

Title: Systems Biology, Emerging Technologies and The Transformation from Reactive to Proactive (P4) Medicine

Date: May 04, 2011 07:00 PM

URL: <http://www.pirsa.org/11050071>

Abstract: Imagine medicine that is predictive, personalized, preventive and participatory

Systems Biology, Emerging Technologies and the Transition from Reactive to Proactive (P4) Medicine

Predictive, personalized, preventive and participatory

Medicine is a bottom-up informational science

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P4 Medicine Employs Staggering Amounts of Information--In 10 years Billions of Data Points Will Surround Each Individual

TeleHealth

110101000
101010101
101010101
001000101
101010001
101010001

Phenome

Na143 K 3.7
BP 110/70
HCT32 BUN
12.9 Pulse
110 PLT150
WBC 9200
HbC 92

Social Media

110101000
101010101
101010101
001000101
101010001
101010001

Epigenome

110101000
101010101
101010101
001000101
101010001
101010001

Genome

GCGTAG
ATGCGTAG
GCATGCAT
GCCATTAT
ACCTTC



Transcriptome

UUAGUG
AUGCGUCU
AGGCAUGC
AUGCC

Proteome

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

Transactional

110101000
101010101
101010101
001000101
101010001

Single Cell

110101000
101010101
101010101
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101010001

iPS Cells

110101000
101010101
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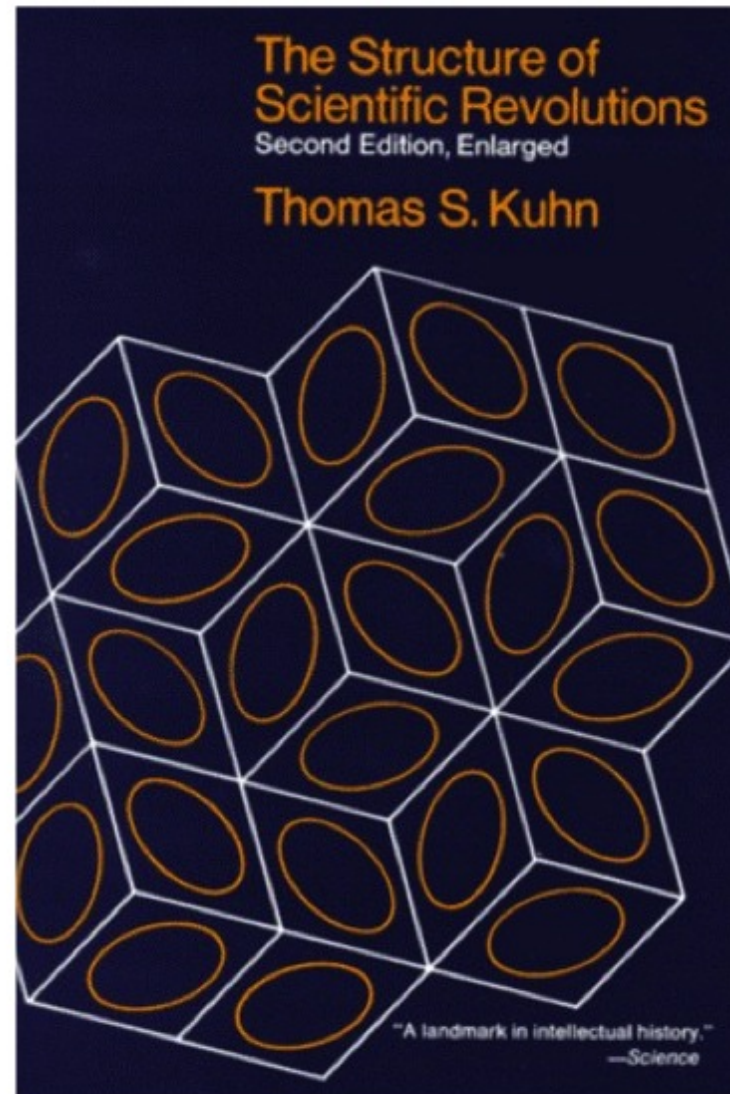
Outline of Lecture

- Complexity and paradigm changes
- Science and technology of P4 medicine
- Implications for you (the patient)
- Implications for society and for science

The Grand Challenge of the 21st Century in Science and Technology Is Complexity

- New concepts, strategies and technologies permit biologists to successfully begin to attack biological complexity
 - View biology as an **informational science**
 - **Systems approaches** permit one to attack complexity effectively
 - Evolving current and **emerging technologies** permit the exploration of new areas of data space (and improve the old)
 - **Computation and mathematical tools** permit one to acquire, store, transmit, integrate, mine and create predictive models.
- These approaches will allow us to effectively attack some of society's most vexing challenges—all big problems—**healthcare (P4 medicine), global health, environment, energy, nutrition, agriculture, etc.**

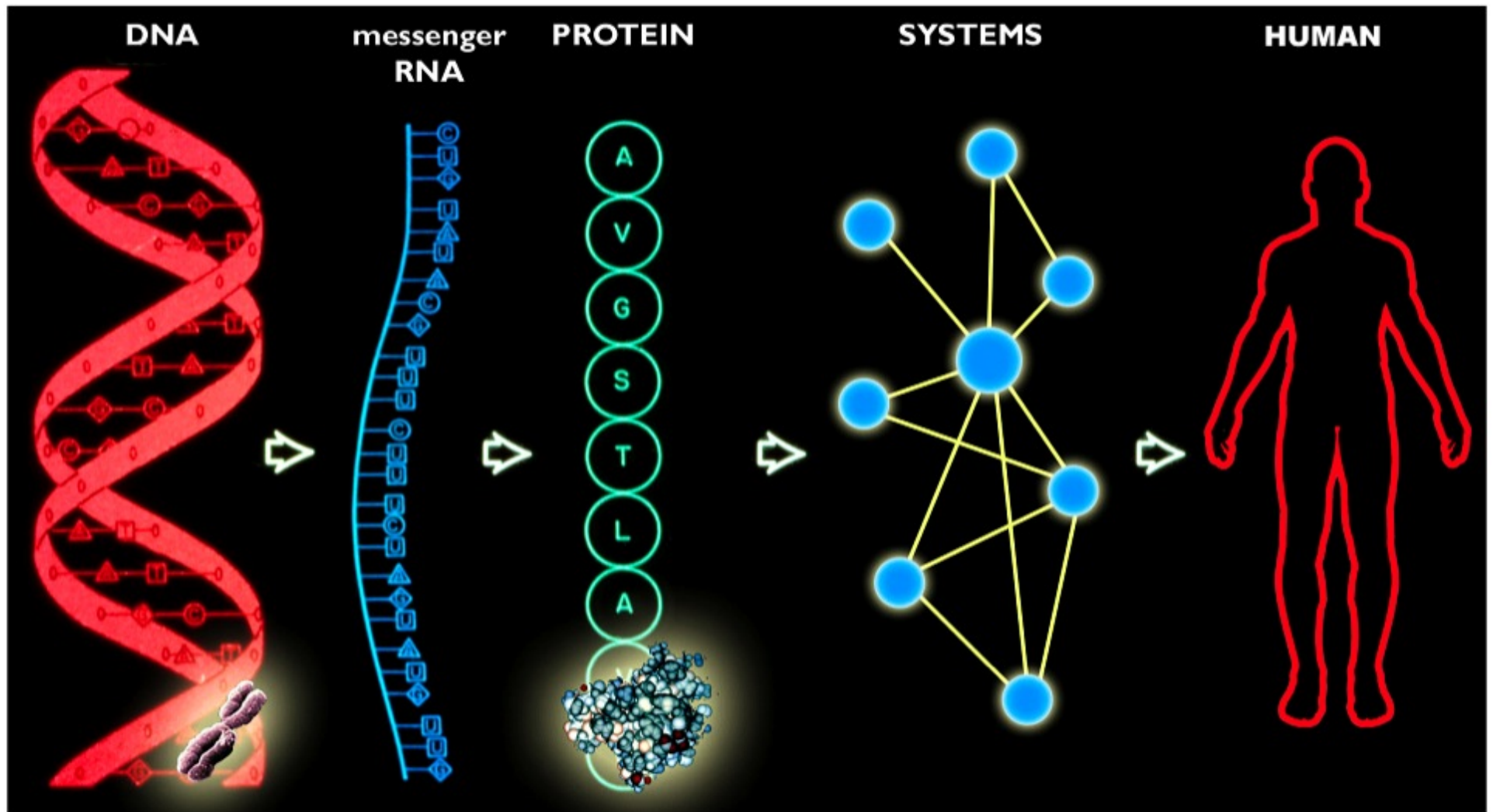
Paradigm Changes Drive Radical Changes in Science



I Participated in Four Paradigm Changes in Biology from 1970 to 2011 Leading to a Fifth Paradigm Change--P4 Medicine

- Bringing engineering to biology (high throughput biology)

Information in Biology in 1970



Five Instruments Developed in the Hood Laboratory

Protein Sequencer+
Protein Synthesizer+
DNA Sequencer+
DNA Synthesizer+

Ink-jet DNA Array Synthesizer*

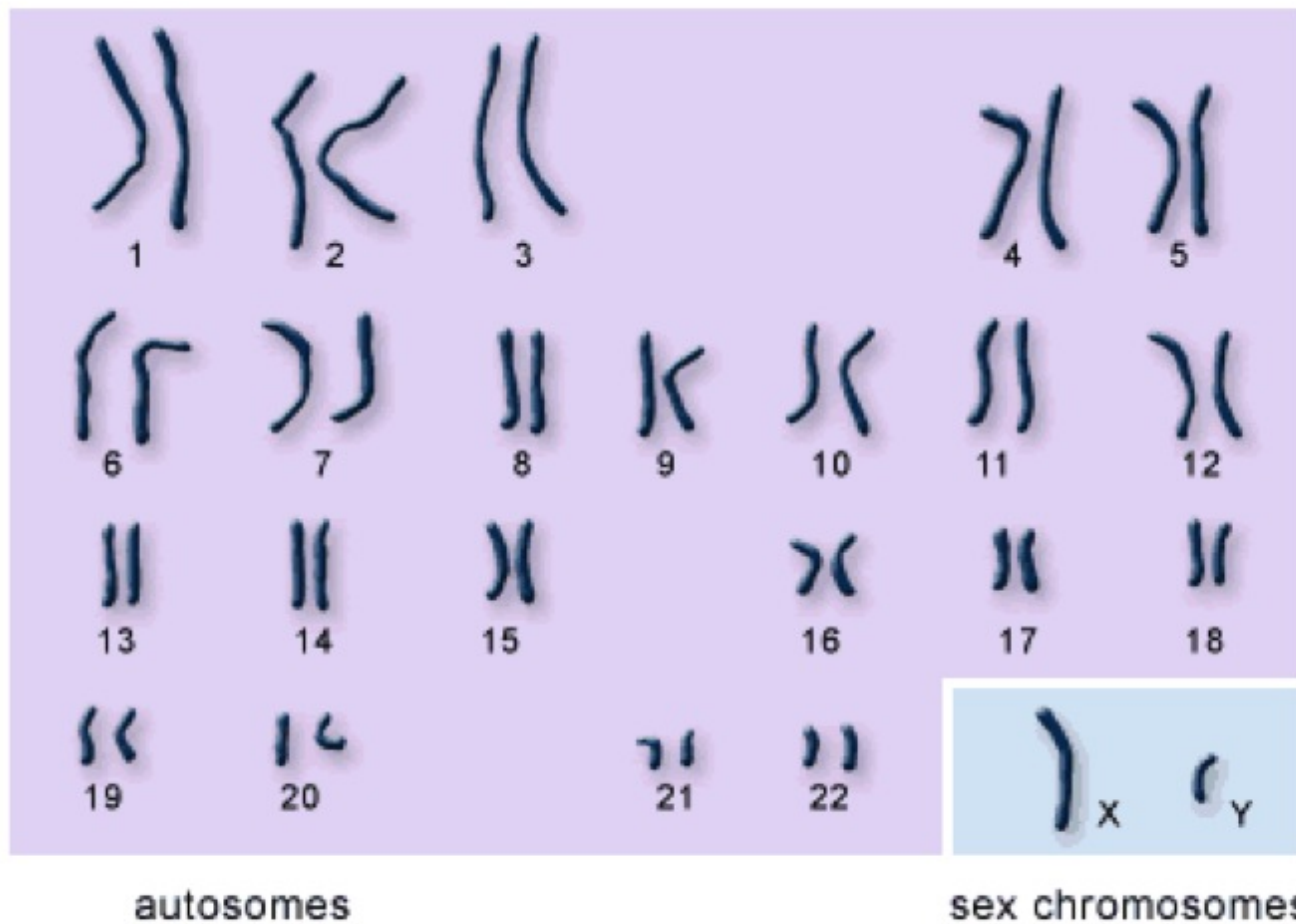
+Caltech—commercialized by Applied Biosystems

*University of Washington—commercialized by Agilent

I Participated in Four Paradigm Changes in Biology from 1970 to 2011 Leading to P4 Medicine

- Bringing engineering to biology (high throughput biology)
- The human genome project

The Human Genome



Your body has 10^{14} cells and 6 billion letters of DNA are in the nucleus of each cell—6 meters of DNA

Your body has DNA that would reach to the sun and back—2000 times.



How Did the Genome Project Transform Biology?

- Provided a complete parts list of genes (and proteins)—enabled systems biology
- Made all genes (and all other potentially interesting regions of the genome) available to all scientists—democratization of genome
- High throughput sequencing and other technologies drove the development of high throughput data generation platforms—next step in bringing engineering to biology
- Enable mass-spectrometry-based proteomics (global study of proteins)
- Drove the development of sophisticated computational and mathematical approaches to biology—brought computer scientists/mathematicians to biology
- Instituted the vision of immediate open data access
- Demanded a high level of data quality
- Provided genomic access to plants, animals and microbe
- Transformed our understanding of evolution
- Transformed medical diagnostics—pharmacogenomics and disease diagnosis
- Directed the use of therapies for cancer
- Ushered in the world of personalized (P4) medicine
- Introduced to biologists the idea of big science vs. small science
- Spent 5% budget on social, ethical and legal issues—science must be socially responsible

I Participated in Four Paradigm Changes in Biology from 1970 to 2011 Leading to P4 Medicine

- Bringing engineering to biology (high throughput biology)
- The human genome project
- Cross-disciplinary biology
- Systems biology

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

- Each fundamentally changed how we think about biology and medicine.
- Each was met initially with enormous skepticism and generally took 10-15 years to realize.
- Each new idea needed new organizational structure.

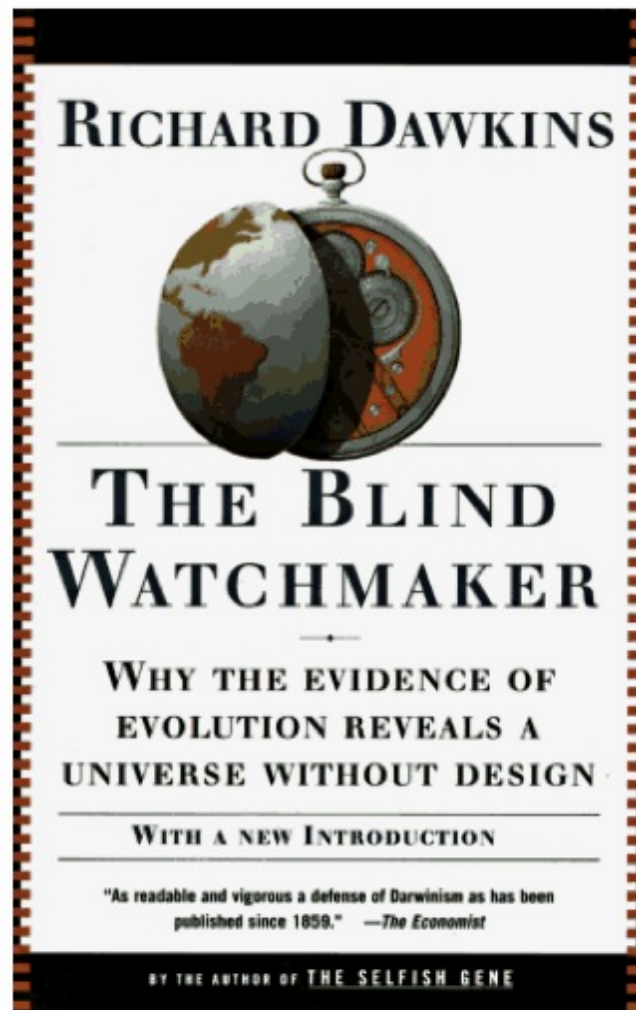
The Foundations of Systems Biology and Systems (P4) Medicine – Four Pillars

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

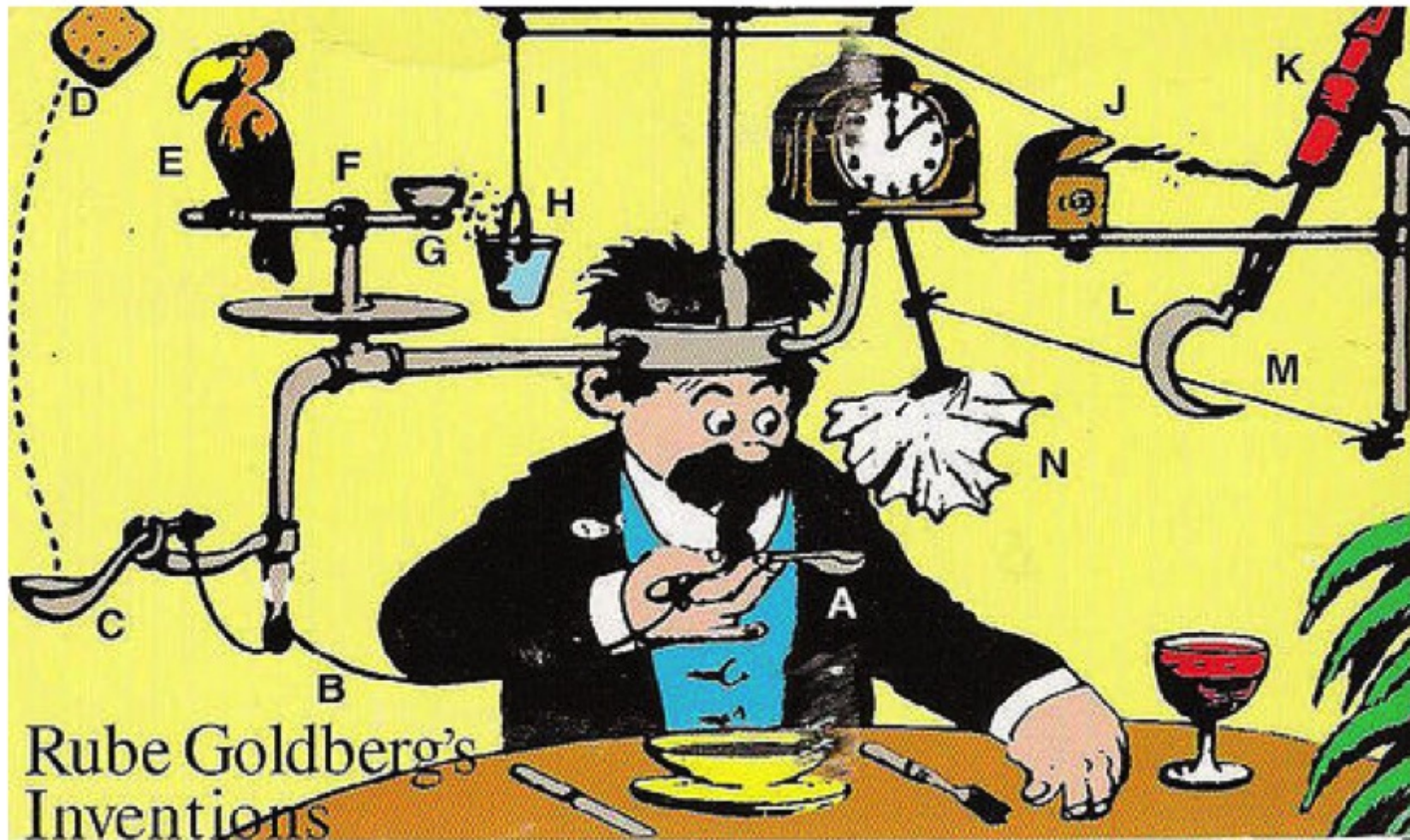
Biology and Medicine are Information Sciences



Evolution arises from random mutations, is driven by environmental challenges and selects solutions building on past successes



Evolution accounts for the magnitude of biological complexity



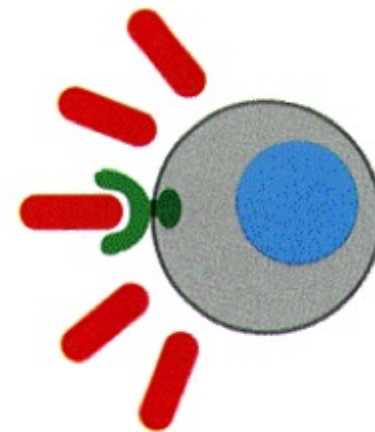
Biological modularity is one key to deciphering complexity



Human Phenotypes are Specified by Two Types of Biological Information

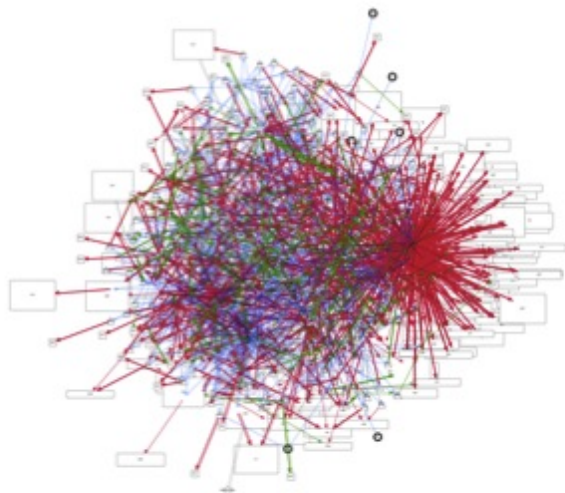
- The **digital information** of the genome
- The **environmental information** that impinges upon and modifies the digital information

```
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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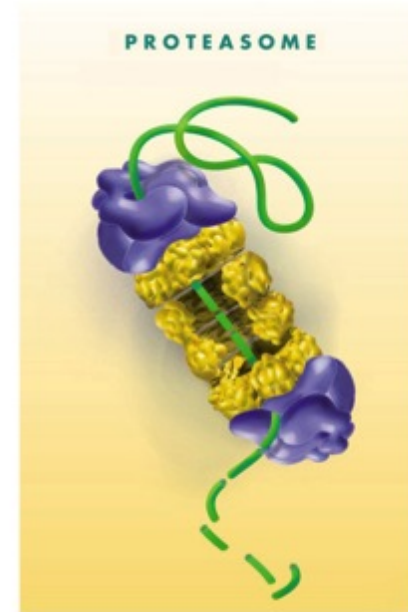


Two General Biological Structures Connect the Genotype/Environment and Phenotype

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



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Left Index Fingerprints from Identical Twins Are Distinct



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

DNA

RNA

Protein

Protein interactions and biomodules

Protein and gene networks

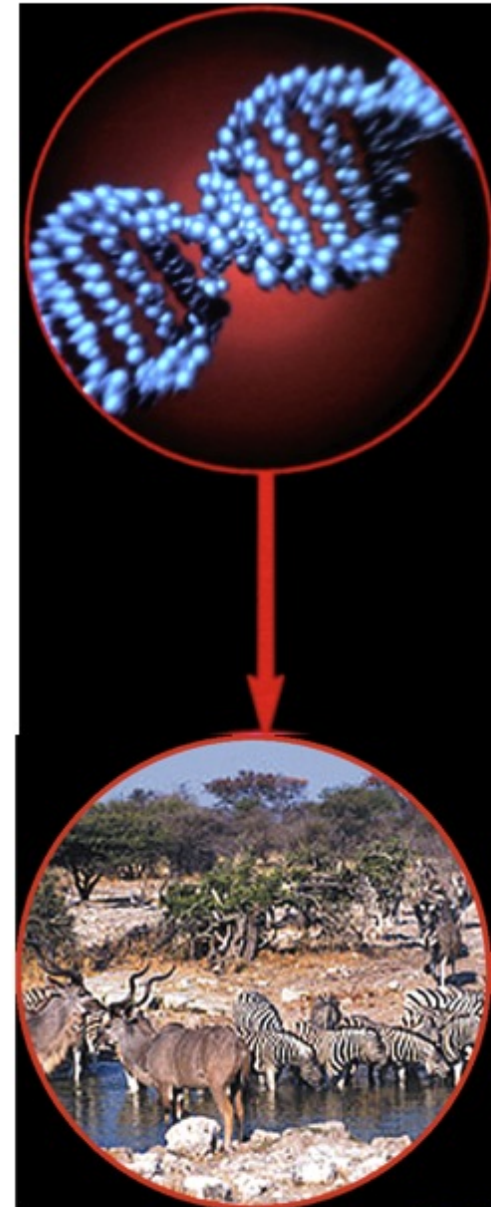
Cells

Organs

Individuals

Populations

Ecologies



The Foundations of Systems Biology and Systems Medicine—Four Pillars

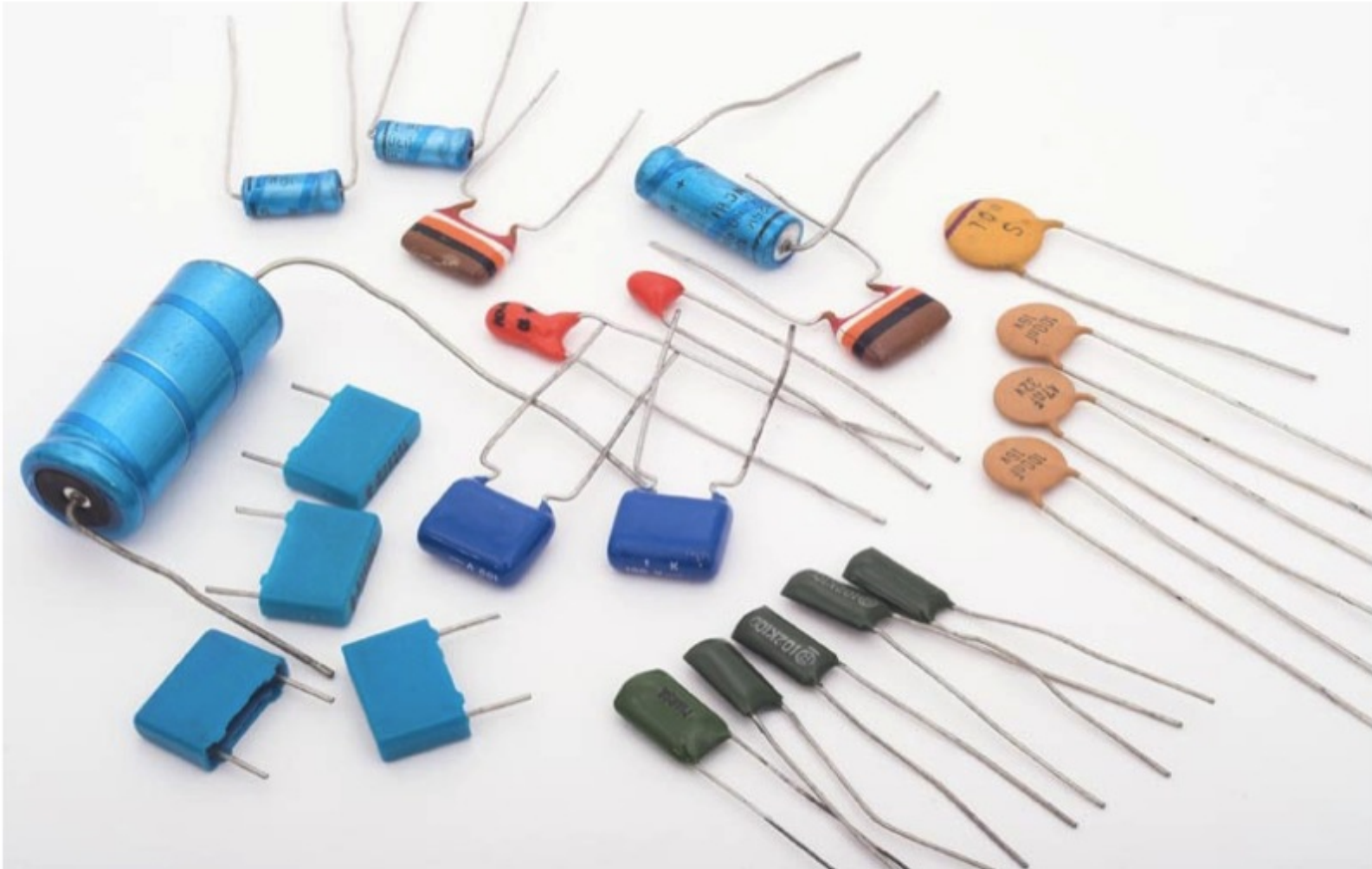
1. View medicine as an informational science
2. **Systems approaches** allow one to understand wellness and disease—holist rather than atomistic approach (systems biology and systems medicine)
3. Emerging technologies will allow us to explore new dimensions of patient data space
4. Transforming analytic tools will allow us to decipher the billions of data points for the individual--sculpting in exquisite detail wellness and disease

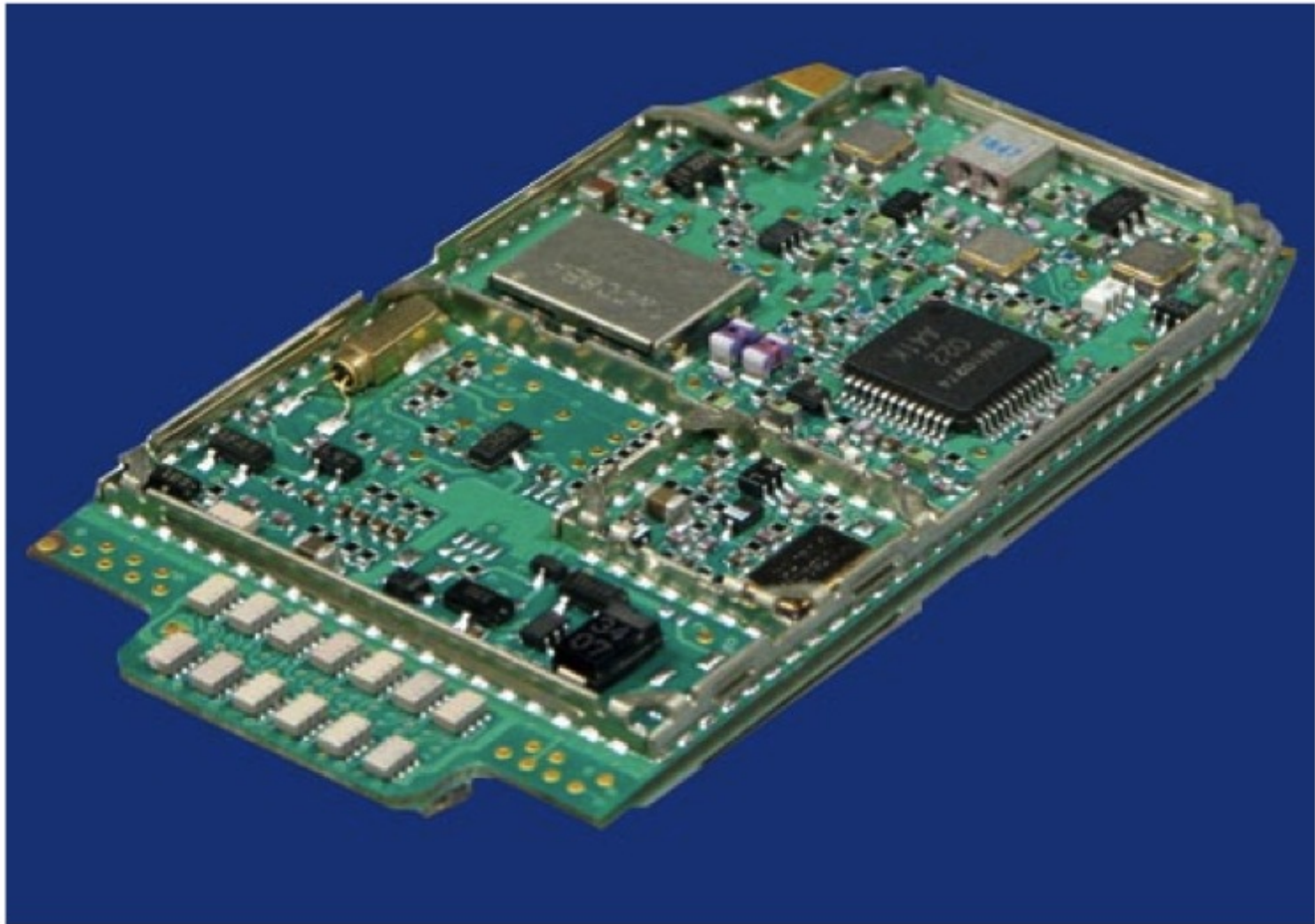
How Might an Engineer Think About a Systems Approach?

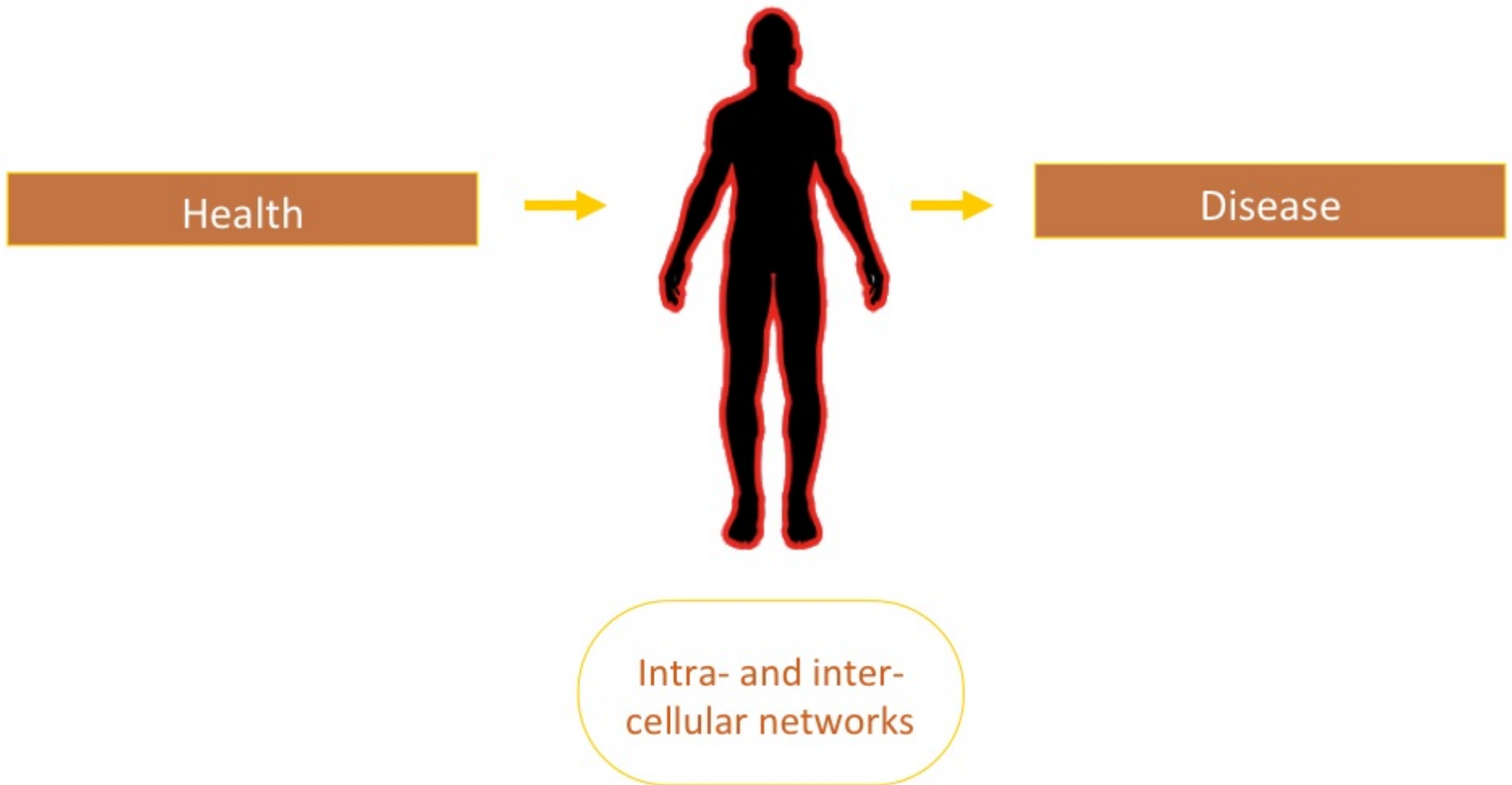
Radio Waves



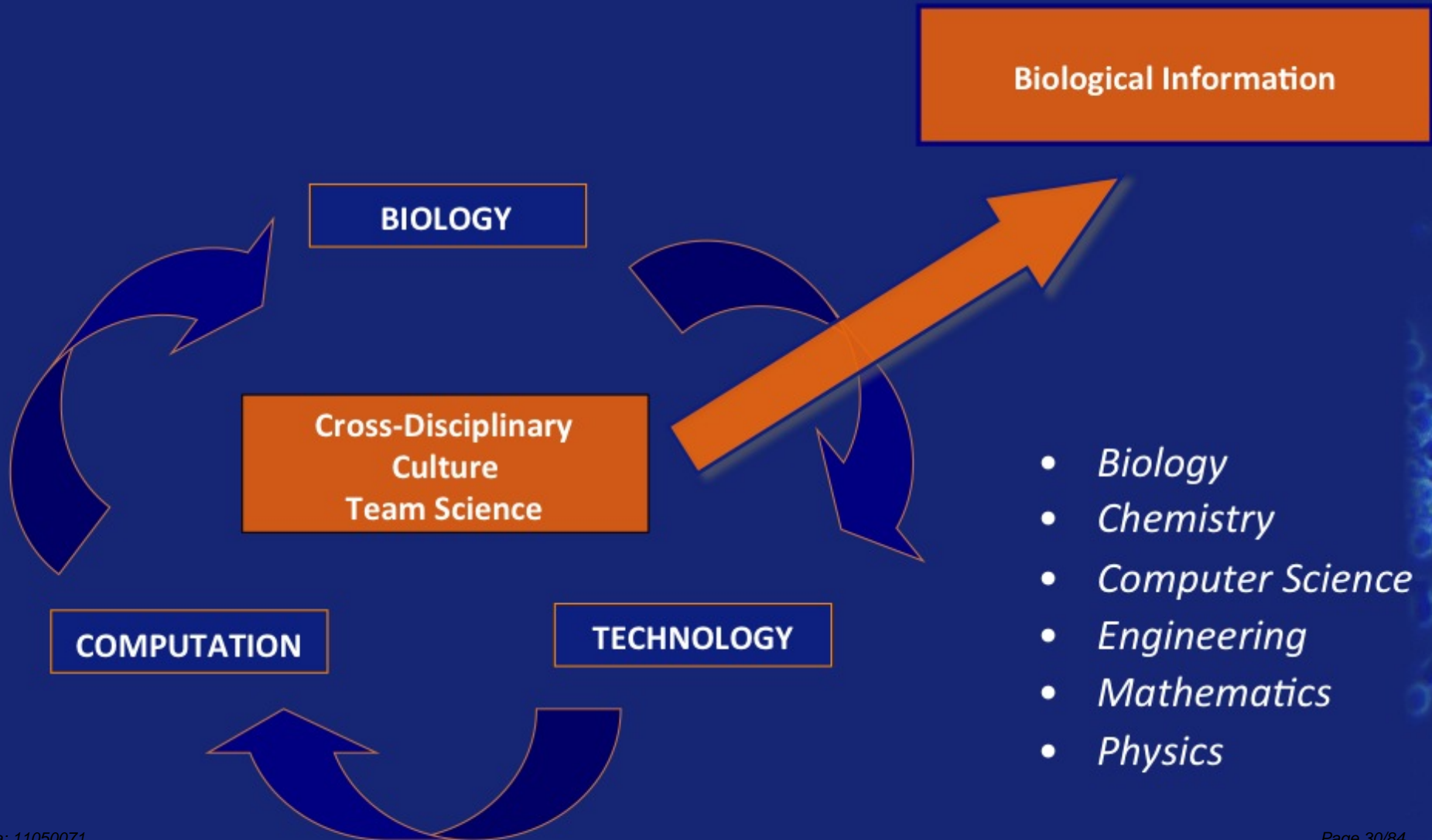
Sound Waves

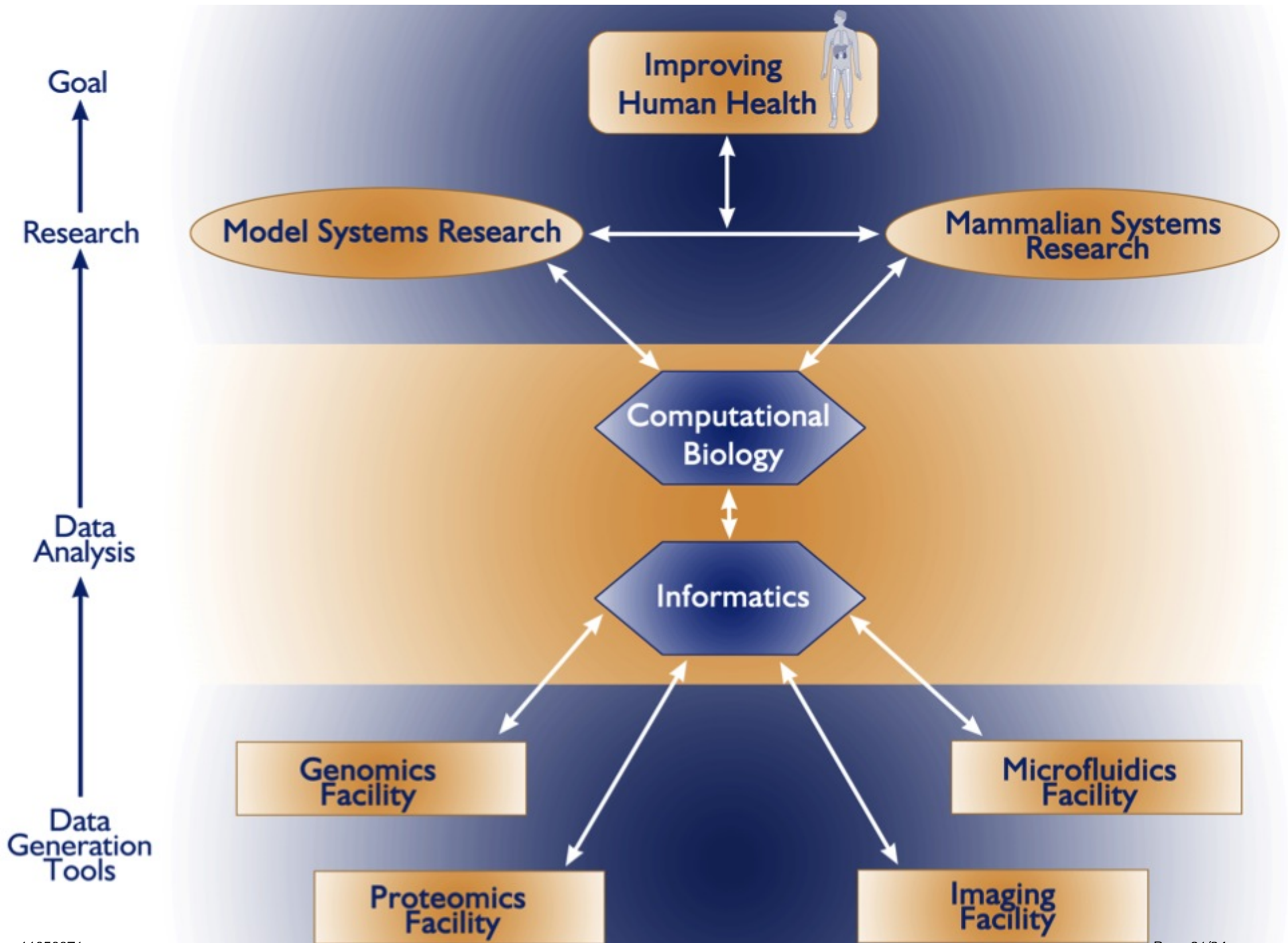






Agenda: Use biology to drive technology and computation.
Need to create a cross-disciplinary culture.

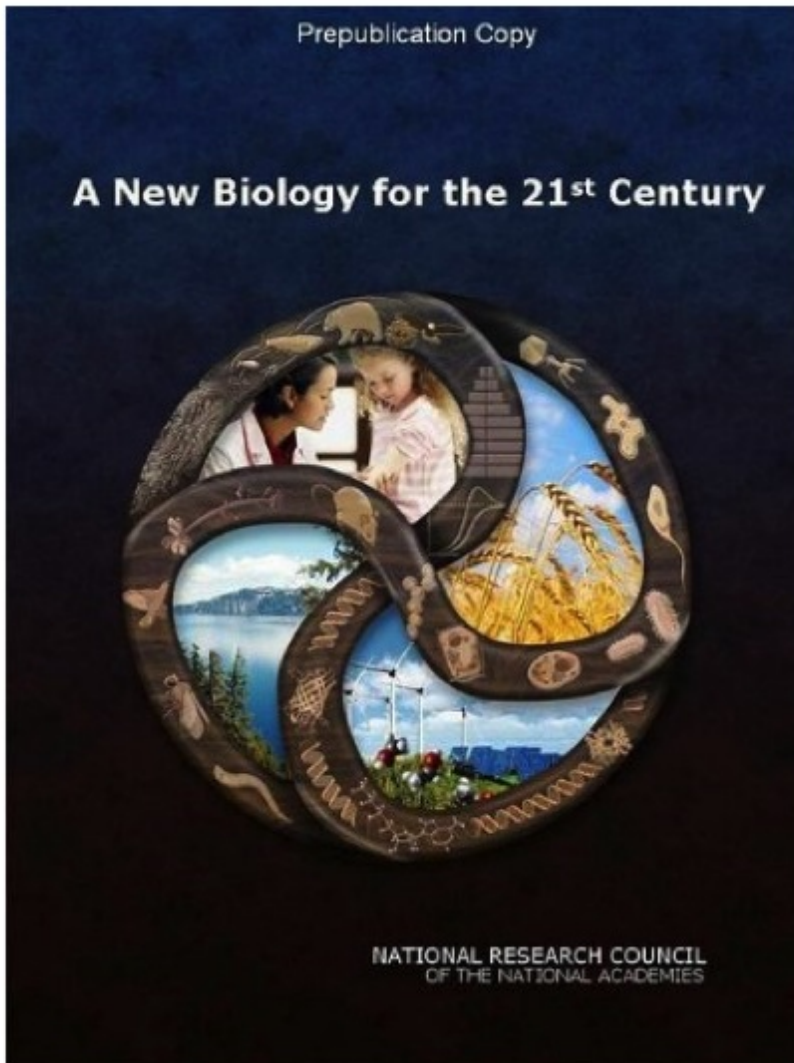




Institute for Systems Biology Founded 2000—10th Anniversary



ISB has 12 faculty and 300 staff

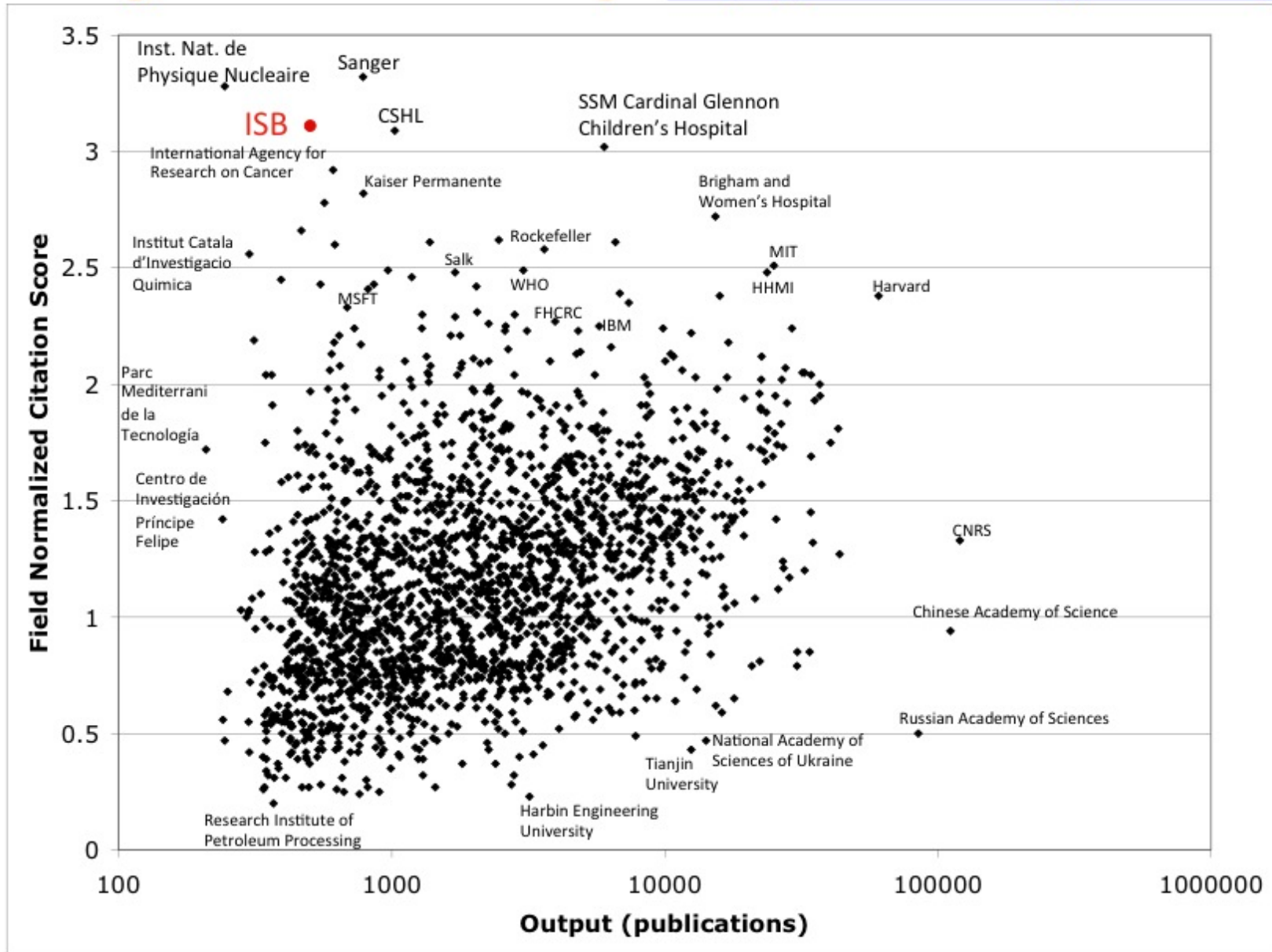


ISB's description of systems biology in 2000 is virtually identical to that of this National Academy of Sciences 2010 report entitled the "New Biology".

ISB was the first Systems Biology organization in 2000—today there are more than 70 world wide

Report predicted that systems approaches would drive the biology and medicine of the future

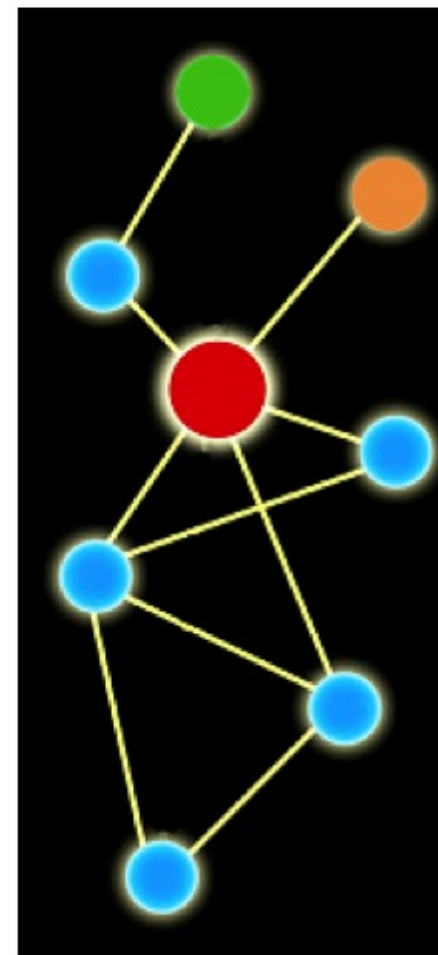
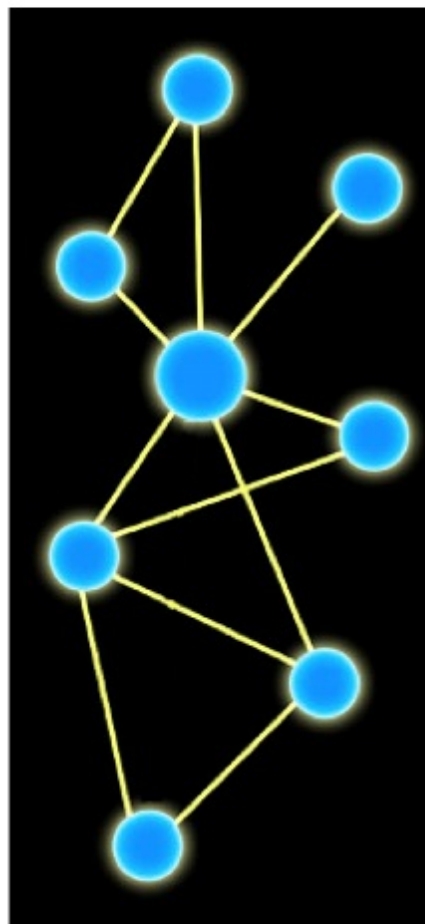
SCImago Institutions Rankings: <http://www.scimagoir.com/>



ISB 1st in US and 3rd in World for Impact of Papers

A Systems View of Disease

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

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

Time-course array analysis: subtrative analyses to DEGs

Prion strains:

- RML
- 301V

Mouse strains:

- C57BL/6J
- FVB/NCr
- BL6.I
- FVB/B4053

Inoculate w/ Prions

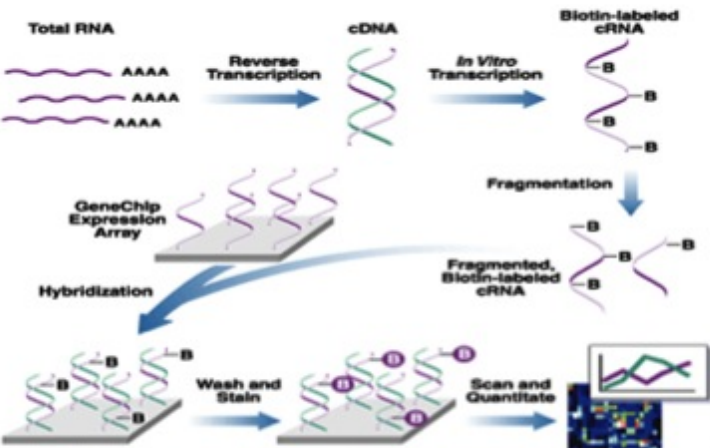


Prion infected brain



Uninfected brain

RNA
from brain
homogenate



Mouse Genome array:

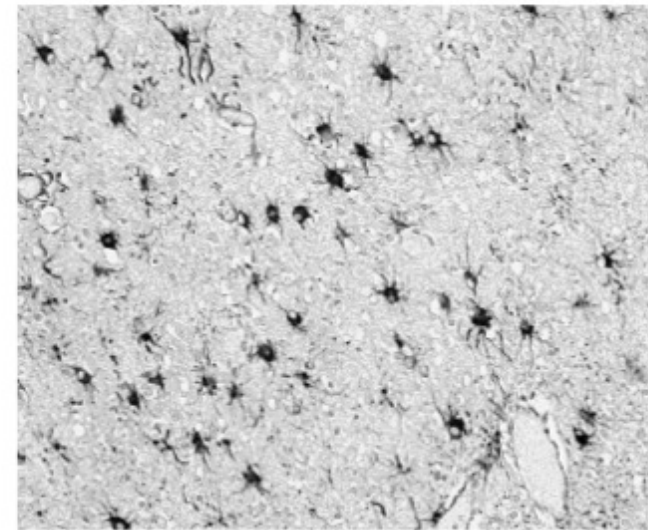
45,000 probe sets
~22,000 mouse genes.

Neuropathology Identifies 4 Major Disease- Perturbed Networks for Prion Disease

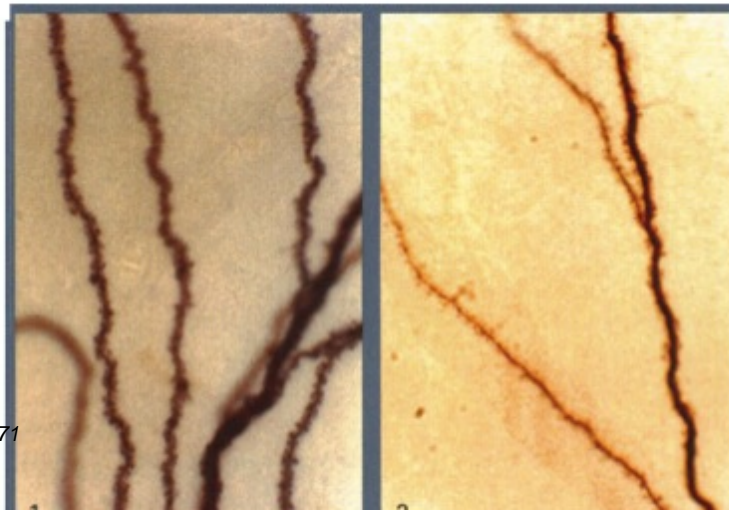
PrP accumulation



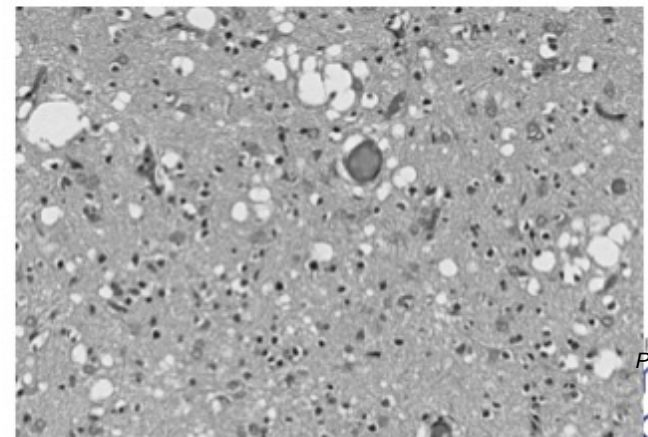
**Microglia / Astrocyte
activation**



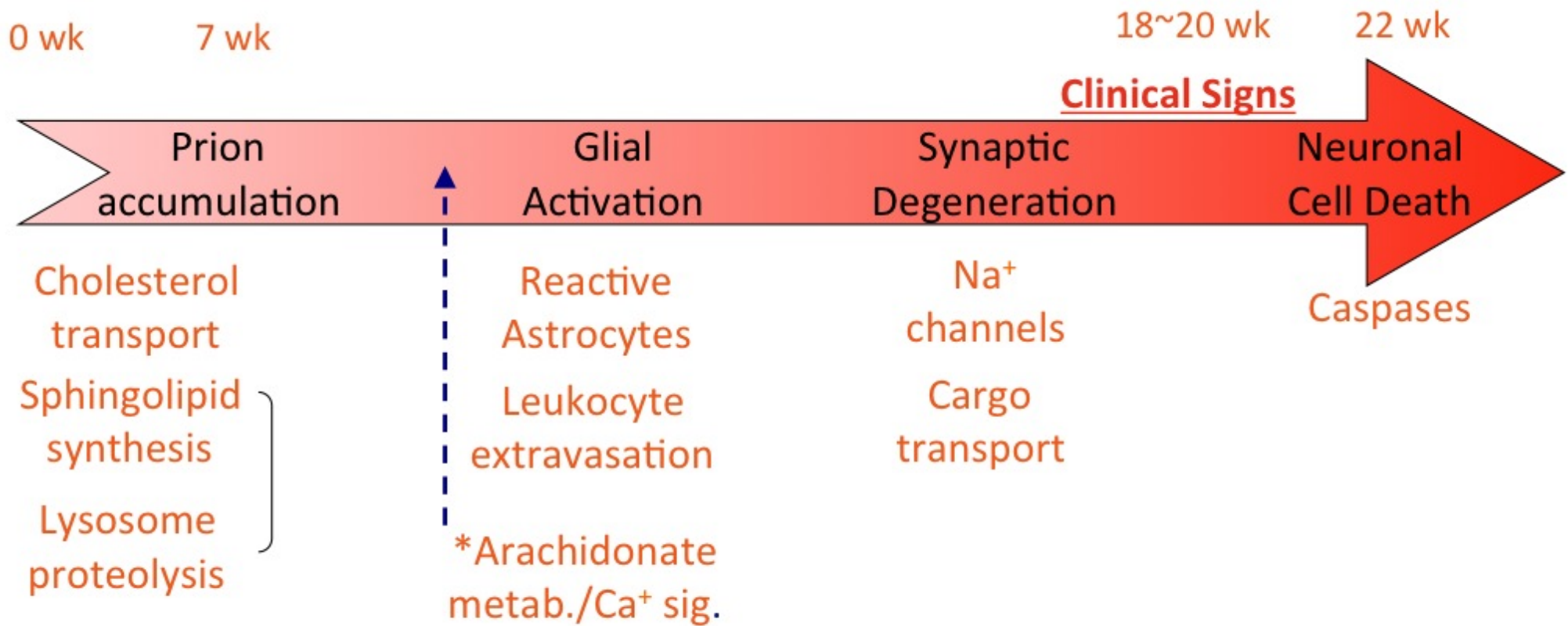
Synaptic Degeneration



Nerve cell death



Sequential Disease-Perturbation of the Four Networks of Prion Disease



Dynamics of a Brain Network in Prion Neurodegenerative Disease in Mice

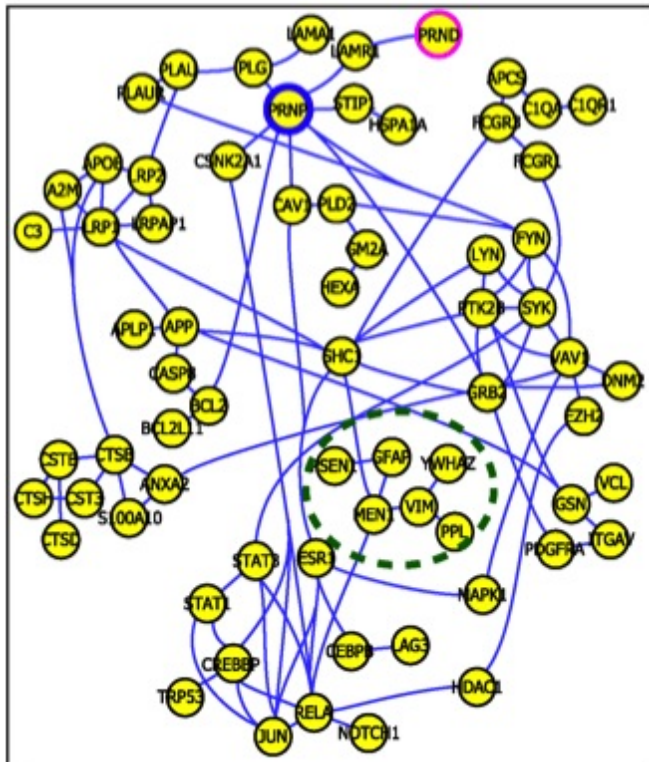
Prion accumulation network

18 wks

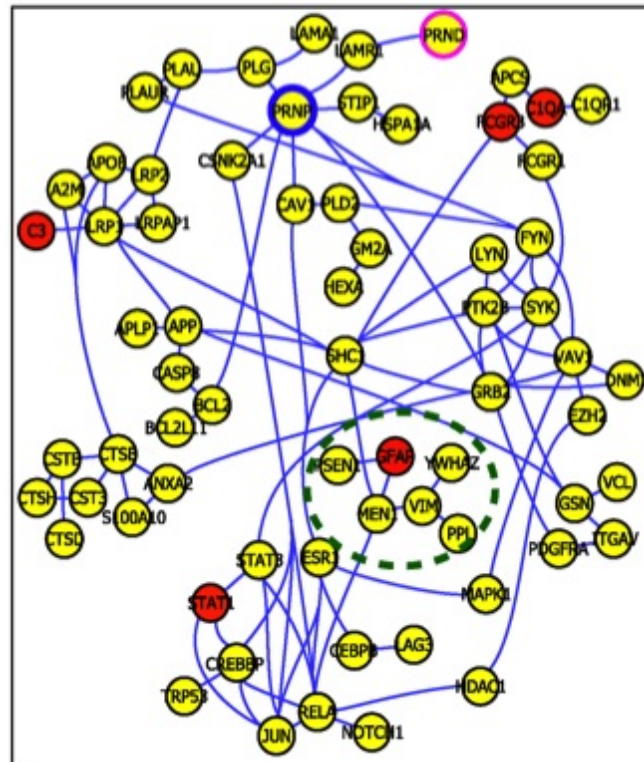
22 wks

No Clinical Signs

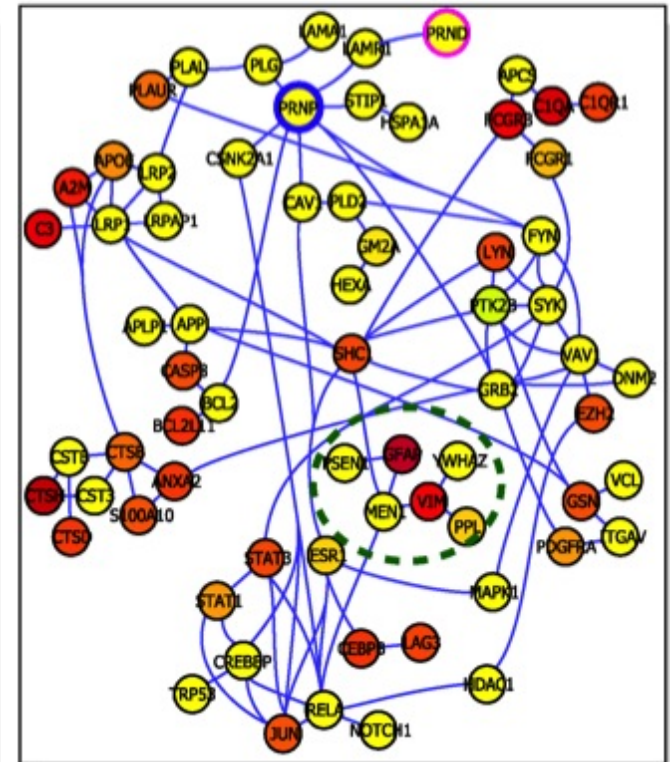
Clinical Signs



2 wks



12 wks

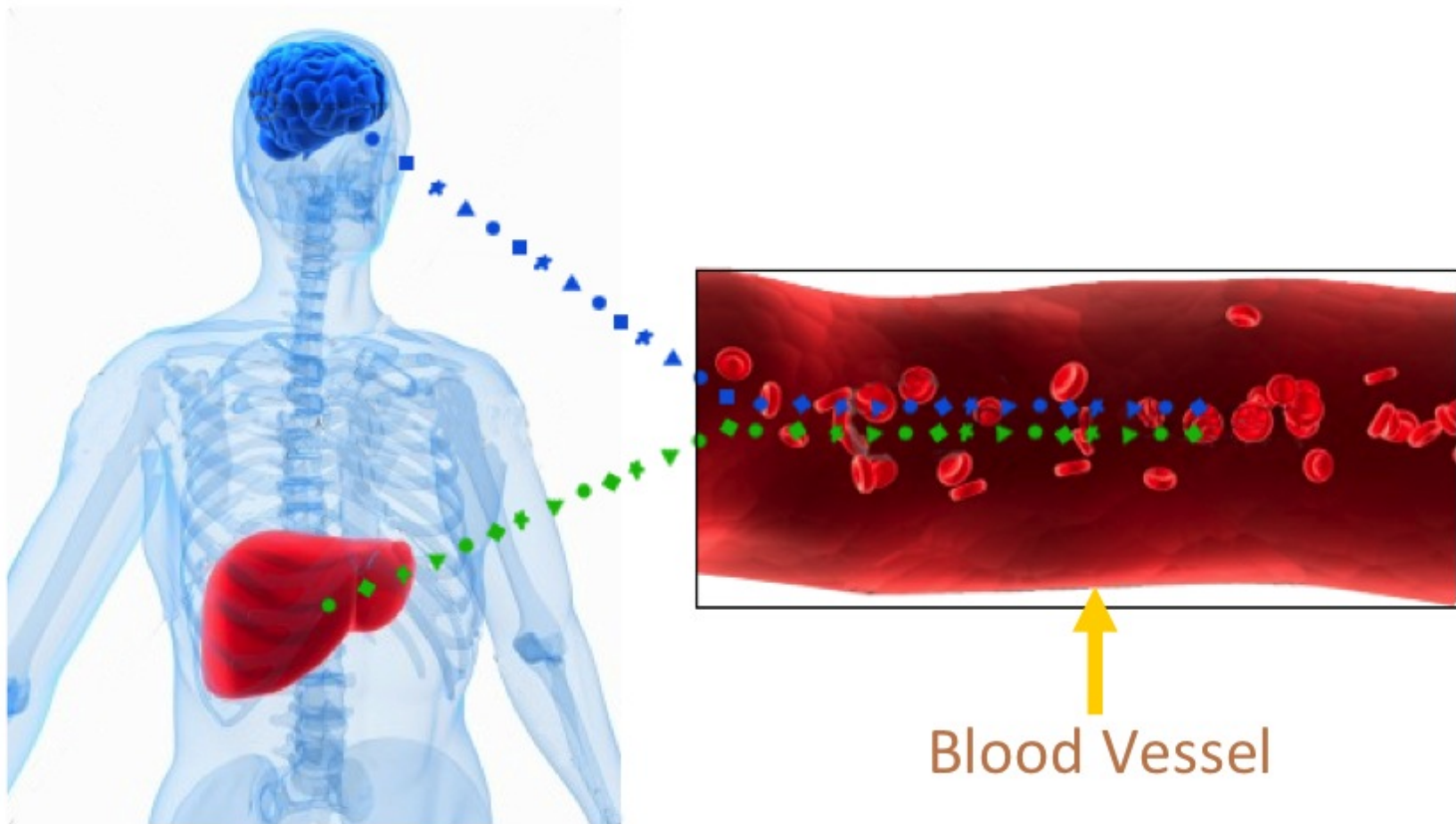


20 wks

300 genes encode the core prion disease response—map to 4 major networks
 Network dynamics explains all disease pathophysiology

Making Blood A Window Distinguishing Health and Disease

Organ-specific Blood Proteins



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

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

Integrated Diagnostics

The Foundations of Systems Biology and Systems Medicine—Four Pillars

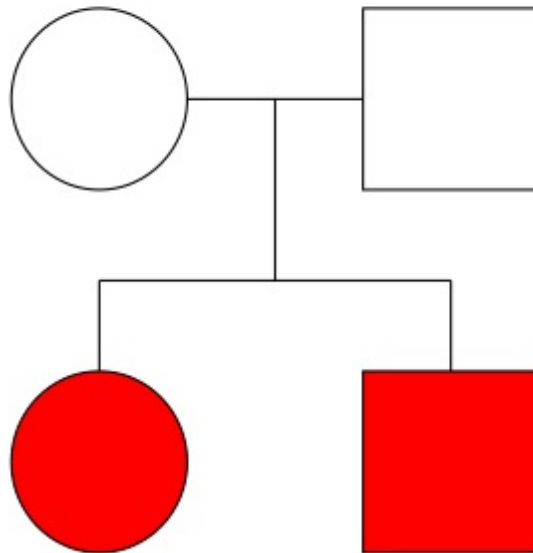
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Four ISB Technology-Driven New Big Projects

- Complete genome sequencing of families—sequences and **new stratifications** to identify disease genes—1000s individuals
- 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

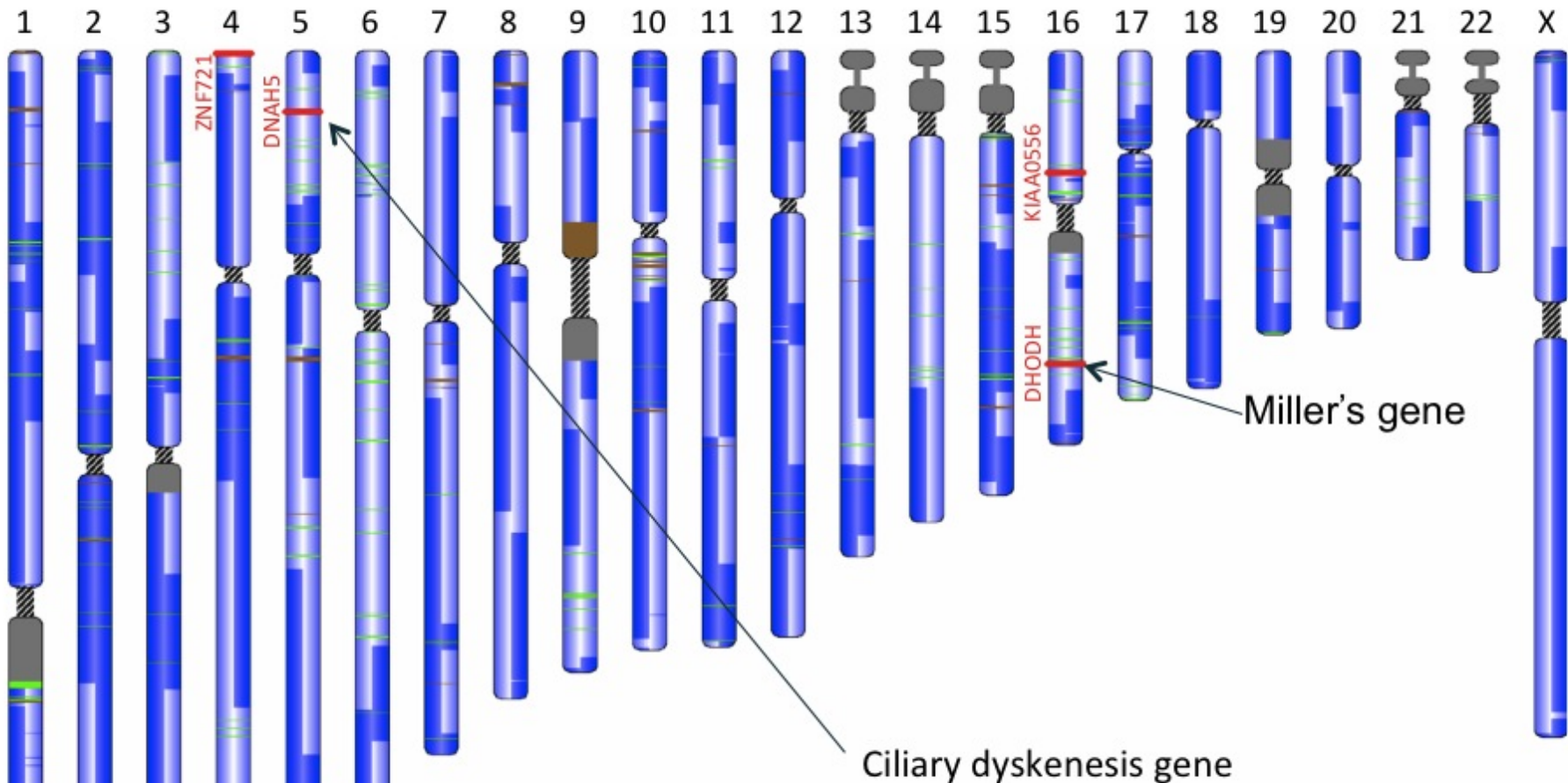
Whole Genome Sequencing of Family—Integration of Genetics and Genomics

Unaffected parents

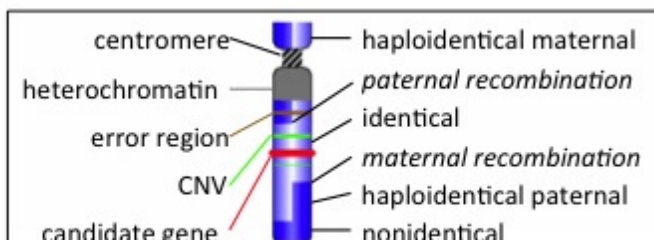


Children with craniofacial
and limb malformation (Miller Syndrome)
and lung disease (Ciliary Dyskenesis)

Family Genome Sequencing Facilitates Finding Disease Genes



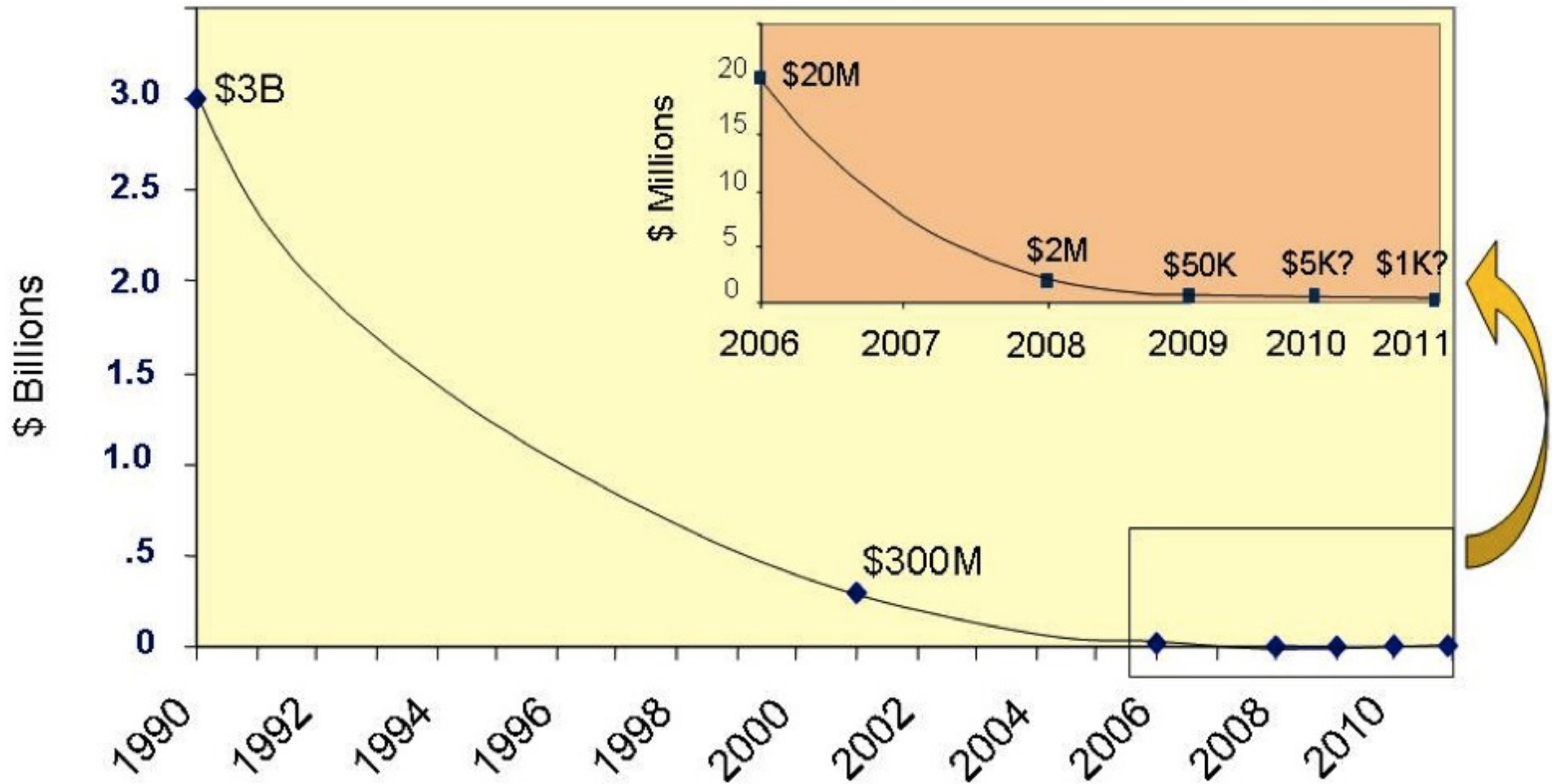
Sibling genomes are identical across ~25% of their length (23.2% here)



Family Genome Sequencing May Facilitate Finding

- Simple (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

Game Changer-- Declining Cost of Sequencing Genomes: A Part of Your Medical Record in 10 Years

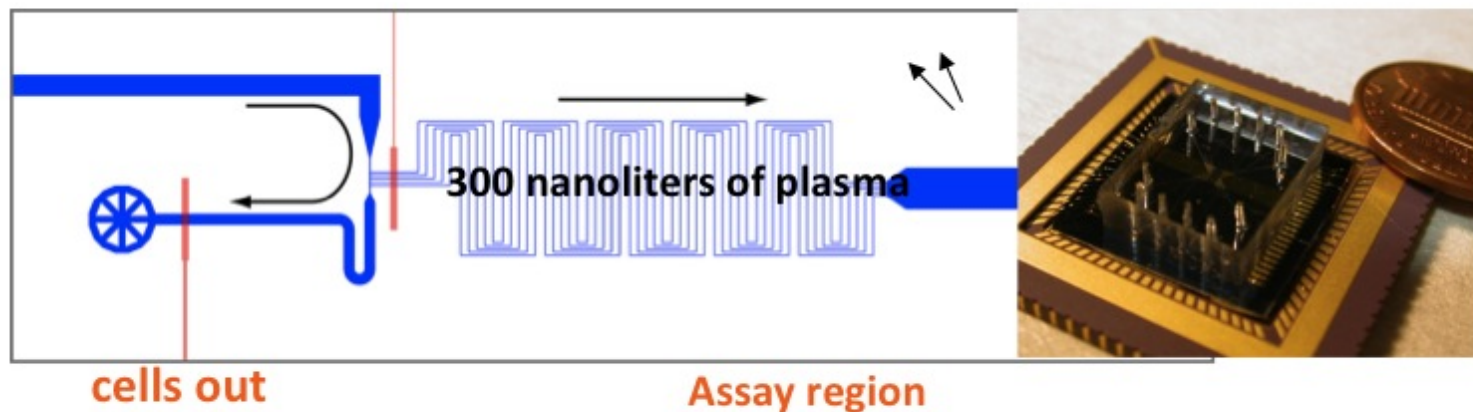


Making Blood a Window into Health and Disease for 100s millions of patients:

50 organ-specific blood proteins from each of 50 organs



Integrated nanotech/microfluidics platform



1. Uses fraction of droplet of blood
2. Measures 50 proteins
3. Assay takes 5 minutes
4. Procedure in hospitals

Technologies for Exploring New Dimensions of Patient Data Space

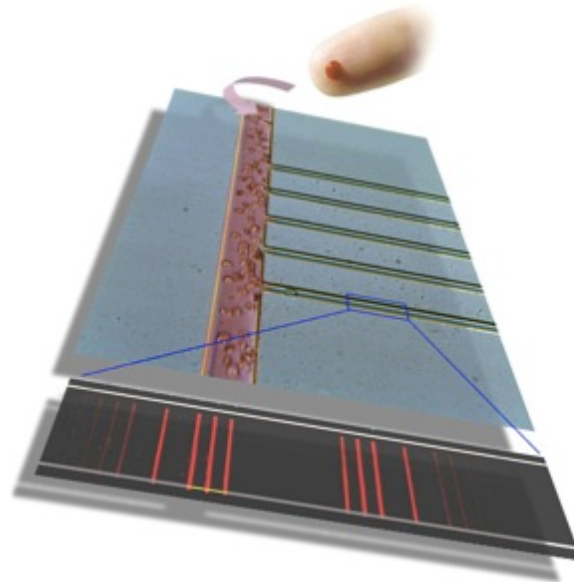
- 16 genomic, proteomic, and cell assays for patients

Actionable Gene Variants: Genomic Assay

- There are 106 disease genes that if identified in a patient could lead to actionable consequences.
- Example: Leiden Factor V
 - 5% of population has
 - Leads to deep vein thromboses
 - Pregnant women are especially susceptible
 - In normal population—1/1000 has thromboses
 - With one bad copy of Leiden Factor V—1/100 affected
 - With two bad copies of Leiden Factor V—1/10 affected

Predictive, Personalized, Preventive and Participatory (P4) Medicine

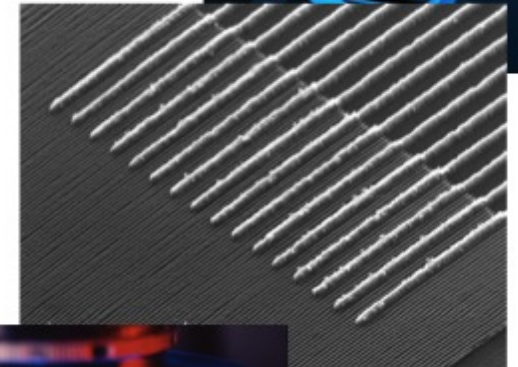
- Driven by systems approaches to disease, new measurement (nanotechnology) and visualization technologies and powerful new computational tools, P4 medicine will emerge over the next 10-20 years



P4 Medicine

- Predictive

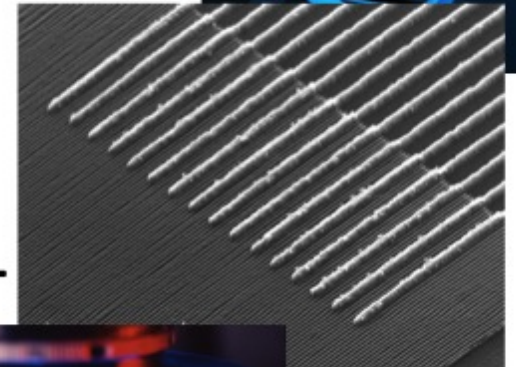
- Probabilistic health history--DNA sequence
- Biannual multi-parameter blood protein measurements
- Stratification of disease and match with drugs



P4 Medicine

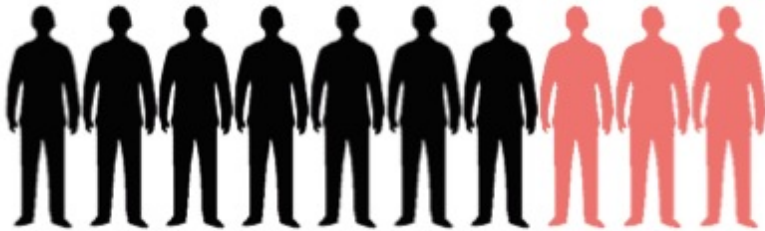
- Personalized

- Unique individual human genetic variation mandates individual treatment
- Stratification of the individual's disease and match with effective drugs
- 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

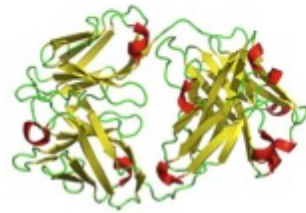


Example of Personalized Medicine – Disease Stratification of Breast Cancer and the Success of the Drug Herceptin

Target treatment...



Some women with metastatic breast cancer have tumors that overexpress the *HER2* gene and have a poorer response to chemotherapy



Herceptin +

Pathway®
HercepTest®

} IHC

PathVysion®

FISH

HER2 pharmDx™



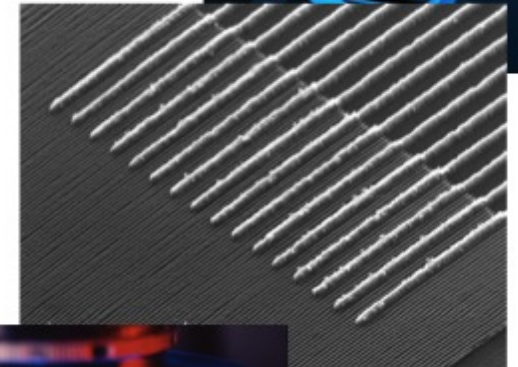
Identifying HER2+ patients with genetic (FISH) or immunological (IHC) tests and targeting with Herceptin improves treatment.

50% reduced risk of recurrence
after one year

P4 Medicine

- **Preventive**

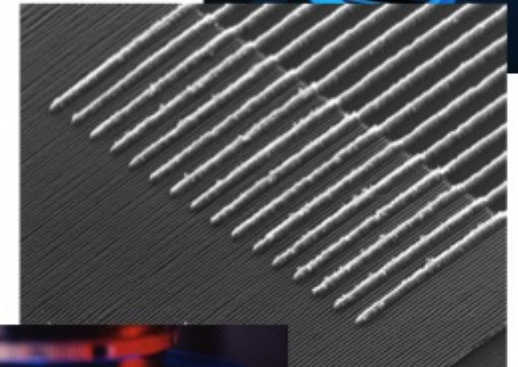
- Design of therapeutic and preventive drugs via systems approaches
- Systems approaches to creating effective vaccines will transform prevention of infectious diseases
- Transition from a focus on disease to a focus on wellness



P4 Medicine

- Participatory

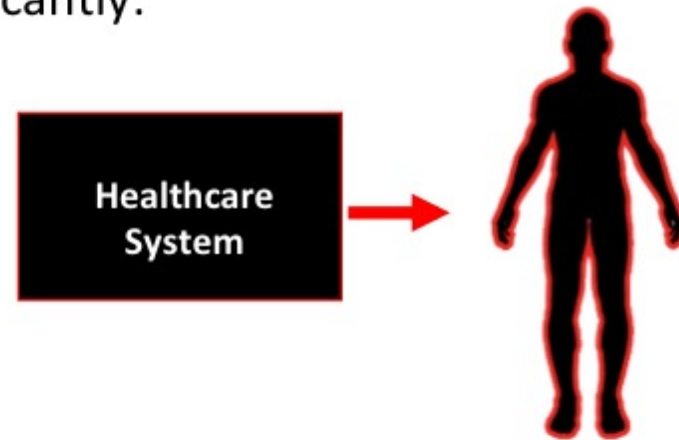
- Patient understands and participates in medical choices
- Physicians trained before P4 will have to understand it
- Medical community—interconnected and educated
- Create IT for healthcare to handle billions of data points for 100s of millions



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



New ideas generally need new organizational structures

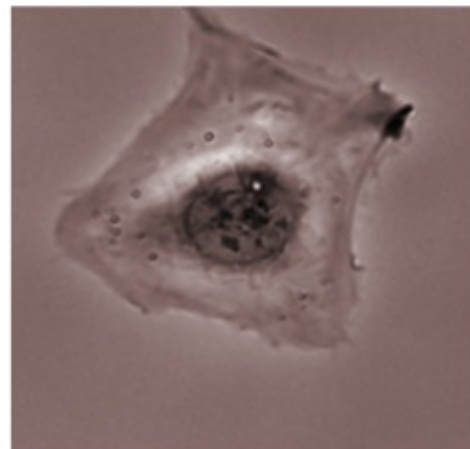
Digitalization of Medicine Will Be Transformational

- Analysis of single molecules, single cells, single organs and single individuals—actionable consequences
- Handling billions of data points for each individual
- 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

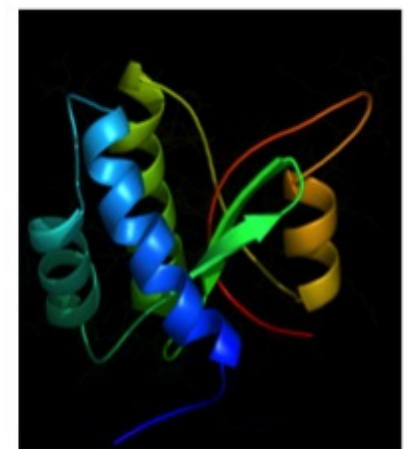
Single individual



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 normalcy **with drugs**—new and less expensive strategy for drug target discovery
- **Benefits of wellness**-- survey biannually 2500 blood organ-specific protein measurements—50 from each of 50 organs—global early detection of the transition from health to disease
- **Technologies exponentially increasing in measurement potential and decreasing in cost (digitalization of medicine)**--sculpt for individuals the dimensions of health/disease while dramatically decreasing measurement costs, 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.

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

- Savings on healthcare
- 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

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

Inventing the Future



- Analyzing one gene and one small problem at a time

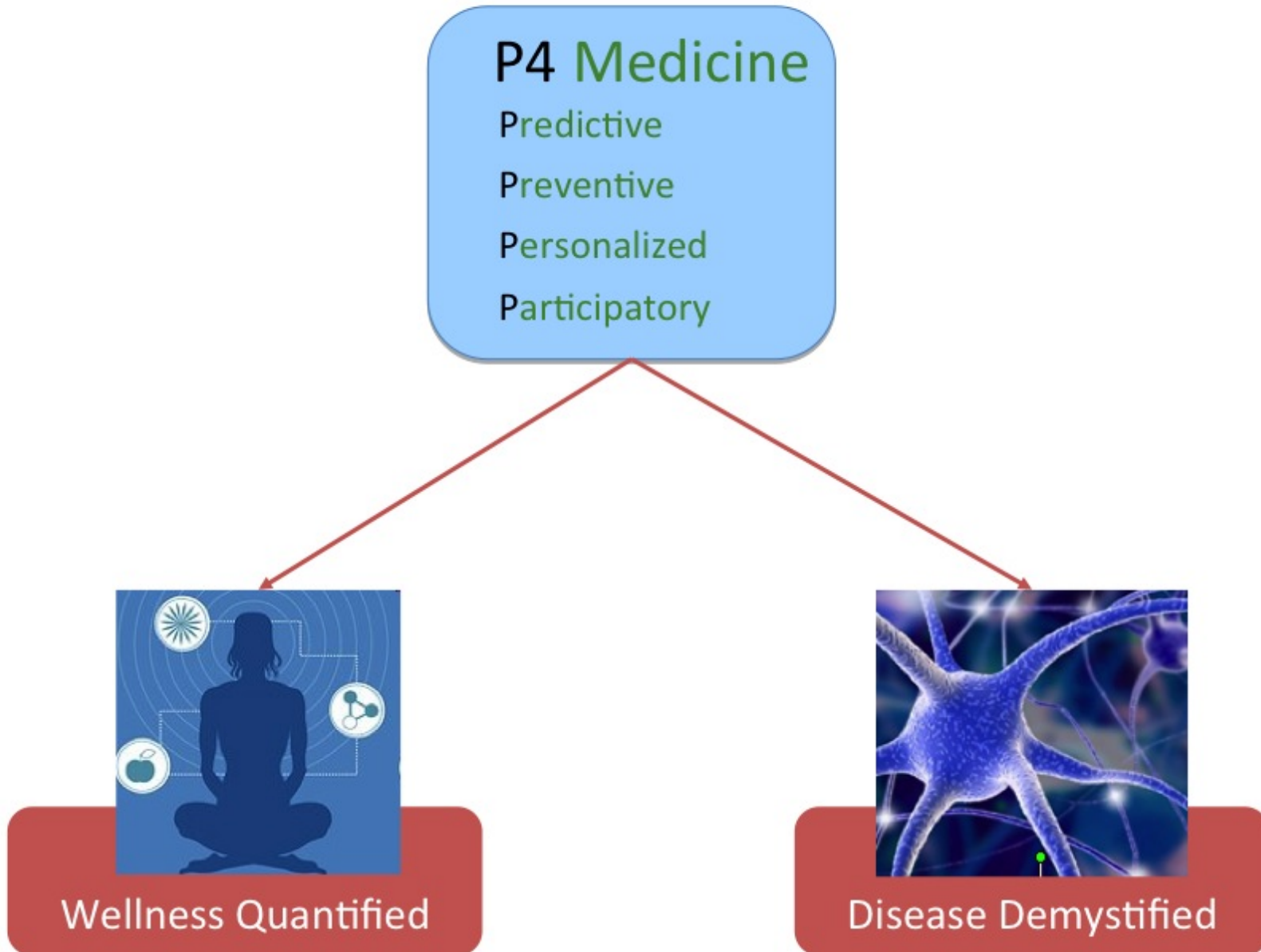
- Systems analysis of biology and medicine--e.g., predictive, preventive, personalized and participatory (P4) medicine
- Technology development
- Pioneer computational tools
- Transferring knowledge to society--joining academics and industry--changing K-12 science education--P4 medicine and society
- **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

Essence of P4 Medicine

Conceptual Themes of P4 Medicine



Interesting Issues for Biology (Science)

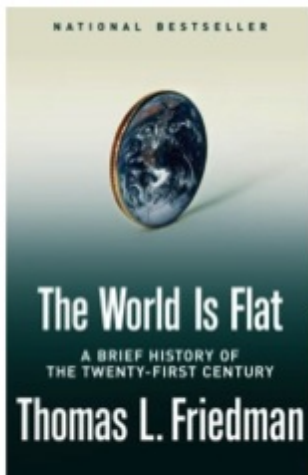
New Ideas (paradigm changes) Need New Organizational Structures and ISB Will Catalyze Some of These

- Bringing engineering to biology--**Applied Biosystems**
- The human genome project--**new NIH and DOE Institutes**
- Cross disciplinary biology--**UW Department of Molecular Biotechnology**
- Systems biology--**ISB**

- Predictive, preventive, personalized and participatory medicine--**Integrated Diagnostics, P4 Medicine Institute, many others**

The Flattening of Many Worlds: Strategic Partnerships and the Globalization of Science

The worlds of systems science, technology, health are flattening.
Tremendous opportunities for national and international
**strategic partnerships in science and technology
to attack “Big Problems”.**



- **Strategic partnerships: a network of interacting complementary, institutions led by a unitary vision**

- Attack big scientific problems—P4
- Recruiting the best world talent
- Gathering scientists and engineers with complementary skills and technologies
- New patient populations, records and the ability to analyze data
- New approaches to cross-disciplinary training
- New fundraising opportunities

P4 Medicine is a Big Scientific Problem

Big Problems Require an Integrative,
Cross Disciplinary Approach



Small Biology

The Grand Challenge of the 21st Century in Science and Technology Is Complexity

- New concepts, strategies and technologies permit biologists to successfully begin to attack biological complexity
 - View biology as an **informational science**
 - **Systems or holistic approaches** permit one to attack complexity effectively
 - Evolving current and **emerging technologies** permit the exploration of new areas of data space (and improve the old)
 - **Computation and mathematical tools** permit one to acquire, store, transmit, integrate, mine and create predictive models.
- These approaches will allow us to effectively attack some of society's most vexing challenges—**healthcare (P4 Medicine), global health, environment, energy, nutrition, agriculture, etc.**

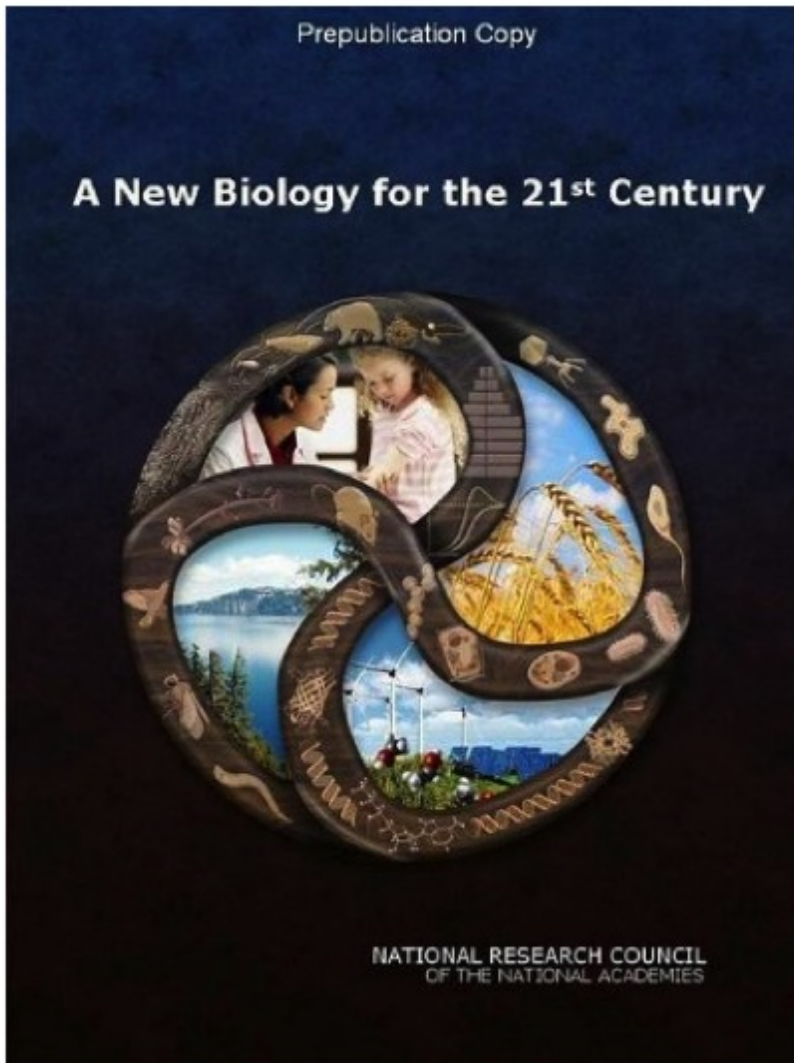
Implications of Human Genome Project's Book of Life for Society

- Humans are one race—and differences arise from poverty and lack of education, healthcare or jobs —not genetics.
- Humans are interconnected to all living creatures —and have an obligation to create a sustainable environment for all.
- We all have a obligation to understand science and technology—to help make wise decisions for the future—and to educate our fellow citizens.

Institute for Systems Biology Founded 2000—10th Anniversary



ISB has 12 faculty and 300 staff

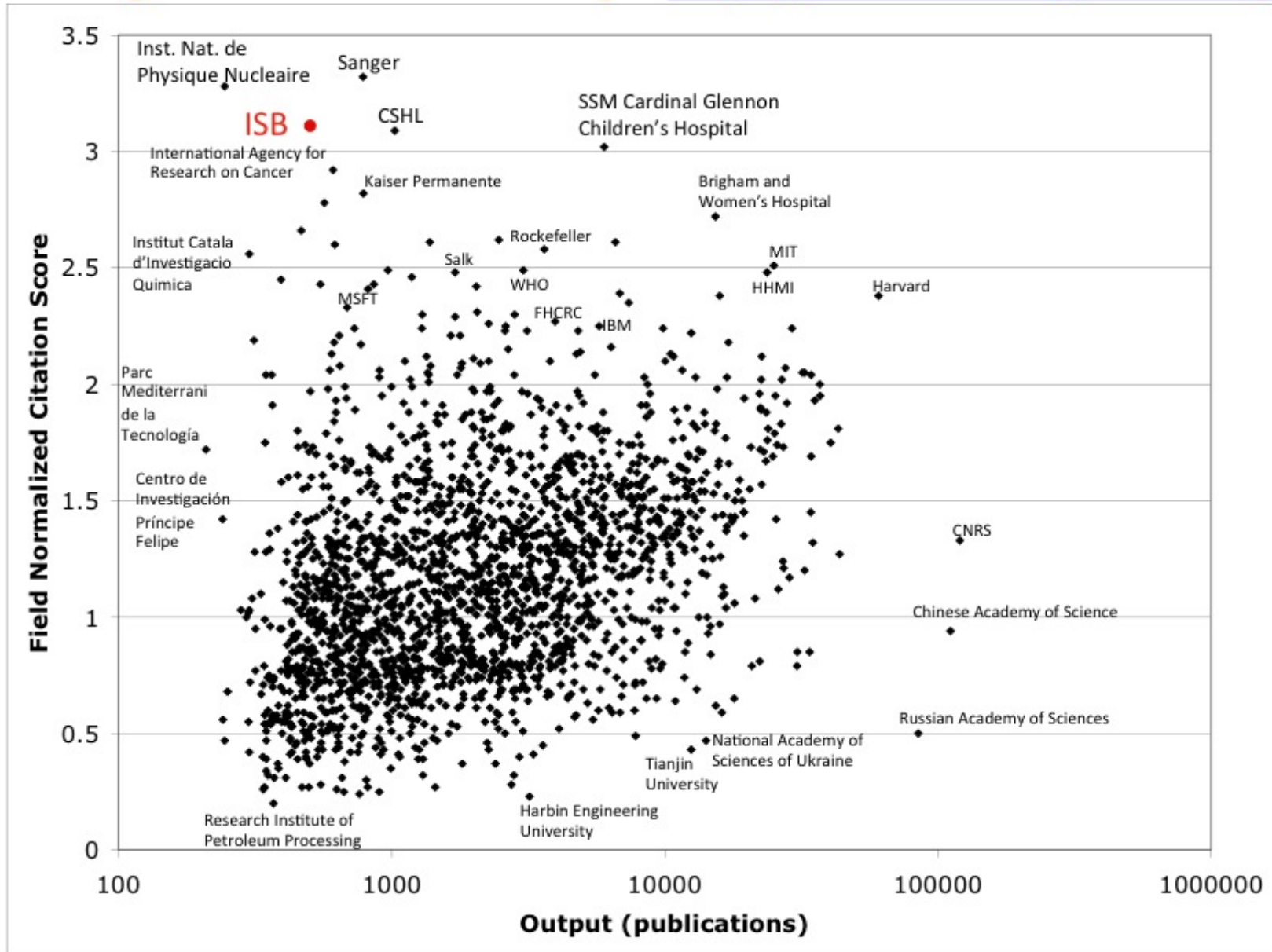


ISB's description of systems biology in 2000 is virtually identical to that of this National Academy of Sciences 2010 report entitled the "New Biology".

ISB was the first Systems Biology organization in 2000—today there are more than 70 world wide

Report predicted that systems approaches would drive the biology and medicine of the future

SCImago Institutions Rankings: <http://www.scimagoir.com/>



ISB 1st in US and 3rd in World for Impact of Papers

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

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P4 Medicine has Four Societal Implications

- Force a revision of business plans of every sector of healthcare industry—**enormous economic opportunity**
- **Digitalize medicine**—a larger revolution than the digitization of information technologies and communication
- Turn sharply around escalating costs of **healthcare** and export to the developing world
- P4 Medicine will **create significant wealth**

Elements of Systems Approach to Biology Education

- Conceptual teaching--biology as an informational science
- Systems view of biology--evolution, development, physiology and disease-- and other disciplines
- Good training in physics, chemistry and mathematics and statistics
- Cross-disciplinary--dual majors
- Learn to think analytically--quantitative problems
- Use new approaches to teaching--computational tools
- Learn to think outside the box--computer games
- Mini-courses for breadth and to learn the other languages of science
- Societal implications of science--deal with anti-intellectualism and anti-science

Whole Genome Sequencing of Families: A New Genomic Strategy Integrating Genetics and Genomics

Sequencing by a company Complete Genomics

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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