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 new Chief Executive Officer Dr. Edward H. Snell, 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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OUTGOING CHIEF EXECUTIVE OFFICER’S MESSAGE

My term as CEO officially ended on November 30, 2014, so I write this to you having concluded the 2014 fiscal year and having handed the reins over to Ed Snell, a principal research scientist with HWI with a very distinguished scientific career already. In retrospect, I have seen great strides in the last 6 1/2 years with management of day-to-day operations as well as continuing efforts of long-range projects. Overall, my time was invigorating and truly enjoyable having been a part of a remarkable institution with a tremendous legacy.

As I look back in a broad way at what has happened over my time at HWI I would like to mention a few of what I see are our most significant accomplishments.

• Development of new and potential revenue streams not dependent on R01-type grants
  • Our relationship with IMCA-CAT and their team
  • The establishment of HWI's subsidiary HarkerBIO

• HWI being the primary impetus in securing the National Science Foundation BioXFEL Science and Technology Center

• The appointment of Michael Malkowski as a tenured UB professor serving as interim chair in the Department of Structural Biology situated at HWI

HWI does still face challenges like any organization moving into the future and your support is always critical for helping the organization navigate through both the good and the bad. Challenges always present opportunities and ways in which you can support HWI and poise it well for future growth I’ve suggested below.

• Consider coming in for a tour and get in touch with our team of researchers; your advocacy and knowledge of HWI in our community is a tremendous asset for the Institute

• Consider a gift to HWI; both large and small gifts enable us to support our researchers as they need funding to start new projects and collect data before they can apply for federal support

• Consider sharing your talents and perhaps volunteer at HWI; our building is vast and our team is small, we always appreciate the knowledge and expertise of friends of HWI helping us in ways that would not be feasible within a small organization

I have high hopes for the outcome of the strategic planning process that began recently, and for HWI to play a major role in the entrepreneurial and academic expansion at the BNMC. From this vantage point Ed Snell, our new CEO, is doing a wonderful, aggressive job. I am still here at HWI and leading the BioXFEL Center, and I look forward to seeing much more come to fruition.

Respectfully submitted,
Eaton Lattman, PhD
CEO emeritus

FROM THE CHAIRMAN OF THE BOARD

Dear friends of Hauptman-Woodward,

I am very pleased to announce the selection of HWI’s new Board Officers, effective June 2015.

Judy Feldman, Board Chair
Peter McCauley, Vice-Chair
John Horn, Secretary
Charles Lannon, Finance Chair

The Board of Directors unanimously approved this slate at our Board Meeting held in June and I would like to thank the new Officers for their willingness to serve the Institute in this capacity. HWI continues with their leadership on the path toward supporting major scientific discovery and innovation, as well as greater financial strength.

2014 has been a successful year for the Institute with changes and advances in many facets of the organization. First, I would like to recognize and thank Ed Lattman for his service as HWI’s CEO for the past 7 years. Under his leadership, HWI saw the successful awarding of a prestigious National Science Foundation Science and Technology Center; a financially and scientifically advantageous relationship with IMCA-CAT; as well as the launch of HarkerBIO. Each of these is a tremendous undertaking and represents great forward momentum for the Institute. I am also more than encouraged by the Board’s selection of Edward Snell to step into the CEO role. An internationally recognized scientist in his own right, Ed Snell brings the scientific and administrative talents necessary to lead HWI towards a promising future.

After nearly 10 years, I am officially stepping down from my own position on the HWI Board, of which 4 years were spent serving as your Chair. I would like to take this opportunity to thank each of you for the support you’ve given to the Institute and the Board during this time. Thank you for making this a very fulfilling and engaging experience. I have enjoyed the chance to serve in this capacity and to learn more about the tremendous work being done by HWI researchers. Their tenacity and commitment to the work they do, even through the most challenging of funding periods, is a testament to their dedication to contribute to future cures.

As we embark on 2016, HWI will be celebrating its 60th anniversary since Helen Woodward Rivas gave her founding gift of $3 million in 1956 to support the leading edge research of Dr. George Koenig (the equivalent of a $26 million gift in today’s economy). I am pleased to see the impact that HWI has had over this time period and how well poised it is to have significant impact in the future. It is my hope she would feel the same. I do plan to actively participate in this promising future as a friend to the Institute and it is my hope that you will continue to do the same.

With sincere appreciation,
Richard Aubrecht, PhD
Departing Board Chair

OUTGOING CHIEF EXECUTIVE OFFICER’S MESSAGE

Respectfully submitted,
Eaton Lattman, PhD
CEO emeritus
Our consolidated accrual basis net loss for the year ended October 31, 2014 was $116k and was
driven mainly by depreciation expense on our research facility as well as a continued reduction of our federal grant revenue base. Cash flow remained flush with the prior year positively impacted by payments on outstanding receivables. Controllable expenses were maintained within budget. Non operating gains of $536k include realized and unrealized investment performance as well as the fair value of the derivative arrangement on our outstanding debt. During the course of the year, HWI formed a for-profit subsidiary named HarkerBIO, LLC. HarkerBIO’s mission is to work with clients to improve and optimize the process of drug discovery through structural biology methods developed at the Institute. HWI invested $250k of capital into the company this year for a majority of the membership units. The establishment of HarkerBIO will enhance and expand HWI’s scientific footprint as well as generate new revenue streams for the Institute.

On the balance sheet, our total assets are approximately $26M. This includes $7.8M in investments of which our permanent endowment represents $2.3M. We have set aside another $100k in a Reserve for Replacement as required by our covenants with our lender. This effectively brings our replacement reserve up to $1M and satisfies the covenant in full. Lastly, we once again received a favorable “unqualified” report from our auditors. There were no deficiencies noted in accounting controls or major research programs.

Respectfully submitted,

Anne M. Kent
Vice President of Finance

### Significant Financial Statement Elements

<table>
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<tr>
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<th>10/31/2014</th>
<th>10/31/2013</th>
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</thead>
<tbody>
<tr>
<td>Total Assets</td>
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<td>Total Liabilities</td>
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<td>Total Net Assets</td>
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<tr>
<td>Total Revenues &amp; Other Support</td>
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<td>Total Operating Expenses</td>
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<tr>
<td>Net Operating Loss</td>
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<td>Non Operating Gains/(Losses)</td>
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<td>$ 621,810</td>
</tr>
<tr>
<td>Net Loss</td>
<td>$ (116,355)</td>
<td>$ 649</td>
</tr>
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</table>

1 Source: The audited financial statements of the Hauptman Woodward Medical Research Institute, Inc.

### 2014 RESEARCH HIGHLIGHTS

#### Dr. Vivian Cody’s Laboratory

The primary focus of Dr. Cody’s research is to understand how drugs or hormones are recognized by their protein targets and how their interactions can be optimized to help design more effective drug treatments for diseases such as cancer, AIDS-related pneumonia, and thyroid hormone disorders.

One on-going study is aimed at finding inhibitors of dihydrofolate reductase (DHFR), a critical enzyme responsible for the synthesis of nucleic acids and proteins. This enzyme drives protein synthesis, and therefore, cell growth. The major focus of this work is to identify inhibitors that can selectively target DHFR from pathogens rather than the human enzyme, for the treatment of such diseases as *Pneumocystis pneumonia*, malaria, bacterial infections, and cancer.

Another area of focus is on 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 amyloidic polyneuropathy, is the result of 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 make the body’s organs 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 which has designed novel compounds that can stabilize human TTR. She 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 a Professor in the School of Medicine and Biomedical Sciences, UB and is currently Secretary of the School of Medicine Faculty Council.
The Gewirth Lab studies the structure and mechanism of proteins involved in cancer. A major focus of this group is Hsp90 chaperones. These chaperones are proteins, and their job is to help other proteins survive in the crowded and hostile cellular environment. They do this by helping other, newly made proteins, assume their functional folded shape, or by sequestering damaged proteins for subsequent removal.

Among the ‘client’ proteins that Hsp90 acts on are many of the key proteins required for tumor growth. Inhibitors of Hsp90 are currently under intensive study because of their great potential as powerful anti-cancer drugs. Dr. Gewirth also investigates steroid and nuclear hormone receptors, in particular the androgen receptor and its role in the regulation of prostate cancer. Although normally slow growing and benign, in some men prostate cancer becomes aggressive and life threatening. For these patients, anti-androgens are used to counter the growth and spread of the disease. Over time, however, this treatment inevitably becomes ineffective as mutations in the androgen receptor render it insensitive to castration treatments. The goal of Dr. Gewirth’s research, carried out in collaboration with scientists in Minnesota and Vancouver, is to develop drugs that target new parts of the androgen receptor. The hope is that these inhibitors will suppress cancer cells even after the cells become resistant to the current drug treatments available.

Dr. Gewirth is Chair of the HWI Scientific Governance Council and represents the faculty on the HWI Board of Directors.

2014 RESEARCH HIGHLIGHTS

Dr. Daniel T. Gewirth’s Laboratory

Dr. Andrew M. Gulick’s Laboratory

Many pharmaceuticals, including the anti-cancer agent bleomycin and the antibiotics penicillin and vancomycin, are naturally produced by bacteria and fungi. The Gulick Lab is studying the enzymes that are involved in the production of these active natural products by a family of proteins called Non-Ribosomal Peptide Synthetases (NRPSs). The goal of this work is to understand the basic strategy of how these enzymes function, which may allow bioengineering approaches to produce new active compounds. Additionally, many bacteria harbor NRPSs for which the product is unknown. A better understanding of how these enzymes work could allow us to discover new natural products with new activities. Finally, other NRPS proteins are responsible for the virulence of human pathogens and the Gulick lab is discovering compounds that block NRPS function to prevent the bacteria from making these molecules that allow them to grow. Important additional studies this year led to publications with collaborators from several groups from the University at Buffalo to study important proteins in the human pathogens Klebsiella pneumoniae and Mycobacterium tuberculosis.

Dr. Gulick was recently named HWI’s Vice President for Research.
Joseph R. Luft’s Laboratory

The Luft Laboratory aims to bring scientific rigor to the means of growing protein crystals; these crystals are used to determine three-dimensional structures to see proteins and learn how they function. Crystallization conditions are identified by combining a protein with hundreds of different chemicals and then looking for indications of crystals. The high-throughput crystallization laboratory at HWI can set up 1,536 of these experiments in minutes and now has a state-of-the-art imaging system, the SONICC was acquired through a generous anonymous gift as well as with funds from Empire State Development. The SONICC can detect crystals that would otherwise be missed because they are too small to be seen with a microscope. The laboratory continues to improve upon technologies through collaborative scientific research and to date has screened more than 15,000 proteins for crystallization.

The Malkowski Laboratory is focused on structure-function studies of integral membrane enzymes, specifically those involved in lipid metabolism and the oxygenation of polyunsaturated fatty acids. One of the key families of enzymes under current study is the Cyclooxygenases (COX-1 and COX-2). Changes in COX-mediated prostaglandin biosynthesis are associated with various disease pathologies, including inflammation, cardiovascular disease, and cancer. COX-1 and COX-2 are the targets of aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDs), and COX-2 selective inhibitors (coxibs) such as Celebrex. These compounds are some of the most heavily utilized drugs in the world, used to decrease acute and chronic inflammation, protect against adverse cardiovascular events, and reduce the risk of developing certain cancers. However, NSAID and coxib use is not without risk. Over 15,000 deaths per year can be ascribed to harmful effects derived from their consumption, the molecular basis of which is unknown. Dr. Malkowski’s laboratory is interested in understanding the molecular basis of how these drugs interact with the enzyme, with the ultimate goal of providing a foundation for the development of new drugs and repurposing existing ones to provide maximum efficacy while minimizing risks.

The Luft lab is playing an integral role in the launch of HWI’s HarkerBIO.

Dr. Michael G. Malkowski’s Laboratory

Dr. Malkowski was recently named Interim Chairman for the Department of Structural Biology at the University at Buffalo School of Medicine and Biological Sciences which is housed at HWI.
Crystallography is the dominant technique for visualizing biological macromolecules and understanding how they work. The existence of high-quality crystals is a key requirement. However, the growth of such crystals is often a major obstacle. Therefore, one of the major goals of the Snell laboratory is to develop greater understanding of the crystallization process and to improve the methodology for elucidating the structure, function and dynamics of large biological molecules. Complementary techniques are also being developed where crystallization is not successful or to add additional information to the crystallographic structure.

The Snell laboratory is situated adjacent to HWI’s high-throughput crystallization screening laboratory, directed by Joseph Luft; the two labs work together to develop practical approaches for initial crystallization screening, to examine different methods of evaluating experimental outcome, and to make use of the crystals that result. More often than not, crystallization attempts initially fail or samples remain recalcitrant to crystallization. In cases like these where satisfactory crystallographic work is not possible, the Snell lab has developed algorithms and techniques in Small-Angle X-ray Scattering (SAXS), to extend the information that can be derived from this complementary technique.

The Snell lab has multiple collaborations in combining complementary methods: for example, they have made use of neutron scattering to study enzymes, SAXS as a tool to validate basic shape information, and Nuclear Magnetic Resonance (NMR) in combination with computational modeling to understand structure. Of particular importance is the combination of crystallography, SAXS, and molecular dynamics to provide structural and mechanistic information.

Dr. Snell was recently named Chief Executive Officer of HWI.

Dr. Timothy Umland explores how animal viruses mutate to gain the ability to productively infect human cells through evasion of the innate immune system. Many viruses have evolved responses that allow them to either remain undetected by, or to disable a host’s first-line innate immune responses. Discovering how animal viruses mutate to “match” with key innate immunity proteins present in a new host cell may eventually lead to antiviral drugs or the ability to enhance surveillance for emerging pathogenic viruses. The Umland Lab, in collaboration with Thomas Russo, M.D (University of Buffalo and VA Medical Center), has also identified proteins that are essential during infection for the growth and survival of Acinetobacter baumannii, a bacterium that exhibits extreme-drug resistance that primarily affects medical health center patients. This is a first step in an effort to develop new antibiotics capable of combating multi-, and extreme drug-resistant bacteria.

Dr. Umland hopes to lay the groundwork for developing new antibiotics to treat drug-resistant bacteria.
2014 PUBLICATIONS


The nonsteroidal anti-inflammatory drug ibuprofen bound to Cyclooxygenase-2. Solved by the Malkowski Laboratory
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.

**Board of Directors and Officers**

The People of the Hauptman-Woodward Medical Research Institute

Hauptman-Woodward plays a role in ensuring the organization’s current and future successes.
We would like to thank and acknowledge the following donors

Gifts received between January 1, 2014 and December 31, 2014

$50,000 - $99,999
- Richard W. and Mae Stone Goodie Trust
- Richard W. and Mae Stone Goodie Trust

$40,000 - $99,999
- E.J. and Martha H. Bechtel
- Community Foundation for Greater Buffalo
- Edith M. Flanigan
- Downtown Buffalo Liquor

$20,000 - $49,999
- Mr. and Mrs. Peter L. McCauley
- KeyBank
- Dr. George N. Phillips, Jr.

$10,000 - $19,999
- Mr. and Mrs. Reginald M. Newman, II
- New Era Cap
- Mr. and Mrs. Lewis D. McCauley

$500 - $9,999
- Mr. and Mrs. James T. Ford
- Mr. and Mrs. Anthony M. Ford
- Dr. and Mrs. William H. Ford

$100 - $249
- Mr. and Mrs. Michael L. Ford
- Buffalo Bills Alumni Foundation
- Mrs. Elizabeth M. Fisk

$50,000 - $99,999
- Dr. and Mrs. Robert E. Ford
- Community Foundation of Greater Buffalo
- Buffalo Bisons

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The sixth annual Hauptman Society gathering took place on April 16, 2015. 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,” 2015 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 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.