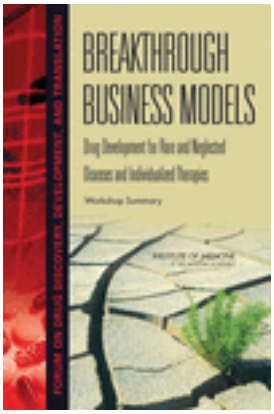

Breakthrough Business Models: Drug Development for Rare and Neglected Diseases and Individualized Therapies: Workshop Summary

Theresa Wizeman, Sally Robinson, and Robert Giffin, Forum on Drug Discovery, Development, and Translation, Institute of Medicine

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6

Strategies for Navigating Intellectual Property

The new models for funding research and sharing materials and data discussed previously necessitate newer and more effective strategies for addressing issues of intellectual property. An overview of the current intellectual property environment for rare disease research was provided to set the stage for three complementary panel perspectives: one from industry; one from a patient-led, disease-specific foundation; and a third from the technology transfer office of a major research university. An overview of the strategic alliance and intellectual property strategies of each of these organizations is provided in Box 6-1.

OVERVIEW: CREATING AN ENABLING INTELLECTUAL PROPERTY ENVIRONMENT FOR RARE AND NEGLECTED DISEASES[1]

The ownership and sharing of knowledge play an important role in scientific innovation, drug development, and the creation of affordable access to health technologies. Establishing intellectual property rights protects proprietary interests so that sufficient financial incentive exists to fuel innovation. By definition, however, drugs for rare and neglected diseases serve small or resource-limited markets, and market exclusivity may be less lucrative. Dr. So and other presenters in this session discussed how

[1]This section is based on the presentation of Anthony So, M.D., Professor of the Practice of Public Policy Studies and Director, Program in Global Health and Technology Access, Terry Sanford Institute of Public Policy, Duke University.

BOX 6-1
Managing Strategic Alliances, Licensing, and Intellectual Property: Company, Foundation, and University Perspectives

VERTEX PHARMACEUTICALS
Founded in 1989 by current Chairman, President, and CEO Joshua Boger, Ph.D, Vertex has more than 1,200 employees across three research and development sites in Cambridge, Massachusetts; San Diego, California; and Oxford, United Kingdom.

Goals
- To build a major drug company through the development and commercialization of both Vertex-driven products and products developed in collaboration with major pharmaceutical companies.
- To identify more efficiently promising drug candidates that address significant unmet medical needs.

Lessons Learned for Alliance Partners
Coordinating partner (customer)
- Provide intellectual incentives for partner.
- Avoid harsh or inappropriate acquisitiveness.
- Listen, and welcome new ideas or approaches.
- Be patient, and expect to walk before running.
- Explicitly define (and quantify) any dissatisfactions.
- Do not assume anything about the partner.
- Find the right balance of parallel and serial actions.
- Meet the partner team and maximize face-to-face communications.
- Be aware that sometimes it really is best to let partners do it their way.

Executing partner (vendor)
- Allow no internal commercial conflicts.
- Solve operational problems with confidence.
- Communicate troubleshooting strategies.
- Strive to demonstrate wise independence.
- Don't be afraid to ask clarifying questions.
- Don't be afraid to suggest changes or innovations.
- Remember execution problems are yours to solve.
- Constantly inquire to recalibrate partner priorities.
- Listen for when partners really must have it done their way.

Cross-cutting
- Be honest and aware of your own strengths and weaknesses.
- Understand your partner's culture and personality.
- Adapt your communication style to the partner's personality.
- Define roles and metrics of success clearly and explicitly.

http://www.vpharm.com

THE MYELIN REPAIR FOUNDATION (MRF)
Founded in 2002 by a multiple sclerosis (MS) patient, MRF is dedicated to discovering and developing effective treatments for MS.

Structure
MRF is run like a start-up business, designed to maximize results, minimize costs, and prioritize scientific quality. Targets are validated; steps are taken to protect intellectual property; and a partnership for development is then formed with a biopharmaceutical company, with the goal of translating discoveries into clinical trials within 5 years.

The MRF Collaborative Research Process®
Rather than trying to understand MS in its entirety, MRF is focused exclusively on understanding how the body produces myelin, how MS disrupts this process, and how the body's natural ability to repair myelin can be restored. MRF has assembled an interdisciplinary team of leading scientists, laboratories, and institutions, and provides them with a collaborative infrastructure that allows them to identify and validate promising therapeutic candidates quickly. MRF establishes milestone-driven sponsored research agreements with all of the participating universities, negotiating critical terms up front, defining goals and objectives clearly, and including partners in the planning process. MRF makes its Collaborative Research Process® available to other medical research organizations to help them increase productivity and decrease time to market for new treatments.

http://www.myelinrepair.org

UNIVERSITY OF CALIFORNIA AT BERKELEY, OFFICE OF INTELLECTUAL PROPERTY AND INDUSTRY RESEARCH ALLIANCES (IPIRA)
IPIRA was created in 2004 to provide a single entry point for industry research partners to interact with University of California at Berkeley (UC Berkeley) research programs.

Structure
Two offices report to the Assistant Vice Chancellor for IPIRA, ensuring coordination:

- The Office of Technology Licensing in IPIRA engages in "technology push," patenting and copyrighting intellectual property and licensing patent rights and copyrights to the private sector for commercial development.
- The Industry Alliances Office in IPIRA is engaged in "technology pull," bringing personnel, materials, and resources back into UC Berkeley from the private sector.

Relationship Model of Technology Transfer
Technology transfer is part of a relationship continuum, with many points of interaction and engagement with multiple parties over time. Partnerships and collaborations are critical to success. In a successful transaction:

continued

BOX 6-1 Continued

- Rights and knowledge flow in both directions.
- Acceleration, innovation, translation, and deployment are enabled.
- The impact of the research is maximized. IPIRA engages in double-bottom-line accounting, considering social impact to be as important a metric as financial gain.

IPIRA employs a full spectrum of intellectual property management strategies, from gifting, where there are no intellectual property considerations, to sponsored research agreements, which are intellectual property–intensive. Different approaches can be applied for different purposes, and a given activity is not undertaken at the expense of another.

UC Berkeley Socially Responsible Licensing Program (SRLP)
Owners of intellectual property must demonstrate good stewardship of intellectual property rights, using the resources for public benefit and societal change. Helping the developing world is a moral imperative, and countries with resources should help those that are resource poor. The Berkeley SRLP:

- Maximizes the societal impact of Berkeley research, especially in the developing world.
- Brings resources for research to Berkeley in exchange for the future grant of a nonexclusive royalty-free license in defined locations.
- Allows the university to elect not to patent, or to patent only in certain locations.
- Stimulates funding from a broader base of research support.
- Shares revenue or other benefits with collaborators, including indigenous peoples and communities that contribute local knowledge, and gives proper attribution to collaborators or sources.

http://www.ipira.berkeley.edu

creative management of intellectual property rights can serve both public and private interests relative to rare diseases of industrialized countries and neglected diseases endemic to developing countries.

The typical market life cycle of a drug begins with a period of sunken research and development (R&D) investment, followed by a period of return on investment after the drug enters the market. The return on investment diminishes as competing products enter the market, and is exacerbated when generic competition begins upon expiration of the patent period.

The system of innovation in the United States is driven largely by intellectual property. In addition to protecting proprietary knowledge that might hold off competition, intellectual property rights impact the affordability of patented end products, even when there has been significant public

funding of their development. To address the latter problem, a variety of largely public and philanthropic funding models or financing mechanisms have evolved. These models and mechanisms can be considered broadly in two categories. The first is push mechanisms—paying for inputs into the research process. The usual push solutions have included National Institutes of Health (NIH) and other research grants, as well as R&D tax credits; panelist Carol Mimura of the University of California at Berkeley illustrated an innovative approach involving "bootstrap philanthropy."[2] Another example is licensing a drug to an entity that can produce it at reduced cost, such as a company in the developing world, rather than to a large private-sector company. Alternatively, there are pull mechanisms that work to pay for the outputs of R&D processes. One model is advanced market commitments that guarantee revenue return, such as those for vaccines for developing countries. Other pull mechanisms involve prizes and patent buyouts. In exchange for the prize awarded, the intellectual property might be licensed for generic production, which could create competition among multiple firms, or it could be adapted by others for better targeted use in developing countries.

When considering intellectual property, one must take into account the multiple layers of innovation: scientific collaborations, data sharing, material transfers, and, of course, patents and licenses. So offered two questions for consideration as the various model approaches were presented by the panel. First, does the approach improve the access to and use of intellectual property case by case or more systematically? Craig Sorsensen of Vertex Pharmaceuticals discussed the value of pooling intellectual property, creating an opportunity to move beyond the case-by-case approach and transform how scientific communities work together, particularly in the precompetitive stage. Second, does the approach improve the access to and use of intellectual property in one layer of innovation or in multiple layers at the same time? Rusty Bromley of the Myelin Repair Foundation described a model in which norms established early in the scientific collaboration layer may extend downstream in the R&D process.

Dual Markets

For rare and neglected diseases, there is too often a reliance on dual markets, whereby a higher-paying or sufficiently large market allows for a second market segment in which a product might be priced more affordably. The product might be produced because of sufficient economies of scale in the first market, or the patent license might be treated differently,

[2] "Bootstrap philanthropy" is a term used to describe funding for a start-up or other new enterprise that comes from a charitable source, such as a foundation.

perhaps royalty-free, in the second market. The larger market could be in an industrialized country, a veterinary market, or another application of the technology. So provided three examples of serendipitous dual markets: ASAQ, a new malaria combination drug that segments the market by price; eflornithine, a product that has different uses in industrialized and developing-country markets; and a nonprofit vaccine firm that seeks to license its intellectual property differently in industrialized and developing countries (see Box 6-2).

Normative Influences

Key stakeholders, including funders, universities, product development partnerships, and industry, all play a role in shaping innovative arrangements. Normative influences on each of these stakeholders help create an enabling intellectual property environment for neglected and rare diseases. Funders can play a key role in shaping this environment through guidance to grantees and grant agreements. Under guidance entitled "The Bermuda Rules," for example, the Wellcome Trust and NIH encouraged the leading sequence centers for the Human Genome Project to deposit all sequence stretches of greater than 1,000 base pairs in the publicly available GenBank database within 24 hours of completion of sequencing. This guideline maximizes access to gene sequences and discourages patenting of sequenced genes.

Some grant agreements have humanitarian access provisions. Under grant agreements for point-of-care HIV/AIDS diagnostics in resource-limited settings with a host of institutions, the Doris Duke Charitable Foundation (DDCF) retained a nonexclusive, royalty-free, irrevocable license to inventions arising from DDCF-funded research to meet the charitable objective of ensuring affordable access to those HIV/AIDS monitoring technologies in developing countries. DDCF also retained the ability to sublicense any resulting intellectual property to ensure that the affordable care objective would be met. More recently, the Gates Foundation has put forth related principles in sample language for its global access agreements (see Box 6-3). In his presentation, summarized below, Bromley described how his patient-led, disease-specific foundation sets the norms in its scientific community.

Some universities have institutional policies supporting access for neglected diseases, and some have completed licensing agreements that offer examples of humanitarian access provisions for developing countries. In her presentation, summarized below, Carol Mimura of the University of California at Berkeley gave examples of the university's socially responsible licensing.

Industry has expressed concern about overlapping patent protections,

BOX 6-2
Examples of Serendipitous Dual Markets

DUAL MARKET PRICING: ASAQ

Product/Technology
A new fixed-dose combination of artesunate and amodiaquine (ASAQ) to treat malaria in sub-Saharan Africa
Partners
Drugs for Neglected Diseases initiative (DNDi) and Sanofi Aventis
Dual-Price Markets
- Public market—once-a-day dosing, preferential no-profit/no-loss price to public organizations in endemic countries of <$1.00 for full treatment
- Private market—under the brand name Coarsucam, at $3–4 for full treatment

Intellectual Property Approach
The product purposely was not patented. DNDi receives a percentage of the revenues from the sales of Coarsucam, which it uses toward lowering the preferential price of ASAQ in the public market.

DUAL MARKETS FOR A PRODUCT: EFLORNITHINE

Product/Technology
Eflornithine
Partners
Bristol-Myers Squibb (BMS)/Gillette and Aventis Pharma
Dual-Product Markets
- Public market—eflornithine for the treatment of African sleeping sickness (trypanosomiasis)
- Private market—under the brand name Vaniqa, a cream for slowing the growth of unwanted facial hair in women

Intellectual Property Approach
BMS and Gillette market Vaniqa under a license from Aventis Pharma. BMS funds the bulk material costs for producing 60,000 vials of eflornithine.

DUAL MARKETS FOR LICENSING: GLOBAL VACCINES, INC.

Product/Technology
Novel vaccine technologies
Partners
Global Vaccines, Inc. (GVI) and the University of North Carolina (UNC)
Dual-Licensing Markets
- Public market—noncommercial vaccine markets and/or orphan vaccines
- Private market—commercial vaccine markets and/or nonvaccine applications

Intellectual Property Approach
GVI secured a license from UNC for royalty-free application and use of its vaccine technology in noncommercial or orphan vaccine markets. Concurrently, GVI can apply this technology to commercial vaccine markets or nonvaccine applications, returning licensing revenues to both GVI and the university.

SOURCE: So, 2008.

BOX 6-3
Gates Foundation Global Access Agreements

The Parties recognize that there are a number of potential intellectual property management strategies for ensuring that Developing Countries benefit from the Grant . . .

Possible strategies include:

(a) not patenting in Developing Countries, thereby allowing free access to any company to manufacture and market for no royalties; and

(b) providing non-exclusive licenses to a number of companies to market these products with minimal royalties to the developers or identify a partner willing to produce the vaccines for the developing world with specific reference to the fact that the licensing party must implement the invention for the benefit of the developing world consistent with the Gates Foundation Charitable Objective.

SOURCE: Private communication between So and the Gates Foundation.

sometimes called "patent thickets," that can make it difficult to sort out intellectual property ownership and access necessary technology for development. To help combat this problem, Merck, for example, initiated the Merck Gene Index, releasing hundreds of expressed sequence tags to the public domain. Similarly, various industry groups have partnered with several universities and the Wellcome Trust to lower the cross-licensing costs associated with research on single nucleotide polymorphisms (SNPs) that are important to genetic mapping.

Finally, product development partnerships can also have a normative influence on intellectual property deployment. The Institute for OneWorld Health and DNDi are both developing paromomycin, a drug no longer under patent, for treatment of visceral leishmaniasis in India and Africa, respectively. The pooling arrangements made by the International AIDS Vaccine Initiative (IAVI) Neutralizing Antibody Consortium suggest another approach. The consortium funds basic research in exchange for mandated sharing of data and any benefits resulting from intellectual property holdings. The responsible investigator receives proportionately more of the reward, but all consortium members collect a share of any revenues from royalty streams.

Technology Trusts

Institutional efforts such as IAVI's Neutralizing Antibody Consortium highlight the need to go beyond the actions of individual institutions and private-sector firms to collective action. The experiences of the Malaria Vaccine Initiative demonstrate the complex patent landscape that can result when institutions act as individuals, rather than collectively. For 10 key malaria antigens, there were 167 patent families filed by 75 different organizations. Considering just the moderate- to high-priority patents, 39 of the 167 patent families fell into that category, and they were held by 21 organizations. Of the moderate- to high-priority patents, 69 percent (27) had originally been filed by a public entity. At the time of the study, only 21 percent of those patents (8) remained available for licensing from the public entity (Shotwell, 2007).

As noted above, these types of patent thickets can stifle innovation. An alternative approach involving collective action is the use of patent pools to alter the traditional one patentee–one licensee relationship by encouraging a many-to-many exchange of intellectual property. So highlighted a program at Duke University that is working to conceptualize how a technology trust might create an enabling intellectual property environment for rare and neglected diseases (see Figure 6-1). Such a trust would not only use pool-

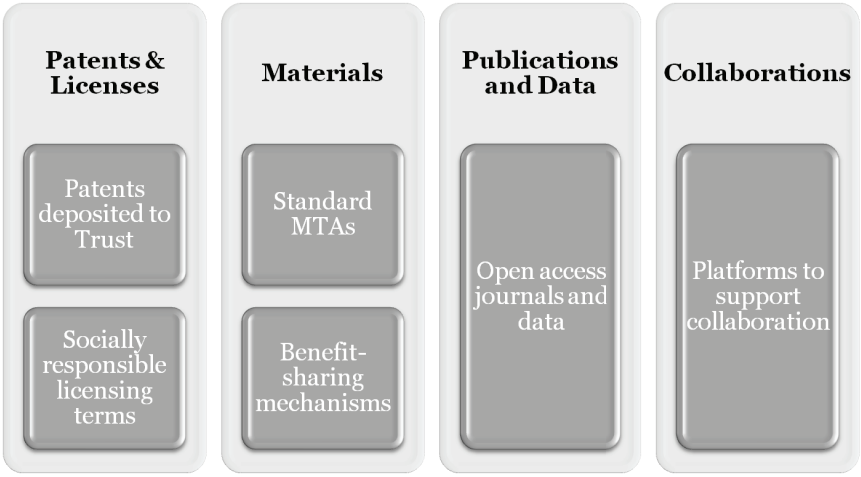

FIGURE 6-1 Duke University concept of how a technology trust might create an enabling intellectual property environment for rare and neglected diseases.
NOTE: MTA = material transfer agreement.
SOURCE: So, 2008.

ing mechanisms, but also seek to align the norms of public-sector collective action to deploy intellectual property in a way that would support public health aims.

Presentations throughout the workshop provided examples across the spectrum from pooling of intellectual property to its deposit in a trust and use of socially responsible licensing terms and technology transfer, from standard material transfer agreements (MTAs) to new benefit-sharing arrangements, and from open access to data to new platforms for supporting collaboration. Now, So said, it is essential to enable collective action by the public sector in concert with private-sector stakeholders, to pool intellectual property and cultivate collective norms, to speed innovation, and to improve the affordability of these health technologies. Together, these actions can facilitate much-needed development to treat rare and neglected diseases.

INNOVATION IN ALLIANCES AND LICENSING: VERTEX PHARMACEUTICALS TRANSFORMING NOW FOR THE FUTURE[3]

Vertex Pharmaceuticals was founded in 1989 by a scientist who remains CEO today. A heightened sense of social responsibility permeates the company. Vertex continues to have a productive relationship with the Cystic Fibrosis Foundation and, more recently, based on a similar model, a relationship with the CHDI Foundation. The company is also involved in an internal effort addressing new, different, and transforming approaches to treatment of tuberculosis.

The industry today is at an interesting juncture, Sorensen noted—a "post-genomic challenge." The sequencing of the human genome resulted in the identification of numerous targets, enabling the pharmaceutical and biotechnology industries to develop drugs based on novel targets. The challenge, however, is determining how to develop a safe and effective drug for such a target. At least some of the problems that the pharmaceutical industry is facing, Sorensen said, stem from the dictum "fail fast, fail early, fail often," which means the industry focuses a great deal of its time on failing. Novel drug development is also hindered by industry's emphasis on the development of second-generation drugs and products that fail to address current needs. In many cases, research and development do not fit seamlessly together.

Sorensen stressed that there is a need across industry for more consolidation, downsizing, and focus. Pharmaceutical companies have become too diffuse and too large, and they need to concentrate once again on

[3]This section is based on the presentation of Craig Sorensen, Ph.D., Senior Director, Strategic Research Alliances, Vertex Pharmaceuticals Incorporated.

what they do best and avoid the temptation to try to do everything. The industry needs to outsource more activities—not just the usual ones such as manufacturing or toxicology, but also certain aspects of discovery. There is increasing competition in all aspects of development, and the industry needs to find new solutions. Many organizations have focused first on their operational issues, but to remain competitive, they now need to shift their emphasis to strategic research licensing.

The twentieth century was driven largely by the technology revolution, with two camps evolving—the pharmaceutical/biotechnology camp and "everyone else." In the twenty-first century, a synergism is emerging that involves recognizing the needs of the other party and introducing the concept of patent pooling to achieve common goals, resulting in greater freedom to operate for everyone involved in the discovery process. This synergism gives industry access to world-class technology on a global scale and allows companies to remain focused on building internal core competencies. In the end, long-term cost savings will result from casting a broader net for more opportunities, thereby increasing the competitive advantage overall.

Innovative Alliances and Licensing

The industry needs to do a better job of licensing, patenting, and forming strategic alliances if it is to meet the challenges of drug discovery for rare and neglected diseases. The traditional approach of a closed, internalized model of pharmaceutical R&D needs to be updated to a network approach, incorporating strategic alliances, distributed risks, and greater flexibility. In forming strategic research alliances and outsourcing, the most important criteria for success are speed, flexibility, and the right partner. The right partner is not necessarily a large organization; it may be a collection of small organizations that pool their abilities and resources, including intellectual property, as needed.

Strategic research alliances and outsourcing are, in the end, aimed at bringing innovative medicines to patients. As noted, innovation and flexibility are at the core of a successful approach. But there must also be an alignment of vision, an understanding of what the other party needs to achieve its goals, and the building of a relationship of mutual trust. Combining the unique strengths of industry, academia, and nonprofit organizations can only add value and speed to the overall process.

Alliances and outsourcing derive from both motivating and facilitating factors. Motivating factors include the need to obtain access to complementary knowledge and expertise; to find practical solutions to address increasing competition; and to improve flexibility and complex adaptation, including reassessment of the value and role of current patenting and licensing strategies. Facilitating factors, which make it possible to meet the moti-

vating needs, include the organizational structure, ability, and reputation of the partner; the earned and shared vision and trust; the mutual benefit of the arrangement to both partners; communication; and leveraging of new information technologies and virtual organizational tools to break down old barriers, whether real or perceived.

To develop these new models for bridging gaps and building sustainable alliances, it is necessary to identify the areas that need attention. The philosophy employed must be strategic, not reactive, establishing whether the relationship is cooperative or controlling and whether the goal is long-term or short-term return on investment. The parties must agree on relative value and on patenting and licensing goals early in the process. Success requires understanding that the value of the alliance is directly related to the degree to which the overall vision is shared by the individual partners. Different partners may have different visions, and all parties should understand that it may be in everyone's best interest to walk away and find a more compatible partner. It is also important to acknowledge and reduce risks so energy can be focused on the desired benefits. For a successful, synergistic alliance, complementary organizational structures and contributions should be blended: one party may have the funding, another may have the ideas, and another may have access to patient pools or information.

Perceived risks are associated with alliances and licensing, including concerns about the manageability of complex projects, the internal atrophy of critical skills, the loss of hands-on experience, and the potential to lose intellectual property or be boxed in by the competition. These perceived risks collectively translate into a loss of control. But most of these risks, Sorensen suggested, are not real or can be managed. On the other hand, the benefits of alliances are quite real: access to world-class technology and focused, flexible discovery infrastructures; expanded horizons and new opportunities; and lower capital investment and more effective resource allocation. Together, these real benefits lead to a gain of control. Concessions may be required on the part of each of the members of the collaboration. In the end, however, if the work has been done right, if there is a process for mediating conflicts, and if open communication is maintained, all parties win.

Collaborators' insight is important, and alliance partners should have nonoverlapping expertise. Successful alliances leverage the skills and expertise of each member and identify evolving needs (see Figure 6-2). Alliance networks should also be global, tapping the best and the brightest worldwide.

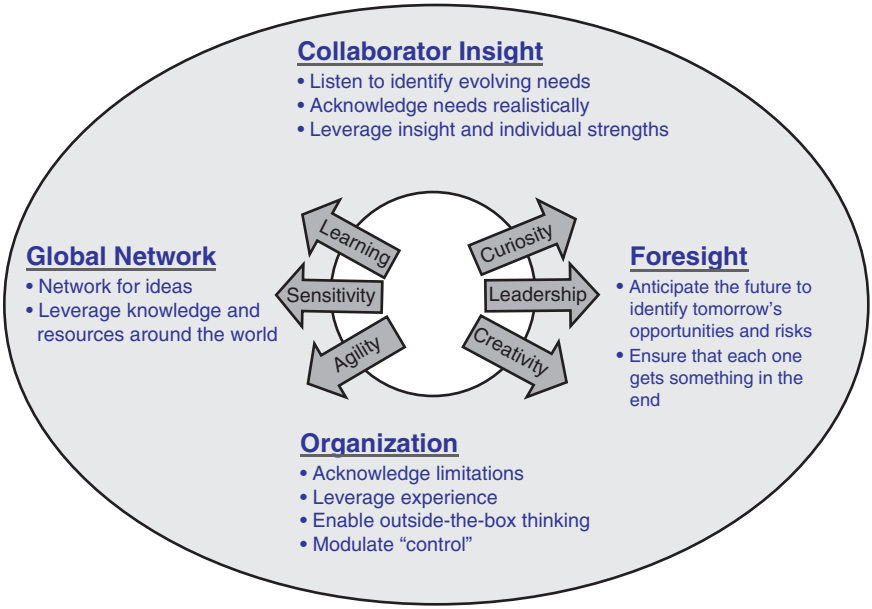

FIGURE 6-2 Vertex approach to maintaining strategic research alliances. Building and maintaining healthy alliances is a dynamic balance. Having the foresight to anticipate what one wants or needs to achieve and then casting a global net to acquire the various pieces of the puzzle is the first step. Once in place, however, the relationship must continually be fine-tuned. This means listening to what partners are really saying and then leveraging that experience to develop out-of-the-box solutions, a process that in turn feeds back into being able to anticipate tomorrow's opportunities today.
SOURCE: Sorensen, 2008.

THE MYELIN REPAIR FOUNDATION: ACCELERATING INTELLECTUAL PROPERTY SHARING TO FACILITATE TRANSLATION[4]

Prior to establishing the Myelin Repair Foundation (MRF), the founder, who has had multiple sclerosis (MS) for 35 years, had no background in the biomedical research enterprise; his expertise was in technology start-ups. As he began to look at how new treatments came to market, he found that there were (1) basic academic research scientists who were making

[4]This section is based on the presentation of Rusty Bromley, Chief Operating Officer, Myelin Repair Foundation.

individual discoveries focused on expanding the base of knowledge about MS, and (2) pharmaceutical companies that were focused on developing products for profit, which required extensive validation and preclinical testing before being tested as therapeutics. As noted repeatedly throughout the workshop, these two parties have moved further apart over time, leaving a gap between discovery and treatment.

The vision of the founder of MRF, Bromley said, is a world in which accelerated scientific discoveries are streamed rapidly into the drug pipeline and delivered to patients who cannot afford to wait. Acceleration means lower cost and faster time to market for treatments for which the need is greatest. The MRF strategy is to reduce risk to the point where commercial entities with the resources to bring these new targets to market can be engaged.

Managing Intellectual Property

One of the key elements of MRF's success over the last 5 years has been the ability to assess what intellectual property—including data, publications, materials, knowledge, and patents—needs to be shared to facilitate translation. MRF starts with the end in mind, looking to negotiate win–win relationships with the various constituencies. MRF approached a number of academic institutions to recruit scientists to participate in a novel research process. The organization considered the barriers to sharing, including competition in the forms of publications, funding, and peer review, and understood that building a culture of trust would be essential.

MRF also recognized who the stakeholders are. In addition to those discussed earlier, including patients, the public, and government interests, taking discoveries to the translational level requires considering the interests of the investigators and the universities, including the often conflicting needs of the university research contracts office, technology transfer office, and office of the general counsel.

The MRF strategy includes bringing together multiple disciplines and ensuring that all partners have clear goals and cooperate at every level of the process, beginning far upstream with intellectual cooperation during experimental design. It is also important to share resources and rewards. MRF shares the relevant intellectual property—whether materials, knowledge, or patents—among the team, acting as an agent to pool resources for the benefit of all the participants. Through the contracts with the universities, all intellectual property that is generated through the partnership is available to the nonprofit research community on a nonexclusive, royalty-free basis. Any tools developed are likewise available on a nonexclusive basis, both to industry and to the nonprofit research sector.

Operational Strategy

Even though MRF is a foundation, it does not make traditional grants. Instead, it operates under milestone-driven sponsored research agreements with all of the participating universities. Under the agreements, MRF is responsible for identifying and protecting any resulting intellectual property, and the universities hold the patents. MRF has a master agreement that it will freely share with anyone who is interested. Because it is a sponsored research agreement, there are annual research plans with each of the investigators. Each program sponsored by MRF has specific milestones that must be accomplished, and partners are held accountable. This is why it is important to negotiate critical terms up front, to define goals and objectives clearly, and to include partners in the planning process. From MRF's perspective, the only objective is getting new therapies into clinical trials, and individual targets and programs are selected on the basis of which provide the strongest opportunity to achieve this objective as quickly as possible (an approach similar to that of the Cystic Fibrosis Foundation).

Communication is also key to accelerating translational research. Basic science tends to be fairly secretive, as the first to publish receives the recognition. MRF provides secure data sharing, opportunities for joint publications that serve the needs of both the foundation and the participants, and facilities for teleconferencing and web conferencing. Human interaction is critical to building trust, and therefore MRF also facilitates face-to-face team meetings.

Organizational Structure

MRF's mission is to find novel myelin repair treatment targets for MS. The initial organizational structure of its collaborative research process is shown in Figure 6-3. This process is the standard operating procedure for interaction between the laboratories, and according to Bromley it has been very useful. MRF also established electronic links to facilitate communication between laboratories. The research plan was an interactive process aimed at creating a set of boundary conditions, and because the scientists participated in this process, they have been very good about meeting those conditions. MRF provided resources, including a scientific advisory board, a board of directors, management, and external collaborative resources, to help address any issues on which the core team lacked the necessary competencies. Also, as noted earlier, MRF acts as a pooling agent for any resulting intellectual property.

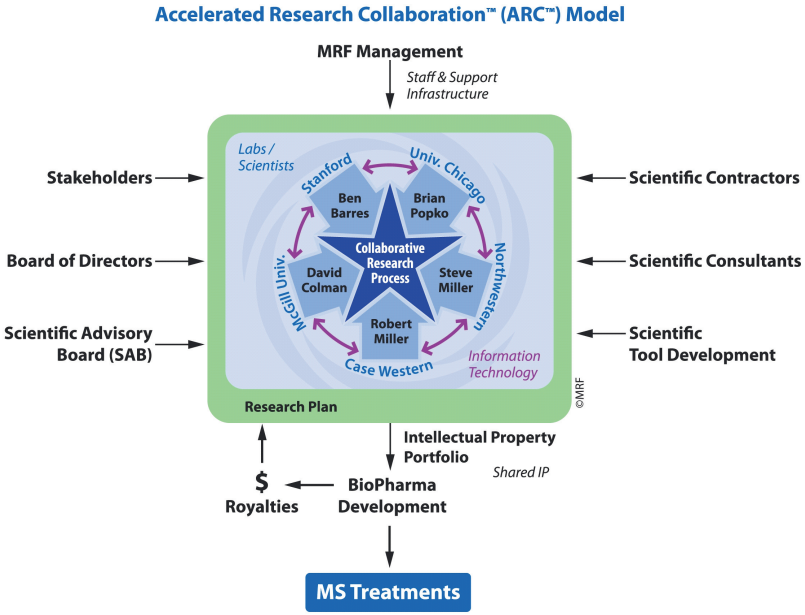

FIGURE 6-3 The Myelin Research Foundation's collaborative research process. SOURCE: Bromley, 2008.

Moving Forward

In the 4 years since MRF began conducting research, 19 novel targets have been identified. Some of these targets are currently undergoing a validation process, and two cellular therapies are slated to enter Phase I investigator-directed clinical trials in late 2008. MRF began this process by aligning the research team and providing a foundation for the collaboration in an effort to develop compounds and dramatically increase the numbers of new drugs in the pipeline. Since then, MRF has also recognized the gap between discovery and treatment (see Figure 6-4). A number of external resources need to be brought to bear because many of the best people and best technologies in this area reside in commercial organizations. While a number of academic centers have entered the drug discovery enterprise, many specialized skills are necessary to accelerate the process, and there may be a long learning curve for some of these skills. One of the barriers MRF encountered was the difficulty of obtaining funding for the development of tools. As a result, about 40 percent of the MRF research budget

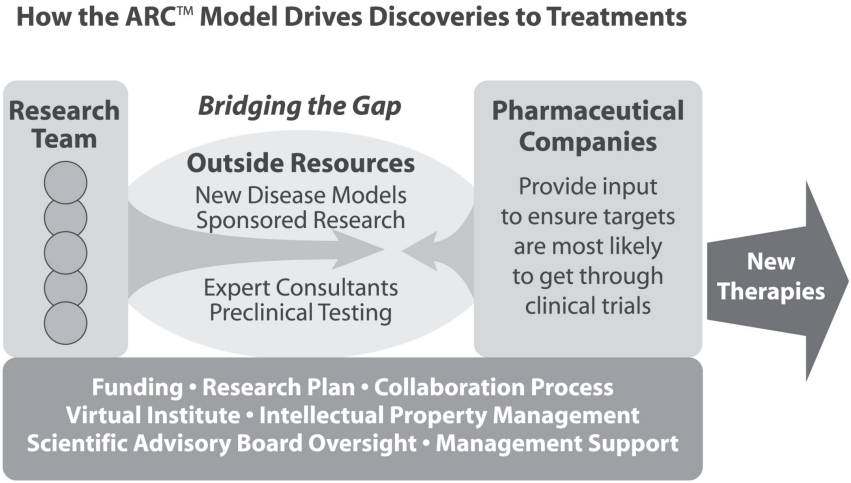

FIGURE 6-4 Bridging the translational research gap between discovery and treatment.
SOURCE: Bromley, 2008.

has been used to develop new assays, new animal models, gene expression databases, and other tools to facilitate the drug discovery process.

In the postdiscovery arena, a number of translational challenges lie ahead. One is identifying new collaborators and capabilities, including contractors, commercial entities, university organizations, and government in the form of the Patent Office and the Food and Drug Administration. Another challenge is that these stakeholders have differing motivations, including education, the public good, and profit. If a partnership is to be successful, interests, capabilities, and motivations need to be carefully aligned among the stakeholders.

THE UNIVERSITY OF CALIFORNIA AT BERKELEY'S APPROACH TO MANAGEMENT OF INTELLECTUAL PROPERTY[5]

The mission of the University of California (UC) encompasses teaching, public service, the dissemination of information, and research. In fact, a recent study showed that the 10 campuses within the UC system were responsible for 7 percent of the R&D activity in the state of California.

[5]This section is based on the presentation of Carol Mimura, Ph.D., Assistant Vice Chancellor for Intellectual Property and Industry Research Alliances, University of California at Berkeley.

The university, Mimura said, has a duty to ensure that applications derived from basic research that can benefit society are publicly transmitted and deployed. Partnerships between the university and industry have the potential to accelerate innovation, translate research for public benefit, bring resources back into the university, and fuel economic growth.

The Office of Intellectual Property and Industry Research Alliances (IPIRA) at University of California at Berkeley (UC Berkeley) was created in 2004 to serve as the portal through which all industry partners would interact with the Berkeley research enterprise. As part of IPIRA, the Office of Technology Licensing engages in "technology push," patenting and copyrighting, and licensing of patent rights and copyrights to the private sector for commercial development. The Industry Alliances Office is engaged in "technology pull," bringing personnel, materials, and resources back into UC Berkeley from the private sector. Both offices report to the Assistant Vice Chancellor for IPIRA, ensuring coordination.

The Relationship Model of Technology Transfer

Traditionally, technology transfer is thought of as involving outgoing transactions only. Under the IPIRA organizational structure, technology transfer consists of a relationship continuum over time, with many points of interaction and engagement with multiple parties and a flow of rights and knowledge in both directions. Adopting a relationship model can break down cultural and negotiation barriers and establish an overall comfort level that attracts funding, promotes collaboration, and facilitates the completion of transactions or gifting to the institution.

The model of technology transfer that most universities have used to date is the biotechnology model, which emphasizes protection of intellectual property; long R&D timelines; exclusive licensing; and running royalties, milestone payments, and multiple payments, with the goal of maximizing licensing revenues. In contrast, the ultimate goal of IPIRA is maximizing the impact of research. UC Berkeley recognized that if success were measured only by the volume of patents obtained, licenses signed, and royalties and fees brought in, the organization would favor only those outcomes. Instead, IPIRA operates under a system in which no single model for technology transfer relationships is preferred over another. The goals are social impact, translational efficiency, sharing, reputational gains, affiliations, strategic partnerships, collaborations, and optimal speed and efficacy of the above. To these ends, flexible approaches can be taken to contracting, addressing industry-specific needs. Also under this philosophy, what were considered in the past to be alternatives to technology transfer (such as patent pooling, royalty-free licensing, and not patenting or not

patenting in certain locations) are all impactful and therefore all equally viable options.

A double-bottom-line accounting approach to measuring success places equal value on societal impact and the financial bottom line. While it is easy to collect data for the financial bottom line (such as number of licenses and patents, license revenues, or number of start-up ventures), assessing social impact is more of a challenge. Metrics such as neglected or tropical disease research funded, lives saved, medical costs reduced, software distributed, research tools shared, collaborations enabled, and knowledge and expertise transferred can be difficult to measure, especially when they are separated both spatially and temporally from causative transactions in IPIRA. Therefore, economists and other scholars are needed to assist in measuring impact under IPIRA's new paradigm. Another challenge is that, while increases in certain metrics can be measured, including qualitative goals such as reputational gains, there is no baseline against which to compare these measures because prior data were collected using traditional means and are primarily quantitative in nature.

An innovative feature of the IPIRA model is that in the traditional system, basic research is funded by state or federal agencies, innovations are patented, and universities make licensing arrangements with biotechnology companies. Following several years of development, a biotechnology company must then partner with a pharmaceutical company to commercialize the end product. IPIRA partners all of the collaborators at the outset with the goal of reducing translational research gaps. This approach eliminates future transaction costs, uncertainty in finding the next partner, and gaps between development stages, resulting in seamless transitions that accelerate bench-to-bedside translational research.

As a result of the philosophy and intellectual property management approach at UC Berkeley, the university has benefited financially. Corporate-sponsored research funding has increased about fourfold, foundation funding has grown, gift funding has increased from both private and foundation sources, and a larger number and variety of public–private partnerships exist at the university than ever before.

Intellectual Property Management Strategies

IPIRA employs a full spectrum of intellectual property management strategies (see Figure 6-5A), from gifting, whereby a donor gives a gift with no contingencies and intellectual property considerations are completely moot, to sponsored research agreements, whereby a company funds a particular project and retains an exclusive license to commercialize the results. There are creative opportunities for intellectual property management at all points along this spectrum, including industry affiliate programs,

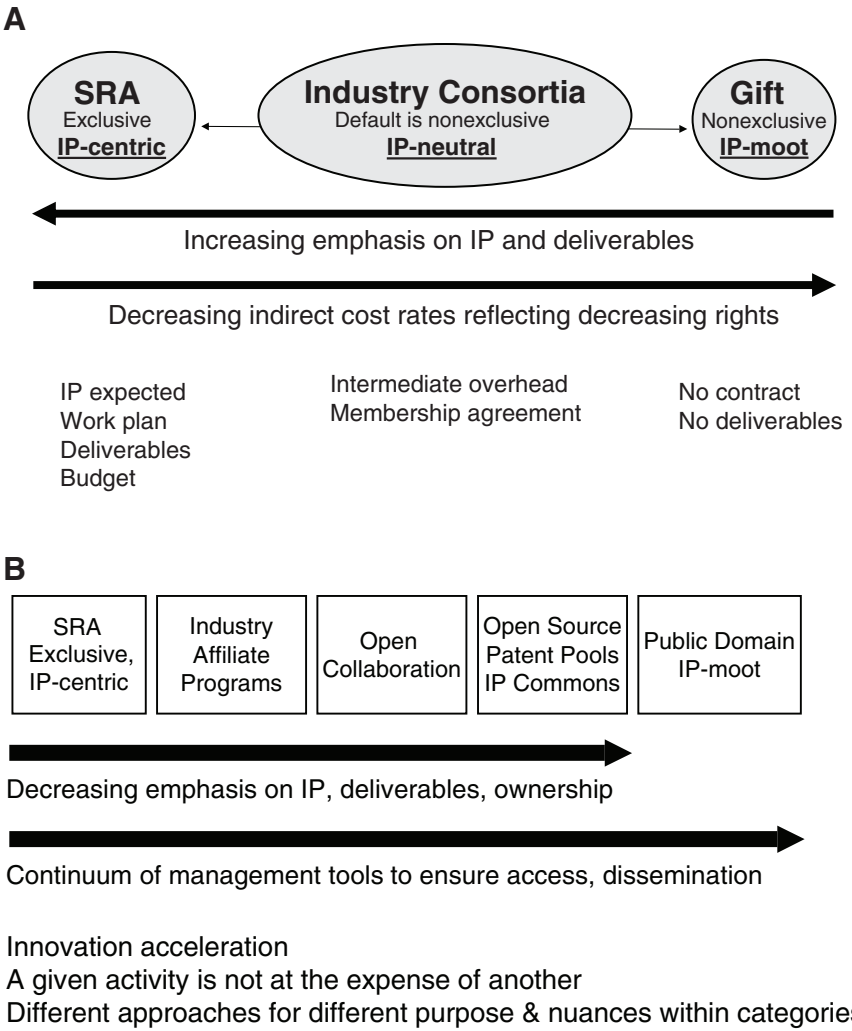

FIGURE 6-5 UC Berkeley IPIRA intellectual property management models. (A) A full spectrum of models is employed to achieve maximum impact, access, uptake, and dissemination. (B) The management strategy is geared toward achieving translation of research results. By applying new metrics, the goal of impact can be achieved in many ways.
NOTE: IP = intellectual property; SRA = sponsored research agreement.
SOURCE: Mimura, 2008.

an intellectual property–neutral approach whereby the main deliverable is relationships and information. UC Berkeley may elect not to patent a given invention if this is deemed to be the best way to achieve impact (keeping in mind that patents may ultimately be filed by research sponsors, such as the federal government). Different approaches can be applied for different purposes, and a given activity is not undertaken at the expense of another (see Figure 6-5B). For example, the grant of a royalty-free, nonexclusive license is not detrimental to the Office of Technology Licensing's bottom line in IPIRA if it supports the goal of social impact or if the license stimulates research funding that would go to IPIRA's Industry Alliances Office. Open-source licensing and patent pooling are also considered impactful end points when the goal of societal benefit is achieved through sharing of the information.

The Socially Responsible Licensing Program[6]

Another IPIRA management strategy for intellectual property is UC Berkeley's Socially Responsible Licensing Program (SRLP). The goal of this program is to maximize the impact of UC Berkeley research to benefit the neediest populations, such as those in the developing world. Some agreements in SRLP bring resources for research to UC Berkeley in exchange for the future grant of a nonexclusive, royalty-free license for humanitarian purposes in defined locations. Under the program, the university can also elect not to patent or to patent only in certain locations. In addition to making drugs and therapies affordable and accessible in the developing world, SRLP is concerned about attribution and revenue sharing, especially when local experts (such as a shaman) provide assistance.

UC Berkeley believes that helping the developing world is a moral imperative, and countries with resources should help those that are resource poor. The opportunity cost of, for example, providing university-generated therapies for free in the developing world is low compared with the societal benefit, and the university is not harmed because the goal is consistent with defining the success of technology transfer as maximizing impact. Examples of innovations licensed and/or funded under SRLP are shown in Box 6-4.

One high-profile example is the public–private partnership among the Institute for OneWorld Health, UC Berkeley, and Amyris Biotechnologies, Inc. (a Berkeley start-up company). The partnership is funded by the Bill and Melinda Gates Foundation to produce low-cost artemisinic acid-based combination therapies to treat malaria.[7] Berkeley licensed to both Amyris

[6]More detailed information on the UC Berkeley Socially Responsible Licensing Program can be found in Mimura, 2006.

[7]Further detail on the malaria drug development partnership can be found in Daviss, 2005.

BOX 6-4
Examples of Innovations Licensed and/or Funded Under the Socially Responsible Licensing Program (SLRP) at UC Berkeley

DIAGNOSTIC
Handheld MEMS (micro-electro-mechanical systems) device for the diagnosis of dengue fever in Nicaragua, in association with Sustainable Sciences Institute (SSI, a nonprofit). License to SSI granting royalty-free sales for as long as SSI remains a nonprofit in certain countries. Achieves the mutual goal of bringing a low-cost diagnostic to the developing world.

THERAPEUTIC
Research collaboration and revenue sharing (if a drug is commercialized) with the Commonwealth of Samoa for a potential HIV drug, an antiviral compound derived from native Mamala tree bark. Half of any revenue generated will be portioned out to the government of Samoa, several local villages, and the descendents of the healers who identified the medicinal properties of the Mamala bark.

AGRICULTURAL
Agricultural–biotechnology company license to commercialize disease-resistant crops. No-cost sublicenses in Africa.

VACCINATION
Tuberculosis vaccine research agreement stipulating that if a vaccine is invented with company-funded research at UC Berkeley, vaccine distribution will be royalty-free in defined countries.

NUTRITIONAL
Development of a more nutritious and more digestible sorghum in collaboration with Africa Harvest Biotechnology Foundation International, funded by the Gates Foundation. Advance commitment to allow royalty-free sales in Africa.

SOURCE: Mimura, 2006.

Biotechnologies, Inc. and the Institute for OneWorld Health patent rights based on synthetic biology that results in cloning and overproduction of artemisinic acid in yeast and *E. coli*. Through a three-party collaboration agreement and two license agreements, UC Berkeley received about $8 million to perform basic research (a great deal more, Mimura noted, than would be expected from an NIH grant, even if NIH had funded this very project). Amyris Biotechnologies received about $12 million to perform translational research (much more than the typical start-up company usually has at its inception), and the Institute for OneWorld Health retained

about $22 million to conduct the more expensive clinical, regulatory, and distribution activities.

The license from UC Berkeley to Amyris Biotechnologies (a for-profit company) is granted in defined countries in the developed world. It stipulates that the company cannot make a profit on the malaria drug, but it also grants rights to use the same intellectual property for revenue-generating commercial applications (e.g., flavors, fragrances) in the developed world. The Institute for OneWorld Health received the reciprocal license in the developing world and is field-of-use limited to the malaria drug.

None of the partners alone could have attained the goal of lowering the existing drug cost 10-fold, from $2.40 to $0.24. The Gates Foundation funded the project based on assurances that the dual goals of access and affordability in target countries could be met. Amyris and the Institute for OneWorld Health have granted sublicenses to Sanofi Aventis, which will ultimately distribute the affordable treatment in the target locations around 2010. The compressed timeline of 6 years from signature to delivery is an example of expedited bench-to-bedside translational research. The generosity and vision of the Bill and Melinda Gates Foundation enabled basic and translational research projects to proceed in parallel, rather than in sequence, and represents an example of bootstrap philanthropy in a start-up company. In this case, Amyris Biotechnologies did well by doing good.

Good Stewardship of Intellectual Property Ownership

Mimura referred workshop participants to "Nine Points to Consider in Licensing University Technology." This white paper, drafted by 11 universities and the Association of American Medical Colleges and endorsed by numerous additional institutions, offers best practices for university technology transfer activities (see Box 6-5) (AUTM, 2007).

Mimura observed that in many cases, those assessing intellectual property issues are quick to attribute problems to the Bayh–Dole Act, which gives universities, small businesses, and nonprofits the right to patent and license out the intellectual property arising from their U.S. government–funded research. It is not the ability to own intellectual property that is the problem, however, but how those rights are employed that makes the difference. When universities elect to make rights proprietary through patenting and other means, they must demonstrate good stewardship of those rights. This means preserving public access to inventions while retaining the right to use them on the university's behalf (and on behalf of other nonprofit organizations) for teaching and research purposes, even when they have been licensed out. Also, several agreements in the SRLP include provisions for sharing revenue and giving attribution to collaborative contributors.

From a legal perspective, it is often necessary to analyze the antitrust

BOX 6-5
Highlights of "In the Public Interest: Nine Points to Consider in Licensing University Technology"

1. Universities should reserve the right to practice licensed inventions, and to allow other nonprofit and governmental organizations to do so.
2. Exclusive licenses should be structured in a manner that encourages technology development and use.
3. Strive to minimize the licensing of "future improvements."
4. Universities should anticipate and help to manage technology transfer related conflicts of interest.
5. Ensure broad access to research tools.
6. Enforcement action should be carefully considered.
7. Be mindful of export regulations.
8. Be mindful of the implications of working with patent aggregators.
9. Consider including provisions that address unmet needs, such as those of neglected patient populations or geographic areas, giving particular attention to improved therapeutics, diagnostics, and agricultural technologies for the developing world.

SOURCE: AUTM, 2007.

implications of an agreement, given that the collaborators are mutually setting a future price for a given humanitarian use in a defined location. Often under the SRLP at UC Berkeley, the price is set at zero, and the university is forgoing revenue. Inventors are consulted so the royalty-free licenses can be implemented. Mimura said it would be helpful to have a formal legal opinion confirming that this collegial interaction is not anticompetitive, but procompetitive.

Finally, with regard to funding sources, while UC Berkeley is grateful to foundation donors for funding research, those projects must be kept separate from others to meet the mutual expectations of the university and the sponsor. Thus researchers who are funded by one foundation cannot use their intellectual property in a project for another foundation.

OPEN DISCUSSION

During the open discussion, participants raised additional points regarding who pays the fees for patent applications and maintenance, and what cultural obstacles might be faced in attempting to implement a bold new intellectual property management strategy such as that of UC Berkeley.

Further examples of intellectual property strategies were also offered. Overall, participants confirmed the importance of defining and agreeing upon expectations and responsibilities early on and in a face-to-face meeting, thereby establishing a strong, ongoing relationship among the partners.

Patent Application and Maintenance Fees for Intellectual Property

Bromley suggested that an organization wishing to be the focal point for intellectual property resulting from a project and to make it available to the academic and for-profit communities must be prepared to fund the patent process. Technology transfer offices at universities are generally understaffed and underfunded, and large universities can be so diverse that it is impossible for them to have people with expertise in every field. Coming to the table with the appropriate counsel and the necessary funding can give an organization a real advantage. MRF's limited resources are, in fact, focused mainly on patent filing and maintenance fees. Bromley noted that MRF receives most of its legal services pro bono, and encouraged other organizations to seek out such support. Mimura agreed, adding that universities typically do not wish to be obliged to file a patent application unless they have one or more licensees in a position to reimburse them. A patent application is necessary only if the private-sector partner needs the intellectual property right to exclude others or to justify the magnitude of its investment in the project.

Cultural Obstacles

In 2001, UC Berkeley convened task forces involving industry, other universities, and internal faculty to review processes for interactions with industry, particularly research contracts. The resulting recommendations ultimately led to the formation of IPIRA. Certainly, granting a license at no cost is preferable to faculty members who value research funding over the slim possibility of someday seeing patent royalties. Culturally, however, many universities say they cannot afford IPIRA's approach; most of these are universities with highly profitable drugs. Mimura said that a colleague once told her the only reason UC Berkeley can take this approach is that it does not have a medical school. There is a dynamic tension within a university when the medical school views technology transfer as being about profits and about finding the next blockbuster drug. But UC Berkeley also has strong agricultural–biotechnology roots and a preeminent engineering school with a tradition of offering open-source software licenses, including the Berkeley Software Distribution (BSD) license. Mimura suggested as well that it is often less difficult to take unconventional approaches at UC Berkeley than elsewhere. The university has a culture of sharing and

engagement, and the chancellor and vice chancellor support IPIRA's role. By contrast, many technology transfer offices are now being run by people with a background in finance or venture capital who wish to run the office as a profit center.

Additional Examples

An example of successful intellectual property management at the national level is the Canadian Stem Cell Program, operated under the auspices of the Canadian Genome Project. According to one participant, the program pooled the intellectual property related to stem cell biology throughout Canada, establishing a central source with which Canadian scientists can negotiate to establish a company and obtain any necessary licenses. In 2007, the Canadian program formed an alliance with the California stem cell initiative that would not have been possible had there not been a pooling of the intellectual property related to stem cell biology.

Mimura mentioned other models IPIRA is assessing, with the goal of expediting translational research through public–private partnerships. One is a "technology sandbox" concept, whereby companies that are not direct competitors are selected for a project. For example, to develop a handheld diagnostic tool that could be carried into the jungle and would still work if dropped in a river, IPIRA would engage a fluid mechanics company, an enzyme company, a chip company, and the university, working together under a short-term intellectual property pooling arrangement that would include an agreement that no one collaborator would assert its intellectual property rights against the others. Through this cooperative arrangement, initial advances could be achieved that would otherwise not be possible. After a certain point, the collaborators would part to pursue their own projects in house.

Diana Wetmore of Cystic Fibrosis Foundation Therapeutics (CFFT) supported the idea of having a range of intellectual property strategies. She noted that CFFT often finds itself in the middle, trying to help a company and a university come to a mutual agreement so that CFFT's goals can be met. She offered one example of a strategy CFFT has tried. The CFTR gene and the delta F mutation, the most common mutation present in cystic fibrosis, were patented by the University of Michigan and the Hospital for Sick Children in Toronto in 1989. CFFT's interpretation of the patent literature was that drug screening using the gene in any transformed-cell type of tool system was covered. The University of Michigan was collecting royalties from diagnostics. CFFT engaged the university in a dialogue, stressing that it wanted the companies it funded to be in compliance with the patent but did not want to take a year to negotiate a license and delay drug discov-

ery. As the solution, the university and the hospital issued the foundation a sublicensable license; CFFT has issued five of these sublicenses to date. The drawback is that CFFT has assumed the administrative burden, spending a great deal of time with the business offices of the companies explaining the sublicense terms. Overall, however, the approach has resulted in a win–win solution. CFFT reports annually to the university on what parties are operating under the sublicenses. The university gains recognition that its patent is broadly accepted as valid and receives a nominal fee from CFFT. When well-defined intellectual property is necessary to advance research on a given condition, this approach may be one option to consider.