REVOLUTIONIZING SCIENCE. ENHANCING OUR LIVES.

Institute for Systems Biology 2006 Annual Report

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REPORT FROM THE CHAIRMAN

The report that you have in your hands charts the remarkable progress that we have made at the Institute for Systems Biology (ISB). Indeed, in just a few short years, ISB has become a global leader in the advancement of "systems biology" research. In its simplest form, systems biology provides a framework for thinking about how the building blocks of biological machines interact to yield the properties that we associate with living organisms.

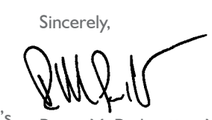
Having participated in the sequencing of human and other genomes in the 1990s, Lee Hood, together with immunologist Alan Aderem and proteomics specialist Ruedi Aebersold, recognized that a new sort of research entity would be required to fully realize the potential benefit to human health created by advances in our understanding of genetics. It would need to be a place where physicists, chemists, mathematicians, computer scientists and biologists could work together to build the tools necessary to understand the emergent properties of living systems.

Lee, Alan and Ruedi created just such a place in ISB. In six short years the Institute has tripled in size to more than 200 employees. It now occupies 65,000 square feet of state-of-the-art laboratories at the north end of Seattle's Lake Union and in 2006 ISB maintained an operating budget of $25 million. In addition, the faculty and senior scientists published 79 peer-reviewed articles and attracted $25.4 million in new grants from government funding agencies. Private grants, gifts and commitments to the Institute yielded an additional $6.2 million.

This annual report provides persuasive evidence of the importance of the vision originally articulated by Drs. Hood, Aderem and Aebersold. As Lee Hood notes in his letter, ISB is focusing increasing effort on the application of tools developed through systems biology research to the realization of personalized, predictive, preventive and participatory (P4) medicine.

Recognizing that research grants, especially given current federal budget constraints, cannot possibly support the full development of the Institute for Systems Biology, the ISB Board of Directors has, together with management, chartered a process aimed at developing new sources of long-range funding. I look forward to sharing the details of this plan with you next year. In the meantime, the attached summary of our activities in 2006 makes plain that the Institute for Systems Biology has adopted a truly pioneering approach, one that will dramatically advance biomedical research and, ultimately, the practice of medicine.

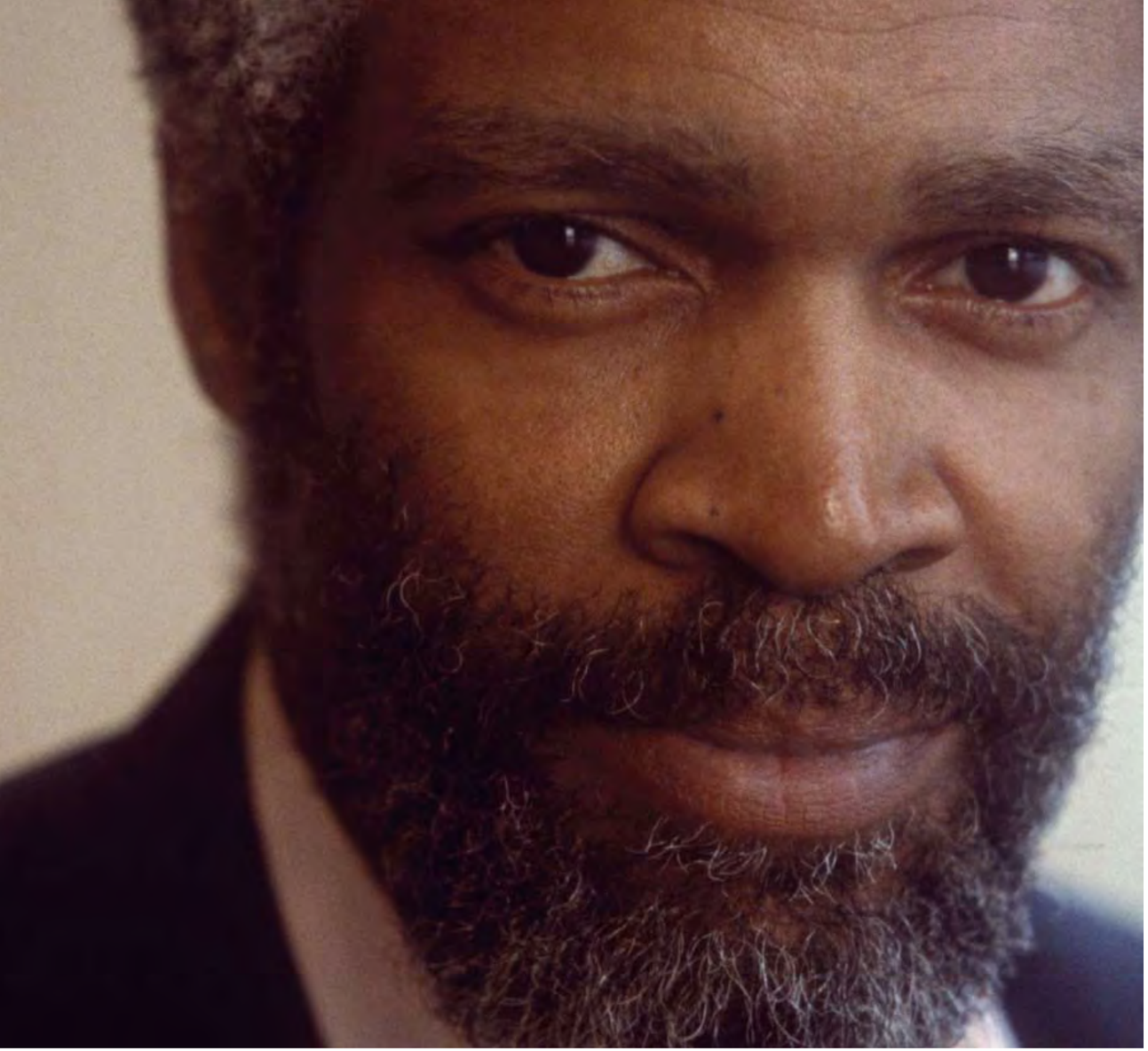
Sincerely,



Roger M. Perlmutter, MD, PhD
Chairman of the Board

P4 MEDICINE

Medicine of the future will be personalized, predictive, preventive and participatory, examining the unique biology of an individual to assess their probability of developing various illnesses and then designing appropriate treatments, even before the onset of disease.



"My DNA will be a crystal ball, allowing me to see into my health future."

REPORT FROM THE PRESIDENT

One of the grand challenges of the 21st century is to decipher the complexity of the biological systems upon which our life depends. Systems biology, pioneered by ISB, is the most powerful approach to meeting that challenge, understanding the intricacy of biological function, and harnessing the body's biological networks to improve human health.

Until recently, biologists largely studied cellular and molecular phenomena without observing or measuring their extraordinary connectivity. The complexity of that connectivity within human biological networks requires approaching biology as an information science. Each component of the biological systems — proteins, DNA, RNA — can be represented as digital information. Using measurement technologies to generate data and computer analyses, and modeling to test hypotheses, scientists can develop strategies for predicting what happens to the functioning of a biological system when one or more elements is destroyed or mutates. That understanding will allow us to think about new strategies for early diagnosis (and hence the cure of most cancers) as well as new strategies for designing drugs for therapy, or even the prevention of cancers, neurological disorders, Type 1 Diabetes and many more diseases.

Disease arises from environmentally or genetically perturbed networks that do not return to their normal states. Thus, studying biological network malfunctions and determining how to re-engineer them to restore healthy function will provide new insights into diagnosis, therapy and prevention.

This is the basis of the new medicine based on systems biology: a medicine that will quickly evolve over the next generation from a reactive practice to a predictive, personalized, preventive and participatory (P4) process.

At ISB the systems approach is producing spectacular results. We have demonstrated how perturbed biological networks function abnormally, explaining many features of prostate cancer and mad cow disease (in mice). We are making significant progress on new technologies for vaccine development. We have demonstrated that our organs secrete protein biomarkers into the blood that allow one to distinguish health from disease, and in fact, which type of disease is present. Our scientists are developing nanotechnologies that will enable the measurement of thousands of these proteins from a droplet of blood. We are working to develop new DNA sequencing methods, which will enable us to sequence inexpensively entire individual genomes within 10 years. Finally, ISB is working on new computational and mathematical approaches to the analyses of genomes and blood protein content.

Together, these and many other advances represent the excitement and the immense promise of ISB's research community. They constitute a driving force for the emergence of P4 medicine.

Lee Hood

Leroy Hood, MD, PhD
President

PREDICTIVE

One drop of blood is all it will take. One drop on a chip placed into a handheld device in your physician's office will tell you if you have an 85 percent chance of developing heart disease, a 12 percent chance of developing diabetes, a 70 percent chance of developing Parkinson's disease, or cancer, or virtually any other disease influenced by your genetic makeup. That knowledge will give you power.

"My DNA may reveal that I have an 85 percent chance of developing breast cancer. Knowing that gives me options and could save my life."

SCIENTIFIC ACHIEVEMENTS

ISB researchers made significant progress in 2006, publishing nearly 80 peer-reviewed articles in scientific journals, receiving substantial government awards to advance systems biology approaches, broadening the scope of ISB's strategic partnerships and receiving worldwide recognition for the excellence of their work.

A new window on inflammatory disease

Using a systems approach, scientists at ISB discovered that the absence of the transcription factor ATF3 leads to inflammatory disease in mice. The inflammatory response is required for immune responses to infection, but uncontrolled, it leads to a variety of illnesses such as rheumatoid arthritis and lupus. ATF3 appears to control the balance between the beneficial and destructive arms of inflammation, and a complete understanding of this regulation could point to novel therapeutics for these diseases. These findings were published in *Nature*.

Mutations in immune system genes increase risk for infectious diseases and point the way to better drugs and vaccines

ISB researchers found significant links between mutations in innate immune genes and human susceptibility to a number of infectious diseases. The mutations are in a family of molecules called Toll-like receptors (TLRs), which alert the body to the presence of infectious agents. The results suggest new drug targets and vaccine strategies. The studies demonstrate, for example, that a mutation in TLR9 leads to rapid progression from HIV infection to the development of AIDS and a mutation in TLR2 predisposes patients to genital herpes, tuberculosis and leprosy. These observations were published in the *Proceedings of the National Academy of Sciences*, *The Journal of Experimental Medicine*, *The Journal of Infectious Diseases*, *The Journal of Immunology and AIDS*.

Gene mutation a potential herald of Type 1 Diabetes

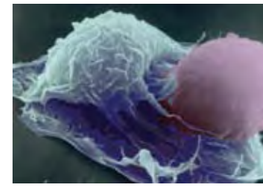
In the October 2006 issue of *The American Journal of Human Genetics* ISB researchers identified a gene, ITPR3, which is associated with Type 1 Diabetes. ITPR3 regulates calcium flow within cells and had not previously been associated with diabetes. This finding gives deeper insight into mechanisms underlying Type 1 Diabetes, a debilitating illness which generally strikes the young.

New means of defense against E. coli and Salmonella promise new therapies

ISB researchers identified two new mechanisms by which the immune system defends us from infection. In the first, reported in *Nature*, the scientists found that immune cells secrete a protein, lipocalin, which limits E. coli infections by competing with the bacterium for iron. In the second, reported in *Nature Immunology*, investigators identified a protein, Ipaf, which detects the flagella of Salmonella and triggers a robust immune response to the bacteria. Knowledge of these novel pathways could lead to the development of new antibiotics.

Computational methods facilitate development of new approaches to P4 medicine

The prediction of traits, including diseases and responses to therapies, is greatly complicated by the intricate ways in which combinations of gene variants interact. This complexity underlies the genetic challenges of predictive and personalized medicine. ISB researchers have developed computational methods that accurately predict genome-wide gene activity and precise trait outcomes



PREVENTIVE

If your genetic structure tells doctors you have a 95 percent chance of developing Parkinson's disease, and you know that by taking a pill and exercising starting at age 20 you could reduce that chance to less than three percent, what would you do? If protein biomarkers in your blood told physicians that your pancreas cells were beginning to mutate and become cancerous, would you take a drug that would tell your immune system to attack those cells and cure you before you experienced even a single symptom?

SCIENTIFIC ACHIEVEMENTS
(continued)

for combinations of mutations. This work, reported in *Molecular Systems Biology*, provides a core strategy for the systems biology of complex genetics.

Mathematical models lead to a better understanding of genetic diseases

ISB scientists developed a mathematical model for the genetic program leading to the formation of an essential organelle, the peroxisome. Peroxisomes have a variety of metabolic roles that implicate them in many human health concerns, including aging, neuropathology, cancer, heart disease, obesity and diabetes. These findings were reported in *Molecular Systems Biology*.

Metals research could lead to remedy for some genetic diseases

ISB researchers developed a model that explains how cells respond to metals in the environment. These results, and the systems biology approach used to map the process, may be useful in understanding the pathophysiology of a number of genetic maladies that are known to be linked to metals, such as Menkes and Wilson's diseases. This work was reported in *Genome Research*.

Quantitative methods developed to identify biomarkers

Blood biomarkers form one of the cornerstones of P4 medicine. In 2006 ISB scientists developed new methods to identify and quantify molecules in the blood that can serve as early diagnostic markers for cancer, heart disease, and the efficacy of vaccines. This work was reported in *Proteomics*, *Science*, *Genome Biology*, *Nature Biotechnology*, and *Nature Methods*.

Genetic diversity of TB bacteria influences disease transmission

ISB researchers demonstrated that mycobacterial lineages adapt to particular human populations, and that host-pathogen co-evolution impacts the transmission of tuberculosis. This led to the further observation that strain genetic diversity can influence the transmission of drug-resistant bacteria. These are important findings for the design of new tuberculosis diagnostics, drugs and vaccines. These observations were published in *Science*, the *Proceedings of the National Academies of Science* and *PLOS Pathogens*.

ISB selected by NIH to host national Center for Systems Biology

In spring 2006, ISB received a five-year, $16.3 million grant from the National Institutes of Health (NIH) to fund a Center for Systems Biology. The Center provides professional development in systems biology approaches and fosters collaboration among the diverse researchers at the Institute: biologists, chemists, computer scientists, engineers, mathematicians and physicists. Core research funded by the grant includes genomics, proteomics, microfluidics and imaging, and informatics. The Center also provides support for K-12 education in inquiry-based science. The NIH is funding six additional centers to support systems biology work pioneered at institutes like ISB.

Alan Aderem, PhD
Co-Founder and Director

"In the future I will be cured by medications designed just for me."

PERSONALIZED

In the future, having your genetic structure will allow physicians to provide you with medicine made for you and no one else. Not one of the hundreds of thousands of other people who share your disease but not your personal biology. These medicines will have no side-effects. They will eliminate the need for trial and error treatments that allow for disease progression, and they will cure you before you know you are sick. Having your genetic structure will give you knowledge, and that knowledge will give you the power to live intentionally rather than reactively, and to live longer and more fully.

TRANSFERENCE OF KNOWLEDGE TO THE COMMUNITY

ISB enhances people's lives and improves the human condition by transferring knowledge gained through its research to the community. It accomplishes this through support of science and math education in public schools and the transfer of new technologies to the commercial sector.

Growing new biotech companies: Accelerator Corporation

A key component of ISB's commitment to the community is Accelerator Corporation, a novel partnership among ISB and life science leaders Amgen Ventures, ARCH Venture Partners, MPM Capital, OVP Venture Partners, Versant Ventures and Alexandria Real Estate Equities, Inc. Accelerator creates early-stage companies arising from scientific discovery at the Institute and elsewhere.

Accelerator grew five emerging biotechnology companies in 2006: VieVax Corp., VLST Corp., Spaltudaq Corp., Homestead Clinical Corp. and Allozyne, Inc. These companies focus on:

- novel approaches to vaccine development;
- faster development of effective therapeutics for inflammatory and autoimmune diseases;
- developing tumor-specific therapeutic antibodies to treat cancer;
- commercializing ISB technologies with broad utility for developing diagnostic, prognostic and theranostic tools;
- commercializing technologies that improve the efficacy of protein-based therapeutics.

VLST Corp., focused on developing therapeutics for autoimmune and inflammatory disorders, raised $55 million during 2006 as the first Accelerator company to receive series B financing.

Building scientific literacy: Center for Inquiry Science

ISB's Center for Inquiry Science (CIS) exemplifies the Institute's commitment to improving science education for every child in the state. Excellence in science education for K-12 students is critical for providing the skilled employees Washington's research and development sectors require in the next generation, as well as equipping an educated citizenry to make wise choices about the many scientifically related challenges facing our society.

Mission of CIS

To enable schools and districts to have the capacity to produce scientifically literate and capable students by creating and supporting a statewide infrastructure, comprised of collaborative and regional partnerships among schools, districts, and community partnerships that will train and support science educators.

CIS 2006 highlights

- Programming supported teachers and administrators in 21 districts representing 24 percent of Washington state's student population.
- CIS developed, coordinated and/or facilitated 76 professional development events serving 1,135 science educators.
- CIS generated more than $800,000 in grants, gifts and fee-based revenue, approximately $543,000 of which came from outside Washington state, to help schools build strong, inquiry-based scientific literacy among the state's student population. Grants were provided by such organizations as the National Institutes of Health, the Boeing Company, the National Science Foundation, the Washington State Office of the Superintendent of Public Instruction/Pacific Science Center and the Arthur Vining Davis Foundations.

"One day my DNA could reveal that I'm highly likely to die young of heart disease. If it does, I'll work with my doctors to create a different future."

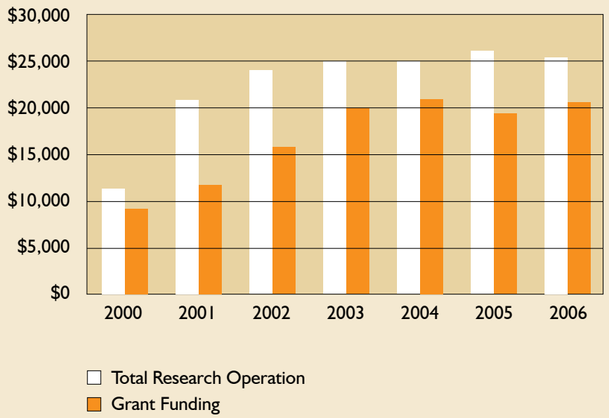
PARTICIPATORY

P4 Medicine will give you more information, more choices and more control than any other healthcare advance in history. You will control whether your genome is sequenced. You will control who gets to view your genetic makeup. You will sign up for biomarker tests every six months and you — no one else — will adhere to therapies (whether physical, nutritional or medicinal) to cheat your genetic destiny. Or you won't. That's the participatory part. You will have the power, and the responsibility, of using resources never before available to live your longest and best life.

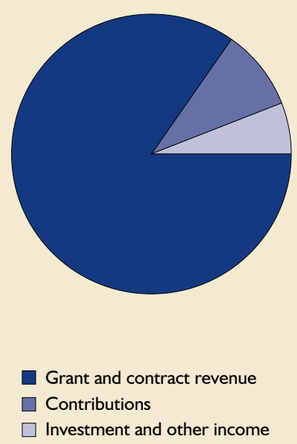
FINANCIAL TABLES

Fiscal Year Ended December 31, 2006
(Dollars in thousands)

GROWTH IN OPERATIONS
Over A Seven Year Period



REVENUES
FY 2006



FINANCIAL STATEMENTS

Balance Sheet	
Cash and investments	11,662
Other assets	7,440
Property and equipment, net	8,094
Total Assets	**27,195**
Accounts payable and accrued expenses	1,964
Deferred revenues	913
Notes payable	11,337
Total Liabilities	**14,213**
Unrestricted net assets	891
Temporarily restricted net assets	3,419
Permanently restricted net assets	8,672
Total Net Assets	**12,982**

UNRESTRICTED REVENUES & EXPENDITURES

Revenues	
Grant and contract revenue	20,364
Contributions	2,222
Investment and other income	1,414
Total Revenues	**24,000**
Expenditures	
Research and direct costs	19,447
Management and general	5,305
Fundraising and other	433
Total Expenditures	**25,185**
Decrease in Net Assets	**(1,185)**

FINANCIAL HIGHLIGHTS

Revenue from grants and contracts, the Institute's major source of funding, increased $1.4 million to $20.4 million in 2006, a seven percent increase over 2005.

This positive outcome was very welcome, as 2006 was a fiscally challenging year for independent research institutions such as ISB, which heavily depend on government grants and contracts. Nationally, awards from the National Institutes of Health (NIH), the largest source of biomedical research funding, dropped slightly in inflation-adjusted terms for the second year in a row. Furthermore, it remained very difficult for younger investigators to receive grant funding, which made the climate particularly competitive for our relatively young cadre of investigators.

The excellence of the Institute's science countered these market forces, however.

ISB was awarded more than $25 million in new government grants during 2006, including a prestigious center grant in systems biology from the NIH, which will bring ISB $16.3 million over the next five years. In addition, ISB received new grants and contracts from private sources totaling more than $6.2 million, including seven-figure awards from the Bill and Melinda Gates Foundation and The Boeing Corporation. Unrestricted gifts totaled more than $2.0 million, and investment and other income exceeded $1.4 million, a 30 percent increase over 2005.

ISB invested just over $800,000 in new equipment and equipment upgrades in 2006. Proteomics is a core competency of the Institute, and almost half of these funds were spent to acquire a triple quadrupole/linear ion trap mass spectrometer ideal for drug discovery and development, protein discovery, protein identification and biomarker validation. ISB also invested significantly in two state-of-the-art Leica microscopes to enhance image analysis.

Looking to grow and diversify its revenue sources to advance its mission, ISB began in 2006 to expand its fundraising and marketing efforts, hiring a Vice President for Development and other related staff. Building on the successes of 2006, ISB faculty and administrators began developing a new strategic plan for the next decade and beyond.

Gary Raisl, EdD
Vice President of Finance and Administration

AWARDS AND RECOGNITION

ISB co-founder and president Lee Hood received the 2006 Heinz Award in Technology, the Economy and Employment. Hood and ISB co-founder Reudi Aebersold were elected to the prestigious European Molecular Biology Organization. ISB co-founder Alan Aderem was recognized by the Society for Biomolecular Sciences for the most outstanding paper at the organization's 2006 conference in Seattle.

DEVELOPMENT AND PUBLIC RELATIONS

Since its founding in 2000, more than $50 million in gifts and grants have been awarded to ISB by the private sector. This philanthropic investment has unleashed systems biology as the model for biological inquiry and discovery in the 21st century, leveraged millions of dollars in government grants and contracts for our scientists, and enabled ISB to build key strategic partnerships. ISB is truly a remarkable example of the power of philanthropy.

In 2006, the Institute recorded $2.6 million in cash income from private sources. Nearly $2.1 million was in unrestricted funds, which are invaluable in that they help launch the research and careers of our junior faculty and meet costs of other research and administrative opportunities. Program support totaled almost $500,000, primarily advancing the work of ISB's Center for Inquiry Science, Washington's premier center of training and support for secondary school science teachers. In addition, we received a commitment of $1 million from the Boeing Foundation, payable over four years, to support CIS. The McDonnell Foundation provided another major gift.

Sponsorship income of more than $60,000 supported the 5th Annual ISB International Symposium, "Systems Biology and Medicine." This two-day event in April attracted more than 250 attendees, the Institute's most successful symposium ever.

Looking to ISB's future, the board of directors in 2006 decided to professionalize operations in development and public relations. The position of vice president of development was established, and I was delighted to join the Institute in September. ISB immediately began to increase substantially the number of individuals, corporations and foundations to whom the Institute can turn for gifts and grants, to boost unrestricted gift income, focus fund-raising on strategic objectives, and begin a concerted effort to raise endowment funds. All these endeavors are integrated with ISB's strategic planning, which began in late fall. The Institute is also launching a communications program to educate the public about ISB's achievements and the impact of our systems approaches on future medical care.

ISB intends to continue providing many opportunities for visionary and generous donors who want to enhance lives through our revolutionary science.

Laurence W. Herron
Vice President for Development

Major Donors

Anonymous
Alexandria Real Estate Equities, Inc.
Allen Institute for Brain Science
Amgen Foundation
Bill and Melinda Gates Foundation
The Boeing Company
California Institute of Technology
Cancer Research Institute
Fermentas, Inc.
Frederick Frank
GVA Kidder Matthews
Harbor Properties, Inc.
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IDT
Invitrogen
James S. McDonnell Foundation
Lake Union Travel
Valerie Logan and Leroy Hood
Merck & Co., Inc.
OVP Venture Partners
Pacific Northwest National Laboratory
Roger M. Perlmutter
Puget Sound Refrigeration
Henry Riggs
The Runstad Foundation
University of Washington
Vulcan, Inc.

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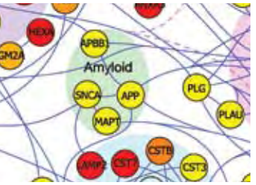
STRATEGIC PARTNERSHIPS: BRIDGING ACADEMIA AND INDUSTRY



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ISB's academic collaborations leverage an array of expertise to undertake comprehensive analyses of scientific problems. ISB's partnerships with industry demonstrate how non-profit and for-profit alliances can rapidly develop and disseminate new methods and technologies with global impact in predicting and preventing diseases.

In 2006, ISB maintained partnerships with the following organizations:

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California Institute of Technology

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Helicos

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The Nanosystems Biology Alliance

The Rockefeller University

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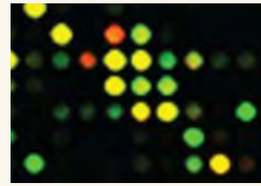
Examples of 2006 strategic partner initiatives

- GenoLogics Life Sciences Software Inc., in partnership with ISB, announced integrated open source software that broadened the dissemination of new technologies and computational tools for proteomics research to scientists and labs worldwide.
- In October, Lumera Corporation and ISB extended their productive relationship to develop detection methods for an array of diagnostic biomarkers aimed at various types of cancer.
- Helicos Biosciences Corporation and ISB established a partnership that employs the company's new high throughput DNA sequencing platform to study the transcriptomes (populations of mRNAs in cells or tissues) of normal and cancer cells.



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