A Creative Gap in the Medical Science Fight Against Diseases of Poverty

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Among the most arresting realities in the fight against diseases of poverty is the absence of a proven socioeconomic model that translates basic scientific discoveries to improved patient care for the impoverished. Without this model, the research engine of the pharmaceutical industry decelerates before addressing the most pressing health problems of the planet.

In affluent parts of the world, pharmaceutical development effectively occurs in three stages. First, basic research is carried out in laboratories around the world with public and private investment to create discoveries with general applications for a range of diseases. Second, the prospect of economic profit drives scientists, engineers, venture capitalists, and other entrepreneurs to translate research discoveries into clinical treatments in a way that lowers the financial risk of later-stage development by pharmaceutical companies. This "lowering of risk" is often achieved by incorporating "delivery technologies," which help make early-stage drugs and vaccines easier to produce, deliver, and sell. They may confer advantages related to ease of manufacture, cost, safety, and so forth—in short, they improve the commercial product profile of the drugs and vaccines. Third, pharmaceutical and large biotechnology companies license these products from the smaller entrepreneurial organizations and subsequently invest the hundreds of millions of dollars per drug or vaccine required to commercialize pharmaceutical products to meet the needs of intended users. Drugs and vaccines reach and remain in

David Edwards is a Harvard professor and founder of *Le Laboratoire*, a new innovation space in downtown Paris, where artists and scientists perform collaborative experiments. The outcomes of these experiments are exhibited to the public in the form of contemporary art and design installations. Since its opening in October 2007, *Laboratoire* exhibitions have attracted international media attention. The principal of *Le Laboratoire* as an artscience catalyst for innovation is described in Edward's recent book, *Artscience: Creativity in the post-Google Generation*. David is also a founder of many for-profit and not-for-profit organizations, including the Cloud Foundation—a Boston based foundation that oversees Cloud Place, a dynamic center for urban youth arts—and Medicine in Need—or MEND, a global health not for profit funded by the Bill and Melinda Gates Foundation. MEND is based in Boston, Paris, and Pretoria.

the market because researchers, entrepreneurs, private companies, healthcare providers, and patients participate in a complex development and implementation chain that has evolved over the last century in the United States, Europe, and other countries with developed economies.

For diseases that primarily confront less affluent parts of the world, pharmaceutical development, from discovery to implementation, is a more recent global effort. Discovery research—largely driven by government and philanthropic institutions like the National Institutes of Health, the Bill & Melinda Gates Foundation, the Global Fund, and the Wellcome Trust—now occurs vigorously around the world. This activity mirrors the first stage of pharmaceutical development in the "classical model" described above. Mirroring the third phase of the classical pharmaceutical development model, pharmaceutical companies in India, Brazil, Africa, and China are increasingly finding economic value in commercialization of drugs and vaccines that target developing country populations.

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Where is the second stage? Lacking the large economic incentive that motivates entrepreneurs to translate discoveries into practical medications according to pharmaceutical norms, clinical research tends to remain exploratory. Furthermore, without this funding, there is little incentive to incorporate the range of technologies that make early-stage drugs and vaccines practically useful and affordable. This stagnancy diminishes public and corporate appreciation of the value of investing in the overall medical science discovery and development effort aimed at diseases of poverty. As a result, while the classical pharmaceutical model has led to the approval of 383 new drugs and vaccines since 1996[1] for diseases ranging from heart disease to diabetes, the last vaccine approved for tuberculosis (TB) was 87 years ago, and to date we have no viable vaccines for HIV/AIDS and malaria. Yet HIV/AIDS, TB, and malaria combined are presently estimated to account for more than 7 million deaths per year, primarily in impoverished regions of the world.

We believe it possible to fill this "pharmaceutical development gap," at least in part, through the growth of an international, collaborative nonprofit organization aimed at translating early stage discoveries from the bench into the clinic. This organization, based significantly in the developing world, would incorporate delivery technologies to improve the economic viability of potential products and their suitability for development, sale and distribution in developing countries. It would work closely with existing nonprofit and for-profit organizations and aim to inject the energy, innovation,

and passion that entrepreneurs bring to classical pharmaceutical development through unusual "experiments" between medical scientists and artists, longstanding partners with scientists in the fight against AIDS and other diseases of poverty.

An Entrepreneurial Technology Translator for the Developing World

Based on our recent research, of the 55 vaccines currently under development for the three principle infectious disease killers (HIV/AIDS, TB, and malaria) today, only one is in advanced clinical testing (by the French pharmaceutical company Sanofi-Pasteur). The other 54 candidates are pursued by 47 distinct for-profit and nonprofit organizations. This group of 47 includes large and small for-profit pharmaceutical companies in the developed world, African universities, U.S. and European nonprofits, and the World Health Organization (WHO), among others. Well over half of these organizations have only one candidate, while only six have four or more. Of these six organizations, three are nonprofit organizations backed by the Bill & Melinda Gates Foundation (the International Aids Vaccine Initiative, or IAVI; the Malaria Vaccine Initiative, or MVI; and the Aeras TB Vaccine Foundation), one is a major pharmaceutical company (GlaxoSmithKline), another is the *Institut Pasteur* in France, and the last is the National Institute for Allergies and Infectious Disease (NIAID). Encouragingly, these numbers reveal that vaccines aimed at diseases of poverty are actively under development, including a major effort to develop a new TB vaccine by the European and Developing Countries Clinical Trial Partnership (EDCTP). However, the fragmentation of the development effort reflects a nascent global effort and relatively limited overall resources devoted to the cause. Lacking clear economic potential, preclinical, and clinical medical solutions for HIV/AIDS, TB, and malaria received—as estimated in 2005—less than $10 billion annually relative to greater than $200 billion annually for diabetes related R&D alone.[2]

What will it take to build the kind of economic sustainability that might encourage greater investment from the private sector? In February 2008, the nonprofit Medicine in Need (MEND), formed in 2002 as a student and faculty initiative at Harvard University, gathered around 70 research scientists, healthcare workers, and funders of pharmaceutical development for a two-day conference to explore this question in the context of medical science technology. Funded by the Bill & Melinda Gates Foundation and the French *Agence Nationale de Recherche contre le Sida* and hosted at the art and science innovation center *Le Laboratoire* in central Paris, this conference convened various for-profit and nonprofit organizations.[3]

From this meeting three principles emerged to respond to this specific question and the general unmet need:

1) **Lowering product risk in early stage development.** This means early integration of a range of advanced delivery technologies to improve potential sustainability of drug and vaccine candidates by significantly improving the product's profile. Developments include providing lower manufacturing cost, better shelf-life stability, shorter dosing regimens, and alternate routes of administration. Such integration occurs in developed world markets by the community of venture capitalists and entrepreneurs who propel research discoveries into the clinic. Without this community during the effort to develop drugs and vaccines for diseases of poverty, development tends to remain largely academic: success is often measured more by publication-worthy outcomes such as drug and vaccine safety and efficacy rather than by what can be viewed as the less remarkable achievements of manufacturability, shelf stability, low cost, or ease of use.

2) **Investing in local developing world infrastructure.** Revenue potential for new drug and vaccine development for diseases of poverty may be small given the market needs of major international pharmaceutical companies, but it remains attractive to emerging pharmaceutical companies in the developing world. As shown in a recent article by Peter A. Singer, Abdallah Daar, and their colleagues,[4] companies such as Shantha Pharmaceuticals in Hyderabad, India, the first Indian biotech company to produce its own recombinant DNA product (Hepatitis B antigen), are not solely focused on products able to generate annual revenues of billions of dollars. Novel partnerships with not-for-profit entities have permitted Shantha and other Indian pharmaceutical companies, like Biocon, to commercialize vaccines and drugs (insulin in the case of Biocon) that enter the developing world market at far lower prices than in the developed world. While lowering prices and improving access, these developing world pharmaceutical companies then create an encouraging commercialization pathway for new medical science innovations aimed at diseases of poverty.

3) **Creating an innovation culture.** The entrepreneurs who help the traditional pharmaceutical industry create and maintain an innovation culture are often relatively freethinking risk-takers who know, or learn, how to manage the risk of a creative endeavor up to the stage where there is almost no risk at all. Creating a similar culture without the economic dynamism of developed world markets is a major challenge. In at least one way it resembles the challenge that faced Xerox, in its maturity, when the company decided in part to recreate the innovation culture of its early days by the artist experiment called PARC. [5] Xerox turned to proposing residencies in Silicon Valley for leading artists (themselves freethinking

risk takers able to effectively manage risky projects). The collaboration between artists and scientists would encourage the creative spirit Xerox needed to succeed. As developed below, we see this as an equally meaningful strategy for the global health pharmaceutical development community—an incentive for innovation among collaborating medical scientists and a forum for communication with the public.

Investing in Delivery Technologies

Delivery technologies for vaccines and drugs potentially improve the performance of medical compounds of interest at any point in their lifecycle. Such technologies target improved manufacturing ease, better stability at high temperatures during transit and storage, and lower costs. They also target more efficacious formulations (e.g., controlled release or better drug solubility), dosing, and routes of administration. Examples include technologies which produce drugs and vaccines in dry powder forms, through spray drying operations; deliver drugs and vaccines into the blood stream without injections and through transdermal patches; and package drugs and vaccines in water-resistant, low cost, environmentally safe containers. These and other technologies are routinely and systematically employed during early development for products in the developed economies of North America, Europe, and Asia by global pharmaceutical and "big-biotech" corporate entities, which are driven by fundamental economics and risk management. Because these organizations can count on significant revenue and profit margins from the sale of successful drugs, they can also invest the appropriate resources into R&D budgets. Such investment enables them to address and optimize uncertainties in formulation and manufacturing at an early stage, in addition to eliminating products without sufficient promise.

There is obviously no single delivery technology that can assure sustainability of all drugs and vaccines. Moreover, early stage clinical development is so complicated that to even consider the technology needs of new drugs and vaccines—let alone to assure their economic viability—is hard to achieve given the currently nonprofit nature of the international effort aimed at diseases of poverty.

For these reasons we advocate the creation of a highly collaborative nonprofit focused on delivery technology integration into drug and vaccine development and limited to early stage clinical development. This nonprofit, which we envision as the emerging organization MEND, would facilitate the "hand-off" of drug and vaccine candidates—licenses of intellectual property—to developing world pharmaceutical companies by assuring that critical issues of manufacturing and control, dosing, production scale, and stability are addressed early on. Such a nonprofit would provide

to partner organizations resources including patent assessment, preclinical feasibility, "good manufacturing process" production, and regulatory and business development. Enabled with a sophisticated product management function, this organization might facilitate clinical development of drug and vaccine products to pharmaceutical industry standards and significantly address the current development gap in the effort to find medical science solutions for diseases of poverty.

Investing in Developing World Research & Development

The future of drug and vaccine development for developing world diseases clearly lies in our ability to help form in the developing world something resembling the sophisticated community of researchers, healthcare workers, financial experts, patients, and governments that enable the traditional pharmaceutical industry.

For this reason we believe it necessary to accelerate investment in developing world research and development labs, already growing in Africa, Asia, and South America. Beyond this there is a need to heighten the visibility of "delivery challenges" and to direct attention—within the R&D community and among the broader public—to the effectiveness of technologies that address these challenges. Researchers actively involved in the development of new drugs and vaccines often work without awareness of the efforts of researchers who are actively involved in the development of new delivery technologies, the latter typically housed in traditional engineering environments. Lacking effective community, researchers are either unfamiliar with, or lack the access to, any other option than the most expedient and simple formulation or route of delivery available. This communication challenge grows as research and development activities expand in the Southern Hemisphere, owing to geographical and cultural barriers, among others. A need exists to improve dialogue between these different groups of researchers and between the Northern and Southern Hemispheres.

Investing in Creativity: The Surprising Role of Art

The choice to invest resources in creative scientific research aimed at future healthcare solutions as opposed to implementation of available solutions today is both a bet on the value of human creativity and a recognition of the importance of hope in healthcare today. We *create* through a kind of experimentation that synthesizes processes of aesthetic and analytical thought, embracing uncertainty while succeeding to frame problems, inducing and deducing, dreaming, and analyzing.

This "artscience" process shows up increasingly in industry, society, culture, and education.[6] However, the demands of specialization are such that the substance of

innovation is often pushed out of our institutions, where "aesthetic" and "analytical" processes of thought tend to be encouraged in discrete departments, enclosed within tight mission statements and limited by specialized value systems. We may encourage imagination in a design curriculum and analytical ability in an engineering curriculum, but the simultaneous ability to dream and analyze, characteristic of the most innovative designers and engineers, is hard to teach. This hampers our ability to learn innovation and ultimately to produce it.

How can an innovation culture be created in the effort to develop medical science solutions for diseases of poverty? Xerox once ran its "PARC" experiment in Silicon Valley, where artists took residence among computer scientists—aiming to catalyze innovation.[4] Artist collaborations of this kind have become more frequent in recent years in some of the most creative science environments. The Broad Institute in Cambridge, Massachusetts, invited the artist Daniel Kohn to establish residence among its genetic scientists three years ago. Harvard Medical School has recently done a similar residency with the artist Brian Knepp. Between these two institutions, MIT's well-known Media Lab has an entire building dedicated to artist, scientist, and designer collaborations. All these efforts aim to create innovative environments by bringing artists and scientists together in places and around projects that inspire both.

We propose to invite artists to engage in a similar kind of residency with researchers and healthcare workers dedicated to the medical science fight against infectious disease. Art activists have long played a role in international community-building and resource mobilization for AIDS and other diseases of poverty, from film actor Rock Hudson's disclosure of his AIDS condition in 1985 to Nelson Mandela's 46664 Concert in November 2003, named after his prisoner number on Robben Island. Mandela's 46664, which led to other concerts, engaged performing artists to raise awareness about the spread of AIDS in South Africa.

The idea of artists "residing" with scientists who work in disparate labs around the world implies the existence of a common project, what we have come to think of as "experiments."

Such experiments between artists and scientists are within the mission of a new art and design experimentation center in Paris, France, called *Le Laboratoire*.[7] Open since 2007, this new center has led experiments between plastic artists and bioengineers, chefs and colloid scientists, digital composers and number theorists—along with many others in various stages of development. These experiments lead to innovative processes that provide

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rich educational context for Harvard University students (and others from Paris design schools and Trinity College, Dublin), training and inspiration for young urban high school students from Boston and Paris, groundwork for innovation programs at companies like BNP Paribas, and an innovative community for medical scientists and healthcare workers.

MEND

We are currently growing the nonprofit MEND—which has bases in Cambridge, Massachusetts; Paris, France; and Pretoria, South Africa—to provide the innovative, early-stage, technology translator organization described in this article.

Its primary manufacturing base is in South Africa and run by South Africans. While major clinical sites exist in the developing world for the purpose of testing new drugs and vaccines for diseases of poverty, sophisticated sites for research and development of new drugs and vaccines are less common. This is the objective of MEND's base in Pretoria, South Africa, a collaboration with the South African Medical Research Council to build manufacturing capabilities for preparing low-cost, high-volume, stable vaccine formulations for new experimental vaccines developed at Harvard University and elsewhere.

MEND's administrative base is in Cambridge, Massachusetts, near my Harvard lab, where early MEND work took place. From the Cambridge base, MEND recruits and manages various technology collaborations to meet the needs of drug and vaccine projects early in the clinic or in preclinical development. One current project is with the Aeras Global TB Vaccine Foundation, where we are bringing a technology we developed for preparing inhaled vaccine material to bear on a new TB vaccine. A second project involves the for-profit Sanaria, which is developing a new malaria vaccine. MEND is beginning to work with MIT's Alex Klibanov and another corporate partner to bring stabilization technology to prepare a more commercially viable Sanaria product. A third project involves an off-patent TB drug of Eli Lilly. Eli Lilly remains charitably engaged in getting this drug to regions of high TB burden. We have developed a new inhaled formulation, using other technology created in my lab, to develop a new non-injectable treatment for MDR-TB. More broadly, through the creation of Steering Committees in affected regions around the world, MEND intends to monitor policy, development projects, and organizational process through local leadership. It plans to protect and manage intellectual property and extract from this resource that can help sustain the overall charitable goal, manage programs, and promote dialog and expand technology collaborations.

MEND's European base is at *Le Laboratoire* in Paris, a convening site for interna-

tional technology meetings and the facilitator of annual global health art and science experiments. Our first "experiment" took place around the February meeting that led to the vision described in this article. It involved James Nachtwey, one of the leading photojournalists working today. Most recognized as a war photographer, whose photographs appear on covers of *Time* magazine and in prestigious art galleries, James began to work with us two years ago on an "experiment" with medical scientists. Working with *Le Laboratoire*, we proposed a collaboration where the poignant work of the artist might catalyze the creative work of the scientist, and where the insight of scientist might alter the lens of the artist. This led to a public exhibition, inaugurated by Michel Kazatchkine, director of the Global Fund, and provided a moving context for our February meeting.

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Being an experiment, the Nachtwey project has continued to evolve. In October 2008, it appears in Bangkok as part of the Annual Meeting for the Bill & Melinda Gates Grand Challenge Program and the Keystone Conference on Infectious Disease. Around the walls of the main meeting spaces of the Sheraton Hotel are images, films, and words. Many of these images, such as images of war, are hard to look at. Look more closely and you see healing hands—hands of medical scientists, often, and of others, like an unsung hero outside Bangkok who cares for patients suffering from AIDS and tuberculosis. These hands, and the words and films that accompany them, testify to a principal reason why medical science researchers do what they do. Passion to help those who cannot help themselves drives much of the creative work of medical science, perhaps especially in the largely humanitarian context of infectious disease research. This passion often goes unspoken. The collaboration between James Nachtwey and medical science researchers gives it a voice, quite literally in the powerful film portraits by New York artist Asa Mader of Peter Singer, Abdallah Daar, Anne Goldfeld, and Ed Nardell.

Nachtwey's experiment was a first. Our second involves the Indian artist Shilpa Gupta, who is working with medical science researchers on the subject of mental health—the context for MEND's second international meeting on global health technologies—in India and the broader developing world. We propose to develop such annual cultural projects that cut across lines of culture, geography, language barriers, and health systems. Our "experiments" aim to enrich the creative process in which we are investing and to communicate to the public the idea of healthcare as a complex, creative, and human process.

David Edwards

Conclusion

Accelerating the development of drugs and vaccines for diseases of poverty will require intense collaboration between the private and public sectors and between innovators around the world. It will require active, sustained dialog all along the discovery-delivery value chain. We believe this can happen as current international efforts move increasingly toward a socioeconomic model that builds confidence among investors and the public that investing in scientific discovery and new drug and vaccine development can appreciably alleviate the health crises of low-income regions of the world. The growth of a collaborative nonprofit organization that integrates enabling technologies, orients products toward commercial partners, and recruits innovators from North and South into the medical science fight is one potential step forward. WA

Notes

1. Bethan Hughes, "2007 FDA drug approvals: a year of flux," *Nature Reviews Drug Discovery* 7, no. 2 (February 2008): 107–109.

2. Ann Pettifor, Conrad Barwa, and Paul Zeitz, "Global Fund Debt Conversion Report: A Joint Report from Advocacy International and the Global AIDS Alliance" (July 2005), http://www.theglobalfund.org/en/media_center/press/news_050726.asp.

3. These organizations include: Emory University, Georgia Tech, Harvard Medical School, Harvard University, Massachusetts Institute of Technology, Max Planck Institut, Universite de Paris Sud, University of North Carolina, University of California at Santa Barbary, University of Geneva, University of Michigan, University of Parma, University of Queensland, University of Santiago, University of Strasbourg, University of Toronto, Accenture Technology Consulting, Advancell, Booz Allen Hamilton, CEREP, Lagray Chemical, NanoBio Corporation, Polaris Venture Partners, Pulmatrix, Sanaria, Shantha Pharmaceuticals, TransForm Pharmaceuticals/J&J, Vaxlnnate Corporation, Wolfe Laboratories, Inc., *Institut Pasteur*, International AIDS Vaccine Initiative, Massachusetts General Hospital, Medicine in Need, PATH, Seattle Biomedical Research Institute, TB-VAC, The Bill & Melinda Gates Foundation, UNICEF, *Agence Nationale de Recherche sur le Sida et les hepatites virales*, Foundation for the National Institutes of Health, *Statens Serum Institut*, and the World Health Organization.

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