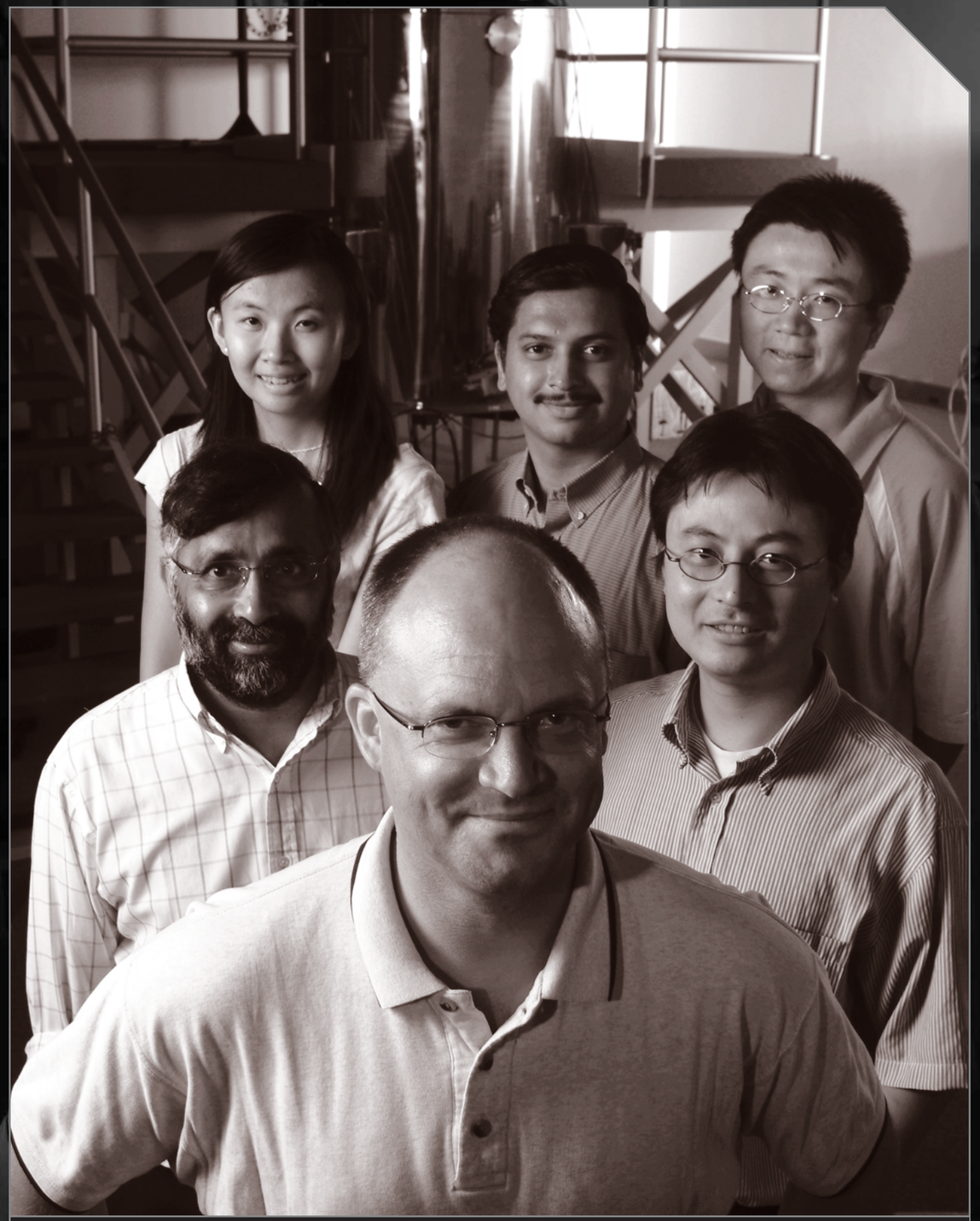


Photos by Doug Levere

Thomas Szyperski, PhD, **FRONT,** and his team. **MIDDLE ROW, LEFT TO RIGHT,** are Dinesh Sukumaran, PhD, and Gaohua Liu, PhD; **BACK ROW, LEFT TO RIGHT,** are Ying Shao, Hanudatta Atreya, PhD, and Yang Shen.

a picture of things to come

NEW METHOD TRANSFORMS PROTEIN MODELING

A University at Buffalo scientist created a stir in 2003 when he announced a much faster, more precise and far less expensive method of obtaining nuclear magnetic resonance (NMR) data to map a protein's atomic structure. Genomics researchers were fascinated, but some also were skeptical.

Not anymore.

By Ellen Goldbaum

In a paper published online in the *Proceedings of the National Academy of Sciences* on July 18, 2005, Thomas A. Szyperski, PhD, UB professor of chemistry, and a team of scientists described how they determined the structures of eight proteins in just 10 to 20 days per protein. Typically, researchers require an average of six to 12 months to solve a single protein using conventional NMR methods.

The paper proves the efficacy of Szyperski's patented protocol to solve protein structures, with the ultimate goal of developing new medicines and treatments.

It also marks the beginning of wider dissemination and use of his method, called G-matrix Fourier Transform NMR (GFT-NMR), to solve protein structures, including membrane proteins, considered by some to be the "holy grail" of structural genomics and highly prized in rational drug design.

The authors of the paper were supported by the Northeast Structural Genomics Consortium, which is part of the Protein Structure Initiative of the National Institute of General Medical Sciences at the National Institutes of Health (NIH).

Szyperski's GFT-NMR method has now been selected as a standard protocol for NMR structural determination by the consortium, whose other members include Columbia, Cornell and Rutgers universities and the Hauptman-Woodward Medical Research Institute.

"The [July 18] paper in the *Proceedings of the National Academy of Sciences* completes the story by showing that the GFT-NMR method works almost better than we expected and is applicable broadly to solve structures of proteins with 200 amino acid residues or more," says Szyperski, who was named one of *Scientific American* magazine's top 50 technology leaders in 2003.

In reference to GFT-NMR, John Norvell, PhD, director of the Protein Structure Initiative, says, "It is the development of this type of innovative methodology that's crucial for achieving the goals of the Protein Structure Initiative and advancing structural biology."

Already, Szyperski's method has been used to solve more than a dozen structures, and he expects his lab at UB to solve between 12 and 15 structures per year, using GFT-NMR.

NMR machines use very powerful magnetic fields to determine macromolecular structures via a two-step process: first, using NMR spectra experiments, the chemical shifts, or "resonance frequencies," of a structure's atomic nuclei are measured and correlated.

This is done by using the NMR machine's powerful magnetic field to grab hold of protein molecules, which are then bombarded with radio waves that measure the signature reverberations shed by each atom in the molecule as it returns to alignment with the magnetic field.

Once these measurements are obtained, they are then used to calculate distances between protons in order to determine the molecular structure.

GFT-NMR can be used for both steps, as described in three papers that the UB group published in 2004 and 2005 in the *Proceedings of the National Academy of Sciences* and the *Journal of the American Chemical Society.*

COLLABORATION WITH CRYSTALLOGRAPHERS

"It's been clear for quite awhile that NMR is a very nice complement to X-ray crystallography," says Szyperski, who has joint appointments in the departments of biochemistry and structural biology in the UB School of Medicine and Biomedical Sciences, as well as in the College of Arts and Sciences. "There are many high-profile proteins that don't crystallize or don't do so easily. For X-ray crystallography-based, high-throughput structural biology, this is a major obstacle."

Due to collaborations between faculty at UB, Hauptman-Woodward Medical Research Institute and Roswell Park Cancer Institute—partners in the new Life Sciences Complex on the Buffalo Niagara Medical Campus—structural genomic researchers in Buffalo are helping to foster new interactions between the disciplines of NMR and crystallography.

For example, Szyperski's recent paper was communicated* for publication in the *Proceedings of the National Academy of Sciences* by Wayne A. Hendrickson, PhD, a leading developer of X-ray crystallography methodology who is University Professor of Biochemistry and Molecular Biophysics at Columbia University.

Similarly, related papers Szyperski published in 2002 and 2004 in the *Proceedings of the National Academy of Sciences* were communicated by Herbert A. Hauptman, PhD, Nobel Prize winner and president of Hauptman-Woodward Medical Research Institute, whose research has revolutionized X-ray crystallography.

"Traditionally, X-ray crystallographers were among the somewhat more skeptical peers when it came to judging the value of NMR for protein-structure determination," explains Szyperski. "So it's significant that both of these papers were communicated by famous crystallographers."

In another paper, which will be published in an upcoming issue of *Proteins,* Szyperski's lab used GFT-NMR to solve in just two weeks a protein target that the Midwest Center for Structural Genomics, a major center of the Protein Structure Initiative, had been unable to solve using X-ray crystallography.

NMR'S ROLE IN THE EQUATION

Szyperski, who is director of the Northeast Structural Genomics Consortium's NMR division, notes that the consortium is the only large-scale center funded by the Protein Structure Initiative with a strong NMR component.

"The Northeast Structural Genomics Consortium is starting to operate as an NMR branch for the other structural genomics consortia that are focused exclusively on crystallography," explains Gaetano T. Montelione, PhD, professor of molecular biology and biochemistry at Rutgers, the State University of New Jersey, director of the Northeast Structural Genomics Consortium and a co-author.

"The protocol described in the paper in the *Proceedings of the National Academy of Sciences* is of high value

* "Communicated for publication" refers to one of the three ways a paper can be submitted to the *Proceedings of the National Academy of Sciences.* It involves an academy member obtaining outside reviews of the paper from at least two qualified referees, each from a different institution and not from the authors' institutions.

"The [July 18] paper in the *Proceedings of the National Academy of Sciences* completes the story by showing that the GFT-NMR method works almost better than we expected and is applicable broadly to solve structures of proteins with 200 amino acid residues or more," says Szyperski, who was named one of *Scientific American* magazine's top 50 technology leaders in 2003.

Thomas Szyperski, PhD, professor in the Department of Chemistry, UB College of Arts and Sciences, also holds joint appointments in the departments of biochemistry and structural biology in the School of Medicine and Biomedical Sciences.

In this syringe is a solution containing a protein that will be inserted in the nuclear magnetic resonance machine, as shown on page 8.

for NMR-based structural genomics pursued by the NMR division of the Northeast Structural Genomics Consortium," says Montelione, "and it nicely exemplifies the combined use of GFT-NMR, highly sensitive modern NMR spectrometers equipped with 'cryogenic probes' and methodology for semi-automated data analysis."

Montelione's laboratory at Rutgers was the major supplier of proteins for the research published in the *Proceedings of the National Academy of Sciences*. The Rutgers group also has developed some of the essential tools for semi-automated analysis of NMR data used in the work.

Proteins also were supplied by a team led by Cheryl Arrowsmith, PhD, professor in the Department of Medical Biophysics at the University of Toronto, whose team included Adelinda Yee, PhD, scientific associate, and Alexander Lemak, PhD, research associate, co-authors of the paper.

"Our labs collaborate very intensely on developing methodologies for semi-automated data analysis, an important cross fertilization for efficient structure calculation," explains Szyperski.

"Using our automated analysis methods, initial 3D protein structures could be generated soon after data collection and then refined by manual data-analysis methods," adds Montelione.

"At the end of the day," says Szyperski, "high-throughput protein-structure determination in the framework of structural genomics projects promises to semi-empirically solve the enigmatic 'protein-folding problem' for naturally occurring proteins so that 3D structural information of proteins is made readily available from DNA sequence information alone. This is the central mission of the NIH Protein Structure Initiative."

WESTERN NEW YORK SYNERGY

In 2005 alone, Szyperski's UB laboratory has attracted approximately $4 million in new federal research funds over the next five years. The support comes from a variety of sources, including the Protein Structure Initiative; the New York Center on Membrane Protein Structure, an NIH-funded center of the Protein Structure Initiative; and the National Science Foundation's Molecular and Cellular Biophysics Division, led by Kamal Shukla, PhD, program director.

Continued on Page 8

A Proteomics Primer

SO, WHY IS IT IMPORTANT that we discover faster, more precise and far less expensive methods of obtaining data to map a protein's atomic structure, as described in the accompanying article?

To grasp the full import of the work being conducted by Thomas Szyperski, PhD, and colleagues, it is helpful to step back and look at what these genomics researchers are trying to accomplish with tools such as nuclear magnetic resonance (NMR) and crystallography, in combination with data obtained through the new science of bioinformatics.

As a result of the Human Genome Project, experts now estimate that humans have some 30,000 genes that are responsible for churning out thousands of different proteins. The challenge is that, in most cases, the function of these genes and their proteins is a mystery.

Toward the goal of unlocking the secrets of proteins, a new scientific field called proteomics has sprung into being, the aim of which is to discover the structure and interactions of all proteins in a given cell. By studying the proteomic landscape of healthy and diseased cells, researchers may better understand the complex ways in which cells communicate at a molecular level, which in turn can lead to a better understanding of our body's metabolic pathways.

Once these mysteries are deduced, pharmaceutical companies can collaborate with basic scientists to develop more sophisticated diagnostic devices, as well as new drug targets. In this new world of pharmacogenetics and pharmacodynamics, scientists will attempt to identify which misguided protein needs targeting and design drugs that bind to it in order to turn it on or off—a form of treatment that because of its specificity is predicted to produce few, if any, side effects. (See page 10 for an article describing the work of UB Professor William Jusko, PhD, a leader in the fields of pharmacokinetics and pharmacodynamics.)

Although scientists do not know the details surrounding how proteins function, what they do understand is that a protein's function often is tied to its shape; in other words, the way in which a protein interacts with other molecules is in many cases determined by its three-dimensional structure.

In this post-genomic era, therefore, much attention and tremendous resources are being marshaled toward the goal of modeling the three-dimensional structure of as many proteins as possible. More specifically, scientists who have expertise in structural biology are seeking to devise ways to better understand, and even predict, how a gene's DNA directs amino acids to fold in order to create a protein's three-dimensional shape. (Based on current knowledge, scientists estimate that there are several thousand different classes of protein folds.)

Over the past few decades, scientists have devised a number of laboriously painstaking techniques to determine the shape of a protein. One of these techniques is crystallography, which involves bombarding single crystals of protein molecules with X-ray beams. The beams are diffracted by the atoms of the protein molecule, thereby generating the diffraction pattern. The pattern is then analyzed by computer to define the protein's molecular structure. A second technique involves nuclear magnetic resonance (NMR) spectroscopy, which uses powerful magnets to determine the chemical shifts of nearly all atoms of the protein. Knowledge of these shifts enables scientists to measure the distances between protons, from which protein structure can be calculated.

Like the Human Genome Project, the success of proteomics depends heavily on the ability of scientists to automate and greatly accelerate these and other protein-modeling techniques, which is exactly what Szyperski's new method, called GFT-NMR, accomplishes, as described in the accompanying article.

Integral to this automation effort is the tandem development of new generations of robotic systems and supercomputers.

Underpinning this entire post-genomic quest is the burgeoning new field of bioinformatics, where computer scientists and biologists work side by side toward the goal of harvesting information produced by the genome and proteome projects in order to provide medical researchers with knowledge they will need to move forward with discoveries.

At the University at Buffalo, computing power for the calculation of so many structures in a short a time—as required by Szyperski's GFT-NMR method—is provided by the Center for Computational Research, part of UB's New York State Center of Excellence in Bioinformatics and Life Sciences (see "Data Crunch, New Computer Cluster Expands Research Capacity," on page 10).

The new building for the Center of Excellence, located on the Buffalo Niagara Medical Campus, will open early next year and will be reported on in an upcoming issue of *Buffalo Physician*. BP

—S. A. Unger

Continued from Page 7

The advances made possible by Szyperski's GFT-NMR method come at a time when Hauptman-Woodward Medical Research Institute—another protein-structure determination powerhouse in Western New York—also has grabbed the national spotlight by winning a prestigious $16.9 million grant under the Protein Structure Initiative for its new Center for High-Throughput Structural Biology.

Principal investigator for the grant is George T. DeTitta, PhD, executive director and chief executive officer for Hauptman-Woodward Medical Research Institute, and chair of the UB Department of Structural Biology. (For more information on this grant and the Hauptman-Woodward Research Institute—which also is a research partner in the New York State Center of Excellence in Bioinformatics and Life Sciences—visit the web site at http://www.hwi.buffalo.edu/.)

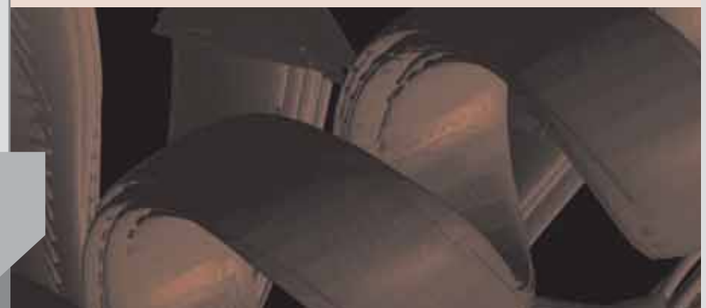
Both Hauptman-Woodward's efforts in X-ray crystallography and the UB team's efforts in NMR are driving forward the current mission of the Protein Structure Initiative to cut costs and production times so that protein structures can be determined more quickly, with less cost.

By improving the methodology used to determine the structure of proteins, genomics researchers in Buffalo are at the leading edge of efforts aimed at giving scientists the tools they need to better understand cell signaling and metabolic pathways (see "A Proteomics Primer" on page 6). This understanding is pivotal to the work being done by pharmaceutical companies to develop new diagnostic tests and to attain the highly coveted goal of rational drug design. BP

A sample tube with a solution containing a protein is inserted in the magnet. Once the nuclear magnetic resonance data is collected, it will eventually be used to solve the three-dimensional structure of the protein.

It is the development of this type of innovative methodology that's crucial for achieving the goals of the Protein Structure Initiative and advancing structural biology.

—JOHN NORVELL, PHD, DIRECTOR OF THE PROTEIN STRUCTURE INITIATIVE NATIONAL INSTITUTES OF HEALTH



Additional UB co-authors on the July 2005 paper in Proceedings of the National Academy of Sciences *and members of the Szyperski lab are Hanudatta S. Atreya, PhD, and Gaohua Liu, PhD, senior research scientists; Yang Shen, Ying Shao and David Parish, graduate students, and Dinesh K. Sukumaran, PhD, director of the Magnetic Resonance Center in the Department of Chemistry.*

Co-authors at the Center for Advanced Biotechnology and Medicine, a joint operation of Rutgers and the University of Medicine and Dentistry of New Jersey, are Rong Xiao, laboratory researcher; Aneerban Bhattacharya, doctoral candidate, and Thomas Acton, PhD, assistant research professor.

Global 'Protein Structure Olympics'

UB RESEARCHERS WIN TOP SPOTS

FOR ANY INSTITUTION that is home to even a single winner in the international "protein structure olympics," winning a top spot means automatic bragging rights.

But until the most recent competition, it was unprecedented for three research teams from the same institution to make the most accurate blind predictions of an unknown protein structure.

In the Sixth Community Wide Experiment on the Critical Assessment of Techniques for Protein Structure Prediction (CASP), three of the 17 winning predictor teams were from the University at Buffalo, and two of them are affiliated with UB's New York State Center of Excellence in Bioinformatics and Life Sciences. A total of 150 predictor teams from universities and scientific institutes around the world participated in the competition.

Scientific papers by the winning teams will be published in a forthcoming special issue of the journal *Proteins*.

The ultimate purpose of CASP is to find the very best computational methods to elucidate three-dimensional protein structures.

"This really puts UB and its New York State Center of Excellence in Bioinformatics and Life Sciences on the map," says Daniel Fischer, PhD, associate professor in the Department of Computer Science and Engineering, UB School of Engineering and Applied Sciences, who is affiliated with the center and was one of the UB winners in the competition.

The other winning UB teams were: Jeffrey Skolnick, PhD, professor of structural biology, and Yang Zhang, PhD, assistant professor, both members of the Data Intensive Analytical Bioinformatics Core Group in the Center of Excellence; and Yaoqi Zhou, PhD, associate professor, and Hongyi Zhou, PhD, research assistant professor, both in the Department of Physiology and Biophysics in the UB School of Medicine and Biomedical Sciences.

In the biennial competition, several dozen protein amino acid sequences are provided to bioinformatics scientists who compete with one another—and with automated computer servers using algorithms written by humans—to complete the three-dimensional structures of the same mystery protein.

Skolnick's predictions won in the contest among humans, while Fischer and the team of Yaoqi Zhou and Hongyi Zhou each won for the predictions of their separate computer servers.

"This has established that Buffalo is on the frontlines of protein-structure prediction," Fischer notes.

Predicting structures has been a top priority since the sequencing of the human genome in 2003. The National Institutes of Health has allocated millions of dollars to solve between 10,000 and 20,000 structures experimentally during the next 10 years.

At stake is a far greater understanding of proteins, how they interact and cause disease and how new drugs might be developed rationally to fight them.

"Because there isn't enough money or time or people to complete an experimental structure for each protein in the world, the idea is to have representative sets of experimental structures so that those for which we don't have structures can be generated computationally," explains Fischer.

In 2000, Fischer was responsible for introducing into CASP the participation of fully automated computer servers. Since then, he has been the organizer of the parallel competition, CAFASP—Critical Assessment of Fully Automated Structure Prediction.

"I wanted to find out how capable automatic programs are in making blind predictions without any human intervention," he says. "The beauty of this is to find which humans are better, which programs are better and what the difference is between humans and programs. So now we have humans versus humans, servers versus humans and servers versus servers, all working to determine the structure of the same proteins. The availability of fully automated programs allows thousands of non-expert biologists to be able to predict the structures of their proteins of interest."

He noted that while the servers are getting better all the time, five to 10 human experts still perform better than the best automated programs.

"But the gap is likely to narrow in the future," predicts Fischer. "I would not be surprised to see the programs win in the next 'olympics,' similar to what happened in the famous chess match between Kasparov and Big Blue." BP

"This really puts UB and its New York State Center of Excellence in Bioinformatics and Life Sciences on the map," says Daniel Fischer, PhD, one of the UB winners in the competition.

Jusko Receives MERIT Award

By Mary Cochrane

PHARMACOKINETIC AND PHARMACODYNAMIC RESEARCH

THE NATIONAL INSTITUTES OF HEALTH of the U.S. Department of Health and Human Services has selected a University at Buffalo researcher to receive one of its coveted MERIT (Method to Extend Research in Time) awards, totalling $3 million over its first five years.

William J. Jusko, PhD, professor and chair of the Department of Pharmaceutical Sciences in the School of Pharmacy and Pharmaceutical Sciences, received the award, which offers support for up to 10 years, for his ongoing research in corticosteroid pharmacokinetics and pharmacodynamics. Fewer than 5 percent of NIH-funded investigators are selected to receive MERIT Awards.

The NIH gives MERIT awards to provide long-term, stable grant support, rather than the usual three or four years, to investigators "whose research competence and productivity are distinctly superior," according to Richard T. Okita, program director for the National Institute of General Medical Sciences.

"Dr. William Jusko is a major leader in the field of pharmacokinetics and pharmacodynamics whose work over the past 20 years has led to significant advances in the modeling of the time course of events that follow drug administration," says Okita. "Providing support to such investigators is expected to foster their continued creativity and spare them the administrative burdens associated with submission of full-length research grant applications. This may allow them the opportunity to take greater risks, be more adventurous in their lines of inquiry or take the time to develop new techniques."

Jusko, who is editor-in-chief of the *Journal of Pharmacokinetics and Pharmacodynamics,* has had NIH funding for his research for the past 28 years. Along with his collaborators—Richard R. Almon, PhD, UB professor of biological sciences and adjunct professor of pharmaceutics, and Debra C. Dubois, PhD, UB research assistant professor of pharmaceutics—Jusko examines a cascade of biomarkers that control pharmacologic and metabolic effects of corticosteroids.

The team has a special interest in pharmacodynamics—the study of the action of drugs on the body—and seeks to reveal the rules of biology that govern the time course of drug action, according to Jusko.

"Our latest award was triggered by the realization that corticosteroids act by changing the functioning of hundreds of genes in numerous tissues and the interplay offers amazing complexity, which we are seeking to better understand. There are various ways that drugs alter body functions to produce their effects, and we seek to find mathematical methods of quantitating and predicting drug responses," says Jusko says. "This support will continue much of the research pursued over the past 10 years, but expands it to a higher level, seeking to integrate several body systems affected by these drugs."

Corticosteroids are "important therapeutic agents" used in the treatment of many diseases, including asthma, lupus, kidney disease and others, Jusko explains, "but their myriad adverse effects severely limit their long-term use.

"Our research is seeking to find ways of improving the beneficial effects and reducing the adverse effects of these essential drugs," he adds.

Jusko says he is extremely pleased to have been selected for a MERIT award. "The NIH only occasionally bestows a MERIT award for established investigators in areas of special scientific need," he says. "I feel highly honored and privileged to receive one of these awards."

In July 2005, The American Association of Colleges of Pharmacy (AACP) selected Jusko as this year's recipient of its Volwiler Research Achievement Award. Considered the AACP's premier research award, the honor recognizes outstanding research conducted by a pharmaceutical scientist/educator. BP

> Dr. William Jusko is a major leader in the field of pharmacokinetics and pharmacodynamics whose work over the past 20 years has led to significant advances in the modeling of the time course of events which follow drug administration.

By Ellen Goldbaum

Data Crunch

New computer cluster expands research capacity

IN RESPONSE TO THE SOARING DEMAND for computational power by the hundreds of researchers who depend on it, University at Buffalo has expanded the computing capacity of the Center for Computational Research (CCR) in its New York State Center of Excellence in Bioinformatics and Life Sciences with the installation of a new Dell high-performance computing cluster. The cluster, with 1,668 processors, nearly doubles the Center of Excellence's computing capacity.

"The Center of Excellence has been working diligently over the past year to establish the necessary programs and infrastructure to pursue quantum leap approaches in medical discovery," says Bruce A. Holm, PhD, executive director of the Center of Excellence and UB senior vice provost.

In addition to supporting the work of researchers affiliated with the Center of Excellence, the new cluster will support UB faculty members working in a wide variety of areas ranging from chemistry and engineering to visualization and data mining.

The cluster was purchased with $2.3 million in federal funds appropriated for the Center of Excellence as a result of the efforts of Representative Thomas M. Reynolds, Senator Hillary Rodham Clinton and Senator Charles E. Schumer.

"This installation will increase dramatically the pace of research and discovery at UB," says Russ Miller, PhD, director of CCR and UB Distinguished Professor in the Department of Computer Science and Engineering in the UB School of Engineering and Applied Sciences. "The expansion effectively will double our processing speed. It will expand the capability of computing we can offer to our users, where large numbers of processors are used simultaneously to solve an individual problem, as well as our capacity computing, where the results of many independent, single-processor results are combined to solve a problem.

"This increase in throughput will enable researchers to undertake calculations at an entirely new scale," he continues. "Researchers will be able to tackle larger problems, consider them in more detail, and address problems that would have been intractable without such a system."

To learn more about the new Dell cluster described above, go to www.buffalo.edu/news/ and search "CCR Dell cluster."

For more information about the UB Center for Computational Research, visit http://www.ccr.buffalo.edu/. BP