STRUCTURES

A PUBLICATION OF HAUPTMAN-WOODWARD INSTITUTE SUMMER/FALL 2017

HOPE for new developments in breast cancer treatment

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"Human health and molecules seem chaotic, but underlying the mess is a set of simple chemical rules that govern them..." p.10

IN THIS ISSUE

cure·osity

HISTORY

Marking HWI's 60th Anniversary with Growth

The $4 million Fund for Cure•osity enables HWI to recruit new scientific groups who will enhance our international leadership in the study of biomedical interactions – how life works and how drugs can help that process. This philanthropic investment will allow us to add four laboratories, each led by a scientist whose discoveries will develop the cures for the future in areas including cancer, Alzheimer's, Parkinson's, and the treatment of infection.

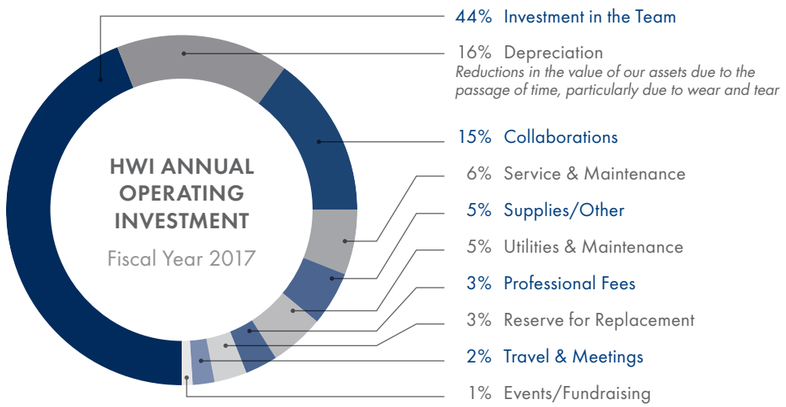
Start-up support leads to self-sustaining growth.
Starting a successful new research group takes approximately $1 million. This funds the costs of a new investigator, the scientific personnel of their laboratory, equipment, and supplies for a period of three to five years. While federal funding supports the science of mature investigators, it does not pay to bring the next generation of investigators on board – that's why support from partners and philanthropists to fund these four new research groups is crucial. This support buys the time needed to generate exciting results that can be parlayed into Federal support and then lead to a self-sustaining research effort. As evidence, a generous gift of $5.75 million from a local foundation has leveraged nearly $50 million in federal research grants led by HWI investigators. The return on investment of this philanthropy is tremendous and brings resources and recognition back to the Western New York community.

HWI discoveries are the catalyst for cures here in Buffalo and beyond.
The research findings that come from our laboratories are shared in the public domain for scientists worldwide to build upon. By expanding our capabilities with four new laboratories, we exponentially increase the amount of valuable data we can share with world-class research centers working toward cures around the country.

We are the backbone of the Buffalo Niagara Medical Campus.
As the biotechnology boom in Buffalo blossoms, the Institute has played an important role in the Region's rebound. As the first new construction on Buffalo Niagara Medical Campus, we've watched as other local institutions have joined us in building Buffalo's medical legacy beam by beam. By bringing new talent into Buffalo, HWI can lead the research that provides the foundation for the cures of tomorrow.

BUILDING A NEW RESEARCH GROUP

Principal investigator	$544,000
Staff, such as students or technicians	245,000
Supplies, travel, publication costs, etc.	79,000
Core overhead	465,000
TOTAL OVER 5 YEARS	**$1,333,000**



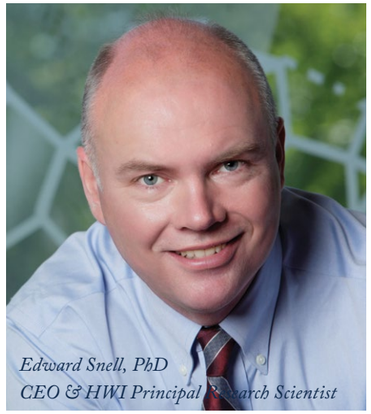
In the spirit of expanding interactions with our Campus partners, we will seek researchers that strengthen current research in cancer, age-related diseases, infection, and other areas to leverage existing expertise within the Institute and the growing Medical Campus.

Our continued success belongs to the community.
A private gift of $3 million founded the Institute 60 years ago and attracted the pioneering work of Herbert Hauptman, who earned a Nobel Prize for his discoveries and catapulted HWI to premier standing among research institutes worldwide. Since then we've grown to become an organization marked by efficiency, passionate local leadership, and favorable international reputation within the scientific community. But we couldn't have done this without the initial – and continued – support and generosity of friends and neighbors. We need your help to deepen our impact on foundational research, discovery of cures, and to bring the spotlight to what we are achieving in Buffalo.

Make a difference for the future – support The Fund for Cure•osity today. This monumental capital campaign will help us find the cures for the future so that diseases that cannot be successfully treated today can be tackled for the benefit of our children and grandchildren. Please consider being a part of this important work.

SCIENCE

HWI Research that is out of this world



Edward Snell, PhD
CEO & HWI Principal Research Scientist

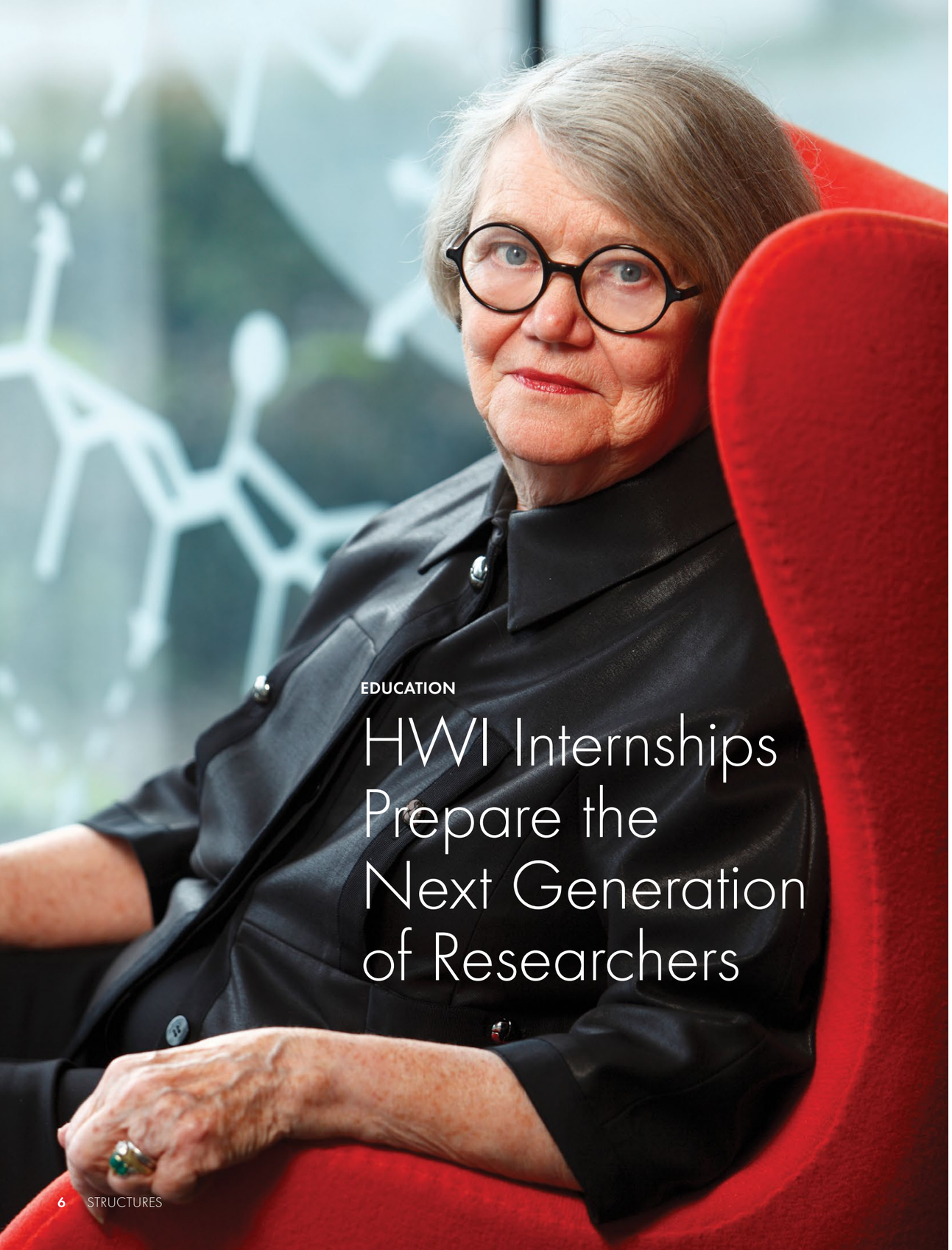
Two television shows, Star Trek and Carl Sagan's Cosmos cemented my interest in science. Despite being a child of the Apollo era (just) and working at NASA for over 10 years, my interest went from outer space to inner space. There are just as many mysteries about how life works on earth as there are when you look out to the stars. Those mysteries of inner space are a lot closer and have an immediate impact on those we care about. Sometimes it seems that nature smiles – mathematically outer space and inner space are very similar. When you combine looking at inner space by using outer space as a tool to a biophysics nerd this is paradise - when we add X-ray lasers, it shifts to Nirvana, making use of the most technologically advanced tools anywhere in the world.

So beyond the sheer joy of the experiment, what are we doing with them? Let me first make a simple statement about a complex technique. If we want understand the targets of drugs, we have to use complex processes to do so. The most productive method is to build crystals of those targets and shine X-rays at them. Trust me on this, almost thirty Nobel Prizes have been awarded in the development and use of this area, including that of our namesake, Herb Hauptman. It's complex, totally amazing, and yields profound insight into nature at the most basic level. The key is the crystal. The better the crystal is then the better the information that results. As an analogy, imagine trying to find a house on a map of the state – the map would not provide enough detail to find the street let alone the house number. Zooming in provides the detail and allows us to find the house. Better quality crystals are like zoomed in maps – we can find the house and deliver the package, and in our case **hopefully a drug that cures a disease.**

We use space to grow better crystals. Since the days of Spacelab shortly after Apollo, scientists have experimented with growing crystals in space. In a small but significant number of cases, the quality of the resulting crystal has been greatly improved. Crystals grow larger and better for the same reasons you see astronauts floating. Rather than dropping to the bottom of the beaker, the crystal remains suspended and can grow larger. The internal construction becomes easier. At the Institute we think we can identify those crystals that benefit from space by using a simple test on the ground. Imagine that the components making up a crystal are either building blocks or jelly beans. The building blocks can be formed into just as good a crystal on the ground as they can in space but the jelly beans really need that 'weightlessness' to build into an object. We are performing measurements on the ground that identify the building block from the jelly bean and now, testing if our idea is correct. Currently every 90 minutes a crystal from Buffalo flies overhead.

The Institute focuses on innovation, discovery, and education. Our work with NASA shows some of the innovation. If we can identify which targets we should fly, we can make very efficient use of the International Space Station while advancing our understanding on earth. If the targets are disease targets we don't have the detailed map for, space born experiments may help us obtain them. This will be our next experiment to launch – targets where improved structural knowledge will help us understand how to develop better cancer treatments or improve radiation therapy processes. Our innovation drives discovery. It also drives education, it is gratifying to see a student's eyes light up when you talk about space experiments. You capture their interest, especially when you can show them the samples that have been on the Space Station already.

In avoiding much of the scientific jargon, I hope I have lifted the curtain on some of the magic. We are using our results to try and improve a process for all. The structural knowledge we gain on targets for cancer drugs and improvement of radiation therapy will also help astronauts go a lot further than the moon. In developing tools, we help advance the science of space, and use them for our own discoveries.



EDUCATION

HWI Internships Prepare the Next Generation of Researchers

As Buffalo builds its reputation as a scientific research hub, it is becoming increasingly important to attract and retain researchers and scientists to the local area. Cultivating the next generation of researchers and keeping them in Western New York is a key focus of HWI through its summer internship programs.

HWI offers a 10-week summer apprentice program that pairs students with PhD level scientists to work on specific research projects in molecular biology, crystal growth, X-ray diffraction and computerized data analysis. The internship requires hands-on research, completion of challenging experiments, and a presentation of findings to the entire scientific staff at the completion of the program. Top students vie for these coveted positions and have a chance to gain real world experience and a better understanding of what a career in scientific research might be like. HWI also manages the National Science Foundation BioXFEL Summer Research Internship program, which focuses on a broader range of STEM fields and places students not just at HWI, but also at the University of Buffalo, Arizona State University and University of Wisconsin-Milwaukee.

In addition to gaining experience working with world-renowned scientists and state-of-the-art equipment, HWI interns learn more about Buffalo's growing list of companies and institutions connected to the field of structural biology. According to William Bauer, PhD who oversees HWI's internship programs, "Many students don't know about the growing number of companies that are located in Western New York and on the Medical Campus and they generally come away enthused about their career prospects. At the same time, these companies and research institutions need a pipeline of qualified researchers, so this is a benefit for all."

The internship program, created in the early 1970's, started as a way for researchers to have another set of hands in the laboratory. More than 350 students have served as interns, many choosing careers in scientific research and some, such as Dr. Bauer (once an HWI intern) have continued their careers at HWI. At least eight have chosen to do their graduate work though HWI as well.

Many students begin the internship without a clear sense of their career interests and whether or not research is a good fit. Working as an intern provides a short-term opportunity to test the field out.

Jane Griffin, PhD, Emeritus Principal Research Scientist at HWI, who ran the program for more than two decades before her retirement last year, says that students find the real world of research to be much different than the classroom setting. According to Dr. Griffin, "One of the biggest lessons students learn is just how difficult it is to do research. Students learn from both positive and negative research outcomes. For some, it becomes a career choice, while others determine that this is not for them. Both valuable lessons."

The number of participating students varies each year depending on funding and many students return for another summer or to participate in other programs. Under Dr. Bauer's leadership, additional programs on presentation communications and securing funding have been added so that students can gain a better understanding of the skills necessary for a career in research. Also planned is more tracking of interns after their work with HWI to continue to offer support and networking opportunities in an effort to encourage them to stay true to their Buffalo roots.

A unique opportunity for high school students and undergraduates.

To date more than **300 students from 45 area high schools** have participated.

For **nearly 50 years,** HWI has hosted university undergraduates for summer internships.

More than 350 undergraduate students have had the opportunity to work with world-renowned HWI scientists.

Pictured left is Dr. Jane Griffin, HWI emeritus researcher.

"I regard this summer at the Hauptman-Woodward Medical Research Institute as one of my most meaningful life experiences and the single largest motivator for me in pursuing a medical education. Being a part of the research process and contributing first hand to therapies that will be used to save lives is an amazingly powerful and motivating force."

Sam Wopperer, HWI Intern 2011

The Jane F. Griffin Fund for Science Education

The fund was established in October of 2016 when the Institute, upon its 60th anniversary, recognized Dr. Griffin for over 40 years of leadership in growing and nurturing its education programs. This fund supports summer interns, educational workshops and can assist graduate students in the UB Department of Structural Biology.

Dr. Griffin, a longtime collaborator of Dr. Herbert Hauptman believes that teaching and mentoring future scientists is a worthwhile and noble pursuit. Critical foundational research at HWI is shared worldwide and provides knowledge to help cure critical diseases. In a similar fashion, helping students recognize and develop their interests in scientific pursuits creates future generations of researchers. The impact and success of the program has been an important part of our mission. Its continuation is a priority of the Institute and recognizes and honors the wonderful contributions of Dr. Griffin."

Gifts can be made in Dr. Griffin's honor via Michael Madonia, HWI Director of Development at 716.898.8636 or via email at mmadonia@hwi.buffalo.edu

UB Collegiate Science and Technology Entry Program (CSTEP) Students

CSTEP Students visit HWI to learn more about structural biology and HWI educational offerings. Pictured above with William Bauer, PhD, (far left) HWI Director of Education and Diversity programs.

HWI 2017 Summer Undergraduate Interns

Back row: Kailey Ferger, University of Rochester '19; Frances Heredia, University of Puerto Rico Mayaguez '19; Shirley Yuen, University at Buffalo '16

Front row: Jermel Griffin, University at Buffalo '18; William Schultz, Geneseo '20; Bill Bauer, HWI Education Director, University at Buffalo '08; Abigail Schwenk, Canisius College '18; Efrain Rodriguez Ocasio, University of Puerto Rico Mayaguez '18; Not Pictured: Armond June, University at Buffalo '18

ON THE COVER

HOPE: Chaperoning new developments in breast cancer treatment

Principal Research Scientist Daniel Gewirth, PhD, studies a special class of proteins with tremendous potential

Growing up in Chicago, Dr. Daniel Gewirth was very interested in science, something for which he credits his dad (a philosopher), his mom (who studied biology), and a litany of good science teachers. His fascination lies in the puzzle aspects of science – examining the nature of individual pieces and figuring out how things fit together to form something bigger.

"Human health and molecules seem chaotic, but underlying the mess is a set of simple chemical rules that govern them – in the end it should all make sense, so we have hope of figuring out exactly how."

The intellectual puzzles Dr. Gewirth has been studying for 16 years are centered on disease, specifically breast cancer – what happens when the pieces don't fit correctly and something goes wrong? The precise piece in his puzzle is called Grp94, and it's part of a special class of proteins known as hsp90 chaperones.

Chaperones act as housekeepers within the cells of the human body, making sure other proteins are doing what they're supposed to be doing. In order to function correctly, proteins have to be folded into a certain active form; chaperones assist with that folding. When proteins age or become damaged, they need to be disposed of properly; chaperones come in to take out the trash. When either duty – folding or disposing – doesn't happen, it causes a cellular malfunction that leads to diseases such as cancer, neurodegeneration, and infection.

Drugs that selectively target individual members of the chaperone machinery have great potential to treat disease. The goal of Dr. Gewirth's lab, formed in 2005 when he joined the ranks at HWI, having been recruited from Duke University, is to understand these chaperone systems and apply those insights to develop new treatments.

Last November, Dr. Gewirth was invited to present his research at The 8th International Conference on the hsp90 Chaperone Machine held in Abbey Seeon, Germany. His talk, "The structure of the activated confirmation of Grp94," was shared among an audience of nearly 120 scientists from around the world who all study the specific functions of hsp90 chaperones.

"The presentation is a great way to promote our work, hear what other people are doing, and establish collaborations and connections with people to work on a specific problem," Dr. Gewirth explains. "It also allows us to put a face to a name; you know people by reputation after reading their papers, but it's nice to meet them and hear common scientific interests."

Continued on page 12

Dr. Gewirth receives $300,000 grant from the AVON Foundation

The lab of Dr. Daniel Gewirth has been awarded $300,000 by the AVON Breast Cancer Crusade, which will support his group's continued research on examining how a patient's immune system can be a powerful tool for fighting metastatic breast cancer. By studying how proteins extracted from tumor cells can lead to an immune response, they hope to help the patient's immune system recognize and attack the cancer.

The grant gives the lab two years to work on an idea they've had for quite some time about the specific role of GRP94, and allow Dr. Gewirth and his staff to carry out experiments to see if the idea has any merit. So far, preliminary experiments conducted under the grant show promise. The lab will also be able to use the AVON grant as seed money to parlay into a larger federal grant to do further research.

The grant is funded by The Walk to End Breast Cancer, the largest fund-raising event for the AVON Breast Cancer Crusade. Since its launch by the AVON Foundation for Women in 2003, more than 220,000 participants have trekked 6,868,000 miles and raised nearly $590,000,000 in the fight to end breast cancer. Funds raised at each event provide direct impact in the area where the event takes place, and also help make sure that care and research programs nationwide have adequate resources to make the most progress possible.

"It's definitely not the kind of work for the impatient... we're trying to work on therapies that will be important in 20 years' time."

Daniel Gewirth, PhD

The work of Dr. Gewirth and fellow scientists in this field doesn't offer immediate insights or fast answers; instead, their research is slow and tedious. Countless hours are dedicated to preparing proteins and running multiple series of routine and experimental tests to investigate parts of a hypothesis, often over and over again until a theory is confirmed (or denied). It may take weeks, months, and even years to reach a conclusion.

"It's definitely not the kind of work for the impatient," Dr. Gewirth says with a smile. "We're trying to work on therapies that will be important in 20 years' time. We're not bringing a drug to market next week."

When Dr. Gewirth's lab uncovers a new piece of data, it shares its findings with organic chemists at other institutions like Memorial Sloan Kettering and the Medical University of South Carolina, where researchers synthesize compounds and test them for potential drug applications. If the result isn't a good fit for developing a new drug, it might help form the basis of further experiments moving forward.

Back in the lab at HWI, a staff scientist, a technician, and a graduate student work alongside Dr. Gewirth, who also has a joint appointment as a faculty member in the Department of Structural Biology at the University at Buffalo, where he mentors the next generation of researchers through the school's graduate program, founded at HWI in 2001. Some of his PhD students have gone on to become a staff scientist at a leading biotech firm in Boston, work on the regulatory side of drugs at the FDA, pursue post doctoral studies with a well-known scientist in California, and opt for teaching roles in academic research.

When he's not running experiments or working with students, Dr. Gewirth spends his time working on a different kind of puzzle – rehabbing a 1915 home near the Parkside neighborhood. He enjoys woodworking, and says the quick, noticeable results of home improvement offer a good balance to the less visible, longer-term nature of his research.

His home is only a few blocks away from the growing Buffalo Niagara Medical Campus, something Dr. Gewirth counts as a huge asset for this area.

"The big game changer is the movement of the medical school down here – all the people we work with will be right here," he says. "I can just walk over and participate in seminar programs. The proximity will encourage us to branch out more, and potentially expand the scope of our research. I'm anticipating great things."

BioXFEL

A National Science Foundation Science and Technology Center

5th International Conference

New Orleans, Louisiana USA

February 13-15, 2018

The National Science Foundation BioXFEL Science and Technology Center is entering its 5th year. The Center holds an annual conference of international accord and this year is no exception. The meeting draws world renowned researchers as well as up and coming students and postdocs.

The Institute's newest scientist, Dr. Sarah Bowman, was first introduced to HWI at the 2016 Conference in San Juan, Puerto Rico. At the time, Dr. Bowman was a postdoc at MIT under the conference's keynote speaker, Dr. Cathy Drennan.

"When I attended the conference, I was excited because the experiments being done with XFELs is so cutting edge and opening whole new avenues for understanding structural biology. As a postdoc, these types of conferences are amazing opportunities to gain exposure to the real forefront of research. It also put HWI on my radar as a place where this incredible work was happening and as a top-notch research facility."

The conference has given the Institute access to great talent and has enabled us to facilitate educational opportunities for underserved communities, in particular, students of the University of Puerto Rico. These students have limited access to researchers, facilities, and supplies. This gives them opportunity to bring knowledge back to their institutions as well as create new collaborations. Many take part in our undergraduate summer internship program at HWI, ASU, or UWM, as well as, our UB graduate program located at HWI. The training they receive here has given them the tools to secure internships at other prestigious institutions, such as, Cornell, Harvard, and Stanford.

BioXFEL's annual international meeting is quickly becoming the premiere conference on Biology with X-ray Free Electron Lasers. We strive to bring the most cutting edge results to the greater scientific community and create an amicable free flowing atmosphere in which to share information.

2017 BioXFEL Travel Scholars: Undergraduate and Graduate Students from University of Puerto Rico Mayaguez and Rio Piedras Campuses.

2017 HIGHLIGHTS

181 participants attended 6 sessions.

62.6% came from outside the Center.

Attendees traveled from 8 countries and 12 states.

Thought leadership across the globe and beyond!

HWI researchers have traveled the globe and beyond for invited talks and to advance their research in the last few months. The Institute's excellent reputation internationally was cemented in our early years and continues through today. This time invested fosters further global conversations and collaborations on the path toward cures.

1 Buffalo, New York
HWI hosts a successful site visit for the NSF BioXFEL Center. More than 60 participants attended to present on the Center's most recent achievements.

2 San Juan, Puerto Rico
Bill Bauer gives a workshop on structural biology techniques to University of Puerto Rico students. UPR is a partner in the NSF BioXFEL Center.

3 Houston, Texas
An introduction to structural biology is given to summer interns at Rice University.

4 Tempe, Arizona
Scientific career options are presented to groups of undergraduate students interested in pursuing a research path.

5 Milwaukee, Wisconsin
Ed Snell gives a talk to biophysicists at the University of Wisconsin-Milwaukee.

6 Las Vegas, Nevada
Nearly 200 attendees participate in the NSF BioXFEL Center's 4th annual conference. Experts from all across the globe come to present their cutting-edge research.

7 University of Warwick, Coventry, United Kingdom
Andrew Gulick presents to over 200 attendees at a meeting sponsored by the Royal Society of Chemistry.

8 Abbey Seeon, Germany
Dan Gewirth gives an invited talk to over 100 scientists and students about his most recent advances in breast cancer research.

9 Charleston, South Carolina
At the Hollings Cancer Center 2017 Spring Research Symposium on the Integration of Protein Folding, Immunity, and Cancer, Dan Gewirth presents to leaders in the field.

10 Lund, Sweden
HWI CEO, Ed Snell gives a talk as an invited speaker, drawing on his expertise in structural biology.

11 Denver, Colorado
As a program chair for the annual meeting of the American Crystallographic Association, Ed Snell led the coordination of the talks and workshops for over 500 attendees.

12 Stanford, California
Numerous members of HWI attend the LCLS Users' Meeting at the LCLS X-Ray Free Electron Laser at Stanford University.

13 Oxford, United Kingdom
Ed Snell participates in a group reviewing the UK's scientific operations of the beamlines at the Diamond Light Source.

14 Tokyo, Japan
Ed Snell is invited to give a talk at the University of Tokyo to biophysicists.

15 New Orleans, Louisiana
HWI and BioXFEL researchers give talks at the American Crystallograpic Association Annual Meeting.

16 Granada, Spain
An invited talk is given by Ed Snell in addition to his leading 4 practical workshops at the International School on Biological Crystallization.

17 Cleveland, Ohio
HWI Snell Lab sends crystals to space with NASA.

18 NASA Space Station
Experiments are performed on HWI samples by NASA astronauts at the International Space Station.

PARTNERSHIPS

Collaboration Makes IMCA-CAT Unique

The world of pharmaceutical research can be incredibly competitive as companies race to research and develop new drugs that can ease pain and save lives. A unique collaboration among pharmaceutical companies, managed by the Hauptman-Woodward Institute (HWI), has a successful 25-year track record providing the facilities, equipment, and researchers for the use of macromolecular crystallography as a tool in drug discovery and product development.

The Industrial Macromolecular Crystallography Association (IMCA) is the consortium of five pharmaceutical companies that support the Collaborative Access Team (CAT), collectively known as IMCA-CAT. The organization owns and operates an experimental station, sector 17, at the Advanced Photon Source (APS) at Argonne National Laboratory, just outside of Chicago, that plays a crucial role in drug research. Current members of the consortium include AbbVie, Bristol-Myers Squibb, Merck, Novartis, and Pfizer.

According to Lisa Keefe, Director of IMCA-CAT and Vice President for Advancing Therapeutics at HWI, the collaboration began when several researchers at competing firms recognized an opportunity to combine resources to build a facility where proprietary research could be conducted while minimizing their overall investment. According to Dr. Keefe, "It is truly remarkable that this unique collaboration has continued for so long and has had such an impact in drug discovery. It has caught the attention of researchers around the globe, but has not been replicated successfully anywhere else."

While the research is complex, IMCA-CAT's premise is straightforward: All members support the endeavor financially, serve as voting board members, and have access to the facility and its research. Since 2010, the facility has been staffed and run by HWI and the research HWI conducts on behalf of pharmaceutical companies remains proprietary. HWI also represents IMCA to the APS, monitors performance and safety, and serves as the interface between the needs of the companies and the staff. There are no government dollars involved and the facility is completely financed by the consortium.

Lisa Keefe, PhD, HWI Director of IMCA-CAT and Vice President for Advancing Therapeutics

By collaborating in this way, the individual companies do not have to build, staff, or run their own research labs, saving time and manpower. They simply send their samples to IMCA-CAT and HWI researchers conduct the research on their behalf. The individual companies benefit by having access to the state-of-the-art facility that is faster, and allows for higher quality data collection because of the power of the synchrotron technology.

Dr. Keefe describes the research conducted at IMCA-CAT as akin to finding the right key for a particular lock. The research helps to determine the internal structure of a target so that it is possible to design a drug that is highly specific and highly effective. By understanding the key components of a disease, it becomes possible to develop chemical components that can bind to it with the goal of slowing or stopping the disease. This research, using the synchrotron for X-ray crystallography, provides a foundation from which to find possible drugs that can address a particular disease.

Since the facility is located at the Argonne National Laboratory that is supported by the Department of Energy, IMCA-CAT is required to allocate some time at the facility to general users such as academics and other researchers who are not working on proprietary studies. HWI researchers, who must be vetted through a peer-reviewed process in order to use the facility, have been able to have access for their work there as well.

"It is truly remarkable that this unique collaboration has continued for so long and has had such an impact in drug discovery. It has caught the attention of researchers around the globe, but has not been replicated successfully anywhere else."

According to Dr. Keefe, the collaboration has worked so well because the members recognize the great impact it has had on drug discovery, that it provides their company access to cutting edge technology, and the speed and quality of the data collection allows them to tackle more challenging diseases. For HWI, the benefits are in supporting the private sector in finding cures and the ability to conduct its own research here as well.

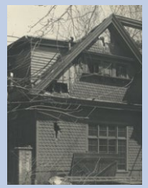
Pictured left is the Argonne National Laboratory's Advanced Photon Source

HWI Builds on its Legacy After 60 Years

1956

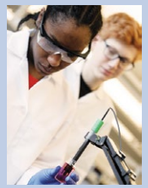
The Medical Foundation of Buffalo is established through the vision of George Koepf and philanthropy of Helen Woodward Rivas

1959



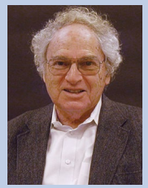
The carriage house, first home to the laboratory, burns to the ground and plans commence for new construction on Ellicott and High Streets

1967



A program for undergraduate interns is established through which more than 350 students have had the opportunity to explore science in an internationally recognized institution

1970

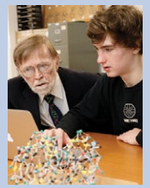


Future Nobel Laureate, Herbert Hauptman, is recruited to Buffalo by lab director Dorita Norton to join the crystallographic group

1985

Herb Hauptman is awarded the Nobel Prize in Chemistry for his mathematical applications for protein structure determination, still utilized globally to this day

1991



Bill Duax begins the Institute's program for high school student interns which has hosted more than 300 students from over 45 area high schools

1994

The Medical Foundation of Buffalo is renamed the Hauptman-Woodward Medical Research Institute to recognize the partnership and synergy between science and philanthropy

2000

The High Throughput Center is founded by George DeTitta as the first to pioneer an automated process to grow and visualize crystals - to date the Center has received over 2,000 samples from scientists in more than a dozen different countries

2001

HWI partners with the University at Buffalo to establish the Department of Structural Biology which has graduated more than 20 PhD students

2005

The Institute opens the doors to its 73,000 square-foot state of the art research facility, the first new construction on the Buffalo Niagara Medical Campus

2014

HarkerBio was founded in 2014 as a spin-off of HWI, commercializing our structural biology expertise for industry

2017

NSF approves the renewal of the BioXFEL Science and Technology Center for an additional 5 years and $25M

For more than 60 years, the Hauptman-Woodward Medical Research Institute (HWI) has remained true to its roots as an independent research institution, while at the same time recognizing that the key to evolution and growth is to continually adapt.

The research organization came to fruition with a conversation between friends. Dr. George Koepf, an endocrinologist working on thyroid disease, shared his vision of creating an independent research foundation with his friend and patient, Helen Woodward Rivas. As an heir to the Genesee Pure Food Co. that owned the unique recipe for Jell-O, Helen had the means to make his dream a reality. She anonymously pledged $3 million (equivalent to $26 million today) to establish the Medical Foundation of Buffalo in 1956. According to Dr. Koepf's son David, the foundation's independence was important to his father so that researchers could be free to follow where their investigations took them.

Dr. Koepf simultaneously ran the Foundation, dedicated to studying the causes of disease with a focus on biology, while practicing medicine at the Buffalo Medical Group. The Foundation needed to adapt early on as a near-devastating fire in the Foundation's first lab on Delaware Avenue necessitated a move to High Street across from Buffalo General Hospital. What began with two researchers in addition to Dr. Koepf, came to focus on growth and also to shift its research expertise towards crystallography.

In 1970, Dr. Herbert A. Hauptman joined the Foundation's crystallography group and went on to serve as Research Director and President. His work and that of his colleagues during this period helped to raise the national and international profile of HWI, particularly after Dr. Hauptman was awarded the Nobel Prize in Chemistry in 1985. He was honored for his innovative mathematical methods for analyzing crystallographic diffraction data, which has since been used to study thousands of previously inaccessible molecular structures and is now the foundational tool for finding cures for disease.

According to Emily Constantine Doren, current HWI board member and great-granddaughter of Ms. Rivas, the organization has always been a marriage of science and philanthropy. To that end, the Foundation was renamed in 1994 the Hauptman-Woodward Research Institute to honor Dr. Hauptman's contributions and those of the Foundation's initial benefactor.

As the competition for recruiting top scientists and research dollars began to increase, HWI embarked on a capital campaign to build a new facility in 2003 that was designed with scientists in mind. The Ellicott Street facility, in what is now the heart of the Buffalo Niagara Medical Campus, was a symbol of the Institute's and the community's commitment to science and research and is a significant tool in bringing top scientists to Buffalo. Around the same time, HWI became one of the founding members of the Medical Campus, continuing a tradition of collaboration with the University at Buffalo, Roswell Park Cancer Institute and other member institutions.

Today, HWI has become one of the longest established independent research institutes in the country and it has built a global reputation for high quality scientific research in the field of structural biology. Despite its success and international reputation, the Institute knows it must continue to adapt to new realities and challenges in research to further its work. As federal grant funding is increasingly competitive, HWI finds innovative ways to expand its expertise and diversify its revenue streams- from a spin off corporation, to an industry collaboration in Chicago, to the highly competitive National Science Foundation BioXFEL Science and Technology Center - HWI is at the cutting edge of foundational research.

Celebrating 60 years, HWI's faculty have contributed over 2,200 publications to science, received over 32 awards, been bestowed 13 honorary degrees, an NSF Science and Technology Center, AND a Nobel Prize.

The ultimate gift in the truest sense of the word

G. David and Susan J. Koepf have made a legacy commitment that will ensure the Koepf name stays connected to HWI in perpetuity. David's father, Dr. George F. Koepf, combined his vision with Helen Woodward Rivas' tremendous philanthropic work, to establish HWI in 1956.

"I think my father would be very pleased with how far HWI has come and how much it has achieved since he started it," says David. "The fact that the Institute has remained private is important; that independence is key to directing the organization's future."

The Koepf's, as longtime supporters of HWI, have made a planned gift to support the Institute as new members of the Helen Woodward Rivas Society. The Society recognizes contributions made through bequests, trusts, charitable gift annuities and other planned giving instruments.

David and Susan believe this gift is the ultimate testament of their confidence in the impact of work being done at Hauptman-Woodward Medical Research Institute.

We are touched by their generosity.

SEE YOUR GENEROSITY IN ACTION

A tax-saving way to help the Hauptman-Woodward Medical Research Institute

If you are 70½ years old or older, you can take advantage of a simple way to benefit HWI and receive tax benefits in return. You can contribute up to $100,000 from your IRA directly to HWI without having to pay income taxes on the gift.

This law no longer has an expiration date so you are free to make annual gifts to the Institute this year and well into the future.

Why consider this gift?

• Your gift will be put to use today, allowing you to see the impact of your generosity.

• You pay no income taxes on the gift. The transfer generates neither taxable income nor a tax deduction, so you benefit even if you do not itemize your deductions.

• HWI has a rich history of leveraging every dollar of philanthropy into $13 of funded research, and in many cases even more.

Can my gift to HWI be used as my required minimum distribution under the law?

Yes, absolutely. If you have not yet taken your required minimum distribution, the IRA charitable rollover gift can satisfy all or part of that requirement. Contact your IRA custodian to complete the gift.

For more information or if you have questions, contact Michael Madonia, Director of Development at 716-898-8636 or mmadonia@hwi.buffalo.edu

HWI WELCOMES NEW BOARD MEMBERS

"HWI has benefited from a strong, active board, clearly a strategic asset to the Institute. We are pleased to continue to mature, adding diversity of thought, breadth of experience and new advocacy for HWI's critical work. We welcome Christina Arthurs and James Obletz."

Judith Feldman, HWI Board Chair

Christina Arthurs

Works at: Lippes Mathias Wexler Freedman LLP as an attorney specializing in trusts, estates and family business

Lives in: Elmwood Village

Christina's introduction to HWI
Christina Arthurs first heard about HWI when friends invited her as their guest to the Riedel wine tasting event, HWI's annual fundraiser. Shortly after, she joined the planning committee for the event and helped grow visibility and revenues with the team for the next three years. Her work didn't go unnoticed, and when a fellow board member asked if she'd like to get more involved, she jumped at the chance.

"I said 'absolutely' – the more you learn about the work HWI does, the more you want to be a part of it," she explains. As someone who started her undergraduate education and early career in the environment and ecology field, she finds the science itself very intriguing.

"They're doing the work in the initial stages where you might not see the results right away, but it'll all lead to cures and new medications to help with various issues in the future. These are the groundbreaking stages; it's very fascinating."

Her initial impressions of the Board
"It's a very well-run, efficient and sophisticated board with a variety of backgrounds – finance people, attorneys, science people, a variety of ages and experience levels. People take it very seriously. It's refreshing to see a board that's so well run; it stems from the dedication within the organization itself. Everyone I've met who works at HWI is really down-to-earth, easy to talk to, and great to work with. If you're going to volunteer, it's wonderful to do it with a group who respects your time and appreciates it."

Community involvement
Christina previously served as a board member with United Church Home retirement community. Through her workplace, she participates in community work with Say Yes to Education Buffalo and helps provide free legal clinics for families of public school students.

Strategy moving forward
"The organization has an aggressive strategic vision – I would love to help them achieve it through development and fundraising," she says. "It's been a cornerstone of the Buffalo Niagara Medical Campus from the beginning with great partnerships. And as the Buffalo community grows, it would be gratifying to help everyone understand what HWI does in a way that helps us meet fundraising goals."

James Obletz

Works at: Delaware North as Vice President of Corporate Business Development, developing and implementing strategies for corporate business expansion

Lives in: Elmwood Village

Jamie's HWI connection
Jamie (as his friends call him) Obletz says he had known about HWI anecdotally as someone who grew up in Buffalo, but never really knew the details of what the organization does. When he moved back to the region last fall, he got a call from a long-time friend and current board member, who invited him for coffee and a chat about the organization.

She explained more about the Institute's research focus and groundbreaking work, and caught Jamie's attention with the idea that HWI is a hidden asset bringing talented scientific resources to the area and developing strong partnerships within the community. When he was invited to join the board, he saw a welcome opportunity to lend some of his business and strategic acumen to the organization.

His initial impressions of the HWI Board
"From my vantage point, they have the right mix of visionaries/strategic thinkers and 'doers' – people who run with things," he says. "There's excellent diversity – medical and scientific minds, bankers, business owners, men, women, all ages, new and veteran members."

Jamie about Western New York
Obletz jumped back into the Buffalo community this past spring, joining the boards of the Westminster Community Charter School, the Richardson Center Corporation, and Invest Buffalo Niagara; this fall he'll join the board of the Park School, his alma mater.

Where he sees HWI headed in the next few years
"On an informal level, I'd like to help get the word out, make sure the community is aware of the Institute and its benefits to human health and the global good," he says. "I'd like to help more people understand how much of an asset HWI is for the city. It has great success and great promise, but it's not widely known. It would be wonderful to broaden that awareness, and I'd like to be an ambassador."

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The Hauptman Society 2017

Founded in 2008, the Society recognizes individuals, corporations, foundations and organizations that made annual gifts of $1,000 and above. These gifts support HWI's mission and the pursuit of life-altering research.

Membership advantages include:

- Annual member event
- Invitation to exclusive speaker series
- Behind the scenes tour of HWI and the diffraction lab, upon request
- Name on the Hauptman Society plaque in the lobby

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Continued on page 28

MOOG Honored for Longstanding Support of HWI

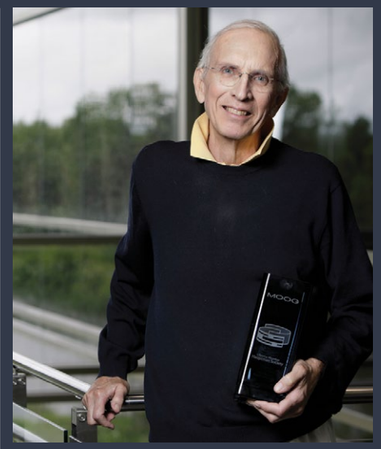
MOOG, Inc., a supporter of the Hauptman-Woodward Institute for over two decades, was honored this spring with the Lifetime Hauptman Society Award for their support of HWI and in recognition of the company's belief in the importance of medical research. Presented to Dr. Richard Aubrecht, MOOG Vice President of Strategy and Technology, on behalf of the technology-based company, it was the sole award presented at the Hauptman Society's annual meeting and reception. The Hauptman Society honors corporations and individual donors who contribute unrestricted gifts of $1,000 or more annually.

Based in East Aurora, N.Y., MOOG uses motion control technology to enhance performance in a variety of industries and applications including aircraft, space, defense, components and medical technology.

According to Dr. Aubrecht, a former HWI board member and Board Chair, MOOG became interested in HWI years ago as an organization that was succeeding in innovation. While HWI's work is at the front end of medical research in finding cures and producing knowledge, MOOG's work is typically at the delivery or end stage, although both companies work strategically and with innovation in mind.

"The people who guide HWI work to stay relevant by continuing to develop new tools and processes to develop cures for the next generation. They have built consistently on Dr. Hauptman's work and we are confident that they will continue to do so. While we don't need recognition for our partnership, we are pleased to know that we have made a difference," commented Dr. Aubrecht.

In his presentation of the award, Michael Madonia, HWI Director of Development, highlighted the special relationship between the two organizations and noted MOOG's support of medical research in finding cures and in increasing scientific knowledge that continues to inspire.



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Andrew Gulick, HWI Principal Research Scientist

Gulick lab paper published in *Nature*

The Gulick lab recently authored a paper entitled "Structures of Two Distinct Conformations of *holo*-Non-Ribosomal Peptide Synthetases" that was published in *Nature*, one of the most high-impact journals in the scientific community. Playing key roles in the new study were Eric Drake and Bradley Miller, as well as members of the labs of Georgios Skiniotis, Professor of Biochemistry at the University of Michigan, and Courtney Aldrich, Professor of Medicinal Chemistry at the University of Minnesota.

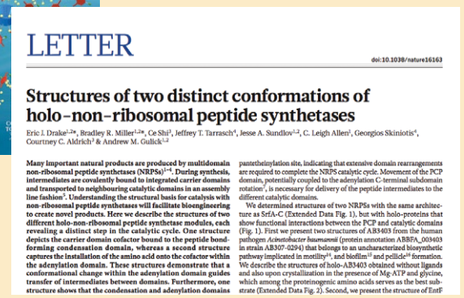
Many drugs that we currently use were inspired by "natural products," small chemicals that are produced by bacteria, fungi, and plants. These organisms evolved to produce the natural products, which confer on them advantages that include competition or communication with other organisms, or adaptation to a unique environment. One example of this is penicillin, an antibiotic that destroys the bacterial cell wall. Penicillin is produced by bacteria and fungi to create a hostile environment for their competitors.

There are many different kinds of natural products. One important family of them includes some anticancer agents and antibiotics (including penicillin). They are produced by a family of unusual proteins called *Nonribosomal Peptide Synthetases* (NRPSs). The NRPSs contain multiple components that function together to make their final product. To make a peptide antibiotic, specific protein regions called *peptidyl carrier proteins* migrate to different parts of the NRPS protein, transporting the molecule that is being built.

The NRPSs are often compared to an assembly line. In a factory, a series of machines might fill empty jars, secure the lids, attach labels, and then place the jars in a carton for shipping to the grocery store. With an NRPS assembly line, each part of the machine carries out a chemical change to the growing natural product, making and breaking chemical bonds in an orderly fashion.

Understanding how the NRPSs work has been a goal for many years. While we knew what each part of the NRPS looked like, we did not know how the complete assembly line functioned. To extend our analogy, we knew how the labels were attached but we didn't know how the jars went from the filling station, to the labeling station, and then to the sorting box. We also did not know how the timing was controlled. You would not want to put a lid on before a jar was filled.

Recently, the Gulick lab published a paper that explained how some important NRPSs work. Drake and Miller each determined the atomic structure of two related NRPS proteins. The two proteins were captured at different stages of the assembly line. This identified how the regions of the protein interact and what features of the chemical reaction drive the delivery of the carrier protein. Aldrich and his colleagues provided intricate chemical tools that allowed the NRPS to be trapped in a particular state. Skiniotis and members of his lab used a complementary technique called Electron Microscopy to support the observed structural movements.


LETTER

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Structures of two distinct conformations of holo-non-ribosomal peptide synthetases

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Many important natural products are produced by multidomain non-ribosomal peptide synthetases (NRPSs)[1–4]. During synthesis, intermediates are covalently bound to integrated carrier domains and transported to neighbouring catalytic domains in an assembly line fashion[5]. Understanding the structural basis for catalysis with non-ribosomal peptide synthetases will facilitate bioengineering to create novel products. Here we describe the structures of two different holo-non-ribosomal peptide synthetase modules, each revealing a distinct step in the catalytic cycle. One structure depicts the carrier domain cofactor bound to the peptide bond-forming condensation domain, whereas a second structure captures the installation of the amino acid onto the cofactor within the adenylation domain. These structures demonstrate that a conformational change within the adenylation domain guides transfer of intermediates between domains. Furthermore, one structure shows that the condensation and adenylation domains

pantetheinylation site, indicating that extensive domain rearrangements are required to complete the NRPS catalytic cycle. Movement of the PCP domain, potentially coupled to the adenylation C-terminal subdomain rotation[3], is necessary for delivery of the peptide intermediates to the different catalytic domains.

We determined structures of two NRPSs with the same architecture as SrfA-C (Extended Data Fig. 1), but with holo-proteins that show functional interactions between the PCP and catalytic domains (Fig. 1). First we present two structures of AB3403 from the human pathogen *Acinetobacter baumannii* (protein annotation ABBFA_003403 in strain AB307-0294) that belongs to an uncharacterized biosynthetic pathway implicated in motility[6,7], and biofilm[7,8] and pellicle[8] formation. We describe the structures of holo-AB3403 obtained without ligands and also upon crystallization in the presence of Mg·ATP and glycine, which among the proteinogenic amino acids serves as the best substrate (Extended Data Fig. 2). Second, we present the structure of EntF

The work provided exciting new views of NRPS enzymes. Because the NRPS products are often used as pharmaceuticals, these insights raise the possibility of being able to predict the structures of newly identified NRPSs from unusual bacteria. Additionally, some scientists are trying to engineer NRPS assembly lines to force them to make novel drugs. An understanding of the structural features that direct how the different parts of the NRPS interact is a critical step toward the identification or design of new natural products that could be used as the next generation of pharmaceuticals. "This was a very important study," said Gulick, "and it represents the culmination of a long series of experiments by many members of my lab over the last 15 years in our effort to understand how bacteria make molecules that we can exploit as pharmaceuticals. We have, additionally, been working with Courtney for over a decade and have teamed up to provide what I believe are some of the most important structures in the NRPS field."

Work in the Gulick lab is currently funded by the Institutes of General Medical Sciences and of Allergy and Infectious Diseases, within the National Institutes of Health, as well as the Richard W. and Mae Stone Goode Foundation.

The exceptional painting featured on the cover is Buffalo-based international artist Alixandra Martin's interpretation of a protein structure determined by the Gewirth group at HWI. This laboratory is studying this structure's anti-tumor properties related to breast cancer. They are driven by the desire to save the lives of our family and friends affected by this indiscriminate and horrid disease. Contact HWI if you are interested in purchasing a limited run print of this artwork.

HWI research is advanced by the combination of determination, scientific talent, and generous support from our enlightened donors. This vibrant palette of bold strokes comes together to create things of beauty – treatments and cures for diseases that touch all of our lives. Thank you for helping make this important work possible.

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