blocks can be moved very fast, potentially offering gigahertz bandwidth switching. The first generation of randomly accessible reconfigurable metamaterials or nanomembranes, providing control in a single spatial dimension, have been realized and can function as refocusable lenses or dynamic diffraction gratings.

Phase change is another technology that can work for metamolecular-level switching. Initially developed for rewritable optical discs, it offers a mechanism for nonvolatile switching of optical properties within a nanoscale volume (*11*). This provides a new platform for creating optical components that are written, erased, and rewritten as two-dimensional binary or grayscale patterns into a film of chalcogenide glass using tailored trains of femtosecond pulses. Reconfigurable bichromatic and multifocus Fresnel zone plates, superoscillatory lenses with subwavelength focus, grayscale holograms, and a dielectric metamaterial with on-demand resonances have been demonstrated.

Another emerging technology for controlling and switching the manifestation of optical properties in metamaterials is coherent control. A highly absorbing plasmonic metamaterial film of subwavelength thickness that is placed in the node of a standing wave formed by counterpropagating control and signal waves will see zero electric field and so will not absorb the light. Any change in the phase or intensity of the control wave will distort the standing wave pattern and destroy the regime of zero absorption. This effect can underpin various forms of optical switching (*12*) operating down to the level of a few photons and with a modulation bandwidth up to 100 THz, presenting powerful opportunities for laser spectroscopies, image processing, and data handling in the locally coherent networks that are increasingly part of the mainstream telecommunications agenda. ■

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INFECTIOUS DISEASES

Overcoming neglect of kinetoplastid diseases

Drug development offers hope for controlling diseases that affect millions of people worldwide

By **Graeme Bilbe**

Of the 17 neglected tropical diseases listed by the World Health Organization (WHO) (*1*), three are caused by parasitic kinetoplastid protozoa: human African trypanosomiasis (HAT; also known as sleeping sickness), leishmaniasis, and Chagas disease. The three diseases are responsible for high mortality and morbidity among the world's poorest populations. Although these and other neglected diseases have received increased attention over the past decade, new drugs are still scarce: From 2000 to 2011, only 4% of new drugs and vaccines were registered for neglected diseases (*2*). However, the drug development pipeline, with sustained resources and research efforts, should see the delivery of new drugs for these diseases over the next decade.

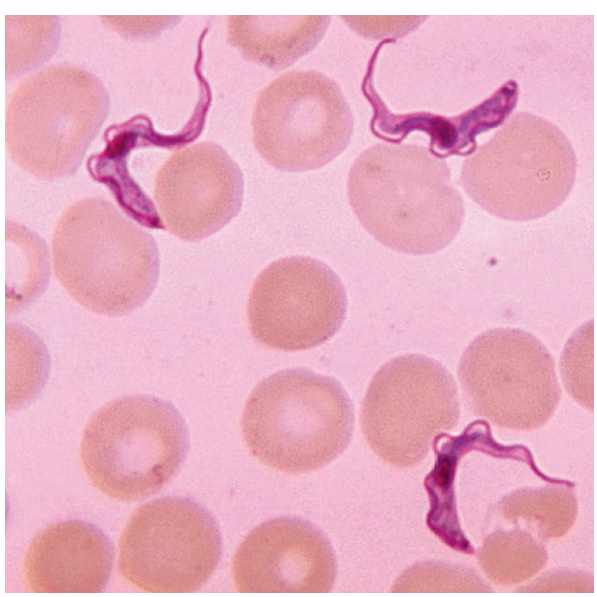
INFECTIOUS DISEASE SERIES

KINETOPLASTID DISEASES. Transmitted by insects, these poverty-related infectious diseases are genetically highly diverse. They cause a spectrum of often chronic visceral and disfiguring skin diseases that can be fatal and that exact a high socioeconomic burden on patients and their families. Most cases occur in impoverished countries with poor health resources, but the diseases are also reemerging in Europe and the United States.

HAT is caused by *Trypanosoma brucei* (see the first figure). It is transmitted by the bite of an infected tsetse fly and is fatal without treatment. Active case detection and treatment have led to a fall in the number of cases, currently estimated at 20,000, and sustained efforts are vital to ensure that the WHO's target to eliminate HAT as a public health problem by 2020 is achieved and maintained. The initial hemolymphatic phase of the disease generally goes undiagnosed without active surveillance.

Leishmaniasis is caused by *Leishmania* parasites that are transmitted by phlebotomine sandflies. Visceral leishmaniasis (fatal without treatment) and cutaneous leishmaniasis are the two most common forms of the disease, which is prevalent in 98 countries with 350 million people at risk. Leishmaniasis was long considered not to be a public health threat to high-income countries, but population increases, migration, and climate change may be spreading it, as highlighted by a recent serious outbreak in Madrid, Spain (*3*). Of even greater concern is the change in epidemiology of the more serious visceral form due to the spread of HIV (*4*).

Chagas disease is caused by *T. cruzi* parasites. An estimated 6 million to 7 million people worldwide are infected with the parasite. The disease is endemic in 21 countries of Latin America, where it causes more deaths than malaria, but can remain asymp-



Trypanosoma sp. parasites in blood smear from a patient with African trypanosomiasis. The parasites are about 16 to 42 μm long.

ILLUSTRATION: C. SMITH/*SCIENCE*; IMAGE: CDC/MYRON G. SCHULTZ

tomatic for many years. Chronic symptomatic disease, which most often affects the heart and digestive tract, develops in up to 30% of cases.

DRUG DISCOVERY CHALLENGES. There is a need for affordable treatments that are adapted for use in resource-poor settings and can withstand the environmental conditions of endemic countries. Challenges to drug discovery and development include a lack of understanding of drug targets and obstacles to developing high-throughput screening technologies. In addition, there is a paucity of animal models predicting efficacy in patients, with further challenges in performing clinical studies that meet international standards in resource-poor settings.

Given the relatedness of the kinetoplastids, it is hoped that future oral therapies developed for one species may have utility against another. However, this goal remains unmet, because the biology of the parasites during disease and the essential biological pathways necessary for parasite survival in the host are not well understood, and selection of lethal drug targets unique to the parasite has not been possible to date. For leishmaniasis, varying levels of drug efficacy are documented for South Asian, East African, and Latin American patient populations (*5*, *6*), illustrating the lack of understanding of parasite diversity and parasite-host interaction in the action of therapeutic agents.

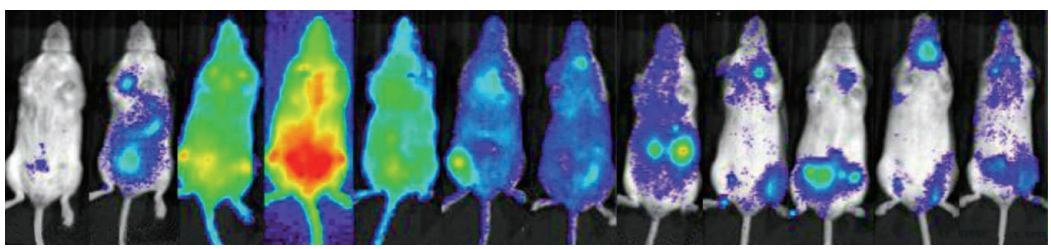
Translation into the clinic is a further challenge for kinetoplastid disease therapies. Kinetoplastid parasites are accomplished evaders of host immune response, complicating animal testing of drugs and the interpretation of animal test data. Lack of knowledge about parasite evasion mechanisms and the complexities of drug action in animal models can lead to an overestimation of "cure" in humans. Lewis *et al.* have used noninvasive bioluminescence imaging to show how *T. cruzi* parasite load varies by tissue type over time (see the second figure) (*7*). The results highlight the need for serial sampling of accessible tissue compartments to demonstrate the absence of parasites in patients during and after treatment, as well as for improved biomarkers and diagnostics for Chagas disease.

Not all drug candidates will advance unhindered through development, and resistance to new drugs may render new tools quickly ineffective in therapeutic settings. Alternatives will thus be needed. However, the rise of resistance can be countered by developing combinations of drugs with different mechanisms of action, as has been shown with older drug combinations such as NECT (nifurtimox-eflornithine combination therapy) for HAT or sodium stibogluconate and paromomycin for visceral leishmaniasis. Only new drugs will overcome the remaining serious issues of drug administration and toxicity.

Further challenges are faced as candidate drugs progress into clinical studies. A human experimentally induced infection model for malaria (*8*) allows rapid testing of promising candidates in healthy volunteers inoculated with low numbers of parasites and treated with a test drug. Should the test substance show lack of efficacy against the parasite, a proven treatment is administered to prevent the development of full-blown disease in healthy volunteers. Combining safety and efficacy tests in this way can expedite progress to large-scale field trials in patients. Unfortunately, drugs for kinetoplastid diseases cannot currently be tested in this way, and new treatments require lengthy follow-up to demonstrate sustained recovery by the patient.

It is also crucial that evidence-based clinical research in endemic countries is conducted to the same standards as those demanded in the developed world. Careful consideration is needed to ensure that patient consent is properly obtained. Local ethical requirements need to be met and cultural needs respected. It is often necessary to improve site infrastructure by equipping sites with solar energy or generators to run laboratory equipment and to guarantee the cold chain required for samples, together with Internet access for the transmission of clinical data. Local personnel need to be trained in the conduct of clinical trials to conform to international standards, and accessing sites can be difficult, especially during the rainy season.

There is also a continued need for rapid, sensitive, and specific diagnostic tests for patient screening and to confirm parasitological cure following treatment. In the case of HAT, although a first generation of rapid diagnostic tests (RDTs) with high sensitivity and specificity has been developed, they still need to be deployed, particularly in order to extend passive screening in fixed health facilities. A second generation of RDTs based on recombinant antigens is in development, but the need to find a confirmatory surrogate marker of parasitological cure following treatment remains. The need for rapid tests goes beyond clinical trials; for instance, by mobile teams in Africa who travel to villages far from treatment centers to screen, diagnose, and determine the state of HAT progression. Disease staging requires examination of cerebrospinal fluid obtained by lumbar punctures, and needs to be carried out at diagnosis and after treatment. Ultimately, rapid tests will become part of the tool kit needed to carry out a "test and treat" strategy at the village level for disease elimination.



Hide and seek. Bioluminescence imaging of mice infected with *T. cruzi* parasites shows that infection is highly dynamic in space and time (*7*). The figure shows snapshots of infection in the same mouse over the course of 140 days. The colors indicate the bioluminescence intensity from low (blue) to high (red).

THE DRUG PIPELINE. Until 2009, therapies for the advanced, neurologic phase of HAT were toxic or difficult to administer. The main treatment, the arsenic compound melarsoprol, required 10 painful daily injections, with ~5% treatment-related mortality. The current combination of oral nifurtimox and infusions of eflornithine (NECT) is a vast improvement, but requires patient hospitalization. Two compounds undergoing clinical evaluation may become the first oral-only treatments: fexinidazole and SCYX-7158 are in phase IIb/III and phase I trials, respectively (*9*), and are potentially useful for both stages of the disease.

Pentavalent antimonials have long been used to treat visceral leishmaniasis despite requiring slow, painful injections or infusions; side effects include cardiotoxicity and pancreatitis. Parasite resistance to such therapies is on the increase. New formulations and alternative treatments (including

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liposomal amphotericin B, miltefosine, and low-cost paromomycin) have become available over the past decade, but each has disadvantages, such as difficult administration, toxicity, or cost. There are also regional differences in response to therapy. Exploratory studies are evaluating the efficacy of fexinidazole in visceral leishmaniasis patients, and several potential oral drug candidates are undergoing preclinical evaluation.

Benznidazole and nifurtimox are the only available treatments with potential to cure Chagas disease, but have many side effects. Recent trials with two azole class compounds—posaconazole and the ravuconazole pro-drug E1224—showed neither to be sufficiently effective alone (*10*, *11*), although benznidazole monotherapy did show sustained effect for 12 months and longer. More clinical studies are under way to determine the efficacy and tolerability of benznidazole at lower doses and/or with altered treatment duration, and in combination with E1224.

OUTLOOK. Neglected diseases still lack sufficient investment. Attempts to mitigate the lack of resources through collaborations, open sharing of information to avoid duplication of research effort, and harnessing new technologies to enhance discovery programs are ongoing. However, sustainable funding is needed to ensure the development of a new generation of orally active therapies. Progress toward effective oral therapies for Chagas disease and visceral leishmaniasis is slow and will require continued efforts in discovery and development for at least another decade. However, notable advances have been made in the development of HAT treatments, with orally active therapies close to finishing pivotal clinical trials. These drugs should become part of the arsenal in ongoing efforts to eliminate this deadly disease. ■

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IMMUNOLOGY

Expanding the role of metabolism in T cells

A protein links mitochondrial energetics to T cell proliferation

By **David O'Sullivan** *and* **Erika L. Pearce**

Understanding the mechanistic processes that govern T cell responses is crucial to enhancing immunotherapies against human disease. Naïve CD8 T cells extensively proliferate in response to antigen, creating a large pool of effector T cells that clear tumors or infected cells. During this process, T cells metabolically reprogram to meet energy demands and supply biosynthetic precursors necessary for proliferation (*1*). On page 995 of this issue, Okoye *et al*. (*2*) identify lymphocyte expansion molecule (LEM), a protein that targets T cell metabolism and enhances proliferation. LEM improved CD8 T cell–mediated viral and tumor clearance and boosted memory T cell numbers. These findings suggest that modulating T cell metabolism by targeting LEM could alter the course of cancer, autoimmunity, or infection.

Okoye *et al*. identified LEM by analyzing antiviral CD8 T cell responses in mice that had chemically induced germline mutations. Increased numbers of virus-specific CD8 T cells were found in one mouse (called Retro). The enhanced expression of LEM in this mouse was consistent with a mutation in the *BC055111* gene. Through a series of experiments, the authors predicted that this mutation led to stabilization of LEM messenger RNA (mRNA) through the loss of an alternative splicing factor/splice factor 2 (ASF/SF2) binding site, and a subsequent reduction in nonsense-mediated decay, a targeted process that can degrade mRNA.

Okoye *et al*. infected Retro mice with lymphocytic choriomeningitis (LCMV) clone 13, which establishes a chronic infection, and found reduced viral titers that correlated with increased numbers of virus-specific CD8 T cells and lysis of infected cells. On a per cell basis, killing by Retro CD8 T cells was identical to that of wild-type cells, indicating that the greater antiviral immunity in Retro mice was not due to enhanced function as a consequence of LEM, but rather due to increased numbers of CD8 T cells.

Although Retro mice exhibited enhanced T cell responses and reduced viral titers, they died 2 weeks after infection, whereas all wild-type mice survived. Elevated effector T cell–mediated cytolysis in Retro mice suggested a pathology resulting in a fatal loss of vascular integrity (*3*). There is a trade-off between killing infected cells and limiting damage to healthy tissue. Reaching the right balance is crucial for an effective immune response and is context dependent. Consistent with this idea, in contrast to infection with LCMV clone 13, Retro mice infected with LCMV Armstrong, which causes an acute infection, exhibited no mortality, despite still having appreciably more effector CD8 T cells. Of note, Retro CD8 T cells exhibited reduced programmed cell death–1 (PD-1) expression after LCMV clone 13 infection. PD-1 negatively regulates T cell activation, and lower expression can cause sustained effector T cell responses (*4*). Reduced PD-1 expression with increased proliferation (and thus a larger CD8 T cell response) in Retro mice may be a deadly combination in chronic infection. In infections like LCMV clone 13, where antigen expression is sustained, PD-1 mediated signaling and T cell exhaustion may be a protective mechanism to limit pathologic T cell responses (*3*, *5*).

> ***"...metabolism can determine biological outcomes in the immune system."***

Although reduced PD-1 expression and enhanced CD8 T cell proliferation could be detrimental during chronic infection, they are likely to be favorable in cancer or acute infection. In a B16 melanoma mouse model, CD8 T cells from Retro mice reduced tumor burden. Also, memory T cells increased after infection with LCMV Armstrong. This may be due not to a direct function of LEM in memory T cells, but to the larger primary immune response, from which memory T cells emerge. This is supported by the decrease in LEM in both wild-type and Retro CD8 T cells 8 days after infection, when effector T cells begin to die and memory T cells persist; it is also consistent with the lower frequency of memory T cell precursors in Retro mice, despite their greater numbers.

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