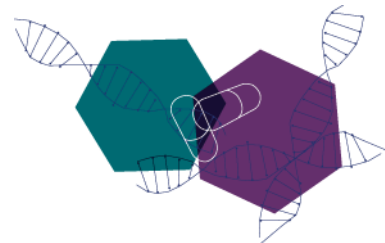


Catalyzing Innovation Through Collaboration

IOM Round Table, D.C.– June 5, 2013

Dr. Krishna “Balki” Balakrishnan
Senior Technology Manager, Office of Strategic Alliances
National Center for Advancing Translational Sciences, NIH
Email: Balki@nih.gov



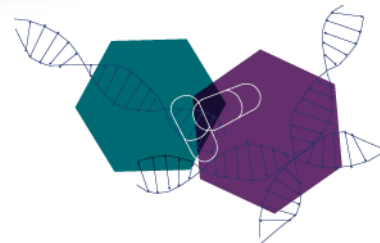
Creation of the National Center for Advancing Translational Sciences (NCATS)

- Established on December 23, 2011
- Part of Consolidated Appropriations Act 2012 (PL 112-74)



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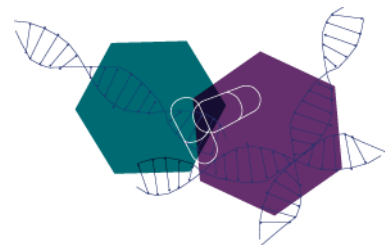
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NCATS Mission

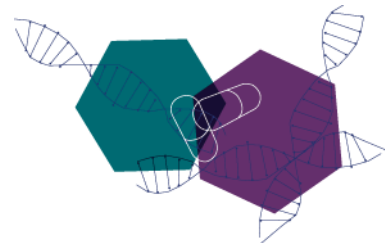


To catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.



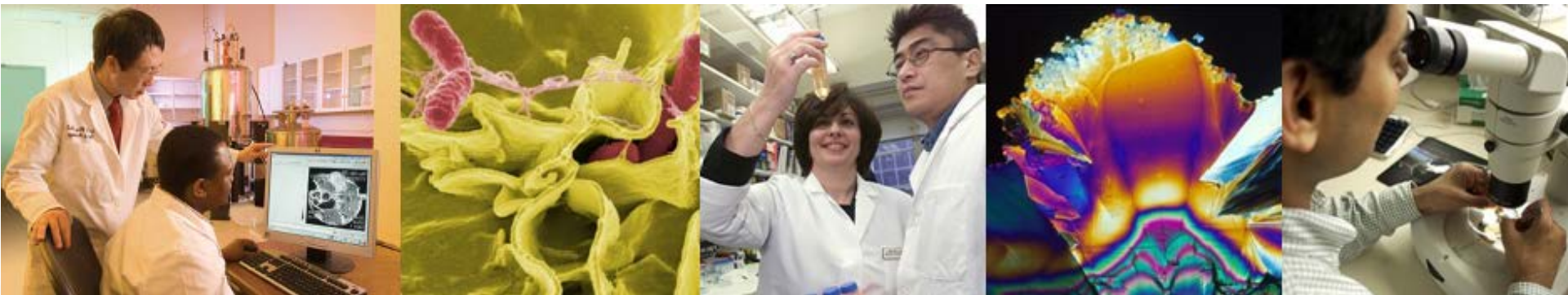
NCATS Approach to Collaboration

- Realize that problems are of massive scale
- Define problems clearly
- Define responsibilities clearly and align goals
- Look for synergies and complementary assets
- Be transparent and share glory
- Position NCATS as an “Honest Broker”
- Serve an “Adapter” function
- Be willing to disengage when appropriate



Catalyzing Collaboration **Within** NCATS

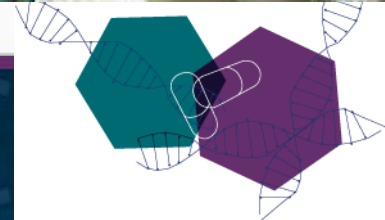
- Collaboration (like charity) starts at home
- Cross functional teams- Biology, Chemistry and Bioinformatics
- Instill collaborative DNA throughout organization
 - Develop common vision
 - Reduce the burden of collaboration and make it a habit
 - Be transparent and over-communicate
 - Reward teamwork and share glory



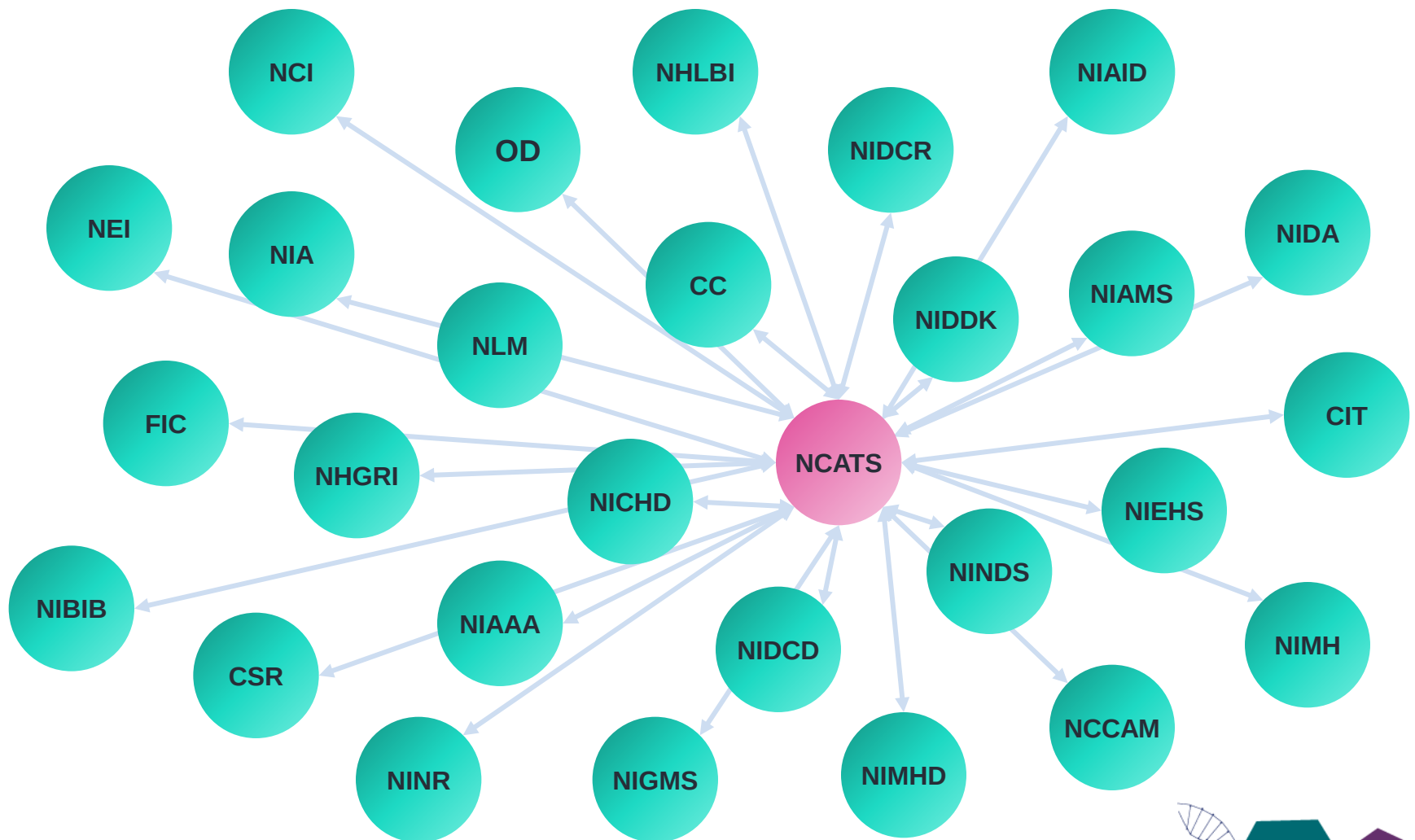
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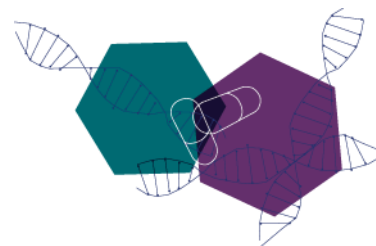


Catalyzing Collaborations **Within** NIH

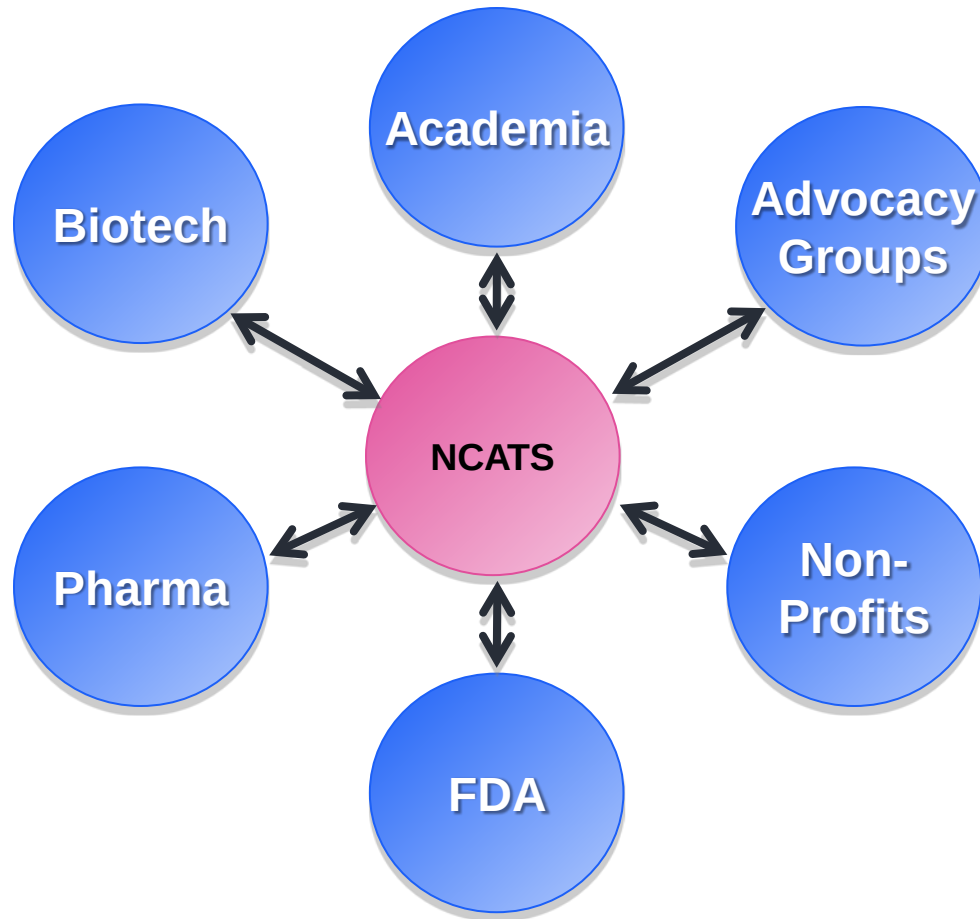


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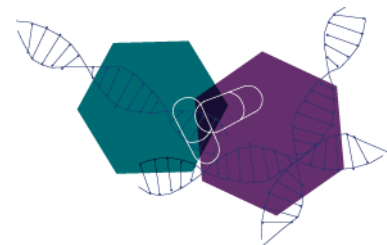
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Catalyzing Collaborations **Outside** NIH

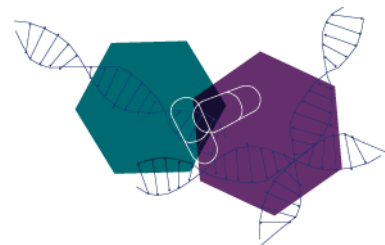


- Complement — not compete with — the work of others
- Revolutionize the process of translation by promoting innovative research
- Expand the precompetitive space
- Support and augment regulatory science and its application
- Galvanize and support new partnerships



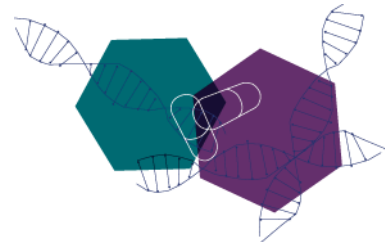
NCATS Approach to Industry Collaborations

- Science drives the collaboration and partner
- Projects focus on new technologies, enabling tools, and dissemination; de-risking novel therapeutic approaches for industry adoption; pre-competitive area
- Most projects are selected via a solicitation or review process
- Projects follow NIH policies and laws regarding the implementation of industry collaborations, handling and licensing of IP



Collaborating within the COI framework

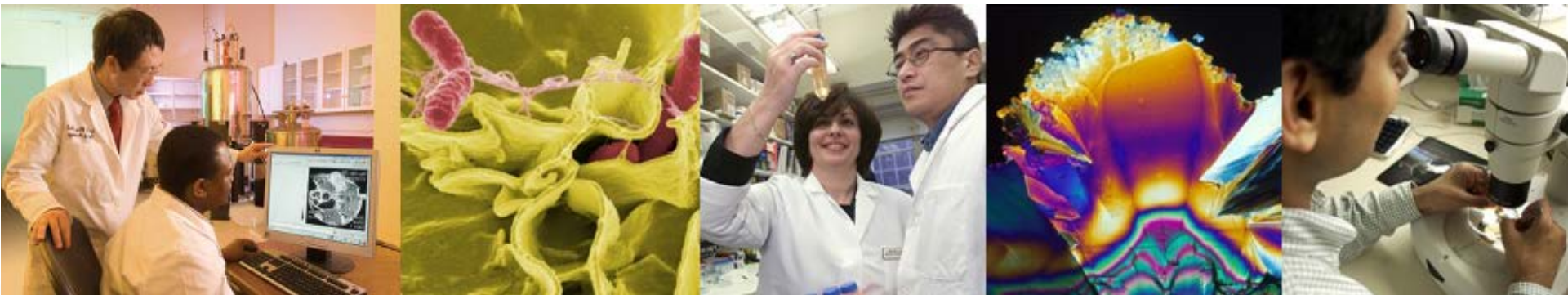
- Disseminate project solicitation process widely
- Utilize objective review process for project selection
- Formalize collaboration and make it official
- Standardize and streamline collaborative procedures wherever possible- make it easy to collaborate
- Clearly communicate and follow NIH policies and laws regarding all aspects of collaboration
- Duplication of efforts and paperwork may sometime be a necessary burden



Overcoming Challenges Through Collaboration

NCATS Case Studies

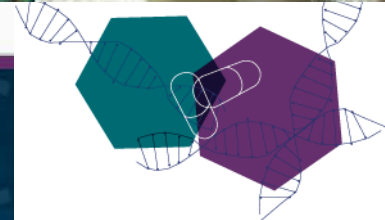
- TRND- Risky programs, lack of incentives
- Drug Rescue and Repurposing program- Crowdsourcing, multiple partners, risk averseness of partners, lack of clear rewards
- Tissue Chip- Massive scale, risk, need for multiple partners, new platform technology development



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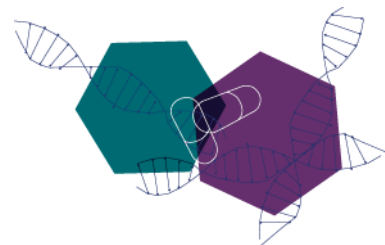
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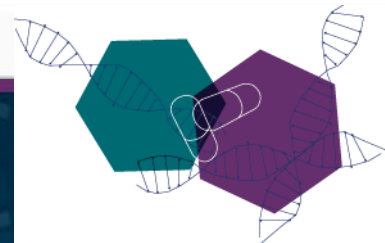
Therapeutics for Rare and Neglected Diseases (TRND)- De-Risking via teamwork

- Drug development collaboration between NCATS and extramural partners with disease-area / target expertise
- Projects may enter at various stages of preclinical development
- Disease must meet FDA orphan or WHO neglected tropical disease criteria
- De-risk projects through “Valley of Death”- Max Phase IIa
- Transparent project management and governance
- Multifunctional project teams and independent Joint Research Committee
- Milestone driven project management



TRND Highlights

- 15 projects adopted since 2009
 - Mix of small molecules and biologics
 - Two innovative platform technologies
- **4 investigational drugs taken into humans in 16 months**
 - Chronic Lymphocytic Leukemia: Phase I trial, 9/2011
 - Sickle Cell Disease: Phase I trial, 12/2011
 - Hereditary Inclusion Body Myopathy: Phase 1 trial in patients, 9/2012
 - Niemann-Pick Type C Disease: Phase 1 trial in patients, 1/2013
- Initiated first natural history study
 - HIBM: NIH Clinical Center, 1st patient enrolled in 9/2011
- **Every project is a unique public-private partnership**
 - Many include foundation and patient advocacy input



TRND

Pulmonary Alveolar Proteinosis

- **Collaborators**

- Bruce Trapnell (Cincinnati Children's Hospital) and Genzyme

- **Clinical Manifestation**

- Ultra-rare; 7 per million
- Accumulation of surfactant fluid in lungs; can lead to respiratory failure

- **Current Treatment**

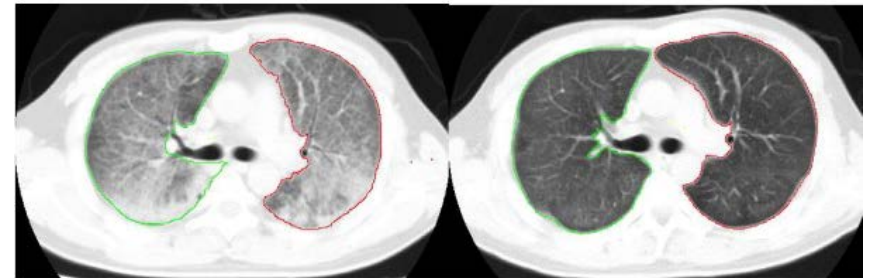
- Whole lung lavage under general anesthesia
- Technically challenging, invasive, pediatric safety concerns

- **Alternative: Leukine (GM-CSF)**

- Possibly generate alveolar macrophages to scavenge surfactants and clear liquid
- Currently approved in IV form for Myeloid reconstitution after bone marrow transplant

- **Path Forward/Gaps**

- Need toxicology data on inhaled form of drug
- TRND funded GLP toxicology study with Genzyme donated drug



PAP infiltration

4 days post lavage

Eur J Radiol 2011, May 26; <http://dx.doi.org/10.1016/j.ejrad.2011.05.005>

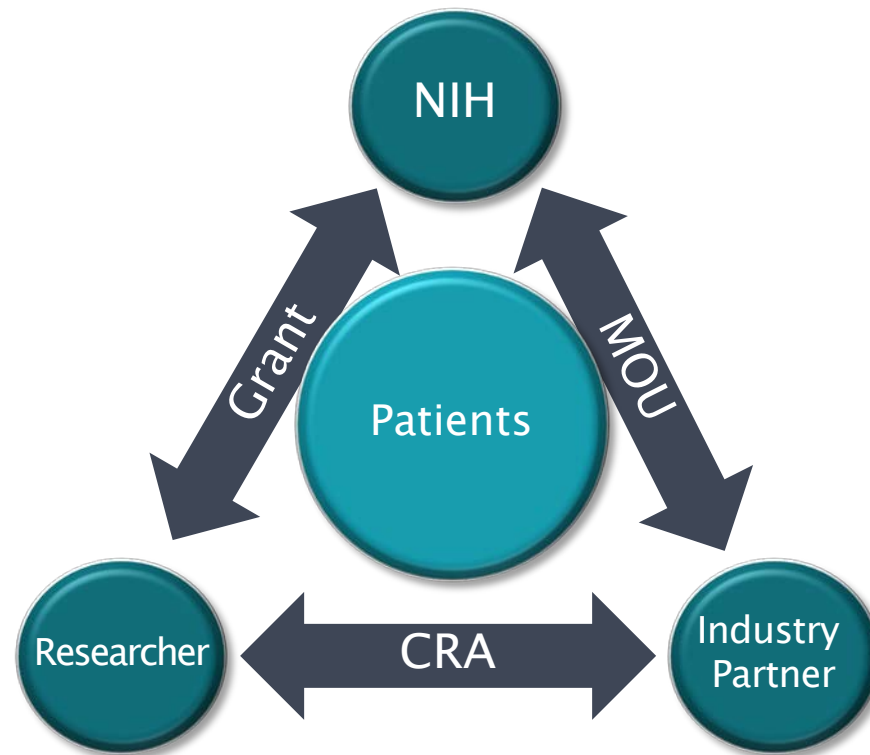


Whole Lung Lavage Fluid

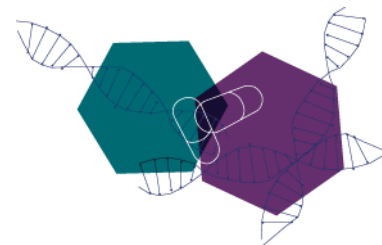
N Engl J Med 2007; 357:e21

Discovering New Therapeutic Uses for Existing Molecules (Therapeutics Discovery)

NIH - Industry Pilot Program: Launched May 2012
Synergy through crowdsourcing

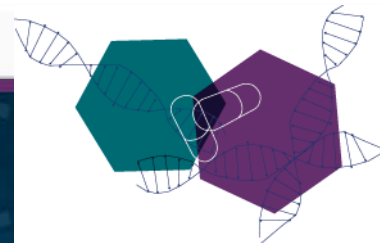


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Therapeutics Discovery

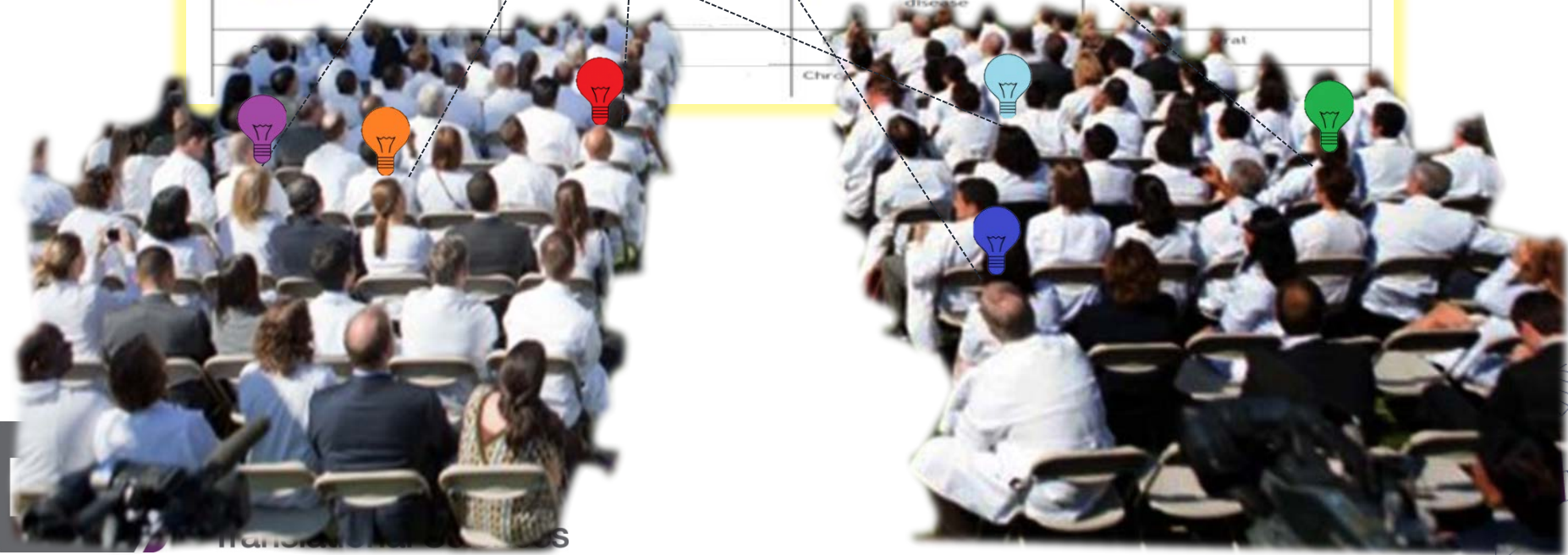
- Use NCATS funds to “rescue” forgotten compounds in Pharma’s “medical attic” through innovative ideas from researchers
- 8 companies have contributed 58 compounds
- Pfizer, AstraZeneca, Lilly, Abbott, BMS, GSK, Janssen and Sanofi
- Memorandum of Understanding – Between NIH and Industry Partners
- Confidential Disclosure Agreement and Collaborative Research Agreement Templates - Between the Pharmaceutical Company Partner and the Applicant



Therapeutics Discovery

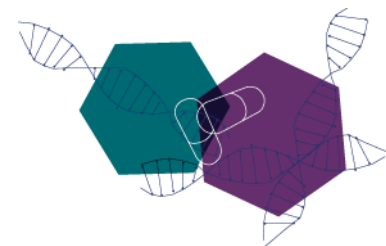
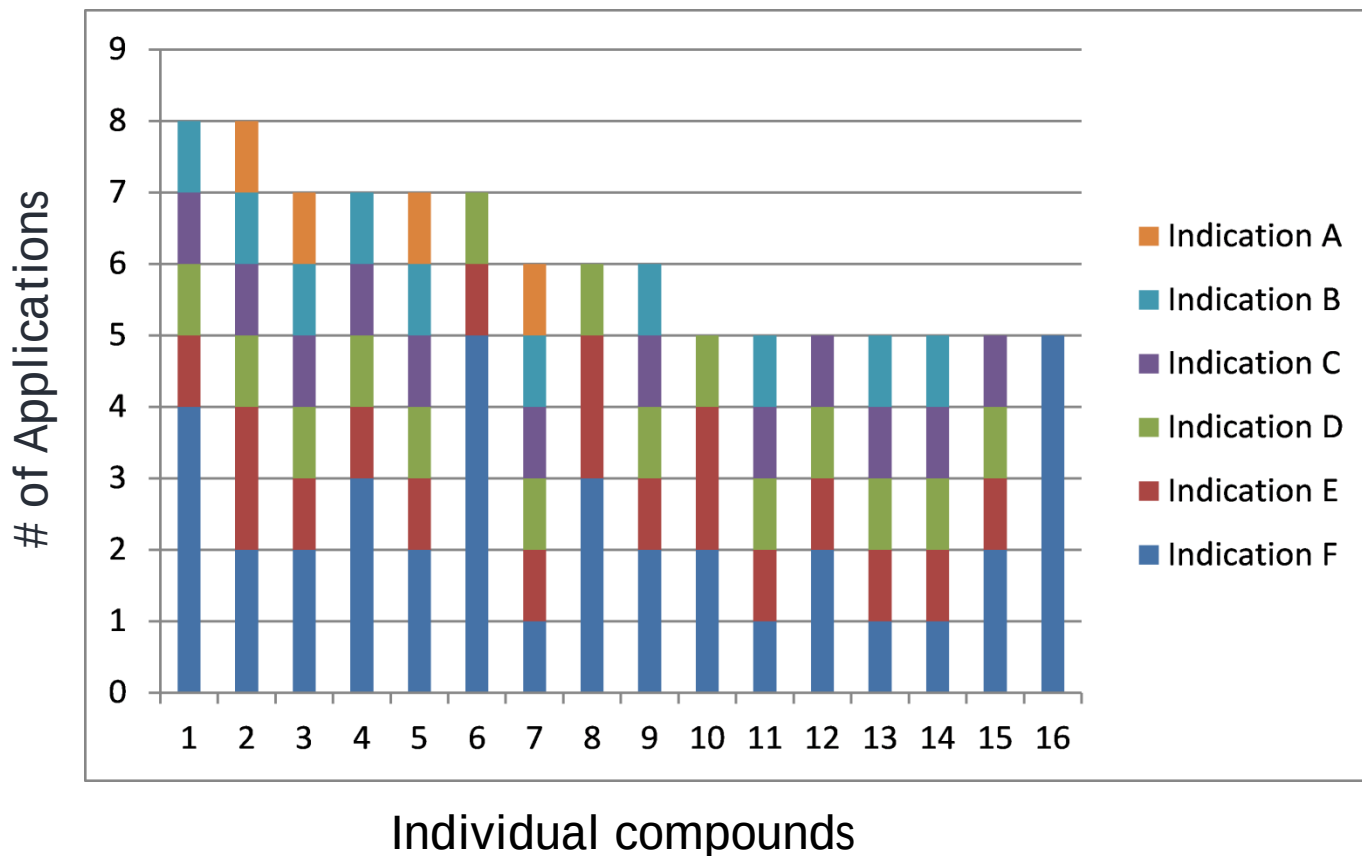
Crowdsourcing- some think alike others don't!

Code Number & Link to More Information	Mechanism of Action	Original Development Indication(s)	Route of Administration Formulation Available (CNS Penetrant [†])
Compound 1	MoA 1	Hypercholesterolemia	Oral
Compound 2	MoA 2	Maintenance of sinus rhythm in atrial fibrillation patients Prevention of shocks and major clinical outcomes in patients with implanted cardiac defibrillator	Oral
Compound 3	MoA 3	Sickle cell disease	Oral
Compound 4	MoA 4	Asthma	Oral (Yes)
Compound 5	MoA 5	Pain	Oral (Yes)
Compound 6	MoA 6	Obesity	Oral (Yes)
Compound 7	MoA 7	Osteoarthritis pain	Oral (Yes)
		Asthma	Oral
		Chronic obstructive pulmonary disease	Oral
		Chronic	Oral

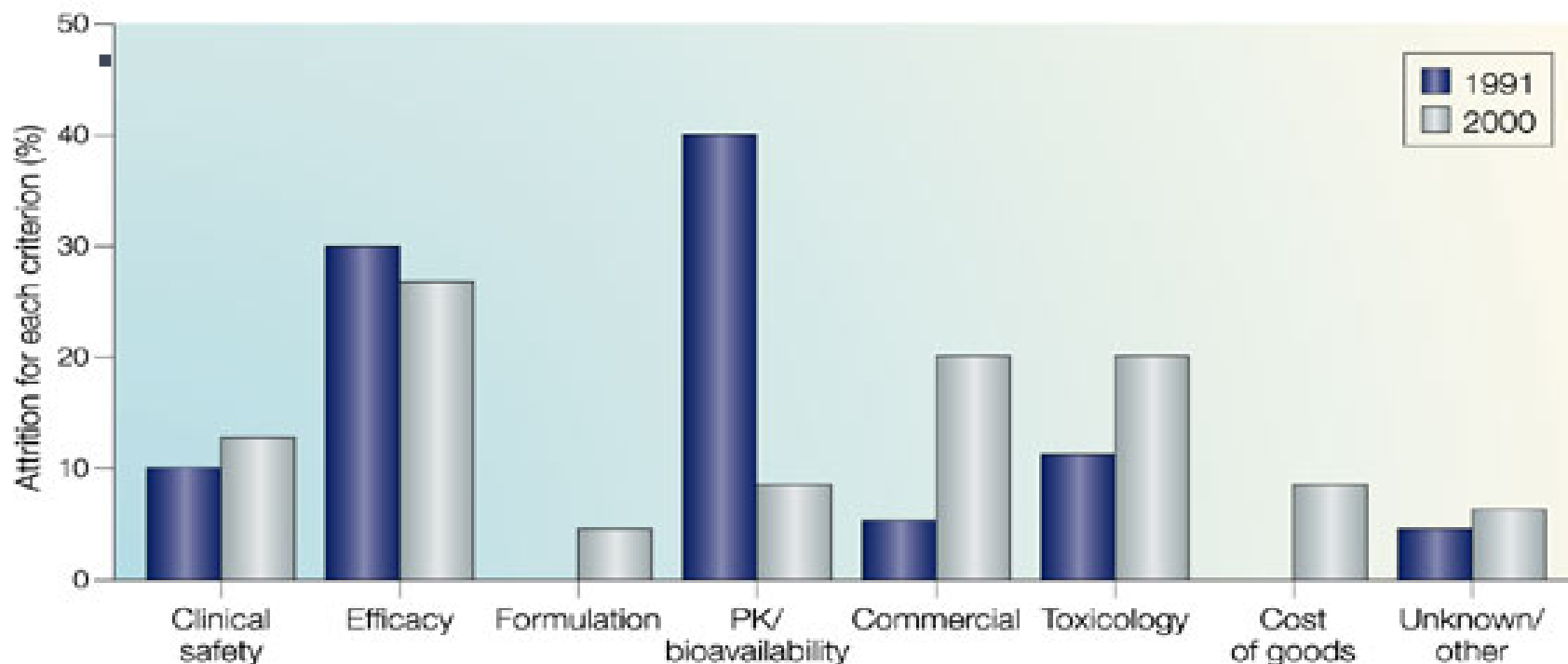


Therapeutics Discovery

Impact of Crowdsourcing



Lack of Efficacy and Toxicity – Top Reasons for Drug Development Failure; Can Tissue Chips Help?



Preclinical (21%) + Clinical (12%) Tox = 33% of all failures and coupled with 28% failure in efficacy account for majority of causes of attrition

Nature Reviews | Drug Discovery

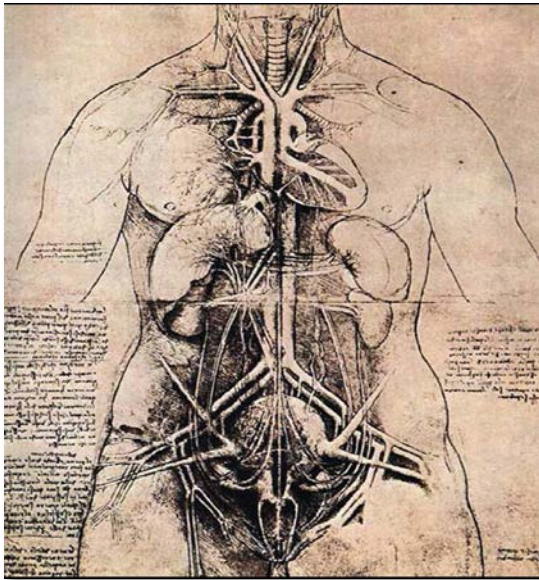
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Tissue Chip Program

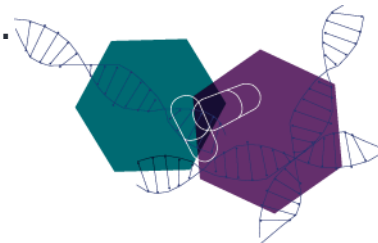
GOAL: Develop an *in vitro* platform that uses human tissues instead of whole animals to predict drug efficacy, pharmacokinetics and safety.



- All ten human physiological systems will be functionally represented:
 - Circulatory
 - Endocrine
 - Gastrointestinal
 - Immune
 - Integumentary
- Physiologically relevant, genetically diverse and pathologically meaningful.
- Modular, reconfigurable platform for easy integration.
- Tissue viability for at least 4 weeks.
- Community-wide access.

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Generalized Building Blocks for Organs-on-Chips

Scaffold

- purified ECM
- synthetic polymers
- composites

Cells

- stem/progenitor
- differentiated
- mixed cell types

Structure

- porosity
- topography
- stiffness

Spatial/Temporal Patterning

- cytokine gradients
- controlled release

Perfusion

- embedded channels
- vascularization

Bioreactors

- optimized culture conditions
- biomechanics

Computational Design

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

Functional Readout

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

Host Response

- generalized inflammation
- specific immunity

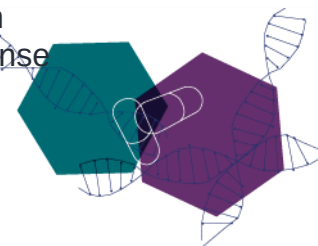
Innervation

- signal propagation
- coordinated response

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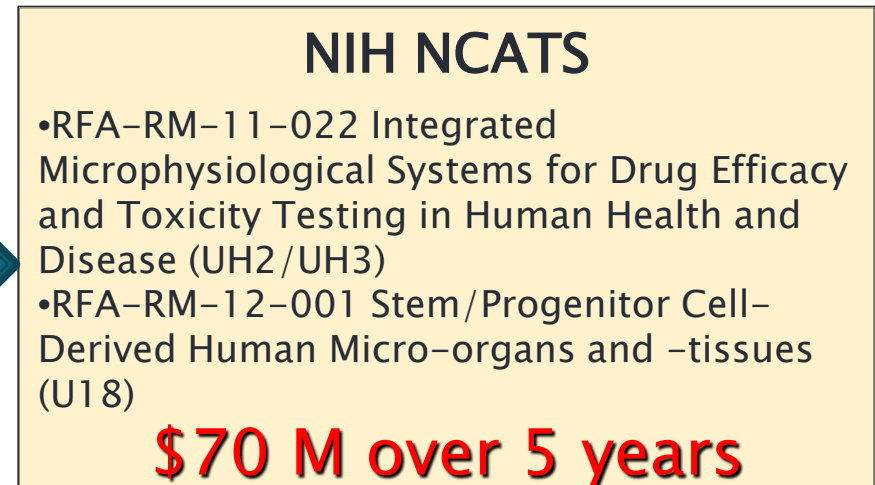
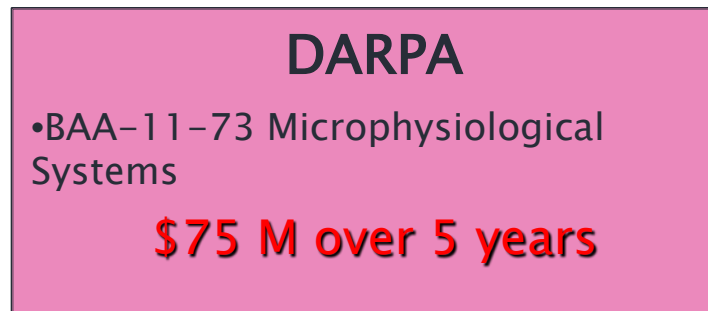
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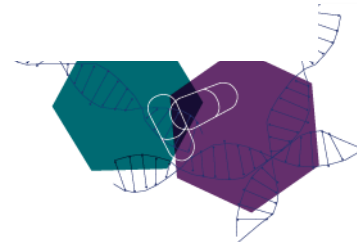
The Tissue-Chip Partnership

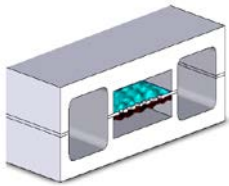
Develop tissue chips that mimic human physiology to screen for safe, effective drugs using best ideas in engineering, biology, toxicology



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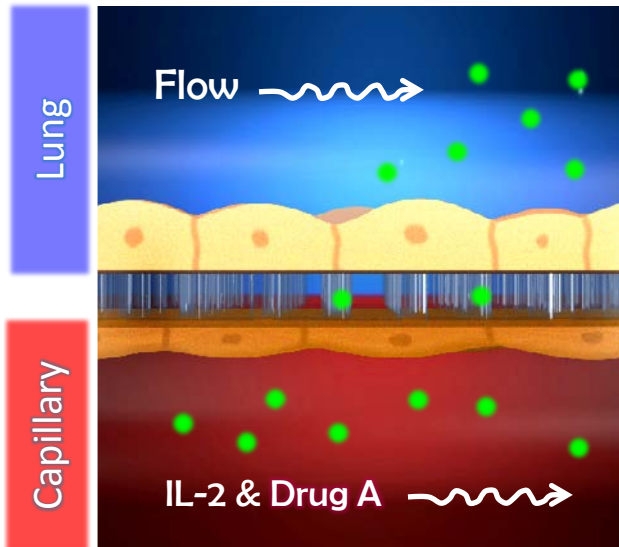
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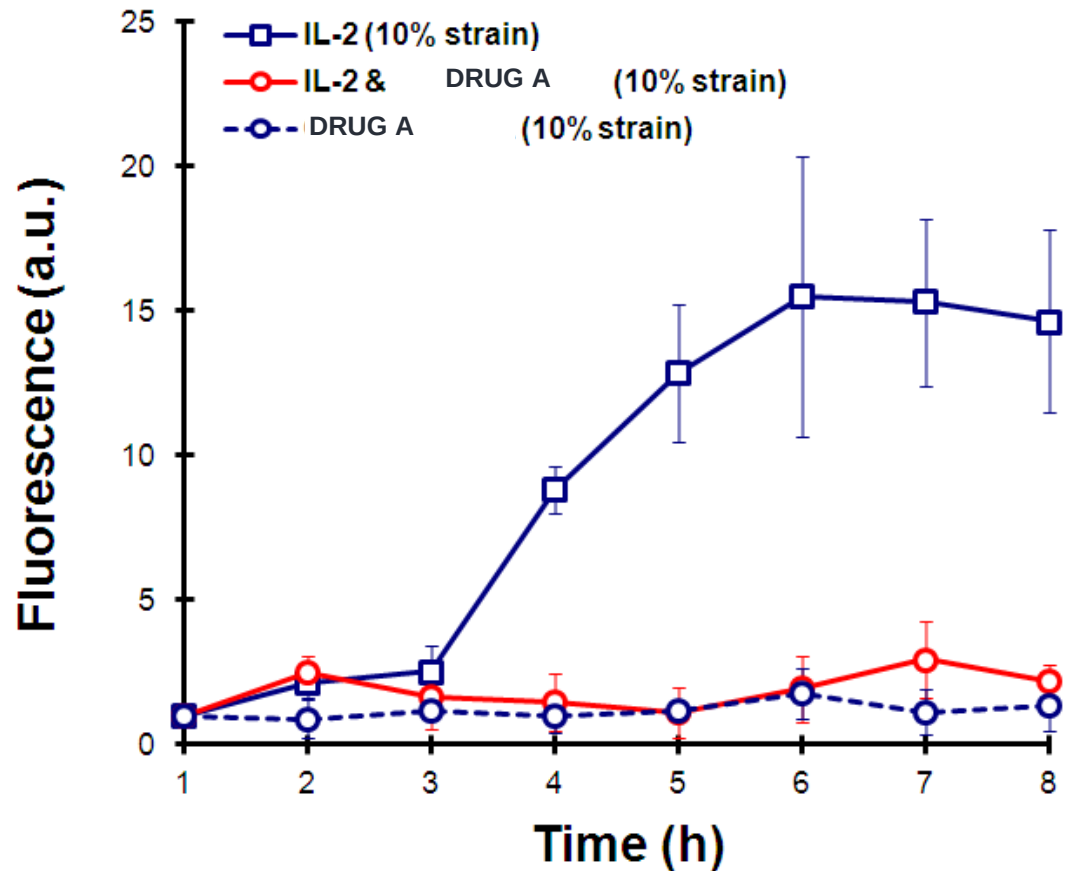


Lung-on-a-Chip: Predicting Drug Efficacy

- Common side effect of IL-2 chemotherapy is vascular leak syndrome or edema



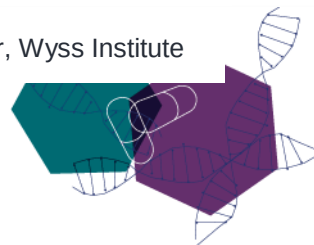
● FITC-inulin



Data provided by Dr. Don Ingber, Wyss Institute

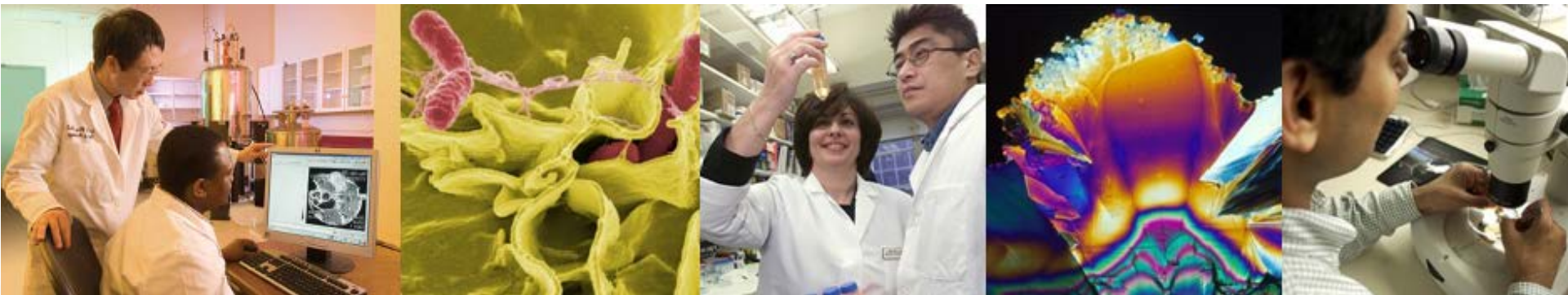
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Overcoming Challenges Through Collaboration

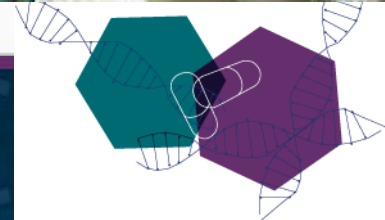
- TRND- **Program risk, Lack of incentives**
- Therapeutics Discovery- Crowdsourcing, **Multiple partners, Risk averseness** of partners, **Lack of clear rewards**
- Tissue Chip- **Massive scale, Risk, Multiple partners, New platform** technology development



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