6th INSTITUTE FOR SYSTEMS BIOLOGY International Symposium

Systems Biology & the Environment

April 22–23 2007

INSTITUTE FOR
Systems
Biology
Revolutionizing science. Enhancing life.

1441 North 34TH Street | Seattle, Washington 98103 | www.systemsbiology.org

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Area of expertise: Tuberculosis, comparative genomics, bacterial population genetics

Symposium Welcome

Dear colleagues:

On behalf of the Institute for Systems Biology (ISB) and our co-hosts at the University of Washington's Biology Department, we welcome you to our sixth annual international symposium.

The 21st century presents and enormous challenge for biology—namely how do we deal with the bewildering complexity of biological systems. It is clear that the fundamental paradigm change that will let us deal with this complexity is the simple idea biology is an informational science. There are two fundamental types of biological information—the digital information of our genomes and the environmental information that impinges on the core digital information—and the interplay of both lead to the development of living organisms and their responses to our environment. Hence one of the great challenges in 21st century biology in this interplay between our genes (the digital information) and the environment in molding and shaping living organisms. The emerging field of systems biology promises completely new systems approaches to the study of genes and environment—the topic of this years International ISB Symposium. This symposium will explore many different topics in this domain—how small organisms can impact the enviroment in a striking manner; how the history of our evolution can be read from our genes; the ecophysiology of microorganisms; how infectious agents trigger disease; how we may use environmental perturbations to gain a deep understanding of the biological networks of life; how we can use the interactions of the sun with living organisms to provide our energy needs; and many more topics. These interactions between genes and the environment pose some of the most pressing scientific challenges of the 21st century—and the powerful approach of systems biology may provide us with tools we need to meet these challenges.

We know that the powerful combination of our knowledge of the genome, advancing measurement tools, high-speed computers, the systems view of the interactions between our genes and the environment and growing interdisciplinary collaborations are giving us the opportunity to make new scientific and technical breakthroughs at an ever faster pace—certainly more rapidly than in any new field of biology in the 20th century. We are delighted to have you join us for a birds-eye view of Systems Biology and the Environment.

Thank you for joining us this year. We look forward to your participation.

Sincerely,

Lee Hood

Leroy Hood, President

Sunday

April 22, 2007

2:00 pm

Registration

3:00 pm

Welcoming Remarks

Leroy Hood M.D., Ph.D., President President
Institute for Systems Biology (ISB)

3:30 pm

Keynote Address

Sallie Chisholm Ph.D., Massachusetts Institute for Technology
Tiny Cells, Global Impact: What Prochlorococcus Can Teach Us about Systems Biology

4:30 pm

Break

5:00 pm

Session I

John Delaney Ph. D., University of Washington
Transforming Ocean and Earth Sciences with Distributed Submarine Sensor Networks Wired to Next-Generation Internet

5:45 pm

Steve Koonin Ph.D., BP p.l.c.
Challenges in Energy Biosciences

6:30 pm

Session Closing

6:45 pm

Opening Reception

Ponti Seafood Grill
3014 3rd Avenue North in Seattle
Ponti is a five minute drive from ISB.
Directions will be available at the registration table.

Shuttle service from ISB will be provided.

Monday

April 23, 2007

8:00 am

Continental Breakfast

8:30 am

Session II

Chair: Ilya Shmulevich ISB

Antoine Danchin Ph.D., Institut Pasteur
The Bacterial Core Genome is an Archive of the Origin of Life

9:15 am

Elliott Meyerowitz Ph.D., California Institute of Technology
Regulated Morphogen Transport: A Novel Mechanism of Development

10:00 am

Break

10:30 am

Session III

Chair: Tim Galitski ISB

Jim Fredrickson Ph.D., Pacific Northwest National Laboratory
Integrated Genome-Based Investigations of Shewanella Ecophysiology

11:15 am

Nitin Baliga Ph.D., Institute for Systems Biology
Systems Approaches to Statistically Learn Regulatory Circuits Underlying Responses to Diverse Environmental Insults

12:00 pm

Break

Lunch, ISB Tours and Poster Session

1:30 pm

Session IV

Chair: John Aitchison ISB

Ben Kerr Ph.D., University of Washington
The Evolution of a 'Tragedy of the Commons' within Host-pathogen Population Networks

2:15 pm

Steve Briggs Ph.D., University of California, San Diego
Global Proteome Changes Caused by Nematode Infection

3:00 pm

Break

3:30 pm

Session V

Chair: Alan Aderem Director, ISB

John Groopman Ph.D., Johns Hopkins University
From Biomarkers to Pathobiology: The Chemical-Viral Conspiracy in Liver Cancer

4:15 pm

David Cox M.D., Ph.D., Perlegen Sciences, Inc.
Human DNA Variation, Environmental Exposure, and Common Human Disease

5:00 pm

Closing Comments

Alan Aderem

Sallie Chisholm Ph.D.

Presentation Title

Tiny Cells, Global Impact: What Prochlorococcus Can Teach Us about Systems Biology

Sunday / Keynote Address

Lee and Geraldine Martin Professor of Environmental Studies
Massachusetts Institute of Technology

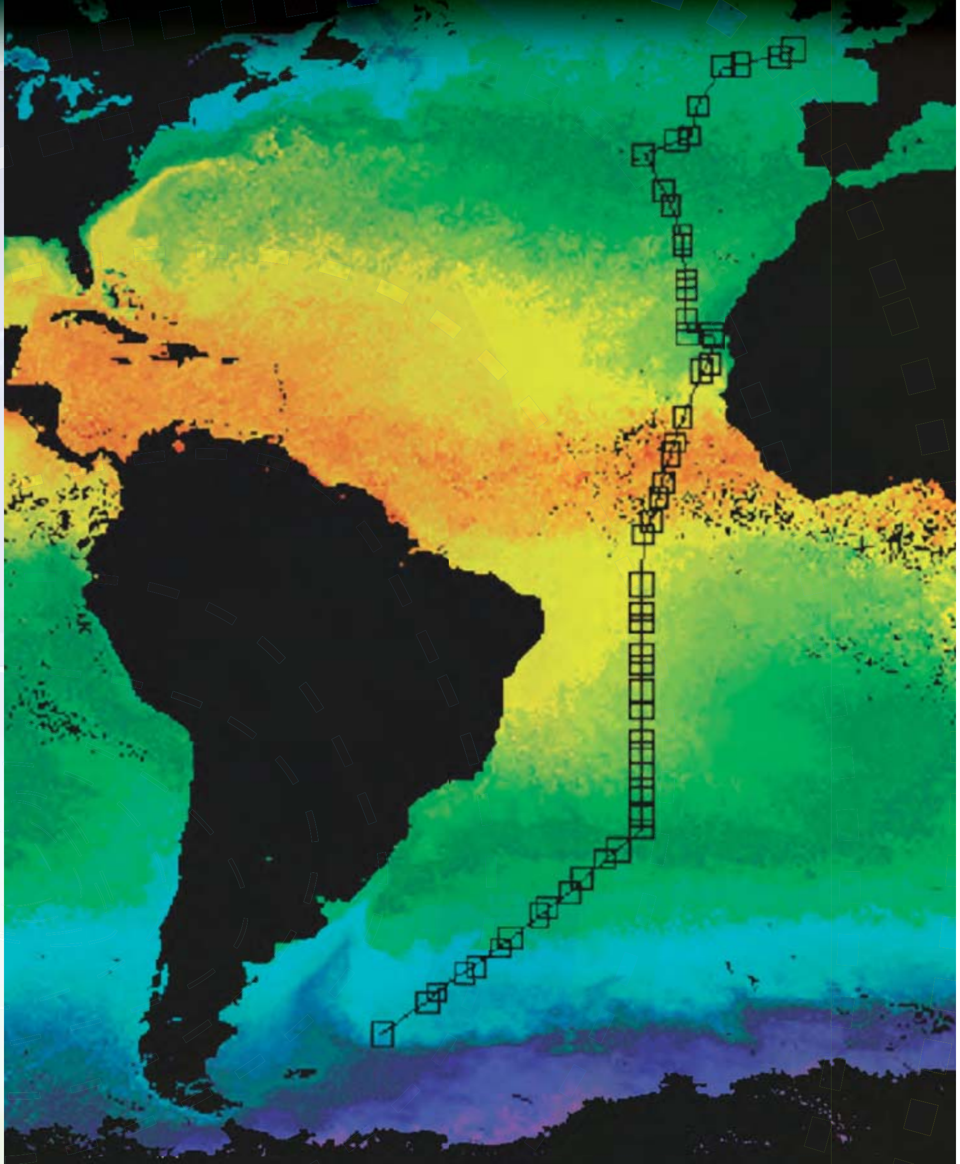
Dr. Chisholm is a biological oceanographer, whose research over the past decade has focused on the ecology and evolution of *Prochlorococcus*—the smallest, and numerically dominant photosynthetic microbe in the sea. Her group's work on *Prochlorococcus* spans all scales of biological organization—from the genome to the ecosystem—and represents an attempt to understand the cross-scale systems biology of a single organism.

The Chisholm lab strives to understand the ecology of phytoplankton in the oceans and the biogeochemical cycles that they mediate. The focus of their research is the cyanobacterium *Prochlorococcus* as a model system. It is the most abundant photosynthetic microbe in the sea and can account for up to half of the photosynthetic biomass over vast oceanic regions. *Prochlorococcus* is a "minimal phototroph," which means that it converts CO2, solar energy and inorganic nutrients into a living cell with approximately 1,700 genes. It is a useful model for understanding the autotrophic mode of life, for studies of comparative genomics and metabolic reconstruction, and for investigating the role of microdiversity in shaping the structure and evolution of microbial communities.

The global abundance of *Prochlorococcus* arises in part from the existence of physiologically and genetically distinct "ecotypes" that require different light intensities for growth and have adapted to life under different conditions in the oceans. The genomes of eleven *Prochlorococcus* strains have been sequenced, allowing us to compare differences in genomic architecture within and between ecotypes, the core genes shared by all, and the genes that are unique in each strain. Some of these unique genes have obvious roles in determining relative fitness in different environments; others have unknown functions, and likely hold clues to unknown agents of natural selection in the oceans.

Ultimately, the goal is to understand how genomic and metabolic differences among *Prochlorococcus* ecotypes determine their global distributions in the oceans. The challenge will be to link our understanding of their biology at fundamentally different scales, and to work toward a unified understanding of this one small representative of the diversity of life on earth.

Next year in 2008 marks the 20th anniversary of the discovery of *Prochlorococcus*. Dr. Chisholm's believes in the next decade it will be possible to develop and distribute the *Prochlorococcus* model system to it can serve as the foundation for developing integrative systems biology.



> "As a microbial ecologist, I think of life on earth as a system of systems, cross cutting many time and special scales, from cellular metabolic networks to the biosphere. The genomic and post-genomic era has made tractable not only cellular systems biology, but the study of life processes on a global scale. It is changing our view of the Earth as a living planet."

Sallie Chisholm Ph.D.
Lee and Geraldine Martin Professor of Environmental Studies
Massachusetts Institute of Technology

Nitin Baliga Ph.D.

Presentation Title

Systems Approaches to Statistically Learn Regulatory Circuits Underlying Responses to Diverse Environmental Insults

Monday / Session III

Faculty Member

Institute for Systems Biology

Dr. Baliga is particularly interested in crafting systems level approaches to understand how organisms mount responses to complex changes in their environment. He holds an undergraduate degree in Microbiology from Ruia College, India, and an M.Sc. in Marine Biotechnology from Goa University, India. Dr. Baliga conducted his doctoral studies in Microbiology at University of Massachusetts at Amherst and his postdoctoral studies in systems biology with Dr. Leroy Hood at ISB. During his predoctoral studies, he won two competitive awards from the government of India: the Council for Scientific and Industrial Research Fellowship, and a fellowship from the Department of Biotechnology.

Current research in Dr. Baliga's laboratory is geared towards elucidating complete sets of genetic circuits in *Halobacterium NRC-1* that specify its robust behavior in an ever-changing hypersaline (saturated salt) environment. His research involves scientists of varied expertise in diverse areas such as environmental molecular microbiology, structural biology, and computational biology.

Dr. Baliga has also made significant contributions to improving biology education in high schools throughout the greater Seattle area. His primary goal is to develop mind stimulating inquiry modules that teach high school students novel concepts in biology such as systems biology. Research in Dr. Baliga's laboratory is supported by research grants from the National Science Foundation, the Department of Defense, the NASA, and Department of Energy.

Steven P. Briggs Ph.D.

Presentation Title

Global Proteome Changes Caused by Nematode Infection

Monday / Session IV

Professor of Cell and Developmental Biology

University of California, San Diego

Dr. Briggs received his Ph.D. from Michigan State University and spent the first half of his career in industry, most recently as Sr. Vice President for Corporate Research at Diversa. Previously he was President of Torrey Mesa Research Institute and before that he was Director at Pioneer/DuPont for several research areas including genomics. Dr. Briggs has been Co-editor of The Plant Cell; he serves on the Scientific Advisory Board, Keystone Symposia and the Board of Advisors, Plant Sciences Institute, Iowa State University; he is a member of the National Academy of Sciences.

Dr. Briggs was the first to isolate and characterize a plant gene for resistance to infectious disease. He was also the first to discover a natural mechanism for plant resistance to infection. In 1998, Dr. Briggs founded the Torrey Mesa Research Institute (originally named the Novartis Agricultural Discovery Institute) with funding from the Novartis Research Foundation. While there, he produced a draft sequence of the rice genome. This enabled comparative genomics in plants by reference to the recently completed arabidopsis genome sequence, and it provided a framework for genomics in all of the other grass crops (maize, wheat, barley, oats, rye, and sugarcane). Under Dr. Briggs' direction, the staff at TMRI created the first plant (arabidopsis) GeneChip, which was released for public use and is still popular; the first reverse genetics technology for arabidopsis, which was followed by and incorporated into the Salk T-DNA collection; the first crop GeneChip (for rice); the first all-exon GeneChip (for arabidopsis); and the first plant proteome (for rice; this remains the most comprehensive plant proteome in the literature).

David Cox M.D. | Ph.D.

Presentation Title

Human DNA Variation, Environmental Exposure, and Common Human Disease

Monday / Session V

Chief Scientific Officer and Co-founder

Perlegen Sciences, Inc.

Dr. Cox is internationally recognized for his research on the molecular basis of human genetic disease.

After receiving his B.A. and M.S. degrees from Brown University in Rhode Island, Dr. Cox obtained his M.D. and Ph.D. degrees from the University of Washington, Seattle. He then completed his Pediatric Residency at the Yale-New Haven Hospital in New Haven, Connecticut, and was a Fellow in both genetics and pediatrics at the University of California San Francisco. From 1980 to 1993, Dr. Cox held faculty positions in the Departments of Pediatrics, Biochemistry, and Psychiatry at the University of California San Francisco. In 1993, he accepted a position as a Professor of Genetics and Pediatrics at the Stanford University School of Medicine, as well as the Co-director of the Stanford Genome Center. In October of 2000, Dr. Cox left his position at Stanford University to become the Chief Scientific Officer of Perlegen Sciences, Inc.

Dr. Cox is certified by both the American Board of Pediatrics and the American Board of Medical Genetics.

He has served on several international and national councils and commissions including the Council of the Human Genome Organization (HUGO) and the National Bioethics Advisory Commission (NBAC). He presently serves as a member of the Health Sciences Policy Board of the Institute of Medicine.

Dr. Cox's honors include election to the Institute of Medicine of the National Academy of Sciences.

Antoine Danchin Ph.D.

Presentation Title

The Bacterial Core Genome is an Archive of the Origin of Life

Monday / Session II

Directeur, Genomes and Genetics Department

Institut Pasteur

Dr. Danchin was originally trained as a mathematician and a physicist, but became an experimental microbiologist in the early seventies. The main goal of his research has always been to try to understand how genes function collectively in the cell.

In 1985, he collaborated with computer scientists to study integrated problems in molecular genetics. This convinced him that it was time to investigate the genome as a whole provided that an important effort in computer sciences was initiated in parallel. Early in 1987 he proposed that a sequencing program should be undertaken for Bacillus subtilis. This proposal was actualized by a European joint effort on this genome in 1988. The complete sequence was published in 1997. The first significant and unexpected discovery of the sequence was the many genes (at that time half of the genes) were of completely unknown function. It has been discovered that genomes are structures that are much more orderly than previously suspected, and that there exists a strong interaction between the organization of the genes in the genome and the cell's architecture.

Dr. Danchin has published more than 450 articles and four books, including a book on the origin of life, and a book on genomes (The Delphic Boat, Harvard University Press, 2003). He has a continuous interest in philosophy and in exchanges with other civilizations (formation of a Chinese-European University Without Walls in 1990).

He promoted genome research in Hong Kong where he created the HKU-Pasteur Research Centre in 2000. He stayed in Hong Kong for three years and set up there a working seminar with the Department of Mathematics of Hong Kong University to discuss epistemological and ethical problems raised by the recent status of biology in human knowledge.

John Delaney Ph.D.

Presentation Title

Transforming Ocean and Earth Sciences with Distributed Submarine Sensor Networks Wired to Next-Generation Internet

Sunday / Session I

Director, NEPTUNE Program

Jerome M. Paros Endowed Chair in Sensor Networks

Professor of Oceanography

University of Washington

Dr. Delaney is a passionate advocate for launching next-generation ocean science and education: submarine distributed robot-sensor networks that enable adaptive, real-time interactive research on natural processes operating throughout the world's oceans. He has directed the NEPTUNE ocean observatory program since 1997 when he led the effort that confirmed the feasibility of using electro-optical cable to wire the entire Juan de Fuca tectonic plate off the coasts of Washington, Oregon, and British Columbia. Wired to the Internet, the NEPTUNE system will allow millions of land-based observers to virtually experience events, both catastrophic and gradual, that are continually remaking the ocean and seafloor environments.

Dr. Delaney worked as a mining geologist early in his professional career, then spent nearly six months living inside the active volcanoes of the Galapagos Islands in 1970–72. He completed his Ph.D. in Geosciences at the University of Arizona and took a position in the University of Washington's School of Oceanography in 1977.

In 1987, Dr. Delaney served as the first Chairman of the RIDGE Program and initial co-chairman of the international InterRIDGE. Both programs were designed to foster intensive studies of the physical, chemical, and biological interactions that characterize the vigorous volcanic and hydrothermal activity along the 70,000-kilometer mid-ocean ridge system.

Dr. Delaney's research focuses on deep-sea volcanic activity in the northeast Pacific Ocean. He has served as chief scientist on over forty oceanographic research cruises and has published more than 160 scientific papers and articles.

Jim Fredrickson Ph.D.

Presentation Title

Integrated Genome-Based Investigations of Shewanella Ecophysiology

Monday / Session III

Laboratory Fellow and Chief Scientist

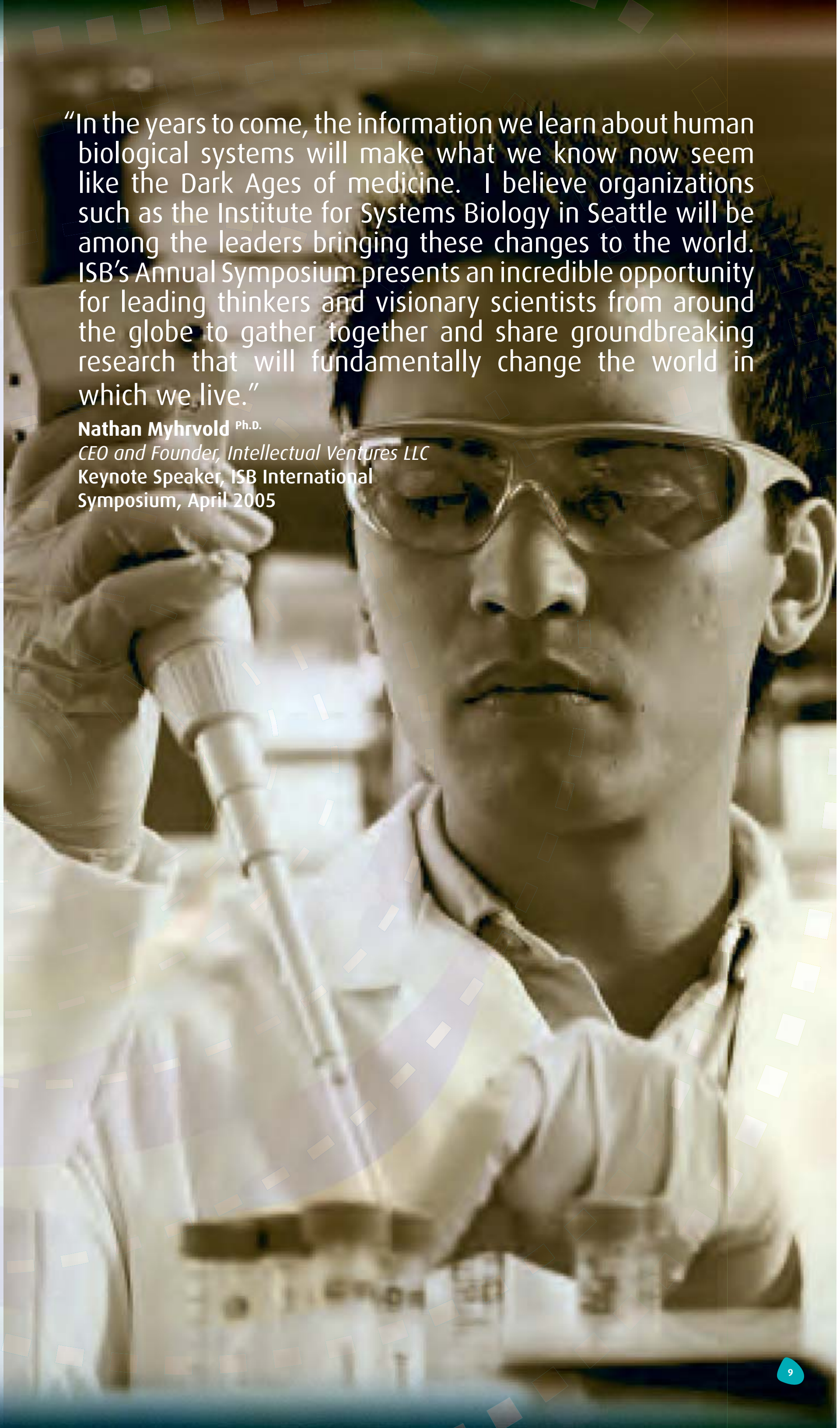
Pacific Northwest National Laboratory

Dr. Fredrickson specializes in microbial ecology and environmental microbiology. Since joining Pacific Northwest National Laboratory in 1985, he has focused his research efforts in subsurface microbiology and biogeochemistry. He has been responsible for laboratory and field research programs investigating the microbial ecology and biogeochemistry of geologically diverse subsurface environments and is recognized nationally and internationally for these efforts.

In 2005, Dr. Fredrickson was appointed Chief Scientist for the U.S. Department of Energy's Genomics: GTL program. In this capacity, he serves as a spokesperson for the GTL program to the science community and provides technical guidance to DOE. He also serves as the national coordinator for the Shewanella Federation, a multi-institutional, multi-disciplinary research team focused on the systems biology of dissimilatory metal-reducing bacteria of the genus Shewanella.

Since 2005, Dr. Fredrickson has been co-lead of a DOE Biogeochemistry Grand Challenge at DOE's W.R. Wiley Environmental Molecular Sciences Laboratory, located at PNNL. This innovative, multi-disciplinary project involves 25 researchers from the U.S., Canada, and United Kingdom who are probing the fundamental question of how subsurface metal-reducing bacteria interact with and transfer electrons to the mineral surfaces on which they live.

Dr. Fredrickson served as a member of the National Research Council's Committee on the Astrobiology Strategy for the Exploration of Mars and is a member of the American Society for Microbiology and the American Chemical Society. He is a Fellow of the American Academy of Microbiology and of the American Association for the Advancement of Science. He served for more than 10 years as Editor-in-Chief of Microbial Ecology and currently is on the editorial boards of Environmental Microbiology and Microbial Biotechnology.



> "In the years to come, the information we learn about human biological systems will make what we know now seem like the Dark Ages of medicine. I believe organizations such as the Institute for Systems Biology in Seattle will be among the leaders bringing these changes to the world. ISB's Annual Symposium presents an incredible opportunity for leading thinkers and visionary scientists from around the globe to gather together and share groundbreaking research that will fundamentally change the world in which we live."
>
> **Nathan Myhrvold Ph.D.**
> *CEO and Founder, Intellectual Ventures LLC*
> **Keynote Speaker, ISB International Symposium, April 2005**

John Groopman Ph.D.

Presentation Title

From Biomarkers to Pathobiology:
The Chemical-Viral Conspiracy in Liver Cancer

Monday / Session V

Anna M. Baetjer Professor and Chair

Department of Environmental Health Sciences

Bloomberg School of Public Health

Johns Hopkins University

Dr. Groopman's research involves the development, validation and application of molecular biomarkers of exposure, dose, and effect from environmental carcinogens to high-risk populations. The environmental carcinogens studied include agents that are naturally occurring in the diet as well as those produced as a result of cooking practices. A major emphasis of the research has been in the elucidation of the role of aflatoxins, a common contaminate of the food supply, in the induction of liver cancer in high-risk populations living in Asia and Africa. This work has led to the identification of a very strong chemical-viral interaction between aflatoxin and the human hepatitis B virus in the induction of liver cancer. These biomarkers have also been used in many collaborative molecular epidemiology studies of liver cancer risk and recently employed to assess the efficacy of a number of chemopreventive agents in trials in high-risk aflatoxin-hepatitis B virus exposed populations. This research is now being extended to develop genetic biomarkers of p53 mutations and viral mutations in human samples as early detection of disease biomarkers using a novel mass spectroscopy based method for genotyping developed in the laboratory.

Dr. Groopman received his Ph.D. degree from the Massachusetts Institute of Technology and was also a post-doctoral fellow at MIT. He received further training as a staff fellow at the National Cancer Institute in the Laboratory of Human Carcinogenesis. Dr. Groopman was the Associate Dean at the Boston University School of Public Health. In 1992 I was appointed Chair of the Department of Environmental Health Sciences in the School of public health.

Ben Kerr Ph.D.

Presentation Title

The Evolution of a 'Tragedy of the Commons' within Host-pathogen Population Networks

Monday / Session IV

Assistant Professor, UW Biology

University of Washington

Dr. Kerr received his Ph.D. in Biological Sciences from Stanford University in 2002. While at Stanford, he worked with Marcus Feldman on modeling the evolution of flammability in resprouting plants, the evolution of animal learning, and the evolution of altruism. He also worked with Brendan Bohannan on experimental evolution within microbial systems and with Peter Godfrey-Smith on some philosophical issues arising in the levels of selection controversy. Dr. Kerr spent three years as a postdoctoral research associate at the University of Minnesota, where he worked with David Stephens on modeling impulsive behavior in blue jays, with Tony Dean on the evolution of cooperation within a microbial host-pathogen system, and with Claudia Neuhauser on spatial dynamics within model population genetic systems. He joined the faculty of the Biology Department at the University of Washington in 2005.

Dr. Kerr's current research generally focuses on the consequences of organismal effects on their environment. One of the hallmarks of living organisms is the change they induce in their abiotic and biotic environments. Using a combination of analytical, simulation-based and lab-experimental techniques, Dr. Kerr has studied several biological systems that possess strong niche construction elements: **1**) fire-prone flora with plant traits that enhance flammability, **2**) learning organisms that alter the form and frequency of their stimuli, **3**) bacteria that produce anti-bacterial toxins, and **4**) hosts and pathogens that continually coevolve. Recently, he has focused on how the incorporation of spatial structure can drastically affect the eco-evolutionary dynamics of these and other niche construction systems. He has also explored (both theoretically and experimentally) how altruistic forms of niche construction evolve in relation to various forms of population structure.

Steven E. Koonin Ph.D.

Presentation Title

Challenges in Energy Biosciences

Sunday / Session I

Chief Scientist

BP p.l.c.

Dr. Koonin was born in Brooklyn, New York and educated at Caltech (B.S. in physics) and MIT (Ph.D. in theoretical physics). He joined the Caltech faculty in 1975, becoming a full professor in 1981 and serving as the Institute's Provost from 1995 - 2004.

Dr. Koonin left Caltech in March 2004 to become BP's Chief Scientist. BP is the world's second largest independent oil company, producing some 4% of the world's oil and gas. It refines and markets petroleum products in more than 100 countries and serves more than 13 million customers each day. Among the well-know BP brands in the US are Arco, Amoco, and Castrol.

In his capacity as Chief Scientist, Dr. Koonin is responsible for BP's long range technology plans and activities, particularly those "beyond petroleum." He also has purview over BP's major university research programs around the world, and provides technical advice to BP's senior executives on matters on Group significance.

Dr. Koonin is a fellow of the American Physical Society, the American Association for the Advancement of Science, and the American Academy of Arts and Sciences, as well as a member of the Council on Foreign Relations and the Trilateral Commission. He has served on numerous advisory bodies for the National Science Foundation, the Department of Defense, and the Department of Energy and its various national laboratories. His research interests have included theoretical nuclear, many-body, and computational physics, nuclear astrophysics, and global environmental science.

Elliott Meyerowitz Ph.D.

Presentation Title

Regulated Morphogen Transport:
A Novel Mechanism of Development

Monday / Session II

George W. Beadle Professor of Biology

Chair, Division of Biology

California Institute of Technology

Dr. Meyerowitz has been a member of the faculty of the California Institute of Technology since 1980. He studies the genetics of flowering plants, especially Arabidopsis thaliana. Dr. Meyerowitz's laboratory has identified and cloned homeotic flower development genes, leading to the "ABC Model" of floral organ specification, and was the first to clone plant hormone receptors. Their current work combines studies of gene expression and cell division patterns with computational models, to understand plant growth.

Among Dr. Meyerowitz's honors are the Pelton Award of the Botanical Society of America and the Conservation Research Foundation (1994); the Gibbs Medal of the American Society of Plant Physiologists (1995); the Genetics Society of America Medal (1996); the International Prize for Biology of the Japan Society for the Promotion of Science (1997); the Lounsbery Award of the National Academy of Sciences (1999); the Wilbur Cross Medal of Yale University (2001); and the R.G. Harrison Prize from the International Society of Developmental Biologists (2005).

Dr. Meyerowitz is past president of the International Society for Plant Molecular Biology (1995-97) and the Genetics Society of America (1999), and is president (2005-06) of the Society for Developmental Biology. He is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, the American Philosophical Society, a foreign associate of the Académie des Sciences of France, and a foreign member of the Royal Society.

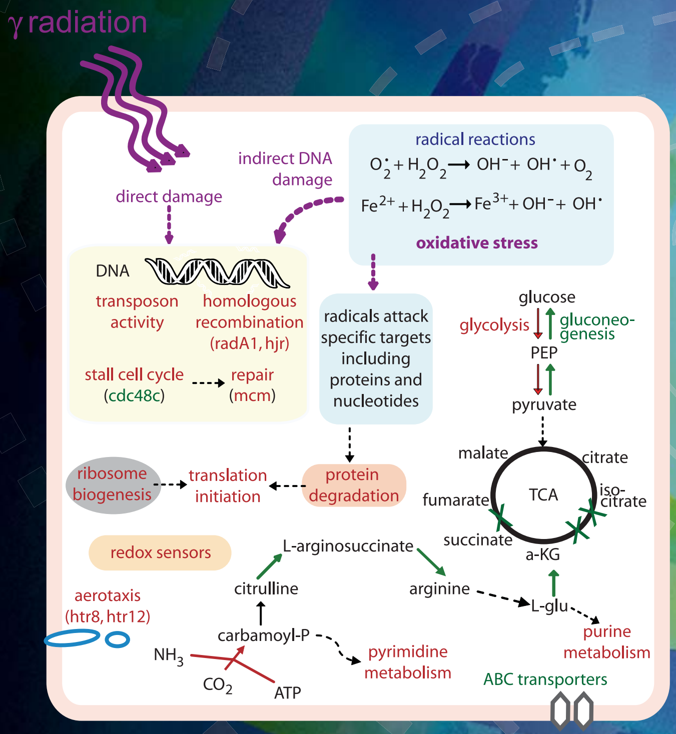
> "The most significant advances in medicine in the late 20th century will pale in comparison to the impact that systems biology will have on our ability to predict and prevent diseases in the 21st century. It's an historic time in science and the Institute for Systems Biology is at the forefront."

George Rathmann PhD
Biotehnology pioneer and member, ISB Board of Directors
Sunnyvale, California

Systems Biology & The Environment At ISB

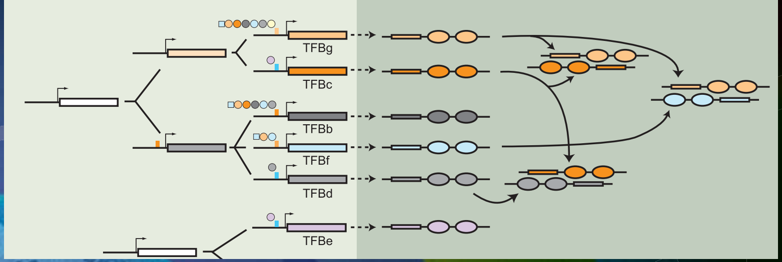
The Institute for Systems Biology (ISB) was co-founded in 2000 by Ruedi Aebersold, Alan Aderem, and Leroy Hood. In six years it has grown to more than 200 staff members, including 12 faculty members and their laboratory groups.

Because a systems approach to disease requires the seamless integration of biology, technology, and computation, ISB has developed a philosophy, an infrastructure, and an administrative structure that is designed to break down traditional organizational and disciplinary barriers. Researchers collaborate across the boundaries of their disciplines and reach outside organizational boundaries to share and leverage knowledge and expertise with partners in academia and industry. Systems biology recognizes the complex multi-scale organization of biological systems from molecules to ecosystems and the environment. ISB scientists conduct leading research in the areas of infectious disease, toxicology, and biological responses to extreme environments.



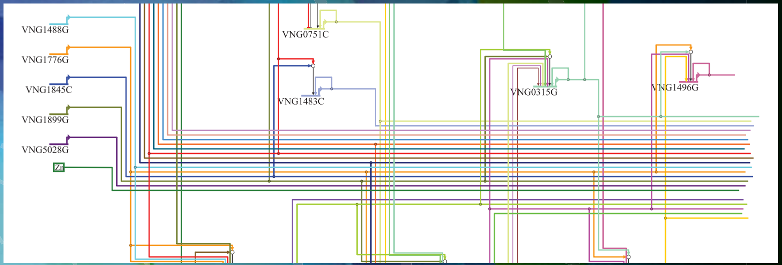
Molecular Systems Analysis of Cellular Responses to the Environment

All organisms can sense and process complex changes in the environment through a web of intricate information processing pathways to adapt their behavior appropriately. At ISB, high throughput global technologies in concert with traditional genetic and biochemical approaches are providing fascinating insights into how this process tailors physiological responses in face of environmental stress. Specifically, using *Halobacterium salinarum* NRC-1 an extremophilic organism that proliferates in a saturated salt environment, scientists at ISB are delineating cellular circuits for negotiating excessive metals, DNA damaging UV and gamma radiation, excessive oxidative stress, dynamic fluctuations in oxygen availability and routine adjustments to the day/night cycle.



Evolution of Gene Regulatory Mechanisms

Life on this planet has been classified using molecular phylogeny into three major domains. While many principles of gene regulation have been discovered from the Bacteria and the Eukaryotes, for the first time systems approaches applied to *Halobacterium* are providing insights into how this process has evolved in organisms of the third domain of life –the Archaea. Organisms of this domain are better known for their ability to grow in unusual environments including above boiling temperatures, enormous pressures, and hypersaline conditions. Research at ISB has shown that through the duplication and evolution of no more than two families of general transcription factors these organisms have assembled sophisticated global gene regulatory programs.



Modeling Cellular Networks with Machine Learning Algorithms

Biological systems are extraordinarily complex with exponentially larger sets of possible cellular network architectures with increasing numbers of genes. Although global technologies are generating ever increasing amounts of data associated with information processing highways in cellular networks, sophisticated computational approaches are necessary to construct meaningful biological networks from these data. Using machine learning algorithms scientists at ISB are integrating the large amounts of data from individual cell response studies into unified comprehensive models for gene regulatory programs governing physiological changes. These models are serving as blueprints for re-engineering cellular networks and predicting cellular responses in new environments.

The Liver and Toxic Chemicals

At ISB scientists are using systems approaches to identify blood molecular fingerprints whose protein concentrations reflect the status of the organ from which they are derived (organ-specific blood proteins). They are using this approach to study the response of the liver to toxic chemicals in the blood. The liver is the largest organ in the human body. It filters the blood often removing chemicals that may be deleterious to life. In some occasions these chemicals may poison the liver itself. Recently ISB has studied the effects of Tylenol overdoses (toxicity) in mice through an analysis of dynamically changing concentrations of proteins in the liver-specific blood fingerprints at different time points after the poisoning. These fingerprints allow us to measure the changing degrees of liver toxicity and are beginning to provide fundamental insights into the nature of metabolic changes introduce by the toxin. Thus the systems approaches will be very powerful in studying the interactions of the environment (in the form of toxic chemicals) and living organisms such as humans.

Global Phylogeography and Population Genetics of *Mycobacterium tuberculosis*

At ISB scientists study the nature and consequence of genetic variability in *Mycobacterium tuberculosis*, which they address from both a micro- and macro-evolutionary perspective. This perspective comprises evaluating the effect of bacterial genetics and compensatory evolution on the relative fitness and transmission dynamics of drug-resistant *M. tuberculosis*. This work integrates the use of experimental evolution and competitive fitness assays with molecular epidemiological studies in clinical settings. The macro-evolutionary perspective focuses on the global phylogeography and population genetics of *M. tuberculosis*, and on the effect of mycobacterial variation on the host-pathogen interaction. These research efforts rely on ISB's high-throughput DNA sequencing to define the global diversity of *M. tuberculosis*, and on cytokine assays and gene expression profiling to study the effect of strain variation on host immune signaling.

Centers Of Excellence At ISB

Center for Systems Biology

The Center for Systems Biology (**www.centerforsystemsbiology.org**) funded is pioneering the study of molecular network dynamics in model systems and disease systems. Application of this approach to disease will revolutionize medicine in that very early diagnoses may be made from a blood test that detects network perturbations—thus improving the efficacy of existing treatments and enabling the development of new treatments. Over the next 5 to 20 years, systems biology will serve as the foundation for predictive, preventive and personalized medicine.

Seattle Proteome Center

The goal of the Seattle Proteome Center (**www.proteomecenter.org**), supported by the National Heart, Lung, and Blood Institute, is to develop innovative proteomic technologies and apply them to biological questions. The research focus of the Center is an array of new, systematic assays to comprehensively study the dynamics of cells in health and disease. The long-term focus of this Center is to apply these technologies to the biology of the macrophage - a cell of central importance in chronic inflammatory responses that lead to disabling human diseases, which include atherosclerosis and chronic fibrotic lung diseases.

Center for Inquiry Science

The Center for Inquiry Science is a team of science educators uniquely hosted at the nonprofit research institution, the Institute for Systems Biology. While drawing from and contributing to educational research, the Center for Inquiry Science's efforts support K-12 inquiry-based science education within the Puget Sound region and often, if requested, across Washington State. The services offered by the Center for Inquiry Science include development, facilitation, and coordination of professional development and consultation for teachers and administrators.

Strategic Partnerships

The ISB is a scientific catalyst and a hub of strategic partnerships driving the impacts of systems biology.

Helicos BioSciences Corporation

The ISB is a partner with Helicos BioSciences (**www.helicosbio.com**), a pioneer in high-speed, high-sensitivity sequencing. This union allows us access to Helicos' True Single Molecule Sequencing (tSMSTM) technology and protocols for use in its scientifically groundbreaking research projects. The tSMSTM technology enables researchers to rapidly and accurately sequence individual molecules of DNA and RNA and promises to provide both maximum efficiency and cost-savings. We have begun applying the capabilities of true single molecule sequencing technology in the area of cancer research. The tSMSTM technology will allow us to address questions in the field of oncology that have, up until this point, remained elusive.

NanoSystems Biology Alliance

With Caltech and UCLA, the ISB is a partner in the NanoSystems Biology Alliance that is dedicated to using the needs of systems medicine to drive new in vitro and in vivo measurement technologies. One aspect of the alliance in the Nanotechnology/Cancer Center funded by the National Cancer Institute. This Center (**www.caltechcancer.org**) is organized to take advantage of the state-of-the-art in chemistry, materials, and physics of nanotechnology science and engineering, the state-of-the-art in the systems biology approach to health and disease, and the state-of-the-art in the science, technology, and clinical applications of cancer biology.

Systems Approach to Innate Immunity-Inflammation-Sepsis

With The Scripps Research Institute and Rockefeller University, the ISB is a partner in a long-term collaborative NIAID-funded project to study the systems biology of the innate immune response to infection (**www.septicshock.org**). The pathophysiology of severe sepsis/shock is exceedingly complex. The only means to approach such a complex system is to use appropriate cellular and animal model systems and apply the principles of systems biology in their analysis. This interdisciplinary collaboration will substantially expand the formulation of new concepts for this field. These studies will also identify potential new drug targets that could lead to new therapies for sepsis and shock.

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