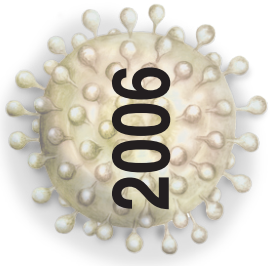

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Message from the President

Charles W. Steger

VirginiaTech
Invent the Future

Virginia Tech has embraced its mission as a land-grant university for more than a century, helping to transform the world around us through the benefits of knowledge. We can be extremely proud of the robust research university that we continue to build, a university that advances the land-grant values of discovery, learning, and outreach. These missions are as relevant in the 21st Century as they were when our university took its first steps along its long path of development.

At the beginning of this decade, our university developed a forward-looking strategic plan expressing our goal to be among the best universities anywhere. This year we re-examined and updated that blueprint for the future. Through our growing eminence in discovery, learning and engagement, we can increase our impact on the world around us. This year we reached an important milestone in our efforts to communicate the Virginia Tech story as we announced the creation of a branding campaign that gives new voice and clarity to the university's future. The resulting "Invent The Future" statement is a succinct expression of the forward-looking objectives of Virginia Tech.

In the area of discovery, the strategic plan identifies four broad areas for emphasis: energy, materials, and environment; health, food, and nutrition; social and individual transformation; and innovative technologies and complex systems, in which the Virginia Bioinformatics Institute plays a pivotal role.

The Institute's contributions to research, technology development and education are paving the way to a brighter future arising from a climate of innovative discovery. It will be exciting to watch new developments unfold in the years ahead and to see how an entrepreneurial approach to the life sciences positively transforms individuals and communities.

Virginia Tech remains committed to the highest standards of excellence. Every day we witness the transformative power of knowledge. Education and the creation of knowledge can invent a bright future for all of us. Our efforts inspire lives and communities, help assure a strong economic future for our state and the nation, safeguard our ideals, and enrich the lives of people across the globe.

It is my sincere belief that the Virginia Bioinformatics Institute has a key role to play in our exciting initiatives to "invent the future."

Charles W. Steger

Charles W. Steger, Ph.D.
President
Virginia Polytechnic Institute and State University

Letter from the Director

Bruno W.S. Sobral

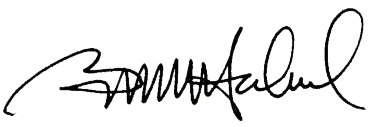
Building a successful research institute requires making a commitment to the future and change. As we enter the seventh year of the Virginia Bioinformatics Institute (VBI), it is extremely rewarding to observe the considerable progress that has been made at our Institute as we pursue our objectives. At VBI, we continue to advance our science base in a way that reflects our mandate to channel innovation into research projects that emphasize the importance of team-based science and knowledge generation in the context of problem-solving. In just over six years, we have grown into a transdisciplinary research institute with over 220 employees supporting research efforts in biomedicine, agriculture, bioinformatics, as well as synthetic, systems and computational biology.

The research platform of VBI is primarily centered on the "disease triangle" of host-pathogen-environment interactions. Pathogens, the infectious organisms that may cause diseases in their hosts, are the unifying theme of this year's annual report. In the context of infectious diseases, we place considerable emphasis on research to find new approaches that will assist in the development of drugs, vaccines and diagnostics – the problems to be solved. VBI research involves diverse disciplines such as mathematics, computer science, biology, plant pathology, biochemistry, and statistics. Our nationally and internationally recognized faculty in these disciplines have over the past 12 months engaged in groundbreaking research, some of the highlights of which are presented in our 2006 annual report.

As part of our growth plan, it has been particularly rewarding to see VBI reach another critical milestone in its development. The recent opening of our new facility at Virginia Tech's operations in the National Capital Region is the first step in a strategic effort to build a larger presence in the greater Washington D.C. area. The new offices provide resources to expand the research, development and outreach activities of our institute and will enable VBI to forge closer links with federal agencies, researchers, foundations and business development partners. The facility also provides space and resources for present and future faculty and staff to work in the greater Washington area. Further information on this exciting initiative is included in this annual report.

As we look ahead, our objectives remain to foster excellence in transdisciplinary research through far-reaching scientific projects involving diverse collaborations with various types of organizations. In this way, we hope to drive growth in knowledge, innovation, and scientific discoveries in an integrative manner.

As part of Virginia Tech, we share the university's commitment to inventing the future. This creative undertaking is based on credible research initiatives and sound science. We hope you will join us in sharing our enthusiasm for this endeavor.



Bruno W.S. Sobral, Ph.D.
Executive and Scientific Director
Virginia Bioinformatics Institute at Virginia Tech

Achievements

July
VBI researcher receives USDA grant

September
Simulation sciences at VBI

October
Dr. João Setubal named VBI deputy director

Students and VBI faculty participate in high school days

NSF supports cyberinfrastructure education and outreach initiative

November
Novel protein complex enables survival in hostile environment

December
VBI and VT College of Agriculture and Life Sciences award research fellowships to undergraduates

First VBI scientific report released

VBI's Core Laboratory Facility holds Open House Event for proteomic and genomic services

January
VBI designated Affymetrix National Custom Array Center

VBI receives $2.5 million for global pathogen portal project

February

New method enables gene disruption in destructive fungal pathogen

Orion and VBI announce collaboration to develop computational diagnostics

High school students learn about research at VBI

Dr. Lincoln Stein speaks at VBI First Annual Research Symposium

VBI researchers present at the annual meeting of the American Mathematical Society

March

VBI launches microbial database

High-efficiency transformation of strawberry

April

VBI hosts international alphaproteobacteria symposium

VBI develops Tomato Metabolite Database

May

FIOCRUZ and VBI sign agreement

Research group launched at Synthetic Biology 2.0 meeting

June

EML Research and VBI launch COPASI simulation software

Highlights

July 2005

VBI researcher receives USDA grant

Brett Tyler, research professor at the Virginia Bioinformatics Institute, is awarded a three-year, $980,000 grant from the United States Department of Agriculture to identify ways in which the plant pathogen *Phytophthora sojae* overcomes the defenses of its host, the economically important soybean crop.

September 2005

Simulation sciences at VBI

VBI announces that The Network Dynamics and Simulation Science Laboratory is up and running on the Virginia Tech campus. The laboratory, which is led by Dr. Christopher L. Barrett, designs and analyzes simulations of extremely large systems and implements them on high-performance computer systems for research on biological, information, social and technological systems.

October 2005

Dr. João Setubal named VBI deputy director

Dr. João Setubal is appointed as the Institute's Deputy Director, acting on behalf of VBI's executive and scientific director, Bruno Sobral, in handling internal administrative functions, as well as scientific decision making.

NSF supports cyberinfrastructure education and outreach initiative

Bluefield State College, the Galileo Magnet High School in Danville, VA, and VBI receive a $250 000 grant to support a forward-looking initiative for education in cyberinfrastructure. The funds from the National Science Foundation will be used over a period of two years to develop and implement the new course, broaden access of high school and undergraduate students to computer-related technologies, and encourage trained students to pursue careers in informatics-related projects.

Students and VBI faculty participate in high school days

Approximately 50 students from Auburn and Blacksburg high schools participate in "VBI High School Days" program, which exposes students to bioinformatics and encourages interest in science and mathematics. Faculty members Karen Duca, Reinhard Laubenbacher, Chris Lawrence, Iuliana Lazar, Dharmendar Rathore, Bruno Sobral, Brett Tyler and their research groups introduced the students to research programs at VBI.

November 2005

Novel protein complex enables survival in hostile environment

Biswarup Mukhopadhyay and Eric Johnson from VBI discover a novel enzyme that represents an ancient detoxification system and provides a clue to the development of early metabolism on earth. The research appeared in the Nov. 18, 2005 issue of the *Journal of Biological Chemistry*. The newly discovered enzyme links biological methanogenesis and sulfate reduction, two most ancient respiratory metabolisms, in a unique way.

December 2005

VBI and VT College of Agriculture and Life Sciences award research fellowships to undergraduates

VBI and Virginia Tech's College of Agriculture and Life Sciences each award one systems biology summer research internship to an undergraduate student poster presenter at the Society for Advancement of Chicanos and Native Americans in Science (SACNAS) Annual Conference. The awards give the students the opportunity to work side by side with Virginia Tech researchers for ten weeks during the summer of 2006.

January 2006

VBI designated Affymetrix National Custom Array Center

VBI signs an agreement with Affymetrix Inc. for the not-for-profit use of Affymetrix' GeneChip® technology. Under the terms of the agreement, the Institute's Core Laboratory Facility (CLF) is granted the status of National Custom Array Center for custom microarray design, sample processing and analytical services. Affymetrix custom microarrays offer researchers the flexibility to design arrays that can analyze the genome sequence of any organism.

VBI receives $2.5 million for global pathogen portal project

VBI is allocated $2.5 million for its pathogen portal project (PathPort) in the Defense Appropriations Bill for 2006. The new funding will enable researchers at VBI to continue the planned expansion and deployment of PathPort, an Internet portal that allows scientists around the globe to access the very latest research tools as well as use vital information on key pathogens and infectious diseases.

February 2006

New method enables gene disruption in destructive fungal pathogen

Researchers at VBI, Colorado State University and Duke University Medical Center develop a new method to determine gene function on a genome-wide scale in the fungal pathogen *Alternaria brassicicola*.

A. brassicicola, which causes black spot disease in cultivated Brassica, is a destructive fungus that may lead to considerable leaf loss in economically important crops including canola, cabbage, and broccoli.

Orion and VBI announce collaboration to develop computational diagnostics

VBI and Orion Integrated Biosciences Inc. sign an agreement to facilitate the development of new diagnostic methods for key viral pathogens. Under the terms of the agreement, information on encephalic and hemorrhagic viruses from VBI's PathPort project will be integrated into Orion's Integrated Computational Analysis System, a high-performance, portable computational tool that allows users to store, retrieve and exchange molecular and diagnostic data on viral pathogens.

High school students learn about research at VBI

Students from Montgomery County Schools' High School/High Tech program and the Korea Science Academy visit VBI to learn more about the Institute. High School/High Tech is a community-based partnership designed to encourage students with physical, sensory, and learning disabilities to explore career opportunities in the fields of science, engineering, and technology. The students from the Korea Science Academy are participating in an exchange program with the Roanoke Valley Governor's School of Science and Technology and attended a presentation from Professor Reinhard Laubenbacher on the role of mathematics in biology.

Dr. Lincoln Stein speaks at VBI First Annual Research Symposium

VBI welcomes Dr. Lincoln Stein, professor of bioinformatics at Cold Spring Harbor Laboratory in Cold Spring Harbor, New York, to the Virginia Tech campus as part of the Institute's First Annual Research Symposium. Stein, whose pioneering work

in the field of bioinformatics has spurred the development of several powerful computer-based methods for analyzing a wide variety of biological data, gives the plenary lecture on Reactome, an open source database of biological pathways, to a packed VBI Conference Center. Reactome is a joint collaboration between Cold Spring Harbor Laboratory, The European Bioinformatics Institute, and the Gene Ontology Consortium.

Highlights

VBI researchers present at the annual meeting of the American Mathematical Society

Researchers from VBI present at a workshop entitled "Modeling and Simulation of Biological Networks". The workshop, which was organized and introduced by VBI Professor Reinhard Laubenbacher at the annual meeting of the American Mathematical Society in San Antonio, Texas, presented state-of-the-art examples of the use of mathematics, statistics, and computer science to understand biological systems. Madhav Marathe and Pedro Mendes of VBI, and Brandilyn Stigler, postdoctoral fellow at the Mathematical Biosciences Institute at The Ohio State University and former VBI graduate researcher, also gave presentations at the workshop.

March 2006

VBI launches microbial database

Researchers at VBI launch a publicly-available microbial database to host a range of microbial genome sequences. The VBI Microbial Database (VMD) contains genome sequence and annotation data for the plant pathogens *Phytophthora sojae* and *Phytophthora ramorum*. The purpose of the database is to make widely available to researchers the recently completed genome sequences of these pathogens as well as powerful analytical tools in one integrated resource.

The work described in the paper was completed by VBI researchers Sucheta Tripathy, Varun Pandey, Bing Fang, and Fidel Salas, and led by Brett Tyler, VBI professor and professor of Plant Pathology, Physiology, and Weed Science at Virginia Tech. The VMD database was featured in *Science*, the flagship journal of the American Association of the Advancement of *Science* (vol. 311, no. 5768, 24 March 2006, page 1685).

High-efficiency transformation of strawberry

Researchers at VBI and the Department of Horticulture in the College of Agriculture and Life Sciences at Virginia Tech develop a new procedure for the efficient transfer of specific DNA sequences into the genome of strawberry. The scientists have used *Agrobacterium tumefaciens*, nature's genetic engineer, to introduce DNA into the woodland or alpine strawberry *Fragaria vesca*. The work was funded by a Virginia Tech ASPIRES grant.

April 2006

VBI hosts international alpha-proteobacteria symposium

VBI hosts an international group of scientists for a research symposium at the VBI Conference Center. The "International Symposium on the Comparative Biology of the Alpha-Proteobacteria" examined the very latest research and findings on the alpha-proteobacteria, a group of diverse organisms whose members have successfully adopted different lifestyle and energy-yielding strategies in the course of evolution. The symposium comprised around 30 presentations from leading experts from around the globe. Siv Andersson, professor in Molecular Evolution and head of the Department of Evolution, Genomics and Systematics at Uppsala University, delivers the plenary lecture on expansion and reduction of the alpha-proteobacterial genome.

VBI develops Tomato Metabolite Database

A researcher at VBI develops a database and computational tools to help scientists learn more about how certain genes in tomatoes affect the crop's flavor and nutritional value. The Tomato Metabolite Database will be used as a resource to identify key genes involved in the synthesis of essential metabolites that impact tomato flavor and the quality of its nutrients.

The work is part of a collaboration with the University of Florida, the Boyce Thompson Institute at Cornell University and the United States Department of Agriculture (USDA). The work is funded by a $2-million grant from the National Science Foundation.

May 2006

FIOCRUZ and VBI sign agreement

VBI and the Oswaldo Cruz Foundation (FIOCRUZ) sign an agreement to accelerate the development of new health products and technologies. The initial three-year agreement is intended to facilitate the development of drugs, vaccines, diagnostics and other technologies that may reduce the global burden of infectious diseases. The collaboration includes innovative research and development initiatives targeting healthcare solutions for dengue fever, hepatitis C, HIV/AIDS, influenza, malaria, and pneumonia.

Dr. Bruno Sobral, executive and scientific director of VBI, remarked: "This agreement reflects a compelling need for new ways to tackle the global threat of infectious diseases. It also represents what we see as a highly innovative framework for new partnerships in the public health arena."

Research group launched at Synthetic Biology 2.0 meeting

VBI sets up a research group that will focus on the emerging field of synthetic biology. The announcement coincides with the recent arrival of Dr. Jean Peccoud, a computational biologist from Pioneer Hi-Bred International, a fully owned subsidiary of DuPont, as well as the Second International Conference on Synthetic Biology, which took place on May 20-22, 2006, at the University of California, Berkeley. Synthetic biology involves the design and construction of new biological parts, devices and systems as well as the redesign of existing, natural biological systems for useful purposes.

June 2006

EML Research and VBI launch COPASI simulation software

VBI and EML Research announce the launch of the COPASI simulation software. COPASI (Complex Pathway Simulator) is a major software package that allows users to model, simulate and analyze biochemical and systems biology networks. COPASI, which supports the Systems Biology Markup Language (SBML) standard for systems biology software, enables researchers to investigate how a system is working by allowing them to construct biochemical models, reproduce experimental results and justify the validity of the chosen model. The software may be freely downloaded at www.copasi.org for non-commercial purposes.

EML Research

Focus on pathogens

New disease epidemics, the risk of pandemics and the threat of bioterrorism mean that society has to intensify its research efforts to develop vaccines, diagnostics and therapeutics. Society must also explore new approaches to prevent the onset of disease, model impacts of disease outbreaks and deploy countermeasures to disease outbreaks.

Epidemics associated with emerging and re-emerging infectious diseases are now occurring in historically unprecedented numbers. Since 2001, the World Health Organization has verified more than 1100 epidemics of international importance. Over 70% of new and emerging diseases originate in animals.

Society needs unique mechanisms to address some of the key global challenges in public health posed by existing and emerging biological pathogens. This should also help to remove some of the gross inequities in disease burden that currently exist between developed and developing countries.

Researchers at VBI are involved in a wide range of biomedical, agricultural, environmental and bioinformatics projects that may integrate various disciplinary components to tackle infectious diseases. The tools and methods under development are being used to investigate plant and animal pathogens, push the boundaries of infectious disease research and better understand biological processes from the molecule to the system.

"Over the next few decades the most important biomedical advances will come from focusing interdisciplinary methodologies on specific problem areas."

Phil Green,
Member of the US National Academy of Sciences

16 June 2006, VBI Faculty Retreat

Features:

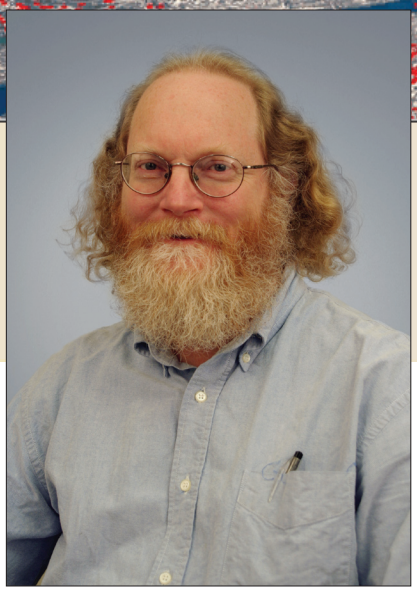
- Modeling and simulation of pandemic influenza
- Sequences reveal benign origin of deadly plant pathogens

This negative stained transmission electron micrograph (TEM) shows recreated 1918 influenza virions that were collected from supernatants of 1918-infected Madin-Darby Canine Kidney (MDCK) cells cultures 18 hours after infection. Adapted from the CDC Public Health Image Library. Credit Cynthia Goldsmith

Modeling and simulation of pandemic influenza

"One of the key objectives of the MIDAS group is to look in detail at how results from the computer modeling and simulation of infectious disease outbreaks can be most effectively transformed into public policy."

The impact (right) of staying at home on an influenza outbreak in Portland, Oregon.



"Infectious diseases pose one of the most significant threats to public health worldwide. Computer simulations that include the response of populations to a disease outbreak can help to estimate how an outbreak might spread and how interventions may help to alleviate disease burden."

Stephen Eubank

Stephen Eubank is deputy director of the Network Dynamics and Simulation Science Laboratory at VBI. Since earning his Ph.D. in theoretical physics, his research interests have focused on complex non-linear systems. He is currently a Principal Investigator for MIDAS (Models of Infectious Disease Agent Study), a collaboration of research and informatics groups developing computational models to investigate how infectious diseases emerge and spread through large populations.

MIDAS is a research partnership with a mandate to develop computational models for policy makers, public health workers and other researchers. The computational models developed by partners in the MIDAS network are used to assist in making better-informed decisions about natural or intentionally caused emerging infectious diseases. MIDAS also plays a role in planning for national emergencies or acts of bioterrorism.

The devil lies in the detail

Eubank remarked: "Perhaps one of the best ways to visualize the work of MIDAS is to consider one of the many simulations that we have performed to date for some cities in the United States. For a city of a million or so population like Portland, Oregon, we have been able to show the influence that responses like staying at home or interventions like vaccination can have on a simulated epidemic of influenza. The simulations show that the behavior of individuals can have a large impact on how quickly a disease will spread through a population."

The models being developed by the Network Dynamics and Simulation Science Laboratory consist of "synthetic individuals" that each represent a single person with a set of activities to carry out at different locations. Eubank believes that models require a high level of detail about individuals' interactions in order to come up with effective, workable strategies to mitigate disease outbreaks. The challenge is to balance the demand for detail with the availability of data and capacity of current computational methods. He remarked: "We have used Portland, Chicago, Houston and Dallas for simulations and have been able to run detailed analyses for these populations that provide useful information at the local urban level. We have now reached a point where we can model 300 million synthetic individuals which corresponds to the population of the United States. Clearly the demand for computational resources is higher in this scenario but it is feasible to run diseases like pandemic influenza for populations of this size."

The power of networks

The MIDAS network consists of principal investigators, scientific collaborators, programmers, data and computer experts, as well as students from research and informatics groups across the country. In addition to the Virginia Bioinformatics Institute, MIDAS co-workers can be found at the University of Pittsburgh's Graduate School of Public Health, University of Maryland, Brookings Institute, Fred Hutchinson Cancer Research Center, University of Washington, Harvard Medical School, Brigham and Women's Hospital, Massachusetts Department of Public Health, Kaiser Permanente Northern California, Harvard School of Public Health, University of Pennsylvania School of Veterinary Medicine, Harvard School of Public Health, The University of California at Irvine and the Centers for Disease Control and Prevention. International partners are also found at the University of Warwick and Imperial College of London.

The network of MIDAS collaborators has a mission to further its work by catalyzing discussions among modelers, policymakers, and the public health community that involves setting priorities and designing studies. This involves taking leadership to ensure that MIDAS software is translated into useful tools for the public health community. It also encompasses sharing results and resources with the MIDAS network, policymakers, public health officials, and the scientific community. MIDAS takes advantage of the intellectual capital within the group to undertake projects that would be impossible for any single group.

Eubank adds: "We've been working hard as a group for a number of years now. It's exciting to see many of our undertakings reaching fruition and a point in their development path where they may be used as tools for informed decision making."

About Models of Infectious Disease Agent Study (MIDAS)

- MIDAS improves the nation's ability to respond to biological threats promptly and effectively by:
  - Developing useful computational tools and models of emerging infectious diseases
  - Building models in response to real or anticipated outbreaks
  - Making tools and models available to policymakers, public health professionals, and researchers
- MIDAS is a collaboration of research and informatics groups established to develop computational models of:
  - Interactions between infectious agents and their hosts
  - Disease spread
  - Prediction systems
  - Response strategies
- The MIDAS network may be called upon to develop specific models to aid public officials in their decision-making processes if there were to be a disease outbreak
- MIDAS researchers are currently working on modeling outbreaks of influenza, a disease that could pose a serious challenge to global public health if a new pandemic were to occur
- MIDAS is funded by the National Institute of General Medical Sciences (NIGMS), which is part of the National Institutes of Health

MIDAS
Models of Infectious Disease Agent Study

http://www.nigms.nih.gov/Initiatives/MIDAS/

Sequences reveal benign origin of deadly plant pathogens

Draft genome sequences of two deadly plant pathogens were featured in the September 1 issue of *Science* in the article "*Phytophthora* genome sequences uncover evolutionary origins and mechanisms of pathogenesis." (vol. 313, no. 5791, 2006)

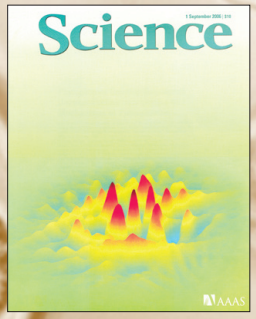


Photo credit: Matteo Garbelotto Laboratory, University of California, Berkeley

"The sequencing of these pathogens will help researchers better understand the genome makeup of these deadly organisms and identify valuable information to help control and prevent disease."

Brett Tyler

VBI's Brett Tyler and his research group, along with an international team of collaborators, have uncovered information about two plant pathogens that could potentially have a tremendous impact on the United States' economic and environmental future. This important genetic information was revealed publicly when the draft genome sequences of *Phytophthora ramorum* and *Phytophthora sojae* were featured in the September 1 issue of *Science*.

Phytophthora species and related pathogens cause tens of billions of dollars of damage every year to a wide range of agriculturally important plants, and also cause severe damage to forests and threaten entire natural ecosystems. More specifically, *P. sojae* causes damage to soybean crops and costs U.S. commercial farmers, which produce nearly half of the world's soybeans, $1 to $2 million in annual losses. *P. ramorum*, which causes sudden oak death, has attacked and killed tens of thousands of oak trees in California and Oregon.

The sequencing of these pathogens will help researchers better understand the genome makeup of these organisms and identify valuable information to help control and prevent plant disease. The work of Tyler and his collaborators has helped to trace the evolutionary path of *Phytophthora*, beginning as a benign photosynthetic ancestor and transforming into a sophisticated, plant-killing machine. The sequences have also revealed that *P. sojae* and *P. ramorum* have a large number of genes compared to counterparts such as pathogenic fungi.

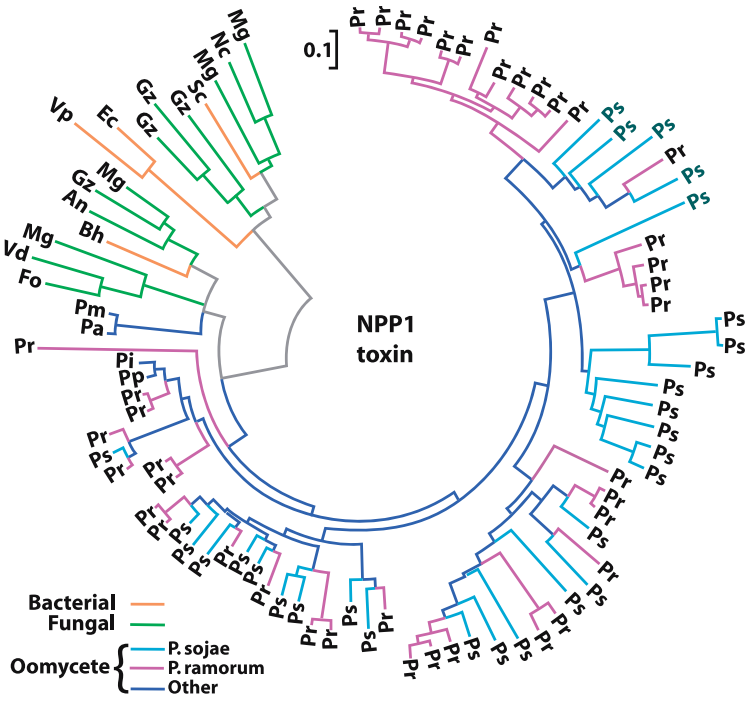
In *P. sojae,* 19 027 likely genes were identified, while 15 743 were identified in *P. ramorum*. One reason for the pathogens' additional number of genes was discovered after comparing the genomes of the two *Phytophthora* species. The comparison showed a rapid expansion and diversification of many protein families linked to plant infection, including toxins, protein inhibitors, and enzymes. The additional genes are needed to support the pathogens' abilities to generate these substances used to invade plants. Both *P. sojae* and *P. ramorum* are armed with an arsenal of these proteins, helping to break down cell walls to infiltrate their hosts.

"What is extraordinary about the *Phytophthora* genomes is that almost half of the genes contained in them show signs of rapid adaptation," Tyler explains. "We speculate that the rapidly changing genes are being driven to evolve by pressure from the defense systems of the pathogens' host plants. The unprecedented level of genetic flexibility in these organisms gives us insights into how these pathogens have become successful. At the same time, it has helped us identify weak points in the organisms that can be targeted to control them."

According to Professor Jeffrey Boore, a co-leader of the project from the US Department of Energy (DOE) Joint Genome Institute "This has been a ground-breaking, large-scale, collaborative project. As a resource for the entire scientific community, it is already having an immediate impact on plant pathogen research. To take one example, the *P. ramorum* sequence has over 13 000 single nucleotide polymorphisms, which has already led to the development of genetic markers for population studies and for tracking the movement of different strains of *P. ramorum*."

In order to develop improved methods for controlling *Phytophthora* infection, it is important to understand how these pathogens break down the plants' defenses. This should allow researchers to develop plants with improved resistance against the pathogen. By using the genetic markers to identify the species and map their paths as they invade different regions of their hosts, researchers will be able to determine patterns in the geographic movement of the pathogens, making it possible for them to design strategies to counter their migration.

"The sequences are a fundamental resource with wide-ranging applications for the *Phytophthora* community. We will be pursuing our investigations of the secreted proteins linked to damage of the plant host in the hope of developing much needed countermeasures against these deadly pathogens," Tyler says.

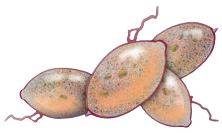


Sequence divergence of the NPP1 or Nep1-like protein toxin family

*Source: Science **313**(5791):1261-1266.*

Genome sequences of *P. ramorum* and *P. sojae*

- Project to sequence the genomes began in 2002
- Sequencing of *P. ramorum* represents the fastest sequencing of a newly emerged pathogen other than Severe Acute Respiratory Syndrome (SARS) virus
- *P. ramorum* was identified in 2000 and its draft sequence was complete by 2004
- Work has been funded by the National Science Foundation, the National Research Initiative of the USDA Cooperative State Research, Education and Extension Service, and the Department of Energy
- Project has been carried out by an international team of scientists led by the DOE Joint Genome Institute and the Virginia Bioinformatics Institute



Resources and People

Core Facilities

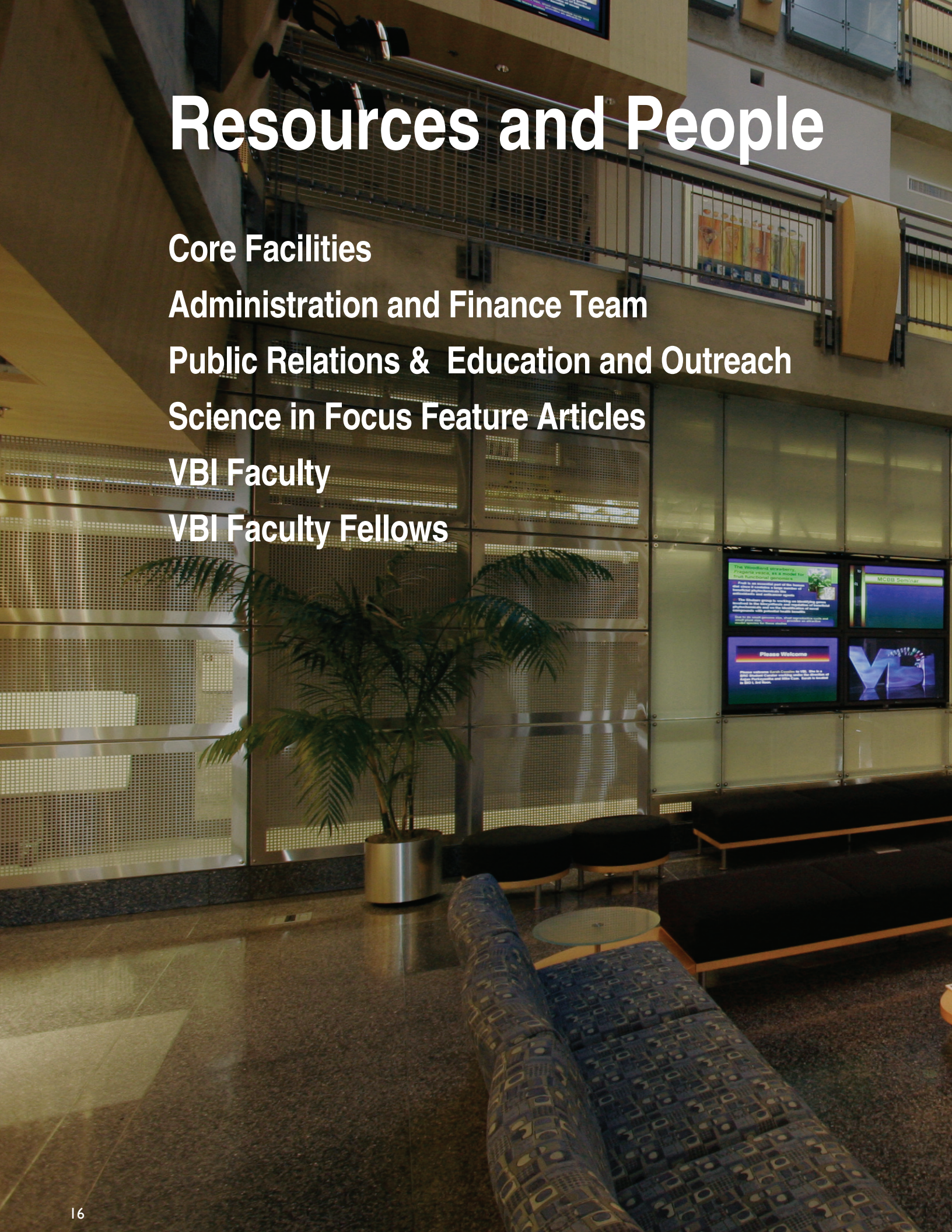
Administration and Finance Team

Public Relations & Education and Outreach

Science in Focus Feature Articles

VBI Faculty

VBI Faculty Fellows

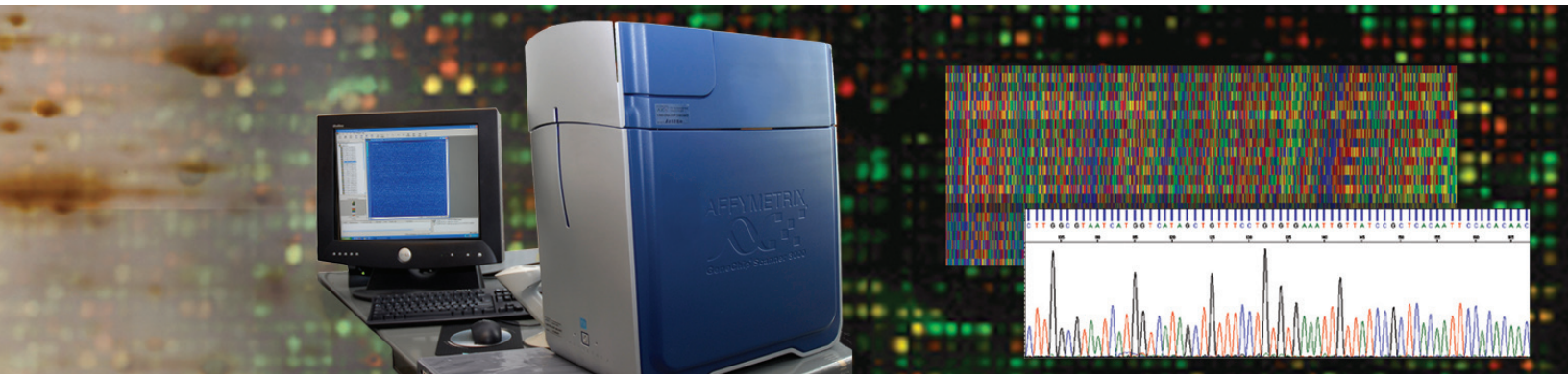


Virginia Bioinformatics Institute main lobby

Core Laboratory Facility

The Virginia Bioinformatics Institute's Core Facility is a state-of-the-art resource delivering a wide range of services and data to the global life science community. By integrating multi-user resources, the Core Facility combines high-throughput data generation from the Core Laboratory Facility (CLF) with the data analysis capabilities of the Core Computational Facility (CCF). This makes the Core Facility a one-stop, full-service shop that provides the staff, infrastructure, software and hardware systems needed for some of the most challenging applications in the biomedical, agricultural and computational sciences. VBI's Core Facility provides researchers with access to the latest technology platforms for the generation of data, as well as the computational tools needed for extensive data analysis on a cost-recovery basis.

CLF personnel (left to right):
Clive Evans (Core Laboratory Facility Manager), Bin Fang, Kristal Cooper, Brad Howard, Megan Blauvelt, Kris Lee, Don Shaw, Jeannine Roney, Adam Jerauld



Core Laboratory Facility

The Core Laboratory Facility (CLF) functions as a multi-user resource dedicated to the development and application of various high-throughput technologies. The Institute offers essential key services for clientele working at Virginia Tech as well as other universities, institutions, and private sector companies. It provides services and expertise at all stages of gene expression experimentation, from designing the actual experiment to interpreting the data. The CLF currently provides analysis platforms for DNA sequencing and genotyping, gene expression analysis, and proteomics.

The CLF also offers a selection of molecular biology applications, for example, colony picking, cloning, and DNA/RNA isolations. It is the combination of application and development that allows the CLF to be a leader in partnering with researchers to enable a complete systems biology approach to their science.

The CLF continually upgrades equipment, processes, and software and expands its staff to meet the growing demands for offered services, ensuring high quality production and workflow capabilities, as well as the availability of dedicated professionals to assist users in the successful application of technologies.

Virginia Bioinformatics Institute gains National Customer Array Center status

The Virginia Bioinformatics Institute at Virginia Polytechnic Institute and State University is an Affymetrix National Custom Array Center for custom array design, sample processing, and analytical services. By way of an agreement signed with Affymetrix towards the end of 2005, the Institute's Core Laboratory Facility has been able to expand its offerings of Affymetrix technologies and services, further integrating breakthrough genomic tools to its portfolio of services.

The GeneChip® technology platform consists of high-density microarrays and tools to help process and analyze microarrays. GeneChip microarrays consist of small DNA fragments that are chemically synthesized at specific locations, referred to as features, on a coated quartz surface; millions of features can be contained on one array. By extracting and labeling nucleic acids from experimental samples, and hybridizing those prepared samples to the array, the amount of label can be monitored at each feature, enabling a wide range of applications on a whole-genome scale. Typical applications include gene- and exon-level expression analysis, novel transcript discovery, genotyping, and resequencing.

Laboratory Information Management System

The CLF is supported by a custom Laboratory Information Management System (LIMS), designed and built by GraphLogic, Inc. of Branford, Connecticut, that provides an easy-to-use, secure interface for sample submission and data retrieval. The combination of application and development at the CLF helps researchers take a complete systems biology approach to their science.

Behind the scenes, the LIMS supports the CLF production environment with its ability to store, retrieve, and manage information related to: projects, clients, workflows, samples, equipment, reagents, inventory, and associated costs.

The LIMS is fully supported by the Core Computational Facility (CCF) to ensure secure and efficient data storage and retrieval capabilities. The seamless link between the CLF and the CCF provides VBI's clientele with a simple and effective connection between data generation and data analysis.

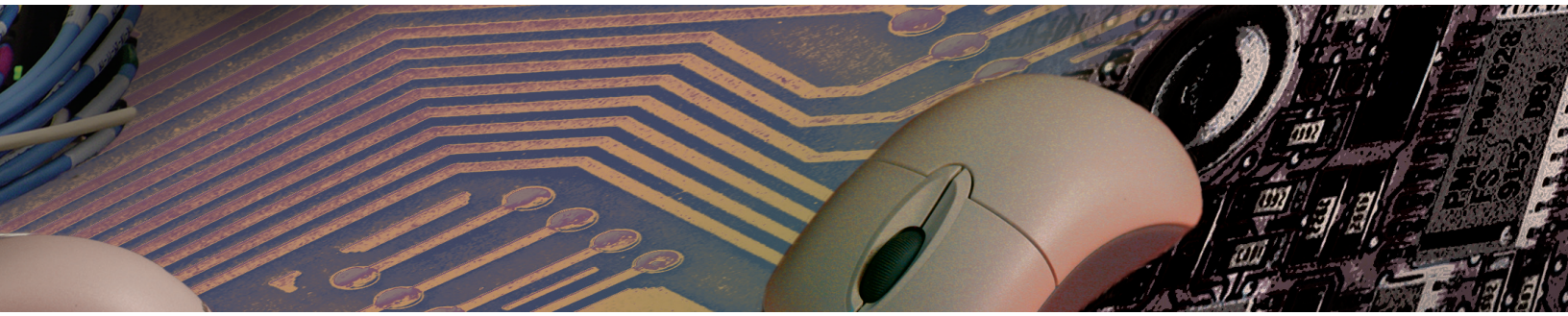
Core Computational Facility

The Core Computational Facility (CCF) is the data management and analysis machine of the VBI Core Facility. The CCF provides high performance computing resources to support data visualization, data mining, and a wide range of biological applications. A team of dedicated information technology professionals guarantee that the CCF remains a state-of-the-art facility. The services currently offered by the CCF include:

- Computational Processing
- Compound Services (analysis applications via webservices, website hosting)
- Database and System Administration
- Data Storage and Backup

These services are designed to assist researchers in the study of large-scale biological systems involving genes, proteins, and their interactions, as well as metabolic networks (systems biology).

CCF personnel (left to right):
Jeremy Johnson, William Shank, David Bynum, Doug McMaster, Ryan Chase, Mark DiFilippo, Dominik Borkowski, Sally Waldon, Clark Gaylord, Dustan Yates, Guy Cormier (Chief Information Officer)



Computational processing

Powerful supercomputers, including a Sun Enterprise 15000 and an IBM Power 4, are at the center of the CCF's computational processing, providing resources that can be used for a wide variety of applications. Comprehensive data backup and recovery systems guarantee the integrity and availability of CCF services. An IBM Storage Area Network (SAN) provides over 35 terabytes of combined disk and tape storage, including an off-site copy for added security. The CCF uses gigabit Ethernet as its communication backbone and has a dedicated, scalable, and high-speed connection to the Internet, Internet2 and the National LambdaRail.

Generating huge amounts of data is getting easier to do each day making it even more critical to have a solid computational infrastructure in place. Recent additions to the CCF continue to strengthen the Core Facility's best-in-class capabilities. Its newest cluster, an IBM Power 4, has an extensive set of tools and applications for biologists, all available via webservices and the CCF website. The CCF also provides production hosting of websites and web-based applications.

Administration and Finance

The groups that comprise VBI's Administration and Finance Team internally support the research mission of the Institute by providing administrative support, business services, financial reporting, facilities services, human resources, and grants and contracts management. The team provides a solid infrastructure for the Institute's dynamic research environment, allowing for continued growth and success.

Administration personnel (left to right, back row):
Shannon Worringham, Otto Folkerts, Lauren Coble, James Vest, Jodi Lewis, Carol Volker, Lynn Byrd, David Martin, Cory Byrd, and Bruno Sobral.
Front row:
Jim Walke, Jana Cranwell, Barbara Waller, Patricia Seeley, and Kim Borkowski.

Administration

VBI's Administrative Team maintains a strong foundation for the Institute, overseeing a wide variety of functions central to the operation of the Institute. The members of the team provide general support for VBI faculty and their research groups and apply their expertise to many areas, including administrative assistance, financial management, and human resources. With such a wide range of roles, the team includes a very diverse group of professionals with extensive backgrounds and experience.

Facilities

VBI's Facilities Team is an integral part of continued growth and evolution of the Institute. The team is actively working with faculty and staff members at VBI, handling space configurations and facilities operations. In addition, the team coordinates with various external authorities and departments in the design, construction, renovation, operation, and maintenance of VBI's facilities. The members of the Facilities Team support all aspects of the Institute's daily functions and are closely involved in all long-term planning.

Left to right: Susan Huckle, Dawn Maxey, Linda Correll, Wilson Barnes, Sheryl Locascio, David Gibbs

Finance

The Finance Team at VBI serves as an important component in the overall financial management of the Institute. Members of the team provide a wide variety of professional financial and support services, including accounting, financial reporting, purchasing, invoice processing, and account reconciliations. The team is comprised of business professionals dedicated to administering sound business and financial management practices to ensure the continued overall success and growth of VBI.

Left to right, back row: Alesha Johnson, Deb Williams, Shelana Ryan
Front row: Kelly O'Rourke, Tina Lawrence, Stacey Walton

Grants and Contracts

VBI's Grants and Contracts Team plays a key role in securing funding for the Institute's transdisciplinary research projects. The team administers guidance and assistance throughout the entire process, beginning with researching and identifying funding opportunities from both federal and private agencies. The team works closely with the Institute's faculty members to provide technical writing, editing, and graphic design assistance, as well as financial reporting and coordination services. Post-award reporting and coordination is also handled by VBI's Grants and Contracts Team, completing this comprehensive support system for the funding process.

Left to right: Darleen Baker, Lauren Coble, Sharon Lawson, June Mullins

Public Relations & Education and Outreach

Left to right:
Barry Whyte, Susan Faulkner, Ivan Morozov, Susan Bland, June Mullins, Morgan Maurer, Alana Manzini, Lea Hamblin

Public Relations

VBI's Public Relations group identifies key audiences for the Institute and implements a research-driven communication program to ensure information about VBI reaches its target groups. Managing the information flow for the Institute to both internal and external audiences is one of the primary responsibilities for this service-oriented group.

VBI e_Connections

In the spring of 2006, the group launched the first issue of VBI e_Connections, VBI's quarterly electronic newsletter. The newsletter serves as an informational resource for VBI's audiences and includes feature articles, technology updates, a review of recent news, as well as a section featuring interviews with individuals connected to the life sciences, such as researchers, authors, faculty, and students.

Institute's second Scientific Annual Report

The group produced VBI's second annual scientific report, which showcases the latest accomplishments of VBI's research faculty during the fiscal year. Researchers at VBI are engaged in a wide range of transdisciplinary research projects that bring together diverse disciplines such as mathematics, computer science, biology, plant pathology, biochemistry, statistics and economics. The report highlights the work of the Institute's researchers and the use of team-based science to implement new innovations and discoveries in many scientific areas including bioinformatics and systems biology.

Services provided by Public Relations

- Media relations
- Annual reports
- Graphic design and illustrations
- Photography
- Editing/proofreading/writing
- Presentations
- Website design and management
- Promotional and marketing materials
- Tours

Media coverage

In the past fiscal year, VBI's communication program resulted in coverage in the following media outlets: Affymetrix User Forum, Bio-Inform newsletter, Bio-IT World, Blue Ridge Business Journal, Clinica, The Collegiate Times, First Science. Com, GenomeWeb News, Ivanhoe Newswire, Medical Technology Business Europe, PC Magazine, The Roanoke Times, Science magazine, Supercomputing online, United Press International, VA newswire (Virginia Biotechnology Association newsletter), WVTF Public Radio (NPR), and other publications. Some of VBI's news has been featured in on-line publications in countries across the globe including Australia, Canada, Germany and the Republic of China. Three special spotlights on innovation were also featured on the Virginia Tech web site and an article entitled "Cyberinfrastructure underpins infectious disease research" appeared in the Virginia Tech Research Magazine.

Education and Outreach

VBI's Education and Outreach group is committed to building strong connections with external audiences and developing education programs that serve as integral components of the Institute's success. The group promotes VBI's involvement in a wide variety of educational programs to the Virginia Tech community and beyond.

Educational opportunities

K through 12

The group hosted VBI's first annual "VBI High School Days" event, with approximately 50 students from area high schools participating in the program, which is designed to encourage interest in science and mathematics. Seven VBI faculty members and their research groups were involved in the activities. The group also coordinates VBI's participation in Montgomery County Public Schools' High School/High Tech program, which is designed to provide students with various types of disabilities with opportunities to explore careers in science, mathematics, and technology.

Two VBI faculty members participated in the Roanoke Valley Governor's School "Research Day," sharing their professional experiences and discussing possible areas of research with students. Chris Lawrence visited the school and gave the students an overview of VBI and his research group, while six students from the school's modeling and simulation course visited VBI. Faculty member Reinhard Laubenbacher met with the students and discussed modeling and simulation of gene regulatory networks.

Undergraduate

VBI has partnered with Bluefield State College and the Galileo Magnet School as part of a $250,000 grant from the National Science Foundation (NSF) to support a forward-looking initiative in education in cyberinfrastructure. Funds from the project have been used to develop and implement an introductory cyberinfrastructure course, broaden students' access to computer-related technologies, and encourage students to pursue careers in informatics-related projects.

The Institute also coordinated systems biology summer research internships for undergraduate student poster presenters at the Society for Advancement of Chicanos and Native Americans in Science (SACNAS) Annual Conference. The SACNAS interns were sponsored by VBI and Virginia Tech's College of Agriculture and Life Sciences.

Summer internships

During the summer of 2006, VBI's faculty and administration members hosted 15 high school and undergraduate interns. These students assisted in a variety of positions, completing laboratory, computational, and administrative duties for the Institute.

Research experiences for teachers

In conjunction with the NSF grant awarded to VBI, Bluefield State College, and Galileo Magnet School to develop a cyberinfrastructure education initiative, three teachers were presented with funding from NSF to provide teacher support for the project, allowing them to work with VBI researchers to develop cyberinfrastructure curriculum.

MARCE training

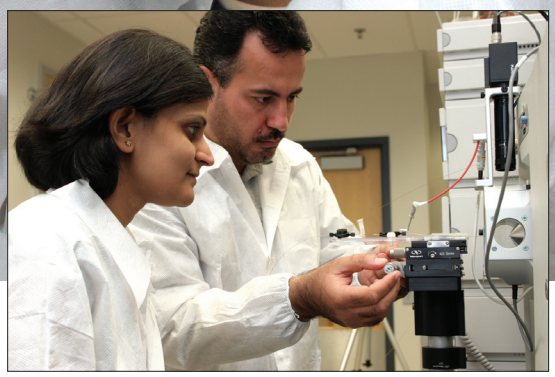
Researchers from VBI's Cyberinfrastructure Group host training sessions for members of the Middle Atlantic Regional Center of Excellence for Biodefense and Emerging Infectious Diseases (MARCE). The group held a comparative genomics training session with 11 attendees from the University of Maryland working on countermeasures against biodefense-related infectious agents.

Conference awards

The group was awarded $15,000 from NSF and $3,000 from the National Institutes of Health for travel and registration expenses associated with the International Symposium on the Comparative Biology of the Alpha-Proteobacteria. This conference focused on the evolutionary adaptations of the genomes of these species and the mechanisms used by these organisms to respond to changes in their environment.

Lab-on-a-chip technology development at VBI

Microfluidic devices have emerged as powerful and reliable analysis platforms for proteomic applications and biomarker screening. The miniature format and ability to manipulate small amounts of sample result in short analysis times and significant reductions in cost.



"The lab-on-a-chip integrates a pump, valve, separation column, and detection interface onto a 3- by 1-inch glass microchip and delivers a performance to match benchtop instrumentation typically occupying a few square feet of lab space."

Iuliana Lazar

The Lazar research group at VBI is working on the development of fully integrated, stand-alone microfluidic devices that integrate mass spectrometric detection for high-throughput proteomic investigations. Iuliana Lazar, assistant professor at VBI and of biology at Virginia Tech, and her group, which consists of microfluidics and mass spectrometry specialist Abdulilah Dawoud and graduate research assistants Nileshwari Vaghela and Yang Xu, are creating such a platform for high-throughput screening and discovery of biomarkers in cancer cells and tissues.

Disposable microchip

The group's efforts have resulted in the development of a disposable microchip that replaces space-consuming instrumentation with fast, cost-effective, lab-on-a-chip technology. This work should open the door for large-scale screening of disease-related protein biomarkers, which are useful as "molecular indicators" for a wide range of diseases. The lab-on-a-chip integrates a pump, valve, separation column, and detection interface onto a 3-by-1-inch glass microchip and delivers a performance to match benchtop instrumentation typically occupying a few square feet of lab space.

Under the research umbrella

"Lab-on-a-chip is still new technology and mostly under the research umbrella," research group member Dawoud explains. "It has the advantage of low-cost and high-speed analysis. We are trying to take it to another level by demonstrating that it can be used in real applications, such as disease-screening, where conventional systems have been used."

According to Lazar, sample, injection, separation, labeling and detection of important biomolecules can be performed with this new technology in only a few minutes, but adds that short analysis time isn't the only advantage to using the microchip. Lazar explains that "Increased specificity and sensitivity are paving the way for high-throughput testing that will, in time, permit screening at the population level for prognostic or diagnostic markers for a whole range of diseases."

Microfluidic device

Microfabrication is emerging as one of the most significant trends in analytical chemistry instrumentation. Microfluidic devices present unique opportunities for integration, multiplexing and handling small sample quantities, and represent an optimal platform for proteomic applications. Progressively smaller, faster, and "smarter" devices with integrated complex detection systems, such as the disposable microchip developed by the Lazar group, are being designed to accommodate the accelerating demand for information-producing, high-throughput instrumentation.

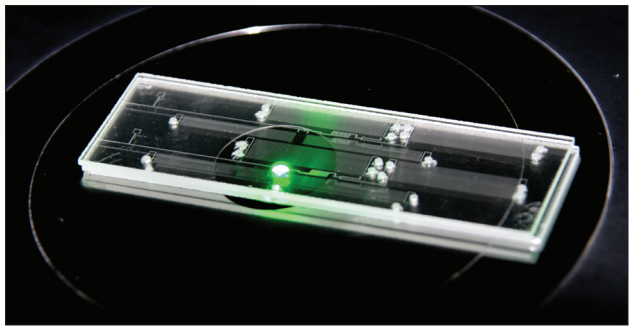
The system designed by Lazar and her team combines liquid chromatographic separation of proteins driven by hundreds of parallel micro- and nanochannels. These channels, which have dimensions in the micrometer domain, serve to generate an electroosmotic flow. This flow of liquid helps to separate the proteins which are then identified by state-of-the-art mass spectrometric detection instruments. To date, researchers in Lazar's laboratory used the microchip to detect more than 2,000 cancer biomarkers in cellular extracts generated from the MCF7 breast cancer cell line. Seventy-seven proteins were identified with confidence, five of which are known to be cancer-specific biomarkers. The fully integrated microfluidic liquid chromatography system has been shown to be suitable for the detection of multiple disease-specific biomarkers.

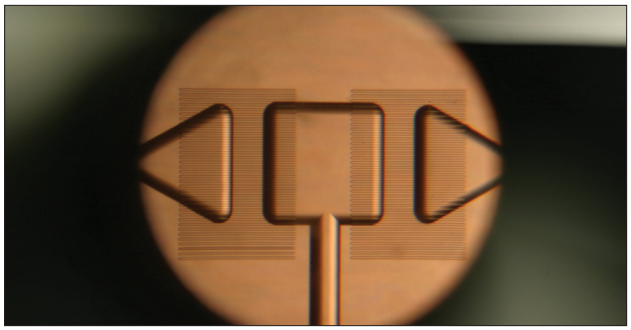
In the future, this approach should pave the way for low-cost, disposable microfluidic platforms suitable for high-throughput screening and discovery of a wide range of biological markers which, in turn, would significantly impact how diseases like breast cancer are diagnosed and treated.

Lazar IM, Trisiripisal P, Sarvaiya HA (2006) Microfluidic liquid chromatography system for proteomic applications and biomarker screening, *Analytical Chemistry*, vol. 78, no. 15: 5513-5524.

About the lab-on-a-chip technology

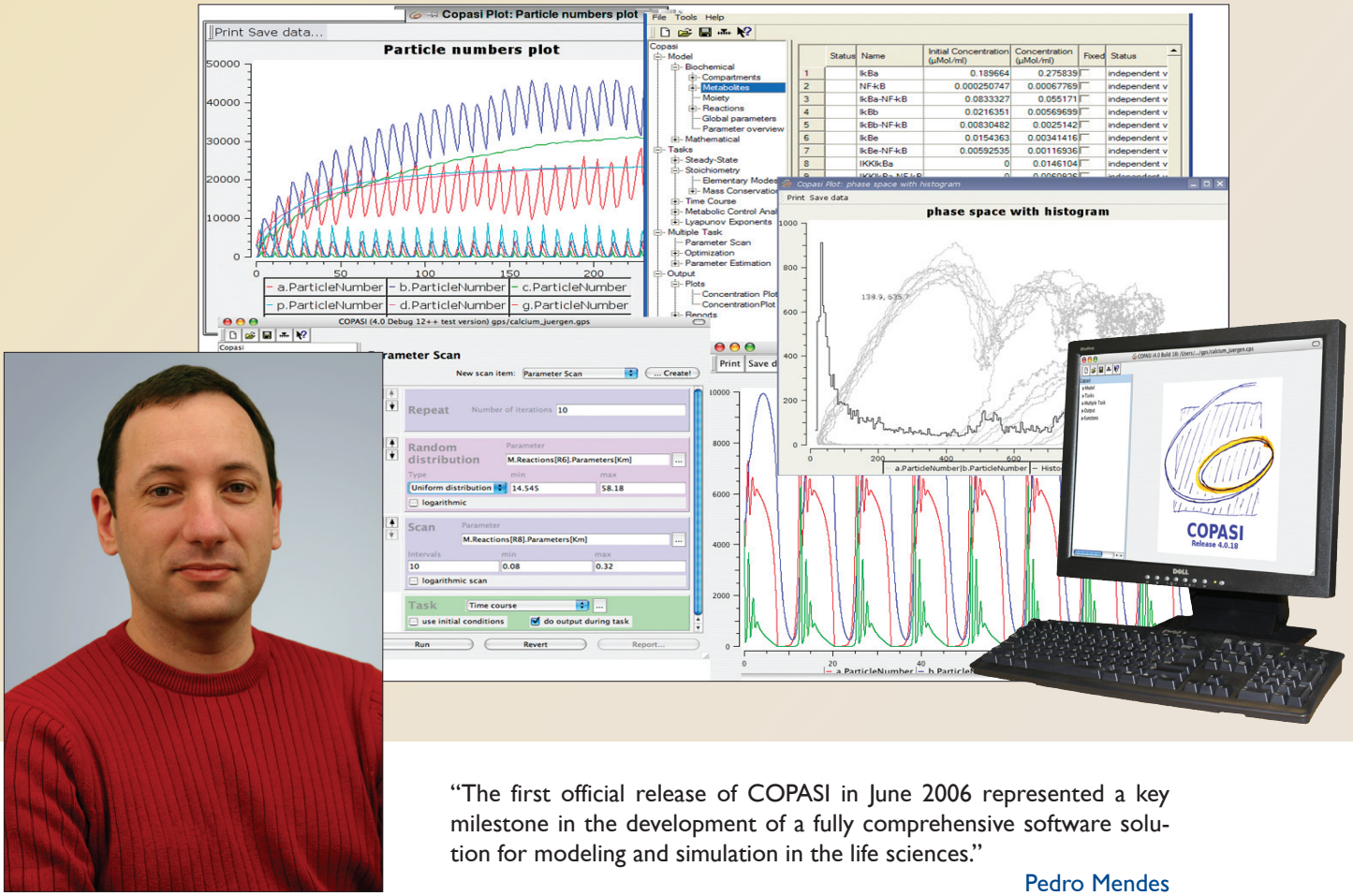
- The system combines liquid chromatographic separation of proteins driven by hundreds of parallel micro- and nanochannels
- The channels, which have dimensions in the micrometer domain, serve to generate an electroosmotic flow
- The electroosmotic flow helps to separate the proteins which are then identified by state-of-the-art mass spectrometric detection instruments
- The microchip is used to detect cancer biomarkers in cellular extracts generated from the MCF7 breast cancer cell line
- 77 proteins have been identified with confidence, five of which are known to be cancer-specific biomarkers
- The fully integrated microfluidic liquid chromatography system has been shown to be suitable for the detection of multiple disease-specific biomarkers





International partnership supports launch of COPASI simulation software

COPASI is a powerful software package that allows users to model, simulate and analyze biochemical and systems biology networks



"The first official release of COPASI in June 2006 represented a key milestone in the development of a fully comprehensive software solution for modeling and simulation in the life sciences."

Pedro Mendes

For EML Research gGmbH in Germany and the Virginia Bioinformatics Institute, June 2006 was a key month in the development of a major software package for biochemical and systems biology modeling. The official launch of the COPASI simulation software was the culmination of six years of intense development work to deliver a versatile, high-performance software package that meets the real needs of the life science community.

COPASI (Complex Pathway Simulator) is a software package that allows scientists to model, simulate and analyze biochemical and systems biology networks. One of the key objectives in launching COPASI has been to make available an easy to use software tool that targets the wider biological community. Cells are complex, dynamic structures that undergo a myriad of biochemical reactions. To understand the behavior of the molecules that make up these systems, scientists need tools that can model and simulate the many reactions taking place. Modeling and simulation allow scientists not only to improve their understanding of these systems but also serve as a starting point to develop practical applications for their research.

Modeling involves identifying the chemical players in specific metabolic reactions and specifying the chemical reactions that either consume or produce those substances. Once a mathematical description of the rate of change of these reactions can be determined, a computer can be used to simulate the model under investigation. COPASI strives to provide an easy-to-use interface that can be used by scientists that may not have expert knowledge of the advanced algorithms or set of mathematical instructions that lie behind the COPASI interface.

A versatile tool

COPASI, which supports the Systems Biology Markup Language (SBML) standard for systems biology software, enables researchers to investigate how a system is working by allowing them to construct biochemical models, reproduce experimental results and justify the validity of the chosen model. COPASI simplifies the task of model building by assisting the user in translating the language of chemistry (reactions) to mathematics (matrices and differential equations). The user-friendly interface is combined with a set of sophisticated numerical algorithms that assure the results are obtained quickly and accurately. COPASI simulates the kinetics of systems of biochemical reactions and provides a number of tools to fit models to data, optimize any function of the model, and perform metabolic control analysis and linear stability analysis.

International collaboration

The launch of COPASI has been made possible by an international collaboration between EML Research, Germany, and the Virginia Bioinformatics Institute. Pedro Mendes, associate professor at VBI, remarked: "We have been working closely with Ursula Kummer's group at EML Research to deliver an open-source software package that aids in the understanding of cellular and molecular behavior and which facilitates the quantitative interpretation of modern experiments. Today, the research community that we hope to reach with COPASI is a global one. The further development of COPASI will involve collaboration from scientists in different countries and in different disciplines. Transdisciplinary research of this type is part of the mandate of our Institute."

Situated in Heidelberg, Germany, EML Research gGmbH is a non-profit institute conducting research in information technology and its applications. The institute has a strong focus on bioinformatics and research is carried out in close collaboration with universities and other research institutes. EML Research projects are supported by the Klaus Tschira Foundation, as well as by the European Union, the German Ministry of Research and Education and by the German Research Foundation. The institute is housed in the Villa Bosch in Heidelberg, the former residence of Nobel Prize laureate Carl Bosch.

Dr. Ursula Kummer, principal investigator at EML Research, commented: "Simulation and modeling are becoming increasingly important tools in systems biology research and can be used to test the physical and chemical limitations as well as feasibility of a wide range of biochemical reactions. We anticipate that COPASI will prove invaluable to researchers not only in simulating increasingly complex networks but also in helping to understand how external factors, for example drugs, impact metabolic systems." She added: "We have already seen many applications from our existing user community and expect many more due to COPASI's inherent flexibility for top-down and bottom-up modeling."

The software may be freely downloaded at www.copasi.org for non-commercial purposes.

Systems Biology at VBI

Systems biology research at VBI is a core component of the Institute's transdisciplinary scientific program. For example, Dr. Pedro Mendes, Dr. Reinhard Laubenbacher and Dr. Vladimir Shulaev of VBI are jointly engaged in a yeast systems biology project to infer biochemical networks from systems-wide experimental measurements. This project integrates modeling and data generation processes by focusing on the regulatory network in *Saccharomyces cerevisiae* which is involved in the response to oxidative stress. Modeling and simulation of biochemical networks are essential activities to aid in the understanding of cellular behavior and to facilitate quantitative interpretation of modern systems biology-oriented experiments.

Photo: Peter Saueressig/EML Research

Left to right: Jilan Stoleriu, Femke Mensonides, Ralph Gauges, Juergen Pahle, Sven Sahle, Irina Surotsova, Ursula Kummer, Tim Johann, Andreas Weidemaier, Natalia Simus, Ursula Rost

About COPASI (Complex Pathway Simulator)

- Software package that allows the simulation and detailed analysis of biochemical networks
- Available for use on Windows, Macintosh, Linux and Solaris operating systems
- Based on original software developed by Pedro Mendes (Gepasi) and on the STODE software developed at EML Research
- The main authors of COPASI are Drs. Stefan Hoops, Sven Sahle, and Ralph Gauges
- Incorporates a model editor, different simulation techniques (e.g. deterministic and stochastic), optimization routines, sensitivity analysis and user-friendly visualization techniques
- Supports the Systems Biology Markup Language (SBML) standard for systems biology software

Research groups

Dr. Christopher Barrett

Dr. Allan Dickerman

Dr. Ina Hoeschele

Dr. Reinhard Laubenbacher

Dr. Christopher Lawrence

Dr. Iuliana Lazar

Dr. Pedro Mendes

Dr. Biswarup Mukhopadhyay

Dr. Dharmendar Rathore

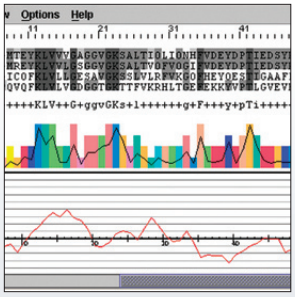
Dr. David Samuels

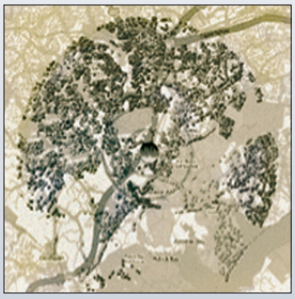
Dr. João Setubal

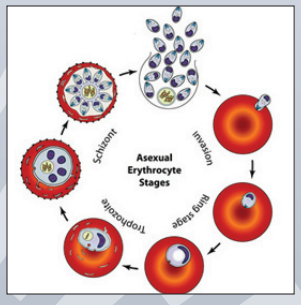
Dr. Vladimir Shulaev

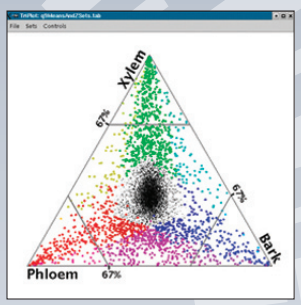
Dr. Bruno Sobral

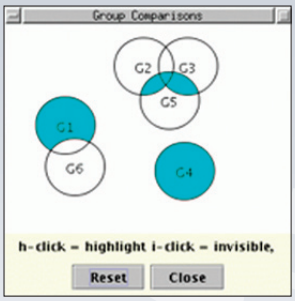
Dr. Brett Tyler

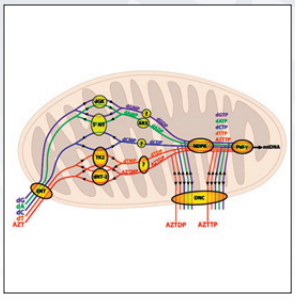












Dr. C. Barrett

Network Dynamics and Simulation Science Laboratory

Left to right, back row:
Christopher Barrett, Richard Beckman, Stephen Eubank, Henning Mortveit, Anil Kumar Vullikanti, Bryan Lewis, Martin Holzer
Front row:
Julia Paul, Keith Bisset, Madhav Marathe, Paula Stretz, Achla Marathe, Karla Atkins, Jiangzhuo Chen

Extremely detailed, multi-scale computer simulations allow formal and experimental investigation of large-scale systems.

The Network Dynamics and Simulation Science Laboratory designs, develops and implements simulation tools to understand large biological, information, social, and technological systems. For many reasons, which range from practical difficulty to the possibility of great harm, simulations are a uniquely capable medium in which representation and analysis can be performed. The need for simulations is derived from questions posed by scientists, policy makers, and planners involved with very large complex systems. Extremely detailed, multi-scale computer simulations allow formal and experimental investigation of large-scale systems. By enabling individuals to explore the potential impact of different interventions or strategies on the course of a disease outbreak or a specific transportation scenario, for example, important information can be prioritized as to the potential merits of different interventions.

The Network Dynamics and Simulation Science Laboratory is currently pursuing projects in the following programmatic areas: integrated high-performance simulation and data service architectures; human population dynamics and associated social networks in urban environments and at the national scale; epidemiology and the spread of infectious diseases; computational and behavioral economics and commodity markets; next generation computing and telecommunication systems; and computational systems biology.

The group has developed Simfrastructure, a service- and grid computing-oriented modeling tool for socio-technical, biological, and information systems and Simdemics, a scalable high-performance computing-based service environment for general reaction diffusion systems. Other recent milestones include the successful development of scalable algorithms for simulating epidemics and other reaction diffusion systems. A synthetic population has been created consisting of 300 million individuals endowed with daily activity patterns where the activities are performed at real locations. The EpiSims tool is being used by the National Institutes of Health Models of Infectious Disease Agent Study to support preparedness for potential disease pandemics.

Research Interests

- Interaction-based simulation for modeling very large complex systems
- Parallel and distributed computing
- Simulation, modeling and analysis of infectious diseases, epidemiology and public health issues
- Large social and biological networks, molecular and system biology
- Population dynamics
- Cognitive science and decision support
- Theoretical computer science, computational complexity and probabilistic, distributed and approximation algorithms, formal specifications
- Combinatorics, algebra, discrete dynamical systems
- Statistics and design of simulation experiments
- Computational and behavioral economics, commodity and energy markets

Publications

Barrett C, Eubank S, Marathe M (2006) Modeling and simulation of large biological, information and socio-technical systems: an interaction based approach. In *Interactive Computing: A New Paradigm*, Goldin D, Smolka S, Wegner P (eds) Springer Verlag.

Bisset K, Eubank S, Marathe M, Mortveit M (2005) The design and implementation of Simdemics. *NDSSL Technical Report*. 05-017.

Bisset K, Atkins K, Barrett C, Beckman R, Eubank S, Marathe M, Marathe A, Mortveit H, Stretz P, Anil Kumar VS (2006) Synthetic data products for societal infrastructures and proto-populations: Data Set 1.0. *NDSSL Technical Report*. 06-006: January 24.

Network Dynamics and Simulation Science Laboratory

Faculty members working with Chris Barrett in the Network Dynamics and Simulation Science Laboratory.

Stephen Eubank

Stephen Eubank is deputy director, Network Dynamics and Simulation Science Laboratory and adjunct professor, Department of Physics at Virginia Tech. His work includes fluid turbulence; nonlinear dynamics and chaos; time series analysis of markets (as a founder of Prediction Company); natural language processing (as Visiting Scientist at ATR in Kyoto, Japan); and simulations of large interaction-based systems. As a staff member at Los Alamos National Laboratory, he played a leading role in the development of the traffic microsimulation component of the Transportation Analysis and Simulation System (TRANSIMS), developed the Epidemiological Simulation (EpiSims) project, and served as team leader for the Urban Infrastructure Suite (UIS), of which both TRANSIMS and EpiSims are parts. Since arriving at VBI in January, 2005, he has pursued interests both in developing advanced technology for the study of realistic socio-technical systems and also in understanding how the dynamics of diffusive processes on networks, e.g. disease transmission, are related to the structure of the underlying networks. He is the Principal investigator on one of the research groups making up the NIH's MIDAS (Modeling Infectious Disease Agent Study) network.

Achla Marathe

Achla Marathe joined the Virginia Bioinformatics Institute and Virginia Tech's Department of Agricultural and Applied Economics as an associate professor in January 2005. She received her B.A. (Honors) in Economics from Delhi University, India, and a Ph.D. in Economics from the University at Albany. Before joining Virginia Tech, she worked at Los Alamos National Laboratory for ten years, initially as a postdoctoral fellow and then as a technical staff member. At Los Alamos, Dr. Marathe worked on and led a number of projects in economics and data mining. Prior to joining Los Alamos National Laboratory, Dr. Marathe consulted for International Finance Corporation, World Bank Group, where her work focused on emerging equity markets.

Henning Mortveit

Henning Mortveit joined Virginia Tech in 2005 as a senior research associate in the Network Dynamics and Simulation Science Laboratory at the Virginia Bioinformatics Institute, and assistant professor in the Department of Mathematics at Virginia Tech. Mortveit received his doctorate in mathematics from the Norwegian University of Science and Technology in 2000, and spent five years at Los Alamos National Laboratory, first as a postdoctoral fellow and then as a technical staff member. His current research is focused on the area of finite dynamical systems, with an emphasis on sequential dynamical systems and generalized cellular automata. This class of systems represents a natural framework and modeling tool for biological systems, social systems, and distributed systems. He is also involved in the study and implementation of large-scale, generalized cellular automata on new computing architectures such as field programmable gate arrays.

Madhav Marathe

Madhav Marathe is a professor of Computer Science at Virginia Tech and deputy director of the Network Dynamics and Simulation Science Laboratory. He obtained his Bachelor of Technology degree in 1989 in Computer Science and Engineering from the Indian Institute of Technology, Madras, and his Ph.D. in 1994 in Computer Science from the University at Albany. Before coming to Virginia Tech in 2005, he worked in the Basic and Applied Simulation Science group (CCS-5) in the Computer and Computational Sciences division at Los Alamos National Laboratory, where he was team leader in a theory-based, advanced simulation program to represent, design, and analyze extremely large socio-technical and critical infrastructure systems. He has over eight years of experience in project leadership and technology development, specializing in population dynamics, telecommunication systems, epidemiology, design and architecture of the data grid, design and analysis of algorithms for data manipulation, design of services-oriented architectures, and socio-technical systems.

Anil Vullikanti

Anil Vullikanti is senior research associate in the Network Dynamics and Simulation Science Laboratory at the Virginia Bioinformatics Institute, and assistant professor in the Department of Computer Science at Virginia Tech. He received his Ph.D. in Computer Science from the Indian Institute of Science in 1999 and was a postdoctoral associate at the Max-Planck Institute and at the Los Alamos National Laboratory, where he became a technical staff member in 2003. His current interests are at the interface of theoretical computer science and modeling and simulation of social and infrastructure systems, epidemiology, and mobile computing.

Dr. A. Dickerman

Phylogenomics Research Group

Left to right:
Johanna Craig, Allan Dickerman, Elena Shulaeva

By using phylogenetic models, researchers can identify patterns of diversification in gene sequences that relate to changes in function.

Research Interests

- Phylogenetic approaches to comparative genomics
- Gene expression programs in *Arabidopsis* embryogenesis
- Pathogen identification by microarrays of rRNA probes

Publications

Tyler BM, Tripathy S, Zhang X, Dehal P, Jiang RHY, Aerts A, Arredondo F, Baxter L, Bensasson D, Beynon JL, Chapman J, Damasceno CMB, Dickerman A, Dorrance AE, Dou D, Dubchak I, Garbelotto M, Gijzen M, Gordon S, Govers F, Grunwald N, Huang W, Ivors K, Jones RW, Kamoun S, Krampis K, Lamour K, Lee MK, McDonald WH, Medina M, Meijer HJG, Nordberg E, Maclean DJ, Ospina-Giraldo MD, Morris P, Phuntumart V, Putnam N, Rash S, Rose JKC, Sakihama Y, Salamov A, Savidor A, Scheuring C, Smith B, Sobral BWS, Terry A, Torto-Alalibo T, Win J, Xu Z, Zhang H, Grigoriev I, Rokhsar D, Boore J (2006) *Phytophthora* genome sequences uncover evolutionary origins and mechanisms of pathogenesis. *Science* **313**(5791)1261-1266.

Zhao C, Craig JC, Petzold HE, Dickerman AW, Beers EP (2005) The xylem and phloem transcriptomes from secondary tissues of the *Arabidopsis* root-hypocotyl. *Plant Physiol.* **138**(2): 803-818.

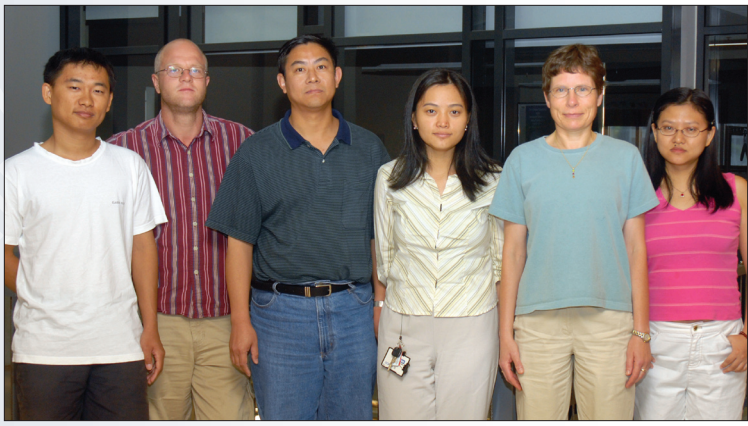
Phylogenomics involves the study of evolutionary relatedness among various groups of organisms. The idea that a common ancestry links all living organisms has been an integral part of biological research long before it became possible to compare sequence information. Full gene sequences of many organisms have now been completed, providing researchers with opportunities to identify more specific ancestral connections using genes, chromosomes and whole genome sequences. Phylogenomics is thus enabling the analysis of the similarities and differences of many species in an evolutionary context. By using phylogenetic models, researchers can identify patterns of diversification in gene sequences that relate to changes in function.

A major focus of Dr. Allan Dickerman's Research Group is the creation of analysis tools needed to construct the history of common ancestry for all of the components of genomes within a particular area of interest. For this purpose, the "GeneTrees" database focuses on the alignment of protein sequences in an effort to obtain evolutionary histories. This project has created external collaborations with scientists interested in a wide range of organisms and their classification. In addition, the group's "SeedGenes" project is near completion. This project focuses on the bioinformatic and functional analysis of genes active in the early development of plant seeds. More specifically, "SeedGenes" was developed to examine essential gene functions of the model organism *Arabidopsis thaliana* and includes a web interface that offers information on all the proven early developmental lethal mutations in *Arabidopsis*. This coordinated effort has resulted in the collection and analysis of information related to the function of *A. thaliana's* genes and the results have been synthesized for efficient use by the scientific community.

Dr. I. Hoeschele

Statistical Genetics Research Group

Left to right:
Hailong Cui, Alberto De La Fuente, Yongcai Mao, Bing Liu, Ina Hoeschele, Lucia Gan



The common thread of research in Dr. Hoeschele's group is the desire to understand how the joint action and interaction of multiple genes determines complex phenotypes.

Statistical genetics provides a way to understand how the joint action and interaction of many genes determines complex traits and diseases in animal, human and plant populations. Dr. Ina Hoeschele's group designs and analyzes large-scale gene expression experiments, including linear mixed model analysis of complex designs and inference of gene interaction networks. A continued, long-standing interest of the group is the development of statistical and computational methods for haplotype inference and joint linkage and linkage disequilibrium mapping of quantitative trait loci (QTL) in complex pedigrees. Researchers in Dr. Hoeschele's group have recently compared methods for the mapping of expression QTL (eQTL) in genetical genomics experiments, and designed statistical algorithms using local structural models for inference of a causal, encompassing gene network based on eQTL analysis. The group is investigating structural equation modeling for inference of sparse, causal networks in genetical genomics and systems genetics experiments.

These statistical and computational methods are currently being applied to a genetical genomics experiment conducted in the laboratory of Professor Brett Tyler at VBI in collaboration with Virginia Tech and The Ohio State University researchers, in which a soybean recombinant inbred line population infected with the pathogen *Phytophthora sojae* is phenotyped for quantitative disease resistance, genotyped for genetic markers, and expression profiled using an Affymetrix GeneChip® containing comprehensive probe sets for soybean and *P. sojae*. Another application is a mouse model of human lung cancer developed by researchers in the Department of Cancer Biology at Wake Forest University.

Research Interests

- Quantitative trait locus (QTL) mapping in inbred line crosses and complex pedigrees
- Statistical design and analysis of microarray expression experiments
- Expression QTL mapping
- Reconstruction of causal gene networks in genetical genomics experiments
- (Co)Variance components estimation in mixed models and Markov chain Monte Carlo simulation

Publications

Betthauser JM, Pfister-Genskow M, Xu H, Gouleke PJ, Lacson JC, Koopang RW, Liu B, Hoeschele I, Eilertsen KJ, Leno GH (2006) Nucleoplasmin facilitates reprogramming and *in vivo* development of bovine nuclear transfer embryos. *Molecular Reproduction and Development* **73**(8):977-986

Bing N, Hoeschele I (2005) Genetical genomics analysis of a yeast segregant population for transcription network inference. *Genetics* **170**: 533-542.

Gao G, Hoeschele I (2005) Approximating identity-by-descent matrices using multiple haplotype configurations on pedigrees. *Genetics* **171**: 365-376.

Dr. R. Laubenbacher

Applied Discrete Mathematics Research Group

Left to right, seated:
Dedra LaShawn Wright, Abdul Salam Jarrah, Paola Vera-Licona
Standing:
Miguel Colón-Velez, Alan Veliz-Cuba, Reinhard Laubenbacher, Blessilda Raposa, Elena Dimitrova, Edgar Delgado-Eckert

One of the fundamental challenges in systems biology is to infer biochemical networks from system-wide experimental measurements.

Research Interests

- Modeling and simulation of biological networks
- Dynamical systems theory
- Reverse-engineering of networks
- Yeast systems biology

Publications

Babson E, Barcelo H, Delongueville M, Laubenbacher R (2006) Homotopy theory of graphs, *J.Algebraic Combinatorics* http://arxiv.org/abs/math/0403146.

Garcia L, Jarrah AS, Laubenbacher R (2006) Sequential dynamical systems over words, *Appl. Math.Comp.* **174**: 500-510.

Laubenbacher R (2005) System identification of biochemical networks using discrete models. In *Computation of Biochemical Pathways and Networks*, Kummer U (ed), pp. 87-94. Berlin: Petronius Verlag.

Laubenbacher R (2005) Algebraic models in systems biology. In *Algebraic Biology 2005*, Anai H, Horimoto K (eds) pp. 33-40. Tokyo: Universal Academy Press, Inc.

Laubenbacher R, Mendes P (2005) A discrete approach to top-down modeling of biochemical networks. In *Computational Systems Biology*, Eils R, Kriete A (eds) pp. 229-247. Burlington, MA: Elsevier.

Laubenbacher R, Pareigis B (2006) Update schedules of sequential dynamical systems, *Discr.Appl. Math.* 54: 980-994.

Researchers are looking at the relationships and interactions between the various parts of biological systems in an effort to understand their entirety. However, creating a comprehensive picture of biochemical networks by examining the components of systems, such as gene regulatory, metabolic, protein, and signaling networks, is one of the major hurdles in the area of systems biology. The Applied Discrete Mathematics Group, which is led by Dr. Reinhard Laubenbacher, is developing mathematical tools to help solve this problem. The group uses system-level experiments, such as the collection of time course data from DNA microarray measurements, to design mathematical models of the biochemical networks that influence these measurements. This construction of network structure models using high-throughput data is referred to as "top-down" modeling.

The group uses techniques from discrete mathematics and symbolic computation that are utilized in open-source symbolic computation software. Researchers in the group are currently working with VBI faculty members Drs. Pedro Mendes and Vladimir Shulaev on a project involving the creation of a new modeling approach to biochemical networks. Dr. Laubenbacher's group is developing computation methods to reverse-engineer biochemical networks which are then applied to genomic, proteomic, and metabolomic data with a specific focus on the oxidative stress network in the yeast *Saccharomyces cerevisiae*. In another project, mathematical tools developed by the group are being used for the analysis of agent-based models of immune response to Epstein-Barr virus infection. The long-term goal is to create systematic methods for determining interventions that modify immune response in order to achieve desired outcomes.

The Applied Discrete Mathematics Group is currently focusing on the theoretical aspects of their methods and is also working to develop a comprehensive, user-friendly software package for the reverse-engineering of biochemical networks.

Dr. C. Lawrence Research Group

Left to right, standing:
Mihaela Babiceanu, Mauricio La Rota, Graciela Santopietro, Chris Lawrence and Kwang-Hyung Kim
Seated:
Derrick Scott and Yangrae Cho

Necrotrophs comprise the largest class of fungal plant pathogens and have a negative economic impact on important crops including canola, cabbage and broccoli.

The Lawrence research group studies the way in which necrotrophic fungi lead to plant and human disease. Infection with necrotrophic fungi can result in some of the most destructive of plant diseases that are sometimes referred to as the "rots". In humans, exposure to airborne fungi may result in chronic airway diseases such as asthma, allergy and chronic rhinosinusitis. Necrotrophs comprise the largest class of fungal plant pathogens and have a negative economic impact on important crops including canola, cabbage and broccoli. Although they represent just 4% of fungal diversity, necrotrophs cause around 80% of foliar losses due to fungal diseases in some parts of the world. Necrotrophic fungi inflict substantial tissue damage on their hosts since most of the nutrients required for completion of their lifecycle arise from dying or dead tissue.

To study the plant-pathogen interaction, researchers in the Lawrence laboratory examine the way the necrotrophic fungus *Alternaria brassicicola* interacts with the model flowering plant *Arabidopsis* as well as closely related *Brassica* crops. Functional genomic methods are used to dissect the molecular events involved in infection, identify fungal genes involved in pathogenesis, and determine the plant genes involved in disease susceptibility and resistance.

Humans are constantly exposed to *Alternaria* and other airborne fungi. The Lawrence group, in collaboration with the Mayo Medical School, studies the role of *Alternaria* in chronic airway diseases such as asthma, allergy, and chronic rhinosinusitis. The goal of this research is to help in the understanding of the role of fungi in modulating immune responses in humans and, ultimately, assist in the design and discovery of novel therapeutics for treating fungal-associated conditions.

By closely studying the interactions of fungi with plants and humans, the Lawrence research group hopes to significantly advance the current level of understanding of host-pathogen interactions and open up new opportunities for biomedical and agricultural research.

Research Interests

- The *Alternaria-Brassicaceae* pathosystem as a model for necrotrophic fungal-plant interactions
- The genome sequence of the model nectrophic fungus *Alternaria brassicicola*
- The role of *Alternaria* in chronic respiratory disorders
- Fungal biotechnology

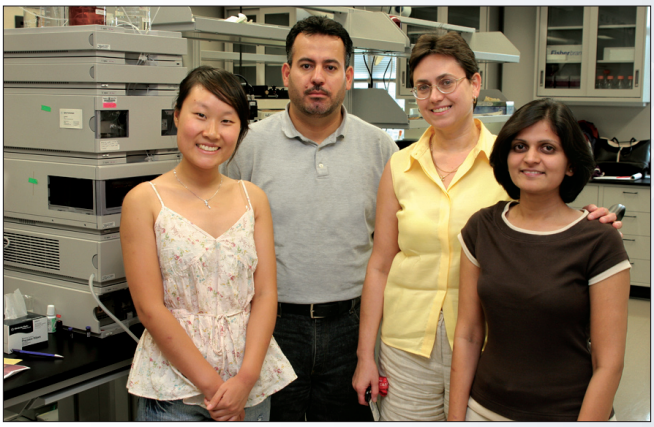
Publications

Cramer RA, La Rota CM, Thon M, Cho Y, Craven KD, Knudson DL, Mitchell TK, Lawrence, CB (2006) Bioinformatic analysis of expressed sequence tags derived from a compatible *Alternaria brassicicola– Brassica oleracea* interaction. *Molecular Plant Pathology* **7**: 113-124.

Cho Y, Davis JW, Kim K, Wang J, Sun Q, Cramer RA, Lawrence, CB (2006) A high throughput targeted gene disruption method for *Alternaria* functional genomics using Linear Minimal Element (LME) constructs. *Molecular Plant-Microbe Interact.* **19**: 7-15.

Hong SG, Cramer RC, Lawrence CB, Pryor BM (2005) Alta1 allergen homologs from *Alternaria* and related taxa:analysis of phylogenetic content and secondary structure. *Fungal Genetics and Biology* **42**: 119-129.

Li Q-S, Lawrence CB, Xing H, Davies M, Everett NP (2006) Increased pathogen resistance and yield in transgenic plants expressing combinations of the modified antimicrobial peptides based on indolicidin and magainin. *Planta* **223**: 1024-1032.



Dr. I. Lazar

Research Group

Left to right:
Yang Xu, Abdulilah Dawoud, Iuliana Lazar, Nileshwari Vaghela

The long-term objective in the Lazar research group is to develop a microfluidic platform that integrates mass spectrometry detection.

Research Interests

- Development of fully integrated, stand-alone microfluidic devices with mass spectrometry (MS) detection for high-throughput proteomic investigations
- Development of bioanalytical strategies for global proteomic profiling of cancer cells and tissues: qualitative profiling, differential protein expression analysis, and characterization of post-translational modifications
- Development of microfluidic-mass spectrometric platforms for cancer biomarker discovery and screening

Publications

Lazar IM, Grym J, Foret F (2006) Microfabricated devices: a new sample introduction approach to mass spectrometry. *Mass Spectrom. Rev.* **25**(4): 573-594.

Lazar IM, Trisiripisal P, Sarvaiya HA (2006) Microfluidic liquid chromatography system for proteomic applications and biomarker screening, *Analytical Chemistry* **78**(15): 5513-5524.

MCF7 Cell Line-Proteome Profile and Cancer Biomarkers, the HUPO 2nd Annual Conference, Boston, MA, USA, March 11-15, 2006.

Microfluidic Architectures for Novel Separation Designs, 28th International Symposium on Capillary Chromatography and Electrophoresis, Las Vegas, NV, USA, May 22-25, 2005.

Microfluidic LC System for the Analysis of Proteomic Constituents in Cancerous Cell Lines, 53rd Conference on Mass Spectrometry and Allied Topics, San Antonio, TX, USA, June 5-9, 2005.

Microfluidic Devices for the Identification of Biomarkers from Cancerous Cell Lines, the National Cancer Institute (NCI) sponsored conference on Moving Biosensors to Point-of-Care Cancer Diagnostics, Rockville, MD, USA, June 8-9, 2005.

New technologies are urgently needed to enable the fast and cost-effective discovery of biological disease markers. The detection, prevention and treatment of disease would be significantly improved if these devices could offer improved specificity and sensitivity of measurement compared with existing technologies.

The long term objective of Dr. Lazar's research is to combine the emerging technology of microfluidics with state-of-the-art mass spectrometry detection to enhance capacity for analyzing the molecular mechanisms that contribute to cancer on-set and development. This high-throughput platform would be used for the screening and possible discovery of biomarkers in cancer cells and tissues. In spite of intense research, very few biomarkers are used in clinical practice. The discovery of new molecular markers for the early detection of different forms of cancer would have a profound effect on the survival rates of cancer patients.

Research in Dr. Lazar's laboratory focuses on two main areas: the development of fully integrated, stand-alone microfluidic devices that integrate mass spectrometric detection for high-throughput proteomic investigations and the development of bioanalytical strategies for the global profiling of proteins in cancer cells and tissues. These microfluidic devices, which can be made from glass, allow increased sensitivity and specificity for proteomic assays. Microfluidic chips can be easily integrated into mass spectrometric instruments. In the Lazar laboratory, more than 2000 proteins have been identified in breast cancer cell line MCF7 using an internally developed protocol for such a system. Two hundred and twenty of these proteins were deduced to be involved in cancer-related processes by examining their biological function; 25 of these proteins were previously described in scientific publications as putative cancer biomarkers. The use of microfluidic liquid chromatography-mass spectrometric analysis enabled 39 proteins and five cancer-specific biomarkers to be identified in a protein rich sub-fraction obtained from the MCF7 cell line. In the future, this approach should pave the way for low-cost, disposable microfluidic platforms suitable for high-throughput screening and discovery of biological markers. This should significantly impact the detection, prevention and treatment of diseases like breast cancer.

Dr. P. Mendes

Biochemical Networks Modeling Group

Left to right, back row:
Pedro Mendes, Stefan Hoops, Revonda Pokrzywa, Kimberly Heard, Aejaaz Kamal, Diogo Camacho, Autumn Clapp, Bharat Mehrotra
Front row:
Xing Jing Li, Hui Cheng, Saroj Mohapatra, Ana Martins, Adaoha Ihekwaba

Dr. Pedro Mendes' Research Group focuses on computer modeling, simulation and the analysis of biochemical networks.

Modeling and simulation of biochemical networks are invaluable tools used by researchers to investigate cellular behavior and help in the interpretation of data arising from quantitative experiments. Systems biology brings together modeling, simulation and quantitative experiments under one umbrella, allowing researchers to use the data of one of these approaches to repeatedly define the framework of the other approaches.

Dr. Pedro Mendes' Research Group focuses on computer simulation and the analysis of biochemical networks. Researchers in Dr. Mendes' laboratory, in collaboration with the Kummer group at EML Research, have developed the COPASI software to model and simulate biochemical networks. COPASI, which supports the Systems Biology Markup Language standard for systems biology software, enables researchers to investigate how a system is working by allowing them to construct biochemical models. One of COPASI's main features is the ability to automatically adjust model parameters to reproduce experimental results, which helps to justify the validity of the chosen model.

Bottom-up and top-down modeling are the two main methods used to create models of biochemical networks. Bottom-up modeling uses *in vitro* kinetic properties of enzymes in the network to form a model of the entire pathway. In collaboration with VBI faculty members Drs. Reinhard Laubenbacher and Vladimir Shulaev, the group is developing a method to characterize every isoenzyme of an important pathway in yeast that plays a major role in metabolism and the response of yeast to various stresses, particularly oxidative stress. This work will aid the group in building a comprehensive model of the pentose-phosphate pathway. Top-down modeling is based on reverse-engineering the pathway dynamics using measurements of the system's response to environmental or genetic perturbations. The group has continued work in this area, developing a database to store large-scale systems biology data, applying several algorithms for data analysis and reduction, and developing a method for inference of biochemical models from time course data.

The ability to organize and analyze data from large-scale technologies is another important task in the area of systems biology. Dr. Mendes' group provides the tools needed to manage this type of data and is continuing to develop DOME, a client-server system that manages and integrates transcriptomic, proteomic and metabolomic data.

Research Interests

- Biochemical modeling and simulation software development
- Bottom-up model building based on enzyme kinetics
- Top-down model building based on "omic" data sets
- Management and analysis of functional genomic and systems biology data sets
- Metabolomic data analysis using statistical and machine learning methods

Publications

Cramer GR, Cushman JC, Schooley DA, Quilici D, Vincent D, Bohlman MC, Ergul A, Tattersall EAR, Tillett R, Evans J, Delacruz R, Schlauch K, Mendes P (2005) Progress in bioinformatics – the challenge of integrating transcriptomic, proteomic and metabolomic information. In *Proceedings of the VII International Symposium on Grapevine Physiology and Biotechnology,* International Society for Horticultural Science, *Acta Horticulturae* vol. 689 Williams LE (ed) pp. 417-425.

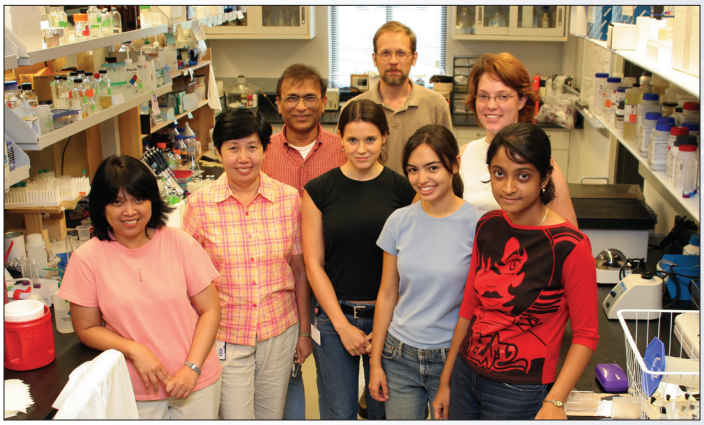
Laubenbacher R, Mendes P (2005) A discrete approach to top-down modeling of biochemical networks. In *Computational Systems Biology,* Eils R, Kriete A (eds) pp. 229-247. Burlington, MA: Elsevier.

Lei Z, Elmer AM, Watson BS, Dixon RA, Mendes P, Sumner LW (2005) A two-dimensional electrophoresis proteomic reference map and systematic identification of 1367 proteins from a cell suspension culture of the model legume *Medicago truncatula*. *Mol. Cell. Proteomics* **4**: 1812-1825.

Mendes P, Camacho D, de la Fuente A (2005) Modelling and simulation for metabolomics data analysis. *Biochem. Soc. Trans.* **33**: 1427-1429.

Novere NL, Finney A, Hucka M, Bhalla US, Campagne F, Collado-Vides J, Crampin EJ, Halstead M, Klipp E, Mendes P, Nielsen P, Sauro H, Shapiro B, Snoep JL, Spence HD, Wanner BL (2005) Minimum information requested in the annotation of biochemical models (MIRIAM). *Nature Biotechnol.* **23**: 1509-1515.

Rodriguez-Fernandez M, Mendes P, Banga JR (2005) A hybrid approach for efficient and robust parameter estimation in biochemical pathways. *Biosystems* **83**: 248-265.



Dr. B. Mukhopadhyay

Research Group

Left to right, front row:
Endang Purwantini, Francisca Tanoerahardjo, Hannah Glasson, Jennifer Stieber, Lakshmi Dharmarajan
Back row:
Biswarup Mukhopadhyay, Eric Johnson, Jessica Kraszewski

Additional laboratory members are shown below

Microorganisms have adopted diverse strategies and biochemical mechanisms to survive hostile environments.

Research Interests

- Remnants of ancient metabolism in archaea
- Evolution of metabolism
- Methanogenesis
- Coal bioconversion to methane and mitigation of methane-induced mine explosion
- Tuberculosis
- Type 2 diabetes
- Phosphoenolpyruvate carboxylase and phosphoenolpyruvate carboxykinase

Publications

Johnson EF, Mukhopadhyay B (2005) A new type of sulfite reductase, a novel coenzyme F420-dependent enzyme, from the methanarchaeon *Methanocaldococcus jannaschii*. *J. Biol. Chem*. **280**: 38 776-38 786.

Left to right, top row:
Christopher Case, Deanna Colton, Caitlyn Criss, Ashley Hoffman
Bottom row:
Karla Piedl, Ashley Shifflett, Dwi Susanti, Ban Wang

Dr. Biswarup Mukhopadhyay's research group studies the biochemical mechanisms used by microorganisms to survive under extreme conditions. Research in the laboratory focuses on methanogenic archaea, tuberculosis, coalbed methane and type 2 diabetes.

Methanocaldococcus jannaschii is a methane-producing organism found in submarine hydrothermal vents. The Mukhopadhyay research group has discovered that *M. jannaschii* possesses a new type of enzyme, a sulfite reductase, which represents an ancient detoxification system. This is the first time methane production and sulfite reduction have been shown not to be mutually exclusive processes. *M. jannaschii* can carry out both processes because it contains a system to detoxify the otherwise toxic sulfite. It is possible that at one time methanogenesis and sulfate reduction existed in one organism, which performed both methanogenesis and sulfate-dependent anaerobic oxidation of methane.

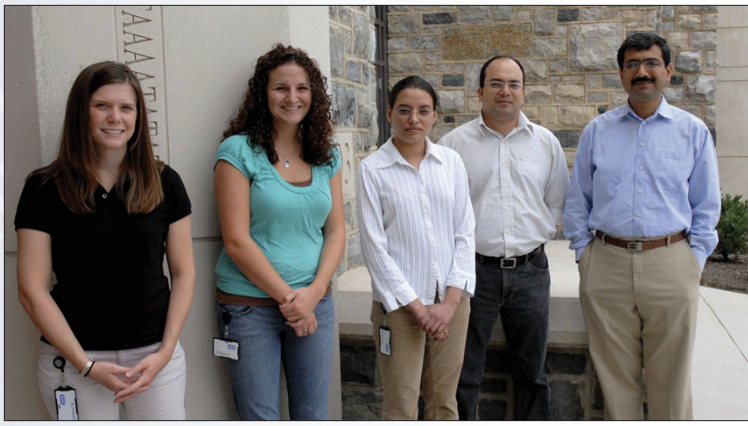
In collaboration with the Johns Hopkins University, Rotinsulu Pulmonary Hospital (Bandung, Indonesia), and Institut Teknolgi (Bandung, Indonesia) Dr. Mukhopadhyay and coworkers are also developing diagnostics, vaccines and therapeutics for tuberculosis. The team has identified 30 clinically unique strains of *Mycobacterium tuberculosis* and is investigating these strains for genomic and antigenic differences. This work should help to facilitate the development of vaccines and diagnostics for tuberculosis which kills approximately 1.7 million people annually (World Health Organization).

The Mukhopadhyay research group is also exploring the use of microbial organisms to convert coal to methane and reduce the risk of methane-induced mine explosion. This work is being carried out in collaboration with the Altuda Energy Corporation in San Antonio, Texas. In addition, studies of human phosphoenolpyruvate carboxykinase and an archaeal-type phosphoenolpyruvate carboxylase are allowing new avenues to be explored for designing drugs for treating type 2 diabetes and infections caused by *Clostridium perfringens*.

Dr. D. Rathore

Research Group

Left to right:
Kiley Walawender, Kristal Cooper, Dewal Jani, Rana Nagarkatti, Dharmendar Rathore



Using a genomics approach, Dr. Rathore's research group has identified and characterized several malaria parasite antigens that play a role in initiating malarial infection.

Malaria, a devastating disease caused by *Plasmodium* parasites, is responsible for 10% of all the disease-associated mortality in children under the age of five. The majority of these fatalities are caused by infections with *Plasmodium falciparum*, the most lethal form of the human malaria parasite. Dr. Rathore's research group is actively pursuing a genomics approach towards the identification of parasite factors that lead to the successful onset and sustenance of malaria infection in its human host and can be developed either as a vaccine or a drug target.

While malaria infection begins with the invasion of hepatocytes by *Plasmodium* sporozoites inoculated by an infected mosquito, clinical symptoms of malaria, which include high fever, chills and anemia, are due to the subsequent infection and rapid multiplication of the parasite inside red blood cells. To sustain its rapid pace of development, the parasite cannibalizes hemoglobin, which represents 90% of the total protein present inside a red blood cell; approximately 75% of which is degraded during the erythrocytic stage of development.

The degradation of hemoglobin releases heme, which is extremely toxic to the parasite. To protect itself, the parasite rapidly detoxifies heme into a crystalline product called hemozoin.

Dr. Rathore's research group has identified a novel malaria protein that plays an important role in the detoxification of heme into hemozoin. As heme detoxification is critical for the survival of the parasite, this protein is now being investigated as a target for antimalarial drug discovery.

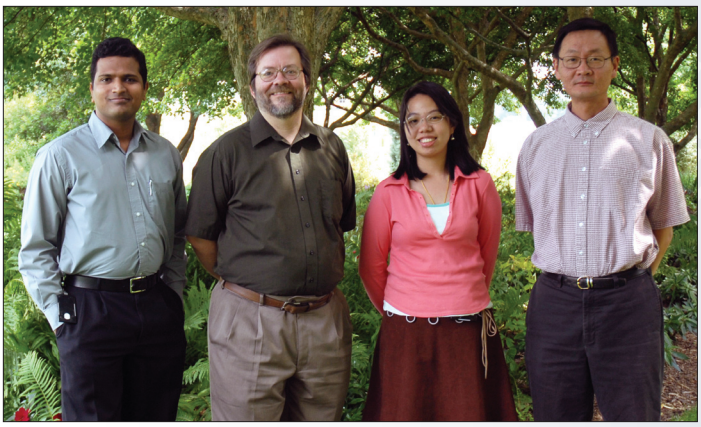
Research Interests

- Investigation of malarial pathogenesis
- Antimalarial drug development
- Fungal antigens in chronic rhinosinusitis

Publications

Rathore D, Jani D, Nagarkatti R, Kumar S (2006) Heme detoxification and antimalarial drugs: known mechanisms and future prospects. *Drug Discov. Today: Therapeutic Strategies* **3**(2): 153-158.

Rathore D, McCutchan TF, Sullivan M, Kumar S (2005) Antimalarial drugs: current status and new developments. *Expert Opin. Investig. Drugs*. **14**(7): 871-883.



Dr. D. Samuels

Research Group

Left to right:
Harsha Rajasimha, David Samuels, Passorn Wonnapinij, Jonghoon Kang

Dr. Samuels' research group uses bioinformatics and computational biology to study diseases involving the function of mitochondria.

Research Interests

- Toxicity of nucleoside analogs, such as AZT, used as antiviral drugs
- Metabolism of DNA precursors in mitochondria
- Physical properties of DNA and mutation mechanisms
- The role of mitochondria in aging
- The interaction of pathogens with the host mitochondria

Publications

Bradshaw PC, Li JX, Samuels DC (2005) A computational model of mitochondrial AZT metabolism. *Biochem. J.* **392**: 363-373.

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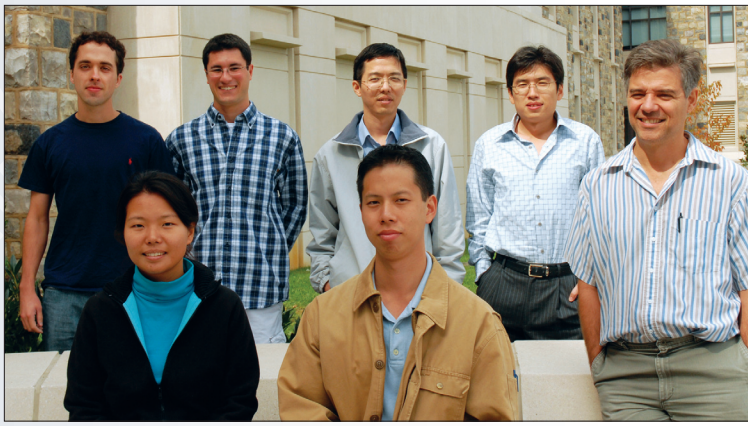
The first successful treatment for human immunodeficiency virus infection was AZT (azidothymidine; zidovudine), which is one example of a class of drugs known as nucleoside analogs. The current AIDS therapy is Highly Active Anti-Retroviral Therapy (HAART), which typically uses two nucleoside analogs in combination with one other drug. These drugs can affect a patient's mitochondria and the mutation of the DNA of a cell's mitochondria can lead to a loss of cell function. Such drugs enter the mitochondria and can disturb the small but critical amount of DNA located there. Many anti-AIDS drugs that seemed promising in the lab have been found in clinical trials to have serious and sometimes fatal complications because of their effects on the patient's mitochondrial DNA. The fundamental mechanism for the toxicity of nucleoside analogs is not clear. A systems biology approach to this problem is needed to understand the interactions between coupled metabolic pathways and explore the combined effects of multiple mechanisms of toxicity.

Dr. Samuels' research group uses bioinformatics and computational biology to study diseases involving the function of mitochondria. Mitochondria possess their own genome that is distinct from the nuclear genome. Mutations within the mitochondrial genome may lead to a loss of energy within a cell and, in turn, the loss of cell function. This loss of function may have severe clinical repercussions and contribute to different neurodegenerative diseases. The accumulation of mutations in mitochondrial DNA may also be linked to the decrease in the ability of a cell to function as an organism ages. Dr. Samuels' research group is working to identify the major pathways and events responsible for the damage to mitochondria.

Dr. J. Setubal

Research Group

Left to right, back row:
Andrew Warren, Chris Lasher, Jian Sun, Jian Tu
front row:
Zheng Cai, Tsai–Tien Tseng, João Setubal



Dr. Setubal's research group develops bioinformatics infrastructure for the genomic analysis of multiple microorganisms.

The Setubal research group works primarily on bioinformatics for bacterial genome annotation and sequence analysis. Three projects are in progress directly related to bioinformatics for sequencing efforts. First, the genomes of two species of the well known plant pathogen and biotechnology agent *Agrobacterium* are being sequenced and analyzed in partnership with other universities and institutions. The careful comparison of these two new genomes with others already known should provide insight into the way in which *Agrobacteria* infect and interact with the host plant. The second project focuses on *Azotobacter vinelandii*, a free-living, nitrogen-fixing bacterium found in soils worldwide, and which is also an important laboratory organism for biochemistry studies. The third project studies two strains of *Xanthomonas* that cause various forms of citrus canker, a disease that results in severe losses for the citrus industry in many parts of the world, including the United States.

In order to effectively support sequencing-related projects, the Setubal research group develops bioinformatics tools for the annotation of sequence data. Annotation is the process whereby the genetic information contained in genome sequences is made clear and useful for further studies. The Genome Annotation Tool (GAT) allows the storage of multiple genomes and includes a database and web-based interface for viewing and editing annotations. The Genome Reverse Compiler (GRC) is a computer program for fast automated annotation of bacterial genomes. The combination of GRC and GAT allows genome sequences to be studied in an efficient and effective way.

Other projects include a study of the bacterial evolution of *Pseudomonas syringae* that should give rise to new tools for detailed whole-genome analysis, the development of gene ontology terms for standardized annotation of plant-associated microbe genomes, and the further development of PATRIC (PathoSystems Resource Integration Center), a web-based bioinformatics resource for biodefense priority pathogens such as *Brucella, Rickettsia*, coronaviruses and others. The long-term objective is to facilitate the development of vaccines, diagnostics and therapeutics for the diseases caused by these organisms. Examples of these diseases are brucellosis, spotted fever, and Severe Acute Respiratory Syndrome.

Research Interests

- Computational tools for genome annotation and analysis
- Algorithms for problems in computational biology
- Bacterial genome evolution

Publications

Setubal JC, Reis M, Matsunaga J, Haake DA (2006) Lipoprotein computational prediction in spirochaetal genomes. *Microbiology* **152**:113-121.

Setubal JC, Verjovski-Almeida S (eds) Advances in Bioinformatics and Computational Biology. Proceedings of the Brazilian Symposium on Bioinformatics, BSB 2005. Lecture Notes in Bioinformatics, vol. 3594. Berlin: Springer-Verlag, 2005.

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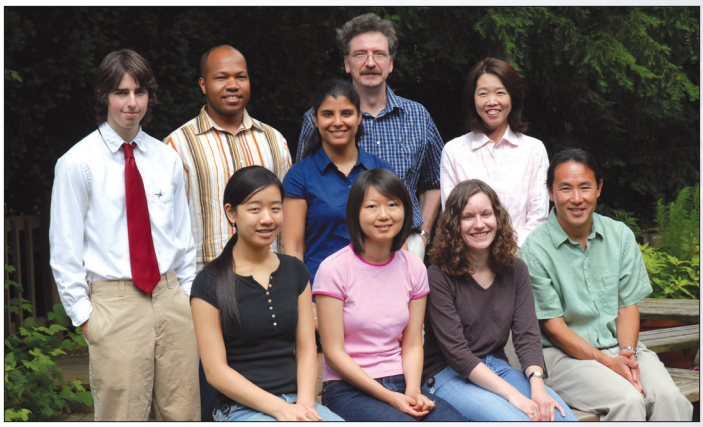

Dr. V. Shulaev

Research Group

Left to right, back row:
Christopher Estes, Diego Cortes, Leepika Tuli, Vladimir Shulaev, Teruko Oosumi
Front row:
Laura Wang, Wei Sha, Holly Johnson, Joel Shuman

Metabolomics has emerged as a powerful tool to complement large-scale genomic and proteomic technologies.

Research Interests

- Applications of metabolomics to functional genomics
- Metabolomics and yeast systems biology
- Woodland strawberry (*Fragaria vesca*) as a model for fruit functional genomics
- Metabolomics and cancer
- Application of metabolomics to study gene function in *Arabidopsis*

Publications

Gadjev I, Vanderauwera S, Gechev TS, Laloi C, Minkov IN, Shulaev V, Apel K, Inze D, Mittler R, Van Breusegem F (2006) Transcriptomic footprints disclose specificity of reactive oxygen species signaling in *Arabidopsis*. *Plant Physiol.* **141**: 436-445.

Shimada T, Nakano R, Shulaev V, Sadka A, Blumwald E (2006) Vacuolar citrate/H(+) symporter of citrus juice cells. *Planta* **224**(2): 472-480.

Shulaev V (2006) Metabolomics technology and bioinformatics. *Brief. Bioinform.* **7**(2): 128-139.

Suzuki N, Rizhsky L, Liang H, Shuman J, Shulaev V, Mittler R (2005) Enhanced tolerance to environmental stress in transgenic plants expressing the transcriptional coactivator multiprotein bridging factor 1c. *Plant Physiol.* **139**: 1313-1322.

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Oosumi T, Gruszewski HA, Blischak LA, Baxter AJ, Wadl PA, Shuman JL, Veilleux RE, Shulaev V. (2006) High-efficiency transformation of the diploid strawberry (*Fragaria vesca*) for functional genomics. *Planta* **223**: 1219-1230.

Shulaev V, Oliver DJ (2006) Metabolic and proteomic markers for oxidative stress. New tools for reactive oxygen species research. *Plant Physiol.* **141**: 367-372.

Metabolomics involves the global analysis of all cellular metabolites, which are small-molecule products of the chemical processes occurring in living organisms. This type of analysis is becoming more popular in genomics research, complementing other commonly used techniques to look at genes and proteins on a large scale. Although metabolomics has emerged as a powerful tool for functional genomics, it is now being applied to other areas. For example, metabolomics is being used by researchers to study mutant phenotypes, evaluate responses to environmental stress, further drug discovery work and conduct human disease and nutrition research. Metabolomics is also being applied as a systems biology tool.

Dr. Vladimir Shulaev's Research Group is interested in developing metabolomics technology and applying high-throughput metabolite profiling to study stress response in microorganisms, plants and animals. In collaboration with VBI faculty members Drs. Reinhard Laubenbacher and Pedro Mendes, the group is working on a project involving the use of a systems biology approach to study the oxidative stress response in the yeast *Saccharomyces cerevisiae*. The group is also performing functional genomic studies of fruit crops using *Fragaria vesca* (woodland strawberry) as a model. Fruit contain a large number of beneficial phytochemicals such as antioxidants and anticancer agents.

The Shulaev group is identifying the genes involved in the biosynthesis and regulation of these phytochemicals, as well as novel compounds with potential health benefits. In other projects, the group is studying the early stages of transformation of normal cells to cancerous cells (malignancy) in human breast epithelial cells using a combination of mass spectrometry-based metabolomics and transcriptomic approaches. The group also collaborates with Johns Hopkins University on a National Institutes of Health-funded project to study malaria. The Shulaev group is also looking at the application of metabolomics to study gene function in the commonly used model plant *Arabidopsis*.

Dr. B. Tyler

Research Group

Left to right, back row:
Konstantinos Krampis, Ken Tian, Daolong Dou, Lee Falin, Marcus Chibucos, Trudy Torto
Front row: Layomi Fakunmoju, Regina Hanlon, Rays Jiang, Brett Tyler, Sucheta Tripathy, Bryndan Durham, Lecong Zhou, Felipe Arredondo.
Not shown: Adriana Fereira, Nick Galloway, Xia Wang, Brian Smith, Lachelle Waller, Rajat Singhania

Understanding the host-pathogen-environment triangle requires knowing in intimate detail the genomic make-up that helps Phytophthora recognize and infect its host.

Plant pathogens from the genus *Phytophthora* cause destructive diseases in a large variety of crop plants and forest ecosystems. The potato pathogen *Phytophthora infestans* was responsible for the Irish potato famine, *Phytophthora ramorum* is attacking trees and shrubs of coastal oak forests in California and the soybean pathogen *Phytophthora sojae* is causing serious losses to the United States soybean crop. *Phytophthora* pathogens are oomycetes, which are organisms that resemble fungi but belong to a kingdom of life called Stramenopiles. Stramenopiles are more closely related to algae such as kelp and diatoms. Because of this, conventional fungal control measures often do not work when used to target these pathogens. Oomycetes include many other destructive plant pathogens, such as the downy mildews and more than 100 species of the genus *Pythium*.

Dr. Brett Tyler's Research Group is working to identify and characterize the genes and biological mechanisms that enable these pathogens to recognize and overcome the defense of their plant hosts. The group is using approaches involving genome-wide technologies to identify pathogen and host genes that participate in the interaction and predict the functional interactions among the products of those genes that determine the outcome of infections. More specifically, the group has used these technologies to identify many rapidly diversifying gene families in *P. sojae* that encode potential pathogenicity factors, including protein toxins and a class of proteins that appear to have the ability to penetrate plant cells. Analysis of quantitative or multigenic resistance against *P. sojae* in soybean has revealed that there are widespread adjustments in host gene expression in response to infection, and that some responses are unique to particular resistant varieties of plants.

These observations lay the foundation for uncovering the interplay between pathogen and host genes during infection at a whole-genome level.

Research Interests

- Comparative and functional genomics of oomycete plant pathogens
- Molecular analysis of oomycete virulence proteins
- Functional genomics of quantitative disease resistance and infection responses in plants
- Computational prediction of gene functions
- Mathematical modeling of complex cellular responses

Publications

Jiang RHY, Tyler BM, Whisson SC, Hardham AR, Govers F (2006) Ancient origin of elicitin gene clusters in *Phytophthora* genomes. *Mol. Biol. Evol.* **23**(2): 338-351.

Tripathy S, Pandey VN, Fang B, Salas F, Tyler BM (2006) VMD: A community annotation database for microbial genomes. *Nucl. Acids Res.* **34**: D379–D381.

Tyler BM (2006) Genomics of fungal plant pathogens. In *Encyclopedia of Plant and Crop Science,* Goodman RM (ed), Marcel Dekker, New York, USA (in press).

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Dr. B. Sobral

PathoSystems Biology Research Group

Left to right, back row Timothy Driscoll, Chunxia Wang, Endang Purwantini, Chunhong Mao, Xiaoyan Sheng
Front: row: Raymie Equi, Bruno Sobral, Matt Dyer

Dr. Bruno Sobral and coworkers' research comprises the collective efforts of the PathoSystems Biology and Cyberinfrastructure groups at VBI. The research activities of these groups focus on using the α-proteobacteria as a starting point for increasing knowledge of infectious diseases in different biological systems. The alpha-proteobacteria represent one of the most abundant bacterial groups found in the environment. They include pathogens of humans and domestic animals as well as insects and plant hosts. In the course of evolution, the alpha-proteobacteria have successfully adopted different lifestyle and energy-yielding strategies. According to the National Center for Biotechnology Information (NCBI), 48 α-proteobacterial genomes have been completed and 69 are in progress (www.ncbi.nlm.nih.gov/genomes/lproks.cgi accessed 24 August 2006). The α-proteobacteria are also of interest since some genes found in eukaryotic cells are derived directly from α-proteobacteria, especially those related to mitochondria. By investigating the interactions between hosts, pathogens and their environment — the so-called "disease triangle" — researchers in Dr. Sobral's team hope to bring a new level of understanding to infectious disease research.

Research Interests

- Development and deployment of cyberinfrastructure supporting infectious disease research
- Alpha-proteobacteria, using the *Sinorhizobium meliloti–Medicago truncatula* symbiosis as a model system, and their strategies and success as intracellular bacteria
- Comparative biology of intra- and extracellular forms of alpha-proteobacteria
- Comparative genomics, especially of alpha-proteobacteria, focused on evolution and dynamics of intracellular lifestyles across multiple bacterial–host systems
- Transdisciplinary partnerships aimed at supporting the development of vaccines, diagnostics and therapeutics against infectious agents

PathoSystems Biology Group

The primary focus of the PathoSystems Biology Group is to look in detail at the α-proteobacterial genomes from the bias of the Rhizobiales. Rhizobiales is a sub-division of the α-proteobacteria that includes many bacteria living in close association with plants. For example, it comprises some of the soil bacteria that fix nitrogen from the atmosphere and which live symbiotically inside the nodules of certain legumes. The goal of the research in the PathoSystems Biology Group is to try and compare the biological systems found in Rhizobiales across different species, but mostly within the group.

Technological platforms have been established to allow such studies, including custom gene expression arrays, proteomics and other approaches, as well as the development of informatics resources. Specific databases for the Rhizobiales as well as data analysis pipelines are also being developed that should facilitate research into this biologically important group of organisms.

Projects underway in the PathoSystems Biology Group include the study of polyhydroxybutyrate synthesis in *Sinorhizobium meliloti* and proteomic analysis of the enzymes involved in this process, the development of RhizoBRC as an integrated bioinformatics resource for rhizobia-legume symbiosis research, the development of the NodMutDB database, and comparative modeling of the cell cycle from *Caulobacter crescentus*.

NodMutDB (nodmutdb.vbi.vt.edu) is a comprehensive database for plant and bacterial mutants and genes that affect nodulation and nitrogen fixation. The collected data are curated from the scientific literature. The NodMutDB serves as a one-stop-shop for researchers looking to acquire the very latest information on the genes and mutants of nitrogen-fixing bacteria. The Rhizobiales Bioinformatics Resource Center (RhizoBRC, http://rhizobia.vbi.vt.edu) is a fully-fledged web-based resource for genomic and related information on several Rhizobiales, including many species of *Agrobacterium*, *Bartonella, Bradyrhizobium, Brucella, Rhizobium, Rhodopseudomonas,* and *Sinorhizobium*. RhizoBRC uses a robust technology infrastructure developed in-house as part of the PATRIC project (patric.vbi.vt.edu).

Dr. B. Sobral

Cyberinfrastructure Research Group

Left to right, back row: Nishant Vaghela, Chengdong Zhang, Harsha Rajasimha, Jeetendra Soneja, Herman Formadi, Mark Scott, Eric Nordberg, Dan Sullivan, Lucas Mackasmiel, Mark Hance, Cory Byrd, Kelly Williams
Middle Row: Shamira Shallom, Ranjan Jha, Debby Hix, Boyu Yang, George Abramochkin, Anjan Purkayastha, Nataraj Dongre Vishnubhat, Oswald Crasta, Ron Kenyon, Nithiwat Kampanya
Front row: Susan Baker, Nirali Vaghela, Maulik Shukla, Tony Zhang, Mike Czar, Yan Zhang, Rebecca Will, Dan Liu, Joe Gabbard, Patty Seeley

By investigating the interactions between hosts, pathogens and their environment - the so-called "disease triangle" - researchers in Dr. Sobral's team hope to bring a new level of understanding to infectious disease research in plants, humans and other animals.

Cyberinfrastructure Group

The approach used for research in the Cyberinfrastructure (CI) Group is transdisciplinary, uniting diverse initiatives to address some of key challenges in the biomedical, environmental and agricultural sciences. Cyberinfrastructure, which underpins infectious disease research in Dr. Sobral's group, refers to new research environments that support advanced data acquisition, storage, management, integration, mining, visualization and other computing and information processing services via computing infrastructure. As such, cyberinfrastructure is a technological solution to the problem of efficiently connecting data, computers, and people with the goal of generating new scientific theories and knowledge.

The bioinformatics resources developed by the CI Group include tools for the curation of the genomes and pathogen systems of a wide range of infectious organisms, database systems for acquiring, storing, and disseminating high-throughput data generated from the study of pathosystems biology, and software systems for analysis and visualization of the data. Integrated into this effort are education and outreach activities that include the training of current and future generations of scientists as well as collaborative research activities.

Some of the projects of the CI Group include:

- PATRIC (patric.vbi.vt.edu)
- PathPort (pathport.vbi.vt.edu)
- Proteomics Biodefense (proteinbank.vbi.vt.edu/bprc)
- Mid-Atlantic Regional Center of Excellence in Biodefense and Emerging Infectious Disease (MARCE; marce.vbi.vt.edu)

Some of the resources offered by the CI Group include:

- Genome Curation Infrastructure (GCI)
- Document information systems that integrate and disseminate published information on pathogens in a machine-readable format
- Database systems, web visualization and bioinformatic tools for microarray and proteomic applications

Genome Curation Infrastructure consists of analytical services and web pages that have been developed for nucleotide and protein level annotation of microbial genomes. The document information systems of the CI Group include documents that present information on 40 pathogen species in an integrated and published format also available via the PATRIC portal. The database system and web visualization tools have been developed to integrate and disseminate experimental data on microarrays and several proteomics data types.

Disease resistance, the emergence of new infectious agents, and the possibility of the deliberate use of viruses, bacteria, or other agents to start disease epidemics are the driving forces behind the need for effective cyberinfrastructure. By targeting the disease triangle - the combination of interactions between host, pathogen, and environment - the CI Group is looking to enable the prevention, diagnosis and treatment of many key pathogen-related diseases. This should help researchers worldwide in their efforts to discover much needed vaccine, drug and diagnostic targets.

Publications

He Y, Reichow S, Ramamoorthy S, Ding X, Lathigra R, Craig JC, Sobral BWS, Schurig GG, Sriranganathan N, Boyle SM (2006) *Brucella melitensis* triggers time-dependent modulation of apoptosis and downregulation of mitochondria-associated gene expression in mouse macrophages. *Infect. Immun.* **74**(9): 5035-5046.

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Dr. T. M. Murali

VBI Faculty Fellow

Dr. T.M. Murali and colleagues are computing the building blocks of cellular networks and developing tools to predict the roles of genes in sequenced genomes that have unknown or poorly understood functions.

Research Interests

- Computational and comparative systems biology
- Data-driven construction of network legos
- Prediction of gene function
- Large-scale data integration and mining
- Algorithms and data structures

Publications

Grothaus G, Mufti A, Murali TM (2006) Automatic layout and visualisation of biclusters. *Algorithms in Molecular Biology* **1**:15, doi:10.1186/1748-7188-1-15

Li P, Sioson A, Mane S, Ulanov A, Grothaus G, Heath L, Murali TM, Bohnert H, Grene R (2006) Response diversity of *Arabidopsis thaliana* ecotypes in elevated CO_2 in the field. *Plant Mol. Biol.* **62**(4-5):593-609.

Massjouni N, Rivera CG, Murali TM (2006) VIRGO: Computational prediction of gene functions. *Nucleic Acids Res.* Web server issue, **34**:W340-W344.

Murali TM (2006) Hierarchically-consistent prediction of gene functions. *Proceedings of the Second Automated Function Prediction Meeting* (in press).

Pati A, Vasquez-Robinet C, Heath LS, Grene R, Murali TM (2006) XcisClique: Analysis of regulatory bicliques in *Arabidopsis thaliana*. *BMC Bioinformatics* **7**: 218.

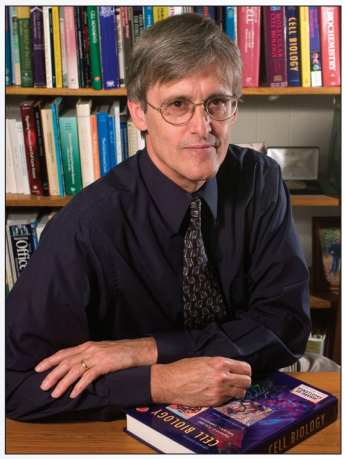
Dr. T. M. Murali is assistant professor of Computer Science at Virginia Tech and a VBI faculty fellow. Dr. Murali's research group is looking at two major challenges in the field of systems biology. The first is computing the building blocks of cellular networks and investigating how they relate to each other. The second involves predicting the roles of genes in sequenced genomes that have unknown or poorly understood functions. Both of these challenges require the use of data-driven methods based on graph theory, discrete algorithms, data mining and machine learning.

The cell is a vast network of molecules that interact with each other. One approach to study this complex network involves methods that integrate different types of data, for example genomic or proteomic data, to find the building blocks of the biological networks. The identification of these building blocks allows scientists to not only reconstruct networks but also to investigate what happens when these networks are challenged with a specific stimulus. Researchers in Dr. Murali's group develop data-driven methods that compare the response of the cell to different stimuli for this purpose. The longer-term objective is to provide new insights into cellular machinery and processes.

Dr. Murali's research group is also interested in the automated prediction of gene function. The rapid surge in the amount of sequence information for different organisms means that the function of many genes is unknown or poorly understood. The GAIN system (Gene Annotation using Integrated Networks) predicts gene functions by integrating gene expression data with molecular interaction networks. Dr. Murali's research group works closely with VBI researchers on biological applications of the new gene function prediction methods. This collaboration includes methods to simultaneously annotate the genomes of sequenced microbial organisms and determine the response pathways to oxidative stress in model eukaryotic organisms such as *Arabidopsis*, yeast and the plant pathogen *Phytophthora*.

Dr. J. Tyson

VBI Faculty Fellow



Dr. John Tyson's Research Group is converting network diagrams into dynamical models and exploring these models using analytical and computational methods.

The fundamental goal of molecular cell biology is to understand how the information encoded in a genome is used to direct a cell's complex physiological response to its environment. One major achievement in molecular biology has been the identification and characterization of the molecular components of a living organism; the complete sequencing of the human genome is one notable example. A challenge for post-genomic cell biology, however, is to assemble all of these components into a working model of a living cell to demonstrate how the physiological properties of a cell are derived from its underlying molecular machinery.

Complex networks of interacting proteins control the physiological properties of a cell, including metabolism, reproduction, motility and signaling. Diagrams of these networks can be useful in classifying the results of the hundreds or more of observations that occur during experiments, but one difficulty is developing tools that will help researchers understand the dynamics of such control systems.

Using basic principles of biochemical kinetics, Dr. John Tyson's Research Group is converting network diagrams into dynamical models and exploring the models using analytical and computational methods. Of particular interest to the group are the mechanisms that control cell division in prokaryotes and eukaryotes, ranging from beneficial and parasitic bacteria to cancerous tumors. More specifically, the group is investigating a molecular mechanism controlling the cell cycle in *Caulobacter crescentus*. *C. crescentus* is a bacterium that has two distinct stages in its life cycle. It inhabits freshwater, seawater and soils where it plays an important role in global carbon cycling by mineralizing dissolved organic material. Dr. Tyson and colleagues have created a model that accounts for important details of the physiology, biochemistry and genetics of cell cycle control in *C. crescentus*. Other areas of interest for the group include signal transduction in mammalian cells and circadian rhythms in cyanobacteria, fungi and animals.

Research Interests

- Spatial and temporal organization of biological systems
- Network dynamics and systems biology
- Cell division cycle in bacteria and yeast
- Bifurcation analysis, stochastic modeling and parameter estimation

Publications

Sible JC, Tyson JJ (2006) Application of mathematical modeling to cell cycle questions. *Methods* (in press).

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Finance and Administration

Completed in 1991, the cable-stayed Talmadge Memorial Bridge replaced the old cantilever truss bridge that had become a danger for large shipping entering the port of Savannah, Georgia. The new infrastructure carries four lanes of traffic over the Savannah River with great beauty and style. At the Virginia Bioinformatics Institute, the development of new infrastructure - for example computing tools, information channels or administrative support systems - drives growth and research excellence.

INFRASTRUCTURE

Lauren Coble

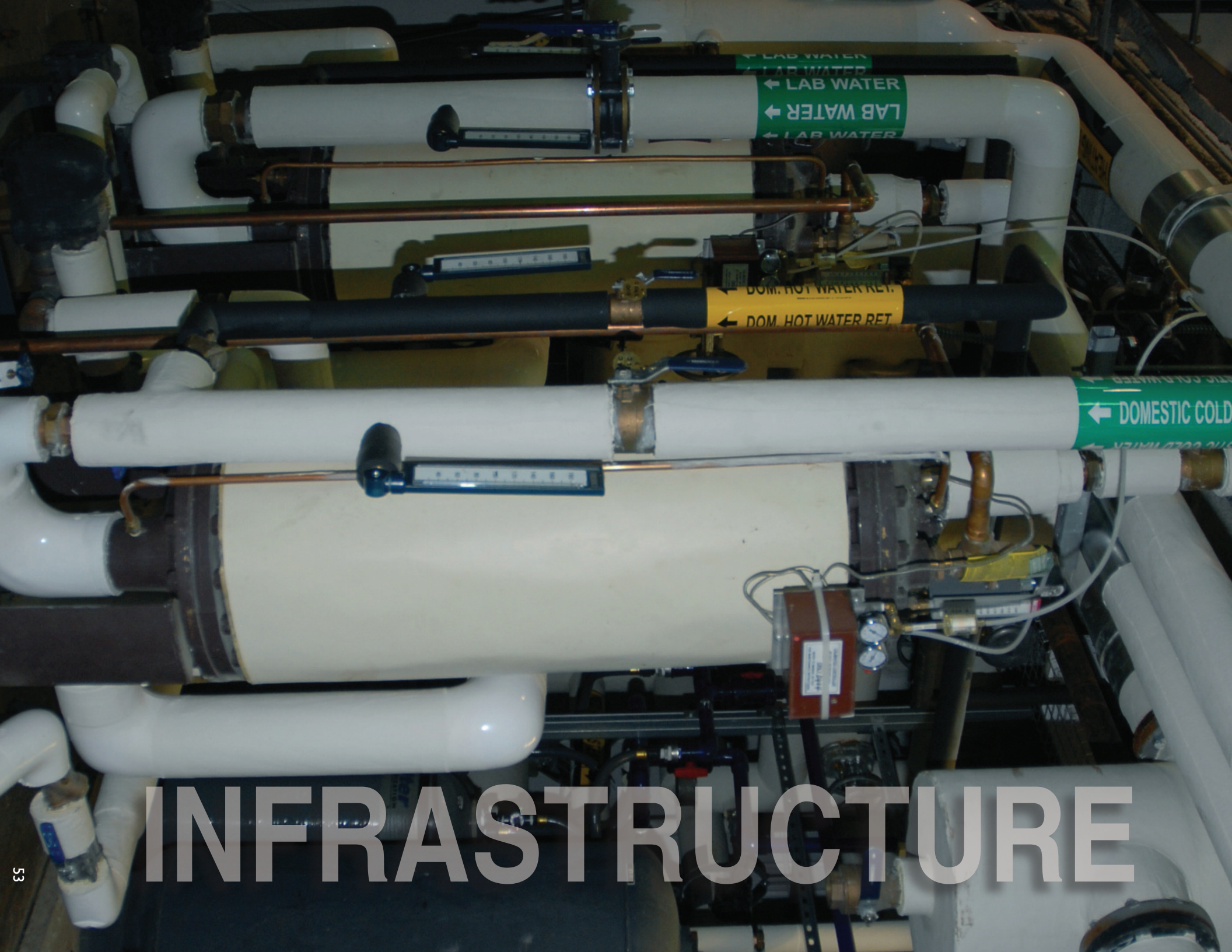
Here at the Virginia Bioinformatics Institute we continually work to strengthen and develop resources to make our Institute more competitive in a global context. People are at the heart of our venture; over 220 employees form the foundation of our research enterprise and support our scientific initiatives.

VBI continues to be a leader in financial performance for Virginia Tech. The Office of the Vice President for Research publishes all awards greater than one million dollars awarded to the university community. Three of the faculty at the Institute contributed 25% (more than $ 9.62 million) of the top 20 awards in the fiscal year that ended June 30, 2006. The Institute ranked fourth overall in proposals submitted, awards received and sponsored expenditures. VBI was third in overhead earned per dollar of university research support. In addition, the Institute was second in sponsored expenditures and overhead generated per square foot of research space.

The diversity of our financial support, which includes a broad sponsor base comprising the National Institutes of Health, the National Science Foundation, the United States Department of Defense, the United States Department of Agriculture, and other leading sponsors, is particularly pleasing.

We would like to thank everyone associated with VBI for the commitment they have shown in making these achievements possible. In the years ahead, we will be investing further in our people, infrastructure, and other resources as we realize the university's vision of inventing the future. The Institute is in an ideal position to continue to deliver outstanding results and to contribute to the university's goal to become one of the best research universities worldwide.

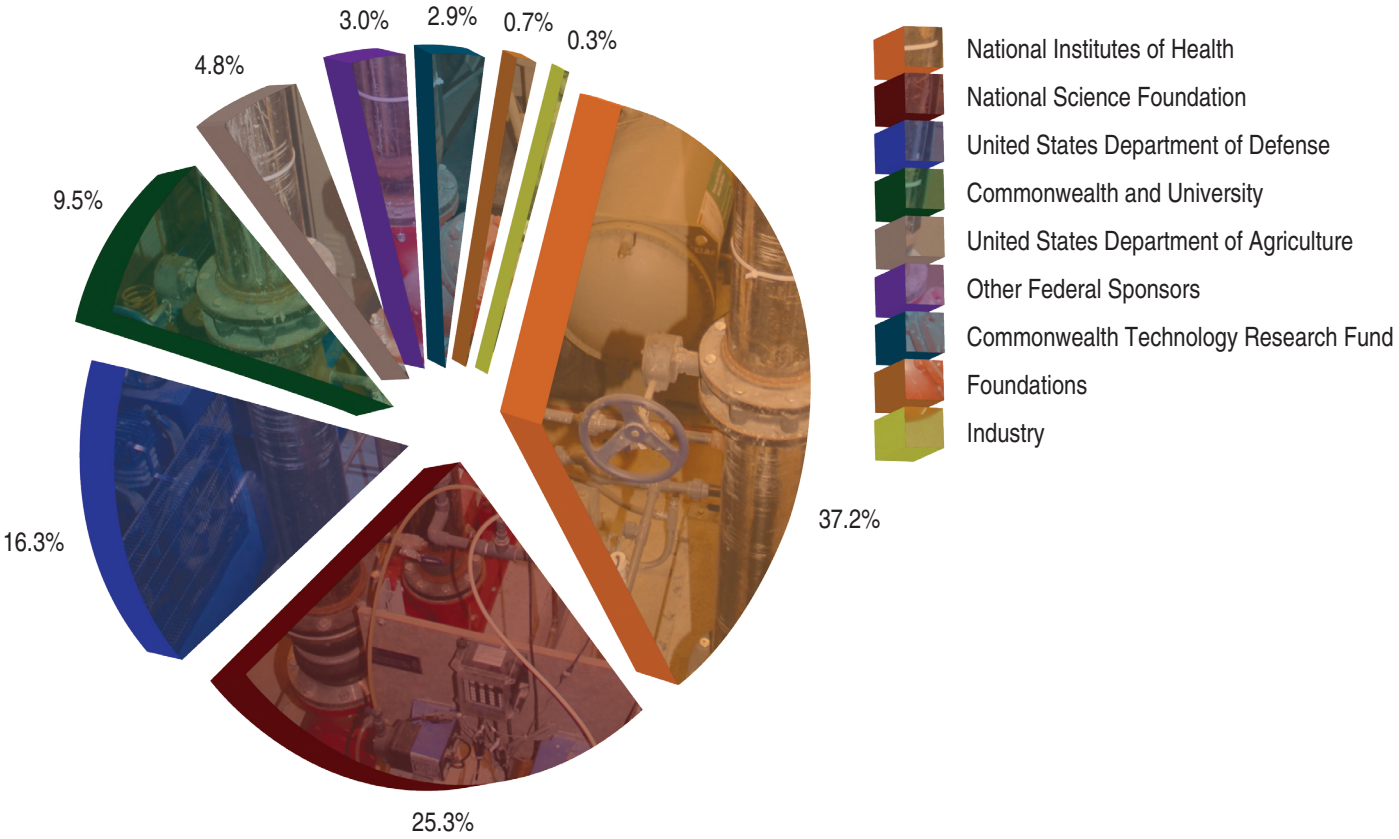
Lauren Coble
Associate Director, Administration and Finance



INFRASTRUCTURE

Active Research Grants and Contracts

as of June 30, 2006



Total Active Awards by Sponsor

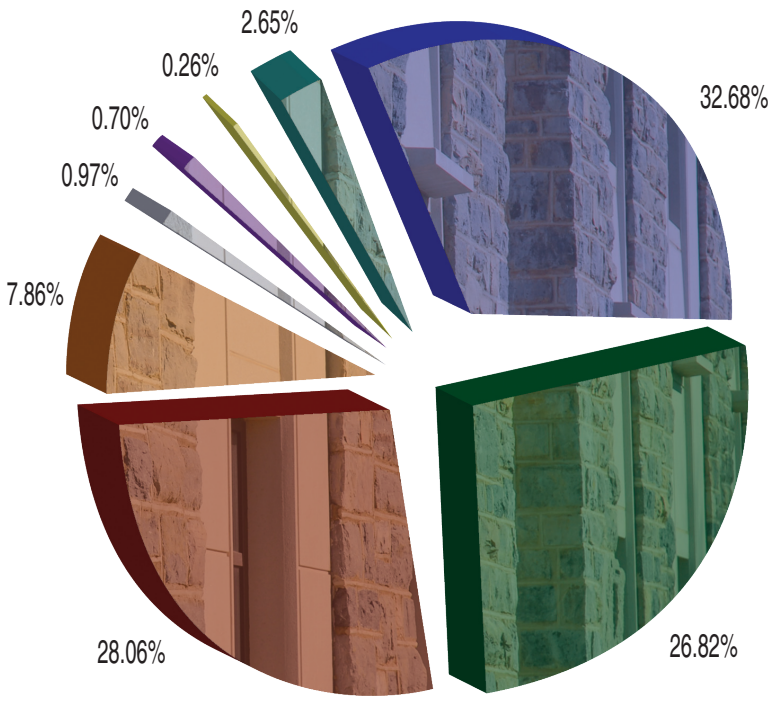
as of June 30, 2006

National Institutes of Health	$ 20,164,345
National Science Foundation	13,706,549
United States Department of Defense	8,865,816
Commonwealth and University	5,160,419
United States Department of Agriculture	2,597,035
Other Federal Sponsors	1,637,689
Commonwealth Technology Research Fund	1,547,210
Foundations	375,000
Industry	156,263
Total active awards	$ 54,210,326

2006 Research Expenditures by Sponsor

as of June 30, 2006

National Institutes of Health	$ 4,927,884
National Science Foundation	4,043,065
United States Department of Defense	4,230,506
United States Department of Agriculture	1,185,257
United States Department of Transportation	146,173
United States Department of Energy	106,640
Other sponsors	38,452
Commonwealth and university sources	399,011
Total extramural expenses	$ 15,076,988



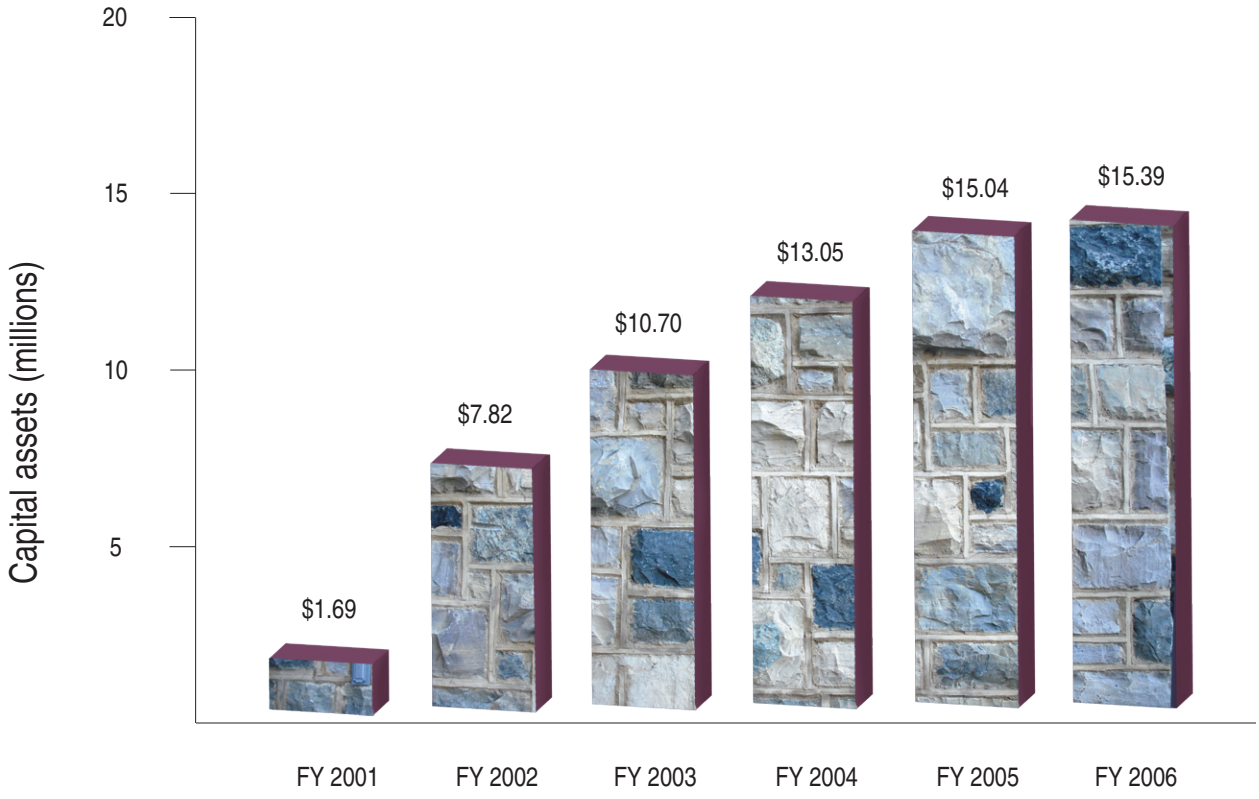
Financial Operating Activity

for the years ended June 30, 2006 and 2005

Revenues	FY 2006	FY 2005
Grants and contracts		
National Science Foundation	$ 3,115,413	$ 3,252,492
United States Department of Defense	4,123,852	2,605,195
National Institutes of Health	5,539,237	2,267,910
United States Department of Agriculture	1,147,850	402,104
United States Department of Energy	388,097	332,151
United States Department of Transportation	126,924	
Foundations	24,424	60,648
National Aeronautics and Space Administration	6,029	
Industry	4,810	284,628
Other federal sources	10,169	
Total grants and contracts	14,486,805	9,205,128
Commonwealth and university sources	3,111,826	3,167,004
Total operating revenue	17,598,631	12,372,132
Expenses		
Personnel expenses	14,602,596	12,037,942
Operating expenses		
Contractual services	941,619	815,176
Information technology	634,856	317,919
Travel and other	617,214	595,814
Supplies and materials	1,750,613	1,321,426
Building and other rentals	58,856	1,005,595
Subcontracts	1,752,777	1,474,891
Equipment	580,623	220,536
Total operating expenses	6,336,558	5,751,357
Indirect expenses	4,096,187	2,574,144
Total expenses	25,035,341	20,363,443
Non-operating sources		
University support	8,509,015	8,349,457
Gain in net assets	$ 1,072,305	$ 358,146

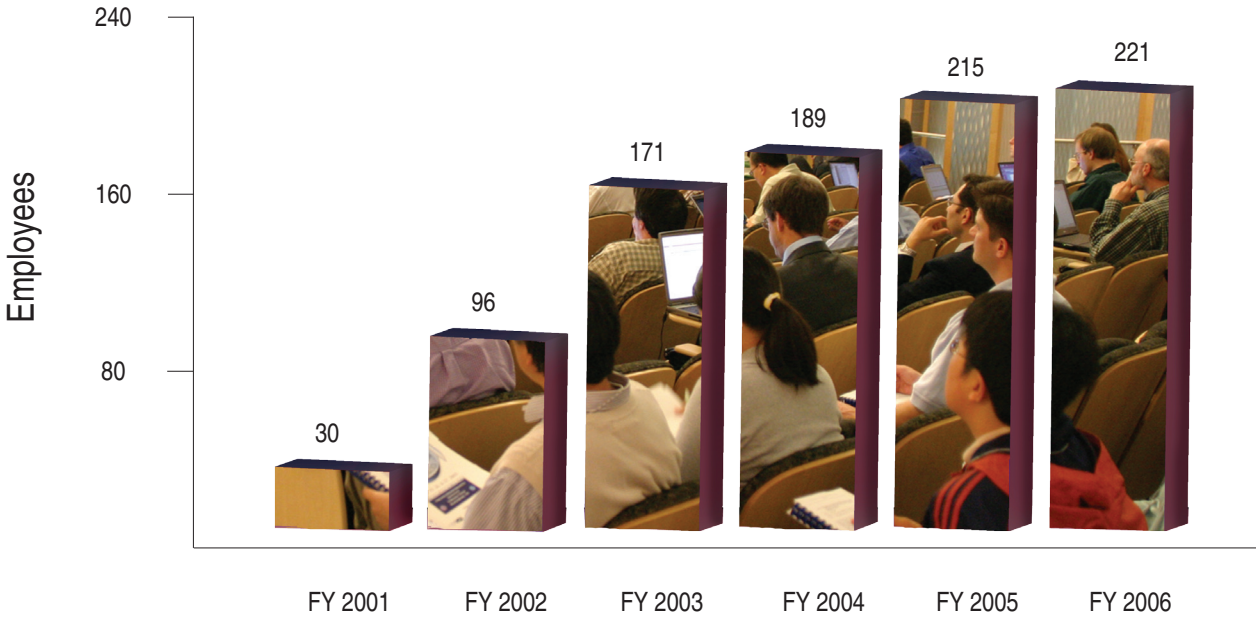
Capital Assets

for fiscal years 2001-2006



Personnel

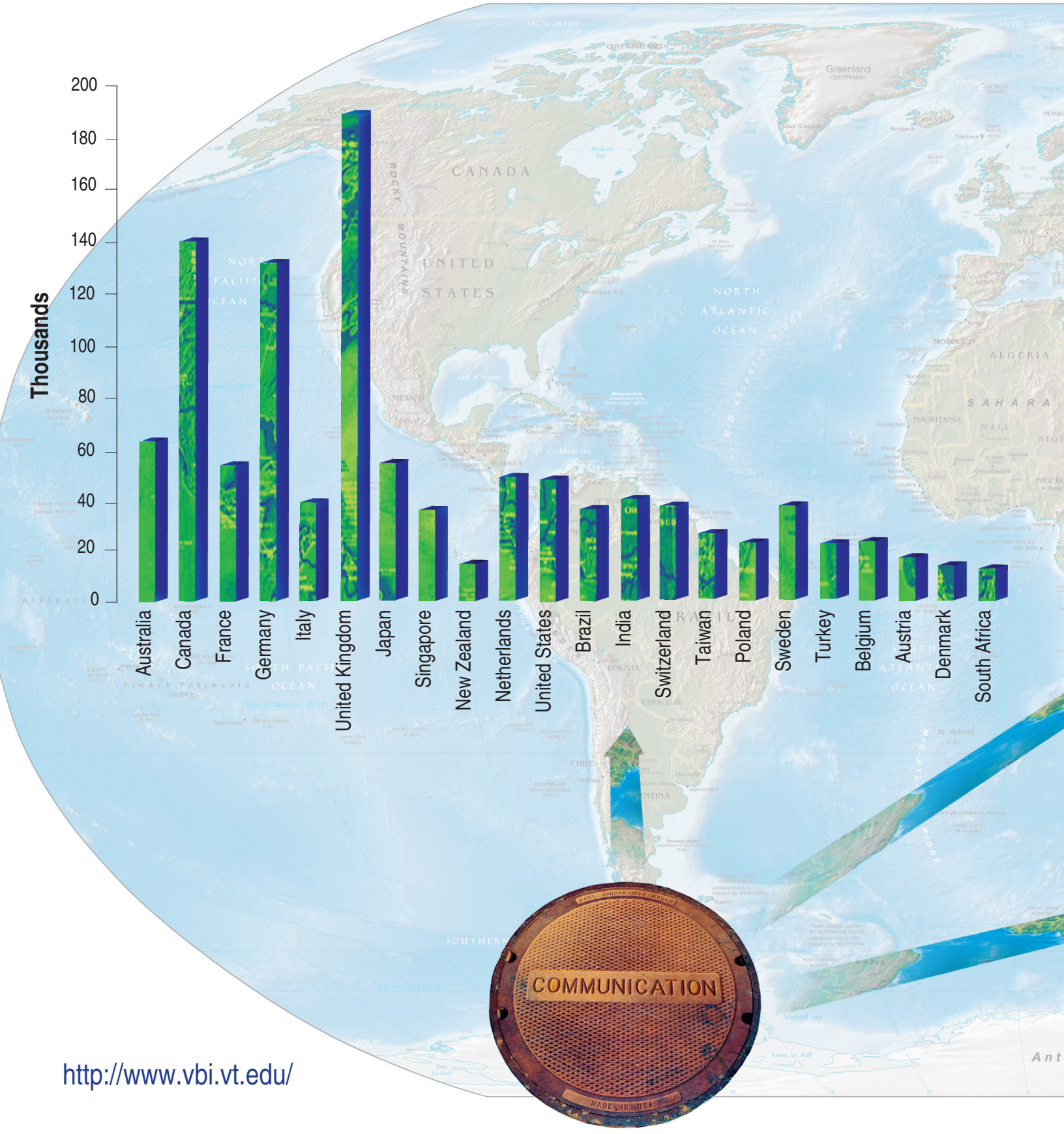
for fiscal years 2001-2006



Communication infrastructure

Number of web site page requests by country

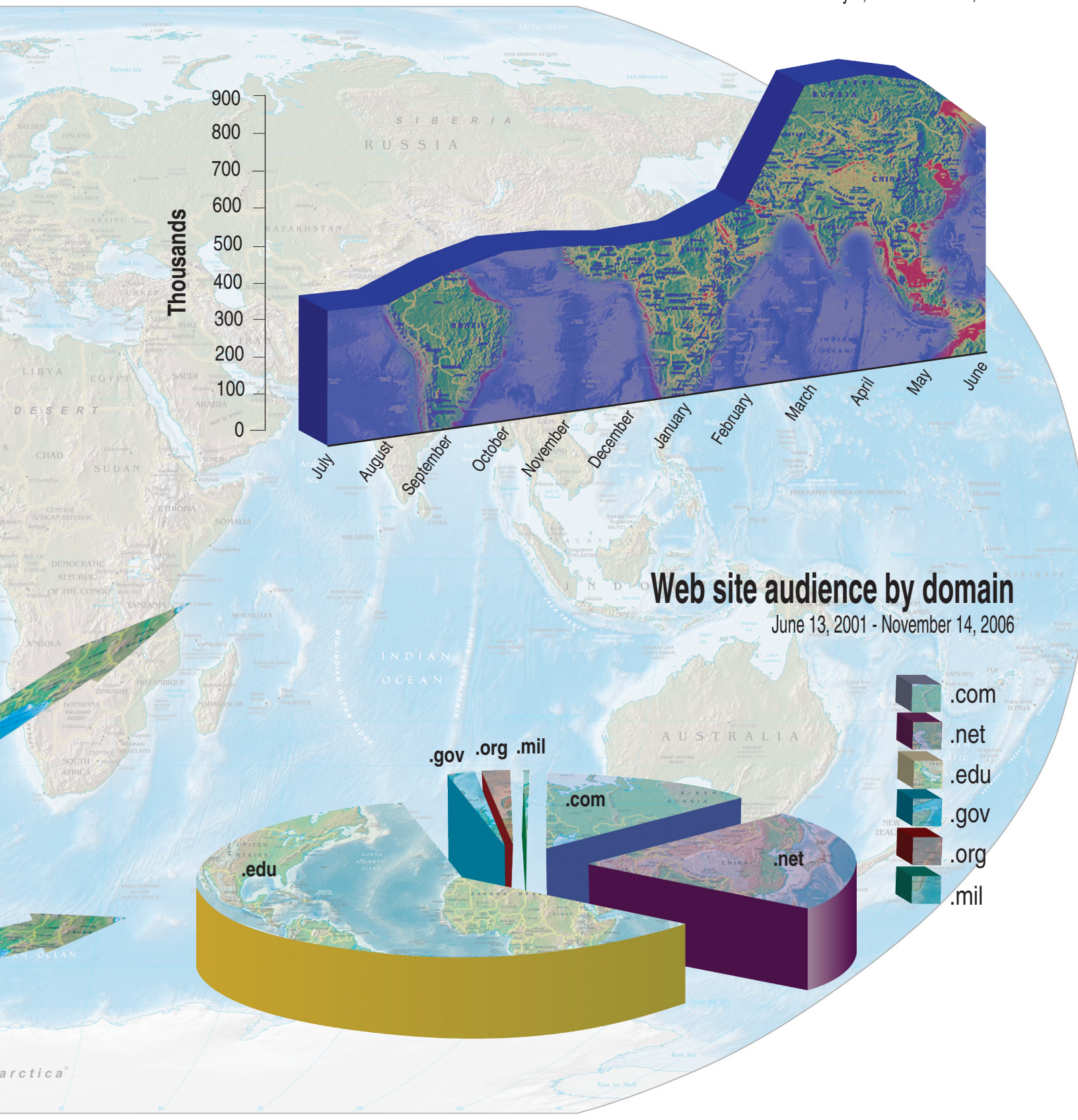
June 13, 2001 - November 14, 2006



http://www.vbi.vt.edu/

Number of web site page requests by month

July 1, 2005 - June 30, 2006



Web site audience by domain

June 13, 2001 - November 14, 2006

Development

Technology

Outreach

Looking to the Future

Technology development at VBI

"The Virginia Bioinformatics Institute is continually producing research innovations that can lead to the development of new products, technologies and services."

Otto Folkerts, Associate Director, Technology Development

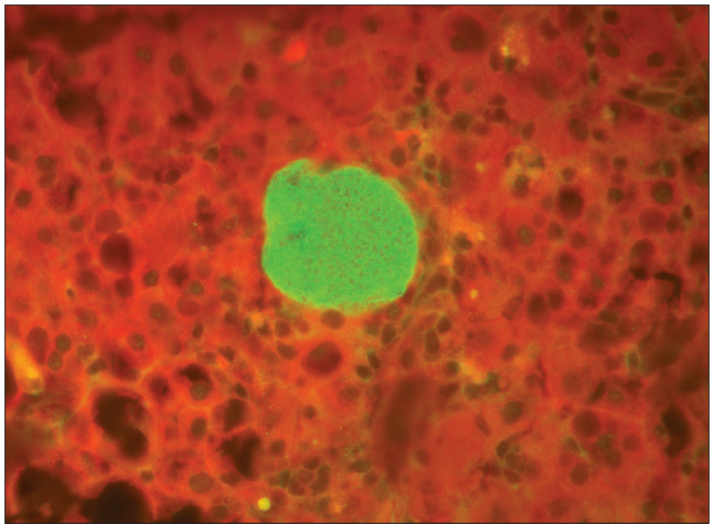
As a research center with a significant critical mass in basic and applied research, VBI is continually producing research innovations that can lead to the development of new products, technologies and services. The lengthy process of developing and commercializing these discoveries is commonly referred to as "Technology Development". It is a continuum of activities consisting of:

- Identifying new discoveries, technology, know-how, and intellectual property that have commercial potential
- Protecting the intellectual property by filing invention disclosures with the university, and patent applications with the US Patent and Trademark Office
- Identifying opportunities and hurdles for product or technology development, and determining which enabling technologies or critical path activities are necessary
- Finding partners who can assist in and fund commercial development
- In select cases, determine the potential to start new business ventures around technology

The main focus of activities during the fiscal year that ended June 30, 2006, was on identifying new technologies and establishing an efficient process for protecting intellectual property. Working with the appropriate individuals at Virginia Tech, and in partnership with Virginia Tech Intellectual Properties, Inc. and outside law firms, six Invention Disclosures, one Provisional Patent Application and one US Utility Application were filed (see table).

Case study: Malaria

Malaria is a potentially fatal disease that is responsible for 10% of all disease-associated deaths of children under the age of five worldwide. According to the Medicines for Malaria Venture, the disease is estimated to kill a child every 30 seconds and to cause up to 600 million new infections worldwide annually. The malaria parasite, *Plasmodium falciparum*, is transmitted through the bite of an infected mosquito, and undergoes a complex life cycle that spans the vector (mosquito) and different stages within infected individuals (see illustration). This complex life cycle and the tenacity of the parasite pose considerable challenges to scientists looking to create new therapeutics or develop a vaccine against the disease agent.

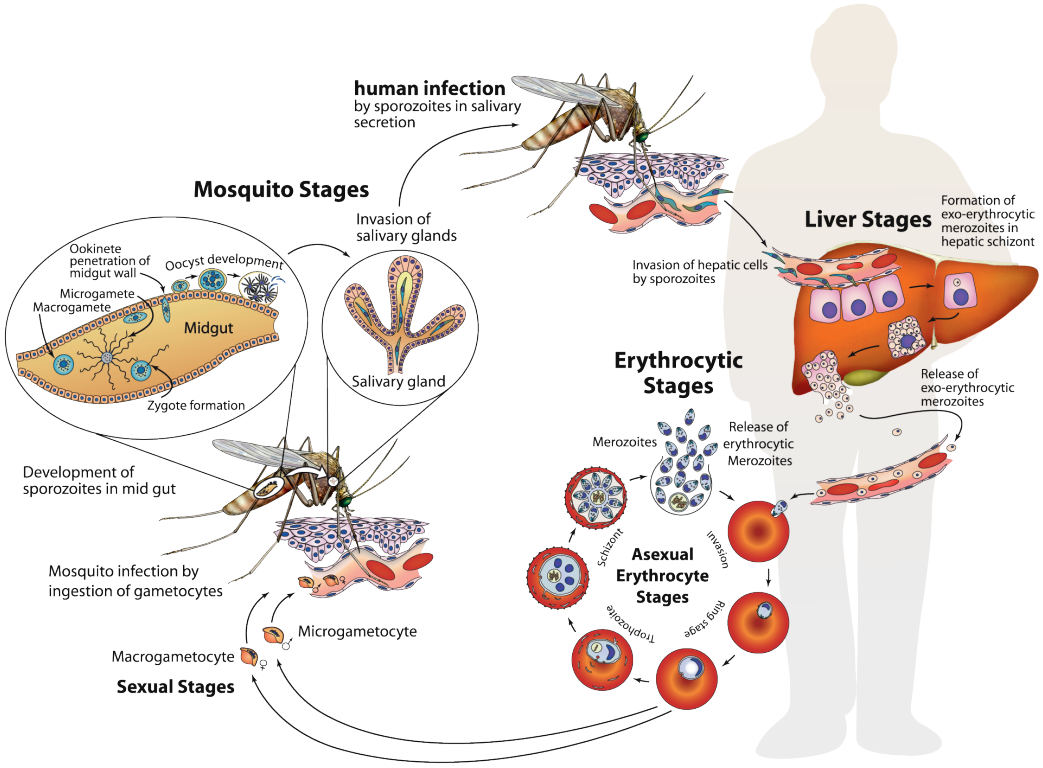


Liver stage malarial parasite expressing heme detoxification protein.

Using a genomics approach, Dr. Dharmendar Rathore's research group at VBI has identified and characterized several malaria parasite antigens that play a role in initiating malaria infection. Bioinformatic tools that allow proteins to be identified on the surface of the parasite have been instrumental in this approach. The group is working to identify components of the malaria parasite that could be developed as a vaccine for malaria prevention, or as drug targets for the development of medications that prevent or treat active malaria infection. Specifically a protein known as heme detoxification protein (HDP) is being studied as a potential drug target and vaccine candidate. HDP is present in all members of the *Plasmodium* genus, plays an important role in the onset of infection and represents a novel target for drug and vaccine development.

The work by Dr. Rathore is a good illustration of the technology development opportunities that can arise from research at VBI. During the fiscal year ended June 30, 2006, a disclosure was made to Virginia Tech, and a US Utility Patent Application was filed with the US Patent and Trademark Office on this newly characterized protein that has potential for the development of new malaria vaccines or anti-malaria drugs. Subsequent to the filing of the patent application, several pharmaceutical and biotechnology companies were approached to determine the potential for development and to identify a possible partner. In addition, the Medicines for Malaria Venture was approached for funding. A high-throughput screening project has been started at the Broad Institute at the Massachusetts Institute of Technology in Boston to identify inhibitors of this potential drug target that can be further optimized and developed as drug candidates.

Malaria Life Cycle

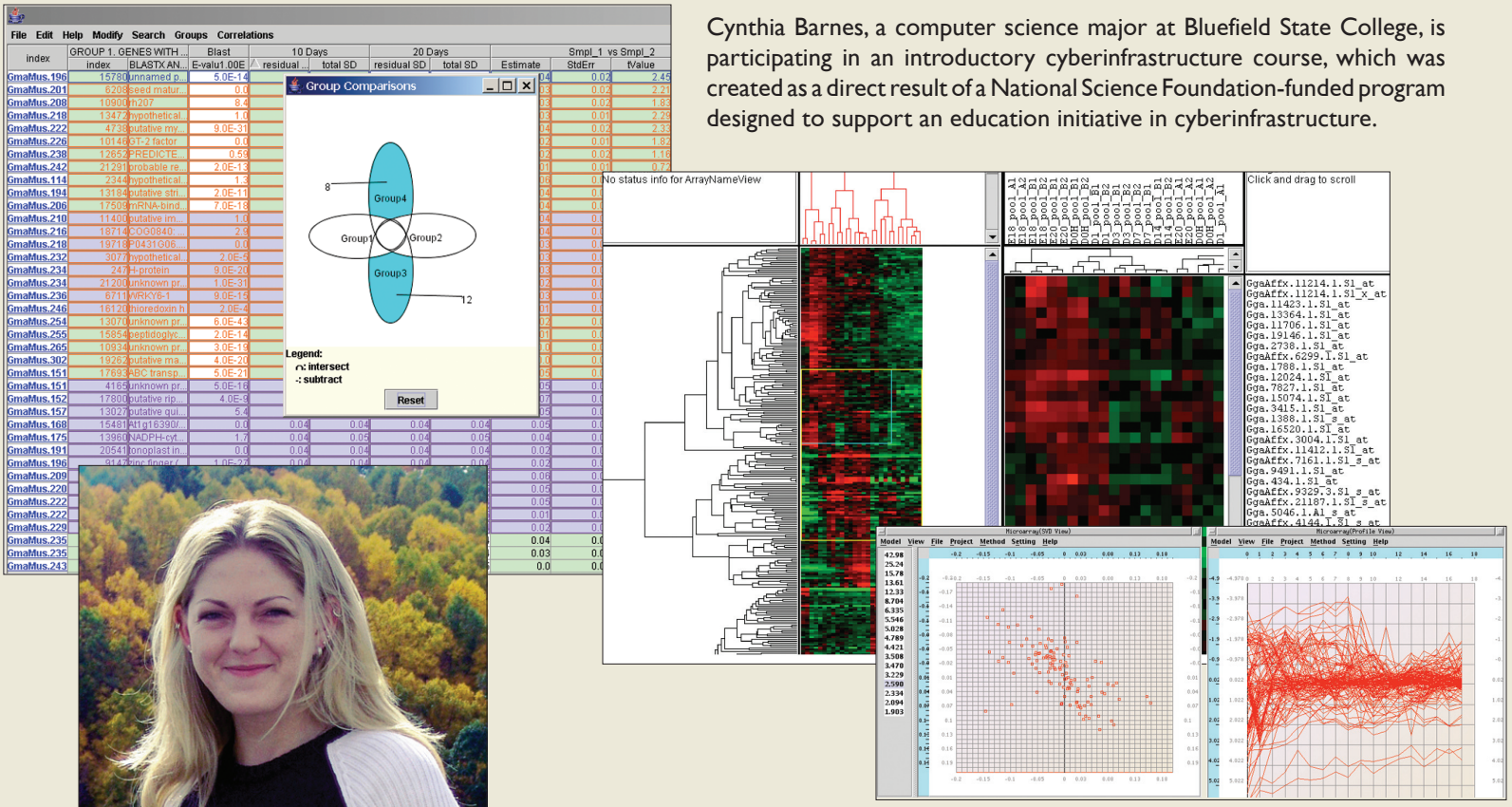


Invention disclosures, provisional patent applications and US utility applications in the fiscal year ended June 30, 2006, at VBI.

VT Disclosure Number	Principal Investigator	Filing Date	Title
Invention Disclosures			
05.062	Dharmendar Rathore	09/30/2005	FRAP: a drug and vaccine target for malaria and other parasitic diseases
05.071	João Setubal	10/07/2005	GAT: Genome Annotation Tool
06.026	Chris Lawrence	03/17/2006	Fungal Biotechnology Platform
06.057	Iuliana Lazar	05/12/2006	Microfluidic device with MALDI-MS detection for complex sample processing
06.058	Bruno Sobral	05/18/2006	Scrum tool
06.059	Chris Lawrence	05/23/2006	Drug targets for fungal associated respiratory diseases
US Utility Applications			
05.062	Dharmendar Rathore	10/14/2005	A novel therapeutic target for protozoal diseases
Provisional Applications			
06.026	Chris Lawrence	03/15/2006	Targeted disruption and expression using linear minimal element constructs

Outreach development

Education initiative in cyberinfrastructure benefits undergraduate



Cynthia Barnes, a computer science major at Bluefield State College, is participating in an introductory cyberinfrastructure course, which was created as a direct result of a National Science Foundation-funded program designed to support an education initiative in cyberinfrastructure.

"I had intended on going into network administration/network security after graduation, but I must say this class is opening up my eyes to new things. I would like to continue my education and work on my Master's degree at Virginia Tech, and I am now very interested in obtaining a student internship at VBI."

Cynthia Barnes

In 2005, VBI, Bluefield State College in Bluefield, WV, and the Galileo Magnet High School in Danville, VA received a $250,000 grant from the National Science Foundation (NSF) to support an education initiative in cyberinfrastructure. The goal of the project is to introduce high school and undergraduate students to the science of bioinformatics and, in particular, the concept and practice of cyberinfrastructure. The program is specifically designed for students who might not normally have the chance to receive formal training in bioinformatics.

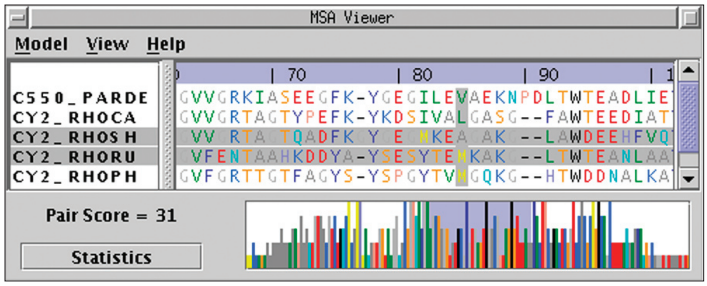
This initiative is perfectly suited for Bluefield State College student Cynthia Barnes. Barnes, a computer science major at the college, participated this semester in an introductory cyberinfrastructure course, which was created as a direct result of the NSF-funded program. The course helps students from a diverse array of academic backgrounds, including mathematics, biology, computer science, and engineering, learn more about bioinformatics while retaining their own unique perspectives. While this new class isn't a requirement for computer science majors at Bluefield State College, Barnes was attracted to the uniqueness of the class and wanted to be a part of something that was "a first" for the college.

"Since the course is interdisciplinary, we have four instructors and that is definitely something I've never experienced before," Barnes explained. "We have a biology professor, computer science professor, project management professor, and a physics professor all working together to teach us about cyberinfrastructure as it pertains to bioinformatics specifically. Also, all of the students in the class are involved in different fields, which brings an interesting perspective to the class."

Students enrolled in the course explore the relevant literature through discussions and forum postings, helping to emphasize interdisciplinary teamwork in both face-to-face and online environments. Each week, the students are given a topic related to cyberinfrastructure and bioinformatics to discuss in an online forum. Each student posts his or her opinion to spark a discussion on the topic. The first topic assigned to the class involved a report from NSF's Blue-Ribbon Advisory Panel on Cyberinfrastructure authored by Daniel Atkins and colleagues, which is also referred to as the Atkins Report.[1] The accompanying box shows Barnes' contribution to the Atkins Report discussion. Her thoughts, she explained, originated from thinking about the Advanced Cyberinfrastructure Program discussed in the report.

Barnes says she hopes the class will help her to be successful and efficient working in a team environment. She seems confident that the class will have a positive impact on her future.

"I had intended on going into network administration/network security after graduation, but I must say this class is opening up my eyes to new things," Barnes said. "I would like to continue my education and work on my Master's degree at Virginia Tech, and I am now very interested in obtaining a student internship at VBI."



Atkins Report Class Discussion,

by Cynthia Barnes

Cyberinfrastructure was a brand new term to me when this class started and though I could speculate as to its meaning I was looking for a good definition while reading the Atkins Report.[1] I picked up the meaning but didn't really find what I wanted. I did, however, find a definition in a report called "Our Cultural Commonwealth." They state that, "cyberinfrastructure is meant to denote the layer of information, expertise, standards, policies, tools, and services that are shared broadly across communities of inquiry but developed for specific scholarly purposes."[2] So it's something more specific than a network but more general than a tool. The base technologies of cyberinfrastructure are computation, storage, and communication. Without these integrated electro-optical components, cyberinfrastructure wouldn't be.

The whole point, as I understand it and as is stated in the Atkins Report, is to revolutionize what people can do, how they do it, and who participates by enabling them to share and collaborate over time and over geographic, organizational, and disciplinary distance. Without the base technologies there wouldn't be much progress, time and money would be wasted. I think achieving the vision of the Advanced Cyberinfrastructure Program will be so beneficial to all fields of study that's it's worth the extra $1 billion annual budget. Like we discussed in class, when it comes to bioinformatics, the collaboration of cyberinfrastructure is needed to find out what is really going on in a living organism. This fact was backed up in *Science* in an article called "Cyberinfrastructure: Empowering a 'Third Way' in Biomedical Research", where it said, "Biomedicine is at the precipice of unlocking the very essence of biologic life and enabling a new generation of medicine. Development and deployment of cyberinfrastructure may prove to be on the critical path to obtaining these goals".[3]

References:

1. Atkins D, Droegemeier K, Feldman SI, Garcia-Molina H, Klein ML, Messerschmitt DG, Messina P, Ostriker JP, Wright MH (2003) Revolutionizing science and engineering through cyberinfrastructure: Report of the National Science Foundation Blue-Ribbon Advisory Panel on Cyberinfrastructure, National Science Foundation.
2. Our cultural commonwealth: The Report of the ACLS Commission on Cyberinfrastructure for the Humanities and Social Sciences, July 18, 2006
3. Buetow, K (2005) Cyberinfrastructure: empowering a "third way" in biomedical research. *Science* **308**(5723): 821-824.

Looking to the future: Expansion in the National Capital Region

"The opening of our new offices in the greater Washington area represents a key milestone in the development of our Institute. Through this initiative, we will not only be able to forge closer links with federal agencies, researchers, foundations and business development partners, but also provide space and resources for present and future faculty and staff to work in the Washington DC area."

Bruno W.S. Sobral,
Scientific and executive director of the Virginia Bioinformatics Institute

On September 28, 2006, the Virginia Bioinformatics Institute inaugurated its new office space in the National Capital Region. VBI's presence in the National Capital Region is an important step in the continued expansion of the Institute. The National Capital Region location will help VBI promote and foster relations with federal agencies, create additional research and business development opportunities, and provide space for faculty who wish to work in the area.

Partnership opportunities

The opening ceremony took place in Virginia Tech's National Capital Region Operations at King Street, Alexandria, and featured remarks from George W. Korch Jr, United States Army Medical Research Institute of Infectious Diseases, Maria Giovanni, National Institute of Allergy and Infectious Diseases, Karl A. Western, National Institutes of Health, and Machi F. Dilworth, National Science Foundation. The opening addresses, which focused on partnership opportunities, infectious disease research, and new synergies, were followed by a tour of the new office space.

Commenting on the initiative, Dr. Charles Steger, president of Virginia Tech, remarked: "For over 30 years, Virginia Tech has witnessed steady growth in its offerings for instruction, research and outreach in the Washington DC area. In this time, we have been able to strengthen relationships with public and private sector partners that support our diverse research and education programs. The development and planned expansion of the Virginia Bioinformatics Institute in the greater Washington area confirm the commitment of the university to promote our growing scientific and technical know-how with interested parties in the greater Washington area and beyond."

State-of-the-art facility

The initial facility comprises nine offices for executive staff and faculty. It includes a state-of-the-art executive meeting space and an access node grid to enable group-to-group communications. This powerful suite of multimedia facilities is suitable for large-scale distributed meetings, collaborative workstations, seminars, lectures, tutorials and training. It will also ensure close integration between the northern Virginia and Blacksburg resources of VBI.

Dr. Sobral remarked: "In just over six years, we have grown into a transdisciplinary research institute with over 220 employees supporting research efforts in biomedicine, agriculture, bioinformatics and synthetic, systems and computational biology. This forward-looking move in the National Capital Region is the next phase in our exciting plans for the expansion of VBI and opens up further opportunities for research, commercializing innovative discoveries and networking with partners."

In the years ahead, VBI is poised for further growth to support its research efforts in biomedicine, agriculture, and bioinformatics. All of the planned initiatives are designed to drive growth in knowledge, innovation, and scientific discoveries.

The new facility in the National Capital Region is the first step in a strategic move to build a larger presence in the greater Washington area.

VBI POLICY BOARD

The Policy Board of the Virginia Bioinformatics Institute was established in 2000 to help guide the Institute in its efforts to produce economically beneficial research to the Commonwealth of Virginia and beyond. The Policy Advisory Board exercises its authority principally in policy-making and oversight, serving in an advisory role to the university administration and helping develop, secure, and enhance resources for the Institute. The role of the Policy Advisory Board is instrumental in helping to advance the economic development components of the Institute's mission.

Members of the Board of Visitors

George C. Nolen, Chair
Ben J. Davenport, Jr.

At-large
Recommended by the University
Mr. John Alderson
Dr. Brad Fenwick
Mr. Lawrence H. Framme, III
The Honorable Thomas D. Rust

Representative from the Tobacco Indemnification and Community Revitalization Commission

Mr. Clarence D. Bryant, III

Recommended by the Governor

Dr. Christoph von Arb
Mr. Buddy G. Beck
Mr. R.J. Kirk

Ex-officio

Dr. Charles Steger
Mr. James A. Hyatt
Dr. Mark McNamee
Dr. Bruno Sobral

Others/Senior Staff

Mr. M. Dwight Shelton, Jr.
Mr. Ralph M. Byers
Ms. Lauren Coble
Dr. Otto Folkerts
Dr. João Setubal