Catalyzing A Revolution

ANNUAL REPORT 2016

INSTITUTE FOR SYSTEMS BIOLOGY

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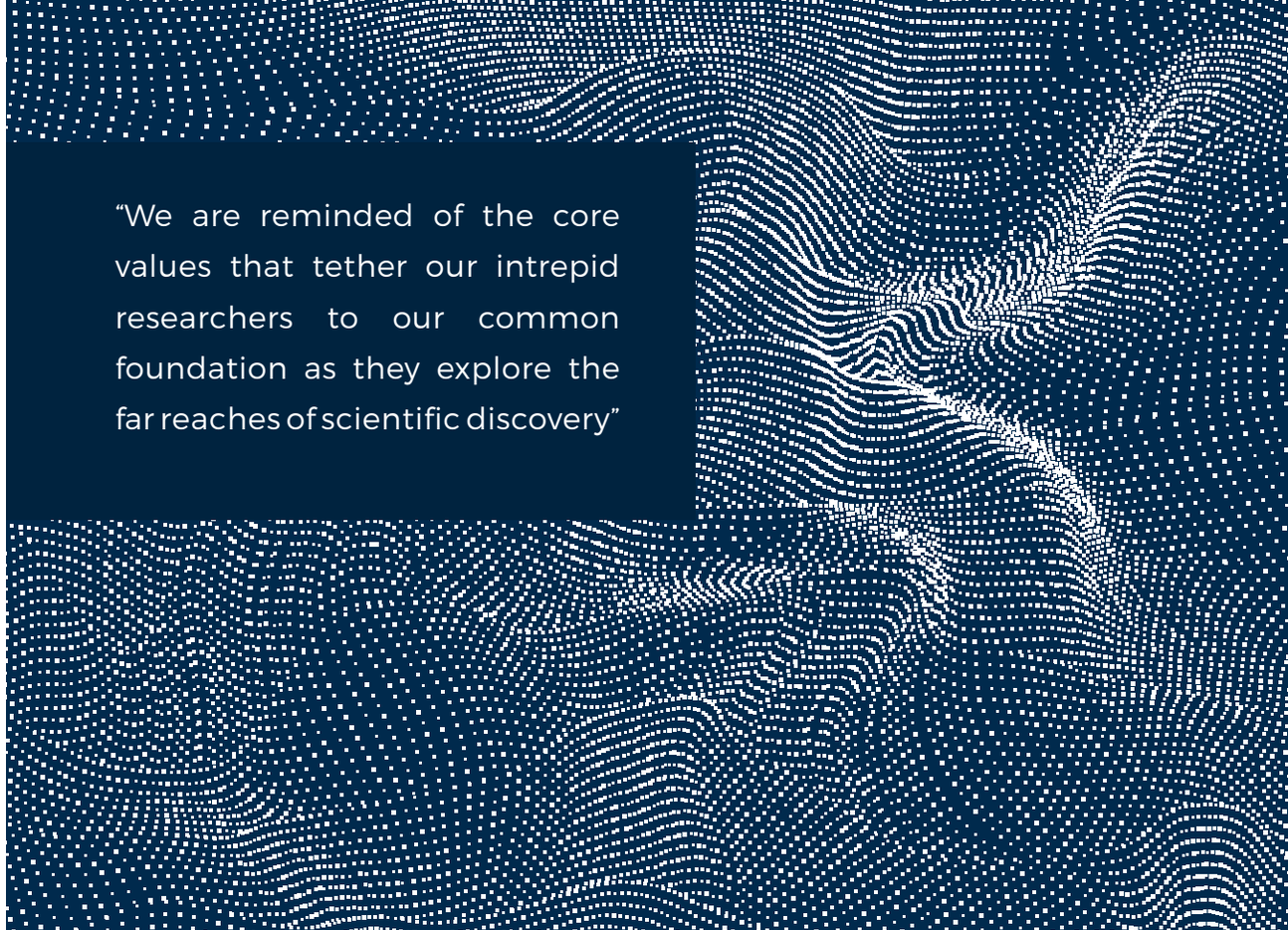
Institute for Systems Biology

WELCOME

ISB's compass has always been oriented toward the future. Even when we reflect on the past year for each annual report, it's always through the lens of what's on the horizon. We are remarkably consistent in that regard, which is in no small part due to our president Dr. Lee Hood, whose vision is perpetually a decade – at least – ahead of everyone else.

In this year's letter, Dr. Hood offers a treatise on the momentum that has tipped his every prediction into a new reality. As we contemplate his vision for the future of healthcare and scientific wellness, we are reminded of the core values that tether our intrepid researchers to our common foundation as they explore the far reaches of scientific discovery: We cherish intellectual freedom, value collaboration, share what we learn, create roadmaps, and we expect to invent the future of human health, scientific wellness, and environmental sustainability.

What lies ahead is a stretch of this roadmap. Travel with us.



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P4 Medicine and Scientific Wellness:

Catalyzing A Revolution in 21st Century Healthcare

Lee Hood, MD, PhD

Starting in the early 2000s, ISB pioneered the concept of a medicine that is predictive, preventive, personal and participatory (P4). 2016 gave us a profoundly deeper understanding of why we stand at a P4 tipping point.

A tipping point, as defined by Malcolm Gladwell, "is that ***magic moment*** when an idea, trend, or social behavior crosses a threshold, tips, and spreads like wildfire."

As a result of our ongoing exploration of scientific wellness and a systems approach to disease, that magic moment in healthcare is upon us. In April 2016, ISB affiliated with Providence St. Joseph Health (PSJH), one of the largest not-for-profit healthcare systems in the U.S. This affiliation, which made ISB the research arm of PSJH and me its Senior Vice President and Chief Science Officer, accelerates the momentum toward the broad incorporation of P4 medicine into the American healthcare system.

TWO TIPPING POINTS IN U.S. HEALTHCARE SEPARATED BY ALMOST A CENTURY

The first tipping point in U.S. medicine was the Flexner Report of 1910. There were 165 medical schools at that time that were mostly trade schools with little science and inadequate mentoring. The Carnegie Institute asked Abraham Flexner to lead a report about the state of American and Canadian medicine. He visited each of the then existing medical schools and wrote a scathing report that suggested there should be a dramatic cut in the number of medical (trade) schools and that science should be brought to both clinical practice and medical education.

Johns Hopkins Medical School pioneered these ideas and, over the next 30 years or so, established itself as a premier, science-based medical school—a ranking it retains today. Having the courage to catalyze and lead this tipping point had enormous benefits for Johns Hopkins.

Today P4 healthcare and scientific wellness, in my view, constitute a similar transformational tipping point to the Flexner Report. Scientific wellness embodies the very essence of P4 medicine:

1 PREDICTIVE

Individual genetic risk for many diseases, the earliest indicators of transitions from wellness, and predicators of the effects of disease and our interventions to control it are being determined using wellness approaches.

2 PREVENTIVE

The wellness approach allows individuals to avoid disease transitions and to identify the earliest indications of disease transition when it is most reversible by therapies arising in the future from systems-based strategies. This is the preventive medicine of the 21st century.

3 PERSONALIZED

The focus of wellness approaches to healthcare is on the individual, and how to optimize his/her wellness rather than on analyses of populations that assume homogeneity among the humans in the context of wellness or disease.

4 PARTICIPATORY

Patients who are well informed about their health will make their own healthcare decisions, making medicine far more efficient.

In the intervening period between 1910 and today, there have been many advances that have transformed various aspects of healthcare—clean water, antibiotics, vaccines, chemotherapies—but none of these has had the potential, as P4 medicine and scientific wellness do, to broadly transform the entire structure of modern healthcare, shifting it from an almost complete focus on disease to one that has a major focus on wellness, with striking implications for the virtualization of healthcare by bringing it to the home.

THE EVOLUTION OF PARADIGM CHANGES AND CONCEPTS LEADING TO SYSTEMS MEDICINE AND P4 HEALTHCARE

In the 2015 annual report, I discussed the multiple paradigm changes I participated in over my career dealing with biological complexity and leading to our current vision of P4 healthcare. These include:

- Bringing **engineering to biology** to create instruments that initiate large numbers of measurements in biology and big data;
- The **Human Genome Project** that defined all the human genes and proteins, enabled the beginnings of an understanding of how genetic variation correlates both with wellness and disease, and enabled systems thinking about human biology and disease;
- The creation of the **Institute for Systems Biology**, which catalyzed, through systems approaches to disease, the emergence of the disciplines of **systems medicine and P4 healthcare**;
- The 2014 pilot project in P4 healthcare with 108 individuals that defined and demonstrated the power of **scientific wellness** both to improve individual health and provide the data that will let us invent the future of medicine; and
- The **affiliation of ISB and PSJH** that permitted P4 medicine to be transferred to patients and the contemporary healthcare system.

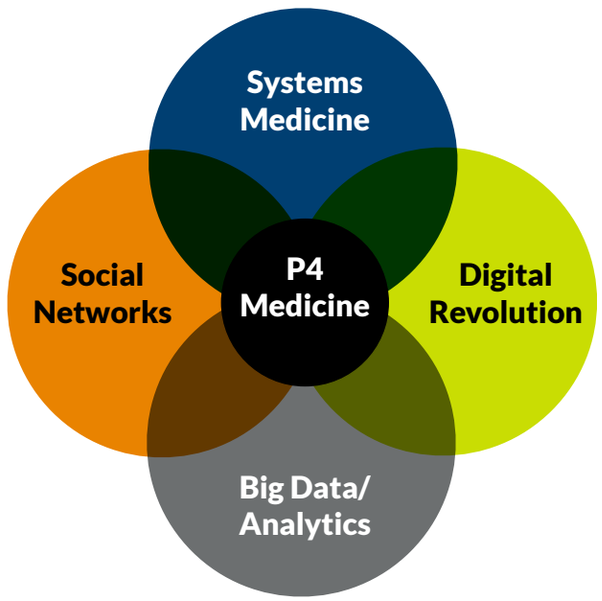
SYSTEMS THINKING CONTRIBUTED FOUR IMPORTANT APPROACHES TO SYSTEMS MEDICINE

1 Systems thinking led to an idea that is central to systems medicine: **dense, dynamic, personal data clouds**. These clouds are essential to assessing the two major contributions to health: an individual's genetics and environment/lifestyle. Billions of data points of many different types (mostly from genome sequence) are generated for each individual and these data can be analyzed to reveal individual actionable possibilities. If acted upon, these actionable possibilities will improve an individual's wellness or ability to avoid disease.

2 The data from the individual data clouds can be converted into **biological networks**—the information conduits that regulate human development, physiology and aging—that, if perturbed, cause disease. Knowing how normal and disease-perturbed networks differ allows scientists to understand the mechanisms of disease and identify biomarker and drug target candidates.

3 At ISB, we have developed more than 10 **systems-driven technologies**, such as targeted proteomics and single-cell and single molecule analyses. We have also developed many systems-driven strategies—that is, one or more technologies embedded in an analytic and semi-automated platform to handle the data and convert it into actionable possibilities (e.g. family genome sequencing to identify disease genes, biomarker discovery for diagnostics, dense, dynamic and personal data clouds to study the particular features of wellness or disease, etc.). These technologies and strategies truly revolutionize how disease can be attacked and constitute an important aspect of the P4 tipping point.

4 At ISB, we stress four important aspects of **data generation and data analyses**: data should be global (comprehensive), dynamical (measured over time and space to assess changes) and integrative (in simple terms bringing data into network-like inferences relevant to biology). Finally, systems thinking can be used to deal with the enormous signal-to-noise problems inherent in big data. Complex systems theory allows researchers to draw simple inferences from very complex data sets.



THE EMERGENCE OF P4 HEALTHCARE

In 2014, there was a convergence of four strategies: systems medicine; individual digital measurements (quantified self); big data and its analytics; and a broad range of connectivities, including social networks, that allowed us to define P4 medicine more precisely.

The differences between P4 medicine and contemporary medicine are striking. P4 medicine:

- Is proactive rather than reactive.
- Focuses on the individual rather than populations.
- Includes wellness rather than just disease, as is true of most contemporary medicine.
- Employs dense, dynamic, personal data clouds to study wellness and disease and assess for the individual both the genetic and environmental contributions to health.
- Envisions drug trials that use personalized data clouds rather than averaged large populations, recognizing that individuals differ from one another genetically and environmentally and, so, reducing the problems with low signal-to-noise ratios that arise from averaging the features of disparate humans in a population.
- Employ social networks to educate patients, students, and healthcare professionals about the coming revolution in P4 medicine.

APPLICATIONS OF DENSE, DYNAMIC, PERSONAL DATA CLOUDS

One of the most important contributions of a systems approach to medicine has been the many applications of dense, dynamic, personal data clouds which allow us to:

- Optimize wellness.
- Follow the progression of disease.
- Carry out clinical trials with the ability to stratify individuals into responders versus non-responders, to stratify disease into different subtypes, and to identify off-target drug reactions.
- Conduct N=1 experiments to deconvolute the complexities of disease and biological processes (e.g., nutrition) in ways that would otherwise be impossible.
- By following large populations, we will see, over time, wellness-to-disease transitions for all of the common diseases. This will enable us to identify biomarkers to detect these transitions and use network biology to identify interventions, including drug target candidates that could reverse the disease before it ever manifests itself phenotypically.

This is the preventive medicine of the 21st century.

SCIENTIFIC WELLNESS AND THE TRANSFORMATION OF HEALTHCARE

In 2014, we conducted a nine-month scientific wellness experiment using 108 well individuals (self defined) or "pioneers" as we termed them. The complete genome sequence was determined for each pioneer and blood draws were taken every three months for clinical chemistries, metabolites and proteins. The gut microbiome was quantified every three months, and we recorded quantified-self data, such as blood pressure and pulse rate, and used a wearable device (Fitbits) to determine activity and quality of sleep. These data were analyzed and integrated for each individual.

We found that each pioneer had multiple actionable possibilities to improve wellness or avoid disease. Scientific wellness coaches delivered these actionable possibilities to the pioneers, both explaining them and putting them in the context of each pioneer's own health objectives. The coaches achieved a remarkable success–70% compliance—and were a vital part of the scientific wellness program.

As the amount of data increased for the pioneers, more and more actionable possibilities were discovered to improve their wellness. Many of the pioneers felt this was the "***experience of a lifetime.***"

Scientific wellness should be a lifetime journey bringing most individuals to parity with a group of elderly people described by Eric Topol, of the Scripps Translational Science Institute, as "wellderly." These are individuals in their 80s and 90s who have never been seriously ill, never been to a hospital, never taken a drug, and who move into their 90s mentally alert and physically capable.

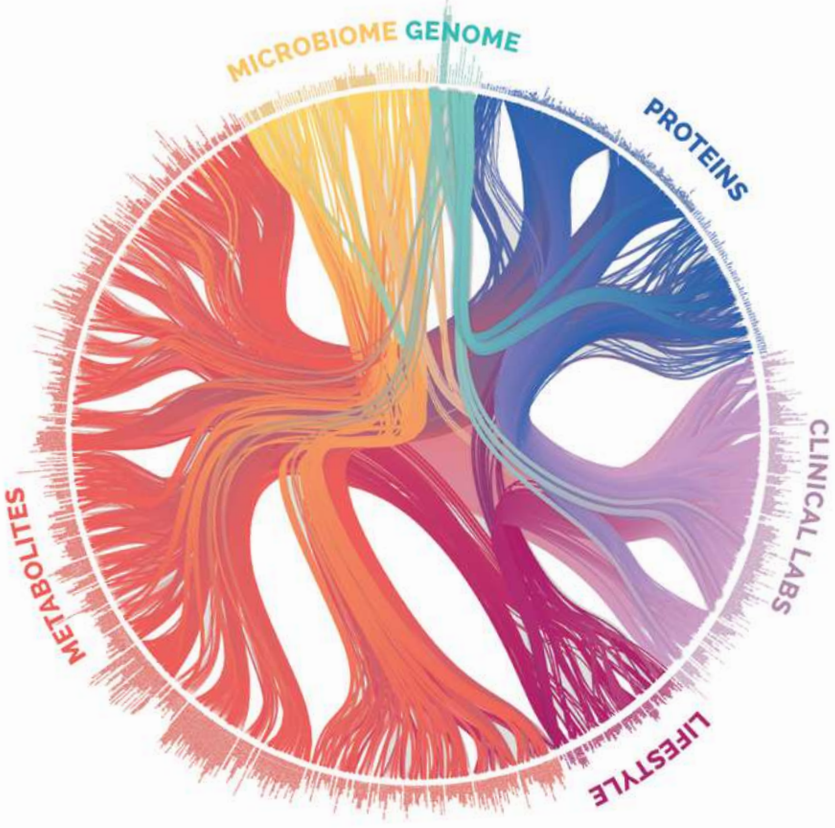
In 2015, to follow up on the success of the 2014 pioneer project, ISB spun out a company, Arivale, to bring scientific wellness to consumers. Today it has more than 2000 enrollees—including many of the original 108 pioneers. This is already about 20 times as many enrollees as in the first study. We are now beginning to see wellness to disease transitions quite regularly among the 2000 individuals.

The Arivale program of scientific wellness is now available in Washington, Oregon and California. Arivale is using dense, dynamic, personal data clouds in conjunction with ISB and PSJH to carry out clinical trials on scientific wellness and a variety of diseases. The data that Arivale is generating will transform how healthcare companies—pharma, biotech, diagnostic and nutrition companies—will carry out their research in the future. Arivale is one of the first companies to populate the new healthcare sector of scientific wellness.

DATA FROM THE DENSE, DYNAMIC, PERSONAL DATA CLOUDS WILL TRANSFORM SCIENTIFIC WELLNESS AND OUR UNDERSTANDING OF HUMAN BIOLOGY AND DISEASE

The data from the 2014 pioneer study has been analyzed and recently accepted for publication in the journal *Nature Biotechnology*. We feel these data are akin to the Hubble telescope, which scanned the heavens with a resolution never before possible. Similar to the Hubble telescope, these data clouds let us view human biology and human disease with a resolution that has never before been seen in a discrete population. These data lead to three fascinating observations.

- The data were analyzed in six data types (microbiome, genome, proteins, clinical labs, lifestyle and metabolites). We analyzed data bits from one data type against the data bits in the other data types. We observed more than 4000 statistical correlations that lead to fascinating hints at the identification of new biomarkers for disease detection and possible drug target candidates. We observed more than 4000 statistical correlations that lead to fascinating hints at the identification of new biomarkers for disease detection and possible drug target candidates.
- We can estimate the genetic risk of an individual for about 60 different diseases that have been studied in genome-wide-association studies. In 21 cases, we were able to demonstrate a correlation between genetic risk and the magnitude of a disease phenotype (e.g. LDL levels to high cholesterol risks). We can identify proteins, metabolites, clinical chemistries and even gut microbes that correlate with the disease risks, raising the possibility in the future that proper treatment of these analytes might mitigate high genetic risks for a multitude of diseases.
- We see wellness-to-disease and disease-to-wellness transitions for many common diseases. This gives us the possibility of being able to identify biomarkers for these transitions at their earliest stage and, later, we can employ disease-perturbed network approaches to determine drug target candidates that may reverse these diseases before they ever get started. It also lets us follow pioneers at high risk for major diseases very closely to identify and hopefully eventually reverse their earliest disease transitions.



JOINING SYSTEMS BIOLOGY AND SYSTEMS MEDICINE WITH CLINICAL MEDICINE—AN AFFILIATION BETWEEN ISB AND PSJH

In 2016, Rod Hochman, MD, CEO of PSJH, asked me whether I would consider making ISB the research arm of PSJH. Rod also proposed that I become PSJH's chief science officer. Hochman clearly understood the power of P4 medicine and scientific wellness and wanted to bring them to the Providence system. We accepted this dual offer and that has opened up a series of exciting possibilities to bring P4 to the U.S. healthcare system.

We immediately realized this affiliation offered unique opportunities: carrying out a series of translational pillars, as well as bringing an understanding of P4 medicine and scientific wellness to healthcare professionals (including physicians), students (K-12 students, undergraduates and graduates), and citizens (patients). The affiliation will also allow us to develop a technology platform for executing dense, dynamic, personal data clouds more effectively and inexpensively. We will also bring P4 medicine and scientific wellness to other large healthcare systems, both in the U.S. and abroad.

To begin, we proposed a series of seven translational pillars using systems technologies and strategies, and dense, dynamic personal data clouds to study scientific wellness and several important diseases (Alzheimer's disease, diabetes, wellness for breast cancer patients, fatty liver disease, multiple sclerosis, and maternal fetal health).

The scientific wellness pillar project started in January 2017. For this pillar, 1000 PSJH employees are enrolling in the Arivale program for three years. We will analyze the resulting data to determine the health and economic benefits of the Arivale scientific wellness program—which we anticipate will be very significant. This economic data are essential evidence payers will need to agree to pay for scientific wellness.

I have created a PSJH Science Advisory Council that advises me with 23 scientists and clinician researchers selected from throughout the PSJH system and from ISB. We want to advance understanding within PSJH that "***investing in research***" is the key to inventing the future of medicine and transforming healthcare.

LARGE NUMBERS OF PERSONAL DATA CLOUDS OVER TIME WILL TRANSFORM HOW THE HEALTHCARE INDUSTRY OPERATES

Large numbers of personal data clouds will transform how pharma, biotech, diagnostic and nutrition companies operate. The ability to develop novel correlations between different data types (i.e. the microbiome to genetics or disease), to identify proteins, metabolites, and clinical chemistries with known genomic disease risks, and to pinpoint transitions between wellness and disease will advance each of these businesses. In large measure, this is because the precision of these measurements allow signal-to-noise issues to be dealt with effectively in a manner that was heretofore impossible.

We also believe that scientific wellness will become a rapidly growing sector of the healthcare industry in itself. Arivale and some of the digital health efforts now under way are initial examples of companies that will populate this space. We also believe that many of the translational pillars, if strikingly successful, could become the basis of new scientific wellness companies.

SCIENTIFIC WELLNESS WILL BE DEMOCRATIZED

Currently the cost of scientific wellness is very high— roughly $4000 per individual per year. This is primarily driven by the cost of the assays (genome sequence, blood chemistries, gut microbiome analyses, etc.). I believe that within the next 10 years, these costs will approach a few hundred dollars—reflecting a Moore's Law decline in the cost of these measurements. That cost reduction coupled with the fact that government or private payers will support scientific wellness, because of the cost savings it will bring to healthcare, should bring it in reach of all areas of society— the poor, middle class and rich. In time, scientific wellness can be exported to developing countries as well as the developed countries—leading to a true worldwide democratization of scientific wellness.

HOW SCIENTIFIC WELLNESS WILL REDUCE HEALTHCARE COSTS

Scientific wellness will reduce the cost of healthcare in many ways, including by:

- Optimizing wellness to avoid many initial disease transitions that most individuals experience.
- Identifying those at high risk for particular diseases and initiate possible preventive measures that will move individuals from high to low risk.
- Identifying very early indicators of transition from wellness to disease for ordinary individuals and then using systems approaches to generate transition point biomarkers and eventually the drugs that will reverse the disease at its transition point before it ever manifests itself as a disease phenotype—if we can do this for major diseases such as cancer, diabetes, cardiovascular, and neurodegenerative disease—scientific wellness will generate striking savings for the healthcare system.
- Providing the incentive for developing increasingly less expensive digital devices for measuring simple and complex phenotypes— these will be very useful in reducing dimensionality of assays necessary to assess scientific wellness.
- A benefit that is hard to evaluate is the enormous contribution that these individual data clouds will, collectively, provide for creating the informational medicine of the future, which, over the next 10-20 years, will allow us to transform medicine from a trial and error approach to an informational science that will improve the health of our children and grandchildren in revolutionary new ways.

A Moore's Law decline in the cost of wellness assays— with miniaturization, parallelization, integration, automation, real-time measurements— will continue. As an example, the cost of DNA sequencing declined a million-fold from 2003 to 2016 (from $1 billion to $1000 for an entire genome sequence). Within 10 years, a genome sequence will cost $100/genome. Indeed, I can foresee a time when people will have devices at home that will make thousands of wellness-relevant measurements from a drop of blood, transmit the measurements to an analytical center, which will, in turn, then send these results to you and your physician with relevant actionable recommendations. Thus healthcare will be executed at home and not in a hospital.

U.S. healthcare costs are about 18% of the GNP, and 86% of healthcare dollars are spent on chronic diseases. Scientific wellness will eventually eliminate most chronic diseases by stopping them at their earliest transition points before the disease ever manifests itself. Progress in preventing Alzheimer's disease, for example, which now costs the American healthcare system about $260 billion per year and is expected to rise exponentially in the near future, would by itself represent an enormous savings.

There will be also be enormous saving as individuals begin to take control of their own healthcare decisions because they are informed about their health. This is, of course, the fourth "P" (participatory) of P4 medicine.

P4 HEALTHCARE WILL CHANGE THE STRUCTURE OF 21ST CENTURY HEALTHCARE

Healthcare will be transformed from a focus almost entirely on disease to a focus on scientific wellness which will be covered by payers— both government and private. We anticipate many changes, including these:

- The frequency of many chronic diseases will be greatly reduced by scientific wellness (e.g., neurodegeneration, cardiovascular disease, diabetes, obesity, many cancers, etc.).
- A primary care doctor will be able to handle scientific wellness for perhaps 1000 patients in conjunction with three-to-four wellness coaches. Coaches will handle scientific wellness and physicians will handle disease transitions, trauma and other problems that require their specialized training.
- Telecommunication will be even more important in physician practices than it is now.
- Diseases themselves will increasingly be caught early and often treated at home.
- Hospitals will become more virtual as care migrates to wellness and homecare.
- Scientific wellness coaches will be an important new healthcare profession— and represent a unique new professional opportunity for young students.
- Physicians and other healthcare professionals will receive training in scientific wellness and P4 medicine.
- It will be commonplace for individuals to reach their 90s physically active and mentally alert.

PSJH HAS AN OPPORTUNITY TO CATALYZE AND LEAD THE NEW MEDICAL REVOLUTION REPRESENTED BY THE P4 MEDICINE TIPPING POINT

PSJH is one of the largest not-for-profit health systems in the nation, operating 50 hospitals and 239 clinics in seven states (Alaska, California, Montana, New Mexico, Oregon, Texas and Washington). The system has 106,000 employees, including 23,000 physicians and 23 million admissions/doctor visits annually.

With ISB's affiliation with PSJH, I became the system's Senior Vice President and Chief Science Officer. I have had a chance to visit nearly every major region in the PSJH system and have interacted with hundreds of Providence staff. They are an outstanding group, with many highly skilled clinical researchers—often excited about pushing forward with new translational research agendas (e.g., translational pillars).

When combined with the enormous talent at ISB and our groundbreaking work in scientific wellness, P4 healthcare and systems biology, PSJH, not unlike Johns Hopkins in 1910, is at the fulcrum of a major P4 tipping point in U.S. healthcare: the broad introduction of P4 medicine and scientific wellness. These will lead to improved quality of health (wellness) for each individual and to enormous savings for the healthcare system. We see the dawning of a new era of healthcare—one that is predictive, preventive, personal and participatory, and focuses primarily on wellness and not just on disease.

Lee Hood, MD, PhD

Co-founder and President, Institute for Systems Biology
Senior Vice President and Chief Science Officer, Providence St. Joseph Health

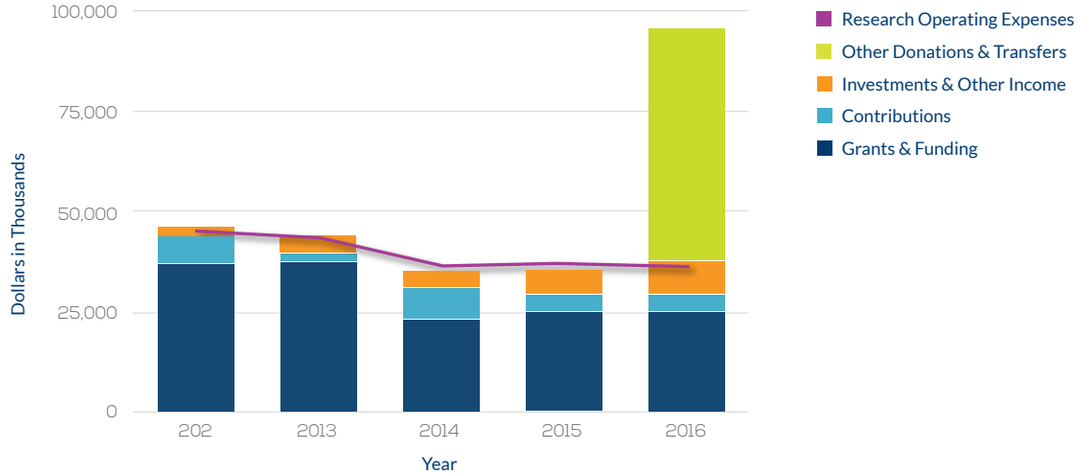
Dr. Hood's outstanding contributions have had a resounding effect on the advancement of science since the 1960s. Throughout his career, he has adhered to the advice of his mentor, Dr. William J. Dreyer: "***If you want to practice biology, do it on the leading edge, and if you want to be on the leading edge, invent new tools for deciphering biological information.***"

Financials

Year ending December 31, 2016

5-YEAR OVERVIEW

Research Operating Expenses vs. Total Revenue



BALANCE SHEET

Dollars in Thousands

ASSETS	$
Cash & Investments	68,476
Other Assets	8,357
Property & Equipment (Net)	7,032
Total Assets	**83,865**

LIABILITIES	$
Accounts Payable & Accrued Expenses	11,652
Deferred Revenues	1,340
Total Liabilities	**12,992**

NET ASSETS	$
Unrestricted Net Assets	57,591
Temporarily Restricted Net Assets	4,610
Permanently Restricted Net Assets	8,672
Total Net Assets	**70,873**

STATEMENT OF ACTIVITIES

Dollars in Thousands

REVENUES	$	%
Grants & Contract Revenue	24,155	25.5
Contributions	4,437	4.7
Investments & Other Income	8,283	8.7
Other Donations & Transfers	57,860	61.1
Total Revenues	**94,735**	**100.0**

EXPENDITURES	$
Research & Other Direct Costs	23,840
Management & General	12,377
Fundraising & Other	162
Total Expenditures	**36,379**
Increase in Net Assets	**58,356**

Quantitating the Complete Human Proteome

Robert Moritz, PhD, Professor

SUMMARY POINTS

1. ISB scientists collaborate with ETH Zurich to develop the Human SRMAtlas, a compendium of mass spectrometry assays for any human protein.
2. ISB releases protein assay parameters freely to the scientific community for the ability to assay any human protein without restriction.
3. Through the use of the ISB Human SRMAtlas, biomarker candidates, wellness markers and protein networks can be quickly evaluated to provide quantitative results on disease, wellness and biological processes.

Reporting in the journal *Cell*, Senior Research Scientist Dr. Ulrike Kusebauch, of the Dr. Robert Moritz Lab at ISB, describes the results of a collaboration between scientists at ISB, ETH Zurich and a number of other contributing institutes to develop the Human SRMAtlas. The Human SRMAtlas is a compendium of highly specific mass spectrometry assays for the targeted identification and reproducible quantification of any protein in the predicted human proteome, including assays for many spliced variants, non-synonymous mutations and post-translational modifications. The team used selected reaction monitoring (SRM) on 166,174 well-characterized, chemically synthesized proteotypic peptides to develop the assays. With such a resource, the prospect of measuring any protein is now a reality.

Although the Human Genome Project in 2003 created an inventory of all human genes, the majority of protein research is still focused on the same relatively small subset of proteins that were explored before the human genome was sequenced. To move beyond this stagnated proteogenomic research approach, the development of highly specific assays for essentially every human protein was needed. The Human SRMAtlas provides verified mass spectrometry assays based on SRM technology developed in a uniform and consistent process for essentially every protein of the human proteome. These assays can be rapidly deployed in systems biology and biomedical studies to identify and quantify any human protein with high sensitivity and high selectivity, and to navigate complete proteome maps to understand their biological functions.

The ability to reliably and reproducibly measure any protein of the human proteome in any tissue or cell-type is transformative for understanding systems-level properties as well as specific pathways in physiology and disease. The Human SRMAtlas provides definitive assay coordinates that can conclusively identify the respective peptide in biological samples and allow quantification of 99.7% of the 20,277 annotated human proteins.

Personalized medicine will depend on molecular signatures to monitor health status and provide signals to identify changes in wellness trajectories and information to match the right patients to the right drugs, first in clinical trials, then in clinical practice. The Human SRMAtlas initiative pushes proteomics firmly into the forefront and provides further ammunition for proteomics to play a large role in increasingly worldwide efforts of the Cancer Moonshot.

The SRMAtlas resource is free and publicly available at ***www.srmatlas.org*** and will equally benefit focused, hypothesis-driven and large proteome-scale studies. The team expects this resource will significantly advance protein-based experimental biology to understand disease transitions and wellness trajectories because any human protein can now, in principle, be identified and quantified in any sample.

READ THE PAPER: ***ISB.IO/HP16***

Speeding Up Drug Discovery to Fight Tuberculosis

Eliza Peterson, PhD, Baliga Lab

Seattle researchers created a genetic blueprint of the cunning tuberculosis bacteria, then used it to predict and rank potential drug targets.

The rise in multi-drug resistant (MDR) and extremely drug resistant (XDR) strains of *Mycobacterium tuberculosis* (MTB) is becoming a major cause of global health concern for treating tuberculosis, which affects a third of the global population. In fact, the number of worldwide deaths caused by tuberculosis has surpassed HIV/AIDS, and there is greater sense of urgency than ever before to find effective drug cocktails to outsmart MTB.

In a landmark study published on June 6, 2016, in *Nature Microbiology*, researchers at Institute for Systems Biology and the Center for Infectious Disease Research (CIDR) in Seattle demonstrated a systems biology approach that has the potential to rationally predict combinations of drugs that will disrupt tolerance networks in MTB making it even more susceptible to antibiotic therapy.

"The incredibly large number of possible drug combinations taken together with the difficulty of growing MTB in the laboratory make discovery of effective combination therapy extremely challenging. We hope that our systems-based strategy will accelerate TB drug discovery by helping researchers prioritize combinations that are more likely to be effective," said Nitin Baliga, Senior Vice President of Institute for Systems Biology and the senior author on the paper.

The success of MTB is largely due to its ability to alter gene expression to counteract host defense and anti-tubercular drug treatment. An extended period of tolerance gives MTB a window of opportunity to mutate and evolve longer term resistance.

Previously, researchers in the Baliga lab at ISB and in the Sherman lab at CIDR published a genome-wide regulatory network model that could predict how MTB senses and responds to changes in its environment, including anti-tubercular treatment.

In this study, they used the network model to understand how MTB tolerates killing by the drug bedaquiline, which in 2012 was the first drug in 40 years to be approved by the FDA. They used this network-enabled knowledge to find a second drug (pretomanid) to counteract tolerance against bedaquiline.

They went on to demonstrate that making the tolerance network hyperactive abolished the effectiveness of the combination therapy, confirming the mechanism of combined action of bedaquiline and pretomanid. The success of this systems biology-based method to find drug combinations has the potential to revolutionize and rapidly accelerate efforts towards TB drug discovery.

SUMMARY POINTS

1. Researchers at the Institute for Systems Biology and Center for Infectious Disease Research have deciphered how the human pathogen *Mycobacterium tuberculosis* is able to tolerate the recently approved FDA drug.

2. The study demonstrated that silencing certain regulatory genes in the bacteria, or pairing with a second drug, pretomanid, disrupts a tolerance gene network to improve efficacy of killing by bedaquiline.

3. This systems-approach to rational drug discovery represents significant advance in the fight against tuberculosis, which affects a third of the global population, surpassing HIV/AIDS in the number of deaths worldwide.

READ THE PAPER: ***ISB.IO/TB16***

Stitching Together Insight For Deadly Brain Cancer

Christopher Plaisier, PhD, Baliga Lab

SUMMARY POINTS

1. Using data from TCGA and ENCODE, ISB researchers developed an integrative database and analysis platform that provides insight into the underpinnings of glioblastoma multiforme (GBM).

2. Researchers developed a way to intelligently discover combinations of small RNA molecules and drugs that can lead to synergistic effects.

3. They also identified a never before seen association between increased levels of immune molecules, tumor immune cell infiltration, and decreased patient survival.

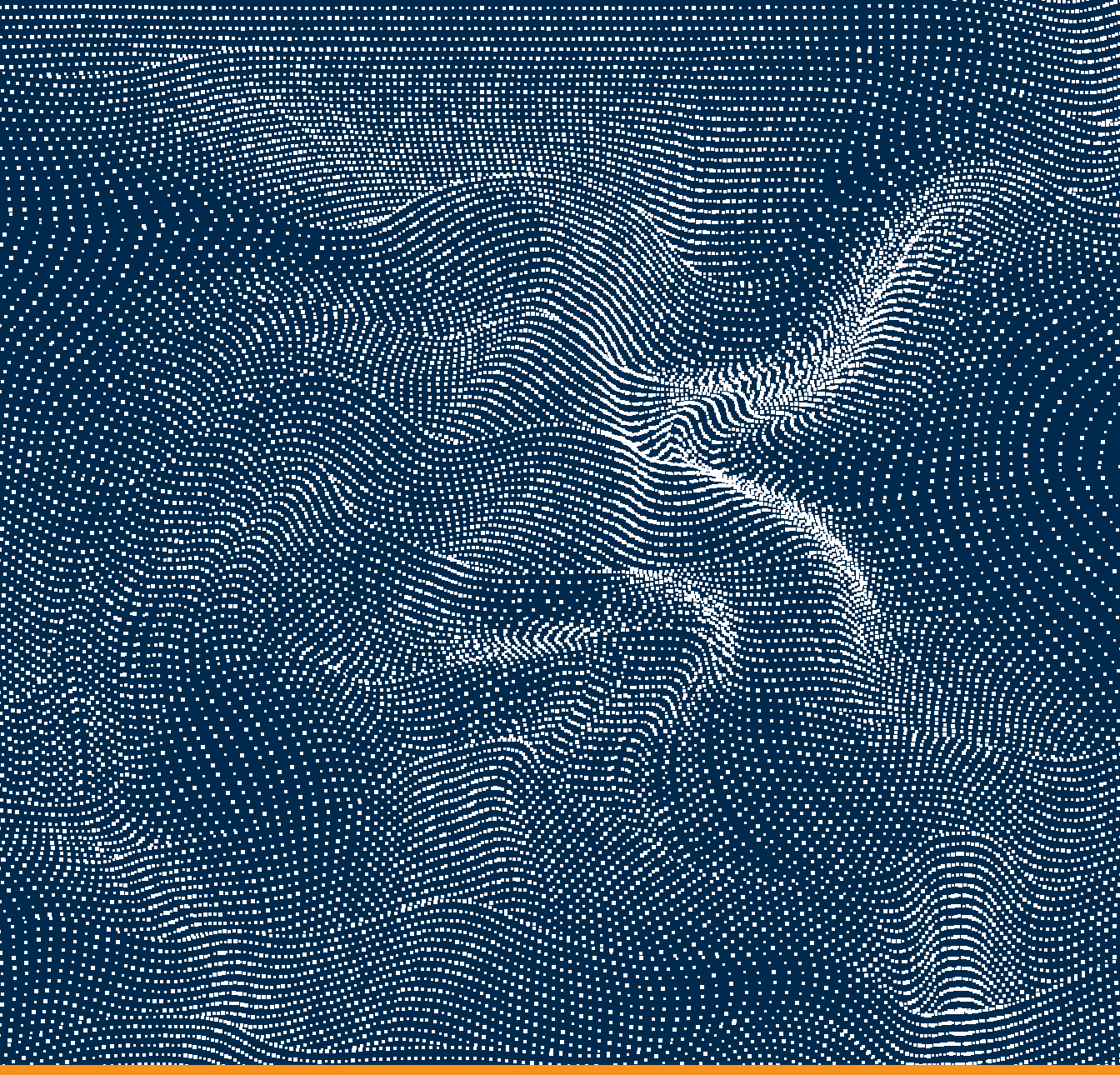
In a study published in *Cell Systems* on July 14, 2016, researchers at the Institute for Systems Biology have developed a platform for integrating somatic mutations and gene expression from patient data into a mechanistically based transcriptional regulatory network. They applied this approach to construct the most comprehensive regulatory network for the deadly brain cancer glioblastoma multiforme (GBM).

Researchers used data from a large consortium (TCGA and ENCODE) to develop a highly integrative approach which they demonstrate can be used to discover the underlying topology of regulatory interactions, potential drug targets, and dissect the biological underpinnings of disease traits (e.g. tumor lymphocyte infiltration). For the first time, their network suggests a regulatory mechanism for how increased cellular immune proteins are associated with increased tumor lymphocyte infiltration and decreased patient survival in GBM.

With the hope that they will catalyze innovative treatments and cures the Cancer Genome Atlas (TCGA) has assembled clinical, transcriptomic, and genomic data for a large cohort of patient GBM tumors. The challenge with these data has been that each patient tumor contributes only a single snapshot, which is insufficient to provide insight into causal or mechanistic underpinnings of the disease within that patient. They hypothesized that patients with similarly perturbed oncogenic processes would have conserved genomic and molecular patterns, based on which they could be sub-grouped to provide the statistical power required to map the underlying dysfunctional network and identify points of intervention to halt oncogenic processes.

This was the impetus for developing the TF-target gene database and the SYstems Genetics Network AnaLysis (SYGNAL) pipeline. Through their studies applying these new tools to GBM, the researchers have demonstrated that multi-omic data from each patient can be stitched together into a gbmSYGNAL transcriptional regulatory network to gain clinically/biologically meaningful insights. And that the network structure and integration with orthogonal information (drug targets) can be used to discover intervention points that can lead to synergistic interactions. This demonstrates that ISB's new SYGNAL pipeline can become a data integration platform that explains the etiology of a disease and provides the knobs which can be turned to maneuver the system back to a healthier state.

READ THE PAPER: ***ISB.IO/GBM16***



Institute for Systems Biology

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