# Transforming Academic Knowledge for Drug Innovation: A Practice-Based View of Objects, Entrepreneurs, and Institutions

By

Yun Su

A Dissertation submitted to the

Graduate School- Newark

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

for the degree of

Doctor of Management and Global Business

Graduate Program in Rutgers Business School

written under the direction of

Professor Deborah J. Dougherty

And approved by

Professor Michelle Gittelman

Professor Arturo Osorio

Professor Lee Clarke

Newark, New Jersey

May 2013

## DISSERTATION ABSTRACT

**Transforming Academic Knowledge for Drug Innovation: A Practice-Based View of Objects, Entrepreneurs, and Institutions**

**By Yun Su**

**Dissertation Director: Professor Deborah J. Dougherty**

Academic-industry partnerships in biopharmaceuticals have been commonly arranged through firms licensing academic patents and universities receiving research grants and royalties. However, this arrangement does not accommodate the complexity in science. The research question of this dissertation is what kinds of social arrangements transform academic knowledge for complex innovation. I conducted interviews and field observations with scientists involved in drug discovery research. I developed a grounded theory on three dimensions of knowledge that characterize the boundaries for science-based complex innovation.

One dimension is the materiality of complex knowledge, which emphasizes on the situated and contextualized learning about how drugs work in the realities of human biology. Another is the epistemic dimension, which highlights the ever-emergent nature of knowledge that motivates scientists to keep asking questions and drawing on rich scientific theories. The third is the activity dimension that directs a purpose of multidisciplinary collaboration among scientists. These dimensions reveal how scientists in the basic and clinical research communities go about creating and commercializing research for innovation. I further examined how the current academic-industry arrangements bridge the two forms of boundaries, and concluded that social arrangements have to support scientists participating in situated learning, raising questions, and engaging in activities to iteratively validate emergent findings.

The contribution of this dissertation is threefold. My theory develops a deeper understanding of the content and substance of knowledge for biopharmaceutical innovation. My in-depth examination of how academic discoveries mediate practices among scientists suggests that these dimensions can create a common ground for scientists, business managers, and investors to collaborate. I also suggest the kinds of knowledge transformation that academic-industry partnerships need to accommodate to promote more effective collaboration.

**ACKNOLWEDGEMENTS**

I would never have been able to finish my dissertation without the support of my dissertation chair, committee members, family, and husband.

I would like to express my deepest appreciation to my advisor, Dr. Deborah J. Dougherty for her tremendous guidance and persistence while providing me with the intellectual freedom to conduct my research. She helped me overcome my challenges and execute my vision. Without her, my Ph.D. would not have been possible. I am also grateful to Dr. Michelle Gittelman for her unyielding support and extraordinary insights. I would also like to thank Dr. Arturo Osorio and Dr. Lee Clarke for their direction and commitment in preparing me to conduct fieldwork.

I am greatly indebted to Dr. Thomas Richardson and Dr. Jennifer Henry for their assistance with my data collection. My gratitude is also extended to all the participants for their time and dedication to my research. I'd also like to express my gratefulness towards the Technology Management Research Center at Rutgers Business School for its financial support. The data collection process would not have been possible without all of your help.

In addition, I'd like to extend my love and appreciation to my father for his support and confidence in choosing this career path for me. I am committed to conduct research in innovation management and hope to contribute to the field for many more years to come. I would also like to thank my husband who is my biggest cheerleader and stood by me throughout the process. Lastly, I would like to express my deepest love to my mother for her words of wisdom and encouragement in our daily phone conversations. Thank you for being in this research process with me.

## TABLE OF CONTENTS

## LIST OF TABLES

# Chapter 1: Introduction

Biopharmaceutical companies collaborate with universities through the licensing of patents and the contracting of research projects. Collaborations with academics benefit companies by allowing access to cutting-edge scientific research and specialized laboratory facilities, as well as co-authorship with academic scientists. Around 2008, these partnerships began to face pressure for change. Because biopharmaceutical companies are facing a productivity crisis from a lack of emerging products in their pipelines, they have increasingly turned to academic labs for new ideas and discoveries. At the same time, the National Institutes for Health (NIH) launched several funding programs to encourage translational science in universities (Collins 2011;Tralau-Stewart, Wyatt, Kleyn, Ayad 2009; Wadman 2010). In conjunction, recent studies from the field of technology transfer have raised skepticism as to whether a transactional relationship is the optimal arrangement between academic and industry partners. For example, pharmaceutical firms prefer to build relationships with universities on projects of exploratory innovation rather than of transactional mechanisms such as, patent licensing or sponsored research (Bercovitz and Feldman 2006, 2007; Milne and Malins 2012). Accordingly, academic-industry partnerships in biomedical fields are experiencing changes at institutional, organizational and practical levels.

One of the critical problems for drug discovery research in the academic-industry collaboration is how to integrate distinctive sets of knowledge and practices between these two groups, while maintaining the goal of producing a safe and effective drug. The integration of distinctive sets of knowledge is especially problematic when it comes to complex innovation. Scientists in biopharmaceutical firms and academia have very

distinct knowledge and practices. On the one hand, industrial scientists apply and contextualize their knowledge, while they focus on developing a safe and effective new drug. On the other hand, academic scientists use theoretical and conceptual knowledge, with the goal of exploring the frontiers of their respective disciplines.

The differences in knowledge and practice create a gap known as the 'valley of death' in drug discovery. It refers to the difficulty of exploiting newly discovered breakthrough knowledge for application. The early stage research of academic laboratories is too premature for industrial scientists to apply directly to their innovation projects. Consequently, we have basic scientific research that discovers the fundamental causes of disease, but we do not have research centers and companies doing the "grunt work that turns such breakthroughs into drugs" (Begley and Carmichael, 2010). The impetus to study this problem is straightforward. The budget for medical research has doubled but the number of new viable drugs launched to the market has decreased by more than half (Scannell, Blackley, Bolden, and Warrington, 2012). In order to bridge the knowledge gap in the biopharmaceutical, this dissertation aims to gain a deep understanding of the dimensions of the complex knowledge that separates the academic and industrial scientists in drug discovery.

The concept of a pragmatic boundary helps to conceptualize the knowledge boundary in an academic-industry partnership. A pragmatic boundary, also known as political boundary, refers to the discontinuities in practices, in which both groups not only have different knowledge-producing practices and conflicting interests, but also have strong dependencies to accomplish a common goal (Carlile, 2004; Dougherty and Dunne, 2012). In terms of knowledge-producing practices, academic scientists publish

novel research results based on their discoveries, while industry scientists integrate established research results for a safe and effective drug. To a certain degree, they have conflicting motivations. Industrial scientists are driven to produce products, while academic scientists are motivated to publish research. At this pragmatic boundary, novel research that is conceptual and abstract needs to be validated and transformed to fit a bigger product system. Members of the both communities understand how knowledge from the other fits within the context of their own work. For biopharmaceutical firms to draw on academic knowledge for product development, knowledge must be transformed from the original academic context to become a part of a complex product system.

The research question of this dissertation is what types of social arrangements enable the transformation of academic knowledge for complex innovation. My goal is to develop a theory about the dimensions of knowledge for complex innovation, in order to gain an understanding about whether or not current social arrangements are sufficient to accommodate this complexity in science. In the next chapter I will set the foundation and discuss the concepts of academic-industry relations as a pragmatic boundary. The pragmatic boundary concept proposes that knowledge has to be transformed when two groups with significantly different knowledge coming together for a common goal. The current literature on academic-industry partnership has not adequately addressed how knowledge is transformed and what it takes to transform knowledge.

My approach to the research question is first to delineate the dimensions of academic discoveries by introducing a new framework, namely a pluralistic framework of objects. I build on the large literature in the sociology of science and innovation management on objects to better understand the nature of knowledge for complex

innovation. I conceptualize academic discoveries with pluralistic dimensions that mediate the interactions among industry, academic scientists, universities and entrepreneurs. The three dimensions of academic discoveries are materiality, epistemic, and activity, which invoke differences in knowledge and practices among different communities in academic drug discovery. Then, I identify whether social boundaries exist among scientists, and determine whether organizational arrangements exist to bridge those boundaries.

## Chapter 2: Theoretical Framework

Discovering a drug that is a safe and effective treatment for a disease is a complex innovation. First, the human biological system is comprised of many parts that interact in complex ways, even in the absence of disease. The relationship between the causes and effects of a disease are complex and only partially understood, so the knowledge required for drug discovery either does not exist or is incomplete. Second, developmental trajectories for complex innovation are non-linear, which means that feedback loops shift from positive to negative and connections shift from loose to tight without warning (Boisot and McKelvey 2010). Minor adjustments can generate enormous changes, and some small perturbations will escalate into major opportunities or problems. For drug discovery, a change in a functional group on a molecule can make the molecule toxic, while other changes may lead to surprising new opportunities. Third, because of the unknowns of human biology and disease, drug discovery scientists deal with very tacit knowledge that they must continually interpret.

The pragmatic boundary framework as defined by Carlile (2004) refers to a type of knowledge boundary. There is a significant difference in knowledge accumulated by the actors, and strong dependencies in activities among the actors are required but not clearly indicated. The variations in knowledge create different interests among actors, and they have to transform domain-specific knowledge to relate to their common knowledge. This concept sheds light on the limitations of the current arrangements for transforming distinctive academic and industrial knowledge. Of the current social arrangements for transferring knowledge, the first involves transferring patents. Companies spend a lot of money modifying technologies to fit their projects after

academic patents are internalized. The second involves academic scientists sitting on the advisory boards of biopharmaceutical companies, but those scientists provide knowledge on an ad hoc basis and are not fully engaged throughout the drug development process. The third involves academic scientists starting up a company based on their discoveries, but start-up companies face constant resource constraints and usually need to seek pharmaceutical companies for merger and acquisition opportunities. Next, I will draw on the framework of the pragmatic boundary to discuss the limitations of these arrangements in more detail.

## ACADEMIC-INDUSTRY PARTNERSHIP AS A PRAGMATIC BOUNDARY

Existing studies from two dominant views of academic-industry partnerships have focused on transacting patents and citing publications as the major knowledge transferring mechanism. These studies measured either the number of citations of academic patents or publications in industry patents (e.g., Jaffe 1986; Jaffe, Trajtenberg and Henderson 1993) or the number of academic licenses in industry products to transfer and translate academic knowledge to the industry (e.g., Colyvas et al. 2002; Mowery et al. 2001). Transferring knowledge through patents enables companies to license academic inventions and integrate them into their innovation projects. Patents define the utility and application of academic inventions in a universal language, which reduces confusion and costs of applying the invention in specific contexts. For example, when a company licenses an academic patent (including utility or design patents), its scientists follow the procedures indicated in the patent and apply them in their projects. Transferring knowledge through patents also implies that the knowledge codified in the patent

sufficiently specifies the differences between the academic knowledge and the firm's innovation projects. In other words, academic knowledge as presented in a patent is ready to "plug into" a company's product development projects, and modification of the procedure will not be necessary.

Transfer of knowledge from academic to industry settings is facilitated both by geographical proximity and social networks. For example, proximity to universities allows companies to gain access to academic research and transfer knowledge for industrial innovation. Some studies have shown that research productivity is positively associated with a shorter distance between a firm and universities (Cockburn and Henderson 1998; Furman et al. 2006). As firms actively reach out to universities searching for novel product ideas, close geographic proximity makes it convenient for firms to tap into academic research trends and inventions. Participation of firms in professional or contractual networks also facilitates the transfer of knowledge from academia. Owen-Smith and Powell (2004) found that membership of biotech companies in a network dominated by public research organizations positively affects their innovations, as correlated to the numbers of patents applied for. Network ties signal their commitment to open-science, the belief in public service, and their reliability. Together, these attributes make scientists comfortable with sharing knowledge without fear that others will profit from it. Shared network ties between industrial and academic scientists enable them to share knowledge or fine-grained information about research (Liebeskind et al. 1996).

The implication from two dominant views is that when academic knowledge is transferred across the academic-industry boundary, a common language in patent

licensing contracts and patents themselves sufficiently explains how companies would apply academic knowledge to innovation. Transferring knowledge, however, becomes problematic when the context of where the knowledge is produced and applied is different. The common language is no longer sufficient to explain the novelty of knowledge (Carlile 2004). Knowledge from the academic and industrial sectors is different. Academics scientists are oriented around breakthroughs and new discoveries (Grinnell 2009). They tend to have deep, specialized knowledge of a specific scientific area with the goal of pushing the knowledge frontier (Stokes 1997). On the other hand, the knowledge practices for industrial scientists are product-oriented, they have a more generalized knowledge of several biological systems, and they integrate various aspects to put together a coherent drug profile. Science published in high-impact journals does not equal feasible innovations with commercial value (Gittelman and Kogut 2003). The assumptions behind academic-industry partnerships are that there is no need for academic scientists to coordinate with industry scientists for the execution of invention and it is not necessary to discuss patent usage or engage in problem-solving with respect to patents. Firms take the active role of defining and shaping the innovation context, and there is no need for academic scientists to change their knowledge transfer practices.

Theoretical knowledge does indeed provide a general direction for solving a problem conceptually, but it does not detail specific solutions for empirical problems. As Pisano points out, companies license in technologies that fit with their existing technological capabilities and product strategies. They look for specific needs to fill in their portfolio. However, universities offer cutting-edge science that may not always fit with a firm's immediate demand (2006: p. 133-134). Thursby, Jesen, and Thursby (2001)

found that only 12% of technology that is licensed is ready for commercialization because the technology is too premature for market launch. The majority of licensed research from universities requires companies to invest significant development work and maintain ongoing cooperation with faculty members to advance the academic invention to a commercial product (Pisano and Teece 2007; Pisano 2006; Bercovitz and Feldmann, 2006). As a consequence, academic-industry partnerships based on licensing patents are important but insufficient to fully exploit academic research for industry's problem solving for specific innovation problems.

The dependency aspect of the pragmatic boundary framework is that actors from different groups are dependent on each other, which is a condition where they "must take each other into account" to fulfill a common goal (Carlile, 2004). In an ideal situation, when an academic scientist and a company enter a partnership, there is a mutual dependence. The industry-related work is incorporated into the academic scientist's day-to-day research activities, and the work performed by the academic scientist will affect the company's product development plan. This working partnership is difficult for academic and industrial scientists to achieve because of their divergent interests. Academics are evaluated by their institutions based on the number of papers published and the amount of research funding received. As such, they dedicate most of their time to writing papers, submitting grants and advising students (Smitth-Doerr 2005). They are less familiar with the timeline for delivering new products and coordinating team members. Industrial scientists, who tend to be grouped in teams, work on a pipeline directed at the delivery of a new drug, so they are constantly considering issues such as feasibility, safety, and efficacy (Dunne and Dougherty, 2010). It becomes difficult to

build relationships between them as their work life and institutional values are distinct.

Some studies have suggested that academic and industrial scientists would develop co-learning behaviors once they work alongside each other. For example, research has suggested that face-to-face interaction facilitates product innovation because innovators across organizational boundaries can discuss, communicate and establish a common vision in their projects. Gittelman (2007) found that close geographical distance enhances innovation outcomes because partners can easily travel for face-to-face interactions. Cockburn and Henderson (1998) found that co-authorship between industry and academic scientists provided an opportunity for learning, discussion and joint problem-solving between academic and industrial partners. In other words, academic and industrial scientists work well together once they reach an agreement on the topic and goal. However, it is unclear what types of institutional arrangements are in place to foster their dependencies. The practice of academic and industrial scientists co-authoring papers is different from the development of feasible products (Gittelman and Kogut, 2003). Therefore, we are unclear as to how they would coordinate and work on a product together.

To resolve the differences in knowledge between academic and industrial partners, active academic entrepreneurs translate the knowledge from academic to industrial contexts. Active academic entrepreneurs are known as star scientists and achieve prominence in universities by publishing in top-tier journals while contributing significantly to industrial innovation (Zucker, Darby, and Armstrong 1994; 2002). Star scientists translate their hands-on research knowledge for industrial innovation through several social arrangements. For example, they start companies based on their discoveries

(Zucker, Darby and Brewer 1998), or they consult as part of an advisory board providing advice to the firm who licensed their patents (Murray 2002; 2004). They may also actively promote their academic patents by strategically framing and justifying the value of their research to biotech firms, venture capital firms, universities, and lawyers (Kaplan and Murray 2008; Shane and Stuart 2002). Through their engagements in both academic and industrial communities, they translate break-through science theories into industrial solutions and have the capacity to mobilize and negotiate interests with industrial partners (Murray 2004).

Social arrangements such as networking relationships or advisory board memberships are more likely to develop dependencies between academic and industrial scientists. As product systems become more complex, "managing dependencies requires the capacity to develop an *adequate* common knowledge" (Carlile 2004). The underlying complexity in science-based products, such as drugs, is tremendous. Biological pathways and objects are connected, and the details about the causes of many diseases are unknown. The knowledge and practices of academic and industrial scientists are dependent upon each other. For example, they divide the task to assess potential compounds and a particular drug target; they share their detailed observations of the compound and the target; and they are in tune with the progress. The "adequate common knowledge" that they develop would be specific to a disease context, such as an aspect of a disease they are targeting, a list of potential molecules, and a tacit emergent observation of biological interactions. In the case of networking or advisory board membership, the dependency between the company and the academic scientist could be on an ad hoc basis. For example, the academic scientists fill in the gaps in the industrial scientists'

observations or advise them on a general direction or potential drug target. The ad hoc consultation through advisory board membership may not develop the "adequate common knowledge" to sustain the dependency.

The last aspect of the pragmatic boundary is novelty, which recognizes that the knowledge at the boundary is very specialized and unique. The actors in different groups do not have an equal understanding to assess the specific novel knowledge. Especially with science-based products, novel ideas create a tremendous amount of uncertainty about the potential to materialize the idea into a product. For example, consider an academic scientist who identifies a protein as a potential drug target for a rare neurodegenerative disease. The knowledge about the novelty of this protein implies that its mechanisms and characteristics are unexplored, and biopharmaceutical firms and investors view this uncertainty as a risk. Companies are less likely to license the protein and develop it as a drug target. As a consequence, the scientist may be more likely to start his own firm to develop and commercialize the protein. The academic scientist possesses hands-on knowledge about this protein that others do not have access to. The novel understanding is rooted in the scientist's lab and close networks.

The challenge that academic scientists face when starting a company is their need for financial and technical capital to perform systematic experiments to confirm that a novel protein has product potential. Shifting from the laboratory setting to business in the boardroom, academic scientists must demonstrate market potential and value by materializing research into tangible products (Murray 2004; Kaplan and Murray 2008). For example, they would need to produce a product profile based on their research, including its concept and objective, design blueprints, manuals, or databases and present

it to potential investors for funding. In addition, empirical studies focusing on star scientists starting new firms overlook the notion that innovation requires collective action and contribution rather than star scientists alone (Rothaermel and Hess 2007). Technological and product innovations are social, collective processes of transforming inputs into goods to increase firms' values and do not rely on a category of innovators, but the organization of innovators, supporting staff and managers (e.g., Tornatzky 1991; Leonard-Barton 1995). Statistical results have shown that it is not only the star scientists that produce scientific results at a firm, but also non-star scientists that mediate their productivity (Rothaermel and Hess 2007). While star scientists focus their energy on fundraising, non-stars perform work to develop novel research into tangible products. Successful product innovation requires star scientists working with non-stars, and the lengthy drug discovery process requires scientists to be highly dependent on each other.

In summary, through the lens of the pragmatic boundary, I discussed three limitations of academic scientists applying their research for drug innovation. The first limitation is that social arrangements such as transferring patents do not sufficiently account for how companies resolve the difference between academic conceptual knowledge and contextualized knowledge for product development. Companies still spend money and effort to transform academic knowledge and adapt their product development. What sort of research knowledge is most useful for drug innovation? What sorts of research outcomes are readily applied and useful for drug discovery? Second, it is insufficient for star scientists being advisory board members to develop the stable dependencies required throughout the lengthy drug development process. How do they develop the capability to connect with firms? What about those academic scientists

without connections to firms, do they participate in the general innovation process? Lastly, scientists starting small companies face constant resource constraints in their effort to systematically confirm their novel ideas have market potential, as they also engage in both patenting and publishing. What sorts of institutional arrangements enable a scientist to do so? While existing studies provide important insights, we do not have a complete understanding about the process. How do these practices transform knowledge for innovation across academic-industry boundary? It becomes clear that we require a new framework, theoretical and empirical, to understand the process of transforming academic knowledge for complex innovation.

The research question of this dissertation is what are the social arrangements in transforming academic knowledge for science-based complex products? From the point of view of academic scientists, this research builds a theory about the kinds of social arrangements based on the dimensions of knowledge for complex innovation that may or may not enable academic scientists to adapt their discoveries to innovation. In the following sections, I will first discuss what it means to transform knowledge from the practice-based perspective, which proposes that common ground and objects are involved in this transformation process. Next, I draw on a pluralistic framework on objects to conceptualize academic discoveries as objects with multiple dimensions in order to put together a holistic picture of practices that academic scientists engage in to adapt their discoveries to industrial innovation.

## TRANSFORMING KNOWLEDGE AT PRAGMATIC BOUNDARIES

Thus far, I have argued that the knowledge in academic-industry partnerships for

drug discovery is conceptualized as pragmatic and that the current partnership arrangements only support the transfer and translation of knowledge. Next, I will discuss how knowledge is transformed at pragmatic boundaries. The pragmatic boundary framework argues that the transformation of knowledge takes place in the practices that produce knowledge. This conceptualization is drawn from the practice-based perspective of innovation management. Practices are considered a set of coordinated activities among individuals and groups working together for understanding, whether it is the study of an epistemic object (i.e., a molecule, a protein or DNA segment) or a material artifact (Cook and Brown, 1999). The coordinated activities consist of a repertoire of actions, such as "learning, organizing, understanding, belonging, and translating" to generate knowledge (Nicolini, Gherardi, Yanow 2003). Knowledge arises from everyday interactions, from active participation and interactions with tasks, technologies, sciences, resources, and others (Bartel and Garud 2009) and is situated in a particular context. Knowledge is not an objective entity to be transferred or exchanged, but it is situated in the everyday practices of innovating including problem-setting and -solving, identifying and exploring alternatives, interpreting intermediate results and reframing the problems (Dougherty 1992; Orlikowski 2002). Together, the transformation of knowledge at a pragmatic boundary means that a repertoire of actions is transformed so that others understand.

A few recent studies have discussed what it requires to transform knowledge at the practical level. Transformation of knowledge is a process where occupational groups come to understand each other and change their understanding and practices. Carlile (2004) defined the transformation of knowledge as the process by which motor engine designers' domain-specific knowledge became relevant to the common knowledge of

safety, engines and climate control groups. Bechky (2003a) gave an example of the transformation of understanding as a member of one community came to recognize how knowledge from another community fit within the context of his own work (p. 321). Dougherty and Dunne (2012) saw transformation in practice as digital and therapeutic scientists use their expertise to develop a problem space to guide their innovation activities. There are three elements enabling knowledge transformation to occur. First, an organizational structure allows face-to-face interactions for occupational groups to physically demonstrate how to execute the work at hand. Second, a common ground allows occupational groups to contribute their understanding. Third, the presence of objects, both material and intellectual, motivates actors to work together. The consequence of transforming knowledge is that the individual's understanding of product, process or organization becomes broader and more diverse (Bechky 2003a).

The first element to enable transforming knowledge is an organizational structure that allows occupational groups to demonstrate and execute work. Innovators are essentially working with their hands, developing hands-on skills manipulating artifacts and putting emphasis on quality of the work (Sennett, 2008). Innovators from different occupational group have different skills for manipulating the artifact. For example, digital scientists work with computers, while therapeutic scientists work with cellular and animal systems. Engineers work with drawings, while assemblers work with automobile parts. Because they have different skills and relationships with the same artifact, an organizational structure that creates a workshop space allows innovators to work together and deal with their skill differences face-to-face. In Carlile's 2004 study, the design group finished designing the computational fluid dynamic tool (CFD) and subsequently

went to four other groups (i.e., vehicle styling, engine, climate control, and safety groups) to teach them how to use the new CFD. For each individual group, the design group demonstrated the CFD, identified the differences in reading new measurements, and developed a common language with all four groups. In a similar vein, Bechky (2003a) observed that physical demonstration is an important interaction in which each group can iteratively "try on" alternatives, make adjustments and verify that the new design is functional. Transformation of knowledge takes place when physical demonstration enables an occupational group to understand how others work on the same artifact.

The second element that enables transforming knowledge is a common ground (i.e., a common subject, topic) or an open problem space, in which different occupational groups contribute their own understanding. In Bechky's study (2003a), tangible definitions of the machine were the common ground, and the three occupational communities, engineers, technicians and assemblers, contributed to and altered their own understanding of the machine. While engineers had a conceptual understanding of the machine based on drawings, assemblers had a concrete understanding of the machine based on physical interaction around the machine. Technicians understood the machine based on drawings and physical parts of the machine, and are able to communicate between engineers and assemblers. When engineers and assemblers did not understand each other with respect to fixing parts, the technicians physically demonstrated to the engineers what the assemblers meant. The physical demonstration is important to develop a tangible definition that enabled engineers and assemblers to understand each other. Common ground provides a guideline for different occupational groups to proceed with their work.

Dougherty and Dunne (2012) extended Bechky's notion of common ground and saw it as an open problem space rather than tangible definitions. In their interpretation, the transformation of innovation activities takes place when innovators form new questions and alter their activities to pursue those new questions. Because complex innovation like drug discovery contains an unlimited amount of interdependent elements that interact autonomously, innovation problems or product concepts cannot be precisely defined. They found that drug discovery scientists developed a problem space based on rich scientific theories about diseases and defined their exploration of possibilities within the problem space. For example, an open problem space allowed digital and therapeutic scientists to add their expertise, explore partial models of product architecture and examine a variety of alternatives. Rather than predefining a product concept, an open problem space allowed scientists to recognize "emergent patterns" and reformulate new partial models to incorporate those patterns. A common ground, either tangible definitions or an open problem space, provides a guide for different occupational groups to contribute and integrate their own knowledge for a complete understanding.

The last element contributing to transforming knowledge is the presence of objects that require interpretation among different occupational groups. In both Bechky (2003a) and Carlile's (2004) studies, boundary objects, such as drawings, maps, images and test resulted from the CFD tool, were devices that specified the differences in knowledge, and were used to help different occupational groups improve their own understanding. Boundary objects are known as "artifacts that inhabit several intersecting social worlds and satisfy the information requirements of each of them" (Star and Griesemer 1989). For example, Bechky (2003a, b) suggested that drawings, maps or

machinery objects are boundary objects, in which each provides information and requires interpretation from engineers, technicians and assemblers. Bechky further argued that boundary objects generating tangible definitions serve as common ground and transform the understanding among different groups.

Boundary objects may mediate problem-solving across occupational groups, but there is no clear condition on how boundary objects are effective in transforming knowledge at pragmatic boundaries. Bechky stated that not all boundary objects are useful for creating common ground for sharing. In some cases, they could even serve as constraints. As emphasized by Carlile (2004), occupational groups have varying capacities to understand the boundary object. For example, in Bechky's study, assemblers found the engineer's drawing too abstract, so technicians had to physically interact with assemblers and engineers. In Carlile's study, the safety, engine and climate control groups had different interpretations of the measurements produced by the CFD tool, and the design group had to explain the measurements to each individual group. Carlile pointed out that a boundary object is not a "magic bullet" to transform knowledge across pragmatic boundaries (2002, 2004), and the use of boundary objects to manage pragmatic boundaries cannot be taken for granted. Boundary objects are only effective when problems are clearly defined and all occupational groups agree that they are useful for problem solving. In Dougherty and Dunne's study (2012), the common problem space enabled transformation. They argued that "transformation of innovation activities are [is] necessary *before* competencies and boundary objects can work in complex innovation" (2012: p. 14). In other words, using boundary objects to develop tangible definitions comes *after* and *not before* an open problem space is developed. Even though Dougherty

and Dunne did not address the particular role of boundary objects in transforming knowledge, their theory suggests that identifying the discontinuity in practice and having a rich set of alternatives in an open problem space is more important than using boundary objects for transforming knowledge.

Through the lens of transforming knowledge at pragmatic boundaries, previous studies in academic-industry partnerships have not adequately discussed the common problem space for academic and industrial scientists to contribute their own knowledge for a complete understanding. As the these studies have focused on knowledge transfer through licensing patents and co-writing papers, patents and publications are considered the boundary objects that represent information and implications. They are also flexible enough for different occupational groups to have their own interpretations. For example, scientific publications and patents are available, but scientists often have different interpretations and different goals of how they want to apply the information. In the drug discovery context, cause and effect relationships within the disease, the body and the potential drug are unknown. Small adjustments might generate enormous changes as many interdependent elements interact autonomously. Reading papers and patents are insufficient to apply the codified knowledge to drug innovation, as product concepts cannot be pre-defined in a complex system (Simon, 1996; Dougherty and Dunne, 2011). Scientists must use their hands to manipulate scientific objects and use experiments to assess the unknowns and observe the change. Therefore, patents and publications as boundary objects are not enough and cannot be considered a “magic bullet” to transform knowledge across pragmatic boundaries.

With studies of innovation management in the for-profit sector, it is straightforward to comprehend new products or technology as the object of innovation. We take it for granted and assume that scientists also see new products and technologies as objects of their activities. Academic scientists conducting research and working in a scholarly enterprise are pursuing the knowledge frontier. Scientists are curious about nature and ask questions about biological objects. The paths of conducting scientific research are ambiguous, convoluted and ill-defined (Grinell 2009; Firestein 2012). Using boundary objects as a common ground to transform academic knowledge for innovation only provides a limited explanation. We need a new framework to understand what comprises academic knowledge. In the next section, I will draw on a pluralistic framework of objects to understand the common grounds for transforming academic knowledge for complex innovation. The pluralistic framework of objects incorporates multiple theoretical perspectives to understand the role of objects in cross-disciplinary collaboration (Nicolini, Mengis, and Swan, 2011). This framework is pertinent to my research question because unless we have a deep understanding of the nature of academic discovery, our management of academic-industry collaboration will remain superficial.

## USING PLURALISTIC FRAMEWORK OF OBJECTS TO UNDERSTAND ACADEMIC DISCOVERIES

To formulate a better understanding of what social arrangements enable transforming academic knowledge for drug innovation, I draw on a pluralistic framework of objects to conceptualize the nature of academic discovery. The pluralistic framework

of objects integrates various theoretical perspectives, such as boundary objects, epistemic objects and historical activity theory, to explain how and why cross-disciplinary collaboration occurs. Objects refer to a material entity that mediates between social groups, and can be interacted with (Star 2010). Objects can also be conceptualized as processes and projections that warrant attention in different domains (Knorr Cetina and Bruegger 2000). When objects are used in social settings, they represent what people know, mediate practices between communities and reveal differences among them.

In the context of drug discovery, academic discoveries (usually scientific entities or artifacts) are considered as objects that embody scientists' practices and representations of their knowledge. Most academic scientists spend many years studying the object that they have discovered. Their knowledge about the object is represented in their day-to-day practice, interactions, publications, presentations and dialogue with their colleagues. Scientists from different disciplines may be working on one particular gene, may read each other's published work and continue to work on this gene without directly interacting with each other. Scientists across the world may also discuss a particular gene and share a common understanding. They also use the object of discovery to connect with their colleagues, industry and the commercialization process. Essentially, scientists use objects as a means to present themselves as members of a culture.

When objects assume a social function and mediate interactions, analyzing objects reveals the practices of knowing that object and provides concrete means to learn about differences between communities. For example, Bechky (2003b) demonstrated how two objects–engineering drawings and machines–represent different knowledge and practices. There was a context for professional jurisdiction between engineers and

assemblers. The engineers found drawings representing what they know about how the machine would look and how the parts would fit together. The drawings represented their professional jurisdiction because all information needed for building the machine had to be approved by them. The assemblers saw machines as the concrete representation of what they know and found the engineering drawings abstract and mistrustful. By examining the practices around the objects, the use of these artifacts as tools reinforced the knowledge claims (p. 734).

In addition, a recent study conducted by McGivern and Dopson (2010) analyzed the transformation of epistemic objects into technical objects. By analyzing the political interactions among three epistemic communities, medical academics, a government agency and a health service community, McGivern and Dopson argued that objects were created as the outcome of their political struggles. As the three communities competed for scientific credibility, in order to settle their political competition, they transformed their epistemic knowledge into a set of technical objects such as genetic test results and patient care protocols. As objects come in different forms, either material or abstract, they usually remain in the shadow of practices and interactions. When we incorporate objects into our analysis, then we demonstrate a clearer understanding of the complexity of social interactions.

The pluralistic framework of objects provides a lens to conceptualize academic discoveries acting as material, epistemic and activity objects. Discoveries are scientific entities (e.g., a molecule, a receptor, a mechanism, a pathway, a protein etc.) that have potential for drug application and are objects by nature. First and foremost, an object is a thing, a material entity composed of more or less well-structured stuff (Star 2010). The

material aspect of objects refers to their concrete structural form that can be observed, touched and manipulated with hands. For example, as scientists conduct experiments on laboratory objects (i.e., a protein, a DNA sequence), the objects contain concrete, structural forms that can be observed, but making such observation requires experience and hands-on manipulation of the object. Consider this example. Warren and Marshall observed a type of spiral bacteria, *Helicobacter pylori,* and postulated its association with stomach diseases (Thagard, 1999). To test their hypothesis, they conducted studies to measure the correlation between the bacteria and the biopsy specimens from one hundred patients (Thagard, 1999). As a material object, *H. pylori* is a concrete entity, but it was unknown that it causes stomach ulcers (Thagard, 1999). The connection of *H. pylori* to a medical problem was possible when Warren and Marshall employed microscopes, used biopsies and designed a set of procedures to identify its relationship to stomach problems. Their practice to observe and manipulate the bacteria required empirical knowledge for preparing the experiments and testing the theory. The series of actions to observe the entity developed knowledge through the relationship with the object (Latour, 1986; Knorr Cetina, 2001; Nicolini et al., 2003; Orlikowski, 2002). Academic discoveries in biology or chemistry are objects existing in the natural environment, but observing these objects is only possible with work of scientists. The ability to observe and learn about objects is situated and contextualized in specific settings.

Epistemic and activity objects are considered as primary objects that motivate and fuel cross-disciplinary collaboration. They contain properties that are fragmented and emergent and require different types of knowledge and techniques to formulate a complete understanding. Epistemic objects refer to scientific entities (materials or

artifacts) for which scientists have a lack of understanding. For scientists, it is the category of epistemic entities, such as disease, proteins, DNA, or other scientific entities, which drives them to learn more (Knorr Cetina 1999; Knorr Cetina and Bruegger 2001). For example, the structure of DNA is an epistemic object that motivated Francis Crick and James Watson to determine its three-dimensional structure. It prompted their discussions and activities to determine the structure of DNA. When Louis Pasteur studied infectious disease, he was studying the microbes from infected animals. Pasteur collected microbial samples from farmers, distillers, veterinarians, and surgeons and studied the microbes under different conditions (Latour 1988).

Epistemic objects trigger questions, and it is those very questions that motivate the search for an understanding. A real-life practicing neuroscientist, Dr. Stuart Firestein wrote,

> "Scientists use ignorance to program their work, to identify what should be done, what the next steps are, where they should concentrate their energies…. And ignorance is a condition of knowledge [where there is] the absence of facts or understanding. It is not an individual lack of information but a communal gap in knowledge. It is a case where data don't exist, where the existing data don't add up to a coherent explanation, cannot be used to make prediction or statement about some event" (Firestein 2012; p. 44- 45).

Scientists are innovators, knowledgeable about scientific theories, equipped with experimental skills and techniques, and motivated by a passion to know and to uncover nature. They must be able to identify the most pertinent questions, in order to pursue their desired course of study and to uncover the answers.

Let us consider drug discovery as an example. One of the ways to discover a new drug involves the identification of a biological target that impacts a particular disease and finding compounds that act on that particular target. Scientists are working with

incomplete knowledge of our biological systems. They raise questions about the biological mechanisms, the disease and the symptoms. The questions structure their activities and search for answers. For instance, a scientist may ask, "What is the underlying mechanism of the disease?" or "What are the pathways involved?" Once scientists have identified some enzymes as possible drug targets, they face another set of interrelated questions, such as "Are these enzymes druggable?" "What are the structures of these proteins?" and "What is the relationship between this enzyme and the disease?" Answers to these questions require coordinated efforts from scientists from multiple disciplines. Scientists conduct experiments in either dry (theoretical) or wet (practical) labs, but they cannot predict what the answers are. Epistemic objects are associated with uncertainty, questions, and the lack of knowledge of what scientists will find by studying the object. Only by working with the object and observing its unfolding patterns would a scientist gain new understandings. Firestein said, "things happen or don't, that redirect your thinking; [scientists] reveal new results that require you to revise your idea; results from your own experiments are not what you expected and you revise new interpretations and new strategies" (p. 45). In other words, scientists' day-to-day practices have already incorporated the epistemic characteristic of the object. As scientists work on questions, results emerge that help them gain a greater understanding and revise their existing strategies.

The third form of an object is an activity object, which refers to artifacts that "enable purposeful action and connect agents to their surroundings" (Nicolini et al. 2011: p. 9). Activity objects can be conceptualized as a project, a campaign, a new product, or object, where many people contribute their knowledge and activities to make it concrete

in the real world. Activity objects share attributes with epistemic objects. They both contain emergent characteristics that motivate different experts to work on the object and formulate an understanding. The practices around an activity object follow a guideline, or a series of steps to materialize the object and make it concrete and observable in the real world. Referring to Bechky's study (2003b), the large semiconductor-manufacturing machine that assemblers, technicians and engineers were building is an activity object to which they contribute their expertise and solving-problems. During the process of building the machine, the machine generated questions for technicians and assemblers to discuss, but a real machine would be the concrete outcome in the end of their work. In Dougherty and Dunne's study (2012), the drug that digital and therapeutic scientists were discovering is an activity object, as they contributed their techniques and models for a coherent drug configuration. As different occupational groups contribute activities and understandings, the activity object is also "prospective outcomes that motivate and direct activities" (Nicolini et al. 2011: p. 9). An activity object is not just an idea but rather is an outcome of the idea in a material form that is concretely present in the world.

Comparing academic and industry scientists, they may be working on the same epistemic object, for example a protein, and both face a set of questions about the structure and bioactivity of this protein. However, academic and industrial scientists have different objectives with respect to the protein, and thus engage in different activities to present their knowledge of this protein. To academic scientists, this protein remains an epistemic object as they continually raise questions, pursuing the protein's emerging patterns and publishing their findings in academic papers. On the other hand, industrial scientists see that this protein may have the potential to be developed into a

drug target. They would conduct pre-clinical experiments to analyze safety and efficacy of compounds targeted for this proteins. They follow a series of steps to determine the feasibility of a drug target and accompanying compound(s). There is a definite answer in the end of their search.

To summarize, academic discoveries are conceptualized as objects with three dimensions: material, epistemic, and activity. Academic discoveries are concrete materials, with structural forms that require hands-on manipulation to observe them. They are also epistemic with aspects that scientists do not yet know and are motivated to determine. The activity aspect of academic discoveries involves a series of steps to present in the real world. This framework helps us to visualize the dimensions of academic knowledge and to reveal where boundaries exist across different communities of scientists. In the next section, I will outline my approach to the research question and the analysis for the rest of the dissertation.

## WHAT LIES AHEAD

To answer my research question about how social arrangements enable the transformation of academic knowledge for complex innovation, I conceptualize academic discoveries (e.g., a molecule, a receptor, a mechanism, or a pathway) as scientific entities with pluralistic forms, both as epistemic and activity objects that require individual and collective work supported by material infrastructures. Academic discoveries are concrete scientific entities that can be touched, visualized and manipulated. When an academic scientist discovers a protein, enzyme, gene, or any kind of biological entity and it is being

considered as a potential drug element, it has potential for drug discovery processes. It is called potential drug element because the scientific entity is not yet a drug (or drug target), nor is it the drug, but only a part of a drug. A drug consists of a chemical compound that has the capacity to bind selectively and specifically to a biological target that impact a particular disease. The interaction between the compound and the target would change the state of the disease. Therefore, a potential drug element refers to either a biological target or a compound. After the compound goes through a phase of validation, it becomes a drug possibility and may enter clinical trials. The terms drug element and scientific entity are used interchangeably, because scientists do not always know immediately whether their discoveries are useful for industrial application.

The nature of the drug discovery process is transformative throughout different stages. The scientific entities are first discovered in a lab, studied and examined as potential drug elements, being validated as drug possibilities, and then developed and manufactured as a viable drug. In the early stages of drug discovery, a potential drug element (i.e., target or compound) contains epistemic characteristics, where a lot of its biological mechanisms are unknown to scientists but have the potential to use for therapy. Scientists are working with their hands to reveal its characteristics and understand its mechanisms in different contexts and biological situations. The understanding of how the drug element would be useful for treating a disease is deeply embedded in the day-to-day research practice of the scientists and their laboratory settings. Scientists' knowledge of the drug element is in the social interaction with their colleagues while discussing observations, problems, and questions. The potential drug element is also an activity

object that fuels collaboration among scientists of multiple disciplines to validate its connections with a disease.

By using the pluralistic framework of objects, I am putting academic discovery in various forms (i.e., scientific entity, drug elements, and drug possibilities) as the focal point of the analysis. It is at the center where academic and industrial scientists interact to seek a social order among organizations of knowledge practices, people, and technologies. The unit of analysis is scientists' practices of knowing the object. The analysis focuses on the ongoing process of knowing an object in which scientists continuously acquire new properties, definitions and understanding. Put differently, knowing the academic discovery as a potential drug element is the primary purpose of the practices and interactions between academic and industrial scientists. When we recognize that academic discoveries contain emerging qualities in which scientists have an incomplete understanding, we would understand *why* experts and companies collaborate. They want to find out about drug elements and compensate their differences in knowledge to achieve a common goal (Nicolini et al. 2011). For example, companies would license another company's technology to analyze their compounds, or they may work with an academic scientist who tests the compounds in his/her experimental system. Academic scientists engaging in networking activities or starting firms are social arrangements for gaining a better understanding of their discoveries.

My analysis of practices of knowing academic discoveries reveals two forms of boundaries in transforming academic knowledge for innovation: one in the discontinuities of practice and the other in the fragmented commercialization process. In Chapter 4, my analysis first delineates the dimensions of knowledge for drug possibilities. The three

dimensions serve as pillars to see where practices of knowing are discontinuous and fragmented. The material dimension suggests the complex function of the human biology and disease. The epistemic dimension opens the ever-emergent nature of knowledge that motivates scientists to ask questions drawing on rich scientific theories to answer them. The activity dimension directs the purpose of knowing practices and guides the direction of multidisciplinary collaboration among scientists. Chapter 5 reveals the discontinuities of practice of knowing that separate basic science research from those of clinical research. Practices within basic science consist of raising questions about mechanisms, making implications to a general disease area and continuously moving to new observations. In contrast, practices of clinical science raises questions about therapeutic functions of the object, making connections with a disease, and following the emerging patterns. Chapter 6 discusses the fragmented commercialization process, where industrial entrepreneurs evaluate the drug possibility based on its legitimacy, monetary mechanisms, and the specificity of disease context and users. The evaluation criteria disrupt the process of knowing because academic scientists forgo the control of their research directions while satisfying the evaluation criteria set by the industrial entrepreneurs.

Chapter 7 presents evidence showing that both sectors seek changes in their partnership arrangements, and alternative institutional arrangements in addition to patent transactions are in place to bridge the knowledge gap. My data include four models institutional arrangements of academic-industry partnerships, such as linear model, academic medical centers, disease-focused venture philanthropy, and industry initiated drug discovery partnership. Collaboration under new arrangements would allow

academic scientists to expand their local understanding of their discoveries to a global understanding between the discovery and the biological system as a whole.

My dissertation contributes to the discipline of innovation management in three ways. The first contribution is to create stronger theory about how and why collaborations in complex, science-based innovation are challenging, and how to deal with those challenges. Although the knowledge is complex, it is not an incoherent, ill-structured mess that is explored randomly, but rather contains three dimensions that different communities can work along. Innovation in this century will be increasingly accomplished in such ecologies, because no one organization can harbor all the necessary expertise or create the necessary knowledge. The second contribution is the in-depth examination of objects that are the primary mediating devices in complex innovation. Analyzing drug possibilities as objects reveal the discontinuities of practices between basic and clinical research, which contribute to the persistent knowledge boundary in the drug discovery ecology. These dimensions of knowing constitute the common ground between basic and applied science for drug discovery, structure ill-defined domain of work, and delineate the differences in practice between the two communities of science. There may be additional dimensions of knowing that exist in these complex domains, but these three are central ones. My third contribution is to suggest the kinds of knowledge transformations that social arrangements for collaboration need to accommodate to promote more effective collaboration. I propose that for academic knowledge to be useful for innovation, transformation has to occur at three levels: practices of knowing, social interaction between the scientist and industrial entrepreneurs, and institutional arrangements of academic-industry partnerships.

## Chapter 3: Data Collection and Coding

The research question in this dissertation is what kinds of social arrangements enable transformation of academic knowledge for complex innovation. Based on current literature, I have established that transformation of knowledge at a pragmatic boundary involves three aspects: organizational structure that allows different occupational groups to demonstrate and execute work, a common ground or an open problem space where different occupational groups contribute their own understanding, and the presence of objects that require interpretation among different groups. Having discussed how current studies of academic-industry relations are limited in addressing the aspects of common ground and objects, I draw on a pluralistic framework of objects to bring new insight for conceptualizing the nature of academic discoveries.

My research approach is to investigate the underlying practices surrounding drug possibilities as objects, identify whether social boundaries exist among scientists, and determine whether there organizational arrangements exist to bridge those boundaries. To answer my research question, I have proposed using grounded theory building (GTB) as a qualitative research method to build a theory concerning the transformation of academic knowledge for complex innovation. This method is appropriate to the research question because it is useful in investigating how academic scientists make sense of their research for innovation purposes and how they go about research and commercialization activities in the organizational context shaped by policy institutions and firms in biopharmaceutical sector. GTB is an iterative analytical process connecting data collection with analysis, leading to more questions about the phenomenon and indicating further areas for more data collection, and culminating in analysis that leads to concepts

(Bailyn 1977; Corbin and Strauss 2008). Therefore, rather than collecting the entire set of data before analysis, I cycled between data collection and analysis so that I could hone in on key concepts and themes grounded in the data and discover how those concepts vary under different conditions (Corbin and Strauss 2008: p.144). From time to time, I compared my field observation with existing studies on academic-industry relations. The constant comparison technique indicated the gap and connections between findings from the current studies and the actual practices in the real world.

In the following sections, I provide background of the research context, describe the data sources, and outline my data analysis process.

*RESEARCH SETTING*

The empirical context for investigating my research question is academic scientists participating in drug-related research. Drug discovery represents the first phase in creating new drugs, which involves the first 6 years of a process that takes 12 years, on average. Historically, drug discovery has evolved through several search paradigms, from a serendipity-based approach in the 19th century, to antibiotics discovery in the early 20th century, then to patient-oriented research in which major medical discoveries have been made through clinical observation (Gittelman 2012). Since 1990s and early 2000s, four distinctive players have been separately conducting research on drug discovery and development: pharmaceutical firms, biotechnology companies, academic institutions, and the National Health Institutes (Fishburn 2012). Since the emergence of biotechnologies in 1970s, pharmaceutical firms have adopted a more systematic approach, "rational drug design," so that they can design and engineer compounds and screen them with high

throughput sequences. Currently, the community of drug discovery scientists emphasizes "translational" research and "omics" research as new paradigms to drug discovery, both of which seek to target mechanisms that underlie issues of diseases and design drugs to address those issues directly (Fisburn 2012).

The drug discovery process is essentially complex. A human biological system consists of 20 million proteins or more, interacting semi-autonomously and dynamically to ensure a functional order in the body. A new drug entering the human body interacts with the proteins in the body, causing numerous unpredictable side effects. Drug discovery scientists are faced with an almost infinite number of possibilities from the complex biology, and they do not have simple criteria for success (Dunne and Dougherty 2010). They need to have a deep understanding of how a disease works and the biological pathway through which the disease evolves and manifests itself in the human body. They also need to know how the compound would interact with the disease and show how the new drug would improve the performance of existing drugs (Pisano 2006).

Because of the complexity of the process, the underlying uncertainty is enormous, making drug discovery an innovation that is highly capital intensive and risky. The cost of discovering and developing a new drug amounts to $1.5 billion. Pharmaceutical firms have a long history of collaborating with universities because academic knowledge helps frame ill-structured problems and is the basis for new drugs (Pisano 2006). However, these partnership arrangements have been facing pressure for change since the economic crisis in 2008. Biopharmaceutical companies have been experiencing a productivity crisis because of a lack of new products in their pipelines. At the same time, the NIH has launched several funding programs to accelerate therapeutic treatments from "bench to

bedside." In other words, universities, industry, and government agencies are creating new social arrangements to enable true collaboration across this knowledge boundary, not just traditional contract relations, to translate research discoveries into new products that are available to patients (Wadman 2010).

The incentive to change the current partnership arrangement is mutual between the industry and the academic-scientists community (Fishburn 2012). One of the critical problems for many large pharmaceutical firms is that several patents of their highly effective and lucrative drugs are about to expire and they face the lack of new molecular entities in their product pipelines. In addition, facing the current economic constraints, biopharmaceutical companies no longer have the financial capital to support early stages of exploring drug candidates. Therefore, the incentive for biopharmaceutical companies to partner with universities is that academic scientists have the expertise and freedom to discover new scientific entities and mechanisms in human biology. In one of his keynote speeches, Dr. Marc Tessier-Lavigne, the current President of Rockefeller University and previously the CEO of Genetech, argued a point about drug discovery: "Genetech has 200 people that are doing target discovery, but Rockefeller University has 1200 people doing that." Being a thought leader in the industry and academia, Dr. Tessier-Lavigne shapes the vision that the future of target discovery will be in academia (Tessier-Lavigne, 2011 October, Memorial Sloan-Kettering Academic Convocation). Therefore, partnerships with academia are a valuable resource for pharmaceutical companies in identifying new drug possibilities, driving them to reform their partnership arrangements with universities and academic labs.

On the other hand, the incentive for a university to partner with biopharmaceutical firms is not only a diversification of their research funding as the federal agencies have tightened their budgets, but also a pursuit of a social mission of developing products that would improve public healthcare. For example, the NIH sees a pressing need to accelerate the development of new therapies for the increasingly aging population and, thus, has been reducing budgets for basic science research while increasing grants for translational research in universities (Colins 2011; Wadman 2010). The NIH launched the Clinical &Translational Science Awards (CTSA) and National Center for Advancing Translational Sciences (NCATS) programs to encourage universities to establish translational research centers, promote translational research, and provide drug discovery training for academic scientists. It is important to note that the focus of academic research remains on identifying new targets and compounds as drug elements for disease. Such research does not generate actual drugs but identifies drug elements and possibilities that pharmaceutical companies can develop into viable drugs. In short, academic research has moved from an "important but distant foundation for drug discovery to a critically important source of immediate useful knowledge and technique" (Cockburn and Henderson 2001). Given the ongoing changes in the institutional landscape, this context for the academic-industry partnership in drug discovery offers a rich and fertile ground for research.

*DATA COLLECTION*

The primary source of data is interviews with scientists who have been involved in academic-industry collaboration. Originally, I had planned to interview only academic

scientists in universities and nonprofit research organizations that conduct research in diseases or therapeutic areas or have been involved in drug discovery projects with firms. However, industry scientists showed interest in participating in my study, so some were included in my sample.

I conducted 55 interviews and 4 group discussions; among them, 34 were with academic scientists, eight were with academic scientists who previously worked in industry, 10 were with industry scientists, and three were with directors in technology transfer offices at three universities (See Table 1 for details). All scientists interviewed had experience with or are currently conducting research in diseases or conducting drug discovery programs in the New York, New Jersey, or Philadelphia regions. They worked in various disease areas, such as cancer, neurodegerative diseases, and infectious diseases.

The interviews were conducted in an open-ended format, which is designed to reveal the process of how the participant approaches drug discovery or drug-related research. Interview questions included asking participants to describe their research areas, the major research questions they wanted to address, and the research experiences that had led them to their current questions. In addition, I asked how they made their research available for the drug discovery process and what they did to apply their research in a clinical setting. For confidentiality reasons, interviews were focused on the research process in general and not soliciting information on specific projects they were working on. All interviews averaged about an hour. Forty-seven interviews were conducted at the participants' work sites and six were conducted via telephone.

Interviews were taped (with the participants' permission) and transcribed; otherwise, detailed notes were taken.

In addition, I drew on three data sources as supplements: research profiles, unstructured observations at the participants' labs, and field observations at conferences. Prior to my interview with a participant, I reviewed his or her C.V. or research profile. Doing so helped me familiarize with the participant's research interests, education, and career background. Another data source was unstructured observation of the participants' laboratories with their permission. The unstructured observation was supplementary but important because I gained a better understanding of the setting and could put the interviews in the context of the academic scientists' work sites.

I also attended 10 science conferences and meetings covering such topics as cancer, Alzheimer's disease, and industry-academic partnerships (See Table 2 for a list of conferences). Most of the science conferences and meetings were attended by academic and industry scientists, providing a valuable source to observe their institutional connections in real time. The panel discussions at the conferences were tape-recorded, and detailed notes on the presentations were taken; the tape-recorded panel discussions were also later transcribed. In addition, I took notes for ethnographic interviews with conference attendees. These notes are included in the data analysis. At the conference, when time allowed, I would ask participants open-ended questions about why they attended the conference, whether they had found the conference useful, and what they thought of academic-industry partnership in drug discovery.

My data from interviews and field observation contain two limitations. First, not all researchers in my sample are doing drug discovery per se, but rather doing research

related to a drug, such as understanding a scientific entity or disease mechanisms that may contribute to a drug concept, developing ways to intervene the disease, or developing ways to deliver a drug. As mentioned earlier, since there are many ways to discover drugs and therapies, my data are not limited to a particular way to approach drug-related research. Second, the interview data is a more direct observation of the social actions and practices than large sample studies, but they are based on the subjects' reflections and what they choose to reveal. Their description of their everyday practices of research and interaction might be exposed to a problem where interviewees unconsciously or consciously reveal a story to maintain positive self-images (Singleton and Straits 2005). To establish coherence, I would triangulate the interview data with field observation at conferences as well as talking to industry scientists. I would also refer to current existing literature to evaluate the validity of the interviews (Dougherty, 2002). As Corbin and Strauss (2008) argue, when talking about qualitative research, credibility instead of validity and reliability, is the key dimension to judge the research, which indicates the trustworthiness of the finding, so that it reflects participants', researchers', and readers' experiences with the phenomenon (p. 302). Considering these limitations, I am giving a story about the practices and social interaction that academic scientists are involved in when connecting their research to innovation, and my goal is to convey my experience with the phenomenon and connect it with existing literature.

*DATA ANALYSIS*

I used methods described in Corbin and Strauss (2008) to proceed with data analysis. The essence of grounded theory building is identifying contrast among different

categories of practice. The process of iterative coding and comparison divided my analysis into three levels, from the microlevel of practices of knowing through which scientists produce knowledge through their interaction with drug possibilities, at the network level of practices through which scientists with institutional entrepreneurs to commercialize academic discoveries, and at the macrolevel of practices of working with the industry under various models of academic-industry partnership.

I noticed that most scientists discussed their research in terms of scientific entities, such as proteins, genes, and estrogen, and I realized that these entities are their objects of work. Then, I focused on the scientific entities and the questions that scientists raise in order to distinguish the three dimensions. I distinguished the material dimension by identifying questions about the scientific entity as a potential drug—"Where is the binding site of this protein?" and "How can we group the molecule to change its structure to reduce its side effect?"—Or questions to understand how the drug would function in the body—"Is the protein targetable? Can drugs bind there and get there?" or "Does the drug interact with other medications that the patient is taking?" I identified the epistemic dimension by looking for questions about the scientific entity itself, such as "What is this gene's cell cycle, and what controls its growth and signaling?" or "What are the pathways to get to this protein?" For the activity dimension, I looked for questions that scientists ask to structure their subsequent activities, such as "If this works in a mouse, does the same thing happen in a human?" or "If this protein is making bones, then how do you know it's not killing muscle cells?" or "If this molecule doesn't harm the kidney, what about the heart?" Scientists essentially know the scientific entity by raising questions, and they produce knowledge by answering questions. The questions about a scientific

entity also change as the entity moves from the lab to commercialization and then innovation.

The interview participants that included academic and industry scientists represented a wide range of possible practices of knowing. In the beginning of data analysis, I began to observe a difference among the scientists in terms of how they viewed drug-related research in general. I looked for their institutional affiliations, whether they were in a disease-focused department or a research center, and whether they had ties with hospitals, clinicians, and patients. I differentiated basic academic researchers from clinical researchers according to their approaches to drug discovery research, which reflected the two quadrants of research indicated in Stoke's model (1997). The two quadrants are Borh's quadrant, which refers to basic research concerning a quest for fundamental understanding without consideration of use, and Pasteur's quadrant, which refers to research concerning a quest for fundamental understanding but inspired by considerations of use. I categorized the scientists who did basic research as basic research scientists and those who did use-inspired research as clinical research scientists.

Between the two categories of scientists, I developed a theme based on their distinctive practices of knowing drug possibilities. I identified how their research practices were different in terms of the three dimensions. The materiality dimension has to do with whether scientists relate drug possibilities with a disease context and see a specific purpose. I looked for whether their research addressed a specific disease and whether their research on a drug possibility was situated in a specific disease context or a general implication for a therapeutic area. I coded for how extensively they conducted

experiments in a specific disease context. The epistemic dimension has to do with the types of research questions pursued. I looked for descriptions about participants' research trajectories, such as how they made discoveries and what kind of research questions and hypotheses they raised. I then coded the data for what research questions they raised about their scientific entities, whether the questions were simple and mechanistic or relational and conditional, and whether they examined the entity in itself or examined it under certain conditions. The activity dimension has to do with how scientists follow up on their research questions and how they make their research publically available. I coded for participants' approaches to designing their experiments, such as whether they shifted between cell systems and animals systems or whether they used new technologies to conduct an experiment.

Shifting my attention on practices of knowing at the microlevel, I noticed that drug possibilities were also objects concerning which scientists engaged with their peers and technology transfer offices. I then developed two themes—commercialization and academic-industry partnership—with the former relating to academic scientists drawing on their universities' resources to commercialize and the latter relating to their practices of collaborating with industry scientists in various ways in the institutional arrangements. The commercialization process, in which academic scientists intend to bring their discoveries to the market, consists of the interaction between academic scientists and industrial entrepreneurs concerning the drug possibility. The process begins when academic scientists bring their discoveries to the university's technology transfer office (TTO)and the TTO suggests what the scientists should do to commercialize the discovery. The TTO then decides how it wants to proceed with the commercialization.

Differences concerning which institutional entrepreneurs evaluate the drug possibility emerged, and I coded them as evaluation criteria.

Again, the three dimensions guided the iterative categorization of the evaluation criteria. The materiality dimension has to do with the material forms in which drug possibilities are presented to the institutional entrepreneurs and the mechanisms that institutional entrepreneurs monetize from the drug possibility. I looked for practices of academic scientists in presenting a drug possibility in its material form, such as filing for disclosure, applying for patent protection, building up a patent portfolio, or starting a company. Because the epistemic dimension encompasses questions and curiosity surrounding drug possibilities, I coded the practices of publishing and patenting as institutional mechanisms that legitimize the questions they raise. Finally, the activity dimension includes the directions, goals, and objectives scientists seek to find in the commercialization process; therefore, I coded whether scientists promoted their discoveries, why they did or did not, and what they learned from the commercialization process.

The last theme identified is academic-industry partnership at the institutional level. By attending conferences and seminars, I encountered various models of academic-industry partnership that have emerged recently, such as Pfizer's Center for Translational Innovation and Eli Lily's $PD^2$, as well as venture philanthropy foundations. I decided to gather more data from scientists who had participated in these models so that I could compare how practices of knowing are different for those not involved in these models. Four models of academic-industry partnership were identified in my sample: linear market-oriented, industry-initiated, disease-focused venture philanthropy, and

academic medical centers. Other forms of partnership may have emerged (Tralau-Stewart, Wyatt, Kleyn, and Ayad 2009), but these four were available in my data collection process. I compared these models in terms of various dimensions, such as how they handle their intellectual property, the stage when they reach out to the industry, the stage of the drug possibility when they partner with the industry, and the coordination of work among the scientists. I also took into account the objectives that these models have for the collaboration. In general, the linear market-oriented model and AMCs have transacting patents as the main objective while industry-initiated drug discovery partnerships and venture philanthropy foundations focus on conducting proof-of-concepts or proof-of-principals.

To analyze the practices of knowing in these various models, I investigated how academic and industry scientists interacted and collaborated along the three dimensions. For example, the material dimension has to do with contextualized drug possibilities and developing a drug possibility into a functional application in the body. I considered the kinds of practices academic and industry scientists shared when they collaborated, how they contextualized drug possibilities what they learned from each other by working together. Because the epistemic dimension has to do with raising questions about the drug possibility, I focused on who defined the question in the partnership and how questions were defined in each model. With the activity dimension, I compared the extensiveness of validation scientists conducted in each model.

# Chapter 4: Understanding drug possibilities as pluralistic objects

The pluralistic framework of objects provides an analytical lens to delineate the multiple dimensions of drug possibilities, which is important in understanding why and what make science-based complex innovation challenging. Drug possibilities as objects of scientific discovery contain three dimensions: materiality, epistemic, and activity. The material dimension drills down into the complex functioning of human biology and diseases. The epistemic dimension opens up the ever-emergent nature of science that motivates scientists to keep asking questions and drawing on scientific theories to answer those queries. The activity dimension guides the direction and purpose of knowing drug possibilities. In the beginning of this analysis, I noticed that scientists discussed their discoveries in terms of scientific entities (i.e., protein, gene, estrogen, amyloid, or dendrite branching) and so structure their research practices around these units. I developed a theme on scientific discoveries relevant to drug possibilities and looked for the scientists' descriptions of those discoveries found in the lab, in the drug discovery context, and in the innovation process.

A delineation of three dimensions of drug possibilities deepens our understanding of why complex innovation is challenging (see Table 3 for a summary of dimensions). The materiality dimension of drug possibilities refers to the concrete, material form of a drug as an outcome of the discovery process. Drug possibilities involve a specific purpose. They are dependent on a particular context such as a disease, a set of symptoms or patient conditions, and require hands-on manipulation to observe their characteristics. This materiality dimension highlights the challenge for innovation where drug discovery scientists must define specific purposes for a drug possibility among the complex

interaction of the disease and human biology. In addition, because drugs have specific functions and are effective only for patients with those conditions, learning and knowledge is highly situated and contextualized. The epistemic dimension of drug possibilities refers to the emergence of properties, as they often derive from objects of nature and biology. Properties are emergent and not completely understood by scientists, which makes it hard for them to capture observations. This dimension triggers questions and motivates collaboration across disciplines to reveal drug properties. However, because of the complexity in human biology, there are unlimited questions that scientists can pursue; therefore, the challenge for innovation is to determine relevant questions for the drug possibility and disease. Lastly, the activity dimension of drug possibilities refers to a series of scientific work to reveal feasibility and efficacy in the human body. The scientific work involves technical studies to obtain a more thorough understanding. The innovation challenge associated with this dimension involves limited mechanisms and incentives for academic scientists to extend their work beyond discovery.

## THE MATERIALITY DIMENSION OF DRUG POSSIBILITIES

The first dimension of drug possibilities is their materiality otherwise known as the concrete structure and observable form. I derived this dimension and its categories from analyzing aspects of drug targets or compounds that are a part of drug possibilities, and I looked for what scientists said about the connections among diseases, targets, compounds, and human biology. Three categories consist of the materiality dimension, including the specific purpose of the drug possibility, the need to work with hands, and the dependence on disease and patient contexts. Drugs fulfill a specific purpose, such as

treating a disease, alleviating symptoms, or killing the pathogens that trigger the disease. As drug elements come from objects that may already exist in nature, scientists work with their hands to identify the properties and potential therapeutic purposes of these compounds. Also, drugs are effective when given to patients with the appropriate condition using the right mechanisms; therefore, each drug possibility is context-dependent on patients' experiences and physiological conditions. When considering all characteristics together, the innovation challenge is to identify the connections of compounds and targets with a disease and to find the biological pathways and combinations of compounds that may intervene in the disease process.

*DRUG POSSIBILITIES FULFILL SPECIFIC PURPOSES*

On the surface, drugs look like simple products that come in many forms, liquid, gel, or pills, but they fulfill a specific purpose in the body. However, the innovation challenge is to identify how these supposedly "simple" drugs fulfill specific purposes when they enter the human body as a complex biological system. A cancer biologist said, "all drugs are specific," meaning that a drug has to go through complex interconnections in our body and hit the target without triggering any adverse effects. Drugs become a part of our biology when they enter the human body. They are dissolved in the bloodstream, get digested in the system, and interact with millions of proteins. Moreover, efficacy and safety of the drug possibility are two ongoing issues that scientists have to be aware of throughout the drug discovery process. A drug is safe and effective means that the target in the body is targetable, that potential compound would hit the right target in the body, and intervene in the disease without binding to other

targets and creating adverse side effects. This is difficult because there are so many interactions in the body that any small change might cause side effects, make the drug ineffective, or change the action of the drug. The compound might bind to another target that has a similar structure to the desired target but very different action. Therefore, the challenge is to determine specific purposes of biological or chemical objects to treat a disease and deliver them into the body safely and effectively.

In addition, the lack of full knowledge about the causes and interactive factors that impact a disease makes it challenging to define specific purposes for a drug possibility. A disease is a complex phenomenon, which consists not only of observable symptoms, but also some underlying interconnections in our body not working properly. A professor infectious disease said, "A lot of times, when humans feel sick and have many symptoms, for example, when you have a cold, you feel chills, fever, headache, those are caused by the host response to the virus (WS500080, interview)." Diseases are complex and each has specific stages of manifestation. For example, Alzheimer's disease symptoms do not appear until years into the disease process, so once someone experiences the symptoms; it is already too late for effective treatment because the neurodegeneration process has already began. Unfortunately, the causes of a lot of diseases remain unknown or some of those causes are ambiguous, which makes it extremely challenging to identify both targets and compounds. For example, Alzheimer's is a complex disease where patients experience memory loss, impairment of cognition, and loss of the ability to speak, write, and make judgments. Although scientists have established that Alzheimer's disease is correlated with the increasing level of amyloid-beta, amyloid-beta is only one part of disease process, because there are other

factors, such as genetics and environmental factors that affect the neurodegeneration process. As a result, the lack of complete understanding of diseases and the complexity of human biology make uncovering specific functions for drug possibilities very challenging.

*DRUG POSSIBILITIES ARE SPECIFIC TO DISEASE CONTEXTS*

As drug possibilities aim to treat a disease, they are effective when given to patients with the right condition through the right biological mechanisms. The effectiveness of drug possibilities depends on the intimate understanding of the disease and the patients' experience with the disease in order to know how the drug possibility would trigger desirable biological effects. Therefore, the knowledge to understand the function of drug possibilities is highly contextualized and situated in a particular disease. Drug possibilities rather than existing in abstract biology actually "have meanings" as they reflect physiological conditions of patients who are taking the drug (WS500052, presentation). Sir Colin, a prominent scientist in both academic and industry communities, talks about the meaning of target for drug discovery:

> "For most people who are in discovery, a target means something like this could be a receptor for an antagonist * antibody, or could be an enzyme. It is a single neuronal nuclear target and that is what people target. You have to remember, that target sits in a protein not a single channel. In fact, it is always a complex system. …the protein sends out signals and interacts with other proteins and generate symptoms. In the sense, that is not the end of the story about what you think about as a target… targets are in networks…. Ultimately we are interested in the role of the target and the human. Let's suppose that this drug we are taking through is designed in some way to benefit heart failure by increasing the output of the heart. We do a study on a healthy normal man and it may work quite well in achieving that aim. But most of our patients are more likely to have a failure, reflective of this individual. Now, he does have heart failure, he's got a big heart, and the drug is less effective. In fact, probably, it is causing problems with cardiac arrhythmias because it is not increasing the output of the heart…. You

> have to think about the physiological disorder of the systems in the patient in which you are looking at the effects at the time" (WS500052, presentation).

Dr. Colin's quote makes two points about the context of drug possibilities. First, targets play a role in the manifestation of a disease. An example of a target is a protein that "sends out signals and interacts with other proteins that generate symptoms," which means that targets are interconnected with other parts in the body and contribute to making a disease takes place. While targets have their own structures, such as neuronal, nuclear target, or receptor, most drug discovery scientists see targets as biological objects isolated from their interconnections in the body; however, they are also a part of the complex system rendering a disease. The second point is that each target has a physiological context, which reflects patients' symptoms and physiological conditions, such as age, weight, diet, and living habits. Patients' living conditions such as demography, medical history, gender, diet and living habits all also have something to do with the biological targets. Dr. Colin emphasized that drug discovery scientists are "ultimately interested in the role of the target and the human." Consider an overweight patient with heart failure. Because he is overweight, his heart might have be enlarged, which causes him to have an irregular, abnormal heart beat. While many patients with heart failure would take a drug to increase the output of the heart, this type of drug will not be effective for him because it doesn't help to regulate his heart beat. Therefore, drug possibilities need to address to a specific problem in the body, and knowing the context is important to find what problem needs to be addressed.

Identifying how drug compounds are useful for a disease involves highly contextualized understanding, from knowing the disease mechanisms to chemical compositions; moreover, the discovery process is also highly complex. Scientists would

not know how to proceed with the discovery process if they are not fully engaged. A professor in pharmacology recalled his experience collaborating with a pharmaceutical company, where he was to analyze one of the company's compounds. The company provided him information about the compound's number and weight, but did not provide information about the compound structure, usage and function; nor did the company give him information about the biological mechanisms for which the compound was interacting with. At the end of the collaboration, he said, "I just handed over the data and result" without knowing what it is for (WS500007, interview). Because the company did not provide him any information about the disease and the compound structure, he perceived no meaning from the compound. I also asked a group of three industry scientists whether academic scientists would be able to help them selecting which drug targets to go after. They said, "academic scientists are not equipped to do that, because companies would not provide them a lot of proprietary information about the chemical compound" (WS500029, group discussion). These two examples reflect that because the drug discovery process is so complex, scientists would not be able to engage with the process without knowing the contexts.

### *DRUG POSSIBILITIES REQIRE HANDS-ON MANIPULATION TO REVEAL THEIR PROPERTIES*

The third characteristic of the materiality of drug possibilities is that scientists are essentially working with their hands to understand them. The important aspect of working with their hands means that they visualize, touch, smell, and feel the object of work; they have physical contact with the object and have intimate experience with the object. Both scientists in "wet labs" and "dry labs" work with their hands. Scientists in

"wet labs" set up equipment for an experiment, feel and manipulate organisms, and observe the object's performance in the experiment. Scientists in "dry lab" also work with their hands to understand the nature of biological objects and translate it into computer codes. By working on the object with their hands, they develop a unique personal skill from handling the object; they also develop a rhythm, coordination, and habit of manipulating the object. When I asked a professor in molecular physiology about how he recognized his discovery, he said,

> "You can't plan for this. I take the discovery in three ways. One is you have your theory. You read your books and then you will learn the technique. The technique is writing on a paper. For example, you are taught from your childhood how to write alphabets. That's the learning scale. Your technique is how you hold the pen and how to write in a line so that people can understand. But here is a third one. What we call the skill. The skill is: you write in your own code. I write in my own code. So your skill is based upon your technique and your learning. If you don't have these two, you don't have a skill. Then your discoveries, you apply all these three things and then design your experiments. I say "look, here is a technique which I know, and here is a skill I can tweak it. And I have my background." So based on that, that's how I redesign… with my experiment, some people said, "Break the leg, but don't inject into the fracture; inject into the arm…. if you put it here for a fracture here, will it still cure it?" You don't know it. So you need to do that. …But these are not answered unless you do it. And you do it and you repeat it many times to make sure it works" (WS500014, interview).

Working with their hands brings a series of tacit experiences with the object. This scientist was referring to a protein that he discovered, which stimulates bone growth, and he was testing to see if this protein grows bone in animals with bone fracture. When deciding where on the animal to inject the protein, his decision is based on his experience with the protein, the disease, and the animal. He was working with his hands to find out the best place to inject the protein that would give the best result. Scientists cannot plan for a discovery, but they rely on their understanding of a theory, skills, and techniques that they have accumulated over the years, and apply them at unexpected situations.

Furthermore, working with their hands also suggests that the drug possibility is malleable and transformable. Scientists working in laboratories are based upon the premise that objects are not fixed entities and taken "as they are" (Knorr Cetina, 1999). Remember, drug possibilities consist of targets and compounds that work together to trigger therapeutic effects in our body. Borrowed from Pisano's analogy, they are like a key and a lock working together to unlock the door. If biologists are searching which doors to open to treat the disease, then chemists are like the locksmith figuring out how to make a key to fit into the lock. Say that biologists identify a protein as a disease target and need to find out its function in cell cycles, they have to transform the protein (i.e., incubate, purify, inject color solution etc.) to visualize its activities. Also, when chemists identify a lead compound that might bind to the desired target, they have to synthesize and create many modified versions of the compound to see which version fits with the target. This is also a process that requires hands-on manipulation to transform the compound.

Because scientists work with their hands to manipulate the drug possibility, it becomes very costly for them to codify the procedures in patents or papers. For example, a pathology researcher specialized in ophthalmology revealed to me that the technical part of testing a target's mechanism is not written in the patent application, so even if licensees license his patent, they still wouldn't know how to test compounds on his target because they need to know how the mechanism works, in order to inject the compound (WS500031, interview). Also, some procedures become very complicated so it is also very costly for others to replicate them. When companies evaluate a potential patent for licensing, they take into consideration the number of steps to synthesize compounds; the

more complicated it is to synthesize the compound, the more likely errors would occur in the process, so the less likely they will license the patent.

## THE EPISTEMIC DIMENSION DRUG POSSIBILITIES

The second dimension of drug possibilities includes epistemic and embodied qualities that we do not completely understand, because they contain biological and chemical elements of nature. This dimension and its characteristics are derived from scientist descriptions of discoveries, questions that are pursued, doubts, and speculations faced regarding discoveries and the desire to investigate. Three characteristics contribute to the epistemic dimension of drug possibilities, first being emerging qualities, second being trigger questions, and third being motivating scientists to pursue answers to questions. The epistemic dimension motivates scientists to ask questions in order to understand emerging qualities. The innovation challenge is to determine the relevant questions for drug possibilities and diseases. Also, this dimension makes it difficult for knowledge to be transferred through patents or translated between social contexts without direct communal interactions. Drug elements come from biological and chemical entities, and their properties only become apparent under certain conditions. Because scientists learn to see epistemic objects through microscopes, chemical reactions, or other indirect means, the process of observation is complex. If there is a minor change in the technical process of analyzing the object, then the scientist might not observe the appropriate/same properties. For example, the same blood cell, derived from different preparations, may appear dissimilar as an artifact of the preparatory method. Therefore, a

lack of consistent observation and complete understanding of the object will make it challenging to codify and transfer knowledge through patents.

*THE PROPERTIES OF A DRUG POSSIBILITY EMERGE*

Drug possibilities are epistemic objects that come from elements in nature, and scientists will not understand their qualities unless they perform work to reveal them. At the same time, the emergence of their qualities is unpredictable but also informative, which then make it challenging to plan the innovation process. The following is an example of an academic scientist who took a series of actions to answer his questions about a drug possibility for Alzheimer's disease. With regard to Alzheimer's, many studies have found that the accumulation of amyloid is associated with the disease. Amyloid is formed by two kinds of enzyme, beta secretase and gamma secretase and ATP is a energy source for those enzymes to function properly. Therefore, a strategy to treat Alzheimer's would be to reduce the accumulation of amyloid by stopping the activity of one of the two enzymes, or by inhibiting the ATP. This neuroscience researcher specializing in Alzheimer's disease has been studying how Amyloid is formed. His questions about using amyloid as a drug target motivated him to raise more questions about it and search for possible compounds. As he performed work on amyloid, the interaction between a drug compound (Gleevec) and amyloid emerged, which helped him learn more about amyloid. He describes his experience of exploring this drug possibility for treating Alzheimer's.

> "I said to myself, we've all said — if we could inhibit the ATP then we could inhibit amyloid production. The ATP is used with different proteins in the cell and totally different processes, it's impossible to do that without killing a person. And then, and I read basically what is ATP blocker, basically it is an inhibitor; and

> what Gleevec is a protein that binds ATP, and then hydrolyzes ATP…. But the point is that I said how could Gleevac do this and be so safe at the same time? So, because it was a very select inhibitor of the ATP, but I didn't believe that; partially because I was naive…when I looked at the evolutionary relationships between the positive kinases…but they were distantly related to each other; distantly related in terms of where the domain of the proteins with the ATP defined. And I said well, maybe this means that Gleevac is promiscuous; and as it turns out, it is because it binds to just about anything in the cell. I don't know why but it does, and the miracle about it is that it doesn't kill a person or make them sick" (WS500064, interview).

This story illustrates that this neuroscience researcher performing work on ATP allows its biochemical interactions to emerge, and those interactions are unpredictable but also informative. After working on amyloid for so long, he wanted to find a compound that targets ATP in order to stop amyloid from accumulating. However, the problem is that inhibiting ATP blocker would stop many enzymes from functioning and might cause severe side effects. Gleevac happens to be a protein binding to ATP blocker "without killing people", but he didn't believe this effect, which essentially motivated him to test and to find out. He found out that Gleevac hydrolyzes ATP and that the nature of Gleevac as potentially promiscuous and might make it useful to treat Alzheimer's. Right now, knowing more about the interaction between Gleevac and ATP, this neuroscience researcher is working on a prototype of Gleevac that will be able to go into the brain and inhibit ATP production. The point of the story is that a lot of proteins, enzymes, and receptors in our bodies have potential to be drug targets and these potentials would emerge when more work is performed; scientists will not know unless they perform work.

*EMERGENT PROPERTIES TRIGGER QUESTIONS*

As epistemic objects, drug possibilities embody questions that are crucial to the process of searching and learning; however, there is an unlimited number of ways to ask questions, which makes innovation challenging to decide which questions are relevant to a drug possibility and the disease. Consequently, scientists are more likely to raise questions where equipment and techniques are available to them to answer those questions. When scientists have questions about biological or chemical objects, they experience a feeling of unease and hunches about the object (Locke et al., 2008). Refer back to Dr. BN's example, when he learned that amyloid accumulation would stop when ATP is inhibited, he felt the urge of wanting to find a compound that binds to ATP. He somehow made a connection that Gleevac might be a compound that would bind to ATP, but he had doubts that how can Gleevac bind to ATP without causing severe side effects. Therefore, he performed work by obtaining samples of Gleevac, testing it on ATP, and collecting data. Questions and doubts about new discoveries help scientists to generate actions and initiate a series of practices to come to know, to uncover, the object in order to resolve the underlying doubts. It is also this very doubt and questioning that motivate scientists to investigate, to search for possibilities, try them out, modify, and transform them (Locke et al., 2008). A practicing scientist and a professor of neuroscience at Columbia wrote,

> "Questions are more relevant than answers. Questions are bigger than answers. One good question can give rise to several layers of answers, can inspire decades-long searches for solutions, can generate whole new fields of inquiry, and can prompt changes in entrenched thinking. Answers, on the other hand, often end the process" (Firestein, 2012, p.11).

In short, questions about a potential drug essentially drive scientists to search for ways to turn it into a drug in reality.

Because of the complex interconnections in our biological systems, scientists have an unlimited number of ways to ask questions about an object. They could ask about its fundamental mechanisms or about its interactions with certain chemicals. Questions about the object shape the process of selecting a target for a disease. A postdoc researcher in cancer biology who is working in a lab specializing in systems biology, talks about the questions involved in the process of selecting drug targets for a particular type of cancer. She said,

> "I studied EGFR, the epidermal growth factor receptor that is known to be involved in cancer, specifically in retinoblastoma. There are tons of drugs targeting EGFR, but those tons of drugs don't work that well. The reason is that there may be a signaling pathway that gets unregulated, or there is a gene at the downstream of EGFR is mutated… by asking the question about "here is the EGFR signaling network in this cancer, if we hit it with this drug, this gene way over here gets unregulated and how does it work?" and that's something that signaling network analysis could tell you. And you can ask this question a bunch of different ways, looking for resistance against a drug, looking at what's driving the cancer, or looking for the difference between cancer, stem cells, and the general progenitor of the tumor population. There are a lot of ways asking about hidden signaling genes"(WS500048, interview).

The first part of the quote illustrates again that objects are situated in complex networks connected with many genes functioning in multiple pathways. The complexity triggers a lot of questions for scientists to consider, such as the biological interactions between specific proteins and genes, or the biochemical interaction between the drug and the EGFR. The complex connections in our human biology triggers infinite number of questions for scientists to pursue. The second part of the quote has to do with selecting methods to answer questions. For example, this postdoc researcher is a "wet lab" scientist, skilled in the experimental method, but she is also surrounded by "dry lab" scientists; therefore, she could employ a combination of experimental and system biology approaches to identify and validate a target. She said,

> "I could just roll my finger around and land on one of [the genes] and maybe test all of those neighbors, … or I can do this more sophisticated, mathematical analysis and give some kind of score to all those genes in the network, which the score would say that these 10 genes are probably most important and test those 10" (WS500048, interview)

She was referring to the choice of method for selecting drug targets for retinoblastoma. From a "wet lab" approach, she could randomly choose a certain number of genes as drug targets and conduct experiments with lab animals to evaluate each of those genes as potential drug targets. On the other hand, by adopting a "dry lab" approach that calculates the probabilities of those genes being associated with the disease, she would narrow her focus down to a smaller number of genes and have a better chance of identifying ones that are important. Alternatively, she could combine both methods, using "wet lab" and "dry lab" approaches, which would provide her a "bottom up" and "top down" perspective to increase the chances of selecting the appropriate gene.

The questions that scientists raise largely depend on their laboratory settings. The equipment and facilities in academic labs tend to be more specialized based on the scientist's skills, background, and specialty. Each scientist is more likely to raise questions that can be investigated by the equipment available to him or her, and thus tends to focus on specific areas of biology or chemistry. As a result, the questions they raise would be more specialized and mechanistic. While it is becoming more common for scientists to work together in multidisciplinary groups, each individual tends to be restricted by their own expertise.

### *EMERGENT PROPERTIES FUEL CROSS-DISCIPLINARY COLLABORATION*

The last characteristic of the epistemic dimension is that the questions motivate scientists to collaborate. Cross-disciplinary collaboration that integrates diverse

knowledge and technologies becomes necessary to reveal the complex emergent characteristics of a drug possibility. A drug itself is essentially an integrated product where the compound consists of active ingredients and inactive ingredients to trigger a desirable effect. When a drug interacts with its target, a variety of unpredictable outcomes are possible. From the formulation of drug compounds to the mechanisms of delivering the compound to the target, drug discovery scientists face all different kinds of questions, such as: Is this a feasible target to affect the disease? What are the components of this pathway? What are the details of the potential target's structure? What genes are involved? Where can a drug molecule bind to this target, and what would be a desirable therapeutic effect? A wide variety of disciplines and techniques will need to be used to fully reveal the properties of a drug possibility. Cross-disciplinary collaboration becomes necessary to answer these questions. Consider the following statement from Dr. Lipinski, a very pronounced medicinal chemist,

> "When you're stuck in a project and you can't get it. You're making no progress at all. What do you do? You take a very experienced medicinal chemist who is uncontaminated by any of the thinking of the current project. You bring that person in and he or she very often makes a breakthrough because they see something in the current chemistry. They say 'you know seven years ago I was working on something like this and I think the chemistry would work. And I know the biology is completely different but I'm going to try it anyway' and it works. It's this conservation of biology motifs translated into conservation of chemistry motifs that's the explanation for it…. And to do this, you've got to go into the chemistry side. You can't get this by going into the biology side" (WS500083 presentation).

Dr. Lipinski's quote exemplifies a collaboration in action, when a biologist brings his drug possibility for a chemist to take a look at it, and the chemist would see the drug possibility from a different perspective. Because the properties of a drug possibility emerge from different technical procedures and conditions, scientists bringing another

area of expertise would reveal other hidden properties. When a biologist has to decide whether a set of proteins can be drug targets, by collaborating with chemists, he/she would learn more about the target's chemical interactions, such as its sensitivity and stability to compounds. By the same token, if a chemist wants to find out what disease the compound is suitable for, collaboration with biologists would help him find out what disease conditions respond to the compound.

Furthermore, a multidisciplinary team including patent lawyers and clinicians becomes necessary as the drug element moves toward lead compound identification and selection. At this stage, chemists perform various types of screening and possibly make variations of the candidate compound. Biologists would conduct experiments to demonstrate pharmacological and pharmacodynamic effects, as well as biological mechanisms of the compound interacting with the target (WS500083, 84 presentations). Patent lawyers and regulators can provide an understanding about the path of developing the drug possibility into a viable product that can be sold to patients, including the competitive landscape for the potential drug. Clinicians provide insights on whether the drug possibility would be effective for patients, what symptoms or situations might make a person a candidate to receive the new drug, and how the drug possibility might affect symptoms (WS500087, presentation).

## THE ACTIVITY DIMENSION OF DRUG POSSIBILITIES

The third dimension of drug possibilities emphasizes the direction and purpose of collaboration among scientists, which consist of a series of multi-disciplinary interactions to unveil this dimension and determine the materiality dimension. Many times drug

possibilities come from an idea or a concept. However, the process to determine whether this idea is safe, sound and functional needs to be conducted in rigorous experimental settings. The innovation challenge is to establish scientific reliability and validity that if the drug possibilities work in experimental settings, and then it would work in the human. This is a capital-intensive process, yet the outcome is highly uncertain with a probability of failure as high as 99%. Biopharmaceutical companies and drug discovery centers invest in a wide range of technologies and experiments to produce information about the compound's toxicology and adverse effects. The drug development process also requires targets and compounds to show efficacy *in vitro* (in cellular systems) and *in vivo* (in animal models) before the drug possibilities can even be considered for clinical trials in humans. In other words, when drug possibilities are discovered in laboratory settings, there is still a long way to go to develop the novel drug possibility into a safe and effective drug.

In order to tease out the activity dimension, I put drug possibilities in the broader context of innovation and asked questions such as, what does this drug possibility mean in the innovation process, and how do biopharmaceutical firms form collaborations with academic scientists to help them with understanding drug potential. I also reviewed the activities that scientists engage in to determine whether a drug possibility has potential. This dimension consists of three categories including transforming novelty to innovation, shifting drug possibilities between experimental settings, and the uncertainty of drug possibilities in the innovation process.

*ACTIVITIES TO TRANSFORM NOVELTY TO INNOVATION*

When scientists identify a target (i.e., protein, enzyme, gene, receptor) or a drug element, these objects are novel but also epistemic, as they have not been previously identified and are not well understood. Essentially, this drug possibility triggers a lot of questions, and it requires a direction and multi-disciplinary work to reveal the characteristics. Say that a drug possibility comes from identifying a target. There are a lot of biological questions to be resolved, such as, how does this target play a role in the disease mechanism? What is the pathway leading to this target? What are the genes that trigger this target and how do they interact? What is the structure of this target, is it a "druggable" target that compounds can bind and will not interact with other proteins? In addition, one who is concerned with bringing the drug possibility to the market for this target would also be asking "What is the disease population?", and "Is this target going to be present in this patient population?" Are there existing drugs that will compete with this drug possibility? Answering these scientific questions not only requires a lot of work and knowledge from multiple disciplines, but also requires time and investment that cannot be afforded by one single sector. The activity dimension involves activities to transform individual novelty into a feasible, functional product.

However, it is not always clear to determine a product vision and to guide the multi-disciplinary work. A clinician as well as an academic drug discovery consultant, said:

> "You want to end it with a vision of molecule, you got to have a profile, a plan, even though it could evolve over time, you should be thinking about early clinical aspects. Your aspirational goals will yield a product profile and you want to confirm the mechanisms related to the biology and pharmacologies and there are methodologies for you to do that" (WS500084, presentation).

While, at the point of discovery, a drug possibility is epistemic and emergent, as more questions are answered and more properties revealed, the drug possibility becomes more like a product with a "product profile" that indicates its specific purpose and disease contexts. This transition requires the participation of specialists in many different disciplines.

Dr. Howard Fillit, a prominent medical doctor and a founder of a venture philanthropy foundation said,

> "[Pointing at a diagram] Basic research would be sort of off the scale here to your left. And that's where targets are discovered, new pathways. But that's not really what leads to drugs. And what I would like to say is that the principles and practice of basic scientific research, basic neurobiology, are incredibly different from the science of drug discovery where we need medicinal chemistry, pharmacology and all those other disciplines to actually create a drug, which is actually an incredibly hard thing to do and especially for neurodegenerative diseases which are complex and multi-faceted in origin. In a drug discovery program, depending on how you go about it, you might start out with 10,000 to a million compounds and that even go into a high frequent screening campaign. But in this case, the biology is really looking at these perspective drugs on cells and trying to refine molecules. But this is really the point in which innovation comes from in terms of new drugs" (WS500084, presentation)

This quote underscores the difference between novel target discovery and drug innovation, which is at the heart of bring basic research to clinical science. The diagram referenced by Dr. Fillit represents the so-called "valley of death", which refers to a knowledge gap between basic research and drug innovation. Basic research discovers novel targets and pathways, identifies their functions and mechanisms related to a disease. This is only the first step of drug discovery. Dr. Fillit said that the principles and practices of basic scientific research are "incredibly different from science of drug discovery," which requires knowledge and practice from multiple disciplines. Innovation in drug discovery really takes place through understanding drug possibilities from

multiple perspectives. According to Dr. Fillit, when biologists identify the targets, pathways and mechanisms, they really need to draw on other perspectives and technologies (e.g., compound screenings, medicinal chemistry, pharmacology) to look at the targets and how the targets interact with compounds in different experimental settings. From the scientists' perspective, when they advance drug possibilities through stages of drug discovery, the focus on their individual creativity and the target's novelty will shift toward safety, efficacy, and applicability.

Academic scientists are always passionate about discovering novelty in the biology and publishing their discoveries, as they have always been discovering novel objects in human biology and working to understand their basic mechanisms. However, innovation doesn't come from identifying novel objects, but comes from integrating different perspectives to understand the novel object. Assessment of a target or compound requires consideration of all kinds of scenarios because our body is so complex. A professor in molecular physiology said,

> "If [academics] are constantly looking for novelty in what you find or what you publish, you will lead to shocking gaps; it's not going to work. Academics need to do an in-depth correct assessment of the target, this is an academic investigation, not an industrial investigation" (WS500038, field note)

Basic academic scientists make novel discoveries and publish them without specifying their function and determining how they interact with other systems (will discuss this in detail in Chapter 5). The "shocking gap" refers to the knowledge gap between the early state of the art in the biological or chemical objects and actual applicability of these objects as a drug. The "in-depth assessment" of the target and compound refers to combining multiple disciplines and perspectives to figure out the likelihood that a target/ compound can be a drug possibility.

The process of transforming a drug possibility into a product also contains a tremendous amount of uncertainty. The uncertainty lies in the fact that scientists may not find out about adverse effects until many years after initial drug development, because the drug's properties continue to emerge in unexpected conditions. For example, certain drugs work very well except when the patient has an apparently unrelated underlying condition. For those few patients, the drug may not work, or may have severe side effects. For example, drugs such as Crestor and Pravachol that lower cholesterol were launched in early 2000s and mid-1990s respectively. These drugs contain statins as their active ingredients increases liver enzyme and may cause severe liver damages. However, it's only until now that studies have identified men above age 45 with heart disease are more likely to expose to liver damages. The long time horizons for the drug's full effects to emerge are one major source of uncertainty. The other challenge is clearly defining a purpose of a target or compound given the complex interdependencies in our body. For example, a drug that was supposed to treat cancer may turn out to be effective for treating a neurodegenerative disease, or anti-seizure drugs used to treat epilepsy is also effective in treating bipolar disorder and migraines. The context is hard to define because the detailed causes of many diseases remain unknown, which then results in uncertainty in innovation. All of these uncertainties point to difficulties for developing drug possibilities into a viable drug.

### *UNCERTAINTY FROM SHIFTING DRUG POSSIBILITIES BETWEEN EXPERIMENTAL SETTINGS*

One critical set of activities to bring drug possibilities into innovation is translating observations of these drug possibilities to different experimental settings,

which involves high level of technical uncertainty. For drug elements to move forward from laboratory settings to clinical application, they have to be translated into animal models and laboratory settings similar to actual human systems. Most of the time, scientists rely on cellular systems to identify a lot of novel biological mechanisms because they are relatively cheaper and easier to manipulate. Once potential targets and drug possibilities have been identified in cellular systems, further study is required to evaluate how those molecules function in humans, and this is usually done in animal model systems. However, this process of translation is not only very costly, but also requires scientists' tacit and specialized skills as well as sufficient translational facilities. It may take scientists up to a year to develop models and obtain the appropriate material that accurately mimic human biology. Academic scientists most of the time face a lot of resource constraints for making such translation possible. Academic labs are smaller, more specialized than industrial labs, and are tailored to the scientist's specialties, and are less likely to be able to afford high-speed or cutting-edge equipment (WS500041, WS500048 interviews).

In addition, the human biological system is much more complex than any single cell culture model. Use of animal models more closely mimics the complexity of an integrated biological system, but any given animal model will have essential differences from human systems. For example, the blood-brain-barrier is a critical mechanism where membranes on the brain's capillaries prevent certain drugs from entering brain tissues. I asked a young scientist who studies this topic about whether we have enough knowledge to exploit this mechanism for drug delivery. She said, "There is definitely enough knowledge to exploit the blood brain barrier for drug delivery, the principals are

in place, but the problem is how to apply in the clinic. It's easy to do it in animals, and we already have a lot of tools, data, and approaches, but there is still a long way to go and test them in humans" (WS500042 field note). The drug discovery community has already accumulated a lot of technologies, research approaches, and tools to answer questions in biology; however, the knowledge has to be translated into human settings to be able to know for sure that the biological mechanism indeed exists in human and can be exploited for problem-solving. Consider this story from a medical doctor who is also a researcher specializing in Schizophrenia:

> "So for example there's this thing that's called P50 gating. When you hear the sort of history of P50 gating the more you know about it, the less real it is, the less important it is. So seeing my patients and being able to say to them, 'look I read this paragraph that says that you hear all these like extraneous signals in the background, and that keeps you from being able to filter out the environment.' They look at you and go, 'no, I don't have that problem. That doesn't happen to me.' On the other hand you talk to patients about what the real barriers in their lives are, what the real problems are, and then you can go and try to fix those things in the lab" (WS500068, interview)

P50 sensory gating is a neurological process that filters out redundant or unnecessary stimuli in the brain. Recent studies conducted in human setting show that patients with schizophrenia are more likely to have a deficiency in sensory gating, which is interpreted to mean that their brains are overloaded with stimuli from the environment. This doctor, who has treated patients with schizophrenia for more than 20 years, constantly makes a connection between what he reads in academic papers and the physiological conditions experienced by his patients. He said that he would ask his patients about whether they would extract messages from meaningless noises, and his patients told him that they didn't have that experience. Consequently, he believes that the literature on P50 sensory gating is only suggestive but does not reflect patients' reality. When novel insights are

published in academic journals, the uncertainty rests in how much practical relevance those insights have with empirical application.

When practitioners such as clinicians or industry scientists read academic journals, the first thing they want do know is whether these papers help them to solve specific problems quickly (McGahan, 2007). However, the goals of academic research are to generate novel ideas and potentials for targets, and many of these potentials will not have identical functions in humans or are inapplicable to clinical settings. It's not because the academic papers are wrong, but it's because they employ technical apparatus or carefully controlled conditions that do not reflect patients' reality. Because these studies are based on lab experiments rather than patients' lived experiences, knowledge published in the paper is not directly applicable to patients. This lack of direct applicability creates a layer of uncertainty in translating knowledge of drug possibilities from lab experiments to clinical settings.

Industrial scientists often rely on academic journals searching for novel targets; however, because of the challenges in translating drug possibilities between different contexts and experimental settings, patents and publications for industry scientists to learn about the nuances of drug possibilities become limited. Most pharmaceutical companies have set up in-house target validation programs to increase the confidence in those projects (Prinz et al., 2011), because pharmaceutical companies have to consider safety and efficacy of the product in humans. However, the cost and time of validating the target are enormous. At the point of transferring projects from an academic to a company setting, the focus changes from 'interesting" to "feasible/marketable" (Prinz et al., 2011). As a result, uncertainty comes from an inability to directly translate

observations from animal to human settings, which creates additional challenges in commercializing academic discoveries.

*RISKS IN THE INNOVATION PROCESS*

The uncertainty of whether a drug possibility will become a viable, marketable drug is considered as risk for companies and investors. Their investment suffers from no return when the drug possibility fails to go through clinical trials and reach the market. The probability of failure for finding a drug is extremely high. Only approximately 1-in 5000 drug possibilities will work and can be turned into a commercially viable drug (Pisano, 2006). There are many reasons why drug possibilities would fail. A compound might cause toxicities and damage parts in the body; the compound might affect other targets that have similar structure with the one desired, or the compound might not go through certain mechanisms in the body and may be metabolized differently than expected. A lot of times, reasons behind why drug possibilities fail cannot be predicted unless trials are performed.

When companies enter collaboration with academic scientists, they face two scenarios that put them at risk. First, companies are exposed to contractual risks when academic scientists do not conduct experiments as indicated in the contract. At the stage of target validation, it is more cost effective for companies to collaborate with academic labs that have specialized experimental settings, rather than the company's scientists learning the technique and designing follow-up experiment themselves. However, companies are exposed to risk in case the academic scientists don't execute the experiment as indicated in the contract A lot of times, it's the students (i.e., PhD student

or post-docs) who execute the experiment rather than the academic scientists, which increases the likelihood of errors and inconsistency (WS500040, WS500029 interviews). Consequently the company would find the results inapplicable for its purpose and the product development is stalled because they cannot use the results. For example, a pharmacology scientist recalled that her company once collaborated with an academic scientist because the company wanted to test its compound with the academic lab's primate model. However, the academic scientist didn't control the experiment property, so the data were inapplicable for their disease context. The company ended up paying for data that they could not use.

The other type of risk that companies face is that they are not sure if the drug possibility behind the academic patent is applicable for their purposes. It is very common for academic scientists reach out to companies with the hope that the company will license their academic patents. The situation of information asymmetry puts the company at risk because the academic scientist has more knowledge about the drug possibility than the company does. Companies have to go through a process of validation, repeating the procedures indicated on the patent to make sure that the drug possibility is reproducible. For example, a scientist works in a large pharmaceutical company who evaluates academic projects as potential licensors said,

> "So when we want to license, it helps to understand both academic research and the drug discovery process. A little company would bring its idea with some data in mouse model and sell them to a big company. Then we have to evaluate whether this model really predicts, so we need a lot of understanding of how the research was done and we go through process to validate whether those molecules and models really have potentials to become a drug. The small companies can afford to develop something new, and they hope to partner with big companies. Even things get to Phase I, 95% of it fail, and 99% of them fail when it gets to Phase III, so we are trying to pick the best one. Small companies can do pretty science stuff, very creative, which is very good because we don't have the

> capacity to do that much, but we can take some of those stuff to validate it and develop it" (WS500023, interview).

Here, this pharmaceutical scientist was talking about her company being selective with what drug possibilities they internalize and in what they invest. She refers to small academic start-ups as "a little company," which implies that the start-ups are very small in size and capability in comparison with big pharmaceutical firms. The small companies do not understand the complexity of drug discovery that the big companies have to deal with. Her story also suggests that small academics start-up have a simplified expectation that big pharmaceutical firms would be willing to invest in their drug possibility. It's very common for small start-ups to seek large pharmaceutical firms to finance their drug possibilities; however, big pharmaceutical firms are skeptical and cautious to invest in those ideas because they cannot afford to pursue novel ideas without validation of "those molecules and models".

Large pharmaceutical companies are very risk adverse in terms of their choices to invest and develop new drug possibilities. Instead of understanding the emergent properties of a drug possibility, they would rather rely on other innovation mechanisms, such as academic translational centers, venture capital, or small biotech start-ups to investigate those emerging properties. Consequently, smaller organizations that do the initial discovery work thus become a necessary innovation mechanism for big pharmaceutical firms to reduce uncertainty in the translational process.

## SUMMARY

In this chapter, I focused solely on drug possibilities as an object and delineated three dimensions. As a concrete material with specific purposes, the outcome of drug

possibilities would address a particular medical need. A drug possibility is also an epistemic object because it comes from nature/biology. It is also an activity object, as it motivates collaboration within multiple disciplines to reveal emerging properties. It is important to recognize these characteristics in order to understand how the current social arrangements for drug discovery are necessary but limited in many ways. Patent protection on drug possibilities is important to protect the inventor and legitimize the commercialization potential. However, academic- industry partnerships based on patent transactions restricts scientists from pursuing multiple questions about a drug possibility. Moreover, the language codified in patents could be limited to explain the specialized craft of manipulating the object. Additionally, although citing papers and patents are a way to learn about academic research, industry scientists still have to translate the academic research into specific disease contexts and this translational process is costly and requires specialized skills. Lastly, the arrangement where academic scientists start up companies enables them to engage in hands-on translation of drug possibilities into different experimental settings, but the innovation process still requires many technologies and tools that would be difficult to obtain for a single company. Understanding the nature of drug possibilities allows us to reflect on the problems with existing social arrangements of academic-industry partnership.

In the next chapter, I shall present information regarding the practice of knowing the objective among academic scientists, where I distinguish between basic and clinical research scientists. As I shall discuss, the clinical research scientist often produces knowledge that is more relevant to drug innovation.

# Chapter 5: Discontinuities in the practices of knowing drug possibilities - basic research vs. clinical research

In the previous chapter, I depicted the theoretical framework of objects to analyze drug possibilities that consist of potential targets and potentially active compounds. With the materiality dimension, drug possibilities are not just an idea but have concrete structure and observable form to fulfill specific purposes in the body. With epistemic dimensions, drug possibilities contain emergent characteristics and generate questions, which motivate scientists to find answers. With the activity dimension, drug possibilities provide a purpose and direction for a series of steps to determine efficacy and feasibility in the human body. In this chapter, I shift my focus from drug possibilities to scientists' practices of knowing drug elements or drug possibilities, and I find that discontinuities in practices exist between basic and clinical researchers.

The three dimensions have guided my analysis of practices of knowing, which refer to a set of activities to produce new knowledge. Scientists learn something new by raising questions, conducting experiments, making observations, interpreting results, writing, and engaging in discussions. I categorized scientists who do basic research as "basic research scientists," and those who perform use-inspired research as "clinical research scientists." For the materiality dimension, I looked for the context where scientists are studying the particular drug element of their interest. I also sought descriptions regarding why it is important to know this drug element, whether they connect it with a disease, or how they understand the drug possibility in terms of a disease. For the epistemic dimension, I analyzed the structure of the research questions to ascertain if there was a desire to understand a drug element on its own or in a

relationship. I also compared how they came up with research questions (i.e., is it an extension of their Ph.D. work, is it because they noticed something in the science that did not make sense, or is it because they want to change a disease state?). For the activity dimension, I investigated how scientists make use of their newly developed understanding of the drug possibility. For example, do they publish new findings immediately or do they "play" with the data, and how do they deal with the emerging characteristics of the drug element (i.e., do they share with their colleagues about what they have found, or do they just move along with their research) (see Table 4 for a summery of the findings).

In the process of analyzing the practices around knowing drug possibilities, I also noticed a contrast or discontinuity within each dimension. Thus, I matched practices of knowing with the scientists' research interests and institutional affiliations and drew the conclusion that two distinctive sets of practices of knowing represent basic and clinical approaches to science. The knowledge from basic research scientists is considered in the Bohr's Quadrant where scientists embark on a voyage of discovery to obtain a fundamental understanding without consideration of practical use (Stokes, 1997). In contrast, knowledge from clinical research scientists belongs in the Pasteur's Quadrant, which seeks to extend the frontier of understanding but is also inspired by the consideration of use (Stokes, 1997, p. 74). This distinction also suggests that the clinical research practice of knowing produces knowledge that is directly relevant to drug innovation. First, basic academic scientists investigate a drug element in the absence of a disease context while clinical research scientists make direct connections between the element and a disease. Second, as these two groups of scientists raise different research

questions about drug elements, basic academic scientists pursue open-ended questions while clinical research scientists define therapeutic functions of the element. Third, as a drug element's properties emerge through experimentation, academic scientists quickly publish those promising properties while clinical research scientists follow up and conduct more experiments to validate the information. As a result, clinical scientists are more likely to recognize drug possibilities than basic academic scientists.

To illustrate these different approaches, imagine two scientists, Dr. John and Dr. Bill. Both conduct research in academic labs and both come across a new protein, P123, which has something to do with melanoma. Dr. John wants to know how P123 works, specifically whether it connects to other proteins, receptors, or DNA fragments that cause melanoma. He would study P123 in a cellular system. Once he finds out that P123 is connected with Receptor 123, Dr. John would publish this finding, and move on to search for another aspect about P123, such as how it sends signals to Receptor 123 and form cancerous cells. He would again conduct experiments *in vitro* and publish the results. In contrast, Dr. Bill also wants to know what P123 has to do with melanoma and how P123 interacts with other genes or proteins that were already found related to melanoma. In addition to *in vitro* experiments, he would find out about the relation between P123 and melanoma *in vivo* (i.e., animal models) and then he would compare tissues between healthy patients and patients that died from melanoma. He might think about publishing those findings if the results are a statistically significant relationship between P123 and melanoma, but what he really wants to find out is whether P123 can be a drug target to treat melanoma. In this way, he makes the transition from basic to clinical research.

Both Dr. John and Dr. Bill are curious about the function of a protein in the human body that they don't completely understand. On a day-to-day basis, their work on P123, which consists of observing the protein, manipulating it, and reconfiguring it to know more about it, might be the same. However, their practices of knowing P123 are different in that Dr. John's knowledge about the protein is basic and general whereas Dr. Bill's knowledge is directed toward a therapeutic purpose, treating a disease. This chapter presents the three key aspects that distinguish practices of knowing and draws the implication that the clinical practice of knowing is more relevant to drug innovation.

## MATERIALITY DIMENSION: THE CONTEXT OF KNOWING THE OBJECT

As mentioned in the previous chapter, a drug possibility fulfills a specific purpose of changing the state of a disease and has a meaningful function in human biology. Because of the complexity in human biology, the innovation challenge is to define a specific purpose of the drug possibility among the interdependent biological connections and pathways. Therefore, a disease serves as the context of knowing, which gives meanings to the interactions of the biological objects in the body that manifest the symptoms of a disease. For example, when people have a cold, they feel chills, fever, and headaches; these symptoms are the bodily responses to the virus. When a drug possibility enters the body, it interacts and becomes a part of human biology that would reflect the disease experience. Disease contexts help making connections between the drug possibility and the large number of interdependencies, so that drug discovery scientists have a point of reference to weed out connections. Having this in mind, I coded practices of situating the understanding in a disease as "engage with a disease" and

practices of putting a disease in a background as "disengage from a disease." This materiality dimension reveals a contrast between how scientists contextualize the drug possibility of their interests. In comparison, the practice of basic research makes remote connections between the drug possibility and a disease context, whereas the practice of clinical research situates the knowing in a disease context.

*BASIC RESEARCHERS DISENGAGE FROM A DISEASE*

Academic scientists tend to investigate the object without connecting it with a disease context. A professor specialized in protein biology who studies the process of neurodegeneration said that he and his lab are doing "in depth stuff on a particular protein function and structure." I asked him whether he is concerned with how this protein is relevant to a disease, he said,

> "It might. And it might not ever be relevant. But at this point, we might want to try and engineer the protein and make it more therapeutically efficacious… And all the stuff we do is just pushing along the basic knowledge of that protein could be relevant. I could say, well that's not relevant at all" (WS500015, interview).

His everyday practice is studying this protein, its structure and function, and he is less concerned whether or not this protein is directly connected to a disease. His object of discovery is "this protein" and he wants to know everything about it. One way he might learn more is designing the protein by changing its structure and function, in order to see the effect of specific changes. Like Professor John in the example in from the beginning of the chapter, the protein biology professor studies the object of discovery in absence of a disease context, although his protein engineering may lead to improved therapeutic efficacy. Maybe this protein could be connected with one or multiple diseases, but this is not the focus of his knowing. A genetics professor specialized in neuroscience said that,

> "We are really discovering things on a very basic level that we need to do all this ground work before [companies] are able to apply it… Because for autism, we don't need to know what genes, protein pathways are affected…we are able to discover things that can then be more informative to drug companies so that they can target different pathways, different genes, and different proteins. We contribute to the knowledge base and if a pharmaceutical company wants to take our information and develop a drug, I don't care" (WS500017, interview)

The genetics professor said that that they are doing all the "ground work" by identifying everything about this gene, its mechanisms, its signals, and its variations. In other words, he would be an expert on this gene. Let us consider a scenario, suppose that a drug company is developing a drug to treat an aspect of Autism, and this drug would interact with a protein and thus affects the signaling of this gene, then this genetics professor would be able to provide information on the mechanisms of this gene, which would help the company in its decision-making. However, in his mind, there is "no need" to know how genes, proteins, and other organisms working in conjunction to manifest autism. It is a drug company's job to put together the pieces to see how they trigger autism and whether a specific target can be used as a drug possibility. Moreover, he does not care how drug companies use the basic knowledge that he has identified, whether for drug innovation or other purposes.

The implication from the two stories above is that academic scientists understand the object in the absence of a disease context, and they see the object as an individual part separate from a connection to a disease. The possibility of using an object in our body is very slim; therefore, there is "no need" to know how the gene and other things work together to manifest a disease. A disease is a complex problem with many genes, proteins, and different parts acting together to manifest a disease. Basic academic scientists are specialized to look at only one part of a disease. Given the complex

interdependencies in the body, there is a long way to go to integrate all the pieces together to understand how different parts render the disease. Consequently, basic scientists are only concerned with one part and not about *what* discovery is utilized or *how* that discovery is utilized in drug innovation. An MD/PhD student said to me at a conference coffee break:

> "Researchers asking basic research questions tend to make implications to a disease, but the implications are usually very far. Scientists who are asking basic science questions feel the pressure to make disease implications, but the research itself is not relevant or even built in the disease. There is still a long way to really find out about a disease if questions are raised from basic research perspective" (WS500038, field note).

"Making far implications," means that it takes a long time to establish a correlation between a drug possibility and a disease. Explanation of a disease usually begins by scientists noticing associations between the disease and possible causal factors (Thagard 1999). The knowledge of those associations would progress and evolve as more researchers make similar observations, accumulate understanding of the mechanisms, then develop causal hypotheses, and then test those hypotheses (Thagard, 1999). It takes a long time to accumulate knowledge of a disease, and scientists usually structure their research to fill in one segment of a long process. Conducting research built in a disease context is different from making implications to a disease. The former involves designing experiments that reflect a particular stage of a disease, using disease-based cell systems or animal models, and employing technical procedures to simulate the disease progression in the experiment. In other words, the work involved is complicated and expensive; therefore, the ability academic scientists conduct research built in a disease context is limited by their access to disease-based material. They would conduct the

research based on the material and equipment that is available to them and draw disease implications, which would subsequently require other researchers to verify those implications with experiments designed in the disease context. An academic molecular biologist said, "What happened was that people usually put a 'standard stamp' in their grant applications by saying 'my research has implication to such-and-such disease.'" Using a standard stamp implies that it is a standard practice among basic academic scientists to signal their research identity to the grant review committee. By stating that the research has "implication to such and such disease," they make a suggestive rather than definitive connection with the disease. Another interpretation is that the federal grant institutions do not require basic scientists to demonstrate rigorous connections between the basic research question and a disease, and thus basic science research only makes suggestive and implicit connections to a disease context.

*CLINICAL RESEARCHER ENGAGES WITH A DISEASE*

For clinical researchers, their knowing practices are built in the context of a problem, and the problem could be a disease, the symptoms from a disease, or a problem of delivering a drug to the body. A disease context connects their observations in the lab with their understanding of patients' conditions. A faculty member of infectious disease at a large research university, a professor studying infectious diseases, said that understanding the disease mechanisms prevent scientists from "getting sidetracked," so that they can recognize what to look for in an experiment (WS500081, interview). When scientists perform experiments to understand a particular object, the experiments are stages of actions that may or may not reflect real-life phenomenon (Knorr Cetina, 1999).

According to this infectious disease professor, scientists might get "sidetracked" by something interesting they see, but which is not relevant to real-life phenomena. She said, "When you use a model, you need to be very clear of what you want and what you want to observe."

Setting a disease as a context of knowing would guide the process and help to make the connection between the reality in the lab and the reality in patients. A cancer biologist, who was doing basic research and transitioned to translational research said,

> "If you start with the disease and you want to go back and see what are the causes or driving factors in the disease and how to block it. That is really your endpoint, is how to treat the disease" (WS500060 interview).

The drug discovery process is like a process of exploring unknown interdependencies among the moving parts. This does not necessarily follow a linear pattern and is rather chaotic and iterative. Cheng and Van de Ven (1996) describe this as an "expanding and diverging process…. in chaotic conditions, and follows a narrowing and converging process of testing the action-outcome relations (1996: 607). Scientists raising open-ended questions start the learning process at the diverging stage by "uncovering the unknown". However, when scientists begin connecting the knowing with a specific function, their learning process enters the converging stage, so that they "work it backward to see how to fix [a disease]." The clinical path of inquiry tends to be directed toward a solution and the knowledge would be contextualized.

Furthermore, being exposed to patients is another aspect for making the knowing concrete and contextualized. Another infectious disease academic researcher who works closely with the pharmaceutical industry described that he would visit clinics, talk to

patients, or even observe how people behave in subway stations as his ways to understand diseases. He said,

> "You have to understand the disease, why these pathogens cause disease, how do they cause disease, how do you intervene? When you interview, how patient behaves tells you what is it that you are doing in the laboratory that can impact this disease. Translational research, that's what we emphasize. For me, it's incredibly valuable [to talk to patients] because then when I'm in the lab, I can think about these patients and look at what we do in the laboratory and look at it and say, 'What is it that we're doing here today that is going to help that patient?' If you don't understand the disease and how it is affecting the patient, then you can't really impact the disease. You do basic science because you want to understand at the most fundamental level how things work. But I argue that if I want to impact what happens in the patients, the more I understand about the biology, the better, because I understand intervention points, I understand where there are potential side effects and what we can do to be novel, creative, and think creatively about how to deal with the problem" (WS500011, interview).

His experience reflects the clinical practice of knowing that is situated in a context, and that the knowing is connected between the labs and patients. By traveling to clinics and talking to patients, Dr. PR uses many sources to know the pathogens in all contexts, not just from the staged setting in the lab. He also puts pathogens in the context of disease and patient conditions, so that he knows what else he can do to manipulate the object in the lab. Like Pasteur, who collected samples from different places such as farmers and distillers in order to understand the disease, scientists who practice translational science would make a patient's problem relevant to the lab and vice versa.

Furthermore, academic scientists who are also clinicians are more likely to keep their practices of knowing in the lab relevant to diseases and patient conditions. Clinicians who have first hand knowledge of patient conditions and diseases are able to quickly make the connections of knowing from patients to work objects. For example, a medical doctor in psychiatry as well as an academic researcher in neuroscience said that he would not do an experiment unless it would help a patient (WS500068, interview). He

and his lab members are constantly directing their questions to "What is real, what are the patients actually needing? What is actually going on in the clinic?" Scientists working with patients would move the work object from bedside to the lab and back again. When work objects are manipulated in a controlled setting, patient's conditions or the disease context are often not taken fully into account in the experiments. The observation of the biological object would be separated from patients' real experiences about the disease. His approach to research is that the experiment he conducted in the lab must address patients' problems. He would incorporate the disease context and patients' condition into his experimental designs, so that his observation of the work object would reflect patients' conditions.

All objects of discovery are a part of the human body and they are interconnected in the body. A disease takes place when parts of the human body are not working properly, a group of genes, proteins, and pathways working together to manifest its symptoms. This process is not only complex but also evolves over time. Like the genetics professor said, academic scientists find "no need" to know how an object connects with other parts to manifest the disease; they are also less likely to connect the object with the entire body. In contrast, clinical research scientists not only see the object in the context of a disease but also take an extra step to validate that connection.

## EPISTEMIC DIMENSION: RISING QUESTIONS ABOUT THE DRUG POSSIBILITY

As epistemic objects, drug possibilities contain characteristics that nobody completely understands. The emergence of characteristics is unpredictable because scientists cannot plan when they will make an observation. Therefore, raising questions and being engaged with emerging patterns is a process of learning more about the drug possibility. This dimension reveals two different kinds of questions, which associate with distinctive ways of knowing the drug possibility. The first kind is open-ended questions to unfold fundamental mechanisms and the second kind is relational questions to define therapeutic function relevant to a disease. By comparison, basic research practice involves asking questions about the possible fundamental mechanisms and patterns of a drug element. Scientists with this practice employ techniques and skills to discover novel aspects and generate an explanatory body of knowledge that can be applied in various contexts (Stokes, 1997). On the other hand, clinical research practice involves defining a therapeutic function for the drug element and raising questions to determine applicability. Scientists with clinical research practice draw on existing knowledge of a drug possibility published in literature and employ these drugs to intervene a disease process. They are making use-inspired knowledge that is fundamental yet also fulfills the purpose of treating a disease.

*BASIC RESEARCHERS RAISE OPEN-ENDED QUESTIONS*

Raising open-ended questions refers to a research process that explores a scientific entity with a limited consideration of use. Scientists practicing basic research raise open-ended questions about a drug element and aim to explain its fundamental mechanisms. An academic researcher in neuroscience for 30 years has been pursuing the

fundamental research question "What is the non-genomic function of estrogen?" Estrogen is a hormone that dictates the development and function of the female reproduction system. The neuroscience researcher's research question focuses on the non-genomic function of estrogen, which sends out signals without altering gene expression and stimulating cell growth, but not its genomic function, which stimulates growth in living cells. Studies have found that even though estrogen's non-genomic effects might be helpful to protect cardiac muscle and prevent heart attack and memory loss, the genomic function of estrogen increases risk of cancer. Therefore, he believes that by understanding how to trigger only the non-genomic function of estrogen would improve estrogen's therapeutic effect. Therefore, he has been learning about the mechanisms of estrogen, its pathways and it's signaling through different pathways. He has also been trying out different substances such as glutamate and histamine to trigger estrogen's impact along specific channels to direct its non-genomic effect. Open-ended research questions imply an exploratory process of knowing the object. Even though there is a goal of improving women's health in general, there is still a long research process to scientifically demonstrate the non-genomic function of estrogen, and then translating them into specific treatments that can be tested in animal experiments and only rarely into a clinical trial. Open-ended research questions produce knowledge that is fundamental and applicable to a wide variety of contexts, from tumors, depression, to cardiac diseases.

Scientists with open-ended questions hone in on a drug element. Honing in means that scientists examine the element's mechanisms and behavior by holding other parts in the biology constant. For example, a genetics professor specialized in

neuroscience said that, "there are many many genes that contribute to autism" and his lab focuses on "one gene, and how this gene, when it gets disrupted, affects other genes" (WS500017, interview). He would zero in on one element, one of the genes that impact autism, and examines a variety of behaviors of this gene, such as increased expression levels of the gene and regulation of downstream targets, and how these behaviors relate to autism. A disease, such as autism, is a complex phenomenon that involves not only a group of genes, proteins, but also neurons or brain tissues interacting together to manifest the disease. However, basic scientists hone in on one of many moving parts and examine factors that contribute to the disease one at a time. Suppose that this genetics professor participated in a multi-disciplinary team of industry and academic scientists for discovering a drug for autism. If the drug interacts with this gene that he is working on, then he would be able to tell the team what happens if a drug hits this gene, but he probably wouldn't know how to deliver the drug to the gene or how would a change in this gene affect autism.

Our body is composed of many sub-systems (i.e., the heart, brain, skin, etc.), but academic scientists fix the knowing within a sub-system as they uncover everything within a sub-system to its entirely, including functions, behavioral patterns, and mechanisms. For example, a neuroscientist who specialized in brain functioning has recently discovered a novel protein (call it Protein A) that relates to formation of neural connections that affect learning and memory. When I asked her how she took further steps to make the connection with neurological diseases, she said,

> "I'm looking at it from the inside and outside. I look at what impacts formation of these neural connections, and what binds to Protein A that changes the pattern of connections. So this led me to the next research question, which is to look at the specific role of Protein A in regulating

> neural patterning. I found that Protein A interacts with PSD95 to stabilize newly formed neuron branches.... Then I want to see what other kinds of proteins bind with Protein A and I found that Protein B increases as neuron development slows down. So the conclusion is that overexpression of Protein B affects Protein A and thus slows down formation of the neural connections important for memory and learning" (WS500075, interview).

She hones in on Protein A and neural patterning of learning and memory functions in the brain. Her observation is fixed on the connection between Protein A and neural patterning in the brain and she looks "from the inside and outside" to see what other aspects of brain development are affecting this connection. "Looking from the inside and outside," suggests that she broadens her observation to explore other components interacting with Protein A, and she also honed in on the local connection between Protein A and learning and memory, and has made a novel observation. The novel observation is that Protein B is connected with Protein A in determining the patterning of this specific area of the brain. She hones the observation in the nervous connections within the brain and lets the patterns to guide the process of knowing.

In a similar vein, an academic scientist specializing in cancer metabolism describes the autophagy mechanism, a process by which cancer cells survive when they encounter stress. She explains that the main goal of her lab was to determine the functional role of autophagy in cancer, so she really hones in on the autophagy, its architecture, pathway, function, and mechanisms. She presented her findings in a cancer metabolomics conference, she said,

> "Autophagy is a stress-activated pathway. When cells are confronted with starvation, damage, and stress of any kind from cancer therapy, they will activate this pathway where cells will eat themselves. They will form a double-membrane vesicle called and autophagozome that will capture intracellular cytoplasmic debris, and combine with a lysosome to degrade the contents. Once the damaged proteins and organelles are broken down

> into basic building blocks, these breakdown products are released from the lysosome into the cytoplasm where they can be re-utilized by the cell. The main function of the autophagy pathway is to allow cells to bide their time when there is a period of nutrient interruption and to recycle components to sustain their metabolism (WS500080, presentation)"

The autophagocytic mechanism is important because it allows cells to survive under mal-nutrient conditions. The implication is that, when cancer cells are starved rather than disintegrated by cancer therapy, cancer cells can actually sustain themselves due to the autophagy mechanisms. If cancer cells are better at autophagy than normal cells, the cancer therapy will cause more harm than good. This quote illustrates the in-depth knowledge about the autophagy mechanism, such as what it looks like and how it works. She tells a story about autophagy like peeling an onion, layer after layer, first with an understanding of cancer cell growth and mechanisms to respond to stress. She then describes what the autophagocytic pathway looks like, what happens when cells move through the pathway, and how damaged proteins and organelles are broken down when autophagy is activated.

The in-depth knowledge is useful as background knowledge for scientists to design applications associated with the autophagocytic mechanisms. She said that, "if autophagy is indeed the survival pathway for tumor cells, then scientists can target the autophagy pathway for cancer therapy – inhibition of autophagy should compromise the ability of tumor cells to survive under stress." The ultimate purpose of knowing about autophagy is to be able to stop the autophagocytic mechanism so that cancer cells can be destroyed by cancer therapy, limiting the opportunity for relapse. However, there is still a long research process to reach that point. She said, "autophagy can be a new mechanism to target RAS-driven cancer (a type of genetic mutation), so what are we

working towards? Well, we don't know yet… we don't know in vivo how mouse autophagy is playing a role in maintaining their metabolism…we need a better understanding how autophagy contributes to tumor metabolism under physiological conditions." Most of the autophagy studies are conducted in animal experimental settings and there is a variety of autophagy processes, so we know exactly which of the processes observed in animal setting really takes place in humans. Moreover, cancer is caused by mutations in a variety of genes, and the relative role of autophagy in each kind of cancer is not understood. Does the mechanism work the same way in human as it does in animal models? How do we identify autophagy in actual cancer patients and how does it affect their physiological conditions? There are still a lot of questions as well as uncertainty about applying the understanding of autophagy to enhance cancer treatment

Scientists applying an understanding of autophagy for a cancer therapy face a different kind of research question, such as "which biological pathway can inhibit autophagy in cancer cells," or "how to prevent autophagy from being activated?" Scientists would combine the knowledge of autophagy mechanisms and the characteristics of a particular cancer to design a therapeutic strategy to stop cancer cell growth. They would also consider whether the autophagy mechanism operates differently in different stages of cancer. However, there is a translational gap between finding answers in animal experimental settings and applying the answer to clinical settings. Scientists need a different set of techniques and questions to identify autophagy in cancer patients and be able to connect the theoretical mechanism with their physiological symptoms in order to know the point of intervention to inhibit autophagy in cancer cells.

*CLINICAL RESEARCHERS RAISE THERAPEUTIC-FOCUSED QUESTIONS*

Both academic and transitional scientists want to know the basic mechanisms of the drug element of their study; however, scientists practicing clinical research raise questions that focus on an application rather than further exploring the element. In other words, clinical research scientists ask questions about the drug element with an attempt to make use of the element to change a disease state. Comparing Dr. John and Dr. Bill again, Dr. John would focus on knowing the mechanisms of P123 and looking at it from "inside and outside." Dr. Bill, as a translational scientist, would focus on how P123 triggers melanoma and whether P123 might be a therapeutic target for disease treatment. The knowing practice of clinical research scientists starts with defining a therapeutic function for the drug element, such as changing a disease state or alleviating symptoms of a disease. A research question that aims to define a therapeutic function has a specific endpoint to the research. Scientists would search for means to the end, so that they would know whether the element could be a drug possibility or not at the end of the research progress. On the other hand, an open-ended question merely guides the research process where the scientists explore the element and see where it takes them.

A medical doctor as well as an academic researcher in respiratory diseases, who previously worked in industry but is now at a university, illustrates what it means by a research question with a therapeutic endpoint. For example, he said, a research question with a therapeutic endpoint would be "what biological pathway would lead to a disease-modifying agent?" (WS500054, interview) A disease-modifying agent would be a drug possibility (i.e., a target that could be a protein, enzyme, or receptor) in our human body

that can change the state of a disease. He described a hypothetical research process that a scientist would undertake with this research question. For example, the scientist would learn about the disease mechanisms and study how the disease progression could be altered, by looking at genes and pathways connected to the target. Then, he would find out how those genes and pathways and the target manifest the disease, and determine which pathway would be a point of intervening the disease. At the same time, he would also consider the consequences for the disease and for the patient when the disease-modifying agent is inhibited. As described here, although clinical research scientists define a function of a biological element in terms of a disease or treatment, the research still creates a lot of fundamental understanding of biological mechanisms, and therefore also contributes to the knowledge frontier of a field.

Because clinical research scientists have a specific endpoint in mind, they don't always discover new drug possibilities but rather draw on existing possibilities that have been identified in the literature. Then, they would find a therapeutic intervention based on that object. For example, existing studies in cancer have shown that the CD19 antibody is an attractive target for stimulating the immune system to destroy leukemia. Since our body is already producing CD19 antibody, a common approach for treating antigen-related cancer is to engineer an anti-CD19 antibody to boost its function. Building on this line of research, a cancer biologist specialized in lymphoma conducted a research to investigate how CD19 antibody can be used as therapeutic intervention for leukemia (WS500038, field note). His research question was "What agent and receptor, combined with CD19 antibody, can inhibit leukemic cells?" He first conducted experiments in a cell culture system to find a receptor site where CD19 can bind. Then,

he engineered the CD19 antibodies and he translated the antibody from cellular system to animal system to see their interaction. At the same time, he is involved in testing the concept in a small-scale clinical trial with three patients. The outcome of this research question aims to improve the patients' immune responses to combat the growth of leukemic cells.

The point about this cancer biologist's story is that he defined a therapeutic function of a target that was previously identified in existing research. CD19 antibody was already identified; a lot of its basic mechanisms, functions, and properties had also been identified. Therefore, the translational research question about the object is to understand how to apply and make use of the object to solve a problem. Also, antibody therapy for cancer is a common therapeutic approach, and he draws on this common approach and applies it to work on an existing-known object to treat a specific kind of leukemia. Compared to basic academic scientists, clinical research scientists shift away from discovering new elements toward combining existing techniques and tools and making use out of elements that have been identified and validated. In the case when the discovery has already been established, scientists can quickly build on prior art and apply it for problem solving.

Furthermore, clinical research scientists see drug possibilities as being interdependent and connected with many moving parts and pathways in our body. Their path of inquiry focuses on the interactions and interconnections of the drug possibilities with different parts to manifest a disease. I asked a pathology researcher specialized in ophthalmology to describe his research process (WS500033, interview), who has recently identified a target for treating retinoblastoma (tumor of the retina). He described that he

first came across a biological target that has been described in the literature, and he wondered if the target could be used as a drug target to treat for retinoblastoma (tumor of the retina). His path of inquiry began with understanding the basic mechanisms of the target, such as how it relates to the origin of the retinoblastoma tumor, its cellular mechanisms, and its signaling pathways, all of which are different parts working in conjunction to manifest the disease. Subsequently, he found out that this target is only useful for one of the two mutations that cause retinoblastoma. He further looked for the binding site where compounds could be best attached to the target. Then, he sought to collaborate with a pharmacologist and conducted high-throughput screening to figure out what kind of compound would bind to the target. His research path suggests that he has not only pursued an understanding of the fundamental mechanism of the drug target, but also defined the conditions in which the target is applicable for the disease.

In comparison, open-ended questions about a drug element produce important understanding about its fundamental mechanisms whereas defining a therapeutic function of a drug element is more likely to produce knowledge about using the drug element to change a disease. When drug elements are defined with a use, scientists would employ tools and technologies such as screening and imaging to understand as well as to validate the global interconnections between the drug element and the surrounding biological systems.

## ACTIVITY DIMENSION: PURSUING EMERGENCE OF DRUG POSSIBILITIES

So far, I have discussed the contrast between basic academic and clinical research practices in terms of material and epistemic dimensions. Lastly, the activity dimension involves a set of technical procedures and steps necessary to materialize the drug possibility. Because a drug possibility's properties are emergent, particularly true for targets in the human body, observations may not be consistent under varying circumstances and translating the object into different experimental settings may create uncertainty in the technical procedures.

This dimension reveals a major difference between two sets of practice in terms of what scientists do with their findings. I looked for the activities that scientists engage in to make their findings available publically. I coded scientists who immediately publish their finding as "moving on from emergence" and scientists who employ other techniques to test their finding as "following up with emergence." On the one hand, scientists that practice basic research publish the result about drug possibilities after making a new observation and move on to search for another novel aspect of the object. On the other hand, scientists that practice clinical research would verify observations in various experimental settings and continue to use other technologies to validate those observations. For example, if both Dr. John and Dr. Bill made the same observation about P123, Dr. John would publish the observation and move on to search for new observations, while Dr. Bill would follow up with the emergent property and find other techniques to validate the observation. The stories below will better illustrate this point.

*BASIC RESEARCHERS MOVE ON FROM EMERGENCE*

As basic scientists raise open-ended questions about a drug element, they make an observation on its newly discovered aspects and then they move on to searching for another new aspect. They are constantly searching for new aspects of a drug element or for a new element, so that they don't dwell on the emergence. An academic researcher specializing in leprosy illustrated what it means to "move on" to the next scientific questions. In her earlier studies using a drug molecule TH on leprosy, she finds that ENL, a kind of leprosy, is caused by a sudden increase in TNF enzyme. She said,

> "The next question is what causes the increase in TNF enzyme. The role of [drug molecule TH] would be less interesting to me, because I've used it as a tool to understand what causes, how the disease involves. Under normal circumstances, I would leave drug molecule TH aside and go on to examine why is there sudden TNF enzyme increase in these patients, move on to the next scientific question, unless I'm specifically interested in trying to develop drugs that would work" (WS500011, interview)

The TNF enzyme and its role in leprosy is her object of discovery. The drug molecule TH is not her object of discovery; it's only a tool for her to find out about the TNF enzyme that she was interested in. Academic scientists in general are interested in the human biology but not in the interaction between drug molecules and the human biology, hence she said, "under normal circumstances, I would have left the drug molecule alone and gone onto examined why the sudden change in TNF enzyme in patients", which is the next scientific question she would have pursued. In their minds, the scientific question pertains the specific object, its mechanisms and function in a disease, but not its interaction with drug compounds.

She continued to explain, "Basic scientists usually focus on a question, a mechanism, on a biological system that they are trying to understand. When they come

up with new ideas, new mechanisms, new observations, they would sort of move on, and they might or might not use that finding beyond its implication to the research" (WS500011, interview). The implication here is that academic scientists focus on one question about the drug element and they are always searching for new aspects about the element. Drug possibilities contain epistemic characteristics of which no one has complete understanding, so when there are technical procedures done on the possibility, its new properties would appear and we would learn more about it. Therefore, when the property of the element emerges and scientists make observation of that emerging property, they "move on" to search for other new properties to emerge.

Consider another example. A genetics professor described his path of knowing his object of discovery, which is a gene that has to do with autism. He said,

> "My hypothesis initially was whether this gene is involved in autism. So the answer was yes. Then the next question is – what is the DNA variant that contributes to it and how is it function. We answered that. The question after that is well, if it's function, when, where, and how is it function *in vivo*. We are answering that. If it's truly functional, what are the downstream effects? That is where we are going. So one question leads to another question which leads to another question (WS500017 interview)."

This story first shows that this gene could be a drug element that is involved in autism, and the emergence of the gene's property shapes and guides the research path in a piecemeal fashion, first with the DNA variant of the gene and its function, how the variant functions *in vivo*, then its downstream effects. Dr. JM emphasized the linear progression of knowing the work object when he said, "one question leads to another question which leads to another question," which suggests that the emergence takes them from one question to the other and that they do not dwell on the emergence.

Scientists "moving on" from emerging properties suggest a practice of constantly searching for new properties without validating those properties. In other words, they are searching for novelty and new aspects, which is the focus of their everyday practice. Repeating experiments is not a part of day-to-day practice for basic academic scientists, because it costs money and sacrifices their time for new research; moreover, results produced from repeated experiments have no intellectual value for publication and grant application. However, the lack of repeating experiments makes scientific results irreproducible, which hinders future application and innovation. A professor in molecular biology described his experience collaborating with a scientist in a prestigious academic lab.

> "You rarely just go and repeat experiments because that's boring. So what you normally do is you go to the next step.. If "a" is true, then I'm going to start doing "b" and "c," so we started with "b" and "c" and then we got to "d" and then everything failed. We went back to "a" that was published and it didn't work. We contacted the scientist and he admitted that he had not been able to reproduce the data (WS500007, interview)."

He said that "it's rare" to repeat experiments, which suggests that once scientists make an observation of an emergent property, they rarely repeat the same experiment to make sure if the observation is consistent. This leads to a lack of iterative validation in the academic practice of knowing. Moreover, studies published in academic journals are generally assumed to have a certain level of science integrity, so that other scientists expect to be able to reproduce the experiment and get the same result. However, his experiment was stalled because he thought that "a" was reproducible when it actually was not, so that he could not move on to "b, c, and d". The story also shows that when scientists move on from emergent properties of objects, the lack of validation and follow-

up on the emergence not only contaminate the integrity and reproducibility of science but also can slow the innovation progress.

Institutional pressure from the disciplinary fields drives scientists to move on from emerging properties and to constantly seek new observations. If they don't, then they would lose security in funding and advantage in the field. The molecular biology professor further said,

> "If you are looking for [some techniques] that you think you can sacrifice some weeks or months of lost productivity, because you can think that you're going to get a better publication; and in any case, the field technology moves on. The field moves on and if you don't move on, you're going to lose your funding at some point, and your edge in the field (WS500007, interview)."

Because of the funding pressure, basic academic scientists who rely on federal funding are less likely to pick up new skills or conduct experiments with unfamiliar techniques. For example, if they conduct experiments in cell cultures, they are less likely to conduct experiments in animals because they have to "move on" to the next scientific questions.

The way they move on from the emerging property to the next science question is by publishing their new observation. In their minds, publishing is the endpoint of their involvement in drug innovation, and they may or may not be concerned with how their drug element could be a drug possibility or not. For example, a protein biology researcher specialized in neurodegeneration process said,

> "Once we made that discovery [of the gene that causes a common hereditary neurodegenerative disease], it's just a question of how to actually solve the problem of delivering [the enzyme encoded by that gene]. We let the gene therapists who… are real specialists, so we don't go into that field. We help them with their research (WS500015, interview)."

After he discovered the particular gene as the cause of the disease, the next problem of finding a drug is delivering the enzyme missing in the disease, which he considered to be gene therapists' problem. He sees replacing the missing enzyme as an easy problem for gene therapists to solve and he doesn't have to get into the field of gene therapy. He also assumes that his research will be picked up by gene therapists and be applied to solve the problem. Therefore, by publishing the discovery of that gene in academic journals, he is "helping gene therapists" with their research. The goal of academic scientists is to disseminate findings through publications, so that experts from other disciplines can pick up the knowledge from journals and plug into their innovation process. In other words, publication is a taken-for-granted channel for academic scientists to participate in a general innovation process.

A post-doc who previous worked in industry but now is in academia confirmed this pattern when she said, "If you have discovered a molecule and just kind of publish it, and you're like, 'ok, that's it, there's nothing else, we are not going to do trials for one of these.' Her quote illustrates a common behavior for academic scientists, who publish their discoveries and then move on to another discovery, without doing trials-such as confirming the discovery in *in vivo* for exploring alternatives for making the molecule into a drug possibility. Her story implies that an academic's involvement in innovation stops once they have made a discovery. They publish the finding without continuing to work on the same discovery.

In addition to the institutional pressure from the publishing system, another institutional force from the funding agencies might shape the pattern of asking open-

ended questions and moving on from emergence. According to a cancer biology researcher,

> "A lot of times at NIH, you can get a grant if you to know the idea you propose. As long as you basically answer something that is related to it, that's fine. You publish your papers and you get to the next question. You are further in your research. However, further in your research and answering a directed question are very different" (WS500060, interview).

The institutional pressure from the funding agency, such as the NIH, also shapes scientists to move away from emerging properties and searching for new ones. As Dr. JK's quote implies here, federal grant agencies like the NIH do not review the direct connection between the research and a particular disease context but rather look for novelty in the research. Therefore, academic scientists are able to ask open-ended questions and explore the drug element, which is a different practice from answering a specific question. Answering a specific question implies that the knowledge produced leads to actions and what kind of actions. Referring back to Dr. John and Dr. Bill, by discovering P123, Dr. John is furthering his research on melanoma while Dr. Bill is answering a specific question whether P123 is a druggable target. In the following, I will discuss how clinical research scientists follow up and validate those emerging properties of work objects. To some extent, they are concerned with a specific question, so once they come across an emerging property, they follow up with the property and translate that observation to different settings. A lot of time, they go out of their way to find new methodological approaches to validate their observation.

*CLINICAL RESEARCHERS FOLLOW UP WITH EMERGENCE*

Rather than moving on from the emergent property and searching for the next new property of the drug element, clinical research scientists draw on multiple experimental settings and techniques to validate the observation they have made. Clinical research scientists are concerned with the interrelations between the drug element and different parts of the human biology; therefore, they conduct in-depth assessments of the relationships in multiple experimental settings. Translating observations from one experimental setting to the other produces additional signals about the drug element and teases out the unknown effects. For example, a faculty member who specializes in melanoma identified two DNA fragments that trigger the formation of melanoma in cell systems. She was not sure whether these two DNA fragments really cause melanoma in humans. To prove her hypothesis, she created mouse models to see if the same observation appeared in animals. At the same time, she contacted a medical doctor and asked for human specimens in order to further assess her observation in humans. The shifting between experimental settings from cells, to animals, and to human specimens increases the validity of her observations. Shifting between experimental settings transforms conceptual knowing in laboratory situations to real-world problems.

Clinical research scientists are more likely to combine experimental methods and digital technologies to understand the object's interactions and interdependencies in the context of a disease. Scientists using experimental methods are considered as working in the wet lab where they manipulate and visualize the object of study. On the other hand, digital technologies, which include statistics and mathematical modeling, simulate a structural view of biological processes and provide a more accurate prediction of the range of targets and signaling pathways, as well as the potential effects when they are

targeted. Because these techniques are highly specialized, scientists familiar with one often don't know the other; therefore, they have to collaborate in order to integrate the methods for one research agenda. For example, a cancer biology researcher specialized in lung cancer sets out to understand the signaling mechanism of the Erythropoietin Receptor (EPo), which plays a role in many lung cancer treatments. Regulatory agencies and clinicians have been speculating that many lung cancer treatments contain too much EPo, which causes adverse side effects in patients; therefore, she started a research program to address this concern. She first started with understanding the basic mechanisms of EPo (i.e., regulation of cell growth cycles and division) and the relationship between EPo and lung cancer cells. Then she wanted to understand how EPo behaves in lung cancer. She said that it's a very complicated process so she combined quantitative math modeling, differential equations, and experimental methods to show how EPo is responsible for lung cancer cell proliferation. I asked her about how she combined the two methods with digital technologies and experimental methods.

> "I am working with a physics scientist and I have Post-Docs who specialize in math modeling and system biology. We work very close together and we need a constant back-and-forth, and sometimes we work side-by-side. The hardest part is how to interpret errors, because there are variations in cell lines [from the experimental method] and in the expression profiling [from the network analysis]. Therefore, when you need to interpret those variations, she said that establishing reliability is always very hard. In the end, you have to narrow down and select the one that is closest to the lung cancer context (WS500053, field note)"

The point here is that clinical research scientists would go out of their way to collaborate with experts with different methodologies to comprehensively examine the EPo in lung cancer. They take into account of the networks and interdependencies and thus seek rigorous methods to account for a holistic picture of the drug element and its context. According to her, the difficult part of combining the two methods is "establishing

reliability," because the results from math modeling have to correspond with the result from experiments. For example, she and her team conducted experiments to show the dynamic properties of two signaling cancer cells and the EPo's binding site on those cancer cells, while the physicist used math modeling to predict the best dose of medicine that triggers EPo. The meaning of the variables in the math model is translated to experiments and vice versa, and the two methods are validating one another. Therefore, rather than moving on from the emergence, clinical research scientists are more likely to employ additional methods and technologies to follow up and further understand the emerging properties.

Another clinical research scientist, who discovered a protein that potentially treats osteoporosis, describes the path of assessing that protein in depth. He first tested the protein using bone cells; then he translated the same experiment from cell systems to animals. Later, he used many techniques, such as x-rays, imaging, histomorphometry, and amino acid chemistry to validate that the protein he has discovered does indeed treat osteoporosis. He said,

> "You need to repeat your experiment. You cannot just give it as a one-shot thing and you say, "Oh, this is good." But you need to have appropriate controls, design the experiment to make sure you're not missing anything in the big picture. And when all the stars are aligned and everything works in the right directions many times, that's when you say, "ok, we're on the right track" (WS500014, interview).

Here, we see a contrast between clinical research scientists repeating experiments and the molecular biology professor who would "rarely just go and repeat experiment." On the other hand, this clinical research scientist repeats the experiment many times and makes sure that the results from different experiments would confirm that his concept is feasible. Using multiple skills and technologies to assess a scientific observation is not merely

repeating the same experiment, but establishes a new level of understanding for the complex system. This clinical research scientist picked up many techniques, such as "x-rays, imaging, histomorphometric, and amino chemistry" to validate the drug possibility. Shifting between experimental settings makes meaning out of the chaotic variety in biology, and each setting produces new meanings that can be integrated into a new level of understanding.

The iterative trial and error is a routine to identify new meaning and new alternatives that can be used to guide further search (Simon 1996; Carlile 2004). A translational practice of knowing consists of making a functional connection between the object and the disease context, and iteratively validating that connection. Validating the observation by shifting between experimental settings is a process of "making meaning out of noises" (Tsoukas 2005). Human biology is a complex system with many biological interactions and numerous interdependencies. There are noises in any complex system that disrupt order, create interference and uncertainty (Tsoukas 2005). However, by making meaning out of the noise using multiple experimental settings, a scientist is also "inventing new codes which may be seen as part of a new signifying structure and be integrated into a new level of understanding" (Tsoukas 2005: p. 286).

After scientists make a new discovery, the practice of validating observations in different experimental settings differentiates academic scientists from translational scientists. Academic scientists move on to new scientific questions once a new observation is made, while clinical research scientists utilize multiple experimental settings to validate the new observation. When a new discovery is made, the practice of validation and verification is a critical step to "transform discovery claims into scientific

discoveries" (Grinnell 2009: p. 60), where discovery claims contain components of subjectivity that cannot escape the potential for misinterpretation and error. As a standard practice in the scientists' community, validation and verification consist of checking a hypothesis with more data, using different techniques to make sure that the initial observation can be repeated (Tullock 1966). This practice is particularly important to tease out the unknown properties of the new discovery that could be a drug possibility for a disease. Since a drug possibility is a configuration of target and compound that interacts with all the complex parts of the biology, it has to treat the disease without disrupting biological order in the body. If a drug possibility is effective in killing disease cells in cellular settings, it does not mean that it would cure the disease in humans. There are a lot of uncertainties in translating a drug possibility from cellular system to animal models that will eventually work in human. Because of the emergent properties of a drug possibility, each experimental setting will produce new understanding. Cellular systems demonstrate the preliminary patterns of the drug possibility in a simplified setting, and animal models demonstrate its mechanisms and interactions, so that scientists would get a closer understanding of how it works. Iterative employment of technologies, such as x-rays, imaging, high-throughput screening, and informatics in the "dry lab" is to confirm the observation. The different experimental systems are to tease out the ambiguity and emergent properties of the discovery.

## SUMMARY

This chapter compares two distinctive sets practice of knowing, basic research and clinical research based on the three dimensions of drug possibilities. The materiality

dimension highlights the concrete nature and specific purpose of drug possibilities in the human body. All scientists understand the concrete nature of drug possibilities and actively situate their practices of knowing in the complex biology of the human body. However, they diverge over the biological situation they concentrate on and how they engage in this situated learning. With the epistemic dimension, the characteristics of drug possibility emerge and trigger questions that motivate scientists to identify new possibilities. All scientists are motivated to work on what they do not yet know, but they diverge over the kinds of questions they ask and the paths they follow to track down emerging insights. With activity dimension, drug possibilities provide a purpose and direction for a series of steps to determine their efficacy and feasibility in human body. Scientists diverge over the steps they take and the sense they make of those processes.

Because drug possibilities embody epistemic characteristics, their properties are not completely understood and would continue to emerge as more work is performed. The aspect of "moving on" from the emerging properties consequently hinders academic discoveries from becoming drug possibilities. Scientists want to be the first in making discoveries and disclosing the discoveries to receive recognition (Merton 1973). Their rewards and recognitions are structured based on being the first to disclose novel knowledge in their fields. However, the haste to publish creates a "gap" in the knowledge between novelty and application, which leads to inefficiency in science research and innovation process (Dasgupta and David 1994). In contrast, the practice of following up on the emerging properties is about drawing on multiple technologies and experimental settings to validate their observations iteratively. As academic scientists (both basic and clinical) are discovering new biological and chemical objects, by

following- up on their emerging properties with technologies and tools, they are exploring the potential of transforming biological objects into drug possibilities. The aspect of iterative validation and follow-up with an emergent property is more than repeating the same experiment, but is a practice of making new understandings from complexity. Because our biological system is complex, iterative assessment and validation may be a key practice to develop the appropriate configuration in the complex system. The practice of clinical research not only requires a wide range of translational facilities but also financial capital and institutional environment to enable such practice. In the next two chapters, I will shift focus to discuss the practices of academic scientists making their research available to drug innovation through the commercialization process.

# Ch. 6: Commercialization Process: Industrial Entrepreneurs and Academics Scientists Around Drug Possibilities

Previously, I identified the discontinuities in practice between basic research and clinical research scientists in terms of how they approach the three dimensions of drug possibilities. The scientists differ their approach to the materiality dimension with basic research scientists situating their understanding of drug elements in a general therapeutic area while clinical research scientists situate the learning in a specific disease. Basic and clinical research scientists also approach the epistemic dimension differently because basic research scientists raise open-ended questions to explore the drug element's fundamental mechanisms while clinical research scientists raise specific questions to understand the relationship between the drug element and a disease. The practices for the activity dimension also differ. On the one hand, basic research scientists move on from the emerging patterns; on the other hand, clinical research scientists follow up on the emerging patterns by repeating experiments with different methods and technologies.

Shifting from looking at the practices of knowing in the lab, this chapter focuses on the commercialization process, in which academic scientists and their universities bring potential drug possibilities beyond research settings into the marketplace. In short, commercialization is difficult for academic scientists. Not only do they face the lack of funding throughout the process, but they also have to learn about patent policies and how to communicate with the industry. During this process, academic scientists interact with industrial entrepreneurs with the goal to seek funding and users for the drug possibilities that they have discovered. Industrial entrepreneurs are skilled professionals from large institutions, such as university technology transfer offices (TTOs), venture philanthropy

foundations, venture capital firms, or pharmaceutical companies, and they draw on institutional resources to influence the commercialization process. While academic scientists rely on industrial entrepreneurs for financial and technological support to commercialize their discoveries, the commercialization process disrupts their practices of knowing the discoveries because they have to meet the evaluation criteria of those entrepreneurs.

This chapter presents an analysis of the criteria that industrial entrepreneurs use in evaluating drug possibilities and the practices that academic scientists engage in to meet those criteria (See Table 5 for a summary). The evaluation criteria reflect the three dimensions of drug possibilities. First, a drug possibility's materiality refers to the function and disease context in which it is applicable; industrial entrepreneurs evaluate this dimension based on the mechanisms that they can monetize from the drug possibility in its final form. Industrial entrepreneurs see academic discoveries for commercialization as investment opportunities, so they would be able to profit from the discoveries when they are packaged into intellectual properties. If the discovery is a single technology, then filing a patent and licensing it to companies constitute the appropriate monetary mechanism. If the discovery is a platform, then starting up a company is the appropriate mechanism to monetize and develop the discovery into a complete product family. To code the practices that academic scientists engage in to meet the criteria, I looked for what they do to present the drug possibility in its material form, such as filing for patent disclosure, applying for patent protection, building a patent portfolio, or starting a company, all of which represent what they know about the drug possibility and its practical functions. I also looked for what academic scientists do to develop a patent

portfolio, the rational behind starting a company, and what it means for them to start-up a company.

Second, the epistemic dimension refers to scientific questions of a drug possibility; industrial entrepreneurs evaluate this dimension based on the legitimacy of the scientific questions and innovation purposes through publications and patents on the drug possibilities. Publications legitimize scientific questions and signal the drug possibility is scientifically sound, and patents legitimize the drug possibility for commercial application. To code for this dimension, I looked for their rationale behind applying for patents, what kind of research questions they pursue for publications and for patents, how do they pursue the two institutional requirements, and whether or not there is a tension. Lastly, industrial entrepreneurs evaluate the commercial potential of a drug possibility based on its market size, which is determined by its patient population. Therefore, the activity dimension in the commercialization process refers to how well academic scientists define the industrial users and disease population. For this dimension, I coded whether or not, and how academic scientists promote their patents, and their learning experiences from the commercialization process.

Two issues that academic scientists face in the commercialization process are a lack of funding and the selection of drug possibilities by industrial entrepreneurs. First, academic scientists encounter so called the "chicken or the egg" problem, where they face the lack of funding to validate the therapeutic purpose of the drug possibility with epistemic uncertainty. For example, when a molecule or a compound is first discovered in an academic lab, it is novel, unique, unexplored, and undefined. Pre-clinical investigation requires a wide range of technologies and expertise, which small academic

labs cannot often afford. Academic scientists need financial and technical resources to find out more about the drug possibility, develop it, and present it in a way that satisfies the evaluation criteria from those in the industry. However, funding for validating academic discovery is limited as the funding from federal agencies primarily supports research with breakthrough contributions. Among my interview subjects, 22 out of 38 academic scientists (58%) actively seek non-NIH [1]funding for pre-clinical development to develop patents and make their research commercially applicable. The "chicken or the egg" problem is that funding agencies want to see results from pre-clinical development to decide whether to fund the academic scientists; yet the scientists lack funding to produce those results. As a consequence, academic discoveries are often trapped in the "valley of death" where discoveries with therapeutic potential cannot be developed due to lack of financial support.

The second issue is that industrial entrepreneurs, such as universities' technology transfer offices, venture capitalists, and representatives of biopharmaceutical companies, are gatekeepers that determine which drug elements can make it to commercialization. The drug discovery process contains sources of uncertainty embedded in the very nature of drug possibilities, but these are also considered investment risks for industrial entrepreneurs. As academic scientists bring their discovery forward to the commercialization process, industrial entrepreneurs evaluate and try to monetize it as its properties continue to emerge. Together, the lack of funding and the nature of the

[1] It's until recently that the NIH has launched several funding programs to support pre-clinical investigations, such as the Small Business Innovative Research funds (SBIR) and Clinical Translational Science Awards. In addition, there are non-NIH grants from venture philanthropy foundations.

evaluation process make it difficult for academic drug possibilities to become applicable for drug innovation.

## INDUSTRIAL ENTREPRENEURS EVALUATE ACADEMIC DISCOVERIES

The commercialization process is structured in a way that academic scientists bring forward what they have discovered, and the industry (i.e., large pharmaceutical companies, venture capitalists, and practitioners) evaluates those discoveries and thus decide whether or not they want to commercialize those discoveries. Industrial entrepreneurs consist of TTO staff, venture capitalists, venture philanthropy foundations, and large pharmaceutical companies, and these entrepreneurs determine what academic discoveries get funded and developed through the commercialization process. They play a vital role in providing financial capital and technical support to bridge between lab discoveries and the market for drug innovation (Pisano, 2006). Having the financial capital and market knowledge, industrial entrepreneurs evaluate whether drug possibilities have market potential as a way to enact their professional jurisdiction.

Industrial entrepreneurs serve as a kind of resource for academic scientists by offering them market information, advice, and managerial expertise to go through commercialization. As the most accessible industrial entrepreneurs for academic scientists, universities TTOs are often the first unit approached in the commercialization process. TTOs provide information about patent applications and business opportunities, and connect academic scientists with different business networks. They evaluate drug elements discovered in academic labs based on their scientific legitimacy and whether there are market interests. The second type of industrial entrepreneur is the venture

philanthropy foundation, which provides funding for disease-specific drug elements in their early stages. As venture philanthropies are non-profit organizations that do not take ownership of intellectual property, they evaluate the drug elements based on whether they are relevant to a specific disease and its patient population.

The third type of industrial entrepreneurs is venture capitalists that are not as accessible for academic scientists in comparison to venture philanthropy foundations. A lot of venture capitalists have PhDs in life sciences, so they not only have the background knowledge to judge the craftsmanship and the integrity of the science, but they also have knowledge about the market and financial resources through their connections with institutional investors and large pharmaceutical companies. Venture capital firms provide funding and managerial expertise for academic scientists to start up companies *if* they are interested in the academic drug elements. Their evaluation emphasizes not only scientific legitimacy, but also the completeness of patent claims, and the presence of market interests. Funds of venture capital come from wealthy organizations and institutions that invest in up-and-coming academic projects with the goal that that these institutional investors would enjoy a return on their investment. Academic scientists, who start up a company to commercialize their drug possibilities, would seek venture capitalists to help them raise funds and bring managerial expertise for the start-ups. Venture capital firms finance the start-up on the basis of milestones where the drug possibility is proven to reach certain stages of maturity. To venture capital firms, start-ups are an "investment opportunity," so they make profits by selling the start-ups to large pharmaceutical companies once the drug elements from the academic lab are matured into a viable drug. They gain profits when large pharmaceutical companies acquire their

start-ups; therefore, venture capital investors evaluate the drug possibilities based on the interests and demands of large pharmaceutical companies.

Lastly, large biopharmaceutical companies have the most capacity to commercialize academic discoveries, but they are also the least accessible industrial entrepreneurs to academic scientists. As large pharmaceutical companies' productivity has been suffering from the lack of new molecules in their product pipelines, they are reaching out to universities and academic communities for new targets and compounds. A few large pharmaceutical companies are developing new models for collaborations with academic scientists, such as Eli Lily's Open Innovation model and Pfizer's Clinical Translational Innovation model (CTI). A representative from one of these pharmaceutical firm, said that the model allows them to "pick and choose the best things and to deliver them to their customers" (interview, WS500055). "Pick and choose" implies that the company engages in a process of evaluating and selecting promising academic drug possibilities that can be taken to the market. The model is set up to invite academic proposals, evaluate them, and make arrangements with the academic scientist if his/her proposal is accepted. If an academic proposal is accepted, then the pharmaceutical firm would finance pre-clinical development.

Even though industrial entrepreneurs provide a vital source of funding, the evaluation process sets a high bar for academic scientists to move their discoveries through the "valley of death." In the next section, I move on to discuss the underlying practices in which academic scientists engage to commercialize their discoveries in the pharmaceutical industry. The commercialization process is fragmented so that academic scientists find it difficult to bring their drug possibilities forward to innovation if they do

not meet the evaluation criteria. To meet the material dimension, which represents the monetary mechanisms of the drug possibility, scientists either start up a company or develop a portfolio of patents around their discoveries. This set of practices creates a tension in which scientists need financial support from industrial entrepreneurs while wanting to maintain control of their drug possibilities. The second set of practices in the epistemic dimension is legitimizing scientific questions through publishing and patenting. Pursuing patenting and publishing disrupts scientists' day-to-day practice of knowing because they have two sets of experiments that do not align, one set of experiments that demonstrate biological mechanisms for high impact journals and the other set to demonstrate functions for patent application. To fulfill the activity dimension that consists of defining the industry users and market size of the drug possibilities, academic scientists establish ties with the industry to promote their patents while they learn to do business with the industry.

## THE MATERIALITY DETERMINES THE MONETARY MECHANISMS

The materiality dimension determines the mechanisms from which industrial entrepreneurs would monetize the drug possibility in its final form. This aspect of the evaluation is challenging for academic scientists because defining a specific purpose for the drug possibility is not an obvious and straightforward process. Defining a commercial purpose for the drug possibility depends on the academic scientists' knowledge of what the industry wants from the drug possibility, which is not entirely clear to all academic scientists. At the same time, academic scientists lack the funding to continue to develop the drug possibility. When they present their drug possibilities to

industrial entrepreneurs for financial opportunities, the entrepreneurs are thinking, "How can I make money from this? What is the best model to appropriate this protein?" Industrial entrepreneurs evaluate the drug possibility based on its potential monetary mechanisms. Consequently, academic scientists are caught in this tension. On the one hand, they want to maintain control of the drug possibility that they have worked on for so long; on the other hand, they must define its commercial purpose for industrial entrepreneurs to monetize the drug possibilities. The two practices to fulfill the materiality dimension are "building the IP fence" around the drug possibility so that industrial entrepreneurs can monetize from licensing the patent to different companies or "starting a company" to develop multiple products based on the drug possibility.

### *"BUILDING THE IP FENCE" FOR THE DRUG POSSIBILITIES*

The process of "building the IP fence" is technical that requires various specialized techniques and facilities; it is not straightforward whether the drug element can be developed into a single or multiple products. It is a process where the discovery is defined commercially and legally as a product for sale or transfer. However, it is not always obvious for academic scientists to define what the drug elements they are working on are useful for commercially. For example, consider an academic scientist who has identified a nucleic acid molecule whose sequence has not been published prior to the filing of the patent application. Identifying this nucleic acid molecule is a discovery, not an invention. When the academic scientist defines a purpose for the nucleic acid molecule in treatment or diagnosis of an infectious disease, then the scientist can file a claim on the utility of the molecule. Moreover, if the academic scientist adopts

"inventive steps," which are procedures "not obvious" to reveal the nucleic acid molecule, then the scientist can also file a claim for the inventive step (Hubel, Schmelcher, and Storz, 2012).

Several academic scientists share their experiences about the path of discovering and defining their discoveries for commercialization. A researcher specialized in nucleic acid and his collaborators first came up with a technique to reproduce and amplify certain RNAs, known as "molecular beacons," so they filed a patent on the beacons. Then, they applied this technique to create a diagnostic assay, which is a use-IP. Then, they designed two probe simplexes from the RNA that can bind to a target, so this is another claim around the original patent of the molecular beacon. The expanding IP claims came from a series of research studies that he and his collaborators had done for 10 years (WS500013 interview). A neurology physician and researcher started up a company based on his discovery of a small molecule that inhibits one of the signaling pathways involved in Alzheimer's disease. As he continued to conduct pre-clinical investigations on the small molecule, he filed a series of use IP applications. Subsequently, as he identified lead molecules and produced their derivatives, his patent claims expanded to "composition of matter", which indicates that the molecule is synthesized into a chemical compound (WS500089 presentation). A pathologist specializes in cancer briefly mentioned that he is in the process of applying for patent protection for using a compound that already exists in the market to treat retinoblastoma. Even though the compound already exists in the market to treat a disease, the patent he files is specifically using this compound to treat retinoblastoma for a particular genetic mutation. He further

said that he wanted to file for another patent protection on the procedure of testing a retinoblastoma drug target that he has discovered (WS500031 interview).

These stories suggest that the categories of the patent claims expand from utility through process and technique, and then to design and manufacturing as academic scientists build the IP fence. A single drug element is being developed into a product family or a product portfolio. Because new aspects of the drug element continue to emerge, the emerging process brings academic scientists new knowledge and understanding on the usefulness and function of the discovery as a potential drug element. Essentially, academic scientists build the IP fence based on research data that has been accumulating for a long period of time. In addition, when academic scientists are writing their patent claims, they are codifying their tacit knowledge and experience in the patent and emphasize the element's distinguishable features and usefulness. The writing process requires a deep understanding of what the drug element is useful for, what problem it addresses, and its inventive steps. This is a collaborative process that involves the academic scientists talking to the TTO and his collaborators from other disciplines.

The hands-on knowledge generated during the development of the first product could have subsequent product development opportunities. For example, it is possible that a technique of producing humanized monoclonal antibodies could be a core product applicable to many diseases and developed into many products, even though the prototype antibody with unique properties is only suitable for a single product (Shimasaki 2009, p. 30). Therefore, having discussions with scientists and clinicians from other disciplines, and other companies helps academic scientists to gain insights about other

opportunities to develop the drug element into other related products. By talking to companies, they learn about the various product types and applications for which the drug element could be useful, which in turn helps the scientist to classify licenses into different categories of usage and package the research into a product family. Also, because each company has its own portfolio of existing products and capabilities, talking to companies informally is a way for scientists to figure out how their discoveries would fit with the companies' existing portfolios.

When venture capital investors evaluate academic drug elements, they receive a package that contains a codified, well put-together, and "attractive" product profile of the drug element. The package indicates the status of intellectual property and intellectual asset that incudes drawings, data, or blueprints to present the soundness and potential. The completeness of the patent is critical to their decisions to finance a start-up, meaning that the academic scientists have filed a full patent application based on the academic invention. The academic inventor should have developed a complete patent family, the items claimed in the patent must be defined appropriately, and some assurance made that others have not infringed on those domains.

*STARTING A COMPANY*

Besides building the IP fence, academic scientists may consider starting up a company based on their discovery as another mechanism to materialize it as potential drug elements. Academic scientists are attached to their discovery that they have worked for a long period of time, and they would like to continue to mature and further the research. At this early stage of discovery, only the academic scientists and the tech

transfer office have direct knowledge of the research. Companies are less likely to license or sponsor the early stage drug element because they don't have direct knowledge to determine the commercial viability of the drug element. Therefore, the options is to continue maturing the discovery into a potential drug element by starting up a company that gathers funding from universities and venture capital to develop the research.

By starting up a company, the academic scientist would be able to integrate information and knowledge from various experiments to produce the potential drug element from their discoveries. The work involved includes performing pre-clinical investigation of the drug element (i.e., animal model testing, compound screening), identifying lead compounds and performing basic pharmacological testing, synthesizing the target and molecules, and building a prototype of the compound. A professor in molecular genetics, who participated in starting up a company, said that the amount of work takes 20 people for several years. At the same time, the academic scientist as the CEO of the start-up has to look for funding to support the pre-clinical work. Ultimately, the output produced from the start-up is "an attractive asset package" that includes patents and other legally recognized property as well as drawings, designs, blueprints, protocols, software programs, and databases. The goal of producing an attractive asset package is to sell the start-up company to a large pharmaceutical company, so that the large company would be able to produce the product based on the codified asset package.

Academic scientists starting up a company is not only a vehicle to commercialize science research, but also a source of revenue for universities. Pisano indicates that a university with start-up programs could hold an equity position in 41 percent of biotech firms that did an IPO in 2004 (Pisano, 2006). A lot of universities these days have

incubator programs and start-up programs, which systematically commercialize their intellectual properties. The way university start-up programs works is that an academic scientist applies for patents based on his discovery, and the ownership of the patent remains in his university. The university would license out the patent to the start-up company that the academic scientist has started, so that he could work on the drug element further. For example, a professor of molecular physiology started up a small company, licensed the patent, and paid the university licensing fees to further develop the drug element. Universities receive licensing fees as well as royalty fees when the product goes on sale in the market. It is a mechanism for the university to monetize its IP as well as a means to materialize the potential drug element.

The molecular physiology professor, who started his company based on his discovery, described the monetizing process from his perspective. He said,

> "We invented a diagnostic kit and the university filed a patent. And after one year, the university said, "Looks like nobody wants it. You can take it." They give it back to the inventor. And I took it and went outside and formed my own company. So in the company, I am the dishwasher, I am the CEO, I am my own secretary. It went on for six months and then I learned about what is a company, what is an LLC,… how do you have a board of directors, what are their rights, how do you get the investments. I learned all those things. Then I brought in a couple of people, because I am a faculty, I cannot go full time and work in a company. Then I brought in a CEO, who said, "Okay. I'll work, but you give me a salary." I said, "I don't have money." Then he said, "Okay. Give me part of your company." I said, "How much?" "25 percent." So the idea is the company. The CEO took the 25 percent and his job is to raise money to develop this idea, to development some of the basic ideas in the product. … So that is what happened, the starting person who holds 100 percent slowly goes down. We raised $200,000 for patent costs, small research costs…then $200,000 just evaporate. And then we got a venture capitalist, who comes in and says, "We'll give you two million dollars, and you are out of your board. We are taking away your equity." And you make a deal with them…. So I'm out of my own company's board, and I don't have any say in it…. We have a diagnostic kit manufacturing company. I started it but I was pushed out. Now the company is run by itself in Connecticut but I have my equity; I get my consultant fee and I just sit quietly until it becomes a product." (WS500014 interview)

This is a snapshot of how an academic scientist started a company based on a patented research idea that he filed and then licensed from the university. In the beginning, it was a one-man company and he had to "learn what *is* a company," such as how it operates, what kind of structure, what the management entails. As he hired CEO and employees, his ownership of the company got "thinned out". The CEO and the employees executed his idea indicated in the patent, carried out the experiments, ran the analysis, developed the product configuration, and contacted manufacturers to produce it. What this shows is that it takes a company to materialize an academic discovery into a product. In addition, because the company needs money to run these operations, the CEO is constantly seeking funding until a point where a venture capital firm is willing to fund the company. At that point, the venture capital will likely hold the majority of the company's ownership, and the academic scientist's ownership becomes diluted.

Academic scientists are generally attached to their discoveries and have worked on for their entire research career. To them, technology transfer implies that a company is taking away their discoveries and that they lose the control to work. This molecular physiology professor, a basic scientist by training, summarizes the motivation behind engagement of many academic scientists in the commercialization process.

> "Where is the funding coming from to do all these things? You need to get this funding. And how I learned was—I don't know anything about law. I don't know anything about talking to business people, but when my first invention was taking up by that, I started learning. I started working with a patent attorney. I said, "I never had a clue of what a patent provisional application is. But because my product is being taken up as something, I have to go and learn about it." Some people take additional courses. You have paralegal courses, you can talk to friends, you can go on the Internet. You can learn. That's a process. The other people, what they do is they actually just give it up and say I don't know anything about this and let the tech transfer office deal with. But normally as scientists, we

> want to know. So I would rather know everything rather than somebody take all my stuff" (WS500014, interview)

As a result of this mindset and his learning experiences, he became the director of the translational research center of his university some years ago. His story reflects two things academic scientists are concerned about in terms of commercializing their discoveries: funding, and the ownership of intellectual property. Like him, many academic scientists learn about the commercialization process on their own, and a lot of them find the process overwhelming and confusing. Here, this professor would rather "know everything than somebody take all of my stuff," which suggests that he feels that handing his research to the tech transfer office would take him away from his discoveries and then he would have no control over the discovery. For many academic scientists, commercializing their discoveries means that the industry buys their discoveries, so that they will be unable to work on the discovery in the future. Therefore, choosing to commercialize is a practice to retain some control over how their discoveries will be developed.

If they license the drug element to companies, they fear that it would not be properly promoted and developed. Champions in big pharmaceutical companies are therefore critical to make sure that the licensed academic technologies are in the company's agenda. An academic scientist who started his own company expressed his concern, "Unless there is really a passionate internal champion, you know your technology may just sit on a shelf and not be prioritized. Who knows, every Monday the priorities can change, and you may play a role or you may not." His story reflects the lack of control that academics have on their technology once it is licensed to a company. Also, at a panel discussion, a large pharmaceutical company licensing director revealed

the names of committee members who reviewed certain academic technologies to be licensed into the company (WS500089 presentation). This inside information is critical for academic scientists to identify internal champions. Without a champion in large pharmaceutical companies, it's very likely that the academic patent will fall out of the company's bureaucracy and agenda; therefore, starting a company is an option to retain control of their research.

Among the scientists I interviewed, only 3 out of 38 scientists (7%) started their own companies to develop and promote their patents. Even though my sample size is limited, starting a company does not appear to be a favorable choice for academic scientists on the path to commercializing their discoveries. As Pisano (2006) points out, academic scientists face a career dilemma on whether to start up a company to commercialize their discovery. On the one hand, starting up a company requires a lot of commitment, which takes them away from research. Pre-clinical development requires a lot of work and the academic scientists would have to quit their research job and be fully committed to commercialization, which would end their research career in academia. On the other hand, they fear losing control of their discovery if a company licenses it.

However, starting up a company is only a temporary mechanism to develop the discovery. Ultimately, a small start-up has limited capacity to sustain itself in the long run. Therefore, the small startup company has to work with the university TTO and venture capital firms to identify potential buyers. A professor in cancer biology commented on the reality of academic scientists starting up a company to commercialize their objects. She said,

> For instance, Dr. XX has his own little company, with 1 person working on it. It's a little company. One day if he proved his thing is really good, some big company

> like Merck or Bristol Meyers are going to come and going to buy him out. But that's what big pharmas do. They buy small ones out. But meanwhile is he struggling trying to get money? Trying to do his work? He is. Is he forming partnership with a big pharma? No he's not. You don't see big pharma supporting his work, even though he has a small company. Say if something I studied today, big pharma can never come and buy me. They can't buy me out, because I don't have a company. So I would never be getting these millions of dollars because this. But he will, because he has a company. (WS500031, interview)

So, although starting up companies is a mechanism to develop a more complete product based on the discovery, start-ups constantly face the lack of cash flow to support their research and development, and "raising money for a start-up company may be the single most arduous, and time-consuming activity undertaken during one's career" (Shimasaki, 2009). Academic scientists seek funding from various sources, including angel investors, venture capital, peer-review grant funding, or state and local financing programs; they could sell the company to a large pharmaceutical company as an alternative. However, the ownership of their start-up will gradually be diluted in the fundraising process, and eventually they will not be able to participate in developing the discovery into a drug element. A director of an academic translational center said that "it's not realistic for academic scientists to start up their own companies" because of the amount of work and the challenge to sustain the company. When starting a company, academic scientists face a dilemma: on the one hand, they want to develop their discoveries, but on the other hand, they don't have sufficient means to do so (WS500043 interview). As a consequence, they find it easier to publish the discovery and move on to make more discoveries.

## PATENTS AND PUBLICATIONS DETERMINE THE LEGITIMACY OF EPISTEMIC QUESTIONS

As the epistemic dimension refers to questions that scientists raise about the drug possibility, patents and publications are institutional mechanisms for scientists to legitimize their questions. To develop this dimension, I analyze the practices of knowledge disclosure, which are considered as the "first step" for contributing knowledge for innovation (O'Mahnoy and Murray, 2010). The peer-review process in the publication system would legitimize and ensure the drug possibility to be scientifically sound. The patent system indicates that the drug possibility contains commercial value. There is nothing new that academic scientists engage in patenting and publishing simultaneously at the same idea. My data show that some scientists would "play the two" systems by withholding novel techniques in publications but disclose them in patents, so that licensees would pay a premium to access the technique. In addition, it is the university's TTO not the academic scientists who decide whether the academic discovery should or should not be patented. The two practices to fulfill scientific and commercial legitimacy are "advertise drug possibilities through publications" and "TTO determines the patenting process."

### *ADVERTISE DRUG POSSIBILITIES THROUGH PUBLICATIONS*

From the standpoint of a drug possibility, publication is a process to legitimize an academic discovery as well as advertising its existence in the scientific community. There is no doubt that all academic scientists have to publish, as the saying goes, "publish or perish." When scientists discover a new biological or chemical element, it is often a

personal experience that most likely includes elements of subjectivity (Grinnell, 2009; p. 60). However, the practice of publishing the knowledge on the elements transforms personal experiences into scientific statements. In the process of publishing a paper, an academic scientist would turn to his peers, refer to their findings, and establish a connection between his discovery and their work. When the paper goes through rounds of peer review, the peers also make sure that academic discovery is novel and does not contradict with previous scientific knowledge. This is not only a process of establishing the credibility of the new observation but also legitimizing it as a scientific discovery.

Publication is also necessary for academic scientists to apply for patent protection. Since patent examiners conduct literature searches and review the drug possibility in terms of its level of novelty, credibility, and usefulness, publication in peer-reviewed journals therefore signals the drug possibility's credibility and novelty. For example, when a neuroscience researcher, who studies the non-genomic function of estrogen, wanted to apply for patent protection on a mechanism he observed, he sought advice on the process of applying for a patent from his university's TTO. The TTO told him that he had to publish a few papers based on the finding before he can apply for patent protection (WS500034 interview). A drug possibility going through the peer-review process demonstrates its scientific credibility and integrity as a novel science discovery. In addition, universities especially put an emphasis on publication not only because the research prestige of the university is based on the number of faculty publications but also to protect their intellectual property. For example, a postdoc in cancer biology, who wanted to apply for opportunities to collaborate with a large pharmaceutical company based on a novel observation she made about a drug possibility, found that her

university's TTO advised her to publish and file a patent disclosure before she applied for funding from pharmaceutical companies. She said, "The TTO wants to make sure that the ownership of [my project] remains in the university before it reaches to "the other side" (i.e., the industry) (WS500048, interview). The university wants to get the "credit" of novel research before the drug possibility become applied in industrial innovation.

In addition, publication is a channel to establish visibility of their research to the scientific community. For example, a computer science consultant for an academic lab helped to develop a software program based on a discovery from the academic lab. He said that the team has published the discovery and the software in academic papers after filing for patent protection. He said,

> "I work on this software which can take * from any organism, and convert into DNA for any event. Let's say you can take elephant DNA and put it in a frog; my software could do it. I built it in 2002, but we didn't publish it till 2005, because it took us a year to work with patent lawyers to get it patented, and to build brand new technology to make drugs. There were many pieces, chemistry, biology, and then there was software. We have to put all of this into a patent; so it took us about a year, year-and-a-half to work on the patent. Once we got it patented, then the [principal investigator] said okay, now you can publish, so we published it. When we had patented it, nobody knew about it, because it was still in house information. But after publishing, we started getting a lot of inquiries to use the software to collaborate with us. So, at one point, I had people from different universities using my software…. If we hadn't published, as many people would not have come up" (WS500069, interview)

This story is an evidence that publication establishes visibility for novel research, because peer reviewed journals are widely read and circulated within the scientific community. Publications make research findings public and noticeable for scientists from different sectors and disciplines. On the other hand, patents are not widely circulated and distributed; the target audience would only review patents when they want to apply the knowledge for their specific purposes. Therefore, even when academic scientists file for

patent application, publications would help to publicize their findings and discoveries to the community.

The publication system is also used to maintain one's advantage in research. In a presentation discussing systems biology and experimental methods for drug discovery, a scientist in the audience mentioned that he used a novel technique that was disclosed in the patent but not in his publications. The presenter said, "You should disclose the technique in the publication because it will be very useful for other people" (WS500087, field note). This incident reflects how scientists may be cautious and strategic when sharing information with each other because of the patent application policy. When an academic scientist discloses his/her novel techniques in publications, other scientists can replicate and apply them, but this also means that the scientist would lose his/her "edge." Arora, Fosfuri, and Gambardella who refer this as "privatization of knowledge," where academic scientists withhold new findings in publications in order to increase future payoffs from patent protections (2001). When novel techniques are disclosed in patents, licensees pay a premium to the inventor for using the technique, and thus the accessibility of the novel technique is more limited than if it were presented in publications. The scientist inventor balances the potential future monetary payoffs from licensing the patent against the current payoff of publishing the novel finding. As a consequence, scientists may be dis-incentivized to publish until patent protection secures their novelty. When scientists in general pursue dual routes of disclosure by simultaneously filing patent application and publication, they are more likely to "play the two systems."

*TTO DETERMINES THE PATENTING PROCESS*

Patents are considered as a common currency for transferring knowledge and technologies from universities to the industry. By definition, patents specify utility and application of a technology (i.e., device, material, method, a composition of matter, or a process of making something a product). Knowledge and content in the patent is stated in standardized language, with the purpose to simplify interpretation among the parties and makes it less costly for transfer of technology across organizational and institutional boundaries. In most cases, industrial entrepreneurs will not consider academic discoveries if they are not patented, which suggests that companies are only willing to internalize codified knowledge in a standardized format.

Even though the filing for patent protection is a prevalent mechanism for academic scientists to commercialize their discoveries, the TTO is the decision-maker to determine whether a discovery would be patented. When academic scientists disclose their discoveries to the TTO, the first requirement to evaluate whether it should proceed with a full patent application is publication. When the research is published in peer-reviewed journals, it means that it has gone through rounds of review process and that the research is legitimate for further development. Publication in peer-reviewed journals also means that the scientists can claim the intellectual ownership of the research. Therefore, when TTOs evaluate whether the invention brought forward by academic scientists can be patented, they would look for whether the scientists have published on such invention.

Second, when the discovery is qualified for TTO to apply for a full patent protection, most university TTOs[2] encourage academic scientists to identify companies

[2] Each university's TTO has a different agenda and technology transfer policy that is set by the university. Generally speaking, if there is no company willing to license the patent, the university

that would be interested in the technology before filing a full application for the patent. When companies are interested in the discovery before full patent application is filed, the TTO could make sure that companies will buy the license to cover the patent application costs. Moreover, companies' interests also give TTO the confidence that someone will use the discovery (WS500043, 51, 90 interviews). If there is no company showing interest in the academic discovery, then the TTO may prefer to file a provisional patent application. Consider this experience of a pharmacology professor with filing patents with TTO. She said,

> "I submitted eight, nine, or ten provisional patent applications to the TTO, and provisional patent applications are very cheap. What my school wants to do, they submit the provisional patent application and waited one year.. They want me to find company who will like it in the future and buy the license. What happened is that they don't want to risk, they want to make sure that someone will buy the license when they file the patent. I talked with companies and told them what I have are provisional patent and I have this data. But companies told me that this is too early, you don't have patent yet, get a patent and we will talk with you" (WS500082 interview)

Her experience illustrates the obstacle that academic scientists face when they intend to develop their patents. Because patent application process contains legal fees, maintenance costs, and research funds, TTOs take all these costs into account when they evaluate whether the research is worth patenting or not. TTO proceeds with full patent applications for academic scientists with the condition that companies show interest in licensing their discoveries. Because the legal fees for full patent applications and maintaining the patents are expensive, the university TTO would prefer to be sure that companies will want to license the patent. It then becomes critical for academic scientists to have existing ties with companies so that the company would have first-hand

---

must pay for legal fees to maintain the patents. Therefore, to be cost efficient, TTO would first determine whether there is market interest and potential licensees before it goes ahead to file the patent for the academic scientists.

information on the early discovery and be willing to fund the academic discovery. As a consequence, academic scientists who have not identified industry users would find it more difficult to apply for full patent protection for their potential drug elements and thus make commercialization difficult or impossible.

Furthermore, the process of applying for a patent imposes a disruption on the scientists' day-to-day practice in research. Scientists applying for patent protect for a drug possibility must demonstrate that it is "unique" and "non-obvious," and they write out the description in a relatively standardized language and format. This codifying process to demonstrate the "unique" and "non-obvious" inventive steps does not align with their practices to publish. Consider a cancer biology postdoc's recollection about the process,

> "When I was working on this project which technically isn't published yet but it is patented. When you want to patent something, you hold of publishing it. You file first; make a disclosure agreement so that they know that you want to patent it. [The TTO] might say well, in order to get the patent past, we are probably going to need these five things. Do you think you could do this? So there is a push and pull between they may be asking me to do experiments that I really don't want to do but I want to patent it so I'll do them. There is a push and pull from the tech transfer office. We're also pressing on with experiments to get pushed and answer the more academic questions" (WS500048, interview)

She described the "push and pull" tension, where on the one hand, the TTO exerts a "pull" for more data that she did not want to perform but needed to in order to complete the patent application. On the other hand, she wanted to perform other kinds of experiments that would answer more academic questions to "push" the publication out. Because the research questions addressed in publications are different from the criteria required in the patent, academic scientists have to perform different sets of experiments to satisfy each institutional logics.

The co-existence of patent and publishing systems creates contradictions in the day-to-day practice of knowing as they divide their attention about what to patent and what to publish. A director of an academic translational research center said that

> "I struggle for a balance of what to publish, what not to publish and how long you can wait for it to be published so that it can come out as a product…. All these things, I struggle with it everyday, trying to make a balance between an academic life and an inventor." (WS500014, interview)

According to this faculty member, he has to wait to publish because he was in the process of filing a patent application; therefore, making a balance between what to patent and what to publish is a part of his everyday knowing process. This faculty member reflects on the life under the institutional tension between the norm of full disclosure from the patent system and the urge to be the first to publish from the publication system (Dasgupta and David, 1994).

Because the patent system is a necessary mechanism to participate in commercialization, academic scientists would develop a portfolio of research questions where they would pursue basic research as well as commercially viable research. It is more likely that when scientists define research for a particular therapeutic function, they recognize the commercial potential and establish relevance between research and clinical application. A genetics faculty member who works on discovering therapeutic agents to treat neuropathic pain said that when he picks a research topic, he "is clearly aware the potential whether this is just an avant-garde academic interest or a is really a medical problem which needs knowledge to help the eventual drug discovery and drug development" (WS500019, interview). By the same token, a medical doctor conducting academic research on schizophrenia said that he has two lines of research in his lab, one of which has commercial value by developing long-term drug discovery systems for

schizophrenia. In this line, he actively engages with clinicians, the institution's technology transfer office, and a few companies to develop a patent. The other research stream is to publish anything he has found that is not relevant to the patent application. In his mind, he sets a clear distinction between the research with commercial value and the research with theoretical appeal. He believes that it is his duty "as a citizen" to patent and his duty for the academic community to publish.

## ACTIVITIES TO DEFINE INDUSTRY USERS AND MARKETS

The activity dimension, which refers to the direction and purpose of collaboration, consists of practices to define industry users and potential markets for the drug possibilities. By presenting the discovery to the public through the commercialization process, academic scientists and their institutions are also searching for industry users and markets. It is not easy for academic scientists to establish connections with managers and scientists from the industry. Academic scientists who possess ties with the industry are more likely to seek users than academic scientists without any industry ties. Close ties with companies give academic scientists the advantage in getting the information they need to develop the discovery into drug elements according to the company's product portfolio and to make sure that the academic discovery remains a priority in the company's product development. As a consequence, many academic scientists would rather publish the finding and move on to the next scientific question instead of going through the commercialization process. The two practices associated with this dimension are "promoting patents through industry ties" and "learning to do business with the industry."

*PROMOTING PATENTS THROUGH INDUSTRY TIES*

In general, academic scientists file patents for their discoveries because they believe that the discovery can be utilized and applied; however, academic scientists don't know what and how exactly the discovery is useful for. Having ties with the industry would help them better define its function and use. Among the 38 academic scientists in my sample, 27 (71%) of them have filed patents and 17 (63%) of them actually have promoted their patents by initiating "monetizing campaigns". Among the 38 scientists, only 10 of them have pre-existing ties with companies, meaning that they know their industry partners from before, and 17 of them put in efforts to reach out to companies to promote their patents.

Establishing ties with the industry is a challenge for many academic scientists because they in general don't have connections with the industry. They have not had any experience working in the industry because they have been in academia after their receiving their PhDs. They either contact the companies through letters, or through the university TTO. A researcher in infectious disease and his partners have invented the 'molecular beacon,' which is an RNA probe that finds and detects target DNA sequences. He described the story of their "monetizing campaign" of reaching out to companies and negotiating licensing deals.

> "We had the idea in 1992, and we put in a patent application in 1993. We did some experiments to see how to design the beacons properly. And then after applying for the patent, we spent two more years doing experiments. And before the patent was to be published and before we published a paper, we wrote letters to 10 companies who we thought could use molecular beacons, 10 very large companies. We signed letters of confidentiality with them and we spoke with them. And of those 10, I think maybe six of them approximately said yes. And probably five of them are now our licensees for the beacons although it took quite

> a bit of time. So we started to speak to the companies in '95. Just scientists. We had no idea how to license, so we asked them, "How would you like to license this?" And ultimately the first license was taken in 1997. So one of the first things we had to decide is should we license the technology to one company, or should we license non-exclusively? We came to the conclusions from talking to the companies. First of all, many companies were interested. They could use it. The second thing they told us is that they want to exclusively license the beacon, but because they have to commit time, money and people to develop this technology, they will not pay for up-front payment and will pay for large royalty. (WS500013, interview)

The infectious disease researcher emphasized that he and his colleagues had never worked in the industry and didn't have any business experience; moreover, they had no idea how to reach out to companies or promote their invention, and they really wanted to know whether their invention was useful for the industry. Therefore, they decided on the traditional way of writing letters to the scientists in large companies and asking them whether the company would find their academic invention useful. When academics develop their own invention, they conceptualize the invention in a laboratory setting, so that they don't know whether the invention fits with the practical problem faced by practitioners. Connecting with industry scientists is a channel to understand the day-to-day innovation problems they face, so that academic scientists can shape their invention to address industrial problems. In addition, his story illustrates a negotiation process with the industry, where the company's interests were not aligned to theirs with exclusive licenses and large royalty fees in the future. He said, "This does not fit with our own academic business model. We needed money now, and we really want people to use molecular beacons" and "we really want to give incentives for people to use it" (WS500013, interview). In order to incentivize companies to use their invention, the infectious disease researcher and his team allow any scientists including the industry to try their products, and the industrial scientists can visit his and try it out at no cost.

This infectious disease professor's story reflects the spectrum of activities to reach out to companies and create incentives for them to license his academic inventions. Academic scientists file patents because they want the industry to be interested in their discovery. But to develop a product that will be used by the industry, academic scientists have to know the interests and demand of the industry and the specific innovation problems that the industry faces. Even though academic scientists conduct research for their own research interests, a two-way dialogue would nevertheless allow academic scientists to define the context and function for their discoveries. Academic scientists who don't have existing ties with the industry have to create opportunities to connect with the industry, and connection with the industry helps them to define the usefulness of their academic invention.

However, learning about what the industry needs is a challenge for academic scientists without industry ties. Among my interview subjects, three scientists who filed patents said that the patents are meaningless for their research because they do not know how to develop those patents nor do they know who would license those patents. For example, I asked a neuroscience faculty whether she structures her research for patent or publication purposes, she said, "I always do research to publish first, and feel that there is a disconnect. I don't know what to do with these patents and whom to go to" (WS500075 interview). A professor in infectious disease expressed similar concern and said "I don't know whom to contact in the industry once I get my patent" (WS500066 interview). Without ties with companies, academic scientists would not know how to develop usage out of their discovery. Even though university's TTOs serve as brokers

between their academic scientists and the industry, academic scientists still have to motivate the TTOs to build ties with the industry to promote their patents.

Moreover, for most academic scientists, talking to companies without existing ties is difficult because conversation with companies is protected by confidentiality agreements that restrict the academic scientist from learning about the company's internal product capability. For example, a representative from a big pharmaceutical company who scouts academic inventions said, "anything you share with me is appropriately covered by a confidentiality agreement if necessary" (WS500089, panel). A confidentiality agreement restricts the two parties from sharing specific information discussed with other parties as well as restricting others to have access to that information. Though it is a very common practice in academic-industry partnerships, the confidentiality agreement suggests the need to build trust between both academic and industry partners. Say that academic scientists are interested in knowing more about what pharmaceutical companies in general are doing, but it is difficult for them to obtain general knowledge about the industry because a confidentiality agreement might guard a normal day-to-day conversation. The pharmaceutical representative further said that she is very careful "not to accept an invitation to share information that would contaminate an internal program" of her company and that she is the "first filter of anything that is coming into her company" (WS500089 panel). Because of restrictive dialogues with pharmaceutical companies, academic scientists are limited in learning about the industry's product capabilities and the criteria that the companies are looking for in their discoveries.

Even though patents are the currency for technology transfer, having ties with the industry helps academic scientists to understand how to shape their academic invention to appeal to specific industry innovation problems. Academic scientists without industry ties don't have the "inside knowledge" about what companies are looking for in their discoveries and are sometimes clueless about how to develop their patents into products.

*LEARNING TO DO BUSINESS*

When academic scientists do take their discoveries through the commercialization process, they work with various types of experts for information about funding, patent application, and the market to determine the best developmental path for their discoveries. For most academic scientists, making science discoveries determines their day-to-day activities; however, the commercialization process is complex and may require skills and knowledge that they do not possess. When academic scientists patent their invention, they learn about how to draft the patent license, the agreement to negotiate a license, and the patent license agreement. For many academic scientists, writing business agreements and proposals is a completely new experience. Similarly, when academic scientists start companies, they learn what it is like to work in a company, and how to handle the fundraising, founding, operation, and management. Since many of them have stayed in academia throughout their career, learning how to do business may be very foreign. For example, a professor in molecular genetics was involved in starting a company based on his discoveries. He said that he learned about hiring, fundraising, and putting together a management team. He also acknowledged that the process of making his discovery into a product was much more complicated than he had expected.

Commercialization requires a lot of commitment from full-time faculty members who conduct research, write grant applications, teach, and advise students. In addition, learning about patent protection policies and structures of license agreements is overwhelming for academic scientists. A biochemistry professor who started his company to commercialize his discovery, recalls,

> "The commercialization process is enormously complicated for a PI to grasp what is the property, how quickly they make a mistake you know disclose something publically before you disclosed it to your tech transfer office, which could instantly invalidate your ability to commercialize. There is a list of specifics about how much time you have and how people understand the technology, and the list just goes on and on…. I visited my technology transfer office 10 times for 10 months for two hours each time. It's very complicated" (WS500040, panel).

His story illustrates the difficulty and extensive commitment for academic scientists to commercialize their discoveries. Consequently, many academic scientists are discouraged to commercialize. The second aspect of this story is that academic scientists have traditionally disseminated novel knowledge through publications, and they enjoy the freedom to share ideas in conferences and presentations. However, because of the patent protection policies, it's very easy for academic scientists to make mistakes by publically disclosing novel findings that are in the patent application process. As a result, academic scientists are working with two institutional systems that contradict with each other to some extent. On the one hand, academic scientists enjoy publishing and the autonomy to disseminate novel knowledge for their peers; on the other hand, they are restricted in disclosing certain aspects of their research in order to comply with patent protection policies. In the following section, I will discuss these aspects in more detail and how they affect the commercialization process.

## SUMMARY

This chapter reveals the difficulties for general academic scientists to commercialize their academic discoveries. Academic discoveries from labs are in the early state of art and require a tremendous amount of work to develop them into commercially viable products. Academic scientists have to rely on industrial entrepreneurs for financial, technical resources, and also to determine who would be using those discoveries. Industrial entrepreneurs playing the broker between universities and the industry are looking for business opportunities from the drug possibilities. Moreover, their evaluation of academic discoveries disrupts academic scientists' day-to-day practices of knowing, such as starting a company or losing control of the discovery, or striking a balance between patent and publications. The existing literature has discussed these practices by which general academic scientists make their research available for the innovation process, such as disclosing knowledge through patent and publications, developing and promoting patents (including sitting on advisory board to consult), and starting a company. These practices are essentially ways of presenting academic discoveries to the public and fulfilling the criteria set by the industrial entrepreneurs. The three practices need to be understood as interdependent because they together drive how academic knowledge flows into industrial innovation.

In the next chapter, I shall discuss the institutional arrangements that may facilitate academic scientists to bridge these barriers and bring their academic discoveries more directly to drug innovation.

# Chapter 7: Four Models of Academic-Industry Partnership: Bridging the Boundaries

In the previous chapters, I identified two forms of boundaries in the practices of knowing and in the commercialization process. One form of boundary is situated in the discontinuities between basic and clinical research practices in terms of defining specific or general functions, raising questions, and following up on or moving beyond the emerging patterns. The second form of boundary is in the commercialization process, which is fragmented because the resources to commercialize available to drug possibilities address specific disease context and are legitimated with patents and publications, whose industrial users are well defined. Moving beyond the two forms of boundaries, this chapter addresses the social arrangements in the current models of academic-industry partnership that bridge those boundaries. Because both academia and the industry are recognizing a need to change their partnership arrangements to deal with the productivity crisis, my analysis reflects on how new changes address the discontinuities in practices and fragmented commercialization process.

This chapter is organized as follows. I first describe four types of academic-industry partnership models. Then, I revisit my analysis of the practices of knowing under which academic and industry collaborate in the four models. I focus on whether and how the four models bridge those boundaries in practices and in commercialization. There are four collaboration arrangements in my sample: a market-oriented linear model, academic medical centers (AMCs), industry-initiated partnerships, and venture philanthropy foundations. To identify these four collaboration arrangements, I first categorized the institutions to which scientists belonged, whether their research

institutions were affiliated with hospitals or translational facilities and whether the institutions focused on a particular therapeutic area. Then, I compared the role of the institutions' TTOs and the stage at which the office becomes involved. Finally, I compared the patent management and publication policies under which scientists collaborate with the industry. (See Table 6 for a comparison of the four models.)

The three dimensions of drug possibilities direct the sorting of three aspects in the partnership arrangements that bridge the boundaries in the practices and commercialization process (See Table 7 for a summery). Because the materiality dimension includes a specific function that the drug possibility fulfills in the human body, I looked for practices that enable situated learning and contextualizing drug possibilities for a specific function. It has long been established that academics and industry follow different incentive and reward structures, with academic scientists producing publications while biopharmaceutical firms produce products. How do the new partnership arrangements resolve this difference? If patents are necessary for academics to partner with industry, how do these new models enable universities to develop a complete patent portfolio? I found that AMCs and venture philanthropy foundations are converging their interests to develop a product vision to bring drug possibilities to the market more efficiently from their collaboration with the industry. In addition, industry-initiated partnerships that allow academic and industry scientists to work side-by-side in the lab help to contextualize learning for academic scientists so that they become more aware of how to bring drug possibilities to humans.

Second, the epistemic dimension includes scientific questions concerning the drug possibility. We know that scientists are driven by questions, but what kind of questions

do they pursue when they collaborate, and who gets to define the questions? Comparing the four models, I found that, in partnerships in the linear model, the scientific question and procedures have been defined prior to collaborating with academic scientists so that the scientists do not have the capacity to explore. On the other hand, a change is occurring among the new partnership arrangements, with academic and industry scientists collectively exercising their science capabilities to decide what therapeutic questions to pursue by making such decisions together.

Third, the activity dimension includes a set of technical procedures to materialize drug possibilities. I previously indicated that academic scientists face the lack of technological support to perform pre-clinical experiments and that a need exists to verify and follow up on emergent findings. The question is how partnership arrangements enable such activities. In addition, what is the extent of access that academic scientists have to the translational facilities? I found that the partnership models have become more flexible in their institutional arrangements, with companies and universities finding alternative way to manage IP and exploring contractual language so that barriers from legal language do not inhibit access to material and translational facilities.

In the following section, I describe four types of partnership models. The first type is the linear market-oriented model, in which the collaboration has been based on a one-time transaction. Biopharmaceutical firms outsource experiments to academic labs, or academic scientists rely on the market and seek buyers of their patents. The second type is academic medical centers (AMCs), which usually specialize in one or two disease areas. AMCs adopt a hierarchical form of governance in which the research centers centralize their control of research from discovery to proof-of concept. My sample

includes six AMCs that reflect the changing orientations of academics conducting drug-related research. The third collaboration model, industry-initiated partnerships, is like a hybrid model with network and vertical integration. These organizations, such as Pfizer's Center for Therapeutics Innovation (CTI) or Eli Lily's $PD^2$, are formed with the intention of developing closer relationships between industry and academic scientists. The last model includes disease-focused venture philanthropy foundations (e.g., Michael J. Fox Foundation, Bill and Melinda Gates Foundation), which are a fairly new organizational form that convenes academic scientists and private enterprises to further therapeutic research for a particular disease. Research organizations of this type are considered to be a network form of governance in which the foundation hosts a network of researchers, venders, and industry partners.

## FOUR MODELS OF ACADEMIC-INDUSTRY PARTNERSHIPS

In this section, I discuss three aspects of each of the four models, their general structure in terms of academic-industry partnership, university's technology transfer office's (TTO) involvement, and the IP governance. Besides the linear market-oriented model, the three new models are moving away from transacting patents for royalty fees and towards academic and industry scientists working together. Tufts Center for the Study of Drug Development recently released a report that indicates that arrangements such as start-up programs, academic drug discovery centers, and pre-competitive collaboration between universities and industry have become increasingly popular and are likely to become dominant in the future (Milne and Malin 2012). As academic-industry partnership gains importance in companies' strategies and universities' missions,

both sectors are exploring new approaches to manage IP, such as joint IP ownership and open source data depositories. As described below, institutional changes that are taking place not only foster involvement of academics in pre-clinical investigations but also facilitate academic-industry collaboration.

*I: LINEAR MARKET-ORIENTED MODEL*

The arrangement of academic-industry collaboration has been based on the company licensing a university's patents for the rights to modify the technology and the university receives royalties and research grants. This kind of collaboration is based on a one-time transaction; the academic patent inventors are not involved in negotiating with the company nor do they provide consultation once the licensing deal is complete. As the company internalizes the patent, it spends time and money to develop the academic invention so that it would fit with its product portfolio and capabilities. Another common collaboration arrangement is when a company needs to test their drug possibilities in a specialized experimental system in an academic lab. Under confidentiality agreements, companies would contact the academic scientist with the specialized systems and skills to conduct the experiment. This is usually a one-time only collaboration where academic scientists conduct testing of the company's compounds or targets and hand off the testing results in exchange for direct payments of research funds.

*IP Governance*. Under the linear model, academic scientists in general have a passive role in handling IP. When an academic scientist files for patent protection, his university possesses the right to license out the patent. When the patent is licensed to a company, the academic scientist would no longer be involved in developing the technology, unless

he/she sits on the advisory board of the company. Academic scientists cannot publish the results of experiments on the compound or target provided by the company, because these materials are the company's proprietary assets that have not yet been released to the market. Only in the exceptional situation where the company's proprietary invention is already in the market would the academic scientists be able to publish their results. As a consequence, academic scientists are less willing to collaborate with the industry because of the limitation on publications.

*II: ACADEMIC MEDICAL CENTERS- HIERARCHY FORM OF GOVERNANCE*

From the 10 research institutions where my interview subjects are affiliated, I categorized the institutions with hospitals or their own translational research centers as academic medical centers (AMC). AMCs in my sample include Memorial Sloan Kettering Cancer Center, Rockefeller University, Institute for Translational Medicine and Therapeutics at University of Pennsylvania, and the Medical Center at Kansas University. Medical centers of this type specialize in one to two therapeutic areas, such as cancer or neurodegenerative diseases, and they conduct early stage drug discovery by combining basic, translational, and clinical science all in one roof. Since 2006, the NIH has launched programs (i.e., CTSA and NCATS) to encourage translational research in universities, and there are now more than 60 translational research centers in universities across the U.S. Although the NIH is their primary funding source, AMCs also form partnerships with industries through patent licensing, clinical trials, and joint educational programs (Milne and Malins 2012).

Generally speaking, science researchers in AMCs come from multiple disciplines, but all are studying a set of diseases in a therapeutic area. For example, AMCs like Memorial Sloan Kettering Cancer Center or New Jersey Cancer Institute contain biologists, chemists, protein biologists, geneticists and scientists of various other disciplines, who are all studying cancer. Disease-focused AMCs have translational facilities such as compound libraries focusing on a therapeutic area, high through-put compound screenings facilities, imaging facilities, and lab space to breed animals. Their affiliation with hospitals also allows scientists to obtain patient samples, access clinical trials, and acquire existing drugs in the market. Like most universities, researchers are evaluated by their publications as well as their performance in the lab. Within the institution, researchers have the autonomy to seek collaborators for developing new targets and running clinical trials.

Even though AMCs in the U.S. are all under the NIH umbrella, each of them has different structures and strategies of project management. Several respondents in my sample are affiliated with MSKCC and they conduct cancer research from basic (i.e., cancer biology, pathology, and cancer metabolomics) to applied (i.e., molecular pharmacology epidemiology, integrative medicine, and radiation therapy). An AMC scientist doing research on neuroblastoma in pediatric patients said, "My institution is almost the same as a drug company, we are making drugs, but we go after the diseases that pharmas do not go after. If they are going after the same disease as us, then we wouldn't be able to compete"(WS500035 interview). This comment reflects the fact that the researchers and the facilities for conducting drug discovery research in the AMC are not comparable to the ones in the pharmaceutical industry. Moreover, AMC researchers

are aware of the safety and efficacy issues of drug possibilities. Furthermore, two researchers from MSKCC said that the institution provides them a clear objective of discovering drugs for cancer. The institution evaluates their performance based on the number of publications and the effort to discover drugs (WS500035, WS500047, interviews).

It has become common for industry scientists to switch their career path and move to AMCs as project leaders. An AMC director said that his center recently recruited more than 200 scientists from the pharmaceutical industry, who helped by guiding drug discovery projects from the start. He described the operation of his AMC as a project management team model by saying,

> "We put a team of academic researchers with a pharmaceutical experience researcher who leads the project. Each project has strong components of multi-disciplines and multiple organizations. The industry-experienced scientists would guide the team, and the teams would make go-no-go decisions, pre-define the criteria for decision-making, the costs and the kind of data they need, and what experiments to make the go-no-go decisions" (WS500043, interview).

The go/ no-go decisions is a model that a lot of biopharmaceutical companies adopt to decide whether they should move forward with developing a drug possibility or not. In pre-clinical stages, a go/ no-go decisions model is a set of specific questions that help scientists to narrow down which ones to pursue. Examples of question in go/ no-go decision model include which target alters the disease, is this target safer than others, and is this target effective for the patient population. In the team environment, academic scientists and industry-experienced scientists coming from multiple disciplines would come up with a set of specific questions to pursue and make collective decisions about selecting targets. The multi-disciplinary team allows scientists to pay attention to emerging properties and they have more people who follow up and validate those

emerging properties. The AMC model provides an integrated organizational structure where academic scientists get to be involved in a project from conceptualizing the idea to execution of clinical trials.

*IP Governance*. Like the traditional model, AMCs patent their drug possibilities and license them to biopharmaceutical firms who can take those possibilities to clinical trials. Two major differences between the AMC and the traditional model are 1) a TTO takes on an active role in helping the drug discovery team to identify potential licensees and market, and 2) the company that licenses the patent might conduct clinical trials in the AMCs' affiliated hospitals, so that the key academic inventor might still be involved in developing the drug possibilities.

### *III: INDUSTRY-INITIATED DRUG DISCOVERY PARTNERSHIP- HYBRID FORM OF GOVERNANCE*

As pharmaceutical companies are facing patent cliffs and the lack of new molecular entities in their product pipelines, they see that the discoveries made by academic scientists in universities could bring new possibilities for new products. Pharmaceutical companies have been forming collaborations with universities whose institutional arrangements depart from the traditionally transaction-oriented model. One recent example is the partnership between AstraZeneca and the Center for Neurodegenerative Disease Research at UPenn Medical School, where they partner to share resources for discovering and developing drug candidates for Alzheimer's disease. Another example is the partnership between GlaxoSmithKline and several academic labs at Yale to develop targets for disease-causing proteins in several therapeutic areas. The

institutional arrangement of the collaboration has been modified so that academic and industry scientists can work together to co-develop potential products.

One of the innovative collaborative arrangements in my sample is organized by Pfizer's CTI, which aims to "correct all the mistakes they made in the past in partnering with academics" (WS500055 interview). Currently, there are four CTI sites in different biotech clusters in the U.S., including Boston, San Francisco, San Diego, and New York. Each CTI is a small, semi-autonomous unit locating in close proximity to top-tier biomedical research universities. The process of setting up a partnership begins with CTI representatives inviting academics to submit a short non-confidential proposal. The site will select the proposals that fit the best with the company's portfolio. Once the pre-proposal is accepted, a CTI scientist and the academic scientist will write a full proposal together, which specifies all the experiments, procedures, and milestones that will be executed during the partnership. The CTI scientist will help the academic scientists to design experiments that translate their discovered targets into clinically relevant experiments. This is the stage where the industry and academic scientists will work side-by-side. A joint steering committee (with academic and industry experts) will review the full proposal. The partnership will begin if the full proposal is accepted. During the time of collaboration, academic scientists will have access to the company's compound library and equipment, the CTI scientists will synthesize and produce the molecules for experiments, and both academic and industry scientists get to work side-by-side.

*IP Governance*. In this example, IP ownership is divided 50-50 between the company and the university. The academic scientist and the CTI scientists conduct early stage

proof-of mechanism in the first year, and then the company will have a year to decide whether they want to buy the other 50% of the patent from the university. If the target does not work out, then the CTI will return 100% of the research and the idea to the academics. In addition, academics can publish their research with CTI as long as the CTI site approves the manuscript 2 weeks before submission.

### *IV: DISEASE-FOCUSED VENTURE PHILANTHROPY FOUNDATION- NETWORKED FORM OF GOVERNANCE*

Another partnership arrangement is disease-focused venture philanthropy, which is a hybrid institutional arrangement that combines elements of not-for-profit philanthropy and venture capital. They are not-for-profit philanthropy as their funding comes from the private sector, and they focus on a specific agenda, usually advancing treatments for specific diseases. Like venture capitalists, they review the scientist's research progress on the basis of milestone and provide funding contingent on reaching certain milestone before the next stage is awarded. Unlike other forms of partnership, venture philanthropy foundations are very patient-centered, with the primary goal of improving patients' lives with new and improved therapies. Therefore, they fund research projects focusing on various aspects of a specific disease. For example, as the largest private funder of Parkinson's disease research, the Michael J. Fox Foundation (MJFF) funds research in various areas of Parkinson's, such as genetic links with neuropathological features, causes and treatments of cognitive impairment due to Parkinson's, and side-effects of Parkinson's treatments.

Venture philanthropy foundations award funds to scientists, who then become a part of the foundation's network that convenes drug discovery scientists, clinicians,

vendors, and patients. One of the directors of the Michael J. Fox Foundation described the foundation's role in convening stakeholders:

> "Because we're focused solely on the patient, we have a very unique role as a mutual convener. We're very open, and we have that trust with different stakeholders, so we're able to convene them and we're able to bring them around the table and talk about different research hurdles that are affecting drug development. That could take many different forms. It could be a meeting where you're having brain-storming sessions and thinking about problems such as clinical trial design. It could be about bringing players together in the pre-competitive spirit to develop tools" (WS500089, panel).

Because of its non-profit and patient oriented mission, venture philanthropy foundations cultivate relationships with many stakeholders without getting involved in the process of negotiating contracts and patents. Therefore, the foundation can bring in various stakeholders to discuss problems that their grant recipients encounter. In this structure, once a scientist receives grants from venture philanthropy foundations, he/she gains access to its networks that help them with their research.

*IP Governance*. Unlike AMC or the traditional collaboration model, venture philanthropy foundations do not take any IP ownership, which means that the IP resides with the scientist and his/her university.

Thus far, I have outlined four different models of collaboration between academic institutions and biopharmaceutical companies, all of which have a goal of allowing the two sectors to draw on each other's strengths to identify and validate academic discoveries and develop them into drug possibilities. These sectors have complementary capabilities. On the one hand, biopharmaceutical companies possess cutting-edge facilities to synthesize, engineer, and screen compounds in large volumes; on the other

hand, academic labs have specialized expertise applied in experiments and deep conceptual knowledge in biological mechanisms. By working together, members of an academic-industry partnership would be able to access complementary knowledge and capabilities for advancing therapies for unmet medical needs. With the pressing need for developing new treatments for the increasing aging population, the new models of partnership are shifting toward pursuing a social mission of accelerating the development of treatments for unmet medical needs.

In the next section, my analysis returns to the practice of knowing when academic and industry scientists collaborate within these four models. The first aspect that enables the materiality dimension—defining a drug possibility with a specific function—is converging interest in developing product visions. This aspect consists of "developing the drug possibilities in the best shape possible" and "contextualized learning by working in the lab." The partnership arrangements, such as AMCs and venture philanthropy foundations, show evidence that academia and industry are converging their different interests to co-develop drug possibilities. The second aspect that enables the epistemic dimension among the partnership arrangements is allowing more autonomy for academic scientists to exercise their science capabilities. This aspect consists of "pursuing therapeutic questions together for a more complete understanding" and "making scientific decisions together." The third aspect that enables the activity dimension, such as a series of activities to materialize the product vision, is flexibility in institutional arrangements so that academic and industry scientists have access to translational facilities. This aspect consists of "changing the IP ownership structure to allow continuous practice of

knowing" and "exploring new contractual language" to overcome the legal barriers in the process of forming a collaboration.

## CONVERGING INTEREST IN DEVELOPING DRUG POSSIBILITIES AS A PRODUCT ENABLES THE MATERIALITY DIMENSION

The first aspect of new institutional arrangements is converging interest between academics and industry in developing product visions from the drug possibilities. Evidence shows that AMCs and venture philanthropy foundations have revised their goals from research to developing drug possibilities in their best shape possible so that those drug possibilities can be further developed in the industry. Two practices are associated with converging interests, such as "developing the drug possibilities in the best shape possible" and "contextualized learning from working alongside with industry scientists." Academic and industry scientists working side-by-side in labs is especially important for collaboration in drug innovation because experimental techniques are not easily transferrable through patents and publications. The industry-initiated partnership allowing such collaboration would open up more opportunities for academic and industry scientists to learn each other's techniques in manipulating drug possibilities.

In the linear model, academic scientists' involvement in the product development process is limited. One scenario is that a company does not provide academic scientists proprietary information, so the scientists conduct experiments on the drug possibility without knowing what it is for; moreover, academic scientists cannot publish findings from the industry-specific experiments. Another scenario is that, when academic scientists patent their discoveries and license them to the industry, they are no longer

involved in developing the discovery unless they begin their own companies or sit on the company's advisory board. Consequently, academic scientists are not exposed to the innovation process, nor do they appreciate what the process entails.

*DEVELOPING DRUG POSSIBILITIES IN THE "BEST SHAPE POSSIBLE"*

One of the social missions for AMCs and venture philanthropy foundations is that they perform pre-clinical investigations with the goal that those drug possibilities can become a ready-to-use product and "handed off" to the industry through patent licensing. A drug possibility being "in its best shape possible" indicates that scientists have defined its disease context; they have identified the patient population, understand its mechanisms and biochemical interactions, and preliminary compound screenings have been conducted. The strength of academic science is discovering and identifying targets that have potential for drug possibilities; however, universities and their scientists generally do not have the resources to develop drug possibilities into viable drugs—the actual product that patients use. For drug possibilities to reach patients, universities and research institutions realize that they need to package their research in a product portfolio with a complete patent family based on the drug possibility. Therefore, a more intimate partnership between academics and industry will allow each to leverage the other's capabilities.

An AMC director said, "[T]hose in academia can't do it alone. We are beginning to figure out the recipe for success and the recipe for failure. The open-source model is good to share information, and it opens a pre-competitive space. But I really think that at some point, it needs to cross over into the competitive space" (WS500043, interview).

Even though working in academic setting, this AMC director had more than 20 years of experience in drug discovery in the pharmaceutical industry. He wanted to bring his expertise from the industry to academia and guide academics in learning and practicing pre-clinical research. He knows that drug discovery is not an innovation to be conducted in a single sector but requires partnerships among industry, academic, and government agencies, with each having its own unique capabilities and being dependent on the others. Therefore, the role of academic scientists in drug discovery is to bring a drug possibility to the "best shape possible" and hand it off to the industry that can deliver it to patients.

During coffee breaks in a conference on translational medicine, I talked to staff members representing two AMCs and asked them about the role of academia in the future of drug discovery. One said, "They have to have a role because the industry is running out of money and they are turning to academia, and academia has a lot of resources, its knowledge and research." The other said, "Academia needs to build a pipeline, get the pre-clinical research done well, and get it ready to move to the industry" (WS500038, field note). Furthermore, a director from MJFF said that the foundation's mission is "to financially support pre-clinical research to a point that [drug possibilities] can be handed off to an actor who may have more money than the foundation and who has development expertise to bring it to the market" (WS500089). Many AMCs and venture philanthropy foundations are becoming involved in supporting pre-clinical research for academic scientists. Their collective goal is to develop drug possibilities to the point that many questions have been answered, disease and patient contexts are defined, and a patent family is developed so that pharmaceutical companies can license them and bring them to clinical trials.

In a panel discussing the topic of academic-industry partnership for drug discovery, a pharmaceutical company representative shared his vision for the future of academic-industry partnership,

> "I think we are going to a trend toward big institutional broad agreements between companies and universities. . . . [T]he new type of agreement that focuses on drug discovery has a lot of financial incentives to succeed and brings together pre-clinical and clinical research to bridge this translational gap; that is the source of most interaction in the industry. I think we'll see big agreements with the universities that focus on certain disease areas like cancer, where companies have established interests and strategies. We don't really want to do agreements where we gain access to academic knowledge but not necessarily produce anything. Even the universities are saying, "What was the point of that? Thanks for the money, but it didn't advance our social mission and we are not interested in those agreements anymore." We are seeing more focus on innovation that can be turned into products. This is consistent with at least part of the universities' mission and within the interest of the companies. (WS500040, panel discussion)

This comment sums up the ongoing changes in how academia and the industry approach collaboration agreements. In the linear model, academics and industry collaborate based on academic scientists providing research that is funded by the industry, or academics patent their discoveries hoping that companies will license them. This pharmaceutical industry representative was saying that neither the university nor the industry wants to continue the transactional-based approach to collaboration. Their interests are converging to an extent that they both want to be involved in producing products together. Therefore, the newly emerged collaboration agreements are focused on pooling the strengths and capabilities of both parties.

However, not all academic scientists are willing to participate in developing drug possibilities to the "best shape possible." In AMCs, where academic scientists' promotion is based on grants and publications, they are more likely to hesitate in participating in drug discovery projects. An AMC director said that the teams in his

translational research center consist of academic researchers and industry-experienced researchers who jointly decide on go/no-go decisions. However, even though they are in a team environment, the director said,

> "The biggest difference is that, in industry, we report to bosses, and the bosses define targets, give us the marching order. On the other hand, our academic folks focus on promotion, tenure, and their major focus is really about getting grants. It's very hard to get federal grants. So we have conflict and competing priorities. If academic folks are getting grants, . . . we can't really go talk to them and tell them to kill a project that they are pursuing for federal grants" (WS500043, interview)

Despite the new institutional arrangements such as working in teams in AMCs, this director's comments indicate that the institutional norm of achieving communal reputation through publications is deep rooted in academic scientists' practices. Academic scientists are still more accustomed to working on publications and writing grants than they are to working on team projects.

### *CONTEXTUALIZED LEARNING BY WORKING ALONGSIDE INDUSTRY SCIENTISTS*

The other practice that enables the materiality aspect is that of academic and industry scientists working side-by-side in the lab, a situation that provides opportunities to contextualize learning and see drug possibilities materialize in human settings. Among the four partnership models, the industry-initiated partnership creates a social space in which academic and industry scientists work together in a lab. One of the capabilities of academic scientists is discovering new targets and pathways, and the corresponding capability of industry scientists is to investigate whether these elements are effective and how to translate them into clinical settings. The skills to manipulate scientific entities are not easily transferrable but require scientists to be physically in the lab performing

experiments. Being in the lab together, academic and industry scientists shift their attention from commercial interests to knowing science together, and doing so helps to resolve their differences in scientific skills and rationales. When they work in laboratories, they realize that they are using the same technique or scientific rationale but applying it for different reasons.

For example, the CTI arrangement offers a place for academic scientists to translate contexts from laboratory to clinical settings. Because large pharmaceutical companies have a great deal of technological resources, one of the strengths of industry scientists is designing experiments that reflect human disease contexts. To translate drug elements and their possibilities to clinical settings, scientists need disease samples, equipment for animal models, imaging facilities, and the expertise to conduct *in vivo* experiments. A CTI scientist specializes in cancer biology is in the stage of writing a proposal with an academic scientist. I asked her about the kind of research questions that drive her and her academic collaborators to work together. She responded,

> "A lot of [academic] labs have been working on [a target] for years. It is kind of like their baby. It is more exciting to them to still be involved in the process of testing it rather than in the past you sold it to a company and they took over. I think the motivation was already there when they wrote the proposal. It is probably scary to them because you're going to test it. This is it. . . . For both of us, it is proof of principle or proof of concept. You're starting with a hypothesis . . .. And you're saying that your target that you've been studying for a long time, and we are testing it. You're going to see what that does to the disease. I think it is a common goal for both sides to see" (WS500060, interview).

Her comment indicated that it is "very exciting" for academic scientists to see the drug target they have been studying actually be tested and applied in an empirical problem. Academic scientists usually generate hypotheses or conceptual understandings of what a target might do, but they do not have the resources to demonstrate what it really does.

They either do not have the facility and material (e.g., samples from diseased cells and tissues), or there is pressure to publish, so consequently they must move on to the next scientific question. However, if there is an opportunity for academic scientists to learn how to use the drug possibilities in an empirical problem, it's "very exciting" for them.

We know that academic and industry scientists are oriented toward different productive outcomes, with academic scientists publishing academic papers while industry scientists develop products. Because writing papers and developing products involve two different sets of practices, having academic scientists working in a lab with industry scientists provides an opportunity to learn what it takes to develop a product. By working with industry scientists, academic scientists learn about contextualizing their understanding of drug possibilities and think about the connection between drug possibilities and the human body. As CTI scientist specializes in cardiovascular disease said,

> You have to think about just the nuts and bolts of giving a drug in a real world. . . . Writing a paper that ends with this discovery could help us to understand the mechanisms of cancer, but that is very different than trying to understand how I'm going to give this drug to this patient. What is the competitive landscape? What else are they taking? How are we going to screen these patients? What biopsies can we get? Is it blood draw, surgery? How are they going to get the drug; is it a pill or injection? What is the disease you are trying to cure? How is this going to positively impact this patient's life? (WS500062, interview)

His comment highlights the difference between writing a paper and developing a product because many later criteria have to be considered when materializing drug elements and possibilities. Even though many of these criteria, including competing with drugs in the market, manufacturing, and administering the drugs to patients, are not incorporated in the academic practice of science, working with industry scientists would enable academics to learn about these aspects of the drug discovery process.

Furthermore, the CTI arrangement offers a place for academic scientists to translate contexts from laboratory to clinical settings. For example, according to a CTI cancer biologist,

> "Say you have a molecule that is mutated or something in cancers. You think that if you can get at this molecule, then you can cure the cancer. There is a lot of different ways that molecule might be working. How do you want to target that molecule? Do you want that molecule to have effective function where you are killing the cell? Do you just think that molecule is maybe providing the cancer cell with the ability to get growth signals and you just have to block that effect? The drug can have a bunch of different actions, and neutralizing it can actually be a self-killing mechanism. I think there are strengths and weaknesses to different ones and side effects. If you're going to be delivering something systemically or locally. So I think we can help with all of that" (WS500060, interview).

To translate drug elements and their possibilities to clinical settings, scientists need disease samples, equipment for animal models, imaging facilities, and the expertise to conduct *in vivo* experiments. Moreover, there are many ways to devise a molecule to treat cancer, either killing the cancer cells or blocking the growth signals of the cancer cells. There are also many different ways that a drug element interacts with the patient's biology, such as different ways to deliver the molecule to the desirable disease target. One of the strengths of industry scientists is designing experiments that reflect human disease contexts. She said that "we can help with all that," meaning that industry scientists can help academic scientists to approach the complex interdependencies and interactions and become familiar with what it takes to develop drug possibilities for use in the human body.

Moreover, this learning is two-sided because the industry scientists also want to learn from academic scientists by working closely in the lab. When I had a small group discussion with four industry scientists about what improvements they would they like to see in academic-industry partnerships, one of them said,

> "The drug discovery has to start getting animal models. It would be better to get some academic people to actually come into the company and do it and show you. Because it's hard to develop animal models, and if they have already developed it, it's a lot easier to come in and have somebody absolutely familiar with it to show you exactly what you have to do, rather than you try and do it yourself" (WS500028, discussion).

Another industry scientist, followed up on the comment, saying, "I think more of that would be very very helpful for discovery. I don't think it's done as much as it could be" (WS500028, discussion).

In the linear model, the company would transfer materials to academic labs and have the academic scientists perform the experiment in their own labs. In this situation, industry scientists do not learn about the exact procedures, and the academic scientists perform the experiment in their own timeline. According to these two industrial scientists, instead of passing material and data back and forth, if academic and industry scientists were able to share lab space and coordinate on performing experiments, they would share common questions about the drug possibilities and co-develop knowledge.

Whether scientists are working in the industry or in academic labs, they have gone through similar type of educational training, surrounded by experiments, working in labs and under advisors. They share a common language in scientific methods and techniques even though they are using the same technique for different purposes. A pharmaceutical scientist specializes in neurodegenerative diseases, described a dynamic he had with his academic collaborator:

> "We wanted to go after this molecule for multiple sclerosis, so we set up collaboration with an academic scientist to go after this molecule. The academic collaborator suggested testing the target in EAE model, but the EAE model takes 60 days to run, which is a very long time. We introduced the academics [to] a tier model to test the mechanism of action; it's not a disease model, but a model to test the action as a way to give therapeutic indicator. . . . Then later, the academic collaborator was showing me this procedure and injected some fluids into the

> brain tissue to turn off the receptor in the brain, and six hours later, we could see the signal from the therapeutic indicator. As it turns out, they were doing the same procedure for science reason, but we can use this technique as a biomarker for us. So we both got the benefits" (WS500039, interview)

From this dynamic in the lab, he and his academic collaborator realized that they knew the same technique even though they were using it for different reasons. Their common language was their techniques, which they demonstrate in laboratories. This pharmaceutical scientist further said,

> "They are teaching us more about science, and we are teaching them how to do drug discovery. We use the science for practical reason and they have the rationale for theory" (WS500039, interview).

For interview subjects who have worked alongside with industry/ academic scientists, they said that they have no problem in reaching scientific consensus once they are engaged in scientific questions (WS500062 interview). When their interaction is situated in the lab and they both know the science, academic and industry scientists realize that they share similar scientific techniques and rationales but for different purposes, one for advancing scientific theory and the other for product development.

## INCREASE AUTONOMY TO ENABLE THE EPISTEMIC DIMENSION

The second aspect of partnership arrangements is increasing the autonomy that would enable academic scientists to exercise their science capabilities. This aspect constitutes "academic and industry scientists raising therapeutic questions together to arrive at a complete understanding" and "making scientific decisions together". In the linear model, academic scientists collaborate with companies based on a one-time service in which they conduct industry-specific experiments that address certain questions related to the company's product. For example, a company intends to find answers for a specific

question, such as "Does compound Y work in plague X?" (WS500039, interview), so when an academic scientist possesses samples of plague X, the company would contract with the academic scientist and have him test compound Y. The company has already decided the scientific question and experiment, and there is no room for academic scientists to exercise their creativity and research capability. Consequently, academic scientists find it "not interesting" to conduct industry-specific experiments (WS500040 panel, WS500090 interview). In comparison, the new institutional arrangements are becoming more flexible so that academic and industry scientists have more autonomy to search and explore a common set of questions about the drug possibility.

### *PURSUING THERAPEUTIC QUESTIONS TOGETHER FOR A MORE COMPLETE UNDERSTNADING*

New models of industry-initiated partnership now have structures that enable academic scientists to investigate the drug possibility in various perspectives. Because neither the industry nor academic scientists have a complete understanding of the drug possibility and its role in the complex biology, combining their expertise and knowledge enables them to obtain a more complete understanding of the drug possibility. Companies adopting non-linear partnerships reach out to academic scientists as a way to raise questions and search for answers with the academic scientists. As a cancer biologist commented, "For both of us it is proof of principal or proof of concept. You're starting with a hypothesis, . . . and we are testing it. I think it is a common goal for both sides to see" (WS500060, interview). The CTI arrangement is set up in a way that the company's scientists and the academic scientists are conducting "proof of principle" together, which is the "common goal for both sides." In other words, the company is no longer

deterministic about what questions academic scientists pursue in their collaboration, but they are collectively defining and answering the questions.

Large pharmaceutical companies reach out to academic scientists because they have deep insights about the particular drug possibilities that the companies do not have. Companies having open dialogues with academic scientists concerning the drug possibility would not only benefit from their deep insights but also fill gaps in the companies' own practical knowledge. For example, a large pharmaceutical company contacted a professor in neurobiology to check on a compound that was already in Phase 3 clinical trials. This company had a compound to treat dyskinesia, but it was about to fail the Phase 3 clinical trial, and they wanted to know why it failed and how it failed when it attached to dopamine receptors. Therefore, the company contacted the neurobiology professor, who had studied dopamine receptors in schizophrenia and Huntington's disease for 15 years. He said,

> "One of the reasons that [the pharma] came to us [was] because they were trying to find a biological reason for why they were getting certain human results [from the compound]. They were trying to figure out, . . . 'Does it have something to do with the dosing?' . . . So they saw that this compound had a very narrow therapeutic window. Like you couldn't go below a certain dose; you couldn't go above a certain dose. You had to work within a certain range. And the patients have to know that they cannot take less, they cannot take more. So they solved this property of this particular compound, and they were trying to understand why that was, at least from the basic science point of view, and we were trying to come up with theories based on our data, a cause to why it might behave that way" (WS5000012, interview).

The company contributed the compound and materials while the neurobiology professor contributed his expertise and skills in manipulating the cell line. Even though the company's scientists knew something about the compound, they did not fully understand the details of how it interacted with the receptor. This professor, who had studied all five

different dopamine receptors, had a deep knowledge about how to handle the receptors and the kind of experimental systems to observe them. He could explain nuances of the compound interacting with the receptors to the company. In particular, the narrow dosing range of the compound was an emergent property because scientists could not know about it until they tested the compound in humans. By working on the experiment together, they were able to observe the unfolding interaction between the compound and dopamine receptors.

Because biopharmaceutical firms lack deep knowledge about drug possibilities, they collaborate with academic scientists to develop a complete understanding of a compound's safety and efficacy. A few academic scientists said that they were "filling the gap" for the company's practical knowledge concerning a drug possibility. When a company's understanding of a drug possibility has reached a limit, especially concerning the issue of efficacy, which requires deep knowledge, they reach out to academic scientists.

The CTI arrangement allows academic scientists to continue working on their projects, and they are able to learn about how their conceptualizations are executed and actualized. When academic scientists and industry scientists pursue a scientific question together, their knowledge and practices complement each other. Academic scientists offer their intimate knowledge about targets and their mechanisms while pharmaceutical firms and their scientists contribute the resources and execute the experiments. A director from one of the CTI branches said that the proposal-writing stage in the CTI model is focused on co-developing a product with academic scientists and helping them to gain an appreciation for the drug discovery process. She said,

> I need academics to know what they don't know. There are a lot of stuff that they don't know, and I need them to know that they don't know everything. I want them to continue doing their basic science, asking basic mechanistic questions, because that is what they are good at. It's helping them to gain an appreciation. They only have to know what they don't know and when to ask those questions and what to focus [on]. (WS500055, interview)

Because academic scientists have been working on their specializations for a long time, they may overlook other parts in the biological system that they do not know. However, one cannot possibly know everything, and having complete knowledge prevents one from working with others. As this CTI director suggested, academic scientists knowing what they do not know would facilitate their collaboration with industry scientists so that they can help each other with their complementary knowledge. When academic and industry scientists focus on a particular problem, such as designing an experiment to test a drug target, working together enables them to be aware of what they actually do not know, becoming an opportunity for co-learning. Academic scientists obtain an understanding about the global connections between the drug possibility and the whole body, while industry scientists learn about new mechanisms and the subtlety of the drug possibility.

*MAKING SCIENTIFIC DECISIONS TOGETHER*

Compared with the traditional model, the new institutional arrangements enable joint decision making between academic and industry scientists, and the academic scientists become more involved with planning the direction of a given industry project. A pharmaceutical scientist recalled that collaboration with academics was like "contracting the academics to do the model and tell them what to do. This doesn't work out well because it was not very satisfying for the industry and academic scientists to have a dichotomy like this" (WS500039, interview). As mentioned earlier, with the

traditional model, the company has already decided the experiment and the question to pursue and then contracted academics to perform the experiment, so the academic scientist works alone like an "outside contractor" to whom the company outsourced experiments for its projects. An industrial scientist specializes in neurodegenerative diseases said,

> "Now things have changed a little, where there is more creativity and more risk sharing from the academics side. We would work on developing compounds together, sharing information on the biologics and compounds, and then the industry would pay by milestones. Academics are not interested in receiving royalties because it usually takes too long to make a drug, and they would receive the royalties from the drug" (WS500039, interview).

He pointed out that the traditional collaboration model, in which the company has already decided the question and the experiment, is not intellectually satisfying for either the company or the academic scientists because neither side is learning from the other. As the industry and academics are making adjustments in their collaboration arrangements, some companies have begun to share more proprietary information with academic scientists and allow them to contribute insights about designing experiments, as well as conducting experiments together. In this case, academic scientists are allowed to apply their tacit, hands-on knowledge to a specific problem, and they participate in deciding which experiment to conduct. As academic and industry scientists solve problems together, opportunities for learning from each other increase.

With the CTI arrangement, in addition to academic and industry scientists writing the proposal together, academic scientists and CTI scientists and managers collectively decide which proposals to accept and how to strategize the project. The alliance manager of CTI branch said, "Every decision is made together, not only from the proposals, but also the selections of milestone to marketing. It's all decided by a joint steering

committee which is made up of 50% of Pfizer and 50% of academics; no decision will go forward unless it is agreed upon both sides" (WS500063, interview). In the traditional model, the pharmaceutical company has already made most of the scientific, business, and strategic decisions prior to consulting with academic scientists, who may sit on an advisory board and provide their advice on an ad hoc basis. In such cases, their participation in the drug-discovery process is limited to science, and they are not involved in other aspects of the innovation. With the CTI arrangement, input and advice from academic scientists are considered throughout the drug-discovery process; there is an actual co-development of a product, rather than consultation through sitting on an advisory board.

## FLEXIBLE INSTITUTIONAL ARRANGEMENTS TO ENABLE THE ACTIVITY DIMENSION

The third aspect of the new partnership arrangements is flexible institutional arrangements that enable academic and industry scientists to collaborate more quickly and allow access to translational facilities. This aspect of the partnership is associated with two practices, such as "universities and the industry exploring creative contractual language" and "changing IP ownership structure to facilitate collaboration." My interviews with several industry scientists revealed that the negotiation process between lawyers from the companies and universities slows down the collaboration or sometimes causes it to be abandoned because the lawyers disagree on the contractual language. For example, companies forbid academic scientists to publish findings using their proprietary material, or the university wants to file for patent protection for a part of the technology

scientists develop with the company. Issues involving intellectual property often get in the way of collaboration. Learning from past mistakes, universities, along with AMCs and industry-initiated partnerships, are exploring new institutional structures to overcome the legal barrier to facilitate collaboration.

### *EXPLORING CONTRACTUAL LANGUAGE TO ENABLE ACCESS TO TRANSLATIONAL FACILITIES*

To change the activity dimension so that both academic and industry scientists can pursue a set of purposeful activities, universities and companies are exploring more creative contractual terms to accommodate their partnerships. One of the major administrative obstacles in academic-industry partnerships is that lawyers from both sides spend a good deal of time negotiating contracts from scratch. They negotiate detailed items, including the right to publish, intellectual property of the product and material that belongs to university or the company, locations for conducting experiments, and transferring of materials used in experiments. The negotiation process is not only costly to the project but also holds up the collaboration, and it is usually a primary reason for many collaboration deals failing to go through because lawyers from both the university and the company could not agree on the terms. Therefore, many universities have begun to adopt a master agreement to which a company that wants to collaborate with the university can refer; the company and the university can make adjustments to the contract based on the project. For example, several AMCs in my sample had adopted a master agreement for collaborating with local biotech firms. In addition, industry-initiated partnerships like Pfizer CTI and Eli Lily's $PD^2$ innovation projects use master agreements with more than a dozen universities.

Both universities and companies have begun to be more creative with the language they use in these contracts. In a panel on academic-industry partnership, with representatives from a university TTO, a large pharmaceutical company, and a biotech firm, the representatives discussed the complexity of legal documents not only increasing chances of mistakes but also requiring long periods of negotiation. The panel participants agreed that both universities and companies are becoming more creative in using new terms in their contracts. For example, an AMC director described her experience with biopharmaceutical representatives in drafting a new master agreement:

> "What gets us caught up very often, is the language of the contracts and what that language means. So let's think about what are the basic problems? One is publications; academics want to publish sometimes, and industry doesn't. Let's find some language that would be a compromise on this. Indemnification: let's find some language it would be a compromise on that. The next issue is intellectual property because after the Bayh-Dole Act of 1980, the universities are allowed to own their intellectual properties. So that's been a big problem for industry. And, so let's find language that would be appropriate for that. And if we can find language to put together a master template, there'll always be a few little things that you may have to negotiate. So, just having those dialogs is really, really, important. . . . We sent [the master template] to the biotech folks, who were not lawyers. They loved it. We loved it. We brought it to faculty; everybody loved it" (WS500081, interview).

This AMC director sending the master template to the biotech folks instead of lawyers indicated that scientists and managers are becoming more active in shaping the conditions of the collaboration rather than having lawyers handle the contract. In some cases, even though academic and industry scientists may agree to collaborate, the lawyers from the university and the company could not agree on the contractual language, so the negotiation was unsuccessful, thereby harming the partnership and innovation process (WS500023, WS500029 interviews). Moreover, as scientists and managers become more involved in shaping contracts, they are also using new terms to accommodate the

complexity of their work as well as the task dependencies between academics and industry scientists.

Testing a drug possibility requires a wide range of technologies and facilities to validate whether it has the potential to be a viable drug. Making such facilities available to academic scientists would encourage those scientists to raise translational questions and repeat experiments to validate emerging patterns. Many academic labs tend to be smaller and specialized according to the scientists' expertise, and university laboratories are usually not equipped with industry-standard facilities, such as high-speed screening or large-volume compound libraries. Even though this is the nature of the academic research setting, the technological capacity would affect the questions that academic scientists pursue and the experiments they can conduct. For example, if an academic scientist wants to verify her observation from animal models in human tissue, she has to obtain samples of human tissues; however, only research hospitals would possess such samples. If the university she works for is not affiliated with a research hospital or if she does not know anyone with such samples, she would not be able to verify her observation. In a panel that discussed translational medicine, a well-known medical doctor and researcher emphasized the same argument:

> "It's pretty clear to me that the availability of the compounds is a problem [to conducting translational science research in universities]. I do believe that universities, if they are going to do this, either open up all of their technology to the target discovery process or come together and find a [way] to handle the equipment. Otherwise, I don't think we are going to go forward" (WS500045 presentation).

Compound screening is an important process of hitting a target with already-known compounds to investigate the target's pharmacological qualities, such as its binding site, sensitivity, and dosing window. This is a preliminary step to determining whether the

target is “druggable” or not. Most universities have limited or no compound library and screening facilities. Recently, however, some universities and AMCs are starting to purchase these technologies with financial support from the NIH.

The three newer models of partnership arrangement enable academic scientists to access translational technologies and facilities. When academic scientists know that translational facilities are available to them, they shift their research questions from mechanistic to application to disease contexts. Many translational facilities are expensive, and animal models are difficult to design and execute. Therefore, providing academic scientists access to models and tool kits would save a good deal of time and money and would encourage scientists to conduct in-depth assessment of the discovery and explore its potential as a drug element. The Michael J. Fox Foundation distributes research tools and works with various vendors and contractors to develop those tools and distribute them to its grant recipients. By receiving grants from philanthropy foundations, academic scientists gain access to a wide range of research tools, such as different variations of animal models, antibodies for protein detection, disease-specific gene databases, and samples of patient tissues.

### *CHANGING IP OWNERSHIP STRUCTURE TO ENABLE COLLABORATION AND CONTINUOUS PRACTICE OF KNOWING*

As universities and companies are converging some of their missions and interests in developing new therapeutic products, they are also exploring creative ways to reach collaboration agreements. Each sector is finding new approaches to handling IP ownership. Traditionally, biopharmaceutical companies funded academic research and wanted to claim 100% of the IP and restrict the academic scientists from publishing

anything related to the funded research because the company financially supported the research. As a CTI scientist said, "I think [this arrangement] has been one-sided. With the CTI model, we want to collaboratively see what the steps are. We've agreed that if the company agrees not to continue, all of the academics' work will return back to them and they can move forward how they see fit" (WS500062 interview). Therefore, the CTI arrangement is that, if the drug element proposed by the academic scientists does not work out, the CTI will return the project in its entirety to the scientist. Often, graduate students and post-doctoral fellows do the lab work on the initial discoveries. Although the discovery may not work as a drug element, it can still provide a topic of study for the students and fellows in the lab so they can continue doing research.

Several thought leaders in academia advocate for an open-source approach or an approach of filing for patent protection at a later stage of discovery, which would better facilitate cross-disciplinary collaboration. For example, an open-source consortium based in the U.K. and funded by Oxford University and the pharmaceutical industry analyzes proteins and deposits the data in its online database. The consortium adopts a model that files patents at the relatively late point of discovery when the drug target is defined and validated clinically. The director of this consortium advocates for applying patent protection at a later stage of discovery because, as he put it, "What is the point of generating IP on 90% of the targets that are destined to fail?" (WS500051 presentation) Moreover, he said that not filing IP at early stages enables the consortium to "collaborate quickly with any scientists, any labs, or any institutions on the planet. We can work closely with multiple private organizations on the same project. If I were applying for IP, I would be spending most of my time sorting deals with Pfizer and GSK" (WS500051,

presentation). Filing for patent protection before the discovery has been verified in terms of its therapeutic functions prevents scientists from collaborating with other disciplines because disclosing the knowledge about the discovery would violate the patent application policies. However, the emergent properties of the discovery require multiple disciplines to reveal their characteristics. If cross-disciplinary collaboration were restricted, then a full understanding of many possibilities would also be limited.

## SUMMARY

In this chapter, I have discussed the current institutional arrangements for academic-industry partnerships and how they bridge two forms of boundaries in practices and commercialization process. Compared with the linear model, the new institutional arrangements allow academic and industry scientists to investigate a common set of questions about a discovery with potential to be a drug element and enable the scientists to share lab space and technologies. The new institutional arrangements also show evidence that both sectors are searching for creative approaches to manage IP ownership, as well as streamlining the negotiation process so it will not jeopardize their partnerships.

With the opportunities offered by the new partnership models, universities and their academic scientists could expand their research portfolios and capabilities by being more involved in pre-clinical research. Universities still are learning and searching for strategies to collaborate with industry while preserving their own focus on research. Several industry scientists with whom I talked said that they did not want academics to develop drugs, but they wanted academics to be more involved in the drug-discovery research (WS500055, interviews; WS500082, interviews; WS500056, discussion). One

representative from a large pharmaceutical company indicated that there is “no point for universities replicating what Pharma has been doing, . . . and universities should be aware and not naive” (WS500040, panel). With the ongoing institutional changes in drug discovery and academic-industry partnerships, different aspects of change in academia are inevitable in terms of faculty promotion evaluation, IP management, and improving translational facilities. This is an important time for universities to develop and strengthen their research capabilities to manage risk.

# Chapter 8: Grounded Theory Building Discussion

Data analysis from previous chapters demonstrates two forms of boundaries referred to as discontinuities in practices and the fragmented commercialization process. These forms function in the process of transforming academic knowledge for drug innovation. Chapter 4 delineated the dimension of knowledge for drug possibilities, which deepens the understanding on the content and substance of knowledge for science-based innovation. The material dimension drills down into the complex functioning of the human biology and diseases. The epistemic dimension opens up the ever-emergent nature of the knowledge that motivates scientists to keep asking questions drawing on rich scientific theories for answers. The activity dimension directs the purpose of knowing and guides the direction of multidisciplinary collaboration among scientists. The three dimensions also serve as pillars to identify where practices are discontinuous and fragmented, which prevent academic research from being directly applicable for innovation. In Chapter 7, I presented new evidence on aspects of institutional arrangements that may facilitate side-by-side collaboration of academic and industry scientists. My analysis highlighted the aspects from new institutional arrangements that may help to bridge the boundaries.

In this chapter, I use the grounded theory method theorizing the data to answer the research question of this dissertation: "What kinds of social arrangements enable academic and industrial scientists to transform academic knowledge for complex innovation?" This is an important question for gaining a deeper understanding of how to improve collaboration between the two sectors, because complex innovation in this century will rely on multiple institutions and organizations collaborating. The

transformation of academic knowledge for drug innovation could take place at three levels including practice of knowing, in the relationships between academic scientists and industrial entrepreneurs, and in the institutions of knowledge accumulation. At the practice level, transformation of academic knowledge takes place when research questions change from raising open-ended about a drug element to questions about its connection to a disease. In the relationships between academic scientists and industrial entrepreneurs, transformation of academic knowledge takes place when research capabilities are bundled to address a market need. Lastly, transformation of knowledge would occur when novel emergent findings are iteratively validated for innovation purposes. These transformations need not to occur in academia, as industry also has to transform its practices to collaborate with academics, but it is important to identify the underlying boundaries and possible transformation, to understand how and why the transformation is necessary in the biopharmaceutical sector. In the following, I will elaborate on the two forms of boundaries and discuss how knowledge might be transformed at academic-industry partnership to enable innovation.

## DISCONTINUITIES IN PRACTICE: PRACTICE OF BASIC RESEARCH VERSUS PRACTICE OF CLINICAL RESEARCH

The first boundary in the process of transforming academic knowledge for innovation is in the discontinuities of practice of knowing objects. The practices of basic research and clinical research diverge in three dimensions. In the materiality dimension, basic research practice focuses on human biology in general and its specific purpose is to know everything about that single element. Clinical researchers situate their knowing in

a particular disease process and search for a therapeutic function. These researchers explicitly incorporate a disease context in their knowing by conducting experiments with disease-based materials. Basic academic researchers and clinical researchers also diverge in terms of their approach to epistemic objects by following paths of emergence around their element and asking open-ended questions that trace mechanisms. Such an approach produces detailed mechanistic knowledge that is important to drug innovation because it is necessary to know all the facts for application purposes. On the other hand, clinical scientists follow paths of emergence that connect drug possibilities to diseases and ask questions that develop these specific relationships. Whether the epistemic object is new or previously discovered, scientists using this approach define how the object may be useful for a therapeutic purpose.

Furthermore, practices of basic and clinical research diverge in the activity dimension, which directs the purpose of knowing. All scientists are motivated to work on what they do not yet know, but they diverge in the steps they take to materialize the object. Scientists practicing basic research tend not to repeat experiments in different contexts to validate drug elements and they do not work toward the objective of materializing an efficacious drug. Clinical research scientists interact directly with clinicians and patients, and more importantly, they make a connection between patients' experiences with the disease and scientific laboratory observations.

The implication about the activity dimension is that "moving on" from the emerging properties would consequently hinder academic discoveries from becoming useful for drug innovation. Many recent studies have pointed out that, "at least 50% of published studies, even those in top-tier academic journals, can't be repeated with the

same conclusion by an industrial lab" (Prinz et al. 2011). Since the pharmaceutical industry relies on studies that identify new targets for drug development, industry scientists spend time and money trying to replicate the published studies but do not find the same results (Kahn 2012). The inability to replicate academic research is associated with two reasons, one being that the experimental procedures are so specialized they cannot be codified, and second being the priority rule to publish. Scientists want to be the first in making discoveries and disclosing the discoveries to receive recognition (Merton 1973). Their rewards and recognitions are structured based on being the first to disclose novel knowledge in their fields. However, the haste to publish creates a "gap" in the knowledge between novelty and application, which leads to inefficiencies in the science research and innovation process (Dasgupta & David 1994). Because biology and diseases are complex, unlimited possibilities and unpredictable events exist. Therefore, following up on emerging patterns and iteratively validating them becomes critically important to make sure that an observation is reliable in real-world conditions.

Another issue of academic-industry partnerships based on patent transactions is that scientists are restricted to pursue questions about a drug possibility together. In the linear market-oriented model where firms contract academic scientists to perform a one-time experiment, firms have already pre-defined the questions and thus restrict new possibilities. Also, while citing papers and patents are a way to learn about academic research, the language codified in these documents could be limited to explain the specialized craft of manipulating the object. Industry scientists still have to translate the academic research into specific disease contexts and this translational process is costly and requires specialized skills.

These practices, both basic and clinical, are a part of the innovation ecology. Scientists are not limited in one kind of practice because many explore various types of questions and engage in entrepreneurial activities by diversifying research portfolios through collaborations (Dasgupta & David 1994). However, when it comes to commercialization and drug innovation, knowledge produced by clinical research practices is believed as more directly relevant. The comparison between basic academic and clinical research practices suggests that knowledge produced from clinical research practices is more likely to be useful for drug innovation.

## FRAGMENTED COMMERCIALIZATION PROCESS THAT DISRUPTS PRACTICES OF KNOWING

The second boundary in the transformation of academic knowledge for complex innovation is situated in the commercialization process. Commercialization is fragmented because resources to commercialize drug possibilities are available to those in a specific disease context, legitimated by patents and publications, and directly applied to specific industry users and patient populations. A drug possibility's materiality is represented by its monetary mechanisms in the forms of patent portfolios or start-up companies. Publications and patents determine a drug possibility's legitimacy in science and innovation, as publications signal that the research is scientifically sound and patents indicate it has potential commercial usage. Academic scientists' social connections with the industry dictate their activities to define industry users and potential disease populations. In short, drug possibilities would not be commercialized without meeting these three criteria.

My conceptualization of the drug commercialization process involves the interaction between academic scientists and industrial entrepreneurs. While academic scientists engage in these activities, the evaluation criteria are also mechanisms to filter potential discoveries. On the one hand, academic scientists engage with the commercialization process through their research on drug possibilities, which entails what they know and what questions they want to pursue. As they inform the TTO of the university that their discoveries may have market potential, they are also seeking financial support to develop the discovery into commercializable products. On the other hand, industrial entrepreneurs enact the professional jurisdiction as they evaluate drug possibilities and determine which can and cannot be commercialized (Ferlie, Fitzgerald, Wood, & Hawkins, 2005; Bechky, 2003b).

Existing studies on academic-industry partnerships suggest three major practices by which general academic scientists make their research available for the innovation process including disclosing knowledge through patents and publications, developing and promoting patents (including sitting on advisory board to consult), and starting a company. However, these practices are essentially ways of presenting academic discoveries to the public, and industrial entrepreneurs evaluate them in terms of their commercialization potential. The underlying assumption among these studies is that the academic scientists who participate in commercialization are driven by profits. I find that academic scientists engage in commercialization because they want to maintain control of the drug possibilities. These three practices need to be considered as interdependent because together they drive how academic knowledge flows into industrial innovation.

Furthermore, the commercialization process is set up in a linear structure, which makes it relatively low cost for firms and the industry to internalize academic research in the form of patents or start-up companies. However, it is rather difficult for academic scientists to bring their discoveries into innovation because of cost issues. The practices that academic scientists engage in to fulfill the evaluation criteria disrupt their day-to-day practices of knowing in research. For example, the process where academic scientists build a product family based on their discoveries requires an accumulation of research over many years. This process is not linear, nor is it straightforward and obvious. The challenge that academic scientists face is how to package potential products from their research when they do not know what they are going to find. For example, the use of a combination of genes to assess the risk of breast cancer recurrence could be a single product, but the expertise generated can be applied to development of similar products for colon or prostate cancer (Shimasaki, 2009). Because a discovery contains epistemic characteristics, its potential uses and functions continue to emerge over time. Scientists would not know how to package a discovery into different product categories unless they conduct the work, manipulate the discovery, and then talk to other experts, such as TTO, clinicians, or industry insiders. Academic scientists who participate in commercialization are often caught in the dilemma of whether to stay in academia or be fully committed to building the start-up.

Additionally, drug possibilities with the epistemic dimension contain unlimited number of questions, and it is a challenge to determine what questions are relevant to the application. Since industrial entrepreneurs possess financial capital and market knowledge, they may end up defining the questions that academic scientists pursue in

order to commercialize drug possibilities. For example, venture capital investors buy into the expected values of drug possibilities, which may both facilitate and constrain emerging new potentials (Bercowitz & Feldman 2006). Their funding principal is milestone based: they would tell academic scientists "if you can do X, Y, and Z, then we will give you N amount of money" (WS500089 panel). Venture capital[3] is a governance structure to create incentives for scientists to follow-up and develop findings. However, this is also a mechanism where industrial entrepreneurs determine the questions. If academic scientists diverge from the questions initiated by the entrepreneurs, they will eventually lose control of their funding and drug possibilities.

Lastly, biopharmaceutical companies rely on the patent system to reduce uncertainties and conduct a selection process within the company to determine which patents to internalize and develop further. For example, firms have regular meetings to discuss what technologies and products to develop in their portfolios. Even though a firm has already internalized a particular academic patent, the academic inventor worries about whether his patent has a champion in the company to make sure that the patent is next in line for development (WS500089 panel). If the academic technology does not have a champion or is not in the company's product development agenda, the technology would likely sit on a shelf and go undeveloped. Because the selection process has not been transparent, academic scientists do not always know what companies want and how they select the academic discoveries for commercialization. Moreover, venture capital investors and large pharmaceutical firms exercise the lowest level of risk tolerance as

---

[3] While venture capital usually lasts on average of 3 years, Pisano (2010) pointed out that the time-span of three years is too limited for the grunt work for drug discovery and development, as it usually takes at least 5-7 years. Therefore, academic scientists starting up a company to develop their discoveries are constantly seeking funding.

they select academic discoveries based on the potential patient population size, which determines the market volume of a potential product. In many aspects, venture capital firms echo the interests of large pharmaceutical companies when they evaluate academic discoveries. For example, large pharmaceutical companies and venture capital firms are desperately looking into the academic scientific community for new drug elements for Alzheimer's disease, due to the increasing population of aging individuals around the world. In short, information about a firm's internal selection process and preferences for market are unclear to academics, which make commercialization difficult.

Despite the discontinuities in practices and fragmented commercialization processes, the three dimensions of drug possibilities also provide insights about the social arrangements that would enable transformation of academic knowledge for complex innovation. I find that the three dimensions of knowing and objects together structure the complex space of creating, combining, and recombining knowledge for drug discovery. These dimensions constitute the common ground upon which all scientists, entrepreneurs, and business managers can collaborate. I propose that industrial entrepreneurs and scientists work along the activity dimension to define the purpose and direction that would determine a drug possibility's function, potential users, and markets. Transformation of academic knowledge would take place when research capabilities are bundled to address certain market needs. By involving industrial entrepreneurs in their day-to-day practice of research, academic scientists would be able to draw on their knowledge about markets and industry and thus align their understandings of biological mechanisms with commercial purposes and functions. I also propose that academic-industry partnerships are established for diseases, so that academic and industry scientists

would work along the materiality dimension by searching for the specific purpose of the drug possibility. Institutional arrangements between universities and firms have to be flexible so that academic and industry scientists can open up the emergent nature of the knowledge and be motivated to draw on rich scientific theories. When academic and industry scientists work closely in the lab, transformation of academic knowledge will take place when research questions are posed in a context and bring opportunities for situated learning. Lastly, I propose that social arrangements need to allow academic researchers to collaborate with a larger variety of experts that are not normally accessible to academics and there needs to have an alternative knowledge accumulation system to deposit knowledge produced from replicating experiments. I discuss the three propositions in details below.

## TRANSFORMING RESEARCH CAPABILITIES INTO PRODUCT INNOVATION

Transformation of academic knowledge occurs when research capabilities are bundled to address certain market needs. Because scientists are organized by questions, I propose industrial entrepreneurs to be actively involved in the day-to-day practice of defining questions with academic scientists. The current commercialization process for academic discovery is that academic scientists bring their discovery to the TTO and other industrial entrepreneurs decide whether those discoveries are commercializable or not. Academic scientists who are unfamiliar with conducting business with the industry could rely on industrial entrepreneurs to broker information. Consequently, instead of defining

the questions *with* them, industrial entrepreneurs are defining the questions *for* the scientists.

Industrial entrepreneurs could strategically frame potential market demands and align them with the scientists' "communal gap of knowledge." An experienced biotech entrepreneur, Dr. Craig Shimasaki (2009), said that no matter how novel and ground-breaking the science is, if there is not a significant viable industry market for the resulting product, it would almost be impossible to identify channels to develop drug discovery through to commercialization (p. 28). Industrial entrepreneurs, including university TTOs, are resources that help academic scientists identify their research capabilities to match market demands. TTO entrepreneurs knowledgeable about science can guide academic scientists to evaluate the question "Is there a viable product for this discovery," "Who would benefit from this product," and "Are there unmet needs that this potential product can address." This issue needs to be considered early on, even before the scientist applies for patents. When TTO entrepreneurs understand science research, they can guide the scientists' process of raising questions about the diseases in the direction of market needs. Gradually, their relationship would become a resource for academic scientists to identify the application, therapeutic function, and commercial purpose of their research directly.

More universities are establishing business alliance offices in addition to technology transfer offices, to establish connections with the industry. However, unless university entrepreneurs "tap into" the research of academic scientists and continuously frame research for innovation, creating bureaucratic units would not facilitate commercialization. In their paper, Dougherty and Dunne (2011) suggest that managers

continuously frame activities for innovation by bundling capabilities into businesses and matching those businesses with market opportunities, which is one of the principles for organizing knowledge ecologies for complex innovation. Because the product architecture cannot be pre-determined, managers must focus on the process and actively understand the firm's internal capabilities while connecting those competencies across disciplines to identify market opportunities. Like business managers, TTO entrepreneurs play a vital role in transforming research capabilities to product innovation by "matchmaking" academic researchers with industry projects. TTOs build relationships with biopharmaceutical companies and identify what companies need as market opportunities. At the same time, they could frame industry-oriented work as novel contributions to science in order to incentivize academic scientists to appreciate innovation objectives.

My data suggest that it is rather difficult for average academic scientists to grasp strategic framing including the goals of business enterprises or value creation for customers. A TTO director helps academic scientists appreciate industry-specific experiments as "investigating novel tools to understand different biology so that as the technology improves, the science proceeds" (WS500090 interview). To frame research activity for product innovation continuously, TTO entrepreneurs must be involved in the day-to-day practice of academic scientists, in tune with the research projects and specialization, and able to define how the research capability contains innovative values. Rather than waiting for academic scientists to approach the TTO, the TTO entrepreneurs can "tap into" academic research and help scientists establish connections between their research and diseases or opportunities for therapeutic application.

Furthermore, resources (i.e., financial capital, industry information, and social contacts) in the commercialization process are highly disorganized and unevenly distributed. The result is that academic scientists are discovering drug targets, potential compounds, or therapies in which large pharmaceutical companies are not interested, and biopharmaceutical firms cannot convene networks of academic scientists to collaborate. In a discussion panel on commercializing academic drug discovery, a medical doctor as well as a academic researcher who started up a company mentioned several times that, "I wish someone had told me what were the funding options, or someone could put all the information about the funding options, the appropriate intellectual property for technology, all in one slide" (WS500089 panel). This view is not one-sided. Representatives from large pharmaceutical companies found that "information in universities is siloed" or "information on faculty's websites or tech transfer offices website is not enough" (WS500040 panel discussion). There is actually no "road map" that guides academic scientists through the commercialization process that includes patent applications, selecting funding sources, and conducting market analyses. While academic scientists find it difficult to obtain direct information from the large companies and to understand market demands, biopharmaceutical firms also find it confusing to navigate faculty information across universities. Social arrangements need to enable dialogues in both directions, so that academic research can understand, what the industry and patient groups want and the industry can understand what academic researchers can accomplish.

## TRANSFORMING QUESTIONS IN THE PROCESS OF KNOWING

I propose that diseases could be a common ground for academic-industry partnerships, which would foster contextualized learning. Knowledge transformation would take place when questions about a specific drug element move to questions about how it interacts with other issues related to the disease. Because product specifications cannot be precisely defined for complex innovation systems and innovators are searching for answers in an open problem space (Simon 1996; Dougherty & Dunne 2012), questions about the connection between the object and disease context would give guidance on how to search in the open problem space. Given the complexity in human biology, there are an infinite number of ways to raise questions. When selecting a drug target for a disease, scientists could ask questions about fundamental mechanisms at a micro-level (e.g., what is the target's cell growth cycle, what signaling patterns does the target cell use), or questions about biochemical interactions at a macro-level (e.g., what kind of therapeutic effect will the drug have, is this target druggable for old-age patients). All these questions could be relevant and need to be included in the common ground of the academic-industry partnership.

When academic and industry scientists collaborate, their partnership organized by a particular disease context would allow them to explore both fundamental and pragmatic questions in various directions. Both academic and industry scientists do not find it intellectually satisfying when their partnerships are based on transactions. Academic scientists enter collaboration with the industry because it is important for them to know and develop a complete understanding of the drug possibility. Scientific techniques are the common language in the lab and scientists realize that they share similar scientific

rationales but for different purposes, one for expanding scientific knowledge and the other for product development. Academic and industry scientists working alongside each other in a lab "had fun together" (WS500013 interview), and they did not have problems working together and reaching a scientific consensus (WS500007; WS500061 interviews). Working in laboratories generates more opportunities for academic scientists to "fill in the gap" for the understanding of industry scientists because both would speak about what they want to know and what they do not know during informal interactions. Allen (1977) points out that as technology defines a problem for science, the advance of technology is also contingent upon the pursuit of "gap-filling science." When the connection between science and technology develops a close coupling for a short period, the transfer of knowledge would speed up, technology would find new solutions, and science would find new streams of research. Therefore, partnership arrangements set on a disease context with flexible coordination would be able to leverage the motivation of pursuing questions and foster more opportunities for "close coupling" between industry and academic scientists.

Furthermore, at the practice level, the transformation of academic knowledge would take place when questions about drug possibilities are contextualized, situated in specific biological situations, and drill into the connections between the drug possibilities and the human body. Having clinical experiences, industry scientists are more likely to define contextualized problems that reflect real-life events and they begin questions with defining an endpoint, which is how to treat the disease. Although they still ask open-ended questions to explore basic mechanisms, their goal is to change the state of a disease. Transformation of abstract knowledge takes place when the problem is defined

as how to achieve an effect (e.g., the desirable effect is to trigger autophagy; Grandori, 2010). For example, an open-ended question about autophagy would be "how does autophagy function," but a question that defines an endpoint would be "which biological pathway can inhibit autophagy in cancer cells?" This change of questions exemplifies a transformation of knowledge by moving the question about a drug element to the question about the element's interaction in a disease. A cancer biologist said, "if you start with a disease and connect the discovery with the disease, scientists can work their way back to see what are the causes or driving factors in the disease and how to block it" (WS500060 interview). A common ground that is organized by disease context would allow basic researchers who wish to collaborate more effectively to move their practices of knowing closer to those of the clinical scientists.

## TRANSFORMING "MOVING ON" INTO "FOLLOWING UP" WITH EMERGENT FINDINGS

Lastly, I propose that social arrangements for collaboration need to allow basic researchers to collaborate with a larger variety of experts including medicinal chemists, physiologists, and pharmacologists that are not normally accessible. Collaborative entities must also provide the lab equipment and facilities needed for validation, since basic researchers in universities often do not have access to the specialized (and expensive) equipment and expertise needed for validation studies. Working on drug possibilities as activity objects, collaborative basic researchers need to work more on validating specific discoveries in a variety of experimental settings (e.g., in animal and human models), rather than move on from one novel discovery to the next.

Transformation of academic knowledge for complex innovation would take place when a discovery is iteratively validated and replicated. Basic scientists are keen to identify a discovery but then they move on to new patterns, new mechanisms, and new scientific entities. Because of the "publish or perish" pressure on academic scientists, they may not feel the need to repeat experiments once they have identified a result.

However, because the system is complex, with unlimited possible outcomes, iteration is more than repetition; it can deliver new meanings out of the noise present in initial observations. A complex system also contains a large amount of information; therefore, making meaning out of information in an iterative manner becomes critical for understanding the complexity. For example, when a scientist conducts an experiment the first time, he only observes X, because his mind only accepts a certain level of complexity. When he conducts the same experiment iteratively, his skills get better and his mind can read a higher level of complexity and he observes $X_1$ and $X_2$, and he pays attention to Y and Z. Additional iteration would enable the scientist to not only confirm $X_{1, 2 \ldots n}$ with Y and Z, but also reinterpret known facts and make new interpretations from the high volume of information. Because we cannot eliminate uncertainty or prevent unpredictable events, the best way to "cope with the unknown and the unforeseen [is] by seeking not so much to predict as to act and transform" (Tsoukas 2005: p. 288). Tsoukas' argument is that complexity and randomness is also a kind of order, which can be made meaningful and by acting on the complex information, iterative validation, and interpretation allow transformation of randomness to order. Transformation of knowledge takes place through incorporating trial and error in the routine and making new assessments and adjustments for problem solving at the pragmatic boundary (Carlile

2004: p. 563)

Iteratively validating emerging patterns comes with a price, as experiments require significant time and money. As the data herein revealed, the lack of translational facilities and funding in the academic environment in addition to the "publish or perish" norm discourage these scientists from following up with emerging patterns through iterative validation studies. For example, from Chapter 5, a professor in molecular biology said, "you rarely repeat experiments" because spending time to learn new techniques sacrifices time to write papers and publish results. Academic scientists in general face a lack of incentive to validate finding because they are rewarded for being first to publish newly discovered findings. Moreover, iterative validation requires translational facilities and multidisciplinary teams of scientists and technicians to conduct the work. A professor in molecular physiology repetitively conducted his experiments by using different methods and technologies to assess the same observation because he was located in a research center with facilities and hospitals. Therefore, academic scientists without access to such facilities and techniques are less likely to follow up and iteratively validate emerging patterns so they would move on to finding new observations.

Another aspect that discourages academic scientists from iterative validation of data is that there is no institutional system that rewards them for conducting validation on their findings, and there is no outlet for them to publish those results. From Chapter 5, a cancer biology postdoc said that academic scientists tend to discover something and then publish it without taking it to preclinical trial. Bringing a drug possibility to a pre-clinical trial is not only very expensive, but also the results cannot be published in high-ranking journal. She said,

> Those results [from pre-clinical experiments] do not have real academic value when we publish it in some journal of toxicology or something. Even though those results would contribute to getting the regulatory documents together, it is not really valuable to academics. (WS500048 interview)

This comment highlights the lack of institutional mechanisms to incentivize academics to validate new findings for pre-clinical trials. Because academic scientists are recognized for publishing their discoveries in high-ranking journals, they are discouraged from repeating experiments that produce results that do not complete a "perfect story" for it is when the data is not perfect; scientists are forced to publish in low-ranking journals (Kahn, 2012).

The by-product of institutional reward through publication is that tacit knowledge, including negative findings, is not published and remains sitting in laboratories. Pisano points out that the "deeper understanding" from iterative validation may be critical to further development but it is generally not patentable, nor is it often publishable (Pisano, 2010: p. 474). The reason is that there is a lack of institutional mechanisms to accumulate practical knowledge other than through publication. For example, a pharmaceutical scientist specializes in neurodegenerative diseases commented that journals do not accept negative findings (WS500041 interview). Also, a neuroscience researcher said that lab notes are laboratory property and never are disclosed to the public. Even when a technician or post-doc leaves a lab, their notes remain with the principal investigators (WS500034 interview). The implication is that the publication system, which defines scientist rewards, does not encourage scientists to pursue emergent knowledge about drug possibilities, and there are no systematic mechanisms for accumulating validated results about drug possibilities.

Universities and biopharmaceutical companies are exploring creative ways to handle IP ownership. Industry-initiated drug discovery partnerships such as Pfizer's CTI are sharing 50% of the ownership with the university where the academic scientist works. More open-source consortiums are established to allow free deposition of and access to data. There is a gradual movement of changing IP management from the industry and academic scientists. It remains unclear as to how these top-down changes would influence the day-to-day practice of academic scientists, as we see that practices of patenting and publishing continue to compete with each other. Future research could continue to examine how these institutional forces impact science entrepreneurship and the day-to-day practice of knowing.

# Chapter 9: Conclusion

In this last chapter, I will conclude with my contributions and suggestions for future research. By drawing on the pluralistic framework of objects, I delineated the three dimensions of knowledge boundary for drug possibilities as a way to characterize the substance and content of knowledge in bio-pharmaceutical research. The three-dimension framework contains important theoretical and practical contributions. As a theoretical contribution in innovation management, my theory strengthens our understanding about how and why collaborations in complex, science-based innovation are challenging, and how to deal with those challenges. Although the knowledge is complex, it is not incoherent and ill structured, but actually contain material, epistemic, and activity dimensions. There may be additional dimensions exist in this complex innovation, but these are the central ones, which can also be applied to other kinds of complex, science-based innovation. Also, these three dimensions can be generalized to reveal commonalities and conflicts between scientists, business managers, investors, and regulators in drug innovation.

For practice, the three dimensions contribute to a deeper understanding about how to organize collaboration among scientists, entrepreneurs, managers, and regulatory agencies for drug discovery and development. The material dimension drills down into the complex functioning of the human biology and diseases, and the challenge is to define the specific purpose for a drug possibility among the complex interdependencies in biology. In practice, local and international research consortiums can focus on specific diseases in order to provide an intellectual space for scientists and clinicians across multiple disciplines and identify new therapeutic possibilities. The epistemic dimension

opens up the ever-emergent nature of the knowledge that motivates scientists to keep asking questions and drawing on rich scientific theories to answer them. The innovation challenge associated with this dimension is to decide which paths to explore. To put into practice, communities such as venture philanthropists and industrial scientists can help frame paths of inquiry, identify good questions, and make sense of results. Lastly, the activity dimension directs the purpose of knowing and guides the direction of multidisciplinary collaboration among scientists, but the challenges are the uneven resources for commercialization and the intellectual property arrangements with the industry. There is a grass-root movement among academic and industrial scientists to promote open-source data depository platforms and regional research networks, which may encourage data sharing and provide alternative institutional mechanism to accumulate knowledge. The three dimensions can be drawn as common grounds for collaboration among different communities in the drug discovery ecologies. All these possibilities require additional study.

The limitations of the data from interviews and field observation open up future research directions. I was unable to directly observe academic and industrial scientists working side-by-side, and the interviews with the scientists only revealed their memories from working with each other. Future studies can collect field observation at scientific conferences, seminars, and workshops to directly observe their interactions. In addition, the materiality and activity dimensions need more research. For example, I find that hands-on manipulations are an important part of the materiality dimension. I also find that a routine of iterative verification as practiced by clinical researchers would help identify new alternatives. These everyday processes are very tacit, based on experience,

and developed idiosyncratically by individual scientists. Ethnographic research that looks very closely at routines and physical surroundings with laboratory infrastructure would add more important insights to the two dimensions.

Lastly, my study not only pinpoints the limitations of using patent transactions to transfer academic knowledge for industrial innovation, but also shows evidence that alternative forms of academic-industry partnerships have emerged. The practices of knowing drug possibilities involve processes that are very tacit and require intimate understanding of specific disease contexts. Relying solely on patents as the main mechanisms of knowledge transfer not only restricts transferring of tacit knowledge, but also limits the opportunities to explore new alternatives and possibilities for new solutions. As seen in my data, new models of academic-industry partnership in drug discovery will continue to emerge, including pre-competitive research consortiums and disease-focused venture philanthropy foundations. Future research can explore how these new models operate, how communities of scientists accumulate knowledge through these models, and how these models enforce or modify the institutional norms of science. These new models that depart from linear patent transactions between universities and the industry will provide vast opportunities for research in innovation management.

## List of Tables

Table 1: Number of interviews with subjects based on their institutional affiliations.

| **Interviews** | **Counts** |
|---|---|
| Academics Scientists | 34 |
| Academics previously worked in industry | 8 |
| Industry Scientists | 10 |
| TTO directors | 3 |
| Group Discussion | 4 |
| Total Data Points | 59 |

Table 2: Description of the science conferences and meetings attended.

| **Conference topic** | **Orientation** | **# of panel discussions** | **# of days** |
|---|---|---|---|
| Animal models for drug discovery | Industry & academic | 3 | 2 |
| Personalized Medicine | Academic | 1 | 1 |
| Epigenetics for Alzheimer's Disease | Academic | 1 | 1 |
| Academic- industry partnership | Industry & academic | 1 | 1 |
| Translational medicine | Academic | 4 | 2 |
| Brain barrier for neurological diseases | Academic | 1 | 1 |
| Drug Discovery | Academic | 2 | 1 |
| Pre-symptomatic markers for Alzheimers' | Academic | 2 | 1 |
| Cancer Metabolomics | Academic | 2 | 1 |
| Drug Discovery for Alzheimer's | Academic | 3 | 2 |

Table 3: Drug possibilities as pluralistic objects.

| Dimensions of drug possibilities | Definitions | Innovation challenge |
|---|---|---|
| **Materiality** | • Concrete observable structure<br>• Context-dependent to fulfill a specific purpose in the body<br>• Require hands-on manipulation | • Define a specific purpose for the drug among the complex interdependencies in the human biology |
| **Epistemic** | • Emerging characteristics<br>• Trigger questions<br>• Fuel cross-disciplinary collaboration | • Facing unlimited number of questions and not knowing which question to pursue |
| **Activity** | • Direct a purpose to the ongoing work<br>• Shifting across different experimental settings<br>• Reduce uncertainties | • Make sure that the same thing work in animals also work in humans |

Table 4: Discontinuities of practices between basic and clinical researcher.

| Dimensions of drug possibilities | Practices of basic research | Practices of clinical research |
|---|---|---|
| **Materiality** | • Distant from a disease | • Situated in a disease |
| **Epistemic** | • Open-ended questions | • Relational questions |
| **Activity** | • Move on from emerging patterns | • Follow up with emerging patterns |

Table 5: Practices of commercialization to fulfill the evaluation criteria.

| **Evaluation Criteria** | **Industrial Entrepreneurs** | | | |
|---|---|---|---|---|
| | **TTO** | **Venture Capital** | **Venture Philanthropy** | **Pharmaceutical firms** |
| **Materiality** Monetizing mechanisms | • Patents<br>• Start-ups | • Patents<br>• Start-ups | • No monetization of the intellectual property | • Patents<br>• Start -ups |
| **Epistemic** Legitimacy of the questions for science and for innovation | • Patents<br>• Publications | • A complete patent family<br>• The technical soundness of the start-up | • Publications<br>• Novel drug elements or possibilities for a specific disease area | • An attractive package (with patents, data from pre-clinical experiments) |
| **Activity** Defining potential markets and users | • Identify potential licensors before patent application | • Present business proposal<br>• Target big therapeutic areas (i.e., CNS, cancer, diabetes) | • Application to foundation, present work at conferences | • Need champions and connections |

Table 6: Four models of academic- industry partnerships

| Models of academic-industry partnership | Linear Model | Academic medical centers | Industry-initiated Partnership | Disease-Focused Venture Philanthropy |
|---|---|---|---|---|
| **IP ownership** | • University holds the IP | • AMC holds full IP | • Joint ownership | • No IP ownership |
| **Publication policies** | • Limited publication on the company's proprietary material | • No limitation | • Minimum limitation; company reviews and approves 30 days before submission | • No limitation |
| **What kinds of discovery get selected** | • Depends on the company's strategy, capabilities | • Specialized biopharmaceutical company; specific patient populations | • Depends on the company's therapeutic focus, and its product portfolio | • Disease specific; specific patient populations |
| **Governance (i.e., coordination, organization of work)** | • One-time transaction<br>• Academic scientists look for partners through the market | • Hierarchy<br>• Multi-disciplinary teams<br>• Affiliated with hospitals | • Hybrid<br>• Company has multi-disciplinary teams<br>• Co-locate to share lab space | • Network-based<br>• Convenes experts to study the drug possibility<br>• Connect the scientists with Pharma or VC |
| **Stage of TTO's involvement** | • Later stage when faculty has identified potential licensors | • Early to define potential markets, buyers, IP and regulatory strategies | • Early<br>• Set up "master agreement" | • Minimum involvement |

Table 7: Practices of knowing under which academic and industry scientists collaborate in the four models

| | **Linear model** | **Academic Medical Centers** | **Industry-Initiated Partnerships** | **Disease Focused Venture philanthropy** |
|---|---|---|---|---|
| **Materiality**<br>1) Developing a product vision<br><br>2) Contextualized learning | • Limited learning<br>• Limited knowledge about the proprietary product | • Develop drug possibilities "best shape possible"<br>• Bring the drug possibility to the market | • Learn to translate drug possibilities *in vitro, in vivo*, to human<br>• Work side-by-side | • Deliver drug possibilities to patients |
| **Epistemic**<br>1) Collectively decide on questions<br><br>2) Make decisions together | • Experiments defined by the industry | • Multi-disciplinary teams decide on go/ no-go decisions | • Proof of principal between drug possibilities and a disease | • Validate the connections between drug possibilities and the disease |
| **Activity**<br><br>1) Flexible contracts to access facilities<br><br>2) IP ownership | • Companies supply the material<br>• Disagree on publishing policies | • Translational facilities for pre-clinical experiments<br>• Licensing patents to industry | • Validate the drug possibility for therapeutic purpose<br>• Joint IP ownership | • Access the foundation's network and facilities<br>• No holding of IP |

## Bibliography

Allen, T. J. (1977). Managing the Flow of Technology. Boston, MA, MIT Press.

Amann, K., and K. Knorr Cetina (1990). The Fixation of (visual) Evidence. Representation in Scientific Practice. M. a. S. W. Lynch. Boston, MA, The MIT Press.

Arora, A., A. Fosfuri, and A. Gambardelle (2001). Markets for technology: The economics of innovation and corporate strategy. Cambridge, MA, The MIT Press.

Bailyn, L. (1977). "Research as a cognitive process: Implications for data analysis." Quality and Quantity **11**(2).

Bartel, C., and Raghu Garud (2009). "The role of narratives in sustaining organizational innovation." Organization Science **20**(1).

Bechky, B. (2003a). "Sharing meaning across occupational communities: the transformation of understanding on a production floor." Organization Science **14**(3): 312- 330.

Bechky, B. (2003b). "Object Lessons: workplace artifacts as representation of occupational jurisdiction." American Journal of Sociology **109**(3): 720-752.

Begley, S., and Carmichael, Mary (2010). "Desperately seeking cures: How the road from promising scientific breakthrough to real-world remedy has become all but a dead end." Newsweek **155**(22).

Bercovitz, J. E. L., and Maryann P. Feldman (2006). "Entrepreneurial universities and technology transfer: A conceptual framework for understanding knowledge-based economic development." Journal of Technology Transfer **31**: 175-188.

Bercovitz, J. E. L., and Maryann P. Feldman (2007). "Fishing upstream: Firm innovation strategy and university research alliances." Research Policy **36**: 930-948.

Boisot, M., and Bill McKelvey (2010). "Integrating Modernist and Post-modernist Perspectives on Organizations: A Complexity Science Bridge." Academy of Management Review **35**(3): 415-433.

Brown, J. S., and Paul Duguid (1991). "Organizational Learning and Communities- of-Practice: Toward a unified view of working, learning, and innovation." Organization Science **2**(1).

Carlile, P. (2002). "A pragmatic view of knowledge and boundaries: Boundary objects in new product development." Organization Science **13**(4).

Carlile, P. (2004). "Transferring, translating, and transforming: An integrative framework for managing knowledge across boundaries." Organization Science **15**(5): 555-568.

Cheng, Y. T., and A. Van de Ven (1996). "Learning the innovation journey: Order out of chaos?" Organization Science **7**(6).

Cockburn, I. M., and Rebecca M. Henderson (1998). "Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery." The Journal of Industrial Economics.

Cockburn, I. M., and Rebecca M. Henderson (2001). Publicly Funded Science and the Productivity of the Pharmaceutical INdustry. Innovation Policy and the Economy. A. Jaffe, and Josh Lerner, and Scott Stern. Boston, MA, MIT Press. **1**.

Collins, F. (2011). "Re-engineering translational science: the time is right." Science Translational Medicine **3**(90).

Colyvas, J., and Michael Crow, Annetine Gelijns, Roberto Mazzoleni, Richard Nelson, Nathan Rosenberg, and Bhaven Sampat (2002). "How do university inventions get into practice? ." Management Science **48**(1).

Cook, S., and John Seely Brown (1999). "Bridging Epistemologies: The Generative Dance Between Organization Knowledge and Organizational Knowing." Organization Science **10**(4).

Corbin, J., and Anselm Strauss (2008). Basics of Qualitative Research, Sage Publications, Inc.

Dasgupta, P., and P. David (1994). "Toward a new economics of science." Research Policy **23**.

Dougherty, D., and Daniellete Dunne (2011). "Organizing Ecologies of Complex Innovation." Organization Science **22**(5): 1214-1223.

Dougherty, D., and Daniellete Dunne (2012). "Digital Science and Knowledge Boundaries in Complex Innovation." Organization Science **23**(5).

Dunne, D., and Deborah Dougherty (2010). "Searching for Clues: A process theory of exploratory product innovation." working paper.

Ferlie, E., L. Fitzgerald, M. Wood., and C. Hawkins (2005). "The non-spread of innovations: The mediating role of professionals." Academy of Management Journal **48**(1).

Firestein, S. (2012). Ignorance: how it drives science. New York, Oxford University Press.

Fishburn, C. S. (2013). "Translational Research: The changing landscape of drug discovery." Drug Discovery Today.

Frye, S., M. Crosby., T. Edwards., and R. Juliano (2011). "U.S. Academic Drug Discovery." Nature Reviews: Drug Discovery **10**: 409-410.

Garud, R., and Cynthia Hardy, Steve Maguire (2007). "Institutional Entrepreneurship as Embedded Agency: An Introduction to the Special Issue." Organizational Studies **28**(7).

Gittelman, M., and Bruce Kogut (2003). "Does Good Science Lead to Valuable Knowledge? Biotechnology Firms and the Evolutionary Logic of Citation Patterns." Management Science **49**(4): 366-382.

Gittelman, M. (2007). "Does Geography Matter for Science-Based Firms? Epistemic Communities and the Geography of Research and Patenting in Biotechnology." Organization Science **18**(4): 724-741.

Gittelman, M. (2009). "Fortune Favors the Well-Located Firm: Absorptive Capacity and the Geography of Inter-firm alliances." **under review**.

Gittelman, M. (2012). The revolution that never arrived: Clinical and genetic paradigms in bio-medical discovery and the R&D productivity paradox. Working paper.

Grandori, A. (2010). "A rational heuristic model of economic decision making." Rationality and Society **22**(4).

Grinnell, F. (2009). Everyday Practice of Science: Where Intuition and Passion Meet Objectivity and Logic. NY, Oxford University Press.

Hubel, A., and Thilo Schmelcher, and Ulrich Storz (2012). Biopatent Law: Patent Strategies and Patent Management. Duesseldorf, Springer.

Jaffe, A. (1986). "Technological opportunity and spillovers of R&D: Evidence from firms' patents, profits and market value." American Economic Review **79**.

Jaffe, A., and Manuel Trajtenberg, and Rebecca Henderson (1993). "Geographic Localization of Knowledge Spillovers as Evidence by Patent Citations."

Kahn, J. (2012). "Connecting the dots in translational research." Nature Reviews Drug Discovery **24**.

Kaplan, S., and Fiona Murray (2008). "Entrepreneurship and the construction of value in biotechnology." Research in the Sociology of Organizations.

Knorr Cetina, K., and Urs Bruegger (2000). "The market as an object of attachment: Exploring postsocial relations in financial markets." Canadian Journal of Sociology **25**(2).

Knorr Cetina, K. (2001). Objectual practice. The Practice Turn in Contemporary Theory. T. Schatzki, and Knorr Cetina, K., and von Savigny, E. London, United Kingdom, Routledge.

Knorr-Cetina, K. (1999). Epistemic Cultures: how the sciences make knowledge. Cambridge, Harvard University Press.

Latour, B., and Steve Woolgar (1986). Laboratory Life: The construction of scientific facts. Princeton, New Jersey, Princeton University Press.

Lawrence, T., and Suddaby, R (2006). "Institutional work". Handbook of Organizational Studies. C. H. S. Clegg, and T. Lawrence London, Sage

Leonard- Barton, D. (1992). "Core Capabilities and Core Rigidities: A Paradox in Managing New Product Development." Strategic Management Journal **13**.

Liebeskind, J. P., and Amalya L. Oliver, Lynn Zucker, and Marilynn Brewer (1996). "Social Networks, Learning, and Flexibility: Sourcing Scientific Knowledge in New Biotechnology Firms." Organization Science **7**(4).

Locke, K., K. Golden-Biddle, and M. S. Feldman (2008). "Making doubt generative: Rethinking the role of doubt in the research process." Organization Science **19**(6): 907-918.

McGahan, A. (2007). "Academic Research That Matters to Managers: On Zebra, Dogs, Lemmings, Hammers, and Turnips." Academy of Management Journal **50**(4).

McGivern, G., and Sue Dopson (2010). "Inter-epistemic power and transforming knowledge objects in a biomedical network." Organization Studies **31**: 1667- 1686.

Merton., R. K. (1973). The sociology of science: Theoretical and Empirical Investigations. Chicago, IL, Chicago Press.

Milne, C. P., and Ashley Malins (2012). Academic-Industry Partnerships for Biopharmaceutical Research and Development: Advancing Medical Science in the U.S. Boston, MA, Tufts Center for the Study of Drug Development, Tufts University School of Medicine.

Mowery, D., and Bhaven N. Sampat (2005). University in national innovation systems. The Oxford Handbook of Innovation. D. Mowery, and Bhaven Sampat. Oxford, Oxford University Press.

Murray, F. (2002). "Innovation as Co-evolution of Scientific and Technological Networks: Exploring tissue engineering." Research Policy **31**: 1389-1403.

Murray, F. (2004). "The role of academic inventors in entrepreneurial firms: sharing the laboratory life." Research Policy **33**: 643-659.

Murray, F., and Siobhan O'Mahony (2007). "Exploring the Foundations of Cumulative Innovation: Implications for Organization Science." Organization Science **18**(6): 1006-1021.

Nicolini, D., and S. Gherardi, D. Yanow (2003). Introduction: Toward a practice-based view of knowing and learning in organizations. Knowing in Organizations: A Practice-based Approach. D. NIcolini, and S. Gherardi, D. Yanow. New York, M.E. Sharpe.

Nicolini, D., and Jeanne Mengis, Jacky Swan (2011). "Understanding the role of objects in cross-disciplinary collaboration." Organization Science(Articles in advance): 1-18.

Orlikowski, W. (2002). "Knowing in Practice: Enacting a Collective Capability in Distributed Organizing." Organization Science **13**(3): 249-273.

Owen-Smith, J., and Walter Powell (2004). "Knowledge Networks as Channels and Conduits: The Effects of Spillovers in the Boston Biotechnology Community." Organization Science **15**(1): 5-21.

Pisano, G. (2006). Science Business: the promise, the reality, and the future of biotech Boston, MA, Harvard Business School Press.

Pisano, G. (2006). "Profiting from innovation and the intellectual property revolution." Research Policy **35**: 1122-1130.

Pisano, G., and David J. Teece (2007). "How to capture value from innovation: Shaping intellectual property and industry architecture." California Management Review **50**(1).

Pisano, G. (2010). "The evolution of science-baed business: innovating how we innovate." Industrial and Corporate Change **19**(2): 465- 482.

Powell, W. W., Koput, K.W. and Smith-Doerr, L. (1996). "Inter-organizational collaboration and the locus of innovation: networks of learning in biotechnology." Administrative Science Quarterly **41**: 116-145.

Prinz, F., T. Schlange, and K. Asaullah (2011). "Believe it or not: How much can we rely on published data on potential drug targets? ." Nature Reviews: Drug Discovery **10**(712).

Scannell, J., Blanckley, A., Bolden, H., and Warrington, B (2012). "Diagnosing the Decline in Pharmaceutical R&D Efficiency." Nature Reviews Drug Discovery **11**: 191-200.

Sennett, R. (2008). The Craftsman. New Haven, Yale University Press.

Shane, S., and T. Stuart (2002). "Organizational endowment and the performance of university start-up." Management Science **48**(1).

Shimasaki, C. D. (2009). The business of bioscience: what goes into making a biotechnology product. New York, Springer.

Simon, H. (1996). The Sciences of the Artificial. Cambridge, MA, MIT Press.

Singleton, R. A. J., and Bruce Straits (2005). Approaches to Social Research. New York, Oxford University Press.

Smith-Doerr, L. (2005). "Institutionalizing the Network Form: How Life Scientists Legitimate Work in the Biotechnology Industry." Sociological Forum **20**(2).

Star, S. L., and James R. Griesemer (1989). "Institutional Ecology, "translations" and Boundary Objects: Amateurs and Professionals in Berkeley's Museum of Vertebrate Zoology, 1907-39." Social Studies of Science **19**: 387-420.

Star, S. L. (2010). "This is not a boundary object: reflections on the origin of a concept." Science, Technology and Human Values **35**(601).

Stokes, D. E. (1997). Pasteur's Quadrant: Basic Science and Technological Innovation. Washington, D.C. , Brookings Institution Press.

Tessier-Lavigne, M. (2011). Memorial Sloan-Kettering Academic Convocation. Memorial Sloan-Kettering Center News Magazine. New York, Memorial Sloan-Kettering. **October**.

Thagard, P. (2000). How scientists explain disease. Princeton, New Jersey, Princeton University Press.

Thursby, J. G., and R. Jensen, and M. Thursby (2001). "Objectives, characteristics and outcomes of university licensing: A survey of major U.S. Universities." Journal of Technology Transfer **26**: 59-72.

Tornatzky, L. G., and Fleisher, M (1990). The Process of Technological Innovation, Lexington Books.

Tralau-Stewart, C., and Colin A. Wyatt, Dominique E. Kleyn and Alex Ayad (2009). "Drug discovery: new models for industry-academic partnerships." Drug Discovery Today **14**(1/2).

Tsoukas., H. (2005). Complex Knowledge: Studies in organizational epistemology. Oxford, Oxford University Press.

Tullock, G. (1966). The organization of inquiry. Durham, North Carolina, Duke University Press.

Zucker, L. G., and Michael Darby, and Jeff Armstrong (1994). "Intellectual Capital and the Firm: The Technology of Geographically Localized Knowledge Spillovers." NBER Working Paper Series # 4946.

Zucker, L. G., and Michael Darby, and M. Brewer (1998). "Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises." American Economic Review **88**.

Zucker, L. G., and Michael Darby, and Jeff Armstrong (2002). "Commercializing knowledge: university science, knowledge capture, and firm performance in biotechnology." Management Science **48**(1).

Yun Su
Rutgers University, Department of Management & Global Business
1 Washington Park Newark, NJ 07102
yunsu@pegasus.rutgers.edu USA: 646.241.4368

## DATE AND PLACE OF BIRTH

August 5, 1979
Taipei, Taiwan

## EDUCATION

**Taipei American School, Taipei, Taiwan, May 1998**
High School Diploma

**New York University, New York, May 2002**
B.A., Economics and Sociology

**New York University, New York, 2005**
M.A., Economics

**Columbia University, New York, 2008**
M.A., MPhil. Sociology

**Rutgers University, New Jersey (expected May, 2013)**
Ph.D. Candidate, Major: Organization Management
Minor: Strategic Management

## PUBLICATIONS

Dougherty, D. Yun Su and K. Chung (2012). Qualitative Research and Data Analysis in *Empirical Methods for Research in Organization and Management* 2nd edition (in Chinese), edited by Chen, Xiao-Ping., and Anne Tsui and Larry Farh

## RESEARCH EXPERIENCE

05/ 2004- 09/ 2004. Research assistant. Institute of Economics, Academia Sinica, Taipei, Taiwan. Professor Shin-Kun Peng, Research Fellow and Deputy Director.

09/ 2006- 05/ 2007. Research assistant. Department of Sociology, Columbia University, New York. Contributed to a book project, White, Harrison (2008). *Identity and Control: How social formations emerge*. Princeton University Press., Princeton, New Jersey.

05/ 2009 – 09/2009. Research assistant. Department of Management and Global Business, Rutgers University, New Jersey. Organized and reviewed qualitative data, Professor Deborah Dougherty.