Seed Grant Yields Bountiful Harvest
U of M-Mayo-IBM collaboration provides proof-of-principle for larger grant

Darrin York, Ph.D., develops computational methods for simulating the catalysis of chemical reactions mediated by RNA. Yuan-Ping Pang, Ph.D., explores the subcellular mechanisms behind complex physiological processes. Carlos Sosa, Ph.D., is advancing applications for ultra-fast computers that hold huge promise for unlocking the mysteries of molecular interactions.

After BICB gave the three researchers an opportunity to talk at a networking event just over a year ago, they decided to combine forces. They applied for and received a $100,000 BICB seed grant to apply IBM computational chemist Sosa’s emerging high-speed computing capabilities, and the multi-scale quantum modeling approaches developed by York, an associate professor of chemistry at the University of Minnesota, to solve questions Pang, a professor of pharmacology at the Mayo Clinic, is asking related to rational drug design of reactivators and irreversible inhibitors.

“The expertise in computational methods development for quantum simulations here at the U of M was a perfect marriage with high-performance computing architectures of IBM to go after high impact problems in rational drug design spearheaded at the Mayo Clinic,” York says. “These problems require accurate modeling of molecular recognition and chemical bond formation and cleavage events in complex biological environments.”

The outcome is the epitome of what cross-disciplinary, cross-institutional research is all about. Results of research funded by the seed grant allowed York to add some key “just in time” findings to a proposal he had previously submitted to the National Institutes of Health (NIH). The proposal subsequently yielded a four-year, $1.1 million NIH grant, and York is convinced the proof-of-principle results from the BICB seed grant gave him the competitive edge he needed. The first series of papers highlighting the new simulation methods was published this past spring in *Journal of the American Chemical Society* and *Chemistry & Biology*.

York also credits BICB for catalyzing the collaboration with Sosa and Pang. Though the three knew of and were interested in each other’s work, he says, “In this financial climate, it’s a real challenge to take already overcommitted externally funded research groups and get them together to nucleate around a new idea, and then actually follow it through.”

continued on page 3

*The York group has pioneered multi-scale quantum simulation methods to study the molecular mechanisms of RNA enzymes, such as the hammerhead and hairpin ribozymes, and elucidate the origin of their catalytic capability.*
Welcome

Welcome to the first issue of the BICB Research Bulletin. We are enthusiastic about the many things we have going on, and happy to have the opportunity to share the excitement and momentum with you. This bulletin provides an overview of some of the accomplishments that arose from the first year of BICB’s existence, as well as a preview of what’s ahead.

The Biomedical Informatics and Computational Biology (BICB) program is sponsored by the University of Minnesota Rochester. The U of M, in collaboration with the Hormel Institute, Mayo Clinic, and IBM, established the BICB program as a way to harness the Rochester region’s strong resources in education, medicine, and technology to create world-class graduate and research programs in two of bioscience’s fastest-growing fields: biomedical informatics and computational biology.

Our first round of seed grants and traineeships has yielded results even beyond our optimistic projections. More than 40 investigators have invested the resources we have provided to initiate exciting new interdisciplinary and multi-institutional research projects. Their collaborations have opened the door to new lines of research, new interactions, and even to new resources in the form of federal competitive grant funding.

Rich opportunities for interaction were provided by three symposia we sponsored for 2007–08. These symposia brought scientists and scholars together from business, industry, and academia, sparking new ideas for partnerships to advance discovery.

The University of Minnesota is moving to set in place a graduate program that will train the leaders of tomorrow in biomedical informatics and computational biology. The proposal to create M.S. and Ph.D. programs in this vibrant and fast-paced field will go to the Board of Regents for approval in July, and we anticipate a favorable outcome.

We are now gearing up to select and fund the 2008-09 seed grants and traineeships, as well launch a postdoctoral research fellowship program (see announcement on page 6), and moving into our next round of interdisciplinary collaborative symposia. Please join us as we look forward to a bright future for BICB, Rochester, and the quest for better health through biomedical informatics and computational biology.

Trainee Profile

Andrew Norgan

How can we keep deadly viruses from replicating? Mayo Clinic M.D.-Ph.D. student Andrew Norgan is pursuing the answer with the help of a two-year BICB traineeship.

Norgan is one of 10 graduate students awarded financial support during BICB’s first granting round last year. His research focuses on applying computational methodology to screen for chemicals that can inhibit budding, part of viral replication. What he discovers may prove useful in developing drugs that inhibit HIV and other viruses from replicating. Norgan is working with Carlos Sosa, Ph.D., of IBM; David Katzmann, Ph.D., and Jean-Pierre Kocher, Ph.D., of Mayo Clinic; and Claudia Neuhauser, Ph.D., of the University of Minnesota.

“The BICB program has been really helpful,” Norgan says. “It establishes a framework for scientific collaboration, and that in turn has allowed me to go places with my research that I wouldn’t otherwise be able to go.”
Seed Grant Yields Bountiful Harvest
continued from page 1

up by devoting the required resources so that they might demonstrate sufficient feasibility and promise to secure large-scale sustained funding and make real breakthroughs.” By providing researchers with an open forum to explore how their efforts might interface, and the opportunity to compete for seed project support, the BICB program lowered the activation barrier for launching a promising interdisciplinary collaboration.

For More Information
Contact:

Michael Olesen
Program Director for Bioscience, UMR
UMTC Telephone: 612-625-6414
UMR Telephone: 507-280-4647
E-mail: oles001@umn.edu

Jim Clausen
Program Management Consultant for Bioscience, UMR
Telephone: 507-280-4630
E-mail: claus158@umn.edu

BICB Web Site
www.r.umn.edu/bicb

A Match Made in . . . Rochester

Over the history of scientific inquiry, some of the most fertile collaborations have arisen by chance, as investigators from different disciplines or different institutions discover connections between their efforts during casual conversation. But chance is slow, too slow for fast-evolving, interdisciplinary endeavors such as biomedical informatics and computational biology. That is why last spring BICB gave chance a hand up by giving researchers from IBM, Mayo Clinic, the University of Minnesota Twin Cities, and the Hormel Institute the opportunity to explore opportunities for future collaboration.

Modeled after speed dating, the first such effort brought together approximately 40 scientists and researchers in March 2007 in Rochester to meet and discuss how their interests and investigations might dovetail. Afterwards, the BICB program provided seed funding for five collaborations involving 25 researchers (see page 4) and for 10 graduate traineeship projects.

“I found the BICB symposium beneficial,” commented participant Carlos Sosa, Ph.D., of IBM. “It provided an opportunity to present some of the research that is funded through BICB grants and also served as a catalyst for researchers to discuss potential collaborations among the different groups. It provided a valuable forum for this type of interaction.”

The next “speed collaboration” session is scheduled for June 20, 2008, with a focus on collaborative, interdisciplinary biomedical research in the areas of medical imaging informatics, biomedical informatics and bioinformatics, computational biology, computational approaches to genomics and proteomics, and integration of data types with genomic emphasis.
Multi-modality Data Mining: Accelerating Discovery
Kelvin Lim, M.D. (UM); Vipin Kumar, Ph.D. (UM); Monica Luciana, Ph.D. (UM); Tim Mullins (IBM); Richard Mushlin, Ph.D. (IBM); Michael Steinbach, Ph.D. (UM); Tushar Garg (UM), and Ben Mayer (UM)

In order to discover patterns that can lead to the development of hypotheses about relationships among genetics, brain structure, and cognition in adolescents, this seed grant aims to develop new computational tools to analyze massive amounts of neuroimaging, cognitive, and genotype data, collected from roughly 200 subjects who are part of a federally funded research project. The investigators have made encouraging progress towards accelerating the processing of brain images by reengineering existing open-source image processing software for IBM’s Cell processor. In addition, the application of high-powered computational tools to data analysis has begun to reveal intriguing correlations among cognitive and neuroimaging features, which provide preliminary evidence for interesting differences due to gender and age.

Large-scale Virtual Screening for the Design of Selective Inhibitors of the Oncogenic ERK Pathway
Zigang Dong, M.D., Dr.P.H. (UM); Ann Bode, Ph.D. (UM); Angelo Pugliese (UM); and Carlos Sosa, Ph.D. (IBM)

Improving the understanding of cancer at the molecular and atomic level is a key aim of structure-based drug discovery. In this study, researchers are using computational tools to identify small molecules that might be used as drugs to inhibit a protein known as ERK 2, that they suspect contributes to malignant cell proliferation. Their goal is to do so in a way that does not also inhibit ERK1, a very similar protein that is thought to have tumor suppression capabilities.

Analysis of the crystal structure of ERK2 has identified two promising sites on the molecule where drugs could potentially interact with it and inhibit its function. In phase one of this study, the researchers are applying supercomputer modeling (using Minnesota’s first IBM Blue Gene supercomputer, part of the University of Minnesota’s Hormel Institute) and molecular and cellular biology approaches to test millions of small molecules in search of ones that hold promise for disabling ERK2, then refining those that do to enhance their efficacy as ERK2 inhibitors. The next step will be to test selected molecules in vitro and in vivo to confirm the in silico (computer-based) predictions of their ability to inhibit ERK2.

Several manuscripts have been published, are in press, or are in preparation that have been coauthored by Pugliese, who is receiving a stipend from the seed grant. These publications correspond with many of the techniques needed and used for this project.

Computational Models for Analysis of iTRAQ™ Global Proteomic Mass Spectrometry Data
Yan Asmann, Ph.D. (Mayo Clinic), R.H. Bergen, Ph.D. (Mayo Clinic), Jeanette Eckel-Passow, Ph.D. (Mayo Clinic), LeeAnn Higgins, Ph.D. (UM), Vipin Kumar, Ph.D. (UM), Gary Nelsestuen, Ph.D. (UM), Ann Oberg, Ph.D. (Mayo Clinic), Michael Steinbach, Ph.D. (UM), Terry Therneau, Ph.D. (Mayo Clinic), Baolin Wu, Ph.D. (UM), Douglas Mahoney (Mayo Clinic), Christopher Mason (Mayo Clinic), and Gaurav Pandey (UM)

This research group has worked out optimal parameters for two mass spectrometry platforms, the 4800 MALDI TOF/TOF and the ESI-LTQ Orbitrap. In addition, they have performed an evaluation of variability on two mass spectrometry platforms utilizing the iTRAQ labeling system.

A complex peptide mixture from yeast proteins was analyzed on three MS systems: 1) 4800 TOF/TOF at University of Michigan 2) 4800 TOF/TOF at UM, and on the Orbitrap at Mayo Clinic;
BICB Supported Research Reports

BICB 2008/01
Origin of Mutational Effects at the C3 and G8 Positions on Hammerhead Ribozyme Catalysis from Molecular Dynamics Simulations
Tai-Sung Lee and Darrin M. York

BICB 2008/02
Solvent Structure and Hammerhead Ribozyme Catalysis
Monika Martick, Tai-Sung Lee, Darrin M. York, and William G. Scott

BICB 2008/03
Role of Mg2+ in Hammerhead Ribozyme Catalysis from Molecular Simulation
Tai-Sung Lee, Carlos Silva-Lopez, George M. Giambasu, Monika Martick, William G. Scott, and Darrin M. York

BICB 2008/04
Quantum Mechanical/Molecular Simulation Study of the Mechanism of Hairpin Ribozyme Catalysis
Kwangho Nam, Jiali Gao, and Darrin M. York

BICB 2008/05
Contracted Auxiliary Gaussian Basis Integral and Derivative Evaluation
Timothy J. Giese and Darrin M. York

BICB 2008/06
Charge-dependent model for many-body polarization, exchange and dispersion interactions in hybrid QM/MM calculations
Timothy J. Giese and Darrin M. York

BICB 2008/07
Publications Quantitative Evaluation of Approximate Frequent Pattern Mining Algorithms
Rohit Gupta, Gang Fang, Blaine Field, Michael Steinbach, and Vipin Kumar

BICB 2008/08
Raf and MEK Protein Kinases are Direct Molecular Targets for the Chemopreventive Effect of Quercetin, a Major Flavonol in Red Wine

BICB 2008/09
The Resveratrol Analogue 3,5,3′,4′,5′-Pentahydroxy-Transtilbene Inhibits Cell Transformation via MEK

BICB 2008/10
High Throughput Computing Validation for Drug Discovery Using the DOCK Program on a Massively Parallel System
Peters, A., M. Lundberg, Lang, T., and Sosa, C. P.

BICB 2008/11
iTRAQ Reagent-Based Quantitative Proteomic Analysis on a Linear Ion Trap Mass Spectrometer
Griffin TJ, Xie H, Bandhakavi S, Popko J, Mohan A, Carlis JV, and Higgins L.

BICB 2008/12
Statistical Analysis of Relative Labeled Mass Spectrometry Data from Complex Samples using ANOVA
Oberg, AL, Mahoney, DW, Eckel-Passow, JE, Malone, CJ, Wolfinger, RD, Hill, EG, Cooper, LT, Onuma, OK, Spiro, C, Therneau, TM, and Bergen, HR III

To request BICB Research Reports, please send email requesting the publication by BICB report number (i.e., BICB 2008/XX) to Cindy Holton at holto003@umn.edu.
Call for Proposals and Nominations

BICB is currently accepting proposals from multi-institutional teams for collaborative seed grants of up to $100,000 in the areas of medical imaging informatics, biomedical informatics, computational biology, computational approaches to genomics and proteomics, and integration of data types with a genomic emphasis. Nominations are also being accepted for collaborative traineeships for graduate students and postdoctoral research fellowships for 2008-09. Statements of intent to submit a seed grant proposal are due July 3, 2008. The submission deadline for nominations and proposals is July 15, 2008. For more information see: www.r.umn.edu/19_BICB_2008-09_Call.htm.

Urine samples were processed utilizing both the eight-plex and four-plex stable isotope labeling iTRAQ™ technology on the 4800 TOF/TOF.

Conclusions:
• The Orbitrap is able to detect nearly twice as many proteins as the 4800 in approximately one-fifth of the amount of time and from approximately one-tenth of the amount of sample, and has a wider dynamic range when compared to the 4800.
• When comparing the full data sets, average overall variability in Orbitrap data is substantially larger than in 4800 data.
• When sub-setting the Orbi data to an abundance range similar to that of the entire 4800 data, the two platforms detect a similar number of proteins and the CVs are similar between the two platforms.

It appears that fewer proteins are detected on the eight-plex, although further data is required in order to have a definitive conclusion since the results may be sample dependent and dynamic range dependent.