DRUG DISCOVERY

Driving Drug Discovery: The Fundamental Role of Academic Labs

B. Michael Silber

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Academic labs have been responsible for virtually all of the basic science discoveries that translate into the discovery and development of innovative new medicines. There is a growing concern that large pharmaceutical and biotechnology companies are not able to sustain research pipelines that bring new compounds into drug development that translate into innovative new medicines, especially in areas with high unmet medical need. To address the needs of patients, caregivers, and society, academic labs have played and can continue to play an important role at one or more stages in the development of innovative medicines, both directly and through collaborations with researchers in pharmaceutical and biotechnology companies. Collaboration is in the best interests of patients and society if it accelerates the translation of basic science discoveries to new medicines that address unmet medical needs.

INTRODUCTION

Virtually all basic science research that contributes to the discovery of an innovative medicine occurs in academic labs and research institutes. An innovative medicine is a new chemical entity (NCE) that affects (or "hits") a previously unused drug target and is shown to be efficacious, safe, and approvable for a specific indication in a patient population. Alternatively, it may be an already approved medicine used for an unexpected indication or disease. Such innovative medicines are distinct from "copycat" drugs that hit precedented targets and work by the same mechanism of action (MOA) as other approved drugs.

A typical NCE R&D program is complex, lengthy, and multidisciplinary (Fig. 1). After potential drug targets—disease-associated structures or molecules—are identified, functional information is gathered to validate them as clinically relevant targets. A variety of methods are then used to identify or design molecules that will modulate that target. Using assays that have been developed and validated, often in a high-throughput format, chemical libraries are screened to identify "hits," which are compounds that produce the desired effect. If the assay is cell-based, a hit will be confirmed through retesting and demonstration that the effect is not simply a result of nonspecific cell death. Confirmed hits are then organized by chemical type to identify "leads" or chemical scaffolds for additional refinement. Leads are further evaluated by screening chemical analogs identified through catalog purchase or by a structure activity relationship (SAR) approach, during which a series of structurally related compounds are synthesized and tested. After potential leads have been selected, they are chemically optimized using SARs to develop potential NCEs that have good drug-like properties (appropriate solubility, ability to enter the cell, pharmacokinetics, toxicology, and delivery to target). Extensive preclinical studies in vitro and in animal models are then performed to test the safety and efficacy of these optimized leads to select those that may enter clinical testing. Phase I clinical trials are the first step for testing the safety and pharmacokinetics of a drug in humans, typically a small group of healthy volunteers. Phase II trials involve larger groups and aim to test dosing requirements and pharmacodynamic relationships in target patient populations. A successful outcome in a phase IIa trial would support proof of concept (POC), demonstrating that modulating the target leads to a desirable clinical outcome with an acceptable therapeutic index (safety-to-efficacy ratio). Phase III trials, which are randomized controlled trials involving large groups of patients, are done to determine definitively whether the drug is better than the current gold standard treatment, and are the most expensive and lengthy phase.

Institute for Neurodegenerative Diseases and Departments of Neurology and Bioengineering and Therapeutic Sciences, University of California San Francisco Schools of Medicine and Pharmacy, San Francisco, CA 94143, USA. E-mail: msilber@ind.ucsf.edu

Most reports indicate that, for an established company, an R&D program for the discovery, development, and approval of a drug hitting an unprecedented target requires up to 15 years and costs up to $1.5 billion or more, on average (*1*–*8*); recent analysis suggests that the cost may be much higher (*9*). However, most of the cost of developing one successful drug is attributable to the cost of accumulated failures, including wasted investment on targets and drugs before establishing efficacy and safety in POC phase IIa clinical trials (*10*). The cost of getting one NCE-based medicine to approval, ignoring the failures, is typically between $100 million and $300 million. The overall probability of getting a drug to the regulatory approval stage is at most 0.6% (for a new/unprecedented target) and 6% (for a fully precedented target) (*10*). The challenge is to find the one drug that is worth a substantial investment, without making large investments in targets and drugs that will ultimately fail.

EXAMPLE: HMG-CoA REDUCTASE AS A DRUG TARGET

Brown and Goldstein's identification of the crucial role played by 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase in the cholesterol biosynthetic pathway is an example of basic research performed in academic labs that had a profound effect on drug discovery (*11*), resulting in the selection of this enzyme as a target for drug discovery to lower levels of low-density lipoprotein cholesterol and treat atherosclerosis. Merck translated this basic research to discover, develop, and gain regulatory approval for lovastatin (Mevacor), the first approved HMG-CoA reductase inhibitor, as well as simvastatin (Zocor), a second-generation (more potent) statin drug. HMG-CoA reductase inhibitors have revolutionized the treatment of elevated blood lipid concentrations and atherosclerosis.

The confidence in rationale (CIR) and confidence in safety (CIS) in a target reflect the presence or absence of evidence that hitting a particular target results in an effective and safe desired endpoint in patients. The CIR and CIS would be high for a medicine that had been approved for a particular indication and would be low when there was no medicine for that target that had been shown to be effective, safe, and approvable. The CIR and CIS for HMG-CoA reductase had to be proven in the clinic. Inhibitors of this enzyme were effective and safe in

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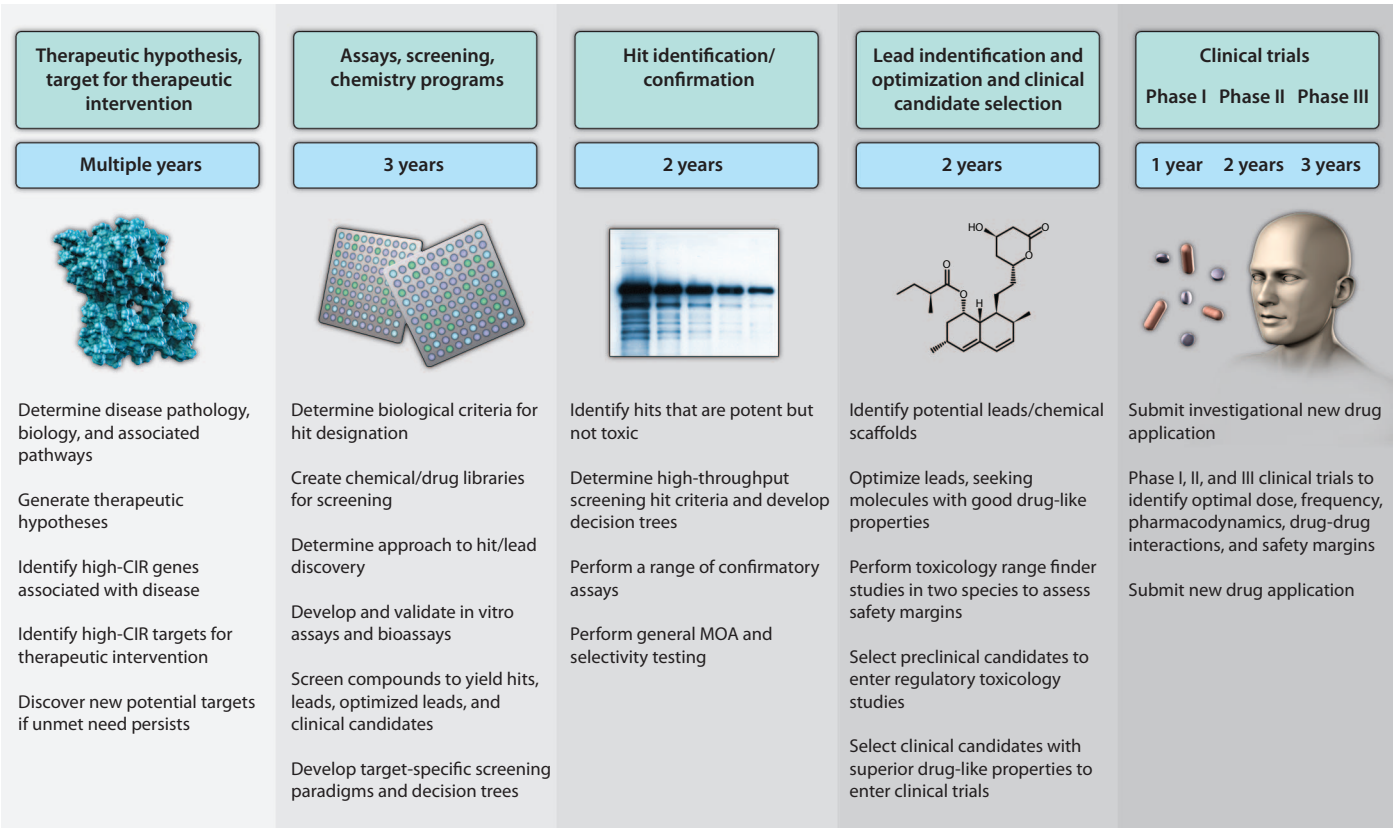

Fig. 1. Drug discovery R&D paradigm. For a more detailed version of this figure, see the supporting online material.

people, but the formation of liver tumors in rodents almost derailed the program and the target. In retrospect, the safety issues were rodent-specific, illustrating the challenge of overinterpreting safety findings in animals and translating them to humans, especially for new targets.

Merck had to persevere to bring lovastatin to patients, after which at least five other statins were approved, which differed in their potency, pharmacokinetics, and metabolism. One was subsequently withdrawn from the market because of toxicity. In 2009, statins were used to treat 30 million people and generate $30 billion in sales annually worldwide; one of them (atorvastatin) is the most popular medicine in the world. Some say that these statins are copycat drugs that, although chemically distinct, work by an identical MOA as lovastatin, providing only marginal improvements in efficacy, safety, or both.

SUCCESSES AND CHALLENGES FOR DRUG DISCOVERY EFFORTS

Basic research from academic labs and the efforts of industry have led to the discovery of scores of new therapies that effectively treat many diseases. As a result, conditions such as hypertension and atherosclerosis have been substantially blunted and delayed as causes of death. Osteoporosis and benign prostatic hypertrophy are now preventable or treatable. Symptoms of serious inflammatory diseases such as Crohn's can be substantially improved for many patients, something unheard of 20 years ago. Organ transplantation has become common partly because of the discovery of reasonably tolerated antirejection medicines. Psychosis, depression, and anxiety can be improved in a subset of patients. Many bacterial, fungal, and viral illnesses are treatable and in some cases curable; infection with human immunodeficiency virus and hepatitis C virus, both virtual death sentences even 15 years ago, can be controlled with mixtures of three to four medicines today. These are just a few examples of the results of pharmaceutical R&D in the past 50 to 60 years, driven by discoveries from academic labs.

New uses for drugs already approved for other indications have also been made first by academic labs. For example, Hauser *et al.* recently reported that rituximab (Rituxan) is efficacious in patients with multiple sclerosis, an indication not originally described by Biogen or Genentech as part of the approval of the drug for cancer (*12*).

Furthermore, new technologies discovered in academic labs can also inform drug discovery. Two crucial discoveries illustrate the promise and challenges of such technology. First, small interfering RNA (siRNA), discovered in academic labs, is already playing a vital role in the discovery and validation of targets (*13*, *14*), whereas therapeutics employing the technology are challenged by factors including drug delivery issues. Second, the use of embryonic stem cells and inducible pluripotent stem cells is contributing to the availability of cells for the development of in vitro models of disease and drug safety and the identification of new disease-related targets and biomarkers of drug response (*15*–*17*); their use in regenerative medicine still faces many challenges.

In spite of these discoveries, we lack effective therapies for many diseases, because we still don't understand enough about them. There remains a paucity of high-impact "druggable" targets: proteins or pathways that play key disease-related roles, which can be effectively modulated with small

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molecules. Overwhelming evidence indicates that in spite of unprecedented spending on R&D, research innovation and productivity continue to decline inside established pharmaceutical and biotechnology companies, which is a serious problem for the sustainability of the traditional R&D model. In contrast, major advances in basic science by academic labs continue to uncover critical knowledge about fundamental processes in health and disease. The challenge is translating the discoveries into medicines. The National Institutes of Health Roadmap and other initiatives have proposed innovative approaches to enhance the discovery of new medicines and facilitate more contributions by academic labs.

COLLABORATIONS BETWEEN INDUSTRY AND ACADEMIA

Recently, because of a dearth of research innovation and high-quality experimental candidates from discovery research pipelines, the strategy at most established pharmaceutical and biotechnology companies has changed. Now the aim is to create and sustain research innovation by increasing collaboration with academic labs and institutes and startup companies. Most companies are now focused on licensing new drug targets, assays and screening methods, and preclinical and clinical drug candidates, especially those at later stages of development (*18*). The established companies excel at later-stage processes in drug development that work well at large scale, such as phase II and III clinical trials and the scale-up of drug supplies for large-scale studies. These companies typically need to generate two to three new drug approvals per year to meet their stated growth objectives. None of them has ever approached this level of productivity.

WHY DRUGS FAIL

The root cause of drug attrition and failure is understood; approaches to reduce risk and cause attrition to happen earlier in the approval process when less money has been invested have been proposed (*10*). Such approaches might increase the rate of drug discovery and decrease its costs. Toxicity in animals is the largest cause of drug attrition during early research, when up to 70% of optimized leads never progress beyond dose range-finding or regulatory toxicology studies. Between such trials, animal pharmacology studies exploring efficacy, pharmacokinetics, and pharmacodynamics help define the doses and concentrations needed to achieve and sustain the desired response. However, animal models of many diseases (including cancer; obesity; diabetes; hypertension; and lipid, respiratory, cardiovascular, and neurological disorders) are frequently poor indicators of outcomes in patients and have led to false-positive conclusions about the validity, CIR, and CIS of a new target.

During drug development, most failures occur during phase II (when up to 70% of drug candidates stop their progression) and phase III (when 50% stop their progression) clinical trials. As a result, the drug and its target are often abandoned because of inadequate efficacy, unacceptable safety issues, or other reasons. In contrast, attrition during phase I, which is focused on the pharmacokinetics and safety of single and multiple doses (over 2 to 4 weeks), is generally less than 25%. Pfizer's withdrawal of torcetrapib from regulatory review at the end of a phase III trial is one example of a costly and late-stage failure. Torcetrapib was developed to inhibit cholesteryl ester transferase protein (CETP), a new drug target. Although Pfizer and others confirmed that CETP inhibitors lead to changes in blood lipid concentrations, most have also reported an associated increase in blood pressure and no change in atherosclerosis, and in a trial of a combination of torcetrapib and atorvastatin, an increase in adverse cardiovascular events and mortality. Torcetrapib was withdrawn after an investment of almost $1 billion in R&D. It is still unclear whether the hypertension was related to the target, the chemical structure of the drug, or both; it is also unclear why this effect was not observed preclinically. Although at least two companies (Roche and Merck) are still investigating CETP inhibitors in late-stage clinical trials, most have abandoned CETP as a drug target. This example emphasizes the high risk involved in pursuing a drug discovery R&D program and the risk of predicting efficacy and safety in humans from preclinical studies involving a new versus a precedented target.

In contrast, the major cause of attrition in drug discovery programs targeting clinically validated or precedented targets is too small a therapeutic index in animal models and/or in the intended patient population, a lack of sufficient differentiation from a marketed product, or both. Safety-related issues may be due to mechanism- or (chemical) structure-based toxicity. Overall, drug discovery programs that pursue precedented drug targets have at least a 10- to 20-fold higher probability of success than those that pursue new drug targets, while also having a much higher probability of finding a copycat drug with few to no innovative advantages (*10*). It is not always simple to define a drug as truly innovative or a copycat. For example, drugs that target peroxisome proliferator–activated receptor γ (PPARγ), which plays a role in glucose metabolism and fatty acid storage, have been developed to treat diabetes mellitus. The originally approved innovative drug was withdrawn from the market because of serious life-threatening effects. At least two additional drugs targeting this receptor were approved and could have been defined as copycats. Recent reports suggest that one may be much safer than the other and have already led to drug labeling changes. If one of these is ultimately withdrawn or its use curtailed, that would leave only one drug targeting PPARγ for the treatment of the disease. In this case, safety issues after drug approval weighed heavily and could ultimately result in the third (not the first) approved drug acting by this MOA actually remaining as an innovative treatment for the disease.

RELEVANT AREAS OF RESEARCH IN ACADEMIC LABS

Table 1 provides a small but representative sampling of some of the institutions where academic labs aim to contribute to one or more stages of the drug discovery process. These and other labs and institutes seek to (i) develop biochemical, cell, and other in vitro assays to screen small molecules; (ii) create peptide, fragment, small-molecule, and other libraries in search of hits, leads, and chemical scaffolds; (iii) develop moderate- to high-throughput screening platforms for drug discovery; (iv) understand SARs by studying analogs purchased from chemical catalogs and through synthetic chemistry; (v) pursue drug metabolism, pharmacokinetic, drug delivery, formulation, and toxicology studies both in vitro and in vivo to identify experimental compounds with good drug-like properties; (vi) develop animal models of disease to screen for pharmacologic and pharmacodynamic effects in vivo; and (vii) identify and test clinical candidates for phase I and II trials.

Although many academic labs pursue basic research that may yield potentially translatable discoveries, few do early drug discovery R&D, and even fewer pursue the identification of hits, leads, and optimized leads. An even smaller number are pursuing

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Table 1. Illustrative examples of academic labs that are contributing to the drug discovery process. IDs, infectious diseases; CVs, cardiovascular diseases.

		Areas of basic research and drug discovery															
Institution	Illustrative disease focus	Disease biology/ gene discovery	Chemical biology/ pathways	Disease target identification	Drug target identification	Drug target validation	Development of assays to screen compounds	High-throughput screening	Identification of chemical hits and leads	Lead testing in animal models	SAR/lead optimization	Preclinical candidate identification	Clinical candidate selection	Dose range-finding toxicology	Phase I	Phase II	Phase III
Broad Institute	Aging, cancer, diabetes, IDs	*	*	*	*	*	*	*	*	*	*	*	*				
Burnham Institute	Cancer, diabetes, obesity	*	*	*	*	*	*	*	*	*	*	*	*				
Cal Tech	Addiction	*	*	*			*	*									
Case Western Reserve	Cancer	*	*	*	*	*	*	*	*	*	*	*					
Columbia U.	Cancer, CVs, neurological diseases, IDs	*	*	*	*	*	*		*	*	*						
Duke U.	Aging, cancer	*	*	*	*	*	*	*	*	*	*	*	*		*	*	
Emory U.	Cancer, IDs, inflammation	*	*	*	*	*	*	*	*	*	*	*	*				
Georgetown U.	Cancer	*	*	*	*	*		*									
Harvard U.	Cancer, CVs, NDDs	*	*	*	*	*	*	*	*	*	*	*	*				
Memorial Sloan-Kettering	Cancer	*	*	*	*	*	*	*	*	*	*						
MIT	Aging, cancer	*	*	*	*	*											
Mt. Sinai	Cancer	*	*	*	*	*	*	*	*	*	*				*		
Northwestern U.	Cancer	*	*	*	*	*											
Ohio State U.	Cancer	*	*	*	*	*	*	*	*	*	*	*	*		*	*	
Purdue U.	Cancer	*	*	*	*	*			*	*							
Rockefeller U.	Cancer, obesity	*	*	*	*	*											
Scripps Institute	Cancer, CVs, immune diseases, IDs	*	*	*	*	*	*	*	*	*							
Stanford U.	Cancer, others	*	*	*	*	*			*	*	*	*	*				
U. of Chicago	Cancer	*	*	*	*			*			*						
U. of Cincinnati	Cancer, diabetes, obesity	*	*	*	*	*	*	*	*								
U. of Colorado	Pain/general	*	*	*													
U. of Georgia	Cancer, IDs	*	*	*				*									
U. of Kansas	Cancer	*	*	*	*	*	*	*	*	*	*	*	*	*			
U. of Michigan	Alzheimer's disease, cancer, diabetes	*	*	*	*	*	*	*									
U. of Minnesota	Cancer	*	*	*		*	*	*	*	*	*	*	*				
U. of North Carolina	Cancer	*	*	*		*	*										
U. of Pensylvania	Cancer	*	*	*	*	*		*	*	*							
U. of Pittsburgh	Orphan/neglected diseases	*	*	*	*	*	*	*	*	*	*						
U. of Texas Southwestern	CVs, neurogenesis	*	*	*	*	*		*	*								
U. of Utah	Cancer	*	*	*		*											
U. of Washington	Cancer	*	*	*	*												
U. of Wisconsin	IDs	*	*	*	*	*	*	*									
UC Berkeley	AIDS, cancer, diabetes, IDs	*	*	*	*	*	*										
UC Los Angeles	Aging, diabetes, obesity	*	*	*	*	*	*	*	*	*							
UC San Diego	Pediatric diseases	*	*	*	*												
UC San Francisco	Cancer, CVs, immune diseases, IDs, metabolic diseases, NDDs	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	
UC Santa Cruz	Cancer, viral	*	*	*													
Vanderbilt U.	Cancer, obesity	*	*	*	*			*	*								
Washington U.	Aging, cancer	*	*	*	*	*											

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clinical candidates for phase I and II trials or actually performing these trials. Therefore, very few academic labs are pursuing the entire drug discovery process from bench to bedside. Nevertheless, the potential opportunity for academic labs to translate their basic science discoveries to the drug discovery process has never been higher.

Because of advances in robotics, fluidics, miniaturization, high-speed chemistry, bioinformatics, high-throughput screening assay formats and detection systems, and data mining techniques, academic labs and institutes may have the opportunity to create and screen libraries of compounds in search of hits and leads and participate in the early stages of drug discovery. Medicinal chemistry; SAR-related work; studies involving pharmacokinetics, drug metabolism, drug formulation, and toxicology; and clinical trials are still often rate-limiting for academic labs. In contrast to established pharmaceutical companies where many diseases and drug discovery programs are pursued, academic labs generally focus on one disease area.

INNOVATIVE WORK ON DRUG DISCOVERY AND DEVELOPMENT IN ACADEMIC LABS

Many academic labs are currently involved in gene discovery and attempting to link genes and proteins to disease. Some are also involved in developing and using chemical biology approaches and attempting to apply these to drug discovery programs. For example, researchers at the Broad Institute are using an innovative chemistry approach called diversity-oriented synthesis (*19*). In this approach, chiral, natural product–like molecules are made efficiently, providing access to all of the stereoisomers of a given compound. Many of these molecules will not be druglike in composition or physical properties, but they will have potential for yielding useful design information for compounds that could have druglike properties. Investigators at the Scripps Research Institute are designing, synthesizing, and evaluating α-helix mimetic libraries targeting protein-protein interactions (*20*). Similarly, scientists at the University of Wisconsin are synthesizing new structures with beta peptides that have antimicrobial properties (*21*). Additionally, the University of California San Francisco (UCSF) is involved in gene discovery, disease biology, chemical biology, and target identification for a large number of diseases. The Institute for Neurodegenerative Diseases, based at UCSF, is one of the few institutions in the United States focused on the entire drug discovery process. It aims to discover new medicines for neurodegenerative diseases (NDDs), performing steps from the hypothesis-generation stage to POC phase II clinical trials, with special emphasis on innovative targets and indications in which CIR and CIS may be high. NDDs such as Alzheimer's disease, Parkinson's disease, frontotemporal dementia, and prion diseases such as Creutzfeldt-Jakob disease have proven an especially difficult class of disorders to treat.

CHALLENGES OF DRUG DISCOVERY FOR NEURODEGENERATIVE DISEASES

It is disappointing that the pharmaceutical industry has been so unsuccessful in developing drugs to treat neurological or NDDs (*22*–*25*), but perhaps this should not be surprising. The development of drugs to treat brain diseases is difficult: Only about 200 (or 10%) of the approximately 2000 drugs approved by the U.S. Food and Drug Administration (FDA) target brain disorders, primarily pain, depression, psychosis, and epilepsy; many if not most are copycat medicines. Less than 20 of the drugs are approved for the treatment of NDDs. Many are targeting precedented targets yielding copycat drugs; none have shown disease-modifying properties. New targets with high CIR and CIS are needed to ensure that we find new, effective, and safe medicines for these NDDs.

In addition to all of the usual causes of attrition, the difficulty of discovering medicines for brain diseases is compounded by the fact that effective drugs must in general cross the blood/brain barrier (BBB) to achieve and maintain effective drug concentrations. It has been estimated that less than 1% of approved drugs achieve significant concentrations in the brain, possibly because they were not originally designed to have suitable physicochemical properties amenable to crossing the BBB or are substrates for the P-glycoprotein efflux pump that transports drugs out of the brain (*26*).

RECOMMENDATIONS FOR ACADEMIC LABS

Industry tends to devote substantial resources to developing drugs that hit precedented targets, often leading to copycat drugs. Johnston and Hauser reported in 2006 that of the 22 drugs approved by the U.S. FDA in the 5 prior years for neurological indications, 17 were essentially copycat drugs (*27*). All of the top 10 best-selling drugs on the market at that time were copycats. They further reported that not a single drug used to treat neurological disease was approved in 2005 that acted by a new MOA. Academic labs that are doing basic science and are interested in applying their discoveries to drug discoveries should focus on innovative targets and therapeutics to find cures for diseases with high unmet medical need.

To be effective, academic labs must also use innovative science and technology to drive basic research discoveries that may play a role in the drug discovery process. Some may try to establish bench-to-bedside programs, but such attempts will be challenging for many reasons, including cost, space, and the need to coordinate across many scientific disciplines. In addition to basic research that directly drives drug discovery, there are many areas of technology that enable and increase the ultimate likelihood of success of drugs that will pass early discovery R&D milestones, including early predictors of human absorption, distribution, metabolism, excretion, and toxicology properties and in vitro tissue-specific toxicology assays. Furthermore, some enabling technologies can affect early drug development milestones, including (i) cell models of disease; (ii) chemistry and synthesis platforms; (iii) early predictors of human response, such as predictive cell-based models; (iv) predictive animal models of efficacy; (v) predictors of pharmacokinetics, drug transport, and toxicology; (vi) means of providing accurate readouts of both animal and human responses to therapeutics, such as molecular imaging and biomarkers; (vii) formulation and drug delivery methods; for example, for siRNA; (viii) approaches for drug delivery across the BBB and to specific tissues; and (ix) platforms for combination therapies. In almost all cases, academic labs are driving basic research and discoveries that are yielding critical breakthroughs in these enabling technologies, allowing them to be applied by industry.

Academic labs and institutes are actively engaged in basic research that has, and will have, major impact on the drug discovery process. Academic labs should avoid focusing on precedented targets or the discovery of copycat medicines. Rather, they should concentrate on basic research that may lead to the discovery of innovative targets and experimental medicines providing new therapeutic approaches. Keeping in mind the need to have good CIR and CIS, researchers

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should focus on bringing a drug candidate to phase IIa POC before substantial investments are made. Academic labs can also contribute substantially to basic research by developing and applying new technologies, such as the bioluminescence imaging that was developed for prion disease (*28*). Academic labs can, therefore, contribute to bringing innovative medicines to patients in various ways, a goal that may also be enhanced through collaboration with industry. Collaboration is in the best interests of patients and society if it promotes open and early publication of results and accelerates the translation of basic science discoveries to important new medicines addressing unmet medical needs.

SUPPORTING ONLINE MATERIAL

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Fig. S1. Drug discovery R&D paradigm.

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B. Michael Silber

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