Viruses vs. Cancer

Innovative BICB research proposal chosen for Minnesota Partnership grant

A BICB-based proposal to improve viruses’ ability to selectively kill cancer cells has garnered a $451,610 grant from the Minnesota Partnership for Biotechnology and Medical Genomics.

The two-year grant was awarded in February to a research team led by three BICB faculty members: David Dingli, M.D., Ph.D. (Mayo Clinic), Claudia Neuhauser, Ph.D. (University of Minnesota Rochester), and Zeljko Bajzer, Ph.D. (Mayo Clinic). It stems from observations that certain viruses have the ability to selectively seek, find, and destroy cancer cells while leaving healthy tissue intact. One big challenge to clinical application is the need to quantitatively understand interactions among virus, malignant tissue, and immune system over time and space. The grant, “Applying Network Theory to Optimize Cancer Virotherapy,” will apply computational approaches developed for modeling stochastic processes in ecology and evolutionary biology to better understand the interplay between the configuration of cancers and the ability of viruses to selectively target, infiltrate, and debilitate them.

“Tumors are quite complicated. They’re not just blobs of cells,” says Neuhauser. “We have to understand what kinds of growth dynamics, what kind of architecture they have.”

Also involved in the project are George Paulik, Ph.D. (IBM, BICB faculty member) and BICB graduate student Yaming Chen. Neuhauser, who earned her Ph.D. in mathematics, says the project is a perfect example of the value-added of BICB-based collaborations. “It’s very close to my research specialty, stochastic processes, but I’m not an oncologist,” she says. “Putting together the clinical expertise with the mathematical expertise, that’s what allows us to do the work. None of us could do that by ourselves.”

The Minnesota Partnership, a collaboration among the University of Minnesota, Mayo Clinic, and the state of Minnesota, was established in 2003 to stimulate economic development through biomedical research in Minnesota. To learn more about the partnership, go to www.minnesotapartnership.info.

Save the Date

BICB Research Symposium
June 25, 2010
Rochester, Minnesota
http://www.r.umn.edu/research/bicb/events/summer2010
Program Update

If you’ve ever waited with anticipation for bulbs you planted to come up, you have a sense of the mood surrounding the BICB program these days. After sowing the seeds of collaboration with 9 multi-institution seed grants and 15 collaborative traineeships in 2008 and 2009, we are now seeing some exciting activity emerge, with new research findings, numerous scientific presentations and publications (including a recent one in Science), prestigious fellowships, and even federally sponsored grant awards emerging from the sponsored research teams. Check out Collaborative Seed Grant Progress Reports on page 5 for details.

Our educational programs are booming and blooming as well. We now have 11 students on the University of Minnesota Rochester campus, including 3 in the Ph.D. program. An additional 6 Ph.D. and 2 M.S. students are working on degree programs from the Twin Cities campus, with another 8 to 10 planning to enroll in fall 2010.

With these emerging successes, we would like to acknowledge our supporters once again. Start-up funding, including fellowships, has been provided by UMR and the Graduate School through the University of Minnesota Interdisciplinary Informatics initiative. Funding for the BICB graduate traineeships and the collaborative seed grants has been provided by the state of Minnesota’s U of M Rochester Signature Programs in Technology Health Science award and UMR.

As we turn the corner from spring into summer, we’d also like to express a hearty thank you to program management consultant Jim Clausen, whose leadership has been invaluable in envisioning and shaping BICB into an interdisciplinary, multi-institutional graduate and research program that leverages the University of Minnesota’s academic and research capabilities in partnership with IBM, Mayo Clinic, Hormel Institute, and other industry leaders. Jim retired from the BICB program in January after more than three years of helping to create and guide BICB. We wish him all the best in his future endeavors.

BICB will be holding its seventh research symposium on June 25, 2010, in Rochester, Minn. With BICB entering its fourth year, and the research and academic programs it has fostered beginning to gain significant momentum, we are looking to focus this symposium on the impact BICB can have on economic development in southeastern Minnesota and the entire state. We plan to do this through, in addition to scientific presentations, a panel discussion on entrepreneurship in the context of the biomedical industries and a keynote address on how to foster innovation and business development. More information about the symposium is available at www.r.umn.edu/research/bicb/events/summer2010/index.htm. We look forward to seeing you there.

—The BICB Planning Team: Vipin Kumar, Ph.D.; Claudia Neuhauser, Ph.D.; Michael Olsen; Erin Spencer

Graduate Student Profile: From Biostatistics to BICB

When Yaming Chen moved from California to Rochester, Minn., two years ago, he had his sights set on earning a master’s degree in biostatistics. When he heard about the BICB program, however, he realized he’d run into an even better idea. His first love is mathematical modeling, and he’s very interested in applying modeling to research aimed at helping advance cancer therapy. BICB seemed a perfect fit.

“I just looked at it and thought, that’s the program I want to get into,” Chen says. He applied, and began Ph.D. studies in biomedical informatics and computational biology in 2009.

Under coadvisors Claudia Neuhauser, Ph.D., of UMR and Mayo Clinic faculty member Zeljko Bajzer, Ph.D., Chen will use his mathematical expertise to improve the application of viruses to destroying tumor cells. In the growing field of virotherapy, a major challenge is precisely modeling the movement of virus into the tumor in order to maximize tumor exposure while minimizing risk to surrounding cells. Chen will apply network theory to model three-dimensional spatial relationships among virus, tumor, and normal cells in a way that allows fine-tuning of therapy timing and dose. Also guiding him are Mayo Clinic researcher David Dingli, M.D., Ph.D., and George Paulik, Ph.D., of IBM Rochester.

“I’m very excited about this opportunity,” Chen says. “People in the BICB program are from very different backgrounds. We can come together. And for me, mathematics and computation can come together in my Ph.D. research.”

Chen’s long-term career goal is to continue research in an academic environment. In the meanwhile, he’s enthusiastic about the opportunities the BICB program offers.

“It’s unique and it’s combined the different areas together,” he says, “so it gives me the opportunity to work on a very exciting project.”
Progress and Plans

January research symposium at UMR highlights discovery to date, cultivates conversations for new collaborations

Three years ago, a vision of bringing new economic growth to the Rochester area and new, computational solutions to health care challenges took root in the form of a unique public-private partnership among the University of Minnesota Rochester (UMR), University of Minnesota Twin Cities (UMTC), Mayo Clinic, the Hormel Institute, and IBM—the Biomedical Informatics and Computational Biology program (BICB). If the recent BICB Winter Research Symposium is any indication, the idea not only has taken root, but is beginning to blossom. In mid-January, more than 120 research scientists, students, and others from southern Minnesota gathered at UMR to share updates on BICB-sponsored research, float ideas for new collaborations, and brainstorm ways to make the BICB vision even better.

“It was great to see so many diverse individuals with a common interest come together, share success stories, and make plans for future progress,” said Michael Olesen, director of information technology, bioscience program, and research for UMR. “The symposium truly exemplified what the BICB program is all about and showcased what has been accomplished.”

The daylong event began with a welcome by UMR chancellor Stephen Lehmkuhle, Ph.D., and vice chancellor Claudia Neuhauser, Ph.D. Neuhauser recognized BICB program management consultant Jim Clausen for his exceptional service and contributions to BICB. Clausen retired at the end of January from the BICB program.

Drew Flaada of IBM began the day with a keynote speech on the growing role of high-power computing in health-care research.

Drew Flaada, director of Emerging Solutions Development for IBM and a key manager of the IBM/Mayo Clinic collaboration, presented the keynote speech, “Computers for Cures.” After describing the origins of the BICB program—he was part of the governor’s commission that led to its creation—Flaada noted that a major challenge in health-care research today is the amount of information being produced. For BICB, “the problem is the opportunity,” Flaada said. “We live in a time when the information is not only exploding, the ability to deal with it is exploding, too.”

Flaada discussed the application of IBM’s Blue Gene supercomputers to searching for molecules with specific traits. He also spoke of the promise of individualized medicine, and of the potential for applying high-power computing to sophisticated medical pursuits such as identifying potential brain aneurism hot spots. He noted that IBM has contributed some $1.3 million worth of computing time to BICB projects since the program began.

“The ideas you all are working on excite me to no end,” Flaada told the audience. “The collaborations are really exciting—the kinds of discoveries, but also the kinds of relationships developed as well.”

Following Flaada’s keynote, four research teams receiving BICB support provided updates on their investigations:

**Predicting Transplant Outcomes.** UMTC electrical and computer engineering professor Vladimir Cherkassky, Ph.D., spoke on using computation to predict the likelihood of graft-versus-host disease and transplant-related mortality in candidates for bone marrow or blood transplants. Collaborators in the project are Feng Cai; Daniel Weisdorf, M.D.; Mukta Arora,
M.D.; Brian Van Ness, Ph.D.; and Bharat Thyagarajan, M.D., all of UMTC. The researchers have analyzed one data set and are exploring the clinical utility of applying their findings to predicting the likelihood of transplantation success based on patients’ age and genomic characteristics.

**Beating Viruses at Their Game.** Jean-Pierre Kocher, Ph.D., assistant professor, College of Medicine, Mayo Clinic, and Andrew Norgan, an M.D.-Ph.D. student at Mayo Clinic and a BICB trainee, provided an update on a project looking at ways to use small molecules to inhibit replication in HIV and Ebola viruses. The research team has used theoretical analyses and computational models to predict which molecules in a library of more than 2,500 would be best suited to throw a wrench in the works of a key viral protein. The next step for the research is to acquire the most promising candidate molecules and test their effectiveness against the actual virus. Collaborators are Carlos Sosa, Ph.D., IBM/UMTC; Kendall Byler, Ph.D., Mayo Clinic; Eric Poeschla, M.D., Mayo Clinic; David Katzmann, Ph.D., Mayo Clinic; Emilia Wu, Ph.D., UMTC; and Yiannis Kaznessis, Ph.D., UMTC.

**New Approach to Killing Cancer.** Chad Myers, Ph.D., assistant professor of computer science at UMTC; and Mayo Clinic researcher Dennis Wigle, M.D., Ph.D., described their collaboration aimed at developing a targeted way to kill cancer cells by identifying lethal combinations of mutations using high-speed computing to rapidly process massive amounts of data. The researchers have identified a number of deadly combinations in yeast, and are now working on using that knowledge to find lethal combinations in the human genome. Wigle noted that the research collaboration arose from ideas the two shared at a previous BICB gathering. “A casual conversation in the hallway turned into all of this,” he said.

**Figuring Out p53.** UMTC senior scientist Tai-Sung Lee, Ph.D., presented results of research to date on a multi-institutional project aimed at understanding the connections between structure and function in the tumor suppressor protein p53. Using a computational approach and newly identified crystal structure of p53, he and his colleagues have explored how phosphorylation of a serine residue on the protein inhibits its ability to bind DNA. Collaborators on the project are Darrin York, Ph.D., UMTC; Zigang Dong, M.D., Dr.P.H., and Anne Bode, Ph.D., the Hormel Institute; Paul Limburg, M.D., Mayo Clinic; and Carlos Sosa, Ph.D., IBM/UMTC.

To wrap up the day, scientists and students took part in a panel moderated by Vice Chancellor Neuhauser on the rewards and challenges of the BICB program’s unique approach to fostering interdisciplinary and inter-institutional collaboration.

UMTC associate professor of chemistry Darrin York, Ph.D., began by addressing the challenges of bridging the divide between physical and clinical sciences. He noted that undergraduate education is still strongly departmentalized. “We need to have some progressive free thinkers who are interested in pioneering a new model,” he said. “I think it’s going to be our BICB grads who end up becoming leaders in the field.”

For panelist Ann Oberg, Ph.D., a Mayo Clinic statistician, areas to address include juggling competing priorities and communicating effectively across the miles. Noting the explosion in availability of research data, Oberg pointed to inter-institutional collaboration as a valuable tool for enhancing the statistical rigor of studies.

UMTC computer science graduate student Rohit Gupta, who has been involved in inter-institutional research characterizing colonoscopy success rates, said the opportunity BICB provides to gather insights and input from a broad range of individuals when formulating and carrying out a research project can be both beneficial and challenging. “One thing I learned,” he said, “is to have a lot of patience.” Andrew Norgan, an M.D.-Ph.D. student at Mayo Clinic and a BICB trainee, described the challenges of starting with the life sciences and adding computer science to the mix as he pursued his research in drug discovery. He said he’s found instant messaging to be valuable in facilitating communication among widely dispersed members of a research team. He also predicted that personalized medicine would be the wave of the future in health care.

Finally, Flaada discussed differences in culture and focus between industry and academic research. “In academia what’s important is discovery of new ideas, the ability to publish, the ability to land public grants,” he says. “That’s not our business; IBM is a profit-driven corporation.” Flaada noted the need for collaborations to

continued on page 6
Collaborative Seed Grant Progress Reports

An update on research collaborations initiated with the assistance of BICB seed grant funding

Mining Genetic Determinants of Human Disease
Jean-Pierre Kocher, Ph.D. (Mayo Clinic); Hugues Sicotte, Ph.D. (Mayo Clinic); Dennis Wigle, M.D., Ph.D. (Mayo Clinic); Rui Kuang, Ph.D. (UM); Michael Steinbach, Ph.D. (UM); Vipin Kumar, Ph.D. (UM); Richard Mushlin, Ph.D. (IBM)

Research Update
The research team has finished the collection and quality control of clinical data, as well as the bioinformatics data processing of the genetic, genomic, and transcriptomic data. Team members described the system they built to manage large multi-data type datasets in a presentation entitled “Biologically Oriented Repository Architecture (BORA) for Integrative Molecular Analysis (IMA) of Cancer.” Collaborator Hugues Sicotte, R. Kuang, D. Wigle, V. Kumar, T. Hwang, M. Steinbach, E. Will, and J.-P. Kocher. 2010. Collaborator Hugues Sicotte received a two-year bioinformatics career development award from the Mayo Clinic Center for Individualized Medicine beginning in February 2010. The research plan for this award leveraged the BORA system developed as part of this collaboration.

Conference Presentation

Reliable Biomarkers for Prediction of Transplant-Related Mortality
Vladimir Cherkassky, Ph.D. (UM); Daniel Weisdorf, M.D. (UM); Mukta Arora, M.D. (UM); Brian Van Ness, Ph.D. (UM); Mark Litzow, M.D. (Mayo Clinic); Walter Kremers, Ph.D. (Mayo Clinic); Brooke L. Fridley, Ph.D. (Mayo Clinic)

Research Update
Analysis of factors predicting successful outcome of blood and marrow transplantation and computer-aided diagnosing of graft-versus-host disease can aid patient counseling and medical decision-making and identify patients needing specialized approaches to improve their outcome. This project investigates application of machine learning methods that incorporate both genomic and nongenomic information into a predictive diagnostic model for predicting transplant-related mortality. The researchers applied standard support vector machine (SVM) classifiers for data-analytic modeling of transplant-related mortality (TRM). The goal is to predict the binary output TRM (alive or dead) from a set of genetic and clinical inputs.

Classification decision rule is estimated using the SVM approach appropriate for such sparse multivariate data. The study compares several feature selection techniques for modeling TRM and objectively evaluates the quality of feature selection via prediction accuracy of the corresponding SVM classifiers. Results of this comparison are currently under discussion with collaborators at Mayo Clinic and the University of Minnesota Medical School.

Papers and Presentations


Predictive learning and the nature of scientific discovery. V. Cherkassky Invited talk presented at the Center for Cognitive Sciences, 11 February, University of Minnesota, Minneapolis, 2010

Support vector machines and predictive data modeling methodology. V. Cherkassky Short course organized by Chicago Chapter of the American Statistical Association (ASA), 26 March, Chicago, 2010

Cancer Drug Target Discovery Through Computational Prediction of Generic Interactions
Chad Myers, Ph.D. (UM); Dennis Wigle, M.D. (Mayo Clinic)

Research Reports

continued on next page
Characterization of systems-level organization through mining large-scale genetic interaction networks.
Bellay J., B. VanderSluis, Y. Kim, S. Bandyopadhyay, and C. L. Myers

New Models for Cancer Targets From Clinical Data
Darrin York, Ph.D. (UM); Tai-Sung Lee, Ph.D. (UM); Zigang Dong M.D., Dr.P.H. (Hormel Institute); Ann Bode, Ph.D. (Hormel Institute); Paul Limburg, M.D. (Mayo Clinic); Carlos Sosa, Ph.D. (IBM)

Presentations
Large scale virtual screening to identify novel inhibitors of Fyn as potential drugs for cancer treatment.
Madhusoodanan Mottamal
Poster presentation, AACR annual meeting, 17–21 April, Washington D.C., 2010

Computers for cures, IBM innovation supporting the biosciences: Projects overview.
C. P. Sosa
Cellworks, Inc, 12 July, Minneapolis, 2009

Virtual screening for designing inhibitors of the oncogenic ERK2 kinase.
C. P. Sosa, M. Mottamal, G. Giambasu, A. Pugliese, A. M. Bode, and Z. Dong
BICB Research Symposium, 16 January, Rochester, Minnesota, 2009

Federal Grant
Proposed Study Employing Computer Simulations and Screening, $500,000 NIH award to Zigang Dong, M.D., Dr. P.H., and Ann M. Bode, Ph.D. 12/01/09–05/31/11. The objective of the proposal is to examine the potential use of high-performance computer modeling, simulation, and screening methods to assist in the search for potential effective chemopreventive agents based on in silico methods. The agents to be examined are of two different classes: 1) cyclooxygenase (COX) inhibitors; and 2) epidermal growth factor receptor (EGFR) inhibitors, both of which are validated targets in multiple organs of both animals and humans. A great deal of information is available regarding these two classes of agents and therefore results derived from computational methods can be compared with results obtained by other investigators using other techniques. The proposed work comprises three main goals for identifying and characterizing COX1, COX2 or EGFR inhibitors by in silico methods: (1) to examine known agents for COX1 and COX2 (or EGFR) inhibitory activity; (2) to examine known COX1 and COX2 (or EGFR) inhibitory activity; (3) to examine a drug library to identify additional agents for their ability to bind COX1 or COX2 (or EGFR).

Progress and Plans continued from page 4

lead to greater demand for IBM products and services. He agreed with the value of instant messaging in long-distance collaboration, but underscored the importance of at least occasional face-to-face gatherings.

The question-and-answer session that followed elaborated on the panelists’ comments. One prominent theme was the need for soft skills in addition to scientific expertise. “We need people who know how to be teammates, to get things done on time,” one audience member observed.

The BICB program holds research symposia each January and June. The next event is scheduled for June 25, 2010.
BICB Research Reports

BICB 2010/01
The Genetic Landscape of a Cell

BICB 2010/02
Characterization of Systems-level Organization Through Mining Large-scale Genetic Interaction Networks
Bellay J., B. VanderSluis, Y. Kim, S. Bandyopadhyay, and C. L. Myers

BICB 2010/03
An RDF-base Normalized Model for Biomedical Lexical Grid
Tao C., J. Pathak., H. R. Solbrig W. Q. Wei, and C. G. Chute

BICB 2010/04
Semantic Measurement for SNOMED Sub-domains: A Pilot Study Using Clinical Notes
Wei W. Q., C. Tao, G. Jiang, and C. G. Chute
AMIA Summit on Clinical Research Informatics (CRI), San Francisco, March 2010

BICB 2010/05
Identification of Type 2 Diabetes Mellitus Patients by SNOMED CT Concept Frequency
Wei W. Q., and C. G. Chute
AMIA 2009 Annual Symposium, San Francisco, November 2009

BICB 2010/06
LexRDF-based Unified Model for Heterogeneous Biomedical Ontologies
Tao C., J. Pathak, H. R. Solbrig, W. Q. Wei and C. G. Chute

A complete list of BICB Research Reports is available at www.r.umn.edu/bicb. To request a report, please send an email requesting the publication by BICB report number (e.g., BICB 2009/XX) to Erin Spencer at spenc320@umn.edu

BICB Trainee Wins Prestigious IBM Fellowship

Congratulations to 2007 BICB trainee Dimitrije Jevremovic, who was recently chosen to receive a prestigious IBM Ph.D. Fellowship. The internationally competitive award will support Jevremovic’s thesis research during 2010–11 on analysis of metabolic pathways in biochemical reaction networks.

“Dimitrije has shown remarkable progress in only a short time in our Ph.D. program,” says computer science and engineering professor Daniel Boley, Ph.D., Jevremovic’s advisor and the person who nominated him for the award. “I am very happy that he received this award. I hope it will encourage continued close cooperation with IBM in this research. It will certainly allow Dimitrije to make rapid progress on his Ph.D. program and advance our research program in the mathematical and computational issues in metabolic network analysis.”

The research Jevremovic will pursue under the fellowship is a direct outgrowth of work he began in fall 2007 as part of his BICB traineeship. The fellowship will provide a stipend and cover educational expenses as well as a paid internship at IBM, and will help ensure access to MSI and IBM computing resources for computation of metabolic pathways. Jevremovic is working toward a Ph.D. in computer science with a BICB minor.

“It is encouraging for both our research group and me as a graduate student that IBM with this fellowship has recognized the importance of the research in biological network analysis of which metabolic networks are part,” he says. “Inherently, problems of metabolic pathway computation and analysis require advanced computing algorithms and resources.”

Jevremovic’s IBM mentor for the fellowship will be Carlos Sosa, Ph.D., a member of his Ph.D. committee who has been coadvising him in the area of parallel computing and use of supercomputing resources.

“I was particularly pleased that Dimitrije’s hard work was rewarded with this prestigious fellowship,” says Sosa, a computational chemist with IBM and the University of Minnesota. “It shows IBM’s commitment to assist and nurture young talents. BICB has helped open the door not only to develop this type of collaboration but also to be part of this program.”

Carlos Sosa, Dimitrije Jevremovic, and Daniel Boley
Working in Parallel

For BICB graduate student Haitao Sun, job and school make the perfect pair

Keep working or earn a doctoral degree? Haitao Sun didn’t have to choose. While browsing the Internet, he discovered that he could pursue his Ph.D. while continuing his job as a software developer at IBM in Rochester by enrolling in the BICB graduate program. A 10-year IBM employee, Haitao began progress toward his degree last year, advised by Carlos P. Sosa, Ph.D., of IBM and UMR, and University of Minnesota Twin Cities chemistry faculty Jiali Gao, Ph.D., and Donald Truhlar, Ph.D.

Haitao’s dissertation research will focus on developing parallel computer code based on a method developed by Gao, Truhlar, and their coworkers for biomolecular simulations. He will deliver a paralleled simulation software, as well as develop new parallel techniques for life science applications. Thanks to relationships established through the BICB program, he is able to apply high-performance computing systems located in Rochester and at the Minnesota Supercomputing Institute in the Twin Cities to his Ph.D. research.

Haitao says the degree program is helping him to advance his supercomputer skills, parallel techniques, biology knowledge, and database expertise, as well as develop skills related to carrying out research and publishing research papers.

“The BICB program is a very good program and really fits in with my needs and expectations,” Haitao says. “It allowed me to pursue my Ph.D. degree while working at IBM full time. And what I’m learning at the University of Minnesota is helpful for what I am doing at IBM.”