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Sarah H. Beachy, Samuel G. Johnson, Steve Olson, and Adam C. Berger, Rapporteurs; Roundtable on Translating Genomic-Based Research for Health; Board on Health Sciences Policy; Institute of Medicine

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DRUG REPURPOSING AND REPOSITIONING

WORKSHOP SUMMARY

Sarah H. Beachy, Samuel G. Johnson, Steve Olson, and
Adam C. Berger, *Rapporteurs*

Roundtable on Translating Genomic-Based
Research for Health

Board on Health Sciences Policy

INSTITUTE OF MEDICINE
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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the report before its release. The review of this report was overseen by **Elena Nightingale,** The George Washington School of Medicine and Health Sciences and Georgetown University School of Medicine. Appointed by the Institute of Medicine, she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the rapporteurs and the institution.

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Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ALS	amyotrophic lateral sclerosis
BMS	Bristol-Myers Squibb
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CMS	Centers for Medicare & Medicaid Services
CRO	contract research organization
DNA	deoxyribonucleic acid
EMR	electronic medical record
ENL	erythema nodosum leprosum
ERK	extracellular-signal-regulated kinase
FDA	U.S. Food and Drug Administration
GWAS	genome-wide association study
HIV	human immunodeficiency virus
HPBCD	2-hydroxypropyl-b-cyclodextrin
ImmPort	Immunology Database and Analysis Portal
IOM	Institute of Medicine
IRB	institutional review board

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LINCS	Library of Integrated Network-Based Cellular Signals
LOD	logarithm of odds
MODDERN	Modernizing Our Drug and Diagnostic Evaluation and Regulatory Network
MRC	Medical Research Council
NCATS	National Center for Advancing Translational Sciences
NeuroNEXT	Network for Excellence in Neuroscience Clinical Trials
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
R&D	research and development
TGF	transforming growth factor
TNF	tumor necrosis factor
TRND	Therapeutics for Rare and Neglected Diseases
UK	United Kingdom
U.S.	United States

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1

Introduction and Themes of the Workshop[1]

Drug development can be time-consuming and expensive. Recent estimates suggest that, on average, it takes 10 years and at least $1 billion to bring a drug to market (Paul et al., 2010). Given the time and expense of developing drugs de novo, pharmaceutical companies have become increasingly interested in finding new uses for existing drugs (a process referred to as drug *repurposing* or *repositioning*)[2] (for an overview of this topic, see Barratt and Frail, 2011).

Finding a new use for an existing compound holds many appeals. Typically the safety, efficacy, and toxicity of an existing drug have been extensively studied, and, therefore, data have already been accumulated toward gaining approval by the U.S. Food and Drug Administration (FDA) for a specific indication. Because data have already been acquired, repurposing a drug can save time and money compared with the process of developing a drug de novo; repurposed drugs are generally approved in shorter timeframes (3 to 12 years) and at about 60 percent of the typical development cost (Ashburn and Thor, 2004; Chong and Sullivan, 2007). While approximately 10 percent of new drug applica-

[1]The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, are not necessarily endorsed or verified by the Institute of Medicine, and should not be construed as reflecting any group consensus.

[2]*Drug repurposing* is the use of an approved drug or a drug under development for a different indication than that for which it was originally developed. *Drug repositioning* has recently been used to describe the novel use of a drug that was previously discontinued for development. For the purposes of this workshop summary, drug *repurposing* and *repositioning* are used interchangeably.

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tions gain market approval, it is estimated that nearly 30 percent of repurposed drugs are approved, which gives companies a significant market-driven incentive for finding ways to repurpose existing drugs (Ashburn and Thor, 2004; Kaiser, 2011).

Historically, drug repurposing has been largely an unintentional, serendipitous process that took place when a drug was found to have an off-target effect or a previously unrecognized on-target effect that could be used for identifying a new indication. Perhaps the most recognizable example of such a successful repositioning effort is sildenafil. Originally developed as an anti-hypertensive, sildenafil, marketed as Viagra® and under other trade names, has been repurposed for the treatment of erectile dysfunction and pulmonary arterial hypertension. Viagra® generated more than $2 billion worldwide in 2012 (Pfizer, 2013) and has recently been studied for the treatment of heart failure (Bishu et al., 2011). Another drug, thalidomide, was essentially removed from the market after its connection to serious fetal limb defects was discovered (Kim and Scialli, 2011). However, recent research has shown it to be an effective treatment for leprosy and multiple myeloma (Huang et al., 2011).

These and other success stories have prompted pharmaceutical companies to add repurposing projects to their research portfolios and the National Institutes of Health (NIH) to test an award program for identifying new uses for existing molecules (Thayer, 2012). In addition, technological advances and the increasing availability of genomic data and computational systems have resulted in new methods to systematically identify both drug targets and pathways for linking drugs with secondary—and sometimes seemingly unrelated—indications (Sirota et al., 2011).

Given the widespread interest in drug repurposing, the Roundtable on Translating Genomic-Based Research for Health of the Institute of Medicine (IOM) hosted a workshop on June 24, 2013, in Washington, DC, to assess the current landscape of drug repurposing activities in industry, academia, and government. Stakeholders, including government officials, pharmaceutical company representatives, academic researchers, regulators, funders, and patients, were invited to present their perspectives and to participate in workshop discussions. Box 1-1 lists the goals of the workshop.[3] As several of the individual workshop speakers noted, many of the drug repurposing strategies they discussed are broadly applica-

[3]The workshop agenda, speaker biographical sketches, full statement of task, and list of registered attendees can be found in Appendixes A–D, respectively.

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BOX 1-1
Workshop Objectives

- To assess the current landscape of drug repurposing activities in industry, academia, and government.
- To examine enabling tools and technology for drug repurposing.
- To evaluate the business models and economic incentives for pursuing a repurposing approach.
- To discuss how genomic and genetic research could be positioned to better enable a drug repurposing paradigm.

ble across disciplines, inclusive of, but not specific only to genomics. For example, improving access to compounds and data, encouraging collaborative efforts, dedicating teams to repurposing (as highlighted in Chapter 2) and using high-throughput screening technologies, gaining a better understanding of disease mechanisms, employing collaborative models, and data sharing techniques (discussed in Chapters 3 and 4) were examined as potential strategies to increase the success of drug repurposing efforts. While genomics could be an extremely useful enabler of many of these approaches, these strategies are not specific only to the field of genomics.

WORKSHOP THEMES

The high failure rate of drugs in development and the fact that most drugs have multiple indications are powerful arguments for repurposing and repositioning. Chapter 2 of this workshop summary explores this reasoning within the current state of the science. Industry, academic, and governmental perspectives are presented, with an extended discussion of Marfan syndrome as an example of the ways in which these stakeholder roles overlap during the development process. Though orphan drugs are used by relatively few patients, they can still be profitable for companies and have been a major target of repurposing and repositioning efforts. Barriers to drug repositioning are also discussed, including reluctance to explore alternate indications, the need to update clinical regulatory documents, and considerations relating to the limited patent life of repurposed drugs.

In Chapter 3 the roles of new tools and technologies in drug repurposing are considered; the discussion includes a look at genomics-based technologies that have enabled the identification of new indications for

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drugs as well as screening technologies that can generate new ideas about targets and drugs. This chapter also examines the vast new stores of publicly available data that can accelerate the discovery process for repurposing drugs. There is a description of new collaborative models that combine the strengths of pharmaceutical companies, biotechnology companies, academic researchers, venture capitalists, and others. These models call for, among other elements, enhanced coordination and communication to engage patients and clinicians during the drug development process.

Chapter 4 addresses the question of whether the value proposition for companies is sufficient for them to pursue repurposing as a profitable business opportunity. Although returns on research and development (R&D) investments have been declining in the pharmaceutical industry, the investigation of new targets and mechanisms for existing drugs with known safety profiles may add value to the business model and bring more therapies to market for patients. Governmental incentives for drug development are also discussed, but they may not always provide the most attractive business opportunity for pharmaceutical companies. Finally, the drug development process is considered, with a particular focus on the idea that disease indications need to be re-evaluated throughout the discovery, development, and life-cycle management of a compound.

Chapter 5 presents research and policy initiatives that have been undertaken to encourage repurposing activities; such initiatives often take the form of partnerships involving academic researchers, companies, and government agencies. The strategy of crowdsourcing candidate compounds for repurposing is discussed in the context of how it can generate ideas about new mechanisms of action and potential applications. The release of information about potential compounds for repurposing is emphasized in a discussion about the goal of striking a balance between confidentiality and providing sufficient information to attract the best research proposals. Finally there is a discussion of how a trusted intermediary often participates to spur collaboration and to provide the infrastructure needed for institutions to work together.

In Chapter 6 the role that genomics plays in drug repurposing is considered, along with other potential research tools such as the electronic medical record (EMR). Barriers to drug repurposing are discussed, including the sharing of drug data, return on investments, and intellectual property concerns. This last chapter also outlines the potential roles that academia, industry, government, regulators, and patient advocacy groups can play in improving repurposing collaboration. Individual workshop

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speakers and many participants who spoke stated that drug repurposing has the potential to change the lives of patients by providing another path for drug development.

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2

The State of the Science

Important Points Highlighted by Individual Speakers

- Gaining access to compounds and their data, having a willingness to explore other indications, and forming collaborative partnerships are key components of a successful repurposing program.
- Establishing internal, dedicated teams to repurposing and improving the efficiency of the process by which drug data are organized and updated may encourage more of those in industry to explore drug repurposing as part of their business models.
- Industry–academia collaborations can provide both valuable access to drugs and information to use for finding therapies for patients in need.
- The use of animal models can be useful for elucidating mechanisms of disease, such as in Marfan syndrome, and these insights can guide therapeutic development for the initial disease of study as well as for additional disorders.

Academia, industry, and government stakeholders each have a distinct set of concerns regarding the state of the science for drug repurposing, but workshop speakers emphasized that because each of those groups has its own strengths, if they work together it can increase the likelihood of the successful translation of a repurposed drug. Many of the examples cited by individual speakers in this session—and throughout the workshop—involved rare diseases, which have been a focus of re-

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purposing efforts to date. For example, Marfan syndrome was discussed as an example of the potential of repurposing in a broad range of Mendelian disorders.

INDUSTRY REPURPOSING EFFORTS

Three strategic elements are key to drug repositioning, said Don Frail, vice president of science at AstraZeneca. The first is having access to compounds, which typically involves access not just to the compound itself but to all of the information associated with that compound, such as safety data and clinical study reports.

The second element is exploring the indication space—whether broad or narrow—to include both core areas and opportunistic indications. Within pharmaceutical companies, project teams can be focused on therapeutic areas, or groups can be dedicated to repurposing across therapeutic areas. Biotechnology companies often take the latter approach because they are interested in maximizing the value of their compounds and will often explore opportunities in broader treatment areas.

The third key element is maximizing the generation of ideas, in part through partnerships with others. It is increasingly more common for some nonprofit organizations to support repositioning or repurposing efforts, Frail said. For example, the nonprofit organization Cures Within Reach[1] uses a model of providing small grants to repurpose drugs and devices already on the market to quickly deliver safe and affordable treatments and cures for both common and rare disorders for which no effective treatments currently exist.

AstraZeneca is working on all three elements through a partnership with the Medical Research Council (MRC) in the United Kingdom. The objective of the partnership is to provide MRC investigators with access to well-characterized compounds for the discovery of new indications, Frail said. (Chapter 5 covers this program in greater detail.) Data on 22 compounds attracted more than 100 clinical and preclinical proposals from 37 UK institutions, and in 2012, 8 preclinical and 7 clinical projects were selected for funding by the MRC at a level of about $10 million, Frail said. This partnership has been recognized internationally and serves as a model for future collaborations in translational research.

[1]For more information about Cures Within Reach, see http://cureswithinreach.org (accessed January 21, 2014).

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AstraZeneca also has developed open innovation partnerships with the eye care company Alcon and the dermatology company Galderma, Frail said. These companies have access to AstraZeneca's compound collections and are developing therapies in two areas where AstraZeneca is not active, allowing the company to maximize the value of its compounds.

Potential Barriers

There are several barriers to drug repurposing, Frail said. Companies are typically focused on certain disease areas, so they sometimes miss opportunities to follow the biology of a compound into different areas. Repositioning can also be a distraction to current project teams and organizations that are focused on specific disease areas. A discontinued compound does not have a project team, and an active project team typically is dedicated to getting a drug to work on its current indication rather than exploring different indications. Furthermore, individuals in a company may view drug repositioning as less innovative than developing an entirely new drug.

Companies have a limited number of compounds with which to work, and they may have limited capital to invest in projects, Frail said. The response to limited resources is to focus one's efforts, which can work against repositioning. Other reasons that a project might not proceed include a company not having an appropriate compound, a project having a low probability of success, reimbursement by payers posing challenges, the market being too small, or regulatory approval endpoints having not been defined, Frail said.

Repositioning can also raise complex issues about regulatory filings, pricing, and other considerations, all of which can serve as deterrents to project teams. For example, in collaborations an investigator will often request updated clinical regulatory documents, such as an investigational new drug application, and it can be time-consuming to collect all of the updated information and make the changes to the existing document, Frail said. A clinical study may have closed before all the data were in, or a new set of pharmacokinetic data or chemistry, manufacturing, and control sections may need to be generated. Safety reporting and pharmacovigilence also can be complicated for such projects, Frail said.

Investigator-initiated studies or out-licensing may require a support infrastructure and legal agreements. Patent exclusivity or remaining patent life can be major considerations, as can data exclusivity, which is another way—in addition to patenting a product—of obtaining market

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exclusivity. In Frail's view, the U.S. data exclusivity regulations are some of the least accommodating in the world, and he suggested that the waiting period for data exclusivity for small molecules (currently 5 years) should be the same as the waiting period for biologics (12 years) (Goldman et al., 2011; see also Chapter 5 for more discussion on patents).

RARE DISEASES

According to the NIH Office of Rare Diseases Research, about 6,800 diseases with limited therapeutic options affect between an estimated 25 and 30 million Americans. Most of them affect fewer than 200,000 people in the United States and most are single-gene diseases. Since the passage of the Orphan Drug Act in 1983, about 250 pharmaceuticals have been developed to treat an estimated 13 million Americans (FDA, 2012). Orphan diseases are definitely of interest to the pharmaceutical industry, especially as more specialty care markets develop. Overall, 11 percent of pharmaceutical companies' total revenues are from drugs used for orphan diseases, Frail said. Sometimes working on orphan diseases has been profitable for companies, despite the fact that drugs for these diseases are needed by a relatively small number of patients. One benefit of repurposing drugs for orphan diseases is that they have data exclusivity for a longer period than other drugs, Frail said.

Indeed, more than 30 percent of the drugs approved by the U.S. Food and Drug Administration (FDA) in each of the past 6 years have been for rare diseases, said Weida Tong, director of the Division of Bioinformatics and Biostatistics at the National Center for Toxicological Research at FDA. For example, in 2013, 9 of 27 drugs approved by the FDA Center for Drug Evaluation and Research were for the treatment of rare diseases (FDA, 2013a). Tong and his group use computational means to determine drug similarity as one way of meeting the agency's goal of identifying new indications of marketed drugs for rare and neglected diseases, for diseases for which safer or less expensive drugs are needed, and for diseases for which drug shortages exist (Liu et al., 2013). The fundamental principle behind drug repositioning is straightforward, Tong said: If two drugs are similar, both drugs could treat the same disease, and if two diseases are similar, a drug that treats one disease could be equally effective for the other disease. The challenge, he said, is how to define or determine "similarity."

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The FDA's Office of Orphan Products Development aims to advance the evaluation and development of products that demonstrate promise for the diagnosis or treatment of rare diseases or conditions, said Tong. For example, the office has established a Rare Disease Repurposing Database containing drugs that have received orphan status designation (that is, they have been found promising for treating a rare disease) or that have been approved for the treatment of another disease (FDA, 2013b).

Drug Repositioning in Cystic Fibrosis

Tong cited his group's work on cystic fibrosis (CF) as an example of how a genomic approach can be used for drug repositioning. CF is a Mendelian disease that affects the lung and digestive systems. In the United States about 30,000 patients have been diagnosed with CF, and every year about 1,000 new cases are reported. The predicted median age to which a patient with CF will survive is the early 40s (Cystic Fibrosis Foundation, 2014).

Kalydeco™ was developed with the help of $75 million from the Cystic Fibrosis Foundation and was approved by FDA in 2012, Tong said. However, it is only for patients above age 6 who have a particular CF mutation (G551D) in the CF transmembrane conductance regulator gene (*CFTR*). Kalydeco also costs about $5,700 per week, which has generated reluctance among insurance companies to cover such drugs (O'Sullivan et al., 2013).

The hypothesis being evaluated is that CFTR, a protein channel involved in transport, is regulated by a set of feed-forward loops and that drugs that interfere with these loops can serve as treatments, Tong explained. His group is using a genomic approach in combination with bioinformatics to delineate feed-forward loops, and drugs have been tested to determine which may have the potential to treat the disease. So far, this research has identified about 15 feed-forward loops and about 40 drugs that could be effective, safe, and affordable, he said.

POTENTIAL OPPORTUNITIES FOR DRUG DISCOVERY

Mendelian disorders represent a great opportunity in drug discovery, said Harry Dietz, the Victor A. McKusick professor of pediatrics, medicine, and molecular biology and genetics at the Institute of Genetic Medicine at the Johns Hopkins University School of Medicine. While individually

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rare, Mendelian disorders are collectively common and personally burdensome, he said. Patients with these disorders have disproportionately fueled progress in human genetics and molecular therapeutics, often at personal cost to themselves despite little chance of personal advantage. Mendelian disorders facilitate the identification of genetic modifiers in people and in experimental models, which can lead to surprising and appealing treatment strategies. Genetically defined animal models of rare diseases allow for genetic or pharmacologic perturbations that allow mechanisms to be refined. In addition, animal models aid in the development of assays and biomarkers for use in small molecule screens. Finally, Mendelian disorders offer the potential to explore the mechanisms and treatments in more common presentations of component phenotypes.

Marfan Syndrome

Marfan syndrome provides an example of all these opportunities. A systemic disorder of connective tissue with dominant inheritance and a prevalence of about 1 in 5,000, Marfan syndrome is characterized by effects in the ocular, skeletal, and cardiovascular systems, including lens dislocation, overgrowth of the long bones, and progressive dilatation of the root of the aorta (Dietz, 2011). If left untreated, early death can result from aortic rupture (Judge and Dietz, 2005).

In 1991 Dietz and his colleagues demonstrated that mutations in the gene encoding the connective tissue protein fibrillin 1 cause Marfan syndrome (Dietz et al., 1991). "Fibrillin 1 monomers [normally] aggregate to form complex extracellular structures called microfibrils that cluster around the maturing ends of elastic fibers during embryonic growth," Dietz said. Without these microfibrils, those with Marfan syndrome have a structural predisposition for tissues to fail as they age.

Animal models showed that these microfibrils also serve a separate important regulatory function, Dietz said. They bind the large inactive complex of the multi-potential growth factor TGF (transforming growth factor)-beta and suppress TGF-beta release or activation. In the presence of insufficient microfibrils, matrix sequestration of latent TGF-beta is not sufficient. Free TGF-beta then interacts with its cell surface receptor and activates an intracellular signaling cascade that mediates transcriptional responses and can lead to stretching of the aorta (Holm et al., 2011).

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Repositioning a Blood Pressure Medication

Aortic aneurysm, emphysema, mitral valve prolapse, and skeletal muscle myopathy were greatly attenuated or even prevented in mouse models of Marfan syndrome after treatment with TGF-beta neutralizing antibody, Dietz said (see Cohn et al., 2007; Habashi et al., 2006). This led to the question of whether there was an FDA-approved drug that would mimic these protective effects. Losartan, which is an angiotensin II, type 1 receptor blocker that lowers blood pressure and has been approved for the treatment of hypertension, had been shown to attenuate TGF-beta signaling in rodent models of chronic kidney disease. Treatment of Marfan mice with losartan led to attenuation of disease phenotypes, making them indistinguishable from wild-type littermates. Losartan also induced a dramatic rescue in aortic root growth that correlated with weakened TGF-beta signaling (Habashi et al., 2006).

Remarkably, losartan also addressed manifestations outside of the cardiovascular system. In mouse models, it caused improvement in distal alveolar septation, a process by which surface area for gas exchange is increased in the lung, and it prevented developmental emphysema, Dietz said. It also improved skeletal muscle architecture and function in mouse models of Marfan syndrome that show a distinct skeletal muscle myopathy.

Nine clinical trials of losartan in Marfan syndrome are ongoing, and the two whose outcomes have been reported have produced promising results, Dietz said. He and his colleagues have focused on treating a subset of children with the most severe and rapidly progressive form of Marfan syndrome; these children normally exhibit unrelenting aortic root growth despite maximal treatment with beta blockers and/or angiotensin-converting enzyme (ACE) inhibitors. After two treatments with losartan, the children exhibited no further aortic root growth (Brooke et al., 2008; Lacro et al., 2013).

Access to information from pharmaceutical companies about the effects of angiotensin receptor blockers on the TGF-beta signaling cascade has been a tremendous advantage in this research, Dietz said. Dietz's group has also gained access to a selective and potent extracellular-signal-regulated kinase (ERK) antagonist in collaboration with the Therapeutics for Rare and Neglected Disorders program at NIH; this drug has been as effective as losartan in preventing abnormal aortic growth in Marfan syndrome (Holm et al., 2011). Indeed, mice treated with this therapy show a slight but statistically significant decrease in aortic size over time.

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Treating Marfan Syndrome in Pregnant Women

There is a high risk of aortic dissection in women with Marfan syndrome if they become pregnant, Dietz said. This risk had been attributed to high stress from circulating blood, but the majority of dissections occur within the weeks after delivery; the risk was not affected by C-section or antihypertensive agents. Because the oxytocin receptor is up-regulated in the aorta in response to estrogen in pregnancy, Dietz's group hypothesized that oxytocin, which stimulates uterine contraction and milk release, might play a role in these pathogenic events. The oxytocin receptor is up-regulated in the aorta in response to estrogen in pregnancy, and oxytocin mediates its effects on peripheral tissues.

With mice that have 95 percent death due to aortic dissection within 3 weeks after delivery, the removal of the pups immediately after birth prevented lactation-induced oxytocin release and improved survival from 5 percent to 74 percent (Habashi et al., 2012). When oxytocin is delivered to non-pregnant Marfan mice, aortic growth and death due to aortic dissection are dramatically increased, Dietz said.

Most recently, Dietz and his colleagues studied a selective oxytocin antagonist that has 150 times greater potency for the oxytocin receptor than for the vasopressant receptor. When mice were treated 2 weeks into pregnancy and through delivery with this agent, survival transitioned from 0 percent to 100 percent. "These data suggest that oxytocin antagonists such as atosiban, which is approved for use in pre-term labor in other countries, may find utility in the treatment of aortic aneurysm and aortic tear," Dietz said.

Genetic Modifiers

In five exceptional families that showed discrete intrafamilial variation in phenotypic severity, where half of the mutation carriers died because of aortic dissection by the age of 15 and the other half had no vascular manifestation of Marfan syndrome at the age of 60, linkage analysis revealed a protective locus on human chromosome 6 with a logarithm-of-odds (LOD)[2] score of greater than 4. All 20 individuals with the protective locus shared a four-megabase haplotype between selected markers on chromo-

[2]The LOD score is a statistic that provides information about whether two genes are located near each other on a chromosome and whether they are likely to be inherited together. A score of greater than or equal to 3 typically means two genes are located near each other.

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some 6, while only 2 of 19 affected individuals without the protective locus carried this haplotype, Dietz explained.

Of the 32 genes in this critical interval, attention is being focused on *MAS1*, which encodes the receptor for angiotensin-(1-7) as the most likely candidate to be involved with this protective effect. Mouse models also demonstrated a comparable modification of the Marfan phenotype on certain genetic backgrounds, which led to the discovery of a single locus on mouse chromosome 9 with a LOD score of more than 9 at a map position coincident with the gene encoding the type 2 subunit of the TGF-beta receptor, Dietz said. This finding also provides a target for therapeutic intervention, he said.

Implications Beyond Marfan Syndrome

The relevance of these drug repurposing findings extends well beyond Marfan syndrome, Dietz said. For example, compounds related to those effective in Marfan syndrome have been shown to attenuate vascular disease in multiple TGF-beta vasculopathies, including common conditions such as bicuspid aortic valve with aneurysm, which affects 1 percent of the general population, he said. TGF-beta-induced suppression of muscle regeneration also contributes to both rare and common myopathic states, and the angiotensin receptor blockers are protective in mouse models of Duchenne muscular dystrophy or immobility associated with muscle atrophy and weakness (Ennen et al., 2013). Finally, losartan improves total lung capacity in patients with chronic obstructive pulmonary disease and also reduces lung damage associated with cigarette exposure in mice (Podowski et al., 2012).

Lessons Learned

Rare disease studies highlight the fact that diseases can be treated without necessarily correcting the original defect, Dietz said. Correcting the integrity of the connective tissues throughout the body would be challenging if not impossible, but focusing on disease pathogenesis led to an understanding of downstream effects of matrix deficiency that were easier to address with therapeutics. The use of mouse models may not necessarily be the best way to test drugs, but it can reveal details of mechanisms of pathogenesis that create new therapeutic opportunities. “Virtually every hypothesis that we test in the lab derives from a clinical encounter,” Dietz said. Finally, the study of a single rare disorder can lead to many therapeutic insights, and these experiences could be repeated with other disorders.

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3

Enabling Tools and Technology

Important Points Highlighted by Individual Speakers

- By sharing data publicly in databases, drug repositioning efforts can be accelerated by using already existing data for discovery of new drugs and targets.
- In addition to testing drug effectiveness and studying disease mechanisms, academic researchers can contribute to repurposing efforts by developing new computational tools and technologies for screening drugs and drug targets in a high-throughput format.
- New collaborative models that draw on the strengths of pharmaceutical companies biotechnology companies, academic researchers, venture capitalists, and others will be needed if repurposing is to be successful.
- Progress can be made in the area of drug development if innovative thinking is used by all stakeholders to address intellectual property and data sharing and transparency issues related to repurposing.
- Tools such as electronic medical records could be valuable for understanding drug effectiveness, drug safety, and patient outcomes and could improve the statistical power of studies.
- High-throughput drug screening technologies are another way to quickly generate new ideas about drug targets. Industry–academia–government collaborations can help alleviate the often high costs associated with obtaining the necessary drugs for the screen.
- Enhanced coordination and communication are needed to engage patients with clinicians in the collection of quality treatment data, especially for rare diseases for which a lack of treatment options can be a source of frustration. Engaging patients in activities such as working groups and data safety monitoring boards can contribute to the development of drugs when innovative protocols or nontraditional trials are explored.

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Repurposing and repositioning have gained new momentum in part because of the development of new tools and technologies, individual speakers at the workshop said. Large databases, genome-based informatics capabilities, and contract research organizations (CROs) have all enabled advances in drug development. These tools and the development of other technologies can aid in repurposing and repositioning efforts.

DISCOVERY USING PUBLICLY AVAILABLE DATA

In 2001 journals began to require that authors using microarrays deposit their data into repositories, said Atul Butte, chief of the division of systems medicine at Stanford University's Center for Pediatric Bioinformatics. Since then more than 1 million microarray datasets have become publicly available, and the number is doubling about every 2 years (Baker, 2012). Many other kinds of data are becoming publicly available at comparable rates, including molecular, clinical, and epidemiological data. These data could be used to find new uses for existing therapeutics. More data are always better, but data are already plentiful today and should be used even if they are not perfect, Butte said, because using what is currently available is a better option than waiting for perfect data.

For more than 2 years Butte's laboratory has been analyzing publicly available gene expression data from individuals with diseases and from healthy controls along with data from biological samples treated with drugs and from untreated samples. By comparing the datasets and using a method based on the Connectivity Map strategy, Butte and his colleagues have been able to identify possible drug targets for diseases of interest (Lamb et al., 2006; Sirota et al., 2011). Disease-based computational strategies for drug repurposing have been used by Butte and several other groups as well (Dudley et al., 2011a).

To follow up on promising computational leads, Butte's laboratory has been contracting out for research services through commercial websites such as assaydepot.com. The CROs also provide access to a wide variety of animal disease models, including a mouse model of diabetes that Butte's laboratory has used extensively. For example, results from a 16-mouse diabetes drug study that include data on fasting blood sugar, glucose tolerance, insulin tolerance, and other measures can be delivered within weeks for $9,000. Butte and his colleagues design the protocols, but they no longer have to do the experiments themselves. If the robustness of the results needs to be verified, the researchers simply have a test done in more than one laboratory, he said.

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Using publicly available data to identify drug targets and then testing these targets by outsourcing the animal work is an extremely fast way to test and reposition drugs, Butte said. As an example from his own laboratory, he described the prediction that the epilepsy drug topiramate could help treat inflammatory bowel disease or Crohn's disease (Dudley et al., 2011b). Parts of this work were outsourced to other laboratories and to CROs, including a laboratory in Massachusetts that performs rat colonoscopies. Other drug repositioning efforts are also under way, such as an ongoing study of an antidepressant effective against small-cell lung cancer in mice. Just 15 months after the computational prediction was made, institutional review board (IRB) approval for clinical trials was obtained, and two patients at Stanford are already on the trial, Butte said.

A Data-Rich Future

In the future it will be much more common for drug repurposing to be accelerated by findings from existing public data, predicted Butte, who has co-founded a company to commercialize discoveries made in his laboratory. One contributing factor will be the steadily increasing quantities of data available through PubChem, the Library of Integrated Network-Based Cellular Signals (LINCS) of NIH, the Immunology Database and Analysis Portal (ImmPort), and many other databases. Clinical trial data also will become increasingly available, including data from trials that fail but still yield data useful for drug repositioning.

Discoveries of ways to repurpose drugs do not happen automatically, Butte said. Ensuring such discoveries will require the development of a new generation of investigators who "own" their research findings and follow them through to validation, which in turn may require the cultivation of investigators who are interested in this kind of work and the creation of incentives to encourage researchers to share their data openly.

ROLE OF BASIC SCIENCE FOR TRANSLATION

The typical mission of a university researcher is to focus on research, service, and education, which leads to publications, funding, tenure, and, increasingly, a stake in intellectual property, said Larry Sklar, regents professor of pathology at the University of New Mexico. In recent years the translation of research results to clinical applications has also become a significant priority for university professors. The translation process

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has many components, including commercialization, technology transfer, and economic development, Sklar said.

The increased emphasis on translation has changed the way that research scientists work. Collaborators, funding agencies, and patients all have become clients in the context of the academic mission, Sklar said. At the University of New Mexico School of Medicine, for instance, cycles of opportunity have occurred for the development of instrumentation, involvement with NIH programs, and the creation of molecular libraries. These opportunities corresponded with a steady stream of new programs at NIH focused on translation, including the biomedical engineering consortia, the Molecular Libraries Program, the National Cancer Institute Experimental Therapeutics Program, and the Clinical and Translational Science Award consortia. These programs provided a motivation for academicians to "move molecules to clinical trials," Sklar said. Simultaneously, translation was driven by an increase in drug discovery meetings, funding initiatives, compound collections, and screening technologies; the development of new pharmaceutical and biotechnology business models; and activities sponsored by such groups as the Academic Drug Discovery Consortium and the International Chemical Biology Society.

Technology-Enabled Repurposing

The University of New Mexico School of Medicine has used these new initiatives to move aggressively into drug repurposing by using computer modeling and informatics approaches. As one example, Sklar cited the use of a database called DRUGS database, a licensed resource developed at the University of New Mexico Health Sciences Center that contains 4,414 active pharmaceutical ingredients, accumulated from more than 44,000 FDA drug labels and about 58,000 National Drug Codes, which are annotated to 3,117 protein targets.[1] Sklar and colleagues have successfully used this database to map drugs, indications, and targets using chemical structures of drugs and target bioactivity (Oprea et al., 2011b).

Academic research contributes to repurposing in various ways other than simply testing drugs against already known targets and already available screening technologies. In particular, academic research also contributes to the development and application of new technologies. For

[1]Database contents as of January 27, 2014 (personal communication with Larry Sklar). The database is available to academic collaborators and on a fee basis for industry users.

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example, a high-throughput flow cytometry technology developed at the University of New Mexico School of Medicine has been used to find new targets for existing drugs, Sklar reported (Kuckuck et al., 2001). Flow cytometric analyses of competitive inhibitors that bind to small molecular weight GTPases (enzymes that hydrolyze guanosine triphosphate) on fluorescent beads have identified new uses for ketorolac (Oprea et al., 2011a). Ketorolac is a nonsteriodal anti-inflammatory drug approved for the treatment of acute pain. By using this flow cytometry approach, it was also discovered that ketorolac may inhibit GTPase signaling to regulate cell growth in ovarian cancer (Agola et al., 2012; University of New Mexico Cancer Center, 2012).

Through the use of computational analysis to model the docking of compounds into metnase, raltegravir, a DNA (deoxyribonucleic acid) repair enzyme that is associated with chemotherapy resistance when overexpressed in malignant cells was found to inhibit metnase activity (Williamson et al., 2012). Raltegravir was originally approved as an integrase inhibitor for the treatment of HIV infections. Currently raltegravir is being evaluated for its effectiveness as an adjuvant in treating squamous cell carcinoma of the head and neck,[2] Sklar said.

It is typical to find new activities for existing drugs during repurposing screens and mechanism of action studies, Sklar said. Academicians can play a significant role in contributing to this type of translational research, and resources that support discovery technologies and collaborations among basic scientists and clinicians are helpful in achieving this role.

DATA MINING

Although drug development is a complex and intricate process, it generally follows one of two basic approaches, explained Lon Cardon, senior vice president of alternative discovery and development at GlaxoSmithKline. The first approach is to start with a target and then try to find chemical entities that alter the target. The second is to begin with a phenotype and work toward the identification of a target and mechanism that can be altered.

In order to repurpose a drug it is important to understand both the drug's targets and the mechanisms of its action, Cardon said. New re-

[2]Pilot Study of Raltegravir and Cisplatin in Squamous Cell Carcinoma of Head and Neck (ClinicalTrials.gov identifier, NCT01275183).

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search findings, animal model experiments, and modifications of existing therapies are all ways of developing information on targets, but today this approach is far from optimal. If a drug is going to fail in development, Cardon said, it should fail early instead of late in order to reduce the costs of developing drugs that do not work in the first place. However, it is often the case that not enough information is available about targets and mechanisms to predict which drugs ultimately will fail.

Pharmaceutical companies already invest a fair amount in repurposing, but it is not necessarily easier to repurpose a drug than to develop one de novo, Cardon said. A single drug target may be the focus of five to seven projects looking at different indications, but little may emerge from the efforts.

The Potential for Genomics to Guide Repurposing

The recent study of genomics has been following what Cardon referred to as the "hype cycle."[3] In the early 1990s, many geneticists predicted that genomics would revolutionize medicine by identifying new drug targets and personalizing treatments, but when these predictions did not soon become a reality, the enthusiasm surrounding the field faded. Since reaching a low point in 2006, the field has continued to make progress and is now gaining momentum in what Cardon referred to as the "enlightenment phase" of the hype cycle. For example, data from genome-wide association studies (GWAS), which not long ago were being characterized as often disappointing and lacking biological relevance, have become more valuable. A catalog of GWAS can identify genes associated with diseases, such as type 2 diabetes, that are also the targets of ongoing drug development efforts (NHGRI, 2014). By combining this type of information, drug development and repositioning efforts can become more efficacious, Cardon said (Sanseau et al., 2012).

As more data are generated and made available, the number of repurposing hypotheses that can be constructed will increase dramatically, Cardon noted. These can be integrated to reveal new targets and new drugs for repositioning that were never considered before. In particular,

[3]The hype cycle is a graphical representation of the interest and enthusiasm related to an emerging technology as it matures through its life cycle. The information can be used as a tool to manage the commercial viability of a product. The hype cycle was described by Gartner, Inc. (Stamford, Connecticut) (Fenn and Raskino, 2008).

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Cardon said, resequencing can uncover genetic variants that might point to new indications even for well known therapeutics.

Collaboration Models

Drug repurposing is a challenging process and is neither straightforward nor guaranteed, but the chances of success can be increased by collaboration. Drug development is not the exclusive domain of either industry or academia, Cardon said. Efforts such as the Innovative Medicines Initiative in Europe and the National Center for Advancing Translational Sciences (NCATS) in the United States are demonstrating that an effective way to develop drugs is through collaborations. Rapid progress may require rethinking established practice in such areas as intellectual property, data sharing, and transparency. Industry cannot just support academic researchers and hope that something of value is generated, and academic researchers cannot just look for industrial funds to support what they were already doing. New models are needed that will play to the strengths of pharmaceutical companies, biotechnology companies, academic researchers, venture capitalists, and others, which will require give and take from all sides, Cardon said.

Pharmaceutical companies have data from high-throughput screening that academic researchers do not have, Cardon said. The barriers to the use of those data have to be broken down, so that the two groups can work collaboratively rather than on parallel tracks. For example, several years ago GlaxoSmithKline put its high-throughput screens for potential malaria drugs into the public domain. If ways could be found to make such data available for common chronic conditions, research would take a huge step forward.

Electronic Medical Records and Biobanks

EMRs can be important tools for identifying new uses for existing drugs (Hurle et al., 2013). These records could be another source of data on patient outcomes after treatment if ways could be found for researchers to access that information, Butte said. (See Chapter 6 for further discussion on EMRs.) Furthermore, Butte said, the use of data from EMRs could provide the statistical power needed to better understand drug effectiveness, but improved ways to mine the data contained in these records are needed.

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The China Kadoorie Biobank[4] study enrolled more than 500,000 adults and is collecting clinical data and biospecimens with the goal of identifying risk factors for chronic disease, Cardon said. The data collected from this study could also be a valuable tool for identifying new indications for drugs. For example, GlaxoSmithKline is evaluating cardiovascular outcomes for patients taking darapladib, an Lp-PLA2 inhibitor used to treat coronary heart disease, for the treatment of atherosclerosis.[5] Because the prevalence of a loss-of-function mutation in phospholipase A2, group VII in some Asian populations is more than 10 percent, Cardon suggested that by examining the genotypes in the Kadoorie study and querying corresponding EMRs, useful information about safety and other indications for Lp-PLA2 may be obtained (Jang et al., 2011). Information from studies that collect biological specimens and EMRs may also provide opportunities for targeted trial recruitment and for the study of other rare loss-of-function variants.

REPURPOSING AT NCATS

The Therapeutics for Rare and Neglected Diseases (TRND) program is a collaborative drug discovery and development research program, not a grant program, in the preclinical development space, said John McKew, acting scientific director in the Division of Pre-Clinical Innovation at NCATS. Projects may enter at various stages of preclinical development, but the diseases being studied must meet FDA orphan or World Health Organization neglected tropical disease criteria, he said. Using either internal resources or government contracts, collaborative projects are taken to the stage of the development process needed to attract an external organization that can complete clinical development and registration. A wide range of small molecules and biologics have been investigated, and a wide range of collaborators are involved. The program also serves to develop new, generally applicable platform technologies and paradigms for drug discovery, including informatics, communications, and collaboration tools that could have widespread benefits for drug repurposing.

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[4]China Kadoorie Biobank, http://www.ckbiobank.org (accessed January 29, 2014).

[5]In November 2013, GlaxoSmithKline announced that darapladib did not reach the primary endpoint of a statistically significant difference between treatment groups (i.e., time to a first major adverse cardiovascular event). The company indicated that it would continue to examine the role of Lp-PLA2 inhibition in heart disease and for other indications (see GSK, 2013).

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Screening-Enabled Repurposing

Four projects within the TRND portfolio are focused exclusively on repurposing, McKew said: three small molecule repurposing projects and one biologics repurposing project. An important technique used for these projects is screening-based repurposing.

The screening strategy at TRND is to use phenotypic cell-based assays, such as immunofluorescence imaging, as useful tools for scanning the collection of drugs. Using a high-throughput screening assay, compounds are tested in vitro on cells containing reporter genes whose products produce light when the drug reacts in the cell. The initial screen uses primary patient-derived cells that express the disease phenotype; recently, induced pluripotent stem cells that are differentiated to the appropriate cell types have been used. When it is possible to use, McKew said, this approach is the best way to examine the potential of a compound in vitro.

Screening can have several outcomes, McKew said. It can serve as a tool to probe disease pharmacology or new targets, it can identify a compound that acts as a starting point for a chemistry optimization program, or it can yield an approved drug that can be tested directly in patients in the clinic, though existing data and intellectual property protections might need to be weighed in order to decide the path forward. For example, is it a weakly potent molecule that may require significant additional data to augment the existing drug master file? Can method-of-treatment claims or other intellectual property patents be filed? Overall, the drug screening process identifies interesting molecules and helps build a package that can attract partners to finish the development of the molecules.

As an example of new technologies that can advance repurposing, McKew mentioned matrix screening, or mechanism interrogation plates, which searches for drug synergy among compounds with known mechanisms of action. Identifying drug synergies can make it possible to use less of an individual drug, which can allay concerns about toxicity.

Niemann–Pick Type C Disease

McKew described the Niemann–Pick Type C project, which has been conducted through a collaboration among Johnson & Johnson, the Albert Einstein College of Medicine, the University of Pennsylvania, Washington University, and several NIH institutes. The repurposing screening set consists of about 4,000 molecules representing approved

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drugs in Canada, Europe, and the United States (Huang et al., 2011), which has more recently been augmented with late-stage clinical compounds. Niemann–Pick Type C disease is an autosomal recessive disorder with a prevalence of about 1 in 150,000 in western Europe, and patients with this disease usually survive until the second or third decade of life (Patterson, 2013). Defects associated with Niemann–Pick disease, Type C1 or Niemann–Pick Type C2 cause cholesterol and other lipids to accumulate in lysosomes. This aberrant lipid accumulation leads to an enlargement of the spleen and liver and progressive neurological deficiencies, including cerebellar ataxia, dysarthria, dysphagia, tremor, and seizures. No FDA-approved therapies exist; miglustat has been approved in Europe, but it is not a target-specific treatment, McKew said.

Through a grant from the Ara Parseghian Medical Research Foundation, the repurposing collection was screened. This collection included 60 drugs reported in the literature to have an impact on Niemann–Pick Type C disease, McKew said. Skin biopsies from 58 different patients had been genotyped, so the underlying genetic defect was known, and multiple patient lines were used for the screening. A number of phenotypic imaging assays were used to measure accumulated cholesterol and the size of the lysosomes.

The most promising molecule that emerged from the screen, known as 2-hydroxypropyl-b-cyclodextrin (HPBCD), had been approved not as a therapeutic but as an excipient, which added to the challenge of approving the drug, McKew said. HPBCD does not cross the blood–brain barrier, so the treatment had to be adapted for a neurological disorder. This involved working with FDA to demonstrate that the drug would not be toxic if injected into the central nervous system. The drug received an orphan designation from FDA and the European Medicines Agency in 2013, and a Phase I clinical trial had just begun at the NIH Clinical Center at the time of the workshop, McKew said. The intention, he said, is to put together a package of data and incentives that will motivate a drug developer to take the project forward.

Challenges

Cost-related issues of drug repurposing can be a challenge, said McKew. The screening drug collection has been expensive to create and maintain. Because the screening plates are not distributed, researchers must work in collaboration with NIH to gain access to the plates, McKew said. Furthermore, incentives may not exist to move a generic

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compound through enough clinical study to effect a label change. A robust, published study may result in the drug being prescribed off-label, and this reduces the incentive for a company to spend the money to change the label with the FDA. In addition, the costs of some repurposing candidates can be prohibitive if the originator is not willing to participate by donating the molecule, McKew said.

PATIENT-REPORTED DATA

Drug repurposing projects have uncovered dysfunction in the clinical research enterprise, said Petra Kaufmann, director of the Office of Clinical Research at the National Institute of Neurological Disorders and Stroke (NINDS). The most important stakeholders—that is, patients—can be frustrated with the lack of treatment options and therefore are often willing to bypass parts of the current drug development process.

Lithium is a mood stabilizer with presumed neuroprotective properties that is thought to promote autophagy, a process of cellular destruction, Kaufmann explained. Mouse studies suggested that lithium could increase survival in patients with amyotrophic lateral sclerosis (ALS), and a small trial in humans found a delayed progression of the disease (Fornai et al., 2008). The morning after the results of this trial were released, Kaufmann said, her phone did not stop ringing, and her patients could not understand why she was not comfortable prescribing lithium for them. But with only 44 patients in the trial—16 of whom received riluzole (a drug used to slow the progression of ALS) and lithium, and 28 of whom received riluzole only—the trial did not have enough power to establish efficacy, Kaufmann said, especially with a disease as variable as ALS.

Many of Kaufmann's patients obtained lithium from another source and started taking it anyway. Patients using lithium would share their ALS Function Ratings Scale—a measure of a patient's ability to complete daily living activities—on the website PatientsLikeMe. Within a few months more than 100 people on the site reported taking lithium for ALS, but the results were not interpretable, Kaufmann said. A user of PatientsLikeMe wrote this about the online study: "The study is what it is, whether you are a proponent or a critic makes no difference at the end of the day. Does it have its flaws? Sure. Does it have its redeeming points? Sure. It is a piece of evidence for people to use in their own judgments, nothing more, nothing less" (Frost et al., 2008).

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At the same time NINDS, the ALS Society, and the ALS Society of Canada funded a randomized, controlled, double-blind study of 84 patients, which was stopped for futility at the first pre-planned interim analysis (Aggarwal et al., 2010). Other trials conducted in the Netherlands, the United Kingdom, and the United States did not find a benefit to treating ALS with lithium (Chio and Mora, 2013). Close to 700 patients were enrolled in these trials, with many more taking lithium outside of trials.

Patient Engagement

Having enough rare disease patients to fill a traditional large-scale, longer-term clinical trial can be difficult, Kaufmann said. Because recruitment takes a long time, patients can become frustrated and decide not to participate. Innovative approaches for evaluating drugs, such as a futility trial, which seeks to show that a drug does not work rather than to prove it does, requires fewer patients, less time, and less statistical power. This is the kind of innovative protocol that needs to be used for rare diseases, she said.

Opportunities to gain information from the compassionate use of drugs should be used, even though such data are often difficult to interpret, Kaufmann said. Instead of compassionate use, patients could be offered engagement in nontraditional trial designs. The key is to be more nimble in getting patients access to medicine while getting data that can be used as evidence to evaluate whether something works, which will require cooperation among regulators, funders, researchers, and patients. Innovative models that feature transparency and communication can connect stakeholders, including clearinghouses, crowdsourcing, and coordination through patient organizations or funders.

The critical element is public engagement, Kaufmann said. Patients and clinicians need a seat at the table during the development of the disease treatment concept and protocol, she said. For example, in some of the projects supported by the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) program at NINDS, researchers are required to involve patients from the beginning of the drug study.[6] This bidirectional communication makes research projects more successful and aids in information dissemination. Patients feel more comfortable and confident being part of research endeavors, including the repurpos-

[6]More information about the program is available at www.neuronext.org (accessed May 1, 2014).

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ing of existing drugs. Furthermore, rare diseases have so few patients that great efficiency is needed both in enlisting subjects for studies and in conducting studies.

One way to overcome the interpretation issues of self-reported data encountered in the ALS efforts is to use a different approach to using social media to learn more about potential treatments, Kaufmann said. In general, she said, patients need more opportunities to participate in working groups, data monitoring boards, and other activities that can speed up drug development. But patients also often need clear instruction regarding what kinds of data are needed, or the quality of the data and follow-up may suffer. It works well when patients and clinicians work together to participate in a research opportunity so that data are more objective and curated. For example, through the use of a restricted social media group known as Ning,[7] patients affected by ALS can ask questions about alternative off-label treatments and receive information from ALS researchers and physicians who are part of this group membership (Bedlack and Hardiman, 2009). The researchers or physicians would help assess the treatments and share the information they gather with patients.

[7]Available at ning.com (accessed January 30, 2014).

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4

Value Propositions for Drug Repurposing

Important Points Highlighted by Individual Speakers

- High-throughput genomics-based data are helping to elucidate disease mechanisms and targets, which provides optimism for the identification of new indications for a shelved compound.
- Opportunities for new indications for drugs need to be reevaluated throughout the discovery, development, and life-cycle management of a compound.
- Government incentives for drug development can be important for industry, but it is challenging to make an unattractive business opportunity more attractive.
- Understanding disease mechanisms and collecting clinical data are important components of identifying new indications for a drug.

Patients receive effective treatments when private companies are engaged and using their expertise to facilitate the regulatory approval, manufacturing, and distribution of drugs. Repurposing and repositioning therefore needs to make economic sense for companies if drugs are to become available for new indications. In a market where drug development is costly, pharmaceutical companies carefully consider their strategies for which drugs and targets to pursue, individual speakers said. The repurposing of thalidomide is provided as an example of the importance of understanding drug and disease mechanisms coupled with clinical data.

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BUSINESS MODELS

Drug repurposing offers grounds for pessimism and optimism, said Michael Ringel, partner and managing director for the Boston Consulting Group. For the past six decades, the number of new drugs developed per billion dollars invested in R&D has undergone an exponential decline—a trend known as Eroom's law (or Moore's law written in reverse) (see Figure 4-1) (Moore, 1965). As a result, the average cost to bring a drug to market has increased from a few hundred million dollars in the 1990s to more than $2 billion today, Ringel said. Today, for every dollar spent by the pharmaceutical industry on R&D, less than a dollar of value is returned, suggesting that future R&D expenditures by companies will decline.

One cause of the declining return on investment is the high failure rate of drug candidates in all phases of development. An obvious response would be for drugs to "fail earlier" in the development process so as to minimize the time and resources spent to determine that a drug will

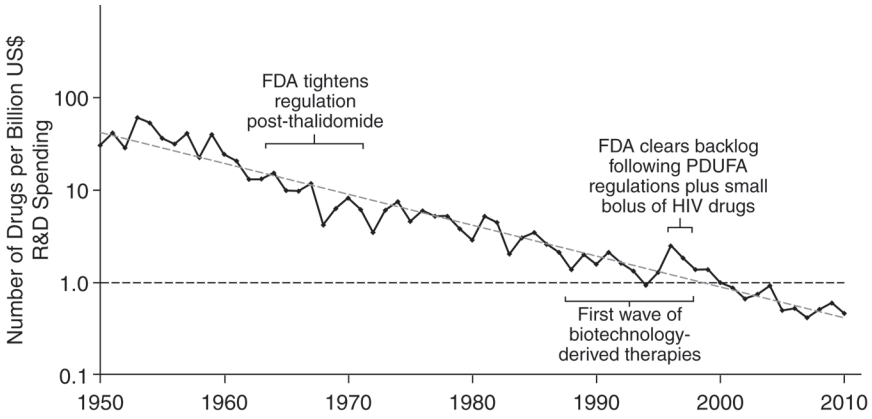

FIGURE 4-1 Eroom's Law in pharmaceutical R&D (spending adjusted for inflation).
NOTE: FDA, U.S. Food and Drug Administration; HIV, human immunodeficiency virus; PDUFA, Prescription Drug User Fee Act; R&D, research and development; US, United States.
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not be successful; however, behavioral disincentives (e.g., optimism about drug development data, market forces, job security) often interfere. The application of behavioral economics theory suggests that humans also are temperamentally biased toward continuing to invest in projects that already have considerable costs that may not be recouped. As Daniel Kahneman has written, there is a tendency to gamble on a gain even when taking that chance is more likely to lead to a greater loss (Kahneman, 2013).

These observations should point toward a cautious approach for drug repurposing, Ringel said. A drug that has already failed and is sitting on the shelf does not seem to be a good bet for alternative uses, he said, if, for example, the drug failed because of toxicity issues.

However, that challenge is balanced with reasons for optimism in genomics-enabled repurposing. GWAS data offer new ways to identify more promising targets. High-throughput biological data are uncovering the mechanistic pathways involved in disease. Precision medicine is becoming more successful, Ringel said—for example, in subdividing non-small-cell lung cancer into molecular subcategories responsive to targeted treatments (Ou et al., 2012).

Finding the Right Drug for a Disease Target

Thinking about drug development in a different way could establish a reasonable path forward for repurposing, Ringel suggested. Gaining a better understanding of disease targets and mechanisms can overcome market imperfections that impede repurposing. Some companies are developing platform tools to build matrices of diseases and molecules that might treat those diseases. Other companies are developing drugs specifically for out-licensing.

Drug developers could use imperfect drugs as probes to validate research hypotheses about the mechanisms of a disease, Ringel said. With this information, developers could then refine their research to design a molecule that works more effectively on the target to potentially treat the disease. As in the case of thalidomide (discussed later in this chapter), investigative molecular entities can act as probes for more effective or targeted molecules. Consortia, whether public or supported by government, can work on a larger scale than independent private efforts and can overcome loss-of-exclusivity issues.

Though returns on R&D investments have been declining in the pharmaceutical industry, Ringel said that he is an optimist about technol-

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ogy curves. Insights into new therapeutic targets and pathophysiologic mechanisms portend new drug indications.

REPURPOSING DRUGS CURRENTLY IN DEVELOPMENT

Translating scientific insights into novel therapies requires identifying the area where scientific innovation, unmet needs, and commercial attractiveness overlap, observed Simeon Taylor, vice president for research and scientific affairs at Bristol-Myers Squibb (BMS).

At least two factors contribute to the commercial attractiveness of a therapeutic, Taylor said. One is the existence of a sufficiently large number of patients to make a drug profitable. In that context, rare diseases can present a challenge, though the challenge can be offset to a certain degree by the price of the drug per patient.

The second factor contributing to commercial attractiveness is the synergy of expertise that is created through collaborations between academia and industry, Taylor said. Academia can provide innovative insights linking pharmacologic and disease mechanisms to drug indications. Industry can facilitate execution across stage development, regulatory approval, manufacturing, and commercialization.

Evaluating Disease Indications

The terms *purposing* or *positioning* are preferable to *repurposing* and *repositioning*, Taylor said, because the process of selecting a disease indication should be evaluated at every point in the discovery, development, and life-cycle management of a product. Even when an initial disease indication is selected, knowledge about the mechanism or the target may be relatively limited. Over the course of drug development, there may be numerous opportunities to re-evaluate indications. In addition, a safety concern that may not be manageable in one context may be manageable or acceptable in another, such as a more serious disease that leads to negative outcomes in patients when a suitable treatment is not available.

Dasatinib, an antineoplastic agent, was originally developed from a BMS program targeting the tryosine kinase Lck. During the study of dasatinib, researchers noticed that the drug had off-target effects against other tyrosine kinases, including Abl, which is involved in Philadelphia chromosome positive leukemia. In collaboration with Charles Sawyer at

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the University of California, Los Angeles, BMS researchers optimized dasatinib for Abl, which led to FDA approval for its use in treating imatinib-resistant Philadelphia chromosome-positive leukemia as well as consideration for first-line treatment (Das et al., 2006; Shah et al., 2004; Talpaz et al., 2006). In this case, academic–industry collaboration was essential for producing a dramatic shift from one target and indication early in the drug development process to another, Taylor said.

Another example involves lomitapide, which was recently approved as a treatment for familial hypercholesterolemia. The basic scientific research conducted largely at BMS relied on animal models and found that the compound effectively improved lipid profiles, Taylor said. However, the drug's significant adverse reactions, especially the accumulation of fat in the liver, were deemed unacceptable because patients with common dyslipidemia had access to numerous therapeutic alternatives. At that point, an academic researcher at the University of Pennsylvania suggested that the drug could be used to treat patients with rare homozygous familial hypercholesterolemia in cases where effective treatments are not available. Researchers moved forward successfully (using the drug donated by BMS) and founded a separate biotechnology company, Aegerion Pharmaceuticals, for handling the regulatory approval, mass manufacturing, and efficient distribution of the drug. During a Phase III study, lomitapide was found to be effective in lowering low density lipoproteins in patients (Cuchel et al., 2013).

Understanding the reasons the development of a particular drug failed can help in the repositioning of the drug in a context where it is less likely to fail, such as using it for defined patient subgroups, Taylor said. Metreleptin, a modified version of the hormone leptin, was originally developed by Amgen to promote weight loss for people with a genetic deficiency in leptin (Farooqi and O'Rahilly, 2006; Farooqi et al., 1999; Zhang et al., 1994). However, most people who are obese have sufficient endogenous leptin and are resistant to its effects, which led Amgen to stop drug development. At the time, Taylor said, he was working at the National Institute of Diabetes and Digestive and Kidney Diseases, and Taylor and his team reached out to Amgen to consider repurposing metreleptin for patients with lipoatrophy who have no fat (except for significant deposits in the liver) and no leptin. It was subsequently demonstrated that metreleptin significantly reduced circulating triglyceride levels and deposition of fat in the liver, which reduced the prevalence of serious clinical sequelae, including steatohepatitis (Oral et al., 2002). The leptin program has been acquired by other companies over time and the

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hope is that patients could be resensitized to leptin, thus learning from past failures in a way that repositions the drug for success.[1]

Considerations for Development

Taylor underscored the importance of financial incentives to companies by positing that the number of patients multiplied by the price for a drug must attain a certain minimum level in order for it to make financial sense for a company to invest in the drug (although companies may provide drugs for philanthropic reasons). The company must also take into account how long the drug will be under patent protection, Ringel said. If the patent on a drug has expired or is close to expiring, the cumulative revenues available from that drug will be much less than for a drug with significant patent life, he noted.

The federal government incentivizes drug development for orphan diseases; however, Taylor said, some diseases are still more likely to attract interest than others. A disease affecting 199,000 patients is naturally a more attractive target than a disease with only 100 patients, he said. While government incentives certainly matter to companies, they may not make a clearly unattractive business opportunity attractive enough to pursue.

There is also some reluctance to explore repurposing collaborations, Taylor said. Transferring technology is also often time-consuming and costly, and biotechnology company partners may lack sufficient capital resources to successfully invest in the compound to see through its development. There is a perception that the odds are slim that a viable product line will result for any given drug. For these reasons, BMS infrequently engages in these types of repurposing efforts, Taylor said.

THALIDOMIDE: REPURPOSING A DRUG THAT WAS NOT SUCCESSFUL FOR ITS FIRST INDICATION

Thalidomide was initially marketed as a sedative to address symptoms of morning sickness in pregnant women and was first offered as an over-the-counter product in 1957 by the German pharmaceutical company

[1]On February 24, 2014, FDA approved Myalept (metreleptin) for patients with congenital generalized or acquired generalized lipodystrophy. See *FDA approves Myalept to treat rare metabolic disease*. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm387060.htm (accessed February 27, 2014).

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Grünenthal, said Thomas Daniel, executive vice president for global research and early development at Celgene. However, sporadic reports had surfaced of phocomelia, a congenital deformity resulting in short limbs so that the hands and feet are in close proximity to the trunk, in children born of women who had taken the drug. The first affected patient was recognized in December 1956, but not until 1961 in a letter from William McBride in *Lancet* was there a published account of the correlation between thalidomide and birth defects (McBride, 1961). In the United States, FDA reviewer Frances Oldham Kelsey had delayed approval of the drug until a more complete data package was made available, which saved many U.S. women and families from devastating outcomes. For her role she was honored with the President's Award for the Distinguished Federal Civilian Service by President Kennedy in 1962 (FDA, 2013c).

After its withdrawal as a sedative, thalidomide was discovered in the 1960s to be an effective anti-inflammatory treatment for patients with leprosy, Daniel said. In the 1990s, Gilla Kaplan at Rockefeller University had an interest in thalidomide as an active inhibitor of tumor necrosis factor (TNF)-alpha production. At the same time, there was interest from the international AIDS community for using thalidomide because HIV/AIDS patients have elevated levels of TNF-alpha, although FDA voiced concern about development in unauthorized markets. It was not until 1998 that thalidomide was approved by FDA for use in patients with erythema nodosum leprosum (ENL), a type of leprosy reaction. This fueled aggressive efforts to identify additional applications and alternative drugs with reduced safety liabilities. Celgene therefore set out to reposition thalidomide for new indications and to develop analogues that lacked teratogenicity and other side effects.

New Indications

The first two new indications for thalidomide were for hematologic applications far removed from its anti-inflammatory effects in ENL, Daniel said. Thalidomide proved to be effective in treating refractory multiple myeloma (Singhal et al., 1999) and refractory anemia with excessive blasts, a type of myelodysplastic syndrome. These successes enhanced development efforts for the second-generation compounds lenalidomide and pamolidomide, Daniel said.

A prominent part of that research endeavor was the identification of targets and mechanisms for thalidomide and related compounds. Because

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thalidomide has pleiotropic effects on plasma cells, on the stromal cells that support them within bone marrow, and on the immune system, early evidence pointed to differential co-stimulation of T-cells by thalidomide and related compounds, Daniel said. In addition, in 2010, the primary target of teratogenicity was identified (Ito et al., 2010), which elucidated the immunomodulatory effects related to some of the common adverse reactions. This expanded understanding of the pharmacologic mechanisms facilitated the development of new thalidomide analogues, each with different pharmacodynamic properties, for further study. For example, a molecule called CC-122 is in late Phase I studies showing dramatic activity in B cell malignancies, in hepatocellular carcinomas, and in anaplastic astrocytoma, Daniel said.

Data Coupling Is Key

An understanding of disease mechanisms and therapeutic targets can dramatically narrow the hunt for clinical indications and provide paths for regulatory approval, Daniel said; however, clinical observations remain important for drug repurposing, as demonstrated by the use of thalidomide for leprosy and other conditions. Though the development of thalidomide and related compounds was not enabled by genomics, it is an example of how coupling systems biology to phenotypic assays can reveal differential activities, produce new intellectual property, and create new indications and value propositions.

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5

Policy Approaches and Legal Framework

Important Points Highlighted by Individual Speakers

- A trusted intermediary is often useful to initiate collaborations and provide the infrastructure and resources for academia and industry to work together.
- Crowdsourcing of candidate compounds for repurposing can generate ideas about new mechanisms of action and potential applications.
- Template collaborative research agreements can be beneficial for initiating a partnership and providing a catalyst to help projects move forward quickly.
- The release of information about potential compounds for repurposing has to strike a balance between confidentiality and providing sufficient information to attract the best research scientist and proposals.
- A less formal program for investigators who could use a small amount of a compound for a cell culture or animal experiment may also have a significant impact on assisting in the identification of new uses for existing drugs.

The success of repurposing and repositioning depends on the participating academic research and industry partners as well as on the contractual agreements and strategies enlisted by the programs. However, the biotechnology and pharmaceutical industries have been resistant to collaborative research because intellectual property is so important in this sector, said Arti Rai, Elvin R. Latty Professor at Duke University. The expense of clinical trials changes the business model for the biopharmaceutical industry, creating a need for more procedural and legal formalities involving patents, trade secrecy, and contractual mechanisms.

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Academic and industry researchers have different research focuses, expectations regarding publication, and styles of negotiation, Rai said. For this reason, a trusted intermediary is often needed to spur collaboration, fund projects, and provide the infrastructure needed for working together, such as template agreements.

Programs undertaken by NIH in the United States and the MRC in the United Kingdom have been developed to foster innovation in drug repurposing and to increase the understanding of disease mechanisms by promoting collaborations between pharmaceutical companies and academic researchers, Rai said.

OVERCOMING BARRIERS TO DRUG REPURPOSING AT NCATS

The mission of NCATS is "to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions,"[1] said Christine Colvis, director of extramural therapeutics discovery at NCATS. As part of that mission, NCATS has launched a Therapeutic Discovery Pilot program with the goal of identifying "new therapeutic uses of proprietary compounds and biologics across a broad range of human diseases in areas of medical need," Colvis said.

Eight pharmaceutical company partners—AbbVie (formerly Abbot), AstraZeneca, BMS, Eli Lilly, GlaxoSmithKline, Janssen, Pfizer, and Sanofi—have collectively made 58 compounds available, Colvis said. All are in early stages of development and are not approved drugs, and in most cases academic researchers would typically have been unaware of the existence of these compounds. NCATS listed the compounds with their known mechanisms of action, original indications, route of administration, penetration into the central nervous system, safety and tolerability data, and clinical trial information. The intention was to provide enough information for a researcher to determine whether a drug might be appropriate for a disease of interest.

[1]NCATS Mission Statement, http://www.ncats.nih.gov/about/mission.html (accessed February 26, 2014).

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In order to be included in the program, a company needed to have at least three compounds it could offer, and each company had different philosophies and strategies for selecting compounds, Colvis said. In sending compounds to NCATS, BMS chose only compounds that were safe because it felt uncomfortable putting compounds with significant concerns about safety into the hands of people outside the company, given that BMS would have no control over how the drugs would be used, said Taylor. The company also chose compounds with enough patent life that if a positive study occurred, BMS would have the financial incentive to continue study of that compound, which would be needed for the compound to be manufactured and distributed. Only three compounds met these criteria, Taylor said, although the company has had far more than three failures in drug development.

The intent of the NCATS program was to match candidate agents from the pharmaceutical partners with members of the research community who have innovative ideas for using shelved compounds for new indications. Each match represents a three-part interaction among NIH, industry, and academic researchers. NIH provides template collaborative research agreements, confidential disclosure agreements, mechanisms for peer review, funding, and oversight of the program. The pharmaceutical partners provide therapeutic compounds and relevant drug data along with in-kind support. Academic research partners provide disease biology knowledge, new ideas for different drug indications, and access to patients. The program is designed to be a collaborative process that should ultimately benefit patients, Colvis emphasized, and it does not involve simply handing over compounds for study.

Crowdsourcing Ideas

The program's goal in making the drug information publicly available, Colvis said, was to crowdsource the compounds in order to generate ideas about potential targets and indications for use. Within about 60 days NCATS received almost 160 pre-applications for potential new uses, many of which were for different indications using the same compound. For instance, a single compound might generate interest from various academic researchers as a treatment for arthritis, cancer, kidney failure, Alzheimer's disease, and the management of pain.

At NCATS the review was remarkably fast, even with managing the conflicts that arose. Only 7 weeks passed between the application due date and the completion of the reviews, Colvis said. About 1,000 review-

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ers were pre-recruited, and they were given 1 week to conduct their reviews. Each application was seen by reviewers with clinical expertise, knowledge of the mechanism of action, and drug development experience. The applications were short—just six pages—so the primary consideration was whether the scientific rationale was sound. Reviewers also were asked whether this was the right team for the project and whether the team members had the expertise to start work immediately.

After peer review, the top-rated applicants were put in contact with the company for the first time. At this point the partners could make a joint decision about whether or not to go forward and execute collaborative research agreements and confidential disclosure agreements. These agreements would enable the exchange of data, after which an investigator could decide whether to submit a full application for a research project. The agreements between companies and researchers were critical in enabling projects to proceed, Colvis said. The first agreements were hardest to negotiate, while subsequent agreements were much easier to arrange. Furthermore, Colvis said, having a template for the agreements made it possible to move quickly, which would not have been the case if each agreement had to be negotiated de novo.

In June 2013, nine awards were announced, which totaled $12.7 million in funding for the first year. Eight diseases were covered: alcoholism, Alzheimer's disease, calcific aortic valve stenosis, Duchenne muscular dystrophy, lymphangioleiomyomatosis, peripheral artery disease, schizophrenia (two applications), and smoking cessation.

Signs of Success

The receipt of 160 applications within 2 months was a very positive sign, Colvis said. The willingness of eight potential competitors to participate in a single program was also a sign of success. Although a handful of awards will make only a small difference to the overall problem, demonstrating that a strategy can work—even if just a few compounds make it as far as Phase II trials—could lead to a much broader application of that strategy.

NCATS was also collecting feedback from the community so that it could consider converting the pilot program into a full program. Several other parties should be involved in future efforts, including FDA and patient advocacy groups, Colvis said. One complication with repurposing, she pointed out, is that a new indication may move a compound from one part of FDA to another, with different people and requirements

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becoming involved, though working with FDA could help smooth any such transitions.

OVERCOMING BARRIERS TO DRUG REPURPOSING AT THE MRC

The MRC is the United Kingdom's largest public funder of medical research both in universities and hospitals and in the MRC's own intramural program, said Christopher Watkins, director of translational research and industry at the MRC. One of seven research councils in the United Kingdom, the MRC is funded by the UK government but is free to support whichever science it chooses, with the exception that it cannot directly support R&D for companies. As part of its translational strategy, it focuses on research performed in humans for identifying mechanisms of disease and demonstrating proof-of-concept evidence of the validity and importance of new discoveries or treatments. The overall strategy is to ensure that the science it supports is of relevance to human health.

Under the Mechanisms of Disease Initiative, the MRC has been working with AstraZeneca to provide academic researchers access to compounds that AstraZeneca has deprioritized and is therefore no longer developing (Wadman, 2012). The goals of the program are to gain a better understanding of human disease mechanisms, to develop potential therapeutic interventions, and to stimulate relationships between academia and industry. The molecules were chosen so as not to duplicate active company research, ensuring that the MRC was supporting research that would not otherwise have been done, Watkins said. Relatively well developed toxicological information was available for the molecules, but some of the deprioritized compounds were cancer drugs for which the toxicology profile may not have been appropriate for chronic administration in other patient groups.

The call for proposals generated more than 100 applications, Watkins said. The proposals were assessed on the basis of the scientific rationale for using the compound, the availability and supply of the compound, the novelty of the study, clinical trial design, and the risks and benefits for patients. Out of 25 applicants invited to submit full proposals, 15 projects were funded at the end of 2012, 8 of which were clinical projects and 7 pre-clinical. Research areas ranged from common illnesses to orphan diseases, including an investigation of whether a compound originally designed for prostate cancer could delay Alzheimer's disease progression,

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a heartburn medication reused for chronic cough treatment, and the repurposing of a lung disease drug to treat muscular dystrophies, Watkins said.

The MRC specified that scientific excellence was the most important consideration, and the peer review was international, Watkins explained. As part of the agreement with AstraZeneca, none of the reviewers were industry scientists. The review mechanism was designed appropriately for its intention, with the goal of having the right experts asking the right questions in order to aid in the selection of successful research, Watkins said.

Repurposing compounds from AstraZeneca is not the explicit objective of the initiative, Watkins said. Rather, the compounds have been used as probes to investigate disease mechanisms, validate targets, and reveal new therapeutic opportunities. The program does not involve the screening of a compound library. Rather, researchers use compounds to test hypotheses. All the projects took the form of collaborative efforts between AstraZeneca scientists and academic scientists.

Similarities and Differences Between NCATS and MRC Programs

The NCATS and MRC programs have many similarities. They both have used template agreements and have served as trusted intermediaries, Rai said. The agencies also both use a two-stage process, with relatively open crowdsourcing followed by a more closed second stage that is governed by cooperative agreements. NCATS and MRC both have detailed provisions for publication, and both draw a distinction between background, including existing intellectual property protections, and the research results that could emerge from the collaboration.

The programs being conducted by the two agencies differ in several key ways, however, said Rai. The cooperative research agreements used by NIH are formally bipartite between the researcher and company, although modifications to the agreement necessitate the approval of NIH, and the agreements cannot supersede the terms and conditions of NIH grants. By contrast the MRC grant is a contract between the university and the MRC, with separate project agreements between the university and AstraZeneca. The MRC approach allows for greater confidentiality of applicant information in the first stage.

A larger difference, Rai said, is that the MRC collaboration aims to validate targets and increase the understanding of disease biology using humans as an experimental model, whereas NCATS is more focused specifically on repurposing. With NCATS, the model templates are

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directed to situations where molecules are repurposed and become commercially valuable as a consequence. Also, licensing provisions for the intellectual property in the results are specified in detail in advance, while AstraZeneca has the right to negotiate either exclusive or nonexclusive rights to the intellectual property retained by the academic organization.

Lessons Learned

Including industry and academic researchers as full co-applicants on all the proposals created true collaborations in which each party benefited from the study, Watkins said. AstraZeneca benefited by revisiting compounds that would not have otherwise been explored further. The researchers benefited by gaining access to the compounds as well as the related toxicology and safety data. By working together, academic researchers and industry capitalized on their unique strengths to improve their understanding of the underlying basis of human disease and aided in the development of potential therapeutic interventions.

As was the case with the NCATS programs, confidentiality template agreements were extremely beneficial for beginning collaborations, Watkins said. The agreements sped up the process well beyond what is usual for industry–academia collaboration. In particular, the use of a template known as the Model Industry Collaborative Research Agreement, which has been approved by a wide range of stakeholders, made it possible for the research agreements to be signed within 4 months of the announcement of funding decisions.

COMPOUND AVAILABILITY

A smaller and less formal program for investigators who need a small amount of a compound to do a quick cell culture or animal experiment would be very helpful, Dietz said. Such a program could leverage the infrastructure, trust, and connections built by NCATS and the MRC. Discussions are being held with other companies concerning the creation of such a program, although the mechanisms for such a program would have to be established, Watkins said. He noted that AstraZeneca put significant time and effort into establishing the program with the MRC, and future programs should try to reduce the amount of bureaucracy necessary. The idea would be to have the best scientists in academia working

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with the best scientists in industry, and the program would not be "just a reagent catalog," Watkins said.

LEGAL AND INTELLECTUAL PROPERTY ISSUES

Collaborative research agreements usually include provisions on how to deal with existing technologies—that is, what the parties had developed prior to the collaboration—along with provisions on the technology developments or results from the collaboration and the intellectual property rights associated with those developments or results, Rai said.

The release of information about the deprioritized drugs had to strike a balance between the need to provide confidentiality and the need to disclose sufficient information to attract the best research proposals, Watkins said. This information included data about the nature of the target, specificity, selectivity, and toxicology. The information did not, however, include details about whether the drug crossed the blood–brain barrier, which in retrospect was an oversight, he said.

An important issue was protecting the intellectual property of potential applications so that investigators would not be worried that companies would infringe upon their ideas. Confidentiality agreements were necessary among all partners in order to allow for the protection of some of the more detailed information, the sharing of information necessary for choosing the right molecules, the protection of the intellectual property of potential applicants, and the assuring of confidentiality from the peer reviewers, Watkins said.

AstraZeneca retains the intellectual property on its molecules, Watkins said, while any intellectual property resulting from the research is to be retained by the research organizations. AstraZeneca will be able to negotiate intellectual property protections once the studies are complete. The partners also agreed to publish the study results within 6 months so that information from the initiative enters into the public domain.

Method-of-Use Patents

Some molecules may serve simply as "parent" molecules, with patents filed on compounds derived from them, Rai said. If the compounds do not have much patent life left, it may be possible to acquire some protection through process or method-of-use patents.

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One question, Rai said, is whether method patents provide sufficient incentives to complete the testing that would be necessary for FDA approval of a new use. If the molecule is already being marketed for another use, which in this case is unlikely, then the compound could simply be used off-label. If the compound is not being marketed, a method-of-use patent provides more exclusivity, though the level of exclusivity depends on the strength of the method-of-use patent.

An alternative intellectual property approach may be needed, given that the patent system is not now working optimally for the biopharmaceutical industry, Rai said. In the future, compounds may need a "therapeutic only" exclusivity comparable to the data exclusivity that biologics have. For example, the proposed Modernizing Our Drug and Diagnostic Evaluation and Regulatory Network (MODDERN) Cures Act of 2011[2] would have allowed the Secretary of Health and Human Services to designate a particular therapy or potential therapy as addressing an unmet medical need and thereby provide 15 years of exclusivity.

[2]MODDERN Cures Act of 2011, H.R. 3497, 112th Congress, 1st session (November 18, 2011). The bill was re-introduced in 2013 as MODDERN Cures Act of 2013, H.R. 3116, 113th Congress, 1st session (September 17, 2013).

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6

Increasing the Efficiency and Success of Repurposing

Repurposing and repositioning have gained considerable attention from a range of stakeholders, including NIH, academic institutions, pharmaceutical companies, and even some technology companies, for its potential to improve human health, particularly in rare diseases, said Aidan Power, vice president and head of PharmaTx Precision Medicine at Pfizer. When these stakeholders have joined together in collaborations, they have achieved notable successes in finding new and sometimes unexpected uses for existing drugs, he said. (The suggested best practices and opportunities that individual speakers offered concerning drug repurposing are found in Box 6-1.) Indeed, given the degree of success experienced with repositioning for rare diseases, global strategies could be instituted to pursue this approach, Power said.

Initial drug discovery and repurposing are not very different from each other in the sense that they share some of the same challenges encountered during the drug development process, Cardon said. When thinking about drug development, the initial approach may be to focus on the drug itself, but with drug repurposing in rare diseases the thought process is different and the approach typically begins with a focus on the disease pathology, and clinical insights remain critical, Cardon said.

BOX 6-1
Suggested Proposals Made by Individual Speakers

These suggested proposals should not be seen as recommendations of the workshop, but they are promising ideas for further discussion.

continued

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BOX 6-1
Continued

Suggested Best Practices for Drug Repurposing from Individual Speakers

- Successful drug development calls for an understanding of both disease biology and clinical observational data. (Daniel, Ringel)
- Academia can provide significant technological innovation for drug repurposing through the development of high-throughput assays and computational approaches. (Sklar)
- A key element to repurposing is to maximize the generation of ideas through partnerships among academia, industry, nonprofit groups, and others. (Cardon, Frail, McKew)
- Possibilities for new indications for drugs should be reassessed throughout all developmental stages of a compound. (Taylor)
- Collaborative research agreements can serve as catalysts for efficiently initiating industry-academia partnerships and for setting expectations for repurposing programs. (Colvis, Watkins)
- Knowing how a drug works in humans should be a focus in drug development if the goal is to ultimately use the treatment in patients. (Power, Watkins)

Possible Strategies and Opportunities for Consideration from Individual Speakers

- A less formal mechanism for sharing small amounts of drugs with academic laboratories for testing in vitro and in vivo is necessary. (Dietz)
- Increasing the public availability of data can accelerate the process of drug repurposing, but incentives are needed to encourage more scientists to share their data. (Butte)
- Innovative thinking about intellectual property and data sharing issues is needed in order to maximize the synergy among the different strengths of academia and industry for repurposing. (Cardon)
- Treatments will be developed more quickly if innovative approaches for clinical trials and patient input are used while still maintaining the quality and objectiveness that can come from longer, more traditional trial designs. (Kaufmann)
- The search for new indications should be expanded to active drugs and not just deprioritized ones. (Colvis)
- A centralized system of technology transfer offices that work with universities on a contractual basis to provide specialization in technology and negotiation may be an alternative way to facilitate academia-industry partnerships by providing expertise. (Rai)

continued

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BOX 6-1
Continued

- Genomics can be used as a tool throughout the drug repurposing effort to identify drug targets and bring greater understanding to disease mechanisms. (Bartek)
- EMRs need to evolve into usable tools that enable the study of patient outcomes and therapeutic effectiveness. (Butte, Cardon, Ginsburg, Kaufmann)
- Collaborations, such as clearinghouses, are needed to facilitate drug repurposing by enabling the exchange and distribution of drug information. (Bartek)
- Negative or less interesting data are still valuable and should be shared with the larger drug repurposing community so that the specific reasons for drug failures are clear. (Bartek)
- Key stakeholders such as CMS, private payers, FDA, and patient groups need to be involved in future drug repurposing projects. (Colvis, Pacanowski, Tong)
- Drug repurposing efforts should focus on unmet medical needs, such as developing treatments for rare diseases. (Bartek, Pacanowski)

THE ROLE OF GENOMICS

An integrated approach to drug repurposing that is not focused specifically on genomics or other omics-based research will be the most successful approach for finding new indications, Cardon said. But genomics and other new technologies add a dimension to repurposing that could greatly speed progress. With diseases such as cancer, for example, immense quantities of data are being generated that can foster innovation, both in the kinds of compounds that are being developed and in the specific treatments used for molecularly profiled diseases.

Genomics can be used throughout the repurposing process to identify therapeutic approaches and disease pathways, said Ronald Bartek, president of Friedreich's Ataxia Research Alliance. The technology is a tool for developing an understanding of mechanisms and for gaining clues as to why some patients respond to drugs during clinical trials while others do not, said Allen Roses, the Jefferson–Pilot Professor of Neurobiology and Genetics at Duke University. Dietz agreed, adding that in the case of failed trials, genomics may enable the identification of the patient populations in which a drug is effective.

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Collecting Other Types of Data

Geoffrey Ginsburg, director of the Center for Genomic Medicine at Duke University's Institute for Genomic Sciences, asked whether it makes sense to monitor the entirety of the transcriptome, metabolome, proteome, immunome, and anything else that could be informative about the diversity of actions of a drug. The answer to that question involves looking at relative costs and benefits, Frail said. Even analyzing just the metabolome is quite expensive, and the returns from such an investment are uncertain. Genetic studies, whether of the genome or of the transcriptome, are more cost-effective, but the cost of analyzing the data still can be prohibitive. The difficulty arises from the need to screen large numbers of compounds in individual patients, although such screens may be possible with a more limited number of compounds, McKew said.

While biological understanding can drive drug development and the choice of treatments, clinical data also can inform research activities, observed Ringel. The most promising approach, individual participants observed, is an integrated one that combines genomics, clinical observations, basic research, animal models, and clinical trials. However, Power reminded the group, all approaches need to culminate in human experiments if drugs are to be used in patients.

USE OF ELECTRONIC MEDICAL RECORDS

Early experiences have shown that EMRs can be used for research, Ginsburg said, even though they have not been designed for that purpose. EMRs could be especially valuable if the information they contain were coordinated so that signals from the data more clearly emerged from the noise, Ringel added.

However, the use of EMRs is still in its infancy, Cardon said. Much depends on the quality and quantity of the clinical information available. As Kaufmann pointed out, EMRs have been constructed more for compliance and billing purposes than for research, and the information they contain often is proprietary. Where EMRs could be helpful in working with rare diseases would be identifying patients or linking clinicians with trial opportunities, she said. However, with so few patients the data would probably not be good enough to generate useful results.

The current weaknesses of EMRs provide an opportunity to think about which stakeholders should be at the table in deciding about their

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future evolution, Kaufmann continued. If more research capabilities were built into these systems, they could prove to be valuable. Ginsburg also pointed out that patient-reported datasets are becoming more common, and it may be possible to derive information from such datasets that is not available from EMRs.

EXISTING BARRIERS

Repurposing and repositioning are still in their early stages, Ginsburg said. Many strategies are being pursued, none of which has been described as ideal. Furthermore, the stakeholders involved in repurposing and repositioning have different interests, and no obvious way yet exists to harmonize these interests.

A number of barriers to repurposing exist. One is that companies may decline to release information out of a fear that a blockbuster drug will be tarnished if a repurposing program uncovers safety or efficacy issues, said Michael Pacanowski, acting associate director for genomics of the Center for Drug Evaluation and Research at FDA. For rare or severe diseases, in contrast, the bar may not be set as high with regard to safety; thus, in this regard repurposing is less risky for these indications, although such drugs also produce lower returns on investment because of their limited patient populations. However, Taylor noted that companies do not measure returns on investment just in terms of dollars. An organization may be willing to accept financial risks if the patients it represents have a personal stake in the undertaking.

Pharmaceutical companies continue to have problems with intellectual property protections and with the costs of transactions for licensing, Rai said. Other industries share information without the formality seen in drug development, but this is because clinical trials are so expensive. An alternative would be to publicly fund trials, but this is not likely to happen, she said. Ringel pointed out that there have been success stories of companies transferring rights among themselves, but these success stories are rare. Sometimes, when another company expresses interest in a compound, the company owning the rights to the drug will renew its own internal effort. In addition, each company has its own disease area strategy, and it can be hard to get traction within the company if an idea is outside that area.

Difficulties can occur in gaining timely IRB approval for fast-turnaround studies using social media, Kaufmann said. People who self-

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enlist in such studies are information altruists who want their data to be used, while the medical system has the goal of protecting their data. Centralized IRBs that see more and larger projects may be more forthcoming with approvals.

POSSIBLE NEXT STEPS

Collaborations, such as consortia, represent an opportunity to create a clearinghouse or other means of information exchange and dissemination designed to expedite drug repurposing programs, Bartek said. A venue where ideas, resources, and knowledge can be freely shared without excessive procedural and legal formality could maximize the number of drugs being tested for different drug targets, Dietz said.

Technology transfer officers have different levels of expertise in negotiating complex arrangements with private companies and government, and they are often overburdened at their jobs, Rai said. An alternative model that has been discussed is to centralize the technology transfer process so that a smaller number of technology transfer officers with expertise in particular areas represent a number of universities. In such a case, technology transfer officers could be experts not only in negotiating contracts but in the technology covered by the contract.

Frail emphasized how much can be learned from negative, or less interesting, findings. Journals are more receptive to publishing such studies now than they have been in the past, and clinical trial results are now more transparent. Colvis observed that negative data are really just data, especially in the context of repurposing, where information about what does not work and why can be extremely valuable. Bartek noted that it would be helpful to know whether the drug itself or the clinical trial failed. Colvis pointed out, though, that data of value can sometimes be difficult to share.

Though NCATS and the MRC have begun demonstrating what is possible, many other government agencies could do more to promote repurposing and repositioning, Bartek said. First, NCATS is not the only supporter of translational science at NIH. All the other institutes have their own translational and clinical programs that could become engaged with drug repurposing, and these programs could be especially productive if they were coordinated within NIH to accelerate translational science. NIH could potentially play a role as a clearinghouse with academia for identifying points of contact for learning more about how drug repur-

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posing technologies are being used for specific diseases, Bartek said.

Pacanowski observed that FDA has large quantities of data that could be extremely useful if they were integrated and synthesized. In addition, the further development of regulatory science will allow science to inform the regulatory process, observed Tong. Government agencies can coordinate efforts to address issues related to emerging technologies, as with quality control of microarray applications. CMS and other public and private healthcare payers also could advance repositioning, particularly through collaborations with other stakeholders in the drug development ecosystem, Tong suggested.

Patient groups have an important role to play, said a workshop participant. Although patient groups do not receive a funding stream in the current drug development system, they can quickly put together cohorts and provide samples that are matched to genotypes, phenotypes, and available compounds. Kaufmann added that patient data will be subject to some selection bias in terms of who decides to volunteer information, but the opportunity is sufficiently great that this limitation needs to be accommodated. Researchers will need to work with patient organizations to make sure that patients feel comfortable and that privacy concerns are adequately understood. Data quality is also a consideration, but simple measures, such as an app that asks patients to report on their pain level, can offer good ways of collecting information, even if not all data will be useful in, for example, securing a label change from FDA. Kaufmann pointed out that common data elements and outcome analyses would facilitate future meta-analyses. Even better would be coordinating studies from the beginning rather than doing studies separately.

As an example of what patient groups can do, Frail cited the Polycystic Kidney Disease Foundation, which set up a small scientific advisory board that could provide guidance on compounds and animal models to test. Similarly, the Michael J. Fox Foundation has supported drug repositioning for Parkinson's disease. In that case, the foundation brought together industry and academic partners to pursue promising leads. However, such collaborations need to harmonize with the business model of a company.

FUTURE REPURPOSING EFFORTS

Drug developers and their partners in government and in the patient community should continue to pursue low-hanging fruit, especially with

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rare diseases, Bartek said. New technologies can lead to a better understanding of disease mechanisms and molecular pathways and can continue to create new opportunities to repurpose and reposition drugs for alternative targets. Even after a high-throughput screen has detected hits for diseases such as Friedreich's ataxia, new assays or better cell models can create new possibilities, he said.

An emphasis should be placed on unmet medical needs as opposed to searching for convenient discoveries, Pacanowski said, and investments should be made where they will have the biggest impact on public health instead. Colvis urged that repositioning programs be broadened to include active as well as deprioritized compounds. Preventive disease strategies and therapeutics should also be included when thinking about drug repurposing, a workshop participant added.

Finally, individual workshop participants who spoke stated that the ultimate measure of success is improved health. As Ringel put it, by creating value for patients, repositioning can change people's lives.

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A

Workshop Agenda

Drug Repurposing and Repositioning
A Workshop

June 24, 2013

The Keck Center of the National Academies, Room 100
500 Fifth Street, NW
Washington, DC 20001

Workshop Objectives:

- To assess the current landscape of drug repurposing activities in industry, academia, and government.
- To examine enabling tools and technology for drug repurposing.
- To evaluate the business models and economic incentives for pursuing a repurposing approach.
- To discuss how genomic and genetic research could be positioned to better enable a drug repurposing paradigm.

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8:30–8:35 A.M. **Welcoming Remarks**

Sharon F. Terry, Roundtable Co-Chair
President and Chief Executive Officer Genetic Alliance

Geoffrey Ginsburg, Roundtable Co-Chair
Director, Genomic Medicine, Duke Institute for Genome Sciences & Policy; Executive Director, Center for Personalized Medicine, Duke Medicine; Professor of Medicine and Pathology, Duke University Medical Center

8:35–8:40 A.M. **Charge to Workshop Speakers and Participants**

Aidan Power, Workshop Chair
Vice President and Head, PharmaTx Precision Medicine
Pfizer Inc.

8:40–10:20 A.M. **SESSION I: CURRENT LANDSCAPE**

Moderator: *Gabriela Lavezzari*
Assistant Vice President, Scientific Affairs
PhRMA

8:40–8:55 A.M. **State of the Science: Academia**

Larry Sklar
Distinguished Professor
Director, Center for Molecular Discovery
Associate Director, Cancer Center
University of New Mexico School of Medicine

8:55–9:10 A.M. **State of the Science: Industry**

Don Frail
Vice President of Science
New Opportunities Innovative Medicines Unit
AstraZeneca

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9:10–9:25 A.M. **State of the Science: FDA**

Weida Tong
Director, Division of Bioinformatics and Biostatistics
National Center for Toxicological Research
U.S. Food and Drug Administration

9:25–9:40 A.M. **State of the Science: Rare Disease**

Hal Dietz
Victor A. McKusick Professor of Medicine and Genetics
Institute of Genetic Medicine
Investigator, Howard Hughes Medical Institute
Johns Hopkins University School of Medicine

9:40–10:20 A.M. **Discussion with Speakers and Attendees**

10:20–10:35 A.M. BREAK

10:35 A.M. –12:30 P.M. SESSION II: ENABLING TOOLS AND TECHNOLOGY

Moderator: *Geoffrey Ginsburg*
Director, Genomic Medicine, Duke Institute for Genome Sciences & Policy; Executive Director, Center for Personalized Medicine, Duke Medicine; Professor of Medicine and Pathology, Duke University Medical Center

10:35–10:55 A.M. **Computational Strategies (modeling, literature-based discovery)**

Atul Butte
Chief and Associate Professor of Systems Medicine
Department of Pediatrics
Stanford University School of Medicine

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10:55–11:15 A.M. **Data Mining (post-market surveillance, high-throughput screening, databases)**

Lon Cardon
Senior Vice President, Alternative Discovery and Development
GlaxoSmithKline

11:15–11:30 A.M. **Government-Sponsored Efforts: NCATS**

John McKew
Acting Director, Division of Pre-Clinical Innovation
National Center for Advancing Translational Sciences

11:30–11:45 A.M. **Government-Sponsored Efforts: NINDS**

Petra Kaufmann
Director, Office of Clinical Research
National Institute of Neurological Disorders and Stroke

11:45 A.M. –12:30 P.M. **Discussion with Speakers and Attendees**

12:30–1:20 P.M. **WORKING LUNCH**

1:20–2:45 P.M. **SESSION III: VALUE PROPOSITION FOR REPURPOSING**

Moderator: *Allen Roses*
Jefferson–Pilot Professor of Neurobiology and Genetics
Professor of Medicine (Neurology)
Director, Deane Drug Discovery Institute
Senior Scholar, Fuqua School of Business
R. David Thomas Executive Training Center
Duke University

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1:20–1:35 P.M. **Business Model/Economic Incentives**

Michael Ringel
Partner and Managing Director
The Boston Consulting Group

1:35–1:50 P.M. **Repurposing Drugs Currently in Development**

Simeon Taylor
Vice President, Research and Scientific Affairs
Bristol-Myers Squibb

1:50–2:05 P.M. **Repurposing Drugs That Were Not Successful for Their First Indication**

Thomas O. Daniel
Executive Vice President
President, Global Research and Early Development
Celgene Corporation

2:05–2:45 P.M. **Discussion with Speakers and Attendees**

2:45–3:00 P.M. **BREAK**

3:00–4:25 P.M. **SESSION IV: POLICY APPROACHES AND LEGAL FRAMEWORK**

Moderator: *Arti Rai*
Elvin R. Latty Professor of Law
Duke University

3:00–3:15 P.M. **Strategies for Overcoming Barriers to Drug Repurposing: NCATS**

Christine Colvis
Director, Extramural Therapeutics Discovery
National Center for Advancing Translational Sciences

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3:15–3:30 P.M. **Strategies for Overcoming Barriers to Drug Repurposing: MRC/AZ**

Chris Watkins
Director, Translational Research and Industry
Medical Research Council

3:30–3:45 P.M. **Legal/Intellectual Property**

Arti Rai
Elvin R. Latty Professor of Law
Duke University

3:45–4:25 P.M. **Discussion with Speakers and Attendees**

4:25–5:15 P.M. SESSION V: INCREASING THE EFFICIENCY AND SUCCESS OF REPURPOSING

4:25–5:15 P.M. **Advancing Repurposing Efforts**

Moderator: *Aidan Power, Workshop Chair*
Vice President and Head, PharmaTx Precision Medicine
Pfizer Inc.

Respondents:

Ronald J. Bartek
President
Friedreich's Ataxia Research Alliance

Lon Cardon
Senior Vice President, Alternative Discovery and Development
GlaxoSmithKline

Christine Colvis
Director, Extramural Therapeutics Discovery
National Center for Advancing Translational Sciences

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Hal Dietz
Victor A. McKusick Professor of Medicine and Genetics
Institute of Genetic Medicine
Investigator, Howard Hughes Medical Institute
Johns Hopkins University School of Medicine

Michael Pacanowski
Acting Associate Director for Genomics
Center for Drug Evaluation and Research
Office of Clinical Pharmacology
U.S. Food and Drug Administration

Arti Rai
Elvin R. Latty Professor of Law
Duke University

Michael Ringel
Partner and Managing Director
The Boston Consulting Group

5:15–5:30 P.M. **SESSION VI: CONCLUSION**

5:15–5:30 P.M. **CONCLUDING REMARKS**

Aidan Power, Workshop Chair
Vice President and Head, PharmaTx Precision Medicine
Pfizer Inc.

5:30 P.M. **ADJOURN**

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B

Speaker Biographical Sketches

Ronald J. Bartek, M.A., is co-founder and president at Friedreich's Ataxia Research Alliance; chairman of the board of the National Organization for Rare Disorders; 4-year member of the National Advisory Neurological Disorders and Stroke Council at the National Institutes of Health; and former partner and president of a business and technology development, consulting, and government affairs firm. Mr. Bartek's professional experience also includes 20 years of federal executive branch and legislative branch service in defense, foreign policy, and intelligence, including 6 years on the policy staff of the House Armed Services Committee; 4 years at the State Department's Bureau of Politico-Military Affairs, including a year as a negotiator on the U.S. Delegation to the Intermediate-Range Nuclear Forces Treaty talks in Geneva; 6 years as a Central Intelligence Agency analyst of political–military aspects of the East–West balance, including 1 year as an intelligence community representative to the interagency groups charged with U.S. arms control policy; and former director of the American Friends of the Czech Republic. Following graduation from the U.S. Military Academy at West Point, Mr. Bartek spent 4 years as an Army officer, serving as a company commander in Korea and an infantry and military intelligence officer in Vietnam. He has a master's degree in Russian area studies from Georgetown University.

Atul Butte, M.D., Ph.D., is chief of the Division of Systems Medicine in the Department of Pediatrics and an associate professor in pediatrics, medicine, and, by courtesy, computer science at Stanford University and the Lucile Packard Children's Hospital, and he is a pediatric endocrinologist. Dr. Butte received his undergraduate degree in computer science

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from Brown University, and he worked in several stints as a software engineer at Apple Computer (on the System 7 team) and Microsoft Corporation (on the Excel team). He graduated from the Brown University School of Medicine. He completed his residency in pediatrics and his fellowship in pediatric endocrinology, both at Children's Hospital, Boston. Dr. Butte received a Ph.D. in health sciences and technology from the Medical Engineering/Medical Physics Program in the Division of Health Sciences and Technology at Harvard Medical School and the Massachusetts Institute of Technology. The Butte Laboratory builds and applies tools that convert more than 300 billion points of molecular, clinical, and epidemiological data—measured by researchers and clinicians over the past decade—into diagnostics, therapeutics, and new insights into disease. Examples of this method includes work on cancer drug discovery published in the *Proceedings of the National Academy of Sciences of the United States of America* (2000), on type 2 diabetes published in the *Proceedings of the National Academy of Sciences of the United States of America* (2003), on fat cell formation published in *Nature Cell Biology* (2005), on obesity in *Bioinformatics* (2007), and in transplantation published in *Proceedings of the National Academy of Science*s *of the United States of America* (2009). To facilitate this, the Butte Lab has developed tools to automatically index and find genomic datasets based on the phenotypic and contextual details of each experiment, published in *Nature Biotechnology* (2006); to re-map microarray data, published in *Nature Methods* (2007); to deconvolve multi-cellular samples, published in *Nature Methods* (2010); and to perform these calculations on the Internet "cloud," as published in *Nature Biotechnology* (2010). The Butte Lab has also been developing novel methods for comparing clinical data from electronic health record systems with gene expression data, as described in *Science* (2008), and it was part of the team performing the first clinical annotation of a patient presenting with a whole genome, as described in *Lancet* (2010). The Butte Laboratory currently has been funded by the Howard Hughes Medical Institute and the National Institutes of Health.

Lon Cardon, Ph.D., joined GlaxoSmithKline (GSK) in 2008, initially as head of genetics, and now holds the position of head of alternative discovery and development, a pan-therapeutic division focused on nontraditional approaches for drug discovery and development. The unit takes on new diseases for GSK, such as ophthalmology and rare diseases; new modalities, including gene therapy, stem cells, and oligonucleotides; and bespoke academic and biotechnology partnership models. Prior to join-

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ing GSK, Dr. Cardon was a senior academic in the United Kingdom and the United States, as professor of bioinformatics at the University of Oxford until 2006 and then as professor of biostatistics at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle. He received his Ph.D. training from the Institute for Behavioral Genetics at the University of Colorado and conducted his postdoctoral research in the Department of Mathematics at Stanford University. He has received a number of scientific awards, including election to the United Kingdom's Academy of Medical Sciences in 2005. He has authored more than 200 scientific publications and 15 books and chapters.

Christine Colvis, Ph.D., joined the National Center for Advanced Translational Sciences (NCATS) in June 2012 to lead the National Institutes of Health (NIH)-Industry Pilot Program: Discovering New Therapeutic Uses for Existing Molecules, which tests a new model for public–private partnership collaborations, including template agreements to shorten the time it takes to establish collaborations between an academic institution and a pharmaceutical company and move more rapidly into the actual research. The pilot involves eight pharmaceutical companies that made 58 assets available for repurposing by the broader research community. Collaborations established between academic institutions and the company will test ideas for new therapeutic uses, with the ultimate goal of identifying promising new treatments for patients. Before joining NCATS, Dr. Colvis had been a program director at the National Institute on Drug Abuse (NIDA) beginning in 2001 and later its director of program integration. She led NIDA's management of the American Recovery and Reinvestment Act, which resulted in commitments of more than $300 million made by the Institute in 7 months. She has also been a leader and advisor for complex NIH programs, such as the molecular libraries and the NIH epigenomics programs. Before becoming a program director, Dr. Colvis had done a short postdoc at the National Eye Institute in its intramural program after receiving her Ph.D. from Oregon Health Sciences University in Portland.

Thomas O. Daniel, M.D., is executive vice president and president of research and early development at Celgene Corporation. Dr. Daniel has more than 2 decades of medical and pharmaceutical research leadership experience. He served as chief scientific officer and director at Ambrx Inc., a biotechnology company focused on discovering and developing protein-based therapeutics. As vice president of research at Amgen Inc., he was

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research site head of AmgenWashington and therapeutic area head of inflammation. Prior to Amgen's acquisition of Immunex, Dr. Daniel served as senior vice president of discovery research. At Immunex, he consolidated and built programs in oncology and vascular biology, advanced candidate therapeutics in those areas, and forged programmatic emphasis on antibody therapeutics. Dr. Daniel is a member of the Therapeutic Advisory Board of aTyr Pharma Inc. and is a director of Epizyme and Ferrumax. A nephrologist and former academic investigator, Dr. Daniel was previously the K.M. Hakim Professor of Medicine and Cell Biology at Vanderbilt University and the director of the Vanderbilt Center for Vascular Biology. He conducted research in the Howard Hughes Medical Institute at the University of California, San Francisco. He earned an M.D. from University of Texas, Southwestern, and completed a medical residency at Massachusetts General Hospital.

Harry (Hal) C. Dietz, III, M.D., is Victor A. McKusick Professor of Pediatrics, Medicine, and Molecular Biology and Genetics in the Institute of Genetic Medicine at the Johns Hopkins University School of Medicine. He is also an investigator in the Howard Hughes Medical Institute. His undergraduate training in biomedical engineering was performed at Duke University, and his M.D. degree was received from the Health Sciences University of Syracuse. Clinical and research training in pediatrics, pediatric cardiology, and genetics occurred at Johns Hopkins University School of Medicine. Dr. Dietz heads a multidisciplinary clinic for the diagnosis and management of individuals with heritable forms of cardiovascular disease, with a special emphasis on Marfan syndrome and related connective tissue disorders. He is director of the William S. Smilow Center for Marfan Research, a group of dedicated molecular biologists focused on improvement of the lives of individuals with Marfan syndrome and related disorders through the development of novel diagnostic and treatment strategies. Dr. Dietz has received multiple prestigious awards, including the Curt Stern Award from the American Society of Human Genetics and the Taubman Prize for excellence in translational medical science. He is an inductee of the American Society for Clinical Investigation, the American Association for the Advancement of Science, the Institute of Medicine, the Association of American Physicians, and the National Academy of Sciences.

Don Frail, Ph.D., is the vice president of science with AstraZeneca (AZ). He leads the science group in the New Opportunities iMed, which

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seeks new opportunities complementary to AZ core areas through drug repositioning and open innovation partnerships. Recently, the team implemented groundbreaking partnerships with the United Kingdom's Medical Research Council and the National Institutes of Health to collaborate with investigators to explore the use of AZ development compounds in new indications. Don recently coauthored the book *Drug Repositioning: Bringing New Life to Shelved Assets and Existing Drugs*. Prior to joining AZ, Dr. Frail held several leadership positions, including founder and chief scientific officer of the Indications Discovery Unit at Pfizer, head of Pfizer's St. Louis research and development site, vice president of biology for the St. Louis site, and head of discovery neurosciences in Pharmacia.

Geoffrey Ginsburg, M.D., Ph.D., is the founding director for genomic medicine at Duke University and assumed his current position in the Duke Institute for Genome Sciences & Policy in 2004. He is also the founding executive director of the Center for Personalized Medicine established in the Duke University Health System in 2010. He is currently professor of medicine and pathology at Duke University Medical Center.

While at Duke, Dr. Ginsburg has pioneered translational genomics, initiating programs in genome-enabled biomarker discovery, longitudinal registries with linked molecular and clinical data, biomarker-informed clinical trials, and the development of novel practice models and implementation research for the integration of genomic tools in heath care systems. With a strong commitment to interdisciplinary science, he has led projects to develop predictive models for common complex diseases using high-dimensional genomic data as well as collaborations with engineering groups to develop novel point of care sensors. His work spans oncology, infectious diseases, cardiovascular disease, and metabolic disorders, and his research is addressing the challenges for translating genomic information into medical practice using new and innovative paradigms and the integration of personalized medicine into health care. He is an internationally recognized expert in genomics and personalized medicine with more than 200 published papers and funding from the National Institutes of Health, the Department of Defense, the Defense Advanced Research Projects Agency, the Gates Foundation, and industry.

In 1990 he joined the faculty of Harvard Medical School, where he was director of preventive cardiology at Beth Israel Hospital and led a laboratory in applied genetics of cardiovascular disease at Children's Hospital. In 1997 he joined Millennium Pharmaceuticals Inc. as senior

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program director for cardiovascular diseases, and he was eventually appointed vice president of molecular and personalized medicine, where he was responsible for developing pharmacogenomic strategies for therapeutics as well as biomarkers for disease and the implementation of those biomarkers in the drug development process.

He has received a number of awards for his research accomplishments, including the Innovator in Medicine Award from Millennium in 2004 and the Basic Research Achievement Award in Cardiovascular Medicine from Duke in 2005. He is a founding member and former board member of the Personalized Medicine Coalition, a senior consulting editor for the *Journal of the American College of Cardiology*, an editor for the *HUGO Journal*, and an editorial advisor for *Science Translational Medicine*. In addition he is the editor of *Genomic and Personalized Medicine* (Elsevier), the first edition of which was published in 2009.

He has been a member of the Secretary of Veterans Affairs Advisory Council on Genomic Medicine and the National Advisory Council for Human Genome Research at the National Institutes of Health (NIH). He is currently an international expert panel member for Genome Canada; a member of the board of external experts for the National Heart, Lung, and Blood Institute; a member of the Institute of Medicine's Roundtable on Translating Genomic-Based Research for Health; and a member of the external scientific panel for the Pharmacogenomics Research Network. He has recently been appointed to the advisory council for the newly established National Center for Advancing Translational Sciences at NIH. He has recently been nominated to serve on the World Economics Forum's Global Agenda Council on Personalized and Precision Medicine.

He received his M.D. and a Ph.D. in biophysics from Boston University and completed an internal medicine residency at Beth Israel Hospital in Boston, Massachusetts. Subsequently, he pursued postdoctoral training in clinical cardiovascular medicine at Beth Israel Hospital and in molecular biology at Children's Hospital as a Bugher Foundation Fellow of the American Heart Association.

Petra Kaufmann, M.D., M.Sc., is director of the Office of Clinical Research (OCR) at the National Institute of Neurological Disorders and Stroke (NINDS). In this capacity she oversees the clinical research programs funded by NINDS. The OCR fosters clinical research that increases our understanding of the cause, diagnosis, treatment, and prevention

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of neurological diseases and translates scientific discoveries into improved therapies for people living with neurological diseases worldwide.

Prior to joining NINDS, Dr. Kaufmann was a tenured associate professor of neurology at Columbia University in New York City. She earned her medical degree from the University of Bonn, Germany, and a master of science degree in biostatistics from Columbia's Mailman School of Public Health. She completed an internship in medicine at St. Luke's/Roosevelt Hospital in New York City and trained in neurology and clinical neurophysiology at Columbia University. She did a postdoctoral fellowship in molecular biology of mitochondrial diseases at Columbia's H. Houston Merritt Center for Muscular Dystrophies and Related Diseases. While on the faculty of Columbia University, she worked clinically in the neuromuscular division, the electromyography laboratories, and the pediatric neuromuscular clinic. Her research focused on the clinical investigation of spinal muscular atrophy, amyotrophic lateral sclerosis, and mitochondrial diseases.

Gabriela Lavezzari, Ph.D., M.B.A., joined P*h*RMA in July 2012 as assistant vice president, scientific affairs. In this role Dr. Lavezzari is the primary staff lead for a variety of strategic initiatives aimed at establishing P*h*RMA as a valuable source of scientific expertise in innovative biopharmaceutical research and development within the Scientific & Regulatory Affairs (S&RA) division of P*h*RMA. Dr. Lavezzari brings to P*h*RMA more than 10 years of combined research experience in the government and industry, with multidisciplinary expertise in personalized medicine.

Prior to joining P*h*RMA, Dr. Lavezzari served as director of extramural development at the Medco Research Institute, a subsidiary of Medco Health Solutions, where she led clinical utility and cost-effectiveness research to create value-based reimbursement decisions in a variety of different therapeutic areas. Prior to Medco, Dr. Lavezzari spent a few years at Theranostics Health, a proteomic-based diagnostics company where she led the laboratory operations and the oncology product development. Prior to Theranostics, Dr. Lavezzari worked at Social Scientific Systems, where she provided scientific support to and managed multiple AIDS clinical trials group, laboratory science, laboratory technical, and specialty laboratory committees, subcommittees, and working groups.

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In addition to her experience in industry, Dr. Lavezzari spent almost 6 years in research at the National Institutes of Health and at Georgetown University, where she completed her postdoctoral training.

Dr. Lavezzari received her Ph.D. in biological sciences from the University of Milano (Italy) and received her M.B.A. from the New York Institute of Technology.

John C. McKew, Ph.D., has been branch chief of the Therapeutic Development Branch at the National Institutes of Health (NIH) Center for Translational Therapeutics (NCTT) and the director of chemistry for the NCTT. His responsibilities include developing the Therapeutics for Rare and Neglected Disease Program and the Bridging Interventional Development Gaps Program (formerly the NIH-RAID Program). Both of these programs focus on novel public–private partnerships to advance collaborative drug discovery projects through pre-clinical development into early clinical development. Prior to joining NIH, Dr. McKew held a director-level position at Wyeth Research, and he began his career at Genetics Institute in Cambridge, Massachusetts, spending a total of 17 years between the two. At Wyeth he led a chemistry group to identify promising compounds for cardiovascular, musculoskeletal, and metabolic disease therapeutic areas. Prior to that, Dr. McKew spent 10 years working in the inflammation therapeutic area, with his work resulting in multiple compounds entering clinical evaluation. His research interests include rare and neglected diseases, medicinal chemistry, synthetic methodology, and tool compounds to probe biology. These interests have resulted in more than 20 publications, 10 granted U.S. patents, and multiple podium presentations. Dr. McKew also enjoys sharing his passion for science with others. This has prompted him to become course director and lecturer in GMS PM 881, Drug Discovery and Development, a graduate-level course in the Department of Pharmacology and Experimental Therapeutics, which resulted in his appointment as an adjunct associate professor at the Boston University School of Medicine. He has also taken an active role in the Northeastern Section of the American Chemical Society and has served as the chair-elect, chair, and the immediate past chair. Dr. McKew graduated from the State University of New York at Stony Brook with B.S. degrees in chemistry and biochemistry. He completed his Ph.D. in organic chemistry at the University of California, Davis, and held postdoctoral research positions at the University of Geneva and Firmenich, S.A.

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Michael A. Pacanowski, Pharm.D., M.P.H., is the acting associate director for genomics in the Office of Clinical Pharmacology at the U.S. Food and Drug Administration (FDA). Dr. Pacanowski received his Pharm.D. from the Philadelphia College of Pharmacy. He then completed clinical training at Bassett Healthcare in Cooperstown, New York, and a clinical research fellowship in cardiovascular pharmacogenomics at the University of Florida, where he also received his M.P.H. Dr. Pacanowski's expertise is in the area of genetic epidemiology and public health genomics, specifically as related to pharmacogenomic strategies in drug development and utilization. At FDA, he oversees review of investigational and new drug applications, contributes to regulatory policy development, and conducts research that supports FDA's core public health mission.

Aidan Power, M.B., B.Ch., M.Sc., M.R.C.Psych., has been vice president and head of PharmaTx Precision Medicine since January 2008. Precision medicine represents a synthesis of all the emerging technologies and operations (computational science, imaging, pharmacogenomics, metabolomics, proteomics, physiological measurements, and diagnostics) that form the scientific basis of emerging approaches to the development of personalized medicine. Graduating in medicine from University College Cork, Ireland, Dr. Power trained as a psychiatrist in England and joined Pfizer in the United Kingdom in 1993, working on the antidepressant sertraline and the antipsychotic ziprasidone. In 2002 Dr. Power relocated to Pfizer's global research and development headquarters in New London, Connecticut, where he headed clinical pharmacogenomics. For the past 3 years he has headed up molecular medicine (now PharmaTx Precision Medicine), which has been integrating molecular studies across disease areas as well as developing diagnostics for critical programs in the Pfizer product pipeline.

Arti Rai, J.D., the Elvin R. Latty Professor of Law, is an internationally recognized expert in intellectual property (IP) law, administrative law, and health policy. Ms. Rai has also taught at Harvard, Yale, and the University of Pennsylvania law schools. Her research on IP law and policy in biotechnology, pharmaceuticals, and software has been funded by the National Institutes of Health and the Kauffman Foundation. She has published more than 50 articles, essays, and book chapters on IP law, administrative law, and health policy. Her publications have appeared in both peer-reviewed journals and law reviews, including the *New England*

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Journal of Medicine, the *Journal of Legal Studies*, *Nature Biotechnology*, and the Columbia, Georgetown, and Northwestern law reviews. She is the editor of *Intellectual Property Law and Biotechnology: Critical Concepts* (Edward Elgar, 2011), the coauthor of a 2012 Kauffman Foundation monograph on cost-effective health care innovation, and the coauthor of a casebook on law and the mental health system.

From 2009 to 2010 she served as the administrator of the Office of External Affairs at the U.S. Patent and Trademark Office (USPTO). As external affairs administrator, Ms. Rai led policy analysis of the patent reform legislation that ultimately became the America Invents Act and worked to establish the USPTO's Office of the Chief Economist. Prior to that time, she had served on President-Elect Obama's transition team reviewing the USPTO. Prior to entering academia, Ms. Rai clerked for the Honorable Marilyn Hall Patel of the U.S. District Court for the Northern District of California, was a litigation associate at Jenner & Block (doing patent litigation as well as other litigation), and was a litigator at the Federal Programs Branch of the U.S. Department of Justice's Civil Division.

Ms. Rai regularly testifies before Congress and relevant administrative bodies on IP law and policy issues and regularly advises federal agencies on IP policy issues raised by the research that they fund. Recently her work has focused on advising the Defense Advanced Research Projects Agency and the National Human Genome Research Institute. She is currently co-chair of the IP Committee of the Administrative Law Section of the American Bar Assocation. She also serves as a member of the Institute of Medicine's Committee on Understanding the Global Public Health Implications of Substandard, Falsified, and Counterfeit Medical Products. In 2011 Ms. Rai won the World Technology Network Award for Law.

Ms. Rai graduated from Harvard College magna cum laude with a B.A. in biochemistry and history (history and science), she attended Harvard Medical School for the 1987–1988 academic year, and she received her J.D. cum laude from Harvard Law School in 1991. Ms. Rai's moot court team at Harvard Law School won best brief and team honors at the school's prestigious Ames Moot Court Competition.

Michael Ringel, Ph.D., is a partner and managing director in the Boston office of the Boston Consulting Group (BCG) and is BCG's global topic leader on research and development (R&D) productivity in biopharmaceuticals. Dr. Ringel has worked for a range of biotech and pharmaceutical

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clients, with the bulk of his work focused on R&D strategy, operations, and organization. He has worked on topics such as disease area strategy, transformation and process optimization, sourcing/partnerships, and organizational design as well as mergers and acquisitions/licensing strategy, valuation, and post-merger integration. Prior to joining the firm, Dr. Ringel worked in academia, pursuing research in theoretical population dynamics and conducting field experiments in the Amazon basin near Manaus, Brazil.

Dr. Ringel has a B.A. summa cum laude in biology from Princeton University, a Ph.D. in biology from Imperial College and a J.D. cum laude from Harvard Law School. He sits on the Board of The Nature Conservancy in Massachusetts.

Allen D. Roses, M.D., is president and chief executive officer of Cabernet, Shiraz, and Zinfandel Pharmaceutical Companies. Dr. Roses has established an international reputation for his work in pharmacogenetics, exploratory drug discovery, and clinical neuroscience. He founded Cabernet Pharmaceuticals in 2008 to provide pharmacogenetics (PGx) and project-management services to pharmaceutical and biotechnology companies, clinical research, and managed health care organizations and to academic institutions. He has formed a team of consultants with deep experience in the practical application of PGx to drug development.

Dr. Roses also serves in several capacities at Duke University: as Jefferson–Pilot Professor of Neurobiology and Genetics, as professor of medicine (neurology), as director of the Deane Drug Discovery Institute, and as senior scholar at the Fuqua School of Business. He recently returned to Duke after a decade-long career as a senior vice president at GlaxoSmithKline (GSK) and its corporate predecessor GlaxoWellcome (GW). Upon joining GW in 1997, he organized genetic strategies for susceptibility-gene discovery, pharmacogenetics strategy and implementation, and integration of genetics into medicine discovery and development. Subsequently at GSK, he headed research in genetics, genomics, proteomics, and bioinformatics in support of the entire research and development pipeline. Among the specific activities of his group at GSK were proof-of-principle experiments using linkage-disequilibrium mapping to identify susceptibility loci for drug-associated adverse events. With respect to hypersensitivity to the HIV/AIDS drug abacavir, for example, GSK identified the HLA-*B5701 locus with candidate-gene analyses and then prospectively established the sensitivity (97 percent) and specificity (>99 percent) of this genetic risk marker.

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During his previous tenure at Duke, Dr. Roses was Jefferson–Pilot Professor of Neurobiology and Neurology, founding director of the Joseph and Kathleen Bryan Alzheimer's Disease Research Center, chief of the Division of Neurology, and director of the Center for Human Genetics. He was one of the first clinical neurologists to apply molecular genetic strategies to neurological diseases. His laboratory reported the chromosomal location for more than 15 diseases, including several muscular dystrophies and Lou Gehrig's disease. He led the team that in 1992 identified Apolipoprotein E (APOE) as a major, widely confirmed susceptibility gene in common late-onset Alzheimer's disease. Translation of these findings to metabolic-pathway analyses and drug discovery and development continued in GSK, leading to Phase 3 trials now under way to evaluate the drug rosiglitazone for the treatment of Alzheimer's disease.

Dr. Roses was a member of the science board of the U.S. Food and Drug Administration (FDA) between 2003 and 2007. He was a member of the board's Subcommittee on Science and Technology that in 2007 authored the report *FDA Science and Mission at Risk*. He continues to consult with FDA and other regulatory agencies in the field of pharmacogenetics and companion diagnostics.

Recently Dr. Roses described the association of a variable polyT repeat [rs10524523] with the age of onset distribution of Alzheimer's disease. The data enhanced the accuracy of the prior age of onset curves based solely on APOE genotypes (also developed by Dr. Roses at Duke in 1992). Shiraz Pharma was founded in 2009 to commercialize the intellectual property from this new discovery. Zinfandel Pharma was also founded in 2009 to plan and execute a prospective validation of the "523" diagnostic for predicting risk of Alzheimer's disease onset in the next 5 to 7 years for individuals aged 60 to 87 years. A combination diagnostic validation study and prevention (delay of age of onset) clinical trial in epidemiologic-selected populations is currently in progress, having completed a voluntary genomic data submission discussion with FDA regarding the design of the clinical trial. Five epidemiology-based recruitment sites for Caucasians without cognitive impairment have been organized and are piloting subject recruitment in order to decrease the recruitment time once the trial commences.

Larry A. Sklar, Ph.D., is principal investigator and director of the University of New Mexico (UNM) Center for Molecular Discovery for the Roadmap Molecular Libraries Initiative of the National Institutes of Health.

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He is Regents Professor of Pathology, Distinguished University Professor, Maralyn S. Budke Endowed Chair in Cancer Drug Discovery in the National Cancer Institute–designated UNM Cancer Center, and co-director of translational technology in the UNM Clinical and Translational Science Center. He has more than 360 publications and patents in leukocyte biology, molecular assembly in signal transduction, and cell adhesion as well as high-throughput flow cytometry for drug discovery and repurposing. He is co-inventor of the HyperCyt high-throughput flow cytometry platform and co-founder of IntelliCyt. Dr. Sklar received his Ph.D. in physical chemistry from Stanford University.

Simeon Taylor, M.D., Ph.D., received his education at Harvard University, from which he received a B.A. in chemistry, Ph.D. in biological chemistry, and an M.D. degree. He completed clinical training at Massachusetts General Hospital with a specialty in internal medicine and a subspecialty in endocrinology and metabolism. He joined the Diabetes Branch in the Division of Intramural Research at the National Institutes of Health (NIH) in 1979, where he rose to the position of branch chief, a position he held for 11 years (1989–2000). In addition, he served as director of the NIH Inter-Institute Clinical Training Program in Endocrinology and Metabolism (1995–1998). During his time at NIH, Dr. Taylor's research was directed toward elucidating the molecular mechanisms of insulin action and also toward understanding the causes of insulin resistance in human diseases such as diabetes and obesity. This work resulted in more than 200 publications in the scientific literature. Dr. Taylor's contributions have been recognized by several awards, including the Outstanding Service Award of the U.S. Public Health Service (1990) and the American Diabetes Association's Outstanding Scientific Achievement Award ("Lilly Award") (1992). In addition, he has served on the editorial boards of numerous journals, including the *Journal of Clinical Investigation*; *Journal of Clinical Endocrinology and Metabolism*; *Journal of Biological Chemistry, Endocrinology, Molecular Endocrinology*; and *Endocrine Reviews*. After 21 years at NIH, Dr. Taylor moved to Eli Lilly and Co., where he was a Lilly Research Fellow in the Department of Endocrine Research (2000–2002). In 2002 Dr. Taylor was appointed as vice president, discovery biology at the Hopewell, New Jersey, site of the Bristol-Myers Squibb Company, where he led drug discovery biology in cardiovascular and metabolic diseases (2002–2010). In addition, he served as co-chair of the cardiovascular and metabolic dis-

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ease strategy team (2002–2008) and currently serves as co-chair of the cardiovascular disease early asset team.

Sharon Terry, M.A., is president and chief executive officer of the Genetic Alliance, a network of more than 10,000 organizations, 1,200 of which are disease advocacy organizations. Genetic Alliance improves health through the authentic engagement of communities and individuals. It develops innovative solutions through novel partnerships, connecting consumers to smart services. Ms. Terry is also the founding chief executive officer of PXE International, a research advocacy organization for the genetic condition pseudoxanthoma elasticum (PXE). As co-discoverer of the gene associated with PXE, she holds the patent for ABCC6 and has assigned her rights to the foundation. She developed a diagnostic test and is conducting clinical trials. Ms. Terry is also a co-founder of the Genetic Alliance Registry and Biobank. She is the author of more than 90 peer-reviewed articles. In her focus at the forefront of consumer participation in genetics research, services, and policy, she serves in a leadership role on many of the major international and national organizations, including the Institute of Medicine (IOM) Health Sciences Policy Board, the National Coalition for Health Professional Education in Genetics board, and the International Rare Disease Research Consortium Interim Executive Committee, and she is a member of the IOM Roundtable on Translating Genomic-Based Research for Health. She is on the editorial boards of several journals. She was instrumental in the passage of the Genetic Information Nondiscrimination Act. In 2005 she received an honorary doctorate from Iona College for her work in community engagement; the first Patient Service Award from the University of North Carolina Institute for Pharmacogenomics and Individualized Therapy in 2007, the Research!America Distinguished Organization Advocacy Award in 2009, and the Clinical Research Forum and Foundation's Annual Award for Leadership in Public Advocacy in 2011. She is an Ashoka Fellow.

Weida Tong, Ph.D., is director of the Division of Bioinformatics and Biostatistics at the U.S. Food and Drug Administration's National Center for Toxicological Research. He also holds several adjunct positions at universities, including that of associate professor at the University of Medicine and Dentistry of New Jersey. His division at the Food and Drug Administration (FDA) develops bioinformatic methodologies and standards to support FDA research and regulation and advances

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regulatory science and personalized medicine. The most visible projects from his group are (1) development of the FDA bioinformatics system, ArrayTrack™ suite, to support FDA review and research on pharmacogenomics; (2) leading the effort on the Microarray Quality Control Consortium to develop standards for translational science and personalized medicine; (3) development of liver toxicity knowledge base for drug safety; and (4) in silico drug repositioning. In addition, his group also specializes in molecular modeling and quantitative structure–activity relationships with specific interest in estrogen, androgen, and endocrine disruptor. Dr. Tong has published more than 180 papers and book chapters.

Christopher S. Watkins, Ph.D., is director of translational research and industry at the Medical Research Council (MRC) in the United Kingdom. The MRC is the largest public funder of biomedical research in the United Kingdom, with an annual budget of more than £750 million. The MRC supports and advances medical research in three main ways: by providing research grants and career awards to scientists in UK universities and hospitals, by funding research centers in partnership with universities, and through its own research facilities. Dr. Watkins' role is leading the development and implementation of the MRC's translational research and industry liaison strategies, which include activities such as the MRC/TSB Biomedical Catalyst, the multiple partner consortia in stratified medicine, and the recent MRC/AstraZeneca compound access initiative. After undergraduate and postgraduate studies at Imperial College, Dr. Watkins undertook postdoctoral research at the Royal Free Hospital, London, and the MRC National Institute for Medical Research. He has been engaged in research administration at the MRC head office since 1999, with previous roles including responsibility for the MRC's clinical trials portfolio and the MRC's Health Services and Public Health Research Board, before leading its translational research activities beginning in 2008.

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C

Statement of Task

An ad hoc planning committee will plan and conduct a public workshop to examine and discuss genomics-based approaches to repurposing existing or developing therapeutics. The goal of the workshop will be to assess the current landscape of drug repurposing activities in industry, academia, and government; examine enabling tools and technology; evaluate the business models and economic incentives; and advance discussions among a broad array of stakeholders that may include government officials, pharmaceutical company representatives, academic researchers, regulators, funders, and patients. The planning committee will develop the workshop agenda, select and invite speakers and discussants, and moderate the discussions. An individually authored summary of the workshop will be prepared by a designated rapporteur in accordance with institutional policy and procedures.

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D

Registered Attendees

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Private citizen

Naomi Aronson
Blue Cross and Blue Shield Association

Mike Bailey
Legg Mason

Ronald Bartek
Friedreich Ataxia Research Alliance

Andrea Bennett
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