Nontoxic Drug Therapy for Chagas' Disease and Malaria: University of Washington and Yale University

Some of the world's most intractable diseases are predominantly in the developing world. These illnesses are known as neglected diseases because they receive little attention from the medical community and the pharmaceutical industry, even though they have a significant impact on vulnerable populations. One of these neglected killers is Chagas' disease.

According to the World Health Organization, Chagas' disease is an insect-borne, parasitic illness that infects and kills millions of people every year. Chagas' disease is endemic in 21 Latin American countries and is a major cause of heart failure in the region. Caused by the parasite *Trypanasoma cruzi*, Chagas' disease is most often transmitted by an insect known as the kissing bug, which tends to feed on people's faces. Humans, as well as wild and domestic animals, carry the parasite, and insects infected with *T. cruzi* frequently live in the thatched walls and roofs of homes, making it especially challenging to eradicate.

Controlling the disease is difficult, costly, and risky: it depends largely on treating homes in affected areas with residual insecticides and, in general, improving housing by replacing traditional thatched-roof dwellings with more modern, plastered walls and metal roofs. Management of the illness now involves blood screening to prevent transmission through transfusion. Some drug treatments are available as well.

COLLABORATING TO FIND A TREATMENT

But the standard drug treatments for Chagas' disease leave much to be desired. Most are aimed at fighting the infection, which spreads inside the heart and gastrointestinal tract of the victim. Drugs are difficult to administer and highly toxic, leading to severe side effects in many patients. And no existing medicines have consistently cured patients, according to a report from the Institute for OneWorld Health, a nonprofit pharmaceutical company the goal of which is to develop affordable treatments for neglected infectious diseases around the world.

A collaborative research effort among scientists at the University of Washington and Yale University recently brought forth a nontoxic drug therapy for Chagas' disease. The team included Andy Hamilton and Junko Ohkanda, both chemists at Yale, and Fred Buckner and Wesley Van Voorhis, infectious disease experts, and Michael Gelb and Kohei Yokoyama, chemists, at University of Washington.

"It was a wonderful collaboration between organic chemists and parasite biologists that came about through reading the literature and recognizing potential connections," said principal investigator Hamilton, who has since become a provost at Yale. "Big problems nearly always involve collaborative solutions because no one person or institution can have all the answers."

Buckner, of the University of Washington Medical School, agreed. He has worked for years with a group of chemists led by Gelb to develop compounds to treat infectious diseases caused by protozoan pathogens.

"They would make the compounds and we would test them against the parasites to see if they would do

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anything," Buckner said. "Some turned out to be active against targets that were different than what we designed them to do, but we determined the mechanism of action and showed them to be active in an animal model."

APPROACHING THE PROBLEM FROM DIFFERENT ANGLES

The original patent application described "compounds and methods for treating infections caused by bacterial protozoal and fungal agents," said Aline Flower, of University of Washington TechTransfer Invention Licensing.

When asked about the potential application of the compound, Hamilton said, "we developed, in collaboration with parasitologists, compounds that target the Chagas' disease agent in animal models, and we are seeing some very encouraging data."

Buckner and his colleagues had made inroads targeting these diseases, working toward cures or vaccines. "We had discovered that protozoan parasites contain the enzyme protein farnesyltransferase," said Buckner. "This same enzyme plays an important role in cancer cells, which meant a lot of research laboratories were developing drugs against it. We were working on the hypothesis that protein farnesyltransferase inhibitors might work against parasites."

In the meantime, Hamilton and Ohkanda were working on a similar problem from another angle. "This was the result of many years of fundamental research in trying to get a novel molecular structure to target a specific enzyme," Hamilton said. "It's a question of how one synthetic molecule could recognize a biological molecule in a process called molecular recognition."

According to Hamilton, the two universities and the nonprofit pharmaceutical company developed an integrated model for drug development, perhaps just as important as the chemical compound the researchers had discovered. "We hope, as we make progress in the pre-clinical stage, OneWorld Health will help us pull together the necessary funding to allow the clinical and preclinical development of these compounds," said Hamilton.

The Yale Office of Cooperative Research senior licensing associate Alan Carr explained that an interinstitutional agreement between the University of Washington and Yale University enabled the institutions to structure a deal with OneWorld Health to license the compound affordably.

Like the drug compound, the model for drug development, borne of innovative university technology transfer, could well have a lasting impact on people around the world. ■