Leveraging University Research to Advance Global Health

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THE WORLD'S DESTITUTE SICK FACE A PERILOUS DISADvantage in accessing essential medicines. The crisis stems from 2 related problems. First, for the billion people affected by neglected diseases such as trypanosomiasis and cholera, few safe and effective treatment options exist. Because these neglected diseases predominantly affect the poor, they attract little research and development funding, leading to a paucity of therapies.[1] Second, for other diseases, several interlinked factors impede access to medicines that do exist: high prices, underfunded and uncoordinated health care systems, and drug formulations ill-suited to resource-poor settings.

Generic competition has lowered the price of antiretroviral therapy for human immunodeficiency virus (HIV) from more than $15 000 per patient-year 6 years ago to $99 today.[2] Concomitant with this decrease in prices has been an increase in funding and political will to address the HIV/AIDS pandemic. This has shifted the debate from whether antiretroviral therapy is possible in resource-poor settings to how to strengthen health infrastructure to provide comprehensive care.[3]

Despite the progress demonstrated for antiretroviral therapy in poor countries, there is, as yet, neither a comprehensive nor a lasting solution to ensure that patients in poor countries pay less for medicines than patients in rich countries. Even antiretrovirals, generally heralded as a success story for differential pricing, show the evanescence of any progress that has been made. Implementing new first-line HIV treatment guidelines from the World Health Organization would cost 5 times more per patient-year than the older, first-line treatment regimen; second-line therapies are even more expensive.[2] Meanwhile, major generic-producing countries like India must now enforce product patents to comply with the World Trade Organization's Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement.[4] The US government is pushing further still for expanded intellectual property protection by systematically negotiating so-called TRIPS-plus provisions into bilateral free-trade agreements.[5] Taken together, these developments threaten to undermine gains for the health of the underserved that have been made by reforms to the international intellectual property system.

The Role of Universities

Research universities have an opportunity to intervene in the access-to-medicines crisis in poor countries. By virtue of their upstream contribution to the drug development pipeline—estimated at $19.6 billion in 2002 for the United States alone—universities have considerable untapped influence.[6] Both the number of patents held and the number of license agreements executed by universities more than doubled between 1991 and 2005.[7] The case for university action becomes more tangible when considering actual medicines. For instance, the patent rights contributing to several currently marketed HIV drugs are held by universities: stavudine (Yale University), abacavir (University of Minnesota), lamivudine (Emory University), emtricitabine (Emory University), and enfuvirtide (Duke University). Overall, university patents are associated with 10 of the 30 HIV drugs approved by the US Food and Drug Administration between 1987 and 2007.[8]

Several institutions—both private and public—have demonstrated that it is possible to leverage ownership of intellectual property to improve access to medicines. For example, in 2001, Yale University negotiated price concessions from Bristol-Myers Squibb for stavudine in South Africa.[9] Similarly, the Bill and Melinda Gates Foundation, through its Grand Challenges in Global Health initiative, requires grantees to ensure that any health products created with Grand Challenges funds will be available at affordable prices in poor countries.[10] The grants call for principal investigators to outline *ex ante* intellectual property ownership issues, licensing strategies, and potential commercial partners. The US National Institutes of Health (NIH) has also pioneered proactive management of its intellectual property to benefit the developing world. For technologies with a worldwide market (such as new antiretrovirals), the NIH has adopted license terms that require companies in North America or Europe to provide a marketing plan for making products available in developing countries.[11]

Public-sector research and licensing practices have implications extending beyond HIV medicines. Of the 35 million deaths from chronic disease that occurred in 2005, 80% occurred in low- and middle-income countries.[12] Expanding access to primary care treatments for chronic illnesses like diabetes and cardiovascular disease could have an immediate effect, both for patients and for the structure of limited or unstable health care systems. Vaccine-preventable diseases also exemplify the magnitude of the opportunity. Human papillomavirus vaccine was originally developed at the Univer-

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sity of Rochester, Georgetown University, Queensland University, and the US National Cancer Institute. Research on rotavirus vaccine was originally conducted at the Wistar Institute and the Children's Hospital of Philadelphia. Both of these vaccines were recently licensed for use in the industrialized world without a clear strategy for access to the vaccines in poor countries, where the vast majority of deaths due to cervical cancer and diarrhea occur.

Ensuring access to university-derived medicines in poor countries would have a demonstrable effect on global health only if pro-access policies are adopted collectively by major research universities. An important step toward consensus was taken recently when the Association of American Medical Colleges (AAMC) and 18 research institutions called for ensuring access to university innovations in the developing world.[13] The AAMC and collaborating universities joined committees of the World Health Organization[14] and the American Association of Arts and Sciences[15] that previously espoused this same principle. What follows are policy recommendations for operationalizing that principle.

Promoting Equal Access to Research

When university-owned intellectual property is necessary for the development of a potential health-related product such as a drug, a vaccine, or a diagnostic test, universities could either require the inclusion of licensing terms in exclusive technology transfer agreements that ensure low-cost access to health-related innovations in the developing world; or develop a transparent, case-by-case global access strategy to ensure access when licensing provisions will not serve access objectives.

The licensing transaction between a university, and, for example, a biotechnology company represents an important point of leverage for access considerations. A critical lesson learned from the first round of price reductions for antiretroviral agents was that generic competition is the most effective mechanism for lowering prices.[4] An effective licensing policy would engender such generic competition. One example of this type of policy is the equitable access license (EAL), developed by Universities Allied for Essential Medicines. The EAL is a nonexclusive, open licensing arrangement that provides a means to capture any downstream licensee improvements for the purpose of supplying developing-country markets.[16,17] The EAL applies to countries classified as low- or middle-income by the World Bank and permits multiple producers to compete in these countries simply by notifying the university and its licensee.

An advantage of the EAL is that, by relying on the market for generic production, the administrative burden on the university is minimized. However, this parsimony may not be well-suited to certain situations. For example, biologics (eg, vaccines and macromolecules such as monoclonal antibodies) and medical devices are subject to different scientific and technical constraints than are synthetic small molecules (eg, antiretrovirals such as stavudine) and may require different methods to ensure access. Universities ought to implement open licensing solutions like the EAL where possible but could pursue alternative global access strategies for predefined situations in which open licensing may not be the best solution. While intellectual property ownership is an important and tangible point of influence, it is not the only leverage available to public institutions such as universities.

The term "global access strategy" derives directly from the Gates Foundation's guidance on intellectual property management for the Grand Challenges in Global Health.[10] Among other provisions, the guidance requires that the grantee's intellectual property revert to the Gates Foundation if the patented innovation is found to be inaccessible in poor countries. The purpose of the global access strategy, however, is to prevent this situation from arising in the first place by negotiating in advance a feasible plan to ensure access to innovations where they are needed most. Potential components of a global access strategy include: (1) stipulations for voluntary licenses to generic manufacturers and mandatory sublicensing requirements to alternative manufacturers when access objectives are not being met; (2) clauses requiring the licensee to make products developed from a university innovation available at a reduced cost in developing countries; (3) actively seeking third-party organizations to participate in development and distribution for the developing-world market; and (4) participating in patent pools (ie, joining with other institutions and companies to cross-license patents) that are organized in the interest of public health.[15]

Promoting Research and Development for Neglected Diseases

Neglected diseases are those for which treatment options are inadequate or do not exist and for which drug-market potential is insufficient to attract a private-sector response. To promote research and development in treatments for neglected diseases, universities could adopt needs-based medical research policies, such as promoting in-house neglected-disease research; engaging with nontraditional partners to create new opportunities for neglected-disease drug development; and carving out a neglected-disease research exemption for any patents held or licenses executed.

Internally, university decision makers setting the research agenda could purposefully include work on neglected diseases in their deliberations. While funding sources and faculty interests govern the research agenda to some degree, steps can be taken to cultivate neglected-disease research. Capital investments by universities such as the $30 million committed to found the Duke Global Health Institute—an interdisciplinary initiative combining education, research, and service missions—are too few and far between.[18] Even simple structural changes, such as the creation of a Center for Neglected Diseases, and marketing of neglected-disease research capacity can help attract talented researchers and new sources of funding, as seen in the cases of the George Washington University and the University of California at Berkeley.[19,20] One way that all universities could start is by formalizing annual review practices aimed at identifying new or currently shelved technologies with promising potential for application to neglected diseases.

University policy makers might also take note of the external developments that have changed the landscape of neglected-disease drug development. Product-development partnerships like the Medicines for Malaria Venture and the Drugs for Neglected Diseases Initiative have attracted hundreds of millions of dollars in funding, the majority of which is contributed by the Gates Foundation.[21] Universities could actively seek privately funded but targeted partnerships—as well as partnerships with developing-country companies and research institutions—to develop technologies applicable to neglected diseases.

In addition, when patented innovations have not yet been licensed for further development, universities could allow, as a matter of policy, other nonprofit institutions to use them in research for neglected diseases. One way to operationalize this research freedom could be to contribute to a comprehensive molecular screening library for neglected diseases.[22] When innovations have been externally licensed, universities could include an exemption for neglected-disease research in their licensing agreements. These agreements can be structured as a "dual-market" opportunity, permitting the universities to partner with companies for markets in industrialized countries while a nonprofit entity retains the rights to develop the compounds for patients in developing countries.[23]

Measuring Research Success According to Effect on Global Public Health

University technology transfer operations are usually evaluated using simple, quantifiable criteria such as patents applied for and received, licenses granted, and licensing revenue generated. The focus on these types of statistics may partly explain why technology transfer objectives are often misaligned with the broader public mission of universities.[24] Yet perhaps surprisingly, licensing revenue from academic research is, in the majority of cases, not a lucrative investment. For example, among US institutions, the ratio of licensing income to sponsored research funding was reported to be 5% or less in 2005.[25] Thus, the positive social effect of university innovations—particularly in poor countries—would go largely unnoticed if the success of technology transfer were measured in dollars alone. To rectify this situation, universities could collect and report data on university intellectual property practices related to global health access. Furthermore, universities could collaborate to develop more robust technology transfer metrics that better gauge access to public health goods and innovation in neglected-disease research.

Even though perfectly sound technology transfer metrics may not yet exist, universities can make the nonmonetary benefits of technologies for global health more transparent. For example, universities could disclose all health care–related products in which they hold intellectual property rights. Universities could also publish information on patents applied for or granted in all developing countries, the number and nature of licensing agreements that include access-minded provisions, and reports of nontraditional partnerships for neglected-disease research and development.

University mission statements typically include the noble idea of creating and disseminating knowledge in the public interest. Holding universities to these standards is a critical means to fulfilling an even loftier principle, codified in the Universal Declaration of Human Rights: providing access to medical care and treatment as a basic human right.

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