

# NCATS' Roles in NIH HEAL Initiative

Christine Colvis, Ph.D.

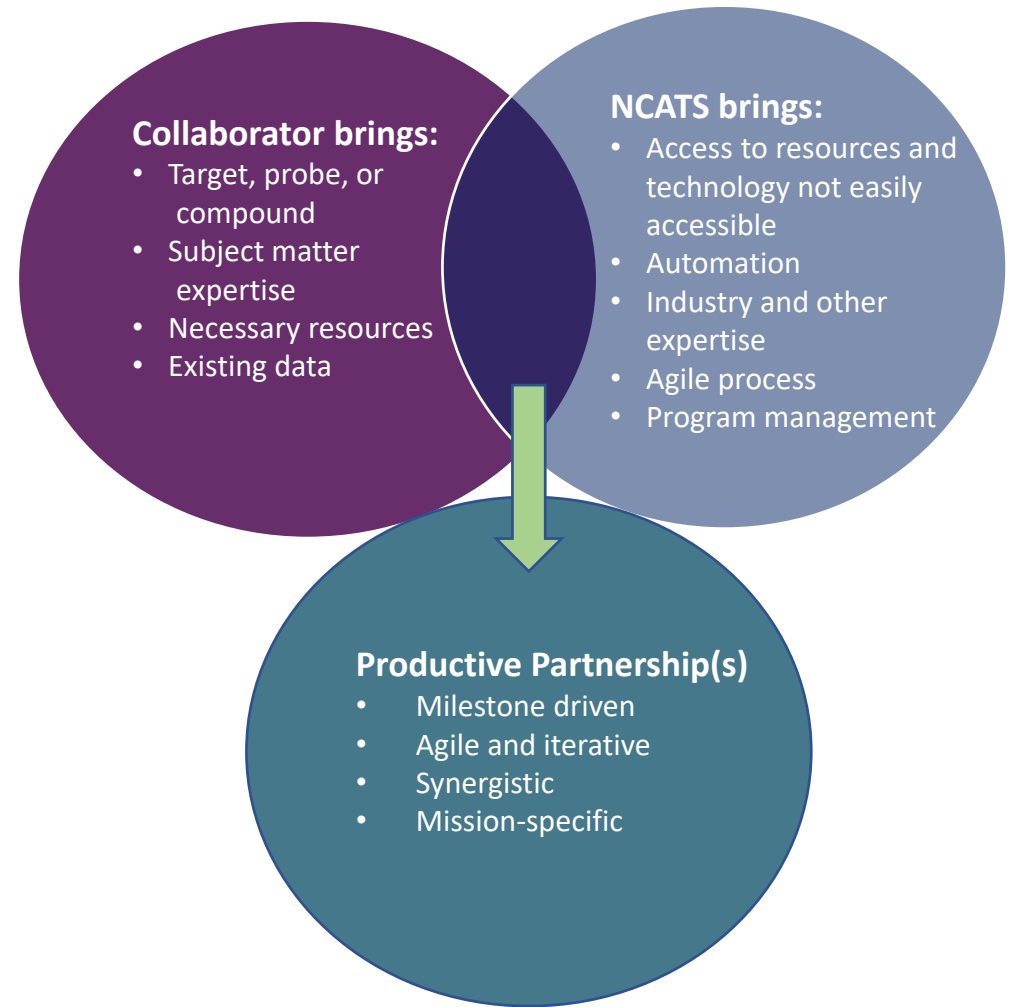


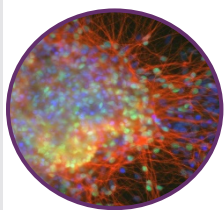


# NCATS Intramural Research Program in the HEAL Initiative: Developing Human-based Testing Platforms and Novel Drugs for Pain, Addiction, and Overdose

[NOT-TR-19-018](#) *NCATS is accepting pre-proposal applications!*

Mission: Speed and facilitate the development of new treatments  
for pain, opioid misuse and opioid overdose

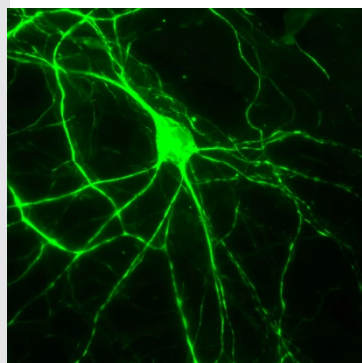




# Human iPSC-Derived Neurons for Pain and Reward Pathways

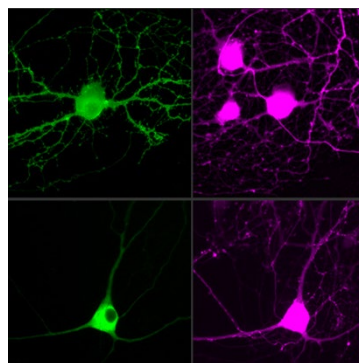
Collaborators can work with NCATS Stem Cell Translation Lab to develop iPSC-derived cellular platforms for improved prediction of *in vivo* human effects of lead compounds

## Capabilities:



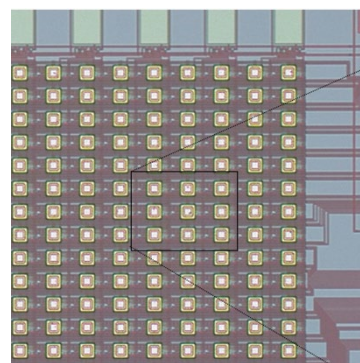
Access to relevant human cell types

*Sensory neurons (nociceptors) and other neuronal subtypes*



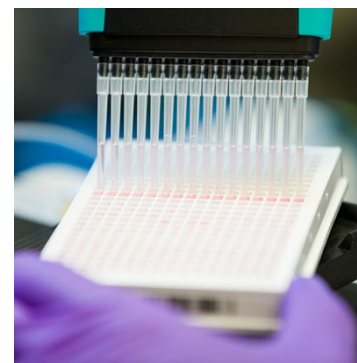
Advanced imaging technologies for functional cell characterization

*High-content confocal, calcium imaging, optogenetics*



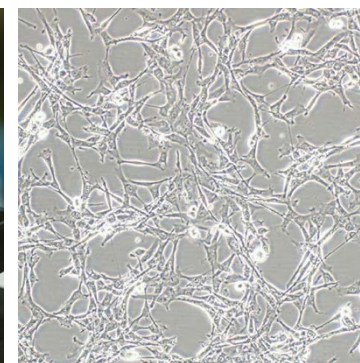
High-throughput electrophysiology methods

*High-density multi-electrode arrays  
26,400 electrodes/well*



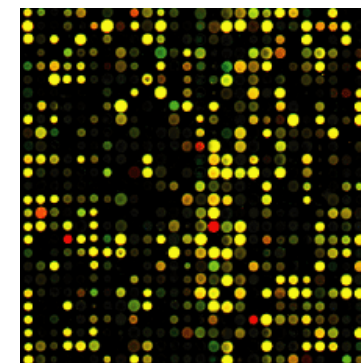
Measurement of signaling pathways, metabolism & specific targets

*Cyclic AMP, PKA activity, CREB phosphorylation, energy metabolism*



Longitudinal tracking of cell behavior

*Multiple measurements over days, weeks or months*



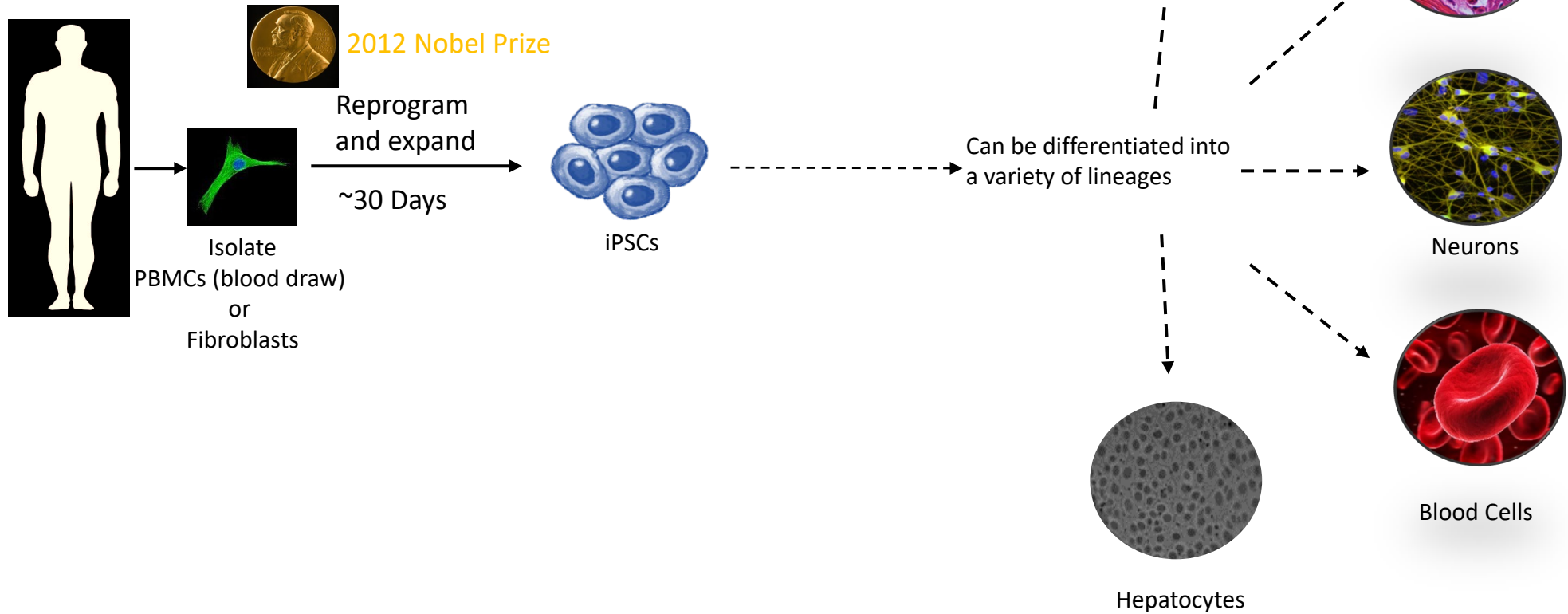
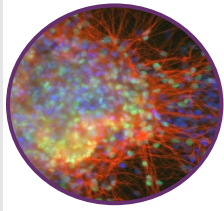
Combined single-cell transcriptomic & proteomic analyses

*Drug response in individual nociceptors and other neuronal phenotypes*

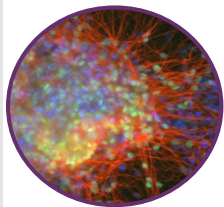


National Center  
for Advancing  
Translational Sciences

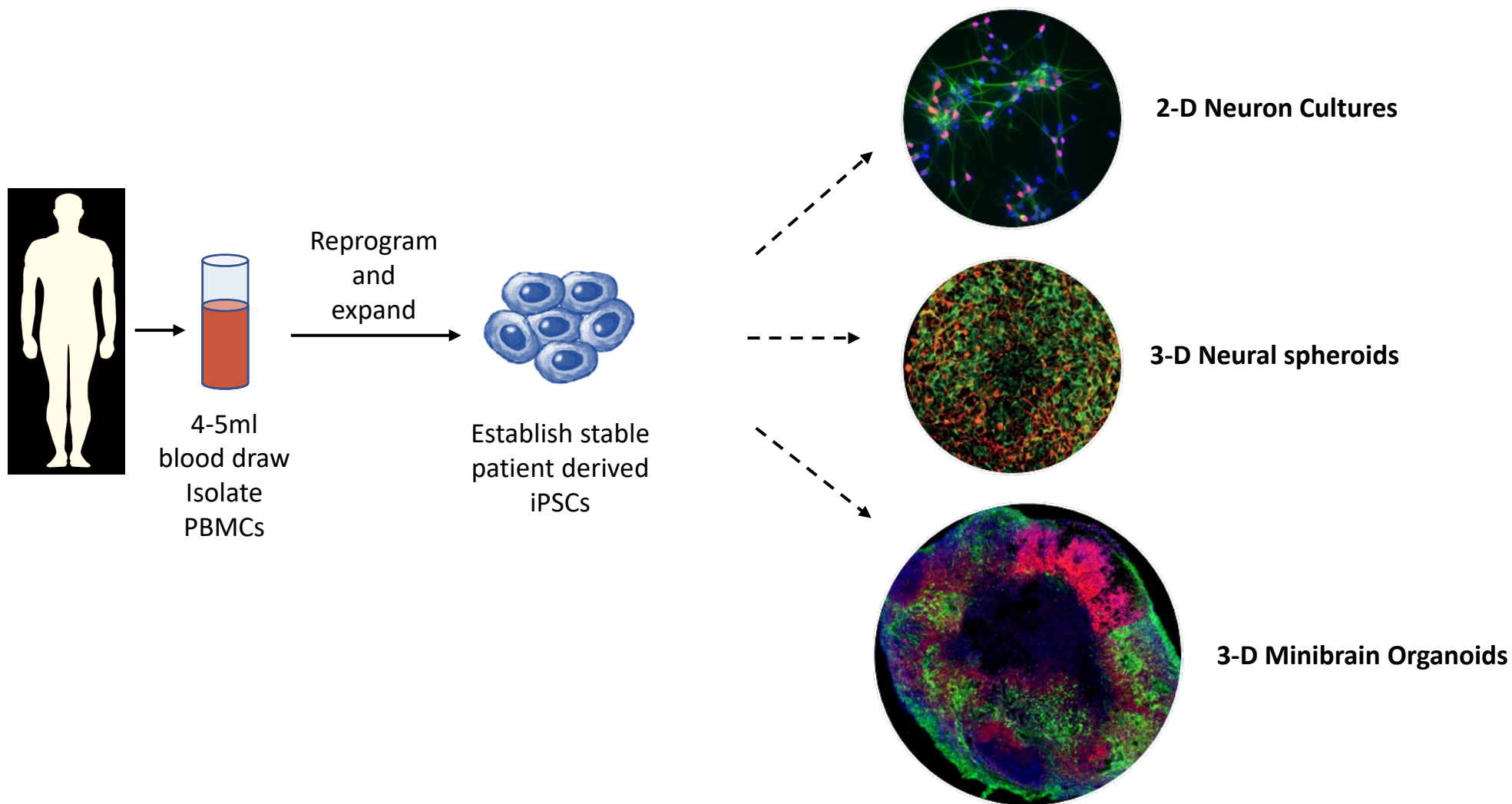
# Induced Pluripotent Stem Cells (iPSCs)



National Center  
for Advancing  
Translational Sciences

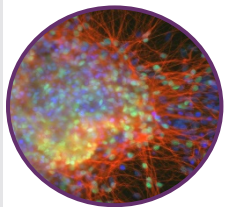


# Generation of Human iPSCs for the NIH HEAL Initiative

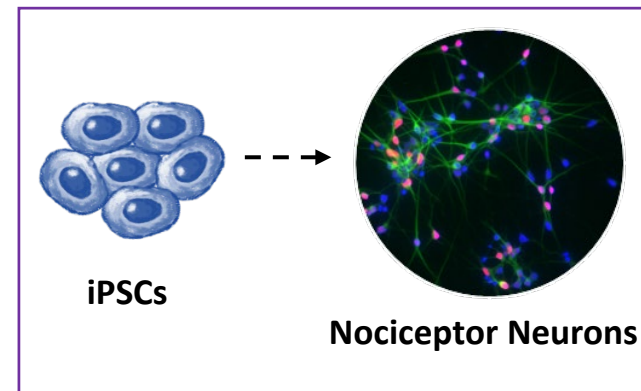


National Center  
for Advancing  
Translational Sciences

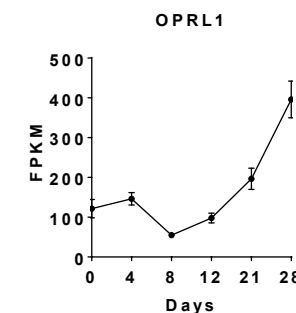
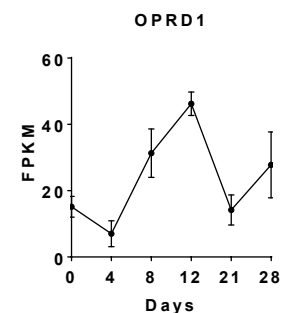
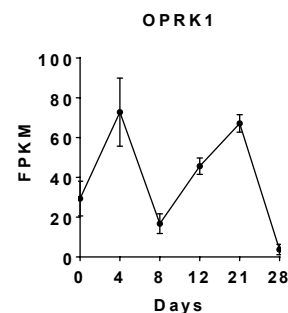
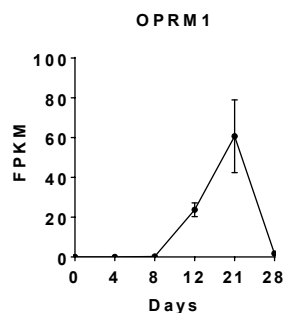
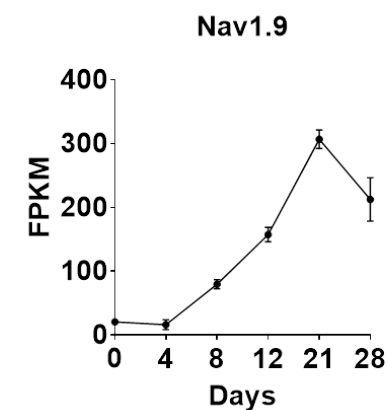
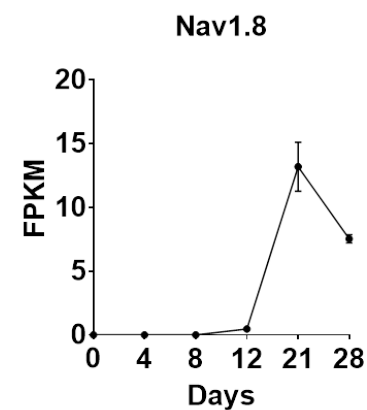
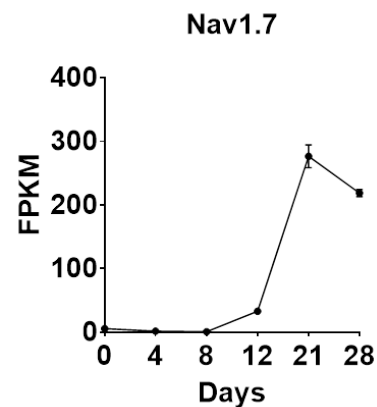
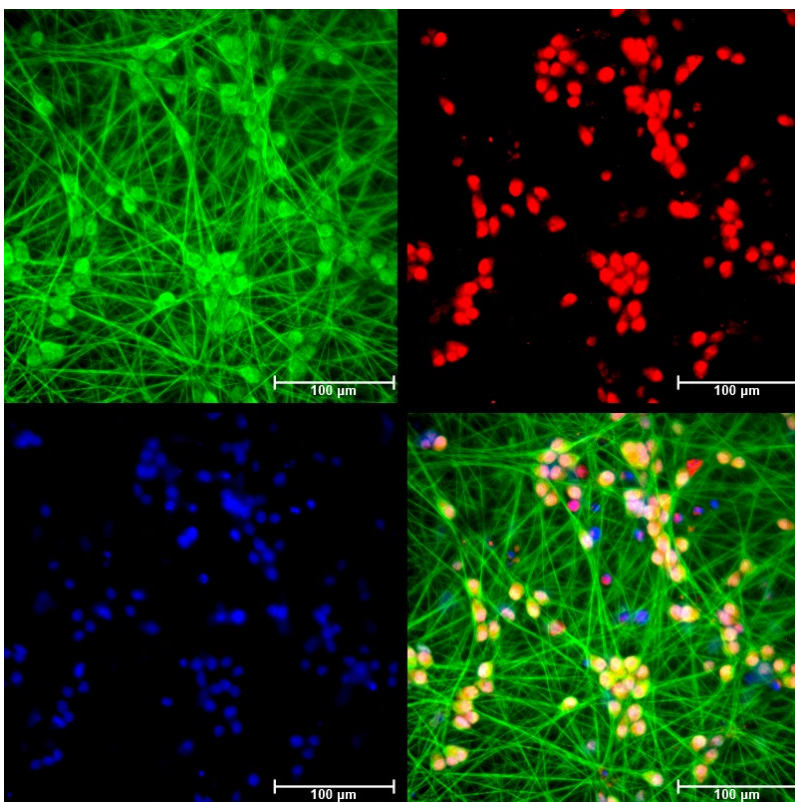




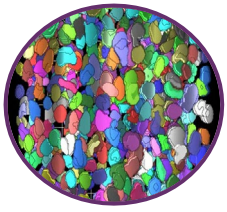
# Highly Efficient Human Nociceptor Differentiation Protocol



NF200/BRN3A/DNA



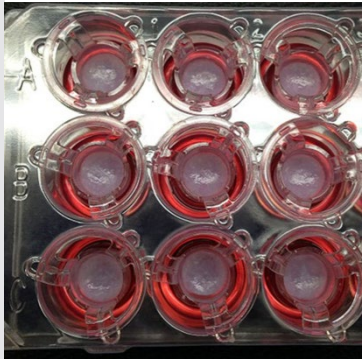
National Center  
for Advancing  
Translational Sciences



# 3-D Bioprinted Tissue Models

Collaborators can work with NCATS 3-D Biofabrication Laboratory to biofabricate multicellular functional tissues using human primary or iPSC-derived cells that are better models of human disease state and response to new drugs

## Capabilities



**Tissue engineering technologies**

*Development of tissues-in-a-well*



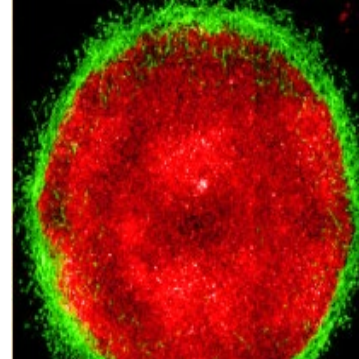
**Automated production of iPS cell-derived cells**

*To reproducibly scale up production of human tissue relevant cells*

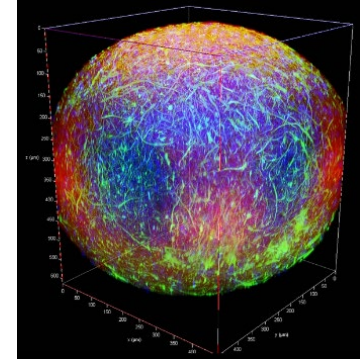


**3D bioprinters**

*To create spatial cellular patterns in tissues, e.g., neuronal circuits, neurovascular unit, innervated tissues*

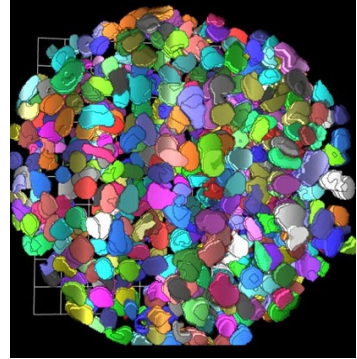


**Spatially defined and physiologically relevant tissue models**



**Validation of 3D organoid cultures**

*Neural spheroids for compound screening*



**Assays using 3D tissue models**

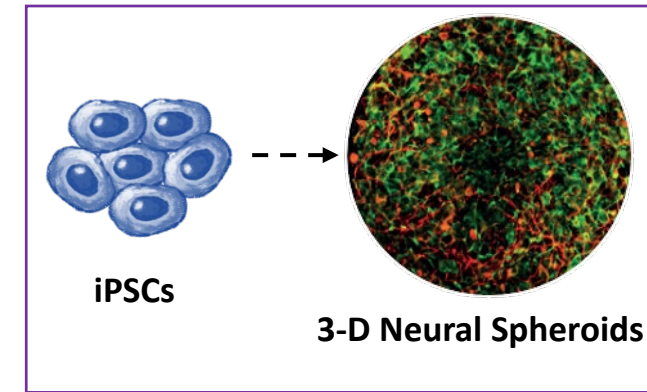
*High-content confocal, calcium imaging, optogenetics, multielectrode arrays, neurotransmitters biosensors*



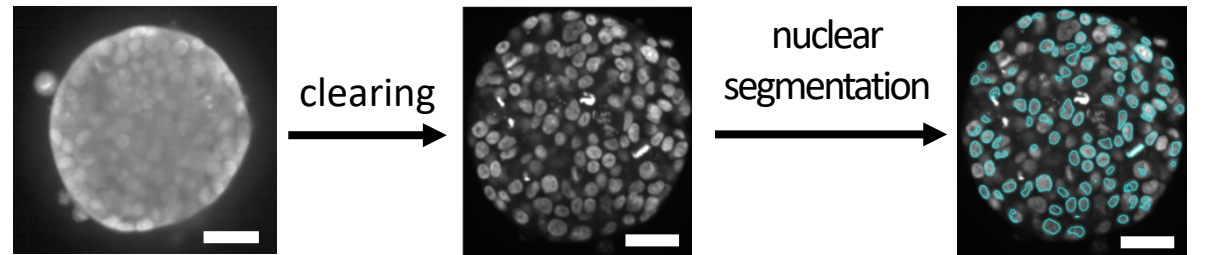
National Center  
for Advancing  
Translational Sciences



# Development of high-throughput tissue clearing protocols for high-content, image and functional activity analyses in human iPSC-derived neural spheroids

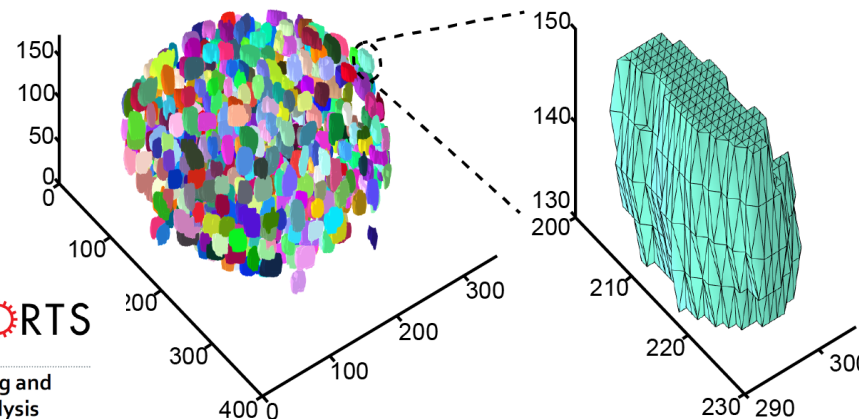


Clearing can be used to improve 3D tissue visualization and analysis



3D view of segmented nuclei

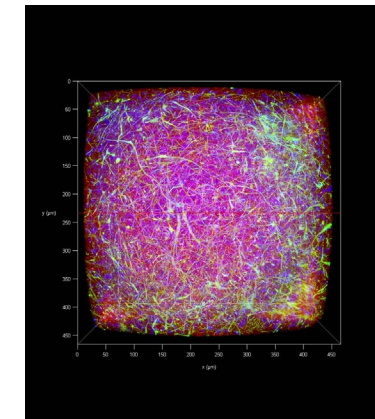
Single nuclei



Boutin, et al, Sci Rep, 2018

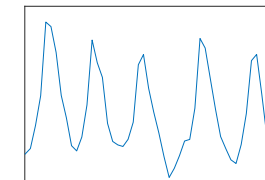
Application of clearing to iPSC-derived neural spheroids

neurons astrocytes nuclei

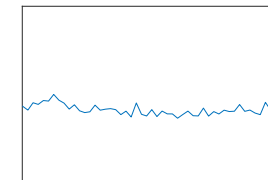


Functional imaging of spontaneous and synchronized calcium oscillations in iPSC-derived neural spheroids:

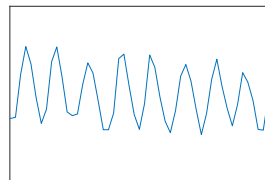
Untreated



Compound 1



Compound 2



National Center  
for Advancing  
Translational Sciences

SCIENTIFIC REPORTS

OPEN

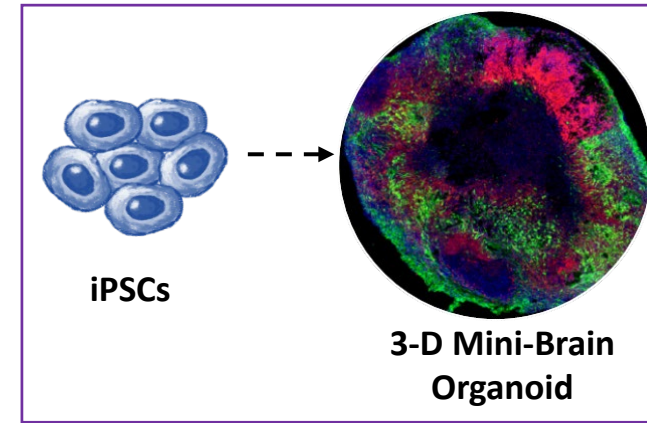
A high-throughput imaging and  
nuclear segmentation analysis  
protocol for cleared 3D culture  
models

Received: 19 January 2018  
Accepted: 6 July 2018  
Published online: 24 July 2018

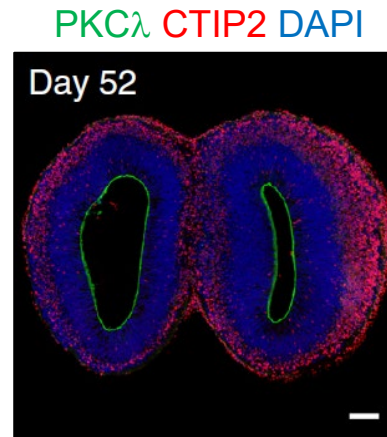
Molly E. Boutin, Ty C. Voss, Steven A. Titus, Kenzie Cruz-Gutierrez, Sam Michael & Marc Ferrer



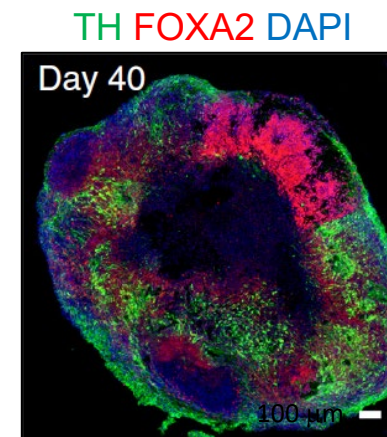
# Human iPSC-Derived Advanced Brain Organoid Models



iPSCs → Differentiation, embryoid body formation, further maturation under agitation/stirring →



Forebrain Organoid



Midbrain Organoid

- ✓ 3-Dimensional
- ✓ *In vivo* architecture
- ✓ Cell-identity

Protocol adapted from Qian et al., Nature Prot. 2018; Cell 2016



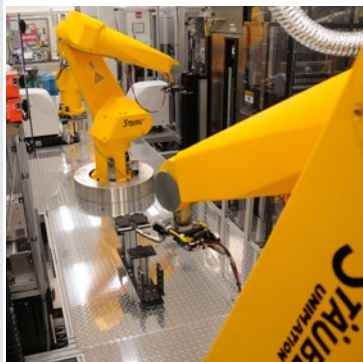
National Center  
for Advancing  
Translational Sciences



# Development of Pharmacological Probes for Novel Targets

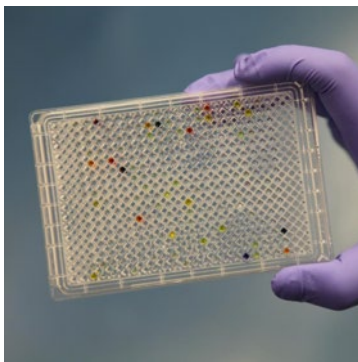
Access NCATS resources and expertise in assay development and quantitative high-throughput screening to identify promising compounds to modulate novel targets; optimize compound properties to probe novel targets.

## Capabilities



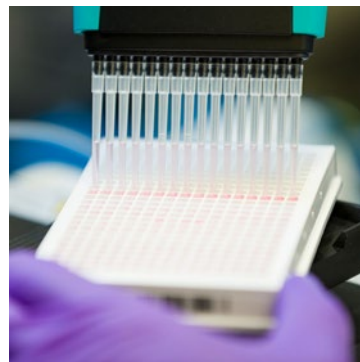
### HTS assay adaptation, development

*GPCR and ion channel assays and high-content image-based assays*



### Drug repurposing libraries

*All FDA approved compounds (>2,400), as well as >150,000 in annotated/diversity collections, HEAL-focused library*



### Counterscreen & confirmatory assays



### Cheminformatics platforms

*Molecular modeling and docking, Machine learning, High content image analysis*



### Medicinal chemistry

*Largest medicinal chemistry program at NIH, > 30 fume hoods, > 20,000 molecules made*



### ADMET Assays

*Aqueous kinetic solubility, rodent & human liver microsomal stability & PAMPA permeability*



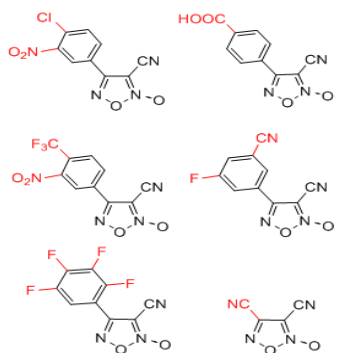
National Center  
for Advancing  
Translational Sciences



# Development of Investigational Drugs Ready for Clinical Testing

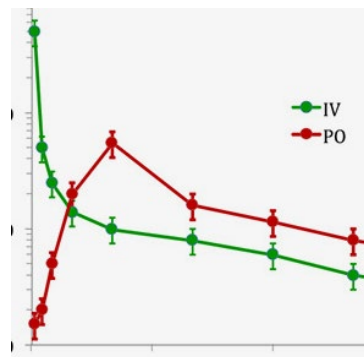
Joint project teams develop prototype therapeutics into IND-enabled small molecules, biologics, and gene and cell therapies ready for clinical testing.

## Capabilities

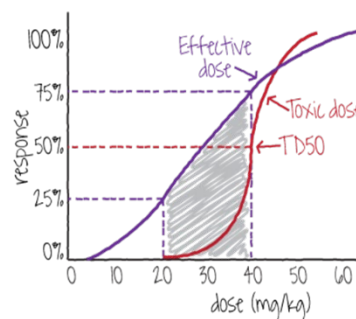


Target validation  
and lead  
optimization

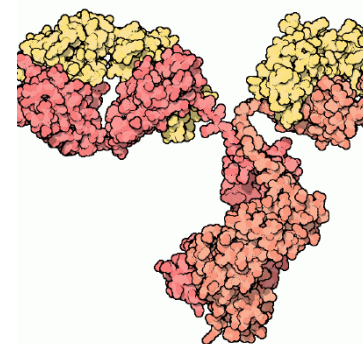
*To finalize declaration  
of clinical candidates*



Pharmacokinetics/  
pharmacodynamics



GLP safety  
evaluation and  
toxicology



Therapeutic  
modality expertise

*Including small  
molecules, biologics  
and gene and cell  
therapies*



GMP  
manufacturing  
and formulation

*To scale up the  
production of the  
compound for clinical  
testing*

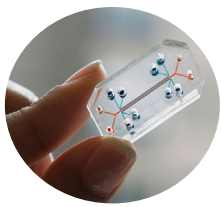


Repurposing of  
approved  
therapies



National Center  
for Advancing  
Translational Sciences

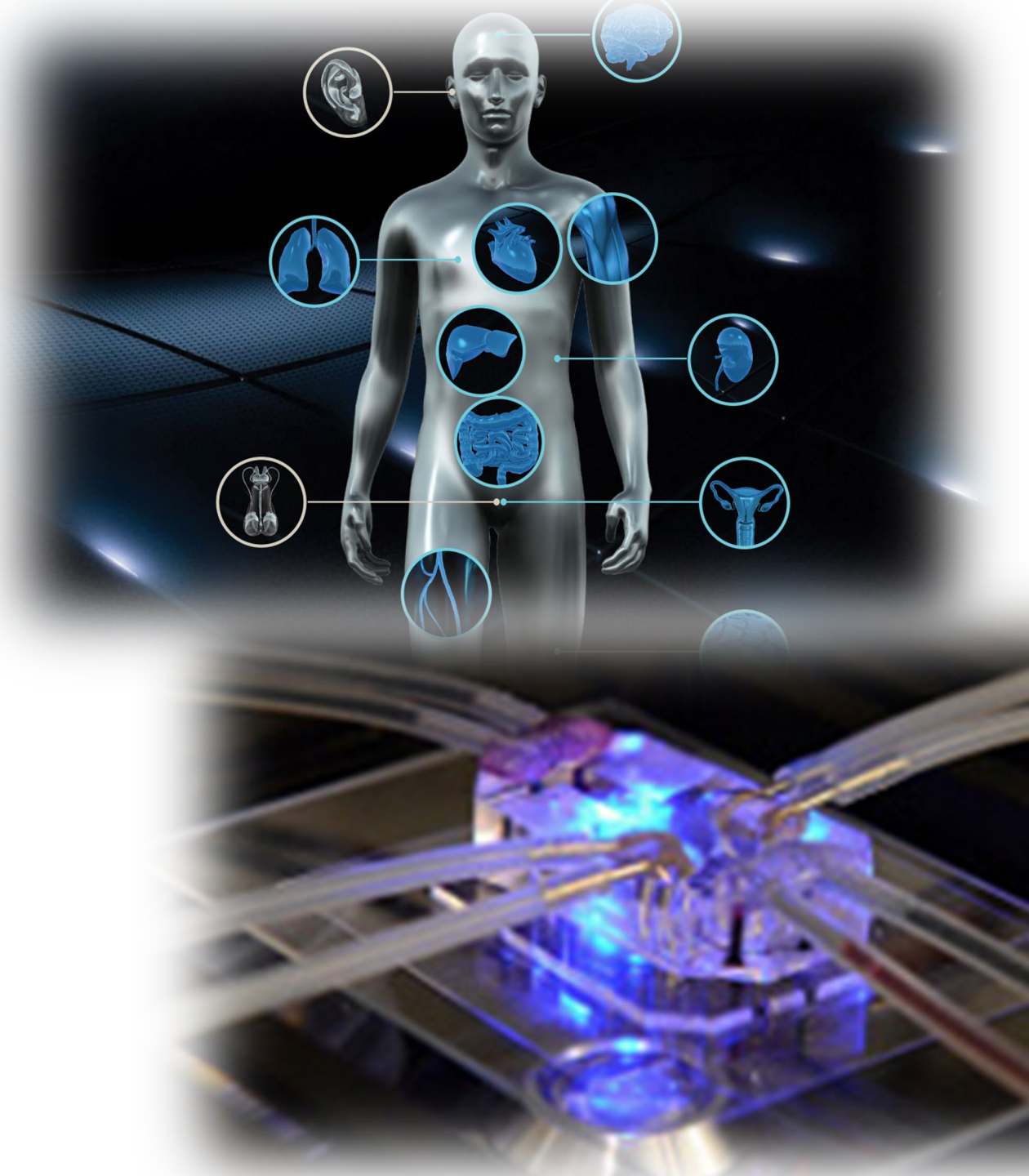




# Tissue Chip

RFA TR-19-003

The goal of this FOA is to promote the development of in vitro microphysiological systems to model human nervous and non-nervous tissues that recapitulate the mechanisms or effects of nociception/pain-relevant signaling, addiction, or opioid use disorders (OUDs), and/or their respective therapies and treatments.



National Center  
for Advancing  
Translational Sciences