17 Annual Daniel Nathans Lecture

A Tipping Point for Healthcare: Systems Medicine, Big Data and Scientific Wellness

Lee Hood, President and Co-founder
Institute for Systems Biology, Seattle

Senior Vice President and Chief Science Officer
Providence St. Joseph Health

April 6, 2017

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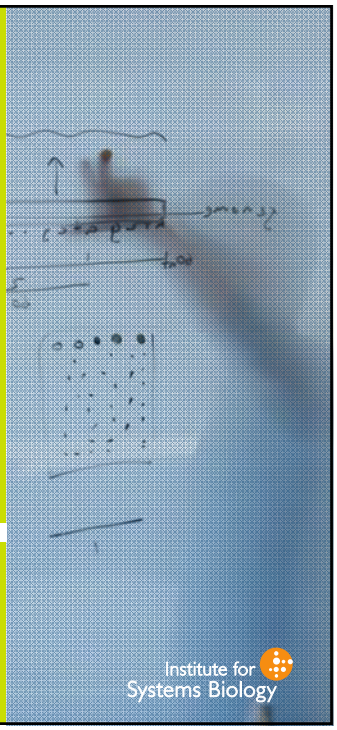
The grand challenge for biology and medicine: Deciphering biological complexity



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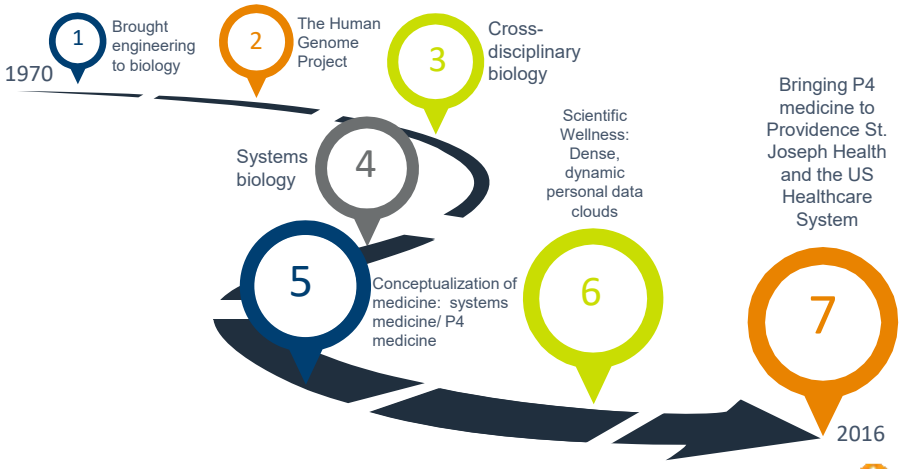
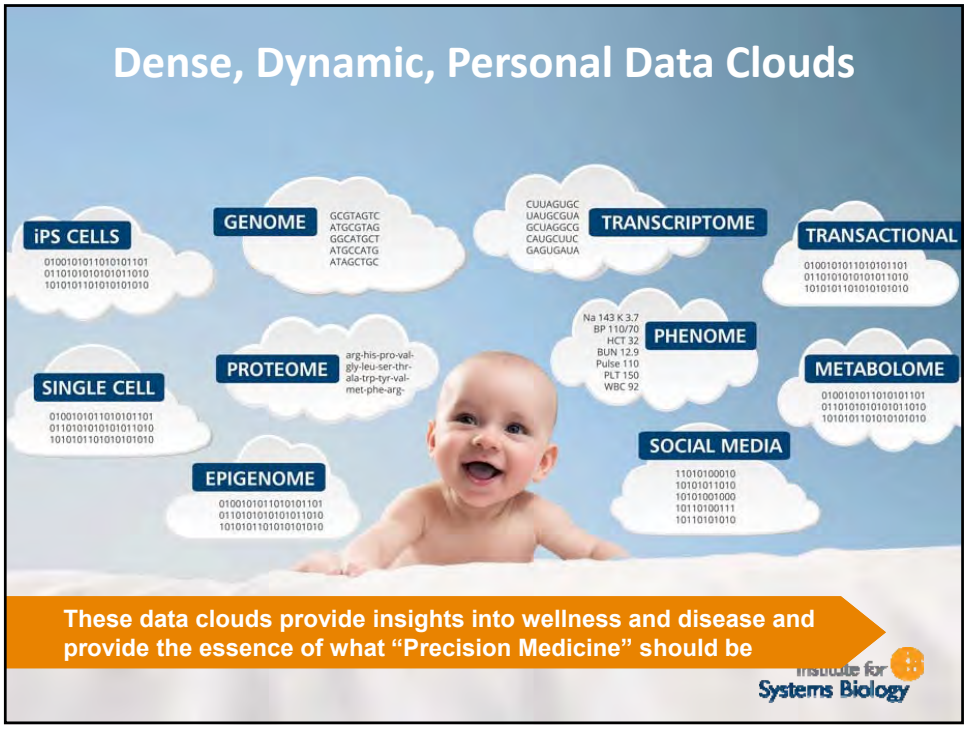
I Participated in Seven Paradigm Changes in Biology Dealing with Complexity



Four Contributions of Systems Biology To Systems (P4) Medicine

- ***Dense, dynamic, personal, data clouds***
- ***Dynamic network biology***
- ***Systems-driven technologies and systems-driven strategies***
- ***A systems view of data***


Dense, Dynamic, Personal Data Clouds
iPS CELLS
GENOME
GCGTAGTC
ATGCGTAG
GGCATGCT
ATGCCATG
ATAGCTGC
CUUAGUGC
UAUGCGUA
GCUAGGCG
CAUGCUUC
GAGUGAUA
TRANSCRIPTOME
TRANSACTIONAL
PHENOME
Na 143 K 3.7
BP 110/70
HCT 32
BUN 12.9
Pulse 110
PLT 150
WBC 92
PROTEOME
arg-his-pro-val-
gly-leu-ser-thr-
ala-trp-tyr-val-
met-phe-arg-
METABOLOME
SINGLE CELL
SOCIAL MEDIA
EPIGENOME
These data clouds provide insights into wellness and disease and provide the essence of what "Precision Medicine" should be
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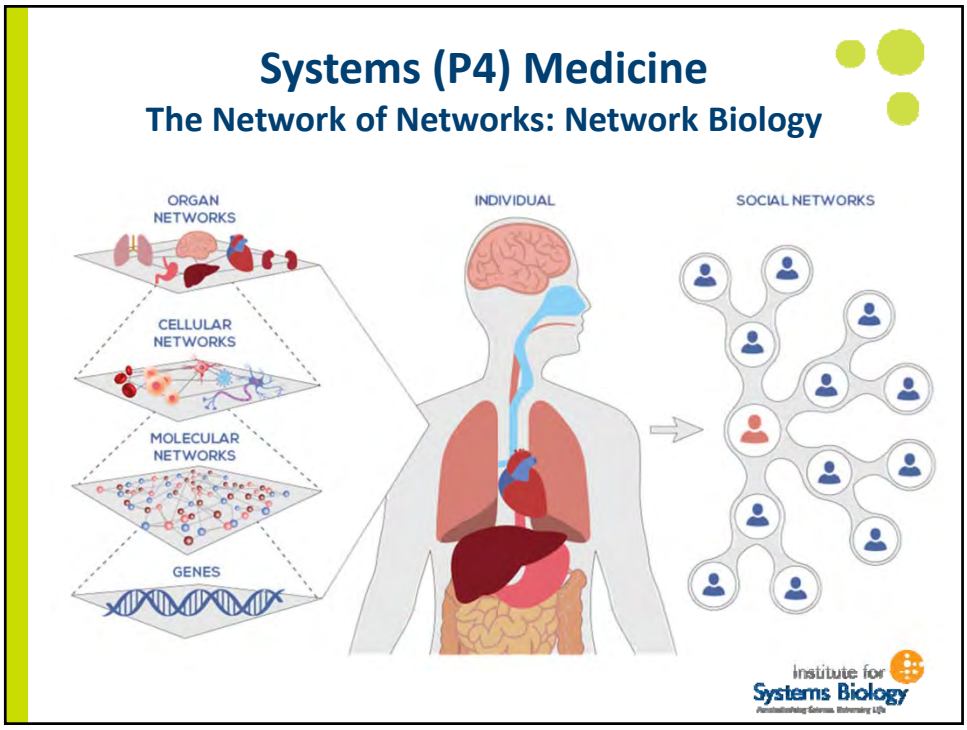
Systems (P4) Medicine
The Network of Networks: Network Biology
ORGAN NETWORKS
CELLULAR NETWORKS
MOLECULAR NETWORKS
GENES
INDIVIDUAL
SOCIAL NETWORKS
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Systems-Driven Technologies and Strategies

- **Technologies**
  - **3rd generation DNA sequencing** ($100 genome)
  - **Targeted proteomics** (blood biomarkers)—SRM Atlas
  - **Peptide protein-capture agents** (replace antibodies as diagnostics and drugs)
  - **Single-cell analyses** (deciphering biological complexities)
- **Strategies**
  - **Family genome sequencing** (identify disease genes and compare 1000s of genomes)
  - **Animal model disease dynamics** (identify earliest disease-perturbed networks)
  - **Blood biomarker discovery** ((cancer, preterm birth, PTSD, liver disease)
  - **Organ-specific blood proteins** for wellness and disease
  - **Dense, dynamic, personal data clouds** to analyze wellness and disease
  - **Billions of natural synthetic products as drugs**
  - Translating data to **disease-perturbed networks** and their analysis to identify **drug target candidates**
  - Use **disease-perturbed networks** to identify **drug target candidates**
  - **Blood is a window into the dynamics of human biology and disease (**separate/analyze molecules of blood, vesicles, cells)

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A Systems View of Big Data:

Dealing with Biological Complexity of Complex Systems

- **Global analyses** of all components—DNA, RNA protein, etc.
- **Dynamics of systems** (networks)—temporal and spatial
- **Integration** of different data types from the system
- Use of **theoretical conceptual approaches** for new insights into biology: dynamical systems theory and thermodynamical phase transitions in biology
- Development of **platforms** for **systems-driven technologies and strategies** is key (family genome sequencing)
- Large data sets reflect two types of **noise—biological and technical**

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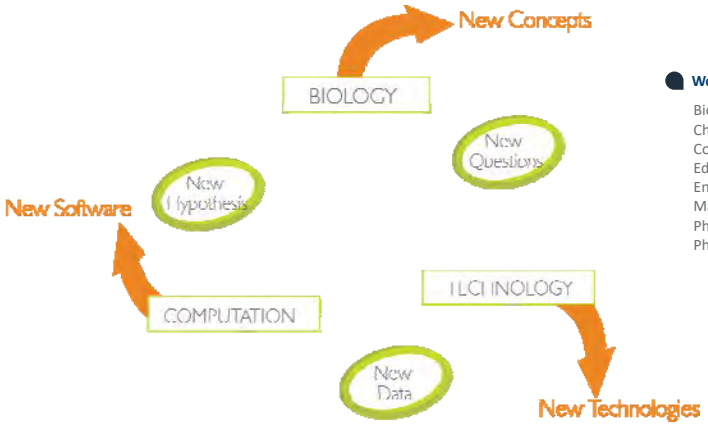
Discovery and Innovation Engine for Systems Biology



Working together:

- Biologists
- Chemists
- Computer Scientists
- Educators
- Engineers
- Mathematicians
- Physicists
- Physicians

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Systems-Driven Technologies and Strategies

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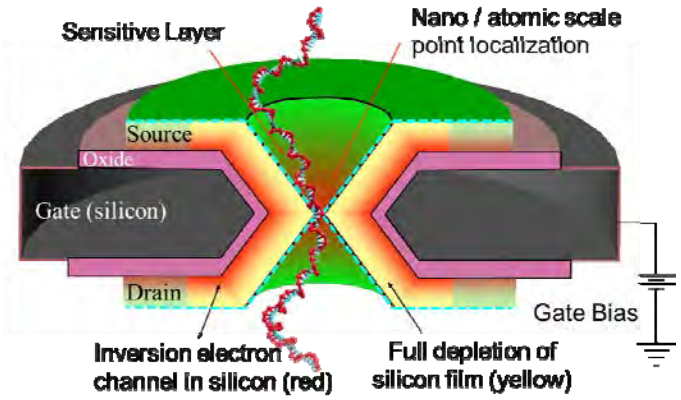
3rd Generation DNA Sequencing

- Ease of sample preparation
- Single molecule analysis
- Nanopore sequencer
- Electronic detection
- Detect 16 epigenetic modifications of DNA
- In principle could sequence RNA as well as DNA
- Enormous parallelization and minaturization
- Whole human genome sequence in 15 minutes for less than $100

Field Effect Nanopore Transistor Sequencer



Bharath Takulapalli
INanoBio Inc.

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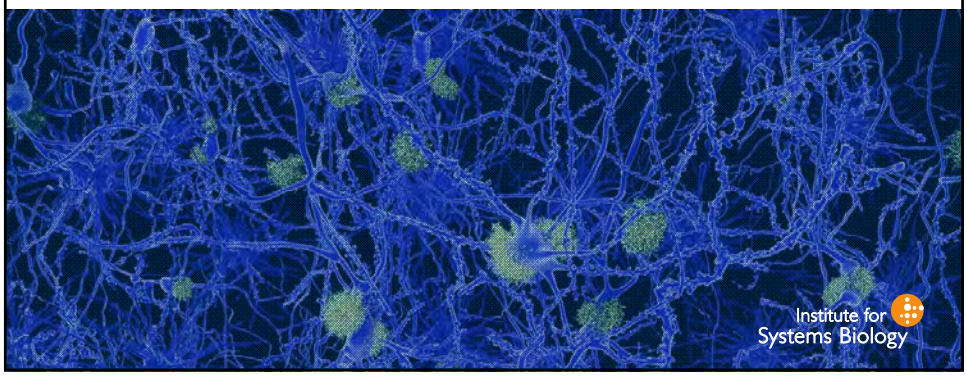
Prion-Induce Neurodegeneration: An Animal Model for Studying the Dynamics of a Disease

Dawhee Huang, Inyoul Lee, George Carlson, Lee Hood



Global and Subtractive Brain Transcriptome Analysis—Differentially Expressed Genes (DEGs)

Prion strains:
- RML
- 301V

Mouse strains:
- C57BL/6J
- FVB/NCr
- BL6.I
- FVB/B4053

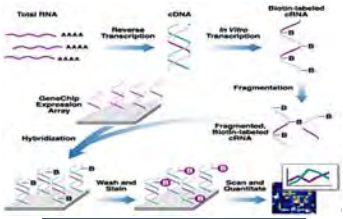
Inoculate with Prions

Prion infected brain

Uninfected brain

RNA from brain homogenate

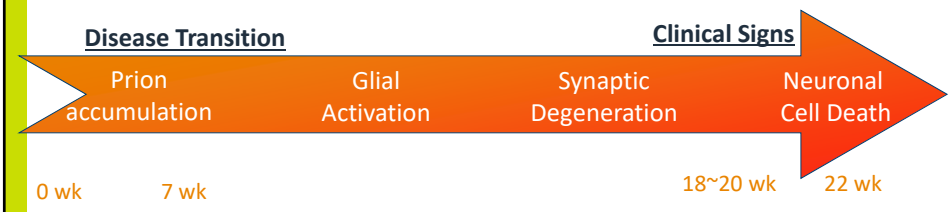
Time-course array analysis: subtrative analyses to DEGs
- **C57BL/6J-RML**: 12 time points
- **FVB/NCr-RML**: 11 time points
- **BL6.I-301V**: 9 time points
- **FVB/B4053-RML**: 8 time points



Mouse Genome array:
45,000 probe sets
~22,000 mouse genes.

7400 DEGs–signal to noise issues–biological/technical–deep biology—300 DEGs encode the prion neurodegenerative response

Sequential Disease-Perturbation of the Four Major Networks of Prion-Induced Neurodegeneration in Mice



Analyzed with 10 Brain transcriptomes across the 22 weeks of disease progression

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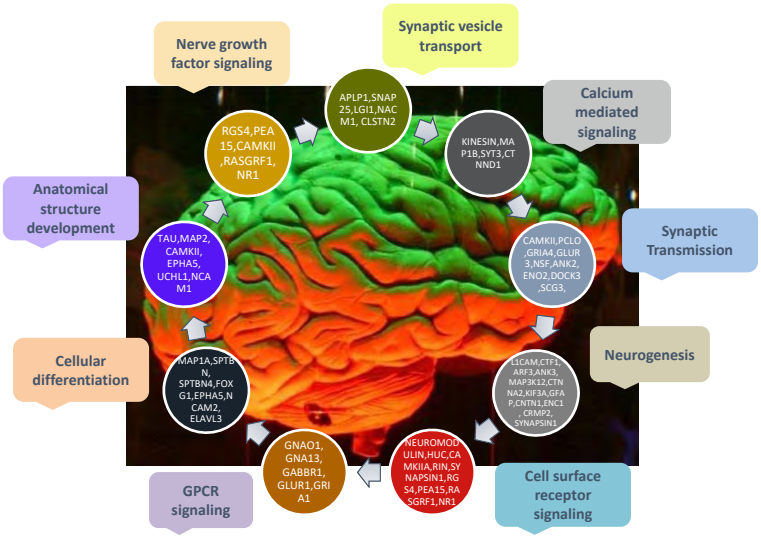
100 Brain-Specific Blood Transcripts (Proteins) Reflect Key Networks (SRM assays)



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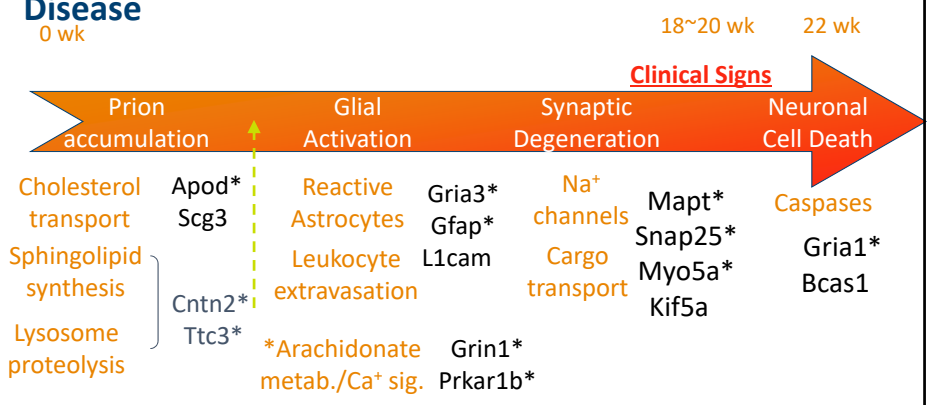
11 Brain-Specific Blood Proteins Reflect the early Initiation and Progression of Prion Disease-Perturbed Networks: Blood is a Window into Wellness and Disease



- Indicates brain-specific blood proteins
- An example of "blood is a window into health and disease

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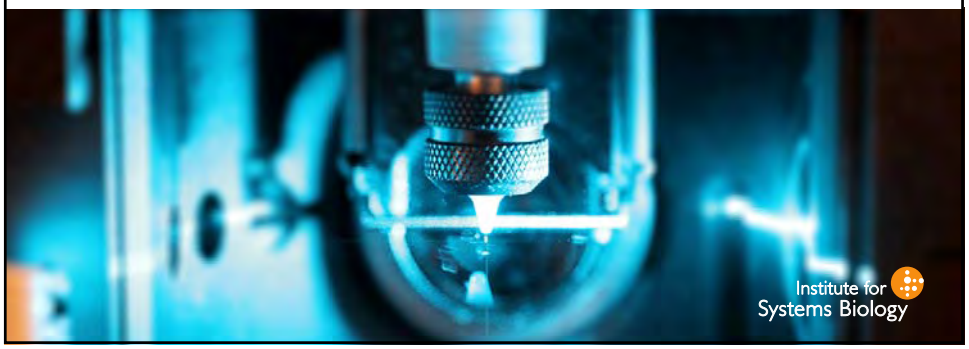
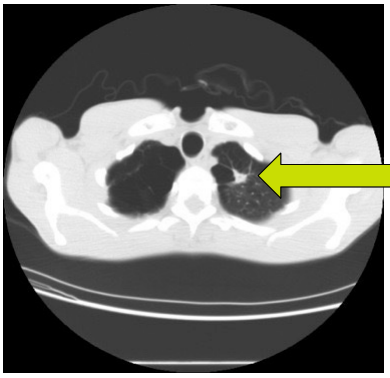
Systems-Driven Approaches to Blood Biomarker Discovery

Paul Kearney, Nathan Price, Lee Hood

Integrated Diagnostics & Institute for Systems Biology



Indeterminate Pulmonary Nodules



Patrick Nana-Sinkham, MD Ohio State University

Is this cancer?

~3 million cases annually in the USA

Integrated Diagnostics

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Systems Approach to Distinguishing Benign from Malignant Lung Cancer Nodules (with Integrated Diagnostics)

- 371 SRM assays for lung cancer tissue/190 detectable in the blood
  - **Differentially secreted (normal vs. neoplastic)**
  - **Differentially shed from cell surface (normal vs. neoplastic)**
  - Candidates captured from the literature
- Discovery samples—analyze all 190 detectable proteins
  - 72 cancer vs. 72 benign–**from four sites**
- **Discovery algorithm for "cooperative" proteins**
  - Select the 32 (out of 190) best proteins for distinguishing nodules
  - A million random panels of 10 of 32 best proteins were scored
  - Identified 13 proteins that were highly "cooperative"—generally in most effective panels
- Validation study—13-protein panel—identifies 36% of benign nodules
  - 52 cancer vs. 52 benign–**from 4 old sites plus 1 new site**
  - **Identifies 36% of the benign lung nodules**
- Integrated Diagnostics commercialize the panel of 13 blood proteins in Q4 2013
- Integrated Diagnostics develops a **two-protein blood panel** that identifies more than 50% of the benign lung nodules 2016

Bold Blue indicates systems-driven approaches.

X. Li et.al. Science Translation Medicine: 5, 207, 2013

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Systems Driven Blood Targeted Human Blood Protein Biomarkers

Validated

- **Distinguish benign and neoplastic lung nodules**—two blood proteins can identify with more than 95% specificity more than 50% benign nodules—saving US healthcare more that $4.5 billion/year
- **Preterm birth** —two blood proteins can distinguish at 19 weeks mothers destined to have preterm birth from those with normal births (Sera Prognostics in Salt Lake City)—in time for actionable therapy

Discovery

- **Post traumatic stress disorder** (PTSD)—2 blood proteins that allow one to distinguish from plasma 50 normal Afghanistan soldiers and 50 PTSD Afghanistan soldiers (ISB)
- **Glioblastoma**—4 blood proteins distinguish normal from patients with glioblastoma
- **Liver disease**—4 proteins identify AIDS-induced fibrosis and multiple proteins identify liver toxicity—acetaminophin poisoning

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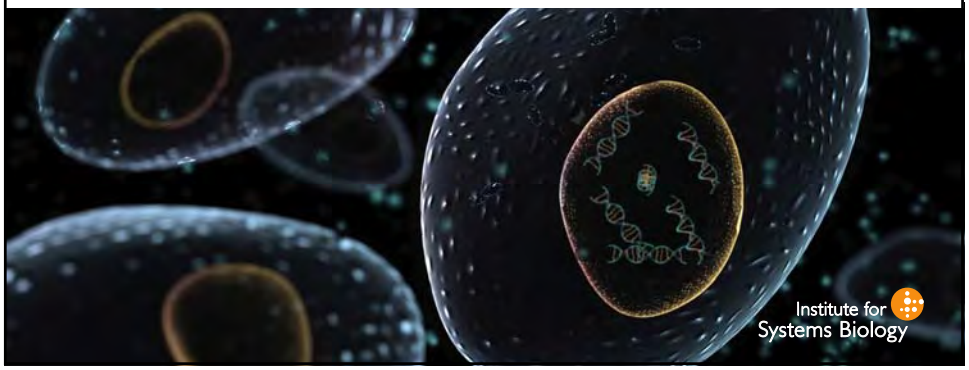
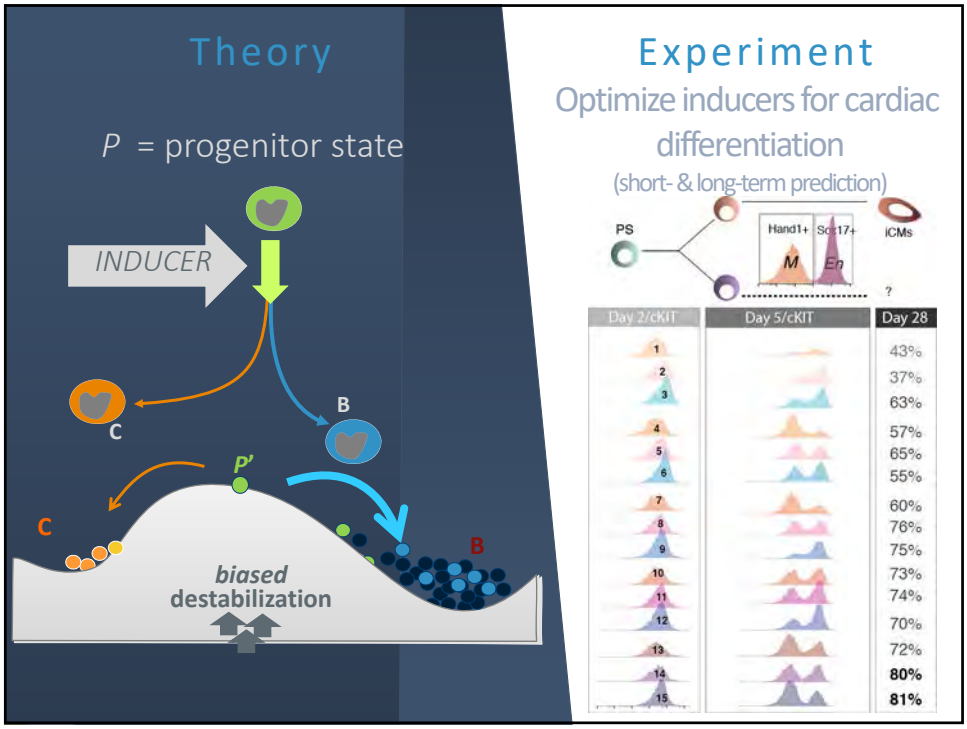
Single Cell Analyses Following the Development of iPS Cells to Cardiomyocytes

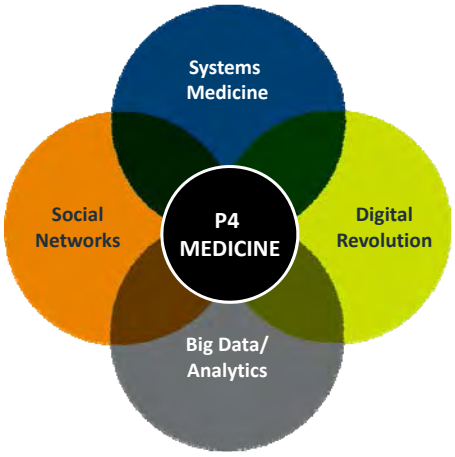
Kalli Trachana, Rhishi Bargaje, Martin Shelton
Sui Huang, Lee Hood




Theory
P = progenitor state
INDUCER
C
B
P'
C
B
biased
destabilization
Experiment
Optimize inducers for cardiac differentiation
(short- & long-term prediction)
PS
Hand1+
Sox17+
iCMs
M
En
?
Day 2/cKIT
Day 5/cKIT
Day 28
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
43%
37%
63%
57%
65%
55%
60%
76%
75%
73%
74%
70%
72%
80%
81%


"New directions in science are launched by new tools (and strategies) much more often than by new concepts."
"The effect of a concept-driven revolution is to explain old things in new ways."
"The effect of a tool-driven revolution is to discover new things that have to be explained."
- Freeman Dyson, Imagined Worlds

The Emergence of P4 Medicine



Converging Megatrends

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P4 Medicine

- Proactive
- Individual
- Wellness & disease
- Personalized data clouds
- Personalized data clouds for clinical trials (N=1 experiments)
- Patient activated social networks

Contemporary Medicine

- Reactive
- Population
- Only disease
- Averaged patient populations
- Averaged patient populations for clinical trials

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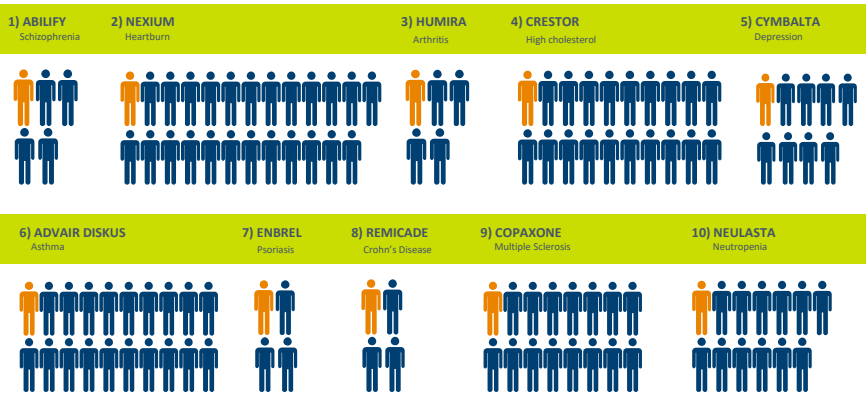
Imprecision Medicine:

Time for N=1 Drug Trials to Stratify Disease Subtypes



For every person in the US that the 10 highest grossing drugs do help (orange), they fail to improve the conditions of between 3 - 24 people (blue).

Schork, Nicholas. Time for one-person trials. Nature. Vol 520. April 2015

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Conceptual Themes of P4 Medicine

P4 MEDICINE
Predictive, Preventive, Personalized, Participatory

WELLNESS QUANTIFIED
Scientific Wellness Industry

DISEASE DEMYSTIFIED
Disease Industry (Current healthcare)

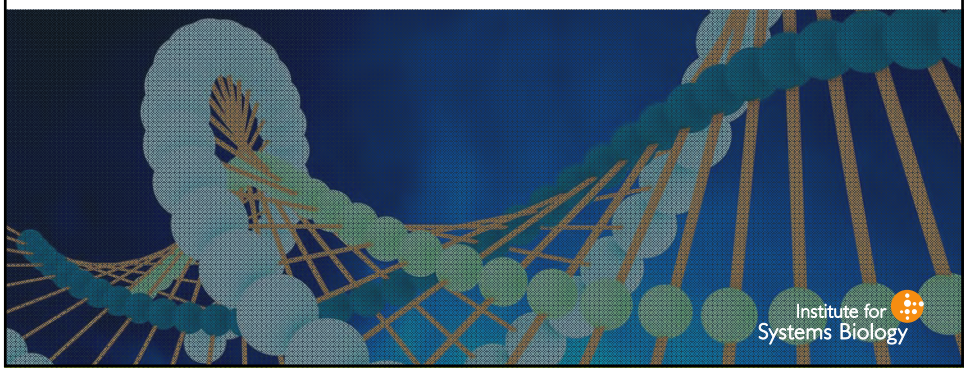
Dense, dynamic, personal data clouds will enable us to:

- Optimize human potential / wellness
- Follow disease, response to therapy and return to health (follow high risk individuals)
- Identify earliest wellness to disease transitions—reverse preventive medicine 21st century
- N=1 experiments are key to deconvoluting biological complexity

The 108 Person Wellness Project 2014 (Pioneers)

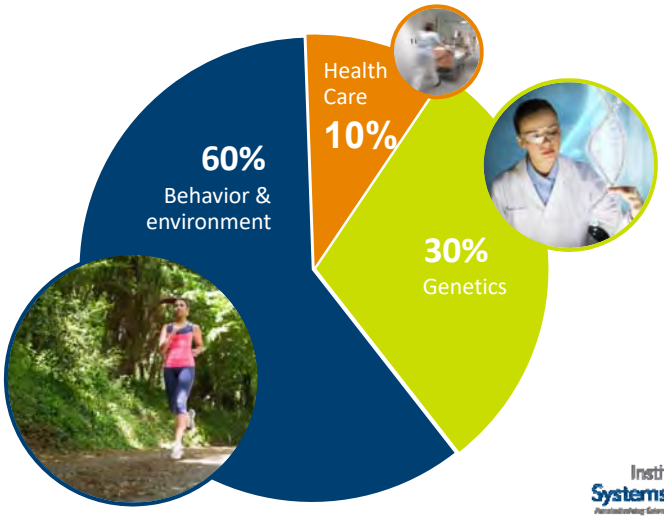
Principal Investigators: Lee Hood and Nathan Price
Using dense, dynamic, personal data clouds for wellness

IRB approved study



Determinants of Health in U.S.

Dense, dynamic, personal data clouds assess the integration of individual genetics and environment



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Assays / Measurements for 108 Pioneers

Creating dense, dynamic, personal data clouds

GENOME

Whole Genome Sequencing
SNPs Millions

LABS

Detailed lab tests 3x (blood, urine, saliva)
Clinical chem. 150
Metabolites 1700
Proteins 400

SELF-TRACKING

Continual self-tracking & lifestyle monitoring

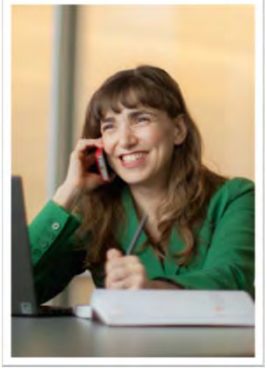
MICROBIOME

Gut Microbiome 3x

Wellness Coaching for HPWP Participants

A Critical Component of Scientific Wellness

Wellness Coach



Sandi Kaplan, MS, RD

Study Physician

Craig Keebler, MD

Long term longitudinal recruitment of pioneers

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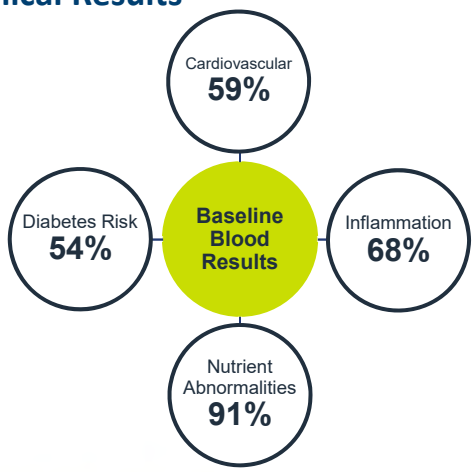
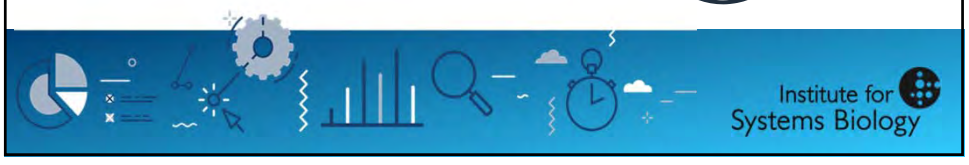
Initial Clinical Labs Discovery:
High Rate of Actionable Clinical Results

- The 108 "well" participants had a high rate of initial abnormal lab results
- **100%** of the participants had actionable recommendations from their blood results





Vitamin D Deficiency:
Arising from Both Genetics and Environment—*N=1 Experiments Key*

- Vitamin D – 90/108 Pioneers were low
- Six genetic variants from 3 genes block Vitamin D absorption
- Those with multiple blocking variants and presumably unknown variants, need **mega-doses** of Vitamin D
- Unknown blocking factors

Risks associated with low Vitamin D

- Ricketts– improper bone mineralization
- Increased risk of death from cardiovascular disease
- Cognitive impairment in older adults– Alzheimer's
- Severe asthma in children
- Cancer

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Pioneer with 3 years of Neuralgia and Facial Bell's Palsy

Almost no blood vitamin B12

Actionable Possibility: Intramuscular injections of B12 and reversed completely in 3 months

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108 Pioneers: Insights

I can take control of my health with the proper data/coaching.

Your genome does not control your destiny – just your potential.

We are less well than we think. Everyone has multiple actionable possibilities.

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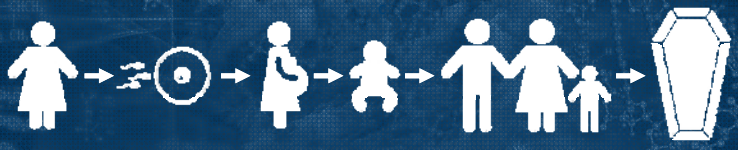
Where Do You Reside On The Wellness Staircase?

Scientific wellness is a life long journey

Increasing Scientific Wellness

Scientific wellness will be a life-long journey—from conception to death



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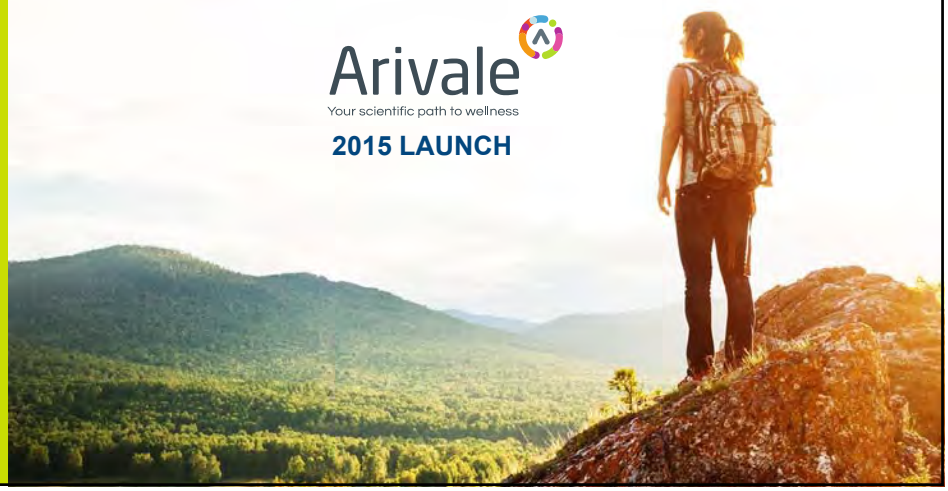
Creation of a Consumer-Based Scientific Wellness Company

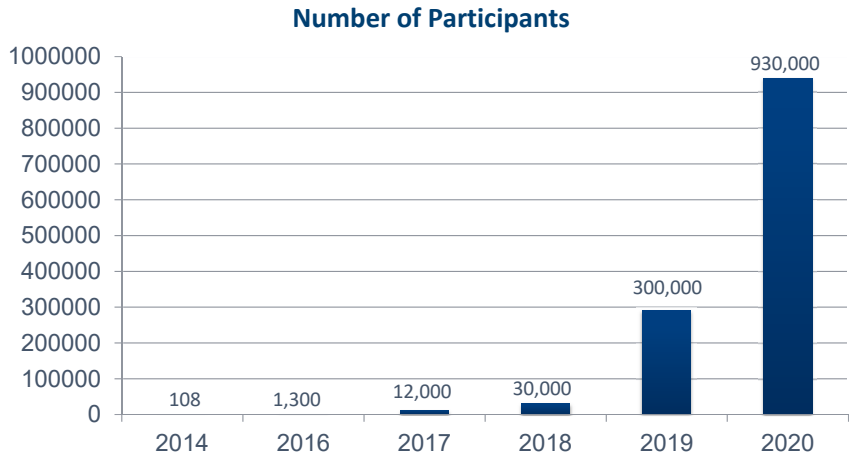
Arivale

Your scientific path to wellness

2015 LAUNCH



Arivale Scaling of Individuals with Dense, Dynamic, Personal Data Clouds



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Dense, Dynamic. Personal Data Clouds: Probing the Dark Matter of Wellness And Disease

The Hubble Telescope allows us to probe the dark matter of the universe just as dense and dynamic personal data clouds allow us to probe the dark matter of human biology and disease.

Nature Biotech, in press

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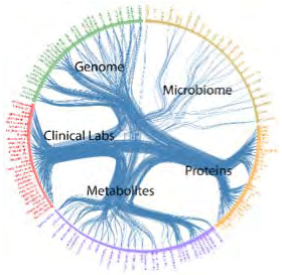
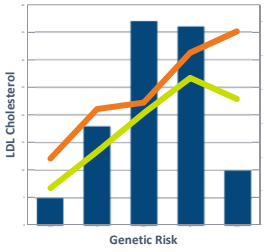
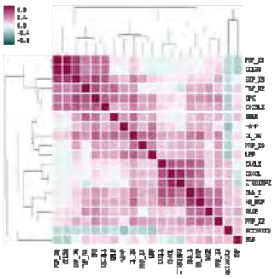
The Power of Integrative Analysis on Multiple Data Quadrants

Nature Biotechnology, in press







Statistical Correlations between all of our data quadrants for 108 individuals

Determination of genetic risk and correlation with disease phenotype

State transitions For wellness and disease states

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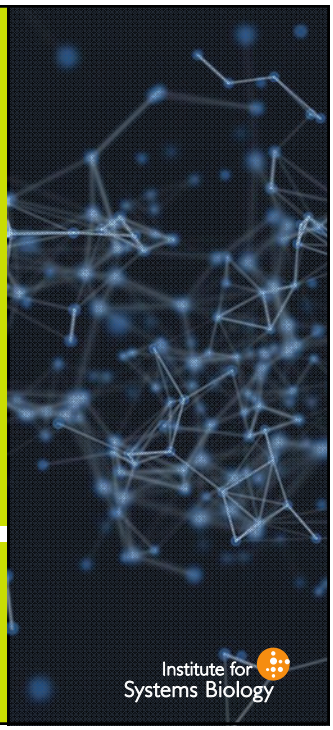
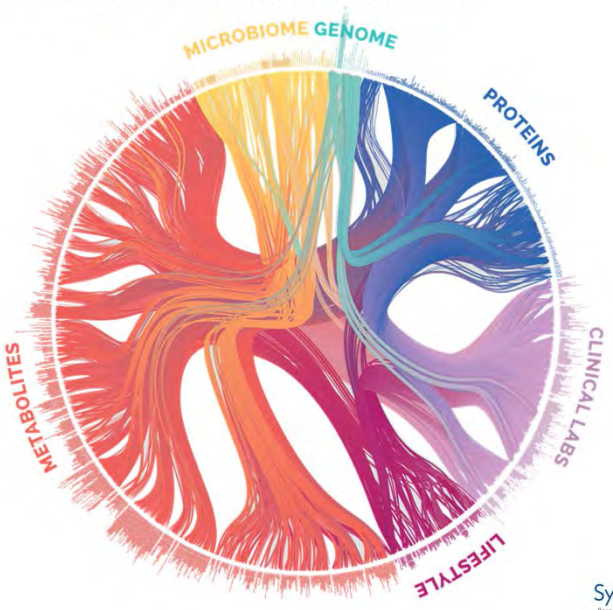
Statistical Correlations



Multi-Omic Correlation Network



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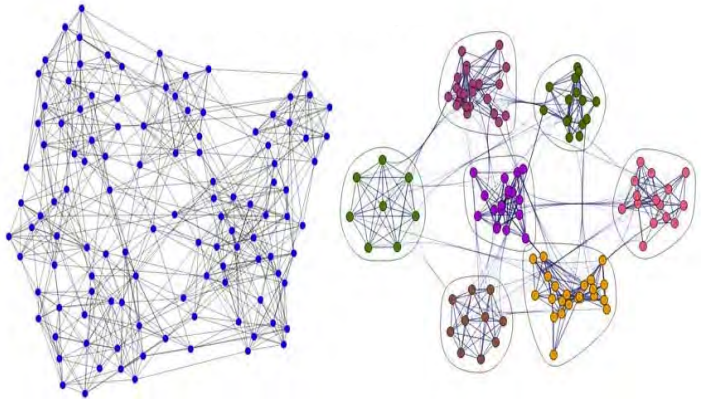
Substructures of the Correlation Network

We identify 'communities' in the correlation network – sets of analytes that are more connected with each other than with the rest of the network.



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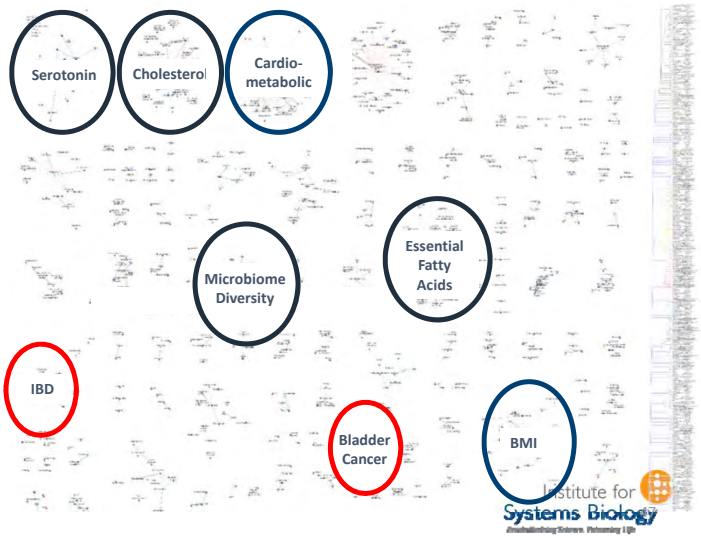
Identification of Multi-Omic 'Functional Modules' in the Correlation Network

Metabolism

Biomarkers

Diseases



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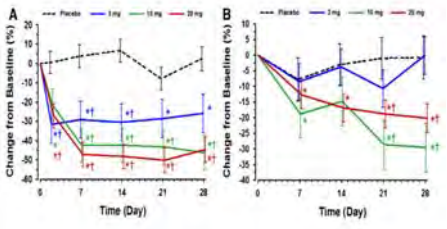
Association of FGF-21 and 'Cardiometabolic' Community

Triglycerides

LDL cholesterol

'Cardiometabolic' community



Red: Negative Coefficient Blue: Positive Coefficient

Gaich, G. et al (2013). The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. Cell Metab. *18*, 333–340.

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Association of FGF-21 and 'Cardiometabolic' Community

We identified a significant negative relationship between the protein Fibroblast Growth Factor 21 and levels of triglycerides, HOMA-IR, and c-peptide.

FGF21 is a recently discovered metabolic regulator. Obese diabetic patients treated with an FGF21 analog showed improvements (decreases) in triglycerides and LDL cholesterol. **This analog is in clinical trials by the pharmaceutical company Eli Lilly (A Study of LY2405319 in Participants With Type 2 Diabetes).**

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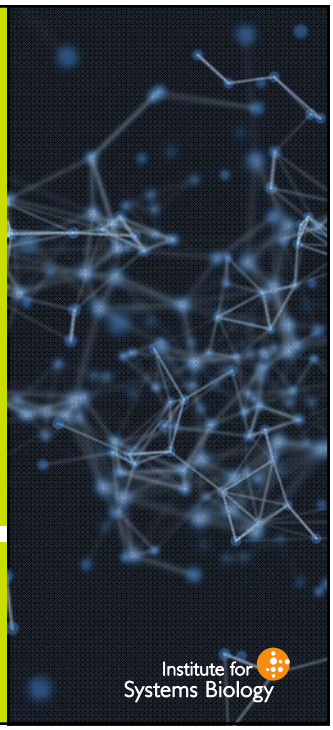
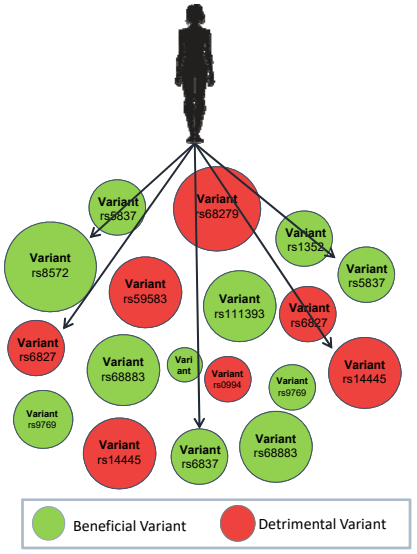
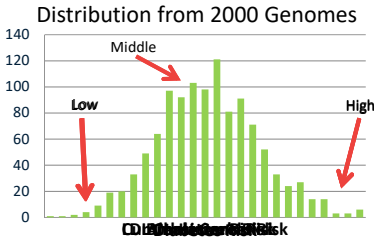
We can determine your genetic risk for at least 60 diseases.



GWAS Variants Have Been Determined for About 60 Diseases and Traits





Estimated **risk** for the disease or trait relative to a **population**

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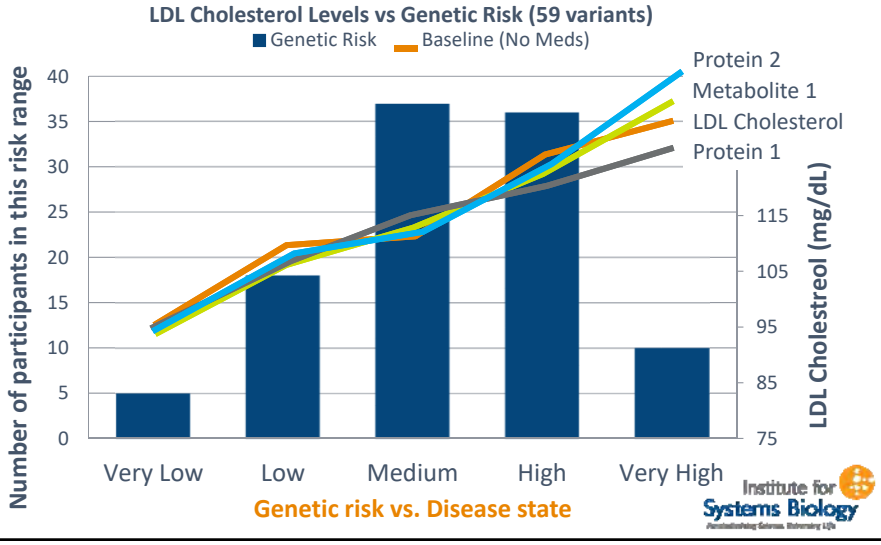
LDL cholesterol in Participants Shows Monotonic Relationship with 'Genetic Risk'



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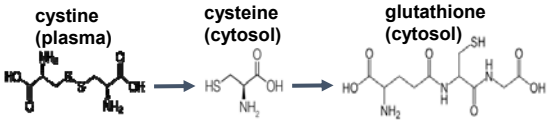
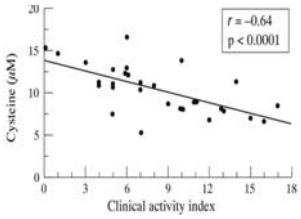
Cystine Negatively Correlated the Severity of IBD and with Genetic Predisposition for IBD

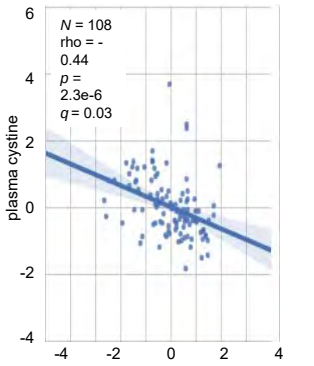


	Cystine
Control (n=65)	61.3 (1.7)
Crohn's disease (n=33)	
Before surgery	42.8 (2.4)***
10 days after surgery	56.0 (3.0)
3 months after surgery	52.7 (2.8)1-160
Ulcerative colitis (n=33)	
Before surgery	47.3 (1.8)***
10 days after surgery	64.3 (2.4)
3 months after surgery	64.5 (3.6)

Ulcerative colitis activity



Correlation of Risk



Nature Biotechnology (in press)

Sido, B., Hack, V., Hochlehnert, A., Lipps, H., Herfarth, C., and Dröge, W. (1998). Impairment of intestinal glutathione synthesis in patients with inflammatory bowel disease. Gut *42*, 485–492.

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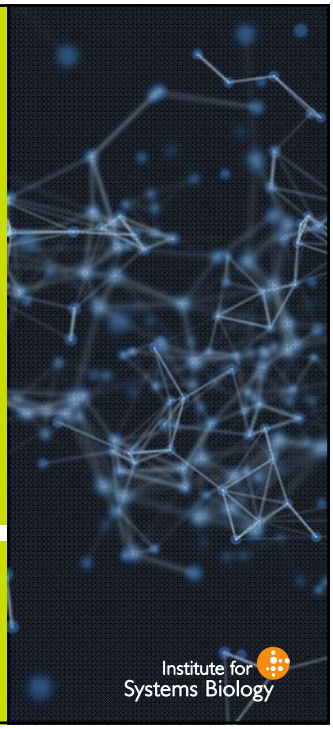
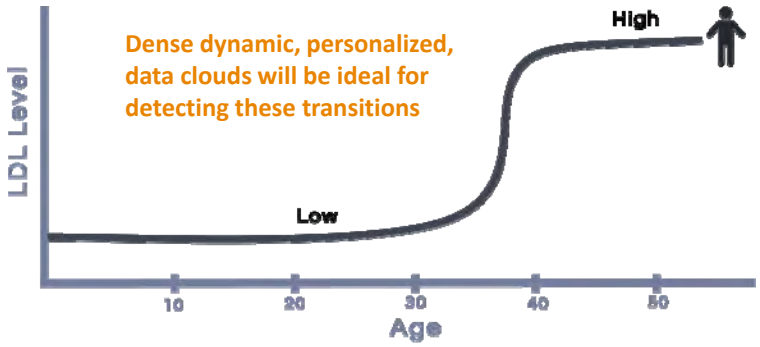
GWAS Variants Have Been Determined for About 60 Diseases and Disease Traits

ADHD	COPD	Myopia
Alzheimer's disease	Crohn's disease	Obesity
Anorexia	Esophageal cancer	Osteoarthritis
Asthma	Gout	Osteoporosis
Atrial fibrillation	Grave's disease	Ovarian cancer
Breast cancer	Hematocrit	Pancreatic cancer
Bipolar disorder	Hypertension	Parkinson's disease
Blood pressure	Hypothyroidism	Primary biliary cirrhosis
Bone mineral density	Inflammatory bowel disease	Prostate cancer
Inflammation	Iron levels	Psoriasis
Calcium	Lung Cancer	Rheumatoid arthritis
Cardiovascular disease	Lupus	Schizophrenia
Celiac disease	Macular degeneration	Stroke
Cholesterol levels	Magnesium levels	Type 1 Diabetes
Chronic kidney disease	Metabolic syndrome	Type 2 Diabetes
Colorectal cancer	Migraine	Ulcerative colitis
Coronary heart disease	Multiple sclerosis	Urate levels

State Transitions: Wellness to Disease



At Middle Age, We Begin to See Increasing Numbers of Wellness to Disease (or Disease Phenotype) Transitions



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Early Wellness to Disease Transitions: Arivale

Disease	Diagnosed	Pre-diagnosis blood draws*	Post diagnosis blood draws*
Diverticulosis	February 2017	1	0
Prostate cancer	June 2016	5	2
Melanoma	January 2017	3	0
Aortic aneurysm (fatal)	September 2016	3	-
Hypertension	February 2017	7	0
Hypertension	March 2017	5	0
Eosinophilic esophagitis	February 2016	1	3
Melanoma	September 2016	1	0
Colon Cancer	September 2016	2	0
Oral cancer	June 2016	1	1
Squamous cell carcinoma	December 2016	2	0
Hemorrhagic stroke	March 2017	2	0

* Approximately 6 months between draws

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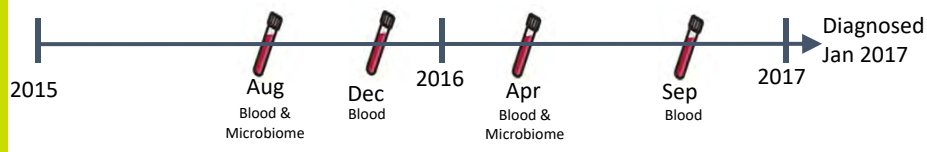
Pioneer Diagnosed with Stage 4 Pancreatic Cancer

- Female, 57 years old, Caucasian, non-Hispanic
- Diagnosed January 2017
- Four historical blood draws and two microbiome samples available

Can we find anything detectable in plasma that could have indicated the cancer was present?



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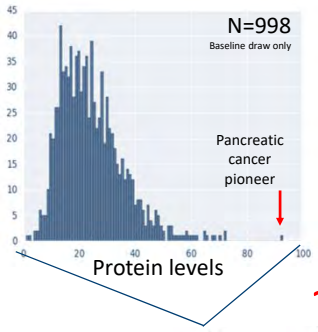
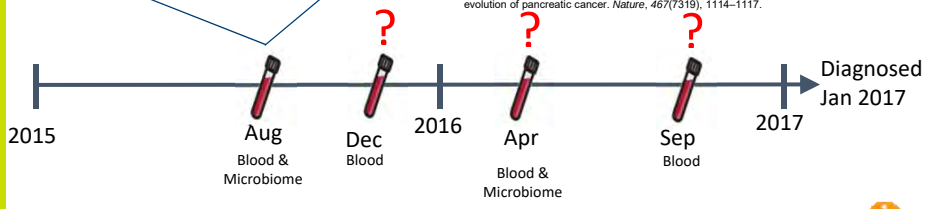
Pioneer Diagnosed with Stage 4 Pancreatic Cancer



- Notch signaling pathway
- Regulator of cell growth and neuroendocrine differentiation
- Expressed in beta cells of the islets of Langerhans in the adult pancreas
- Early immunotherapy for a cure ?

A 2010 study by Bert Vogelstein estimates at least 5 years between parental, non-metastatic founder cell and metastatic ability in pancreatic cancer.

Yachida, S et al. (2010). Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature*, *467*(7319), 1114–1117.



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Early Disease Reversal:

Preventive Medicine of the 21st Century

- In following 10,000 or more patients over an extended time period, we will start to see wellness to **early disease transitions** for all common diseases (as measured by blood analytes).
- Use systems approaches to develop blood biomarkers for early transitions for each disease and disease-perturbed network biology for therapies to reverse the disease at the earliest transition.
- Thus individuals will have diseases reversed before the diseases manifest themselves a disease phenotype—preventive medicine of the 21st century.

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State Transition:
Aging

Quantitative Blood Metrics for Wellness

- Two approaches
  - Follow individuals from wellness to greater wellness and follow what changes in the data clouds. Promising possibilities with blood proteins and metabolites.
  - Follow individuals as they age (variability in range of omic measurements increases significantly)
- We believe that we can do this for both physiological and psychological wellness
- Physiological vs. chronological age
- These approaches will provide powerful metrics against which wellness improvements for individuals can be assessed.

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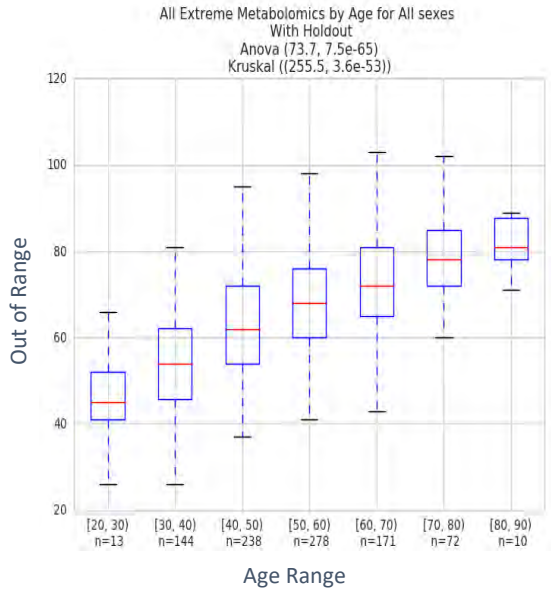
Observe Increasing Range of Divergence of Metabolites with Age



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Providence St. Joseph Health & ISB Affiliation

- *ISB is the research arm of Providence*
- *Lee Hood is SVP and Chief Science Officer of Providence*
- *Initiating Translational Pillars*
- *Bringing P4 medicine to physicians and healthcare professionals*
- *Bringing P4 medicine to patients*
- *Develop an appropriate technology platform*

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ISB & Providence St. Joseph Health Affiliation

Alaska, California, Oregon, Montana, Washington, New Mexico, Texas

States served	7
Hospitals	50
Physicians	7500
RNs	36,000
Unique patients served each year	5 million
Total Assets	$20 billion

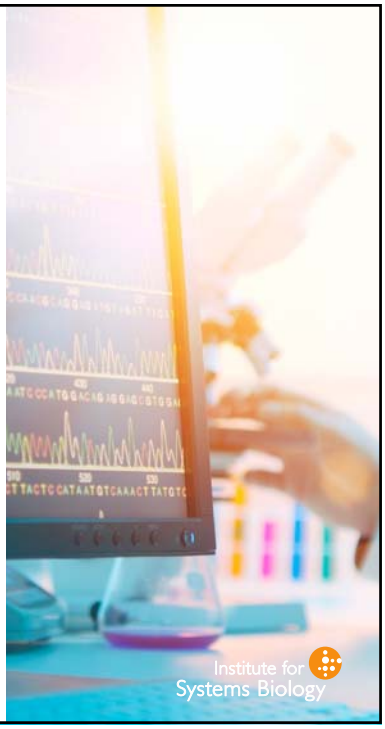
Largest not-for-profit healthcare system in the US
Integrated Medical Electronic Health Records for 30 million patients

Translational Pillars

1. Scientific wellness
2. Alzheimer's
3. Type 2 diabetes
4. Glioblastoma
5. Wellness for breast cancer survivors
6. Liver disease
7. Multiple sclerosis

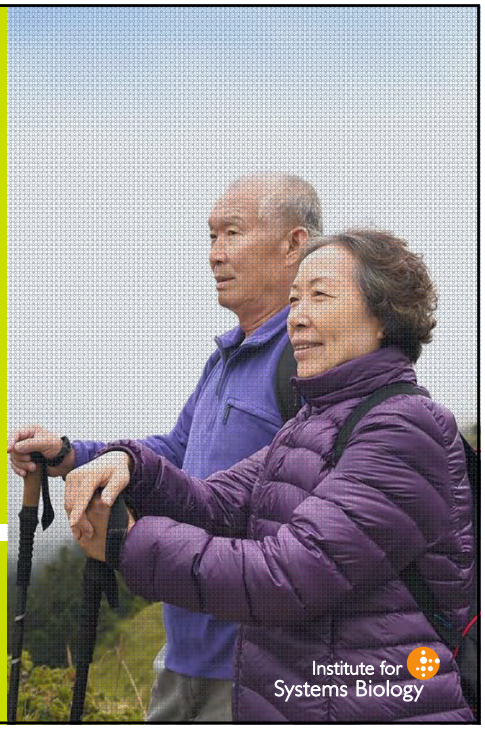
Strategies

Systems-driven technologies and strategies
Dense, dynamic, personal data clouds



TRANSLATIONAL PILLAR:

Scientific Wellness



TRANSLATIONAL PILLAR:

Alzheimer's Disease

The Future of Healthcare

- Bringing P4 medicine and scientific wellness to the healthcare system
- Precision medicine—employ dense, dynamic data clouds for each individual to allow one to explore interactions between genetics and environment
- Optimize wellness through actionable possibilities
- Reverse disease at its earliest transition point: Prevention of the 21st century
- Scientific Wellness: A lifetime journey
- Healthcare costs dramatically reduced
- Creation of a Scientific Wellness Industry
- Transformation of biotech, pharma, diagnostic, nutrition industries
- Democratization of healthcare

ISB Hundred Person Wellness Project: Team

Special thanks to our funders: Robert Wood Johnson Foundation, M.J. Murdock Charitable Trust, Maveron and ISB

Project Leadership
- Leroy Hood, MD, PhD
- Nathan Price, PhD
- Clayton Lewis
- Sean Bell, Business Director

Participant Engagement
- Jennifer Lovejoy, PhD, VP Clinical Affairs
- Sandi Kaplan, Wellness Coach
- Craig Keebler, MD, Study Physician

Data Analytics
- Nathan Price, PhD – Analytics Lead
  Gustavo Glusman, PhD, Genomics
- Andrew Magis, PhD, Multi-omics
- John Earls, Data integration

Project Management
- Kristin Brogaard, PhD Project Manager
- Sara Mecca, Project Assistant
- Mary Brunkow, PhD, Project Coordinator

Communications
- Gretchen Sorenson, Consultant
- Hsiao-Ching Chou, Comm. Director

Medical Advisory Board
- Robert Green, MD
- Jane Guiltinan, ND
- Michael Raff, MD
- Sarah Speck, MD
- Gil Omenn MD

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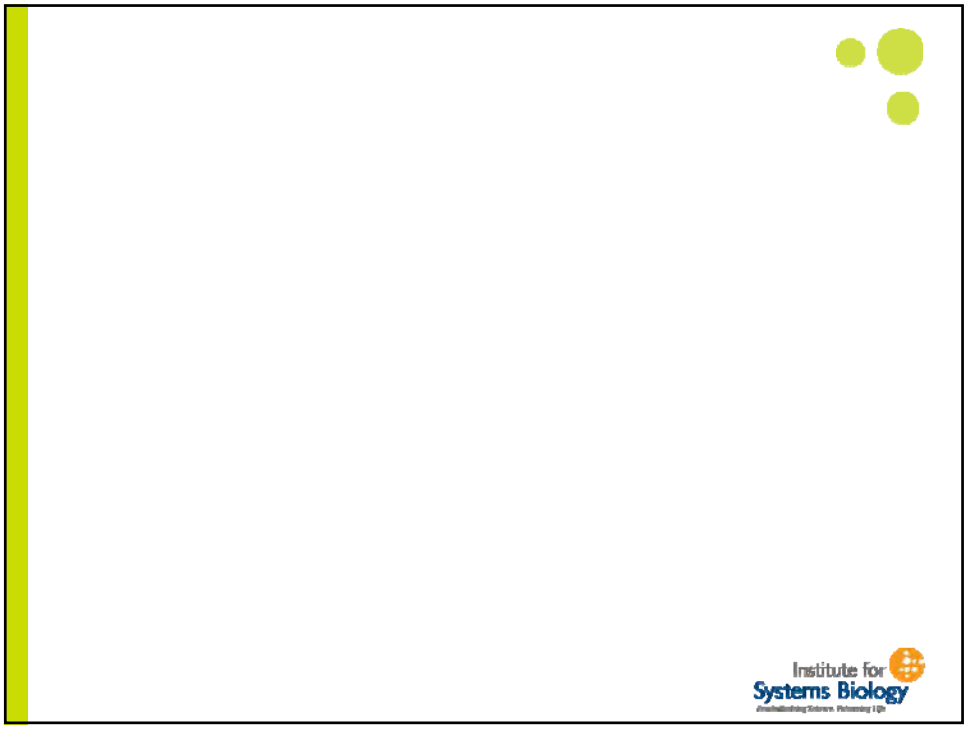
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Systems Biology
Non-profit scientific research organization founded in 2000
2017
• 10 faculty, 200 staff
• $35 million annual budget
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Inventing the Future with Systems Biology

- **Reductionist**
  Analyzing one gene and one small problem at a time

ISB FOUNDED in 2000

- Integrative Systems Analysis
- Systems-Driven Technology and Systems-Driven Strategies
- Pioneering Computational Tools
- Cross-Disciplinary Environment
- Employs Big Science to Attack Large-Scale Integrative Biological Problems
- Strategic Partnerships
- Transferring Knowledge to Society

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I Participated in Seven Paradigm Changes in Biology Dealing with Complexity

1970 — 1 — Brought engineering to biology

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Six Instruments Developed by Hood Laboratory

1970 — 1 — Brought engineering to biology

1. **Protein Sequencer**
   Caltech—**Applied Biosystems**
2. **Protein Synthesizer**
   Caltech—**Applied Biosystems**
3. **DNA Sequencer**
   Caltech—**Applied Biosystems**
   DNA Synthesizer
   Caltech—**Applied Biosystems**
4. **Ink-jet oligonucleotide DNA synthesizer**
   MBT/UW—**Rosetta** then Agilent
5. **Nanostring nCounter**
   ISB—**Nanostring**

***Hood startup companies**

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It will be important to measure complex phenotypes in the future—to assay the contributions of multiple systems to wellness (and disease)

- Heart rate variability
- Computer key board strokes
- Facial recognition analyses
- EEG—longitudinal analyses of brain waves
- EKG—longitudinal analyses of heart waves
- Whole body imaging—omics blood analyses will eliminate signal to noise problems

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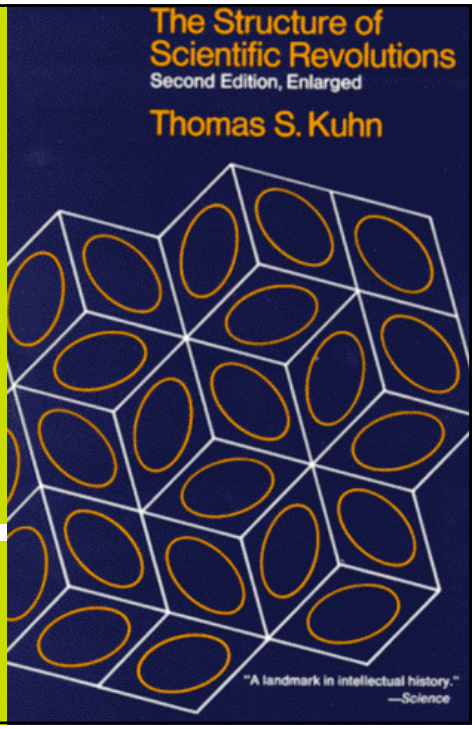
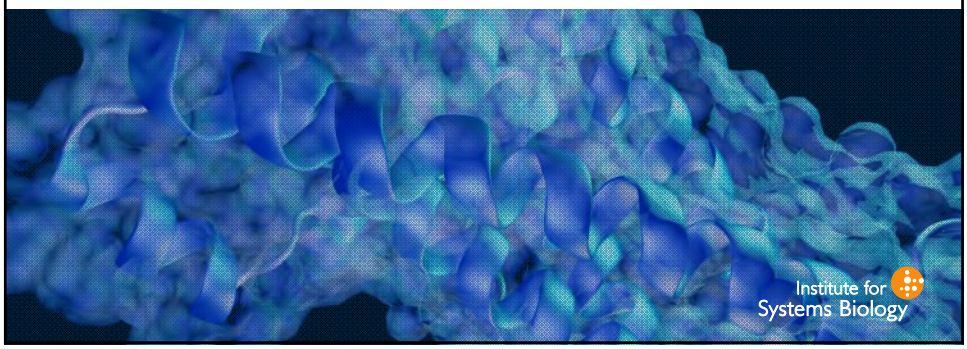
Paradigm Shifts Drive Radical Changes *in Science*



Organ-Specific Blood Proteins: Blood As a Window Into the Dynamics of Human Biology and Disease

Shizen Qin, Yong Zhou, Lee Hood



Organ-Specific Blood Transcripts (Proteins)

20 protein and transcriptome data bases employed

Organs	Number of Transcripts
adipose	9
brain	746
Breast	15
colon	46
esophagus	19
heart	80
kidney	131
liver	301
lung	68
overay	14
pancreas	66
placenta	100
prostate	19
skeletal muscle	124
skin	166
small intestine	38
uterus	12

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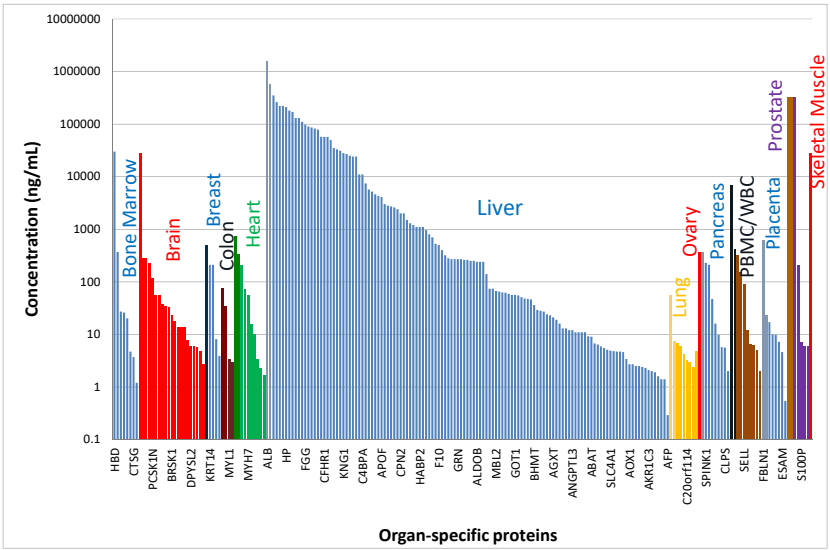
Organ-Specific Proteins Covering a Dynamic Range of Six Order of Magnitude in Blood

PeptideAtlas MS Data



Organ-Specific Transcripts and Proteins

- Identified organ-specific (organ-enriched) transcript lists for **19** major human organs (**1600** transcripts from more than 20 different protein and transcriptome databases)
- Developed refined SRM assays to measure OSPs in the blood–**745** proteins/**1,421** peptides, and identified **211** proteins from **19** organs
- Why organ-specific proteins are missing in blood–two reasons--low levels or are not in blood
- Used to study liver fibrosis, liver toxicity and Lyme Disease (5 organs affected)
- Our goal is to develop a single blood-based test to monitor about 50 major organs with 10-20 organ-specific proteins for each organ as a wellness assay
- **Blood as a window into the dynamics of human biology and disease**

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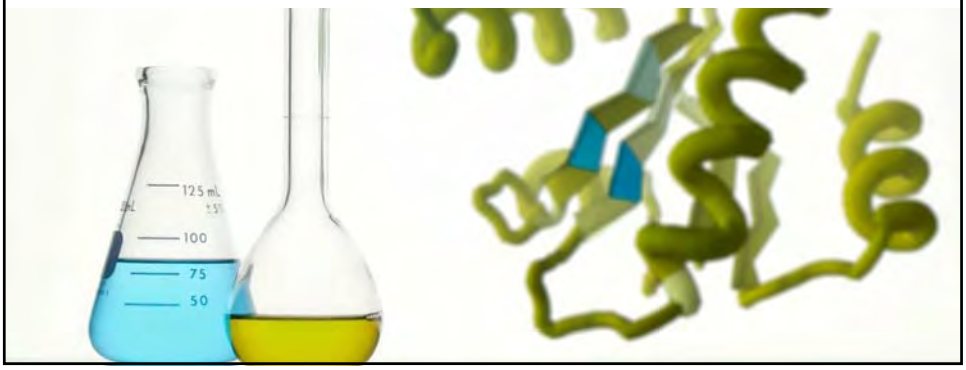
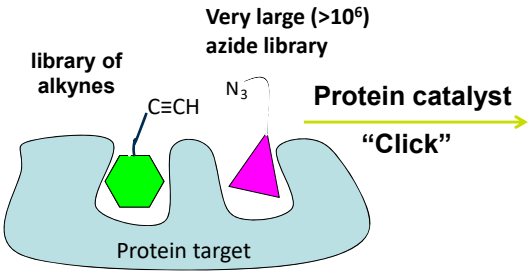
Peptide Protein-Capture Agents will Replace Antibodies

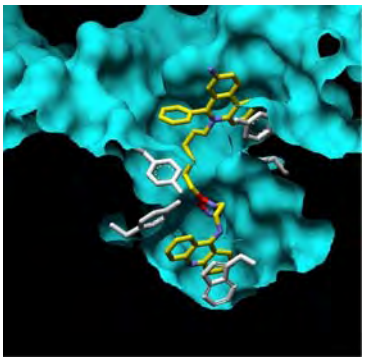
Jim Heath, Caltech

Indi Molecular



Circular 5-mer D Amino Acid Peptides are Positioned on a Protein and Joined Together with Click Chemistry





Protein selectively couples only those peptide library elements that fit onto its surface in just the right fashion

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Peptide Protein Capture Agents–Features

- **Stable**—send to Africa in an envelop
- **Sensitive**—each monomer a log increase in sensitivity
- **Digital**–synthesize unlimited quantities
- **Minimum cross reactivity**--can be precisely directed at epitopes—hence avoids much of the cross-reactivities that plague antibodies
- Can be adapted to **large-scale production** through automation—easy to produce
- Functions
  - In vitro diagnosis
  - In vivo diagnosis
  - Therapeutic reagents—possibly lacking cross reactivities
- Prediction—will replace monoclonal antibodies with 10-15 years

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Understanding Scientific Wellness is Key
More than half of all children born today in developed countries can expect to celebrate their 100th birthday.
Christensen, Ageing Populations: The Challenges Ahead, Lancet , 2009
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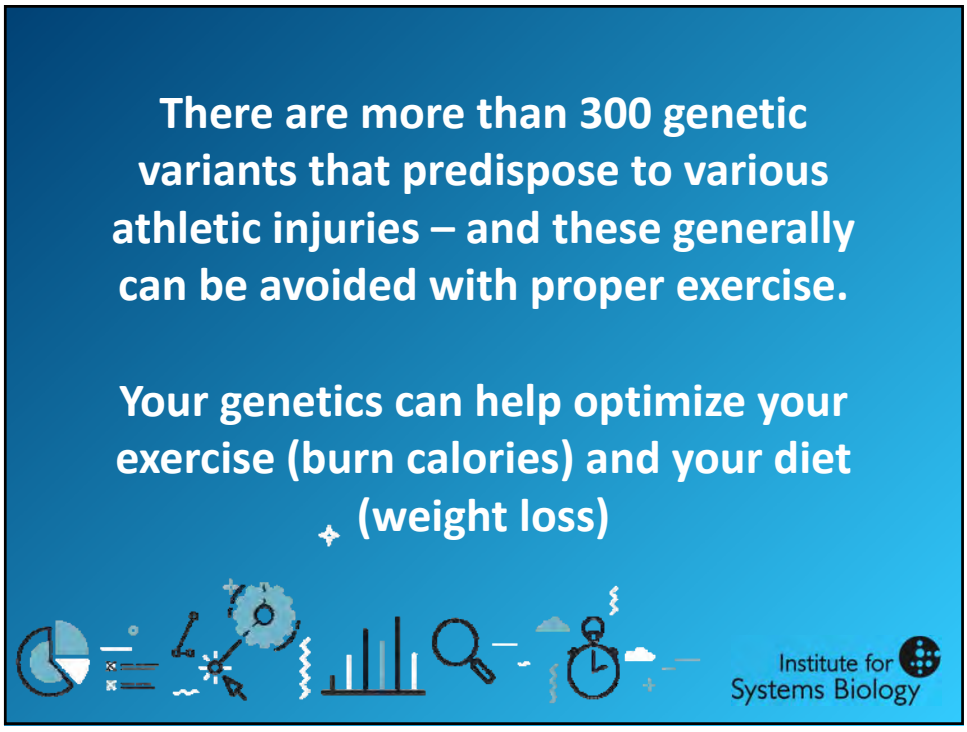
There are more than 300 genetic variants that predispose to various athletic injuries – and these generally can be avoided with proper exercise.
Your genetics can help optimize your exercise (burn calories) and your diet (weight loss)
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Increasing Loss of Ability to Concentrate and Motivation for a High-Powered Science Career

Almost no blood iron

Actionable Possibility: Replace blood iron and reverse symptoms within weeks

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Three Pioneers Had High Levels of Blood Mercury

Potential harm: Brain damage

Actionable Possibility: Do not eat tuna sushi & replace amalgam fillings

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Arivale Management

- Clayton Lewis – CEO
- Sean Bell – CBO
- Jennifer Lovejoy – CTSO
- Michael Kaplan – Director, Clinical Science
- Andrew Magis – Sr. Bioinformatics Scientist
- Isabelle Lucas-Beckett – Translational Geneticist
- Sandi Kaplan – Sr. Director, Coaching
- Ashley Wells – Director, Product Development

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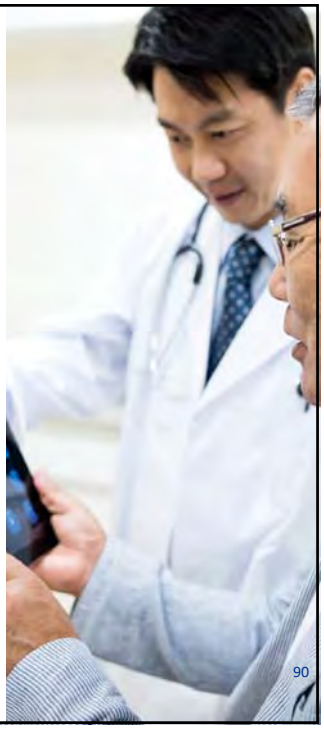
Democratization of Scientific Wellness

- Todays major limitation for scientific wellness is the cost of the assays
- In 10 years, the annual cost of scientific wellness will decline from $5,000 to less than $100
- Avatars and apps will leverage wellness coaches and digital devices are emerging for measurements of simple and complex phenotypes
- Scientific wellness will be covered by health insurance and government payers.
- This coverage will allow the poor, middle-class and rich to be covered for scientific wellness



Scientific Wellness Will Strikingly Reduce Healthcare Costs

- Optimize wellness—and thus avoid many initial disease transitions
- Identify diseases in newly enrolled pioneers and reverse them early—hemachromatosis, diabetes, cardiovascular disease, etc.
- Identify and reverse earliest disease transitions before they manifest as disease phenotype—preventive medicine of 21st century
- Increasing inexpensive digital devices measure simple and complex phenotypes—useful in reducing dimensionality of assays
- Increasing knowledge of wellness will allow us to focus and target measurements—again reducing dimensionality from billions to say 5,000
- Moore's law decline in cost of wellness assays—with miniaturization, parallelization, integration, automation, etc.
- Follow closely potential early disease transitions in individuals at high risk for particular diseases
- Metrics for wellness—helping to efficiently optimize wellness for individual
- Healthcare 20% GNP; 86% healthcare dollars are spent on chronic disease
- Scale of obesity, diabetes, etc.
- Over whole life—prevent Alzheimer's, diabetes, cardiovascular, etc
- Value of that data for discovery of improved healthcare and transformation of the healthcare industry. Many factors in calculus of $s savings

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Strategic Partners in First Translational Pillars

- **ISB**—project design, analytics, develop better assays (cheaper and low volumes sample), analytics
- **Providence**—clinical expertise, patients, electronic medical records
- **Arivale**—execute dense, dynamics, personal data clouds, coaching, analytics
- **MultiScale**—extract patient records from clinical data base (Epic) and place in cloud queryable by Jupiter work stations

Novel Approach to Drug Discovery– Creation of Large Synthetic Natural Products Library—and High Throughput Screens

Mike Tyers–Montreal

The Idea

- Synthesize a billion synthetic natural products rapidly
- Screen a library of a billion natural products for selected drug targets rapidly

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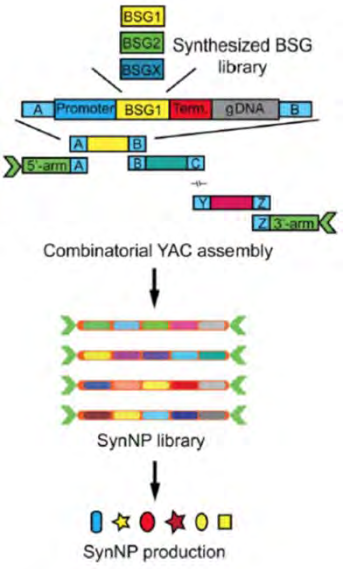
Genetically-Encoded Combinatorial Diversity Produced in Yeast Cell Microfactories



- Published biosynthetic genes (BSGs) across many NP classes optimized for GC content and synthesized at low cost
- BSGs reassembled in yeast artificial chromosomes (YACs) to create **chimeric biosynthetic pathways (BSPs) producing NP variants never observed in nature**
- Each BSP combination produces unique natural product-like compounds, termed synthetic natural products (SynNPs)
- Libraries are modular and are being continuously expanded (currently 1600 enzymes, >10^7 combinations)

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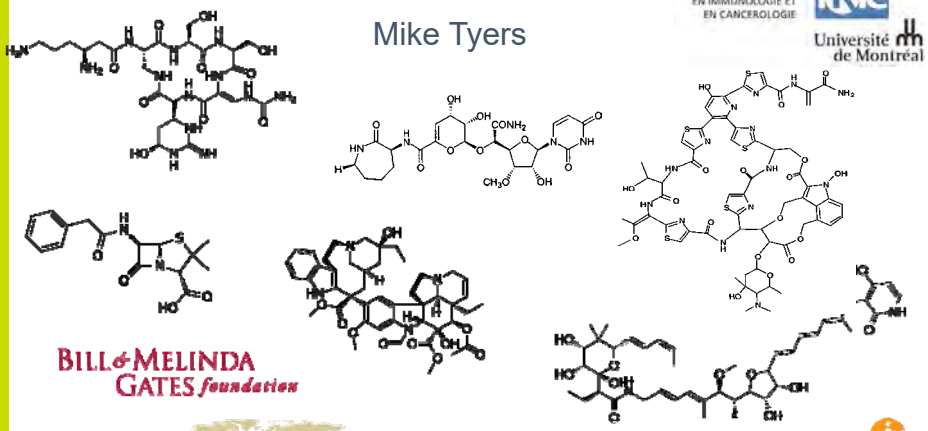
Synthetic Natural Products: A New Concept for Drug Discovery

Mike Tyers



INSTITUT DE RECHERCHE EN IMMUNOLOGIE ET EN CANCEROLOGIE
IRIC
Université de Montréal

BILL & MELINDA GATES foundation

Grand Challenges in Global Health

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70 Self-Reported Diseases/Conditions are Currently Represented in the Arivale Research Platform (1200 pioneers)

Allergy	32.2%	Type 2 diabetes	2.6%	Lupis	0.8%
High cholesterol	17.7%	Alcohol abuse	2.5%	Multiple sclerosis	0.8%
Arthritis/osteoarthritis	13.3%	Arthritis rheumatoid	2.5%	Gallbladder disease	0.7%
Gastroesophageal disease	13.0%	Gynecological other	2.4%	Epilepsy	0.7%
Hypertension	12.3%	Cancer other	2.3%	Blood transfusion	0.7%
Hypothyroidism	11.9%	Thyroid nodule	2.2%	Blood clot (leg)	0.7%
Sleep apnea	11.1%	Celiac disease	1.9%	Grave's disease	0.6%
Migraine	9.0%	Concussion	1.8%	Hepatitis A	0.6%
Depression	8.2%	Fibromyalgia	1.8%	Stomach ulcer	0.6%
Skin eczema	7.9%	Coronary artery disease	1.7%	Type 1 diabetes	0.5%
Asthma	7.4%	Glaucoma	1.7%	Recent heart attack	0.5%
Chicken pox	6.0%	Chronic fatigue syndrome	1.7%	Hip fracture	0.4%
Irritable bowel syndrome	5.2%	PTSD	1.6%	Stroke	0.4%
Fractures	5.1%	Kidney stones	1.6%	Blood clot (lung)	0.3%
Bladder disease	5.0%	Hyperthyroidism	1.5%	Emphysema	0.3%
Colon polyp	4.6%	Inflammatory bowel disease	1.5%	Hepatitis C	0.3%
Osteoporosis	4.1%	Pneumonia	1.5%	Ovarian cancer	0.3%
Skin abnormal moles	4.1%	Gout	1.4%	Prostate nodules	0.2%
Skin psoriasis	4.1%	Bipolar disease	1.4%	Hepatitis other	0.2%
Anemia	3.2%	Kidney disease	1.2%	Colon cancer	0.2%
Prostate enlargement	3.2%	Liver disease	1.1%	Hepatitis B	0.2%
Cataracts	3.1%	Gynecological endometriosis	1.1%		
Gynecological fibroids	2.9%	Lyme disease	0.9%		
Breast lump	2.8%	Prostate cancer	0.9%		
Diverticulosis	2.6%	Breast cancer	0.8%		

Translational Pillars

"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

Luxembourg: Catalyze the development of about 10 ISB technologies and systems-driven strategies with $100 million over 5 years.