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Health Innovation Networks to Help Developing Countries Address Neglected Diseases

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Gross inequities in disease burden between developed and developing countries are now the subject of intense global attention. Public and private donors have marshaled resources and created organizational structures to accelerate the development of new health products and to procure and distribute drugs and vaccines for the poor. Despite these encouraging efforts directed primarily from and funded by industrialized countries, sufficiency and sustainability remain enormous challenges because of the sheer magnitude of the problem. Here we highlight a complementary and increasingly important means to improve health equity: the growing ability of some developing countries to undertake health innovation.

Improving the health of the poorest people in the developing world depends on the development and deployment of many varieties of health innovations, including new drugs, vaccines, devices, and diagnostics, as well as new techniques in process engineering and manufacturing, management approaches, software, and policies in health systems and services. In developed countries, philanthropic and government donors have created and invested more than \$1 billion in global product development partnerships (PDPs) to develop and help to ensure access to new drugs, vaccines, and diagnostics for diseases of the poor (1). These PDPs have made major progress in a relatively short time period (2) but continue to face many challenges.

All developing countries can undertake health innovation to varying degrees. Some

developing countries, however, are more scientifically advanced than others and are starting to reap benefits from decades of investments in education, health research infrastructure, and manufacturing capacity. We refer to these as innovative developing countries (IDCs) (3, 4).

It is a challenge to get complete data on health research spending. According to the most recent available data, public spending on health research by developing countries totaled at least \$2 billion (5). This number does not include China, for which data were not available. That investment, which has already led to important innovations, is projected to continue to grow (3, 5–7). Furthermore, lower labor and other costs have the potential to magnify the impact of this investment. To put it in a different perspective, just 1/10th of these IDC public health research re-

sources amounts to more than all that was spent in 2004 by the above-mentioned PDPs engaged in the development of drugs, vaccines, and diagnostics for diseases of the poor (8, 9).

Patents and well-cited publications indicate the productivity of research investments, and in this light, IDCs have made major progress. The number of U.S. patents per capita is a common proxy used to measure the relative innovation efficiency of countries, but we believe that this computation underestimates the innovative capacity of developing countries, because it fails to detect the productivity of highly capable centers of excellence within countries with large populations. Adjusting for both relative economic status and population (U.S. patents per gross domestic product per capita) (10), the top 25 most productive countries in the world include India, China, Brazil, South Africa, Thailand, Argentina, Malaysia, Mexico, and Indonesia (10). For Brazil, China, India, and South Africa, the number of highly cited academic papers rose nearly two-fold from 1993–1997 to 1997–2001 (11), whereas the number of U.S. patents has increased 10-fold (12).

Academic research, publications, and patents do not help the poor (or anyone else) unless they are turned into tangible products or improved practices and policies. Detailed analyses and comparisons of countries' performance in turning ideas into innovations are limited (13), but there are case examples that imply growing capabilities. IDCs have a publication intensity that is much higher than the global average in health biotechnology fields that are relevant to the health needs of their own populations (14). As far as specific products now on the market, the list includes the following: (i) the first effective meningitis B vaccine, developed at the Cuban Finlay Institute and recently licensed to GlaxoSmithKline (15); (ii) new innovative processes for engineering local versions of the recombinant hepatitis B vaccine in Cuba, Korea, and India (16); and (iii) the antimalarial drug arteether (a semi-synthetic artemisinin derivative), developed at India's Central Drug Research Institute and transferred to Themis Chemicals for commercial development, now sold under the brand name E-mal in 48 countries (17). In terms of innovative health programs, Brazil's human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) program stands

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out, because it has combined the local manufacturing of antiretrovirals and government financing to provide free access to all who need the drugs (18). A number of companies from IDCs are working on new products in collaboration with the global PDPs, including FIOCRUZ/Bio-Manguinhos and Butantan Institute of Brazil with the Human Hookworm Vaccine Initiative (19), Ranbaxy and Bharat Biotech in India with the Malaria Vaccine Initiative, and the Serum Institute of India with the Meningitis Vaccine Initiative.

Developing countries also play an increasingly important role in manufacturing health products to meet global health needs. China is the world's leading producer of penicillin. The Serum Institute of India is the world's leading manufacturer of diphtheria-pertussis-tetanus vaccine. Over 60% of the United Nations Children's Fund's vaccine requirements for the Expanded Programme on Immunization are met by Brazil, Cuba, India, and Indonesia (20, 21). In dollar terms, 67% of India's drug exports and 74% of Brazil's drug exports go to other developing countries, whereas 63% of Uganda's drug imports and 54% of Tanzania's drug imports come from other developing countries (22). By volume, India is now the fourth largest producer of pharmaceuticals in the world (23).

Some observers have emphasized the need for developing countries to "build their own capacity to develop drugs, particularly in the case of neglected diseases ... for which multinational pharmaceutical companies may have little interest in investing because the market is unlikely to provide adequate returns" (24). Yet there may be tensions between national health priorities and the desire for economic development (25). Al-

though the Commission on Macroeconomics and Health has emphasized the direct link between health and economic development (26), others underscore the need to consciously align innovation policies and health priorities in a way that is consistent with the legitimate goals of wealth and job creation (27).

These perspectives help to highlight specific questions that require further study. For example: Under what conditions might a market that seems unattractive to a developed-country company be attractive to its developing-country counterpart? Under what circumstances might companies in the individual IDCs build a business based on national health needs, as opposed to global diseases with blockbuster profit potential? Are there opportunities for IDCs to help least-developed countries, either through the manufacture and export of low-cost products or through technical assistance and capacity building (28)? Is it in their economic interest to do so? In considering such questions, we raise the following points, each of which is based on observations that require further study

1) Public-sector infrastructure. Unlike in wealthier countries, most health research (and some manufacturing) in developing countries is funded by and conducted in the public sector and therefore may be driven more by public health goals (5, 29, 30).

2) Low-cost production. C. K. Prahalad points out (31) that some manufacturers in developing countries pursue a business model in which they specialize in high-volume, low-margin production, which leads to low-cost products, and they often explicitly develop products with the goal of distributing them to the poor in

developing-country markets. Manufacturing cost advantages (32) mean that products produced in developing countries may be more affordable, an important factor in access to medicines.

3) Acceptability and social conscience. Those closest to the needs of the poor are the affected communities, scientists, policymakers, and institutions in developing countries. This proximity may motivate innovation for treating diseases of the poor. IDC products may also be more acceptable to governments and consumers in developing countries.

A recent study of innovation systems in health biotechnology in developing countries found that policies and practices affecting local public-private partnerships (PPPs), sustained government support for research, the retention and expansion of the scientific corps, the availability of venture capital, and manufacturing and regulatory approvals are particularly important factors in innovation to meet national health needs (6). Given that currently most of the infrastructure for health research in developing countries resides in the public sector (5, 29, 30), we believe that innovation through partnering of local public and private research organizations deserves particular attention. National innovation policies to encourage such partnerships, and capacity building in the management of intellectual property, among other competencies, can help make such partnerships more effective.

In 2002, the U.K. Commission on Intellectual Property Rights suggested the need for "a network of the public-private partnerships in developing countries, taking advantage of the concentration of research resources in public sector institutions but also the opportunity to build research capacity in the private sector" (33). Given the large and growing investments by IDCs in health research, we strongly advocate a network for health innovation in developing countries that promotes policy research, local innovation, South-to-South learning, and information sharing (Fig. 1).

Several networks have already formed, focusing on individual diseases, technologies, or components of health innovation systems. In April 1994, FIOCRUZ and the Special Programme for Research and Training in Tropical Diseases (TDR) organized in Rio de Janeiro the first Parasite Genome Network Planning Meeting (Fig. 2). The Developing Country Vaccine Manufacturers' Network, established in November 2000, includes both state-owned and private producers in Brazil, Cuba, China, India, Indonesia, and Mexico that are prequalified by the World Health Organization (WHO) for sale to United Nations (UN) agencies. The South-South Initiative (SSI) in tropical diseases research, a TDR initiative begun in 1991, is designed to facilitate sharing of resources among research groups in Latin America, Asia, and Africa in order to increase competitiveness and optimize scientific opportunities. The SSI currently in its full operation is managed by a coordinating committee representing African, Asian, and Latin American

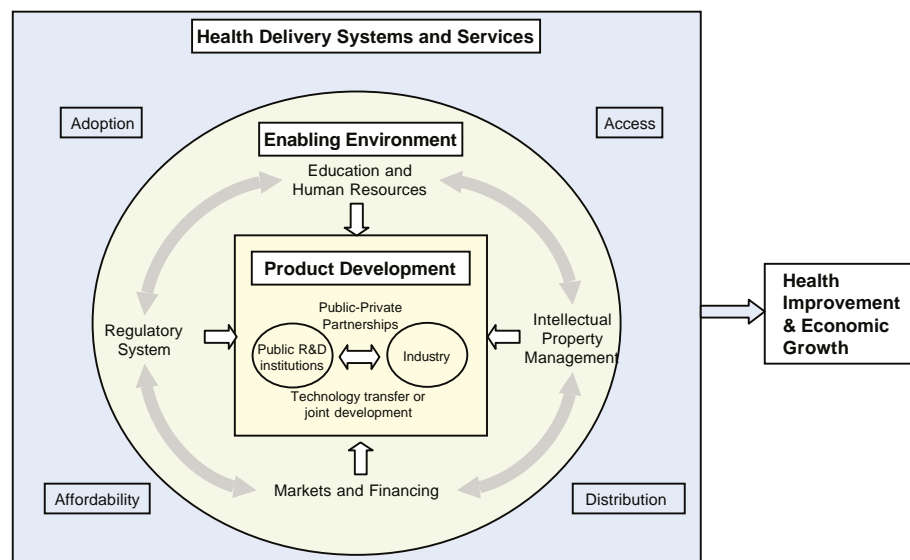


Fig. 1. Health innovation systems have multiple components, operating in both the public and private sectors, including the following: education, research, financing, manufacturing, technology management practices, intellectual property rules, regulatory rules, and domestic and export markets (including public procurement). The system refers not only to these components but also to the technical, commercial, legal, social, and financial interactions; the interlinkages among components; and the policies and practices that guide them. The function (or dysfunction) of and dynamic linkages among these components contribute to the production and delivery of health products and services to people—or lack thereof.



Fig. 2. Group photograph of the participants of the FIOCRUZ-TDR Parasite Genome Network Planning Meeting, held in Rio de Janeiro, Brazil, on 14 and 15 April 1994. This international meeting, attended by 40 scientists and 5 representatives from WHO, selected the three parasite strains whose genome sequences are published in this issue of *Science* by the Tritryp project.

investigators (34). The India–Brazil–South Africa Dialogue Forum, established in June 2003, includes a focus on intellectual property and access to medicine, traditional medicine, and R&D on vaccines and pharmaceutical products to address national health priorities. The Technological Network on HIV/AIDS, which was announced in Bangkok during the July 2004 International AIDS Conference, includes Brazil, China, Cuba, Nigeria, Russia, Thailand, and Ukraine (with perhaps India and South Africa joining in the near future). The Network supports research and South-South technology transfer to develop and manufacture antiretroviral drugs and new drug formulations, male and female condoms, microbicides, and HIV vaccines. Finally, the WHO Developing Countries' Vaccine Regulators Network, created in September 2004, involves Brazil, China, Cuba, India, Indonesia, Russia, South Africa, South Korea, and Thailand.

Broader networks could expand linkages to other like-minded organizations (35). We believe that more frequent robust exchanges of know-how among an expanding universe of public- and private-sector players would accelerate innovation and expedite the translation of knowledge about diseases of the poor while also reflecting national sensitivities, changing contexts, and the concomitant desire for economic growth. This goal will also require bringing together two communities whose communication has been, in our opinion, far from optimal. A growing body of scholarly economic studies has examined innovation systems in developing countries (6, 20, 36–38). This work tends to equate well-being with wealth creation, and it is built largely on case studies from the electronics, information technology, engineering, and other nonhealth manufacturing industries. At the same time, global health professionals concerned with the discovery, development, and introduction of new health technologies—who are, in fact, working to address challenges that are directly related to the components of health innovation systems—have not systematically applied concepts and methodologies from the field of innovation systems in their work. A network approach could

help maximize substantial existing investments in health research made by IDCs and also complement global efforts to address health disparities and achieve the Millennium Development Goals.

We have sought to highlight two points: (i) A rapidly evolving phenomenon: IDCs are increasingly capable of health innovation to address their national health priorities and to help meet the needs of less advanced developing countries. (ii) A knowledge gap: Innovation systems theory has rarely been applied to global health problems, whereas the global health community has rarely focused on innovation systems (39). We believe that new insights may arise at the intersection of these two cultures and research communities (40).

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Supporting Online Material

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Materials and Methods
 Fig. S1

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RESEARCH ARTICLE

Comparative Genomics of Trypanosomatid Parasitic Protozoa

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A comparison of gene content and genome architecture of *Trypanosoma brucei*, *Trypanosoma cruzi*, and *Leishmania major*, three related pathogens with different life cycles and disease pathology, revealed a conserved core proteome of about 6200 genes in large syntenic polycistronic gene clusters. Many species-specific genes, especially large surface antigen families, occur at nonsyntenic chromosome-internal and subtelomeric regions. Retroelements, structural RNAs, and gene family expansion are often associated with syntenic discontinuities that—along with gene divergence, acquisition and loss, and rearrangement within the syntenic regions—have shaped the genomes of each parasite. Contrary to recent reports, our analyses reveal no evidence that these species are descended from an ancestor that contained a photosynthetic endosymbiont.

The protozoan pathogens *Leishmania major*, *Trypanosoma cruzi*, and *Trypanosoma brucei* (family *Trypanosomatidae*, order *Kinetoplastida*) collectively cause disease and death in millions of humans and countless infections in other mammals, primarily in developing countries in tropical and subtropical regions (1). There are no vaccines for these diseases and only a few drugs, which are inadequate because of toxicity and resistance. Although the three pathogens (referred to here as the “Trityps”) share many general characteristics, including subcellular structures such as the kinetoplast and glycosomes, each is transmitted by a different insect and has its own life-cycle features, different target tissues, and distinct disease pathogenesis in their mammalian host [box 1 in (2) and fig. S1]. They also use different immune evasion strategies: *L. major* alters the function of the macrophages it infects, *T. cruzi* expresses a complex variety of surface antigens from within the cells it infects, and *T. brucei* remains extracellular but circumvents the host immune response by the periodic switching of its major surface protein (3).

The availability of the three draft genome sequences (4–6) allows better understanding of the genetic and evolutionary bases of the shared and distinct parasitic modes and lifestyles of

these pathogens. In the accompanying Research Articles, the discussion of each species reflects the current state of knowledge for each organism. Thus, the Research Article by Berriman *et al.* (4) emphasizes metabolism and biochemical pathways of *T. brucei*; the Research Article by Ivens *et al.* (5) highlights fundamental aspects of molecular biology (transcription, translation, post-translational modification, and proteolysis) of *L. major*; and the Research Article by El-Sayed *et al.* (6) focuses on repeats and retroelements, DNA replication and repair, and signaling pathways of *T. cruzi*. Here, we compare gene content and genome architecture, composition, and organization of protein domains encoded by each genome and offer an analysis of the rates of gene evolution.

Core proteome. The *T. brucei*, *L. major*, and *T. cruzi* haploid genomes contain between 25 and 55 megabases (Mb) distributed over 11 to 36 (generally) diploid chromosomes, and encode about 8100, 8300, and 12,000 protein-coding genes, respectively (Table 1). An “all-versus-all” basic local alignment search tool (BlastP) comparison of the predicted protein sequences within each of the three genomes was made using a suite of algorithms designed to collapse closely related paralogous genes. In the case of *T.*

cruzi, all alleles were included because of the hybrid nature of this genome (2, 6). The mutual best BlastP hits between the three collapsed proteomes were grouped as clusters of orthologous genes (COGs). Iteration of this process with manual inspection and reannotation, especially of two-way COGs (i.e., those with members in only two of the Trityps), resulted in 6158 three-way COGs, which defined the Trityp core proteome, as well as 1014 two-way COGs (Table 1,

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