GAME MODELS OF THE DEFECTION DILEMMA IN BIOPHARMACEUTICAL DISCOVERY RESEARCH

Minna Allarakhia [1], D. Marc Kilgour [2], J. D. Fuller[3]

[1] Corresponding Author;
University of Waterloo, Department of Management Sciences, 200 University Avenue West, Waterloo, ON, N2L 3G1, Canada

[2] Wilfrid Laurier University, Department of Mathematics, 75 University Avenue West, Waterloo, Ontario, N2L 3C5, Canada

[3] University of Waterloo, Department of Management Sciences, 200 University Avenue West, Waterloo, ON, N2L 3G1, Canada

Abstract

Recent trends in biopharmaceutical discovery research toward the systems biology paradigm have created a need for interdisciplinary teams with a wide range of skills. Success, especially economic success, will depend on the ability of team members to learn from each other. The mechanisms used for knowledge transfer and the motives of team members during knowledge production are crucial to this sharing of knowledge. Moreover, the timing of appropriation may determine whether downstream developments can be pursued.

In this article 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.

Keywords: patents, systems biology, game models, discovery research

Introduction

In the winner take all situation, the incentive to race to achieve patent priority is strong [25, 33]. 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 [39, 51].

Under existing patent law, biological information is considered a new article of manufacture or composition of matter [12, 13]. However, patent examiners are increasingly finding it difficult to apply the chemical patent law doctrines to biological information. The consequence of this has been the granting of and enforcement of broad patents on biotechnological entities that perhaps should not be enclosed [47, 58]. 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 research dependent on upstream research [1, 9, 16, 51, 52]. A patent system that was developed for a discrete model of innovation and an essentially linear relationship between knowledge elements may no longer be optimal for a knowledge-based, cumulative model of innovation.

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 behavior and relationships of all units of knowledge in a particular biological system from a functional perspective [23, 27, 28]. Genomes are now being described as consisting of complex, intersecting systems rather than unitary collections of separately functioning structures [13, 22]. 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 systems paradigm, many biopharmaceutical companies are reconsidering their competitive strategies with respect to upstream genomic discovery research [7, 15].

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 [1, 39]. 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 [20].

Grant and Baden-Fuller (2004) contend that the primary basis for knowledge-based alliances is knowledge access rather than knowledge acquisition [2, 10, 18, 24, 31, 41, 42, 43]. Such alliances contribute to the efficient integration of knowledge into the development of products and the efficient utilization of knowledge. 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 [18]. 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 [18, 34]. 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 [18].

The capacity of a knowledge network or collaborative alliance to generate new wealth, however, depends on the ability of researchers to learn from each other. Moreover, the structure of mechanisms for knowledge transfer and the transparency of motives during knowledge production are crucial to this sharing of knowledge [31]. In this article we use game models to represent and analyze interactions between partners in collaborative alliances. Our contention is

that cooperate-versus-defect decisions in upstream knowledge production and subsequent knowledge dissemination determine whether researchers can equitably pursue downstream opportunities. These decisions therefore determine a researcher's "freedom to operate" in downstream medical application development.

A Game-Theory Perspective on Discovery Research Interactions

A game of strategy is a model of an "interactive decision problem" in which each of two or more players (decision makers) must choose one from two or more alternatives [48]. Here we assume two players making simultaneous choices, which together determine the outcome. The players' preferences over the possible outcomes are usually different; Rapoport and Chammah (1965) suggest that the most psychologically interesting games are those in which the players' interests are partly opposed and partly coincident, for then the tension between cooperating and competing may throw light on the players' inner conflicts.

Game models provide a useful representation for this tension in the early stages of drug discovery research. 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. 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.

Table 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

	C_2	**D_2**

C_1	3, 3	1, 4
D_1	4, 1	2, 2

In the model of Table 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) [48].

A crucial feature of PD is that the players' incentives drive them toward mutual defection. As is easy to verify in Table 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, 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 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 [3, 6].

It is important to note the societal effects of the situation modeled in Table 1. The U.S. is the world's largest market for biopharmaceuticals, and U.S. patents are crucial to downstream investment and product development. Enclosing discovery knowledge may reduce downstream activities, whereas open disclosure of discovery knowledge – which we identify with the mutual cooperation outcome – would make it readily available to multiple researchers for medical applications.

The Era of the Genome-A Dilemma of Defection

We have argued that any research partner may have an incentive to defect, and that a researcher who expects a partner to defect can do no better than defect as well. Yet both sides know that mutual cooperation is preferable to mutual defection. How can cooperation be stabilized? Credible signals that a researcher intends to cooperate are one approach [30]. For example, researchers may signal their quality as allies by disclosing private knowledge with no assurance of reciprocal benefits. Costly signaling may not only provide a basis for cooperation, but also helps a relationship resist invasion by selfish outsiders or free riders [17]. Sequences of

alternating decisions often provide the opportunity to signal cooperation, and are the basis of the famous tit-for-tat strategy [30]. But sequences of signals depend for their success on repeated interactions by individuals who know each other's identities and maintain records of past behavior [4]. Knowing that their interaction will continue into the future encourages researchers to keep the future in mind; as the possibility of being held accountable reduces the temptation to behave selfishly [30].

Collaborative alliances require maintenance, of course. The incentive to continue to invest in collaboration must be measured against its evolving benefits, common and private. Common benefits are those that accrue to a partner from collective learning and collective application of knowledge generated. Private benefits are those that a partner earns unilaterally, for example by learning from a partner. Yet private benefits can jeopardize the alliance. By pooling a partner's knowledge with internal, unshared knowledge, a researcher may gain competitive advantage with respect to downstream activities. Thus, a researcher who has learned a great deal from a partner may be motivated to withdraw from the alliance. It is not surprising, therefore, that researchers often attempt to gain knowledge from their partner as rapidly as possible [26].

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

Table 2 is a game model that can be used to understand this dilemma. In this game, the benefits of being the sole defector have been removed. Mutual cooperation is now the best possible outcome for everyone, but a sole cooperator is still in a bad position. This feature reflects that a cooperating researcher risks being unable to bargain for access to enclosed knowledge, or being forced to pay high royalties for access. 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. Merges (1996) argues that each researcher will find defection (in this case, privately appropriating knowledge) in his or her own interest, and will therefore expect the partner to similarly defect [40].

Table 2: The Dilemma of Defection in Upstream Discovery Research

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

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

In their analysis of patents on biological research tools, Walsh *et al*. also discuss the concept of "defensive patenting" [54]. Biotechnology and pharmaceutical executives have confirmed that defensive patenting programs are in play 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."

Overall, about a third of industry respondents reported increased patenting of gene sequences, assays, and other research tools as a response to the patenting behavior of other researchers, so as to augment their own freedom to engage in downstream activities [58].

As discovery knowledge has become increasingly complementary and application possibilities have broadened, patents provide a strong bargaining position *vis-à-vis* other researchers who need access to protected knowledge. The dilemma discussed above becomes severe as the defector's uncertainty about the future increases. Another consideration is that, while defecting improves an individual researcher's bargaining position with respect to the protected knowledge, researchers who defect earlier in time may meet reduced success in bargaining with others who remember past actions and may not be so eager to bargain with a defector. In this event, the defector's freedom to operate remains compromised.

Merck Gene Index: Changing the Game

The *transition point* in discovery research is 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 key then to understanding the behavior of research organizations is to recognize this transition point.

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. During the Human Genome Project, Merck decided to finance a separate program to identify sequences in May of 1994, with all sequences available publicly without delay or commitment regarding use. Merck provided financing in the range of $10 million U.S.D. to Washington University, to produce hundreds of thousands of human sequences [29]. The development of the Merck Gene Index created prior art data with the intention of defeating competitor intentions of enclosing human sequences.

In October of 1994, when Britain's Wellcome Trust hosted a meeting with genome leaders to discuss whether or not 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 provided their support to the initiative that had been proposed by Merck [11]. Analysts note that Merck's decision was not entirely "altruistic". Merck wanted to challenge competitor SmithKline-Beecham's hold over a private database. Merck, like other big pharma companies, had been completely shut out of the private database [11, 37]. In this sense, Merck unilaterally moved the transition point using a pre-emptive disclosure strategy as shown in table 3. In this game model, preferences over outcomes are given ordinally.

Table 3: Unilaterally Moving the Transition Point

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

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

Parchomovsky (2000) argues that the prospect of pre-empting the patent rights of a rival can motivate a researcher who is losing an ongoing patent race to publish results. Such a researcher is better off publishing incomplete research results that are not sufficient for a patent application but enough to render the rival's more complete results obvious and therefore unpatentable. Thus, pre-emptive publication permits both researchers to compete in the market for the unpatented product [46].

Merck's pre-emptive strategy was a *response* to a competitor's defection. In other scenarios, players can choose to pre-empt rivals from the outset of research activities. 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, the Broad Institute of MIT, and Harvard announced a joint project to decipher the genetic causes of type 2 diabetes. The Broad-Novartis Diabetes Initiative decided to place all findings about type 2 diabetes directly onto the Internet. Novartis assumed 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", stated Mark Fishman, President of Novartis's biomedical efforts. "You gain much more by being open." 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 [32].

Genomic Consortia-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 unilaterally or jointly defect (Table 4; preferences are given ordinally). 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 [30, 44, 50].

Table 4: Jointly Moving the Transition Point

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

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

The success of the Human Genome Project highlighted the advantages of the consortium. Ostrom et al. (1994) discusses the roles 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. Rule changes 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 [45].

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 [37] Eisenberg uses this theory to also 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 [16, 29]. 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 would not enclose this vital knowledge.

Fears that this promising new technology might be tied up in commercial claims were discussed in 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 & Co., of Whitehouse Station, New Jersey, the group discussed what Williamson called a "pre-emptive strike" against the commercialization of SNPs. Some panelists wanted NHGRI to issue a manifesto aimed at discouraging such patents. But the majority said that NHGRI should simply assemble a new repository of human genetic SNPs and release them unconditionally to the public [37].

Systems Biology Consortia-An Industry Model?

The development of other such open-source initiatives can be traced from the time of the 1990s gene races to present day involving researchers, institutions, and organizations from across the world [31, 53]. Table 5 provides an overview of systems biology consortia, the participants in each consortium, the focus of knowledge in each consortium, the characteristics of the knowledge, and timing and focus of appropriation of knowledge. These consortia use rules and binding agreements to defer appropriation until the characteristics of knowledge warrant patenting to ensure that downstream products are developed. Where tools, reagents, or biological materials are produced or contributed, rules are established with respect to the licensing of this knowledge for non-commercial use. These rules and agreements essentially seek to level the playing field for all downstream researchers in an increasingly complex knowledge environment.

Table 5: Analyzing Open Source Initiatives in the Systems Biology Era [a, b, c]

Alliance	Focus of Knowledge	Knowledge Characteristics	Knowledge Appropriation
Research Collaboratory for Structural Bioinformatics; PUB; Est. 1998	3-D Structure of Biological Macromolecules	HC, NS, HA, D	ODS
SNP Consortium; PPP; Est. 1999	Human Genome Variation Analysis	HC, NS, HA, D	ODS
Beta Cell Biology Consortium (BCBC); PUB; Est. 2001	Pancreatic Islet Cell Development	HC, S (Tools)/NS (Data), HA, E (Tools)/D (Data)	FDLNC
Cell Migration Consortium; PUB; Est. 2001	Cell Migration (Reagents, Technologies and Data)	HC, S (Reagents)/NS (Data), HA, E (Reagents)/D (Data)	ODS; FDLNC
Consortium for Functional Genomics; PUB; Est. 2001	Role of Carbohydrate-Protein Interactions at the Cell Surface	HC, S (Tools)/NS (Data), HA, E (Tools)/D (Data)	FDLNC
Alliance for Cellular Signaling; PPP Est. 2002	Cellular Signaling	HC, NS, HA, D	ODS
DopaNet; PUB; Est. 2002	Neurotransmission	HC, NS, HA, D	ODS
The Lipid MAPS Consortium; PPP; Est. 2003	Study of Lipidomics	HC, NS, HA, D	ODS
Structural Genomics Consortium; PPP; Est. 2003	Three-Dimensional Structure of Proteins	HC, NS, HA, D	ODS
HepatoSys; PPP; Est. 2004	Systems Biology of Liver	HC, S (Tools)/NS (Data), HA, E (Tools)/D (Data)	ODS
International Genomics Consortium; PPP; Est. 2004	Gene Expression Analysis (Cancer Tissue)	HC, NS, HA, D	ODS
SYMBIONIC; PPP; Est. 2004	Systems Biology of the Neuronal Cell	HC, NS, HA, D	ODS
International Molecular Exchange Consortium; PUB; Est. 2005	Molecular Data Exchange	HC, NS, HA, D	ODS
Receptor Tyrosine Kinase (RTK) Networks Consortium; PUB; Est. 2005	RTK Signaling Pathways	HC, NS, HA, D	ODS
Yeast Systems Biology Network; PPP; Est. 2005	Systems Biology Research using the Yeast Saccharomyces cerevisiae Model	HC, NS, HA, D	ODS

[a)] **Participant type** is assessed as follows:

PUB=Public participants only.
PPP=Public-Private Partnership.

[b)] In this analysis of consortia, we assess **knowledge characteristics** as follows:

Complementarity- Confirmation that knowledge production is conditional on the identification and integration of diverse and disperse units acting as inputs (Scale of Low to High Complementarity; HC=High Complementarity, LC=Low Complementarity).

Substitutability-Confirmation that the knowledge can be replicated through human processes with complete preservation of biological form and/or biological function (0 or 1; S=Substitutable, NS=Nonsubstitutable).

Applicability-Confirmation that the knowledge is involved in more than one biological intervention pathway and/or domain (Scale of Low to High Applicability; HA=High Applicability, LA=Low Applicability).

Embodiment-Confirmation that knowledge application and product development are the central goals of the alliance. (0 or 1; D=Disembodied Knowledge, E=Embodied Knowledge).

[c)] **Knowledge Appropriation** is assessed as follows:
ODS=Open Data Sharing.
OTD=Open Technology Development.
FDLNC=Royalty-Free Distribution or License for Non-Commercial Use with reference to tools, biological materials, reagents, and technology.

In the management of systems biology teams and partnerships, the research outcomes to be disseminated, the format for dissemination, and the knowledge that should be privatized for appropriation, should be clearly understood by all the participants [21]. Internal rules or mechanisms used to promote cooperative behavior 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 [19]. Formalizing the requirements to join the network by asking for a sacrificing pre-commitment, can serve as a signal of cooperation to other participants. The shadow of the future and the possibility of interacting with participants during downstream activities may further temper a participant's need to defect particularly during knowledge dissemination. Repeated interactions will foster the expectation that reciprocity between participants will occur, particularly as trust develops [4, 53]. If information about a participant's behavior is then shared with group members, the development of reputations will be possible, motivating individuals to behave cooperatively [30].

Studies also demonstrate the positive effects of communication on cooperation. Across a wide variety of studies, when individuals are provided with the opportunity to communicate with each

other, cooperation increases significantly [30]. While monitoring and sanctioning can be costly to implement, closely interacting groups can use reputations, records of past behavior as determining future interactions, and banishment from groups as means to encourage cooperation during knowledge production and dissemination [4]. An authority that regulates access to knowledge can ensure that a fair and efficient knowledge governance strategy is used [45]. In the social network, characterized by norms of trustworthy behavior in exchanges of information, reciprocity and honesty in research facilitates the production and disclosure of reliable, valuable information, enabling a domain to develop rapidly and at a reasonable cost [34].

Drug Development-Encouraging Downstream Competition

Cooperative enterprises may use binding agreements with respect to their role during knowledge production and then their commitments during knowledge dissemination. Joint ventures spread risk and development costs for new therapeutics. Together, these structures are socially beneficial because they provide efficient access to knowledge and facilitate the development of therapeutics that would probably not be developed by individual firms. In contrast, cooperative strategies that result in collusion are tantamount to monopolies and cartels. In fact, such collusion can appear in the later stages of a drug's life cycle, as brand companies and generic drug manufacturers collude to keep generics off the market.

Competition that results in overinvestment in R&D, as occurred in the Human Genome Project, is wasteful and results in redundant research. Racing for discovery, which eventually results in a lock-up of research domains, can cause dropout due to the heavy costs of accessing knowledge, is likewise detrimental to the consumer, as crucial therapies might not be developed [35].

A balance between cooperation and competition is clearly necessary. Competition may be socially wasteful during the early stages of research when the rapid, open flow of knowledge is

beneficial – an ideal achieved by research consortia, as discussed above [15]. But in the development phase, competition between firms with different approaches can be beneficial, especially if the exclusivity period for the first break-through drug is relatively short, so that "me-too" brand drugs become available rapidly, providing the consumer with access to alternatives at competitive prices. Once application development predominates, the advantages of being first to market make defection inevitable. In Table 6 as in Table 1, each player strongly prefers unilateral defection. But in Table 6 mutual defection is better for both than mutual cooperation. So at least in this latter scenario, individual incentives tend toward a collectively better outcome. Moreover, this outcome is socially optimal if this results in multiple products being introduced to the market.

Table 6: Encouraging Downstream Competition

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

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

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 U.S. 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 [5].

Discussion and Conclusion

The game models developed in this paper provides an effective illustration of changing incentives to cooperate or defect in knowledge production and/or dissemination.

Table 7 summarizes the outcome of the games analyzed in this paper and the implications in terms of discovery research and/or downstream development. From this table, it becomes clear that upstream discovery races can result in the premature enclosure of discovery knowledge-possibly limiting downstream research to the patent holder and licensees that agree to the licensing terms set by the licensor. Unfortunately, in the genomics era, researchers may be forced to prematurely appropriate discovery knowledge in order to ensure a seat on the bargaining table.

Realizing the problems associated with the premature enclosure of knowledge, some firms are unilaterally opting to pre-empt rival firms from patenting through the strategic disclosure of discovery knowledge or cooperatively establishing rules with respect to the patenting of this knowledge. While the appropriation of upstream discovery research can limit downstream product development, we contend that it is imperative to encourage downstream competition (defection in our game model); in this case, competition may result in multiple products entering the market, with a shorter exclusivity period for the first break-through product to enter the market.

Table 7: Strategic Implications from Our Game Analysis

Game Strategy	Outcome of Game	Implications
The Discovery Race	Mutual Defection	Premature appropriation of discovery knowledge.
Dilemma of Defection	Mutual Cooperation or Mutual Defection	Signaling cooperation may be necessary to move away from mutual defection during discovery research.
Changing the Game	Unilateral Cooperation	Pre-emption of patent rights of a rival; Postponement of appropriation to downstream product development.
Changing the Rules	Mutual Cooperation	Rules may be necessary to enable cooperation in discovery research.
The Downstream Race	Mutual Defection	Competition should be encouraged in downstream product development; Consumers provided with alternatives.

The Human Genome Project has dramatically changed how researchers view and practice biology. The Human Genome Project has strengthened the view that biology is an information science with both static and dynamic elements. Systems biology seeks to understand the various hierarchies of biological information, the complex networks of genes and proteins, and the key nodes in a system where perturbations can have a profound impact during medical intervention. Platform technologies will take advantage of central intervention nodes and pathways found in multiple systems.

The Human Genome Project has also emphasized the need for interdisciplinary researchers. To complete the sequence map of the Human Genome required breakthroughs in understanding computational sciences, measurement technologies, statistics, and data management [22, 27]. Tools enabling high-through quantitative measurements of biological information were developed from this collective understanding. Computer science, mathematics, and statistics were also employed to handle, store, disseminate as well as analyze biological information.

Biologists are no longer satisfied with the simple inventory of genomic structures, but are working toward understanding how these structures collectively work together in biological systems that control the development and function of organisms. Biological systems are being analyzed *in silico* and in real time experiments. The objective is to dissect these models in the search for common pathways and mechanisms that can be controlled or redesigned for medical intervention. 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. 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.

Shared research programs, real-time learning-by-doing opportunities, attendance at meetings, presentations, joint publications, and the review of written work, all enable for collective learning and create more opportunities to create new knowledge. Collaborative institutes and academic programs are also increasingly seeking to bring together the complementary assets of science and engineering for systems-based research. Within such institutes and academic programs, faculty and industry participants should define the strategies to be used to generate knowledge as well as the mechanisms to be used to disseminate knowledge. Technology transfer officers at these the collaborating institutions will have to learn if possible, how to parcel out intellectual property rights fairly across institutions, departments, or laboratories. The benefits from assignment of an exclusive license versus the costs to downstream knowledge generation should be weighed before these institutions issue such licenses.

Funding agencies can enable not only the development of the above large-scale collaborative systems-based alliances, but also encourage the open dissemination of any research results. 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. However, should institutions seek patents, federal funding agencies can further advocate public institutions to issue non-exclusive licenses to enable for broad dissemination of the knowledge.

Scientific journals are similarly compelling scientists to submit information to databases prior to publishing and receiving credit for their discoveries. A policy making journal publication contingent on DNA sequence database submission was first implemented by Nucleic Acids Research in 1988, compelling many other journals to follow suit [38].

The United States Patent and Trademark Office (USPTO) also has an essential role during the appropriation of systems-based knowledge. As an example, US 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 [47]. 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 [36]. 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 [8]. Furthermore, in June 2005, the US Patent and Trademark Office (USPTO) commenced a reexamination of the US patent. In the reexamination, the USPTO has asserted that there exists a substantial new question of patentability for certain claims of the patent [49]. From this case, it has become increasingly evident that it is no longer just up to the courts to decide patent rights, but great care must be taken during the initial assignment of broad patent rights by the USPTO.

For industry stakeholders, it is anticipated that an understanding of upstream knowledge characteristics should enable firms to better understand how to manage their strategic alliances and associated knowledge outcomes. In determining alliance structure, managers should examine the goals of knowledge production, namely knowledge discovery versus knowledge application. These goals can be mapped onto the physical form of knowledge to be generated and then optimal alliance structure. Through the correct valuation of knowledge, given a firm's product development goals, managers will also be in a more strategic position to correctly and efficiently appropriate knowledge. Developing the capability to conceptualize and efficiently manage these complexities in systems biology research is fundamentally necessary to ensure that multiple firms (regardless of size and location) can exploit the technological opportunities presented by this new drug discovery and development paradigm.

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