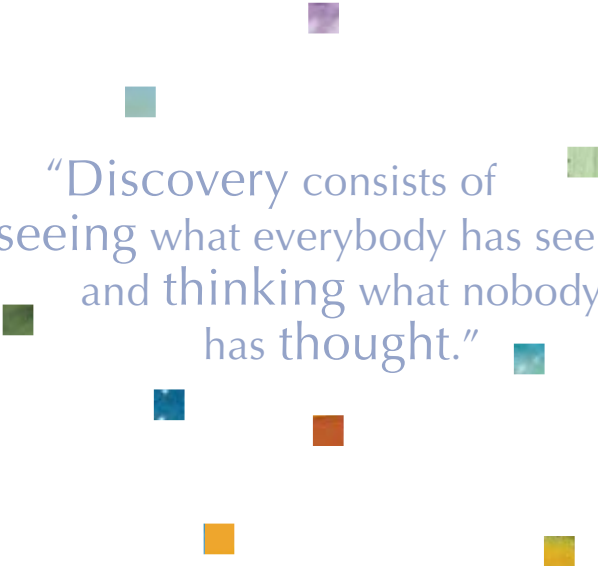


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“Discovery consists of
seeing what everybody has seen
and thinking what nobody
has thought.”

KAUFFMAN Thoughtbook 2009

Fourth in an ongoing series, the *Kauffman Thoughtbook 2009* captures what we are thinking, learning, and discovering about education, entrepreneurship, and advancing innovation. This collection of more than forty essays is written by the talented Kauffman Foundation associates, partners, and experts who are pursuing the principles and vision set by our founder, Ewing Kauffman.

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A Cure for the Drug Discovery Gap

FRANK L. DOUGLAS, Ph.D., M.D.

Partner, Pure Tech Ventures; Founder, MIT Center for Biomedical Innovation;

Senior Fellow, Ewing Marion Kauffman Foundation

Recently, the Kauffman Foundation launched a new focus on translational medicine—the process of turning scientific breakthroughs in the lab into new drugs and other patient therapies, often delivered by startup companies.

Despite the growing sophistication and promise of health care technology research, fewer and fewer breakthrough ideas are finding their way out of research institutions and into the hands of experienced clinicians and medical product development teams. Patients suffer as a result, because promising research and innovation are not being translated into new treatments.

Progress is being stifled by a crucial gap in the current research and development pipeline: expertise and funding for early-stage innovations. Many of the biotech startups, academic institutions, and government research centers that perform critical early-stage work do not have the resources to move their breakthroughs further along the commercialization pipeline. At the same time, large pharmaceutical companies and venture capitalists are reluctant to invest in early-stage research that lacks proven market potential and requires a longer period of time to produce returns on investment. And federal investment in medical research is tight—the 2008 budget for the National Institutes of Health is only about 1 percent higher than its 2007 budget.

In the following essay, Frank Douglas, a senior fellow at the Kauffman Foundation and a physician with extensive experience in pharmaceutical innovation and research, sheds light on the lengthy timeframe between breakthrough discoveries and new treatment options. He also explores one idea for catalyzing medical research to help bridge the gap between the laboratory and the bedside.

Several years ago, I coauthored (with Peter Tolman and Malcolm McKenzie of the strategy consulting firm, Monitor) an article for the medicine and business magazine *In Vivo*. Our article tackled the question of how to spend a billion dollars in research and development. At the time, the highest yearly R&D budget among pharmaceutical companies was \$547 million. And most companies, regardless of the size of their budgets, aspired to produce two discoveries capable of being approved by the FDA as a “new chemical entity” each year. More than ten years later, in spite of R&D budgets that routinely range between \$3 billion and \$8 billion a year, few companies have been able to reach this benchmark.

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This lack of productivity has resulted in a mixture of public consternation and more vocal calls for action by government agencies. The deciphering of the human genome eighteen years ago increased hope that a genomics revolution would accelerate the discovery of new drugs. Yet few genome-based drugs have made it to market.

Why this delay in getting potential therapies from the laboratory to the patient? Noted economist Manuel Trajtenberg described two timeframes that are crucial to realizing the potential of a fundamentally new technology. One is the time

from discovery to the horizon—when new products are actually developed. The second is the time from discovery to application—when a new concept can be turned into a tool that can be used to produce a commercial product. These timeframes are clearly evident in the use of new technologies to find novel drugs.

The horizon timeframe in drug discovery and development comprises several critical steps, including the selection of a target receptor or enzyme; the molecular validation of the relevance of that target to the disease; the identification of a lead compound that is selectively active against the target; the optimization of that compound through pharmacological, toxicological, and

New R&D Models Gaining Ground

The *In Vivo* article I authored with Tolman and McKenzie pointed out that the major companies pursued one of two R&D models, which we called “scale-based” and “capabilities-based.” Scale-based organizations sought to have all research and development disciplines at-scale in-house. Capabilities-based organizations sought to have research and early development at-scale in-house, but in-house late-stage development was restricted to critical capabilities, with other development work performed by Contract Research Organizations (CROs).

Today, most companies are moving away from a scale-based R&D organization and embracing a capabilities-based organization, for reasons including the overall cost of R&D; the growth of biotechnology companies, many of which do not have the resources and experience to perform the extensive late-stage clinical development programs that are needed for regulatory approval of a drug;

the proliferation of CROs; the rise of low-cost alternatives in India and China; and the increasing government-sponsored (NIH and FDA), academic-industry consortia to find biomarkers or develop special models that will improve the ability to predict efficacy and safety.

A potential third model is the “discovery cluster.” In this model, large pharmaceutical companies perform their discovery through loose consortia of academic and institute laboratories, and small biotech companies focused on technology platforms or therapeutic areas, each of which has common goals and specified deliverables for integration and further development by the large pharmaceutical company.

Capabilities-based R&D organizations and discovery clusters can improve the development of novel drugs, but they’re not sufficient to accelerate the horizon time.

human *in vivo* studies (conducted on living patients); the clinical proof of the concept in a target patient population; and, finally, the large clinical trials needed to demonstrate efficacy and appropriate safety (the final validation of the target) in patients. This process takes, on average, ten to thirteen years—and only then is the new therapy submitted to regulatory agents for marketing approval.

The application timeframe, on the other hand, can be as little as a few months from discovery to impact. For example, the decoding of the genome enabled the rapid growth of proteomics, the study of proteins, and metabolomics, which are integral to cell metabolism. Proteomics, genomics, and their application to systems biology are having a significant impact on identification and validation of new targets. Pharmacogenomics and pharmacogenetics are improving the understanding of patient susceptibility to specific pharmacological agents.

All of these “omics” are contributing to finding biomarkers that can potentially predict and monitor the efficacy or safety of any specific drug candidate. However, it will require the coordinated and simultaneous application of all of these technologies against a disease to significantly shorten the overall horizon time—the time it takes to create new therapies.

How can we facilitate a shortening of the horizon time?

What we need is a challenging, overarching problem that clearly requires the coordinated engagement of academia, large pharmaceutical companies, therapeutic- and technology-based biotechnology companies, and hospitals and specialized clinics—a challenge such as curing cancer.

Cancer has common features, but also requisite complexity because many mechanisms drive the disease. It also has a combination of genetic and environmental factors that contribute to its etiology or cause, as well as a high personal and societal burden. And, as yet, there are few adequate therapies for treating cancer.

We often hear officials and advocates talk about our nation's fight against cancer, but a potentially more effective solution would be to wage the fight in a state with the required medical-scientific infrastructure to accommodate it. A state such as Massachusetts, which has more than 300 biotech companies and startups, several

Translational Medicine Alliance Tackles Bench to Bedside Challenges

Overcoming the obstacles facing translational medicine requires cooperation among all major stakeholders—the medical product development industry, philanthropies and research-oriented nonprofits, academia, the investment community, and the federal government. In 2007, the Kauffman Foundation joined a host of organizations active in the field of translational medicine to launch the Translational Medicine Alliance. The goal of the Alliance is to tap into thought leaders' best ideas and develop an integrated strategy to support and advance the most promising technologies.

The Alliance's first national forum was held in September 2007 to facilitate discussions about translational issues and to discuss how stakeholders can work together to accelerate commercialization of medical products. Participants discussed the critical areas of funding, R&D collaboration, education, and institutional policy. They also examined specific translational issues in various therapeutic areas, as well as medical

devices, and new tools and technologies to facilitate research.

Through ongoing collaboration, the Translational Medicine Alliance seeks to build connections between stakeholders in the field, helping to raise awareness of the challenges faced in each sector (academic, corporate, nonprofit, government, etc.), while devising innovative solutions to overcome them. Members of the Alliance also will advocate for greater accountability from government and research institutions, to make the translation of breakthrough research into new therapies the benchmark of success. And the Translational Medicine Alliance will keep the most important stakeholders—patients—at the center of the discussion. The duty of everyone involved in translational medicine is to find creative and expeditious ways to save and improve patients' lives.

For more information on the Translational Medicine Alliance, visit translationalmedicinealliance.org.

renowned academic institutions and schools, renowned hospitals and clinical centers, and research centers of large pharmaceutical companies, would be an excellent candidate.

A real breakthrough in the horizon time for the cure of cancer could be achieved if, for example, Massachusetts became the “Cure Cancer within a Decade” state. It could do this by appointing a Cancer Czar who would bring together multiple organizations to work collaboratively to solve specific cancers. This would enable standardization of research methods and assays, and accelerate the adoption of, for example, personalized health records, and stratified or personalized medicine.

While we cannot predict the outcome of such a venture, it is reasonable to believe that a concerted effort, with a widely agreed-upon goal on a fixed timeline, would spur the kind of coordinated engagement necessary to accelerate the development of new treatments and finally bring the promise of genomic medicine to the patient’s bedside.