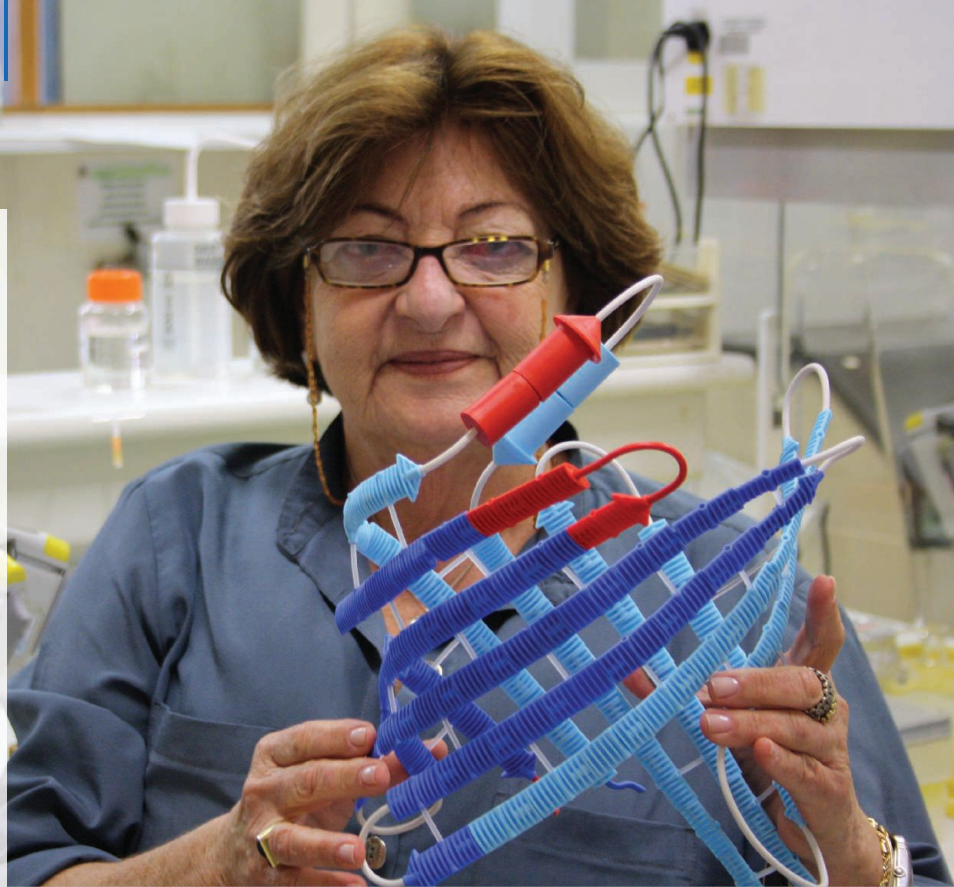


A Worm Vaccine, Coming at A Snail's Pace

The long struggle to develop a schistosomiasis vaccine badly needs new money



RIO DE JANEIRO, BRAZIL—Miriam Tendler has not moved her lab in more than 20 years. Her office is cramped and filled with stacks of paper, and the hallways are lined with big filing cabinets. Yet Tendler has stayed in this old, low building on the campus of the Oswaldo Cruz Foundation, she explains, because she is afraid of doing anything that could disturb the life cycle of the microscopic worm that she has carefully nurtured in her lab all these years. Tendler has devoted her career to developing a vaccine against this worm, a pernicious parasite that is a scourge of people in eastern Brazil: *Schistosoma mansoni*.

Her target is one of at least six flatworms that cause a debilitating human disease called schistosomiasis. The worms can live for decades in blood vessels, shedding eggs that cause pain, severe blood loss, and malnutrition and that can damage the liver, kidneys, and spleen. Half of their unusual life cycle takes place in freshwater snails, which is why one room in Tendler's lab houses dozens of aquariums.

According to the World Health Organization (WHO), schistosomiasis, also known as bilharzia, is the second most devastating parasitic disease in the world, after malaria. Some 200 million people are estimated to be infected, most of them children, and another 600 million are at risk. Mortality estimates vary widely, but Lester Chitsulo, who heads

WHO's Schistosomiasis Control Programme in Geneva, Switzerland, says that there are probably almost 300,000 deaths a year in sub-Saharan Africa alone.

Vaccines could be powerful weapons against schistosomiasis, but a lack of interest and money, combined with the fact that a cheap, effective drug is available, has hampered research. "We have limped along with small amounts of money," says Alex Loukas of James Cook University, Cairns, in Australia. That could change if, as researchers hope, the Bill & Melinda Gates Foundation joins the fight. Next month, the foundation will bring experts to Seattle for a 2-day meeting to discuss schistosomiasis vaccines. If it decides to fund the research, everything could change, Loukas says.

There has been some progress; two vaccines are now in clinical trials. But there are questions about both. Bilhvac, developed at the Pasteur Institute in Lille, France, targets *S. haematobium*, a species that causes urogenital schistosomiasis and is common in Africa and the Middle East. But despite extensive trials, very little has been published so far, leading other scientists to wonder what's going on.

The other is Tendler's candidate against *S. mansoni*, backed by the Brazilian government through a public-private partnership. The vaccine, the only one from a country where *Schistosoma* is endemic, may enter

phase II trials this year. (It's based on a protein called Sm14, which a worm uses to ferry a host's fatty acids into its own cells.) But some groups have been unable to replicate the high level of protection that Tendler has shown in mouse studies.

What's more, vaccines are needed for other *Schistosoma* species as well, as there is no one-size-fits-all vaccine. "We need to develop a pipeline," says Peter Hotez, dean of Baylor College of Medicine's National School of Tropical Medicine in Houston, Texas. Hotez is working on a vaccine candidate named Sm-TSP-2 that has yet to reach the clinic; another candidate, Sm-p80, is also being developed in the United States.

Into the groove

Different *Schistosoma* species cause different patterns of symptoms, but the parasites essentially follow the same lifecycle. They reproduce in freshwater snails that release large numbers of free-swimming larvae, called cercariae, into the water. When these find a human, for instance a child playing in the water, they burrow through that person's skin with their head. The larvae then lose their tail and migrate through the blood vessels and the lung into the liver, where they mature into adult worms and mate. The larger male worm forms a groove, which the thinner female slips into.

Together, the couple moves into veins

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Eyes on the target. Miriam Tendler's vaccine candidate is based on Sm14, a crucial *Schistosoma* protein.

in different parts of the body, depending on the species: *S. mansoni* and *S. japonicum* reside in the bowel and rectum, for instance, whereas *S. haematobium* migrates to the bladder. The females start producing hundreds of eggs daily, sometimes for many years. Most of them are shed in urine and feces, and they can infect new snails if they end up in lakes or rivers. But some get trapped in the liver or other organs, causing an immune response that leads to the typical symptoms and sometimes death.

Public health officials tried for decades to get rid of schistosomiasis by targeting the snails. Despite sporadic successes, that strategy has proved too daunting in rivers like the Nile and the big lakes in Africa. Since the 1980s, a drug called praziquantel, which kills the worms in a person's body, has been the weapon of choice. In many endemic areas, all schoolchildren get the drug annually; Merck has provided praziquantel to WHO for free since 2007 and recently pledged to increase its annual donation to 250 million tablets.

But scientists worry that such widespread use will fuel resistance against praziquantel, the only drug available. Moreover, people in endemic areas usually get reinfected within months of treatment, so there is little long-term progress. "I think people are finally realizing that drugs alone are unlikely to control schistosomiasis," Loukas says.

Vaccines would probably not prevent human infections, but they could reduce the number of eggs that female worms produce, which in turn would reduce symptoms and slow transmission, says Maria Yazdanbakhsh of Leiden University Medical Center in the Netherlands, who heads a European project to find a vaccine against *S. mansoni*. "If the worms produce fewer eggs, the water will be less infested, and that will slowly reduce transmission." Studies suggest this is possible. Adults in endemic areas have been found to be partially immune to reinfection, and in animals, vaccines were shown to reduce the number of eggs by about half.

Hotez thinks support for a vaccine is now growing, in part because of schistosomiasis's role in the HIV epidemic: Female genital schistosomiasis increases the risk of con-

tracting HIV three- or fourfold. If the Gates Foundation steps in, it would raise the disease's profile, Yazdanbakhsh says, and that could encourage national governments to donate as well. So far, the foundation has made no commitment, and it would not comment to *Science*.

Painful rashes

Even if more money becomes available, there are obstacles to a successful vaccine. One of them emerged in 2007 during a trial of a vaccine against a different group of parasites called hookworms. Healthy U.S. volunteers tolerated the shots well, but a study conducted in an area of Brazil where hookworm infection is common had to be suspended when three of the first seven volunteers developed painful rashes on their head,

the two in clinical trials—such data have yet to be presented.

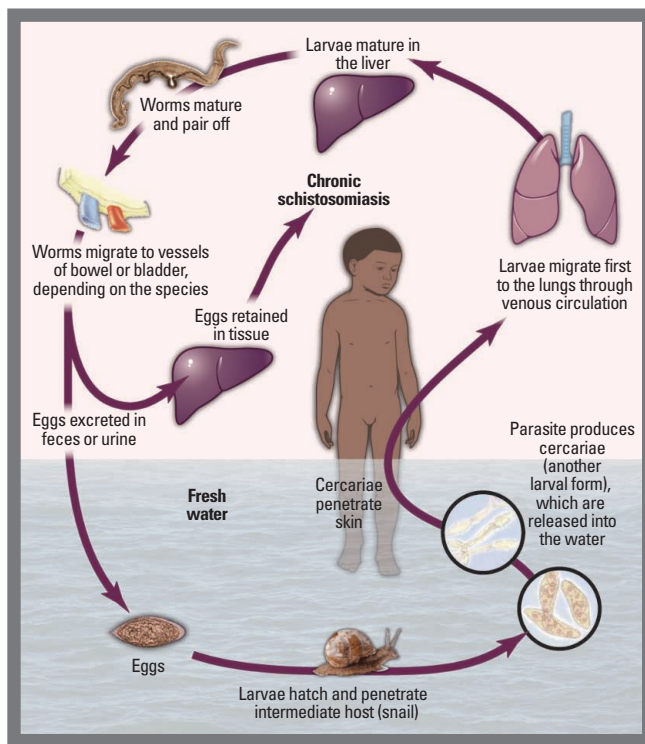
Another difficulty is that the results of several promising studies in mice—including Tendler's Sm14 vaccine—have not been replicated by researchers in other labs, for reasons that aren't clear. "This is a problem that has plagued the schistosomiasis field for many years and it has done the field an enormous amount of harm," Loukas says. How well results in mice translate to humans is also unclear. Although *S. mansoni* infects mice readily, the rodent is not a natural host; in terms of sheer size, one pair of worms in a mouse is equivalent to a very heavy infection in humans. Some researchers have switched to other animal models, such as baboons, which require special facilities and are more expensive.

The French vaccine, meanwhile, is a bit of a dark horse. A phase I trial, done in 1998 and 1999 in France, was not published until July 2012; phase II and phase III studies, both completed, have yet to appear. The team's original strategy was to go through all the phases before publishing anything, Gilles Riveau of the Pasteur Institute writes in an e-mail to *Science*. "I think today that we were wrong," he adds, saying that results on phase II may be out soon.

Others are betting on new targets, and the genomes of *S. mansoni* and *S. haematobium*, both now sequenced, have given them a wealth of choices. Yazdanbakhsh and colleagues are aiming at the earliest form of the worm that the immune system encounters: the larvae passing through the skin. Scientists in the consortium have identified genes that are turned on only in this stage; by targeting these proteins, they hope to catch the worm before it has its defenses up. Such a vaccine, they hope, might prevent infection altogether.

Loukas's group, meanwhile, has developed an array of *Schistosoma*'s surface proteins, which they have screened against the blood of resistant individuals to see which antigens are recognized by their immune system. A new vaccine candidate will be published soon, he says.

With so much new technology available, developing a vaccine is now primarily a question of political will, Tendler argues. "This is not a bet, this is not a game, this is not magic. It is just work." **—KAI KUPFERSCHMIDT**



Circle of life. *Schistosoma*'s life cycle takes it from freshwater snails to human blood vessels and back.

neck, and shoulders. The rash was caused by a class of antibodies called IgE, which the volunteers had developed during prior hookworm infections, says Loukas, who was involved in the trial.

To prevent such nasty surprises with *Schistosoma*, Loukas says, any new vaccine candidate needs to be screened to see whether people in endemic areas might have IgE in their blood that reacts with it. "If they do, we immediately throw the candidate out," he says. For some of the candidates already in development—including