Scientists at The Scripps Research Institute Discover Mechanism of Action of Drug Used to Treat Schistosomiasis, a Worldwide Health Problem

La Jolla, CA. February 10, 1995 — A team of biophysicists led by John Tainer, Ph.D., at The Scripps Research Institute, have reported a discovery in understanding the mechanism of action of the leading drug used to treat a parasitic worm disease that afflicts more than 275 million people worldwide, largely in developing countries. This finding may lead to the design of new and more effective drugs to treat the disease.

Second only to malaria in the number of people it affects throughout the world, schistosomiasis, also known as "snail fever," is a lethal parasitic infection responsible for as many as 200,000 deaths annually. Despite an increase in concerted efforts to fight the disease, the incidence of schistosomiasis is increasing.

Using a technique known as x-ray crystallography -- in which x-rays are projected through crystals of pure protein to create a distinctive pattern that can be analyzed to measure the exact position of each atom -- the scientists determined the three-dimensional structure of one of the parasite's defensive proteins, an enzyme called glutathione S-transferase. The scientists' findings show for the first time that the enzyme, known to be responsible for the elimination of many toxins and crucial to the worm's survival, binds to the drug praziquantel which is the drug of
choice for the treatment of schistosomiasis and also is used to treat other parasitic worm infections.

According to Fred Cohen, M.D., Ph.D., in the Department of Pharmaceutical Chemistry and Medicine at the University of California, San Francisco, "This is an important finding because it identifies the molecular target for praziquantel with atomic precision. This will help researchers in their quest to make variants of the drug that may be more effective and less expensive, while overcoming the problem of resistance to the medication."

The study was published in the February 10 issue of the Journal of Molecular Biology in an article entitled, "Crystal Structures of a Schistosomal Drug and Vaccine Target: Glutathione S-Transferase from Schistosoma japonica and its Complex with the Leading Antischistosomal Drug Praziquantel," by Michele A. McTigue, DeWight R. Williams and John A. Tainer.

"The binding of praziquantel to glutathione S-transferase suggests that the drug may kill the parasite by inhibiting the enzyme which would cause a lethal buildup of toxins within the parasite," noted Tainer. "Knowing its atomic structure with praziquantel bound may also allow the design of new drugs for the treatment of this debilitating disease, a situation made more critical by the increasing reports of the parasites becoming resistant to known therapeutics."

As of 1991, the World Health Organization recognized 76 nations as endemic for schistosomiasis, including countries in Africa, Asia and the Far East, South America and the Middle East. It is estimated that more than 400,000 people with schistosomiasis are living in the United States today.
The disease is caused by waterborne *Schistosoma* blood flukes (a type of flatworm) that develop in certain species of snails and then exit the snails to infect humans by burrowing through their skin while they are wading or swimming. Once inside the human body, the worms mature in the blood vessels and then produce eggs, which can be life-threatening when they are trapped in the liver, bladder, brain or other vital organs.

Within endemic countries, transmission is most intense in rural areas where inadequate water supplies, limited sanitation and frequent human contact with fresh water are the norm. However, transmission has occurred in large cities in Brazil and Africa. Symptoms of the disease include high fever, abdominal pain, diarrhea, weight loss, myalgia, arthralgia, and in severe cases, renal failure and cirrhosis of the liver.

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