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Local News: Monday, July 22, 2002

## UW scientists lead study of proteins to treat diseases

By **Eran Karmon**  
*Seattle Times staff reporter*

A University of Washington student walks into tropical-disease specialist Wes Van Voorhis' clinic with a button-sized, red-and-white crater just below his right eye.

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Van Voorhis diagnoses a parasitic infection and prescribes the latest available: 20 injections of a drug containing heavy metals, administered over three weeks.

The treatment fails. After an even heavier regimen of shots, the infection finally retreats, to the student's relief.

He was lucky. Many of the 2 million people worldwide who catch leishmaniasis go without treatment, and for many it can be fatal.

The lengthy series of shots, while painful, are not nearly as bad as treatments for some other common tropical diseases, some of which sometimes kill the patient before the parasites.

Researchers at the UW and elsewhere last October began a \$15 million, four-year project that they hope will lead one day to a host of powerful new drugs to kill a range of parasites that collectively infect half a billion people and kill as many as 3 million annually.

Scientists involved in the new Structural Genomics of Pathogenic Protozoa project think a good place to look for new drugs is inside the parasites — specifically in certain parasite proteins.

An increasingly popular approach to drug development, one used to make many HIV drugs, is identifying key proteins in a pathogen and then making drugs that disrupt the way the proteins function.

"Proteins perform so many important functions, so they are very important drug targets. If you clobber up, mix up, block an important function of a protein in a parasite, then you have a drug," said Wim Hol, UW professor of biochemistry and the project's director.

The 18-member and growing group includes nine UW scientists and two researchers from the Seattle Biomedical Research Institute.

The diseases targeted are malaria, sleeping sickness, leishmaniasis and Chagas'



disease — the single largest infectious cause of heart disease, with 18 million cases in Central and South America.

The need for new therapies is immediate and grave.

"The drugs we have don't work, and we need new ones," says UW genetics professor and malaria expert Carol Sibley, who twice contracted malaria while working in Africa.

Many previously effective malaria drugs no longer do the job because of resistant parasites, Sibley said. Studies announced last week in the journal *Nature* suggest such resistance may be a bigger problem than previously thought.

Because most people contracting tropical diseases are among the world's poor, there's little market incentive for developing new cures, so academic initiatives have to pick up the slack, like the genomics project or philanthropic organizations like the Bill & Melinda Gates Foundation, which last Wednesday pledged \$30 million to combat schistosomiasis and also funds malaria, tuberculosis and AIDS prevention.

"It's the bottom line. It's not an anti-impotence drug, so the drug companies know they aren't going to make a billion dollars on it," said Van Voorhis, a professor of medicine at UW and project member.

While identifying important proteins is a start, it's a long way from developing new drugs, said Ken Stuart, project member and director of the Seattle Biomedical Research Institute.

Even if a certain drug blocks and inhibits the function of a protein, it may be toxic to the patient, or it may not work within the complex biological machinery of a human body.

"It's very difficult to get a good drug. It is not easy. It's possible to get very nice inhibitors, but drugs are very precious compounds. They are not very toxic for humans, while they are very toxic for the parasite, and that is a very special property," Hol says.

To find compounds with that special property, researchers are taking what Hol calls a "low-hanging fruit approach." They plan to identify and find the structure of as many new parasite proteins as possible.

"The key is many," said Mike Gelb, project member and UW chemistry professor, "because a lot of (drugs) fail."

Since October, the group has been busy producing protein in the laboratory and putting together a team of experts from around the country. The real results, said Hol, will come in the next two or three years.

Proteins can be finicky. Sometimes it's difficult to produce large amounts of them for study, or to prepare them for the X-ray process used to assess their structure. Hol said that if the researchers find a protein that doesn't easily comply, they'll cut bait and move on to the next one.

The effort is aided by a wealth of genomic information. The complete DNA blueprint that codes for every single protein in the malaria parasite, for example, has been found by an American-British consortium and should be submitted for the scientific peer-review process at the end of this month, according to Jane Carlton, a scientist with the Institute for Genomic Research in Rockville, Md., one of the institutions involved in the malaria study.

Hol says that about 40 parasite-protein shapes are currently known. He hopes the genomic effort will increase that number to several hundred.

Gelb and Van Voorhis have an \$800,000 grant from the Medicines for Malaria Venture — a global push for new drugs that receives funding from the Gates Foundation — to

develop a certain type of cancer drug for malaria use. Gelb said that in about two years, they should have a drug suitable for use in human clinical trials.

Researchers agree that a multi-pronged approach is necessary to ease the tropical-disease plague, including basic research like the genomics project, more direct efforts to develop new medications like Gelb's cancer-drug work, and educating people about ways to prevent the diseases.

Sibley likens the effort to a military campaign.

"If you go to Kenya, as I do often, and see five children lying crosswise on a bed because they have serious forms of malaria, you start to believe that a military metaphor is appropriate."

*Eran Karmon can be reached at 206-464-2155 or [ekarmon@seattletimes.com](mailto:ekarmon@seattletimes.com)*

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