Institute for Systems Biology

SHIFT-ING PARA-DIGMS

2015 ANNUAL REPORT

systemsbiology.org/annualreport

Institute for Systems Biology

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WELCOME

For ISB's 2015 Annual Report, we begin with "ISB & Tipping Points" from our President Dr. Lee Hood. He describes the six paradigm shifts that mark his career, the most recent of which is bringing P4 medicine to Providence Health & Services and the U.S. healthcare system. Dr. Hood makes a compelling case that ISB's leadership in the arena of scientific wellness will engender vast opportunities for innovation.

In our commitment to catalyzing a new sustainable future, our Director and Senior Vice President Dr. Nitin Baliga and his colleagues are tackling questions about the environment's ability to support a global population spike to 10 billion people. Dr. Baliga addresses some of the complex, pressing issues and how his team has begun to make an impact.

The belief that we must transfer our knowledge to the public and champion equitable access to quality science education is so intrinsic to ISB that we have known no other way. In 2015, we began a partnership to grow our impact beyond K-12 school districts into community college-level instruction. Dr. Jen Eklund shares some of the successes in that crucial work.

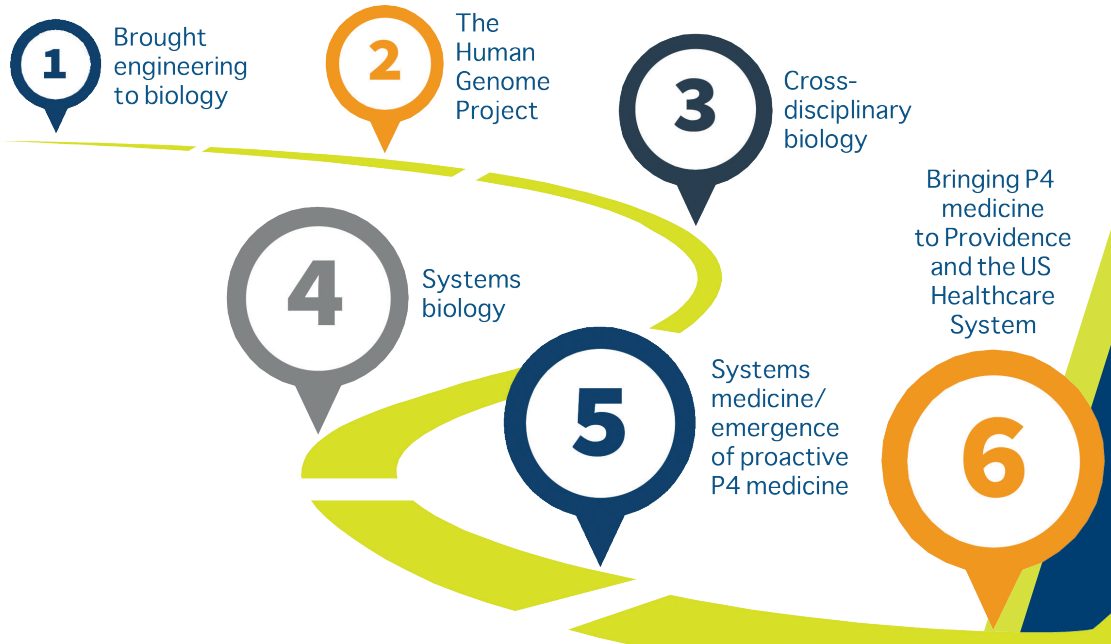
ISB's generous supporters have made all the difference in how we diversify our funding sources. Our Director of Development Nick Newcombe offers a report on one of our marquee research projects on Lyme disease, which has received $6.3 million in gifts and pledges.

Throughout the report, we have shared research headlines from 2015. We encourage you to explore them further online at: ***systemsbiology.org/annualreport***.

Institute for Systems Biology

ISB & TIPPING POINTS

LEE HOOD, MD, PHD
President & Co-founder, Institute for Systems Biology
Senior Vice President & Chief Science Officer, Providence Health & Services



Institute for Systems Biology

> The tipping point is that magic moment when an idea, trend, or social behavior crosses a threshold, tips, and spreads like wildfire.
>
> *– Malcolm Gladwell, The Tipping Point*

I participated in **six major changes** in biology - from bringing engineering to biology in the 1970s to, in 2016, bringing medicine that is predictive, preventive, personalized and participatory (P4 Medicine) to the U.S. healthcare system. This change, the most recent ISB tipping point, is the result an affiliation between ISB and Providence Health & Services.

VISION OF THE INSTITUTE FOR SYSTEMS BIOLOGY

Major advances in science and technology from 1970 through the 1990s led to the creation of ISB in 2000. In the 1970s when I was at Caltech, we began to understand that big science requires not just biologists but also chemists, engineers, and other types of scientists. The Human Genome Project was the first successful application of the concept of big science and, in the 1990s, these concepts were further advanced by the establishment of the cross-disciplinary Department of Molecular Biology at the University of Washington.

In 2000, three well-established senior scientists departed from their conventional and cloistered academic careers. They started a non-profit research organization – ISB – dedicated to pioneering the emerging discipline of systems biology – which entails a global or holistic approach to deciphering the complexities of biology and disease.

ISB was launched with the conviction that leading-edge systems biology would require the development of new technologies and systems-driven strategies to more effectively generate data and explore untapped areas of data space in living organisms (molecules, cells, organs, individuals). This also required developing the analytical tools to capture, standardize, analyze, integrate and model these data to reveal deep insights into biological and disease mechanisms. ISB strongly believes that these technologies, data and analytical tools should be made widely available to the scientific community in a timely manner – a policy of open data and open software.

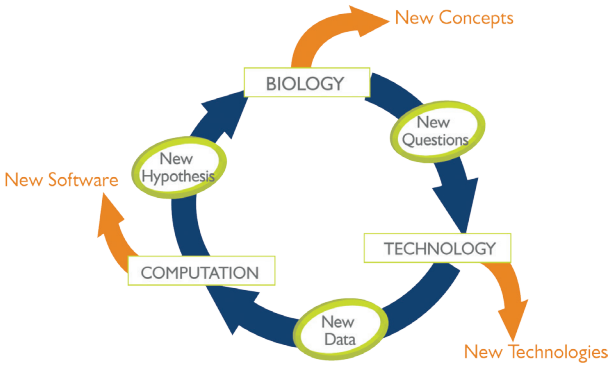
***TIPPING POINT** - ISB defined systems biology and catalyzed a revolution in how biology is done. In 2000, ISB was the first institute devoted to systems biology. Today, there are more than 100 systems biology centers, institutes and departments worldwide. Systems approaches are recognized throughout the life sciences as key to unraveling the complexities of biology and disease.*

THE FEATURES OF ISB THAT HAVE CATALYZED A VARIETY OF TIPPING POINTS ARE:

CROSS-DISCIPLINARY ENVIRONMENT

To achieve our vision of systems biology, we created a cross-disciplinary environment, bringing together biologists, chemists, computer scientists, engineers, mathematicians, physicists and academic physicians in close proximity at ISB. They learned one another's languages and how to effectively work together in teams.

Working collaboratively across disciplines enables leading-edge biology to drive the development of relevant technologies. In turn, the resulting data can catalyze the pioneering of analytical tools. Thus, a fundamental mantra of ISB is "biology drives technologies and technologies drive analytical tools." When these are seamlessly integrated around a biological challenge, game-changing concepts, technologies and analytical tools emerge and catalyze both scientific discovery and innovation.



CREATION OF NEW CONCEPTS

ISB has played a major role in conceptualizing and reducing to practice a variety of new concepts in biology and medicine:

- Systems biology, systems medicine (a systems approach to disease)
- P4 medicine: a predictive, preventive, personalized and participatory approach to healthcare
- Scientific wellness, which employs and assesses dense, dynamic, personal data clouds for each individual, focusing on the so-revealed interactions of one's genetics and environment to identify "actionable possibilities" that, if acted upon promote wellness or avoid disease

BIG VS. SMALL SCIENCE

The complexity of biology led to the distinction between big vs. small science. Small science is generally a single investigator and a laboratory group working on a very discrete and focused problem (e.g. what does the cancer molecule P53 do?).

On the contrary, complex biological challenges often require an **integrative** and coordinated "big science" strategy that includes a **systems-driven** approach to attacking a difficult problem, combined with a **cross-disciplinary** environment of scientists and engineers that can take on the many different dimensions of the challenge. Big science also requires the integration of technologies, diverse types of data and appropriate analytical tools. Big science must be driven by an integrated vision, **milestones** and appropriate timelines.

The Human Genome Project (HGP) was biology's first "big science" project – and the largest single undertaking in the history of biological science. The HGP provided a vision and a roadmap for success, which included generating technologies essential for scaling up the sequencing and related analyses, assembly of a global, cross-disciplinary team of scientists, and a laser-focused execution of that vision. The combined elements enabled the scientific community to bring the human genome sequence to society faster than anyone thought possible. The HGP transformed virtually every aspect of the life sciences.

ISB has successfully employed these approaches for a wide variety of big science problems that has enabled ISB to transform the global understanding of human diseases and to pioneer the emerging sector of scientific wellness.

Some examples:

- Developing the tools and strategies for P4 medicine in collaboration with the nation of Luxembourg
- The Cancer Genome Atlas (TCGA) project in collaboration with the National Cancer Institute and the National Human Genome Research Institute
- United States Army project to study Post-Traumatic Stress Disorder
- Department of Defense (DTRA) project on sepsis

TRANSFERRING KNOWLEDGE TO SOCIETY

Since ISB's inception, a fundamental principle has been our commitment for all scientists to transfer the useful and relevant knowledge they gain to society. In this regard we have:

- Fostered K-12 science education throughout the Puget Sound region and beyond through the Logan Center for Education, the Systems Education Experiences program and the Center for Systems Biology
- Spun out 8 companies – all successful and all running effectively
  - » These companies have returned more than $6 million to ISB for research support
  - » Several of these companies have the potential to provide an endowment to ISB in the future

> ISB has a very flat organization, little bureaucracy, focused leadership and an excellent administrative staff. Decisions can be made rapidly in order to take on big and small projects.

SCIENCE AND TECHNOLOGY

ISB has made important advances in technology. ISB has pioneered:

- Targeted and global (SWATH) mass spectrometry
- Single molecule measurements of nucleic acids through the company Nanostring
- Inkjet printer technology - which Agilent commercialized - that allows large amounts of DNA to be rapidly synthesized and DNA arrays to be readily manufactured
- Use of single-cell analysis to interrogate the complexities of human development and cancer
- Developing peptide protein-capture agents by co-founding a company (Indi Molecular) that is developing agents that will in 10 years replace monoclonal antibodies because they are stable, digital, high affinity and can be designed to lack cross reactivity – and they can be employed as *in vitro* or *in vivo* diagnostic reagents or as drugs

SYSTEMS-DRIVEN STRATEGIES

ISB has also pioneered a series of systems-driven strategies:

- The complete genome sequence analyses of families allows us to readily identify disease genes
- We have made blood a window into health and disease by employing targeted mass spectrometry to identify protein biomarkers for diseases (e.g., lung cancer and preterm birth)
- We pioneered the use of dense, dynamic, personal data clouds to investigate scientific wellness, wellness-to-disease transitions and the progression and treatment of disease itself
- We employ computational methods with disease-perturbed biological networks to identify possible disease drug targets

LUXEMBOURG PARTNERSHIP & SCIENTIFIC WELLNESS

ISB enters into strategic partnerships with government, industry and philanthropy that:

- Provide scientific and technical talent and expertise to address a big science problem
- Bring new technologies, strategies and analytical tools to ISB
- Bring additional funding sources
- Enable the very best scientists in the world to combine with those at ISB in attacking challenging big problems

In 2008, ISB began a five-year strategic partnership with the nation of Luxembourg – to bring biotechnology and healthcare to the newly founded University of Luxembourg in the form of a new Center for Systems Biomedicine, which today is one of the leading such institutes in Europe. In return, Luxembourg provided ISB $100 million over five years to invent the technologies and strategies of systems (P4) medicine. This funding generated 10 new technologies and systems-driven strategies, and allowed ISB to explore the patient data space in powerful and innovative new ways.

***TIPPING POINT** – The ten new technologies and strategies developed by the Luxembourg partnership placed ISB at a tipping point in systems medicine and allowed us to explore patient data space in powerful and innovative new ways.*

HEADLINES 2015

Pushing the Molecular Switches of Tuberculosis into Overdrive to Map Interactions

BALIGA & PRICE LABS

Open-Source Software to Analyze Digital Footprint of Protein Data Released

MORITZ LAB

Mixture of Markers from Two Distinct Cell Types Indicates Poor Prognosis in Breast Cancer

HUANG LAB

LAUNCHING A NEW INDUSTRY – SCIENTIFIC WELLNESS

In 2014, ISB partnered with Maveron, a consumer-only venture firm to conduct the **Hundred Person Wellness Project**, a 10-month scientific study on 108 individuals. Dense, dynamic, personal data clouds were generated for each individual from whole genome sequences, clinical chemistries, metabolites and proteins from blood obtained every three months, gut microbiome bacterial quantification from stool samples every three months and quantified-self measurements for activity and sleep quality from a Fitbit.

These data were analyzed and integrated for each individual, and through behavioral coaching, actionable recommendations were made to the participants to optimize their wellness or avoid disease. Seventy percent of the participants were compliant with the coaching recommendations. The data, on a de-identified basis, have been transformational in providing insights both into human biology and disease. We termed this transformational approach "scientific wellness."

In July, 2015, in partnership with venture firms ARCH Venture Partners, Polaris Partners and Maveron, ISB co-founded Arivale, a consumer-focused, scientific wellness company.

***TIPPING POINT** - We believe Arivale will create an entirely new thrust in healthcare – scientific wellness. It is our view that in a 10- to 15-year period, the market cap of the scientific wellness sector will far exceed that of the current healthcare (or disease care) industry.*

ISB AFFILIATION WITH PROVIDENCE HEALTH & SERVICES

With the goal of bringing P4 medicine to every patient, Providence Health & Services and ISB affiliated in April 2016. Together ISB and Providence will transform healthcare to a proactive mode that is focused on keeping patients well and identifying the earliest opportunities to reverse or even prevent disease.

This exciting new relationship will enable ISB to expand its research capacity during the next few years and recruit outstanding new faculty in the areas of systems biology, technology development, data and analytics, and translational medicine. Further, it will enable us for the first time ever to apply ISB-driven systems approaches for optimizing wellness and minimizing disease to patient care.

We will combine our basic research with the clinical expertise at Providence, bringing P4 medicine directly to the patient's bedside through an initial four translational pillars, each employing the platform of dense, dynamic, de-identified personal data clouds:

- Scientific wellness
- Cancer survivorship
- Alzheimer's disease
- Brain cancer (glioblastoma)

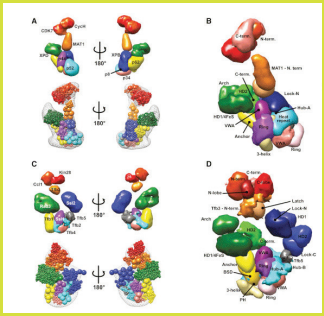
With each of these translational pillars, we will employ innovative approaches made possible by ISB's new technologies, systems-driven strategies and new conceptual approaches.

***TIPPING POINT** – The affiliation between ISB and Providence will bring systems medicine that is predictive, preventive, personalized and participatory (P4) to a major health system and ultimately to U.S. healthcare more broadly.*

HEADLINES 2015

ISB'S Cancer Genomics Cloud Team Launches BigQuery Platform

SHMULEVICH LAB



Architecture of a Macromolecular Complex Regulating Gene Expression and DNA Repair Determined

RANISH LAB

Results Released for the Most Powerful Tool for Reconstructing a Gene Network

BALIGA LAB

THE FUTURE OF HEALTHCARE

ISB has opened the possibility of transforming some of society's most challenging problems by:

- Employing P4 medicine to greatly reduce the cost of healthcare and thus begin to change one of the biggest challenges to all nations – the runaway costs of healthcare
- Using scientific wellness to greatly diminish the challenges of aging and ensure each individual life-long wellness

Scientific wellness will create a new healthcare industry and – if Washington State or the U.S. is the center of this industry, as it is now, it will provide enormous economic benefits and possibilities for innovation.

***TIPPING POINT OF THE FUTURE** - As the cost of scientific wellness diminishes significantly (just as the cost of DNA sequencing has diminished by a million-fold over the course of about 12 years), then we can bring this opportunity to the poor as well as the rich nations of the world, leading to a democratization of healthcare unimaginable even a few years ago.*

CODA

Recall once again Gladwell's opening quote: *"The tipping point is that magic moment when an idea, trend, or social behavior crosses a threshold, tips, and spreads like wildfire."*

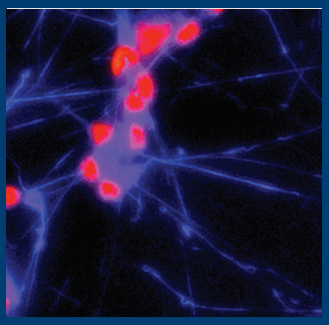
From my vantage point, it is fair to say that ISB has catalyzed many tipping points – some of which have spread like wildfire. So the future will continue to see the evolution of ISB-catalyzed tipping points, and it will be fascinating to determine just how long some of the most interesting take to spread like wildfire.

Lee Hood

Lee Hood, MD, PhD
President & Co-founder, ISB
SVP & CSO, Providence Health & Services

World's Largest Public Catalog of Human Genomic Variations Released

HOOD LAB



Understanding the Genetic 'Architecture' of Bipolar Disorder

PRICE LAB

Researchers Find Key Protein Tied to Production of 'Good' Cholesterol

RANISH LAB

HEADLINES 2015

A NEW SUSTAINABLE FUTURE

NITIN BALIGA, PHD
Senior Vice President & Director
Institute for Systems Biology

A human crisis of unprecedented proportions is in the making. Diminishing arable land, water shortage and expected population growth to 10 billion portend a catastrophic food security crisis by 2030. This threat requires a dramatic reduction of the environmental footprint of agricultural practices. A paradigm shift to the food supply chain is necessary to meet an expected 70 percent or more increase in food demand.

Advances in precision agriculture and the development of higher-yielding, disease-resistant crops are addressing a number of these issues. For example, there are technologies to minimize the application of pesticides and fertilizers and optimize water usage. But these advances alone will not cut it. Even with improvements in the efficiency of water usage, it is estimated that there will be about a 30 percent shortage in water supply by 2030. Agriculture alone will require approximately 4.5 trillion cubic meters of water, but the total supply of fresh water is just 4.2 trillion cubic meters – and this does not take into account home and industrial water needs. Shrinking arable land due to desertification and salination, and projected water shortages, both exacerbated by climate change, are threatening food security. This is a multi-scale systems problem that will require concerted advances in technologies for sustainable production of food, as well as responsible consumption of natural resources and food.

ISB launched Project Feed 1010 (10^{10}=10 billion) to catalyze this paradigm shift and create a new sustainable agriculture economy. PF1010 is pioneering a crowd-sourced network of scientists, teachers, students and farmers to optimize aquaponics – a sustainable food production solution that combines aquaculture (fish farming) and hydroponics (growing plants in water) to

In just one year of existence, PF1010 has created an international network that has made tremendous, impactful contributions toward training hundreds of teachers and students across the United States and beyond.

support year-round crop production with up to 90 percent less water usage than conventional agriculture. This project aims to make scientific breakthroughs for scaling up sustainable agriculture while transforming STEM education to generate a massive workforce and entrepreneurs for a new economy. We dream of a future where every unused urban space is repurposed for sustainable food production, where everyone is a citizen scientist, and we are all prosumers (producers + consumers) in a smart food supply chain.

This is an audacious and bold vision that requires an approach that is rapidly scalable and one that integrates education, research and farming – nationally and internationally. PF1010 is developing a network of educators, farmers and scientists to coordinate and leverage simultaneous advancements in teaching and curriculum development, research and innovation, and agricultural practices.

We recognized the importance of targeting high school students, because nearly 47 percent of mid-scale jobs, most of which require a high-school diploma, are predicted to be at high risk of being replaced by technology and automation. By targeting this segment of the population, we could create awareness of the food security crisis, its underlying causes and potential solutions, and simultaneously address the massive unemployment crisis by preparing these students to enter the workforce in the sustainable agricultural economy of the future. In just one year of existence, PF1010 has created an international network that has made tremendous, impactful contributions toward training hundreds of teachers and students across the United States and beyond, while engaging students across high schools, skill centers, colleges and universities in the development of key components of the education and research infrastructure.

PF1010 is laying the foundation for a sustainable future. A new paradigm is emerging. By engaging students in the development of solutions for real-world problems we are transforming them into producers, and not just consumers of knowledge. More importantly, the students are directly involved in innovating new solutions to a complex problem that threatens us all: creating proficient and creative problem solvers who are prepared to immediately participate in the workforce of a new sustainable economy they are helping create.

ISB Receives $1.7 Million to Study Cancer Drug Resistance

HUANG LAB

ISB Launches 3-Year Wilke Cohen Lyme Disease Project

HOOD, MORITZ, PRICE & SUBRAMANIAN LABS

Washington Research Foundation Gifts $2 million to ISB to Advance P4 Medicine

ISB

HEADLINES 2015

KEY PF1010 MILESTONES INCLUDE:

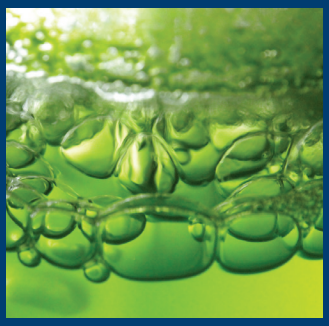
- Partnering with Northeastern University to develop a modularized post-graduate course in advanced software development focused on creating cloud infrastructure of databases, web/iOS/Android apps, data analytics, visualization, and social networking for monitoring and coordinating sustainable agricultural systems across a network.

- Establishing a network of high school science educators to implement ISB-developed curriculum on sustainable agriculture and providing personalized support to integrate systems education principles.

- Partnering with Washington Network for Innovative Careers to offer a year-long high school course for students in which they participated as citizen scientists to innovate designs for aquaponics systems. Through this program, the students were invited to participate in the Bill and Melinda Gates Teen Action Fair, the Environmental and Adventure School's Healthy Choices Fair, and the University of Washington's 2016 Earth Day celebration.

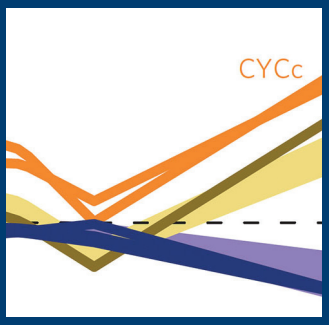
- Partnering with the National Science Foundation to create an Ambassadors of Change training program for high school and undergraduate students (pictured right) to learn about sustainable agriculture through Project Feed 1010 and how to transfer that knowledge to their respective schools and communities.

- Inspiring and supporting the Florida high school team that incorporated PF1010 curriculum into their science classes and took first place in the Global Change Challenge with their aquaponics project.



Microalgae as BioFactories of a Sustainable Future

BALIGA LAB



Genetic Switch May Help Marine Microalgae Respond to Higher Carbon Dioxide Levels

BALIGA LAB

Researcher Expounds on the Captivating World of Microbes

BALIGA LAB

HEADLINES 2015

INSPIRING CHANGE IN EDUCATION

JEN EKLUND
Interim Director & Education Liaison
Logan Center for Education
Institute for Systems Biology

The paradigm shifts in science, technology, engineering and mathematics (STEM) fields are leading to abounding opportunities for STEM careers and a need for all people to have STEM literacy to participate in decisions that affect their own health, the health of their communities and the health of our environment.

Shifting paradigms in classrooms is challenging and STEM educators need support to integrate adjustments that reflect the profound changes in STEM fields.

In 2015, ISB's Logan Center for Education continued to play an important role in leading our region to provide educators with the knowledge and resources to inspire paradigm shifts in science classrooms. Those shifts include implementing new standards in math and science, integrating engineering into science learning, and developing quantitative reasoning skills that students will need in all STEM careers of the future.

Sixth grade science teachers in the Renton school district worked with a biologist from the University of Washington to explore local phenomena that would support students to engage their curiosity and explore the characteristics of living things. Middle school science teachers in the Renton School district partnered with the Logan Center for Education to continue the implementation of Washington State's new science standards.

The new standards push students beyond memorizing facts and "cookbook" experiments; they ask students to think, behave and interact as scientists and engineers do. This new perspective in the classroom allows students in the Renton School District to be the STEM professionals and STEM literate citizens of the future.

The new standards push students beyond memorizing facts and "cookbook" experiments; the new standards ask students to think, behave, and interact as scientists and engineers do.

This year, elementary, middle and high school teachers from the Marysville school district worked with the Logan Center team and engineers from the University of Washington and Edmonds College to develop a suite of experiences and lessons like this. Students in Marysville are learning that engineering is more than tinkering; engineering requires an understanding of science to address real-world problems.

At Lower Columbia College, non-major biology students wrestled with data from The Cancer Genome Atlas project to develop a deeper understanding of the role of gene regulation in cancer. The assignment gave students a sense of the landscape of contemporary biological research exemplified by ISB and asked students to begin the practice of using **quantitative reasoning (QR)** and systems thinking skills that have not traditionally been part of undergraduate biology courses.

Through its partnership with Washington's State Board of Community and Technical Colleges, the Logan Center has strategically expanded its education work to the postsecondary level in 2015. This partnership uniquely applies the Logan Center's knowledge and experience of educator professional development with ISB scientists expertise in contemporary biology. The work supports community and technical college faculty to make instructional shifts to include QR skills comprised of accessing data (big data and multi-scale data), analyzing and interpreting data (mathematics and statistics, computational modeling, and simulation), and organizing and communicating data (for visualization, presentation, and publication) in their courses. Students in these courses will be better prepared for STEM careers that rely increasingly on QR skills.

Community College Faculty Learn about Big Data from ISB Researchers to Integrate into Curriculum

LOGAN CENTER FOR EDUCATION

Ginny Ruffner's "Aesthetic Engineering" Exhibit Installed at ISB

CONSILIENCE PROGRAM

Valerie Logan Luncheon Raises More than $92,000 to Support Science Educators

LOGAN CENTER FOR EDUCATION

HEADLINES 2015

BATTLING LYME

NICK NEWCOMBE
Director of Development, Institute for Systems Biology

In 2015, ISB embarked on a comprehensive study of Lyme disease, which is a highly complex and often misdiagnosed disease that can be debilitating for those who do not respond to a standard course of antibiotics. This important research was spearheaded by Liesl and Jeff Wilke and their magnanimous gifts. Since then, thanks to their generosity and that of the Steven & Alexandra Cohen Foundation, Jeff and MacKenzie Bezos, and the Bay Area Lyme Foundation, the project has received a total of $6.3 million.

The Wilke Cohen Lyme Disease Project is a three-year study that is leveraging the tools and technologies of systems biology to understand the fundamentals of Lyme, identify biomarkers, and gain insights about the genomics and proteomics of the infecting Borrelia organism. Of the research on Lyme disease currently under way in the U.S., ISB's Wilke Cohen Lyme Disease Project is one of the most prolifically funded by private philanthropy.

There's a great void of knowledge in the world of Lyme. I believe that only the biggest, most elegant computational science can fill it, and ISB is uniquely positioned to do just that.

-Liesl Wilke

We believe in ISB's holistic, systems approach and share their commitment to finding more effective diagnostics and treatments.

-Alexandra Cohen

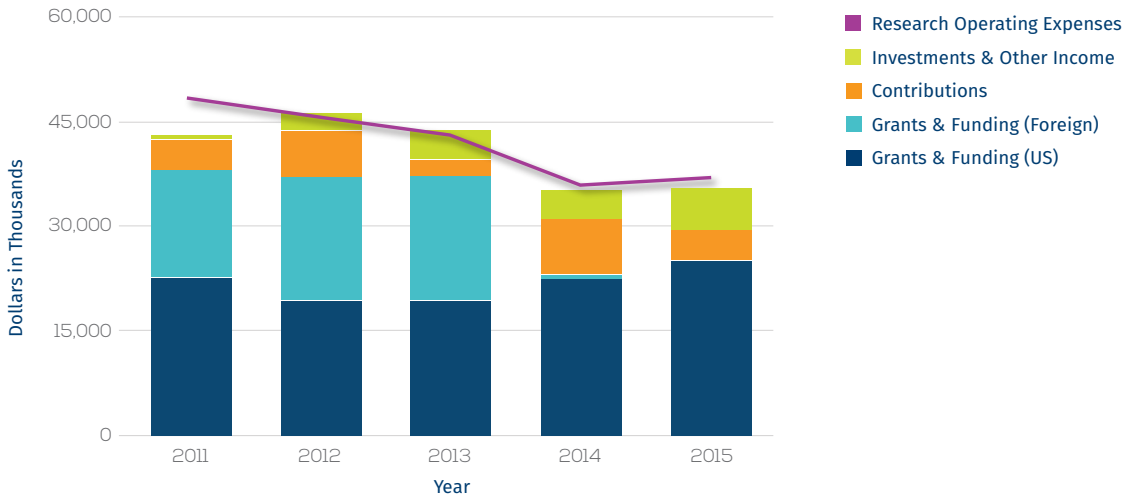
Institute for Systems Biology

FINANCIALS

Year ending December 31, 2015

5-YEAR OVERVIEW

Research Operating Expenses vs. Total Revenue



BALANCE SHEET

Dollars in Thousands

Assets	$
Cash & Investments	16,816
Other Assets	13,462
Property & Equipment (Net)	8,662
Total Assets	**38,940**

Liabilities	$
Accounts Payable & Accrued Expenses	13,624
Deferred Revenues	3,024
Notes Payable	7,782
Total Liabilities	**24,430**

Net Assets	$
Unrestricted Net Assets	(1,373)
Temporarily Restricted Net Assets	7,211
Permanently Restricted Net Assets	8,672
Total Net Assets	**14,510**

STATEMENT OF ACTIVITIES

Dollars in Thousands

Revenues	$	%
Grants & Contract Revenue	25,081	70.2
Contributions	4,465	12.5
Investments & Other Income	6,188	17.3
Total Revenues	**35,734**	**100.0**

Expenditures	$
Research & Other Direct Costs	24,894
Management & General	11,862
Fundraising & Other	153
Total Expenditures	**36,909**
Decrease in Net Assets	**(1,175)**

ADDRESS

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ONLINE

systemsbiology.org

Institute for Systems Biology

Founded in 2000, the Institute for Systems Biology is a nonprofit 501(c)(3) biomedical research organization based in Seattle, Washington.