BREAKTHROUGH BUSINESS MODELS

Drug Development for Rare and Neglected Diseases and Individualized Therapies

Workshop Summary

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Forum on Drug Discovery, Development, and Translation
Board on Health Sciences Policy

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Willing is not enough; we must do."
—Goethe

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Preface

The research and development process for new drug and biologic products has become extraordinarily expensive and time-consuming. Even for large pharmaceutical companies working to develop potential blockbuster drugs, many consider the current model to be unsustainable. While developing drugs to treat rare and neglected diseases can be just as expensive and time consuming as it is for blockbuster drugs, the products are often far less commercially viable to certain sectors of the pharmaceutical industry. Recognizing that patient advocacy groups can play a vital role in the development of new drugs to treat rare and neglected diseases, the Forum held a workshop in September 2007 entitled "From Patient Needs to New Drug Therapies: Can We Improve the Pathway." The workshop featured the work of four patient-focused organizations: the National Breast Cancer Coalition, the Cystic Fibrosis Foundation, the Arthritis Foundation, and the American Diabetes Association.

To better understand the innovative approaches being used by these organizations to help advance drug development, the Forum hosted a public workshop on June 23, 2008, titled "Breakthrough Business Models: Drug Development for Rare and Neglected Diseases and Individualized Therapies." Investors, policy makers, and companies seeking to develop therapies for smaller markets came together to discuss innovative strategies being implemented to expedite the development of products for these less commercially viable conditions. The intent of the workshop was first to raise awareness of these new models. Additionally, participants discussed approaches for reducing the risk of such investments by both filling critical

funding gaps along the drug development pathway and pursuing highly targeted approaches to early-phase development.

The workshop had several objectives. The first was to lay a foundation for the discussions by describing the changes that have taken place in the translational research process over the past 10 years, such as the 10-fold increase in investment by philanthropic organizations since 2000. The second objective was to discuss successful "venture philanthropy" models for funding translational research. Beyond new funding models, some philanthropic organizations and for-profit groups have undertaken innovative strategies to help expedite the development of safe and effective drugs for rare and neglected diseases by, for example, funding trials directly, supporting resources such as tissue banks, and negotiating intellectual property. A third objective was to explore whether such strategies are successful and could be implemented more broadly. Finally, workshop participants were asked to examine regulatory, legislative, and institutional policy tools currently in place to help advance the development of therapies for rare or neglected diseases.

The workshop provided an opportunity for participants to share ideas and identify potential collaborative activities. It is our hope that this workshop summary will serve as a resource for all organizations interested in advancing the drug development process for rare and neglected conditions, as well as individualized therapies.

Nancy Sung
Workshop Chair and Member
Forum on Drug Discovery, Development, and Translation

Stephen Groft
Member
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Introduction and Overview*

An objective look at current statistics characterizing the state of drug development paints a gloomy picture. The traditional process for developing a new drug or biologic product and bringing it to market has become exceedingly expensive and lengthy—estimated to cost between $800 million and $1.3 billion, and to take approximately 10–15 years. Only 8 percent of investigational new drugs entering Phase I clinical trials run the full course of development and receive U.S. Food and Drug Administration (FDA) approval, and of those, about 4 percent are eventually removed from the market. In addition, the number of new drug approvals has been slowly declining over the last 11 years—from 53 new molecular entities approved in 1996, to an average of 28 per year between 1999 and 2005, and to a mere 17 in 2007. A recent editorial outlines many of these issues and concludes that "the conventional business model appears fallible" and that "both industry and academia are poorly positioned to respond in the [current] financial landscape" (FitzGerald, 2008). Even considering the potential for blockbuster drugs, this lengthy, high-cost, low-success-rate model is likely to prove unsustainable; for those far less commercially attractive drugs used to treat rare and neglected diseases,[1] it is simply infeasible.

*The planning committee's role was limited to planning the workshop, and this summary was prepared by the workshop rapporteur and the Drug Forum staff as a factual summary of what occurred at the workshop.

[1]For the purposes of this report, rare diseases are defined as diseases that affect small patient populations, and neglected diseases are defined as diseases that are concentrated in poor or developing countries.

Twenty-five years ago, Congress formally recognized the lack of available treatments for rare and neglected diseases and the difficulty of finding companies to develop them. Congress reasoned that if adequate financial incentives were created, companies might be more willing to assume the large risks associated with developing drugs for these conditions. Accordingly, in 1983 Congress passed the Orphan Drug Act,[2] which allows FDA to provide incentives for companies to bring such drugs to market. Recently, Congress introduced additional incentives in the 2007 Food and Drug Administration Amendments Act. Current incentives include grants, tax credits, a waiver of the $1 million Prescription Drug User Fee Act filing fee, FDA assistance with protocol development, priority review of new drug applications (a 6-month review rather than the standard 10-month review), and a 7-year U.S. market exclusivity following approval of a designated orphan product.[3]

Patient groups, disease foundations, and philanthropic organizations have long recognized that the conventional drug development model is less effective in yielding treatments for rare and neglected diseases, and have therefore devised a range of financial and operational strategies for filling this gap. As a result, the outlook for the development of drugs for rare and neglected diseases is arguably far better today than was the case a decade ago.

The riskiest period of drug development, and the one most difficult to fund, is that between basic discovery, generally funded by government, and late-stage development, generally funded by large pharmaceutical companies. This period, often referred to as the "valley of death," includes expensive preclinical animal safety testing, pilot manufacturing, and early-stage safety and proof-of-concept efficacy clinical trials. Many not-for-profit organizations are advancing the development of drugs for rare and neglected diseases through a broad array of financial and operational strategies aimed at decreasing the risk of investment during this period. Some organizations, such as the Cystic Fibrosis Foundation, have launched entire virtual companies to manage all aspects of the development of new therapies for a single

[2]The FDA Orphan Drug Program is discussed further in Chapter 3.

[3]Therapies for rare and neglected diseases may be designated as orphan products if one of the following conditions is met: (1) the disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year as specified in 21 CFR § 316.21(b); or (2) for a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in 21 CFR § 316.21(c).

disease, such as funding, intellectual property, patient registries, and clinical trials. Other organizations take a more focused approach; the Muscular Dystrophy Association, for example, aims to advance drug development for 40 neuromuscular diseases primarily through targeted funding and a process to facilitate access to patients with these diseases.

Such innovative approaches are increasingly relevant to the development of mainstream drugs, which may lead to targeted therapies, for which fewer patients are eligible. For example, Genentech's Herceptin (trastuzumab) is a monoclonal antibody therapy for breast cancer—but only for HER2-positive breast cancer. It is not an effective treatment for breast cancer patients whose tumors do not overexpress the HER2 protein. There are several other targeted therapies on the market today, mainly in the fields of oncology and HIV/AIDS, and it is expected that as this trend continues, an increasing number of products will have reduced markets and may qualify as orphan products.

SCOPE OF THE WORKSHOP

In this context, the Institute of Medicine's Forum on Drug Discovery, Development, and Translation held a public workshop on June 23, 2008, titled "Breakthrough Business Models: Drug Development for Rare and Neglected Diseases and Individualized Therapies." The purpose of the workshop was to explore innovative strategies for orphan drug development. As outlined by workshop chair Nancy Sung,[4] the workshop was designed to:

- provide an overview of how drug development is financed;
- review the state of orphan product development at FDA;
- explore new models for funding translational research and technologies; and
- examine and discuss the adequacy of the regulatory, legislative, and policy tools currently in place to help advance the development of drugs for rare and neglected diseases.

The workshop presentations and discussions considered a range of strategies for reducing the risk to industry and venture capitalists of investing in the development of such therapies by filling critical funding gaps along the drug development pathway and pursuing highly targeted approaches to early-phase development. Such strategies include sharing data and materials, managing intellectual property, launching clinical trials, and incorporating progress milestones. Speakers and participants examined the factors that

[4]Nancy Sung, Ph.D., is a Senior Program Officer for the Burroughs Wellcome Fund.

contribute to successful approaches. They further discussed the use of these approaches by other organizations and in other disease areas in order to accelerate research on rare and neglected diseases. In addition, the workshop provided an opportunity for organizations with an interest in such diseases to share ideas and identify potential collaborative activities.

KEY THEMES

Over the course of the workshop several key themes emerged:

- **Collaboration—**Developing a drug for a rare or neglected disease is often prohibitive for any single organization. Establishing alliances is advantageous and can result in expanded access to innovative technology and to additional resources, including funding, intellectual property, disease experts, and patient communities. Several speakers stated that relationship building is paramount, and a successful relationship requires that knowledge and intellectual property rights flow in both directions to enable acceleration, innovation, translation, and deployment.
- **Sustainability—**The workshop discussions encompassed a broad spectrum of funding models, including philanthropy, pharmaceutical partnerships, venture capital, angel investors, and social investors, as well as product revenues and traditional sources such as loans, grants, and Cooperative Research and Development Agreements. Regardless of which models are pursued, the key to an organization's long-term success and the success of its product pipeline is sustainability. Of the approaches discussed, those that had been in operation the longest used a diverse array of funding mechanisms to achieve sustainability.
- **Sharing of data and materials—**Making data and materials available and accessible is critical to progress. Establishing publically accessible repositories of tissue, nucleotide sequences, or clinical data for particular diseases is vitally important. These repositories facilitate sharing by requiring standardization of entries, validation of data, and the capability for direct input of data and samples by patients. Also important is the implementation of user agreements mandating that those accessing data or materials must share as well. Negotiations for sharing can be made more efficient through the use of standardized agreements.
- **Global reach—**When dealing with rare diseases affecting extremely small numbers of people, it is important to try to identify every patient afflicted worldwide. Doing so can make it possible to gather a large enough population for clinical trials and can also help deter-

mine the market for a product, aiding in the assessment of pricing and access.

- **Communication with FDA—**Drug sponsors have a legal right to meet with FDA regarding drugs in development. Early and frequent communication with FDA throughout the development process can increase the chances of a smooth, efficient process and a successful application. FDA can advise on trial planning and execution, such as the selection of appropriate end points for the indications desired.

ORGANIZATION OF THE REPORT

The chapters that follow summarize the presentations and discussions that took place during the workshop:

- **Chapter 2** provides an overview of the current financial landscape at the various stages of drug development, including the investors at each stage, the drivers of investment for those funders, and the current state of investments.
- **Chapter 3** reviews the regulations and opportunities that currently exist through FDA's Orphan Drug Program, and describes strategies for accelerating the development of therapies for rare and neglected diseases.
- **Chapter 4** is the first of four chapters offering specific examples of business models for the development of drugs for rare and neglected diseases. The funding models of four organizations are described: the Institute for OneWorld Health, a nonprofit pharmaceutical company; Cystic Fibrosis Foundation Therapeutics, a disease foundation that functions as a virtual drug company; Genzyme, a for-profit biotechnology company; and Celtic Therapeutics, a global private equity firm that functions as a virtual pharmaceutical company.
- **Chapter 5** addresses strategies to facilitate the sharing of data and research materials. Two successful models are highlighted: the Alzheimer's Disease Neuroimaging Initiative, a public–private partnership that is conducting a large observational longitudinal study of Alzheimer's, and the Genetic Alliance BioBank, a centralized repository for disease-specific clinical data and biological samples, as well as medical records, DNA/RNA, self-reported patient information, cell lines, tissue, and organs.
- **Chapter 6** provides examples of innovative ways in which intellectual property has been used to advance drug development for rare diseases. Examples discussed include pooling intellectual property,

depositing it into a trust, allowing open access to data, implementing socially responsible licensing, standardizing material transfer agreements, and creating new benefit-sharing arrangements.

- **Chapter 7** describes strategies for facilitating clinical trials. It reviews the regulatory tools available to assist with orphan drug development and approval processes, including fast track designation; accelerated approval; priority review; and early and frequent communication with FDA through such vehicles as Type A, B, or C formal meetings, special protocol assessments, or informal meetings.
- **Chapter 8** outlines areas identified as needing further discussion: (1) business models for the development of drugs for rare and neglected diseases, as it is still too soon to be able to distill broadly applicable lessons and best practices, and new models will continue to be created; (2) the current state of data and resource sharing and public access, with a focus on distilling best practices; (3) intellectual property issues as they relate to orphan drugs and rare and neglected diseases; and (4) policies applied to the review of orphan drug applications, with consideration of what new or revised policies might better facilitate the approval of such drugs.
- Finally, a number of resources mentioned throughout the workshop are available on the Internet. **Appendix C** provides a list of websites for those interested in the development of drugs for rare and neglected diseases.

2

Current Model for Financing Drug Development: From Concept Through Approval[1]

The cost of developing a new drug has been estimated to be more than $1 billion. Development of this scale involves multiple financing mechanisms, as well as the involvement of numerous partners throughout the process. As background for the workshop discussions, Dr. Caskey provided an overview of the current financial landscape at various stages of drug development, including the investors at each stage and the current state of investments, and put forth several suggestions for ways to facilitate drug development.

INVESTORS IN DRUG DEVELOPMENT

The principal investors in drug development differ at each stage. While basic discovery research is funded primarily by government and by philanthropic organizations, late-stage development is funded mainly by pharmaceutical companies or venture capitalists. The period between discovery and proof of concept, however, is considered extremely risky and therefore has been difficult to fund. Several initiatives discussed below have been undertaken to overcome this funding gap.

[1]This chapter is based on the presentation of C. Thomas Caskey, M.D., Director and Chief Executive Officer and Chief Operating Officer of the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases at the University of Texas Health Science Center.

Early- and Late-Stage Development

Historically, the largest government investments in basic drug discovery research have been made by the National Institutes of Health (NIH). The Defense Advanced Research Projects Agency (DARPA) has also contributed to the discovery stage by taking on some relatively high-risk biologic projects. Moreover, in part as a result of the public's impatience with the slow pace of the discovery process, state governments are increasingly taking the initiative in this area. One such example is the California Institute for Regenerative Medicine, a state agency established in 2005 by the California Stem Cell Research and Cures Initiative, which provides grants and loans for stem cell research and facilities at California's research institutions and universities. Another example is the Texas Cancer Initiative, under which state funds are dedicated to cancer research conducted in Texas. Beyond these public investments, private foundations are also taking a significant financial interest in the discovery process, facilitating progress by funding research in their particular areas of interest.

At the other end of the continuum is late-stage development, which is funded primarily by pharmaceutical companies or venture capitalists with some collaborative support from government sources, such as NIH. Such partnerships are critical in the transition from proof of concept to clinical development.

Translational Research: Discovery Through Proof of Concept

Between basic discovery research and late-stage development lies the critical step of proving the utility of a proposed drug. The funding gap that often occurs in this period has been referred to as the "valley of death." The risks are great and may be considered as not worth taking for products designed to treat rare and neglected diseases, which may ultimately yield a very limited return on investment. To help fill this funding gap, U.S.-based foundations have increased their investments in discovery and development for new drugs specific to their diseases of interest. In 2007 such groups invested approximately $75 million in biopharmaceutical companies, a 10-fold increase since 2000 (Gambrill, 2007).

At the government level, the Department of Health and Human Services' Small Business Innovation Research and Small Business Technology Transfer programs provide financial assistance to small companies attempting to advance their initial discoveries to commercial development. In recent years, NIH has significantly increased its focus on translational research. For example, NIH's National Center for Research Resources administers the Clinical and Translational Science Awards, which fund a national consortium of medical research centers that train physicians in

the drug development process. Likewise, the Food and Drug Administration (FDA) encourages the use of Cooperative Research and Development Agreements (CRADAs) to foster public–private partnerships in targeted areas of interest to the agency. Initiatives are taking place at the state level as well. The Texas Emerging Technology Fund, for example, is designed specifically to help companies finance proof-of-concept research. The fund invests in biologic sciences and biotechnology, as well as engineering, materials science, and information technology, and has committed funding to individual companies ranging from $500,000 to $10 million. The aforementioned Texas Cancer Initiative and California Stem Cell Research and Cures Initiative support research through this phase as well. In addition to government programs and philanthropy- and state-funded initiatives, many start-up companies, launched to develop discoveries emerging from academic laboratories, are being supported initially by venture capitalists and "angel investors."

CURRENT STATUS OF INVESTMENTS

Inhibitors of Development

Caskey argued that, despite the desire for development of new therapies, several environmental factors negatively affect new investments in drug development. Examples include decreased funding for basic research, regulatory barriers, and problems with drug safety that lead to product withdrawals. Elaborating on these points, Caskey emphasized first that the investment in basic research has been essentially flat in recent years. NIH funding has not increased significantly since its budget doubled from $13 billion in 1998 to $26 billion in 2003, and given inflation, its investment power has actually diminished over the last 5 years, in effect reducing the dollars available for funding new research. Fewer investments in basic research can result in fewer new drug therapy candidates, which in turn can result in fewer investments by private industry to advance promising candidates.

Second, navigating novel products or technologies through the existing regulatory pathways is challenging as scientific advances are made and regulations continue to evolve. In light of the increasing uncertainty of the regulatory process and possible increases in regulatory requirements throughout the development process, investors may shy away from investing in a product before there is clear evidence of its safety and effectiveness. An example is FDA's initiative to address biomarker evaluation. Although FDA currently allows the use of biomarkers as surrogate end points in some cases, evaluation of biomarkers is difficult, and the agency is working to

determine the best approach to the regulatory assessment of biomarker data.

Finally, Caskey argued that lawsuits following product withdrawals greatly affect new investments in development. For example, individual and class-action lawsuits following the withdrawal of Fen-Phen led to settlements of $20–30 billion (Caskey, 2007). This amount of money could potentially have funded the development of 30 to 40 new drugs.

Opportunities to Improve the Financial Landscape

When a program fails in Phase III clinical trials because of either a lack of efficacy or problems with safety, a great amount of money and time that have already been spent go to waste. Thorough identification and validation of drug targets is a critical step in early discovery research that can drastically reduce late-stage drug failures. However, even though a target may be validated and a drug may appear to have an acceptable safety profile, one can never know all of the safety issues that may arise when a new therapeutic is introduced into broad use in the market.

In addition to funding for the discovery and development of drug candidates, funding is needed for research on new technology platforms for validating targets and therapeutics. Recently, venture capitalists have taken an interest in companies developing new platforms. These new technologies can play a significant role in facilitating drug discovery and enhancing drug safety.[2] High-throughput screening platforms that evaluate DNA, RNA, or proteins have already advanced the art of drug discovery. One example is mRNA expression profiling, a powerful micro-array technology platform that was discovered by an academic laboratory, received additional research funding from NIH, and was then commercialized by industry. Profiling of mRNA expression can indicate the phenotype of cells and be used to characterize cancers, but has also been employed successfully in the drug discovery process to identify and validate new targets and measure the responsiveness of a target to a drug. Another platform example is biochemical pathway analysis using mass spectrometry to measure analytes, rather than nucleic acid methods or proteomics. Such a high-throughput method for assessing numerous markers and pathways associated with a disease or drug action can contribute to efficacy and safety analysis prior to clinical use of a drug.

[2]For more detailed discussion of technologies that are improving the efficiency of drug development and the safety of new products, see Caskey, 2007.

WAYS TO FACILITATE DRUG DEVELOPMENT

Caskey put forth a number of suggestions for overcoming the impediments to new drug discovery and development:

- **Academic initiatives**
  - The academic research community needs to increase investments in technology that can improve target validation and drug safety.
- **Government initiatives**
  - Government research funding aimed at addressing health challenges needs to be more focused on forecast morbidity and the cost of care in the United States.
  - FDA needs to be adequately funded so it can partner with drug developers and direct the research being performed toward answering important regulatory questions.
- **Private initiatives**
  - Small Business Innovation Research and Small Business Technology Transfer regulations need to be revisited and revised to allow for greater investment.
  - New incentives for high-risk investors need to be created, perhaps through tax law.
  - Private disease foundations' provision of support to the academic community for discovery and to industry for development is beneficial and should be embraced.
  - Experienced investors need to be brought into the innovation process earlier.
  - The pharmaceutical industry and academia need to work together to build a stronger U.S. industry.

3

The Food and Drug Administration's Orphan Drug Program[1]

New business models for the development of products to treat rare and neglected diseases have developed within a legal and regulatory framework that has been shaped largely by the 1983 Orphan Drug Act. Dr. Coté provided an overview of the Food and Drug Administration's (FDA) orphan drug program.

The year 2008 marks the twenty-fifth anniversary of the passage of the Orphan Drug Act and the establishment of the FDA's Office of Orphan Products Development (OOPD). In the decades before 1983, those with rare diseases suffered what Coté termed "pharmacologic neglect." It was impossible for pharma to earn a reasonable return on its research investment in therapies for such conditions given the small number of patients who would benefit. Academic laboratories would occasionally discover promising new therapies, but without the capital required to conduct the clinical trials necessary for FDA approval and without the interest of a pharmaceutical company in bringing these compounds to market, these potential new products remained undeveloped. While the science of drug discovery progressed rapidly during this period, yielding powerful insights into human biology and the pathologic processes of diseases, rarely were these insights applied to research on rare diseases.

The irony is that rare diseases provide a critically important window into disease processes that can be of benefit across the full range of medical research. For example, much has been learned about hemoglobin from

[1]This chapter is based on the presentation of Timothy Coté, M.D., M.P.H., Director, FDA Office of Orphan Products Development.

people with hemoglobinopathies, such as sickle cell anemia and thalassemia. Understanding of the urea cycle was gleaned from the experiences of patients with urea cycle disorders. Patients with diseases such as phenylketonuria (PKU) provided knowledge about amino acid metabolism. These are but a few of the hundreds of known examples. Absent patients with rare diseases, many basic aspects of medical science would be less well understood. Despite these benefits, however, opportunities for research on rare diseases and the ability of patients to receive licensed therapies for these illnesses have historically been limited.

In this context emerged the National Organization for Rare Disorders (NORD), a powerful political movement founded by grassroots organizer Abbey Meyers. She knew that rare diseases were individually infrequent but collectively common. Meyers and several others who shared her vision drafted legislation that would change the way drugs are developed. The most important feature was an allowance for 7 years of market exclusivity, during which a company could recoup some of the expense of drug development. Additionally, tax credits and exemptions from fees made it possible to build a sound business model on investments in products for rare diseases. Clarifying terminology, Coté explained that "rare" is defined by regulation as diseases that affect fewer than 200,000 people in the United States; "neglected" is the term used by the tropical medicine community. While tropical diseases have significant impact in the developing world, all tropical diseases are rare diseases as defined in the U.S. Orphan Drug Act.

Biotechnology as an industry was propelled into a major expansion by the Orphan Drug Act. Thousands of scientific, commercial, and humanitarian opportunities were made possible by the act that could otherwise not have existed. Historically, pharma has been less than fully responsive to these opportunities, but this situation is changing as the country's larger scientific and fiscal drug enterprise recognizes the value of investing in orphan drug development.

The crafters of the Orphan Drug Act also intended to jumpstart the science behind rare diseases. The establishment of the National Institutes of Health's Office of Rare Diseases is a prime example of this. Congress also established the Orphan Products Grant Program at FDA, administered by OOPD, which Coté believes "has become the single most tangibly productive grants program in the entire U.S. government." The program is currently funded at only $14 million per year and has been declining in buying power over the past 15 years; nonetheless, it has yielded 41 FDA-approved therapies.

During the 25-year history of OOPD, the program has been successful, granting more than 1,850 orphan drug designations, 326 of which have received full FDA marketing approval (see Figure 3-1). And as noted above, 41 of these drugs came out of the OOPD grants program. FDA

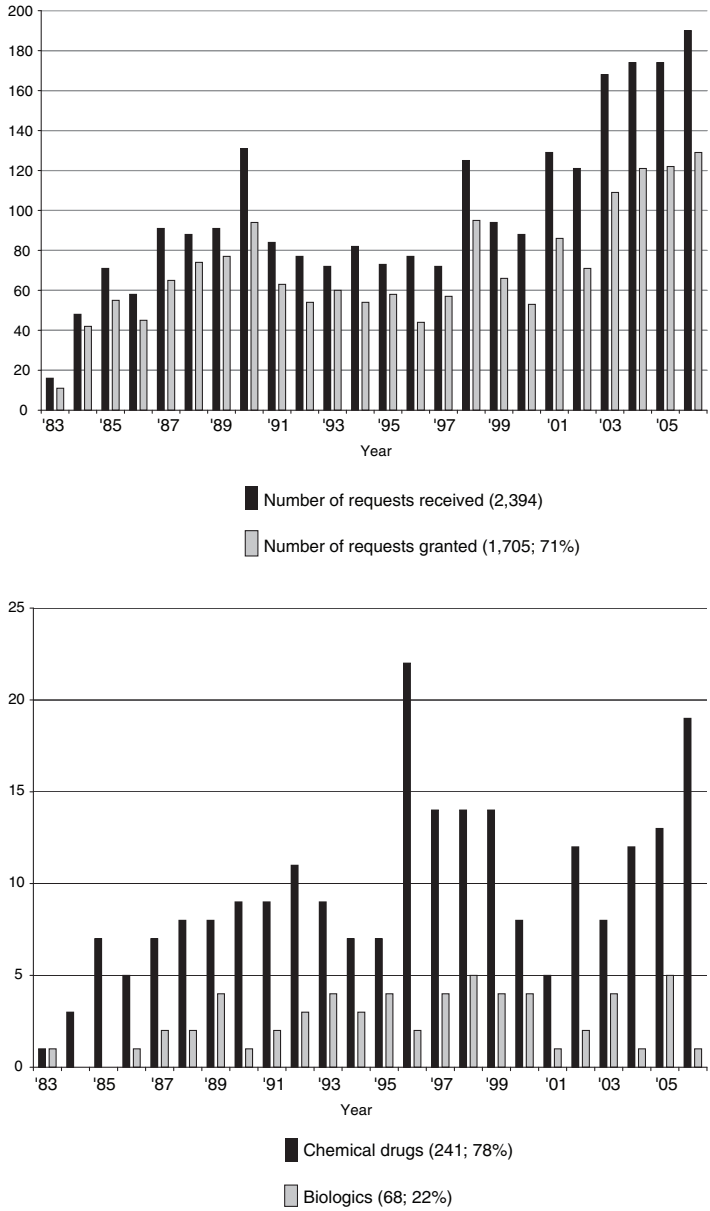

FIGURE 3-1 The number of products that received orphan designation and the number of new drugs approved from 1983 to 2005. Note that the numbers on the charts do not match the numbers in the text because the charts show data only through 2005, while Dr. Coté presented data through 2008.
SOURCE: Coté, 2008.

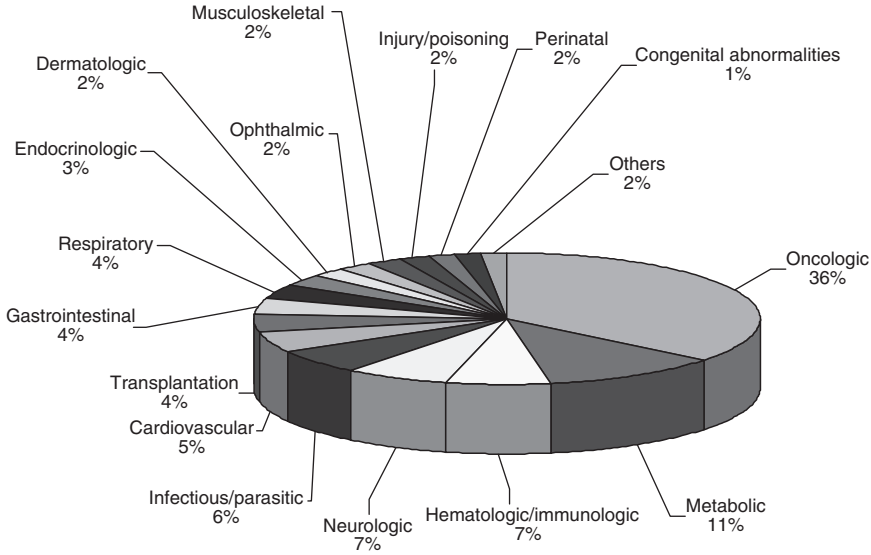

FIGURE 3-2 Diseases treated by orphan drugs, 2000 to 2006.
SOURCE: Coté, 2008.

estimates that collectively, these therapies have benefited about 12 million Americans with rare diseases, many of them children. Despite the program's accomplishments it has only resulted in therapies for less than 10 percent of such diseases—approximately 6,000 diseases are designated as rare. If one looks at orphan drug designations by organ system, the largest category is oncology drugs, but virtually every organ system has been impacted by an orphan drug designation (see Figure 3-2). As noted in the introduction to the workshop, FDA approvals overall have been decreasing. However, the proportion of FDA approvals for orphan drugs has been increasing, and now amounts to roughly one-third of all FDA approvals.

STRATEGIES

Coté emphasized that the objective of the workshop, and of his office, is to accelerate the development of therapies for rare and neglected diseases. To this end, he offered ten strategies for consideration.

Don't fix what isn't broken. The Orphan Drug Act is working well through the core activities of OOPD—making orphan designations, awarding grants, providing advocacy, and shepherding products through the FDA approval process. OOPD connects sponsors with the relevant review

divisions, which can advise on the design of clinical trials. It also protects the spirit of the Orphan Drug Act, considering all designations carefully to prevent specious products.

Nurture and expand FDA's relationships with industry. There are a host of reasons why pharma needs to be more involved in the development of orphan products. While the vast majority of the 1,850 orphan compounds came from academia and biotechnology companies, pharma has greater resources to develop these compounds and bring them to market. Orphan drugs can be part of a viable business model, as evidenced by the 326 orphan drug approvals, and can yield the occasional blockbuster (e.g., Gleevec®, Botox®, and synthetic erythropoetin [EPO], all of which started as orphan products). And for an industry currently struggling with its public image, there can be a positive payoff from addressing the unmet medical needs of people with rare diseases. In addition, the orphan drug process is an intermediate step in the growth of personalized medicine. Mastering the development of orphan drugs positions a company to develop products for smaller and smaller populations—the essence of personalized medicine. Moreover, individual pharmaceutical companies have vast libraries of compounds that have not yet been developed, primarily for commercial reasons.

Work together, and make the other party's job easier. OOPD wants new orphan drugs to reach those who need them, and sponsors want to have new products in their portfolio. OOPD needs the help of all applicants to advance the process as effectively as possible. With designation applications, for example, brevity is key. Although applicants must demonstrate that a drug has potential efficacy for a rare disease or condition that affects fewer than 200,000 people in the United States, Coté suggested this could be done succinctly in two or three pages. In addition, FDA needs to make the process more transparent to applicants by, for example, issuing guidance and performing more outreach. With regard to involving patients and patient advocates, although OOPD does work with patient advocacy groups, there are 6,000 rare diseases, while OOPD has a staff of 25. Therefore, the office relies on interactions with umbrella organizations, such as NORD and the Genetic Alliance.

Understand the value of the grants program. As noted earlier, 41 drug approvals came out of OOPD's grants program, a clear demonstration of its significant success. Yet the total budget for the program has remained essentially flat when inflation and the increasing costs of conducting clinical trials are taken into account, and the program is currently funded at only $14 million. During the open discussion following Coté's presentation, one participant who is not currently a federal employee urged workshop participants to discuss with their members of Congress how increasing the grants funding for OOPD could yield a substantial payoff for human health.

Focus on tropical infectious diseases. The last 50 years has seen very limited development of anti-infective drugs for the developing world. However, with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the establishment of the priority review voucher, this situation could finally change. The priority review voucher uses current market forces to create new development incentives. Prior to FDAAA, once FDA had approved a new orphan drug to treat a tropical disease, the sponsor found itself in the difficult position of having a lifesaving new drug that it could not sell since the people who needed it could not afford it. Under FDAAA, the sponsor of a New Drug Application (NDA)/Biological License Application (BLA) for a drug to treat a tropical disease receives a priority review voucher that is redeemed on a subsequent NDA/BLA and ensures review and action by the agency within 6 months of submission of that application. The critical aspect of the priority review voucher is that it is transferable and can be sold to another sponsor, which can then apply it to any other drug. Getting a product to market more rapidly can be highly valuable to a large pharmaceutical company with a potential blockbuster in the pipeline (some say a blockbuster can earn $5–10 billion per year), and selling the voucher generates income for the sponsor of the orphan drug. In addition to the new priority review voucher system, FDA is working with the World Health Organization (WHO), OneWorld Health, the Sabin Institute, and the Gates Foundation on the possibility of establishing an "orphanage" of early-stage drug candidates for tropical diseases. This entity would be housed within an existing nongovernmental organization and created fairly rapidly, perhaps through a workshop involving no more than 12 professionals who would generate 40–50 orphan designation applications over the course of 1 week. Drug candidates entered into the orphanage would already be eligible for the priority review voucher and have both FDA and European Medicines Agency (EMEA) orphan status, making this a valuable resource for pharmaceutical and biotechnology companies wishing to acquire orphan drug candidates for the purposes of obtaining their own priority review vouchers.

Know thyself. While the numbers of orphan designations and approvals are known, there are other important statistics that OOPD has not tracked. Moving forward, OOPD plans to determine the proportion of designated orphans for which Investigational New Drug (IND) applications have been submitted; the number of NDAs or BLAs that have been filed; the phase of development of each product and the locations of ongoing clinical trials; and the projected timeline for progression between development Phases I, II, and III. Lastly, OOPD plans to explore whether it can identify predictors for successful development and approval.

Know the disposition of all designees. Over 1,850 products have received orphan designation. Although 326 orphan products have been

approved, OOPD is interested in determining the status of the remaining 1,525 orphans that have not yet received approval. While some are probably in development, others have been abandoned for various scientific or business reasons, and it is likely that some of these designees still hold promise. OOPD plans to develop criteria that could be used to screen the regulatory submissions for the remaining designated orphans to determine which hold promise.

Explore the possibility of orphan policy in drug review. There is no special policy for the review of drugs to treat rare diseases; prior to approval, all drugs are required to have shown "substantial evidence of effectiveness" (21 CFR § 314.50). And while the FDA review divisions have, according to Coté, sense, sensibility, and sensitivity with regard to the issues surrounding orphan drugs, the level of understanding is not homogeneous. FDA would like to consider what if any policies might be needed to better facilitate the review of orphan drugs and is beginning discussions to that end internally and with Institute of Medicine (IOM) leadership.

Mentor the review divisions in the fundamental science underlying small clinical trials. In 2001, the IOM released a report on conducting and interpreting small clinical trials (IOM, 2001). Expanding on this study, OOPD would like to establish a curriculum to enhance the knowledge of reviewers regarding the fundamental science underlying small clinical trials. As highlighted in the IOM report, there are new methodologies, each with its own strengths and weaknesses, with which reviewers should be familiar. OOPD hopes to create a cadre of go-to reviewers who would have expertise in small clinical trials and interpretation of the data that orphan drug sponsors would submit, and would employ these new methodologies.

Act globally. OOPD has worked to establish relationships with regulatory agencies around the world, particularly EMEA. Globally, there are patients with the same diseases and researchers working to understand the same underlying science. EMEA passed its own orphan drug act in 1999, and while there are some important differences, the EMEA and U.S. acts have many similarities. EMEA and FDA now share a joint application form for orphan product designation that can be submitted to either or both EMEA and FDA. The processes are still independent, but the agencies hold monthly teleconferences and are reviewing many of the same applications. There is also an exchange program whereby people from the European orphan drug office and OOPD meet to learn how each operates. Coté noted that OOPD has not yet reached out significantly to Japan and other countries, but that such interactions are planned for the future.

4

Diverse Funding Models

There are multiple potential approaches to funding the discovery and development of drugs to treat rare and neglected diseases. The four speakers in this workshop session described their organizations' unique approaches to facilitating drug development for rare and neglected diseases: a not-for-profit pharmaceutical company model, a disease foundation that operates a virtual company linking investors with biopharmaceutical companies, a for-profit company with a vested interest in rare diseases, and a global private-equity fund dedicated to advancing drug discovery. Highlights of each of the four models are provided in Box 4-1.

INSTITUTE FOR ONEWORLD HEALTH: A NOT-FOR-PROFIT PHARMACEUTICAL COMPANY[1]

Ten million children around the world die every year. More than one-third of childhood deaths occur in the neonatal period. Children who survive past infancy succumb to a variety of diseases, including pneumonia, diarrhea, malaria, measles, and AIDS; malnutrition is an underlying contributor in more than half of these cases (Bryce et al., 2005). These statistics were striking and unacceptable to Dr. Hale, and inspired her to found the Institute for OneWorld Health, a not-for-profit pharmaceutical company focused on neglected diseases in the developing world. Such diseases are not

[1]This section is based on the presentation of Victoria Hale, Ph.D., Founder and Chair of the Board of Directors, Institute for OneWorld Health.

BOX 4-1
Examples of Business Models for Funding the Development of Drugs to Treat Rare and Neglected Diseases

INSTITUTE FOR ONEWORLD HEALTH (IOWH)

Business Model
Not-for-profit pharmaceutical company

Structure
A small team of pharmaceutical company experts, founded in 2000 with seed funding from the Bill and Melinda Gates Foundation.

Approach
Identify promising drug candidates, complete clinical trials, secure local manufacturing and regulatory approval in countries in which target diseases are endemic, and form partnerships to ensure drug distribution. IOWH strives to be opportunistic and flexible, engage industry partners, bridge industry and the public sector, focus on development, not duplicate available global resources, and ensure local government support.

Strategies
- Find new approaches to old diseases.
- Focus on high-risk, high-reward projects.
- Start with parasitic diseases (for which there are no vaccines).
- Seek to find new uses for older, off-patent drugs.

Portfolio
- Public health tools—for disease elimination programs (e.g., paromomycin, a cure for visceral leishmaniasis)
- Consumer products—the mother as the decision maker and purchaser (e.g., antidiarrheal medication)
- Prescription drugs—accessed through the formal health care system (e.g., Chagas drug)
- Active pharmaceutical ingredients—supplier to industry (e.g., biosynthetic artemisinin analogues)

CYSTIC FIBROSIS FOUNDATION THERAPEUTICS, INC. (CFFT)

Business Model
"Venture philanthropy"

Structure
Wholly owned, nonprofit drug discovery and development subsidiary of the Cystic Fibrosis Foundation with eight staff members.

Approach
Establishes business relationships with biotechnology and pharmaceutical companies and works with them to reduce the risk of their investment in cystic fibrosis treatments by providing financial support, access to leading cystic fibrosis experts and research tools, and access to the Cystic Fibrosis Therapeutic Development Network of Cystic Fibrosis Care Centers for facilitation of clinical trials.

General Elements of Alliance Agreements
- Funds are provided on a matching basis for preclinical and clinical development.
- Awards are milestone driven.
- A scientific advisory council oversees progress.
- Upon approval of a drug, CFFT receives a multiple of its investment (or a royalty based on sales), which it can then reinvest in new products.

GENZYME

Business Model
For-profit company

Structure
Biotechnology company founded in 1981. Currently more than 10,000 employees worldwide and annual revenues exceeding $3 billion.

Approach
A sustainable business model for drug development for rare and neglected diseases requires three basic elements:
- The therapy must be effective and address an unmet medical need, presumably treatment for a disease that causes a life-threatening, severe morbidity.
- There needs to be a global market.
- The price must be sustainable.

Research and Development Philosophy
- Genzyme pursues areas in which there is a severe, unmet medical need.
- The therapy must be disease modifying and/or lifesaving.
- The therapy must be testable.
- Post-approval, Genzyme is committed to optimizing patient care and access.

CELTIC THERAPEUTICS, LLLP

Business Model
Global private equity firm

Structure
A "virtual pharmaceutical company" comprising a management company that runs a private equity fund and a biomedical development organization that devel-

continued

BOX 4-1 Continued

ops the firm's strategy and manages the outsourcing of all product development components.

Approach

The company seeks to acquire and invest in novel therapeutic drug candidates that can address unmet medical needs. It buys, licenses, or forms an alliance with a biotechnology company for one of its promising product candidates for a rare or neglected disease that is in Phase IIA, develops the product to the point at which a large pharmaceutical partner will be interested, and then sells it at auction to a pharmaceutical company. A key feature of a "virtual pharma" is that traditional fixed costs (e.g., human resources and facilities) are converted to variable costs (e.g., contract research organizations and consultants). The model can provide returns to investors following commercial distribution by a pharmaceutical partner, or can help fulfill the mission of a philanthropic organization by facilitating noncommercial distribution through a public–private partnership.

necessarily rare in those areas of the world.[2] Intestinal worms, for example, are rare in the United States but affect 3 billion people globally. Likewise, although almost unheard of in the United States, malaria affects 500 million people worldwide, lymphatic filariasis 90 million, and leishmaniasis 14 million.

Research and discovery can occur in a variety of venues, but bringing a product to market requires the involvement of a biopharmaceutical company. Blockbuster drugs have made the industry highly profitable, but the business need to develop the next blockbuster means that few if any company resources are available for addressing global health inequities and diseases of the poor. The discoveries, technologies, and expertise exist, and there is a desire on the part of pharmaceutical professionals to address global health issues, but a new model is needed for the development of affordable drugs to treat infectious diseases in the developing world.

Creative Funding and Social Enterprise

OneWorld Health was launched in 2000 as an experiment, modeled after the pharmaceutical industry but eliminating the profit requirement

[2]As noted by Coté in Chapter 3, "rare" is defined in the U.S. Orphan Drug Act as diseases that affect fewer than 200,000 people in the United States. "Neglected" and tropical diseases have significant impact in the developing world, but all are rare diseases as defined in the U.S. Orphan Drug Act.

from the business plan. There is little venture capital interest in these markets, and start-up activities were deliberately funded primarily through philanthropy. There are no shareholders or returns to be paid, and the company cannot be bought, merged, or acquired. The primary target is neglected diseases of the poor resulting from infectious agents or vectors that are not generally prevalent in the developed world.

Initial program funding was provided by the Bill and Melinda Gates Foundation. OneWorld Health now has the task of convincing new funders that there are worthwhile investments to be made in research and product development addressing neglected diseases. The optimal business model would be self-sustaining and would not rely exclusively on philanthropy. Ultimately, Hale imagines a hybrid organization that would be socially driven and could support itself either wholly or in part with revenues. She would like to see the emergence of a not-for-profit pharmaceutical sector, and to that end, OneWorld Health has helped start nine nonprofit organizations focused on the development of drugs, vaccines, and diagnostics.

Hale suggested that somewhere between the not-for-profit and for-profit models lies a realm of new business model possibilities. Although philanthropy enables a significant amount of research and development in the global health sector, pharmaceutical partnerships are increasingly expected. One emerging funding source is social investors—people who have money to loan or invest and want to use it to drive social change, and who have a strong desire to be engaged and understand how their money is being used.

Regardless of the funding source and whether a company is for-profit or not-for-profit, the key to a successful business model is sustainability. Funding from a single source does not result in a sustainable model. Therefore, having a diversity of funding sources is important, and organizations should strive to obtain loans and grants in addition to philanthropic funds. A principal strategy of OneWorld Health is varying its approach depending on the project and remaining flexible, nimble, and nonbureaucratic. The organization is opportunistic and pragmatic, and adapts as necessary to move a particular technology forward.

Intellectual Property

All intellectual property is potentially profitable. It is now generally accepted, however, that when it comes to global infectious disease technology, intellectual property is royalty free for countries that rank in the bottom two-thirds of the World Bank's ranking of countries by economic development (which often includes India and China). The movement to this end began with a few progressive investigators and universities, and others followed. Today under Gates Foundation leadership, neglected tropical dis-

eases are generally acknowledged to be not-for-profit territory with respect to intellectual property.

What Defines Success?

In the short term, OneWorld Health has demonstrated that people can work together through a not-for-profit company to develop a medicine for a neglected disease. For example, OneWorld Heath developed a new use for paromomycin, an antibiotic already on the market for 30 years, as a lifelong cure for visceral leishmaniasis, a parasitic infection.[3]

While regulatory approval of a new product or a new use of an existing product is necessary for success, it is not sufficient. To be successful in the medium term, the product must have impact, which means it must save lives. And to do that, the product has to reach those who need it, many of whom live in very rural areas. Accomplishing this requires partnerships with social entrepreneurs. For the long term, the mark of success will be a sector that is sustainable, with broad corporate and government engagement and acknowledgment that work on some diseases simply will not be profitable.

Hale encouraged the orphan drug development community to be bold and disruptive with regard to both systems and people: engage the public; engage the government, including the Food and Drug Administration (FDA) and Congress; and challenge the current experts and leaders in the field to break existing boundaries.

CYSTIC FIBROSIS FOUNDATION THERAPEUTICS, INC. (CFFT): A VIRTUAL COMPANY FOR MANAGING DRUG DISCOVERY AND DEVELOPMENT ALLIANCES[4]

The Cystic Fibrosis Foundation was established in 1955 by a group of parents of children with cystic fibrosis seeking to ensure that their children would get the best of care. At the time, the mechanism of the disease was unknown. In 1989 a team of researchers, supported in part by funding from the foundation, identified the gene responsible for the disease. This gene normally produces a protein now known as the cystic fibrosis conductance transmembrane regulator, or CFTR. A defect in the CFTR gene leads to defective mucociliary clearance in the lung, setting up a cycle of

[3]Paromomycin was approved as a treatment for visceral leishmaniasis by the Drug-Controller General of India in September 2006.

[4]This section is based on the presentation of Diana Wetmore, Ph.D., Vice President of Alliance Management, Cystic Fibrosis Foundation Therapeutics, Inc.

mucus obstruction, infection, and inflammation that ultimately leads to lung destruction and death.

Following elucidation of the pathogenesis of cystic fibrosis, Pulmozyme, an enzyme for thinning and clearing mucus and the first drug in 30 years to be developed specifically to treat cystic fibrosis, came to market in 1994. The anti-infectives tobramycin (TOBI) and azithromycin reached the market in 1998 and 2002, respectively, and in 2004, hypertonic saline became available to aid mucus clearance. Today there are three CFTR-targeted candidates currently in clinical trials (see Figure 4-1).

The Cystic Fibrosis Foundation measures the success of research and development efforts by whether they translate to increased length of survival or significantly enhanced quality of life for cystic fibrosis patients. Each year since 1985 has seen an increase in the expected life span of patients with the disease, and over the last several years the slope of that curve has increased. Although full statistics are not yet available, the foundation believes this is due in part to the use of TOBI, Pulmozyme, and hypertonic saline. Given the complexity of the disease, these drugs span a range of therapeutic targets. Disease-preventing therapies, introduced at a very early age to prevent damage to the lung, include gene therapy, CFTR protein modulation, and restoration of ion transport. At the other end of the spectrum are disease-modifying therapies that help manage the manifestation and progression of the disease; they include drugs that thin and clear mucus, anti-inflammatory and anti-infective drugs, products that can increase the success of lung transplantation, and nutritional supplements.

CFFT, established in 2000, is a wholly owned nonprofit drug discovery and development subsidiary of the main foundation. Its primary mission is to convince biopharmaceutical companies to develop drugs for a disease that affects only 30,000 people in the United States and 70,000 worldwide. The primary strategy involves reducing the risk to development partners of entering the cystic fibrosis field and making products more attractive from a business perspective. Keys to success include:

- understanding the basic defect, the underlying science, and the pathophysiology of cystic fibrosis;
- establishing a business relationship with the partner; and
- providing access to patient populations and information systems to support clinical development.

Risk is a combination of uncertainty, cost, and timing. CFFT works to reduce risk to partners by sharing the financial burden and by working with the cystic fibrosis research community to validate therapeutic targets, develop clinically relevant disease models, and validate assays and discovery tools. In addition, the organization understands the proof-of-concept pro-

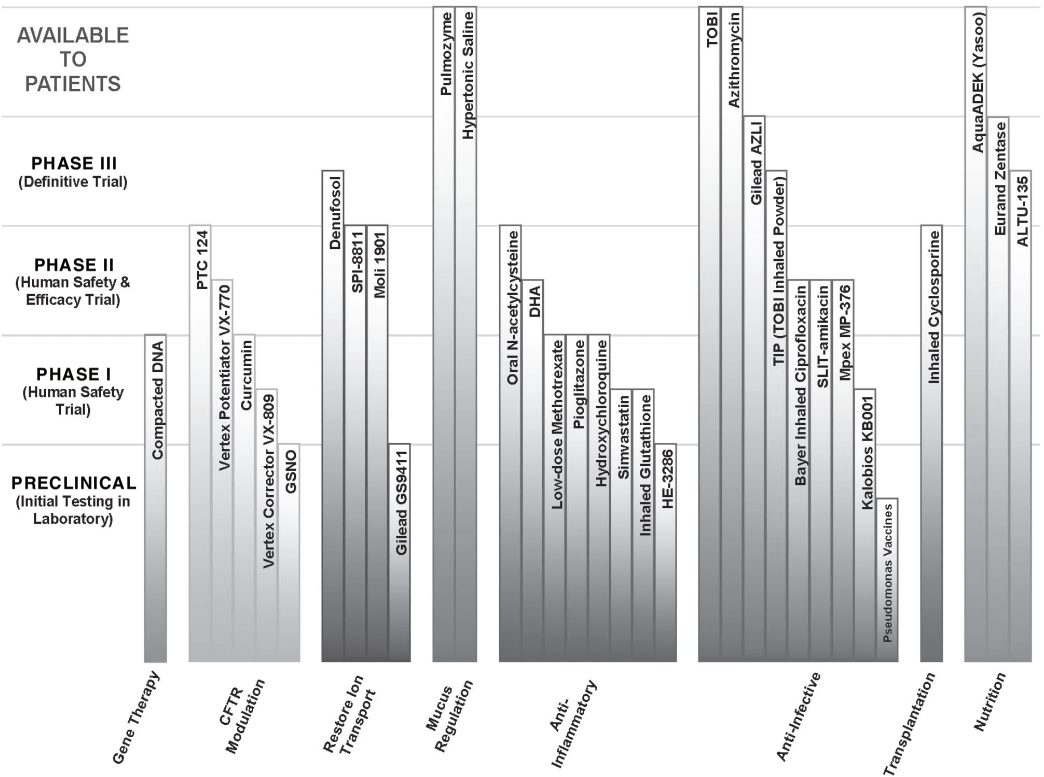

FIGURE 4-1 Breadth and depth of the Cystic Fibrosis Foundation Therapeutics pipeline as of April 30, 2008. Three cystic fibrosis conductance transmembrane regulator (CFTR)–targeted candidates are in Phase III clinical trials.
SOURCE: Wetmore, 2008.

cess and has created a Therapeutics Development Network of cystic fibrosis clinical care centers with experience in the design and conduct of clinical trials for and access to patients, which can improve enrollment efficiency (see Figure 4-2). This infrastructure assures partners that if their products are ready for clinical development, CFFT will help streamline the clinical trial process. The clinical care centers in the network receive grant support from CFFT to ensure that they are not only providing excellent care, but also training their staff in the conduct of clinical trials. In addition, the network includes an independent data safety monitoring board whose members are familiar with the clinical development of drugs for cystic fibrosis.

It is important to understand that, although CFFT is a virtual company and necessarily functions through the actions of others, it does not simply provide funding and expertise. The alliances formed are truly business relationships, and there is a peer-reviewed, milestone-driven mechanism to enable evaluation of promising therapies. CFFT agrees to provide funds on a matching basis for preclinical development and for initial clinical trials, and negotiated portions of the monetary awards are dependent on the achievement of predetermined milestones. A scientific advisory council comprising CFFT and sponsor representatives provides oversight and progress reports. CFFT does expect a return on investment. The organization was designed to shoulder risk, and it is understood that there is no return on investment if a drug is not approved. If a drug makes it to market, however, CFFT expects its investment to be repaid so it can reinvest in the pipeline, and the agreements made ensure that CFFT receives a multiple of its original investment (or a royalty payment based on net sales). As an adjunct, CFFT has created a Technology Access Program that provides funding for the development and validation of new technology platforms.

After the development agreement with a sponsor is in place, CFFT functions as an external expert advisor, enabling, facilitating, and troubleshooting. For example, CFFT can save a business partner 6 months on the learning curve by having validated assays available at contract research organizations or by providing access to positive control compounds or cellular, antibody, or protein reagents. CFFT can also facilitate collaborations between a sponsor and academic partners, as well as access to intellectual property. And through regular advisory meetings, CFFT can assist in resolving issues and connect a sponsor with experts in pharmaceutical development. These elements of CFFT's approach create an acceptable level of risk for industry partners, and help ensure that the pipeline of cystic fibrosis treatments remains full and that promising products eventually reach patients.

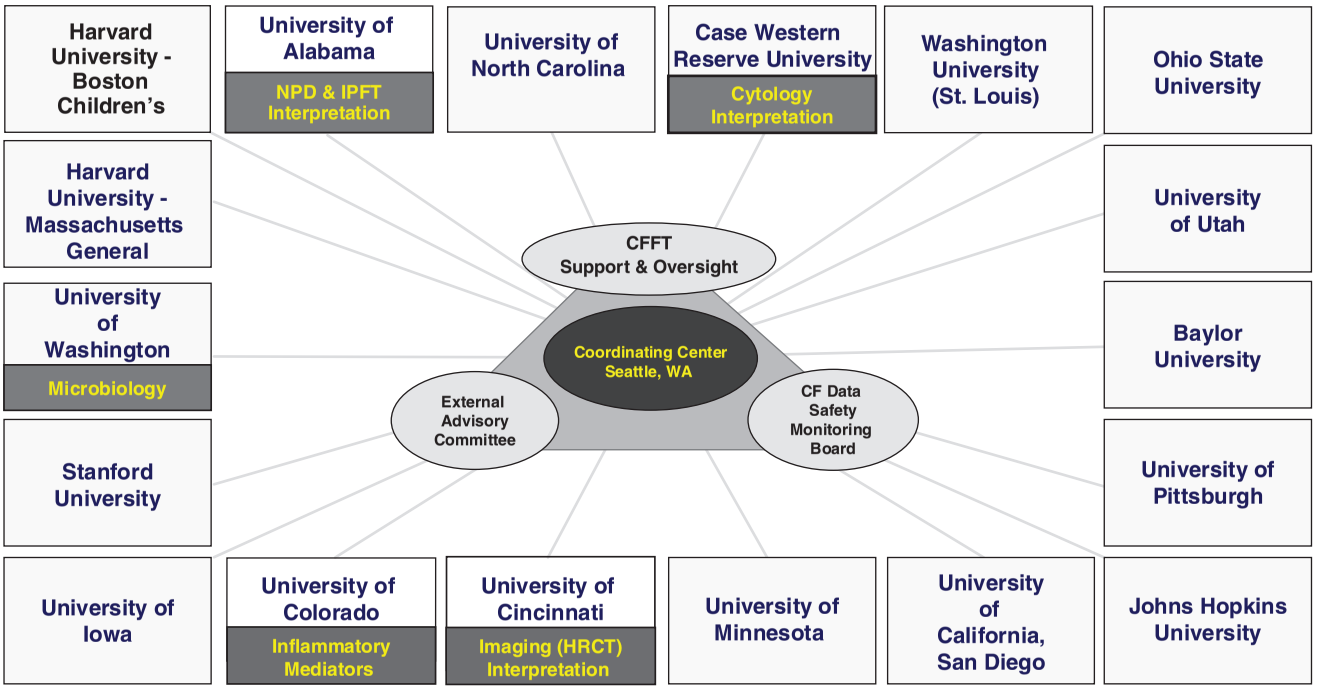

FIGURE 4-2 The Therapeutics Development Network of cystic fibrosis clinical care centers. Principal investigators and staff have experience in the design and conduct of clinical trials for cystic fibrosis and access to patients for trial enrollment.
NOTE: CF = cystic fibrosis; CFFT = Cystic Fibrosis Foundation Therapeutics, Inc.; HRCT = high-resolution computed tomography; IPFT = infant pulmonary function testing; NPD = nasal potential difference test.
SOURCE: Wetmore, 2008.

GENZYME: SURVIVING AND THRIVING AS A FOR-PROFIT COMPANY IN THE RARE DISEASE ARENA[5]

Gaucher disease affects fewer than 1 in 1,000 individuals of Ashkenazi Jewish descent and 1 in 100,000 of the larger population. Those affected are missing an enzyme without which lipid accumulates in the liver and the spleen, as well as the bone marrow, ultimately resulting in a crippling bone disease and early mortality.

Cerezyme, an enzyme replacement therapy for Gaucher marketed by Genzyme, produced revenues in excess of $1 billion in 2007. In light of this remarkable success, Dr. Meeker raised two questions for consideration. First, is this a reproducible model? And second, is it necessarily a good thing that a product for an orphan disease can yield $1 billion in revenue?

Genzyme was founded in 1981. In 1988 it was a small bulk manufacturer of pharmaceuticals and also had a nascent cystic fibrosis research program. With survival of the company as the primary goal, its leadership made a decision to devote all resources to pursuing one therapy for one disease, and saw Gaucher disease as offering that opportunity. In 1991 Genzyme's first Gaucher treatment, Ceredase, was approved on the basis of a 12-patient pivotal trial, with the dose and the total number of patients enrolled being chosen primarily on the basis of the amount of enzyme the company had available.

At that time, the approach of investing all resources in one drug for one disease was regarded as unsustainable, and the company's plan for the longer term was to pursue more conventional targets. In 1993, the CFTR gene had recently been cloned, and venture capitalists were willing to invest $85 million in a Genzyme cystic fibrosis program over a 5-year period. Part of the reason, Meeker believes, was recognition not only that the Orphan Drug Act had opened doors for drug approval, but also that the model for Gaucher disease had shown that a company could make a viable business out of treating a small population.

Ceredase was a human-derived product; 22,000 human placentas were required to harvest enough enzyme to treat one patient for 1 year. Its approval coincided with the peak of the AIDS epidemic, and a manufacturing process requiring such a massive quantity of pooled placentas posed a significant safety and regulatory challenge. In 1994, a recombinant plant protein version of the product, called Cerezyme, was approved, eliminating the need for human tissue. Today, Gaucher patients treated early, before significant damage has occurred, have every prospect of living a normal life.

[5]This section is based on the presentation of David Meeker, M.D., President, Lysosomal Storage Disorder Therapeutics, Genzyme.

The first Gaucher patient treated in a clinical trial in 1983 is now married with children.

For-Profit Model and Philosophy

In Genzyme's view, a sustainable business model for the development of drugs to treat orphan diseases requires three basic elements:

- The therapy must be effective and must address an unmet medical need, presumably one involving a life-threatening, severe morbidity.
- There needs to be a global market.
- The price must be sustainable.

The company philosophy that evolved from the Ceredase/Cerezyme experience was that Genzyme would pursue areas in which there was a severe unmet medical need. A therapy would have to be disease modifying and/or lifesaving. And it would have to be testable—a challenge given the small populations involved when one is dealing with rare diseases.

Post-approval, Genzyme is committed to optimizing patient care, as opposed to simply convincing physicians that the treatment for their Gaucher patients is Ceredase. Thus the company seeks to facilitate an environment in which patients with Gaucher disease have a reasonable expectation of being seen and diagnosed by a disease expert so informed decisions can be made about therapy. Ultimately, accomplishing this means fostering the development of sustainable health care systems around the world capable of caring for patients with rare diseases. The nature of such diseases is that systems are not set up to deal with them or staffed with the necessary experts, nor are these conditions a priority for payers.

The industry recognizes that if a company has a lifesaving therapy for a disease such as Gaucher, it has a global responsibility. This is particularly true for very high-priced products, which many countries cannot afford. Providing drugs free of charge is not a sustainable solution. To help create a sustainable model, Genzyme seeks to establish in-country partnerships that demonstrate a commitment on the part of the country.

Challenges

The science of rare diseases is the primary challenge faced by companies seeking to develop therapies for such conditions. There are many diseases that affect the central nervous system (CNS), for example, for which there simply is not enough scientific information available to enable the development of safe and effective treatments. Once the mechanism of a disease

is understood, moreover, a proposed therapy must be testable. Cerezyme reverses the effect of Gaucher, but there are a number of diseases whose damage is not reversible, and the goal of a therapy is to slow the progression of the disease. Demonstrating decreased progression is very different statistically from showing reversal.

Another challenge, alluded to earlier, is the practicality of running a clinical trial when the patient population is extremely small. One example is Niemann-Pick B disease, a genetic condition, much like Gaucher, affecting 500 to 1,000 patients worldwide. Genzyme began a Phase I trial of a therapy for this condition in January 2007 at a single center in New York City. Patients are also being screened in the United Kingdom, Germany, Chile, Brazil, Saudi Arabia, and New Zealand. Only eight patients have been enrolled to date. Upon completion of Phase I, more patients will be needed for Phase II, and it is unclear whether gathering these subjects will even be possible.

A third challenge can be manufacturing enough product, even for a small population. For example, the dose of Myozyme for Pompe disease is 20 mg/kg, an amount requiring significantly more protein production than is necessary for Genzyme's other therapies, which are administered at doses of about 1 mg/kg. Genzyme knows this is a potentially lifesaving drug, and is in the process of scaling up production from 160 to 2,000 liters and ultimately to 4,000 liters. The company is providing the drug free in many places, including the United States, while it works through the process of scaling up production and meeting regulatory requirements. To date, Genzyme has invested more than $600 million in developing this drug.

Indeed, cost and pricing represent a final, critical challenge for companies seeking to develop drugs to treat rare diseases. Given the success of Cerezyme, some might suppose that a company can develop a therapy for a rare disease, charge a high price, and be successful. However, this is a simplistic view. For many rare diseases, the total number of affected patients is unknown. Moreover, global access is uncertain, and while a company may receive broad approval of a drug, its business model will not be sustainable if the company is reimbursed in only one country. Ultimately, the reason Cerezyme revenues total $1 billion today, 15 years after the product's launch, is not the price; it is the fact that Cerezyme is treating 5,000 patients in 90 countries around the world (1,500 within and 3,500 outside of the United States).

With respect to pricing, the cost of production and the cost of development are factors, but the most important driver is rarity. In 2004, for example, 14 million individuals were prescribed Nexium, 8,000 were prescribed the orphan drug Gleevec, and approximately 1,500 were prescribed Cerezyme. If there were 100,000 patients with Gaucher disease, the cost of Cerezyme would be 1–10 percent of what it is today ($200,000 per year).

In the developing world, even for such a costly treatment, partnerships can facilitate access. The per-patient cost is extremely high, but the total cost for a country to treat its affected population is a negligible proportion of its overall health care budget. Sustainable pricing and a global market are key to the development of drugs for rare diseases.

Another orphan disease therapy in the Genzyme portfolio is Aldurazyme, a treatment for mucopolysaccharidosis I (MPS I), which is even rarer than Gaucher disease. With CNS involvement, MPS I leads to death before age 5. A more intermediate phenotype with no CNS involvement leads to death by age 10. Aldurazyme does not treat the CNS aspects of the disease, but if patients are treated early, it can significantly prolong life by alleviating systemic manifestations. In developing Aldurazyme, Genzyme partnered with BioMarin; given the rarity of the disease, neither company alone could have developed the product. After 5 years on the market, Aldurazyme is expected to have grossed $140 million globally in 2007. The cost of maintaining production of a treatment for a rare disease is significant, so the profit derived from Aldurazyme is very small, but the costs are shared by the two companies. This arrangement works for a product that is part of a larger portfolio, but would not be suitable for a company producing a single product.

Summary

Whether a drug indication under study benefits a large or a small population, therapies must make a difference. A sustainable business model for the production of drugs to treat rare diseases is a shared responsibility between industry and the health care system. Pricing must be viewed as a function of rarity, and future investment depends on a viable market. While funding research is important, the real driver is at the other end of the continuum, when there can be a guaranteed market for these drugs. Regardless of the size of the market, any product that is approvable, suggested Meeker, can become a valuable part of a company's portfolio.

CELTIC THERAPEUTICS, LLLP: A PRIVATE-EQUITY MODEL FOR ADDRESSING GLOBAL HEALTH[6]

As discussed previously, along the drug development continuum between early discovery/early development and late-stage development/approval lies a substantial gap in which sufficient funding is lacking. Dr. Corr elaborated on this concept by discussing the imbalance of resources between drug

[6]This section is based on the presentation of Peter Corr, Ph.D., Co-founder and General Partner, Celtic Therapeutics Management, LLLP.

candidates in small biotechnology companies and the resources allocated to research and development by large biotech and pharma companies. He then discussed approaches to bridging this gap, including that taken by his company, Celtic Therapeutics, LLLP.

Opportunities in the Gap

Venture capitalists tend to support emerging companies through initial proof-of-concept, but the price of development increases after that stage and continues to do so through advanced development to approval. Pharmaceutical companies do consider early-stage licensing but are often on a fixed budget for early-stage research, and bringing in products from the outside can mean eliminating an existing program. Furthermore, in Phase II many questions about compounds remain, and only 30–40 percent make it to the next phase, a fact that discourages many companies from investing in compounds that are in early development. Generally, a smaller biotechnology company that cannot afford to move forward with a compound on its own may discuss an agreement with a large pharmaceutical company, but such discussions may extend for up to 18 months, during which time the biotechnology company must continue to spend money and consume critical patent life of a potential product.

One method of bridging the funding gap during this period is by forming precompetitive alliances with organizations such as the Critical Path Institute (C-Path), the Genetic Association Information Network (GAIN), and the Biomarkers Consortium. C-Path, which was created to support FDA in implementing the Critical Path Initiative, facilitates collaborative projects among FDA, academia, and industry that accelerate product development. GAIN brings together corporate partners and the National Institutes of Health (NIH), in association with the Foundation for the NIH, to fund the genetic analysis of thousands of patients and allow researchers to identify genetic causes for the 20 most common diseases in the United States. The Biomarkers Consortium is a collaboration among FDA, industry, NIH, and the Foundation for the NIH aimed at identifying quantitative biological markers that aid researchers and regulators in developing and assessing treatments.

Pharmaceutical companies also form alliances with biotechnology companies. Examples are the Wyeth–Elan collaboration on an Alzheimer's vaccine; the Merck–GTx alliance on selective androgen receptor molecules (SARMs) to treat muscle loss; and the Pfizer Incubator in La Jolla, which provides resources and support to promising entrepreneurs and facilitates the commercialization of innovative products.

Thus a number of models for successful alliances exist. Corr suggested,

however, that new models are needed, particularly for rare diseases, for which the markets are small.

The Celtic Therapeutics "Virtual Pharma" Model

Corr and colleagues founded the global private equity firm Celtic Therapeutics to bridge the gap between discovery/preclinical development and late-stage clinical trials and approval (see Figure 4-3). To this end, the firm will function as a virtual pharmaceutical company, acquiring or investing in novel therapeutic candidates. A compound should not proceed to Phase III clinical trials unless there is a clear understanding of the dose, the right formulation, and the basic safety profile. CelticTherapeutics plans to fund the development of promising candidates that are in Phase II to the point at which a large pharmaceutical partner will be interested, often at the end of Phase III.

The Celtic Therapeutics "virtual pharma" comprises a management company that runs a private equity fund and a biomedical development organization that manages the outsourcing of all components of product development. The development organization consists of a small core of very experienced drug development professionals who develop the firm's strategy for each product, and a small group of experts that manages product development execution through outside vendors and consultants, such as contract research organizations (CROs). There is also a Celtic Therapeutics employee acting as a full-time project leader. Celtic Therpeutics' strategy is to buy, license, or form an alliance with a biotechnology company for one of its products; develop the product; and then sell it at auction to a pharmaceutical company.

A key feature of the Celtic model is that traditional fixed costs, such as employees, human resources, and facilities, can be converted to variable costs, such as CROs, consultants, chief medical officers, and key opinion leaders. This approach provides several advantages. Costs associated with human resources and facilities are significantly reduced. Project-specific experts are engaged as needed, in lieu of a large cadre of highly paid experts maintained on staff in case they are needed. Decisions are based on the science and outcomes, and because the organization is structurally flat, can be made quickly by the core team. And cash can be moved rapidly for acquisition of a potential product or acceleration of development of a potential product already acquired.

Based on the results with Celtic Therapeutics' predecessor firm, Celtic Pharma, the model has already been validated, and the next step is to take the company to a new level and verify whether this model is applicable to a large portfolio. Traditionally, investors participate for the returns and royalties that result from commercial distribution through a pharmaceuti-

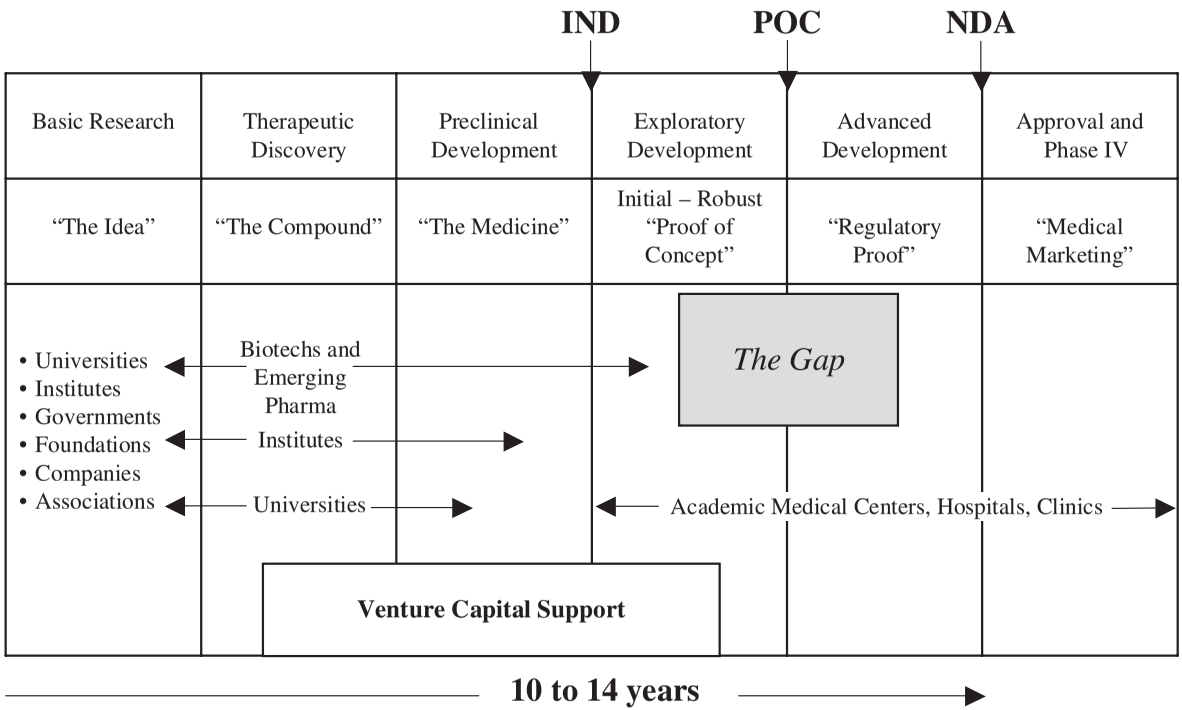

FIGURE 4-3 Defining the gap in biomedical research, from idea to patent expiration. Celtic Therapeutics funds and facilitates the development of promising product candidates to the point of submission of an NDA or a major increase in value of the potential product.
NOTE: IND = initial new drug; NDA = New Drug Application; POC = proof of concept.
SOURCE: Corr, 2008.

cal partner. But Corr believes a development organization that is making a profit for its investors can also develop a product on behalf of a philanthropic organization and facilitate noncommercial distribution through a public–private partnership, or return the product to the originator. Once Celtic's infrastructure and staff have been established, plans are to allow their use by developers of drugs for neglected diseases at cost plus 10 percent. Celtic has several major funders who are very interested in this aspect of the firm's model.

Addressing Neglected Diseases

The global burden of disease is on the rise, and diseases of the developed and developing worlds are converging. For example, as countries develop and economies improve, cardiovascular disease rises. And infectious diseases that were isolated 15 years ago have become global as a result of air travel. Drugs to treat neglected diseases are therefore a global need. What are the truly neglected diseases? With 127 compounds in development, HIV/AIDS is not a neglected disease. For malaria there are only 30 drugs in development, many of which are in the early stages and have a high risk of failure. For tuberculosis (TB), and particularly drug-resistant TB, only 22 candidate drugs are in the pipeline. For truly neglected diseases, such as human African trypanosomiasis, Chagas disease, and dengue fever, the pipeline is very limited, including 5, 7, and 8 compounds, respectively. To deliver new therapies for neglected diseases, Corr recommended the following:

- Explore new business models and new sources of capital.
- Establish public–private partnerships to build and maintain a medical infrastructure.
- Create new incentives to train and retain health care professionals in developing countries in performing clinical trials at a level that is acceptable for regulatory approval.
- Utilize the most advanced distribution systems.
- Ensure political will and a global community to deal with corruption in the developing world and enforce intellectual property rights.
- Advocate for policies that sustain and stimulate innovation.

In conclusion, Corr suggested that, through collaboration across sectors and through new and innovative business models, it will be possible to address not only the issues related to rare and neglected diseases, but also global disparities in health.

PANEL DISCUSSION[7]

Following the presentation of the above four models, an expert panel provided additional perspective on funding for research and development on drugs to treat rare and neglected diseases.

Mr. Onsi described the approach of HealthCare Ventures, an early-stage venture capital firm that has been investing since 1985, participating in the start-ups of Human Genome Sciences, MedImmune, Leukosite, and FoldRx. The firm looks for a combination of strong science, key talent, and a business plan that makes sense—defined as a reasonable probability that a company can achieve milestones that will result in someone's investing in or buying the company later at a higher valuation. Onsi stressed three points regarding working with venture capitalists:

- Institutions and patient foundations have an important role to play in helping venture organizations understand the probability of technical success of a particular therapeutic candidate and how patients for trials can be found. As a result, venture investors can make better decisions about such investments.
- Venture capitalists have varying interests. To be successful in attracting a venture capitalist to an organization's cause, it is important to match the interests of the two. Some investors, for example, may be interested in early-stage development and wish to be involved in building a company, while others may be seeking later-stage product opportunities and want clinical proof of concept.
- Venture organizations encounter many more opportunities than they can assess. Those that arise through existing relationships generally receive more attention. Fundamentally, however, it is critical to help the venture organization understand clearly the opportunity, the management, and the people who are going to do the work.

Dr. Khosla described how his effort to develop therapies for celiac disease (for which no medicines currently exist) through a nonprofit charity failed in its primary goal because of an inability to bridge a different gap from that previously described. The costs of the chemistry, manufacturing,

[7]This section is based on the remarks of Doug Onsi, J.D., Venture Partner, HealthCare Ventures; Chaitan Khosla, Ph.D., Professor, Departments of Chemistry, Chemical Engineering, and Biochemistry, Stanford University; Mark Batshaw, M.D., Chief Academic Officer, Children's National Medical Center; Marleen Haffner, M.D., Ph.D., Executive Director, Global Regulatory Intelligence and Policy, Amgen; and Gail Cassell, Ph.D., Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company.

and controls (CMC); toxicology; and regulatory activities necessary to bring these molecules to human trials were insurmountable for a philanthropic organization. The project was eventually taken on by a venture-backed company. Within the first year of formation, that company was able to raise more than 10-fold what the charity was able to raise through donations and completed the necessary preclinical activities. Technically, the charity was successful as it helped identify a drug that is currently in clinical trials, and it also aided research on two biomarkers that could be used in those trials. Khosla cautioned that without the development of new business models for preclinical and early clinical drug development, the rare and neglected disease community will have difficulty developing new molecular entities, and will be limited to evaluating old entities with existing CMC capabilities and toxicology profiles.

Dr. Batshaw described one way in which NIH, philanthropic organizations, and pharmaceutical companies can come together to bring rare disease treatments to the market. Under the authority of the Rare Disease Act of 2002, the Office of Rare Diseases at NIH administers a grant program that supports collaborative clinical research in rare diseases and training of clinical investigators in rare disease research. The funding and time to conduct the studies are limited, and to enhance its chance of success, Batshaw's rare disease center turned to philanthropy. Many donors that support rare disease research have family members who are affected, and they look to NIH as the gold standard of medical research. At Batshaw's center, which focuses on urea cycle disorders, three families committed to matching the amount of money awarded to the center by the NIH grant program. The additional funding and the alliance with the families allowed the center to expand its network so that in the 2-year period during which the study was open, it was able to capture about 20 percent of all patients in the United States currently being treated for these disorders. This capability also makes the center attractive to pharmaceutical companies because it allows them access to enough patients with these rare diseases to conduct trials rapidly.

Dr. Haffner made several observations based on her 20 years of experience running the Office of Orphan Products Development (OOPD) at FDA. First, a drug that works well, has clear-cut results, and truly makes a difference in treating a disease and consequently in patients' lives can be developed and approved even with very few patients. She gave an example of one drug that was approved to treat a disease that affected only 12 patients in the United States and 54 worldwide based on a pivotal trial of 6 patients.

Second, personalized medicine will result in significant changes in disease paradigms as the human genome continues to be deciphered. As this information allows for better targeting of therapies, many diseases are likely

to meet the criterion of fewer than 200,000 cases in the United States, and companies will be able to profit from producing products that successfully treat those diseases.

Third, the new Food and Drug Administration Amendments Act of 2007 rewards a sponsor for developing a drug for a neglected tropical disease with a transferable priority review voucher that can be applied to any drug (see Chapter 3). Haffner explained that while this voucher may encourage sponsors to develop drugs that are expected to yield a small return on investment, more will need to be done. Haffner also raised the issue of funding for the OOPD grants program, stressing that at $14 million it is very small, and the need is much greater than the program can meet.

Dr. Cassell suggested that the United States cannot afford to be investing $29 billion in federal funds in biomedical research without fostering partnerships to develop drugs for rare diseases. She encouraged the rare disease community to think about how best to involve government—both intramural NIH scientists and NIH-funded investigators. Cassell described such a partnership, whereby Eli Lilly worked with the National Institute of Allergy and Infectious Diseases (NIAID) to establish a not-for-profit organization for the discovery of early-phase TB drugs. FDA provided several of its most experienced staff to serve on the advisory board, and Eli Lilly and Merck allowed the nonprofit to use its compound libraries and its senior toxicology chemists. The organization provides no funds for licensing, but instead adds value to the compounds others have developed by identifying new indications.

OPEN DISCUSSION

The open discussion that followed the presentations and panel discussion raised additional points regarding sustainability, as well as two other issues relevant to all models: publications and patents, and concerns about counterfeit products and reimportation into primary markets of donated or reduced-cost products intended for developing countries.

Sustainability

Several workshop participants suggested ways in which companies interested in the development of drugs for rare and neglected diseases can enhance the sustainability of their efforts. Forum member Les Benet noted that patents can be a source not of income, but of the involvement of collaborators or an industry partner. The Institute for OneWorld Health, for example, is not making any money from its patents, but has been able to attract pharmaceutical companies as partners because they can realize benefits from access to the patents.

Cassell noted that in some cases, income can be generated in the developed world for a product that is used to treat a tropical disease in the developing world. She cited antibiotics as an example, which may have applicability for diarrheal diseases.

Meeker pointed out that there is increasing incentive in the developed world to ensure that the health care problems of the developing world are addressed. This incentive increases the possibility that a market could be created in developing countries.

Finally, Hale drew attention to the fact that some neglected diseases are more neglected than others. African sleeping sickness and visceral leishmaniasis, for example, are at the bottom of the list when it comes to drug development efforts. In the drive to be self-sustaining, there is a temptation not to address diseases affecting the poorest of the poor, and it is important to resist that temptation when working to achieve sustainability.

Publications and Patents

Sharon Hesterlee of the Muscular Dystrophy Association noted that, in the association's experience, securing funding from nonprofit partners through grants or other mechanisms often requires that research be published. Under marketing or licensing arrangements with companies, however, there may be a restriction on publishing. Hale agreed that there is need for academicians to publish to advance their careers or for funders to see publications that serve as evidence of their investment in action, but intellectual property and marketing issues also need to be considered. Corr observed that if a company is supporting research in an academic laboratory or clinical trial, the contract usually gives the company a 30-day period to review any manuscript and determine whether it raises critical intellectual property issues and if so, to initiate a patent application. Doing so generally requires the involvement of patent attorneys, which can be expensive, but it may be possible to find attorneys willing to work pro bono given the nature of the work. Hale agreed, noting that OneWorld Health has worked with pro bono patent attorneys. Khosla suggested that misconceptions often exist about the cost of filing an initial patent application, explaining that he has been helping people file provisional patent applications for $250 (although subsequent revisions do add to the cost).

Counterfeiting and Reimportation

Richard Rogers of FDA stated that counterfeiting of pharmaceuticals is increasingly prevalent in the developing world, and undercuts the building of global markets and robust health care delivery systems. Cassell sec-

onded the need for reliable authentication methods for pharmaceuticals. She noted that some of the countries most affected by the problem are beginning to address counterfeiting and are placing greater emphasis on drug quality. Hale has observed that when poor people are very sick and fear they may die, they ask for injections instead of oral products because in their experience, oral products are of poor quality. This is why OneWorld Health developed an injectable intramuscular paromomycin for visceral leishmaniasis. Corr cited two approaches to the problems of counterfeiting and reimportation currently being used by pharmaceutical companies: manufacturing pills that are shipped to developing countries in a different color, which decreases the pills' reimportation into the developed world, and radiofrequency identification tagging, which can now be done on a capsule or ampule.

5

Strategies for Facilitating Sharing of Research Materials and Data

In the biological and biomedical sciences, it is essential that research materials and data be shared if progress is to be achieved. The discussions summarized here described strategies for leveraging time and resources to meet this crucial need. While not all of these strategies are specifically geared to the development of drugs for rare and neglected diseases, they were presented with the idea that they could potentially be employed with that focus.

FINDING AND BARGAINING FOR RESEARCH MATERIALS AND DATA[1]

Dr. Mowatt explained that the sharing process is relatively simple: request, negotiate, and receive. Successful execution of a complex research project often requires that multiple parties share materials and information. The acquisition of these "ingredients" can be challenging, resulting in an iterative process during which difficulties are likely to be encountered. Mowatt described two barriers to sharing of research materials and data—finding and bargaining for them—and ways in which those barriers can be overcome.

[1]This section is based on the presentation of Michael Mowatt, Ph.D., Director, Office of Technology Development, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Finding Materials and Data

Determining where to look and whom to contact for research materials or data may seem simple, but this often is not the case. Certainly it is easiest to find something when all resources of potential interest are located in the same place. One approach to collecting resources is through the development of repositories, whether for reagents and materials or for data.

Repositories have a number of characteristics that facilitate the exchange of materials and data. In general, they are set up to be searchable. Once created, a repository can alleviate the technical, logistical, and administrative burdens associated with sharing, such as propagating vectors, aliquoting materials, managing paperwork for shipping, and completing the material transfer agreement (MTA). Most repositories require users to register to make a withdrawal, and this registration usually serves as the standardized agreement under which withdrawals are made. Users understand the terms associated with transfers to them or to the repository and the use of those materials before they make a request or a donation. Another benefit of repositories is that the distribution and use of materials can easily be tracked, and their impact on research can be assessed. The National Institutes of Health (NIH) has supported a number of successful repositories, such as the NIH AIDS Research and Reference Reagent Program, the Malaria Research and Reference Reagent Resource Center (MR4), and the Biodefense and Emerging Infections Research Resources Repository (BEI Resources) (see Table 5-1).

Another model for sharing is a virtual repository, consisting of an electronic material-transfer system functioning in some ways similarly to eBay or the marketplace on Amazon.com. The repository contains information about available materials and facilitates the transactions necessary to acquire those materials, but the materials themselves are not maintained

TABLE 5-1 Examples of Repositories of Materials and Data Supported by the National Institutes of Health

	AIDS Reagent Program*	MR4	BEI Resources
Year of inception	1988	1998	2003
Unique materials contributed	>8,500	>1,200	>10,000
Requests in 2007	>15,000	1,600	6,700
Countries of requesters	65	66	30
Registrants	>3,800	650	677

NOTES: Data are for 2008. BEI Resources = Biodefense and Emerging Infections Research Resources Repository; MR4 = Malaria Research and Reference Reagent Resource Center.
*The AIDS Reagent Program is described further in Cohen, 2008.
SOURCE: Mowatt, 2008.

by the repository. Like a standard repository, this mechanism provides an infrastructure for finding materials, as well as for negotiating and for tracking impact. The materials are then distributed by the owner. An example is the Biological Materials Transfer Agreement Project of Science Commons, which is striving to make materials easier to find on the web and easier to obtain.

Bargaining

Bargaining relates to negotiation of the terms and conditions of the transfer of materials or data, which generally involves an MTA. As discussed earlier, the publication of research results is a priority for all research institutions, and the dissemination or use of research results should be addressed when an MTA is negotiated. Intellectual property issues, such as who retains the rights to inventions developed during an investigator's use of shared materials, may be covered by an MTA. Another concern is the liability of the provider as a result of the use of the materials by the requester.

Contention in negotiations often derives from the provider's and recipient's differing perceptions of the value of the material, whether it be a tool, a drug, or a reagent needed to conduct research. There can be disagreement on the proposed use of the shared material (e.g., for discovery, preclinical, or clinical research). Conflicting interests and obligations also occur because the cultures and priorities of academia and industry, while overlapping, are quite distinct.

Negotiation of MTAs can be very labor-intensive. Given the diverse nature of the materials the parties may want to share, these agreements contain many nonstandard terms. As a result, the recipient organization must review each agreement meticulously. This process typically involves the technology transfer office of a university or the business development office of a company, as well as legal counsel and the researchers. As with negotiations in any venue, the process often entails cycles of offers and rejections or counteroffers, making the process resource-intensive and iterative and leading to high transaction costs. This time and these resources are consumed at the expense of other opportunities.

The bargaining process could be facilitated through the use of standardized agreements, which would theoretically eliminate the need to conduct de novo legal reviews of MTAs and transfer agreements. An example is the Uniform Biological Material Transfer Agreement (UBMTA), developed and implemented by NIH and others in 1995. This master agreement embodies a set of terms that 331 organizations to date have agreed to as those under which material transfers will be made. The UBMTA itself is lengthy and

detailed, but to simplify the transactions that utilize it, the terms of the transfer are referenced in a one-page implementing letter signed by representatives of the receiving and providing organizations. The UBMTA and implementing letter have streamlined the transfer of research materials, and the fact that so many institutions have accepted its terms is a good indicator that those terms are broadly acceptable. But the large number of signatories does not reflect the frequency with which the UBMTA is used, and in the experience of the National Institute of Allergy and Infectious Diseases, its use is not common. Its principal users have been nonprofit and public organizations.

As a follow-up to the launch of the UBMTA, in 1999 NIH published guidelines for disseminating research resources developed with NIH funding. These guidelines articulate the expectation that recipients of NIH funding will use a Simple Letter Agreement for exchanges of unpatented research tools. The Simple Letter Agreement is used more frequently than the UBMTA, but there is still a need to negotiate nonstandard agreements, sometimes with universities, but most commonly with industry.

Another approach to streamline the exchange of essential research materials and information to accelerate research has been implemented by the Collaboration for AIDS Vaccine Discovery (CAVD), a program of the Bill and Melinda Gates Foundation consisting of a network of centers and consortia. Participants in the program are expected to agree to and comply with certain principles for the sharing of materials and data, as well as to use a master MTA and a confidential disclosure agreement for exchanges of materials and information among the various CAVD awardees and collaborators.

THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI): A PUBLIC–PRIVATE PARTNERSHIP[2]

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a public–private partnership that grew out of a need for validated biomarkers for clinical trials targeting Alzheimer's disease (Box 5-1). Current Alzheimer's trials use clinical or cognitive outcome measures that have a slow rate of change over time and therefore cannot easily be used to determine the disease-modifying effects of treatments. In addition, such trials usually require large sample sizes and are time-intensive and costly. Dr. Ryan said the hope is that using imaging and biochemical biomarkers will improve the speed and efficiency of clinical trials of therapies for Alzheimer's disease.

[2]This section is based on the presentation of Laurie Ryan, Ph.D., Program Director, Alzheimer's Disease Clinical Trials, Division of Neuroscience, National Institute on Aging, National Institutes of Health.

BOX 5-1
Examples of Data Sharing Models for Biomedical Research

THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI)

ADNI is a 5-year longitudinal, multisite observational study designed to collect clinical and imaging data, and assess these data for rates of change in cognition, function, brain structure and function, and biomarkers so as to identify the best markers for following disease progression and monitoring treatment response. The study (which began in 2005) includes 200 subjects with Alzheimer's disease, 400 subjects with mild cognitive impairment, and 200 elderly controls across 57 performance sites.

ADNI comprises several core groups: an administrative core; a clinical core based at the University of California at San Diego (UCSD); a neuroimaging core (magnetic resonance imaging [MRI] and positron-emission technology [PET]) and an informatics core, housed at the University of California at Los Angeles (UCLA) in the Laboratory of Neuroimaging (LONI); a biomarker core; a neuropathology core; a statistics core; and an industry scientific advisory board (ISAB).

- The LONI image data archive facilitates deidentification and pooling of image data from multiple institutions, making the data available to all authorized investigators. The clinical and biomarker database is housed at UCSD and linked to LONI.
- A key feature of ADNI is rapid public access to all raw and processed data. New data are quarantined for a maximum of 30 days for quality control review prior to posting.
- An ADNI data-use agreement is a prerequisite for obtaining data, and a user table lists everyone who is accessing ADNI data. All qualified investigators have equal access; ADNI study investigators do not have priority access. There is also a data-sharing and publication committee.
- Biological sample sharing is facilitated by a resource allocation review commit-

ADNI is a longitudinal, multisite observational study. Its primary goal is to collect data and biological samples to establish a brain imaging, biomarker, and clinical database that will enable identification of the best markers for following disease progression and monitoring treatment response. The study is also focused on determining the optimum methods for acquiring, processing, and distributing images and biomarkers in conjunction with clinical and cognitive data in a multisite context, and on validating the imaging and biomarker data through correlation with the clinical and cognitive data. A key feature of ADNI is rapid public access to all data.

tee. Requests are reviewed for significance, scientific quality, lack of duplication among projects, and a commitment to sharing by the investigators. The decision to allocate biological samples rests with the National Institute on Aging.

http://www.adni-info.org,
http://www.loni.ucla.edu/ADNI/

GENETIC ALLIANCE BIOBANK

Launched in 2004 by seven genetic disease advocacy organizations, the Genetic Alliance Biobank is modeled after the PXE International Blood and Tissue Bank, which was established in 1995. The primary goal is to revolutionize access to resources and data and to enable translation of research into diagnostics, drugs, and services that support individualized decision making.

The BioBank is a repository for clinical data and biological samples, owned by advocacy organizations, housing medical records, DNA/RNA, self-reported patient information, cell lines, tissue, and organs. The degree of open access to each collection is determined by the managing organization. The BioBank:

- centralizes the standardized collection and archiving of both clinical data and biological samples;
- maintains the integrity of each advocacy organization's collections and data;
- enables institutional review board (IRB)-approved investigator research;
- ensures appropriate use of data and samples;
- enables ethical recontact and follow-up for phenotype/genotype correlations and natural history and longitudinal studies;
- allows for regular communications with key constituents; and
- facilitates stewardship and benefit sharing among advocacy organizations.

http://biobank.org

Design and Launch of the ADNI Study

ADNI was launched in 2002 with informational and advisory meetings, followed by the formation of four working groups to address magnetic resonance imaging (MRI), positron-emission tomography (PET), study design, and biological measures. In July 2003, a meeting was held with industry representatives, advocacy groups, the Food and Drug Administration (FDA), and the Foundation for the NIH, and in October 2003, a request for applications was issued. By the end of 2004, funding had been awarded, and recruitment for the study began in September 2005.

As noted, a goal of ADNI is to identify markers of disease progression,

primarily at the transition between normal cognition and Alzheimer's disease. The study was designed to include 400 subjects with mild cognitive impairment—200 with Alzheimer's disease and 200 as controls. Currently, 822 subjects are enrolled in 57 sites. All studies are to be completed by summer 2010, with most analyses completed by the end of 2010. Throughout the trial, at various time points from zero to 36 months, standard cognitive and clinical measures are taken. In addition, biological samples are collected, and pathological markers of Alzheimer's disease are analyzed. The study comprises several core groups: an administrative core; a clinical core that is based at the University of California at San Diego (UCSD); a neuroimaging core, including MRI and PET; an informatics core, which is housed at the University of California at Los Angeles (UCLA) in the Laboratory of Neuroimaging (LONI); a biomarker core; a neuropathology core; a statistics core; and an industry scientific advisory board (ISAB).

ADNI Funding and Operation

ADNI is funded through a cooperative agreement at $12 million per year for 5 years. However, total funding currently exceeds $60 million, with $40 million in NIH funds and nearly $25 million raised by the Foundation for the NIH from 17 organizations, 15 companies, and 2 nonprofit organizations. All industry sponsors have representation on the ADNI ISAB and steering committee. Funding has also been provided for a number of additional ancillary studies. One of these studies is aimed at identifying analytical methods for cerebrospinal fluid (CSF) analysis. Amyloid imaging is funded with a supplement of $2.6 million, sponsored by the Alzheimer's Association and GE Healthcare. Blood is also being collected for genome-wide genotyping and genetic analysis, and this promises to be one of the most robust and extensive Alzheimer's disease genotyping databases available.

Key Features of the ADNI Model for Open Sharing of Data and Samples

ADNI is truly a public–private partnership. Common, specific goals were clearly defined at the outset, and resources, both financial and intellectual, are being pooled. The heart of ADNI is open sharing of data and samples, which includes:

- rapid public access to all raw and processed data;
- a central repository for all quality-assured MRI and PET images through LONI;
- a clinical database, housed at UCSD and linked to LONI;
- databases that are in the public domain and available to all qualified investigators;

- no special access privileges (i.e., ADNI investigators do not have priority access, and data become public nearly in real time, immediately following quality assurance);
- a data-sharing and publication committee, an ADNI data-use agreement that is a prerequisite for obtaining the data, and a user table that lists everyone who is accessing ADNI data; and
- biological sample sharing, facilitated by a resource allocation review committee that assesses applications for significance, scientific quality, lack of duplication among projects, a commitment to sharing by the investigators, and the investigator and environment (following the assessment, the decision to allocate biological samples rests with the National Institute on Aging).

The Global Reach of ADNI Data

ADNI data are being utilized worldwide, well beyond what was expected. In the 22 months after the first application for data use was approved, there were more than 270,000 image downloads by 265 investigators, and clinical data were downloaded by 203 investigators. Figure 5-1 shows the downloads by country. Not surprisingly, the most downloads have been by researchers in the United States, with the United Kingdom and Canada also being very active. But Ryan noted that it was surprising to observe nearly 8,000 downloads from China and to see interest and download activity from such countries as Turkey and India. The sources of the applications received by the ADNI database are shown in Figure 5-2. Most are academic sites, but use by the pharmaceutical industry has increased 400 percent in the last year. Another interesting outcome is that the ADNI methodology has sparked similar efforts in Japan, Australia, and Europe, and the hope is that data can someday be compared across these international efforts.

ADNI is meeting or exceeding all expectations, and there are many opportunities for analysis and publication and for studies using ADNI data as controls or for comparison. ADNI hopes to establish the optimum methods for multisite Alzheimer's clinical trials and to identify imaging and biomarker techniques that have high rates of change, small standard deviations, high power, and correlation with the clinical measures. These imaging and biomarker techniques will be used in Phase II and III studies and validated in treatment settings. ADNI results may allow for the use of prior information in the design and analysis of trials, potentially increasing statistical power, and it is hoped that FDA will give greater weight to ADNI-evaluated imaging and biomarkers. The ultimate goal of ADNI is to facilitate the development of effective disease-modifying therapies for the

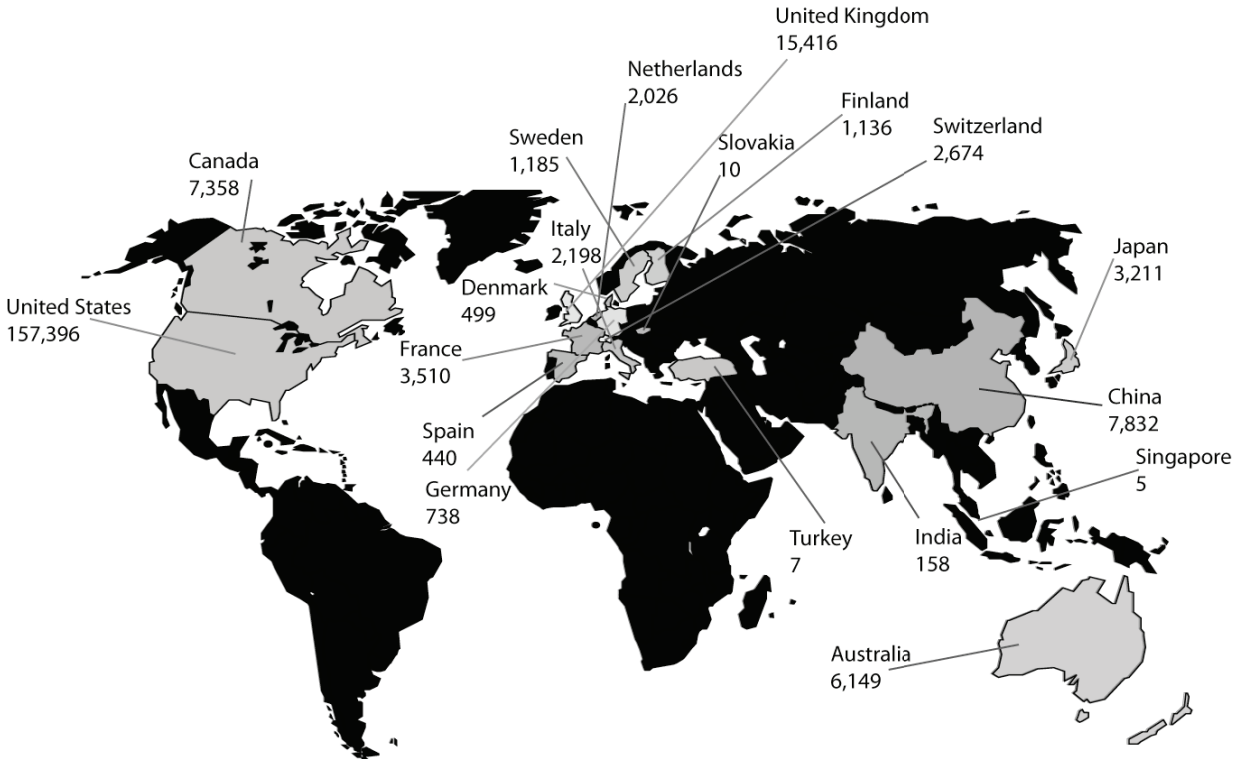

FIGURE 5-1 Worldwide use of ADNI data. More than 270,000 image downloads by 265 investigators occurred in the 22 months following the database's inception, and clinical data were downloaded by 203 investigators.
SOURCE: Ryan, 2008.

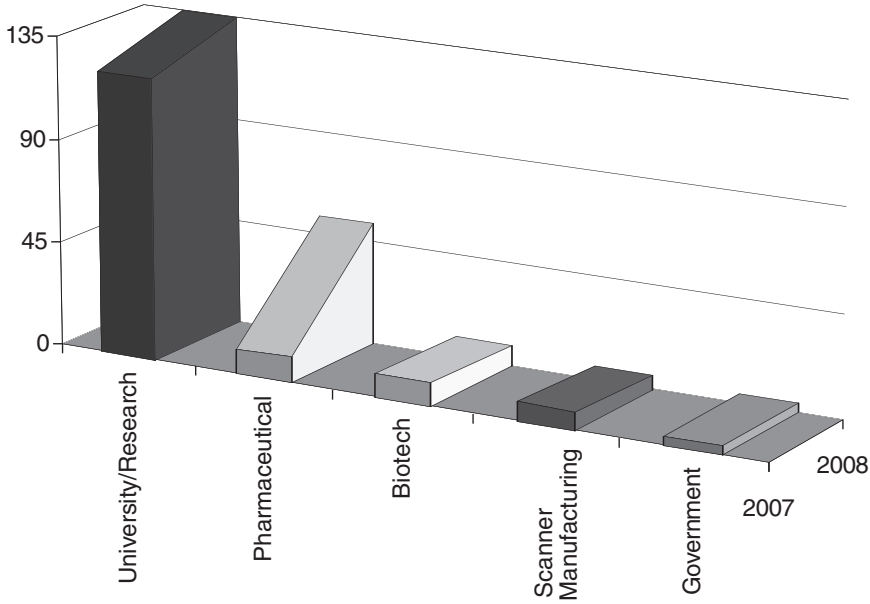

FIGURE 5-2 Sources of applications for use of the ADNI database. While most are academic institutions, use by the pharmaceutical industry increased 400 percent from 2007 to 2008.
SOURCE: Ryan, 2008.

treatment of Alzheimer's disease, the delay of disease progression, or the prevention of the disease.

GENETIC ALLIANCE BIOBANK[3]

Genetic Alliance was founded 22 years ago by a social worker as a place for disease advocacy groups to support one another (Box 5-1). More recently, the organization has matured to promote an environment of openness aimed at transforming health through genetics. The Alliance brings together diverse stakeholders to establish novel partnerships in advocacy, integrating individual, family, and community perspectives to improve health systems. By revolutionizing access to genetic information, the Alliance hopes to enable the translation of biomedical research into health services and to facilitate better individual decision making.

[3]This section is based on the presentation of Sharon Terry, M.A., President and CEO, Genetic Alliance, and founding Executive Director of PXE International.

Genesis of the BioBank[4]

In 1994, Terry's children were diagnosed with a rare disease called pseudoxanthoma elasticum (PXE). Within 2 months of the diagnosis, Terry, a college chaplain, and her husband, a fire protection engineer, had read everything that had been written on PXE—about 400 articles—and realized that there was no coordinated plan to address the disease. They took action by founding PXE International and the PXE International Blood and Tissue Bank. The foundation-owned and -managed bank was the first of its kind and served as the model for the Genetic Alliance BioBank, which was founded in 2003.

Key Characteristics of the BioBank

The vision of the Genetic Alliance BioBank is to revolutionize access to the information and resources needed to enable the translation of research into diagnostics, drugs, and services that support individualized decision making. The needs to be met are quite clear, and Genetic Alliance seeks to address those needs by providing the following:

- access to well-annotated samples;
- the ability to obtain consent and reconsent from study participants dynamically;
- longitudinal clinical data collection;
- a clinical health information registry;
- medical record collection;
- interoperability with electronic medical records/personal health records;
- archival exchange with the database of Genotype and Phenotype (dbGaP), which is part of the NIH system for genotype/phenotype correlations; and
- compliance with good manufacturing practices.

The Genetic Alliance BioBank is a cooperative model that provides infrastructure for clinical records and images; research questionnaires; and biological materials such as DNA, tissue samples, and cell lines. A web-based interactive system enables the collection of self-reported data from patients. The BioBank is owned by advocacy organizations, and the disease-specific organizations manage their own collection and facilitate the distribution of information and materials. The BioBank currently contains

[4]For additional information about PXE International and the creation of the Genetic Alliance Biobank, see Terry et al., 2007.

about 10,000 physical samples—encompassing all types of tissue, blood, and cell lines, including whole-body harvest—and about 20,000 clinical records for seven diseases. Some of the collections are virtual, meaning they are recorded in this system but housed elsewhere.

Structurally, the BioBank creates a firewall between researchers and many of burdensome administrative tasks associated with working with patients (see Figure 5-3). The BioBank provides scientists with all the information they need with respect to samples, clinical data, and medical records, as well as standardized MTAs and publishing rights. Because the organizations themselves maintain control, they are able to broker with their researchers regarding the most productive use of these rare samples. Another important element is that the BioBank has its own institutional review board, so transactional issues are standardized, saving time and energy. Additionally, the BioBank is able to recontact patients and to conduct longitudinal studies that would not be possible in other situations. The system also gives back to participants by providing them with information that results from the studies. This is a public trust, and

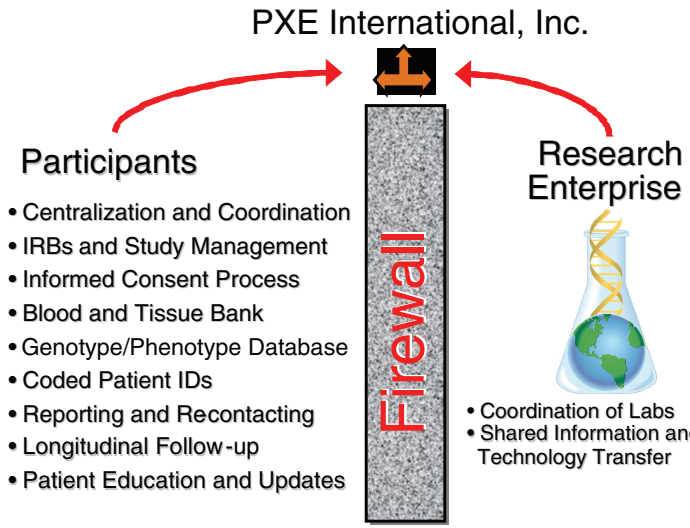

FIGURE 5-3 PXE International, Inc., BioBank model. The Genetic Alliance BioBank, modeled after the PXE International model, creates a firewall between researchers and many of the costly and time-consuming administrative tasks associated with working with patients.
NOTE: IRB = institutional review board.
SOURCE: Terry, 2008.

advocates are included in all steps of the design so that processes such as informed consent, cohort accrual, and participant retention are simplified and improved.

The primary interest of Genetic Alliance constituents is to ensure that the experimental treatments used in the clinical trials are effective. Constituents are willing to assume additional safety risks if a treatment is effective—an approach to drug development that reflects the unique needs of people living with a rare disease. Ultimately, a new, flexible paradigm is needed that:

- is forward looking and takes into account the rapid changes in research and industry;
- is well coordinated across federal agencies and companies;
- has safe harbors for high risk, encourages publishing of negative results, and allows companies to take risks without fear of being penalized as they might be under the current regulatory regime;
- is transparent and open; and
- is characterized by more common registries and more shared data.

In addition, intellectual property issues must be addressed to enable win–win situations. And sharing failures is critical to save others from wasting resources. In conclusion, Terry stressed the need for bold leadership to dissolve old boundaries and accelerate the adoption of this new paradigm.

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-

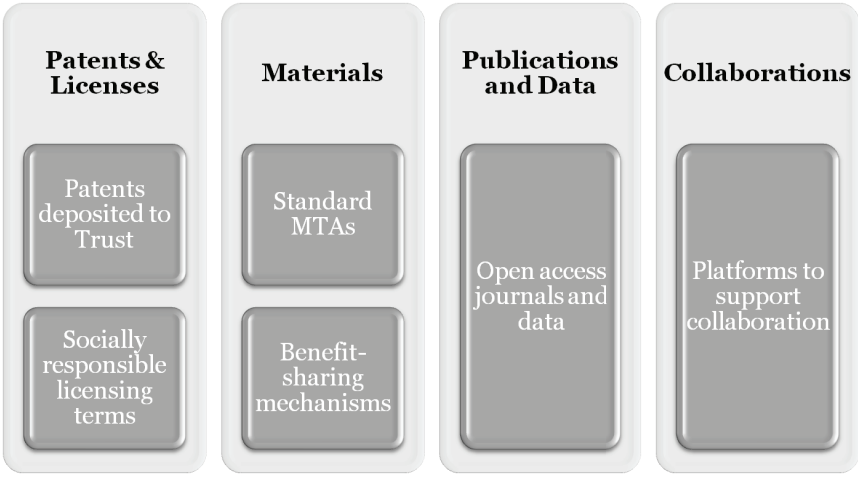

FIGURE 6-1 Duke University concept of how a technology trust might create an enabling intellectual property environment for rare and neglected diseases.
NOTE: MTA = material transfer agreement.
SOURCE: So, 2008.

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.

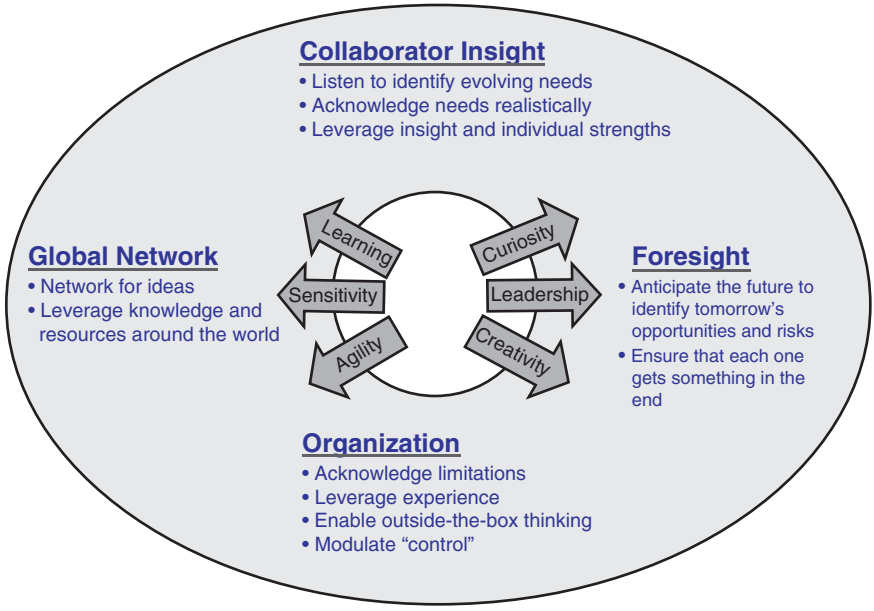

FIGURE 6-2 Vertex approach to maintaining strategic research alliances. Building and maintaining healthy alliances is a dynamic balance. Having the foresight to anticipate what one wants or needs to achieve and then casting a global net to acquire the various pieces of the puzzle is the first step. Once 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.

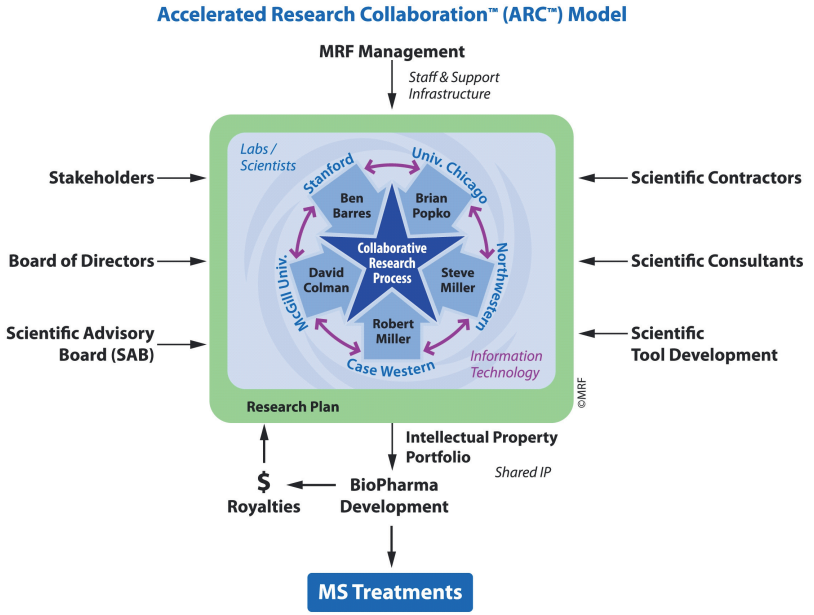

FIGURE 6-3 The Myelin Research Foundation's collaborative research process. SOURCE: Bromley, 2008.

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

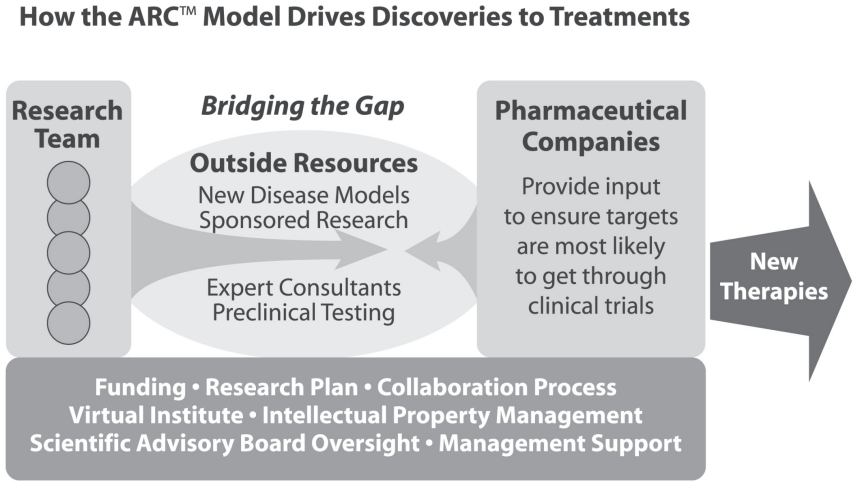

FIGURE 6-4 Bridging the translational research gap between discovery and treatment.
SOURCE: Bromley, 2008.

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,

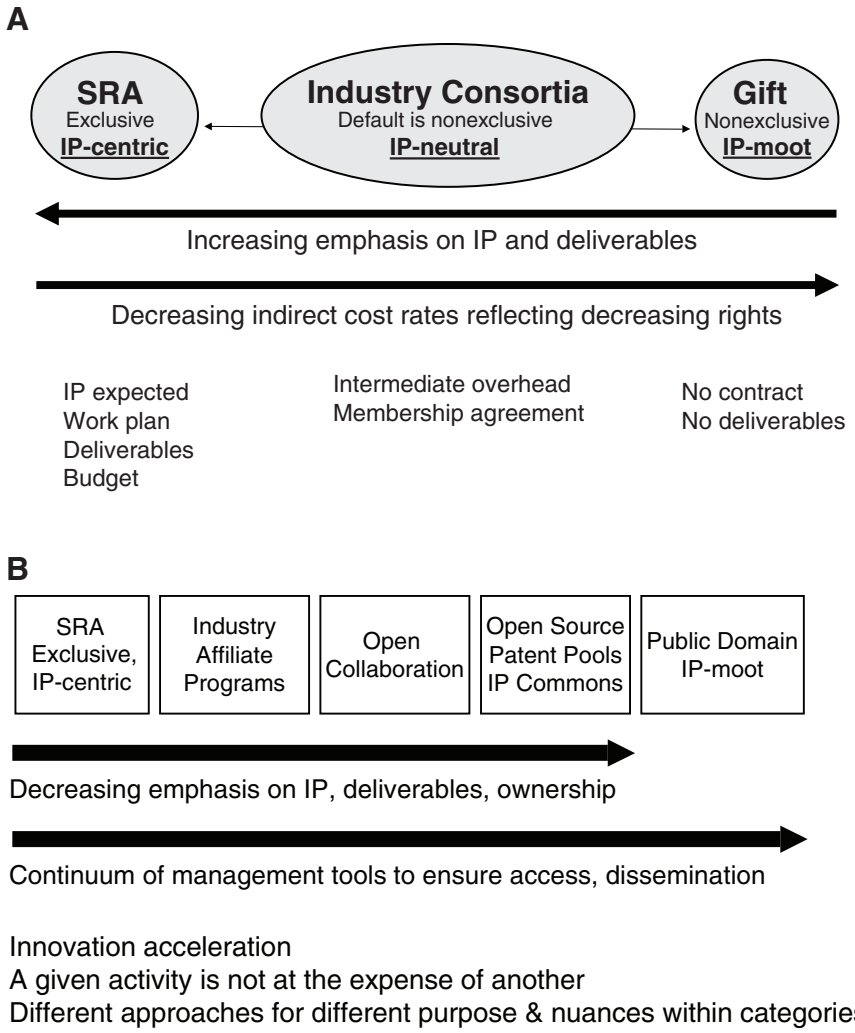

FIGURE 6-5 UC Berkeley IPIRA intellectual property management models. (A) A full spectrum of models is employed to achieve maximum impact, access, uptake, and dissemination. (B) The management strategy is geared toward achieving translation of research results. By applying new metrics, the goal of impact 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.

7

Strategies for Facilitating Clinical Trials

There are three common misperceptions about clinical trials for therapies for rare and neglected diseases: (1) there is a lack of interest in these conditions and research to address them, (2) there is a lack of information on these conditions, and (3) there is a lack of access to clinicians with salient experience.[1] In fact, however, tremendous progress has been made. Investments in research and development on therapies for rare and neglected diseases are being made around the world, stimulated in large part by the interest and action of patient advocacy groups. Contrary to popular belief, there is considerable information available on these conditions, and one responsibility of the rare and neglected disease community is teaching the public and patients how to search for that information. Patients should not feel isolated or stigmatized by the diagnosis of such a disease.

All therapies must be proven safe and effective in clinical trials with human subjects before they can be approved for broad use, regardless of the size of the target population. The three speakers in this session discussed strategies for streamlining the clinical trial process. Highlights of these strategies are presented in Box 7-1.

[1]This introductory section is based on the presentation of session moderator Stephen Groft, Pharm.D., Director, Office of Rare Disease Research, National Institutes of Health.

FDA REVIEW AND REGULATION OF SMALL CLINICAL TRIALS: SUCCESSES, BARRIERS, AND DIRECTIONS FOR THE FUTURE[2,3]

From the regulatory/legislative perspective, there are special challenges associated with Food and Drug Administration (FDA) review and approval of products to treat rare diseases. The majority of New Drug Applications (NDAs) for orphan drugs are based on small clinical trials, some with as few as 20 patients. As noted by Coté earlier in the workshop, the Orphan Drug Act provides for predominantly financial incentives for orphan drug development. Orphan drugs are not held to different or less stringent standards than other drugs. Marketing approval for all drugs requires, by law, "substantial evidence of effectiveness" (21 CFR § 314.50). But exactly how that evidence is provided is negotiable, and communications with FDA can help ensure the most effective use of the sponsor's limited financial and human (i.e., patient) resources.

Regulatory Tools

The Orphan Drug Act has been successfully implemented, resulting in the approval of 326 products to treat rare and neglected diseases over the past 25 years.[4] There are additional tools pertaining to the regulation of nonorphan drugs, such as the Prescription Drug User Fee Act (PDUFA) and the FDA Modernization Act of 1997 (FDAMA), that can also help advance the development of orphan products (see Box 7-2). For example:

- Fast-track designation can be given to a drug product that is both intended to treat a serious/life-threatening condition and claimed to address an unmet medical need. Fast-track designation allows for more involvement with FDA through scheduled meetings and permits rolling review, whereby the NDA can be submitted in sections.
- Accelerated approval is based on a surrogate end point rather than a clinical outcome. For example, a surrogate end point for treatment of HIV could be a decrease in viral titers rather than demonstration of clinical improvement or extension of patient life span. Proof of a clinically meaningful benefit, which can take a

[2]This section is based on the presentation of Anne Pariser, M.D., Medical Team Leader, Inborn Errors of Metabolism Team, Division of Gastroenterology Products, Center for Drug Evaluation and Research, FDA.

[3]Dr. Pariser's presentation focused on conducting clinical trials for drugs to treat rare diseases and drugs that have been designated as orphan products. It is important to note that some of the discussion may not apply to drugs for neglected diseases.

[4]The Orphan Drug Act is discussed in detail in Chapter 3.

BOX 7-1
Examples of Disease Foundation Strategies for Facilitating Clinical Trials

MULTIPLE MYELOMA RESEARCH FOUNDATION (MMRF)
Founded in 1998 by a newly diagnosed multiple myeloma patient, Kathy Giusti, and her sister, Karen Andrews, MMRF's mission is to urgently and aggressively fund research that will lead to the development of new treatments for multiple myeloma.

As part of its long-, mid-, and short-term research strategies, MMRF funds a portfolio of research worldwide comprising the basic science of multiple myeloma, validation, and Phase I and II clinical trials (conducted by MMRC; see below).

http://www.multiplemyeloma.org

MULTIPLE MYELOMA RESEARCH CONSORTIUM (MMRC)
A sister organization to MMRF, founded in 2004 by Kathy Giusti, MMRC has as its mission accelerating the development of novel and combination treatments for multiple myeloma by facilitating clinical trials and correlative studies. MMRC integrates the research efforts of 15 member institutions that represent the leading myeloma centers in the United States and the world. Centers are bound by a common membership agreement.

MMRC is designed to operate like a drug development organization. Its leadership team includes:

- A chief executive officer with 10 years of experience in drug commercialization at two major pharmaceutical companies (also the founder and a myeloma patient).
- A chief scientific officer with 16 years of industry experience in drug and target discovery.
- A chief medical officer who is a trained hematologist/oncologist with more than 20 years of clinical research and drug development experience in industry.

The MMRC Progress Review Committee comprises experts from the member institutions, and selects and prioritizes targets. The MMRC Tissue Bank integrates myeloma tissue samples with corresponding genomic and clinical data. To facilitate accrual, MMRC has a program in place to allow patients to donate tissue directly. The MMRC Data Bank enables sharing of standardized data among consortium member institutions.

Metrics and reward systems are implemented to improve processes and to enforce accountability:

- A scorecard tracks the number and quality of tissue samples provided to the tissue bank, the time required to open and accrue clinical trials, and the engagement of principal investigators (monitoring activities such as participation in monthly calls and face-to-face meetings or bringing new ideas to the consortium).
- Tier one centers, those performing in the top one-third, receive funding to cover the full salary of a clinical research coordinator who provides dedicated oversight of all MMRC clinical trials (100 percent full-time equivalent [FTE]). The second tier receives 50 percent of an FTE and the third tier 25 percent.

http://www.themmrc.org

MUSCULAR DYSTROPHY ASSOCIATION (MDA)

MDA was founded in 1950 by a group of patients and parents of young patients with muscular dystrophy and a researcher studying the disease. MDA is an umbrella organization covering 40 rare neuromuscular diseases and is the largest nongovernmental sponsor of neuromuscular disease research. It also provides numerous services to patients (such as buying and repairing wheelchairs and leg braces and running free summer camps for children), facilitates meetings of MDA support groups, and sponsors public and professional education programs. MDA is funded almost exclusively through individual, private contributions.

MDA has more than 200 offices nationwide, sponsors 230 hospital-affiliated clinics across the United States, and supports nearly 400 research projects worldwide, distributing funding across basic research, target identification, proof-of-principle testing in animals, translational research and preclinical development, and clinical research. MDA is also working to develop, validate, and standardize end points.

MDA works through private–private partnerships with other nonprofit organizations, such as the TREAT-NMD neuromuscular network in Europe, the International Coordinating Committee for Spinal Muscular Atrophy Clinical Trials, and the Duchenne Research Collaborative International.

http://www.mda.org

BOX 7-2
FDA Review: Opportunities to Facilitate the Drug Development and Approval Processes

FAST-TRACK DESIGNATION
- Drug product must be intended to treat a serious/life-threatening condition and address an unmet medical need.
- Allows for:
  - Scheduled meetings to obtain agency input on development plans
  - Rolling review option to submit NDA in sections rather than all at once
- Allowed by law under Section 112 of FDAMA.
- FDA guidance available: *Guidance for Industry Fast Track Drug Development Programs—Designation, Development, and Application Review* (http://www.fda.gov/Cder/Guidance/5645fnl.pdf).

ACCELERATED APPROVAL
- FDA approval is based on a surrogate end point (e.g., a laboratory measure or physical sign rather than a clinical outcome).
- Allowed by law under agency regulations:
  - Drugs: 21 CFR § 314.500 (Subpart H)
  - Biologics: 21 § CFR 601.40 (Subpart E)

PRIORITY REVIEW
- Sets the goal date for FDA action on the marketing application at 6 months, rather than the standard review goal date of 10 months.
- Designation is made after the marketing application is submitted.
- Must be requested by the sponsor.
- Allowed by agency procedure:
  - Drugs: CDER MaPP 6020.3R (http://www.fda.gov/cder/mapp/6020.3R.pdf)
  - Biologics: CBER SOPP 8405 (http://www.fda.gov/CbER/regsopp/8405.htm)

COMMUNICATIONS
- Early and frequent communication with FDA is encouraged by the agency to "aid in the evaluation of the drug and in the solution of scientific problems. . . ." Includes "free, full, and open communication . . ." (21 CFR § 312.47).
- The Review Division should be contacted for information; must be requested by the sponsor.

long time, is not required at the time of the accelerated approval, and verification studies are conducted post-approval.

- Priority review can be requested at the time a sponsor submits a marketing application and if granted, commits FDA to a PDUFA goal date of 6 months, rather than the standard 10-month review cycle.

- The consistent point of contact for the sponsor is the regulatory project manager (RPM).

FORMAL MEETINGS

- FDA guidance available: *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products* (http://www.fda.gov/cder/guidance/2125fnl.pdf).
- Type A
  - Immediately necessary for a program to move forward.
  - For dispute resolution (e.g., Clinical Hold, Refuse-to-File).
  - To occur within 30 days of FDA's receipt of sponsor request for meeting.
- Type B
  - Held at specified clinical stages or milestones.
    - Pre-IND (21 CFR § 312.82)
    - End of Phase II (21 CFR § 312.47)
    - Pre-NDA/BLA (21 CFR § 312.47)
  - To occur within 60 days of FDA's receipt of sponsor request for meeting.
- Type C
  - Any meeting that is not type A or B.
  - To occur within 75 days of FDA's receipt of sponsor request for meeting.

SPECIAL PROTOCOL ASSESSMENTS

- FDA's evaluation of the adequacy of a protocol's design, conduct, and analysis relative to regulatory requirements for approval.
- FDA response issued within 45 days.
- Available only for certain types of protocols.
- Allowed by law under Section 119(a) of FDAMA 1997.
- FDA guidance available: *Guidance for Industry: Special Protocol Assessment* (http://www.fda.gov/cder/guidance/3764fnl.pdf).

INFORMAL MEETINGS

- Usually response to a limited number of specific questions that may require only yes/no answers, or brief clarifications of previous responses.
- Arranged through the RPM and usually involve only a few members of the review team.
- No written communications are issued.

Communication with FDA

Regardless of whether a product is designated as an orphan drug or has fast-track designation, early, frequent, and quality communication between FDA and the drug developer is crucial. There are a variety of opportunities for communication with FDA; however, small companies and individual

academic investigators often do not realize that they are entitled by law to these communications. It is important to note that FDA cannot initiate such a meeting; the party developing a new drug must request it, following the procedures detailed in guidance documents (see Box 7-2). Opportunities include formal meetings, informal meetings, and special protocol assessments (SPAs). An advantage of formal meetings is that FDA will issue written minutes, usually within 30 days of the meeting, documenting the advice given and verifying agreements that are reached, helping to speed the process and offering a better likelihood of success. There are three types of formal meetings—A, B, and C (see Box 7-2). Note that type B meetings, which are clinical-stage or milestone meetings, can be requested even before the initial Investigational New Drug (IND) protocol is submitted. Such early communication can make the clinical process run more smoothly and help prevent delays. Pariser urged applicants to request meetings with FDA, noting that the agency is usually very willing to grant such requests.

Pre-IND Challenges

In the pre-IND stage, problems arise that, while not unique to orphan drugs, are due to the limited resources of the small companies and academic institutions that sponsor the drugs. Before a sponsor can initiate an IND, much often expensive work must be completed. Chemistry, manufacturing, and controls (CMC) of the drug must be adequately characterized. This is especially challenging for biologics, which are generally large molecules that are difficult to characterize. Working assays, such as immunogenicity assays, must be in place during development. While CMC can be outsourced to contract organizations, funding for such services can be a nearly insurmountable barrier for small companies and academic investigators. Animal pharmacology studies are also required before a product can be administered to humans in clinical trials—another topic that should be discussed during a pre-IND meeting. And if there is previous human experience, it must be of sufficient quality to support safety and proposed dosing.

Pivotal Study Design

Another common roadblock to approval is an inadequate pivotal study. The studies for orphan drugs are usually small. For a given product, FDA may see one Phase I/II study addressing safety, pharmacokinetics/pharmacodynamics (PK/PD), and exploratory efficacy that might include just 8–12 patients. There may then be only one pivotal trial, as opposed to a pivotal trial followed by a confirmatory trial, as is typically the case for nonorphan drugs. On occasion, a sponsor will initiate an IND, not communicate with the agency for 5–7 years, and then submit an NDA with a

pivotal trial that is inadequate. For a nonorphan indication, the study may have to be disregarded, and the sponsor may have to begin over again. But for an orphan drug, this is a heartbreaking situation, Pariser said, given that conducting a second pivotal trial may be an almost insurmountable problem because of a lack of funds, of trial participants, or even of additional drug product. One way to overcome these obstacles is to maintain regular communication with the agency throughout the development process.

What constitutes an adequate and well-controlled study will vary depending on the disease in question, and there may be more flexibility for rare diseases as a result of the small populations and lack of statistical certainty involved. The best approach is to work with FDA to determine what the acceptable end points are and agree on the study design in advance. Accelerated approvals that rely on surrogate end points are also a possibility, but these approvals require a postapproval verification study that demonstrates clinically meaningful benefit (a postmarketing or Phase IV study). "Well-controlled" does not necessarily mean a placebo control. The choice of control groups is determined on the basis of available standard therapies, other available therapies, adequacy to support the chosen design, and ethical considerations. The control arm of a study is unique to the disease. In general, randomized controlled trials include control and test groups chosen from the same population treated concurrently, and the controls may be placebo, no-treatment, dose-response, or active comparator controls. In some circumstances, it may be possible to use a historical control, although this is an unusual situation, and such studies must be carefully designed.

NDA/BLA Issues

Some of the issues FDA encounters frequently with NDAs and Biological Licensing Applications (BLAs) for orphan drugs arise from misunderstandings about what is required for an orphan drug. Incomplete submissions, from both large and small companies, are relatively common. Sponsors have told the agency they thought a particular component of the submission was not required because their product was an orphan drug. As noted earlier, all drugs are held to the same standard of "substantial evidence of effectiveness." All components of the NDA or BLA must be completed unless there is an agreement from FDA in writing to the contrary. An incomplete application will not always be prevented from moving forward, but it can result in an unwanted delay. Again, the components of the application can be discussed at a pre-NDA meeting, or earlier.

FDA Recommendations to Sponsors

Based on FDA's experience in working with sponsors of orphan drugs, Pariser offered the following recommendations:

- *Meet with FDA early and often.* Sponsors should take advantage of all opportunities for meetings and communication. The agency favors open communication with both drug developers and patient groups. FDA does meet with patient groups, either alone or with the drug developer; however, all information regarding a drug product under IND is confidential, and FDA cannot discuss it with patient groups without permission from the drug developer.
- *Formulate the clinical program as early as possible.* Understanding the natural history of a disease and determining whether there are biomarkers that can be used can aid in designing the pivotal study, especially since there is a limited patient population available for study, and many orphan diseases are not well understood.
- *Do not overlook the value of early-phase trials.* Sponsors should consider animal models, exploratory end points, PK/PD parameters, and surrogate end points/biomarkers in the design of early-phase studies.
- *Submit an SPA for the pivotal study.* FDA will review it and provide comments. An agreed-upon SPA is a binding agreement, so if the sponsor's trial meets the predetermined end point, the likelihood of approval is increased.
- *Rigorously control study conduct.* Training study personnel and developing a comprehensive study manual can decrease variability in study-related procedures. This can be accomplished more easily for small trials in a limited number of centers, with experts in the field or specialists as principal investigators.
- *Conduct a natural history study.* Such a study can be either retrospective or prospective. Given a limited number of patients, it is important to recognize end points, preferably ones that are apparent in the shorter term. Patient groups can facilitate natural history studies. The published literature, such as case reports, is often inadequate for rare diseases. The most severe cases tend to be published and may not be representative of the broader affected population and/or attenuated presentations.
- *Be attentive to the rights and welfare of medically vulnerable patients with no (or few) other treatment options.* Among its patient protection provisions, the Declaration of Helsinki addresses vulnerable populations who need special protection. Sponsors should

consider using an independent safety monitoring board or other oversight committee when conducting the pivotal study.

- *Remember that the drug will be labeled only for the populations/indications studied.* Orphan drugs can be very expensive, and insurance will not pay for them unless their use is approved by FDA and they are labeled for that particular population and indication. Since FDA needs substantial evidence of benefit before it can approve a label indication for a population, it is important to be as inclusive as possible early on. The target population and how the drug will be used should be carefully defined to ensure that patients will have access to the drug.
- *For biologics, discuss characterization, assays, and antibody testing with FDA's Office of Biotechnology Products as early as possible.* Sponsors can contact the review division for help in setting up a meeting with that office if necessary.

Directions for the Future

FDA is sharing knowledge with international regulatory agencies such as the European Medicines Agency (EMEA) and Health Canada and working to increase international collaboration. The agency is also attempting to increase the involvement of patient groups. For example, review divisions may have patient consultants participate in meetings, or patients may serve on advisory committees as special employees of the government. As discussed earlier, patient advocacy foundations have contributed significantly to the funding of clinical trials. Patient groups can also play an active role in planning studies, advising on barriers to enrollment, or addressing safety concerns related to a study. Post-approval, drug developers often collect data on patient safety and efficacy through orphan drug registries, which are often required by FDA as a condition of approval for a product.

APPROACHES TO ACCELERATING CLINICAL TRIALS[5]

An oncology compound that is entering Phase I has about a 5 percent chance of ultimately achieving FDA approval (Sharpless and DePinho, 2006). In addition, oncology trials tend to be inefficient. Dilts and Sandler at Vanderbilt University reviewed 300 oncology trials conducted at their center and found that on average, almost 10 months elapsed between final protocol and first patient dosed (Dilts and Sandler, 2006).

[5]This section is based on the presentation of Anne Quinn Young, M.P.H., Program Director, Multiple Myeloma Research Foundation.

For multiple myeloma, four new drugs have been approved over the past 5 years, and there are nearly 40 additional compounds in development. The importance of collaboration in moving drug development forward was highlighted throughout the workshop. Bringing four new myeloma drugs to patients has been the result of a successful collaboration between the Multiple Myeloma Research Foundation (MMRF) and the Multiple Myeloma Research Consortium (MMRC), working with partners in industry; academia; government, including the National Cancer Institute (NCI) and FDA; and most important, the patients who participate in trials, donate funding to disease foundations, and provide tissue so that correlative studies can take place.

MMRF and MMRC are sister organizations. MMRF funds a portfolio of research worldwide, including investments in the basic science of multiple myeloma; validation of targets; translational research; and Phase I and II clinical trials, which are conducted by MMRC. Early on, MMRF determined that to accelerate drug development, it needed to operate like a drug development company. The leadership team consists of the CEO and founder, who is a myeloma patient with 10 years of experience in drug commercialization at two major pharmaceutical companies; a chief scientific officer with 16 years of industry experience in drug and target discovery; and a chief medical officer, who is a trained hematologist/oncologist with more than 20 years of industry experience in clinical research and drug development.

MMRC integrates the research efforts of 15 leading academic centers, with the common goal of facilitating and accelerating Phase I and II clinical trials and banking tissue. These are the leading myeloma centers in the United States and the world, and are bound by a common membership agreement. MMRC is focused on high-quality trials of drugs and combinations. Targets are prioritized by a committee of experts from the 15 centers, and new projects undergo a stringent review process. MMRC brings expertise to small biotechnology companies that often have limited resources and clinical experience, working with the company to develop a strong regulatory plan. MMRC also has a Good Laboratory Practices (GLP)–quality tissue bank, which enables correlative studies to be conducted with all of the trials. Speed and efficiency are a priority, and MMRC has set aggressive goals for the timing of protocol development (3 months); contracting, which is often the biggest factor in delaying trials (2 months); institutional review board (IRB) approval (3 months); and patient accrual (8–14 months).

Metrics and reward systems are implemented to improve processes and enforce accountability. MMRC has instituted a scorecard that is used to track the number and quality of tissue samples provided to the tissue bank; the time required to initiate clinical trials and accrue patients; and

the engagement of principal investigators, including such activities as participating in monthly calls and face-to-face meetings or bringing new ideas to the consortium. Use of the scorecard has led to improvements. Following the release of the first scorecard results at the end of 2007, 100 percent of principal investigators participated in the monthly call for the first time. Using the scorecard, MMRC ranks the centers in three tiers and links financial rewards to performance. The top third of the 15 centers are placed in tier one and receive funding to cover 100 percent of a full-time equivalent (FTE) clinical trials coordinator. The second tier receives 50 percent of an FTE and the third tier 25 percent. The top center, which in 2007 was Emory University, also benefits from the publicity and enhanced credibility gained from being designated Center of the Year.

To date, MMRC has initiated 14 clinical trials. The portfolio is balanced in terms of Phase I and II trials, as well as independent investigator and industry-sponsored studies. MMRC is now in a position where it can be more selective about the trials that are undertaken, ensuring that only those that advance its objectives are selected.

MMRC has assessed and devised solutions to barriers commonly encountered in the clinical trials process. During concept and protocol development, for example, MMRC brings sponsors and centers together in weekly teleconferences, and it is developing a standard protocol template. With regard to site selection, MMRC knows the number of its own trials that are open at each site, as well as the total number of myeloma trials and the number of myeloma patients seen by each center. As a result, MMRC can work with sponsors to identify the best sites for an expeditious trial. For the contracting stage, MMRC has a standard membership agreement for those institutions that are part of the consortium and a standard clinical trials agreement. It negotiates with companies on behalf of all of the centers as a single entity, as opposed to companies having to negotiate contracts with each center independently. In-house counsel and an outside attorney work closely to facilitate contracts. MMRC recently brought together industry partners and academic attorneys to review the clinical trials agreement and revise it as necessary to address the needs of both industry and academia and make the process even more efficient.

As noted above, MMRC fully or partially funds coordinators at each site based on the site's performance tier. For the IRB approval process, these coordinators ensure that consortium trials receive priority, even hand-delivering the IRB submission from one desk to another as needed, significantly reducing the duration of the process. The MMRC-funded site coordinators also facilitate patient accrual, aided by the MMRF database of almost 30,000 patients. In terms of FDA approval and communications, MMRC holds roundtables in collaboration with the agency, bringing biotechnology companies together the day before the roundtable

to discuss real and perceived barriers to drug development and approval. MMRF also conducts continuing medical education and patient education programs.

MMRC is now focused on ensuring that 100 percent of the trials conducted within its purview have a correlative science component. To date, this has been the case for about two-thirds to three-quarters of the trials. The resulting information can help companies understand who the target population is and who is most likely to benefit from the drug, and bring drugs that truly work in a given population to the market more quickly.

MUSCULAR DYSTROPHY ASSOCIATION'S APPROACH TO MAXIMIZING ASSETS IN CLINICAL TRIALS[6]

The Muscular Dystrophy Association (MDA) is an umbrella organization addressing 40 rare neuromuscular diseases, ranging from muscular dystrophy, to spinal muscular atrophy, to amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). Dr. Hesterlee said that MDA faces the same challenges as single-disease organizations, but multiplied 40 times over. It cannot take the same approach as those other organizations to managing clinical research networks and clinical trials because it is dealing with so many different diseases. MDA's mission is to develop therapies or cures for all of these diseases, so it seeks creative ways to leverage its resources. It operates on a program budget of $120 million per year, distributing funding across basic research, target identification, proof-of-principle testing in animals, translational research and preclinical development, and clinical research. Currently, basic research receives the largest share of the funding, but in the next year MDA plans to shift its focus and spend significantly more money on translational and clinical research.

Barriers to Clinical Trials of Drugs for Rare Diseases

When a company has a promising therapeutic candidate, one of the first steps it takes is to calculate the net present value of the therapy going forward, looking at cash flow and applying a discount rate to account for inflation during development. Data inputs for this kind of model include revenue and the factors that influence it, such as patient flow (which for a rare disease is going to be low), price, length of therapy, and number of disease episodes per year. It also includes expenditures, such as development, sales force, cost of goods sold, NDA application costs, and milestone payments. Risk is an additional factor considered.

[6]This section is based on the presentation of Sharon Hesterlee, Ph.D., Vice President of Translational Research, Muscular Dystrophy Foundation.

Clinical trial costs are a key component of development expenditures. These costs may include study and protocol development, site and patient enrollment, statistical analysis, report writing, and CMC. Even with a promising product and knowledge of what costs must be considered, issues often arise of not knowing how many patients have a particular rare disease or what the burden of disease is. The sponsor of the drug may find that the natural history data are inadequate, or that the academic community has been running clinical trials with end points that have not been validated or that the FDA does not accept. All of these issues add complexity to the development of an economic model.

Finding trial participants is critical in a small market, and may require identifying every patient with a rare disease to make the economic model viable. Another common barrier is ownership of or access to data, networks, methodology, funding, or patient populations on the part of those who are unwilling to share resources.

Solutions: Partnerships and Collaborative Structures

While there has been much discussion about public–private partnerships, MDA functions primarily through private–private partnerships, collaborating with other nonprofit organizations, notably those with which MDA competes for funding. Hesterlee described three examples of collaborative partnerships in which MDA is involved.

The TREAT-NMD neuromuscular network in Europe links 21 partner organizations and more than 300 doctors, researchers, and other professionals throughout 11 European countries. This European Union–funded network enables experts to work together to share best practices and develop consensus in diagnosis, standards of care, validated outcome measures, uniform patient databases, and a clinical research network. The member countries are currently establishing registries of patients with Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA). A key aspect of these registries is that they contain core data elements agreed upon by those who maintain the various national databases, and there are specifications regarding what data are to be collected and how. Beyond these mandatory data are data that are highly encouraged, and countries may also collect whatever additional data they desire for their own registries. The ultimate goal is for all of the national patient registries to provide the core data to a central, global database. An industry drug sponsor would then be able to run a quick search of the database to determine how many eligible patients exist in multiple countries across the world.

Another collaboration in which MDA is involved is the International Coordinating Committee for Spinal Muscular Atrophy Clinical Trials. The group includes academic and National Institutes of Health (NIH) investiga-

tors and representatives of at least four patient advocacy groups (Families of SMA, Fight SMA, MDA, and the SMA Foundation), working on committees to address outcome measures, clinical trial design, biomarkers, standards of care, and a patient registry, as well as a patient advisory committee. Begun by Families of SMA, the organization was transitioned to joint ownership by the group of SMA disease organizations, and funding for the patient registry is divided among them. MDA asked the SMA groups to ensure that all of the core elements of the registry would be compatible with the TREAT-NMD standards so it would be able to join the global registry. To date, the organization has published and disseminated standards of care and launched a biomarker initiative.

A third collaboration example is the Duchenne Research Collaborative International, comprising four organizations: MDA; the Association Française contre les Myopathies (AFM, the MDA sister organization in France); Parent Project Muscular Dystrophy (PPMD), based in the United States; and United Parent Project Muscular Dystrophy, based in the Netherlands. Together, these organizations have identified a series of projects, including a clearinghouse for research investments and resources, a global clinical trial network, and a global patient registry. The clearinghouse, a "Research Crossroads" site, will be a for-profit website that aggregates data on funding and research. The vision is that from this joint grants database, researchers and patients will be able to access research grants from NIH, MDA, AFM, PPMD, and other groups, cross-referenced with listings for patient registries and other research resources. One of the difficulties encountered has been reaching agreement on a single contract among the four organizations and their lawyers and the lawyer for the website company.

In addition to these collaborative efforts, MDA funds 230 clinics across the United States, where a neuromuscular specialist will see anyone with one of the 40 neuromuscular diseases covered by the program. These are primarily medical clinics, but some of them participate in research as well. Given that clinical research networks already exist for such diseases as ALS, SMA, and DMD, MDA decided that it would work with these networks, augmenting their efforts by funding an FTE clinical coordinator at 10 ALS and DMD centers.[7] MDA plans to expand this funding to include five clinics focused on SMA next year, with the ultimate goal of funding 50 clinics in the network.

Finally, MDA is actively working to develop, validate, and standardize end points. Two meetings have been held for this purpose, in 2005 and 2007. These meetings brought together stakeholders, including FDA, NIH, academic investigators, and companies, to discuss the current state of end

[7]Since the workshop was held, five ALS centers and five DMD centers have received funding for this purpose.

points for particular diseases, whether the natural history of the diseases is known, and steps that need to be taken to move forward. Based on the results of those meetings, MDA has issued requests for applications and is funding projects to fill the identified gaps. For example, MDA funded a project at the University of Rochester to develop a survey instrument on the natural history of myotonic dystrophy.

OPEN DISCUSSION

The open discussion in this session expanded on the concept of collaboration among disease foundations that compete directly for funding, and on the importance of considering issues of affordability and access when foundations fund the development of new drugs.

Collaboration Among Foundations

Hesterlee noted that collaborating on the same disease can be difficult because of fundraising issues. It is easier, however, to collaborate across different diseases—for example, looking at common mechanisms. Young pointed out that MMRC recently announced a collaboration with the Leukemia and Lymphoma Society, an organization with which MMRC competes directly for funding. The collaboration is focused on stem cell research, identifying and targeting the myeloma stem cell. Young suggested that collaboration works best in a high-risk area, an area that is unlikely to lead to any therapies in the near term, and one that is somewhat outside of both organizations' direct missions. With regard to exploring common mechanisms, Pariser stressed the need for caution in designing trials. Diseases such as the muscular dystrophies may look the same, and some, such as progressive muscular weakness, may have a great deal in common, but if their etiologies differ, responses may differ as well, and the desired end points may not be achieved.

Affordability and Access

So inquired how MMRC and MDA are handling the issue of affordability at the end of the pipeline. Hesterlee responded that MDA is considering this issue, and internal discussions are focused on whether the association is going to advocate for Medicare and Medicaid coverage. Part of the plan is to address affordability from the outset by absorbing some of the infrastructure costs. Young noted that there is a limited number of new and expensive drugs for myeloma. Until 4 years ago, patients were treated with chemotherapy and steroids that were all generic. The mission of MMRC is research, and while access has not yet been an issue, it will have to be considered as more drugs become available.

8

Summary[1]

The main objectives of the workshop were to understand how translational research is changing; to explore different models for funding translational research and technologies; and to discuss current policies and regulations and consider whether they are adequate, or if revisions are needed in light of new funding models. In the final session of the workshop, Dr. Bond summarized the highlights of the day and outlined four areas in which further discussion is needed.

SCIENTIFIC AND REGULATORY ELEMENTS OF THE TRANSLATIONAL RESEARCH PROCESS

The last several years have seen a remarkable culture change that has created a new environment in which translational research is highly valued. Still, barriers to progress persist. Tom Caskey reviewed financial barriers to orphan drug development during discovery, utility or proof of concept, and clinical development, and discussed drivers of investment (see Chapter 2). He proposed solutions to help speed the development of new drugs: more defined focus of government research, adequate funding of the Food and Drug Administration (FDA), possible revision of the Small Business Innovation Research and Small Business Technology Transfer regulations, new incentives for high-risk investors, early engagement of experienced investors, and building of a stronger U.S. industry through partnerships with

[1]This chapter is based on the closing remarks of Enriqueta C. Bond, Ph.D., President, Burroughs Wellcome Fund.

academia. He also stressed the need for better target validation and safety at all levels. Tim Coté reviewed the history of the orphan drug law and its current status. He also presented ten strategies for moving orphan drug development forward more rapidly and efficiently (see Chapter 3).

DIVERSE FUNDING ORGANIZATIONS

Four models for drug development were described: a not-for-profit pharmaceutical company, a foundation that operates a virtual company linking investors with biopharmaceutical companies, a for-profit company with a vested interest in rare diseases, and a global private-equity fund dedicated to advancing drug discovery (see Chapter 4).

The Institute for OneWorld Health, the not-for-profit pharmaceutical company, eliminated the profit requirement from its business plan. Seed money was provided by the Gates Foundation. Acknowledging that a single funding source is not a sustainable model, the Institute is now seeking additional funders, with the ultimate goal of being able to support itself partially or fully with revenues from marketed products.

Cystic Fibrosis Foundation Therapeutics (CFFT) has shown how a disease-oriented foundation can become a virtual drug company. CFFT establishes business partnerships with pharmaceutical companies, lowering their risk in the development of drugs for rare disorders by providing financial support, access to leading cystic fibrosis experts and research tools, and access to the Cystic Fibrosis Therapeutic Development Network of Cystic Fibrosis Care Centers for facilitation of clinical trials.

Genzyme approaches the development of drugs for rare diseases as a for-profit venture. There are several keys to the sustainability of this model: the therapy must be effective and must address an unmet medical need, presumably one involving a condition that is life-threatening or causes severe morbidity; there must be a global market; and the price must be sustainable. Partnerships can allow for the development of a product that would not be possible for a single company, and less profitable drugs can be developed if they are part of a larger portfolio.

Celtic Therapeutics is a global private equity firm that functions as a virtual pharmaceutical company, acquiring or investing in novel therapeutic candidates to bridge the gap between discovery and preclinical development and late-phase clinical trials/approval. As well-financed pharmaceutical company pipelines dwindle, underfinanced biotechnology companies have drug candidates but lack the resources to develop them. This new venture management group plans to fill a portion of its portfolio with promising drug candidates for rare or neglected diseases that are in Phase II, develop the products to the point at which a large pharmaceutical partner would be interested, and sell them at auction to pharmaceutical companies. An

expert reaction panel provided further examples of funding models. The venture capital community is ready and willing to invest in new therapies, but needs rare disease foundations to help lower the risks involved by assisting the venture organizations in fully understanding the opportunities, including the probability of technical success for a particular therapeutic candidate, the likelihood of finding patients for trials, and the scientific talent required.

As genomic information allows for better targeting of therapies, personalized medicine will create numerous opportunities for the development of new orphan drugs by leading to the identification of diseases that affect fewer than 200,000 people in the United States. Being able to develop such drugs may require the broad adoption of some of the models discussed in the workshop.

SHARING OF MATERIALS AND DATA

Michael Mowatt said the barriers to sharing resources fall into two main categories: finding (i.e., determining where to look and whom to contact for materials or data), and bargaining (i.e., negotiating the terms and conditions of the transfer of those resources). He discussed a variety of mechanisms for reducing barriers to sharing, such as standardized material transfer agreements (MTAs) or letters of agreement, and repositories that provide easy access to materials or data (see Chapter 5).

To facilitate sharing, the National Institute on Aging established the Alzheimer's Disease Neuroimaging Initiative—a public–private partnership that is conducting a large observational study following 822 subjects, including patients with Alzheimer's disease, those with cognitive impairment placing them at risk for the disease, and elderly controls. All data, including images, biological samples, and clinical data, will be available in a public global database.

The Genetic Alliance BioBank is an advocacy-owned repository for clinical data and biological samples, designed so as to create a firewall between researchers and many of the burdensome administrative and regulatory tasks associated with working with patients. The BioBank provides infrastructure for disease-specific organizations that manage their own collections of materials and data and facilitates their distribution. Sharon Terry of the Alliance said that patients with rare diseases need therapies and are therefore willing to accept a higher degree of risk. They are eager to engage in discussions aimed at making drug development more of a social-entrepreneurial venture, contributing, for example, by increasing participation in clinical trials.

INTELLECTUAL PROPERTY STRATEGIES

With regard to intellectual property strategies, Anthony So noted the gap between drug company priorities and public health needs. He provided a number of examples of innovative ways in which intellectual property has been used to advance drug development for rare diseases, such as pooling intellectual property, depositing it in a trust, allowing open access to data, using socially responsible licensing terms, standardizing MTAs, and instituting new benefit-sharing arrangements. So encouraged collective action by the public and private sectors to pool intellectual property, and suggested the creation of a technology trust as a strategy for creating an enabling intellectual property environment for rare and neglected diseases (see Chapter 6).

The recurring theme of the three presentations in this area—from industry, from a patient-led disease-specific foundation, and from a university technology-transfer office—was the need to create new alliances and partnerships. Vertex Pharmaceuticals stressed alliances as the way forward and offered a list of lessons learned for alliance partners. The Myelin Repair Foundation, which has structured itself like a start-up business, showed how it was able to build networks, establish patient repositories, and share intellectual property to accelerate drug development. The message from the University of California at Berkeley was that university technology-transfer offices need to take a new approach to facilitate sharing and research. The university employs a relationship-based model that shifts the focus from maximizing licensing revenue to maximizing the societal impact of research, and assesses both financial income and public good in quantifying success.

APPROACHES TO FACILITATING CLINICAL TRIALS

Anne Pariser offered an overview of the regulatory process, noting that FDA is eager to facilitate the development of orphan drugs. While orphan drug regulations provide financial incentives for drug sponsors, they do not make it easier to navigate the regulatory process. Pariser offered nine recommendations to sponsors of orphan drug applications and described opportunities for facilitating development, including fast-track designation, accelerated approval, priority review, and early and frequent communication with FDA (see Chapter 7).

To help researchers overcome regulatory barriers, the Multiple Myeloma Research Foundation established the Multiple Myeloma Research Consortium (MMRC), a group of 15 leading academic centers focused on high-quality trials of myeloma products and correlative studies. MMRC also created repositories for tissue samples and data. A scorecard approach is

used to track the number and quality of tissue samples each center provides to the tissue bank, its speed in initiating and accruing patients for clinical trials, and the overall engagement of principal investigators. Centers are rewarded accordingly with funding for all or part of the cost of a full-time equivalent clinical coordinator.

The Muscular Dystrophy Association, an umbrella organization addressing 40 rare neuromuscular diseases, has focused on establishing partnerships with other private-sector groups and developing patient registries, research clearinghouses, and international resources and standards. It also convenes collaborating groups in face-to-face meetings.

Bond challenged the participants to consider whether each individual disease-oriented group needs to develop approaches to facilitate regulatory processes, or this is something universities could be doing, building that capacity at an institutional level. Currently, disease-oriented groups must replicate these approaches for the diseases on which they focus.

AREAS FOR FURTHER DISCUSSION

In concluding, Bond highlighted four potential areas for further discussion:

- **Business models**—A variety of models for drug development were discussed during the workshop. While this discussion was interesting and informative, and these models have been successful in their own venues, Bond suggested that it is too soon to distill broadly applicable lessons and best practices from these approaches and that new models will continue to emerge. She recommended that the Forum on Drug Discovery, Development, and Translation revisit the topic of business models for the development of drugs to treat rare and neglected diseases on a recurring basis, perhaps every couple of years.
- **Data sharing and public access**—Several interesting new models for sharing resources were presented during the workshop. Models such as the Public Library of Science, public access to information derived from National Institutes of Health–funded research, and requirements that centers involved in the Human Genome Project deposit sequence data into GenBank in a timely fashion are evidence that a new, favorable climate for the sharing of resources is emerging. Bond suggested that it would be valuable to conduct a study to explore the terrain of resource sharing and distill best practices.
- **Intellectual property**—A variety of models for the management of intellectual property were discussed during the workshop, but

many intellectual property issues related to drugs for rare and neglected diseases remain. Bond concluded that a full workshop or study on this topic alone would be valuable.

- **Designated orphan drugs**—As noted by Coté (see Chapter 3), there have been over 1,850 orphan designations and 326 orphan drug approvals, leaving 1,525 orphan drugs in development or abandoned for various scientific or business reasons. Some of these compounds may still hold promise, and an assessment of their current disposition is needed. Bond suggested as a further area for discussion policies applied to the review of orphan drugs and what new or revised policies might facilitate the approval of such drugs.

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Appendix A

Agenda

Objectives: The broad objectives of this 1-day workshop will be to:

- Outline changes in the translational research (discovery through Phase II) process that have taken place over the past 10 years and why.
- Discuss new models for funding translational research and new technologies and consider their impact on the process.
- Examine regulatory, legislative, and institutional policy tools currently in place to help advance therapeutic development for rare or neglected diseases and individualized therapies, and discuss whether these tools are adequate or whether new ones are needed in light of these new funding models.

8:30 Welcome, Background, and Introduction of Workshop Objectives

Nancy Sung (Workshop Chair, Drug Forum Member)
Senior Program Officer
Burroughs Wellcome Fund

8:45 Keynote: Changes in the Translational Research (Discovery–Phase II) Process

- What are the scientific and regulatory elements/requirements of the translational process?

- Are the current approaches for fulfilling these requirements adequate to advance development of drugs for rare or neglected diseases and individualized therapies?
- Where along the continuum is investment needed?

Innovative Safe New Drugs—Financial Sectoring

Tom Caskey (Drug Forum Member)
Chief Operating Officer and Director/Chief Executive Officer
University of Texas Health Science Center at Houston

Q&A

9:05 Session 1: Diverse Funding Organizations—Business Cases

- Why were new approaches or models needed, and what are their advantages?
- Are these models effective at helping to speed development and how might their impact be measured?
- Are these viable models for advancing products in the context of individualized therapies?
- Are federal regulatory policies adequate for helping speed development and approval of drugs for rare diseases?

Moderator: Timothy Coetzee
Executive Director
Fast Forward, LLC

9:10 OneWorld Health: A Not-for-Profit Pharmaceutical Company

Victoria Hale
Founder and Chair of the Board of Directors
Institute for OneWorld Health

9:25 Cystic Fibrosis Foundation Therapeutics' Pipeline Approach to CFTR Drug Discovery and Development

Diana Wetmore
Vice President of Alliance Management
Cystic Fibrosis Foundation Therapeutics

9:40 Surviving as a For-Profit Company in the Rare Disease World

David Meeker
President, Lysosomal Storage Disorder Therapeutics
Genzyme

9:55 New Business Models Addressing Global Health: A Framework for Private Equity

Peter Corr (Drug Forum Member)
Co-founder and General Partner
Celtic Therapeutics

10:10 Reaction Panel

Gail Cassell (Drug Forum Co-chair)
Vice President, Scientific Affairs, and Distinguished Lilly Research Scholar for Infectious Diseases
Eli Lilly and Company

Marlene Haffner (Drug Forum Member)
Executive Director, Global Regulatory Intelligence and Policy
Amgen

Mark Batshaw
Chief Academic Officer
Children's National Medical Center

Chaitan Khosla
Professor, Departments of Chemistry, Chemical Engineering, and Biochemistry
Stanford University

Doug Onsi
Venture Partner
HealthCare Ventures

Q&A

11:15 Break

11:30 Session 2: Strategies for Facilitating Sharing of Research Materials and Data

- How have funding organizations controlled data and materials to facilitate open access and sharing?
- Are open-access databases and repositories making a difference? How might their use be broadened?
- What are the opportunities and challenges of managing these resources?
- Are federal regulatory policies adequate for helping speed development and approval of drugs for rare diseases?

Moderator: Margaret Anderson
Chief Operating Officer
FasterCures

11:35 Agreements for Research and Materials Sharing

Michael Mowatt
Director, Office of Technology Development
National Institute of Allergy and Infectious Diseases, NIH

11:50 The Alzheimer's Disease Neuroimaging Initiative (ADNI): A Public–Private Partnership

Laurie Ryan
Program Director, Alzheimer's Disease Clinical Trials
Division of Neuroscience, National Institute on Aging, NIH

12:05 Genetic Alliance BioBank or Herding the Cats

Sharon Terry
President and Chief Executive Officer
Genetic Alliance

Q&A

12:30 Lunch Break

12:50 Luncheon Keynote

The FDA Orphan Drug Program: A Proven Model

Tim Coté
Director, Office of Orphan Products Development
U.S. Food and Drug Administration

1:30 Break

1:45 Session 3: Strategies for Navigating Intellectual Property

- Are existing policies adequate to facilitate efficient management of intellectual property throughout the development process?
- Which novel strategies have been implemented in recent years to manage intellectual property in light of new funding models?

Moderator: Anthony So
Professor of the Practice of Public Policy Studies
Director, Program in Global Health and Technology Access
Terry Sanford Institute of Public Policy, Duke University

1:45 Creating an Enabling Intellectual Property Environment for Neglected and Rare Diseases

Anthony So

2:05 Innovation in Alliances and Licensing: Transforming Now for the Future

Craig Sorensen
Senior Director, Strategic Research Alliances
Vertex Pharmaceuticals Incorporated

2:25 Accelerating Intellectual Property Sharing to Facilitate Translation

Rusty Bromley
Chief Operating Officer
Myelin Repair Foundation

2:45 UC Berkeley's Approach to Intellectual Property Management: Multiple Strategies Are Required to Deploy Innovations for Maximal Impact

Carol Mimura
Assistant Vice Chancellor for Intellectual Property and Industry Research Alliances (IPIRA)
University of California at Berkeley

Q&A

3:45 Break

4:00 Session 4: Strategies for Facilitating Clinical Trials

- What do patient groups and disease organizations need to know about working with FDA toward approval of new therapies?
- How are patient groups and disease foundations helping to facilitate trial launch?
- Are there innovative methods for conducting efficient multicenter clinical trials with small numbers of patients?

Moderator: Stephen Groft (Drug Forum Member)
Director, Office of Rare Disease Research
National Institutes of Health

4:05 FDA Review and Regulation of Small Clinical Trials: Successes, Barriers, and Directions for the Future

Anne Pariser
Medical Team Leader, Inborn Errors of Metabolism Team
Division of Gastroenterology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

4:20 Accelerating Clinical Trials: The MMRF and MMRC Model

Anne Quinn Young
Program Director
Multiple Myeloma Research Foundation

4:35 Maximizing Your Assets in Clinical Trials: Economies of Scale and Standardization

Sharon Hesterlee
Vice President, Translational Research
Muscular Dystrophy Foundation

Q&A

5:15 Session 5: Recap of Key Points Made Throughout the Day

Enriqueta Bond
President
Burroughs Wellcome Fund

5:30 Adjourn

Appendix B

Speaker Biographies

Margaret A. Anderson, M.A., joined FasterCures in June 2004 as Chief Operating Officer. She came to the organization after 5 years at the Academy for Educational Development (AED) in Washington, DC. At AED, she was Deputy Director and a Team Leader in the Center on AIDS and Community Health. In that capacity, she assisted the Senior Vice President in managing a 70-person domestic and international staff. Her responsibilities included financial and budget oversight; management of a team, projects, and staff; and strategic planning. She managed a portfolio that consisted of grants and contracts from the Centers for Disease Control and Prevention (CDC), the Ford Foundation, and the Annie E. Casey Foundation. Project activities included a Diffusion of Effective Behavioral Interventions (DEBI) project, which provided curriculum development and training on eight proven effective HIV prevention interventions; an anti-HIV/AIDS stigma project; an annual health summit for community health agencies; and more than 20 other CDC task order projects. Between 1995 and 1998, Ms. Anderson was Program Director for the Society for Women's Health Research. At the Society, she managed grant-funded programs including the start-up planning for the multiyear campaign Some Things Only a Women Can Do, aimed at increasing women's awareness of and participation in clinical trials; the Get Real: Straight Talk about Women's Health campaign for college campuses, focused on improving young women's health; the Vive La Difference video and facilitator's guide, which provide information about sex-based biology; and the annual Scientific Advisory Meeting. Prior to joining the Society, Ms. Anderson was a health science analyst at the American Public Health Association (APHA) from 1992 to 1995, where

she managed a programmatic portfolio on HIV/AIDS and other sexually transmitted diseases, infectious diseases, women's health, and public health infrastructure issues. From 1987 to 1991, she was an Analyst and Project Director at the Congressional Office of Technology Assessment. Ms. Anderson currently serves as a member of the Whitman-Walker Clinic Institutional Review Board and has held numerous committee and coalition memberships for federal agencies and professional associations in the biomedical and public health arena. She holds a bachelor's degree from the University of Maryland and a master's degree in science, technology, and public policy from The George Washington University's Elliott School of International Affairs.

Mark L. Batshaw, M.D., is the "Fight for Children" Chair of Academic Medicine and Chief Academic Officer at the Children's National Medical Center (CNMC) in Washington, DC, and Professor and Chairman of Pediatrics and Associate Dean for Academic Affairs at The George Washington University School of Medicine and Health Sciences, also in Washington, DC. Dr. Batshaw is a graduate of the University of Pennsylvania and the University of Chicago Pritzker School of Medicine. Following pediatric residency at the Hospital for Sick Children in Toronto, he completed a fellowship in developmental pediatrics at the the Johns Hopkins Medical Institutions. Dr. Batshaw is Director of the National Institutes of Health (NIH)–funded Rare Diseases Clinical Research Center at CNMC and continues to pursue his research on innovative treatments for inborn errors of metabolism, including gene therapy. He has published more than 150 articles, chapters, and reviews on his research interests and on the medical aspects of the care of children with disabilities.

Enriqueta C. Bond, Ph.D., is President of the Burroughs Wellcome Fund. She received her undergraduate degree from Wellesley College, her M.A. from the University of Virginia, and her Ph.D. in molecular biology and biochemical genetics from Georgetown University. She is a member of the Institute of Medicine (IOM), the American Association for the Advancement of Science, the American Society for Microbiology, and the APHA. Dr. Bond chairs the National Academies' Board on Capacity Development of African Academies of Science and serves on the Report Review Committee for the National Academies. She serves on the board and executive committee of the Research Triangle Park Foundation, on the board of the National Institute for Statistical Sciences, on the board of the Northeast Biodefense Center and the New England Center of Excellence in Biodefense and Emerging Infectious Diseases, and on the council of the National Institute of Child Health and Human Development. Prior to being named President of the Burroughs Wellcome Fund in 1994,

Dr. Bond had served on the staff of the IOM since 1979, becoming IOM Executive Officer in 1989.

Russell (Rusty) Bromley is Chief Operating Officer of the Myelin Repair Foundation (MRF). Since joining MRF in September 2003, he has been instrumental in the creation and evolution of the MRF Accelerated Research Collaboration™ model. His principal responsibilities include development and execution of the MRF research plan, identification and protection of resulting intellectual property, and development of relationships with a broad range of academic and commercial organizations. Prior to joining MRF, Mr. Bromley was CEO of LabVelocity, Inc., and spent 17 years with American Hospital Supply Corporation and Baxter Healthcare, where he was President of the Burdick and Jackson division. Mr. Bromley holds a degree in biochemistry from Rice University.

C. Thomas Caskey, M.D. (member, IOM Forum on Drug Discovery, Development, and Translation), is Director and Chief Executive Officer and Chief Operating Officer of the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM) at the University of Texas Health Science Center at Houston. Dr. Caskey was founding director of Houston-based Cogene Biotech Ventures and Cogene Ventures, venture capital funds supporting early-stage biotechnology and life sciences companies. He has received numerous academic and industry-related honors. He is a member of the National Academy of Sciences and the IOM. He has served as President of the American Society of Human Genetics; the Human Genome Organization; and The Academy of Medicine, Engineering and Science of Texas (TAMEST). Dr. Caskey served as Senior Vice President for Human Genetics and Vaccines Discovery at Merck Research Laboratories from 1994 to 2000 and as President of the Merck Genome Research Institute from 1998 to 2000. His genetic research documented the universality of the genetic code, discovered the mechanism of peptide chain termination, identified the genetic basis of 10 major heritable diseases, opened understanding of triplet repeat diseases (Fragile X, myotonic dystrophy, and others), developed the STR method of DNA-based personal identification (now used worldwide) for forensic studies, and developed a viral vector vaccine for HIV. Dr. Caskey received the Distinguished Texas Geneticist Award from the Texas Genetics Society in 1998 and serves on Texas Governor Rick Perry's Council on Science and Biotechnology, which makes funding recommendations for the $200 million Texas Emerging Technology Fund. He earned his medical degree from Duke University School of Medicine and his undergraduate degree from the University of South Carolina. He is board certified in internal medicine, clinical genetics, metabolic diseases, and molecular diagnostics.

Gail H. Cassell, Ph.D. (Co-chair, IOM Forum on Drug Discovery, Development, and Translation), is currently Vice President, Scientific Affairs, and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company, Indianapolis, Indiana. She is former Charles H. McCauley Professor and Chair of the Department of Microbiology, University of Alabama Schools of Medicine and Dentistry at Birmingham, a department that ranked first in research funding from NIH during the decade of her leadership. She obtained her B.S. from the University of Alabama in Tuscaloosa and in 1993 was selected as one of the top 31 female graduates of the twentieth century. She obtained her Ph.D. in microbiology from the University of Alabama at Birmingham and was selected as its 2003 Distinguished Alumnus. She is past President of the American Society for Microbiology (the oldest and single largest life sciences organization, with a membership of more than 42,000). She was a member of the NIH Director's Advisory Committee and of the Advisory Council of the National Institute of Allergy and Infectious Diseases (NIAID). She was named to the original Board of Scientific Councilors of the Center for Infectious Diseases, CDC, and served as chair of the board. She recently served a 3-year term on the advisory board of the Director of CDC and as a member of the Secretary of Health and Human Services' Advisory Council of Public Health Preparedness. Currently she is a member of the Science Board of the U.S. Food and Drug Administration (FDA). Since 1996 she has been a member of the U.S.–Japan Cooperative Medical Science Program, responsible for advising the respective governments (U.S. State Department/Japanese Ministry of Foreign Affairs) on joint research agendas. She has served on several editorial boards of scientific journals and has authored more than 250 articles and book chapters. Dr. Cassell has received national and international awards and an honorary degree for her research in infectious diseases. She is a member of the IOM and is currently serving a 3-year term on the IOM Council, the institution's governing board. Dr. Cassell has been intimately involved in the formulation of science policy and legislation related to biomedical research and public health. For 9 years she was chair of the Public and Scientific Affairs Board of the American Society for Microbiology. She has served as an advisor on infectious diseases and indirect costs of research to the White House Office of Science and Technology Policy, and has been an invited participant in numerous congressional hearings and briefings related to infectious diseases, antimicrobial resistance, and biomedical research. She has served two terms on the Liaison Committee on Medical Education (LCME), the accrediting body for U.S. medical schools, as well as other national committees involved in establishing policies on training in the biomedical sciences. She recently completed a term on the Leadership Council of the School of Public Health of Harvard University. Currently she is a member of the Executive Committee of the Board of Visitors of

Columbia University School of Medicine, the Executive Committee of the Board of Directors of the Burroughs Wellcome Fund, Research!America, and the Advisory Council of the Johns Hopkins School of Nursing.

Timothy Coetzee, Ph.D., is Executive Director of Fast Forward, LLC, a venture philanthropy of the National Multiple Sclerosis (MS) Society. In this capacity, he is responsible for the Society's strategic funding of biotechnology and pharmaceutical companies, as well as partnerships with the financial and business communities. Prior to assuming his current position, he led the Society's translational research initiatives on nervous system repair and protection in MS, as well as its programs to recruit and train physicians and scientists in MS research. Dr. Coetzee received his Ph.D. in molecular biology from Albany Medical College in 1993 and has since been involved in the field of MS research. He was a research fellow in the laboratory of Society grantee Dr. Brian Popko at the University of North Carolina at Chapel Hill, where he received an Advanced Postdoctoral Fellowship Award from the Society. After completing his training with Dr. Popko, Dr. Coetzee joined the faculty of the Department of Neuroscience at the University of Connecticut School of Medicine, where he conducted research that applied new technologies to understanding how myelin is formed in the nervous system. He is the author of a number of research publications on the structure and function of myelin. Dr. Coetzee joined the National MS Society's Home Office staff in fall 2000.

Peter Corr, Ph.D. (member, IOM Forum on Drug Discovery, Development, and Translation), is Co-founder and General Partner of Celtic Therapeutics Management Company, LLLP. He retired from Pfizer Inc. in January 2007, where he was Senior Vice President for Science and Technology with strategic responsibility for advancing the company's human health business through licensing and business development, science, technology, and medical outreach and advocacy, including global medical professional relations and science policy. In 2002 and 2003, he also headed worldwide pharmaceutical research and development for Pfizer. Dr. Corr was a member of the Pfizer Human Health Leadership Team, an executive body responsible for managing Pfizer's global human health business, and the Pfizer Leadership Council. He previously served as Executive Vice President, Pfizer Global Research and Development, and President, Worldwide Development. Before joining Pfizer in 2000, he held leadership positions in industry as Senior Vice President, Discovery Research, at Monsanto/Searle, and then as President of Pharmaceutical Research and Development at Warner Lambert/Parke Davis until the merger with Pfizer in 2000. Dr. Corr, who received his doctorate from Georgetown University School of Medicine, spent 18 years as a researcher in molecular biology and pharmacol-

ogy at both the basic science and clinical levels at Washington University in St. Louis. When he left the university, he was Professor, Department of Medicine (Cardiology), and Professor, Department of Pharmacology and Molecular Biology. His research has been published in more than 160 scientific manuscripts. Dr. Corr is the recipient of numerous awards, including membership in the Alpha Omega Alpha National Medical Honorary Society, an Established Investigator Award from the American Heart Association, and a Research Career Development Award from NIH. He received the Washington University School of Medicine Teacher of the Year Award on several occasions and, in 1990, the Washington University Distinguished Faculty Award. In 2004, he was named a William Pitt Fellow at Pembroke College, Cambridge University, Cambridge, UK. In addition to his work at Pfizer, Dr. Corr was Chairman of the Science and Regulatory Executive Committee of Pharmaceutical Research and Manufacturers of America (PhRMA); Chairman of the PhRMA Foundation Board of Directors; and Chairman of the Hever Group, representing chief scientific officers across the European and U.S.-based pharmaceutical industry. He is a Governor of the New York Academy of Sciences (and immediate past Chairman of the Board of Governors) and a member of the Board of Regents of Georgetown University. Additionally, he serves on the boards of C-PATH Institute in Tucson, Arizona; the International Partnership for Microbicides; CBio, an Australian biotechnology firm; Global Edit, Inc.; and the African Leadership Congress. He is a Trustee of the Joyce Theatre Foundation in New York City, and a member of the IOM Committee on Conflict of Interest in Medical Research, Education and Practice, as well as the IOM Forum on Drug Discovery, Development, and Translation.

Timothy Coté, M.D., M.P.H., has served as Director of FDA's Office of Orphan Product Development since September 2007. He received a bachelor's degree from Syracuse University, a medical doctorate from the Howard University College of Medicine, and a master's in public health from Harvard School of Public Health. He has completed residencies and is board certified in both preventive medicine and anatomic pathology. Dr. Coté began his federal service in 1989 with CDC's Epidemiology Investigation Service (EIS) and has since continued as an officer in the U.S. Public Health Service Commissioned Corps, assigned to wide variety of positions at CDC, NIH, the U.S. Department of Agriculture, and FDA. Most recently he served as CDC Chief of Mission in Kigali, Rwanda, where he implemented the President's Emergency Plan for AIDS Relief. He has authored or coauthored more than 60 publications on infectious and neoplastic diseases.

Stephen Groft, Pharm.D. (member, IOM Forum on Drug Discovery, Development, and Translation), is Director, Office of Rare Diseases, at NIH. He

started his career as a commissioned officer in the U.S. Public Health Service as a pharmacist in the Indian Health Service, with assignments in South Dakota and Oklahoma. From 1982 to 1986, he served in the Office of Orphan Products Development (OOPD) at FDA, and from 1986 to 1989, he was with the Department of Health and Human Services as Executive Director of the National Commission on Orphan Diseases. As Director of NIH's Office of Rare Diseases, he has devoted particular attention to efforts to stimulate research on these diseases and develop information for the rare disease community. The office has cosponsored approximately 725 scientific workshops and symposia with the NIH Research Institutes and Centers and patient support groups. Dr. Groft received both his bachelor of science in pharmacy (1968) and doctor of pharmacy (1979) degrees from Duquesne University.

Marlene E. Haffner, M.D., Ph.D. (member, IOM Forum on Drug Discovery, Development, and Translation) has been involved in patient access and therapies for those in need for her entire medical and public health career. She began her career on the Navajo Reservation, where she was responsible for the provision of comprehensive care to the 100,000 Navajo Indians. For 20 years she directed the OOPD at FDA. While in that position, she was involved in the development of orphan product programs around the globe, including the European Union, Japan, Australia, and Taiwan. Dr. Haffner is a graduate of The George Washington University School of Medicine and the Johns Hopkins University Bloomberg School of Public Health. She is trained in internal medicine, dermatology, and hematology. Her passion is making a difference in the health of people so their lives can be healthier and more productive. Since 2007 Dr. Haffner has been Executive Director, Global Regulatory Intelligence and Policy, at Amgen, Inc., where, in addition to her work in regulatory policy, she maintains her interest and involvement in orphan drugs, rare diseases, and access by patients to needed therapies.

Victoria Hale, Ph.D., is Founder and Chair of the Board of Directors of OneWorld Health. She established her expertise in all stages of biopharmaceutical drug development at FDA's Center for Drug Evaluation and Research and at Genentech, Inc., the world's first biotechnology company. She presently maintains an Adjunct Associate Professorship in Biopharmaceutical Sciences at the University of California at San Francisco (UCSF); is an Advisor to the World Health Organization (WHO) for building ethical review capacity in the developing world; and has served as an expert reviewer to NIH on the topic of biodiversity. Dr. Hale's recent honors include being elected to membership in the IOM in 2007; being named a John D. and Catherine T. MacArthur Foundation Fellow in 2006;

and being selected as an Ashoka Fellow for work in leading social innovation, also in 2006. In 2005, *The Economist* named Dr. Hale the recipient of its Social and Economic Innovation award, and *Esquire* magazine named her "Exec of the Year." That same year, OneWorld Health was awarded the Social Responsibility Award at the prestigious Pharmaceutical Achievement Awards competition and received the Skoll Award for Social Entrepreneurship. In 2004, Dr. Hale was named one of the Most Outstanding Social Entrepreneurs by the Schwab Foundation for Social Entrepreneurship. Also in 2004, Dr. Hale and OneWorld Health were included in the *Scientific American* 50, the magazine's annual list recognizing outstanding acts of leadership in science and technology.

Sharon Hesterlee, Ph.D., is Vice President, Translational Research, for the Muscular Dystrophy Association. She received her Ph.D. in neuroscience in 1999 from the University of Arizona, where she studied neural development and received funding from a Flinn Foundation Training Grant. From 2000 to 2006, she served as the Muscular Dystrophy Association's Director of Research Development. In that position, she developed and oversaw an $8 million translational research program aimed at increasing industry participation in drug development for rare diseases. She has been involved in the planning of several meetings to identify and remove barriers to therapy development for neuromuscular diseases and serves on numerous advisory boards, including the Department of Health and Human Services' Federal Advisory Committee for muscular dystrophy. In 2006 Dr. Hesterlee was appointed Vice President of Translational Research, and in addition to overseeing that program, she is currently directing major collaborations in the areas of Duchenne muscular dystrophy, Friedreich's ataxia, spinal muscular atrophy, and amyotrophic lateral sclerosis (ALS).

Chaitan Khosla, Ph.D., is Professor of Chemistry, Chemical Engineering, and Biochemistry at Stanford University. He received his Ph.D. in 1990 at the California Institute of Technology. After completing postdoctoral studies at the John Innes Centre in the United Kingdom, he joined Stanford in 1992. His research interests focus on the interface of chemistry, engineering, and medicine. Over the past decade he has studied polyketide synthases as paradigms for modular biosynthesis and has sought to exploit their properties for engineering novel antibiotics. More recently, he has investigated the chemical underpinnings of Celiac Sprue pathogenesis, with the goal of developing therapeutic alternatives for this widespread but overlooked disease. He has co-authored more than 200 publications and is the recipient of several awards and honors, including a Camille and Henry Dreyfus New Investigator Award (1991), a National Science Foundation Young Investigator Award (1994), a David and Lucile Packard Fellowship for Science

and Engineering (1994), the Allan P. Colburn Award from the American Institute of Chemical Engineers (1997), the Eli Lilly Award in Biological Chemistry (1999), the Pure Chemistry Award (2000) from the American Chemical Society, and the Alan T. Waterman Award from the National Science Foundation (1999). He is also the recipient of a Distinguished Alumnus Award from his undergraduate (Indian Institute of Technology) and graduate (Caltech) alma maters. He is a member of the American Academy of Arts and Sciences and a Fellow of the American Association for the Advancement of Science.

David P. Meeker, M.D., is Executive Vice President, Therapeutics, Biosurgery and Transplant, at Genzyme. He joined Genzyme in 1994 as Medical Director to work on the Cystic Fibrosis Gene Therapy program. Subsequently, as Vice President, Medical Affairs, and prior to his promotion to Senior Vice President in 1998, he was responsible for the development of therapeutic products, including products in the current lyosomal storage disease (LSD) portfolio. In 2000 he assumed the position of Business Unit Leader for Genzyme's LSD and Thyrogen® programs in Europe. In March 2003 he was promoted to President of the Global LSD Business Unit. Dr. Meeker has overseen the global launches of Aldurazyme®, Fabrazyme®, and Myozyme®. In May 2008, he was promoted to Executive Vice President and now oversees the Biosurgery and Transplant Business Units in addition to Therapeutics. Prior to joining Genzyme, Dr. Meeker was Director of the Pulmonary Critical Care Fellowship at the Cleveland Clinic Foundation. He has authored more than 40 articles and multiple book chapters. He is currently a member of the Board of Penwest Pharmaceuticals Inc. and a member of the Scientific Advisory Board of Prize4Life, an organization dedicated exclusively to promoting research and development objectives in ALS. Dr. Meeker attended Dartmouth College and received his M.D. from the University of Vermont Medical School. He completed an internal medicine residency at Beth Israel Hospital in Boston and a pulmonary/critical care fellowship at Boston University. He completed the Advanced Management Program at Harvard Business School in 2000.

Carol Mimura, Ph.D., is Assistant Vice Chancellor for Intellectual Property and Industry Research Alliances (IPIRA) at the University of California at Berkeley (UC Berkeley). IPIRA is the portal for industry access to Berkeley's preeminent faculty and research capabilities. Dr. Mimura holds a bachelor of science degree from Yale University in molecular biophysics and biochemistry and a Ph.D. in biology (biochemistry and microbiology concentration) from Boston University. She was an NIH-sponsored postdoctoral fellow and research scientist at UC Berkeley in biochemistry and in chemical biodynamics. She served on the board of directors of the Children's Hospi-

tal Research Institute in Oakland, California, and as a member of the board (the Chancellor's alternate) of BayBio, the regional voice of biotechnology in northern California. She is former Executive Director of UC Berkeley's Office of Technology Licensing. Prior to her positions at UC Berkeley, Dr. Mimura was an Analyst at Technology Forecasters and a consultant to Cor Therapeutics and Genomyx, and wrote for the *Genetic Engineering News*. Her scholarly publications include articles on the sucrose phosphotransferase system in *Streptococcus mutans* and the histidine permease in *Salmonella typhimurium* in the *Journal of Biological Chemistry,* the *Proceedings of the National Academy of Sciences, Infection and Immunity, Analytical Biochemistry, Biochimica and Biophysica Acta, Journal of Cellular Biochemistry, FEMS Microbiological Reviews, Advances in Enzymology,* and *Abstracts of the American Society for Microbiology*. She also authored an article in the fall 2006 *Journal of the Association of the University Technology Managers*, "Technology Licensing for the Benefit of the Developing World: UC Berkeley's Socially Responsible Licensing Program," which was reprinted in *Industry and Higher Education* (August 2007).

Michael R. Mowatt, Ph.D., is Director, Office of Technology Development, at NIAID. He has directed NIAID's Office of Technology Development (OTD) since 2001. He has more than 12 years of experience in technology transfer, intellectual property management, and the development of partnership agreements. Dr. Mowatt leads a staff of nearly 30 professionals in support of NIAID's research mission to conduct and support basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. In addition to managing the intellectual property portfolio of NIAID and promoting the development and commercialization of NIAID's inventions, OTD is responsible for negotiating and managing transactional agreements, including Material Transfer Agreements, Cooperative Research and Development Agreements, and other collaboration agreements that enable NIAID to execute successful and effective research and R&D programs around the world. He and his staff have negotiated a wide variety of agreements with NIAID partners, which include universities, nongovernmental organizations, other U.S. government agencies, and philanthropic organizations such as the Bill and Melinda Gates Foundation, as well as commercial concerns ranging from large pharmaceutical companies with bureaucracies that rival that of the U.S. government to small biotechnology companies. Dr. Mowatt joined OTD in 1995 after completing postdoctoral training in molecular and cellular biology and parasitology in the Laboratory of Parasitic Diseases at NIAID and in the Laboratory of Molecular Parasitology at the Rockefeller University in New York City. He received a Ph.D. in microbiology and immunology at the University of Michigan in 1985 and a B.S. in microbiology at the

University of Notre Dame in 1980. He has authored more than 30 original scientific papers, reviews, book chapters, and book reviews in the disciplines of molecular and cellular biology, immunology, and parasitology. In addition to the daily challenges of promoting and negotiating partnerships between the private sector and NIAID, Dr. Mowatt has overseen the tripling in size and restructuring of his office to support the growing and evolving needs of NIAID's biodefense and emerging infectious diseases research initiatives.

Douglas E. Onsi, J.D., is a Venture Partner of HealthCare Ventures. Prior to joining HealthCare Ventures in 2007, he served as Vice President, Campath Product Operations and Oncology Portfolio Management, and as Vice President, Business Development, at Genzyme Corporation. Before joining Genzyme, Mr. Onsi was Chief Financial Officer and Vice President, Business Development, of TolerRx, Inc. Prior to joining TolerRx, he held a senior business development position at LeukoSite, Inc., which was merged with Millennium Pharmaceuticals, Inc. He has also practiced corporate law at Bingham Dana, LLP. Mr. Onsi received his J.D. from the University of Michigan Law School and his B.S. in biology from Cornell University.

Anne R. Pariser, M.D., is Medical Team Leader for the Inborn Errors of Metabolism team in the Division of Gastroenterology Products, Office of New Drugs, at the Center for Drug Evaluation and Research, FDA. She has been at FDA since 2000 as a Medical Officer and Medical Team Leader, and has been responsible for clinical reviews for drugs and biologic products for a wide variety of indications. In recent years, she has worked almost exclusively with rare diseases such as LSD, urea cycle disorders, and many others. She is actively involved in working within FDA and with industry, patient groups, and other stakeholders for the development of drugs and biologic products for rare diseases, and her work focuses on regulatory decisions and policy affecting the clinical development and approval of these products.

Anne Quinn Young, M.P.H., is Program Director at the Multiple Myeloma Research Foundation (MMRF), where she oversees all communication efforts for the foundation and for its sister organization, the Multiple Myeloma Research Consortium (MMRC). In this role, she works closely with founder and CEO Kathy Giusti to communicate the organizations' success in breaking down barriers to drug development and building collaborations with industry and academia to deliver much-needed new and effective treatments to patients. In addition, she oversees the organization's extensive educational programming for and outreach to patients and health care providers, which includes a number of continuing medical education (CME)–accredited programs. Ms. Quinn Young currently serves on

the Cancer Leadership Council (CLC) and as principal investigator on a multiyear grant from CDC focused on reaching underserved populations and their health care providers with critical information on how best to treat multiple myeloma. Prior to joining the MMRF, she was a consultant in the Healthcare Practice of Datamonitor, a global market research and business intelligence company, where she focused predominantly on oncology. Ms. Quinn Young previously worked in health care public relations at Burson-Marsteller and Chandler Chicco Agency, where she developed disease awareness campaigns for a number of disorders following a postgraduate internship at the Department of Justice, Antitrust Division. She holds a master of public health degree from the Mailman School of Public Health of Columbia University and graduated cum laude from Dartmouth College with a B.A. in government.

Laurie M. Ryan, Ph.D., is Program Director, Alzheimer's Disease Clinical Trials, for the Division of Neuroscience, National Institute on Aging, NIH. She received her bachelor of arts degree in human development from St. Mary's College of Maryland in 1986 and went on to obtain her master's degree in psychology from Loyola College in Maryland in 1991. During that time, she worked at NIH for the National Institute of Neurological Disorders and Stroke in the Neuropsychology Service of the Clinical Epilepsy Branch, where she was mentored by Dr. Paul Fedio. Following completion of her master's degree, she attended Louisiana State University (LSU) in Baton Rouge for doctoral training in clinical psychology, with specialty training in neuropsychology, under the mentorship of Dr. W. Drew Gouvier. During her doctoral training at LSU, she maintained an active research program focused on the nature and sequelae of mild traumatic brain injury (TBI). Dr. Ryan went on to complete a neuropsychology-focused internship at the Medical University of South Carolina/Department of Veterans' Affairs Medical Center in Charleston, South Carolina. During her internship, she broadened her research experience to include disorders affecting geriatric populations, such as dementia. Her primary research project focused on identifying distinctive neuropsychological correlates of Alzheimer's dementia that distinguish it from vascular dementia. She completed her internship and obtained her Ph.D. in 1997. She then went on to the Thomas Jefferson University/Jefferson Medical College in Philadelphia to complete her 2-year postdoctoral fellowship in clinical neuropsychology. During her fellowship, she continued to gain both clinical and research experience. She was involved with research projects addressing the neurocognitive and emotional changes associated with focal epilepsy and epilepsy surgery, and neurocognitive functioning in aging and dementia. In 1999, Dr. Ryan joined the Defense and Veterans Brain Injury Center

(DVBIC) at the Walter Reed Army Medical Center in Washington, DC, as clinical neuropsychologist. In January 2003, she became Assistant Director for Research and Senior Neuropsychologist for DVBIC, where she was responsible for overseeing clinical research development and implementation across sites, with a particular focus on clinical trials. In September 2005, Dr. Ryan accepted her current position with NIH. As Program Director, she is responsible for the management and development of the clinical trials portfolio for Alzheimer's and other dementias. This portfolio currently includes 23 trials plus the Alzheimer's Disease Cooperative Study (ADCS), a large clinical trials consortium. The interventions under study include both pharmacologic and nonpharmacologic approaches and both prevention and treatment strategies.

Anthony So, M.D., serves as Professor of the Practice of Public Policy Studies at Duke University's Terry Sanford Institute of Public Policy, where he started the Program on Global Health and Technology Access in 2004. The program focuses on issues of globalization and health, particularly innovation and access to essential medicines. Dr. So's research on the ownership of knowledge and how it is best harnessed to improve the public's health ranges from conceptualizing a technology trust and patent pools to reengineering the value chain from R&D to the delivery of health technologies for developing countries. Previously Dr. So served as Associate Director of the Rockefeller Foundation's Health Equity program, where he co-founded a cross-thematic program on charting a fairer course for intellectual property rights; shaped the foundation's work on policy on access to medicines in developing countries; and launched a multicountry program in Southeast Asia, "Trading Tobacco for Health," focused on enabling countries to respond on their own terms and for the long term to the challenge of tobacco use. Prior to joining the foundation, Dr. So served as Senior Advisor to the Administrator at the Agency for Health Care Policy and Research, U.S. Department of Health and Human Services, and from 1995 to 1996, he served as Secretary Donna Shalala's White House Fellow. A general internist by training, he also earned his M.P.A. from Princeton University as a Woodrow Wilson Scholar and completed a fellowship in the Robert Wood Johnson Clinical Scholars Program at the University of California at San Francisco/Stanford. He presently serves on the Board of Directors for Community Catalyst, a U.S.-based national advocacy organization working to ensure quality affordable health care for all; sits on the Advisory Board for TropIKA, a new web-based research and policy portal from the Special Programme for Research and Training in Tropical Diseases (TDR); and is a member of the Advisory Board for Universities Allied for Essential Medicines, a student organization committed to improved access to medicines in developing countries, particularly by ensuring a socially responsible role for universities.

Craig M. Sorensen, Ph.D., is currently Senior Director, Strategic Research Alliances, at Vertex Pharmaceuticals Incorporated, where he is responsible for establishing strategic research collaborations and alliances worldwide in both core and emerging scientific areas to address global health problems. Dr. Sorensen holds a B.S. in microbiology and in biochemistry from the University of Illinois and a Ph.D. in immunology and pathology from Washington University in St. Louis. After receiving his graduate degree, he was an Assistant Professor of pathology at Washington University Medical School in St. Louis, Missouri. After leaving academia, he held various research and business strategic planning positions in the biotechnology/biopharma industry before joining Vertex in 2001. Dr. Sorensen is a member of Sigma Xi and serves on the NIH Immunology IRG Special Emphasis Panel.

Nancy Sung, Ph.D. (member, IOM Forum on Drug Discovery, Development, and Translation), is a Senior Program Officer with the Burroughs Wellcome Fund (BWF), having joined its staff in 1997. She oversees grantmaking of $13–15 million annually in the areas of translational research and interfaces in science. This portfolio includes programs ranging from individual bridging awards for postdoctoral fellows, to midcareer awards for clinical investigators, to institutional awards for interdisciplinary training programs that bridge the physical/mathematical and biological sciences. She has also shaped BWF's funding and activities in the areas of clinical research policy and workforce development. Dr. Sung earned her undergraduate degree from the University of Pennsylvania and a Ph.D. in microbiology and immunology from the University of North Carolina at Chapel Hill. Prior to joining the BWF staff, she was a Visiting Fellow at the Chinese Academy of Preventive Medicine's Institute of Virology in Beijing, with the support of WHO and NIH–NCI. Dr. Sung is Founding Chair of the Health Research Alliance, a growing consortium of private foundations and voluntary health agencies with a shared interest in fostering basic science discoveries and removing barriers that prevent those discoveries from being translated into clinical studies and then into better health. She has served as a member of several IOM panels, including the Clinical Research Roundtable.

Sharon Terry, M.A., is President and CEO of the Genetic Alliance, a network focused on transforming health by promoting an environment of openness centered on the health of individuals, families, and communities. She is founding Executive Director of PXE International, a research advocacy organization for the genetic condition pseudoxanthoma elasticum (PXE). She codirects a 33-laboratory research consortium and manages 52 offices worldwide for PXE International. Ms. Terry is a co-founder of the Genetic Alliance BioBank. She serves as a member of many of the major

governmental advisory committees on medical research and services, and is liaison to the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children and the National Advisory Council for National Human Genome Research Institute (NHGRI), NIH. She is on the steering committees of the Genetic Association Information Network of NHGRI, the Collaboration, Education and Test Translation (CETT) program, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Stakeholders Group, and the Google Health Advisory Board. She serves on the boards of the Biotechnology Institute, DNA Direct, the National Coalition of Health Professional Education in Genetics, and the Coalition for 21st Century Medicine. She is Chair of the Coalition for Genetic Fairness, which was instrumental in the passage of the Genetic Information Nondiscrimination Act. She is a member of the IOM Roundtable on Translating Genomic-Based Research for Health. She is also Chair of the Social Issues Committee of the American Society of Human Genetics. In 2005, she received an honorary doctorate from Iona College for her work in community engagement and haplotype mapping, and in 2007 she received the first Patient Service Award from the University of North Carolina Institute for Pharmacogenomics and Individualized Therapy.

Diana R. Wetmore, Ph.D., is Vice President of Alliance Management for Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT). Since joining CFFT in 2003, she has managed the strategic planning process for the CF Foundation–supported therapeutics pipeline, identified and launched multiple new discovery and development projects with industry collaborators, and provided ongoing project management support for CFFTs discovery and development projects. Some of the projects directed by Dr. Wetmore include the CFFT discovery collaborations with EPIX Pharmaceuticals, SGX Pharmaceuticals, and FoldRx, and development collaborations with PTC Therapeutics, Transave, and Mpex. Additional projects managed in her group include the CFFT Specimen Bank with ProMedDx, the MetaMiner CF informatics platform with GeneGo, and the CF Biomarker validation initiative. As a business-oriented scientist, Dr. Wetmore has had a successful career managing complex multidisciplinary drug discovery projects and teams. She obtained her Ph.D. in biochemistry at the University of Calgary in Canada, where her interest was in studying the contributions of ligand binding to protein folding and stability. Prior to joining CFFT, she held positions in the pharmaceutical and biotechnology industries. At Dupont Merck Pharmaceuticals (now Bristol Myers Squibb), she was part of the crystallography group and studied protein–protein and protein–ligand interactions using calorimetric methods. During her 5-year tenure at Scriptgen Pharmaceuticals, now Anadys, she led the bifunctional drug design group before becoming Senior Director of R&D Project Management. At Geneprot, Inc., she served as Chief Technical Officer

Appendix C

Resources

A number of resources mentioned throughout the workshop are available on the internet. The following list is provided as a starting point for those interested in the development of drugs for rare and neglected diseases. The Forum does not endorse any particular programs, publications, or websites.

ORGANIZATIONS AND INITIATIVES

National Organization for Rare Disorders (NORD)
http://www.rarediseases.org/

FasterCures, The Center for Accelerating Medical Solutions
http://www.fastercures.org/
See white paper: *Entrepreneurs for Cures: The Critical Need for Innovative Approaches to Disease Research,* May 30, 2008.
http://www.fastercures.org/objects/pdfs/white_papers/FastercuresWP_Innovation_052808.pdf

Drugs for Neglected Diseases initiative (DNDi)
http://www.dndi.org/

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

FDA
http://www.fda.gov/

FDA Office of Orphan Products Development
http://www.fda.gov/orphan/

Funding

FDA Orphan Products Grants Program
http://www.fda.gov/orphan/grants/index.htm

FDA Cooperative Research and Development Agreements
http://www.fda.gov/oc/ofacs/partnership/techtran/default.htm

Guidance for Industry

Fast Track Drug Development Programs—Designation, Development, and Application Review
http://www.fda.gov/cder/guidance/5645fnl.pdf

Formal Meetings with Sponsors and Applicants for PDUFA Products
http://www.fda.gov/cder/guidance/2125fnl.pdf

E 10 Choice of Control Group and Related Issues in Clinical Trials
http://www.fda.gov/cder/guidance/4155fnl.pdf

Special Protocol Assessment
http://www.fda.gov/cder/guidance/3764fnl.PDF

Code of Federal Regulations (CFR) and Federal Food, Drug, and Cosmetic Act (FFDCA)

Title 21: Food and Drugs (21 CFR) Chapter I: Food and Drug Administration, Department of Health and Human Services (Parts 1–1299)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

21 CFR § 316 Orphan Drugs
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=316

Priority Review and Priority Review Voucher, FFDCA, Section 524
http://www.fda.gov/opacom/laws/fdcact/fdcact5b.htm

NATIONAL INSTITUTES OF HEALTH (NIH)

NIH Office of Rare Diseases
http://rarediseases.info.nih.gov/

Funding

NIH National Center for Research Resources (NCRR), Clinical and Translational Science Awards (CTSA)
http://www.ncrr.nih.gov/clinical_research_resources/clinical_and_translational_science_awards/

Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs
http://grants1.nih.gov/grants/funding/sbirsttr_programs.htm

Guidelines and Standardized Agreements

Uniform Biological Material Transfer Agreement (UBMTA)
http://www.autm.net/aboutTT/aboutTT_umbta.cfm

Principles and Guidelines for Recipients of NIH Research Grants and Contract on Obtaining and Disseminating Biomedical Research Resources
http://www.ott.nih.gov/policy/reasearch_toolarchive.html

EXAMPLES OF DATA AND MATERIALS SHARING REPOSITORIES

NIH AIDS Research and Reference Reagent Repository
https://www.aidsreagent.org/Index.cfm

MR4: Malaria Research and Reference Reagent Resources Program
http://www.mr4.org/

BEI Resources: Biodefense and Emerging Infectious Diseases Research Resources Repository
http://www.beiresources.org/

ScienceCommons Biological Materials Transfer Project
http://sciencecommons.org/projects/licensing/

LONI Image Data Archive
https://ida.loni.ucla.edu/login.jsp?project=ADNI%2f

Genetic Alliance BioBank
http://biobank.org

INTELLECTUAL PROPERTY MANAGEMENT

Socially Responsible Licensing at Berkeley—Humanitarian Use Clauses in Contracts
http://ipira.berkeley.edu/—then "Socially Responsible IP Management" link

CLINICAL TRIALS

Small Clinical Trials: Issues and Challenges (IOM report, full text free online)
http://www.iom.edu/CMS/3740/5483.aspx

ClinicalTrials.gov Registry
http://clinicaltrials.gov/

Declaration of Helsinki, the World Medical Association
http://www.wma.net/e/policy/b3.htm