (AfCS)	HC, NS, HA	Database Deposit; Publication	Reagent Sharing for AfCS Research
Beta Cell Biology Consortium (BCBC)	HC, NS, HA		Freely Distributed to Academics for Non-Commercial Use
Biological Innovation for Open Society (BIOS)	HC, S, HA		Royalty Free, Non-Exclusive Licenses Among Participants
Cancer Vaccine Consortium	HC, S, HA	Publication	
Cell Migration Consortium	HC, NS, HA	Database Deposit; Publication	Royalty Free, Non-Exclusive Licenses for Non-Commercial Use
Collaborative Cross	HC, S, HA	Database Development	Repository; Open Subscription to Mouse Repository
Combinatorial Chemistry Consortium	HC, S, HA	Exclusive Access to Data	Exclusive Access to Licensed Software
Consortium for Functional Glycomics (CFG)	HC, NS, HA	Database Deposit; Publication	Material Sharing for Consortium Research; Royalty Free, Non-Commercial Use
DopaNet	HC, NS, HA	Database Deposit; Publication	
Functional Proteomics Consortium	HC, NS, HA	Exclusive Access to Annotated Data	
HepatoSys	HC, NS, HA	Database Development; Publication	
Human Epigenome Consortium	HC, NS, HA	Database Deposit; Publication	
Human Genome Consortium	HC, NS, HA	Database Deposit; Publication	
International Genomics Consortium	HC, NS, HA	Database Deposit	

Consortium	Knowledge Characteristics	Rules or Mechanisms used to Disseminate Data	Rules Regarding Sharing of Tools, Biomaterials, and Reagents
International HapMap Project	HC, NS, HA	Database Deposit; Publication	
International Molecular Exchange Consortium	HC, S, HA	Database Deposit/Management	Creative Commons Copyright Licensing Advocated
International Regulome Consortium	HC, NS, HA	Database Deposit; Publication	
International Rice Functional Genomics Consortium	HC, NS, HA	Database Development	Sharing of Materials
International Rice Genome Sequencing Project	HC, NS, HA	Database Deposit; Publication	
International Sequencing Consortium	HC, NS, HA	Database Deposit	
Knockout Mouse Project	HC, S, HA	Database Development	Public Repository for Biomaterial; Patent Pooling Advocated
MalariaGEN	HC, NS, HA	Data Management Addressed	Restricted Licensing; Geographic Restrictions
MitoCheck Consortium	HC, NS, HA	Database Development	
Mouse Genome Sequencing Consortium (MGSC)	HC, NS, HA	Database Deposit; Publication	
Mouse Models of Human Cancers Consortium (MMHCC)	HC, S, HA	Database Deposit; Publication	Repository for Biomaterials; Reagent Distribution through Open Biosystems
Nanotechnology Consortium	HC, S, HA	Exclusive Access to Data	Exclusive Access to Licensed Software
Novartis Institutes for Biomedical Research-Broad Institute Alliance	HC, NS, HA	Database Deposit; Publication	
Osteoarthritis Initiative	HC, NS, HA	Data Repository	Research Tools Wide Available; Limited Materials Priority Distribution
Public Population Project in Genomics	HC, S, HA	BioBanks-Database; Publication	
Receptor Tyrosine Kinase (RTK) Networks	HC, NS, HA	Database Deposit; Publication	

Consortium	Knowledge Characteristics	Rules or Mechanisms used to Disseminate Data	Rules Regarding Sharing of Tools, Biomaterials, and Reagents
Consortium			
Research Collaboratory for Structural BioInformatics (RCSB)	HC, NS, HA	Data Bank; Publication	
RNAi Consortium (TRC)	HC, S, HA		Distribution through Sigma Aldrich and Open Biosystems
SNP Consortium	HC, NS, HA	Database Deposit; Publication	
Structural Genomics Consortium	HC, NS, HA	Database Deposit; Publication	
SYMBIONIC	HC, NS, HA	Database Development; Publication	
TB Structural Genomics Consortium	HC, NS, HA	Database Deposit; Publication	
The Lipid MAPS Consortium	HC, NS, HA	Database Deposit; Publication	

Table 6.6: Analyzing Consortium Structures and Rules for the Dissemination of Data and the Sharing of Tools, Biomaterials, and Reagents

C=Complementarity (H=High); S=Substitutable; NS=Non-substitutable; A=Applicability (H=High)

Consortium	Appropriation Scenarios	Licenses Advocated by Consortium
Agilent-Industry Open Microarray Design Program	Appropriation Possible	Based on Consortium Rules
Beta Cell Biology Consortium (BCBC)	Appropriation Possible	Freely Distributed to Academic for Non-Commercial Use; NIH Grants Policy on Sharing of Unique Research Resources
Biological Innovation for Open Society (BIOS)	Appropriation Possible	Royalty Free, Non-Exclusive Licenses Among Participants
Cancer Vaccine Consortium	Y(I), N(C)	
Cell Migration Consortium	Y(I), N(C)	Royalty Free, Non-Exclusive Licenses for Non-Commercial Use
Combinatorial Chemistry Consortium	Y	Non-Exclusive License for Members Only
Consortium for Functional Glycomics (CFG)	Y(I), N(C)	Royalty Free, Non-Commercial Use
DopaNet	Copyright License for Dataset	MIT License
Functional Proteomics Consortium	Appropriation Possible	
Human Epigenome Consortium	Appropriation Possible	Wellcome Trust Intellectual Property Policy
International HapMap Project		Initially Click-Wrap License to Access Genotypic Data
International Molecular Exchange Consortium	Copyright License for Dataset	Creative Commons License
International Regulome Consortium	Y(As Approved by SC)	
Knockout Mouse Project		Patent Pooling Advocated to Manage Existing Intellectual Property
MalariaGEN	Y(I), N(C)	Restricted Licensing Based on Geographical Applicability
Mouse Models of Human Cancers Consortium (MMHCC)	Y(I), N(C)	Limited-Use License by Open Biosystems
Nanotechnology Consortium	Y	Non-Exclusive License for Members Only
Public Population Project in Genomics	Y(I), N(C)	
RNAi Consortium (TRC)	Y(P), N(C)	Limited-Use License by Open Biosystems

Consortium	Appropriation Scenarios	Licenses Advocated by Consortium
SNP Consortium	Y(P), N(C)	Upstream Provisional Patents (Prior Art Creation); Downstream Patents on Products Permitted
Structural Genomics Consortium	Y(P), N(C)	

Table 6.7: Appropriation of Knowledge and Licensing Strategies

Y=Yes; N=No; C=Consortium; I=Institution that hosts researcher; SC=Steering Committee; P=Private;
Y(X)=Appropriation possible by X party; N(X)=No Appropriation by X party

Chapter 7: Modeling the Decision to Participate in Alliances

7.1 Introduction

As discussed in Chapter 6, the decision to participate in knowledge networks is affected by the degree of accessibility of the associated knowledge. Open access ensures that knowledge will be available to all participants in future downstream research regardless of participation. In this case, other participants may free-ride by enjoying knowledge disclosed at little or no cost, and without contributing knowledge to the alliance. Closed access, in contrast, ensures that knowledge is available only to contributing members of the alliance, network, or consortium; therefore, a researcher outside the alliance may be unable to pool its own knowledge with that of the alliance, or may do so only at a cost that varies according to the market power of the closed group.

The ability to join a consortium or alliance is also tempered by the existence of informal or formal rules of participation [Ostrom et al., 1994]. Entrance fees may facilitate research and development activities and at the same time signal cooperation and commitment to the commons, network, or consortium. Entrance costs or participation rules can also create trust through a visible signal. For example, a commitment of resources in advance makes other participants and researchers considering future participation aware of a researcher's intentions [Gulati et al., 1994]. In scenarios where

(1) cooperation occurs only when a researcher is assured that a partner will also cooperate and

(2) the best choice for a researcher who believes that the partner will defect is to defect as well,

costly signals demonstrating participation can assure other participants that a researcher intends to cooperate [Kollock, 1998]. Several studies have analyzed the impact of unilateral benefits to group members. Partners who provide such a benefit to other group members, or who provide more of the benefit, signal their quality as allies. This signal can then alter the behaviour of other group members, encouraging them to act in ways that can provide a positive payoff to the signaler, for example by preferring signalers as

allies. Costly signaling may therefore provide a mechanism for the evolution of cooperation and provide stability against invasion by selfish participants or free-riders [Gintis et al., 2001].

In this chapter, we model the decision to participate in a consortium when knowledge is accessible to the public at large (public access setting), and when knowledge is accessible only to consortium members (restricted access setting). Common benefits are those that accrue to each player that joins a consortium and adheres to the rules regarding knowledge dissemination. Therefore, the synthesis of knowledge in a consortium will create a common value, *CV*, related to the knowledge units jointly generated by or contributed to the consortium. Private benefits are those that a player can earn by unilaterally pursuing research (knowledge generation) activities. Knowledge that is unilaterally generated and *held in secrecy* will have a private value, *PV*, for its owner. The decision to patent knowledge is not considered in this model, but is modeled in Chapter 8.

We consider how the decision to participate in a consortium and share knowledge depend on access. In the public access setting, which applies for the majority of the consortia analyzed in Chapter 6, knowledge is accessible by consortium members as well as the public at large (i.e. non-members); we assume that consortium rules determine how knowledge is shared with the public at large. Therefore, in the public access setting, a player that chooses not to participate in a consortium and share knowledge will still be able to pool consortium knowledge with internal firm knowledge, possibly gaining a competitive advantage in downstream activities. In contrast, in the restricted access setting, knowledge is accessible only to consortium members; this is the case for the Accelrys consortia analyzed in Chapter 6. Under restricted access, the player that chooses to cooperate by joining the consortium and adhering to the rules regarding internal knowledge dissemination, will continue to enjoy the common value *CV* related to the knowledge units jointly generated or contributed within the consortium. The player that chooses to pursue research activities unilaterally will, however, no longer have access to

consortium knowledge; therefore, this player will obtain private value only through unilateral activities.

An interesting situation arises even when there are only two players. Each player must decide whether to participate in the consortium and share knowledge or not to participate and hold its knowledge in secrecy. Only when both players choose to cooperate can a consortium form; if both players choose to defect and not join the consortium, a consortium does not form. An obvious problem arises when one player wants to cooperate and the other player does not. While a consortium cannot form in this situation, we must still consider the strategic decision to cooperate. As technological complexities increase, it may be the case that the player who chooses unilateral cooperation will openly share knowledge to pre-empt a rival in downstream activities, signal a future need to cooperate, or facilitate the development of a technological standard around which this player can develop alternative products. In this case, the common value *CV* derives from disclosure and deposit of knowledge into an open or closed pool.

A modified version of this two-player model is the game in which each player decides whether to participate in an existing consortium. The common value then derives from units jointly generated, contributed, and combined with existing consortium knowledge. In this case, an additional parameter may be required to encompass existing consortium knowledge to which a new participant can add. In the sections that follow, we validate our model using various case scenarios to explain firm behaviour, including the decision to participate in the consortia analyzed in Chapter 6. As we discussed in Chapter 6, these consortia are initiatives with the objectives of joint knowledge production and in most cases open knowledge dissemination. We use the models developed in this chapter to understand the strategic decisions made by firms to join and participate in these consortia as a function of access setting—public access versus restricted access. (Analysis 7.1)

7.2 Model Parameters

We define the following notation for our model (Table 7.1).

Notation	Definition
Index *i and j*.	Two researchers 1 and 2.
$\bigcup$	Union.
$\bigcap$	Intersection.
K_i	The knowledge contributed or held by researcher *i*.
$CV_i(K_i)$	The payoff (utility) to researcher *i* for sharing knowledge (K_i).
K_c	Knowledge within an existing consortium, rather than one formed by *i* and *j*.
$PV_i(K_i)$	The payoff (utility) to researcher *i* for withholding knowledge (K_i) through secrecy.
$K_i - K_j = \{x \in K_i : x \notin K_j\}$	Knowledge unilaterally available to researcher *i*.
$K_i \bigcap K_j$	Knowledge jointly known by the researchers.

Table 7.1: Participation Game Model Notation

In order to define the game models, we adopt the following set notation:

We use the parameters *X*, *Y*, and *Z* to represent the knowledge held by the researchers. For example, the knowledge held by researcher 1 includes the union of what is known unilaterally (*X*) and what is jointly known with researcher 2 (*Y*). Similarly, the knowledge held by researcher 2 includes the union of what 2 knows unilaterally (*Z*) and what is jointly known with researcher 1 (*Y*). *Y* thus represents the intersection of researcher 1's and researcher's 2 knowledge sets. For knowledge in *Y*, what is known by one researcher is also known by the other, i.e., with no difference in perception.

$K_1 \bigcup K_2 = X \bigcup Y \bigcup Z$ where $X \bigcap Y = X \bigcap Z = Y \bigcap Z = \varnothing$

$K_1 = X \bigcup Y$

$K_2 = Y \bigcup Z$

$K_1 - K_2 = X$

$K_2 - K_1 = Z$

$K_1 \bigcap K_2 = Y$

These parameters are illustrated in the following Venn diagram:

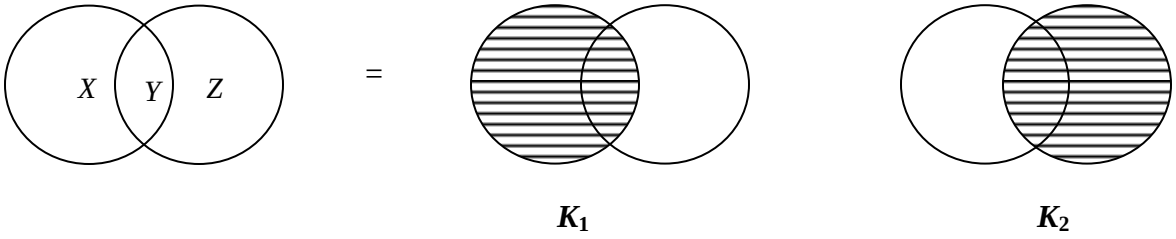


Figure 7.1: Graphical Representation of Knowledge in the Model

We make the following assumptions:

1. Decisions are simultaneous.
2. The total value of knowledge in a set is equal to the sum of values of the individual knowledge units that comprise the set.
3. $CV_1 (K_1 \cup K_2) = CV_1 (X) + CV_1 (Y) + CV_1 (Z)$ and $CV_2 (K_1 \cup K_2) = CV_2 (X) + CV_2 (Y) + CV_2 (Z)$ where X, Y, and Z are as defined in the Venn diagram. The payoff (utility) to researcher i for participating and contributing knowledge, is a function of the joint contribution by both players. (By assumption 2, the payoff is a simple additive function: in other words, the common value of joint knowledge units derives from the addition of the individual common values of X, Y, and Z. Alternatively, the common value of joint knowledge could be greater than the sum of the individual common values, i.e., knowledge of all parts could be worth more than the sum of the worth of the individual parts.)
4. $PV_1 (K_1) = PV_1 (X) + PV_1 (Y)$ and that $PV_2 (K_2) = PV_2 (Z) + PV_2 (Y)$ where X, Y, and Z are as defined above. (Again by assumption 2, the payoff is a simple additive function, implying that the private value of knowledge units derives from the addition of the individual private values of X or Z for players 1 and 2 respectively (knowledge that is known unilaterally and not disclosed) and Y (knowledge that is jointly known but not disclosed). Alternatively, the private value of knowledge could be greater than the sum of the individual private values, i.e., knowledge of all parts could be worth more than the sum of the worth of the individual parts.)

7.3 Access Setting Models

We consider the decision to participate in a consortium and share knowledge as a function of access setting. In the public access setting, knowledge is available to consortium members as well as the public at large (i.e. non-members); we assume that consortium rules will determine how knowledge is shared with the public at large. In contrast, in the restricted access setting, knowledge is available only to consortium members as determined by consortium rules.

Model 7.1: Public Access; No Existing Consortium

Model 7.1 reflects the public access setting. We also assume that there are only two players and that no effective consortium is in existence.

Strategies.

Join=player enjoys the common value of the knowledge shared; we assume that sharing of knowledge is mandated by the rules of the consortium and is available as soon as a player joins.

Does Not Join= player enjoys the private value of his/her knowledge.

	Player 2 Joins	**Player 2 Does Not Join**
Player 1 Joins	$CV_1(K_1 \cup K_2)$, $CV_2(K_1 \cup K_2)$	$CV_1(K_1)$, $PV_2(K_2 - K_1) + CV_2(K_1)$
Player 1 Does Not Join	$PV_1(K_1 - K_2) + CV_1(K_2)$, $CV_2(K_2)$	$PV_1(K_1)$, $PV_2(K_2)$

Table 7.2: Participating in the Public Access Setting; No Existing Consortium

Note on Strategic Form Games: Each player makes a choice. The choices by both players determine a cell representing an outcome. In the cells are written the players' values at the outcomes; player 1's values are first and player 2's values are second. In our analysis, we focus on whether players would prefer to join a consortium if the common values of

knowledge exceed their private values; we looks for the case where the choice of joining a consortium is a player's dominant strategy. Formally, we will look for strictly dominant strategies (for one or both players) or, failing that, Nash equilibria [Kilgour, 2006]. (See Chapter 3)

First we analyze Player 1's preferences:

Assume Player 2 Joins (Column 1)

Row 1 is preferred to row 2 iff

7A)

$$CV_1(X) + CV_1(Y) + CV_1(Z) > PV_1(X) + CV_1(Y) + CV_1(Z)$$

which is equivalent to $CV_1(X) > PV_1(X)$ that is, when the common value of knowledge X is greater than the private value of knowledge X, player 1 will prefer row 1 (cooperation).

Assume Player 2 Does Not Join (Column 2)

Row 1 is preferred to row 2 iff

7B)

$$CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$$

that is, when the common value of knowledge X and Y (what is unilaterally known and what is jointly known, respectively) is greater than the private value of knowledge X and Y, player 1 will prefer row 1 (cooperation).

The analysis of player 2's actions will be similar to what is given above for player 1, with the only change being the replacement of parameter X with parameter Z i.e., knowledge that is unilaterally known by player 2. In each of the models that follow below, we only describe player 1's preferences keeping in mind that player 2's preferences will be similar with the replacement of parameter X with Z where appropriate.

Suppose that $CV_1(X) > PV_1(X)$ and $CV_1(Y) > PV_1(Y)$. Then $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$ so both 7A and 7B hold. Therefore, joining is a strictly dominant strategy for player 1; player 1 rationally joins regardless of player 2's choice.

If however, $CV_1(X) > PV_1(X)$ but $PV_1(Y) > CV_1(Y)$, joining may no longer be a strictly dominant strategy for player 1; 7A holds but 7B may not, so the outcome may depend on player 2's choice. The same condition follows if $CV_1(Y) > PV_1(Y)$ but $PV_1(X) > CV_1(X)$. In both cases, however, $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$ may still hold true, and if so, joining will be a strictly dominant strategy for player 1.

If we consider the possible synergy between knowledge units, it may be possible to assume that $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$, even if $CV_1(X) > PV_1(X)$ but $PV_1(Y) > CV_1(Y)$ or $CV_1(Y) > PV_1(Y)$ but $PV_1(X) > CV_1(X)$ as the total value of knowledge in the set may greater than the sum of the values of the individual knowledge units that comprise the set. Future research will assess this synergy between knowledge units.

However, in the simple case of no synergy, both joining is a Nash Equilibrium if $CV_1(X) > PV_1(X)$ and $CV_2(Z) > PV_2(Z)$. Player 1 joins (strictly dominant strategy) if $CV_1(X) > PV_1(X)$ and $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$.

Conclusion: $CV_1(X) > PV_1(X)$ and $CV_2(Z) > PV_2(Z)$ are (jointly) sufficient for both joining to be a Nash equilibrium. In other words, for both to join, each player's common value of knowledge is greater than his/her private value of knowledge; hence, greater value is attained when knowledge is known to and shared by all players.

Model 7.2: Public Access; Acting Consortium in Existence

A modified version of Model 7.1 may include an existing consortium, rather than the formation of a new consortium including only players 1 and 2. In this case, the parameter K_c is used to encompass existing consortium knowledge as follows:

	Player 2 Joins	**Player 2 Does Not Join**
Player 1 Joins	$CV_1(K_1 \cup K_2 \cup K_c)$, $CV_2(K_1 \cup K_2 \cup K_c)$	$CV_1(K_1 \cup K_c)$, $PV_2(K_2 - K_1) + CV_2(K_1 \cup K_c)$
Player 1 Does Not Join	$PV_1(K_1 - K_2) + CV_1(K_2 \cup K_c)$, $CV_2(K_2 \cup K_c)$	$PV_1(K_1) + CV_1(K_c)$, $PV_2(K_2) + CV_2(K_c)$

Table 7.3: Participating in the Public Access Setting; Consortium in Existence

These parameters are illustrated in the following Venn diagram:

In this case K_c represents the knowledge that is held by the existing consortium and is isolated from the knowledge known by players 1 and 2. The common value of knowledge will therefore, derive from K_c as well knowledge contributed to the consortium by researchers 1 and 2 if they both join.

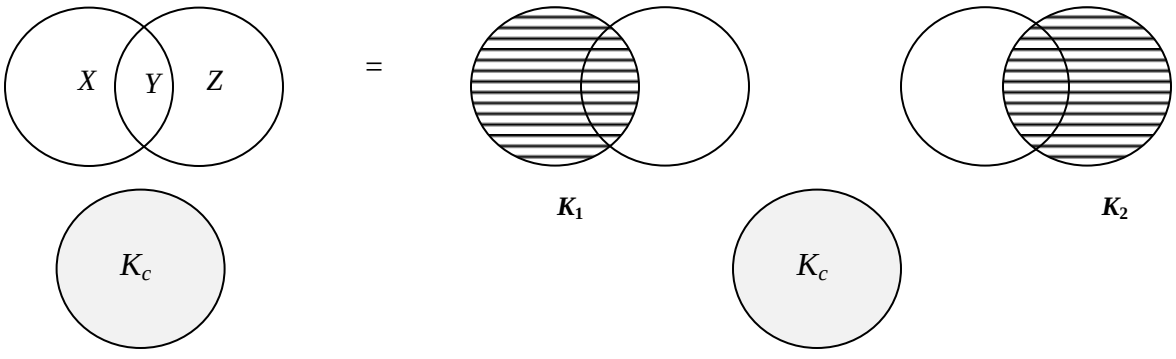


Figure 7.2: Graphical Representation of Knowledge in the Modified Model

In this case, the players' preferences remain the same; quantity $CV(K_c)$ appears on both sides of each of the above inequalities and so has no effect (based on assumption 2 assuming there is no synergy between individual units of knowledge held by researchers 1 and 2). Intuitively, given that the above situation reflects the public access setting, where what is known by the consortium is openly shared with members and the public at large, K_c is enjoyed by both players regardless of choice made, and as such, is not a factor in the decision taken by each player.

Both joining is a Nash Equilibrium if $CV_1(X) > PV_1(X)$ and $CV_2(Z) > PV_2(Z)$. Player 1 joins (strictly dominant strategy) if $CV_1(X) > PV_1(X)$ and $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$.

Conclusion: $CV_1(X) > PV_1(X)$ and $CV_2(Z) > PV_2(Z)$ are (jointly) sufficient for both joining to be a Nash equilibrium. Hence, greater value is attained when knowledge is known to and shared by all players.

Model 7.3: Restricted Access; No Existing Consortium

Model 7.3 reflects the restricted access setting. In this model, we assume that there are only two players and no existing consortium.

Strategies.

Join=player enjoys the common value of the knowledge shared; we assume that sharing of knowledge is mandated by the rules of the consortium and is available as soon as a player joins.

Does Not Join= player enjoys the private value of his/her knowledge.

	Player 2 Joins	**Player 2 Does Not Join**
Player 1 Joins	$CV_1(K_1 \cup K_2)$, $CV_2(K_1 \cup K_2)$	$CV_1(K_1)$, $PV_2(K_2)$
Player 1 Does Not Join	$PV_1(K_1)$, $CV_2(K_2)$	$PV_1(K_1)$, $PV_2(K_2)$

Table 7.4: Participating in the Restricted Access Setting; No Existing Consortium

Player 1's preferences:

Assume Player 2 Joins (Column 1)

Row 1 is preferred to row 2 iff

7C)

$CV_1(X) + CV_1(Y) + CV_1(Z) > PV_1(X) + PV_1(Y)$

that is, when the common value of pooled knowledge *X*, *Y*, and *Z* is greater than the private value of knowledge held by player 1 *X* and *Y*, player 1 will choose row 1 (cooperation).

Assume Player 2 Does Not Join (Column 2)

Row 1 is preferred to row 2 iff

7D)

$CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$

that is, when the common value of knowledge held by player 1 *X* and *Y* is greater than the private value of knowledge *X* and *Y*, player 1 will choose row 1 (cooperation).

The analysis of player 2's actions will be similar to what is given above for player 1, with the only change being the replacement of parameter *X* with parameter *Z* i.e., knowledge that is unilaterally known by player 2. In each of the models that follow below, we only

describe player 1's preferences keeping in mind that player 2's preferences will be similar with the replacement of parameter X with Z where appropriate.

Suppose that $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$. Then, since $CV_1(Z) > 0$, $CV_1(X) + CV_1(Y) + CV_1(Z) > PV_1(X) + PV_1(Y)$ so both 7C and 7D hold. Therefore, joining is a strictly dominant strategy for player 1; player 1 joins regardless of player 2's choice.

In particular, if $CV_1(X) > PV_1(X)$ and $CV_1(Y) > PV_1(Y)$, then the condition $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$ holds, so joining is a strictly dominant strategy for player 1. Note that this condition is necessary for joining to be a strictly dominant strategy in Model 7.1. Therefore, joining is at least as likely in the restricted access setting as in the public access setting.

If however, $CV_1(X) > PV_1(X)$ but $PV_1(Y) > CV_1(Y)$, joining may no longer be a strictly dominant strategy for player 1; in fact, both 7C and 7D may fail so the outcome generally depends on player 2's choice and on $CV_1(Z)$. The situation is similar if $CV_1(Y) > PV_1(Y)$ but $PV_1(X) > CV_1(X)$. In both cases, if however, $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$ still holds true, then joining will be a strictly dominant strategy for player 1; alternatively, as long as $CV_1(X) + CV_1(Y) + CV_1(Z) > PV_1(X) + PV_1(Y)$, given the value assigned to $CV_1(Z)$, then joining will continue to be a strictly dominant strategy for player 1.

Again, if we consider the possible synergy between knowledge units, it may be possible to assume that $CV_1(X) + CV_1(Y) + CV_1(Z) > PV_1(X) + PV_1(Y)$, even if $CV_1(X) > PV_1(X)$ but $PV_1(Y) > CV_1(Y)$ or $CV_1(Y) > PV_1(Y)$ but $PV_1(X) > CV_1(X)$ given the value assigned to $CV_1(Z)$, as the total value of knowledge in the set may greater than the sum of values of the individual knowledge units that comprise the set.

In the simple case of no synergy, both joining is a Nash Equilibrium if $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$ and $CV_2(Z) + CV_2(Y) > PV_2(Z) + PV_2(Y)$.

Conclusion: $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$ and $CV_2(Z) + CV_2(Y) > PV_2(Z) + PV_2(Y)$ are (jointly) sufficient for both joining to be a Nash equilibrium.

A modified version of Model 7.3 assumes an existing consortium, rather than a possible new consortium formed by players 1 and 2 only. In this case, the parameter K_c is used to encompass existing consortium knowledge as follows.

Model 7.4: Restricted Access; Acting Consortium in Existence

A modified version of Model 7.3 may include an existing consortium rather than the formation of a new consortium including only players 1 and 2. In this case, the parameter K_c is used to encompass existing consortium knowledge as follows:

	Player 2 Joins	**Player 2 Does Not Join**
Player 1 Joins	$CV_1(K_1 \cup K_2 \cup K_c)$, $CV_2(K_1 \cup K_2 \cup K_c)$	$CV_1(K_1 \cup K_c)$, $PV_2(K_2)$
Player 1 Does Not Join	$PV_1(K_1)$, $CV_2(K_2 \cup K_c)$	$PV_1(K_1)$, $PV_2(K_2)$

Table 7.5: Participating in the Restricted Access Setting; Consortium in Existence

In the restricted access setting, as only members can enjoy the common value of consortium knowledge, the parameter K_c is mathematically significant and can be a factor in the decisions taken by each player. For simplicity, we assume that

$K_c \cup (K_1 \cup K_2) = \varnothing$; future research will consider the intersection of knowledge between a consortium of researchers and players 1 and 2.

Player 1's Preferences:

Assume Player 2 Joins (Column 1)

Row 1 is preferred to Row 2 iff

7E)

$CV_1(X) + CV_1(Y) + CV_1(Z) + CV_1(K_c) > PV_1(X) + PV_1(Y)$

that is, when the common value of pooled knowledge *X*, *Y*, *Z*, and K_c is greater than the private value of knowledge *X* and *Y* held by player 1, player 1 will choose row 1 (cooperation).

Assume Player 2 Does Not Join (Column 2)

Row 1 is preferred to Row 2 iff

7F)

$CV_1(X) + CV_1(Y) + CV_1(K_c) > PV_1(X) + PV_1(Y)$

that is, when the common value of knowledge *X* and *Y* held by player 1 and pooled with consortium knowledge K_c, is greater than the private value of knowledge *X* and *Y*, player 1 will choose row 1 (cooperation).

The analysis of player 2's actions will be similar to what is given above for player 1, with the only change being the replacement of parameter *X* with parameter *Z* i.e., knowledge that is unilaterally known by player 2. In each of the models that follow below, we only describe player 1's preferences keeping in mind that player 2's preferences will be similar with the replacement of parameter *X* with *Z* where appropriate.

Suppose $CV_1(X) > PV_1(X)$ and $CV_1(Y) > PV_1(Y)$. Since $CV_1(Z)$ and $CV_1(K_c) > 0$ then $CV_1(X) + CV_1(Y) + CV_1(Z) + CV_1(K_c) > PV_1(X) + PV_1(Y)$, so both 7E and 7F hold. Therefore, joining is a strictly dominant strategy for player 1; player 1 joins regardless of player 2's choice.

If however, $CV_1(X) > PV_1(X)$ but $PV_1(Y) > CV_1(Y)$, joining may no longer be a strictly dominant strategy for player 1; now the outcome may depend on the common value of consortium knowledge K_c and/or the common value of Z or player 2's choice. The same conclusion follows if $CV_1(Y) > PV_1(Y)$ but $PV_1(X) > CV_1(X)$. In both cases, however, if $CV_1(X) + CV_1(Y) + CV_1(K_c) > PV_1(X) + PV_1(Y)$ given the value assigned to $CV_1(Z)$, still holds true, then joining will be a strictly dominant strategy for player 1.

Again, if we consider the possible synergy between knowledge units, it may be possible to assume that $CV_1(X) + CV_1(Y) + CV_1(K_c) > PV_1(X) + PV_1(Y)$, even if $CV_1(X) > PV_1(X)$ but $PV_1(Y) > CV_1(Y)$ or $CV_1(Y) > PV_1(Y)$ but $PV_1(X) > CV_1(X)$ given the value assigned to $CV_1(Z)$, as the total value of knowledge in the set may greater than the sum of values of the individual knowledge units that comprise the set.

In the simple case of no synergy, both joining is a Nash Equilibrium if $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$ and $CV_2(Z) + CV_2(Y) > PV_2(Z) + PV_2(Y)$.

Conclusion: $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$ and $CV_2(Z) + CV_2(Y) > PV_2(Z) + PV_2(Y)$ are (jointly) sufficient for both joining to be a Nash equilibrium.

In the sections that follow, we consider various scenarios where each quadrant is a possible stable equilibrium by changing the common and private values of knowledge. For simplicity, we evaluate decisions in the two-player setting where a consortium is not in existence (from the outset) i.e., Models 7.1 and 7.3. Players can cooperate (C) by

joining/forming a consortium and adhering to consortium rules regarding knowledge dissemination or can defect (*D*) by not joining/forming a consortium and withholding knowledge. We use numerical values for the common and private values of knowledge to demonstrate the utility of the models developed in section 7.3 to the biopharmaceutical industry—with specific reference to the formation of large-scale consortium in the post-genome era.

7.4 Signaling Intentions

In this example, we consider the situation where the private value of knowledge is greater than the common value of knowledge. This might reflect the scenario where researchers have moved further downstream into product development and knowledge while high in complementarity, possibly high in applicability, is substitutable. Hence, researchers should avoid disclosing this knowledge for fear of providing competitors an advantage in downstream development. Once this knowledge is disclosed, a competitor may easily come up with an alternative solution or product that may not have been possible prior to disclosure.

$PV_i\,(X) > CV_i\,(X)$

$PV_i\,(Y) > CV_i\,(Y)$

$PV_i\,(Z) > CV_i\,(Z)$

For simplicity, we assume that both players can equivalently exploit the knowledge—hence the common and private values of knowledge are equivalently expressed for both players.

$CV(X) = 5;\ CV(Y) = 3;\ CV(Z) = 6$

$PV(X) = 9;\ PV(Y) = 4;\ PV(Z) = 8$

Example 1: PUBLIC ACCESS

	C_2	D_2
C_1	14, 14	8, 16
D_1	18, 9	13, 12 *

Table 7.6: Private Value of Knowledge Exceeds Common Value of Knowledge in the Public Access Setting
Researcher 1 chooses C_1 or D_1; the first number in each cell is Researcher 1's payoff.
Researcher 2 chooses C_2 or D_2; the second number in each cell is Researcher 2's payoff.
C=Join; D=Does Not Join; * indicates Nash Equilibrium

Example 2: RESTRICTED ACCESS

	C_2	D_2
C_1	14, 14 *	8, 12
D_1	13, 9	13, 12 *

Table 7.7: Private Value of Knowledge Exceeds Common Value of Knowledge in the Restricted Access Setting
Researcher 1 chooses C_1 or D_1; the first number in each cell is Researcher 1's payoff.
Researcher 2 chooses C_2 or D_2; the second number in each cell is Researcher 2's payoff.
C=Join; D=Does Not Join; * indicates Nash Equilibrium

In the public access setting (Example 1) where free-riding is possible with respect to an opponent's knowledge and the unilateral private value of knowledge exceeds the common value of knowledge both researchers can have an incentive to defect. Interestingly in the restricted access setting (Example 2), without the ability to free-ride, cooperation can be very attractive if it is mutual, but defecting is proof against being a "sucker" (ending up at one's worst outcome), which explains why players may defect unless the opponent's cooperation is assured. In this game known as Assurance, the greatest potential payoff is associated with mutual cooperation; both sides know that mutual cooperation is preferable to mutual defection. Therefore how can cooperation be stabilized? Credible signals that a researcher intends to cooperate are one approach [Kollock, 1998]. For example, researchers may signal their quality as allies by disclosing private knowledge without the assurance of reciprocal benefits. Costly signaling may not only provide a basis for cooperation, but can also help a relationship resist invasion by

selfish outsiders or free-riders [Gintis et al., 2001]. Sequences of alternating decisions often provide the opportunity to signal cooperation, and are the basis of the famous tit-for-tat strategy [Axelrod, 1984; Kollock, 1998]. But sequences of signals depend for their success on repeated interactions by individuals who know each other's identities and maintain records of past behaviour. Hence, accountability reduces the temptation to behave selfishly [Axelrod, 1984; Kollock, 1998].

Signaling Commitment: Monetary commitments, formal commitments to the mandate and policies of the consortium, and mandatory licensing of products used within the consortium, are all examples of signals of cooperation. Upfront monetary commitments tend to support large-scale research, consortium management, or data management. In some initiatives such as the SNP Consortium, large upfront payments were made to support research, in other instances, such as the International Structural Biology Consortium, membership fees are imposed. These membership fees entitle a member to access beta-version software, experimental instruments, and technology that are developed by associated research labs and institutions. From a game perspective, these provisions reduced the private value of knowledge for both players, enough so as to make cooperation a Nash equilibrium. A similar situation could arise with an exit fee; requiring members who prematurely exit a consortium to pay an exit fee would reduce the temptation of the private payoff from "defecting".

Where formal commitments are made to the mandate and policies of the initiative, as in the case of the International Regulome Consortium, a typical participation by-law reads as follows:

> "The applicants for incorporation of the Corporation, as well as any person from universities, university hospital centres, research institutes and centres, any government, funding agencies and organizations from the public and private sectors, that are committed to (i) complying with the objectives of the Corporation and to providing the Corporation with the benefit of his knowledge; (ii) respecting the confidentiality of contributors as well as all applicable legal and ethical

obligations; and (iii) satisfying the conditions of admission set forth in the present by-law and in any enacted membership policy of the Corporation, may become members of the Corporation, upon application to the Board of Directors and acceptance by the Board of Directors having full discretion in that respect, the whole subject to the provisions of the present by law with respect to the suspension and expulsion, and resignation of the members."
[www.internationalregulomeconsortium.ca, 2007].

In the case of the Accelrys Combinatorial Chemistry, Accelrys Functional Proteomics Consortium, and Accelrys Nanotechnology Consortia, members are required to maintain licenses to a number of products which form the core of Consortium technology

7.5 Technological Complexities

We now consider the situation where the common value of knowledge is greater than the private value of knowledge. This might reflect the scenario where researchers are pursuing upstream research i.e., discovery of upstream knowledge that is significantly high in complementarity, possibly high in applicability, and likely low in substitutability. Given the complementary nature of the knowledge, technological complexities associated with discovery research, and the need for technological standards to enable comparative upstream research to occur, researchers may benefit greatly from the collective production and dissemination of knowledge. This now assumes

$CV_i\ (X) > PV_i\ (X)$

$CV_i\ (Y) > PV_i\ (Y)$

$CV_i\ (Z) > PV_i\ (Z)$

For simplicity, we assume that both players can equivalently exploit the knowledge—hence the common and private values of knowledge are equivalently expressed for both players.

CV(X) =9*; CV(Y)* =4*; CV(Z)* =8

PV(X) =5*; PV(Y)* =3*; PV(Z)* =6

Example 3: PUBLIC ACCESS

	C_2	D_2
C_1	21, 21*	13, 19
D_1	17, 12	8, 9

Table 7.8: Common Value of Knowledge Exceeds Private Value of Knowledge in the Public Access Setting

Example 4: RESTRICTED ACCESS

	C_2	D_2
C_1	21, 21 *	13, 9
D_1	8, 12	8, 9

Table 7.9: Common Value of Knowledge Exceeds Private Value of Knowledge in the Restricted Access Setting

As the common value of knowledge is greater than the private value of knowledge, cooperation strictly dominates defection in examples 3 and 4, and a researcher always does better by cooperating regardless of access setting.

Technological Uncertainties: Drug discovery research has become associated with a high level of complexity as the sources of knowledge are increasingly diverse and derive from a wide variety of scientific fields and technological competencies. Pharmaceutical companies and even the larger biotechnology companies adapting to the information paradigm, are forming alliances with academic institutions and the smaller biotechnology companies that are often significantly further down the molecular biology and genomics learning curves, accessing both disembodied knowledge and embodied knowledge in the

form of therapeutics or supportive tools [Bower and Whittaker, 1992; Liebeskind et al., 1996; Powell et al., 1996; Blumenthal et al., 1997]. Pharmaceutical firms may also need to form strategic alliances with their traditional competitors to similarly manage the complexities associated with chemical-based technologies.

From our analysis in Chapter 6, it is apparent given the interconnectivity between large biological datasets, the need to develop tools to support complex upstream discovery research, and the challenges associated with downstream product development, that the consortium enables geographically separated researchers to collectively pool human capital and resources to achieve pre-defined goals. (Table 7.10) Cooperation becomes a Nash equilibrium as the common value of pooled knowledge exceeds the private value associated with secrecy or non-disclosure of knowledge. Furthermore, given these complexities, it is anticpated that cooperation will continue to dominate regardless of completion of consortium goals, as participants move into drug discovery. As long as the common benefits of cooperation outweight the private benefits of unilateral knowledge production, these participants will choose to cooperate.

Technological Uncertainty Driving Consortium Participation	Example Consortium
Scale of Analysis	Functional Proteomics Consortium; HapMap Project; Human Epigenome Consortium; Human Genome Consortium; Mouse Genome Sequencing Project; Structural Genomics Consortium
Interconnectivity of Biological Knowledge	AfCS; Hepatosys; CFG; International Molecular Exchange Consortium; Lipid Maps Consortium
Tool Development to Support Complex Upstream Discovery Research	Collaborative Cross; Combinatorial Chemistry Consortium; Knockout Mouse Project; MMHCC
Downstream Product Development Challenges	Cancer Vaccine Consortium; International Genomics Consortium; Osteoarthritis Initiative

Table 7.10: Technological Uncertainties Driving Consortium Participation

Establishing a Technology Standard: To encourage the adoption of supportive tools, companies such as Agilent are enabling the formation of open innovation communities via the Agilent shared-design microarray program. The program facilitates a novel way of doing business with Agilent; scientists share their custom microarray designs with designated groups while either maintaining control of their intellectual property or sharing knowledge with the scientific community at large. Although the technology is highly substitutable, Agilent's program hopes to lock researchers into its technology by developing complementary linkages to knowledge databases and convincing researchers of the breadth of application of its microarray technology [Arthur, 1989]. By ensuring compatibility with software and flexibility in microarray customization, and by encouraging adoption within research consortia, Agilent is effectively trying to tip the market toward its technology—assuring researchers that there are increasing returns to adoption of its microarray technology [Arthur, 1989]. In this case, Agilent is encouraging cooperation and increasing the common value of knowledge to establish a technology standard on the market.

7.6 Differential Values for Knowledge

We now modify our assumption that both players can equivalently exploit knowledge. Rather, the situation may arise that one player may not have the internal resources or capabilities to privately exploit knowledge or due to project planning issues may not equivalently value knowledge for private, downstream development. Then the common values of knowledge will be the same for both players, but the private values may differ.

$CV_1(X) = 7;\ CV_1(Y) = 4;\ CV_1(Z) = 9$

$CV_2(X) = 7;\ CV_2(Y) = 4;\ CV_2(Z) = 9$

$PV_1(X) = 5;\ PV_1(Y) = 2;\ PV_1(Z) = 6$

$PV_2(X) = 8;\ PV_2(Y) = 5;\ PV_2(Z) = 10$

Example 5: PUBLIC ACCESS

	C_2	D_2
C_1	20, 20	11, 21*
D_1	18, 13	7, 15

Table 7.11: Differential Valuation of Knowledge in the Public Access Setting

In this game (example 5), player 1 strongly prefers to cooperate whereas player 2 strongly prefers to defect.

Free-Riding: In the case of the Human Genome Project, public sector researchers agreed that by publicly disclosing genomic data, greater value would be created through the scrutiny and validation of knowledge. Celera on the other hand, was accountable to its private shareholders. For Celera, maintaining shareholder value did not include cooperation through openness of research data, but meant paid access to a proprietary sequence database and a set of tools to mine the information. In this case, Celera was better off defecting.

With the formal release of two versions of the Human Genome sequence on February 12th 2001, many viewers agreed that Celera's genome was more accurate, easier to read, and more complete than the public Human Genome version. Scientists who had started using Celera's map further asserted that it is "fast becoming the preferred way to search for genes…" [Hensley, 2001]. However, public sector researchers argued that Celera's database was clearly enriched by access to public databases and that without such access, Celera could not have created its database as effectively [Davies, 2001].

Example 6: RESTRICTED ACCESS

	C_2	D_2
C_1	20, 20*	11, 15
D_1	7, 13	7, 15

Table 7.12: Differential Valuation of Knowledge in the Restricted Access Setting

Continuing with the above example, if Celera's efforts were indeed made more effective by the public sector initiative, then in the restricted access setting—without access to public data—Celera may not have enjoyed the same private payoffs from defection. Hence, in example 6, both players' payoffs favour cooperation.

7.7 Increasing the Common Value of Joint Knowledge

In this case, we consider the impact of increasing the common value of what is jointly knowledge by both players.

$PV_i\,(X) > CV_i\,(X)$

$PV_i\,(Z) > CV_i\,(Z)$

$CV_i\,(Y) > PV_i\,(Y)$

For simplicity, we assume that both players can equivalently exploit the knowledge—hence the common and private values of knowledge are equivalently expressed for both players.

$CV(X) = 5;\ CV(Y) = 10;\ CV(Z) = 6$

$PV(X) = 9;\ PV(Y) = 4;\ PV(Z) = 8$

Example 7: PUBLIC ACCESS

	C_2	D_2
C_1	21, 21	15, 23*
D_1	25, 16*	13, 12

Table 7.13: Increasing the Common Value of Joint Knowledge in the Public Access Setting

In the above game (example 7), which is equivalent to Chicken, both players receive the largest payoff when unilaterally defecting. While player 1 receives a payoff of 25 by unilaterally defecting, player 2 receives the payoff of 16 (more than he/she would receive if both defected). Similarly, when player 2 defects and receives the payoff of 23, player 1 receives the payoff of 15 (again, larger than the payoff he/she would receive if both defected). Although both players would be better off cooperating, given the public access setting, each player can openly enjoy the common value of what is known by the other player, including what is jointly known, without having to disclose knowledge *X* or *Z* respectively. If however, we change the access setting, unilateral defection no longer pays as well.

Example 8: RESTRICTED ACCESS

	C_2	D_2
C_1	21, 21*	15, 12
D_1	13, 16	13, 12

Table 7.14: Increasing the Common Value of Joint Knowledge in the Restricted Access Setting

In the restricted access setting, should a player choose defection, this player can only enjoy the private value of knowledge i.e., the common value of knowledge including knowledge unit *Y*, can only be enjoyed by members. Hence, it no longer pays to defect

unilaterally. Mutual cooperation is instead a Nash equilibrium in this game; in fact, cooperation is a strictly dominant strategy for both players.

Building Absorptive Capacity: Given the complexities associated with drug discovery and development technologies, members can have the opportunity to access knowledge and technology early in the discovery process through membership in knowledge networks. Accelerated access to complex technologies as well as the absorptive capacity developed in a collaborative learning-by-doing setting can enable members to competitively manage both their cost and time to market during product development [Cohen and Levinthal, 1990].

The Accelrys Nanotechnology Consortium for example (as is the case for all three Accelrys Consortia), provides a project framework that addresses the challenges of rational nanomaterials and nanodevice design. The Consortium gives members an edge in their R&D, increasing both its efficiency and effectiveness. It will further enhance the impact of software tools, contributing to R&D cost savings, supporting patent applications, facilitating interdisciplinary research, and supporting a smooth ongoing 'lab to fab' transition.

7.8 Discussion

The game models developed and validated in this chapter provide an effective illustration of the implications of changing incentives to participate in cooperative alliances. (Table 7.15) Interestingly, in most cases, the incentive is to cooperate via participation in an alliance in the restricted access setting—thereby accessing required knowledge. But when the private value of knowledge exceeds its common value, the incentive to cooperate is assured only if another researcher also cooperates (row 1, Table 7.15). Therefore, signaling one's intentions to cooperate may be necessary to ensure that mutual cooperation is the outcome of this game.

Understandably, if knowledge can be readily accessed without participation, and the private value of knowledge is greater than the common value of knowledge, defection is generally the outcome (row 1, Table 7.15); similarly, when the common value of knowledge exceeds the private value of knowledge, mutual cooperation is the preferred outcome (row 2, Table 7.15). In the case where players 1 and 2 differentially value knowledge, i.e., for player 1 the common value of knowledge exceeds the private value of knowledge and vice versa for player 2 (row 3, Table 7.15), player 1 is the sole cooperator. When the common value of joint knowledge is increased (row 4 Table 7.15), and both players would benefit from mutual cooperation, a player that chooses unilateral cooperation still enjoys a larger payoff by cooperating rather than defecting; mutual cooperation is instead assured in the restricted access setting.

Test	Outcome of Game-Public Access	Outcome of Game-Restricted Access
$PV_i\ (X,Y,Z) > CV_i\ (X,Y,Z)$	Defection	Cooperation or Defection
$CV_i\ (X,Y,Z) > PV_i\ (X,Y,Z)$	Cooperation	Cooperation
$CV_1(X,Y,Z) > PV_1(X,Y,Z);$ $PV_2(X,Y,Z) > CV_2(X,Y,Z)$	Unilateral Defection by Player 2	Cooperation
$PV_i\ (X,Z) > CV_i\ (X,Z);$ $CV_i\ (Y) > PV_i\ (Y)$	Unilateral Defection	Cooperation

Table 7.15: Summary of Outcomes from the Participation Game Model

In this chapter, we have analyzed different incentives to join (form) a consortium given the knowledge access setting. Models 7.1 to 7.4 reflect changing payoffs as both the access setting is changed and whether or not players 1 and 2 form a new consortium or join an existing consortium. Using numerical examples to demonstrate the utility of these models, and with reference to the analysis conducted in Chapter 6, we better understand the behavioural and technological drivers for cooperation. Assuming that both players join a consortium, in Chapter 8, we consider the decision to privately appropriate knowledge from the consortium via the filing of patents.

Chapter 8: Modeling the Decision to Appropriate from Alliances

8.1 Introduction

Once a commitment is made to participate in a knowledge network, researchers will face the decision on whether and when to privately appropriate knowledge from the network. In the case of biotechnology, appropriation most often occurs through the filing of patents. The common benefits from contributing to versus the private benefits associated with appropriating knowledge will determine when a participant will choose to signal his/her departure from the alliance. For example, when the private benefits from filing patents are higher than the common benefits from open knowledge dissemination, researchers will likely choose depart from the alliance [Khanna et al., 1998].

In our model, the synthesis of knowledge in an alliance will create a common value *CV* related to the knowledge units jointly generated and contributed to the alliance. Private benefits are those that a firm can obtain unilaterally by learning from another firm. By pooling a partner's knowledge with internal firm knowledge, a firm can gain a competitive advantage in downstream activities. The knowledge that is held unilaterally will have a private value *PV* for its owner. We assume in our model that a firm has the option of capturing these private benefits by seeking a patent on the knowledge.

The probability of receiving a patent will depend on whether the knowledge is nonobvious, novel, and has utility assuming that the patent examiner can correctly assess this from the existing prior art; it can also be affected by a rival firm's disclosure through the creation of patent-defeating prior art [Parchomovsky, 2000]. From a knowledge perspective, the value *CV* will derive from the characteristics associated with the knowledge and the value from collectively holding all of the knowledge in the public domain. Equivalently, the value *PV* derives from the characteristics of knowledge—namely the level of substitutability, complementarity, and applicability.

In this chapter, we use our game model to understand the strategic decisions made by firms regarding the timing of appropriation activities. The game model not only models the decision to file a patent, but through the use of case studies as presented in Chapter 6, models the decision to pre-empt rivals through disclosure—thereby preventing firms from prematurely enclosing upstream knowledge. (Analysis 8.1)

8.2 Model Parameters

We define the following new notation for our model (Table 8.1; see Table 7.1 for additional notation):

Notation	Definition
$CV_i\ (K_1 \cup K_2)$	The payoff (utility) to researcher *i* for contributing knowledge to the public domain is a function of the joint contribution by both researchers.
$PV_i\ (K_i)$	The payoff (utility) to researcher *i* for withholding and patenting knowledge (K_i); this private payoff can derive from internal exploitation or licensing of the knowledge.
p_i	Probability of researcher *i* receiving a patent on K_i or K_i - K_j (see assumption 4).
q_i	Probability of researcher *i* receiving a patent on the intersection set $K_i \cap K_j$. (see assumption 5).

Table 8.1: Appropriation Game Model Notation

In order to define the game models, we adopt the following set notation:

We use the parameters *X*, *Y*, and *Z* to represent the knowledge held by the researchers. For example, the knowledge held by researcher 1 includes the union of what is known unilaterally (*X*) and what is jointly known with researcher 2 (*Y*). Similarly, the knowledge held by researcher 2 includes the union of what 2 knows unilaterally (*Z*) and what is jointly known with researcher 1 (*Y*). *Y* thus represents the intersection of researcher 1's and researcher's 2 knowledge sets. For knowledge in *Y*, what is known by one researcher is also known by the other, i.e., with no difference in perception.

$K_1 \cup K_2 = X \cup Y \cup Z$ where $X \cap Y = X \cap Z = Y \cap Z = \varnothing$

$K_1 = X \cup Y$

$K_2 = Y \cup Z$

$K_1 - K_2 = X$

$K_2 - K_1 = Z$

$K_1 \cap K_2 = Y$

These parameters are illustrated in the following Venn diagram:

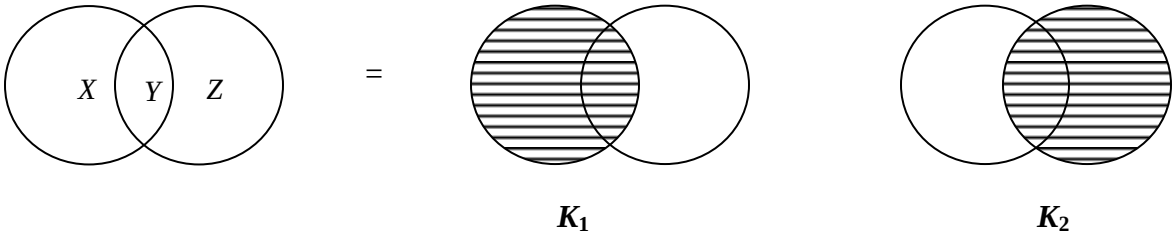


Figure 8.1: Graphical Representation of Knowledge in the Model

We make the following assumptions:

1. Decisions are simultaneous.
2. No communication takes place with the exception of the game presented in Table 8.10.
3. Each participant is able to appropriate the full value of the consortium's knowledge.
4. The probability of receiving a patent depends on the researcher's probability of crossing the threshold to patent, i.e., knowledge is novel, nonobvious, and has utility.
5. Only one firm wins the patent on knowledge $K_1 \cap K_2$; in the event that both researchers file for patents, the patent is awarded to one winner for $K_1 \cap K_2$, so $q_1 + q_2 = 1$.
6. The total value of knowledge in a set is equal to the sum of values of the individual knowledge units that comprise the set.

7. $CV_1 (K_1 \cup K_2) = CV_1 (X) + CV_1 (Y) + CV_1 (Z)$ and $CV_2 (K_1 \cup K_2) = CV_2 (X) + CV_2 (Y) + CV_2 (Z)$ where *X*, *Y*, and *Z* are as defined in the Venn diagram. The payoff (utility) to researcher *i* for participating and contributing knowledge, is a function of the joint contribution by both players. (By assumption 6, the payoff is a simple additive function: in other words, the common value of joint knowledge units derives from the addition of the individual common values of *X*, *Y*, and *Z*. Alternatively, the common value of joint knowledge could be greater than the sum of the individual common values, i.e., knowledge of all parts could be worth more than the sum of the worth of the individual parts.)
8. $PV_1 (K_1) = PV_1 (X) + PV_1 (Y)$ and $PV_2 (K_2) = PV_2 (Z) + PV_2 (Y)$ where *X*, *Y*, and *Z* are as defined above. (Again by assumption 6, the payoff is a simple additive function, implying that the private value of knowledge units derives from the addition of the individual private values of *X* or *Z* for players 1 and 2 respectively (knowledge that is known unilaterally and not disclosed) and *Y* (knowledge that is jointly known but not disclosed). Alternatively, the private value of knowledge could be greater than the sum of the individual private values, i.e., knowledge of all parts could be worth more than the sum of the worth of the individual parts.)

8.3 The Appropriation Model

We propose the following game model to illustrate the payoffs available to players as a function of the characteristics associated with knowledge and the probabilities of appropriating knowledge.

Model 8.1: Patenting Consortium Knowledge

In this model, we consider the decision to patent consortium knowledge. As in Chapter 7, we consider a consortium with two players, researchers 1 and 2.

Strategies.

Share Knowledge=player enjoys the common value of the knowledge shared.

Patent Knowledge= player enjoys the private value of his/her knowledge.

	Player 2 Shares Knowledge	**Player 2 Patents Knowledge**
Player 1 Shares Knowledge	$CV_1(K_1 \cup K_2)$, $CV_2(K_1 \cup K_2)$	$p_2CV_1(K_1) + (1 - p_2)CV_1(K_2 \cup K_1)$, $p_2[PV_2(K_2 - K_1) + CV_2(K_1)] + (1 - p_2)CV_2(K_2 \cup K_1)$
Player 1 Patents Knowledge	$p_1[PV_1(K_1 - K_2) + CV_1(K_2)] + (1 - p_1)CV_1(K_1 \cup K_2)$, $p_1CV_2(K_2) + (1 - p_1)CV_2(K_1 \cup K_2)$	$p_1\, p_2[q_1PV_1(K_1) + (1\text{-}q_1)PV_1(K_1 - K_2)] + p_1(1 - p_2)[PV_1(K_1 - K_2) + CV_1(K_2)] + (1 - p_1)\, p_2\, CV_1(K_1) + (1 - p_1)(1 - p_2)\, CV_1(K_1 \cup K_2)$, $p_2\, p_1[q_2PV_2(K_2) + (1\text{-}q_2)PV_2(K_2 - K_1)] + p_2(1 - p_1)[PV_2(K_2 - K_1) + CV_2(K_1)] + (1 - p_2)\, p_1\, CV_2(K_2) + (1 - p_2)(1 - p_1)\, CV_2(K_1 \cup K_2)$

Table 8.2: A Knowledge-Based Appropriation Game Model

We first analyze Player 1's Preferences:

Assume Player 2 Shares Knowledge (Column 1)

Row 1 is preferred to row 2 iff

8A)

$CV_1(X) + CV_1(Y) + CV_1(Z) > p_1\,[PV_1(X) + CV_1(Y) + CV_1(Z)] + (1 - p_1)[CV_1(X) + CV_1(Y) + CV_1(Z)]$

which is equivalent to $CV_1(X) > PV_1(X)$ (assuming p_1=1 for simplicity) that is, when the when the common value of knowledge X is greater than the private value of knowledge X, player 1 will choose row 1 (cooperation). In the case that p_1=0, player 1 will be indifferent to the choice of sharing knowledge vs. the choice of patenting knowledge (assuming that player 2 shares knowledge) as both strategies result in the same payoff.

Assume Player 2 Patents Knowledge (Column 2)

Row 1 is preferred to row 2 iff

8B)

$p_2 [CV_1(X) + CV_1(Y)] + (1 - p_2) [CV_1(X) + CV_1(Y) + CV_1(Z)] > p_1 p_2[q_1(PV_1(X) + PV_1(Y)) + (1 - q_1)PV_1(X)] + p_1 (1 - p_2) [PV_1(X) + CV_1(Y) + CV_1(Z)] + (1-p_1) p_2 [CV_1(X) + CV_1(Y)] + (1 - p_1)(1 - p_2) [CV_1(X) + CV_1(Y) + CV_1(Z)]$
which is equivalent to $p_1CV_1(X) + p_1p_2 CV_1(Y) > p_1PV_1(X) + p_1p_2q_1PV_1(Y)$ and simplifies to $CV_1(X) + p_2 CV_1(Y) > PV_1(X) + p_2q_1PV_1(Y)$ given assumptions 7 and 8.

When $p_{2=}0$ then player 1 chooses row 1 (cooperation) when the common value of X is greater than the private value of X. In this case, cooperation is a strictly dominant strategy for player 1; player 1 joins regardless of player 2's choice.

When $p_{2=}1$, but $q_1=0$, then player 1 chooses row 1 (cooperation) when the common values of X and Y are greater than the private value of X. If $CV_1(X) > PV_1(X)$, cooperation is a strictly dominant strategy for player 1 since $CV_1(Y) > 0$; player 1 shares knowledge regardless of player 2's choice.

Finally, when $p_2 =1$ and $q_1 =1$, then player 1 chooses row 1 (cooperation) when the common values of X and Y are greater than the private values of X and Y. If $CV_1(X) > PV_1(X)$ and $CV_1(Y) > PV_1(Y)$, then $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$. Therefore, sharing knowledge is a strictly dominant strategy for player 1; player 1 shares knowledge regardless of player 2's choice.

If however, $CV_1(X) > PV_1(X)$ but $PV_1(Y) > CV_1(Y)$, sharing knowledge may no longer be a strictly dominant strategy for player 1; now the actual outcome may depend on player 2's choice. The situation is similar if $CV_1(Y) > PV_1(Y)$ but $PV_1(X) > CV_1(X)$.

If we consider the possible synergy between knowledge units, it may be possible to assume that $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$, even if $CV_1(X) > PV_1(X)$ but

$PV_1(Y) > CV_1(Y)$ or $CV_1(Y) > PV_1(Y)$ but $PV_1(X) > CV_1(X)$ as the total value of knowledge in the set may greater than the sum of values of the individual knowledge units that comprise the set. Future research will assess this synergy between knowledge units.

Equivalently, Player 2's Preferences:

When p_1=0 then player 2 chooses column 1 (cooperation) when the common value of *Z* is greater than the private value of *Z*. In this case, cooperation is a strictly dominant strategy for player 2; player 2 shares knowledge regardless of player 1's choice.

When $p_{1=}1$, but q_2=0, then player 2 chooses column 1 or cooperation when the common values of *Z* and *Y* are greater than the private value of *Z*. If $CV_2(Z) > PV_2(Z)$ cooperation is a strictly dominant strategy for player 2 since $CV_2(Y) > 0$; player 2 shares knowledge regardless of player 1's choice.

Finally, when $p_{1=}1$ and q_2=1, then player 2 chooses column 1 or cooperation when the common values of *Z* and *Y* are greater than the private values of *Z* and *Y*. If $CV_2(Z) > PV_2(Z)$ and $CV_2(Y) > PV_2(Y)$, then $CV_2(Z) + CV_2(Y) > PV_2(Z) + PV_2(Y)$.

Therefore, sharing knowledge is a strictly dominant strategy for player 2; player 2 shares knowledge regardless of player 1's choice.

If however, $CV_2(Z) > PV_2(Z)$ but $PV_2(Y) > CV_2(Y)$, sharing knowledge may no longer be a strictly dominant strategy for player 2; now the actual outcome may depend on player 1's choice. The situation is similar if $CV_2(Y) > PV_2(Y)$ but $PV_2(Z) > CV_2(Z)$.

If we consider the possible synergy between knowledge units, it may be possible to assume that $CV_2(Z) + CV_2(Y) > PV_2(Z) + PV_2(Y)$, even if $CV_2(Z) > PV_2(Z)$ but $PV_2(Y) > CV_2(Y)$ or $CV_2(Y) > PV_2(Y)$ but $PV_2(Z) > CV_2(Z)$ as the total value of

knowledge in the set may greater than the sum of values of the individual knowledge units that comprise the set.

When p_1=0 and p_2=0 players are indifferent to the choice of sharing knowledge vs. the choice of patenting knowledge as both strategies result in the same respective payoff.
When p_1=1, q_1=1 (hence q_2=0) and p_2=1 both sharing knowledge is a Nash Equilibrium if $CV_1(X) + CV_1(Y) > PV_1(X) + PV_1(Y)$ *and* $CV_2(Z) > PV_2(Z)$.
When p_1=1, q_2 =1 (hence q_1=0) and p_2=1 both sharing knowledge is a Nash Equilibrium if $CV_1(X) > PV_1(X)$ *and* $CV_2(Z) + CV_2(Y) > PV_2(Z) + PV_2(Y)$
When p_1=1 and p_2=0 both sharing knowledge is a Nash Equilibrium if $CV_1(X) > PV_1(X)$
When p_1=0 and p_2=1 sharing knowledge is a Nash Equilibrium if $CV_2(Z) > PV_2(Z)$

Conclusion: $CV_1(X) > PV_1(X)$ and $CV_2(Z) > PV_2(Z)$ are (jointly) sufficient for both sharing to be a Nash equilibrium

Figure 8.2 provides an extensive form representation of the events in our model.

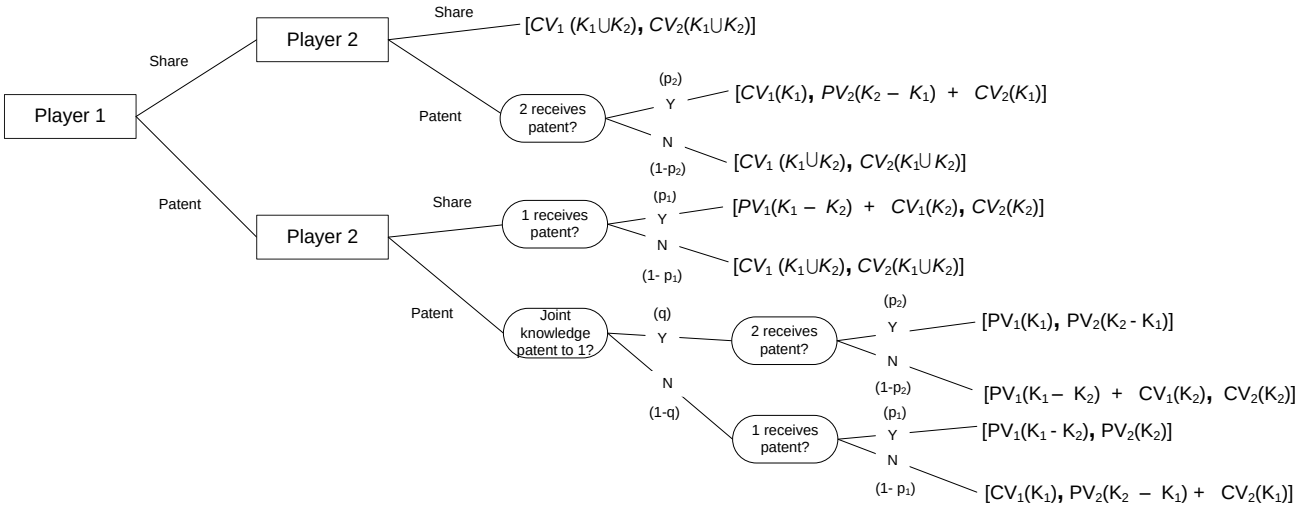


Figure 8.2: Graphical Representation of the Events in the Appropriation Model

We validate our model by showing that payoffs exist that are consistent with the previous discussion and that yield the outcomes observed in our case examples. In our models, two researchers can either cooperate (*C*) through full knowledge dissemination, or defect (*D*) by patenting and privatizing knowledge. Payoffs are expressed as numerical values. With respect to the probability of receiving a patent, for simplicity, we assume that both players can patent knowledge with probability 1 (although this is not always the case and future research will consider varied probabilities for patenting knowledge) and in most cases player 2 wins the right to patent knowledge that is jointly known.

8.4 Enjoying the Private Value of Knowledge

First, we study the implication of private values for knowledge that are higher than the corresponding common values.

$PV_i\ (X) > CV_i\ (X)$

$PV_i\ (Y) > CV_i\ (Y)$

$PV_i\ (Z) > CV_i\ (Z)$

For simplicity, we assume that both players can equivalently exploit the knowledge—hence the common and private values of knowledge are equivalently expressed for both players.

Example 1:

$p_1=1$; $p_2=1$

$q_1=0$; $q_2=1$

$CV(X)=5$; $CV(Y)=2$; $CV(Z)=6$

$PV(X)=9$; $PV(Y)=4$; $PV(Z)=8$

	C_2	D_2
C_1	13, 13	7, 15
D_1	17, 8	9, 12*

Table 8.3: Private Knowledge Exceeds Common Knowledge
Researcher 1 chooses C_1 or D_1; the first number in each cell is Researcher 1's numerical payoff.
Researcher 2 chooses C_2 or D_2; the second number in each cell is Researcher 2's numerical payoff.
C=Cooperate; D=Defect; * indicates Nash Equilibrium

In example 1 (Table 8.3), both players can choose to file a patent on knowledge. Given that the private values of knowledge are greater than the common values, the best decision for both players is to defect. From the perspective of knowledge types, the above model is (at least we advocate should be) typical in the downstream development of drugs, diagnostics, and tools. In the genomics era, although drugs may be highly dependent on complementary upstream knowledge, drugs are substitutable by both competitor brands and generics. Interestingly, the incentive to race to market a drug first will be stronger as the market size (or applicability) increases.

In the development phase, competition between firms with different approaches can be beneficial, especially if the exclusivity period for a first break-through drug is relatively short, with "me-too" brand drugs rapidly available so that consumers have access to competitively-priced alternatives. As Table 8.3 shows, although each player may strongly prefer unilateral defection, both players are better off defecting. Of course both are better off cooperating, but it is no surprise that this outcome is highly unstable since the game is a version of Prisoner's Dilemma (see Chapters 1 and 2).

Consider the example of Tagamet, a breakthrough drug in antiulcer therapies that was introduced in 1977. Tagamet was the first drug to relieve ulcers by blocking the histamine 2 (H2) receptors in the lining of the stomach from stimulating acid production by the parietal cells. Six years after Tagamet became available, a second H2 antagonist, Zantac, was approved; it eventually became the largest-selling drug in both the United States and the world. By 1989, two additional H2 antagonists, Pepcid and Axid, were

available. Thus, four slightly different drugs using the same therapeutic mechanism (blocking the H2 receptor) were all patentable, and the breakthrough drug had only six years of market exclusivity before being challenged by a competitor using a similar compound [Berndt et al., 1994]. According to the Pharmaceutical Care Management Association in Washington, as many as 70 brand-name drugs will lose their patent protection over the next five years, enabling for strong generic competition. Some popular drugs that are currently open to generic imitators include Ambien, a sleep aid, antidepressants Wellbutrin, Zoloft, and Xanax, and Zocor, a cholesterol-lowering drug [Mighty Statins, 2006].

Similarly, although tools that support drug discovery and development and diagnostics that predict drug response or identify disease may be highly dependent on complementary upstream knowledge, such as gene sequences, SNPs, or drug targets, these downstream products may be substituted by competing products. In each of these cases, we argue that competition may be beneficial since the target of knowledge appropriation will be downstream products and not the upstream knowledge itself. Interestingly, the Cancer Vaccine Consortium and the Biological Innovation for Open Society (BIOS) both focus on downstream product development, but have opted for collective knowledge production and dissemination.

To address the networking, clinical, and regulatory needs of corporations, organizations, and researchers working in cancer vaccines, the Sabin Vaccine Institute organized the Cancer Vaccine Consortium. The goal of the consortium is to accelerate the process of bringing cancer vaccines from the development stage to the clinic. The members of the consortium benefit from dynamic exchanges of data, standardization of assays, potential identification of combination therapies, and shared knowledge management. Overall benefits also include accelerated vaccine development and reduced product development costs, as the Cancer Vaccine Consortium fosters networking among members [www.sabin.org, 2007].

The BiOS Initiative enables open access to patented and patentable technologies for public benefit. Under a BiOS-compliant agreement, a user must agree to conditions that encourage cooperation and development of the technology instead of royalties or other conditions that discourage creation of products. For example, licensees cannot appropriate core technology and improvements exclusively. The base technology remains the property of the original inventor, but improvements can be shared with others supporting the development of a protected commons around the technology; all those who agree to the terms of sharing obtain access to improvements and other information [www.bios.net, 2007].

8.5 Enjoying the Common Value of Knowledge

Here we study the implication of common values for knowledge that are higher than the corresponding private values.

$CV_i(X) > PV_i(X)$

$CV_i(Y) > PV_i(Y)$

$CV_i(Z) > PV_i(Z)$

For simplicity, we assume that both players can equivalently exploit the knowledge—hence the common and private values of knowledge are equivalently expressed for both players.

Example 2:

$p_1=1$; $p_2=1$

$q_1=0$; $q_2=1$

$CV(X)=7$; $CV(Y)=4$; $CV(Z)=9$

$PV(X)=5$; $PV(Y)=2$; $PV(Z)=6$

	C_2	D_2
C_1	20, 20*	11, 17
D_1	18, 13	5, 8

Table 8.4: Common Knowledge Exceeds Private Knowledge

In example 2 (Table 8.4), both players can choose to file a patent on knowledge. However, given that the common values of knowledge are greater than the private values, the best decision for both players is to cooperate. From the perspective of knowledge types, the above model is (at least we advocate should be) typical of upstream discovery research. In the systems biology era, upstream knowledge has become increasingly complex, highly complementary, and applicable across multiple diseases and human biological processes. Furthermore, genomic sequences, protein sequences, and biological systems are not substitutable (despite being analyzed in artificial form). The knowledge embodied in these biological components cannot be duplicated. As such, we advocate that to ensure downstream technological opportunities are preserved for multiple researchers, this knowledge should be openly disclosed or at least readily accessible through favourable licensing terms as is the case for many of the consortia analyzed in Chapter 6 [Merges, 1996; Maurer, 2003; Nelson 2003; Walsh et al., 2003].

8.6 Differential Valuation of Knowledge

In this example, we study the implication of differential values for the common and private values for knowledge for players 1 and 2.

$CV_1 (X) > PV_1 (X)$

$CV_1 (Y) > PV_1 (Y)$

$CV_1 (Z) > PV_1 (Z)$

$PV_2 (X) > CV_2 (X)$

$PV_2 (Y) > CV_2 (Y)$

$PV_2 (Z) > CV_2 (Z)$

Example 3:

p_1=1; p_2=1

q_1=0; q_2=1

$CV_1(X)$ =7; $CV_1(Y)$ =4; $CV_1(Z)$ =9

$CV_2(X)$ =7; $CV_2(Y)$ =4; $CV_2(Z)$ =9

$PV_1(X)$ =5; $PV_1(Y)$ =2; $PV_1(Z)$ =6

$PV_2(X)$=8; $PV_2(Y)$ =5; $PV_2(Z)$ =10

	C_2	D_2
C_1	20, 20	11, 21*
D_1	18, 13	5, 15

Table 8.5: Differential Values for Private Knowledge

In example 3 (Table 8.5), we assume that the players are different, giving them different preferences over private and public knowledge. For player 1, the common value of knowledge exceeds the private value of knowledge. Consequently, player 1 strongly prefers cooperation. Conversely, for player 2, the private value of knowledge is greater than the common value of knowledge, so player 2 strongly prefers defection. At the unique Nash equilibrium, player 1 ends up being the sole cooperator.

As an example, although gene sequences are complementary in nature, non-substitutable, and high in applicability in downstream research activities, researchers may differentially exploit them. In the above model, player 1 may not be able to privately use these sequences (or even perceive the private value given the current state of knowledge), whereas player 2 may be able to use these exact sequences to develop a genomic-based drug, a microarray tool with the sequences spotted on the solid matrix used in probing biological samples, or even a diagnostic that uses the sequences to predict drug response

or disease development. Player 2 will likely patent not only the drug, tool, or diagnostic, but also the sequences physically embodied in these products (or to be embodied at a future date) to maximize on (future) private value.

In the case of *Laboratory Corporation vs. Metabolite Laboratories*, at stake is the validity of a patent held by Metabolite Laboratories that claims a monopoly over a basic scientific relationship used in diagnosis and medical treatment [Eisenberg, 2006]. Justice Breyer outlines in his Supreme Court Opinion:

> "This case involves a patent that claims a process for helping to diagnose deficiencies of two vitamins, folate and cobalamin. The process consists of using any test (whether patented or unpatented) to measure the level in a body fluid of an amino acid called homocysteine and then noticing whether its level is elevated above the norm; if so, a vitamin deficiency is likely.
>
> The lower courts held that the patent claim is valid. They also found the petitioner, Laboratory Corporation of America Holdings (LabCorp), liable for inducing infringement of the claim when it encouraged doctors to order diagnostic tests for measuring homocysteine. The courts assessed damages. And they enjoined LabCorp from using any tests that would lead the doctors it serves to find a vitamin deficiency by taking account of elevated homocysteine levels." [Breyer, Supreme Court Opinion, 2006].

Breyer argues that this is a matter of a correlation between the presence of homocysteine and the relevant vitamin deficiencies (clearly a natural phenomenon), and is not convinced by Metabolite's argument that the patent claim is actually an application of this unprotectable relationship [Breyer, Supreme Court Opinion, 2006]. On June 23rd 2006, the Supreme Court dismissed the case from its docket, saving the decision for another day on whether a naturally occurring scientific relationship can be patented [Mauro, 2006].

8.7 The Dilemma of Defection in Upstream Discovery Research

Where intellectual property rights are the major consideration, the timing of appropriation may determine whether all downstream medical opportunities can be exploited. Fully disclosing knowledge will facilitate future collaboration, while appropriating knowledge strengthens a researcher's bargaining position for trading knowledge. The former choice is cooperation—the researcher places knowledge in the public domain where it is readily accessible for downstream application development. The latter choice is defection—the researcher has the option of using enclosed knowledge as a bargaining tool, i.e., to trade for knowledge held by others.

Example 4 (Table 8.6) is a game model that can be used to understand this dilemma. There are no particular gains to an individual who defects, but a researcher who is the sole cooperator risks being unable to bargain for access to enclosed knowledge, or may be forced to pay large royalties for access. Despite the greater payoff from cooperation, defecting is proof against the "sucker" outcome (the lowest payoff) [Merges, 1996]. Minimax (sometimes minmax) is a strategy for minimizing the maximum possible loss. Alternatively, it can be thought of as maximizing the minimum gain (maximin). For example in the Prisoner's Dilemma, the minimax strategy for each prisoner is to betray the other even though they would each do better if neither confessed their guilt. In example 4, therefore, the minimax strategy is to defect as proof against receiving the sucker payoff, despite the higher payoff associated with cooperation.

Example 4:

	C_2	D_2
C_1	4, 4*	1, 3
D_1	3, 1	2, 2*

Table 8.6: The Dilemma of Defection in Upstream Discovery Research

As discovery knowledge becomes increasingly complementary and broadly applicable, patents provide a strong bargaining position *vis-à-vis* other researchers who need access

to the protected knowledge. The above dilemma becomes severe as the defector's uncertainty about the future increases. Although researchers may improve their bargaining position with respect to protected knowledge, researchers who defect earlier in time may be less able to bargain in the future, as researchers who remember past actions and who hold vital knowledge may not be so eager to bargain with the defector [Kollock, 1998]. Hence, a defector's freedom to operate may be compromised in any case.

The key to understanding the behaviour of research organizations is to recognize the transition point—when knowledge characteristics change to make the gains during downstream development activities from privatization more valuable than the benefits from knowledge disclosure. As discussed earlier, once the development of medical products and applications predominates, the greater gains associated with being first to market will make defection inevitable.

8.8 Changing the Game

Companies can unilaterally force other competitors to delay their appropriation activities to when the characteristics of knowledge change so that privatization of knowledge is of strategic value for all parties. During the Human Genome Project, Merck financed a separate program to identify sequences in May of 1994, making all sequences publicly available without delay or commitment regarding use. Merck provided financing, in the range of $10 million to Washington University, to produce hundreds of thousands of human sequences [Kluge, 2003]. The development of the Merck Gene Index created prior art data with the intention of defeating competitor intentions to enclose human sequences.

In October of 1994, Britain's Wellcome Trust hosted a meeting with genome leaders to discuss whether to use a private collection of sequences as part of the large-scale effort to map the location of genes. Leaders strongly opposed using these sequences and instead supported the initiative that had been proposed by Merck [Davies, 2001]. Analysts note that Merck's decision was not entirely "altruistic"; Merck wanted to challenge competitor SmithKline-Beecham's hold over a private database. Like other big pharma companies,

Merck did not have access to the private database [Marshall, 1996; Davies, 2001]. In this sense, Merck unilaterally moved the transition point by using a pre-emptive disclosure strategy as shown in Table 8.8.

Example 5:

p_1=1; p_2=1

q_1=0*;* q_2=1

CV(X) =5*; CV(Y)* =3*; CV(Z)* =2

PV(X) =6*; PV(Y)* =9*; PV(Z)* =4

	C_2	D_2
C_1	10, 10	8, 12*
D_1	11, 5	6, 13

Table 8.8: Pre-empting Rivals through Disclosure

In example 5 (Table 8.8), both players can choose to patent. However, only player 2 strongly prefers to do so. To prevent player 2 from achieving the payoff 13 via patenting both *Y* and *Z* knowledge units and leaving player 1 with the private payoff of 6 from *X* knowledge unit, player 1 pre-empts player 2 by disclosing *X and Y* and placing them in the public domain.

Merck's pre-emptive strategy was a *response* to a competitor's defection. In other scenarios, players sometimes pre-empt rivals at the outset of research. An example of an upfront strategic move (to level the playing field in downstream research and development activities) is the Broad-Novartis Diabetes Initiative. In October 2004, Novartis, MIT's Broad Institute, and Harvard announced a joint project to decipher the genetic causes of type 2 diabetes. The Broad-Novartis Diabetes Initiative planned to

place all findings about type 2 diabetes directly onto the Internet. Novartis believed that the benefits of openness would outweigh those of secrecy: "I'm doing this to make a statement in the world of medical science that the patient should come first. You gain much more by being open", stated Mark Fishman, President of Novartis' biomedical efforts. While the team would not file patents on the database, it would allow others to patent new therapies or diagnostic tests (delaying appropriation to downstream activities) based on the shared information [Lawler, 2004].

An interesting situation also arises when we simply reverse the common and private payoffs for knowledge unit Y as shown in Table 8.9.

Example 6:

p_1=1; p_2=1

q_1=0; q_2=1

CV(X) =5; *CV(Y)* =9; *CV(Z)* =2

PV(X) =6; *PV(Y)* =3; *PV(Z)* =4

	C_2	D_2
C_1	16, 16	14, 18*
D_1	17, 11*	6, 7

Table 8.9: Multiple Equilibria

In example 6 (Table 8.9), with an increase in the common value of knowledge unit *Y*, we have multiple equilibria. If player 1 chooses defection, player 2's best strategy is to choose cooperation, placing both knowledge units *Y* and *Z* into the public domain. Alternatively, if player 2 chooses defection, player 1's best strategy is to choose cooperation, placing both knowledge units *X* and *Y* into the public domain. It is the common value of *Y* that encourages a player to seek cooperation when the opponent

chooses privatization. Player 1 enjoys the payoff of 14 from the common values of *X* and *Y* when choosing cooperation against player 2's decision to defect, rather than also defecting to receive the payoff of 6.

8.9 Changing the Rules

Cooperative enterprises such as consortia have explicit rules about sharing research. The use of binding agreements ensures that the incentive to cooperate dominates the incentive to defect as shown in example 7 (Table 8.10).

Example 7:

	C_2	D_2
C_1	4, 4*	3, 1
D_1	1, 3	2, 2

Table 8.10: Jointly Moving the Transition Point

The success of the Human Genome Project highlighted the advantages of the consortium structure. Ostrom et al. (1994) discusses the role in consortia of deontological statements, which define what is obligatory, permitted, or forbidden. Obligations can affect the structure of an interaction, producing incentives that change the outcome. Rules may reflect conscious choices by actors, or may evolve with time as participants develop a shared understanding of which actions led to better outcomes in the past [Ostrom, et al., 1994].

In the Human Genome Project, for instance, the accelerated timetable for entry of new DNA sequences into a publicly accessible database under the "Bermuda rules" (within 24 hours of discovery), made it difficult for grantees to file patent applications prior to public disclosure [Marshall, 2001]. Eisenberg uses a similar idea to explain the motivation of the SNP Consortium, whose members could not obtain access to any components of the SNP map prior to their public release. The Consortium members filed

provisional patents to record the date of each SNP at the United States Patent and Trade Office (USPTO), serving as proof of priority in the event of any future claims for ownership [Eisenberg, 2000; Kluge 2003]. However, others argue that the SNP Consortium pre-emptively chose to place the SNPs into the public domain and mark the dates of priority so that competitors such as Abbott Laboratories of Chicago and Genset of Paris could not enclose this vital knowledge.

Fears that this promising new technology might be tied up in commercial claims were discussed at a meeting of the advisory council to the National Human Genome Research Institute (NHGRI) in 1997. In a session moderated by Alan Williamson, Vice President for research strategy worldwide of Merck, the group discussed what Williamson called a "pre-emptive strike" against the commercialization of SNPs. While some panelists wanted NHGRI to issue a manifesto aimed at discouraging such patents, the majority suggested that NHGRI simply assemble a new repository of human genetic SNPs and release them unconditionally to the public [Marshall, 1997].

In Chapter 6, we discussed the strategies used by 39 consortia to manage complex knowledge production. The rules and agreements used by selected consortia, essentially seek to level the playing field for downstream researchers both inside and outside the consortia. In other cases, while members exclusively enjoy the benefits of collective knowledge production, the object of these consortia is enable members to gain early access to complex technologies while pre-empting rivals outside the consortia during product development.

Table 8.11 compares the knowledge management strategies adopted by various consortia from the perspective of our appropriation model. In the majority of cases, consortia have as their objective the cooperative generation and dissemination of upstream knowledge. In a few cases, consortia appear to have been established to pre-empt downstream rivals. For example, the Accelrys Combinatorial Chemistry Consortium, the Accelrys Functional Proteomics Consortium, and the Accelrys Nanotechnology Consortia seem to

have been established to pre-empt downstream rivals through selective cooperation and knowledge dissemination.

Consortium	Knowledge Management Strategy Adopted
Agilent-Industry Open Microarray Design Program; Est. 2005	Pre-empting Rivals and Standard Creation via Cooperation
Alliance for Cellular Signaling (AfCS); Est. 2002	Increasing the Common Value of Knowledge via Cooperation
Beta Cell Biology Consortium (BCBC); Est. 2001	Increasing the Common Value of Knowledge via Cooperation
Biological Innovation for Open Society (BIOS); Est. 2004	Increasing the Common Value of Knowledge via Cooperation
Cancer Vaccine Consortium; Est. 2002	Increasing the Common Value of Knowledge via Cooperation
Cell Migration Consortium; Est. 2001	Increasing the Common Value of Knowledge via Cooperation
Collaborative Cross; Est. 2005	Increasing the Common Value of Knowledge via Cooperation
Combinatorial Chemistry Consortium; Est. 1996	Pre-empting Rivals during Downstream Development via *Selective Cooperation*
Consortium for Functional Glycomics (CFG); Est. 2001	Increasing the Common Value of Knowledge via Cooperation
Functional Proteomics Consortium; Est. 2000	Increasing the Common Value of Knowledge via *Selective Cooperation*
Human Epigenome Consortium; Est. 2003	Increasing the Common Value of Knowledge via Cooperation
Human Genome Consortium; Est. 1990	Increasing the Common Value of Knowledge via Cooperation
International Genomics Consortium; Est. 2004	Increasing the Common Value of Knowledge via Cooperation
International HapMap Project; Est. 2002	Increasing the Common Value of Knowledge via Cooperation
International Regulome Consortium; Est. 2004	Increasing the Common Value of Knowledge via Cooperation
Knockout Mouse Project; Est. 2006	Increasing the Common Value of Knowledge via Cooperation
MalariaGEN; Est. 2005	Increasing the Common Value of Knowledge via Cooperation
Mouse Genome Sequencing Consortium (MGSC); Est. 2000	Increasing the Common Value of Knowledge via Cooperation
Mouse Models of Human Cancers Consortium (MMHCC); Est. 1999	Increasing the Common Value of Knowledge via Cooperation
Nanotechnology Consortium; Est. 2004	Pre-empting Rivals during Downstream Development via *Selective Cooperation*
Novartis Institutes for Biomedical Research-Broad Institute Alliance; Est. 2004	Pre-empting Rivals; Increasing the Common Value of Knowledge via Cooperation
Osteoarthritis Initiative; Est. 2001	Increasing the Common Value of Knowledge via Cooperation
Public Population Project in Genomics; Est. 2004	Increasing the Common Value of Knowledge via Cooperation
RNAi Consortium (TRC); Est. 2005	Increasing the Common Value of Knowledge via Cooperation
SNP Consortium; Est. 1999	Pre-empting Rivals; Increasing the Common Value of Knowledge via Cooperation
Structural Genomics Consortium; Est. 2003	Increasing the Common Value of Knowledge via Cooperation
The Lipid MAPS Consortium; Est. 2003	Increasing the Common Value of Knowledge via Cooperation

Table 8.11: Analyzing the Knowledge Management Strategies Adopted by Consortia from the Perspective of our Appropriation Model

8.10 Discussion

The game models developed and validated in this chapter provide an effective illustration of changing incentives to cooperate or defect in knowledge production and dissemination as knowledge structures evolve. (Table 8.12)

Example	Outcome of Game
$PV_i\ (X,Y,Z) > CV_i\ (X,Y,Z)$ $p_1=1;\ p_2=1$ $q_1=0;\ q_2=1$	Defection
$CV_i\ (X,Y,Z) > PV_i\ (X,Y,Z)$ $p_1=1;\ p_2=1$ $q_1=0;\ q_2=1$	Cooperation
$CV_1(X,Y,Z) > PV_1(X,Y,Z)$ $PV_2(X,Y,Z) > CV_2(X,Y,Z)$ $p_1=1;\ p_2=1$ $q_1=0;\ q_2=1$	Player 1 sole cooperator
$PV_i\ (X,Y,Z) > CV_i\ (X,Y,Z)$ *But* $CV_i\ (X) + CV_i\ (Y) > PV_i\ (X)$ $p_1=1;\ p_2=1$ $q_1=0;\ q_2=1$	Pre-emptive disclosure
$PV_i\ (X, Z) > CV_i\ (X, Z)$, $CV_i\ (Y) > PV_i\ (Y)$ $p_1=1;\ p_2=1$ $q_1=0;\ q_2=1$	Multiple Equilibria

Table 8.12: Summary of Outcomes from the Appropriation Game Model

It is our contention that as biological knowledge structures become complex, researchers and firms should cautiously determine their strategies with respect to upstream discovery research. The greater the complementarity between knowledge structures and applicability across systems, models, or diseases, the greater the need for multiple researchers to access these knowledge structures for downstream product development.

Cognitive biases can lead to the overvaluation of knowledge, specifically, its private value in *future* downstream activities [Heller and Eisenberg, 1998]. Furthermore, firms with stronger financial resources and human capital may be in a better position to exploit upstream knowledge in downstream activities [Heller and Eisenberg, 1998]. Although these firms may not be in position to exploit the knowledge immediately, the anticipation of its future value to the firm may drive the firm to overestimate the private value of

upstream knowledge. This overvaluation would provide the incentive to defect. However, if the overvaluation is incorrect, knowledge may be prematurely appropriated and a downstream user may decline any license to the overvalued patent (and associated knowledge) [Merges, 1994].

In their analysis of patents on biological research tools, Walsh et al. also discuss the concept of "defensive patenting" [Walsh, et al., 2003]. Biotechnology and pharmaceutical executives have confirmed that patenting programs are sometimes defensive with respect to genomics-based technology, as follows:

> We have a defensive patent program in genomics. It is the same as in the Japanese electronics industry. There they patent every nut and screw on a copier, camera, and build a huge portfolio, so Sony never sues Panasonic and Panasonic never sues Sony. There is a little of that going on in genomics. That way, if an IP issue ever arose, we have some cards in our hand.…
>
> I supposed because we see everyone else doing it in part. Sort of like the great Oklahoma Land Rush. If you don't do it you're not going to have any place to set up a tent, eventually [Walsh et al., 2003].

Overall, about a third of industry respondents reported increased patenting of gene sequences, assays, and other research tools as a response to the patenting behaviour of other researchers, so as to augment their own freedom to engage in downstream activities [Walsh et al., 2003].

Merges (1996) argues that each researcher may find defection in his or her own interest, and will therefore expect a partner to similarly defect, unless cooperation is assured. However, unlike the tit-for-tat strategy in the Prisoner's Dilemma game, where a player will always cooperate unless provoked and will retaliate, but quickly forgives the opponent if provoked, the player who is "suckered" may not be so forgiving [Axelrod, 1984]. Players who defect earlier in time may meet reduced success in bargaining with

others who remember past actions. Pre-emptive disclosure as shown in Table 8.8 may be one option to ensure the freedom to operate in downstream development for both players.

An interesting situation arises however, when the common value of what is jointly known increases. In this case, multiple equilibria exist in our game model (Table 8.9). If player 1 chooses defection, player 2's best strategy is to cooperate, and vice versa. Similar to the game of Chicken, if both players choose to defect, both are worse off, receiving the lower payoffs (despite the fact that the private value of what is unilaterally known may be higher than the common value of this knowledge).

While our model begins to demonstrate the importance of evaluating biological knowledge structures as driving the strategic behaviour of firms during knowledge production and dissemination activities, future research is required to augment the model. We need to determine how best to evaluate private and collective knowledge units. Furthermore, we have assumed that the collective value of knowledge is simply the sum of the individual parts; our model may provide alternative insight if we modify the collective value of knowledge to derive from not only the individual parts, but also from the synergy between knowledge units.

In Chapter 9, we assume that knowledge has been patented and consider the licensing options available to both the licensor and potential licensee as knowledge structures change.

Chapter 9: Modeling the Bargaining Process for Appropriated Knowledge

9.1 Introduction

Our model of the strategic licensing environment is adapted from Scotchmer (2004). Figure 9.1 is an extensive form game model of the licensing environment where first inventions have commercial value and are complementary to second generation product development. In other cases, first inventions may have no commercial value (e.g. upstream discoveries) and therefore, the first inventor can only derive value from licensing the technology. In our model, we consider the impact of changing knowledge structures on the licensing decisions taken by the licensor and licensee.

In the model, two players conduct research in sequence. Player 1 develops an invention at a cost of c_1. If the invention is patented for time period T, the discounted private value of this first invention (profit) is x_T (where x_T is only a simple parameter to capture the value of the first invention; future research will consider issues such as the period over the life of the patent during which profits are actually earned and the impact of other competitor products on profits earned). This will be the patent holder's profit. But if the first invention is basic research (upstream research) and will enable downstream product development, it may have no commercial value and therefore x_T=0.

Suppose that player 2 has an idea (y, c_2) for a second generation product that builds on the first invention, where y_T is the discounted private value (profit) of the second generation product (where is y_T only a simple parameter to capture the value of the second generation product), patented for time period T at development cost c_2. In reality, although patents are for 20 years from the date of application, profits may not be earned immediately; products will have to be tested and then manufactured before profits can be earned on the market. Since the second generation invention is facilitated by the first invention, the second invention although patentable, may infringe on the first patent. In this case, player 2 can develop the second generation product without a license on the first invention, but cannot commercialize it. Only if player 2 can substitute for player 1's

invention without infringing the associated patent, can player 2 commercialize the second generation product without a license. In this case, there will be no incentive to bargain with player 1, and player 2 may cut into player 1's profits. If player 2 is able to substitute for the first invention, player 1's profits are now βx_T, where β is the fraction of the market captured by player 1, so that player 2's profits are augmented by $(1-\beta)x_T$.

The two players can either sign a license agreement ex-ante, that is, before player 2 invests c_2 (but after the first innovation has been made) or ex-post, after player 2 invests c_2. The terms of the license will be the outcome of bargaining, which will depend on the threat points for each player and bargaining surplus. The threat point, each player's BATNA (Best Alternative to Negotiated Agreement), is the expected profit it can guarantee if it leaves the bargaining table. The bargaining surplus is the total amount by which the players will be richer if bargaining is successful. For example, ex-post, the two players' threat points are $x_T - c_1$ and $-c_2$ respectively because, without a license, the second generation product cannot come to market as it is blocked by the patent on the first invention. On the other hand, if a license is issued, player 1 and 2 can add αy_T and $(1-\alpha)y_T$ respectively to their profits, where α is the fraction of the bargaining surplus going to player 1. Each player can guarantee itself at least the amount of the threat point. However, central to a successful outcome (where success refers to the option of pursuing downstream product development) is how to divide the bargaining surplus. In our model, this bargaining surplus will vary with type of license issued (non-exclusive or exclusive) and the timing of the license (ex-ante or ex-post). Ideally, a system should ensure that both players are rewarded for their contributions. In particular, the investment made to develop the first invention should permit the second generation product to be developed and profitable.

Whether or not a license is issued and accepted ex-ante will be depend on the division of the bargaining surplus, the cost of developing the second generation product, and the ability of player 2 to substitute for the first invention. Furthermore, if player 1 is relatively uninformed about the value and costs associated with the development of the second generation product ex-ante, he/she may be unwilling to allow ex-ante licensing.

In our model, we explore the impact of knowledge characteristics on the licensing process. (Analysis 9.1) We consider various scenarios in which the first invention has no commercial value alone, in which the first invention is substitutable without infringement, in which the cost of production of the second generation is high and the market applicability low, and in which there is asymmetric information regarding the value of the second generation product. We present the case where $x_T>0$ in Figure 9.1; however, by setting $x_T=0$ in Figure 9.1, we can derive the licensing model where the first invention has no commercial value.

9.2 Model Parameters

We define the following notation in our model (Table 9.1):

Notation	Definition
x_T	Discounted Value of First Invention (Private Profit earned over the Life of the Patent)
y_T	Discounted Value of Second Generation Product (Private Profit earned over the Life of the Patent)
T	Length of Patent
α	Fraction of Bargaining Surplus
NE	Non-Exclusive
E	Exclusive
$\alpha_{NE(ex\text{-}ante/ex\text{-}post)}$	Fraction of Bargaining Surplus from a Non-Exclusive license (assigned either ex-ante or ex-post)
$\alpha_{E(ex\text{-}ante/ex\text{-}post)}$	Fraction of Bargaining Surplus from an Exclusive license (assigned either ex-ante or ex-post)
c_1	Cost of First Invention
c_2	Cost of Second Generation Product
c_d	Cost of Duplication of First Invention
C	Complementary
S	Substitutable
NS	Non-substitutable
HA	High Applicability
LA	Low Applicability
β	Fraction of Market Captured by Player 1
p_d	Probability of Duplication

Table 9.1: Bargaining Game Model Notation

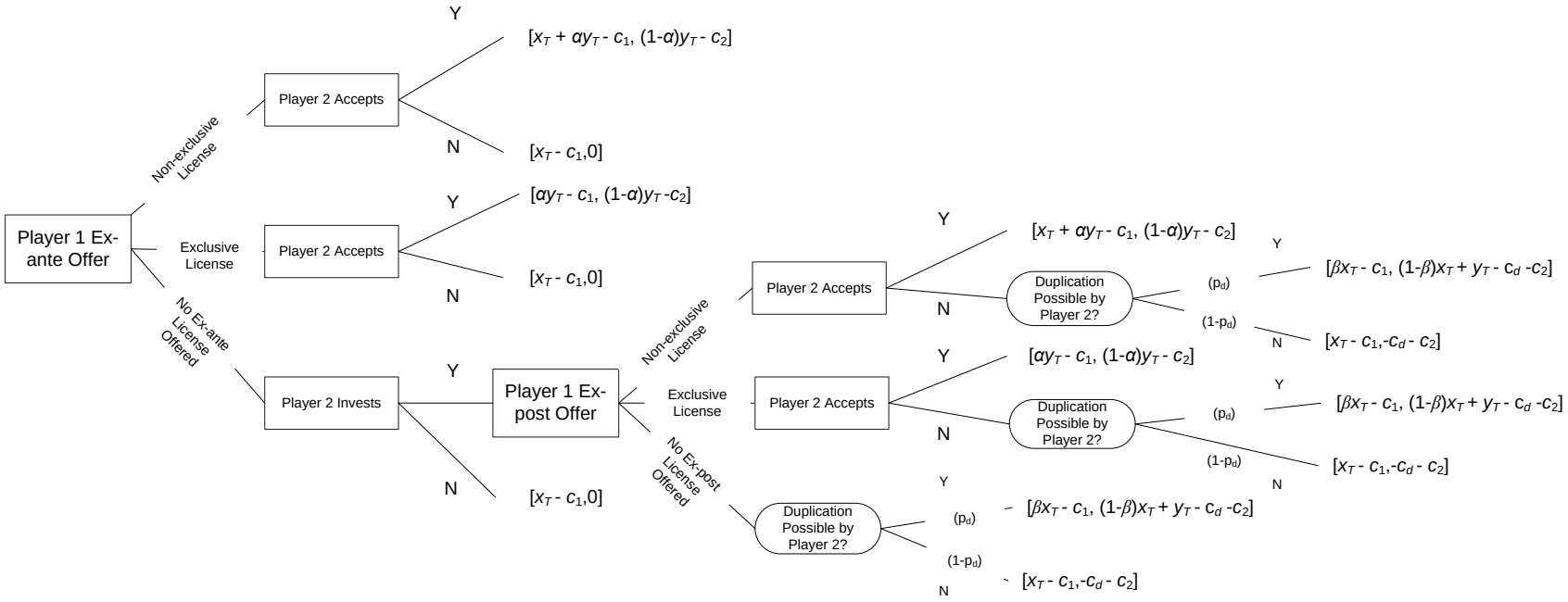


Figure 9.1: Strategic Licensing Process where x_T>0

9.3 Model Analysis

In this section, we analyze possible outcomes if player 1 offers a license ex-ante (before player 2 makes an investment), if player 1 offers a license ex-post (after player 2 makes an investment), or if player 1 chooses not to offer a license.

9.3.1 Ex-ante Licensing

If player 1 chooses to offer a non-exclusive license to player 2 for the first invention, then player 2 will accept this license if $(1 - \alpha_{NE})y_T - c_2 > 0$.

If player 1 chooses to offer an exclusive license to player 2 for the first invention, then player 2 will accept this license if $(1 - \alpha_E)y_T - c_2 > 0$.

We assume that the fraction of the bargaining surplus offered to player 2 will be different in the non-exclusive (NE) vs. exclusive (E) license setting. Generally, player 1 will demand a larger fraction of the bargaining surplus if an exclusive license is offered.

Player 1 will choose to offer a non-exclusive license rather than an exclusive license if $x_T - \alpha_{NE}y_T - c_1 > \alpha_E y_T - c_1$, which is equivalent to $x_T - \alpha_{NE}y_T > \alpha_E y_T$; player 1 will offer an exclusive license if the reverse inequality is true.

9.3.2 Player 2's Decision to Invest Ex-post

If player 1 opts not to offer an ex-ante license (assuming that he/she will be able to receive a larger fraction of the bargaining surplus once player 2 invests c_2), player 2 will have to decide whether to invest in research on the second invention assuming that the first invention is complementary to the second invention and a license will be required (in order to commercialize the second invention). We assume that player 2 will not know if duplication of or a work-around solution for the first invention is possible until an investment is made and research is conducted.

In the case that duplication is not possible and a license is required from player 1, player 2 will invest in research if $(1 - \alpha_{NE})y_T - c_2 > 0$ in the case that a non-exclusive license is issued; or if $(1 - \alpha_E)y_T - c_2 > 0$ in the case that an exclusive license is issue.

In the case that duplication or a work-around solution is possible, player 2 will invest in research as long as $(1 - \beta)x_T + y_T - c_d - c_2 > 0$, where if β is the fraction of the market that is captured by player 1 and $(1-\beta)$ is the fraction of the market that is captured by player 2 for the (duplicated, non-fringing) first invention.

9.3.3 Ex-post Licensing

Once player 2 decides to make an investment in research, player 1 will either offer an ex-post exclusive license, an ex-post non-exclusive license, or will opt not to offer an ex-post license altogether.

In the case that duplication is not possible and a license is required for the first invention, if player 1 chooses to offer a non-exclusive license to player 2 for the first invention, then player 2 will accept this license if $(1 - \alpha_{NE})y_T - c_2 > 0$.

In the case that duplication is possible, in the simple case we assume the probability of duplication or work-around (p_d) equals 1, as long as $(1 - \beta)x_T + y_T - c_d - c_2 > (1 - \alpha_{NE})y_T - c_2$, which is equivalent to $(1 - \beta)x_T + y_T - c_d > (1 - \alpha_{NE})y_T$, then there is no incentive for player 2 to bargain for a non-exclusive license with player 2. However, as the cost of duplication rises and the probability of duplication decreases, then player 2's incentive to bargain for a license will likely increase.

In the case that duplication is not possible and a license is required for the first invention, if player 1 chooses to offer an exclusive license to player 2 for the first invention, then player 2 will accept this license if $(1 - \alpha_E)y_T - c_2 > 0$.

In the case that duplication is possible, in the simple case we assume the probability of duplication or work-around (p_d) equals 1, as long as $(1 - \beta)x_T + y_T - c_d - c_2 > (1-\alpha_E)y_T - c_2$,

which is equivalent to $(1 - \beta)x_T + y_T - c_d > (1 - \alpha_E)y_T$, then there is no incentive for player 2 to bargain for an exclusive license with player 2. However, as the cost of duplication rises and the probability of duplication decreases, then player 2's incentive to bargain for a license will likely increase.

Player 1 will choose to offer a non-exclusive license rather than an exclusive license (assuming that duplication by player 2 is not possible) if $x_T - \alpha_{NE}y_T - c_1 > \alpha_E y_T - c_1$, which is equivalent to $x_T - \alpha_{NE}y_T > \alpha_E y_T$; player 1 will offer an exclusive license if the reverse inequality is true.

In the case that player 2 is able to duplicate or work-around the first invention without infringing it, then player 1 will be left with the payoff of $\beta x_T - c_1$ regardless of license setting (non-exclusive vs. exclusive).

9.3.4 Player 1's Decision to Not Offer an Ex-Post License

Assuming that duplication is not possible, player 1 may opt not to offer a license to the first invention even ex-post after player 2 has made an investment. This may be the case when the first invention has high stand-alone commercial value or will have high commercial value once player 1 completes further development work. In either case, the first invention can be assumed to have high value for player 1.

In the case of opting not to offer an ex-post exclusive license, this will be true when $x_T - c_1 > \alpha_E y_T - c_1$, which is equivalent to $x_T > \alpha_E y_T$; therefore, as long as the payoff attained by player 1 from internal commercial exploitation is greater than the payoff attained through exclusive licensing, then player 1 will opt to not offer an ex-post exclusive license.

In the case of an ex-post non-exclusive license, player 1 will have to choose whether the additional income gained from licensing is of value in comparison to just internal commercial exploitation of the first invention, since $x_T + \alpha_{NE}y_T - c_1$ will always be greater than $x_T - c_1$.

9.3.5 Player 1's Decision to Offer an Ex-Ante vs. Ex-Post License

Player 1 will have to decide whether to offer an ex-ante license, an ex-post license, or no license (these are the decisions available to player 1 at the first node).

An ex-ante non-exclusive license will be offered if

$(x_T + \alpha_{NE \text{ ex-ante}}\, y_T - c_1) > (\alpha_{E \text{ ex-ante}}\, y_T - c_1)$ **and**

$(x_T + \alpha_{NE \text{ ex-ante}}\, y_T - c_1) > (x_T + \alpha_{NE \text{ ex-post}}\, y_T - c_1)$ or $> (\alpha_{E \text{ ex-post}}\, y_T - c_1)$ or $> (x_T - c_1)$ or $> (\beta x_T - c_1)$

An ex-ante exclusive license will be offered if

$(\alpha_{E \text{ ex-ante}}\, y_T - c_1) > (x_T + \alpha_{NE \text{ ex-ante}}\, y_T - c_1)$ **and**

$(\alpha_{E \text{ ex-ante}}\, y_T - c_1) > (x_T + \alpha_{NE \text{ ex-post}}\, y_T - c_1)$ or $> (\alpha_{E \text{ ex-post}}\, y_T - c_1)$ or $> (x_T - c_1)$ or $> (\beta x_T - c_1)$

An ex-post non-exclusive license will be offered assuming player 2 invests in research, but duplication of the first invention is not possible, if

$(x_T + \alpha_{NE \text{ ex-post}}\, y_T - c_1) > (\alpha_{E \text{ ex-post}}\, y_T - c_1)$ **or** $> (x_T - c_1)$ **and**

$(x_T + \alpha_{NE \text{ ex-post}}\, y_T - c_1) > (x_T + \alpha_{NE \text{ ex-ante}}\, y_T - c_1)$ **or** $> (\alpha_{E \text{ ex-ante}}\, y_T - c_1)$

An ex-post exclusive license will be offered assuming player 2 invests in research but duplication of the first invention is not possible, if

$(\alpha_{E \text{ ex-post}}\, y_T - c_1) > (x_T + \alpha_{NE \text{ ex-post}}\, y_T - c_1)$ **or** $> (x_T - c_1)$ **and**

$(\alpha_{E \text{ ex-post}}\, y_T - c_1) > (x_T + \alpha_{NE \text{ ex-ante}}\, y_T - c_1)$ **or** $> (\alpha_{E \text{ex-ante}}\, y_T - c_1)$

If duplication is possible, then the outcome will depend on p_d. If p_d equals 1, then player 1 will have no choice but to accept $(\beta x_T - c_1)$ ex-post. Player 1 will then have to analyze which payoff is greater—an ex-ante non-exclusive license or an ex-ante exclusive license, given that player 2 can duplicate or work-around the first invention. As p_d decreases or the cost of duplication (c_d) increases, an ex-post license may be accepted by player 2 as described in section 9.3.3.

9.4 Bargaining for Upstream Knowledge

In this section, we analyze the licensing strategy adopted for upstream knowledge as we vary the underlying knowledge characteristics of the first invention—namely, substitutability, and applicability. We assign values to the parameters outlined in Table 9.1 to illustrate the bargaining process when the initial discovery has no commercial value.

A first invention may represent a research input e.g. gene or drug target. The follow-on inventor may use the research input to develop a downstream product e.g., diagnostic based on the gene, or a drug that binds to the target discovered by the first innovator. In this case, the first invention has high complementarity, high applicability, and is non-substitutable. Therefore, the follow-on innovator will require a license in order to progress downstream into product development. Given these knowledge characteristics, it would be in player 1's best interests to issue an exclusive license after player 2 has made an investment into product development. In this case, player 1 will be able to demand a larger share of the bargaining surplus by issuing an ex-post exclusive license. In Model 1 (Figure 9.2), given the values set for the model parameters, player 1 indeed receives the largest payoff by offering an ex-post exclusive license to player 2.

If this game model is broken into "sub-games" containing a sub-set of all the available choices in the main game, it is possible to find a subgame perfect Nash equilibrium strategy. In this case, if the players play any smaller game that consists of only one part of the larger game and their behaviour represents a Nash equilibrium of the smaller game, then their behaviour is a subgame perfect equilibrium of the larger game. A subgame perfect equilibrium is a prescription for rational behaviour. [Kilgour, 2006] In model 1, the subgame perfect equilibrium is the path through *player 1 not offering an ex-ante license, but player 2 making an investment, player 1 then offering an exclusive license and player 2 accepting the ex-post exclusive license* with utility [21, 1]. This outcome then assumes that both players are behaving rationally from a game perspective. Given the characteristics of knowledge in this game model, the decision to offer an ex-post exclusive license should indeed be the strategy chosen by the players.

In contrast, 30 out of the 39 consortia analyzed in Chapter 6, use or plan to use databases to provide access to upstream genomic, proteomic, systems, biochemical and/or cell biology information. As this data is often high in complementarity, non-substitutable, and high in downstream applicability, these consortia address the open dissemination of data as part of their rules for the sharing of information with members and with the public at large. (Table 6.6)

In Model 2 (Figure 9.3), the first invention represents a research input with no commercial value—highly complementary and non-substitutable, however in this case, the target market to which the follow-on innovator can apply this knowledge in downstream products is small. Hence, the first invention has low applicability. In this case, player 2 may choose not to invest in the development of the second-generation product. Hence, player 1 will be left with a loss since the first invention does not have commercial value on its own. Consequently, player 1 may have to bargain with player 2 over the surplus to be shared, i.e., to provide player 2 with an incentive to invest in downstream product development. In model 2, the subgame perfect equilibrium is the path through *player 2 not accepting an ex-ante non-exclusive or exclusive license or the path through player 2 not investing* with utility [-10, 0]. Given the characteristics of knowledge and the costs associated with development of invention 2, player 2 should not invest in this innovation; unless player 1 provides an incentive that will be enable player 2 to recoup his/her costs and enjoy a positive return, player 2 will not invest in any R&D activities, leaving player 1 with a payoff of -10.

In the United States, an orphan drug is a drug developed to treat rare diseases ("orphan diseases"), defined as diseases affecting fewer than 200,000 people in the United States [www.fda.gov, 2007]. Since developing drugs to treat such diseases is financially disadvantageous, companies engaging in such development activities are rewarded with tax reductions and marketing exclusivity on such drugs for an extended time period (seven years post-approval). These incentives are thought to encourage companies to invest in research activities targeting these small markets. The model we present in Figure 9.4 demonstrates this need to provide incentives to player 2 to engage in

downstream product development given the high costs and likely low profits associated with the downstream market.

Ex-ante
x_T=0
α_{NE}=2/5
α_E=3/5
y_T=30
c_1 =3
c_2 =5

Model 1

Knowledge Type
x_T=0; C, NS, HA
e.g. research input-gene or drug target

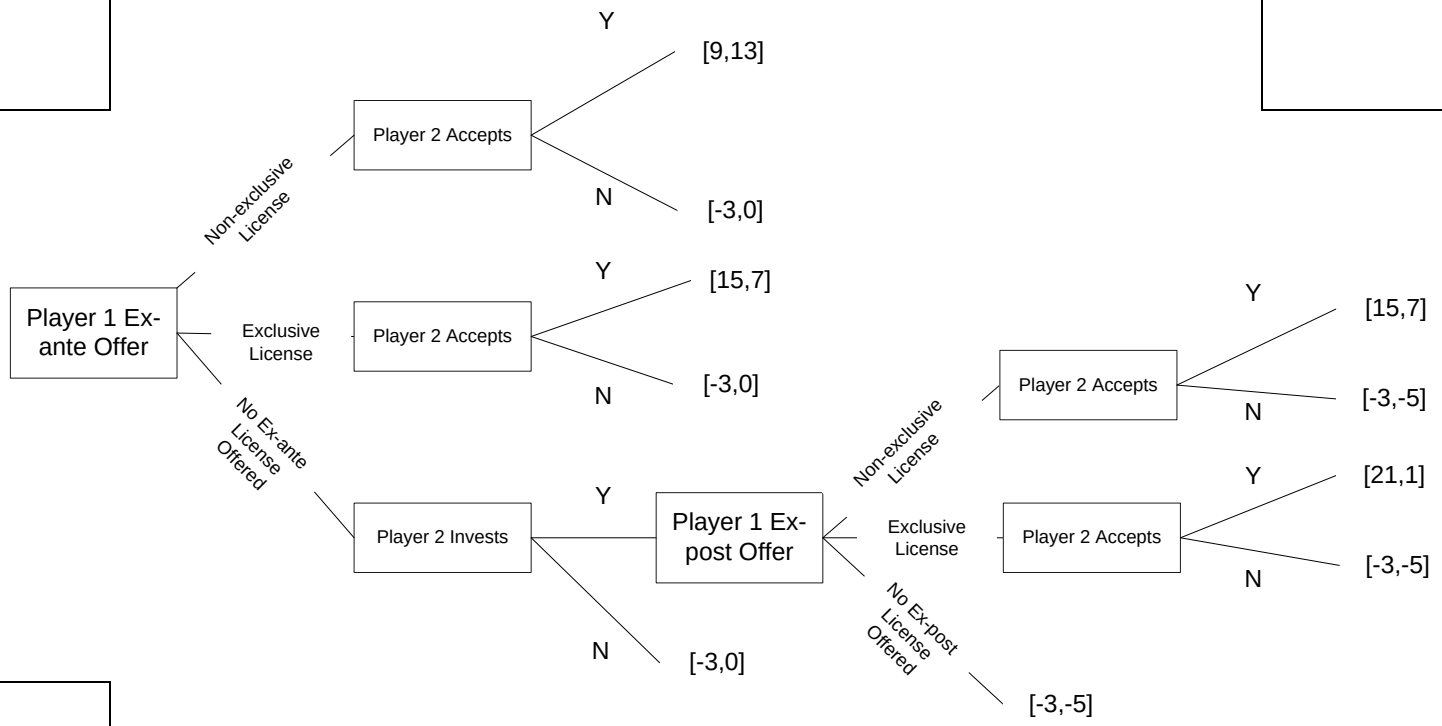


Figure 9.2: Licensing a Non-Substitutable Research Input

Ex-post
xT=0
α_{NE}=3/5
α_E=4/5
yT=30
c_1 =3
c_2 =5
Substitutable =NO

Ex-ante
x_T=0
α_{NE}=3/5
α_E=4/5
y_T=20
c_1 =10
c_2 =15

Model 2

Knowledge Type
x_T=0; C, NS, LA;
Target Market
Small

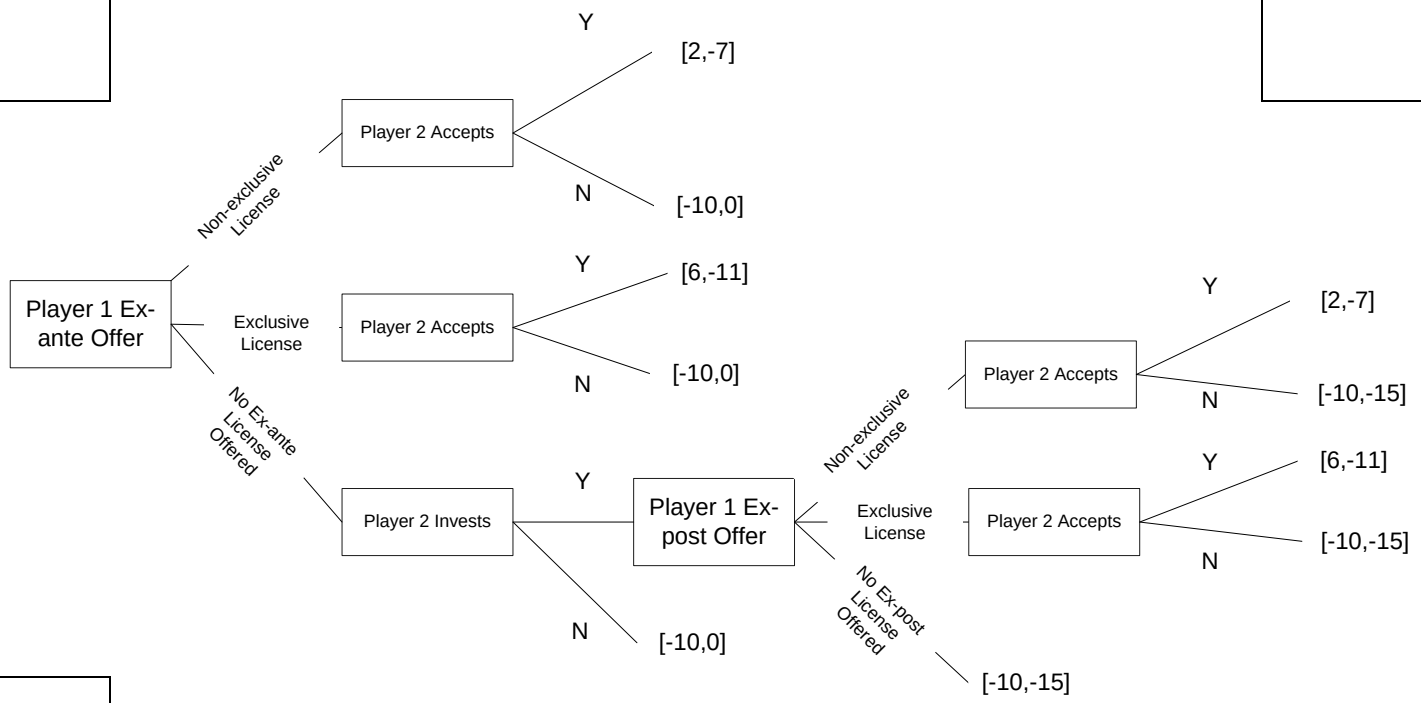


Figure 9.3: Licensing a Non-Substitutable Research Input with Low Applicability

Ex-post
x_T=0
α_{NE}=3/5
α_E=4/5
y_T=20
c_1 =10
c_2 =15
Substitutable =NO

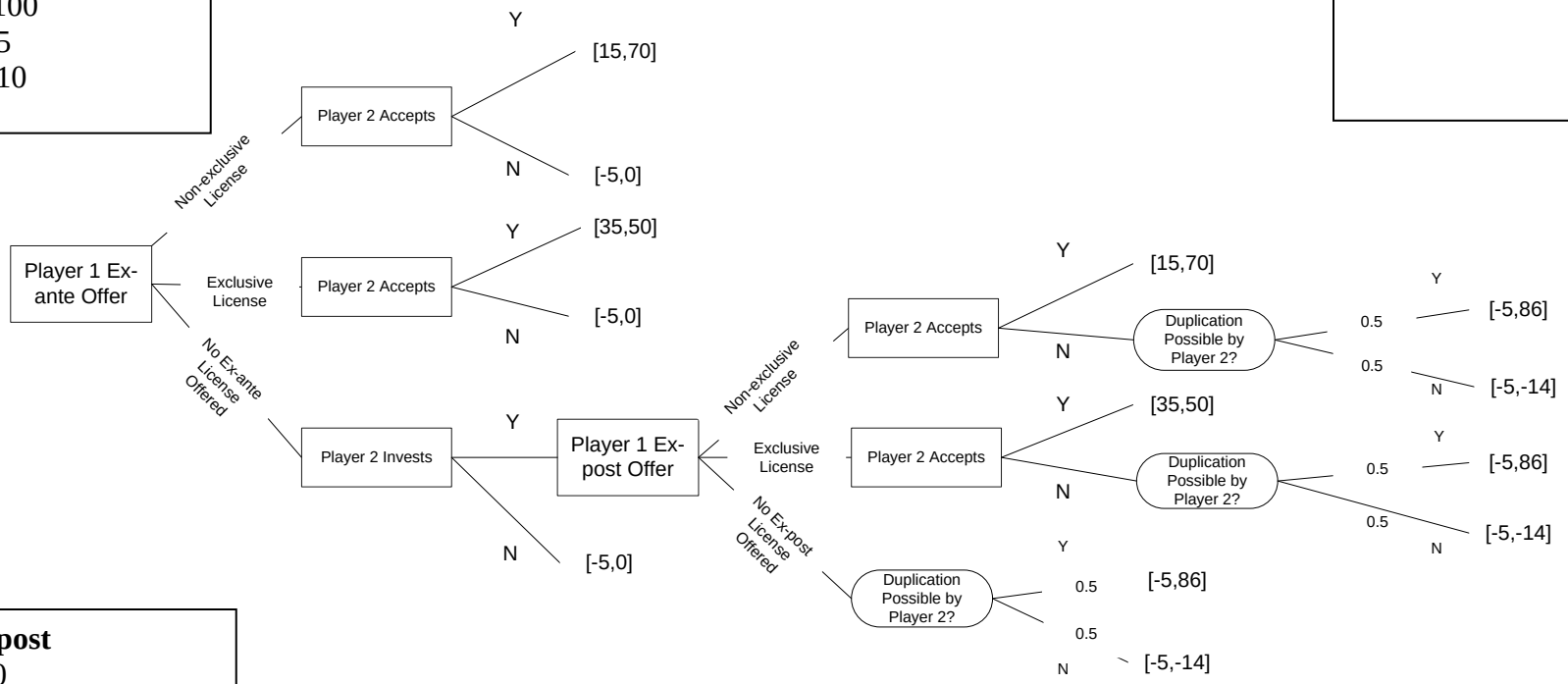
In Model 3 (Figure 9.4), once again the first invention represents a research input with no commercial value—high in complementarity and applicability, but now substitutable by player 2. Here we introduce the possibility that player 2 can duplicate the first invention (or develop a work-around solution without infringing on player 1's patent) with probability p_d. When p_d equals 1, there is no uncertainty associated with duplicating or creating a work-around solution for the first invention; thus, player 2 no longer has an incentive to bargain with player 1 for a license. When p_d equals 0.5, player 1 has an incentive to offer an ex-ante non-exclusive license to player 2 for the research input—thereby ensuring a share of the large private value (profits) associated with the follow-on invention. In model 3, interestingly, the subgame perfect equilibrium is the path through *player 1 offering an ex-ante exclusive license and player 2 accepting this license* with utility [35, 50]. If player 1 however, chooses to instead offer an ex-ante non-exclusive license for the above reasons, player 1 is off the equilibrium pathway. [Kilgour, 2006]

From our consortium analysis, we identified 16 consortia where tools, biomaterials, and/or reagents (high in complementarity, in applicability, and in substitutability) are a either a direct outcome or byproduct of consortia member research. In these consortia, rules exist to address the sharing of these items with members and the public at large. These rules advocate sharing of materials for consortium research, ensuring access to open repositories where animal models are housed, or providing for the wide, public dissemination of materials via non-exclusive, royalty-free licenses; only in a few cases is access to tools restricted to members. (Table 6.6)

Ex-ante
x_T=0
α_{NE}=1/5
α_E=2/5
y_T=100
c_1 =5
c_2 =10

Model 3

Knowledge Type
x_T=0; C, S, HA



Ex-post
x_T=0
α_{NE}=1/5
α_E=2/5
y_T=100
c_1 =5
c_2 =10
c_d =4
Substitutable =YES
β =N/A (operating in different markets)
p_d =0.5

Figure 9.4: Licensing a Substitutable Research Input

While player 1 may be better off by offering an ex-post exclusive license in the case where the first invention has no commercial value but is high in applicability and is non-substitutable, this option is not the best one when the size of the market changes and if player 2 can substitute for the first invention. As the market size changes in Model 2, with higher costs and lower profits associated with downstream development, player 1 may be better off to offer an ex-ante license with a bargaining surplus that favours downstream development. If player 2 can substitute for the first invention—the case for Model 3, assuming that there is some uncertainty associated with duplication—player 1 is better off by offering an ex-ante *non-exclusive* license to player 2. Clearly, player 1 needs to evaluate the knowledge characteristics associated with the first invention in deciding the best licensing approach. As the only source of revenue from the first invention in these cases is licensing, player 1 needs to set licensing terms that encourages downstream product development.

In section 9.5 we now consider licensing scenarios where the first invention has commercial value for both player 1 and player 2.

9.5 Bargaining for Downstream Knowledge

Models 4 through to Models 7 (Figures 9.5 to 9.8) analyze the bargaining process when the first invention has commercial value. In some cases the first invention is non-substitutable, whereas in others player 2 can substitute for the first invention. We also analyze the impact of the licensing strategy adopted when the technologies are compatible with each other and are appropriate for joint marketing, and by giving players asymmetric information regarding the value of the second invention.

In Model 4 (Figure 9.5) we assume that a downstream technology is being licensed by player 2. For example, player 2 may be licensing the right to develop and use a slightly different diagnostic that depends on a technology patented by player 1. In this case, player 1 is better off offering an ex-post non-exclusive license—whereby he/she can generate additional rent from player 2. It is the non-substitutability of the first invention

and the fact that player 1 can also pursue downstream development that allows player 1 to demand an ex-post non-exclusive license. In model 4, the subgame perfect equilibrium is the path through *player 1 not offering an ex-ante license, but player 2 investing, player 1 then offering an ex-post non-exclusive license and player 2 accepting this license* with utility [43, 5].

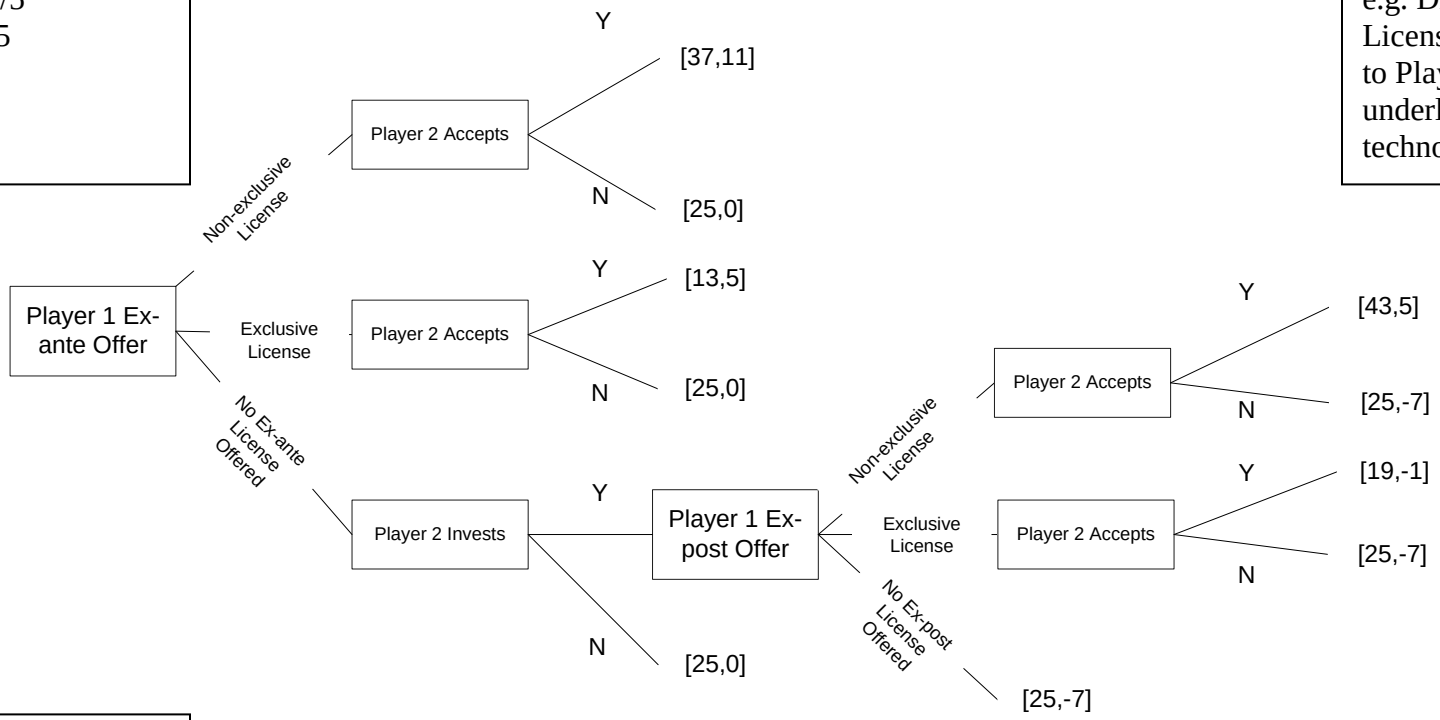
In Model 5 (Figure 9.6), the first invention is substitutable. We set p_d to 1—indicating that player 2 is guaranteed a successful outcome from duplication or a work-around strategy. In this case, we assume that player 2 will operate in the same market as player 1 with the understanding that there may be a fraction of this market split between the two players—with player 2 able to tap into player 1's profits. With the threat of guaranteed duplication by player 2, player 1 will have to be flexible on the bargaining surplus split between the two players, as there is no real incentive for player 2 to enter into bargaining. We anticipate, however that as the cost of duplication increases, the incentive to enter into bargaining will increase as well. Player 1 is better off in this case by offering an ex-ante non-exclusive license. In model 5 with p_d set to 1, the subgame perfect equilibrium is the path through *player 1 not offering an ex-ante non-exclusive or exclusive license, but player 2 investing and duplicating or working-around the first invention* with utility [26, 39]. If player 1 chooses to offer an ex-ante non-exclusive license, although he/she is off the equilibrium pathway, player 1 may make plans at this node in order to ensure that bargaining can take place between the two players. If we set p_d set to 0.5, interestingly the subgame perfect equilibrium is the path through *player 1 not offering an ex-ante non-exclusive or exclusive license, but player 2 investing, player 1 then offering an ex-post non-exclusive license and player 2 accepting this license* with utility [50, 19].

Therefore, in Models 4 and 5 while player 1 is better by offering a non-exclusive license so that he/she can also develop and market the first invention, the substitutability of the first invention will determine whether an ex-post or ex-ante non-exclusive license is issued.

Model 4

Ex-ante
x_T=30
α_{NE}=2/5
α_E=3/5
y_T=30
c_1 =5
c_2 =7

Knowledge Type
x_T>0; C, NS, HA
e.g. Diagnostic; License is issued to Player 2 to use underlying technology



Ex-post
x_T=30
α_{NE}=3/5
α_E=4/5
y_T=30
c_1 =5
c_2 =7
Substitutable=NO

Figure 9.5: Licensing a Non-Substitutable Downstream Technology

Ex-ante
x_T=40
α_{NE}=1/5
α_E=3/5
y_T=40
c_1 =6
c_2 =5

Model 5

Knowledge Type
x_T>0; C, S, HA
e.g. RNAi Technology vs. Gene Silencing; Both target the same market

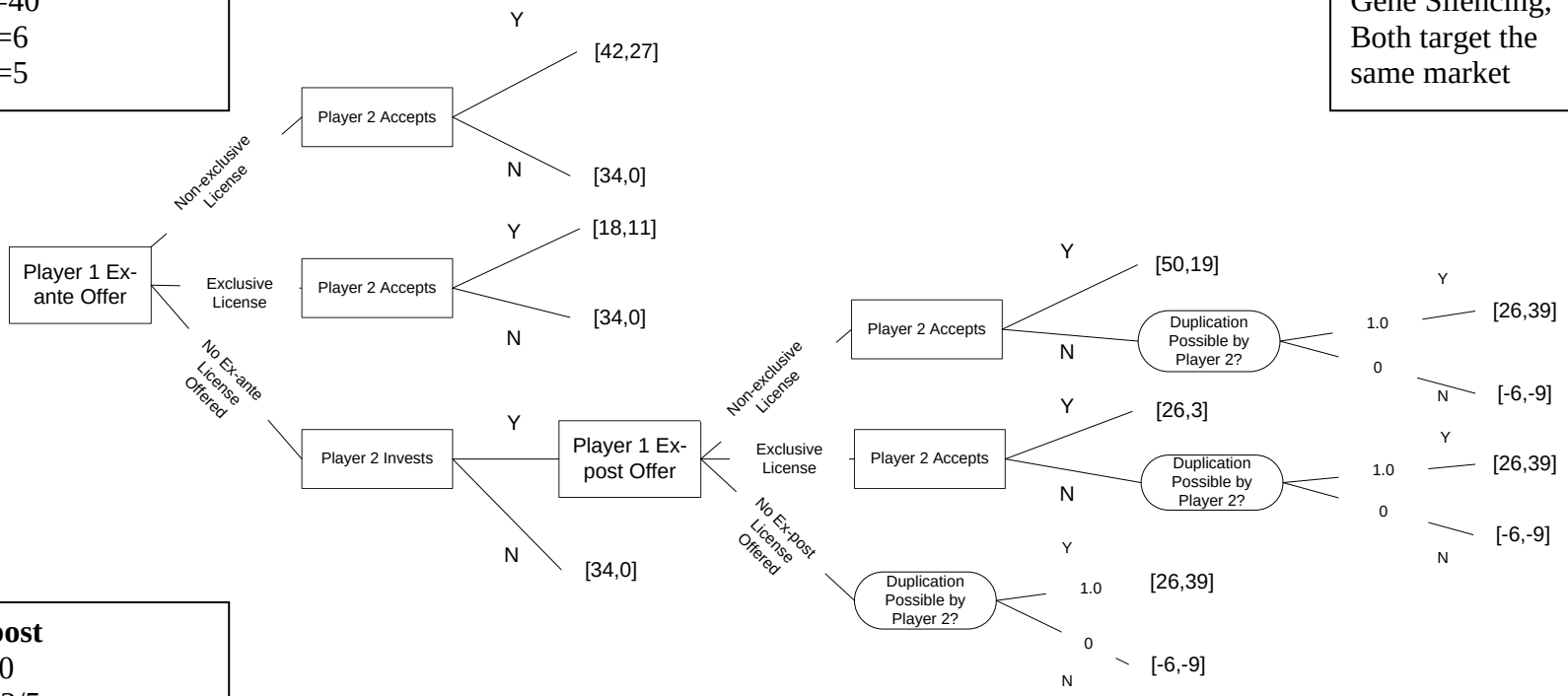


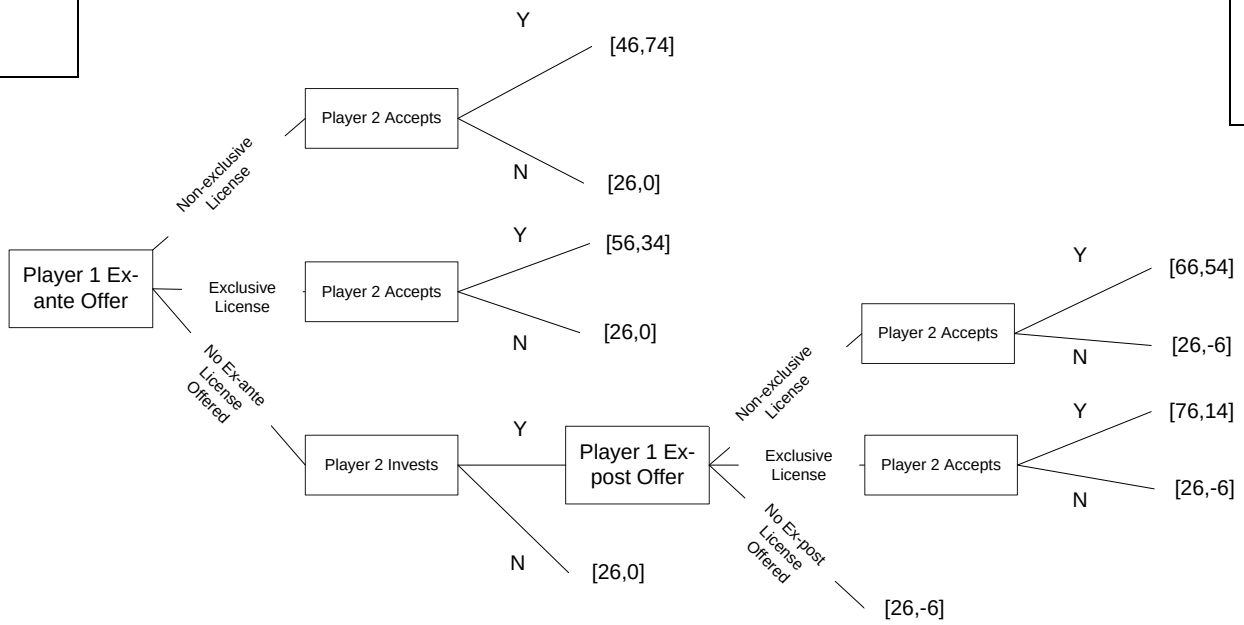
Figure 9.6: Licensing a Substitutable Downstream Technology

Ex-post
x_T=40
α_{NE}=2/5
α_E=4/5
y_T=40
c_1 =6
c_2 =5
c_d =4
Substitutable =YES
β =4/5 (Same Market)
p_d =1

As medical treatment becomes more complex, a situation may arise where multiple technologies are used by a doctor to diagnose and then treat a disease. Pharmacogenomics is the study of the genetic variations or single nucleotide polymorphisms (SNP) between individuals that are associated with common diseases and linked to drug responses [Akhtar, 2002]. Pharmacogenomics will identify candidate genes and polymorphisms, predict drug responses and clinical outcomes in order to reduce adverse reaction events, and enable for doses of therapeutic drugs to be decided on the basis of a patient's genotype [Akhtar, 2002]. Pharmacogenomics will change the current drug discovery and development process as customized drugs are developed for defined sub-populations of patients and perhaps even tailored for specific individuals. In the age of personalized medicine, there may soon be a market where patients are first screened for disease susceptibility based on genomic profile and then treated accordingly. Consequently, medical diagnostic and biopharmaceutical companies may align to jointly develop and market the appropriate technologies. In Model 6 (Figure 9.7), we assume that greater value is attained through the joint marketing of the first invention and follow-on invention. With y_T also large, player 1 receives a larger payoff by offering an ex-post exclusive license to player 2, so that he/she can jointly market the two products. In Model 6, the subgame perfect equilibrium is the path through *player 1 not offering an ex-ante license, but player 2 making an investment, player 1 then offering an exclusive license and player 2 accepting the ex-post exclusive license* with utility [76, 14].

Ex-ante
x_T=30
α_{NE}=1/5
α_E=3/5
y_T=100
c_1 =4
c_2 =6

Model 6



Knowledge Type
x_T>0; C, NS, HA
e.g. SNP Based Diagnostic; Greater Value from Joint Marketing

Ex-post
x_T=30
α_{NE}=2/5
α_E=4/5
y_T=100
c_1 =4
c_2 =6
Substitutable =NO

Figure 9.7: Licensing Downstream Compatible Technology

In Model 7 (Figure 9.8) player 1 has private information regarding the value of y_T. Player 1 knows that the follow-on invention has high applicability and hence high profit potential. As a result of this prior information, player 1's probability that the second invention has high applicability and high profit is greater than player 2's probability. As a result of this asymmetry, and based on our assumptions regarding parameter values, player 1 may choose to offer an exclusive license while player 2 expects a non-exclusive license. Player 1 must handle this asymmetry in information carefully in order to maximize his payoff—as player 2 will be expecting a payoff of 33 from a non-exclusive license versus a payoff of 17 from an exclusive license. In Model 7, from player 1's perspective the subgame perfect equilibrium is the path through *player 1 offering an exclusive license with player 2 accepting this license* with utility [230 (38), 145(17); depending on player perspective]. From player 2's perspective the subgame perfect equilibrium is the path through player 1 offering a non-exclusive license and player 2 accepting this license with utility [190 (62), 225 (33); depending on player perspective].

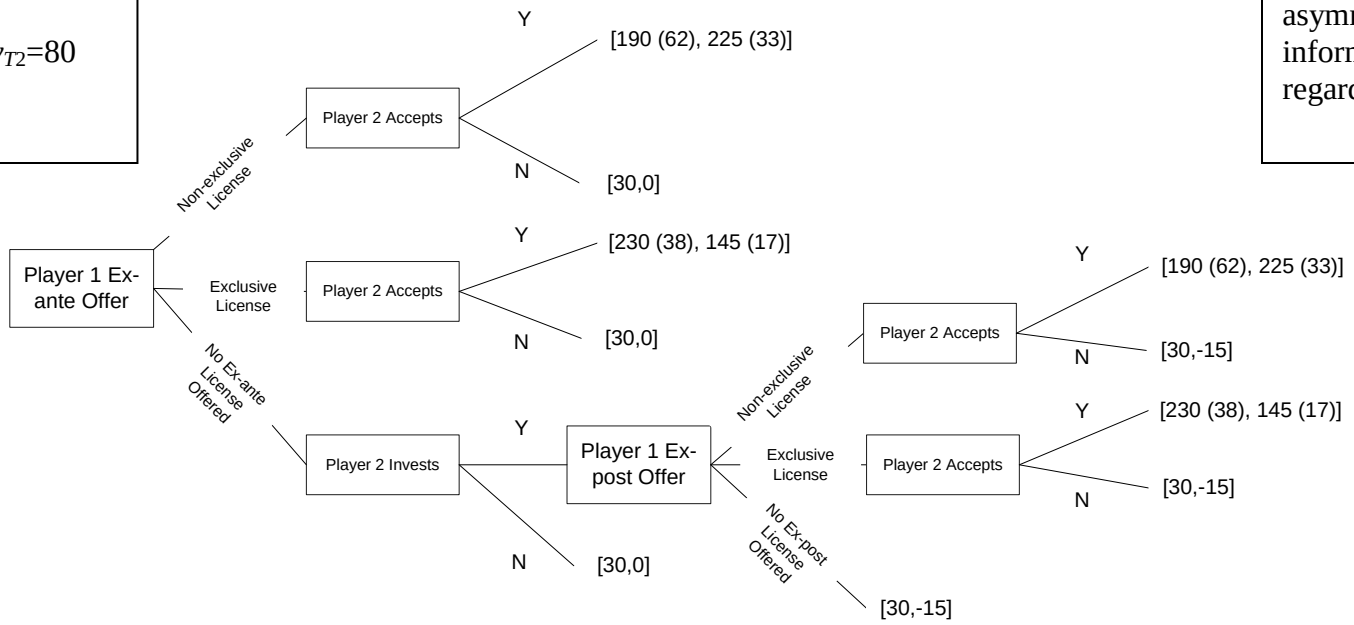
Differences in the ability to tolerate the transaction costs associated with licensing complicate the bargaining process. Large corporations with substantial resources will be in a better position to negotiate licenses on a case-by-case basis than public sector institutions or small startup firms. This asymmetry may make it difficult to develop mutually advantageous licensing agreements [Heller and Eisenberg, 1998]. Heller and Eisenberg also discuss that "cognitive biases" can cause a patent holder to overvalue his/her patent for future downstream research [Heller and Eisenberg, 1998]. The downstream user may decline the knowledge, with the possibility that critical technological opportunities will not be exploited in downstream research and product development.

The majority of consortia studied in Chapter 6 have as their objective the collective production of upstream disembodied or upstream embodied knowledge in the form of research inputs or tools. The models in this chapter, however, provide insight on how consortium members individually or collectively focus on downstream product development. Once consortium objectives are achieved and membership is terminated,

firms can easily become competitors on the product marketplace. It is at this *transition point* that the licensing strategies adopted by firms can be expected to maximize the private value of their knowledge.

Ex-ante
x_T=40
α_{NE}=2/5
α_E=3/5
y_{T1}=400; y_{T2}=80
c_1 =10
c_2 =15

Model 7



Knowledge Type
x_T>0; C, NS, HA; Player 1 has asymmetric information regarding y_T

Ex-post
x_T=40
α_{NE}=2/5
α_E=3/5
y_{T1}=400; y_{T2}=80
c_1 =10
c_2 =15
Substitutable =NO

Figure 9.8: Licensing Downstream Technology with Asymmetric Information

9.6 Discussion

The sequence of bargaining models is our attempt to explore the implications of licensing as knowledge structures and paradigms evolve. Table 9.2 summarizes outcomes of various licensing scenarios according to our analysis, given our assumption regarding the value of first innovations and second-generation products, as well ex-ante and ex-post bargaining surplus divisions.

Licensing Scenario	Outcome
Licensing a Non-substitutable Research Input; x_T=0; C, NS, HA	Ex-post exclusive license
Licensing a Non-substitutable Research Input with Low Downstream Applicability; x_T=0; C, NS, LA	No investment by player 2; Room for bargaining by player 1
Licensing a Substitutable Research Input; x_T=0; C, S, HA	Ex-ante non-exclusive license
Licensing a Non-substitutable Downstream Technology; x_T>0; C, NS, HA	Ex-post non-exclusive license
Licensing Substitutable Downstream Technology; x_T>0; C, S, HA	Ex-ante non-exclusive license
Licensing Downstream Compatible Technology; x_T>0; C, NS, HA	Ex-post exclusive license
Licensing Downstream Technology with Asymmetric Information; x_T>0; C, NS, HA	Player 1 offers an exclusive license; Player 2 expects a non-exclusive license

Table 9.2: Summary of Outcomes from the Bargaining Model

From the consortium analysis, we determined how various licensing agreements are employed to disseminate (in most cases) embodied knowledge in the form of tools, biomaterials, and reagents, as well as copyrighted material. Options include: the nonexclusive license to share tools, biomaterials, and reagents; the MIT license or Creative Commons license to share copyrighted materials such as software code or databases; the BIOS license to enable downstream product development; the Click-wrap license to indicate agreement to the terms set by a consortium; the Patent pool as a means of bypassing the complexities associated with intellectual property negotiations; and geographic-based licensing to provide an incentive for a licensee to develop a product for specific regional markets. (See Chapter 6)

Table 9.3 compares and contrasts the strategies used by the consortia to manage various knowledge structures and the strategies suggested by our bargaining model as a function of these knowledge structures. From this analysis, it appears that the consortia are using rules that encourage licensing strategies with the greatest *collective* value (and in turn greatest social value), rather than providing the greatest unilateral, private value to a single firm—as is the case with our model.

Consortium	Knowledge Characteristic	Licenses Advocated by Consortium	Licenses Advocated by Bargaining Model
Beta Cell Biology Consortium (BCBC)	HC, NS, HA	Freely Distributed to Academic for Non-Commercial Use	Licensing a Research Input; x_T=0; C, NS, HA; Ex-Post, Exclusive License
Biological Innovation for Open Society (BIOS)	HC, S, HA	Royalty Free, Non-Exclusive Licenses Among Participants	Licensing Substitutable Downstream Technology for Use in Different Markets; x_T>0; C, S, HA; Ex-Ante, Non-Exclusive License
Cell Migration Consortium	HC, NS, HA	Royalty Free, Non-Exclusive Licenses for Non-Commercial Use	Licensing a Research Input; x_T=0; C, NS, HA; Ex-Post, Exclusive License
Combinatorial Chemistry Consortium	HC, S, HA	Non-Exclusive License for Members Only	Licensing Substitutable Downstream Technology for Use in Different Markets; x_T>0; C, S, HA; Ex-Ante, Non-Exclusive License
Consortium for Functional Glycomics (CFG)	HC, NS, HA	Royalty Free, Non-Commercial Use	Licensing a Research Input; x_T=0; C, NS, HA; Ex-Post, Exclusive License
DopaNet	HC, NS, HA	MIT License	Licensing a Research Input; x_T=0; C, NS, HA; Ex-Post, Exclusive License
International HapMap Project	HC, NS, HA	Initially Click-Wrap License to Access Genotypic Data	Licensing a Research Input; x_T=0; C, NS, HA; Ex-Post, Exclusive License
International Molecular Exchange Consortium	HC, S, HA	Creative Commons License	Licensing a Substitutable Research Input; x_T=0; C, S, HA; Ex-Ante, Non-Exclusive License
Knockout Mouse Project	HC, S, HA	Patent Pooling Advocated to Manage Existing IP	Licensing a Substitutable Research Input; x_T=0; C, S, HA; Ex-Ante, Non-Exclusive License
MalariaGEN	HC, NS, HA	Restricted Licensing Based on Geographical Applicability	Licensing a Research Input; x_T=0; C, NS, HA; Ex-Post, Exclusive License
Mouse Models of Human Cancers Consortium (MMHCC)	HC, S, HA	Limited-Use License by Open Biosystems	Licensing a Substitutable Research Input; x_T=0; C, S, HA; Ex-Ante, Non-Exclusive License
Nanotechnology Consortium	HC, S, HA	Non-Exclusive License for Members Only	Licensing Substitutable Downstream Technology for Use in Different Markets; x_T>0; C, S, HA; Ex-Ante, Non-Exclusive License
RNAi Consortium (TRC)	HC, S, HA	Limited-Use License by Open Biosystems	Licensing a Substitutable Research Input; x_T=0; C, S, HA; Ex-Ante, Non-Exclusive License
SNP Consortium	HC, NS, HA	Upstream Provisional Patents (Prior Art Creation)	Licensing a Research Input; x_T=0; C, NS, HA; Ex-Post, Exclusive License

Table 9.3: Comparing Licensing Strategies Suggested by Consortia and By Bargaining Models

Chapter 10: Discussion

10.1 The Knowledge Framework

From the review in Chapter 2, it is evident that the current literature is filled with many insightful contributions regarding the economics of knowledge and intellectual property. However, in this thesis, we make a novel contribution to the existing literature by linking knowledge structures and intellectual property. We expand the notion of knowledge as being a public good or a quasi private good and consider the underlying characteristics of knowledge as impacting downstream opportunities for product development. Specifically, we consider the complementarity, substitutability, and applicability of knowledge as impacting knowledge production processes and knowledge dissemination practices. By looking more closely at the classes of knowledge—research inputs, tools, drugs, and diagnostics, we are also better able to understand the motivation of strategic alliances increasingly sought to generate and manage upstream (both disembodied information and embodied in the form of research tools) and downstream knowledge (embodied as products such as drugs and diagnostics). Finally, we consider the evolution of strategic alliance formation and intellectual property practices across major drug discovery and development paradigms—the chemical, the biological, and the information paradigms. Across paradigms, as new sources of profit have emerged for the firm, the focus of knowledge generation as well as intellectual property has evolved—from new medicinal entities to research tools and data, and now possibly new life forms as the synthetic biology paradigm emerges. Table 10.1 outlines the use of the above knowledge parameters in this thesis.

In Chapter 4, we discuss the current systems biology paradigm extensively and analyze current intellectual property strategies. By selecting seven biologically significant systems, we hoped to uncover problems on the horizon as a result of the application of the traditional "chemical" intellectual property doctrine. We categorized patents according to phase of research and paradigm focus. While the majority of patents filed on these biological systems focus on downstream applications and with a mixture of paradigm focus—chemical, biological and in some cases information, the most alarming case is that of the GPCR cell signaling system. More than half of the patents on the GPCR cell signaling systems are upstream-based, and discovery oriented patent applications; hence the dominance of the information paradigm. Of the 133

GPCR patents analyzed, 77 focus on the structural aspects of the systems thereby adhering to the information paradigm. Of further concern, is the fact that almost half of the patents on these systems are owned by a concentrated number of private organizations and public institutions. GPCRs constitute a large and diverse family of proteins whose primary function is to transduce extracellular stimuli into intracellular signals. They are among the largest and most diverse protein families in mammalian genomes and are the largest class of targets for modern drug development [Beaumont and Negulescu, 1999].

Knowledge Parameter		**Analysis**
Knowledge Characteristics	Complementarity	Impact on Participation, Appropriation, and Bargaining Decisions
	Substitutability	
	Applicability	
Knowledge Class	Research Input	Impact on Participation, Appropriation, and Bargaining Decisions
	Tool	
	Drug	
	Diagnostic	
Knowledge Form	Disembodied	Value of Knowledge (Anticipated Transition Point)
	Embodied	
Knowledge Phase	Upstream	Timing and Focus of Appropriation
	Downstream	
Knowledge Paradigm	Chemical	Focus of Knowledge Generation Activities and Intellectual Property Strategies
	Biological	
	Information	

Table 10.1: Use of Knowledge Framework to Understand Strategic Firm Behaviour

As we see in the case of the NF-κB cell signaling system, where Ariad Pharmaceuticals is able to reach into the past to claim that Eli Lilly's drugs that act along the cell signaling system infringe their 2002 patent, the case may exist that a GPCR patent holder could similarly reach not only into the past but also the future to exploit the product development of *other* researchers. The completion of the Human Genome Project is proving to be a driving force for the growing role of GPCRs in drug discovery. This project has yielded a treasure trove of putative GPCRs with unknown functions and ligands, better known as "orphan GPCRs". Given that nearly 70% of all drugs currently marketed worldwide are targeted against GPCRs, clearly there is enormous potential to validate these "orphan GPCR's" as drug targets and reap the benefits of the blockbuster drugs of the past and tomorrow [GPCRs, 2002].

While lawmakers and the USPTO are revising the utility and obviousness bars for patents, and changes are on the horizon with respect to the Patent Reform Act, industry stakeholders should be cautious in this current paradigm with their intellectual property strategies. It is understandable that firms will need to acquire intellectual property in the systems paradigm to ensure the possibility of downstream product development via internal development efforts or through external licensing. However, these firms should be flexible with respect to their own licensing strategies. The shadow of the future should be kept in mind as multiple licenses may be required to progress into downstream development in the systems paradigm. If critical cell signaling system patents are held by one or two major firms, and if these firms are unable to fully exploit all opportunities associated with a cell signaling system, private and social benefits may warrant a broad licensing strategy. If cell signaling system patents are held by multiple firms, a cooperative licensing strategy can minimize both the licensing fees and any other associated transactions. However, we contend that by understanding the transition point—where the characteristics of knowledge warrant privatization of knowledge, firms may opt to wait to patent biological and/or chemical therapeutics that can act along the cell signaling systems, rather than simply the structures associated with the systems and putative functions.

In Chapter 5, a knowledge structures perspective of upstream strategic alliances provides interesting results. While strategic alliances have traditionally been analyzed from a resource-based theory perspective, a knowledge acquisition, or a knowledge access perspective, we contribute to the literature on strategic alliances by considering a nuanced, knowledge structures perspective. Here we specifically consider the paradigm, phase, and subject matter focus of upstream public-private and private strategic alliances as well as the associated licenses.

By analyzing the paradigm focus across strategic alliances and periods, we were able to determine the focus of knowledge generation activities in each type of alliance. While the biological paradigm and increasingly the information paradigm are the focus of public-private alliances, the chemical paradigm appears to continue to be of importance in private alliances. Of concern within public-private alliances, however, is the number of licenses issued to upstream oriented knowledge when the focus is on the information paradigm. This is not surprising given

the trends observed during the Human Genome Project with the patenting of gene fragments and genes, the patenting of drug target families, and the patenting of structural aspects of cell signaling systems in the current paradigm [Allarakhia 2001; Allarakhia and Wensley, 2005]. We find further support from our subject matter analysis for the notion that in the current information paradigm, the focus of research is on pre-discovery (upstream research) within public-private alliances. Hence, it may be the case that given the current state of knowledge, the patents that are currently being issued in the information paradigm are on upstream knowledge. Interestingly, within private alliances, although pre-discovery is a notable subject matter for these alliances (with the majority of pre-discovery research following the information paradigm), tool development dominates within the information paradigm. It is therefore possible that the private sector has progressed further downstream into product development albeit even if the focus is on supportive upstream tool development. The fact that an equivalent number of licenses are issued to upstream and downstream research when alliances adhere to the information paradigm, may be supportive of this notion that the private sector has moved further downstream.

10.2 The Consortium Analysis

Systems biology will transform biological research into a more quantitative discipline, needing even more sophisticated tools to measure biological processes and manage the resulting data. Discoveries are made at the intersection of once disparate disciplines [Gershon, 2000]. The intellectual and technological challenges associated with understanding biological systems require collective effort from multiple research arenas. As such, the scope of these interactions has broadened considerably since the completion of the Human Genome Project.

Managing the various scientific and technical cultures of systems biology is in itself a challenge. New initiatives and programs dedicated to systems biology are enabling for networking and collaboration between the disparate disciplines. Institutions are physically bringing together scientists and engineers from various laboratories located within their boundaries. Other networks are enabling for virtual collaboration between researchers dispersed globally through the use of information technologies. These institutions and networks are charged with the responsibility of breaking down the traditional cultural and bureaucratic barriers associated with

the disciplines. At the heart of the matter is the need to enable for knowledge production, communication between disciplines based on a common scientific language, and the need for knowledge dissemination. Within communities of interdisciplinary researchers, all participants must understand conventions regarding knowledge production and dissemination.

Several funding agencies including the NIH, Genome Canada, and the Wellcome Trust have played a significant role in enabling large-scale collaborative projects such as those discussed in Chapter 6. For example, the National Institute of General Medical Sciences Glue Grant provides resources for the formation of research teams to tackle complex problems that are of central importance to biomedical science, but that are beyond the means of any one research group. Resources may be requested to allow participating investigators to form a consortium to address the research problem in a comprehensive and highly integrated fashion [www.nigms.nih.gov, 2007].

Genome Canada's International Consortium Initiative (ICI) was established in October 2002. The ICI similarly provides an opportunity to fund unique international projects that will have significant impact on Canadian science and further enhance the status of Canada and Canadian scientists in the global community. Proposed projects must involve a formally constituted international consortium of research partners [Genome Canada, 2004].

By supporting such collaborations, funding agencies can indirectly encourage the norm of disclosure. Guarantees of disclosure and descriptions of mechanisms for knowledge dissemination are often components of the grant application. The Wellcome Trust for example, sponsored a meeting in January 2003 to discuss how pre-publication data release can promote the best interests of science and help to maximize the public benefit to be gained from genomics research. In attendance were large-scale sequence producers, sequence users including computational biologists, representatives of the major nucleotide sequence databases, journal editors, and scientists interested in other large-scale data sets [Wellcome Trust, 2003].

The meeting concluded that pre-publication release of sequence data by the International Human

Genome Sequencing Consortium, and other sequence producers, has been of tremendous benefit to the scientific research community in general. While not all were in a position to make commitments for their funding agencies, the meeting attendees were in broad agreement that, to encourage the continuation of such benefits, sequence producers, sequence users, and funding agencies should recognize and implement a system based on tripartite responsibility [Wellcome Trust, 2003].

Specifically,

- The meeting attendees reaffirmed the 1996 Bermuda Principles, which expressly called for rapid release to the public international DNA sequence databases (GenBank, EMBL, and DDBJ) of sequence assemblies of 2 Kb or greater by large-scale sequencing efforts and recommended that that agreement be extended to apply to all sequence data [Wellcome Trust, 2003].
- The attendees recommended that the principle of rapid pre-publication release should apply to other types of data from other large-scale production centres specifically established as "community resource projects". A community resource project is a research project specifically devised and implemented to create a set of data, reagents or other material whose primary utility will be as a resource for the broad scientific community [Wellcome Trust, 2003].
- The attendees recognized that pre-publication data release might conflict with a fundamental scientific incentive—publishing the first analysis of one's own data. The attendees noted that it would not be possible to absolutely guarantee this incentive without applying restrictions that would undermine the rationale for rapid, unrestricted release of data from community resources. Therefore, it was understood that the contributions and interests of the large-scale data producers should be recognized and respected by the users of the data, and the ability of production centres to analyze and publish their own data should be supported by their funding agencies [Wellcome Trust, 2003].

From our own analysis of research consortia in Chapter 6, we determined that many of the consortia themselves use rules and binding agreements to defer appropriation until the characteristics of knowledge warrant patenting to ensure that downstream products are developed. Consortia differentiate between disembodied knowledge in the form of raw data and embodied knowledge created by consortium members in the form of tools, biomaterials, and reagents. Although data that is high in complementarity and applicability, but low in substitutability is mandated in most cases for almost immediate release, tools, biomaterials, and reagents (in most cases, high in complementarity and applicability, as well as in substitutability) may be appropriated and licensed to consortium members and the public at large. Interestingly in most cases, appropriation is also regulated by the provision of rules regarding licensing terms. Specifically, by adhering to data and materials sharing policies provided by the NIH, the Wellcome Trust, the Creative Commons, the Biological Innovation for Open Society, and even private sector firms such as Open Biosystems, has enabled for relatively easy access to disembodied and embodied knowledge created within consortia. Table 10.2 comparatively analyzes the recommendations made by participants at the Wellcome Trust meeting held in 2003 and the recommendations (including rules) implemented by the consortia discussed in Chapter 6. We see from this analysis that the recommendations suggested at the meeting are being followed (in some form) by the various consortia dedicated to large-scale scientific research.

Consortium/Community Resource Project Issue	Wellcome Trust 2003 Meeting Outcome	Consortium Analysis Outcome
Resource Producers	Timeline for data production goals and publication should be established.	Rules established in most cases with respect to participation, knowledge production, and dissemination.
Resource Users	No restriction on use of data; Citation of data.	Infrastructure established in most cases to enable open data access; Citation of data required by users.
Data	Data generated by community project should be released immediately.	Data mandated in most cases for almost immediate release.
Research Materials and Tools	Develop practical approaches to use timely and rapid access to materials and tools.	Materials and tools may be appropriated and licensed in most cases via royalty-free, non-exclusive licensing.

Table 10.2: Comparatively Analyzing Funding Agency Recommendations and Rule Implementation by Consortia

While the consortia in Chapter 6 use rules to encourage licensing that provides the greatest *collective* value (and in turn greatest social value) to members and/or the public at large, the participants in our bargaining game model will rationally choose the outcome with the greatest unilateral value. For example, many of the consortia analyzed advocate the use of royalty-free non-exclusive licenses, whereas our game model advocates the use of non-exclusive licenses where the characteristics of knowledge—namely complementarity, substitutability, and applicability warrant such licenses. Where technology has commercial value on its own, a patent holder may choose a non-exclusive license so as to be able to sell the technology on the product marketplace alongside licensees. Furthermore, where technology can be substituted through non-infringing work-around solutions, a patent holder will also have an incentive to offer a non-exclusive license, rather than face competition without any possible compensation for his/her initial discovery. Alternatively, in cases where the market for technology is relatively small with technology having zero standalone commercial value, a patent holder may need to offer a non-exclusive license to ensure that a downstream developer will use the technology in products, thereby enabling the patent holder to reap the rewards of his/her original discovery. In each case, the strategy chosen will rationally maximize the benefits reaped by the patent holder or the first discover. Perhaps however, through the use of similar binding agreements regarding the division of the bargaining surplus and/or the costs of research, as issued by the consortia, the NIH, and the Wellcome Trust, the players in our bargaining game model may choose strategies that will maximize the collective value for both players.

10.3 The Games

10.3.1 The Participation Games

The game models developed and validated in Chapter 7 provide an effective illustration of the implications of changing incentives to participate in cooperative alliances including large-scale research consortia. By using numerical values for the common and private values of knowledge, we demonstrate the utility of the models to the biopharmaceutical industry—with specific reference to the formation of large-scale consortia in the post-genome era.

Interestingly in most cases, in our two-player model, the incentive is to cooperate via participation in an alliance in the restricted access setting—thereby accessing required knowledge. But when the private value of knowledge exceeds its common value, the incentive to cooperate is assured only if another researcher also cooperates. Understandably, if knowledge can be readily accessed without participation, and the private value of knowledge is greater than the common value of knowledge, defection is generally the outcome; similarly, when the common value of knowledge exceeds the private value of knowledge, mutual cooperation is the preferred outcome. When the common value of joint knowledge is increased, and both players would benefit from mutual cooperation, although a player that chooses unilateral cooperation still enjoys a larger payoff by cooperating rather than defecting—mutual cooperation is instead only assured in the restricted access setting. (Table 7.15)

A modified version of our two-player model involves a game of two players who each decide whether to participate in an existing consortium. The common value derives from units jointly generated, contributed, and combined with existing consortium knowledge. In this case, an additional parameter (K_c) is required to encompass existing consortium knowledge to which a new participant can add. We see from our model that in the public access setting, where what is known by the consortium is openly shared with members and the public at large, K_c is enjoyed by both players regardless of choice made and as such, not a factor in the decision taken by each player. In the restricted access setting however, as only members can enjoy the common value of consortium knowledge, the parameter K_c is (mathematically) significant and can be a factor in the decisions taken by each player. Future models should therefore consider the decision to join an existing consortium in the restricted access setting.

10.3.2 The Appropriation Game

In Chapter 8, we developed a two-player game model to understand the strategic decisions made by firms regarding the timing of appropriation activities. The game model not only models the decision to file a patent, but through the use of case studies as presented in Chapter 6, models the decision to pre-empt rivals through disclosure—thereby preventing firms from prematurely enclosing upstream knowledge. It is our contention that as biological knowledge structures become complex, researchers and firms should cautiously determine their strategies with respect

to upstream discovery research. The greater the complementarity between knowledge structures and applicability across systems, models, or diseases, the greater the need for multiple researchers to access these knowledge structures for downstream product development.

Merges (1996) argues that each researcher may find defection in his or her own interest, and will therefore expect a partner to similarly defect, unless cooperation is assured. (Table 8.12) However, unlike the tit-for-tat strategy in the Prisoner's Dilemma game, where a player will always cooperate unless provoked and will retaliate, but quickly forgives the opponent if provoked, the player who is "suckered" may not be so forgiving [Axelrod, 1984]. Players who defect earlier in time may meet reduced success in bargaining with others who remember past actions. In this case, pre-emptive disclosure may be one option to ensure the freedom to operate in downstream development for both players. (Table 8.8)

From our consortium analysis, we determined that the majority of consortia have as their objective the cooperative generation and dissemination of upstream knowledge. In a few cases, consortia appear to have been established to pre-empt downstream rivals. For example, the Accelrys Combinatorial Chemistry Consortium, the Accelrys Functional Proteomics Consortium, and the Accelrys Nanotechnology Consortia appear to have been established to pre-empt downstream rivals through selective cooperation and knowledge dissemination.

An interesting situation arises however, when the common value of what is jointly known increases. In this case, multiple equilibria exist in our game model. If player 1 chooses defection, player 2's best strategy is to cooperate, and vice versa. Similar to the game of Chicken, if both players choose to defect, both are worse off, receiving the lower payoffs (despite the fact that the private value of what is unilaterally known may be higher than the common value of this knowledge). (Table 8.9)

While our model begins to demonstrate the importance of evaluating biological knowledge structures as driving strategic behaviour of firms during knowledge production and dissemination activities, future research is required to augment the model. We need to assess how best to evaluate private and collective knowledge units. Furthermore, we have assumed that

the collective value of knowledge is simply the sum of the individual parts; our model may provide alternative insight if we modify the collective value of knowledge to derive from not only the individual parts, but also from the synergy between knowledge units. (See Chapters 7 and 8 for a preliminary analysis.)

10.3.3 The Bargaining Game

In Chapter 9, we assume that knowledge has been patented and consider the licensing options available to both the licensor and potential licensee as knowledge structures change. Figure 9.1 is an extensive form game model of the licensing environment where a first invention has commercial value and is complementary to second generation product development.

The threat point, each player's BATNA (Best Alternative to Negotiated Agreement), is the expected profit it can guarantee if it leaves the bargaining table. The bargaining surplus is the total amount by which the players will be richer if bargaining is successful. Each player can guarantee itself at least the amount of the threat point. However, central to a successful outcome (where success refers to the option of pursuing downstream product development) is how to divide the bargaining surplus. In our model, this bargaining surplus will vary with type of license issued (non-exclusive or exclusive) and whether the license is issued ex-ante or ex-post. Ideally, a system should ensure that both players are rewarded for their contributions and in particular, that the investment made to develop the first invention permits the second generation product to be developed and profitable.

Whether or not a license is issued and accepted ex-ante will be depend on the division of the bargaining surplus, the cost of developing the second generation product, and the ability of player 2 to substitute for the first invention. Furthermore, if player 1 is relatively uninformed about the value and costs associated with the development of the second generation product ex-ante, he/she may be unwilling to allow ex-ante licensing. With the threat of duplication by player 2, player 1 will have to be flexible on the bargaining surplus split between the two players, as there is no real incentive for player 2 to enter into bargaining. We anticipate that however, as the cost of duplication increases, the incentive to enter into bargaining will equivalently increase. Similarly, if the downstream product market size is small, our model demonstrates that player 1

may need to provide player 2 an incentive to engage in product development particularly as the costs of development rise in relation to profits.

The models in Chapter 9 provide insight on how consortium members individually or collectively focus on downstream product development. Once consortium objectives are achieved and membership is terminated, firms can easily become competitors on the product marketplace. It is at this *transition point* that the licensing strategies adopted by firms can be expected to maximize the private value of their knowledge.

Future models should enable for cross-licensing to understand the change in licensing strategy adopted by the licensor or licensee as knowledge is traded. A particularly interesting scenario will arise with the cross-licensing of asymmetrically valued knowledge. Complementarity between the sale of disembodied knowledge and internal embodiment occurs when knowledge possesses high applicability and it is possible to operate in different markets from other licensees of the knowledge [Teece, 1986; Arora and Fosfuri, 2003, Foray, 2004]. In this case, cross-licensing may also be an effective strategy [Shapiro, 2001]. With downstream activities dependent on the recombination of a variety of knowledge, the cost of the coordination including accumulation of the full range of required knowledge may be too high for one researcher [Antonelli, 2003; Burk and Lemley, 2003]. Specifically, the capabilities of the one researcher may only cover a portion of the research domain. Consequently, researchers may find it profitable to engage in cross-licensing for knowledge. However, the ability for each researcher to access knowledge depends of the amount and type of proprietary knowledge each one is able to contribute in any bargaining event [Antonelli, 2003].

Shapiro (2001) also discusses that when two or more companies control patents necessary to make a given product, a patent pool or a package license can be the solution. Under a patent pool, an entire group of patents is licensed in a package, either by one of the patent holders or by a new entity established for this purpose, usually to anyone willing to pay the associated royalties [Shapiro, 2001]. Under a package license, two or more patent holders agree to the terms on which they will jointly license their complementary patents and divide up the proceeds [Shapiro, 2001].

10.4 Understanding the Future from the Past

Dyes that preferentially stained tissues led to the birth of chemotherapy. Chemical affinities between dyes and tissues—cells or cellular components, led to the exploration of the binding properties of biological structures and chemical compounds in living organisms. Researchers postulated that cells carry on their surfaces and then eventually in their interior, receptors that preferentially bind to certain chemical compounds. The challenge for chemotherapy would be to find chemical compounds that would only bind to cells that a therapist would hope to eliminate from the body of a diseased patient [Drews, 1998; Dutfield, 2003; PhRMA 2007].

From the perspective of pharmacology, receptors are viewed as signal receivers. These targets interact selectively with a signal and transmit the signal information to intracellular effector organelles. It is this biochemical understanding of receptors, enzymes, and even ion channels (all targets for intervention by pharmaceuticals) that was responsible for the drug revolution in the 1950s and 1960s, resulting in the production of numerous medicines [Drews, 1998; Dutfield, 2003].

The biotechnology industry originated in the 1970s, based largely on new recombinant DNA techniques developed by Stanley Cohen of Stanford University and Herbert Boyer of the University of California, San Francisco [BIO.org, 2007]. The understanding of disease from a molecular perspective and the use of molecular techniques to create recombinant DNA has produced a vast number of drugs such as vaccines, monoclonal antibodies, recombinant products, and gene-based drugs [BIO.org, 2007].

Biotechnology companies have come to play a significant role in discovering an ever-increasing proportion of the new molecular entities (NMEs) launched every year. In the past, most drugs have been discovered either by isolating the active ingredient from traditional remedies or by serendipitous discovery. Modern biotechnology often focuses on understanding the metabolic pathways related to a disease state, and manipulating these pathways using molecular biology or biochemistry. Therefore, biotechnology companies assist in bringing not only the traditional chemical based—new small-molecule drugs to market, but also biological based products [BIO.org, 2007; PhRMA, 2007].

Once researchers understand the underlying cause of a disease, researchers select a "target" for a potential new medicine. A target is generally a single molecule, such as a gene or protein, which is involved in a particular disease. Even at this early stage in drug discovery, it is critical that researchers pick a target that is "druggable," i.e., one that can potentially interact with and be affected by a drug molecule [PhRMA, 2007]. Researchers search for a molecule, or "lead compound," that may act on their target to alter the disease course. There are a few ways to find a lead compound:

- **Nature:** Until recently, scientists usually turned to nature to find compounds. Bacteria found in soil and moldy plants have both served as sources of new compounds. While, nature still offers many useful substances, there are other approaches to drug discovery [PhRMA, 2007].
- **De novo:** Given advances in chemistry, scientists can create molecules from scratch. Using sophisticated computer modeling researchers are able to predict what type of molecule may serve as a lead [PhRMA, 2007].
- **High-throughput Screening:** This process is the most common technique used to discover leads. Advances in robotics and computational power allow researchers to test hundreds of thousands of compounds against the target to identify any that might be promising. Based on the results, several lead compounds are usually selected for further study [PhRMA, 2007].
- **Biotechnology:** Scientists can also genetically engineer living systems to produce biological molecules [PhRMA, 2007].

While small-molecule drugs have chemical compositions, biologics include recombinant proteins, monoclonal antibodies, vaccines, antisense products, as well as cell and gene therapies. A 2006 report from the Pharmaceutical Research and Manufacturers of America (PhRMA) found 418 medicines and vaccines—developed through biotechnology—were being tested to treat more than 100 diseases. These biotechnology medicines include 210 medicines to treat cancer, 50 to treat infectious disease, 44 to treat autoimmune disorders, 22 to treat HIV Infection and related-conditions, and 22 to treat cardiovascular diseases [PhRMA, 2006]. These potential medicines,

all of which are either in human clinical trials or under review by the Food and Drug Administration, will add to the list of 125 biotechnology medicines already approved and available to patients [PhRMA, 2006]. In fact, in 2006, 29 new medicines were approved by FDA. These new medicines include 18 new chemical-based drugs, four new therapeutic biologics, and seven other biologics [PhRMA, 2006].

From the above analysis, we see the evolution of profits models for the pharmaceutical and now biopharmaceutical industry—from chemical-based drugs discovered from nature or serendipitously, to chemical-based drugs discovered through modern biotechnology, to both chemical- and biological-based drugs arising from traditional chemical techniques and novel biotechnology processes.

To complete the sequence map of the Human Genome also required breakthroughs in understanding computational sciences, measurement technologies, statistics, and data management [Hood, 2000; Kitano, 2001]. Tool companies have therefore enabled high-through quantitative measurements of biological information based on computer science, mathematics, and statistics. Biotechnology is also responsible for hundreds of medical diagnostic tests used in health care management and disease diagnosis.

In parallel, during the sequencing of the Human Genome, several proprietary genomic databases were created by the private sector. These databases contained genomic information and the necessary tools and software to view, browse, and analyze genetic data, for the purposes of finding new discoveries and breakthroughs in medicine. Bioinformatics companies provided the necessary high performance software and scientific expertise for biological sequence data mining.

As the industry evolves to incorporate the systems paradigm, it is anticipated that the drug discovery and development feedback cycle will further incorporate novel technologies and disciplines. Global observations made during discovery research will be matched to model predictions or hypotheses in an iterative manner, leading to new patient models, predictions, and methods of patient experimentation [Ideker et al., 2001]. Computational experiments will

identify and virtually screen lead compounds. Successful leads will be synthesized and then tested via *in vitro* and *in vivo* experiments as well as clinical studies [Kitano, 2002].

As shown in Figure 10.1, we contend that with paradigm shifts, new profit models have emerged. To capture new market shares, the targets of intellectual property have also evolved with paradigms—from chemical compositions, to biologics, to biological materials and genomics-based tools, diagnostics, and now biological information. Unfortunately, patent examiners are increasingly finding it difficult to apply the chemical patent law doctrines to biological information. As such, the time has come to re-evaluate the current patent system to not only accommodate new processes as is the case with the 2007 U.S. Patent Reform Act, but new categories of goods. With the move toward "synthetic biology" i.e., the creation of new life forms by starting at the genetic level, this re-evaluation has reached a stage of urgency. Rai and Boyle (2007) discuss that synthetic biologists hope to create an array of modular biological parts that can be easily synthesized and mixed in different combinations. Synthetic biology will further bring together various systems, devices, parts, and DNA to create new products and hence targets for intellectual property. These components occupy various levels in the knowledge hierarchy to be associated with synthetic biology. Systems for example consist of devices and devices may consist of parts composed of DNA [Rai and Boyle, 2007]. Once again, as is the case for systems biology, complicating the matter is the hierarchical nature of synthetic biology knowledge. At any level in this hierarchy, patents may exist. Depending on the breadth of patents filed at a particular level, these patents can dominate over other hierarchical levels of information. Unfortunately, the combination of synthetic and non-synthetic materials (depending on perspective taken with respect to DNA) will add new complexities for a patent system that already needs reform. Rai and Boyle (2007) discuss one solution—the MIT Registry of Standard Biological Parts—an open initiative to place parts into the public domain—that makes parts not only unpatentable, but will also prevent the patenting of trivial improvements. Such open initiatives may be just as effective for managing the complexities of this new paradigm as they appear to be for the systems paradigm, particularly in the early stages of knowledge development.

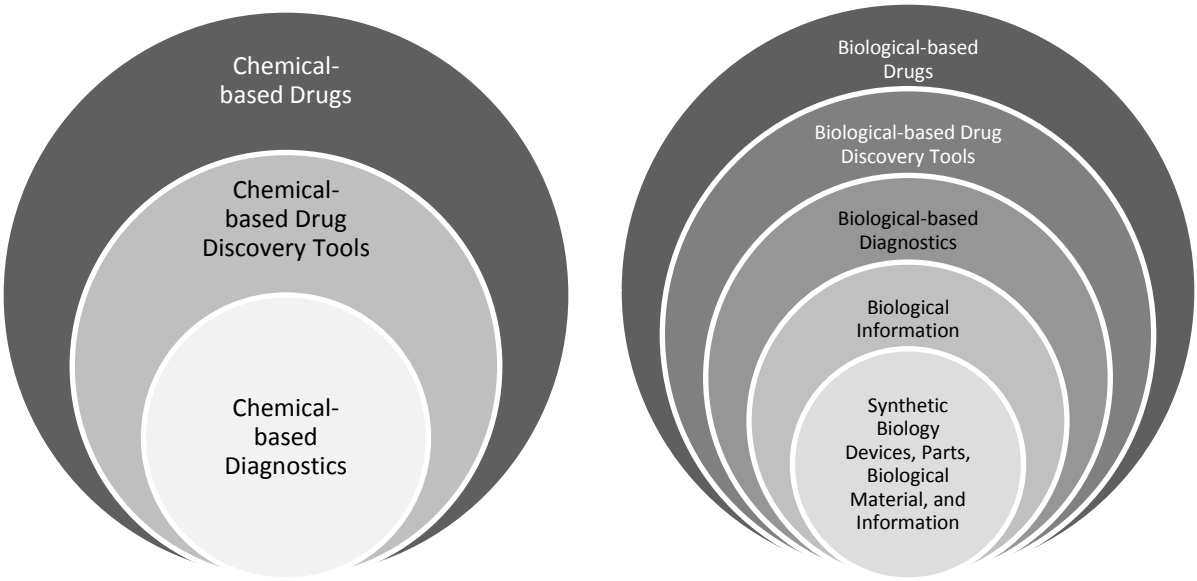


Figure 10.1: Evolving Profit Models and Targets of Intellectual Property in the Chemical and Biological-Based Paradigms

Chapter 11: Current Outlook

11.1 Changing Incentives and the Bayh Dole Act

Powell and Owen-Smith (1998) argue that the separation of the scientist in the academic world and the technologist in the private arena no longer holds in the life sciences. Universities have become much more oriented to the commercialization of research. The shift is argued to be a result of changing incentives favouring the commercialization of research. With the 1980 Patent and Trademark Law Amendments Act, also known as the U.S. Bayh-Dole Act, universities were given the right to retain property rights to inventions derived from federally funded research. The intent of Congress was to promote collaboration between commercial enterprises and academic institutions. In 1984, the rights of universities were more broadly expanded to permit universities to assign their property rights to others [Powell and Owen-Smith, 1998]. Powell and Owen-Smith (1998) explain that many of the legislative changes of the 1980s and 1990s sparked a considerable upsurge in licensing, as well as the growth in the number of university-industry research centres, consortia, and agreements. Universities were given the right to grant licenses including exclusive licenses to their inventions to private firms. It was anticipated that such licenses were necessary to provide private firms the incentive to invest in the downstream development of commercial products [Rai and Eisenberg, 2003].

Encouraged by the success of the Bayh-Dole Act, the Japanese Government enacted the Law for Promoting University-Industry Technology Transfer in 1998. The law provided for the establishment of Technology Licensing Offices (TLOs), which would receive financial assistance from the government to encourage technology transfer partnerships between universities and the private sector [Institute of Intellectual Property, 2001]. In Canada, while many universities retain ownership of intellectual property generated from public funds or share it with researchers, other universities turn over full rights to the researchers. The concern is that legislation such as the Bayh-Dole Act might not be effective in maintaining the open scholarship stance of Canadian universities; as well, it is not entirely clear whether spending on commercialization might be the best solution with respect to benefiting more from Canadian investment in university-based research [Kondro, 1999].

Rai and Eisenberg (2003) also argue that the U.S. Bayh-Dole Act should be reformed to give funding agencies greater discretion to determine when to mandate that publicly-funded research discoveries be placed into the public domain. These authors explain that the Bayh-Dole Act does not presume that patents are necessary to motivate grantees to perform research with federal funds, but rather that patents will promote the usage and commercialization of inventions arising from federally supported research. The reasoning behind this presumption is that patents and exclusive licenses are essential to attract the private investment for product development. However, no distinction has been made between knowledge types—upstream research inputs and upstream tools versus downstream diagnostics and drugs—and knowledge form—disembodied, pure knowledge versus embodied knowledge. As well, the Bayh-Dole Act does not encompass the notion of changing paradigms and knowledge structures and the impact of patents or exclusive licenses on downstream opportunities. Clearly, discussion is required to understand under what circumstances adherence to the Bayh-Dole Act is required to provide incentives for downstream product development and alternatively, when the private and public sectors are better served by the broad dissemination of knowledge.

On a number of occasions, the NIH has been able to use strategies to convince academic institutions to act collectively to keep basic research information in the public domain. For example, leaders of the National Human Genome Research Institute (NHGRI), together with the Wellcome Trust, and academic researchers at the major human genome mapping centres, resolved in February 1996 that "all human genomic DNA sequence information generated by centres funded for large-scale human sequencing should be freely available and in the public domain in order to encourage research and development" [Marshall, 1996]. NHGRI followed up with an April 1996 policy statement making "rapid release of data into public databases" a condition for grants for large-scale human genome sequencing [NHGRI, 1996]. NHGRI also warned that it would monitor whether grantees were patenting "large blocks of primary human genomic DNA sequence" and might invoke the "exceptional circumstances" limitation (to restrict patenting) in future grants [NHGRI, 1996]. A more general statement of "Principles and Guidelines for Sharing of Biomedical Research Resources," adopted by NIH in December 1999, also attempted to guide NIH grantees in their appropriation activities. We determined from our

consortium study that many consortia opted to use these guidelines to guide their members' patenting and licensing activities. These principles state that:

> The use of patents and exclusive licenses is not the only, nor in some cases the most appropriate means of implementing the Bayh-Dole Act. Where the subject invention is useful primarily as a research tool, inappropriate licensing practices are likely to thwart rather than promote utilization, commercialization, and public availability [NIH 1999].

These guidelines and statements seek to encourage cooperation during knowledge production and dissemination. Of further encouragement is the National Institute of General Medical Sciences Glue Grant—providing resources for the formation of research teams to tackle complex problems that are of central importance to biomedical science, but that are beyond the means of any one research group. Resources may be requested to allow participating investigators to form a consortium to address the research problem in a comprehensive and highly integrated fashion. Such grants provide researchers with incentives to cooperate earlier in time—during knowledge production.

Similarly, on September 4th 2007, the Canadian Institutes of Health Research (CIHR) announced a new policy to promote public access to the results of funded research. CIHR will require its researchers to ensure that their original research articles are freely available online within six months of publication. Researchers can deposit their article in an archive, such as PubMed Central or an institutional repository, and/or by publishing results in an open access journal. In addition, grant recipients are now required to deposit bioinformatics, atomic, and molecular coordinate data, already required by most journals, into the most appropriate public database immediately upon publication of research results [CIHR, 2007]. "Timely and unrestricted access to research findings is a defining feature of science, and is essential for advancing knowledge and accelerating our understanding of human health and disease", stated Dr. Alan Bernstein, President of the Canadian Institutes of Health Research [CIHR, 2007].

11.2 Reforming the Patent System

Earlier this year, the U.S. Senate Judiciary Committee Chairman Patrick Leahy (D-Vt.), and Senator Orrin Hatch (R-Utah), a senior member of the panel, joined with Rep. Howard Berman (D-Calif.), chairman of the House Judiciary Committee's Subcommittee on Courts, the Internet, and Intellectual Property and Rep. Lamar Smith (R-Texas), ranking member of the House Judiciary Committee, introduced the Patent Reform Act of 2007. These changes serve as legal mechanisms to change the incentives for appropriation and the probabilities associated with receiving patents.

The bill will create a pure "first-to-file" patent system. The American system is the only one in the world that still grants patents to the first inventor rather than the first to file an application. The bill also creates a more streamlined and effective way of challenging the validity and enforceability of patents [Leahy, 2007]. "If we are to maintain our position at the forefront of the world's economy and continue to lead the globe in innovation and production, then we must have an efficient and streamlined patent system to allow for high quality patents that limits counterproductive litigation," said Leahy. "This bill is an important step towards achieving that goal." [Leahy, 2007].

The United States Patent Office currently uses an interference proceeding to determine which party was first to "invent" the claimed invention where competing claims arise. The determination is apparently intensely fact-specific and costly to resolve [Leahy, 2007]. The bill converts the United States' patent system into a first-to-file system, giving priority to the earlier-filed application for a claimed invention. Interference proceedings will be replaced with derivation proceedings to determine whether the applicant of an earlier-filed application was not the proper applicant for the claimed invention. It is hoped that a derivation proceeding will be faster and less expensive than the interference proceeding. This bill also encourages the sharing of information by providing a grace period for publicly disclosing the subject matter of the claimed invention without losing priority [Leahy, 2007]. The Biotechnology Industry Organization (BIO)—the largest advocacy group representing the industry—supports this transition to the first-to-file system [BIO, 2007]. While this reform is expected to bring consistency and clarity to the U.S. system in comparison to global patent systems, we argue that

it may also change the perception of the "transition point". Inventors will have to reconsider when they apply for patents. The change could encourage inventors to file patent applications earlier than they would presently do, and file applications more often to preserve downstream product development opportunities including a seat at the bargaining table.

Leahy, Berman, and Smith indicate in the bill, that as products have become more complex, often involving hundreds or even thousands of patents, litigation has not reliably produced damages awards in infringement cases that correspond to the true value of the infringed patent. While the bill preserves the current rule that mandates that damages award shall not be less than a "reasonable royalty" for the infringed patent, it further requires the court to conduct an analysis to ensure that, when a "reasonable royalty" is the award, it reflects only the economic value of the patent's "specific contribution over the prior art", i.e., "the truly new thing that the patent reflects" [Leahy, 2007]. Interestingly, the court is encouraged to consider any non-exclusive marketplace licensing of the invention, if there is such a history, in determining a reasonable royalty [Leahy, 2007].

BIO opposes these provisions, arguing that this approach ignores the fundamental facts that virtually all inventions are, to some degree, based on prior art, and that many patented components may be essential to the functionality of the overall infringing product [BIO, 2007]. We offer the same argument regarding the complementarity of knowledge in this thesis to limit the scope and timing of patenting. From a game perspective, the limitation of damages to the "true new thing of the patent" is expected to decrease the private value of appropriation. While BIO argues that the resulting royalties would be lower than the reasonable royalties calculated under current law and would compensate patent owners for only a portion of their invention, rather than its' whole, thereby making infringement cheaper and perhaps ultimately discouraging investment into R&D, we argue that the private and social impacts are yet to be seen.

This bill also creates a new, post-grant review that provides an effective and efficient system for considering challenges to the validity of patents. The bill specifically amends the reexamination procedures to provide that, within three months of a request for reexamination of a patent by the patent owner, or at any time on the Director's own initiative, the Director may determine

whether a substantial new question of patentability is raised by patents discovered by him/her or cited by any other person [Leahy, 2007]. BIO opposes provisions that would create a limitless opportunity to broadly challenge a patent administratively at any time during the life of the patent—claiming that this post-grant review provision would cast a cloud of uncertainty over issued patents [BIO, 2007]. In BIO's view, in order to prevent abuse and misuse of any new post-grant opposition system, any administrative alternative to patent validity litigation must maintain the presumption of validity of patent claims that were issued by the USPTO. Further, any post-grant opposition system must include incentives to bring validity challenges early in patent life, and contain limits on the ability of challengers [BIO, 2007]. Such a post-grant system again could limit the private value of appropriation, prompting firms to cautiously craft out patent claims; perhaps the problems associated with the first-to-file transition could then be mitigated by this post-grant review system. Although, the U.S. House of Representatives passed, in a 220 to 175 vote on September 7th 2007, its version of the Patent Reform Act of 2007, several changes are expected to the House bill before the Bush administration authorizes full passage.

U.S. Supreme Court decisions regarding utility and recently, obviousness, have also raised the bar for receiving patents—and from a game perspective have likely decreased the probability of receiving the patent. The key issue in patenting genetic material has always revolved around the utility of the claimed genes and fragments. The 1999 Revised Interim Utility Guidelines established a heightened standard for utility [USPTO, 1999]. Under the 1999 standard, "credible utility" was not sufficient without an additional indication of "specific" and "substantial" utility [USPTO, 1999]. The policy of this heightened standard was based on the USPTO's adoption of the U.S. Supreme Court's position in Brenner vs. Manson that a patent is not given as a reward for the search of an invention's utility but, rather, a reward for actually discovering that utility [Brenner v. Manson, 383 U.S. 519, 536, 1966].

In its KSR vs. Teleflex decision, the U.S. Supreme Court acknowledged that nearly all innovations rely upon building blocks discovered in the past, but ruled that patentability requires more than predictable combinations of prior art [Nature Drug Discovery, 2007]. The impact of this change in obviousness definition is already being felt in the biopharmaceutical industry. In

an opinion released in June of this year, Judge William H. Pauley III of the U.S. District Court for the Southern District of New York ruled that Merck's (MRK) patent on the formulation for Pepcid Complete is invalid as obvious, clearing the way for Perrigo Co. (PRGO) to sell its own generic version of the medication [Nature Drug Discovery, 2007]. The decision is one of the first pharmaceutical patent decisions to rely on, and quote extensively from the Supreme Court's April 30th 2007 decision in KSR v. Teleflex (TFX). Pepcid Complete is an over-the-counter product intended for the treatment of heartburn. Judge Pauley refers to the following in his decision:

> Under KSR, the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. The '340 patent does no more than combine the predictable results of Davis and Wolfe with the predictable results of the '072 and '114 patents (two prior art patents) [Barkoff, 2007].

While innovators in the life sciences and chemical industries often cannot reasonably predict the outcome from a combination of particular elements from prior art, we have yet to see the full impact on the biotechnology and pharmaceutical industries [Kintisch, 2007]. Currently, it is anticipated that closely related imitation drugs may be deemed obvious even if they offer substantial improvement, and drug companies may be limited in their attempt to extend patents and the life of their drugs with minor improvements.

Dr. Richard Gold and Tina Piper of the Centre for Intellectual Property Policy (CIPP; 2006) also recommend revisions to Canadian patent law. Dr. Gold states for example that the Australian Law Reform Commission has recommended 50 changes to Australian patent law to meet challenges posed by new technologies. The European Union has also doggedly attempted to streamline its patent process to create a European-wide patent. Japan similarly revamped its patent laws in the 1980s [Gold and Piper, 2006]. While innovators seeking protection for their inventions in Canada, the U.S., Europe, and Japan must file for a patent in each place, most Canadian companies are likely to first patent inventions in the much larger U.S. market and may not even bother patenting in Canada at all [Gold, 2006]. Gold and Piper explain that American

companies both invent and sell in the U.S., while Canadian companies typically invent at home and sell abroad. Keeping this in mind, Gold and Piper propose the following:

> First, because Canada's strategic advantage lies in research and not the size of the market it offers, our patent laws should encourage public and private sector researchers to invent in Canada and sell abroad. Canadians patents should be carefully scrutinized before they are granted to ensure that the monopoly they create does not restrict access to knowledge and research tools. In other words, our researchers should be left free to innovate with relatively few impediments [Gold and Piper, 2006].
>
> Second, patent law should not obstruct the administration of our public health care system. Since Canada's share of the technology market is so small, it is unlikely that broader patent rights would attract outside investors seeking to profit on new medical technologies created in this country. On the other hand, expanded patent rights would lead to more medical products being sold to the Canadian health system at monopoly prices. Canada should therefore be capable of weighing potential benefits associated with increased patent protection against costs to the health care system that would be created if such protection was introduced [Gold and Piper, 2006].

11.3 Patients Changing the Rules of the Game

In Federal District Court in Chicago on October 30th, 2000, the law offices of Chicago-Kent College of Law filed a lawsuit against Miami Children's Hospital (MCH) and Dr. Reuben Matalon on behalf of parents of children afflicted with Canavan disease and Canavan Foundation, Dor Yeshorim, and National Tay-Sachs and Allied Diseases Association, Inc. (NTSAD). The case involves an alliance between parents and not-for-profit organizations who sought the help of researchers to develop prenatal and carrier testing for Canavan disease to be made accessible and affordable to the public [caravanfoundation.org, 2007]. The suit alleges that unbeknownst to the Canavan families and organizations, Dr. Matalon and his employer—the Miami Children's Hospital, secretly obtained a patent for the Canavan disease gene they discovered using the genetic information and financial resources provided by the Canavan

families and organizations [caravanfoundation.org, 2007]. Upon receiving the patent, Dr. Matalon and MCH started to charge royalties and limit the availability of testing. The six-count lawsuit, the first of its kind, alleges breach of informed consent, breach of fiduciary duty, unjust enrichment, fraudulent concealment, conversion, and misappropriation of trade secrets [caravanfoundation.org, 2007].

Based on the patent, doctors were prohibited from testing or examining patients for the Canavan disease gene despite the fact that the doctors could do so using traditional medical practices and such testing or examination would not require the use of any product or device invented by Dr. Matalon or MCH [caravanfoundation.org, 2007]. At stake was the possibility that royalties for the Canavan test would either cause a price increase in the series of tests doctors offered in their testing program or force its removal from any premarital screening program. In the lawsuit, the Canavan families and organizations primarily sought injunctive relief to prevent Miami Children's Hospital from restricting access to prenatal and carrier testing for Canavan disease and from impeding research on finding a cure or therapies for Canavan disease through enforcement of its patent [caravanfoundation.org, 2007].

The case was eventually settled between the parties. The patient group agreed not to further challenge the patent. While Miami Children's Hospital would continue to license and collect royalty fees for clinical testing for the Canavan gene mutation, the settlement also allowed license free use of the Canavan gene in research to cure Canavan disease, including gene therapy research, genetic testing in pure research, and in mice used to research Canavan disease [caravanfoundation.org, 2007].

Interestingly in another case, involving a genetic disorder that causes connective tissue in the skins, eyes, and arteries to calcify, a disorder known as pseudoxanthoma elasticum (PXE), PXE International received a joint patent with the researchers who isolated the disease causing gene. PXE International provided scientists at the University of Hawaii with blood and tissue samples from patients with the disorder [Smaglik, 2000]. In return, the patient advocacy group received joint patent rights to the disease causing gene. Sharon Terry, president of PXE International stated that the group sought joint patent rights to ensure that licenses for any resulting gene tests

would be widely available and at a low cost [Smaglik, 2000]. The Canavan case clearly raised concerns regarding the ownership of discoveries made with the assistance of subjects afflicted with the disease. The U.S. National Bioethics Advisory Commission also started encouraging the sharing of benefits with subjects who enabled discoveries [Smaglik, 2000]. Smaglik (2000) also anticipated that other genetic disease groups would follow the PXE model.

In both of these cases, the power of social groups is evident. From a game perspective, these social groups reduced the payoff associated with unilateral defection through the use of lawsuits and negative publicity. Social groups can therefore, encourage cooperation by threatening to punish defectors. The patient advocacy groups involved in the Canavan case was retroactively able to change the rules associated with appropriation of research results. Alternatively, the PXE alliance could become a model for proactively handling intellectual property rights emerging from cooperations between patient groups and researchers [Smaglik, 2000].

11.4 The Developing Market

As economies such India, China, Brazil, South Africa enter the biopharmaceutical arena, it is essential that developed economies share not only technology expertise, but also their experiences regarding collaborative knowledge production, technology transfer, and intellectual property management. The goal should be to enable these economies to participate on a level playing field to protect local knowledge and enable access to global knowledge as well as technology. It is anticipated that North-South partnerships will enable these emerging economies to better understand international technology transfer, licensing, and commercialization of technologies, as well as effective cross-broader public–private partnerships. Regional partnerships will be necessary to enable for capacity building namely via bioscience cluster development including public institutions, government laboratories, incubators, local and international private sector firms.

Beyond North-South partnerships and local capacity building, it is necessary that researchers and technology transfer officers take greater caution in the patenting and licensing of technologies that have significant application in developing and under-developed markets. Maintaining and

building the public domain with particular attention to knowledge that is of benefit to these economics can enable researchers to quickly and cost-effectively access knowledge. Open licensing, geographic-based licensing, assigning fair-royalties are all options being employed to assist researchers in developing economies access technologies that address for example neglected diseases or local health needs.

Local governments also have a role to play. Through the development of innovation policies with reference to patenting publicly funded research, governments can ensure not only the protection of local resources and local capacity building, but also a seat for these researchers at the international bargaining table.

An example of the role of government in balancing the needs of its local researchers and firms with its obligations as member of the World Trade Organization (and the Trade Related Aspects of Intellectual Property Rights) is the case of Novartis vs. the Government of India. In August of 2007, an Indian court ruled that the country's pharmaceutical industry could continue producing cheap generic drugs for diseases such as HIV/AIDS, malaria, and tuberculosis [Ward, 2007]. The case stemmed from the Indian Government's rejection of a patent application submitted by the pharmaceutical company Novartis for its new leukemia drug, Gleevec. In issuing its rejection, the Indian government asserted that the leukemia drug Gleevec does not differ sufficiently from earlier versions of the drug [Ward, 2007]. Under current Indian patent law, pharmaceuticals must be either a new invention or offer a significant improvement on existing medications to qualify for patent. A victory for Novartis in the Gleevec case would have set an important precedent preventing the production of many other generic medicines, greatly reducing the $5 billion Indian pharmaceutical industry's ability to supply drugs to aid agencies and low income countries in Asia, Africa, and Latin America [Ward, 2007].

We anticipate that our knowledge perspective and game models will provide a preliminary framework for understanding the increased complexities associated with product development for developed, developing, and even under-developed markets. Through the correct management of novel strategic alliances and the knowledge assets developed within such alliances,

biopharmaceutical companies can gain access to new economies with the objectives of gaining private benefits as well as providing social benefits to their new consumers.

11.5 Theoretical and Practical Outcomes

The knowledge framework developed in this thesis should enable firms to better understand the underlying structure and state of knowledge. While we discuss the chemical, biological, and information paradigms in this thesis, this framework has considerable applicability as the synthetic biology paradigm evolves—where the biological, information, and devices paradigms intersect. Many of the issues discussed for the information paradigm will have even more serious consequence as these firms seek patents over biological materials that may be placed into synthetic devices or as genomic information is manipulated to develop new organisms. Furthermore, as new theories underlying biological processes emerge and researchers re-evaluate their assumptions regarding the value of old knowledge, the strength of patents filed on older knowledge may change. For example, what was once thought of as "junk" DNA may become critical in our understanding of biological and disease processes. Patents that have placed little value on this upstream knowledge may not offer as strong protection over downstream product domains. In other cases, broad patents including claims on such knowledge may now offer new players a stronger seat at the bargaining table. Hence, we contend that researchers and firms should bear in mind that the state of knowledge is constantly changing and as such, our knowledge framework provides a first glance at the strategies that should be used to evaluate biological knowledge structures and the types of alliances that can be formed to acquire, access, and generate new knowledge.

As new paradigms and knowledge structures emerge, we should also keep in mind that developing markets and new industries will offer once isolated firms the opportunity to develop products. Here, government including public funding agencies and patent systems, may need to work together in order to ensure an equitable opportunity for these weaker players to enter research arenas. Programs that enable for cross-border research alliances and train researchers in the areas of technology transfer and commercialization can use the lessons learned from our consortium analysis to determine the best alliance structures, the rules for knowledge production

and dissemination, as well as the best strategies for appropriating knowledge. Of interest will be the continued use of the open source strategies analyzed in Chapter 6 as the biotechnology industry expands its focus on new energy sources and sustainable development.

Patent systems can provide support as paradigms and knowledge structures evolve in terms of 1) breadth of claims approved in patent applications—ensuring that high standards of utility, obviousness, and written enablement are used, 2) the pre-grant and post-grant review processes used to contest new patent applications—ensuring that uncertainty surrounding patents is resolved earlier in time, and 3) the information available to patent officers regarding the characteristics of knowledge underlying patent applications—keeping knowledge domains open for multiple researchers and firms through the mechanisms outlined above. The use of open source strategies by various stakeholders, including the private sector, is perhaps a signal to patent authorities that the time has come to reform not only the U.S., but perhaps also global patent systems.

Our game models provide a simple but elegant framework for understanding the impact of changing knowledge structures on the payoffs associated with cooperation and defection in knowledge production and appropriation. As new paradigms and knowledges structures emerge, we anticipate that our game models will continue to provide valuable insight. A comparative analysis of the management of common pool resources should closely observe the underlying structures associated with each resource as well as the mechanisms and payoffs associated with cooperation. As the structures underlying these resources change, we contend that the source of profits will also evolve. While some model will be adopted permanently, others profit models will change as knowledge structures change. Of interest therefore, will be observing the evolution of these profit models and the impact on the payoffs associated with cooperation and defection including the occurrence of the transition point. From a social perspective, the transition point can be defined as the moment when the characteristics associated with upstream knowledge change so that downstream competitive behaviour will in fact increase the substitutive value of products for consumers. Therefore, with a correctly timed transition point, we suggest that both the private and social benefits of downstream product development should be maximized.

APPENDIX 1:

CELL SIGNALING SYSTEMS
PATENT ANALYSIS DATA

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
7,122,527	Use of antisense oligonucleotides to inhibit the expression of human Akt-1	USE	Downstream	Biological	Rexahn Corporation (Potomac, MD)
7,098,208	Inhibitors of Akt activity	INH	Downstream	Chemical	Merck & Co., Inc. (Rahway, NJ)
7,071,316	Human Akt-3	STRUCTURAL	Upstream	Information	Janssen Pharmaceutica N.V. (Beerse, BE)
7,034,026	Inhibitors of Akt activity	INH	Downstream	Chemical	Merck & Co., Inc. (Rahway, NJ)
6,960,584	Inhibitors of Akt activity	INH	Downstream	Chemical	Merck & Co., Inc. (Rahway, NJ)
6,958,334	Inhibitors of Akt activity	INH	Downstream	Chemical	Merck & Co., Inc. (Rahway, NJ)
6,881,555	AKT nucleic acids, polypeptides, and uses thereof	USE	Downstream	Biological	Aventis Pharmaceuticals Inc. (Bridgewater, NJ)
6,187,586	Antisense modulation of AKT-3 expression	MOD	Downstream	Biological	Isis Pharmaceuticals, Inc. (Carlsbad, CA)
6,043,090	Antisense inhibition of human Akt-2 expression	INH	Downstream	Biological	Isis Pharmaceuticals Inc. (Carlsbad, CA)
5,958,773	Antisense modulation of AKT-1 expression	MOD	Downstream	Biological	Isis Pharmaceuticals Inc. (Carlsbad, CA)

Appendix Table 1: Patent Analysis of the Akt Cell Signaling System

INH=Inhibitor; MOD=Modulator

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
6,537,804	BCR-ABL directed compositions and uses for inhibiting Philadelphia chromesome stimulated cell growth	INH	Downstream	Biological	Board of Regents, The University of Texas Systems (Austin, TX)
6,107,457	Bcr-Abl directed compositions and uses for inhibiting Philadelphia chromosome stimulated cell growth	INH	Downstream	Biological	Board of Regents, The University of Texas System (Austin, TX)
6,066,463	Method and compositions for treatment of BCR-ABL associated leukemias and other cell proliferative disorders	USE	Downstream	Biological	New York University (New York, NY); Duke University (Durham, NC); Sugen, Inc. (South San Francisco, CA)
5,652,222	Selective inhibition of leukemic cell proliferation by bcr-abl antisense oligonucleotides	USE	Downstream	Biological	Temple University-of The Commonwealth System of Higher Education (Philadelphia, PA)
5,369,008	Methods for the detection of BCR-ABL and abnormal ABL proteins in leukemia patients	METHOD	Downstream	Biological	Board of Regents, The University of Texas System (Austin, TX)

Appendix Table 2: Patent Analysis of the Bcr Cell Signaling System

INH=Inhibitor; MOD=Modulator

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
H2,136	Nucleic acids encoding G protein-coupled receptors	STRUCTURAL	Upstream	Information	Affymetrix, Inc. (Santa Clara, CA)
7,122,570	Tetrahydrocarbazol derivatives as ligands for G-protein-coupled receptors (GPCR)	USE	Downstream	Chemical	Zentaris AG (Frankfurt, DE)
7,119,190	Endogenous and non-endogenous versions of human G protein-coupled receptors	STRUCTURAL	Upstream	Information	Arena Pharmaceuticals, Inc. (San Diego, CA)
7,115,724	Murine genomic polynucleotide sequence encoding a G-protein coupled receptor and methods of use therefor	USE	Downstream	Biological	Wyeth (Madison, NJ)
7,115,377	Cell-based assays for G-protein-coupled receptor-mediated activities	METHOD	Downstream	Biological	Atto Bioscience, Inc. (Rockville, MD)
7,108,991	Human orphan G protein-coupled receptors	STRUCTURAL	Upstream	Information	Arena Pharmaceuticals, Inc. (San Diego, CA)
7,105,488	G protein-coupled receptor antagonists	INH	Downstream	Biological	The United States of America as represented by the Department of Health and Human Services (Washington, DC)
7,097,969	Non-endogenous, constitutively activated known G protein-coupled receptors	MOD	Downstream	Chemical	Arena Pharmaceuticals, Inc. (San Diego, CA)
7,094,593	Method for improving the function of heterologous G protein-coupled receptors	METHOD	Downstream	Biological	BASF Aktiengesellschaft (DE)/The United States of America as represented by the Department of Health (Washington, DC)
7,094,572	Polynucleotide encoding a novel human G-protein coupled receptor variant of HM74, HGPRBMY74	STRUCTURAL	Upstream	Information	Bristol-Myers Squibb (Princeton, NJ)
7,087,735	Bivalent binding molecules of 7 transmembrane G protein-coupled receptors	STRUCTURAL	Upstream	Information	Gilead Sciences, Inc. (Foster City, CA)

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
7,084,259	G-protein coupled receptors	STRUCTURAL	Upstream	Information	Amgen Inc. (Thousand Oaks, CA)
7,081,360	Expression of G protein-coupled receptors with altered ligand binding and/or coupling properties	USE	Downstream	Biological	Cadus Technologies, Inc. (New York, NY)
7,063,966	Chimeric G protein coupled receptors	STRUCTURAL	Upstream	Information	SRI International (Menlo Park, CA)
7,057,028	14273 Receptor, a novel G-protein coupled receptor	STRUCTURAL	Upstream	Information	Millennium Pharmaceuticals, Inc. (Cambridge, MA)
7,049,096	Polynucleotides encoding a novel human G-protein coupled receptor splice variant HGPRBMY29sv1	STRUCTURAL	Upstream	Information	Bristol-Meyers Squibb Company (Princeton, NJ)
7,037,891	Methods of modulating G-protein-coupled receptor kinase-associated signal transduction	MOD	Downstream	Biological	Children's Medical Center Corporation (Boston, MA)/Yissum Research and Development (Jerusalem, IL)
7,033,773	Screening assays for G protein coupled receptor agonists and antagonists	METHOD	Downstream	Biological	The General Hospital Corporation (Boston, MA)
7,018,812	Modified G-protein coupled receptors	STRUCTURAL	Upstream	Information	Duke University (Durham, NC)
6,998,255	Human G-protein coupled receptor	STRUCTURAL	Upstream	Information	Solvay Pharmaceuticals B.V. (CP Weesp, NL)
6,902,902	Human G protein-coupled receptors and modulators thereof for the treatment of metabolic-related disorders	USE	Downstream	Chemical	Arena Pharmaceuticals, Inc. (San Diego, CA)
6,893,827	Receptor function assay for G-protein coupled receptors and orphan receptors by reporter enzyme mutant complementation	ASSAY	Downstream	Biological	Applera Corporation (Bedford, MA)
6,890,731	Isolated human G-protein coupled receptors that are members of the aminergic subfamily, nucleic acid molecules encoding human GPCR proteins, and uses thereof	STRUCTURAL	Upstream	Information	Applera Corporation (Bedford, MA)

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
6,887,683	Human G-protein coupled receptors	STRUCTURAL	Upstream	Information	Human Genome Sciences, Inc. (Rockville, MD)
6,864,229	G protein coupled receptor (GPCR) agonists and antagonists and methods of activating and inhibiting GPCR using the same	INH	Downstream	Chemical	New England Medical Center Hospitals, Inc. (Boston, MA)
6,855,807	Heterodimeric opioid G-protein coupled receptors	STRUCTURAL	Upstream	Information	New York University (New York, NY)
6,855,550	Expression of G protein coupled receptors in yeast	USE	Downstream	Biological	Duke University (Durham, NC)
6,838,275	Human G-coupled protein receptor kinases and polynucleotides encoding the same	STRUCTURAL	Upstream	Information	Lexicon Genetics Incorporated (The Woodlands, TX)
6,838,258	G protein-coupled receptor up-regulated in prostate cancer and uses thereof	USE	Downstream	Biological	Agensys, Inc. (Santa Monica, CA)
6,835,546	Drosophila G protein coupled receptors, nucleic acids, and methods related to the same	STRUCTURAL	Upstream	Information	Pharmacia & Upjohn Company (Kalamazoo, MI)
6,824,990	Methods of detecting and modulating oligomerization of G protein-coupled receptors	METHOD	Downstream	Biological	Washington University (St. Louis, MO)
6,821,950	Cyclic agonists and antagonists of C5a receptors and G protein-coupled receptors	MOD	Downstream	Chemical	The University of Queensland (Brisbane, AU)
6,806,061	G protein-coupled receptor gene and methods of use therefor	USE	Downstream	Biological	Children's Medical Center Corporation (Boston, MA); Millennium Pharmaceuticals, Inc. (Cambridges, MA); Brigham and Women's Hospital (Boston, MA)
6,806,054	Non-endogenous, constitutively activated known G protein-coupled receptors	STRUCTURAL	Upstream	Information	Arena Pharmaceuticals, Inc. (San Diego, CA)
6,800,749	G-protein coupled receptor	STRUCTURAL	Upstream	Information	AstraZeneca Canada Inc. (Mississauga, CA)

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
6,800,445	Systems for sensitive detection of G-protein coupled receptor and orphan receptor function using reporter enzyme mutant complementation	METHOD	Downstream	Biological	Applera Corporation (Bedford, MA)
6,790,631	G protein-coupled receptor up-regulated in prostate cancer and uses thereof	USE	Downstream	Biological	Agensys, Inc. (Santa Monica, CA)
6,733,990	Nucleic acid encoding 15571, a GPCR-like molecule of the secretin-like family	STRUCTURAL	Upstream	Information	Millennium Pharmaceuticals, Inc. (Cambridge, MA)
6,709,830	Methods for modulating the activation of a lymphocyte expressed G protein coupled receptor involved in cell proliferation, autoimmunity and inflammation	MOD	Downstream	Biological	The Regents of the University of California (Oakland, CA)
6,699,965	Peptides that activate the G-protein coupled receptor protein, 0T7T175	ACTIVATOR	Downstream	Biological	Takeda Chemical Industries, Ltd. (Osaka, JP)
6,696,257	G protein-coupled receptors from the rat and human	STRUCTURAL	Upstream	Information	National Research Council of Canada (Ottawa, CA)
6,696,244	G-coupled receptors associated with retroviral entry into cells, and therapeutic uses thereof	USE	Downstream	Biological	New York University (New York, NY)
6,682,886	Bivalent binding molecules of 7 transmembrane G protein-coupled receptors	STRUCTURAL	Upstream	Information	Gilead Sciences, Inc. (Foster City, CA)
6,653,086	Endogenous constitutively activated G protein-coupled orphan receptors	STRUCTURAL	Upstream	Information	Arena Pharmaceuticals, Inc. (San Diego, CA)
6,638,733	G-protein coupled receptors amplified in breast cancer	STRUCTURAL	Upstream	Information	Tularik Inc. (South San Francisco, CA)
6,635,741	G-protein coupled receptor BCA-GPCR-3	STRUCTURAL	Upstream	Information	Tularik Inc. (South San Francisco, CA)
6,632,621	G protein-coupled receptor-like receptors and modulators thereof	MOD	Downstream	Biological	Pharmacia & Upjohn Company (Kalamazoo, MI)

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
6,620,615	G-protein coupled receptor--encoding nucleic acids	STRUCTURAL	Upstream	Information	CuraGen Corporation (New Haven, CT)
6,607,906	Heterologous G protein coupled receptors expressed in yeast, their fusion with G proteins and use thereof in bioassay	USE	Downstream	Biological	BASF Aktiengesellschaft (Ludwigshafen, DE)
6,602,699	Promotor for functional characterization of G-protein coupled receptors in the yeast saccharomyces cerevisiae	STRUCTURAL	Upstream	Information	Aventis Pharma Deutschland GmbH (Frankfurt, DE)
6,586,205	43239 a novel GPCR-like molecule and uses thereof	USE	Downstream	Biological	Millennium Pharmaceuticals, Inc. (Cambridge, MA)
6,569,995	Identification of a G protein-coupled receptor transcriptionally regulated by protein tyrosine kinase signaling in hematopoietic cells	METHOD	Downstream	Biological	The Regents of the University of California (Oakland, CA)
6,538,107	G protein coupled receptor protein production, and use thereof	USE	Downstream	Biological	Takeda Chemical Industries, Ltd. (Osaka, JP)
6,521,418	G protein-coupled receptor with an enlarged extracellular domain	STRUCTURAL	Upstream	Information	The Scripps Research Institute (La Jolla, CA)
6,518,480	Selective target cell activation by expression of a G protein-coupled receptor activated superiorly by synthetic ligand	ACTIVATOR	Downstream	Biological	The Regents of the University of California (Oakland, CA)
6,518,414	Molecular cloning and expression of G-protein coupled receptors	USE	Downstream	Biological	Individual
6,514,696	Transcriptionally regulated G protein-coupled receptor G2A	STRUCTURAL	Upstream	Information	The Regents of The University of California (Oakland, CA)
6,500,934	Bivalent agonists for G-protein coupled receptors	STRUCTURAL	Upstream	Information	Individual
6,448,005	14723 Receptor, a novel G-protein coupled receptor	STRUCTURAL	Upstream	Information	Millennium Pharmaceuticals, Inc. (Cambridge, MA)
6,444,456	Human G-coupled protein receptor kinases and polynucleotides	STRUCTURAL	Upstream	Information	Lexicon Genetics Incorporated (The

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
	encoding the same				Woodlands, TX)
6,420,563	Small molecule modulators of G protein-coupled receptor six	MOD	Downstream	Chemical	Arena Pharmaceuticals, Inc. (San Diego, CA)
6,406,871	Method for detecting ligand binding to G protein coupled receptors	METHOD	Downstream	Biological	BASF Aktiengesellschaft (Ludwigshafen, DE)
6,403,767	Polypeptide molecules of the G protein-coupled heptahelical receptor superfamily and uses therefor	USE	Downstream	Biological	Millenium Pharmaceuticals, Inc. (Cambridge, MA); CRC Technology Limited (London, GB)
6,403,305	Methods of identifying peptide agonists or negative antagonists of a G protein coupled receptor	METHOD	Downstream	Biological	Cornell Research Foundation, Inc. (Ithaca, NY)
6,395,877	14273 receptor, a novel G-protein coupled receptor	STRUCTURAL	Upstream	Information	Millennium Pharmaceuticals, Inc. (Cambridge, MA)
6,383,778	Nucleic acids encoding a G-protein coupled receptor involved in sensory transduction	STRUCTURAL	Upstream	Information	The Regents of the University of California (Oakland, CA)
6,383,761	Methods and compositions for identifying modulators of G-protein-coupled receptors	METHOD	Downstream	Biological	The Regents of the University of California (Oakland, CA); National Institutes of Health (Rockville, MD)
6,383,760	Transcriptionally regulated G protein-coupled receptor	STRUCTURAL	Upstream	Information	The Regents of the University of California (Oakland, CA)
6,368,848	Compositions to identify plant proteins that function in G-protein coupled systems	USE	Downstream	Biological	BASF Aktiengesellschaft (DE)
6,361,967	Axor10, a g-protein coupled receptor	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA); SmithKline Beecham plc (Brentford, GB)
6,344,342	Human G protein coupled lysophosphatidic acid receptor	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA)

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
6,300,312	Antagonists of G-protein-coupled receptor	STRUCTURAL	Upstream	Information	Hôpital Sainte-Justine (Montreal, CA)
6,291,177	Assay for agents which alter G-protein coupled receptor activity	ASSAY	Downstream	Biological	Millennium Pharmaceuticals, Inc. (Cambridge, MA)
6,287,801	Nucleic acids encoding the G-protein coupled receptor HNFDS78	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA)
6,280,934	Assay for agents which alter G-protein coupled receptor activity	ASSAY	Downstream	Biological	Millennium Pharmaceuticals, Inc. (Cambridge, MA)
6,258,527	Methods of identifying g-coupled receptors associated with macrophage-trophic HIV, and diagnostic and therapeutic uses thereof	METHOD	Downstream	Biological	The Aaron Diamond Aids Research Center (New York, NY); New York University (New York, NY)
6,255,069	Compositions and methods for modulating the activity of G protein-coupled receptor kinases GPK5 and GRK6	METHOD	Downstream	Biological	Thomas Jefferson University (Philadelphia, PA)
6,255,059	Methods for identifying G protein coupled receptor effectors	METHOD	Downstream	Biological	Cadus Pharmaceutical Corporation (Tarrytown, NY)
6,251,582	Alternative G-coupled receptors associated with retroviral entry into cells, methods of identifying the same, and diagnostic and therapeutic uses thereof	USE	Downstream	Biological	New York University (New York, NY)
6,242,572	Human G protein coupled lysophosphatidic acid receptor	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA)
6,232,123	Monoclonal antibodies against leucocyte-specific G protein-coupled receptors	USE	Downstream	Biological	Individual
6,218,376	Uracil compounds as P2-purinoreceptor 7-transmembrane G-protein coupled receptor antagonists	USE	Downstream	Chemical	AstraZeneca UK Limited (London, GB)

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
6,214,562	Transcriptionally regualted G protein-coupled receptor	STRUCTURAL	Upstream	Information	The Regents of the University of California (Oakland, CA)
6,207,412	Identification of a G protein-coupled receptor transcriptionally regulated by protein tyrosine kinase signaling in hematopoietic cells	USE	Downstream	Biological	The Regents of the University of California (Oakland, CA)
6,183,974	Screening assays for G protein coupled receptor agonists and antagonists	ASSAY	Downstream	Biological	The General Hospital Corporation (Boston, MA)
6,168,927	Expression of G protein coupled receptors in yeast	USE	Downstream	Biological	Duke University (Durham, NC)
6,114,139	G-protein coupled receptor protein and a DNA encoding the receptor	STRUCTURAL	Upstream	Information	Takeda Chemical Industries, Ltd. (Osaka, JP)
6,111,076	Human G-protein coupled receptor (HIBCD07)	STRUCTURAL	Upstream	Information	Takeda Chemical Industries, Ltd. (Osaka, JP)
6,096,868	ECR 673: A 7-transmembrane G-protein coupled receptor	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA)
6,090,575	Polynucleotides encoding human G-protein coupled receptor GPR1	STRUCTURAL	Upstream	Information	Human Genome Sciences, Inc. (Rockville, MD)
6,087,115	Methods of identifying negative antagonists for G protein coupled receptors	METHOD	Downstream	Biological	Cornell Research Foundation, Inc. (Ithaca, NY)
6,071,722	Nucleic acids encoding a G-protein coupled 7TM receptor (AXOR-1)	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA)
6,071,719	DNA encoding ECR 673: A 7-transmembrane G-protein coupled receptor	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA)
6,063,596	G-protein coupled receptors associated with immune response	STRUCTURAL	Upstream	Information	Incyte Pharmaceuticals, Inc. (Palo Alto, CA)
6,060,272	Human G-protein coupled receptors	STRUCTURAL	Upstream	Information	Human Genome Sciences, Inc. (Rockville, MD)

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
6,048,711	Human G-protein coupled receptor polynucleotides	STRUCTURAL	Upstream	Information	Takeda Chemical Industries, Ltd. (Tsukuba Ibaraki, JP)
6,020,158	Isolated polynucleotide for novel G-protein coupled receptor	STRUCTURAL	Upstream	Information	Allelix Biopharmaceuticals, Inc. (Ontario, CA)
6,013,479	Human Emr1-like G protein coupled receptor	STRUCTURAL	Upstream	Information	Incyte Pharmaceuticals, Inc. (Palo Alto, CA)
6,001,972	Splicing variant of the epstein-barr virus-induced G-protein coupled receptor	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA)
5,998,164	Polynucleotides encoding human G-protein coupled receptor GPRZ	STRUCTURAL	Upstream	Information	Human Genome Sciences, Inc. (Rockville, MD)
5,994,097	Polynucleotide encoding human G-protein coupled receptor	STRUCTURAL	Upstream	Information	Incyte Pharmaceuticals, Inc. (Palo Alto, CA)
5,985,584	Method to identify plant proteins that function in G protein coupled systems and compositions therefor	METHOD	Downstream	Biological	American Cyanamid Company (Madison, NY)
5,955,575	Antagonists of G-protein-coupled receptor	STRUCTURAL	Upstream	Information	Hopital Sainte-Justine (Montreal, CA)
5,955,309	Polynucleotide encoding G-protein coupled receptor (H7TBA62)	STRUCTURAL	Upstream	Information	Smithkline Beecham Corporation (Philadelphia, PA)
5,945,307	Isolated nucleic acid molecules encoding a G-protein coupled receptor showing homology to the 5HT family of receptors	STRUCTURAL	Upstream	Information	Millennium Pharmaceuticals, Inc. (Cambridge, MA)
5,942,414	Polynucleotides encoding human G-protein coupled receptor HIBEF51	STRUCTURAL	Upstream	Information	Human Genome Sciences, Inc. (Rockville, MD)
5,939,320	G-coupled receptors associated with macrophage-trophic HIV, and diagnostic and therapeutic uses thereof	USE	Downstream	Biological	New York University (New York, NY); The Aaron Diamond Aids Research Center (New York, NY)
5,932,702	Human G-protein coupled receptor	STRUCTURAL	Upstream	Information	Human Gene Sciences (Rockville, MD); Takeda (Osaka, JP)

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
5,925,549	Soluble 7-transmembrane domain G-protein-coupled receptor compositions and methods	METHOD	Downstream	Biological	The Board of Trustees of the Leland Stanford Junior University (Stanford, CA)
5,912,335	G-protein coupled receptor HUVCT36	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA)
5,910,430	Isolated nucleic acid encoding G-protein coupled receptor (HTADX50)	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA)
5,891,720	Isolated DNA encoding a novel human G-protein coupled receptor	STRUCTURAL	Upstream	Information	Millennium Pharmaceuticals, Inc. (Cambridge, MA)
5,882,944	Methods for G protein coupled receptor activity screening	METHOD	Downstream	Biological	The Regents of the University of California (Oakland, CA)
5,874,252	Splicing variant of the Epstein-Barr virus-induced G-protein coupled receptor	STRUCTURAL	Upstream	Information	Smithkline Beecham Corporation (Philadelphia, PA)
5,874,245	Human G-protein coupled receptor (HIBCD07)	STRUCTURAL	Upstream	Information	Takeda Chemical Industries, Ltd. (Osaka, JP)
5,871,967	Cloning of a novel G-Protein coupled 7TM receptor	USE	Downstream	Biological	SmithKline Beecham Corporation (Philadelphia, PA)
5,869,609	G protein coupled glutamate receptors	STRUCTURAL	Upstream	Information	Zymogenetics, Inc. (Seattle, WA); The Board of Regents of the University of Washington (Seattle, WA)
5,856,443	Molecular cloning and expression of G-protein coupled receptors	USE	Downstream	Biological	Individual
5,834,587	G-protein coupled receptor, HLTEX 11	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA)
5,783,402	Method of identifying ligands and anatgonists of G-protein coupled receptor	METHOD	Downstream	Biological	The United States of America as represented by the Secretary of the

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
					(Washington, DC)
5,763,218	Nucleic acid encoding novel human G-protein coupled receptor	STRUCTURAL	Upstream	Information	Human Genome Science, Inc. (Rockville, MD); Takeda (Osaka, JP)
5,747,267	Method for identifying a G protein coupled glutamate receptor agonist and antagonist	METHOD	Downstream	Biological	Zymogenetics, Inc. (Seattle, WA); The Board of Regents of the University of Washington (Seattle, WA)
5,739,029	Vectors for expression of G protein coupled receptors in yeast	STRUCTURAL	Upstream	Information	Duke University (Durham, NC)
5,721,107	Antibodies to G protein coupled glutamate receptors	USE	Downstream	Biological	The Board of Regents of the University of Washington (Seattle, WA); Zymogenetics, Inc. (Seattle, WA)
5,691,188	Transformed yeast cells expressing heterologous G-protein coupled receptor	USE	Downstream	Biological	American Cyanamid Company (Madison, NJ)
5,591,618	G protein-coupled receptor kinase GRK6	STRUCTURAL	Upstream	Information	ICOS Corporation (Bothell, WA)
5,585,476	Molecular cloning and expression of G-protein coupled receptors	USE	Downstream	Biological	Individual
5,576,210	Mammalian/yeast hybrid G protein-coupled receptors	STRUCTURAL	Upstream	Information	ZymoGenetics, Inc. (Seattle, WA)
5,532,157	Host cell line LVIP2.0Zc, useful in assays to identify ligands and ant agonists of G protein-coupled receptors	ASSAY	Downstream	Biological	The United States of America as represented by the Secretary, Department (Washington, DC)
5,532,151	G protein-coupled receptor kinase GRK6	STRUCTURAL	Upstream	Information	ICOS Corporation (Bothell, WA)
5,482,835	Methods of testing in yeast cells for agonists and antagonists of mammal G-protein coupled receptors	METHOD	Downstream	Biological	Duke University (Durham, NC)
5,385,831	Method for producing a mammalian	METHOD	Downstream	Biological	Zymogenetics, Inc.

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
	G protein coupled glutamate receptor				(Seattle, WA); The Board of Regents of the University of Washington (Seattle, WA)
5,284,746	Methods of producing hybrid G protein-coupled receptors	METHOD	Downstream	Biological	ZymoGenetics, Inc. (Seattle, WA)

Appendix Table 3: Patent Analysis of the GPCR Cell Signaling System

INH=Inhibitor; MOD=Modulator

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
7,122,552	Inhibitors of JAK and CDK2 protein kinases	INH	Downstream	Chemical	Vertex Pharmaceuticals Incorporated (Cambridge, MA)
6,969,760	Jak kinases and regulation of cytokine signal transduction	MOD	Downstream	Biological	St. Jude Children's Research Hospital (Memphis, TN)
6,933,300	JAK-3 inhibitors for treating allergic disorders	INH	Downstream	Chemical	Parker Hughes Institute (Roseville, MN)
6,800,649	Method for inhibiting c-jun expression using JAK-3 inhibitors	INH	Downstream	Chemical	Parker Hughes Institute (St. Paul, MN)
6,452,005	JAK-3 inhibitors for treating allergic disorders	INH	Downstream	Chemical	Parker Hughes Institute (Roseville, MN)
6,326,373	JAK-3 inhibitors for treating allergic disorders	INH	Downstream	Chemical	Parker Hughes Institute (Roseville, MN)
6,313,130	JAK-3 inhibitors for treating allergic disorders	INH	Downstream	Chemical	Parker Hughes Institute (Roseville, MN)
6,265,160	Method of identifying inhibitors of the Jak-Stat signal transduction pathway	METHOD	Downstream	Biological	Department of Health and (Washington, DC)
6,210,654	Jak kinases and regulation of cytokine signal transduction	MOD	Downstream	Biological	St. Jude Children's Hospital (Memphis, TN)
6,177,433	JAK-3 inhibitors for treating allergic disorders	INH	Downstream	Chemical	Parker Hughes Institute (Roseville, MN)
6,136,595	Jak kinases and regulations of cytokine signal transduction	MOD	Downstream	Biological	St. Jude Children's Hospital (Memphis, TN)
6,080,748	Therapeutic use of JAK-3 inhibitors	INH	Downstream	Chemical	Parker Hughes Institute (Roseville, MN)
6,080,747	JAK-3 inhibitors for treating allergic disorders	INH	Downstream	Chemical	Hughes Institute (Roseville, MN)
5,728,536	Jak kinases and regulation of Cytokine signal transduction	MOD	Downstream	Biological	St. Jude Children's Research Hospital (Memphis, TN)

Appendix Table 4: Patent Analysis of the Jak Cell Signaling System

INH=Inhibitor; MOD=Modulator

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
6,900,043	Phosphatases which activate map kinase pathways	ACTIVATE	Downstream	Biological	Amgen Inc. (Thousand Oaks, CA)
6,984,646	Imidazopyridinones as p38 map kinase inhibitors	INH	Downstream	Chemical	Bayer Healhcare AG (Leverkusen, DE)
6,979,693	Pyrazole derivatives-p38 MAP kinase inhibitors	INH	Downstream	Chemical	Syntex (U.S.A.) LLC (Palo Alto, CA)
6,962,933	Method for inhibiting p38 MAP kinase or TNF-a production using a 1,3-thiazole	INH	Downstream	Chemical	Takeda Pharmaceutical Company Limited (Osaka, JP)
6,630,485	p38 map kinase inhibitors	INH	Downstream	Chemical	Syntex (U.S.A.) LLC (Palo Alto, CA)
6,479,507	p38 MAP kinase inhibitors	INH	Downstream	Chemical	Syntex (U.S.A.) LLC (Palo Alto, CA)
6,444,696	Pyrazole derivatives P38 MAP kinase inhibitors	INH	Downstream	Chemical	Syntex (U.S.A.) LLC (Palo Alto, CA)
6,376,527	Pyrazole derivatives-p38 map kinase inhibitors	INH	Downstream	Chemical	Syntex (U.S.A.) LLC (Palo Alto, CA)
6,316,466	Pyrazole derivatives P-38 MAP kinase inhibitors	INH	Downstream	Chemical	Syntex (U.S.A.) LLC (Palo Alto, CA)
6,316,464	P38 MAP kinase inhibitors	INH	Downstream	Chemical	Syntex (U.S.A.) LLC (Palo Alto, CA)
6,147,107	Specific inhibition of the P42/44 mitogen activated protein (map) kinase cascade sensitizes tumor cells	INH	Downstream	Chemical	Virginia Commonwealth University (Richmond, VA)
6,033,910	Antisense inhibition of MAP kinase kinase 6 expression	INH	Downstream	Biological	Isis Pharmaceuticals Inc. (Carlsbad, CA)
6,566,081	Methods of identifying a compound which modulates the non-transcriptional non-map-kinase induced effects of steroid hormones	METHOD	Downstream	Chemical	The Brigham and Women's Hospital, Inc. (Boston, MA)
6,010,856	Assay systems and methods for measuring P38 map kinase, and modulators thereof	METHOD	Downstream	Biological	The Scripps Research Institute (La Jolla, CA)
6,001,580	Method for assaying ERK2 map kinase	METHOD	Downstream	Biological	Takeda Chemical Industries, Inc. (Osaka, JP)

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
6,806,293	Use of pheromone compounds having MAP kinase modulating activity	MOD	Downstream	Chemical	Darley Pharmaceuticals LTD (Tel Aviv, IL)
6,537,996	Modulators of p38 MAP kinase	MOD	Downstream	Chemical	Iconix Pharmaceuticals, Inc. (Mountain View, CA)
6,706,869	Map kinase phosphatases and polynucleotides encoding them	STRUCTURAL	Upstream	Information	Wyeth (MA)
6,566,511	MAP kinase phosphatase mutant	STRUCTURAL	Upstream	Information	Syngenta AG (Basel, CH)
6,376,747	Plant-derived map kinase kinase	STRUCTURAL	Upstream	Information	Her Majesty the Queen in right of Canada as represented by the Minister of (CA)
6,376,214	DNA encoding a novel homolog of CSBP/p38 MAP kinase	STRUCTURAL	Upstream	Information	SmithKline Beecham Corporation (Philadelphia, PA)
6,190,663	Human MAP kinase homolog	STRUCTURAL	Upstream	Information	Incyte Genomics, Inc. (Palo Alto, CA)
5,989,885	Specific mutations of map kinase 4 (MKK4) in human tumor cell lines identify it as a tumor suppressor in various types of cancer	STRUCTURAL	Upstream	Information	Myriad Genetics, Inc. (Salt Lake City, UT)
5,846,778	Human map kinase homolog	STRUCTURAL	Upstream	Information	Incyte Pharmaceuticals, Inc. (Palo Alto, CA)
5,663,313	Human map kinase homolog	STRUCTURAL	Upstream	Information	Incyte Pharmaceuticals, Inc. (Palo Alto, CA)
6,765,128	Method of using a pathogen-activatable map kinase to enhance disease resistance in plants	USE	Downstream	Biological	Rutgers, The State University of New Jersey (New Brunswick, NJ)
5,977,442	Salicylic acid induced map kinase and its use for enhanced disease resistance in plants	USE	Downstream	Biological	Rutgers, The State University of New Jersey (New Brunswick, NJ)

Appendix Table 5: Patent Analysis of the MAP Kinase Cell Signaling System

INH=Inhibitor; MOD=Modulator

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
7,081,343	Methods for identifying modulators of NF-KB activity	METHOD	Downstream	Biological	The Regents of the University of California (Oakland, CA)
6,740,522	Antibodies against ligand for receptor activator of NF-kB	USE	Downstream	Biological	Immunex Corporation (Seattle, WA)
6,696,498	2-cyclopenten-1-one and its derivatives as inhibitors of the NF-kB factor	INH	Downstream	Chemical	Consiglio Nazionale Della Richerche (Rome, IT)
6,660,268	Proteasome regulation of NF-KB activity	MOD	Downstream	Biological	The President and Fellows of Harvard College (Cambridge, MA)
6,642,215	Method of modulating NF-kB activity	MOD	Downstream	Chemical	Leo Pharma A/S (Ballerup, DK)
6,545,027	Methods of modulating NF-kB transcription factor	MOD	Downstream	Chemical	Eli Lilly and Company (Indianapolis, IN)
6,410,516	Nuclear Factors associated with transcriptional regulation	STRUCTURAL	Upstream	Information/ Biological	President & Fellows of Harvard College (Cambridge, MA); Massachusetts Institute of Technology (Cambridge, MA); Whitehead Instittue for Biomedical Research (Cambridge, MA)
6,392,100	2-Cyclopenten-1-one as inhibitors of the NF-KB factor	INH	Downstream	Chemical	Consiglio Nazionale Delle Richerche (Rome, IT)
6,123,943	NF-KB activity inhibitor	INH	Downstream	Chemical	Kaken Shoyaku Co., Ltd. (Tokyo, JP)
6,509,377	Use of a 2-hydroxy-4-trifluoromethylbenzoic acid derivatives as inhibitors of the activation of the nuclear transcription factor NF-.kappa.B	INH	Downstream	Chemical	J. Uriach & Cia, S.A. (Barcelona, ES)
6,498,147	Suppression of nuclear factor-.kappa.b dependent processes using oligonucleotides	INH	Downstream	Biological	The Scripps Research Institute (La Jolla, CA)

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
5,981,583	Inhibition of nuclear transcription factor NF-.kappa.B by caffeic acid phenethyl ester (CAPE), derivatives of CAPE, capsaicin (8-methyl-N-vanillyl-6-nonenamide) and resiniferatoxin	INH	Downstream	Chemical	Research Development Foundation (Carson City, NV)
5,591,840	Antisense oligonucleotides directed against nucleic acids encoding NFKB transcription factor	STRUCTURAL	Upstream	Information/ Biological	Hoffmann-La Roche Inc. (Nutley, NJ)

Appendix Table 6: Patent Analysis of the NF-κB Cell Signaling System

INH=Inhibitor; MOD=Modulator

U.S. Patent No.	Patent Title	Patent Categorization	Phase	Paradigm	Patent Assignee
6,815,176	Assays for sensory modulators using a sensory cell specific phospholipase C	METHOD	Downstream	Biological	The Regents of the University of California (Oakland, CA)
5,847,074	Phospholipase C-inhibiting peptides	INH	Downstream	Biological	Kyowa Hakko Kogyo Co., Ltd. (Tokyo, JP)
5,677,420	Phospholipase c-inhibiting peptides	INH	Downstream	Biological	Kyowa Hakko Kogyo Co., Ltd. (Tokyo, JP)
5,580,956	Phospholipase C-inhibiting peptides	INH	Downstream	Biological	Kyowa Hakko Kogyo Co., Ltd. (Tokyo, JP)
5,474,921	Expression and purification of phosphoinositide-specific phospholipase C-.gamma.	METHOD	Downstream	Biological	Merck & Co., Inc. (Rahway, NJ)
6,235,729	Uses of phospholipase C inhibitors	INH	Downstream	Chemical	UAB Research Foundation (Birmingham, AL)
5,519,163	Inhibitors of phosphoinositide-specific phospholipase C	INH	Downstream	Chemical	Merck & Co., Inc. (Rahway, NJ)
5,352,810	Phosphatidylinositol analogues, inhibitors of phosphatidylinositol specific phospholipase C	INH	Downstream	Chemical	Mediolanum Farmaceutici S.p.A. (Milan, IT)
6,958,152	Human phospholipase C delta 5	STRUCTURAL	Upstream	Information	Merck Patent GmbH (Darmstadt, DE)
6,897,056	32544, a novel human phospholipase C and uses thereof	STRUCTURAL	Upstream	Information	Millennium Pharmaceuticals, Inc. (Cambridge, MA)
6,534,301	16835, a novel human phospholipase C family member and uses thereof	STRUCTURAL	Upstream	Information	Millennium Pharmaceuticals, Inc. (Cambridge, MA)
6,060,302	Human phospholipase C-.alpha. and DNA sequence encoding the same	STRUCTURAL	Upstream	Information	Shionogi & Co., Ltd. (Osaka, JP); Hirano; Naoto (Tokyo, JP)
5,676,946	Phospholipase C homolog	STRUCTURAL	Upstream	Information	Incyte Pharmaceuticals, Inc. (Palo Alto, CA)
5,587,306	Phospholipase C homolog	STRUCTURAL	Upstream	Information	Incyte Pharmaceuticals, Inc. (Palo Alto, CA)

Appendix Table 7: Patent Analysis of the Phospholipase C Cell Signaling System

INH=Inhibitor; MOD=Modulator

APPENDIX 2:
SAMPLE RECOMBINANT CAPITAL ALLIANCE PARADIGM CATEGORIZATION DATA

Partnership	Phase Categorization	Paradigm Categorization
Aging & Age-related Disease	U	BP
Collaboration for Diabetes Research	U	BP
Protein Crystallography to Advance Drug Discovery	U	BP
Human Neural Crest Stem Cells in Human Transplantation	U	BP
Beta Amyloid for Alzheimer's	U	BP
Profile Liver Progenitor Stem Cells	U	BP
Infectious Disease Collaboration	U	BP
Type II Diabetes Cell Biology	U	BP
Peptide Chemistry	U	BP
Stem Cell Clones for Gene Trap Mutations	U	BP
Drug Discovery for Inflammatory Diseases	U	CP
TTP Translational Technology for Drug Discovery Worldwide	U	CP
Drug Discovery Collaboration	U	CP
Discovery & Preclinical Development of New Kinase Inhibitors	U	CP
Drug Discovery Collaboration	U	CP
Drug Discovery Collaboration	U	CP
Small Molecule Drug Discovery Program	U	CP
Drug Discovery Collaboration	U	CP
Drug Discovery Collaboration for Bone & Joint Disease	U	CP
Drug Discovery Collaboration	U	CP
Development of Next Generation Proteins & Peptides	U	IP
Prostate Cancer Drug Target Discovery	U	IP
Target Discovery for Metabolic Diseases	U	IP
High-density Whole Genome Analysis	U	IP
Novel Biomarkers for Lung Cancer	U	IP
Biomarker Study for Toxicity	U	IP

Partnership	Phase Categorization	Paradigm Categorization
Cancer Biomarkers	U	IP
Drug Targets for CNS Diseases	U	IP
Glycomics Collaboration	U	IP
Systems Biology Collaboration	U	IP
Antibody Collaboration & Cross-license	D	BP
Antibody Identification & Production	D	BP
Oral RNA-Directed Therapeutics	D	BP
Gene Therapy Alliance	D	BP
MAbs for Alzheimer's Disease	D	BP
RNAi as Therapeutic Agents	D	BP
Natural Compounds for Disease Prevention	D	BP
Cancer MAbs Discovery & Development	D	BP
MAbs for Rheumatoid Arthritis (RA) & Inflammatory Diseases	D	BP
Sirna-027 and RNAi Products for Ophthalmology	D	BP
FieldFocus Compounds Development	D	CP
Selective Removal of Target Molecules from Fluid Mixtures	D	CP
Human Response Prediction platform for Clinical Drug Response Prediction	D	CP
Biopharmaceutical Research Services	D	CP
DrugMatrix Chemogenomics system & Drug Signatures® Library	D	CP
SoftFocus® for Hepatitis and HIV Programs	D	CP
Macrozyme's Library of Glucosylceramide Synthase Inhibitors	D	CP
PDE10 inhibitors for Neurological & Psychiatric Disorders	D	CP
Library Compounds from SoftFocus® collection	D	CP
Protein Kinase C (PKC) Modulators	D	CP
CRADA for Biomarkers Associated with Chemical Warfare Agents Exposure	D	IP
siRNAs in Hearing Restoration	D	IP
Proteins and Peptides Production Technology	D	IP-Tech
SilenceSelect Technology for Drug Target Validation	D	IP-Tech

Partnership	Phase Categorization	Paradigm Categorization
Protein Crystallography Service Agreement	D	IP-Tech
Access PharmaCarta(TM)	D	IP-Tech
Crystallography Technology For Drug Discovery	D	IP-Tech
High Content and High Throughput Screening Software	D	IP-Tech
Genedata Expressionist Software	D	IP-Tech
Bioinformatics Software Products	D	IP-Tech

Appendix Table 8: Recombinant Capital Alliance Paradigm Categorization Data

U=Upstream, D=Downstream; BP=Biological Paradigm, CP=Chemical Paradigm,
IP=Information Paradigm, IP-Tech=Information Paradigm (Technology Development)

APPENDIX 3:
SAMPLE RECOMBINANT CAPITAL ALLIANCE SUBJECT CATEGORIZATION DATA

Partnership	Paradigm Categorization	Subject Categorization
Infectious Disease Collaboration	BP	Biological Information
Angiogenesis for Cancer	BP	Disease
Genomics-based Drug Discovery Collaboration	BP	Drug Discovery
Genotyping Services for SNP analysis	BP	Other
Antibody Production	BP	Process
Peptide Screening	BP	Screening
Ex vivo Cell Therapy for Leukemia	BP	Therapeutic
Transgenic Models of Alzheimer's	BP	Tool
Combinatorial Chemistry and High Throughput Screening	CP	Combinatorial Chemistry
Small Molecule Discovery for Hepatitis	CP	Drug Discovery
Molecular In Vivo Imaging Agents for Cancer Detection	CP	Other
Screening of Chiron Peptoids	CP	Screening
M20-2 as IL-1 Inhibitor	CP	Therapeutic
PharmaCarta Chemogenomics Platform	CP	Tool
Human Genes Required for Malaria Infection Process	IP	Biological Information
Molecular Mechanisms of Spinal Muscular Atrophy	IP	Disease
Proteins and Peptides Production Technology	IP	Process
Whole Genome Wide siRNA Library	IP	Tool
Transcription-based Assay Technology	IP-Tech	Information Technology
Assay Development and Target Screening	IP-Tech	Screening

Appendix Table 9: Recombinant Capital Alliance Subject Categorization Data

BP=Biological Paradigm, CP=Chemical Paradigm, IP=Information Paradigm,
IP-Tech=Information Paradigm (Technology Development)

APPENDIX 4:
DATA SOURCES FOR CONSORTIUM ANALYSIS

Consortium	Consortium Website	Peer-Reviewed Publication	Press Release	Other
Affymetrix-National Alliance for Autism Research	√		√	
Agilent-Industry Open Microarray Design Program (TRC)	√		√	
Alliance for Cellular Signaling (AfCS)	√	√		
Beta Cell Biology Consortium (BCBC)	√	√		
Biological Innovation for Open Society (BIOS)	√	√		
Cancer Vaccine Consortium	√		√	
Cell Migration Consortium	√	√		
Collaborative Cross		√		
Combinatorial Chemistry Consortium	√			√
Consortium for Functional Glycomics (CFG)	√		√	
DopaNet	√		√	
Functional Proteomics Consortium	√	√		√
HepatoSys	√		√	
Human Epigenome Consortium	√	√	√	
Human Genome Consortium	√	√	√	
International Genomics Consortium	√		√	
International HapMap Project	√	√		
International Molecular Exchange Consortium	√		√	
International Regulome Consortium	√		√	√
International Rice Functional Genomics Consortium	√		√	
International Rice Genome Sequencing Project	√		√	
International Sequencing Consortium	√		√	
Knockout Mouse Project	√	√		
MalariaGEN	√	√		
MitoCheck Consortium	√	√		
Mouse Genome Sequencing Consortium (MGSC)	√	√	√	

Consortium	Consortium Website	Peer-Reviewed Publication	Press Release	Other
Mouse Models of Human Cancers Consortium (MMHCC)	√			√
Nanotechnology Consortium	√		√	
Novartis Institutes for Biomedical Research-Broad Institute Alliance	√	√	√	
Osteoarthritis Initiative	√		√	
Public Population Project in Genomics	√			√
Receptor Tyrosine Kinase (RTK) Networks Consortium	√			√
Research Collaboratory for Structural BioInformatics (RCSB)	√			√
RNAi Consortium	√	√	√	
SNP Consortium	√	√		
Structural Genomics Consortium	√	√		√
SYMBIONIC	√			√
TB Structural Genomics Consortium	√	√		
The Lipid MAPS Consortium	√		√	

Appendix Table 10: Data Sources for Consortium Analysis

Other=Survey, Director Presentation, Consortium Annual Report

APPENDIX 5: CONSORTIUM SURVEY

Objectives and Outcomes:

1) Indicate from the list provided below the type of research generated by the consortium:

A. Drug discovery research
B. Drug discovery tools
C. Preclinical research
D. Clinical research
E. Other: _____

2) Describe the objectives of the research consortium:

_____
_____
_____
_____
_____

3) To date, indicate what has been accomplished by the research consortium:

_____
_____
_____
_____
_____

Participants and Organization:

4) Indicate who the significant participants (from a time or resource perspective) are within the research consortium (check all answers that are applicable):

A. Academic Institutions
B. Non-profit Research Organizations
C. Government Laboratories
D. Private Firms
E. Other: _____

5) Indicate the geographic location of these participants:

A. Within province or state only
   Indicate province or state: _____
B. Within country only

Indicate country: _____

C. International locations
Indicate locations for only significant participants: _____

6.1) Are there specific organizational divisions within the research consortium?

A. Yes
B. No

6.2) If you answered yes to question number 6.1, are the divisions determined by:

A. Project
B. Technology
C. Location
D. Other: _____

7) What communication strategies are used by the research consortium participants (check all answers that are applicable)?

A. In Person
B. Telephone
C. Online
D. Email
E. Mail
F. Other: _____

Research Generation, Research Dissemination, and Rules:

8.1) Are there rules associated with joining the research consortium?

A. Yes
B. No

8.2) If you answered yes to question number 8.1, how can members join the research consortium?

_____
_____
_____
_____
_____

9.1) Are there rules associated with exiting the research consortium?

A. Yes
B. No

9.2) If you answered yes to question number 9.1, how can members exit the consortium?

_____
_____
_____
_____
_____

10.1) Are there rules to determine the allocation of research-based tasks?

A. Yes
B. No

10.2) If you answered yes to question number 10.1, describe the rules that determine how research-based tasks are allocated; please provide specific details of the tasks in your answer:

_____
_____
_____
_____
_____

10.3) Are there mechanisms to address non-compliance to the rules described in question number 10.1?

A. Yes
B. No

10.4) If you answered yes to question number 10.3, describe the mechanisms that exist to address non-compliance to the rules regarding responsibility for conducting research:

_____
_____
_____
_____
_____

11.1) Are there rules to determine how research results are disseminated within the consortium?

A. Yes
B. No

11.2) If you answered yes to question number 11.1, describe the rules that exist to address the dissemination of research within the consortium:

_____
_____
_____
_____
_____

11.3) Are there rules to determine how research results are shared with the public at large?

A. Yes
B. No

11.4) If you answered yes to question number 11.3, describe the rules that exist to address the dissemination of research rules with the public at large:

_____
_____
_____
_____
_____

11.5) Are there mechanisms to address non-compliance to the rules regarding research dissemination?

A. Yes
B. No

11.6) If you answered yes to question number 11.5, describe the mechanisms that exist to address non-compliance to rules regarding research dissemination:

_____
_____
_____
_____
_____

12) What mechanisms are used to share research results with the members of the consortium and/or public at large (check all answers that are applicable)?

A. Publications
B. Database
C. Conferences
D. Internet
E. Other: _____

13) To date, indicate what research i.e., specifically the type and number of biological components that have been disseminated by the research consortium either within the consortium itself or to the public at large?

_____
_____
_____
_____
_____

External Partnerships:

14) What sources of funding are used by the consortium (check all answers that are applicable)?

A. Public grants
B. Private grants
C. Other: _____

15.1) Does the consortium have any external partnerships i.e. beyond the membership itself?

A. Yes
B. No

15.2) If you answered yes to question 15.1, what role do these partners play with respect to conducting the research and/or disseminating the research?

_____
_____
_____
_____
_____

Intellectual Property and Research Usage:

16.1) Are patents filed for the research generated by the consortium?

A. Yes
B. No

16.2) If you answered yes to question 16.1, when are patents filed?

_____
_____
_____
_____
_____

16.3) If you answered yes to question 16.1, indicate who has filed for patents?

_____
_____
_____
_____
_____

16.4) Have any patents been assigned to the research generated by the consortium?

A. Yes
B. No

16.5) If you answered yes to question 16.1, please provide the corresponding patent numbers:

_____
_____
_____
_____
_____

17) How have members used the research generated by the consortium?

_____
_____
_____
_____
_____

APPENDIX 6: DESCRIPTION OF CONSORTIA

1) **Affymetrix-National Alliance for Autism Research-**The National Alliance for Autism Research launched the NAAR Autism Genome Project to find the genes associated with inherited risk for Autism.

2) **Agilent Shared Design Microarray Initiative-**The Agilent shared-design microarray program provides an intellectual forum for researchers to work together using custom microarrays and share them with the global community as needed.

3) **Alliance for Cellular Signaling (AfCS)-**This Alliance was formed to study the mechanisms that cells use to communicate with each other to determine their functions and actions. Investigators at 21 institutions are collectively utilizing their knowledge and expertise to determine how cells interpret signals in a context specific manner.

4) **Beta Cell Biology Consortium (BCBC)-**The Beta Cell Biology Consortium (BCBC) was formed to facilitate interdisciplinary approaches to advance an understanding of pancreatic islet development and function with the long-term goal of developing a cell-based therapy for insulin delivery.

5) **BIOS-**The Biological Innovation for Open Society (BIOS), is a new initiative to extend the concepts of Open Source to biotechnology and other forms of innovation in biology.

6) **Cancer Vaccine Consortium-**The Sabin Vaccine Institute has organized the Cancer Vaccine Consortium to address the networking, clinical, and regulatory needs of corporations, organizations, and researchers working in cancer vaccines. The goal of the consortium is to accelerate the process of bringing cancer vaccines from the development stage to the clinic.

7) **Cell Migration Consortium-**The Cell Migration Consortium is dedicated to accelerating progress in migration-related research by fostering multi-disciplinary research activities and producing novel reagents and information.

8) **Collaborative Cross-** The goal of the Consortium is to promote the development of mouse-based resources that can be used to understand, treat, and ultimately prevent human diseases.

9) **Combinatorial Chemistry Consortium-**The Accelrys Combinatorial Chemistry Consortium was organized with the objective to develop tools for high-throughput drug discovery modeling.

10) **Consortium for Functional Glycomics (CFG)-**The Consortium for Functional Glycomics (CFG) was established to understand the role of carbohydrate-protein interactions at the cell surface in cell-cell communication.

11) **DopaNet-** This network's goal is to investigate precisely and quantitatively all the aspects of neurotransmission—at the levels of the molecule, the supra-molecular assembly, the neuronal cell, and the neuronal network— in a specific neuronal system, involved in many neuropathologies, such as Parkinson's disease, schizophrenia and drug abuse.

12) **Functional Proteomics Consortium-**The purpose of this Accelrys Consortium was to offer members exclusive access to the most complete collection available of protein sequences having assigned function.

13) **HepatoSys-**HepatoSys focuses on a quantitative understanding of complex and dynamic cellular processes in detoxification, endocytosis, iron regulation, and regeneration in mammalian hepatocytes.

14) **Human Epigenome Consortium-**A public/private collaboration that aims to identify and catalogue Methylation Variable Positions (MVPs) in the human genome with the goal of providing insight into the complex relationship between genetics and epigenetics that underlies both normal cellular homeostasis and disease states.

15) **Human Genome Consortium-**The Human Genome Project was officially launched in October of 1990. The project resulted in the identification of many genes, the development of a physical map of the genome, and the sequencing of the 3 billion letters comprising the genome.

16) **International Genomics Consortium-**The International Genomics Consortium is a non-profit medical research organization that is building on the discoveries of the Human Genome Project. This first project called expO will provide biomedical investigators with information on which gene activities are increased or decreased in patient tumour samples.

17) **International HapMap Project-**A partnership of scientists and funding agencies from Canada, China, Japan, Nigeria, the U.K., and the U.S. with the objective to develop a public resource that will enable researchers to find genes associated with human disease and response to pharmaceuticals. A haplotype map (sets of associated SNP alleles in a region of a chromosome) of the human genome—the HapMap, will describe the common patterns of human DNA sequence variation.

18) **International Molecular Exchange Consortium-** The IMEx consortium is a group of major public interaction data providers sharing curation efforts and exchanging completed records on molecular interaction data, similar to successful global collaborations for protein and DNA sequences, as well as for macromolecular structures.

19) **International Regulome Consortium-**This consortium is conducting what is known as the third generation genomics project to completely map the regulatory networks that control gene expression.

20) **International Rice Genome Sequencing Project and International Rice Functional Genomics Working Group**-Public and private sector participants contributed to the completion of draft sequences from two rice subtypes in 2002; the rice community further decided that a similarly structured consortium that would facilitate research in the post-sequencing functional genomics era was necessary.

21) **International Sequencing Consortium-**The International Sequencing Consortium (ISC) was established to provide a forum for genomic sequencing groups and their funding agencies to share information, coordinate research efforts, and address common issues raised by genomic sequencing, such as data release and data quality.

22) **Knockout Mouse Project-**The Knockout Mouse Project is a trans-NIH initiative that aims to generate a comprehensive and public resource comprised of mouse embryonic stem (ES) cells containing a null mutation in every gene in the mouse genome.

23) **MalariaGEN-** The aim of MalariaGEN is to bring together expert scientists to explore and identify critical mechanisms of protective immunity against malaria which could lead to successful malaria vaccine development.

24) **Mitocheck Consortium-**MitoCheck is an integrated research project which brings together leading European research groups to study systematically the regulation of mitosis in human cells.

25) **Mouse Genome Sequencing Consortium (MGSC)-**The Mouse Genome Sequencing Consortium (MGSC), a public-private partnership of institutes, was modeled after the SNP consortium with the aim to accelerate, facilitate, and coordinate global mouse genomic sequencing efforts.

26) **Mouse Models of Human Cancers Consortium (MMHCC)-**The Mouse Models of Human Cancers Consortium (MMHCC) is a collaborative program designed to derive and characterize mouse models, and to generate resources, information, and innovative approaches to the application of mouse models in cancer research.

27) **Nanotechnology Consortium-** The Accelrys Nanotechnology Consortium aims to extend existing and create new software tools for the investigation of materials at the nanoscale.

28) **Novartis Institutes for Biomedical Research-Broad Institute Alliance-**Novartis, the Broad Institute of MIT, and Harvard developed this joint project to decipher the genetic causes of type 2 diabetes. The team plans to make its findings freely available to scientists worldwide.

29) **Osteoarthritis Initiative-**The Osteoarthritis Initiative (OAI) is a public-private partnership that brings together resources to help find biological and structural markers (biomarkers) associated with the development and progression of the joint disease.

30) **Public Population Project in Genomics**-The Public Population Project in Genomics (P3G) aims to create an international consortium to foster collaboration between researchers in the field of population genomics with the goal of understanding the interaction between genes, environment, lifestyle, and disease.

31) **Receptor Tyrosine Kinase (RTK) Networks Consortium**-The Receptor Tyrosine Kinase (RTK) Networks Consortium is an organization to facilitate and coordinate international efforts for the continued understanding of RTK signaling pathways and its relationship to human pathologies.

32) **Research Collaboratory for Structural BioInformatics (RCSB)**-The Research Collaboratory for Structural Bioinformatics (RCSB) is a non-profit consortium dedicated to improving the scientific community's understanding of the function of biological systems through the study of the 3-D structure of biological macromolecules.

33) **RNAi Consortium**-Investigators from three major pharmaceutical firms, Bristol-Myers Squibb, Eli Lilly & Co., and Novartis AG have joined forces with the Broad Institute and other leading academic centres to create the RNA Interference (RNAi) Consortium. The major goal of the consortium is to produce a comprehensive RNAi toolkit that will enable researchers to specifically shut down expression of some 15,000 genes in both human and mouse cells, thereby enabling an understanding of their relevance to different diseases.

34) **SNP Consortium**-The SNP Consortium Ltd. was a non-profit foundation organized for the purpose of providing public genomic data. Its objective was to discover up to 300,000 SNPs distributed evenly throughout the human genome and to make the information related to these SNPs available to the public without intellectual property restrictions.

35) **Structural Genomics Consortium**-This consortium includes a group of multinational companies together with the Wellcome Trust. This charitable organization will attempt to obtain X-ray structures for a broad representation across families of human proteins.

36) **SYMBIONIC**- Symbionic is a project funded by the European Commission, with the aim of understanding issues related to the systems biology of the neuronal cell.

37) **TB Structural Genome Consortium**-The TB Structural Genomics Consortium was formed with the goal of providing a structural basis for the development of therapeutics for tuberculosis.

38) **The Lipid MAPS Consortium**-The consortium has as its goal the development of the Lipid Metabolites and Pathways Strategy, termed LIPID MAPS, that applies a global integrated approach to the study of lipidomics.

References

" 418 Biotechnology Medicines in Testing Promise to Bolster the Arsenal Against Disease", *PhRMA Report,* July 2006.

"1999 Revised Interim Utility Guidelines", USPTO, December 21 1999.

"Accelrys Nanotechnology Consortium Adds Seven Members, Delivers First Computer-Aided Nanodesign Software Solution, *Accelrys.com*, September 02 2005."

Accelrys Nanotechnology Consortium Summary, *Accelrys.com,* 2004.

Akhtar, S. (2002) "Pharmacogenomics: Are Pharmacists Ready for Genotyped Prescribing", *The Pharmaceutical Journal,* Vol. 268, pp. 296-299.

Allarakhia, M. (2001) "Races in Biotechnology: A Case of Prisoner's Dilemma?", *Master's Thesis,* Waterloo, ON.

Allarakhia, M. and Wensley, A. (2005) "A New Biological Paradigm: Innovation and Intellectual Property Rights in Systems Biology", *Nature Biotechnology,* Vol. 23, No. 12, pp. 1485-148.

Altomare, D.A. and Testa, J.R. (2005) "Perturbations of the AKT signaling pathway in human cancer", *Oncogene*, Vol. 24, pp. 7455-7464.

"Antitrust Guidelines for the Licensing of Intellectual Property (IP Guidelines)", *U.S. Department of Justice and the Federal Trade Commission,* April 6 1995.

Antonelli, C. (2003). "Knowledge complementarity and fungeability: Implications for regional strategy", *Regional Studies,* Vol. 37, No. 6-7, pp. 595-606.

Arora, A. and Fosfuri, A. (2003) "Licensing the market for technology", *Journal of Economic Behavior & Organization,* Vol. 52, No. 2, pp. 277-295.

Arora, A. and Gambardella, A. (1990) "Complementary and external linkages: The strategies of large firms in biotechnology", *Journal of Industrial Economics,* Vol. 38, No. 4, pp. 361-379.

Arrow, K. (1962) "Economic welfare and the allocation of resources for invention", In *The rate of and direction of inventive activity: Economic and social factors (A report of the National Bureau of Economic Research),* Princeton University Press, Princeton NJ.

Arthur, B.W. (1989) "Competing Technologies, Increasing Returns, and Lock-In by Historical Events", *Economic Journal,* Vol. 99, pp. 116-131.

Ashok, K., Takada, Y., Boriek, A.M. and Aggarwal, B.B. (2004) "Nuclear factor-kB: its role in health and disease", *Journal of Molecular Medicine*, Vol. 82, pp. 434-448.

Atkinson, P., Batchelor, C. and Parsons, E. (1998) "Trajectories of collaboration and competition in a medical discovery", *Science, Technology and Human Values*, Vol. 23, No. 3, pp. 259-284.

Austin, C.P. et al. (2004) "The Knockout Mouse Project", *Nature Genetics*, Vol. 36, No. 9, pp. 921-924.

Axelrod, R. (1985) *The Evolution of Cooperation*, Basic Books, New York NY.

Barkoff, A. "Merck's Formulation Patent on Pepcid Complete Invalidated by District Court", *SeekingAlpha.com*, June 07 2007.

Barney, J. (1991) "Firm resources and sustained competitive advantage", *Journal of Management*, Vol. 17, No. 1, pp. 99-120.

Beaumont, K. and Negulescu, P. (1999) "Chipping away at GPCR function", *Nature Biotechnology*, Vol. 17, p. 1060.

Beeley, N. and Berger, A. (2000) "A revolution in drug discovery", *British Medical Journal*, Vol. 321, pp. 581-582.

Berndt E., Bui, L.T., Reiley, D. and Urban, G.A. (1994). "The roles of marketing, product quality and price competition in the growth and composition of the U.S. anti-ulcer drug industry", *National Bureau of Economic Research Working Paper No. 4904*, Cambridge, MA.

"Bioethics and Patent Law: The Case of the Oncomouse", *WIPO Magazine*, June 2006.

Blumenthal, D. (1992) "Academic-industry relationships in the life sciences: Extent, consequences, and management", *Journal of the American Medical Association*, Vol. 268, No. 23, pp. 3344-3349.

Blumenthal, D., Causino, N. and Campbell, E.G. (1997) "Academic-industry research relationships in genetics: A field apart", *Nature Genetics*, Vol. 16, No. 1, pp. 104-108.

Bonn, D. (1999) "International consortium SNPs away at individuality", *The Lancet*, Vol. 353, p. 1684.

Bower, J.D and Whittaker, E. (1992) "Global R&D networks: The case of the pharmaceutical industry", *Journal of Industry Studies*, Vol. 1, No. 1, pp. 50-63.

Brenner v. Manson, 383 U.S. 519, 536, 1966.

Breyer, S. (2006) “Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.”, *Supreme Court Opinion No. 04-607*, June 22, 2006

“Broad, Novartis announce diabetes initiative”, *MIT News*, October 28 2004.

Burk, D.L. and Lemley M.A. (2003), “Biotechnology’s Uncertainty Principle” in *Perspectives on Properties of the Human Genome Project*, Elsevier Academic Press, San Diego CA

Cancer Vaccine Consortium Newsletter, Vol. 1, No. 1, December 2003.

Caskey, T.C. (1996) “Gene patents-a time to balance access and incentives”, *Trends in Biotechnology*, Vol. 14, pp. 298-302.

Cassier, M. (2002) “Private property, collective property, and public property in the age of genomics”, *International Social Science Journal*, Vol. 54, No. 1, pp. 83-98.

Chang, L. and Karin, M. (2001) “Mammalian MAP kinase signalling cascades”, *Nature*, Vol. 410, pp. 37-40.

“Checking Mitosis on a European Scale”, *Institute of Molecular Pathology*, July 14, 2004.

Chesbrough, H.W. (2003) “The Era of Open Innovation”, *MIT Sloan Management Review*, Vol. 44, No. 3, pp. 35-41.

Chesbrough, H.W. (2007) “Why Companies Should Have Open Business Models”, *MIT Sloan Management Review*, Vol. 48, No. 2, pp. 22-28.

Chesbrough, H.W., Vanhaverbeke, W. and West J. (2006) *Open Innovation: Researching a New Paradigm*, Oxford University Press, Oxford.

Chi, T. (1994) “Trading in strategic resources: Necessary conditions, transaction cost problems, and choice of exchange structure”, *Strategic Management Journal*, Vol. 15, No. 4, pp. 271-290.

Child, J. and Faulkner, D. (1998) *Strategies of cooperation: Managing alliances, networks and joint ventures*, Oxford University Press, Oxford.

Chokshi, D.A. Parker, M. and Kwiatkowski, D.P. (2006). “Data sharing and intellectual property in a genomics epidemiology network: Policies for large-scale research collaboration”, *Bulletin of the World Health Organization*, Vol. 84, No. 5, pp. 382-387.

Chuck, E. “Hear No Evil Patents, See No Evil Patents, Speak of No Evil Patents: Research Tool Patents from the Scientist’s Perspective”, *Economics of Innovation PhD seminar paper*, April 2004.

Churchill, G.A. et al. (2004) "The Collaborative Cross, a community resource for the genetic analysis of complex traits", Nature, Vol. 36, No. 11, pp. 1133-1137.

Civil Action No. 02 CV 11280 RWZ, 2006.

Clark, J., Piccolo, J., Stanton, B., Tyson, K., Critharis, M. and Kunin, S. (2000) "Patent Pools: A Solution to the Problem of Access in Biotechnology Patents", *United States Patent and Trademark Office,* December 5 2000.

Cohen, W.M. and Levinthal, D.A. (1990) "Absorptive Capacity: A New Perspective on Learning and Innovation", *Administrative Science Quarterly*, Vol. 35, pp. 128-152.

Combinatorial Chemistry Consortium Summary Presentation, *Accelrys.com*.

Comparative Mouse Genomics Centers Consortium (CMGCC): Mouse Models to Improve Understanding of the Biological Significance of Human Polymorphisms", *Environmental Health Perspectives*, Vol. 113, No. 8, August 2005.

"Consortium for Functional Glycomics awarded $40.7 million 'glue' grant", Scripps *Research Institute,* September 08 2007.

Coutois, G. and Gilmore, T.D. (2006) "Mutations in the NF-κB signaling pathway: implications for human disease", *Oncogene*, Vol. 25, pp. 6831-6843.

Crick, F. (1988) "How to Live with a Golden Helix", excerpt from *What a Mad Pursuit: A Personal View of Scientific Discovery*, Basic Books, New York NY.

Dalrymple, Dana (2003). "Scientific Knowledge as a Global Public Good: Contributions to Innovation and the Economy", in *The Role of Scientific and Technical Data and Information in the Public Domain*, The National Academies Press, Washington, DC.

Das, T.K. and Teng, B.S. (2000) A resource-based theory of strategic alliances, *Journal of Management,* Vol. 26, No. 1, pp. 31-61.

Dasgupta, P. and Stiglitz, J.E. (1980a) "Industrial Structure and the Nature of Innovative Activity", *Economic Journal*, Vol. 90, No. 358, pp. 266-293.

Dasgupta, P. and Stiglitz, J.E. (1980b) "Uncertainty, Industrial Structure and the Speed of R&D", *Bell Journal of Economics,* Vol. 11, No.1, pp. 1-28.

Davies, K. (2001) *Cracking the Genome: Inside the Race to Unlock the Human DNA*, The Free Press, New York NY.

"Doha WTO ministerial declaration on the TRIPS agreement and public health", *World Trade Organization*, 2001.

Drews, J. (1998) *In Quest of Tomorrow's Medicine*, Springer-Verlag, New York NY.

"Drug Discovery and Development: Understanding the Process", *PhRMA*, February 2007.

Dudek, H., Datta, S.R., Franke, T.F., Birnbaum, M.J., Yao, R., Cooper, G.M., Segal, R.A., Kaplan, D.R. and Greenberg, M.E. (1997) "Regulation of neuronal survival by the Serine-Threonine Protein Kinase Akt", *Science*, Vol. 275, pp. 661-665.

Dutfield, G. (2003) *Intellectual property rights and the life sciences industries: A twentieth century history*, Ashgate Publishing Limited, Burlington VT.

Eisenberg, R.S. (1996) "Intellectual property issues in genomics", *Trends in Biotechnology*, Vol. 14, pp. 302-307.

Eisenberg, R.S. (1997) "Patenting Research Tools and the Law", *In Intellectual Property Rights and Research Tools in Molecular Biology*, edited by the National Research Council, National Academy Press, Washington DC.

Eisenberg, R.S. (2000) "Genomics in the public domain: Strategy and policy", *Nature Reviews Genetics*, Vol. 1, No. 1, pp. 70-74.

Eisenhardt, K.M. and Schoonhoven, C.B. (1996) "Resource-based View of Strategic Alliance Formation: Strategic and Social Effects in Entrepreneurial Firms", *Organization Science*, Vol. 7, pp. 136-150

"Experience of Japan: Contribution by the Patent System to Industrial Development of Japan", *Institute of Intellectual Property*, 2001.

"Expression Project for Oncology (expO) completes first phase of standardized gene expression analyses", *International Genomics Consortium*, January 21 2005.

Foray, D. (2004) *The Economics of Knowledge*, MIT Press, Cambridge MA.

Franke, T.F., Kaplan, D.R., Cantley, L.C. and Toker, A. (1997) "Direct regulation of the Akt proto-oncogene product by Phosphatidylinositol-3,4-bisphosphate", *Science*, Vol. 275, pp. 665-668.

"Functional Genomics: Assigning Protein Function using Annotated Protein Structure Models", *Accelrys.com*, May 2000.

Gambardella, A. (1995) *Science and Innovation: The US Pharmaceutical Industry during the 1980s*, Cambridge University Press, Cambridge.

Garber, K. "Homestead 2000: The Genome", *Signals*, March 3 2000.

"Genedata Collaborates with HepatoSys Systems Biology Competence Network", *Genedata*, July 10 2006.

Gershon, D. (2000) "Pushing the frontiers of interdisciplinary research: an idea whose time has come", *Nature*, Vol. 404, No. 6775, pp. 313-315.

Gilbert, R. and Shapiro, C. (1990) "Optimal Patent Length and Breadth", *RAND Journal of Economics*, Vol. 21, No.1, pp. 106-112.

Gintis, H., Alden Smith, E. and Bowles, S. (2001) "Costly Signaling and Cooperation", *Journal of Theoretical Biology*, Vol. 213, pp. 103-119.

Gladwell, M. (2000) *The Tipping Point: How Little Things Can Make a Big Difference*, Little, Brown and Company, Boston, MA.

Gold, R. and Piper, T. "Time for a made-in-Canada solution: What the RIM case shows us about the country's patent laws", *Globe and Mail*, March 2 2006.

Goodman, L. (2004) "Profits of public-private partnerships", *The Journal of Clinical Investigation*, Vol. 114, No. 6, p. 742.

"GPCRs: The Targets of Today's Drugs and Tomorrow's Blockbusters", *Drug and Market Development*, 2002.

Grant, R.M. and Baden-Fuller, C. (2004) "A knowledge accessing theory of strategic alliances", *Journal of Management Studies*, Vol. 41, No. 1, pp. 61-84.

Greis, N.P., Dibner, M.D. and Bean, A.S. (1995) "External partnering as a response to innovation barriers and global competition in biotechnology", *Research Policy*, Vol. 24, pp. 609-630.

Gulati, R. (1995) "Does familiarity breed trust? The implications of repeated ties for contractual choice in alliances", *Academy of Management Journal*, Vol. 38, No. 1, pp. 85-112.

Gulati, R., Khanna, T. and Nohria, N. (1994) "Unilateral commitments and the importance of process in alliances", *Sloan Management Review*, Vol. 35, No. 3, pp. 61-69.

Hacklin, F., Lopperi, K., Bergman, J.P. and Marxt, C. (2004) "Toward an integrated knowledge management cycle in cumulative open innovation networks", Paper presented at *Proceedings of The R&D Management Conference*, Sesimbra, Portugal, RADMA, July 7-9 2004.

Hagedoorn, J. (1993) "Understanding the rational of strategic technology partnering: Inter-organizational modes of cooperation and sectoral differences", *Strategic Management Journal*, Vol. 14, No. 5, pp. 371-385.

Hall, R. (1992) "The strategic analysis of intangible resources", *Strategic Management Journal,* Vol. 13, No. 2, pp. 135-144.

Hamel, G. (1991) "Competition for competence and inter-partner learning within international strategic alliances", *Strategic Management Journal,* Vol. 12, Summer Special Issue, pp. 83-103.

Hardin, Garrett (1968). "The Tragedy of the Commons", *Science,* Vol. 162, No. 3859, pp. 1243-1248.

Heller, M.A. and Eisenberg, R.S. (1998) "Can patents deter innovation? The anticommons in biomedical research", *Science,* Vol. 280, No. 5364, pp. 698-701.

Hemmings, B.A. (1997) "Akt Signaling: Linking membrane events to life and death decisions", *Science*, Vol. 275, pp. 628-630.

Hennart, J.-F. and Reddy, S. (1997) "The choice between mergers/acquisitions and joint ventures: The case of Japanese investors in the United States", *Strategic Management Journal,* Vol. 18, No. 1, pp. 1-12.

Hensley, S. "Celera gene map earns kudos over Human Genome Project version", *Wall Street Journal*, February 12 2001.

Hilgartner, S. (1996) "Access to data and intellectual property: Scientific exchange in genome research", In *Intellectual Property Rights and Research Tools in Molecular Biology,* National Academy Press, Washington DC, 28-39.

Hood, L.E. (2000) "The university office of technology transfer: The inventor/researcher's view", *CASRIP Symposium Publication Series,* No. 5, CASRIP, University of Washington, Seattle WA.

Horwitz, A.R., Watson, N. and Parsons, J.T. (2002) "Breaking barriers through collaboration: the example of the Cell Migration Consortium", *Genome Biology*, Vol. 3, No. 11, pp. 1-4.

Ideker, T.T., Galitski, L. and Hood, L.E. (2001) "A new approach to decoding life: Systems biology," *Annual Review Genomics and Human Genetics*, Vol. 2, pp. 343-372.

Igaz, P., Toth, S. and Falus, A. (2001) "Biological and clinical significance of the JAK-STAT pathway; lessons from knockout mice", *Inflammation Research*, Vol. 50, pp. 435-441.

"IMEx consortium provides new mechanism for improving access to molecular interaction data", *EMBL-EBI,* August 29 2005.

"International Consortium Initiative (ICI)", *Genome Canada*, December 2004.

"International HapMap Consortium Widens Data Access", *NIH News*, December 10 2004.

"Is the alliance deck becoming "anti-stacked" against innovators?", *Signals*, May 29 1998.

Jones, P.A. and Martienssen, R. (2005) "A Blueprint for a Human Epigenome Project: The AACR Human Epigenome Workshop", *Cancer Research*, Vol. 65, No. 24, pp. 11241-11246.

Kale, P., Singh, H. and Perlmutter, H. (2000) "Learning and protection of proprietary assets in strategic alliances: Building relational capital", *Strategic Management Journal*, Vol. 21, No. 1, pp. 212-237.

Kamien, M.I. and Schwartz, N.L. (1974) "Patent Life and R&D Rivalry", *The American Economic Review,* Vol. 64, pp. 183-197.

Kauffmann-Zeh, A., Rodriguez-Viciana, P., Ulrich, E., Gilbert, C., Coffer, P., Downward, J. and Evan, G. (1997) "Suppression of c-Myc-induced apoptosis by Ras signalling through PI(3)K and PKB", *Nature*, Vol. 385, pp. 544-548

Khanna, T., Gulati, R. and Nohria, N. (1998) "The dynamics of learning alliances: Competition, cooperation and relative scope", *Strategic Management Journal,* Vol. 19, No. 3, pp. 193-210.

Kieff, S.F. (ed). (2003) *Perspectives on Properties of the Human Genome Project*, Elsevier Academic Press, San Diego CA.

Kilgour, M.D. (2006) "Introduction to Game Theory", *Laurier Course Package*, Wilfrid Laurier University.

Kintisch, E. "High Court Raises the Patent Bar", *ScienceNow.com,* April 30 2007.

Kitano, H. (2001) "Systems biology: Toward systems-level understanding of biological systems", In H. Kitano (Ed.), *Foundation of systems biology,* MIT Press, Cambridge MA, pp. 1-29.

Kitano, H. (2002) "Systems biology: A brief overview", *Science*, Vol. 295, No. 5560, pp. 1662-1664.

Klemperer, P. (1990) "How broad should the scope of patent protection be?", *RAND Journal of Economics,* Vol. 21, No. 1, pp. 113-130.

Kluge, E-H.W. (2003) "Patenting human genes: When economic interests trump logic and ethics", *Behavioral Science and Medicine*, Vol. 11, No. 2, pp. 119-130.

Kogut, B. (1998) "Joint ventures: Theoretical and empirical perspectives", *Strategic Management Journal,* Vol. 9, No. 4, pp. 319-332.

Kollock, P. (1998) “Social dilemmas: The anatomy of cooperation”, *Annual Review of Sociology,* Vol. 24, pp. 183-214.

Kondro.W. (1999) “Canada: Schools Urged to Boost Technology Transfer”, *Science,* Vol. 24, No. 5415, p. 726.

Kondro, W. (2004) “Consortium Tackles Mouse Regulome”, *Science,* Vol. 304, p. 942.

Kulik, G., Klippel, A., and Weber, M.J. (1997) “Anti-apoptotic signalling by the IGF-I receptor, PI3K and Akt”, *Molecular Cell Biology,* Vol. 17, pp. 1595-1606.

Kurzrock, R., Gutterman, J. and Talpaz, M. (1998) “The molecular genetics of Philadelphia chromosome-positive leukemias”, *New England Journal of Medicine,* Vol. 319, pp. 990-998.

Jackson, B.A. (2003) “Innovation and intellectual property: The case of genomic patenting”, *Journal of Policy Analysis and Management,* Vol. 22, No. 1, pp. 5-25.

Lakhani, K.R. and von Hippel, E. (2003) “How Open Source Software Works: Free User-to-User Assistance”, *Research Policy,* Vol. 32, No. 6, pp. 923-943.

Larsson, R., Bengtsson, L., Henriksson, K. and Sparks, J. (1998) “The interorganizational learning dilemma: Collective knowledge development in strategic alliances”, *Organizational Science,* Vol. 9, No. 3, pp. 285-305.

Lawler, A. (2004) “Broad-Novartis Venture Promises a No-Strings, Public Gene Database”, *Science,* Vol. 306, p. 795.

Le Novère, N. and Donizelli, M. (2004) “The Molecular Pages of the mesotelencephalic dopamine consortium (DopaNet)”, *BMC Bioinformatics,* Vol. 5, No. 174, pp. 1-9.

“Leahy, Hatch, Berman and Smith Introduce Bicameral, Bipartisan Patent Reform Legislation”, *leahy.senate.gov,* April 2007.

Lemley, M. (2002) “Intellectual Property Rights and Standard-Setting Organizations”, *California Law Review,* Vol. 90, pp. 1889-1981.

Lerner, J. (1995) “Patenting in the shadow of competition”, *Journal of Law and Economics,* Vol. 38, No. 2, pp. 463-495.

Liebeskind, J.P., Oliver, A.L., Zucker, L. and Brewer, M. (1996) “Social networks, learning and flexibility: Sourcing scientific knowledge in new biotechnology firms”, *Organization Science,* Vol. 7, No. 4, pp. 428-443.

Lippman, S.A. and McCardle, K.F. (1987) “Dropout behaviour in R&D races with learning”, *The RAND Journal of Economics,* Vol. 18, No. 2 pp. 287-295.

Mack, G.S. (2006) “Ariad Pharmaceuticals wins first round over Eli Lilly, patents on methods can be far-reaching”, *Journal of the National Cancer Institute*, Vol. 98, No. 15, pp. 1028-1030.

Madey v. Duke University, United States Court of Appeals for the Federal Circuit. 01−1567, October 3 2002.

Madhok, A. (1997) Cost, value and foreign market entry mode: The transaction and the firm”, *Strategic Management Journal*, Vol. 18, pp. 39-61.

Marshall, E. (1996) “Genetics: The human gene hunt scales up”, *Science*, Vol. 274, No. 5292, pp. 1456.

Marshall, E. (1997) “The battle Over BRAC1 goes to court, BRAC2 may be next”, *Science*, Vol. 278, No. 5345, p. 1874.

Marshall, E. (2001) “Bermuda Rules: Community spirit, with teeth”, *Science*, Vol. 291, No. 5507, p. 1192.

Masood, E. (1999) “…consortium plans free SNP map of human genome”, *Nature*, Vol. 398, pp. 545-546.

Maurer, S. (2003). “Designing public-private transactions that foster innovation”, in *The Role of Scientific and Technical Data and Information in the Public Domain*, The National Academies Press, Washington, DC.

Mauro, T. “High Court Dismisses Patent Case”, *Legal Times*, June 23 2006.

“Merck’s Pepcid Complete patent obvious”, Nature Drug Discovery, July 2007.

Merges, R. (1994) “Intellectual property rights and bargaining breakdown: The case of blocking patents”, *Tennessee Law Review*, Vol. 62, pp. 75-106.

Merges, R. (1996) “Property rights theory and the commons: The case of scientific research”, *Scientific Innovation, Philosophy and Public Policy*, Vol. 13, pp. 145-167.

Merton, R. (1957) “Priorities in scientific discovery: A Chapter in the sociology of science”, *American Sociological Review*, Vol. 22, No. 6, pp. 635-659.

Merton, R.K. and Lewis, R. (1971) “The competitive pressures (I): The race for priority”, *Impact of Science on Society*, Vol. 21, No. 2, pp. 151-161.

Meyers, T.C., Turano, T.A., Greenhalgh, D.A. and Waller, P.R.H. (2000) “Patent protection for protein structures and databases”, *Nature Structural Biology*, Structural Genomics Supplement, pp. 950-952.

"Mighty statins", *CBC News*, June 30 2006.

Miller, D. and Shamsie, J. (1996) "The resource-based view of the firm in two environments: The Hollywood film studies from 1936-1965", *Academy of Management Journal,* Vol. 39, No. 3, pp. 519-543.

Mody, A. (1993) "Learning through alliances", *Journal of Economic Behaviour and Organization,* Vol. 20, pp. 151-170.

Mowery, D.C., Oxley, J.E. and Silverman, B.S. (1996) "Strategic alliances and interfirm knowledge transfer", *Strategic Management Journal,* Vol. 17, S2, pp. 77-91.

Mowery, D.C., Oxley, J.E. and Silverman, B.S. (1998) Technological overlap and interfirm co-operation: Implications of the resource-based view of the firm", *Research Policy*, Vol. 27, No. 5, pp. 507-523.

"NAAR Launches Largest Autism Genetics Study", *AutismSpeaks.org*, July 19 2004.

Nelson, R. (1959) "The simple economics of basic scientific research", *Journal of Political Economy,* Vol. 67, No. 3, pp. 297-306.

"NHGRI Policy Regarding Intellectual Property of Human Genomic Sequence", *NHGRI*, April 9 1996.

Nicholson, W. (1985). *Microeconomic Theory*, The Dryden Press, Chicago, IL.

"NIGMS Awards $35 Million to UCSD-Led Consortium to Map Metabolic Pathways in Cells", NIGMS, August 11 2003.

Nishizuka, Y. (1992) "Intracellular signaling by hydrolysis of phospholipids and activation of Protein Kinase C", *Science*, Vol. 258, pp. 607–614.

Nishizuka, Y. (1995) "Protein Kinase C and lipid signaling for sustained cellular responses", *FASEB Journal*, Vol. 9, pp. 484–496.

Nordhaus, W.D. (1969) *Invention, Growth, and Welfare: A Theoretical Treatment of Technological Change*, MIT Press, Cambridge MA.

Oltvai, Z. N. and Barabási, A. (2002). "Life's complexity pyramid", *Science*, Vol. 298, No. 5594, pp. 763-764.

"Open access to health research publications: CIHR unveils new policy", *CIHR*, September 4 2007.

O'Shea, J.J., Gadina, M., and Schreiber, R.D. (2002) "Cytokine signaling in 2002: New surprises in the Jak/Stat pathway", *Cell*, Vol. 109 Supplement, pp. S121-S131.

Ostrom, E., Gardner, R. and Walker, J. (1994) *Rules, games and common-pool resources,* The University of Michigan Press, Ann Arbor MI.

Ostrom, V. (1989) "Some Developments in the Study of Market Choice, Public Choice and Institutional Choice", in *Handbook of Public Administration,* New York NY.

Overwalle, G.V, Zimmeren, E.V., Verbeure, B. and Matthijs, G. (2006) "Models for facilitating access to patents on genetic inventions", *Nature Reviews Genetics,* Vol.7, pp. 143-154.

Oxley, J.E. (1999) "Institutional environment and the mechanisms of governance: The impact of intellectual property protection on the structure of inter-firm alliances", *Journal of Economic Behavior and Organization,* Vol. 38, No. 3, pp. 283-310.

Parchomovsky, Gideon. (2000). "Publish or perish", *Michigan Law Review,* Vol. 98, No. 4, pp. 926-952.

"Patent Reform: The Future of American Innovation", *BIO,* June 6 2007.

Peteraf, M.A. (1993) "The cornerstones of competitive advantage: A resource-based view", *Strategic Management Journal,* Vol. 14, No. 3, p. 179-191.

"Pilot Concerning Public Submission of Peer Reviewed Prior Art, *USPTO,* June 6 2007.

Pisano, G., Shan, W. and Teece, D. (1988) "Joint ventures and collaboration in the biotechnology industry", In *International Collaborative Ventures in US Manufacturing,* Mowery D.C. (ed), Ballinger, Cambridge MA, pp. 182-222.

Poundstone, W. (1992) *Prisoner's Dilemma: John Von Neumann, Game Theory, and the Puzzle of the Bomb,* Doubleday, New York, NY.

Powell, W.W. (1990) "Neither market nor hierarchy: Network forms of organization", In *Research in Organizational Behavior,* Staw B.M. and Cummings L.L. (eds), JAI Press, Greenwich CT, pp. 295-336.

Powell, W.W., Koput, K.K. and Smith-Doerr, L. (1996) "Inter-organizational collaboration and the locus of innovation: Network of learning in biotechnology", *Administrative Science Quarterly,* Vol. 41, pp. 116-145.

Powell, W.W. and Owen-Smith, J. (1998) "Universities and the market for intellectual property in the life sciences", *Journal of Policy Analysis and Management,* Vol. 17, No. 2, pp. 253-277.

"Principles and Guidelines for Sharing of Biomedical Research Resources", *NIH,* December 23 1999.

"Public Population Project in Genomics (P3G)" Presentation", *P^3G*, 2005.

"Public-Private Consortium to Accelerate Sequencing of Mouse Genome", *Sanger.ac.uk*, October 6 2000.

"Public-private consortium to create comprehensive tools for uncovering the functions of human, mouse genes", *Broad Institute*, March 15 2005.

Rai, A.K. and Boyle, J. (2007) "Synthetic Biology: Caught between Property Rights, the Public Domain, and the Commons", *PLoS Biology*, Vol. 5, No. 3, pp. 389-392.

Rai, A.K. and Eisenberg, R.S. (2003). "Bayh-Dole Reform and the Progress of Biomedicine", *Law and Contemporary Problems*, Vol. 66, pp. 289-314.

Raman, R., Venkataraman, M., Ramakrishnan, S., Lang, W., Raguram, S. and Sasisekharan, R. (2006) "Advancing glycomics: Implementation strategies at the Consortium for Functional Glycomics", *Glycobiology*, Vol. 16, No. 5, pp. 82R-90R.

Ramanathan, K., Seth, A. and Thomas, H. (1997) "Explaining joint ventures: Alternative theoretical perspectives", In P.W. Beamish and J.P. Killing (eds.), *Cooperative Strategies: Vol. 1 North American Perspectives*, New Lexington Press, San Francisco CA, pp. 51-85.

Rapoport, A. and Chammah, A.M. (1965) *Prisoner's Dilemma*, The University of Michigan Press, Ann Arbor, MI.

Reichman, J. (2003) "A contractually reconstructed research commons for science and innovation", In *The Role of Scientific and Technical Data and Information in the Public Domain*, The National Academies Press, Washington DC, pp. 141-160.

Re-examination C.N. 90/007, 503.

Reid D., Bussiere, D. and Greenway, K. (2001) "Alliance formation issues for knowledge-based enterprises", *International Journal of Management Reviews*, Vol. 3, No. 1, pp. 79-100.

Roberto, M. and Nelson, R.R. (1998) "Economic Theories about the benefits and costs of patents", *Journal of Economic Issues*, Vol. 32, No. 4, pp. 1031-1052.

Rosenberg, N. and Witte, O.N. (1998) "The viral and cellular forms of the Abelson (abl) oncogene", *Advances in Virus Research*, Vol. 35, pp. 39-81.

Roses, A.D. (2002) "Genome-based pharmacogenetics and the pharmaceutical industry", *Nature Reviews Drug Discovery*, Vol. 1, pp. 541-549.

Sabin Vaccine Report, Vol. 6, No. 2, Summer 2003.

Saegusa, A. (1999) “US firm’s bid to sequence rice genome causes stir in Japan”, *Nature*, Vol. 398, p. 545.

Sattler, M. and Griffin, J.D. (2001) “Mechanisms of transformation by the BCR/ABL oncogene”, *International Journal of Hematology*, Vol. 73, pp. 278-91.

Schadt, E.E., Monks, S.A. and Friend, S.H. (2003) “A new paradigm for drug discovery: integrating clinical, genetic and genomic and molecular phenotype data to identify drug targets”, *Drug Discovery and Design*, Vol. 31, No. 2, pp. 437-443.

Scherer, F.M. and Ross, D. (1990) *Industrial Market Structure and Economic Performance*, Houghton Mifflin, Boston MA.

Scherer, F.M. (2000) “The economics of human gene patent”, *Academic Medicine,* Vol. 77, No. 12, pp. 1348-1367.

Scotchmer, S. and Green, J. (1990) “Novelty and disclosure in patent law”, *RAND Journal of Economics*, Vol. 21, No. 1, pp. 131-145+.

Scotchmer, S. (1991) “Standing on the shoulders of giants: Cumulative research and the patent law”, *The Journal of Economic Perspectives,* Vol. 5, No. 1, pp. 29-41.

Scotchmer, S. (2004) *Innovation and Incentives*, MIT Press, Cambridge, MA.

Senker, J. and Sharp, M. (1997) “Organizational learning in cooperative alliances: Some case studies in biotechnology”, *Technology Analysis and Strategic Management*, Vol. 9, No. 1, pp. 35-51.

Sethi, J.K. (2004) “A burst of energy in metabolic disease research”, Genome Biology,Vol. 5, No. 6, Article 327.

Shapiro, C. (2001). “Navigating the Patent Thickets: Cross-Licenses, Patent Pools, and Standard-Setting”, in A. Jaffe, J. Lerner and S. Stern (Eds.), *Innovation Policy and the Economy*, NBER.

“Sharing Data from Large-scale Biological Research Projects: A System of Tripartite Responsibility”, *Wellcome Trust*, January 2003.

“Shared Microarray Design Program enables scientists to collaborate while maintaining control of their IP”, *Agilent.com*, January 13 2005.

Sulston, J. (2006) “Staking claims in the biotechnology Klondike”, Bulletin *of the World Health Organization*, Vol. 84, No. 5, pp. 412-413+.

Smaglik, P. (2000) “Tissue donors use their influence in deal over gene patent terms”, *Nature*, Vol. 407, No. 6806, p. 821.

Starpoli, C. (1998) “Cooperation in R&D in the pharmaceutical industry: The network as an organizational innovation governing technological innovation”, *Technovation*, Vol. 18, No. 1, pp. 13-23.

Stokes, D.E. (1997) *Pasteur’s Quadrant: Basic Science and Technological Innovation*, Brookings Institution Press, Washington DC.

“SYMBIONIC and Lay Line Genomics”, *Lay Line Genomics*, September 3 2004.

Taussig, R., Ranganathan, R., Ross, E.M. and Gilman, A.G. (2002) “Overview of the Alliance for Cellular Signaling”, *Nature*, Vol. 420, pp. 703-706.

Teece, D.J. (1986) “Profiting for technological innovation: Implications for integration, collaboration, licensing and public policy”, *Research Policy*, Vol. 15, No. 6, pp. 785-805.

Teece, D.J. (1992) “Competition, cooperation, and innovation: Organizational arrangements for regimes of rapid technological progress”, *Journal of Economic Behavior and Organization*, Vol. 18, No. 1, pp. 1-25.

Terwilliger, T.C. et al. (2003) “The TB structural genomics consortium: a resource for Mycobacterium tuberculosis biology”, *Tuberculosis*, Vol. 83, pp. 223-249.

“The International HapMap Project”. (2003) *Nature*, Vol. 426, pp. 789-796.

“The International Receptor Tyrosine Kinase Networks Consortium Executive Committee”, White Paper, 2005.

The Meso-telencephalic Dopamine Consortium (DopaNet) Brochure, *European Science Foundation*.

Thigpen, K.G. (2004) “International Sequencing Consortium”, *Environmental Health Perspectives*, Vol. 112, No. 7, p. A406.

Thomas, S.M. (1999) “Genomics and intellectual property rights”, *DDT*, Vol. 4, No. 3, pp. 134-138.

Thorisson, G.A. and Stein, L.D. (2003) “The SNP Consortium website: past, present and future”, *Nucleic Acids Research*, Vol. 31, No. 1, pp. 124-127.

“US Human Epigenome Project”. (2006). *Environmental Health Perspectives*, Vol. 114, No. 3, p. A 165.

Välimäki, M. (2003) “Dual Licensing in Open Source Software Industry”, *Systemes d´Information et Management*, Vol. 8, No. 1, pp. 63-75.

Walsh, J.P., Arora, A. and Cohen, W.M. (2003) “Effects of research tool patents and licensing on biomedical innovation”, In *Patents in the Knowledge-Based Economy*, The National Academies Press, Washington DC, pp. 285-340.

Ward, C. “Indian Court Rules Against Major Pharmaceutical Company, Protects Access to Generic Drugs”, *World Resources Institute*, August 10 2007.

Watson, J.D. (1968) *Double Helix*, Penguin Putnam, New York NY.

West, J. and Dedrick, J. (2001) “Open source standardization: The rise of Linux in the network era”, *Knowledge, Technology & Policy*, Vol. 14, No. 2, pp. 88-112.

West, J. (2003) “How Open is Open Enough? Melding Proprietary and Open Source Platform. Strategies”, *Research Policy*, Vol. 32, No. 7, pp. 1259-1285.

Wheeler-Jones, C.P.D. (2005) “Cell signaling in the cardiovascular system: An overview”, *Heart*, Vol. 991, pp. 1355-1374.

Williamson, A.R. (2000) “Creating a structural genomics consortium”, *Nature Structural Biology*, Vol. 7, No. 11 supplement, p. 953.

“WTO Agreements and Public Health: A joint Study by WHO and the WTO Secretariat”, *World Trade Organization & World Health Organization*, 2002.

www.accelrys.com, accessed 6/2007.
www.afcs.org, accessed 6/2007.
www.affymetrix.com, accessed 6/2007.
www.agilent.com, accessed 6/2007.
www.autismspeaks.org, accessed 6/2007.
www.betacell.org, accessed 6/2007.
www.bio.org, accessed 9/2007.
www.biocarta.com, accessed 5/2007.
www.bios.net, accessed 6/2007.
www.broad.mit.edu, accessed 6/2007.
canavanfoundation.org, accessed 12/2007.
www.cellmigration.org, accessed 6/2007.
creativecommons.org, accessed 6/2007.
www.doe-mbi.ucla.edu/TB, accessed 6/2007.
www.dopanet.org, accessed 6/2007.
www.epigenome.org, accessed 6/2007.
www.fda.gov, accessed 9/2007.
www.functionalglycomics.org, accessed 6/2007.
www.genome.gov, accessed 6/2007.

www.hapmap.org, accessed 6/2007.
imex.sourceforge.net, accessed 6/2007.
www.internationalregulomeconsortium.ca, accessed 6/2007.
www.intgen.org, accessed 6/2007.
www.intlgenome.org, accessed 6/2007.
www.iris.irri.org, accessed 6/2007.
www.lipidmaps.org, accessed 6/2007.
www.malariagen.net, accessed 6/2007.
mouse.ncifcrf.gov , accessed 6/2007.
www.naar.org, accessed 6/2007.
www.nigms.nih.gov, accessed 9/2007.
www.nih.gov/science/models/mouse/knockout, accessed 6/2007.
www.oai.ucsf.edu, accessed 6/2007.
www.openbiosystems.com, accessed 6/2007.
www.opensource.org, accessed 8/2007.
www.p3gconsortium.org, accessed 6/2007.
www.phrma.org, accessed 9/2007.
www.rcsb.org, accessed 6/2007.
www.recap.com, accessed 4/2007.
rgp.dna.affrc.go.jp/IRGSP, accessed 6/2007.
www.rtkconsort.org, accessed 6/2007.
www.sabin.org, accessed 6/2007.
www.sanger.ac.uk, accessed 6/2007.
www.scienceofcollaboratories.org, accessed 2/2005.
www.sgc.utoronto.ca, accessed 6/2007.
snp.cshl.org, accessed 2/2007.
www.symbionicproject.org, accessed 6/2007.
www.systembiologie.de, accessed 6/2007.
www.uspto.gov, accessed 9/2007.
www.wikipedia.org, accessed 9/2007.