

Developing a Safe, Inexpensive Cure for 'Black Fever'

If paromomycin is approved by the Indian drug authorities, it will be the first drug the foundation has played an important role in bringing all the way to regulatory approval.



PHOTO COURTESY OF INSTITUTE FOR ONEWORLD HEALTH.
JONATHAN TOROSOVNIK, PHOTOGRAPHER

Program Area

Global Health

Our Goal

Help the Institute for OneWorld Health (iOWH), a nonprofit pharmaceutical firm, bring an old antibiotic called paromomycin to market for a new use: curing visceral leishmaniasis.

Our Progress in Brief

Thanks to the hard work of our grantee, we are likely to achieve this goal in 2006 (one year later than originally planned). This is a significant milestone for the foundation. If, as expected, paromomycin is approved by the Indian drug authorities, it will be the first drug the foundation has played an important role in bringing all the way to regulatory approval.

The goals for this work have now expanded. Once it became clear that iOWH was likely to succeed in bringing the drug to market, both the foundation and iOWH recognized that for real impact they needed to extend this work beyond regulatory approval to distribution. We are now supporting iOWH's work to ensure that the drug will reach those who need it most—all the way to the village level. We are in the early stages of addressing this new goal.

The Challenge

Visceral leishmaniasis (VL), also known as kala-azar (Hindi for "black fever"), is a deadly parasitic disease that has plagued human beings for at least a thousand years. VL, which is transmitted by the bite of female sand flies, kills as many as 200,000 people every year—more than any parasitic disease other than malaria. The disease is almost always fatal if not treated.

Ninety percent of all VL cases occur in five countries: India, Bangladesh, Brazil, Nepal, and Sudan. About half of all the world's cases occur in one state in India—Bihar, just south of Nepal.

The impact of VL is greatest in poor Bihari villages like Harpur Hardi, where village women work in 110° heat harvesting rice and wheat for about a dollar a day. Here, everyone knows someone who has died of the disease.

Sitting on a straw mat, a weary but self-possessed woman who looks 60 but is probably much younger recently related a story that is all too familiar in her village. Her only daughter took ill at age 10 with an unrelenting fever, lost her appetite, and became very weak. Although the family did not have the benefit of a formal education, they recognized the signs of kala-azar and were terrified. The family did not even have enough rupees for bus fare to the city hospital—much less the money

for a full course of drugs (about \$75–\$100). Without treatment, the daughter soon died.

Doctors currently use a number of drugs to combat VL. But even the least-expensive of these treatments are still too expensive for the poorest of the poor. To make matters worse, several of the drugs are highly toxic, and some have become ineffective as drug-resistant strains of the parasite have emerged. There are a small number of effective drugs with minimal side effects, but they are far beyond the reach of the vast majority of those who are afflicted with VL. For example, the drug liposomal amphotericin B costs more than \$5,000 for a full course of treatment.

Because VL almost always strikes those with the least financial resources, large pharmaceutical companies have had little market incentive to develop new drugs that are safe, effective, and inexpensive. This market problem is by no means unique to VL treatment. Over the past 30 years, 1,556 new drugs were brought to market; only 21 of these drugs target diseases that disproportionately affect the developing world.

The Response

In 2001, Dr. Victoria Hale approached the foundation seeking support for a risky new venture she had started the year before, shortly after leaving the successful biotechnology company Genentech. Dr. Hale's venture, named the Institute for OneWorld Health, was a first in the United States—a nonprofit pharmaceutical firm. Dr. Hale explained that iOWH would focus exclusively on developing new medicines for “diseases of poverty” and would be driven by “global need rather than financial opportunity.”

When Dr. Hale approached us, she had just found her first drug candidate: an antibiotic called paromomycin that she believed could be repurposed as a cure for VL. Equally important, she had found that the government of India was eager to partner with her.

Paromomycin had been patented about 50 years before by an Italian pharmaceutical firm for treating infections unrelated to VL, but the drug had fallen into disuse when new products came to market. Only one small facility in Malta was still producing it and was thinking about closing down production.

In the late 1980s, Kenyan physician Dr. Charles Chunge was able to obtain a modest quantity of the drug and, with the support of the World Health Organization (WHO), tested it as a potential cure for VL. His study found that paromomycin was effective in curing all 53 patients who received it.

Additional small studies in India produced similarly positive results. The WHO reviewed the results of these studies but was not able to secure the funding to follow them up.

That is where Dr. Hale picked up the challenge. In order to bring paromomycin to market for this new use, her firm would have to 1) work with the WHO, the government of India, and private researchers to organize and carry out a large and expensive clinical-trial program and 2) navigate India's challenging regulatory-approval process.

In May 2002, the foundation approved the first of three grants to finance this effort. iOWH then initiated the largest-ever clinical trial for VL with the help of Indian doctors who had been treating this disease for decades.

The clinical trial proved more difficult and time-consuming than we anticipated. As newcomers to the global-health field, the foundation and iOWH both had short track records and were met with hesitation by people on the ground in India as well as by international health organizations. For example, local political figures were not eager to have outsiders shine a spotlight on problems in their communities—even in the context of an offer to help address those problems. More surprising was the fact that an international agency was reluctant to share important data from previous paromomycin trials. (For more on these challenges, see “Key Lessons,” below.)

But when iOWH completed the trial and the results came in, they confirmed iOWH's greatest hopes for the drug: Paromomycin cured 95 percent of the 667 patients in the trial, without causing significant side effects.

Dr. Hale and her team are now working to secure regulatory approval for the drug in India. This month (June 2006), iOWH will hand-deliver a final "dossier" of more than 7,000 pages to the office of the Drug Controller General of India. They hope to receive approval by this fall. If all goes well, they may present a similar dossier to the U.S. Food and Drug Administration (FDA). An endorsement from the FDA would carry weight with health authorities in all the countries where VL exists.

Results

- iOWH's large-scale clinical trial has proved that paromomycin is a safe and effective cure for VL and has significant advantages over the existing treatments. (Its one disadvantage is that it must be injected; there is one treatment that can be administered orally, but it is more expensive and cannot be given to women of childbearing age.)
- With iOWH's help, an Indian pharmaceutical firm has developed a safe and efficient process to produce paromomycin at a price of about \$10 for a full course of treatment, significantly less than any other available treatment.



PHOTO COURTESY OF INSTITUTE FOR ONEWORLD HEALTH, JONATHAN TORGOVNIK, PHOTOGRAPHER

- iOWH's work on paromomycin has proved to us and to others that a nonprofit organization can help correct the "market failure" that results when there are inadequate incentives for private industry to address neglected diseases. Paromomycin would have languished in obscurity if not for iOWH's efforts.
- Even prior to formal approval of the drug, the Indian government, with support from the World Bank, is already looking at ways it can incorporate paromomycin into its countrywide disease-control strategies.

Key Lessons

- **Developing a new drug is important, but it is not a final outcome.** The foundation must not view drug development as an end in itself; it is just one step in a long road toward saving lives. For all of paromomycin's cost and safety advantages, it is conceivable that governments, NGOs, and clinicians will not choose to buy it. (As mentioned earlier, one drawback is the fact that it must be delivered through injections rather than orally.) Like commercial pharmaceutical companies, nonprofits must use every tool at their disposal to understand the market for a new treatment, the attitudes and practices of those who

need treatment, and the smartest ways of building demand. Without these comprehensive efforts, the expense of drug development—and the opportunity to help save thousands of lives—could be lost.

- **We underestimated the funding that would be necessary to bring this product to market.** iOWH has been frugal with its resources and has brought in significant volunteer and in-kind support. But even with careful stewardship, when it comes to neglected diseases, the final stages of drug development are extremely expensive—and not easy to predict with certainty ahead of time. We ask grantees for highly detailed cost projections, but we are learning that we need to allow for uncertainty and flexibility.
- **It is essential for grantees to have a strong, local project manager.** When iOWH initiated its clinical trial, the organization tried to navigate complex local issues from a distance; they didn't have a local project manager with access and credibility on the ground. Fortunately, they were able to rectify this by hiring an outstanding on-site project manager, who worked very effectively with local leaders and scientists. (iOWH is now planning to open two local offices in India, staffed by Indians.) This project taught us that we need to ensure that our grantees have high-caliber local project managers in place at the outset of such efforts—and that we need to be willing to pay for this.
- **The foundation must be willing to step in to mediate disputes (but pick its battles carefully).** At one point, the foundation stepped in to ask an international agency to expedite the release of critical data our grantee needed in order to carry out its trial. That agency felt that we were heavy-handed. We do not take that criticism lightly; we recognize that we need to be very careful if we are to avoid being “a bull in a china shop.” But in this case, we feel that it was an appropriate use of our voice. If a similar scenario presented itself in the future, we would step in sooner.
- **Without our funding, the Institute for OneWorld Health's current funding model would need to change.** iOWH has proven that a nonprofit pharmaceutical firm can develop new medicines for diseases of poverty. However, we must acknowledge that its ability to meet this goal rests heavily on a single source of financial support. The foundation has committed nearly \$180 million to iOWH for a host of different projects, approximately 96 percent of its funding. To ensure that iOWH succeeds over the long term and that other nonprofit organizations join the field, we need to find ways of helping iOWH expand its funding base.
- **Visiting local project sites is essential for the foundation's program officers.** If we had not conducted site visits or had not been granted the ability to speak directly with the local iOWH project manager on a regular basis, we would not have had a full understanding of the nature of the delays in the clinical trial, and we might have pulled back our support prematurely.

Next Steps

In order to help the world combat VL, we need to ensure that paromomycin is put into use as one important component of a broad package of diagnosis, treatment, and prevention efforts targeting every aspect of the disease.

In 2005, we provided significant additional funding to iOWH to launch a pilot program in India that will help identify how to deliver paromomycin in the world's poorest rural settings. As part of this pilot program, some patients will receive paromomycin in government-run district hospitals and clinics. But, in a break from established tradition in India, many others will receive it through nongovernmental organizations, such as the Bihar-based Janani network.

The Janani network was started in 1996 as a set of franchisees selling condoms and oral contraceptives in small shops in Bihar and Jharkhand—two of India's poorest states. Today, thanks in great measure to outside support from the David and Lucille Packard Foundation, Janani franchisees are building more than 40,000 shops and 57,000 rural health centers—nearly one per village. We believe that making VL diagnosis and treatment available through Janani and other nongovernmental clinics will be an effective way to expand access in a setting where public-health services are extremely weak.

We are also working with other grantees to help develop the next generation of VL drugs. Paromomycin is highly effective today, but it is not a silver bullet. There is a small but real chance that the parasite will develop resistance to the drug. Therefore, the wisest public-health strategy is to combine paromomycin with other new drugs—just as doctors do with drugs for malaria, TB, and HIV/AIDS. We have already made one grant, to the University of North Carolina, to work on a new oral drug for VL. A vaccine for VL that would provide a lifetime of immunity would be an even more powerful weapon, and we have made a grant for this purpose to the Infectious Disease Research Institute.



PHOTO COURTESY OF INSTITUTE FOR ONEWORLD HEALTH, JONATHAN TORGOVNIK, PHOTOGRAPHER

Web Sites

- Institute for OneWorld Health:
www.oneworldhealth.org
- Government of India:
<http://namp.gov.in/>
- World Health Organization:
www.who.org
- Janani:
<http://www.janani.org/>
- The World Bank Group:
www.worldbank.org