Ancient Organisms, Modern Scourges

Researchers work to disable parasites that cause sleeping sickness and Chagas disease

Trypanosomes are a family of microscopic parasites, cause a mountain of suffering. Among the trypanosomes’ most virulent weapons is African sleeping sickness, which is responsible for more deaths than HIV/AIDS in sub-Saharan regions.

In all, the disease threatens more than 60 million people in 36 countries on the African continent, and the World Health Organization estimates that, of this population, only four million are under active surveillance or have access to health centers where reliable diagnosis is available.

Chagas disease, caused by a related trypanosome, affects approximately 18 million people in Central and South America. About 25 percent of the 100 million people living in that part of the world are considered at risk.

Both parasites are wily opponents. These ancient organisms have developed ingenious defenses against attack. The African parasite, transmitted by the bite of the tsetse fly, is enclosed in an infinitely changeable protective protein coat. When the trypanosome comes under attack by the host’s immune system or a vaccine, the parasite changes its coat proteins, rendering it impenetrable.

The American parasite, transmitted via the triatomine bug, also known as the assassin bug or kissing bug, has a different type of protein coat and evades the immune system primarily by living in and dividing inside the host cells.

Both defenses make it improbable that a useful vaccine against trypanosomiasis—the general term for these diseases—ever could be created. Unfortunately, the few treatments that do exist are so toxic; they can be worse than the symptoms, which are devastating in the extreme.

Making the situation worse for those in areas where trypanosomiasis is endemic is the fact that its variations are difficult to diagnose, even under the best of circumstances. African sleeping sickness exists in two forms, West African and East African, dictated by the geographic range of the species of tsetse fly that spreads the parasite.

Both infections begin with the insect’s bite, which initially causes mild symptoms, including fever, weakness, headache, joint pains and itching at the site of the bite. East African sleeping sickness progresses from early to advanced stages within days or weeks, making a diagnosis easier.

West African sleeping sickness, in contrast, may become asymptomatic for months or years before entering its advanced stage.

In both forms, the parasite eventually overpowers the immune system and invades the body’s vital systems, including the brain. If sleeping sickness is not treated early, death is inevitable.

Chagas disease, which may remain asymptomatic for decades, primarily attacks the heart, esophagus and colon. Death results eventually from heart failure.

The work of two UB molecular parasitologists, Noreen Williams, PhD, and Laurie Read, PhD, could brighten this dark scenario. Although they work in separate laboratories a few doors apart and are following slightly different routes, both scientists are studying the African sleeping sickness parasite Trypanosoma brucei with the goal of finding promising targets for drugs that could treat both of these devastating diseases.

Because the chances of preventing infection by killing the parasite from the “outside” via a vaccine are close to zero, Williams and Read hope to defeat it from the “inside” by creating a chemical Trojan horse. The researchers are looking for ways to disrupt the parasite’s most basic mechanisms to prevent it from multiplying in its human host.

Williams, a professor of microbiology and immunology, is investigating regulatory events in T. brucei, particularly the role of the enzyme mitochondrial ATP synthase in the parasite’s life cycle. Her work could identify crucial processes that could become targets for drugs to prevent transmission.

Read, associate professor of microbiology and immunology, studies the basic biological mechanisms of T. brucei, concentrating on the processes of RNA editing and RNA turnover. Interrupting any of these events could prevent the parasite from replicating and could identify pathways for drug interventions.

“Our work is very similar, very related,” says Read, “and while we don’t collaborate in the strictest sense of the word, we interact intellectually on a regular basis, to the benefit of both our labs.”
Both Read and Williams are in the top third of UB researchers in terms of active federal grants and together account for more than $7 million in research dollars. Read recently received a $1.5 million grant from the National Institutes of Health to continue studying RNA editing in T. brucei. Publications by Williams and Read on trypanosomes total more than 50.

Williams has studied the life cycle of the trypanosome for 19 years, the last 14 in her laboratory in UB’s Witebsky Center for Malarial Pathogenesis and Immunology. Introduced to the quirky parasite by fellow researchers early in her career, she found it sufficiently intriguing to abandon her purely chemical approach to finding the parasite’s secrets. “It’s a fascinating organism,” she observes.

Read came to UB in 1994 after spending four years as a postdoctoral researcher in molecular parasitology at the Seattle Biomedical Research Institute. She now supervises a master’s student, four doctoral students, two postdoctoral fellows and a technician in her laboratory in the Witebsky Center. “Trypanosomes are important medically because they cause diseases that kill approximately 300,000 people per year,” she says. “They are also of basic biological interest for a number of reasons. They are ancient organisms, so what we learn from trypanosomes can help us understand the evolution of fundamental processes in nucleated cells. In addition, they are model organisms for the study of RNA metabolism—gene regulation at the RNA level.

“Many organisms do a lot of regulation at the level of either making the RNA copy of a gene or not,” she continues. “Trypanosomes don’t regulate this step; they make all the RNAs all the time. They regulate whether the encoded proteins ever get made by either correctly processing the RNA or not, and by specifically regulating the stability of different RNAs under different conditions.”

Trypanosomes provide an especially good model to study RNA metabolism, she points out, because they are specifically geared up to make the transition from one host to another. If you can knock out expression of these essential proteins, the parasites can’t survive and the disease would be prevented.

Read was studying the biochemistry of malaria parasites until she heard a presentation on RNA editing in trypanosomes at a professional meeting and was smitten on the spot. “It’s a fascinating organism,” she observes.

Read and Williams have been studying trypanosomes for 19 years in ways that should enhance such efforts. In 2000, Williams began collaborating with a laboratory headed by Beatriz Garat, PhD, in Montevideo, Uruguay, where Chagas disease is endemic. The work is focused on regulation of gene expression in Trypanosoma cruzi, the Chagas disease agent. Several of Garat’s students have come to UB to work in Williams’ laboratory. One of those students has since established a laboratory in Curitiba, Brazil, and Williams has begun collaboration there as well.

None of these diseases has invaded the U.S., but neither geographical borders nor vast oceans offer protection in the 21st century. “I think most of us have come to recognize” says Read, “that with immigration to the U.S., travel abroad by so many U.S. citizens, and military deployments to exotic locales, that all ‘tropical’ diseases have the potential for significant impact on our lives and our health-care system.” You can’t kill something if you don’t know how it lives. You have to know how it works, how it responds. When you understand these things, you understand what’s essential for the organism’s survival.

— Noreen Williams, PhD

### Trypanosomes

The battle against parasites is being waged by researchers from many disciplines, including biology, ecology, epidemiology, public health, toxicology, microbiology, parasitology, and veterinary sciences.

Trypanosomes, a guide on the UB Health Sciences Library web site at http://ahls.lib.buffalo.edu/ resources/guides/trypanosomes.html provides resources on research to control transmission of African Sleeping Sickness, Chagas disease, and Leishmaniasis.


The University of Cambridge Department of Pathology maintains a site at http://www.mshrc.ox.ac.uk/parasites/ about the world in which to tackle this and emerging infectious diseases that increase as international travel brings humans and organisms together. Also included is a selected bibliography of articles published by UB molecular parasitologists Noreen Williams, PhD, and Laurie Read, PhD, and a list of books and journals available in HSL on the topic.

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