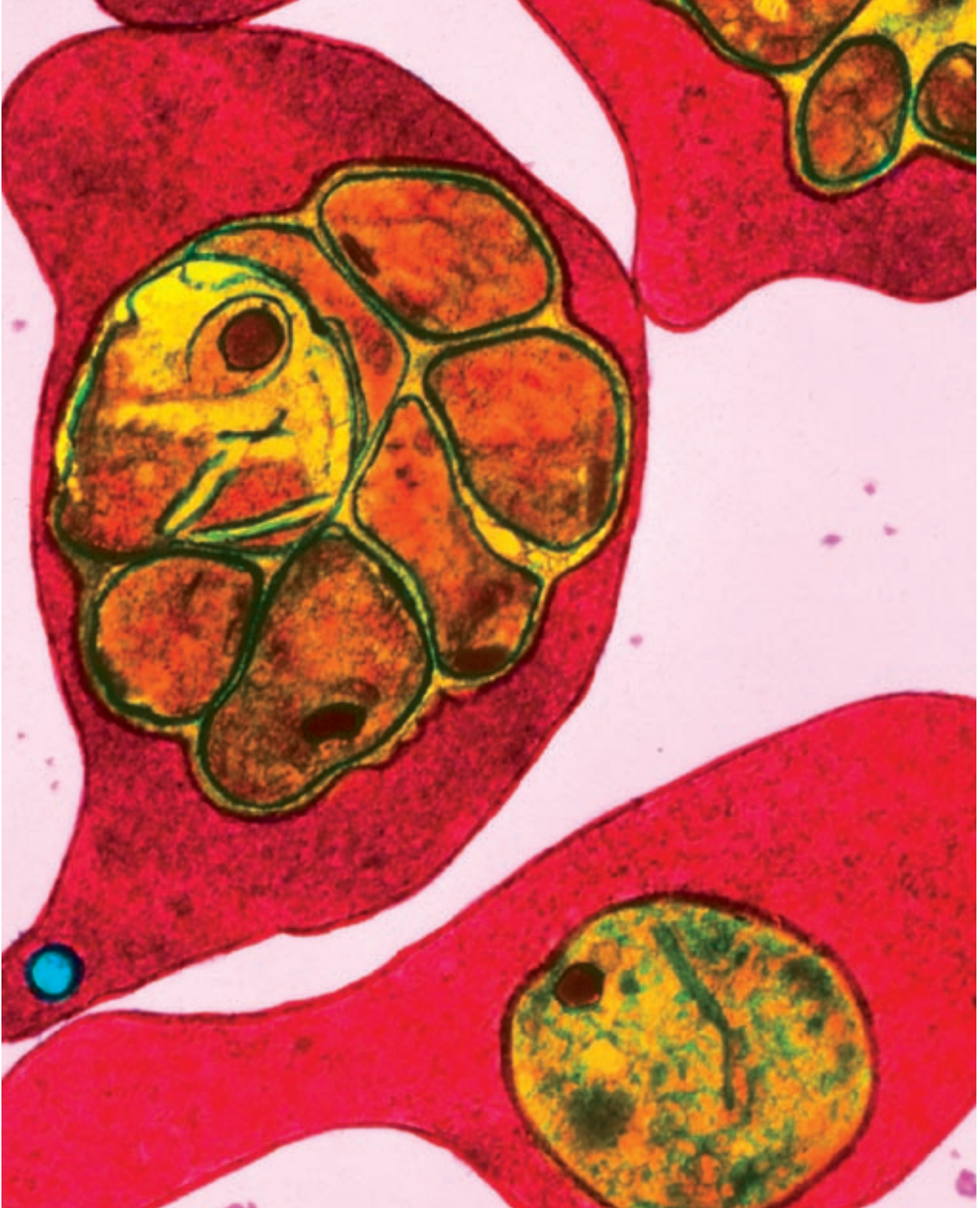


Fighting the Parasites

HHMI international research scholars find promising ways to target Chagas disease and malaria.

BELOW _ MALARIA PARASITES EXIST "CLOAKED" WITHIN RED BLOOD CELLS, WHERE THEY DIVIDE INTO SMALLER CELLS CALLED MEROZOITES THAT ARE RELEASED INTO THE BLOODSTREAM WHEN THE CELL EVENTUALLY BURSTS. (SEE SIDEBAR ON MALARIA, OPPOSITE.)



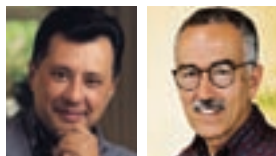
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THE CHALLENGE OF CHAGAS

BIOGRAPHERS AND HISTORIANS GENERALLY believe that Charles Darwin caught Chagas disease during his voyage on *The Beagle* in the early 1830s, and that the disease may have been the root cause of the chronic illnesses that affected Darwin's health until his death in 1882. Today, 123 years later, there is still no effective treatment for the chronic form of Chagas disease, which continues to kill tens of thousands of people annually. But after several decades of research, two scientists think they have found a possible cure.

The disease—caused by the parasite *Trypanosoma cruzi*, which is spread by biting insects known as “kissing bugs”—currently infects between 16 and 18 million people in Central and South America, with 120 million people at risk. Chagas disease occurs in an acute form mainly in children, but in adults there often are no acute symptoms. When the infection reveals itself a decade or two later, irreversible damage has been done to the heart, esophagus, and colon; the

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JULIO A. URBINA,
MIGUEL A. BASOMBRIO



patient gets progressively sicker, usually dying of heart failure. The “kiss” of the parasite’s vector has aptly been called the kiss of death.

The drugs currently used to treat Chagas disease, mainly benznidazole, have serious drawbacks. They don’t work against the chronic form, which kills up to a third of those infected; they can have toxic side effects; and it is common for the parasite to have a natural resistance to them. So an alternative is badly needed. A team led by HHMI international research scholars Julio A. Urbina of the Venezuelan Institute of Scientific Research and Miguel A. Basombrio of the National University of Salta (Argentina) believes it has found that alternative in an experimental compound called TAK-187.

This compound, under investigation for a different therapeutic end as a possible systemic antifungal treatment, turns out to target the Achilles’ heel of *T. cruzi*, which Urbina, Basombrio, and colleagues have discovered from 25 years of studying the basic biology of the parasite. To complete its life cycle, *T. cruzi* needs to synthesize certain types of steroids, called sterols, that are present in nucleated cells. But the parasite cannot make use of the sterol that is most abundant in the tissue of its mammalian host—cholesterol. Instead, it prefers one called ergosterol.

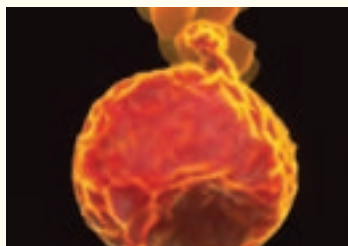
This is where TAK-187 comes in, says Urbina. “It is a compound that blocks the synthesis of ergosterol in the parasite without affecting that of cholesterol in the hosts, and it penetrates into the deep tissues where the parasite thrives.”

His team infected mice with a strain of *T. cruzi*, waited until they showed symptoms in a model of the chronic form of human Chagas disease, and then treated the animals with benznidazole, TAK-187, or a placebo. The two drugs either suppressed the parasite load in the mouse blood and tissue or eliminated *T. cruzi* entirely. But TAK-187 did so at a tenth of the dose, and it worked as well when given every other day, whereas benznidazole had to be administered daily. Postmortem tissue analysis also showed that TAK-187 was more effective than benznidazole at preventing inflammation and damage in the heart and skeletal muscle of the mice.

The researchers, whose work was published in the April 2005 issue of *Antimicrobial Agents and Chemotherapy*, believe the greater efficacy of TAK-187 comes down to the fact that it strikes at the parasite’s ability to replicate and that it is more slowly metabolized by the host, allowing a sustained antiparasitic action. Citing these “potentially interesting” findings together with the “urgent need for new drugs,” John M. Kelly of the London School of Hygiene and Tropical Medicine says that “this preliminary report should point the way to trials on human patients.” ■

— Laura Spinney —

THE CLOAK OF MALARIA



Once in the human body, malarial parasites spread to the liver and multiply in red blood cells such as this one, misshapen and bulging from the malarial parasites within.

In another promising advance against parasitic disease, HHMI international research scholars Alan F. Cowman of the Walter and Eliza Hall Institute of Medical Research, in Melbourne, Australia, and Brendan S. Crabb of the University of Melbourne have peered behind the invisible cloak of the malaria parasite *Plasmodium falciparum*. This parasite invades the host’s red blood cells, from which it exports proteins. Some are virulence factors, aiding the parasite’s spread and colonization of its host; others remodel the surface of the red blood cell, making it undetectable by the host’s immune system.

In a paper published in the December 10, 2004, issue of *Science*, Cowman’s group identified the common mechanism by which the

parasite exports all 400-plus proteins. That mechanism “provides an extremely good target for the development of new drugs,” he says.

In a follow-up paper published in the April 8, 2005, issue of *Cell*, the Cowman and Crabb groups looked specifically at the parasitic proteins that render the red blood cell invisible. The immune system eventually works out what the masking protein is, and it mounts an immune response. But the elusive *P. falciparum* then switches to another protein—and it has a repertoire of at least 50 to choose from. The researchers shed even more light on this trick by showing how the gene for the protein in question is activated while the others are silenced.

—L.S.