



PORTAL
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The Role of Public Funding in the Development of Transformative Drugs

Testimony of:

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Summary of major points

- Point 1

Dear Senator Warren and Congressman Cummings:

My name is Aaron Kesselheim. I am an internal medicine physician, lawyer, and health policy researcher in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital in Boston and an Associate Professor of Medicine at Harvard Medical School. I lead the Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research team studies the intersections between laws and regulations and the development, utilization, and affordability of drugs. I am glad to be able to address the Forum you have organized today about the role of public research funding in discovering our most transformative drugs.

The holy grail of drug research and development are transformative drugs--innovative drugs that have a groundbreaking effect on patient care. There has been a great deal written in the professional and lay press about a perceived decline in the number of new such products emerging from an increasingly cost-intensive drug development process. Recent advances in medical sciences, such as those based on genetics and molecular biology technologies, have not yet led to the large numbers of new treatments that had been expected.

To best encourage transformative new drugs, it is important to understand the sources of these products. But the process of developing therapeutics is poorly understood. A new medication or biotechnology drug usually emerges from a long course of research that starts with pivotal basic science discoveries, followed by translational and applied studies, product development research, and clinical testing. Academic and non-profit research centers are the focus of basic science work, with more than 75% of the work funded by the federal government, foundations, and internal sources.¹ Translational research converts basic science insights into practical applications. Pharmaceutical companies devote an enormous amount of funding to such

research, and National Institutes of Health (NIH) contributes over \$15 billion from its nearly \$30 billion dollar annual budget.² Translational research may occur at academic institutions, start-ups funded by venture capital, and large companies.³ Product development research, including bioavailability and trials to identify the efficacy and safety of a drug, is largely left to the private sector.⁴ Clinical trials encompass over \$20 billion in annual costs, over two-thirds of industry R&D expenditures, and are the fastest growing type of research investment.⁵

Yet not enough is known about the relative importance of these different stages, or of the contributions of members of the biomedical research community, in creating the most highly innovative products we have available for patient care. For example, the pharmaceutical industry has contended that its research leads to most new medicines,⁶ while arguing that public institutions like NIH support medical innovation “distinct from the process of drug development.”⁷ While the contribution of industry-based research to drug development remains vital,⁸ emerging research has also pointed to the valuable, yet under-recognized, role played by public investment. In a study of over 55,000 drug product patents, I found that patents originating in academic, non-profit, and government settings were more likely than industry-based patents to be cited by subsequent patents, a well-established marker of value and the importance of the innovation to the field.⁹

Public investment may be particularly important in the development of transformative “breakthrough” drugs.^{10,11} Sampat recently identified at least 72 drugs approved in the past 25 years whose patents point to involvement by academic inventors, including some of the most novel and clinically useful drugs produced during that time.¹² In the case of the chemotherapy agent paclitaxel (Taxol), the drug with the highest sales in the history of oncology, the General Accounting Office (GAO) estimated that through 2002, NIH invested \$484 million to fund Taxol-related research.¹³ Even after the NIH granted a development agreement to Bristol-Meyers Squibb (BMS), the GAO remarked that “NIH conducted most of the clinical trials associated with the drug. The results of these trials were critical for BMS to secure FDA’s approval.”¹⁴

So where do transformative drugs come from? To help answer the question, in 2012, I led a survey of clinical leaders in 15 different medical specialties from the top 30 academic medical centers in the US to determine what they thought were the most transformative drugs in their specialties to have been approved by the FDA in the past 25 years. From an initial list of over 400 products, the experts came to consensus over the top and second-most transformative product, leading to a final list of 26 drugs and drug classes judged to be transformative. We then examined the developmental history of each drug, based on primary sources, such as the patents, articles published in the peer-reviewed literature, and interviews with key innovators who contributed to the discovery and development of a given drug.

One of the major recurring themes in our results was the centrality of publicly-funded government- and academic-based innovators in the development work. We found that many of the transformative drugs were based on substantial drug discovery and development work performed at publicly funded research centers. This work was sometimes aided by industry collaborators who provided drug samples and other technical or scientific support. Once pivotal clinical trials began, both industry and academic physicians/scientists were almost always both closely involved.

One pattern of interaction involved academic scientists conceptualizing a therapeutic approach based on basic research about disease mechanisms and then demonstrating proof of concept for a given molecule. For example, Gaucher disease is a fatal genetic disease characterized by functional deficiency in the beta-glucocerebrosidase enzyme and accumulation of pathological proteins in the body. A replacement enzyme was first harvested from human placental tissue by researchers at the National Institutes of Health (NIH) and the Scripps Clinic, and tested in small numbers of patients in 1974.¹⁵ Genzyme started supplying

the enzyme in 1981, modifying it and ultimately initiating human clinical trials of the modified enzyme in 1989, leading to the 1991 approval of alglucerase (Ceredase). In the case of Epogen, the recombinant erythropoietin used to treat anemia, over 70 years elapsed between its discovery in the human body and its purification at the University of Chicago laboratory of Eugene Goldwasser in 1971, who also proved its effect in a small, unpublished clinical trial.¹⁶ With Goldwasser's help as a consultant, Amgen researchers cloned the gene over a decade later and produced large quantities of biologically active product, leading to its 1989 approval.¹⁷ Imatinib arose based on the work of Brian Druker at Dana-Farber Cancer Institute who set out to prove the concept that tyrosine kinase inhibitors that could inhibit the *bcr-abl* tyrosine kinase enzyme responsible for chronic myelogenous leukemia (CML). NIH-funded basic science research in the four decades leading up to Druker's work had identified protein translocations in CML, which pointed to protein kinase overactivity. When Druker applied selections from Ciba-Geigy's library of tyrosine kinase inhibitors for activity in his laboratory model, he identified imatinib as an active agent.¹⁸

In one variation on this theme, seminal scientific concepts first arose in university settings, and were later followed up in the industry setting. For example, the discovery of tamsulosin (Flomax) to treat benign prostatic hypertrophy was catalyzed in 1975, when Marco Caine and colleagues at Jerusalem's Hadassah Medical Center described the alpha-adrenergic receptors in prostate smooth muscle and reported that phenoxybenzamine, a nonselective alpha-adrenergic receptor antagonist, was effective in treating prostatic hypertrophy.¹⁹ Toichi Takanaka at Yamnouchi Pharmaceuticals then showed that the alpha-1-adrenergic receptor subtype controlled prostatic smooth muscle. In collaboration with Kazuki Kawabe at University of Tokyo, he searched for a new type of selective antagonist, leading to the initial

discovery of tamsulosin.²⁰ The discovery of SSRI antidepressants dates back to the 1960s, when Arvid Carlsson and his colleagues at the University of Lund in Sweden investigated serotonin's role in depression. They synthesized the first SSRI, zimelidine, and showed its selective effects on serotonin neurons in 1972 and its efficacy in treating depression shortly after.²¹ In parallel, starting in the early 1970s, a research team at Eli Lilly designed and tested fluoxetine (Prozac), which was the first SSRI to be FDA-approved in 1987.²²

The transformative medications in our sample were discovered at different institutions at different times during the 25-year study period, and represented a range of molecular structures. Yet we found three common themes that reveal drivers of successful drug innovation. First, many of the key insights for these transformative products began as publicly-funded basic research in university settings, and were then further developed through collaboration between public and private entities. Second, a substantial number rose to significance after being repurposed from targeting a different indication. Third, a high proportion was designed to treat rare diseases but nonetheless became transformative by opening up new therapeutic pathways or establishing new understanding of pathology.

Our review of transformative medications revealed the crucial role of innovative individual scientists, usually based in academic medical settings but also in some cases based in industry laboratories. Despite the widespread perception that major drug discoveries come from particular manufacturers, our review indicates that for most transformative drugs, the story is much more complex. These findings do not negate the often-vital role played by drug companies in the development of new drugs. In some instances, vital collaborations occurred between industry scientists and academic collaborators to move forward a seminal discovery

into product development. In a few instances, the pivotal insights that led to the creation of a transformative product did indeed arise wholly within the research enterprise of a single company. But our findings do not support the concept of the pharmaceutical industry as the single most important source of transformative drug development.

Correct attribution of source of the discovery of transformative drug products can have important effects on policymaking. The importance of academic centers in pharmaceutical development has been noted in other studies,²³ but is frequently challenged by those who argue that research within pharmaceutical companies is the main source of innovative drug products.^{24 25 26} This claim can justify high prescription drug prices, especially in the US, that will support a continuing supply of innovative products. While companies clearly play a major role in funding and conducting the clinical trials necessary to gain approval, the fraction of pharmaceutical sales that are devoted to total research and development is well under 20%,²⁷ with the amount spent on basic research that often generates truly innovative new compounds estimated to be far less than that.²⁸ Thus, it is not surprising that the insights underlying to the creation and transformative effect of certain drugs, such as the concept that TNF blockers can curb the inflammatory response diseases or that blocking angiogenesis can kill tumors and treat macular degeneration, arose in academic or government-sponsored settings. However, these concepts are not patentable, since ownership under patent law is generally reserved for products. The commercial development of products based on these insights, and the ownership of the resulting intellectual property, therefore often occurs within a pharmaceutical company, leading to subsequent misperception about the origins of these products.

Proposals to promote drug innovation often focus on providing greater incentives for drug producers by extending patents or reducing regulatory barriers for approval, rather than greater support for research that is so often the source of innovative therapeutic ideas. By contrast, reductions in NIH funding and in industry support for its own laboratories in recent years have threatened the funding streams that we found actually did support most transformative drug innovation. Venture capital funds supporting early-stage research are also limited because such work often does not yield immediately patentable products. Policies that support biomedical research, or those that foster idea development, such as open-source drug development, may be more powerful ways of producing more transformative drugs in the future. For example, the World Intellectual Property Organization Re:Search fosters shared intellectual property and resources among its public and private partners to target 19 neglected tropical diseases, malaria, and tuberculosis, to overcome the lack of economic incentive for companies to pursue these areas separately.²⁹ Other solutions that have been proposed include public-private partnerships, such as the NIH's Accelerated Medicines Partnership, an effort to combine companies and academic partners in processing mountainous data on biomarker drug candidates.³⁰

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