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

The grand challenge for biology and medicine: Deciphering biological complexity
I Participated in Seven Paradigm Changes in Biology Dealing with Complexity

1. Brought engineering to biology
2. The Human Genome Project
3. Cross-disciplinary biology
4. Systems biology
5. Conceptualization of medicine: systems medicine/ P4 medicine
6. Scientific Wellness: Dense, dynamic personal data clouds
7. Bringing P4 medicine to Providence St. Joseph Health and the US Healthcare System

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

These data clouds provide insights into wellness and disease and provide the essence of what “Precision Medicine” should be.

Systems (P4) Medicine
The Network of Networks: Network Biology
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)

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
Discovery and Innovation Engine for Systems Biology

Working together:
- Biologists
- Chemists
- Computer Scientists
- Educators
- Engineers
- Mathematicians
- Physicians
- Physicists

Systems-Driven Technologies and Strategies
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 miniaturization
- Whole human genome sequence in 15 minutes for less than $100

Field Effect Nanopore Transistor Sequencer

Bharath Takulapalli
INanoBio Inc.
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

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

Disease Transition

Prion accumulation
Glial Activation
Synaptic Degeneration
Neuronal Cell Death

0 wk 7 wk 18~20 wk 22 wk

Clinical Signs

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

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

Systems-Driven Approaches to Blood Biomarker Discovery

Paul Kearney, Nathan Price, Lee Hood
Integrated Diagnostics & Institute for Systems Biology
Indeterminate Pulmonary Nodules

Is this cancer?

~3 million cases annually in the USA

Patrick Nana-Sinkham, MD  Ohio State University

Integrated Diagnostics

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.
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 than $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

Single Cell Analyses Following the Development of iPS Cells to Cardiomyocytes

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

- Systems Medicine
- Social Networks
- Big Data/Analytics
- Digital Revolution

P4 MEDICINE

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
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).


Conceptual Themes of P4 Medicine

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
**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

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**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
The 108 “well” participants had a high rate of initial abnormal lab results.

100% of the participants had actionable recommendations from their blood results.

**Initial Clinical Labs Discovery:**
High Rate of Actionable Clinical Results

- Cardiovascular: 59%
- Inflammation: 68%
- Diabetes Risk: 54%
- Nutrient Abnormalities: 91%
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
• Rickets – improper bone mineralization
• Increased risk of death from cardiovascular disease
• Cognitive impairment in older adults—Alzheimer’s
• Severe asthma in children
• Cancer

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
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.

Where Do You Reside On The Wellness Staircase?

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

Creation of a Consumer-Based Scientific Wellness Company

Arivale
Your scientific path to wellness
2015 LAUNCH
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
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

Statistical Correlations
Multi-Omic 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.

Substructures of the Correlation Network
Identification of Multi-Omic ‘Functional Modules’ in the Correlation Network

Metabolism

Serotonin
Cholesterol
Cardio-metabolic

Biomarkers

Microbiome Diversity
Essential Fatty Acids

Diseases

IBD
Bladder Cancer
BMI

Association of FGF-21 and ‘Cardiometabolic’ Community

Triglycerides
LDL cholesterol

IBD

Red: Negative Coefficient
Blue: Positive Coefficient

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).

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

LDL cholesterol in Participants Shows Monotonic Relationship with ‘Genetic Risk’
**Cystine Negatively Correlated the Severity of IBD and with Genetic Predisposition for IBD**

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

**Additional Text:**


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

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

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

Dense dynamic, personalized, data clouds will be ideal for detecting these transitions
Early Wellness to Disease Transitions: Arivale

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

* Approximately 6 months between draws

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?
Protein levels
• 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.


2015
Aug
Blood & Microbiome
Dec
Blood
2016
Apr
Blood & Microbiome
Sep
Blood
2017
Diagnosed
Jan 2017

Pioneer Diagnosed with Stage 4 Pancreatic Cancer

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.
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.
Observe Increasing Range of Divergence of Metabolites with Age

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
**ISB & Providence St. Joseph Health Affiliation**

- States served: 7
- Hospitals: 50
- Physicians: 7,500
- 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
Institute for Systems Biology
Non-profit scientific research organization founded in 2000

2017
• 10 faculty, 200 staff
• $35 million annual budget
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

I Participated in Seven Paradigm Changes in Biology Dealing with Complexity

- 1970: Brought engineering to biology
Six Instruments Developed by Hood Laboratory

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

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 keyboard 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
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

<table>
<thead>
<tr>
<th>Organs</th>
<th>Number of Transcripts</th>
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<tbody>
<tr>
<td>adipose</td>
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<td>brain</td>
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<tr>
<td>Breast</td>
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<tr>
<td>colon</td>
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<tr>
<td>esophagus</td>
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<tr>
<td>heart</td>
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<tr>
<td>kidney</td>
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<tr>
<td>liver</td>
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<td>lung</td>
<td>68</td>
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<td>ovary</td>
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<tr>
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<td>skin</td>
<td>166</td>
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<td>small intestine</td>
<td>38</td>
</tr>
<tr>
<td>uterus</td>
<td>12</td>
</tr>
</tbody>
</table>

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

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

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
More than half of all children born today in developed countries can expect to celebrate their 100th birthday.


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)
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

Three Pioneers Had High Levels of Blood Mercury

Potential harm: Brain damage

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

Democratization of Scientific Wellness

- Today’s 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

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
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)

Synthetic Natural Products: A New Concept for Drug Discovery

Mike Tyers

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Allergy</td>
<td>32.2%</td>
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<td>High cholesterol</td>
<td>17.7%</td>
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<tr>
<td>Arthritis/osteoarthritis</td>
<td>13.3%</td>
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<tr>
<td>Gastroesophageal disease</td>
<td>13.0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12.3%</td>
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<td>Chickenpox</td>
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<tr>
<td>Irritable bowel syndrome</td>
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<td>Bladder disease</td>
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<td>Cataracts</td>
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<tr>
<td>Gynecological fibroids</td>
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<td>Breast lump</td>
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<td>Diverticulitis</td>
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<td>Type 2 diabetes</td>
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<tr>
<td>Arthritis rheumatoid</td>
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<tr>
<td>Gynecological other</td>
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<td>Cancer other</td>
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<tr>
<td>Thyroid nodule</td>
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<td>Gout</td>
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<td>Hip fracture</td>
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<tr>
<td>Stroke</td>
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<tr>
<td>Blood clot (lung)</td>
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<tr>
<td>Emphysema</td>
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<tr>
<td>Ovarian cancer</td>
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<tr>
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<tr>
<td>Prostate nodules</td>
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<tr>
<td>Hepatitis other</td>
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<tr>
<td>Colon cancer</td>
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<tr>
<td>Hepatitis B</td>
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</tbody>
</table>

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.