

P4 Medicine: Catalyzing a Revolution from Reactive to Proactive Medicine

Predictive, Personalized, Preventive and Participatory

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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
 - Biology is 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 better 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.

I Participated in Four Paradigm Changes in Biology 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.
- Each new idea needed new organizational structure.

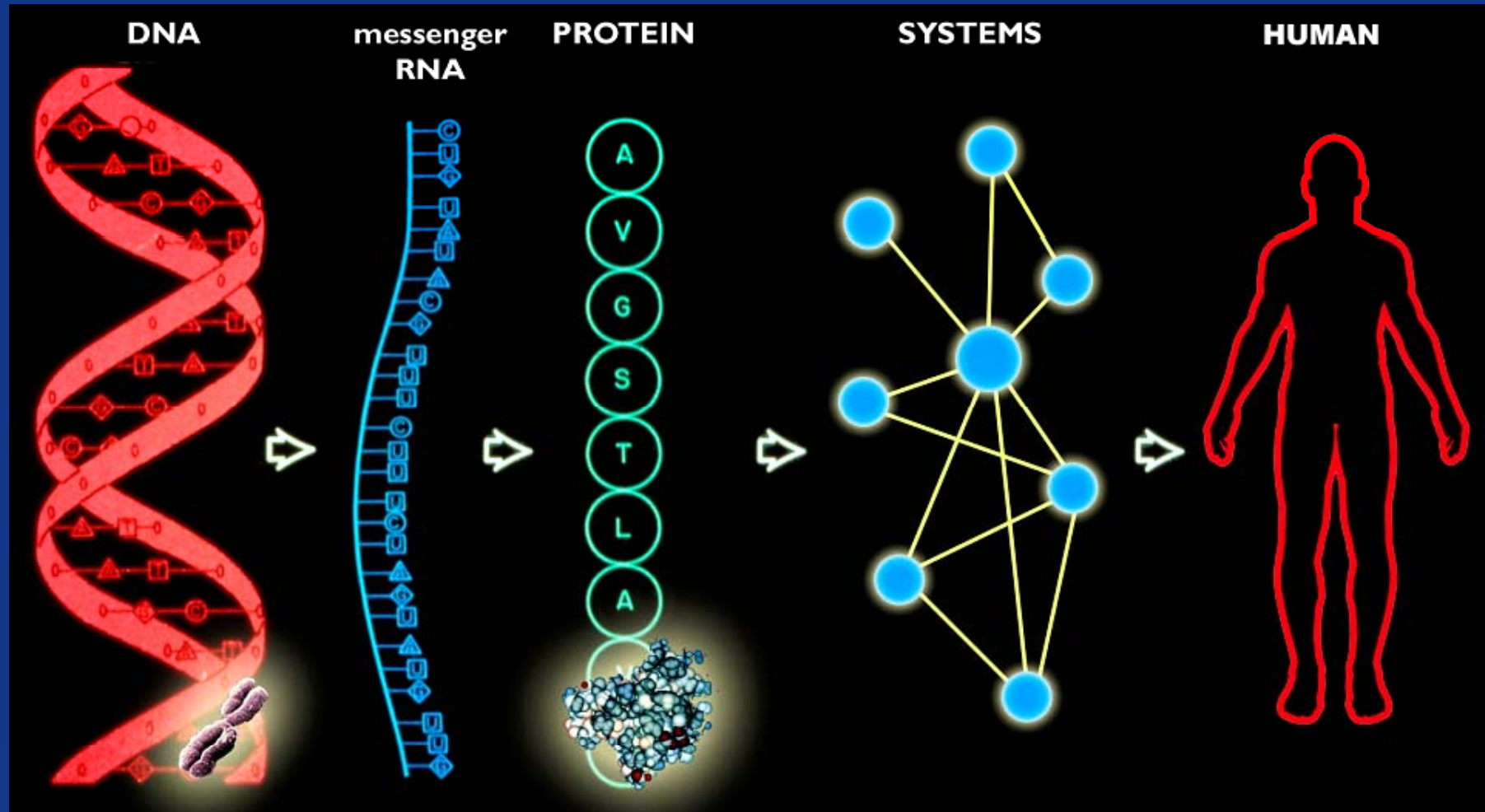
Features of P4 Medicine

- An informational science
- Data driven—each patient billions of data points—predictive medicine
- Each patient their own control for longitudinally assessing transitions from wellness to disease
- P4 medicine is a driver of new technologies
- P4 medicine will drive an economic healthcare revolution
 - Striking lowering of cost of healthcare
 - Transform the nature of the healthcare industry
 - Global wellness will provide enormous economic benefits
- P4 medicine will be for rich and poor alike
- P4 medicine should be the basis for political healthcare decisions

Contemporary Systems Biology is Predicated on Viewing Biology as an Informational Science



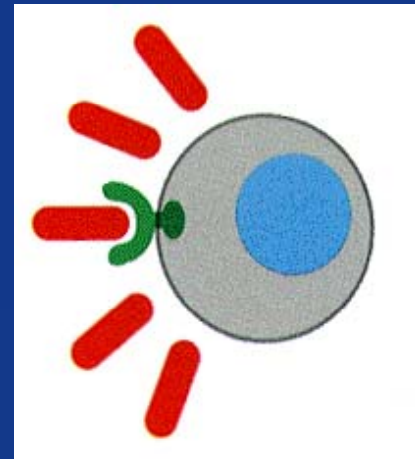
The Flow of Information from DNA to a Human



There are Two Types of Biological Information that Can Lead to Disease

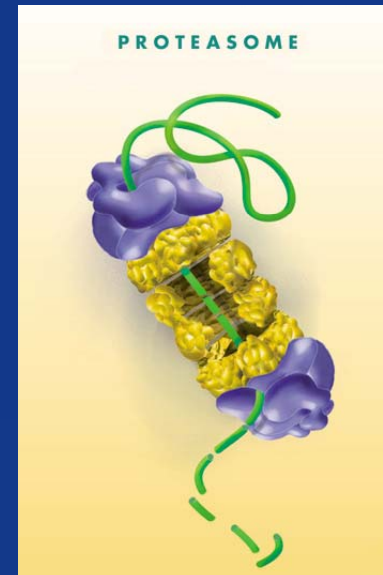
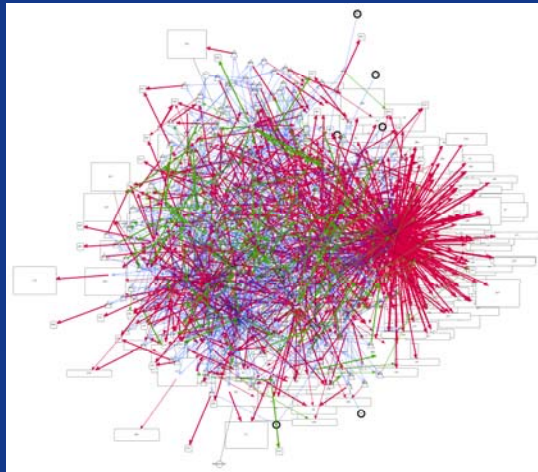
- The **digital information** of the genome
- The **environmental information** that impinges upon and modifies the digital information

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GCAGGGCACA  GGGACAGCCC  CCCTCCACAG
CCAGGAGGTT  GCTTCTTCCA  GGAGGCTTTT
GCTCCCAGCT  GCTGTGAGTG  CTGCACATTC
CACTTCTGGT  GCCCACTGTG  GCCACAGCAA
GCCTCCTGGG  GAGCTGCTGA  CCCTAGGCAG
CACCCCAGTG  TTTGCCAGTG  TTTGCCCGTG
TTTGCTCGCC  AGTGTTCGCC  ACTTGTCCTT
GAAGTTGCAG  GTCCCTCCAG  GACAGTTGGC
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Two General Biological Structures that Handle Information

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



Left Index Fingerprints from Identical Twins



Systems Biology—what is it?

Radio Waves



Sound Waves





Health



Disease

Intra- and inter-cellular networks

ISB's View of Systems Biology and Systems Medicine

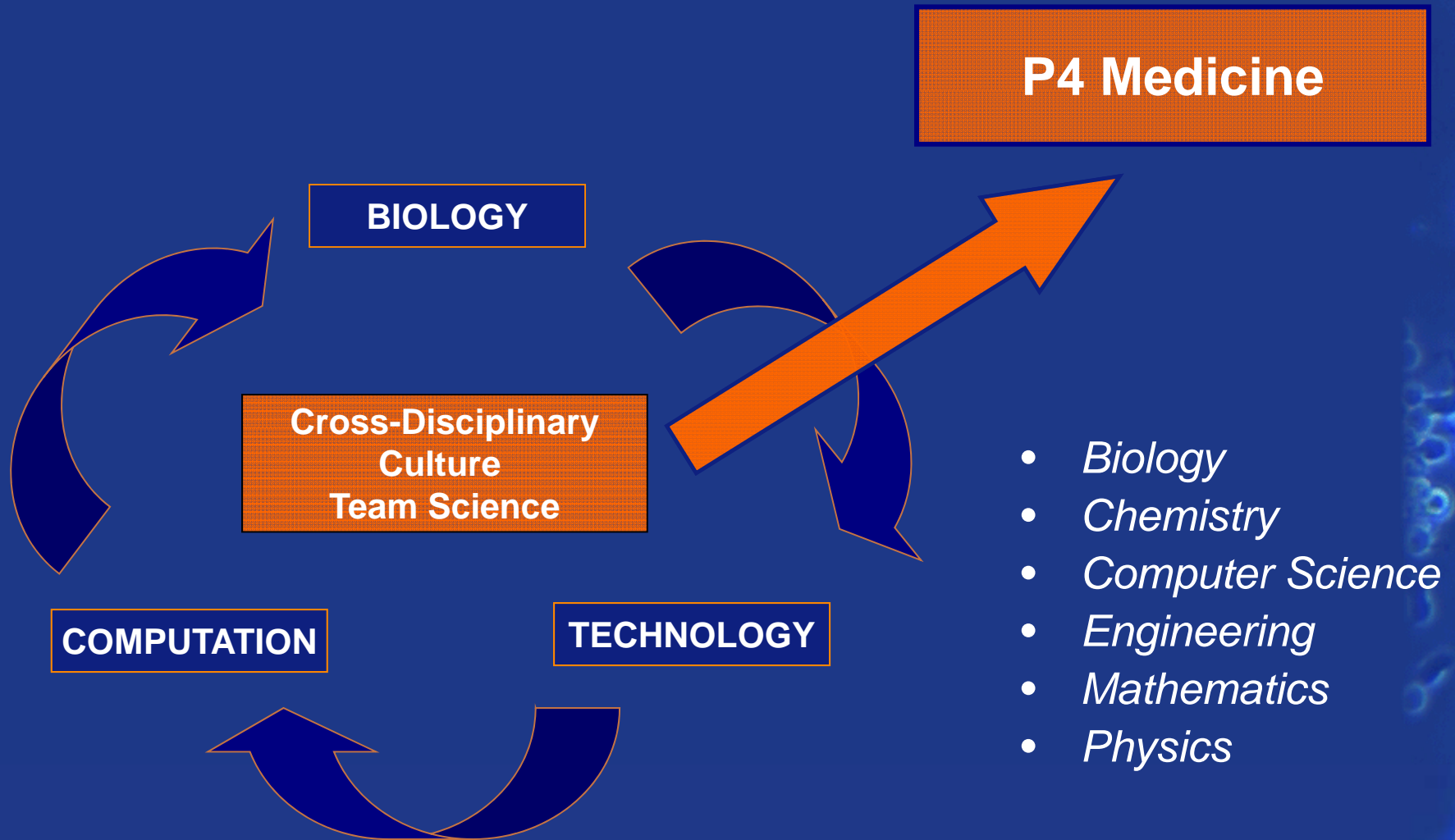
Institute for Systems Biology

Founded 2000



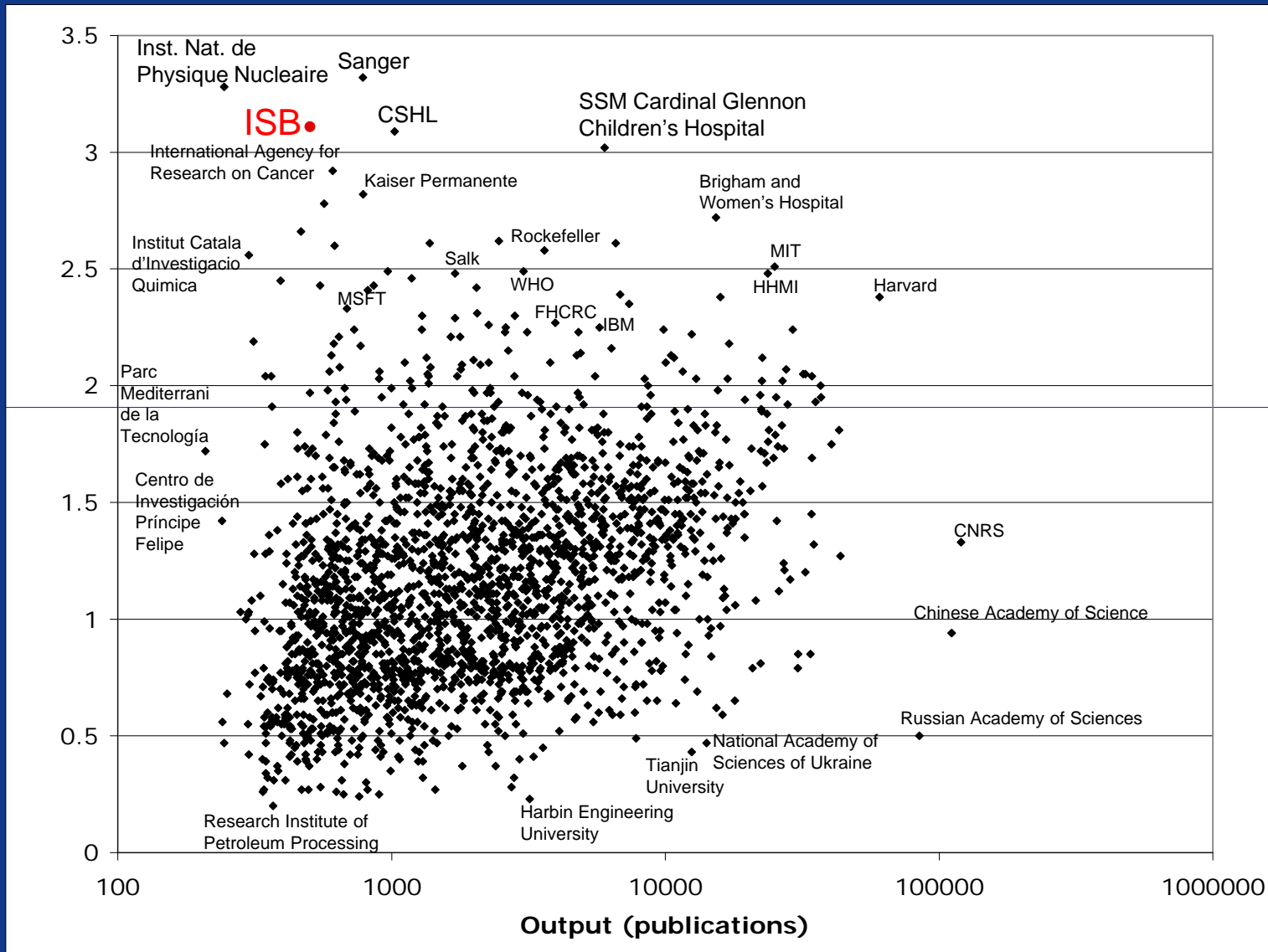
ISB has 13 faculty and 300 staff

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



ISB's 10 Anniversary

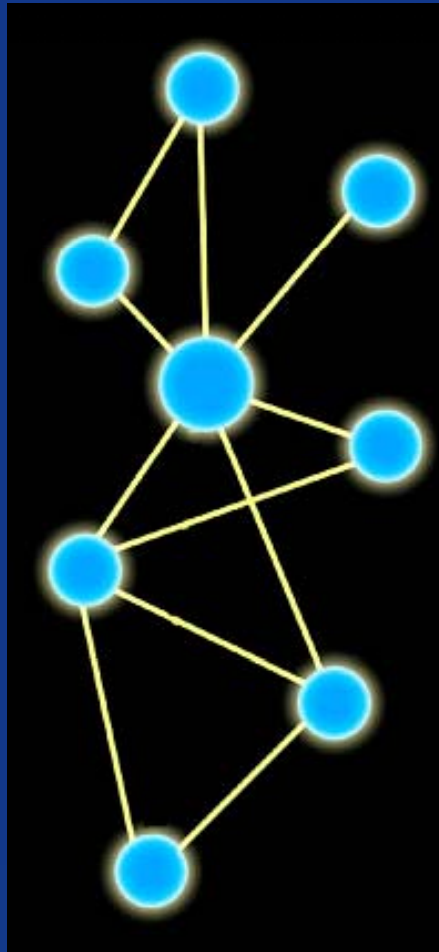
SCImago Institutions Rankings: <http://www.scimagoir.com/>



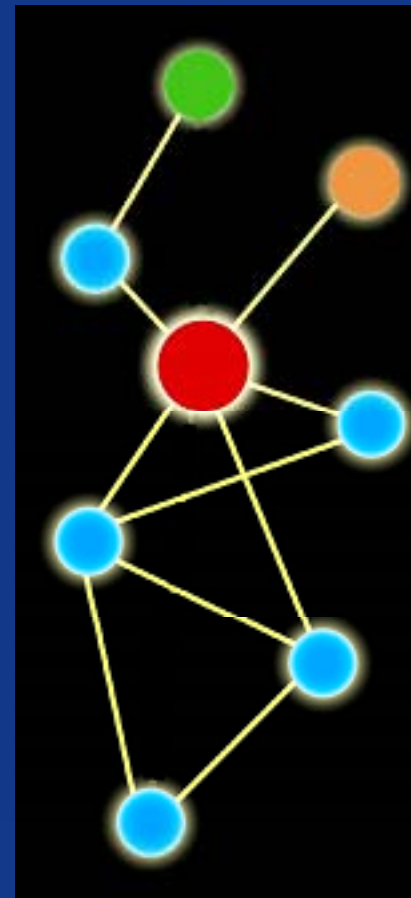
ISB 1st in US and 3rd in World for Impact of Papers

A Systems View of Disease

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



Non-Diseased



Diseased

dynamics of pathophysiology

diagnosis

therapy

prevention

Dynamics of a Neurodegenerative (Prion Disease) Network in Mice

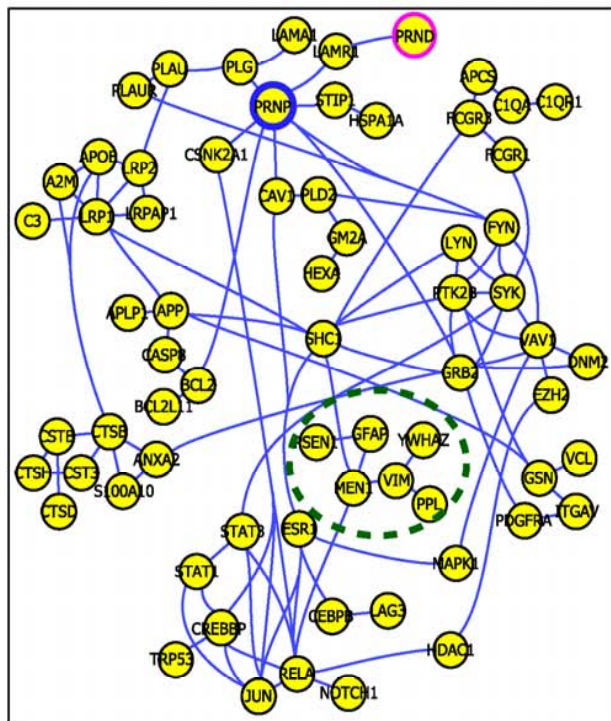
Nerve cell death

18 wks

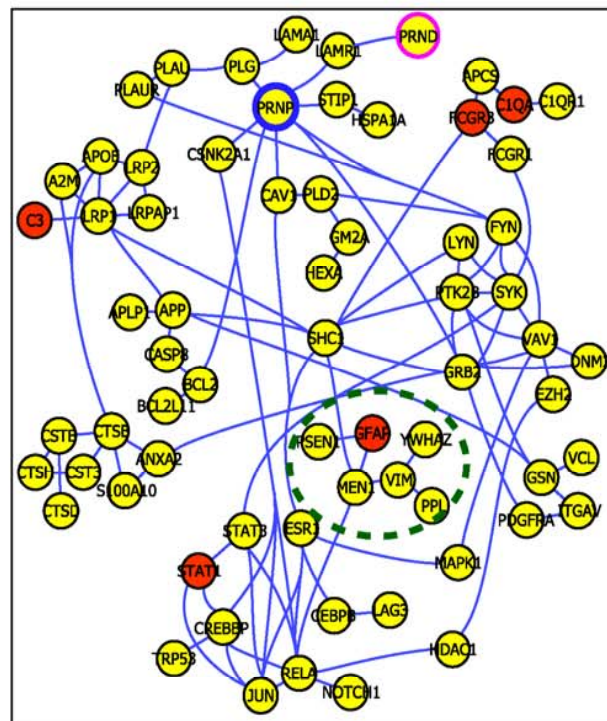
22 wks

No Clinical Signs

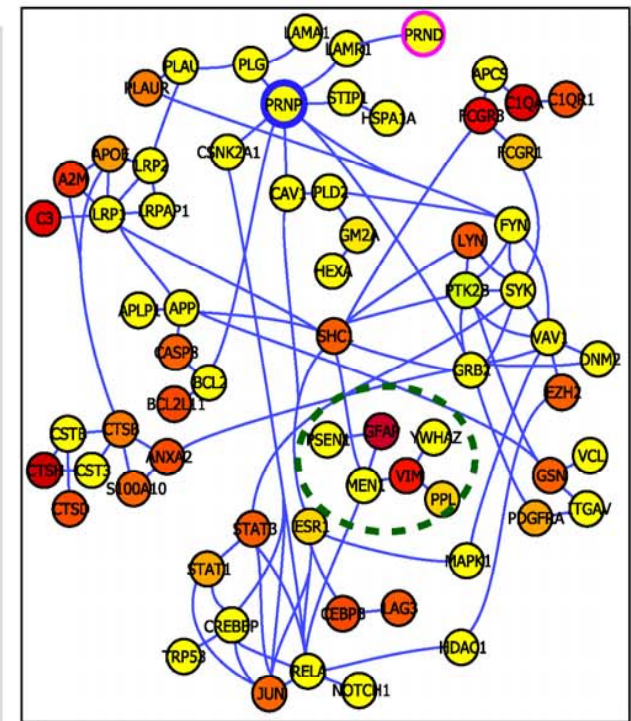
Clinical Signs



2 wks



12 wks



20 wks

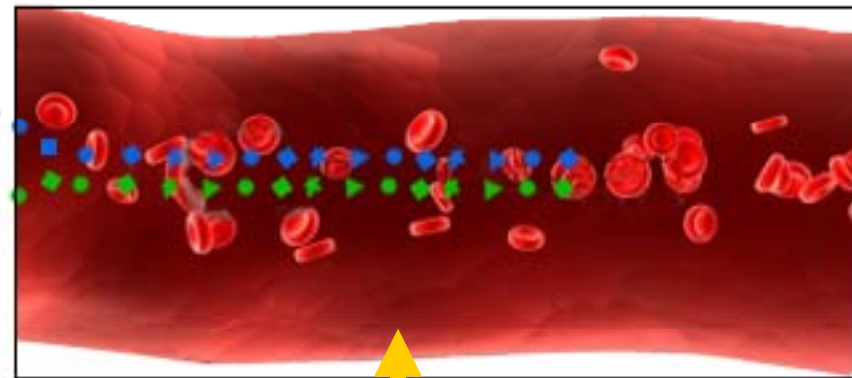
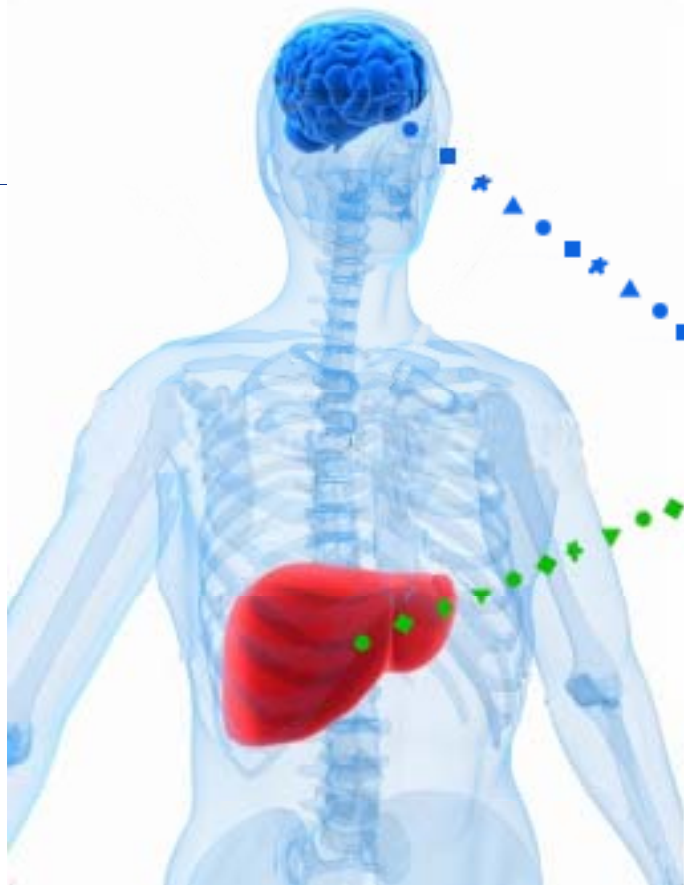
Differentially Expressed Genes (DEGs) Encoding Known and Novel Prion Disease Phenotypes

- About 300 DEGs encode core prion disease
- About 200/300 DEGs encode known disease pathogenic networks
- 100/300 DEGs encode novel pathogenic networks--the dark genes of prion disease
- Re-engineer disease-perturbed networks with drugs—new approach to drug target discovery and systems diagnosis

A Systems Approach to Blood Diagnostics

Organ-Specific Blood Fingerprints

Making Blood A Window Distinguishing Health and Disease



Blood Vessel

Why Blood Diagnostics Will Be the Key to P4 Medicine

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

Integrated Diagnostics—platform company for P4 medicine

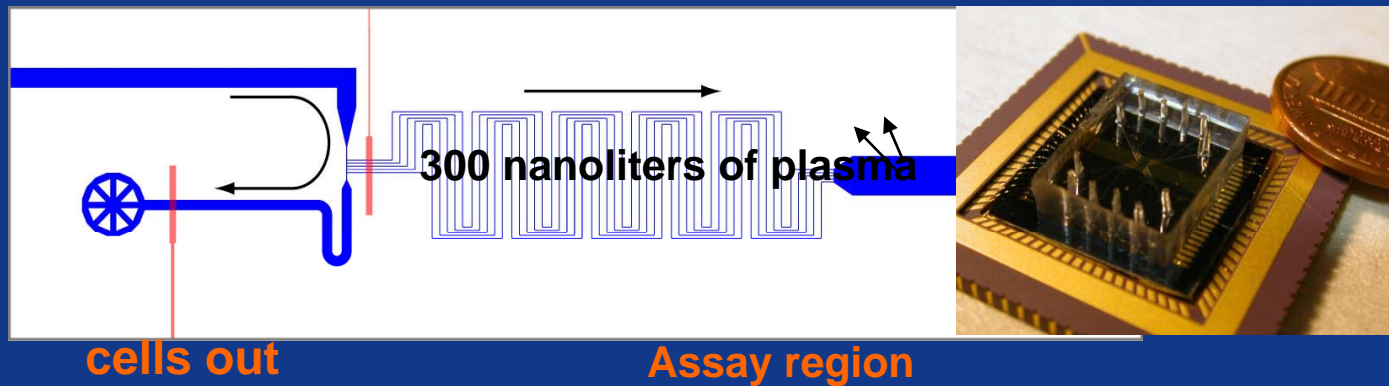
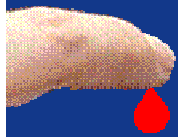
Strategies and Technologies: Exploring New Dimensions of Data Space

Microfluidic Protein Chip:

Assay 2500 Organ-Specific Blood Proteins
from Millions of Patients Using a Drop of Blood

- Jim Heath--Caltech

DEAL for *In vitro* molecular diagnostics: *Integrated nanotech/microfluidics platform*



5 minute measurement

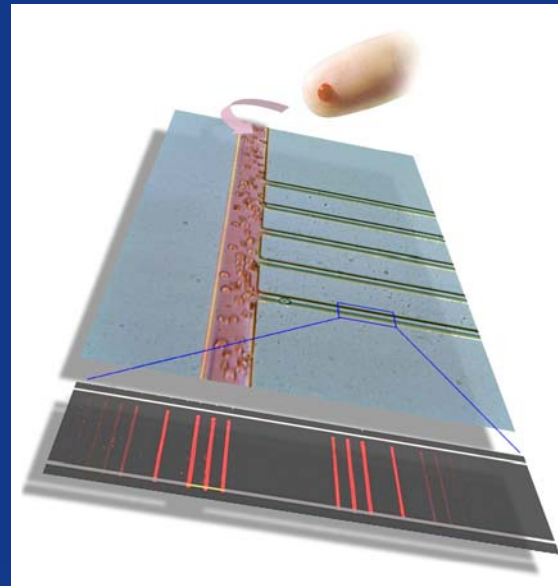
Jim Heath, et al

ISB's Individual Patient Information-Based Assays

- Complete individual genome sequences—predictive health history—will be done sequencing families
- Complete individual genome sequences from a single cell—cancer.
- Complete MHC chromosomal sequence in families—autoimmune disease and allergies
- 200 Actionable SNPs—pharmacogenetics-related and disease-related genes
- Sequence 1000 transcriptomes simultaneously in one DNA sequencing run from single cancer cells to identify quantized cells states and dissect cancer
- 2500 blood organ-specific blood proteins from 300 nanoliters of blood in 5 minutes—twice per year (50 proteins from 50 organs)—wellness assessment.
- Array of 13,000 human proteins—against autoimmune or allergic sera--stratify.
- 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 stem (iPS) cells from each individual differentiated to relevant tissues to get important phenotypic information—molecular, imaging and higher level phenotypic measurements.

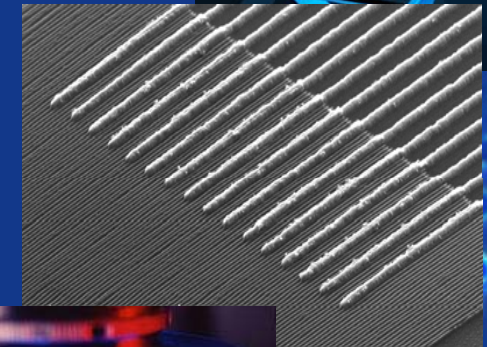
Predictive, Personalized, Preventive and Participatory (P4) Medicine

- 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



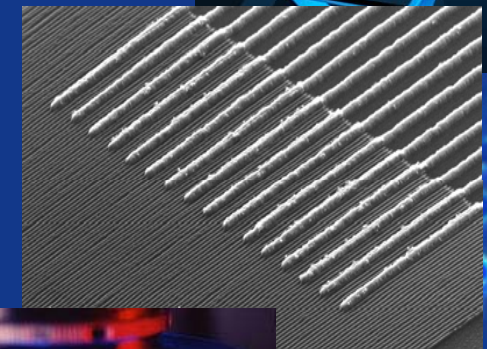
P4 Medicine

- **Predictive:**
 - Probabilistic health history--DNA sequence
 - Biannual multi-parameter blood protein measurements
 - In vivo molecular imaging



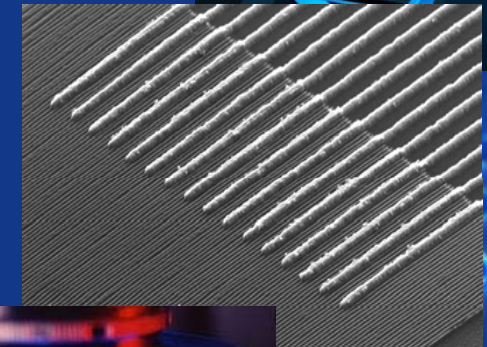
P4 Medicine

- **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
 - 100s millions patients with billions data points



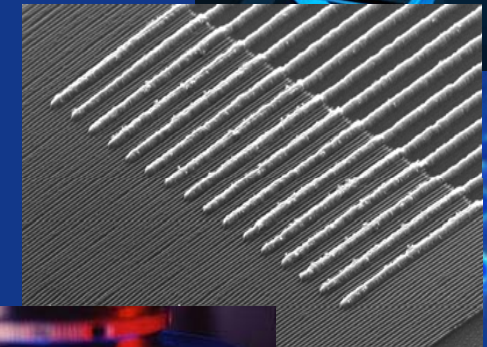
P4 Medicine

- **Preventive:**
 - Design of therapeutic and preventive drugs via systems approaches
 - Systems approaches to vaccines will transform prevention of infectious diseases
 - Transition to wellness assessment



P4 Medicine

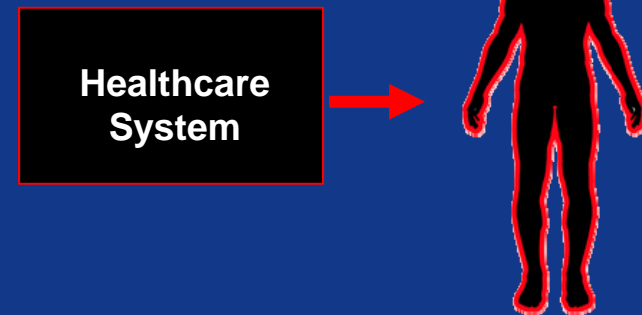
- **Participatory:**
 - Patient understands and participates in medical choices
 - Physicians trained before P4 will have to understand it
 - Medical community—interconnected and educated
 - Create IT for healthcare to handle billions of patients, each with billions of data points



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

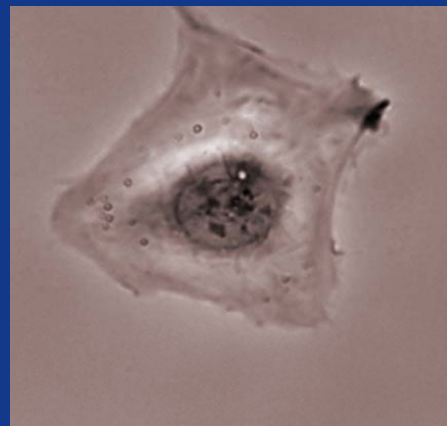
Digitalization of Biology and Medicine Will Transform Medicine

- Analysis of single molecules, single cells, single organs and single individuals
- A revolution that will transform medicine even more than digitalization transformed information technologies and communications
- Digitization of medicine will lead to dramatically lower healthcare costs

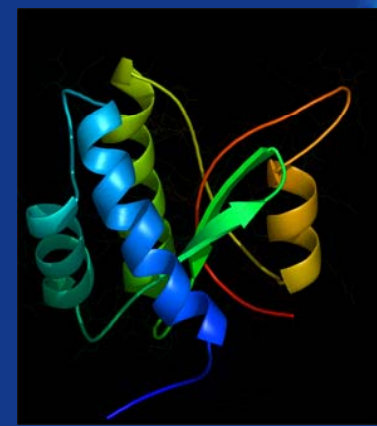
Single individual



Single cell



Single molecule



Why the Digitalization of Medicine and P4 (Systems) Medicine Will Reduce Healthcare Costs

- Diagnosis will stratify disease and impedance match drugs
- Re-engineering disease-perturbed networks to normalcy with drugs—new and less expensive strategy for drug target discovery
- Survey wellness with 2500 blood organ-specific protein measurements biannually—50 from each of 50 organs—global early detection
- Technologies exponentially increasing in the number of measurements they can make and decreasing in cost
- 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

- 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:
 - Predict and prevent disease at the earliest stages
 - Provide the tools for patients to actively participate in optimizing their own wellness
 - Catalyze a new industrial opportunity based on wellness (rather than just disease)

Inventing the Future

20th Century Biomedicine

ISB

21st Century Biomedicine

- 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 hard scientific problems--P4 medicine--industrial, academic, government, international

ISB/Luxembourg Strategic Partnerships

ISB/Luxembourg Strategic Partnership

- Helping to creating a Center for System Medicine similar to ISB—Rudi Balling Director
- Two collaborative research projects--
\$100 million over 5 years
- Helping establish biotech industry in Luxembourg—start ups and established companies--integrated personalized medicine company—Integrated Diagnostics

ISB/Ohio State Strategic Partnership

The P4 Medicine Institute

[\(http://www.P4MI.org\)](http://www.P4MI.org)

- Non-profit 501c3
- ISB and Ohio State founding members
- Committed to bringing P4 medicine to patients—initially through two pilot projects—wellness and lung cancer
- Seeking academic and industrial partners who share the P4 vision and have complementary skills/resources
- Bringing on consultants to analyze the societal challenges of P4 medicine—ethics, security, confidentiality, policy, regulation, economics

P4 Medicine Is Personalized Medicine and Far More!

- P4 medicine is medicine of the **present/near future**.
- P4 medicine is **driven** by **systems approaches** to disease and emerging technologies
- P4 medicine will use **measurements** to **quantify wellness** and its transition into disease
- P4 medicine is **revolutionary** rather than evolutionary or incremental
- 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 be **effective, inexpensive 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.

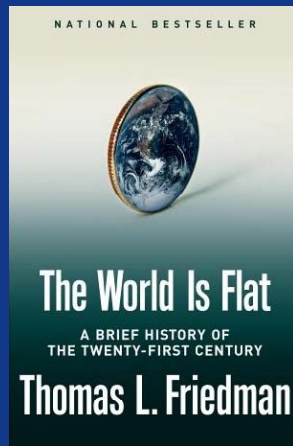
Two Comments on the Economic Implications of the Systems Approaches to Big Problems in Biology

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 - Biology is an **informational science**
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 - Evolving current and **emerging technologies** permit the exploration of new areas of data space (and better 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, global health, environment, energy, nutrition, agriculture**, etc.
- These opportunities will fuel **enormous economic opportunities**

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, technology and education to attack “Big Problems”**.



- Network of interacting complementary, institutions
 - Training in systems biology and recruiting the best world talent
- Transferring and collaborating on new technologies and computational tools
- Strategic partnerships on systems approaches to biology and P4 medicine
- New patient populations
- New fundraising and commercialization opportunities

