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Molecular Medicine

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The Hauptman-Woodward Medical Research Institute, Inc.

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Founded in 1956 as the Medical Foundation of Buffalo (MFB), the Hauptman-Woodward Medical Research Institute, Inc. (HWI) is an independent, non-profit biomedical research facility that specializes in structural biology using the technique of crystallography. The Institute's mission includes dedication to improving the health and well-being of humankind through excellence in basic biomedical research. The Institute's scientists seek to achieve this mission by utilizing two main tracks: (1) studies of the causes of diseases at the molecular level, as well as therapies for the cure and prevention of these diseases; and (2) the expansion and perpetuation of scientific investigation through the training of undergraduate and graduate scientists.

In contrast to clinical research, the main effort of HWI's basic research is to investigate the structures of specific proteins that are related to diseases. These initiatives explore various questions including: What is the three-dimensional structure of a protein? How and with what does the protein react? What controls these interactions? HWI basic research is constantly expanding in an attempt to define these often complex structures through the process of crystallography. The results of these studies provide scientists around the world with the basis for rational drug design. The fundamental research on crystallography, the refinement of methods for structure determination, and the results obtained by Hauptman-Woodward scientists often provide the underpinnings for advances in structural biology and clinical investigations.

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History

The founder of the Hauptman-Woodward Medical Research Institute (formerly the Medical Foundation of Buffalo), Dr. George F. Koepf, was a physician and endocrinologist who received his medical degree from the University of Buffalo in 1937. Dr. Koepf's interest in research and endocrinology peaked during his second year at medical school. At this time, along with another classmate, he discovered that the submaxillary gland beneath the lower jaw of rats contains a substance that could be useful in contracting the human uterus after childbirth. Continuing his research at Johns Hopkins University in 1939, he investigated the role of the cortex of the adrenal gland. Afterwards, while still maintaining a passionate interest in research, he helped begin the first professional medical corporation in Buffalo, which now maintains four offices in the Western New York area.

After being diagnosed with a thyroid disease in 1955, Helen Woodward Rivas, a patient of Dr. Koepf's, expressed interest in funding a medical research effort in Buffalo. With the assistance of Mrs. Rivas' generosity, the dream of Dr. Koepf, the MFB, became a reality. The first site of the MFB was modest with plans to expand in 1960 with the addition of new buildings. Unfortunately, these plans were cut short when a fire ravaged the entire building, sparing most research records. The next two years were spent constructing a new four-story facility, the current location of HWI.

In 1958, Mrs. Rivas suffered a stroke then passed away seven years later, never fully knowing the critical role she played in establishing this facility. In 1977, Dr. Koepf retired from active practice to devote all of his efforts to HWI, including long-range planning and development. Dr. Koepf passed away in 1987, but not before attending the ceremony in which his colleague,

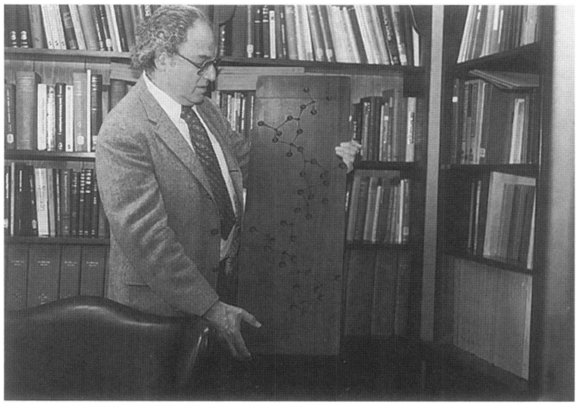

Fig. 1. Dr. Herbert A. Hauptman, president of the Hauptman-Woodward Medical Research Institute, Buffalo, New York holding a wood cutting of the first molecule structure, Colemanite, solved utilizing his direct methods.

Fig. 2. Dr. Douglas Dorset at the electron microscope.

Dr. Herbert A. Hauptman, received the Nobel Prize in Chemistry.

In 1985, the Institute's current president, Dr. Herbert A. Hauptman, received the Nobel Prize in Chemistry for outstanding achievement in the development of direct methods for the determination of crystal structures. This process allows researchers to utilize mathematics and basic crystallographic data to determine the three-dimensional structure of certain molecules. It has changed the whole field of chemistry, opening a new era in research and revolutionizing drug design by allowing the structure of thousands of molecules to be determined. This prize-winning work, once regarded as ridiculous by others, is currently utilized by crystallographers worldwide.

In 1994, to honor the distinction Dr. Hauptman brought to the MFB and to recognize the kindness of our benefactor, Helen Woodward Rivas, the Foundation changed its name to the Hauptman-Woodward Medical Research Institute, Inc. This change was made not only to honor these individuals who made a remarkable contribution, but to exhibit how an integral partnership will always exist between science and philanthropy.

In addition to the work that earned Dr. Hauptman (Fig. 1) a Nobel Prize, the Institute's research over the past 40 years has uncovered other developments in biomedical research which include: the determination of the molecular structure and the mode of action of the antibiotic, gramicidin A—a structure which had been unable to be determined by scientists worldwide for over 40 years; the development of the fetal-viability test that is now used worldwide on mothers at risk for developing hypertension during pregnancy; the development of new and improved crystal growth methods including one patented by two of our scientists; and the provision of critical information to understand a new timed-release insulin therapy, marking the production of the first new diabetic therapy to be produced in more than 75 years.

Methods

In order to decipher the molecular structure of proteins, enzymes, and other molecules, researchers must develop and use methods that will allow them to obtain this vital information (Fig. 2). Through the process of crystallography, researchers are able to determine three-dimensional structures at the molecular level.

Determining molecular structure entails finding the position of atoms from crystallized materials and then using this information to determine their three-dimensional shape. Through the process of x-ray crystallography, this information is obtained by passing x-ray beams through the crystal and then recording the intensities of the diffracted beams. However, during this process only one-half of the necessary information to determine molecular shape is obtained. The missing half, the phase of the beam, is the stumbling block for solving molecular structure. To determine the complete crystal structure, crystallographers are required to solve what is referred to as "the phase problem."

In 1948, work begun by Dr. Hauptman and

his colleague Dr. Jerome Karle slowly proved that the phase information could be obtained from diffracted intensities. By 1953, they developed mathematical equations that allowed this phase data to be retrieved. Initially, their work was rejected, questioned, and criticized by crystallographers. There was minimal acceptance because most crystallographers do not have the mathematical training that would enable them to understand how the phase information could be obtained. This major breakthrough took 15 years and the solution of several complex structures to prove its acceptability to the crystallographic community.

This mathematical method, named direct methods, is used to determine the three-dimensional structures of biologically important materials. It has reduced the time required for molecular analysis from months to hours, it made possible the determination of molecular structures that were previously unable to be solved, and it paved the way for the design of hundreds of drugs. A complete understanding of the molecular structure of all substances involved in diseases allows drugs to be designed that will provide the most effective and specific treatment for those diseases.

HWI's next step is to extend the scope of direct methods to permit the structure determination of macromolecules. HWI has a team of scientists that continues to build and improve upon Dr. Hauptman's work using parallel computers and programming capabilities. This has allowed the creation of *SnB*, a computer program for structure determination that is based on Dr. Hauptman's work.

The emphasis on obtaining these molecular structures at HWI is accomplished not only with x-ray diffraction but also using electron diffraction. Before either of these processes can be used, researchers need to follow a detailed plan, in a particular order to obtain desired results. Initially, the protein or substance being examined must be isolated from the raw material and purified prior to being crystallized. Crystal growth is challenging, because the proteins being studied are becoming larger and more complex making crystallization increasingly difficult. Therefore, crystal growth techniques require both innovation and adaptation on the part of the researcher. HWI scientists are constantly experimenting with and applying new techniques to obtain better and larger crystals. Currently, over a dozen such approaches are being used in both space- and ground-based studies.

After proteins are purified and have been grown into crystals, HWI utilizes both x-ray and electron diffraction in the step-by-step process. Unlike x-ray diffraction, electron diffraction uses an electron microscope to diffract electrons and disclose properties of ultrathin two-dimensional microcrystals. HWI's incorporation of both techniques in this methodology provides the ability to examine certain substances and molecules that do not crystallize well for x-ray methods but do work well when using electron diffraction.

The ability to use both methods, coupled with an experienced and proven group of experts in each area, has earned HWI an international reputation among crystallographic research facilities. Constant questioning and investigation have allowed researchers to improve and refine their methods. Many of these research endeavors have been commended by others, including the National Institutes of Health (NIH), specifically for the Institute's continuous investigation of the phase problem in crystallography, one of the most difficult problems facing crystallographers today.

Current Disease Research

Polycystic Kidney Disease

The most recent research endeavor at HWI deals with the little known but very widespread, polycystic kidney disease (PKD). This disease, which is more prevalent than cystic fibrosis, muscular dystrophy, hemophilia, sickle cell anemia, and multiple sclerosis combined, is a life-threatening genetic disease in which cysts form in and on both kidneys. Through the support of individuals whose family members are afflicted with this disease and their close ties to the Western New York community, HWI has been able to obtain new equipment and additional materials to initiate vital research concerning PKD. By trying to pinpoint the exact cause of PKD through the identification of the proteins that are responsible for kidney failure within these genes, the hope is to determine how they look, how they function, and why they are not working properly.

Diabetes

Currently 16 million Americans suffer from diabetes. At HWI, researchers have been studying the structure of insulin crystals and how certain forms of hexameric insulin (Fig. 3) have the potential to be very slow acting. HWI, in part-

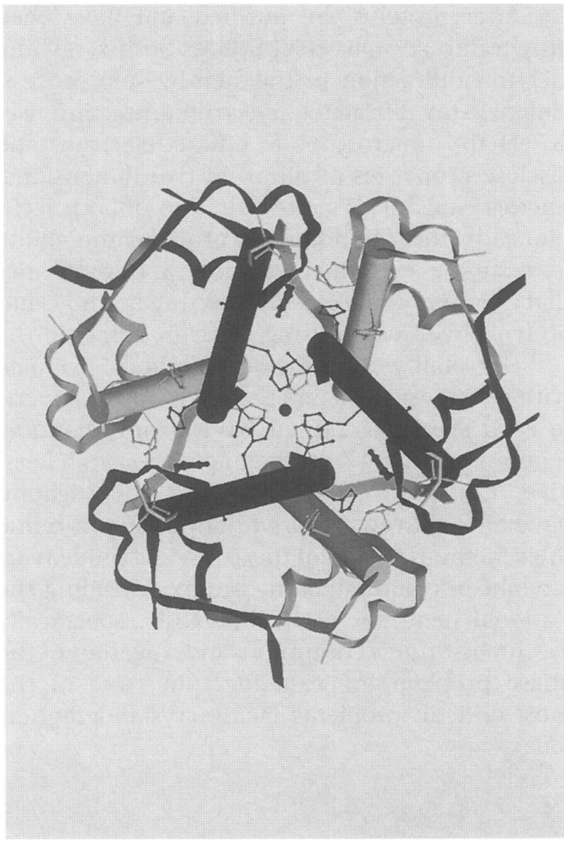

Fig. 3. Crystal structure of hexameric insulin-lispro determined at HWI.

nership with the NASA Center for Macromolecular Crystallography, has grown large perfect insulin crystals in space during recent shuttle missions. These crystals permit knowledge of finer details in the structure. As previously mentioned, a new faster-acting form of insulin has already been developed. By continuing to study these space-grown insulin crystals the expectation is to develop better and slower-acting forms of insulin, including an oral insulin-like drug to replace daily injections.

Breast Cancer

For HWI the focus on breast cancer began over 35 years ago, even before equal time and money was mandated by the government for women's diseases. Concentration in this research area currently deals with the role estrogen plays in supporting tumor growth. By examining enzymes, particularly aromatase and 17β-hydroxysteroid dehydrogenase, involved in estrogen production and the growth and generation of breast tissues, the overall goal is to discover new ways to reduce the active estrogen level in breast tissues. This can lead to improved methods in the control and prevention of tumor growth, allow for early detection in high risk populations, and permit new medications to be developed that would target different enzyme systems than the medications currently available.

HIV and AIDS

Over the past 15 years HIV and AIDS have come to the forefront of the research community. Individuals who are diagnosed with AIDS are susceptible to life-threatening diseases called opportunistic infections. Institute research focuses specifically on *Pneumocystis carinii* (pc) pneumonia, a major cause of infection and mortality in AIDS patients. Researchers are in the process of determining the structure of target enzymes, particularly pc dihydrofolate reductase (DHFR), that can be used to develop new anti-pc agents used to fight AIDS. By identifying the structure, the development of more selective and potent therapeutic agents for the treatment of opportunistic infections can be made.

Science Education

In accordance with HWI's mission, experienced researchers encourage young people to embrace careers in science. Besides offering tours of our facility and various workshop opportunities to area high school students, every summer the Institute hosts more than a dozen students through apprenticeship internships. This program is offered to students at all educational levels who are interested in pursuing a career in the sciences. HWI also participates in a disadvantaged student program funded by the NIH.

The small size of the facility allows the programs offered to students to be unique in several aspects. These include: the inspiring presence and leadership of a Nobel Laureate; a program that has visual appeal and a tangible nature in various areas of study including crystal growth, molecular modeling, and computer graphics and the experience of working one-on-one with researchers, receiving both individual instruction and guidance in the process, as well as the opportunity to see the relevance of the work done in relation to improving human health and well-being.

These internships allow potential scientists to identify challenges and learn the personal satisfaction that is associated with basic biomedical research. In addition to a summer program, current staff members hold faculty appointments at local colleges and universities. Through these relationships, the Institute is able to offer instruction for doctoral students and training for postdoctoral fellows.

Scientific Staff

The core of talent currently at HWI is a diversified team of over 30 scientists hailing from countries all over the world. This group of astute professionals, possessing a combined cumulative experience of 450 years of scientific expertise and commitment to research, has earned worldwide recognition for HWI and themselves within the scientific research community. Most researchers have PhD's from distinguished colleges and universities including Cornell, Ohio State University, the University of Maryland, and the State University of New York at Buffalo.

HWI's established international reputation is due in part to their numerous scientific discoveries and also to the staff's consistent and continuous involvement and contribution to organizations and activities worldwide. This includes holding positions and maintaining memberships in numerous scientific and service organizations. Some of these prestigious organizations include: The National Academy of Sciences, The American Chemical Society (ACS), The American Crystallographic Association (ACA), and the International Union of Crystallography (IUCr). These and other organizations have invited HWI researchers to speak and present their work at various symposia, meetings, and conferences held worldwide.

Each year the research staff continues to collaborate with other scientists on a local, national, and international level. Over the past 40 years HWI staff researchers have collaborated with over 300 scientists at more than 100 institutes in 18 different countries. In total, HWI scientists have either authored or co-authored over 2000 manuscripts, abstracts, chapters, books, and patents. These works contain studies describing the crystal structure determination projects of hundreds of drugs, hormones, and proteins, as well as techniques that have been applied and developed to obtain these crystals and their structures.

HWI's scope of activities extends beyond research that serves the crystallographic and scientific community. The headquarters of the American Crystallographic Association (ACA) is located at HWI. The ACA, currently with over 2300 members, is devoted to serving scientists worldwide who study atomic matter. In addition, the IUCr newsletter, a publication that is distributed to over 10,000 crystallographers throughout the world, is created and produced at HWI.

The Institute offers the crystallographic community access to various services through the World Wide Web. (Vist our website: www.hwi.buffalo.edu) A comprehensive computer program, *SnB,* is offered free of charge to academic users. This program, an extension of direct methods, implements *"Shake and Bake,"* a procedure that permits the structure of larger molecules to be visualized from crystallographic data. HWI also maintains the distribution of the Cambridge Structural Database to U.S. academic sites. This database contains thousands of x-ray structures of organic molecules and information that includes coordinate data and bonding information. This is a vital resource for researchers involved in both basic and applied research.

The Future

Currently, in conjunction with HWI's mission, there are hopes to expand and broaden our current facilities to encompass a center for structural biology. This will allow staff scientists to augment and strengthen the Institute's current role through the increased ability to produce and purify large quantities of biomolecules. This expansion will allow for the recruitment and training of students for future leadership roles. By continuing to grow and extend our capabilities to include international recognition as a structural biology center, the hope is to always have a place in the biomedical research community.