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Editorial

Neglected Tropical Diseases: Research Bites Back

Progress toward the treatment of three major parasitic diseases (sleeping sickness, Chagas disease, and leishmaniasis) was recently demonstrated in an article published online last month in the journal *Nature* (August 8, 2016). Collectively, these three diseases affect 20 million people per year, resulting in 50 thousand deaths. Researchers were able to identify and optimize a small molecule that selectively inhibited the parasite proteasomes, and yet did not inhibit human proteasomes. This gives some hope that with further development, the drug may effectively treat those infected with these parasites without having toxic effects on the patients. These three diseases are known to be caused by genetically similar kinetoplastid parasites, and are part of a larger group of what are referred to as neglected tropical diseases (NTDs). Researchers discovered this promising new compound by screening a library of 3 million small molecules, and found that mice given the optimized drug were able to effectively clear the parasites in preclinical infection models. Although we are still a long way from seeing this drug applied in the clinic, the idea that a single drug could have such broad-spectrum activity against three highly prevalent NTDs is encouraging–particularly since the available treatments for these diseases are not well tolerated and/or easily administered.

NTDs are a diverse group of more than a dozen diseases that collectively affect more than a billion people–mostly the poor–primarily in developing countries with limited resources. Other NTDs include (but are not limited to) schistosomiasis, lymphatic filariasis (elephantiasis), onchocerciasis (river blindness), trachoma, dengue and rabies, as well as helminth-related diseases such as roundworm, whipworm, and hookworm. In 2012, the World Health Organization issued a strategic road map for elimination and/or effective control for many of these NTDs by 2020. This goal has been backed with resources and financial support in collective efforts from major pharmaceutical companies, non-profit agencies such as the Gates Foundation, PATH, and the Drugs for Neglected Diseases Initiative, as well as several academic and governmental agencies. This massive, collaborative effort is of the scale and breadth needed to tackle such as huge undertaking, and the goal is not insurmountable. Treatments for several NTDs are in fact already available, yet will need proper infrastructure for distribution as well as accurate testing and epidemiological analyses for effective implementation and monitoring. Vector and non-human host identification and control, clean water access, and other hygiene and sanitation methods must also be implemented effectively to reach this goal. In addition to these well-defined strategic goals, the complex goals of identifying new treatments and vaccines are likely to require a more in-depth investment of time and resources.

As alluded to above, one reason targeted proteasome inhibition is so exciting as a treatment approach is that the available treatments for these three NTDs are not ideal. Current medicines for late-stage sleeping sickness can be toxic and difficult to administer. Although a combination treatment of nifurtimox and eflornithine has reduced the complexity of eflornithine intravenous regiments, it is effective against only one of two forms of African trypanosomiasis, and the only effective treatment for the *rhodesiense* form is quite toxic, and in fact sometimes deadly. Chagas disease can be treated by both benznidazole and nifurtimox, but patients must be treated early to be effective. Treatment is also counter-indicated in pregnant women and patients with psychiatric disorders or by patients with kidney or liver failure. Treatment for visceral leishmaniasis also has potentially serious side effects, and can be costly. So although drugs are available, there is much room for improvement.

Other NTDs have relatively safe and cost-effective treatments available, such as praziquantel for the treatment of schistosomiasis, and ivermectin (and now possibly doxycycline) for river blindness. The strategy for controlling this category of NTDs has typically been mass, repeated chemotherapy for high-risk populations. The key challenges here are identifying all those at risk and getting them treatment, as well as controlling the vectors (such as snails and black flies) that carry the infectious pathogens. And even though treatment is available for river blindness, there is still a need for new drugs, as co-infection with eye worm can cause adverse reactions to ivermectin. Also, the effectiveness of doxycycline-related inhibition of the adult parasitic worm in preventing blindness needs further study.

Vaccine development for NTDs is another area of great need and opportunity, as even those NTDs with safe and effective drugs will likely need additional preventive measures to fully bolster effective disease control and elimination. Although vaccines are currently under development for several NTDs (such as helminth infections, dengue virus, and kinetoplastid-related diseases), financial support and investment have not nearly approached the scale needed to fully develop, test, and implement vaccines for most NTDs.

We commend the efforts many have made thus far in the battle against this group of diseases that affect the world's neediest. In this issue, we present a paper from Lukehart and colleagues that examines whether flies may play a role as a vector in the transmission of yaws and other treponemal NTDs. At *EBioMedicine*, we aim to contribute the goal of eliminating and controlling NTDs by promoting and publishing studies aimed at optimizing NTD therapies and at identifying new treatments, and by working toward improved measures of monitoring and control of these diseases, their hosts, and their vectors of transmission.

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