"Assessing Effects of Microgravity on Cardiovascular Aging with AI and 3D Organoids"

27th NIH TC Consortium Meeting & CIVM Qualification
Public Workshop: Tissue Chips in Space 2.0

Joseph Wu, MD, PhD (Stanford), Afshin Beheshti, PhD (Pittsburgh)

May 5th, 2025

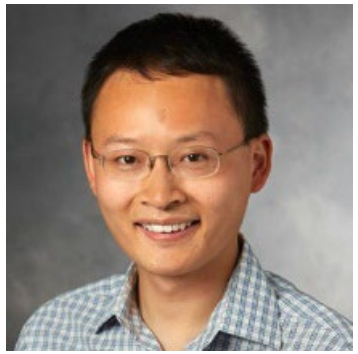
Stanford Cardiovascular Institute

SPACE TANGO

Multidisciplinary Team Members

PI Joseph Wu
iPSC Biology

Co-PI Afshin Beheshti
Space Multi-omics

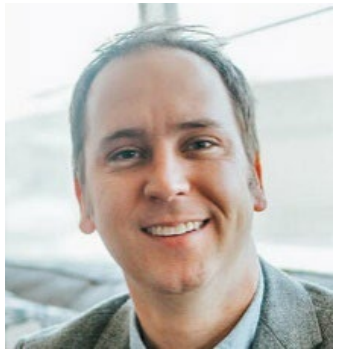


Co-I James Zou
AI/ML

Co-I Sarah Heilshorn
Biomaterial

Co-I Mark Skylar Scott
Biofabrication

Co-I Stanley Qi
Genome Editing



Twyman Clements
Space Tango

Shelby Giza
Space Tango

Amanda Chase
Program Manager

Won Suk Jahng
Postdoc

Renke Tan
Postdoc

Thulaj Meharwade
Postdoc

Stanford Cardiovascular Institute

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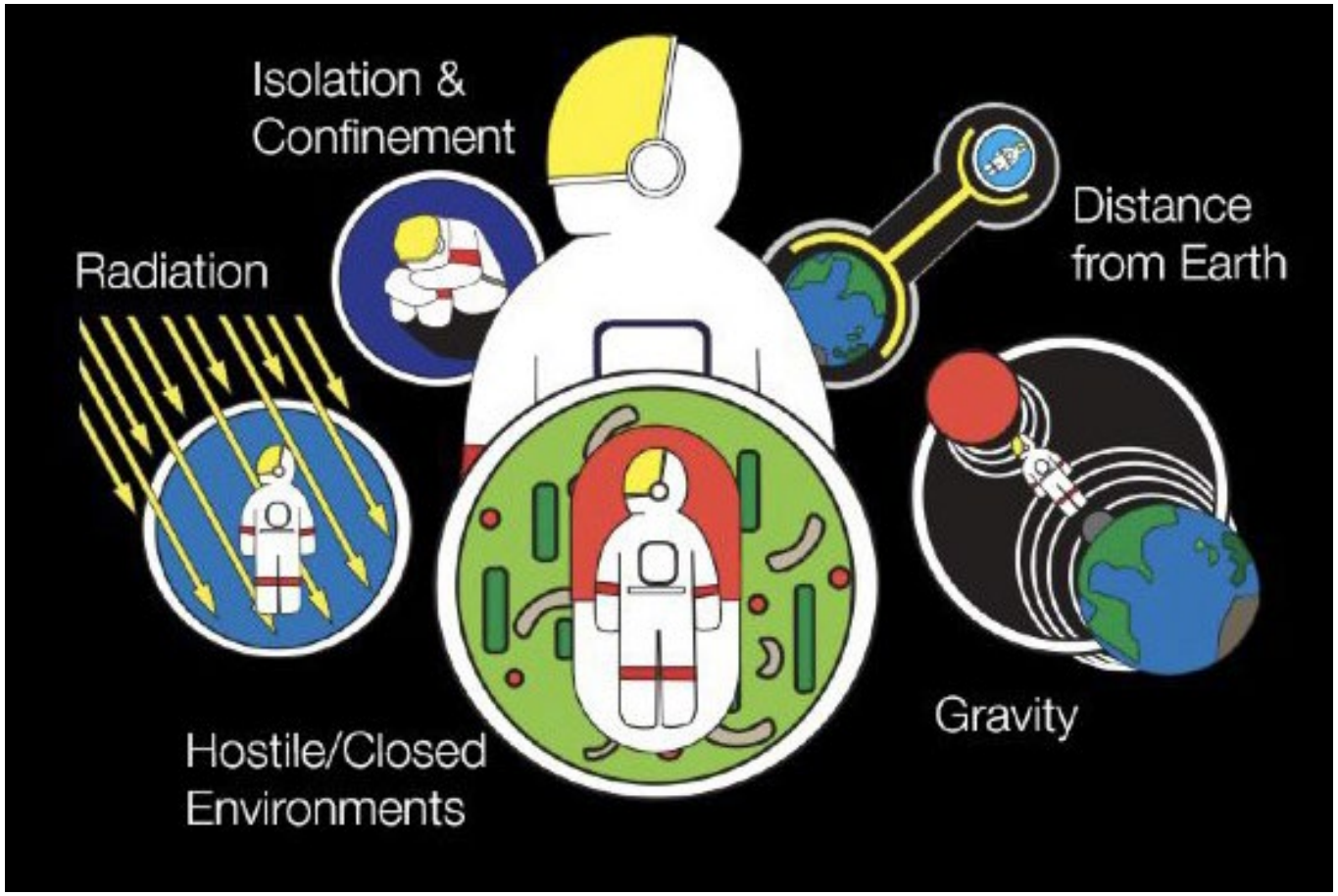
Research Background



Spaceflight Health Hazards

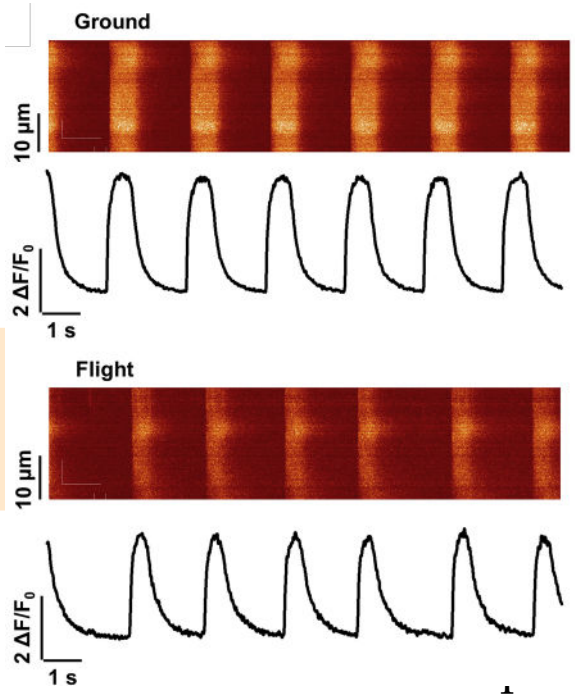
- Microgravity (weightlessness)
- Space radiation
- Cardiovascular & fluid shift
- Sensorimotor & vestibular changes
- Immune system & microbiology
- Psychological & behavorial issues
- Environmental hazards

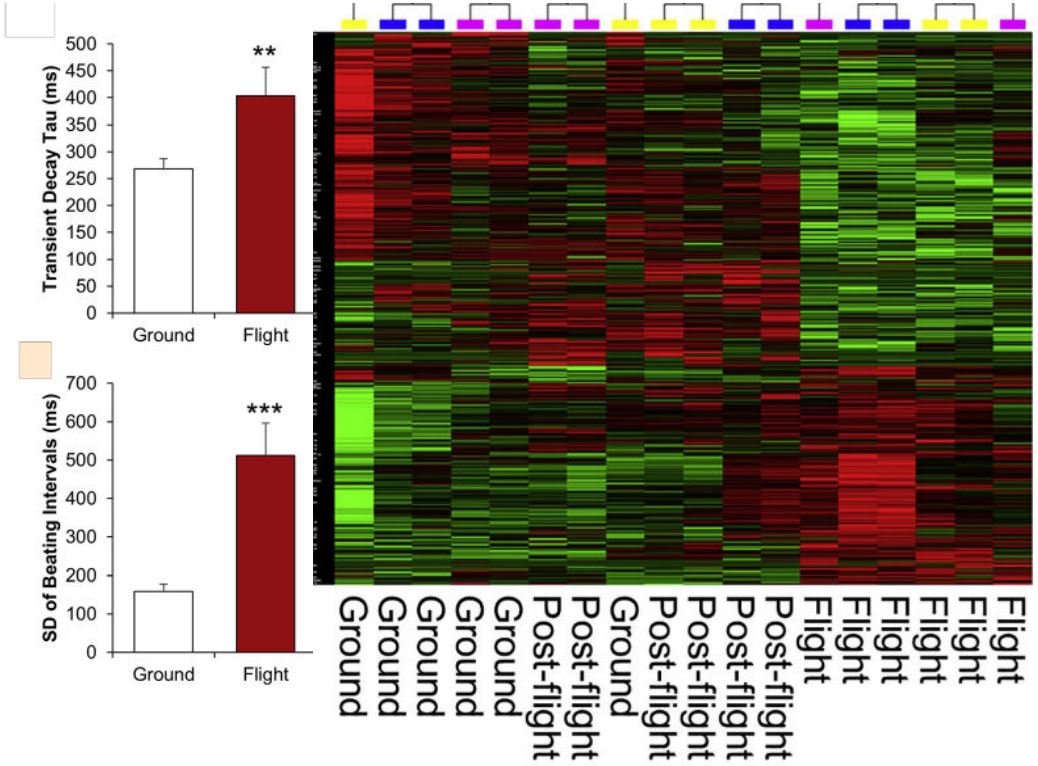
#1 Prior Microgravity Research with 2D iPSC-CMs

2D iPSC-CMs (2016)

- Calcium Mishandling
- Transcriptome Remodeling

Wnorowski & Sharma et al. Stem Cell Reports 2018





- First Flight

SpaceX CRS-9 (July 2016)

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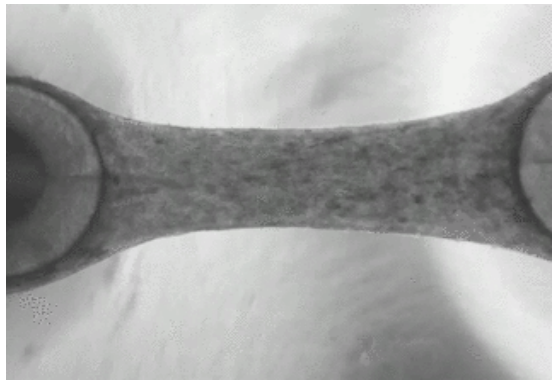
#2 Prior Microgravity Research with 3D iPSC-Engineered Heart Tissues (EHTs)

2D iPSC-CMs (2016)

- Calcium Mishandling
- Mitochondrial Remodeling

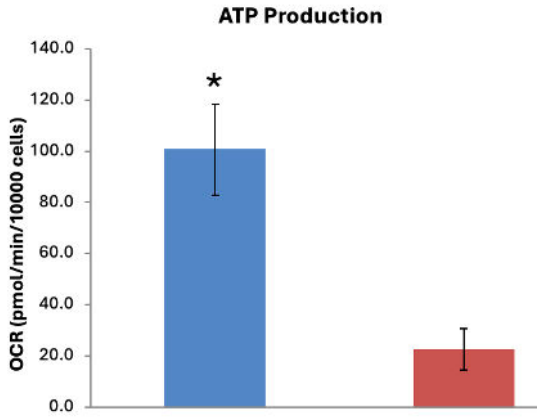
3D Cardiac Spheroids (2023)

- Tissue on a Chip 2.0
- Second Flight



3D EHTs (2019)

- Tissue on a Chip 1.0
- First Flight
- Mitochondrial Remodeling



SpaceX CRS-18 (July 2019)

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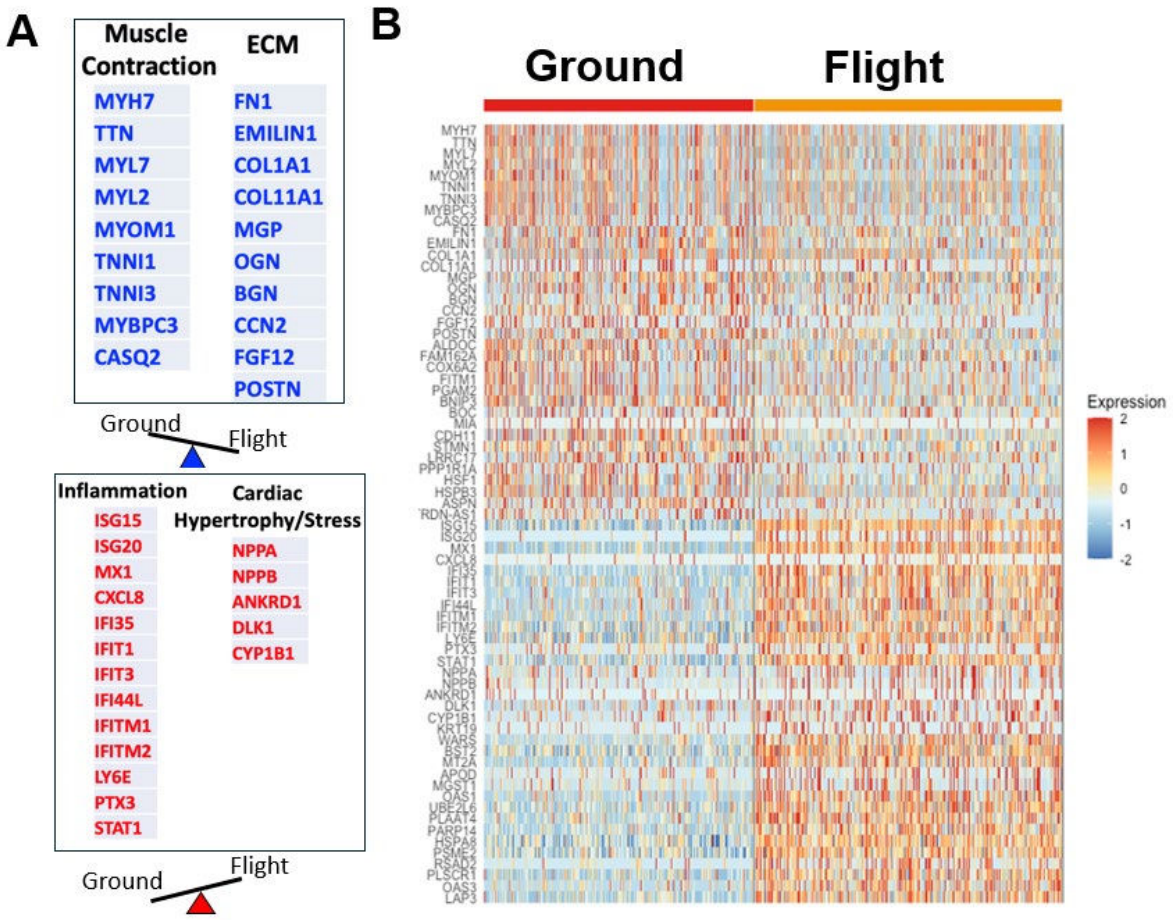
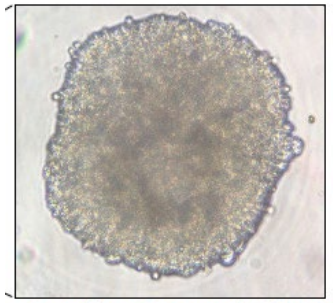
#3 Prior Microgravity Research with 3D iPSC-Cardiac Organoids (COs)



3D Cardiac Spheroids (2023)

- Tissue on a Chip 2.0
- Second Flight
- Increased Makers for Inflammation



Cardiac Organoid (CO)

SpaceX CRS-27 (March 2023)

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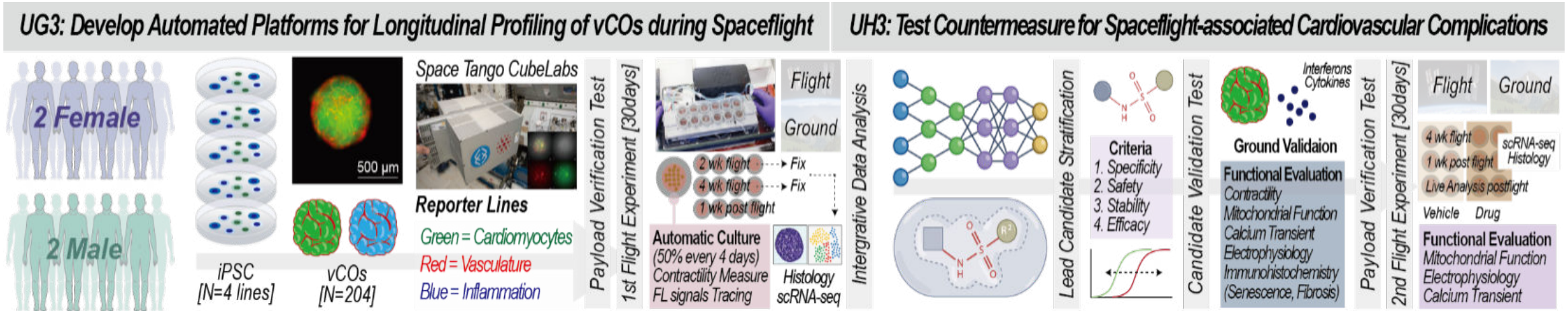
Project Overview

- ✓ **Project Goal**: To understand the impact of microgravity exposure on cardiovascular homeostasis and identify effective countermeasure(s).
- ✓ **UG3 Period**: To develop automated platforms for longitudinal profiling of 3D vascularized cardiac organoid during spaceflight.
- ✓ **UH3 Period**: To test candidate countermeasure for spaceflight-induced cardiovascular complications by inflammation & aging.



Milestones in Aim 1 [Months 1-6]

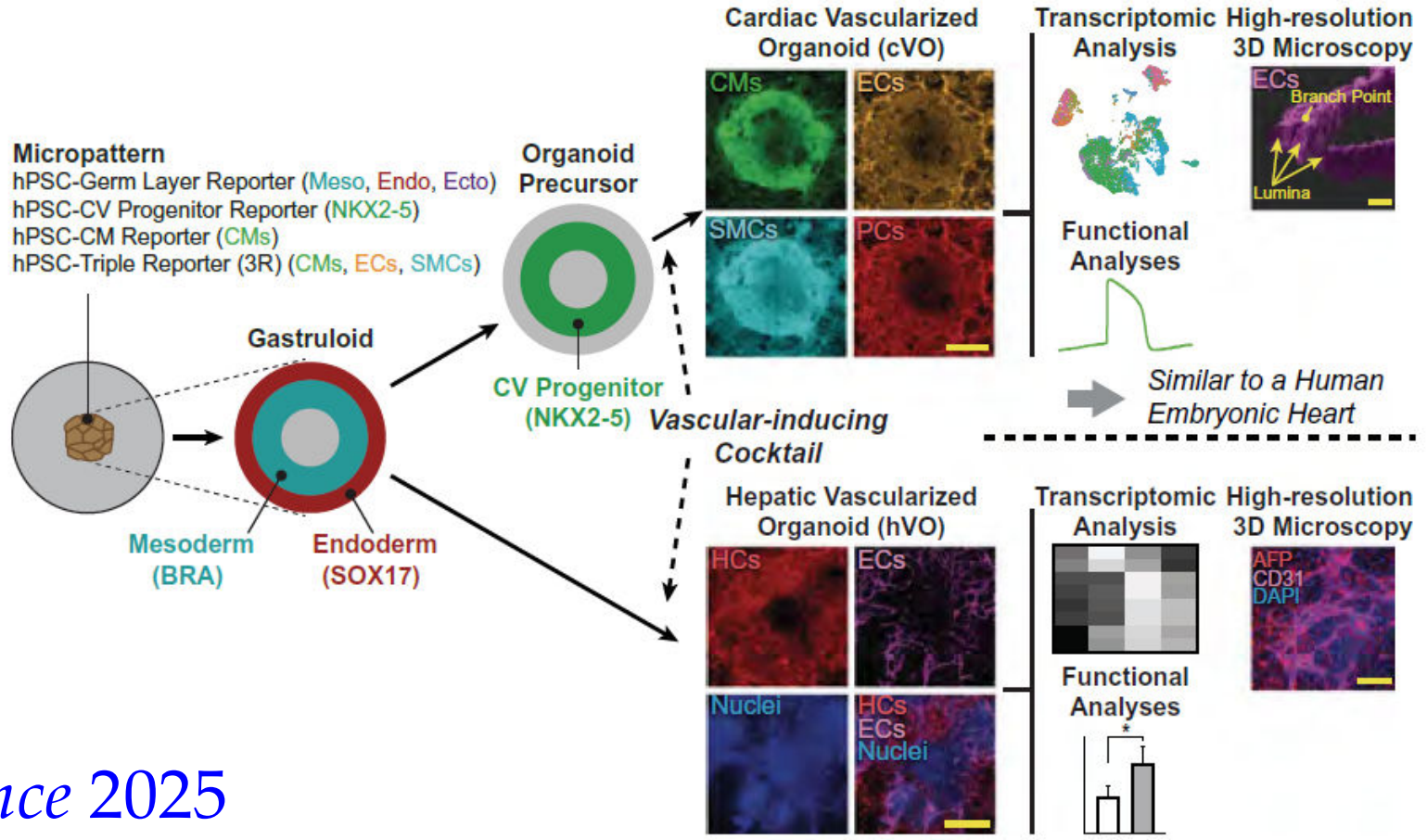
Aim 1: Develop an automated platform to monitor cardiovascular homeostasis and inflammation

- ✓ Generation of triple-reporter iPSC lines
- ✓ TNNT2-eGFP (cardiomyocyte)
- ✓ CDH5-mCherry (endothelial cell)
- ✓ ISRE/GAS-BFP (interferon-stimulated response element)/(gamma-activated sequence
- ✓ Reporter response to IFN-γ, TNF-α, and IL-6 stimuli
- ✓ Differentiation of 3D vascularized iPSC-cardiac organoids

Gastruloids enable modeling of the earliest stages of human cardiac and hepatic vascularization

Oscar J. Abilez†* Huaxiao Yang†, Yuan Guan, Mengcheng Shen, Zehra Yildirim, Yan Zhuge, Ravichandra Venkateshappa, Shane R. Zhao, Angello H. Gomez, Marcel El-Mokahal, Logan Dunkenberger, Yoshikazu Ono, Masafumi Shibata, Peter N. Nwokoye, Lei Tian, Kitchener D. Wilson, Evan H. Lyall, Fangjun Jia, Hung Ta Wo, Gao Zhou, Bryan Aldana, Ioannis Karakikes, Detlef Obal, Gary Peltz, Christopher K. Zarins, Joseph C. Wu*

Micropatterning of four hPSC reporter lines enabled gastruloid, cardiovascular, progenitor, and cVO formation. The identification of a vascular-inducing cocktail of growth factors enabled generation of a spatially organized, branched, and lumenized vascular network within a multilineage cVO. Transcriptomics, high-resolution 3D microscopy, and functional analyses showed that cVOs are similar to a human embryonic heart. The same vascular-inducing cocktail was then used to produce hVOs. CMs, cardiomyocytes; ECs, endothelial cells; SMCs, smooth muscle cells; PCs, pericytes; HCs, hepatocytes.



Science 2025

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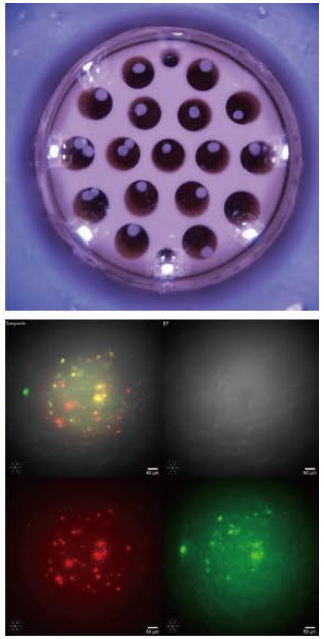
Implementation Partner: Space Tango



Space Tango operates permanent facilities on the ISS, including TangoLab, which houses CubeLab—self-contained, automated units that enable researchers to conduct experiments under microgravity with minimal crew intervention. Each CubeLab is composed of 12 customizable wells, allowing for various cell culture platforms (such as brain organoids). These units are equipped with high-resolution phase contrast and fluorescence cameras, enabling real-time imaging and data capture of experiments conducted in space.

Shared Resources: Human iPSC Biobank

1) World's largest biorepository of **2,500+ iPSC lines** from patients with different medical history, ethnicity, sex, and isogenic lines using CRISPR genome editing.

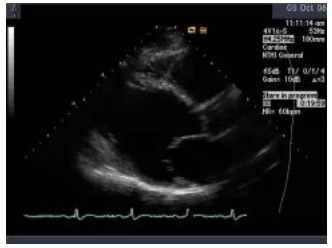
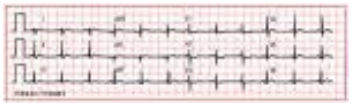
2) Link to medical information using clinical database

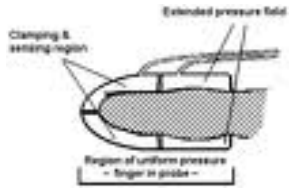
3) Perform multi-omics of human population using iPSC derivatives

4) Understand how human genetic variants impact drug response phenotypes.

5) Working with the FDA CERSI on drug safety testing

6) Robust sharing resource plan with the broader scientific community.



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Shared Resources: AI & Molecular Docking Platforms

Library of compounds

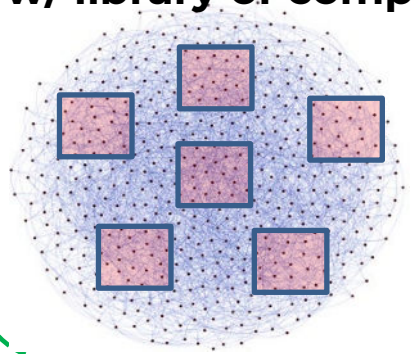
FDA

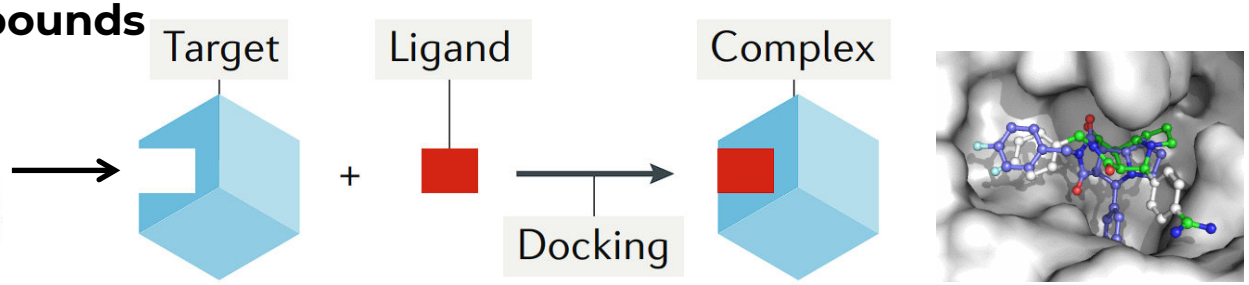
WuXi AppTec

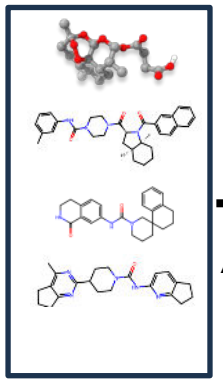
Enamine

Conceptual Overview of Molecular Docking

Sample chemical space w/ library of compounds

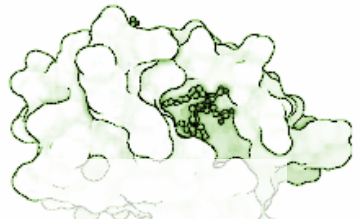




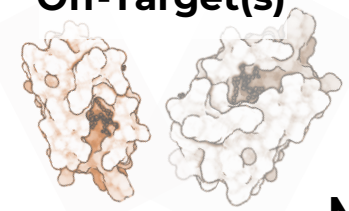


Dock molecules

Autodock Vina



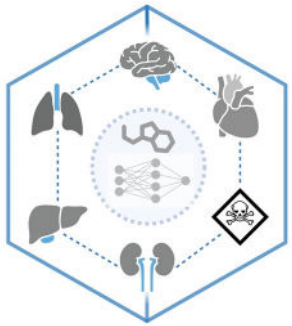
On-Target(s) & Off-Target(s)

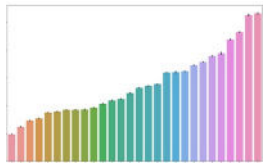


Refine Docking

Boltz-2

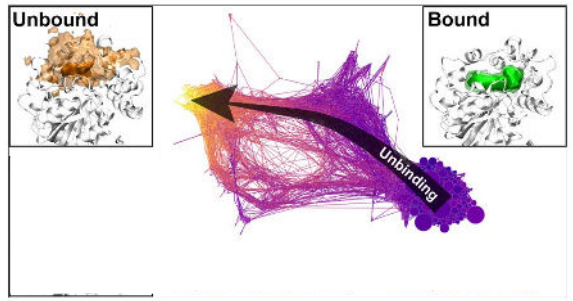
Greenstone ADMET-AI





Score and Rank molecules

Molecular Dynamics (MD) simulations



GROMACS

<u>Multi-dimensional analysis</u> for drug-like properties

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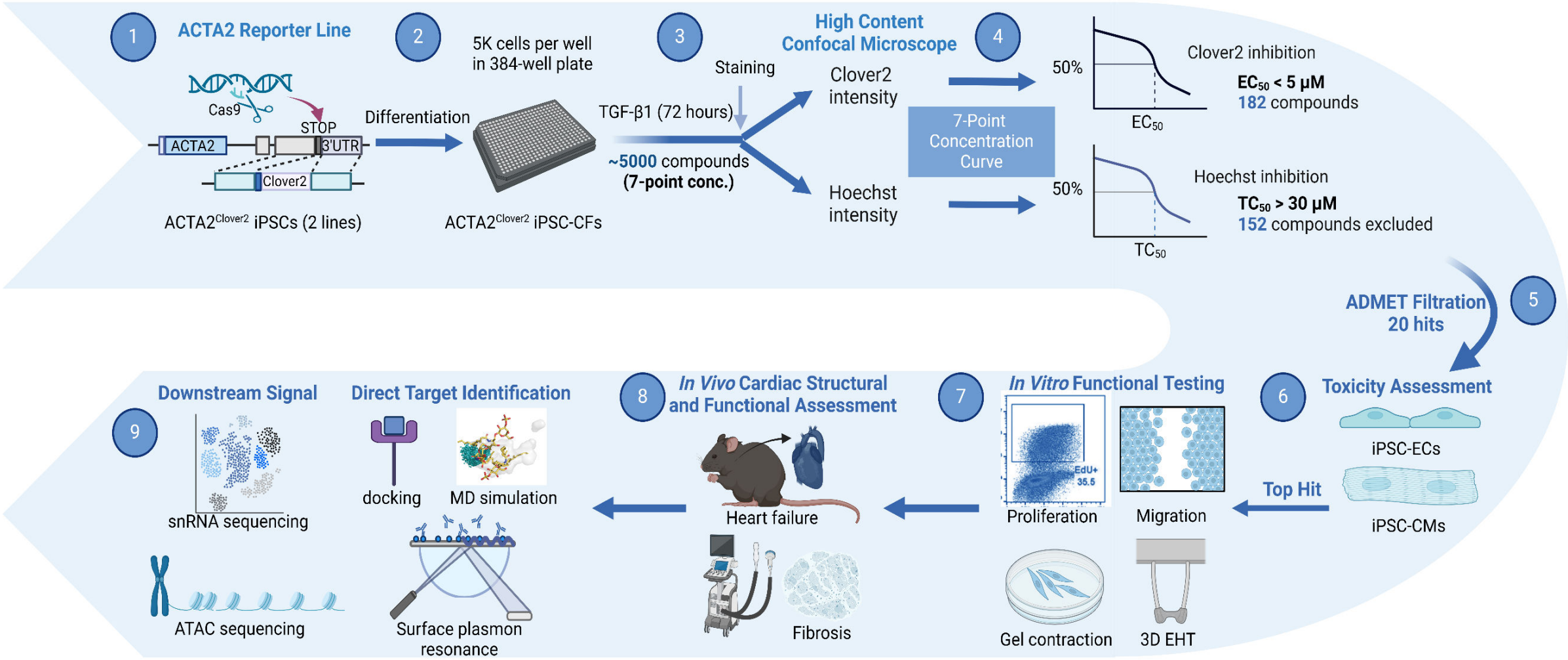
Drug Discovery Pipeline: From Genomics to *In Silico* to *In Chemico* to *In Vivo* Target Validation



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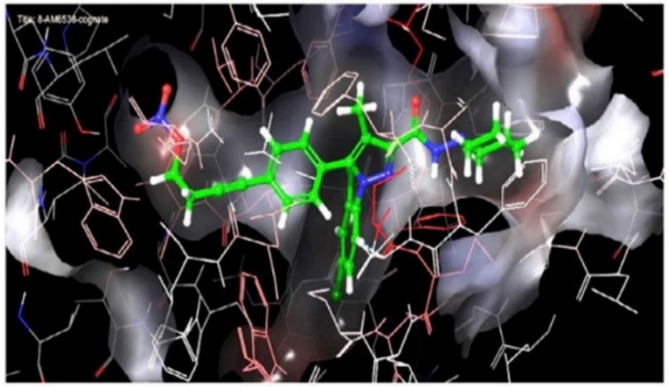
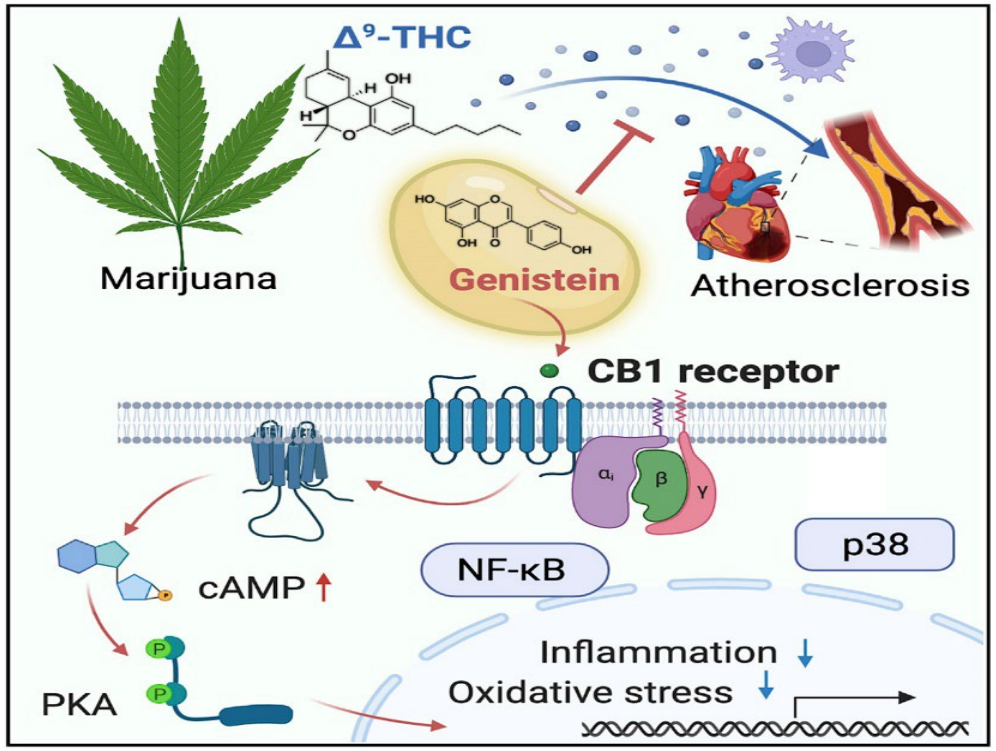
Ex #1

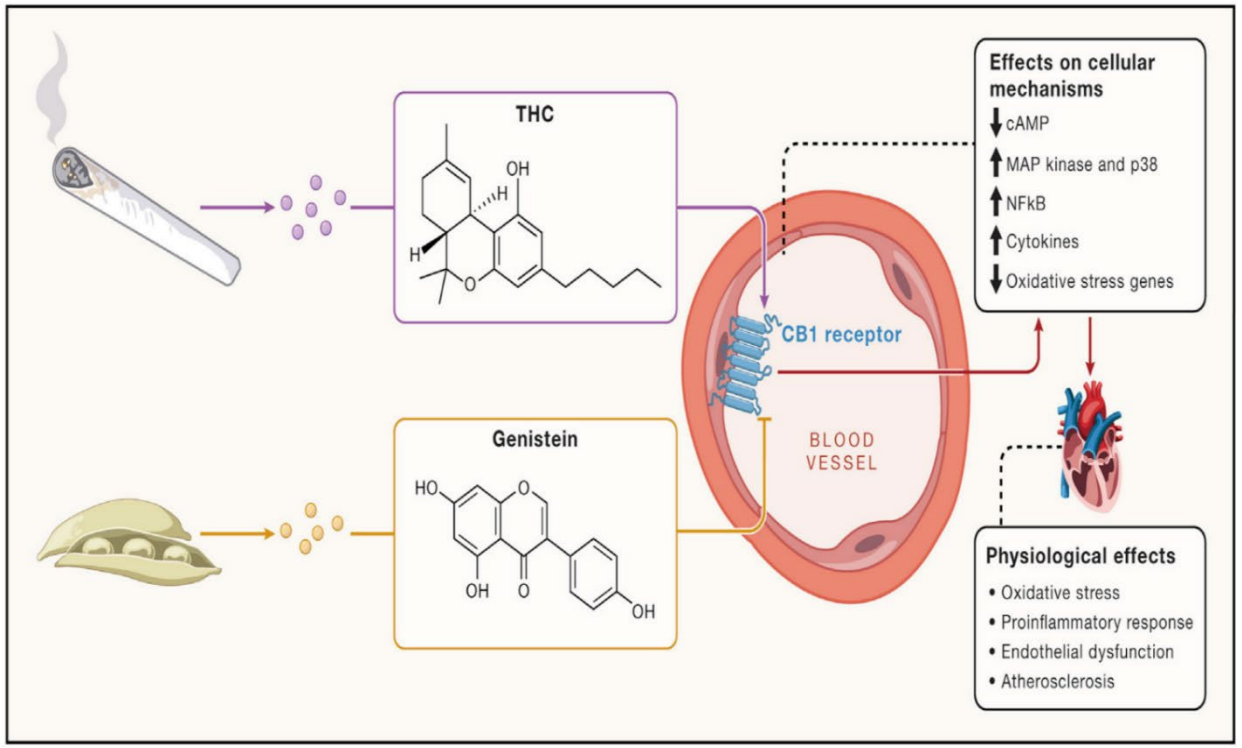
Cannabinoid receptor 1 antagonist genistein attenuates marijuana-induced vascular inflammation

Tzu-Tang Wei,[1,2,3,6,7,17] Mark Chandy,[1,2,3,14,17] Masataka Nishiga,[1,2,3,17] Angela Zhang,[1,2,3] Kaavya Krishna Kumar,[4] Dilip Thomas,[1,2,3] Amit Manhas,[1,2,3] Siyeon Rhee,[1,2,3,14] Johanne Marie Justesen,[2,5,8] Ian Y. Chen,[1,2,3] Hung-Ta Wo,[1,2,3,16] Saereh Khanamiri,[1,2,3] Johnson Y. Yang,[1,2,3] Frederick J. Seidl,[9] Noah Z. Burns,[9] Chun Liu,[1,2,3] Nazish Sayed,[1,2,3] Jiun-Jie Shie,[10] Chih-Fan Yeh,[6,11] Kai-Chien Yang,[6,11] Edward Lau,[12] Kara L. Lynch,[13] Manuel Rivas,[5] Brian K. Kobilka,[4,15] and Joseph C. Wu[1,2,3,14,18,*]

AM6538 (green, blue, red, and white), CB1-R (Gray)







Cell 2022 (Genistein)

Studying the Effects of Cannabis on Vasculature (SECV) NCT05581368

Mark Chandy

ClinicalTrials.gov ID NCT05581368

Sponsor London Health Sciences Centre Research Institute OR Lawson Research Institute of St. Joseph's

Information provided by Mark Chandy, London Health Sciences Centre Research Institute OR Lawson Research Institute of St. Joseph's (Responsible Party)

Last Update Posted 2024-04-10

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Study Overview
Contacts and Locations
Participation Criteria
Study Plan
Collaborators and Investigators
Study Record Dates
More Information

Study Overview

Brief Summary

Cannabis is commonly used globally. It is associated with psychiatric problems, but the effects on the cardiovascular system are unclear. In this project, the investigators plan to study the effects of cannabis on the cardiovascular system. This will be done by using a non-invasive test to measure blood vessel function and by using blood samples to measure inflammation. As a control for this project, the investigators would like to test the blood vessel function and inflammation levels of participants who do not use cannabis. This study will provide important information on the long term cardiovascular effects of cannabis.

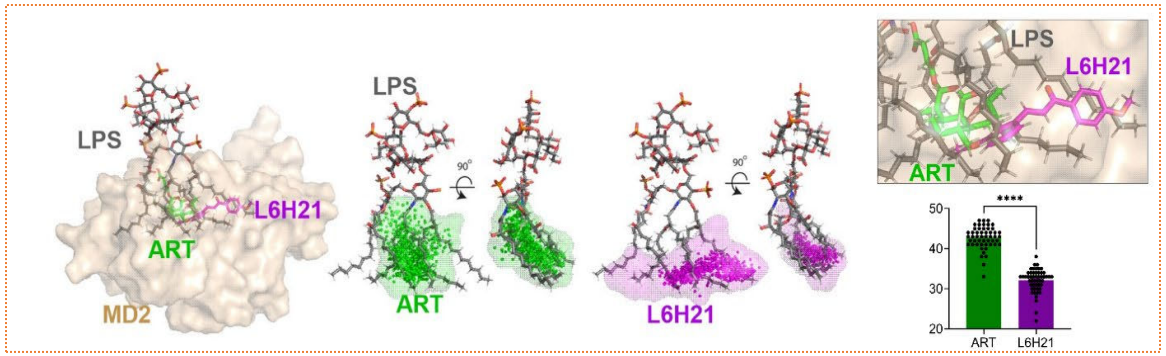
Study Start (Actual)
2023-12-01

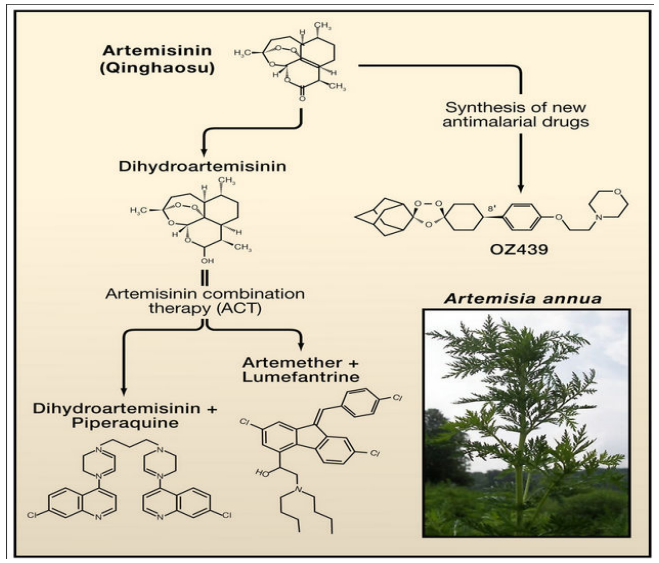
Primary Completion (Estimated)
2024-12

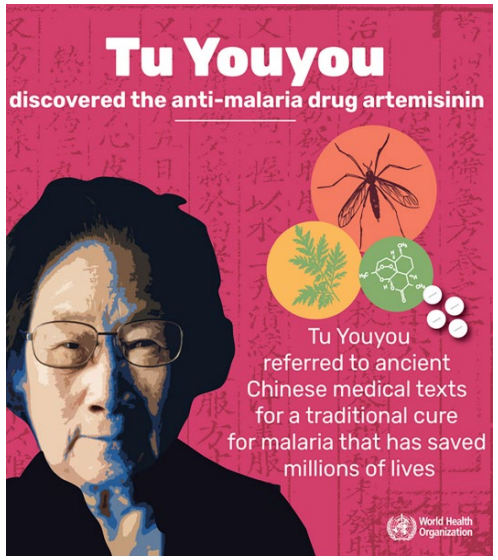
Study Completion (Estimated)
2024-12

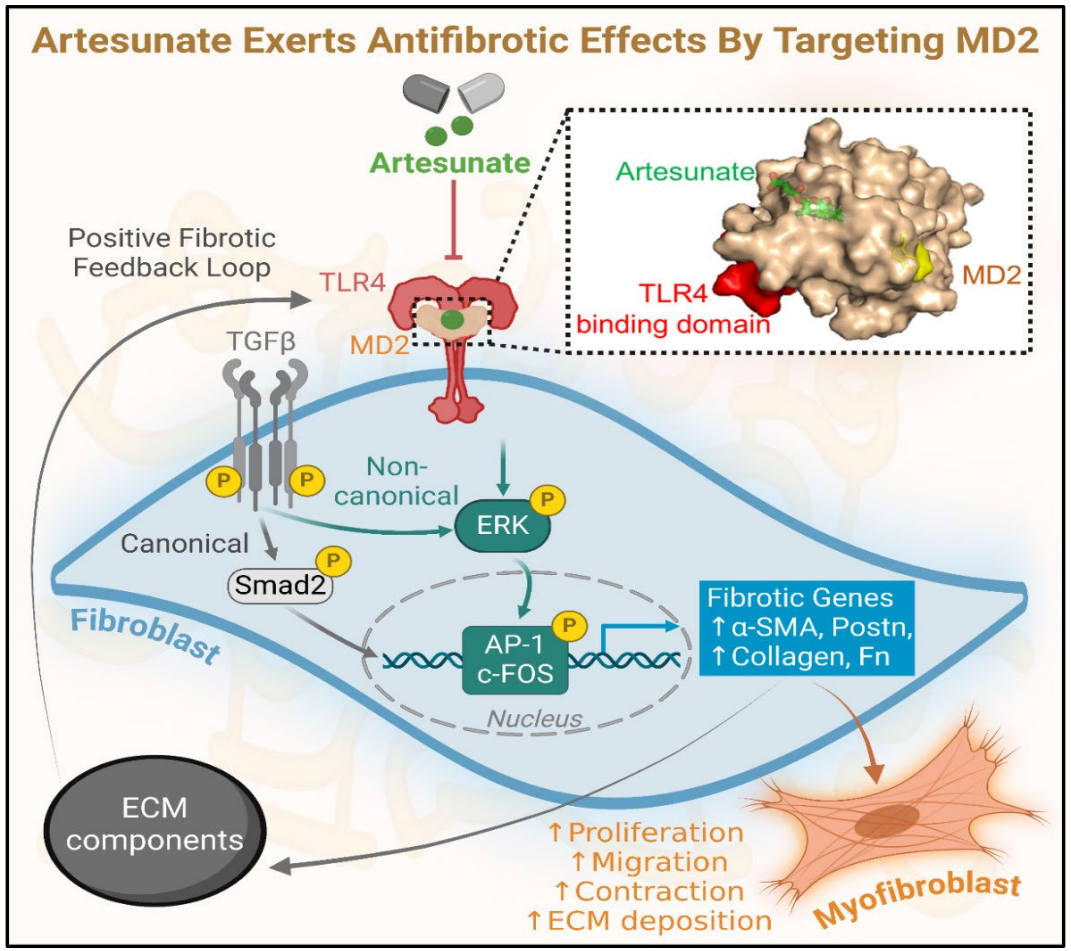
Ex #2 Multiscale Drug Screening for Cardiac Fibrosis Identifies MD2 as a Therapeutic Target

Hao Zhang,[1,2,3,9,*] Phung N. Thai,[4,5,9] Rabindra V. Shivnaraine,[6] Lu Ren,[1,2,3] Xuekun Wu,[1,2,3] Dirk H. Siepe,[7] Yu Liu,[1,2,3] Chengyi Tu,[1,2,3] Hye Sook Shin,[1,2,3] Arianne Caudal,[1,2,3] Souhrid Mukherjee,[6] Jeremy Leitz,[6] Wilson Tan Lek Wen,[1,2,3] Wenqiang Liu,[1,2,3] Wenjuan Zhu,[1,2,3] Nipavan Chiamvimonvat,[4,8] and Joseph C. Wu[1,2,3,10,*]









Open-Label Dose-Escalation Treatment of Patients with Idiopathic Pulmonary Fibrosis (DIAMOND) NCT05988463

Josh Mooney

ClinicalTrials.gov ID NCT05988463

Sponsor Joseph C. Wu

Information provided by Joseph C. Wu, Stanford University (Responsible Party)

Last Update Posted 2024-10-18

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Study Details | Researcher View | No Results Posted | Record History

On this page

- Study Overview
- Contacts and Locations
- Participation Criteria
- Study Plan
- Collaborators and Investigators
- Study Record Dates
- More Information

Study Overview

Brief Summary

Idiopathic Pulmonary Fibrosis (IPF) is a chronic progressive fibrotic lung disease resulting in increasing shortness of breath, cough, and low oxygen levels as a result of lung tissue scarring . The goal of this open-label (no placebo) study is to evaluate the safety and tolerability of artesunate at three different doses in patients with IPF. The secondary goals are to explore the blood biomarkers present in IPF patients at the beginning of the study and to study how those biomarkers change following treatment with artesunate. Participants will have 7 visits to the study site over 20 weeks which will include physician exams, vital signs, questionnaires, research and safety blood samples, and taking artesunate capsules by mouth for 12 weeks.

Study Start (Estimated)
2025-05-01

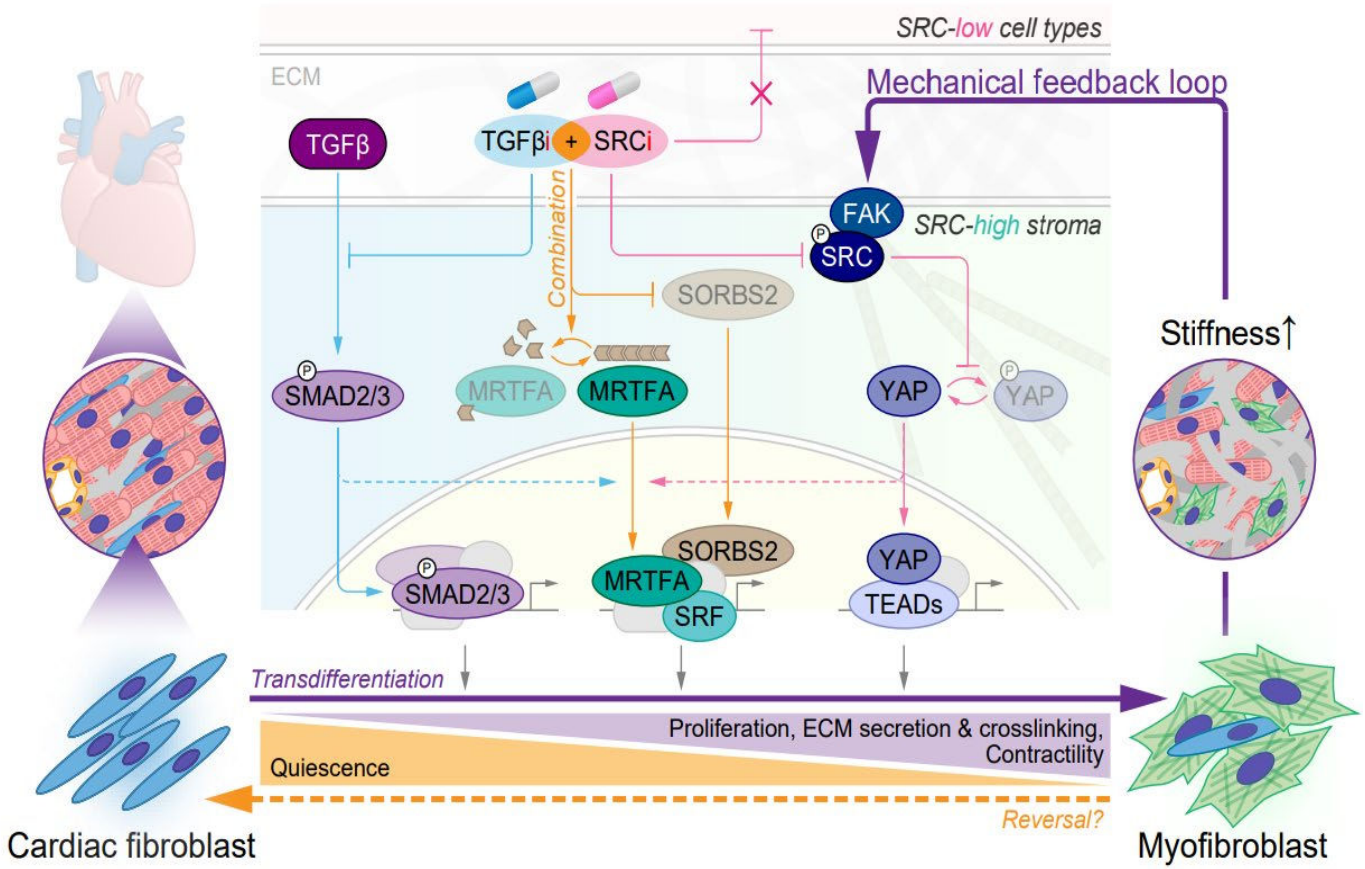
Primary Completion (Estimated)
2026-11-01

Study Completion (Estimated)
2026-11-01

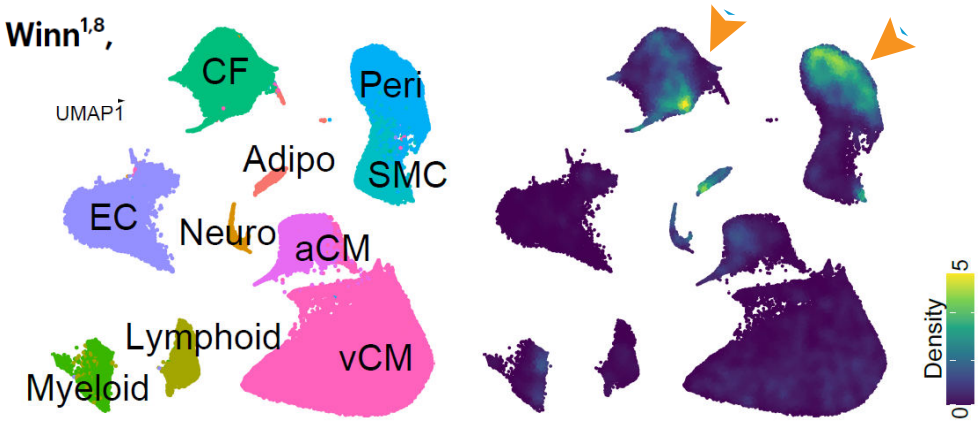
Enrollment (Estimated)

Ex #3 Selective Inhibition of Stromal Mechanosensing Suppresses Cardiac Fibrosis

Sangkyun Cho[1,2,10]✉, Siyeon Rhee[1,2,3,10], Christopher M. Madl[4,5], Arianne Caudal[1,2], Dilip Thomas[1,2], Hyeonyu Kim[1,2], Ana Kojic[1,2], Hye Sook Shin[1,2], Abhay Mahajan[1,2], James W. Jahng[1,2], Xi Wang[6], Phung N. Thai[7], David T. Paik[1,2], Mingqiang Wang[1,2], McKay Mullen[1,2], Natalie M. Baker[1,2], Jeremy Leitz[3], Souhrid Mukherjee[3], Virginia D. Winn[1,8], Y. Joseph Woo[1,9], Helen M. Blau[1,2,4] & Joseph C. Wu[1,2,3]✉

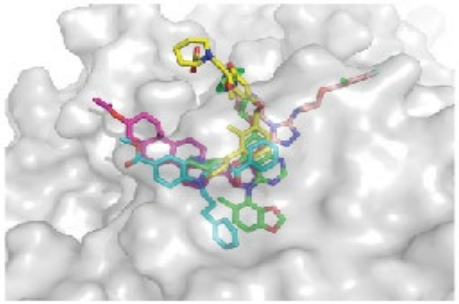


Enriched expression of **mechanosensor *SRC*** in cardiac stroma (vs other cell types)

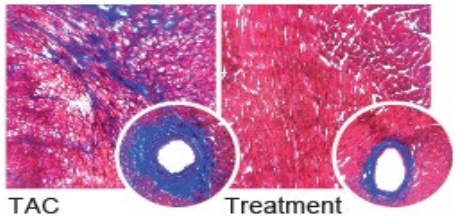


Human Heart Cell Atlas, *Nature* (2020)

Docking screen (>10,000 compounds) & MD simulations → Top candidate SRC inhibitor (SRCi) Saracatinib



Synergy w/ TGFβi in attenuation of fibrosis



Nature 2025 (Saracatinib)

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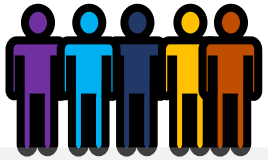
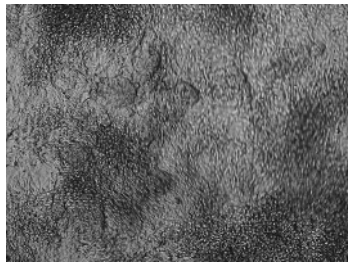
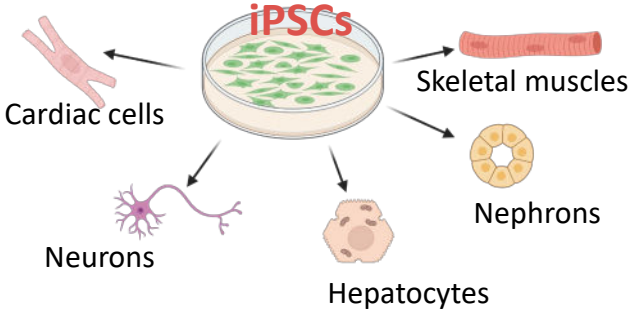
Tissue Chips in Space 2.0: Identify and Develop Therapeutic Targets to Mitigate Microgravity Cardiovascular Inflammation

Patient iPSCs → **Genomics & CRISPR** → **AI/ML** → **Drug Discovery**



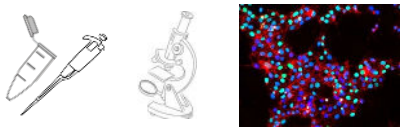
Human iPSC lines = **"biological twin"**





"Digital twin" dataset

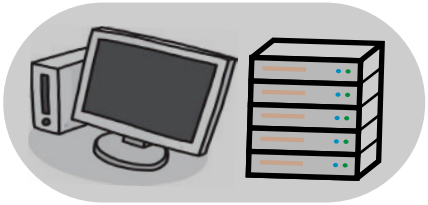
Single cell RNA sequencing



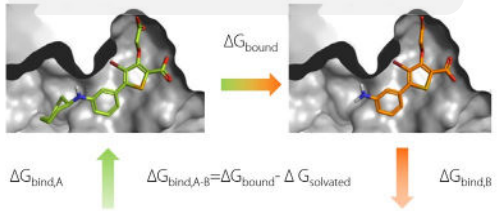
High-throughput wet-lab experiments and imaging

Differential gene expression

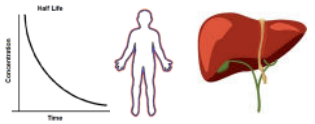
Pathway enrichment analysis



Molecular docking

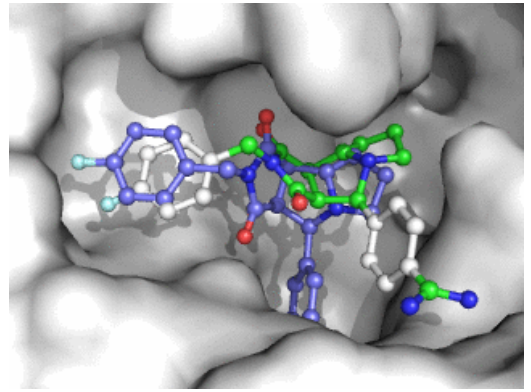


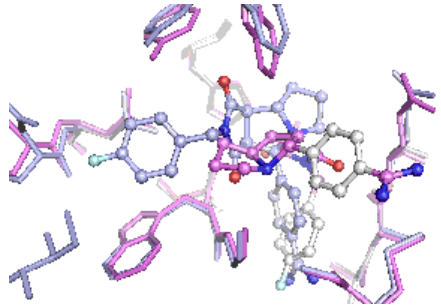
Molecular Dynamics (MD) simulations



In silico ADMET prediction

Novel molecular target
Novel drugs
Repurposing of drugs





Stanford | Cardiovascular Institute

SDDS 2026

Stanford Drug Discovery Symposium

April 27-28, 2026

More Information & Registration

Lifetime Achievement Awardees

Carl June, MD
Richard W. Vague Professor in Immunotherapy in the Department of Pathology and Laboratory Medicine, University of Pennsylvania

Steven Rosenberg, MD, PhD
Chief, Surgery Branch, Center for Cancer Research, National Cancer Institute, NIH

Michel Sadelain, MD, PhD
Herbert and Florence Irving Professor of Medicine, Columbia University

Karen Akinsanya, PhD
President, Head of Therapeutics R&D and Chief Strategy Officer, Partnerships, Schrödinger

David Baker, PhD
2024 Nobel Laureate; Henrietta and Aubrey Davis Endowed Prof of Biochemistry, Univ of Washington School of Medicine

Carolyn Bertozzi, PhD
Nobel Laureate 2022 Baker Family Director of Sarafan ChEM-H

Chris Boshoff, MD, PhD
CSO and President, R&D, Pfizer

James Bradner, MD
Executive Vice President of Research & Development, Amgen

Robert Bradway, MBA
Chairman and CEO, Amgen

Jonathan Cohen
Vice President of Applied Research, NVIDIA

Michael Devoy, MB, BS
CMO and EVP of MedAffairs & Pharmacovigilance, Bayer

Sonia Gupta, MBA
Partner, Co-Head of Biopharma Investment Banking, Goldman Sachs

Alistair Henry, PhD
Executive Vice President & CSO, UCB

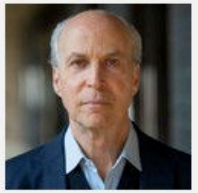
Sandra Horning, MD
Board Member, Gilead; Board Member, Moderna

Thomas Hudson, MD
Venture Partner, Versant Ventures

Joe Jimenez, MBA
Co-Founder and Managing Director, Aditum Bio

Nicole Kleinstreuer, PhD
Acting NIH Deputy Director of Program Coordination, Planning, and Strategic Initiatives

Brian Kobilka, MD
Nobel Laureate 2012; Helene Irwin Fagan Chair of Cardiology, Stanford University



Roger Kornberg, PhD
Nobel Laureate 2006; Mrs. George A. Winzer Professor of Medicine, Stanford University

Jerry Lee, MBA
Partner Managing Director, Investment Banking, Goldman Sachs

Dean Li, MD, PhD
Executive Vice President and President, Merck Research Laboratories

Flavius Martin, MD
Executive Vice President, Research, Gilead

Brett Monia, PhD
CEO, Ionis

Vijay Pande, PhD
Co-Founder and Managing Partner, VZVC

Robert Plenge, MD, PhD
Executive Vice President, Chief Research Officer, Bristol Myers Squibb

Andrew Plump, MD, PhD
President of Research and Development, Takeda

Michael Quigley, PhD
CSO and Global Head of Research, Sanofi

John Reed, MD, PhD
Executive Vice President, Innovation Medicine, R&D, Johnson & Johnson

Aviv Regev, PhD, Msc
Head, Executive Vice President, Genentech Research and Early Development

Randy Schekman, PhD
Nobel Laureate, 2013; Professor of Molecular and Cell Biology, University of California, Berkeley

Amit Sinha, MBA
Partner, CIO and Global Head of Life Sciences Investing, Goldman Sachs

Thomas Südhof, MD
Nobel Laureate 2013; Avram Goldstein Professor and Prof of Neurosurgery, Stanford University

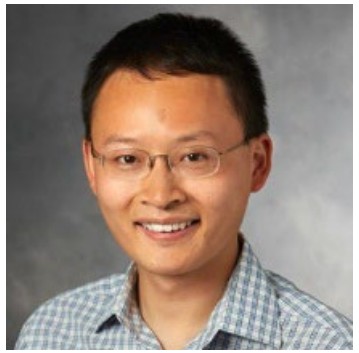
Eric Tokat
Co-President of Investment Banking and Partner, Centerview Partners


THANK YOU

UG3/UH3: "Assessing Effects of Microgravity on Cardiovascular Aging with AI and 3D Organoids"

PI Joseph Wu
Disease Modeling

Co-PI Afshin Beheshti
Space Multi-omics

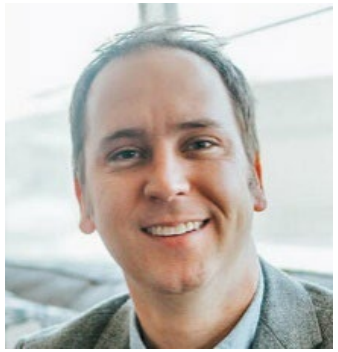


Co-I James Zou
AI/ML

Co-I Sarah Heilshorn
Biomaterial

Co-I Mark Skylar Scott
Biofabrication

Co-I Stanley Qi
Genome Editing



Twyman Clements
Space Tango

Shelby Giza
Space Tango

Amanda Chase
Program Manager

Won Suk Jahng
Postdoc

Renke Tan
Postdoc

Thulaj Meharwade
Postdoc

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