CONNECTING THE DOTS

Institute for Systems Biology

2011 Annual Report

From the Co-Founder & President and the Chairman

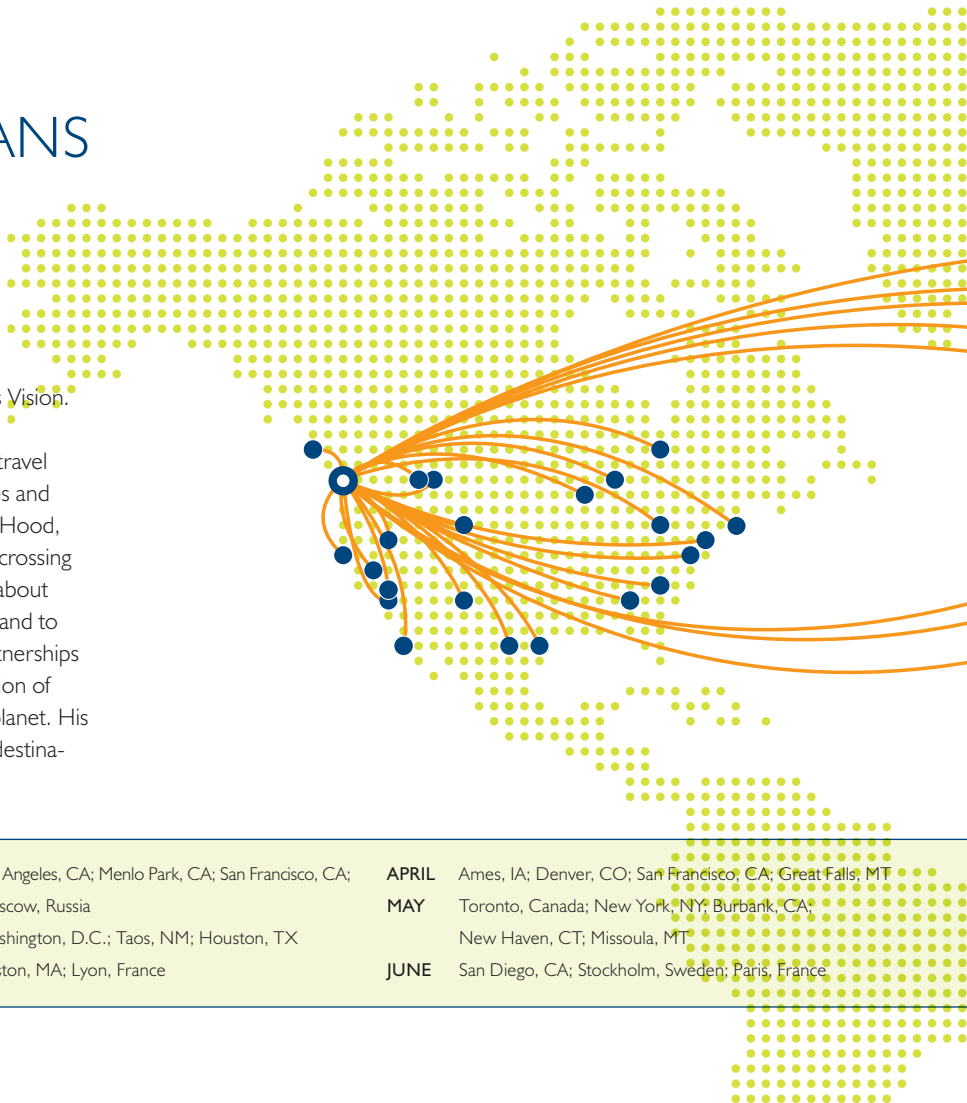
Structuring for the Future

In 2010, ISB celebrated its 10th anniversary and looked back on a decade of pioneering work that expanded the boundaries of research, innovation, knowledge transfer, and national and international strategic partnerships. In 2011, as we stepped into our second decade, we began a shift in structuring that better positions ISB to continue the responsibility of leading the field of systems biology, as well as extending its application to some of society's most challenging areas—healthcare, global health and the environment. All of this is moving forward as ISB faces accommodating the hard realities of diminishing federal resources. A major approach to fostering new opportunities is through greatly expanding strategic partnerships that bring complementary scientific and technical skills, new materials for biological exploration and the opportunity for new approaches to the funding of "big science" projects.

Our year began with preparations for our move in April to our new state-of-the-art facilities in the South Lake Union neighborhood. This area has become a nexus for the life sciences, global health and technology communities in our city, and we are proud to call 401 Terry Ave. N. our home. Since our move, ISB has received LEED Platinum certification, which is the highest designation from the U.S. Green Building Council for environmental sustainability.

In June, we promoted two of our founding faculty members to leadership positions: John Aitchison was named the Senior Vice President and Executive Director for Integrative Biology, and Nitin Baliga was named Director for Integrative Biology.

WELLNESS FOR HUMANS AND THE PLANET



Connecting the World to ISB's Vision.

Our faculty and staff regularly travel to represent ISB at conferences and meetings. Our president, Lee Hood, is our most frequent flier, crisscrossing the globe to grow awareness about the power of systems biology and to explore potential strategic partnerships that can help advance ISB's vision of wellness for humans and the planet. His 2011 itinerary included these destinations:

2011

JANUARY	Los Angeles, CA; Menlo Park, CA; San Francisco, CA; Moscow, Russia	**APRIL**	Ames, IA; Denver, CO; San Francisco, CA; Great Falls, MT
FEBRUARY	Washington, D.C.; Taos, NM; Houston, TX	**MAY**	Toronto, Canada; New York, NY; Burbank, CA; New Haven, CT; Missoula, MT
MARCH	Boston, MA; Lyon, France	**JUNE**	San Diego, CA; Stockholm, Sweden; Paris, France

We are relying on their collective experience, energy and vision to help usher ISB into this next decade. We also brought on two new faculty members, Nathan Price and Sui Huang, to bolster our ability to attack new areas of biology, handle the great challenge of data integration and modeling, and the creation of technologies to explore new dimensions of data space. On the administrative side, we hired Sissy Bouchard as Vice President for Development and Hsiao-Ching Chou as Director of Communications to redouble our efforts to promote a culture of philanthropy and community engagement around our mission to revolutionize science, transform human health and ensure environmental sustainability.

In the fall, we marked another milestone in our strategic partnership with the Grand Duchy of Luxembourg when the Luxembourg Centre for Systems Biomedicine celebrated its grand opening. In just two and a half years, LCSB has become a leading center for systems biology in all of Europe. In addition, we finalized an inter-institutional agreement with Seattle BioMed, which is a global leader in fighting infectious diseases and creating vaccines—and a South Lake Union neighbor—as part of our ongoing structuring for a more collaborative future.

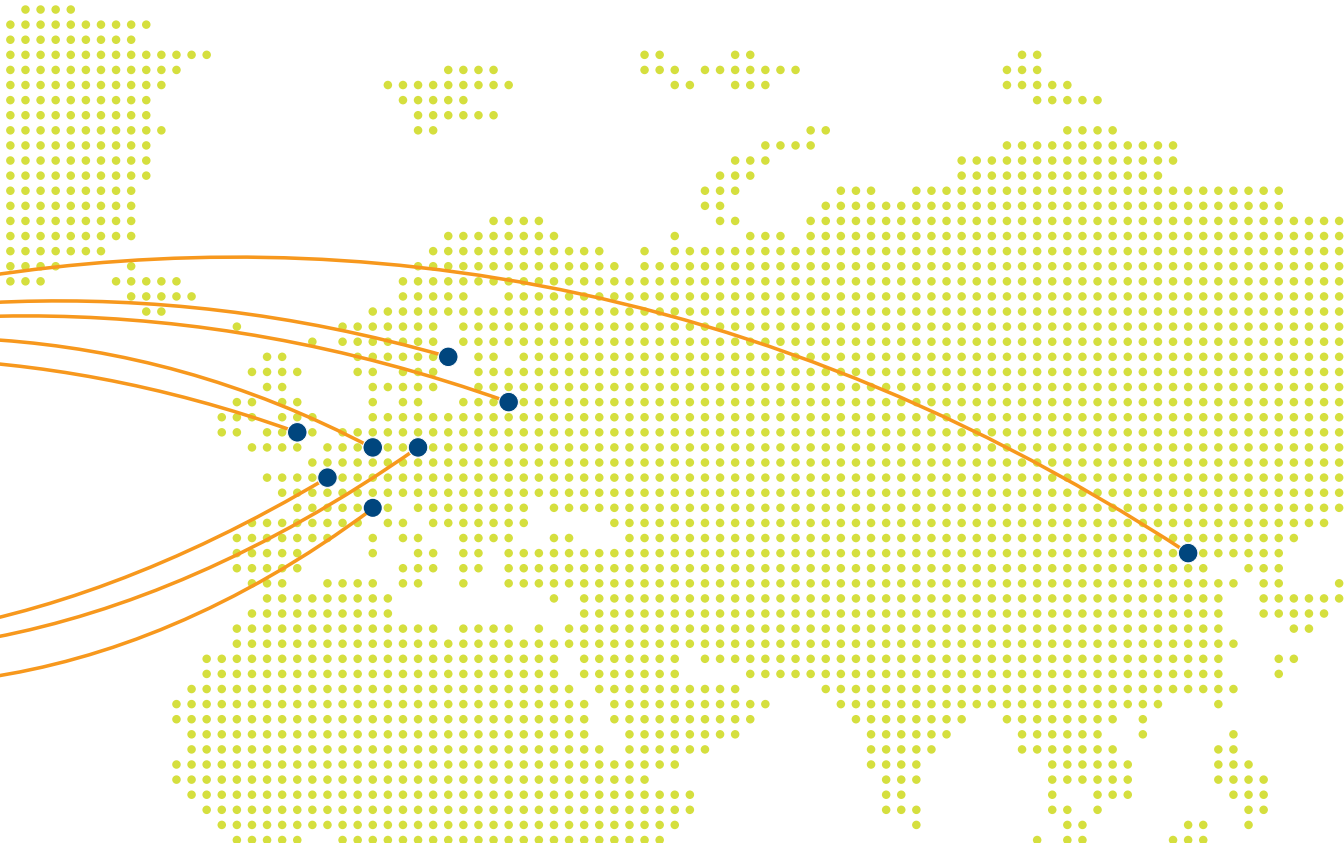
As we look ahead to 2012 and beyond, we believe the future is incredibly promising for ISB and its attempts to pioneer systems science and apply them to challenging societal problems. In this issue, we'd like to draw your attention to the pieces on "The Imperative of Systems Biology" and "Why We Need Single-Cell Analysis"—for they illustrate the very essence of what ISB is all about—and why we deserve your support for helping us change the world.

Lee Hood

Leroy Hood, MD, PhD
Co-founder and President

Lou Lange

Lou Lange,
Chairman of the Board



JULY	San Francisco, CA; Beijing, China; Paris, France	**OCTOBER**	Pittsburgh, PA; Charlotte, NC
AUGUST	Washington, D.C.; Atlanta, GA; Great Falls, MT	**NOVEMBER**	Vancouver, British Columbia; Heidelberg, Germany; Boston, MA
SEPTEMBER	San Antonio, TX; Luxembourg; Washington, D.C.; Menlo Park, CA; San Diego, CA; Reno, NV; London, England	**DECEMBER**	Los Angeles, CA; New York, NY; San Diego, CA; Chicago, IL

ISB's Approach Continues to Pioneer the Field

Dr. Leroy Hood, MD, PhD
Co-Founder and President

ISB was founded in the spring of 2000 to deal with one of the major challenges of the 21st century—biological complexity. This complexity arises as a natural consequence of Darwinian evolution, which acts upon random variation to build complex biological solutions to environmental challenges. One powerful approach to dealing with this complexity is to generate a great deal of data about the system under investigation.

For example, P4 medicine (predictive, preventive, personalized and participatory) deals with the complexities of wellness and disease. My view is that in 10 years, each patient will have a virtual cloud of billions of data points and that we will have the computational tools to reduce this enormous data dimensionality to simple hypotheses about optimizing wellness and dealing with the potential of disease for each individual patient. These data will be of many different types, including genetic, molecular, cellular, organ, and the social networks of individual patients.

The systems-driven science, practiced by ISB, is necessary to handle the enormous complexity of biology and medicine.

The challenges from these huge amounts of data are two-fold: to integrate these data to generate predictive computational models and to deal with the significant signal–to-noise issues. Several of ISB's faculty groups, including Aitchison, Baliga, Price and Shmulevich, are approaching the data integration problem with powerful and innovative solutions.

Noise in the data is of two different types: technical and biological. Technical noise arises from the processes of acquiring the data. Biological noise arises, in part, as a consequence of the random nature of molecular collisions in many biological processes at the cellular level and can, if not averaged out by the large number of cells, show up as variations of the phenotype, which are molecular or descriptive features in a human, such as fingerprints and hair patterns. Biological noise also arises from the fact that in measuring a particular phenotype—a brain transcriptome, for example—the phenotype may arise as a consequence of the integration of multiple inputs from several different biological systems. How to tease these two sources of noise apart to identify the informational elements that encode a "single type of biology" such as neurodegeneration is challenging.

ISB has taken several essential approaches to dealing with signal-to-noise issues;

1. Developing statistical and mathematical tools to deal with technical noise.

2. Conceptualizing biology as an information science, which provides powerful frameworks for dealing with noise: For example, the multi-scale modularity of biology provides deep insights into the organization of complex biological systems.

3. Using clever biology. Having deep domain understanding of biology permits subtractive analyses that allow the separation of the various types of biological noise. The systems approaches provide the ability to undertake dynamical analyses of biological systems in time and space at multiple scales, offering powerful new ways for sorting signal from noise. Modeling also offers powerful approaches for eliminating noise.

4. Employing new technologies permits us to explore new dimensions of data space. As an example, single cell analyses, as discussed elsewhere in this report, are a transformational tool for understanding biological complexity and separating biological from technical noise. The Aitchison, Dudley, Hood, Huang and Ozinsky groups

are exploring this technique. In addition, the global and targeted proteomics strategies being pioneered by the Moritz and Ranish groups will lead to the "democratization" of the study of proteomics.

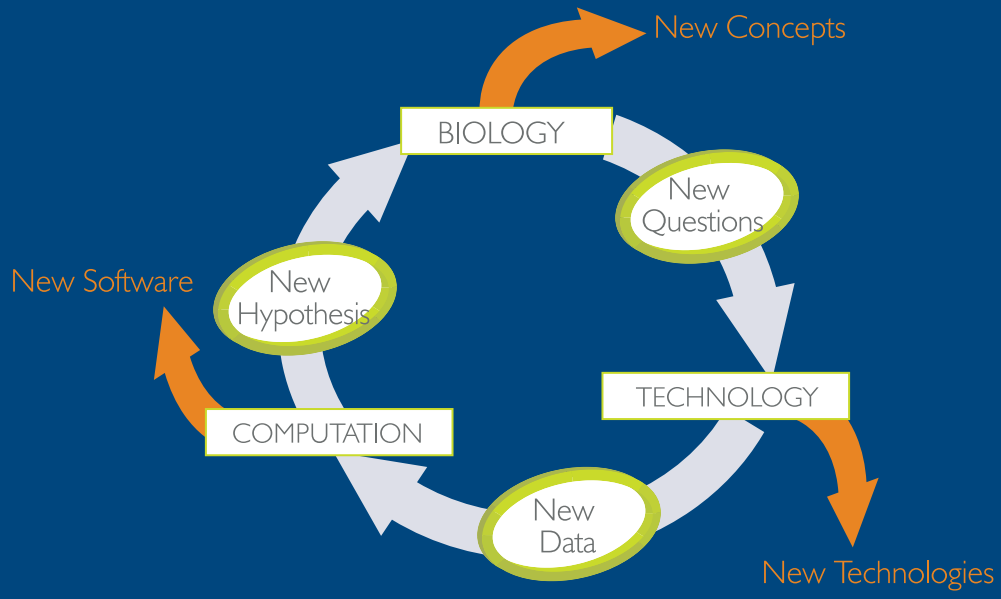
5. Pioneering new computational tools for multiscale data integration into predictive and actionable computational models—as seen in the Aitchison, Baliga, Price and Shmulevich groups.

ISB also has developed a unique infrastructure that facilitates many of the approaches to separating signal from noise as described above. First, a fundamental tenet of systems biology is that solving challenging biological problems always requires the development of new technologies in order to explore new dimensions of data space. Likewise, the development of new data types always requires the pioneering of new analytical tools, both computational and mathematical. To realize the virtuous cycle or holy trinity of "biology drives technology drives computation and mathematics" requires a cross-disciplinary environment where biologists, chemists, computer scientists, engineers, mathematicians, physicists and physicians are all brought together—and learn one another's science languages so that they can work together effectively in teams. This is precisely the environment that ISB has created since its founding. This virtuous cycle is also an "innovation cycle" in that it generates intellectual property that can be spun off as companies. In this regard, ISB has participated in creating 17 companies since 2000—quite a remarkable record.

In addition, ISB has democratized the tools of systems-biology data generation (termed the "omics": genomics, transcriptomics, proteomics, metabolomics, phenomics, etc.) and associated data analyses by making them available to all scientists across groups and disciplines. Accordingly, the systems biologist learns to deal with many types of data. Many of the courses that ISB teaches are focused on broadening this democratization of data generation and data gathering that will enable the "cross-disciplinary" scientists of the future.

Systems approaches to the problems of biology—and medicine—lead quite naturally to the concepts of "big" and "small" science. Small science describes the work of a single scientist and his or her group approaching small and focused problems. Big science describes several different approaches to larger biological problems:

1. Discovery science—attempting to define the "parts lists" of biology. The genome project is the prototypical example that defined the sequence of DNA letters of the 23 different human chromosomes. Parts lists are central to systems biology.



2. Systems-driven science—using an approach that views systems as an entity, and is cross-disciplinary, integrative, milestone-driven and focused. ISB's approach to P4 medicine is an example. Project management and leadership are key elements of this approach.

3. Multi-departmental and multi-institutional program projects or glue grants—attack a big problem with several different laboratories joining together.

4. Large laboratories—these can be national laboratories, such as those of the Department of Energy, or they can represent a single investigator's large laboratory.

Discovery science is essential for defining the biological elements that are the basic substrates of systems

approaches. The systems-driven science, practiced by ISB, is necessary to handle the enormous complexity of biology and medicine. Big science of type 3 often lacks the ability to integrate biology, technology and computation. Type 4 often lacks biological domain expertise, hence failing to achieve the "virtuous cycle." Both types 3 and 4 often fail in their ability to deal effectively with biological complexity.

In principle, big and small science can be powerfully synergistic. Big science can discover the general framework of biological complexity and small science can take on the solution of individual aspects of this complexity. Unfortunately, today there is a clash between big and small science that comes as a consequence of tight federal funding and the fact that the vast majority of biologists practice small science. There are attempts to limit or eliminate big science not understanding that its "systems-science" approaches are essential to dealing with biological complexity. I would argue for a balanced portfolio that integrates big and small science.

Indeed, I would argue that complexity is a fundamental theme of the 21st century for all scientific and engineering disciplines. What is fascinating is that biology has very powerful approaches to dealing with its complexity in the systems-driven big science discussed above. If we consider many of the fundamental problems that society faces today—healthcare, global health, energy, environment, agriculture, nutrition, animal health, etc.—we can see that systems-driven big science will be critical to attacking their respective big-science complexities. ISB has created a systems-driven platform that enables big science while opening new avenues for small science approaches to characterize novel and previously underappreciated biological phenomena.

I think one of the striking challenges for academic and government scientific institutes in the 21st century is to create systems-driven infrastructures (type 2) so that they, too, can participate in effectively attacking some of society's most fundamental big problems. Indeed, society has an obligation to fund the creation of systems-driven, cross-disciplinary science platforms so that these institutions can participate in the deciphering of big science challenges relevant to humankind—just as in the mid-20th century the Department of Energy funded the emergence of large national laboratories to solve challenging technical problems.

I conclude with three important points. First, ISB is unique in its ability to reconcile apparent opposites: big science and small science, as well as systems-driven discovery and hypothesis-driven research. ISB is also unique in an infrastructure that employs the "virtuous cycle" of biology driving technology driving computation. Second, ISB is using its systems-driven platforms to attack three fundamental problems of society—healthcare (P4 medicine), global health and a sustainable environment. The systems platform provides the powerful thrust that enables a small institute of 10 faculty and 230 staff to undertake these major challenges. Finally, we do need support in these audacious endeavors, and we ask you seriously to consider helping ISB continue its pioneering efforts to bring the powerful strategies and technologies of systems biology to society's grand challenges.

ISB is also unique in an infrastructure that employs the "virtuous cycle" of biology driving technology driving computation.

OUR PUBLICATIONS

www.systemsbiology.org/publications

Publications Help Lay the Foundation for Our Scientific Legacy

For scientists, journal publications serve as a crucial metric of success and a powerful tool for transferring knowledge. In 2011, ISB's pioneering scientists added 84 publications to our list for a total of 972 since our founding in 2000. We invite you to marvel at the breadth of our research and the diligence of our scientists by exploring our publications database, which is updated monthly, at https://www.systemsbiology.org/publications. Our 2011 publications appeared in the journals below.

OUR SCIENCE

Systems Biology = Innovation cycle (biology driv
drives computation) and para

P4 MEDICINE

P4 is predictive, preventive, personalized and participatory medicine.

ISB is using systems biology to understand the networks that cause neurodegenerative diseases, cancers, metabolic disorders and genetics. The unprecedented insight we gain from our systems biology approach will help demystify disease and allow patients to quantify their wellness.

P4 medicine will revolutionize healthcare by shifting focus from reactive medicine to prevention and wellness.

GLOBAL HEALTH

ISB's goal of achieving P4 medicine includes sharing this new model of healthcare and focus on an individual's wellness on a global scale. Through partnerships and collaborations, ISB also is using its systems biology approach to address global health concerns such as infectious diseases, vaccine development, and maternal and child health.

Systems biology is essential to understanding the biological mechanisms and processes of pathogens.

OUR MISSION REVOLUTIONIZE SCIENCE, TR
AND ENSURE ENVIRONMENT

ves technology
adigm changes

Future of wellness for
humans and the planet

ENVIRONMENTAL SUSTAINABILITY

Whether we research the trillions of good and bad microbes that exist or we map the functions and dynamics of algae in fuel production, we use systems biology to help understand a given problem and what solution it demands. With our knowledge, we can predict behaviors not only of human diseases but environmental ills, too.

Our research on microorganisms will lead to new solutions related to biofuels, bioremediation, agriculture and medicine.

EDUCATION & OUTREACH

ISB believes that transferring knowledge is an imperative, because the value of cutting-edge research comes in its sharing. It is ingrained in our culture that we must nurture future scientists, so our staff regularly interact with K-12 students and teachers, as well as undergraduate and graduate students through internships, courses, professional training, and our Accelerator biotechnology fellowship.

From K-12 to college and medical schools, the way we teach science needs to change.

RANSFORM HUMAN HEALTH,
TAL SUSTAINABILITY

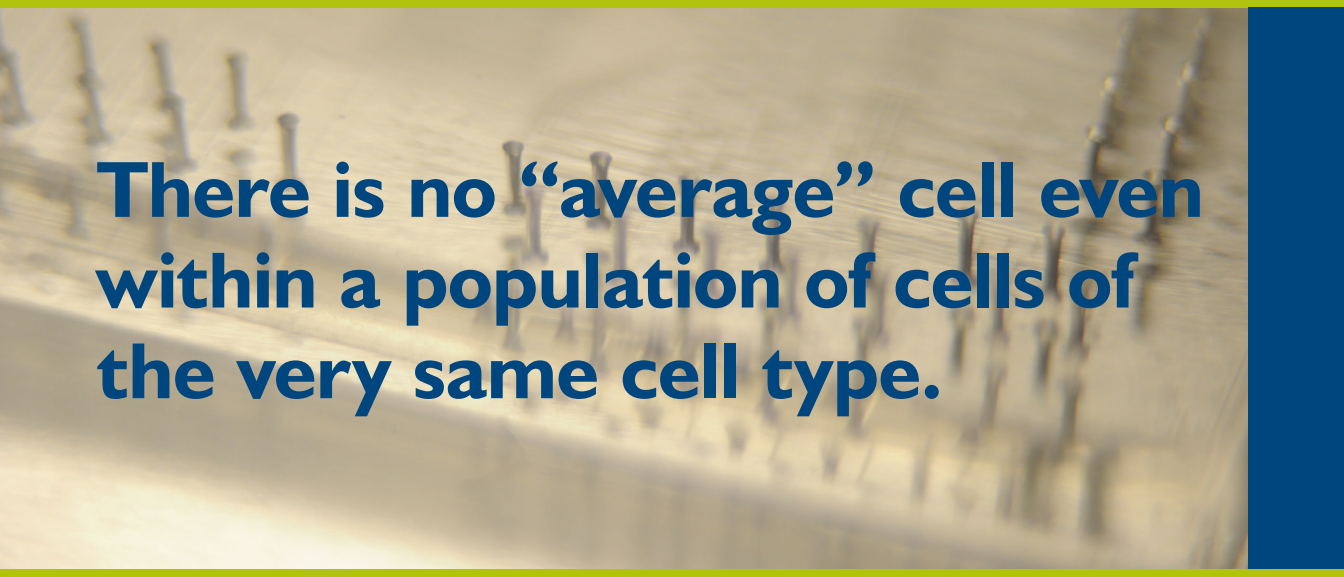
Why we need single-cell analysis

Sui Huang, MD, PhD
Professor

It is now well-known that there is no "average" patient. Therefore, in clinical trials encompassing large groups of patients, one needs to consider the characteristics of each patient, including each person's individual genetic propensity to respond to a drug in a particular way. The statistical analysis of population averages suppresses valuable individual-specific information. The consideration of population heterogeneity due to inevitable patient-to-patient variability is called "stratification" and is at the heart of personalized medicine. Such stratification will allow a proper impedance match against appropriate and effective drugs. So, too, with the cells in tissues and organs.

We now learn that each cell in a cell population of apparently identical cells is a distinct individual. There is no "average" cell even within a population of cells of the very same cell type. Just as one can look at individual patients in a population and identify subtypes of diseases, one can identify "quantized" or "discrete" cell-subtypes in a cell population. The quantized subtypes perform different functions and form a network—much like a social network in human populations. So understanding how an organ works will require understanding the coordinated integration of the functioning of all the quantized cell types.

This awareness of "non-averageable" heterogeneity is taking hold in basic research. Here a chief goal is to expose the "molecular profile" in a diseased tissue, such as a tumor, and look at, for instance, the activity of proteins A, B, C, D and so forth to better understand the cause of diseases at the molecular level. These molecules are interconnected like the cogs in a machine and form a "molecular pathway" [A > B-> C-> D > disease], which offers a material chain of causation and is the basis for the design of modern "target-selective drugs" that operate with molecular precision to suppress the root cause of malfunction.



There is no "average" cell even within a population of cells of the very same cell type.

"Multi-scale" systems biology of complex organisms, one focus at ISB, zooms in to the level of cells and opens a new perspective: the molecular pathways, the very basis of our causal thinking in medicine, are actually also properties of individual cells and each single cell operates within itself its own pathway [A > B-> C-> D-> ...]. The activity of such pathways varies drastically from cell to cell leading to the quantized states within a presumably uniform cell population. There is no average cell that represents our molecular chain causality exactly—much as there is no average person who represents an entire patient population. Because of such cellular heterogeneity, even the most potent target-selective drug will kill only a fraction of tumor cells—explaining the inexorable drug resistance in malignant tumors. This new insight on cellular heterogeneity calls for the measurement of all molecular profiles in individual cells. Tissues must be seen not as an amorphous mass but analyzed as dynamical populations of cells and at single-cell resolution.

Fortunately, this insight coincides with another development at the forefront of technology innovation at the ISB: The analysis of gene expression profiles and other molecular properties in thousands of individual cells. Such high-throughput, high-dimensional single-cell analysis will allow for a stratification of cell populations – precisely like the stratification of patient groups—which in turn will bring molecular analysis to a new level of resolution and redefine our molecular understanding of organisms to the benefit of diagnostics and drug discovery.

401 Terry Ave. N.

Environmental sustainability is one of ISB's core initiatives and integrating efficiencies into our building design not only is beneficial for the planet but makes good financial sense, too. We are happy to announce that our commitment to sustainability has received LEED (Leadership in Energy and Environmental Design) Platinum certification. This is the highest designation from the U.S. Green Building Council, which offers independent, third-party verification that a building was designed with the highest standards regarding human and environmental health. LEED measures an organization's achievements in sustainability, water and energy efficiency, indoor environmental quality and other criteria. Congratulations, too, to our partners in this endeavor: architecture firm Perkins+Will Seattle and general contractor BNBuilders, Inc.

LEED PLATINUM

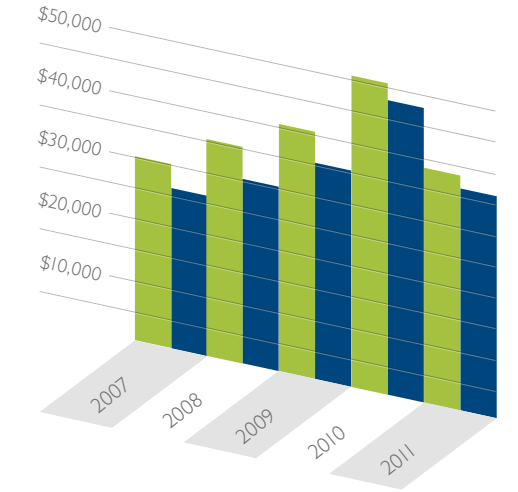
FINANCIAL STATEMENT

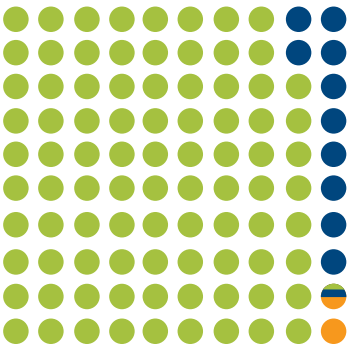
For the Year Ending Dec. 31, 2011 (Dollars in Thousands)

With cuts in U.S. government funding for research and the resulting increase in competition for a smaller number of grants and contracts, 2011 was a challenging year. Despite our successful record, we were not immune to those factors, and our revenue declined for the first time in our history.

As we look to the future, we expect strategic partnerships to continue providing opportunities for research at the same level as in 2011, as organizations in the U.S. and abroad increasingly value our areas of expertise and the abilities of our faculty and staff. And we will continue to be a strong candidate for U.S. government grants and contracts. We look forward to the opportunities that continue to come to us, and to managing our finances and operations in the most productive ways possible.

Jim Ladd
Senior Vice President for Finance and Operations





STATEMENT OF ACTIVITIES

REVENUES	$ AMOUNT	% TOTAL
Grant & contract revenue	38,068	88.4
Contributions	4,378	10.2
Investment & other income	624	1.4
TOTAL REVENUES	**43,070**	**100**
EXPENDITURES		
Research & other direct costs	36,339	
Management & general	12,250	
Fundraising & other	226	
TOTAL EXPENDITURES	**48,815**	
CHANGE IN NET ASSETS	**(5,745)**	

BALANCE SHEET

ASSETS	
Cash & investments	16,151
Other assets	11,214
Preperty & equiptment, net	18,113
TOTAL ASSETS	**45,478**
LIABILITIES	
Accounts payable & accrued expenses	19,567
Deferred revenues	4,209
Notes payable	8,866
TOTAL LIABILITIES	**32,642**
NET ASSETS	
Unrestricted net assets	<980>
Temporarily restricted net assets	5,144
Permanently restricted net assets	8,672
TOTAL NET ASSETS	**12, 836**

2011 REVENUES	% TOTAL
Grant and contract revenue	88.4
Contributions	10.2
Investments & other income	1.4

GOVERNANCE & LEADERSHIP

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Senior Advisor
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Nitin Baliga, PhD
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Sissy Walsh Bouchard, EdD
VP for Development

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Senior Research Engineer

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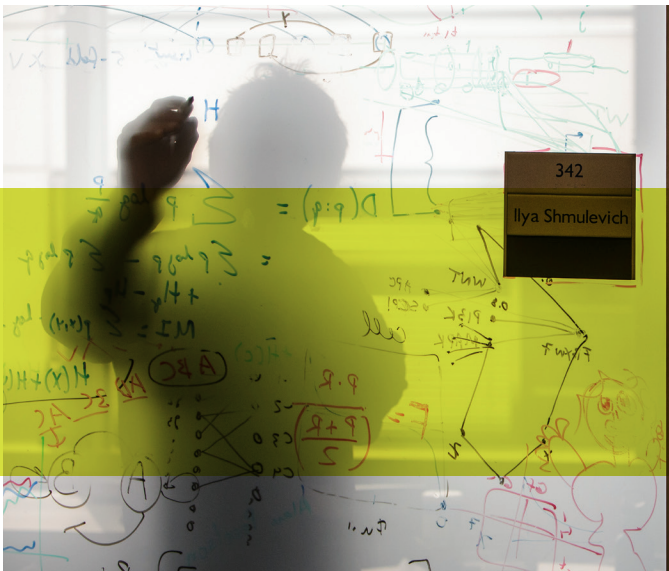

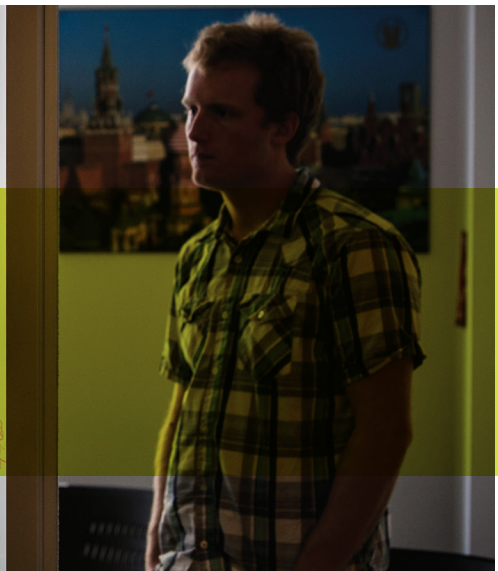

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Victoria VanBruinisse

We are grateful to the above listed individuals and organizations for their commitment to the imperative of systems biology and our educational efforts to transfer knowledge to society. If this piques your philanthropic interests, please dial 206-732-1211 or email Sissy Bouchard at sissy.bouchard@systemsbiology.org to converse. If you would like to give directly, please visit systemsbiology.org/support.

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401 Terry Avenue North
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