Reaching the goals of personalized (P4) medicine: what hills are left to climb?

Predictive, Personalized, Preventive and Participatory

Lee Hood

Institute for Systems Biology, Seattle

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In 10 years P4 Medicine will Generate Billions of Data Points Around Each Individual

TeleHealth

110101000
101010101
101010101
001000101
10101000

Phenome

Na143 K 3.7
BP 110/70
HCT32 BUN
12.9 Pulse
110 PLT150

Social Media

110101000
101010101
101010101
001000101
10101000

Epigenome

110101000
101010101
101010101
001000101
10101000

Genome

GCGTAG
ATGCGTAG
GCATGCAT
GCCATTATA
GCTTCC

Transcriptome

UUAGUG
AUGCGUCU
AGGCAUGC
AUGCC

Proteome

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

Transactional

110101000
101010101
101010101
001000101
10101000

Single Cell

110101000
101010101
101010101
001000101
10101000

iPS Cells

110101000
101010101
101010101
001000101
10101000

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Outline

- What is P4 medicine: the four pillars
  - Medicine is an information science
  - System approaches to disease
  - Emerging technologies
  - Analytic tools (computational/mathematical)
- P4 medicine—personal and societal impacts
- P4 medicine and strategic partnerships

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The Foundations of Systems Biology and Systems Medicine – Four Pillars

1. View medicine as an **informational science**
2. **Systems approaches** allow one to understand wellness and disease—holist rather than atomistic
3. **Emerging technologies** will allow us to explore new dimensions of patient data space
4. **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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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
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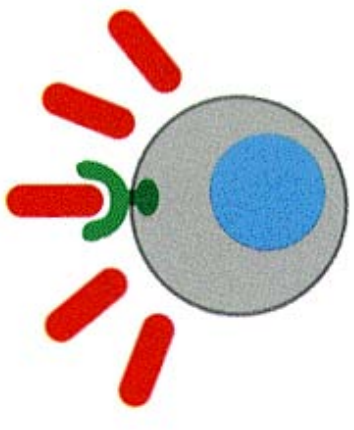
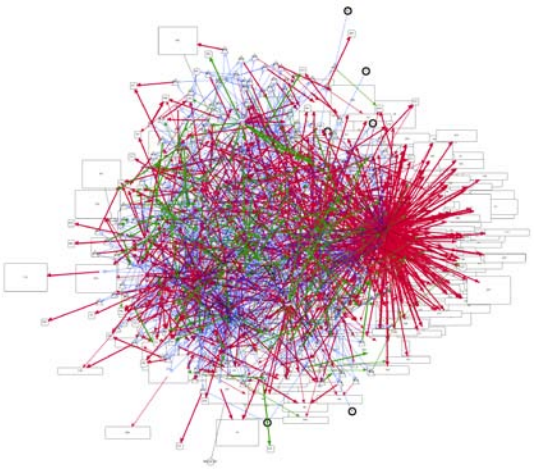
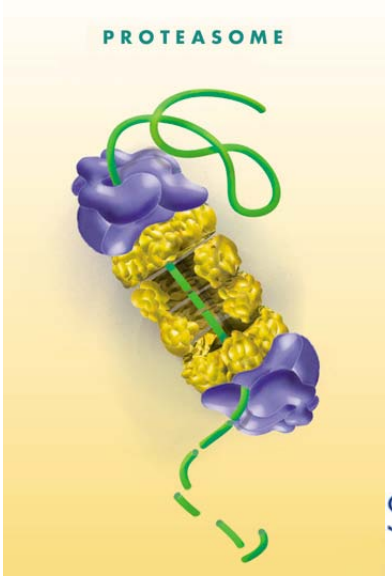


Two General Biological Structures Connect the Genotype/Environment and Phenotype

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





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All Hierarchical or Multiscale Levels of Biological Information—Are Modified by Environmental Signals

DNA

RNA

Protein

Protein interactions and biomodules

Protein and gene networks

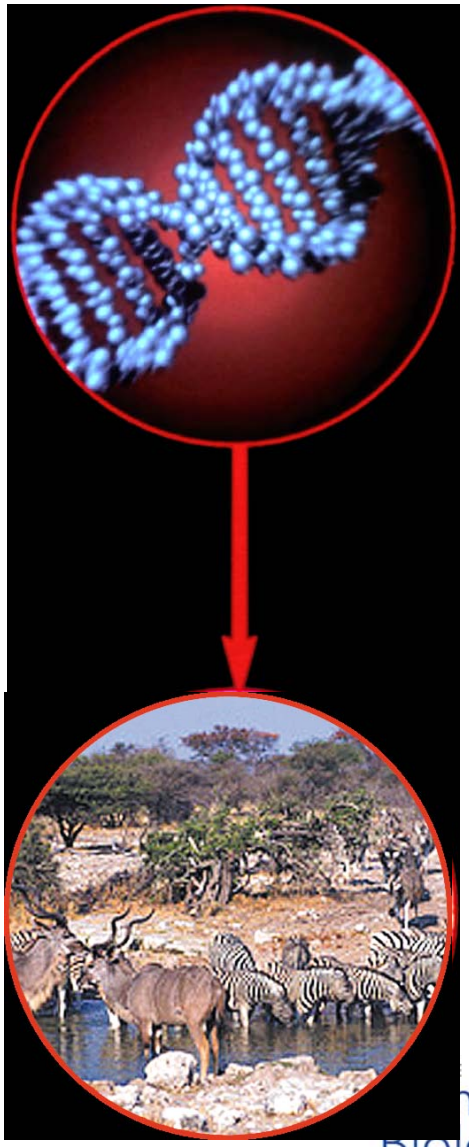
Cells

Organs

Individuals

Populations

Ecologies



The Foundations of Systems Biology and Systems Medicine–Four Pillars

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How Might One Think About a Systems Approach?

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Radio Waves

Sound Waves

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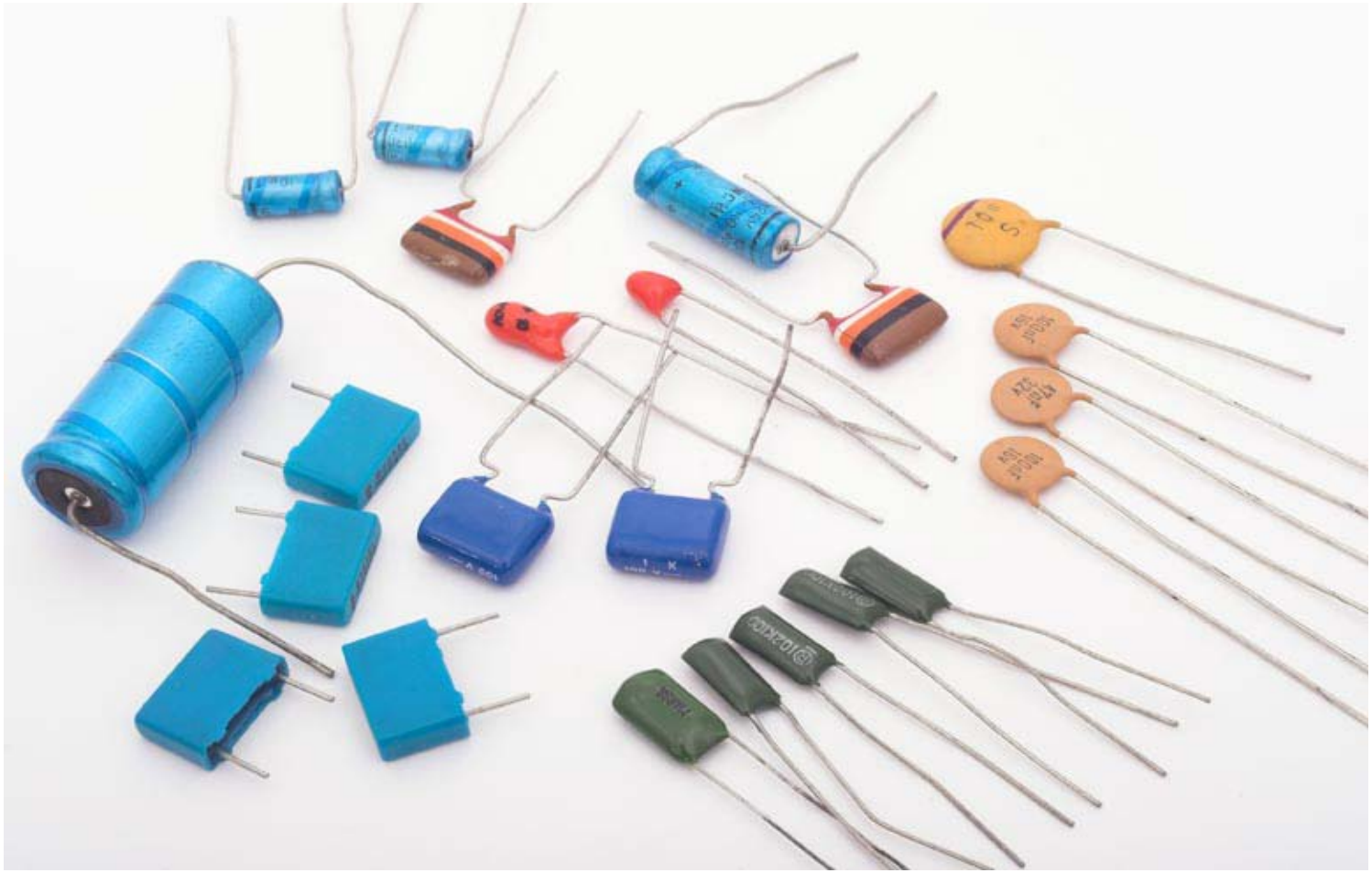
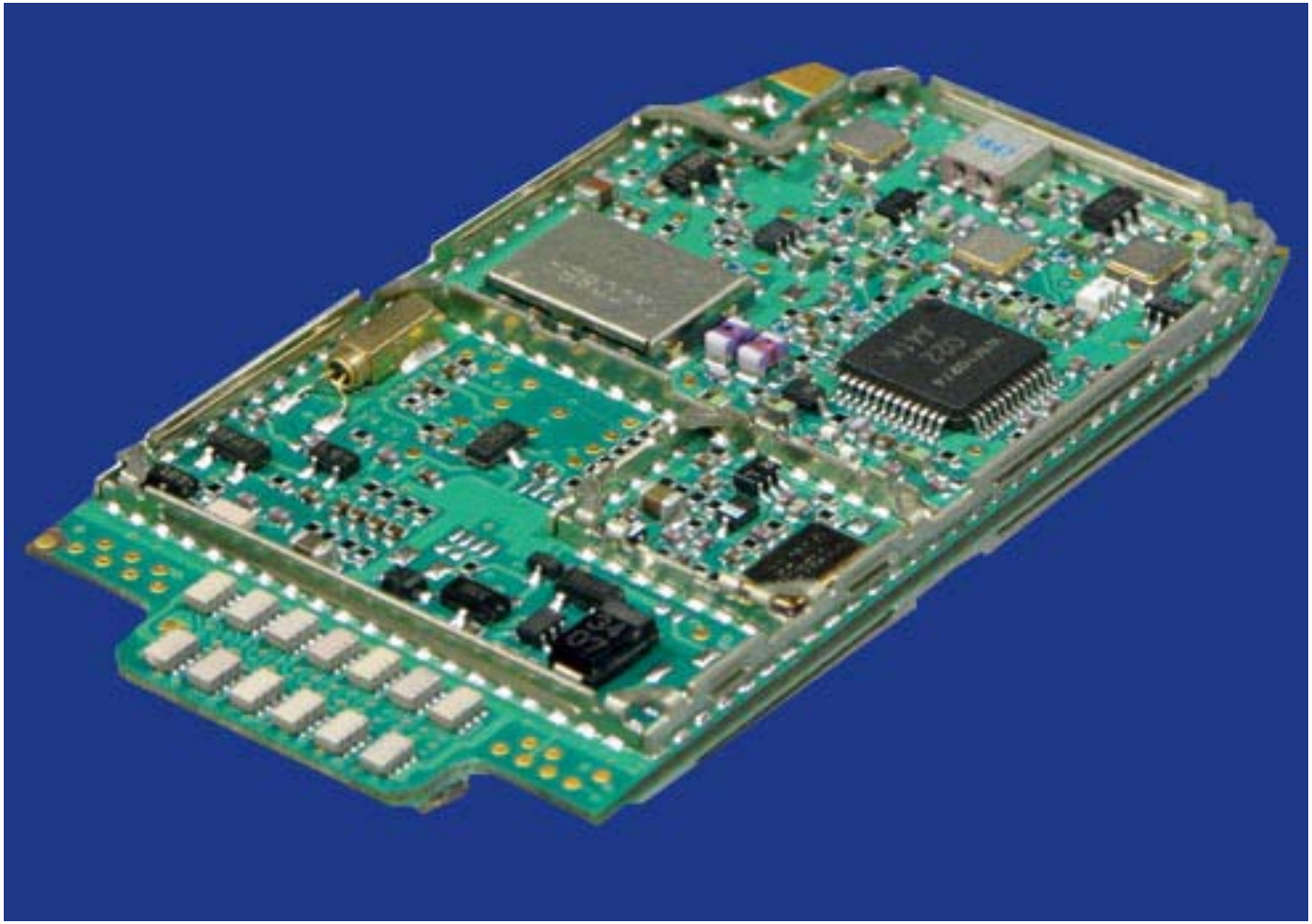
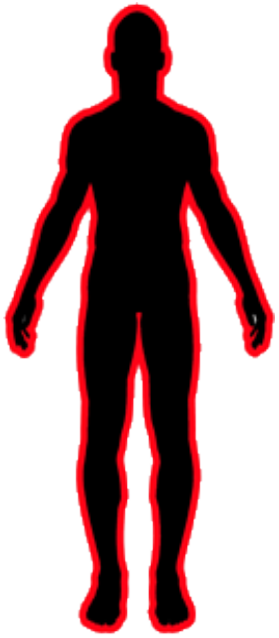




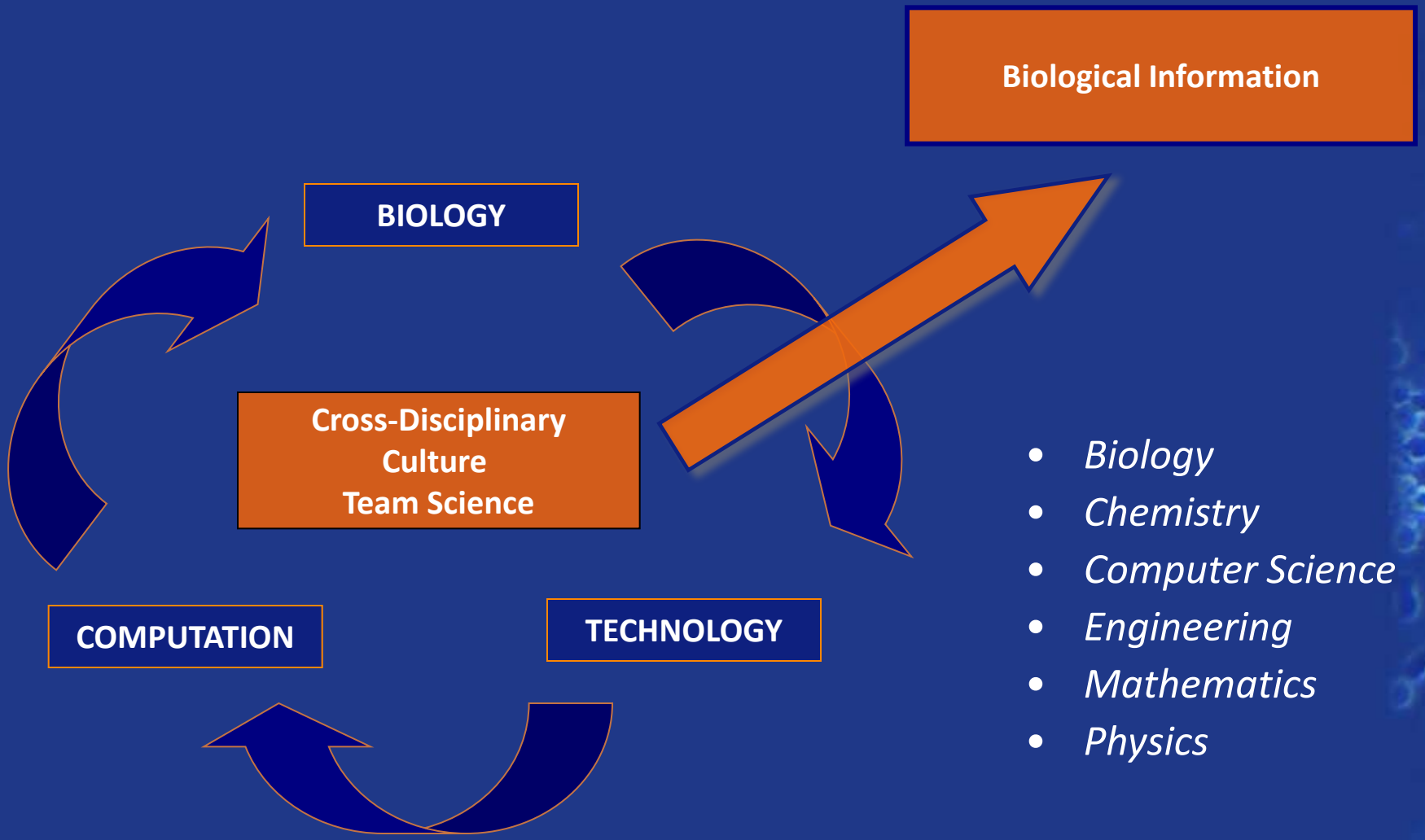
Health



Disease

Intra- and inter-cellular networks

Agenda: Use biology to drive technology and computation.
Need to create a cross-disciplinary culture.



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

A Systems View of Disease

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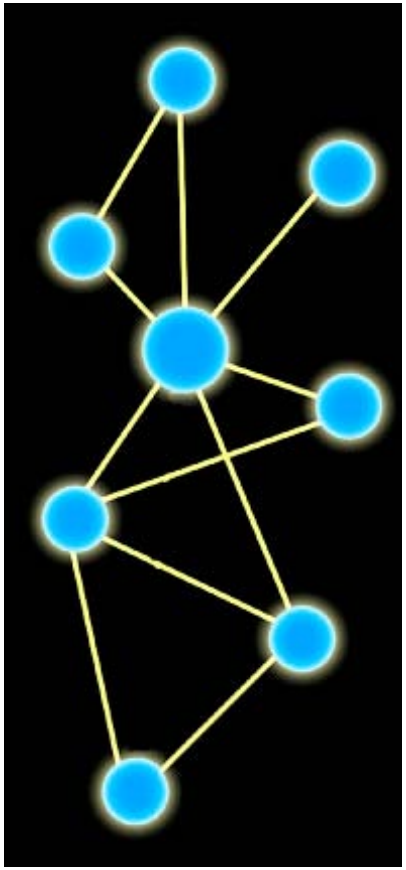
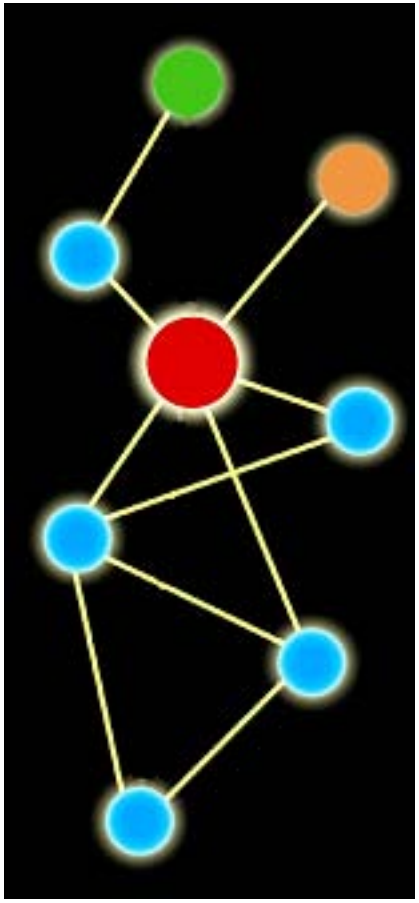
A Systems View of Medicine Postulates that Disease Arises from Disease-Perturbed Networks





dynamics of pathophysiology

diagnosis

therapy

prevention

A Systems Approach to a Neurodegenerative Disease (prion disease) in Mice

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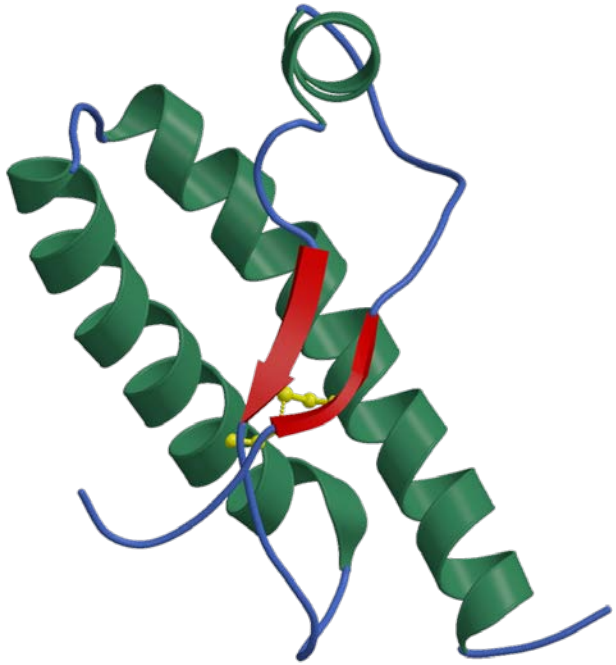
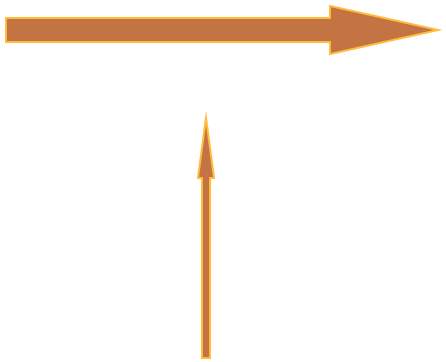
Prion Disease :

Prion Protein Exists in Two Forms



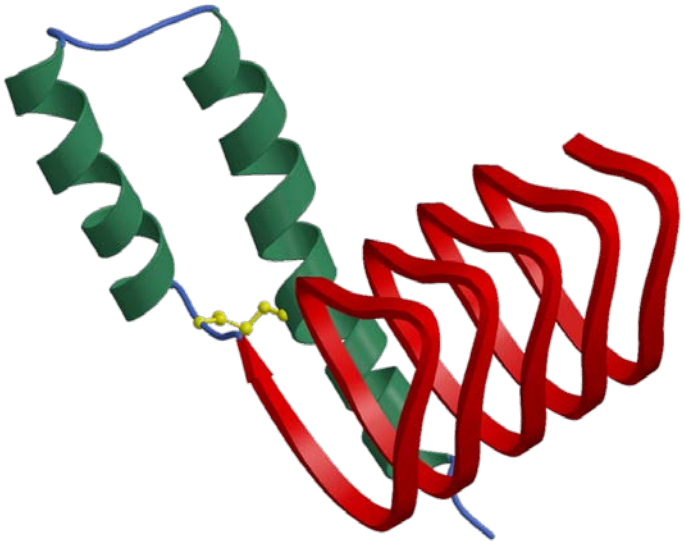
Cellular **PrP^{C}**



PrP Genetic Mutations

PrPSc Infections

Spontaneous conversion



Infectious **PrP^{Sc}**

Initiate the disease (infection) and follow it longitudinally

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

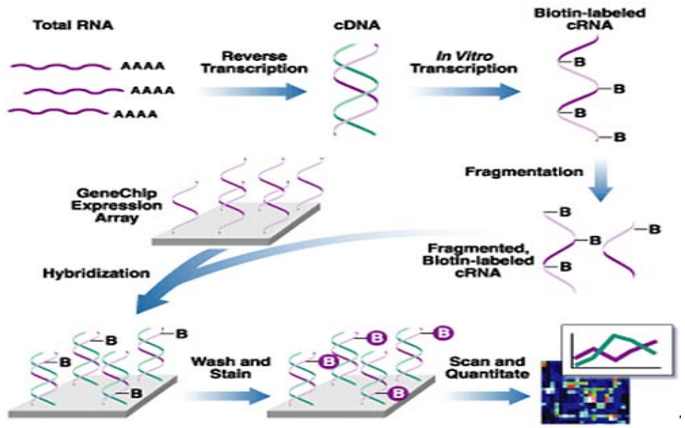
Prion infected brain

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

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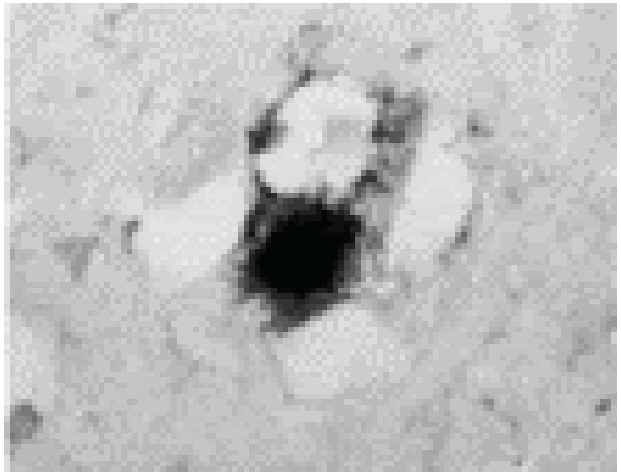
Prion disease in eight mouse strains/prion strain combinations dealing with the biological signal to noise challenge through subtractive analyses

Group	Mouse	*Prnp* Genotype	Prion Strain	Incubation Time (d)
1	C57BL/6J	*a/a*	RML	~150
2	B6.I-1	*b/b*	301V	~120
3	FVB/NCr	*a/a*	RML	~150
4	B6.I-1	*b/b*	RML	~350
5	C57BL/6J	*a/a*	301V	~260
6	(FVB x FVB.129-*Prnp*^{tm1Zrch})	*a/0*	RML	~400
7	Tg(MoPrP-A)B4053	*30 x a*	RML	~60
8	FVB.129-*Prnp*^{tm1Zrch}	*0/0*	RML	No illness

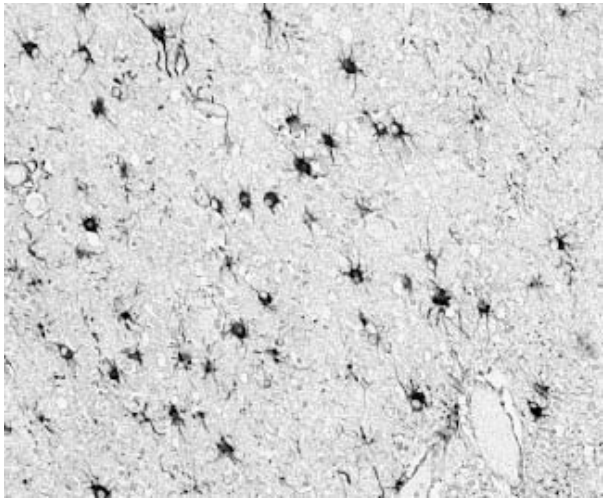
Differentially Expressed Genes--DEGs—from 7400 to 333 encoding the core prion disease response

Neuropathology Identifies 4 Major Disease-Perturbed Networks for Prion Disease

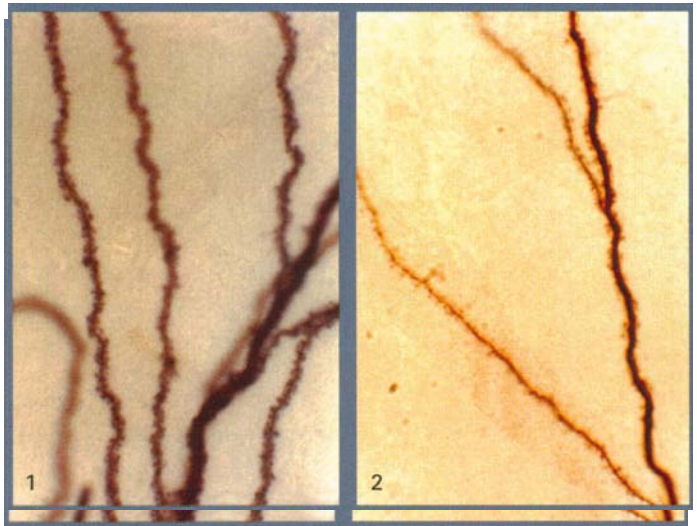
PrP accumulation



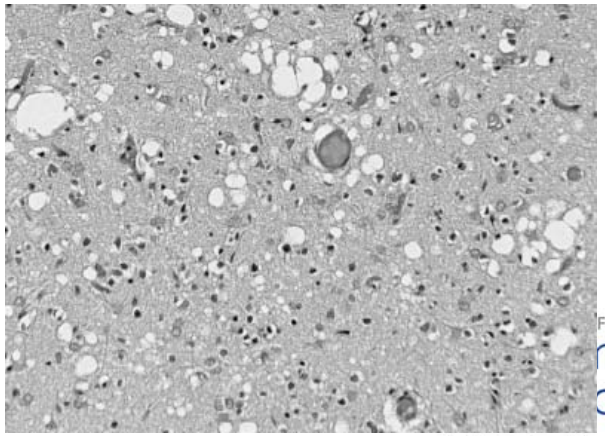
Microglia/astrocyte activation



Synaptic degeneration



Nerve cell death



Integration of Six Data Types for Prion Disease Studies in Mice

- Deep brain transcriptome analyses at 10 time points across disease onset in 8 mouse strains
- Correlate with protein interaction data from known (histopathology) disease-perturbed networks
- Correlation with dynamical histopathological studies
- Spatial distribution of infectious prion protein in the brains across disease progression
- Correlation with clinical signs
- Brain-specific blood protein concentration changes permit following disease

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Examine DEG Dynamics of 4 Prion Disease-Perturbed Networks

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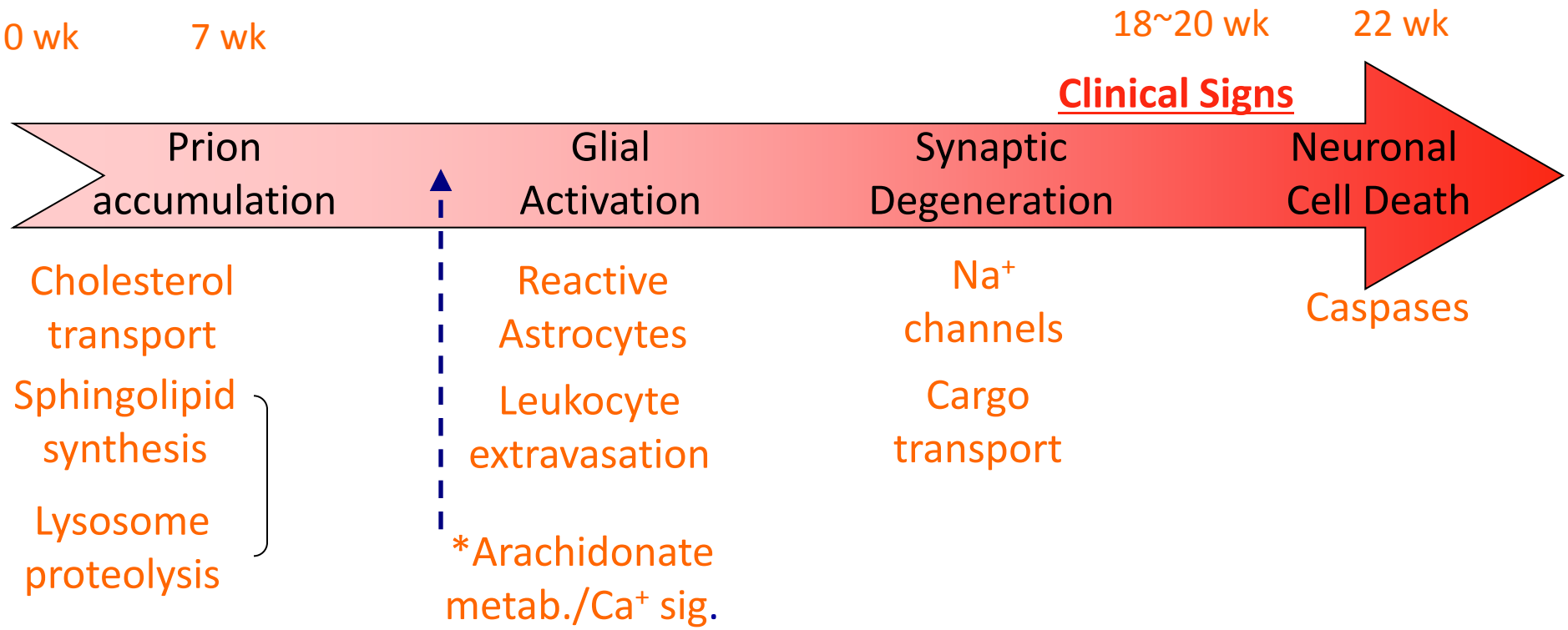
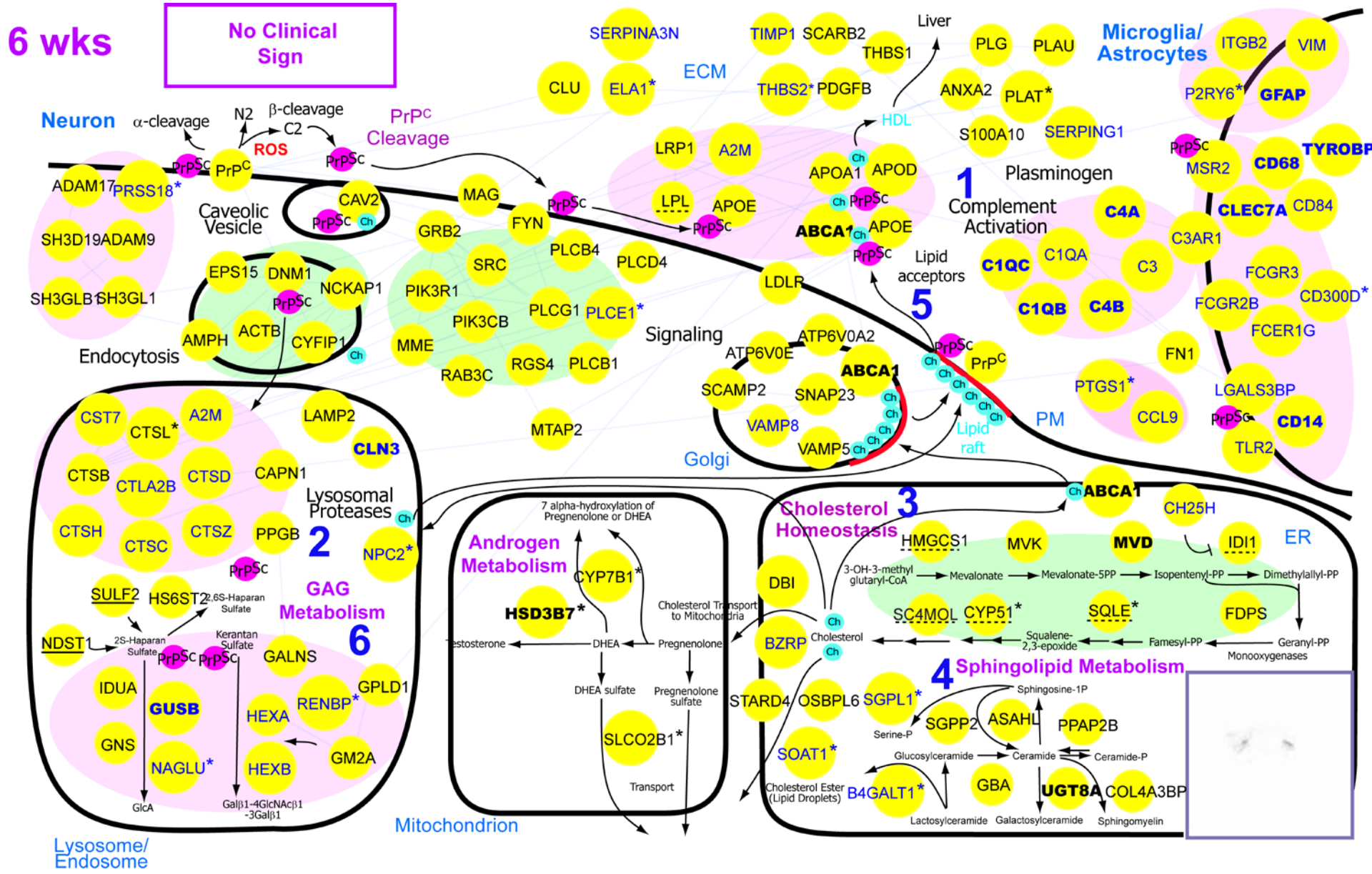
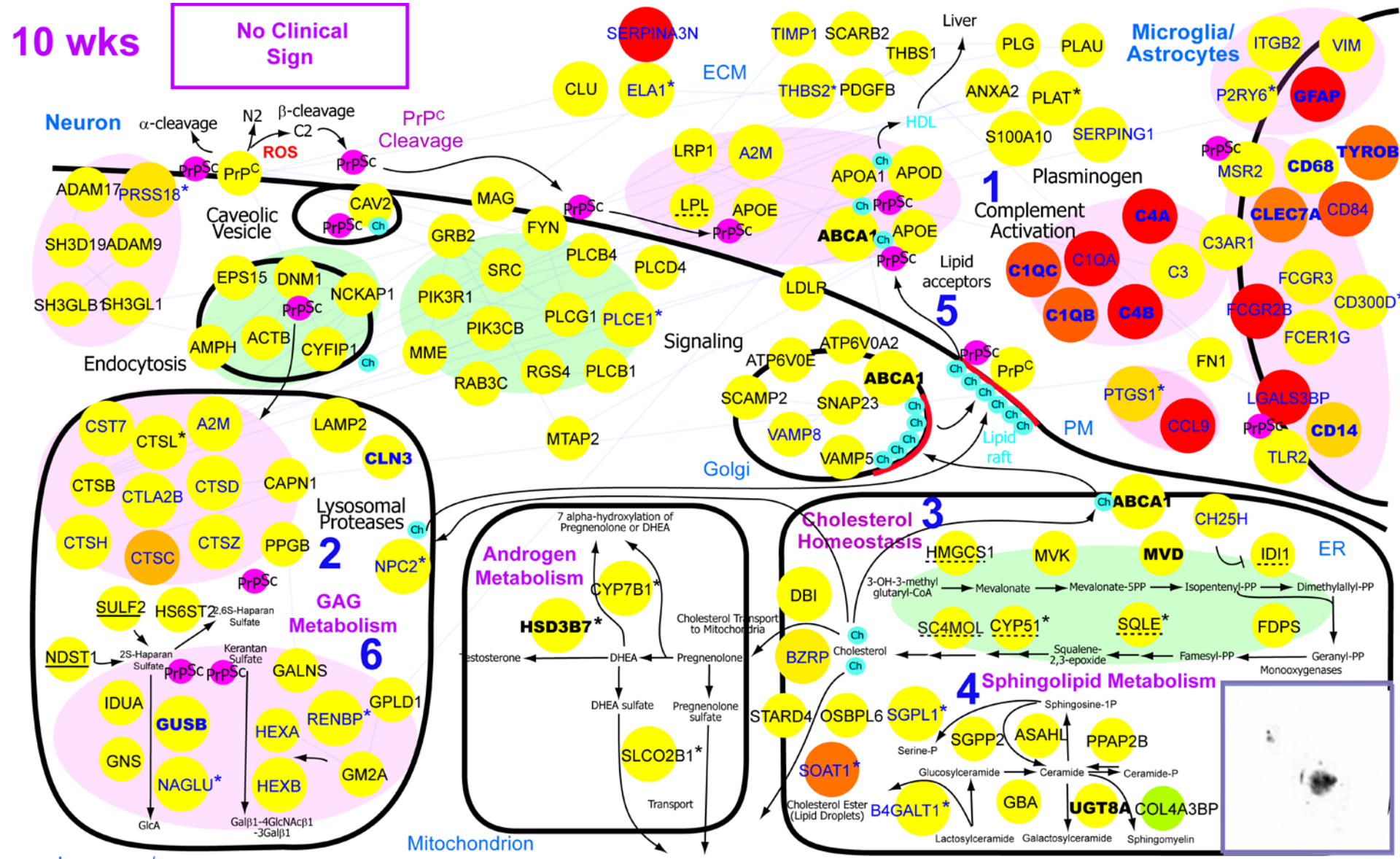
Sequential Disease-Perturbation of the Four Networks of Prion Disease



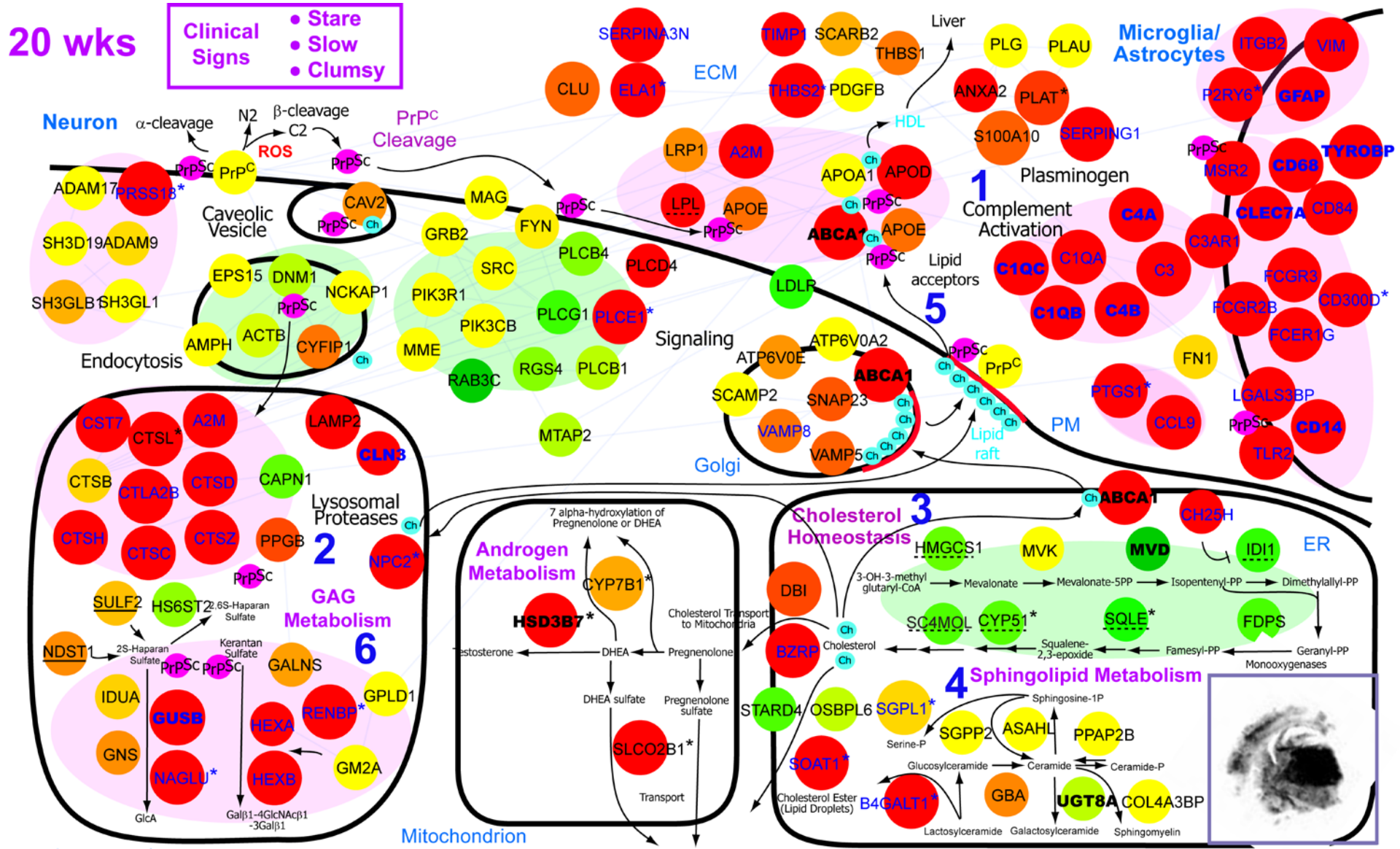
PrP accumulation and replication network—6 weeks



PrP accumulation and replication network—10 weeks



PrP accumulation and replication network—20 weeks



Network Dynamics of DEGs Encoding Known and Novel Prion Disease Phenotypes Provide Striking Insights

- 333 DEGs encode core prion disease
- 231/333 DEGs encode known 4 disease-perturbed networks from histopathology
- 102/333 DEGs encode 6 novel disease-perturbed networks--the dark genes of prion disease
- Disease-perturbed networks sequentially activated
- The dynamics of these disease-perturbed networks explain virtually all of the pathophysiology of prion disease
- New approach to drug target discovery—re-engineer disease-perturbed networks to normalcy with multiple drugs.
- Make blood a window into health and disease—systems diagnostics.

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A Systems Approach to Blood Diagnostics

Making Blood a Window into Health and Disease:

- Blood biomarkers that are chosen from dynamic network analyses—biologically relevant to the biology of the disease
- Blood biomarkers that are organ specific—reflections of disease

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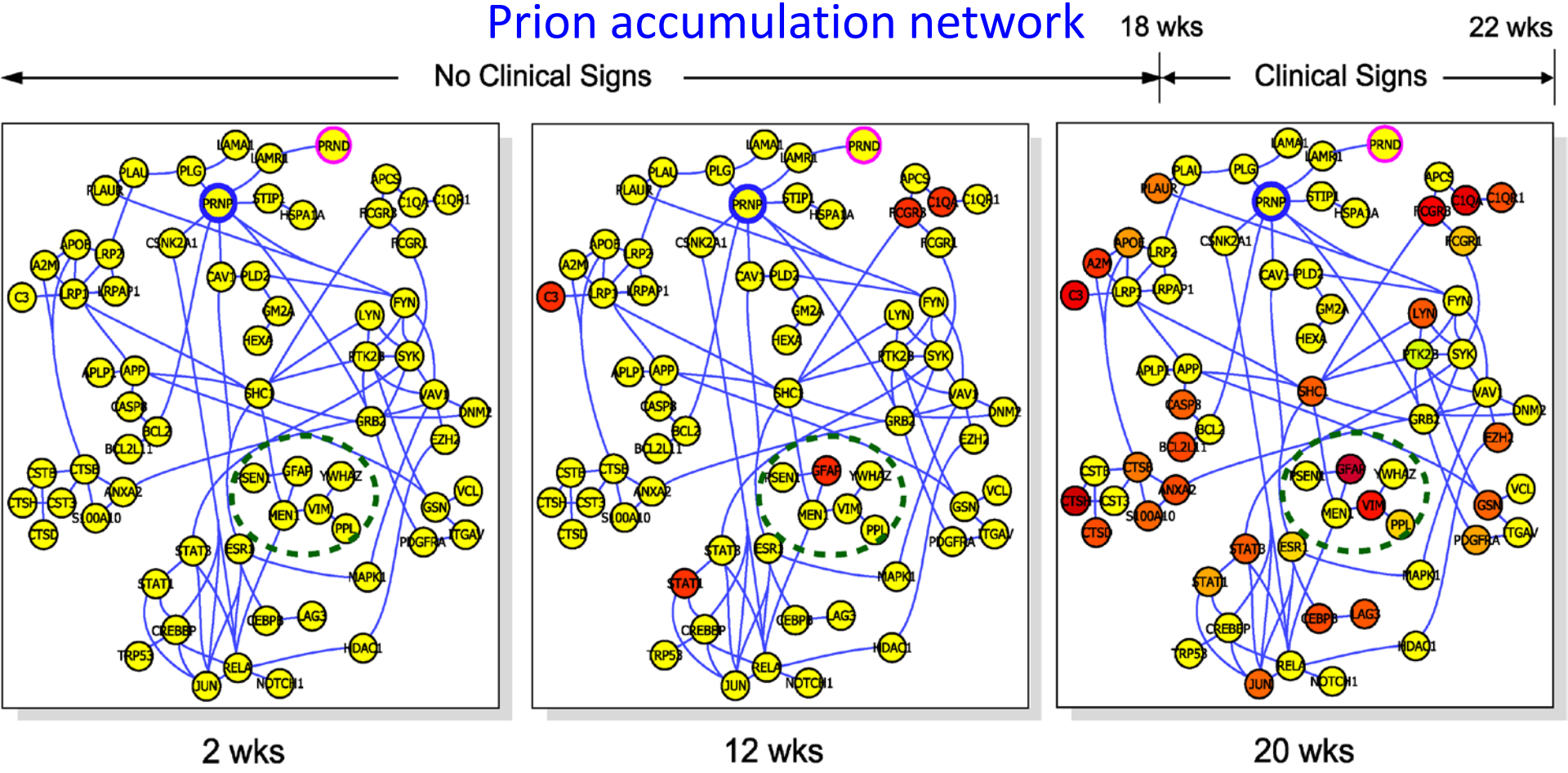
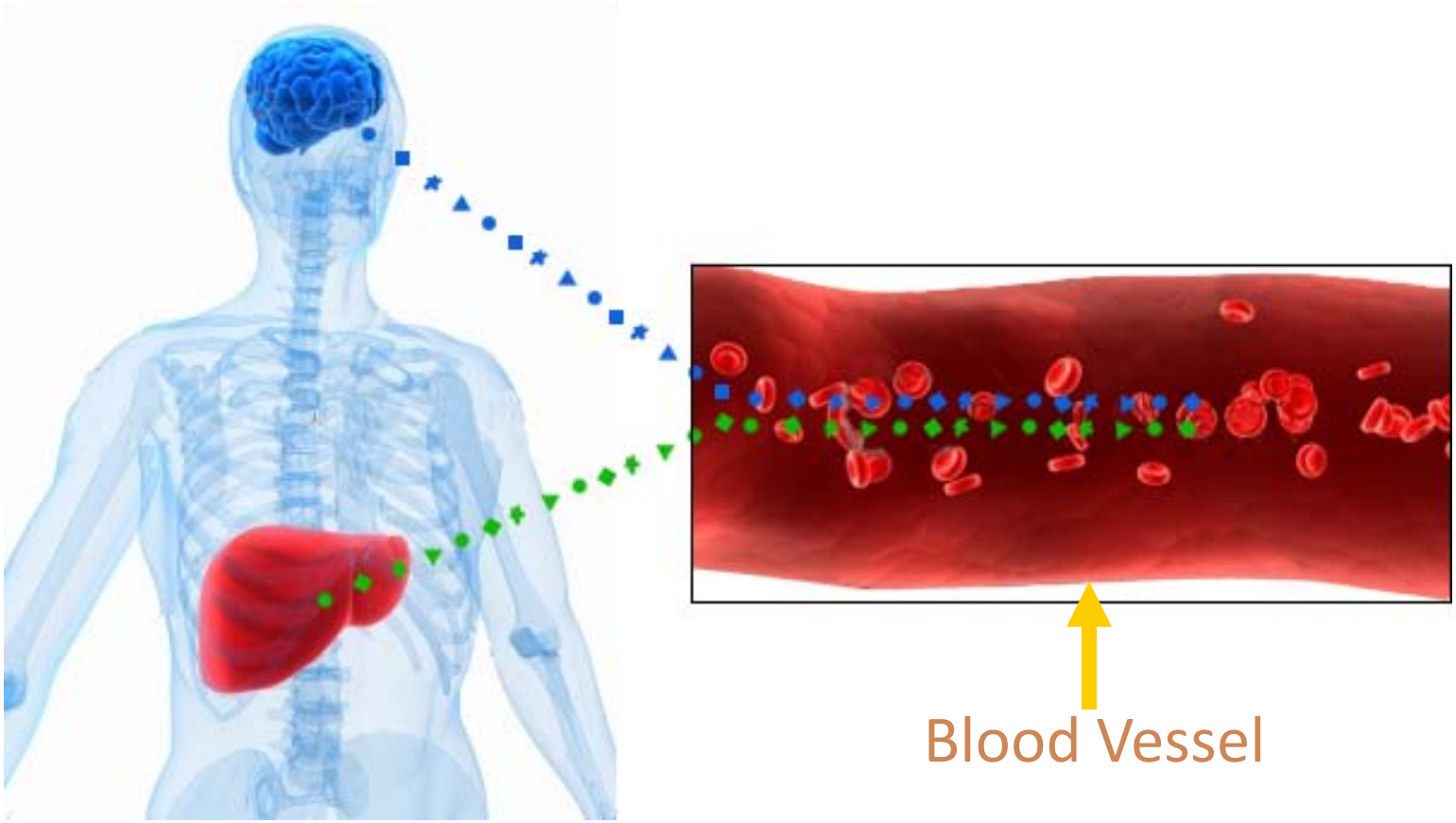
Dynamics of a Brain Network in Prion Neurodegenerative Disease in Mice

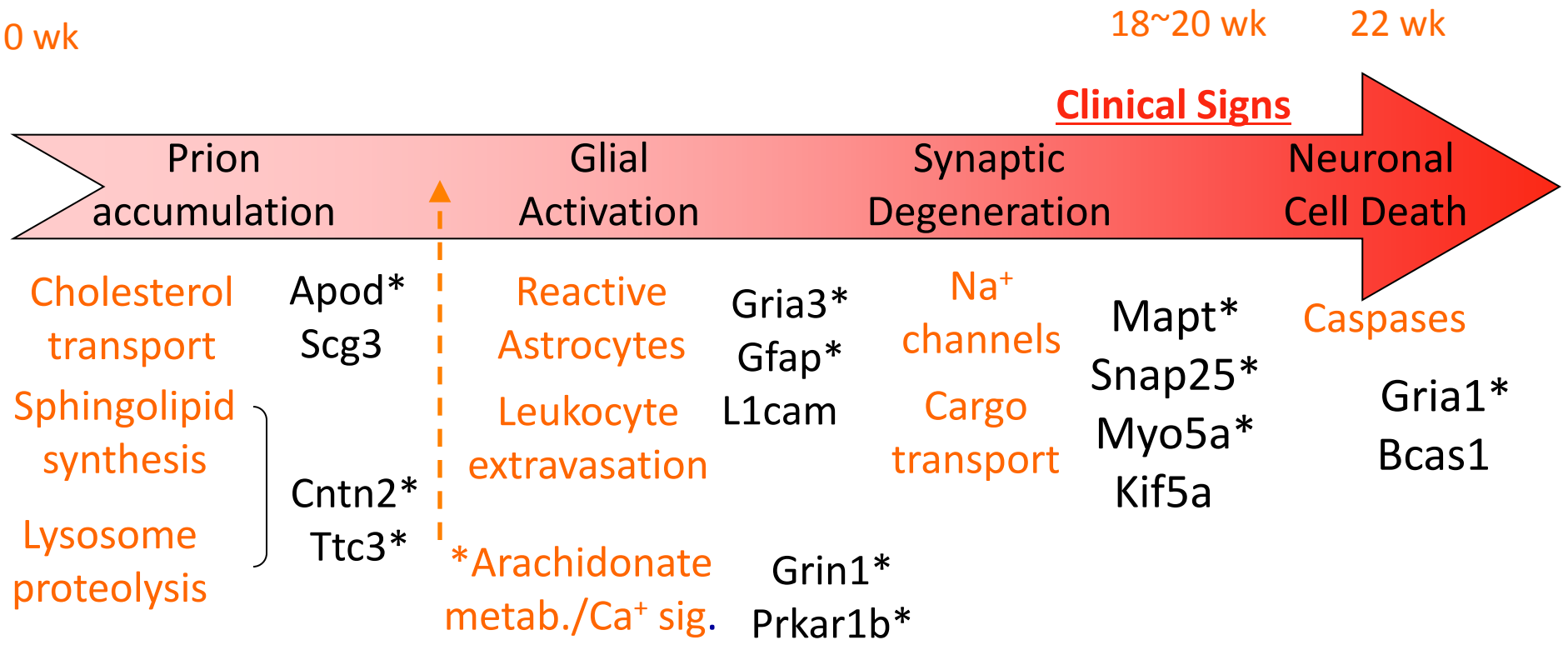


Making Blood A Window Distinguishing Health and Disease

Organ-specific Blood Proteins



15 Brain-Specific Blood Proteins Indicate Timing of Activation of Disease-Perturbed Networks



* indicates brain-specific blood proteins

Why Systems-Driven Blood Diagnostics Will Be the Key to P4 Medicine

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

Integrated Diagnostics

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Four ISB Technology-Driven New Big Projects

- Complete genome sequencing of families—integrating genetics and genomics—an important aspect of systems genetics (connecting genotype/environment to phenotype)
- 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

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Whole Genome Sequencing of Families: Integrating Genetics and Genomics—Systems Genetics

- Sequencing by Complete Genomics, Inc.
- D. Galas, J. Roach, G. Glusman and A. Smit at ISB
- Collaboration with human geneticists at the UW and Utah

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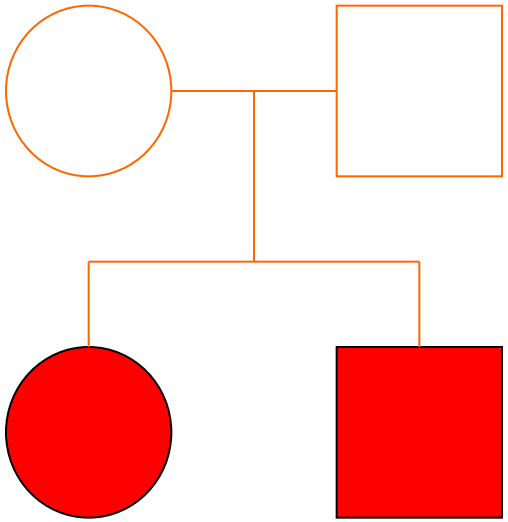
Whole Genome Sequencing of Family of Four



Unaffected parents

Children each with 2 diseases--craniofacial malformation (Miller Syndrome) and lung disease (ciliary dyskinesia)

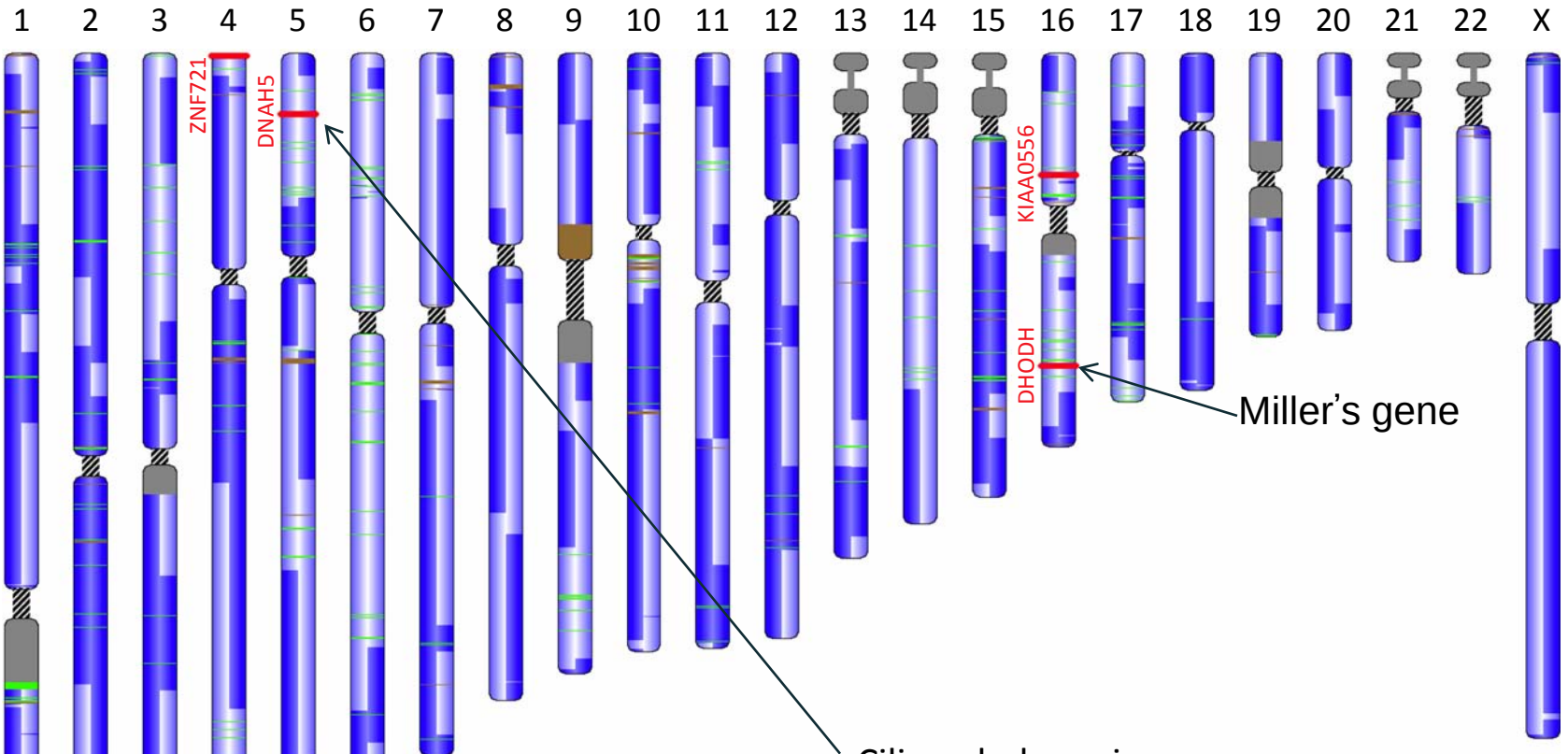
Identify 70% of sequence errors using principles of Mendelian genetics —less than 1/100,000 error rate—now 1/ 1,000,000

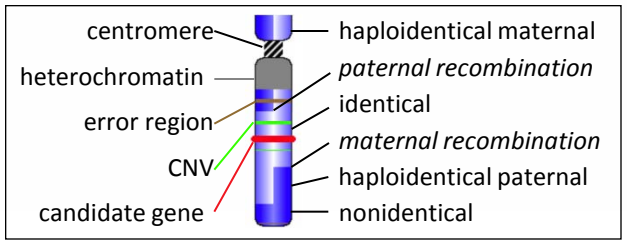
Discovery of about 230,000 rare variants in family—confirmed by identification in two or more family members

Reduce the genome haplotype search space for disease genes—Mendelian haplotype blocks reduce space to ¼ haplotypes for each individual

First time to determine intergenerational mutation rate in humans—30/child

Genomes of kids





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

Family Genome Sequencing May Facilitate Finding

- Mendelian disease genes
- Modifiers of disease genes--sequencing genomes of 65 Huntington's patients from families—mostly finished
- Genes encoding complex genetic diseases after proper patient stratification—Alzheimer's/Parkinson's diseases

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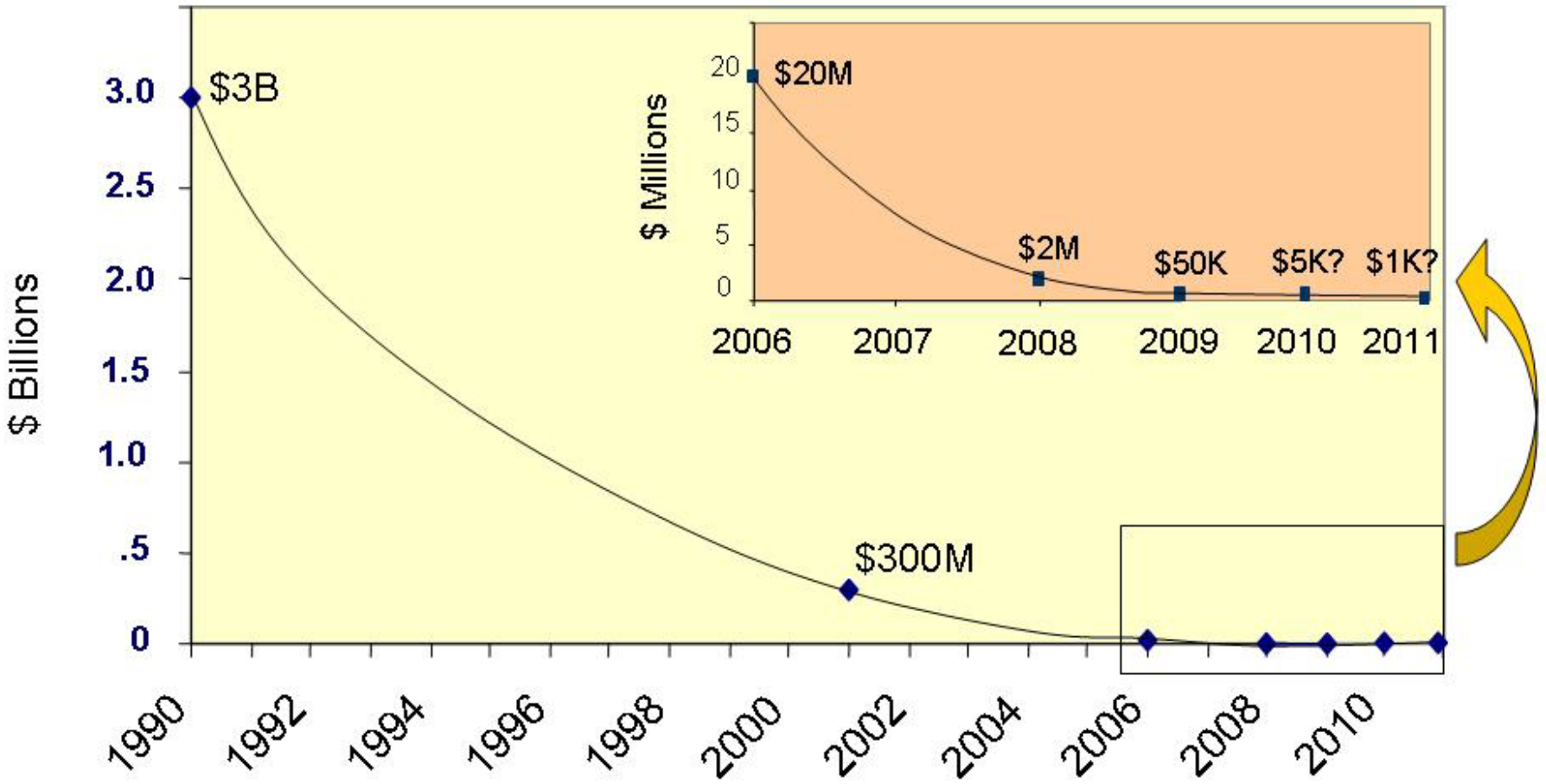
Game Changer--
Declining Cost of Sequencing Genomes: A Part of Your Medical Record



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Making Blood a General Window into Health and Disease

Microfluidic Protein Chips

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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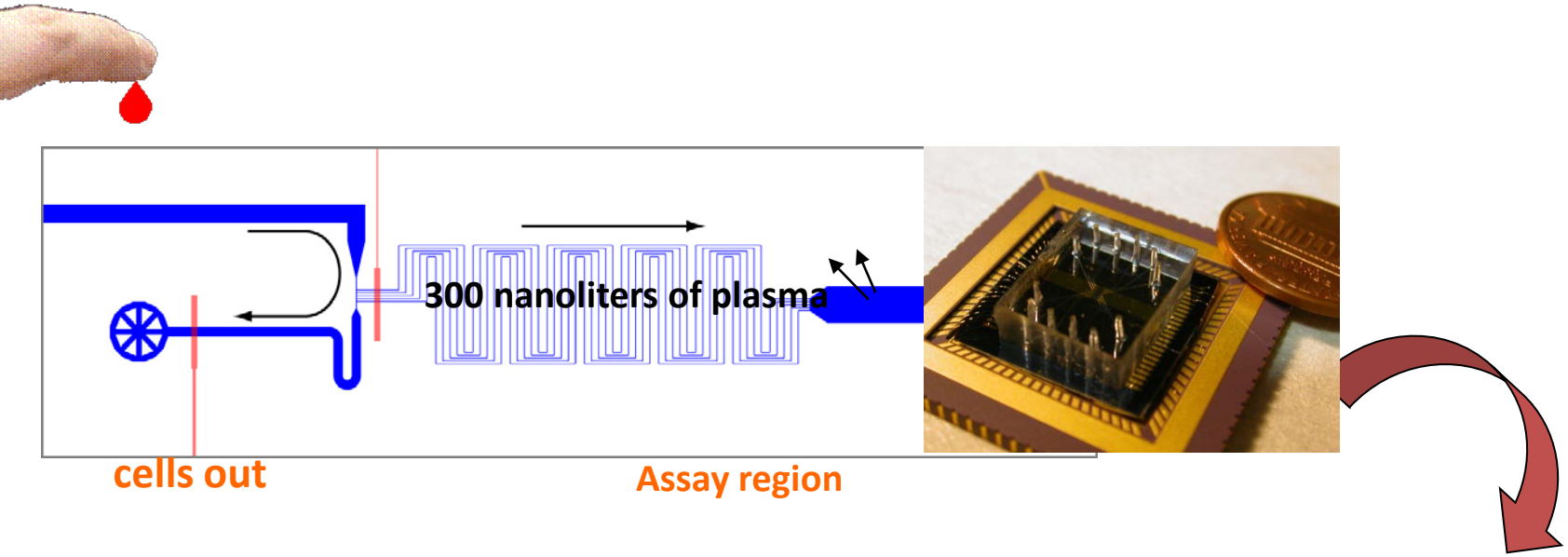
In vitro molecular diagnostics:

Integrated nanotech/microfluidics platform



1. Measure 50 proteins
2. From a fraction of a droplet of blood
3. 5 minute assay
4. 10^6 dynamic range

Jim Heath, et al

Technologies 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
  - 106 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 13,000 human proteins—against autoimmune or allergic sera--stratify.
  - Single molecule protein analyses—blood organ-specific proteins and single cell analyses

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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 epithelial cells from blood cells—cancer

- 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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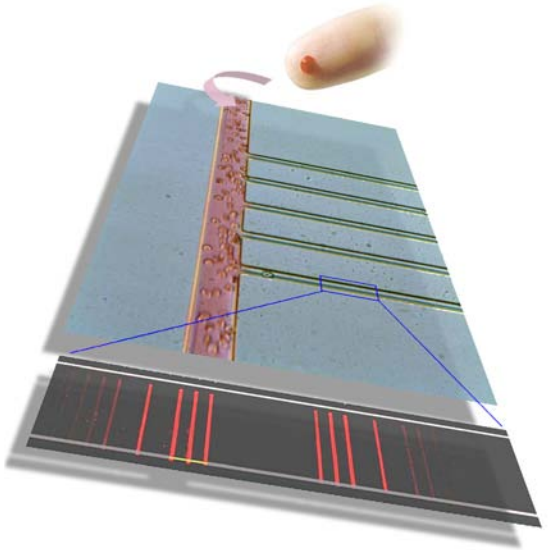
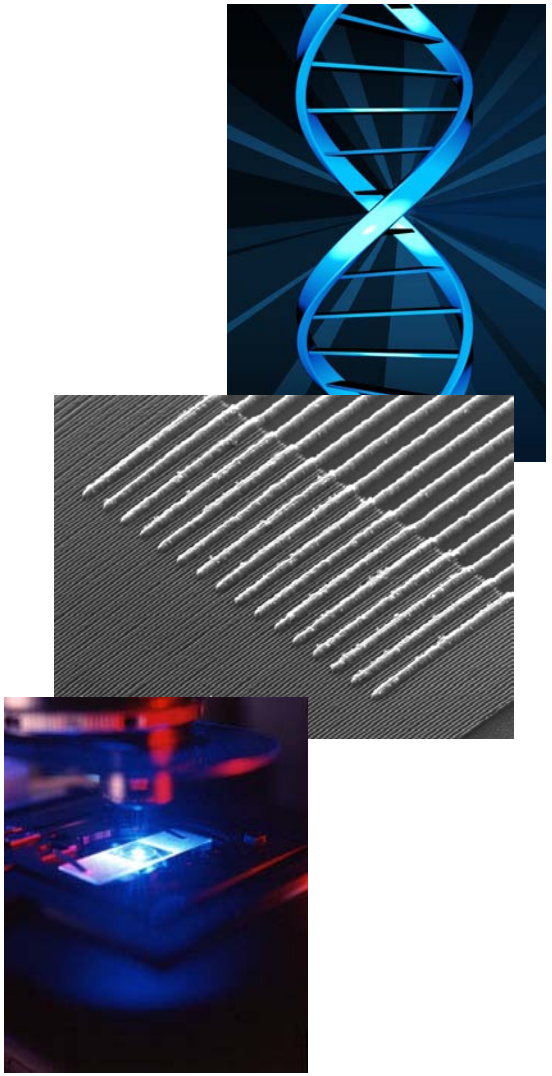
Predictive, Personalized, Preventive and Participatory (P4) Medicine

- Driven by systems approaches to disease, new measurement (nanotechnology) and visualization technologies and powerful new computational tools, P4 medicine will emerge over the next 10-20 years



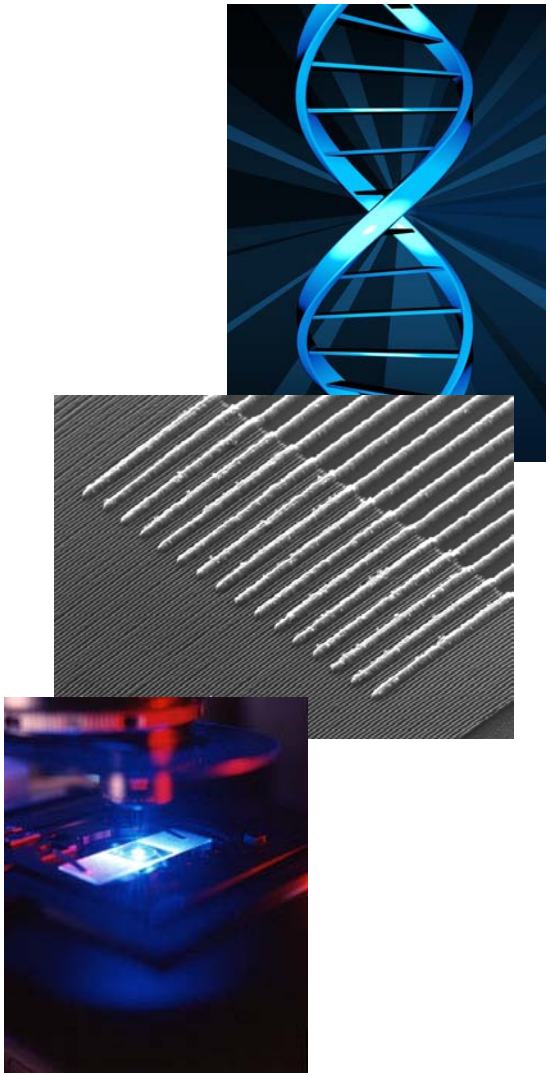
P4 Medicine

- Predictive
  - Probabilistic health history--DNA sequence
  - Biannual multi-parameter blood protein measurements



P4 Medicine

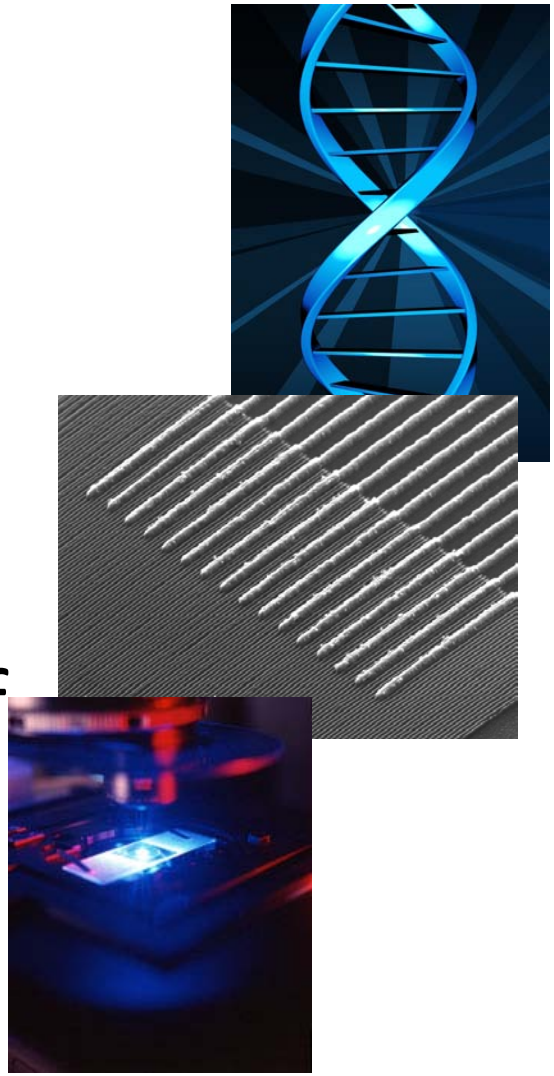
- Personalized
  - Unique individual human genetic variation mandates individual treatment
  - Patient is his or her own control—longitudinal data
  - Billions of data points on each individual
  - Hundreds of millions of patients with billions of data points



P4 Medicine

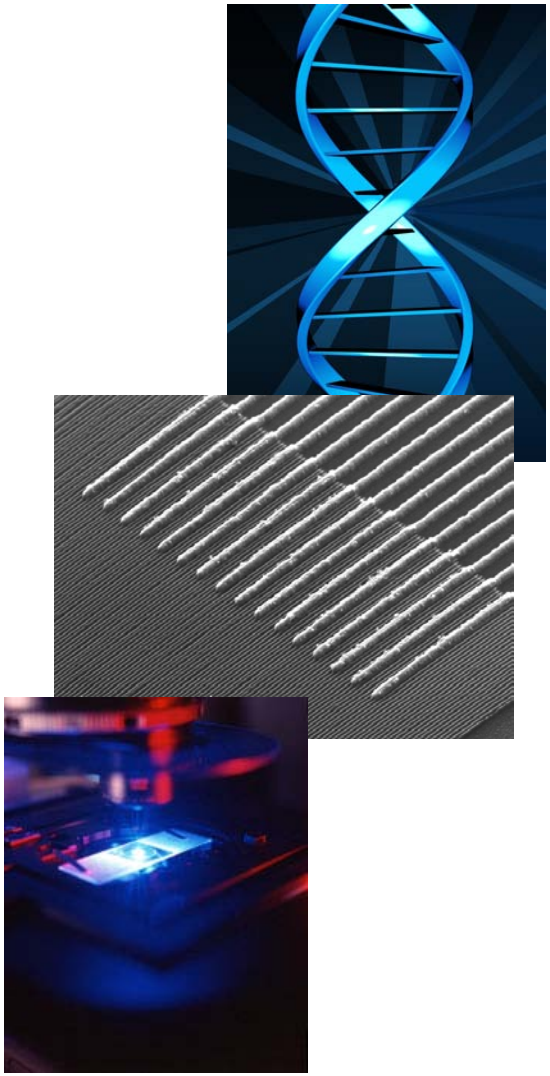
- Preventive
  - Design of therapeutic and preventive drugs

    via systems approaches
  - Systems approaches to creating effective vaccines will transform prevention of infectious diseases
  - Transition from a focus on disease to a focus on wellness



P4 Medicine

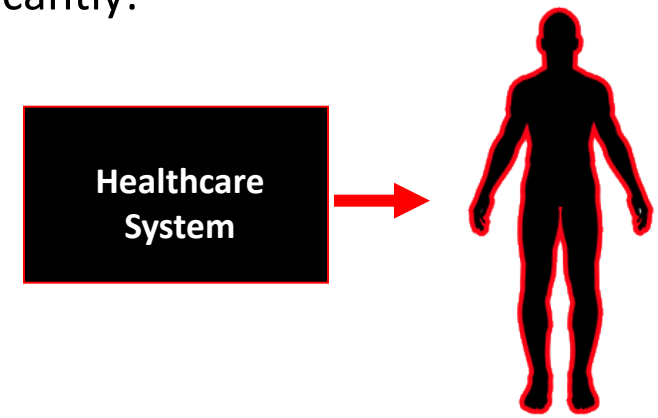
- Participatory
  - Patient understands and participates in medical choices
  - Physicians trained before P4 will have to understand it
  - Medical community—interconnected and educated
  - Create IT for healthcare to handle billions of data points for100s of millions of



P4 Medicine Will Transform the Health Care Industry

Will impact the health care system significantly:

- Pharmaceuticals
- Biotechnology
- Diagnostics
- IT for healthcare
- Healthcare industry
- Health insurance
- Medicine--diagnostics, therapy, prevention, wellness
- Nutrition
- Assessments of environmental toxicities
- Academia and medical schools



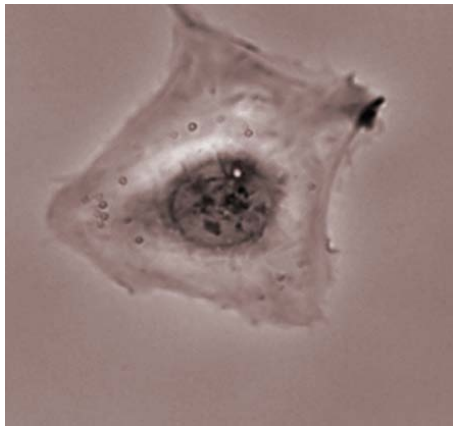
Fundamentally new ideas need new organizational structures

P4 Medicine Will Catalyze the Digitalization of Medicine

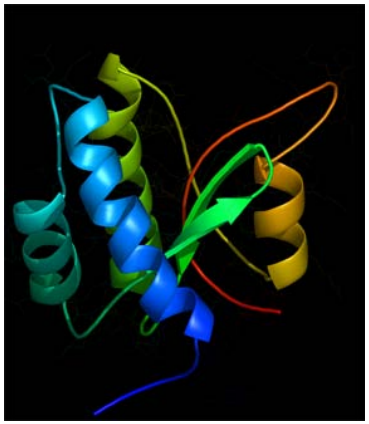
- Analysis of single molecules, single cells, single organs and single individuals—actionable consequences
- Recording patient data routinely on i-phones—easy access by patient and physician—patient centric medicine
- A revolution that will transform medicine even more than digitalization transformed information technologies and communications

Single individual

Single cell



Single molecule



Why the P4 Medicine Will Turn Around the Sharply Escalating Costs of Healthcare

- Diagnosis will stratify disease and create an impedance match effective drugs—companion diagnostics
- Re-engineering disease-perturbed networks to normalicy with drugs—new and less expensive strategy for drug target discovery
- Survey wellness biannually with 2500 blood organ-specific protein measurements—50 from each of 50 organs—global early detection
- Technologies exponentially increasing in measurement potential (digitalization of medicine) to sculpt for individuals the dimensions of health/disease while dramatically decreasing in cost, e.g. sequencing a human genome in 2000 about $300 million dollars; in 2010 about $6000—a 50,000-fold decrease in cost
- Digitalization of medicine
- Other medical advances arising from mechanistic insights—stem cells, neurodegenerative, aging, vaccines, cancer etc.

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P4 Medicine Will Become One of the Most Powerful Public and Private Investments of the 21st Century

- Moving into an information-based economy and society where educated people are the key investment—and their long-term wellness is a critical benefit for increasing productivity.
- P4 medicine will catalyze new healthcare industrial opportunities:
  - Promote an emerging wellness industry by providing the metrics for patients to actively participate in optimizing their own wellness—promote a wellness industry
  - Catalyze a new industrial opportunities based new strategies for dealing with actual or potential disease

Challenges of P4 Medicine

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Two Challenges for P4 Medicine

- Technical—strategies, technologies, computational/mathematical tools
- Societal—ethics, legal, social, security, privacy, policy, regulation, economics, access to patient records and materials for mining the predictive medicine of the future

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Inventing the Future

- Analyzing one gene and one small problem at a time

- Systems analysis of biology and medicine--e.g., predictive, preventive, personalized and participatory (P4) medicine
- Technology development
- Pioneer computational tools
- Transferring knowledge to society--joining academics and industry--changing K-12 science education--P4 medicine and society
- Strategic partnerships—for big scientific problems--P4 medicine--industrial, academic,

ISB's Strategic Partners for P4 Medicine

- Develop the P4 tools and strategies for patient assays—State of Luxembourg--$100 million over 5 years
- Bring P4 medicine to patients with the creation of the non-profit P4 Medical Institute (P4MI) in partnership with Ohio State Medical School—two pilot projects—wellness and heart failure

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The P4 Medicine Institute (http://www.P4MI.org)

- Vision--identify, recruit and integrate strategic partners with ISB to bring P4 medicine to patients.
- Create an network of medical centers, academics and industry partners who share the P4 vision and have complementary skills/resources.
- Create pilot projects at each medical center to validate the power of P4 medicine.
- Communicate the P4 vision to the broader healthcare community.
- Create a network of consultants to meet the societal opportunities and challenges of P4 medicine— social networking, crowd sourcing, ethics, security, confidentiality, policy, regulation, economics, etc.
- Non-profit 501c3--ISB and Ohio State founding members

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Essences of P4 Medicine

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P4 Medicine Is Personalized Medicine and Far More

- P4 medicine is revolutionary rather than evolutionary or incremental
- P4 medicine is medicine of the present/near future.
- P4 medicine is driven by an information view of medicine, systems approaches to disease, emerging technologies and powerful analytic tools
- P4 medicine will use measurements to quantify wellness and its transition into disease
- P4 medicine sees the patient (consumer) as the central focus of healthcare
- Pilot projects with informational assays in patient groups will be necessary to convince skeptics.
- P4 medicine will restructure the business plans of every sector of the healthcare industry—enormous economic opportunities
- P4 medicine will dramatically reverse the ever escalating costs of healthcare and provide enormous economic benefits to economies—readily available to poor and rich.
- The national healthcare debate in the future should be reframed around P4 medicine rather than the old reactive medicine.

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Conceptual Themes of P4 Medicine

P4 Medicine

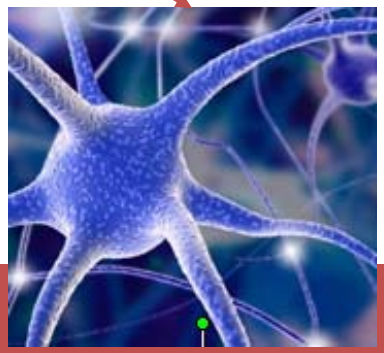
Predictive

Preventive

Personalized

Participatory

Wellness Quantified



Disease Demystified

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Brain imaging—Nathan Price (UI)

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