Disease complexity and the emergence of proactive P4 medicine: convergence of the digital revolution and systems biology

Predictive, Preventive, Personalized and Participatory

Lee Hood, President
Institute for Systems Biology, Seattle

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In 10 years each individual will be surrounded by a virtual cloud of billions of data points—P4 medicine

TeleHealth

11010100
01010101
01101010
10100100

Phenome

Na143 K
3.7 BP
110/70
HCT32 BUN
12.9 Puls

Social Media

11010100
01010101
01101010
10100100

Epigenome

11010100
01010101
01101010
10100100

Genome

GCGTAG
ATGCGTA
GGCATGC
ATGCCAT

Transcriptome

UUAGUG
AUGCGU
CUAGGC
AUGCAU

Proteome

arg-his-pro-
gly-leu-ser-
thr-ala-trp-
tyr-val-
met-phe

Transactional

11010100
01010101
01101010
10100100

Single Cell

11010100
01010101
01101010
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iPS Cells

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01010101
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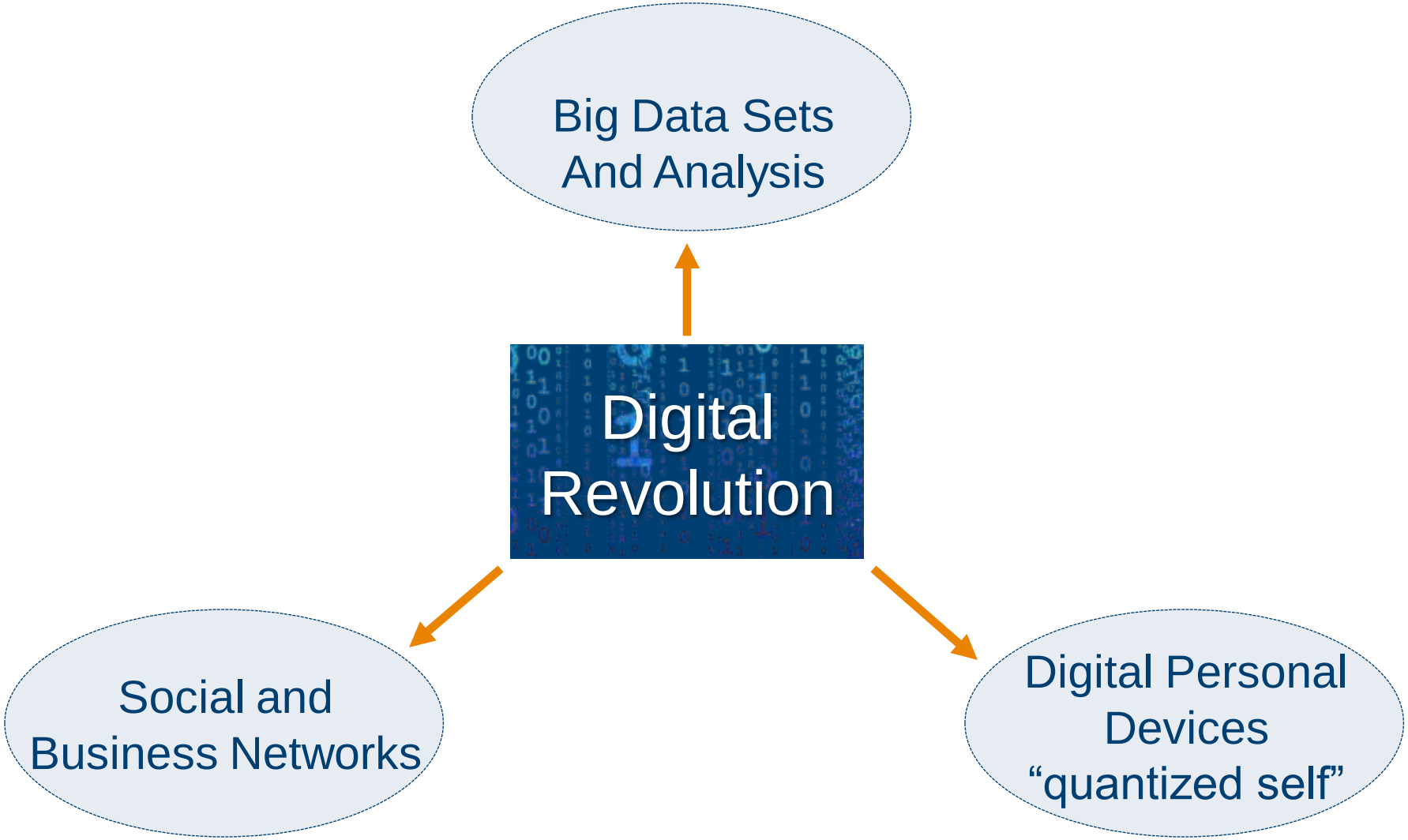
Healthcare and the digital revolution



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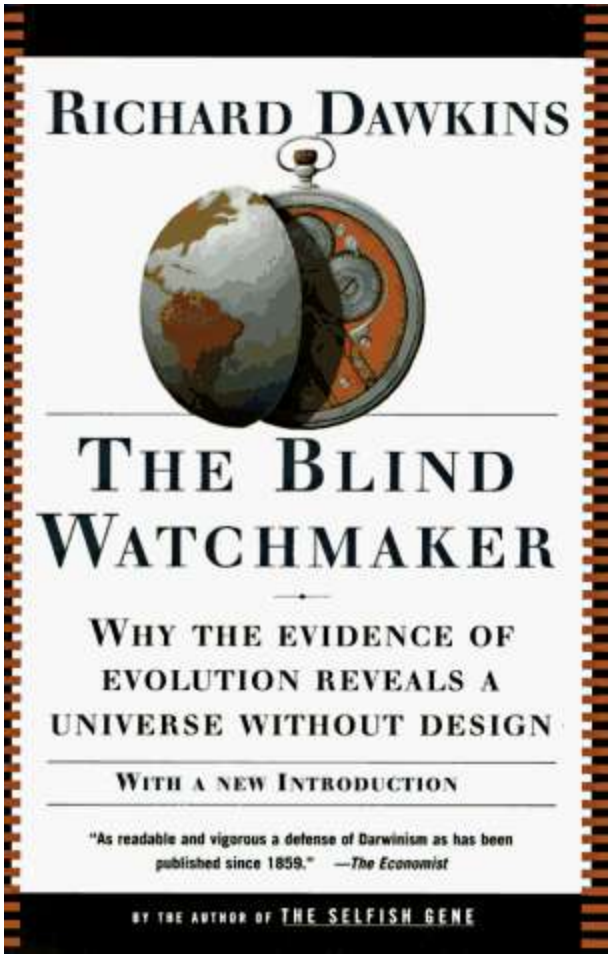
Evolution Generates Biological Complexity

Evolution arises from random mutations, is driven by environmental challenges and selects solutions building on past successes—no law of Occum's Razor



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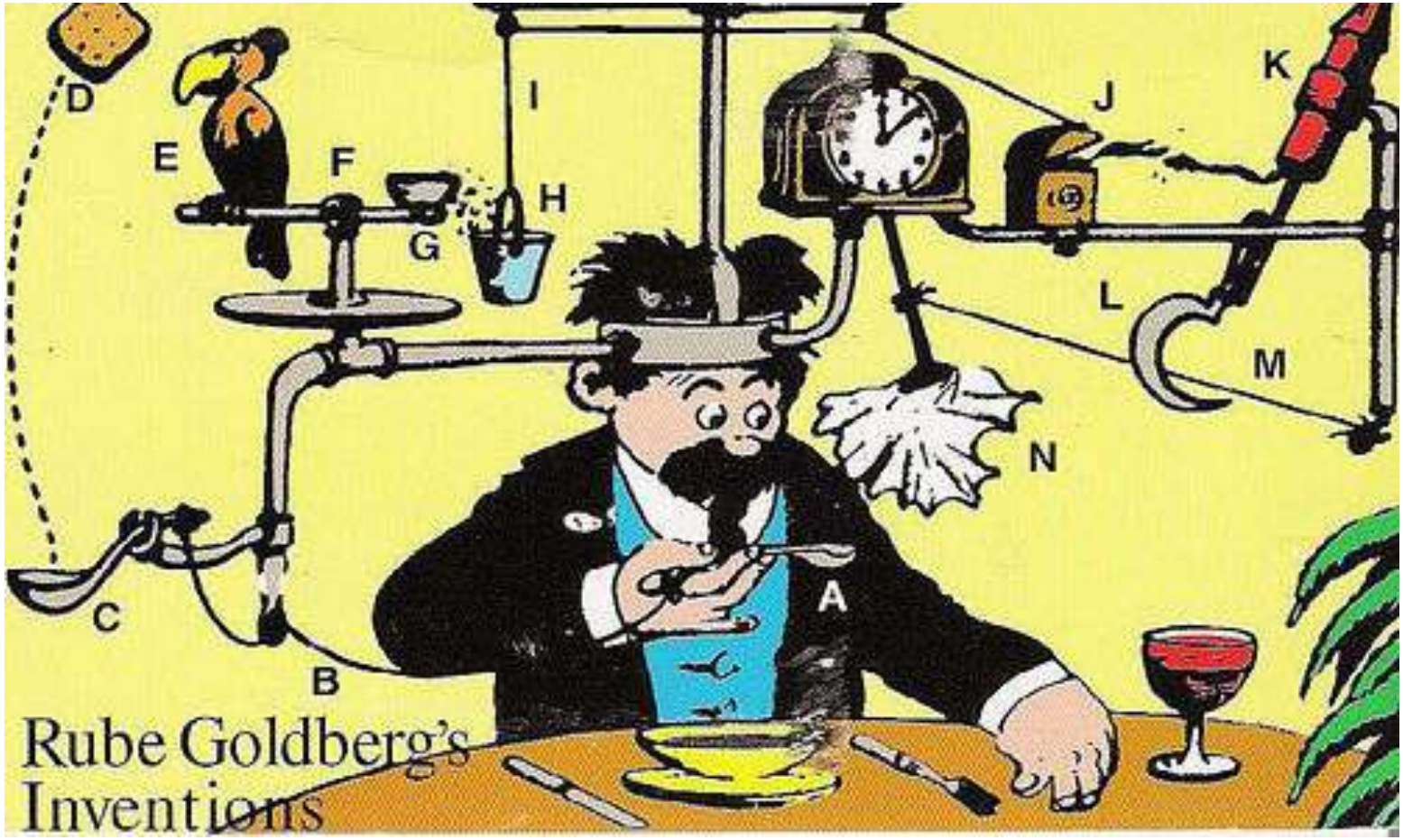
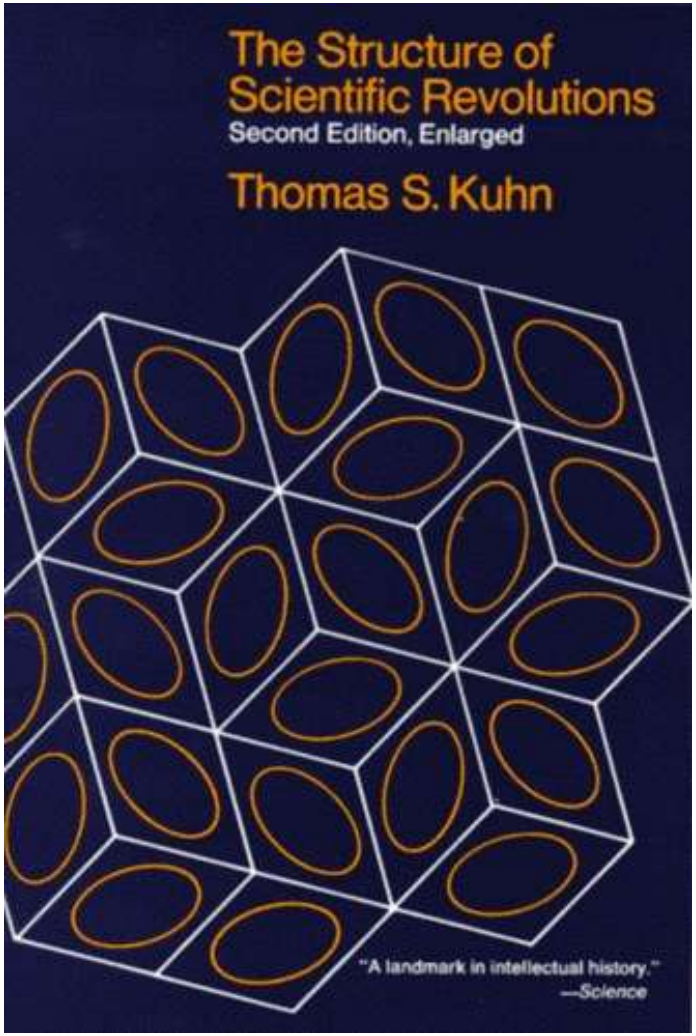
Evolution/Complexity in action



1. How many components?
2. How are they connected?
3. How do they move (dynamics) to cool the soup?

Paradigm Changes Drive Radical Changes in Science



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I Participated in Four Paradigm Changes in Biology over 40 Years Dealing with Biological Complexity Giving Rise to a 5th--P4 Medicine

- Bringing engineering to biology which catalyzed high throughput biology—DNA and protein sequencers and synthesizers
- Helping pioneer and implement the human genome project to democratize genes and create a complete gene parts list for systems biology
- Founding the first cross-disciplinary biology department to couple technology and analytical tool development to leading-edge biology
- Creating the first systems biology institute to present a holistic and integrated approach to dealing with biological complexity
- Conceptualizing and bringing to P4 medicine to patients—to quantify wellness and demystify disease

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Systems approaches to biology, medicine and complexity

- Systems biology—a holistic and integrative approach to biology: where frontier biology drives new technologies and these catalyze novel domain-driven and data-driven computational tools
- Systems medicine—the application of the strategies, technologies and computational tools of systems biology to disease and wellness
- P4 medicine—the clinical applications of systems medicine to patients
- Systems approach essential for deciphering complexity

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An Integrative Systems Approach to Disease Is the Key for Dealing with Complexity–Five Pillars

1. Viewing biology/medicine as an **informational science** is one key to deciphering complexity
2. **Systems biology infrastructure and strategies**— holy trinity of biology, cross-disciplinary culture, democratization of data-generation and data-analysis tools and the power of model organisms to simplify complexity
3. **Holistic, systems experimental approaches** enables deep insights into disease mechanisms and new approaches to diagnosis and therapy
4. **Emerging technologies** provide large-scale data acquisition and permit us to explore new dimensions of patient data space
5. **Pioneering analytic tools** **that** will allow us to decipher the billions of data points for the individual--sculpting in exquisite detail wellness and disease

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Biology and Medicine are Information Sciences

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Human Phenotypes are Specified by Two Types of Biological Information

- The digital information of the genome

- The environmental information that impinges upon and modifies the digital information

```
CCAGAAAGGC CGAGGCTCTG CAGCGGGAGG
GCAGGGCACA GGGACAGCCC CCCTCCACAG
CCAGGAGGTT GCTTCTTCCA GGAGGCTTTT
GCTCCCAGCT GCTGTGAGTG CTGCACATTC
CACTTCTGGT GCCCACTGTG GCCACAGCAA
GCCTCCTGGG GAGCTGCTGA CCCTAGGCAG
CACCCCAGTG TTTGCCAGTG TTTGCCCGTG
TTTGCTCGCC AGTGTTCGCC ACTTGTCCCT
GAAGTTGCAG GTCCCTCCAG GACAGTTGGC
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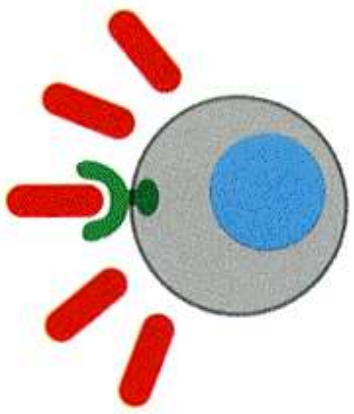
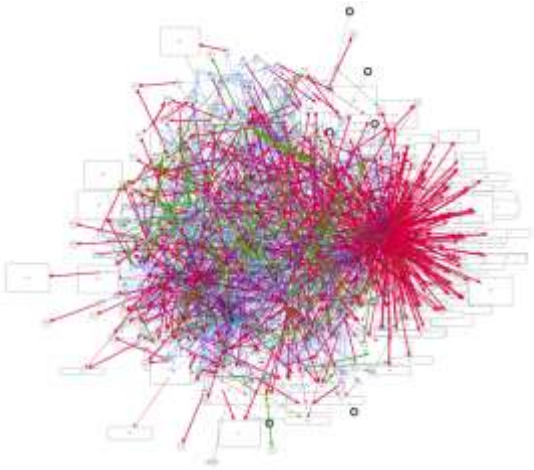
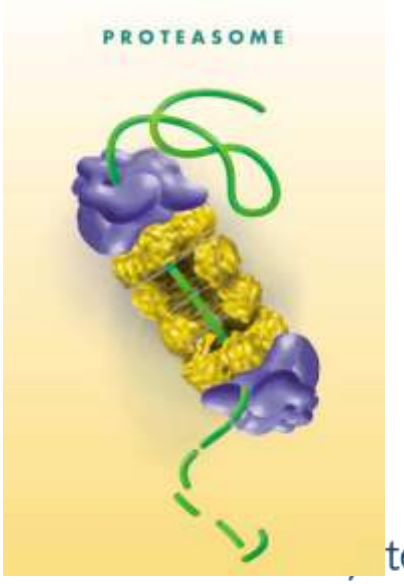


Two General Biological Structures Connect the Genotype/Environment and Phenotype

- Biological networks capture, transmit, process and pass on information
- Simple and complex molecular machines execute biological functions





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All Hierarchical or Multi-scale Levels of Biological Information—Are Modified by Environmental Signals

DNA

RNA

Protein

Protein interactions and biomodules

Protein and gene networks

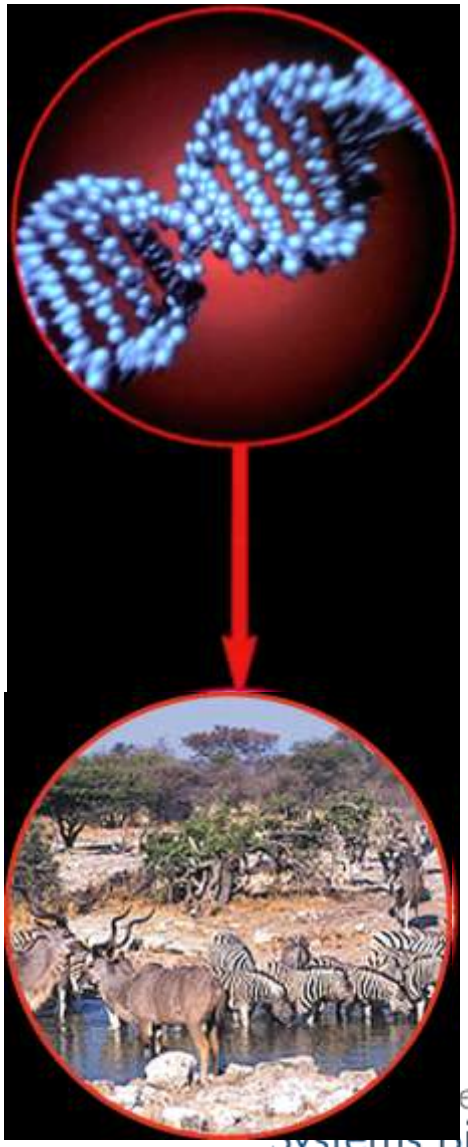
Cells

Organs

Individuals

Populations

Ecologies



Each omic technology will require a domain-driven software pipeline for acquisition, validation, storage, mining, integration, visualization and modeling

- Complete genome sequence (or partials)
- Epigenetic marks
- Transcriptomics
- miRNAomics (and other small RNAs)
- Proteomics
- Metabolomics
- Microfluidics measurements of molecules and cells
- Single-cell analyses—molecular and imaging
- In vitro and in vivo imaging
- Various high throughput phenotypic assays

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A Systems Approach to Disease Is the Key for Dealing with Complexity–Five Pillars

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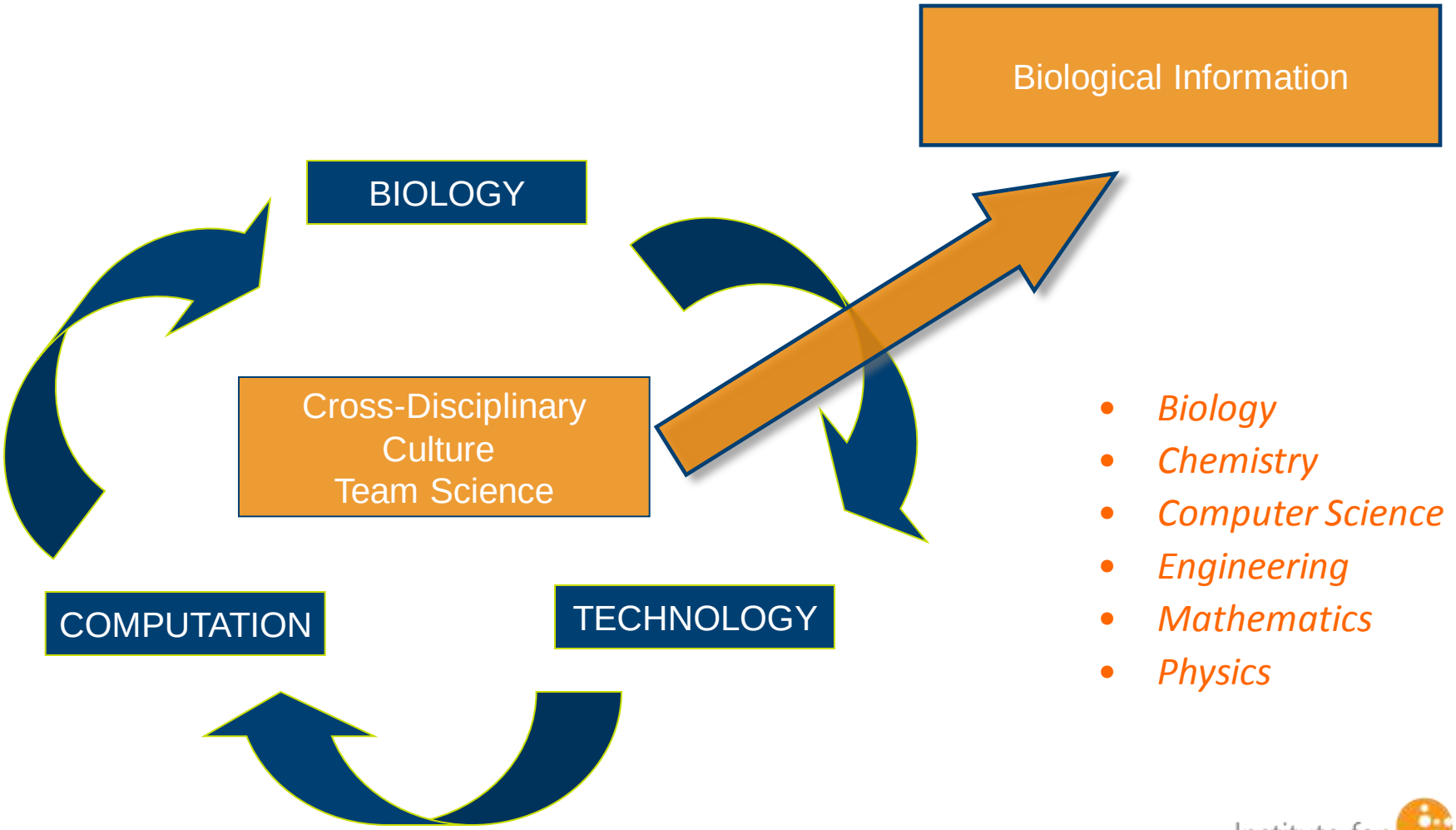
Holy trinity of biology/cross-disciplinary culture

Use biology to drive technology & computation.

Need to create a cross-disciplinary culture.



- *Biology*
- *Chemistry*
- *Computer Science*
- *Engineering*
- *Mathematics*
- *Physics*

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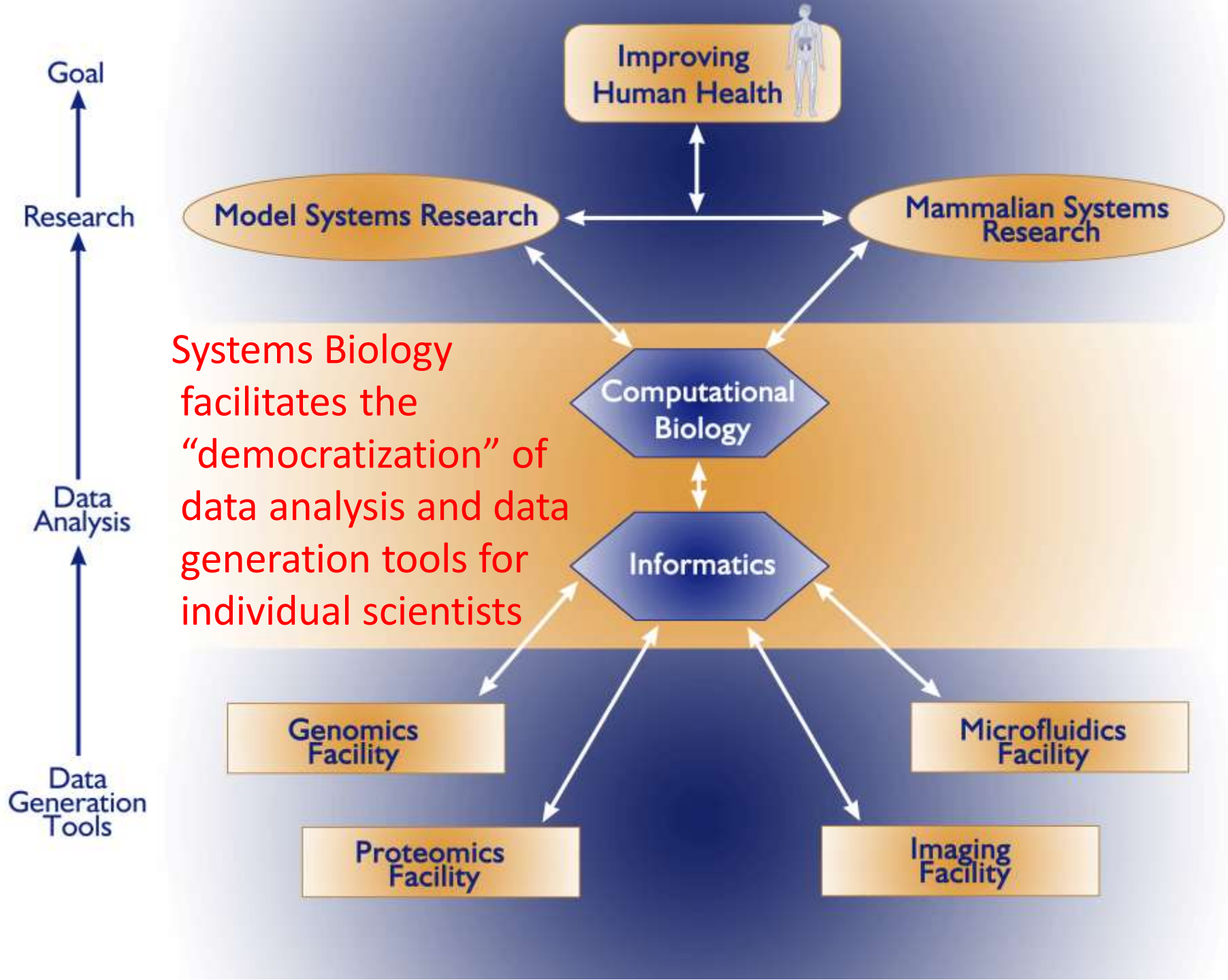
Goal
Research
Data Analysis
Data Generation Tools
Improving Human Health
Model Systems Research
Mammalian Systems Research
Computational Biology
Informatics
Genomics Facility
Microfluidics Facility
Proteomics Facility
Imaging Facility
Systems Biology facilitates the "democratization" of data analysis and data generation tools for individual scientists

A Systems Approach to Biology and Medicine Is the Key for Dealing with Complexity–Five Pillars

1. Viewing biology/medicine as an **informational science** is one key to deciphering complexity
2. **Systems biology infrastructure**—holy trinity of biology, cross-disciplinary culture and democratization of data-generation and data-analysis tools
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A systems approach to understanding a radio

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Radio Waves

Sound Waves

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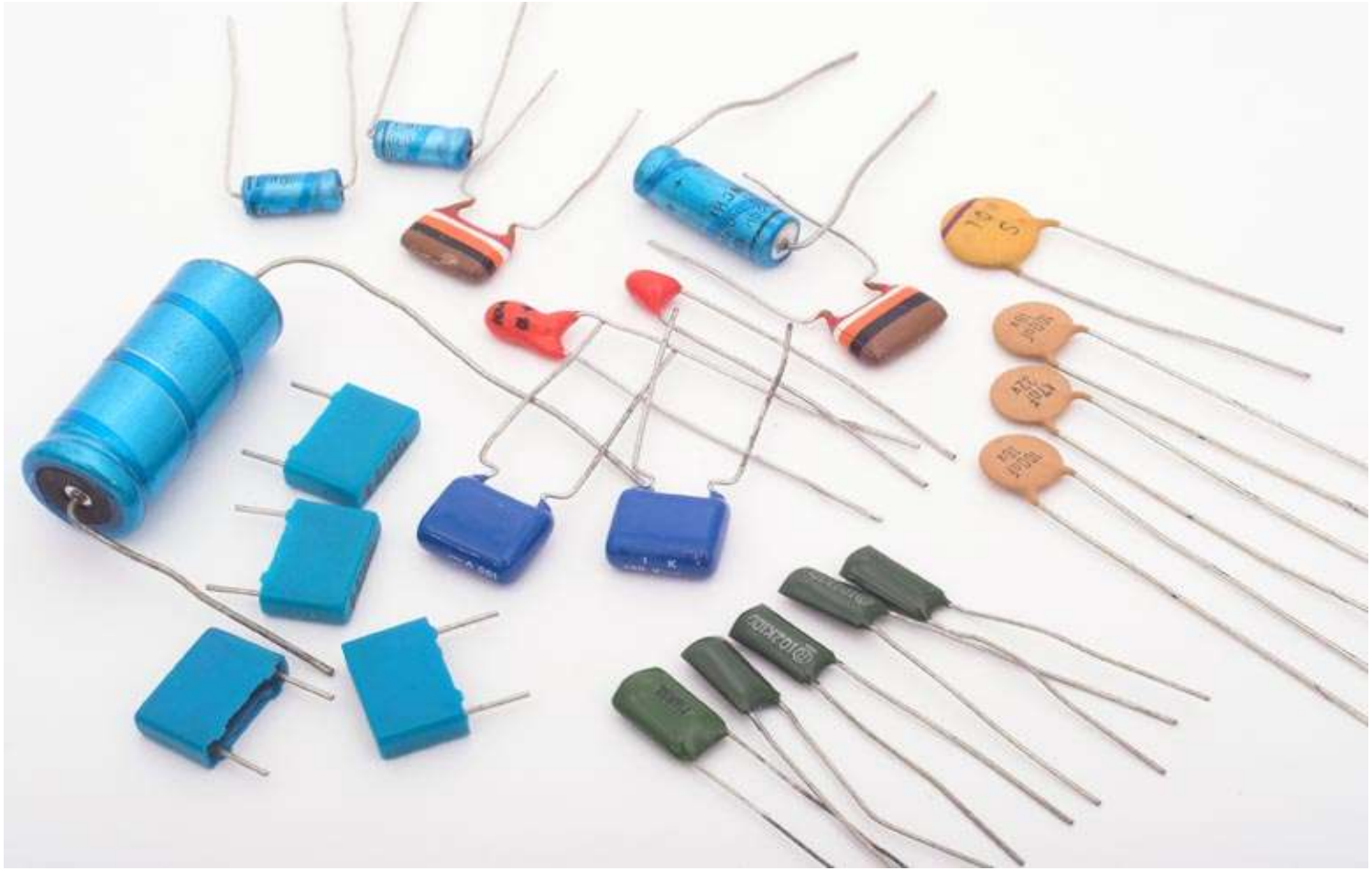

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Health →  → Disease

"networks of networks"

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Essentials of Systems Biology

- Create model from extant data—formulate hypotheses to test model through experimental perturbations of system--hypothesis-driven and hypothesis-generating—generate large data sets
- What are the necessary data features?
  - Global analyses of all components—DNA, RNA protein, etc.
  - Dynamics of systems—temporal and spatial
  - Integration of different data types from the system
  - Large data sets reflect two types of noise—biological and technical
  - Subtractive analyses using a deep understanding of biology and animal models to minimize “biological noise”
- Convert data into knowledge: formulate models, descriptive, graphical or mathematical, that are predictive and actionable.

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A Systems View of Disease

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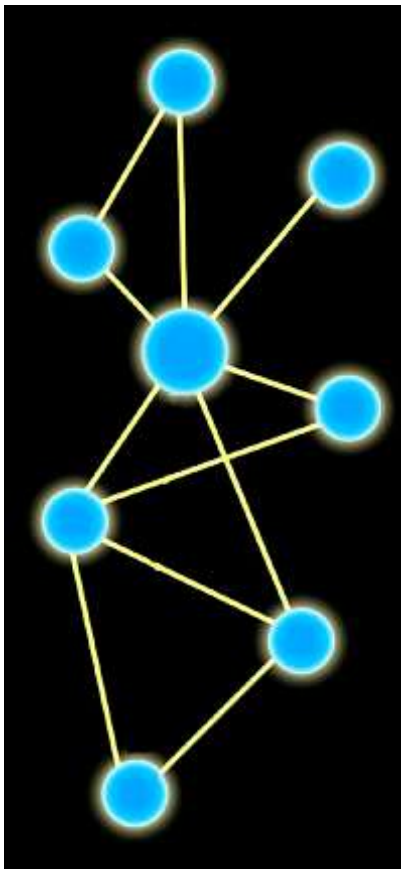
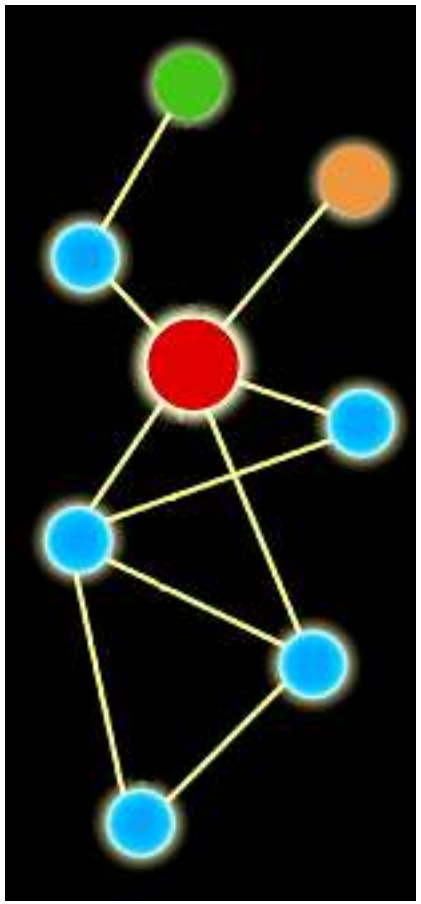
A Systems View of Disease Postulates that Disease Arises from Disease-Perturbed Networks





dynamics of pathophysiology

diagnosis

therapy

prevention

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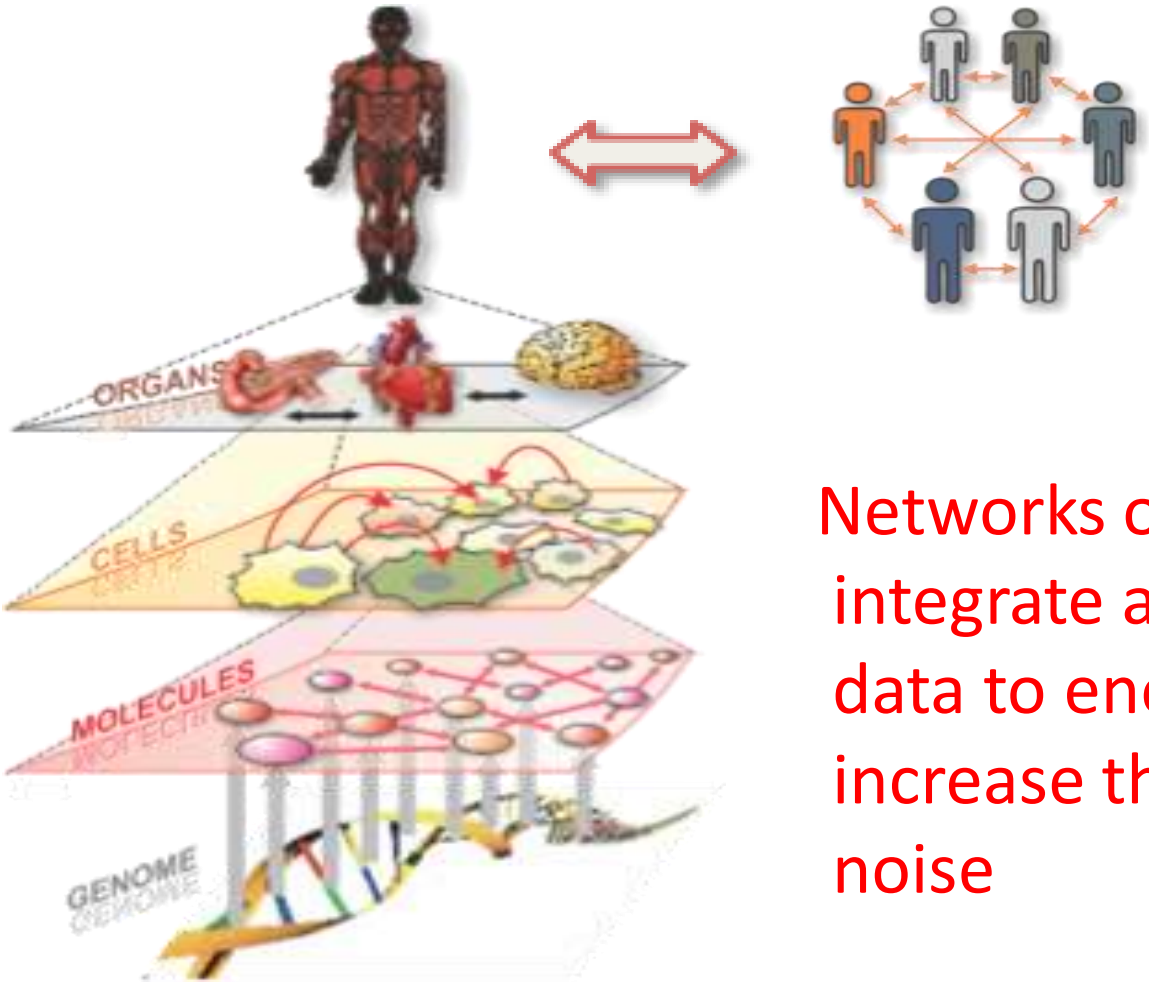
Systems medicine: network of networks



Networks organize, integrate and model data to enormously increase the signal to noise

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Systems approach to neurodegeneration in mouse model system (prion disease)

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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 w/ Prions

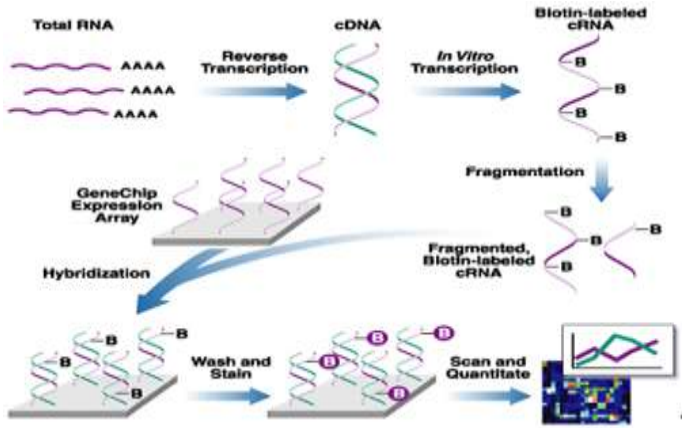
Prion infected brain

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

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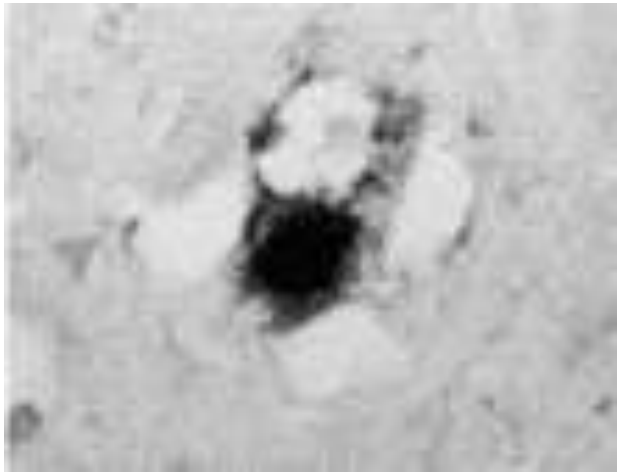
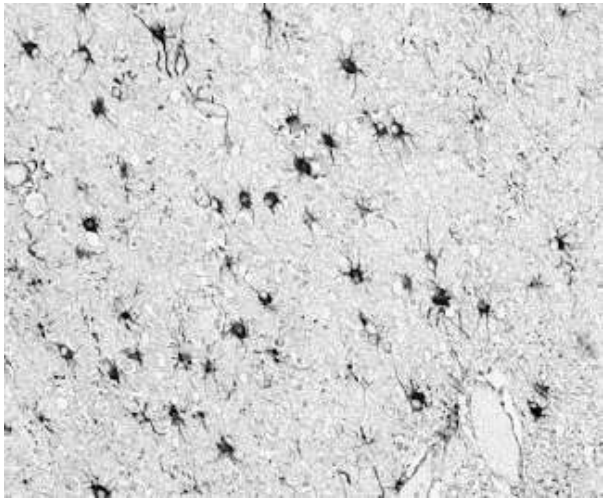
Neuropathology Identifies 4 Major Disease-Perturbed Networks for Prion Disease

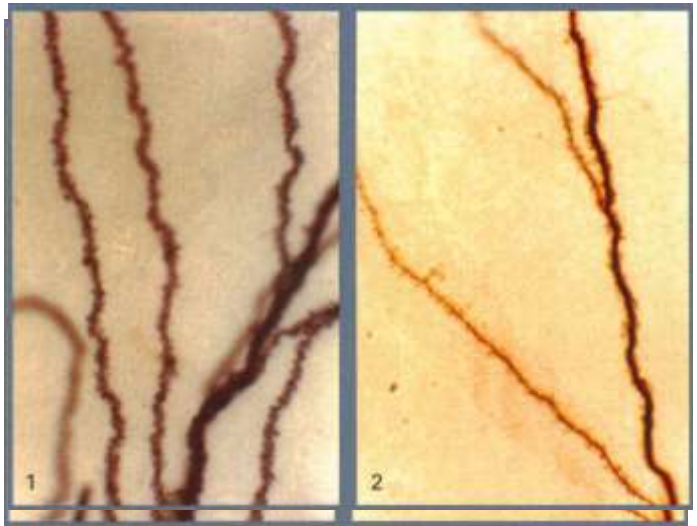
PrP accumulation



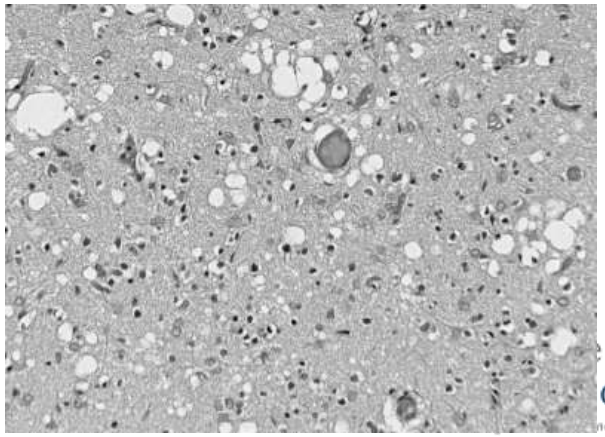
Microglia/astrocyte activation



Synaptic degeneration

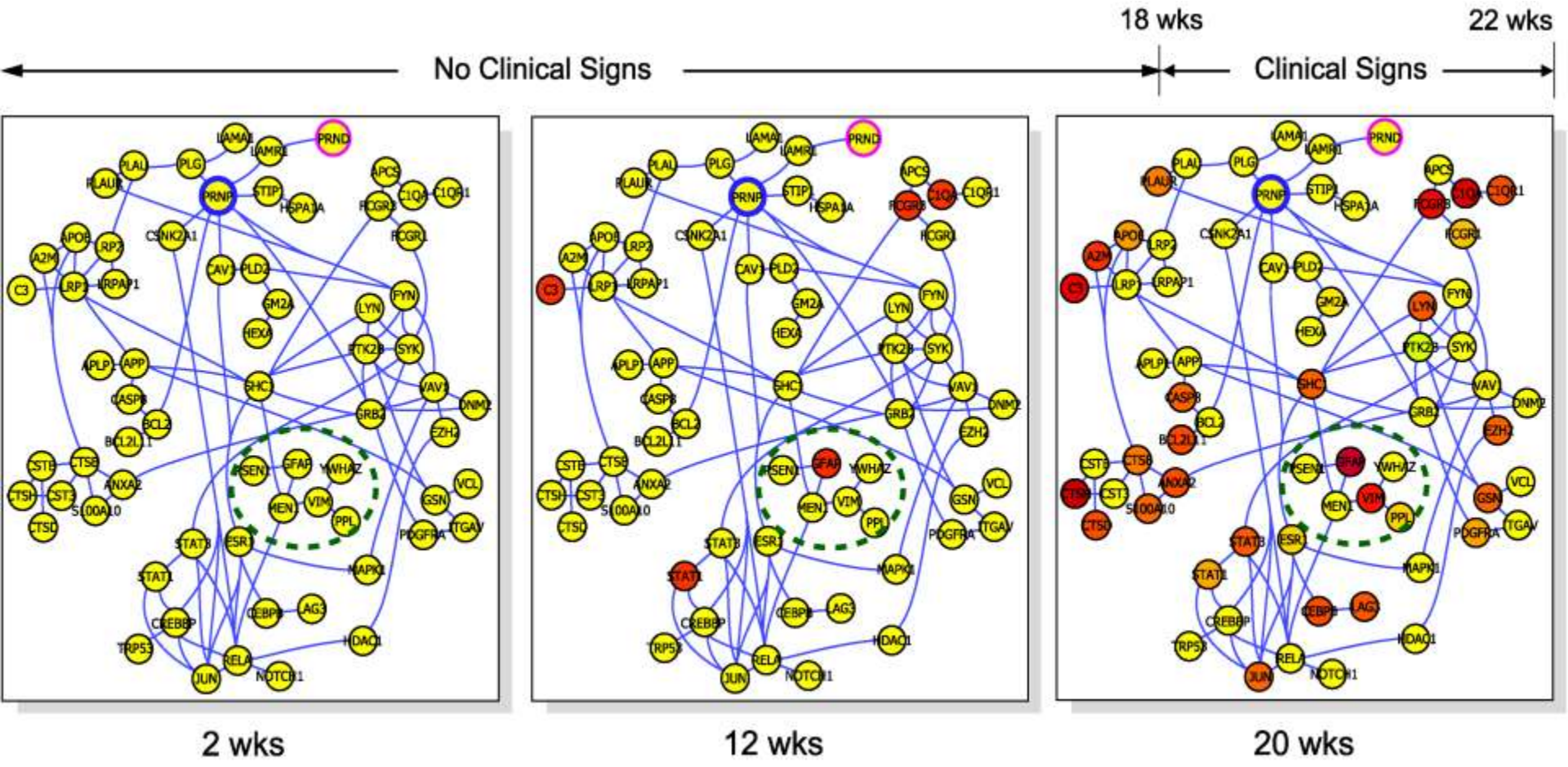


Nerve cell death

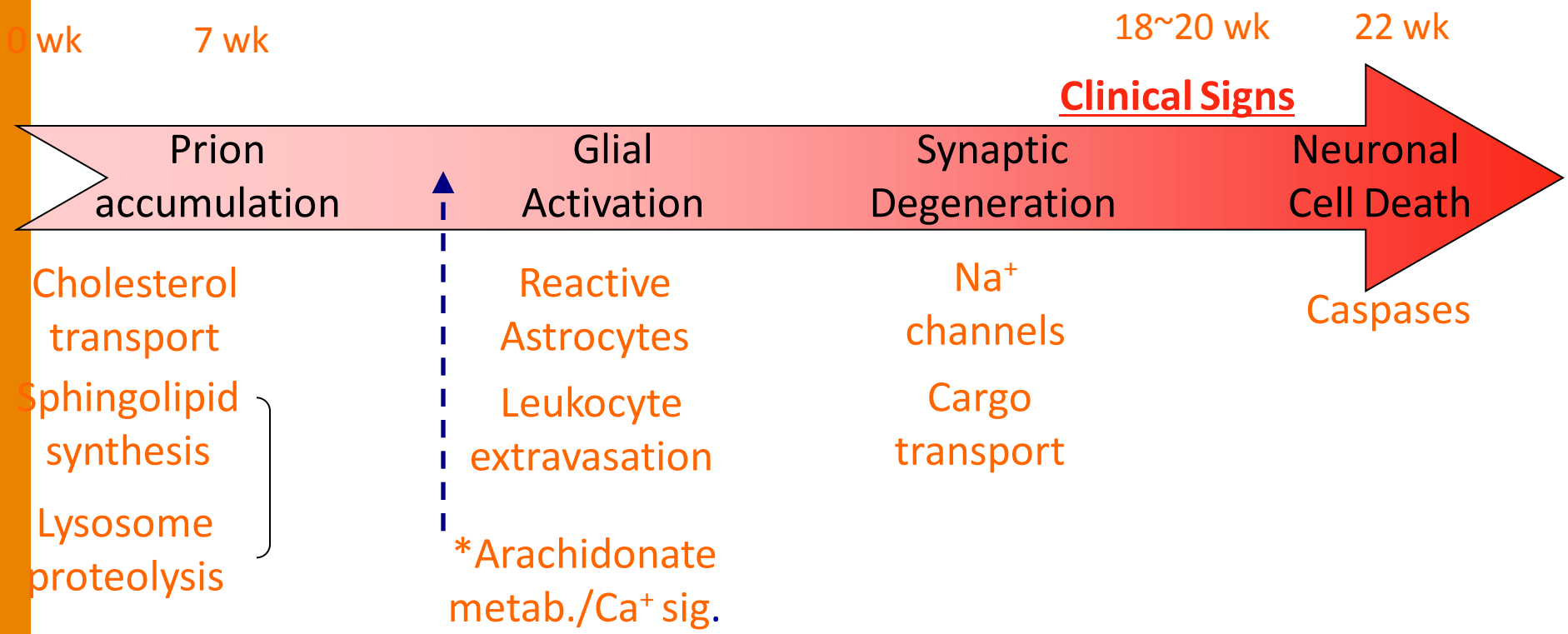


Dynamics of a Brain Network in Prion Neurodegenerative Disease in Mice

Prion accumulation network



Sequential Disease-Perturbation of the Four Networks of Prion Disease



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Conclusions from studies of prion dynamics

- About 200/300 differential expressed genes (DEGs) mapped into the four major networks
- The remaining 100 genes defined 6 new networks—previously unknown participants in prion disease—consequence of global analyses
- There was a sequential disease-perturbation of 10 networks
- The dynamics of these 10 networks explained essentially all of the pathophysiology of prion disease
- These dynamic network analyses led to new approaches to diagnostics

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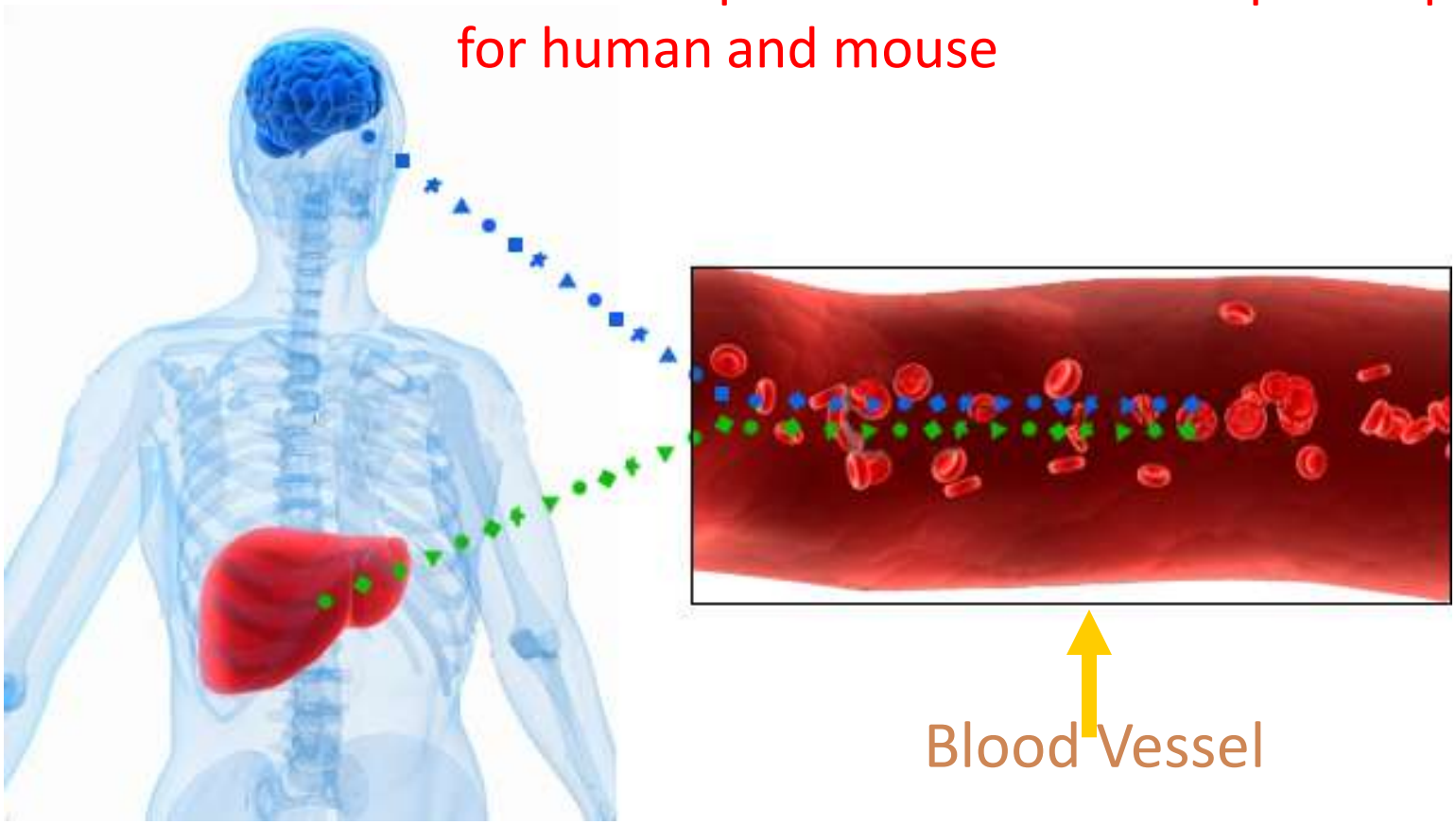
Making Blood A Window Distinguishing Health and Disease

Organ-specific Blood Proteins

100 brain-specific and 100 liver-specific proteins for human and mouse



Why Systems-Driven Blood Diagnostics Will Be the Key to P4 Medicine—Organ-Specific Blood Proteins

- Early detection
- Disease stratification
- Disease progression
- Follow therapy
- Assess reoccurances

Integrated Diagnostics

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Four ISB Technology-Driven New Big Projects with Striking Commercial Applications

- Complete genome sequencing of families—integrating genomics and genetics to find disease genes
- The Human Proteome Project—SRM mass spectrometry assays for all human proteins
- Clinical assays for patients that allow new dimensions of data space to be explored
- The 2nd Human Genome Project—mining all complete human genomes and their phenotypic/clinical data for the predictive medicine of the future

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Family genome sequencing: integrating genetic and genomics

Outsourcing sequencing to Complete Genomics

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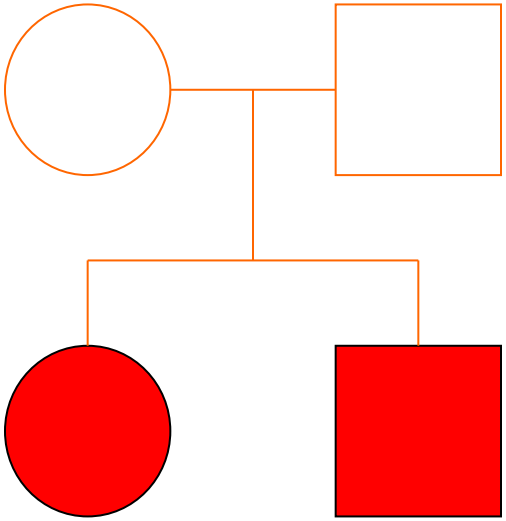
Whole Genome Sequencing of Family of Four



Unaffected parents

Children with craniofacial malformation (Miller Syndrome) and lung disease (ciliary dyskinesia)

- The genome sequences of a family permit one to use the principles of Mendelian genetics to:
  - Identify 70% sequencing errors—current error rate—less than $1/10^6$
  - Identify rare variants
  - Determine chromosomal haplotypes—reduce disease search space
  - Determine intergenerational mutation rate—35 mutations per child
  - Identify candidate genes for simple Mendelian diseases

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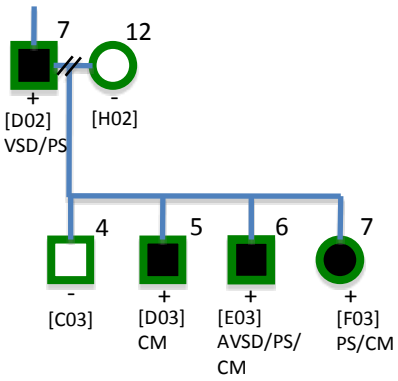
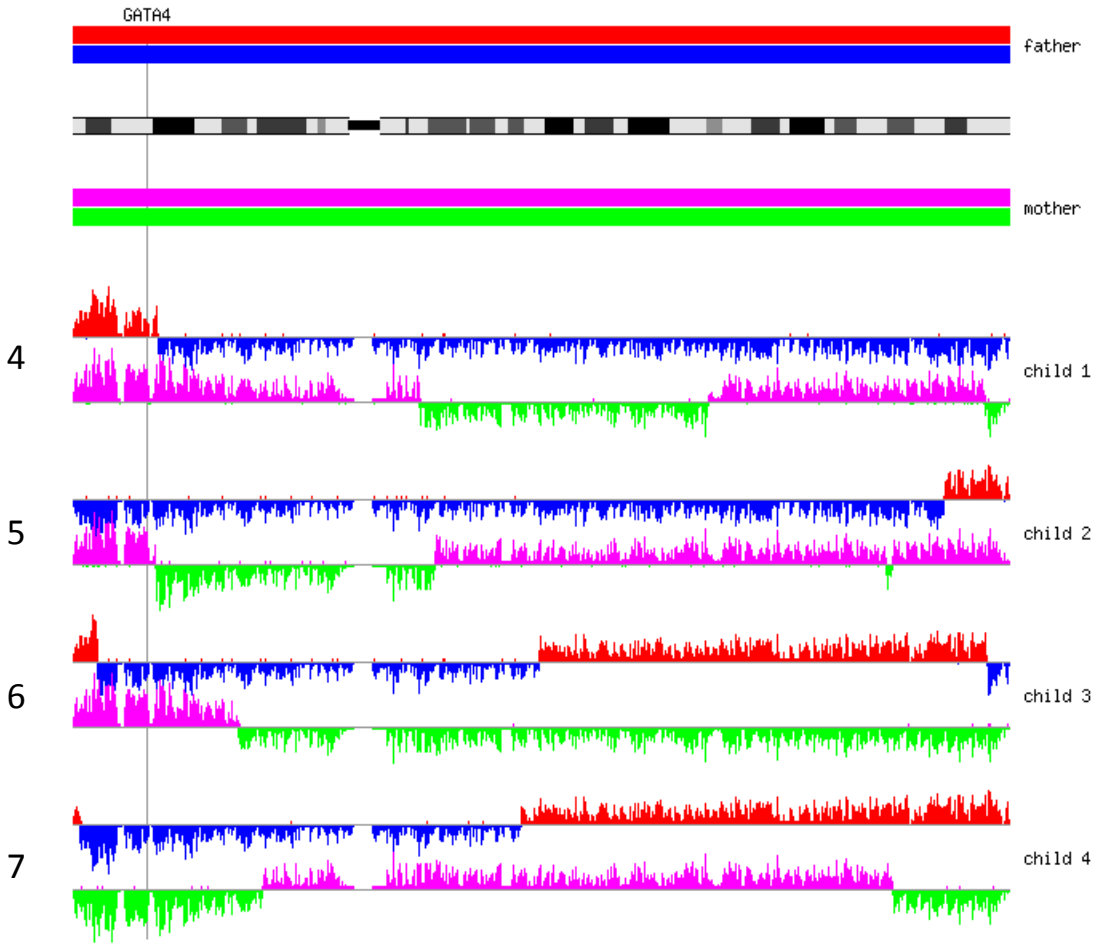
Complete haplotypes: family of six



Family with congenital heart disease caused by a GATA4 mutation



Reduce the chromosomal search space for disease genes

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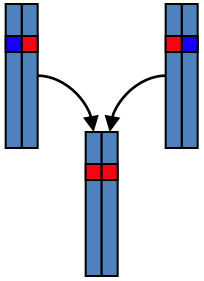
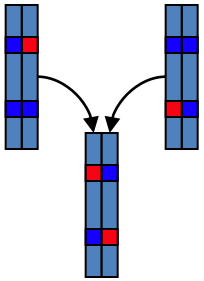
Finding key variants:

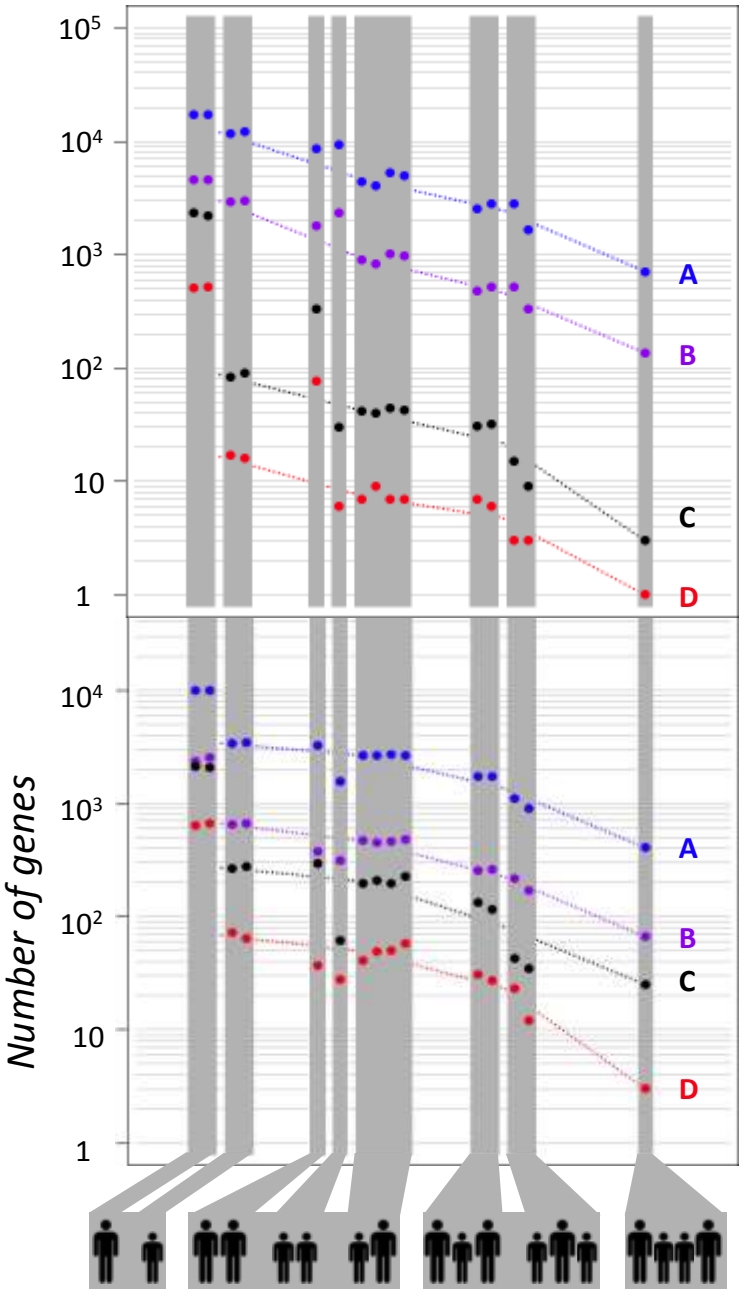
Utility of Constraints & Error Reduction

Simple recessive (SNPs)



Compound heterozygous (genes)





Model constraints:

1. *recessive*
2. *"twin" states*
3. *very rare*
4. *detrimental*

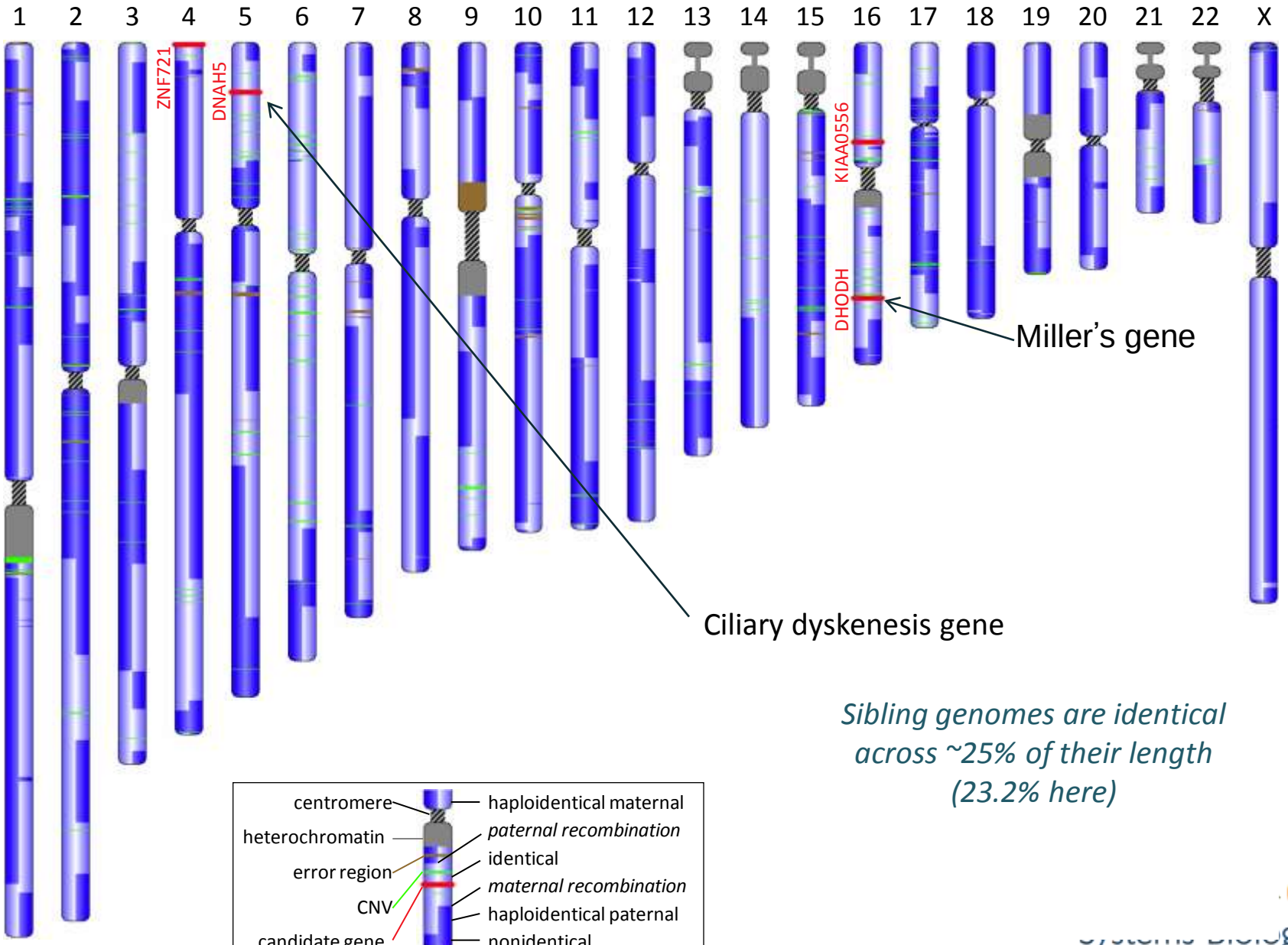
All SNPs, possibly detrimental

All SNPs, probably detrimental
Very rare SNPs, probably detrimental

Very rare SNPs, probably detrimental

Four gene candidates!

Genomes of kids



Sibling genomes are identical across ~25% of their length (23.2% here)

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Human genome will be a part of every patient's medical record in 10 years

- A human genome will cost perhaps $100 in 5 years.
- Genomes should be sequenced in families
- Societal and scientific objections will fade driven by actionable gene variants
- Your genome will be checked yearly for newly discovered actionable gene variants

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ISB Software Packages for Family Genomics
Domain-Expertise and Data-Driven—Bottom Up

Painted Chromosome Figures—visualization of interesting areas

Software to draw a set of chromosomes with the ability to specify painted areas to indicate regions of interest. In addition, specific gene positions can be called out in red.

KAVIAR—catalogue of all published SNPs

A tool that greatly simplifies the assessment of novel variants. Kaviar includes: (i) an integrated and growing database of genomic variation from diverse sources, including over 55 million variants from personal genomes, family genomes, transcriptomes, SNV databases and population surveys; and (ii) software for querying the database efficiently.

Haploscribe—haplotype construction

Haploscribe is a software package that uses Whole Genome Sequencing data from a nuclear family with three or more children to phase the genomic data into haplotypes.

ISCA—checks inheritance consistency—e.g. DNA sequencing errors

ISCA - Inheritance State Consistency Analysis software

MAGMA: Multiobjective Analyzer for Genetic Marker Acquisition

MAGMA employs a multiobjective evolutionary algorithm to select tag SNPs. It is based on a the ECJ evolutionary software package written by Sean Luke and includes the Strength Pareto Evolutionary Algorithm Version 2 changes for multiobjective analysis.

RepeatMasker—identifies repeat sequences

RepeatMasker is a program that screens DNA sequences for interspersed repeats and low complexity DNA sequences. On average, almost 50% of a human genomic DNA sequence currently will be masked by the program.

Proteomics

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The Human Proteome Project

- ISB has pioneered 4 major proteomics advances that led to consideration of a human proteome project
- Strategic partners: ISB (R. Moritz)/ETH (R. Aebersold)/Agilent/AB-Sciex/Origene

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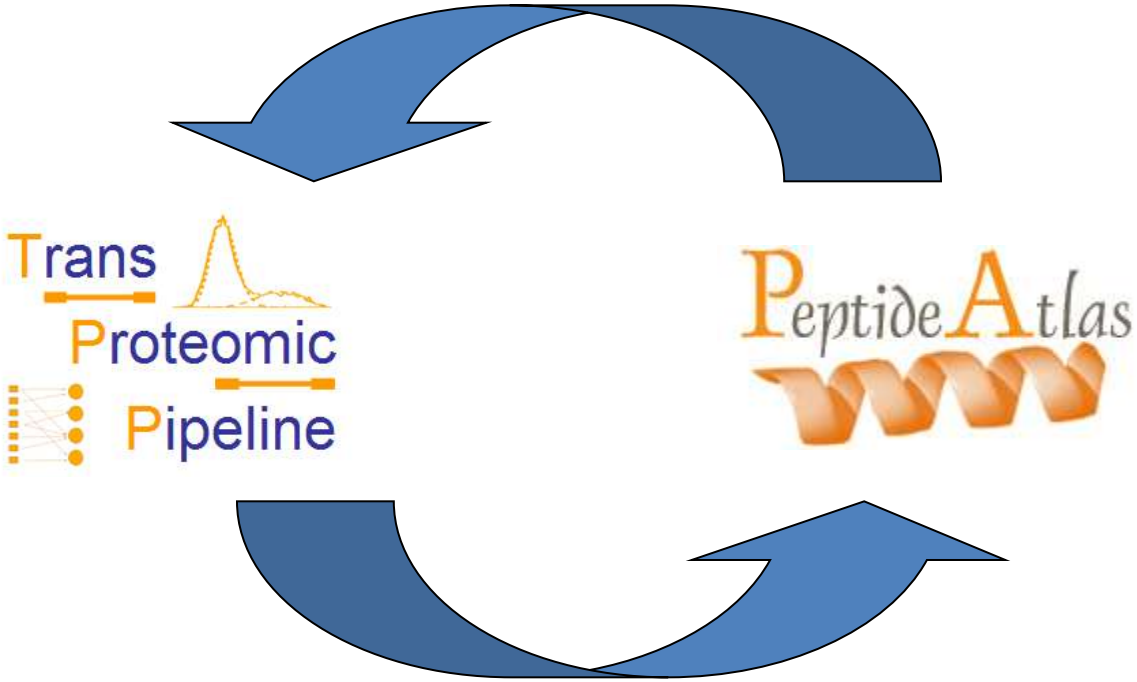
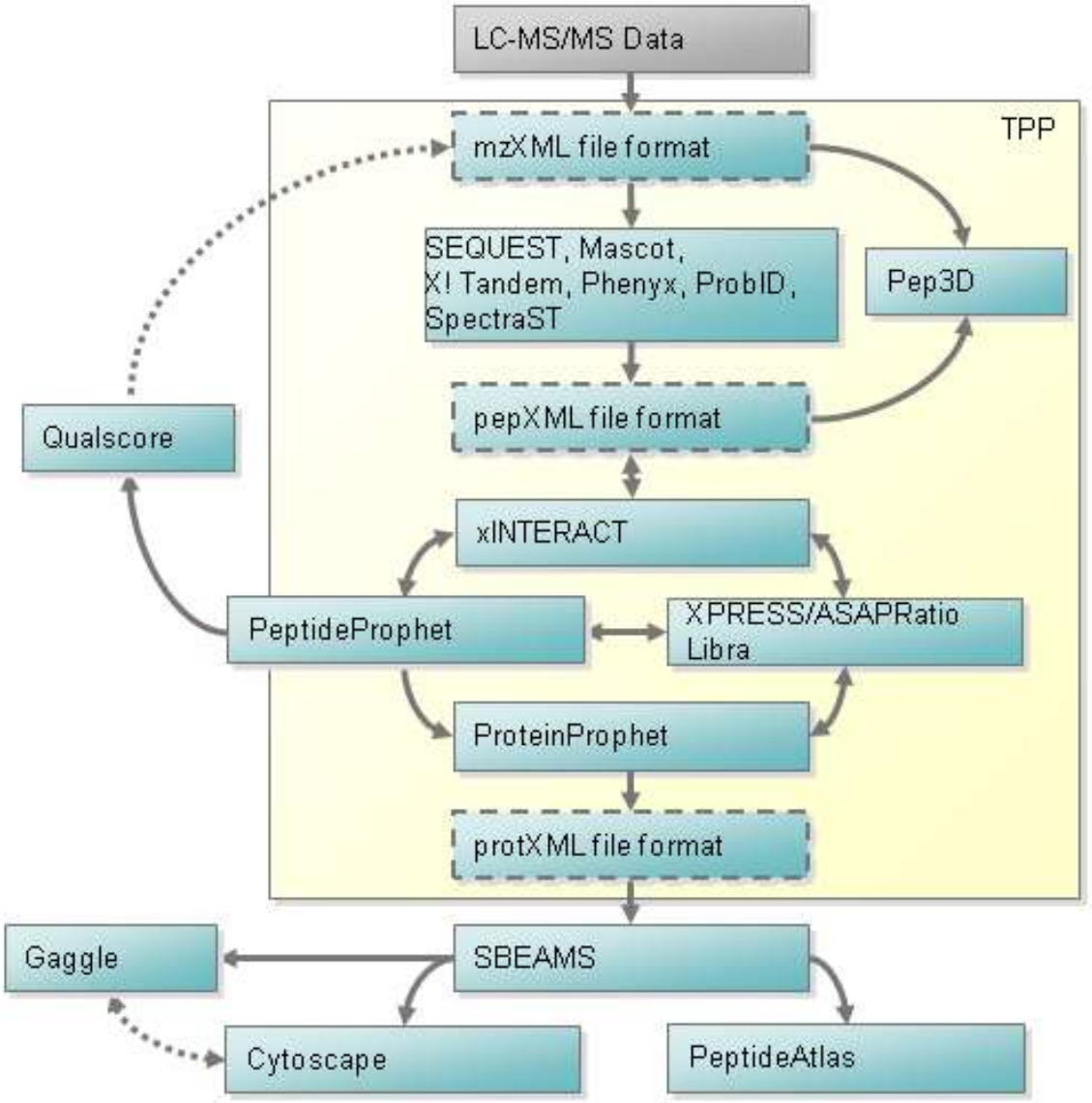
1. Trans Proteomics Pipeline: Foundation for 2. the PeptideAtlas

Drives tool development and optimization



Advanced, uniform processing and evaluation of all data

Trans Proteomic Pipeline (TPP) : Driven by Domain Expertise and Data-Bottom Up Approach



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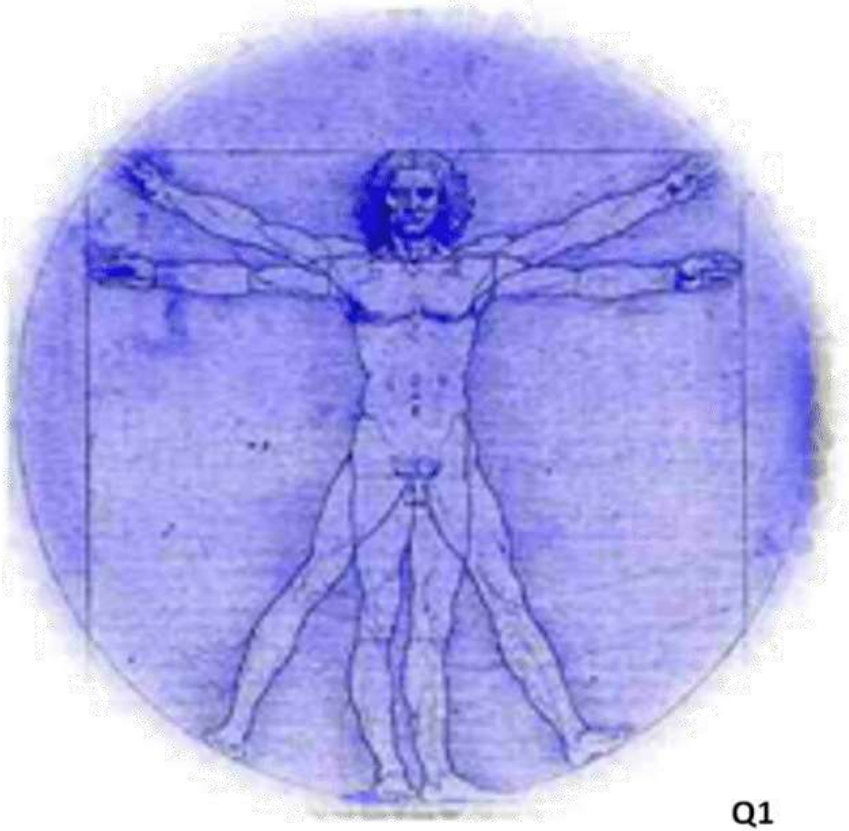
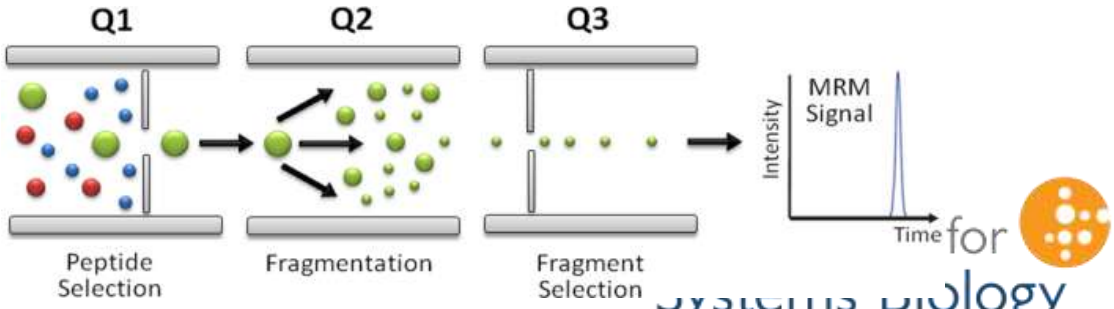
3. Targeted Proteomics: Human SRMAtlas



4. SRM
assays for most of the known 20,333 human proteins

Analyze 100-200 proteins quantitatively in 1 hour
Heavy isotope peptides for Q3 analyses allow quantification



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Current Status of S/MRMAtlas

Democratization of proteins

Species	Peptides synthesized (#)	Proteome coverage (%)
•**Yeast**	28.000	97
• **Human**	170.000	99
• **M Tuberculosis**	12.000	99
• **D. melanogaster**	15.000	40
• **Mouse**	(human orthologs)	>50

Microfluidic protein chips: making blood a window into health and disease for 100s of millions of patients

Assay 2500 organ-specific blood proteins (50 from each of 50 organs) from millions of patients using just a drop of blood—follow health longitudinally and detect transitions from health to disease

- Jim Heath--Caltech

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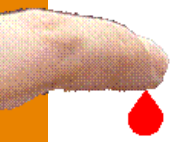
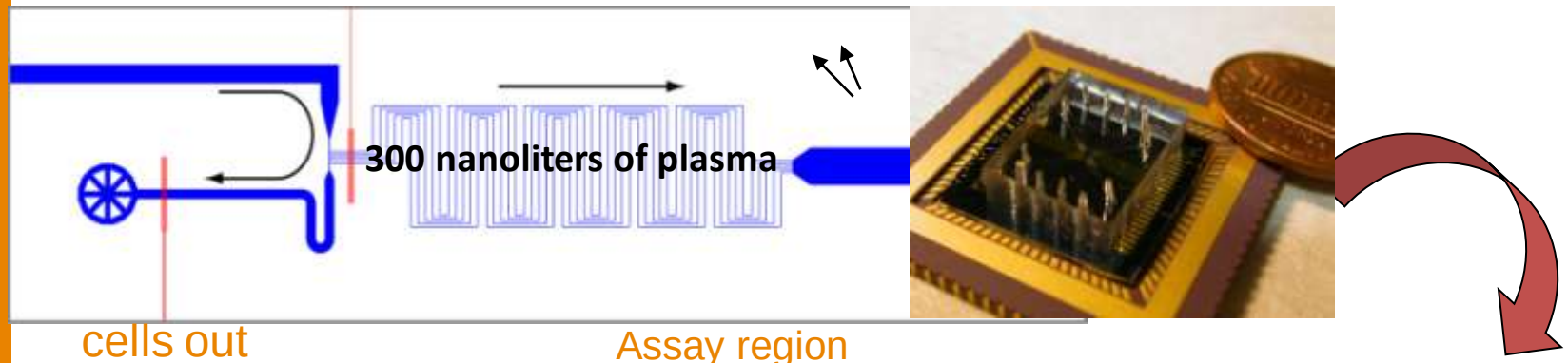
Making Blood a Window into Health and Disease for 100s millions of patients:

50 organ-specific blood proteins from each of 50 organs—measure 2500 blood proteins

Integrated nanotech/microfluidics platform





1. Uses fraction of droplet of blood
2. Assay takes 5 minutes to measure 50 proteins
3. Already being used in hospitals
4. Mid atomole level of sensitivity

Jim Heath, et al

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Clinical Assays for Exploring New Dimensions of Patient Data Space

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Individual Patient Information-Based Assays of the Present/ Future (I)

- Genomics
  - Complete individual genome sequences—predictive health history—will be done sequencing families
  - Complete individual cell genome sequences—cancer.
  - Complete MHC chromosomal sequence in families—autoimmune disease and allergies
  - 206 Actionable SNPs—pharmacogenetics-related and disease-related genes
  - Sequence 1000 transcriptomes—tissues and single cells—stratification disease
  - Analyze aging transcriptome profiles—tissues and single cells—wellness
  - Analyze miRNA profiles—tissues, single cells and blood—disease diagnosis
- Proteomics
  - Organ-specific blood MRM protein assays —110 brain, 80 liver and 20 lung
  - 2500 blood organ-specific blood proteins from 300 nanoliters of blood in 5 minutes—twice per year (50 proteins from 50 organs)—wellness assessment.
  - New protein capture agents.
  - Array of 12,000 human proteins —against autoimmune or allergic sera--stratify.
  - Single molecule protein analyses —blood organ-specific proteins and single cell analyses

Individual Patient Information-Based Assays of the Present/ Future (II)

- Single cells
  - Analyze 10,000 B cells and 10,000 T cells for the functional regions of their immune receptors—past and present immune responsiveness—follow vaccinations—identify autoimmune antibodies.
  - Analyze individual blood macrophages—inflammation, etc.
  - Use pore technology to separate large epithelial cells from smaller white blood cells—cancer/prenatal diagnosis
  - Quantized cell states from cancer cell lines.

- iPS (stem) cells
  - Analyze individual stem (iPS) cells from each individual differentiated to relevant tissues to get important phenotypic information—molecular, imaging and higher level phenotypic measurements.

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Single-cell analyses

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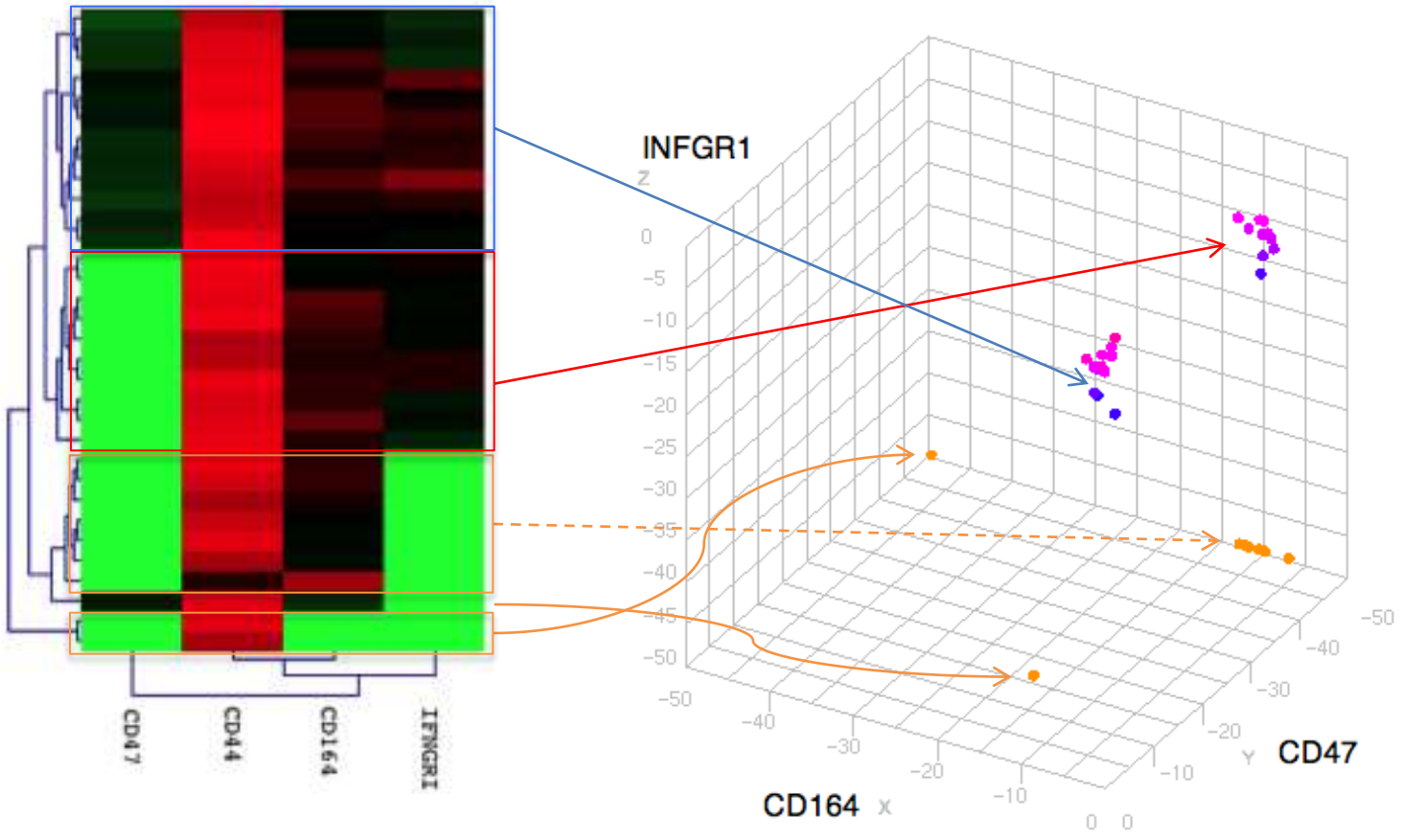
Quantized Cell States: Quantitative transcriptome clustering of single cells from the human glioblastoma cell line U87



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Induced pleuropotential (iPS) cells for biology and diagnostics

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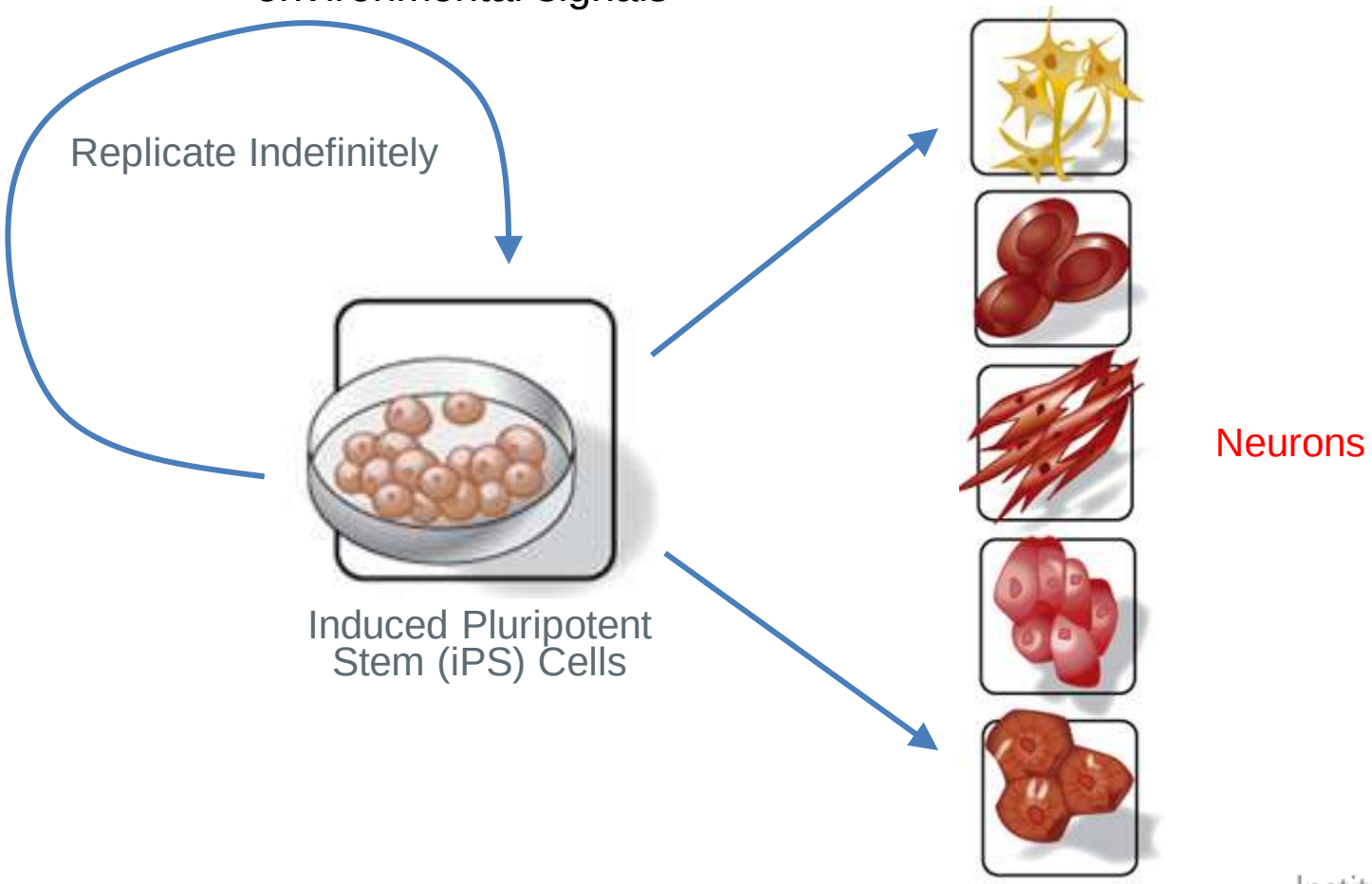
Differentiate Induced Pluripotent Stem Cells to Neurons

Differentiate iPS cells from a normal and a diseased individuals to neurons and probe them with environmental signals



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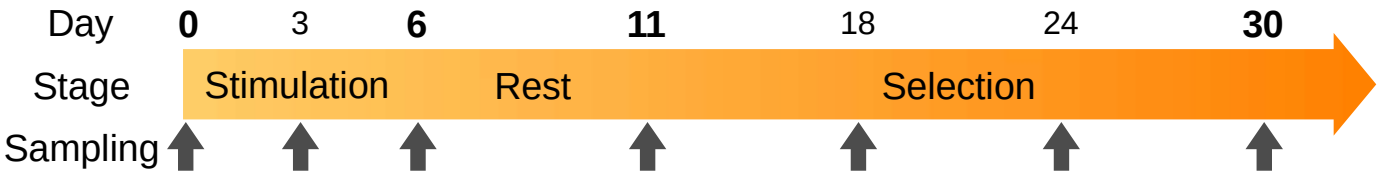
Global and single-cell analyses of neurons development

Use iPS cells from normal and disease patients



Global analysis

Genome
Epigenome
Transcriptome
miRNAome
DNA methylation
Targeted proteome--200
Targeted Metabolome
Targeted Lipidome

Single-cell analysis—8 time points

500 selected mRNAs
Entire miRNAome
Selected DNA methylation
A few proteins
(using immunochemistry)
Cell sort quantized cell populations for omic analyses

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Stratification of Complex Genetic Diseases—e.g., Alzheimer's Disease

- Collect families of patients with the relevant disease (families will stratify disease to certain extent)
- Create iPS cells from each individual in families
- Differentiate iPS cells to neurons in test tubes
- Single-cell analyses to identify and sort quantized cell states
- Probe these sorted neurons (individually or as cell-sorted quantized populations) with ligands, drugs and relevant RNAi's and analyze their transcriptome, miRNAome and selected proteomes—this will stratify different combinations of disease-perturbed (or potentially disease-perturbed) networks
- Sequence family genomes in keeping with their initial stratification types
- Provide Pharma with stratified populations of Alzheimer's patients to test their more than 100 Alzheimer's drugs

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An Integrative Systems Approach to Disease Is the Key for Dealing with Complexity–Five Pillars

1. Viewing biology/medicine as an **informational science** is one key to deciphering complexity
2. **Systems biology infrastructure—**holy trinity of biology, cross-disciplinary culture, democratization of data-generation and data-analysis tools and the power of model organisms to decipher complexity
3. **Holistic, systems experimental approaches** enables deep insights into disease mechanisms and new approaches to diagnosis and therapy
4. **Emerging technologies** provide large-scale data acquisition and permit us to explore new dimensions of patient data space
5. **Domain-driven transforming analytic tools** will allow us to decipher the billions of data points for the individual--sculpting in exquisite detail wellness and disease

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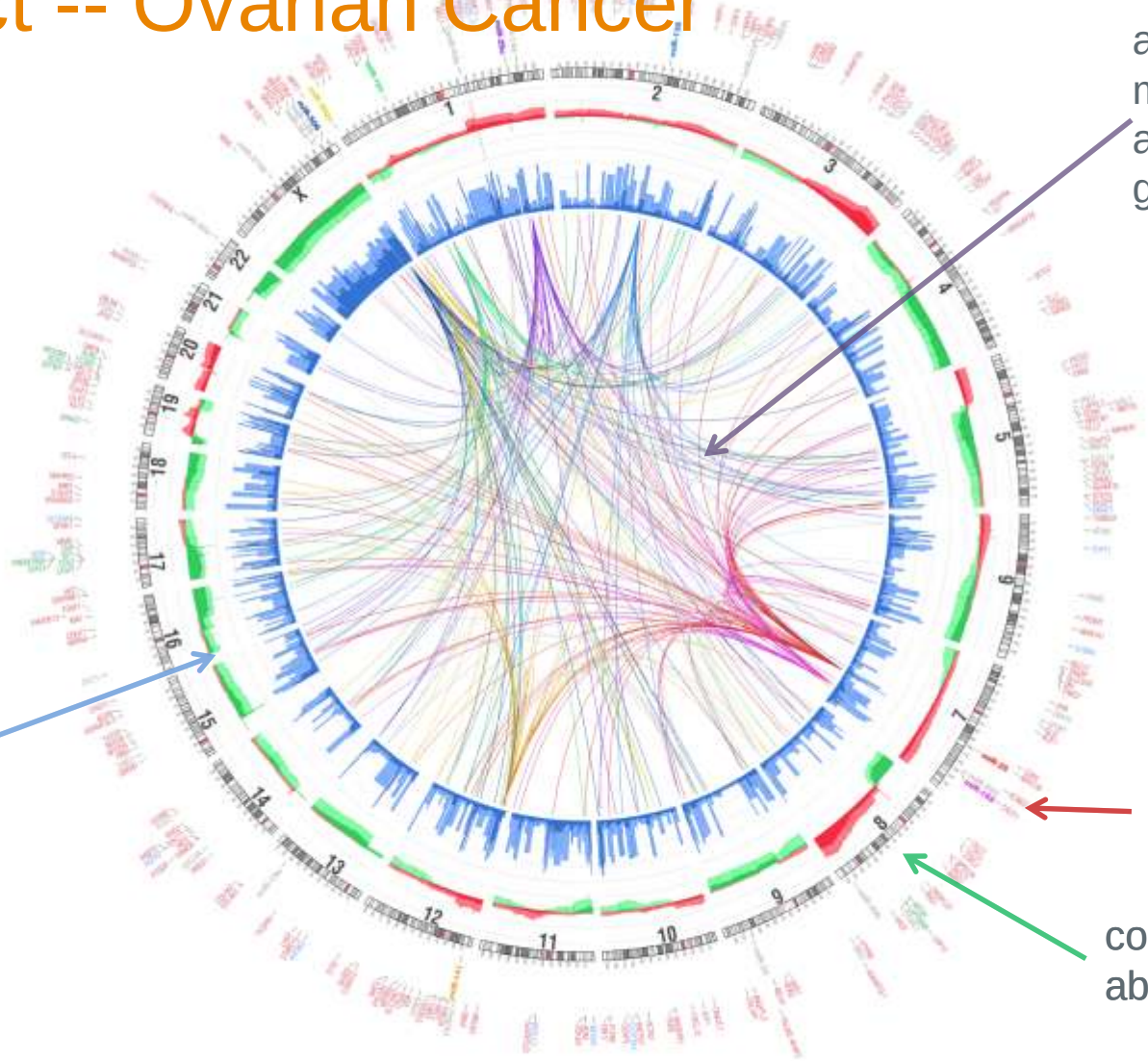
ISB Genomic Data Integration: TCGA Project -- Ovarian Cancer



Shmulevich group, ISB

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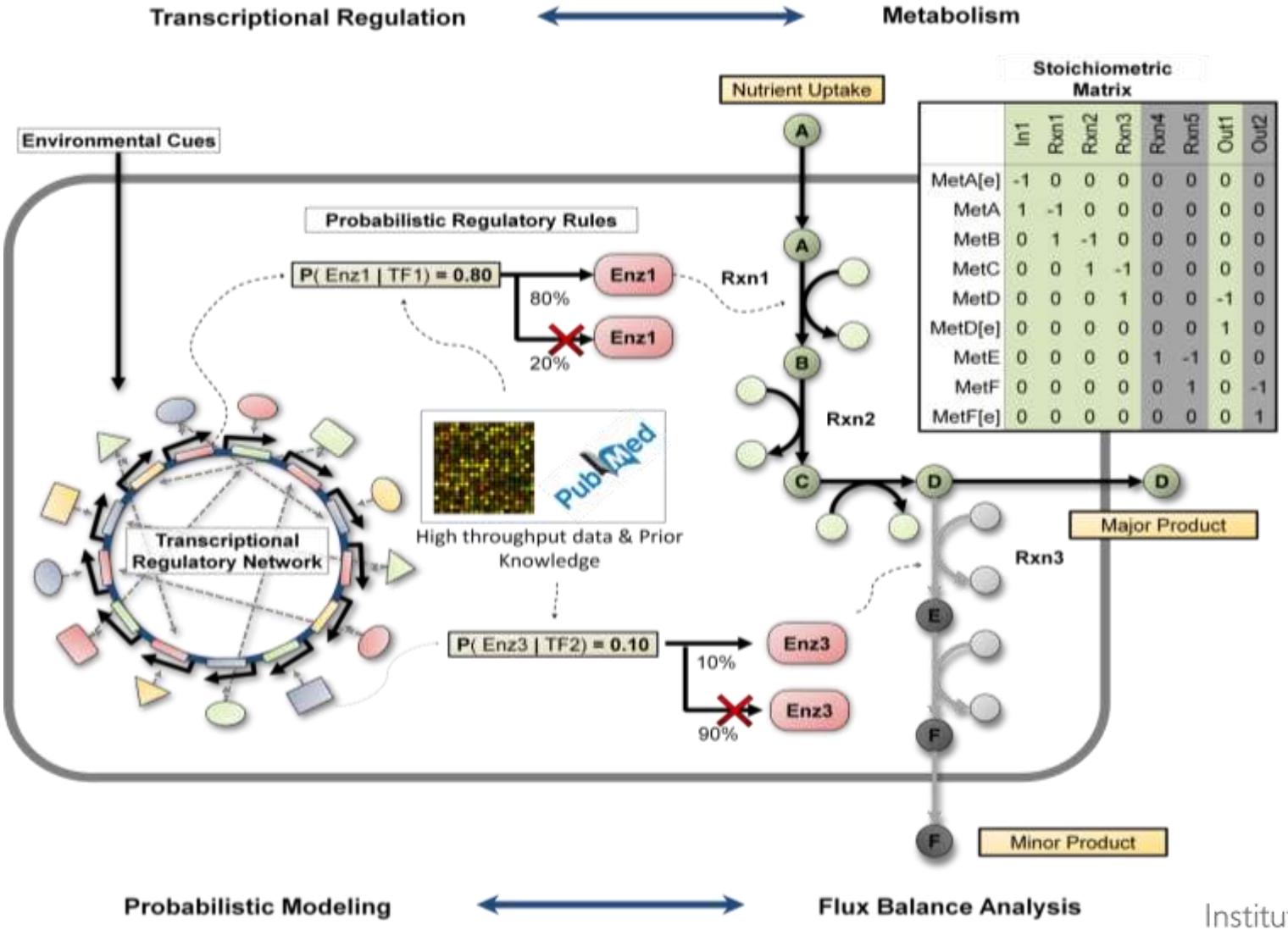
Network integration: genome-scale regulatory and metabolic networks



Chandrasekaran and Price, *PNAS*, 2010

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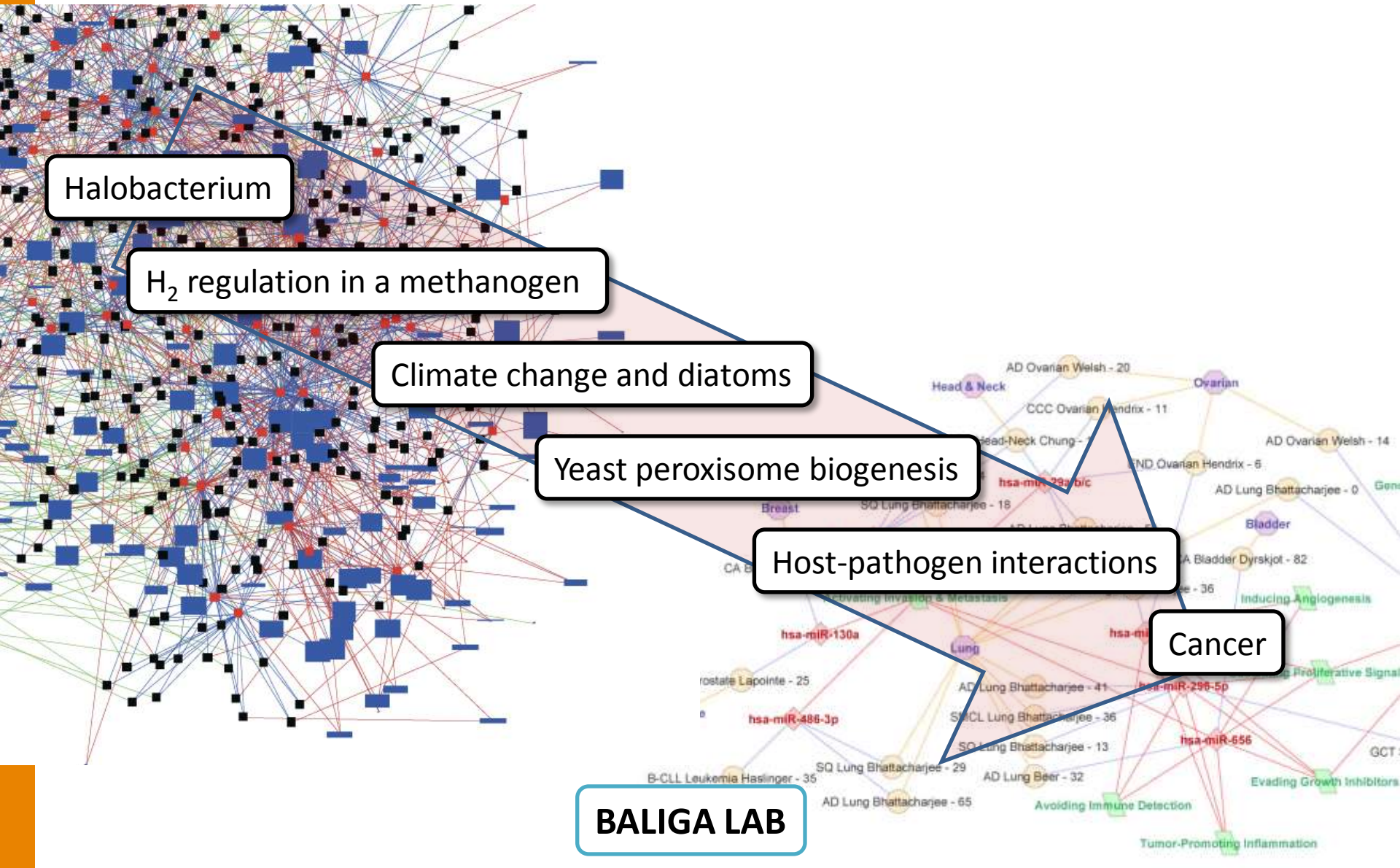
Halo to cancer:

Work on a lesser known microbe drives predictive modeling of environment and health-related biological systems



Biology-Driven and Data-Driven Computational Tools Developed at ISB:

Genomics, Proteomics, Networks, Modeling

- MARLON - Genetic Analysis by Markov Logic Networks
- Addama – light weight data management services
- MRMLIMS – sample management for Human proteome project (100k+ peptides).
- Systems Gentics Platform (SGP) – sample and workflow management for Systems Genetics
- Howdah – high-performance integrative analysis platform primarily used for HTS
- RExS – service designed for the rapid deployment of analysis scripts and tools
- mspecLINE - identifies spectra & associates with disease literature to enable design of targeted proteomics experiments
- Qtips – quantitative proteomic PTM analysis tool
- SeqAdapt – adaptable HTS analysis pipeline primarily used for ChipSeq/RNAseq
- TandemHPC – high-performance parallel proteomic spectra search/scoring system
- SAMQA – high-performance QA pipeline for HTS data analysis
- Fastbreak – structural variation analysis tool for HTS data
- iDirt – mining SILAC mass spec proteomics data to discover temporal protein-protein associations
- TransProt – HTS pipeline to identify transcription anomalies by mapping to both the genome and proteome
- NoMAD – ontology based MEDLINE mining and visualization tool
- FastAlign – tool to enable rapid mapping of thousands of genomes
- Synthetic Cancer – model the genomic development/progression of cancer
- Circvis – interactive genomic feature visualization
- ProtMiner – tool for visual mining of large proteomic repositories and assist in design of targeted experiments
- Cytoscape – desktop network visualization and analysis package
- The Gaggle - framework for exchanging data between independently developed software tools and databases to enable interactive exploration of systems biology data.
- The Firegoose – a toolbar connects the Gaggle to the web.
- cMonkey - learns context-specific (condition-dependent) modules of co-regulated genes by integrating (a) gene expression data, (b) *de novo* detection of *cis*-regulatory DNA motifs, and (c) connectivity in functional association or physical interaction networks.
- Trans Proteomic Pipeline – Validation software for mass spectrometry data
- Protein Atlas – A database for validated mass spectrometry data
- Aebersold, Baliga, Boyle,Galas, Moritz, Shmulevich, et. al.

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Thoughts about the development of software

- Open source for the development of software—both discrete and integrated packages—extensible, interoperable and comprehensive
- Software development driven by domain-expertise, driven by data because of biological complexity (bottom up) and driven by users
- How do we integrate biology expertise with statistical expertise with computational expertise
- How to integrate individual software packages into coherent platforms for comprehensive integration and modeling
- What is the granularity of biological information needed: dealing with disease takes less granularity than understanding biology

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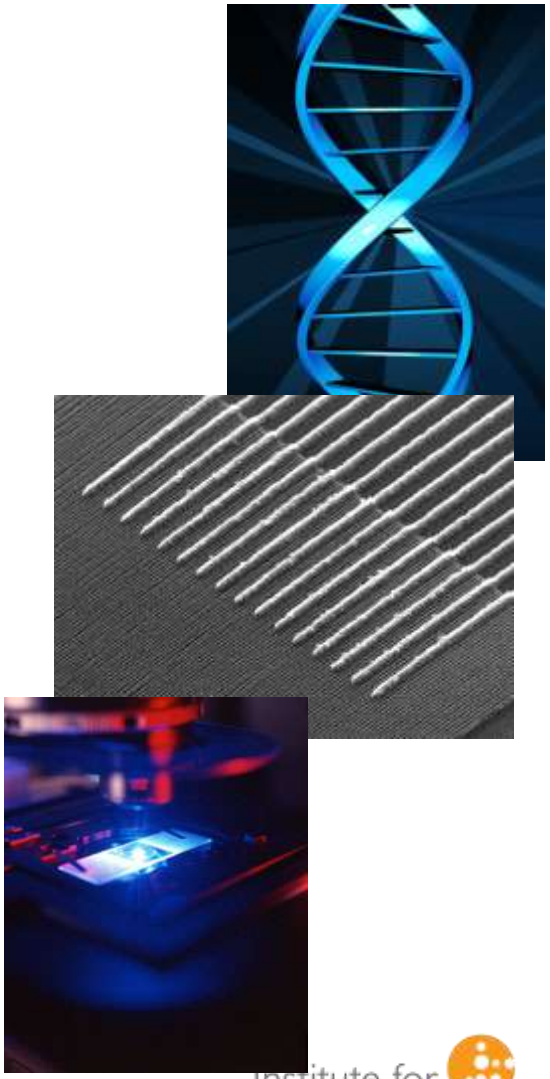
P4 Medicine

- **Predictive**
  - Probabilistic health history
  - DNA sequence & Regular multi-parameter (blood) measurements
- **Preventive**
  - Design of therapeutic and preventive drugs/vaccines via systems approaches
  - Wellness
- **Personalized**
  - Unique individual human genetic variation mandates individual treatment
  - Patient will be their own control for data analyses
- **Participatory**
  - Patient-driven social networks for disease and wellness will be a driving force in P4 medicine
  - Society must access patient data after de-identification and make it available to biologists for pioneering predictive medicine of the future
  - How does one educate patients, physicians and the healthcare community about P4?



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Information Technology for Cancer and Healthcare

- IT infrastructure: sufficient cycles and storage, open source, extensible, interoperative, integrated with technology platforms and analytical tools
- Top down enterprise solutions dangerous—domain-expertise driven, data-driven (bottom up), user acceptable—how to integrate software packages
- Gold standard for internet medical information
- Handle conventional medical records and histories
- Handle molecular, cellular and phenotypic data
- Identify actionable gene variants in the individual genome sequences
- Handle the comparative and subtractive analyses of billions of genomes and their attendant phenotypic data
- Handle the digitization of personal data
- Handle extensive personalized imaging data
- Handle social network data
- Handle longitudinal data gathered on individual patients
- Derive and analyze the dynamical “network of networks” for the individual
- Integrate data/networks and generate predictive and actionable models

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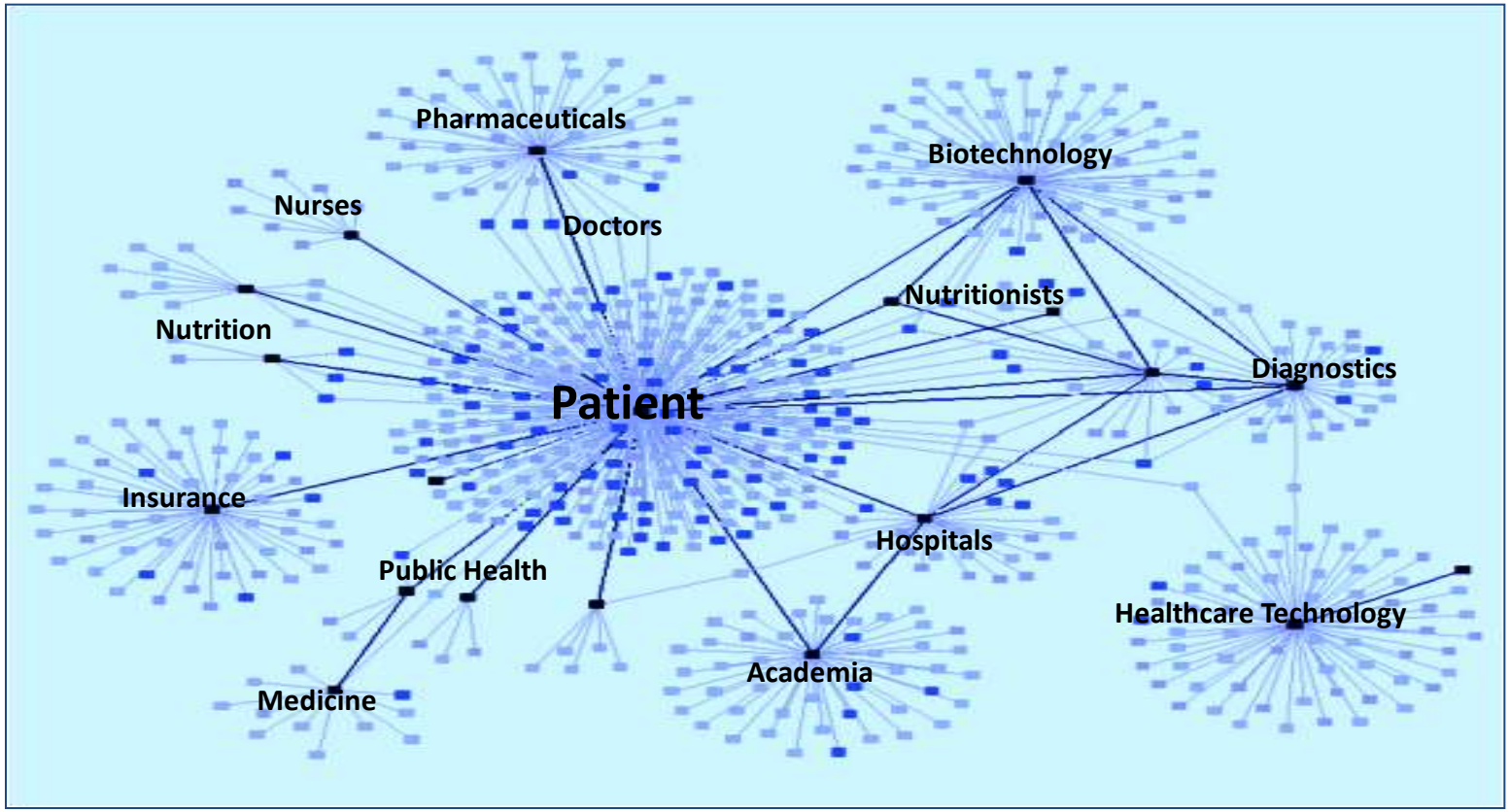
The patient will become the center of the P4 healthcare network and a driver of change through consumer-driven social networks



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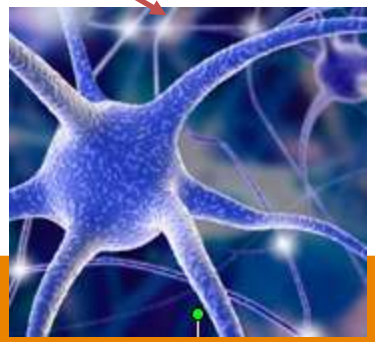
Conceptual Themes of P4 Medicine

P4 Medicine

- Predictive
- Preventive
- Personalized
- Participatory

Wellness Quantified



Disease Demystified

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Systems (P4) Approaches to Disease and Wellness: Transforming Medicine for the Patient

- Systems approaches provide fundamental new insights into disease mechanisms
- The human genome through actionable variant genes provides a means to begin optimizing human health and deal with disease
- Blood as a window into health and disease—disease diagnostics, drug toxicity assessment, wellness assessment, etc.
- Stratification of diseases into their subtypes for a proper impedance match against a patient's disease and discovery of the proper drug
- Assessment of multi-organ response in a disease—organ networks
- New approach to drug target discovery—re-engineer disease-perturbed networks with drugs
- Digitization of individual human parameters—the quantized self--offers the opportunity for providing wellness metrics, optimizing patient treatments and mining for the predictive medicine of the future.

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