THE VIRGINIA BIOINFORMATICS INSTITUTE

2009 annual report

DEPARTMENTS

FEATURES

ABOUT THE COVER

The cover of the 2009 annual report shows *Azotobacter vinelandii* DJ grown under nitrogen-fixing conditions on an agar plate containing Burk's medium. The soil background resembles the organism's natural habitat. Reproduced with the kind permission of the American Society of Microbiology (Copyright 2009).
Final composition of photograph: Ivan Morozov, Virginia Bioinformatics Institute.

Message from the President

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

The Virginia Bioinformatics Institute (VBI) is rapidly approaching its 10th anniversary, an opportunity not only to look back on its many achievements but also to look forward to new opportunities. VBI was established as part of Virginia Tech in 2000. The goal was to create a collaborative research environment that would bring together talented researchers from different disciplines in the life sciences. Expertise, commitment, and an entrepreneurial spirit have been instrumental in shaping what is today an internationally competitive research institute.

The past year has seen changes at VBI. Bruno Sobral, the founding director, has returned to research. Bruno has been the driving force behind the rapid growth of VBI, transforming it from a start-up enterprise into a successful institute with more than 200 highly-qualified employees. He remains at VBI with renewed focus on securing significant funding for the large-scale, transdisciplinary projects that serve as the foundation of the institute, a mission that VBI is uniquely organized to pursue.

As a validation of the benefits offered by this approach, Ninth District Congressman Rick Boucher joined senior Virginia Tech officials in October 2009 to announce the award of approximately $27 million from the National Institutes of Health to Sobral's Cyberinfrastructure Group. The five-year, $27,670,448 contract from the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, is the largest, one-time federal award in the history of Virginia Tech.

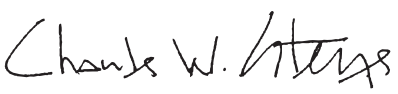
Also in October, VBI and the university welcomed Harold "Skip" Garner as the institute's new executive director. Dr. Garner joined VBI from the University of Texas Southwestern Medical Center, where he was professor of biochemistry and internal medicine and the Philip O'Bryan Montgomery Jr., M.D. Distinguished Chair in Developmental Biology. Before going to the University of Texas Southwestern Medical Center in 1994, he served as a senior staff scientist and founder of the Bioscience Division at General Atomics in San Diego.

Dr. Garner brings an impressive array of skills and experiences to the university at an exciting point in the growth of our research programs. His mandate is to build on VBI's scientific achievements; to strengthen collaborations with our colleges; to foster innovation throughout our campus, including in undergraduate research; and to embrace the research and education possibilities offered by the new Virginia Tech Carilion School of Medicine and Research Institute. Dr. Garner's expertise and fit with Virginia Tech's many innovative scientific programs will be a key asset in moving forward as we look to further developing the institute's significant potential.

Researchers at VBI continue to make discoveries that are transforming our understanding of the natural world. I would like to take this opportunity to thank them all for the commitment they have shown to the university's efforts to advance discovery, learning, and engagement.

The global economy is showing some signs of recovery. However, it remains an extremely challenging time for the higher education community. Virginia Tech is faced with reductions in funding that are very large, but with judicious planning that adheres to our strategic plan and a focus on mission, we will ably manage this significant downturn as we have in the past.

I trust that we will again emerge from the current budgetary crisis as strong as ever. We will endeavor to maintain excellence in our academic enterprise and continue to provide the high-quality research that defines Virginia Tech.



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

Letter from the Director

VIRGINIA BIOINFORMATICS INSTITUTE AT VIRGINIA TECH

Since becoming Executive Director of the Virginia Bioinformatics Institute (VBI) in November 2009, I have had the opportunity to experience in person the collaborative science and talented employees behind the success of the institute. VBI is an excellent example of how to integrate different disciplinary approaches into groundbreaking scientific programs that span policy and decision informatics, cyberinfrastructure, and biosystems research. It also offers many exciting paths for further development.

As the institute's new director, my job is to build on VBI's achievements and identify new opportunities that will provide significant growth. This is a very exciting time to be working at the interface of biology, medicine, and the physical sciences. I believe we are in an ideal position to take advantage of the many exciting developments that are materializing in fields such as genetics, computational biology, and clinical research.

VBI will continue to build on its strengths as one of the leading international institutes for informatics and infectious disease research. Many of the challenges that exist in bioinformatics, computational biology, and biomedicine demand next-generation High Performance Computing environments. We will be working hard to deliver innovative computing solutions and environments that will enable researchers to make sense of the tremendous amounts of new data that are being generated by biological investigations. We will also be pursuing new strategic directions, for example human disease and the use of a wide range of -omics-based research initiatives.

In addition to national and international partnerships, we will be looking closely at the many possibilities for collaborative research on our own doorstep. Opportunities in the life sciences are opening up across the Virginia Tech campus, including possibilities to partner with translational science initiatives at the recently created Virginia Tech Carilion School of Medicine and Research Institute. VBI will work closely with Virginia Tech and key partners as part of its mission to drive science, facilitate policy and decision-making, and produce meaningful outcomes for society. The institute will also be moving ahead with our business development efforts to translate VBI's research achievements into commercial undertakings.

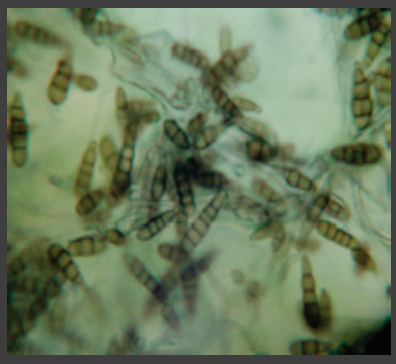
Readers of this annual report will learn how VBI research is helping scientists discover the way pathogens damage plant and animal systems, the impact of large-scale international genome sequencing projects on new applications in biotechnology, as well as how systems biology is poised to improve our clinical understanding of diseases like cancer. The White House has recently emphasized, and is acting upon, its aim to improve the participation of American students in Science, Technology, Engineering, and Math (STEM). This is a key priority if our nation is to remain competitive in the global scientific community. Readers of this report will learn how Virginia Tech initiatives, like Kids' Tech University, are helping to address this need and how educational innovation close to home is encouraging young children to pursue much-needed, technology-related careers.

This is a very exciting time to be joining VBI. I look forward to working with the institute's dedicated employees and partners as we invent the future for this remarkable institute.

Harold "Skip" Garner, Ph.D.
Executive Director, Virginia Bioinformatics Institute

Highlights 2008

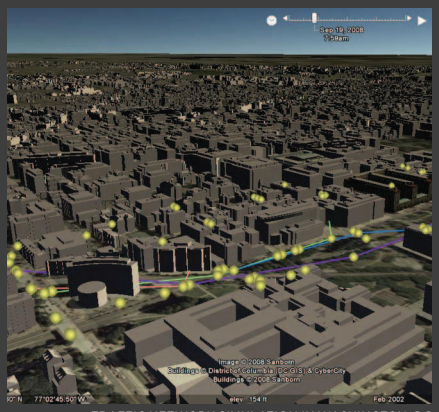
AUGUST // KEY TO VIRULENCE PROTEIN ENTRY INTO HOST CELLS DISCOVERED VBI researchers identify the region of a large family of virulence proteins in oomycete plant pathogens that enables the proteins to enter the cells of their hosts. The protein region contains the amino acid sequence motifs RXLR and dEER and has the ability to carry the virulence proteins across the membrane surrounding plant cells without any additional machinery from the pathogen. Once inside the plant cell, the proteins suppress the immune system of the plant allowing the infection to progress.



SEPTEMBER // INNATE IMMUNE SYSTEM TARGETS ASTHMA-LINKED FUNGUS FOR DESTRUCTION A study completed by researchers at the Mayo Clinic and VBI shows that the innate immune system of humans is capable of killing a fungus linked to airway inflammation, chronic rhinosinusitis and bronchial asthma. Their results revealed that eosinophils, a particular type of white blood cell, exert a strong immune response against the environmental fungus *Alternaria alternata*. These groundbreaking findings shed light on some of the early events involved in the recognition of *A. alternata* by the human immune system.

OCTOBER // BIOTHERAPEUTICS INC. - NEW NUTRACEUTICALS BUSINESS LAUNCHED AT VIRGINIA TECH A new company is created as a spin-off from Virginia Tech to develop nutritional interventions against chronic inflammatory and infectious diseases. BioTherapeutics Inc. promotes health and well-being through the discovery and development of nutraceuticals - naturally occurring molecules that can be integrated into nutritional products and functional food ingredients. The company was founded by VBI Associate Professor Josep Bassaganya-Riera, with the purpose of introducing novel Virginia Tech-developed nutraceutical technologies into the marketplace.

JULY AUGUST SEPTEMBER



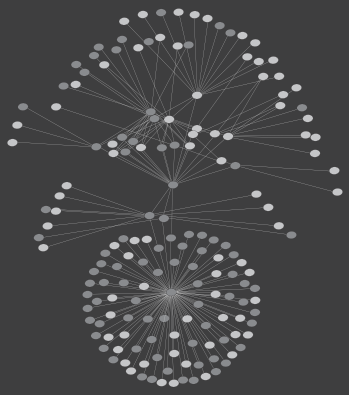
TRAFFIC NETWORK SIMULATION IN WASHINGTON, DC

SEPTEMBER // NSF AWARDS $1,000,000 TO DEVELOP ARTIFICIAL MARKET FOR DYNAMIC SPECTRUM SHARING IN WIRELESS NETWORKS The National Science Foundation (NSF) awards a four-year, $1,000,000 grant to the Network Dynamics and Simulation Science Laboratory (NDSSL) at VBI to develop high-performance computer modeling tools for wireless telecommunication networks. The NDSSL will work with the State University of New York at Stony Brook and Alcatel-Lucent Bell Labs to develop models and algorithms that support the work of policy- and decision-makers who want to design efficient wireless spectrum markets.

OCTOBER // VBI OFFERS FELLOWSHIPS FOR GRADUATE WORK IN TRANSDISCIPLINARY SCIENCE VBI, in collaboration with Virginia Tech's Ph.D. program in Genetics, Bioinformatics, and Computational Biology (GBCB), provides substantial fellowships in support of graduate work in transdisciplinary team science. The Transdisciplinary Team Science Fellowship Program for the Life Sciences was developed for students interested in joining the Virginia Tech GBCB Ph.D. program. With the goal of connecting students with accomplished researchers working in a team science environment, these fellowships cover the costs of the students' first two years in the program.

NOVEMBER // KIDS' TECH UNIVERSITY LAUNCHED AT VIRGINIA TECH A pioneering educational program designed to excite children about science and provide them with a real university experience was offered for the first time in the United States thanks to the efforts of a professor from VBI and his team. Kids' Tech University is a groundbreaking program for kids between the ages of 9 and 12 that gives children the opportunity to participate in a series of engaging scientific activities, including lectures presented by scientific researchers who also have a strong track record in the communication of science. The goal is to expose kids early to cutting edge research in science, math, engineering and technology in a setting that children find both exciting and fun.

DECEMBER // VBI ANNOUNCES PARTNERSHIP WITH MATHEMATICAL BIOSCIENCES INSTITUTE VBI establishes a new partnership with the Mathematical Biosciences Institute (MBI) to provide VBI researchers with further educational and research opportunities. The new initiative supports the development and application of mathematical, statistical, and computational methods for solutions to problems in the biosciences. VBI's participation in the MBI Institute Partner Program will subsidize travel expenses for VBI faculty and students to participate in research and education programs at MBI, as well as provide support for workshops and conferences to be held in Blacksburg.

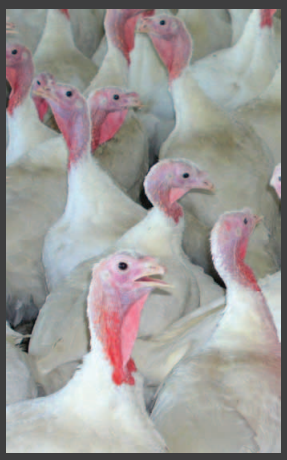


DECEMBER // RESEARCHERS LAUNCH PIG Researchers at VBI and the Department of Computer Science at Virginia Tech launch a publicly available database that allows users to investigate how different proteins interact with each other when pathogens infect their hosts. Protein-protein interactions play a key role in initiating infection for many pathogens. PIG - the pathogen interaction gateway - is a one-stop shop of integrated host-pathogen protein-protein interactions from several public resources. The purpose of the database is to provide researchers with the information and resources needed to facilitate their research on these interactions.

OCTOBER

NOVEMBER

DECEMBER



NOVEMBER // RESEARCH CONSORTIUM TO SEQUENCE TURKEY GENOME An international consortium of researchers begins an effort to sequence the genome of the domesticated turkey, *Meleagris gallopavo*. The genome sequence will be obtained at VBI using the Roche GS-FLX™ sequencing platform and the recently launched Roche GS-FLX Titanium PicoTiterPlate device and reagents. The genome sequence and genomic resources that will be developed from the project should provide turkey breeders with tools needed to improve commercial breeds of turkey for production traits such as meat yield and quality, health and disease resistance, fertility and reproduction and can be compared with the chicken genome sequence to examine similarities and differences in genome organization.

DECEMBER // LAUBENBACHER APPOINTED VICE PRESIDENT FOR SCIENCE POLICY OF SIAM VBI Professor Reinhard Laubenbacher is appointed Vice President for Science Policy of the Society for Industrial and Applied Mathematics (SIAM). The goal of this new position is to strengthen SIAM's commitment to engaging different stakeholders in wider discussions on science policy. In addition to making sure that key information on science policy and funding reaches SIAM's membership, Laubenbacher will help brief policy makers on issues related to SIAM's expertise.

Highlights 2009

JANUARY // COMPARATIVE GENOMICS REVEALS MOLECULAR EVOLUTION OF Q FEVER PATHOGEN Scientists from the National Institute of Allergy and Infectious Diseases, Texas A&M Health Center and VBI uncover genetic clues about why some strains of the pathogen *Coxiella burnetii* are more virulent than others. The researchers compared the sequences of four different strains of *C. burnetii,* an intracellular bacterium that can cause acute and chronic Q fever in humans, to build up a comprehensive picture of the genetic architecture and content of the different genomes. The scientists examined *C. burnetii* strains of differing virulence to unveil clues on the genetic features associated with pathogenicity.

CDC IMAGE LIBRARY

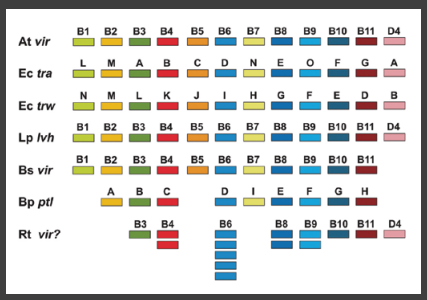
JANUARY // PRESIDENT OF TECHNISCHE UNIVERSITÄT DARMSTADT VISITS VBI The President of the Technische Universität Darmstadt in Germany visited VBI along with other officials from the university as part of a three-day visit to Virginia Tech. The leadership team was given an overview of the activities of VBI as well as a guided tour of the building, including a visit to the Core Laboratory Facility. The visit to VBI was part of a wider Virginia Tech-Technische Universität Darmstadt summit that took place from January 28 through January 31.

FEBRUARY // CAFÉ SCIENTIFIQUE MAKES ITS DEBUT A new event in Blacksburg designed to take scientific research out of the laboratory and deliver it to a more general audience debuts in Blacksburg. Sponsored by VBI, the goal of Café Scientifique is to present science in an informal setting that will encourage public discussion. A 10-20 minute presentation from the featured researcher is followed by a question and answer session from the audience.

MARCH // 200 000 RICE MUTANTS AVAILABLE WORLDWIDE FOR SCIENTIFIC INVESTIGATION Scientists across the world, including Andy Pereira's group at VBI, are building an extensive repository of genetically modified rice plants in the hope of understanding the function of the approximately 57 000 genes that make up the genome of *Oryza sativa*. The International Rice Functional Genomics Consortium announced the public availability of more than 200 000 rice mutant lines, which represent mutations in about half of the known functional genes mapped for rice to date.

MARCH // COENZYME RARE TO BACTERIA CRITICAL TO *MYCOBACTERIUM TUBERCULOSIS* SURVIVAL Coenzyme F_{420}, a small molecule that helps certain enzymes transfer electrons, is found in microorganisms known as methane-producing archaea, some of which thrive in extreme environments. It also helps the bacterium that causes tuberculosis to survive the defenses of the human immune system. Endang Purwantini and Biswarup Mukhopadhyay from VBI have discovered at least one way F_{420} helps to arm the pathogen. Mukhopadhyay's lab specializes in the study of the anaerobic archaea, especially those that produce methane, and has a program on enzymes that utilize coenzyme F_{420}, which is rare in bacteria. Only the Actinobacteria, a group of aerobic microorganisms, contain F_{420}. They include the mycobacteria, which generally live in the soil, except for *Mycobacterium tuberculosis* (Mtb), which causes tuberculosis.

JANUARY FEBRUARY MARCH APRIL

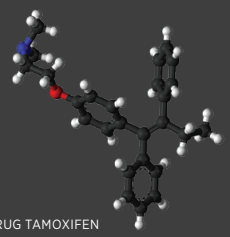


COMPARISON OF GENE SEQUENCES OF DIFFERENT *RICKETTSIA* SPECIES, PLOS ONE

MARCH // BIOINFORMATICS SHEDS LIGHT ON EVOLUTIONARY ORIGIN OF *RICKETTSIA* VIRULENCE GENES Scientists from VBI, the University of Maryland School of Medicine, and the University of Louisville reveal that genes for a specific type of molecular secretion system in *Rickettsia*, a structure that is linked in many cases to virulence, have been conserved over many years of evolution. The scientists compared the gene sequences of 13 *Rickettsia* species to detect a highly conserved type IV secretion system. Type IV secretion systems are membrane-spanning transporters that can act as syringes that inject virulence factors into the cells of their hosts (eukaryotes). Once introduced, these virulence factors compromise the host and may result in harmful disease, for example Legionnaires' disease (*Legionella pneumophila*) and Q fever (*Coxiella burnetii*).

JUNE // VBI RESEARCHERS DEVELOP NEW METHOD FOR BREAST CANCER BIOMARKER DISCOVERY VBI researchers develop and evaluate a new one-step bioanalytical approach that allows them to profile in detail complex cellular extracts of proteins. The method has allowed the scientists to look at how the levels of proteins change in breast cancer cells when they are treated with hormones or cancer drugs like tamoxifen.

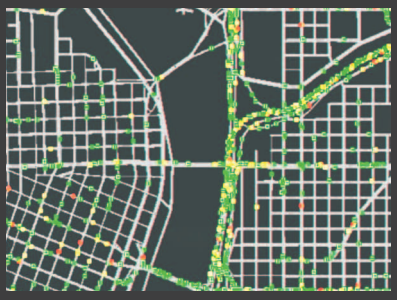
VBI Assistant Professor Iuliana Lazar, along with VBI Professor Ina Hoeschele and VBI Postdoctoral Associate Jenny Armenta, developed the method, which uses proteomic technologies for fast biomarker fingerprinting in complex cellular extracts. The goal of biomarker discovery and screening is to identify changes in the levels of key proteins in the cell in response to the onset or development of a disease. This type of research promises to advance the capabilities of such techniques for early cancer detection, which could significantly reduce the mortality rate from diseases like cancer.



THE DRUG TAMOXIFEN

JUNE // SCIENTISTS SEQUENCE THE GENOME OF THE NITROGEN-FIXING, SOIL-LIVING BACTERIUM *AZOTOBACTER VINELANDII* A collaboration of researchers, which includes scientists at VBI and Virginia Tech, complete the genome sequence of *Azotobacter vinelandii*, uncovering important genetic information that will contribute to a more complete understanding of the biology of this versatile, soil-living bacterium. The work will help advance research on *A. vinelandii's* role as a model study organism for investigation of nitrogen fixation and other biochemical processes. It will also pave the way for new applications in biotechnology, including the possible use of *A. vinelandii* as a "factory" for the production of other proteins, in particular those that may be damaged by the presence of oxygen.

JULY // NDSSL AND COLLABORATORS RECEIVE $1.45 MILLION TO DEVELOP PETASCALE COMPUTER MODELING CAPABILITIES The National Science Foundation awards a four-year, $1.45-million grant to the Network Dynamics and Simulation Science Laboratory at VBI and partners to develop petascale computing environments that model billions of individuals in extremely large social and information networks. The goal of the work is to use new computer technology breakthroughs to study events like disease pandemics, financial crises, as well as the spread of opinions, attitudes or social beliefs, through populations on a global scale. Petascale modeling would make comparable agent-based studies of disease transmission possible for global populations.



TRAFFIC PATTERN SIMULATION

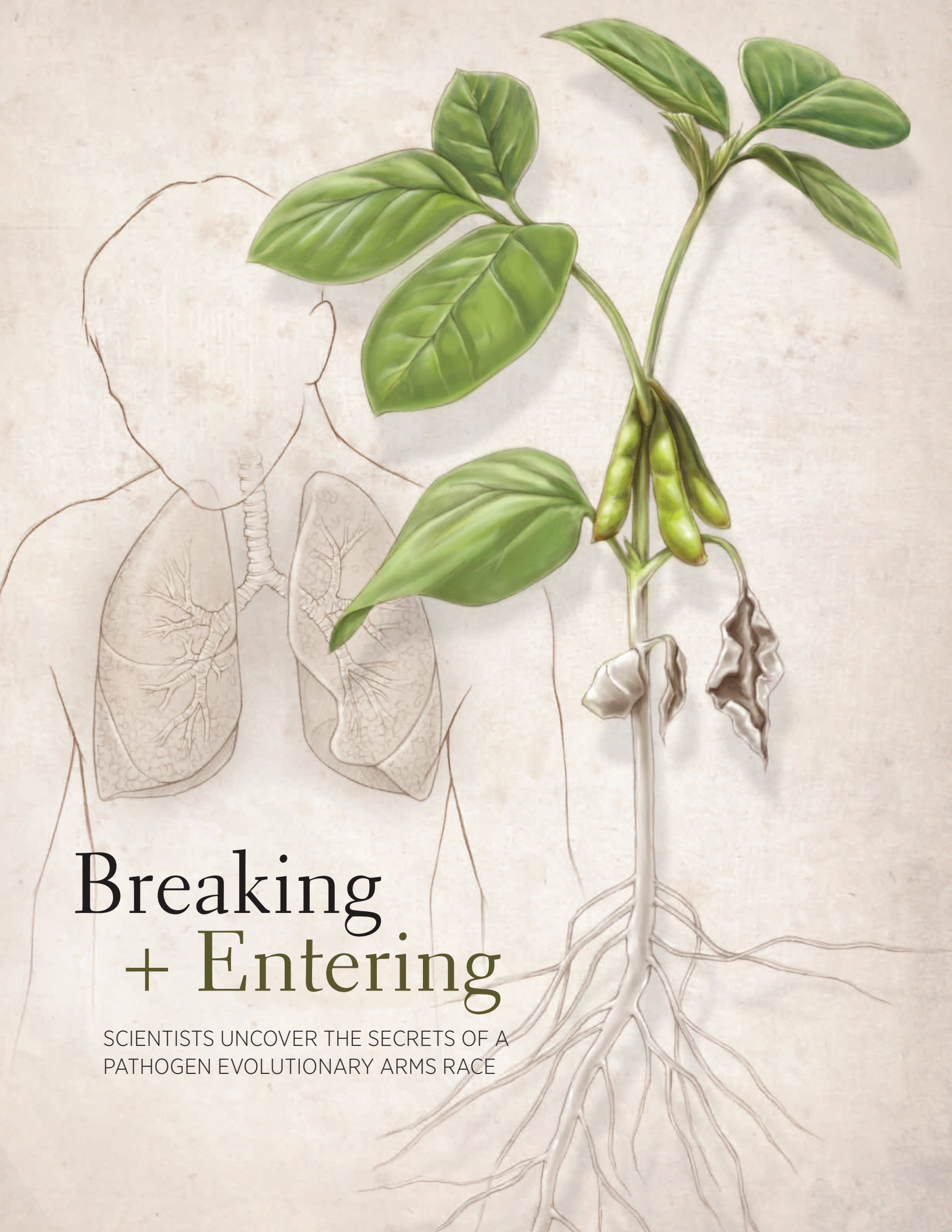
MAY

JUNE

JULY

MARCH // EVOLUTIONARY ORIGIN OF BACTERIAL CHROMOSOMES REVEALED Researchers, including João Setubal's group at VBI, unveil the evolutionary origin of the different chromosomal architectures found in three species of *Agrobacterium*. A comprehensive comparison of the *Agrobacterium* sequence information with the genome sequences of other bacteria suggests a general model for how second chromosomes are formed in bacteria. Agrobacteria are members of the Rhizobiaceae family, which also includes the benign, nitrogen-fixing organisms *Rhizobium* and *Sinorhizobium*. The scientists used the sequence information of the genomes of three types of *Agrobacterium* (biovars), two of which were recently completed, and compared the sequences with those of different bacteria to shed light on the origin of the different chromosomal arrangements.

JULY // SYSTEMS BIOLOGY AS A CLINICAL APPROACH TO CANCER Four VBI researchers and their colleagues at the Wake Forest University School of Medicine advocate the use of systems biology as an innovative clinical approach to cancer. This approach could result in the development of improved diagnostic tools and treatment options, as well as potential new drug targets to help combat the many potentially fatal types of the disease. The team highlights the usefulness of a systems biology approach in developing a comprehensive view of cancer diseases, which will help researchers better understand the complex processes related to cancer progression, diagnosis, and treatment.

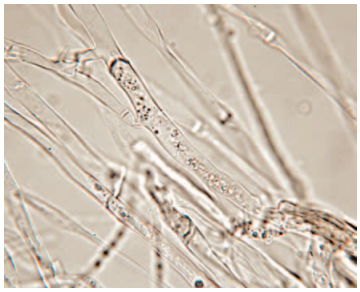


Breaking + Entering

SCIENTISTS UNCOVER THE SECRETS OF A PATHOGEN EVOLUTIONARY ARMS RACE

IN FOCUS | Researchers discover interventions

PROFESSOR BRETT TYLER and collaborators have sequenced the genomes of two deadly *Phytophthora* pathogens, constructed detailed maps of the disease-related genetic networks of host and pathogen, and mined large datasets of information to reveal a fundamental mechanism for the way oomycete pathogens launch their disease-inducing molecules into the cells of their plant hosts. The work suggests a common mechanism for entry of pathogen proteins into the host cells of not only plants but also animals and humans, and points the way towards the development of effective countermeasures. The pay-off in stopping these pathogens in their tracks could be large. Over the years, *Phytophthora sojae* alone has caused billions of dollars of losses for soybean farmers in the United States.



Phytophthora sojae

INVADERS FROM THE SEA

Oomycete plant pathogens are fungal-like organisms that are evolutionarily related to algae in the plant kingdom Stramenopila, a group of plants that also includes golden-brown algae, diatoms, and brown algae such as kelp. 1300 million years ago, an algal relative from this plant kingdom engulfed a red alga and adopted its photosynthetic machinery. Over the course of evolution however, oomycetes abandoned their ability to make food from light, choosing instead to profit from a parasitic lifestyle. Oomycetes became destructive pathogens of aquatic plants and animals, and today remain a major headache for fish and crustacean (shrimp and crab) farmers.

More recently oomycetes have extended their hunting range to land plants. Revealing their aquatic origins, oomycetes are at their most dangerous when the air is cool and misty or the soil is waterlogged. Oomycete plant pathogens destroy many species important to agriculture, forestry, gardens and natural ecosystems. *Phytophthora ramorum*, which causes sudden oak death, has attacked and killed tens of thousands of oak trees in California and Oregon. *Phytophthora sojae* causes severe damage in soybean crops. In the nineteenth century, the potato late blight pathogen *Phytophthora infestans* was responsible for the Irish potato famine. Most of the 90 species of *Phytophthora* are destructive pathogens and scientists want to know how they bring about wide-scale damage in the hope of finding ways to combat infection.

A SYSTEMS-WIDE APPROACH

Most plants have effective defense mechanisms to fight disease and thus they are healthy most of the time. However, evolution has been shaping the attributes of pathogens and plants over many thousands of years in what amounts to an ongoing evolutionary arms race with repeated development of new virulence weaponry in the pathogens and new countermeasures in the hosts.

Sequencing the genomes of pathogens, cataloguing the genes, and analyzing the proteins produced by the host and pathogen are all key steps in understanding how the plant-pathogen system works. The scientists are building genetic networks, integrating data from individual experiments on specific genes, and modeling the way the genes work to help build a picture of how the global network of genes operates.

"We have recently discovered a small molecule that can block the entry of effector proteins into the cell. This significant observation paves the way for the identification of a new class of therapeutic agents that can protect plants, animals and humans from deadly oomycete, fungal, and parasite infections."

Brett Tyler, Professor
Virginia Bioinformatics Institute and Department of Plant Pathology, Physiology and Weed Science, Virginia Tech

Dr. Brett Tyler in his laboratory

Dr. Tyler's group and collaborators are also developing a common language, a gene ontology, to compare the functions of genes across different species. This is helping to model the impact evolution has had on these genes and provide clues for possible disease intervention.

Says Tyler: "To build genetic regulatory networks from biological data, we are putting in place mathematics- and computer-science-based methods for inferring and modeling biological processes. This sheds light on the interconnected genetic regulatory networks that have arisen due to the ongoing co-evolutionary battle between the plant and pathogen."

DEADLY PATHOGEN GENOMES

One of the key pieces of information needed to build up a comprehensive picture of gene networks is the genome sequence of the pathogen. Since 2002, VBI researchers have been working as part of an international team to sequence the genomes of oomycete plant pathogens. In 2006, the draft genome sequences of *Phytophthora sojae* and *Phytophthora ramorum* were published in the journal *Science*. The genome sequences of both organisms provided an important window to the evolutionary history, revealing a recent large expansion and diversification of many deadly genes involved in infection of the plant hosts by *Phytophthora*. The sequence information confirmed how *Phytophthora* has evolved from a benign photosynthetic organism into a sophisticated, plant-killing machine. Says Tyler: "A key finding from this work was the discovery that highly repetitive sequences make up more than one quarter of the pathogen genome. Over the course of evolution there has been a rapid, large-scale expansion of many protein families linked to plant infection, including toxins, protein inhibitors and enzymes that can break down cell walls." Tyler, together with collaborators in the United States and the United Kingdom, are currently working on the genome sequences of two more oomycetes, the downy mildew pathogen *Hyaloperonospora arabidopsidis* and the fish pathogen *Saprolegnia parasitica*.

INTERNATIONAL RESEARCH PARTNERSHIPS

Genome sequences are important resources for biologists but additional data and tools are needed to build a systems-level understanding of host-pathogen interactions. Shared languages known as gene ontologies help scientists to look at and compare the functions of different genes across species. VBI scientists have been working with international collaborators to put in place a powerful language that gives researchers a shared vocabulary to describe disease-related and beneficial interactions between a microbe and its host. By allowing scientists to link experimental results to a computer-readable language, gene ontologies provide scientists with an important bridge between specific experiments that characterize gene function and larger-scale, systems biology efforts to provide a global picture of host-microbe interactions.

The Plant-Associated Microbe Gene Ontology (PAMGO) is a consortium of researchers from Virginia Tech, Cornell University, Wells College, the University of Maryland School of Medicine, North Carolina State University, the University of Wisconsin, Madison, and

the European Bioinformatics Institute in the United Kingdom. The PAMGO Consortium started to develop terms that focus on plant-microbe interactions in 2004. VBI researcher Trudy Torto-Alalibo, who coordinates the PAMGO project, says: "The PAMGO Consortium is an example of how community-driven collaborations amongst different research institutions can benefit the utility of genomic information for scientists working across the globe. PAMGO has contributed more than 800 new Gene Ontology terms to assist in understanding how microbes interact with their hosts. This includes the many relationships of plants with bacteria, fungi, oomycetes, and nematodes."

BREAKING AND ENTERING

When the data sets and tools are in place, scientists can push ahead to understand the biology of plant disease. One of the fundamental questions they want to address is how do oomycete pathogens break and enter plant cells? The answer lies with effector molecules, proteins that can manipulate the physiology of their hosts making them more susceptible to infection. Recently, VBI researchers have identified the region of a large family of virulence proteins in oomycete plant pathogens that enables these proteins to invade the cells of their hosts. The protein region contains "signature" sequences that, in the one-letter code used to describe the amino acids making up proteins, are referred to as RXLR and dEER motifs. The RXLR and dEER motifs are essential to carry the virulence proteins across the membrane surrounding plant cells without any additional machinery from the pathogen. Once inside the plant cell, the proteins suppress the immune system of the plant allowing the infection to progress.

VBI scientists discovered the importance of the RXLR and dEER motifs for infection using an ingenious device for introducing DNA into living tissues that was invented by a Virginia Tech undergraduate, Shiv Kale. Kale, who is now a graduate student in Dr. Tyler's laboratory and was recently awarded a National Science Foundation Graduate Research Fellowship award, says: "The double-barreled Gene Gun enabled us to make much more accurate measurements of effector proteins than were previously possible, which made it practicable to measure the action of the RXLR and dEER motifs."

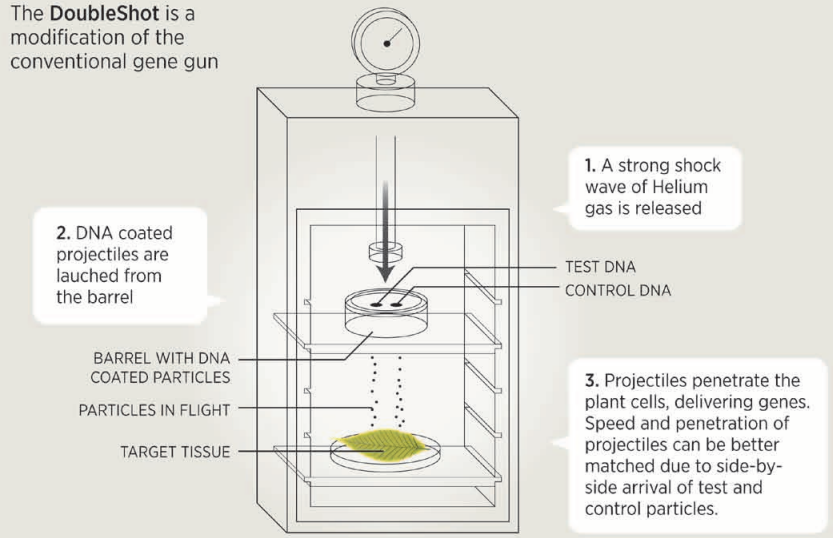
When the researchers probed the published genome sequences of *Phytophthora ramorum* and *Phytophthora sojae* using bioinformatic tools that can look for RXLR and dEER motifs, they identified an enormous superfamily of pathogen genes involved in the infection of plants – the *Avh* superfamily. The results confirm that a single gene from a common ancestor of both pathogen species has spawned hundreds of very different, fast-evolving genes that encode for these highly damaging effector proteins. Given that there are more than 90 species of *Phytophthora* pathogens, these findings imply that there are more than 30,000 members of this deadly superfamily within the genus *Phytophthora*.

THE ROAD AHEAD: FUTURE INTERVENTIONS

The investment in building a systems-wide understanding of *Phytophthora*-plant interactions is starting to pay dividends not only for future disease intervention strategies in plants but also for countermeasures relevant to human disease.

VBI Professor Brett Tyler remarks: "We have recently shown that RXLR and dEER motifs are crucial for entry into both plant and animal cells. The finding that virulence proteins from oomycetes, the malaria parasite *Plasmodium*, and certain fungi use the same entry mechanism means that we may be able to use the same or similar drugs to block infection in all three groups of pathogens."

The reward for finding a common mechanism for entry of pathogen proteins into the host cells of animals, humans, and plants could be considerable. Says Tyler: "We have recently discovered a small molecule that can block the entry of effector proteins into the cell. This significant observation paves the way for the identification of a new class of therapeutic agents that can protect plants, animals and humans from deadly oomycete, fungal, and parasite infections." •



THE GENE GUN. For over 20 years, scientists have used a mechanical device known as a gene gun for the biolistic transformation of living tissue. The gene gun is capable of firing metal particles coated with DNA into plant or animal tissues, allowing for the integration of new genes into different types of cells.

In a new twist to this technology, Shiv Kale, a graduate student at VBI, and Professor Brett Tyler, have invented a double-barreled device by making a simple modification of the conventional gene gun apparatus. DoubleShot allows simultaneous application of control and test DNA from a single shot of helium, the gas used to deliver the projectile into the tissue. This innovation not only saves time but also significantly reduces experimental variation that occurs when successive shots from a single gene gun are used.


ATGTGGGATT
AAGTCAAAGA
CAACCCCAAG
GCCGTGGAAG
CCATCGGCGA
GCTGAGTTGG
CTGCGCCTGA
TGGACCCGGA
GATTCTGGAT
CAGACCTTCG
CCGCCATCGG

IN FOCUS | Researchers discover genome's secrets

A soil-living bacterium's genetic features confirm potential for biotechnology applications

ONE OBSTACLE THAT ALL BIOLOGICAL SYSTEMS ENCOUNTER IS GETTING THEIR HANDS ON USEABLE NITROGEN.

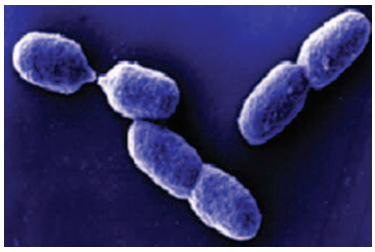
AN INTERNATIONAL TEAM OF RESEARCHERS recently completed the genome sequence of the versatile, soil-living bacterium *Azotobacter vinelandii*. The consortium uncovered a treasure trove of important genetic information, paving the way for new applications in biotechnology and advanced research on nitrogen fixation and other biochemical processes.

In areas where there is a suitable climate and water availability, nitrogen is often the missing component for proper plant growth. One obstacle that all biological systems encounter is getting their hands on useable nitrogen. While there is an abundant supply of nitrogen in the atmosphere, gaseous nitrogen cannot be used directly by plants or animals. With the help of bacterial enzymes called nitrogenases, certain bacteria, such as *A. vinelandii*, have the ability to convert nitrogen from the atmosphere into ammonia. The nitrogen-containing compounds that can arise from ammonia can be used as vital components in the production of DNA and the amino acids that serve as the building blocks of proteins. Adding to the interest in *A. vinelandii's* genome is the fact that it is one of the few bacteria that can fix nitrogen in the presence of oxygen, while simultaneously protecting nitrogenase from oxygen damage.

RESPIRATORY PROTECTION

A. vinelandii is a free-living gamma-proteobacterium that belongs to the family *Pseudomonadaceae*. Found in soils all over the world, it has features of nitrogen and energy metabolism of particular relevance to agriculture. The *Azotobacter vinelandii* genome sequencing project brought together extensive expertise from five independent research groups with significant experience in *Azotobacter* biology, genomics, bioinformatics, and undergraduate education. Supported by the National Science Foundation and M.J. Murdock Charitable Trust Life Sciences Program, the goal of the project was to produce a finished, well-annotated genome sequence of *A. vinelandii* strain DJ and expand an existing undergraduate training platform in genomics technology.

The work of the *A. vinelandii* sequencing project team, which was featured on the cover of the *Journal of Bacteriology*, has identified unique features of the *A. vinelandii* genome that explain how the bacteria is involved in oxygen-sensitive reactions while maintaining strictly aerobic metabolism. With one of the highest respiratory rates of any known bacteria, *A. vinelandii* has the ability to adjust oxygen-consumption rates to help maintain low levels of cytoplasmic oxygen through a process called respiratory protection.

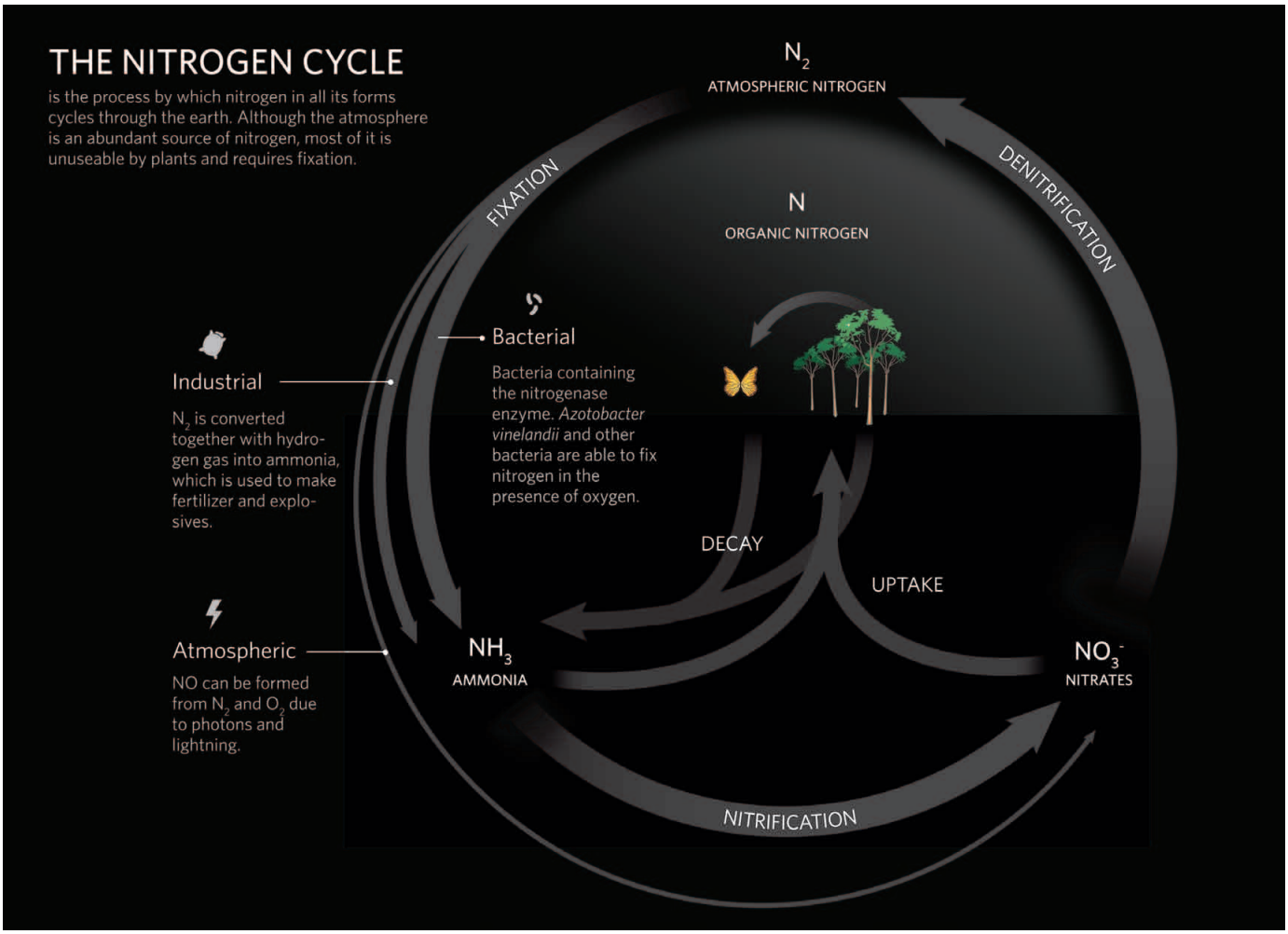


Azotobacter vinelandii

"This genome analysis has allowed us to identify genes involved in respiration and, more specifically, the chromosomal location of three known oxygen-sensitive nitrogenases, as well as genes that code for other oxygen-sensitive enzymes," explained João Setubal, associate professor at VBI and the Department of Computer Science at Virginia Tech. "The sequence has also provided important information about the genes that code for alginate—a polymer that provides additional protection of the organism from excess oxygen by forming a physical barrier

THE *Azotobacter vinelandii* GENOME PROJECT TEAM

NSF PROJECT PRINCIPAL INVESTIGATORS // Derek Wood, Seattle Pacific University / João C. Setubal, Virginia Bioinformatics Institute / Dennis Dean, Virginia Tech / Barry Goldman, Monsanto / Brad Goodner, Hiram College **PARTICIPATING INSTITUTIONS //** Virginia Bioinformatics Institute / Virginia Tech / Wake Forest University / Monsanto / Norwegian University of Science and Technology / Universidad Nacional Autónoma de México / Centro de Biotecnologia y Genomica de Plantas (Spain) / Universidade Federal do Mato Grosso do Sul (Brazil) / Hiram College / Centro de Estudios de Biodiversidad y Biotecnologia (Argentina) / Midwestern University / Seattle Pacific University / University of Arizona / Macquarie University (Australia) / University of Wisconsin-Madison / Sainsbury Laboratory (United Kingdom) / John Innes Centre (United Kingdom) / University of Washington



around the bacterium, limiting the diffusion rate of oxygen into the cells. The ability of *A. vinelandii* to protect its nitrogenase on several fronts is a remarkable adaptation to the organism's external environment and we are now in a position to dissect the genetic contributions to this defense strategy."

The project has also uncovered information about the involvement and regulation of the biosynthetic pathways that help the bacteria adapt its metabolism to diverse sources of nutrients. For example, if no carbon source is present, *A. vinelandii* will undergo a differentiation process, forming cysts that are resistant to desiccation and other chemical and physical challenges.

PRODUCING OXYGEN-SENSITIVE PROTEINS

A. vinelandii has an impressive history as the organism of choice for many investigators interested in the life sciences. The bacterium has been studied in considerable detail for more than a century. Some incisive biochemical experiments with *A vinelandii* predate those performed with *Escherichia coli*, long considered the scientists' workhorse of the molecular biology laboratory. *A vinelandii* can also serve as an excellent source of other proteins, particularly those that may be damaged in the presence of oxygen.

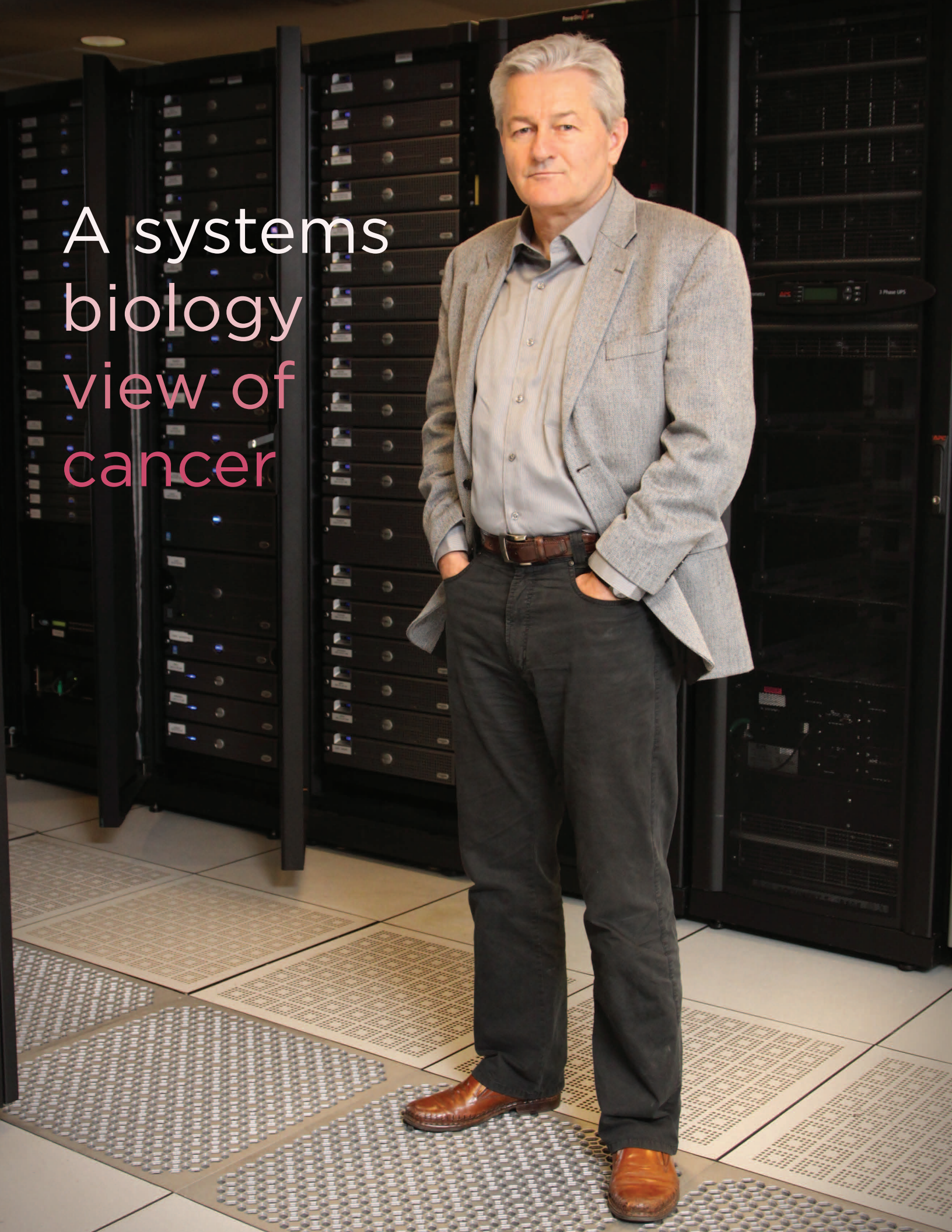
"*A. vinelandii* is an attractive model organism for biochemical studies because of its ability to produce high yields of quality enzymes," said Setubal. "The genome sequence described in this study provides new prospects for the wider application of this bacterium as a factory for the production and characterization of a wide range of oxygen-sensitive proteins through the use of genetic approaches to achieve high-level protein expression."

SHAPING FUTURE SCIENTISTS

Another product of the team's efforts is the opportunity to train new scientists in the fields of genomics and bioinformatics. This research has helped the *A. vinelandii* genome project expand its existing undergraduate training platform in genomics technology, providing students with access to cutting-edge genomics education at both participating and off-site institutions. Undergraduate researchers from around the world worked on many aspects of the project, including the finishing, annotation, bioinformatics, and analytical phases.

"The key to the success of this project was an extremely effective multinational collaboration between *Azotobacter* biologists and our core genomics team," explained Derek Wood, associate professor in Seattle Pacific University's Department of Biology and the University of Washington's Department of Microbiology. "Numerous undergraduate researchers both in the classroom and in the laboratory worked closely with the team on annotation and analyses. This multilevel, interdisciplinary collaboration led to an excellent annotation and informed analysis of this model bacterial system and provided an excellent training platform for our undergraduate partners." •

A systems biology view of cancer



IN FOCUS | Scientists discover cancer networks

Genetic Engineering News published the following PodCast interview, "A Systems Biology View of Cancer," in July 2009. John Sterling, Editor-In-Chief, interviewed Reinhard Laubenbacher, Professor at the Virginia Bioinformatics Institute and the Department of Mathematics at Virginia Tech. The interview is reproduced here with kind permission from Genetic Engineering News.

JOHN STERLING: Dr. Laubenbacher, you and a group of researchers from several universities published an extremely interesting paper in the June 6th, online edition of *Biochimica et Biophysica Acta*.[1] It was entitled, "A Systems Biology View of Cancer." Before we go into some of the details of that paper, what were your main conclusions?

REINHARD LAUBENBACHER: This paper grew out of a collaborative work that involves three research groups at the Virginia Bioinformatics Institute and a group of researchers at Wake Forest University's Comprehensive Cancer Center in North Carolina. Our collaboration focuses primarily on a systems biology approach to breast cancer and brings to the table expertise in cancer biology, metabolomics, and mathematical modeling. The paper is wider in scope and looks beyond breast cancer. Today, the prevalent approach to cancer at the molecular level is what you might call reductionist – the focus is primarily on individual genes and their role in disease. But since there are hundreds of different kinds of cancers and different genetic variants within each type, this approach is very daunting. Many great advances in effective treatments for cancer have been made but despite a strong effort by many people in the last 10–20 years, we have not seen the kind of progress that you might call a cure for these diseases. There are many possible reasons for this. My colleagues and I believe that one of the reasons is the limited capability of the reductionist approach to help us truly understand some of the key mechanisms of cancer pathogenesis. Genes typically do not function alone. They are part of an intricate network that also involves proteins, metabolites, and their many dependencies. In order to understand, for example, the effect of a drug that targets a particular protein, you need to understand the role of this protein within the whole network. In a network, this protein might have several different functions, so this makes it very hard to predict what the cumulative effect of an intervention might be. If you focus on the structure and properties of the network—the whole network—rather than just its parts, I think we will get a better understanding of cancer at the molecular level. Of course that is only part of the picture and it is not sufficient because cancer is a multi-scale disease and its pathogenesis is influenced by many factors at the tissue level, the organism level, and the environmental level. Ultimately, we need to integrate all of these factors.

JS: Let's pick up on this theme here. What is it about systems biology that makes it especially appropriate for a new clinical approach to cancer?

RL: The multiple factors that determine cancer pathogenesis are very complex and they are intricately interwoven across different scales—across different temporal scales and spatial scales, so you have things like intracellular signaling, gene regulation, interaction of a tumor with its microenvironment, the role of the immune system, and others. On top of this, there are environmental factors, such as the exposure to carcinogens, stress, or depression. Without taking a holistic approach, it will be very difficult for us to make progress. Systems biology offers a paradigm for a holistic approach to cancer.

JS: You and your colleagues note that systems biology could result in the development of improved diagnostic tools and treatment options, as well as the discovery of potential new targets. Let's take each of these one by one. How could it lead to improved diagnostics?

RL: An important part of today's research on new diagnostic technique is a focus on biomarkers. Biomarkers are intended to help in the classification of a tissue or a serum sample, for example, into normal or malignant. One type of biomarkers that have been studied for some time are individual genes or small groups of genes, which are typically identified by the analysis of DNA microarray data obtained from large numbers of patient samples. This approach is sometimes useful, but in many cases the biomarkers from a particular data set are difficult to apply to other data sets in a useful fashion. Furthermore, one assumption of this approach is that oncogenes act by differential expression because that is the only way you can pick up differences in DNA microarrays. But we know that this is not always the case. There is evidence that an important difference between normal and malignant cells is not differential expression, but rather an alteration in the molecu-

> "Today, the prevalent approach to cancer at the molecular level is what you might call reductionist – the focus is primarily on individual genes and their role in disease."

> “ The key tools of systems biology are mathematical and statistical models...I think they are the only way to efficiently approach large, complex systems.”

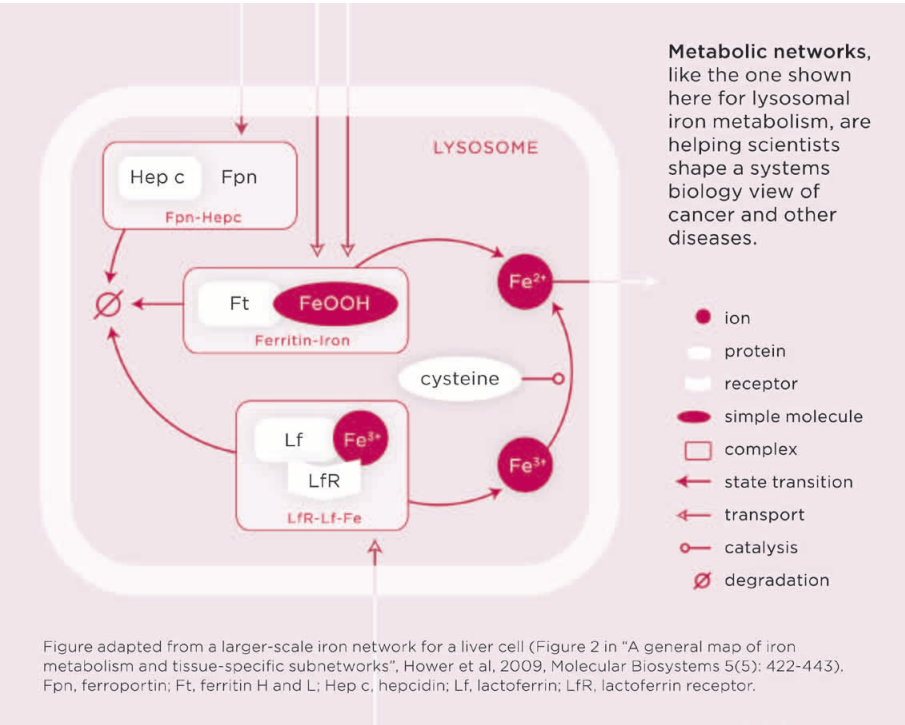
lar network structure, which we can capture by differential regulation. This is one example of how systems biology could contribute to diagnosis.

JS: How about new treatment options?

RL: There are several good examples where the systems approach can lead to the optimization of treatment. The fundamental nature of treatment is control of a certain process. Typically, you want this control to be optimal. For instance, you want to have optimal doses of medication or an optimal dose of radiation treatment. Optimal control is a key ingredient in many engineered systems, such as airplanes or manufacturing robots. And optimal control is a very well developed field of mathematics, which relies on mathematical models of the system that you want to control. Systems biology has an important goal — the construction of mathematical models of biological systems. Cancer systems biology focuses on the complex systems that are relevant to cancer. If the systems biology approach succeeds, then we have a whole new range of mathematical tools available that have been very successful in engineering. We can apply these tools to the control of the networks relevant to cancer—ultimately to the treatment of cancer. And we have some good examples where that has been done successfully.

JS: This leads to my next question because your paper talks about successfully taking a systemic view of cancer and then applying mathematical modeling techniques to study the disease. You go on to provide three examples to support this approach to cancer. Could you briefly describe and give me examples of what you have learned from them?

RL: Our goal was to really provide the reader with some concrete instances of a systems biology approach with enough detail to allow the possibility of the reader thinking about similar approaches in his or her own research. We decided to choose some detailed case studies and we included three papers.[2-4] There are many other good papers we could have chosen. I think these three studies exemplify the added value that the systems biology approach can bring to diagnosis and treatment. The first paper is by Trey Ideker’s group from the University of California, San Diego, and it was published a couple of years ago in *Molecular Systems Biology*. The paper focuses on proposals for a different classification of breast cancer metastasis and starts with a known network of protein-protein interactions — more than 11,000 proteins in the network. Protein-protein interactions are physical interactions between proteins. Ideker’s group uses gene expression data from metastatic and non-metastatic samples and statistical methods to then identify certain sub-networks of this protein-protein interaction network, which allow, as they show, for a better discrimination of samples than just individual collection of genes based on differential expression. I think that’s an excellent example of how systems biology can be applied to disease prognosis.The second paper that we’ve chosen comes from Andrea Califano’s group at Columbia University and it takes a similar network-centric approach to the identification of oncogenes in several different phenotypes of B-cell lymphomas. Again, rather than focusing on differential expression as a key criterion for a classification of a gene as an oncogene, they propose to look instead at changes in how a gene interacts with its neighbors in a particular network. The network that they have constructed, which they call the B-cell Interactome is comprised of several tens of thousands of different types of interactions—protein-protein interactions, protein-DNA interactions, and



Metabolic networks, like the one shown here for lysosomal iron metabolism, are helping scientists shape a systems biology view of cancer and other diseases.

Figure adapted from a larger-scale iron network for a liver cell (Figure 2 in “A general map of iron metabolism and tissue-specific subnetworks”, Hower et al, 2009, Molecular Biosystems 5(5): 422-443). Fpn, ferroportin; Ft, ferritin H and L; Hep c, hepcidin; Lf, lactoferrin; LfR, lactoferrin receptor.

other kinds of regulatory interactions, which are all from a mammalian B-cell. They constructed the network using a wide variety of available data, statistical methods, a very interesting network inference algorithm they designed based on information theory, and some other tools. Using DNA microarray data and some other data sets, the group went on to identify genes whose neighborhood in this B-cell interactome is significantly changed between normal and malignant cell types and they focused on three or four different types of B-cell lymphomas. They discovered in this way some known oncogenes whose expression is significantly changed, but they also discovered some genes whose expression level is not significantly changed between samples but which are known to be involved in pathogenesis. They found other genes whose neighborhood is significantly changed in lymphomas versus normal cells but which could now be studied in terms of what their role really is. I think this approach has a lot of merit and could help us reveal findings that go beyond differential expression.

Finally, the third paper that we chose relates to cancer treatment and it uses a different methodology—a much more strongly mathematical methodology—and it focuses specifically on the development of optimal protocols for radiation therapy. The paper described here comes from Santiago Schnell's group at Indiana University and it constructs a very detailed mathematical model that integrates several different spatial scales, including the intracellular gene regulatory network. It includes a model of the cell cycle and it includes a model of the growing tumor, including blood and nutrient supply. What they do using this model is they simulate the effect of different radiation treatments, different timing of subsequent treatment, and the resulting efficacy of the treatment in terms of the number of cells that are susceptible to it. They draw some very interesting conclusions about how one could improve standard, current treatments. These are the three papers and, as I said, there are many other good examples that we could have used.

> "In the future, we should be able to design cancer therapeutics in the way many engineered systems, like airplanes, are designed today."

JS: To use these models you just talked about effectively, what else is critical?

RL: The key tools of systems biology are mathematical and statistical models, which, of course, as a mathematician by training, make me very happy. I think they are the only way to efficiently approach large, complex systems. Models are only as good as the data we use to build and calibrate them. In my opinion, the most critical needs we have are for more and better data. Most importantly, the design of the experiments to collect such data I think needs to be done by teams that bring together cancer biologists and the mathematical modelers and statisticians, who then use the data to calibrate the model.

JS: At the end of your paper, you and your fellow scientists put forth the vision for systems biology and cancer 20 years from now. Tell us about this vision.

RL: Well, the vision we propose in this paper is really not original to us, but has been suggested earlier by others. In particular, Hanahan and Weinberg have articulated it very well in the influential review paper in *Cell* back in 2000.[5] This vision, in essence, is that we will be able to design cancer therapeutics in the way many engineered systems, like airplanes, are designed today—namely they are designed in a computer based on detailed mathematical models of the system that we have engineered. This would considerably short-circuit the lengthy and very costly process of drug discovery. And, of course, there's also the promise of personalized drug treatments that would allow us to calibrate drug treatment models to the specifications of an individual, or maybe a small group of individuals, which would result in customized treatments. Now whether this is 20 or 50 years off, is not clear to me, but I'm sure it will happen sometime in the not-too-distant future. ▪

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Caitlin Kelleher, assistant professor of Computer Science and Engineering at Washington University in St. Louis and an alumnus of Virginia Tech (Computer Science, 1998) explains why some computer programs can be so frustrating.

IN FOCUS | Children discover science

Kids' Tech University

helps shape the future of science

Many experts agree that children need to be introduced early to the excitement of science, technology, engineering and math if the United States is to remain competitive in the global scientific community. Kids' Tech University (KTU) arose from an idea that the best way to engage children with science is to show them as early as possible how exciting and fun it can really be. KTU provides children between the ages of 9 and 12 semester-long opportunities to attend university lectures, take part in hands-on educational activities on campus, and engage in complementary educational experiences at home.

"We have something special here which I would like to see take root across the country."

Reinhard Laubenbacher
Professor and Deputy Director of Education and Outreach at VBI

Kids' Tech University (KTU), which is principally sponsored by the Virginia Bioinformatics Institute (VBI) at Virginia Tech and the Virginia Cooperative Extension's 4-H Youth Development Program, is the first educational program of its type offered in the United States. Reinhard Laubenbacher, professor and deputy director of education and outreach at VBI, came across the original concept of a children's university in an article published in a German newspaper. Says Laubenbacher, "Hundreds of children have been attending individual lectures on science on the weekend at Universities around Germany, which speaks volumes for the program and the enthusiasm of the kids. I wanted to see if we could build something similar in the United States."

After talking to the people who started the project, Laubenbacher and his team put in place the infrastructure needed for a first semester of KTU. Kids were enrolled to participate in a semester-long series of activities that began in January 2009. Adds Laubenbacher, "We had a huge response from parents and children interested in the program and quickly realized that we were tapping into a significant educational need." Last semester, KTU students were able to attend lectures in a Virginia Tech lecture hall, have lunch in one of the on-campus dining facilities, and take part in hands-on activities to build on the lecture concepts. A key feature of KTU is that the fun and excitement of the university experience continues after the kids leave campus through an online lab component with activities designed to promote a continued interest in the lecture topics, as well as providing a forum area to promote discussion and teamwork.

Says Cathy Sutphin, Virginia 4-H associate director of youth development at the Virginia Cooperative Extension, "A major program focus of 4-H is Science, Technology, Engineering, and Math or STEM. Through hands-on learning, KTU participants apply the ideas that are presented during lectures and explore other avenues. By connecting youth to the university, we increase the chances that they will not only choose a STEM field but that they will also consider attending Virginia Tech."

In the first semester of KTU, students heard from scientists who had engaging stories to tell about their research. Keith Devlin, known as "The Math Guy" on National Public Radio and co-founder and executive director of Stanford's Human-Sciences and Technologies Advanced Research Institute, kicked off

proceedings on 31 January 2009, answering the question "Why are there animals with spotted bodies and striped tails, but no animal with a striped body and a spotted tail?" In subsequent months, Caitlin Kelleher, assistant professor of Computer Science and Engineering at Washington University in St. Louis and an alumnus of Virginia Tech (Computer Science, 1998) explained why some computer programs can be so frustrating and Louis Guillette, professor and director of the Howard Hughes Group Advantaged Training of Research (G.A.T.O.R.) Program at the University of Florida, described how he wrestles alligators in the swamps of Florida to study the effects of environmental contaminants on wildlife. The first semester of KTU ended with an up-close look at what it would take to live on Mars in a lecture from Phil Christensen, Regents Professor and the Ed and Helen Korrick Professor in the Department of Geological Science at Arizona State University.

Says Laubenbacher: "The first semester of KTU was made possible due to contributions by many volunteers from the Virginia Tech community and beyond. Without their help, we would not have been able to put on an event of this scope and their assistance going forward will be a key part of our success."

"We have been able to attract scientists to KTU who have shared their enthusiasm for science in a way that has captivated the children," says Laubenbacher. "Our biggest challenge remains financial support. Despite an oversubscribed program and great feedback from children and parents, the lack of strong connections to formal K-12 education programs has made funding a challenge. With the introduction of teacher workshops we hope to overcome this challenge. We are hoping to secure private and company donations to support our second semester lineup of KTU lectures and hands-on activities."

School's back

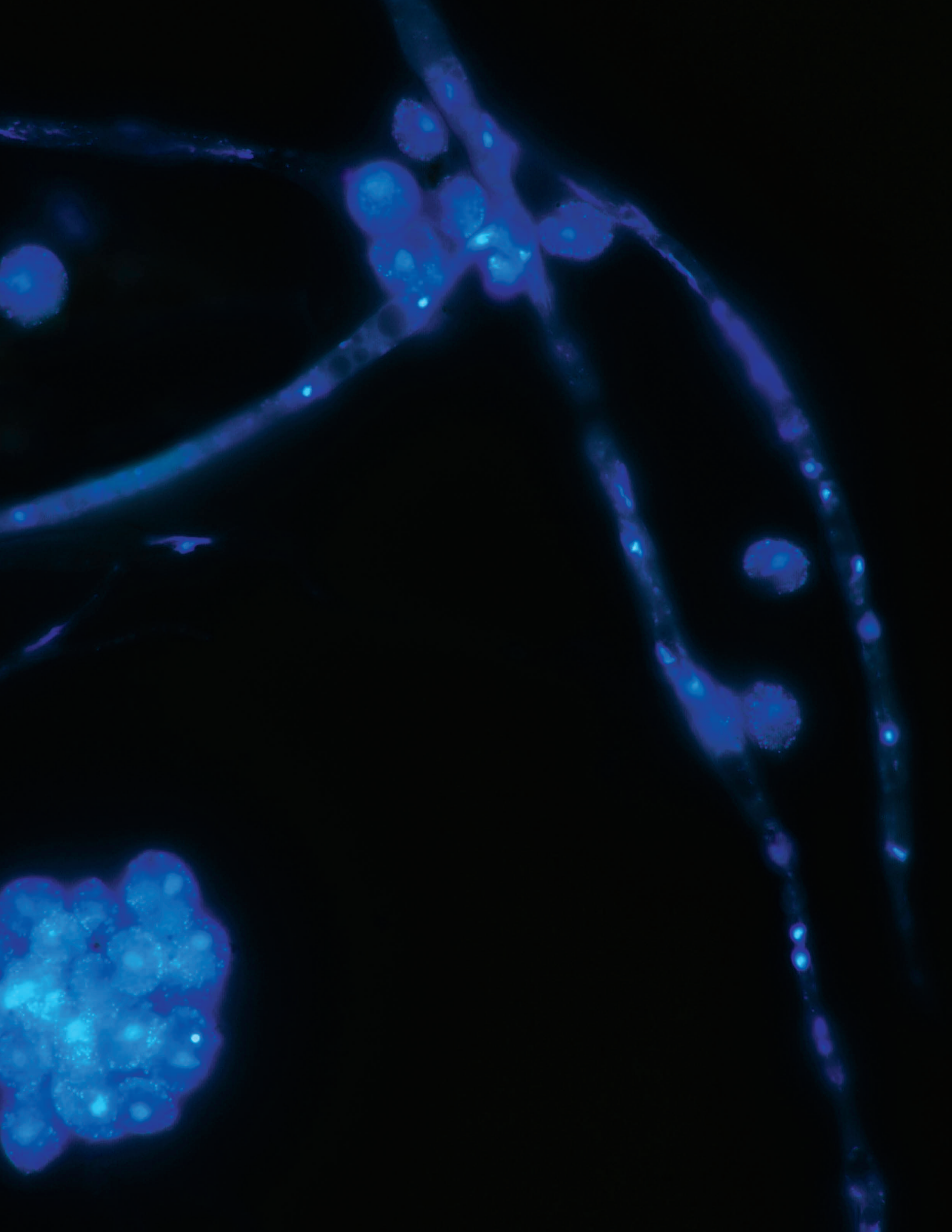
The second semester of KTU begins in January 2010. Kristy DiVittorio, Co-Principal Investigator of KTU at VBI, comments, "This semester KTU has a partnership with Tazewell County Public Schools and Tazewell 4-H to reach and involve economically disadvantaged students and their parents with the KTU program. KTU will also be attending a host of exciting new venues around the Virginia Tech campus." An additional new component of the program will also encompass training of teachers from around the state of Virginia. This will provide opportunities for teachers to acquire Continuing Education Units to advance their professional career development. Kathleen Jamison, Extension Specialist for 4-H Youth Development at the Virginia Cooperative Extension at Virginia Tech, will be spearheading this part of the program.

New and returning children of KTU will be ready to tackle questions like "What is the smallest thing a person can see?" and "Why can't humans walk on water and climb walls with their fingertips like spiders?" Harvey Mudd College Mathematics Professor Arthur Benjamin, who has appeared on *The Today Show*, *CNN*, and *National Public Radio*, will demonstrate his mixture of mathematics and magic, which he calls "Mathemagics," and explain how to mentally solve complex math problems faster than a calculator. Returning KTU lecturer Louis Guillette will explain why alligators are important to the swamps and what they can tell us about the world in which we live.

Says Laubenbacher: "We have something special here which I would like to see take root across the country. We can provide virtual resources that will make it possible for other universities to set up their own KTUs across the United States. In this way, I believe we could take a big step forward for the future of science in this country." •

KTU AT A GLANCE

- 450 kids attended the first KTU event in January, 2009, on the Virginia Tech campus
- First educational program of this type ever offered in the United States
- Real lectures by real researchers in a real university setting
- Diverse hands-on activities to complement lectures
- Encourages kids to pursue science education and careers
- Large unmet need for further, expanded programs



Research Groups

Resources & People

Dr. Chris Barrett

THE NETWORK DYNAMICS AND SIMULATION SCIENCE LABORATORY

Computational Methods for the Study of Large,Complex Network Systems

Left to right: (front) Achla Marathe, Kalyani Nagaraj, Karthik Channakeshava, Katherine Wendelsdorf, Madhav Marathe, Sharon Matchen; (middle) Jonathan Leidig, Kofi Adasi, Mary Williams, Zhengzheng Pan, Fei Huang, Stephen Eubank, Chris Barrett; (back) Rahul Jayaraman, Andrea Apolloni, Keith Bisset, Bryan Lewis, Henning Mortveit

THE NETWORK DYNAMICS and Simulation Science Laboratory (NDSSL) designs, develops and implements modeling tools to understand large biological, information, social, and technological systems. The group's research and development program is advancing the science and engineering of co-evolving complex networks and developing innovative computational tools based on these advances to support the emerging field of policy informatics. The research program comprises four integrated components: Fundamental mathematical and algorithmic principles for composed interactions of heterogeneous entities; Computational methods for the simulation and analysis of large, diverse composed network systems, including composition of intentional agents and co-evolutionary processes; Applications of this theory and technology to real-world problems in social and socio-technical systems; Design and development of high-performance computing based service delivery mechanisms to support application domain experts and decision makers.

NDSSL has established funded programs of more than $20 million in the past four years to study complex systems, including programs with the National Institutes of Health, the Department of Transportation (through AECOM), the Centers for Disease Control and Prevention, the Department of Defense, the National Science Foundation, and the Bill & Melinda Gates Foundation. The group has established a presence in the National Capital Region that plays a leading role in a new institutional initiative in Policy Informatics for Complex Systems.

NDSSL is pursuing new programs in wireless networks, commodity markets, computational economics, energy systems, sustainable interdependent infrastructure design and analysis, and high-performance computing. The group continues to develop advanced high-performance computing based computational tools and methods for reasoning about complex systems. These resources are integrated into web services providing synthetic databases, national scale interaction-based simulations, and analysis tools. NDSSL has used these tools in several stakeholder-designed studies supporting policy planning for pandemics. Four large studies to support pandemic planning for military preparedness were completed for the Defense Threat Reduction Agency of the Department of Defense using a prototype system built by the group, called the Comprehensive National Incident Management System. The Comprehensive National Incident Management System integrates surveillance, simulation-assisted hypothesis testing, and decision support for use in situational awareness and planning in complex systems.

The novel use of high-performance computing assets for addressing practical societal problems represents a unique capability developed by NDSSL.

For the first time, NDSSL transitioned its technology so that public health analysts can now do certain kinds of case studies by using the group's system, via a simple web interface. The novel use of high-performance computing assets for addressing practical societal problems represents a unique capability developed by NDSSL. |

RESEARCH INTERESTS

- Simulation of very large systems
- Theoretical foundations of simulation
- Interaction-based systems, computing, and dynamical systems
- Computational and systems biology
- Computational problems in epidemiology
- Cognitive science and computationally aided reasoning
- Computational economics
- Infrastructure simulation

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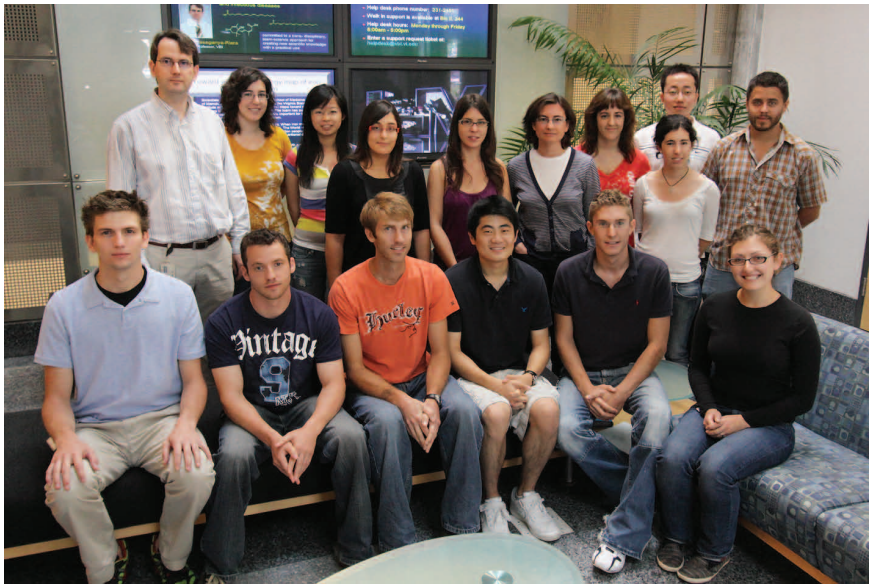
Dr. Josep Bassaganya-Riera

NUTRITIONAL IMMUNOLOGY GROUP

Development of Novel Approaches for Preventing Inflammation in Infectious & Chronic Diseases



Left to right: (front) William Horne, Amir Guri, Nick Evans, Ban Wang, Adria Carbo, Sarah Misyak; (back) Josep Bassaganya-Riera, Cristina Vives, Rong Song, Teresa Salazar, Montse Climent, Raquel Hontecillas, Mar Armengol, Pinyi Lu, Graciela Lopez, Jeff Skoneczka

THE NUTRITIONAL Immunology Research Group is leading research programs on infectious disease, gastrointestinal health, and obesity-related inflammatory complications. The central integrative theme of the group's active areas of research and discovery is to understand the inflammatory processes that underlie various human diseases.

In the area of infectious disease, Dr. Josep Bassaganya-Riera's team is studying the ability of abscisic acid, a growth-inhibiting plant hormone, to reduce the excessive inflammatory response that develops following infection with influenza virus. Influenza-related severe disease is associated with a "cytokine storm," which is a potentially fatal immune reaction between cytokines and immune cells in the lungs. Cytokines are molecules secreted by cells of the immune system, and their purpose is to regulate the immune system. The positive feedback loop created between cytokines and immune cells in influenza causes a type of storm that can lead to excessive pulmonary inflammation and has been linked to flu-related deaths. The group has established that abscisic acid and pioglitazone treatment diminish lung inflammatory lesions induced by influenza virus.

In the area of gastrointestinal health, the group is developing novel therapies against Crohn's disease and ulcerative colitis. These two clinical manifestations of inflammatory bowel disease afflict more than 1 million people in North America and 4 million people worldwide. The Nutritional Immunology group has been working with the Network Dynamics and Simulation Science Laboratory at VBI to create an agent-based model representing a virtual mucosal immune system composed of lymph nodes and a colon. The model can simulate an inflammatory or immunologically tolerant response and will be useful in the development of interventions for regulating gut inflammatory responses as well as host responses to enteric pathogens.

According to recent estimates from the Centers for Disease Control and Prevention, 30% of the United States population is obese and 65% is overweight. Obesity is strongly associated with chronic diseases such as cardiovascular disease, type II diabetes, stroke, obstructive sleep apnea, and colon cancer. The group has been studying the immunological aspects underlying obesity and its association with systemic insulin resistance. It has been shown that macrophages infiltrating white adipose tissue, or white fat, are influential in the inflammation response. The group is investigating therapies that suppress macrophage infiltration and thereby uncouple obesity from its associated diseases (i.e., diabetes, atherosclerosis).

The central integrative theme of the Nutritional Immunology Research Group's research and development is to understand the inflammatory processes that underlie various human diseases.

In October 2008, BioTherapeutics Inc. was created to develop nutritional interventions against chronic inflammatory and infectious diseases. The group continues to develop novel preventive and therapeutic approaches for modulating inflammatory responses in widespread and debilitating diseases. |

RESEARCH INTERESTS

- Nutritional immunology
- Gastrointestinal health
- Obesity-related inflammatory complications
- Modeling immune responses

SELECTED RECENT PUBLICATIONS

Bassaganya-Riera J, Misyak S, Guri AJ, Hontecillas R (2009) PPAR gamma is highly expressed in F4/80(hi) adipose tissue macrophages and dampens adipose-tissue inflammation. *Cellular Immunology* 258(2): 138-146.

Bassaganya-Riera J, Sanchez S, de Horna A, Duran E, Orpi M, Ferrer G, Casagran O, Hontecillas R (2009) F4/80^{hi}CCR2^{hi} macrophage infiltration into the intra-abdominal fat worsens the severity of experimental IBD in obese mice with DSS colitis. *e-SPEN Journal* 4(2): e90-e97.

Hontecillas R, Diguardo M, Duran E, Orpi M, Bassaganya-Riera J (2008) Catalpic acid decreases abdominal fat deposition, improves glucose homeostasis and upregulates PPAR alpha expression in adipose tissue. *Clinical Nutrition* 27(5): 764-772.

Hontecillas R, O'Shea M, Einerhand A, Diguardo M, Bassaganya-Riera J (2009) Activation of PPAR gamma and alpha by punicic acid ameliorates glucose tolerance and suppresses obesity-related inflammation *Journal of the American College of Nutrition* 28(2): 184-195.

Dr. Allan Dickerman

PHYLOGENOMICS RESEARCH GROUP

Phylogenomics & Systems Biology of Plants & Plant Pathogens

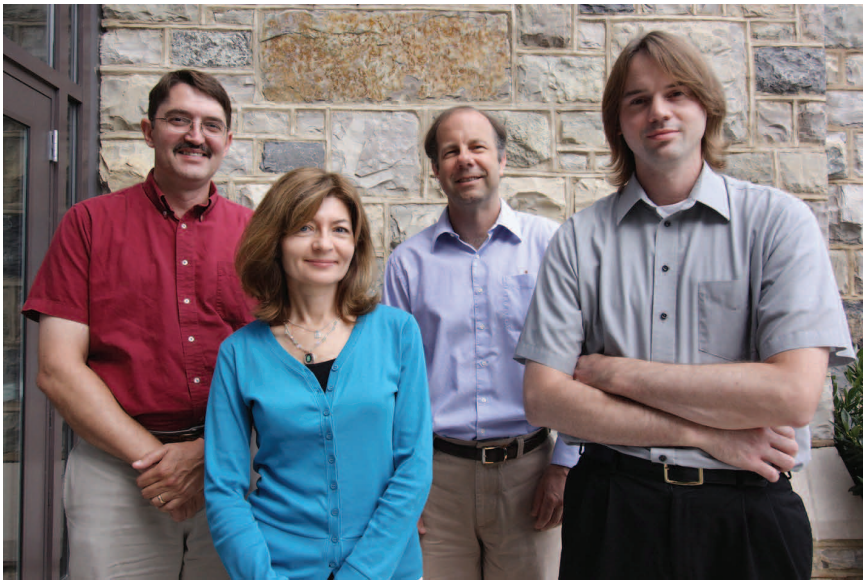
GENOMICS IS PLAYING a greater role in understanding processes important for human health, ecology and economy. The increasingly important science of phylogenomics studies the relationship of a gene's function to its evolution, thus providing greater insight into the mechanisms of both disease and health. In recent work, Dr. Allan Dickerman's Phylogenomics Research Group has been studying such societally important topics as agricultural pathogens, the commensal gut microbiome, and biofuels.

PhytPath is the crop pathogen microarray designed by the group for identification of bacterial and eukaryotic plant pathogens. The chip has been synthesized by Affymetrix and experiments to test its validation and sensitivity are underway. The Dickerman group has also initiated a collaboration with the Virginia Cooperative Extension Plant Disease diagnostic laboratory at Virginia Tech to obtain samples of naturally infected plants to further test the chip on many more plant species and pathogen types.

Phylogenomics is useful for creating very accurate reconstructions of inheritance from common ancestors and gives researchers a way to better understand the evolutionary similarities and differences of species. The Dickerman group is analyzing the phylogeny of all completely sequenced γ-proteobacteria and has been working with the Cyberinfrastructure Group at the Virginia Bioinformatics Institute to prepare a robust phylogenetic tree to resolve the evolutionary history of this important group of bacteria. Multiple phylogenomic projects have involved the Dickerman group with the evolution of plant and animal pathogens and collaborations with other teams have provided opportunities to perform additional phylogenomics analyses of *Agrobacterium*, *Coxiella* and *Liberibacter*, important plant and mammal pathogens.

Phylogenomics is useful for creating very accurate reconstructions of inheritance from common ancestors.

Microbial ecology has a direct impact on human health through the environmental bacteria we contact and by interaction with the individual human microbiome. The Dickerman group continues its analysis of aerial, plant-surface and termite gut bacteria and is beginning to pursue interests in bacterial evolution, horizontal transfer and functional genomics. The group entered the realm of microbial ecology of the mammalian gut flora with metagenomics investigations into the pig gut microbiome, and will study the functional genomics of bacteria during food digestion in a pig model of obesity. The ecological and functional genomics of microbes present many opportunities for research and will form an important component of future work in the Dickerman group. |



Left to Right: Allan Dickerman, Elena Shulaeva, Kelly Williams, Eric Nordberg

RESEARCH INTERESTS

- PhytPath phytopathogen microarray
- Phylogenetic approaches to comparative genomics
- Pathogen identification by microarrays of rRNA probes
- Microbial ecology

SELECTED RECENT PUBLICATIONS

Slater SC, Goldman BS, Goodner B, et al (2009) Genome sequences of three agrobacterium biovars help elucidate the evolution of multichromosome genomes in bacteria. *The Journal of Bacteriology* **191**(8): 2501-2511.

Wattam AR, Williams KP, Snyder EE, et al (2009) Analysis of ten *Brucella* genomes reveals evidence for horizontal gene transfer despite a preferred intracellular lifestyle. *The Journal of Bacteriology* **191**(11): 3569-3579.

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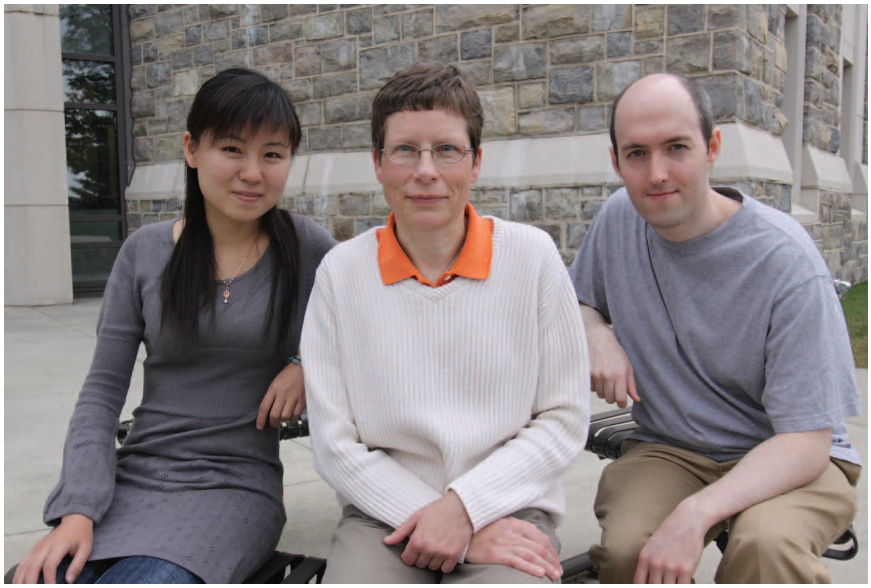
Duan Y, Zhou L, Hall DG, et al (2009) Complete genome sequence of citrus huanglongbing bacterium, '*Candidatus* Liberibacter asiaticus' obtained through metagenomics. *Molecular Plant-Microbe Interactions*: **22**(8): 1011-1020.

Dr. Ina Hoeschele

STATISTICAL GENETICS RESEARCH GROUP

Genetic Architecture of Complex Diseases



Left to right: Hui Yi, Ina Hoeschele, Charles Weeks

THE COMMON THEME of research in the Statistical Genetics Research Group is the statistical design and analysis of genome-wide linkage and association studies and systems genetics experiments. This approach is used to further understand how the joint action and interaction of multiple genes determines complex diseases and biomedical phenotypes of humans, animals and plants. At the present time, the group's main research focus is on developing, implementing and evaluating methods for Quantitative Trait Locus (QTL) mapping of very high-dimensional 'omics phenotypes, gene regulatory and causal network inference in systems genetics experiments, efficient linkage and association mapping in the presence of interactions among genes and among genes and the environment, and identification of pathways from gene expression data affecting biomedical traits of interest.

Statistical genetics allows researchers to make progress in their efforts to understand how the myriad of gene actions and interactions determine complex traits and diseases in animal, human and plant populations.

The group is investigating multivariate, dimension-reduction based methods for high-dimensional quantitative trait loci analysis of 'omics phenotypes, via simulation of systems genetics data and real data analyses to detect the weaker signals of a subset of QTLs jointly regulating a subset of phenotypes. This project is a collaboration with Dr. Alberto de la Fuente at CRS4 Bioinformatica, Italy.

In its work on gene regulatory/causal network inference in systems genetics, the Statistical Genetics Research Group has reconstructed a gene regulatory network using the complete set of yeast genes and yeast genetic markers. This work has been carried out using a sequence-based method for expression QTL mapping, previously developed by the group, and local structural models. The project is a collaboration with former group members Dr. Alberto de la Fuente at CRS4 Bioinformatica, Italy, and Dr. Bing Liu of The Monsanto Company.

The group is using a nonparametric Bayesian method for association and linkage analyses and identification of pathways. This type of approach can be used to identify which pathways affect a continuous biomedical trait or a clinical outcome of interest and can discover any interaction between the genes in a single or in multiple candidate pathways. This project is led by Dr. Fei Zou, Department of Biostatistics, The University of North Carolina at Chapel Hill.

The group is preparing for a genome-wide investigation of expression and DNA methylation in atherosclerosis as part of its work to identify pathways from gene expression data affecting biomedical traits of interest. This analysis of genome-wide expression and DNA methylation data will make use of the Illumina HumanMethylation27 platform. The work is a collaboration with Dr. Yongmei Liu and colleagues, Wake Forest University School of Medicine. |

RESEARCH INTERESTS

- Quantitative and statistical genetics
- Joint linkage and linkage disequilibrium gene mapping
- Genetic parameter estimation
- (Co)variance component estimation
- Generalized linear mixed models
- Nonadditive genetic models
- Design and analysis of microarray transcription profiling experiments

SELECTED RECENT PUBLICATIONS

Bao L, Hoeschele I (2008) Quality assessment for short oligonucleotide microarray data: Comment. *Technometrics* 50: 268-271.

Gao G, Allison DB, Hoeschele I (2008) Haplotyping methods in pedigrees. *Human Heredity* 67: 248-266.

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Dr. Reinhard Laubenbacher

APPLIED DISCRETE MATHEMATICS RESEARCH GROUP

Computational Systems Biology

Left to right: Alan Veliz-Cuba, Shamira Shallom, Katarzyna Świrydowicz, Betsy Williams, Reinhard Laubenbacher, David Murrugarra, Franziska Hinkelmann, Greg Blekherman; (not pictured) Abdul S. Jarrah

DR. REINHARD Laubenbacher's Applied Discrete Mathematics Group is currently focusing on the use of systems biology as an innovative approach to breast cancer research, an effort made possible by the development of new mathematical methods in computational systems biology. Mathematical models, such as finite dynamical systems, are increasingly being used in systems biology to model a variety of biochemical networks. Biochemical networks are central to biological function and models provide a useful way to understand their workings, allowing researchers to design and predict the effect of interventions, such as cancer treatments. The group is currently working with colleagues from VBI, including Drs. Pedro Mendes and Vladimir Shulaev, as well as collaborators from Wake Forest University Comprehensive Cancer Center on several projects. The main application focus of this work is to develop an understanding of malignant changes in the metabolic profile of cells and changes in their iron metabolism.

Evidence suggests that differences in iron metabolism play an important role in cancer risk, survival, and clinical prognosis, especially involving both the development and recurrence of breast cancer in women. The group and its partners are working to develop a systems biology map of iron metabolism. Creating a network of the iron metabolism process would allow researchers to investigate changes in the network under different conditions, serving as a starting point to help identify changes that take place in healthy and diseased tissue. Another project has resulted in the development of new statistical techniques to identify metabolic markers for breast cancer diagnosis.

Before the functional differences between a cancer cell and a normal cell can be understood, an assessment of the overall biochemical network, not just the individual molecular mechanisms involved, is needed.

Other work facilitated by the VBI-Wake Forest partnership highlights the potential benefits of using systems biology as an innovative clinical approach to cancer. Before the functional differences between a cancer cell and a normal cell can be understood, an assessment of the overall biochemical network, not just the individual molecular mechanisms involved, is needed. According to the team, moving the use of systems biology techniques from the laboratory to the clinic could result in the development of improved diagnostic tools and treatment options, as well as potential new drug targets to help combat many potentially fatal types of cancer.

Another research focus of the group is mathematical systems biology, which includes the development of mathematical tools for modeling and simulation of biological networks. The groups has been involved in the creation of parameter estimation methods for Boolean networks, which is available in the software package *Polynome*. Their efforts have also led to a variety of theoretical results about the relationship between the structure and dynamics of discrete network models of such systems. |

RESEARCH INTERESTS

- Mathematical biology
- Applied discrete mathematics
- Symbolic computation
- Systems biology
- Cancer systems biology

SELECTED RECENT PUBLICATIONS

Hower V, Mendes P, Torti FM, Laubenbacher R, Akman S, Shulaev V, Torti SV (2009) A general map of iron metabolism and tissue-specific subnetworks. *Molecular Biosystems* **5**(5): 422-443.

Laubenbacher R, Hower V, Jarrah A, Torti SV, Shulaev V, Mendes P, Torti FM, Akman S (2009) A systems biology view of cancer. *Biochim Biophys Acta* **1796**(2): 129-139.

Laubenbacher, R, Sturmfels, B (2009) Computer algebra in systems biology. *The American Mathematical Monthly* **116**: 882-891.

Sontag E, Veliz-Cuba A, Laubenbacher R, Jarrah A (2008) The effect of negative feedback loops on the dynamics of Boolean network. *Biophysical Journal* **95**(2): 518-526.

Dr. Christopher Lawrence

RESEARCH GROUP

Fungal PathoSystems Biology

Left to right: Kwang-Hyung Kim, Mihaela Babiceanu, Chris Mitelakis, Chris Lawrence, Sang-Wook Park, Amanda Cronin, Ha X. Dang; (not pictured) Rachel Leister

DR. CHRISTOPHER Lawrence's research group studies the ways in which fungi cause diseases of plants and humans. The Lawrence group has been the lead group in the *Alternaria brassicicola* and A. *alternata* genome-sequencing projects. Alternaria is one of the most common molds found on plants and in soil, and is a major plant pathogen. Additionally, these fungi have been clinically linked to human allergic disorders such as asthma and chronic rhinosinusitis. The A. *brassicicola* genome was sequenced in collaboration with Washington University Genome Sequencing Center. The group has also completed sequencing of two A. *alternata* genomes in 2009, using the Roche GS-FLX™ Titanium next generation sequencing platform in the VBI Core Laboratory Facility. Bioinformatic analyses of the genomes were carried out at the Virginia Bioinformatics Institute.

The Lawrence group is using the *Alternaria brassicicola-Brassicaceae* interaction as a system to identify and study fungal pathogenesis and defense responses in plants. Using molecular approaches, coupled with bioinformatic analyses of A. *brassicicola*, the researchers have identified several molecules produced by this plant pathogen that contribute to the development of plant disease.

In contrast to the plant pathogen *Alternaria brassicicola*, the airborne and widely present *Alternaria alternata* species have been especially clinically linked, for almost a century, to human respiratory disorders, including allergy, asthma, and chronic rhinosinusitis. According to the American Lung Association, approximately 34.1 million Americans have been diagnosed with asthma by a health professional during their lifetime, and the World Health Organization estimates that 300 million people worldwide suffer from asthma, with 250,000 annual deaths attributed to the disease in 2005. The Lawrence group is interested in the immunological properties of fungal proteins secreted in the presence of human cells, such as respiratory-tract epithelial cells, antigen presenting cells, macrophages, eosinophils and T helper cells. The group has recently optimized mouse models of *Alternaria* airway inflammation for their studies. The Alternaria genomes sequenced to date have already proven invaluable for the identification of not only virulence factors of plants but allergens and other fungal proteins that cause inflammatory responses in humans. Using the newly completed genome sequences, and through active partnerships with some of the world's leading scientific teams in fungal associated allergic diseases at Mayo Clinic, Rochester, MN and the University of Manchester School of Medicine, Manchester, UK, they will be able to identify pathologically relevant proteins such as novel allergens, immunogenic factors, and, possibly, small molecules that trigger or exacerbate allergic airway inflammation. |

The Alternaria genomes sequenced to date have already proven invaluable for the identification of not only virulence factors of plants, but allergens and other fungal proteins that cause inflammatory responses in humans.

RESEARCH INTERESTS

- *Alternaria* genomics and bioinformatics
- Fungal pathogenesis mechanisms of plants and humans
- Fungal associated allergic airway inflammation and innate immunity

SELECTED RECENT PUBLICATIONS

Kim, K-H, Wilger S, Park SW, Cho Y, Mukhopadhyay B, Cramer RA, Lawrence CB (2009) TmpL, a transmembrane protein required for oxidative stress homeostasis and virulence in a plant and a human fungal pathogen. *PLoS Pathogens* 5(11):e1000653.

Kobayashi T, Koji I, Radhakrishnan S, Mehta V, Vassallo R, Lawrence CB, Cyong J, Pease LR, Oguchi K, Kita H (2009) Asthma-related environmental fungus, *Alternaria*, activates dendritic cells and produces potent Th2 adjuvant activity. *Journal of Immunology* 182: 2502-2510.

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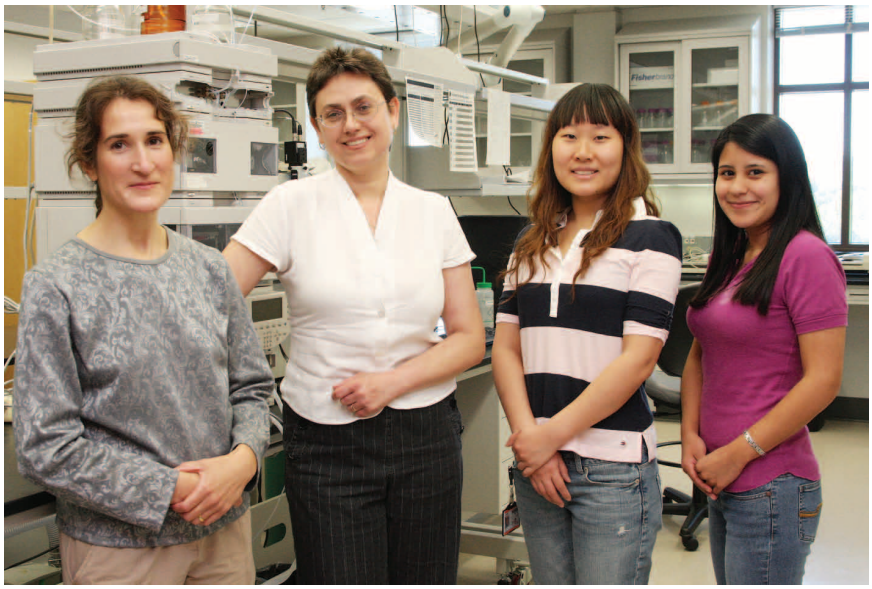
Dr. Iuliana M. Lazar

RESEARCH GROUP

Fast Proteomic Fingerprinting in Cancerous Cells



Left to right: Debby Reed, Iuliana Lazar, Xu Yang, Milagros Perez

MASS SPECTROMETRY is a powerful analytic technique that has become an essential tool in proteomics investigations, providing researchers information about the complexity, concentration, composition, and expression levels of proteomic samples. Biomarker discovery and screening is an expanding field in proteomics that is being developed to identify changes in the levels of key proteins in the cell in response to the onset or development of disease. The scientific community has invested extensive efforts into the development of methods that would allow for the sensitive screening of large panels of biomarkers, instead of just one at a time. This type of research promises to advance the capabilities of early cancer detection, which could significantly reduce the mortality rate due to different types of cancer. Dr. Iuliana Lazar's research group has developed techniques for fast biomarker fingerprinting in complex cellular extracts that demonstrate the power, effectiveness, and reliability of mass spectrometry detection for large-scale biomarker screening in breast cancer research.

Biomarker discovery and screening is an expanding field in proteomics that promises to advance the capabilities for early cancer detection.

A new one-step bioanalytical approach allows the researchers to profile in detail complex cellular extracts of proteins. The group has used the approach for proteomic profiling of MCF-7 breast cancer cells cultured in estradiol, the most abundant circulating estrogen in humans, and tamoxifen, a non-steroidal drug commonly prescribed in hormonal breast cancer therapy. The analysis of labeled protein samples has resulted in the identification of 16 differentially expressed proteins, which has helped establish a link between the proteins and certain cancer-related biological processes, such as cell proliferation, cell death, tumor development, and metastasis.

Working with Dr. Ina Hoeschele at VBI, several innovative developments have been integrated into the one-step bioanalytical approach, including a data acquisition strategy to analyze different cell states and replicates, an advanced way to process the data, and a novel statistical method to check the experimental data. By assessing the expression level changes in the identified proteins, the group hopes to develop a more comprehensive understanding of the complex signaling pathways involved in cancer development, which may shed some light on the ways cancer drugs, like tamoxifen, work to inhibit cell proliferation and induce response to stress at the molecular level. This work will help advance researchers' understanding of how breast cancer cells develop resistance to tamoxifen and could lead to the development of more effective diagnosis and treatment for cancer patients. |

RESEARCH INTERESTS

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

SELECTED RECENT PUBLICATIONS

Armenta JM, Hoeschele I, Lazar IM (2009) Differential protein expression analysis using stable isotope labeling and PQD linear ion trap MS technology. *Journal of The American Society for Mass Spectrometry* **20**(7): 1287-1302.

Yang X, Lazar IM (2009) MRM screening and biomarker discovery: a library of human cancer-specific peptides. *BMC Cancer* **9**(1): 96.

Armenta JM, Dawoud AA, Lazar IM (2009) Microfluidic chips for protein differential expression profiling. *Electrophoresis* **30**(7): 1145-1156.

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Dr. Pedro Mendes

BIOCHEMICAL NETWORKS MODELING GROUP

Software, Standards, & Methods for Computational Systems Biology

Left to right: Revonda Pokrzywa, Pedro Mendes, Stefan Hoops

THE PURPOSE of systems biology is to explore how the interactions between a cell's molecules impact the behavior of the system. By creating models of biochemical networks, researchers are able to better describe and understand the system, as well as the effects of interventions. Biochemical networks require powerful computational support to analyze data, simulate dynamics, and provide a framework to integrate knowledge.

Dr. Pedro Mendes is chair of Computational Systems Biology at the University of Manchester, England, and leads the Biochemical Networks Modeling Group at VBI. The main goal of the group is to develop computational methods as a way to better understand the workings of biochemical networks.

The group has continued its work on COPASI (Complex Pathway Simulator), an open-source software package that allows users with limited experience in mathematics to construct models and simulations of biochemical networks. The group has been developing COPASI for nearly a decade and it is now one of the primary tools used for computational systems biology research. The group has released four new versions of the software in the past year, incorporating new features that have improved its modeling capabilities in several areas.

COPASI now supports MIRIAM (Minimum Information Requested in the Annotation of Biochemical Models)-compliant annotation of models and the application of optimization for sensitivity analysis. These enhancements have allowed the group to develop new modeling methodologies for systems biology, including a new method of global sensitivity analysis. Because biochemical models are not linear, it is difficult to assess how a parameter that changes within a wide range of values will affect the model. Working with colleagues from the University of Heidelberg, the group used the new COPASI features to develop a method that utilizes global optimization algorithms to rapidly assess which parameters have the least effect on the model's outcome.

The study of biochemical networks requires powerful computational support to analyze data, simulate dynamics, and provide a framework to integrate knowledge.

The group also continues to be involved in the creation of community standards of systems biology data in a format compatible with a network model. The Biochemical Networks Modeling Group has created a proposal for the Systems Biology Results Markup Language (SBRML), which provides a way to describe numerical data and associate it with specific elements of a model. SBRML is expected to become a standard way to communicate and store various kinds of systems biology data. |

RESEARCH INTERESTS

- Modeling and simulation of biochemical systems
- Global optimization and inverse problems
- Management and analysis of systems biology data sets
- Oxidative stress and its cellular regulation
- Reverse-engineering of biochemical networks

SELECTED RECENT PUBLICATIONS

Herrgård MJ, Swainston N, Dobson P, et al (2008) A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. *Nature Biotechnology* **26**: 1155-1160.

Hower V, Mendes P, Torti FM, Laubenbacher R, Akman S, Shulaev V, Torti SV (2009) A general map of mammalian iron metabolism and tissue-specific subnetworks. *Molecular Biosystems* **5**(5): 422-443.

Hucka M, Hoops S, Keating S, Le Novère N, Sahle S, Wilkinson D (2008) Systems Biology Markup Language (SBML) Level 2: Structures and facilities for model definitions. *Nature Precedings doi:*10.1038/npre.2008.2715.1.

Dr. Biswarup Mukhopadhyay

RESEARCH GROUP

Redox Biology of Methanogenic Archaea and Mycobacteria, Microbial Gasification of Coal and the Mechanism of Phosphoenolpyruvate Carboxykinase

Left to right: (front) Endang Purwantini, Usha Loganathan, Dwi Susanti, Jennifer Downs; (middle) Karla Piedl, Lindsay Martin, Biswarup Mukhopadhyay, Lakshmi Dharmarajan; (back) Eric Johnson, Jason Rodriguez, Matthew Smith

DR. MUKHOPADHYAY'S laboratory has been investigating coenzyme F_{420} metabolism in the mycobacteria, sulfur metabolism and redox buffering systems in methanogenic archaea, the pathways for oxidation of hydrocarbons and reduction of CO_2 to methane in coal beds, and the mechanism of the enzyme phosphoenolpyruvate carboxykinase (PEPCK).

Mycobacteria, a group of bacteria that includes several pathogens known to cause disease in mammals, produce the enzyme glucose-6-phosphate dehydrogenase (Fgd). This enzyme requires a special coenzyme (F_{420}) for its activity and generates a reduced form of this coenzyme molecule ($F_{420}H_2$) as part of the reaction that it catalyzes. F_{420} is found primarily in the methanogenic archaea, a group of microorganisms that produce methane as a metabolic byproduct. In the bacterial domain, F_{420} is present in the Actinobacteria phylum, a collection of bacteria that include some of the most common soil, freshwater and marine life, and which also includes the mycobacteria. Dr. Mukhopadhyay's team has found that $F_{420}H_2$ chemically reduces nitrogen dioxide (NO_2) to the gas nitrogen monoxide (NO), which could help *Mycobacterium tuberculosis* to combat NO_2 stress; this bacterium causes tuberculosis in humans. *M. tuberculosis* is more sensitive to NO_2 than NO. Since an activated macrophage (a specific type of white blood cell in the body that assists in the defense against invading pathogens) produces NO and converts this compound in its acidified vacuoles or phagosomes to NO_2 for a more aggressive attack, *M. tuberculosis* would use $F_{420}H_2$ to reduce NO_2 back to NO and lower the effectiveness of the antibacterial actions of macrophages.

Dr. Biswarup Mukhopadhyay's research group focuses on the study of methanogenic archaea, bioconversion of coal in coal beds, tuberculosis, and type 2 diabetes.

While investigating the redox buffering systems of *Methanocaldococcus jannaschii*, an ancient methane-producing microbe, the group has characterized a NADH oxidase that appears to be a new member of a group of enzymes known as the group 3 flavin-dependent protein disulfide reductases. The researchers in Dr. Mukhopadhyay's team are also identifying the relevant biochemical pathways that are operational for hydrocarbon degradation in coal bed methane wells.

The work on human liver cytosolic GTP-PEPCK, which is a gluconeogenic enzyme and plays a direct role in type 2 diabetes, has the goal of developing therapeutics that will not inactivate but reduce the activity of the enzyme and thereby lower the blood glucose level in a person with type 2 diabetes, without causing hypoglycemia. Results from the group show that the fully conserved Tyr235 of the human enzyme is not essential for catalysis, but influences the reaction through an anion-quadrupole interaction, a special type of molecular interaction that has been rarely encountered in enzyme catalysis. An interference with this interaction might provide a way to lower the activity of the enzyme. |

RESEARCH INTERESTS

- Metabolism of evolutionarily deeply rooted methanogenic archaea: evolution of sulfite reductases
- Coal bioconversion to methane and mitigation of methane-induced mine explosion
- Structure function studies of phosphoenolpyruvate carboxykinase and Type 2 diabetes
- Structure function studies of a novel archaeal type phosphoenolpyruvate carboxylase
- Tuberculosis – metabolism of coenzyme F_{420} in mycobacteria

SELECTED RECENT PUBLICATIONS

Anderson I, Dharmarajan L, Rodriguez J, et al (2009) The complete genome sequence of *Staphylothermus marinus* reveals differences in sulfur metabolism among heterotrophic Crenarchaeota. *BioMed Central Genomics* **10**: 145.

Case CL, Rodriguez JR, Mukhopadhyay B (2009) Characterization of a NADH oxidase of the flavin-dependent disulfide reductase family from *Methanocaldococcus jannaschii*. *Microbiology* **155**: 69-79.

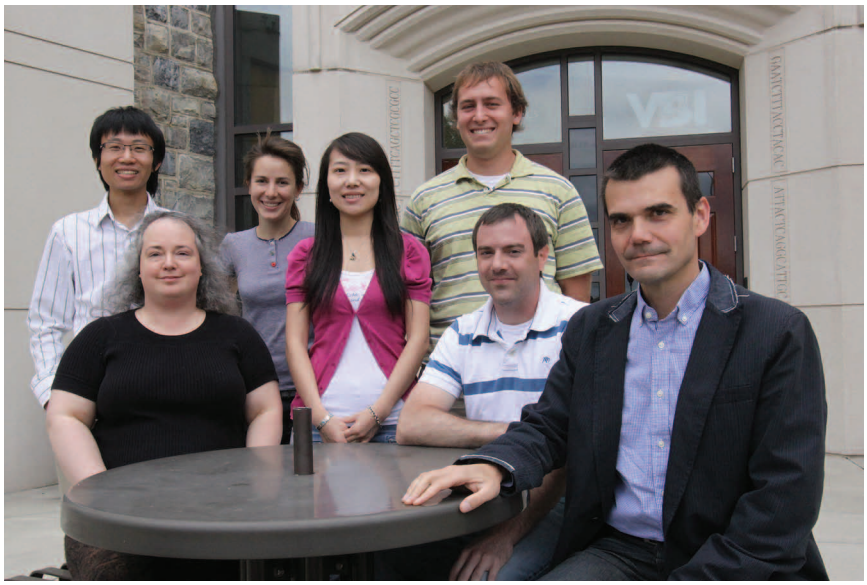
Dharmarajan L, Case CL, Dunten P, Mukhopadhyay B (2008) Tyr^{235} of human cytosolic phosphoenolpyruvate carboxykinase influencing catalysis through an anion-quadrupole interaction with phosphoenolpyruvate. *FEBS Journal* **275**(23): 5810-5819.

Purwantini E, Mukhopadhyay B (2009) Conversion of NO_2 to NO by reduced Coenzyme F_{420} protects mycobacteria from nitrosative damage. *Proceedings of the National Academy of Sciences United States of America* **106**(15): 6333-6338.

Dr. Jean Peccoud

SYNTHETIC BIOLOGY RESEARCH GROUP

Genetic Design Automation



Left to right: Yizhi "Patrick" Cai, Julie Marchand, Laura Adam, Yijing "Sarah" Zheng, Matt Lux, David Ball, Jean Peccoud

THE SYNTHETIC BIOLOGY group at the Virginia Bioinformatics Institute is developing a design automation framework for engineering synthetic biological systems. The successful combination of experimental and computational methods within this framework will unleash the enormous potential of the rapidly emerging field of synthetic biology. In the short term, designing, implementing, and characterizing synthetic DNA sequences provides a new framework to test biological hypotheses and advance biological knowledge. Long-term improved productivity for the biotechnology industry, comparable to what has been achieved by the electronics industry over the last four decades, will result from integrating new computer languages to design DNA sequences, coupling DNA fabrication and design, and engineering a custom imaging platform to evaluate the performance of synthetic DNA molecules.

The Synthetic Biology Group is developing new computer languages to represent complex phenotypes that are encoded in long DNA sequences composed of multiple interacting functional blocks also known as genetic parts. This transformative approach is validated using libraries of related artificial gene networks generated from small libraries of genetic parts.

The group's computational approach is complemented by efforts to collect better data to characterize the dynamics of the gene networks encoded in artificial gene networks. Bacterial or yeast cells are grown and monitored under a microscope for extended periods of time during which images are collected every few minutes. Custom imaging software has been developed to reduce tens of thousands of images typically collected in such experiments to a smaller data set describing the time evolution of regulatory processes in individual cells. In collaboration with Dr. John Tyson's research group, this approach is being applied to the network controlling the cell cycle in yeast. Monitoring individual cells over extended periods of time with a good time resolution leads to new insights into the mechanisms controlling this important biological process.

The successful combination of experimental and computational methods will unleash the enormous potential of the rapidly emerging field of synthetic biology.

Research arising from the Synthetic Biology Group directly translates into applications that can be used by the biomedical and biotechnology communities to better leverage the potential of chemical DNA synthesis. The National Science Foundation recently awarded a three-year $1,421,725 grant to the Synthetic Biology Group to develop GenoCAD - a web-based Computer Assisted Design environment for synthetic biology. GenoCAD, which can be regarded as one of the first Computer Assisted Design systems for synthetic DNA sequences, provides a sequence builder function that guides users through the process of designing a new genetic construct from a database of standard genetic parts. It also includes a sequence verification tool that can be used to ensure that DNA sequences are consistent with a set of predefined design guidelines. GenoCAD is an open source project that will engage members of the synthetic biology community in the specification and development efforts. |

RESEARCH INTERESTS

- Linguistic models of DNA sequences
- High-throughput imaging
- Design automation of synthetic genetic systems

SELECTED RECENT PUBLICATIONS

Goler JA, Bramlett B, Peccoud J (2008) Genetic design: Rising above the sequence. *Trends in Biotechnology* 26: 538-544.

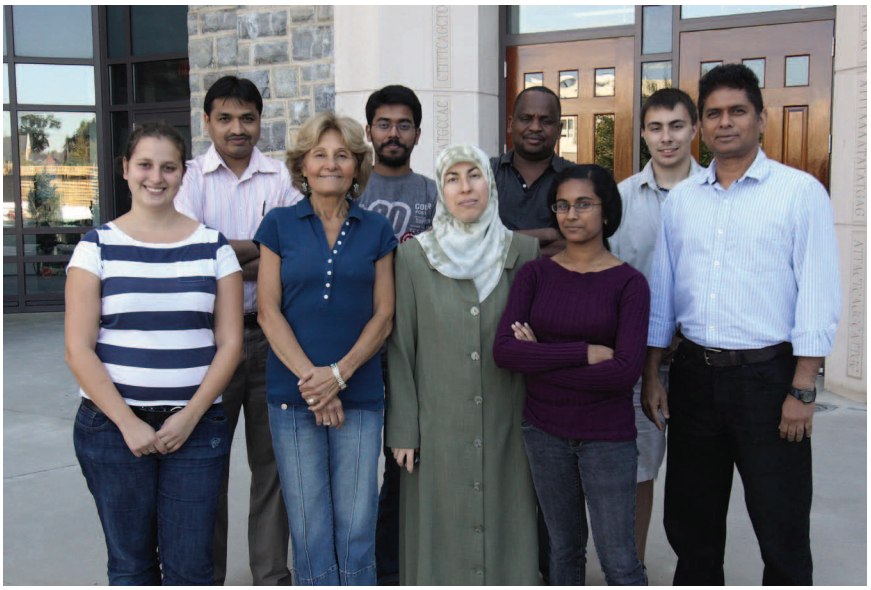
Peccoud J, Blauvelt MF, Cai Y, Cooper KL, Crasta O, DeLalla EC, Evans C, Folkerts O, Lyons BM, Mane SP, Shelton R, Sweede MA, Waldon SA (2008) Targeted development of registries of biological parts. *PLoS ONE* 3(7): e2671.

Czar M, Anderson JC, Bader J, Peccoud J (2009) Gene synthesis demystified. *Trends in Biotechnology* 27(2): 63-72.

Dr. Andy Pereira

RESEARCH GROUP

Gene Interaction Networks for Functional Analysis of Complex Biological Processes



Left to right: (front) Dragana Avirovik, Graciela Santopietro, Amal Harb, Abhi Loganathan, Andy Pereira; (back) Madana Ambavaram, Arjun Krishnan, Utlwang Batlang, Chris Saul; (not pictured) Sarah Misyak, Olivia Crasta, Sherwood Lin, Ankit Gupta

PLANTS HAVE COMPLEX mechanisms for responding to and surviving environmental stresses such as drought, heat, cold, and disease. Analysis of the plant stress responses can provide valuable insight into protective mechanisms and resistance to the plant stresses. The stress response and resistance pathways are complex, involving a variety of factors that must be examined from a systems biology perspective.

The goal of Dr. Andy Pereira's research group is to develop a systems-level view of these complex biological processes through the development of probabilistic functional gene networks. These types of genome-scale networks are constructed by integrating multiple functional genomics data with the results of genetic perturbation experiments, which provide a validated systems view of biological processes that have predictive value. Pereira's group is using this systems biology approach to create drought gene interaction networks. Drought can have significant impacts on crop production, especially when it occurs during essential periods of plant growth. Because the reproductive stage of cereal crops is very sensitive to drought and can have the most significant effect on yield losses, the group has developed an iterative predictive and experimental model system for this drought-sensitive stage, allowing for a comparative analysis of *Arabidopsis* and rice in an effort to better understand this biological process.

A combined bioinformatic and systems biology approach is a powerful way to find those genes that may be modified in some way to improve crop adaptability.

Using functional genomics data from genome-wide comparative transcriptome analysis of drought responses from both plants, the group has been able to identify common regulated gene pathways and genes following exposure to drought-like conditions. This information is then used to create gene interaction networks for *Arabidopsis* and rice. Since plants' perception and resistance to drought has evolved through some common conserved mechanisms, the group can use these networks to experimentally analyze comparative gene functions between *Arabidopsis* and rice and identify how certain genes in the plants regulate other genes. This combined bioinformatic and experimental systems biology approach, which can also be used for comparative analysis of other cereal crops, is a powerful way to find those genes that may be modified in some way to improve crop adaptability, which will contribute to the development of stable food systems worldwide. |

RESEARCH INTERESTS

- Creation and use of gene interaction networks for functional genomics studies in multiple organisms
- Analysis of genetic networks underlying the pathways involved in abiotic stress using various -omics tools
- Development of gain-of-function transposon mutagenesis in *Arabidopsis,* rice and tomato
- Comparative functional genomics between *Arabidopsis*, rice and maize

SELECTED RECENT PUBLICATIONS

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Krishnan A, Guiderdoni E, An G, et al (2009) Mutant resources in rice for functional genomics of the grasses. *Plant Physiology* **149**: 165-170.

Krishnan A, Greco R, Pereira A (2008) Diversity of En/Spm transposons in maize and rice. *Maydica* **53**: 181-187.

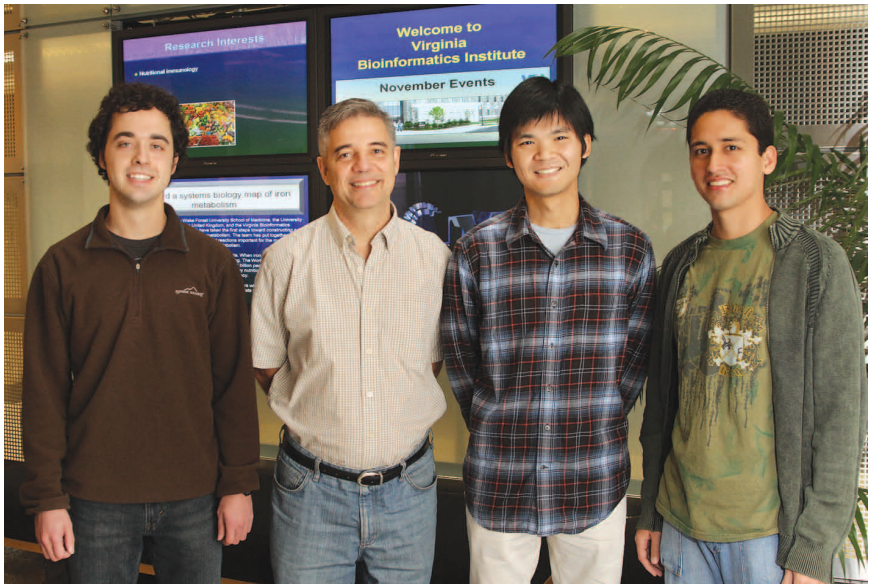
Krishnan A, Pereira A (2008) Integrative approaches for mining transcriptional regulatory programs in *Arabidopsis*. *Briefings in Functional Genomics & Proteomics* **7**: 264-274.

Marsch-Martinez N, Pereira A (2009) Activation tagging for gain-in-function mutants. In *Plant Developmental Biology – Biotechnological Perspectives*, Pua EC, Davey MR (eds) Springer Publishing Company, Berlin, Germany. In press.

Dr. João C. Setubal

RESEARCH GROUP

Bacterial Genomics & Bioinformatics



Left to right: Andrew Warren, João Setubal, Kuan Yang, Ulisses Dias

DR. JOÃO C. SETUBAL'S research group works primarily on bioinformatics for bacterial genome-annotation and sequence analysis, with a focus on facilitating the comparison of genomes. Thanks to new and cheaper DNA sequencing technologies, bacterial genomes continue to become available at a rapid pace, enormously increasing the amount of sequencing data available and creating added pressure and incentive for bioinformaticians to develop new and more efficient sequence analysis computer programs. In addition to work related to specific genomes (which currently cover the genera *Agrobacterium*, *Azotobacter*, *Brucella*, *Pseudomonas*, and *Xanthomonas*), the Setubal research group is interested in automated genome annotation, algorithms to help infer bacterial genome evolution, web-based infrastructure for genome annotation and analysis, and metagenomics.

Pseudomonas syringae is a plant pathogen that has numerous strains that can infect a variety of plants. Some of these strains cause disease in important agricultural crops, such as tomato. The Setubal group collaborates with Boris Vinatzer, Assistant Professor in the Department of Plant Pathology, Physiology, & Weed Science at Virginia Tech, on the genomic analyses of *Pseudomonas syringae* strains. Recently, the two groups identified several genes in strain T1 that likely play a crucial role in its pathogenicity in tomato plants.

The Setubal group developed the Genome Reverse Compiler, a bioinformatic tool that played an important role in the *Pseudomonas syringae* work. This tool is a computer program that efficiently and automatically annotates the genes of bacterial genomes. Gene annotation, the process whereby evidence is inferred about the function of genes, is a key step in genome understanding. Thanks to the Genome Reverse Compiler, the T1 genome was rapidly annotated, thus providing a foundation for additional work on this pathogen.

Brucella is another class of organisms studied by the Setubal group, in collaboration with Stephen Boyle, Professor of microbiology and Director of Virginia Tech's Center for Molecular Medicine and Infectious Diseases. *Brucella* bacteria are pathogens that cause serious respiratory diseases in humans and animals. By doing a careful comparative genomic analysis of 10 different *Brucella* genomes, groups of genes have been discovered that were likely acquired by an ancestral *Brucella* and enabled its descendants to become intracellular pathogens. This discovery was made possible thanks to a novel bioinformatic method developed by the Setubal group to compare genomic regions from different species.

Gene annotation, the process whereby evidence is inferred about the function of genes, is a key step in genome understanding.

In addition to work related to specific genomes, the group is also part of a project with Hamza-El-Dorry, from the American University in Cairo. El-Dorry is leading the Metagenomics Red Sea project, which has collected biological samples from several locations and depths in the Red Sea. The expectation is that interesting discoveries about oceanic microbial biodiversity will be made. |

RESEARCH INTERESTS

- Bioinformatics infrastructure for genome annotation
- Algorithms for genome analysis
- Automated annotation of bacterial genomes
- Bacterial plant pathogens
- Bacterial genome evolution

SELECTED RECENT PUBLICATIONS

Almeida NF, Yan S, Lindeberg M, et al (2009) A draft genome sequence of *Pseudomonas syringae* pv. tomato strain T1 reveals a repertoire of type III related genes significantly divergent from that of *Pseudomonas syringae* pv tomato strain DC3000. *Molecular Microbe-Plant Interactions* 22: 52-62.

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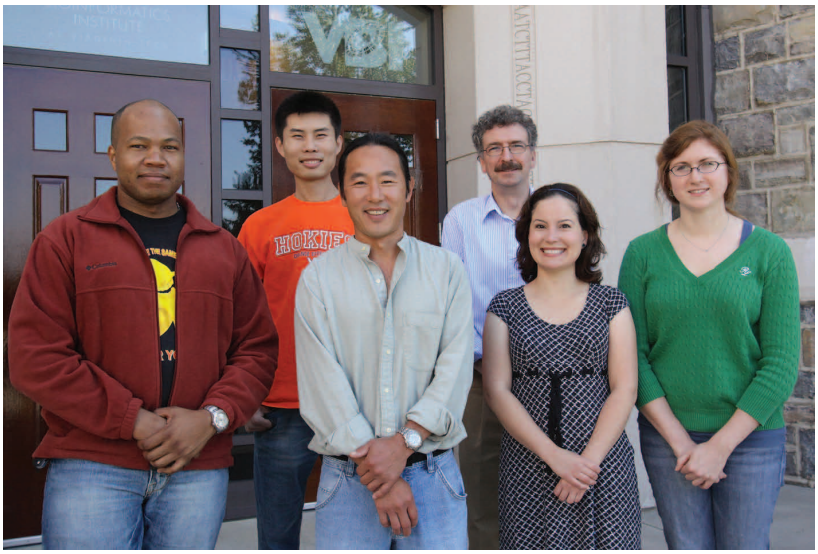
Slater SC, Goldman BS, Goodner B, et al (2009) Genome sequences of three agrobacterium biovars help elucidate the evolution of multichromosome genomes in bacteria. *The Journal of Bacteriology* 191(8): 2501-2511.

Dr. Vladimir Shulaev

BIOCHEMICAL PROFILING RESEARCH GROUP

Metabolomics for System Biology



Left to right: (front) Diego F. Cortes, Joel L. Shuman, Jenny M. Armenta, Sarah H. Holt; (back) Nan Lu, Vladimir Shulaev

THE BIOCHEMICAL Profiling Group at the Virginia Bioinformatics Institute is developing a high-throughput metabolomics platform for systems biology research. This platform can be used for the discovery of metabolic biomarkers and gene function elucidation. Metabolomics is a powerful tool that complements large-scale genomic and proteomic technologies. The metabolomics platform being developed by the group is built on a combination of untargeted metabolite profiling, metabolic fingerprinting, and targeted analysis.

Analytical techniques based on mass spectrometry provide sample analysis with high sensitivity and coverage of a wide range of metabolites. The metabolomics platform under development by the group is being successfully used to elucidate early metabolic responses to abiotic stress in plants, identify unique metabolic signatures associated with the progression of malignancy in human breast epithelium cells, and identify unique metabolic signatures associated with response to various drugs in the malaria parasite *Plasmodium falciparum*.

The group has been using metabolomics to study malaria and identify the mode of action of antimalarial drugs in collaboration with Dr. David Sullivan's group at the W. Harry Feinstone Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health.

A high-throughput metabolomics platform is needed as a tool to understand systems biology, discover metabolic biomarkers, and elucidate gene function.

Information on the metabolic state of different developmental stages of *Plasmodium falciparum* is helping to identify specific metabolic changes associated with drug treatment. Recent metabolomics analysis has shown that antimalarial drugs have different metabolic response patterns and metabolic fingerprinting is being used to classify different antimalarial drugs based on their metabolic response pattern.

In collaboration with Dr. Reinhard Laubenbacher's group at VBI, a new mathematical model is being developed to assign a global signature to each drug-treated *P. falciparum* sample that does not rely on individual markers. This signature can be used to compare signatures in different samples. This new approach is being used on metabolomics data from drug-treated and untreated *P. falciparum*-infected red blood cells to classify known and novel candidate antimalarial drugs.

The Biochemical Profiling Group is a key member of the Rosaceae scientific community. Partnerships with researchers at other leading universities are helping plant breeders in their efforts to improve related Rosaceae crops like apple, peach and pear — high-value nutritional foods of considerable international economic importance. The group has developed a high-throughput genetics platform in the woodland strawberry (*Fragaria vesca*) utilizing a highly efficient plant transformation protocol. This has resulted in a collection of insertional mutant cell lines of value to Rosaceae scientists around the globe. As part of the International Consortium that is sequencing the full genome of *F. vesca*, the group is busy building a portfolio of resources aimed at crop improvement. |

RESEARCH INTERESTS

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

SELECTED RECENT PUBLICATIONS

Koussevitzky S, Suzuki N, Huntington S, Armijo L, Sha W, Cortes D, Shulaev V, Mittler R (2008) Ascorbate peroxidase 1 plays a key role in the response of *Arabidopsis thaliana* to stress combination. *Journal of Biological Chemistry* **283**: 34 197-34 203.

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Shulaev V, Korban KS, Sosinski B, et al (2008) Multiple models for Rosaceae genomics. *Plant Physiology* **147**: 985-1003.

Hower V, Mendes P, Torti FM, Laubenbacher R, Akman S, Shulaev V, Torti SV (2009) A general map of iron metabolism and tissue-specific subnetworks. *Molecular BioSystems* **5**(5): 422-443.

Dr. Bruno W. S. Sobral

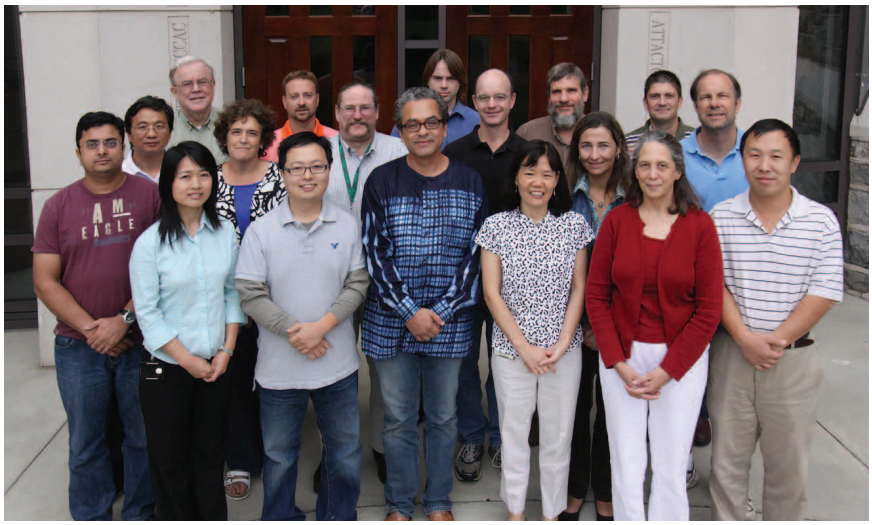
CYBERINFRASTRUCTURE RESEARCH GROUP

THE CYBERINFRASTRUCTURE Group (CIG) at VBI develops methods, infrastructure, and resources to help enable scientific discoveries in infectious disease research and other research fields. The group applies the principles of cyberinfrastructure to integrate data, computational infrastructure, and people. CIG has developed many public resources for curated, diverse molecular and literature data from various infectious disease systems, and implemented the processes, systems, and databases required to support them. It also conducts research by applying its methods and data to make new discoveries.

In September 2009, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), awarded a 5-year, $27,670,448 contract to CIG to support the biomedical research community's work on infectious diseases. The funding is being used to integrate vital information on pathogens, provide key resources and tools to scientists, and help researchers to analyze genomic, proteomic and other data arising from infectious disease research. The new contract covers the development of two web-based resources for biomedical research. The first part of the project supports the development of the Pathogen Portal (http://pathogenportal.org) for the entire Bioinformatics Resource Center (BRC) program, which will serve as an informatics coordinating center and gateway for four newly established BRCs.

The second part of the project supports the development of the PATRIC 2.0 BRC. In June 2004, NIAID awarded CIG a five-year, $10.3 million contract to establish a multi-organism relational database for infectious disease research that focused on biodefense and emerging infectious diseases. The PathoSystems Resource Integration Center (PATRIC; see http://patric.vbi.vt.edu/) was created to serve as a comprehensive web-based resource for an important subset of pathogens - from the set of selected NIAID category A-C priority pathogens. The work supported by the PATRIC 2.0 award spans all bacterial species in the selected NIAID category A-C priority pathogens list and consolidates earlier PATRIC work, as well as the work of other BRC systems that handled bacterial data, into PATRIC 2.0. CIG is building on its successes and experiences gained in executing PATRIC by providing a new, expanded PATRIC 2.0 web-based system that serves as a robust point of entry for access to a host of information, tools and resources for selected NIAID category A-C priority bacterial pathogen species.

In addition, CIG continues to use its model of extensive collaboration with diverse scientific communities across the globe to jointly discover new biological knowledge, as well as focusing internally on biological research that CIG's infrastructure, data and analysis are uniquely positioned to develop. |



Left to right: (front) Maulik Shukla, Chunhong Mao, Harry Yoo, Bruno Sobral, Chunxia Wang, Rebecca Will, Yan Zhang; (middle) Chengdong Zhang, Rebecca Wattam, Eric Snyder, Dan Sullivan, Isabel Da Fonseca, Kelly Williams; (back) Bruce Sharp, Joe Gabbard, Eric Nordberg, Mark Scott, Ron Kenyon

The CyberInfrastructure Group integrates vital information on pathogens, provides key resources and tools to scientists, and helps researchers to analyze genomic, proteomic and other data arising from infectious disease research.

RESEARCH INTERESTS

- Development and deployment of cyberinfrastructure
- Infectious disease research
- Host-pathogen-environment interactions

SELECTED RECENT PUBLICATIONS

Crasta OR, Folkerts O, Fei Z, Mane SP, Evans C, Martino-Catt S, Bricker B, Yu G, Du L, Sobral BW (2008) Genome sequence of *Brucella abortus* vaccine strain S19 compared to virulent strains yields candidate virulence genes. *PLoS ONE* **3**(5): e2193.

Gillespie JJ, Williams K, Shukla M, et al (2008) Rickettsia phylogenomics: unwinding the intricacies of obligate intracellular life. *PLoS ONE* **3**(4): e2018.

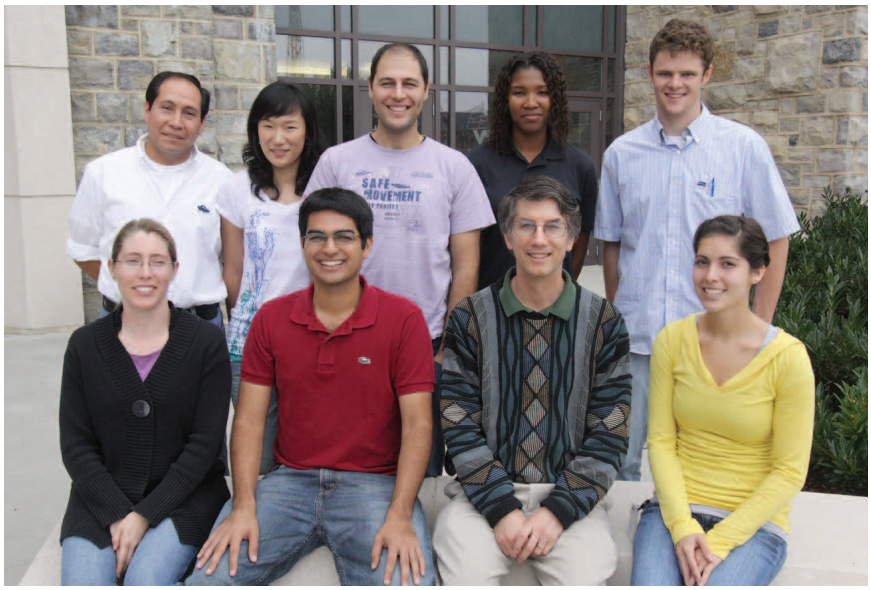
Gillespie JJ, Ammerman NC, Dreher-Lesnick SM, Rahman MS, Worley MJ, Setubal JC, Sobral BS, Azad AF (2009) An anomalous type IV secretion system in Rickettsia is evolutionarily conserved. *PLoS ONE* **4**(3): e4833.

Wattam AR, Williams KP, Snyder EE, et al (2009) Analysis of ten *Brucella* genomes reveals evidence for horizontal gene transfer despite a preferred intracellular lifestyle. *Journal of Bacteriology* **191**(11): 3569-3579.

Dr. Brett M. Tyler

RESEARCH GROUP

Plant-Pathogen Interactions:
From Genome Sequences to
Genetic Networks



Left to right: (front) Regina Hanlon, Shiv Kale, Brett Tyler, Emily Feldman; (back) Felipe Arredondo, Danielle Choi, Enzo Antignani, LaChelle Waller, Todd Brengel; (Not pictured) Sucheta Tripathy, Trudy Torto-Alalibo

INTERCONNECTED GENETIC regulatory networks govern the interactions of hosts and pathogens, due to an ongoing co-evolutionary battle between the organisms. Understanding the structure of these networks will help researchers develop more sophisticated approaches to disease prevention and control. Dr. Brett Tyler's research group is building data collections and tool sets to dissect in detail host-pathogen genetic networks, with a particular focus on oomycete plant pathogens.

Oomycetes are fungal-like organisms related to marine algae that cause tens of billions of dollars of losses to agriculture, forestry, and natural ecosystems every year. The group is sequencing the genomes of several oomycete plant pathogens to uncover their genetic characteristics. They have produced improved sequences of the *Arabidopsis* pathogen *Hyaloperonospora arabidopsidis* and the soybean pathogen *Phytophthora sojae*, sequenced three additional strains of *P. sojae*, and started sequencing the genome of the fish pathogen *Saprolegnia parasitica*.

The discovery of the mechanism used by effector proteins to enter host cells is paving the way for the identification of a new class of therapeutic agents that can protect plants, animals, and humans from oomycete, fungal, and parasite infection.

Functional genomics analysis of these genomes has uncovered a large family of virulence genes that enables proteins to enter the cells of their hosts. Pathogens use effector molecules to manipulate the physiology of their hosts, making them more susceptible to infection. Some of these effectors can be recognized by plant resistance gene products, triggering an effective defense response. The group also discovered a specific protein region containing the amino acid sequence motifs RXLR and dEER that has the ability to carry the virulence proteins across the membrane surrounding plant cells. Once inside, the proteins suppress plant defense reactions, such as programmed cell death, allowing the infection to progress. The work also demonstrated that the RXLR and dEER motifs could be replaced by similar targeting sequences found in effector proteins produced by the malarial parasite *Plasmodium*. The group discovered a small molecule that can block effector protein entry, paving the way for the identification of a new class of therapeutic agents that can protect plants, animals, and humans from oomycete, fungal, and parasite infection.

The group has also completed a project focused on the dynamics of how genes from soybean and its pathogen, *P. sojae*, are expressed during infection. One challenge that occurs when analyzing systems biology data is the process of inferring complex genetic regulatory networks from the data. Dr. Tyler's group is developing mathematics and computer science-based methods for inferring and modeling biological processes, including methods for analyzing data at a whole pathway level and for minimizing uncertainty in inferred models. |

RESEARCH INTERESTS

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

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Dou D, Kale SD, Wang XL, et al (2008) Conserved C-terminal motifs required for avirulence and suppression of cell death by *Phytophthora sojae* effector Avr1b. *Plant Cell* **20**(4): 1118-1133.

Dou D, Kale SD, Wang X, Jiang RHY, Bruce NA, Zhang X, Arredondo FD, Tyler BM (2008) RXLR-mediated entry of *Phytophthora sojae* effector Avr1b into soybean cells does not require pathogen encoded machinery. *Plant Cell* **20**(7): 1930–1947.

Tyler BM (2009) Entering and breaking: virulence effector proteins of oomycete plant pathogens. *Cellular Microbiology* **11**(1): 13-20.

Zhou L, Mideros SX, Bao L, Hanlon R, Arredondo FD, Tripathy S, Krampis K, Jerauld A, Evans C, St. Martin SK, Maroof SMA, Hoeschele I, Dorrance AE, Tyler BM (2009) Infection and genotype remodel the entire soybean transcriptome. *BMC Genomics* **10**:49.

Dr. John Tyson

RESEARCH GROUP

Deterministic and Stochasic Models of Cell Cycle Regulation in Budding Yeast

Left to right: (front) Jianhua Xing, Umma Mobaserra, Teeraphan Laomettachit, Kathy Chen, Janani Ravi, Yan Fu; (middle) Zhanghan Wu, Tongli Zhang, Anael Verdugo, John Tyson, Rajat Singhania, Baris Hancioglu, Sandip Kar; (back) Kartik Subramaniam, Iman Tavassoly, Debashis Barik, Tian Hong, Chun Chen

DR. JOHN TYSON'S RESEARCH Group studies biological systems from a rigorous mathematical perspective, and builds realistic models that help researchers gain a deeper understanding of physiological and molecular events. Most of the group's work is on the mechanism of cell division cycle control as seen in budding yeast, fission yeast, *Xenopus* embryos and egg extracts, *Drosophila* embryos and mammalian cells.

A complex network of interacting genes and proteins controls the cell cycle in budding yeast. Progression through the cell cycle is very rigid in some respects (DNA synthesis, mitosis and cell division always proceed in strict order) and very sloppy in other respects (cells are not too fussy about how big they are or how old they are when they divide). Much of the group's work in the past twelve months has focused on the molecular machinery that accounts for both the robust and noisy characteristics of cell cycle regulation.

Stochastic models developed by Dr. Tyson and collaborators point to low numbers of mRNA molecules as the primary source of noise in the control system and suggest that the experimentally measured abundance and stability of specific mRNA species may be incorrect by 5–10 fold. Deterministic models have uncovered a regulatory motif (feed-forward loops) that may play important roles in coupling the basic cell cycle 'engine' (periodic activation of cyclin-dependent kinases) with the events driven by the engine. A bioinformatic analysis of genomic, transcriptomic, and phosphoproteomic data from budding yeast shows clearly that this regulatory motif occurs much more likely than would be expected by chance and that specific motifs may be playing precisely the signaling role suggested by the group's theory.

One of the grand challenges of post-genomic cellular biology is to assemble a working model of a living cell.

Scientists have successfully been able to build up a comprehensive parts list for the molecules involved in a cell's physiology. The complete sequencing of the human genome is one notable example. One of the grand challenges of post-genomic cellular biology is to assemble a working model of a living cell, a model that gives a reliable account of how the physiological properties of a cell derive from its underlying molecular machinery. Dr. Tyson's research group is converting network diagrams into dynamical models and exploring these models using analytical and computational methods in the hope of shedding light on the many physiological and molecular events that make up the cell's machinery. |

RESEARCH INTERESTS

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

SELECTED RECENT PUBLICATIONS

Barik D, Paul MR, Baumann WT, Cao Y, Tyson JJ (2008) Stochastic simulation of enzyme-catalyzed reactions with disparate time scales. *Biophysical Journal* **95**: 3563-3574.

Csikasz-Nagy A, Kapuy O, Toth A, Pal C, Jensen LJ, Uhlmann F, Tyson JJ, Novak B (2009) Cell cycle regulation by feed-forward loops coupling transcription and phosphorylation. *Molecular Systems Biology* **5**: 236.

Kar S, Baumann W, Paul MR, Tyson JJ (2009) Exploring the roles of noise in the eukaryotic cell cycle. *Proceedings National Academy of Sciences USA* **106**: 6471-6476.

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The Core Laboratory Facility

Providing life science customers worldwide with access to best-in-class technologies for discovery and analysis

Kristal Cooper, Shamira Shallom, Kris Lee, Don Shaw, Clive Evans, Megan Frair, Brad Howard, Bob Settlage, Carmine Graniello

VBI'S CORE LABORATORY FACILITY (CLF) is a dedicated multi-user resource for the development and application of state-of-the-art high-throughput technologies. The CLF is a "one-stop" shop for these technologies, providing researchers access to services and an experienced staff. The goal of the CLF is to provide high quality data in a timely fashion while maintaining excellent customer service.

SERVICES VBI's -omic and computational cores work collaboratively with VBI, Virginia Tech and other international institutions by offering state-of-the-art technologies (deep sequencing, high-throughput microarrays, mass spectroscopy and more) to generate tremendous amounts of new data. A wide range of technology platforms is available for the study of DNA (sequencing and genotyping), RNA (gene expression analysis), and proteins (proteomics). The CLF also offers a selection of molecular biology applications. The large amounts of data generated by this approach are analyzed and interpreted to create new knowledge that is disseminated to the world's scientific, governmental and wider communities.

The CLF occupies 6,500 square feet of laboratory space located at VBI's main building on the Virginia Tech campus. The day-to-day operation of the CLF is supported by a custom Laboratory Information Management System (LIMS) that provides an easy-to-use, secure interface for sample submission and retrieval. The combination of application and development enable the CLF to remain a leader in helping researchers take a complete systems biology approach to their science.

In 2006, the CLF was granted the status of Affymetrix National Custom Array Center for custom microarray design, sample processing and analytical services. This offers customers of VBI's core laboratory the flexibility to design arrays that can analyze the genome sequence of any organism. |

Genomics

GS-FLX™ SEQUENCING

LR70 (Shotgun, Amplicon, Transcriptome, Paired-End Runs)
Titanium (Shotgun, Amplicon, Transcriptome, Paired-End Runs)
Sequence Gap Closures and Assembly

SANGER SEQUENCING

PCR Products
Plasmids
Microsatellites

GENE EXPRESSION ANALYSIS

Affymetrix (Expression, Custom, Exon, SNP, miRNA, Tiling Arrays)
Real-time PCR

Proteomics

PROTEIN EXPRESSION PROFILING

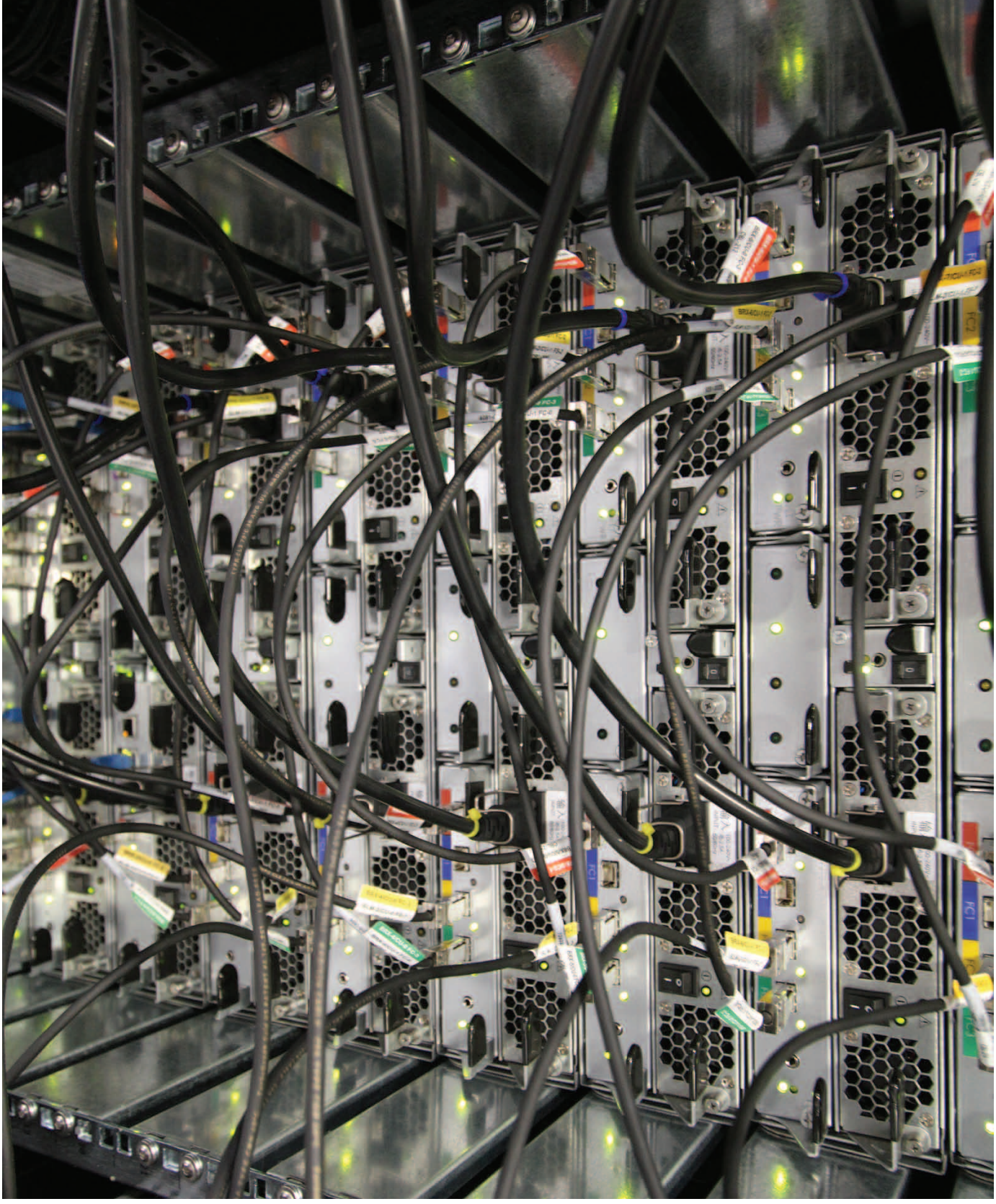
Two-dimensional polyacrylamide gel electrophoresis (2D PAGE, DIGE)
Two-dimensional liquid chromatography (2D LC)
Stable isotope labeling with amino acids in cell culture (SILAC)
Stable Isotope Labeling of Mammals (SILAM)

PEPTIDE/PROTEIN SEQUENCING

Gel spot identification
Complex mixture analysis (pull-downs, lysates)
Post-translational modification identification

PEPTIDE/PROTEIN QUANTITATION

Relative (SILAC, 2D gel, label-free liquid chromatography-mass spectrometry)
Absolute (AQUA, standard peptide curve)



The Core Computational Facility

Providing systems and data management for VBI's core infrastructure by extending information technology solutions to scientific research problems

Left to right: Jason Decker, Anthony Robinson, Dustan Yates, Dominik Borkowski, David Bynum, Jeremy Johnson, Zeb Bowden, Doug McMaster, Mandy Wilson, Jian Lu

THE CORE COMPUTATIONAL FACILITY (CCF) at the Virginia Bioinformatics Institute (VBI) is responsible for providing a secure, stable, and manageable infrastructure supporting data-intensive research. The architecture focuses on scalability and flexibility ensuring fulfillment of future computational and data requirements. The goal of CCF is to enable excellence through proactive technological development and implementation. CCF strives to position VBI at the forefront of life science-oriented computational capabilities.

FACILITIES The computing facilities at VBI include two data centers that occupy 1850 square feet. Current resources encompass more than 1.5 TB of RAM, distributed over more than 650 processor cores, and more than 160 TB of disk storage. The centers host a storage area network ensuring high-speed data access and reliability. Connectivity is achieved via gigabit Ethernet between the desktop and data centers and high-speed paths to Network Virginia and Internet2.

Uninterruptible power is safeguarded by diesel generators, power distribution units, and uninterruptible power supply (UPS) units. Multiple HVAC units control temperature and humidity. Solutions are modular and scalable while maintaining data and power design structures that avoid single points of failure. Aggressive monitoring and ongoing refinement ensure maximum availability in support of scientific efforts across the project life cycle.

The CCF group is poised to introduce further sophisticated applications that require high-performance computing infrastructure, a broad set of embedded, maintained and ready-to-use national and international databases (-omic, text, image and others) as well as a cadre of application development specialists. Combined, these resources will enable basic and clinical biomedical researchers and transdisciplinary scientists to quickly and effectively translate their ideas into solutions. Computationally intensive applications will be made widely available via the web to a broad base of users. |

CCF Services

SERVER
Hosting for dedicated, shared and virtual servers
Engineering and administration

DATABASE
Hosting for Oracle, and MySQL databases
Architecture and administration

HIGH-PERFORMANCE COMPUTING
Sun Microsystems Sunfire 15000
Timelogic DeCypher

STORAGE & BACKUP
80 TB of enterprise storage from Pillar Data Systems, available via both SAN and NAS
On- and off-site backup with IBM Tivoli Storage Manager

PRINTING
Poster printing (up to 42"x60") on high gloss photo paper

APPLICATION DEVELOPMENT, MAINTENANCE & DEPLOYMENT
Assist with the architecture, development, and deployment of High Performance Computing-based applications

CCF TEAM
Computer specialists
Database administrators
System administrators
High Performance Computing application development specialists

HELPDESK
Phone, e-mail and in-person support
Videoconferencing
Conference center, presentation and training lab facilities

Administration and Finance

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

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

Left to right: (front) Jodi Lewis, Sharon Matchen, Joyce Randall, Lauren Coble, Betsy Williams, Kim Borkowski, Traci Roberts; (back) Paul Knox, Lisa Gunderman, Renee Nester, Joyce Bandy, Maureen Lawrence, Stan Hefta

FINANCE | The Finance Team provides a wide variety of professional financial and support services, including accounting, financial reporting, purchasing, invoice processing, and account reconciliations. The team is comprised of business professionals dedicated to administering sound business and financial management practices.

Left to right: (front) Shelana Ryan, Stacey Walton, Deb Williams, Kristin Rasmussen; (back) Richard Webb, Bill Ortega, Ryan Naff

HUMAN RESOURCES | VBI's Human Resources Team ensures staff recruitment, employee relations and resource planning. The group is committed to providing services that support the institute's management and employees, helping them to achieve their goals and the mission of the university.

Left to right: Erin Cassidy, Lynn Byrd, Brian Gittens, Kathy Carrico

OPERATIONS | VBI's Operations Group is responsible for overseeing the security of the Institute, which includes the development of departmental security procedures and policy and departmental communication regarding security issues. The team also coordinates the photocopier management program, shipping and receiving activities, and special events held within VBI facilities.

Left to right: Kim Smith, David Martin, Betty Johnston, Yasmin Evans

GRANTS AND CONTRACTS | VBI's Grants and Contracts Team plays an important role in securing funding for the Institute's multidisciplinary research projects. The team identifies funding opportunities from both federal and private agencies, secures funding for VBI research projects, provides technical writing and editing assistance, and offers post-award reporting and coordination.

Left to right: Jim Walke, Sharon Lawson, Deborah Wray, Carol Volker, Andrew Volker

FACILITIES | VBI's Facilities Team is actively involved with faculty and staff members at VBI, handling space configurations and general operations. The team coordinates the design, construction, renovation, operation, and maintenance of VBI's facilities with various external authorities and departments.

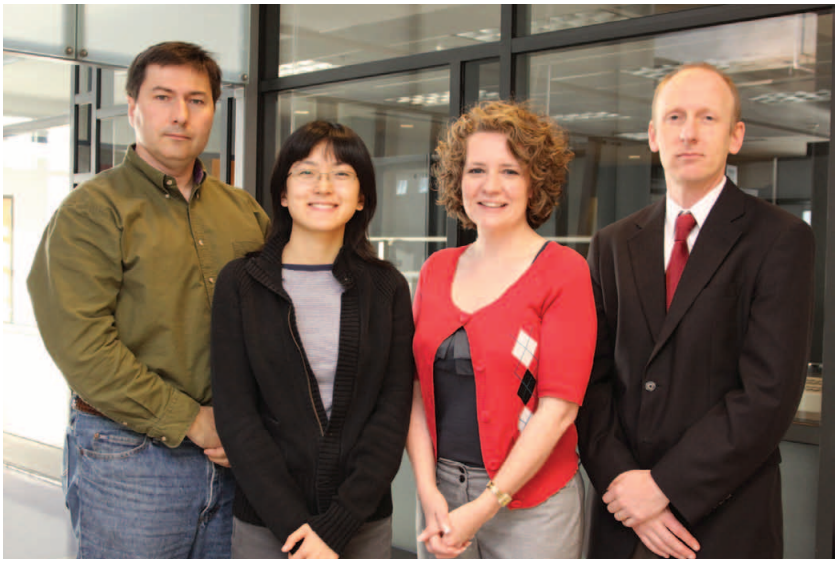
Left to right: (front) Mark DiFilippo, Amy Morrow, Linda Correll, Susan Huckle, Barbara Waller; (back) Wilson Barnes, Sheryl Locascio, David Gibbs, Carmine Graniello

Public Relations

THE PUBLIC RELATIONS TEAM AT THE Virginia Bioinformatics Institute (VBI) identifies key audiences for the Institute and delivers a research-driven communication program to those audiences. The group ensures that information about VBI reaches its public via web-based communication, promotional materials, specialty publications, media outlets, and presentations. Managing the information flow for the Institute to both internal and external audiences is one of the primary responsibilities for this service-oriented group.

In the past 12 months, VBI's media relations' efforts have resulted in coverage in prominent national and international media outlets, including television, radio, print, and multimedia. News releases describing VBI's and Virginia Tech's initiative to sequence the genome of the domesticated turkey, *Meleagris gallopavo*, garnered coverage by the *Richmond Times Dispatch*, News/Talk 960 WFIR (radio), MSNBC, WINA Morning News (radio), GenomeWeb News, In Sequence, United Press International, *The Washington Post* and other media. *The Roanoke Times*, News/Talk 960 WFIR, Associated Press, *Education Week*, and *The Staunton News Leader* featured articles or interviews on Kids' Tech University, a pioneering program developed by VBI in partnership with the Virginia Cooperative Extension's 4-H Youth Development Program to spark children's interest in science, technology, engineering, and mathematics disciplines.

Bruno Sobral, Professor and Director of VBI's Cyberinfrastructure Group, discusses infectious disease research at a Virginia Tech press conference.



Left to right: Ivan Morozov, Jenny Wang, Susan Bland, Barry Whyte

In June 2009, WDBJ Channel 7 ran a television feature describing VBI research to develop a new method for the early detection of breast cancer. *Genetic Engineering News*, which covers international biotechnology news, also featured a PodCast describing the findings of a *Biochimica et Biophysica Acta* paper entitled "A Systems Biology View of Cancer". Four researchers at VBI and colleagues at the Wake Forest University School of Medicine contributed to the paper.

In the course of the fiscal year, GenomeWeb News, the largest online news organization focused on advanced research tools in genomics, proteomics, and bioinformatics, featured several stories on VBI research. These included, amongst others, articles and interviews describing new funding from the National Science Foundation to support work on the DNA-design software tool GenoCAD, the development of a new mathematical model to study cell division in the bacterium *Caulobacter crescentus*, research efforts looking to dissect the molecular secretion system of *Rickettsia* pathogens, as well as VBI and Virginia Tech's work to sequence the turkey genome.

The opinions of VBI researchers on employment opportunities for the next-generation of bioinformaticians were featured nationally in *US News & World Report* in the article "Workers do the shuffle: The labor force is shifting toward science and health" by Liz Wolgemuth.

CLOSER TO HOME

VBI research on modeling pandemic influenza, strawberry genomics, and the impact of *Phytophthora* pathogens on agricultural productivity were also featured in three different articles for Virginia Tech's Research Magazine. In other Virginia Tech media, Kids' Tech University was highlighted in *Outreach Now*, the annual publication of Virginia Tech's Outreach and International Affairs, and the *Virginia Tech Magazine*, both produced by Virginia Tech's University Relations.

More recently, VBI was in the news again, this time the Associated Press (multiple outlets), *The Roanoke Times*, GenomeWeb News, as well as television coverage by WSLS 10 Roanoke, an NBC television affiliate. The media coverage was in response to a press conference held on the Virginia Tech campus where Ninth District Congressman Rick Boucher joined senior Virginia Tech officials to announce the award of approximately $27 million from the National Institutes of Health to VBI. The five-year, $27,670,448 contract from the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, is the largest, one-time federal award in the history of Virginia Tech. The funding is being used by VBI's Cyberinfrastructure Group, which is led by Bruno Sobral, to support infectious disease research across the globe, namely to integrate vital information on pathogens, provide key resources and tools to scientists, and help researchers to analyze genomic, proteomic and other data arising from infectious disease research. |

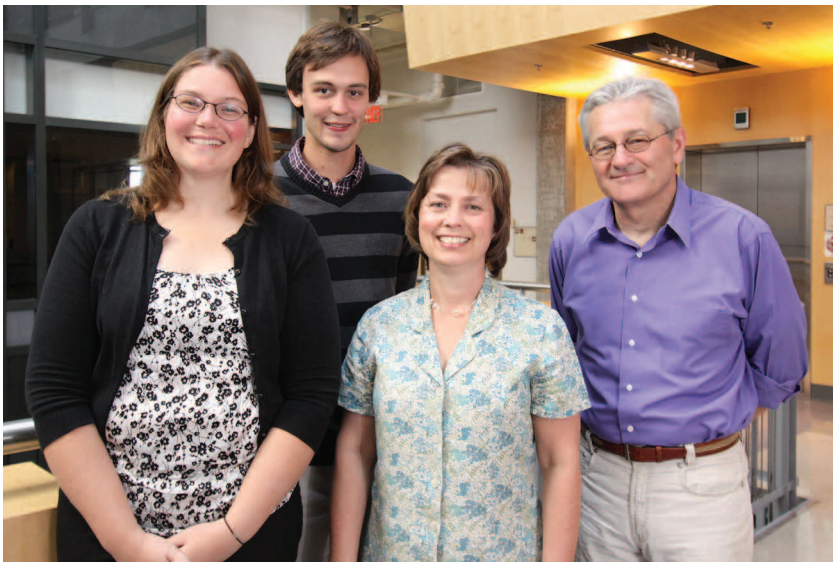
Education and Outreach

VBI'S EDUCATION AND OUTREACH group has been involved in the development and implementation of various programs aimed at encouraging students' interests in scientific research. In addition, the Institute provides training opportunities for science and math teachers at all levels, assisting them with the incorporation of bioinformatics concepts into their curriculums. The group also fosters VBI's strong commitment to outreach. The team builds and maintains strong relationships with the Institute's external audiences, coordinating and promoting VBI's involvement in a wide variety of educational programs in the Virginia Tech community and beyond.

EDUCATIONAL OPPORTUNITIES

K-12 Programs VBI has partnered with the Virginia Cooperative Extension's 4-H Youth Development Program to develop Kids' Tech University (KTU), an educational research program with one primary goal—sparking kids' interest in science, technology, engineering, and mathematics disciplines. Kids between the ages of 9-12 have the opportunity to attend four lectures over the course of a semester. The lectures are given by world-renowned scientists and will address some of the "why?" questions about the world around us. The kids also participate in exciting hands-on activities after the lectures and have access to online lab activities and an interactive kids' forum. The Institute continued its high school summer program developed to help guide students into a research career and recruit the next generation of scientists. Destination: Bioinformatics Research is a week-long program consists of several research activity labs, research related tours, and a discussion/

Top Keith Devlin, known as "The Math Guy" on National Public Radio and co-founder and executive director of Stanford's Human-Sciences and Technologies Advanced Research Institute, explains to Kids' Tech University students why there are animals with spotted bodies and striped tails, but no animal with a striped body and a spotted tail. **Bottom** Students from West Virginia University's Upward Bound program work in teams to extract DNA from strawberries during a visit to VBI.



Left to right: Kristy DiVittorio, Kris Monger, Betsy Williams, Reinhard Laubenbacher

lecture series. Participants get the unique opportunity to explore the world of genomics and bioinformatics with world-renowned research scientists in professional labs. The main objective of the high school program is to positively influence the students' outlook on scientific research. The group also hosted elementary, middle, and high school students enrolled with Virginia Tech's Talent Search and Upward Bound programs, the Upward Bound program at West Virginia State University, and the Higher Achievement Program. The programs provide learning opportunities to underserved students and encourages participants to pursue postsecondary education. The students from the West Virginia State University program got the opportunity to work in a VBI lab extracting DNA from strawberries as part of an activity designed to help the students develop a better understanding of DNA and the link between their hands-on work and the research taking place at VBI.

Undergraduate Programs Over the course of the fiscal year, VBI's Education and Outreach team partnered with other centers and colleges at Virginia Tech to offer unique research opportunities for undergraduate students. The team collaborated with the Virginia Tech-Wake Forest University School of Biomedical Engineering and Science to coordinate the Institute's participation in the Bioengineering and Bioinformatics Summer Institute (BBSI). The program, which is designed for junior or senior undergraduates interested in attending graduate school in biomedical engineering and/or bioinformatics, emphasized four major research areas: Computational Systems Biology, Computational Bio-Imaging, Computational Physiology, and Mathematics. A collaborative effort between VBI and Virginia Tech's Interdisciplinary Center for Applied Mathematics (ICAM) resulted in the Research Experience for Undergraduate (REU) Site: Modeling and Simulation in Systems Biology program, which allowed mathematicians from both groups to serve as mentors to rising juniors and seniors working on research projects involving mathematical modeling and analysis of networks. The REU summer program also allowed the group to further cultivate its Historically Black College and University (HBCU) partnerships, providing an opportunity for two faculty members and three students from Oakwood University to visit the Institute for training.

Graduate Programs VBI continued its work with Virginia Tech's GBCB (Genomics, Bioinformatics, Computational Biology) Graduate Program and awarded three fellowships in support of graduate work in transdisciplinary team science. The Transdisciplinary Team Science Fellowship Program for the Life Sciences was developed for students interested in joining the GBCB program and is intended to connect students with accomplished researchers working in a team science environment. The fellowships cover the costs of the students' first two years in the program plus tuition and fees and requires each recipient to complete a laboratory rotation period, which provides an opportunity to learn more about different research areas and identify an area of interest. |

	EDUCATION & OUTREACH FUNDED PROJECTS 2009	FUNDING AGENCY
K-12	Destination: Bioinformatics Research	USDA
UNDERGRADUATE	Bioengineering/ Bioinformatics Summer Institute (BBSI)	NSF / NIH
UNDERGRADUATE	Research Experiences for Undergraduates Site: Modeling and Simulation in Systems Biology (MSSB)	NSF
GRADUATE	Transdisciplinary Team Science Fellowship Program for the Life Sciences	VBI/ Virginia Tech

Financial Review

July 1, 2008 - June 30, 2009

The Virginia Bioinformatics Institute (VBI) continues to maintain a sound funding base in what remain challenging times for the global economy and the wider research community. For the 2008-2009 fiscal year, VBI research expenditures reached an all time high of $16.9 million on an annual basis. This performance bodes well for the Institute's future.

Total active awards by sponsor for VBI were $95 million at the end of the 2008-2009 fiscal year. Three federal sponsors continue to support the extramural research program of VBI: the National Institutes of Health (36.1%), the United States Department of Defense (35.7%), and the National Science Foundation (16.9%). Other leading federal agencies and academic institutions represent the balance of our funding.

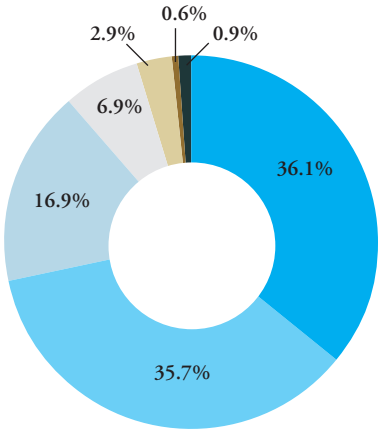
The Institute continues to focus on securing financial support for large-scale, transdisciplinary research projects that will deliver significant opportunities for advancement in the years ahead. This approach has been the catalyst behind the Institute's growth since its inception in 2000. In 2010, we look forward to celebrating the ten-year anniversary of the Institute.

The Institute's success is due to the outstanding commitment that has been shown by its employees over the years. VBI employed 223 highly qualified staff as of June 30, 2009.

I would like to take this opportunity to thank all of our researchers and administrative and support staff for their hard work and many contributions to the progress of VBI.

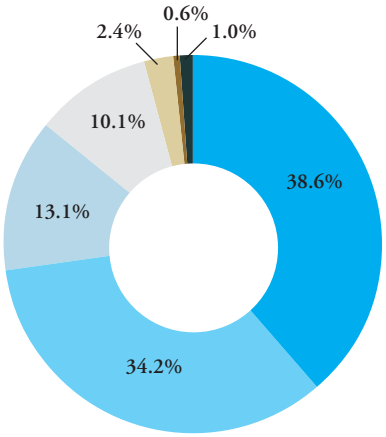
Lauren Coble
Chief Operating Officer

Active Awards by Sponsor



	(IN DOLLARS)
National Institutes of Health	$ 34,215,709
United States Department of Defense	33,910,546
National Science Foundation	16,049,199
United States Department of Agriculture	6,511,411
United States Department of Energy	2,780,659
National Aeronautics and Space Administration	595,153
Other sponsors	884,988
Total active awards	$ 94,947,665

Extramural Research Expenses by Sponsor



	(IN DOLLARS)
National Institutes of Health	$ 6,533,655
United States Department of Defense	5,774,106
National Science Foundation	2,211,182
United States Department of Agriculture	1,699,327
United States Department of Energy	413,204
National Aeronautics and Space Administration	104,374
Other sponsors	172,156
Total extramural expenses	$ 16,908,004

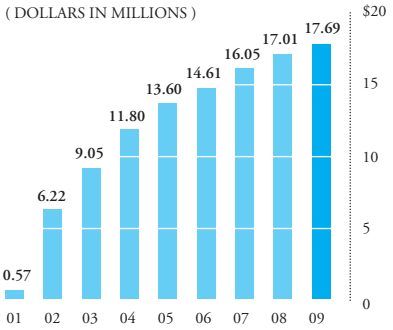
Financial Operating Activity

(FOR THE YEAR ENDED JUNE 30, 2009 & 2008)

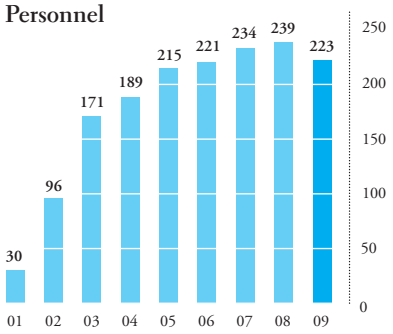
REVENUES	2009	2008
Grants and Contracts		
National Institutes of Health	$ 6,536,043	$ 5,485,416
United States Department of Defense	6,551,164	3,925,768
National Science Foundation	2,179,743	1,255,548
United States Department of Agriculture	1,701,635	1,190,623
United States Department of Energy	227,559	639,970
National Aeronautics & Space Administration	103,851	184,435
Industry	105,172	61,196
Foundations	59,276	57,205
Total grants and contracts	17,464,443	12,800,161
Commonwealth and university sources	3,218,143	3,007,557
Total operating revenue	20,682,586	15,807,718
EXPENSES		
Personnel Expenses	17,588,557	16,430,945
Operating Expenses		
Contractual Services	381,602	858,058
Information Technology	447,486	1,046,744
Travel and Other	566,188	701,258
Supplies and Materials	1,353,053	1,168,824
Building and Other Rentals	806,627	771,534
Subcontracts	1,791,789	999,149
Equipment	762,747	812,596
Total operating expenses	6,109,492	6,358,163
Indirect expenses	4,612,997	4,301,011
Total expenses	28,311,046	27,090,119
Non-Operating Sources		
University support	7,376,859	7,905,588
One Time resource	300,000	–
One Time budget reduction and raise reversions	(116,183)	(197,640)
Commonwealth Research Initiative	150,000	150,000
Total non-operating sources	7,710,676	7,857,948
Gain/(Loss) in Net Assets	$ 82,216	$ (3,424,453)

Capital Assets

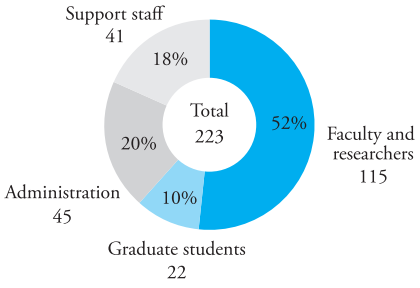
(DOLLARS IN MILLIONS)



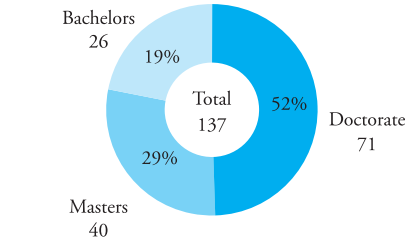
Personnel



Personnel Composition



Graduate & Faculty Breakdown



Scientific Advisory Board

Members of the Scientific Advisory Board of the Virginia Bioinformatics Institute, which include scientific leaders in high-performance computing, biology, bioinformatics, and nanotechnology/engineering, serve as scientific advisors for the Institute. They provide regular external reviews of research strengths as well as guidance on new strategic scientific initiatives and funding opportunities.

From left to right: William J. Feiereisen, Stephan Bieri, Paul Knox (Interim Director), Richard W. Siegel, William Gelbart, Bob Walters. Not pictured: Paul Keim. Paul Knox, University Distinguished Professor at Virginia Tech, served as Interim Director of the Virginia Bioinformatics Institute from March until November 2009.

Acknowledgements

The 2009 annual report of the Virginia Bioinformatics Institute was created and designed by the VBI Public Relations team. The institute recognizes Jenny Wang for the graphic design of the report and Ivan Morozov for photographic contributions. Susan Bland, Darleen Baker, and Barry Whyte facilitated the development of the content in collaboration with the research groups at the Institute. Concept: Barry Whyte, Strategic and Research Communications Officer, Virginia Bioinformatics Institute.

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