National Center for Advancing Translational Sciences:

Catalyzing Translational Innovation

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ADVISORY COMMITTEE TO THE NIH DIRECTOR
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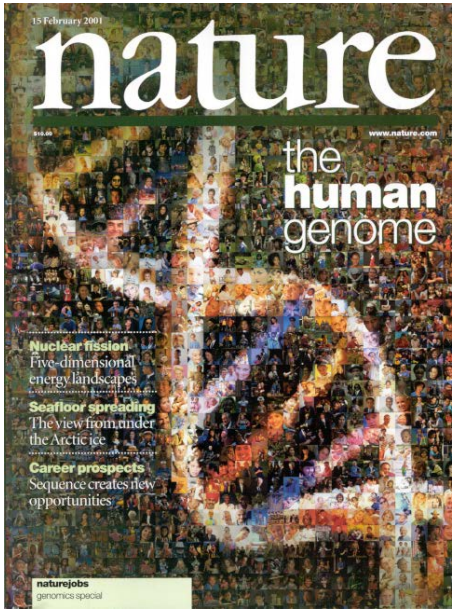
NCATS

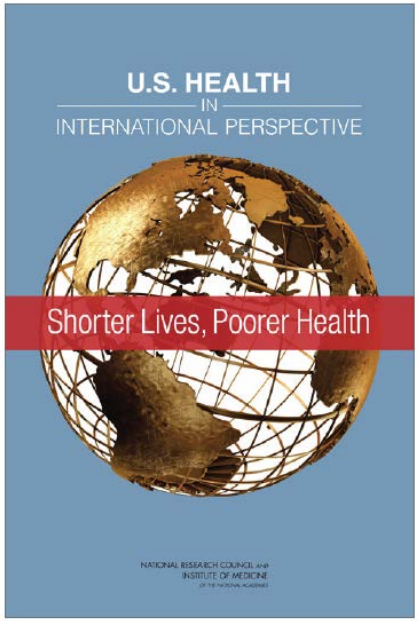
NIH National Center for Advancing Translational Sciences

The Best of Times, the Worst of Times

Fundamental science unprecedentedly advanced, but:

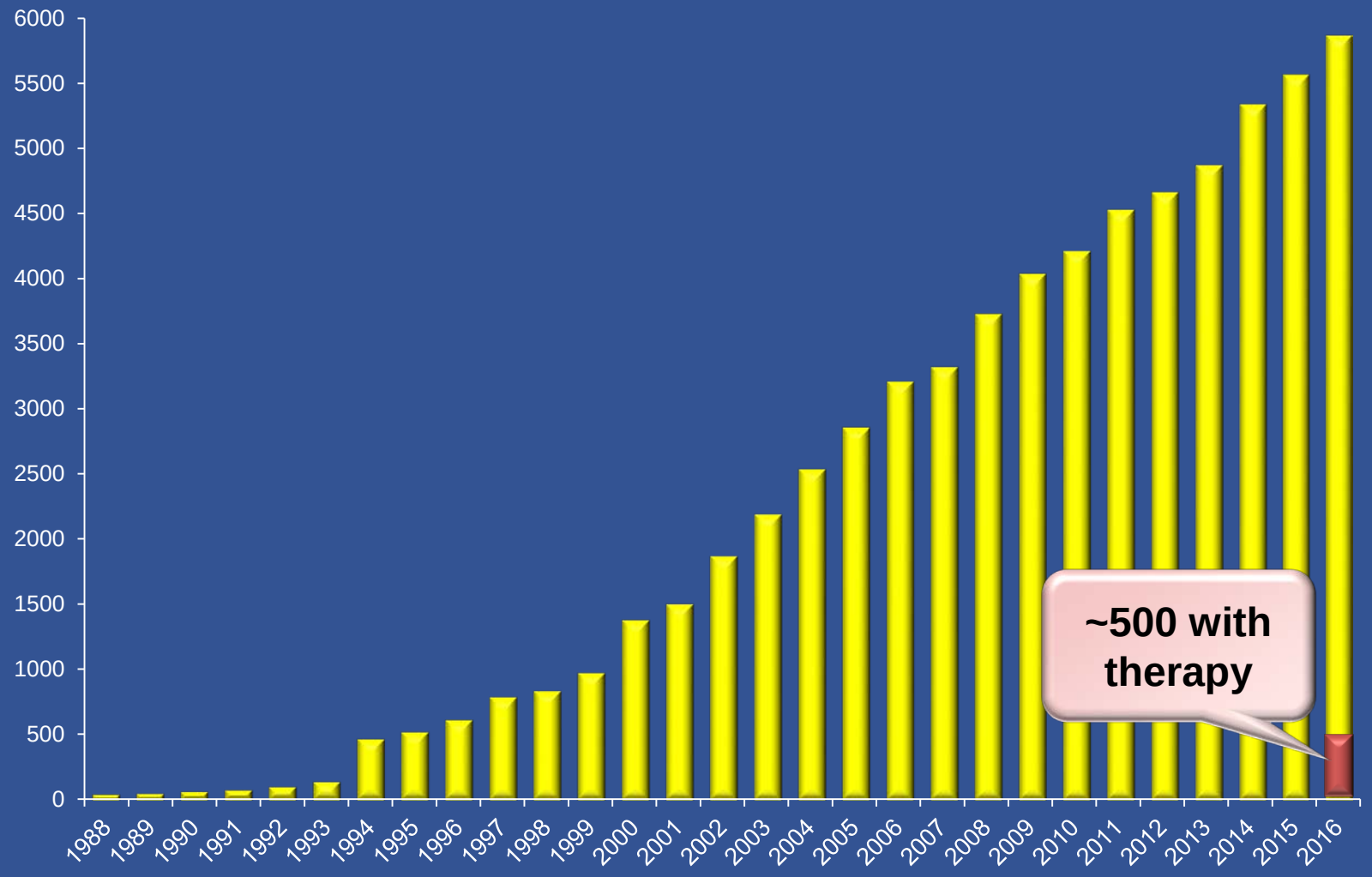


- Poor transition of basic or clinical observations into interventions that tangibly improve human health
- Drug/device/diagnostic development expensive and failure-prone
- Clinical trials system inefficient
- Poor adoption of demonstrably useful interventions



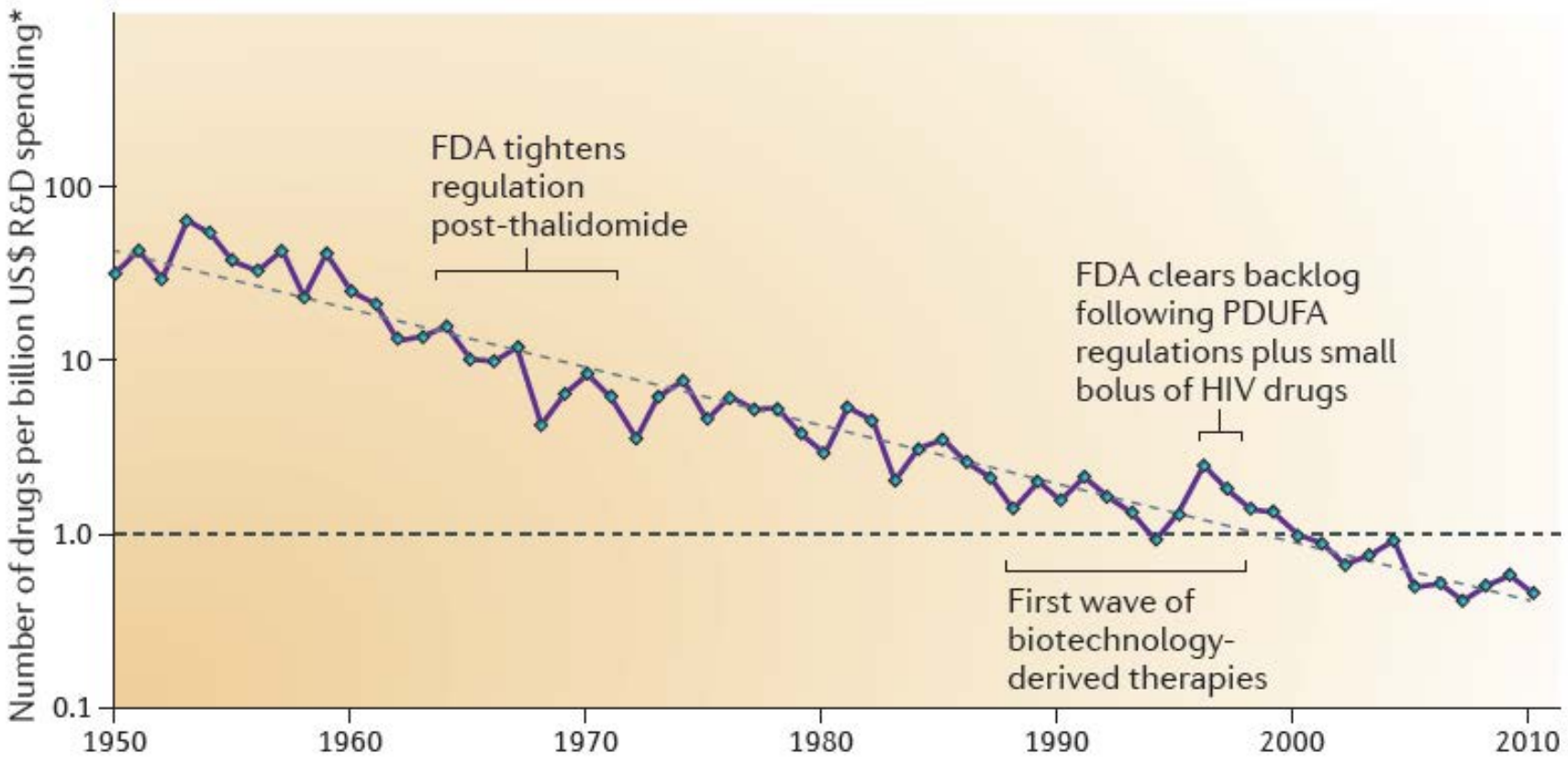
People unhealthier and funders of biomedical research enterprise (public and private) impatient

Human Conditions with Known Molecular Basis



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

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.

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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 scientific 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…

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

- Data transparency/release
- IP management
- Integration of project management
- Incentives/credit for team science
- Incentives/credit for health improvements
- Education/Training (scientific and cultural)
- Collaborative structures
  - » Public-private partnership models

NCATS Scientific Initiatives

- **Clinical Translational Science**
  - » Clinical and Translational Science Awards
  - » Rare Disease Clinical Research Network
  - » New Therapeutic Uses program
- **Preclinical Translational Science**
  - » NCATS Chemical Genomics Center
  - » Therapeutics for Rare and Neglected Diseases program
  - » Bridging Interventional Development Gaps program
- **Re-engineering Translational Sciences**
  - » Toxicology in the 21st Century
  - » Microphysiological Systems (Tissue Chip) program
  - » Office of Rare Diseases Research

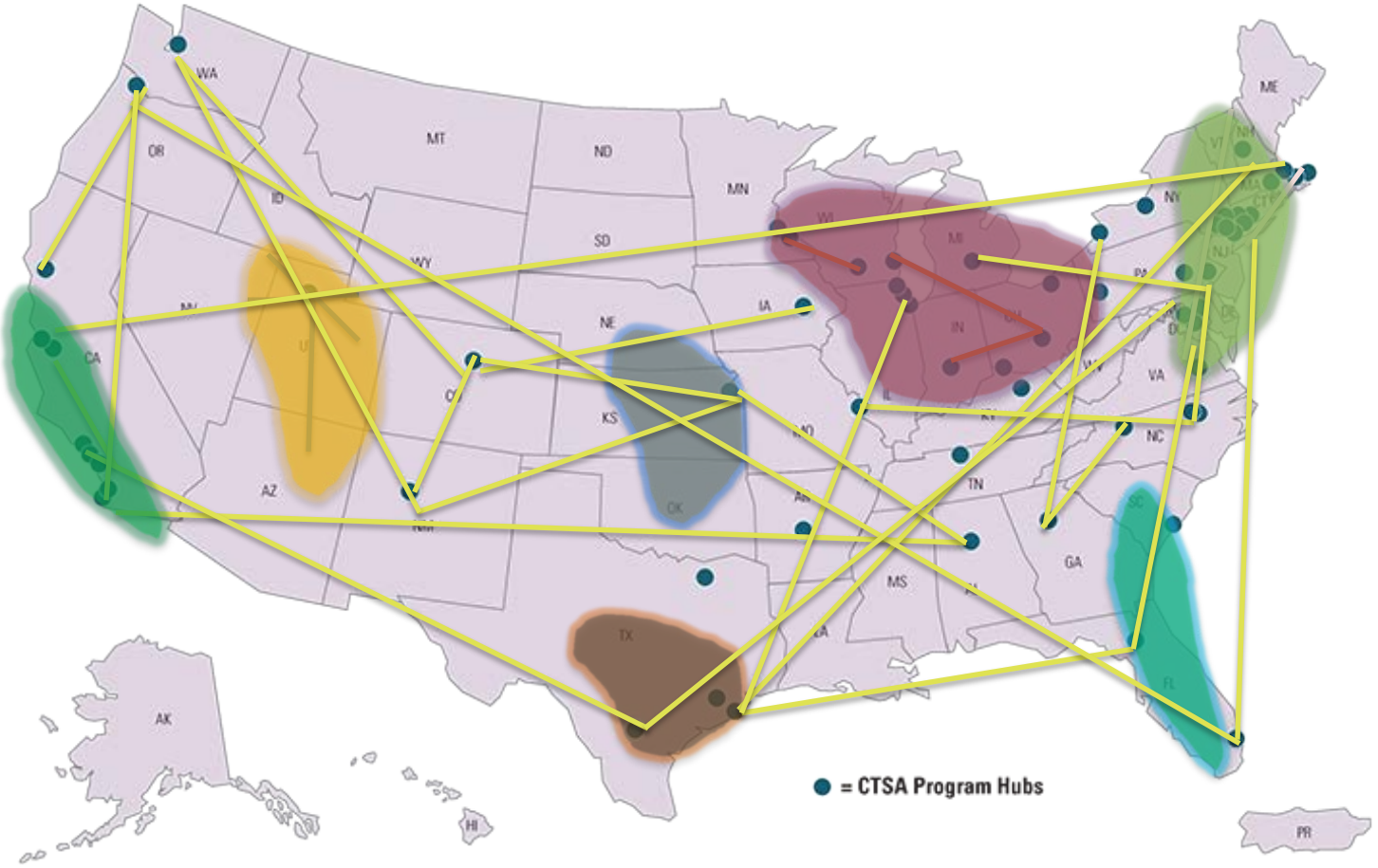
Transforming Clinical Translation:
Clinical and Translational Science Awards (CTSA) Program

- A national consortium of medical research institutions
- Improves the way clinical and translational research is conducted nationwide
- Accelerates the research translation process
- Provides innovative training for clinical and translational researchers

Creating an efficient collaborative national network for translational medicine

- Studies in human subjects are inefficient, limiting to translation of basic discoveries into interventions that improve human health
- NCATS initially (beginning 2013) focused on creating generalized solutions to three limiting factors:
  - » IRB review
  - » Recruitment
  - » Investigator qualification
- **Trial Innovation Network** to be launched shortly

A Collaborative Consortium for Translational Research



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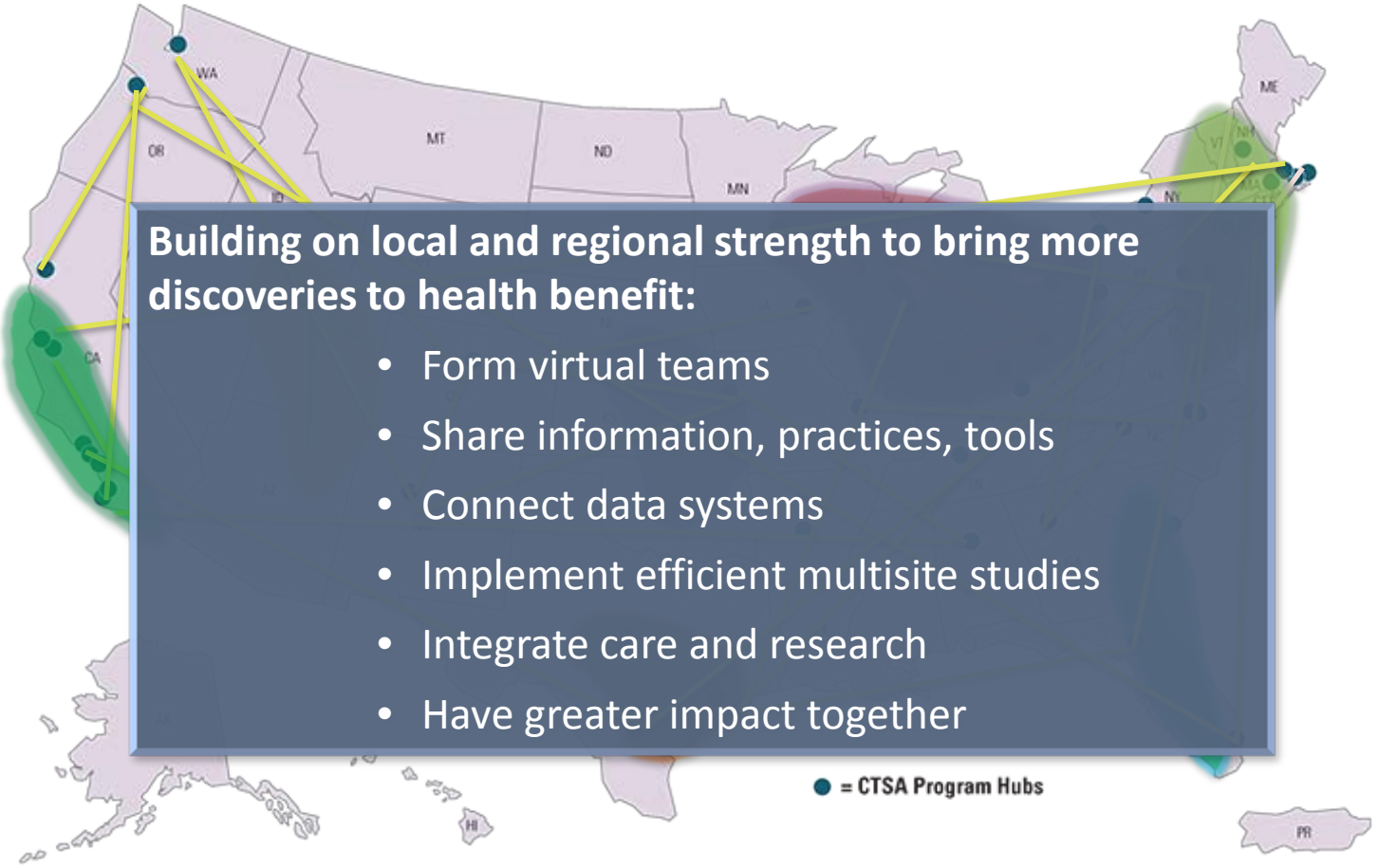
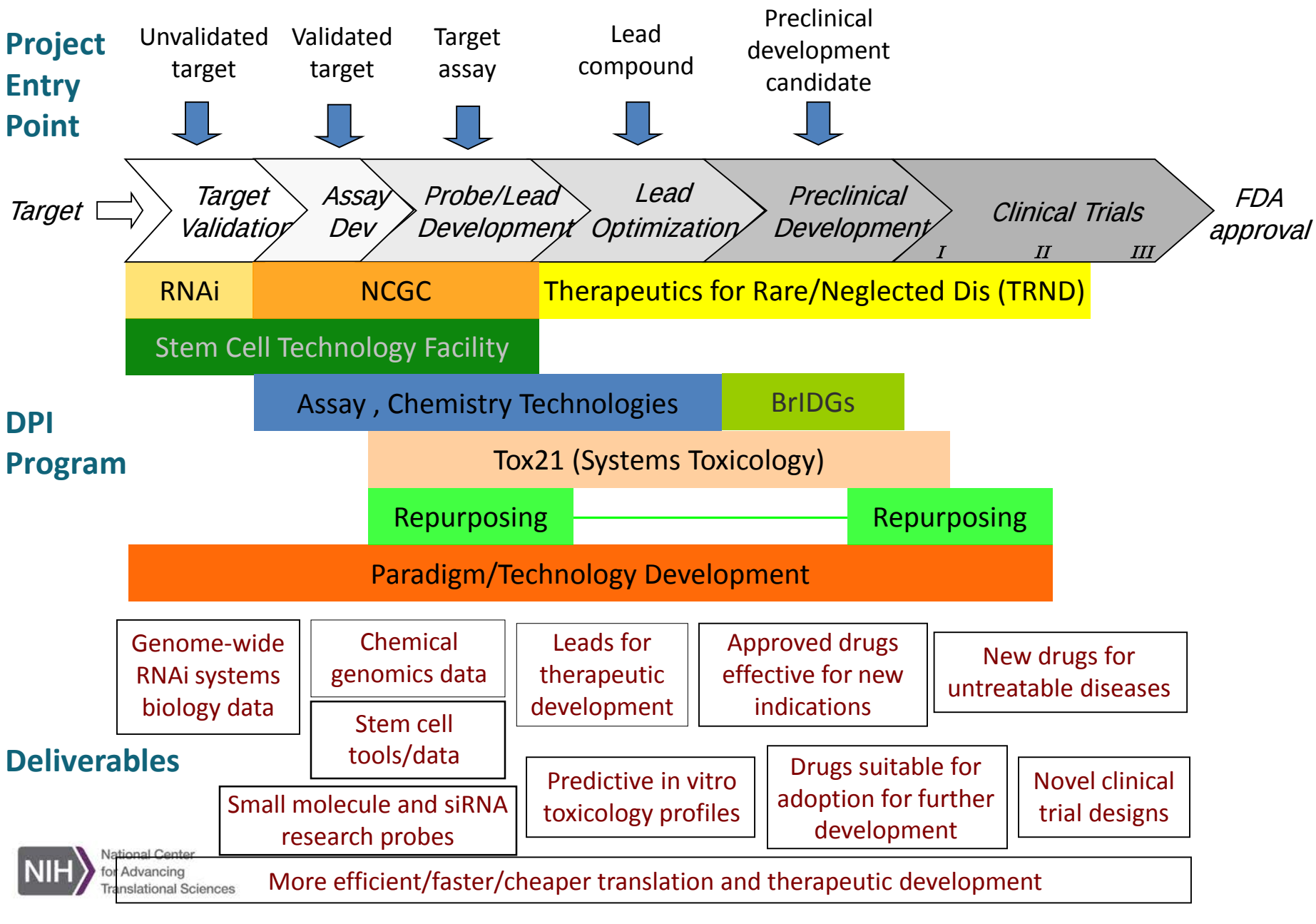


Building on local and regional strength to bring more discoveries to health benefit:

- Form virtual teams
- Share information, practices, tools
- Connect data systems
- Implement efficient multisite studies
- Integrate care and research
- Have greater impact together

NCATS Preclinical Innovation

A collaborative engine



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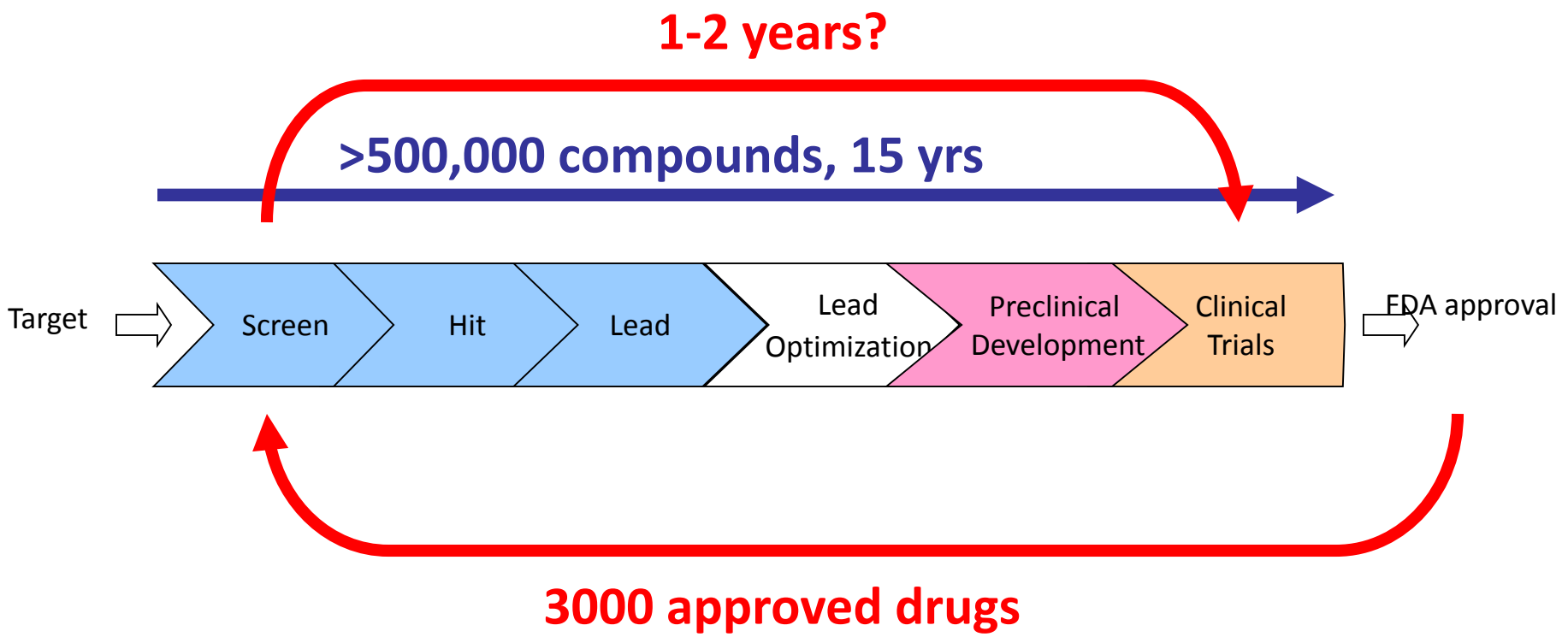
Drug repurposing to increase rate of new drugs



Enabling Comprehensive Repurposing

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

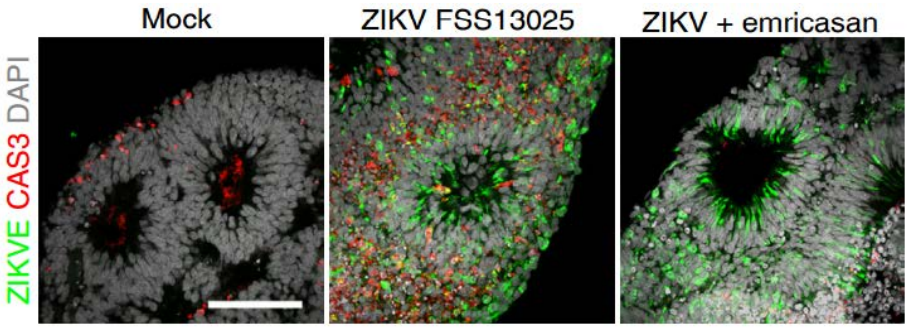
Ruili Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†

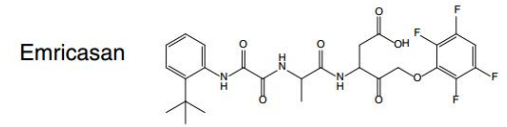
Small-molecule compounds approved for use as drugs may be "repurposed" for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across 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.

NIH National Center for Advancing Translational Sciences www.ScienceTranslationalMedicine.org 27 April 2011 Vol 3 Issue 80 80ps16

Comprehensive repurposing: Zika

- **NCATS rapidly established collaborative team**
  - With investigators at Hopkins and Florida State, identified approved and investigational drugs as starting points for drug development to treat Zika infection
  - Generalized paradigm applicable to public health emergencies, used previously in Ebola, Hep C
- **Assays:** Zika infection-induced cell death, caspase 3/7 activation in hNPCS and 3D human forebrain organoid cultures; Zika virus titer/RNA/protein
- **Compounds**
  - NCATS Pharmaceutical Collection (approved drugs): 2800
  - Investigational drugs and bioactive compounds: 3200
- **Results**
  - Emricasan: investigational pan-caspase inhibitor
    - Also protected hNPCS from cell death
  - Niclosamide: FDA-approved antihelminthic
    - Also inhibited ZIKV replication
  - Ten structurally unrelated inhibitors of CDKs
    - Also inhibited ZIKV replication
- **Combination of neuroprotective and antiviral drugs**
  - Combination of emricasan and CDKi further increased protection of human neuronal progenitors from Zika virus induced cell death





Xu et al., Nature Medicine Aug 2016

Zika drug repurposing

ARTICLES

nature medicine

published online 29 August 2016; doi:10.1038/nm.4184

Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen

Miao Xu[1,2,16], Emily M Lee[3,16], Zhexing Wen[4–7,16], Yichen Cheng[3], Wei-Kai Huang[7,8], Xuyu Qian[7,9], Julia TCW[10], Jennifer Kouznetsova[1], Sarah C Ogden[3], Christy Hammack[3], Fadi Jacob[7,11], Ha Nam Nguyen[7,12], Misha Itkin[1], Catherine Hanna[3], Paul Shinn[1], Chase Allen[3], Samuel G Michael[1], Anton Simeonov[1], Wenwei Huang[1], Kimberly M Christian[7,12], Alison Goate[10], Kristen J Brennand[13], Ruili Huang[1], Menghang Xia[1], Guo-li Ming[7,9,11,12,14,15,17], Wei Zheng[1,17], Hongjun Song[7,9,11,12,15,17] & Hengli Tang[3,17]

In response to the current global health emergency posed by the Zika virus (ZIKV) outbreak and its link to microcephaly and other neurological conditions, we performed a drug repurposing screen of ~6,000 compounds that included approved drugs, clinical trial drug candidates and pharmacologically active compounds; we identified compounds that either inhibit ZIKV infection or suppress infection-induced caspase-3 activity in different neural cells. A pan-caspase inhibitor, emricasan, inhibited ZIKV-induced increases in caspase-3 activity and protected human cortical neural progenitors in both monolayer and three-dimensional organoid cultures. Ten structurally unrelated inhibitors of cyclin-dependent kinases inhibited ZIKV replication. Niclosamide, a category B anthelmintic

All screening results immediately deposited in Pubchem for community use

Improving Drug Development Effectiveness:
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

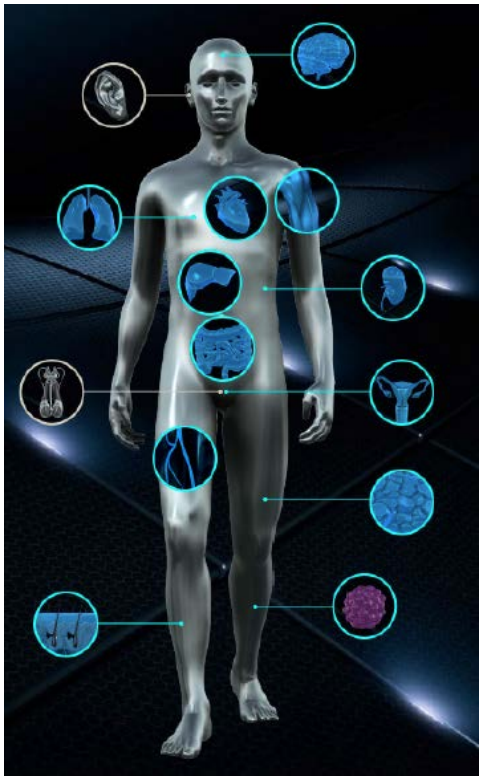
DARPA

DARPA base periods: Organ integration

FDA

****FDA provides insight and expertise throughout the program**

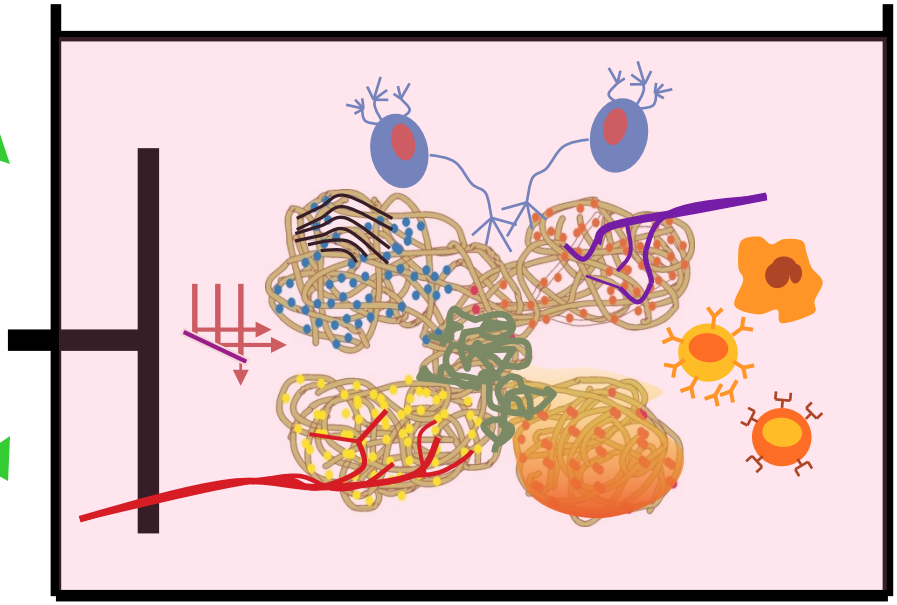
NIH National Institutes of Health



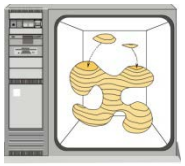
Current Goals:

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

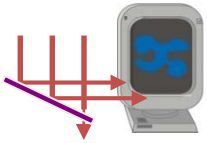
Microphysiological Systems –
A Multidisciplinary, Team-Science Approach



Computational Design
- systems integration
- multi-scale modeling
- simulation
- feedback

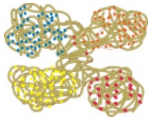


Functional Readout
- real-time, label-free, non-destructive sensing
- imaging

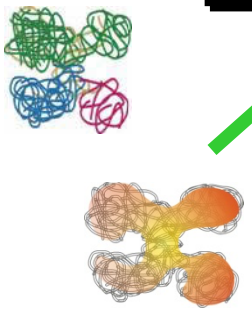


Scaffold
- purified ECM
- synthetic polymers
- composites

Cells
- stem/progenitor
- differentiated
- mixed cell types
- gene editing

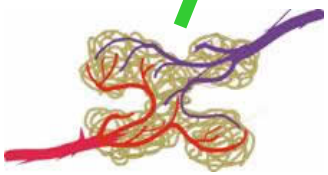


Structure
- porosity
- topography
- stiffness

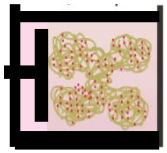


Spatial/Temporal Patterning
- cytokine gradients
- controlled release

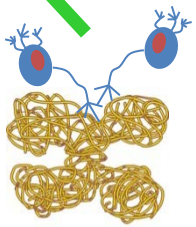
Perfusion
- embedded channels
- vascularization



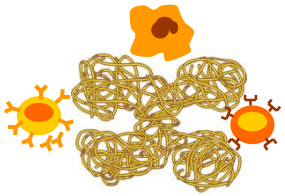
Bioreactors
- optimized culture conditions
- biomechanical properties
- blood mimetics



Innervation
- signal propagation
- coordinated response



Host Response
- generalized inflammation
- specific immunity



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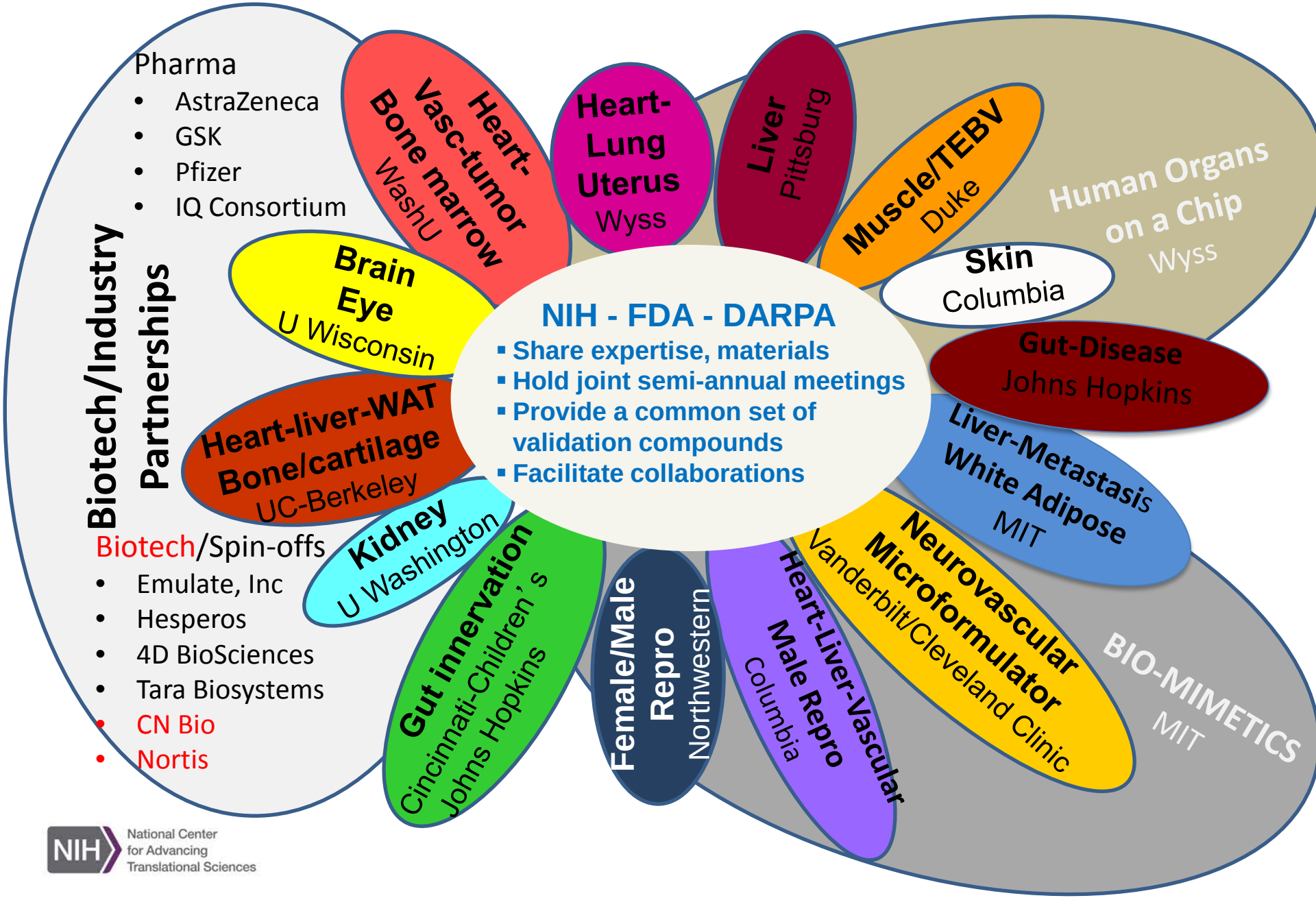
Tissue Chip Consortium



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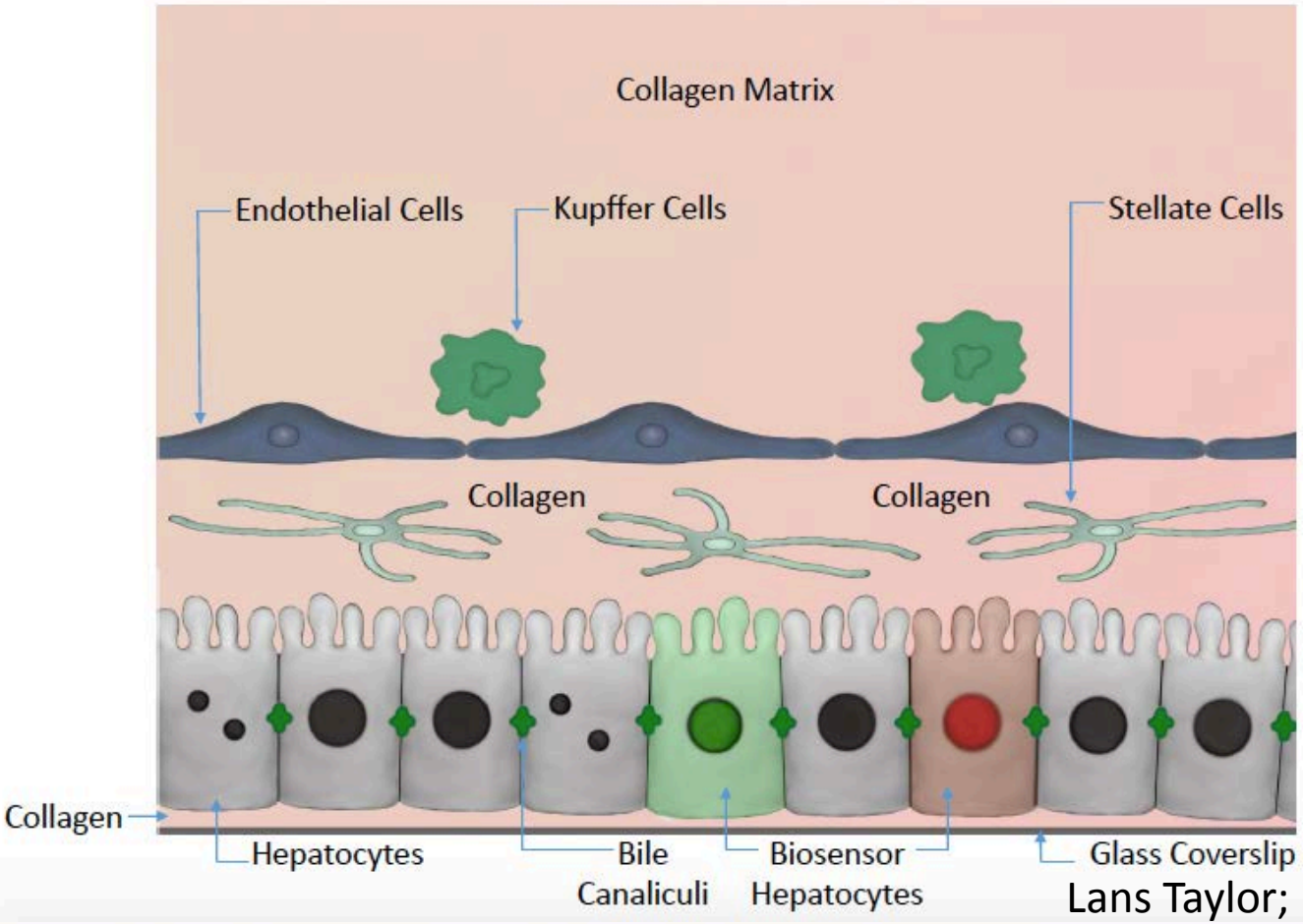
Example: Liver-on-chip

Self-assembly of Hepatocytes and NPC in Nortis MPS



Lans Taylor; Univ. Pittsburgh

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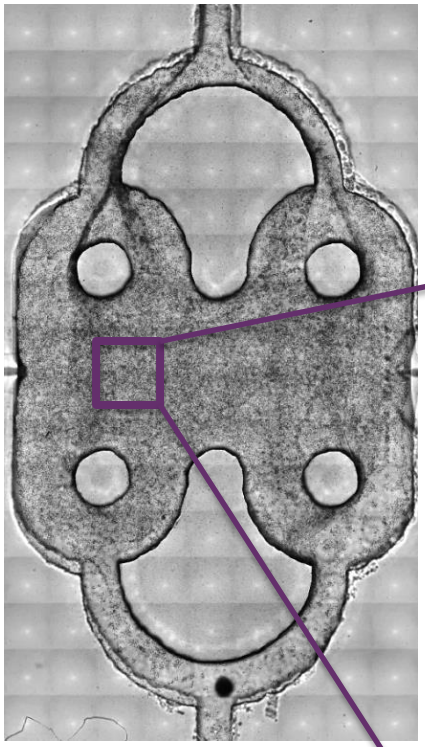
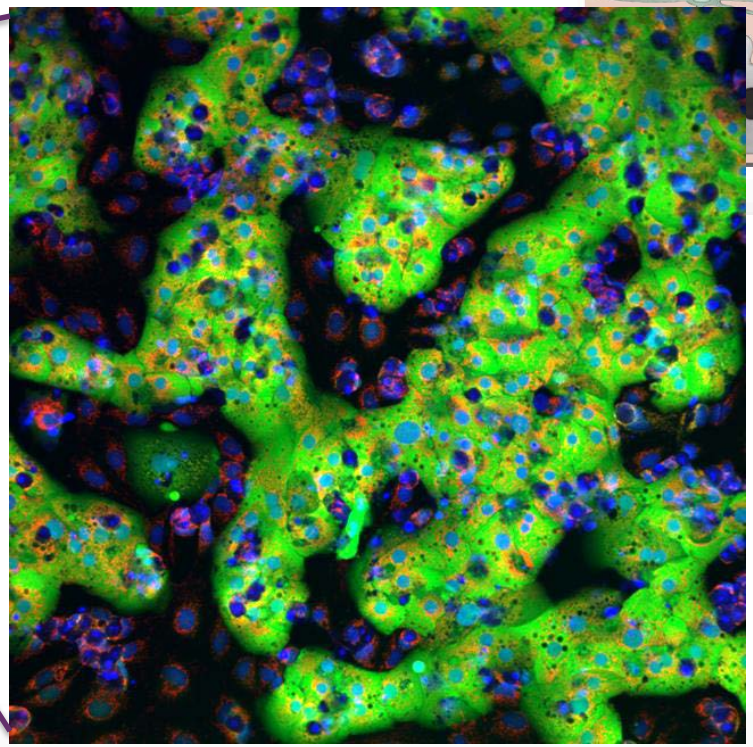
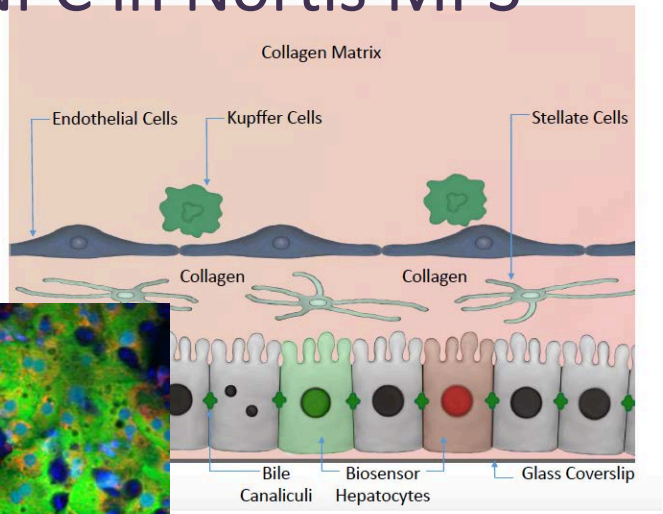


Hepatocyte Cords





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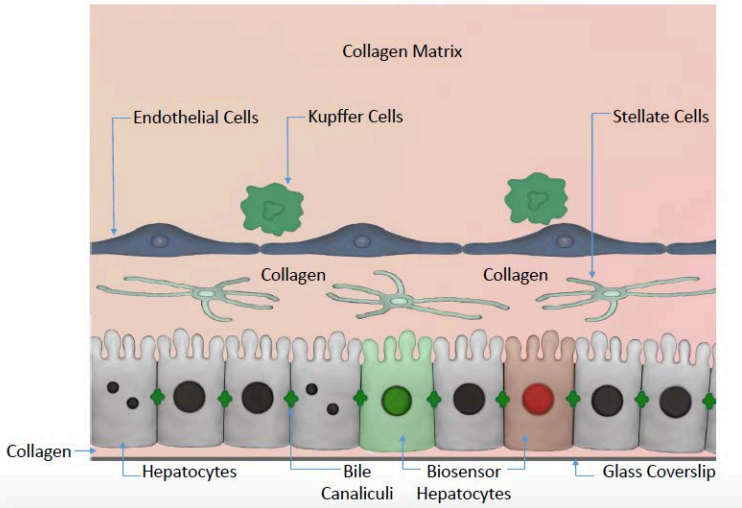
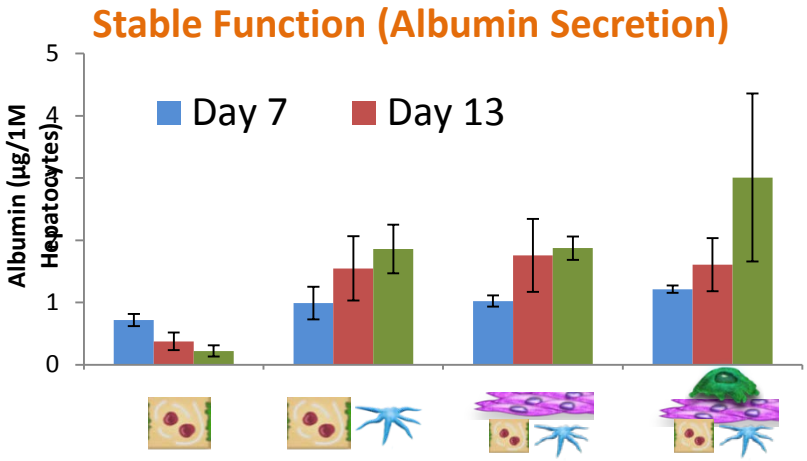
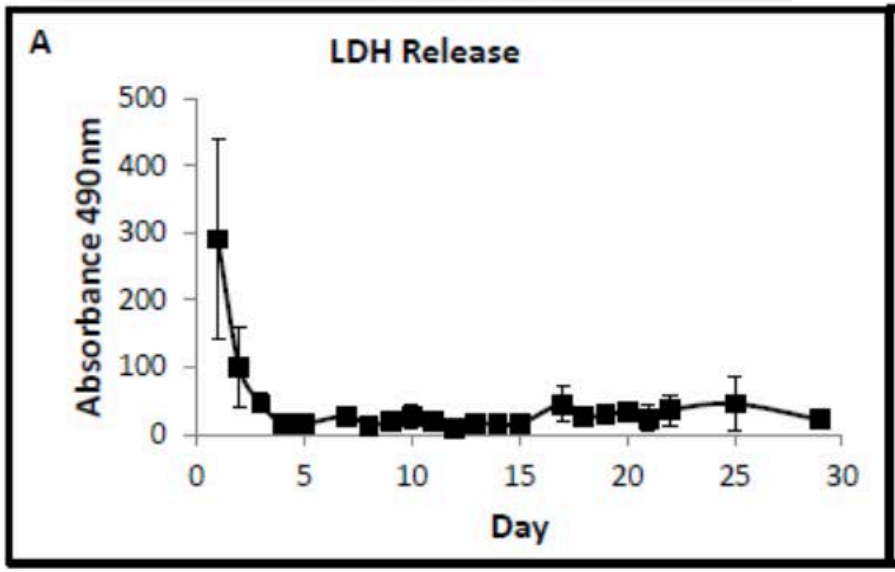
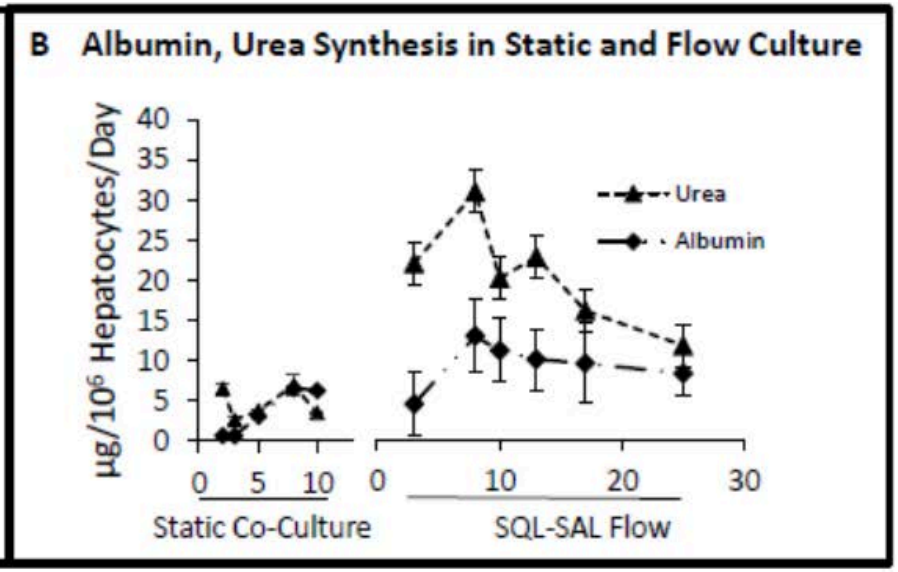
4-week co-culture with NPC and with fluidic flow









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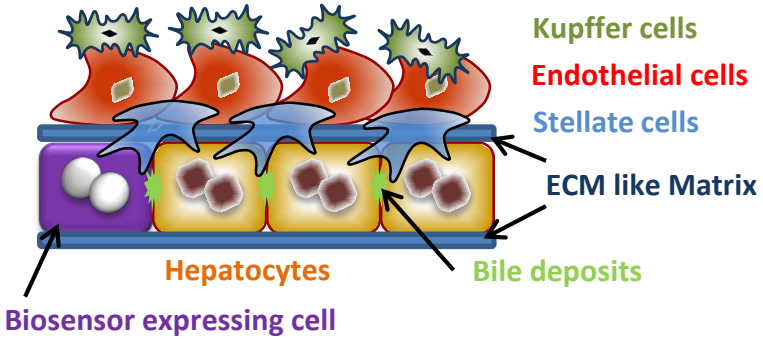
Liver Optogenetic Biosensors

Biosensor	Biosensor Color Options
Nuclear/cell position (Histone H2B)	
Cytochrome C Release: Apoptosis	
Reactive Oxygen Species in Mito. (H_2O_2)	
Mitochondrial Calcium Uptake	
Steatosis (Label-Free)	
Bile canalicular efflux (CMFDA)	
Oxidative Stress in Mito.& Cytoplasm	



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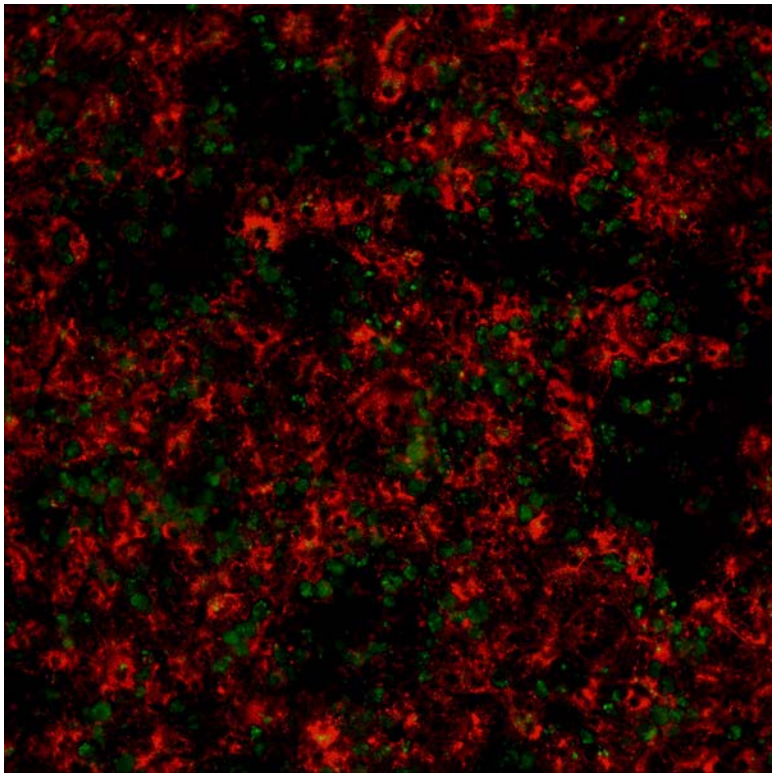
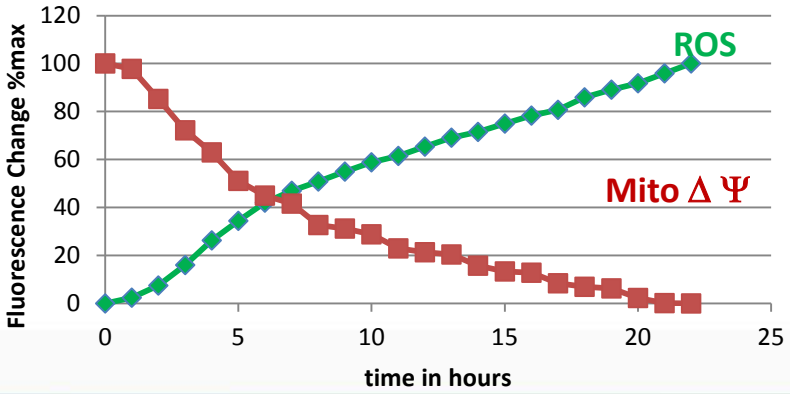


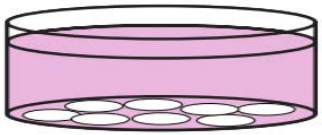


Compounds Tested Using Liver Biosensors

Drug	Cmax	Human/Animal Toxicology	Metabolism dependence	Suggested MOT	Our Results Negative Weak or late positive Strong Positive
Trazodone (in use)	5 uM	extremely rare liver injury Mild ↑transaminases, self eliminating 0.21 incidents/million prescriptions	High clearance drug	No known liver tox	ROS Calcium uptake Mito. membrane potent. Apoptosis bile efflux
Nefazodone (withdrawn US)	0.9 uM	Acute hepatitis Centrilobular (zone 3) necrosis Cholestasis , apoptosis 105 incidents/million prescriptions	High clearance drug, toxic intermediates	Mitochondrial Inhibitor ROS Generation Bile Efflux Inhibition	ROS Calcium uptake Mito. membrane potent. Apoptosis bile efflux
Troglitazone (Withdrawn)	1.8 uM	Moderate to severe ↑ALT,AST Variable necrosis, hepatocellular damage, cholestasis, inflammatory response Up to 1000 incidents/million prescriptions	Impaired clearance	Mitochondrial dysfunction BSEP inhibitor (bile efflux inhibition)	ROS Calcium uptake Mito. membrane potent. Apoptosis bile efflux
Menadione (lead compound-cancer)	Rat 100 mg/kg	Infants: menadione injections produce liver toxicity with hyperbilirubinemia Rat Toxicity (Kidney, Heart, Liver, Lung) IV infusion: Liver: inflammation, degeneration, vacuolization and necrosis MOT identified ROS in liver, calcium uptake into hepatocytes massive liver necrosis in GSH depleted rats	No toxic intermediates known	ROS Mitochondrial Inhibition Calcium uptake	ROS Calcium uptake Mito. membrane potent. Apoptosis bile efflux

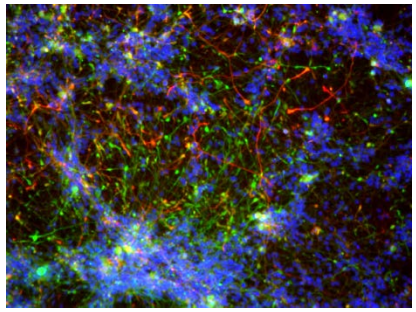
Lans Taylor; Univ. Pittsburgh

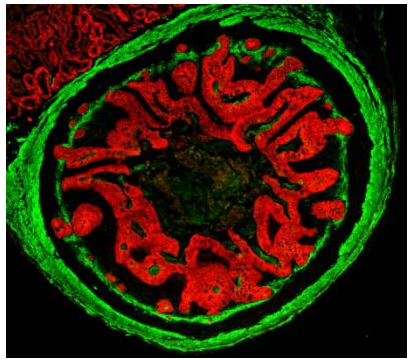
Gut Enteroids



Pluripotent Stem Cells: renewable human cell source

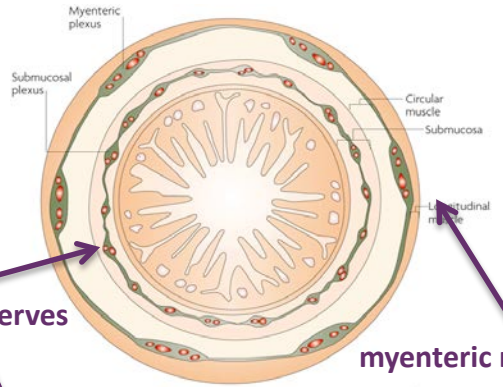
Vagal Neural Crest Cells: peripheral nerve cells





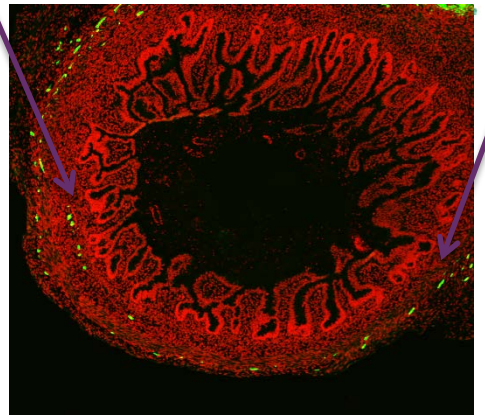
Gut enteroid: 3D multicellular mini gut

Gut Lumen



submucosal nerves

myenteric nerves

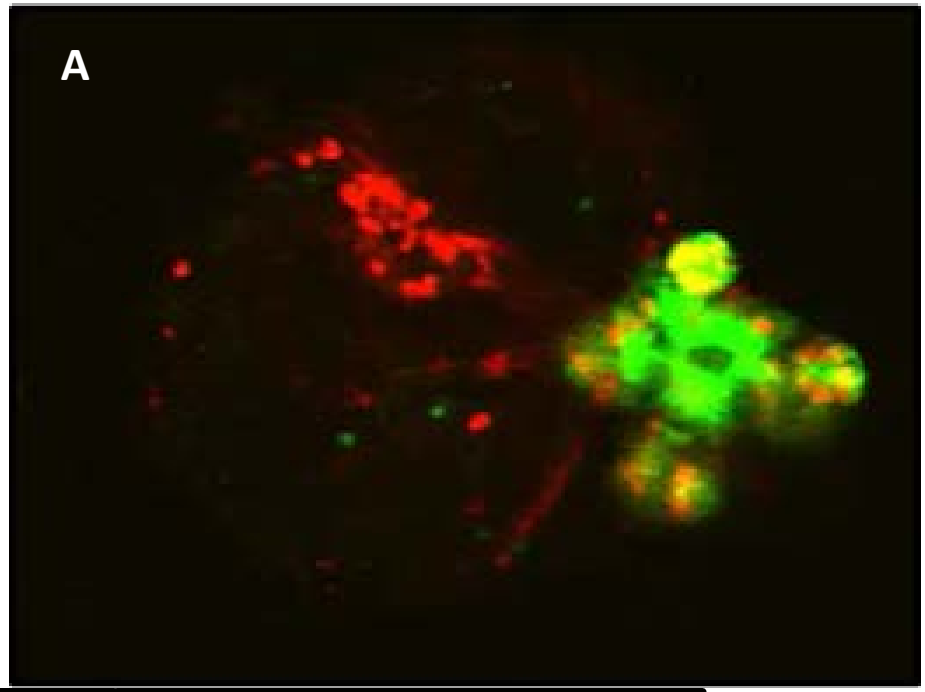


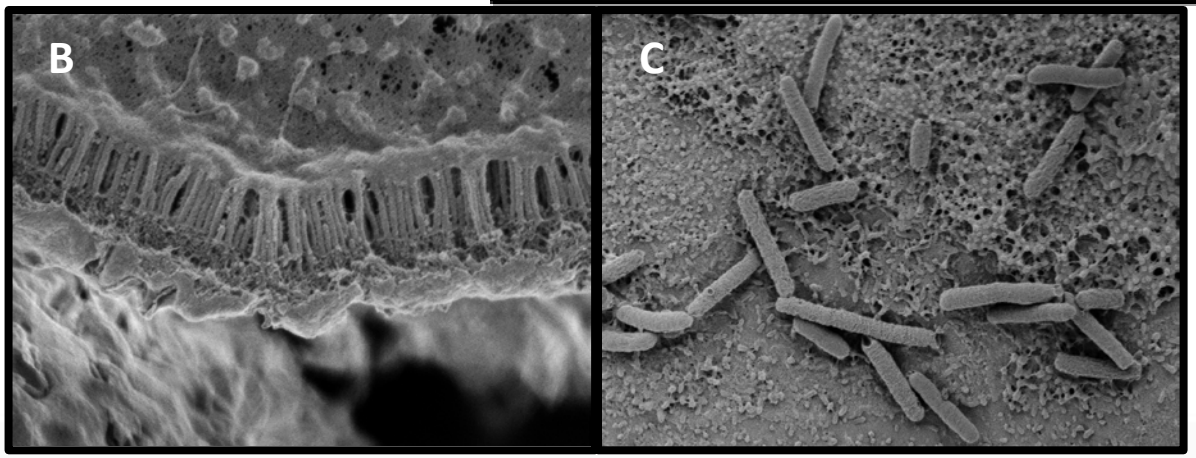
The nervous system in the gut plays a critical role in GI function, including peristalsis (gut contraction). Both nerve and gut tissue can be engineered using renewable human cell sources

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

James Wells, Univ. Cincinnati

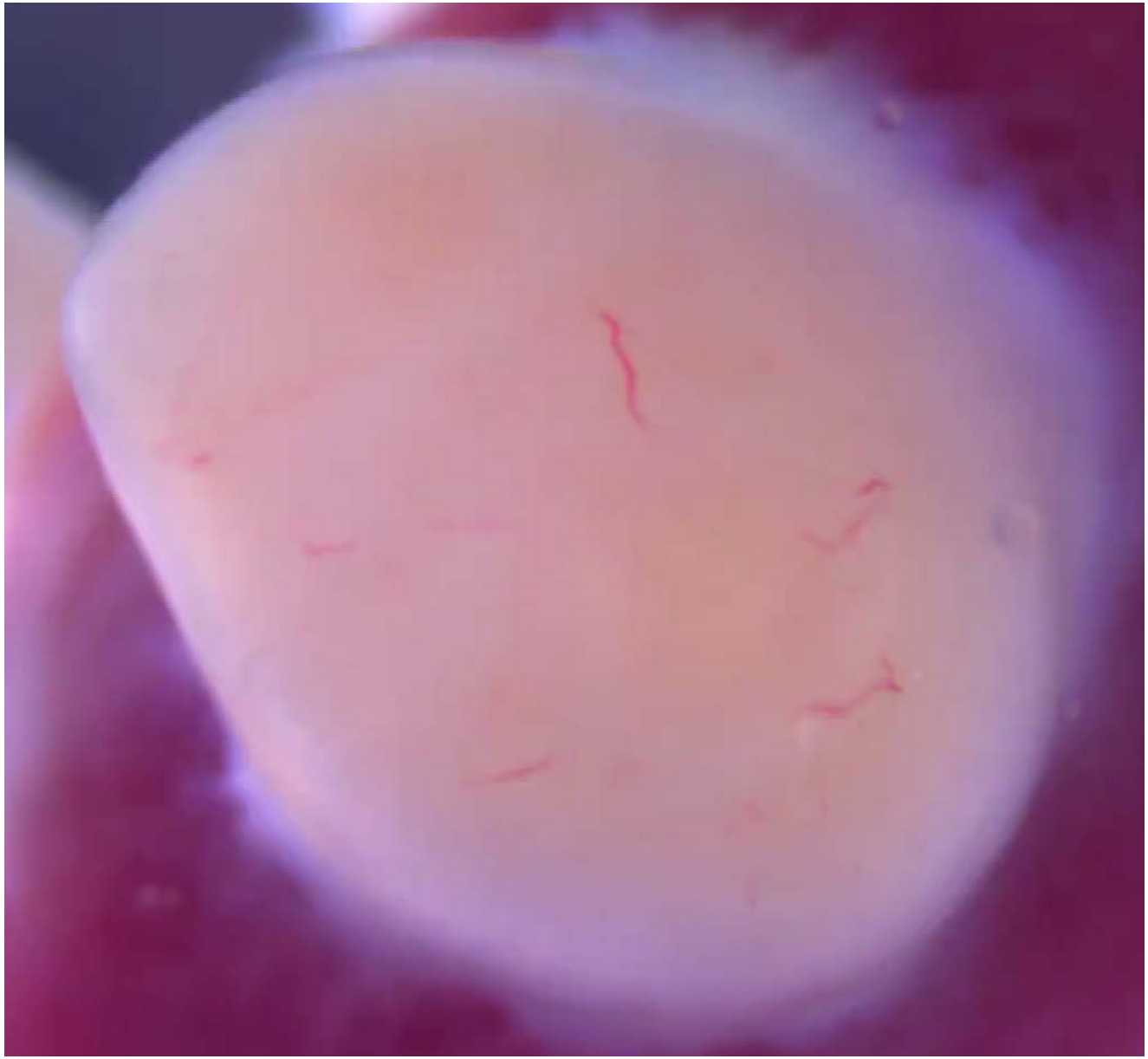
Enteroids mimic gut structure and function





Mark Donowitz, Johns Hopkins

Electrical field stimulation (with ENS)



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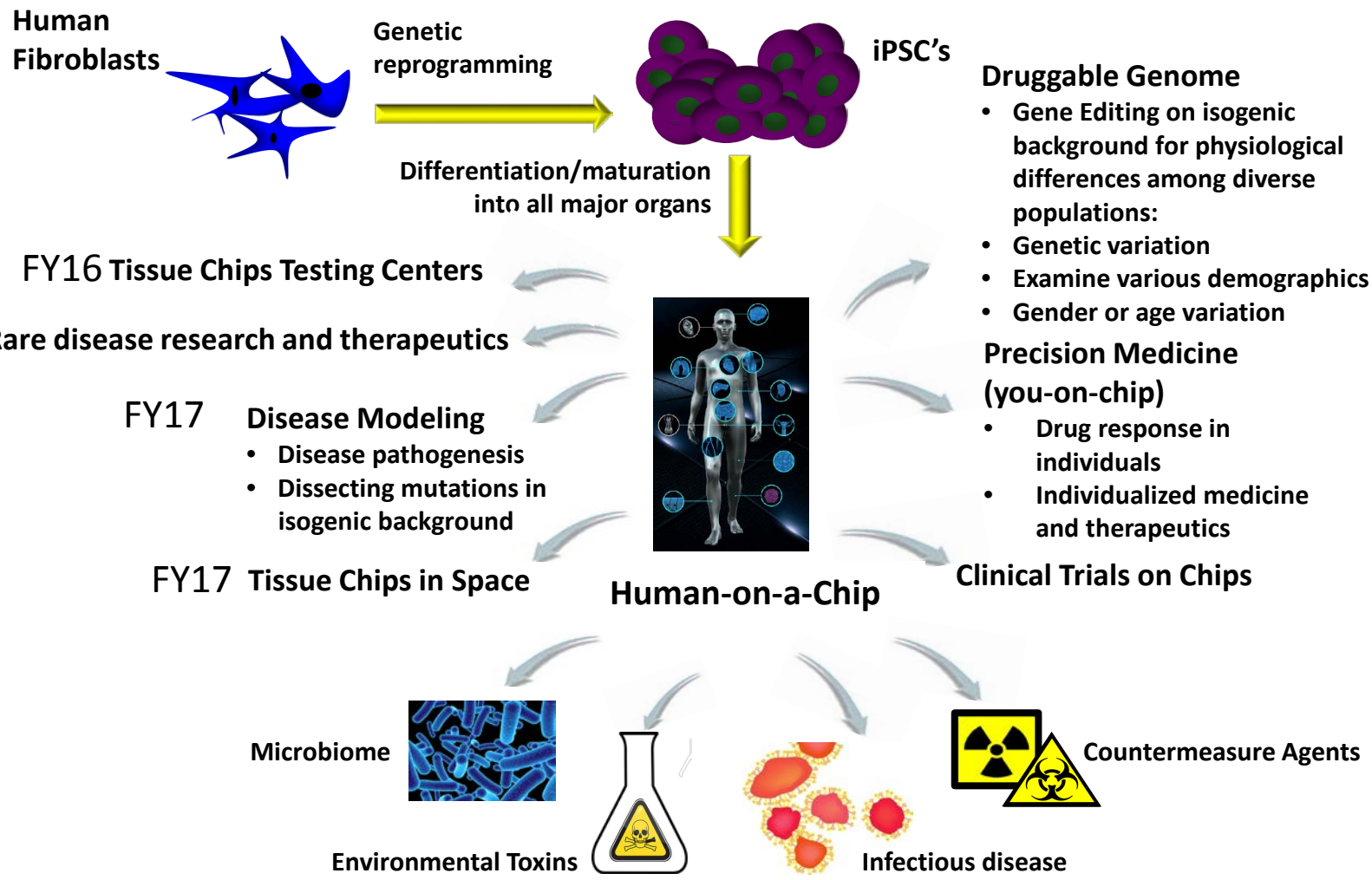
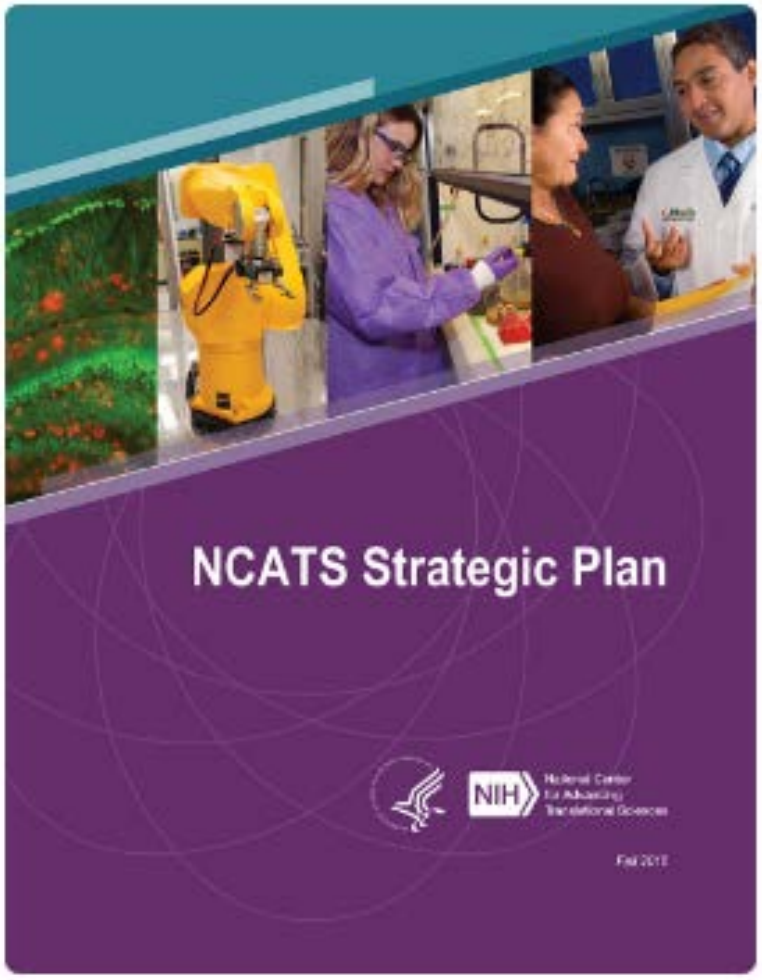
Future Directions in Tissue Chips



NCATS Strategic Plan



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ncats.nih.gov/strategicplan

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