# Advancing Drug Discovery and Toxicology with Human iPSC-Derived 3D Cardiac and Brain Microtissues

Abstract no. #329

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Ncardia

reNEW Novo Nordisk Foundation Center for Stem Cell Medicine

LUMC Leids Universitair Medisch Centrum

## Background

Despite major advances in drug development, attrition rates remain high—particularly for cardiovascular and CNS indications—largely due to the limited predictive power of traditional preclinical models, which often fail to recapitulate human tissue architecture, multicellular interactions, and functional complexity. Human induced pluripotent stem cell (iPSC)–derived 3D microphysiological systems (MPS) offer a promising alternative by enabling more human-relevant assessment of drug efficacy and toxicity.

## Objective

To develop and functionally validate **scalable human iPSC-derived 3D cardiac and brain microtissue platforms** that enable:

- Robust and reproducible modelling of human tissue function
- Disease-relevant phenotyping across CV and CNS systems
- High-throughput, predictive drug discovery and toxicology assessment

## 1. High-Throughput Screening with Ncardia Cardiac Microtissues

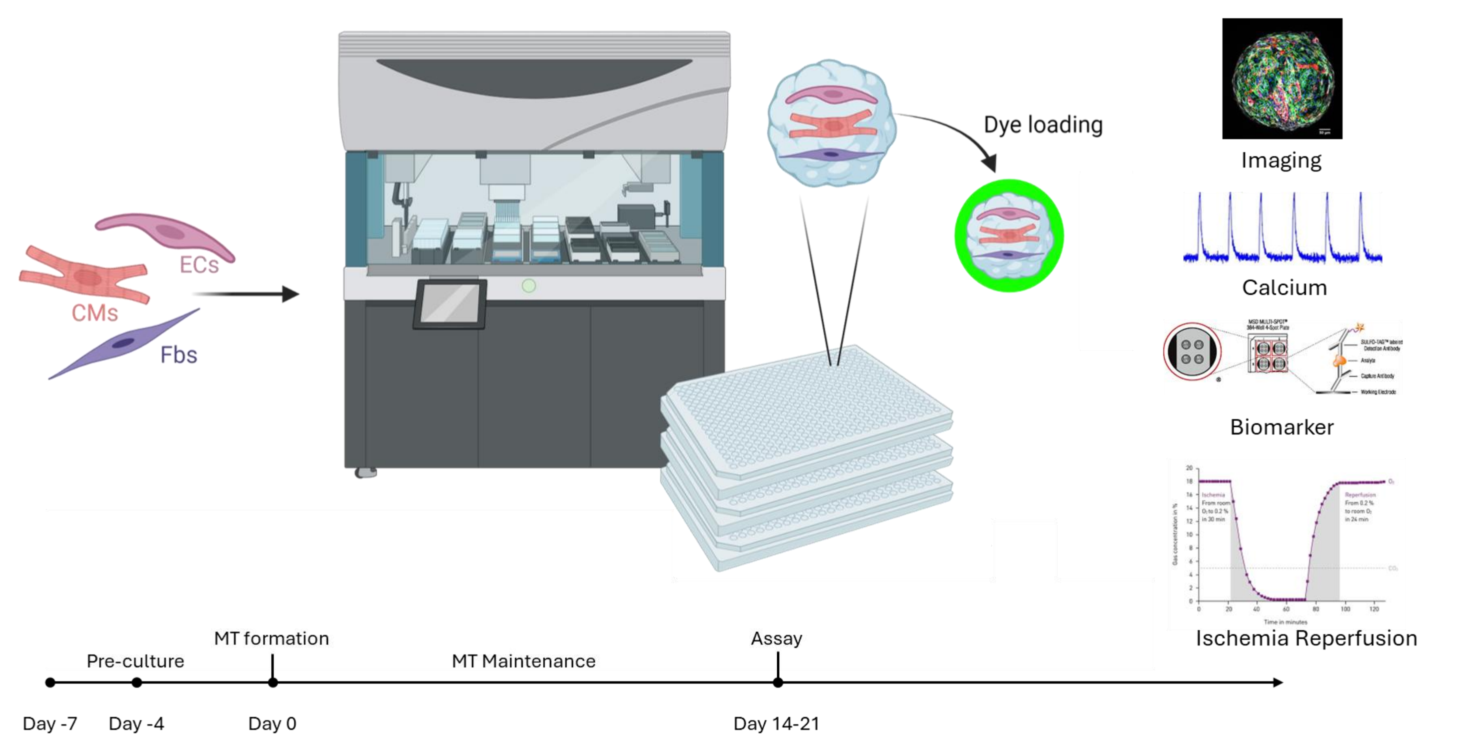


**Figure 1. Workflow illustrating the preparation and use of 3D cardiac microtissues from Ncyte® iPSC-derived cardiomyocytes, endothelial cells and cardiac fibroblasts for high throughput screening** (Modified from https://doi.org/10.1016/j.tibtech.2025.11.016.)

## 2. Heart in Box™: Identity, morphology and functionality

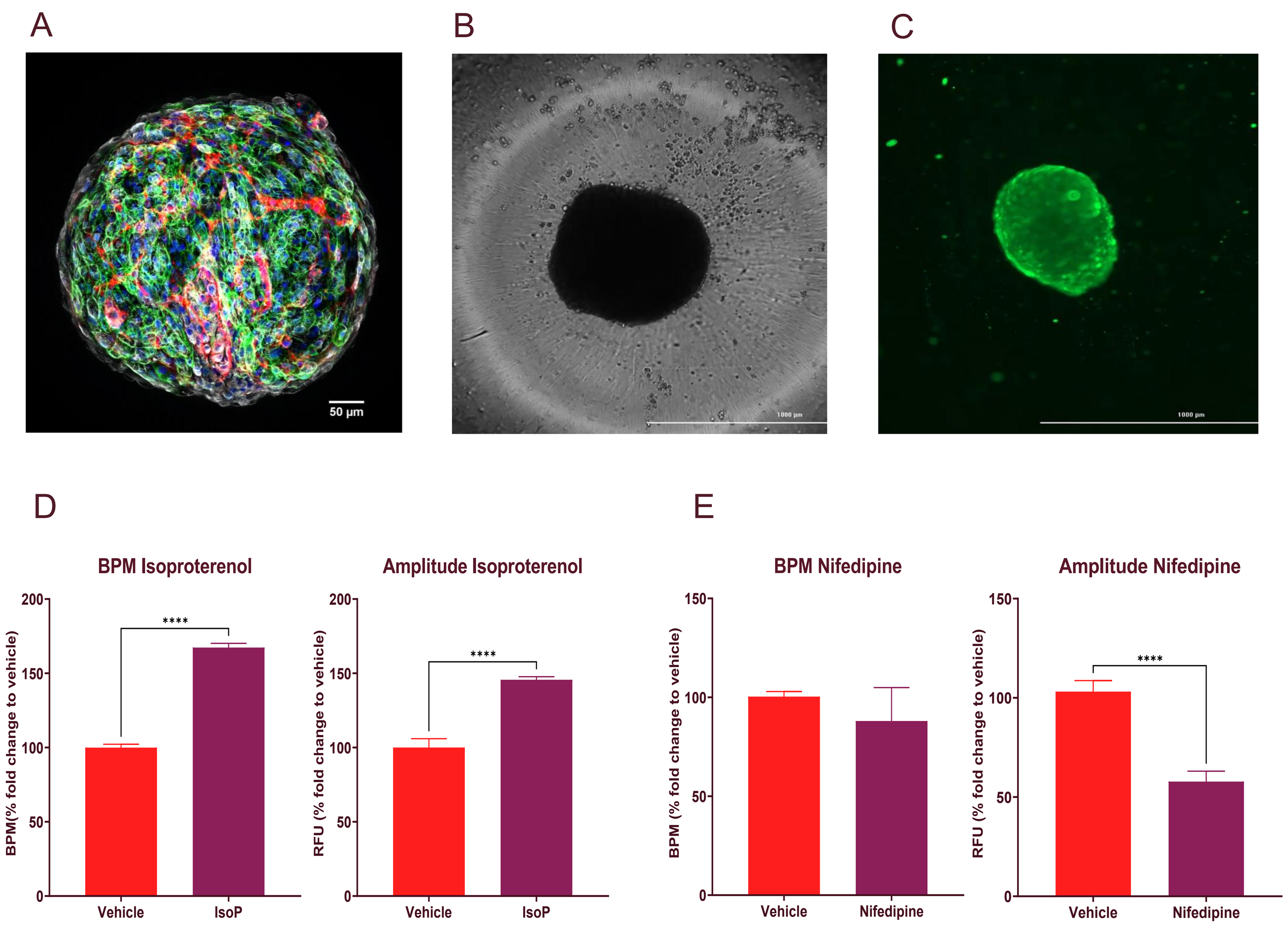


**Figure 2. Identity, morphology and functionality of Heart in Box™ Microtissue.**

A. Immunostaining of Ncyte® Heart in a Box™. Nucleus (blue), Cardiac troponin T (green), CD31 (red), α SMA (white). 20X Image.
B. Brightfield image showing the morphology and structure of a 3D cardiac microtissue.
C. 3D cardiac microtissues stained using FLIPR6 for calcium imaging.
D. Isoproterenol, a β-adrenergic agonist, significantly increases the beating rate (BPM) and amplitude of 3D cardiac microtissues, indicating a positive chronotropic effect.
E. Nifedipine, a calcium channel blocker, shows no effect on the beating rate (BPM) of 3D cardiac microtissues while significantly decreases the amplitude of contraction in CMs, demonstrating a negative inotropic effect.

## 3. Heart in Box™: Disease modelling and Drug screening

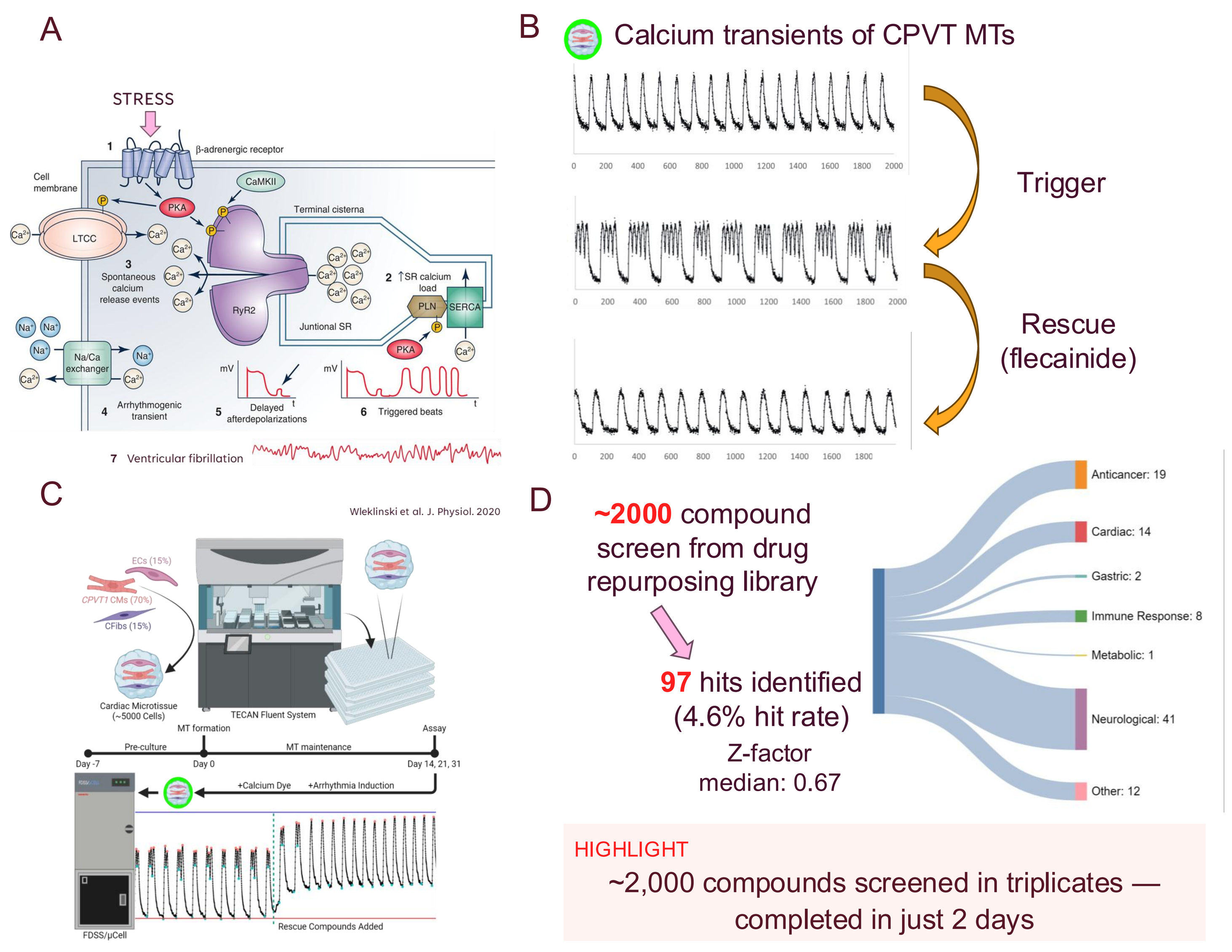


**Figure 3. Disease modeling and High-throughput screen in CPVT1.**

A. Schematic showing how β-adrenergic stimulation in CPVT1 leads to PKA-mediated phosphorylation of RYR2 on the sarcoplasmic reticulum, resulting in leaky channels, abnormal calcium release, and ventricular arrhythmias.
B. Representative calcium traces from CPVT MTs highlight arrhythmic activity and pharmacological correction.
C. Overview of the fully automated system for forming, maintaining, treating, recording and analyzing calcium transients in CPVT microtissues.
D. Alluvial diagram summarizing results from ~2,000-compound screen. 97 hits identified (4.6% hit rate); median Z'-factor of 0.67 confirms assay robustness.

## 4. Brain Microtissues: Generation and Characterization

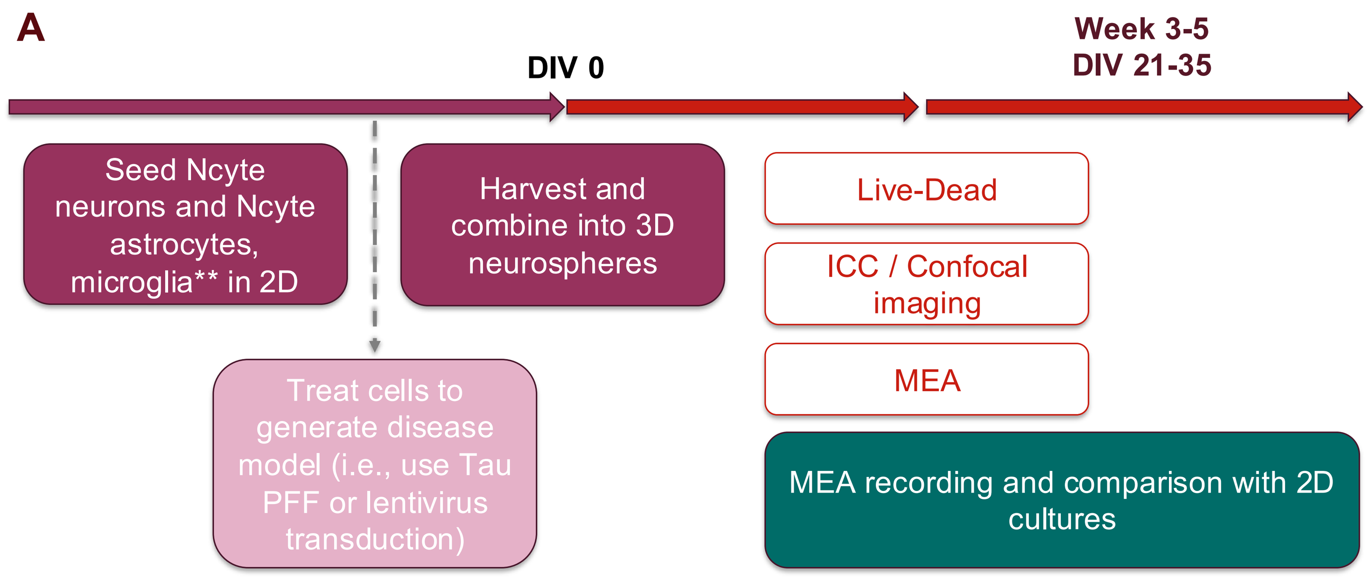


**Figure 4A. Experimental pipeline, timeline and endpoints of Ncardia's Brain Microtissue generation and characterization.** DIV: day in vitro, used to indicate the day of 3D culture.

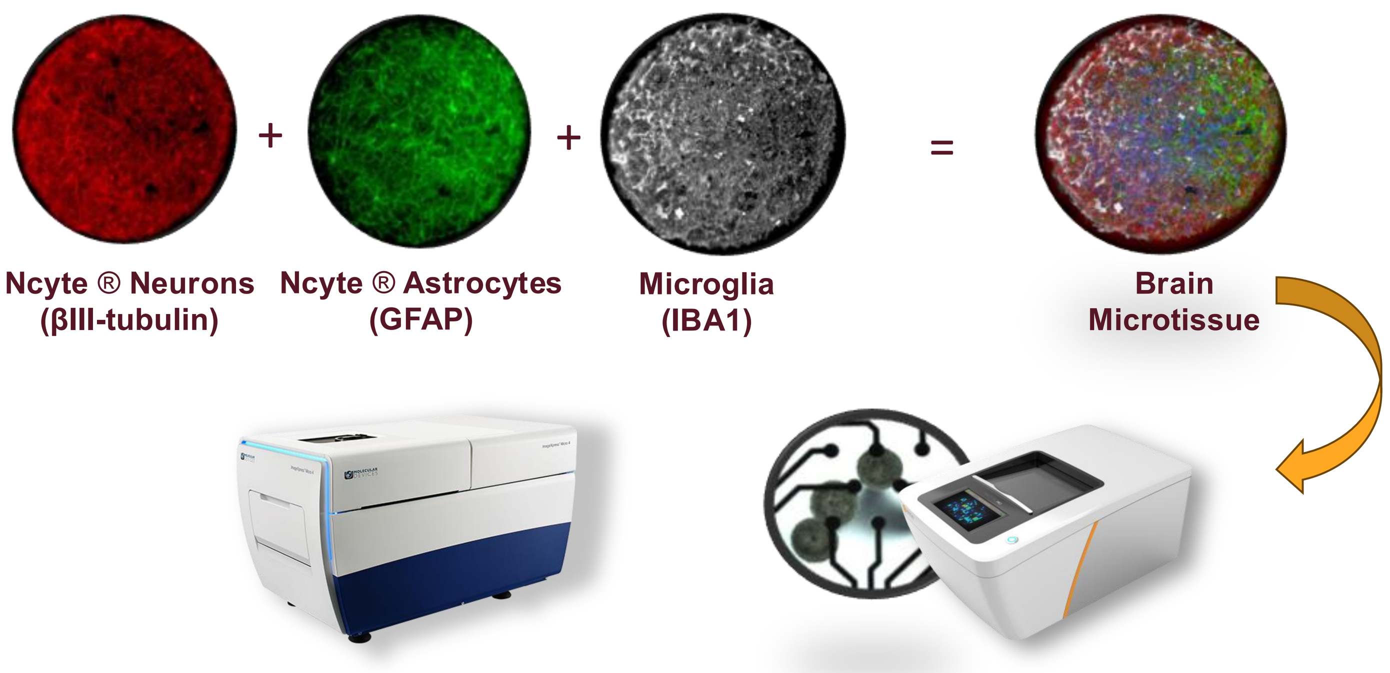


**Figure 4B. Immunofluorescence for cellular markers.** Microtissues were stained for neuronal marker βIII-tubulin (in red) and astrocyte marker GFAP (in green) and microglia marker IBA-1 (in white). Nuclei were stained with DAPI.

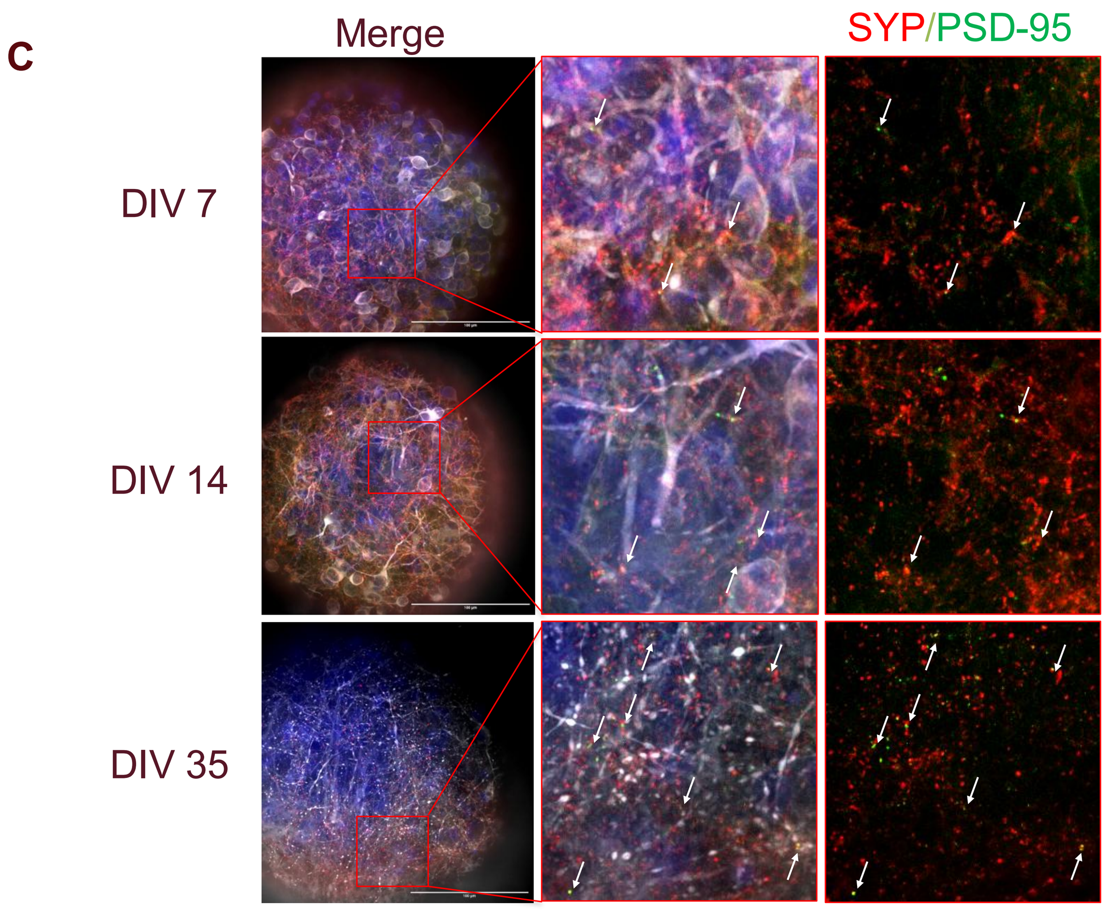


**Figure 4C. Immunofluorescence for synaptic markers.** Microtissues were stained after 1 week in 3D culture (DIV 7), 2 weeks (DIV 14) and 5 weeks (DIV 35) for pre-synaptic marker synaptophysin- SYP (in red), post-synaptic marker PSD-95 (in green) and neuronal marker MAP2 (in grey). Nuclei were stained with DAPI (in blue).

Arrows indicate synaptic structures, expressing SYP and PSD-95. SYP is highly expressed as early as DIV 7 and the expression is consistently maintained throughout culture. Post-synaptic marker PSD-95 is also expressed as early as DIV 7, though at a low level. Expression of PSD-95 is increased in time with highest expression reached at DIV 35. Colocalization of SYP and PSD-95 (in yellow) is also observed. Max projection. Scale bar 100 µm.

## 5. Brain Microtissues: Disease modelling and Drug screening

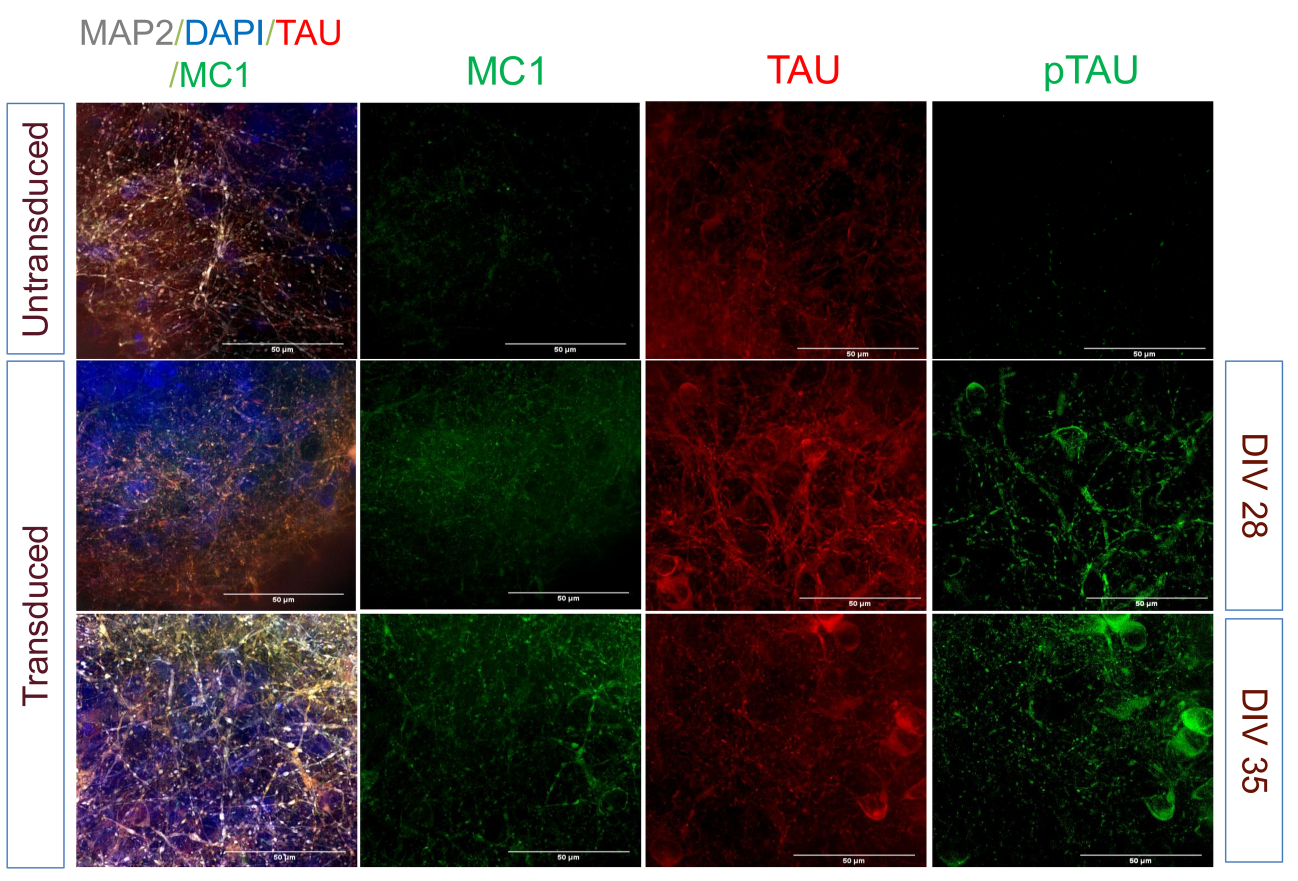


**Figure 6. Immunofluorescence for Tau/pTau/MC-1⁺ TAU.** Transduced microtissues were stained for neuronal marker MAP2, Tau, MC-1 and pTau. Nuclei are stained with DAPI. Untransduced microtissue are used as control. The microtissue show increased TAU and pTAU staining after transduction.

The platform developed at Ncardia can be easily adapted to generate complex 3D disease models that recapitulate better the pathology of the disease observed in patients. At Ncardia we used the in house developed Brain Microtissues to model Tau aggregation often observed in Alzheimer's disease.

## Leading the way in scalable production for Disease Modelling and Therapeutic Development.

- Human iPSC-derived 3D Cardiac and Brain Microtissues provide **scalable, physiologically relevant platforms** that improve the predictive power of preclinical models.
- These systems enable **robust disease modelling, high-throughput drug screening and patient-specific insights**, supporting both **drug discovery and safety assessment.**
- Together, they offer a powerful approach to **bridge the gap between preclinical testing and clinical outcomes** across cardiovascular and CNS indications.

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