NICEATM-ICCVAM Five Year Plan: The role of the National Institutes of Health

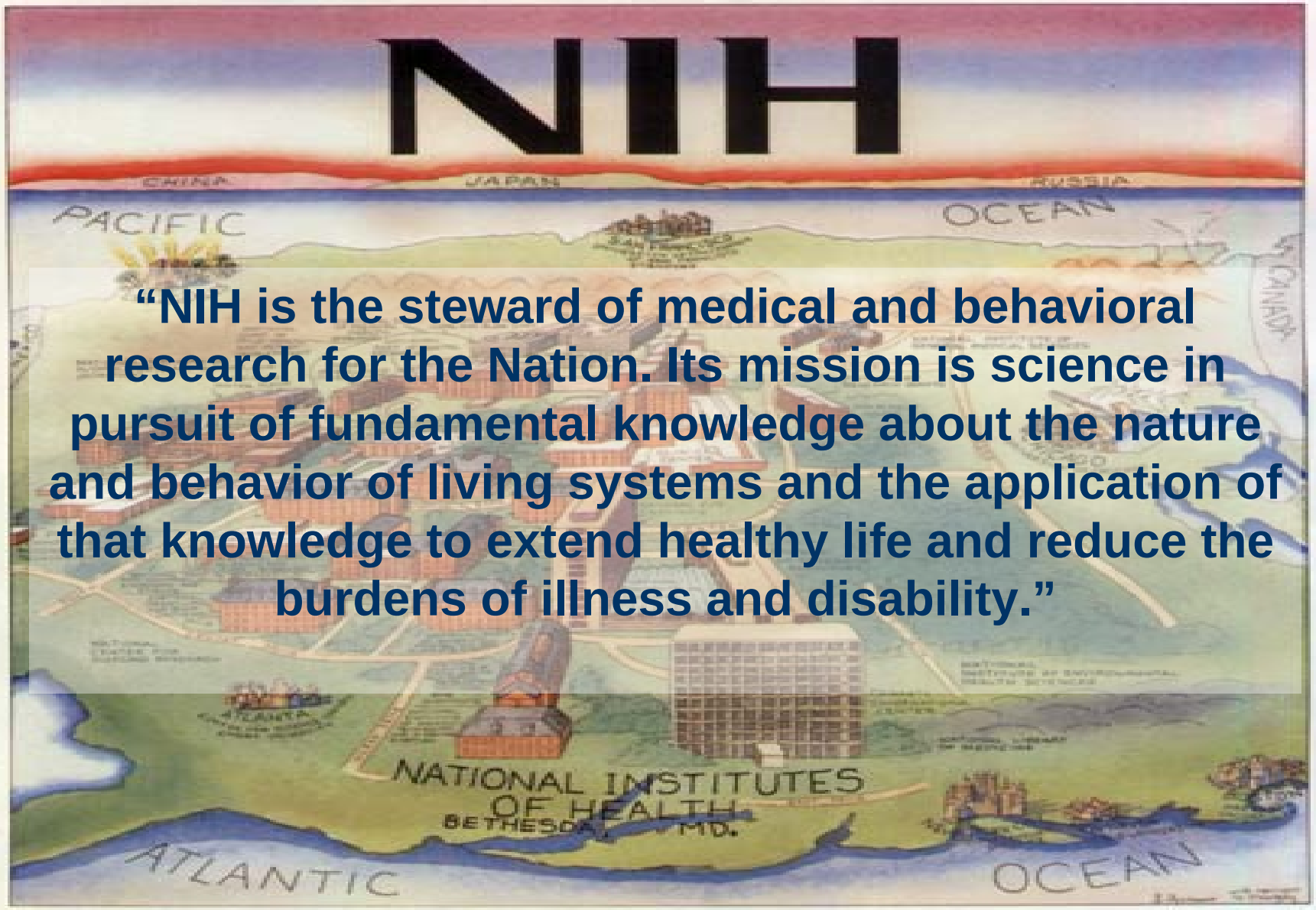
Norka Ruiz Bravo, Ph.D.
NIH Deputy Director for Extramural Research

Presented to the Scientific Advisory Committee on Alternative Toxicological Methods, June 18, 2008

Today's Conversation

- The mission of NIH
- The relationship of NIH basic research to the Five Year Plan
- Current research efforts with implications for toxicology testing

NIH: The Nation's Medical Research Agency



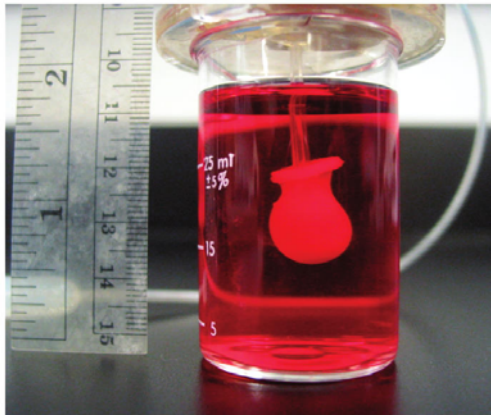
Biomedicine in the 21st century…

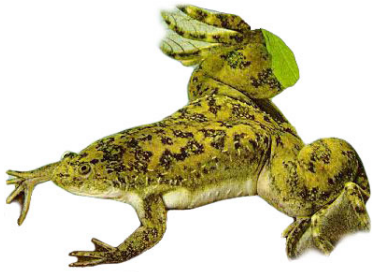
The 4 Ps:
Predictive, Personalized, Preemptive, and Participatory

Predictive ↔ Personalized ↔ Preemptive

Participatory

NIH supports using the best models for the science in question





Evolving public health challenges…

Shift from acute to chronic conditions

Aging population

Health disparities

Emerging and re-emerging infectious diseases

Emerging non-communicable diseases - obesity

Biodefense

The dual nature of NIH…

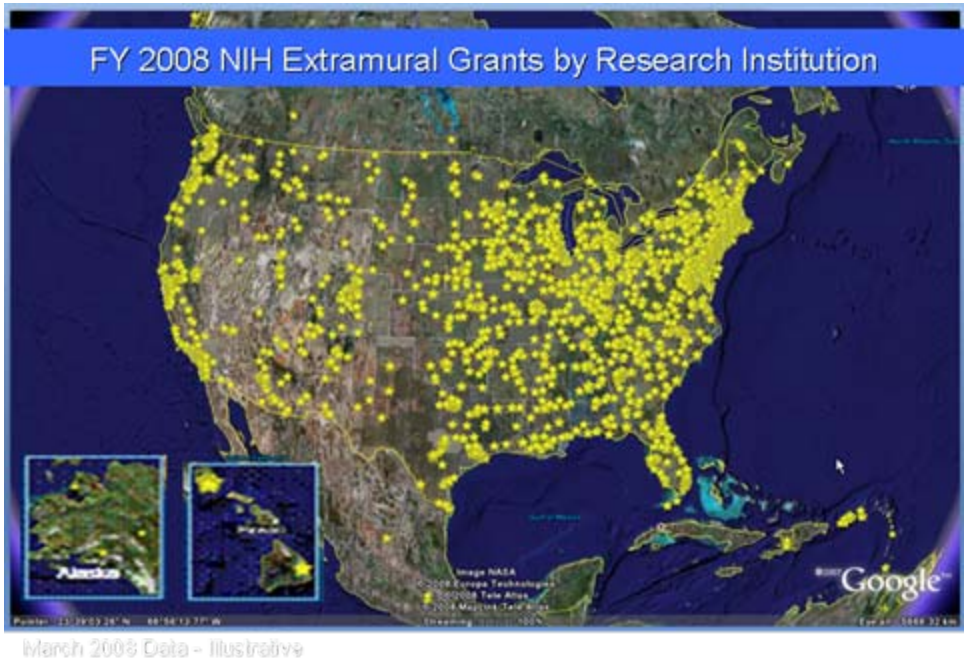
NIH INTRAMURAL RESEARCH

NIH <u>is</u> an institution

- **Supports over 6,000 scientists**
- **Approximately 10% of NIH budget**
- **Primary campus in Bethesda, MD with a few more labs throughout the U.S.**
- **Clinical, Basic, & Translational Research**

NIH EXTRAMURAL RESEARCH

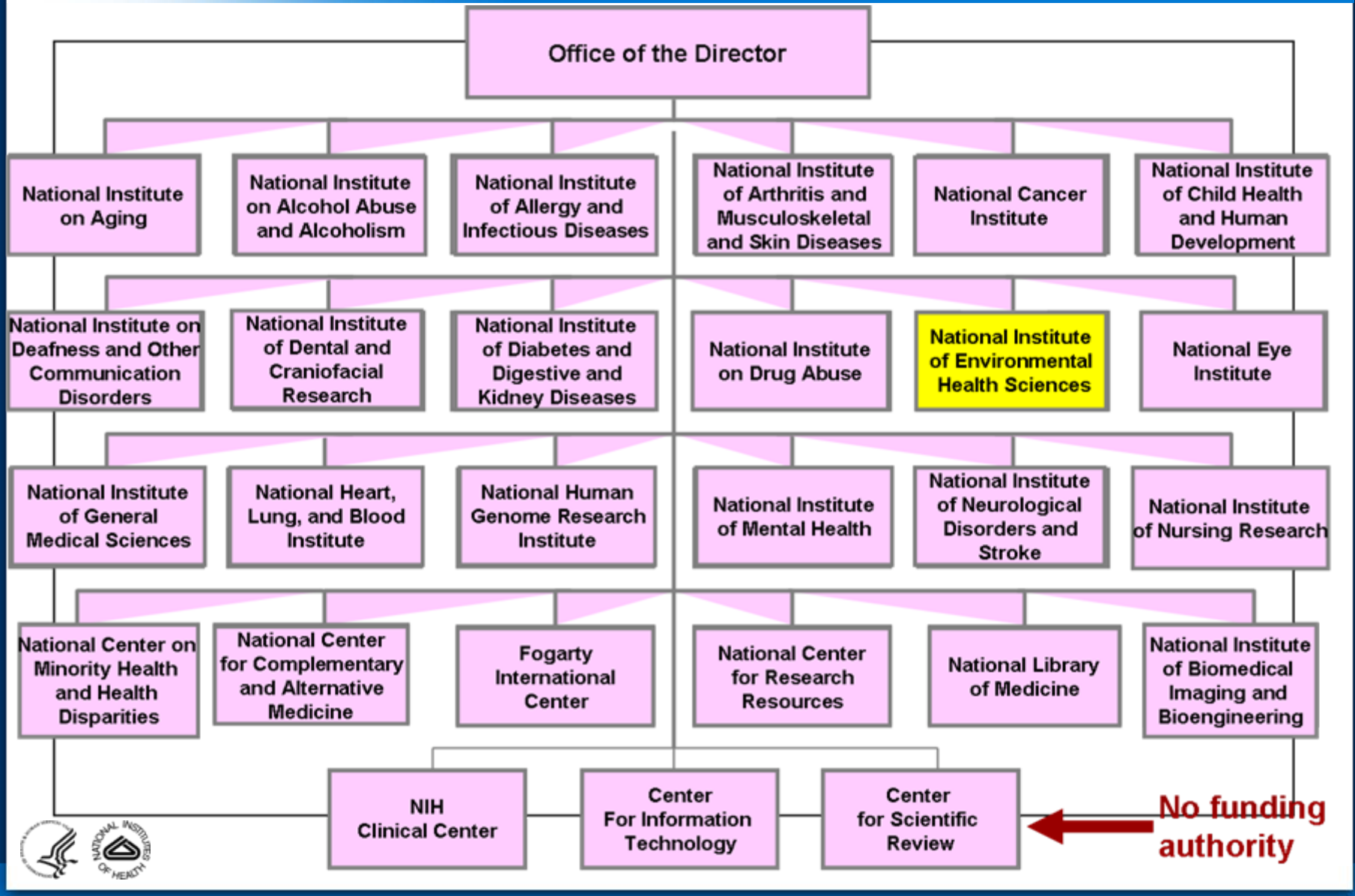
NIH <u>supports</u> institutions



- **Supports over 150,000 PIs & Key Personnel**
- **Approximately 83% of NIH budget**
- **Awards issued to >3,000 institutions in > 100 countries**
- **Clinical, Basic, & Translational Research**

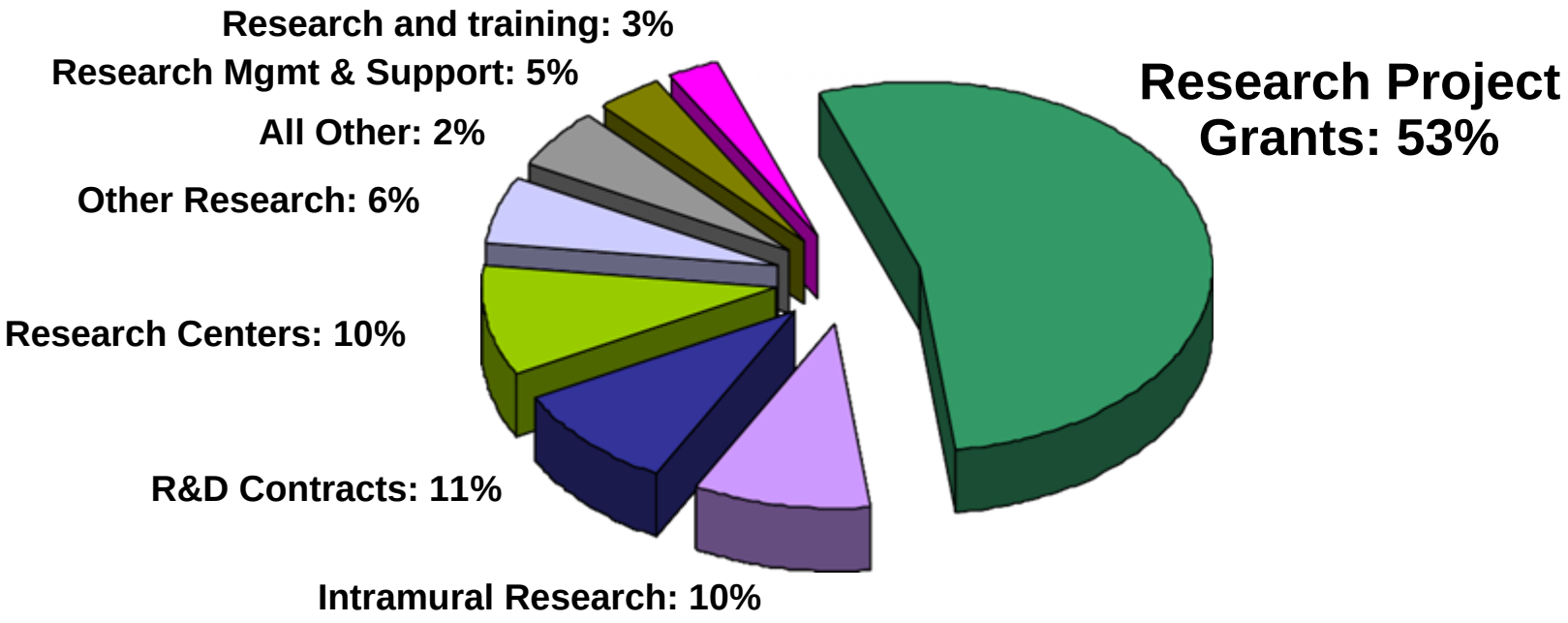
*All figures are estimates.

NIH organizational structure



FY 2008 Enacted Budget

Total NIH Budget Authority: $29.457 Billion



Source: http://www.nih.gov/about/director/budgetrequest/pressinfofy2008.pdf

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

Mission:

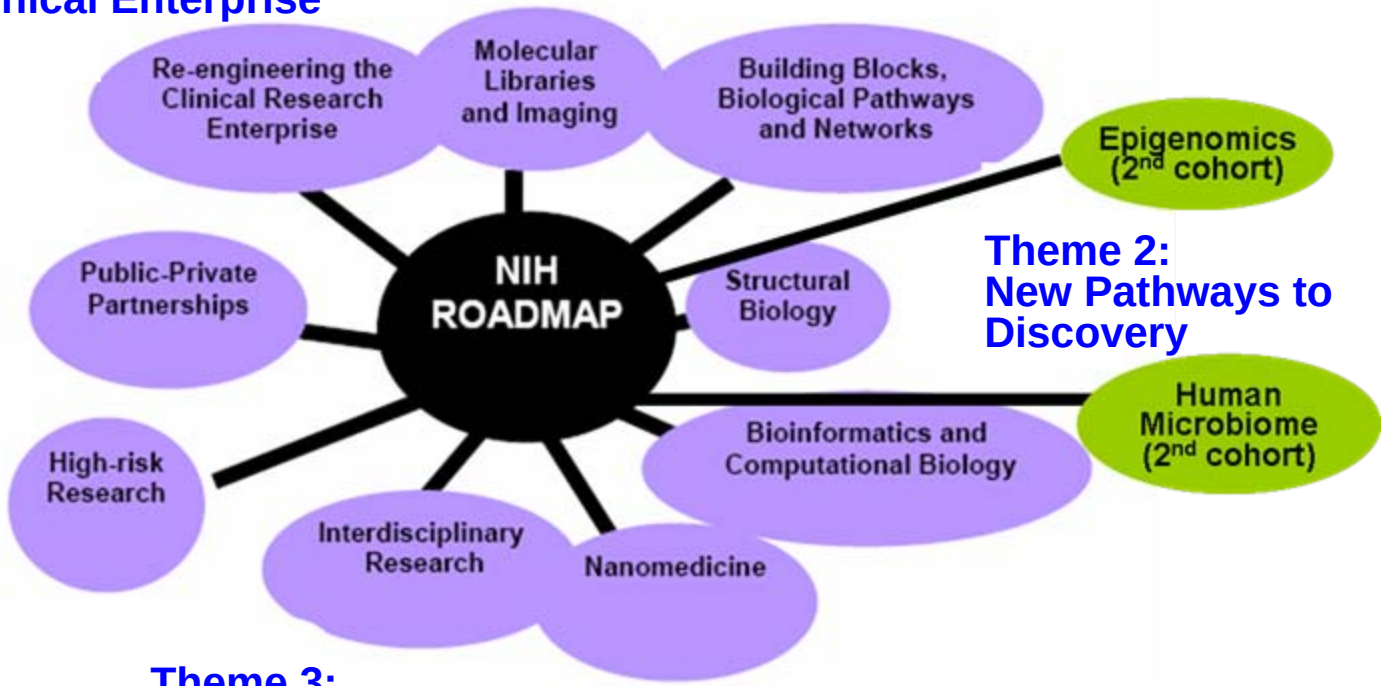
"To facilitate the development, validation and regulatory acceptance of new and revised regulatory test methods that reduce, refine, and replace the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment"

ICCVAM's Five Year Plan (2008-2012) priorities

1. Promoting priority test methods
   - Ocular, dermal, acute toxicity
   - Biologics
2. Incorporating new science and technology
   - NIH science and technology is developed to understand biological systems and promote human health
   - NIH-supported research may open new possibilities for alternative toxicology tests
3. Fostering acceptance and appropriate use of alternative test methods
4. Developing partnerships and strengthening interactions with ICCVAM stakeholders

NIH Roadmap for Medical Research

Theme 1:
Clinical Enterprise



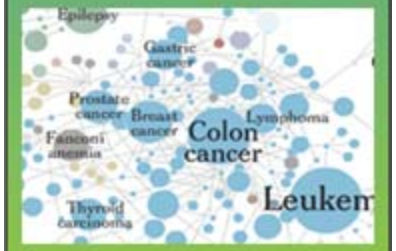
Theme 2:
New Pathways to Discovery

Theme 3:
Research Teams of the Future

Examples from NIH's research portfolio

Zebrafish

NIH Chemical Genomics Center (NCGC)

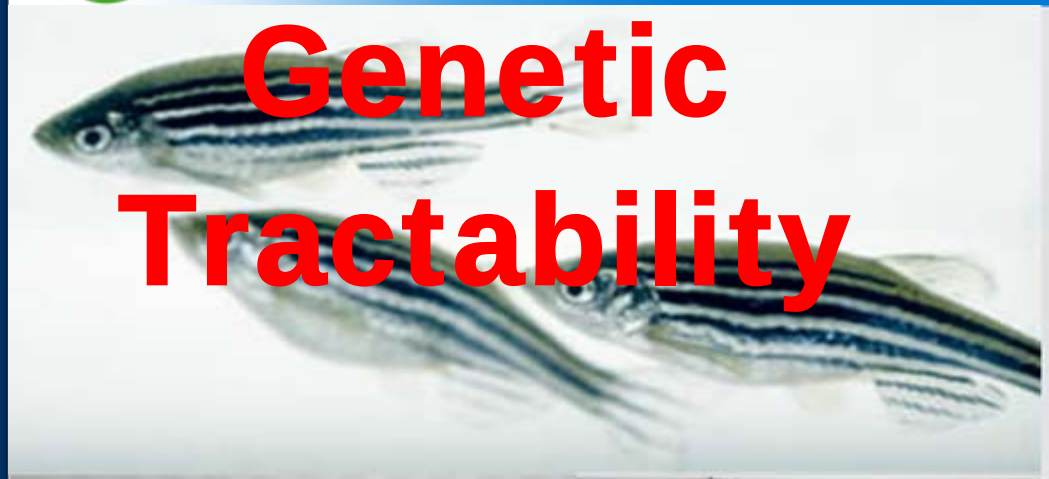


Microarrays/gene chips

3-dimensional tissue modeling and

Small Business Innovation Research (SBIR)

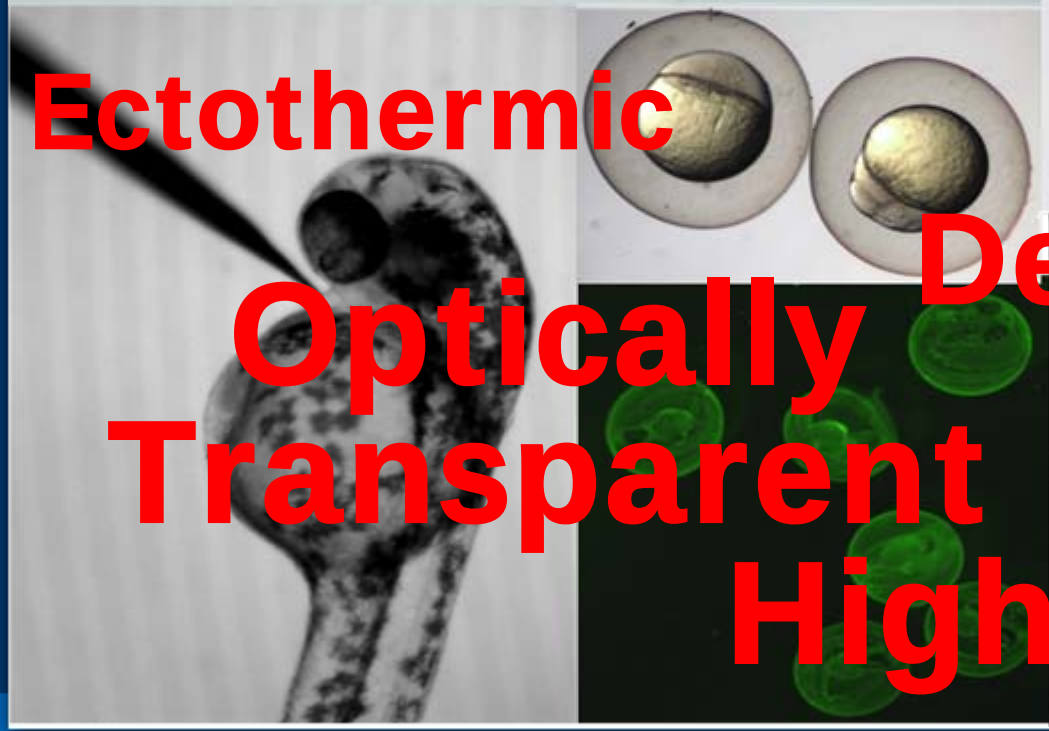
1. Zebra fish in toxicology studies



Genetic Tractability

Small Size

Rapid Development



Ectothermic

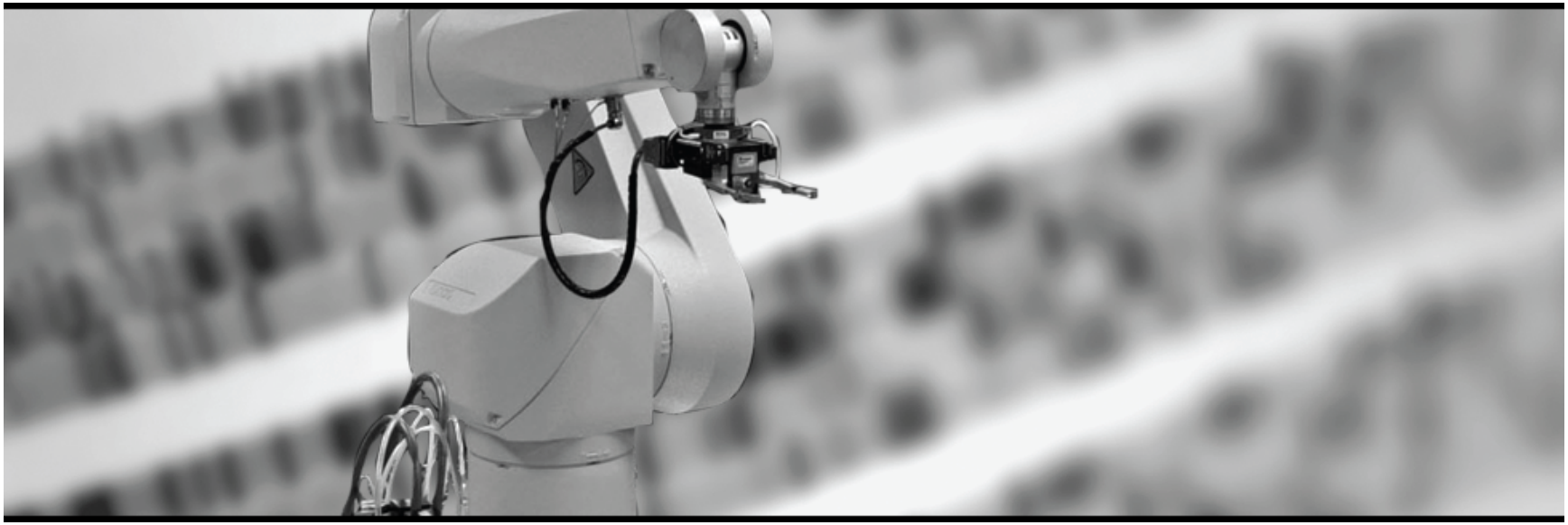
Optically Transparent

Highly Fecund

Slide courtesy of: Jay R. Hove, Ph.D., Dept. of Molecular and Cellular Physiology, University of Cincinnati – College of Medicine

2. NIH Chemical Genomics Center (NCGC)

NIH Chemical Genomics Center



Welcome to the National Institutes of Health (NIH) Chemical Genomics Center (NCGC). This center has been established by the NIH to create a national resource in chemical probe development. The center uses the latest industrial-scale technologies to collect data that is useful for defining the cross-section between chemical space and biological activity.

Source: http://www.ncgc.nih.gov/

NIH-EPA five-year MOU for NCGC

U.S. Department of Health and Human Services

NIH News

National Institutes of Health

NIH Collaborates with EPA to Improve the Safety Testing of Chemicals

New Strategy Aims to Reduce Reliance on Animal Testing

Bethesda, Md., Feb.14, 2008 — Testing the safety of chemicals ranging from pesticides to household cleaners will benefit from new technologies and a plan for collaboration, according to federal scientists from the National Institutes of Health (NIH) and the U.S. Environmental Protection Agency (EPA), who today announced a new toxicity testing agreement. The concept behind this agreement is highlighted in the Feb. 15, 2008 issue of the journal *Science*.

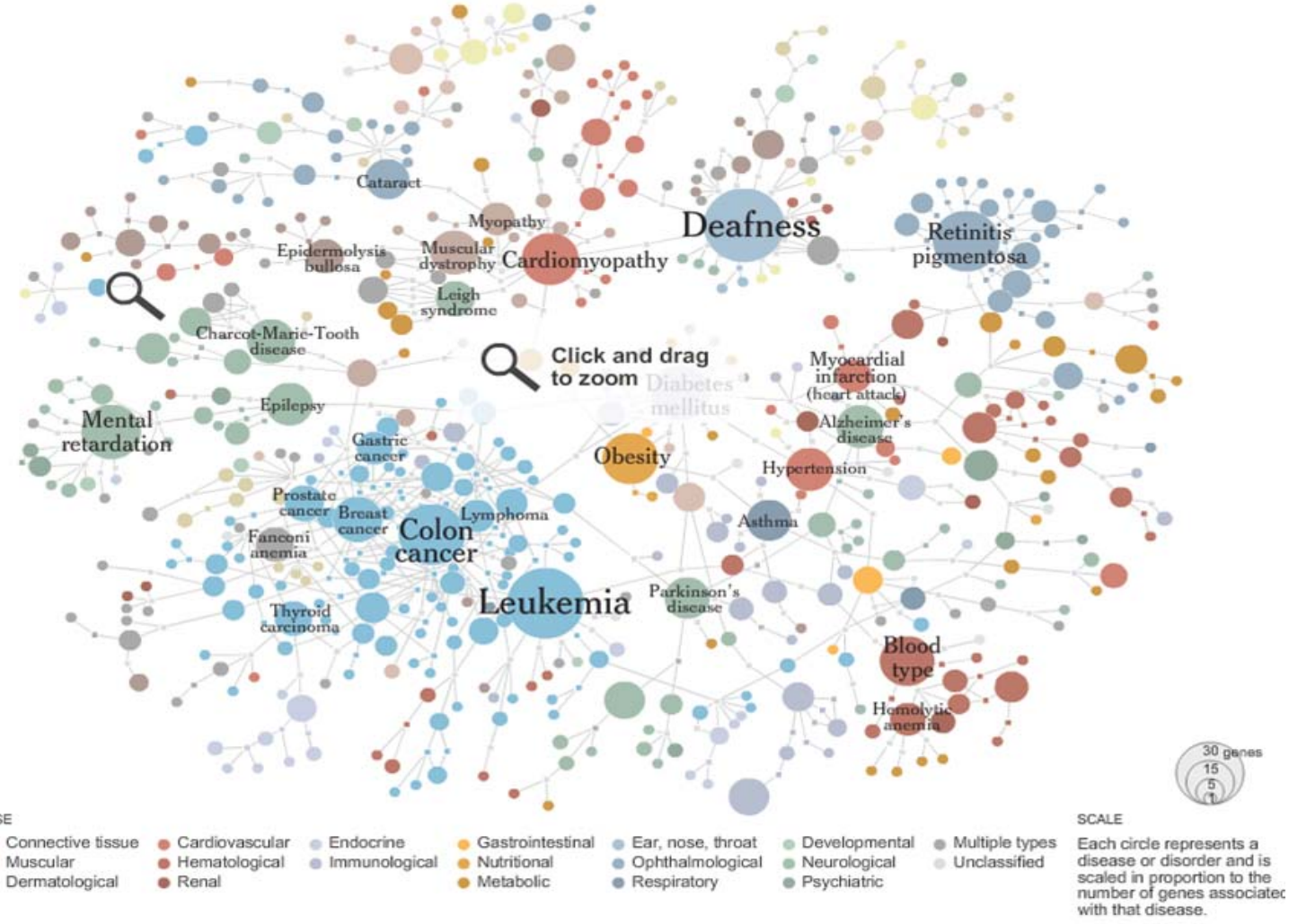
"I launched the NIH Roadmap for Medical Research five years ago to create collaborations between institutes and centers on big projects that none of them could do alone. But I never envisioned a trans-agency collaboration testing for environmental toxins," said NIH Director Elias A. Zerhouni, M.D. "This research collaboration has the potential to make crucial discoveries that will protect the public health by identifying and understanding chemical toxicants to which people are exposed."

Two NIH institutes have formed a collaboration with the EPA to use the NIH Chemical Genomics Center's (NCGC) high-speed, automated screening robots to test suspected toxic compounds using cells and isolated molecular targets instead of laboratory animals. This new, trans-agency collaboration is anticipated to generate data more relevant to humans; expand the number of chemicals that are tested; and reduce the time, money and number of animals involved in testing. Full implementation of the hoped-for paradigm shift in toxicity testing will require validation of the new approaches, a substantial effort that could consume many years.

This collaboration is being made possible through a newly signed, five-year Memorandum of Understanding (MOU) PDF, which leverages the strengths of each organization. The MOU builds on the experimental toxicology expertise at the National Toxicology Program (NTP), headquartered at the National Institute of Environmental Health Sciences (NIEHS), NIH; the high-throughput technology at NCGC, managed by the National Human Genome Research Institute (NHGRI), NIH; and the computational toxicology capabilities at the EPA's recently formed

Source: http://genome.gov/26524913

3. Genomics-based nosology: A new way to understand disease



Source: "Redefining disease, genes and all" by A. Pollack, NY Times 6 may, 2008; image by M. Bloch and J. Corum based on PNAS publication by Goh et al. 22 May, 2007

Gene chips and microarrays

MEDICINE

The Ultimate Model Organism

Atul J. Butte

A deeper understanding of disease requires a database of human traits and disease states that is integrated with molecular information.

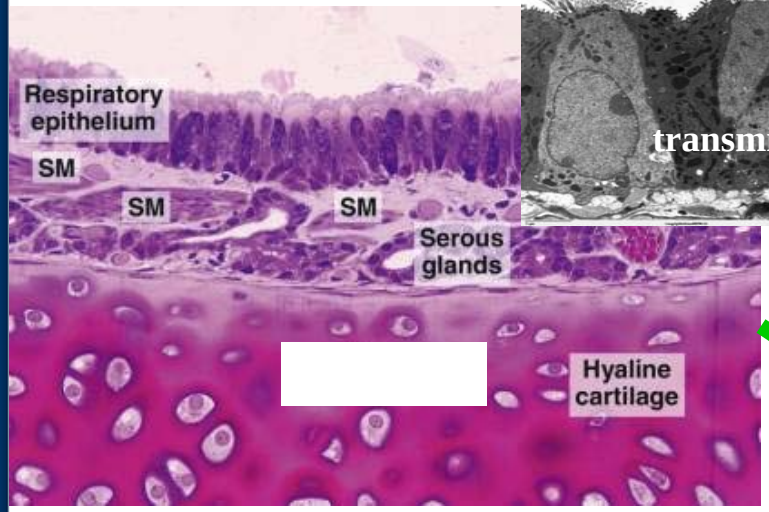
This month, the scientific community celebrates the 25th anniversary of GenBank, the open access database of DNA sequences and the molecules they encode. Heralded as one of the earliest bioinformatics community projects, it has fueled our need to understand how this information can be linked to physiology and disease. Since then, biocomputational, informatics, and statistical methods have been used to relate sequences and molecules to diseases. But as highlighted in meetings such as last month's Summit on Translational Bioinformatics (*1*), the same high-bandwidth measurement style that has accelerated the molecular and genetic study of disease must be practiced in physiology if we are to gain a deeper understanding of normal and impaired health.

Within the last 5 years, systematic studies on the commonalities (*2*) and differences (*3*) across diseases have shown that particular biological signaling pathways and modules share similar properties. Other studies have shown that diseases that resemble each other can share genes with variants (*4*, *5*) or share genes coding for proteins that interact with each other (*6*). So many diseases have now been studied that publicly available data can be used to find genes with common changes in expression for each condition (*7*).

The difficulty with interpreting such analyses lies with how diseases are defined. The definition of a disease is often specified

Stanford Center for Biomedical Informatics Research, Department of Medicine and Department of Pediatrics, Stanford University School of Medicine, Stanford, CA 94305, USA, and Lucile Packard Children's Hospital, Palo Alto, CA 94304, USA. E-mail: abutte@stanford.edu

4. 2-D culture does not mimic *in situ* complexity

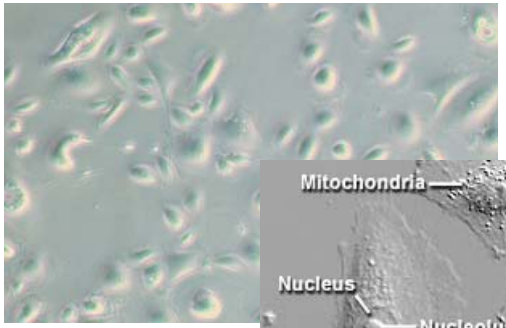


Native Human Lung Histology

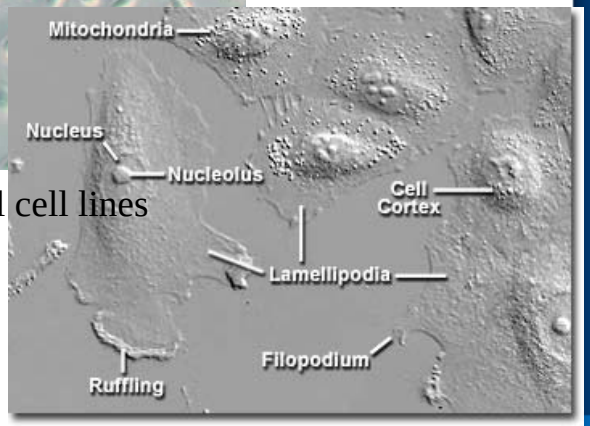
2-D Can Reveal…

- cell surface biomarkers
- gene/protein expression
- intracellular pathway analysis

Standard Cell Culture



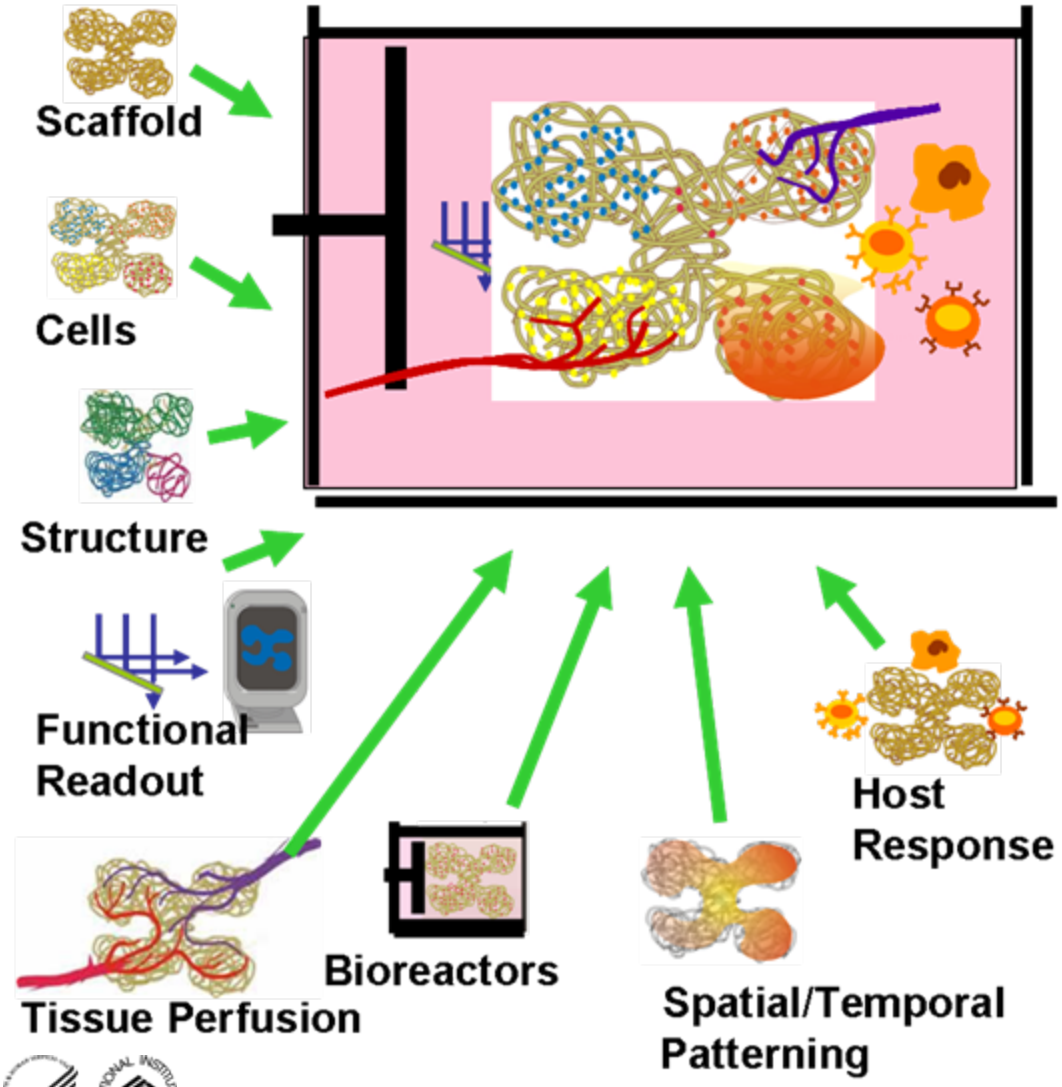
lung epithelial cell lines



… but 3-D data are more physiologically relevant for:

- cell-cell, cell-matrix interactions
- cell polarity and barrier functions
- spatial/temporal gradients
- role of biomechanics
- mixed populations in relevant configurations

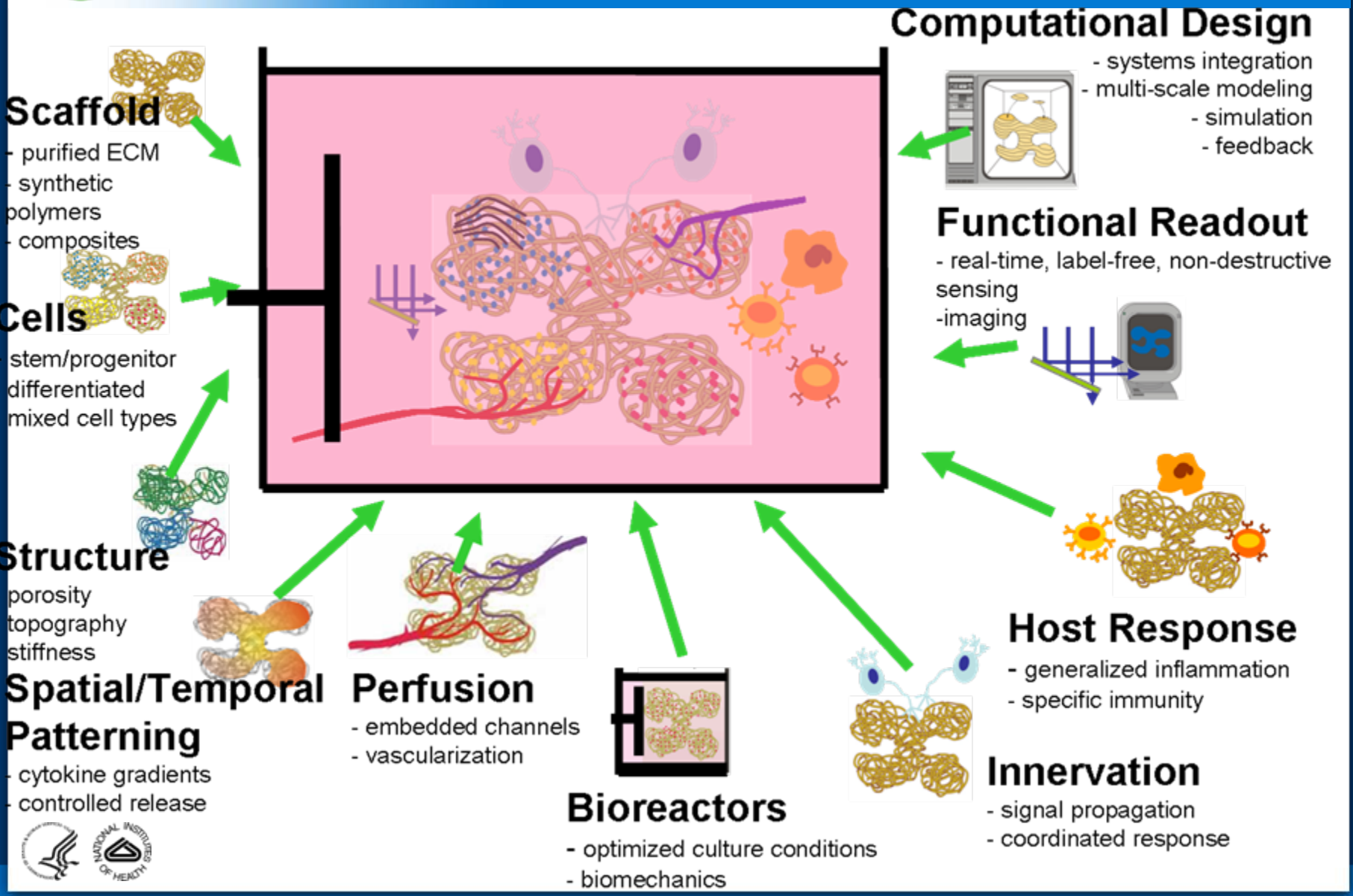
Idealized 3-D tissue model



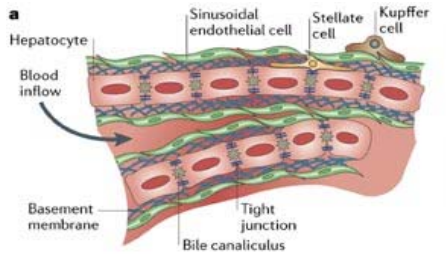
3-D Advantage:

- developmental biology of respiratory tissue
- toxin effects on tissue integrity
- cell polarity and barrier functions
- alveolar gas exchange
- mucosal immunity
- role of cyclic stress in tissue growth and maintenance
- real time monitoring for studying disease progression
- tumor metastasis
- …

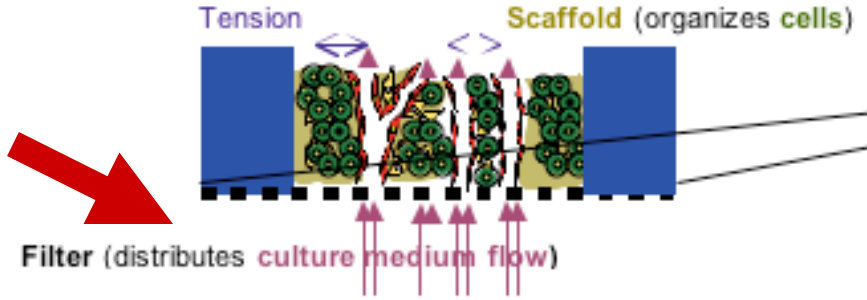
Generalized 3-D tissue model from common building blocks

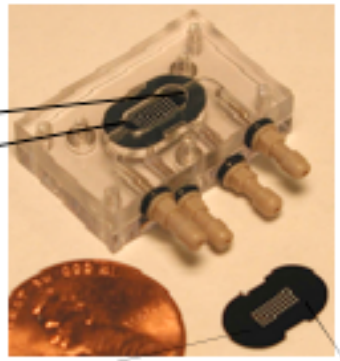


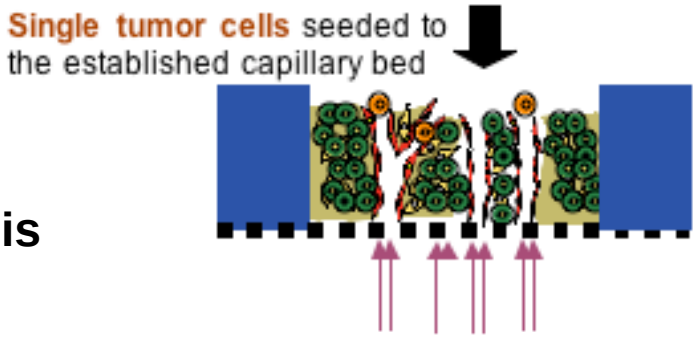
3-D liver models demonstrate feasibility of approach

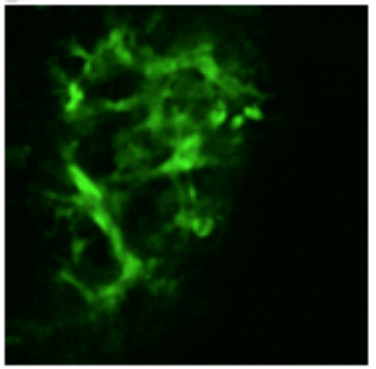


Schematic of the liver

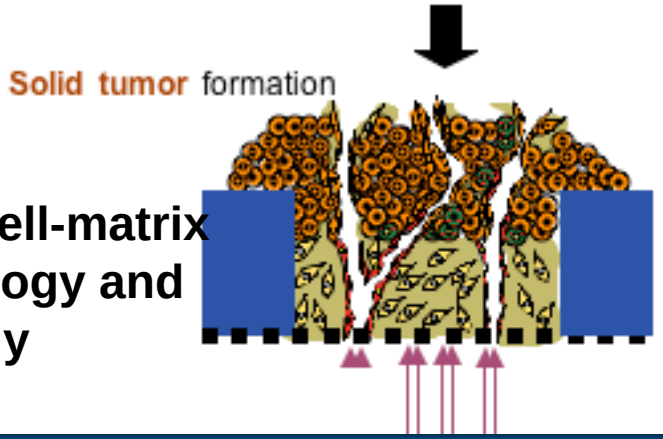


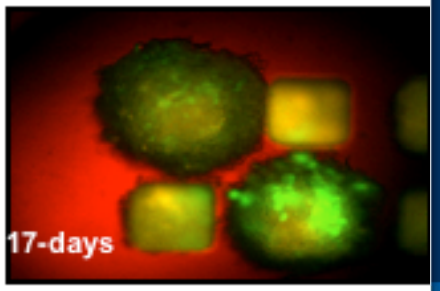






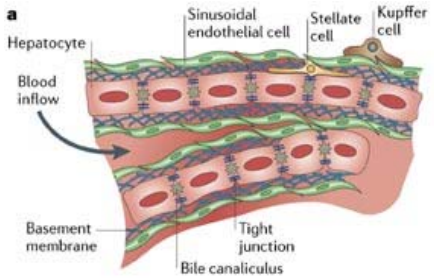
Metastasis model



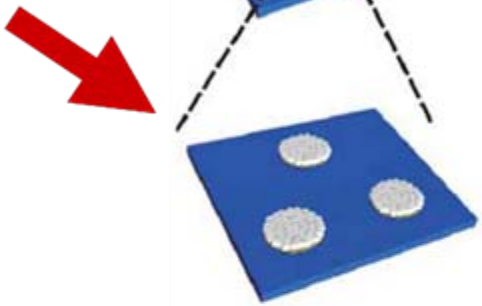


Complex cell-cell and cell-matrix interactions in physiology and pathophysiology

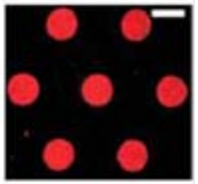
3-D liver models demonstrate feasibility of approach (2)



Schematic of the liver

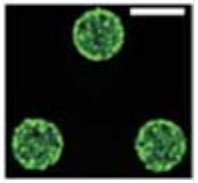


Micropatterned extracellular matrix



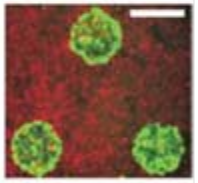
Seed hepatocytes

Micropatterned hepatocytes

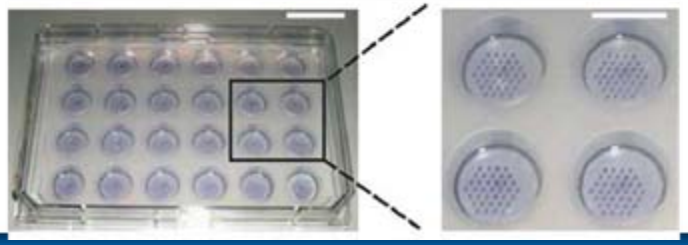


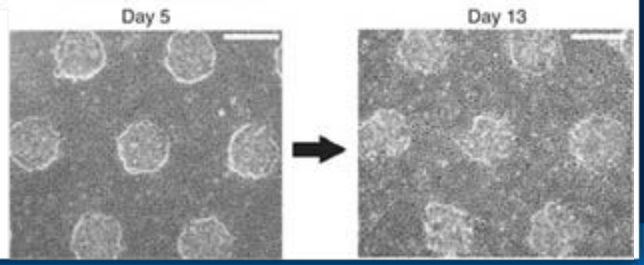
Seed stromal cells

Micropatterned 3-D, mixed cell coculture

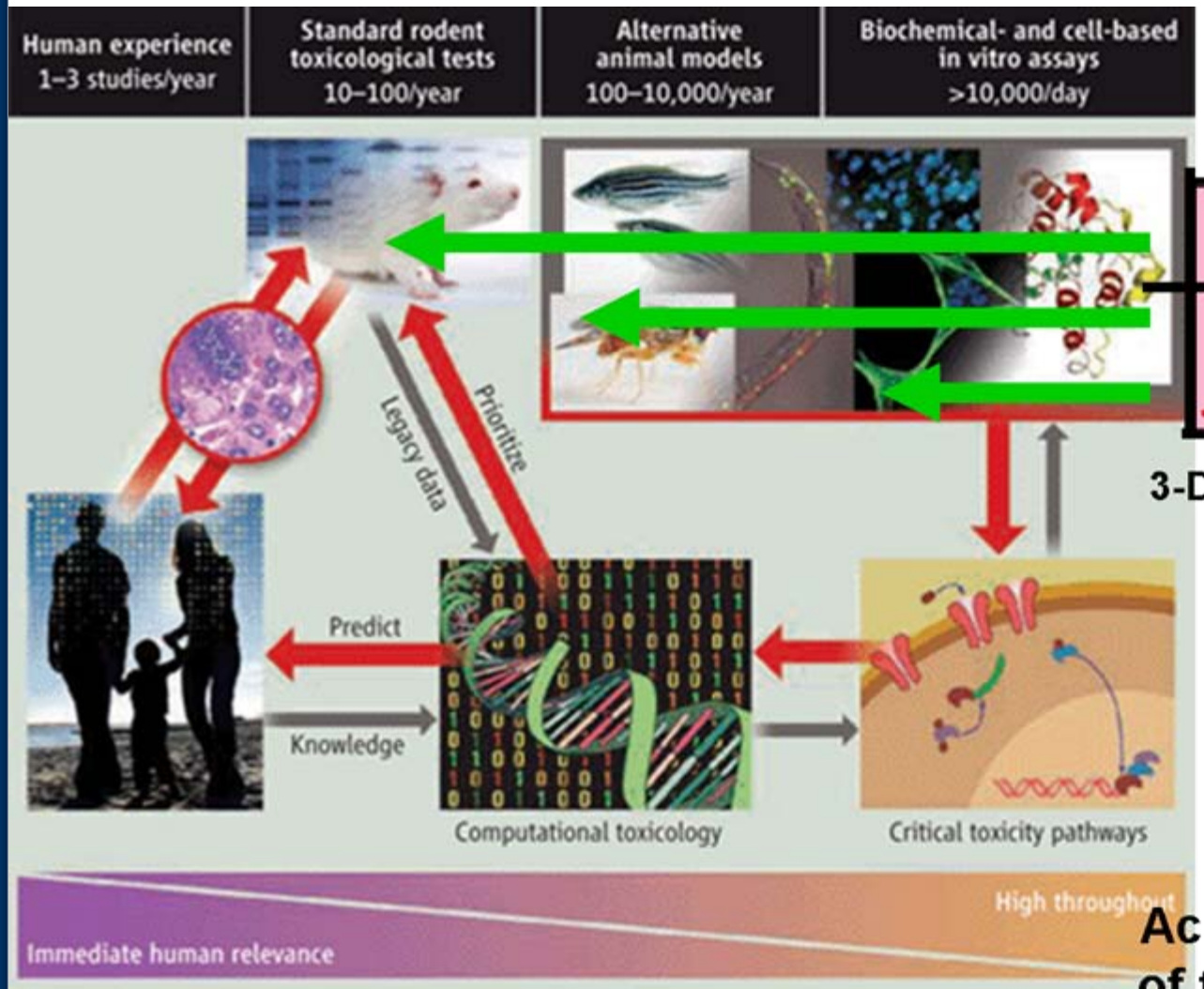


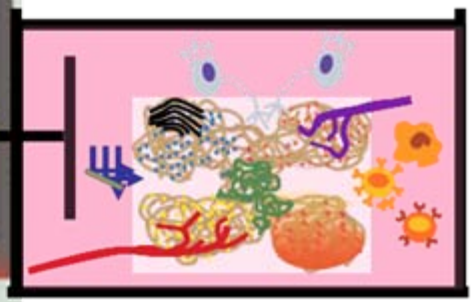
Generating complex tissues via lithography for high throughput screening





Environmental toxicology impact



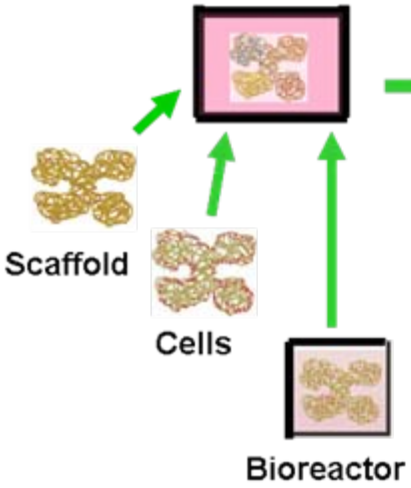


3-D Human Tissue Models

Accelerate discovery of therapeutic agents

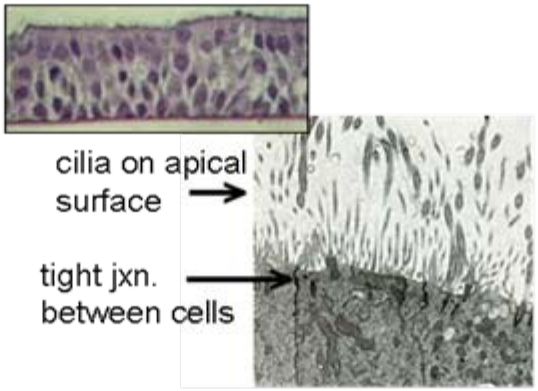
Collins, F, G Gray, J Bucher (2008) Science *319*: 906.

5. NIH SBIR & "First generation" 3-D tissue model

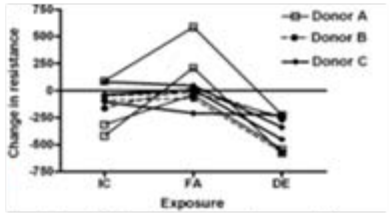


Mattek EpiAirway™ System

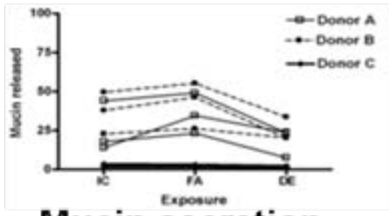
- tissue structure
- physiologic responses
- low Throughput



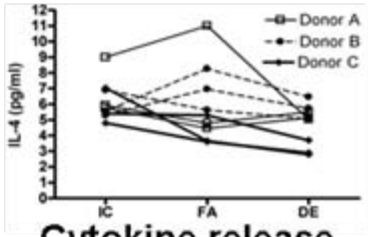
TEM Micrograph



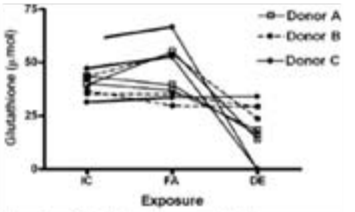
Epithelial Integrity



Mucin secretion



Cytokine release

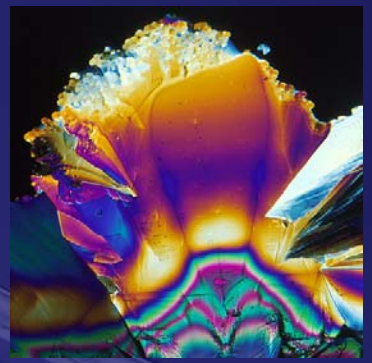


Glutathione Release
(Oxidative stress response)

Functional Assays:

- destructive
- not real time
- limited parameters measured






NIH *Transforming medicine through discovery*