BIOMED21: A human pathways approach to disease research

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DIRECTOR, NCATS

BIOMED21 MEETING
JUNE 26, 2017

NCATS

A career at the ragged edge*

Horner's Syndrome From Hypothalamic Infarction

Christopher P. Austin, MD, Simmons Lessell, MD

• We report a case of Horner's syndrome due to ipsilateral posterior hypothalamic infarction, occurring in the absence of other signs of hypothalamic dysfunction. Associated symptoms of contralateral faciobrachial weakness and dysarthria correlated with the extension of the infarct into the posterior limb of the internal capsule seen by magnetic resonance imaging. The likely vascular anatomy of this lesion is discussed.
(*Arch Neurol.* 1991;48:332-334)

Accepted for publication July 20, 1990.
From the Departments of Neurology (Dr Austin) and Ophthalmology (Dr Lessell), Harvard Medical School, Massachusetts General Hospital and Massachusetts Eye and Ear Infirmary, Boston.
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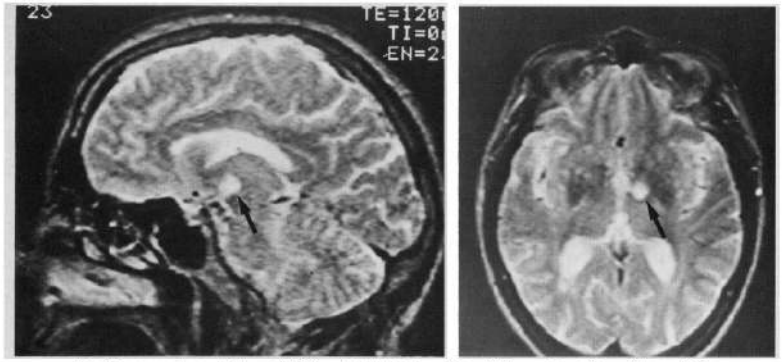
Horner's syndrome can result from interruption of the sympathetic pathway at any point from the hypothalamus to the orbit. The central neuron is involved in as many as 63% of cases,[1-3] most of them at the level of the brain stem; few are caused by lesions that implicate the sympathetic cell bodies in the hypothalamus. We are reporting a case of oculosympathetic paresis from focal, ipsilateral, posterior hypothalamic infarction.

REPORT OF A CASE

A 62-year-old woman with hypertension, diabetes mellitus, and coronary artery disease presented with left-sided occipital headache, left-sided ptosis, and right-sided face and arm weakness of 8 hours' duration.
On the day before admission, she was mildly dysarthric. She was "sleepy" on the day of admission, and, at 6 PM, her left upper eyelid drooped and she complained of left-sided occipital headache. Examination 8 hours later revealed an obese woman with a regular pulse rate of 63 beats per minute, a blood pressure of 135/90 mm Hg, and a crescendo-decrescendo systolic cardiac murmur of grade 3/6. Her mental status was normal, and there was no aphasia. The right pupil measured 4.0 mm and the left 2.0 mm. There was dilatation lag of the left pupil that accentuated the anisocoria when the lights were dimmed, but pupillary reactions were otherwise normal. She had left-sided ptosis, elevation of the left lower eyelid, and decreased sweating over the left side of the forehead. There was slight lingual dysarthria, mild right-sided upper motor neuron facial weakness, right pronator drift, and right arm weakness. Computed tomographic scan of the head, performed



Magnetic resonance images in the sagittal (left) and axial (right) planes (TR = 2000 msec; TE = 120 msec) demonstrating an area of high signal intensity consistent with infarction in the left posterior hypothalamus (arrows).

Development 110, 713–732 (1990)
Printed in Great Britain © The Company of Biologists Limited 1990

Cellular migration patterns in the developing mouse cerebral cortex

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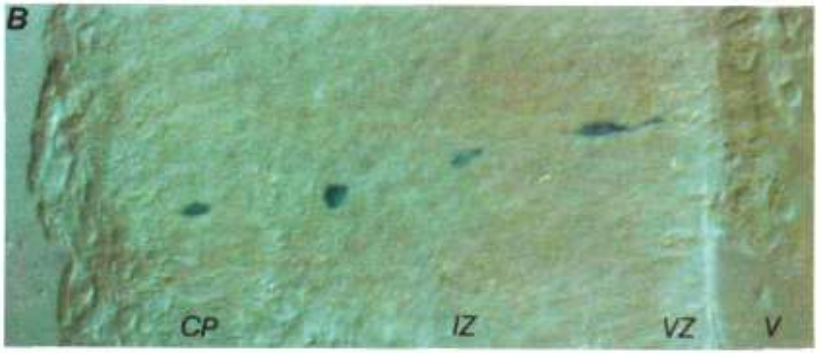
Summary

The migration patterns of embryonic mouse cortical cells were investigated using a replication-incompetent retrovirus vector (BAG). The lateral ventricles of embryonic day 12 mouse embryos were infected with BAG and brains were harvested 2, 3, 4 and 6 days after infection. The location and morphology of all infected cortical cells were recorded from serial sections of entire brains, which were then reconstructed in three dimensions. Examination of the distribution of labelled cells revealed that there were migration patterns characteristic of each medial–lateral domain of the cortex. In the medial and dorsal areas, migration was often radial, although tangential spread increased with survival time, in large part due to ramification of cells in the intermediate zone. In the dorsolateral and lateral areas of the cortex, radial migration was generally not observed. Rather, variable extents of tangential migration occurred, and often resulted in wide separation of cells in the cortical plate. Almost all of the cellular dispersion occurred in the intermediate zone, although a modest degree of dispersion also occurred within the cortical plate itself. Most dispersion occurred in the mediolateral plane, with relatively little dispersion along the anteroposterior axis. Though characteristic migration patterns could be defined, wide variability in the extents of radial migration and tangential separation of cells was seen. The patterns of migration paralleled the distribution of radial glial fibers in all areas, and are most likely a reflection of the role of this network in supporting the migration of cortical neurons. The extent and variability of cellular dispersion supports a lineage-independent mechanism of cortical column ontogenesis.

Key words: cerebral cortex, mouse embryo, migration, retrovirus, cell lineage, three-dimensional reconstruction.



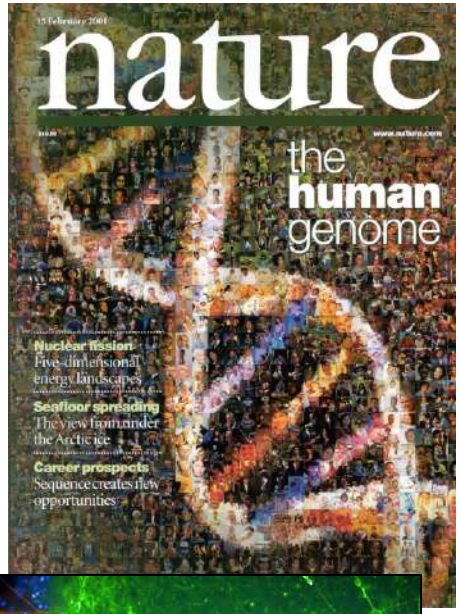
*With apologies to William James

Many would find relief at this point in celebrating the mystery of the Unknowable…Others would rejoice that the finite and separatist view…had at last developed its contradictions, and was about to lead us dialectically upwards to some 'higher synthesis' in which inconsistencies cease from troubling and logic is at rest. It may be a constitutional infirmity, but I can take no comfort in such devices for making a luxury of intellectual defeat. They are but spiritual chloroform. Better live on the ragged edge, better gnaw the file forever!

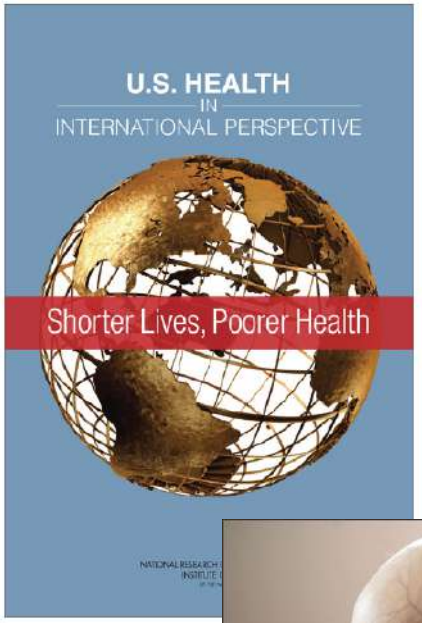
The Principles of Psychology (1890)

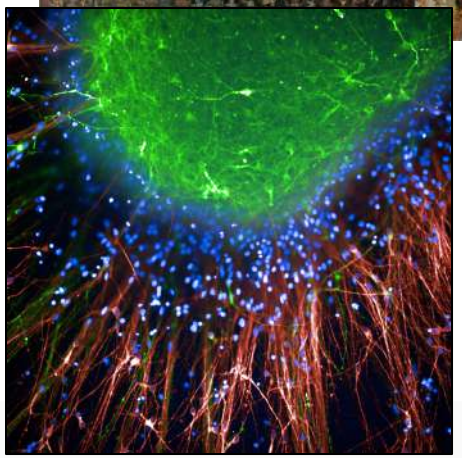
The Best of Times, the Worst of Times

Fundamental science unprecedentedly advanced, but:



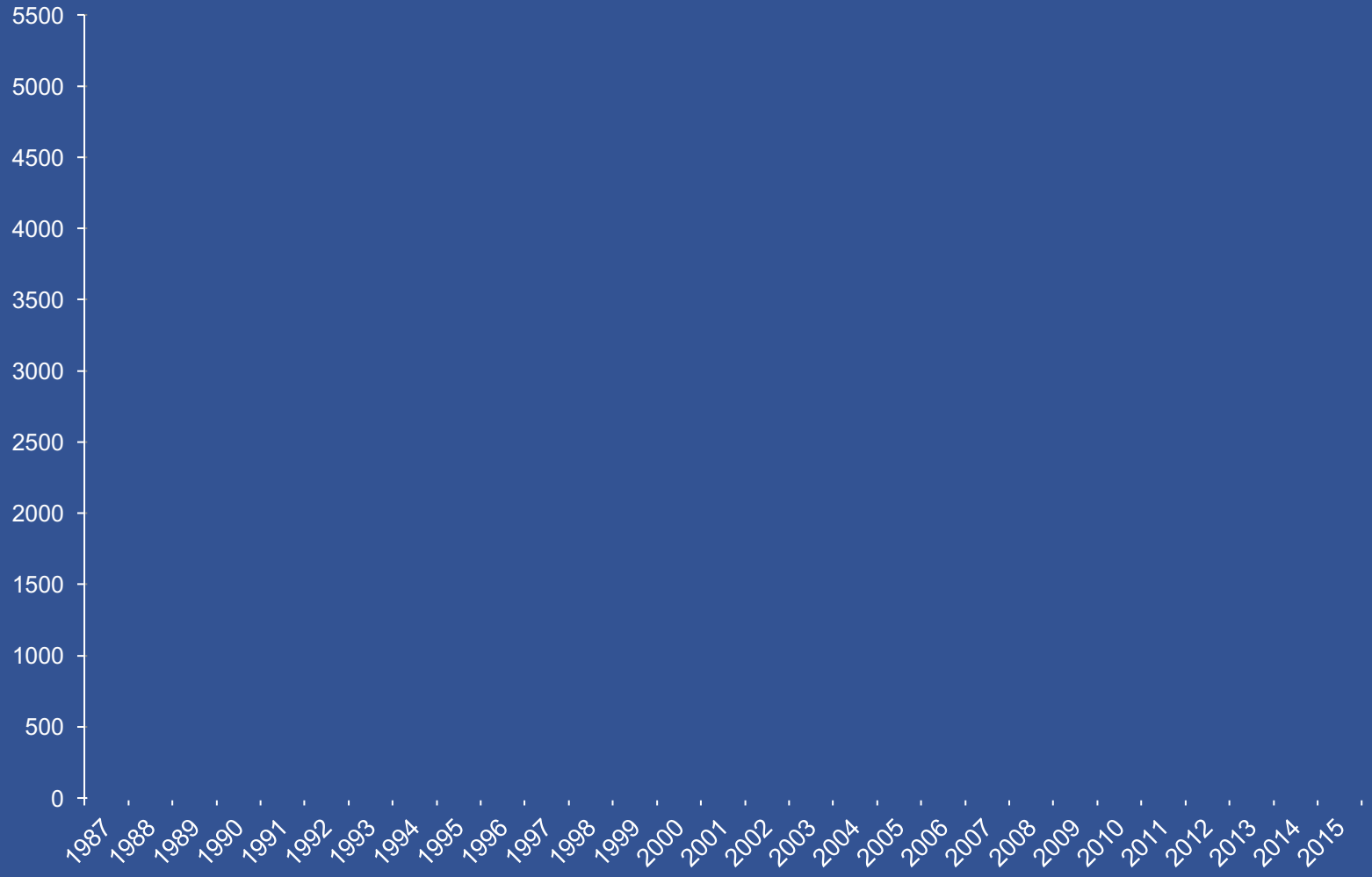
- Poor transition of basic or clinical observations into interventions that tangibly improve human health
- Intervention development failure-prone and expensive
- Poor adoption of demonstrably useful interventions





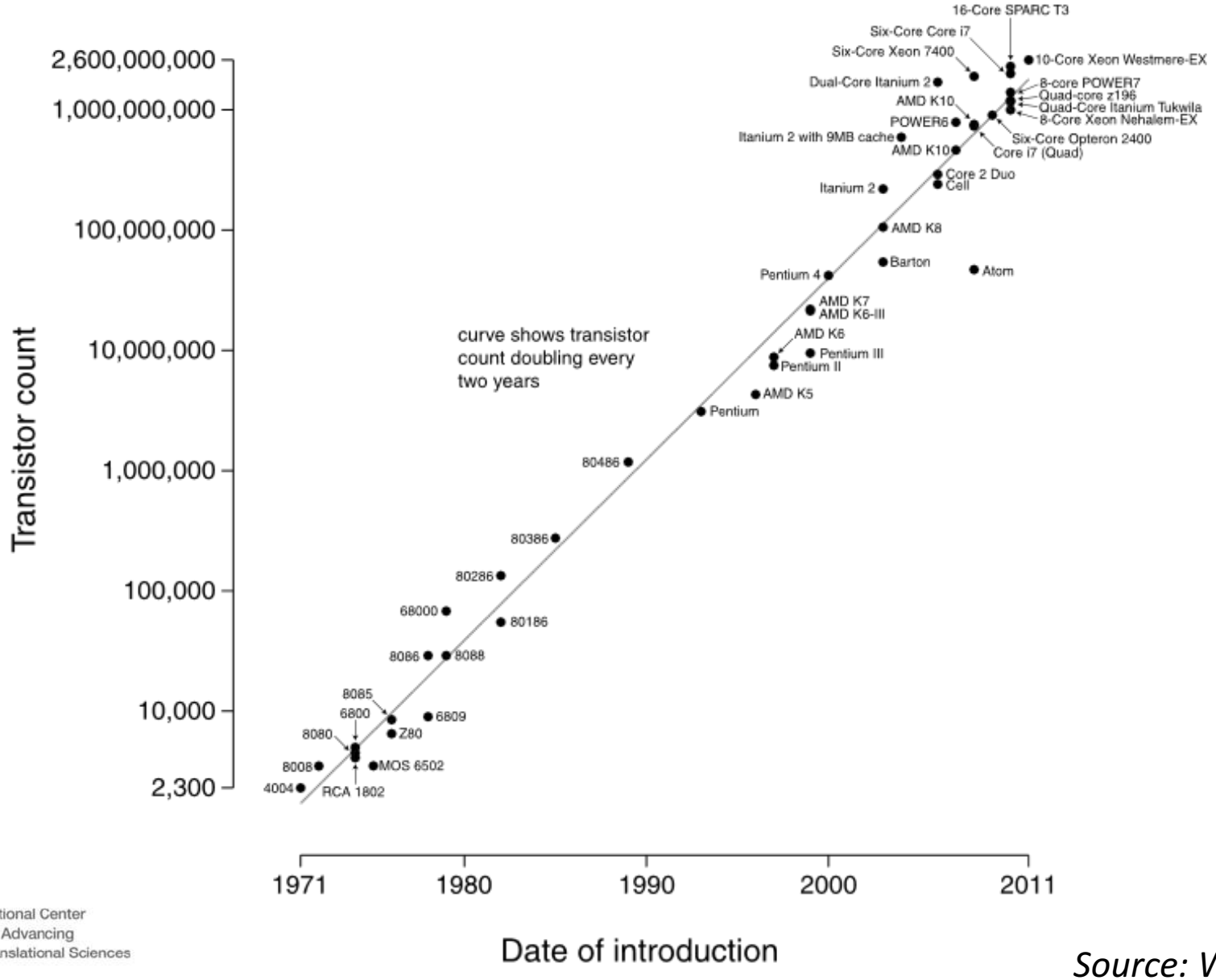
Enormous opportunity/need to deliver on promise of science for patients

Human Conditions with Known Molecular Basis



Source: Online *Mendelian Inheritance in Man*, Morbid Anatomy of the Human Genome

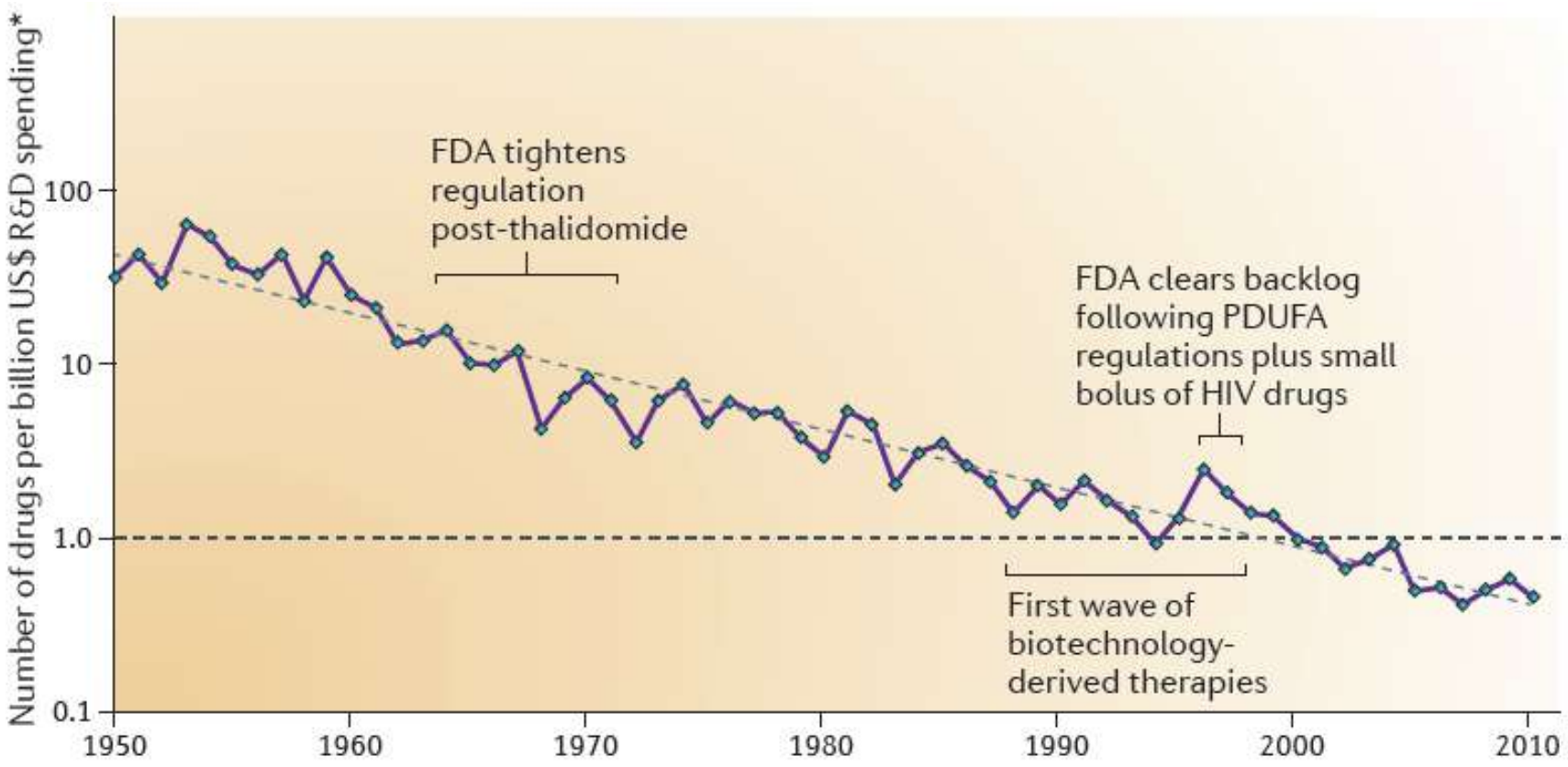
Moore's Law



National Center for Advancing Translational Sciences

Source: Wikipedia

Eroom's Law



The number of new drugs approved by the FDA per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years since 1950.

NIH National Center for Advancing Translational Sciences

Scannell et al., *Nature Reviews Drug Discovery* 11:191, 2012

NCATS Mission

To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

What is Translation?

Translation is the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public - from diagnostics and therapeutics to medical procedures and behavioral changes.

What is Translational Science?

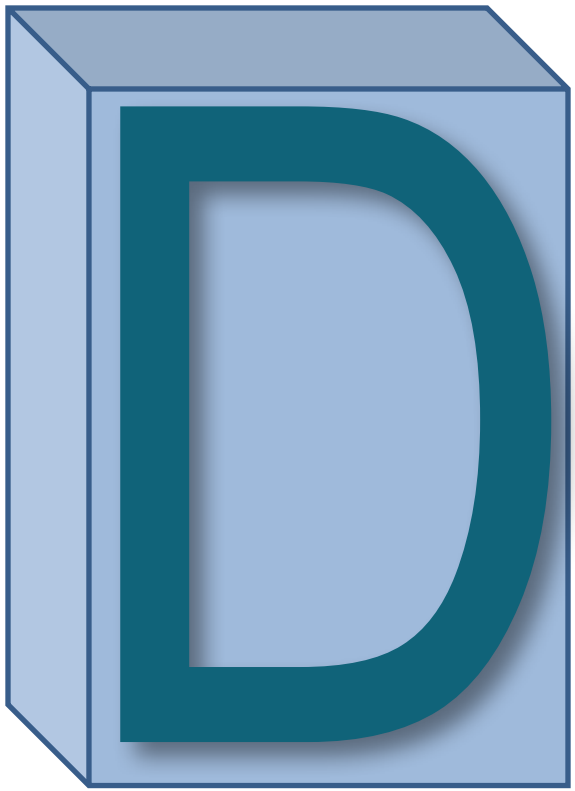
Translational Science is the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process.

NCATS studies translation as a scientific and organizational problem.

Some of the translational problems on NCATS' to-do list

- Predictive toxicology
- Predictive efficacy
- De-risking undruggable targets/untreatable diseases
- Data interoperability
- Biomarker qualification process
- Clinical trial networks
- Patient recruitment
- Electronic Health Records for research
- Harmonized IRBs
- Clinical diagnostic criteria
- Clinical outcome criteria (e.g., PROs)
- Adaptive clinical trial designs
- Shortening time of intervention adoption
- Adherence
- Methods to better measure impact on health…

NCATS "3D's"



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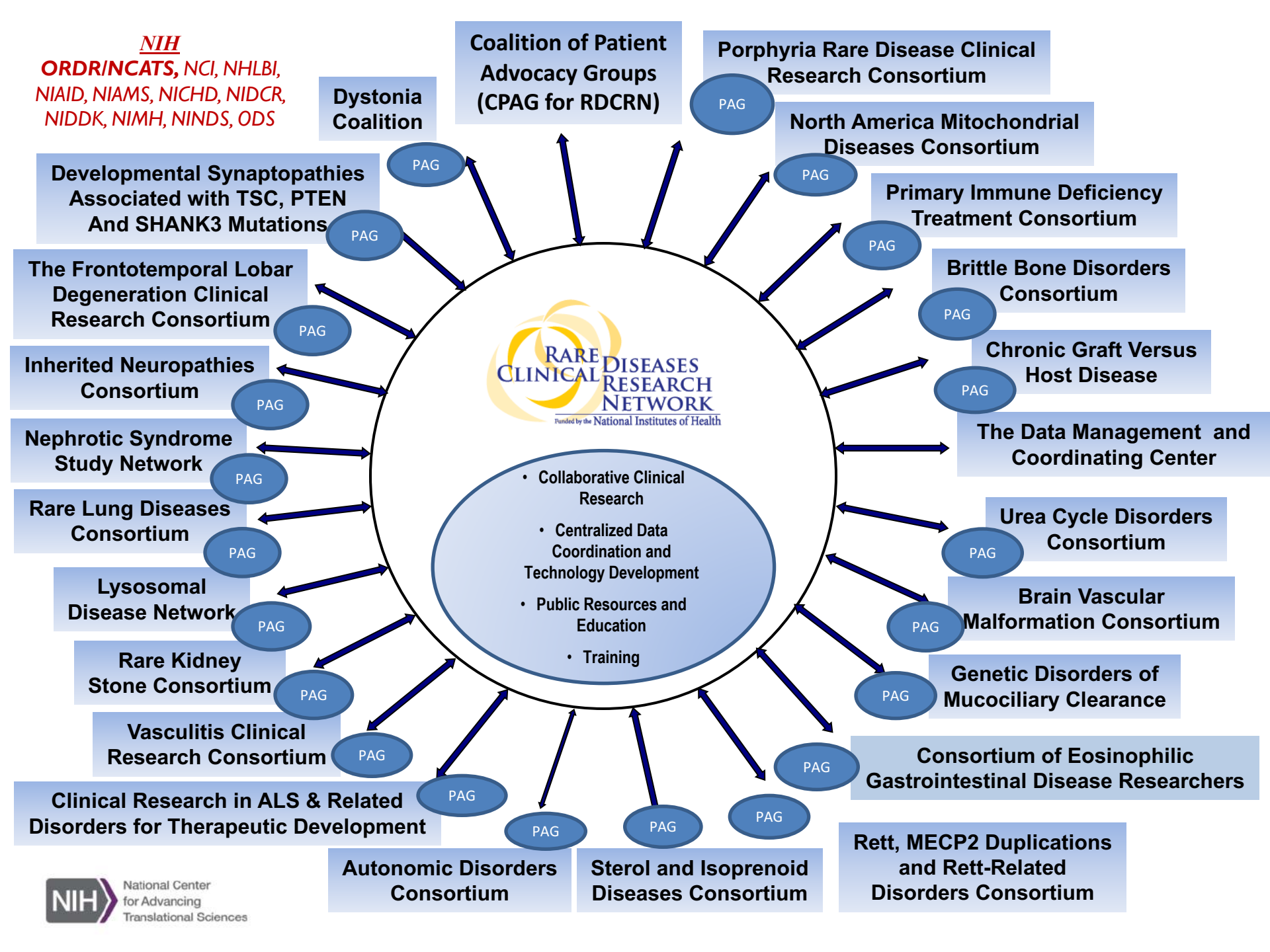
isseminate

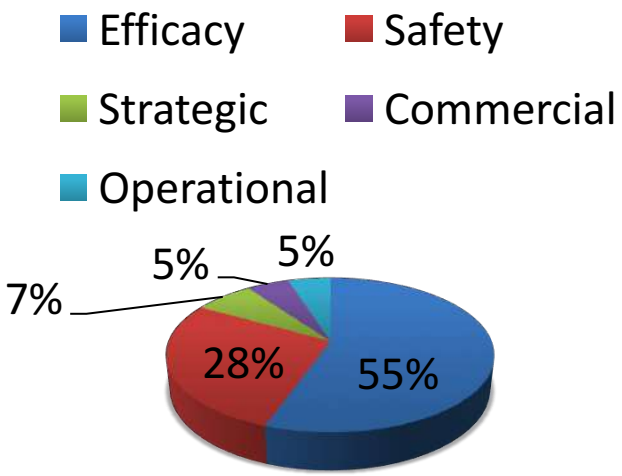
The Problem of Rare Diseases

- ~ 7000 diseases
  - ~250 new rare diseases identified each year
  - ~80% mendelian genetic
  - ~50% onset in childhood
- Population prevalence ~8% (US ~25M; EU ~30M, World 350M)
- Definition of “rare disease” varies by country
  - Absolute prevalence: USA<200,000; Japan<50,000; S Korea <20,000…
  - Percentage prevalence: EU<5 in 10,000; Australia<1 in 2000…
- <5% of rare diseases have a regulatorily approved treatment
  - USA ~300 diseases
  - At current rate 3-5 newly treatable diseases/yr… >1000 yrs to all

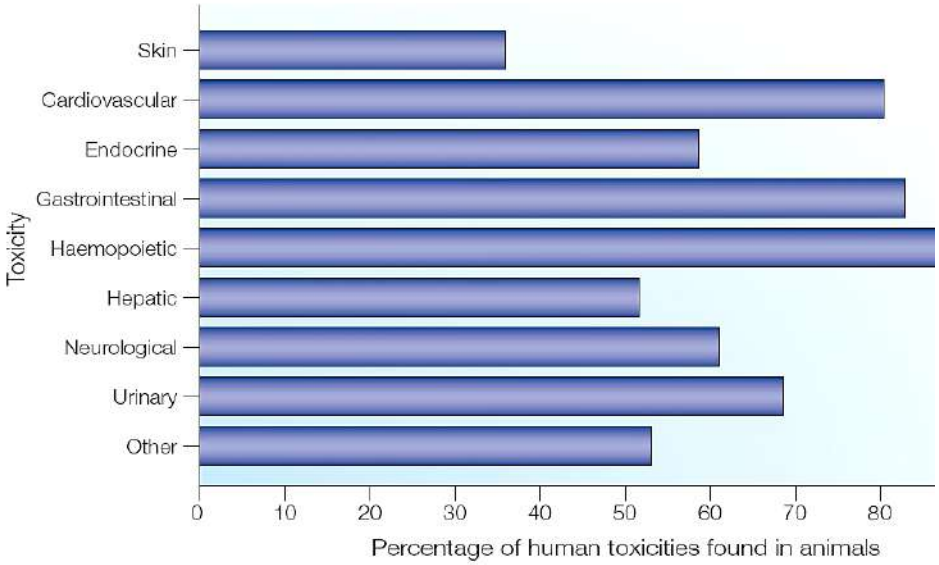

NIH
ORDR/NCATS, NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIDDK, NIMH, NINDS, ODS
Coalition of Patient Advocacy Groups (CPAG for RDCRN)
Porphyria Rare Disease Clinical Research Consortium
Dystonia Coalition
North America Mitochondrial Diseases Consortium
Developmental Synaptopathies Associated with TSC, PTEN And SHANK3 Mutations
Primary Immune Deficiency Treatment Consortium
The Frontotemporal Lobar Degeneration Clinical Research Consortium
Brittle Bone Disorders Consortium
Inherited Neuropathies Consortium
Chronic Graft Versus Host Disease
Nephrotic Syndrome Study Network
The Data Management and Coordinating Center
Rare Lung Diseases Consortium
Urea Cycle Disorders Consortium
Lysosomal Disease Network
Brain Vascular Malformation Consortium
Rare Kidney Stone Consortium
Genetic Disorders of Mucociliary Clearance
Vasculitis Clinical Research Consortium
Consortium of Eosinophilic Gastrointestinal Disease Researchers
Clinical Research in ALS & Related Disorders for Therapeutic Development
Autonomic Disorders Consortium
Sterol and Isoprenoid Diseases Consortium
Rett, MECP2 Duplications and Rett-Related Disorders Consortium
PAG
RARE CLINICAL DISEASES RESEARCH NETWORK
Funded by the National Institutes of Health
• Collaborative Clinical Research
• Centralized Data Coordination and Technology Development
• Public Resources and Education
• Training
NIH National Center for Advancing Translational Sciences

Why drugs fail in development

80% of Phase 2 studies fail; causes:



Human toxicities found in animals



Arrowsmith and Miller, Nature Reviews Drug Discovery, Volume 12, 569 (2013)

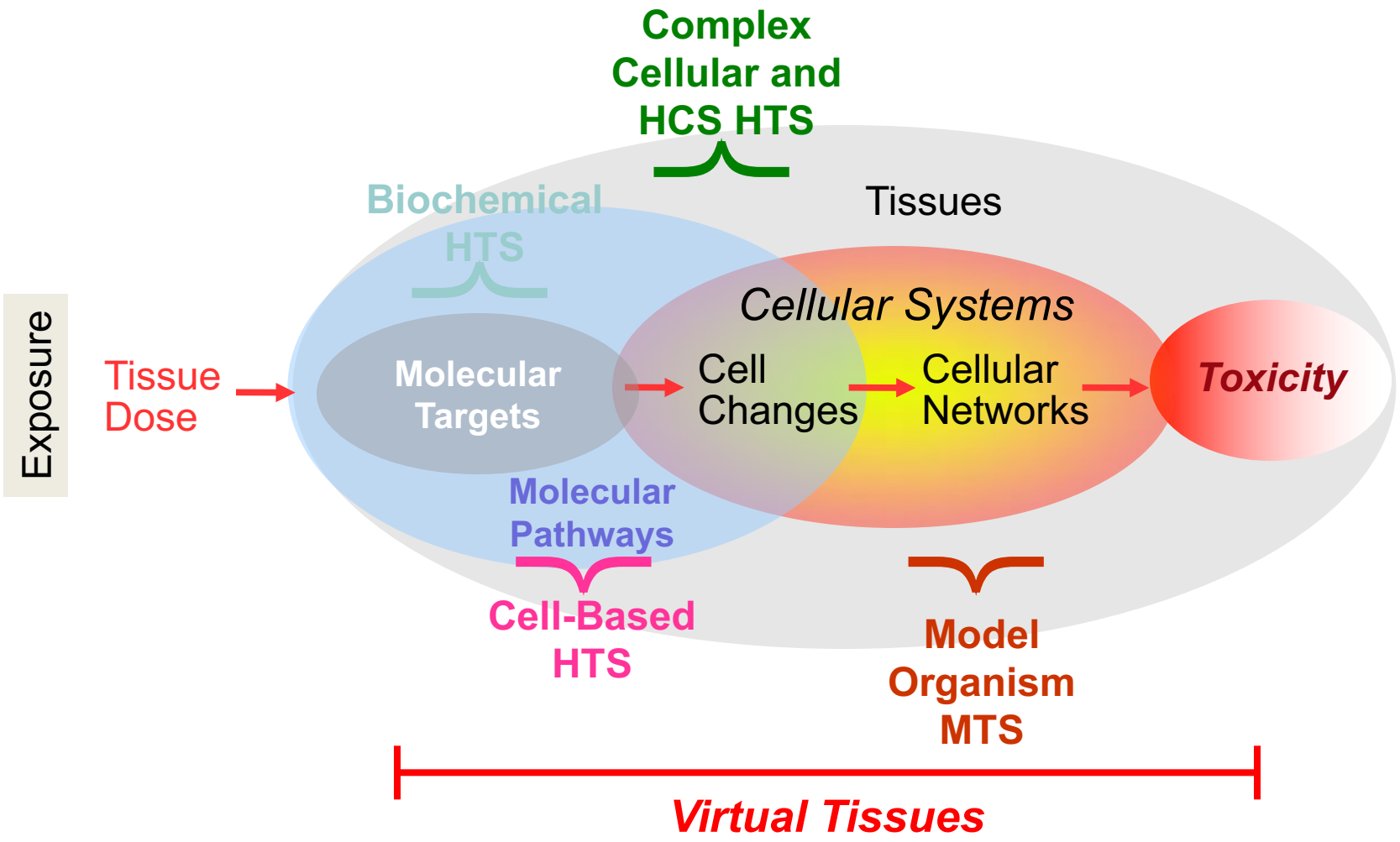
Cook et al., Nature Reviews Drug Discovery, Volume 13, 419 (2014)

Well put…

- "We have moved away from studying human disease in humans. We all drank the Kool-Aid on that one, me included. The problem is that it hasn't worked, and it's time we stopped dancing around the problem…We need to refocus and adapt new methodologies for use in humans to understand disease biology in humans."

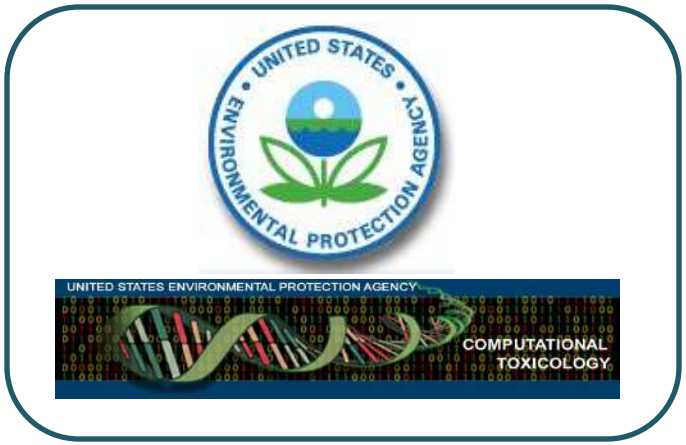
Elias Zerhouni
Lecture at NIH June 2013

A Grand Challenge: Predicting Toxicity



B. Kavlock, EPA

The Toxicology in the 21st Century (Tox21) Program



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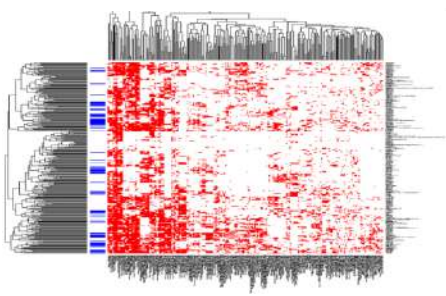
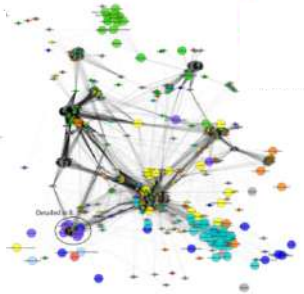
See Anton Simeonov presentation

Tox21 Goals

- Identify patterns of compound-induced biological response in order to:
  - characterize toxicity/disease pathways
  - facilitate cross-species extrapolation
  - model low-dose extrapolation
- Prioritize compounds for more extensive toxicological evaluation
- Develop predictive models for biological response in humans





NCATS Comprehensive Repurposing Program
"Systematizing Serendipity"

The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruili Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†

Small-molecule compounds approved for use as drugs may be "repurposed" for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across human diseases, particularly for rare and neglected diseases, for which the cost and time required for development of a new chemical entity are often prohibitive. Previous efforts to build such a comprehensive collection have been limited by the complexities, redundancies, and semantic inconsistencies of drug naming within and among regulatory agencies worldwide; a lack of clear conceptualization of what constitutes a drug; and a lack of access to physical samples. We report here the creation of a definitive, complete, and nonredundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening.

Improving Drug Development Efficiency:
The Tissue Chip Program

GOAL: Develop an *in vitro* platform that uses <u>human</u> tissues to evaluate the efficacy, safety and toxicity of promising therapies.

NIH National Institutes of Health

Phase 1: Development

Phase 2: Cell incorporation & organ integration

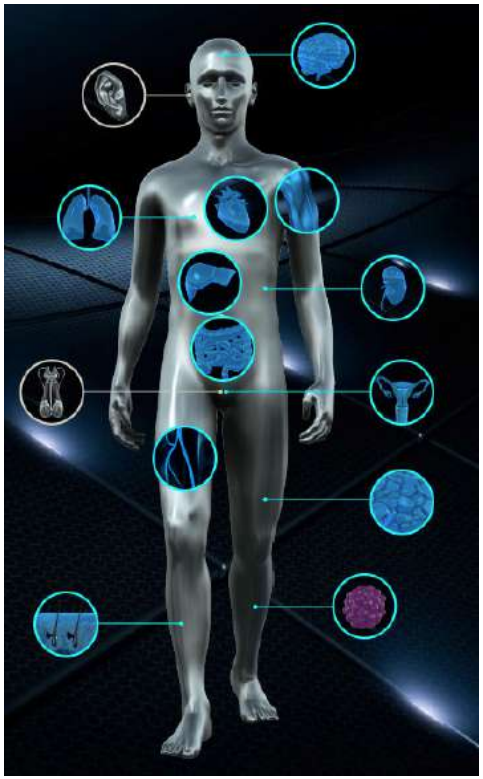
2012-13 | 2013-14 | 2014-15 | 2015-16 | 2016-17

DARPA

DARPA base periods: Organ integration

FDA

FDA provides insight and expertise throughout the program



Current Goals:

- **Integration**
- **Compound testing**
- **Validation**
- **Partnerships**
- **Adoption by community**

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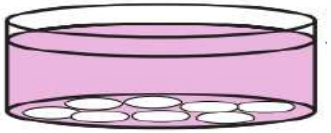
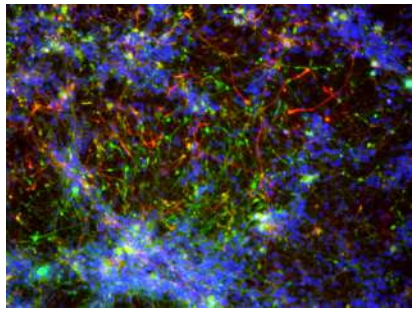
See Dobrila Rudnicki presentation

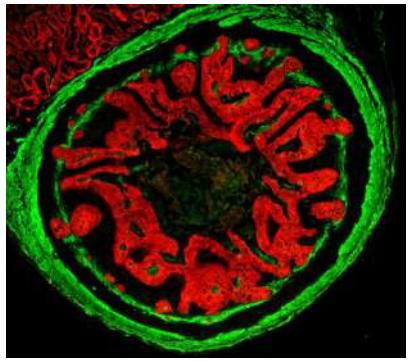
Gut Enteroids



Pluripotent Stem Cells: renewable human cell source

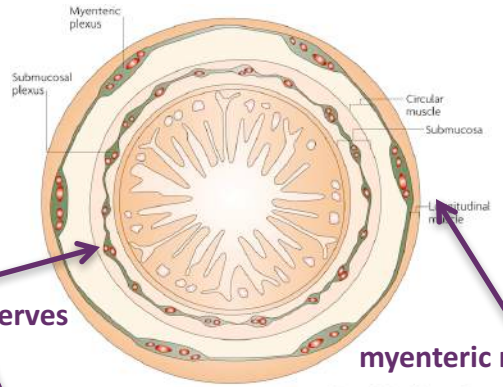
Vagal Neural Crest Cells: peripheral nerve cells





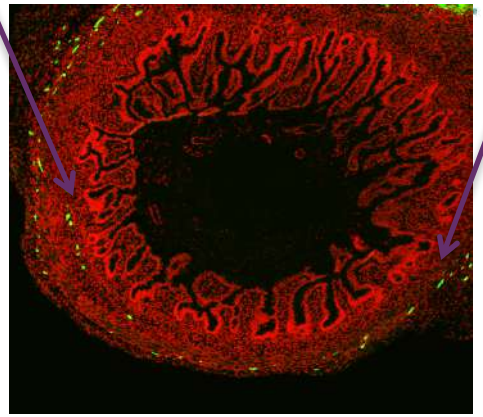
Gut enteroid: 3D mulitcellular mini gut

Gut Lumen



submucosal nerves

myenteric nerves

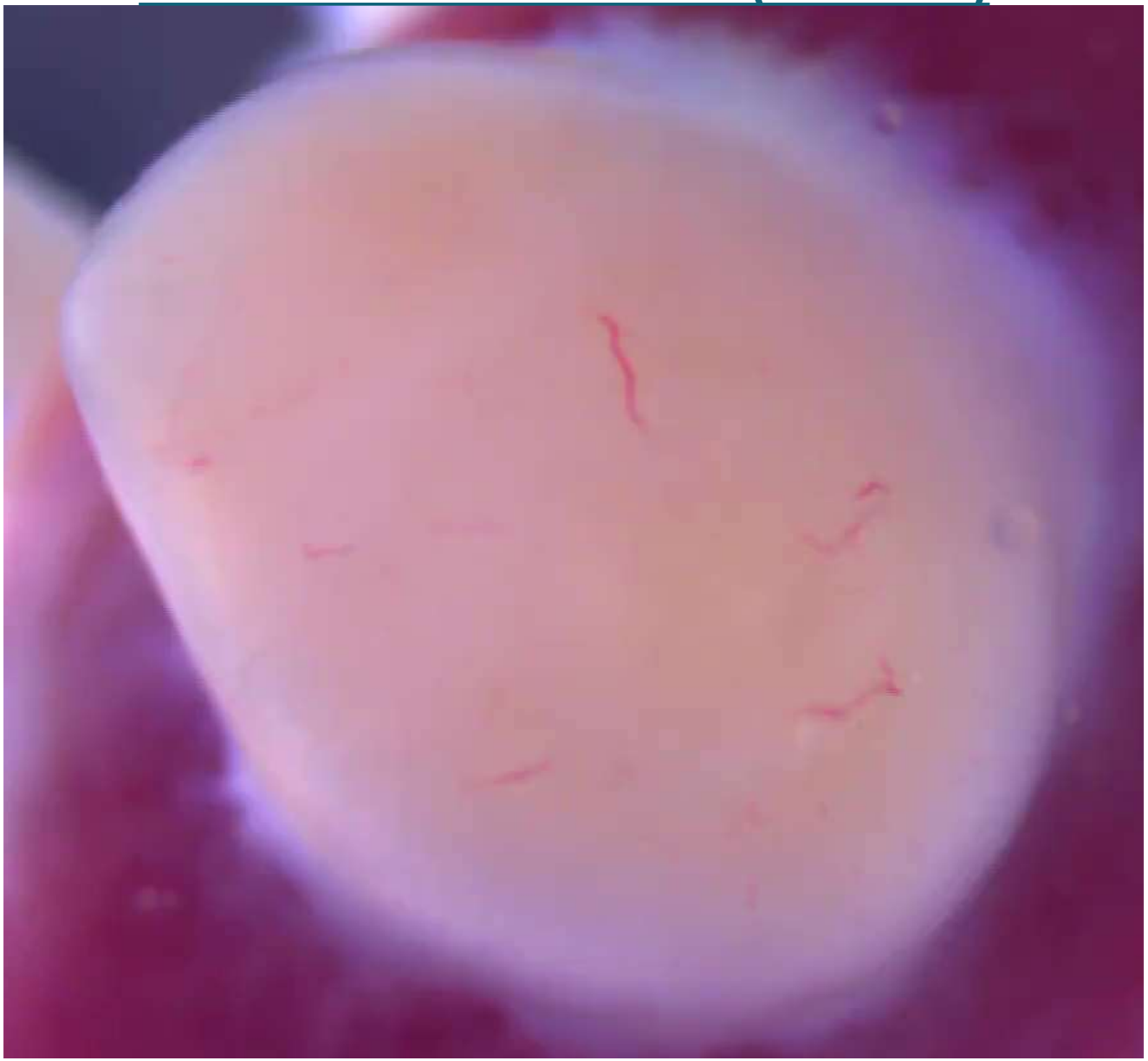


The nervous system in the gut plays a critical role in GI function, including peristalsis (gut contraction). Both nerve and gut tissue can be engineered using renewable human cell sources

As these systems begin to mature, the nerve tissues are added to the GI, creating physiological-like innervated structures

James Wells, Univ. Cincinnati

Electrical field stimulation (with ENS)



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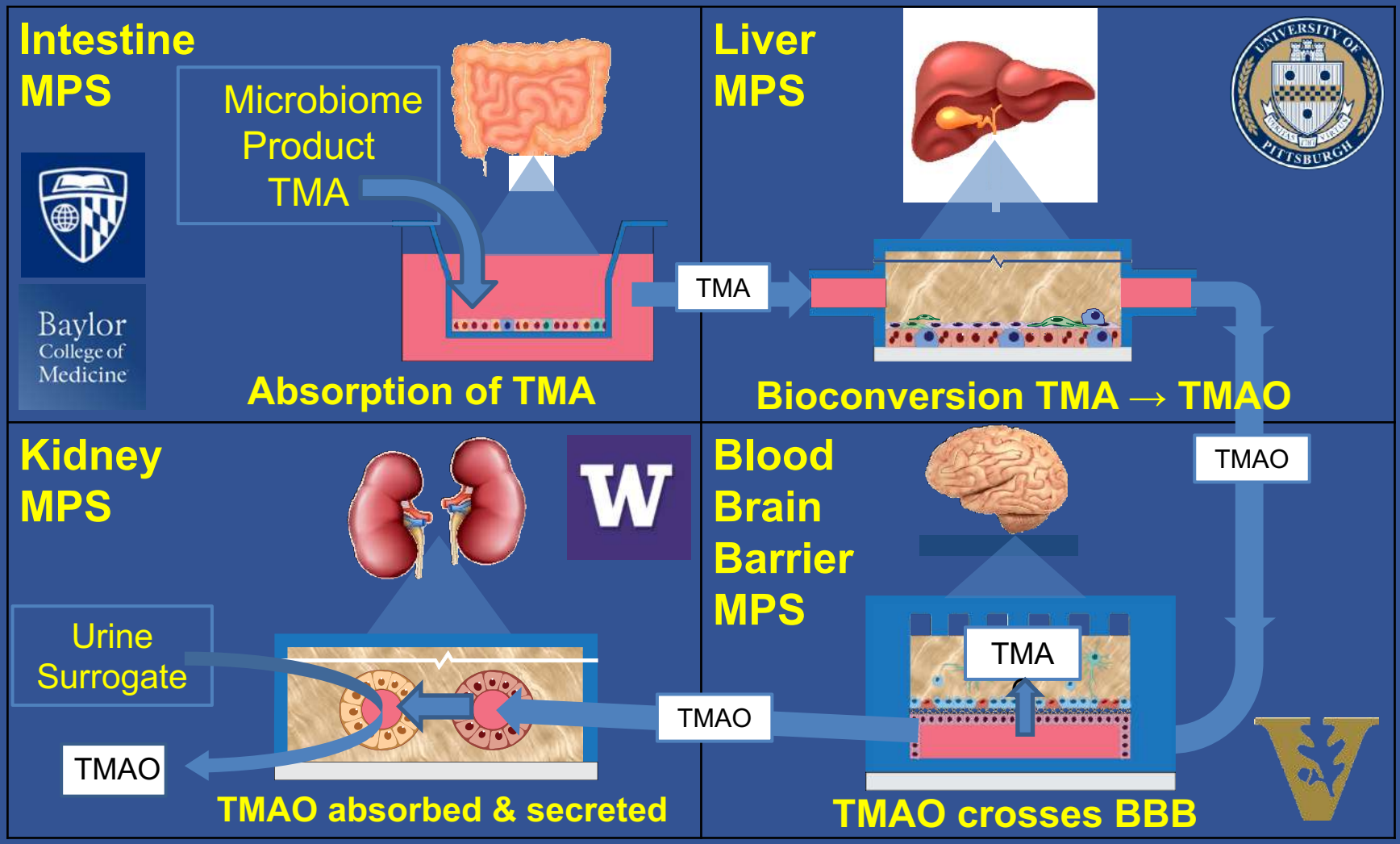
James Wells, Univ. Cincinnati

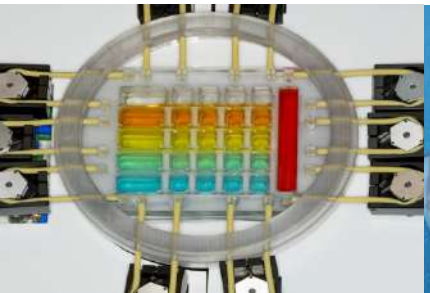
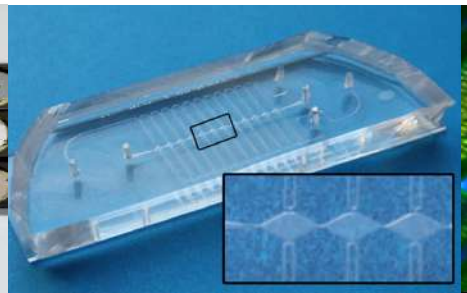
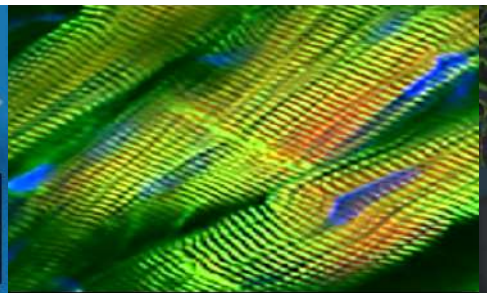
Functional coupling of four chips demonstrates physiological processing of the microbiome product trimethylamine (TMA)



Vernetti L et al (2017) *'Functional Coupling of Human Microphysiology Systems: Intestine, Liver, Kidney Proximal Tubule, Blood-Brain Barrier and Skeletal Muscle'.* Sci Rep 7:42296).

Next Phase Tissue Chip Initiatives

- Tissue Chip Testing Centers *(2016-2018)*
  - » Tech transfer and testing at 2 independent centers (Texas A&M and MIT)
- Tissue Chips for Disease Modeling *(2017-2022)*
  - » Develop tissue chip models of human diseases, particularly rare
    - o Using human primary or induced pluripotent stem cell sources
  - » Use to test effectiveness of candidate therapeutics
- Tissue Chips in Space *(2017-2021)*
  - » Partnership with Center for the Advancement of Science in Space (CASIS)
  - » Adapt, refine chips for on-flight experiments at the International Space Station U.S. National Laboratory
    - o To understand diseases (e.g. bone, muscle, aging) prevalent on earth and accelerated in space

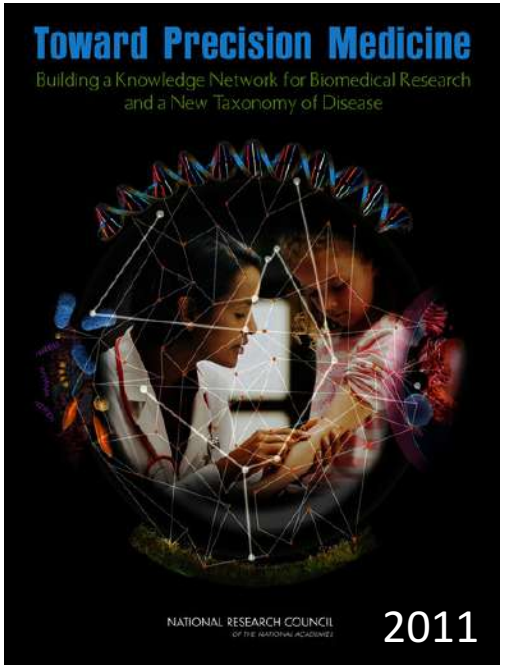
NCATS Biomedical Data Translator
The Vision

- Develop and disseminate a biomedical "data translator" that comprehensively displays and relates all classification schemes used by different groups within the translational research community
  - Distinct languages and cultures of different groups maintain distinct disease concepts that are not easily traversed
- Integrate multiple types of existing data sources relevant to understanding diseases and their potential pathophysiology and treatment
- Enable a user to enter the Translator from any data type and identify all cognates/connections in any other data type
- Open source and completely publicly available

See Christine Colvis presentation

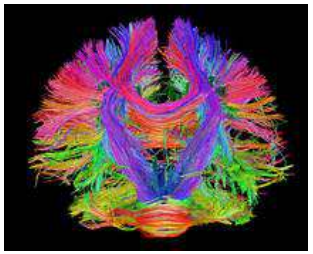
The time is now

- Convergence of data science, engineering, and translational expertise
- Could lead to
  - Greatly accelerated translation
  - Better diagnosis/prognosis
  - New “patient populations”
- For example: is a disorder
  - Schizophrenia (“split-mind”)?
  - A collection of symptoms and typical prognosis?
  - A brain prefrontal-limbic circuit disorder?
  - A synaptic development disorder?
  - A molecular pathway disorder caused by genetic factors combined with environmental induction?
- Answer: Yes.



“Recent advances in biomedical research have caused an explosion of data, offering the potential to develop a "new taxonomy" that defines disease based on underlying molecular and environmental causes, rather than on physical signs and symptoms.”

Some thoughts to get us started



- Animal research has contributed immeasurably to our understanding of biology and disease in many species, including humans
  - Will continue to be critical for the foreseeable future
- However, it is incontrovertible that a model organism is not the organism itself, and that any model is at best an experimental approximation
  - We have sometimes lost sight of this, with predictable results
- New technologies which allow for human models *ex vivo* and non- or minimally-invasive human studies *in vivo* are available or rapidly developing, and their exploration should be pushed as hard as possible while animal model based methods are 3R'ed
  - Analogy to development of new energy sources
- We are going to discover fantastic science in the study of this most complex of animal species!

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