The Hauptman-Woodward Medical Research Institute (HWI) is an independent, not-for-profit, biomedical research facility located in the heart of downtown on the Buffalo Niagara Medical Campus. We are a founding member of the BNMC together with our neighbors Roswell Park Cancer Institute, Kaleida, University at Buffalo, and the Buffalo Medical Group. For more than half a century, HWI scientists have been committed to conducting life-altering research to understand the causes and potential cures of many diseases.

Working under the leadership of Nobel Laureate Herbert Hauptman, HWI scientists are studying a wide range of diseases which include AIDS, arthritis, breast cancer, cardiovascular disease, cystic fibrosis, prostate cancer and many others. In addition, researchers at HWI seek to improve the methods of crystallization and data analysis used by scientists worldwide.

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The past year has been eventful at the Hauptman-Woodward Medical Research Institute.

Our scientists have continued on the path toward discovery – some seeing rather remarkable successes. We have a young scientist – Dr. Andy Gulick - who discovered the structure that will help us understand and hopefully one day block the binding of iron to a protein that helps bacteria thrive in cystic fibrosis patients. Another young scientist – Dr. Dan Gewirth - solved the first high-resolution structure of a mammalian protein that is implicated in certain cancers, sepsis and other critical diseases. And a project that has been more than 30 years in the making in the labs of Dr. Yoshio Osawa and Dr. Deb Ghosh is on the verge of making a difference in the world of estrogen-dependent breast cancers.

It has been a preparatory year for a significant leadership transition. Dr. George DeTitta who has served as our Executive Director and Chief Executive Officer for nine years stepped down effective April 1, 2008 and will be succeeded by Dr. Eaton “Ed” Lattman who will take office effective July 1. Dr. Walter Pangborn, currently serving as Executive Vice President, will serve as interim CEO until Ed takes office and for that we are grateful.

It is appropriate that we acknowledge the outstanding performance of George as CEO during the period of his tenure (1999 to 2008). His time in that office was also a period of transition and one which often was fraught with obstacles and pitfalls. With no prior administrative experience at the level of CEO of a major research institute he undertook his new responsibilities with his characteristically high level of energy and enthusiasm, bringing to bear the lessons learned from his scientific background to overcome the inevitable obstacles which confronted him. He oversaw the expansion of the Hauptman-Woodward Institute from its status as a relatively small research institute to its current role as a major player in the local biomedical research community. This accomplishment required that, among other things, he together with our Board of Directors create and bring together the forces which made possible the creation and construction of our magnificent new state-of-the-art building without which the needed expansion of our scientific staff could not become a reality.

We must not overlook the fact that it was under George's watch that our new CEO was recruited and hired. Ed's present position as Dean of Research and Graduate Education, as well as his role as chair of the Department of Biophysics at John Hopkins University, virtually ensure that he is eminently qualified to discharge like responsibilities at Hauptman-Woodward Institute with distinction.

Thus we thank George for his tireless commitment and dedication to the institute and we thank Walt for his willingness to lead the institute in the interim to ensure a seamless transition for HWI, its staff and collaborators. We also eagerly look forward to Ed’s arrival which we not only view as marking the beginning of an exciting period of further expansion, but have every reason to believe will mark a period of even greater productivity and success than in the recent past.

Herbert A. Hauptman, Ph.D.
Back in July 1997, I slipped out of my lab coat and into the role of Chief Executive Officer for Hauptman-Woodward. In April 2008, I will slip quietly back to the lab and leave the challenges of the executive role to an able successor – of this I am certain. This will be my final Annual Report to you, and I hope you won’t mind if I make you the focus of this report.

Every day I come into a laboratory filled with scientists, students, post-docs and technicians working on the fundamentals of biomedical science, and every day I spend most of my time among those highly talented individuals whose job is to support the science we do. Why do we do the work that we do? It’s certainly not because it’s easy. And it’s certainly not because we get asked for autographs on the street (Herb Hauptman excepted). It’s because we’re curious people who enjoy working out puzzles, and especially puzzles that relate to your health.

Did you ever wonder about all the stars in the firmament that have to line up for your doctor to prescribe something for what ails you? We think about it all the time, as we are at the very beginning of a process that ends with you, your doctor and a treatment. Our contributions are often so many steps away from you and the doctor’s office that you may understandably fail to make the connection between what we do and its ultimate effect on you. How the heck do I explain why the second virial coefficient for dilute solutions of proteins, buffers, polymers and salts has any relevance at all to the development of new treatments for breast cancer? Pretty tough sell, you will have to admit. And what that means is that I am asking you to take it on the word of my word most of the time, if you’re not inclined to spend a couple of years brushing up on your physical chemistry.

Unlike many other human endeavors, however, science has a wonderful in-built correction factor. If I say something of consequence in the biomedical sciences my results will be examined minutely by my scientific peers. They will rather uncannily correct me when I’m wrong, and they will build productively on my efforts when I’m right. So don’t you have to believe me; you can wait for science to speak. And you can follow the thread of the arguments pro and con in the publicly available scientific literature. Ultimately you can go back along a trail of publications that leads you from the new drug to the first stages of basic research that made it all possible. That’s where you find the work of HWI scientists – at the very beginning. But please believe me when I say that we knew you were there waiting for us and our discoveries.

During my entire career at the lab I have stressed the importance of collaboration. It’s become the buzzword for many organizations. Here it is more than a word. Here it is a reality. Camped out as we are in the very heart of the Buffalo Niagara Medical Campus, our natural collaborators are within reach: the University at Buffalo and Roswell Park Cancer Institute. Talented scientists and students in those fine institutions are working with our talented scientists and students to make advances that would be difficult or impossible were we to work in silos. The word I’m after is “synergy” the whole being more than the sum of its parts. We’ve made great progress over the last nine years in this regard. HWI is the home base for the UB Department of Structural Biology, and the departmental faculty members are primarily drawn from the Institute faculty. Joint appointments at HWI and RPCI power some of our most exciting efforts related to cancer. And during my tenure I participated in the creation of a new campus organization, the BNMC, which brings together people from eight not-for-profit institutions spanning the spectrum from basic research to health care delivery. It’s been a pleasure to serve as a director of the BNMC by virtue of my position at HWI.

Finally let me say that we could not have done the work we do without you. You gave to the lab in many ways: your time, your energy, your money, and your moral support. I will always be appreciative of your efforts, and with this message I challenge you to continue to give of yourself to this fine group of curious people. In the end what they do is for you.
Dr. Eaton “Ed” Lattman has been appointed Chief Executive Officer and Executive Director of Hauptman-Woodward effective July 1, 2008. Lattman is an accomplished scientist and successful administrator. He has degrees from Harvard and Johns Hopkins University (JHU). He has published more than seventy articles in the fields of crystallography and structural biology. With Patrick Loll he is a co-author of the recently published book Protein Crystallography: A Concise Guide.

With the exception of a post-doctoral stint in the 1970s, Lattman has spent his entire academic career at the JHU, beginning as a graduate student in Biophysics, and rising through the ranks to become Dean of Research and Graduate Education in the Krieger School of Arts and Sciences. En route he served as Professor of Biophysics in both the Schools of Medicine and of Arts and Sciences, giving him a very broad perspective on university life. He also served as chair of the department from which he gained his Ph.D. degree (and was briefly the supervisor of his own thesis advisor).

He was instrumental in setting up the Hopkins Institute for Biophysical Research, a unit that has served as a focal point for the dramatic growth of biophysics across the whole University. He hired the first women faculty members in the history of his department, and was the principal investigator on the Molecular Biophysics NIH Training Grant awarded to Johns Hopkins.

Lattman was editor-in-chief of the journal Proteins for more than 15 years. He has served, and continues to serve, on many NIH committees. Notably, he was a member of the National Advisory General Medical Sciences Council, and of the NIGMS Advisory Committee on the Protein Structure Initiative (PSI).

His experience and training map almost perfectly onto the profile of HWI. His breadth of knowledge and research experience will be of importance in helping HWI define both directions for expansion and collaborative relations within the Buffalo community.

"... when I was approached about the position of Hauptman-Woodward CEO I was immediately excited by the prospect. The research profile and directions of the HWI faculty are so close to my own training and background that it seemed as though I could talk to most of them in a truly knowledgeable way about what they do. ... This congruence of interests also suggested a role for the CEO as one who enables HWI research from a very informed base. My ability to help faculty find new research directions or mechanisms of support is promoted by detailed understanding of what they do. My first visit to Hauptman Woodward strengthened the good impression I had developed from a distance. One highlight was my interview with Dr. Hauptman. ... I emerged thrilled at having had the conversation ... A second wonderful impression emerged from the set of talks I had with HWI faculty members. ... they all talked about points that were important to HWI or to the faculty as a whole. This collective response demonstrates the high level of esprit de corps that characterizes the Institute. Members respect it and each other. As well, during this visit a lot of wonderful staff work came to my attention ... This commitment from everyone at HWI makes it much easier to attack the real difficulties that face it. This visit also revealed how much the Buffalo community values HWI. ... I look forward to getting to know all of you who are interested in HWI and its work. So I am approaching the job of CEO with zest and intellectual involvement, and with confidence that HWI will prosper in the coming years." — excerpts from Lattman’s remarks at the press announcement of his appointment

Eaton E. Lattman, Ph.D.
We have recently completed our 2007 Fiscal Year (October 31, 2007) and finished with a positive cash flow from operations of roughly $75,000. From an income standpoint, our consolidated accrual basis loss, after depreciation of $1.4M, was $376,000. Expenses have been managed in accord with the budget and income.

On the balance sheet, our total assets are just over $34.8M. In addition to the gain on the sale of 73 High Street, we received $432,000 from the charitable trust left to us by former board member W. Jackson Catt. The Catt funds are permanently restricted in accordance with Mr. Catt’s original intent.

Investment balances continue to be replenished with the payment of capital campaign pledges. We have been able to set aside another $100,000 in a Reserve for Replacement as required by our covenants with our lending bank. This effectively brings our reserve for replacement balance up to $300,000.

We have met all of our covenant requirements as specified in our lending arrangements with the bank regarding our loan for the construction of the laboratory facilities. Additionally, we received a favorable report from our auditors, i.e., there continue to be no material weaknesses or reportable conditions.

As a final note, we recently received word on funding of a grant from the Department of Defense in the amount of $3M. We expect to see these funds at the Institute by late Fiscal 2008 or early Fiscal 2009. The funds are specified to study the transfer of virus from animal to human host and will be expended over a three year period.

Respectfully submitted,

Lisa A. Foti, CPA
Chief Financial Officer
The People of the Hauptman-Woodward Medical Research Institute

Our greatest assets are our people. Hauptman-Woodward is fortunate to be home to some of the most creative minds in science today and has the distinction of offering an investigator-initiated approach that allows our scientists to translate their passion for their work into their everyday experiences. Each employee at Hauptman-Woodward plays a role in ensuring the organization’s current and future successes.

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Senior Research Scientist
Shawn M. Bowman, Ph.D.
Postdoctoral Associate
Margaret Cegeliski
Research Associate
Barnali Chaudhuri, Ph.D.
Research Scientist
Vivian Cedy, Ph.D.
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**AIDS**

**CODY LAB**

Certain infections, often referred to as opportunistic pathogens, prey on people with weakened immune systems such as in AIDS, those undergoing transplant surgery or chemotherapy.

A major focus of the Cody laboratory is to determine the difference between the protein in the pathogen and the existing protein in the human. Understanding the differences will be essential in designing new drugs which will attack only the opportunistic pathogen, while having little effect on the normal human enzyme.

These inhibitors have potential as therapeutic agents for the treatment of AIDS-related pneumonia and other infections in immunocompromised patients.

**POLYCYSTIC KIDNEY DISEASE**

**DUAX LAB**

Polycystic Kidney Disease is one of the most common human genetic diseases with an incidence rate of about 1:1000. The incidence will continue to increase because by the time patients are diagnosed, they are beyond their child-bearing years and as such have already passed it on to their children.

The disease is characterized by the accumulation of fluid-filled cysts in the kidney. The disease results in the loss of renal function leading ultimately to dialysis and transplantation. In addition, the frequency of this disease and the drastic treatment methods that are required place a significant financial burden on the nation’s healthcare infrastructure.

Simply knowing the sequence of a protein does not provide the information needed to understand how mutations cause disease or to design therapies. The three-dimensional structures of the protein products of the genes are the key to understanding what is causing PKD.

The Duax Lab is using pre-existing structural data to create a 3D model of the PKD structure that can be used to locate its most probable mutation sites and to understand why those mutations are happening. Armed with the knowledge of the molecular cause of PKD, we can begin to develop more cost-effective and less invasive drug-based treatments.
Breast cancer is the most common cancer among women in the United States. It is the second leading cause of cancer death in women, after lung cancer.

The chance of a woman having invasive breast cancer some time during her life is about 1 in 8. The chance of dying from breast cancer is about 1 in 35. More than 75 percent of all breast cancer tumors are estrogen-fed. Estrogen is a female sex hormone and androgens are male sex hormones. Regardless of gender, everyone has some percentage of both estrogens and androgens in their bodies.

Aromatase is a unique enzyme that makes estrogens from androgens. It is the only known enzyme in the vertebrate world capable of making estrogens in this manner. All estrogens in the human body are made by aromatase. Drugs, such as Tamoxifen, that prevent aromatase from making estrogens constitute one of the foremost therapies for estrogen-dependent breast cancer. However, these drugs do not discriminate in what they target in the body, which results in significant side effects.

The Ghosh Lab is the first group to unravel the molecular details of how aromatase works. By knowing the structure of aromatase, drugs can be designed to narrowly target aromatase only. This means that results from this research will form the basis for novel breast cancer drugs that are highly specific for aromatase but cause minimal side effects.

The Gewirth Lab is studying this important family of chaperones. Using X-ray crystallography and biochemical analyses, we ask both fundamental questions about hsp90 function and mechanism, as well as practical questions related to the development of novel compounds that can specifically inhibit different members of this family. We are also collaborating with medicinal chemists from Sloan-Kettering to design next generation inhibitors that may soon be used in clinical trials.

Daniel T. Gewirth, Ph.D.
Debashis Ghosh, Ph.D.
MALKOWSKI LAB

Aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase enzymes COX-1 and COX-2 and provide relief to individuals suffering from inflammation, swelling, and pain associated with rheumatoid arthritis and osteoarthritis. These "classical" NSAIDs do not discriminate between COX-1 and COX-2 and thus many individuals experience adverse side effects, such as stomach ulceration and kidney failure, with chronic administration.

The recently approved "COX-2 selective" NSAIDs Celebrex®, Vioxx®, and Bextra® do not cause these gastrointestinal side effects. While COX-2 inhibitors have provided individuals with a drug that allows them to better manage the painful symptoms of arthritis, many still suffer from potentially dangerous NSAID-induced gastrointestinal bleeding.

The goal of this Malkowski Lab research project is to: provide insight into how these NSAID-dependent compounds affect the inflammatory process; and lead to the exploration and development of new therapeutic approaches for the treatment of rheumatoid arthritis, osteoarthritis, and other inflammatory diseases.

GULICK LAB

Cystic Fibrosis is a common disorder, affecting about 1 in 3000 infants born in the U.S. annually. The disease is caused by a defect in a protein in the lungs that results in a clogging of the airways with a thick mucus. This mucus unfortunately becomes a hospitable environment for bacteria. In the CF patient, a particular species of bacteria called Pseudomonas aeruginosa is the most common cause of infections. These infections result in chronic inflammation that ultimately is the major cause of death for most CF patients.

The Gulick lab is studying important biochemical pathways that these bacteria require during the establishment of an infection. For example, bacteria need iron as an essential nutrient to grow. Humans maintain large pools of iron that are tightly sequestered, making it unavailable for bacteria to use. To establish an infection, bacteria need to "steal" this iron.

Pseudomonas makes a molecule which effectively steals the iron and transports the new iron complex back into the bacterial cell. The Gulick lab is studying the many proteins in this pathway to understand how they are used by the bacteria and to identify ways to block these proteins that are essential for the bacteria.

A long-term goal is the development of new antibiotic compounds to inhibit the bacterial infections caused by Cystic Fibrosis and other diseases.

Worldwide, cardiovascular disease and atherosclerosis (hardening of the arteries) are the primary cause of illness and death among adults. The leading cause of coronary artery disease is atherosclerosis. It is well established that inflammation and the accumulation of fat in arterial walls represents the early stages of vascular inflammatory damage that ultimately leads to vessel blockage. The reduction of such blockages through low-dose aspirin treatment is a well-established therapy. An enzyme known as COX-2 is active during the kind of inflammation that occurs in cardiovascular disease. Drugs such as Vioxx® have been developed to target COX-2. Those drugs were designed to control arthritis symptoms. Unfortunately, the drugs were causing heart attacks and other residual health problems. No one truly understand why, so the Malkowski Lab is working toward a better understanding at the molecular level of how these drugs interact with COX-2 and how to stop the problems that are occurring as a result.
Many of the world’s most severe pandemics have resulted when an animal virus acquired the ability to infect humans. The “Spanish flu” of 1918 (500,000 deaths in the US and millions worldwide), the “Asian flu” of 1957 (70,000 deaths in the US), the “Hong Kong flu” of 1968 (34,000 deaths in the US), and HIV (tens of millions of deaths worldwide) are all thought to have evolved from animal viruses. Current concern over avian flu illustrates the continuing threat posed by new human viruses emerging from reservoirs of endemic animal viruses. The main goal of our research is to understand how an animal virus mutates to gain the ability to infect human hosts. We believe that specific virus proteins must mutate to “match” with host cell proteins for a successful infection to be established. This work is at the forefront of biological research and has a long-term goal of antiviral drug design which may also be applied to a broad range of emerging viruses.


• Cody V, Davis PJ, Davis FB. Molecular modeling of the thyroid hormone interactions with alpha v beta 3 integrin. Steroids. 2007 Feb;72(2):165-70.


