

# NCAB ad hoc Subcommittee on Experimental Therapeutics

# Briefing: Current Areas of Interest in Experimental Therapeutics

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## 1. New Alternative Methodologies

### a. NCI/NIH efforts toward developing NAMs

- Organoid models of normal tissues (SOM Center)
- In vitro toxicology assays: DCTD Investigative Toxicology Laboratory
- Tumor organoids

## 2. Highlighted Topics to attract grant proposals

# Policy: Reduce animal testing in drug development & prioritize New Alternative Methodologies (NAMs)

FDA NEWS RELEASE

## FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs

For Immediate Release: April 10, 2025

WORKSHOP | IN PERSON

## FDA-NIH Workshop: Reducing Animal Testing

JULY 7, 2025



Regulatory Toxicology and Pharmacology

Volume 139, March 2023, 105345



## Gaps and challenges in nonclinical assessments of pharmaceuticals: An FDA/CDER perspective on considerations for development of new approach methodologies

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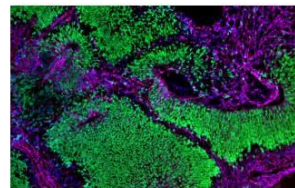
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## NIH Standardized Organoid Modeling (SOM) Center

### Overview

Organoids are small, lab-grown models that mimic the structure and function of human organs and are transforming how researchers study disease and test treatments. Yet most organoid models today are created through trial-and-error, making them difficult to reproduce across labs and slowing their adoption across research and industry. The Standardized Organoid Modeling (SOM) Center will be the nation's first fully integrated platform dedicated to developing standardized organoid-based New Approach Methodologies (NAMs). The initiative is being launched by the NIH Division of Program Coordination, Planning, and Strategic Initiatives, in collaboration with many other NIH Institutes, Centers, and Offices, including the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases' (NIAID) Research Technologies Branch and Center for Human Immunology, Infection and Autoimmunity, the National Human Genome Research Institute



Brain organoid depicting neural stem cells

RESEARCH

Open Access

## Implementing patient derived organoids in functional precision medicine for patients with advanced colorectal cancer



Jérôme Cartry<sup>1\*</sup> , Sabrina Bedja<sup>1</sup>, Alice Boilève<sup>1</sup>, Jacques R. R. Mathieu<sup>1</sup>, Emilie Gontran<sup>1</sup>, Maxime Annereau<sup>2</sup>, Bastien Job<sup>3</sup>, Ali Mouawia<sup>1</sup>, Pierre Mathias<sup>1</sup>, Thierry De Baère<sup>4,5</sup>, Antoine Italiano<sup>6,7</sup>, Benjamin Besse<sup>7,8</sup>, Isabelle Sourrouille<sup>9</sup>, Maximiliano Gelli<sup>1,9</sup>, Mohamed-Amine Bani<sup>10</sup>, Peggy Dartigues<sup>10</sup>, Antoine Hollebecque<sup>6,8</sup>, Cristina Smolenschi<sup>6,8</sup>, Michel Ducreux<sup>1,8</sup>, David Malka<sup>1,8,11</sup> and Fanny Jaulin<sup>1,12\*</sup>

# Policy: Reduce animal testing in drug development & prioritize NAMs

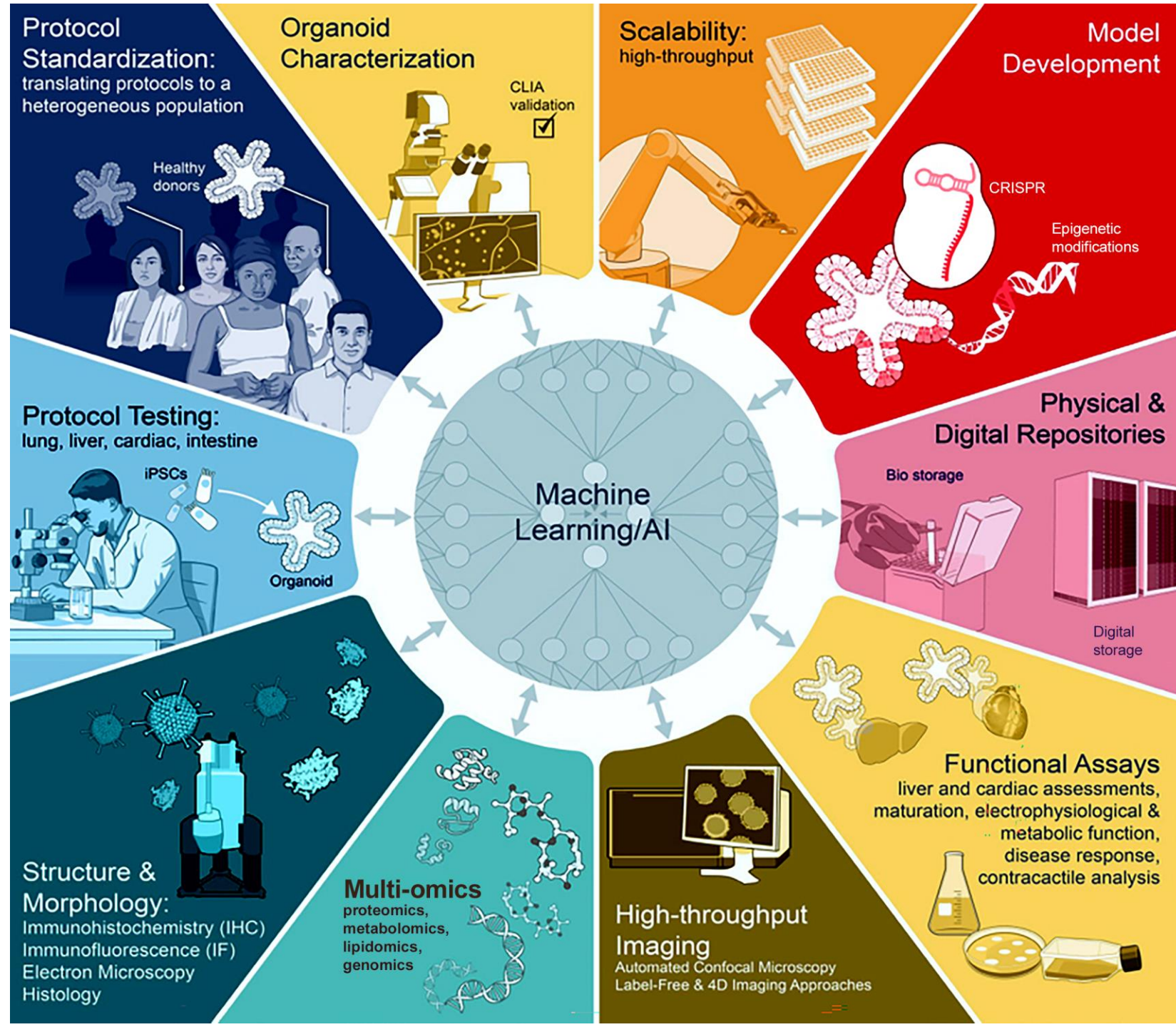
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- In April 2025, the FDA endorses the use of organoid toxicity testing and AI-driven computational models of toxicity and cell lines in pre-clinical research.
- Former FDA Commissioner publicly supports New Alternative Methodologies (NAMs) for pre-clinical testing, coinciding with the FDA's announcement of the Roadmap to Reducing Animal Testing in Preclinical Safety Studies (April 2025).
- Also in April 2025, NIH Director Dr. Jay Bhattacharya highlights NAMs during his Council of Councils address.
- The Physicians Committee for Responsible Medicine submits a letter to Dr. Bhattacharya advocating for innovative non-animal research methods (April 2025).
- The FDA organizes a workshop focused on Reducing Animal Testing in July 2025.
- Dr. Nicole Kleinstreuer, NIH Deputy Director for Program Coordination, Planning, and Strategic Initiatives (DPCPSI), announces that NIH will no longer accept proposals exclusively based on animal models; all new funding opportunities must include language encouraging the consideration of NAMs (July 2025).
- The Standardized Organoid Modeling (SOM) Center is launched at the Frederick National Laboratory for Cancer Research (FNLCR).

# Standardized Organoid Models (SOM) Initiative

## Focus on NORMAL organs/tissues

Establish a National Resource for standardized organoid-based New Approach Methodologies (NAMs), harnessing AI/ML-driven analytics to **deliver robust, reproducible, and patient-centered solutions** transforming drug discovery, disease modeling, and toxicity testing while advancing precision medicine and regulatory science across research and clinical domains.



# The NIH's FFRDC: *Home for SOM Center*

- Established by the National Cancer Act of 1971
- Frederick National Laboratory is **the only FFRDC dedicated solely to biomedical research.**

Frederick National Laboratory



SOM Center Vision and Deliverables: *Standardizing Organoid NAMs to Drive Patient-Centered Innovation, Precision, and Regulatory Confidence*

| Develop                                                                                                                                                     | Deploy                                                                                                                                                    | Establish                                                                                                                                                           | Incorporate                                                                                                                                                | Provide                                                                                                                    | Build                                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| <p>Develop standardized protocols:</p> <p>Create harmonized protocols for over four distinct organoid types to enable reproducible research across labs</p> | <p>AI/ML-informed optimization engine:</p> <p>Deploy AI/ML tools to dynamically refine organoid culture and analysis processes for optimal efficiency</p> | <p>High-throughput robotic production pipelines:</p> <p>Establish automated systems to scale production, reducing human error and increasing output consistency</p> | <p>Integration of Biological Heterogeneity:</p> <p>Incorporate human heterogeneity by standardizing protocols on panels of patient-derived hiPSC lines</p> | <p>Validated NAM for IND filings:</p> <p>Provide NAMs validated for regulatory submissions, streamlining IND processes</p> | <p>National repositories:</p> <p>Build both physical and digital repositories to centralize organoids and related data/protocols</p> |

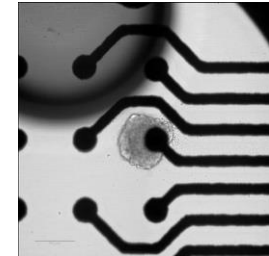
# Safety: In vitro toxicity assays for preclinical evaluation

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## In vitro assessment for cardiovascular safety of candidate drugs

### hiPSC-derived cardiomyocytes (2D)

- General cytotoxicity (morphology, LDH release, Caspase 3/7, troponin)
- Cardiovascular changes (beat rate, spike amplitude, arrhythmia)



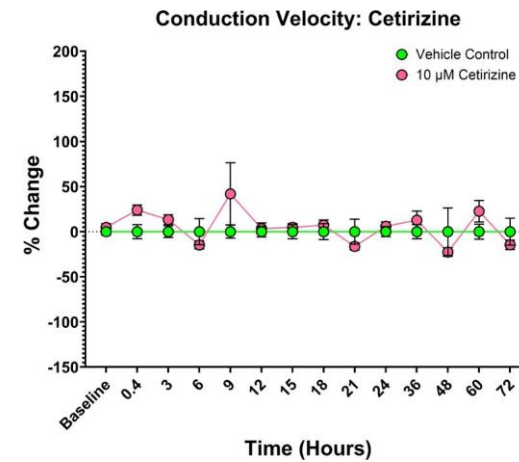
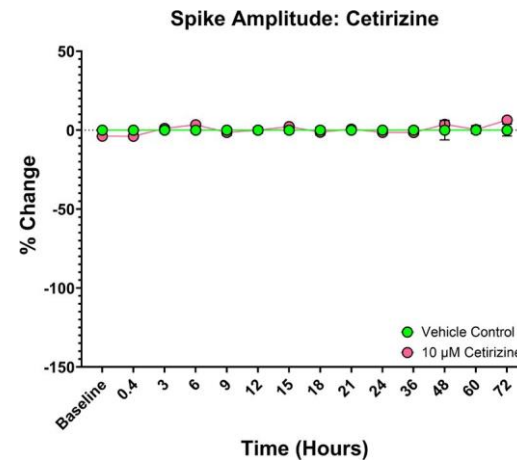
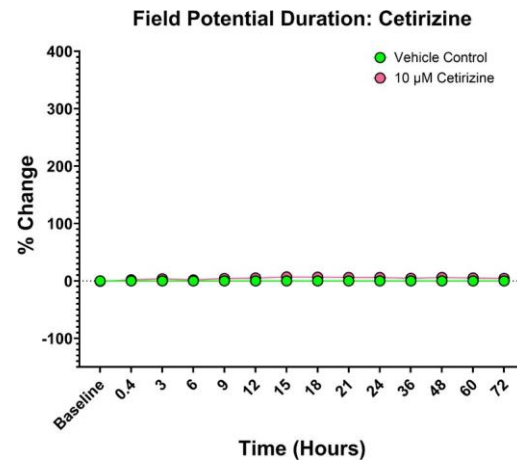
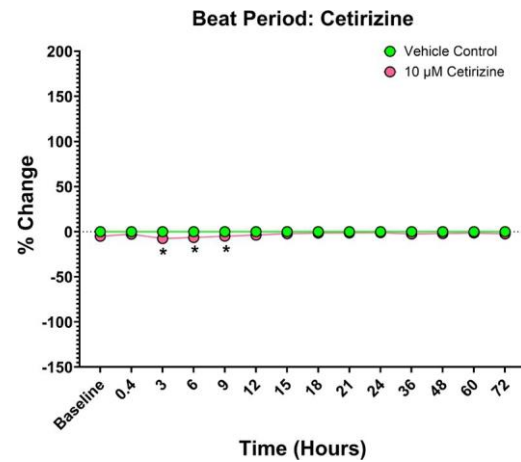
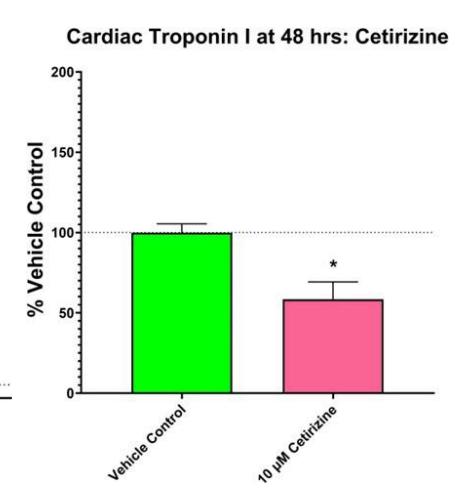
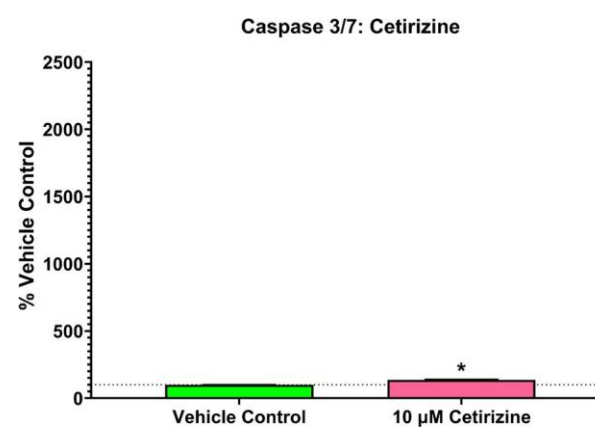
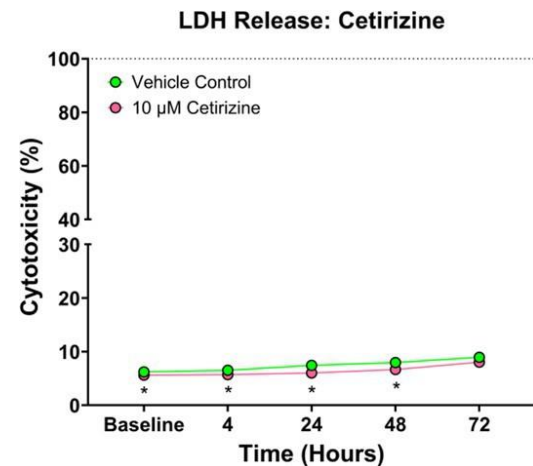
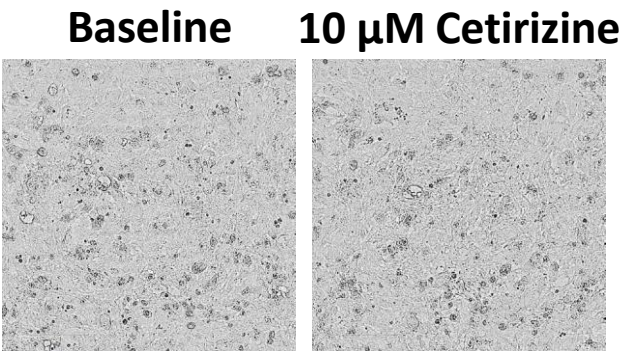
### Cardiac organoids (3D)

- Mixture of hiPSC-cardiomyocytes, hiPSC-cardiac fibroblasts, and hiPSC-endothelial cells

## In vitro assessment of On-Target/Off-Tumor and Off-Tumor/Off-Target toxicity of CAR-T therapies

- hiPSC-Astrocytes
- hiPSC-Cardiomyocytes
- hiPSC-Endothelial cells
- hiPSC-Hepatocytes
- hiPSC-GABAneurons
- hiPSC-Glutaneurons

# Cetirizine: Cardiotoxicity Negative Comparator Compound

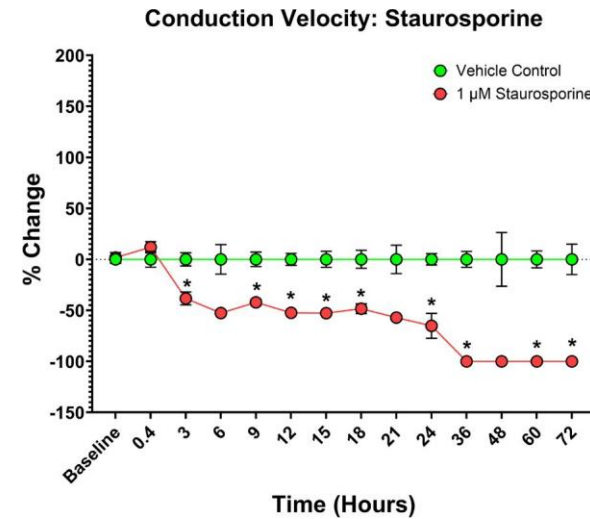
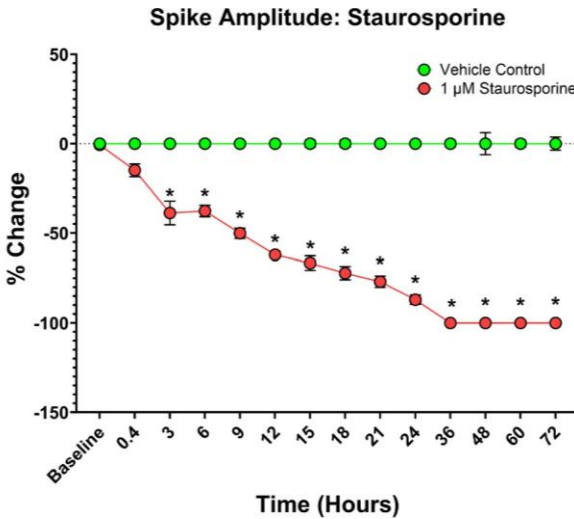
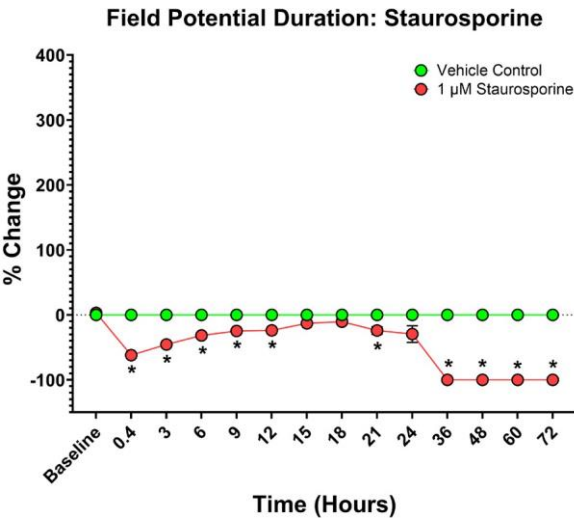
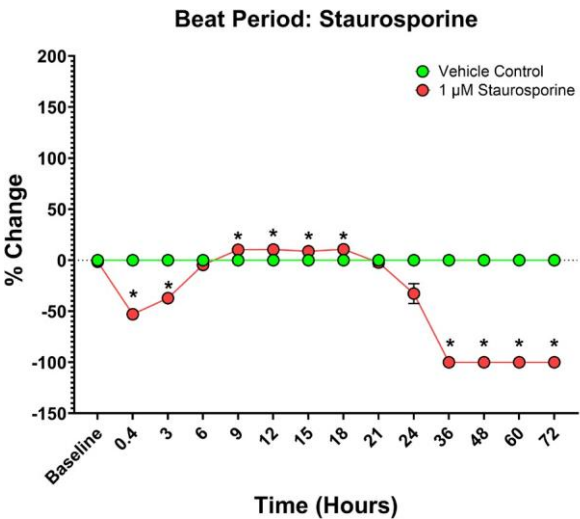
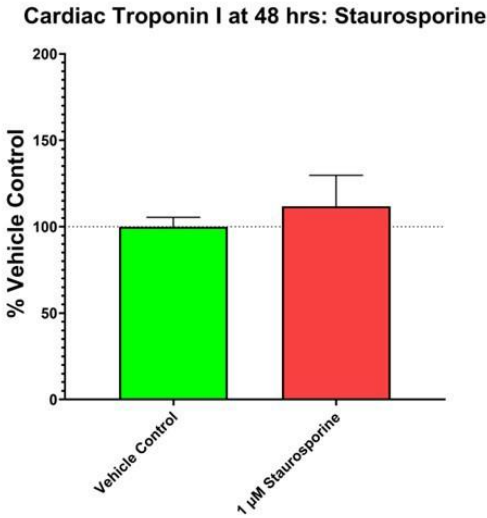
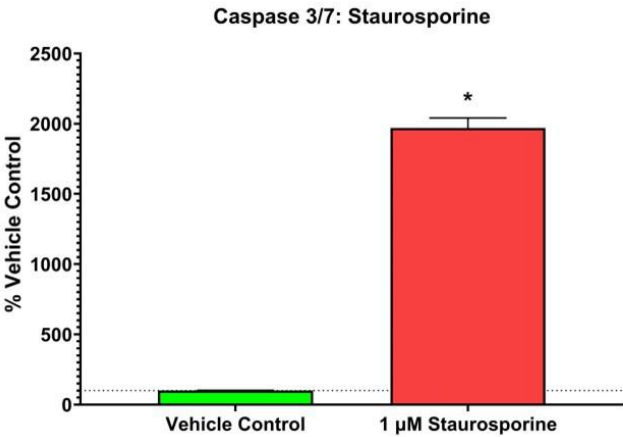
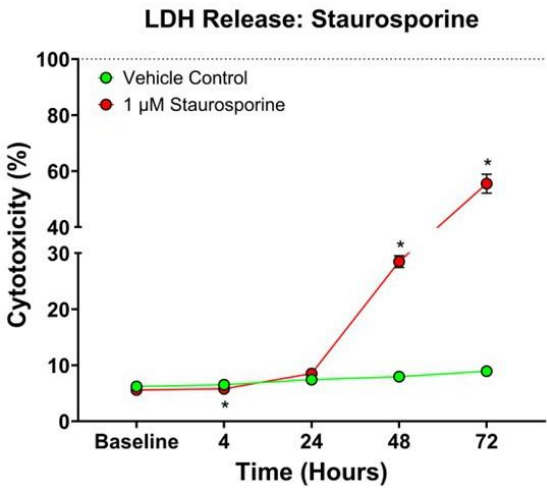
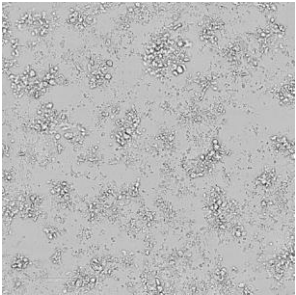
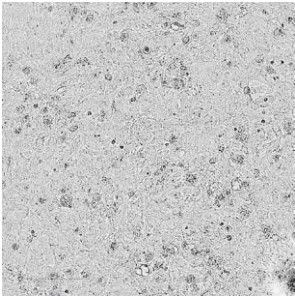


|                       | Baseline | 0.4 HR | 3 HR | 6 HR | 9 HR | 12 HR | 15 HR | 18 HR | 21 HR | 24 HR | 36 HR | 48 HR | 60 HR | 72 HR | Total wells with arrhythmia detected across study |
|-----------------------|----------|--------|------|------|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|---------------------------------------------------|
| Vehicle               | -        | -      | -    | -    | -    | -     | -     | -     | -     | -     | -     | -     | -     | 1/8   | 1/8                                               |
| Cetirizine 10 $\mu$ M | -        | -      | -    | -    | -    | -     | -     | -     | -     | -     | -     | -     | -     | -     | 0/8                                               |

# Staurosporine: Cardiotoxicity Positive Comparator Compound

Baseline

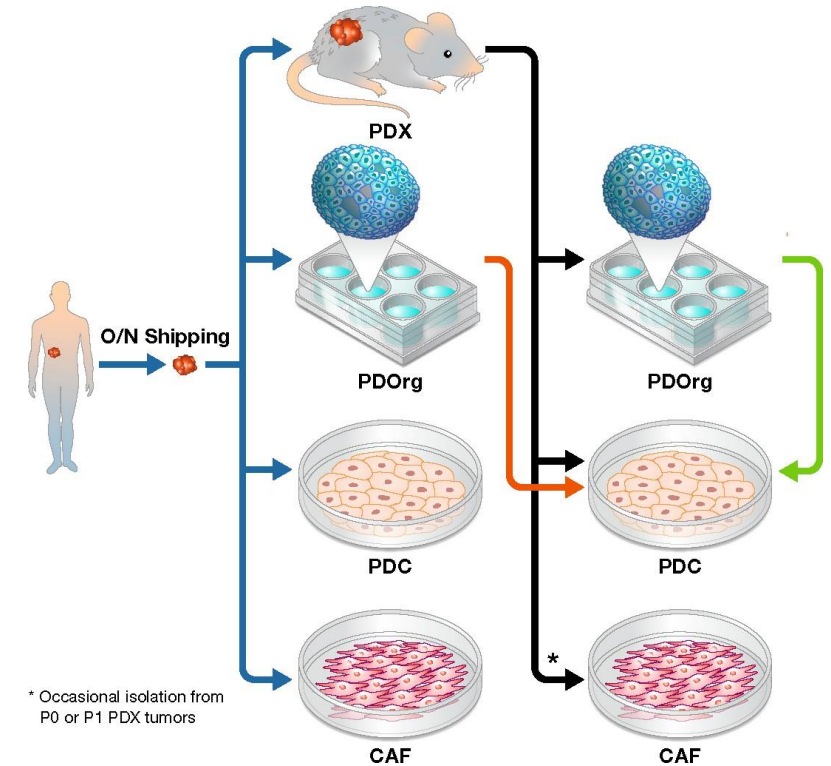
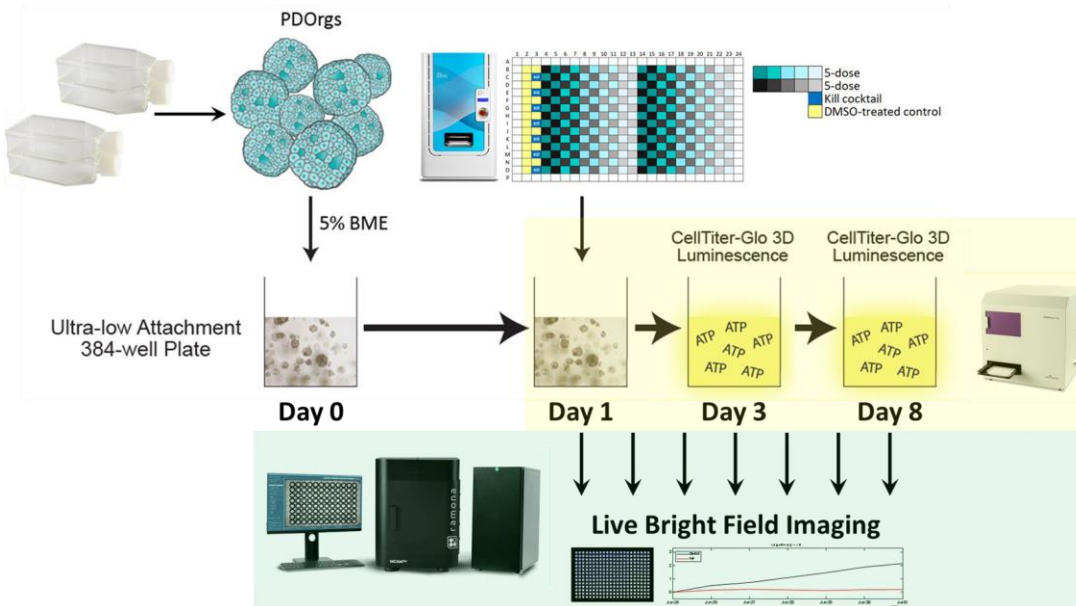
1  $\mu$ M Staurosporine



|                         | Baseline | 0.4 HR | 3 HR | 6 HR | 9 HR | 12 HR | 15 HR | 18 HR | 21 HR | 24 HR | 36 HR | 48 HR | 60 HR | 72 HR | Total wells with arrhythmia detected across study |
|-------------------------|----------|--------|------|------|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|---------------------------------------------------|
| Vehicle                 | -        | -      | -    | -    | -    | -     | -     | -     | -     | -     | -     | -     | -     | 1/8   | 1/8                                               |
| Staurosporine 1 $\mu$ M | -        | -      | -    | -    | -    | -     | -     | 1/8   | 5/8   | 3/8   |       |       |       |       | 6/8                                               |

# Efficacy: Patient-Derived Models & High Throughput Screening of Organoids

- A resource for drug discovery and development
- **Clinically-annotated & early-passage** models with comprehensive **molecular-characterization** and quality control metrics
- Predominantly from solid tumor histologies, both common and rare tumors. Primary and Metastatic lesions. Treatment naïve through heavily pre-treated patient source samples.
- **32 well-characterized colon cancer organoids from the PDMR are ready for HTS screening of novel drugs and drug combinations**



# Novel Alternative Methodologies (NAMs)

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What will it take to fully adopt NAMs?

1. Assay qualification/validation
  1. Reproducible
  2. Robust – assay acceptance criteria (controls, etc)
  3. Representative of human condition (in vivo proof of concept?)
2. Future: All data harnessed to enable AI predictability

## Stimulating research in high-priority areas

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- Grant reviews are consolidated at NIH at the Center for Scientific Review.
- There is a reduction in Notice of Funding Opportunities (NOFO), partly to alleviate the need to convene many Special Emphasis Panels.
- NIH has transitioned to publishing “Highlighted Topics” to inform the research community about priority areas of interest.

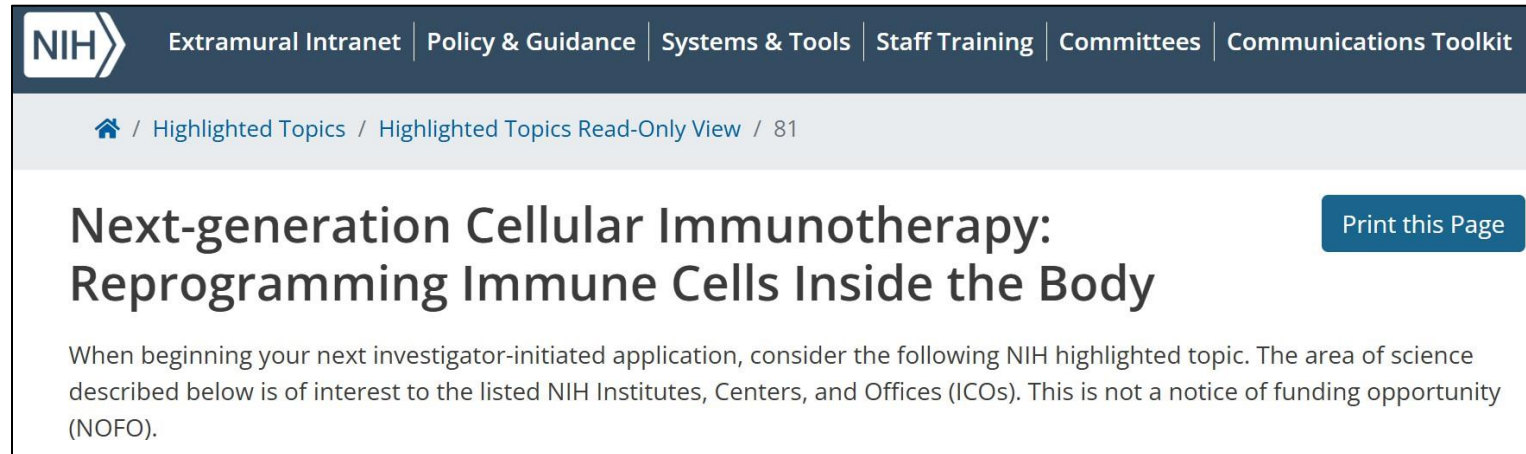
# Highlighted Topics at NIH: <https://grants.nih.gov/funding/find-a-fit-for-your-research/highlighted-topics>

| Bulk Download            | Title                                                                                                                            | Lead ICO | Authored Date ↓ | Shared Interest End Date | Publish Date    | Expiration Date | Status                          |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|--------------------------|-----------------|-----------------|---------------------------------|
| <input type="checkbox"/> | Leveraging Research Resources to Accelerate Innovation and Improve Rigor for Chronic and Comorbid Disease Research and Discovery | NIDDK    | May 25, 2026    | June 8, 2026             |                 |                 | ● Ready for OER Director Review |
| <input type="checkbox"/> | Harnessing Data Science to Address HIV and Co-Occurring Conditions to End the HIV Epidemic in the U.S.                           | NIMH     | May 22, 2026    | June 5, 2026             |                 |                 | ● Ready for OER Director Review |
| <input type="checkbox"/> | Advance the understanding of mechanisms regulating sex differences in response to exercise                                       | NIA      | May 22, 2026    | June 5, 2026             | August 17, 2026 | August 17, 2028 | ● Published                     |
| <input type="checkbox"/> | Building Health through Multidomain Resilience Research from Molecules to Communities: Mechanisms, Measures, and Biomarkers      | NHLBI    | May 21, 2026    | June 4, 2026             |                 |                 | ● Ready for OER Director Review |
| <input type="checkbox"/> | Environmental Contributors to Infertility                                                                                        | NIEHS    | May 19, 2026    | June 2, 2026             | July 20, 2026   | June 11, 2028   | ● Published                     |
| <input type="checkbox"/> | Advanced Biomaterials for Biomedical Research                                                                                    | NCI      | May 15, 2026    | May 29, 2026             |                 |                 | ● Ready for OER Director Review |
| <input type="checkbox"/> | Data Science and Artificial Intelligence Approaches for Biomedical, Biobehavioral and Social Science Research                    | NIDA     | May 14, 2026    | May 28, 2026             | June 25, 2026   | June 25, 2028   | ● Published                     |
| <input type="checkbox"/> | Using Clinical Studies and Human-Based Models to Understand Vaccine Mechanisms Impacting Efficacy and Safety                     | NCATS    | May 11, 2026    | May 25, 2026             | June 3, 2026    | June 3, 2028    | ● Published                     |
| <input type="checkbox"/> | Immune Mechanisms for Disease Prevention                                                                                         | NCI      | May 11, 2026    | May 25, 2026             | August 17, 2026 | August 17, 2028 | ● Published                     |
| <input type="checkbox"/> | Next-generation Cellular Immunotherapy: Reprogramming Immune Cells Inside the Body                                               | NCI      | May 8, 2026     | May 22, 2026             |                 |                 | ● Ready for NIH Director Review |

# Highlighted Topics at NIH: <https://grants.nih.gov/funding/find-a-fit-for-your-research/highlighted-topics>

|                          |                                                                                                               |       |              |              |                 |                 |                               |
|--------------------------|---------------------------------------------------------------------------------------------------------------|-------|--------------|--------------|-----------------|-----------------|-------------------------------|
| <input type="checkbox"/> | Data Science and Artificial Intelligence Approaches for Biomedical, Biobehavioral and Social Science Research | NIDA  | May 14, 2026 | May 28, 2026 | June 25, 2026   | June 25, 2028   | Published                     |
| <input type="checkbox"/> | Using Clinical Studies and Human-Based Models to Understand Vaccine Mechanisms Impacting Efficacy and Safety  | NCATS | May 11, 2026 | May 25, 2026 | June 3, 2026    | June 3, 2028    | Published                     |
| <input type="checkbox"/> | Immune Mechanisms for Disease Prevention                                                                      | NCI   | May 11, 2026 | May 25, 2026 | August 17, 2026 | August 17, 2028 | Published                     |
| <input type="checkbox"/> | Next-generation Cellular Immunotherapy: Reprogramming Immune Cells Inside the Body                            | NCI   | May 8, 2026  | May 22, 2026 |                 |                 | Ready for NIH Director Review |

# Highlighted Topics in Experimental Therapeutics



The screenshot shows the NIH Extramural Intranet interface. At the top is a dark blue navigation bar with the NIH logo and links to 'Extramural Intranet', 'Policy & Guidance', 'Systems & Tools', 'Staff Training', 'Committees', and 'Communications Toolkit'. Below this is a light blue breadcrumb trail: 'Home / Highlighted Topics / Highlighted Topics Read-Only View / 81'. The main content area has a white background. On the left, the title 'Next-generation Cellular Immunotherapy: Reprogramming Immune Cells Inside the Body' is displayed in a large, bold, dark font. To the right of the title is a blue button with white text that says 'Print this Page'. Below the title, a paragraph of text reads: 'When beginning your next investigator-initiated application, consider the following NIH highlighted topic. The area of science described below is of interest to the listed NIH Institutes, Centers, and Offices (ICOs). This is not a notice of funding opportunity (NOFO).'

**Participating ICOs:**  
NIAID, NIAMS, NIBIB,  
NIDCR, ORWH

## NCI emphasis:

- Viral vector-based delivery of DNA fragments carrying tumor-specific CARs, TCRs, costimulatory domains and/or other functional elements
- Nonviral-based delivery using LNPs or other synthetic nanocarriers for mRNA, siRNA and other cargos
- Novel delivery methods such as LNPs, nanocarriers, biodegradable nanomaterials or other delivery vehicles to introduce genetic materials for arming or reprogramming immune cells
- Novel gene editing methods, such as CRISPR/Cas9, base or prime editing, delivered with nanovehicles for genetic editing or epigenetic reprogramming of immune cells
- Preclinical toxicity and safety studies and pilot clinical trials informed by biomarkers
- Combined use with other therapies, such as immune checkpoint blockade or TME-modulating agents

# Pending Highlighted Topics in Experimental Therapeutics

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[Home](#) > [Funding](#) > [Find a Fit for Your Research](#) > [Highlighted Topics](#)

## Advancing Treatment Options using Targeted Degradation Technologies

When beginning your next investigator-initiated application, consider the following NIH highlighted topic. The area of science described below is of interest to the listed NIH Institutes, Centers, and Offices (ICOs). This is not a notice of funding opportunity (NOFO).

- Novel therapeutic approaches to target overexpressed or hyperactivated oncoproteins
- TPD approaches that include PROTACs, LYTACS, and molecular glues
- Improving efficacy, absorption, distribution, metabolism, and toxicity profiles of PROTAC and related drugs using NAMs
- PROTAC linker chemistry
- Expanding these technologies to modulate targets that have not been amenable to traditional drug targeting approaches

# Pending Highlighted Topics in Experimental Therapeutics

## Integrating Immune Aging Research to Improve Therapeutic Outcome

Print this Page

- Quantify immune health status, association with cancer clinical outcomes, & develop immune aging-informed biomarkers
- Advance immune aging biomarker-driven approaches to improve patient stratification & inform clinical decision-making
- Identify immune aging-associated changes at molecular, cellular, tissue, or systemic levels & define how these changes contribute to therapeutic outcomes
- Develop & assess interventions that overcome immune aging-associated changes and/or restore or protect immune health to improve cancer therapy response & mitigate therapy-induced toxicity

### NIA Aged Rodent Colonies

RRID:SCR\_007317

Type: Tool

#### Proper Citation

NIA Aged Rodent Colonies (RRID:SCR\_007317)

#### Resource Information

**URL:** <http://www.nia.nih.gov/research/dab/aged-rodent-colonies-handbook>

**Proper Citation:** NIA Aged Rodent Colonies (RRID:SCR\_007317)

**Description:** Colonies of barrier-raised, Specific Pathogen-Free (SPF) rodents under contractual arrangement with commercial vendors, specifically for use in aging research. They are not available for use as a general source of adult animals for unrelated areas of research. Animals from the NIA aged rodent colonies are available to investigators at academic and non-profit research institutions under the terms described on the Eligibility Criteria page. Orders must be submitted through the online rodent ordering system (ROS) (<http://arc.niapublications.org/acb/stores/1/>). Available strains: \* Inbred Rats: Fischer 344 (F344), Brown Norway (BN) \* Hybrid Rats: F344xBN F1 (F344BN); \* Inbred Mice: BALB/cBy, CBA, C57BL/6, DBA/2 \* Hybrid Mice: CB6F1 (BALB/cBy x C57BL/6), B6D2F1 (C57BL/6 x DBA/2) \* Caloric Restricted Rats: F344 (males only), F344BN F1 (males only) \* Caloric Restricted Mice: C57BL/6; B6D2F1 (males only)

# Pending Highlighted Topics in Experimental Therapeutics

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## Natural Product Discovery and Development for Disease Prevention, Interception and Treatment

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### Plant Extract Library



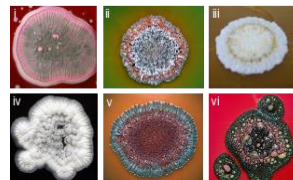
- ~161,000 extracts (organic + aqueous)
- ~44,000 plants, including 81,400 raw materials (leaves, roots, fruit, etc.) collected from Africa and Madagascar, North, Central and South America; and Southeast Asia.

### Marine Extract Library



- ~41,000 extracts (organic + aqueous)
- ~20,500 organisms collected from the Indo-Pacific region.

### Microbial Extract Library



- ~30,000 extracts (organic + aqueous)
- ~16,000 organisms:
  - 4,160 unique genus and species
  - 7,600 unknown organisms

### NCI Natural Products Library

Over 70 collaborations to date

In 2025: 846,912 samples shipped

10,829 sub-fractionated fractions shipped

8,281 1H NMR & 9,624 LCMS experiments

133 purified compounds shipped

# Discussion

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1. NAMs: Opportunities and next steps
2. Recommendations for Highlighted Topics

# With thanks.....

## DTP, DCTD, NCI

Christophe Marchand, PhD

Bev Teicher, PhD

Liz Glaze, PhD

Melinda Hollingshead, DVM, PhD

Sergio Alcoser, PhD

Barry O'Keefe, PhD

Tanja Grkovic, PhD

Sundar Venkatachalam, PhD

Weiwei Chen, PhD

Jennifer Fox, PhD

Zhangzhi Hu, MD

Connie Sommers, PhD

Marco Cardone, PhD

Anju Singh, PhD

Kasia Bourcier, PhD

## SOM Center

Jim Cherry, PhD, NIAID

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## FNLCR Investigative Toxicology Lab

Shari Price, PhD

Krista Zindel, PhD

Su Jeong Lee, PhD

## FNLCR Molecular Pharmacology Lab

Nathan Coussens, PhD

Tom Dexheimer, PhD

Eric Jones

## FNLCR PDMR

Yvonne Evrard, PhD

Dianne Newton, PhD



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