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 Health, 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 our Chief Executive Officer and Executive Director Dr. Eaton E. Lattman, 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 which are critical elements in drug design.

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The People of HWI

Hauptman-Woodward’s Board of Directors
Hauptman-Woodward’s Team

Our Dedicated Donors
Hauptman Society 2013
FROM THE CHAIRMAN OF THE BOARD

For a numbers of years Hauptman-Woodward has faced the challenge that many other independent research institutions, universities and individual researchers face. Funding at the federal level has been strong in the past and has contributed to transformative advances both scientifically and technologically, but in recent years more applicants are applying for dwindling funds. These national resources are not limitless, and now are more competitive than ever. In consideration of this climate, we, HWI’s board of directors and staff have been working diligently to find alternative revenue streams.

In the academic environment, our efforts may be categorized as what many refer to as corporatization of the university, not often in the most favorable way. What this refers to, is the process by which many academic units, and specifically research disciplines, have partnered with industry to bridge this ever increasing gap in funding, and to share resources and knowledge. What does this mean if applied to an institution like HWI which has been modeled in the academic tradition? It means finding alternative methods to expand our revenues to the benefit of our faculty’s research. It means finding strategic partners that allow our research to be supported, applied, and reach the end user more quickly and efficiently. It means more opportunities for those learning at the Institute as they undertake research problems with more than just a theoretical perspective. In many ways it gives the HWI scientific group an opportunity to apply their solutions to problems that are more evident, than elusive. And, it gives them necessary stability in funding.

How have we approached this challenge thus far? We have expanded into management of other scientific facilities. Thanks to Ed Lattman, we administer IMCA, a facility at Argonne National Labs, which is a consortium of pharmaceutical companies committed to the use of macromolecular crystallography as a tool in drug discovery and product development. This brings HWI additional resources of $350,000 annually. As well, we have established a New Business Development committee on our board, chaired by Judy Feldman, which has been working with HWI scientists Joseph Luft, Tim Umland and Wayne Schultz. This group, with other HWI board members, has been tasked with finding a broader market for the High-Throughput Screening lab at HWI. This lab for many years has provided a service to the academic community and industry. Now, this team is looking at ways to broaden the services and market for this lab. Initial investigations of the growth opportunities and a preliminary business plan, look very promising. These efforts will also help support the efforts of the HWI group to advance basic research.

We have ventured as a group into these endeavors with optimism, tempered by caution. We do not want to change the culture of HWI. We are looking for alternative solutions to sustain the HWI culture. We seek to find supplemental funds to support our researchers in their search for answers during difficult times when they need bridge funding, as well as give them additional options to develop new projects, requiring seed funding. We are striving to find ways to stabilize resources, support our faculty, and stimulate their creativity in their search for the solutions to cures.

We thank you always for your support of Hauptman-Woodward in all of these undertakings.

NEW SCIENTIFIC ADVENTURES AT HWI

New Scientific Adventures at HWI

A small independent research Institute like Hauptman-Woodward cannot thrive unless it does something uniquely well, and does it in a way that provides great public benefit. But doing something uniquely well is a moving target. Thus, the Institute has to evolve so that each generation’s claim to fame will be fresh, yet connected to our history and mission.

Dr. Hauptman’s Nobel Prize work in crystallography provided the Institute with unique visibility and prestige in the scientific world. The public benefit arises because, worldwide, virtually every new drug development program in the last 30 years has made use of his discoveries to design or improve the drugs involved.

More recently, George DeTitta, Joe Luft and their colleagues have developed a High-Throughput Crystal-Screening Laboratory, which has provided unique visibility for Hauptman-Woodward along a different dimension. The laboratory comprises a unique resource, helping hundreds of research groups around the U.S., and across the globe, grow crystals of proteins. The operation of this laboratory represents something that we do uniquely well. The public benefit arises because crystals grown in the laboratory have advanced hundreds of research projects in the areas of drug design, as well as in more basic biomedical research.

The discoveries made by Herb Hauptman are now ingrained throughout crystallography and no longer provide unique stature to the Institute. Likewise, the High Throughput Laboratory has been copied in many places, and our original version no longer has the unique visibility that it once did.

What do we do for an encore?

In the broadest sense, the public benefit from these two endeavors was to enable critical research to be carried out at higher and more productive levels. The structures of hundreds of drugs and of hundreds of drug targets are traceable to the discoveries and technologies of Hauptman-Woodward.

In this vein we are truly at the start of a new frontier effort. HWI and UB together, representing a nationwide consortium of eight research universities and institutes, have recently been awarded $25 million from the National Science Foundation to establish a Science Technology Center, nicknamed BioXFEL, for “Biology with X-ray Lasers.” Principal Investigator Eaton E. Lattman and Scientific Director John C.H. Spence, of Arizona State University, are leading the project. See our website at BioXFEL.org.

Science Technology Center awards are very prestigious and competitive. They are announced only once every 4 years. There were 267 applications in the current round, of which only three were funded. The Center is to help advance X-ray laser technology that has been developed at the SLAC National Accelerator Laboratory. This technology is transformative, and will remake the field of structural biology.
Let me mention two examples. First, as you know, the pictures that we make of molecules require that we shoot an X-ray beam at crystals of the molecule in question. The crystallization step is the major bottleneck in the process. Even in our state-of-the-art High Throughput Laboratory less than 20% of proteins yield crystals suitable for X-ray study. The SLAC X-ray laser will greatly mitigate this problem. This X-ray laser is unbelievably bright compared to the X-ray beams we use today. So bright that we can use crystals 1000 times smaller than the ones we use today. Like diamonds, tiny protein crystals are much more common than the larger ones we need right now. So a whole new universe of proteins, molecules that could be targets for drugs, will yield the pictures that reveal how they work.

Much of the HWI research contribution to this Center will be in learning how to grow, handle, and understand these ultra-tiny crystals, which we call nanocrystals.

Second, the X-ray laser beam is actually a stream of unimaginably short pulses that act as flashbulbs that freeze the motions of molecules and allow us to create molecular movies. So we will be able to watch protein molecules pacing through their functional steps.

Being at the forefront of such exciting technology keeps HWI in its special niche of excellence. It will enable new grant funding, stimulate new collaborations, and attract new scientists. And we are having a huge amount of fun in the process.

Our consolidated accrual basis net gain for the year ended October 31, 2013 was $649 compared to a ($990k) loss in the prior year. This is mainly attributable to an increase in research grant income and a decrease in total operating expenses. Controllable expenses were maintained within budget. Non operating gains of $622k include realized and unrealized investment performance as well as the fair market value of the derivative arrangement on our outstanding debt. The purchase of partially state funded equipment resulted in an overall decrease in cash of $28k. We received word in November that Dr. Lattman’s NSF grant proposal was awarded. This grant is a consortium of eight institutions and totals $25M over 5 years. Of the $25M, $5M will remain at the Institute for our part in this collaboration. We continue to respond to numerous solicitations for competitive funding and currently have eight outstanding applications pending.

On the balance sheet, our total assets are just over $26M. This includes $7.7M in investments of which our permanent endowment represents $2.2M. We have set aside another $100k in a Reserve for Replacement as required by our lender. This effectively brings our replacement reserve up to $900k. In that regard, we continue to meet all of our covenant provisions as required in our financing agreements with our lender. Additionally, we once again received a favorable “unqualified” report from our auditors. There were no deficiencies noted in accounting controls or any research programs.

Respectfully submitted,
Anne M. Kent
Controller

<table>
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<th>Significant Financial Statement Elements 1</th>
<th>10/31/2013</th>
<th>10/31/2012</th>
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<td>Net Loss</td>
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</table>

1 Source: The consolidated financial statements of the Hauptman Woodward Medical Research Institute, Inc.
2013 RESEARCH HIGHLIGHTS

Donor Generosity Stimulates New Research Collaboration in Cody Laboratory

How do new projects get started? When researchers receive grant support from various sources (e.g., the National Institutes of Health, the National Science Foundation, or private organizations such as the American Cancer Society, or the American Heart Association), it is in response to a specific proposal of research. Therefore, current funding cannot be used to start new projects. This is a situation when donations from philanthropic individuals can be leveraged to have a greater impact by providing the seed money to initiate new research projects.

Such is the case with Dr. Vivian Cody’s research. Because of the generous support from a long-time Friend of HWI, Dr. Cody is able to initiate studies that will address important questions concerning the function and evolution of transthyretin (TTR), a protein that is responsible for the transport of thyroid hormone throughout the general circulation.

The genetic disease, familial amyloid polyneuropathy, is caused by a series of single mutations in the sequence of human TTR that cause the tetrameric form of the protein to destabilize and form fibrils that cause the body’s organs to look like “Swiss cheese”. There is no cure for amyloid fibril damage. Researchers have focused on understanding why specific mutations result in damage to a specific organ – heart, brain, kidney, or liver. Small molecule drugs have been shown to bind tightly to the thyroid hormone binding site of TTR and stabilize the mutant form of the protein. Dr. Cody is collaborating with a group in Australia who has designed novel compounds that can stabilize human TTR. Dr. Cody has determined the three dimensional crystal structure of human TTR bound with their compound. These data provide insight into the stabilization of TTR.

Dr. Cody is also studying TTR from other animal species whose amino acid sequence naturally contains the same amyloid-forming mutant as observed in human TTR. However, these animals do not form amyloid fibrils. Comparison of the TTR structural data from these species can provide insight into this problem.

Recent data from the Australian collaborators suggest that the TTR gene has evolved from the duplication of the transthyretin-like protein gene (TLP) in early vertebrate evolution. Although similar to TTR in structure, TLP acts as a hydrolase and does not bind thyroid hormone. These data indicate that lamprey TTR has characteristics of both TLP and TTR. Structural studies of human, wallaby, rabbit, and lamprey transthyretin are under investigation to verify these hypotheses.

These preliminary data can be used to leverage the seed funds to obtain support from funding agencies.
Gewirth Lab Receives Grant to Develop New Approaches to Fight Difficult Bacterial Pathogens

Dr. Daniel Gewirth was recently awarded a three-year grant for $150,000 from the Richard W. and Mae Stone Goode Foundation to characterize the interaction between a virulence factor from the bacterium *Clostridium difficile* and its human cell surface receptor. This knowledge will be used to design targeted peptide therapeutics against *C. difficile* infections that have become an increasingly important public health problem. These infections have developed resistance to the first line antibiotics, making the need for new classes of antibiotics crucial.

*Clostridium difficile* infection is a toxin-mediated intestinal disease that results in a spectrum of clinical outcomes from mild diarrhea to toxic mega-colon, sepsis, and death in severe cases. Ironically, this infection can arise as a result of antibiotic use, by disrupting normal gut microflora and enabling *C. difficile* to colonize and cause infection, making it a hospital-acquired infection.

The toxic effect of *C. difficile* is caused by a large protein called Toxin A (TxA) which enters the cell through its outer membrane and initiates a process leading to cell death. Recent work has shown that a surface-localized protein, gp96, is the major cellular receptor for TxA in human cells. Blockage of gp96 by antibodies or depletion of gp96 by small interfering RNA prevents TxA entry into cells.

The Gewirth lab at HWI specializes in studies of gp96. They solved the first crystal structure of this chaperone in 2007 and have led the way in developing small molecule inhibitors directed at this protein, some of which have recently been shown to disrupt an important breast cancer target. The TxA studies, in addition to their application to treating hospital acquired infections, also promise to expand our understanding of the biology of gp96. In particular, gp96 has been reported to be the cellular receptor for other classes of bacterial virulence factors, and the knowledge gained from the TxA study may lead to new approaches to the treatment of other infectious diseases.

When the bacterium *Clostridium difficile* infects humans, it produces a protein called Toxin A. Toxin A is benign until it enters the cells of the gut, where it is cut down into its active form and causes the cell to secrete fluid, leading to cell death. The cellular receptor for Toxin A is gp96. The Gewirth lab is studying how Toxin A recognizes gp96 with the ultimate goal of preventing this interaction and thus stopping toxin from infecting the cells of the gut.
Snell and Luft Receive NASA Grant to Enhance Crystal Growth in Space

One of our major areas of research is to grow crystals of proteins so that we can visualize the three-dimensional structure at the atomic level. This is the same level that pharmaceuticals operate at and the structural knowledge we produce helps us understand the mechanisms involved with life and provides the knowledge to greatly speed up pharmaceutical design. The better the quality of the crystal that we grow, the better the quality of the picture we produce, and the deeper our understanding of the structure.

The National Aeronautics and Space Administration (NASA) has recently awarded Dr. Edward Snell and co-investigator Joseph Luft, a 5-year, $750,000 grant entitled “Growth Rate Dispersion, a Predictive Indicator for Biological Crystal Samples That Improve in Microgravity”. Snell and Luft’s project will involve flights of several experiments from HWI to the International Space Station and is aimed at identifying samples that benefit from crystallization in microgravity, thereby complementing Earth-based studies. As a pioneer in evaluating the influence of reduced acceleration on crystal growth, Dr. Snell, in collaboration with Joseph Luft, will build on this expertise to develop a ground-based technique to predict which crystals can benefit from growth in space versus those that do not.

Crystals grow in solution and as they grow the solution can start flowing past the crystal face stopping the growth or degrading the quality. When NASA flew the Space Shuttle Orbiter and later the International Space Station, the environment onboard was thought to be useful to increase the crystal quality - this flow, driven by convection, was minimized or even eliminated. Larger, higher quality crystals did result but the cases of improvement were not uniform.

Crystallization experiments are small and highly automated, the analysis can be done on the ground, and the potential scientific and commercial payback is high. With this predictive approach, dedicated or parasitic opportunities on space vehicles can be exploited to help life on earth by making use of outer space to study inner space.
2013 PUBLICATIONS


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. The scientific team is supported daily by talented individuals who serve on our boards and a staff which includes individuals with a wide range of talents and experiences. Each employee at Hauptman-Woodward plays a role in ensuring the organization’s current and future successes.
We would like to thank and acknowledge the following donors

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<thead>
<tr>
<th>Gifts received between</th>
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| $250 - $499 |
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| $2,500 - $4,999 |
| $5,000 - $9,999 |
| $10,000 - $24,999 |
| $25,000 - $49,999 |
| $50,000 - $99,999 |
| $100,000+ |

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Dr. Vivian Cody
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Cara Yager
Dr. Vivian Cody
The sixth annual Hauptman Society gathering took place on April 10, 2014. The Hauptman Society was created in 2008 to honor Corporate or Individual donors who contribute leadership unrestricted gifts of $1,000 or more annually. These gifts support HWI’s mission and the pursuit of life-altering research.

“Hauptman-Woodward is honored to receive these important donations which allow HWI scientists to contribute to cures to the diseases that plague our friends and families,” 2014 Chairman Joe Voelkl said.

“Four hundred years ago, no one could possibly have anticipated the enormous strides that science and technology were destined to make in the ensuing centuries. Even as recently as one hundred years ago, who would have predicted the great revolutions in these two areas that the twentieth century held in store for us? Thus the theories of relativity and quantum mechanics, the nature of the structure of matter, molecular biology, and our new understanding of life processes changed forever the way we look at the world around us, and at the same time have irrevocably established the rational mode of inquiry, the quintessential element of the scientific method, as preferred above all others.”

Herbert A. Hauptman, PhD
Nobel Prize in Chemistry, 1985
The Cures Begin Here

The Hauptman-Woodward Medical Research Institute (HWI) creates novel strategies and technologies to promote the understanding, prevention and treatment of many human diseases. Examples of current projects involve finding cures for AIDS, arthritis, cancer, cardiovascular disease, cystic fibrosis, and the transmission of emergent diseases from animals to humans.