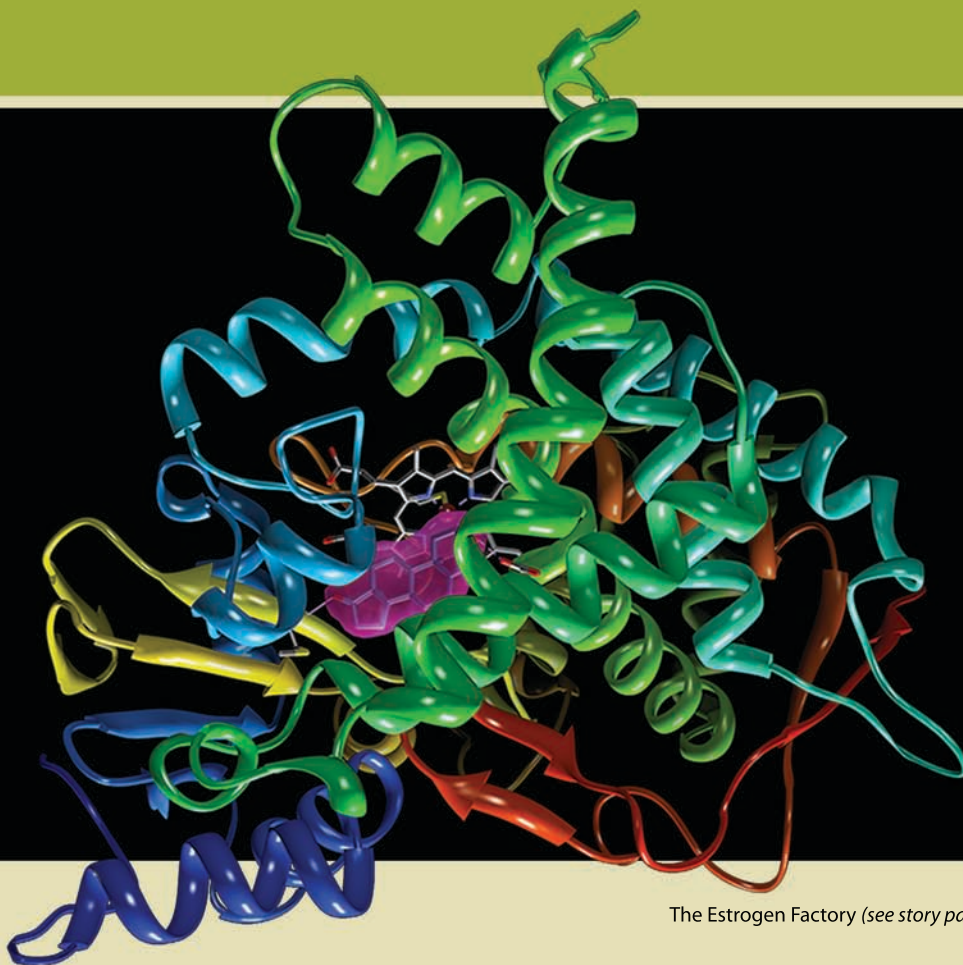


Hauptman-Woodward Institute
2008 Annual Report



The Estrogen Factory (*see story page 6*)

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 Dr. Herbert A. Hauptman and our new 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.

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The cover illustration depicts the structure of human placental aromatase. Aromatase is the key enzyme in producing estrogen. By knowing this structure, drugs can be designed to block the production of estrogen which can help 75 to 80 percent of breast cancer patients.



Herbert A. Hauptman, Ph.D.

A love of science, a dedication to understanding, a generosity of spirit to help the scientific endeavor. Each of these phrases might describe the individuals highlighted as the three main points of my message this year.

A love of science laid the path which led our new Chief Executive Officer and Executive Director Dr. Eaton "Ed" Lattman to find his way to Hauptman-Woodward. Ironically, that same love of science set the path for our former leader Dr. George DeTitta to leave that post and return to the lab. For each of these remarkably gifted scientists, his devotion to science and the role he is interested in playing to support scientific research will be of great benefit not only to HWI, but to the world of science overall. I am confident that our institute is in the most capable of hands with Ed at the helm and that George is providing him sage counsel, guidance and friendship on that journey.

Our scientists and staff members – the backbone of this organization - also are driven by the passion to achieve a greater understanding of our science. They also make sacrifices for the love of science and I continue to be impressed by the commitment of time, energy and creativity our scientific and non-scientific staff bring to the table each day as they try to advance their science and build the strength and success of Hauptman-Woodward. Each of these talented HWI employees is listed on the following pages, and I hope you will join me in applauding their hard work and the successes that have resulted from their investment.

As most of you probably know by now, another key leadership change occurred within the past several months in the ascension to the post of chairman of the board by James Biltekoff in the wake of the tragic death of former board chair Donald Hess and his lovely wife, Victoria. The Hesses were dear friends of so many of us at the Institute; along with our HWI colleagues, my wife Edith and I will mourn for them for a long time to come. But as with everything Don did, his leadership built a legacy and a foundation on which Jim can and is already building for the future. Jim is a capable, talented man whose generosity of spirit is now being dedicated to helping the scientific endeavor at HWI.

Last, but not least I have to mention the dedication to understanding that is at the core of all we do in basic research. Everyone today, in this modern world is seeking easy answers and rapid solutions. But the most rapid route is not always the one which is the most successful. In fact, in the following pages, we are highlighting a project led by Dr. Debashis Ghosh – the solution of the structure of aromatase – which is the culmination of more than 35 years of research at HWI. It was not an overnight sensation, but it will indeed make a difference in the lives of more than 75 percent of the breast cancer victims all over the world.

Of course, I would be remiss not to acknowledge our friends and donors who continue to support us in our effort to succeed and not simply survive. We know that the economy is making this sacrifice even more dear and I thank you on behalf of the Institute because you too play an essential role in improving human health. Together we will continue making breakthroughs for many years to come.

Herbert A. Hauptman, Ph.D.,
Nobel Laureate and President



James R. Biltekoff

2008 was a year of transitions. We celebrated George DeTitta's outstanding service as CEO and Executive Director for nine years, and welcomed our new CEO and Executive Director Ed Lattman, who seems poised to take us to even greater heights. Sadly, we lost three good friends. Don Hess, Chairman of the HWI Board of Directors, is remembered as much for the twinkle in his eye and unassuming manner as for his steady leadership and generosity during the Institute's expansion. Paul Koessler, Vice-Chairman, was a mainstay of wise counsel. Finley Greene, in his former role as Vice President of Development and Communications, played a key role in garnering community support for our successful building campaign.

We cannot replace their talent and enthusiasm, but we can honor their memory by continuing to give our support to this institution they loved so much. Specifically, we can contribute to the Donald and Victoria Hess Endowed Memorial Fund, established and chaired by Don's longtime business partner and friend Chuck Dowdell, to raise permanent funds to further secure the financial strength of the Institute.

I have the great pleasure of working with Ed. He brings to the job intelligence, wit, and vast experience in academic research. He is a natural collaborator who already has reached out to our partners on the BNMC. I am impressed by his ability to see new opportunities where others see only obstacles. Early evidence of Ed's impact can be seen in his initiation of new grant proposals and the creation of our Scientific Advisory Committee. My work, and Ed's, is made easier thanks to the skill, accomplishments, and dedication of our outstanding faculty and professional staff. Thank you, one and all.

Clearly a highlight of 2008 has been Deb Ghosh's breakthrough in solving the structure of an enzyme that plays a key role in the growth of breast cancer tumors. The culmination of more than 35 years of research, Deb's accomplishment is a model of the research process at HWI: years of work lead to the solution of an important structure using techniques developed at and refined at HWI - techniques which now are used around the world. However, embedded in the "solution" is a new challenge for Deb's team: to take the next steps on the road to curing a devastating disease. Let's hope that cure comes in less than 35 years!

I'd like to share with you my top three priorities as chairman: (1) solidify our financial base, by addressing our need for a larger endowment, and by exploring alternative sources of revenue; (2) continued growth through the recruitment of new faculty members and the expansion of our scientific base into the field of computational biology; (3) increase the visibility and reputation of HWI, regionally and nationally. Clearly, our challenge is to achieve these goals in a time of economic stress and curtailed federal grants. For this effort to succeed, we will need help from you, our friends and supporters.

Finally, I would like to share a few thoughts about HWI's role in the BNMC community. The new leaders at UB, Roswell, Kaleida, and HWI are finding ways to collaborate in designing and implementing solutions, and creating new opportunities across the spectrum of scientific research, clinical services and economic development. We will begin to see peer-to-peer collaboration between institutions and among individual scientists, doctors, educators, and professionals in areas as wide-ranging as recruitment and joint hiring, research, grant requests, purchasing, and service delivery. We at HWI are committed to support and promote the spirit of collaboration embodied in the BNMC which benefits us all.

James R. Biltekoff
Chairman of the Board



Eaton E. Lattman, Ph.D.

It is an exciting and sobering moment to sit down and write my first annual report as CEO of Hauptman Woodward. The period encompassed is in fact a good bit less than one year, since I actually began work in the middle of July 2008. But even in those 32 weeks there have been major developments both for HWI, and for me personally. Let me rehearse just a few of the major themes.

Perhaps the most important element in my inaugural period is how smoothly and effectively the transition of the CEO position has gone. Management books will reliably misinform one that having the past CEO in a position to look over the shoulder of the incoming one is a recipe for friction or worse. In fact, George DeTitta is handling this process with the same grace and generosity that he brought to all his other CEO activities. He has spent hours talking to me, and bringing me into the loop on many issues, but has invested no time in telling me what to do. As he pithily said, "I'm going to stay out of your way, but if I think that you are going to walk the plank I'm going to warn you." Thanks, George.

Of all the issues that HWI faculty members raise, perhaps the most troubling has been the level of support provided by the University at Buffalo to Hauptman Woodward for operating the Department of Structural Biology. The faculty members of this department are Hauptman Woodward scientists, and its students are educated in our building. Most faculty members receive no compensation from UB, while a handful of others receive part-time salary. There are difficult issues for both sides in this conversation, issues too complex for this short report. But it is worth noting progress on three fronts. First, I am convinced that Michael Cain, Dean of the School of Medicine, has great respect for our institute and department, and is committed to improving the levels of support. As a concrete example of this, Dean Cain has authorized an international search for a new chair of the Department of Structural Biology, to replace George DeTitta who will be stepping down from that role at the end of June. The advertisement for this position is being distributed as I write this. In addition, Dean Cain has authorized and encouraged consideration of the promotion of Hauptman Woodward scientists who hold research track faculty appointments in the School of Medicine. I look forward to the resolution of additional issues in the coming year.

On a side note, the department is being renamed the Department of Structural and Computational Biology. This is a great opportunity for us to have even more interaction and collaboration with the Center for Computing Resources at the New York State Center of Excellence in Bioinformatics and Life Sciences. We also might see an increased investment in an effort to recruit students with computer systems backgrounds into the program.

Significant changes in the governance of HWI have occurred in the past few months. Of these the most important is the accession of Jim Biltekoff to the post of Chairman of the Institute Board. As you are all keenly aware, this followed the devastatingly sad death of our former chair Don Hess and his wife Vicky. Just recently, under

Jim's leadership the functions of the Hauptman Woodward Foundation Board, which had responsibility for fundraising, were merged into the Institute Board, and all members of the Foundation Board were invited to join the Institute Board. This merger forms part of the process of preparing for a major development effort starting in the next year or two. The Board also authorized the creation of a Scientific Advisory Committee to provide long-term advice about and evaluation of Hauptman Woodward's scientific activities. Already two distinguished scientists from outside Buffalo have agreed to join. I hope that this Advisory Committee will provide a different perspective on the evaluation of our programs and research.

Jim has also instituted the custom of bi-weekly meetings between him and the CEO. These have proved enormously useful and productive, and they are fun too. They also represent an example of the deep sense of involvement and commitment he has brought to his new job.

We have had many exciting research developments this year. As an outstanding representative let me mention only the work by Deb Ghosh and his colleagues in elucidating the three-dimensional structure of the enzyme aromatase. Aromatase is an essential link in the pathway by which women's bodies synthesize the hormone estrogen. Many breast cancer tumors feed on estrogen, and shutting off the supply of estrogen to them can halt or reverse their growth. Knowing the structure of aromatase allows the Ghosh group rationally to develop molecules that bind to aromatase in place of estrogen precursors, and therefore cut off the ability of the aromatase molecule to synthesize estrogen.

There are many issues facing us that I do not have space to mention. Of these perhaps the issue of most significant is the potential effect of the economic downturn on the future of HWI. So far we have been getting along quite well, and we will be energetically pursuing avenues for support made available by the Obama stimulus package. Beyond this, like the rest of the country, we have to wait and see. But I look forward to a continuing and vital HWI, and to making future reports to you about exciting developments in research and education.

Let me conclude on a personal note. Coming to HWI has been an exciting and rejuvenating experience for me. I am impressed by the quality of the science and ideas created by both our faculty and staff, and by the esprit de corps and dedication that they show to the Institute. Although my role was intended to be purely an administrative one, I have been so enthused by my discussions with the faculty, and by our lab meeting presentations that I have submitted a grant of my own. I am having a very good time.

Sincerely,

Eaton E. Lattman, Ph.D.
Chief Executive Officer and Executive Director

HWI Scientist First in World to Solve Structure of Key Breast Cancer Target

The molecular details of Aromatase, the key enzyme required for the body to make estrogen, are no longer a mystery thanks to the structural biology work done by the Ghosh lab at Hauptman-Woodward. Dr. Debashis Ghosh's solution of the 3-D structure of aromatase is the first time that scientists have been able to visualize the mechanism of synthesizing estrogen. His work is so highly acclaimed that it was published in a January issue of the world-renowned journal *Nature*. In addition, Ghosh's work was covered by electronic and print media all over the world and at the time of publication, there were more than 75 media hits on this work. His work is also being recognized by peers who have invited him to speak at conferences in China and Japan, as well as by breast cancer patients, survivors and advocates who have chosen to make him the keynote speaker at this year's Susan G. Komen luncheon in Buffalo, New York.

This breakthrough was not HWI's first foray into the world of estrogen. In fact, the Ghosh lab has determined the structures of all three of the enzymes involved in controlling estrogen levels that can serve as drug targets for estrogen-dependent tumors in breast cancer. In addition to solving the structure of aromatase, the other two enzyme structures determined by the Ghosh lab as part of this project were estrone sulfatase (2003) and 17beta-hydroxysteroid dehydrogenase type 1 (1996). All three enzymes control the levels of estradiol in different tissues.

"This is a dream come true," Dr. Debashis Ghosh, a HWI senior research scientist and a principal investigator who also holds a joint faculty appointment at the Roswell Park Cancer Institute (RPCI), said. "Scientists worldwide have been trying for 35 years to crystallize this membrane-bound enzyme and we are the first to succeed. Now that we know the structures of all three key enzymes implicated in estrogen-dependant breast cancers, our goal is to have a personalized cocktail of inhibitors customized to the specific treatment needs of each patient. Our knowledge about these three enzymes will enable us to develop three mutually exclusive inhibitors customized to each patient's needs which will work in harmony together with minimal side effects."

Why Is This Important?

Most people know that breast cancer is the most common cancer among women in the United States and the second leading cause of cancer death in women, after lung cancer. Many people also may be aware that the chance of a woman having invasive breast cancer some time during her life is about 1 in 8 and the chance of dying from breast cancer is about 1 in 35. But many may not be aware that 75-80 percent of all breast cancer tumors are estrogen-fed. Estrogen is a female sex hormone and androgens are the male sex hormones. Regardless of gender, everyone has some percentage of both estrogens and androgens in their bodies. Each of the enzymes discussed above can individually promote the growth of estrogen-dependent breast cancers, but knowing all three structures opens the door to customized, comprehensive medical treatment.

Aromatase is the only enzyme in the vertebrate world that makes estrogens from androgens. 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. These drugs do not discriminate in what they target in the body, which results in significant side effects. Aromatase inhibitor drugs (AIs) have only been on the market a few years and are targeted to inhibit aromatase specifically. But because the structure was not known, nor the mechanism of androgen to estrogen conversion, the AIs currently in use have been developed using trial and error methods resulting in greater vulnerability to contraindications and side effects.

continued on page 16



Debashis Ghosh, Ph.D.



Lisa A. Foti

Our October 31, 2008 fiscal year ended with an overall positive cash flow of \$71,000. Our consolidated accrual basis net operating loss was \$1.5M and was driven mainly by depreciation expense on our research facility. Controllable expenses were maintained within budget. Significant non operating losses totaling \$891k were reflected in 2008 and largely represent the market decline in our investment portfolio, consistent with overall general economic conditions. If there's a silver lining though, our conservative market strategy resulted in an aggregate loss of only about 9% compared to the 20-25% that the overall market had declined through October 2008.

On the balance sheet, our total assets are \$32.7M and our permanent endowment fund is currently at \$1.7M. We have set aside another \$100,000 in a Reserve for Replacement as required by our covenants with our lender. This effectively brings our replacement reserve up to \$400,000. 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 major research programs.

Finally, in preparation for receipt of our first federal contract through the Department of Defense, we were required to have a separate governmental audit of our accounting systems and controls. The Department of Health and Human Services through the Office of the Inspector General conducted this audit. I am pleased to report that our systems and controls were found to be compliant and according to the defense department program officer, the Inspector General's Office issued an extremely favorable report. This paves the way for additional federal contract work. We expect that this initial contract will be awarded in April 2009. It is a \$2.8M contract over three years to study the transfer of viruses from animals to human hosts.

Lisa A. Foti, CPA
Chief Financial Officer

Significant Financial Statement Elements¹

	<u>10/31/2008</u>	<u>10/31/2007</u>
Total Assets	\$ 32,270,707	\$ 34,742,686
Total Liabilities	\$ 6,893,298	\$ 6,925,086
Total Net Assets	\$ 25,376,779	\$ 27,817,600
Total Revenues & Other Support	\$ 7,391,610	\$ 7,606,446
Total Operating Expenses	\$ 8,940,982	\$ 9,073,947
Net Operating Loss	\$ (1,549,372)	\$ (1,467,501)
Non Operating (Losses)Gains	(891,449)	1,091,924
Net Loss	\$ (2,440,821)	\$ (375,577)

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

We would like to thank and acknowledge the following donors to Hauptman-Woodward making a gift in our fiscal year 2008.

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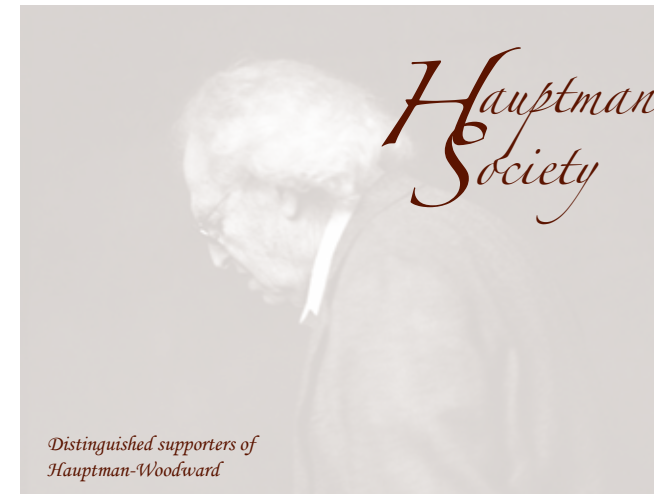


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“Now that the Ghosh Lab has unraveled the molecular details of aromatase, drugs can be designed to specifically target aromatase,” Dr. Walter A. Pangborn, Executive Vice President at HWI, said. “This means that results from this research will form the basis for novel breast cancer drugs that are highly specific for aromatase but cause minimal side effects.”

What Happens Next?

Ghosh now will work to test his hypothesis of the chemical mechanism involved in the conversion of androgens to estrogens. He also will be working with collaborators to develop medicinal complexes for testing. In collaboration with organic synthetic chemist Dr. Huw Davies of Emory University and RPCI colleagues, they will conduct cellular and animal studies of those complexes.

What Was The Project History?

The aromatase and sulfatase projects were started at HWI by Dr. Yoshio Osawa more than 30 years ago. His preliminary work laid the foundation for the eventual solution of the structure of estrone sulfatase. A number of collaborators played a role in the 17 β -hydroxysteroid dehydrogenase project's early work including scientists in Canada, Finland and HWI Hauptman Distinguished Scientist Dr. William Duax. Ghosh and Osawa started to collaborate in 1995. When Osawa retired in 1998, Ghosh took the project over and developed a revolutionary method of purifying and crystallizing these enzymes. “Everyone had given up on crystallizing the enzyme,” Ghosh said. “Using a ‘secret recipe,’ we have been able to crystallize it and identify the structure – knowledge which will be used to make much better drugs.”

About Dr. Debashis Ghosh

In addition to his position as an HWI senior research scientist, Ghosh is an associate member of the Department of Pharmacology and Therapeutics at RPCI and in the Department of Structural Biology of UB. Ghosh received his bachelor's degree with honors in Physics, Chemistry and Mathematics from St. Xavier's College, University of Calcutta, India and his master's degree in Physics from the Indian Institute of Technology, Kharagpur, India. He completed a post-master's fellowship in Biophysics at the Saha Institute of Nuclear Physics in Calcutta, India. Ghosh then earned his doctorate in Crystallography from the University of Pittsburgh and completed his post-doctoral fellowship in Material Science at Carnegie-Mellon University in Pittsburgh, Pennsylvania.

The Ghosh Lab's major research interest involves the structural biology of estrogen and androgen biosynthesis and metabolism using the X-ray crystallographic elucidation of three-dimensional structures of proteins, as well as other biophysical/biochemical techniques. In addition, in collaboration with University of Buffalo ophthalmologist Dr. Federico Gonzalez-Fernandez, his lab is investigating the structure-function relationships of interphotoreceptor retinoid-binding proteins (IRBP) linked to macular degeneration and retinitis pigmentosa. This project is funded by the National Eye Institute. The lab's third project deals with the elucidation of the molecular basis of antigen mimicry by anti-idiotypic antibodies. In collaboration with immunologist Dr. Soldano Ferrone of the University of Pittsburgh Medical Center, they are attempting to design rational peptide mimics of the high-molecular weight, melanoma-associated antigen (HMW-MAA) for possible use as vaccines, a project funded by the National Cancer Institute.



Debashis Ghosh, Ph.D.



"Crystallizing the human aromatase has been a dream! It is now realized!" Senior Research Scientist Dr. Debashis Ghosh, HWI



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