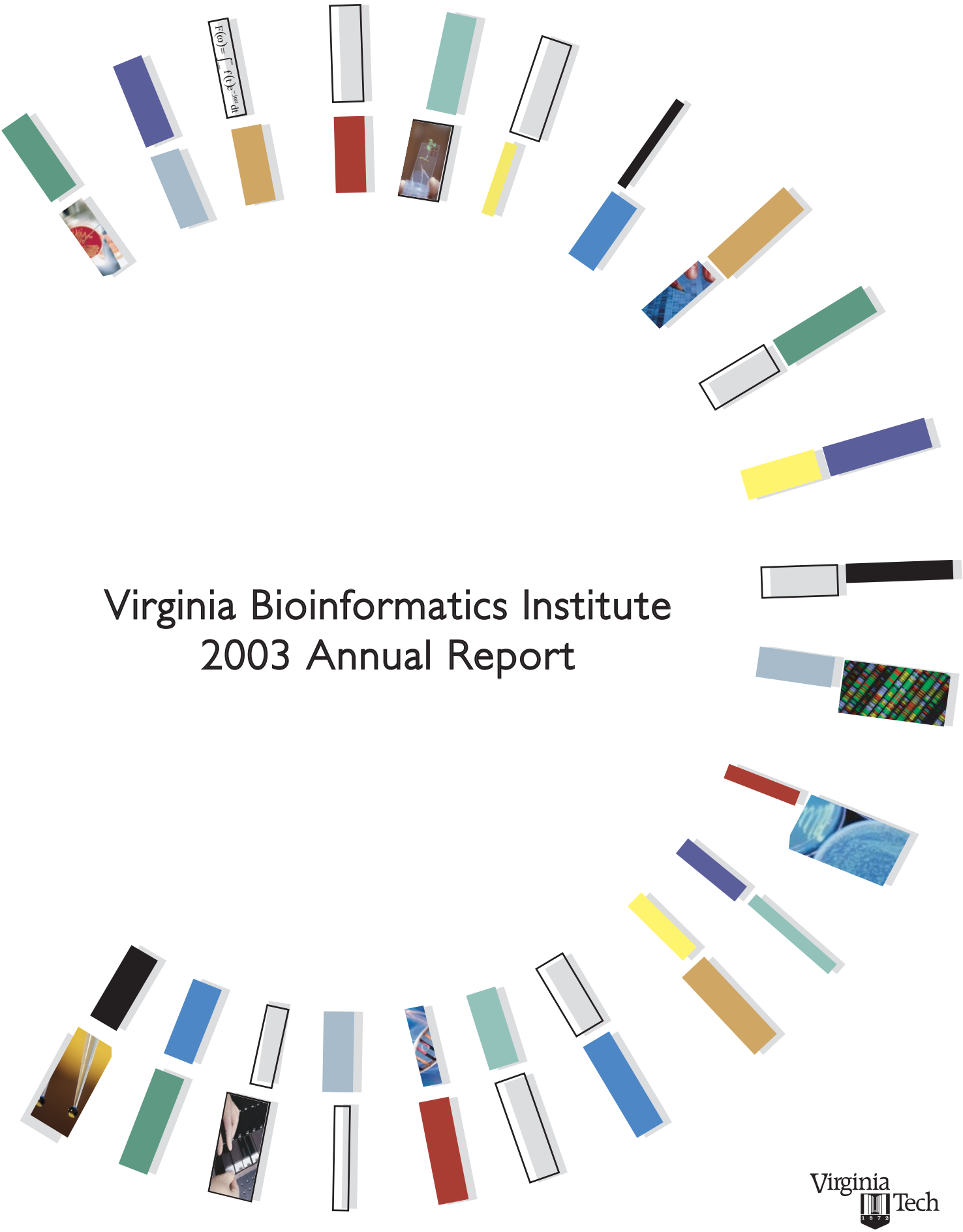
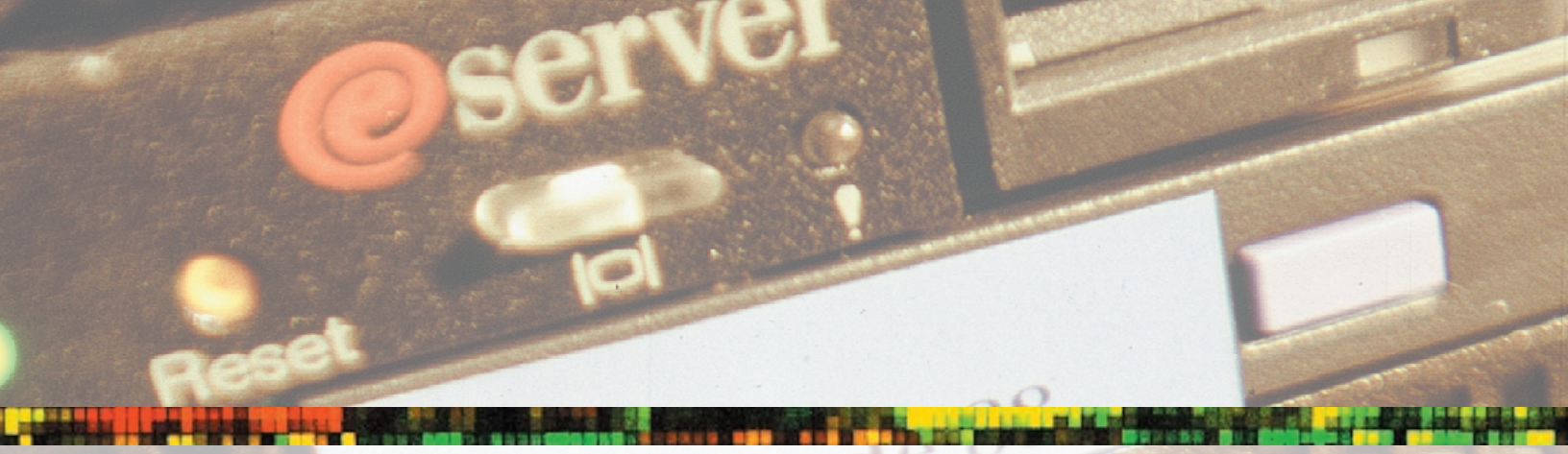


Virginia Bioinformatics Institute
2003 Annual Report

Virginia Tech



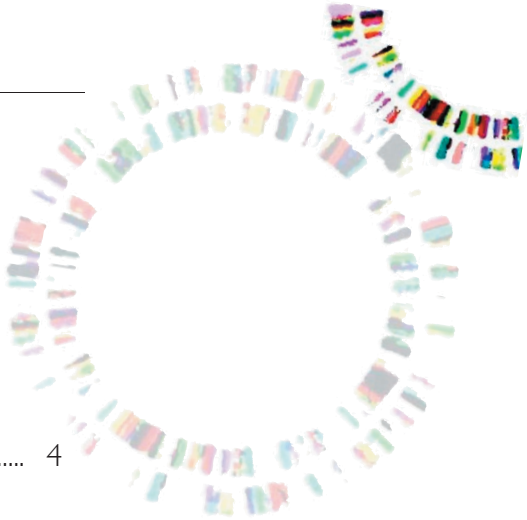
Combining cutting-edge technology and biological research for the advancement of national and global priorities, prosperity, and innovation.

$$F(k\Delta f) = \sum_{n=0}^{N-1} f(n\Delta t) e^{-j(2\pi k \Delta f)(n\Delta t)} \qquad k = 0, 1, 2, \ldots, N$$

$$F(\omega) = \int_{-\infty}^{\infty} f(t) e^{-j\omega t} dt \qquad dR = \frac{\partial R}{\partial x_1} dx_1 + \frac{\partial R}{\partial x_2} dx_2 \ldots = \sum dx_i \frac{\partial R}{\partial x_i}$$

www.vbi.vt.edu

CONTENTS



Venturing Beyond Information

Message from the President

In the tradition of Virginia Tech's motto of *Putting Knowledge to Work*, Virginia Bioinformatics Institute's research platforms continue to power innovative advancements in research and technology as well as economic development for southwestern Virginia and beyond. This document highlights notable achievements in bioinformatics research and education during the past year at VBI. Empowered by many collaborations, VBI continues to gain respect as an epicenter of research excellence founded on the creative energy of a multidisciplinary research faculty and staff, pioneering research approaches, and ever–growing educational programs.

Virginia Bioinformatics Institute's research goals will foster continued growth and new discoveries in bioinformatics. Its continuous energy force comes from a yearning for knowledge—not only to make advances—but leaps in the global bioinformatics community. We look forward to Virginia Bioinformatics Institute's continuing contribution to Virginia Tech's larger momentum as a growing and well–respected research university.

Virginia Tech is delighted to share Virginia Bioinformatics Institute's progress and advancements in this annual report. Looking ahead, Virginia Tech remains committed to investing in the most promising areas of science and engineering research and education. We can be certain that the results will enhance scientific discovery and its application in profound and extraordinary ways.

Regards,

Dr. Charles Steger
President,
Virginia Polytechnic Institute and State University

Letter from the Director

Through this annual report, I invite you to explore the world of Virginia Bioinformatics Institute. Now a fully integrated research institute empowered by a research faculty and staff of more than 160, our research portfolio encompasses almost $30 million in grants and contracts centering on understanding host–pathogen–environment interactions. These research programs are at the frontier of answering important and diverse questions impacting human and animal health, agricultural production, environmental preservation, and technology development.

As we continue to shape our bioinformatics research programs, this report offers the opportunity for us to share our dedication to advances in research and technology, our drive to enhance southwestern Virginia through economic development activities, and our participation in educational programs on many levels. We value the power of partnership in all our endeavors and are pleased to offer cutting–edge technologies and infrastructure via our Core Laboratory and Core Computational Facilities.

Through this report, it is my hope that you take away an understanding of who we are and what we do. As our research endeavors continue to take shape and grow, I welcome you to check in with us from time to time as we continue to *Venture Beyond Information*.

Regards,

Dr. Bruno Sobral
Executive and Scientific Director,
Virginia Bioinformatics Institute

VIRGINIA BIOINFORMATICS INSTITUTE
AT VIRGINIA TECH

VBI in Brief

VBI Building XV at Virginia Tech's Corporate Research Center

Since its inception in July 2000, VBI has become a cutting–edge center for life science and technology research. As an economic catalyst for the commonwealth of Virginia, VBI has developed strategic collaborations with leaders in government, industry, and academia, attracting almost $30 million in research grants and contracts.

VBI has reached major milestones in the past three years, yet the goals for the future continue to lift VBI to new heights and lead it in exciting directions. VBI's bioinformatics and life sciences research meld a unique portfolio of systems biology research focusing on host, pathogen, and environment interactions.

"We sometimes find the most fertile fields for discovery at the intersections of traditional disciplines. VBI's efforts in bioinformatics epitomize this richness."

Dr. Rita R. Colwell
Director
National Science Foundation

VBI: Building for Progress

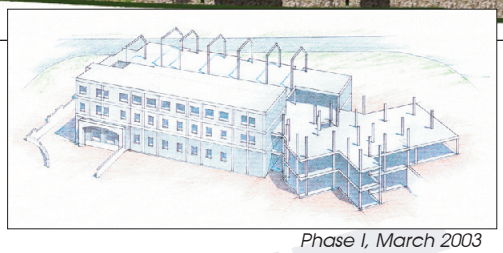
Architect's Rendering, Phases I and II
VBI's Campus Location

Growth and construction have played a major and necessary part of VBI since its inception. With its start in a small sub–leased space in July 2000, the institute now anticipates occupying more than 130,000 square feet within the next two years.

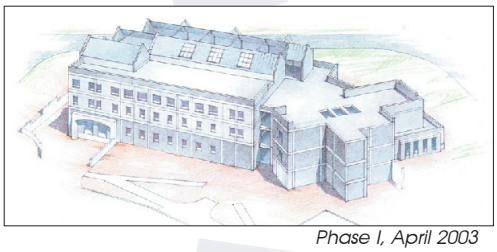
VBI is presently housed in Research Building XV in Virginia Tech's Corporate Research Center, adjacent to the university's campus. The 52,842 square–foot facility offers modern office and laboratory space in a high–quality work environment nestled in an alluring mountain setting.

VBI's growing research programs now underscore the need for additional space. To that end, construction is underway on a new facility on Virginia Tech's campus. In December 2003, over 100 VBI employees will move into the first installment of VBI's permanent home, physically integrating VBI into the Virginia Tech campus community. This building, referred to as Bioinformatics Facility Phase I, comprises 59,000 square feet.

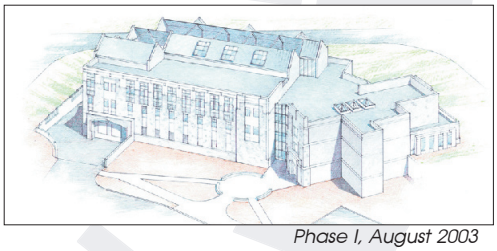
In order to reunite VBI into a common space as well as accommodate future growth, the construction of Phase II began in March 2003. The construction, anticipated to be completed in October 2004, will add an additional 71,560 square feet of space, bringing the total square footage of the institute to more than twice the size of the original facility. This marks the rapid growth and development of VBI.



Phase I, March 2003



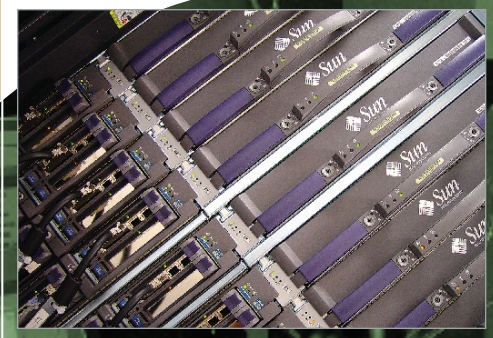
Phase I, April 2003

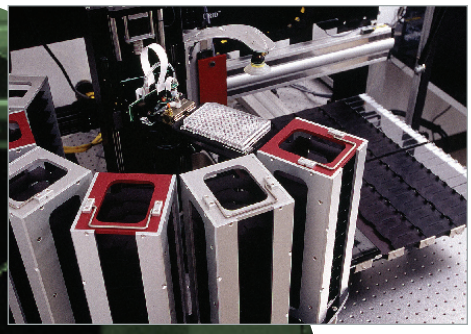


Phase I, August 2003

Construction of VBI Phase I

- Core Laboratory Facility (CLF)
- Core Computational Facility (CCF)





Core Facilities

"The new challenges of understanding systems biology will continue to draw us together across diverse disciplines. The Core Facilities at VBI are pleased to provide cutting–edge platforms and foundations for Virginia and beyond to facilitate this higher purpose of connectivity across science and engineering."

Susan Martino–Catt, Ph.D.
Director, Systems Biology
Virginia Bioinformatics Institute

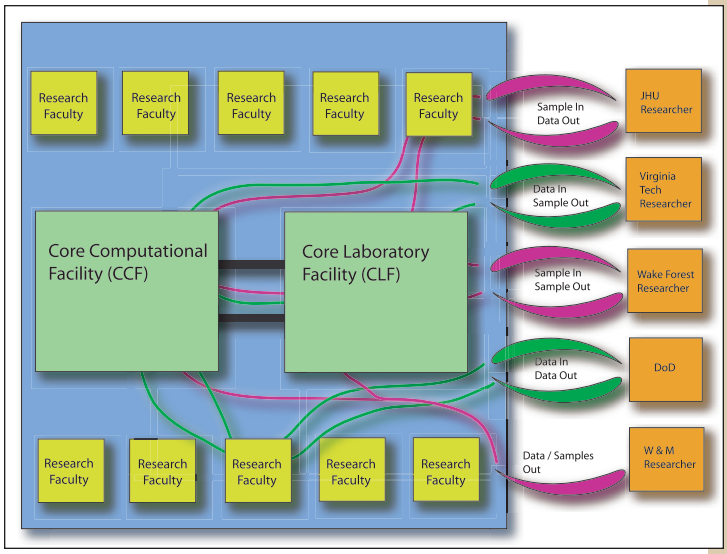
At the heart of VBI's infrastructure are two service-center facilities dedicated to bioinformatics data generation and analysis. Using state-of-the-art technologies, the Core Laboratory Facility (experimental) and the Core Computational Facility (computational) work seamlessly with researchers to catalyze new knowledge.

These Core Facilities ensure that the latest and greatest in bioinformatics technologies and tools are available and accessible on a cost-recovery basis to all facets of the scientific community. Applying this unique approach to bioinformatics research infrastructure synergizes scientific progress and economic development.

Integration of Core Facilities

To effectively address scientific questions posed by infectious disease research in the 21st century, VBI and collaborators quickly recognized the need for integrated state–of–the–art facilities to develop and deliver data and knowledge to stakeholders.

Integrated via a Laboratory Information Management System (LIMS), data generated in the Core Laboratory Facility flows to the Core Computational Facility, providing the computational backbone for research projects.



Role of Core Facilities in Virginia Bioinformatics Institute structure illustrated through a sample of existing partnerships. A Laboratory Information Management System is being implemented to foster data exchange and communication between the Core Facilities. The schematic illustrates the movement of biological samples and data between VBI's Core Facilities, research faculty, and collaborators.

Meet the Core Management

Susan Martino–Catt, Ph.D.
Director, Systems Biology

Susan Martino–Catt, VBI's Director of Systems Biology, focuses on the application and development of genomic technologies through the Core Laboratory Facility and works with researchers to apply these technologies to biological questions.

Dr. Martino–Catt joined VBI from Pioneer Hi–Bred International, Inc. There, she most recently served as Research Coordinator for Genomics at Pioneer—responsible for managing research groups involved in transcript and protein profiling, physical mapping, targeted genetics, and gene discovery. She has held previous positions at the Laboratory of Plant Molecular Biology at the Rockefeller University and the Center for Biological Timing at the University of Virginia. Martino–Catt graduated with her B.S. and M.S. degrees in Biology from Indiana University and Loyola University of Chicago in 1985 and 1987, respectively. She received her Ph.D. in 1991 from the University of Illinois while conducting research at the USDA Photosynthesis Research Unit.

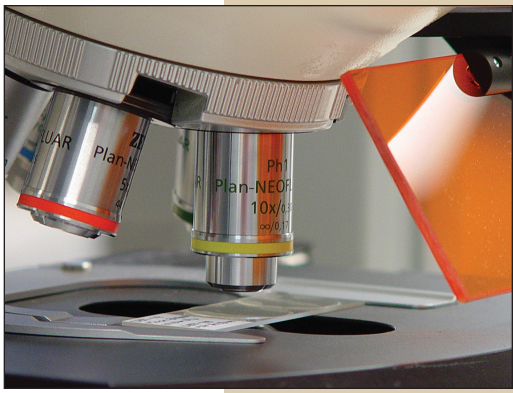
Dustin Machi
Manager, Core Computational Facility

Dustin Machi is the manager of VBI's Core Computational Facility (CCF) and serves as the information technology leader for the institute. His responsibilities include system design, support, security, and recovery, as well as building a cohesive and effective support team. Machi and his team have been instrumental in designing and coordinating the system requirements for the institute.

Machi has his B.S. degree in computer science and computer information systems from Tusculum College in Tennessee, where he served as Director of Information Systems. He has extensive experience with a number of programming languages, operating systems, and database technologies and is familiar with a number of network protocols, methods, and standards. Machi is currently completing his Ph.D. at Virginia Tech in computer science.

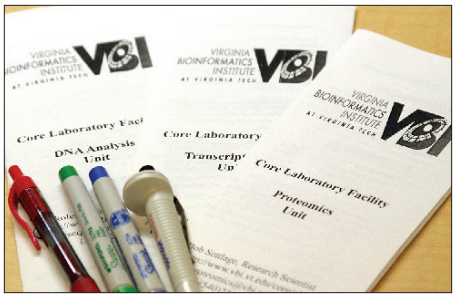
Core Laboratory Facility

The Core Laboratory Facility (CLF) functions as a multi–user resource dedicated to the development and application of various high–throughput technologies to aid in the discovery of biological macromolecules. These types of technologies are quite expensive to operate and maintain, making it difficult for individual laboratories to invest in this type of infrastructure. The CLF model, a "one–stop shop" for these technologies, provides researchers access to both its tools and experienced staff. The CLF's mission is to provide high quality data in a timely fashion and excellent customer service in a collaborative spirit.



The CLF currently provides analysis platforms for DNA (genomics), RNA (transcriptomics), and proteins (proteomics). Metabolic profiling capabilities are expected to be added within the next year. In addition to the ongoing application of existing technologies, the CLF is actively engaged in the development and testing of new technologies as needed.

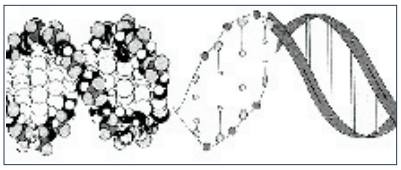
This combination of application and development enables the CLF to remain a leader in helping researchers take a complete systems biology approach to their science.



CLF Staff

CLF Personnel (left to right):
B. Settlage, L. Correll, J. Lennon, S. Martino-Catt, J. Fick, H. Norton, K. Finne, L. Comaratta

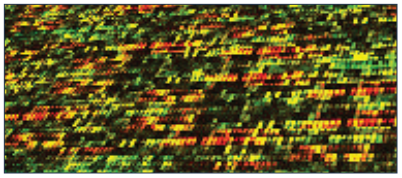
Genomics



Since the discovery of DNA's structure some 50 years ago, many advances have enabled researchers to study and dissect this macromolecule. Precisely unraveling the sequence of nucleotides comprising genes of interest centers gene discovery efforts. The CLF Genomics group focuses on this unraveling process, or DNA sequencing. Customers provide their DNA samples, which are then used in conjunction with template–specific primers (small fragments of DNA in which the sequence is known), fluorescently labeled nucleotides (colored probes that mark specific nucleotides), and DNA polymerase (an enzyme which catalyzes its formation) to generate labeled fragments of complimentary DNA.

These fragments are then analyzed on a fully–automated capillary electrophoresis machine and detected by a laser to generate a string of nucleotides representing the DNA sequence of the starting template. This sequence can then be analyzed and compared to other known sequences by various computational tools provided by VBI's Core Computational Facility (CCF). The Genomics group provides detailed DNA fragment analysis, which is useful when discriminating individuals from each other based on subtle differences in their DNA sequences. The group also performs various types of automated nucleic acid preparations to facilitate researcher needs.

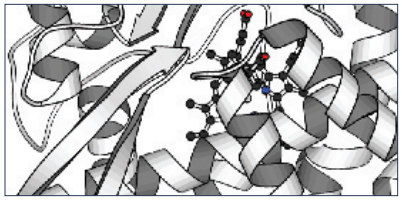
Transcriptomics



Monitoring gene expression—the level at which a gene is active in a living system—is paramount to understanding how biological systems function, how diseases spread, and how people age. While every living cell in an organism has a complete copy of that organism's DNA (or genome), not all DNA is utilized or transcribed equally in a living system to do work. The transcription of DNA (the genetic blueprint) into RNA (the chemical messenger sent from the cell nucleus to do work) depends on many factors including development, tissue type, and environmental stimuli. The Transcriptomics group focuses on detecting which specific pieces of an organism's DNA are transcribed into RNA. By using various types of microarray analysis platforms, researchers can monitor the activity of thousands of genes simultaneously.

VBI's primary microarray is the GeneChip® system provided by Affymetrix. This system has short oligonucleotide representatives of thousands of genes arrayed onto a glass surface. Various techniques are used to isolate and label RNA from specific treatment groups. This RNA is then used to probe the GeneChip® in order to identify what genes are being transcribed into RNA. Custom microarrays can be built for users by designing gene–specific oligonucleotides, which is followed by the use of a robot to carefully array these onto glass slides. Once gene expression data has been compiled, more assistance with the biological validation of this data is provided by using quantitative PCR to accurately measure the amount of RNA present. The combination of microarray data and quantitative PCR validation provides researchers with a strong list of candidate genes for further evaluation in their particular system.

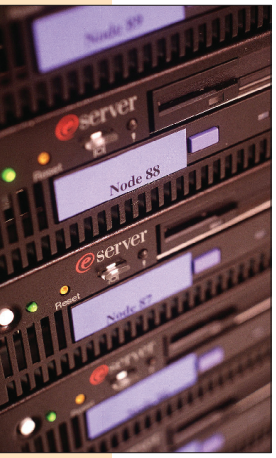
Proteomics



Proteomics, the study of proteins, is the most recent addition to the variety of services provided by the CLF. The technologies of gel electrophoresis and mass spectrometry combine to identify and characterize proteins within a given sample. The CLF is equipped to separate proteins either in a single dimension based on protein size or in two dimensions based on size and charge. Once proteins are separated by gel electrophoresis, extensive analysis of the resulting gel images is performed. Unique protein spots or proteins that appear to be differentially expressed between various treatments can be identified for further analysis.

These unique proteins are treated with various enzymes to generate short peptide fragments that can be analyzed by mass spectrometers to generate both peptide size and amino acid composition. These types of data are then compared against existing databases to provide the researcher with protein identifications. Analysis and management of the proteomic data is performed in collaboration with the CCF.

Core Computational Facility



VBI continues to evolve a holistic IT infrastructure to support computational analysis and systems biology research. VBI's Core Computational Facility (CCF) provides high–performance computational resources to VBI faculty, their collaborators, and the broader community. The CCF also provides systems and database administration for VBI and oversees administrative computing needs for the institute.

In addition, once proof–of–concept software systems are developed through research grants at VBI or elsewhere, the CCF has the capacity to harden and host these systems for VBI scientists or the community. By leveraging partnerships and sponsored research with information technology leaders, such as Sun Microsystems and IBM, the CCF provides a number of services on a cost–recovery basis.

CCF Personnel (left to right):
M. DiFilippo, D. Borkowski, D. Machi, I. Morozov, J. Shah, D. McMaster, R. Chase, N. Galloway

Powerful supercomputers, including a Sun Microsystems SunFire 15000 and an IBM Linux cluster, are at the core of VBI's computational processing. The facility includes an IBM Storage Area Network (SAN) that provides over 13 terabytes of combined disk and tape storage. Comprehensive data backup and recovery systems guarantee the integrity and availability of CCF services.

The CCF utilizes gigabit Ethernet as its communications backbone and has a dedicated, scalable, and high–speed internet connection. The completed construction of VBI's Phase I & II buildings will provide additional space for the CCF to more than double its current size. Staffed by a team of highly dedicated systems administrators, database administrators, and software developers, the CCF provides high performance capabilities to its customers.

Core Computational Facility Services

- **Computational processing** – CPU processing time on both parallel and symmetric multi-processing (SMP) supercomputers provides computational resources appropriate to a wide variety of applications.
- **Data storage and backup** – Data storage provides users with reliable disk storage. Robotic tape back-up systems ensure data availability.
- **Compound services** – Customers are offered packages of multiple services. For example, database services include computational processing, storage, database administration, and application hosting.

CCF Database Group

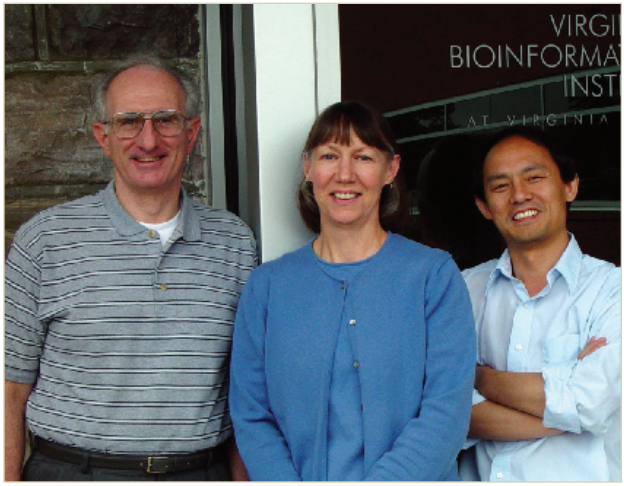
The Core Computational Facility Database Group (CCFDG) works with scientific investigators, laboratory scientists and technicians, and associated collaborators to provide the highest quality, lowest cost database design, analysis, development, and maintenance services in support of basic and applied research. Staffed by professional database system designers and administrators, the CCFDG offers the following services:

- Requirements identification and analysis
- Functional and technical design
- Data modeling
- Development, testing, and implementation
- Backup and recovery
- Project management
- Customer support
- Compliance and quality assurance
- New technology research and development

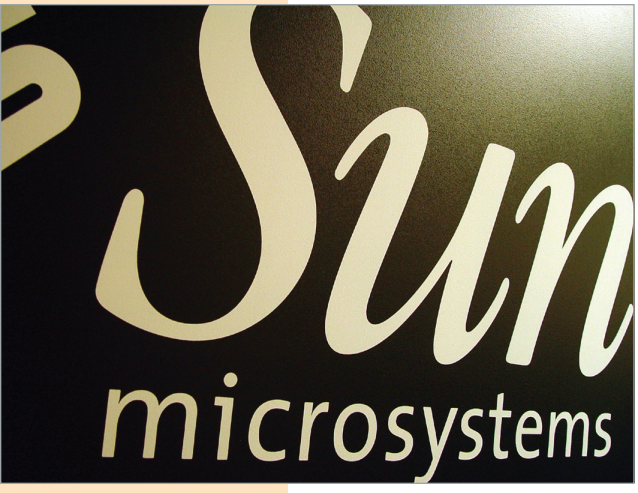
All tasks are performed using software tool sets that employ industry recognized database standards. Mission critical systems are installed on UNIX, Linux, and Microsoft Windows servers hosting Oracle9i, PostgreSQL, and MySQL relational databases. Currently, several major life science research and analysis projects, administrative programs, and open source or commercial laboratory information management systems (LIMSs) are undergoing evaluation, being developed, or are in full production, including the:

- SeedGenes Project
- Expressed Sequence Tag Analysis Pipeline (ESTAP)
- Advanced Computational Research Environment
- Genomics Unified Schema Database
- National Institutes of Health Cancer LIMS, and other LIMSs supplied by the Affymetrix, MicroMass/Bio–Rad, and Advance Chemistry Development Corporations

Each scientific database is designed to support a research project's unique information requirements. Associated data is retrieved from a myriad of sources including domestic and international genome repositories, local and remote laboratory instruments, and recognized scientific publications. Fully protected by an automated suite of Oracle, IBM, and third–party backup and recovery systems, mission critical data is secured and archived in redundant online and offsite storage systems.



CCFDG Personnel (left to right): P. Toffenetti, S. Waldon, D. Kong



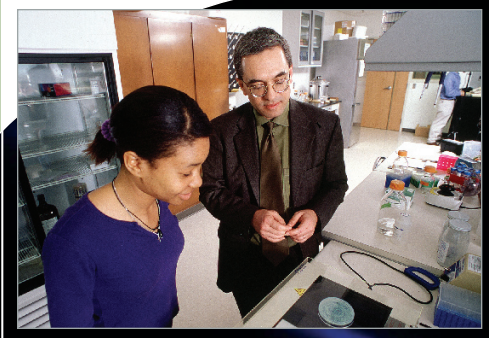
VBI's DeCypher® system is being implemented via a Sun Microsystems SunFire 15K supercomputer.

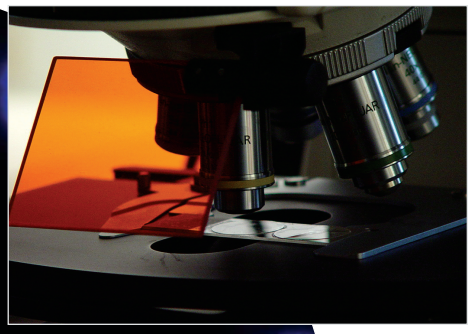
VBI's CCF: Home to World's Largest Academic TimeLogic™ DeCypher® Installation

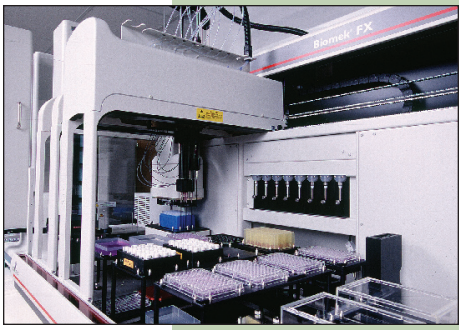
Researchers at VBI now do genome–to–genome comparisons at a much faster rate with the TimeLogic™ DeCypher® system, a configurable system that accelerates computational tasks. VBI's system, the world's largest academic installation, speeds over 30 types of bioinformatics searches.

Composed of six hardware accelerators, the system quickens the analysis of DNA sequences, allowing scientists to understand the actual biological function of DNA much faster and more economically. This technology will be used at VBI to study the evolutionary genetics of organisms and the genetic basis of human, animal, and plant diseases. Implemented within the CCF's Sun Microsystems SunFire 15K supercomputer, the system delivers powerful bioinformatics analysis capabilities that allow broad comparisons among numerous biological systems. Researchers are now able to do DNA sequence comparison against databases and whole genome comparisons at a much faster rate with the system. This DeCypher® system is now available to the research community via VBI's Core Computational Facility on a cost–recovery basis.

- Agriculture and Environment
- Informatics and Modeling
- Biomedicine







Research

"In the same way that society has long depended on connectivity through roadways, power grids, and market systems, the evolution of informatics systems will greatly accelerate the presence of an informed global community."

Bruno Sobral, Ph.D.
Executive and Scientific Director
Virginia Bioinformatics Institute

As our understanding of complex biological systems increases, VBI must utilize an integrated research approach to manage the huge amount of data that results. VBI fosters an interdisciplinary approach to exploring the great scientific questions of today. These efforts center on understanding the disease triangle, or host-pathogen-environment interactions, as a starting point to mathematically model biological systems.

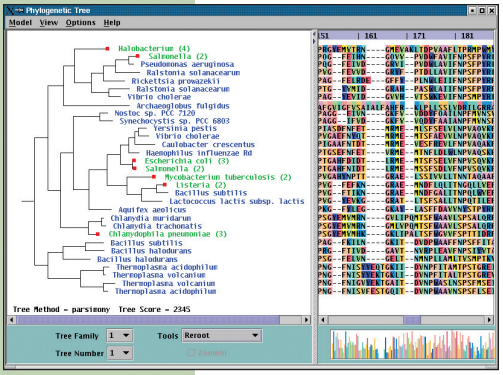
Through collaborations with academia, industry, and government, VBI maximizes resources and creates important partnerships from which the most dynamic bioinformatics research develops.

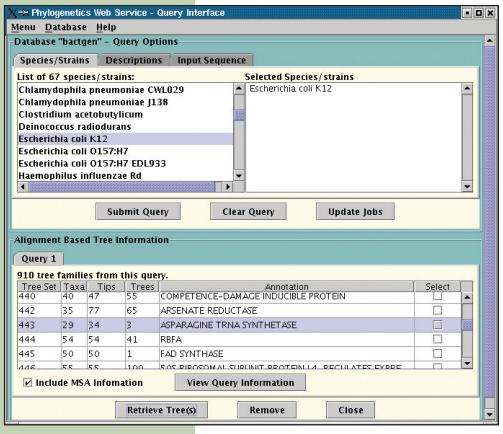
Agriculture and Environment

The goal of agricultural and environmental research projects at VBI is to find solutions to agricultural problems that affect Americans every day, from field to fork. An interdisciplinary approach synergizes research approaches to understand plant and animal traits that affect agricultural production, the environment, and human health and nutrition.

Aided by new tools of biotechnology and bioinformatics, scientists now have the capability to delve into the inner–workings of plants and animals and gain increased understanding of how their biological processes work. From protecting crops and livestock from pests and disease to improving the quality of agricultural products and from sustaining our natural resources to ensuring profitability to farmers, VBI researchers work to provide a framework of new knowledge that will allow society to reap consumption and health–related benefits from plants and animals while sustaining natural resources.

Traversing the Evolutionary Roadmap: Phylogeny Database to Identify Plant Duplication Events





Screenshots of an informatics web service used to analyze evolutionary relationships among organisms.

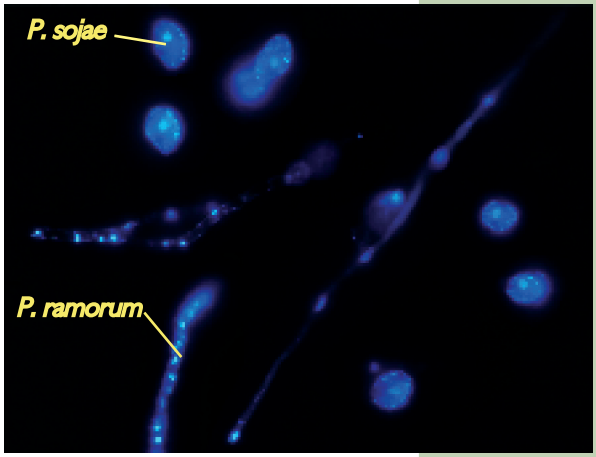
To generate superior genetically engineered crop varieties, scientists must first identify the genes responsible for desired traits. However, crop plant genomes complicate this search because of their polyploidy ancestry. Polyploidy is having one or more sets of extra chromosomes, such that each gene occurs in more than one copy. Over the course of evolution, many of these genes lose function or evolve to perform new roles. Therefore, accurately assessing which plant genes are responsible for a given trait is difficult. Determining the relationship between plants and their evolution has the potential to provide vast benefits to the agricultural community, as crop improvement hinges on first identifying desired genes.

Dr. Allan Dickerman is developing an informatics system to perform phylogenetic analyses using entire genomes of organisms. This phylogenomics approach, or grouping based on ancestry, will aid in the description of the evolutionary history of all genes within particular genomes of interest. The questions that can be uniquely addressed by such a system include analysis of whole or partial genome duplications and subsequent rates of gene loss. The gene–phylogeny approach is also advantageous for gene annotation within gene families. From these data, a phylogenetic tree database can be constructed to detail the lineage of plants in relationship to one another and determine at what point in time a new species branched from their predecessors. The database will also make it possible to target sequence data that can be used to further agricultural development.

The ability to query and visualize data is made possible by a module of the VBI ToolBus software. The Plant Duplication Events effort is funded in part through a USDA/CSREES grant awarded to Drs. Bruno Sobral and Dickerman of VBI and through the VBI PathPort Project.

Structure and Function of *Phytophthora* Genes

Plant pathogens from the genus *Phytophthora* are responsible for destructive diseases affecting an enormous variety of crop plants, such as soybean, strawberry, watermelon, as well as forests and native ecosystems. The potato pathogen, *P. infestans*, was responsible for the infamous Irish potato famine and is now a pathogen of concern from a bioweapons standpoint. The newly emerged pathogen, *P. ramorum*, currently attacks oak trees in California causing sudden oak death syndrome. The soybean pathogen, *P. sojae*, results in serious crop disease costing growers up to $2 million annually. Superficially, *Phytophthora* pathogens resemble fungi, but they belong to a kingdom of life called Stramenopiles. Hence, conventional fungal control measures often fail against these pathogens.



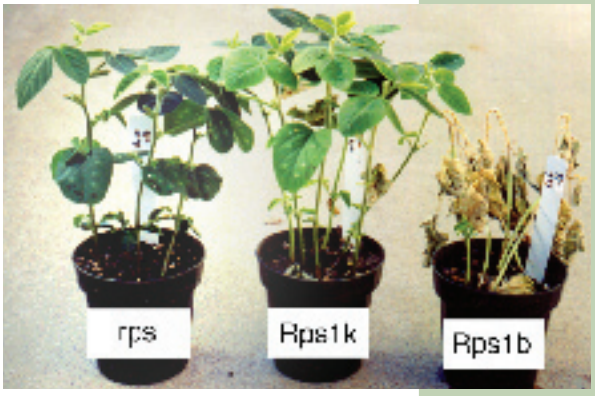
Nuclei containing DNA from the oak pathogen, P. ramorum *(long threads), compared to nuclei containing DNA from the soybean pathogen,* P. sojae *(lemon-shaped spores). Brett Tyler's group is determining the DNA sequences of all the genes in* P. ramorum *and* P. sojae.

Dr. Brett Tyler leads an effort to identify genes in *Phytophthora* species that contribute to its ability to cause infection. Funded by a $1 million grant from the United States Department of Agriculture, VBI scientists have determined the sequences of around 7,000 genes expressed during infection and growth in *P. sojae* and another 4,000 *P. infestans* genes expressed during infection.

In October of 2002, VBI in collaboration with the Department of Energy Joint Genome Institute (JGI) began a $3.8 million project funded by USDA, NSF, and DOE to sequence all genes in *P. sojae* and *P. ramorum*. The VBI–JGI research team will produce and assemble the raw DNA sequence data while the VBI team will create a web–based bioinformatics annotation system allowing *Phytophthora* experts from around the world to access the data. Dr. Tyler's team is also developing a procedure to rapidly test the function of sequenced *Phytophthora* genes via inactivation or alteration of expression timing. This will help elucidate the genes that function during the infection process—leading to new approaches to fight disease.

An Arms Race: The Plant–Pathogen Chase

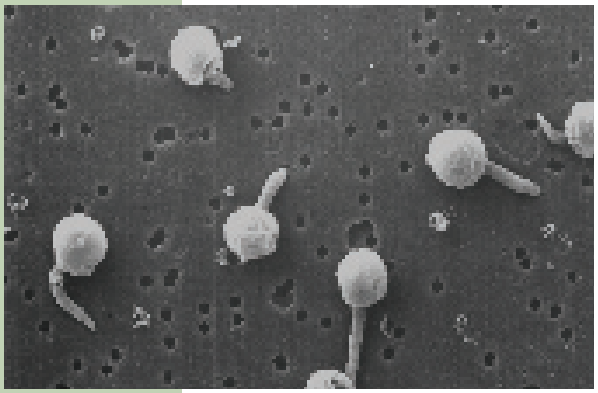
In the ongoing battle between plant and pathogen, plant–pathogenic microbes have evolved special mechanisms to defeat plant defenses. To protect themselves, plants evolve new counter–measures, which result in the evolution of new virulence mechanisms by the pathogen. As a result of this "evolutionary arms race," large numbers of plant genes become involved in the plant's pathogen resistance (called multigenic or quantitative resistance), and a number of pathogen genes contribute to its virulence. Not surprisingly, crop breeders have found that improving multigenic resistance results in longer–lived crop protection than does resistance conferred by a single gene. However, this complexity makes improving disease resistance through conventional breeding quite challenging.



The protein Avr1b, secreted by the soybean pathogen Phytophthora sojae*, kills sensitive plants (Rps1b). Brett Tyler's group is studying how plant pathogens weaken and overcome plant systems.*

In October 2002, VBI and collaborators were awarded $6.7 million from the National Science Foundation to apply genomics and bioinformatics approaches to identify and understand multigenic soybean resistance to *Phytophthora sojae*. Using cutting–edge techniques available in the VBI CLF, the project will ultimately measure the activity level of most genes of soybean and *P. sojae* throughout the infection process. Researchers will hence identify the plant resistance genes concurrently with identifying the pathogen genes that circumvent resistance. Different soybean varieties will then be genetically engineered to narrow down the location of the soybean genes that contribute to multigenic resistance. This collaborative project involves VBI, the Department of Crop and Soil Environmental Sciences at Virginia Tech, and Ohio State University.

Deciphering Pathogen Gene Function



Spores of the soybean pathogen, P. sojae, *invade holes in plastic sheets that resemble indentations on the surface of roots. Brett Tyler's group is studying how plant pathogens recognize susceptible plant species.*

Many diseases affecting humans, animals, and plants are caused by enigmatic or mysterious organisms that are evolutionarily very different from the "model" organisms used by molecular biologists, such as mice, fruit flies, or yeast. Organisms are typically classified in different kingdoms of life with plants, animals, and fungi each forming the distinct kingdoms.

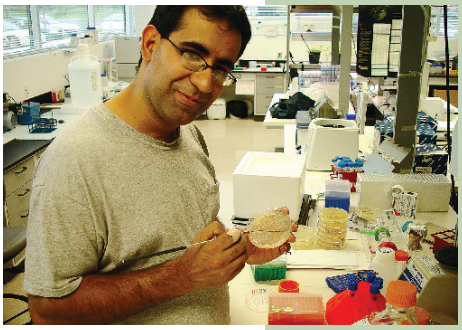
Phytophthora, however, is an example of a plant pathogen in an evolutionarily distant kingdom of life—the Stramenopiles. Because these organisms diverged from model organisms such a long time ago, inferring their gene function by comparing them with genes from model organisms is much more difficult. In partnership with VBI researchers Vladimir Shulaev, Pedro Mendes, and Reinhard Laubenbacher, and with researchers from John Hopkins University Bloomberg School of Public Health, Dr. Brett Tyler is using bioinformatics to discover techniques and rules for identifying functional similarities in genes that may even have come from organisms of different kingdoms.

In particular, this project focuses on identifying genes that protect organisms from oxidative damage. Host organisms often use oxidative damage to defend themselves against pathogens. This mechanism is also the mode of action for several anti–malarial drugs. Oxidative stress genes are being compared among baker's yeast, the model plant *Arabidopsis*, malaria's causal organism, and *Phytophthora sojae*. This will result in an improved understanding of how evolutionarily enigmatic pathogens cause disease. This new knowledge will, in turn, provide the infectious disease community with new information to apply to the development of preventative and therapeutic measures.

Dr. B. Tyler Research Group (left to right): L. Zhou, D. Guo, F. Arredondo, Y. Dan, B. Smith, T. Torto-Alalibo, N. Bruce, B. Tyler, S. Tripathy, R. Hanlon, E. Bush, X. Zhang (not pictured: D. Dao, C. Evans, T. Karkhanis, A. Ko, K. Krampis, L. McCoig, B. Oh, F. Salas, K. Tian, L. Waller)

Perfect Partners: Rhizobia–Legume Symbioses

Microorganisms perform all known biological nitrogen–fixation processes. In particular, bacteria of the genera *Rhizobium* and *Bradyrhizobium* inhabit the root nodules of leguminous plants (e.g., beans, alfalfa, and soybean). These bacteria and leguminous plants have developed a symbiotic relationship, which allow legumes the net benefit of fixing atmospheric oxygen. Understanding this biological process is of great interest from an evolutionary and developmental standpoint. In addition, industrially fixing nitrogen is costly, so an economic incentive for research exists. Dr. Bruno Sobral's wet laboratory research centers on understanding why, in particular, legumes establish the nitrogen–fixing symbiosis at the genomic level of both the pathogen and host.



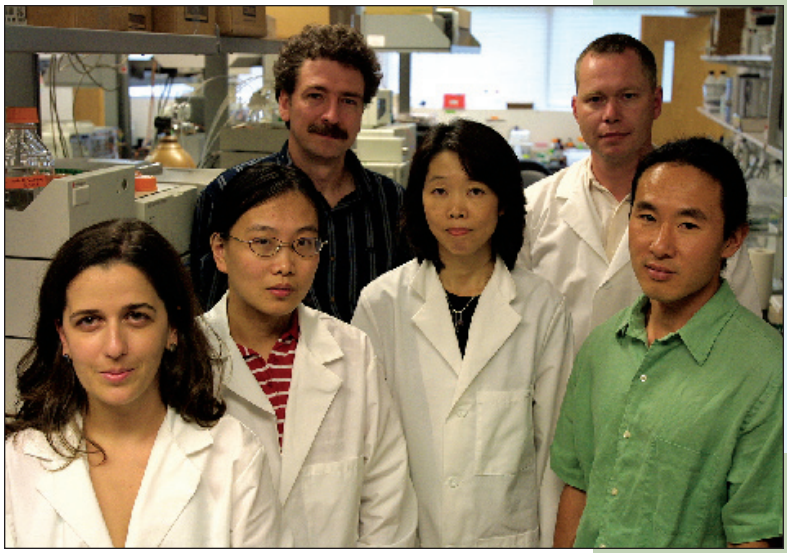
Dr. S. Malhotra studies cultures of Rhizobium *in the Sobral laboratory.*

Early events in the establishment of the symbiotic relationship between rhizobia and legumes seem to be demarcated by some of the same plant genes as those required for the association between plants and mycorrhiza, the beneficial fungi that aid in plant root development. However, mycorrhiza–plant relationships are much older and more widespread than rhizobia–plant symbiosis. The genomes of *Sinorhizobium meloti* and *Brucella* spp. (pathogens of humans, cows, and pigs) also exhibit a high level of similarity to rhizobial genomes, suggesting that certain features for achieving intracellular relationships may be conserved across bacterial species.

By comparing genes, proteins, and metabolites of the legume–rhizobial–like associations, Sobral's research team can pinpoint the similarities and differences within networks, genes, proteins, and metabolites affected during nodule development. This research will increase our understanding of intracellular bacterial pathogens, including information required to determine how other plant cultivars might be developed so they too can naturally fix nitrogen. This, in turn, would decrease our reliability on chemical fertilizers benefitting the agricultural community and the environment alike.

Berry Rich: The Genomics of Fruit

Historically, agricultural research has centered on increasing crop yield, quality, and pest management strategies. Today, however, malnutrition and both infectious– and nutrition–related diseases have also taken center stage as researchers work toward maximizing the dietary value of food and identifying novel compounds with pharmaceutical properties.



Dr. V. Shulaev Research Group (left to right):
A. Martins, J. Qian, V. Shulaev, T. Oosumi, N. Deighton, J. Shuman
(not pictured: V. Arora, D. Cortes)

With funding from the Virginia Tech ASPIRES grant program, Drs. Vladimir Shulaev and Allan Dickerman of VBI along with Drs. Richard Veilleux and Joel Shuman from Virginia Tech's Department of Horticulture, are developing a functional genomics platform for fruit crops using wild strawberry (*Fragaria vesca*) as a model plant species. Wild strawberry's fleshy fruit makes it an ideal model for fruit functional genomics research. This allows for the study of the molecular mechanisms involved in fruit development and ripening, as well as the detailed biochemical study of the fruit's profile at the metabolic level.

In order to elucidate gene functions for economically, medically, and nutritionally relevant phenotypes, this research team is generating a collection of t–DNA insertional mutants in strawberry. They will then screen this collection to identify mutant lines with enhanced disease resistance and improved nutritional composition. The project will enhance the community's knowledge regarding novel genes encoding nutritional and disease resistance attributes in major fruit crops.

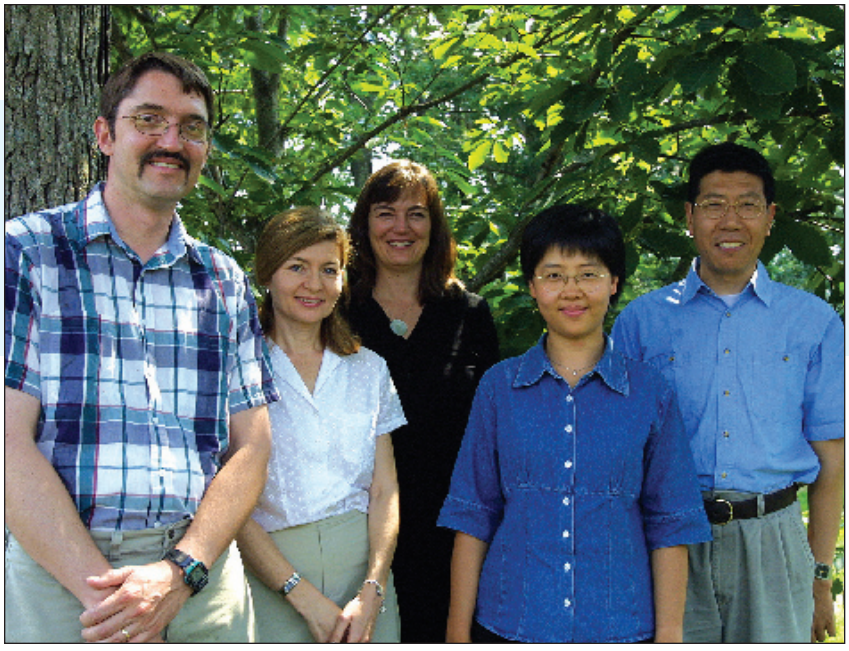
SeedGenes Project: Essential Genes in *Arabidopsis* Seed Development

Arabidopsis thaliana, or mouse–eared cress, is a small flowering plant used widely as a model organism in plant biology. NSF's *Arabidopsis* 2010 Project aims to identify the functions of all genes in this model plant. The SeedGenes Project, one component of this larger effort, centers on identifying and studying every *Arabidopsis* gene essential for seed development. Dr. Allan Dickerman of VBI currently collaborates with Dr. David Meinke at Oklahoma State University and others on this project coined "SeedGenes."

SeedGenes coordinates the collection, analysis, and presentation of information on essential genes that result in a severe seed phenotype when disrupted by mutation. *Arabidopsis* appears to contain about 750 such "essential" genes required for seed development. More than 20% of the genes in the evolving SeedGenes database appear to lack established protein motifs and are predicted to encode proteins with unknown functions. Gene expression analysis using Affymetrix *Arabidopsis* GeneChips® will be conducted to shed light on these "unknown genes" and to infer major regulatory processes in early development.

At present, the SeedGenes Database (www.seedgenes.org) contains two major sections: one includes genes; the other, mutant alleles. The June 2003 release of this database contains information on nearly 220 essential genes and 310 mutants as well as Nomarski micrographs of mutant embryo phenotypes providing a striking visual image of the delayed or otherwise distorted development of these mutants relative to normal wild–type plants. As *Arabidopsis* genes are identified and their function understood, this knowledge will be applied to the improvement of important agricultural commodities.

SeedGenes Project
Essential Genes in Arabidopsis Development
OSU syngenta VBI



Dr. A. Dickerman Research Group (left to right):
A. Dickerman, E. Shulaeva, J. Craig, Y. Tian, L. Yang

The Great Grape: Research Makes It Fruitful

The US produces 10% of the world's grape crop and is the third largest wine consumer country. Although droughts, excess rain, and other environmental stressors affect production, studies have shown that water–stressed vines produce phenomenal tasting wine in spite of stunted growth. To date, however, the molecular and biochemical reasons for both heightened taste and stunted growth are vaguely understood.

VBI's Dr. Pedro Mendes and Drs. John Cushman, Grant Cramer, and David Schooley from the University of Nevada–Reno are conducting research on *Vitis vinifera*, the grape plant commonly used for wine production and produce. With a $3.6 million grant from NSF, this research team will look at grapes on the level of transcripts and proteins and develop an informatics system to store, manage, and organize specific genetic data. This will enable them to identify strategies for increasing the stress tolerance of grape crops. In addition to achieving a better–tasting, longer–lasting grape and facilitating wine production, this research will enhance our understanding of the connection between environmental stressors and crop production on genetic, proteomic, and metabolomic levels.

Dr. P. Mendes leads the Biochemical Networks Modeling Group at VBI.

Informatics: Solving Microbial Mysteries

A wealth of unculturable microbes govern many ecosystem processes in terrestrial, subterranean, and aquatic habitats. However, the majority of these microscopic organisms remain unidentified. In order to better understand the genomics of these bacteria, VBI's Drs. Allan Dickerman and Brett Tyler, with funding from the National Science Foundation, will use bioinformatics to compare multiple genes from a variety of unknown organisms to study their functional genomics concurrently shedding light on their identity based on their function.

A major informatics challenge is data integration from the sequencing of different genes from a mixture of unknown organisms and then assembling a model to identify which genes co–occur within individual species. The VBI research team is developing an informatics–based solution to this problem founded on concordance of gene phylogenies and sequence attributes, such as codon bias and oligonucleotide word frequencies. This system will take anonymous DNA sequences from multiple loci and predict which ones come from the same species.

A successful solution for identifying microbes will enable a new level of sophistication in the way we can study the functional genomics of the largely unknown, unculturable microbes that dominate our natural ecosystems.

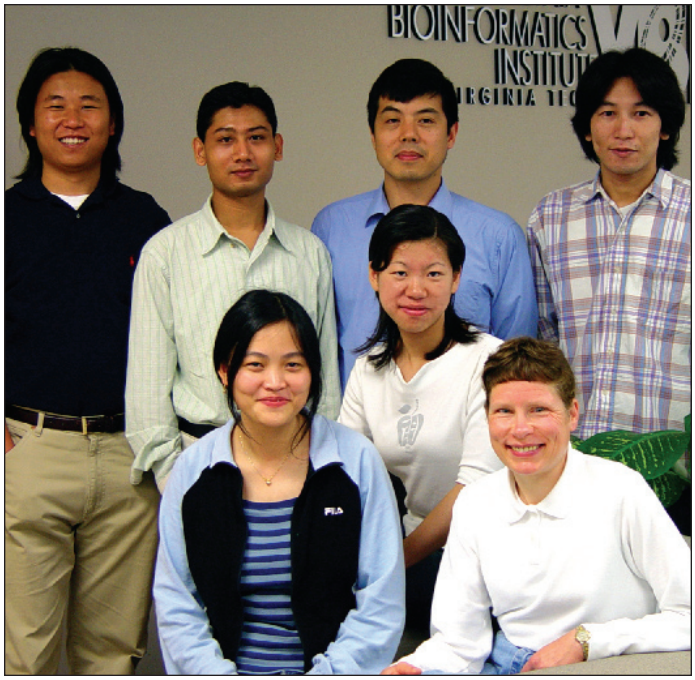
Informatics and Modeling

Since its inception, VBI has adopted a multidisciplinary, systems–oriented view of life sciences research. The quest to integrate, manipulate, and compute on the many disparate forms of molecular biological data is integral to VBI's mission. The long–term goal is to enable increased understanding of the disease triangle and to develop predictive models that span diverse scales of time and space. These can help reorganize biological research and education as well as result in new and faster ways to develop drugs, vaccines, and countermeasures for infectious diseases. A significant portion of this research is advanced by the application of mathematical models, simulations, and visualization tools.

Fine–Mapping of Genes

For VBI Research Professor Ina Hoeschele, comprehending genetic architectures means identifying genes involved in the developmental, physiological, and biochemical pathways leading to the desired trait; rebuilding genetic networks and maintaining biochemical pathways; and identifying subsets of genes that trigger variation between individuals and populations. To that end, researchers in the Hoeschele group, in collaboration with researchers at Boston University, develop statistical methods that pinpoint genome locations as precisely as possible.

One of the primary challenges of genome research is to understand the genetic architecture of quantitative traits, which are influenced by multiple genes, environmental factors, and their interactions. Quantitative traits are common in many complex human diseases, such as heart disease, diabetes, hypertension, and obesity.



Dr. I. Hoeschele Research Group
(top row, left to right): N. Bing, C. Chetia, G. Gao, H. Matsuda
(bottom row, left to right): B. Liu, M. Yan, I. Hoeschele

This NIH research paves the way for identifying underlying DNA sequence variants, crucial data for drug developers, and medical researchers seeking patient–specific treatment. Research in this area develops statistical methods for the fine–mapping of genes in human subjects, which are tested on data structures representing pedigrees and marker maps of the Framingham Heart Study, a 50–year epidemiological study that identified major risk factors associated with heart disease and stroke.

Hoeschele's group collaborates with Infigen Inc., a biotechnology company developing nuclear transfer and genomic technologies for applications in human healthcare. Supported by NIH, the two join forces to investigate the molecular basis of nuclear reprogramming in bovine and porcine embryos. In addition to improving cloning efficiencies, this work will contribute to developing therapeutic approaches for the regeneration of tissues and organs, novel cell–based therapies, tumor reversion, wound healing, and aid in the discovery of new drugs aimed at inducing developmental pathways.

Hoeschele's research also uncovers information of agricultural importance in both plant and animal breeding that can help expedite improvements in productivity, health, nutrition, and food safety. Plant applications include the identification of genes and their interactions in soybean plants presenting resistance to the soybean mosaic virus and the pathogen *Phytophthora sojae* (supported by NSF). Animal applications include developing strategies for the fine–mapping of economic trait genes in Monsanto swine populations. The potential savings of applying these genomic biotechnologies is economically significant as diseases in plant and animal agriculture result in billions of dollars of annual losses.

Using Yeast to Rise: Mathematical Modeling Applied to Oxidative Stress

Oxidative stress affects most organisms—from bacteria to humans—that require oxygen to survive. Oxygen, a very reactive molecule, generates additional reactive and dangerous molecules known as reactive oxygen species (ROS). Highly toxic, ROS are responsible for cellular stress due to highly reactive behavior. A number of human diseases, such as Alzheimer's and Parkinson's, seem to be related to ROS. Aging is also largely attributed to the action of these toxic molecules. Cells have evolved a variety of mechanisms to protect themselves from the damaging effect of ROS and other oxidants. In animals and yeast, one important mechanism involves the molecule glutathione, which is abundant in these cells. Glutathione reacts with ROS transforming them into molecules that are less damaging to the cell.

In its finality, this project will bring together a coherent data set on gene and protein expression levels, concentrations of a number of small molecules of yeast under oxidative stress, and the generation of a mathematical model describing the biochemical network responsible for the cellular response to oxidative stress. Such a model will further our knowledge on the oxidative stress process and provide insight into new ways to combat related diseases.

VBI has been awarded over $1 million from the National Institute of General Medical Sciences to carry out a mathematical modeling project to investigate the response to oxidative stress using a common model system for human disease, baker's yeast (*Saccharomyces cerevisiae*). Drs. Reinhard Laubenbacher, Pedro Mendes, and Vladimir Shulaev are particularly interested in finding the function of several genes and proteins involved in this process. Knowing these gene functions will clarify the mechanism of glutathione degradation and shed light on the possible role of vitamin C in yeast. This four–year project has two objectives: to develop new mathematical modeling methods for systems biology and to improve our knowledge of cellular defenses against oxidative stress. The mathematical approach involves the development of methodologies combining continuous and discrete mathematics, which are applied to data obtained by simultaneous measurements of mRNA, proteins, and metabolites. Experimental results, together with the mathematical frameworks developed, will generate hypotheses about glutathione regulation in yeast. The models will suggest new experimental designs to test those hypotheses.

Yeast Research Group (left to right):
R. Laubenbacher, P. Mendes, A. Martins, V. Shulaev, B. Stigler, A. de la Fuente

Polynomial Models for Biological Networks

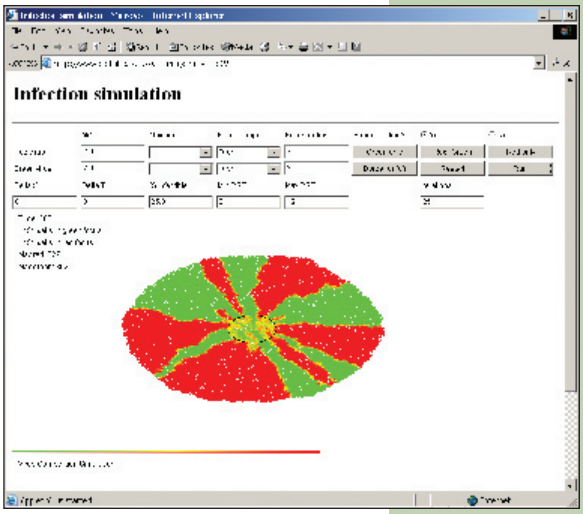
Modeling and simulation have become important tools to study biological networks. Several mathematical frameworks have been employed to model systems at various levels, from gene regulatory networks to the level of ecosystems. The modeling framework being developed by the mathematics group led by Dr. Reinhard Laubenbacher uses time–discrete dynamical systems on finite state sets, which are described by polynomial functions over a finite field. The framework created through polynomial models allows the use of tools from computational algebra and algebraic geometry for the analysis of the relationship between the structure of the simulated polynomials and the resulting dynamics. These theoretical results are being applied to a computer model of immune system response to certain viral pathogens. The goal is to study possible control points that could be used to modify immune system performance in beneficial ways, through drugs, vaccines, and other interventions. The theoretical framework allows the exploration of multiple control inputs.

Algebraic Algorithms for Cell Complexes

The use of cellular complexes as data models represents a novel application of these structures in science and engineering. Computational algebra, combinatorics, and combinatorial topology methods combine to catalyze this unique approach. In collaboration with Bernd Sturmfels at the University of California, Berkeley, and supported by NSF's Computational and Algebraic Representation of Geometric Objects program, Dr. Laubenbacher leads this research concerned with the algorithmic representation of cell complexes, a special type of topological space. These complexes arise as topological models of data and processes in science and engineering. Specific applications of interest involve biological, social, and communications networks, as well as problems in statistics. Topological invariants of the complexes provide measures of certain characteristics of the processes producing the data. One application of these techniques is the development of software tools that allow the rapid comparison of large–scale gene expression measurements, allowing rapid searches to automatically compare gene activity profiles from a great variety of organisms or experimental conditions.

Discrete Mathematics Group (left to right):
N. Polys, R. Laubenbacher, O. Colon-Reyes, B. Stigler, M. Todd, C. Yoo, J. Shah, H. Vastani, R. Luktuke
(not pictured: L. Garcia, D. Potter)

In Vitro Virus Competition



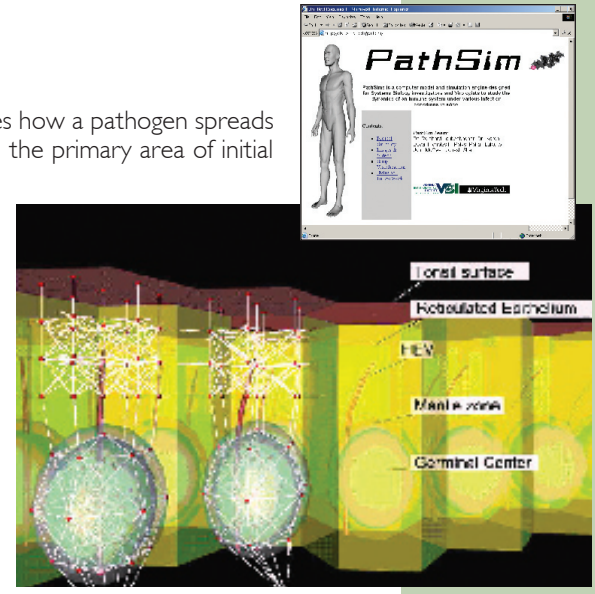
Infection simulation using Sim2Virus. A dual infection (red and green virus) begins in the center of the "cell" monolayer and propagates outward radially.

Many viruses, due to their genetic lability, rapidly evade vaccine–induced immunity. It is important to be prepared to cope with pathogens against which no vaccines have been made. The new tools of biotechnology present opportunities to dissect the entire viral infection process, revealing potential therapeutic intervention points that were previously inaccessible. Competition between pathogen strains within the same host can affect the onset of disease. By combining agent–based simulation with new mathematical methods, the Sim2Virus project at VBI will create an information tool to help answer questions about virus competition. This project, developed by VBI research faculty members Drs. Karen Duca and Reinhard Laubenbacher in collaboration with Dr. A. Jarrah at East Tennessee State University and Dr. A. Blumer at Tufts University, uses computer simulations to study an *in vitro* competition between two strains of murine hepatitis virus: MHV–4 variant 2.2.1 (JHM) and MHV–A59 (A59). Identifying conditions that favor recombination between the two strains under conditions of limited diffusion is a major theme of this project.

Sim2Virus (www.cs.tufts.edu/~ablumer/sim2virus.2), a simulation, models the spread of JHM and A59 on a hexagonal grid of cells. The viruses are distributed randomly into cellular boxes in a single time step. They replicate to generate new viruses that get distributed randomly to the local neighborhood at the next time step. The output of Sim2Virus is graphical and mimics the epimicrographs seen in immunostaining experiments. Initially, a region in the center is infected at random with JHM and A59 in amounts that the user may specify. The user also controls the geometry of the area to be infected.

From this, Duca and Laubenbacher hope to understand the dynamics by identifying steady–state behaviors from certain initializations of the system. Furthermore, new techniques can be used to reduce the dimension of the simulation and the size of its state set, while retaining control over the dynamics. Laboratory experiments will be used to validate the simulations and to verify the predictions derived from the mathematical analysis. This research will help the larger community understand virus behavior.

PathSim Project

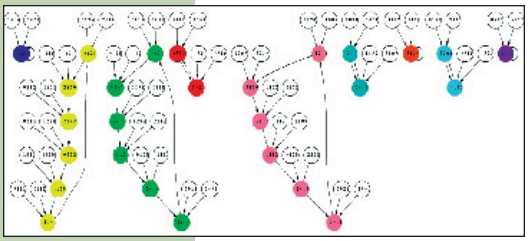


By modeling the human immune system response to infection, VBI's PathSim led by Drs. Laubenbacher and Duca, will understand the incremental stages of an immune response, as well as pinpoint processes that new pharmaceuticals may enhance to ward off illness. Here we see the representation of germinal centers on the epithelium, or top layer, of a tonsil from PathSim.

PathSim, an agent–based computer simulation, visually describes and analyzes how a pathogen spreads from its initial infection in the human body. The simulation tool focuses on the primary area of initial infection, the Waldeyer's ring regions, a ring of lymphoid tissue that encircles the nasopharynx and oropharynx. The Waldeyer's ring is formed by the lymphatic tissue of the pharynx, the palatine tonsil, and the lingual tonsil, as well as other collections of lymph tissue in the area.

The input for this simulation is in XML, selected because of its universal applicability in the exchange of a wide variety of data. The input file describes the anatomy for a particular region of the Waldeyer's ring, creating corresponding data structures. Guided by user specifications and knowledge culled from the literature, viruses and agents may be distributed within the region and simulations run. A rule set governing the behavior of agents is applied to each agent during the simulation run. At every time step in the simulation, an XML output file describing the present state of the system is captured to disk. This output file becomes input to the visualization and analysis tools, which enables study of the infection in greater detail. Collaborators include David Tharley–Lawson from Tufts University's Medical School and Abdul Jarrah from East Tennessee State University. Visit the project at http://www.vbi.vt.edu/~pathsim/3d.html.

Mathematical Foundation of Simulation Science



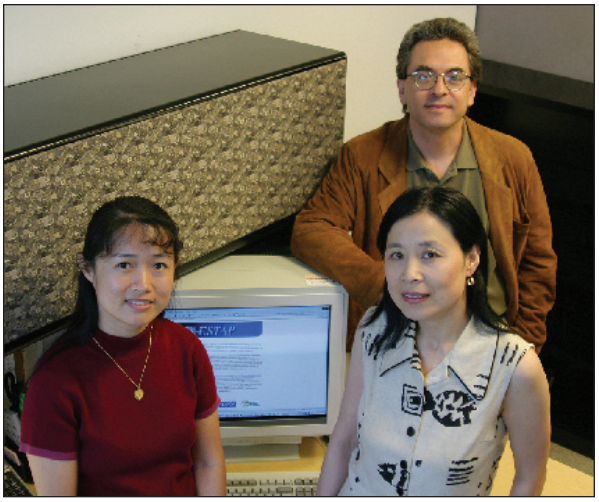
Visualization of network dynamics using the graph-drawing package, GraphViz (www.graphviz.org).

Since the beginning of the twentieth century, the term infrastructure has been used to refer collectively to roads, bridges, railways, and similar works required for an industrial economy to function. The interdependencies of this type of system require a thorough understanding of each component and the role each plays in the effectiveness of the system as a whole. Powerful simulation tools can provide a means for representing and assessing the level of complexity involved in understanding this interaction. These tools will be applied for the design and analysis of PathSim at VBI by Dr. Reinhard Laubenbacher.

This effort is a joint project with the Basic and Applied Simulation Science Group at Los Alamos National Laboratory that grew out of the need for mathematical tools to analyze large–scale computer simulations. Domains of interest include simulations of infrastructure systems and, more recently, epidemiological simulations focusing on the spread of pathogens in urban areas. The approach involves taking the essential ingredients of a simulation and incorporating them into a mathematical object. Mathematical tools can then be developed to help design such simulations and analyze their properties. Results from this work will be applied in the PathSim project for design and analysis. Collaborators include Chris Barrett, Madhav Marathe, Henning Mortveit, and Christian Reidys from the Simulation Science Group at Los Alamos National Laboratory and Bodo Pareigis at the University of Munich.

The EST Analysis Pipeline

Through Expressed Sequence Tag (EST) projects, the scientific community discovers the latest gene functions and studies them more thoroughly. ESTs are markers that denote specific types of genetic material in cells, known as ribonucleic acid (RNA). RNA is the chemical messenger in cells that travels from the cell nucleus to be coded for proteins essential to the structure and function of living organisms.



ESTAP Group (left to right): C. Mao, C. Hao, B. Sobral

The EST Analysis Pipeline (ESTAP) project, developed by Drs. Chunhong Mao and Bruno Sobral of VBI, Dr. Greg May of the Samuel Roberts Noble Foundation, and Dr. John Cushman of the University of Nevada–Reno, is funded by VBI, the University of Nevada at Reno, and the Samuel Roberts Noble Foundation. It provides an automated organizational system that allows researchers to use informatics in their work. Most EST projects involve sequencing 4,000 to 20,000 ESTs, creating an unmanageable amount of data. With ESTAP, a database handles the data and results, quickly and consistently analyzing the sequences.

First released in January 2002, ESTAP has continued to evolve into the most current version containing new features that allow users to analyze their data even more efficiently. This version of ESTAP provides two new features that allow it to handle sequences from a genomic DNA library (up to 10,000 sequences), and clean, BLAST, and assemble the genomic DNA sequences. The software also incorporates InterProScan, a system developed at the European Bioinformatics Institute that combines different protein signature recognition methods into one resource. Visit the ESTAP project at http://staff.vbi.vt.edu/estap.

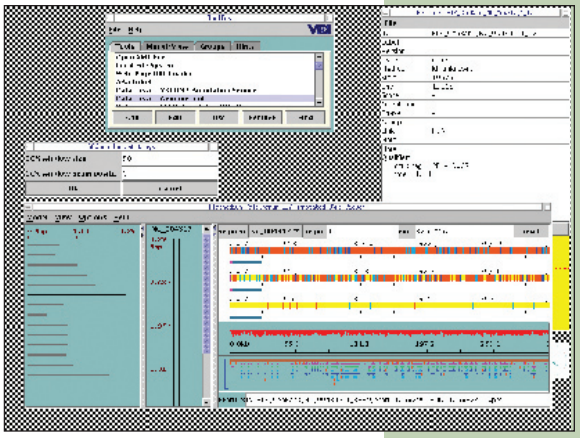
PathPort:
Opening the Door to Comprehensive Pathogen Knowledge

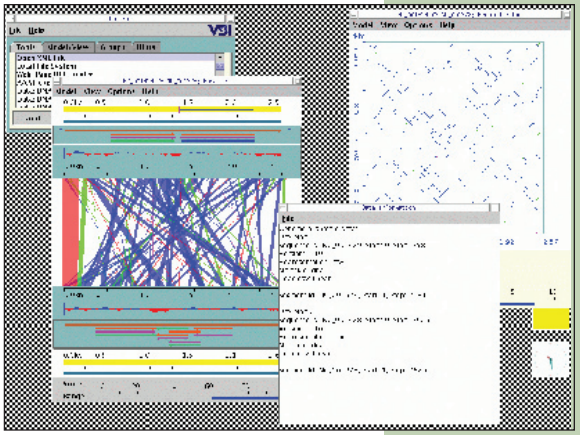
VBI has initiated the PathPort project (short for Pathogen Portal) through a $4 million grant from the Department of Defense. PathPort is opening the door for scientists, government officials, and emergency responders to more effectively combat infectious diseases by providing access to detailed pathogen information databases and bioinformatics tools that allow scientists to more easily gain insight into existing data sets.

Biological data sets are growing exponentially as a result of genome sequencing projects and other new technologies. Drs. Bruno Sobral, Dana Eckart, and Raju Lathigra, together with a team of VBI scientists and information technology specialists, are building PathPort as a set of web services to consolidate, annotate, validate, and analyze available pathogen data from disparate sources through an interoperable cyberinfrastructure. Analytical tools in PathPort allow for the creation of new data models, analysis of genomic data, and discovery of novel inter–data relationships. The VBI–developed software infrastructure supporting PathPort is ToolBus, a client–side "bus" for contacting data and tools and viewing results through a single, consistent user interface. ToolBus helps data management by providing data and tool interoperability. PathPort scientists are working with diverse communities to create a common set of data communication standards to allow scientists across the globe to evaluate data and discover new relationships through a common platform.

Information and data in PathPort focuses on pathogens and their hosts with potential to cause significant harm in either a natural or engineered disease outbreak. PathPort/ToolBus allows researchers to explore curated pathogen information and molecular mechanisms of pathogenesis from diverse sources.

Using its high–performance computational infrastructure and a world–class team of biologists and computer technologists, VBI will continue to develop PathPort as a key to unlock the door to more powerful knowledge for infectious disease research, as well as a crucial enabling cyberinfrastructure for the life sciences.





Visualization tools available via VBI's PathPort system. This web-based system allows users to consolidate, annotate, validate, and visualize existing data sets related to infectious diseases.

PathPort Group (in alphabetical order):
G. Abramochkin, A. Agrawal, B. Chennupati, D. Eckart, H. Formadi, O. He, S. Hoops, P. Jhala, R. Lathigra, D. Machi, M. Ni, E. Nordberg, B. Sobral, W. Sun, Y. Tian, N. Vaghela, R. Vines, R. Wattam, T. Xue, B. Yang, L. Yang, C. Zhang, Z. Zhang, J. Zhao

IBM SUR Awards Aid in Integration of Disparate Genomic Data

Pursuing joint research initiatives enables IBM and VBI to capitalize on complementary strengths and accelerate the development of new technologies for the advancement of the life sciences.

In collaboration with IBM's Watson Research Center, VBI is researching ways to integrate and compile volumes of genomic information. Computational equipment was donated to VBI by two separate IBM Shared University Research Awards. The second of these will advance research using the PathPort system. Currently, biological data (e.g., reference pathogen and host genomes, transcriptomes, proteomes, and metabolomes) are dispersed among many entities including government agencies, corporations, and institutional and university laboratories around the world. A comprehensive system to access, integrate, and manipulate this data to expand our collective knowledgebase as well as combat infectious disease is greatly needed. Issues of data access, format, syntax, security, privacy, and quality need to be resolved. IBM's Enterprise Storage Server, or "Shark," will become a storage facility for data that can be accessed globally. This server and its resident data will support the development and testing of algorithms to analyze and manipulate data.

The *Medicago* Project

From lab results to database curation, the biochemical networks modeling group is producing cutting–edge bioinformatics information with their studies on *Medicago truncatula*, a close relative of alfalfa. This *Medicago* species is a rich source of natural products such as flavonoids, isoflavonoids, and triterpenes, which impact its properties as a forage legume. Dr. Pedro Mendes' team at VBI, partnered with the Plant Biology Division of the Samuel R. Noble Foundation and the Southeastern Oklahoma State University, evaluates the expression of these natural products and other changes in the plant's metabolism by exposing cell cultures to biotic and abiotic elicitors. The ultimate project goal is the generation of a truly functional genomics data set for control and elicited cell cultures. Such data will encompass expressed sequence information and the associated mRNA, protein, and metabolite identities and concentrations. The group will then compare this information regarding gene expression in a homogeneous, inducible system that will lead to a synergistic leap in our understanding of the genetic programming of cellular metabolism.

Funded by the NSF with a $3.6 million grant, the team will also establish integrative models and software to facilitate relational analysis of the data generated across the three biological levels to each other and to previous knowledge on sequences and pathways. The relational database, Biochemical Networks Database (B–Net), allows research group members to compile and sort previously published data and information on this plant. The database curation allows researchers to pinpoint recurring gene expressions and experimental results, and then model the lab findings with the Complex Pathways Simulator (COPASI) modeling system. An expandable analysis server supports the database by processing the information with statistical and numerical algorithms. B–Net's curators access the database through a web interface, which will soon be publicly available, allowing global access to that database's user–friendly interface. The *Medicago* project will bring an increased understanding of the biochemistry of natural products while still increasing plant–disease resistance. This project serves as a flagship for combining genomic, metabolomic, and proteomic data to create a detailed picture of the functioning of biological systems. For more information, visit the project at http://medicago.vbi.vt.edu.

Biochemical Networks Modeling Group (left to right): A. de la Fuente, S. Hoops, P. Mendes, P. Brazhnik, A. Martins, B. Mehrotra, J. Li, W. Sha, A. Kamal, D. Chen, D. Camacho, L. Xu, M. Kulkarni, F. Taliaferro

Biomedicine

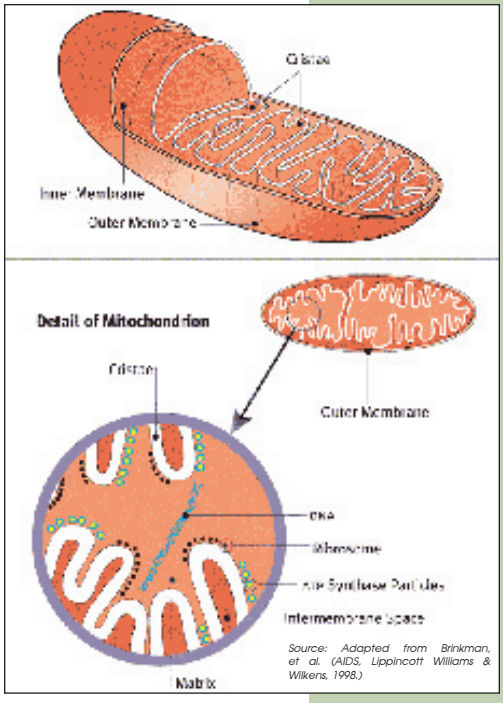
Several global events have reshuffled our nation's public health and biomedical research priorities. With the new era of bioterrorism preparedness, the anthrax scares, the unexpected SARS outbreak, and the growing tuberculosis and AIDS crises, preventing disease transmission in our increasingly global society ranks high among our national priorities. With this sense of urgency comes a charge to develop new and more effective vaccines, drug therapies, and treatments. This charge highlights the need for a better understanding of how infectious diseases affect the processes of biological systems. Researchers at VBI are committed to understanding how the genes of hosts and pathogens interact across a broad spectrum of species and environments, supporting the mission to aid in the rapid detection, identification, prevention, and treatment of disease.

Mitochondria and Aging: Connected through Mutation?

Dr. D. Samuels Research Group (left to right): H. Rajasimha, D. Samuels, A. Rathi

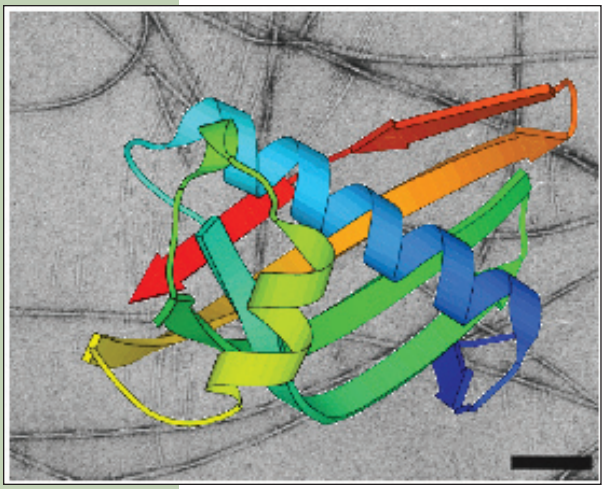
All biosynthetic activities of the cell need energy. The molecule adenosine triphosphate, also known as ATP, serves as a "molecular battery" or chief energy currency for the cell. Most of the ATP used by the cell is formed by organelles called mitochondria. The ancestors of mitochondria were primitive bacteria that developed a symbiotic relationship with cells. As a remnant of their bacterial heritage, mitochondria still contain their own DNA molecules, called mitochondrial DNA (mtDNA), which contains genes for some proteins necessary for forming ATP. Mutations in mitochondrial DNA can cause these proteins to be transformed into a shape unable to produce ATP, leading to a loss of energy and function in the cell. If enough cells fail, the organ will fail. If the cells are in the pancreas, diabetes may occur. If they are in the optic nerve, the result is blindness. If they are in the inner ear, deafness develops.

Mitochondria, known as cell powerhouses, function as ATP generators. However, pollution is produced during ATP generation that appears as reactive oxygen species (ROS), the dangerous chemicals neutralized by anti–oxidants. Since ROS molecules bind easily to DNA, mutations develop. Molecules of mtDNA are damaged because of their close proximity to the ROS–production site. As organisms age, this damage to mtDNA builds up, leading to the gradual failure of cells. This is a universal phenomenon found in the aging of humans, mice, fruit flies, fungi, and other species. At VBI, Dr. David Samuels leads a research team developing models to understand how mtDNA mutations build up in aging cells. By comparing the mitochondrial genomes of different species, Dr. Samuels is beginning to understand why aging occurs at such different rates in different species. This information will be critical in the quest to slow the aging process.



The structure of mitochondria, the powerhouses of the cells.

Using the Power of Proteins in Amyloidosis

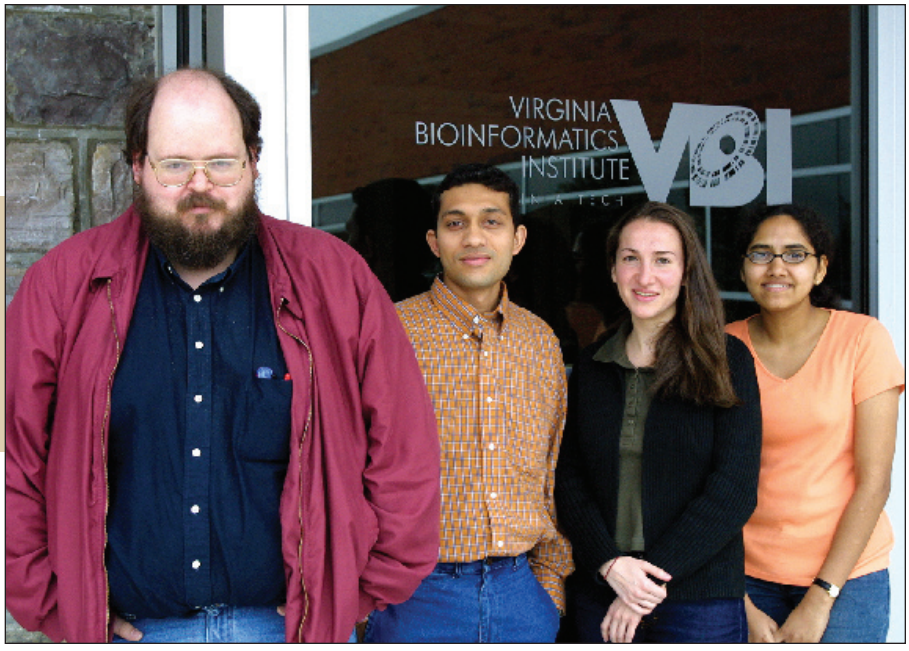


The predicted structure of human cystatin C, a small cysteine protease inhibitor involved in neural development. A single point mutation in the cystatin C gene has been genetically linked to stroke in young adults. Strokes are produced by the aggregation of cystatin C into amyloid fibrils and plaques on the brain blood vessels, weakening them and causing massive hemorrhage (scale=100nm).

As the US population ages, the prevalence of progressive neurodegenerative diseases, such as Alzheimer's and Parkinson's, is expected to increase markedly. As effective treatments are not available for these disorders, they severely impact the quality of life for a large portion of the US population and have a significant economic impact on families that bear the costs of long–term health care. Coupled with the increased incidence of mad cow disease and chronic wasting disease that threaten the safety of food supplies, research into the cause of these diseases is paramount. VBI's Dr. Joel Gillespie leads a research effort doing just that.

The aggregation or grouping of otherwise normal proteins into long fibrillar structures called amyloids causes such diseases. Aggregation depends on adopting a partially unfolded conformation, a process influenced by several genetic and environmental factors. Normally, cells in which such aggregates form have the ability to dissociate and dissolve them, negating any long–term consequences of the aggregate formation. In some cells, however, these housekeeping mechanisms fail. The aggregates continue to grow, eventually killing the cell and surrounding tissue.

The Gillespie lab at VBI studies the mechanisms underlying the formation of these aggregates and the means by which misfolded proteins evade normal cellular housekeeping mechanisms. The role of protein misfolding by cystatin C, a small cysteine protease inhibitor involved in neural development, in precipitating strokes in young adults is of particular interest. The role of Bence–Jones proteins associated with multiple myeloma in systemic amyloidosis is also under investigation. By determining how environmental factors and genetic mutations influence the unfolding of these proteins and initiate amyloid plaque formation, Dr. Gillespie's research will aid in the development of effective treatments for reversing amyloid neuropathies and systemic amyloidosis.



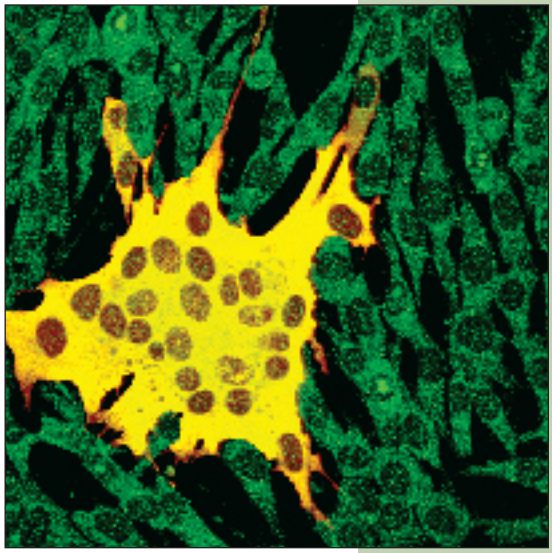
Dr. J. Gillespie Research Group (left to right):
J. Gillespie, K. Shah, M. Raiszadeh, D. Balasubramaniam

Imaging to Understand Viral Infection

Pathogen and host interactions occuring during the complex process of viral infection puzzle researchers. Understanding that process, however, is critical to the next wave of defenses against viral pathogens. VBI's Dr. Karen Duca is assembling a knowledge base from the available literature that incorporates qualitative and quantitative data related to two RNA viruses and their associated disease states.

In order for an animal virus to successfully infect and propagate *in vitro*, several events must occur: a virion must identify and bind to its cellular receptor, become internalized, uncoat, synthesize viral mRNA and protein, replicate its genome, assemble progeny virus, and exit the host cell. While these events are taking place, intrinsic host defenses activate in order to defeat the virus, e.g., activation of enzymatic pathways to degrade foreign RNA, shutdown of host biosynthetic machinery, initiation of the cell "suicide" program, signaling to the local neighborhood, and mobilization of immune cells. Changes in concentrations of distinct host and viral species characterize each event in this complex process.

Associated biochemical signatures and kinetic rate data can be extracted for both virus and host using time–resolved mRNA and protein expression profiling. This complex information is critical to finding the Achilles' heel of viral adversaries in order to develop new approaches in treatment, prevention, and cure. Correctly timed, "system–based" interventions involving multiple mild agents may result in excellent therapeutic outcomes with fewer undesirable side effects.



Delayed brain tumor cells infected with murine hepatits (MHV). Green fluorescence is a tag for RAB8, a marker for vesicle transport between the trans-Golgi and the plasma membrane of the cell. The red fluorescence is a tag for MHV nucleoprotein. Where the two labels are superimposed, the fluorescent image appears yellow.

Novel Ways to Explore New Viral Treatments

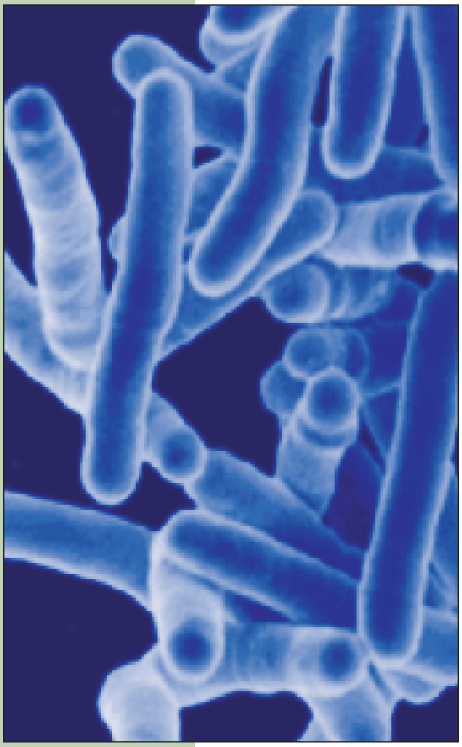
VBI research faculty member Dr. Karen Duca leads imaging research at VBI, which will heighten our understanding of viral function during infection. Guided by profiling experiments, several important molecular players can be labeled with fluorescent tags. The intensity and position of these molecules may be imaged *in vitro* from the time a virus is introduced into a system until the culture is no longer viable. In this manner, important network behavior can be observed directly.

By combining the temporal resolution of the profiling experiments with the spatial resolution of the imaging studies, insights can be gained about system–level viral vulnerabilities that may be exploited to treat active infections. While an *in vitro* model necessarily captures only a small subset of interactions responsible for disease etiology, it serves as the basis for construction of more complete experimental models as understanding increases.

The Duca Lab also investigates the effects of dual perturbation of lung cells by virus and tobacco smoke. Cultured cells are exposed to influenza virus and cigarette smoke condensate and the expression profiles are analyzed relative to control cells. With these methods, the lab investigates how these agents impact important cellular pathways including the interferon pathway of innate immunity, the pathway for apoptosis, and the pathway for repair of damaged DNA. These studies will help determine how these lung–perturbing agents undermine human health when acting individually or together.

Dr. K. Duca Research Group (left to right):
S. Penich, K. Duca, N. Polys, S. Stevens, J. Shah, E. Fulton, J. McGee, and P. Saraiya

Addressing the Global TB Crisis



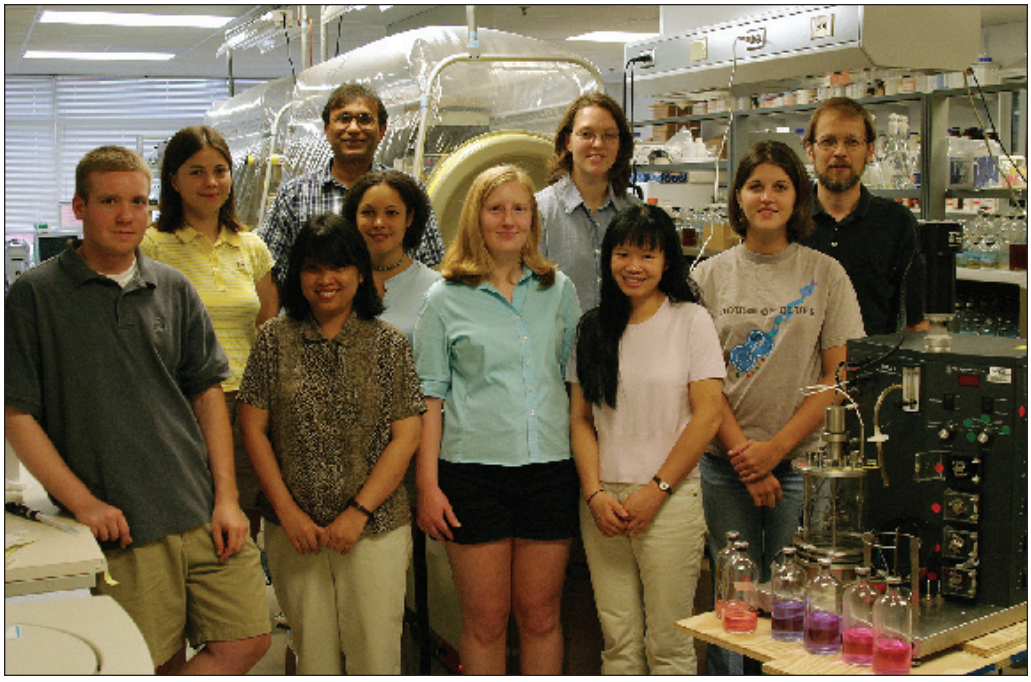
Mycobacterium tuberculosis. (NIAID 2001. Global Health Research Plan)

Five thousand people die of tuberculosis (TB) daily. Despite the availability of drug cocktails to treat the disease, eight million new cases are reported annually. An estimated one–third of the 42 million people living with HIV/AIDS worldwide are co–infected with tuberculosis; this combination of diseases leads to the largest number of AIDS–related deaths.

Mycobacterium tuberculosis, the causal agent of TB, presents complex pathologic mechanisms, making effective treatment difficult. An ability to maintain dormancy allows this pathogen to sustain itself successfully in about one–third of the world's population. Baffling researchers, this pathogen emerges from its dormant state when the carrier's immune system is compromised. Understanding the process that allows mycobacterium to achieve, and subsequently resuscitate, from dormancy would allow researchers to design and develop both more effective pharmaceuticals and an effective vaccine. Since the dormant pathogen is resistant to the pharmaceuticals used to treat TB, a pharmaceutical cocktail therapy typically lasts six to nine months. This long treatment makes compliance difficult for patients, a major reason for the emergence of multi–drug resistant *M. tuberculosis* strains.

Dr. Biswarup Mukhopadhyay's research team at VBI studies the behavior of *M. smegmatis*, a non–pathogenic, close relative of *M. tuberculosis* that grows rapidly in soil and exhibits similar dormancy–related behaviors. More specifically, Mukhopadhyay uses a state–of–the–art bioreactor and a proteomics–based approach that can describe, monitor, and manipulate the environment accurately. The process involves altering oxygen concentrations to induce and then subsequently resuscitate the bacteria. Using proteomics, Mukhopadhyay's group can track the consequential intracellular changes and identify proteins specifically linked to the pathogen's survival.

Mukhopadhyay's approach to microbiology is distinctive and novel. This research approach will shed light on the various mechanisms employed by *M. tuberculosis* to survive over time in human populations and will bring the global community one step closer to finding targets for effective treatments and vaccines.

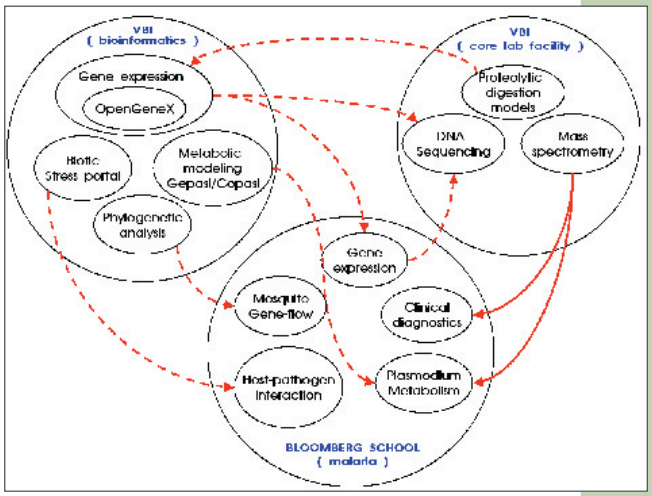


Dr. B. Mukhopadhyay Research Group (left to right): J. Dalton, K. Boswell, E. Purwantini, B. Mukhopadhyay, L. Von Herbulis, B. Nebus, J. Kraszewski, H. Lai, M. Pochyla, and E. Johnson (not pictured: C. Chase and C. Legall)

Combating Infectious Diseases Through Collaboration

In collaboration with Johns Hopkins University's Bloomberg School of Public Health, VBI is studying a number of complex diseases including malaria, AIDS, tuberculosis, type 2 diabetes, brucellosis, and influenza. JHU and VBI are also developing new software, technology, and database capabilities to aid in biomedical research. The studies conducted by this partnership are truly a melding of biology, biochemistry, biomedicine, mathematics, and information technology.

This partnership targets solution development (e.g., knowledge generation, therapeutics, vaccinations) for deadly diseases. Over the course of the five–year collaboration, the research teams will enhance informatics tools and biological models as well as create databases for unmanageable data on disease genomics. To date, ten grant proposals totaling over $5 million have been submitted to support the research efforts of this collaboration. This research team, which pairs premiere biomedical research from JHU with world–class bioinformatics capabilities at VBI, has generated 14 publications and 12 presentations.



VBI-JHU cross-institutional interactions: an example with malaria research.

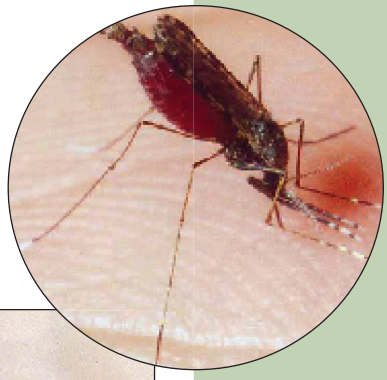
Kiss of the Mosquito

Spread by the *Anopheles* mosquito, the parasite *Plasmodium falciparum* causes 300–500 million new cases of malaria annually, killing 1.5–1.7 million people globally each year. Malaria is presently returning to areas from which it had been eradicated, and spreading to new areas, such as Central Asia and Eastern Europe. Chloroquine, once regarded as a panacea for malaria, has failed in a number of cases, indicating the decline in efficacy of the treatment. Coupled with insecticide resistance developing in mosquitoes spreading this disease, the development of new diagnostic tools, treatment measures, and a vaccine is critical.

VBI's Dr. Allan Dickerman and Johns Hopkins Bloomberg School of Public Health's Dr. David Sullivan are working to develop a new diagnostic method to contribute to our global fight against malaria. Dr. Sullivan has cloned two versions of the histidine–rich protein gene isolated from various strains of *Plasmodium falciparum*, which were then sequenced by VBI's Allan Dickerman. This sequence information will be used to interpret data on the protein's metabolic activity expressed *in vitro* with direct impact on a possible new diagnostic method.

Dr. Vladimir Shulaev's group is currently developing the analytical infrastructure for large–scale metabolite profiling of untreated and antimalarial drug–treated *Plasmodium falciparum*. This will help scientists to identify metabolic changes associated with drug treatment for malaria cases.

Dr. Pedro Mendes, along with four undergraduate students, is developing a molecular biology reference database for *Plasmodium falciparum*. This will serve as a "computerized encyclopedia" for the malaria research community.



The mosquito serves as the vector organism for malaria, which kills over 1.5 million people annually.

Research

Vitamin C

In collaboration with Virginia Tech's Department of Plant Pathology, Physiology, and Weed Science, Dr. Pedro Mendes at VBI is working to increase vitamin C production in fruits and vegetables. Vitamin C, or L–ascorbic acid, is essential to the human body and functions as a natural anti–oxidant. Unfortunately, humans are unable to synthesize vitamin C and therefore must acquire it from fruits and vegetables. Elevated levels of vitamin C may also be of benefit to crop plants by providing protection to environmental stresses. Fresh produce with increased vitamin C could also exhibit a longer shelf life, benefitting both retailers and consumers.

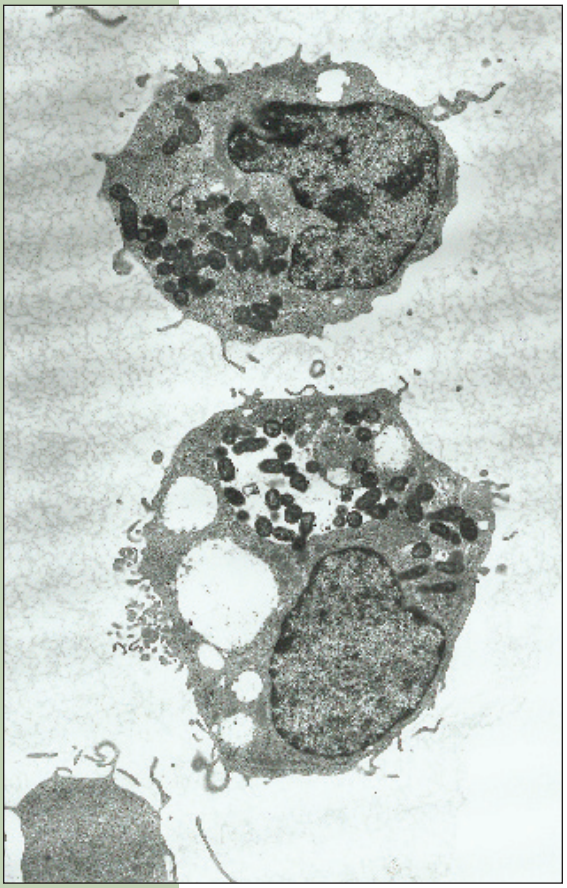
Researchers have known for more than 250 years that plants are an essential source of this 'anti–scurvy' vitamin, but have only just begun to completely understand the biochemical steps involved in its production by plants. Virginia Tech scientists recently discovered a novel plant pathway for vitamin C biosynthesis. By increasing the expression of one of the genes in this pathway, a two to three–fold increase in vitamin C production resulted. With support from the Metabolic Engineering Program at the National Science Foundation and the USDA, the VT–VBI research team is now using the model plant *Arabidopsis thaliana* to study vitamin C production in plants. By striving for a better understanding of the pathways involved in plant vitamin C biosynthesis, this work will aid in the design of plants with increased amounts of this indispensable vitamin. Dr. Pedro Mendes of VBI is providing informatics tools for the project in collaboration with Virginia Tech professors Drs. Craig Nessler and Boris Chevone, who lead the experimental effort.

The model plant Arabidopsis thaliana *used to study vitamin C biosynthesis.*

Teamwork to Tackle Brucellosis

Brucella spp., Gram–negative, facultative, intracellular bacteria, cause brucellosis in humans and farm animals, such as cattle, goats, and swine. Although only 100–200 cases are reported in the United States each year, brucellosis is problematic in developing countries of Asia, Africa, the Caribbean, the Middle East, and the Mediterranean. Closer to home, Mexico has a recurring problem with the spread of *Brucella* and the associated flu–like symptoms of brucellosis. Furthermore, *Brucella* spp. can potentially be used as biological weapons due to their ability to survive in a powder or aerosol form. They are therefore classified as category B priority pathogens by the National Institutes of Allergy and Infectious Diseases and the Centers for Disease Control and Prevention.

The exact mechanisms of host *Brucella* interactions are still unclear. Currently, the genomes of four *Brucella* spp. are completely sequenced, giving scientists new information to apply to the study of this zoonotic pathogen. Researchers at VBI are collaborating with VA–MD Regional College of Veterinary Medicine and Virginia Tech's Department of Biology to better understand the molecular mechanisms of pathogenesis and the associated host responses to infection by *Brucella*. Through this effort, the team also hopes to discover unique species–specific signatures that will allow for better, rapid brucellosis diagnostic methods.



Mouse macrophages, cells of the immune system, infected with Brucella abortus. *This pathogen causes spontaneous abortion in cattle.*

- Outreach
- Education

Public Relations

"Not unlike the way diverse cells in multicellular biological organisms signal their activity and thus coordinate their behavior with unlike cells to ensure the survival of the organism, we as citizens need to do the same. We can learn our place and function in the larger community only by signaling—by explaining ourselves."

The Late Congressman George E. Brown, Jr.
Ranking Minority Member
House Science Committee

The Public Relations and Outreach group is a crucial channel of communication and education. The team focuses on sharing VBI's exciting research with the Virginia Tech community and beyond. This year, the department has developed conferences, workshops, and other educational events for students and professionals.

Also, VBI continues to host high school, graduate, and undergraduate scientists for various short- and long-term learning opportunities. Students may also earn a Ph.D. through Virginia Tech's Genetics, Bioinformatics, and Computational Biology graduate program at VBI. Through these programs as well as facility tours, media interaction, and extensive outreach endeavors, the Public Relations and Outreach group provides colleagues, partners, and others with knowledge and information about the newest developments at VBI.

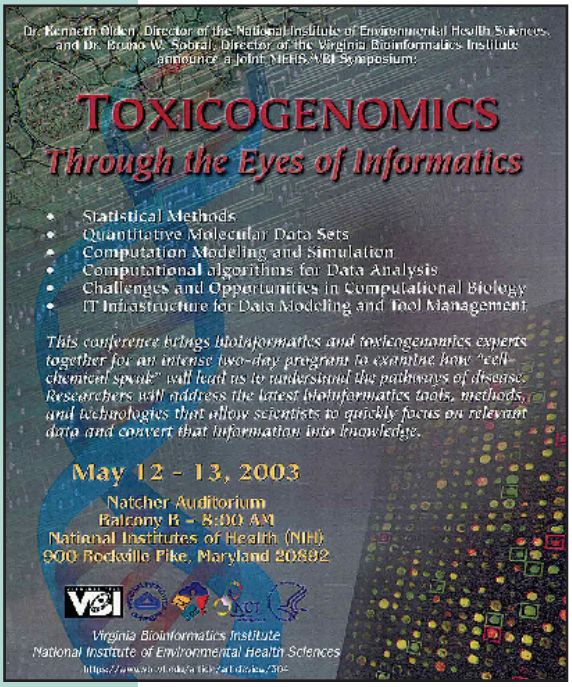
Bioinformatics: A "Case" Worthy of Press

The media professionals participating in the CASE Media Fellowship on a tour of VBI's Core Computational Facility. The fellowship was sponsored by CASE, Virginia Tech University Relations, and VBI.

The Council for Advancement and Support of Education (CASE), an international education association, offers fellowships to journalists each year to provide them with opportunities to interact with renowned scholars, explore the intricacies of important issues, and discover the latest ideas at leading institutions around the world. VBI was awarded the opportunity to host a fellowship program through a competitive review process.

Through this CASE Media Fellowship, eight media professionals spent two days immersed in VBI research programs, learning how they apply to human health, agricultural systems, and national defense. The CASE fellows were introduced to biotechnology data generation and its interpretation through high–performance supercomputers. The visit included hands–on workshops in DNA sequencing, microarray construction, and virus identification via the latest in quantatitative imaging experiments. Additionally, VBI's PathPort project—a global pathogen portal that federates and enables analysis of biological information on known pathogens—served as a ready example of how biotechnology and computer science have merged to create the exciting field of bioinformatics.

Researchers from Around the World Gather for Toxicogenomics Conference



NIEHS and VBI hosted a conference to explore the synergy created by the merger of toxicogenomics and bioinformatics research platforms.

In May 2003, VBI and the National Institute of Environmental Health Sciences (NIEHS) teamed up to hold a conference in Bethesda, Maryland. Entitled "Toxicogenomics Through the Eyes of Informatics," this intense two–day program examined how "cell–chemical speak" will lead us to understand the pathways of disease.

Participants discussed how cells and organisms respond to toxins. By understanding the mechanisms from a genome through a systems view, the risk that toxins pose to humans can be more rationally assessed and evaluated. By integrating experimental studies at the structural, molecular, and cellular level with mathematical and biochemical modeling and informatics, the conference surveyed the integration and merger of advancing technologies.

The conference provided a forum to explore the potential applications and implications of the new technologies centering toxicogenomics research platforms. The conference report can be found at https://www.vbi.vt.edu/conference/niehsvbi2003.

The Interdisciplinary Ph.D. Program in Genetics, Bioinformatics, and Computational Biology

Virginia Bioinformatics Institute is pleased to participate in the new Ph.D. program in Genetics, Bioinformatics, and Computational Biology at Virginia Tech. This new paradigm for bioinformatics education and training cuts across interdisciplinary boundaries to include curricula from nine of Virginia Tech's departments. Research and training environments that produce such a combination of skills are paramount for a new generation of research–oriented professionals. This exciting new program of study encompasses applications of molecular biology, genomics, mathematics, statistics, computer science, and other areas of the life sciences, but allows flexibility and is tailored to students' individual backgrounds.

Students in the program conduct dissertation research projects that cross the boundaries of traditional disciplines. To complement coursework and assist students in developing their dissertation research projects, additional focused research experiences can be required. This interdisciplinary approach to research requires graduates with extensive cross–cultural professional and technical training and provides ample employment opportunities for Ph.D. graduates.

GBCB students (left to right): V. Arora, D. Camacho, K. Lee, C. Chetia, M. Babiceanu, K. Krampis, L. Waller, D. Cortes (not pictured: N. Bing, M. Gajendran, K. Ghosh, P. Jhala, N. Kaufman, B. Liu, H. Ni, H. Rajasimha, B. Smith, B. Vasudevan, J. Zmuda)

VBI faculty members participate in the program on many levels including mentoring students in world–class research programs. Currently, 19 students have been accepted into this new program. Areas of expressed interest include bioinformatics, genomics, human genetics, plant breeding, mathematical modeling, and systems biology.

Tomorrow's Leaders: VBI Graduate and Undergraduate Students

VBI currently employs 26 graduate research assistants and 27 undergraduate student assistants to support the many research projects and internal groups lead by the 13 faculty members, service center directors, and administration. VBI students represent the various undergraduate and graduate programs offered by the university in such fields as computer science, mathematics, human services, finance, and various disciplines in the biological sciences. VBI has benefitted greatly from such a diverse group of student assistants and, in turn, has assisted in their professional development as they prepare for future careers.

Internship Encourages Interest in Research

Simon Stevens is just one example of VBI's cooperative relationships with students. Stevens, who graduated from Danville Community College with a science degree, completed a six–week internship at VBI over the summer. VBI is a partner of Danville's Institute for Advanced Learning and Research, which provides opportunities for collaborations between its partners and students and professionals from Southside, Virginia.

Stevens worked closely with Dr. Karen Duca and other researchers at VBI to compile information about type A influenza in an effort to create a movie demonstrating the effects the flu virus has on a cell. This movie will be used in future research in areas such as drug effectiveness. Stevens is now pursuing a bachelor's degree in biology and says that his work at VBI has inspired him to work towards a Ph.D. in virology.

Simon Stevens, a graduate of Danville Community College, completed a summer internship at VBI. While at VBI, Stevens studied type A influenza.

High School Students Meet Bioinformatics

High school students completing microarray projects in VBI's Core Laboratory Facility.

Four area high school students completed science fair projects with guidance from researchers at VBI.

Felix Kim – Blacksburg High School – "Determining the Effectiveness of the GeneChip® system provided by Affymetrix Standard Target/Assay Protocol by Comparing the Experimental 3' End Signal to 5' End Signal Ratios of Various Genes to Accepted Ratios" – Second place, 2003 Intel Blue Ridge Highlands Regional Science Fair in the Biochemistry Category; Presented at the 2003 Virginia Junior Academy of Science Annual Meeting. Mentors: Heather Norton and Jennifer Fick.

Mark Hickman and Lee Thomas – Cave Spring High School in Roanoke – "The Use of Microarrays to Elucidate Genes Involved in Host Susceptibility to Brucellosis" – Presented at the 2003 Virginia Junior Academy of Science Annual Meeting. Mentor: Heather Norton.

Laura Maxey – Giles High School and Southwest Virginia Governor's School – "Isoxaflutole: Will Grass Prevent this Herbicide from Leaching into the Soil?" – First place, Giles High School; First place, Southwest Virginia Governor's School; Third place, Regional Competition for Governor's Schools. Mentor: Neysa Call.

Working with the Leaders of Tomorrow: High School / High Tech

VBI partners with Montgomery County Schools to provide disabled youth with early exposure to jobs in science and technology–related fields to encourage them to pursue opportunities in higher education. This experience in multifaceted, providing opportunities for realistic career exploration and hands–on research experiences.

This nationwide program emphasizes the development of job skills. In an effort to help cultivate these skills, VBI organized a job skills seminar in April where students attended workshops in resume writing, job interview skills, as well as informational sessions on the field of bioinformatics.

VBI also coordinated on–site visits to expose students to high–tech laboratories and computing infrastructure, and job shadowing experiences.

Dr. Neysa Call hosts a bioinformatics lesson for High School/High Tech students.

Public Relations/Outreach Team

(from left to right)

Susan Light
Technical Communications Editor

Robin Oakes
Public Relations Assistant

Neysa Call
Head, Public Relations and Outreach

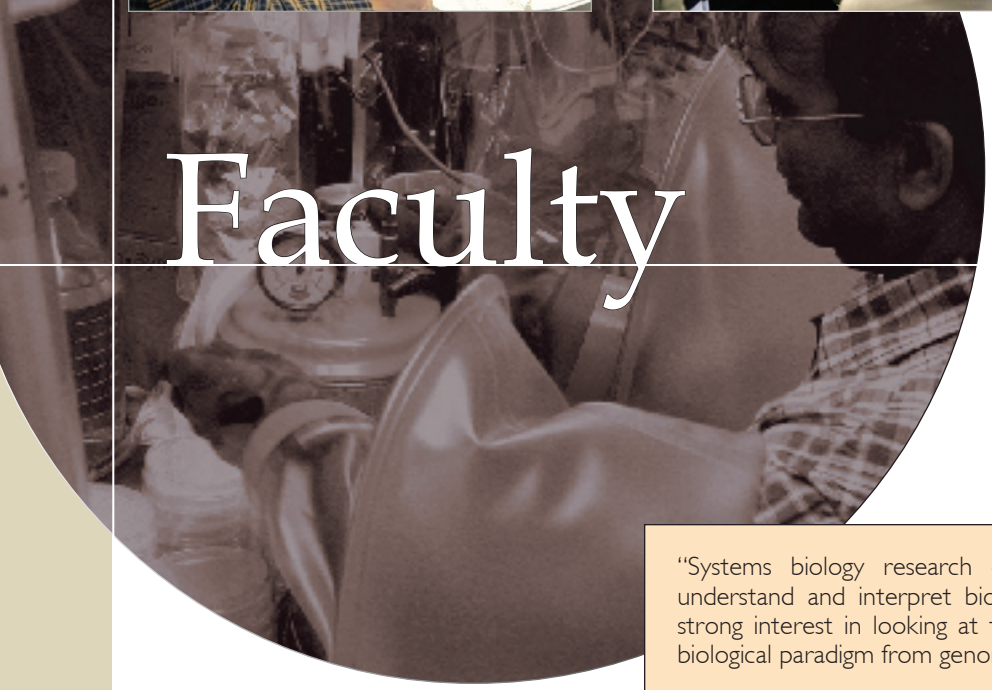
Elaine Fuller
GBCB Coordinator

Candy Baracat
Public Relations Assistant

Andrea Aten
Public Relations Assistant

Not shown:
Ivan Morozov
Web Administrator

VBI's research is solidly founded upon our world–class faculty. Experts in computer science, biology, biochemistry, mathematics, microbiology, plant pathology, and more have joined within the institute to create a unique center for bioinformatics research.



Faculty

"Systems biology research crosses disciplinary boundaries in order to understand and interpret biological systems. VBI's research faculty have a strong interest in looking at the integration of data across all levels of the biological paradigm from genomics to ecosystems."

Brett Tyler, Ph.D.
Research Faculty, VBI
Professor, Plant Pathology, Physiology and Weed Science, Virginia Tech

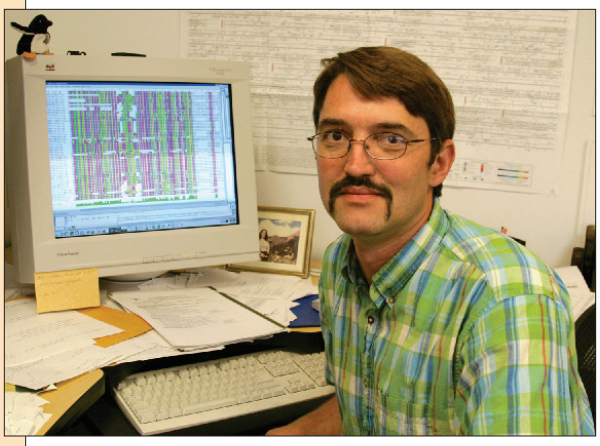
VBI's faculty and staff realize that society's demands on research institutions are expanding. Foremost among VBI's research ideals is the expectation of solving an increasing array of problems for society, from stimulating economic development to enabling the nation to compete in the global marketplace, and from raising our prospects for more productive and satisfying lives to strengthening our national security.

Dr. Allan Dickerman

Research

Dr. Dickerman's research addresses the broad area of genomic sequence analysis from an evolutionary perspective. He focuses on using phylogenetic analyses to describe "interesting" patterns of conservation or diversity in gene sequences. Current collaborative efforts are aimed at using comparative analysis of plant gene sequence to extrapolate functional information from the model dicot *Arabidopsis thaliana* to other species.

In addition to the biological questions addressed through comparative genomic analysis, Dr. Dickerman develops algorithms used in this arena. A common theme in complex genome analysis is the joint inference of correlated phylogenetic models, such as genes evolving within species. Adapting these methods to genome–scale analyses is one of his activities.



Research Assistant Professor, VBI

1992 Ph.D., Zoology,
University of Wisconsin–Madison

Grants

PI. Bioinformatics Prediction of Functions of Unculturable Microbes in Ecosystems. National Science Foundation. 1/1/02–12/31/02: $100,000.

co–PI. Strawberry Functional Genomics. VT ASPIRES. 02/01/03–1/31/05: $100,000.

co–PI. Analysis of Plant Genome Duplication Events and Their Functional Relevance. U.S. Department of Agriculture – Cooperative State, Research, Education, and Extension Service. 4/1/01–3/31/03: $444,230.

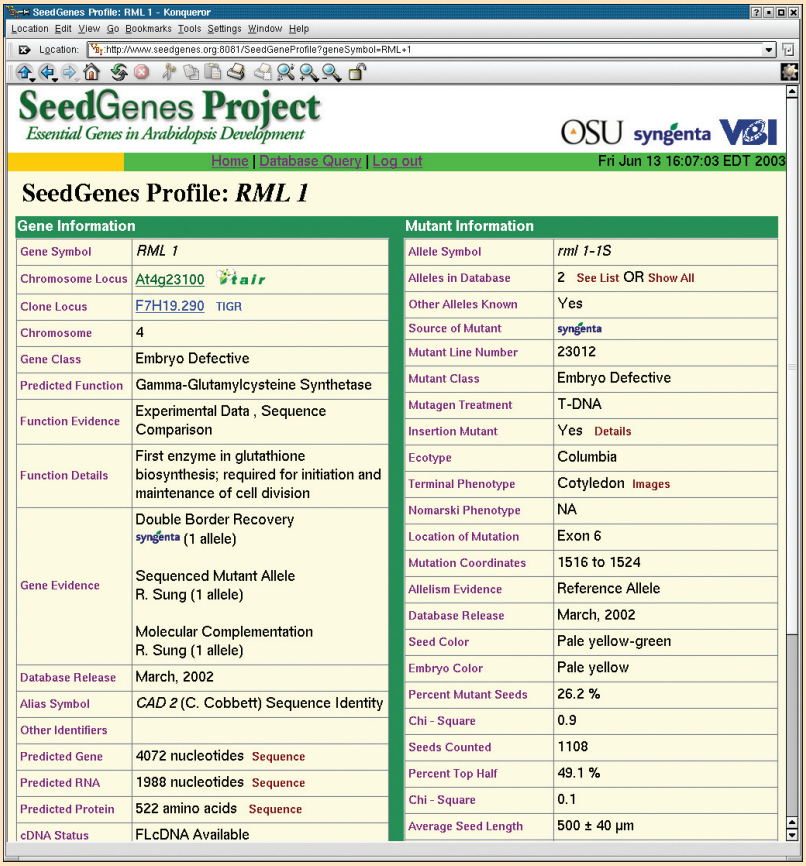
co–PI. Essential Gene Functions in *Arabidopsis* Seed Development. National Science Foundation. 10/1/01–9/30/05: $2,326,667.

Selected Publications

Dickerman, A., Puttegowda, K., Athanas, P., and Park, J. Method for rapid sequence comparison for genetic databases ("Programmable Chip"). Invention/Patent in process.

Huala, E., Dickerman, A., Garcia–Hernandez, M., Weems, D., Reiser, L., LaFond, F., Hanley, D., Kiphart, D., Zhuang, M., Huang, W., Mueller, L., Bhattacharyya, D., Bhaya, D., Sobral, B., Beavis, W., Meinke, D., Town, C., Somerville, C., Rhee, S. 2001. The *Arabidopsis* information resource (TAIR): a comprehensive database and web–based information retrieval, analysis, and visualization system for a model plant. Nucleic Acids Research, 29:102–105.

Meyers, B., Dickerman, A., Michelmore, R., Pecherer, R., Sivaramakrishnan, S., Sobral, B., Young, N. 1999. Plant disease resistance genes encode members of an ancient and diverse protein family within the nucleotide–binding superfamily. The Plant Journal, 20:317–332.



The SeedGenes Project identifies Arabidopsis *genes involved in seed development.*

Dr. Karen Duca

Research Assistant Professor, VBI

1998 Ph.D., Biophysics and Structural Biology, Brandeis University

Grants

PI. Identification of Genes that Predispose Individuals to Smoking–Related Diseases. University of Virginia/ Tobacco Foundation. 7/1/02–6/30/04: $375,000.

Selected Publications

Endler, E., Duca, K., Nealey, P., Whitesides, G., and Yin, J. 2003. Propagation of Viruses on Micropatterned Host Cells. *Biotechnology and Bioengineering*, 81(6):719–725.

Wurtman, J., McDermott, J., Levdusky, P., Duca, K., and Wurtman, R. 2002. The Effect of a Novel Dietary Intervention on Weight Loss in Psychotropic Drug–Induced Obesity. *Psychopharmacology Bulletin*, 36(3): 55–59.

Duca, K., Lam, V., Keren, I., Endler, E., Letchworth, G., Novella, I., and Yin, J. 2001. Quantifying Viral Propagation *in vitro*: Towards a Method for Characterization of Complex Phenotypes. *Biotech Progress*, 17:1156–1165.

Duca, K., Blumer, A., Lokuta, M., and Fleming, J. 2001. MHV Recombination *in vitro* and *in silico*. Second International Conference on Systems Biology, Pasadena, CA.

Duca, K., Chiu, K., Sullivan, T., Berman, S., and Bursztajn, S. 1998. Nuclear Clustering in Myotubes: A Proposed Role in Acetylcholine Receptor mRNA Expression. *Biophysica et Biochimica Acta*, 1401:1–20.

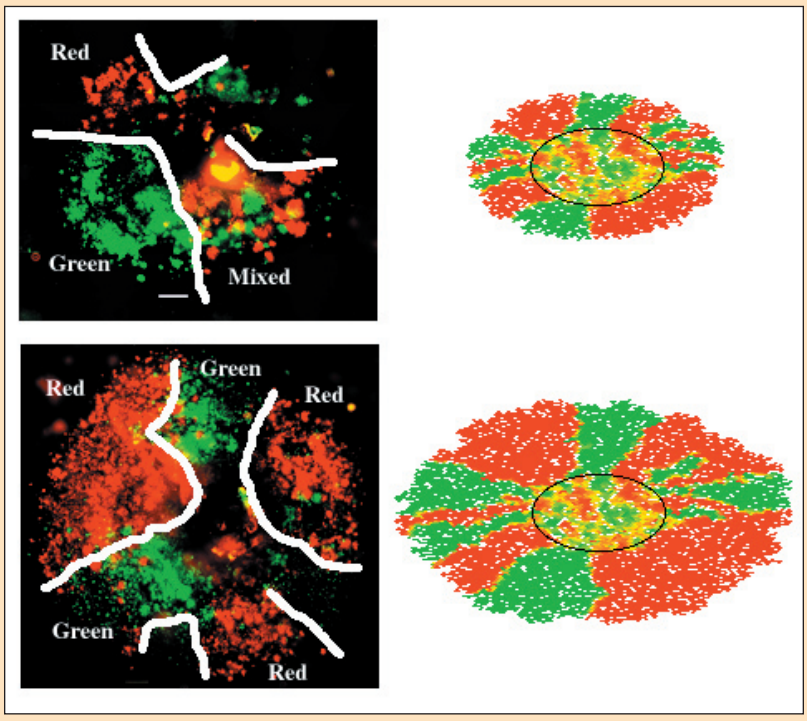
Chiu, K., Duca, K., Berman, S., Sullivan, T., and Bursztajn, S. 1996. A Novel *in situ* Double–Labeling Method for Simultaneous Detection of mRNA and Expressed Protein or Two Different mRNAs. *J of Neuroscience Methods*, 66: 69–79.

Lightfoot, E. and Duca, K. 1999. The Roles of Mass Transfer in Tissue Function in *The Biomedical Engineering Handbook*, 2nd Edition. CRC Press LLC, Boca Raton, FL.

Research

While great strides were made during the twentieth century in treating infectious diseases of bacterial origin, we have not been as successful in controlling viral diseases. The classic approach is preventing infection by prophylactic vaccination. Many viruses, due to their genetic lability, rapidly evade vaccine–induced immunity. Moreover, we live in a world where 30 million people are infected with HIV and the threat of biological terrorism is growing. We must, therefore, be prepared to cope with pathogens against which no vaccines can be made. In addition, therapy must be initiated post–infection. The new tools of biotechnology present opportunities to dissect the entire viral infection process, revealing potential therapeutic intervention points that were previously inaccessible.

Dr. Duca's research program addresses understanding, detecting, and treating infectious diseases caused by viral pathogens. Her main focus is on innate immunity, specifically interferon–activated host responses. Viruses, while simple entities themselves, cause large perturbations in cells, organisms, and populations. The system–level or "emergent" properties of virus–host complexes are notoriously difficult to probe experimentally, as historically most scientific tools rely on reductionist simplification. Engineering disciplines, which excel at conceptualizing large–scale problems and finding solutions in the absence of perfect knowledge, offer different approaches to understand complicated biological phenomena.



Dr. Duca has a keen interest in modeling virus competition experiments in silico. *Figures on the right are epifluorescent micrographs of delayed brain tumor cells infected with two strains of murine hepatitis virus, JHM (green) and A59 (red). Note the clear partitioning of the viruses, which is replicated at right in simulation.*

Dr. Joel Gillespie

Research Assistant Professor, VBI

1997 Ph.D., Biological Chemistry,
Johns Hopkins University School of Medicine

Postdoctoral Training:
University of California, Santa Cruz
Stanford University

Research

Dr. Gillespie's principle research interests are in protein folding, the means by which a protein's amino acid sequence encodes its three–dimensional structure. Research in Dr. Gillespie's laboratory is currently focused on two major projects: the role of protein misfolding in human disease and the design and engineering of proteins with novel catalytic activities.

Protein misfolding has been implicated in the etiology of a variety of different diseases. A few well–known examples include Parkinson's disease, Alzheimer's disease, type II diabetes mellitus, mad cow disease, kuru, and Huntington's disease. All of these diseases have in common the formation of highly ordered, elongated or fibrillar aggregates with a crossed beta–pleated sheet structure believed to be similar to that of silk fibroin, and hence called the "beta–fibrilloses". The long–term goal of Dr. Gillespie's research is to develop a significant understanding of the mechanism by which these pathological aggregates are formed, with the hope that such detailed understanding will lead to better treatments for protein aggregation diseases.

To this end, he has focused on a small cysteine protease inhibitor, cystatin C, and its role in forming pathological aggregates leading to massive strokes in young adults carrying an inherited genetic point mutation in the cystatin C gene on chromosome 20. A significant portion of Dr. Gillespie's research effort is directed toward understanding the mechanism by which such aggregates are formed and the interrelationship between the thermodynamic stability of cystatin C, its amino acid sequence, and its propensity to aggregate. He is also actively studying the relationship between the formation of disordered or amorphous aggregates, and fibrillar aggregates by cystatin C, and their role in disease progression.

A second major thrust of Dr. Gillespie's research involves the design of proteins with novel catalytic activities using both directed molecular evolution and rational design approaches. In this area, Dr. Gillespie's current efforts are aimed at the design of heme oxidoreductases with potential applications to biological remediation of environmental pollutants. Current targets include lignin (LiP) and manganese peroxidase (MnP), two closely related enzymes secreted by the white–rot fungus (*Phanerochaete chrysosporium)* to degrade lignin, a complex phenolic polymer found in woody plant tissue. During wood pulping to make paper, lignin and lignin degradation products are often deposited on cellulose fibers, giving them a dark brown appearance and reducing the value of the paper produced. Removal of lignin usually involves bleaching with Cl_2 (or the more environmentally friendly ClO_2), which can produce a variety of harmful and persistent environmental pollutants including dioxin.

Dr. Gillespie currently uses directed molecular evolution and rational design strategies to produce variants of LiP and MnP that are both stable and have enhanced catalytical activity under a variety of different extrinsic conditions. Such modified enzymes have a variety of potential applications including reducing the environmental impact of paper production and increasing paper yields for recycled materials requiring deinking. He is also *de novo* engineering small proteins with the ability to efficiently oxidize a variety of persistent environmental pollutants, which retain high stereo–selectivity in non–aqueous environments.

Selected Publications

Meyer, A., Gillespie, J., Walther, D., Millett, I., Doniach, S., and Frydman, J. 2003. Closing the folding chamber of the eukaryotic chaperonin requires the transition state of ATP hydrolysis. Cell, 113:369–381.

Abramov, V., et al. 2002. Structural and functional properties of *Yersinia pestis* Caf1 capsular antigen and their possible role in fulminant development of primary pneumonic plague. J. Proteome Res., 1(4)307–315.

Khurana, R., Gillespie, J., Talapatra, A., Minert, L., Ionescu–Zanetti, C., Millett, I., and Fink, A. 2001. Partially folded intermediates as critical precursors of light chain amyloid fibrils and amorphous aggregates. Biochemistry, 40(12): 3525–35.

Uversky, V., Gillespie, J., and Fink, A. 2000. Why are natively unfolded proteins unfolded under physiological conditions? Proteins: Str. Fun. Genetics, 41(3):415–27.

Ionescu–Zanetti, C., Khurana, R., Gillespie, J., Petrick, J., Trabachino, L., Minert, L., Carter, S., and Fink, A. 1999. Monitoring the assembly of Ig light–chain amyloid fibrils by atomic force microscopy. PNAS USA, 96(23):13175–79.

Uversky, V., Talapatra, A., Gillespie, J., and Fink, A. 1999. Protein deposits as the molecular basis of amyloidosis. Part 1: Systemic amylodoses. Med. Sci. Mon., 5(5):1001–13.

Dr. Ina Hoeschele

Research Professor, VBI
Professor of Statistics, VT

1986 Ph.D., Hohenheim University, Stuttgart (Germany)

Grants

PI. Design and Analysis of a Microarray Gene Expression Experiment for Predicting Developmental Competency of Nuclear Transfer Bovine and Porcine Embryos. Infigen Inc. 1/1/00– 12/31/03: $121,386.

PI. Developing Statistical Methods for Fine–Mapping of QTLs in Swine Populations. The Monsanto Company. 1/1/02 – 12/31/03: $139,063.

PI. Polygenic Linkage and Linkage Disequilibrium Mapping. National Institutes of Health. 9/1/2002–8/31/2005: $299,328.

co–PI. Dissecting Soybean Resistance to *Phytophthora* by QTL Analysis of Host and Pathogen Expression Profiles. National Science Foundation. 10/1/2002–9/30/2007: $6,764,465.

Selected Publications

Freyer G., Sorensen, P., Kuhn, C., Weikard, R., and Hoeschele, I. 2003. Search for pleiotropic QTL on chromosome BTA6 affecting milk production traits. J. Dairy Sci., 86:999–1008.

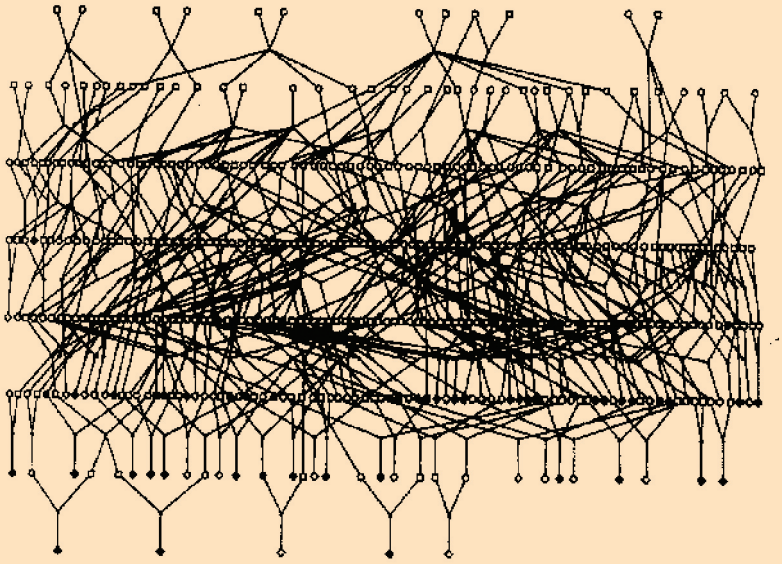
Du, F., Sorensen, P., Thaller, G., and Hoeschele, I. 2002. Joint linkage disequilibrium and linkage mapping of quantitative trait loci. Proc. 7th World Congr. Genet. Appl. Livest. Prod., 32:661–668.

Freyer G., Kuhn, C., Weikard, R., Zhang, Q., Mayer, M., and Hoeschele, I. 2002. Multiple QTL on chromosome six in dairy cattle affecting yield and content traits. J. Anim. Breed. Genet., 119:69–82.

Research

One of the most important problems in post–genome biology is to understand the genetic architecture of quantitative and complex traits, or how genetic variation affects phenotypic variation in humans, plants, and animals. A combination of Quantitative Trait Loci (QTL) mapping on phenotypic traits and gene expression profiles with functional genomics leads to the identification of candidate genes, gene network inference, and the identification of many genes and aspects of metabolism and physiology otherwise missed.

This research has important implications in medicine, agriculture, and functional genomics. Dr. Hoeschele's specific, current research areas include joint linkage and linkage disequilibrium mapping of QTL in complex pedigrees; basic statistical design and analysis of microarray gene expression experiments; and gene network inference using a genetical genomics approach.



Human pedigree analyzed to map genes.

Dr. Reinhard Laubenbacher

Research Professor, VBI
Professor of Mathematics, VT

1985 Ph.D., Mathematics
Northwestern University

Research

Dr. Laubenbacher directs the Discrete Mathematics Group at VBI. This group is interested in the development and application of bioinformatics tools using discrete mathematics, dynamical systems theory, and symbolic computation. Methods from combinatorics and combinatorial topology, as well as computational polynomial algebra are of particular interest.

Mathematical tools for reverse–engineering of biochemical networks are of particular interest to Dr. Laubenbacher. One central problem in systems biology is the design of global models for biochemical networks from experimental data, such as gene regulatory networks from DNA microarray data. Laubenbacher's group has developed a new modeling approach for such networks, based on the framework of discrete dynamical systems in which each variable can take on a finite number of states. The most basic examples of such systems are cellular automata and Boolean networks. Using methods from computational algebra, a method to reverse–engineer gene regulatory networks has been constructed. This tool, combined with tools developed by the Mendes group, is being used in a study of oxidative stress in yeast in collaboration with the Shulaev Laboratory with support from a grant by the National Institutes of Health. Other collaborators include Ed Green from Virginia Tech's Department of Math and Michael Stillman of the Department of Math at Cornell University. This work has been partially supported by an NSF Biocomplexity grant.

Another project is PathSim, a multi–scale computer simulation of immune response to respiratory pathogens. The simulation is based on a mathematical specification that provides the foundation for a built–in control theory. At the systemic level, the immune system is being modeled as a transportation and communication system. At present the project focuses on Epstein–Barr virus and influenza. Collaborators include Karen Duca at VBI; Abdul Jarrah in the Math Department at East Tennessee State University; and David Thorley–Lawson of Tufts University's Medical School. For details see http://www.vbi.vt.edu/~pathsim.

A related project is focused on the development of a mathematical foundation for simulation science as it relates to discrete simulations. The goal of the project is to specify a type of mathematical object that is rich enough to admit a mathematical structure theory and has as incarnations simulations of interest, including the immune system simulation described above. Collaborators include Chris Barrett, Madhav Marathe, Henning Mortveit, and Christian Reidys from the Simulation Science Group at Los Alamos National Laboratory and Bodo Pareigis in the Mathematics Department at the University of Munich, Germany.

Also under development are computational algebra models for Bayesian networks. This is an exploratory project with Bernd Sturmfels of UC Berkeley's Math Department and is supported by an NSF incubation grant from the Computational and Algebraic Representation of Geometric Objects (CARGO) program. The goal of the project is to apply computational algebra techniques to the study of Bayesian networks. In particular, the collection of all probability distributions that are consistent with a given directed graph is represented as a geometric object. This object can then be studied algorithmically with computational algebra techniques. The goal of this project is that general structure theorems can be used in practical applications of Bayesian networks to the reverse–engineering problem for biochemical networks.

Grants

PI. A New Mathematical Modeling Approach to Biochemical Networks, with an Application to Oxidative Stress in Yeast. National Institute of General Medical Sciences. 5/1/03–4/30/07: $1,045,128.

PI. Algebraic Algorithms for Cell Complexes. National Science Foundation. 5/1/02–8/31/04: $100,000.

PI. Mathematical Foundation for Computer Simulation. Los Alamos National Laboratory. 7/2003–4/2004: $100,000.

Selected Publications

Eckart, D., Sobral, B., Laubenbacher, R., and Mendes, P. 2003. The role of bioinformatics in toxicogenomics and proteomics. Proceedings for NATO Advanced Workshop on Toxicogenomics and Proteomics. October 16–20, 2002. Prague, Czech Republic.

Laubenbacher, R. and Pareigis, B. 2003. Decomposition and simulation of sequential dynamical systems, Adv. In Appl. Math., 30:655–678.

Laubenbacher, R., Barcelo, H., Kramer, X. and Weaver, C. 2001. Foundations of a connectivity theory for simplicial complexes. Adv. Appl. Math. 26:97–128.

Jarrah, A., Laubenbacher, R., and Romanovski, V. 2002. The cyclicity problem for two–dimensional polynomial systems, in G. A. Leonov (ed.), Nonlinear Dynamical Systems, Issue 4, St. Petersburg University Press.

Laubenbacher, R. 2003. A computer algebra approach to biological systems. Proc. Intl. Symp. on Symbolic and Algebraic Computation, Assoc. Comp. Mach.

Dr. Iuliana Lazar

Research Assistant Professor, VBI
Assistant Professor, Biology Department, VT

1997 Ph.D., Chemistry
Brigham Young University

Postdoctoral Training
Oak Ridge National Laboratory

Patents

I. M. Lazar and B. L. Karger. Microchip Integrated Multichannel Electroosmotic Pumping System. Patent Application (WO 02/094440 A2, Priority US Application 60/292780).

Selected Publications

Lazar, I. and Karger, B. 2002. Multiple open–channel electroosmotic pumping system for microfluidic sample handling. Anal. Chem., 74(24):6259–6268.

Lazar, I., Foret, F., and Karger, B. Microfabricated devices: a new sample introduction approach to mass spectrometry, chapter submitted to Methods in Enzymology, Biological Mass Spectrometry volume.

Lazar, I. and Karger, B. 2001. Microchip integrated analysis system for electrospray mass spectrometric analysis of complex peptide mixtures in Micro Total Analysis Systems, J. Michael Ramsey and Albert van der Berg, Eds., Kluwer Academic Publishers, Dordrecht, p. 219–221.

Lazar, I., Ramsey, R., and Ramsey, J. 2001. On–chip proteolytic digestion and analysis using 'wrong–way–round' electrospray time–of–flight mass spectrometry. Anal. Chem., 73(8):1733–1739.

Research

Dr. Lazar's research project centers on the development of stand–alone microfluidic analysis platforms with mass spectrometric detection for bioanalytical applications, in particular, proteomics.

Projects include three areas of research:

1. Microchip platform development: design, development, and integration of functional elements (sample propulsion elements, microreactors, separation/infusion channels, MS interfaces, filters, mixers, interconnecting units, microdispensing elements, multiplexed architectures, etc.).

2. Bioanalytical process implementation on the chip: sample cleanup, prefractionation, preconcentration, labeling, digestion, and separation. Emphasis will be placed on developing chemistries based on affinity interactions for capturing, purifying, labeling and immobilizing peptide or protein components.

3. Mass spectrometric (ESI and MALDI) analysis of peptide/protein samples.

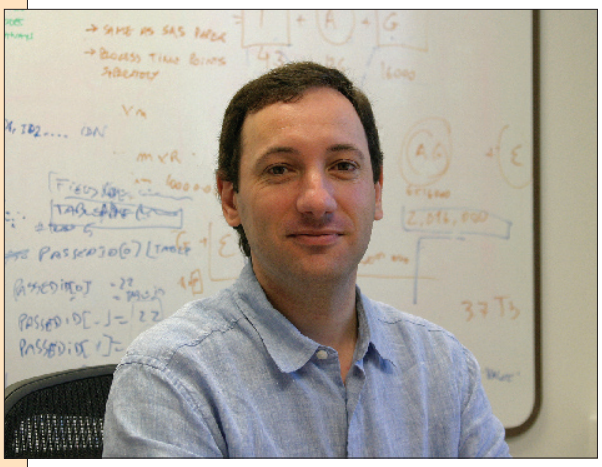
Proteomics is a rapidly developing area of research focused on analyzing the protein content of cells, tissues, and microorganisms. Rapid answers must be provided for questions such as: the identity and level of expression of existing proteins, the nature and site of posttranslational modifications, and the specific functions associated with individual proteins.

Mass spectrometry has evolved into an essential tool in peptide/protein sample analysis. The challenges associated with a "proteomic" sample are numerous: complexity (thousands of proteins/sample), wide range of concentrations (dynamic range of $1{:}10^6$), low level expression for certain components (less than 1000 copies/cell), dynamic composition (different sets of proteins are expressed in various stages of cell development), and availability (final sample for MS analysis at the level of 1–10 L and/or a few nM/pM concentration). Moreover, for one single starting protein mix, the final stage of MS analysis involves the investigation of ten to hundreds of peptide fractions.

Microfabrication is emerging to be one of the most significant trends in analytical chemistry instrumentation. Microfluidic devices present unique opportunities for integration, multiplexing, and capability of handling small sample quantities and represent an optimal platform for proteomic applications.

Progressively smaller, faster, and "smarter" devices with integrated complex detection systems will be designed to accommodate the accelerating demand for information–producing, high–throughput instrumentation.

Dr. Pedro Mendes



Research Assistant Professor, VBI
Adjunct Assistant Professor of Biochemistry, VT

1994 Ph.D., Biochemistry
University of Wales, Aberystwyth (UK)

Research

Dr. Mendes' research focuses on computer simulation and analysis of biochemical networks. It consists of three main components: development of simulation software (Gepasi and COPASI), modeling gene expression in the context of metabolic networks, and bioinformatics support for functional genomics.

Dr. Mendes is the author of the popular biochemical simulation software, Gepasi, in use in many laboratories worldwide. This software facilitates mathematical modeling of biochemical networks without the need to write the mathematics explicitly. Gepasi, a problem–solving environment, allows biochemists to carry out computer simulation without extra programming. Dr. Mendes is also collaborating with European Media Laboratory (EML) in Heidelberg, Germany, to create a new simulator called COPASI. This program will succeed Gepasi with improved functionality for high–performance computers and a user–friendly interface.

Dr. Mendes' group focuses on modeling gene networks together with biochemical pathways. Since gene and biochemical networks are tightly interconnected, it only makes sense to model the two together. An ambitious target of this research has been to uncover these networks from experimental observations of gene expression in proteomics. Progress in this area has proceeded at a steady pace as reported recently in the journal, Trends in Genetics. Work is now expanding to microarray and metabolomics data analysis. Efforts in this area benefit from collaborations with Drs. Hans Westerhoff (Free University of Amsterdam), Jacky Snoep (University of Stellenbosch, South Africa), Dr. Reinhard Laubenbacker (VBI and VT Mathematics Department), Craig Nessler (VT Plant Pathology, Physiology, and Weed Science), Ina Hoeschele (VBI and VT Statistics), and Vladimir Shulaev (VBI and VT Horticulture Department).

In order to integrate genetics with metabolism, whole organism–level measurements of thousands of molecules must be made using novel high–throughput technologies, such as microarrays and mass spectrometry. In particular, measuring the levels of small organic molecules (natural products or metabolites) is important. Such metabolite profiling generates large amounts of data and therefore requires extensive bioinformatics support.

Selected Publications

Eckart, D., Sobral, B., Laubenbacher, R., and Mendes, P. 2003. The role of bioinformatics in toxicogenomics and proteomics. Proceedings for NATO Advanced Workshop on Toxicogenomics and Proteomics. October 16–20, 2002. Prague, Czech Republic.

Sumner, L. W., Mendes, P., and Dixon, R. 2002. Plant metabolomics: large–scale phytochemistry in the functional genomics era. Phytochemistry, 395–398.

Brazhnik, P., de la Fuente, A., and Mendes, P. 2002. Gene networks: how to put the function in genomics. Trends in Biotechnology, 20:467–472.

Mendes, P., de la Fuente, A., and Hoops, S. 2002. Bioinformatics and computational biology for plant functional genomics. Recent Adv. Phytochem., 36:1–13.

de la Fuente, A., Brazhnik, P., and Mendes, P. 2002. Linking the genes: Inferring gene networks from microarray data. Trends Genet., 18: 395–398.

de la Fuente, A., and Mendes, P. 2002. Quantifying gene networks with regulatory strengths. Molecular Biology Reports, 29:73–77.

Grants

PI. An Integrated Approach to Functional Genomics and Bioinformatics in a Model Legume. National Science Foundation.
8/1/01–7/31/05: $3,587,432.

PI. Postdoctoral Fellowship for Bioinformatics Research Training. Samuel Roberts Noble Foundation.
10/15/01–10/14/03: $45,000.

co–PI. Integrated Functional Genomic Resource Development in *Vitis Vinifera*: Abiotic Stress and Wine Quality. University of Nevada–Reno.
8/1/02–7/31/06: $3,609,951.

co–PI. Sun Center of Excellence in Bioinformatics. Sun Microsystems, Inc. 5/1/01–4/30/04: $1,262,486.

co–PI. Metabolic Engineering of Plant Vitamin C Biosynthesis for Improved Nutrition and Health. National Science Foundation and USDA.
9/15/01–8/31/04: $99,999.

co–PI. A New Mathematical Modeling Approach to Biochemical Networks, with an Application to Oxidative Stress in Yeast. National Institute of General Medical Sciences. 5/1/03–4/30/07: $1,045,128.

Dr. Biswarup Mukhopadhyay

Research Assistant Professor, VBI
Adjunct Assistant Professor of Biochemistry and Biology, VT

1993 Ph.D., Microbiology
Laboratory of Prof. Lacy Daniels
University of Iowa, Iowa City

Postdoctoral Training:
Laboratory of Prof. Ralph S. Wolfe,
University of Illinois at Urbana–Champaign

Selected Publications

McInerney, T., Johnson, E., Mukhopadhyay, B., and Borthwick, A. 2003. Analysing 2–D gels at high throughput, data mining with progenesis discovery informatics tool. Genetic Engineering News, 23:31–32, 36.

Galagan, J., Nusbaum, C., Roy, A., Endrizzi, M., Macdonald, P., FitzHugh, W., Calvo, S., Engels, R., Smirnov, S., Atnoor, D., Brown, A., Allen, N., Naylor, J., Stange–Thomann, N., DeArellano, K., Johnson, R., Linton, L., McEwan, P., McKernan, P., Talamas, J., Tirrell, A., Ye, W., Zimmer A., Barber, R., Cann, I., Graham, D., Grahame, D., Guss, A., Hedderich, R., Ingram–Smith, C., Kuettner, H., Krzycki, J., Leigh, J., Li, W., Liu, J., Mukhopadhyay, B., Reeve, J., Smith, K., Springer, T., Umayam, L., White, O., White, R., Conway de Macario, E., Ferry, J., Jarrell, K., Jing, H., Macario, A., Paulsen, I., Pritchett, M., Sowers, K., Swanson, R., Zinder, S., Lander E., Metcalf, W., and Birren, B. 2002. The genome of *M. acetivorans* reveals extensive metabolic and physiological diversity. Genome Res., 12:532–542.

Fabrega, C., Farrow, M., Mukhopadhyay, B., de Crecy–Lagard, V., Ortiz, A., and Schimmel, P. 2001. An aminoacyl tRNA synthetase whose sequence fits into neither of the two known classes. Nature, 411:110–114.

Mukhopadhyay, B., Concar, E., and Wolfe, R. 2001. A GTP–dependent vertebrate–type phosphoenolpyruvate carboxykinase from Mycobacterium smegmatis. J. Biol. Chem., 276:16137–16145.

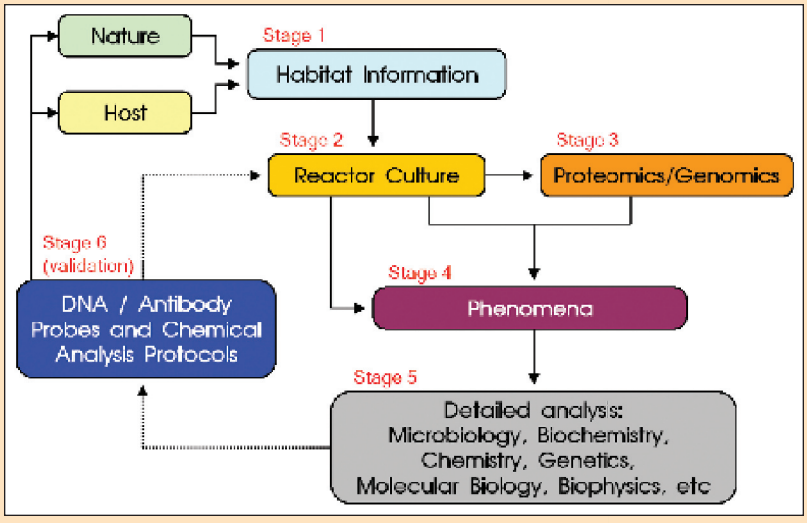
Mukhopadhyay, B., Purwantini, E., Kreder, C., and Wolfe, R. 2001. Oxaloacetate synthesis in the methanarchaeon *Methanosarcina barkeri* : pyruvate carboxylase genes and a putative *Escherichia coli*–type bifunctional biotin protein ligase gene (bpl/birA) exhibit a unique gene organization. J. Bacteriol, 183:3804–3810.

Research

Dr. Biswarup Mukhopadhyay's research falls into two fields: experimental functional genomics and mechanistic biochemistry. The overall goal is to study the ecophysiology of a target microorganism and the biochemical basis of microbial diversity. His work also emphasizes the understanding of evolutionary processes. The figure below summarizes the steps comprising the experimental functional genomics approach. This approach is used to discover environmental stimuli and directed novel behaviors of target microorganisms, and to elucidate their underlying molecular mechanisms. This complete approach makes use of advances in genomics and chemistry and helps to prioritize and provide *in vivo* relevance to *in vitro* biological research. It has aided discovery of certain microbial behaviors that were previously logically unpredictable.

Model organisms for experimental functional genomics projects are *Methanococcus jannaschii*, a hyperthermophilic, strictly anaerobic, hydrogenotrophic, chemolithoautotrophic archaeon that lives in submarine hydrothermal vents, and *Mycobacterium*, major human and animal pathogens as well as inhabitants of the soil.

The mechanistic biochemistry projects involve structure–function analysis and physiological studies in the following systems: oxaloacetate biosynthesis in methanogenic archaea; anaplerotic and gluconeogenesis reactions in the mycobacteria that also serve as models for studying certain aspects of non–insulin–dependent diabetes in vertebrates; evolution of biotin–dependent enzymes; hydrogen sensing, detoxification, and volatilization of selenium; and protein modification in the methanogenic archaeon *M. jannaschii*. The work covers enzyme purification and characterization (structural and kinetic properties), site–directed mutagenesis and design of chimeric proteins (including the development of genetic screens for the mutant or designed proteins), and the design of inhibitors (pharmaceuticals).



An illustration of the experimental functional genomics approach process implemented by Mukhopadhyay's research team.

Dr. Dharmendar Rathore

Research Assistant Professor, VBI

1997 Ph.D., Molecular Biology
National Institute of Immunology
Jawaharlal Nehru University, New Delhi, India

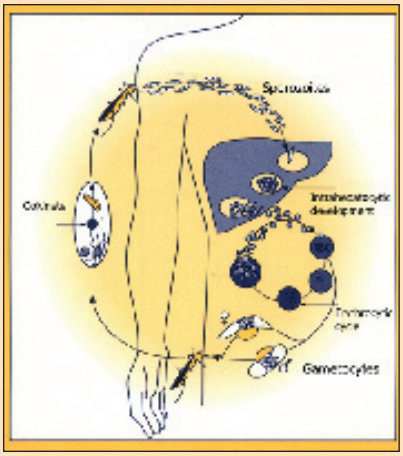
Research

Malaria is one of the 10 most prevalent and deadly diseases. Forty percent of the world's population is at risk. Malaria is transmitted to humans when *Plasmodium* sporozoites are inoculated into the bloodstream by the bite of an infected female mosquito. To devise an effective treatment, whether a vaccine or pharmaceutical, understanding the molecular mechanism of infection and pathogenesis of the etiological agent is of paramount importance.

Dr. Rathore investigates the pathogen and host factors involved in the onset and sustenance of malaria infection. His research elucidated the molecular mechanism of the interaction of Circumsporozoite protein, a predominant sporozoite surface antigen, with host liver cells. He has shown that the protein utilizes its amino terminus for binding and subsequent invasion of liver cells. He has also characterized the nature of the host–cell receptor and identified the minimum binding domain required for the host–parasite interaction. Dr. Rathore now works to identify other sporozoite antigens and their receptors on host cells, which contribute to the successful start of an infection. This effort will lead to a greater understanding of both the parasite and host components involved in infection. In the future, an effective strategy can be devised for disrupting this interaction, which could result in infection control. Dr. Rathore has also investigated drug resistance mechanisms, anti–malarial immune responses, evolutionary relationships, and geographic distribution of the parasite.

Beyond malaria, Dr. Rathore has interests in identifying the common pathways of pathogenesis among various infectious agents. Pathogens, though phenotypically and genotypically different, exploit similar host–cell resources for infection and survival. A wide variety of viruses, parasites, and bacterial pathogens exploit glycosaminoglycan–based host–cell surface receptors for attachment. Exploitation of a common host receptor occurs due to the subtle homologies at the structural level in the surface antigens of these pathogens. Bioinformatics approaches to identify and characterize these surface antigens will be a priority in Rathore's research program at VBI.

Dr. Rathore is also involved in collaborative research projects with the malaria researchers at the National Institute of Allergy and Infectious Diseases, Naval Medical Research Center, and the Bacterial and Parasitic Diseases Laboratory of the Food and Drug Administration.



The cycle of malaria infection studied by Dr. Rathore's team at VBI in order to develop an effective treatment and vaccine.

Selected Publications

Chattopadhyay, R., Rathore, D., Fujioka, H., Kumar, S., De La Vega, P., Haynes, D., Moch, K., Fryauff, D., Wang, R., Carucci, D., and Hoffman, S. 2003. A *Plasmodium falciparum* protein containing an altered Thrombospondin Type I repeat domain is expressed at all stages of the parasite life cycle and is the target of inhibitory antibodies. The Journal of Biological Chemistry, 278:25977–25981.

Rathore, D., Sacci, J., de la Vega, P., and McCutchan, T. 2002. Binding and invasion of liver cells by *Plasmodium falciparum* sporozoites: Essential involvement of the amino terminus of circumsporozoite protein. The Journal of Biological Chemistry, 277:7092–7098.

Rathore, D. and McCutchan, T. 2002. Construction of a gene library with mung bean nuclease treated genomic DNA in malaria methods and protocols. Methods in Molecular Medicine, 72:253–263.

Cummings, L., Rathore, D., and McCutchan, T. 2002. Construction of genomic libraries from the DNA of *Plasmodium* species in malaria methods and protocols. Methods in Molecular Medicine, 72:241–251.

Rathore, D., Kumar, S., Lanar, D., and McCutchan, T. 2001. Disruption of disulfide bonding adjacent to cytotoxic T lymphocyte epitopes of the Plasmodium falciparum Circumsporozoite protein does not alter the cytotoxic and antibody responses in mice. Molecular and Biochemical Parasitology, 118:75–82.

Rathore, D., McCutchan, T., Garboczi, D., Toida, T., Hernaiz, M., LeBrun, L., Lang, S., and Linhardt, R. 2001. Direct measurements of the interactions of glycosaminoglycans and a heparin decasaccharide with the malaria circumsporozoite protein. Biochemistry, 40: 11518–11524.

Dr. David Samuels

Research Assistant Professor, VBI

1990 Ph.D., Physics
University of Oregon

Postdoctoral Training:
Stanford University
NASA Ames and Emory University

Selected Publications

Capps, G., Samuels, D., and Chinnery, P. 2003. A model of the nuclear control of mitochondrial DNA replication. J. of Theoretical Biology, 221:565–583.

Chinnery, P., Samuels, D., Elson, J., and Turnbull, D. 2002. Accumulation of mitochondrial DNA mutations in ageing, cancer, and mitochondrial disease: is there a common mechanism? Lancet, 360:1323–1325.

Elson, J., Samuels, D., Johnson, M., Turnbull, D., and Chinnery, P. 2002. The length of cytochrome c oxidase negative segments in muscle fibres in patients with mtDNA myopathy. Neuromuscular Disorders, 12:858–864.

Elson, J., Samuels, D., Turnbull, D., and Chinnery, P. 2001. Random intracellular drift explains the clonal expansion of mitochondrial DNA mutations with age. American Journal of Human Genetics, 68:802–806.

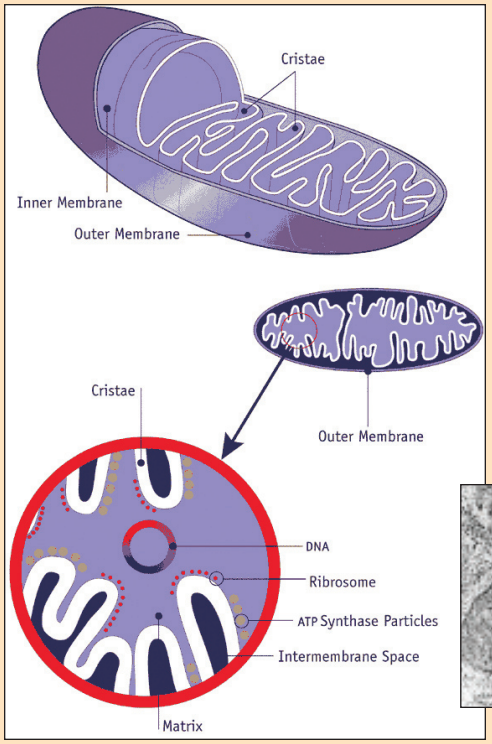
Brown, D., Samuels, D., Michael, E., Turnbull, D., and Chinnery, P. 2001. Random genetic drift determines the level of mutant mitochondrial DNA in human primary oocytes. American Journal of Human Genetics, 68:533–536.

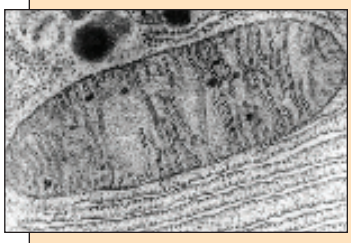
Chinnery, P., Thorburn, D., Samuels, D., White, S., Dahl, H., Turnbull, D., Lightowlers, R., and Howell, N. 2000. The inheritance of mitochondrial DNA heteroplasmy: random drift, selection or both? Trends in Genetics, 16:500–505.

Research

Dr. Samuels' research focuses on cell biology modeling with a biomedical emphasis. His current work is on the modeling of mitochondria, the parts of the cell responsible for generating energy. Mutations in the DNA of mitochondria (mtDNA) lead to loss of energy in the cell and ultimately to the loss of the cell function. This problem is most apparent in cells with high energy requirements, such as neurons and muscle cells. It can take many years, even decades, for mutations in human mtDNA to build up to levels high enough to cause loss of cellular function. Due to these long time scales and the vulnerability of neurons and muscle cells, mutations in mtDNA are often associated with slowly developing neurodegenerative diseases. Dr. Samuels' research uses simulations to understand the development of mtDNA mutations over the human lifetime. His group is analyzing the human mitochondrial genome for sequence characteristics that make the mtDNA susceptible or resistant to mutations. By carrying out these analyses on the genomes, the reasons for the differences in the rate of aging of different species are being investigated.

The current treatment for HIV/AIDS is highly active anti–retroviral therapy (HAART). This therapy involves the use of a drugs that interfere with the replication of the HIV virus. Unfortunately, these therapies may also interfere with the replication of the patient's mitochondrial DNA, leading to the loss of mitochondrial function. Dr. Samuels' group develops models of HAART effects on mitochondria with the goal of determining if these toxic side effects can be minimized or eliminated.





Mitochondria, called the powerhouse of cells, have their own DNA (mtDNA) that is susceptible to mutation over time. These mutations may set the pace for the rate of aging and the onset of certain diseases. (Figure adopted from Brinkman et al., 1998. AIDS 12: 1735-1744)

Dr. Vladimir Shulaev

Research

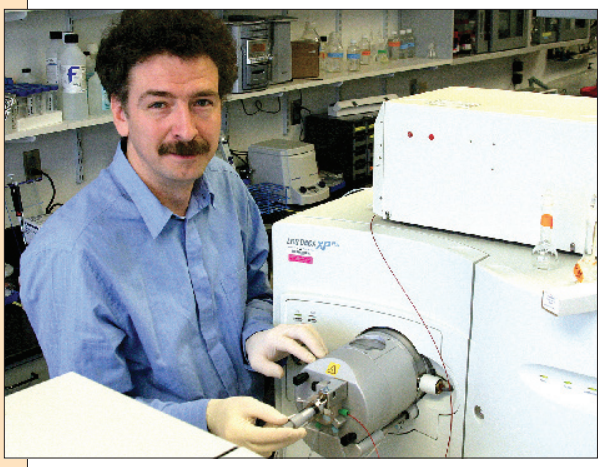
Dr. Shulaev's research program focuses on metabolomics, the quantitative measurement of all low molecular weight metabolites in an organism's cells at a specified time under specific environmental conditions. He applies the fundamentals of this research to various biological systems including plants (strawberry and *Arabidopsis*), malaria, and modeling of oxidative stress in yeast. His strawberry, malaria, and yeast projects are highlighted previously in this report. Using *Arabidopsis* as a model organism to study metabolomics is also central to his research agenda.

Dr. Shulaev studies the biochemical, cellular, and molecular mechanisms of plant responses to biotic and abiotic stress. Susceptibility of crops to stresses—diseases, drought, high salinity, temperature, and others—significantly reduces global agricultural productivity. Efforts to improve plant stress tolerance through traditional breeding or genetic engineering have had limited success due in part to a poor understanding of the basic mechanisms underlying plant adaptive responses. A more mechanistic understanding of the underlying plant responses to environmental stresses is essential in formulating future breeding and engineering strategies aimed at reducing crop losses.

Current research in Dr. Shulaev's lab aims at comprehensive metabolic profiling of plant–derived chemicals involved in stress response in order to identify novel protective metabolites and genes involved in their biosynthesis and regulation. Environmental stress response in plants, an extremely complex trait, is controlled by multiple genes and affected by numerous external factors. Plants respond to stress by dramatically altering both primary and secondary metabolism. These metabolic changes result in the biosynthesis of many specific chemicals designed to protect cells and organs from extreme environmental conditions and pathogens. Numerous plant metabolites are synthesized only in response to a specific stress factor. Many stress–related plant compounds are also traditionally used in pharmaceutical, health, food, cosmetic, agrochemical, and other industries as nutritional supplements, antioxidants, pharmaceuticals, insecticides, and other agents.

For analysis of metabolites, two major analytical platforms are utilized: gas chromatography coupled with mass spectrometry (GC–MS) and high performance liquid chromatography linked to mass spectrometry (LC–MS). Implementation of this dual platform allows simultaneous analysis of a large number of individual compounds with different size, polarity, and other physicochemical properties. Use of *Arabidopsis* as a model system permits rapid identification of genes involved in the biosynthesis and regulation of various classes of compounds. Knowledge of biosynthetic genes and global pathway regulators will improve our ability to manipulate metabolic fluxes toward production of specific products or generate novel compounds with desired properties.

The ultimate goal of Dr. Shulaev's research is the development of new stress–tolerant crops and improving methods of disease control. Biotechnological manipulation of stress metabolites can provide novel ways of engineering plants with desired agronomic traits or increased nutritional value. In addition, finding novel ways to regulate the levels and yield of specific phytochemicals and the identification of novel compounds for human use will be of great benefit and significant economic importance.



Research Associate Professor, VBI
Associate Professor of Horticulture, VT

1987	Ph.D., Biological Sciences Ukraine Academy of Sciences
1995	Ph.D., Plant Biology Rutgers University

Grants

PI. Strawberry functional genomics. Virginia Tech (ASPIRES.) 02/01/03–1/31/05: $100,000.

co–PI. A New Mathematical Modeling Approach to Biochemical Networks, with an Application to Oxidative Stress in Yeast. National Institute of General Medical Sciences. 5/1/03–4/30/07: $1,045,128.

Selected Publications

Nowak, J. and Shulaev, V. 2003. Priming for transplant stress resistance in in vitro propagation. In Vitro Cell. Dev. Biol.–Plant, 39:107–124.

Mittler, R. and Shulaev, V. 2002. Apoptosis in plants yeast and bacteria. *In* Essentials of Apoptosis, A Guide for Basic and Clinical Research, Yin, X.–M. and Dong, Z. eds., Humana Press, Totowa, NJ, 125–134.

Mittler, R., Lam, E., Shulaev, V., and Cohen, M. 1999. Signals controlling the expression of cytosolic ascorbate peroxidase during pathogen–induced programmed cell death in tobacco. Plant Mol. Biol., 39:1025–1035.

Shulaev, V., Silverman, P., and Raskin, I. 1997. Airborne signaling by methyl salicylate in plant pathogen resistance. Nature, 385:718–721.

Dr. Bruno Sobral

Executive and Scientific Director and
Research Professor, VBI

Professor, Plant Pathology, Physiology
and Weed Science, VT

1989 Ph.D., Genetics
Iowa State University

Grants

PI. Shared University Research Grant. IBM Corporation. 2003: $650,000.

PI. PathPort: A Common Asset for Biological Security. U.S. Department of Defense. 4/1/02–3/31/03: $4,000,000.

PI. Sun Center of Excellence in Bioinformatics. Sun Microsystems, Inc. 5/1/01–7/8/04: $1,262,486.

PI. Human Infectious Disease Bioinformatics Collaboratory. VT/Johns Hopkins University Bloomberg School of Public Health. 2/1/02–1/30/07: $10,000,000.

PI. Analysis of Plant Genome Duplication Events and Their Functional Relevance. USDA. 4/1/01–3/31/02: $444,230.

PI. Collaborative Development of an EST Database and Analysis Pipeline. U. of Nevada–Reno/Samuel Roberts Noble Foundation. $323,016.

co–PI. Communication, Training, and Resources for *Phytophthora* Research. NSF. 4/1/02–3/30/07: $497,467.

co–PI. Collaboration with the College of William & Mary and INCOGEN, Inc. Commonwealth Technology Research Fund (CTRF). 1/1/02–12/31/04: $3,251,901.

co–PI. Collaborative Research in Bioinformatics. CTRF. 7/1/01 – 6/30/04: $2,500,201.

co–PI. Genome Sequence of *Phytophthora sojae*. USDA, NSF. 9/15/02 – 9/14/04: $2,334,000.

co–PI. Common Ground for Human Disease Research. NIEHS. 7/01/02 – 10/01/02: $50,000.

co–PI. Virginia Bioinformatics Consortium. CTRF. 11/01/01 – 10/31/04: $1,500,000.

Research

Dr. Bruno Sobral currently serves as Executive and Scientific Director of the Virginia Bioinformatics Institute, as a Research Faculty Member at VBI, and as a Professor of Plant Pathology, Physiology, and Weed Science at Virginia Tech. Under his leadership, VBI has secured almost $30 million in bioinformatics research grants and contracts and has grown to a staff of more than 120. VBI's research platform centers under the umbrella of host–pathogen–environment interactions, in which Dr. Sobral's long–standing interest in reverse engineering living systems, especially in agriculturally or environmentally important organisms, melds appropriately.

His personal research program is two–pronged with both wetlab and cyberinfrastructure programs. His wetlab research entails using comparative genomics, bioinformatics, and proteomics to understand and compare host–pathogen–environment interactions while his cyberinfrastructure research focuses on engineering robust and open frameworks for data and tool interoperability and integration for life sciences. PathPort/ToolBus and ESTAP (EST Analysis Pipeline) are currently being developed by his cyberinfrastructure group at VBI.

Dr. Sobral currently serves on both the NIH Roadmap BECON on Catalyzing Team Science Panel and NSF Cyberinfrastructure Life Sciences Panel. He also serves as an advisor for the development of the U.S. Department of Homeland Security's Special Interest Group in Systems Biology. In addition, he serves as a Panel Member for the Oracle Life Science Advisory Board. He has been active in peer review for research publications in his field and has participated on grant reviews for the Departments of Energy and Agriculture, the National Science Foundation, and the National Institutes of Health.

Selected Publications

Eckart, J. and Sobral, B. 2003. A life scientist's gateway to distributed data management and computing: The PathPort/ToolBus framework. Omics, 7(1): 79–88.

Lathigra, R., He, Y., Vines, R., Nordberg, E., and Sobral, B. 2003. A biologist's view of systems integration for systems biology: The Pathogen Portal Project. Conference Proceedings for Stadler Symposium. Columbia, MO: March 31–April 2.

Eckart, D., Sobral, B., Laubenbacher, R., and Mendes, P. 2003. The role of bioinformatics in toxicogenomics and proteomics. Proceedings for NATO Advanced Workshop on Toxicogenomics and Proteomics. October 16–20, 2002. Prague, Czech Republic.

Huala, E., Dickerman, A., Garcia–Hernandez, M., Weems, D., Reiser, L., LaFond, F., Hanley, D., Kiphart, D., Zhuang, M., Huang, W., Mueller, L., Bhattacharyya, D., Bhaya, D., Sobral, B., Beavis, W., Meinke, D., Town, C., Somerville, C., and Rhee, S. 2001. The *Arabidopsis* Information Resource (TAIR): A comprehensive database and web–based information retrieval, analysis, and visualization system for a model plant. Nucl. Acids Res., 29:102–105.

Sobral, B., Mangalam, H., Siepel, A., Mendes, P., Pecherer, R., and MacLaren, G. 2001. Bioinformatics for rice resources. *In* Rice Biotechnology: Improving Yield, Stress Tolerance and Grain Quality. Wiley: Chichster (Novartis Foundation Symposium 236). 59–84.

Dr. Brett Tyler

Research

Dr. Tyler's research pinpoints genes and molecules that mediate interactions between plants and microbes. These interactions can be beneficial, resulting in increased plant performance, or negative, resulting in plant disease. In either case, the interaction results from the relationship between the two organisms as well as the complex web of signals and responses exchanged among the vast diversity of microbes, microfauna, predators, and competing plants comprising the environment.

The long–term goal of Dr. Tyler's research is to understand the operation of this signaling web sufficiently to enable the design of more sustainable agricultural systems. This will require broad–scale identification of the organisms participating in the communities, the genes they possess, how they use those genes, and the signals they transmit among each other. Dr. Tyler is also interested in the application of similar approaches to the interactions of microbes with animals and humans.

Dr. Tyler's current research centers on identifying and characterizing the signals exchanged between plant pathogens called *Phytophthora* and the plant species they attack, especially soybean. *Phytophthora* pathogens are fungus–like organisms called oomycetes that include the organisms responsible for the Irish potato famine in the 19th century. His research includes a focus on individual genes and signals involved in *Phytophthora*–plant interactions, and whole–genome approaches that include characterizing all the genes in a *Phytophthora* species and determining how they contribute to signaling and pathogenesis. His group also researches the bioinformatic approaches needed to unravel the functioning of complex communities of micro–organisms and their interactions with macro–organisms, such as plants and animals.

Selected Publications

Hirsch, A., Dauer, W., Bird, D., Cullimore, J., Tyler, B., and Yoder, J. 2003. Molecular signals and receptors: controlling rhizosphere interactions between plants and other organisms. Ecology, 84(4):858–868.

Tyler, B. 2002. Molecular basis of recognition between *Phytophthora* species and their hosts. Annual Reviews of Phytopathology, 40:137–167.

Chamnanpunt, J., Shan, W., and Tyler, B. 2001. High frequency mitotic gene conversion in genetic hybrids of the oomycete *Phytophthora sojae*. PNAS, 98(25): 14530–14535.

Tyler, B. 2001. Genetics and genomics of the *Phytophthora*–host interface. Trends in Genetics, 17(11):611–614.

Morris, P., Bone, E., and Tyler, B. 1998. Chemotropic and contact responses of *Phytophthora* sojae hyphae to soybean isoflavonoids and artificial substrates. Plant Physiol., 117(4):1171–1178.

Tyler, B., Wu, M., Wang, J., Cheung, W., and Morris, P. 1996. Chemotactic preferences and strain variation in the response of *Phytophthora sojae* zoospores to host isoflavones. Appl. Environ. Microbiol., 62(8):2811–2817.

Tyler, B., Furster, H., and Coffey, M. 1995. Inheritance of avirulence factors and RFLP markers in outcrosses of the oomycete *Phytophthora sojae*. Mol. Plant–Microbe Ints., 8(4):515–523.

Research Professor, VBI
Professor of Plant Pathology, Physiology, and Weed Science, VT

1981 Ph.D., Molecular Biology, University of Melbourne, Australia

Grants

PI. Communication, Training, and Resources for *Phytophthora* Research. National Science Foundation. 4/1/02–3/30/07: $497,467.

PI. Dissecting Soybean Resistance to *Phytophthora* by QTL Analysis of Host and Pathogen Expression Profiles. National Science Foundation. 10/1/02–9/30/07: $6,764,465.

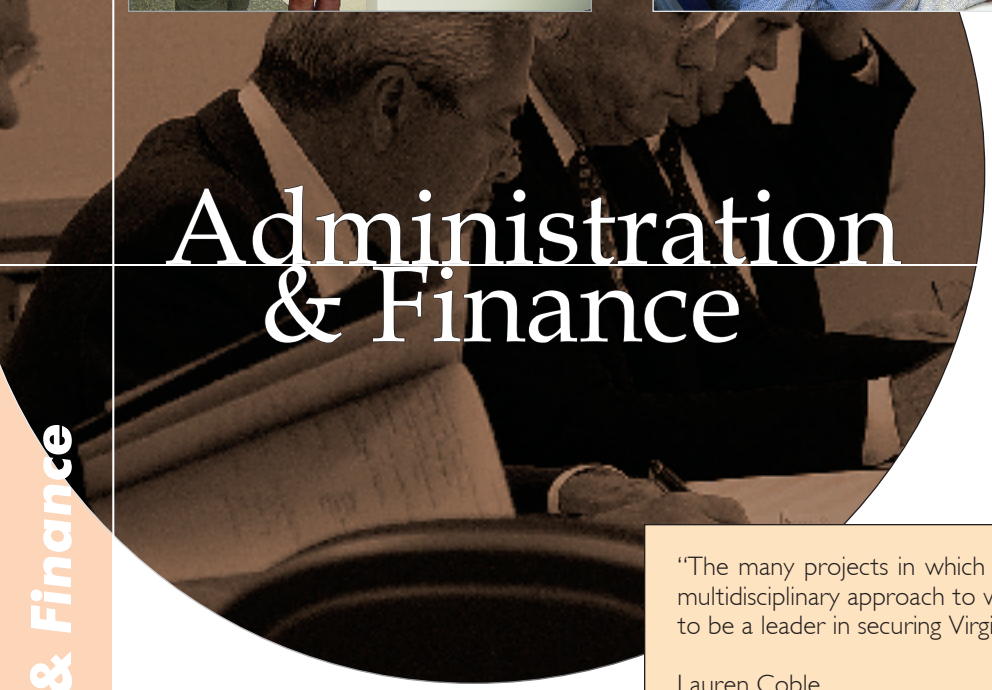
PI. Genome Sequencing of *Phytophthora sojae*. USDA, NSF. 10/1/02–9/30/04: $2,334,000.

PI. *Phytophthora* Genes Expressed During Infection and Propagation. U.S. Department of Agriculture–Cooperative State, Research, Education, and Extension Service. 9/15/00–9/30/03: $1,000,000.

PI. Function of Avirulence Genes in *Phytophthora sojae* Infection of Soybean. U.S. Department of Agriculture. 9/1/01–8/31/04: $230,000.

co–PI. Bioinformatics Prediction of Functions of Unculturable Microbes in Ecosystems. National Science Foundation. 10/1/01–9/30/03: $100,000.

- Administration
- Finance



Administration & Finance

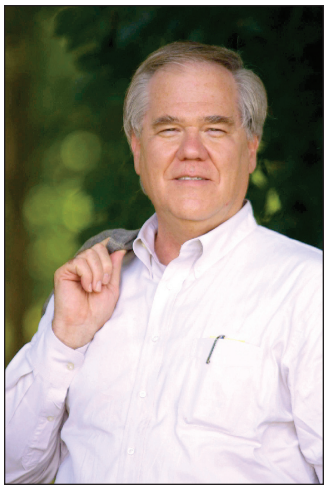
"The many projects in which our research teams collaborate epitomize the multidisciplinary approach to which the institute is dedicated. We are pleased to be a leader in securing Virginia's future."

Lauren Coble
Associate Director, Administration and Finance
Virginia Bioinformatics Institute

VBI's Administration and Finance team provides the infrastructure to support the research mission of the institute's faculty. The team provides centralized services including accounting and finance reporting, facilities management, human resources, and grants and contracts management. The Administration and Finance team's dedication to and enthusiasm for their work is directly linked to the success of the institute; the teamwork necessary to accomplish complex tasks in a dynamic research environment provides the underpinnings of success.

Administrative Staff

Bruno Sobral
Executive and Scientific Director



Dave Sebring
Associate Director of Government and Corporate Relations

Lauren Coble
Associate Director of Administration and Finance

Neysa Call
Head, Public Relations and Outreach

VBI's administrative team handles central administrative issues for the Institute. The team is instrumental to VBI's success and growth as a research institute.

Administration Team Members
(from left to right)

Matt Knefel
Program Support Technician

Shannon Worringham
Executive Assistant to the Director

Catherine Phillips
Office Support Assistant

Barbara Waller
Receptionist/Office Assistant

Stacey Lyons
Fiscal Technician, Sr.

Lauren Coble
Associate Director of Administration and Finance

Lynn Byrd
Human Resources Coordinator

Cory Byrd
Business Analyst

Debi Darnell
Human Resources Recruiter

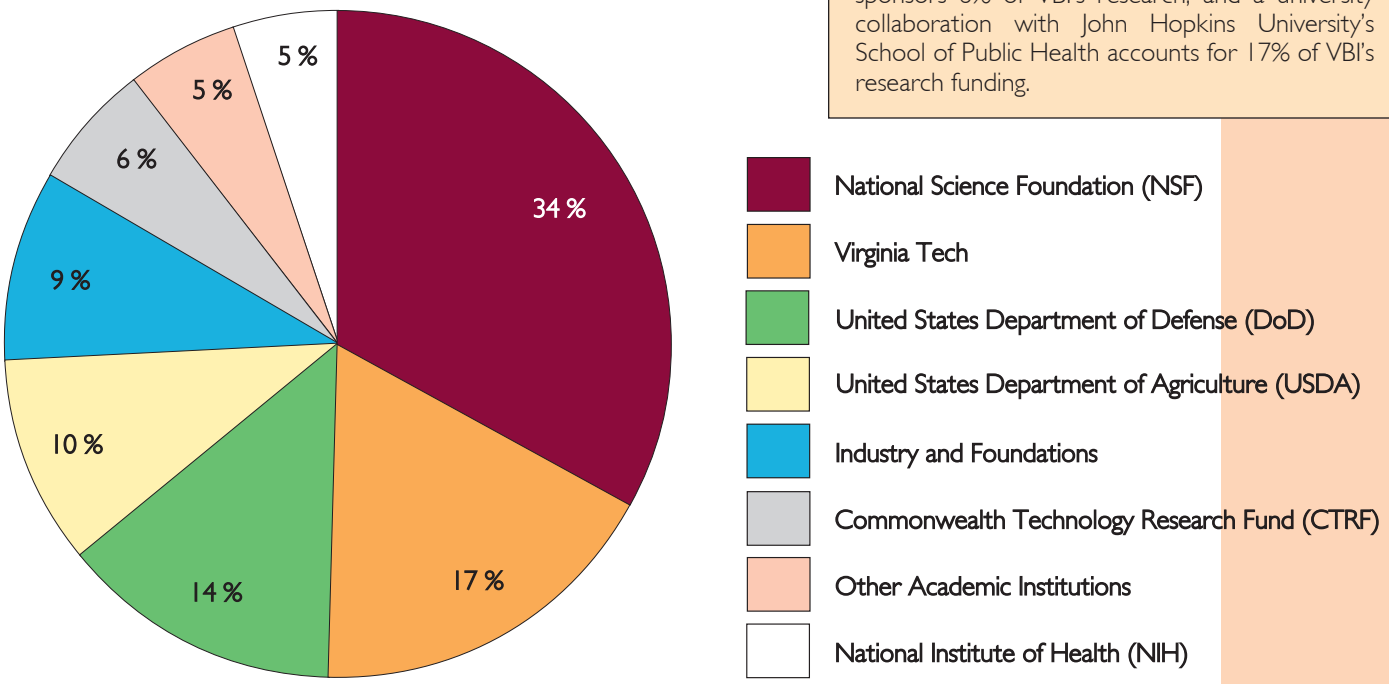
Dawn Maxey
Facilities Manager

Financial Summary

VBI's research portfolio is key to our rapid growth. The institute has supporters and sponsors in a variety of areas, from prominent federal and state government institutions to private foundations and industry leaders. The broad application of bioinformatics research programs provides an environment conducive to innovative thinking and important breakthroughs that could improve the health of people around the world.

VBI Research Portfolio by Funding Source

As of June 30, 2003



VBI has won competitive contracts from four federal agencies, which comprise 63% of VBI's research portfolio. The portfolio distribution of funding is balanced by industry and foundation awards of 9% and awards from other academic institutions of 5%. The Commonwealth of Virginia sponsors 6% of VBI's research, and a university collaboration with John Hopkins University's School of Public Health accounts for 17% of VBI's research funding.

VBI Research Awards by Sponsor

As of June 30, 2003

National Science Foundation (NSF)	$ 9,683,057
Virginia Tech (John Hopkins Univerity collaboration and ASPIRES program)	$ 5,118,537
United States Department of Defense (DoD)	$ 4,429,071
United States Department of Agriculture (USDA)	$ 2,973,614
Industry and Foundations	$ 2,707,955
Commonwealth Technology Research Fund (CTRF)	$ 1,789,058
Other Academic Institutions	$ 1,584,527
National Institute of Health (NIH)	$ 1,491,412
Total	$ 29,777,231

Four federal agencies comprise a total of $18,148,083, or 63% of VBI's total active annual portfolio of $29,777,231.

VBI Proposal and Award Summary

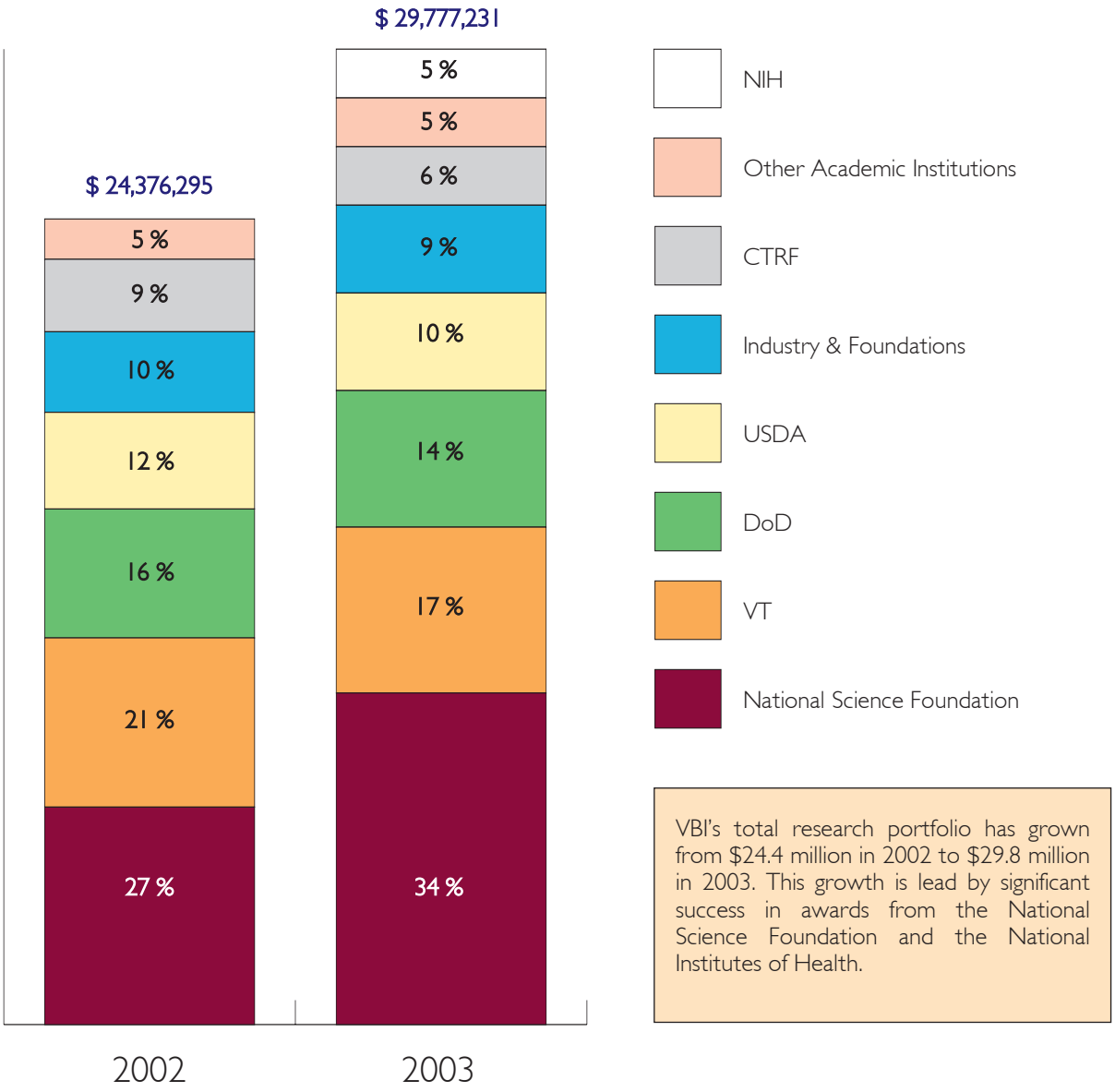
As of June 30, 2003

	Number of Grants and Contracts	Direct	Indirect	Total
Awarded	36	$ 19,779,709	$ 4,997,522	**$ 29,777,231**
Pending	33	$ 38,972,923	$ 13,353,676	**$ 52,326,599**
Not Funded	36	$ 14,831,255	$ 4,011,774	**$ 18,843,029**
Total	105	**$ 73,583,887**	**$ 22,362,972**	**$ 100,946,859**

VBI measures total research activity to provide a benchmark for grant and contract awards. By June 30, 2003, VBI had submitted 105 proposals, totaling over $100 million, of which $29.8 million had been funded. To date, VBI has a 50% funding success rate.

Research Funding Comparison

2002 and 2003



VBI's total research portfolio has grown from $24.4 million in 2002 to $29.8 million in 2003. This growth is lead by significant success in awards from the National Science Foundation and the National Institutes of Health.

VBI's Research Partners and Funded Collaborations

VBI Funded Partnerships

In collaboration with Virginia Bioinformatics Institute, external researchers and institutions have received in excess of $9 million.

College of William and Mary (Williamsburg, VA, USA)
Dept. of Energy Joint Genome Institute (Walnut Creek, CA, USA)
East Tennessee State University (Johnson City, TN, USA)
European Media Laboratory, GMbH (Schloss–Wolfsbrunnenweg, Heidelberg, Germany)
IBM Watson Research Center (Yorktown Heights, NY, USA)
INCOGEN, Inc. (Williamsburg, VA, USA)
INFIGEN, Inc. (DeForest, WI, USA)
Johns Hopkins University, Bloomberg School of Public Health (Baltimore, MD, USA)
Laboratoire Bordelais de Recherche Informatique (LaBRI–Bordelais, France)
Los Alamos National Laboratory (Los Alamos, NM, USA)
Monsanto (St. Louis, MO, USA)
Ohio State University (Columbus, OH, USA)
Oklahoma State University (Stillwater, OK, USA)
Samuel Roberts Noble Foundation (Ardmore, OK, USA)
Sun Microsystems, Inc. (Santa Clara, CA, USA)
TimeLogic, Inc. (Crystal Bay, NV, USA)
Tufts University (Boston, MA, USA)
University of California–Berkeley (Berkeley, CA, USA)
University of Nevada–Reno (Reno, NV, USA)
University of Munich (Munich, Germany)
Virginia Bioinformatics Consortium (University of Virginia, George Mason University, Virginia Commonwealth University, USA)

Virginia Tech

1872

VBI Collaborations with Departments within Virginia Tech

Virginia Tech Departments have garnered over $5 million in funding through collaborations with Virginia Bioinformatics Institute.

Biochemistry	http://www.biochem.vt.edu/
Biology	http://www.biol.vt.edu/
Biomedical Sciences and Pathobiology	http://www.vetmed.vt.edu/Organization/Departments/DBSP/index.asp
Computer Science	http://www.cs.vt.edu/
Crop and Soil Environmental Sciences	http://sudan.cses.vt.edu/
Dairy Science	http://www.dasc.vt.edu/
Electrical and Computer Engineering	http://www.ee.vt.edu/
Fisheries and Wildlife Sciences	http://www.cnr.vt.edu/fisheries/
Horticulture	http://www.hort.vt.edu/
Plant Pathology, Physiology, and Weed Science	http://ipm.ppws.vt.edu/
Statistics	http://www.stat.vt.edu/

Our Partnership Principles

Universities today have evolved from a peripheral role in science and technology to being catalysts for the advancement for innovation. This development, however, has not come independently of cooperation and collaboration with government and industry partners and among universities themselves.

Along with collaboration, growing investments in biotechnology, bioinformatics, and other related fields have spurred new hope and confidence in the importance and relevance of the type of research occuring at VBI. Scientific investment delivers amazing results, and teamwork in the form of collaborations only hearkens that process with greater efficiency. VBI has stepped up to the challenge of cultivating the strength and quality of connections; the scope of our partnerships is invariably equated to our excellence, our leadership in bioinformatics research, and our value to the future of the state and beyond.

Welcoming Partners to VBI

The Institute for Computational Genomics (INCOGEN) relocated its corporate headquarters to Williamsburg, VA from South Carolina as a result of a bioinformatics collaboration with the Commonwealth of Virginia, The College of William and Mary, and the Virginia Bioinformatics Institute.

The collaboration represents a $6.6 million effort funded in part through a $3.2 million grant from Virginia's Commonwealth Technology Research Fund. This relocation has resulted in a prolific research partnership bolstering Virginia's intellectual capabilities in bioinformatics, a goal also central to VBI's economic development mission.

INCOGEN

The College of WILLIAM & MARY

Serving as the home of Virginia Tech and VBI, Blacksburg is located in southwest Virginia. It has a healthy, culturally diverse population of approximately 39,700 citizens living on just over 12,000 acres of land at the foot of the Washington–Jefferson National Forest. The campus is situated on a plateau about 2,100 feet above sea level between the Blue Ridge Mountains to the east and the Allegheny Mountains to the west. The area is especially noted for its scenic and natural beauty, rural tranquility, and outdoor recreation activities. The New River Valley has some of the most spectacular scenery in the east, including the famous Blue Ridge Parkway. Blacksburg provides a harmonious balance of natural beauty and economic opportunity. The town's progressive approach to economic development and the concern for the quality of life of all its citizens were primary factors in Blacksburg being chosen to receive the prestigious award of an *All American City*.

Virginia Tech is a comprehensive university of international prominence. As Virginia's largest university with 25,600 students, it is an institution that firmly embraces a history of putting knowledge to work. Virginia Tech offers more degree programs than any other university in the state with 60 undergraduate and 110 graduate programs and is one of the nation's leaders in developing and using new instructional technologies.

With annual research expenditures of about $170 million, Virginia Tech consistently ranks among the top 50 research universities in the United States. With more than 100 research centers, the university also consistently ranks among the top institutions in industry–supported research and near the top 10 in the number of patents issued each year.

VBI Active Grants

Sponsor	Investigators	Total Award	VBI Award	Project
Commonwealth Technology Research Fund	Dennis Kafura Bruno Sobral	$2,500,201	$1,150,058	Collaborative Research in Bioinformatics
Commonwealth Technology Research Fund	Murray Black Gregory Buck William Pearson Jeffrey Plank Bruno Sobral	$1,500,000	$375,000	Virginia Bioinformatics Consortium
Commonwealth Technology Research Fund	Dennis Manos, et al. Maciek Sasinowski Bruno Sobral	$3,251,901	$264,000	Collaboration with the College of William & Mary and INCOGEN, Inc.
Department of Defense	Bruno Sobral	$4,000,000	$4,000,000	PathPort: A Common Asset for Biological Security
IBM	Bruno Sobral	$650,000	$650,000	Shared University Research Grant
Infigen, Inc.	Ina Hoeschele	$121,386	$121,386	Design and Analysis of a Microarray Gene Expression Experiment for Predicting Developmental Competency of Nuclear Transfer Bovine and Porcine Embryos
Los Alamos National Laboratory	Reinhard Laubenbacher	$100,000	$100,000	Mathematical Foundation for Computer Simulation
Monsanto Company	Ina Hoeschele	$139,063	$139,063	Developing Statistical Methods for Fine–Mapping of Quantitative Trait Loci in Swine Populations
National Institute of Environmental Sciences	Neysa Call Bruno Sobral	$50,000	$50,000	Common Ground for Human Disease Research
National Institute of General Medical Sciences	Reinhard Laubenbacher Pedro Mendes Vladimir Shulaev	$1,045,128	$1,045,128	A New Mathematical Modeling Approach to Biochemical Networks, with an Application to Oxidative Stress in Yeast
National Institute of Health	Zhijian Tu Chunhong Mao	$1,442,364	$60,600	Characterization and Organization of Transposable Elements
National Institute of Health	Ina Hoeschele	$299,328	$299,328	Polygenic Linkage Disequilibrium and Linkage Mapping
National Science Foundation	Allan Dickerman Brett Tyler	$100,000	$72,204	Bioinformatics Prediction of Functions of Unculturable Microbes in Ecosystems
National Science Foundation	David Meinke, et al. Allan Dickerman David Patton, et al.	$2,326,667	$852,207	Essential Gene Functions in *Arabidopsis* Seed Development
National Science Foundation	Reinhard Laudenbacher Bernd Sturmfels	$100,000	$68,362	Algebraic Algorithms for Cell Complexes
National Science Foundation	Pedro Mendes Richard Dixon	$3,587,432	$2,094,705	An Integrated Approach to Functional Genomics and Bioinformatics in a Model Legume

VBI Active Grants

Sponsor	Investigator	Total Award	VBI Award	Project
National Science Foundation, USDA	Craig Nessler Boris Chevone Pedro Mendes	$99,999	$18,371	Metabolic Engineering of Plant Vitamin C Biosynthesis for Improved Nutrition and Health
National Science Foundation	Brett Tyler Bruno Sobral	$497,467	$497,467	Communication, Training, and Resources for *Phytophthora* Research
National Science Foundation	Brett Tyler M.A. Saghai Maroof Glenn Buss Ina Hoeschele Anne Dorrance Steve St. Martin	$6,764,465	$5,940,249	Dissecting Soybean Resistance to *Phytophthora* by QTL Analysis of Host and Pathogen Expression Profiles
Samuel Roberts Noble Foundation	Pedro Mendes	$45,000	$45,000	Postdoctoral Fellowship for Bioinformatics Research Training
Sun Microsystems, Inc.	Bruno Sobral Pedro Mendes	$1,262,486	$1,262,486	Sun Center of Excellence in Bioinformatics
United States Department of Agriculture	Bruno Sobral Allan Dickerman	$444,230	$444,230	Analysis of Plant Genome Duplication Events and Their Functional Relevance
United States Department of Agriculture, National Science Foundation, Department of Energy*	Brett Tyler Bruno Sobral	$2,334,000	$2,334,000	Genome Sequence of *Phytophthora sojae*
United States Department of Agriculture	Brett Tyler	$230,000	$230,000	Function of Avirulence Genes in *Phytophthora sojae* Infection of Soybean
United States Department of Agriculture	Brett Tyler	$1,000,000	$1,000,000	*Phytophthora* Genes Expressed During Infection and Propagation
University of Nevada–Reno	Pedro Mendes	$3,609,951	$3,609,951	Integrative Functional Genomic Resource Development in *Vitis Vinifera*: Abiotic Stress and Wine Quality
University of Nevada–Reno/ Samuel Roberts Noble Foundation	Bruno Sobral John Cushman Greg May	$323,016	$323,016	Collaborative Development of an EST Database and Analysis Pipeline
University of Virginia/ Tobacco Foundation	Karen Duca	$375,000	$375,000	Identification of Genes that Predispose Individuals to Smoking–Related Diseases
VT ASPIRES	Vladimir Shulaev Allan Dickerman Richard Veilleux Joel Shuman	$100,000	$100,000	Strawberry Functional Genomics
Virginia Tech/John Hopkins University Bloomberg School of Public Health	Bruno Sobral, et al. Diane Griffin, et al.	$10,000,000	$5,000,000	Human Infectious Disease Bioinformatics Collaboratory

*Department of Energy has supplied matching funds to this grant.

The VBI 2003 Annual Report was created and designed by the VBI Public Relations and Outreach Team. In particular, the Institute recognizes Ivan Morozov for the report design. Andrea Aten, Candace Baracat, Neysa Call, Elaine Fuller, Amanda Hincker, Susan Light, and Robin Oakes facilitated the development in collaboration with the research teams at VBI.

VT/035800/1103/2.5M/240257

www.vbi.vt.edu

VIRGINIA BIOINFORMATICS INSTITUTE AT VIRGINIA TECH

1880 Pratt Drive, Building XV
Blacksburg, Virginia 24061-0477
Phone: 540.231.2100
Fax: 540.231.2606
Email: bioinfo@vt.edu