Cancer Tissue-on-chip (ToC) technologies for improved preclinical efficacy evaluation of therapies in oncology (*R01, clinical trial not allowed)*

PAR request

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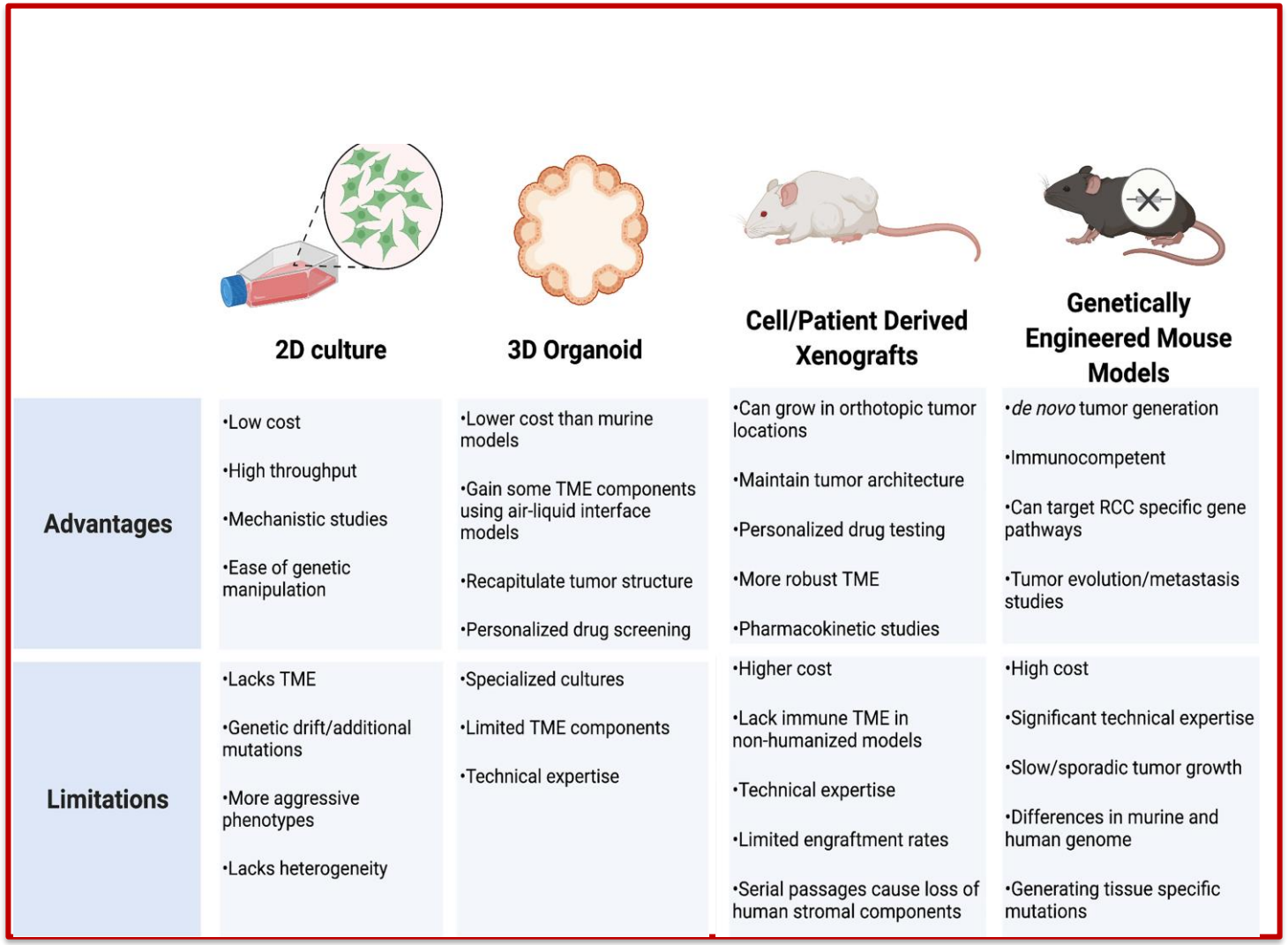
NIH NATIONAL CANCER INSTITUTE

BSA meeting, December 3, 2024

What is the Problem or Challenge?

Majority of compounds tested in cancer clinical trials fail, despite promising results in preclinical testing



	2D culture	3D Organoid	Cell/Patient Derived Xenografts	Genetically Engineered Mouse Models
Advantages	•Low cost •High throughput •Mechanistic studies •Ease of genetic manipulation	•Lower cost than murine models •Gain some TME components using air-liquid interface models •Recapitulate tumor structure •Personalized drug screening	•Can grow in orthotopic tumor locations •Maintain tumor architecture •Personalized drug testing •More robust TME •Pharmacokinetic studies	•*de novo* tumor generation •Immunocompetent •Can target RCC specific gene pathways •Tumor evolution/metastasis studies
Limitations	•Lacks TME •Genetic drift/additional mutations •More aggressive phenotypes •Lacks heterogeneity	•Specialized cultures •Limited TME components •Technical expertise	•Higher cost •Lack immune TME in non-humanized models •Technical expertise •Limited engraftment rates •Serial passages cause loss of human stromal components	•High cost •Significant technical expertise •Slow/sporadic tumor growth •Differences in murine and human genome •Generating tissue specific mutations

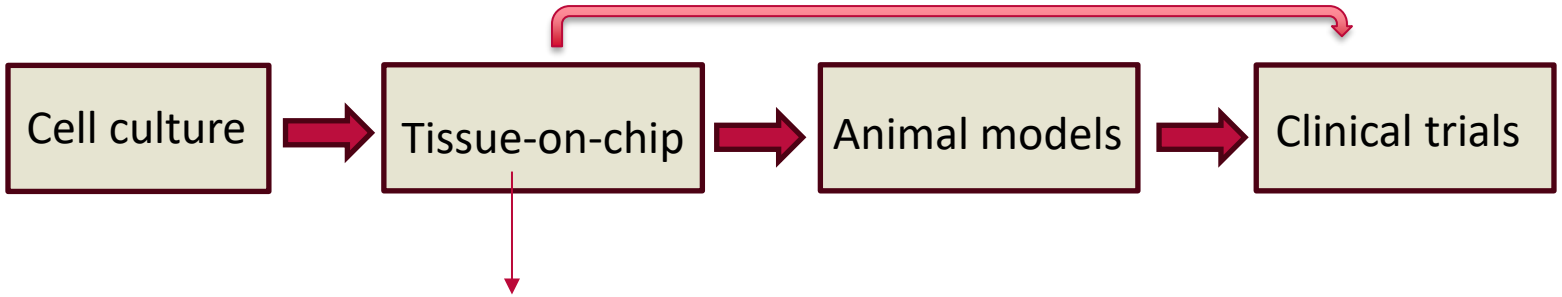
Shapiro, Abel et al. Frontiers in Oncology, 2022

How to Address the Challenge?

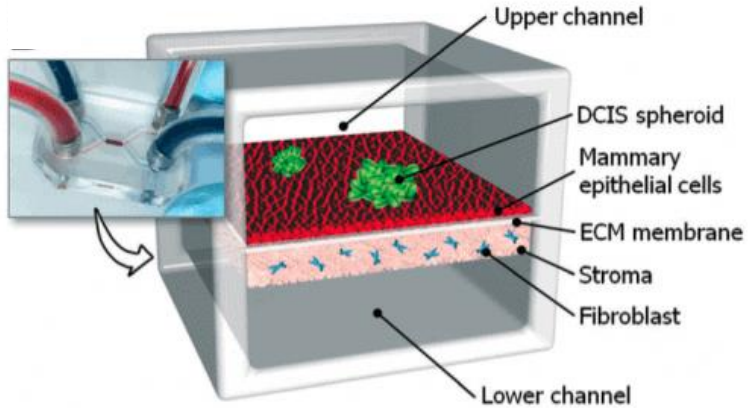
- Continue refining *in vivo* animal models
- Enhance *in silico* modeling in conjunction with AI to improve early selection of APIs for drug development
- Evaluate and further improve tissue-on-chip (ToC) technologies
- Other?

- Tissue-on-chips (ToCs)
  - are a combination of on-chip multi-cell/tissue organotypic (co)culture and engineered microfluidics
  - offer improved mimicry of tumor pathobiology and physiology relative to 'static' 2D or 3D cell cultures

- ToCs can be a viable intermediate model for cancer therapy evaluation, but their full potential is yet to be tapped into



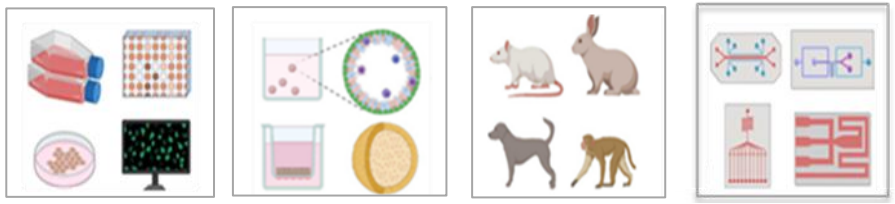
- Dynamic perfusion capability
- Replicating the complex microenvironment
- Controlled biomechanical parameters
- High throughput, parallel multiplexed organotypic cultures
- Continuous monitoring



Example of a ToC design

Sontheimer-Phelps, Ingber Nature Reviews Cancer 2019

Value Added of Tissue-on-chip

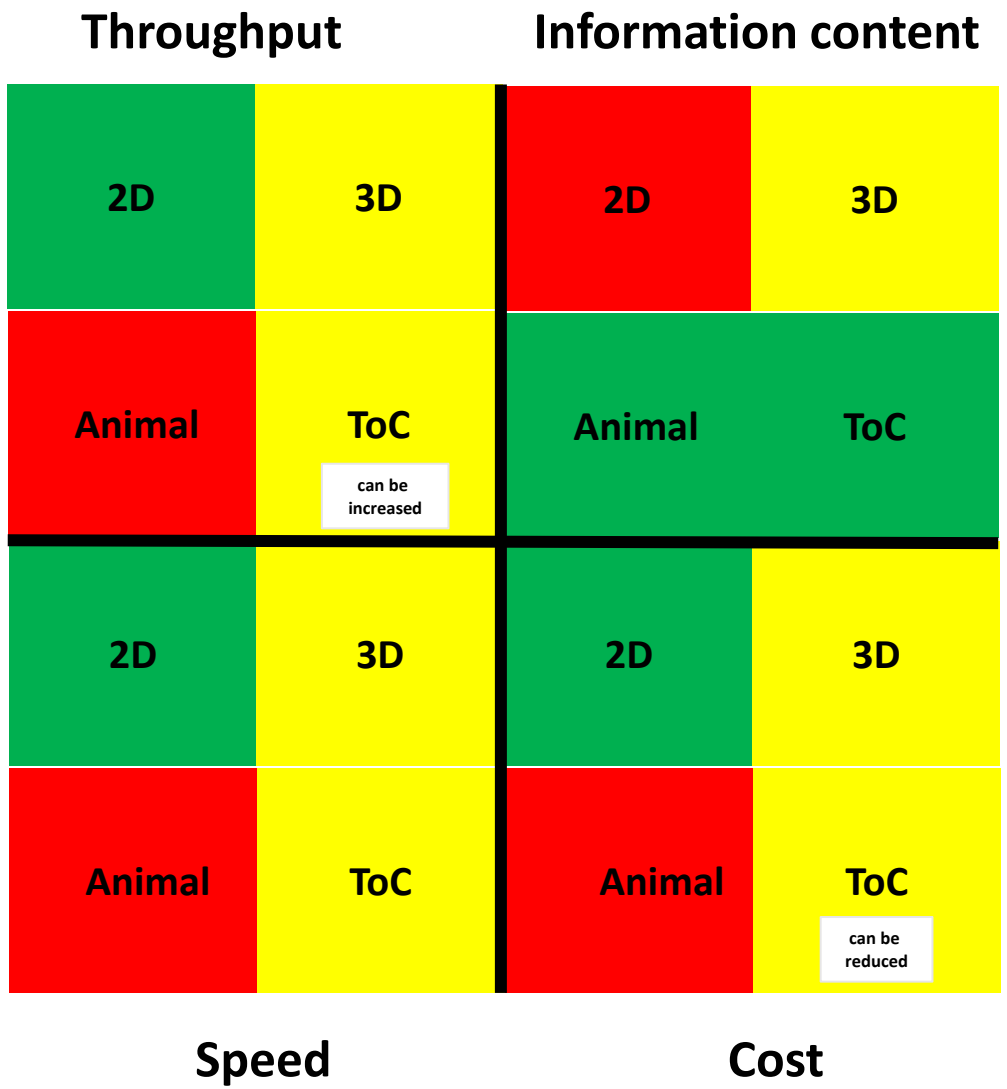


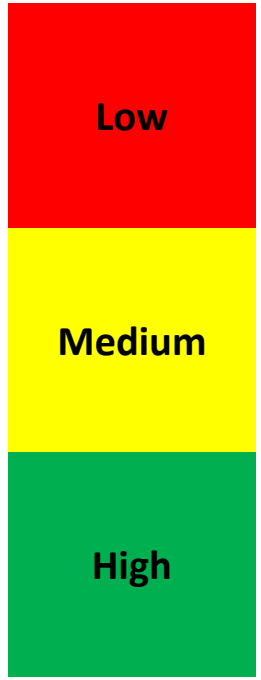
	2D cell culture	3D cell culture	Animal Models	Tissue-on-Chip
Cell-cell interaction	X	0	0	0
Immune cells and stromal cells	X	X/0	0	0
Vascularization	X	X/0	0	0
Microenvironment control	X	X/0	X/0	0
Imitation of human (patho)physiology	X	X/0	X/0	X/0
High-throughput screening	0	0	X	0
Model complexity	X	X/0	0	0
Ethical constraints	0	0	X	X/0

- ✓ More cell-cell interactions and cross-talk
- ✓ Accommodates organotypic/whole-tissue extended cultures
- ✓ Accommodates immune, vascular and stromal cells
- ✓ Better tumor microenvironment replication and control
- ✓ Stimulates fluid shear stress and dynamics
- ✓ Better imitation of human pathology complexity
- ✓ Throughput, automation and reproducibility
- ✓ Accommodates AI in data processing and interpretation
- ✓ Real-time monitoring and time efficiency
- ✓ Less ethical constraints
- ✓ Versatile and customizable
- ✓ Bridges the gap between preclinical testing and human trials
- ✓ Can reduce testing costs

Figure modified from Sokolowska et al. Organoids 2022, and Li et al. SPJ. 2022

ToC Attributes in Preclinical Testing





Early ToC Commercialization

Do we Need more Research?

emulate

Spin-off from Donald Ingber's lab, Wyss Institute, Harvard

- Single- and multi-tissue/organ chips
- Safety toxicity
- Diseases: cancer and infectious diseases

CN-BIO

Spin-off from Linda Griffith's lab, Biological Engineering, MIT

- Single- and multi-tissue/organ chips
- Safety toxicity
- Diseases: nonalcoholic steatohepatitis (NASH), hepatitis B, COVID-19

Needed ToC improvements:

- Validation of cancer tissue/organ chips requires studies different types of cancer drugs that demonstrate similar efficacies and toxicities in tissue/organ chips to those observed *in vivo* and with similar PK;
- Sophistication of ToC analysis depends on inclusion of several cell types (cancer cells, endothelial cells, stromal cells and immune cells) in correct proportions from the same patient into the chip;
- Use of alternate to PDMS materials to build chips needs to be considered.

Organ-on-a-Chip Market Valuation is Set to Skyrocket and Reach US$ 1,665.91 Million By 2032 | Astute Analytica

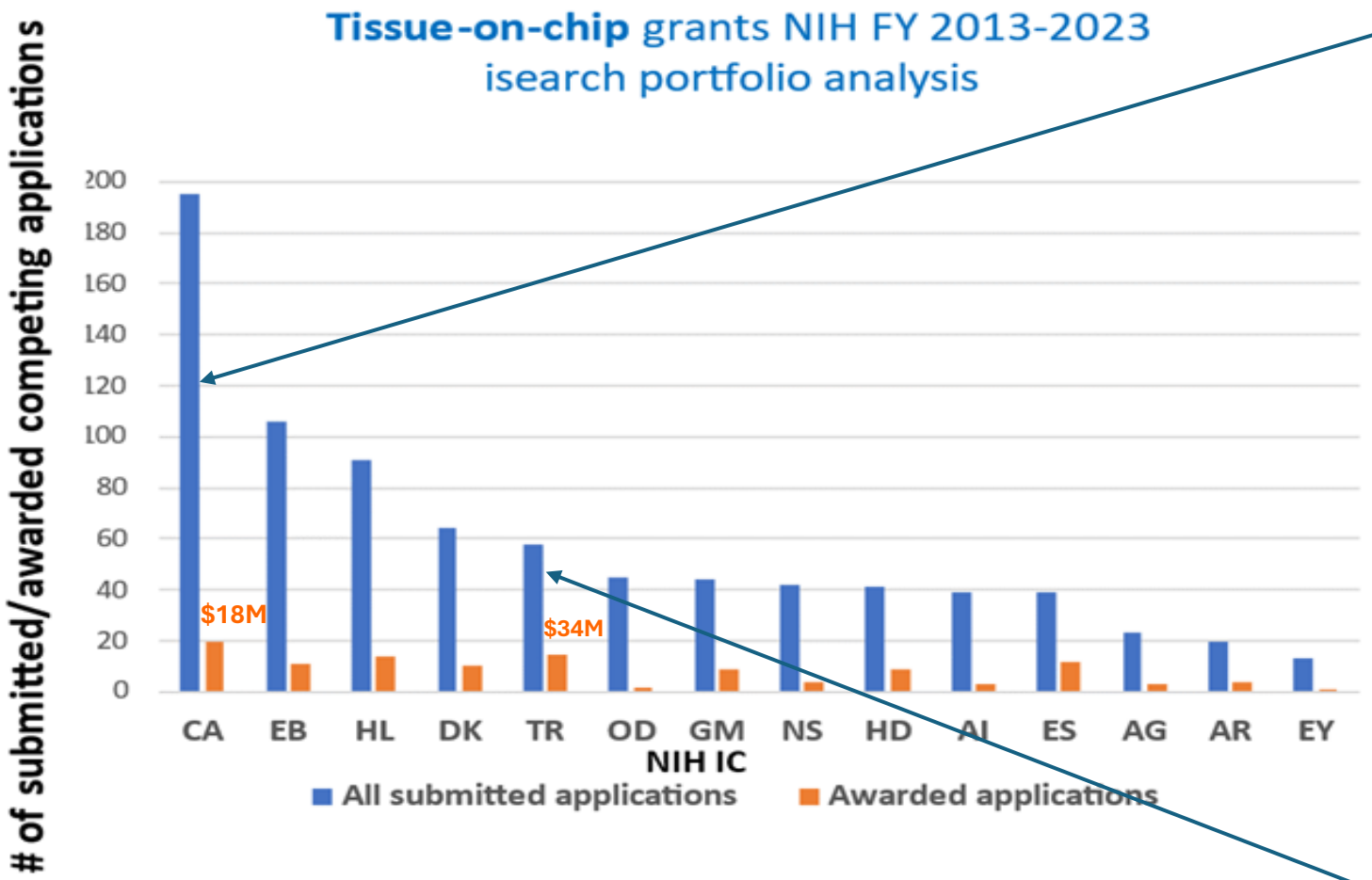
New Initiative – Proposed Goals

The purpose of this proposed PAR is ***to improve pre-clinical efficacy testing of cancer therapies*** utilizing ToCs

- Development and optimization of ToC-based cancer therapy efficacy testing platforms with dynamically controlled environment
  - via implementation of new device design features and integration of imaging and sensing tools
  - via incorporation of mixed-cell cultures, including blood-vessel and immune components, to better mimic *in vivo* conditions
- Comparison of ToC data with that obtained from respective *in vivo* models
- ToC performance proof-of-concept in evaluating different cancer (combination) therapies (chemo/targeted therapies/immunotherapies)

- Achieve wider-spread use of ToC models in (high throughput) cancer therapy efficacy testing
- Improve confidence in ToC assays to be as predictive as established preclinical models
- Understand ToC limitations - how well can complex therapies be assessed in ToCs? Single drug/multi-drug combination therapies/targeted therapies?

Justification for the PAR



Cancer Tissue Engineering Collaborative (TEC), PAR-22-099
Majority of applications and awards are basic mech. science focused
NCI/DCB

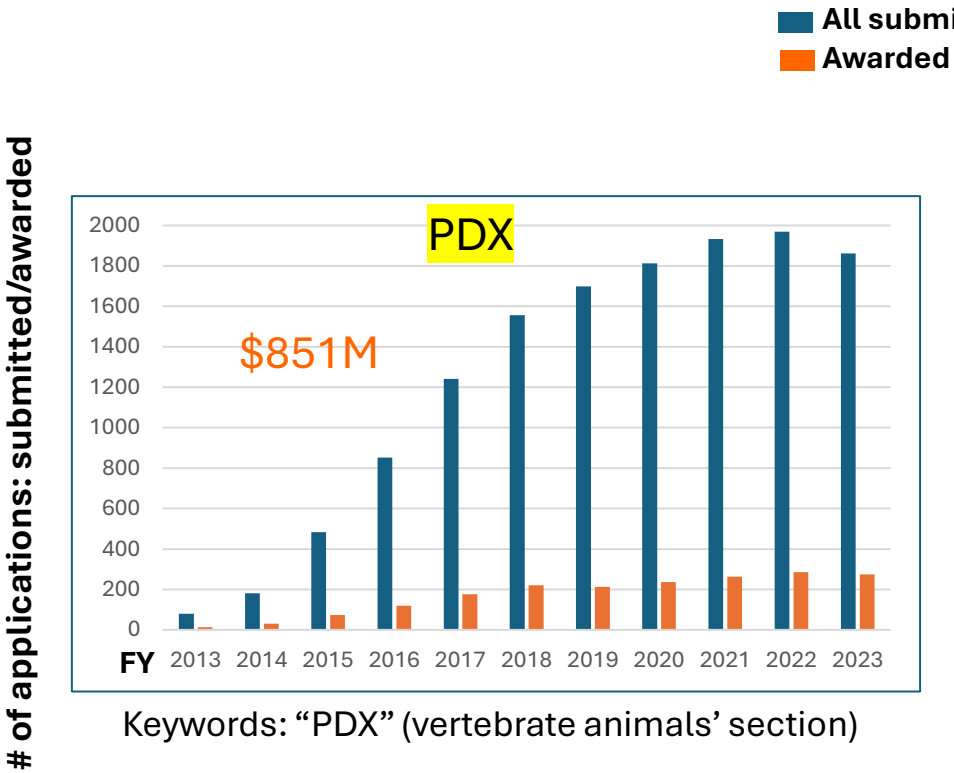
Proposed Cancer ToC PAR
Preclinical efficacy testing
DCTD

Gap

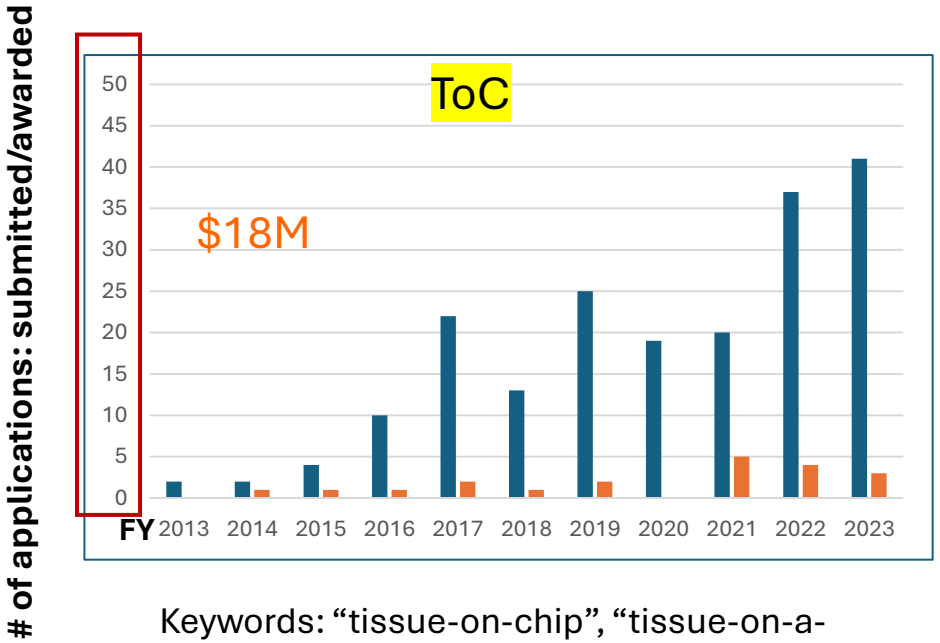
"Clinical Trials" on a Chip, RFA-TR-19-014
Translational Centers for Micro-physiological Systems, RFA-TR-23-001
RFAs - one receipt date only
Tied to existing clinical trails
NCATS

NCATS initiatives funded only 1 UG3/UH3 cancer application

Portfolio Analysis - Other Technologies



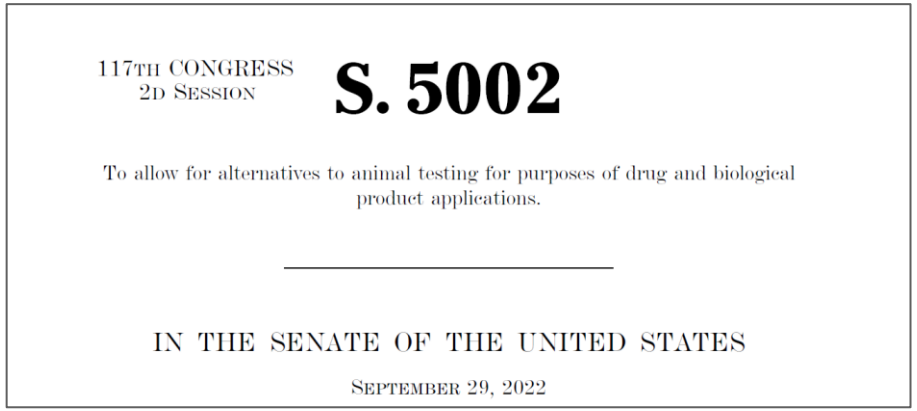
Keywords: “PDX” (vertebrate animals’ section)



Keywords: “tissue-on-chip”, “tissue-on-a-chip”, “organ-on-chip”, “organ-on-a-chip”, "cancer-on-chip", "cancer-on-a-chip" "tumor-on-chip" or "tumor-on-a-chip"

Justification for the PAR

- NCI portfolio analysis shows limited number of ToC-related submitted/awarded applications
- Most of existing NCI applications on ToCs are focused on basic biology mechanistic studies, rather than preclinical drug testing
- Congress-issued FDA modernization Act (2022) and FDA and NIH called for the development of New Alternative Methods (NAMs) to reduce animal testing
- Majority of ToC technologies so far were developed in engineering labs. NCI funding opportunity will enable collaborative efforts with drug developers to strengthen ToC preclinical testing in cancer-adequate environment
- PAR will allow for implementation of Special Review Criteria in NOFO to facilitate focused and adequate review



117TH CONGRESS
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S. 5002

To allow for alternatives to animal testing for purposes of drug and biological product applications.

IN THE SENATE OF THE UNITED STATES

SEPTEMBER 29, 2022

Regulatory Toxicology and Pharmacology 123 (2021) 104953

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journal homepage: www.elsevier.com/locate/yrtph

ELSEVIER

Comprehensive Review

Implementation of the principles of the 3Rs of animal testing at CDER: Past, present and future

Ronald L. Wange *, Paul C. Brown, Karen L. Davis-Bruno

US Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD, USA

Proposed Budget

- This is an new R01 concept, will use the PAR mechanism and will use RPG pool funds
- Expected to start in October 2025 and close in January 2028. Will have 2 receipt dates per year
- We expect around 15-20 submissions per receipt date, 4-6 awards annually

Mechanism	Clinical Trial	Awards	Years of PAR	Direct Costs	Year 1 Total Costs
R01	Not allowed	4-6 per year	3	<500K/year/grant	**$2.0-3.5M**

Thank you!
Questions/comments?

Additional information available in back-up slides below

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www.cancer.gov **www.cancer.gov/espanol**