Institutional Innovations in Global Health: New Approaches to Neglected Diseases

Setting the Context

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Our current research and development system has worked successfully to generate innovation and treatments for diseases that affect large numbers of people in industrialized countries, such as heart disease, stroke, diabetes or cancer. Public and private actors in basic and applied research cooperate to generate scientific breakthroughs leading to new treatment candidates that can eventually be turned into drugs for a large variety of illnesses. Patients have access to these interventions through the health systems in their respective countries.

However, the system has failed to generate the necessary level of innovation in the treatment of diseases that either affect primarily the poor in developing countries, such as malaria and tuberculosis (commonly referred to as "neglected diseases"), or that affect very few people, such as Lou Gehrig's disease (an "orphan disease"). In each case, the dearth of lucrative markets has led to inadequate investment in development with respect to both basic and applied research.

In a nutshell, understanding of these diseases is either insufficient, or, where it has been achieved, it has not translated into tangible benefits for patients suffering from these illnesses. As a consequence, millions die every year.

In the past decade, a number of new approaches have emerged to overcome the challenges of neglected and orphan diseases. The novelty of these approaches lies in their models of cooperation, their work practice, and the incentives they create for actors in the public and private domains.

Three innovators will be present at this panel. The first two, Global Alliance for TB Drug Development (TB Alliance) and the Drugs for Neglected Diseases Initiative (DNDi), share missions to develop treatments for tuberculosis, malaria and other neglected diseases. These organizations rely on new forms of cooperation between public and private partners to identify and test promising drug candidates for the neglected diseases they target. Both organizations have already successfully brought new drugs to the market and are considered to be highly promising examples of the public-private partnership model in global health.

In contrast, Prize4Life pioneers another model that has been receiving increasing

attention in the biomedical domain: that of the inducement prize. Prize4Life targets an orphan disease of unknown cause, ALS (Lou Gehrig's disease). The organization's primary purpose is to induce scientific breakthroughs that could eventually lead to a treatment or cure for this devastating disease. Its strategy is to offer large prizes for defined scientific contributions to ALS research. Prize4Life's experience will have lessons for other health problems across the global health domain.

In this panel, we will examine how these innovators cover a range of basic research and discovery, and development and access to innovations in their respective domains. Among other topics, we will discuss how these approaches differ from earlier approaches to the problems they target, what larger institutional landscape these actors need in order to succeed, how policy makers can help ensure their success, and how these innovators can make sure that the fruits of their labors will actually become available to patients who need them.

William C. Clark is the Harvey Brooks Professor of International Science, Public Policy, and Human Development at the Harvard Kennedy School. Trained as an ecologist, his research focuses on the interactions of environment, development, and security concerns in international affairs. Clark is coauthor of *Adaptive Environmental Assessment and Management*, and coeditor of *Sustainable Development of the Biosphere*; *The Earth as Transformed by Human Action*; *Learning to Manage Global Environmental Risks*; and, *Global Environmental Assessments: Information and Influence*. Dr. Clark is a member of the U.S. National Academy of Sciences and co-chaired the National Research Council study on *Our Common Journey: A Transition toward Sustainability*. He chairs the environmental reporting program of the Heinz Center for Science, Economics, and the Environment, which produces a periodic report on *The State of the Nations Ecosystems*. Dr. Clark is a recipient of the MacArthur Prize, the Humboldt Prize, and the Harvard Kennedy School's Carballo Award for Excellence in Teaching.

New Approaches to Neglected Diseases

Global Alliance for TB Drug Development (TB Alliance): A Public-Private Partnership to Develop Accessible and Faster-Acting TB Medicines

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What was the problem?

Treatment for tuberculosis (TB) takes six to nine months to complete and requires that health-care workers directly observe patients taking their complicated four-drug regime. Because the treatment process is long and cumbersome, multidrug-resistant (MDR) and extensively drug-resistant (XDR) forms of tuberculosis are on the rise worldwide. Despite the clear need for faster and simpler TB treatments, there had been no drug development efforts for decades. Given the very high cost of developing new drugs, and the fact that TB overwhelmingly affects impoverished communities throughout the developing world, there was no incentive for the private sector to embark in TB drug development. The result was a barren pipeline and a world with no new antibiotics to fight the devastating epidemic.

What was the innovation?

In 2000, a group of scientists and physicians representing the public and private sectors from around the world, gathered in South Africa and signed the Cape Town Declaration creating the Global Alliance for TB Drug Development (TB Alliance). With seed money from the Rockefeller and the Bill and Melinda Gates Foundations, the TB Alliance, a not-for-profit corporation, set forth a new business model. Its aim was to produce a new, shorter, and more effective treatment for TB. Length of treatment must be two months or less and be available at an affordable price. The Alliance also committed to make the drugs accessible to those that needed them and to promote their adoption the field. By 2007, the TB Alliance had attracted over $200M in funding from governments and foundations. Using a virtual research platform, with a small staff and low overhead, the TB Alliance identified potential new TB drug candidates from private and public sources, in-licensed them, and developed or co-developed the drug candidates with partners worldwide. Because part of its mandate was to encourage others to embark upon TB drug development, the TB Alliance also invested in platform technologies and basic studies that were broadly disseminated, and served to inform the field.

What were the obstacles?

The obstacles were many and diverse. An early obstacle was overcoming skepticism from all sectors—industry, government, academia, national TB programs, funders, et cetera. There were technical obstacles, such as finding new chemical entities to test because many of the private-sector players had left the infectious disease arena, and much of the data on potential compounds was no longer accessible or available. As the organization grew and the compounds advanced through the drug development pipeline, new challenges arose, including finding appropriate clinical sites, understanding the regulatory hurdles for each country and mapping the value proposition for the best drug combinations, among others. Last, but not least, the difficulty facing all innovative organization models is long-term sustainability. While the TB Alliance is relatively inexpensive for a drug development enterprise, the costs are still high.

What were the results?

The TB Alliance now has the largest TB drug pipeline in history, with two potential drug candidates already in clinical trials. This provides hope for millions of people with TB around the world. Further, the TB Alliance has proven that this new business paradigm can work. Now called the PDP (Product-Development-Partnership) model, it allows for brisk development of drugs for which there is no market pull, using the highest level of regulatory and safety standards. The PDP model also required trailblazing agreements with collaborators worldwide, some of which have won awards for their innovative approaches. These agreements have identified ways in which the public and private sectors can work together in fighting disease in the developing world. Finally, the existence of the TB Alliance catalyzed change in the TB landscape, bringing new corporate, academic and government players into the field so that a new TB drug development strategic plan was adopted and incorporated as part of the Global Plan to Stop TB, launched in Davos, Switzerland, in 2006.

Dr. Maria C. Freire is President of The Albert and Mary Lasker Foundation. Prior to her appointment at the Lasker Foundation, Dr. Freire was the Chief Executive Officer and President of the Global Alliance for TB Drug Development. An internationally recognized expert in technology commercialization, Dr. Freire directed the Office of Technology Transfer at the US National Institutes of Health (NIH) from 1995 to 2001. Before her position at the NIH, Dr. Freire established and headed the Office of Technology Development at the University of Maryland at Baltimore and the University of Maryland, Baltimore County. Dr. Freire trained at the Universidad Peruana Cayetano Heredia in Lima, Peru. She received a doctorate in Biophysics from the University of Virginia and completed post-graduate work in immunology and virology at the University of Virginia and the University of Tennessee, respectively. She is the recipient of a Fulbright Fellowship as well as two US Congressional

Science Fellowships. Dr. Freire has been active on a number of national and international boards and committees. She is the recipient of numerous awards, including the US Department of Health and Human Services Secretary's Award for Distinguished Service, the 1999 Arthur S. Flemming Award, and the 2002 Bayh-Dole Award.

New Approaches to Neglected Diseases

Building Partnerships to Ensure Needs-Driven Research and Development

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What was the problem?

Despite phenomenal changes in medicine over the past half-century, drug discovery for diseases affecting poor populations in the developing world remains a neglected and stagnant field. Parasitic diseases such as malaria, Chagas disease, and African sleeping sickness (human African trypanosomiasis) cause many deaths each year, and yet, because of a combination of market and public policy failures, no clinically useful and effective drugs have emerged to treat them. Of the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis, even though these diseases account for 11.4% of the global disease burden. Furthermore, existing therapies are often toxic, expensive, and administered for long periods by injection, characteristics that are inappropriate for the environments in which they are used. For example, African sleeping sickness, a fatal disease if not treated, threatens more than 50 million people in 36 countries but has limited treatment options using toxic, antiquated drugs. Chagas disease, which affects 18 million, and puts 100 million at risk in Central and South America, has no effective therapy to prevent chronic and debilitating cardiac sequelae that result in up to 30% of those infected.

What was the innovation?

In 2003, the frustrations of treating sick people with inadequate therapies drove innovators from seven organizations around the world to establish the Drugs for Neglected Diseases initiative (DNDi). The DNDi was formed by Brazil's Oswaldo Cruz Foundation, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia, France's Pasteur Institute, Médecins sans Frontières (Doctors without Borders), and the UNDP/World Bank/World Health Organization's Special Program for Research and Training in Tropical Diseases. DNDi began with the understanding that a great deal of academic research had emerged about the parasites that cause these diseases, research that could be coupled with techniques of modern drug discovery to develop accessible treatments for neglected diseases.

DNDi neither maintains research facilities, nor conducts research to develop its treatments; rather, it acts as a virtual pharmaceutical company whereby DNDi personnel with

a range of experience in different aspects of drug discovery manage the outsourcing of research and development. To gather information on local patient needs, capacity, and expertise, DNDi depends on its regional networks of scientists and clinicians actively involved in drug research for neglected diseases in Asia, Africa, and Latin America. The strong clinical presence of Médecins sans Frontières throughout the world enables DNDi to perform trials and distribute new clinical entities in many of these regions. The initiative has also reached agreements with several large pharmaceutical and biotech companies to gain access to research and to benefit from in-kind contributions from these corporations on specific projects. Its virtual organization model limits costs while maximizing flexibility.

In addition to supporting existing capacity in countries where neglected diseases are endemic, DNDi works with its partners to build additional capacity in a sustainable manner through technology transfer for drug research and development. This includes access to chemical diversity, pharmaceutical and clinical development, and working closely with national control programs through, for example, the Leishmaniasis East Africa Platform (LEAP) and Human African Trypanosomiasis (HAT) platforms in Africa.

What were the obstacles?

It is critical to focus efforts on defined, specific disease categories, to identify the optimal balance between research, development, and access to therapies, and to raise the funds needed to make such an effort successful. One organizational challenge for such initiatives is to maintain a pipeline of drugs in different stages of development so that good therapies can emerge relatively quickly, while the search for optimal drug treatments continues. Equally important is the selection of appropriate partners for all stages of the drug discovery process. There are a growing number of players in the field of neglected diseases and different organizations must learn to communicate sufficiently to encourage innovators with different approaches to avoid competition or excessive overlap. Sustainability of such efforts is the biggest concern, as current attention afforded to global health may soon turn to other issues. Public leadership is needed to create policy change that will support funding for, adoption of, and equitable access to, essential health tools.

What were the results?

To give an example of DNDi's achievements, while building DNDi's structure, innovators identified an immediate clinical problem: drug resistance in malaria is an emerging issue worldwide, resulting in a complex treatment regimen of several drugs to reduce the possibility of resistance. To insure that such drugs were taken together, DNDi produced two fixed-dose drug combinations as an initial project to utilize the skills of the DNDi team for an urgent public health need. In addition to the convenience of these anti-malarials (1 to 2 tablets per day over a three-day treatment course), they are also the first such combination therapy to

be available in both adult and pediatric doses. DNDi's industrial partner, Sanofi-aventis, has distributed over 1 million treatments of ASAQ (a combination of artesunate and amodiaquine), and the treatment is now registered in 21 African countries. ASMQ, a fixed-dose combination of artesunate and mefloquine has completed phase 3 clinical trials and has been used in an intervention study of over 15,000 patients in Brazil.

As of late 2007, DNDi has a full pipeline, with drug candidates at all stages of development. There are 18 programs in the initiative's portfolio: six clinical, three preclinical, and nine discovery projects. The insights DNDi has gleaned from developing and delivering ASAQ to Africa will prove invaluable as DNDi moves forward in its goal, not only to deliver new treatments for the most neglected, but also to build a robust portfolio that will produce truly innovative drugs.

Bennett Shapiro, M.D. is currently the Chair of the DNDi (Drugs for Neglected Diseases iniative) North America Board of Directors. Most recently, he was Executive Vice President of Worldwide Licensing and External Research for Merck. Dr. Shapiro joined Merck Research Laboratories in September 1990 as Executive Vice President of Basic Research, Merck Research Laboratories. In this position, he was responsible for all the basic and preclinical research activities at Merck worldwide. Previously, he was Professor and Chairman of the Department of Biochemistry at the University of Washington. Dr. Shapiro has served on many advisory boards and is currently a member of the board of Momenta and Elixir, among other venture-backed companies.

New Approaches to Neglected Diseases

Prize4Life: A Nonprofit Search for a Cure for ALS (Lou Gehrig's Disease)

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What was the problem?

ALS (amyotrophic lateral sclerosis, also known as Lou Gehrig's disease) is a fatal neurodegenerative illness that kills patients within an average of three to five years. Patients become progressively paralyzed until vital functions like breathing can no longer be sustained. Its causes are little understood, and there is no cure. Each year, about five to six thousand Americans are diagnosed with ALS. At any given time, there are relatively few people suffering from ALS because it is so aggressive and progresses rapidly. Because the

disease is relatively rare and the causes unknown, it has attracted fewer research dollars than other diseases. ALS is considered an "orphan disease."

Currently, the only ALS drug on the market prolongs life by an average of a mere two to three months. Systematic large-scale drug development efforts are urgently needed, and many pharmaceutical companies would like to enter the market for ALS treatment, estimated to be worth at least a billion dollars. However, the difficulty of conducting large-scale drug testing on ALS makes clinical trials lengthy and very expensive, discouraging most companies from undertaking further research.

What was the innovation?

Prize4Life was founded by an ALS patient with a mission to accelerate the search for a cure for ALS. Innovators at Prize4Life offer large financial prizes for defined breakthroughs in ALS research. Unlike awards like the Nobel Prize, which honor past scientific achievements, inducement prizes offer money for breakthroughs that are urgently needed but have not yet happened. By offering prizes in ALS research, Prize4Life wants to attract new minds, new attention, and new money to ALS research.

In November 2006, Prize4Life launched its first prize of $1 million for an ALS biomarker; a measure that would allow clinical researchers to track the progression of the disease. Such a biomarker would dramatically reduce the cost of ALS clinical trials and therefore make it easier for clinical investigators to test potential ALS drugs. It would also remove an important obstacle that is currently keeping pharmaceutical companies from entering the ALS field.

What were the obstacles?

Biomedical innovation is a highly complex arena. Breakthroughs almost always depend on the interaction of a variety of players in the research domain. Prize4Life is introducing a results-based model that in many ways turns the traditional research model on its head, and yet it is also interdependent and complementary to existing efforts in ALS research. Among the many challenges that this poses, four stand out. First, clinically oriented biomedical research is very expensive. While the inducement prize does offer a cash reward, individual researchers, or wealthy foundations must still be inspired to invest their own money to undertake their research. Second, many researchers are often more familiar with the upfront funding mechanisms of grants and may first react with skepticism to the idea of inducement prizes. This requires a great amount of communication and outreach work. Third, Prize4Life needs to strike the right balance between competitive and cooperative aspects of the prize model. On one hand, prizes introduce an element of competition and acceleration into the domain in which they operate. On the other hand, they can also lead to the initiation of new collaborations among researchers inside and outside the ALS field.

A final challenge is the general dearth of information and resources in the ALS research field. This hampers researchers' efforts in multiple ways. Prize4Life is currently initiating several projects to improve access to information and infrastructure for the ALS research community. These include a platform for the exchange of research-related information and a database for collecting and pooling patient data.

What were the results?

In the one year since its inception, Prize4Life has already been able to attract new minds and money to the field of ALS. In May 2007, Prize4Life awarded a series of small prizes ($15,000 each) to a number of new and promising approaches to finding an ALS biomarker. Several of these originated outside the immediate ALS field and have led to new interdisciplinary collaborations. The results of the first prize competition will be available in November 2008, when the deadline for the ALS Biomarker Prize arrives. Prize4Life plans to launch two more prizes in 2008.

Nicole Szlezák is a Doctoral Fellow in the Sustainability Science Program at Harvard University's Center for International Development and a doctoral candidate in the Public Policy Program at the Harvard Kennedy School. Her dissertation investigates the role of the Global Fund to Fight AIDS, Tuberculosis, and Malaria and recent changes in China's AIDS policy. She is also interested in institutional arrangements to foster drug development and delivery for diseases that receive little attention in terms of research and development. Together with William Clark, Dr. Szlezák leads the Institutional Innovations for Linking Knowledge with Action in Global Health Project, which studies institutions cooperating in the arena of global health, with a particular focus on lessons from the field of malaria prevention and control. Prior to coming to Harvard, Dr. Szlezák was a clinical researcher at the Institute of Tropical Medicine in Tübingen, Germany, and at the Albert Schweitzer Hospital in Gabon, where her work focused on malaria and schistosomiasis. Dr. Szlezák holds a medical degree from Humboldt University in Berlin, and a Doctor of Medicine degree from the University of Tübingen, Germany. She is also a graduate of the Master in Public Administration Program at the Harvard Kennedy School.