

How Academia and the Pharmaceutical Industry Can Work Together

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Abstract

There is a long history of productive collaboration between biomedical scientists in academia and in the pharmaceutical industry. The primary beneficiary of this collaboration has been the public. Since the middle of the last century, marked advances in the treatment and prevention of disease have been driven by the translational research interactions across these two domains. But

now, at a time when collaboration between academia and industry should be accelerating based on past success, new technology, and ever-increasing need, numerous obstacles to effective collaboration have appeared. In this analysis, based on experience in both academia and industry, the author provides perspective on current obstacles to academic-industrial collaboration, followed by recommendations on how effective collaboration can be renewed and enhanced.

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Introduction

I want to thank Nicholas Hill, M.D., and the American Thoracic Society (ATS) for giving me the honor of the invitation to deliver the 2012 President's Lecture.

I have spent portions of my career in both academia and the pharmaceutical industry. Having done academic research, educated medical students, and participated in industry drug discovery and development efforts, I have developed ideas about how academia and industry should intersect. Here I share my thoughts about research collaboration between academia and the pharmaceutical industry.

A tradition of collaboration between academia and the pharmaceutical industry began with the era of modern therapeutics. Among many possible examples, there are two with great relevance to respiratory medicine. One is the discovery and clinical application of corticosteroids, recognized

with the award of a Nobel Prize to Philip Hench (Mayo Clinic), Tadeus Reichstein (Basel University), and Edward Kendall (Mayo Clinic) (1). The process for large-scale synthesis of cortisone for use in clinical trials was developed by a team at Merck led by Lew Sarrett (2). Another collaboration was initiated by Selman Waksman (Rutgers University), who won the Nobel Prize in 1952 for the discovery of streptomycin (3). He persuaded George Merck to establish a production plant that provided the streptomycin used by Sir Geoffrey Marshall (Medical Research Council, United Kingdom) in what is regarded as the first randomized clinical trial (4).

My colleagues and I would very much like to see this tradition of collaboration between academia and industry continued, as it is of great benefit to our patients. But the world has changed dramatically since the time when steroid hormones and antibiotics were being identified and tested

as therapies. Here I review current challenges facing industry, including our ongoing search for innovation to spur invention of new medicines and vaccines. I will explain the vital role academia plays in industry's mission to generate novel therapeutic agents, identify some obstacles to collaboration, and then describe new models for collaboration between the two domains.

Although I am aware that this journal has an international readership made up of individuals who are primarily either academically or industrially oriented, some of the proposals herein are directed specifically at American colleagues in academia.

The Nature of Drug Invention

The pharmaceutical industry lives and breathes translational research. There are

few organizations on the planet that can do what it has successfully accomplished repeatedly: transform knowledge of a potential drug target into a medicine for patients around the world.

What the pharmaceutical industry does is often referred to as drug discovery. But to me that conjures an image of two old prospectors in a mine. One's shovel hits something hard and he says: "C'mon over here Joe. Tell me if you think what I hit is a drug." In the past, natural molecules that became drugs were typically discovered serendipitously. But today drugs are invented: targets are selected, molecules synthesized, and their properties tested; then, after safety assessment, means for formulation and production are devised. There is a long cycle from idea to product. For comparison, it takes about three times as long to invent a drug as it takes to create an iPad or an iPhone (compare Figure 1 with Reference 5). It is estimated that the pharmaceutical industry spends about \$1 billion to \$2 billion to invent each new drug (6). Merck's annual investment in research and development (R&D) (7) is about eight times that of Apple (8) on a percent of revenue basis.

Outlined in Figure 1 is the process of inventing a drug. The first half of the process begins after years of basic science research in academia that leads to the identification of potential targets for drug invention (Figure 1). Once the drug target

is validated, industry spends the next 3 to 6 years screening compound collections or natural products, then synthesizing new molecules and testing them in biological assays that represent various aspects of healthy and diseased states. This includes *in vitro* testing and evaluation in animal models believed to be predictive of responses in human disease and extensive safety testing. If successful, an equal amount of time is taken evaluating promising molecules in clinical trials and preparing for their large-scale production. The failure rate at this stage is high; 80% of molecules that enter clinical testing do not become drugs. In addition, review by regulatory agencies typically takes 1 additional year. The total time required to invent a drug, from identification of the compound to full regulatory approval, is generally 10 to 15 years. With increasing frequency there also is a period of time in which clinical trials and active surveillance continue postapproval. The process is challenging intellectually, economically, organizationally, and emotionally. But when successful, lives are saved and suffering is alleviated. Figure 2 shows two examples of major drug inventions that resulted in great success on a public health scale.

The number of deaths related to cardiovascular disease in the United States was increasing in runaway mode up until the 1970s. Then, in the 1980s, a variety of

innovations, including the introduction of statins, reversed this trend. Since that time, cardiovascular mortality in the developed world has been in decline (Figure 2A).

Similarly, AIDS had become a deadly global epidemic by the mid-1990s. The invention of anti-HIV medicines by the pharmaceutical industry transformed this nearly universally fatal infection into a largely chronic disease that people in many parts of the world now live with while they return to work and lead nearly normal lives (Figure 2B).

Both of these examples are great public health victories resulting from collaborations between academia and industry. There are many more examples. Perhaps the best examples are vaccines, which have saved the lives of millions, mostly children, in the last 60 years. Few readers of this article have not benefited from a medicine or vaccine invented by the pharmaceutical industry in collaboration with academic colleagues.

The Pharmaceutical Industry Today

Figure 3 shows an important dynamic within the pharmaceutical industry over the last 3 decades. Annual expenditure for R&D relative to income from sales (bars in Figure 3) has increased nearly every year over the last 3 decades, but the return on

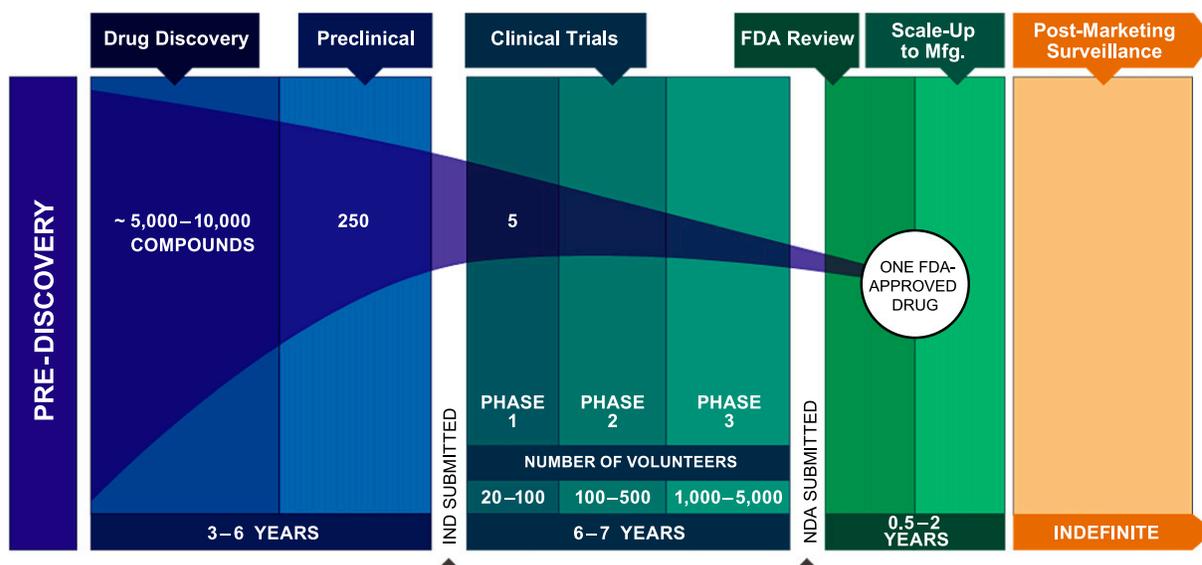


Figure 1. The research and development process. IND = Investigational New Drug Application; Mfg. = manufacture; NDA = New Drug Application. Adapted by permission from Reference 21.

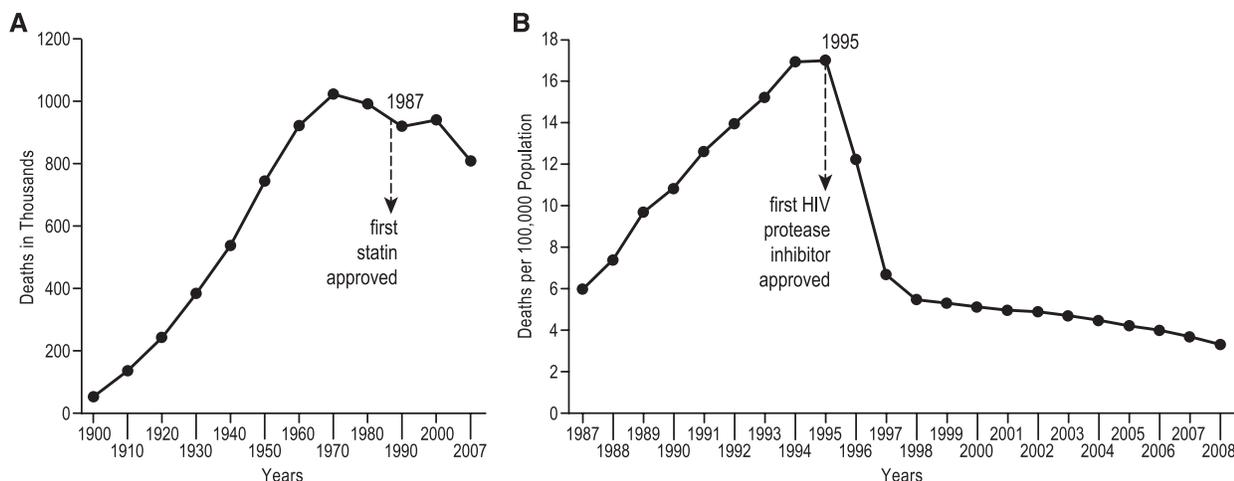


Figure 2. Invention of therapeutic drugs contributes to reduction in deaths from cardiovascular disease (A) and AIDS (B). A, Adapted by permission from Reference 22; B, Adapted by permission from Reference 23.

capitalized R&D investment (dotted line in Figure 3) has decreased. When I started working in the pharmaceutical industry in the early 1980s, \$1 invested in capitalized research returned about \$3 (in sales). This took 10 to 15 years, but there was a clear positive return on investment across the industry. Roughly 30 years later, the financial picture is very different: capitalized R&D returned only \$0.83 per \$1 invested. This is not a sustainable business model, and it has major implications for financing innovation to address unmet medical needs.

Another perspective on productivity is shown in Figure 4. It displays the productivity of three of the oldest and largest pharmaceutical companies—Merck, Lilly, and Roche—over the last 60 years. For all three companies, productivity (as

measured by approved new compounds) has remained generally constant at a rate of approximately one compound per company per year.

Consider the progress that has been made in our understanding of the complexity of biological systems and in the sophistication of our methodologies during the last 60 years. Compare it with the productivity of the pharmaceutical industry. Look back at 1950. A drug approved in 1950 was likely to have been conceived in the late 1930s and developed in the 1940s. In the 1940s, drug invention consisted of chemists making compounds and administering them to animals in hopes of detecting a physiological response. Thirty years later, in the 1970s and 1980s, we entered the period of having true molecular targets: enzymes, receptors, and channels. That time

is perceived as a golden age for the pharmaceutical industry. What happened to productivity at that time? There was no change compared with previous decades; each company continued to produce approximately one compound per year. Two more decades have passed. We are now in the era of “omics” (genomics, proteomics, etc.), yet the yield of new medicines remains approximately one compound per company per year.

The business model of the pharmaceutical industry is relentlessly challenging. Major products in companies’ portfolios today will be gone approximately 10 years from now because of patent expiry, so these companies need to reinvent themselves every decade. Today, pharmaceutical companies fund research through revenues derived from marketed drugs that are

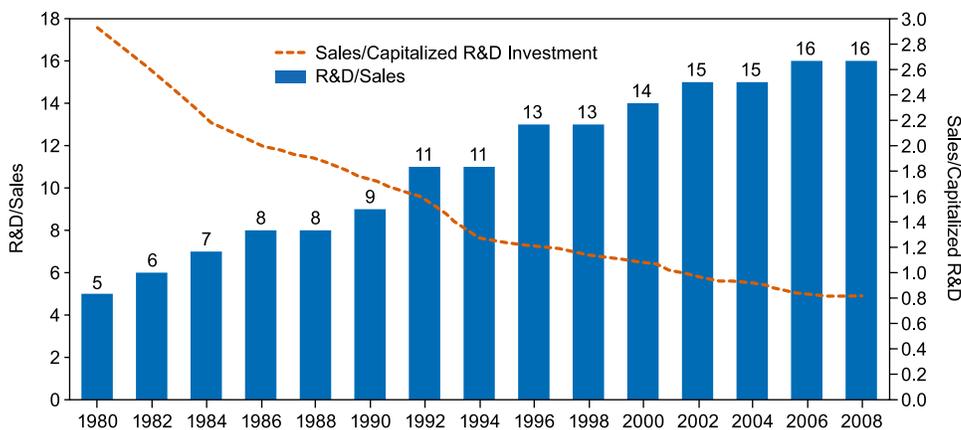


Figure 3. Research and development (R&D) spend/sales and sales/capitalized R&D for top pharmaceutical companies 1980–2008. Note: The capitalized R&D analysis is sales for a given year/R&D spend for 11 years (adjusted for inflation). Adapted by permission from Reference 24.

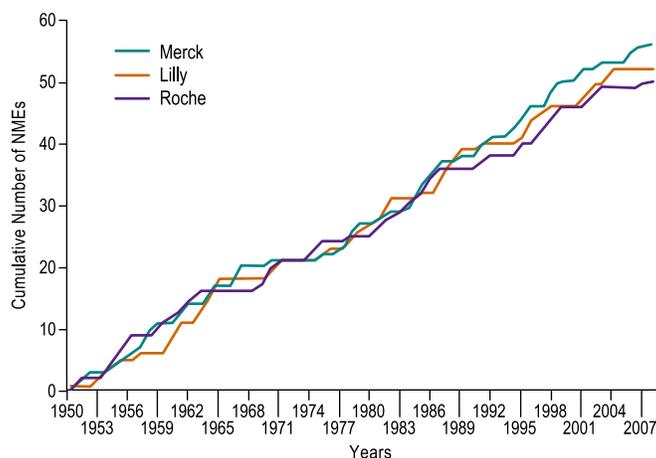


Figure 4. Cumulative new molecular entities (NMEs) produced by three large pharmaceutical companies over 57 years. Adapted by permission from Reference 25.

based on R&D initiated 15 to 20 years ago. Research decisions made by company leadership 10 to 15 years ago determine today's picture. And whatever position a company will occupy in the ecosystem 10 to 15 years from now will depend on decisions that company's leaders are making today.

The Rationale for Collaboration

The pharmaceutical industry's business model depends on innovation, but there is now a growing divide in innovation strategies within the industry. Some companies plan to invest in their own research engine at levels proportionately similar to the past; Merck is one such company. Others are backing away, not willing to take the risk inherent in long-term commitment to internal research and seeking innovation only externally. It will be years before we know the outcome of this big experiment. But despite different approaches to R&D, all major pharmaceutical companies continue looking to academia for sources of innovation beyond their own internal research engine.

Why is there a need for research collaboration between the pharmaceutical industry and academia? Academia and industry have substantive differences, but they share the common goal of improving the health of our patients. Industry relies on academia for basic research that identifies novel molecular targets and for clinical trials

that evaluate the efficacy and safety of inventions from industry. Industry does not have the vast basic research laboratories and hospitals that exist in academia. Conversely, academia is reliant on industry for the medicines and technologies that it uses to take care of patients. In addition, much of the research funding received by academia is part of a covenant with governments and the people that discoveries by academia will be, whenever possible, translated to improve health. In a way, academia and the pharmaceutical industry have complementary enterprises. Currently, a \$33 billion National Institutes of Health (NIH) budget funds mostly basic research, along with translational and clinical research. In contrast, research supported by industry is mostly clinical and translational, with less spent on basic research.

Over the last 2 decades, the relative amount of research supported by the NIH compared with that supported by the pharmaceutical industry has changed dramatically. In the early 1990s, the NIH and industry contributed approximately equally to supporting biomedical research; now the pharmaceutical industry spends 25 to 30% more on research than the NIH (9, 10). This also means there are now more research career opportunities in the pharmaceutical industry than in the past.

Not only is there a natural complementarity between academia and the pharmaceutical industry that should lead to collaboration, but collaboration is the law of the land, at least in the United States. The Bayh-Dole Act (P.L. 96-517, Patent and Trademark Act Amendments of 1980) is

more than 30 years old. It obligates academic institutions that receive federal funding for research to collaborate with industry if they make a discovery that could benefit the health of the American public. The legislation was crafted by Congress because many discoveries made through public support were left sitting on the shelf. Now the NIH clearly endorses collaboration with industry in its Clinical Translational Sciences Institutes and in the new National Center for Advancing Translational Sciences.

Impediments to Collaboration

Before focusing attention on mechanisms for improving research collaborations, I will address several barriers that must be overcome. First, I acknowledge that the interface between the pharmaceutical industry and practicing physicians has been problematic in the past and continues to be a source of tension and distrust. This can create an obstacle to research collaborations because some of the negative attitudes regarding this interface spill over, inappropriately in my view, into the arena of research.

Research-related relationships between the pharmaceutical industry and academia are already considerable and understood to be essential in translating the discoveries of basic biological research into new therapies. Organizations like Research America have documented the public's endorsement of such collaboration (11). But there is a dissonance in understanding the need for such collaborations and their endorsement. Attending a Jewish wedding, I realized that a scene before me (Figure 5) illustrated the state of academia-industry relations.

The community wants us to "dance together" (to collaborate) and be productive. But, as in the wedding scene, where the couple holds a handkerchief between them, we are not supposed to touch each other! I believe academia and industry need to find practical and durable solutions for the best and most appropriate ways to "dance together," to be productive without "touching."

Academia has had conflict of interest rules for decades, but the rules seem to be in a perpetual process of being rewritten. We need to be mindful that constant and unpredictable change creates a regulatory



Figure 5. A Jewish wedding: dancing together without touching.

vacuum. A prolonged process of modification without ultimate resolution creates continuing uncertainty, which keeps good people on the sideline. There is a second barrier to research collaborations. Each academic institution has its own policy concerning collaboration with industry, but the language of most policies is similar. Would it be possible for a group of universities, or pharmaceutical companies, or both, to create a universal template? Some would still need to be individually negotiated, such as royalty rates, payments, and other items that are specific to a particular collaboration. But the availability of a widely adopted template could increase efficiency and speed research.

A third barrier is the growing awareness of the irreproducibility of some data from academia (12, 13). This is a problem for all who work in basic research. Scientists at Bayer recently evaluated about 70 targets that they had worked on. They observed that for almost two-thirds of the targets, the initial basic research data that prompted interest could not be replicated (14). A few months later, Amgen corroborated this finding with its own observations (15). Venture capital firms do not start new companies until they have replicated relevant data (16). This problem needs to be addressed. I think the NIH and academic institutions should take responsibility for solving the problem. Those who do deal with it directly will be in an advantaged position to collaborate with industry.

A fourth barrier is “red tape.” Any successful translational research continuum

requires a strong clinical research component. But clinical research in certain parts of the world is in crisis. Between 2002 and 2007 there was a reduction by approximately one-half in the number of European products in clinical trials that had been developed in the United Kingdom (17). In 2004, 6% of patients participating in clinical trials globally did so in the United Kingdom. But by 2008, this had declined to 2 to 3% (17). It has been suggested that the reason is too much bureaucracy (17). In the United Kingdom it now takes almost 2 years from the time a decision is made to undertake a trial until the first patient enrolls. The United States is not far behind: we have long startup times, high dropout rates, and frequent failure to meet recruiting targets (18). Another discouraging observation is that much time and money is spent training clinical investigators, but almost half of them drop out after their first clinical trial (18), so most first-time investigators are last-time investigators. The environment can be so problematic and frustrating that even the NIH is offshoring clinical trials (18).

Figure 6 shows a dramatic example of the changing geography of clinical trials. The map shows the locations of sites for two of Merck’s Phase III clinical trials. One of these trials, performed in the 1990s, used 58 sites in 20 countries. Another similar trial, begun in 2009, used 387 sites in 40 countries, with proportionately many fewer United States sites.

The clinical trials laboratory is now global. I wonder how many American

academic institutions see this picture clearly. The U.S. biomedical research enterprise is the envy of the world; others are looking for every opportunity to replicate or usurp it. For example, when former President George W. Bush outlawed certain kinds of stem cell research, much of it migrated overseas to the United Kingdom, Singapore, and elsewhere, with astonishing speed. We need to realize that American academic research institutions and global pharmaceutical companies do not form a closed system. The pharmaceutical industry, which is sensitive to inefficiencies, inappropriate barriers, and practices and policies that slow entry of the first patient into a trial, is free and obliged to operate around the world.

How to Move Forward

I believe it is critically important for industry and academia to collaborate, because there remains so much unmet need in most areas of medicine. In thoracic medicine alone, we do not yet have ideal therapies for chronic obstructive pulmonary disease, interstitial lung disease, asthma, lung cancer, and pulmonary hypertension. Other areas of respiratory medicine having unmet needs include AIDS, multidrug-resistant tuberculosis, and a variety of “orphan diseases.”

Despite all the tensions, potential conflicts of interest, and regulatory issues that I describe above, industry-academic partnerships are at an all-time high. Figure 7 shows a timeline of collaborations established between January 2010 and February 2012.

Most of these collaborative arrangements differ from those of the past, which were large, programmatic collaborations embracing entire therapeutic areas, but which, for the most part, were unproductive. Instead, more focused and, in many ways, more thoughtful models are evolving. Joint steering committees decide what will be pursued and what will be postponed, and how much funding should be allocated. Instead of saying “here is a check for 3 years, come back and tell us what you found at the end of that time,” money is now being released based on milestones. Sometimes academia is being asked to “have some skin in the game” or defer rewards. And industry is bringing not only funding to collaborations but also core

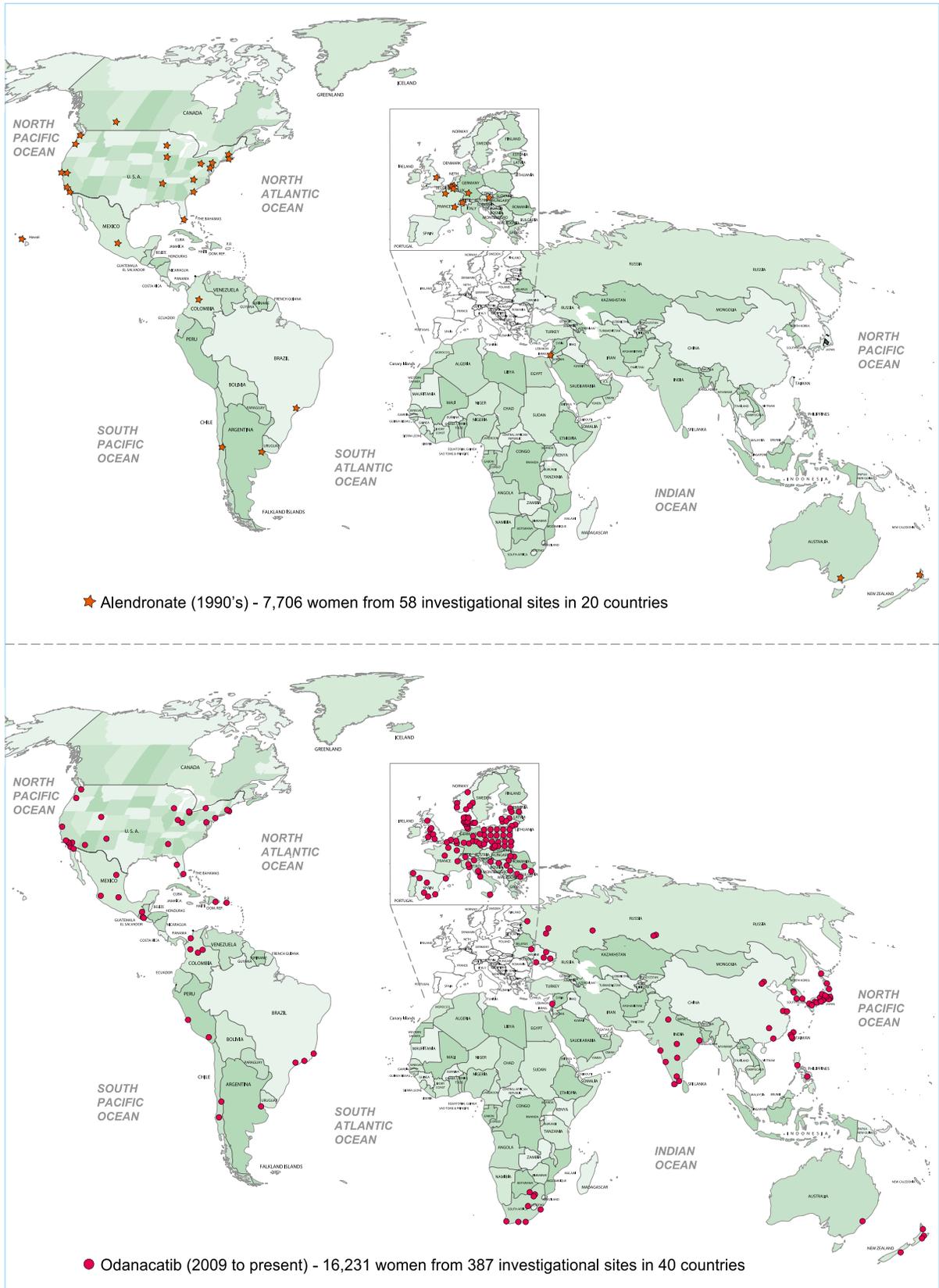


Figure 6. Clinical trials go global. *Red stars* identify cities where clinical trials of alendronate took place in the mid-1990s; *red dots* identify cities where clinical trials of odanacatib took place from 2009–2012.

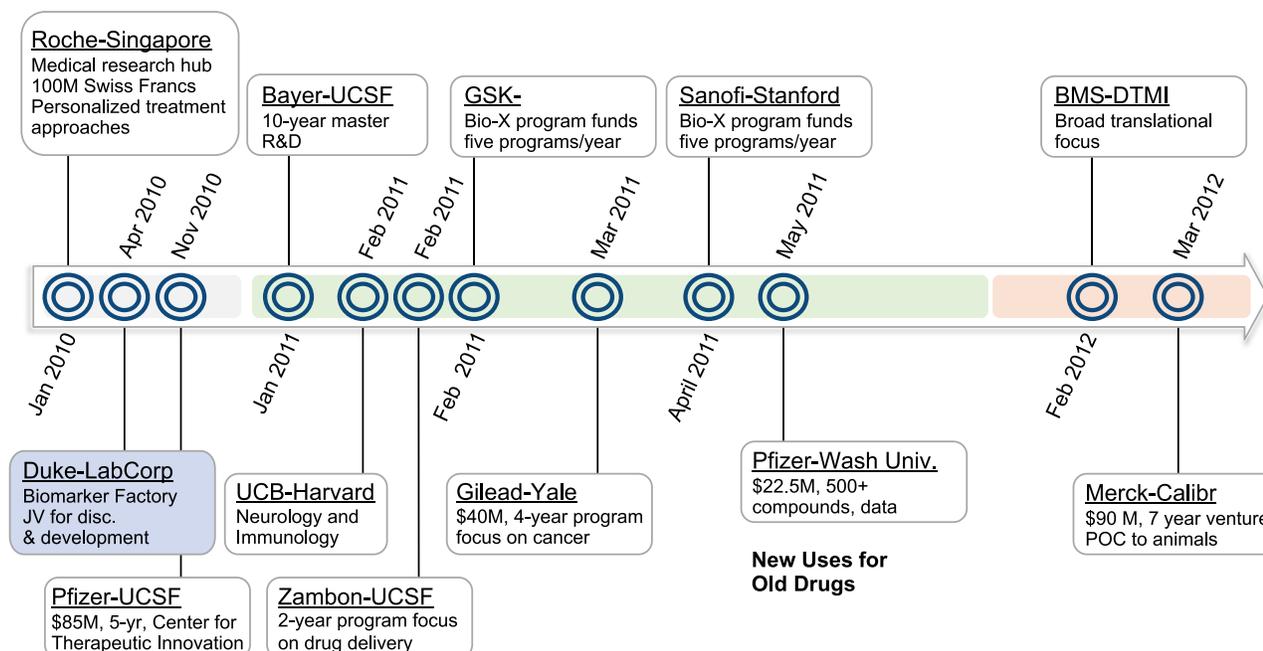


Figure 7. Recently formalized academia–industry partnerships. BMS = Bristol-Myers Squibb; Calibr = California Institute for Biomedical Research; disc. = discovery; DTMI = Duke Translational Medical Institute; GSK = GlaxoSmithKline; JV = joint venture; M = million; POC = proof of concept; R&D = research and development; UCB = University of California, Berkeley; UCSF = University of California, San Francisco; Wash Univ. = Washington University in St. Louis. (Provided by and used with permission of Dr. Robert M. Califf, Duke University Medical Center.)

resources like genetically altered mice, chemical libraries, and cutting-edge imaging methods.

For example, a new model that Merck has just initiated is the California Institute for Biomedical Research (Calibr). Calibr is an independent, not-for-profit organization started March 2012 in San Diego, California. Merck has made a \$92 million commitment to Calibr over the next 7 years. Calibr will provide academic collaborators with a range of industry infrastructure support, such as compound screening and medicinal chemistry. Any investigator, in any country in the world, can approach Calibr. If their project or lead or target is accepted, Calibr will collaborate to bring the concept to proof of principle. Proof of principle will trigger a decision by Merck to become a formal collaborator or to decline interest and return to the academic institution and Calibr the rights to the potential product.

Another example is Pfizer's Centers for Therapeutic Innovation (CTI) located in Boston, New York City, San Francisco, and San Diego and focused on the development of biologic therapies. CTI research staff includes both Pfizer employees and academic scientists, in some cases colocated in the same facility. In addition to financial resources, CTI provides

investigators access to select Pfizer compound libraries, proprietary screening methods, and antibody development technologies. CTI will enable academic career advancement through research and publication, while creating significant financial opportunities through milestones and royalties.

In yet another collaboration, this between Gilead Sciences and Yale School of Medicine, scientists from both organizations will work together to identify novel cancer therapies. Gilead is providing \$40 million in research support and basic science infrastructure development during the initial 4-year period of the collaboration. Gilead will provide a total of up to \$100 million over 10 years should the collaboration be extended through that time frame. Gilead will have the first option to license Yale inventions that result from the collaboration.

What can be done to improve the climate for clinical trials in the United States? I recently coauthored a paper for an Institute of Medicine report on clinical trials (18). We concluded that as the United States is reconfiguring the delivery of medical care under healthcare reform, we have an opportunity to include “clinical research” in the business plan of new

entities such as accountable care organizations. A small tax on healthcare-related revenues could help support this research. In addition, it is critical for medical students and trainees to be educated in the importance and conduct of clinical research.

The leadership of the ATS has been quite explicit in endorsing the views on collaboration between industry and academia espoused by the American Congress and the NIH. The Past-President of the ATS, Dr. Nicholas Hill, and his colleagues, have stated: “...successful collaborative efforts across academia, government, and industry benefit us daily.... We believe it is important for the ATS to rededicate itself to fostering a scientific culture that values inclusiveness—a scientific community of excellence” (19). We encourage other professional societies to adopt policies similar to that of the ATS.

New Opportunities for Collaboration

There are many opportunities for industry–academia collaborations in areas that are precompetitive (genomics, biomarkers,

animal models), in using the “big” databases that healthcare systems have and in the arena of diseases of the developing world. Collaboration will spur innovation in the development of new medicines and vaccines and in healthcare delivery. Merck regards itself as a global company, yet our products reach only 20% of the world’s population. No single sector working alone can bring the needed medicines, vaccines, delivery of care, and infrastructure to prevent and treat diseases in the remaining 80% of the world’s population; collaboration between academia and the pharmaceutical industry is absolutely necessary.

In education we also see opportunities for new kinds of collaboration. Merck has created courses in drug discovery and development, because most doctors have no idea how the medications they prescribe were created or what stands behind these medicines in terms of efficacy and safety data or evaluation by health authorities. A new opportunity in education will be to create training programs in regulatory science.

Francis Peabody said, “The secret in the care of the patient is caring for the patient” (20). I think the secret of a true partnership is acting like you have a true partner. This applies to both academia and

industry. We need to partner for the sake of modern medicine; we need to do it for the sciences fundamental to medicine; and most of all, we need to do it for our patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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