NCATS

COLLABORATE. INNOVATE. ACCELERATE.

Advancing Drug Discovery For Fibrotic Diseases using 3D Tissue Models: 3D-MOFIB TDC

Marc Ferrer
Director
NCATS 3D Tissue Bioprinting Laboratory

ICCVAM Public Forum

29 July 2026

National Center for Advancing Translational Sciences

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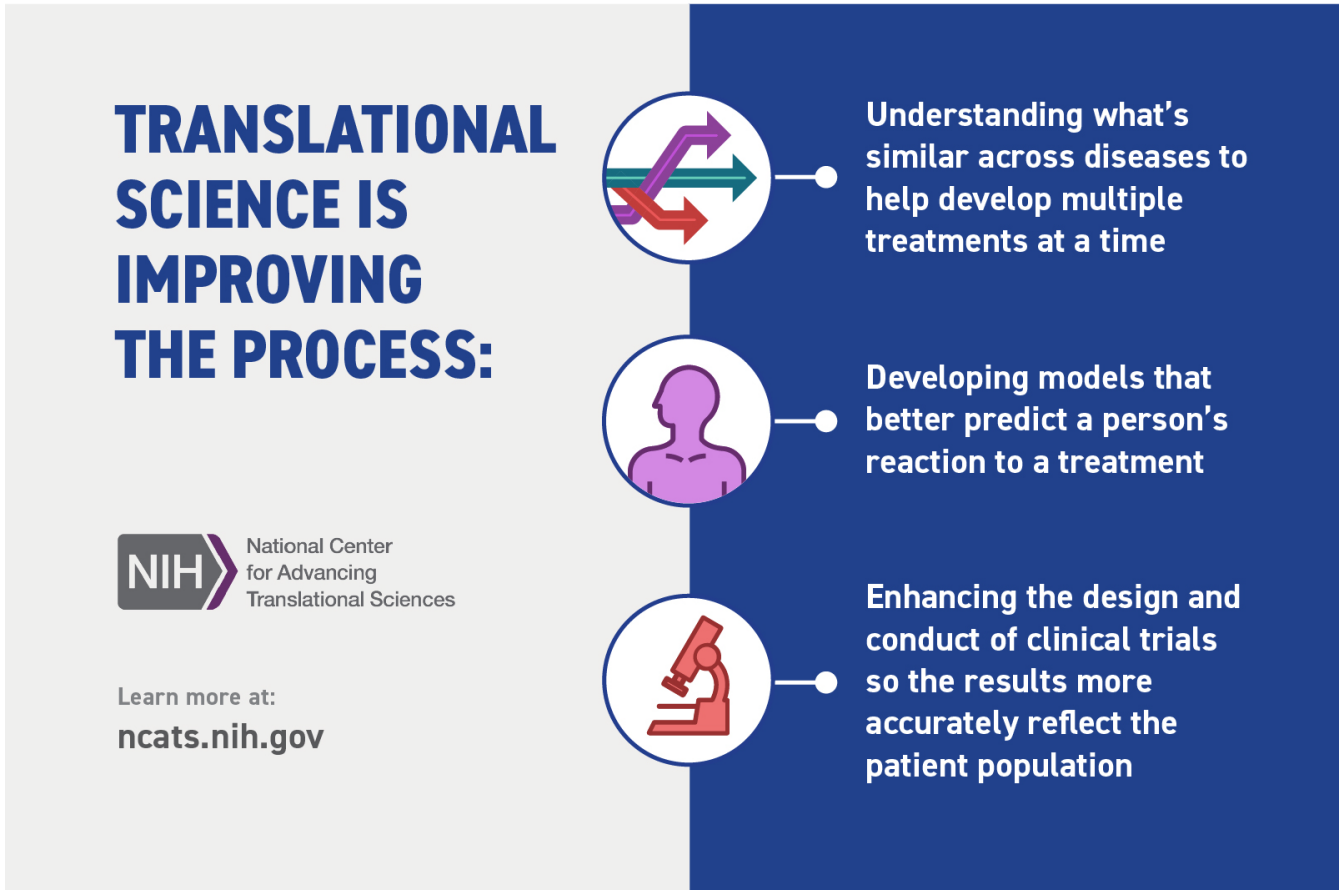
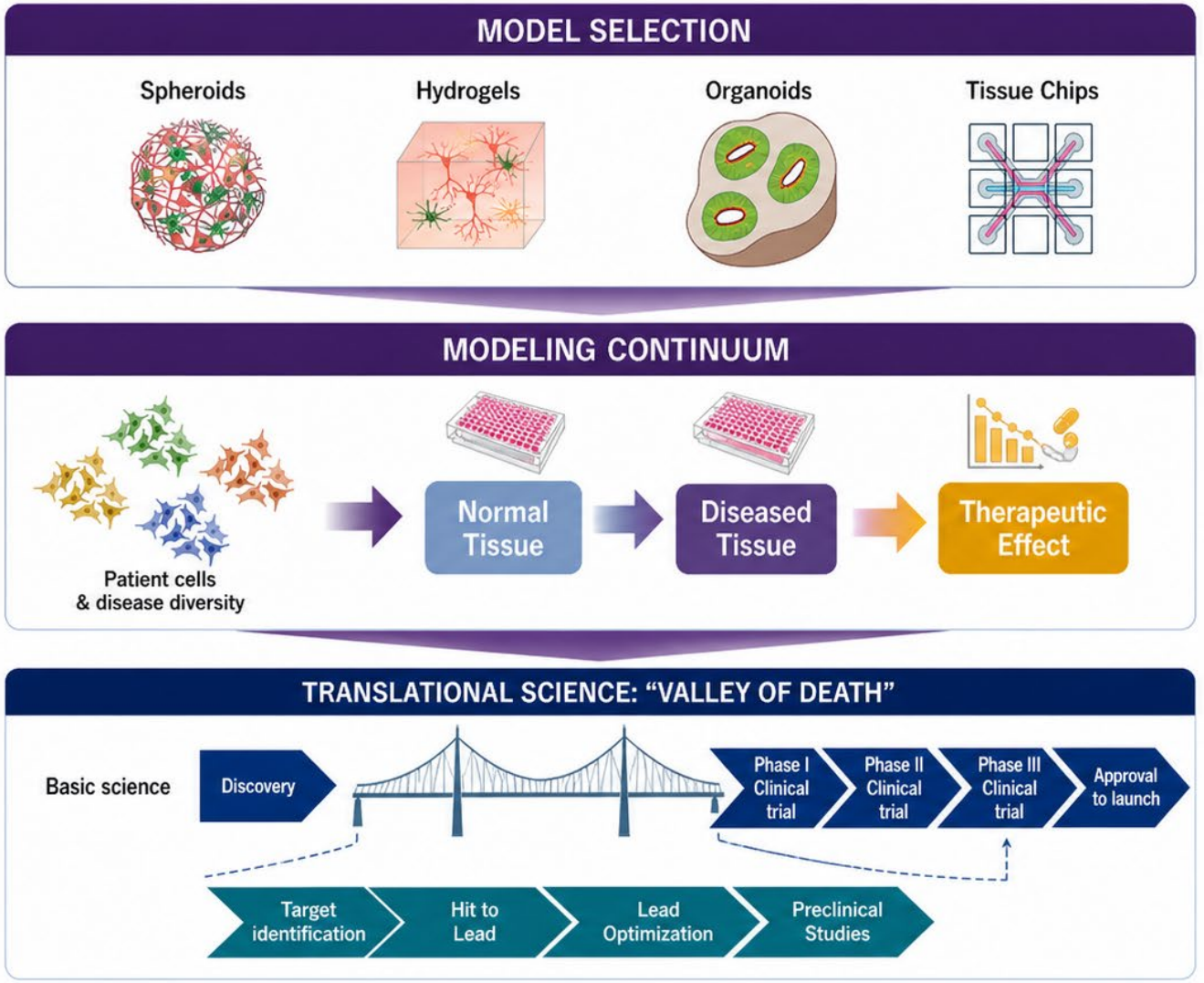
Disease agnostic, technology enabling organization to accelerate the development of new therapies for all patients



NIH
National Center for Advancing Translational Sciences

NCATS 3D Tissue Bioprinting Laboratory

3D “Tissues in a well” to advance New Approach Methodologies (NAMs) as pharmacology and toxicology drug discovery tools



- Define clear **context of use**
- Use a **“Fit for purpose”** approach: **as complex as needed, as simple as possible**
- Demonstrate **predictive performance**

- Biological and physiological validation: **rigorous analysis with harmonized standards**
- Quantitative **functional endpoints** guided by **clinical biomarkers** of physiology and pathology
- **Pharmacological validation**
- Operationalization for HTS as **robust and reliable assays**

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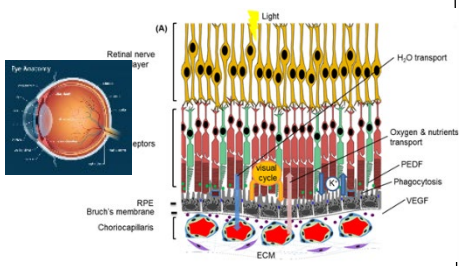
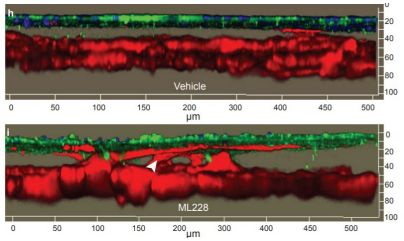
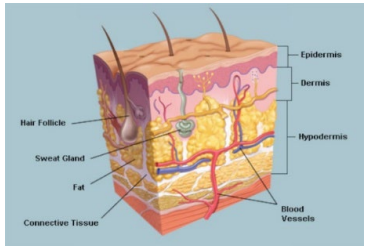
NCATS 3DTBL portfolio of engineered 3D tissue models

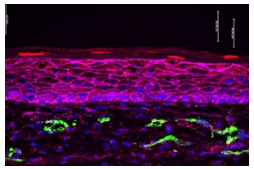
Retina



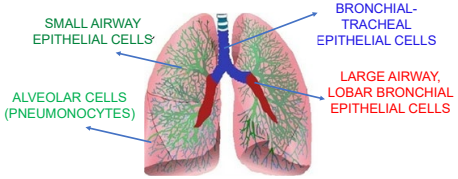


Skin

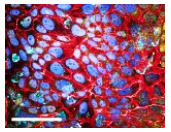




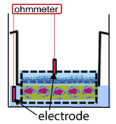
Lung



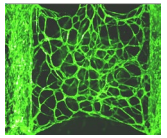
epithelium



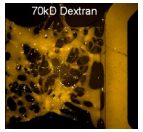
barrier function



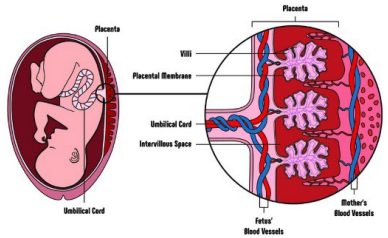
microvessel

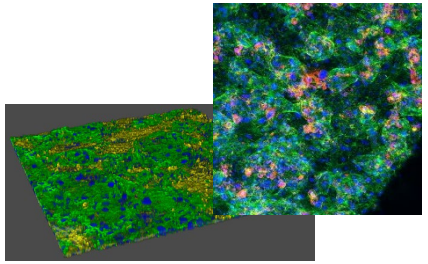


perfusion

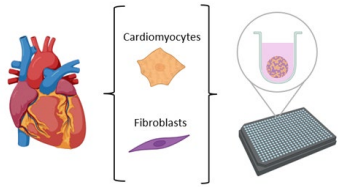


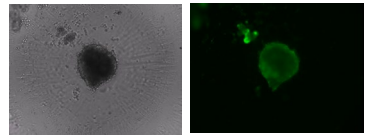
Placenta/fetal barrier



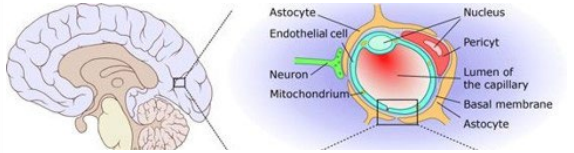


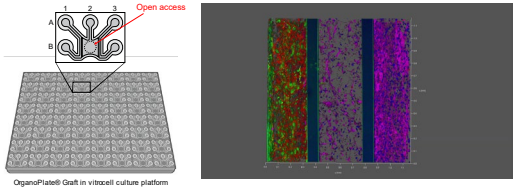
Cardiac

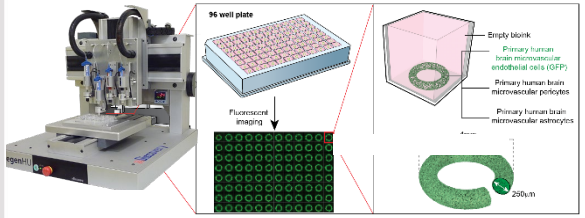




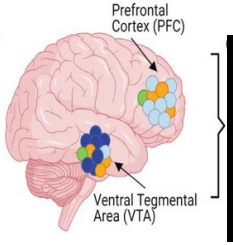
Neurovascular Unit

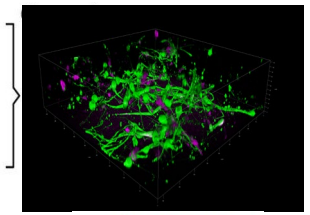


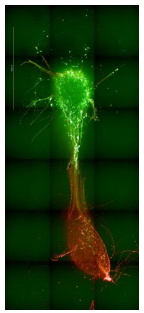


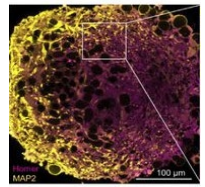


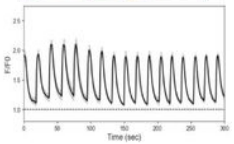
Brain (CNS, PNS)



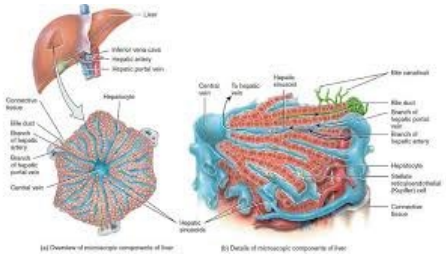


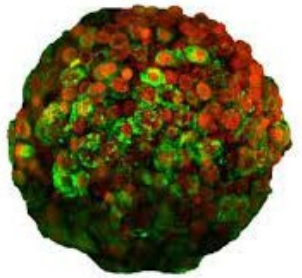




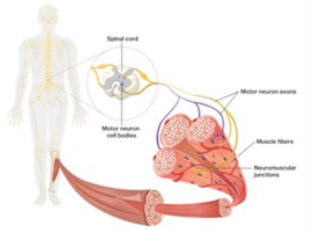


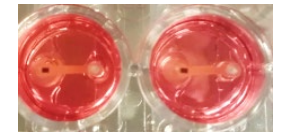
Liver

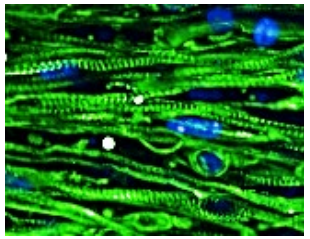


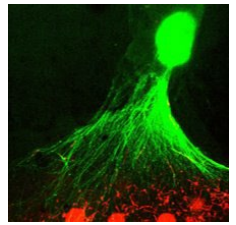


Muscle/ Neuromuscular Junction









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The Complement-AIRE 3D Multi Organotypic models of FIBrosis (3D-MOFIB) Technology Development Center

Integrated NAMs Platform for Anti-Fibrotic Drug Discovery

Multi-dimensional models and data integration to accelerate safe and effective therapies

1 IN VITRO MODELS

3D anti-fibrotic assays

Mechanism-based reporter assays

TGF-β
SMAD2/3
Gene
Reporter

3D toxicity assays

2 MULTIPARAMETRIC READOUTS

High content imaging

Cytokine secretion

Stiffness evaluation

Stiffness (Pa)
Strain (%)

Fluorescence / luminescence

Response (%)
Test compound (M)

FLIPR® Calcium 6 assay

RFU
Time (s)

3 MOLECULAR PROFILING

scRNA-seq

UMAP_2
UMAP_1

Ligand-receptor analysis

Ligand A
Ligand B
Ligand C
Ligand D
Ligand F

Pathway / network analysis

4 PHARMACOLOGY & TOXICOLOGY

Compound libraries

Drug testing

Dose responses

Therapeutic response
Toxic response
Response (%)
Drug concentration (M)

5 IN SILICO MODELS

AI

Computational ligand-based predictive models

Patient populations and unmet needs

EFFICACIOUS AND SAFE TREATMENTS

CLINICAL TRANSLATION

Improved clinical outcomes (e.g., skin fibrosis)

Improved organ function (e.g., pulmonary fibrosis)

A comprehensive, human-relevant platform to de-risk candidate selection and accelerate the path to patients.

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The 3D Multi Organotypic models of FIBrosis (3D-MOFIB) TDC: A Multidisciplinary Team

In vitro NAMs


Dr. Marc Ferrer


Dr. Darlene Dixon


Dr. Menghang Xia


Dr. Erik Tokar


Dr. Stephen Ferguson


Dr. MJ Song


Dr. Yi Wei Lim


Dr. Cristina Antich


Dr. Madison Kirk

In silico NAMs


Dr. David Reif


Dr. Ruili Huang

Research & Clinic

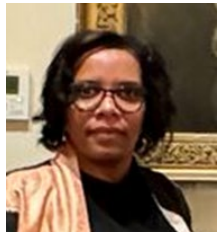

Dr. Resat Cinar


Dr. William Gahl


Dr. John Varga

Pre-clinical development & patient outreach


Dr. Elizabeth Ottinger


Dr. Sharie Haugabook

Training & Education


Dr. Belen Hurle


Dr. Sarine Markossian

Administrative & Project Management


Ms. Anna Rossoshek


Ms. Manju Swaroop


Dr. Dara Zong

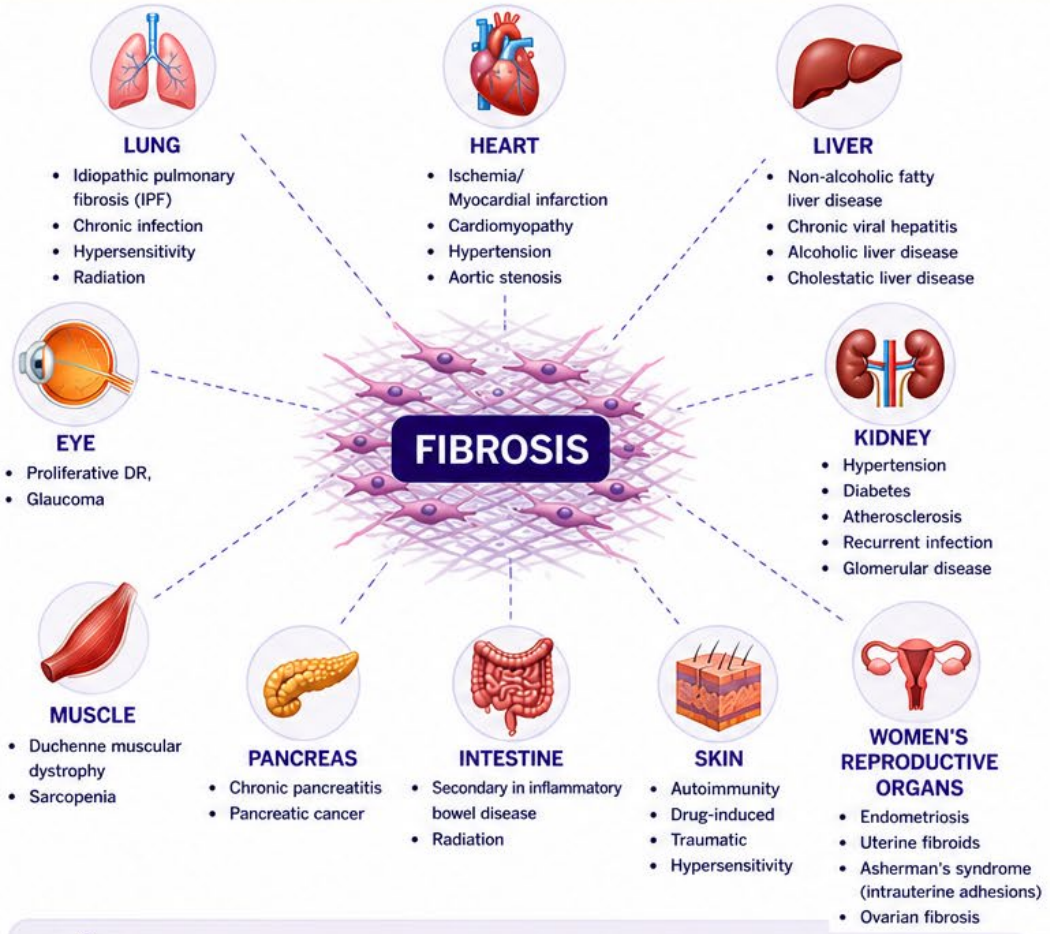
PO


Dr. Doda Rudnicki

Fibrosis: A Common, Underlying Pathology

A pervasive driver of disease across organs — yet few therapeutic options exist

Fibrosis Underlies Many Diseases and Tissues



LUNG
- Idiopathic pulmonary fibrosis (IPF)
- Chronic infection
- Hypersensitivity
- Radiation

HEART
- Ischemia/ Myocardial infarction
- Cardiomyopathy
- Hypertension
- Aortic stenosis

LIVER
- Non-alcoholic fatty liver disease
- Chronic viral hepatitis
- Alcoholic liver disease
- Cholestatic liver disease

EYE
- Proliferative DR,
- Glaucoma

KIDNEY
- Hypertension
- Diabetes
- Atherosclerosis
- Recurrent infection
- Glomerular disease

MUSCLE
- Duchenne muscular dystrophy
- Sarcopenia

PANCREAS
- Chronic pancreatitis
- Pancreatic cancer

INTESTINE
- Secondary in inflammatory bowel disease
- Radiation

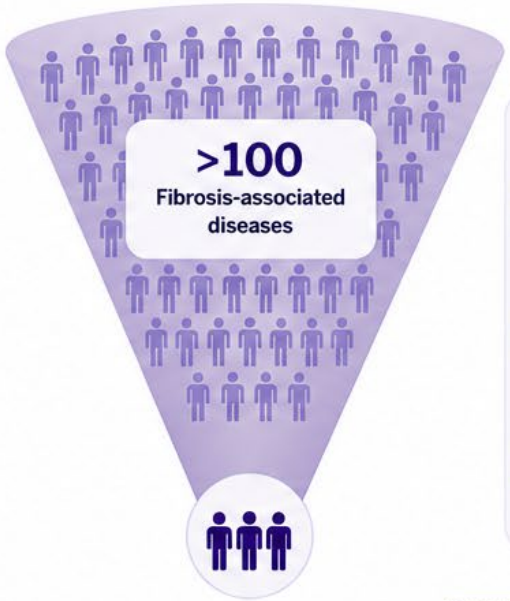
SKIN
- Autoimmunity
- Drug-induced
- Traumatic
- Hypersensitivity

WOMEN'S REPRODUCTIVE ORGANS
- Endometriosis
- Uterine fibroids
- Asherman's syndrome (intrauterine adhesions)
- Ovarian fibrosis

Regardless of the organ or disease, excessive ECM deposition, myofibroblast activation, and chronic inflammation drive fibrosis.

Few Approved Anti-Fibrotic Therapies

Despite fibrosis being central to **>100** diseases, only **3** anti-fibrotic drugs are approved.



3
Approved anti-fibrotic treatments

Approved Anti-Fibrotics

- **Nintedanib** — Idiopathic Pulmonary Fibrosis (IPF)
- **Pirfenidone** — Idiopathic Pulmonary Fibrosis (IPF)
- **Finerenone** — Chronic Kidney Disease (CKD) with T2D

Multiple therapies (e.g., PDE4 inhibitors such as nerandomilast) are in clinical development.

A critical unmet need:
More effective and broadly applicable anti-fibrotic therapies are urgently needed.

Addressing fibrosis has the potential to transform outcomes for millions of patients across a wide range of diseases.

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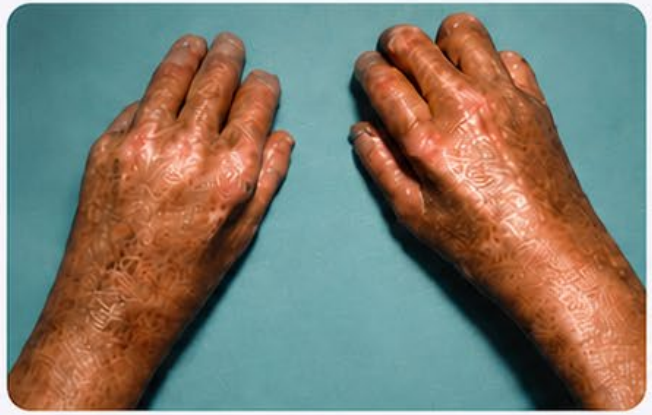
SCLERODERMA

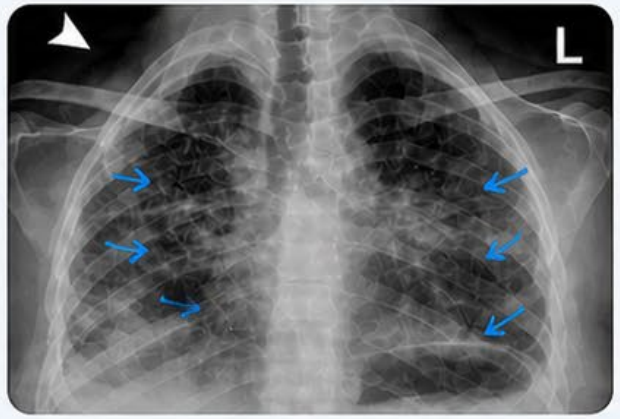


Systemic sclerosis (scleroderma) is a rare chronic autoimmune connective tissue disease.

Localized scleroderma causes excessive collagen deposition leading to thickened, hardened skin.

The exact etiology is not fully understood; both genetic susceptibility and environmental factors contribute.

HERMANSKY–PUDLAK SYNDROME PULMONARY FIBROSIS (HPS-PF)



Hermansky–Pudlak Syndrome (HPS) is a rare autosomal recessive genetic disorder.

HPS causes pulmonary fibrosis (HPS-PF), oculocutaneous albinism, and bleeding disorders.

Caused by mutations in *HSP* genes leading to defective lysosome-related organelles (LROs).

HSP-1 (part of BLOC-3) is critical for LRO biogenesis; nearly 100% of HPS-1 patients develop lung fibrosis.

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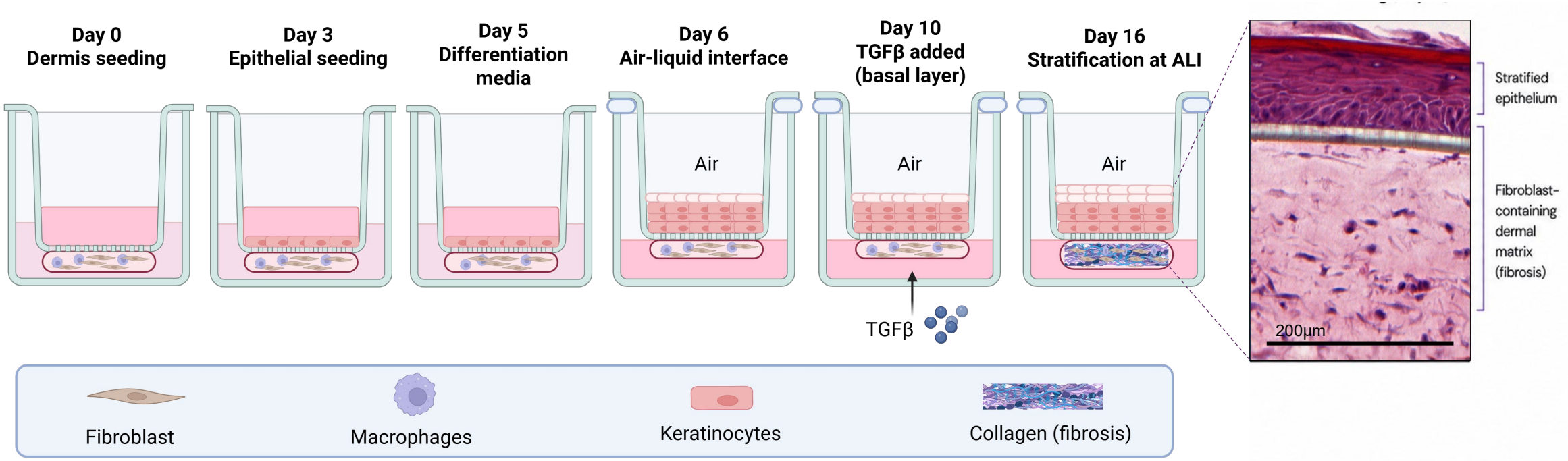
Building an immunocompetent 3D skin fibrosis model for high-throughput drug screening



Created using Biorender

Lim et al., Biofabrication 2024

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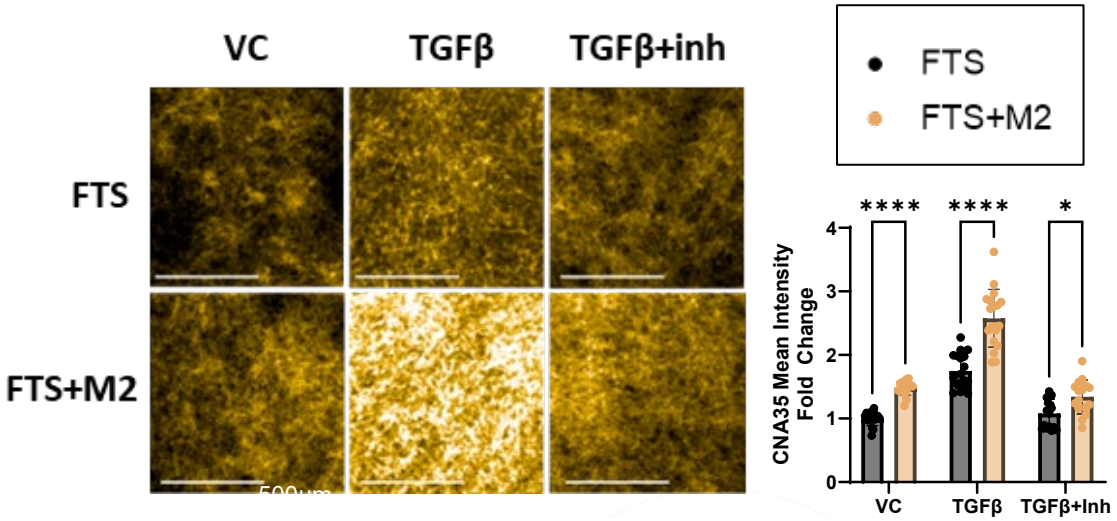
Multiparametric 3D Skin Fibrosis Assay

Goal: Develop immunocompetent 3D skin fibrosis model for high-throughput drug screening

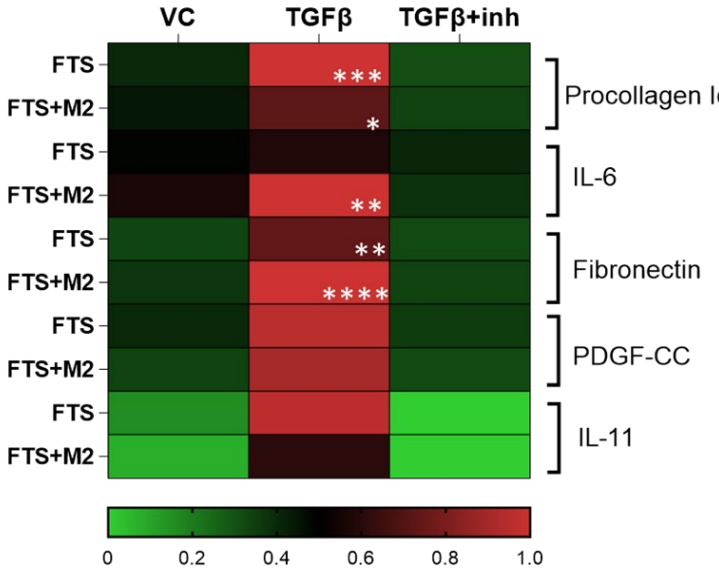
Relevant readouts: ↑collagen ↑fibrosis associated cytokines ↑stiffness

Collagen deposition

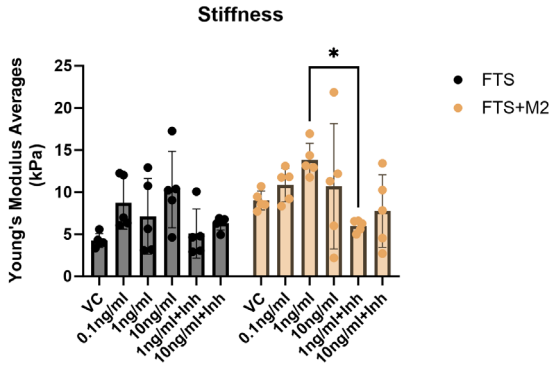


CNA-35: collagen binding protein

Cytokine production



Stiffness



Lim et al., Biofabrication 2024

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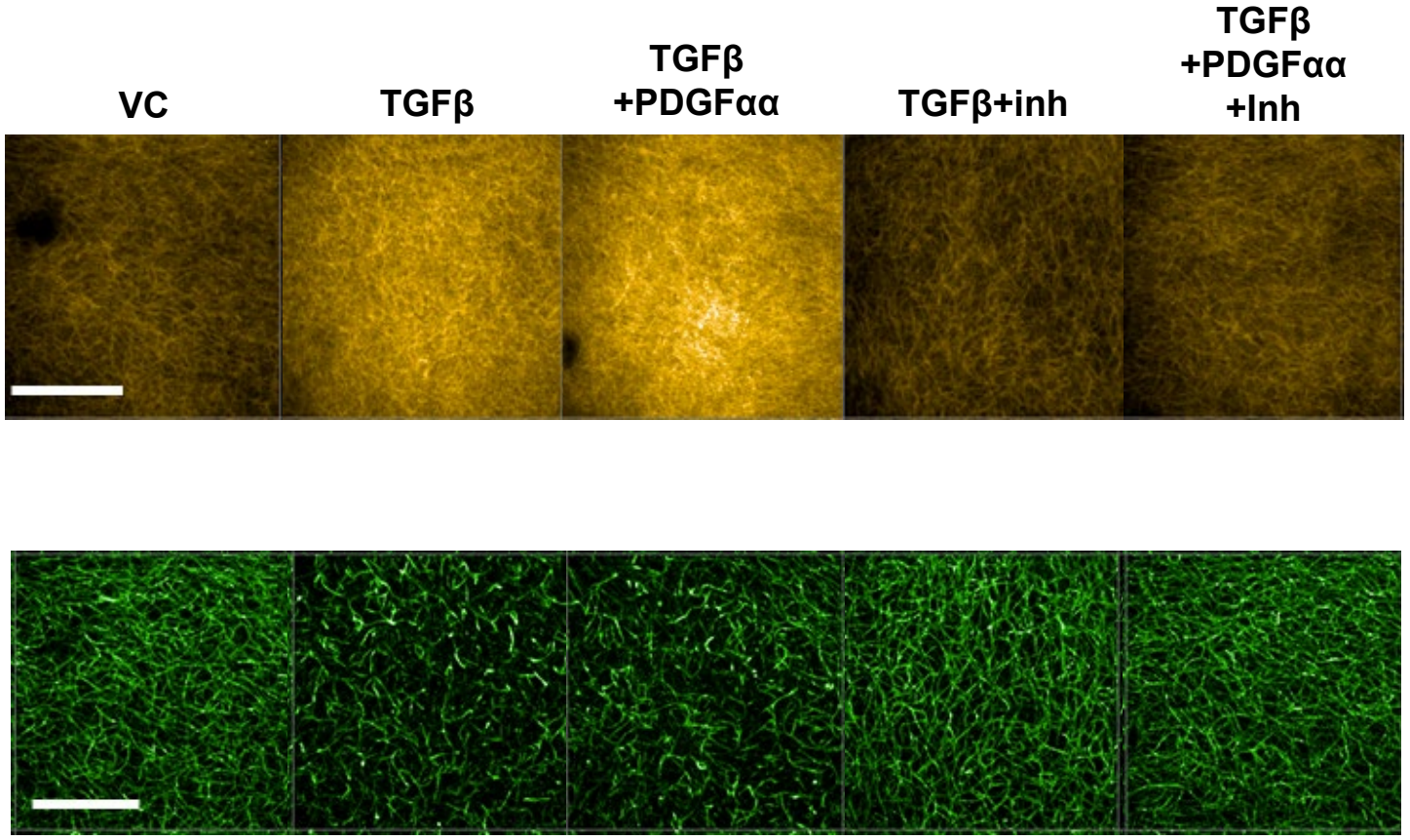
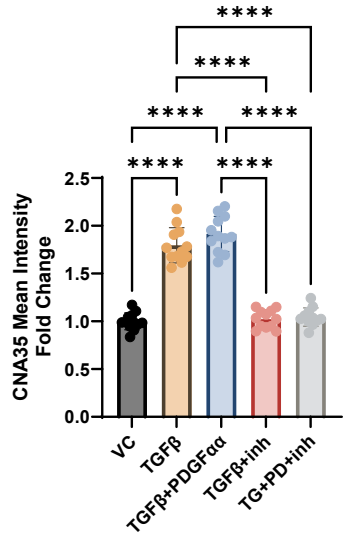
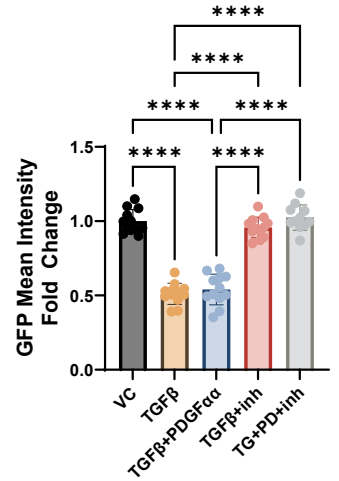
Vascularized Full Thickness Skin Fibrosis Model

CNA-35 (collagen)

Endo-GFP (vasculature)







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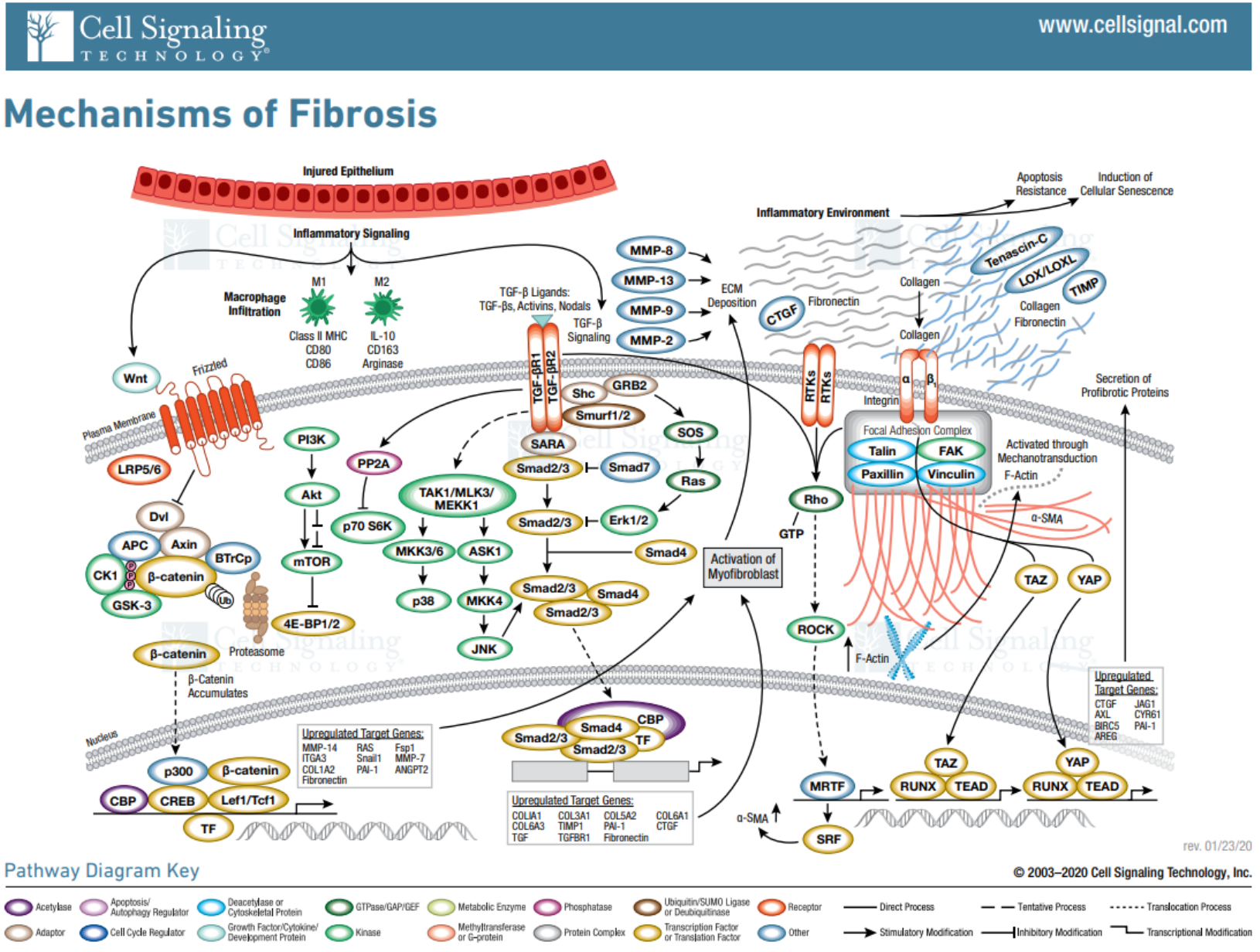
Molecular Mechanisms of Fibrosis



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NCATS toolbox of Pharmacological Collections

Anti-fibrotic (~200)

Drug repurposing (~2800)

Diversity AI (~2000)

	A	B	C	D
1	Number for reference	Name	Target	Structure
2	1	MR-6027 (MORF-57)	integrin inhibitor	Not available
3	2	AZD1236	MMP-9/MMP-12 inhibitor,	C[C@]3(CS(=O)(=O)N1CCC(CC1)OC2=CC=C(Cl)C=N2)NC(=O)NC3=O
4	3	IDL-2965	integrin inhibitor	Not available
5	4	PLN-1474	integrin inhibitor	O=C(O)[C@@H](NC(C1(C)CCOCC1)=O)CCCCCCCC2=NC3=C(CCCN3)C=C2
6	5	PXS-5382	LOX inhibitor	CC1=C(C2=CC=CC(S(=O)(C)=O)=C2)C3=NC(C)=CC=C3N1C/C(F)=C/CN
7	6	PXS-6302	LOX inhibitor	NC/C=C(C(F)(S(=O)(C1=CC=CC=C1)=O)F)\F
8	7	MK571	LTR	O=C(O)CCSC(C1=CC=CC(/C=C/C2=NC3=CC(Cl)=CC=C3C=C2)=C1)SCCC(N(C)C)=O
9	8	Vadimezan	Stimulator of Interferon Genes Protein agonist	CC1=C(C)C2=C(C=C1)C(=O)C3=C(O2)C(CC(O)=O)=CC=C3
10	9	KI-16425	Lysophosphatidic Acid Receptor 1 antagonist	CC(OC(=O)NC1=C(ON=C1C)C2=CC=C(CSCCC(O)=O)C=C2)C3=C(Cl)C=CC=C3
11	10	CL-82198	Matrix Metalloproteinase-13 inhibitor	O=C(NCCCCN1CCOCC1)C2=CC3=CC=CC=C3O2
12	11	PD-166793	Matrix Metalloproteinase-13 inhibitor	CC(C)[C@H](NS(=O)(=O)C1=CC=C(C=C1)C2=CC=C(Br)C=C2)C(O)=O
13	12	SB-3CT	Matrix Metalloproteinase-2 inhibitor	C1C(S1)CS(=O)(=O)C2=CC=C(C=C2)OC3=CC=CC=C3
14	13	CTS-1027	Matrix Metalloproteinase-12 inhibitor	ONC(=O)C3(CS(=O)(=O)C1=CC=C(OC2=CC=C(Cl)C=C2)C=C1)CCOCC3
15	14	PF 00356231	Matrix Metalloproteinase-12 inhibitor	OC(C[C@H](C1=CC=CC=C1)NC(C2=CC(C3=CC=C(C4=CC=NC=C4)C=C3)=CS2)=O)=O
16	15	Cilengitide	Integrin alphavbeta3 (Vitronectin) antagonist	)C(=O)[C@@H](CC2=CC=CC=C2)NC(=O)[C@H](CC(O)=O)NC(=O)CNC(=O)[C@H](C
17	16	ATN-161	Integrin alphavbeta3 (Vitronectin) antagonist	=O)N[C@@H](CC2=CN=CN2)C(=O)N[C@@H](CO)C(=O)N[C@@H](CS)C(=O)N[C
18	17	E-7820	Integrin Receptor antagonist	CC1=CC=C(NS(=O)(=O)C2=CC=CC(=C2)C#N)C3=C1C(=CN3)C#N
19	18	Prinomastat	Matrix Metalloproteinase-9 inhibitor	CC1(C)SCCN([C@H]1C(=O)NO)S(=O)(=O)C2=CC=C(OC3=CC=NC=C3)C=C2
20	19	GLPG-0187	Integrin Receptor antagonist	C=C1)S(=O)(=O)N[C@@H](CNC2=NC(C)=NC(N3CCC(CC3)C4=NC5=C(CCCN5)C=C4)
21	20	Abametapir	Matrix Metalloproteinase-9 inhibitor	CC1=CC=C(N=C1)C2=NC=C(C)C=C2
22	21	Incyclinide	Matrix Metalloproteinase-9 inhibitor	(=O)C1=C(O)C[C@@H]2C[C@@H]3CC4=C(C(O)=CC=C4)C(=O)C3=C(O)[C@]2(O)C
23	22	BMS-986020	Lysophosphatidic Acid Receptor 1 antagonist	H](OC(=O)NC1=C(ON=C1C)C2=CC=C(C=C2)C3=CC=C(C=C3)C4(CC4)C(O)=O)C5=CC
24	23	ADU-S100 (disodium salt)	Stimulator of Interferon Genes Protein agonist	H]4CO[P@](=O)(O[C@@H]5[C@H](O)[C@@H](CO[P@](=O)(O[C@H]4[
25	24	C-178	Stimulator of Interferon Genes Protein agonist	O=C(C1=CC=C([N+]([O-])=O)O1)NC2=CC=C3C(OC4=CC=CC=C34)=C2
26	25	NCGC00650474	Large tumor suppressor kinase 1 (LATS1) inhibitor	CC1=NNC=C1C2=NC3=C(C=CN=C3)C(NC4(C)CC4)=N2
27	26	NCGC00687164	Large tumor suppressor kinase 1 (LATS1) inhibitor	NCC(O)(C1=CC=C(Cl)C=C1)C2=CN=C(C=C2)C3=CC=NC4=C3C=CN4
28	27	TRULI	Large tumor suppressor kinase 1 (LATS1) inhibitor	O=C(C1=CNC2=NC=CC=C12)/N=C(SC=C3)/N3CC4=CC=CC=C4
29	28	Risuteganib (hydrochloride)	Integrin Receptor antagonist	C(=O)[C@H](CS(O)(=O)=O)NC(=O)CNC(=O)[C@H](CCCNC(N)=N)NC(=O)CN)C(=
30	29	Hinokiflavone	Matrix Metalloproteinase-9 inhibitor	C=C1)C2=CC(=O)C3=C(O2)C=C(O)C(OC4=CC=C(C=C4)C5=CC(=O)C6=C(O5)C=C(O)C

anti-fibrosis | DILI | DICT | DICT short | NIEHS Cardiotox | Neurotox

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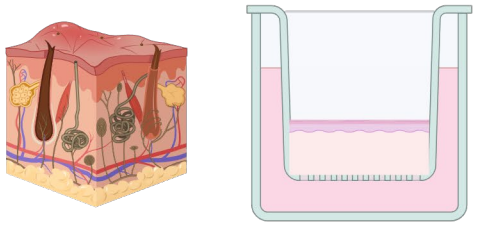
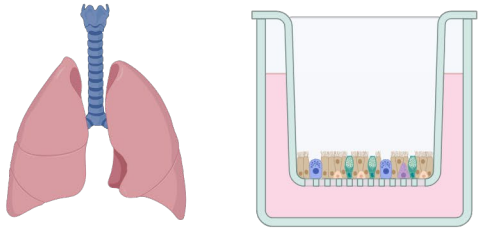
An integrated HTS platform of 3D phenotypic assays and 2D mechanism-based assays for the discovery of anti-fibrotic drugs

Biological Context

Human Skin Model



Human Lung Model



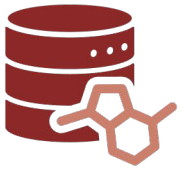
3D Assay Platforms

Anti-fibrotic activity

Anti-fibrosis Library

Repurposing Library

Pharmacogenomics Library



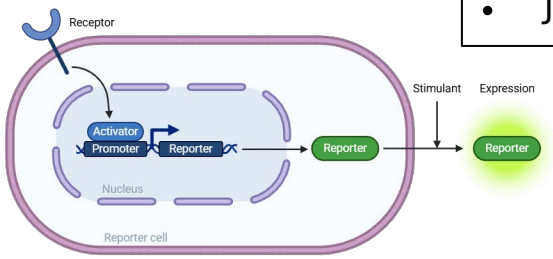
Diversity Library

Mechanism-based activity

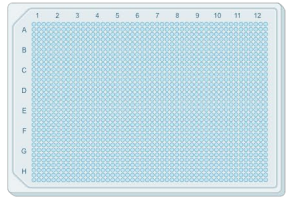
Mechanistic Context

- TGFβ/SMAD
- NF-κB
- Wnt/β-Catenin
- Hippo-YAP/TAZ
- JAK-STAT

Reporter Cell System



High throughput readouts



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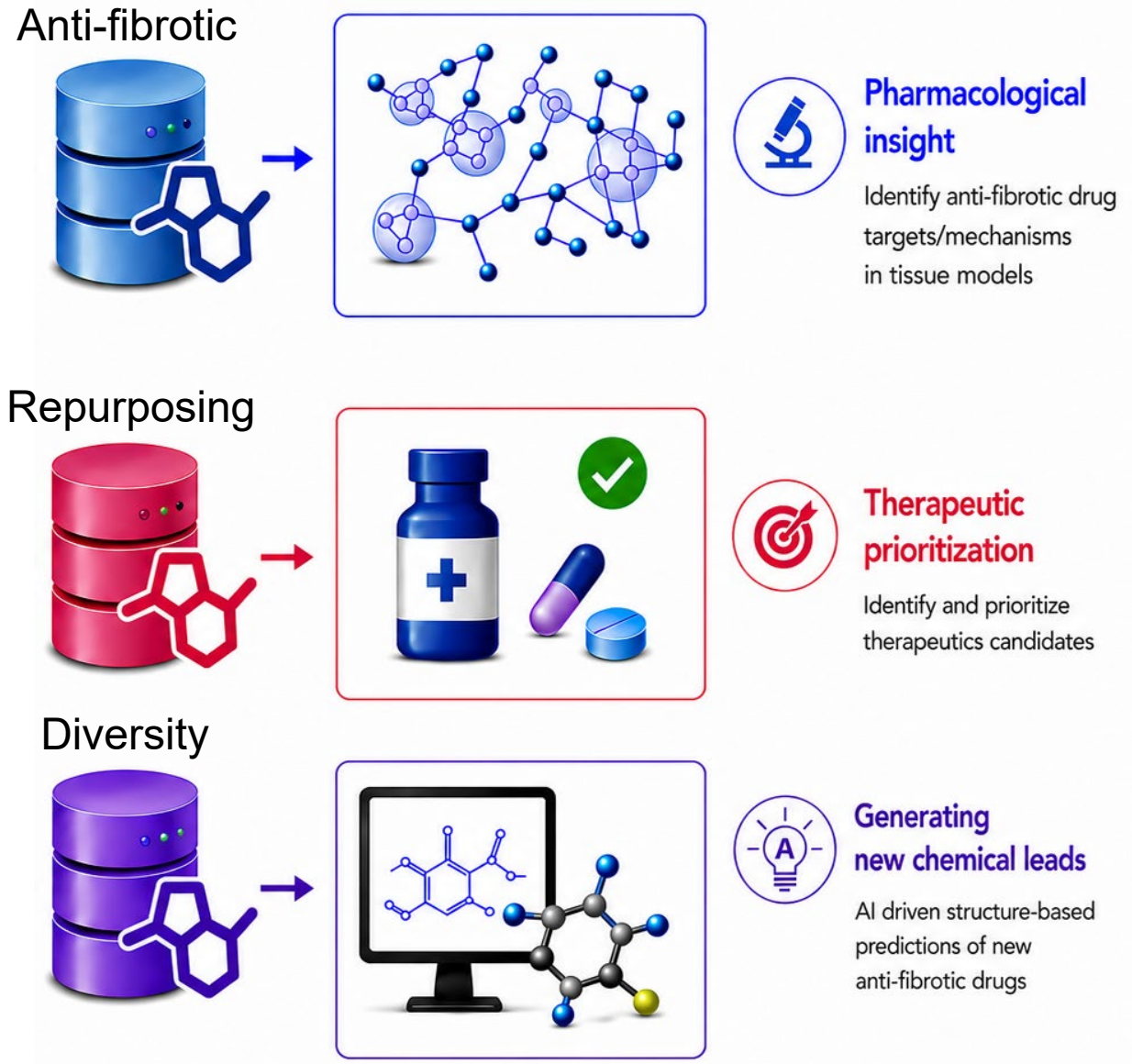
3D-MOFIB Pharmacological Screening Outcomes



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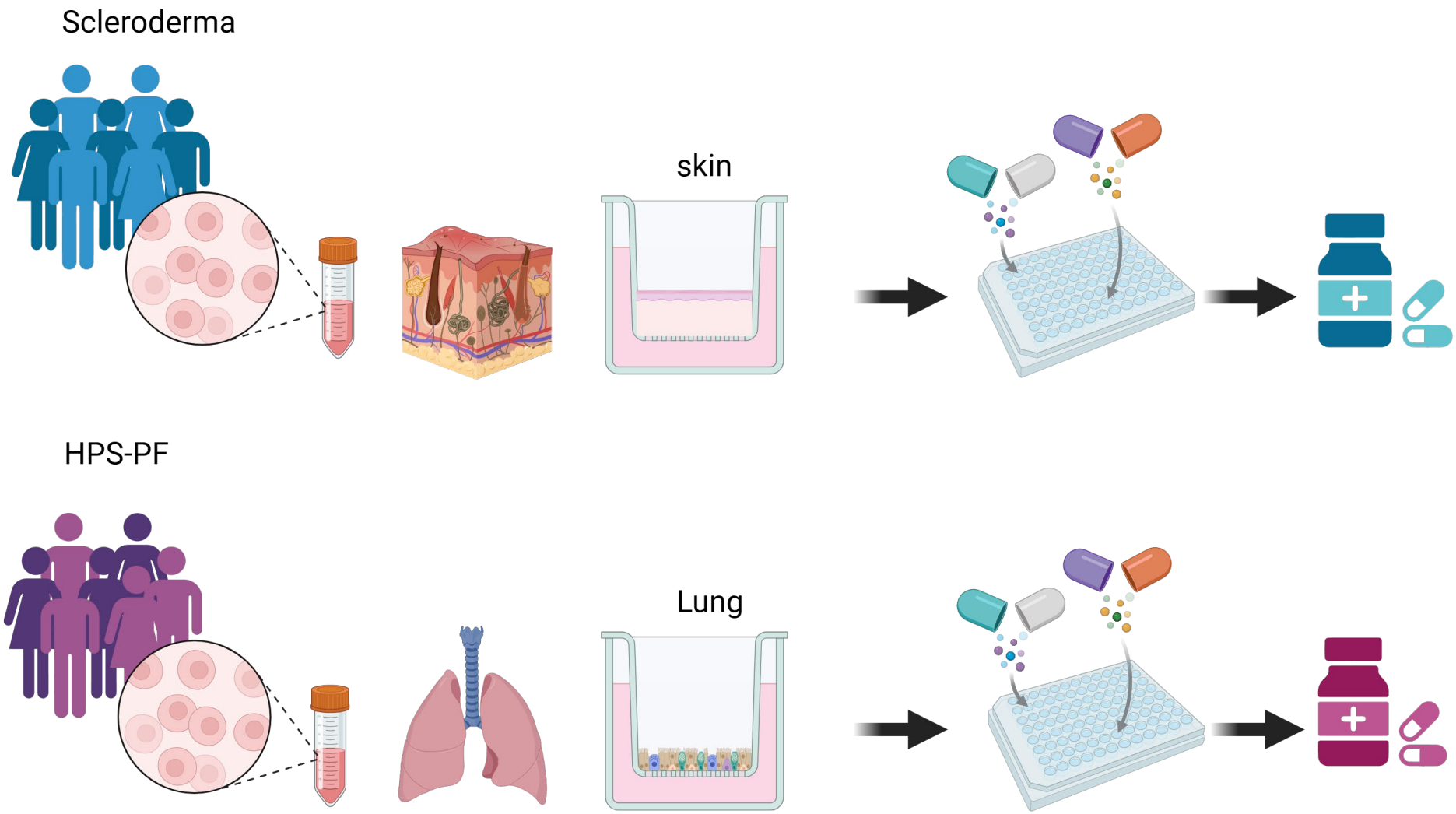
A platform of patient-derived 3D phenotypic assays for the discovery of new anti-fibrotic drugs



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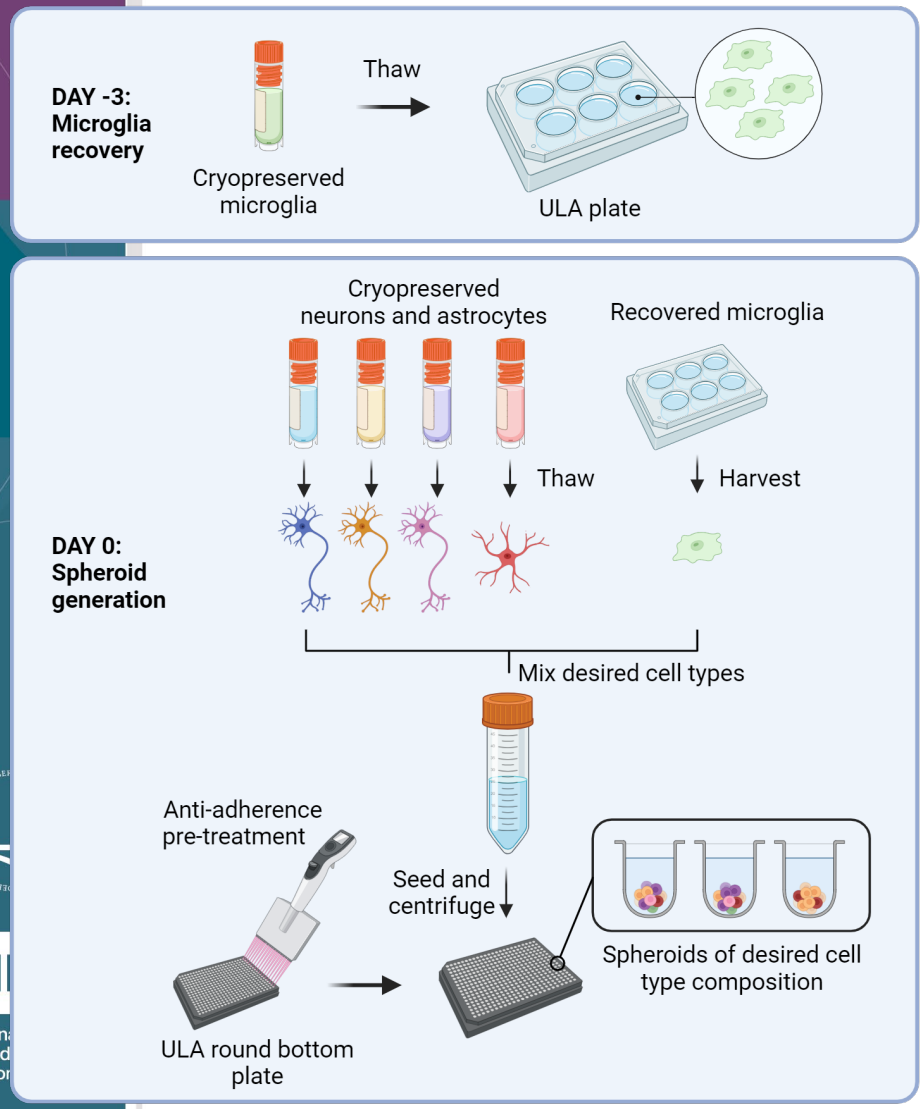
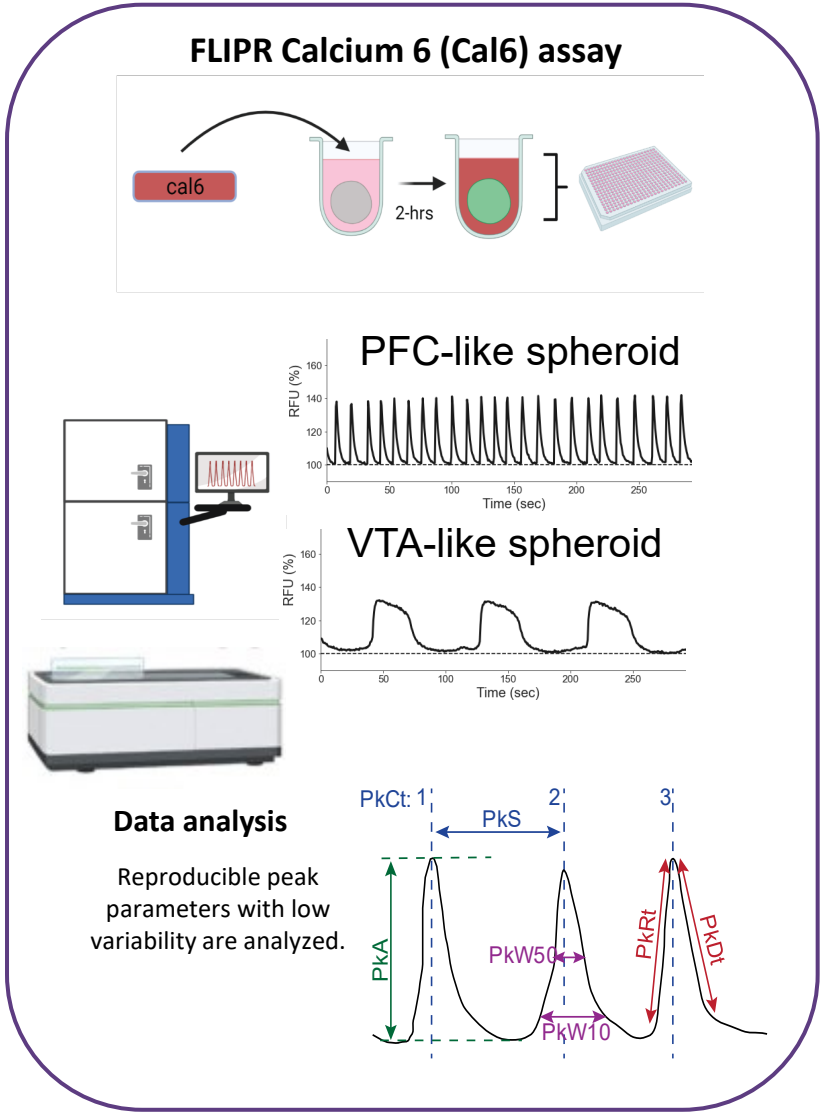
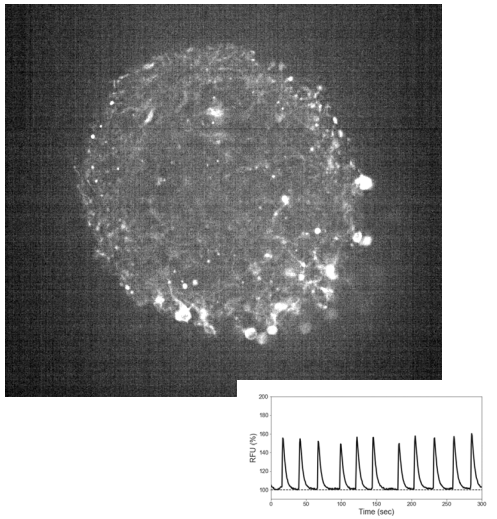
Brain-region–specific neural spheroid platform for neurotoxicity screening (1)



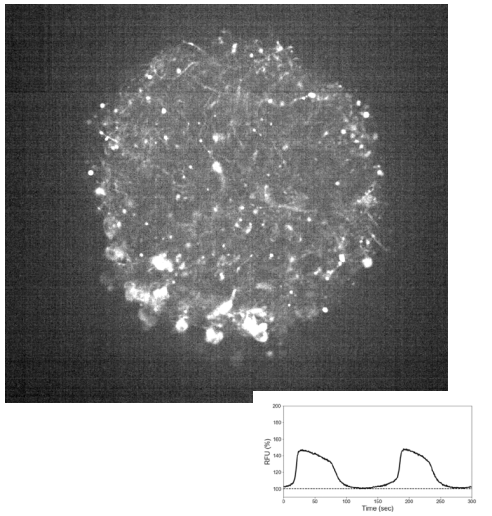
3 weeks



PFC-like

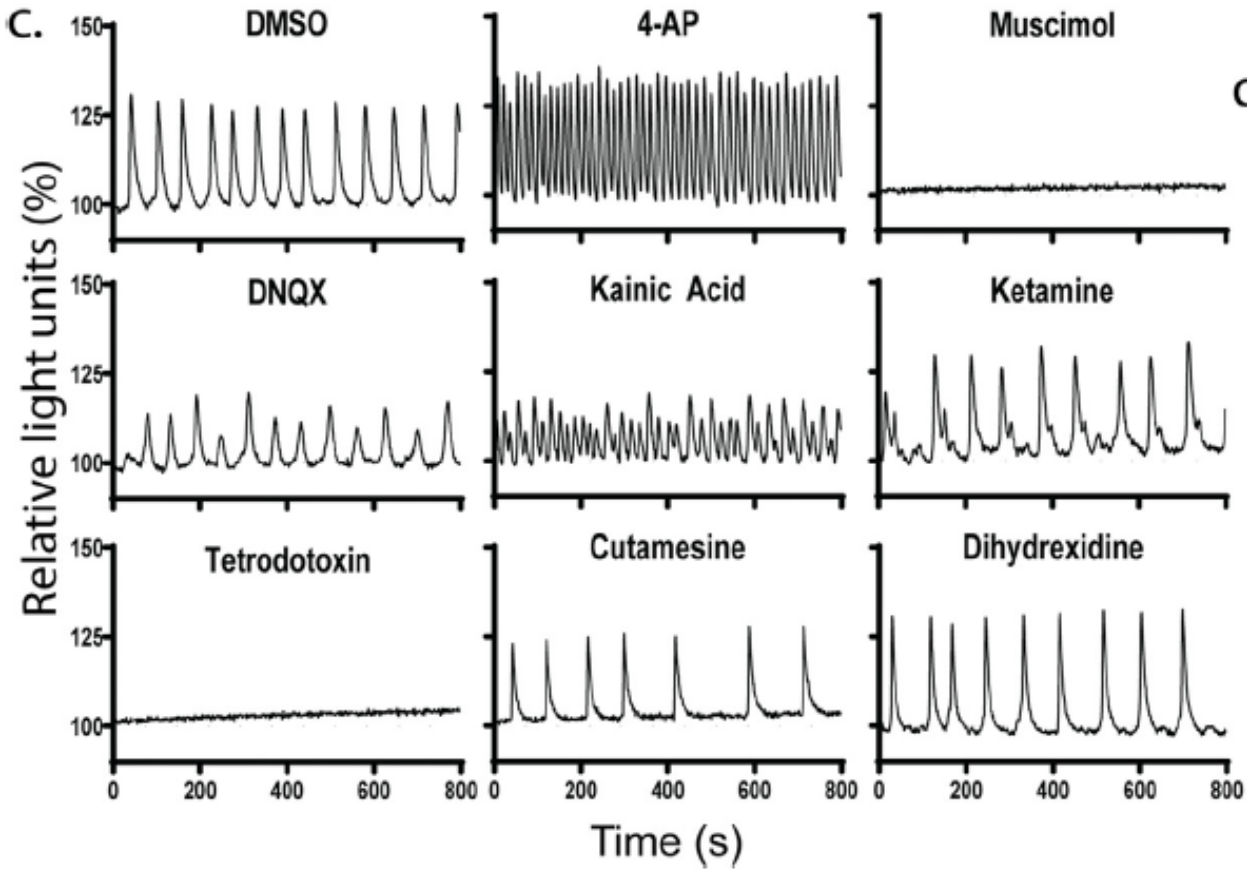


VTA-like



Boutin et al. SLAS Discovery 2022; Strong et al. Comm. Biol.2023; Zhang et al. Comm. Biol. 2026

Brain-region–specific neural spheroid platf;orm for neurotoxicity screening (2)00op’l?O



Boutin et al. SLAS Discovery 2022; Strong et al. Comm. Biol.2023; Zhang et al. Comm. Biol. 2026

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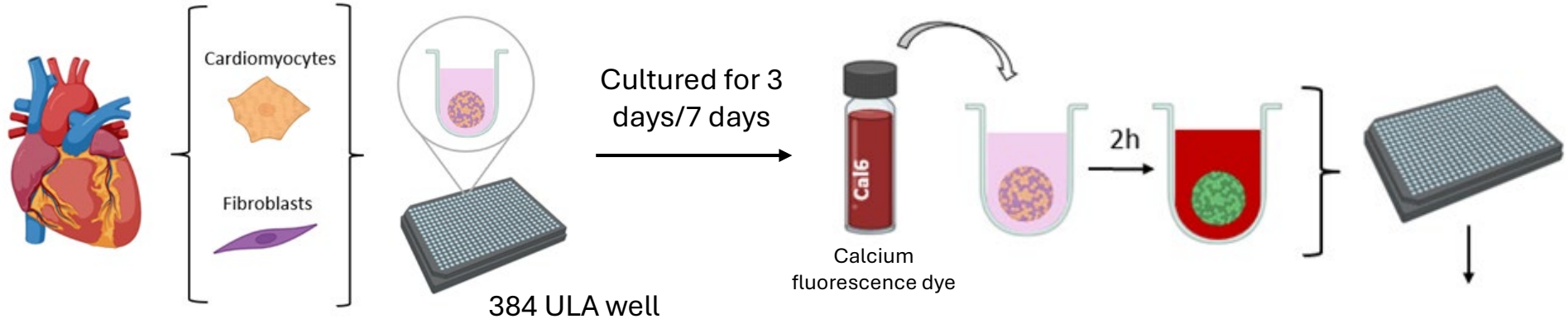
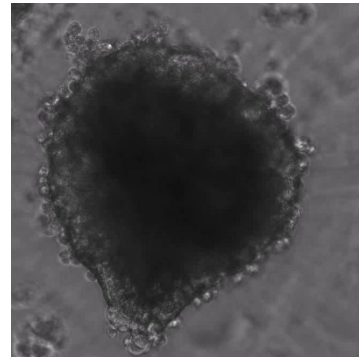
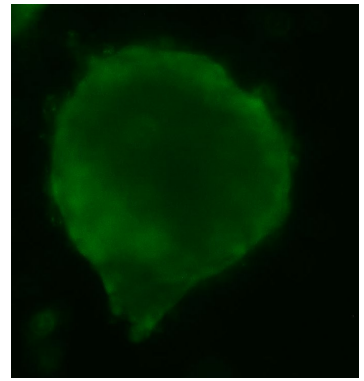
HTS-compatible cardiac spheroid assay for cardiotoxicity (1



384 ULA well plate

iPSC-derived Cardiomyocytes
Primary Fibroblasts

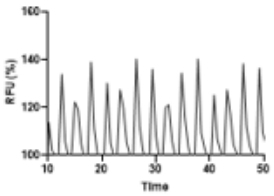




FLIPR

Simultaneous 384w read

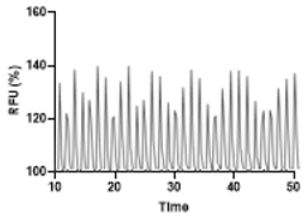
Baseline calcium recording (as RFU)



Compound treatment

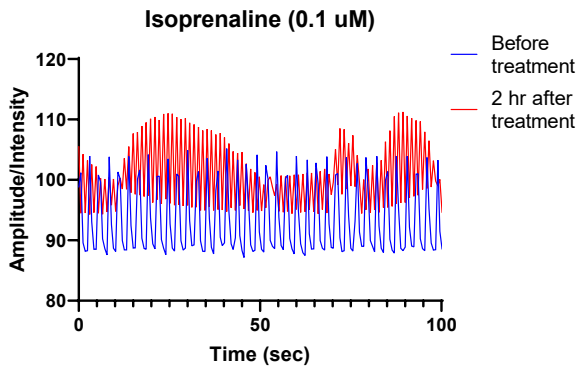
Post drug recording (as RFU)

(0min, 5min, 10min,30min, 1h, 2h)

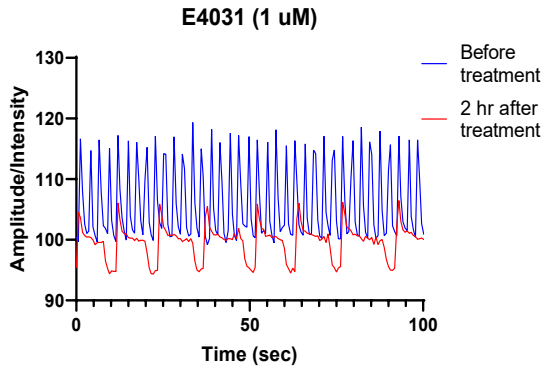


HTS-compatible cardiac spheroid assay for cardiotoxicity (2

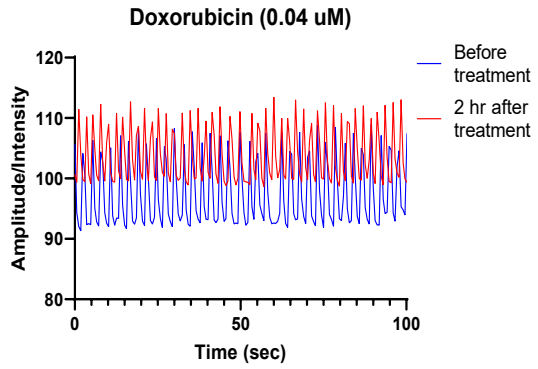
Group 1: Inotropic Modulators



Group 2: Ion Channel Modulators



Group 3: Other Cardiotoxic Compounds



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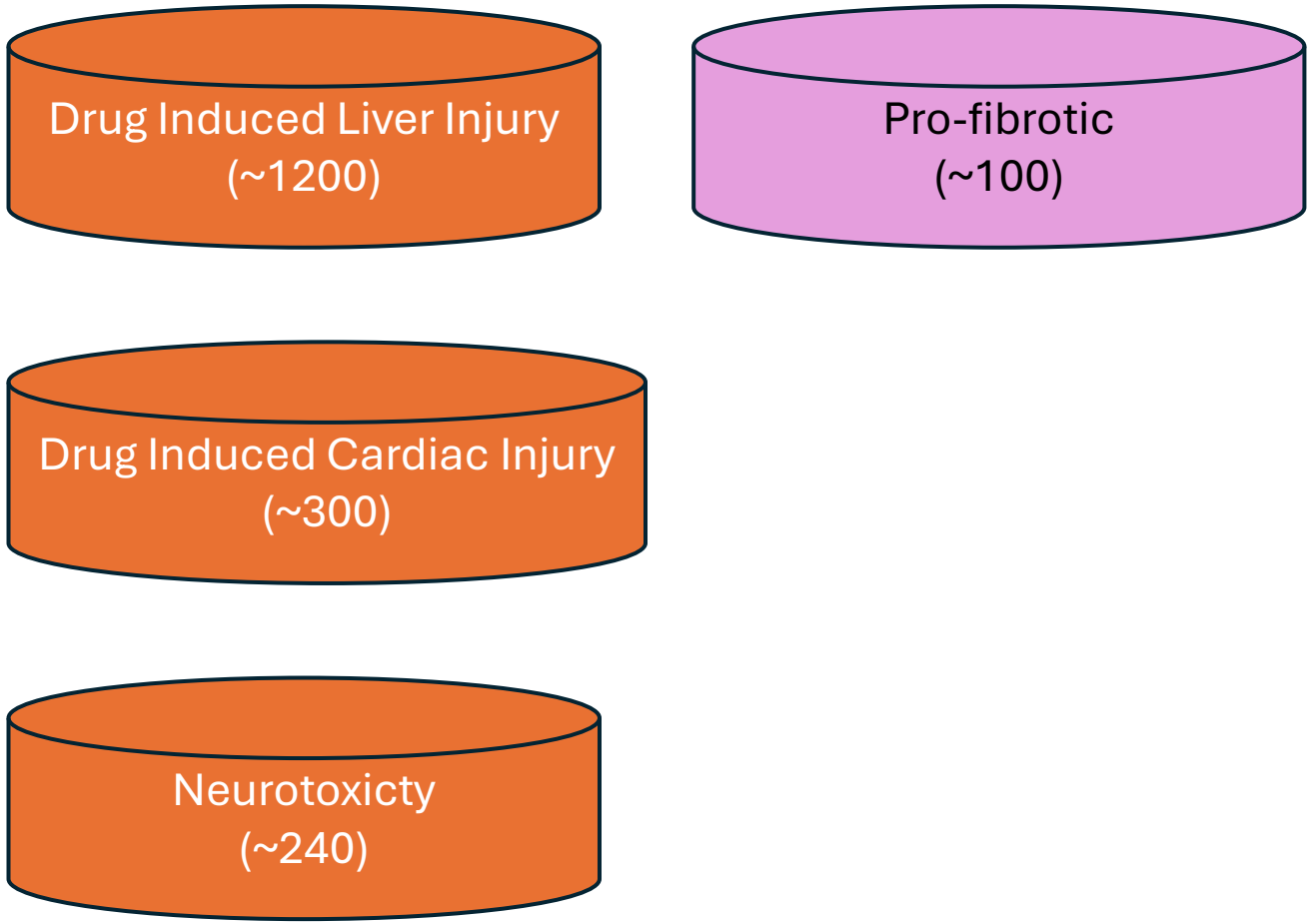
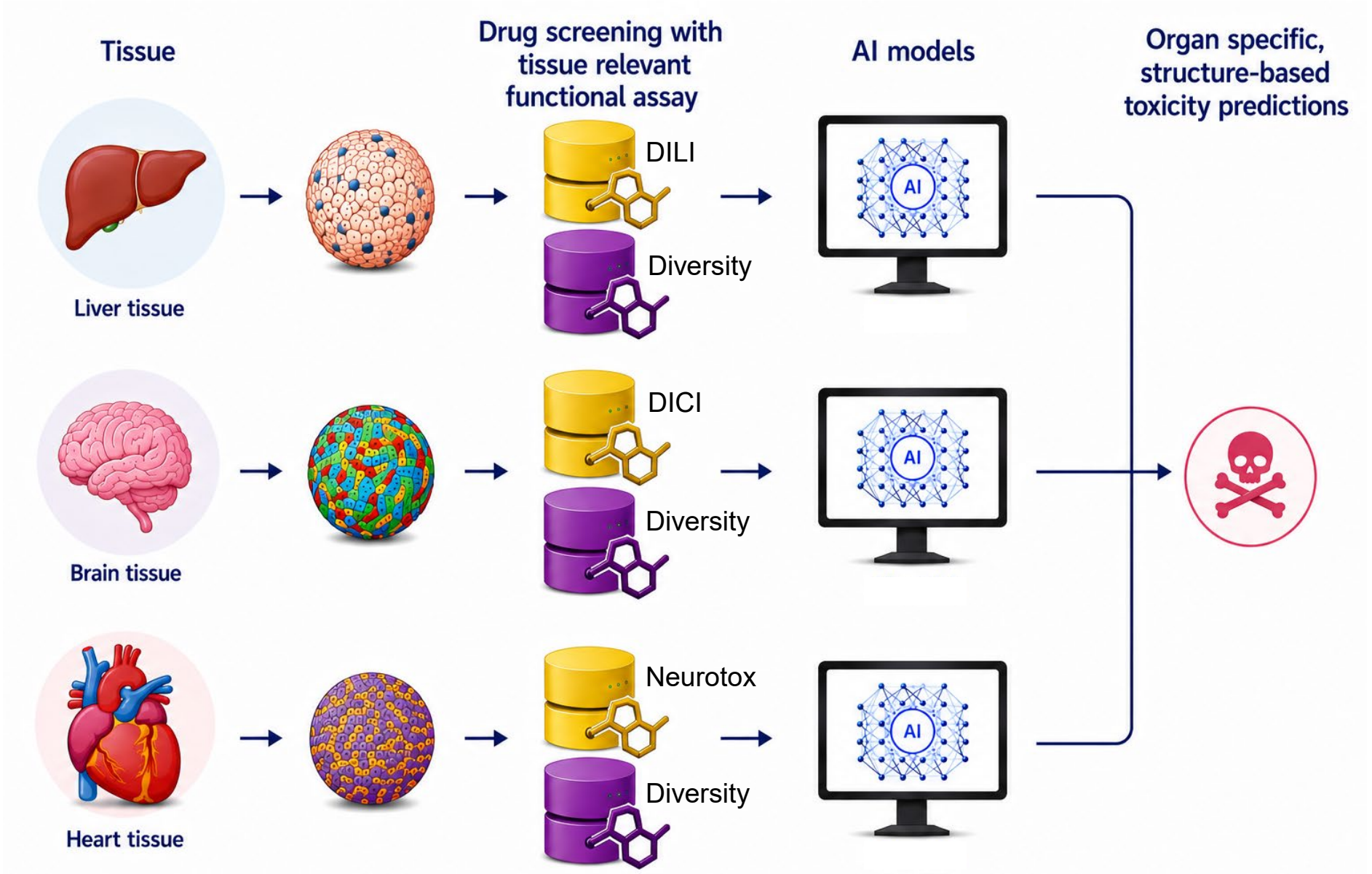
NIEHS/NCATS Toolbox of Toxicology Compound Libraries



3D-MOFIB Toxicology Screening Outcomes



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In Silico Predictions of Drug Toxicology and Efficacy

In vitro assay and chemical structure-based in silico prediction of chemical induced drug toxicity

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Xi Luo, Tuan Xu, Deborah K. Ngan, Menghang Anton Simeonov, Ruili Huang

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Use of *in vitro* methods combined with *in silico* analysis to identify potential skin sensitizers in the Tox21 10K compound library

Zhengxi Wei[1*†], Tuan Xu[1†], Judy Strickland[2], Li Zhang[1], Yuhong Fang[1], Dingyin Tao[1], Anton Simeonov[1], Ruili Huang[1], and Menghang Xia[1*]

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Prediction of drug-induced liver injury and cardiotoxicity using chemical structure and *in vitro* assay data

Lin Ye[a,1], Deborah K. Ngan[a,1], Tuan Xu[a], Zhichao Liu[b], Jinghua Zhao[a], Srilatha Sakamuru[a], Li Zhang[a], Tongan Zhao[a], Menghang Xia[a], Anton Simeonov[a], Ruili Huang[a,*]

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[b] National Center for Toxicological Research, U.S. Food and Drug Administration (FDA), Jefferson, AR 72079, USA

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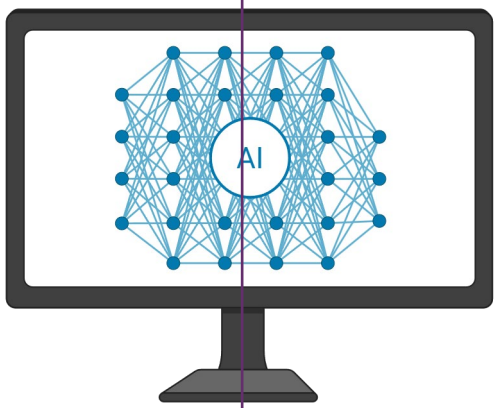

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Morgan Chandler, Sankalp Jain, Justin Halman, Enping Hong, Marina A. Dobrovolskaia, Alexey V. Zakharov, Kirill A. Afonin

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AI-driven discovery of synergistic drug combinations against pancreatic cancer

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The innate and adaptive immune

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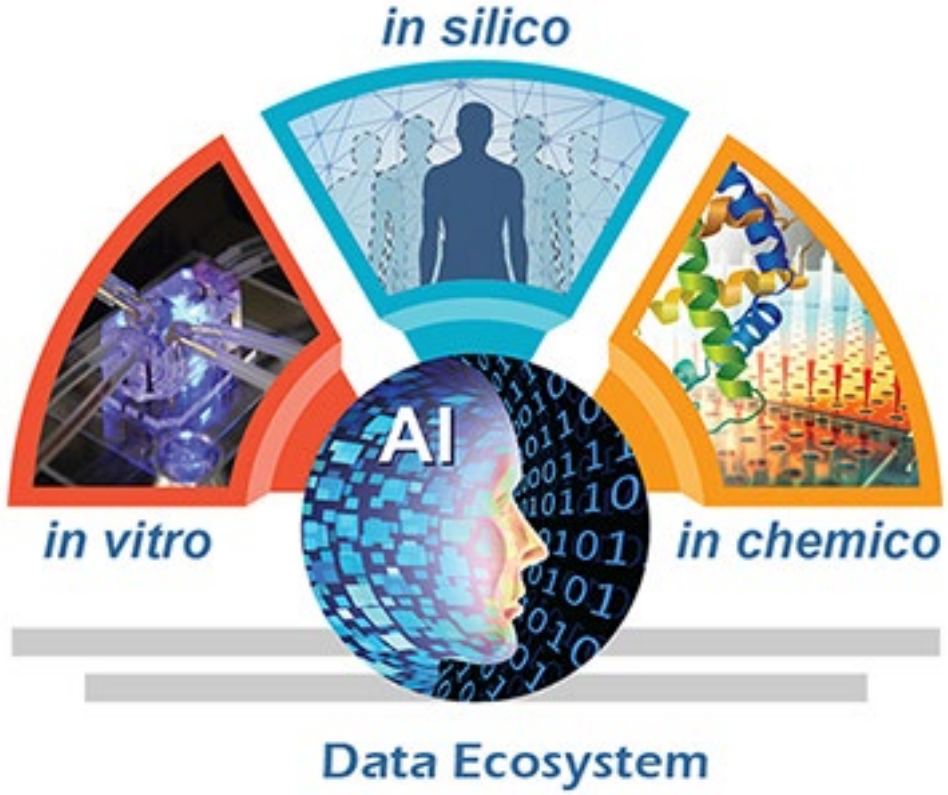

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