GLOBAL HEALTH

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Photo courtesy of IDRI

IDRI scientists at work on products to prevent, detect, and treat neglected diseases

IDRI: Neglected Disease R&D with a Nonprofit Model

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STEVEN REED, FOUNDER

THE PROBLEM/SOLUTION SPACE

More than one billion people—one sixth of the world's population—suffer from neglected diseases.[1] Disproportionately affecting the poor, neglected diseases cause disfigurement, disability, organ damage, and death. Many are infectious diseases that thrive in areas with tropical climates, unsafe drinking water, inadequate sanitation, and minimal access to health care.[2] These diseases, including malaria, elephantiasis, Chagas disease, and schistosomiasis, among others, are classified as neglected because they rarely affect people in developed nations. Moreover, they kill and maim individuals slowly over time, rather than causing swift, lethal outbreaks that make headlines and necessitate widespread attention.[3]

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One particularly grim neglected disease is leishmaniasis—the second most common parasitic killer after malaria.[4] As of 2012, roughly 12 million people were infected with the condition.[5] Spread by the bite of a sand fly, cutaneous leishmaniasis causes skin ulcers on the face, arms, and legs, resulting in scarring and disfigurement. Visceral leishmaniasis attacks the immune system, almost invariably causing death within two years. [6] One to two million people contract leishmaniasis each year, with 500,000 of those individuals suffering from the deadly visceral form. Seventy percent of those who die from leishmaniasis are children. As a result of opportunistic co-infection with HIV/AIDS, the incidence and geographic spread of leishmaniasis are increasing.[7]

Neglected diseases inflict heavy health and economic burdens on low-income nations in Africa, Latin America, parts of Asia, and the Middle East. Despite the dire need for simple diagnostic tests, vaccines, and effective treatments in these regions, for-profit pharmaceutical companies traditionally have not pursued these solutions because of the prohibitive costs of research and development, along with the inability of people in impoverished areas to pay for treatment. Published research estimates that the cost for a major pharmaceutical company to develop a new drug ranges from $802 million[8] to as much as $4-11 billion.[9] In addition, the scientific challenges associated with this work are significant; up to 90 percent of drug candidates fail in the pre-clinical stage.[10] For drug companies that are answerable to shareholders and investors, the steep investment, high risk, and limited potential returns comprise a formidable barrier. While some nonprofit drug development companies have emerged to address neglected diseases, they are often unable to raise the vast sums necessary to initiate drug discovery and fund promising therapies all the way through clinical trials.

Photo courtesy of IDRI

A patient with cutaneous leishmaniasis

ABOUT IDRI

The Infectious Disease Research Institute (IDRI) was founded by immunologist Steve Reed in 1993 as a nonprofit global health research center dedicated to applying advances in immunology to the development of products to prevent, detect, and treat neglected diseases. The institute was distinguished by its emphasis on the practical end goal of getting its products to market. To accomplish this, IDRI drew on the distinct competencies of diverse collaboration partners, including for-profit life science companies, research centers, universities, government organizations, and nongovernmental organizations (NGOs). Under the leadership of CEO H. Stewart Parker, IDRI was focused on eradicating tuberculosis, leishmaniasis, leprosy, malaria and Chagas disease, which together killed more than six million people each year.[11] As of 2012, the company had vaccines, diagnostic, and therapeutic products in various stages for each of these conditions, including a diagnostic product on the market for Chagas disease, and impending clinical trials for TB and leprosy vaccines.[12]

IDRI had made particularly notable headway in its battle against leishmaniasis. Prior to the company's involvement, diagnosing leishmaniasis required performing a lymph node, spleen or bone marrow biopsy; all impractical in resource-limited settings because these tests were invasive, expensive procedures that required hospitalization and access to laboratory facilities.[13] IDRI developed a rapid, point-of-care diagnostic test that could

be used to diagnose more than 98 percent of human visceral leishmaniasis with a single drop of blood.[14] To make this diagnostic widely and inexpensively available, IDRI assigned a series of non-exclusive licenses for the technology, enabling licensing partners to develop tests, pursue approvals, and bring the tests to appropriate markets. To help control and eventually eradicate the disease, IDRI also created the first defined vaccine candidate for visceral leishmaniasis.[15] To date, the first vaccine candidate had been evaluated for human prophylactic and therapeutic indications in clinical trials in South America, India, and Sudan. An additional, improved candidate was also in early safety trials in the U.S., with plans for additional trials in India and other endemic countries. The IDRI vaccines consisted of one or multiple recombinant leishmania protein antigens and a T-cell adjuvant. As part of its vaccine platform, IDRI focused on the development of adjuvants, which were added to vaccine formulations to make them more efficacious, potent, and active at lower doses.

Photo courtesy of IDRI

IDRI founder Steve Reed talks with a healthcare provider about the leishmaniasis diagnostic

ONE CHALLENGE: DRUG R&D WITH A NONPROFIT MODEL

To continue realizing positive results in the neglected disease space, IDRI needed a substantial, ongoing stream of funding. However, as a nonprofit, the organization could not tap into traditional funding sources available to private pharmaceutical firms, such as venture capital.

IDRI felt strongly about maintaining its nonprofit status because of the mission it had defined for the organization. Being a nonprofit also affected how it was perceived in developing countries. According to Parker, in order to enter emerging markets, the organization had to partner with government entities, in-country health organizations, and health and social service personnel. IDRI's nonprofit status paved the way for these partnerships by positioning IDRI as a benefactor to underserved populations, rather than as an entity seeking to exploit them. "That not-for-profit status helps us enter those markets more easily," Parker said.[16] Executive Vice President Erik Iverson added that, on projects where the World Health Organization (WHO) was involved, a strict nonprofit status was necessary if the developer of a technology wanted to stay involved through its implementation. "You can't have any for-profit interest if you want to be included in the downstream discussions on uptake, adoption, and procurement," he noted.

In the absence of venture capital funding, IDRI had turned to grants, many of which were generally unavailable to for-profit entities. For example, funding for the leishmaniasis program had come primarily from the Bill and Melinda Gates Foundation, which had provided almost $40 million toward the effort. "Until fairly recently, the Gates Foundation wasn't funding a lot of companies, so the not-for-profit status allowed us access to resources that would not otherwise have been available," Parker explained. IDRI also received support for its leishmaniasis research through the National Institute of Allergy and Infectious Diseases (NIAID), one of the branches of the National Institutes of Health (NIH), among others.

The main challenge with grants was that the funds were typically designated for a particular development program, and had specific underlying rules governing their use. Accordingly, most grant support could not be used to develop IDRI's infrastructure, or to explore new projects that might enhance current research platforms. These funding constraints made sustaining the company challenging, and limited its strategic growth. IDRI needed to generate additional revenue streams that would allow its management team more freedom in allocating funds to strategic, forward-looking activities.

THE SOLUTION: USING FOR-PROFIT SPINOUTS TO SUPPORT NONPROFIT ACTIVITIES

Reed found the answer in the creation of for-profit development arms to commercialize select IDRI vaccine technologies. Specifically, he devised a model to create for-profit entities related to IDRI to bring forward those technologies that had first-world applications and thus significant profit potential. The approach combined the best of for-profit and nonprofit models; in most cases, IDRI licensed the technology to the for-profit arm, which then raised private funding to accelerate and enhance research and development for commercial applications of that technology. If/when the for-profit company licensed the resulting products to large pharmaceutical companies (or achieved other forms of commercial success in first-world markets), IDRI's portion of those royalties could be used by the organization to further its efforts in developing global health solutions. In some cases, IDRI received an equity ownership in the company as well, so that if the company is successful IDRI can direct the proceeds from its equity back into its mission-centric programs.

There is a tension because your [for-profit] partner wants you to always make sure it's the first priority all the time, and that's probably not going to be the case given our mission-centric programs.

The first such for-profit company was Corixa, which Reed started in 1994 with Steve Gillis, co-founder of Immunex. While also pursuing a cancer drug, Corixa successfully developed the vaccine adjuvant MPL (Monophosphoryl Lipid A), which became a key component in several vaccine candidates developed by GlaxoSmithKline (GSK). In 2005, GSK bought Corixa for $300 million.[17] While the acquisition reduced the collaboration between IDRI and Corixa to a limited exchange of royalties, the early benefits of the relationship were significant. For example, IDRI and Corixa shared lessons learned and best practices stemming from their respective development efforts that enabled both organizations to accelerate their progress.

In 2008, Reed started another for-profit vaccine company, Immune Design, with the goal of leveraging IDRI's adjuvant technology into oncology and developed-world infectious disease applications. In addition to technologies licensed from IDRI, related to a next-generation adjuvant called GLA, Immune Design licensed a lentiviral vector delivery system based on the research of Nobel Laureate David Baltimore at Caltech, which specifically targeted the dendritic cells of the immune system.[18] Dendritic cells played a key role in immune response by capturing antigens and inciting an appropriate immune response.[18] IDRI and Immune Design collaborated closely; IDRI provided regulatory guidance, and Immune Design paid IDRI to make the products for its clinical trials and also upon the achievement of certain milestones. The licensing agreement allowed Immune Design to use IDRI-developed adjuvant technologies to pursue commercial appli-

cations (e.g., flu, Hepatitis C, certain cancers, and HIV), while IDRI used the same technologies in its efforts to find solutions for neglected diseases such as TB and malaria. [19] Any Immune Design products that reached the market would generate a royalty stream for IDRI.

According to Iverson, while taking a technology into a for-profit arm necessitated giving up some control, it was a reasonable tradeoff for more flexible and substantial funding from private sources such as venture capital firms. Another benefit of the for-profit companies was that they could also apply for certain funds like Small Business Innovation Research (SBIR) grants, which were not available to nonprofits. "Those funds actually pay for Erik [Iverson] and me," Parker pointed out, "because we're the kind of overhead that foundation grants don't completely cover."

Photo courtesy of IDRI

Researchers evaluate data from the leishmaniasis diagnostic

In parallel, IDRI pursued other opportunities for realizing flexible revenue streams. For example, it licensed its adjuvant technology to a veterinary health company interested in using it in the canine disease market. That relationship has the potential to generate significant income for what Parker described as IDRI's "unrestricted money pool." "That money is the key for nonprofits because it allows you to be strategic and proactive, and not just be tied to grants," she reiterated.

While the benefits of for-profit spinouts were clear, there were challenges as well. "There is tension because your [for-profit] partner wants you to always make sure it's the first priority all the time, and that's probably not going to be the case given our mission-centric programs," Parker noted. Iverson added, "It can also be challenging with the funders, not only because they are communicating with individuals who bridge both organizations, but because the two entities have fundamentally different goals. On one hand, you have a set of venture funds who are driving towards a particular return on investment, and on the other you have philanthropic or global funders who are looking out for the poor of the world."

Challenges aside, however, Parker concluded, "The biggest hurdle for moving these [vaccine] programs along is funding. A creative approach to solving that problem has really allowed IDRI to advance its products further than a lot of similar organizations might have been able to do."

NOTES

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