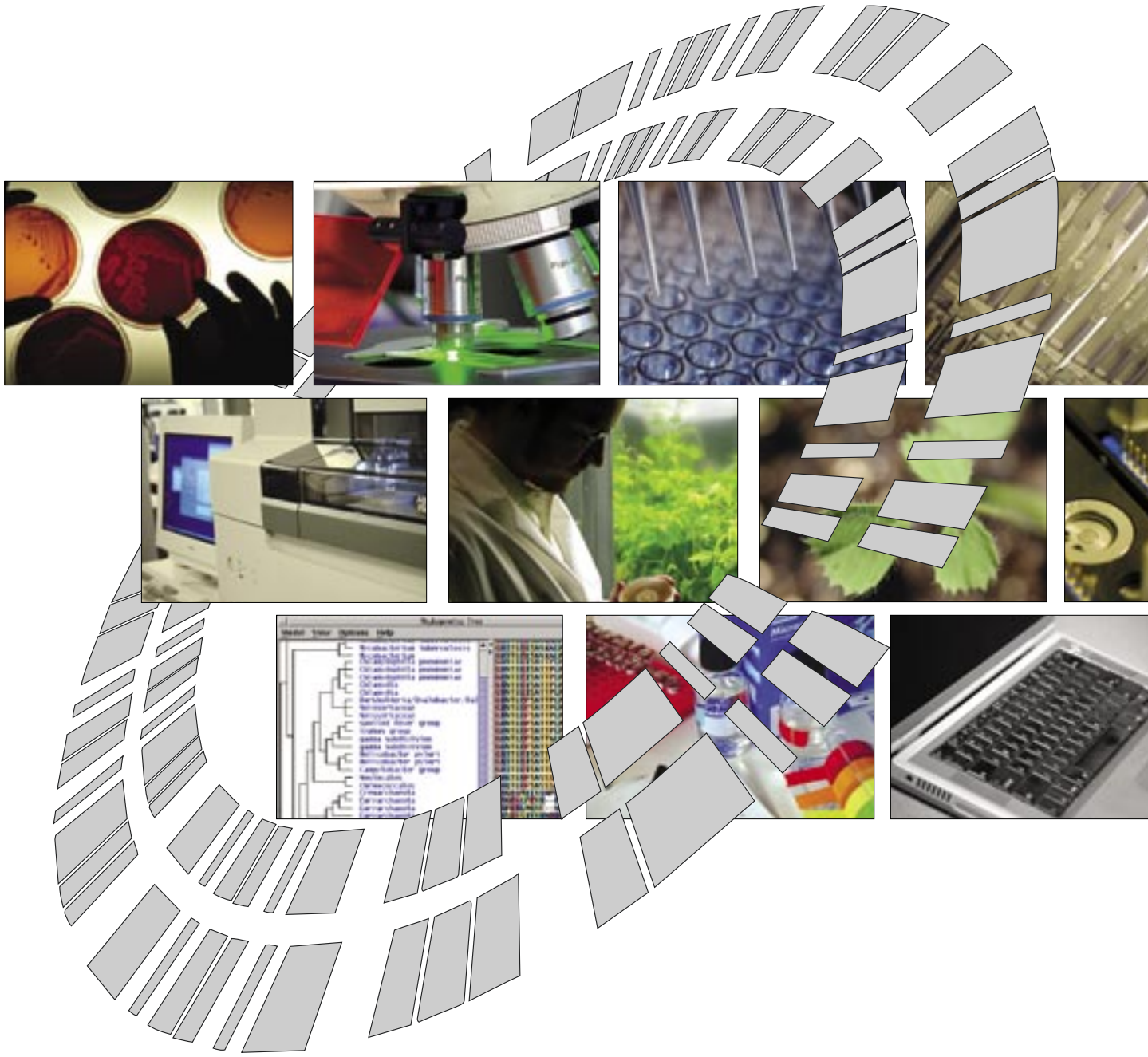

Virginia Bioinformatics Institute
2004 Annual Report

VBI

Virginia Tech

VBI

Venturing Beyond Information

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Message from the President

In its four years of existence, Virginia Bioinformatics Institute (VBI) has helped Virginia Tech maintain its distinguished momentum in research, outreach, teaching, and learning. VBI is also at the forefront of helping Virginia Tech become a top-30 research university. As one of Virginia Tech's premiere research mediums, VBI supports one of the university's pivotal missions—the discovery and dissemination of new knowledge. This document actively serves that mission, highlighting achievements in bioinformatics research and education during the past year.

With VBI's proven accomplishments and solid research portfolio, the Institute will continue to gain respect and overcome bioinformatics obstacles with the help of creative energy from extramural support, new research faculty, and ever-growing education programs. VBI's faculty and support teams continue to move forward in the areas of bioinformatics research and faculty recruitment, and the creation of valued industry partnerships. We are excited about the future of Virginia Tech research and VBI's contributions to the growth of the university.

Virginia Tech is pleased to share VBI's progress and advancements in this Annual Report. Seen through VBI's success, the university strives to invest in the promising areas of science and engineering research and education. We are positive that VBI's work will enhance and expand scientific discoveries and their applications in usable and effective ways for today's society.

Regards,

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

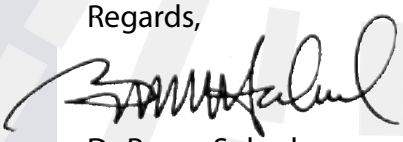
Letter from the Director

Enclosed in this Annual Report, we at Virginia Bioinformatics Institute (VBI) highlight our accomplishments, core scientific priorities, and future directions. Now housed in both Research Building XV at the Corporate Research Center and Bioinformatics Facility I on the Virginia Tech campus, we not only see growth in knowledge, funding bases, and scientific discoveries, but in the Institute's physical and facility sizes as well. With $45.8 million in extramural funding and a faculty and staff of 210 just after four years of existence, VBI continues to focus on host-pathogen-environment interactions.

As we collaborate in such diverse disciplines as mathematics, biology, computer science, biochemistry, statistics, and plant pathology, our work connects once seemingly unrelated fields to develop and deploy new innovations and discoveries in bioinformatics and systems biology. This report confirms the appropriateness and timeliness of such vital explorations, as we seek answers to diverse questions that impact all aspects of life, from human and animal health to technology development. VBI values partnerships and collaborations, as we have leveraged local, national, and global partnerships to tackle some of the world's most complex problems in infectious diseases.

Bioinformatics promises healthy economic growth, intellectual capital, and new discoveries across various sectors. At VBI, we will continue to connect the foundation of past research with modern tools and technologies to create a better world. Through this report, we hope you turn the last page with a better understanding of bioinformatics and VBI's core mission, as VBI continues to "Venture Beyond Information."

Regards,



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

VIRGINIA BIOINFORMATICS INSTITUTE
AT VIRGINIA TECH

What is Bioinformatics?

As a new and promising science, bioinformatics weds biological research with computer science, making way for scientific discoveries from agriculture to genomics. At the interface of biology and information technology, bioinformatics uses computers to analyze, link, organize, and visualize complex sets of biological data including genomic, transcriptomic, proteomic, and metabolomic information.

Bioinformatics includes tasks like mapping an organism's genome and deciphering the raw data with computer science tools. The products of bioinformatics research yield useful information to combat infectious diseases in humans, plants, and animals.

At VBI, scientists and engineers encourage research collaborations to increase the understanding of molecular, cellular, and environmental interactions that affect human health, agricultural systems, and the environment. More specifically, research at VBI focuses on host, pathogen, and environment interactions also known as the disease triangle.

VBI: Building for Progress

VBI began actively integrating into Virginia Tech's campus when approximately 100 of the Institute's employees started the move into VBI's new 59,000 square-foot, on-campus facility named Bioinformatics Facility I in December 2003. As part of Virginia Tech's Founder's Day events, VBI welcomed distinguished speakers Congressmen Rick Boucher, D-9th, and Bob Goodlatte, R-6th, and approximately 250 guests to the Bioinformatics Facility I Grand Opening on April 24, 2004.

The program also featured remarks from Virginia Tech President Charles Steger and Bruno Sobral, VBI's executive and scientific director. An official ribbon-cutting was held directly after the ceremony. Following the ribbon-cutting, guests were entertained with refreshments, live music, and tours of the facility.

The Grant Opening drew coverage from a variety of local news outlets, including Roanoke news stations WDBJ 7, WSLS News Channel 10, and Fox 21/27; VTTV, Virginia Tech's student run television station; the Collegiate Times, Virginia Tech's student newspaper; and HokiE-News, which features information for Virginia Tech faculty and staff.

With its start in a small subleased space in July 2000, VBI anticipates occupying more than 130,000 square-feet upon completion of Bioinformatics Facility II in the early spring of 2005. This construction project adjacent to its sister building 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 its original facility.

Bioinformatics Facility I houses a range of laboratories, including VBI's Core Computational and Core Laboratory Facilities, and many office, meeting, and seminar rooms, all stretched across the three-floor building.

As originally planned, VBI will also retain its lease on the 52,842 square-foot Research Building XV (RBXV) facility located at Virginia Tech's Corporate Research Center (CRC), neighboring the Virginia Tech/Montgomery Executive Airport. Both the CRC and Virginia Tech locations provide modern office and laboratory space in a high-quality work environment, nestled in an attractive mountain setting.

Corporate Partners

With VBI's ever-growing client base and expanding research projects, the Institute appreciates both corporate and private sponsorships and donations. Sponsors like Sun Microsystems, Timelogic, Beckman Coulter, and IBM have greatly contributed to the success of VBI. These partners have partially funded equipment to further the computing and wet-lab research capacities of the Institute.

Sun Microsystems has continuously shown their support of research at VBI since the Institute's inception in 2000. Currently, VBI serves as a Sun Center of Excellence (COE) in bioinformatics. With this COE award, Sun contributed over $1 million in computational resources and support for post-doctoral research during the three-year partnership. Sun's high-performance computing hardware includes 288 gigabytes of memory, 500 gigabytes of internal disk space, and a fiber storage Area network with 1.7 terabytes of storage attached to the Sun Enterprise 15K server. Virginia Tech and VBI both benefit from Sun's partnership, with projects such as Gepasi, COPASI (Complex Pathway Simulator), ESTAP (Expressed Sequence Tag Analysis Pipeline), and the Medicago project directly using this hardware. In addition, Sun was a corporate sponsor of VBI's Bioinformatics Facility I Grand Opening held on April 24, 2004. Sun's continuing support has enhanced both research and outreach capabilities at VBI since the partnership began.

Timelogic has partially funded the world's largest academic installation of the Timelogic DeCypher system, implemented within VBI's Sun Microsystems Sun Fire 15K supercomputer. The DeCypher system delivers powerful bioinformatics analysis capabilities, giving way for comparisons among numerous biological systems and speeding over 30 types of searches. The system is composed of six hardware accelerators that quicken the analysis of DNA sequences, thus allowing scientists to understand the actual biological function of DNA much faster and more economically.

In late 2003, Beckman Coulter awarded Dr. Vladimir Shulaev, VBI associate professor, a $175,373 equipment grant. The equipment included a Biomek 2000 Automation Workstation, Capillary Electrophoresis System, centrifuge, and spectrophometer. This Beckman Coulter donation has expanded the analytical platforms at VBI and contributed to the development of novel tools for metabolite profiling. Shulaev uses the equipment to catalogue small biological molecules, called metabolites, in an effort to further knowledge of human health, disease, and treatment.

IBM has previously supported VBI through two of IBM's Shared University Research (SUR) awards provided to Dr. Bruno Sobral in support of the DoD-funded Pathogen Portal project that Sobral leads. The equipment included an IBM Enterprise Storage Server (code-named Shark) disk storage system, which helped create a state-of-the-art storage facility for a data grid serving the global bioinformatics research community.

Giving to VBI and Virginia Tech

Financial support from alumni and friends of Virginia Tech, whether in the form of an outright gift, pledge, planned gift, or gift-in-kind, is essential to maintaining the quality of education and ongoing research in departments and institutes at Virginia Tech, such as VBI. Donations provide scholarships for students, support for faculty and programs, funding for current operations, and financial assistance for ongoing initiatives.

Private giving has contributed immeasurably to making Virginia Tech a world-class institution. As it prepares for the challenges and opportunities of a new century, Virginia Tech will continue to look to the generosity of donors to help support its land-grant mission of teaching, research, and public service.

The Office of University Development is the fundraising arm of Virginia Tech. As such, University Development works closely with alumni, friends, parents, corporations, and foundations to help determine how and where their support will be of the greatest value to both donors and the university. Gifts can be designated to a specific college or area, such as VBI, or they can be unrestricted, which provides the university with the resources to meet its priority needs.

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

Core Facilities

"With the advent of the genomic age and its resulting data, VBI's Core Facilities create bioinformatics platforms for researchers to visualize, understand, and connect complicated biological processes that are based on complex biochemical networks."

Stefan Hoops, Ph.D.
Associate Director for Scientific Computing
Virginia Bioinformatics Institute

A unique feature of VBI's infrastructure is the integration of multi-user core facilities that integrate high-throughput data generation (Core Laboratory Facility, CLF) and data analysis (Core Computational Facility, CCF) capabilities.

VBI's Core Facilities provide researchers with access to the latest technology platforms as well as to the computational tools needed for extensive analysis of the resulting data sets. The Core Facilities at VBI provide a test bed for emerging technologies, with innovation playing a major role in the success of these facilities.

Integration of Core Facilities

To effectively address scientific questions drawn from infectious disease research in the 21st century, VBI quickly recognized the need for integrated state-of-the-art facilities to develop and deliver data and knowledge to stakeholders. Current wet lab technologies available through the Core Laboratory Facility (CLF) include platforms for the analysis of DNA, RNA, and protein molecules. Data generation is tightly coupled with the Core Computational Facility's (CCF) robust data storage, data visualization and data mining solutions for informatics research.

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 (CLF) and works with researchers to apply these technologies to related biological questions. She received her Ph.D. in 1991 from the University of Illinois while conducting research at the USDA Photosynthesis Research Unit. Martino-Catt spent over nine years in the agricultural biotechnology industry before joining VBI in April 2003.

Stefan Hoops, Ph.D.
Associate Director, Scientific Computing

Stefan Hoops is the manager of VBI's Core Computational Facility (CCF). He received his degree in Mathematical Physics from the Norwegian Institute of Technology. After a career as a commercial software developer, he joined Virginia Bioinformatics Institute (VBI) in December, 2000. Hoops is focused on enabling biological research through the development of new tools and methods.

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 used in the discovery of biological macromolecules. These types of technologies are 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.

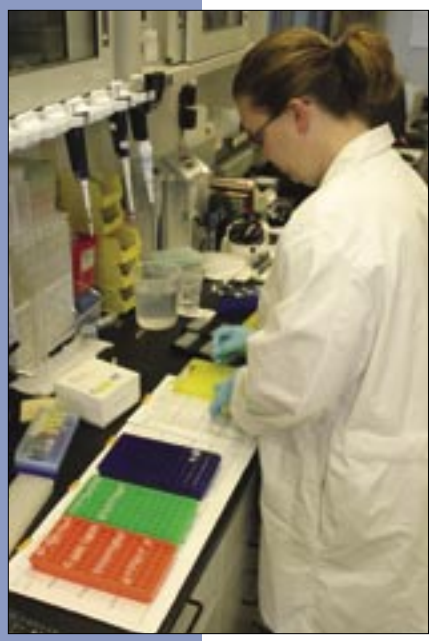
The CLF currently provides analysis platforms for DNA (genomics), RNA (transcriptomics), and proteins (proteomics). Currently, the CLF is working with Dr. Vladimir Shulaev and his group at VBI to establish metabolic profiling capabilities within the CLF. In addition to its ongoing application of existing technologies, the CLF is also actively engaged in the development and testing of new technologies. This two-fold mission helps to ensure that Virginia Tech stays at the cutting edge of bioinformatics technologies, while providing the best possible services to customers. It is this combination of application and development that enables the CLF to remain a leader in helping researchers take a complete systems biology approach to their science.

Overall, the CLF has seen many changes and improvements during the course of this year. The facility has upgraded equipment, processes, and software in order to improve production and workflow capabilities. In addition, the CLF has welcomed many new users this year, including academic collaborators as well as both federal and private biotech companies. The CLF staff has grown to meet the growing demands for the offered services, allowing VBI's CLF to have dedicated professionals available to assist users in the successful application of these technologies. In an ongoing effort to further assist users, the CLF continues to work closely with the Core Computational Facility (CCF) to ensure efficient data management and storage and with Sobral's cyberinfrastructure group to provide input and feedback on data analysis and visualization tools.

CLF Staff

CLF Personnel (left to right):
Front row: S. Martino-Catt, D. Mullins, J. Fick, D. Chisenhall
Back row: C. Evans, C. Umberger, D. Shaw, K. Finne, B. Settlage, J. Lennon

Insets on right (from top to bottom): S. Conrad, A. Jerauld, M. Ferringer



Genomics

In January 2004, the CLF's Genomics group added the ABI3730, a new capillary electrophoresis machine, to the facility. This machine has the ability to analyze 48 DNA sequencing reactions in two hours. Improvements to the CLF's reaction conditions, chemistries, and down-stream sample processing have resulted in increased data generation, with a typical reaction yielding 600-800 base pairs of nucleotide sequence information. The higher throughput of the ABI3730 has allowed the CLF to expand the customer base for DNA sequencing, while maintaining a rapid 24-hour turnaround time. The CLF continues to run the ABI3100 capillary machine alongside the ABI3730, primarily to perform DNA fragment analysis assays for genotyping purposes. The genomics group is also in the process of acquiring additional liquid handling robots to further automate the DNA sequencing process. This automation will allow the CLF to process large projects that are currently in the pipeline, including various EST sequencing projects ranging from 5000-50000 EST clones.

Gene Expression

The CLF's Gene Expression group has also been upgraded this year to increase productivity and efficiency. The main expression platform, the Affymetrix GeneChip® system, continues to be the workhorse technology within the CLF. The CLF upgraded both the laser scanner and the fluidics stations that are part of the Affymetrix system. These upgrades allow the CLF to offer customers the newest arrays being produced by Affymetrix. These new arrays include the full human genome, the full mouse genome and the soybean genome, each displayed on single chips. VBI's CLF is one of the few academic institutions to have the upgraded equipment needed to process these 11 micron feature arrays. The CLF has also been working to streamline the Affymetrix sample labeling process, and the facility has made significant improvements to better manage daily sample flow. These process improvements have resulted in an increase in productivity from 12 chips processed per day to up to 48 chips. To further validate the gene expression data, the CLF began offering real-time PCR assays to customers as an independent technology for assessing gene expression. The CLF continues to optimize the custom oligonucleotide array spotting protocols and expects this service to be fully on-line in the coming months.

Proteomics

The CLF's Proteomics group has had a productive year as well. Many of the technical details of 2D gel processing, image analysis and spot cutting have been optimized. The facility has also added the ThermoFinnegan LTQ ion trap mass spectrometer, which provides rapid and highly sensitive mass analysis and peptide sequencing. Along with the typical proteomics technologies, the CLF has expanded its services to include a non-gel based, liquid assay for the fractionation of complex protein mixtures. The Beckman Coulter ProteomeLab PF 2D protein fractionation system was brought on-line in November, using liquid chromatography as the basis for protein fractionation. This new service has been well received by customers, keeping the machine busy on a daily basis.

Core Computational Facility

VBI's Core Computational Facility (CCF) continues to provide powerful technologies to the bioinformatics research community. While the core infrastructure services, such as computing and storage, have remained available, the CCF also provides higher level services to enhance the scientific capabilities for researchers.

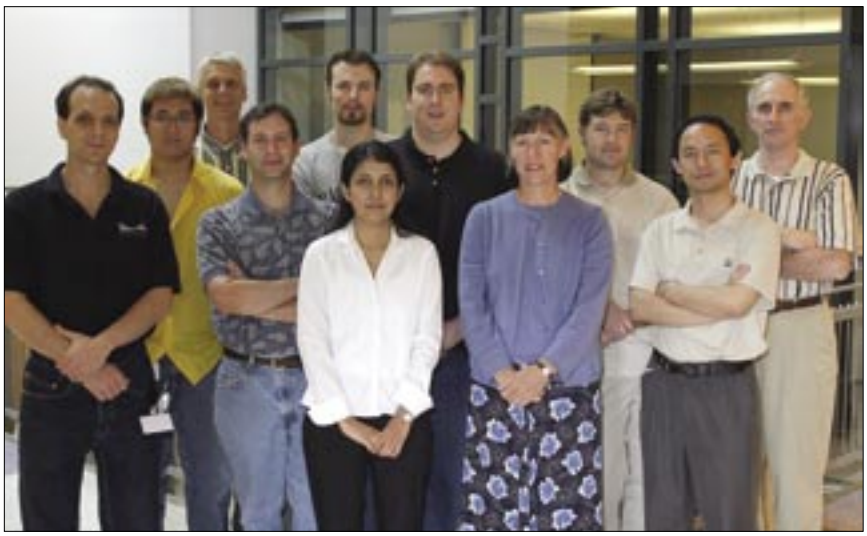
Computationally, VBI continues to make use of a Sun Microsystem SunFire 15000, IBM Linux Cluster, and Storage Area Network with equipment provided by multiple vendors. In addition, the CCF has also brought new hardware online this year, including a new cluster purchased from IBM, consisting of nine 8-processor nodes. Additional storage capabilities have also been added to meet the demands of the high volume data generation that accompanies many experiments today.

An IBM Enterprise Storage Server (ESS) currently provides disk storage to the CCF. With 4 terabytes of storage installed the CCF can provide high speed data storage to any of its servers, including the two supercomputers located on-site.

Data is reliably stored in a disk array providing high performance access through parallel reading of data, as well as reliable access by allowing for disk failure without data or performance loss.

An IBM LTO Tape library provides VBI with up to 12 terabytes of compressed data storage for backups. On a daily basis, the backup systems maintain an off-site copy of all backed up data to ensure the existence of data in the event of a catastrophe.

CCF Staff



CCF Personnel (left to right):
M. DiFilippo, P. Dejsuphong, S. Hoops, D. Machi, D. Borkowski, N. Vaghela, D. McMaster, S. Waldon, R. Chase, D. Kong, P. Toffenetti

CCF's New and Expanded Services

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

This year several new technologies, developed either within or outside of VBI, have been or are being deployed as production services within the CCF. As researchers at VBI and outside the Institute develop new tools and services, the CCF staff is able to take the research quality software, prepare it for production use, and provide as a cost recovered service to the research community.

The EST Analysis Pipeline (ESTAP) software, originally developed at VBI, is an example of how entire research technologies evolve to full production use. Originally funded by several different collaborators, the ESTAP project has been in development at VBI for approximately three years. Over the past year, the CCF has refined this software, allowing it to be used by the broader research community. These refinements include reorienting the system to maintenance mode as opposed to development mode, and developing procedures for deploying the software at another location. VBI faculty have begun to use the system in their own research projects, and the CCF has been contracted to deploy and support the site at a customer location. This service will benefit the researchers and allow the CCF to continue the maintenance cycle of software to ensure its usefulness and availability.

In addition to the new services brought online in the CCF, other services have been expanded. The Timelogic™ DeCypher® system allows researchers to complete high-throughput data analysis, as opposed to using conventional methods of supercomputing, which would make the analysis cost prohibitive. This year the system has been expanded in two different areas. First, additional interfaces are now available to the research community. A web interface has been implemented that allows any researcher in the world to make use of the system, and the Pathport/Toolbus system continues to improve its own interface to the decipher system. In addition to the aforementioned software improvements, the CCF has recently implemented a hardware upgrade that provides an additional 85 percent performance boost to the already fast system.

To meet the growing demands for data storage, the CCF has added equipment to increase storage capacity in a cost-effective manner. For example, a single experiment can have a 100 Gigabyte input file and produce a terabyte of output data. Recently, the CCF added equipment that will nearly double its available disk storage, with further expansions planned in the near future.

The CCF has added a new low-cost disk arrays storage system to address the growing volumes of data being generated by researchers. The CCF now has the ability to provide fast and reliable storage via fiber to equipment, as well as provide low-cost disk storage for equipment and users both within and outside the Institute. With newly available disk arrays, the CCF is able to expand storage very quickly and inexpensively and provide longer term storage of data, while still making the data available to users without the need for administrative overhead.

- Agriculture and Environment
- Informatics Modeling, Theory, & Simulation
- Biomedicine

Research

"Our research projects at VBI are at the frontier of answering important and diverse questions impacting human and animal health, agricultural production, environmental preservation, and technology development."

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

VBI's research efforts center on understanding the disease triangle, or host-pathogen-environment interactions, to mathematically model biological systems. With an integrated research approach, VBI researchers organize, link, analyze, and visualize complex sets of data to produce meaningful knowledge to improve humans' ways of life.

Researchers strive to mathematically describe living systems so they can be understood, with the knowledge then being applied to real-life situations. By applying computational and analytical methods to biological problems, VBI acts as a research, development, and economic engine, with applications in agriculture, environment, modeling, simulation theory, experimentation, and biomedicine.

Agriculture and Environment

VBI's agricultural and environmental research focuses on agricultural problems that affect humans everyday. With interdisciplinary approaches, researchers seek to understand plant and animal traits that affect agricultural production, the environment, and human health and nutrition.

New biotechnology and bioinformatics tools help VBI scientists examine the inner-workings of plants and animals and gain further understanding of how their biological processes work. Researchers' knowledge and results then produce better ways of protecting crops and livestock from pests and disease, while helping to improve the overall quality of agricultural products. 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.

Transcriptomics of *Arabidopsis* Vascular Tissue

Secondary growth in plants produces wood, a resource society uses daily. Although trees serve as the economically important species and house this wood, it is possible to study the basic biology of wood development in the tiny model organism *Arabidopsis thaliana*. Dr. Eric Beers, associate professor of horticulture at Virginia Tech, has developed techniques for isolating the tissues of *Arabidopsis* where secondary growth can be most usefully studied.

Over the last two years, Beers has worked with Dr. Allan Dickerman at VBI to use modern gene chip analysis of the *Arabidopsis* system. Postdoctoral scientists Chengsong Zhao in Virginia Tech's Department of Horticulture, and Johanna Craig from VBI are also part of this team. The research is focused on isolating and measuring mRNA populations in three tissues: xylem, phloem, and outer bark. The team has assembled a data set that shows which genes most strongly differentiate the three tissues by being expressed at a high level in one, but being nearly absent in the remaining two. Many of these tissue-specific genes have known mutants affecting vascular development. Beer's lab has generated new lines that over-express other tissue-specific genes, which have generated interesting new phenotypes that reveal details of vascular tissue development. Overall, these research approaches open new windows into the biology of wood formation.

Perfect Partners: Rhizobia-Legume Symbioses

Microorganisms perform all known biological nitrogen-fixation processes. In particular, Rhizobiaceae bacteria inhabit the root nodules of leguminous plants (e.g., beans, alfalfa, and soybean). These bacteria and legumes have developed a symbiotic relationship, which allow legumes the net benefit of fixing atmospheric dinitrogen, while the bacteria gain photosynthate from the plant. Understanding this biological process is of great interest from an evolutionary and developmental standpoint. In addition, chemical nitrogen fertilizers are costly and can lead to eutrophication, so an economic and environmental incentive for research exists. Dr. Bruno Sobral's Pathosystems Biology Group's research focuses on understanding how rhizobia-legume symbioses are established and maintained.

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.

Sinorhizobium meliloti and *Brucella melitensis* (pathogen of humans and animals) are proteobacteria. Despite their size differences, both genomes share extensive regions of gene synteny, and exhibit a high level of similarity. Symbiosis (*S. meliloti*) and pathogenesis (*B. melitensis*) require intracellular survival and replication of bacteria. By genomic comparison, Sobral's research team has shown many orthologous genes of these two genomes with evident importance in symbiosis and/or pathogenesis. These functionally important orthologs provide new hypotheses in the study of genes and mechanisms in *S. meliloti* symbiosis and *B. melitensis* pathogenesis. Laboratory experiments are being performed to test these predictions. High throughput comparison between *S. meliloti* and *B. melitensis* would lead to further understanding of the molecular evolutionary mechanisms and open new opportunities for symbiosis/pathogenesis research.

By comparing genes, proteins, and metabolites of the legume-rhizobial symbioses, Sobral's research team aims to pinpoint the similarities and differences within networks, genes, proteins, and metabolites affected during nodule development. This research will increase our understanding of intracellular bacteria, the information required to determine how other plants (non-legumes) might be developed so they too can fix nitrogen in symbiosis. This, in turn, will decrease our reliability on chemical fertilizers and have substantial benefit to the improvement of our environment, agriculture, and health care.

Microbial Ecosystems in the Soil

More than 99 percent of the bacterial species in natural environments, such as soil, cannot be grown in the laboratory. Hence researchers know extremely little about how bacterial species contribute to the ecosystems they inhabit. Soil bacteria have a strong influence on the interaction between plant roots and soil-borne pathogens, such as *Phytophthora*. In some cases, bacteria reduce infection either by producing antibiotics or by stimulating the plant's defense responses. In other cases, the bacteria weaken the plant and make it more susceptible.

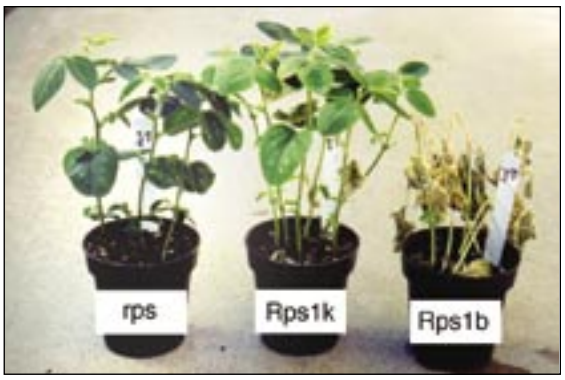
In the project "Bioinformatic predictions of the ecological functions of unculturable microbes," VBI researchers Brett Tyler and Allan Dickerman are developing bioinformatic approaches to identify the species of origin of DNA sequences obtained from DNA extracted directly from soil microbial communities. This project is funded by a $100,000 grant from the National Science Foundation.

Counter-Play of Plant and Pathogen Genes During *Phytophthora* Infection of Soybean

Plant pathogenic microbes have evolved special mechanisms to defeat their hosts' defenses. To protect themselves, plants must evolve additional counter-measures, leading the pathogens to develop new mechanisms of virulence. As a result of this evolutionary "arms race," large numbers of plant genes contribute to natural resistance (also called multigenic or quantitative resistance), and large numbers of pathogen genes contribute to the virulence of the pathogen.

Crop breeders have found that improving multigenic resistance gives protection to crops much longer than single resistance genes, which are quickly overcome by new strains of pathogens. However, because many genes making small contributions create multigenic resistance, this kind of resistance is much harder to improve by conventional breeding. It is also much more difficult to study the molecular mechanisms by which the genes act.

The project "Dissecting Soybean Resistance to Phytophthora by QTL Analysis of Plant and Pathogen Expression Profiles," which began in October 2002 and is funded by a $6.7 million National Science Foundation grant, is using genomics and bioinformatics approaches to identify and understand the contribution of soybean genes to multigenic resistance against *Phytophthora sojae*.



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.*

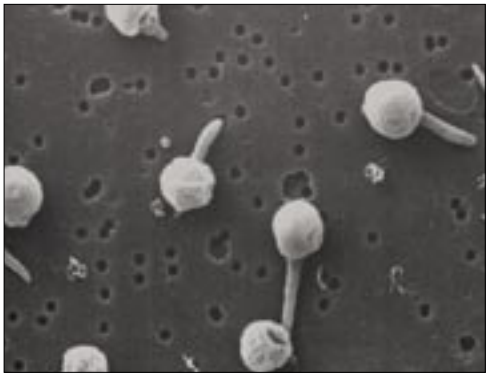
The project measures the activity of most of the soybean and *P. sojae* genes throughout infection, using a technique called microarrays. The activity of the pathogen and plant genes are compared in a number of different soybean varieties with different levels of multigenic resistance in order to identify which genes the plant is using to protect itself, and which genes the pathogen is activating in response. The soybean varieties will then be genetically interbred to narrow down the location of each of the soybean genes contributing to multigenic resistance.

The project is led by Dr. Brett Tyler, research professor at VBI, and also involves VBI faculty Ina Hoeschele and Susan Martino-Catt. Contributing Virginia Tech faculty include Keying Ye from the Department of Statistics and Saghai Maroof from the Department of Crop, Soil, and Environmental Sciences. Also involved with the project are Anne Dorrance and Steve St. Martin from Ohio State University.

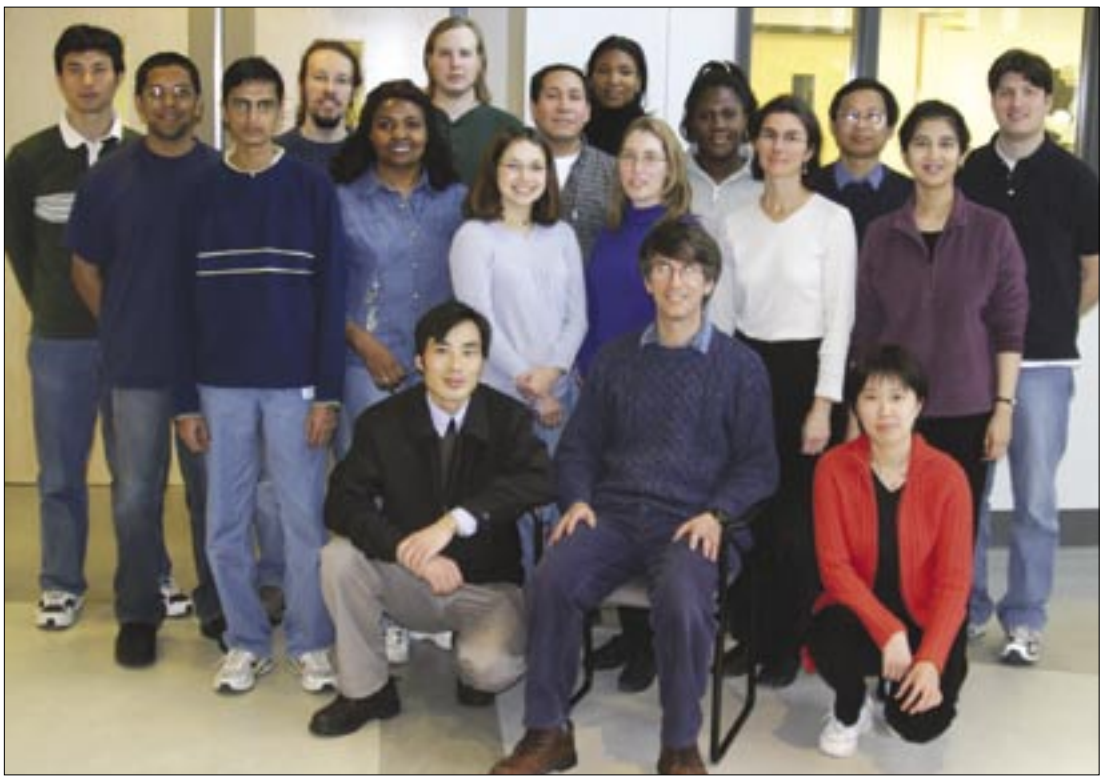
Deciphering Gene Functions in *Phytophthora* and Other Pathogens

Many diseases of humans, animals, and plants are caused by enigmatic organisms that are evolutionarily very different than the "model" organisms that molecular biologists often study, such as mice, fruit flies, and baker's yeast. Taxonomists place them in different kingdoms of life, for example, plants, animals, and fungi each form distinct kingdoms. Some of these enigmatic pathogens include protozoa that cause tropical diseases of humans, such as malaria, leishmaniasis (tropical skin ulcers), and trypanosomiasis (sleeping sickness).

Phytophthora is an example of a plant pathogen that is from an evolutionarily distant kingdom of life. Because these organisms diverged from model organisms such a long time ago, it is much more difficult to infer the functions of their genes simply by comparing them with genes from model organisms. The goal of the project "Deciphering Gene Functions in Malaria and Other Pathogens" is to use experimental genomics and bioinformatics to discover techniques and rules for identifying functional similarities in genes, even when those genes are from organisms in different kingdoms. This project is currently focusing on genes that protect organisms from oxidative damage. Oxidative damage is often used by host organisms to defend against pathogens, and is the mechanism by which several anti-malarial drugs work. Oxidative stress genes are being compared among baker's yeast, the model plant *Arabidopsis*, malaria, and *Phytophthora sojae*. In the project "Application of Hopfield Networks to Cross-species Gene Annotation", VBI researchers Drs. Brett Tyler and Allan Dickerman are collaborating with Virginia Tech computer science researcher T.M. Murali to develop bioinformatics methods for transferring information about gene functions among species from different kingdoms. Together, the research in the two projects will result in an improved ability to understand how evolutionarily enigmatic pathogens, such as malaria and *Phytophthora*, cause disease.



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.*



Dr. B. Tyler Research Group (left to right):
First row: D. Dou, B. Tyler, D. Guo
Second row: V. Srinivasan, B. Kilel, L. McCoig, R. Hanlon, E. Bush, T. Khavhauis
Thrid row: X. Zhang, S. Narayanan, K. Krampis, N, Bruce, F. Arredondo, L. Waller, T. Torto, L. Zhou, B. Smith
Not pictured: Y. Dan, F. Salas, S. Tripathy, C. Evans, A. Ko, K. Tian, N. Galloway

Structure and Function of *Phytophthora* Genes

Plant pathogens from the genus *Phytophthora* cause destructive diseases in an enormous variety of crop plant species, as well as forests and native ecosystems. The potato pathogen *P. infestans* was responsible for the Irish potato famine and is still a destructive pathogen of concern for biosecurity. The newly emerged pathogen in oak trees in California (sudden oak death) is caused by a new *Phytophthora* species, *P. ramorum*.

The soybean pathogen, *P. sojae*, is also a serious disease, causing $1-2 million in damage annually. This species has been used for many basic studies of *Phytophthora* because it is easy to genetically manipulate.

Superficially, *Phytophthora* pathogens resemble fungi, but they belong to the group *Stramenopiles*, which are most closely related to algae such as kelp and diatoms. Hence, conventional fungus control measures often fail against these pathogens.

The objective of the research at VBI involving these pathogens is to identify genes in *Phytophthora* species that contribute to the pathogen's ability to cause infection. In the USDA-funded project "*Phytophthora* Genes Expressed During Infection and Propagation", a team led by Dr. Brett Tyler, research professor at VBI, collaborated with researchers at the University of California, Riverside and North Carolina State University to determine the sequences of around 7,000 *P. sojae* genes expressed during infection and growth and another 4,000 *P. infestans* genes expressed only during infection.

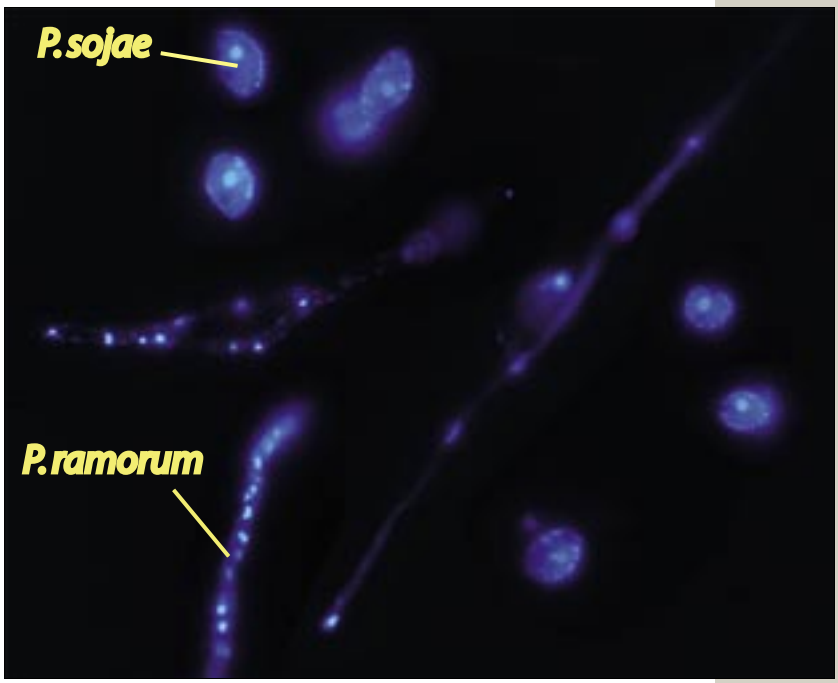
Bioinformatic analysis of the sequences was carried out by a team led by Tyler; Dr. Bruno Sobral, VBI executive and scientific director; and the National Center for Genome Resources.

In October 2002, Tyler and Sobral began a $3.8 million project "Genome Sequence of *P. sojae*" in collaboration with the Department of Energy (DOE) Joint Genome Institute (JGI) in Oakland, California to sequence all the genes of *P. sojae* and *P. ramorum*. This project was funded jointly by the United States Department of Agriculture (USDA), National Science Foundation (NSF), and DOE. The DOE JGI team produced and assembled the raw DNA sequence data, completing the process in May 2004.

Preliminary examination of the sequences has already revealed that *Phytophthora* species have the potential to produce a large and diverse array of protein toxins capable of weakening and subduing the plants they are infecting.

The VBI team has created a Web-based bioinformatics annotation system that will enable *Phytophthora* experts from around the world to log in and interpret the DNA sequence.

In addition, a procedure is being developed to rapidly test the function of sequenced *Phytophthora* genes by inactivating them or altering the timing of their expression.



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.

Berry Rich: The Genomics of Fruit

Recent studies indicate billions of people across the globe suffer from some form of malnutrition or disease. For the past century, efforts in agricultural production have centered on increasing production to feed the growing human population. As malnutrition and both infectious and nutrition-related disease continue to be a problem, however, researchers have begun to focus their efforts on improving the dietary value of foods and identifying novel compounds with pharmaceutical properties.

Most of the gene discovery tools of functional genomics have been developed in studies of the model plant, *Arabidopsis thaliana*. However, there are limitations in transferring gene functions discovered in Arabidopsis to phylogenetically distant plant species. To overcome these limitations, plant scientists have concentrated on new model organisms more closely related to groups of important crops. No comprehensive genomics platform has been developed for fruit crops, despite their significant economic importance and their indispensable role in human nutrition and disease prevention.

Molecular breeding and introduction of desired traits via genetic manipulation have provided a powerful approach for rapid development of new and improved varieties of soybean, corn, potato, and other crops. Application of molecular technologies in small fruit research has increased steadily over the past 10 years, with most of the effort directed towards developing a set of high-density molecular markers that can accelerate breeding through marker-assisted selection. Genetic markers have been developed for many small fruit species including strawberry, blueberry, cranberry, and brambles. But, despite the increased use of molecular approaches in breeding practices, there is no systematic effort for large-scale gene discovery underway for any of the fruit crops.

With funding from the Virginia Tech ASPIRES grant program, Drs. Vladimir Shulaev and Allan Dickerman at VBI, along with Drs. Joel Shuman and Richard Veilleux 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.

Dr. V. Shulaev Research Group (left to right): Front row: E. Mason, J. Qian, A. Martins, J. Shuman, B. Henry
Second row: A. Clapp, H. Gruszewski, V. Shulaev, N. Deighton
Back row: L. Blischak, T. Oosumi, A. Baxter, C. Jiming, D. Cortes

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. This project will enhance the research community's knowledge regarding novel genes encoding nutritional and disease resistance attributes in major fruit crops.

The *Agrobacterium* Biovar Type Strain Sequencing Project

Agrobacterium tumefaciens has attracted the attention of plant biologists, agricultural biotechnology researchers, and, more recently, fungal genetics biotechnology scientists. The generated interest stems from the remarkable ability of *A. tumefaciens* to transfer genes of interest into the nuclear genome of a wide variety of plant species, as well as into many different fungi, algae, and even animal cell lines. Most genetic engineering of plants depends on this natural DNA-transfer mechanism. It is fair to say that without *A. tumefaciens*, plant molecular biology and genetics would probably have bypassed its explosive growth of the past 20 years. Similarly, agricultural biotechnology would not have made such tremendous progress over the same time period.

Thus far only the C58 strain, or biovar, of *A. tumefaciens* has been fully sequenced. This strain causes a tumor-like disease in many plants known as crown gall. Although the disease is harmful to plants, it is generally not considered harmful to crops. This sequenced biovar is also the workhorse for manipulating genes in plants in both academic research laboratories and in agricultural biotech companies. However, both its natural history in the field and the evolutionary relationship of its chromosomes to other species of *Agrobacterium* are unclear. Dr. João C. Setubal, VBI research associate professor, is one of the lead researchers of a project that aims to sequence two additional biovars: *A. rhizogenes* and *A. vitis*. *A. rhizogenes* induces hairy-root formation on a wide variety of plants; it is also an effective biocontrol agent. *A. vitis* induces galls on grapevines. Setubal and his team hope to gain significant new insights into the evolutionary history of the genus *Agrobacterium*, as well as plant disease mechanisms. Each of these organisms is expected to have a genome of approximately 6 Mbp in size.

The *Agrobacterium* Biovar Type Strain Sequencing Project is being conducted in partnership with the University of Washington and the Monsanto Company, among others. Setubal's work on this project is funded by the National Science Foundation (NSF). VBI is responsible for providing the bioinformatics tools for genome annotation and comparative genomics analyses under the leadership of Setubal.

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. As one component of the larger effort, the SeedGenes Project centers on identifying and studying every *Arabidopsis* gene essential for seed development. Dr. Allan Dickerman at VBI currently collaborates with Dr. David Meinke at Oklahoma State University on the SeedGenes project.

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

The SeedGenes Project 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 percent 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 is underway at VBI. Elena Shulaeva and Johanna Craig at VBI are helping Dickerman decipher the gene expression differences between seeds and other known tissues. Thus far, developing seeds have proven to be the second most distinct behind pollen among a range of tissues for which comparable data is publicly available.

The May 2004 database edition presents information on 260 genes and 408 mutants. Included are 251 mutants generated at Syngenta, 30 mutant alleles from the Salk collection, eight mutant alleles from the Versailles collection of INRA/Genoplante, and numerous contributions from the community. More gene identities and a tutorial on screening for seed phenotypes will be released in October 2004.

Informatics Modeling, Theory, and Simulation

VBI's multidisciplinary and systems-oriented view of life sciences research stimulates the Institute's quest to integrate, manipulate, and compute the many disparate forms of molecular biological data. Using mathematical models, simulations, and visualization tools, informatics and modeling researchers hope to better understand the disease triangle and develop predictive disease models that cover diverse scales of time and space. The results of informatics and modeling research can help reorganize biological research and education, while developing better quality drugs, vaccines, and cures for infectious diseases more quickly.

Statistical Genetics and Genomics of Complex Human and Agriculturally Important Traits

Dr. Ina Hoeschele's research focuses on comprehending genetic architectures of complex and quantitative traits. These commonly found traits include many human diseases, such as heart disease, diabetes, hypertension, obesity, and arthritis. More specifically, statistical genetics and genomics of complex traits includes the identification of genes involved in developmental, physiological, and biochemical pathways leading to the traits; the identification of subsets of genes that trigger variation between individuals and populations; and the reconstruction of interactions and networks of genes. In collaboration with researchers at Boston University, the Hoeschele group develops statistical methods that pinpoint genomic locations of unknown genes affecting complex traits as precisely as possible.

In addition, Hoeschele's group collaborates with researchers at the Pennington Biomedical Center in Louisiana to investigate the molecular basis of successful nuclear reprogramming in bovine and porcine embryos.

This work is expected to improve the efficiency of mammalian cloning and has commercial applications including xenotransplantation, biopharmaceutical production, development of animal models of human disease, and the production of therapeutic cell lines. The group also works with researchers at the Comprehensive Cancer Center of Wake Forest University on the analysis of gene expression profiles to understand the molecular basis of lung tumors in mouse models and cancer prevention treatments.

Hoeschele's research also uncovers agriculturally important information in both plant and animal breeding that can help expedite improvements in productivity, health, nutrition, and food safety. This work involves strategies for combining genetic mapping and expression profiling. 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*, which is a project supported by the National Science Foundation. Animal applications include developing strategies for the fine-mapping of economic trait genes in Monsanto swine populations. Applying these genomic biotechnologies to agriculture could potentially save farmers and consumers billions of dollars in annual losses.

Dr. I. Hoeschele Research Group:
Front row: I. Hoeschele
Back from (from left to right): H. Li, C. Chetia, B. Liu, G. Gao

Yeast Systems Biology

An interdisciplinary team headed by Drs. Reinhard Laubenbacher, Pedro Mendes, and Vladimir Shulaev at VBI is conducting yeast systems biology research under a $1 million grant from the National Institute of General Medical Sciences. This project investigates the response of baker's yeast to oxidative stress by using modern technologies of microarrays and metabolomics and by mathematical modeling. Oxidative stress affects most organisms—from bacteria to humans—that require oxygen to survive. Oxygen generates byproducts that are extremely reactive and poisonous to cells, known as reactive oxygen species (ROS), such as hydrogen peroxide. These highly toxic ROS are involved in a number of human diseases, such as cancer, Alzheimer's, and Parkinson's. Aging is also largely attributed to the action of these toxic molecules.

In its finality, the yeast systems biology 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 knowledge on the oxidative stress process and provide insight into new ways to combat related diseases, such as Parkinson's and Alzheimer's.

Cells have evolved a variety of mechanisms to protect themselves from the damaging effect of ROS and other oxidants. These mechanisms in the common baker's yeast, *Saccharomyces cerevisiae*, are very similar to those of animal cells and are based on one important molecule, glutathione. Glutathione reacts with ROS transforming them into molecules that are less damaging to the cell. The yeast systems biology team is using baker's yeast as a model for the oxidative defense mechanisms of animal cells. In the first year, the team has established the optimal experimental conditions for carrying out this study.

This involves using computer-controlled fermentors and a specialized collection device for rapidly cooling the yeast broth. VBI's Core Laboratory Facility (CLF) provides the services to measure expression of genes using microarrays. The team has now submitted two articles for publication describing these optimal experimental conditions that will help other researchers around the world use baker's yeast for systems biology studies.

The use of mathematical and computational methods to interpret and help design experiments is an important characteristic of the systems biology approach in this project. The yeast systems biology team is developing novel mathematical approaches that combine continuous and discrete mathematics. These are applied to data obtained by simultaneous measurements of messenger RNA, 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. While the experiments are proceeding, the team has been assessing the efficiency of the mathematical methods using simulated computational experiments.

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

Even though this project is only in its first year, the yeast systems biology team has already been invited to present research reports at international meetings, namely the 4th International Conference on Systems Biology and the 1st and 2nd International Workshop for Yeast Systems Biology. VBI's yeast systems biology group is now part of an international team that is promoting a worldwide effort for studying yeast systems biology, much like what happened with the Human Genome Project in the 1990s.

Biochemical Networks Modeling Group

VBI's Biochemical Networks Modeling Group, led by Dr. Pedro Mendes, researches how cells work at the biochemical level through computational methods. The group is pursuing several different approaches in different projects, but they all follow the same view of biochemical systems as *networks* of reactions and interactions.

Active projects are:

- A systems biology approach to oxidative stress in yeast—funded by the National Institute of General Medical Sciences, and is a collaboration with the Laubenbacher and Shulaev groups.
- Development of a database and analysis system for large-scale profiling experiments— funded by the National Science Foundation, and is in collaboration with Drs. Rick Dixon (Samuel Roberts Noble Foundation, Ardmore, OK) and Grant Cramer (University of Nevada-Reno).
- Development of generic software for simulation of biochemical networks—a collaboration with Dr. Ursula Kummer at the European Media Labs, in Heidelberg, Germany.
- Analysis of metabolomics data—funded by the National Science Foundation,and is in collaboration with the Shulaev group, and with Dr. Lloyd Sumner (Samuel Roberts Noble Foundation, Ardmore, OK)
- Metabolic engineering of the vitamin C pathway in plants—funded by the National Science Foundation and the United States Department of Agriculture, and is in collaboration with Drs. Craig Nessler and Boris Chevone in the College of Agriculture and Life Sciences at Virginia Tech.

Although the efforts of the group are essentially computational, the projects above are based on experiments with model organisms, namely baker's yeast (*Saccharomyces cerevisiae*), the *Arabidopsis thaliana* plant, the forage legume *Medicago truncatula* (a relative of alfalfa), the common grapevine (*Vitis vinifera*), and the malaria parasite (*Plasmodium falciparum*).

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

The group has published peer-reviewed articles in the journals *Applied Bioinformatics, Bioinformatics, Briefings in Bioinformatics*, *European Journal of Biochemistry*, *Phytochemistry*, *Trends in Biotechnology*, and *Trends in Genetics*. Members of the group are also regular presenters at several conferences, such as the International Conferences on Systems Biology, and the International Conferences on Plant Metabolomics, among many others.

This interdisciplinary group is composed of members from a wide range of scientific areas, namely biology, chemistry, biochemistry, computer science, and mathematics. The group is involved in the following international consortia: The Yeast Systems Biology Network (www.ysbn.org), the Systems Biology Markup Language (www.sbml.org), and the Platform Plant Metabolomics (www.metabolomics.nl).

MicroBlast: A Tool for the Rapid Comparison of High Throughput Profiling Experiments

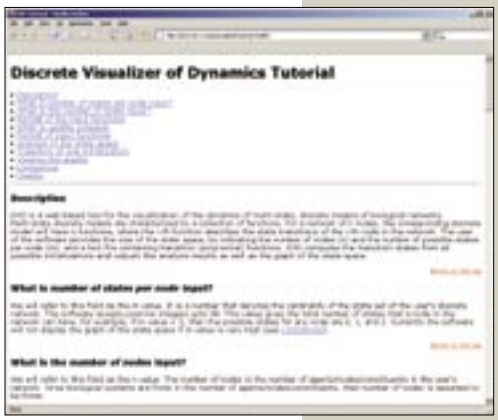
The new "-omics" technologies represent a quantum leap in researchers' ability to experimentally probe gene, protein, and metabolite expression. These technologies are dramatically changing the life sciences in disciplines ranging from agriculture to addiction research. As the number of microarray experiments in the public domain grows, the need for tools that make rapid comparisons between hundreds to thousands of these experiments is becoming increasingly apparent.

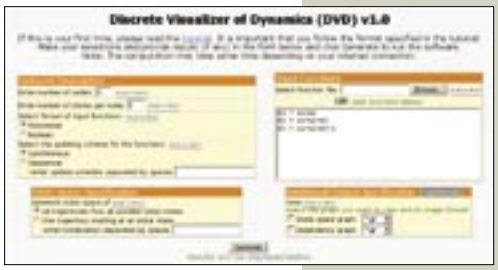
With these needs in mind, a collaboration between Drs. Karen Duca and Reinhard Laubenbacher transpired and gave rise to a project directed by Ph.D. candidate Dustin Potter in which Formal Concept Analysis (FCA), a mathematical method in applied lattice theory, was explored. This work engendered microBlast, a tool that operationally resembles the popular BLAST tool for comparing an input sequence to a large database of sequences. Within the FCA framework, microBlast constructs lattice structures, realized mathematically as graphs, representing gene expression data from functional genomics experiments. Such lattice structure representations allow the use of well-established graph and combinatorial measures to assign numeric signatures to the data. The use of these numeric signatures permits BLAST-like searches for both global and local similarities of a reference microarray experiment against other experiments in a large database.

Mathematical Foundation of Simulation Science Project

Large-scale computer simulations are becoming increasingly important tools in the analysis of highly complex natural and technological systems composed of many interacting entities. Examples of such systems include collections of cells in an organism, for example the immune system, or people in a city transmitting an infectious pathogen. New mathematical tools are needed in order to design and analyze simulations with millions of entities, such as the PathSim project led by VBI researchers Drs. Karen Duca and Reinhard Laubenbacher.

The Mathematical Foundation of Simulation Science project is focused on developing a mathematical foundation for simulations of this type. The basic approach is to represent them as dynamical networks that can be studied with tools from dynamical systems theory, graph theory, and computational algebra. Collaborators include the Basic and Applied Simulation Science Group at Los Alamos National Laboratory and researchers at the University of Munich, Germany.

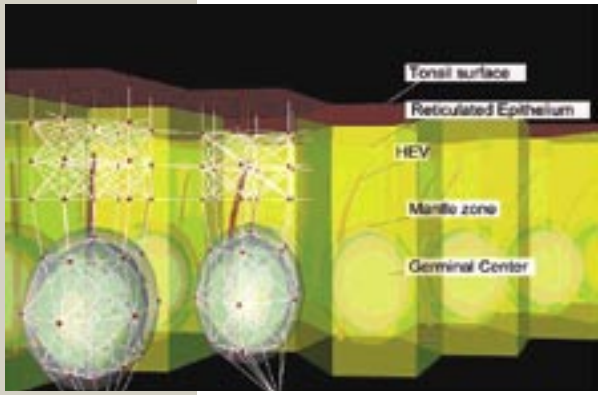




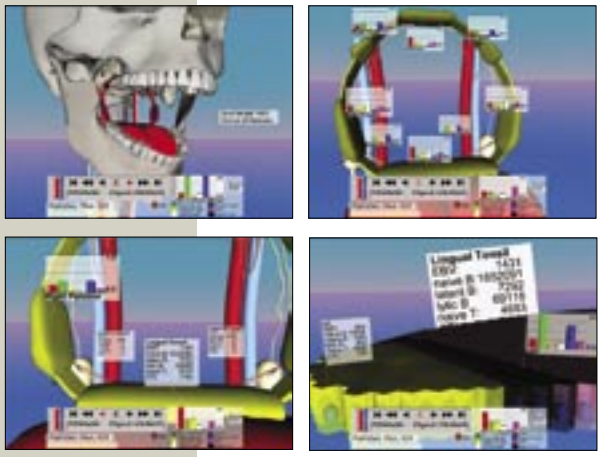
Network dynamics generated by simulator http://dvd.vbi.vt.edu.

Discrete Mathematics Group (left to right):
Front row: A. Jarrah, J. McGee
Back row: D. Dimitrova, H. Vastani, P. Vera-Licona, R. Laubenbacher
Not pictured: N. Polys, O. Colon-Reyes, B. Stigler, D. Potter

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.



VBI researchers Drs. Karen Duca and Reinhard Laubenbacher lead efforts to understand incremental stages of human immune responses to infection. The two collaborate with David Tharley-Lawson from Tufts University's Medical School and Abdul Jarrah from East Tennessee State University to identify cellular processes.

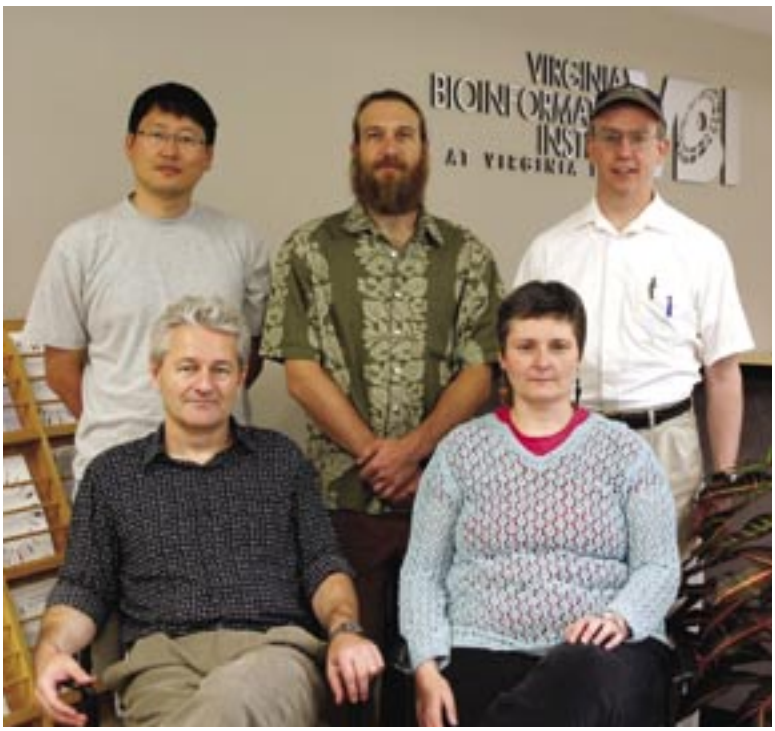
As an agent-based computer simulation, PathSim visualizes and analyzes how a pathogen spreads from its initial point of infection in the human body.

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 current 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.

Visit the project at http://staff.vbi.vt.edu/pathsim/



PathSim Group (left to right): Front row: R. Laubenbacher, K. Duca Back row: K. Lee, N. Polys, J. McGee

In Vitro Virus Competition

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. 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.

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

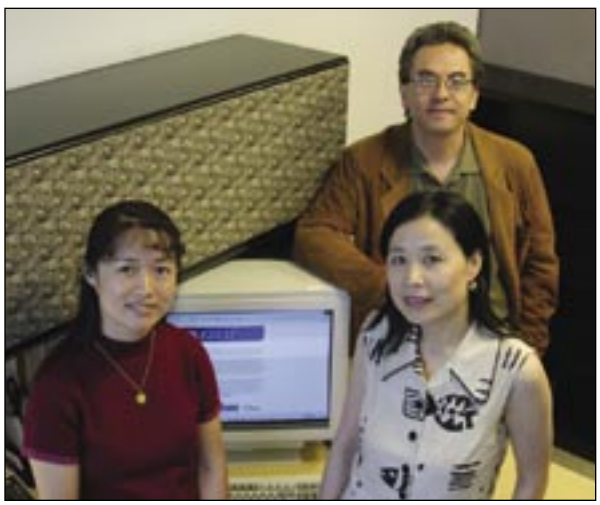
Sim2Virus, a simulation, models the spread of JHM and A59 on a hexagonal grid of cells. The viruses are distributed randomly into cellular boxes in a single time step. They replicate to generate new viruses that get distributed randomly to the local neighborhood at the next time step. The output of Sim2Virus 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, in turn helping the research community understand virus behavior. These new tools of biotechnology present opportunities to dissect the entire viral infection process, revealing potential therapeutic intervention points that were previously inaccessible.

Visit the Sim2Virus website at http://www.cs.tufts.edu/~ablumer/sim2virus.2.

The EST Analysis Pipeline

Expressed Sequence Tag (EST) projects are empowering the scientific community to discover and study gene functions. An EST is a sequence from an expressed gene that characterizes it. For any given cell, thousands of different mRNAs are produced, and the combined effect of the proteins encoded by these mRNAs ultimately yield cell phenotype. Some mRNAs, like the muscle protein actin, are produced in high numbers while others, like hormones, may be manufactured in a few copies. ESTs are used to study the amount and types of mRNA that are produced within a cell. Most EST projects involve sequencing 4,000 to 200,000 ESTs, creating a large amount of data.



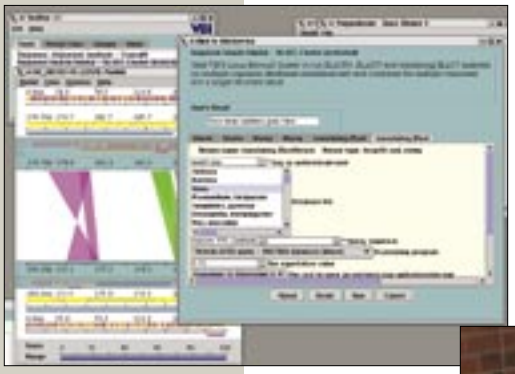
ESTAP Group (left to right): C. Mao, C. Hao, B. Sobral

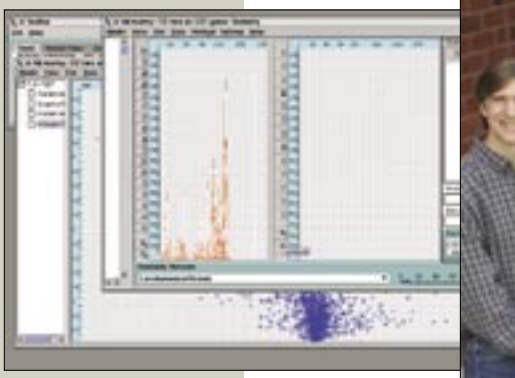
The EST Analysis Pipeline (ESTAP) software, developed by Dr. Sobral's Cyberinfrastructure Group at VBI in collaboration with the Samuel Roberts Noble Foundation (Noble) and the University of Nevada at Reno (UNR), is an automated system for the analysis of EST data. With ESTAP, researchers can rapidly and consistently analyze as well as annotate their ESTs, simultaneously facilitating the discovery of genes and gene functions. ESTAP has been successfully used for analyzing over 200,000 ESTs in more than 60 EST projects, including *Phytophthora* EST projects from the *Phytophtora* Genome Consortium, wine grape EST projects from UNR, and legume EST projects from Noble.

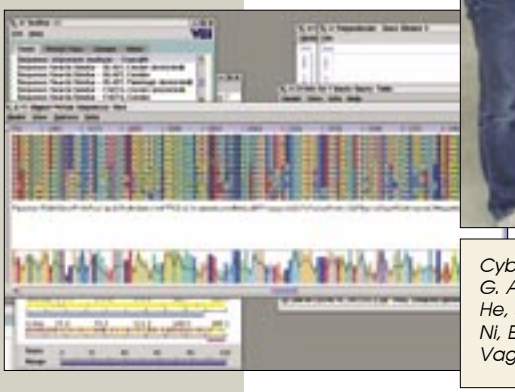
ESTAP service is now available for the public to use through VBI's Computational and Laboratory Core facilities. New ESTs are being processed and analyzed using ESTAP, including the approximately15,000 ESTs from Douglas-fir and Norway-spruce trees provided by University of California.

Visit the ESTAP project at http://staff.vbi.vt.edu/estap.

PathPort: Opening the Door to Comprehensive Pathogen Knowledge







With a total of $9 million in Department of Defense (DoD) funding, VBI continues to develop its already established PathPort (Pathogen Portal) project. PathPort is a life sciences interoperability framework that provides access to biological data from pathogens and their hosts, and the tools to analyze and interpret this data. The DoD-funded project has opened the door for scientists, government officials, and emergency responders to more effectively combat infectious diseases by providing access to relevant data and tools to analyze, manage, visualize, and extend existing and developing data sets. Through integration with VBI's Core Laboratory Facility (CLF), VBI scientists and collaborators have access to a unique infrastructure for data generation, management, analysis, and dissemination.

Cyberinfrastructure Group (in alphabetical order):
G. Abramochkin, S. Cammer, O. Crasta, C. Dharmanolla, A. Dickerman, D. Eckart, Z. Fei, H. Formadi, Y. Guo, O. He, J. Horton, K. Indukuri, P. Jhala, N. Kampanya, N. Kaufman, R. Kenyon, C. Kommidi, B. Lewis, J. Li , H. Liu, H. Ni, E. Nordberg, B. Rajagopalan, H. Rajasimha, G. Santopietro, M. Shukla, B. Sobral, J. Soneja, W. Sun, Y. Tian, N. Vaghela, R. Vines, R. Wattam, E. Wu, T. Xue, B. Yang, Q. Yu, C. Zhang, J. Zhao

Dr. Bruno Sobral and his Cyberinfrastructure Group are building PathPort as a set of Web services to consolidate, annotate, validate, disseminate, and analyze available pathogen data from disparate sources through an interoperable life sciences framework built on open community standards. Current analytical tools in PathPort allow for the creation of new data models; analysis of genomic, transcriptomic, and curated literature data; as well as the discovery of novel inter-data relationships. The client side of PathPort is ToolBus, a "bus" for connecting data and tools and viewing results through a single, consistent user interface.

Currently, data accessible by PathPort largely focus on host-pathogen-environment interactions. ToolBus/PathPort allows researchers to explore curated pathogen information and molecular mechanisms of pathogenesis from diverse sources, however, the system can accomodate any type of data.

Using its high-performance computational infrastructure and a world-class team of biologists and computer technologists, the Cyberinfrastructure Group will continue to develop PathPort as a key to unlock the door to the acquisition of more powerful knowledge for infectious disease research. Additionally, Dr. Sobral's group is providing a crucial enabling cyberinfrastructure for life sciences in general since it is the (selectable) data (and analysis tool) content that chracterizes and makes specific any implementation of ToolBus and associated web services.

Visit the PathPort project at http://pathport.vbi.vt.edu/

National Bioinformatics Resource Centers

VBI was recently named as one of eight national Bioinformatics Resource Centers (BRC). Under this project, VBI will retain high quality curated data on select pathogens and provide relevant tools to enable and facilitate researchers' analytical and visualization needs. Researchers will be able to store, view, display, query, annotate, and analyze genomic and related data and bibliographic information. To effectively address threats posed by infectious diseases in the 21st century, VBI recognizes the pressing need to develop and use molecular biological data (e.g., genomes, proteomes, gene expression, and metabolite profiles of pathogens and their hosts) as integrated, interacting pathosystems rather than simply as independent "pathogen" and "host" data sets. An information system to access, integrate, share, manipulate, and analyze these data is necessary.

Serving as one of the national BRCs, VBI will focus on the following select Category B priority pathogens: Brucella (causes Brucellosis in cattle, pigs, and humans), Caliciviruses (causes many of the viral dysenteries on cruise ships), hepatitis A, Coxiella burnetii/Rickettsias (which cause Q fever, Rocky Mountain spotted fever, and typhus); and Category C priority pathogens: Coronaviruses (SARS) and Rabiesvirus.

The relational database and Pathogen Portal (PathPort) technology at VBI will allow for the collection, analysis, and interpretation of a variety of data types, such as genome sequencing, comparative genomics, genome polymorphisms, gene expression, proteomics, host/pathogen interactions and pathways with state-of-the-art analysis tools. This project will leverage the Web services-based framework developed with PathPort as crucial software infrastructure to achieve data and tool interoperability across the BRCs. In addition, VBI's expertise and tools—acquired in the PathPort project for curating data from the literature—will be used to support curation efforts for the pathosystems selected for this proposal.

VBI and its partners were awarded a five-year, $10.3 million contract from the National Institute of Allergy and Infectious Diseases (NIAID) to establish the BRC. VBI will serve as the lead research group with collaborators at the Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech's Department of Computer Science, Loyola University Medical School, the University of Maryland, and Social and Scientific Systems, Inc. VBI's Professor and Director Bruno Sobral will lead the project, and VBI's Joao Setubal, co-principal investigator for the project, will interact with other Virginia Tech faculty and the scientific communities working on developing countermeasures for these pathogens.

The BRC's VT partnerships provide a powerful scientific basis for moving ahead with cross-cutting collaborations. The bioinformatics and software development team at VBI (Sobral's Cyberinfrastructure Group) will provide software process and engineering management, and the Systems Research Center at Virginia Tech will provide further strengths, applying usability engineering of software tools and systems built for the BRC.

Sobral's Cyberinfrastructure Group will also draw heavily on VBI's Core Computational Facility (CCF) team of systems administrators, database administrators, and network analysts to ensure that data from the BRC are available to the community via two avenues: a browser-accessible system and an application-based system (ToolBus/PathPort). This interaction leverages VBI's existing partnerships with Sun Microsystems, IBM Corporation, and TimeLogic.

Data Management System for Proteomic Research Centers

VBI is partnering with Social & Scientific Systems (SSS) to establish an Administrative Resource for Biodefense Proteomic Research Centers. The Proteomics Research Program will consist of six sites, which will be supported by this Administrative Center. Each site will be composed of a highly interactive, multi-disciplinary research team that applies proteomics technologies to characterize pathogen and/or host cell proteomes.

The primary goal of this research program is to characterize the pathogen and/or host cell proteome by identifying proteins associated with the biology of microbes, mechanisms of microbial pathogenesis, innate and adaptive immune responses to infectious agents, and/or host responses that contribute to microbial pathogenesis.

It is anticipated that the program will identify candidate targets for the next generation of vaccines, therapeutics, and diagnostics, and perform early stage validation of these targets. The sites will be required to include in their studies one or more of the potential agents of bioterrorism and/or pathogens responsible for emerging and re-emerging diseases.

The Administrative Center will design, develop, and maintain a publicly accessible web site and monitor and facilitate the deposition of reagents and protein targets generated by the Proteomic Research sites.

VBI is designing and will implement an integrated National Proteomics Biodefense Database System to collect, store, view, and query proteomics data, including source data, experimental protocols, and novel technologies supplied by the six Proteomics Research Centers. Direct queries and client applications will be enabled through VBI's Pathogen Portal (ToolBus/PathPort) interface and other methods. The availability of an interoperable infrastructure and analysis tools through the PathPort/ToolBus technology allows scientists to use this data to advance scientific research against bioterrorism agents and in the diagnosis, prevention, and treatment of emerging infectious diseases.

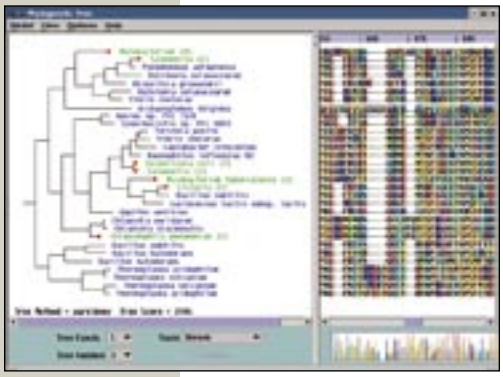
VBI's Core Computational Facility (CCF) will provide disk storage space for raw and processed data. The CCF's six Timelogic DeCypher boards will accelerate specific algorithms related to bioinformatics research, such as BLAST and many more. VBI's recent move into its new Bioinformatics Facility I on the Virginia Tech campus and the Institute's strong computational partners—Sun, IBM, and Timelogic—will help the collaborative team achieve project goals.

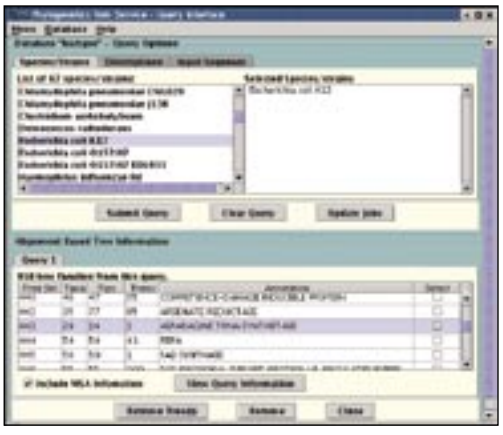
The National Institute of Allergy and Infectious Diseases (NIAID) awarded VBI $2.89 million as part of an $8.74 million contract with SSS. Margaret Moore from SSS is principal investigator (PI) and Dr. Bruno Sobral, VBI's Professor and Director, and Dr. Cathy Wu, from Georgetown University Medical Center, are co-principal investigators (co-PIs) on the project.

Phylogenomics

Phylogenetics is the view that living systems today are products of descent with modification from ancestral systems in the past. This analysis method can describe species as well as components within a single genome. Applying this principle across both species and genomic components comprises the field of phylogenomics. This combination allows one to study the similarities and differences among species in an explicitly evolutionary context.

Dr. Allan Dickerman at VBI has developed a unique analysis method for this information and is building a large database of phylogenetic descriptions of many homologous protein coding gene regions across a set of entire genomes. This provides a resource for delving into various biological questions. This database can be used to study horizontal gene transfer, accelerated or slowed rates of change, and phylogenetic placement of unknown samples. Yuying Tian at VBI is developing a graphical interface to this information in the Toolbus/Pathport project. A web interface is also under construction.





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

Biomedicine

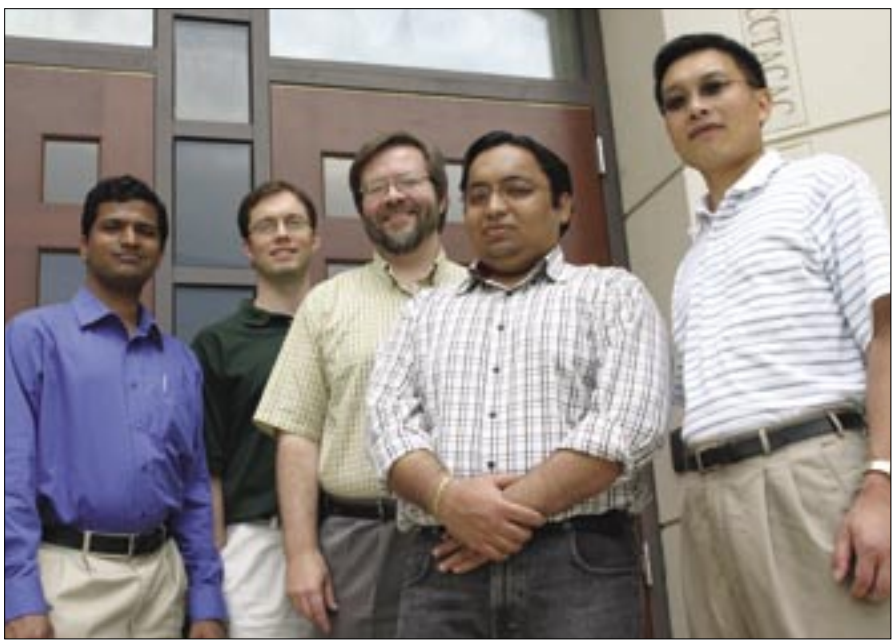
As global citizens face threats of bioterrorism today, researchers are searching for preventative disease transmission measures. With public health and biomedical research near the top of the nation's priority list, researchers must develop new and more effective vaccines, drug therapies, and treatments. Researchers, doctors, and the public health system must have a better understanding of how infectious diseases affect the processes of biological systems. Thus, researchers at VBI are committed to understanding how host and pathogen genes interact across diverse species and environments. The product of this biomedical research will aid in the rapid detection, identification, prevention, and treatment of disease.

Models of Mitochondrial Toxicity in Anti-Viral Treatment for HIV/AIDS

The current treatment for HIV infection is a cocktail of medications called HAART, for "highly active antiretroviral therapy," that includes one or more drugs known to interfere with the replication of viral DNA. These drugs cannot get into the cell nucleus and thus do not interfere with the patient's own nuclear DNA. Unfortunately, the drugs do get into the patient's mitochondria and can affect the small, but critical amount of DNA in the mitochondria (mtDNA). Mitochondria produce the energy for all cellular processes, and if they fail, then organ failure follows. Many anti-AIDS drugs that seemed promising in the lab have been found in clinical trials to have serious and even fatal complications because of their affect on the patient's mitochondrial DNA.

The current AIDS therapy does not remove the HIV virus—it only keeps the virus under control, so the therapy must continue for the rest of the patient's life. Over such a long period of time, even the drugs that passed clinical trials may cause long-term damage to the patient's mitochondria. As HIV therapies improve, patient survival is increasing and the long-term complications of these therapies are becoming even more important. Furthermore, as doctors begin to see older HIV patients, the mtDNA mutations that naturally accumulate with age may affect the severity of the medication's mitochondrial toxicity.

Dr. David Samuels' research group at VBI, including Drs. Jiaxin Li and Patrick Bradshaw, is building a computational model of the metabolism of anti-AIDS drugs in mitochondria. Samuels' group is modeling a class of drugs called nucleoside analogs. Nucleosides are the natural chemicals that are used to build all DNA. These are the letters a, c, g, and t in the familiar genetic code. Nucleoside analogs are chemicals that are just slight modifications of the natural nucleosides. These chemicals have a three-dimensional shape close enough to the natural nucleosides that they can take part in the same chemical reactions, but different enough from the natural nucleosides that they do not make functional DNA. If the nucleoside analogs get into the HIV virus DNA during its replication, then that virus DNA molecule is destroyed and the infection is controlled. However, if an analog gets into the mitochondrial DNA, failure of the mitochondria and then the cell will occur. The aim of Samuels' research group is to identify the metabolic pathways responsible for the majority of the damage to mitochondrial DNA.

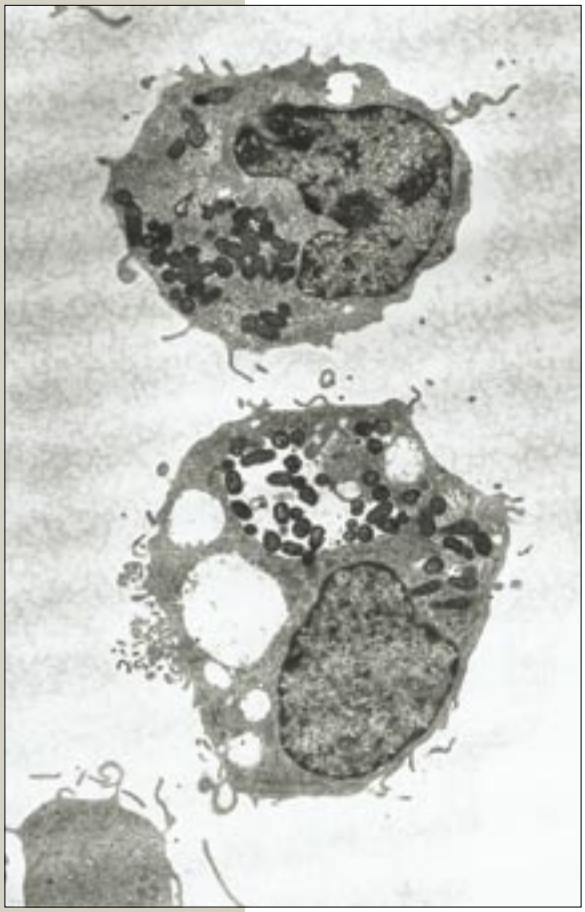


Dr. D. Samuels' Research Group (left to right):
H. Rajasimha, P. Bradshaw, D. Samuels, A. Rathi, J. Li

Teamwork to Tackle Brucellosis

Brucella spp., a gram-negative, facultative, intracellular bacteria, cause brucellosis in humans and farm animals, such as cattle, goats, and swine. Although only 100 to 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.

VIRGINIA-MARYLAND
REGIONAL COLLEGE OF VETERINARY MEDICINE



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

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 and the Virginia-Maryland Regional College of Veterinary Medicine (VMRCVM) have received $300,000 from the National Institutes of Health (NIH) to study brucellosis.

Yongqun "Oliver" He, senior research associate in Sobral's Pathosystems Biology Group, and colleagues will use cutting-edge technology to facilitate the creation of a human vaccine against brucellosis. By using microarray analysis, the scientists will determine which host genes are involved in fighting off the disease process.

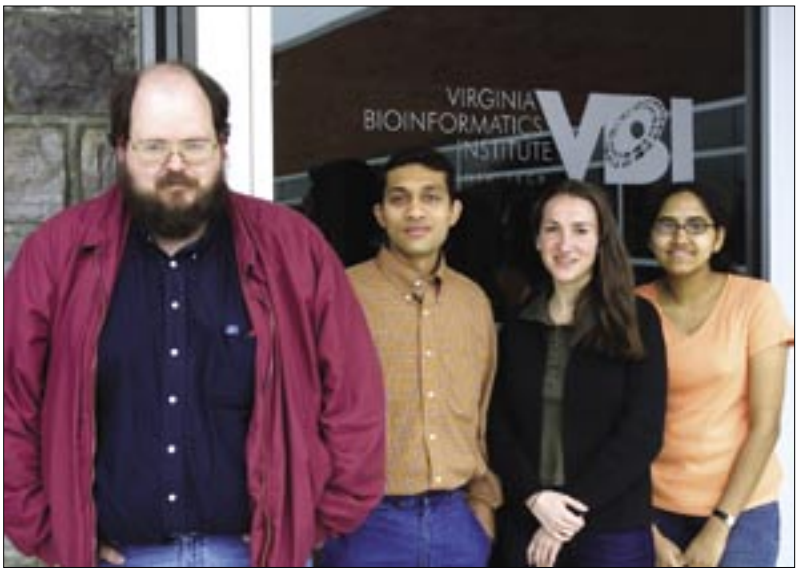
Brucella is one of the few bacteria able to overcome the body's infection-fighting cells, known as macrophages. These large, versatile cells in the immune system are a major player in the body's ability to start a specific defense against infection. *Brucella* bacteria overcome the body's defenses and live inside macrophages. He and project collaborators Stephen Boyle, Gerhardt Schurig, and Nammalwar Sriranganathan from the VMRCVM are studying three species of *Brucella* that infect humans (*B. abortus*, *B. melitensis*, and *B. suis*).

The Office of the Vice Provost for Research at Virginia Tech and the VMRCVM each provided $4,000 to enable the researchers to purchase the supplies necessary to begin the microarray analysis. The resulting data convinced the NIH to fund an extended research project, providing $300,000 this year with potential for a $301,167 renewal next year.

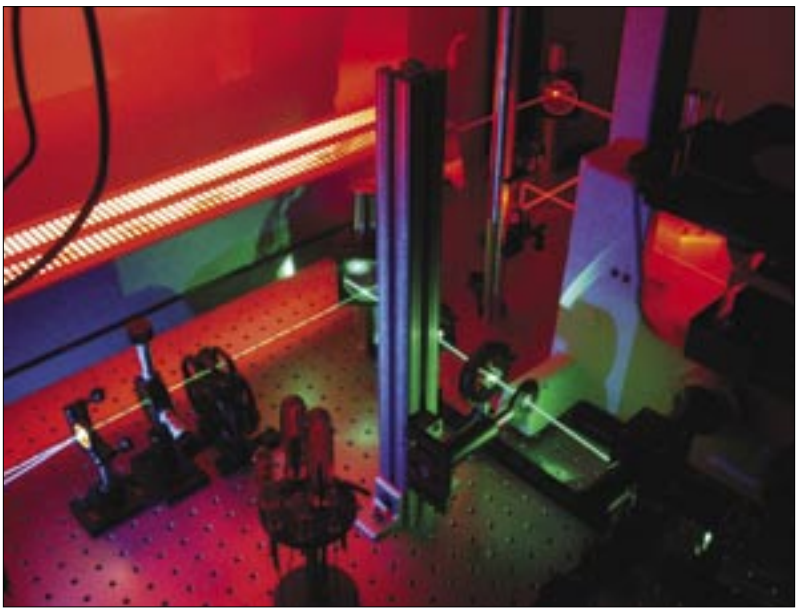
The microarray analysis for this project will be performed at VBI's Core Laboratory Facility (CLF) and software support will be provided by the ToolBus system.

Protein Aggregation Diseases in Humans

Proteins, which can be thought of as chains of amino acids strung together like beads on a string, usually function by adopting a unique three-dimensional structure or fold. When correctly folded, the protein exposes surfaces that can either perform chemistry (catalysis) or recognize and bind other molecules (self-assembly and molecular recognition). When proteins are subjected to destabilizing genetic mutations or certain environmental conditions, some chains can adopt partially folded, misfolded, or meta-stable structures that are prone to aggregate. The structures of these aggregates are the root cause of a variety of progressive degenerative diseases, including neuropathies such as Alzheimer's and Parkinson's diseases. Protein aggregates are secondarily associated with many other diseases, including Type II diabetes, chronic infections (reactive amyloidosis), and some cancers.



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



An optical trapping fluorescence microscope is used to watch single protein molecules fold and unfold over time. Examining the behavior of single molecules can uncover rare and transient structural fluctuations that cannot be detected in bulk samples. Such fluctuations likely are the basis for the formation of protein aggregates in diseases such as Alzheimer's and Parkinson's diseases and provide a direct look into the pathways by which proteins fold and unfold.

Because protein aggregation disease may take years to develop, symptoms are often first noticed in mid-life, though any age can be affected. Therefore, as the population of the United States ages, the prevalence of these protein aggregation diseases is expected to increase markedly. As no effective treatments are available for these disorders and their courses tend to follow a slow progressive degeneration over years, they can severely impact the quality of life for a large portion of the U.S. population and have a significant socioeconomic impact on families that bear the brunt of long-term health care costs and lost earning potential. Furthermore, the increased incidence of transmissible neuropathies, such as mad cow disease and chronic wasting disease in deer and elk herds, potentially threatens the sanctity and safety of food supplies.

Dr. Joel Gillespie's lab at VBI is studying the mechanisms underlying the formation of these pathogenic protein aggregates and the means by which misfolded proteins evade normal cellular housekeeping mechanisms inside cells. Of particular interest is the role of protein misfolding by cystatin C, a small cysteine protease inhibitor involved in neural development in precipitating strokes in young adults (hereditary cerebral amyloid angiopathy) and the role of Bence-Jones proteins associated with multiple myeloma in systemic amyloidosis. The Gillespie lab is determining how environmental factors and genetic mutations influence the unfolding of these proteins and initiate aggregate formation with the long-term aim of developing more effective treatments to stop or reverse the damage caused by protein aggregation.

Identifying Viruses and Their Risks

by freelance writer Eileen Baumann.

VBI research faculty member Karen Duca is collaborating with VBI Faculty Fellow and Electrical and Computer Engineering Associate Professor Amy Bell on a research project with the goal of developing a procedure that may be used to rapidly identify viruses and the illness and mortality risks that they present.

Duca and Bell are studying the response to infection when viruses are introduced to cells in a laboratory dish, or well. Duca is staining and measuring various protein markers that appear in response to the infection. The two are particularly interested in examining the behavior of markers in uninfected host cells for potential defensive strategies. Defensive strategies of uninfected cells may include direct attacks on the virus, recruiting immune cells to the infection site, initiating a suicide program to prevent further viral spread, and signaling to neighboring cells that a virus is coming.

Conventional laboratory studies of viruses generally involve infecting the entire well at once. Duca is infecting the well in the center and studying the response as it spreads outward from ground zero, preserving important spatial information about how the population shares information to protect itself. She is identifying and staining relevant markers from the virus and host with chemical stains that fluoresce when viewed under ultraviolet light. Using a microscope with a low-power lens, the team then captures images of the well at regular time intervals as the infection progresses. By studying the image, they gain valuable information about innate immune responses to viruses.

Bell's goal is to remove the noise from these low-resolution images and derive a clean immunofluorescent intensity signal (IIS). Several sources introduce noise in the images: the microscope and the fluorescent markers are the two primary sources. The microscope cannot capture the entire well at once, so at each time interval, multiple subimages must be taken quickly, then assembled in matrix fashion. Also, at low magnification, the microscope illumination is brighter in the center and dissipates toward the outer edges – creating a montage artifact in the image. Once a montage (composite) image is denoised, it is used to derive a quantitative description of the viral propagation and host-virus interaction: this is the IIS.

Ultimately, the team hopes to develop a quantitative method that derives a characteristic profile – or 'fingerprint' – from the IIS of any host-virus system. A concurrent design goal is to develop fast methods so that laboratory results can be achieved in hours instead of days. The profiles and signal processing techniques could then be used in clinical or field settings to quickly identify known viruses, or to map unknown viruses to existing profiles to better predict their behavior and start appropriate treatment.

Genes that Predispose Individuals to Smoking-Related Diseases

Lung cancer results in more deaths every year than prostate, breast, and colon cancer combined and is the most common cause of cancer death in the United States. The evolution of most lung cancers is believed to be a gradual accumulation of genetic irregularities most often associated with tobacco use. More specifically, many carcinogenic compounds exist in cigarette smoke. Analyzing the expression levels of genes involved in nucleotide excision repair (and other types of DNA repair) could be an effective means to identify risks for developing tobacco-related diseases, such as cancer, cardiovascular disease, and pulmonary disease.

Dr. Karen Duca, research assistant professor at VBI, leads the project, "Identification of Genes that Predispose Individuals to Smoking-Related Diseases," which is funded by the University of Virginia and The Tobacco Foundation. The specific aims of this project are to develop ways to measure the DNA repair status from lung-derived cultured cells, identify and characterize lung-derived cell lines divergent for DNA repair capabilities and measure the expression of genes involved in DNA repair, and determine the candidate genes whose expression profile is most likely to be predictive of DNA repair activity.

More specifically, Duca's lab is investigating 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):
Front row: K. Duca, S. Stevens, J. McGee
Back row: S. Penich, N. Polys, J. Shah, E. Fulton, P. Saraiya

Addressing the Global TB Crisis

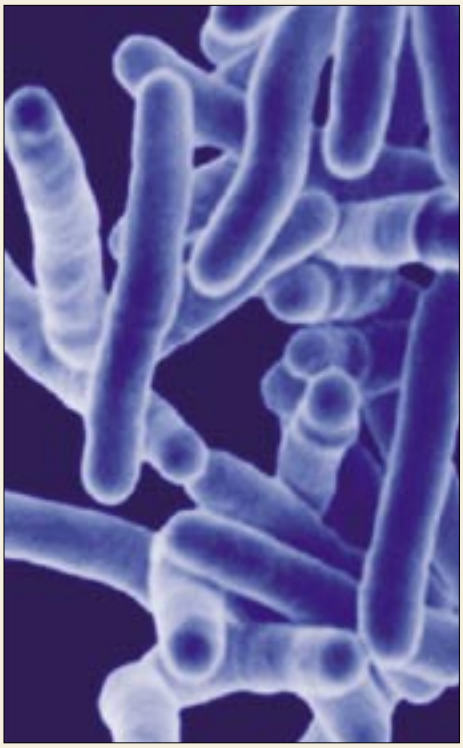
Five thousand people die of tuberculosis (TB) daily. Despite the availability of drug cocktails to treat the disease, eight million new cases are reported annually. *Mycobacterium tuberculosis*, the causal agent of TB, presents complex pathologic mechanisms, making effective treatment difficult. An estimated one-third of the 42 million people living with HIV/AIDS worldwide are co-infected with TB. This combination of diseases leads to the largest number of AIDS-related deaths.

Dr. Biswarup Mukhopadhyay's research group 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. The lab group investigates the mechanisms that *M. tuberculosis* uses to lie dormant within the human body. Common anti-TB drugs do not kill the dormant cells. Using a state-of-the-art bioreactor and a proteomics-based approach, the group can track the consequential intracellular changes and identify proteins specifically linked to the pathogen's survival.

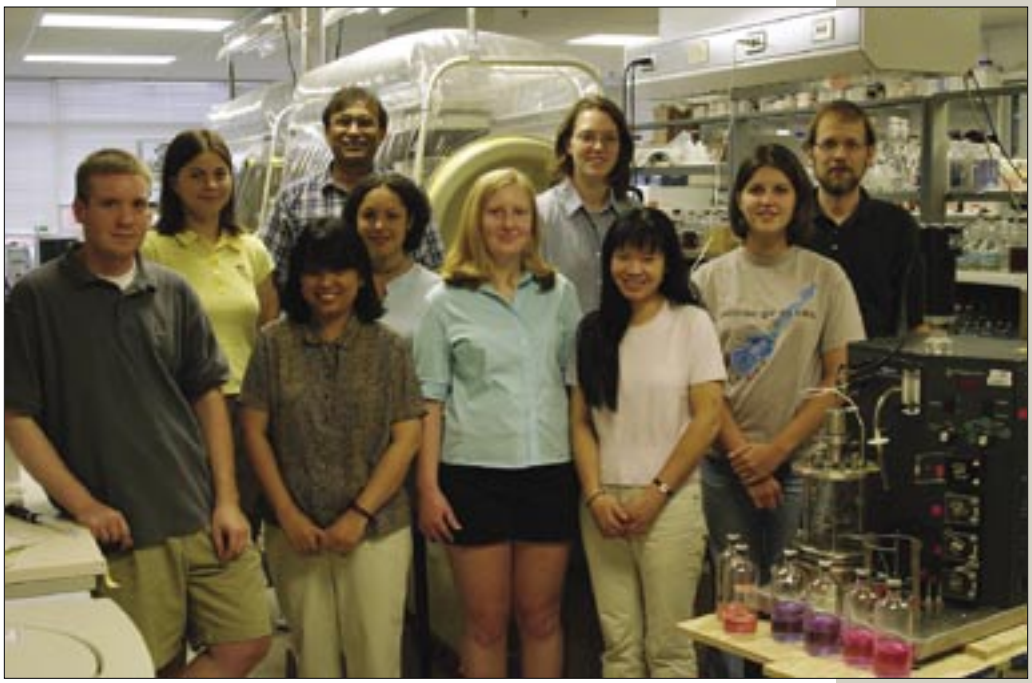
For this study, Mukhopadhyay has formed a partnership with Dr. Ying Zhang at Johns Hopkins University (JHU), who also works on mycobacterial dormancy. Interactions with JHU have helped Mukhopadhyay develop a collaboration with the Division of Tuberculosis Control at the Maryland Department of Health and Mental Hygiene.

In addition, Mukhopadhyay collaborates with Endang Purwantini, a researcher at VBI and a faculty member at the Institute of Technology Bandung (ITB), Indonesia; several researchers at ITB; and a clinician from Sanatorium in Bandung, Indonesia. The researchers are investigating why some people do not get the active disease in an almost fully infected population. They are also interested in the profiles of anti-*M. tuberculosis* antigens in a healthy subject, a person with developing or active TB, and a patient who is responding to an anti-TB drug therapy. Their research is focused on a TB endemic area in Indonesia. The ultimate goal is to develop affordable diagnostic and monitoring reagents and effective vaccines for TB. The team has already secured participation of a TB research group at John Hopkins University and an endorsement from a vaccine company in Indonesia, and has received an international collaboration grant on TB research from the government of Indonesia. This fund will be used to collect initial data on the cell mediated immunity and antigenic profile in TB patients and healthy subjects in a TB endemic area in Indonesia.

Mukhopadhyay's research approach will show how *M. tuberculosis* survives over time in human populations and will bring the global community one step closer to finding targets for effective treatments and vaccines.



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



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 S. Kale

Designing New Drugs and Materials for a New Millennium

Proteins (Greek: proteios, of first importance) are biological macromolecules built from the condensation of amino acids into non-random polymers that typically have complex three-dimensional structures. Proteins are responsible for doing most of the work that takes place in living organisms—they catalyze the chemical reactions that all living things need to metabolize food, move, communicate, and defend themselves. They also play important structural roles, including forming the cytoskeleton of cells, directing the mineralization of bones, forming the outer layers of skin and hair, and even forming the lenses of eyes. Because of the complexity of protein structures, as well as their low thermodynamic stability and strong dependence on interactions with their environment, the rational design of novel proteins is a significant challenge that can only be addressed using both the power of computational biology and the finesse of new experimental biological approaches.

Dr. Joel Gillespie's lab at VBI is developing new strategies and tools for the rational design of proteins with unique and novel functions and properties. Some examples include proteins with the ability to catalyze the oxidation of polycyclic aromatic hydrocarbons (PAHs, an important class of environmental pollutants) and synthetic polymers, such as vulcanized isoprene; proteins that can self-assemble into two-dimensional arrays or rafts when triggered by certain environmental conditions (such as a flash of light or change in pH); and proteins that recognize and bind to other specific proteins in solution and change their shape to signal that binding has occurred.

Such designed proteins have many industrial and biomedical applications, ranging from environmental bioremediation to industrial catalysis to the development of new light-weight fabrics and composite laminates. They can also play an important role in medicine, allowing for the tailored design of new protein and peptide drugs. Such drugs have the potential to be much more selective than traditional drugs, allowing for the dramatic reduction of side effects and toxicity by targeting only diseased cells.

Microfluidics

Ongoing efforts to resolve two major comprehensive projects, the "genome" and the "proteome," have emphasized the necessity to develop simple, compact, and low-cost devices capable of fast, sensitive, and reliable analysis. A significant effort has been invested in the past decade to develop the "lab-on-a-chip" concept. As a result, microfabricated devices have emerged as powerful and reliable analysis platforms. These novel architectures function according to well-established principles and are characterized by several distinguishing features. Together with the capability to manipulate small sample volumes and amounts, the miniature format first results in shorter analysis times and significantly reduced analysis costs. Second, the ability to perform precise and accurate sample handling operations enables process control and automation, and consequently the generation of reliable and high-quality data. Third, microfabrication enables large-scale integration, multiplexing, and thus facilitates high-throughput analysis.

Dr. I. Lazar Research Group (left to right): J. Yoon, I. Lazar, P. Trisiripisal

Microfluidic devices have gained relatively broad acceptance in genomic analysis. However, the same cannot be stated for proteomic applications. A major limitation in this direction relates to the fact that MS detection, while an essential tool in peptide/protein analysis, is not widely utilized with microchips because of the difficulties associated with microchip-MS interfacing. On the other hand, mass spectrometry has evolved into the preferred technique for proteomic identifications since it offers the combined benefits of specificity, sensitivity, and resolving power, and is capable of delivering high-quality structural information.

Dr. Iuliana Lazar's lab at VBI focuses on the development of microfluidic devices with mass spectrometric detection for the handling of a large variety of bioanalytical processes. The value of this approach arises from the superior analytical capabilities of microfabricated devices that can provide the optimum platform for fast, sensitive, and high-throughput handling of minute amounts of samples. These qualities are especially relevant for proteomic investigations.

Combating Infectious Diseases through Collaboration

In collaboration with Johns Hopkins University's (JHU) Bloomberg School of Public Health, VBI is studying complex diseases including tuberculosis (TB), HIV/AIDS, and malaria, as well as developing new technology, software, and database platforms to support biomedical research. Together, scientists at JHU and VBI have submitted 32 grant proposals totaling over $76 million to agencies and foundations such as the National Institutes of Health (NIH), American Diabetes Association, Ellison Medical Foundation, and Global Fund to Fight AIDS, Tuberculosis, and Malaria. As a result of the JHU collaboration, VBI has produced 14 publications and 12 presentations centered on JHU/VBI research.

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Dr. Biswarup Mukhopadhyay (VBI) collaborates with Dr. Ying Zhang (JHU) to research the mechanisms that *Mycobacterium tuberculosis*, the causative agent for TB, employs for lying dormant in the human body and evading the actions of anti-TB drugs. Mukhopadhyay and collaborators have received an international collaboration grant from the government of Indonesia for $80,000, which will be used to collect initial data on the cell mediated immunity and antigenic profile in TB patients and healthy subjects in a TB endemic area.

Dr. Vladimir Shulaev (VBI) collaborates with Dr. David Sullivan (JHU) on developing the analytical infrastructure for large-scale metabolite profiling of untreated and antimalarial drug-treated *Plasmodium facliparum*. This research will identify metabolic changes associated with malarial drug treatment with the aim of identifing metabolic and enzymatic targets. Dr. Pedro Mendes (VBI) is also creating a reference database for *P. falciparum* metabolic network in collaboration with Dr. Fernando Pineda (JHU). Dr. Dharmendar Rathore's (VBI) lab has started cloning and expressing malaria surface antigens in a prokaryotic expression system.

Dr. Bruno Sobral (VBI) leads the Cyberinfrastructure Group, which is developing an open software framework, ToolBus/PathPort, to address data management issues and enable interoperability of bioinformatics analysis tools. Currently, PathInfo documents for pathogens of interest to JHU (*P. falciparum*, *M. tuberculosis*, and HIV) are in development for portrayal through the PathPort system.

The JHU/VBI partnership specifically targets solution development 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.

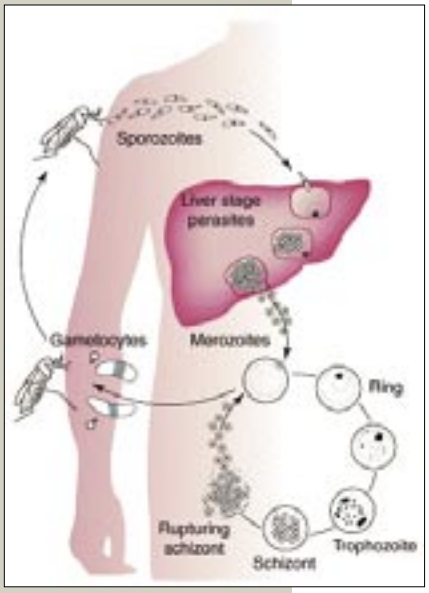
The Molecular Mechanisms of Cryptosporidiosis

Cryptosporidiosis, caused by members of *Cryptosporidium* genus, is a parasitic infection that has emerged as a life-threatening disease in AIDS patients and other immuno-compromised individuals. It is the third major cause of profuse diarrhea, mucosal inflammation, and gastroenteritis in humans. Cryptosporidium oocyst, a dormant stage of the parasite, is fecally shed by the infected host and the fecal contamination of drinking water serves as a vehicle for transmission of this pathogen. The oocysts are long lived, easily transmittable, and resistant to standard water disinfection processes, which has made this parasite a major concern to public health. Because of these concerns, the U.S. National Institutes of Health recently classified Cryptosporidium as a Category-B priority pathogen. In the United States, large scale outbreaks of Cryptosporidiosis have been associated with contamination of community drinking water.

Dr. D. Rathore's Research Group (left to right): R. Nagarkatti, D. Rathore, D. Jani

Once the oocysts have been ingested in the intestinal milieu of the host, they undergo excystation and release sporozoites, the infective form of the parasite. These sporozoites immediately attach to the epithelial microvillus border and are subsequently enveloped by the host apical cell membrane, resulting in a parasitophorous vacuole that contains membrane components from both the host and the parasite. Initial attachment of the parasite to host cells is a prerequisite for the pathophysiological events in infection. The pathogenesis of *Cryptosporidium* is poorly understood due to limited knowledge of the invasion machinery of this parasite. Dr. Dharmendar Rathore at VBI leads an effort to understand the molecular processes that facilitate the interaction between the host and parasite. His laboratory is involved in the identification of parasitic antigens that interact with the host cell epithelium. This work will eventually help in developing new approaches to control this infection.

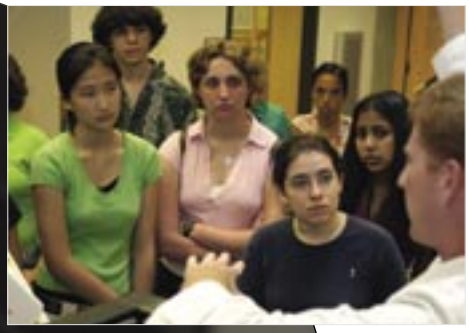
Malaria Vaccine Development



Malaria is a life-threatening parasitic disease causing 300 to 500 million clinical cases annually. Each year, one to three million individuals, mostly children in sub-Saharan Africa, succumb to this disease. Out of the four species of *Plasmodium* that infect humans, *Plasmodium falciparum* is responsible for the most severe form of human malaria and more than 90 percent of the fatalities. In addition to human cost, malaria imposes a massive economic burden, contributing substantially to poverty in developing countries. Malaria is also a major problem for US military, due to their deployment in areas of active malaria transmission.

The complex life-cycle of the parasite poses an enormous challenge in developing an effective vaccine. The only available mechanism to develop consistent protection is immunization with radiation-attenuated whole sporozoites, using the bites of infectious mosquitoes in a laboratory setup. Recently, the complete genome sequence of *Plasmodium falciparum* has become available. It is now imperative to evaluate newly identified proteins for their potential to serve as malarial vaccine candidates. Dr. Dharmendar Rathore's laboratory takes an important step in this direction by investigating the malaria vaccine potential of 17 parasite surface proteins. All 17 molecules have been expressed at the sporozoite stage of the lifecycle, which is responsible for the onset of malaria infection. These molecules are strongly immunogenic, as predicted by *in silico* analysis. The idea is to mimic the protection seen on immunization with irradiated sporozoites, the only working malaria vaccine model. The potential of these proteins to serve as a vaccine candidate is being investigated by screening serum samples obtained from human volunteers immunized with irradiated sporozoites for anti-protein antibodies. Proteins identified by this study will have the potential to serve as a malarial vaccine candidate, either alone, or in combination with other potential antigens.

- 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

VBI's communication, outreach, and education team focuses on sharing the Institute's research and developments with the Virginia Tech community and beyond. The department has developed workshops and conferences, organized the Bioinformatics Facility I Grand Opening, and continued educational outreach activities for students and professionals.

The institute has received extensive press coverage this year, including television and popular journal media highlights. In addition, VBI has published VBI E-News, highlighting important and breaking VBI research and news items. VBI continues to host high school, graduate, and undergraduates students for various short- and long-term learning opportunities. Students may also earn a Ph.D. through Virginia Tech's Genetics, Bioinformatics, and Computational Biology (GBCB) graduate program at VBI. These communications and outreach efforts and education programs, combined with facility tours, provide colleagues, partners, and other community members with knowledge and information about new developments and continuing work at VBI.

Toxicogenomics Conference Meeting Report Published

One year after the May 2003 "Toxicogenomics through the Eyes of Informatics" conference in Bethesda, Maryland, the meeting report article entitled "Toxicogenomics through the Eyes of Informatics: Conference Overview and Recommendations" was published in the May 2004 edition of Environmental Health Perspectives.

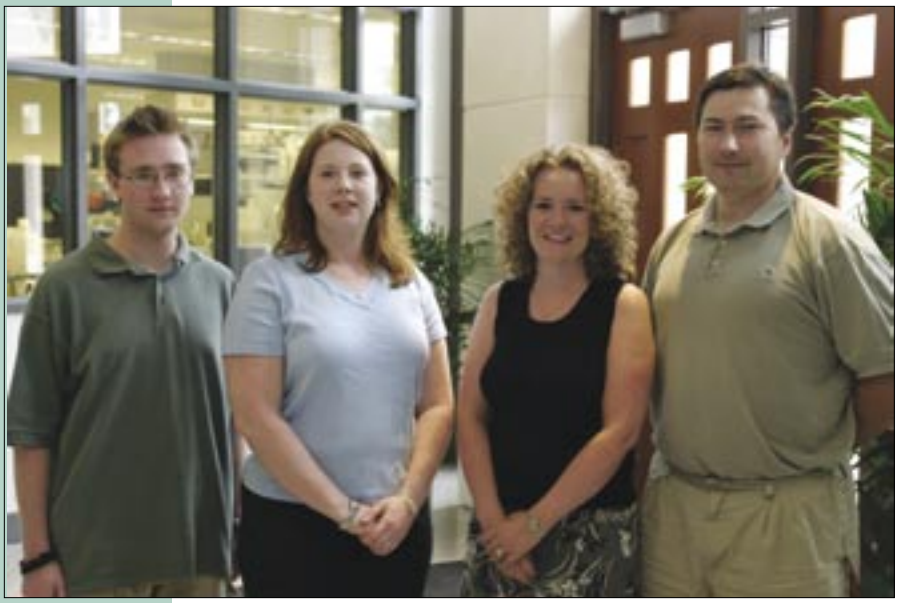
Authors Kenneth Olden, Director of the National Institutes of Environmental Health Science (NIEHS); Neysa Call, Legislative Policy Analyst for the National Science Foundation; Bruno Sobral, Director of Virginia Bioinformatics Institute (VBI); and Robin Oakes, Technical Communications Writer/Editor for VBI, were pleased to view their work in this NIEHS-supported journal. The article highlighted the conference proceedings, presentations, survey results, current toxicogenomics concerns, and future directions of the toxicogenomics community.

At the May 2003 meeting, researchers from around the world met to discuss how the application of bioinformatics tools, methogologies, and technologies will enhance the understanding of how cells and organisms respond to toxins. Conference topics included statistical methods, quantitative molecular data sets, computational algorithms for data analysis, computational modeling and simulation, challenges and opportunities in computational biology, and information technology infrastructure for data and tool management.

VBI Gains Press Coverage from Local and National Media

VBI has gained extensive press coverage throughout the year from both local and national media outlets. The Bioinformatics Facility I Grand Opening, which was held during Virginia Tech's Founder's Day Weekend was highlighted on a variety of local news channels, including Roanoke news stations WDBJ 7, WSLS News Channel 10, and Fox 21/27; VTTV, Virginia Tech's student run television station; the Collegiate Times, Virginia Tech's student newspaper; and HokiE-News, which features information for Virginia Tech faculty and staff.

In addition, the April edition of *Nature Biotechnology* identified Virginia Tech's and VBI's Genetics, Bioinformatics, and Computational Biology (GBCB) Ph.D. program as one of 11 selected programs in North America and 18 around the world offering courses in systems biology. Furthermore, VBI's participation in the Middle Atlantic Regional Center of Excellence (MARCE) for Biodefense and Emerging Infectious Diseases was highlighted in two national media publications, *U.S. Medicine* and *BioInform*.



Public Relations/
Outreach Team
(from left to right)

Andrew Bevins
Graphic Design Intern

Robin Oakes
Technical Communications Writer

Susan Light
Technical Communications Editor

Ivan Morozov
Web Administrator

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

VBI has partnered with the Virginia Tech Graduate School to participate in the interdisciplinary Ph.D. Program in Genetics, Bioinformatics, and Computational Biology (GBCB). Nine Virginia Tech academic departments collaborate to bring a new paradigm for bioinformatics education and training that cuts across boundaries of traditional genetics programs.

The program encompasses molecular biology, genomics, mathematics, statistics and computer science, while applying them to all areas of the life sciences. As a unique feature, the curriculum is tailored to a student's individual background.

Participating students conduct dissertation research projects with mentoring researchers in various traditional science disciplines. To compliment coursework and assist students in developing their dissertation projects, additional focused research experiences can be required. VBI faculty members participate in the program on many levels, including mentoring student in world-class research programs.

The GBCB program prepares researchers for the growing systems biology environment that often requires a new academic training standard – one that creates team-oriented researchers who may be specialists in one area but are literate in several other disciplines. Currently, 17 students are involved in the program.

VBI Graduate and Undergraduate Students

VBI currently employs 13 graduate research assistants and 15 undergraduate student assistants to support the many research projects and internal groups led by the 15 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 benefited greatly from such a diverse group of student assistants and, in turn, has assisted in their professional development as they prepare for future careers.

VBI held a special luncheon to recognize graduating students employed at VBI. Pictured are (left to right): Tom Smith, Laurie Coble (Associate Director of Administration and Finance), Phi Vu, Bruno Sobral (Executive and Scientific Director), Catherine Tuck, Robin Oakes, and Adam Childers.

High School Students Meet Bioinformatics

VBI congratulates Laura Maxey and Yvonne Ng for their participation and success in VBI's high school science project program. VBI's outreach programs, like the high school mentorship program, provide high school and undergraduate students access to cutting-edge technology and experimental guidance.

Two Core Lab Facility (CLF) personnel, Clive Evans and Kathy Finne, mentored Maxey and Ng, respectively. Maxey's project, "Gene Expression of *Arabidopsis thaliana*," won third place at Southwest Virginia Governor's School Science Consortium, first place at the Giles High School Science Fair, and second place at the Blue Ridge Highlands Regional Science Fair. Maxey also presented at the Virginia State Science Fair.

Ng presented her project titled "Determining the Sequence of *Chroma* Bacterium" at the Blue Ridge Highlands Regional Science Fair, where she placed third in the biochemistry division, and at the Virginia Junior Academy of Science Competition.

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

VBI Welcomes Nine Undergraduate Students For Summer

VBI welcomed nine undergraduate students who worked with researchers at the Institute over the summer in conjunction with two Virginia Tech programs – the Multicultural Academic Opportunities Program (MAOP) and the Robert E. McNair Scholars Program.

The students participating in MAOP included: under the advisement of VBI researcher Karen Duca – Nikkida Bundrant (Virginia Tech) and Terrence Hill (Virginia Tech); under the advisement of VBI researcher Brett Tyler – Joyce Curry (Hampton University), Carmine Leggett (Spelman College), Stephanie McBurrough (Fort Valley State University), and Andrew McKinley (Hampton University); and under the advisement of VBI researcher Vladimir Shulaev – Beth Henry (Bluefield State College) and Erica Mason (Virginia Tech). Duca will also be advising Bathsheba Jackson (Virginia Tech), who comes to VBI through the McNair Scholars program.

The mission of the MAOP program is to encourage and support the academic achievement of a diverse student body from Virginia Tech and other institutions across the nation. The program has expanded since its founding more than a decade ago from a focus on recruiting and retaining African American students in Agriculture and Natural Resources, to serving students of every background. Programs and activities serve students from the pre-college through the doctorate level with a continuum of financial, academic, emotional, and social support, and research opportunities. Students participating in MAOP programs have an excellent record of retention, graduation, and enrollment in graduate school.

The Virginia Tech Ronald E. McNair Post-Baccalaureate Achievement Program (commonly known as the McNair Scholars Program) is one of 166 programs across the country designed to prepare first-generation college students and students from ethnic groups underrepresented in higher education to pursue post-baccalaureate degrees. Established and funded by the U.S. Department of Education, and named in honor of Challenger space shuttle astronaut Dr. Ronald E. McNair, the McNair Scholars Program encourages graduate study by providing participants with a mentored research experience, seminars, and workshops on topics relevant to the pursuit of the doctoral degree.

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. This mentorship, in turn, encourages students to pursue opportunities in higher education.

Students are matched on a case-by-case basis with research staff to participate in hands-on research projects. This nationwide program emphasizes job development skills. VBI coordinates on-site visits for students to tour laboratory facilities and the computing infrastructure, while giving opportunities for job shadowing experiences.

Overall, the program is multifaceted, providing opportunities for realistic career exploration and hands-on research experiences in the student's area of interest.

- Research
- Grants
- Selected Publications

Faculty

"Interdisciplinary collaboration is essential to solve the large, complex problems posed by biological systems. Mathematics, statistics, and computer science are rapidly becoming as integral to biological research as these disciplines currently are to physics and astronomy. VBI researchers are actively leading this integration, generating new concepts and tools for understanding life at the molecular level and delivering practical applications in the areas of infectious disease and biosecurity."

Brett Tyler, Ph.D.
Research Professor
Virginia Bioinformatics Institute

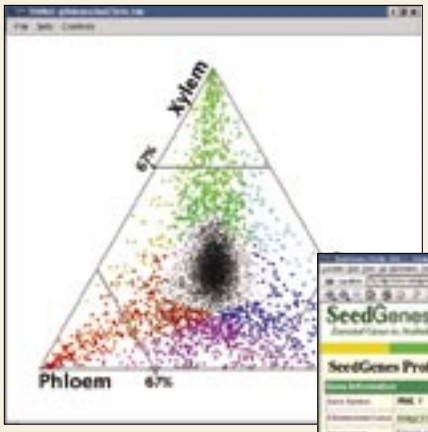
VBI strives to meet society's demands on research institutions by seeking to develop countermeasures for human and agricultural diseases. Through groundbreaking research projects, the Institute's faculty remain updated with emerging threats and the newest technologies.

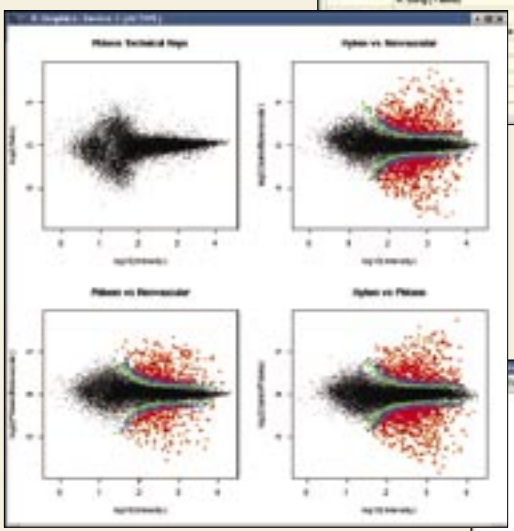
The faculty bring both their personal research interests and years of experience and education to the world-class Institute. As experts in their fields, VBI scientists contribute in the areas of computer science, biology, biochemistry, mathematics, microbiology, plant pathology, and more. Together, the Institute and its faculty create a team-oriented environment for cutting-edge research and development in infectious diseases.

Research

Dr. Dickerman's research addresses the broad area of genomic sequence analysis from an evolutionary perspective. By using phylogenetic analyses, he is able 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 addressing biological questions through comparative genomic analysis, 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. Dickerman adapts these methods to genome-scale analyses.





Dr. Allan Dickerman

Research Assistant Professor, VBI

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

Grants

co-PI. Strawberry Functional Genomics. VT ASPIRES. 01/01/03 - 12/31/04: $22,938.

co-PI. Essential Gene Functions in Arabidopsis Seed Development. National Science Foundation and Oklahoma State University. 9/1/01 - 8/31/05: $852,207.

PI. BDEI: Bioinformatics Prediction of Functions of Unculturable Microbes in Ecosystems. NSF/BDEI. 10/1/01 - 9/30/03. $72,204.

Current Publications

Beers, E., Jones A., and Dickerman A. 2004. The S8 serine, C1A cysteine and A1 aspartic protease families in Arabidopsis. Phytochemistry, 65:43-58.

Tzafrir, I., Pena-Muralla, I., Dickerman, A., Berg, M., Rogers, R., Hutchens, S., Sweeney, T.C., McElver, J., Aux, G., Patton, D., and Meinke, D. 2004. Identification of Genes Required for Embryo Development in Arabidopsis. Plant Physiology, 135: 1206-20.

Tzafrir, I., Dickerman, A., Brazhnik, O., Nguyen, Q., McElver, J., Frye, C., Patton, D., and Meinke, D. 2003. The Arabidopsis SeedGenes Project. Nucleic Acids Res, 31:90-3.

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.

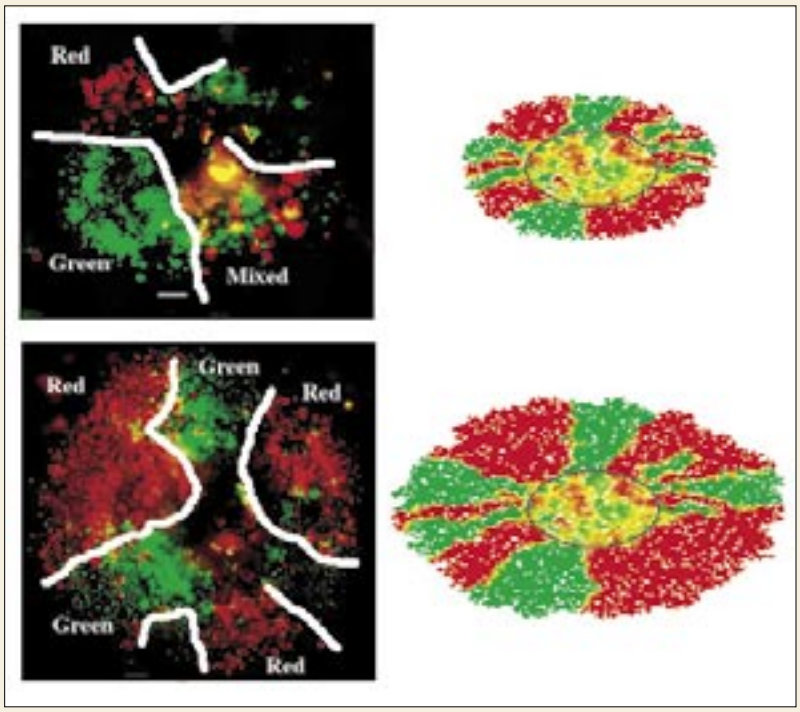
Current Publications

Engler, E., Duca, K., Nealey, P., Whitesides, G., and Yin, J. 2003. Propagation of Viruses on Micropatterned Host Cells. Biotechnology and Bioengineering, 81 (6): 710-725.

Research

While great strides were made during the twentieth century in treating infectious diseases of bacterial origin, researchers and doctors have not been as successful in controlling viral diseases. The classic approach to preventing infection is by prophylactic vaccination. Many viruses, however, because of their genetic lability, rapidly evade vaccine-induced immunity. Moreover, global citizens live in a world where 30 million people are infected with HIV and the threat of biological terrorism is growing. Therefore, the world must be prepared to cope with pathogens with which no vaccines have been 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. Duca focuses 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. 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.*

Research

Dr. Gillespie's principle research interests are in protein folding, molecular recognition, and self-assembly. Research in the Gillespie lab is currently focused on three major projects: the role of protein misfolding in human disease, the design and engineering of proteins with novel catalytic activities and structural properties, and the development of novel drugs for the treatment of infectious diseases.

Protein Misfolding and Aggregation Group
Protein misfolding has been implicated in the etiology of a variety of different diseases in animals and humans. A few well known examples include Parkinson's disease, Alzheimer's disease, and mad cow disease. These diseases each share the common feature of an otherwise normal protein undergoing an inappropriate self-assembly reaction to form insoluble aggregates that are cytotoxic and kill the surrounding cells and tissue. The mechanisms by which these aggregates form, how they kill cells, and how these processes can be reversed or stopped remain a mystery. The protein misfolding and aggregation group is actively seeking to gain a fundamental understanding of how proteins aggregate and how such aggregates affect the cells in which they occur. The group is currently focusing on the mechanism of aggregation for cystatin C, a protein involved in some forms of inherited stroke (human cerebral amyloid angiopathy) and which may be involved in amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), the most common paralytic disease of adults.

Protein Folding and Design Group
A major goal of the protein folding and design group is to understand how protein molecules fold into the complex, three-dimensional shapes that allow them to perform a huge range of functions in living systems, from forming hair to catalyzing chemical reactions. Understanding the complex interplay between the amino acid sequence of a protein, its interactions with the solvent environment, and the physical forces that govern these interactions will eventually allow us to build new proteins from scratch. Such protein molecules can revolutionize fields as diverse as materials science and medicine, allowing for the tailored design of molecules to treat individual patient's diseases or build "intelligent" self-assembling materials. This group is currently working on the design and synthesis of simple models for heme peroxidases, a class of enzymes involved in the electrochemical transformation of a wide-variety of substrates by redox chemistry. A current focus is the ability to engineer "tunability" of redox potentials, allowing for the control of substrate selectivity in enzymes with no well-defined substrate binding site.

Medicinal Chemistry and Infectious Disease Group
The medicinal chemistry and infectious disease group is seeking to understand the molecular mechanisms of bacterial and viral pathogenesis. This group is currently focusing on the mechanism by which members of the species *Yersinia* invade host cells to avoid the host's immune system and how invaded cells respond to the presence of the bacteria. This group is also working to develop novel antiviral agents aimed at the broad-spectrum inhibition of Flavivirus infections. The Flaviviruses include West Nile virus, Yellow Fever virus, Japanese Encephalitis virus and a host of other important human viral pathogens carried by insects.

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

Current Publications

Meyer, A.S., Gillespie, J.R., Walther, D., Millett, I.S., 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.

Dr. Ina Hoeschele

Research Professor, VBI
Professor of Statistics, VT

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

Grants

PI. Marker-assisted Selection in Dairy Cattle. Infigen Inc.09/1/97 – 02/29/04: $121,386.

PI. Developing Statistical Methods for Fine-Mapping of QTLs in Swine Populations. The Monsanto Company. 11/1/00 – 12/31/04: $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.

Current Publications

Freyer G., Sorensen, P., Kuhn, C., Weikard, R., and Hoeschele, I. 2003. Search for pleiotropic QTL on chromosome BTA6

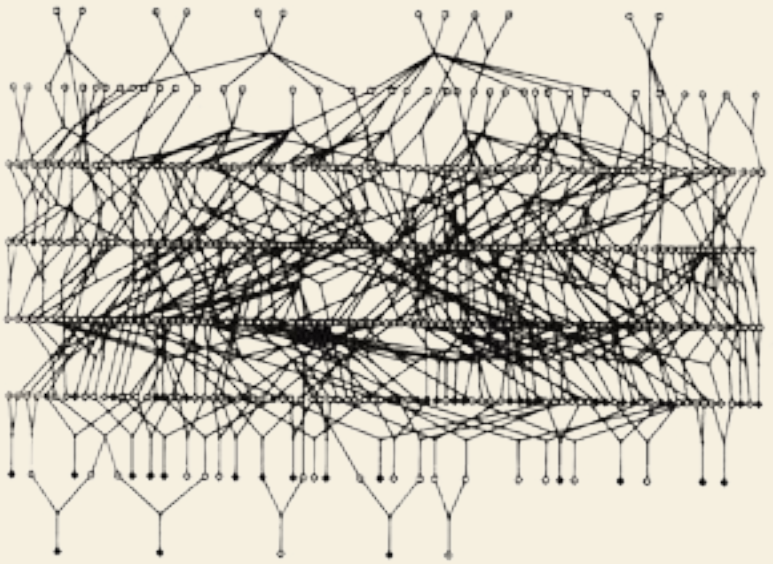
Hoeschele I. 2003. Mapping quantitative trait loci in outbred pedigrees. Handbook of Statistical Genetics, DJ Balding, M Bishop & C Cannings (eds.). Wiley, 477-525.

Gao, G. and Hoeschele, I. 2004. Conditional probability methods for haplotyping in pedigrees. Genetics (in press).

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. Quantitative Trait Locus (QTL) analysis of both phenotypic traits and gene expression profiles leads to the identification of candidate genes, gene network reconstruction, and aspects of metabolism and physiology otherwise missed.

This research has important implications in medicine, agriculture, and functional genomics. Dr. Ina 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. Applications of these methodologies include quantitative disease resistance and host-pathogen interactions in soybeans; design and analysis of gene expression experiments related to reproductive efficiency and nuclear transfer cloning gene mapping in complex human and swine pedigrees; and QTL and expression analysis of mouse models for cancers and cancer prevention treatments.



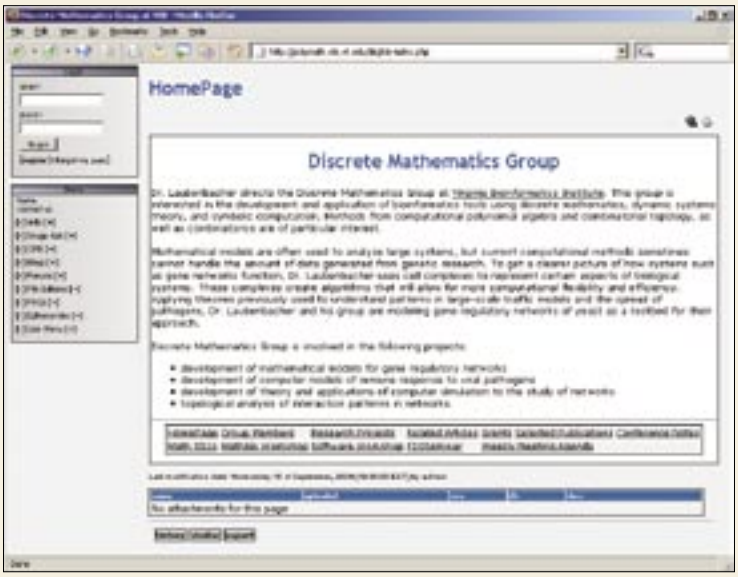
Human pedigree analyzed to map genes.

Research

Dr. Laubenbacher directs the Discrete Mathematics Group at VBI. The research conducted by the group revolves around the application of discrete mathematics and symbolic computation to problems in computational biology.

Projects include the modeling, simulation, and analysis of biochemical networks, modeling of the human immune response to viral pathogens, and the comparative analysis of DNA microarrays. An ongoing mathematical research project on finite dynamical systems supports these applications.

Laubenbacher is on the faculty of the Virginia Tech Mathematics Department and the interdepartmental Ph.D. program, Genetics, Bioinformatics, and Computational Biology (GBCB). He teaches courses on discrete modeling of biological systems and organizes the weekly university-wide Systems Biology seminar series.



Discrete Mathematics Group web site

Dr. Reinhard Laubenbacher

Research Professor, VBI
Professor of Mathematics, VT

1985 Ph.D., Mathematics
Northwestern University

Grants

PI. A New Mathematical Modeling Approach to Biochemical Networks, with an Application to Oxidative Stress in Yeast. NIH/National Institute of General Medical Sciences. 5/1/03 - 4/30/07: $1,306,410.

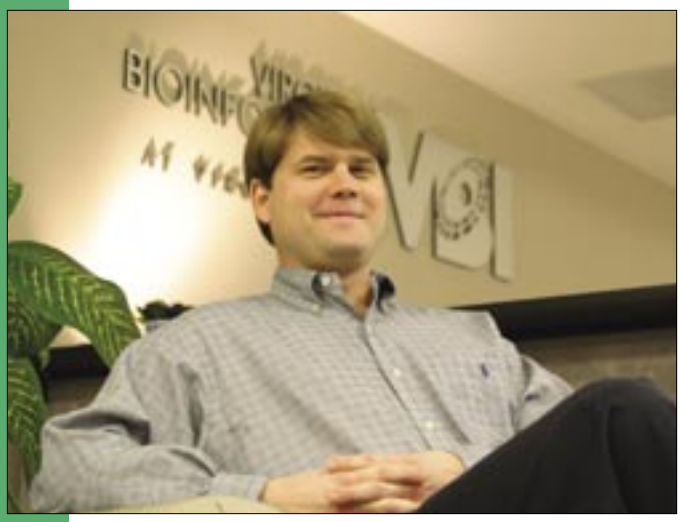
PI. Algebraic Algorithms for Cell Complexes. National Science Foundation/CARGO. 5/1/02 - 8/31/04: $44,777.

PI. Mathematical Foundation Computer Simulation. Los Alamos National Laboratory. 8/30/03 – 6/30/04: $91,459.

Current Publications

Laubenbacher, R. and Stigler, B. 2004. A computational algebra approach to the reverse-engineering of gene regulatory networks. J. Theor. Biol. (in press).

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



Dr. Christopher Lawrence

Research Associate Professor, VBI
Associate Professor of Biology, VT

1998 Ph.D., Plant Pathology
Auburn University

Grants

PI. The *Alternaria*-Brassicaceae Pathosystem as a Model for Necrotrophic Fungal-Plant Interactions. National Science Foundation Young Investigator Award, Plant Genome Program (Award DBI # 0227436). 5/1/04 – 11/30/06: $584,847.

Current Publications

Pruss, G., Lawrence, C., Bass, W., Li, Q., Bowman, L., and Vance, V. 2004. The potyviral suppressor of RNA silencing confers enhanced resistance to multiple pathogens. Virology, 320: 107-120.

Cramer, R. and Lawrence, C. 2004. Identification of *Alternaria brassicicola* genes expressed *in planta* during pathogenesis of *Arabidopsis thaliana.* Fungal Genetics and Biology, 41:115-128.

Geraats, B., Bakker, P., Lawrence, C., Achuo, E., Hofte, M. and van Loon, L. 2003. Ethylene-insensitive tobacco shows differentially altered susceptibility to different pathogens. Phytopathology, 93:813-82.

Pal-Bais, H., Vepachedu, R., Lawrence C., Stermitz, F. and Vivanco, J. 2003. Biochemical and molecular characterization of an enzyme responsible for formation of the anti-depressive compound, hypericin in St. John's wort. Journal of Biological Chemistry, 278: 32413–32422.

Cramer, R. and Lawrence, C. 2003. Cloning of a gene encoding an Alt a 1 isoallergen differentially expressed in the phytopathogenic fungus, *Alternaria brassicicola* during *Arabidopsis* infection. Applied and Environmental Microbiology, 69: 2361-2364.

Research

Dr. Lawrence's research is focused primarily on dissecting the intricate interplay of signaling molecules, effectors, and associated networks in plants and pathogenic microorganisms. In particular, his research centers on developing a model system for necrotrophic fungal plant pathogenesis and host response. The so-called "rots" are among the most destructive of all plant diseases and are caused by necrotrophic fungi that inflict substantial tissue damage on their host in advance of hyphal colonization. These fungi are tremendously important economically. Although the fungi represent just four percent of fungal diversity, they can cause approximately 80 percent of foliar losses in some parts of the world. Importantly, necrotrophs are hard to control with host resistance, which is usually quantitative in nature. Although they are sometimes considered unsophisticated in comparison to the more elegant biotrophs, necrotrophic pathogenic fungi must also be highly specialized in order to successfully avoid, or suppress, host resistance responses.

Lawrence's research is focused on the development of a model pathosystem for exploring interactions between plants and necrotrophic fungi. This pathosystem is being developed utilizing select species found within the plant family Brassicaceae, and the necrotrophic, toxin-producing fungus, *Alternaria brassicicola*. *A. brassicicola* causes black spot disease of cruciferous plants and is of worldwide economic importance in cultivated *Brassica* species such as canola, cabbage, and mustards. Besides being a true pathogen of cultivated plants, *A. brassicicola* can also serve as a "model" necrotroph because of its secretion of toxic proteins, metabolites, and enzymes that degrade plant cell walls during the infection process. No satisfactory resistance has been reported in cultivated species, but high levels of resistance to this fungus have been reported in weedy cruciferous plants, including the model plant, *Arabidopsis thaliana*. This makes the *A. brassicicola-Arabidopsis* pathosystem ideal for dissecting the signaling mechanisms underlying host plant resistance to this important class of pathogens. Knowledge generated from Lawrence's research program may provide critical insight into the design and implementation of novel biotechnology and chemically-based strategies for the control of necrotrophic pathogens in cultivated crops of major economic importance.

The Lawrence lab is also performing research on fungi that cause allergy, asthma, and infections in humans. *Alternaria* and *Aspergillus spp.* are some of the world's most important producers of major allergens in the world. In addition to the research being performed on the biological function of Alternaria allergens, Lawrence's lab is developing a high-throughput *Aspergillus fumigatus* functional genomics platform for a variety of downstream applications. Significantly, *A. fumigatus* can be considered one of the most important human pathogenic fungus worldwide and is responsible for a variety of diseases, including allergy, asthma, and often-fatal systemic mycoses in immuno-compromised patients. Lawrence's research in this area aims to aid in the understanding of fungal pathogenicity, immune response, and the ultimate design and discovery of novel therapeutics for treating fungal infections in humans.

Research

Dr. Lazar's research project is focused on the development of stand-alone microfluidic analysis platforms with mass spectrometric detection for bioanalytical applications.

Projects include the following areas of research:

1. Development of fully integrated microfluidic platforms that contain all the necessary elements for sample preparation prior to mass spectrometric detection: sample propulsion and valving elements, microreactors, separation/infusion channels, filters, mixers, interconnecting units, microdispensing elements.

2. Development of combined microfluidic/microarray structures.

3. Development of microchip-MS interfaces: ESI and MALDI.

4. Development of multiplexed microfluidic structures for high-throughput analysis.

5. Bioanalytical process implementation on the chip: sample cleanup, prefractionation, preconcentration, labeling, digestion, affinity selection, and separation.

6. Application of the above developed microfluidic-MS platforms for:

   a. Global proteomic data generation from cell extracts.

   b. Study of protein phosphorylation/glycosylation in complex proteomic samples.

   c. Cancer proteomics.

Microfluidic architectures for bioanalytical applications

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

Grants

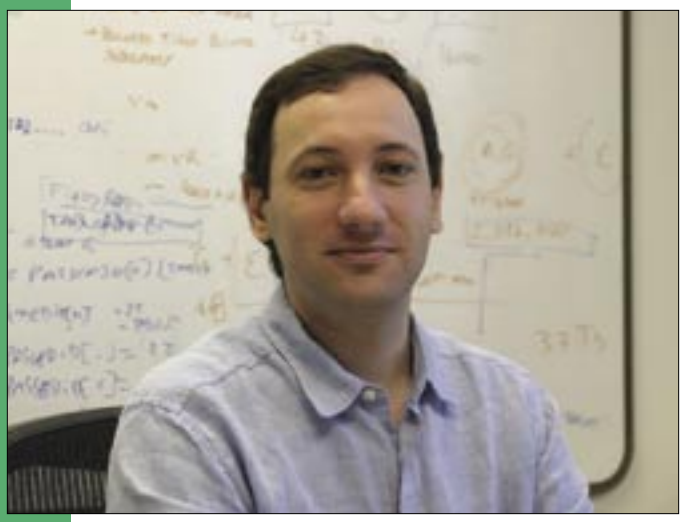
Equipment Donation - Nanospray Ionization Source for the LTQ Mass Spectrometer. Thermo Electron. 1/1/04. $10,000.

Selected Publications

Lazar, I. M., Li, L., Yang, Y., Karger, B.L. 2003. Microfluidic Device for Capillary Electrochromatography-Mass Spectrometry. Electrophoresis, 24(21): 3655-3662.

Patents

Microchip Integrated Multichannel Electroosmotic Pumping System, I. M. Lazar and B. L. Karger. Patent Application (priority US Application 60/292780).



Dr. Pedro Mendes

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

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

Grants

PI. An Integrated Approach to Functional Genomics and Bioinformatics in a Model Legume. National Science Foundation. 9/1/01 - 8/31/05: $1,592,347.

co-PI. Integrative Functional Genomic Resource Development in Vitis vinifera: Abiotic Stress and Wine Quality. University of Nevada-Reno. Two grant amounts -- 9/15/02 – 8/31/06: $886,511, and 9/1/03 – 8/31/04: $86,841. Total -- $973,352.

co-PI. Sun Center of Excellence in Bioinformatics. Sun Microsystems, Inc. 7/9/01 - 7/8/04.

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.

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

Research

Dr. Mendes' research focuses on computer simulation and analysis of biochemical networks, an area that has recently became known as systems biology. His research comprises three major areas: development of simulation software (Gepasi and COPASI), construction and analysis of dynamic models of biochemical networks, and bioinformatics support for functional genomics.

Mendes' software, Gepasi, is widely utilized worldwide for simulation of biochemical networks. This software facilitates mathematical modeling of biochemical networks without the need to program or write the mathematics explicitly. Together with Dr. Ursula Kummer's group at the European Media Laboratory in Heidelberg, Germany, Mendes and his team have been busy developing new simulation software called COPASI. Other research in the area of algorithms for simulation of biochemical networks, was carried out in collaboration with Dr. Julio Banga of the Instituto de Investigaciones Marinas (Vigo, Spain).

The Biochemical Networks Modeling Group, led by Mendes, is also active in constructing, simulating, and analyzing models of biochemical dynamics. One project consisted of creating algorithms for automatic generation of Artificial Gene Networks (AGN). These algorithms are also being used to study the effectiveness of statistical analyses on microarray data. This end is partially being realized through collaboration with Drs. Reinhard Laubenbacher and Vladimir Shulev (both at VBI). In another application of modeling, the group is investigating why some metabolomics data show strong correlations. The results of this inquiry will have application in other projects being pursued by the group, such as two additional projects that are studying the effect of stress on plants, or the Malaria project of Dr. Shulaev, which studies the mode of action in anti-malarial drugs.

While simulation and modeling are strong components of systems biology, large-scale experiments using the techniques of functional genomics are also essential. An approach that Mendes is pioneering with several collaborators is based on integrative studies that use the modern technologies of microarrays and mass spectrometry to measure thousands of molecules simultaneously. Mendes is leading the DOME project, a comprehensive database system to store, analyze, and retrieve such data. This is a multifaceted collaboration, funded through several federal grants, with Drs. Grant Cramer (University of Nevada, Reno), Rick Dixon (S.R. Noble Foundation, Ardmore, OK), Vladimir Shulaev (VBI), and more recently, Dr. Bruno Sobral's PathPort project at VBI.

Current Publications

de la Fuente, A., Brazhnik, P., and Mendes, P. 2004. Regulatory strength analysis for inferring gene networks. in Metabolic engineering in the post-genomics era (Kholodenko, B.N & Westerhoff, H.V. eds.) Horizon Bioscience, Wymondham, UK, pp. 107-137.

Lorence, A., Chevone, B.I., Mendes, P., and Nessler, C.L. 2004. myo-Inositol oxygenase offers a possible entry point into plant ascorbate biosynthesis. Plant Physiology 134, 1200-1205.

Moles, C.G., Mendes, P., and Banga, J.R. 2003. Parameter estimation in biochemical pathways: a comparison of global optimization methods. Genome Research, 13:2467-2474.

Mendes, P., Sha, W., and Ye, K. 2003. Artificial gene networks for objective comparison of analysis algorithms. Bioinformatics, 19: ii122-ii129.

Research

The work of Dr. Mukhopadhyay's laboratory is focused on extreme condition biology, with an emphasis on both fundamental and applied aspects. The growth and survival of microorganisms at high temperatures, as well as in the presence of highly toxic compounds, are the topics of investigation in his laboratory. This research encompasses the fields of experimental functional genomics, evolutionary biology, microbial diversity, and mechanistic biochemistry.

The fundamental research is directed towards understanding how *Methanocaldococcus jannaschii*, an archaeon, thrives at temperatures as high as 94°C and synthesizes a complete cell from hydrogen, carbon dioxide, and inorganic salts. This organism lives within submarine hydrothermal vents and produces methane, a green house gas and potential energy source. The reaction of seawater with hot basalt (1000°C) generates vent fluid that contains nutrients for *M. jannaschii*, as well as several toxic compounds. Mukhopadhyay and colleagues have discovered that *M. jannaschii* uses special tools, such as a novel sulfite reductase, for tolerating and making use of such materials.

Working with the methanogenic archaea, the laboratory has isolated a novel phosphoenolpyruvate carboxylase that is structurally different from the corresponding enzyme in plants. This new enzyme invites further thought on retooling the plant enzyme, a step that holds the promise of greatly improving the photosynthetic productivities in C3 plants such as rice.

Mukhopadhyay's laboratory is also investigating the mechanisms that *Mycobacterium tuberculosis* (the organism that causes tuberculosis, or TB) uses to remain dormant within the human body. These dormant cells are not killed by common anti-TB drugs.

The applied research falls within two areas:
- Natural gas production, mitigation of green house gas production, biodegradation of toxic compounds.
- Diagnosis and vaccine for tuberculosis.

Methane is a major component of natural gas. Recently, coalbed methane production has become an important determinant of the gas supply in the US. Mukhopadhyay's laboratory is investigating the possibility of enhancing coalbed production of methane, by use of the indigenous microbes. A similar effort is underway for eliminating the accumulation of toxic hydrogen sulfide and potentially explosive methane in coalmines. These activities are conducted in collaboration with Altuda Energy Corporation in San Antonio, Texas and with the support of the Department of Energy.

Mukhopadhyay, Dr. Endang Purwantini (Institute of Technology Bandung [ITB], Indonesia and VBI), several researchers at ITB, and a clinician from a sanatorium in Bandung, Indonesia are investigating the apparent TB immunity of some members of an almost fully infected population. In addition, they are profiling anti-*M. tuberculosis* antigens in a healthy subject, a subject with developing or active TB, and one who is responding to anti-TB drug therapy. The research is focused on a TB endemic area in Indonesia. The ultimate goal of the research is to develop affordable diagnostic and monitoring reagents, as well as effective vaccines for TB. The team has endorsement from a major vaccine manufacturer and is working in collaboration with the Division of Tuberculosis Control at the Maryland Department of Health and Mental Hygiene. The Government of Indonesia has awarded the group a grant to initiate this international collaboration.

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

Grants

PI. *In situ* Microbial Conversion of Sequestered Greenhouse Gases. Altuda Energy Corporation. 7/21/03 – 4/20/04: $37,995.

PI. Reduction of non-CO_2 Greenhouse gas emissions through in situ microbial conversion of methane. 7/21/03 – 4/20/04: $36,252.

Current Publications

Patel, H., Kraszewski, J., and Mukhopadhyay, B. The phosphoenolpyruvate carboxylase from *Methanothermobacter thermautotrophicus* has a novel structure. J. Bacteriol., 186:5129-5137.

Patrie, S., Charlebois, J., Quinn, J., Whipple, D., Mukhopadhyay, B., Marshall, A., Hendrickson, C., and Kelleher, N. Construction of a Hybrid Quadrupole/Fourier Transform Ion Cyclotron Resonance Mass Spectrometer for Versatile MS/MS Above 10 kDa. J. Am. Soc. Mass Spect., 15:1099-1108.

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.

Dr. Dharmendar Rathore

Research Assistant Professor, VBI
Adjunct Assistant Professor, Biology, VT

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

Current Publications

McCutchan, T. F., Rathore, D. and Li, J. 2004. Compensatory evolution in the human malaria parasite. Plasmodium ovale Genetics, 166: 637-640.

Rathore, D., Hrstka, S.C.L.,. Sacci, J. B Jr., de la Vega, P., Linhardt, R. J., Kumar, S., and. McCutchan, T. F. 2003. Molecular Mechanism of Host Specificity in *Plasmodium falciparum* Infection: Role of Circumsporozoite Protein. The Journal of Biological Chemistry, 278: 40905-40910.

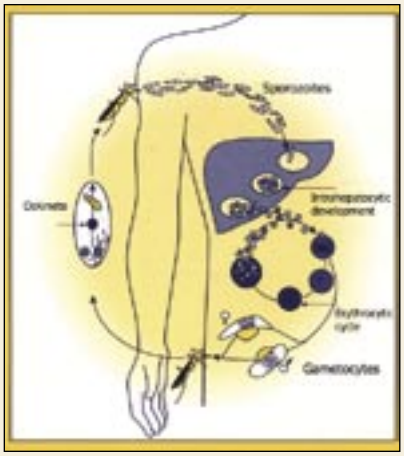
Chattopadhyay, R., Rathore, D., Fujioka, H., Kumar, S., De La Vega, P.,. Haynes, D., Moch, K., Fryauff, D., Wang, R., Carucci, D. J., and Hoffman, S. L. 2003. A *Plasmodium falciparum* protein containing an altered Thrombospondin Type I repeat domain is expressed at all stages of the parasite life cycle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

Research

Dr. Rathore's research is focused on investigating pathogenesis of parasitic organisms. His laboratory is investigating infectivity processes of Malaria and Cryptosporidiosis, two parasitic diseases caused by *Plasmodium* and *Cryptosporidium* parasites, respectively.

Malaria is one of the 10 most prevalent and deadly diseases with 40 percent of the world population at risk. Rathore investigates the pathogen and host factors involved in the onset and sustenance of malaria infection. His research has elucidated the molecular mechanism of interaction between Circumsporozoite protein, a predominant sporozoite surface antigen, and host liver cells. Rathore is now working on identifying other sporozoite antigens and their receptors that contribute towards the successful start of infection. This effort will lead to a greater understanding of both the parasite and host components involved in infectivity.

Cryptosporidiosis, a parasite-induced diarrhea, is a major health issue in immuno-compromised individuals. Cryptosporidiosis is caused by members of *Cryptosporidium* genus, a parasite that is transmitted by contaminated drinking water. Because of its rapid mode of transmission, the pathogen is now classified as a category B priority pathogen. Rathore's laboratory is investigating the mechanisms by which this pathogen is able to initiate an infection. In particular, his laboratory researches pathogen expressed proteins that assist the parasite in binding to the intestinal epithelia.



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

Research

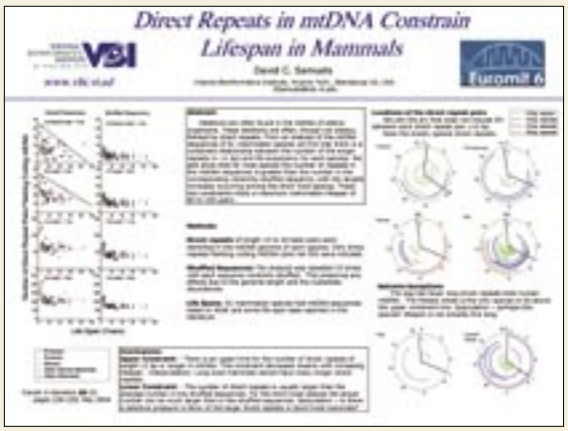
Dr. Samuels applies mathematics and simulation to biomedical research. His current projects involve AIDS medications, several genetic diseases, and degenerative neural diseases.

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 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 levels high enough to cause loss of cellular function. Because of these long time scales and the vulnerability of neurons and muscle cells, mutations in mtDNA are often associated with slowly developing neurodegenerative diseases. Samuels' research uses simulations to understand the development of mtDNA mutations over the human lifetime.

Rate of aging
Samuels' group is analyzing the human mitochondrial genome for sequence characteristics that make mtDNA susceptible or resistant to mutations. Through this analysis, reasons for the differences in the rate of aging between different species are being investigated.

Toxicity of AIDS medications
The current treatment for HIV/AIDS is highly active anti-retroviral therapy (HAART). This therapy involves the use of 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. Samuels' group is developing models of HAART effects on mitochondria with the goal of determining whether these toxic side effects can be minimized or eliminated.

Neuro-degenerative diseases
Many common neurological diseases (Alzheimer's, Huntington's, Lou Gehrig's and others) involve the disruption of axonal transport. Samuels' group is developing simulations of the transport of mitochondria within neurons to understand how this disruption damages the axon, thus causing the disease.



Dr. David Samuels

Research Assistant Professor, VBI

1990 Ph.D., Physics
University of Oregon

Postdoctoral Training:
Stanford University
NASA Ames and Emory University

Current Publications

Samuels, D. 2004. Mitochondrial DNA repeats constrain the life span of mammals. Trends in Genetics, 20(5): 226-229.

Samuels, D., Boys, R., Henderson, D., and Chinnery, P. 2003. A compositional segmentation of the human mitochondrial genome is related to heterogeneities in the guanine mutation rate. Nucleic Acids Research, 31(20): 6043-6052.

Taylor, R., Barron, M., Borthwick, G., Gospel A., Chinnery, P., Samuels, D., Taylor, G., Plusa, S., Needham, S., Greaves, L., Kirkwood, T., and Turnbull, D. 2003. Mitochondrial DNA mutations in human colonic crypt stem cells. Journal of Clinical Investigation, 112(9): 1351-1360.

Dr. João Setubal

Research Associate Professor, VBI

1992 Ph.D., Computer Science
University of Washington

Grants

co-PI. Genome Sequence and Analysis of Two Agrobacterium Biovars. University of Washington. 10/1/03 - 9/30/05: $188,640.

co-PI. Bioinformatic Resource Centers for Biodefense and Emerging/Re-emerging Infectious Diseases. NIH. 6/30/04 - 6/29/09.

Current Publications

Nascimento, A.L.T.O., Ko, A., Setubal, J.C., van Sluys, M.A., et al. 2004. Comparative genomics of two *Leptospira interrogans* serovars reveals novel insights into physiology and pathogenesis. J. Bacteriology, (in press).

Verjovski-Almeida, S., Setubal, J.C., Leite, L.C.C., Dias-Neto, E., et al. 2003. Transcriptome analysis of the acoelomate human parasite *Schistosoma mansoni*. Nature Genetics, 35(2):148-157.

Research

Dr. Setubal's research interests are in the area of computational tools and databases for genome annotation and analysis. The explosive growth of genomic data since 1995 has created exciting challenges for computational biologists. The simple task of managing this information is already daunting, due to the volume of data that exists. In addition, there is the task of extracting useful information from this data. This requires sophisticated computational tools and environments for analysis, comparison, and combination of different kinds of genomic information. It is at this level that Setubal concentrates his research efforts.

Setubal's current research—based on data from several different sources (sequencing data, gene expression data, literature information, etc.)—focuses on providing a single bioinformatics infrastructure for the genomic analysis of multiple microbial organisms.

As part of this infrastructure, Setubal plans to develop new genomics analysis tools. Partly because of his training as a theoretical computer scientist, Setubal is particularly interested in effective and efficient algorithms for solving problems derived from genomics research. In the real world of molecular biology, however, new algorithm design is not enough. An effective algorithm must work hand in hand with a deep understanding of the problem, and be solved with careful statistical analysis to ensure that algorithmic results become meaningful to biologists. Turning algorithms and their statistical basis into practical useful tools requires expertise in programming techniques.

Completing the entire cycle, from bench-derived biological problem to practical, effective computational tool, is one of Setubal's main goals. Examples of problems he is currently working on are computational detection of EST contaminants, improved methods for gene family construction, and computational recognition of bacterial lipoproteins.

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. Shulaev 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 in this report. Using Arabidopsis as a model organism to study metabolomics is also central to his research agenda.

Using traditional breeding or genetic engineering to improve plants' tolerance of stress, such as diseases, drought, high salinity, and temperature, has had limited success because of a poor understanding of the basic mechanisms underlying plant adaptive responses. The susceptibility of crops to these types of stresses directly impacts global agricultural productivity. A 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 Shulaev's group is focused on identifying novel protective metabolites and genes involved in biosynthesis and regulation using comprehensive metabolic profiling of plant-derived chemicals involved in stress response. 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.

In the area of abiotic stress tolerance, major research focus is on understanding the basic mechanisms of plant adaptation to osmotic and oxidative stress using *Arabidopsis thaliana* as model system. Another research area includes investigation of early events in fungal pathogenesis using Arabidopsis interaction with various biotrophic and necrotrophic fungal pathogens. Early events in pathogen recognition are very important in determining the specificity of responses to different pathogens.

Shulaev also uses metabolite profiling to characterize genes in Arabidopsis that currently have no assigned biochemical function. In collaboration with Dr. Eran Pichersky from the Department of Molecular, Cellular, and Developmental Biology at the University of Michigan, and Dr. Joseph P. Noel from Structural Biology Laboratory at the Salk Institute for Biological Studies, Shulaev's group uses metabolomics to elucidate the functions of genes belonging to the SABATH family of methyl transferases in Arabidopsis. Several of the enzymes belonging to this gene family are known to methylate important plant hormones.

Dr. Vladimir Shulaev

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.) 1/1/03 - 12/31/04: $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.

PI. Collaborative Arabidopsis 2010: Toward the characterization of all genes involved in the defense of plants against osidative stress. National Science Foundation (BIO). 9/1/03 – 7/31/07: $440,000.

Current Publications

Rizhsky, L., Shulaev, V., and Mittler, R. 2004. Measuring programmed cell death in plants. Methods Mol Biol., 282: 179-190.

Rizhsky, L., Liang, H., Shuman, J., Shulaev, V., Davletova, S., and Mittler, R. 2004. When defense pathways collide. The response of Arabidopsis to a combination of drought and heat stress. Plant Physiology, 134: 1683-1696.

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

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. Bioinformatic Resource Centers for Biodefense and Emerging/Re-emerging Infectious Diseases. NIH. 6/30/04 - 6/29/09: $10,361,305.

PI. Administrative Resource for Biodefense Proteomic Centers. Social & Scientific Systems, Inc./NIH. 6/30/04 - 6/29/09: $2,891,691.

PI. Development and Implementation of a High-Throughput Gene Annotation Pipeline and Accompanying DNA Sequence/Annotation Visualization System. Philip Morris USA. 4/1/04 - 3/31/05: $302,045.

PI. PathPort: A Common Asset for Biological Security. U.S. Department of Defense/RDECOM. 6/5/02 - 8/10/04: $4,000,000.

PI. Human Infectious Disease Bioinformatics Collaboratory. VT/Johns Hopkins University Bloomberg School of Public Health. 2/1/02 - 1/30/07: $5,000,000.

PI. Mid-Atlantic Regional Center of Excellence (MARCE) for Biodefense and Emerging Infectious Diseases. University of Maryland, NIAID, NIH. 9/4/03 - 9/3/08: $1,292,434.

co-PI. Genome Sequence of Phytophthora Sojae. USDA/CREES. 9/15/02 – 8/31/05.

PI. Commonwealth Technology Research Fund. CTRF Proposal with the College of William & Mary and INCOGEN, Inc. 11/1/01 - 10/31/04: $469,062.

PI. Collaborative Research in Bioinformatics. CTRF. 7/1/01 – 6/30/05: $1,270,058.

PI. ESTAP (Year 3). Noble Foundation (University of Nevada-Reno). 12/1/02 – 11/30/03. $86,841.

PI. 4 in 1 University Proposal/Virginia Bioinformatics Consortium. CTRF. 7/1/01 – 6/30/04: $375,000.

PI. Sun Center of Excellence in Bioinformatics. Sun Microsystems, Inc. 7/9/01 - 7/8/04. $75,000.

Research

Under Dr. Sobral's leadership, VBI has secured $43 million in bioinformatics research grants and contracts, and has grown to a staff of more than 210 in four years. Through collaborative projects, this represents significant economic growth for the Commonwealth of Virginia. VBI's research platform focuses on host-pathogen-environment interactions.

Cyberinfrastructure
Sobral's Cyberinfrastructure Group's research is focused on engineering robust, open frameworks for data and tool interoperability and integration for the life sciences. The Cyberinfrastructure Group strives to bring together data, powerful software programs, and scientific expertise with robust computational methods and hardware, to transform experimental data into knowledge that can be used to advance agricultural, environmental, and biomedical research. Two systems currently being developed, deployed, and leveraged for the various federal agencies include PathPort (a Web services federated platform for host-pathogen-environment data analysis based on client-side software, ToolBus), and ESTAP (Expressed Sequence Tag Analysis Pipeline).

PathoSystems Biology
Dr. Sobral's PathoSystems Biology Group's research applies comparative genomics, bioinformatics, and proteomics to understand and compare host-pathogen-environment interactions. The PathoSystems Biology Group performs integrated and computational experimental studies to understand Medicago truncatula-Sinorhizbium meliloti interactions; Mycobacterium tuberculosis-environment interactions, in collaboration with Dr. Biswarup Mukhopadhyay's Research Group; and Brucella-host interactions, in collaboration with scientists at the Virginia-Maryland Regional College of Veterinary Medicine (VMRCVM).

Continued on next page

Research

Continued from previous page

Dr. Yongqun "Oliver" He, Senior Research Associate in the PathoSystems Biology Group and Principal Investigator of a project, entitled "Gene Expression In Brucella-infected Macrophages," which is funded by the National Institutes of Health (NIH), is collaborating with other researchers at VBI and the Virginia-Maryland Regional College of Veterinary Medicine (VMRCVM) to study brucellosis. By employing microarray analysis, He identifies the host response genes involved in this interaction. The goal is to understand the genetic basis of virulence and host defenses with the eventual aim of developing effective strategies to treat and prevent infections.

In January 2004, Sobral presented testimony before the Federal Infectious Diseases Informatics Working Committee, and in April he presented before the National Interagency Genomics Sequencing Coordination Committee. Both of these meetings were held at the National Science Foundation (NSF) in Arlington, VA and were chaired by Dr. Rita Colwell, NSF Director. At both meetings, Dr. Sobral explained VBI's mission to understand the "disease triangle" (host-pathogen-environment interactions) as well as the importance of having a vigorous systems interoperation infrastructure.

American Phytopathological Society
In April, Sobral and his VBI sub-team members, Drs. Joel Gillespie, Allan Dickerman, and Chris Lawrence, participated in a Microbial Forensics Baseline Study conducted by the Institute for Defense Analyses (IDA). The team provided IDA responses to both technical and strategic questions regarding the analysis needs of bacterial, fungal, viral, prion, and/or associated biologically derived products as it relates to the goal of improving a rapid response to public health threats, including a biological attack. The baseline survey was carried out by IDA to identify the large gaps in knowledge and technological capabilities that must be addressed to help integrate and interpret microbial forensics data as it relates to national security problems involving the intended, planned, or actual use of biological weapons.

Sobral serves on both the NIH Roadmap BECON on the Catalyzing Team Science Panel and the NSF Cyberinfrastructure Life Sciences Panel. He also serves as a member of NIH's Special Interest Group in Systems Biology as well as the Department of Homeland Security's (DHS) National Biodefense Analysis and Counter Measures Center's (NBACC) Biosecurity Knowledge Center (BKC). In addition, he is a Panel Member of 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.

Current Publications

Lathigra, R., He, Y., Vines, R., Nordberg, E. and Sobral, B. 2004. A Biologist's View of Systems Integration for Systems Biology: The Pathogen Portal Project. Plenum Press. (In Press – Stadler Genetics Symposium).

Olden, K., Call, N., Sobral, B., Oakes, R. 2004. Toxicogenomics through the Eyes of Informatics: Conference Overview and Recommendations. Environmental Health Perspectives. Volume 112. 7: 805-807.

Dr. Brett Tyler

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 the Phytophthora Molecular Genetics Community. National Science Foundation. 5/1/02 - 4/30/06: $497,467.

PI. Dissecting Soybean Resistance to Phytophthora by QTL Analysis of Host and Pathogen Expression Profiles. 10/1/02 - 9/30/07: $6,186,049.

PI. Genome Sequence of Phytophthora sojae. U.S. Department of Agriculture-Cooperative State, Research, Education, and Extension Service. 9/15/02-9/14/05 $277,774.

PI. Genome Sequence of Phytophthora sojae. National Science Foundation Microbial Genetics. 9/15/02 – 8/31/05: $272,545.

PI. Function of Avirulence Genes in Phytophthora sojae Infection of Soybean. U.S. Department of Agriculture-Cooperative State, Research, Education, and Extension Service. 9/1/03 – 8/31/04: $144,650.

co-PI. BDEI: Bioinformatic Prediction of Functions of Unculturable Microbes in Ecosystems. NSF/BDEI. 10/1/01 – 9/30/03.

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 end result of the interaction is not just the result of two organisms interacting, but rather the result of a complex web of signals and responses exchanged among the vast diversity of microbes, microfauna, predators, and competing plants that comprise the environment of a plant.

The long-term goal of 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 to each other. Tyler is also interested in the application of similar approaches to the interactions of microbes with animals and humans.

Tyler's current research centers on identifying and characterizing the signals exchanged between plant pathogens (*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 also whole-genome approaches that include characterizing all the genes in a *Phytophthora* species and determining how they contribute to signaling and pathogenesis. His group has also begun research into bioinformatic approaches that will be needed to unravel the functioning of complex communities of micro-organisms and their interactions with macro-organisms, such as plants and animals.

Current Publications

Shan, W-X., Cao, M., Leung, D. and Tyler, B.M. 2004. The *Avr1b* Locus of *Phytophthora sojae* Encodes an Elicitor and A Regulator Required for Avirulence on Soybean Plants Carrying Resistance Gene *Rps1b*" Mol. Plant-Microbe Ints, 17(4): 394-403.

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

Selected Faculty Publications from Prior Years

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.

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.

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.

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.

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

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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.

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.

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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.

Geraats, BP, Bakker, P.A.H.M., Lawrence, C.B., Achuo, E.A. Hofte, M. and van Loon, L.C. 2003. Ethylene-insensitive tobacco shows differentially altered susceptibility to different pathogens. Phytopathology.93:813-821.

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.

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.

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.

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

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.

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- Visiting Professors
- College of Engineering Fellows
- VBI's Funded Partnerships

Collaborations & Partnerships

"Around the globe, collaborative investments in biomedicine and biotechnology have grown with the confidence that the convergence of biology with computing and nanotechnology will yield safer and more effective medicines. VBI partnerships and collaborations further the advancement of these science-to-real-life applications, while bringing the broader research community to southwest Virginia."

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

The advancement for innovation through science and technology depends on research collaborations and partnerships. Whether within the university setting or in conjunction with visiting professors, collaborative relationships give way to successful local, national, and global partnerships. VBI partners with government agencies, industry corporations, and other universities to build a strong multi-disciplinary research base, thus benefiting stakeholders and the public.

Visiting Professors

VBI visiting professors are from different disciplinary backgrounds and share an awareness with our research faculty—that a multi-disciplinary approach to research with fields such as biology, physics, mathematics, engineering, computer science, material science, bioinformatics, and nanotechnology give way to new technologies that have real-life biomedical and health applications.

Visiting professors collaborate with VBI faculty during and after their term at VBI, allowing for continued shared research findings and discoveries.

Dr. Volkan M. Atalay

Research Associate Professor, VBI
Sabbatical with Dr. Bruno Sobral
1993 Ph.D., Computer Science,
Universite René Descartes-Paris V, Paris, France

Dr. Atalay's research efforts at VBI are focused on developing and applying computational techniques for the analysis of biological data and modeling of biological processes at the molecular level. The broad aim of this research is to provide computational tools to assist researchers in understanding, explaining, and predicting the behavior of complex biological systems.

Atalay's approach is based on pattern recognition and statistical machine learning. In an eukaryotic cell, each protein is targeted to its specific cell localization where it is functionally active. Large-scale genome analysis provides a high number of putative genes to be characterized. Therefore, prediction of the subcellular localization of a newly identified protein is invaluable for the characterization of its function. The aim of the P2SL project is to design and develop a system that predicts the subcellular localization of proteins in eukaryotic organisms based on the amino acid content of primary sequences. The approach is to find the distribution of amino acid sub-sequences for each protein (class), and then to use this distribution as a feature for classification. This approach allows a classification independent of the sequence length. Atalay models each localization based on the distribution of sub-sequence occurrences using a self-organizing map (SOM). Class probability distributions are represented by samples as sub-sequence distributions over SOM. The prototype vectors in SOM also provide a normalization for similar sub-sequences, improving the classification rate. The distribution of amino acids can be learned via a neural network, based on their distributions, or can be determined by a support vector machine.

Selected Publications

Erdem, I.A., Erdem, M.E., Atalay, V., and Cetin, A.E. 2004. Vision-based Continuous Graffiti-like Text Entry System. Optical Engineering, 43: 553-558.

Özarar, M., Atalay, V., and Cetin-Atalay, R. 2003. Prediction of Protein Subcellular Localization Based on Primary Sequence Data. Lecture Notes in Computer Science, 2869: 611-618.

Mulayim, A.Y., Ulas, Y., and Atalay, V. 2003. Silhouette-based 3D Model Reconstruction from Multiple Images. IEEE Trans. On Systems, Man, and Cybernetics-Part B, Special Issue on 3D Image Analysis and Modeling, 33(4): 582-591.

Musa, M., de Ridder, D., Duin, R.. and Atalay, V. 2004. Almost autonomous training of mixtures of principal component analyzers,
Volume 25, Issue 9: 1085-1095.

Dr. Rengul Cetin-Atalay

Research Assistant Professor, VBI
Sabbatical with Dr. Bruno Sobral
1997 Ph.D., Biochemistry and Molecular Biology
Université de Paris-Sud, Orsay, France
1992 MD, Hacettepe Medical School, Ankara, Turkey

Dr. Cetin-Atalay's research focuses on the application of computational techniques for the analysis of post genomic data in relation to solid cancers. During the last two decades, genome studies have enabled accessibility of the entire genome. Current studies are now focused on identifying the function of genomes and proteomes in large scale. Genomic and post-genomic research accumulates enormous amounts of raw biomedical data. In this regard, it is essential to develop computational tools for storing, integrating, accessing, and analyzing this data effectively.

Cetin-Atalay has recently been involved in the development of PATIKA, a regulatory signaling database with a graph visualization component. She defined a cell signaling ontology for a comprehensive representation of cellular events, which is used by PATIKA, enabling integration of fragmented, or incomplete, regulatory pathway information, and supporting manipulation and incorporation of the stored data. Cetin-Atalay's current research interest is focused on obtaining an in-depth understanding of *in silico* system behavior in cancer cells under oxidative stress. The gene mutation data are being analyzed using machine-learning methods for construction of distinctive quantified mutation feature data. Such data can be coupled with a regulatory cell signaling network of cancer cells represented by PATIKA ontology. In this model, a node represents a gene where a stimulus is any relevant physical or chemical factor which influences the network and is itself not a gene or gene product. The networks can be modeled as a graph, in which nodes represent proteins, and edges indicate the quantified consequences of mutations on protein functions.

Selected Publications

Demir, E., Babur, O., Dogrusoz, U., Gursoy, A., Ayaz, A., Gulesir, G., Nisanci, G. and Cetin-Atalay, R. 2004. An Ontology for Collaborative Construction and Analysis of Cellular Pathways. Bioinformatics, 20(3): 349–356.

Irmak, M.B., Ince, G., Ozturk, M., and Cetin-Atalay, R. 2003. Acquired tolerance of hepatocellular carcinoma cells to selenium deficiency: a selective survival mechanism. Cancer Res., 63: 6707-6715.

Ozturk, M. and Cetin-Atalay, R. 2003. Biology of Hepatocellular Carcinoma, Gastrointestinal Cancers, A Companion to Sleisenger & Fordtran's GI and Liver Disease, edited by Anil K. Rustgi, James M. Crawford, Chapter 43, W.B. Saunders. Harcourt, Philadelphia.

Kocatas, A., Gursoy, A. and Atalay, R. 2003. Application of Data Mining Techniques to Protein-Protein Interaction Prediction. Lecture Notes in Computer Science, 2869: 316-323.

Dr. Jacky Snoep

VBI International Collaborator
Sabbatical with Dr. Pedro Mendes

Dr. Snoep, appointed at the University of Stellenbosch, South Africa and the Vrije Universiteit in Amsterdam, the Netherlands, has a long-standing collaboration with VBI. Specifically, Snoep has worked with Drs. Pedro Mendes, Reinhard Laubenbacher, and Vladimir Shulaev. His main research interest is in systems biology, where he uses a combined approach of theory, modeling, and experiment to gain a quantitative understanding of cellular processes on a molecular level.

In the second half of 2003, Snoep spent his sabbatical leave at VBI. During this time, he worked with VBI's Core Computational Facility to setup a mirror server for the JWS Online Cellular Modeling project. JWS is a repository of kinetic models that can be accessed and run over the Internet. The project was initiated in 2001 by Snoep and Brett Olivier at the University of Stellenbosch and is linked to the silicon cell project and the yeast systems biology group. JWS is used by international scientific journals and can be accessed from three mirror sites: http://jjj.vbi.vt.edu (USA), http://www.jjj.bio.vu.nl (Netherlands), and the main site, http://jjj.biochem.sun.ac.za (South Africa). During the same sabbatical leave, Snoep set up a fermentation facility at VBI consisting of four fully-controlled bioreactors. Such cultivation techniques are essential for the reproducible experimentation, which is important in many of the "-omics" studies. The equipment is currently being used to run a series of experiments for VBI's yeast systems biology project. Snoep revisited VBI in April 2004 and continues to collaborate with VBI researchers with further visits planned.

College of Engineering Fellows

VBI currently hosts four Virginia Tech College of Engineering (COE) fellows that work closely with VBI researchers on multi-scale modeling, software/hardware engineering, microfluidics, and image and signal process modeling projects. Together, VBI researchers and COE fellows propel their basic research findings into innovations that allow for practical applications, thus improving the quality of life and life expectancy.

Need For Speed: Computational Acceleration for Bioinformatics Applications

The focus of VBI Fellow Peter Athanas' work has been on computational acceleration for bioinformatics applications. Athanas, who is also a professor in Virginia Tech's Bradley Department of Electrical and Computer Engineering, hopes to ultimately enable new techniques of working with data through the use of extreme acceleration, aiming to raise the bar of the computational power available to bioinformatics researchers. These new techniques would enable biologists in both industry and academia to explore genome scale problems with unprecedented speed and thoroughness.

Athanas has worked with VBI's Allan Dickerman on grant proposal preparations to secure funding for necessary lab resources and computing instruments for an interdisciplinary group of students in computer engineering, computer science, and biology. Athanas and Dickerman have targeted Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs opportunities for this funding.

Since the start of his fellowship with VBI, Athanas has quickly identified new areas of possible research collaborations beyond his initial interest in genomic and protein sequence analysis. In the future, Athanas plans to target the research areas of MS/MS process enhancement, phylogenetic tree analysis, and protein folding.

Improving Image Quality: Discovering New Image Denoising Methods

VBI Faculty Fellow and Electrical and Computer Engineering Associate Professor Amy Bell is applying image processing techniques to wide-field, epi-fluorescent microscope images in an effort to understand how viral and host cells interact. Bell works with Satyabrata Rout, a VBI Research Associate, and VBI's Karen Duca. The team has developed a model—rooted in the physics of fluorescence microscopy—that significantly improves the noise mitigation in the images over previously established techniques. The ultimate goal is to transform the denoised images into a quantitative description of the viral propagation and host-virus interaction with signal processing techniques.

Bell and Duca have secured $71,700 through the VBI/Johns Hopkins Collaborative Initiative to identify new signal processing methods for characterizing complex phenotypes in host-virus interactions.

In the future, Bell will focus on investigating signal processing techniques for developing a characteristic profile of any unknown host-virus system, and identifying and investigating significant problems in the development of microdevices for understanding and characterizing viral propagation. In November 2004, Bell presented her team's image denoising research at Asilomar Signals and Systems Conference in Pacific Grove, California.

Models that Traverse Time and Space: Decreasing the Computational and Programming Burden

VBI College of Engineering Fellow Dr. Mark Jones is working on three areas of research at VBI as he maintains his Associate Professor status in the Bradley Department of Electrical and Computer Engineering at Virginia Tech.

First, Jones collaborates with VBI's Karen Duca on methods for multi-scale modeling as they apply to pathogen modeling. The goal of this work is to significantly decrease the computational load and programming burden associated with models that have widely varying time and space scales.

Second, Jones works with VBI's Allan Dickerman and another COE fellow, Peter Athanas, on the use of configurable computing devices (e.g., FPGAs) to accelerate computations in bioinformatics, particularly gene sequencing and ODE-based computations.

Third, Jones models the effects of eating and exercise-related decision making and behavior on aggregate populations using agent-based simulation in collaboration with VBI's Karen Duca and Associate Professor Eloise Coupey of the Virginia Tech Pamplin College of Business.

Jones has also participated as the multi-scale modeling expert for a number of multi-disciplinary VBI proposals submitted to National Science Foundation and National Institutes of Health.

Designing Bio-Analytical System on the Chip: Computational Microfluidic Simulations

VBI Fellow and Aerospace and Ocean Engineering Associate Professor Dr. Joseph Wang is working with VBI's Dr. Iuliana Lazar to develop stand-alone microfluidic analysis platforms with mass spectrometric detection for bioanalytical applications. Wang's research has focused on biofluidics in micro-scale devices. In such devices, the continuum fluid assumption may break down; the flow dynamics is dominated by electrokinetic forces, energy dissipation, and surface interactions; and there are no effective experimental means to diagnose the processes. Wang has developed first-principle based, hybrid fluid-particle simulation models to support experimental research and to explore design options for microfluidic systems. The computer codes are also being ported to run on parallel computers.

Lazar and Wang, along with other collaborators, recently won a university-wide competition to develop the Virginia Tech proposal for the Keck foundation on "The Keck Facility for Microfluidic Mass Spectrometric Analysis of Biological Systems." In the coming year, Wang plans to continue working on microfluidics modeling and microfluidic system design. He will also continue to help Lazar demonstrate the effectiveness of bioanalytical process implementation on the chip for the proteomic characterization of a model organism. Wang also plans to explore new research on nano-technology applications in bio-analytical devices.

VBI's Funded Partnerships

VBI welcomes partnerships from local Virginia Tech departments, national institutions, and global stakeholders. These funded partnerships come from universities, private corporations, and government agencies. Together, VBI and their funded partnerships will continue to venture beyond information by supporting common research missions, consequently allowing their research benefits to more quickly reach the public in a useable form.

Global

Acambis	Merck
Aventis Pasteur	Monsanto
European Media Labs, Heidelberg	Philip Morris - USA
IBM	Shire
I.D. bio	Sun Microsystems COE in Bioinformatics
Laboratoire Bordelais de Recherche Informatique (LaBRI, France)	

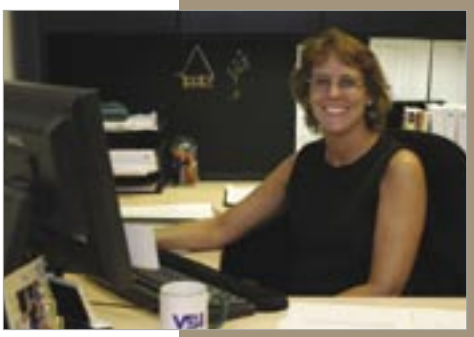
National

Altuda Energy Corporation	Samuel Roberts Noble Foundation
College of William & Mary	RDECOM (DoD)
Department of Energy Joint Genome Institute	Sunol
Drexel University	The Salk Institute for Biological Studies
East Tennessee State University	USAMRIID (DoD)
George Mason University	Uniformed Services University of the Health Sciences (DOD)
George Washington University	Univ. of California-Berkeley
Georgetown University	Univ. of Maryland
INCOGEN	Univ. of Michigan
Infigen, Inc.	Univ. of Missouri
IOMAI Corporation	Univ. of Pennsylvania
Johns Hopkins University	Univ. of Pittsburgh
List Biologicals	University Nevada-Reno
Los Alamos National Laboratory	Univ. of Vermont
MedImmune	Univ. of Virginia
NAV Baxter	Univ. of Washington
Ohio State University	Virginia Commonwealth University
Oklahoma State University	West Virginia University

Virginia Tech Departments

Aerospace and Ocean Engineering	Electrical and Computer Engineering
Biochemistry	Fisheries and Wildlife Science
Biomedical Science and Pathobiology, VMRCVM	Horticulture
Biology	Mathematics
Computer Science	Plant Pathology, Physiology, and Weed Science
Crop and Soil Environmental Sciences	Statistics

- Administration
- Finance



Administration & Finance

"VBI's administrative and finance team actively supports the Institute's multidisciplinary approach by providing services in a team-based environment for diverse research projects and experts in various areas of the sciences. With the institute's many accomplishments, VBI helps secure Virginia's research and economic future."

Lauren Coble
Associate Director, Administration and Finance
Virginia Bioinformatics Institute

VBI's administration and finance team internally supports the research mission of the Institute by providing centralized business services, including accounting and financial reporting, facilities management, human resources, and grant and contracts management. The team, now centrally located in Bioinformatics Facility I, provides a solid infrastructure for the Institute, allowing for continued growth and success. Together, members of the administration and finance team effectively work to accomplish complex tasks in support of VBI's dynamic research environment.

Administrative Staff

VBI's administration and finance team support the institute by handling all business matters, including administration, finance, accounting, facilities, human resources, and grants and contracts management. With their collaborative teamwork, the members help ensure the success and growth of VBI.

Bruno Sobral
Executive and Scientific Director

Lauren Coble
Associate Director of Administration and Finance

Dave Sebring
Associate Director of Government and Corporate Relations

Administration Team Members
(from left to right)

Lauren Coble
Associate Director of Administration and Finance

Cory Byrd
Business Analyst

Debi Darnell
Human Resources Recruiter

Sharon Lawson
Grants and Contracts Manager

Jennifer Craig
Human Resources Assistant

Lynn Byrd
Human Resources Coordinator

Bruno Sobral
Executive and Scientific Director

Catherine Phillips
Office Support Assistant

Matt Knefel
Program Support Technician

Stacey Lyons
Fiscal Technician, Sr.

Dave Sebring
Associate Director of Government and Corporate Relations

Not pictured:
Shannon Worringham
Executive Assistant to the Director

Grants and Contracts Team (GCT)

Securing funding for VBI's multidisciplinary research projects requires a dynamic administrative and financial infrastructure to carry out the complex tasks that accompany that process. The Grants and Contracts Team (GCT) is part of this group and is charged with the responsibility of providing technical assistance to VBI faculty preparing for contract or grant proposal submissions. In addition to providing technical writing, editing, financial reporting and coordination assistance, GCT researches and identifies funding opportunities from both federal and private agencies. The team also assists in the post-award reporting and coordination efforts.

VBI continues to receive competitive grants and contracts, and has thus far received $43 million in total awards. Among the largest grants and contracts to date is a five-year, $10.3 million contract from the National Institute of Allergy and Infectious Diseases (NIAID), a National of Institutes of Health (NIH) agency. The contract establishes a national Bioinformatics Resource Center (BRC) that will direct and coordinate a multi-organism relational database in support of infectious disease research, especially as it affects biodefense and naturally emerging infectious diseases. VBI also recently received $2.9 million from NIAID, as part of an $8.74 million contract with Social & Scientific Systems, Inc. (SSS) to establish an Administrative Resource for Biodefense Proteomic Research Centers. VBI will design and develop an integrated Data Management System to collect, store, view and query proteomics data from all NIAID-funded Proteomics Research Centers. These two contracts as well as the numerous awards won this past year, reveal the importance of VBI's cutting edge research efforts. The Institute's dynamic growth highlights the continued demand for GCT's technical assistance in helping to secure grants and contracts.

Grants and Contracts Team (left to right): D. Baker, D. Carlier, S. Lawson

Facilities Group

With VBI's expansion over the past year, the facilities needs for the institute have become more significant. The Facilities Management group has expanded with the addition of a Senior Facilities Manager, and has continued to evolve and adapt to its growing responsibilities.

Occupancy and readiness of VBI's new Bioinformatics Facility I research building on the Virginia Tech campus was successfully accomplished over the fall of 2003 and the winter and spring of 2004. Extensive preparations have continued in anticipation of the completion and occupancy of VBI's adjoining Bioinformatics Facility II building in the early spring of 2005.

The Facilities Group is actively involved with its internal customers—the researchers and support staff members of VBI—and with all authorities, departments, providers, and administrators in the realms of design, construction, renovation, commissioning, operations, and maintenance. Facilities personnel support all aspects of VBI's daily functions and long-term planning.

Facilities Group (left to right): D. Gibbs, D. Maxey, B. Waller, L. Correll, J. Uerz, E. Allen

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.

Financial Highlights

	2001	2002	2003	2004
Extramural Awards	0	$6,105,736	$13,177,004	$12,661,690
Facilities (square feet)				
Off-Campus	15,231	52,842	52,842	52,842
On-Campus	0	0	59,000	130,560
TOTAL	15,231	52,842	111,842	183,402
Private Gifts *	0	$2,155,706	$175,373	$650,000
Personnel **	25	92	148	210

Notes:

* *For FY 2002, VBI solicited equipment grants from IBM and SUN. In FY 2003, the Development Office facilitated the donation of equipment from Beckman Coulter. For FY 2004, VBI solicited a second equipment grant from IBM.*

** *Includes faculty, staff, graduate, and undergraduate students.*

VBI continues to expand its facilities and personnel in conjunction with its increase in sponsored funding. A significant portion of the extramural awards funds the salaries and fringe benefits of VBI researchers and staff.

VBI faculty have found that the in-house Service Centers, the Core Laboratory Facility, and the Core Computational Facility give an added advantage to their proposals and subsequent research. Travel expenditures encompass trips to conventions and conferences, which promote training and networking, and trips for collaborative meetings to further on-going research initiatives.

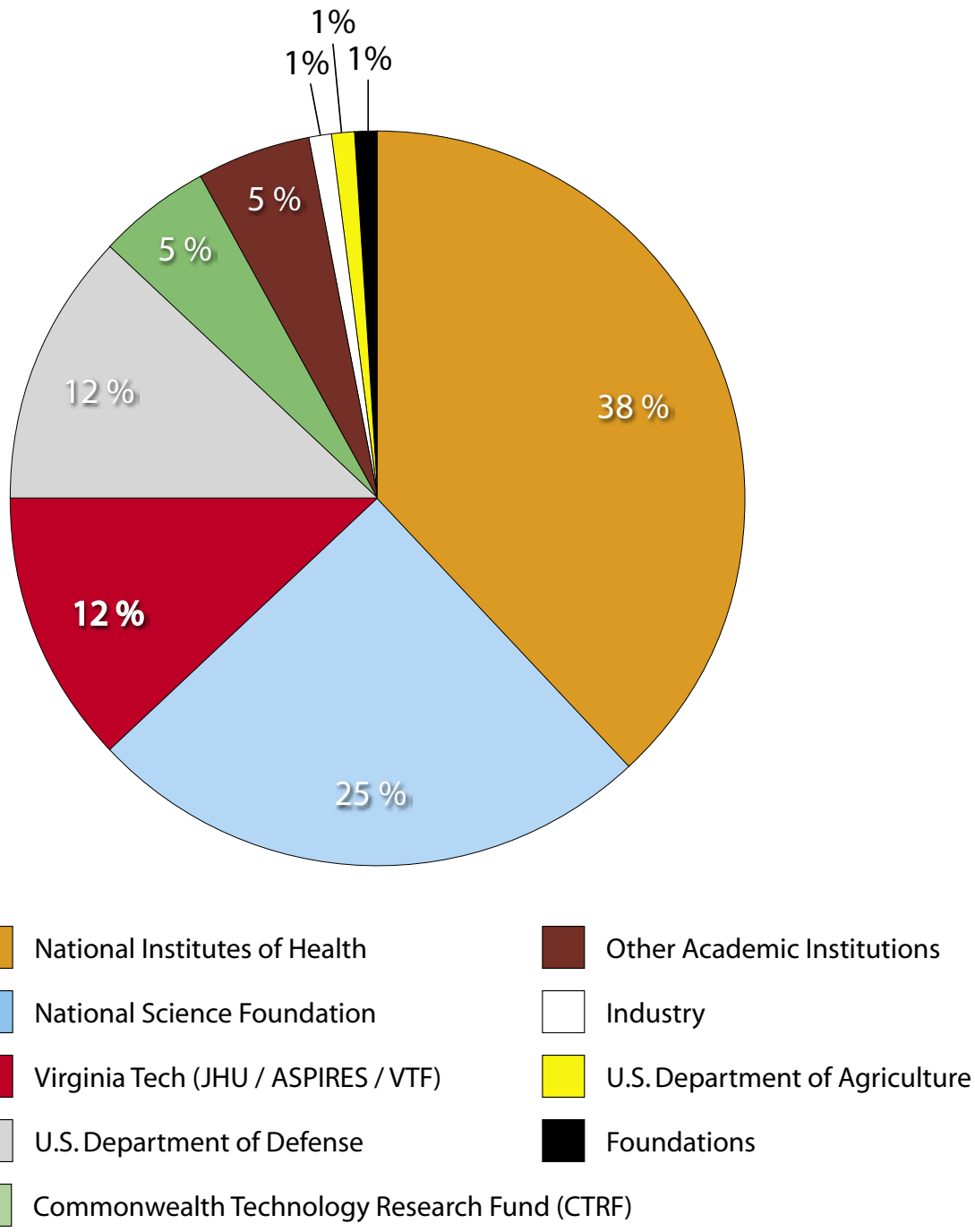
Whenever allowable, faculty purchase additional equipment necessary to perform their research. The facilities space includes laboratory and office space for faculty and their research teams.

VBI Research Portfolio by Funding Source

As of June 30, 2004

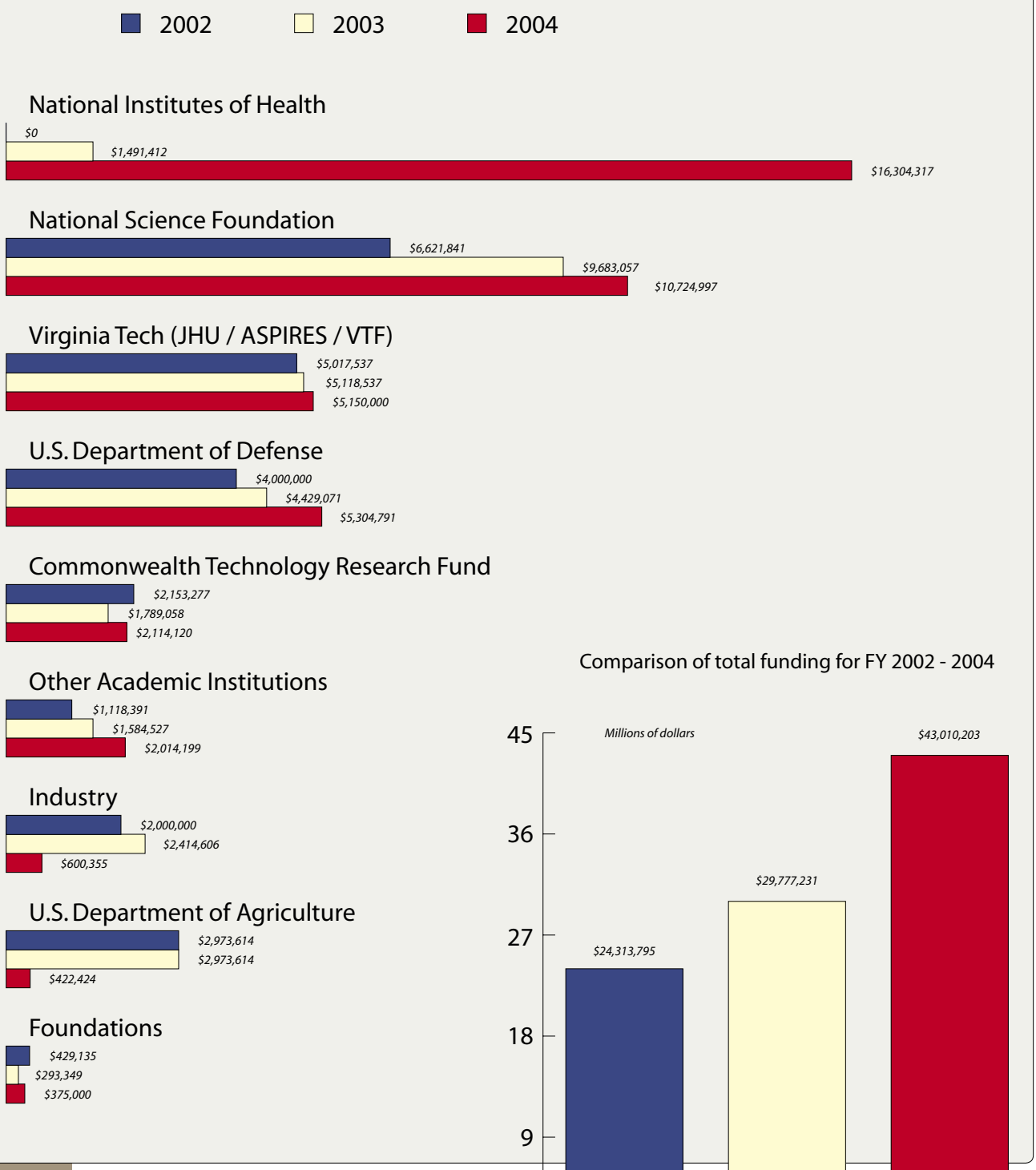
VBI's main source of federal funding in FY2003 was the National Science Foundation. However, in FY2004, VBI has secured two significant contracts from National Institutes of Health, now VBI's leading funding agency. VBI continues to receive significant support from NSF and other agencies and is anticipating an increase in United States Department of Agriculture funding.

Two of the projects are Federal flow-through from the Department of Energy as SBIR Phase I projects and will lead to further funding from this agency. Federal agencies comprise 76% of our total funding.



Three Year Comparison of Research Funding

2002 - 2004



Comparison of total funding for FY 2002 - 2004

VBI Active Grants

Sponsor	Investigators	Total Award	VBI Amount	Project
Altuda Energy Corporation / DoE	Biswarup Mukhopadhyay	$37,995	$37,995	In situ Microbial Conversion of Sequestered Greenhouse Gases
Altuda Energy Corporation / DoE	Biswarup Mukhopadhyay	$36,252	36,252	Reduction of non-CO2 Greenhouse gas emissions through in situ microbial conversion of methane
VT ASPIRES	Allan Dickerman	$22,938	$22,938	Dickerman ASPIRES
CTRF	Dennis Kafura Bruno Sobral	$2,500,201	$1,270,058	Collaborative Research in Bioinformatics
CTRF	Murray Black Gregory Buck William Pearson Jeffrey Plank Bruno Sobral	$1,500,000	$375,000	Virginia Bioinformatics Consortium
CTRF	Dennis Manos, et al. Maciek Sasinowski Bruno Sobral	$3,965,430	$469,062	Collaboration with the College of William & Mary and INCOGEN, Inc.
DoD	Bruno Sobral	$4,000,000	$4,000,000	PathPort: A Common Asset for Biological Security
Infigen, Inc.	Ina Hoeschele	$121,386	$121,386	Marker-assisted Selection in Dairy Cattle
Los Alamos National Laboratory	Reinhard Laubenbacher	$100,000	$91,459	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
NIEHS / NIH	Neysa Call Bruno Sobral	$50,000	$50,000	Common Ground for Human Disease Research
NIH / NIGMS	Reinhard Laubenbacher Pedro Mendes Vladimir Shulaev	$1,306,410	$1,306,410	A New Mathematical Modeling Approach to Biochemical Networks, with an Application to Oxidative Stress in Yeast
NIH / NIAID	Bruno Sobral Joao Setubal	$10,361,305	$8,792,761	Bioinformatics Resource Centers for Biodefense and Emerging/Re-emerging Infectious Diseases
NIH / NIAID	Bruno Sobral Zhijian Tu Chunhong Mao	$1,357,113	$60,600	Characterization and Organization of Transposable Elements
NIH / NIAID	Oliver He	$601,167	$420,817	Gene Expression in Brucella-infected Macrophages
NIH / NIGMS	Ina Hoeschele	$299,328	$299,328	Polygenic Linkage Disequilibrium and Linkage Mapping

DoE - United States Department of Energy
VT ASPIRES - Virginia Tech's A Support Program for Innovative Research Strategies
CTRF - Commonwealth Technology Research Fund
DoD - United States Department of Defense
NIEHS - National Institute of Environmental Health Sciences
NIH - National Institutes of Health
NIGMS - National Institute of General Medical Sciences
NIAID - National Institute of Allergy and Infectious Diseases

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VBI Active Grants

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Sponsor	Investigator	Total Award	VBI Amount	Project
NSF	Allan Dickerman Brett Tyler	$100,000	$72,204	Bioinformatics Prediction of Functions of Unculturable Microbes in Ecosystems
Oklahoma State Univ. / NSF	David Meinke, et al. Allan Dickerman David Patton, et al.	$2,326,667	$852,207	Essential Gene Functions in *Arabidopsis* Seed Development
NSF	Reinhard Laudenbacher Bernd Sturmfels	$100,000	$44,777	Algebraic Algorithms for Cell Complexes
NSF	Pedro Mendes Richard Dixon	$3,587,432	$1,592,347	An Integrated Approach to Functional Genomics and Bioinformatics in a Model Legume
NSF / USDA	Craig Nessler Boris Chevone Pedro Mendes	$199,999	$34,769	Metabolic Engineering of Plant Vitamin C Biosynthesis for Improved Nutrition and Health
NSF	Brett Tyler Bruno Sobral	$497,467	$497,467	Communication, Training, and Resources for the *Phytophthora* Molecular Genetics Community
NSF	Brett Tyler M.A. Saghai Maroof Glenn Buss Ina Hoeschele Anne Dorrance Steve St. Martin	$6,764,465	$6,186,049	Dissecting Soybean Resistance to *Phytophthora* by QTL Analysis of Host and Pathogen Expression Profiles
NSF	Chris Lawrence	$963,008	$584,847	The Alternaria-Brassicaceae Pathosystem: A Model For Necrotrophic Fungal-Plant Interactions
NSF	Vladimir Shulaev	$440,000	$440,000	Collaborative Arabidopsis 2010: Toward the characterization of all genes involved in the defense of plants against oxidative stress
Philip Morris	Bruno Sobral Dana Eckart	$302,054	$302,045	Development and Implementation of a High-throughput Gene Annotation Pipeline and Accompanying DNA Sequence/Annotation Visualization System
Social & Scientific Systems, Inc. / NIH	Bruno Sobral	$8,743,151	$2,891,691	Administrative Resource for Biodefense Proteomic Centers
Sun Microsystems, Inc.	Bruno Sobral Pedro Mendes	$75,000	$75,000	Sun Center of Excellence in Bioinformatics
Thermo Electron	Iuliana Lazar	$10,000	$10,000	Equipment Donation - Lazar - Nanospray Ionization Source for the LTQ Mass Spectrometer

NSF - National Science Foundation
USDA - United States Department of Agriculture
NIH - National Institutes of Health

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VBI Active Grants

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Sponsor	Investigators	Total Award	VBI Amount	Project
USDA/CREES , NSF, DoE*	Brett Tyler Bruno Sobral	$2,334,000	$550,319	Genome Sequence of *Phytophthora sojae*
USDA/CREES	Brett Tyler	$230,000	$144,650	Function of Avirulence Genes in *Phytophthora sojae* Infection of Soybean
Univ. of Maryland / NIH / NIAID	Bruno Sobral	$44,335,674	$1,292,434	RCE: Regional Center for Excellence for Biodefense and Emerging Infectious Disease
Univ. of Nevada-Reno / NSF	Pedro Mendes	$3,609,951	$886,511	Integrative Functional Genomic Resource Development in *Vitis Vinifera*: Abiotic Stress and Wine Quality
Univ. of Nevada-Reno	Pedro Mendes Bruno Sobral	$86,841	$86,841	Integrative Functional Genomic Resource Development in Vitis Vinifera: Abiotic Stress and Wine Quality - ESTAP Portion
Univ. of Nevada-Reno / Samuel Roberts Noble Foundation	Bruno Sobral John Cushman Greg May	$161,508	$161,508	Collaborative Development of an EST Database and Analysis Pipeline
Univ. of Virginia/ Tobacco Foundation	Karen Duca	$375,000	$375,000	Identification of Genes that Predispose Individuals to Smoking-Related Diseases
Univ. of Washington	Joao Setubal	$188,640	$188,640	Genome Sequence and Analysis of Two Agrobacterium Biovars
USAMRIID	Susan Martino-Catt	$47,466	$47,466	Microarray Analysis to Indentify Mechanisms of Action of Bw Agents
VT ASPIRES	Vladimir Shulaev Allan Dickerman Richard Veilleux Joel Shuman	$100,000	$100,000	Strawberry Functional Genomics
VT / John Hopkins Univ. 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.

USDA/CREES - United States Department of Agriculture/Cooperative State Research, Education, and Extension Service
NSF - National Science Foundation
DoE - United States Department of Energy
NIH - National Institutes of Health
NIAID - National Institute of Allergy and Infectious Diseases
USAMRIID - United States Army Medical Research Institute of Infectious Diseases
VT ASPIRES - Virginia Tech's A Support Program for Innovative Research Strategies

Two of the newest projects that have received National Institutes of Health funding involve work in biodefense and will both continue for five years. The largest, with funding from National Institute of Allergy and Infectious Diseases, is to establish a Bioinformatics Resource Center for Biodefense, and will include information on eight pathogens. The other, with VBI as a subcontractor, will allow VBI to help construct a Biodefense Proteomic Center.

Work continues on the Mid-Atlantic Regional Center for Excellence and has helped promote additional collaborations with other institutions. The National Science Foundation (NSF) continues to be a prime source of funding and VBI is exploring further options with shared funding opportunities between NSF and the United States Department of Agriculture. The project with United States Army Medical Research Institute of Infectious Diseases is anticipated to be the first of many future collaborations and will form a bridge for work with other federal agencies.

VBI's Policy Advisory Board

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

Members of the Board of Visitors

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Dr. Hemant Kanakia

At-Large Recommended by the University

Mr. John Alderson

Mr. Lawrence H. Framme, III

The Honorable Thomas D. Rust

Mr. Gary P. Clisham

Representative from the Tobacco Indemnification and Community Revitalization Commission

Mr. Clarence D. Bryant, III

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Dr. Christoph von Arb

Mr. Buddy G. Beck

Mr. R. J. Kirk

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Dr. Charles Steger

Mr. Minnis Ridenour

Dr. Mark McNamee

Dr. Bruno Sobral

Others/Senior Staff

Mr. M. Dwight Shelton, Jr.

Mr. Dave Sebring

Ms. Lauren Coble

The VBI 2004 Annual Report was created and designed by the VBI Public Relations and Outreach Team. The Institute recognizes Ivan Morozov for the report design. Susan Bland, Robin Oakes, and Valencia Person facilitated the development in collaboration with the research teams at VBI.

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