

This story was written by William Holder of the Cornell News Service for publication in the Cornell Chronicle on December 3, 1992.

Fighting AIDS: Scientists seek new drug design route

The Cornell High Energy Synchrotron Source (CHESS) is the centerpiece of a new effort by Cornell University scientists to find a new way to design drugs for AIDS and other diseases.

Armed with a \$3.31 million grant from the National Institutes of General Medical Sciences, a branch of the National Institutes of Health, four faculty members whose laboratories have a high speed electronic link for sharing graphic images of complex molecules and other data will work on an approach to structure based drug design.

Structure based drug design is an ongoing effort in universities and pharmaceutical companies to design drugs on computers, based on a detailed knowledge of the geometry of a target molecule that is crucial in a disease. So far, however, the technique has failed to deliver on its promise. At fault, at least in part, are the complexities of accurately determining the geometry of drugs as they bind with their targets and limitations on computer algorithms, according to Steven Ealick, a Cornell professor of biochemistry who is leading the new effort.

The Cornell team is using a multidisciplinary approach in its search for a new route to drugs for treating AIDS. They will use the Cornell synchrotron, one of the world's most intense sources of X-rays, in an effort to speed up by orders of magnitude the process of acquiring geometric information through X-ray crystallography. CHESS has the only biological isolation facility in the world where crystals of hazardous viruses and proteins can be routinely subjected to intense X-ray beams to determine their three-dimensional structure.

The National Supercomputing Facility at the Cornell Theory Center



Steven Ealick, professor of biochemistry, molecular and cell biology, mounts a film plate in the macromolecular crystallography facility at CHESS, the centerpiece of a \$3.3 million effort by four faculty to develop new drugs for AIDS and other diseases. (Photo: Chris Hildreth/University Photography)

is furnishing the resources for a related effort to more accurately compute how strongly candidate drugs bind to their targets.

Bruce Ganem, a Cornell professor of chemistry, will head the experimental thrust of the program, consisting of chemical synthesis of potential drugs. His work, he said, will provide a "reality check on structure-based design by showing how well candidate drugs actually bind to target molecules.

Other members of the team are David Shalloway and Andrew Karplus, faculty members in the Section of Biochemistry, Molecular and Cell Biology.

"Our approach to AIDS," said Ealick, "is to look at proteins that are related to disease but not produced by the virus." Specifically, they have selected PNP (purine nucleoside phosphorylase), an enzyme present in red blood cells and other tissues that recycles substances required for normal cell growth. Unfortunately

for AIDS therapy, the enzyme also destroys DDI, a newly approved AIDS drug.

"We have good unpublished observations that suggest DDI may work much better in the presence of a supplemental drug that inhibits PNP. Developing such an inhibitor is one of our goals," he said.

Ealick and Ganem hope to take advantage of a new understanding that the old "lock and key" model of interactions between drugs and receptors is inadequate.

Scientists now believe that they need to know what the lock and key look like when the key is inserted and turned, according to Ganem. More technically, they seek a molecule that will mimic the geometry of the interaction between DDI and PNP at a more advanced stage (the transition state) in the reaction that destroys DDI. Their hope is to find a substance that provides a better fit with PNP and therefore leaves DDI to go about its business.

Practitioners of structure based drug design have found the task more complicated because the geometries of both the target molecule and the drug often undergo substantial changes when the two interact. A detailed knowledge of what each looks like by itself may say little about the more important drug-receptor complex.

The team expects its techniques to be applicable to many medical problems. Karplus, for instance, is seeking an inhibitor of an enzyme produced by the parasite that causes sleeping sickness and other widespread and serious disease in tropical countries. A crucial component of this project, one that also has bearing on AIDS, is determining how the presence of water molecules alters the geometry of the drug-target interaction. Karplus expects the synchro-

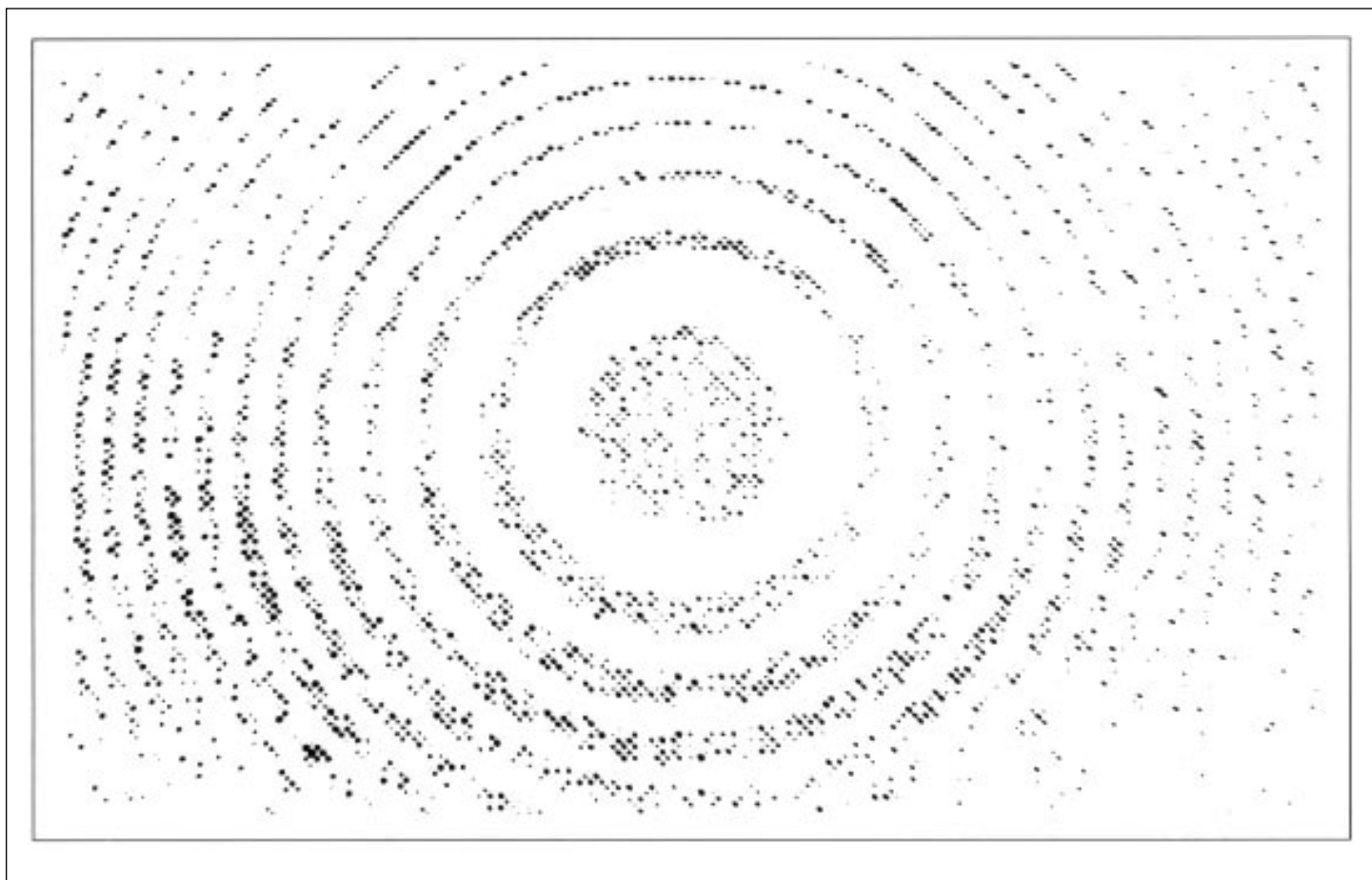
tron to help provide him with the amount of X-ray data he needs to understand that interaction.

One of the most ambitious aspects of the project is an effort, headed by Shalloway, to improve the ability of scientists to compute the strengths of the binding interaction between drugs and targets. More than anything else, it is deficiencies in computational algorithms that are holding up progress in structure-based drug design, he said.

Part of the problem is that computations must take into account the mountains and the molehills of molecular motions. These motions vary from the large and slow vibrations of the whole protein, which take place on the microsecond scale (a millionth of a second or longer), to the ultrafast vibrations of chemical bonds, which occur in femtoseconds (a millionth of

a billionth of a second). Accounting for such disparate scales in the same computer model is a formidable challenge. Shalloway is approaching the problem using techniques he acquired in earlier training as a theoretical physicist.

CHESS is uniquely suited for the experimental component of this work. The X-rays used in this facility are produced by the Cornell Electron Positron Storage Ring, a one-half-mile ring in which counter-rotating beams of electrons and positrons are collided at energies of about 5 billion volts for the study of subatomic particles. The rotating beams produce short bursts of X-rays lasting about one ten-billionth of a second and having an intensity about 1 million times that of a chest X-ray.



Central portion of an HRV16 x-ray diffraction pattern taken on the A1 station ($\lambda=1.56\text{\AA}$) at CHES (Rossmann, Purdue University). The crystal-to-film distance was 100mm, and the exposure time was 10 minutes. The oscillation angle was 0.3° . A similar pattern taken today on the F1 (or new A1) beamline using a Fuji imaging plate and a crystal of about 0.3mm diameter would require about a 10 second exposure time.