Neuronal Models Symposium (NeuMoS) 2026

Organoids, NAMs, and Neural Circuit Assays for Disease and Drug Discovery

16 – 18 September 2026

Zurich

Join the Conversation!

#NeuMoS2026

@MaxWell Biosystems @mxwbio

Welcome

Welcome to the Neuronal Models Symposium (NeuMoS) 2026: Organoids, NAMs, and Neural Circuit Assays for Disease and Drug Discovery!

On behalf of the entire MaxWell Biosystems team, I am delighted to welcome you to Zurich and to NeuMoS 2026. It is wonderful to see so many of you joining us from around the world to exchange ideas, share discoveries, and connect as a community.

This year's symposium is the result of a tremendous collaborative effort with our Scientific Committee, Prof. Giorgia Quadrato, Prof. Yoshiho Ikeuchi, and Dr. Matt Kelley, and builds on the success of our previous editions of the MxW Summits.

The new name, **NeuMoS**, reflects an important evolution of the meeting: from a primarily technology-focused event to a broader, more integrative symposium bringing together the diverse disciplines shaping the future of in vitro neuronal network research.

Over the next two and a half days, our outstanding line-up of speakers will explore the growing convergence of neurotechnology, stem cell biology, organoids and other New Approach Methodologies (NAMs), and computational approaches. Together, we will examine how these advances are enabling increasingly sophisticated models of human neural function and expanding their potential for disease modeling and drug discovery.

Beyond the scientific talks, this year's program includes four hands-on workshops exploring emerging experimental and analytical approaches, from microfluidic patterning and AI-driven analysis to neural stimulation and the functional characterization of neural organoids.

We are also excited to feature special sessions on stem cell research and biomanufacturing in space and on the scientific editorial process. An interactive panel discussion, selected short talks, and poster sessions will create further opportunities to exchange perspectives, spark new ideas, and connect across disciplines.

Our product update will offer a glimpse into the latest developments at MaxWell Biosystems and an opportunity to discuss directly with our team how these innovations can support your research.

We are deeply grateful to our sponsors and partners for their support and for sharing our commitment to advancing in vitro research. By bringing together technology, biology, and diverse scientific perspectives, we hope NeuMoS will continue to grow as a meeting place for an increasingly connected and interdisciplinary community.

Enjoy NeuMoS 2026—and herzlich willkommen in Zürich!

Best,

Urs Frey

CEO of MaxWell Biosystems

Sponsors

Gold Sponsors

bit.bio combines the concepts of cell programming and biology to provide human cells for research, drug discovery, and cell therapy, enabling a new generation of medicines. Its precision human cellular reprogramming technology, opti-ox™, enables consistent, scalable manufacturing of human cells for a broad range of applications.

Open Culture Science develops open and accessible laboratory automation solutions for biological research. By combining hardware, software, and automation, the company aims to make cell culture and experimental workflows more reproducible, scalable, and accessible, helping researchers accelerate experimentation and discovery.

Silver Sponsors

Anatomic provides researchers with access to high-quality, hiPSC-derived human cells to help accelerate drug discovery. By leveraging directed differentiation, the company has developed a scalable platform for manufacturing human cells suitable for high-throughput assays, supporting more relevant and reproducible models for biomedical research and therapeutic development.

Nanion Technologies develops advanced instrumentation for functional cellular analysis and drug discovery. Its portfolio includes automated patch-clamp, impedance-based, and other electrophysiology platforms designed to enable high-quality functional measurements across a range of applications, from ion-channel research to complex cellular models.

Bronze Sponsors

Wunderlichips provides custom fabrication services for silicone elastomer (PDMS) microstructures and microfluidic devices for research in the natural and life sciences. Through expertise in soft lithography, surface treatments, tooling, and chip-to-world interfacing, the company supports researchers in turning their designs into customized microfluidic solutions tailored to their experimental needs.

Scientific Committee

Prof. Dr. Yoshiho Ikeuchi
The University of Tokyo, Japan

After finishing Ph.D. study on RNA modifications at The University of Tokyo, Yoshiho Ikeuchi conducted post-doctoral research in molecular and cellular neuroscience at the Harvard Medical School and Washington University, St. Louis until 2014. After returning to Japan, he has been conducting research on functional interrogation and engineering of neural organoids as a Principal Scientist at the Institute of Industrial Science, The University of Tokyo.

Dr. Matt Kelley
Alexion AstraZeneca, United States

Matt Kelley is a Principal Scientist at Alexion AstraZeneca Rare Disease, where he leads drug discovery programs in rare neurology with the goal of developing innovative and transformational treatments. He also leads Alexion Genomic Medicine's human iPSC-derived neuronal platform, integrating high-throughput molecular readouts with high-density microelectrode array (HD-MEA) electrophysiology to interrogate target engagement and disease-relevant circuit phenotypes on translational human cell models. Prior to Alexion, he held drug discovery program biology lead roles at Pfizer and Voyager Therapeutics, and completed postdoctoral training at Amgen, where he established HD-MEA and in vivo EEG capabilities supporting the Aimovig/erenumab (anti-CGRP) program. He earned his Ph.D. in Neuroscience from Tufts University and his B.S. in Neuroscience from UCLA. He serves on Professional Development Committee for the Society for Neuroscience.

Dr. Giorgia Quadrato
University of Southern California, United States

Giorgia Quadrato is an Associate Professor at USC's Department of Stem Cell Biology and Regenerative Medicine. She is also the Director of the USC CIRM ASCEND Shared Resource Laboratory, dedicated to offering organoids and other stem cell-based models, analyses, consultations, and in-depth education and training. Dr. Quadrato's lab focuses on understanding the cellular and molecular basis of human brain development and disease. By combining emerging models of the human brain with single-cell omics approaches, her lab aims to identify cell-type-specific disease mechanisms and, above all, new treatments for human neurodevelopmental disorders. Quadrato received the 2019 Donald E. and Delia B. Baxter Foundation Faculty Scholar Award, the 2020 Edward Mallinckrodt, Jr. Foundation Early Career Faculty Award, and the 2022 Broad Innovation Award. Since 2024, she has been a member of the Scientific Advisory Board of Cure Syngap1, and Quiver Bioscience.

Table of Contents

Conference Program

Wednesday, September 16

Location: Ambassador House Zürich, Thurgauerstrasse 101, 8152 Opfikon, Switzerland

8:30 - 9:30	Registration and Welcome Coffee	
9:30 - 9:40	Opening Remarks	
nanion	Decoding Neurological Disease with Human Neural Models Chair: Dr. Laura D'Ignazio (MaxWell Biosystems)	
9:40 - 10:25	Keynote Talk	From Genes to Circuits: Convergent Molecular Signatures of Autism Dr. Tom Nowakowski | University of California, San Francisco, United States
10:25 - 10:50	Scientific Talk	Brain Organoids as Platforms for Understanding and Treating Neurological Disorders Dr. Silvia Velasco | Novo Nordisk Foundation Center for Stem Cell Medicine, reNEW Melbourne, Australia
10:50 - 11:00	Short Talk	An Integrated Platform Combining Longitudinal High-Density MEA Electrophysiology and On-Chip Signal-Amplified Spatial Transcriptomics in Human iPSC Neural Networks Aayush Marishi | ETH Zürich, Switzerland
11:00 - 11:20	Product Update	From Activity to Insight: Functional Phenotyping with HD-MEAs Dr. Marie Obien | MaxWell Biosystems
11:20 - 11:50	Morning Coffee Break	
11:50 - 12:00	Short Talk	Isogenic Human Cerebellar Organoids Reveal RNA Processing and Translational Defects Underlying PCH2a Dr. Theresa Kagermeier | Karlsruhe Institut für Technologie, Germany
12:00 - 12:15	Scientific Spotlight	Altered Excitability and Variation of Ion Channel activity in variants of ALS using iPSC-Derived Motor Neurons and High-throughput Automated Patch-Clamp Dr. David Colameo | University of Zürich, Switzerland
12:15 - 12:40	Scientific Talk	High-Throughput Phenotyping and Neural Circuit Analysis in Brain Organoids: Morphology, Neuropharmacology, and Neuromodulation Xinyu Chen | Fudan University, China
12:40 - 13:05	Special Session	Stem Cell Research and Biomanufacturing in Space Dr. Arun Sharma | Cedars-Sinai Medical Center, United States
13:05 - 14:35	Lunch Break and Poster Session	
bit.bio	Neurodevelopment and Neurodegeneration Chair: Dr. Matt Kelley (Alexion AstraZeneca)	
14:35 - 14:40	Sponsor Talk	Why Complexity Matters: Building Consistent Complex Neuronal Models to Enable Human-Relevant Discoveries Dr. Rebecca Northeast | bit.bio, United Kingdom
14:40 - 14:50	Travel Grant Winner	Divergent Paths to Convergent Cortical Hyperactivity in CACNA1A Loss- and Gain-of-Function Forebrain Assembloids Arvin Sarkissian | Emory University, United States

14:50 - 15:15	Scientific Talk	Human Neuronal Models Reveal XPO7 as a Regulator of Sodium Channel Function and Network Activity Dr. Jen Pan | Broad Institute of MIT and Harvard, United States
15:15 - 15:40	Scientific Talk	Contextualizing Molecular Pathology through Network Dynamics in Human Brain Assembloids Dr. Ranmal Samarasinghe | University of California, Los Angeles, United States
15:40 - 16:10	Panel Discussion	Beyond the Bench: Exploring Careers in Science
16:10 - 17:10	Afternoon Coffee Break and Poster Session	
17:10 - 17:20	Short Talk	Electrophysiological Mapping of Human Striatal Microcircuits Enables Parkinson's Disease Stratification Jannes Straub | VIB – KU Leuven, Belgium
17:20 - 17:30	Short Talk	Improving Neurology Drug Discovery Success through High-Density Microelectrode Arrays Dr. Matt Kelley | Alexion AstraZeneca, United States
17:30 - 18:15	Keynote Talk	Cerebral Organoids: Growing Human Brain Tissue from Stem Cells to Study Development and Disease Prof. Jürgen Knoblich | Institute of Molecular Biotechnology, Austria
18:15	Closing Remarks	

Thursday, September 17

Location: Ambassador House Zürich, Thurgauerstrasse 101, 8152 Opfikon, Switzerland

9:00 - 9:30	Welcome Coffee	
9:30 - 9:35	Opening Remarks	
ANATOMIC	Neural Models for Drug Discovery and Screening Chair: Dr. Giorgia Quadrato (University of Southern California)	
9:35 - 10:20	Keynote Talk	Human iPSC-Based Neuronal Models for ALS Disease Modeling, Drug Discovery, and Reverse Translation Prof. Hideyuki Okano | Keio University, Japan
10:20 - 10:45	Scientific Talk	Human Spatial Genomics to Stem Cell Models: Circuit Vulnerability in Alzheimer's Disease Prof. Keri Martinowich | Lieber Institute for Brain Development, United States
10:45 - 10:55	Short Talk	Disease modeling of α-synuclein propagation in human brain assembloids Dr. Kaneyasu Nishimura | Doshisha University, Japan
10:55 - 11:25	Morning Coffee Break	
11:25 - 11:35	Short Talk	Human Enteric Nervous System Organoids: a Platform for Structure-to-Function Phenotyping at the Neuromuscular Interface Dr. Marcella Birtelle | University of Southern California, United States

11:35 - 12:00	Scientific Talk	Village-Based Proliferation and Viability Assays Dr. Michael Wells | University of California, Los Angeles, United States
12:00 - 12:25	Special Session	Publishing with Cell Press: Inside the Editorial Process Dr. Sheila Chari | Cell Stem Cell, United States
12:25 - 13:55	Lunch Break and Poster Session	
Open Culture	Neuroengineering and Bio-Inspired Computing Chair: Prof. Yoshiho Ikeuchi (The University of Tokyo)	
13:55 - 14:05	Short Talk	Dissecting Neurodegeneration Across Engineered Hierarchical Human Neural Circuits Dr. Nicolai Winter-Hjelm | ETH Zürich, Switzerland
14:05 - 14:15	Short Talk	Engineering Vision In Vitro: Functional Light-Evoked Responses in Laminated Retinal Organoids Antonio Ortega | Johns Hopkins University, United States
14:15 - 14:40	Scientific Talk	Engineering Living Neuronal Networks: from Structure-Function Relationships to Bio-Inspired Computing Dr. Mohammed Andres Mostajo-Radji | University of California, Santa Cruz, USA
14:40 - 14:50	Short Talk	Progressive neuronal network reorganisation in glioblastoma drives pathological activity in vitro Giulia Amos | ETH Zürich, Switzerland
14:50 - 15:15	Scientific Talk	Uncovering the origins of human neural syntax Dr. Tal Sharf | University of California, Santa Cruz, United States
15:15 - 15:30	Picture Taking	
15:30 - 16:30	Afternoon Coffee Break and Poster Session	
16:30 - 16:40	Short Talk	Closed-Loop Reinforcement Trains the Spatial Origin of Network Bursts across Days in Cortical Cultures Dr. Wesley Clawson | Tufts University, United States
16:40 - 16:50	Short Talk	Network Architecture Drives Functional Diversification among Connected Cerebral Organoids Prof. Yoshiho Ikeuchi | The University of Tokyo, Japan
16:50 – 17:15	Scientific Talk	Engineering and Decoding Neuronal Circuits Prof. Hideaki Yamamoto | Tohoku University, Japan
17:15 – 18:00	Keynote Talk	Interacting with Neuron Microcircuits 24/7 Prof. Janos Vörös | ETH Zürich, Switzerland
18:00	Closing Remarks	
19:30	Dinner at Zunfthaus zur Meisen	

Friday, September 18

Multiple locations

9:00 - 9:15	Welcome	
9:15 - 14:30	Workshops	
	Wunderlichips Custom microfabrication for the life sciences.	Microfluidic Patterning on High-Density Microelectrode Arrays Dr. Benedikt Mauer, Joël Küchler | ETH Zürich, Switzerland **Location:** Gloriastrasse 37, Zürich, Switzerland
	Open Culture	Plate -> Prompt -> Publish: Toward Full Lab Automation with Open Culture Science Dr. Tjitse van der Molen, Dr. Spencer Seiler | Open Culture Science, United States **Location:** Memox YOND, Albisriederstrasse 199, Zürich, Switzerland
		How to Train your Organoid: An Introduction to BrainDance Dr. Mircea Teodorescu, Dr. Ash Robbins, Hunter Schweiger | University of California Santa Cruz, United States **Location:** Memox YOND, Albisriederstrasse 199, Zürich, Switzerland
		Unlocking Functional Insights from Neural Organoids MaxWell Biosystems' Product & Application Team | MaxWell Biosystems **Location:** Memox YOND, Albisriederstrasse 199, Zürich, Switzerland

Abstracts | Keynote Speakers

Prof. Jürgen Knoblich

Institute of Molecular Biotechnology, Austria

Title | Cerebral Organoids: Growing Human Brain Tissue from Stem Cells to Study Development and Disease

Abstract | The human brain is unique in both its size and complexity. The development of this remarkable organ involves biological processes that are absent or greatly expanded compared to those of most other species. To study these human-specific aspects of brain development, we developed cerebral organoids—three-dimensional stem cell-derived cultures that recapitulate key features of human brain development in vitro. Using this technology, we have identified developmental processes unique to humans, uncovered mechanisms underlying neurological disorders, and reconstituted functional neural network activity in the laboratory (Lancaster et al., Nature 2013; Esk et al., Science 2020; Eichmüller et al., Science 2022; Li et al., Nature 2023).

My presentation will focus on our most recent findings. We have developed organoid models that capture human-specific stages of brain development and reproduce disease-associated abnormalities at the circuit level. I will present our efforts to combine electrophysiology with barcoded connectomics at single-cell resolution to investigate how neural network activity and network architecture are altered in epilepsy. Finally, I will outline how barcoded prime-editing screens enable the systematic functional interrogation of genetic variants that differentiate Homo sapiens from Neanderthals, providing insights into the genetic basis of human brain evolution.

Dr. Tom Nowakowski

University of California, San Francisco, USA

Title | From Genes to Circuits: Convergent Molecular Signatures of Autism

Abstract | Autism is one of the most heritable conditions in medicine, and genetic studies have identified dozens of genes that, when mutated, sharply increase a person's chances of being profoundly autistic. But knowing which genes are involved doesn't yet explain how they lead to autism, or whether their effects can be seen in the brains of the much larger group of autistic people whose diagnosis has no identified genetic cause. Our lab is working to close that gap by following the effects of autism risk genes through three stages: from the molecules they interact with, to the postmortem brain tissue of autistic individuals, to the activity of living brain circuits.

We start by asking whether different autism genes affect the brain through shared machinery. Focusing on one gene often mutated in autism, we found that a disease-linked mutation disrupts its normal partnerships with other proteins, and that recreating this mutation in stem-cell-derived brain tissue causes an overproduction of a specific class of brain cells — a defect shared with a second, related autism gene, suggesting the two act through a common mechanism. We then

asked whether this kind of shared biology could be found directly in postmortem brain tissue from autistic donors — both those with an identified genetic cause and those without one. Comparing gene activity across thousands of individual brain cells, we found that donors with a known genetic diagnosis and those without one shared a common molecular signature. Finally, we ask whether this molecular signature could be related to how the brain works. Using rare recordings from patients undergoing awake brain surgery, we found that these same inhibitory brain cells respond specifically to the onset of speech, connecting molecular change identified in postmortem tissue to brain circuit involved in language, one of the most commonly affected abilities in autism.

Together, this work traces a path from genetic risk, through shared molecular changes in the brain, to circuit-level function — offering a way to link autism's many genetic causes to its shared biology, and eventually, to its clinical features.

Prof. Hideyuki Okano

Keio University Regenerative Medicine Research Center, Japan

Title | Human iPSC-Based Neuronal Models for ALS Disease Modeling, Drug Discovery, and Reverse Translation

Abstract | Human induced pluripotent stem cell (iPSC) technology offers a transformative approach to neurological disease modeling and drug discovery by shifting the starting point of therapeutic development from animal models to human patient-derived cells. This is particularly important for amyotrophic lateral sclerosis (ALS), a clinically and genetically heterogeneous disorder in which many compounds effective in rodent models have failed in clinical trials. Patient-derived iPSCs preserve individual genetic backgrounds and disease risk architectures, enabling “disease in a dish” and, more broadly, “humanity in a dish” as a platform for precision medicine.

In this lecture, I will present our iPSC-based strategy for ALS disease modeling and drug discovery. We established robust protocols to generate spinal motor neurons from ALS patient-derived iPSCs and used these cells to recapitulate disease-relevant phenotypes, including neurite degeneration, mitochondrial dysfunction, oxidative stress, and neuronal hyperexcitability. Screening 1,232 compounds using ALS iPSC-derived motor neurons led to the identification of ropinirole hydrochloride, an approved dopamine D2 receptor agonist for Parkinson’s disease, as a candidate anti-ALS drug. Mechanistic studies showed that ropinirole acts through both D2 receptor-dependent and -independent pathways, including suppression of oxidative stress and modulation of mitochondrial function.

Beyond these mechanisms, our reverse translational studies have revealed a disease pathway linking cholesterol biosynthesis, RNA editing, and motor neuron excitability. Transcriptomic analyses of ropinirole-treated ALS motor neurons indicated suppression of SREBF2-dependent cholesterol biosynthesis. In sporadic ALS iPSC-derived lower motor neurons, cholesterol synthesis-related enzymes were elevated, particularly in ropinirole-responsive lines, suggesting that dysregulated lipid metabolism may define a therapeutically relevant ALS endotype. Ongoing studies further suggest that increased cholesterol biosynthesis can reduce ADAR2 expression and impair A-to-I RNA editing of GRIA2/GluA2, a critical mechanism controlling AMPA receptor calcium

permeability. Reduced editing may therefore increase calcium influx, promote motor neuron hyperexcitability, and contribute to degeneration. High-density microelectrode array recordings support this model by demonstrating abnormal firing activity in ALS neurons and its modulation by ropinirole.

Finally, I will discuss how iPSCs derived from participants in the ROPALS phase 1/2a clinical trial enabled reverse translational research linking in vitro drug responsiveness with clinical progression. I will also introduce cortical–spinal assembloids and organoid-based neural circuit assays as next-generation models for integrating dying-forward and dying-back mechanisms in ALS.

Prof. Janos Vörös

Institute for Biomedical Engineering, Laboratory of Biosensors and Bioelectronics, ETH Zürich, Switzerland

Title | Interacting with Neuron Microcircuits 24/7

Abstract | Networks of neurons fascinate people because we all have them in our heads, but we understand them very little. This talk will introduce how PDMS multicompartment microstructures can be used to build neuron microcircuits on HD-MEAs that allow for both stimulating and recording of their activity. A lid with an embedded water compartment assures 100% humidity while a simple custom incubator allows for 24/7 uninterrupted operation over 40 days with a single media exchange (Maurer, et al., 2026). This allows for a closed-loop optimization of stimulation paradigms to achieve specific performance-goals using reinforcement learning (Clément, et al., 2026). The microstructures are compatible with human induced pluripotent stem cells providing an opportunity to address some of the challenges related to investigating the nervous system and its diseases. Three examples of disease models will be introduced:

- The nociceptory system that is often involved in chronic pain can be replicated to study how the dorsal root ganglia modulate signal propagation from the skin towards the dorsal horn (Clément, et al., 2026).
- The system also allows for observing how glioblastoma-axon interaction causes epileptic behavior in networks of healthy neurons.
- A six-layer hierarchical model of the cortex can be used to study how progerin-induced aging influences the response of the network to amyloid-β exposure (Küchler, et al. 2026).

The custom tools (hardware and software) presented in this talk are all publicly available and we are happy to help scientists to implement them in their own labs.

Abstracts | Invited Speakers

Xinyu Chen
Prof. Lixiang Ma Lab, MRC Laboratory of Molecular Biology (LMB), United Kingdom

Title | High-Throughput Phenotyping and Neural Circuit Analysis in Brain Organoids: Morphology, Neuropharmacology, and Neuromodulation

Abstract | The increasing scale and complexity of brain organoid studies require analytical approaches that support consistent and quantitative comparisons. This presentation will discuss three analytical strategies for morphological characterization, neuropharmacological assessment, and neural circuit analysis in brain organoids.

First, we use CHARM to extend conventional morphological assessment toward high-throughput quantitative analysis. This RGC morphological analysis focuses on image acquisition, feature extraction, and comparison of morphological and histological features across in vitro samples, with particular attention to analytical consistency and sample-to-sample variability. Second, we use high-density microelectrode arrays to examine the neuropharmacological responses of brain organoids. In addition to conventional network-level parameters, we analyze changes in the firing properties of individual neurons following pharmacological perturbation. This strategy allows drug responses to be assessed at both the network and single-neuron levels while retaining information on neuronal response heterogeneity. Finally, we characterize the electrophysiological properties of patient-derived brain organoids carrying DYRK1A mutations and examine neuromodulatory interventions in an assembloid model of interhemispheric cortical connectivity. Local and inter-organoid network activity is recorded before and after intervention. The analysis focuses on identifying electrophysiological features that describe changes in network state and using these features to compare different neuromodulatory conditions.

Together, these approaches highlight the potential of scalable, multimodal analysis to integrate morphological, molecular, and functional readouts in brain organoids and assembloids, enabling a more systematic evaluation of model development, disease-related phenotypes, and responses to intervention. Guided protocols can recapitulate differences in species-specific speeds of brain development which can be observed in vivo. We adapted the cerebral organoid protocol, previously used on human-derived stem cells, for other species including mouse and observed developmental trajectories and neural lineage differentiation that was intrinsically faster compared to human. Further long-term culture at the air-liquid interface facilitated further differentiation of more mature cell populations, and the establishment of neuron and axonal connections and dynamics.

Prof. Keri Martinowich
Lieber Institute for Brain Development, Baltimore, USA

Title | Human Spatial Genomics to Stem Cell Models: Circuit Vulnerability in Alzheimer's Disease

Abstract | Selective vulnerability of interconnected neural circuits is a defining feature of Alzheimer's disease (AD), yet the molecular programs linking genetic risk to early circuit dysfunction remain poorly understood. The locus coeruleus (LC) and entorhinal cortex (ERC) are among the earliest brain regions affected in AD, exhibiting early accumulation of phosphorylated tau pathology prior to

widespread neurodegeneration and cognitive decline. However, how molecular vulnerability emerges across connected brain regions, and how these processes can be modeled experimentally, remains unclear. To address this, we generated paired spatial transcriptomic and single-cell datasets across the LC–ERC circuit using postmortem human brain tissue from middle-aged donors stratified by APOE genotype, ancestry, and sex. In the LC, we identified APOE- and ancestry-associated alterations in astrocytic and neuromelanin-associated transcriptional programs linked to aging, lipid metabolism, oxidative stress, and neuronal vulnerability. In the ERC, AD risk-associated transcriptional changes localized predominantly to oligodendrocyte populations and white matter-associated spatial domains, suggesting disrupted myelination and glial support programs prior to overt disease onset. Because these datasets were generated from the same donors, ongoing work integrates molecular profiles across regions to define circuit-level programs associated with AD risk and early vulnerability. To translate these findings into experimentally tractable systems, we are generating donor-derived induced pluripotent stem cell (iPSC) models from matched postmortem donors used in the human brain studies. These include LC-like noradrenergic neurons, astrocytes, and emerging multicellular systems designed to model region-specific cellular interactions relevant to AD vulnerability. Using these platforms, we are investigating how APOE-associated molecular programs influence neuromelanin accumulation, cellular activity, and glial interactions. Together, these studies establish a framework integrating human spatial genomics with stem cell-based neural models to investigate mechanisms underlying selective circuit vulnerability in Alzheimer's disease.

Dr. Mohammed Andres Mostajo-Radji
Genomics Institute, University of California, Santa Cruz, USA

Title | Engineering and Decoding Neuronal Circuits

Abstract | Engineered forebrain organoids self-organize into functional networks whose architecture reflects their cellular composition, offering a tractable model for how circuits emerge without sensory input. Using longitudinal high-density microelectrode array recordings, I first show that dorsal and ventral forebrain organoids develop distinct network topologies, with refined small-world organization tracking interneuron enrichment. Reading out these dynamics at scale, however, requires extracting what a neuron is, where it sits, and how it participates in a network without features fixed by hand in advance. I then present a representation-learning approach that recovers such structure directly from extracellular waveforms and spiking dynamics, classifying cell types, resolving spatial organization, and exposing network signatures of circuit self-organization and disease.

Dr. Jen Q. Pan
Broad Institute of MIT and Harvard, USA

Title | Human Neuronal Models Reveal XPO7 as a Regulator of Sodium Channel Function and Network Activity

Abstract | Schizophrenia is a highly heritable neuropsychiatric disorder, yet how genetic risk variants disrupt human neuronal function remains poorly understood. Here, we use human induced pluripotent stem cell (iPSC)-derived neurons as a disease model to investigate the cellular consequences of loss of function (LoF) of XPO7, a schizophrenia risk gene identified through recent large-scale exome sequencing studies. By integrating high-resolution electrophysiology, transcriptomics, quantitative proteomics, and imaging with neuronal network assays, we identify convergent molecular and functional phenotypes linking XPO7 deficiency to impaired neuronal excitability.

XPO7 LoF alters voltage-gated sodium channel dynamics and availability, resulting in abnormal action potential generation and disrupted synchrony and regularity of neuronal network. These physiological abnormalities are accompanied by widespread molecular changes affecting nucleocytoplasmic transport, ion channel regulation, and synaptic composition. Notably, the voltage-gated sodium channel Nav1.2 (SCN2A) exhibits altered subcellular localization in XPO7-deficient neurons, providing a potential mechanistic link between XPO7 dysfunction and impaired neuronal signaling.

Together, our findings establish XPO7 as a critical regulator of neuronal excitability and network function and demonstrate how human iPSC-derived neuronal models and circuit-level phenotyping can bridge schizophrenia genetics to disease mechanisms. These results highlight sodium channel dysfunction as a potentially actionable pathway for therapeutic development in neuropsychiatric disorders.

Dr. Ranmal Samarasinghe
Department of Neurology, David Greffen School of Medicine, University of California, Los Angeles, USA

Title | Contextualizing Molecular Pathology through Network Dynamics in Human Brain Assembloids

Abstract | A central challenge in translational neuroscience is bridging the gap between molecular pathology and clinically meaningful dysfunction. I will present a network-centric framework for this problem, using electrophysiological and optical recordings from human iPSC-derived brain assembloids across a progression from neurodevelopmental disease to neurodegeneration. Beginning with cortical-subcortical assembloids in Rett syndrome — where two-photon imaging and local field potential recordings first revealed epileptiform network dynamics in MeCP2-deficient circuits — I will trace how this approach has evolved in scope and resolution. Work in hippocampal assembloids extended LFP-based analysis to region-specific circuit identity and its disruption in channelopathy. More recently, high-density MEA recordings have enabled single-unit resolution in assembloid systems, illuminating network-level mechanisms of anesthetic action and, most strikingly, revealing how tau pathology dismantles ensemble coordination in ways that recapitulate in vivo signatures of neurodegeneration. Across these models, a consistent picture emerges: circuit

dynamics integrate and amplify molecular and cellular changes, making them a privileged and translationally grounded readout for both disease modeling and therapeutic discovery.

Dr. Tal Sharf
University of California, Santa Cruz, USA

Title | Uncovering the Origins of Human Neural Syntax

Abstract | For centuries, philosophers have sought to understand how human neural tissue self-assembles into a physiologic scaffold that generates thought. Recent evidence suggests that neuronal wiring follows developmentally programmed instructions where neurons born from common progenitors preferentially wire and firing together before being recruited into experience-dependent networks. Despite implications for neurodevelopmental disorders such as autism and schizophrenia, we lack a mechanistic understanding of how developing neuronal circuits operate across spatiotemporal scales relevant to computation (ms precision over large networks). Human organoids provide a unique opportunity to investigate human circuit assembly at these scales because they can be engineered and integrated with technology in ways not possible in vivo. Here, we show that fundamental features of cortical computation (including heavy tailed firing-rate and connectivity distributions, reproducible neuronal firing sequences, and the coexistence of low- and high-dimensional subnetworks) emerge spontaneously in human brain organoids and early postnatal mouse cortex but not 2D cultures. These findings suggest that three-dimensional tissue architecture supports an intrinsic neural syntax that precedes sensory experience. Yet cortical development and function cannot be understood without considering directional communication with subcortical structures, particularly the thalamus, the brain's primary sensory relay. I will conclude by presenting our bioengineering approach for controlling interactions between region-specific cortical and thalamic organoids. Using microfluidic devices to establish directional organoid-to-organoid axonal connectivity, we aim to determine how anatomically structured communication shapes the emergence and routing of functional activity across developing human neural circuits.

Dr. Silvia Velasco
Novo Nordisk Foundation Center for Stem Cell Medicine, reNEW Melbourne, Australia

Title | Brain Organoids as Platforms for Understanding and Treating Neurological Disorders

Abstract | Stem cell-derived neural organoids provide a powerful opportunity to study human brain development and disease. We enhanced the utility of these in vitro systems by establishing highly reproducible organoid models that support long-term development and maturation of diverse brain cell types. Using these organoid models in combination with single-cell multi-omic approaches, we investigated cell-type-specific abnormalities associated with neurodevelopmental and neurodegenerative disorders. Finally, we leveraged the reproducibility of these models to develop automated high-throughput organoid screening platforms, enabling the integration of brain organoids into drug discovery pipelines for neurological disorders.

Dr. Michael Wells
UCLA David Greffen School of Medicine, University of California, Los Angeles, USA

Title | Village-Based Proliferation and Viability Assays

Abstract | The capacity of cells to proliferate and survive is central to development and disease. Assays that measure cell fitness are therefore a cornerstone of biology, but traditional techniques lack donor diversity and have high technical variability that impedes scale and reproducibility. To overcome these barriers, we designed and validated a “cell village”-based fitness screening approach using pooled cultures of 12–39 genetically distinct human neural progenitor cell (NPC) lines. We also developed Townlet to establish a foundational statistical framework based on Dirichlet regression for analyzing proportional data from cell villages. Applying these systems, we identified hyperproliferation in NPCs harboring the autism risk factor chromosome 16p11.2 deletion, mapped common genetic variants near ZFHX3 associated with NPC proliferation rate, and discovered genetic modifiers of lead (Pb) sensitivity implicating ARNT2. Together, these experimental and analytical tools advance a scalable, genetically diverse in vitro platform for dissecting human variation in cell fitness and gene-environment interactions.

Prof. Hideaki Yamamoto
Research Institute of Electrical Communication (RIEC), Tohoku University, Japan

Title | Engineering Living Neuronal Networks: from Structure-Function Relationships to Bio-Inspired Computing

Abstract | How does the architecture of neuronal networks give rise to robust and energy-efficient computation in the brain? In vitro neuronal networks are effective tools for addressing this question in a physicochemically defined environment. Furthermore, such cell culture technology can be integrated with semiconductor microfabrication to reconstitute networks that more closely resemble the structures in vivo. In this talk, I will demonstrate how protein micropatterns and microfluidic devices can be used as chemical and physical guidance cues to control the growth of cultured neurons. These platforms provide a unique approach for constructively investigating how biological neurons form structured networks and generate high-dimensional dynamics that can be harnessed for bio-inspired computing.

Abstracts | Special Sessions

Dr. Sheila Chari
Cell Stem Cell, Editor-in-Chief

Title | Publishing with Cell Press: Inside the Editorial Process

Abstract | This talk will introduce Cell Stem Cell's editorial scope, priorities, and role within the broader Cell Press portfolio, with an emphasis on what makes a strong fit for the journal. The session will then focus on practical guidance for navigating the publishing process at Cell Press journals, organized around the questions authors most frequently ask editors. Topics will include selecting the right journal, preparing a cover letter, understanding how editors assess submissions, navigating Cell Press policies on preprints and AI, and responding effectively to reviewer comments. The goal is to demystify the editorial and publication process and provide authors with concrete guidance for preparing and publishing their work in Cell Press journals.

Dr. Arun Sharma
Director, Center for Space Medicine Research, Cedars-Sinai Medical Center, USA

Title | Stem Cell Research and Biomanufacturing in Space

Abstract | Human induced pluripotent stem cells (hiPSCs) provide powerful platforms for modeling cardiovascular disease and advancing regenerative medicine. This talk will highlight how stem cell-derived tissues, organoids, and organ-on-chip systems are being used at Cedars-Sinai to study heart disease, drug-induced cardiotoxicity, and human adaptation to spaceflight. Drawing on pioneering studies performed aboard the International Space Station, Dr. Arun Sharma will discuss how the intersection of stem cell biology and space biosciences is uncovering new insights into human health while creating opportunities for innovation in disease modeling and therapeutic discovery.

Abstracts | Scientific Spotlight

Dr. David Colameo
Senior Scientist at the Electrophysiology Core Facility at the University of Zürich, Switzerland

Title | Altered Excitability and Variation of Ion Channel activity in variants of ALS using iPSC-Derived Motor Neurons and High-throughput Automated Patch-Clamp

Abstract | ALS is caused by diverse genetic mutations, including C9orf72 repeat expansions, SOD1, and TARDBP, that converge on motor neuron dysfunction. Patch clamp remains the gold standard for characterizing excitable cells, but low throughput has limited its use in disease modeling. We addressed this using high-throughput automated patch clamp (SyncroPatch 384, Nanion) to profile iPSC-derived motor neurons from ALS patients (C9orf72, TDP-43 A382T, SOD1 D109Y) and a healthy donor (Axol Biosystems).

The platform allowed simultaneous, unbiased recording of multiple electrophysiological parameters across genetically defined lines and hundreds of sampled motor neurons. Na^+ channel gating kinetics were comparable between healthy and ALS neurons, but ALS neurons showed reduced Na^+ channel current density and decreased excitability, with altered action potential amplitude and firing. Ion channel remodeling extended to reduced K^+ current density and slightly reduced GABA-induced currents, while glutamate and glycine responses were unaffected.

These results demonstrate that HT-APC can resolve disease-relevant electrophysiological phenotypes in hiPSC-derived neurons at a scale unattainable with conventional patch clamp. This positions HT-APC as a scalable tool for mechanistic ALS research and drug discovery.

Abstracts | Sponsored Talks

Dr. Rebecca Northeast
Sr. Portfolio and Partnerships Manager, Neuroscience, bit.bio

Title | Why Complexity Matters: Building Consistent Complex Neuronal Models to Enable Human-Relevant Discoveries

Abstract | The success of neuroscience drug discovery relies on reproducible data and human relevant in vitro models, yet current models struggle with inherent batch-to-batch inconsistencies and physiological relevance. At bit.bio, we are bridging this gap using opti-ox™ technology to generate defined, consistent human iPSC-derived neurons and glia at scale. In this talk, we will explore how these cells can be co-cultured to create robust, electrophysiologically functional networks. Specifically, we will demonstrate how HD-Microelectrode Array (MEA) technology can be used to assess these networks, identify key neuronal characteristics, extract distinct disease phenotypes, and enhance neurocomputing systems. Finally, we will showcase a streamlined workflow for incorporating microglia into 3D brain organoids, offering a physiologically relevant microenvironment for studying neuroinflammation and neurodegeneration.

*Abstract also presented during poster sessions as number #54

Abstracts | Selected Short Talks

PROGRESSIVE NEURONAL NETWORK REORGANISATION IN GLIOBLASTOMA DRIVES PATHOLOGICAL ACTIVITY IN VITRO

Giulia Amos, Luc Jordi, Karan Ahuja, Alexandra Gerber, Gregor Hutter, Janos Voros, Christina M. Tringides, Vaiva Vasiliauskaite

ETH Zürich, Switzerland

Glioblastoma is the most aggressive primary brain tumor and is frequently accompanied by severe neurological symptoms such as epilepsy and cognitive impairment. These symptoms often persist after surgical resection, indicating self-sustaining changes in surrounding neuronal networks [1]. However, the mechanisms by which glioblastoma reshapes network structure and function remain poorly understood. In this work, we investigated how glioblastoma invasion reorganizes neuronal networks using a compartmentalized in vitro platform [2]. iPSC-derived neurons and patient-derived glioblastoma cells were cultured in separate wells connected by microchannels, allowing spatially confined observation of tumor neuron interactions. The system was placed on high-density microelectrode arrays for simultaneous network-wide electrophysiological recording, yielding a longitudinal dataset during tumor progression. Glioblastoma drives reproducible, progressive restructuring of neuronal networks. It first induces the emergence of broadcasting hubs, defined as neurons with disproportionally many outgoing connections, and then the collapse of community structure. A generative network model attributed early reorganization to edge addition via preferential attachment and triad formation, while non-specific neuronal loss explained later-stage structural changes. This reorganization has multifaceted functional consequences. At the whole-network level, structural properties predict epileptiform bursting and hypersynchronisation. At the single-neuron level, broadcasting hub neurons are active at distinct timepoints during network bursts and play a significant role in sustaining pathological activity. Glioblastoma also alters how individual neurons integrate their inputs: late-stage networks show a shift from unique to redundant integration (partial information decomposition [3]). This indicates that neurons increasingly receive overlapping rather than complementary signals from their sources, constraining the network's accessible state space. Together, these findings indicate that glioblastoma does not simply elevate network excitability uniformly, but fundamentally restructures neuronal networks both structurally and functionally, offering hypotheses for why neurological symptoms can persist after tumor resection, as well as suggesting intervention targets.

References: [1] Venkatesh, H.S., et al., Nature, 2019 [2] Amos, G., et al., BioRxiv, 2026 [3] Bertschinger et al., Entropy, 2014

HUMAN ENTERIC NERVOUS SYSTEM ORGANOIDS: A PLATFORM FOR STRUCTURE-TO-FUNCTION PHENOTYPING AT THE NEUROMUSCULAR INTERFACE

Marcella Birtele, Michell Tham, Lydia Park, Alana Snyder, Peter Serles, Giorgia Quadrato

Department of Stem Cell Biology and Regenerative Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA; Eli and Edythe Broad CIRM Center for Regenerative Medicine and Stem Cell Research at USC, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA

Gastrointestinal dysfunction is among the most common comorbidities in neurodevelopmental and neurodegenerative disease, and in disorders such as Parkinson's it can precede neurological symptoms by years. Yet the enteric nervous system (ENS), the intrinsic nervous system of the gut, has received a small fraction of the attention given to the central nervous system, despite comprising the largest collection of neurons outside it. During development, the ENS assembles into a ganglionated plexus with a defined length scale, a geometry that determines how excitation propagates through the network and onto smooth muscle to drive motility. Because ganglion spacing and interganglionic connectivity are quantifiable and functionally interpretable, the ENS offers a tractable human system in which self-organized architecture, network activity, and physiological output can be measured together.

We generated hiPSC-derived ENS organoids via vagal enteric neural crest induction, using size-controlled reaggregation to reduce the variability inherent to embryoid-body approaches. Enteric neural crest is specified by day 12 (CD49D/SOX10), and enteric neuronal subtypes (nNOS, TH, ChAT) emerge by day 35. By day 24, organoids self-organize a HuC/D^{+} ganglionated plexus with honeycomb-like mesh geometry recapitulating the in vivo arrangement of ganglia and interganglionic fibers, providing a quantitative structural readout.

We applied this platform to SYNGAP1 haploinsufficiency, a developmental disorder with intellectual disability and epilepsy, and a top ASD risk gene identified by large-scale sequencing, in which most patients report gastrointestinal dysmotility. Mutant organoids form a plexus with significantly increased mesh perimeter and area compared to isogenic controls but unchanged aspect ratio, consistent with an isotropic expansion of ganglionic spacing rather than a change in shape. Calcium imaging and high-density microelectrode array (HD-MEA) recordings reveal correspondingly altered network activity, suggesting an output impairment onto the muscle.

To connect circuit architecture to physiological output, we assemble ENS organoids with intestinal smooth muscle organoids as a reductionist model of the enteric neuroeffector junction, and combine this with micropatterned grooved scaffolds that impose ganglionic geometry independently of genotype. Together, these genetic and physical perturbations test whether architecture is causal for enteric circuit function, and establish the ENS as a tractable platform for structure-to-function phenotyping at the human neuromuscular interface.

CLOSED-LOOP REINFORCEMENT TRAINS THE SPATIAL ORIGIN OF NETWORK BURSTS ACROSS DAYS IN CORTICAL CULTURES

Wesley Clawson, Caitlin Grasso, Sydney Palmer, Trevor Sullivan, Nathan Wu, Mike Levin

Tufts University, Massachusetts, USA

Can a dissociated cortical network be trained to change not only when it fires, but where its activity begins, and can it hold that change from one day to the next? Learning in cultured networks on microelectrode arrays has almost always been read out in the temporal domain, as the rate or probability of a correct response, and within a single session, leaving both the spatial question and the question of across-day retention open. To address them, we built an open-source closed-loop platform (Holistic Agential Learning, HAL) that detects each network burst on a high-density array, estimates its spatial origin in real time, and applies a deliberately minimal rule under which bursts originating on a goal side go unstimulated while bursts on the wrong side trigger a global aversive signal. Reading learning from the unstimulated pre-training phase, we found that trained cultures shifted the origin of their bursts toward the goal side over days, a movement of the initiation site rather than the burst peak, with gains accruing more across days than within a session in a consolidation-like manner. The side-preference gain itself was modest. Tested against every possible control assignment rather than a single averaged one, it held only as a trend. The sharper and more robust effect was temporal - over training, cultures became markedly better at recovering from an error, climbing back to the goal side after a wrong burst, while the rate of error itself held steady. This asymmetric gain in error-correction depended on intact tissue and, like the spatial shift, accrued across days rather than within a session. We read these results as repositioning burst initiation zones from fixed features of a culture's wiring to plastic, trainable ones, and as evidence that even a minimal network can consolidate an error-correction competency across days.

NETWORK ARCHITECTURE DRIVES FUNCTIONAL DIVERSIFICATION AMONG CONNECTED CEREBRAL ORGANOIDS

Tomoya Duenki, Yoshiho Ikeuchi

Brain organoids possess intricate neuronal networks, but their functional development remains difficult to control because they lack organized macroscopic circuit architecture and structured input. We develop MEA assays to test whether expanding networks by connecting cerebral organoids enhances network function. Repeated stimulation promoted stimulus-specific responses, refined intra- and inter-organoid functional connectivity, and improved signal discrimination, with larger networks showing greater functional enhancement. These suggest that scaling modular connectivity organizes initially equivalent organoids into differentiated functional states, demonstrating that network architecture can drive functional diversification in vitro.

ISOGENIC HUMAN CEREBELLAR ORGANOIDS REVEAL RNA PROCESSING AND TRANSLATIONAL DEFECTS UNDERLYING PCH2A

Theresa Kagermeier*, Francesco Castagnetti*, Lizia Branco, Zeynep Yentur, Daria Andreeva, Isabel Potthof, Pierre Collignon, Simone Mayer

Karlsruhe Institute of Technology, Germany

Pontocerebellar hypoplasia type 2a (PCH2a) is an ultra-rare neurodevelopmental disorder caused by a homozygous founder mutation (A307S) in TSEN54, a core component of the tRNA splicing endonuclease (TSEN) complex. Although impaired pre-tRNA processing is the primary molecular defect, the mechanisms linking defective tRNA splicing to selective cerebellar vulnerability remain poorly understood. To investigate the downstream consequences of TSEN dysfunction in a human developmental context, we generated isogenic induced pluripotent stem cell (iPSC) pairs by introducing the A307S mutation into control cells and correcting the mutation in patient-derived iPSCs using genome editing. Isogenic lines were differentiated into cerebellar organoids and profiled by single-cell RNA sequencing at days 30 and 50 of differentiation. Mutant organoids displayed impaired cerebellar patterning accompanied by widespread transcriptional changes across multiple neural cell populations. Gene set enrichment analyses consistently revealed downregulation of RNA processing and splicing, ribosome biogenesis, and translation-associated pathways. In parallel, mTORC1 signaling, the unfolded protein response (UPR), and ER-associated protein biogenesis were significantly suppressed, indicating a reduced capacity to coordinate protein synthesis with proteostatic and metabolic stress responses during early cerebellar development. These findings suggest that TSEN54 deficiency perturbs a broader RNA homeostasis network extending beyond defective tRNA splicing, resulting in impaired translational control and diminished cellular stress adaptation. Our study provides a mechanistic framework linking defective RNA processing to cerebellar pathogenesis and identifies translational and proteostatic pathways as candidate targets for therapeutic intervention in PCH2a.

IMPROVING NEUROLOGY DRUG DISCOVERY SUCCESS THROUGH HIGH-DENSITY MICROELECTRODE ARRAYS

Matt Kelley

Alexion Genomic Medicine, AstraZeneca Rare Disease

Human iPSC-derived neuronal cultures on high-density microelectrode arrays (HD-MEAs) offer a uniquely translational functional readout for CNS drug discovery, capturing network-level physiology in a patient-relevant genetic background. In practice, however, HD-MEA assays are typically deployed only at the late, hit-validation end of the screening funnel across small molecule and genomic medicine drug discovery programs. The barriers involve multi-week culture and recording timelines, the operational complexity of scaling reproducible advanced neuronal models, and the analytical burden of high-dimensional electrophysiology data.

This talk presents a practical framework, informed by active neurology programs at Alexion Genomic Medicine, for moving HD-MEAs upstream in the discovery cascade. The framework centers on three reinforcing levers that together address the reproducibility and throughput gap. Automation of iPSC neuron plating, feeding, dosing, and MaxTwo recording removes operator-dependent variability and makes weekly, calendar-driven experiments realistic at screening scale. AI-enabled, contemporaneous analysis returns interpretable network phenotypes and QC on the same timescale as the experiment. Pairing HD-MEA experiments with matched RNA sequencing transcriptomics anchors electrophysiological phenotypes to cell-state ground truth, providing a mechanism to detect and de-risk batch-to-batch drift in the underlying neuronal model. The talk will outline where community effort is most likely to transition HD-MEA experiments from specialized to routine primary assays in neurology drug discovery.

AN INTEGRATED PLATFORM COMBINING LONGITUDINAL HIGH-DENSITY MEA ELECTROPHYSIOLOGY AND ON-CHIP SIGNAL-AMPLIFIED SPATIAL TRANSCRIPTOMICS IN HUMAN IPSC NEURAL NETWORKS

Aayush Marishi, Yue Yang Cao, Lorenca Sadiraj, Sreedhar Kumar, Yanxi Chen, Sirvathsan Adivarahan, Stormy J. Chamberlain, Stefanie Alber, Andreas Hierlemann, Andreas Moor, Manuel Schroeter

ETH Zürich, Switzerland

Modelling the pathophysiology of neurodevelopmental disorders requires experimental platforms capable of linking network-scale electrophysiology with spatial gene expression patterns. Traditional in vitro assays typically separate functional recordings from molecular profiling, limiting the ability to correlate phenotypes such as hyperexcitability in autism spectrum disorders (ASD) with underlying transcriptomic markers at cellular resolution. We developed a novel multimodal platform combining forward-programmed human iPSC-derived neurons with an on-chip spatial transcriptomics workflow. Excitatory (iGUTA) and inhibitory (iGABAs) neurons were co-cultured with human astrocytes on high-density microelectrode arrays (HD-MEAs), forming active networks within weeks. Network development was tracked longitudinally using HD-MEA recordings. Standard smFISH methods struggle to resolve single RNA molecules on HD-MEAs due to high background reflectivity from the chip surface. To overcome this optical limitation, we implemented an amplified in situ hybridization protocol directly on the HD-MEA chips. This increased the signal-to-noise ratio, allowing reliable visual resolution of individual transcript spots on the reflective array surface. We evaluated this workflow using a human iPSC model of Chromosome 15q11.2-13.1 duplication syndrome (Dup15q): Functional Dynamics: Longitudinal HD-MEA recordings showed spontaneous activity by week 2, with a distinct divergence in network behavior by week 3. Dup15q networks exhibited a hyperexcitability phenotype, characterized by higher spontaneous firing rates, increased network synchronization, longer burst durations, and shorter interburst intervals compared to isogenic controls. On-Chip Transcript Profiling: Initial qualitative on-chip imaging confirmed that signal-amplified transcript profiling can successfully detect target transcripts directly on the HD-MEA surface. The detected expression patterns aligned directionally with known postmortem patient data, capturing key disease drivers (such as GABRB3, UBE3A) and broader ASD signatures, including glutamatergic receptor dysregulation. This study demonstrates the feasibility of combining longitudinal HD-MEA electrophysiology with signal-amplified spatial transcriptomics on the same chip. By addressing substrate reflection and validating initial feasibility in a Dup15q model, this methodology provides a practical approach for mapping functional and molecular properties in human neural networks.

DISEASE MODELING OF A-SYNUCLEIN PROPAGATION IN HUMAN BRAIN ASSEMBLOIDS

Kaneyasu Nishimura[1], Naoya Amimoto[2], Yuya Sato[3], Mieko Morishima[4], Mamoru Sakaibara[5], Ayana Haratake[6], Mai Nakano[6], Naoko Kaneko[4], Hideaki Yamamoto[5,7], Ayumi Hirano-Iwata[5,7], Takashi Tanii[3], Jun Takahashi[2], Kazuyuki Takata[6], Yoshito Masamizu[1]

[1]Laboratory of Functional Brain Circuit Construction, Graduate School of Brain Science, Doshisha University, Kyotanabe, Japan

[2]Department of Clinical Application, Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan

[3]Faculty of Science and Engineering, Waseda University, Tokyo, Japan

[4]Laboratory of Neuronal Regeneration, Graduate School of Brain Science, Doshisha University, Kyotanabe, Japan

[5]Research Institute of Electrical Communication, Tohoku University, Sendai, Japan

[6]Joint Research Laboratory, Division of Integrated Pharmaceutical Science, Kyoto Pharmaceutical University, Kyoto, Japan

[7]Advanced Institute for Materials Research (WPI-AIMR), Tohoku University, Sendai, Japan

Parkinson's disease (PD) is characterized by progressive degeneration of midbrain dopaminergic neurons and accumulation of α-synuclein pathology. Postmortem studies have suggested that pathological α-synuclein spreads across anatomically connected brain regions, but the cellular and circuit-level mechanisms underlying this interregional propagation in the human brain remain poorly understood.

Previously, we established efficient protocols for generating striatal and midbrain neurons from human ESCs/iPSCs [1,2]. Building on these protocols, we established a human striatal–midbrain assembloid model to investigate interregional α-synuclein propagation [3]. Striatal and midbrain spheroids were generated from hiPSCs and fused to form assembloids containing region-specific neuronal populations and interregional neural connections. Immunocytochemical, electrophysiological, and single-cell RNA-sequencing analyses confirmed the preservation of striatal and ventral midbrain identities with the formation of nigrostriatal-like neural circuits.

To model interregional α-synuclein propagation after assembloid formation, we introduced a doxycycline-inducible system enabling spatially restricted and temporally controlled α-synuclein expression in the striatal region. Induction of α-synuclein after assembloid formation resulted in its appearance in the connected midbrain region, including dopaminergic neurons, demonstrating interregional α-synuclein propagation.

This human assembloid platform provides a controllable experimental system for investigating α-synuclein propagation and the mechanisms underlying synucleinopathy and selective neuronal vulnerability.

References

[1] Amimoto N., Nishimura K. et al., Generation of striatal neurons from human induced pluripotent stem cells by controlling extrinsic signals with small molecules. Stem Cell Res., 55, 102486 (2021).

[2] Nishimura K. et al., Single-cell transcriptomics reveals correct developmental dynamics and high-quality midbrain cell types by improved hESC differentiation. Stem Cell Reports, 18 (1), 337-353 (2023).

[3] Nishimura K. et al., Modeling interregional propagation of α-synuclein in human striatal-midbrain assembloids. bioRxiv, (2026). https://doi.org/10.64898/2026.05.11.723670

ENGINEERING VISION IN VITRO: FUNCTIONAL LIGHT-EVOKED RESPONSES IN LAMINATED RETINAL ORGANOIDS

Antonio J. Ortega, Joanna Hagen, Andrew Chinn, Dowlette-Mary Alam El Din, Benvindo Tye Chicha, Robert J. Johnston, Lena Smirnova

Johns Hopkins University, Baltimore, USA

Retinal organoids offer strong potential for studying the emergence of functional retinal circuitry and its subsequent disruption in disease. Current organoid protocols fall short of recapitulating in vivo retinal architecture and function. Addressing these limitations, we developed the Marmoset Retinal Multi-layered Organoid (MaRMO) protocol using marmoset iPSCs. MaRMOs are retinal organoids that properly laminate, produce, and maintain all major retinal cell types, effectively recreating key features of native retinal tissue. This structural fidelity enables meaningful investigation of retinal circuitry maturation and functional connectivity. MaRMOs displayed light-dependent increases in firing rate, with the response magnitude scaling with stimulus duration. Tracking action potential propagation along individual retinal ganglion cell (RGC) axons revealed conduction velocities consistent with unmyelinated axons. Additionally, distinct retinal ganglion cell response subclasses were functionally identified, including ON, OFF, and ON-OFF RGCs. Lastly, MaRMOs exhibited wavelength-specific response activity, demonstrating the capacity for color perception. Robust responses were detected across stimuli parameters and were consistent across multiple organoids and recording sessions. In contrast, empty well controls showed no measurable response to any light stimulus. Modeling intact retinal circuitry in vitro represents a critical next step for translational vision science which will support the development of therapies aimed at restoring vision.

DIVERGENT PATHS TO CONVERGENT CORTICAL HYPERACTIVITY IN CACNA1A LOSS- AND GAIN-OF-FUNCTION FOREBRAIN ASSEMBLOIDS

Arvin Sarkissian, Cindy Lee, Roy Simamora, Carol Eisenberg, Kaori Graybeal, Alexia King, Alan Emanuel, Fikri Birey

Emory University, United States

CACNA1A (Cav2.1) mutations cause a spectrum of neurological disease, yet gain-of-function (GoF) and loss-of-function (LoF) variants can produce overlapping developmental and epileptic encephalopathies, obscuring how each perturbs neural activity. We used high-density microelectrode array (HD-MEA) recording to ask how these opposing channel defects reshape excitability from the single-neuron to the network level. Isogenic human iPSC-derived forebrain assembloids (fused cortical and subpallial organoids) carrying a CACNA1A GoF (A713T) or LoF (Q680fs) variant, alongside their isogenic control, were recorded on a MaxWell Biosystems MaxTwo HD-MEA. From single-unit spike trains we characterized firing rate and regularity, extracellular spike amplitude, pharmacological dependence (GABA-A, NMDA, and AMPA-receptor blockade), and network-level coupling, assembly structure, and population dimensionality, comparing genotypes across independent wells. Both variants converged on elevated single-neuron firing relative to control, so firing rate alone did not distinguish them — but the cellular basis of that hyperactivity differed. GoF hyperactivity was more synaptically driven: GoF neurons showed larger extracellular spike amplitudes and the strongest responses to disinhibition (GABA-A blockade) and to AMPA-receptor blockade. LoF hyperactivity was more intrinsically driven, with more regular firing that persisted under glutamatergic blockade as receptor-independent activity. These cellular differences were mirrored in network organization: GoF assembloids were more strongly coupled and coordinated — fewer, larger neuronal assemblies and lower-dimensional population activity — whereas LoF assembloids were weakly coupled and fragmented, with assemblies firing largely independently. In isogenic CACNA1A assembloids, GoF and LoF converge on cortical hyperactivity but reach it by divergent routes — GoF through greater synaptic drive and network coordination, LoF through intrinsic, poorly coordinated firing. Resolving these mechanisms across scales offers variant-discriminating functional readouts for CACNA1A channelopathy and a template for HD-MEA-based therapeutic testing. Analyses are ongoing and will be extended for the meeting.

ELECTROPHYSIOLOGICAL MAPPING OF HUMAN STRIATAL MICROCIRCUITS ENABLES PARKINSON'S DISEASE STRATIFICATION

Carles Calatayud Aristoy, Dennis Lambrechts, Jannes Straub, Arne Van Den Kerchove, Julien Verplanken, Sandra Fernandez-Gallego, Christine Michiels, Yiling Yang, Kristofer Davie, Suresh Poovathingal, Alessandra Benz, Jef Swerts, Esther Munoz-Pedrazo, Roman Praschberger, Eliana Nachman, Nicolas Poulvellarie, Keimpe Wierda, Wim Vandenberghe, Birgitt Schuele, Dries Braeken, Patrik Verstreken

VIB-KU Leuven, Belgium

Different molecular alterations lead to neuronal network defects that converge into the motor symptoms of Parkinson’s disease. While symptoms alone do not reveal the underlying molecular etiology, the affected circuits may encode characteristic functional signatures that enable mechanistic stratification of the disease. We built human striatal microcircuits on high-density multielectrode arrays comprising human induced pluripotent stem cell-derived cortical, medium spiny and nigral dopamine neurons. We demonstrate that neurons establish appropriate connectivity, with glutamate driving network activity and dopamine modulating neuronal excitability. We then generated two series of isogenic circuits carrying LRRK2 and GBA mutations associated with disease. Predictive modeling revealed mutation-specific electrophysiological signatures, enabling accurate (>85%) genotype-specific classification. These findings show that LRRK2 and GBA mutant circuits display early and distinct defects, and that combining stem cell-based circuit models with AI-powered computational approaches makes it possible to connect molecular etiologies of disease with motor circuit dysfunction. Our approach thus enables to stratify disease beyond clinical symptomatology.

DISSECTING NEURODEGENERATION ACROSS ENGINEERED HIERARCHICAL HUMAN NEURAL CIRCUITS

Joel Kuchler, Areli Balderas Maza, Giulia Amos, Luc Jordi, Elena Durante, Yara Roth, Vaiva Vasiliauskaite, Benedikt Maurer, Magdalini Polymenidou, Kan Cao, Nicolai Winter-Hjelm

ETH Zürich, Switzerland

Neurodegenerative diseases progress silently for years before the first symptoms emerge. This earliest phase, when intervention would likely be most effective, remains inaccessible to study in patients. How pathology initiates, spreads, and drives adaptive and maladaptive responses across interconnected neural populations is therefore poorly understood. Studying this requires human models that recapitulate the architecture of the circuits where these diseases originate and allow us to continuously probe the networks as pathology unfolds. We present a 33-chamber, six-layer microfluidic platform recapitulating the hierarchical organisation of the neocortex. Spheroids of 50 human iPSC-derived neurons and astrocytes, with defined excitatory/inhibitory ratio, are seeded into individual chambers connected by microchannels only permissible to their axons. Tesla valve microchannel geometries enforce unidirectional inter-layer connectivity, confirmed by transfer entropy-based analysis of functional information flow. The platform is interfaced with a high-density microelectrode array and a custom long-term recording pipeline, enabling continuous electrophysiological monitoring of every connection between the neural populations for weeks. To model Alzheimer's disease-relevant pathology, progerin-induced accelerated ageing in a single chamber establishes a defined disease core, while global amyloid-Î² addition once networks are mature recapitulates diffuse proteinopathy. Continuous recordings revealed progressive, layer-dependent collapse of firing dynamics and network hierarchy, while graph-theoretic analysis revealed an initial compensatory increase in modularity followed by declining global efficiency and community stability. Because every connection between the neural populations is continuously monitored, multiparametric machine learning classification can track the functional state of each population over time, revealing subtle changes that precede overt network deterioration. Progressive separation between disease-affected and control populations emerged from early maturation onward, with populations closer to the disease core diverging earliest and most strongly. By tracking every neural population across a known circuit hierarchy continuously over weeks, this platform allows us to resolve precisely where, when, and in what order electrophysiological signatures of neurodegeneration emerge.

Keynote and Invited Speaker Biographies

Dr. Sheila Chari
Cell Stem Cell, Editor-in-Chief

Sheila Chari, Ph.D, is Editor-in-Chief at Cell Stem Cell and Executive Editor at Cell Press. Her primary responsibilities are knowing and publishing the top stem cell discoveries, driving journal publishing strategy, and managing a global editorial staff. She travels to international scientific conferences and research institutions to be on top of the latest developments and meet with authors, reviewers, and readers. She is a proud member of the stem cell community and an ardent supporter of stem cell research. Sheila holds a doctorate from Northwestern University, where she studied transcriptional control of normal and malignant hematopoiesis. She conducted post-doctoral research on epigenetic regulation of cell fate reprogramming at the University of Chicago. Sheila is based in Los Angeles, California, USA.

Xinyu Chen
Applied and Translational Neurogenomics Group, VIB Center for Molecular Neurology, Belgium

Xinyu Chen is a Ph.D. candidate in the Department of Anatomy, Histology and Embryology at Fudan University School of Basic Medical Sciences. His research focuses on the development of human brain organoid models and their applications in developmental neuroscience and neurological disease research. His work has involved the generation of region-specific brain organoids and assembloid models for studying inter-regional neural connectivity, as well as organoid-based models for investigating neural development, disease-associated phenotypes, and interactions between neural and non-neural cell populations. His current research focuses on developing scalable approaches for quantitative morphological analysis, electrophysiological characterization, neuropharmacological assessment, and neuromodulation in human brain organoids and assembloids.

Dr. David Colameo
Senior Scientist at the Electrophysiology Core Facility at the University of Zürich, Switzerland

David Colameo is a Senior Scientist at the Electrophysiology Core Facility of the University of Zurich. He specializes in high-throughput electrophysiological characterization of in vitro model systems using automated patch clamp and high-density microelectrode arrays, including both excitable and non-excitable cellular models. He received his Bachelor's and Master's degrees in Biology and Neuroscience from the University of Zurich. In the group of Steven Brown, he used single-molecule RNA-FISH to visualize circadian oscillating transcripts at synapses. During his doctoral research in the group of Gerhard Schratt at ETH Zurich, he described a microRNA-based molecular mechanism that controls excitatory and inhibitory synapse strength during homeostatic plasticity and sleep.

Prof. Jürgen Knoblich
Institute of Molecular Biotechnology, Austria

Juergen Knoblich is deputy scientific director at the Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA) and Professor at the Medical University in Vienna. Originally trained as a Drosophila researcher, his research focuses on the development of the human brain and the study of neurodevelopmental disorders. He received his PhD from the University of Tübingen and postdoctoral training in the laboratory of Lily and Yuh-Nung Jan at UCSF, San Francisco. In 2013, the Knoblich group has established cerebral organoids, a groundbreaking new technology that allows reconstitution of human brain development starting from patient iPS cells at unprecedented detail. They have used this system for modelling various neurodevelopmental disorders human brain tissue. They were able to screen through entire sets of disease genes relevant for autism spectrum disorders and could demonstrate that neurodevelopmental disorders can arise from cell types not found in animal models.

Prof. Keri Martinowich
Lieber Institute for Brain Development, Baltimore, USA

Dr. Keri Martinowich is Chief Scientific Officer and Senior Investigator at the Lieber Institute for Brain Development, where she oversees scientific strategy and research integration for the Institute, and Professor of Psychiatry and Behavioral Sciences at the Johns Hopkins University School of Medicine. She received a B.A. in International Relations from George Washington University and a Ph.D. in Neuroscience from the University of California, Los Angeles, followed by postdoctoral training in translational neuropsychiatry at the National Institute of Mental Health. Dr. Martinowich leads a research program focused on defining the molecular and circuit-level architecture of the human brain and its disruption in neuropsychiatric and neurodegenerative disease. Her laboratory integrates spatial transcriptomics, single-cell genomics, computational biology, and experimental model systems to investigate how gene expression programs are organized across cell types, microenvironments, and interconnected brain circuits. Her work emphasizes the use of postmortem human brain tissue to identify molecular and genetic signatures associated with disease vulnerability, with complementary translation into human iPSC-based models and rodent systems. Through these efforts, her research aims to bridge molecular, cellular, and systems-level mechanisms to advance understanding of complex brain disorders and enable development of biologically informed therapeutic strategies.

Dr. Mohammed Andres Mostajo-Radji
Genomics Institute, University of California, Santa Cruz, USA

Mohammed Mostajo-Radji is an Associate Research Scientist at the UC Santa Cruz Genomics Institute, where he directs the Live Cell Biotechnology Discovery Lab. His group builds forebrain organoid models and machine-learning tools to define, track, and decode neuronal identity and circuit function from high-density electrophysiology, with applications to neurodevelopmental and neuropsychiatric disease. A parallel thread of his work develops open, cloud-based platforms to make large-scale neuroscience data and analysis broadly accessible, and to bring hands-on

experimental science to students in underserved communities worldwide. He earned his PhD in Molecular and Cellular Biology at Harvard University with Paola Arlotta, completed postdoctoral training at UC San Francisco with Alex Pollen, and is a Google Cloud Research Innovator.

Prof. Dr. Tom Nowakowski
University of California San Francisco (UCSF), USA

Dr. Tomasz Nowakowski is an Associate Professor of Neurological Surgery, Anatomy, and Psychiatry and Behavioral Sciences at the University of California, San Francisco, and a member of the Eli and Edythe Broad Center for Regeneration Medicine and Stem Cell Research. He earned his Ph.D. in Biomedical Sciences at the University of Edinburgh before joining UCSF for postdoctoral training with Arnold Kriegstein, becoming faculty in 2017.

Dr. Nowakowski's laboratory works to establish the human brain as a primary model system for neuroscience, developing scalable genomic, stem-cell, and viral-vector tools to trace cell lineage, map synaptic connectivity, and study gene regulation directly in human tissue. His research spans human cortical development, brain organoid modeling of neurodevelopmental disorders, and the molecular and circuit-level basis of Autism spectrum disorder.

His work has been published in leading journals and recognized with the Vilcek Prize for Creative Promise in Biomedical Sciences, the Sontag Distinguished Scientist Award, and the Robertson Neuroscience Investigatorship from the New York Stem Cell Foundation, among others. He leads UCSF's role in the CIRM Center for Neuropsychiatric Stem Cell Proteomics and chairs the Developing Brain Working Group of the BRAIN Initiative Cell Atlas Network.

Prof. Hideyuki Okano
Keio University Regenerative Medicine Research Center, Japan

Hideyuki Okano received his M.D. in 1983 and Ph.D. in Medical Science in 1988, both from Keio University. Following a postdoctoral fellowship at the Johns Hopkins University School of Medicine, he became a Professor at the Tsukuba University (1994) and the Osaka University (1997). He returned to Keio University in 2001. He served as a Dean of the Keio University School of Medicine and Graduate School of Medicine from 2007 to 2021 and was appointed Visiting Professor at MIT in 2022. He is currently the Director and Distinguished Professor of Keio University Regenerative Medicine Research Center. He has received numerous honors, including the Medal with Purple Ribbon (2009), the Erwin von Bälz Prize (2014), and the Uehara Prize (2022). In July 2025, he became the president of the International Society for Stem Cell Research (ISSCR). His current research focuses on stem cell therapies for spinal cord injuries, as well as iPSCs-based modeling and drug development for neurodegenerative diseases such as ALS and Alzheimer’s disease.

Dr. Jen Q. Pan
Broad Institute of MIT and Harvard, USA

Jen Q. Pan is an Institute Scientist at the Broad Institute of MIT and Harvard and serves as Director of Translational Neurobiology at the Stanley Center for Psychiatric Research. Her research focuses on understanding how dysfunction of genes implicated in psychiatric disorders contributes to disease mechanisms in the central nervous system, with the goal of identifying novel therapeutic approaches.

Dr. Pan leads the Global Research Initiative of Neurophysiology of Schizophrenia (GRINS) Consortium, which investigates sleep and wake EEG recordings from individuals with psychiatric disorders to identify and validate electrophysiological biomarkers. She has also led multiple academic–industry collaborations to advance translational neuroscience and therapeutic development.

Her research has been supported by the Stanley Family Foundation, National Institutes of Health (NIH), the CACNA1A Foundation, the BD2, Laders2Cures, and industry partnerships. Dr. Pan received her B.S. in Chemistry from Nanjing University and her Ph.D. in Neuroscience from Brown University.

Dr. Ranmal Samarasinghe
Department of Neurology, David Greffen School of Medicine, University of California, Los Angeles, USA

Dr. Ranmal Samarasinghe is an Assistant Professor of Neurology at the David Geffen School of Medicine at UCLA, with clinical interests in epilepsy, autism, and neurophysiologic intraoperative monitoring. He received his medical degree and doctorate from the University of Pittsburgh and completed residency training in adult neurology, postdoctoral research, and a clinical fellowship in neurophysiology, all at UCLA.

His laboratory develops and applies human iPSC-derived brain assembloid models to study neural circuit formation and its disruption in neurological disease. Using a combination of two-photon calcium imaging, local field potential recording, and high-density microelectrode arrays, his group interrogates network dynamics across a spectrum from neurodevelopmental disorders — including Rett syndrome and SCN8A channelopathy — to neurodegeneration. Recent work has extended these approaches to model anesthetic mechanisms and tau pathology in assembloid systems, with findings that recapitulate in vivo electrophysiological signatures of disease. A unifying theme across this research is the use of circuit-level activity as a readout for understanding how molecular and cellular pathology translates into network dysfunction, with direct implications for therapeutic discovery.

Dr. Tal Sharf
University of California, Santa Cruz, USA

Tal Sharf is an Assistant Professor of Biomolecular Engineering at the University of California, Santa Cruz. He earned his B.S. in Physics from UC Santa Barbara, where he studied turbulence in thermally driven convection in the laboratory of Guenter Ahlers. He then pursued doctoral research with Ethan

Minot at Oregon State University, developing biosensors based on carbon nanotube and graphene transistors. Inspired by the BRAIN Initiative, Sharf returned to UC Santa Barbara for postdoctoral training with neurobiologist Kenneth Kosik at the Neuroscience Research Institute, where he was named an Arnold O. Beckman Postdoctoral Fellow. During his postdoctoral work, he generated the first high-resolution map of functional connectivity among neurons in human iPSC-derived brain organoids. In July 2022, Sharf established his laboratory at UC Santa Cruz, where his team integrates physics, biology, and computation to investigate how human brain circuits assemble, wire, and generate function. In 2026, his team reported in Nature Neuroscience the discovery of preconfigured neuronal firing sequences in human brain organoids and the early postnatal rodent brain, suggesting that developing neural circuits contain intrinsic activity patterns that may provide a scaffold for interpreting later experience.

Dr. Arun Sharma
Director, Center for Space Medicine Research; Cedars-Sinai Medical Center, USA

Dr. Arun Sharma, PhD is a stem cell biologist focusing on cardiovascular biology and space biosciences. He is an associate professor at Cedars-Sinai and is the director of the Center for Space Medicine Research. Research in the Sharma laboratory focuses on the applications of human induced pluripotent stem cells (hiPSCs) for modeling cardiovascular disease in-vitro. The lab utilizes hiPSCs, genome editing, cardiac organ-on-chips, and 3D cardiac spheroids/organoids to understand the molecular mechanisms driving cardiovascular disease and heart development. Sharma is also an internationally-recognized leader in the space biosciences field. His laboratory studies the impacts of space on stem cell biology and harnessing microgravity to manufacture unique biomaterials. In 2016, Dr. Sharma led a project that sent human stem cell-derived heart cells to the International Space Station (ISS), the first long-duration cell culture experiment in space. Dr. Sharma and his lab have published articles in leading scientific journals such as Science, Nature Biotechnology, Science Translational Medicine, Circulation Research, Stem Cell Reports, and Cell Stem Cell. He has received numerous awards for his work, including the Sartorius & Science Award in Regenerative Medicine, Forbes 30 Under 30 in Science, the American Heart Association Career Development Award, the Compelling Results Award from NASA, the Igniting Innovation Award from the ISS National Laboratory, and the Donna and Jesse Garber Award for Cancer Research. Dr. Sharma earned his bachelor's degree in biology from Duke University and his PhD in stem cell biology from Stanford University. He completed a postdoctoral research fellowship in cardiovascular genetics at Harvard Medical School.

Dr. Silvia Velasco
Novo Nordisk Foundation Center for Stem Cell Medicine, reNEW Melbourne, Australia

A/Prof. Silvia Velasco leads the Neural Stem Cells Laboratory at the Murdoch Children's Research Institute and is a Principal Investigator at the Novo Nordisk Foundation Center for Stem Cell Medicine (ReNEW) in Melbourne. Her laboratory uses pluripotent stem cell-derived neural organoid models to investigate human brain development and neurological diseases, with the aim of developing safe and effective therapies. A/Prof. Velasco completed postdoctoral training at New York University and the Broad Institute of MIT and Harvard and holds a PhD in Human Biology from the University of Turin.

Prof. Janos Vörös
Institute for Biomedical Engineering, Laboratory of Biosensors and Bioelectronics, ETH Zürich, Switzerland

Janos Vörös is a Professor in the Institute for Biomedical Engineering of the University and ETH Zurich (Department for Information Technology and Electrical Engineering) heading the Laboratory for Biosensors and Bioelectronics since 2006. János Vörös has studied Physics at the Eötvös Loránd University in Budapest. After receiving a diploma in Physics in 1995, he was a doctoral student at the Department of Biological Physics of the Eötvös University (in collaboration with Microvacuum Ltd.) where he received his PhD in Biophysics in 2000. Since 1998 he was a member of the BioInterface group in the Laboratory for Surface Science and Technology at the Department of Materials of ETH Zurich as visiting scientist, postdoc, and from 2004 as group leader of the Dynamic BioInterfaces group until 2006. Prof. Vörös is interested in research and teaching in the areas of bioelectronics, biosensors, and neuroscience. His group focuses on the development of novel biosensor techniques for diagnostics and single molecule sequencing; on bottom-up neuroscience; as well as on stretchable biohybrid electronic devices.

Dr. Michael Wells
UCLA David Greffen School of Medicine, University of California, Los Angeles, USA

Michael F. Wells, PhD is an Assistant Professor in the UCLA Department of Human Genetics. He earned a PhD in Neurobiology from Duke University in 2015 and completed his postdoctoral training at the Broad Institute in Kevin Eggan's lab in 2021. During this time, Dr. Wells co-developed the cell village platform that enables high throughput investigations of human genetic, molecular, and cellular phenotypic variation in shared in vitro environments. His research program at UCLA leverages this technology to understand the mechanisms underlying neurodevelopmental disorders of genetic and environmental origin, and is funded by the National Institutes of Mental Health, the Simons Foundation, and the California Institute for Regenerative Medicine.

Prof. Hideaki Yamamoto
Research Institute of Electrical Communication (RIEC), Tohoku University, Sendai, Japan

Hideaki Yamamoto is a Professor at the Research Institute of Electrical Communication (RIEC), Tohoku University, Sendai, Japan. He obtained a Ph.D. degree in engineering from Waseda University, Japan, in 2009. He was a JSPS Research Fellow at Tokyo University of Agriculture and Technology, and an Assistant Professor at Waseda University, before joining Tohoku University in 2014. In 2020, he was appointed Associate Professor at the RIEC and was promoted to Professor in 2026. His research interests include the use of engineered neuronal cultures as a model system for understanding brain computation, as well as their applications to brain-inspired computing and biomedicine.

Short Talk Presenter Biographies

Giulia Amos
Institute for Biomedical Engineering, Laboratory of Biosensors and Bioelectronics, ETH Zürich, Switzerland

Giulia Amos is a fourth-year Ph.D. candidate in the Laboratory of Biosensors and Bioelectronics at ETH Zurich, working under Prof. János Vörös. Her research investigates how diseases like glioblastoma drive pathological connectivity and information processing in neuronal networks, using compartmentalized human-based in vitro models. Giulia holds an MSc in Health Sciences and Technology from ETH Zurich and was a 2020 ESOP Scholar. During her studies at ETH, she has undertaken research stays at the University of Tokyo, in Singapore, and in Nigeria.

Marcella Birtele
Giorgia Quadrato Lab, University of Southern California, United States

Marcella Birtele completed her PhD in Malin Parmar's lab at Lund University, Sweden, working on the functional and transcriptional profiling of stem cell-derived dopaminergic neurons. As a postdoctoral fellow in Giorgia Quadrato's lab at the University of Southern California, she first used cortical organoids to study the role of SYNGAP1, an autism-associated gene, in human neural development. She now develops human iPSC-derived organoid models of the enteric nervous system to investigate its development and disease mechanisms. She will establish her independent laboratory at the University of California, Irvine, in 2027.

Dr. Wesley Clawson
Tufts University, United States

My research interests revolve around biological organization – how biological dynamics are organized in such a way to support phenomenon such as learning and cognition. Currently, at the Allen Discovery Center at Tufts, my research involves studying neural cultures via a closed-loop system that allows for real-time interaction between a population of neurons and virtual worlds, investigating how cultures learn and adapt via self-organized (or not) change. I also work in the planarian flatworm studying how learning may (or not) persist across whole-brain regeneration. Regardless of the model system, I typically approach things through a practical, embodied cognition approach. Previously, my research focus at the University of Arkansas was on investigating criticality in the visual cortex and its potential functional properties using ex-vivo turtle brains. Mounting evidence indicates that some neural populations may sit at criticality and this statistical phenomenon is tied to certain brain functions. It is a continued area of research for me, where I study the organization of population dynamics in behaving mice through calcium recordings. My PhD research was focused on neural populations and on how they process information and how that is related to computation.

Dr. Theresa Kagermeier
Institute for Systemic Cellular Neurobiology at Karlsruhe Institute of Technology (KIT), Germany

Theresa Kagermeier is a Postdoctoral Researcher at the Institute for Systemic Cellular Neurobiology at Karlsruhe Institute of Technology (KIT), Germany in the lab of Simone Mayer. She gained first research experience with in vitro models at the Max Planck Institute for Molecular Biomedicine in Münster, Germany. Building on that, her doctoral research at the Hertie Institute for Clinical Brain Research in Tübingen, Germany focused on the development and application of regionalized neural organoids as in vitro models for human neurodevelopmental disorders and investigated advanced human stem cell-based models to study mechanisms underlying neurodevelopment and disease. Her research interest lies at the intersection of cellular and molecular neuroscience, human neurodevelopment, and advanced in vitro model systems for neurodevelopmental disorders. Currently she is working on elucidating the mechanisms underlying Pontocerebellar Hypoplasia Type 2A (PCH2A), an ultra-rare neurodevelopmental disorder caused by mutations in the tRNA splicing factor TSEN54, using patient-derived and genome-edited iPSCs and neural organoids.

Aayush Marishi
Department of Biosystems Science and Engineering, ETH Zürich, Switzerland

Aayush Marishi is a PhD student in Biosystems Science and Engineering at ETH Zurich. He holds a master's and bachelor's degree from Goethe University Frankfurt, with expertise in in-vivo and in-vitro electrophysiology ranging from fundamental research to disease modeling.

Dr. Kaneyasu Nishimura
Doshisha University, Japan

Kaneyasu Nishimura is an Associate Professor at Graduate School of Brain Science, Doshisha University, Japan. He received his Ph.D. from Kyoto Pharmaceutical University. He subsequently conducted postdoctoral research at Center for iPS Cell Research and Application (CiRA), Kyoto University, Japan, and at Karolinska Institutet in Sweden.

His research focuses on human pluripotent stem cell-based models of the nervous system, with particular emphasis on neural differentiation, brain organoids and assembloids, and neurodegenerative diseases. His current work aims to reconstruct human brain circuits in vitro and use these models to investigate the mechanisms underlying Parkinson's disease and α-synuclein pathology.

Dr. Rebecca Northeast
bit.bio, United Kingdom

Rebecca received her PhD and post-doctoral training at the University of Manchester where she utilised MEA recordings to study the circadian regulation of metabolic regulators in the brainstem.

Now at bit.bio, Rebecca works with neuroscience researchers across the globe in supporting them to build complex in vitro models for neuroscience with bit.bio's human iPSC-derived cells.

Antonio Ortega
Johns Hopkins University, United States

Antonio Ortega is a PhD candidate in the Center for Alternatives to Animal Testing at the Johns Hopkins School of Medicine. His research centers on developing retinal organoid systems that more faithfully model visual function, advancing organoid architecture and performance to capture essential features of retinal circuitry. He aims to build translational platforms that accelerate therapeutic discovery and support the development of new treatments for retinal disorders.

Arvin Sarkissian
Fikri Birey Lab, Emory University, United States

Arvin Sarkissian is a neuroscience PhD candidate in Fikri Birey's lab at Emory University. His dissertation builds human iPSC-derived brain organoids and forebrain assembloids to model CACNA1A-related disorders, integrating high-density multielectrode array recordings, calcium imaging, transcriptomics, and pharmacology to understand how gain- and loss-of-function variants in the Cav2.1 calcium channel reshape excitatory-inhibitory balance in neurodevelopment.

Jannes Straub
Patrik Verstreken Lab, VIB-KU Leuven, Belgium

Jannes Straub studied Biosciences and Molecular Biosciences with a focus on Neuroscience at the Ruprecht-Karls University in Heidelberg, receiving a M.Sc. degree in 2024. During this time, he completed a research stay at the University of California at Berkeley with Prof. Dirk Hockemeyer, which also marked the start of his work on neurodegenerative diseases. In early 2025, Jannes moved to Patrik Verstreken's lab at VIB-KU Leuven Center for Brain & Disease Research to pursue a PhD studying Parkinson's disease using novel stem cell models. Jannes contributed to several high profile publications during his internships and theses, of which the latter was also recognized with an award by the jGBM. In addition, he is actively involved in institutional responsibilities at his host institutes (student representative) and in tutoring first-year students.

Dr. Nicolai Winter-Hjelm
Institute for Biomedical Engineering, Laboratory of Biosensors and Bioelectronics, ETH Zürich, Switzerland

Nicolai Winter-Hjelm is a Postdoctoral Research Fellow working with Prof. Janos Vörös at the Laboratory of Biosensors and Bioelectronics at ETH Zürich, supported by an ETH Zürich Postdoctoral Fellowship and an ETH Career Seed Award. He received his MSc in Bionanotechnology and his PhD in Medicine from the Norwegian University of Science and Technology (NTNU) in 2020 and 2024 respectively. During his doctoral work, he developed multi-compartment microfluidic platforms with directed connectivity for studying neural circuit function and dysfunction in vitro, with applications to Alzheimer's disease and ALS. At ETH Zürich, his research focuses on engineering human neural

circuit models to study how neurodegenerative disease initiates and propagates across defined hierarchical circuits. As part of this work, he has been a visiting researcher in the laboratory of Prof. Fred Gage at the Salk Institute for Biological Studies, with the goal of integrating novel patient-derived cell models to advance the translational relevance of these platforms. His research interests broadly span the engineering of neural networks with defined topologies to understand how circuit architecture shapes neural computation and dysfunction in health and disease, combining electrophysiological, optical, and molecular approaches.

Abstracts | Poster Presentations

1. AN OPEN, REMOTELY ACCESSIBLE NEUROPLATFORM FOR LONG-TERM CLOSED-LOOP ELECTROPHYSIOLOGY OF HUMAN IPSC-DERIVED BIOLOGICAL NEURAL NETWORKS

F. Jordan, M. Kutter, G. Rebecchi, S. Jaffard, F. Brozzi, J. Comby, E. Kurtys

Finalspark

Wetware computing and organoid intelligence seek to harness living neuronal networks for computation. Unlike artificial neural networks, living networks must be shaped through stimulation, feedback, and environmental modulation, requiring scalable longitudinal experiments. We developed an integrated hardware–software platform for electrophysiology across human iPSC-derived neural spheroids, cortical organoids, assembloids, and 2D neuron–astrocyte co-cultures, collectively termed biological neural networks (BNNs). Depending on the integrated MEA, activity can be monitored for months in 24-hour sessions or continuously, with recording of spontaneous and evoked activity, programmable stimulation, and automated microfluidic medium exchange. A Python API coordinates electrophysiology, pumps, cameras, and UV sources for molecular uncaging, enabling 24/7 closed-loop experiments, remote access, and integration with deep-learning and reinforcement-learning workflows. The modular architecture is designed for air–liquid interface (ALI) and submerged configurations and MEAs ranging from 8-electrode arrays to high-density systems, potentially including MaxWell Biosystems HD-MEAs and Multi Channel Systems platforms. Because the NeuroPlatform is remotely accessible, researchers can perform experiments without establishing their own cell culture laboratory. For example, recordings from forebrain assembloids on a 32-electrode ALI-MEA have been used to reconstruct functional connectivity using a Hawkes process–based method that accounts for the activity of unobserved neurons. To date, the Neuroplatform has been used with over 1,000 neural organoids and has generated over 30 TB of neuronal activity data. These results show how a remotely accessible, MEA-flexible platform can combine long-term experiments with network inference to study plasticity, functional connectivity, and computation across 2D and 3D neural systems.

2. DELAYED MATURATION OF GABAERGIC INTERNEURONS AND PATHOLOGICAL MITOCHONDRIAL DYNAMICS AS KEY DRIVING FACTORS OF EPILEPTIC SEIZURES IN HIPSC DERIVED CORTICAL ORGANOID MODELS OF RETT SYNDROME

S. Raghu, A. Rossetti Carlo, M. Gasparatto, M. Segner, L. Sadiraj, P. Koch, M. Schröter, J. Ladewig

University of Heidelberg

Rett syndrome is an X-linked neurodevelopmental disorder caused by genetic mutations on the MeCP2 gene, which produces a dose-sensitive chromatin associated protein, expressed highly in mature neurons and capable of being both an epigenetic translational repressor and activator. In this project, we tried to model the effects of T158M point mutation on MeCP2, on brain development, using cortical organoids generated from patient derived hiPSCs at the cytoarchitectural, molecular and functional levels. Single nuclear sequencing revealed the presence of a separate progenitor pool in the mutant organoids at the early stages of development and the aberrant and ectopic overexpression of specific GABAergic genes in the excitatory neurons at later stages, both of which resulted in an excitatory-inhibitory imbalance in the T158M mutant organoids. These findings were replicated in organoids generated from other more severe mutant lines like R168X, hence revealing a set of common molecular underpinnings and biomarkers that can be used as potential therapeutic targets across different mutations causing Rett syndrome. Functional characterization of mutant whole brain organoids using HD-MEA and Calcium imaging showed reverberating superbursts reminiscent of seizure like activity in patients. Upon screening of a set of bioactive compounds, a novel mitochondria-targeted drug was shown to successfully reduce the frequency of seizure-like activity in mutant organoids and bring down the global network activity closer to the isogenic control. The mechanism of action of this drug and the effect it has on synaptic and overall neuronal maturation is currently being investigated.

3. HIGH-DENSITY MEA ANALYSIS OF NEURAL NETWORK ACTIVITY, MATURATION AND PLASTICITY IN REGION-SPECIFIC HUMAN BRAIN ORGANOIDS

M. Bertacchi, G. Rebecchi, M. Mugonza, P. Pousinha, M. Studer, I. Bethus, P. Reynaud-Bouret

Université Côte d'Azur, CNRS, LJAD

Institut de Biologie Valrose (iBV) – Inserm U1091, CNRS UMR7277, UniCA – Nice, France

IPMC – Sophia Antipolis, France

Early developmental events that shape the formation of neural circuits in the fetal human brain have been difficult to study due to obvious technical and ethical limitations. Human brain organoids offer a unique opportunity to investigate the formation, maturation, and plasticity of neural circuits under both physiological and pathological conditions within a simplified and accessible in vitro system. Here, we used brain organoids cultured on high-density multi-electrode arrays (HD-MEAs) to monitor the formation of neural networks over time at single-cell resolution, using spontaneous electrical activity as a readout of neural circuit development in vitro. We investigated the effects of FGF8, a key morphogen involved in anteroposterior and dorsoventral brain patterning, by comparing the spontaneous activity of control neocortical organoids with that of FGF8-treated organoids. While control organoids developed a cortical, glutamatergic identity, FGF8 exposure shifted regional specification toward a more ventral fate, generating both excitatory glutamatergic and inhibitory GABAergic neurons. To reconstruct neural circuits and characterize their components, we optimized an analysis pipeline for HD-MEA recordings using Hawkes process models to infer connectivity patterns and quantify excitatory and inhibitory synaptic interactions. In addition, a cross-correlogram-based approach identified and excluded false-positive neuronal units arising from the high electrode density. Our results demonstrate reliable detection of neuronal populations, efficient characterization of excitatory and inhibitory synaptic connections, and discrimination between direct and indirect network interactions, as well as between intra- and inter-organoid connectivity. Importantly, FGF8-treated organoids displayed distinct connectivity profiles, consistent with their proportions of glutamatergic and GABAergic neurons. In collaboration with the biocomputing company FinalSpark, we are now investigating whether established connectivity networks can be reconfigured through electrical or chemical stimulation, thereby reshaping global patterns of spontaneous electrical activity within the organoids. Together, these findings establish an HD-MEA-based platform for both the analysis and modulation of spontaneous neural activity in human brain organoids and provide new insights into the mechanisms underlying the emergence of region-specific neural circuits during early human brain development.

4. SPIKETRAIN SPOTTING: HOW TO INFER SYNAPTIC CONNECTIVITY IN BRAIN ORGANOIDS

G. Rebecchi, M. Mugonza, G. Scarella, C. Phi, M. Bertacchi, M. Studer, I. Bethus, P. Reynaud-Bouret

Université Côte d'Azur

Inferring synaptic connectivity from extracellular spike train recordings is a challenge in neuroscience, with direct implications for understanding how neural circuits learn, adapt, evolve. High-density microelectrode arrays (HD-MEAs) now make it possible to record hundreds to thousands of neurons simultaneously, yet the problem of reliably reconstructing the underlying connectivity from such data remains open. In our work we first benchmark two families of inference methods — covariance-based approaches (GLMCC and Shin-GLMCC) and a Hawkes process-based method defined as STS. In the first part of our work, we simulate spike train data via NEST simulator, testing various network sizes and connectivity densities. We proceed by identifying two benchmarking regimes: an idealistic and often used simulation framework, and a more realistic one. Such benchmarking shows that covariance-based approaches present important limitations concerning accuracy and robustness across different setups and conditions. On the other hand, STS, if adequately tuned through bootstrapping, achieves higher performances. In general, the quality of the reconstruction degrades substantially under realistic conditions, particularly for denser networks. In the second part of this work, we apply STS to MEA recordings, providing human 3d brain organoids connectivity reconstruction, with associated confidence level and error approximation, and categorizing cellular identity based on connectivity properties.

5. A BIOELECTRONIC PLATFORM FOR MODELING FUNCTIONAL CONNECTIONS BETWEEN NEURAL ORGANOIDS

S. Erickson, T. Tunekov, T. Duenki, R. Montero, I. Furfaro, E. Amstad, Y. Ikeuchi, G. Schiavone, S. Lacour

EPFL

Neural organoids are quickly becoming established tools to model human neural tissue and diseases. When allowed to adhere to a substrate, they are known to exhibit cell outgrowth and axon projections that can form connections with other organoids and cells in the vicinity. The goal of this study is to develop a novel bioelectronic platform that harnesses this spontaneous biological phenomenon to create a functional connection between two neural organoids. We designed a custom device composed of two thin-film microelectrode array (MEA) webs connected by a narrow bridge and suspended within a well of cell culture media. We fabricated the MEAs by a standard thin-film microfabrication process using platinum on polyimide. We use photolithography and etching to define the web and bridge outlines, as well as 30 µm diameter via openings to the embedded platinum conductor, creating 32 electrodes for electrophysiology. Electrophysiology is performed by connecting the MEAs to an Intan headstage with a custom connector. An organoid is seeded on each of the two suspended webs, which allows them to be maintained at the air-liquid interface and ensures the organoids have minimal contact with artificial substrates for improved nutrient delivery. The bridge separates the two organoids and provides directionality to promote cell outgrowth from the organoids toward each other. We reinforce this spatial cue by adding a 3D bioprinted biomaterial coating on the bridge, which also greatly improves organoid alignment with the mesh MEA during seeding. This geometric configuration promotes a cellular connection between the organoids that is both confined to a single bridge and accessible to optical/electrical characterization and physical manipulation. We show spiking activity recorded from neural organoids themselves as well as the cells growing between organoids cultured on the MEA. Spikes and bursts were recorded for up to 80 days, and spike sorting and analysis reveal multiunit activity. Within a month on the device, the axonal connection between the two organoids becomes sufficiently strong such that they begin bursting in sync, demonstrating the functionality of the connection. By leveraging the open-access bridge design, we use the platform as a means to model nerve injury, where electrophysiology can serve as the functional readout for healthy, damaged, and repaired tissue. We anticipate our platform to enable novel in vitro models of various tissues of the human nervous system where communication between two nodes is of particular interest. Integration of electrophysiology and optical measurements create a testbed for the evaluation of healthy neural tissues as well as different therapies and regeneration strategies for disease states.

6. DRIVING WITH THE PARKING BRAKE ON. REPAIRING KCNQ2 GAIN-OF-FUNCTION NEURONAL HYPO-EXCITABILITY WITH AN ANTISENSE OLIGONUCLEOTIDE TUNE-UP

M. Kaji, N. Dirkx, N. Zonnekein, L. Carotenuto, E. De Vriendt, S. Weckhuysen

VIB -University of Antwerp

KCNQ2 encodes the Kv7.2 subunit of a neuronal voltage-gated potassium channel that is essential for neurodevelopment and the regulation of neuronal excitability. Heterozygous pathogenic variants can lead to severe dominant-negative loss-of-function (KCNQ2-DN) or, more rarely, gain-of-function (KCNQ2-GOF) disorders, both associated with lifelong developmental delay and intellectual disability. Current treatment is limited to symptomatic seizure management, with no targeted therapies available for KCNQ2 channelopathies and no established treatment options for KCNQ2-GOF. To investigate disease mechanisms and establish a translational platform for therapeutic testing, we generated patient-derived induced pluripotent stem cell (iPSC) models carrying either KCNQ2 loss-of-function (KCNQ2-LOF) or gain-of-function (KCNQ2-GOF) variants and differentiated them into excitatory neurons. Longitudinal functional recordings using high-density microelectrode arrays (HD-MEAs) over two months revealed opposing network phenotypes, with KCNQ2-LOF neurons exhibiting overall hyperexcitability and KCNQ2-GOF neurons displaying hypoexcitability relative to controls. To address the lack of KCNQ2-GOF treatment, we designed gapmer antisense oligonucleotides (ASOs) for pan-allelic KCNQ2 knockdown and assessed their efficacy in iPSC excitatory neurons. Lead KCNQ2 ASOs demonstrated promising potency (IC50 < 100 nM), efficacy (>85% knockdown), on-target selectivity, and favourable in vitro neuronal safety profiles. When KCNQ2-GOF neurons were exposed to KCNQ2-targeting ASOs on HD-MEAs, network development normalized toward wild-type activity across all major affected readouts in a tuneable, concentration-dependent manner (50 nM vs 1 µM). Together, these data provide proof of concept that ASO-mediated reduction of KCNQ2 expression can rescue disease-associated developmental dysfunction in KCNQ2-GOF neurons and warrants further preclinical development as a targeted therapeutic strategy.

7. BEYOND PHENOTYPING: FROM MEA DATA TO MECHANISTIC INSIGHT USING COMPUTATIONAL MODELING

N. Doorn, G. Wiersma, M. Frega, M. van Putten

ETH Zürich - Laboratory of Biosensors and Bioelectronics

MEA recordings of iPSC-derived neuronal networks have become a cornerstone of disease modeling and drug screening. Healthy and patient-derived networks often show clearly distinct activity phenotypes such as differences in burst rate, burst duration, or firing patterns. These phenotypic readouts are typically used as endpoints in themselves. Answering the deeper question—why does the burst duration differ, and what does this mean about what is going on with the cells and circuits—requires laborious follow-up experiments such as patch-clamp or RNA-sequencing. The rich mechanistic information already encoded in MEA activity largely goes untapped. We show that with the right computational tools, MEA data can directly reveal the biological mechanisms driving disease or drug response. We developed a detailed in silico model of iPSC-derived excitatory neuronal networks, configured on virtual electrodes mimicking MEA geometry, with parameters representing properties of ion channels, synapses and network organization. Because biological systems are degenerate (many parameter combinations can produce similar activity), we use simulation-based inference (SBI) rather than traditional parameter fitting. SBI trains a deep neural density estimator on hundreds of thousands of simulations, and can then instantly return the full posterior distribution of biological parameters consistent with any new MEA observation [1]. Crucially, the heavy computations are performed only once; analyzing new data takes seconds. Applying this approach to patient-derived networks, SBI correctly identified reduced sodium and potassium conductances in Dravet Syndrome and GEFS+ networks, as later verified by patch-clamp, and impaired connectivity in CACNA1A haploinsufficient networks. It also detected drug-induced synaptic plasticity changes following Dynasore treatment [2]. A key current limitation is that our model and trained density estimator are tailored to one protocol and a predefined set of research questions. Adapting it to another culture system or question requires redefining the model, generating new simulations, and retraining the estimator. It also forces decisions about relevant mechanisms and model complexity before analysing the data. To overcome this, we are piloting a generalized extension based on PRISM [3], a prior-flexible framework for joint model structure and parameter inference. This would allow researchers to define model components and complexity in a data-driven way at test time, moving from hypothesis-driven parameter testing toward truly open-ended mechanism discovery. Together, this work charts a path from MEA phenotyping towards scalable, data-driven discovery of mechanisms underlying disease and drug response.

References
[1] Gonçalves et al. (2020) eLife 9:e56261 (2020).
[2] Doorn et al., Communications Biology 8:768 (2025)
[3]. Gloeckler et al., arXiv:2603.15292 (2026)

8. PREVENTION OF COGNITIVE IMPAIRMENT AND SYNAPTIC DYSFUNCTION IN ALZHEIMER'S DISEASE

Seth, Miller, Rafiq, F. Deak

Augusta University

We have examined a specific class of proteins – the vesicular membrane associated proteins (VAMPs/synaptobrevins) and their role in synaptic release and Abeta production: a) in human genetic screens single nucleotide polymorphism (SNP) variants of the VAMP1 gene encoding syb1 are significantly associated with late onset AD; b) SNPs associated with increased expression of VAMP1 increase the risk of AD and SNPs associated with lower syb1 expression reduces the risk of AD; c) in neurons of VAMP1 KO mice Abeta40 and Abeta42 production is substantially reduced. d) Lower levels of syb1 protected 18 mo old Tg2576 mice from cognitive impairment, improved their hippocampal synaptic plasticity and reduced amyloid formation in their brains. Conclusions: Based on these observations, we conclude that syb1 is a key coupling protein between vesicular release and APP processing. We propose that variations in synaptobrevin-1 level alter the coupling of synaptic transmission to APP processing and therefore have profound effect on Abeta production and risk of late-onset AD.

9. PHYSIOXIA REGULATES MITOCHONDRIAL DYNAMICS AND PROTECTS DEVELOPING CORTICAL NEURONS FROM HYPOXIA-INDUCED CELL DEATH IN HUMAN BRAIN ORGANOIDS

M. Liput, Z. Kuczynska, P. Leszczynski, E. Metin, L. Buzanska

Mossakowski Medical Research Institute Polish Academy of Sciences

Human corticogenesis requires dynamic metabolic support for neural progenitors and differentiating neurons. Mitochondria are central to ATP production, metabolic signaling, and cellular homeostasis, and their dysfunction contributes to neurodevelopmental and neuropsychiatric disorders. Human iPSC-derived brain organoids recapitulate key features of cortical development, yet most are cultured at atmospheric oxygen levels (21% Oâ,,) rather than at the physiological oxygen concentrations in the developing brain's neurogenic niche (approximately 5% Oâ,,). How oxygen availability influences mitochondrial dynamics and neural development remains poorly understood. To investigate whether oxygen conditions modulate neurodevelopment and mitochondrial dynamics, human cerebral organoids (hCOs) and dorsal forebrain organoids (hDFOs) were cultured at 21% Oâ,, or 5% Oâ,, (â€œphysioxiaâ€). Next, hDFOs cultured under both conditions (21% Oâ,, and 5% Oâ,,) were exposed to short-term hypoxia (48 hours, 1% Oâ,,) to model prenatal hypoxic injury and to determine whether physioxia protects neural populations and mitochondrial homeostasis. In hDFO, physioxia reduced progenitor proliferation (Ki67+) and expanded neuronal rosettes. It also moderately decreased markers of TBR2+ intermediate progenitors, Hopx+ outer radial glia, deep-layer cortical neurons (CTIP2+, TBR1), and synaptic maturation markers (SYP, SYN2). Additionally, physioxia reduced mitochondrial fragmentation, moderately increased network complexity, and decreased mitophagy flux, accompanied by reduced PINK1-Parkin activity in the cortical layer of hDFO. In hDFOs, short-term hypoxia induced mitochondrial fragmentation and activation of the unfolded protein response (UPR). Preconditioning hDFOs at 5% Oâ,, improved the survival of TBR2+ intermediate progenitors, HOPX+ outer radial glia, and cortical neurons. It also attenuated hypoxia-induced mitochondrial fragmentation while activating BNIP3-mediated mitophagy. Transcriptomic analysis of 44-day hCOs showed metabolic reprogramming toward glycolysis and activation of neuroprotective pathways, together with suppression of UPR and pro-apoptotic programs. Alternative splicing analysis further revealed a shift toward anti-apoptotic isoforms. These findings show that physiologic oxygen conditions regulate mitochondrial quality control and enhance the resistance of neural populations to hypoxic injury in the developing brain. They also establish brain organoids as a relevant model for prenatal hypoxic injury, identify physiological normoxia as a viable therapeutic strategy to preserve mitochondrial homeostasis and protect developing neuronal populations from hypoxia-induced damage, and reveal protective mechanisms relevant to hypoxia-associated neurodevelopmental disorders. Acknowledgments: This work was supported by National Science Center Grant 2019/35/B/NZ3/04383 and Statutory Fund of MMRI PAS.

10. SELECTIVE MODULATION OF THE SENESCENCE-ASSOCIATED TRANSCRIPTOME IN HUMAN DORSAL FOREBRAIN ORGANOIDS CULTURED UNDER PHYSIOLOGICAL OXYGEN TENSION

Z. Knapinska, M. Liput, M. Zychowicz, L. Buzanska

Mossakowski Medical Research Institute Polish Academy of Sciences

Cellular senescence is a biological process characterized by irreversible cell cycle arrest and progressive functional decline. Physiological oxygen tension (physioxia, 5% O2) more closely resembles the in vivo cerebral microenvironment than conventional atmospheric oxygen (21% O2) and has been proposed to influence cellular homeostasis and aging. However, its impact on the senescence-associated transcriptome in human brain organoids is not yet completely understood. This study investigated whether culturing human dorsal forebrain organoids for 44 days in physioxic conditions alters the expression of senescence-associated genes compared with standard atmospheric O2 level. It was hypothesized that physioxia would down-regulate molecular pathways associated with cellular senescence. RNA sequencing was performed on dorsal forebrain organoids cultured under 5% O2 and 21%O2. Differential gene expression analysis was integrated with the CellAge database to identify senescence-associated genes exhibiting significant transcriptional changes. Differentially expressed CellAge genes were characterized using volcano plots, hierarchical clustering, and heatmap visualization. Gene Set Enrichment Analysis (GSEA) was subsequently performed using curated CellAge senescence inducer and inhibitor gene sets to evaluate coordinated pathway-level responses. A total of 186 CellAge genes were differentially expressed between experimental conditions, comprising 62 genes upregulated and 124 genes downregulated under physioxia. Both senescence-inducing and senescence-inhibiting regulators were represented among differentially expressed genes, indicating selective remodeling of senescence-associated transcription rather than preferential regulation of a single functional group. Hierarchical clustering demonstrated clear separation of organoids according to oxygen conditions based on the expression of the most significantly altered CellAge genes. In contrast, GSEA revealed no significant coordinated enrichment of either CellAge senescence-inducing (NES = −1.23, FDR = 0.113) or senescence-inhibiting (NES = −0.79, FDR = 0.949) gene sets. These findings demonstrate that physioxic culture conditions selectively alter the expression of senescence-associated genes in human dorsal forebrain organoids. Together, these results suggest that physioxia may influence specific molecular pathways rather than globally regulating cellular senescence. Given the growing evidence linking cellular senescence to neurodegenerative processes, these findings provide a rationale for further investigating the effects of physioxia on additional biological pathways involved in brain homeostasis and disease. In particular, future transcriptomic analyses focusing on neurodegeneration-associated pathways may help elucidate how physiologically relevant oxygen conditions shape molecular mechanisms that connect cellular senescence with neurodegenerative disorders. Acknowledgments: This work was supported by National Science Center Grant 2024/55/I/NZ5/03205 and Statutory Fund of MMRI PAS.

11. FUNCTIONAL PHARMACOLOGY OF BRAIN ORGANOIDS ENABLED BY AUTOMATED MICROFLUIDIC ELECTROPHYSIOLOGY

S. Seiler, K. Voitiuk, T. van der Molen, A. Loehde-Woolard, J. Geng, G. Kaurala, J. LaFemina, H. Schweiger, S. Hernandez, K. Doganyigit, T. Sharf, M. Mostajo-Radji, D. Haussler, S. Salama, M. Teodorescu

University of California, Santa Cruz

For many decades, the culture and study of in vitro neural cultures has been a largely artisanal field. The cultures are moved in and out of incubators, given media changes infrequently, and monitored for treatment effects intermittently. Our automated system performs all of the necessary feeding, dosing, and monitoring to allow for efficient, reliable, and accurate data collection with minimal disturbance. The research we have conducted using this system examines the effects of two compounds known to increase network activity: carbachol, a cholinergic agonist, and gabazine, a GABA-A antagonist, in both cortical and midbrain organoids. Carbachol elicits erratic and rapid bursting that quickly destabilizes the network; this contrasts with the disinhibitory, burst-homogenizing effects of gabazine that induce stable, uniform states. The effects of both compounds were found to be significantly more pronounced in cortical organoids than in midbrain organoids, which were robust to both compounds. All drugs were administered entirely autonomously in-system without disturbing the culture and, through continuous and precise monitoring, we were able to observe temporal dynamics at both the single-unit and population levels that would have been invisible to intermittent methods. This includes initial strong responses to carbachol that rapidly fade as well as latent-state dynamics of both compounds that were analyzed through GPLVM and PCA to further our understanding of the transition between states of activity in brain organoids. These results demonstrate the effectiveness of automated cell culture care systems with integrated monitoring via high-density microelectrode arrays, both in revealing subtle dynamics that would otherwise be missed by intermittent methods and in producing high-quality data with minimal disruption.

12. A SYSTEM FOR UNPERTURBED LONGITUDINAL RECORDING OF NEURONAL NETWORKS THROUGH CONSTANT CULTURING CONDITIONS

B. Maurer, F. Fischer, G. Amos, V. Vasiliauskaitė, J. Vörös

ETH Zurich

In vitro platforms allow investigation of neuronal network dynamics and pharmacological responses under controlled conditions, without the ethical burden associated with in vivo studies. However, longitudinal microelectrode array (MEA) recordings are limited by evaporation-induced drift in culture conditions, exacerbated by heat dissipation from active CMOS-based high-density MEA (HD-MEA) electronics. Existing passive strategies face a fundamental trade-off between suppressing water vapour loss and maintaining the CO2 and O2 exchange required for pH buffering and cell viability. We present a cell culture lid with a water compartment above the liquid–air interface that eliminates evaporation by removing the humidity gradient, whilst preserving gas exchange through two vapour-permeable membranes [1]. Combined with a custom incubator (inkudock) that prevents condensation via independent temperature control of the recording electronics, it enables uninterrupted recordings for weeks without medium exchange, humidity regulation, or perfusion infrastructure. We validated the system with human iPSC-derived neurons patterned into topologically constrained networks on HD-MEAs. Compared to conventional membrane lids, the water compartment lid significantly reduced transient perturbations in firing rate and functional connectivity after medium exchange. This enabled continuous 35-day recordings with a single medium exchange, revealing the emergence, diversification, and consolidation of spatiotemporal firing patterns at single-spike resolution. Tight control over the culturing conditions yields a stable recording baseline. This facilitates a shift towards highly interpretable closed-loop stimulation and drug perturbation studies. It further allows maturation and plasticity to be tracked in the same culture over weeks. All designs and software are publicly available

References

[1] Maurer, B., Fischer, F., Amos, G., Vasiliauskaitė, V., & Vörös, J. (2026). A water compartment cell culture lid enables stable longitudinal recording of neuronal networks in vitro. bioRxiv. https://doi.org/10.64898/2026.04.01.713917

13. HUMAN IPSC-DERIVED MODELS TO UNRAVEL THE ROLE OF GLYPICANS IN SYNAPTIC ALTERATIONS IN SANFILIPPO SYNDROME

A. Girard, D. Colameo, D. Ribas, I. Canals

Kinderspital UZH

Sanfilippo syndrome is a lysosomal storage disorder characterized by early-onset neuronal dysfunction and progressive neurodegeneration. It is caused by mutations in genes encoding enzymes responsible for heparan sulfate (HS) degradation, resulting in HS accumulation. HS is mainly found as HS proteoglycans (HSPGs), which are present on the cell surface and in the extracellular matrix. Among HSPGs, glypicans 4, 5, and 6 are predominantly produced by astrocytes and are important regulators of synaptogenesis. Most studies investigating disease mechanisms have relied on animal models, however, to increase translational relevance, human-based experimental systems are needed to better understand disease mechanisms. To address this limitation, fibroblasts from three patients with Sanfilippo syndrome and three healthy controls were reprogrammed into induced pluripotent stem cells (iPSCs). iPSCs were then differentiated into neurons and astrocytes. Differentiation was achieved via transcription factor overexpression, enabling the rapid generation of neurons and astrocytes that can be cultured in isolation or together in cocultures. Neuronal and astrocytic cell morphology can be assessed using immunocytochemistry, while HS levels can be quantified by mass spectrometry. In cocultures, neuronal and network activity can be examined using multi-electrode array (MEA) recordings. iPSC lines were successfully generated using mRNA-based reprogramming and fully characterized according to ISSCR guidelines. A 2D coculture system combining neurons and astrocytes was established. Network activity was recorded using MEAs, revealing a high degree of batch-dependent variability and potential dysfunctions in Sanfilippo syndrome neuronal networks. To improve consistency of our model, we have implemented a piggyBac-based differentiation towards neurons. Ongoing analysis include HS quantification and synapse number quantification to determine potential differences between healthy control and patient neurons. To model Sanfilippo syndrome, we successfully generated human iPSC lines. Initially, we differentiated the iPSCs using a lentiviral system; however, this approach showed a high level of variability. To reduce this variation, we implemented an alternative piggyBac differentiation strategy, which resulted in improved reproducibility across neuronal differentiations. With this improved system, we can now consistently model the disease to further investigate the underlying mechanisms of Sanfilippo syndrome, particularly at the level of neuron–astrocyte interactions and synaptic function.

14. EFFECTS OF TIME-SERIES LENGTH AND NOISE ON RECURRENCE PLOT ANALYSIS OF DEVELOPMENTAL NEURAL DYNAMICS IN IPS CELL-DERIVED NETWORKS

Y. Uwate, Y. Nishio

Tokushima University

Recurrence plots (RPs) have been widely employed to analyze nonlinear dynamics in biological systems and provide valuable insights into the temporal behavior of neuronal activity. In developing neuronal networks derived from human induced pluripotent stem cells (iPSCs), RP-based analysis has the potential to reveal changes in network dynamics during maturation. However, the reliability of recurrence quantification analysis (RQA) may depend on the preprocessing conditions and the length of the analyzed time series. This study investigates the effects of time-series length and Gaussian filter parameters on RP analysis of spontaneous activity recorded from iPSC-derived neuronal networks cultured on a high-density microelectrode array (HD-MEA). Population firing-rate time series are extracted from recordings obtained at different developmental stages. To evaluate the influence of recording duration, the original time series are analyzed using different observation lengths. In addition, Gaussian filtering with varying parameter settings is applied to examine how different levels of signal smoothing affect recurrence structures and RQA measures. Representative RQA indices, including determinism, entropy, and the longest diagonal line, are compared under different analysis conditions. The proposed investigation aims to clarify the sensitivity of RP-based analysis to recording duration and preprocessing parameters and to provide practical guidelines for selecting appropriate analysis conditions for developmental neuronal dynamics in iPSC-derived networks.

15. DOSAGE-DEPENDENT DISRUPTION OF NEURAL STEM CELL PROLIFERATION AND NEURONAL NETWORK ACTIVITY IN X-CHROMOSOME ANEUPLOIDIES IS MEDIATED BY THE CELL-AUTONOMOUS ZFX–SOX2 AXIS

V. Astro, R. Alghamdi, K. Cardona-Londoño, L. Cortés-Medina, S. Luochen, J. Dilmé-Capó, S. Radío, A. Adamo

KAUST University

Neurodevelopmental deficits in Klinefelter syndrome (47,XXY) and high-grade X-chromosome aneuploidies have been historically attributed to hormonal dysregulation, leaving cell-autonomous mechanisms largely unexplored. Using patient-derived iPSCs spanning the full karyotypic spectrum (46,XY to 49,XXXXY), we show that supernumerary X chromosomes impose a dosage-dependent proliferative brake on neural stem cells (NSCs) and progressively disrupt neuronal morphogenesis and synaptogenesis. To assess the functional consequences of this dosage effect at the network level, we differentiated NSCs of all karyotypes for 8 weeks on high-density multielectrode arrays (HD-MEAs) and recorded spontaneous firing properties. Activity scans across the chip revealed minimal electrical activity in high-grade SCA neurons, whereas 47,XXY neurons retained partially preserved functionality relative to 46,XY controls. Analysis of the highest-firing electrodes showed that only 46,XY and 47,XXY neurons organized into oscillatory circuits defined by synchronous burst events. At the molecular level, allele-specific expression profiling across the iPSC-NSC-neuron trajectory reveals a conserved repertoire of non-pseudoautosomal XCI escape genes that drive the dosage-sensitive transcriptional program, including downregulation of SOX2 and mitotic regulators in NSCs, and of axonogenesis and synaptic genes in neurons. Among escapees, the transcription factor ZFX exhibits the highest dosage sensitivity and represses SOX2 during neural commitment: ZFX overexpression in 46,XY cells phenocopies the aneuploid NSC defect, while ZFX knockdown in 49,XXXXY NSCs restores SOX2 expression and rescues neuronal differentiation. Our findings demonstrate that neurodevelopmental vulnerability in X chromosome aneuploidies is rooted in cell-autonomous transcriptional perturbation and identify the ZFX-SOX2 axis as its mechanistic basis.

16. HUMAN ADHERENT CORTICAL ORGANOIDS DERIVED FROM INDIVIDUALS WITH GREY MATTER HETEROTOPIA

R. Bonrath, S. Cappello, F. de Vrij

Ludwig-Maximilians-University

Human brain organoids are a valuable model system for studying neurodevelopmental disorders (NDDs). However, reproducibility issues and long culture times limit this model system. To address this, we have established adherent cortical organoids that are highly reproducible and reduce the culture time required for electrophysiological readout to 8 weeks. They are derived from neural progenitor cells plated in 384-well plates, offering the opportunity for high-throughput screening. Our goal is to reproduce the migration and electrophysiological phenotypes observed in classic organoids and in patients with grey matter heterotopia, providing a robust and reproducible model to study NDDs. To this end, we cultured control and patient-derived cells for 4 and 8 weeks. Immunohistochemistry, live imaging, morphological reconstruction, and calcium imaging provided an overview of the resulting phenotype. Preliminary data show altered neuronal migration in patient-derived organoids compared to control. These findings support the potential of this scalable, adherent organoid platform to model NDD-relevant phenotypes and enable future high-throughput drug or genetic screening approaches.

17. UNMASKING ENERGETIC AND INTRACELLULAR DYSREGULATION IN HK1-ASSOCIATED NEUROLOGICAL DISORDERS USING IPSC-BASED NEURAL MODELS

P. Carbajal Martin, C. Bürer, M. Güra, J. Crowe, N. Gächter, I. Canals, S. Froese, L. Abela

University of Zurich

Hexokinase 1 (HK1), the predominant brain HK isoform, is primarily mitochondrial-bound and links glucose metabolism to mitochondrial function. De novo heterozygous pathogenic HK1 variants cause a severe neurodevelopmental disorder characterized by epileptic encephalopathy, movement disorder and progressive decline with high morbidity and mortality. Despite partial seizure reduction with ketogenic diet, the disorder remains untreatable, with unknown pathomechanism and no disease-relevant model available. To address this gap, we generated iPSCs from fibroblasts of two unrelated individuals carrying the recurrent c.1370C>T HK1 variant and from one unaffected individual. To control for genetic background, we used prime-editing to correct the c.1370C>T variant in an affected line and introduce it into a control line. To extend the model system, we also engineered a second recurrent, milder variant, c.1334C>T, into the control. All lines were differentiated into human excitatory neurons and astrocytes using lentiviral-induced forward programming with confirmed functional maturation, including spontaneous firing activity by day 14 and coordinated network bursting by day 45 as demonstrated by HD-MEAs. Extracellular flux assays revealed strongly reduced glycolytic activity and oxidative phosphorylation in affected neurons, constituting the first evidence of cellular bioenergetic impairment in this disorder. To understand the underlying dysfunction, we measured enzymatic activity, however, this was unchanged between affected and control lines. Likewise, immunoblotting confirmed unchanged protein abundance, high-resolution confocal microscopy demonstrated preserved mitochondrial localization and RNA expression analyses revealed no compensatory upregulation of other HK isoforms. Thus, the bioenergetic defect may reflect altered HK1 regulation rather than changes in catalytic activity, abundance, or localization. Together, this work establishes a genetically controlled human neuronal model of HK1-associated neurodevelopmental disease, identifies bioenergetic failure as a robust cellular phenotype, and narrows the underlying mechanism.

18. STUDYING FUNCTIONAL NEURAL ACTIVITY IN IPSC-DERIVED BRAIN ORGANOIDS USING MICROELECTRODE ARRAYS

M. Khamaisi, A. Hamdan, A. A. Mansour

Hebrew University of Jerusalem

Brain organoids, derived from induced pluripotent stem cells (iPSCs), are three-dimensional human models that recapitulate key aspects of brain development and function, with particular emphasis on achieving relatively advanced milestones of functional neuronal activity. iPSC- derived brain organoid enables the investigation of complex processes underlying brain function in both health and disease. While neuronal activity is fundamental to understanding nervous system function and dysfunction. We aim to assess dynamic neuronal activity in several neural organoids systems and how they evolve, to address this, We have generated iPSC-derived cortical brain organoids, identified their identity with multiple specific cortical markers and then employed Multielectrode Array (MEA) technology to monitor the development of spontaneous firing activity in cultured organoids across multiple developmental time points. Our results indicate that iPSC-derived cortical organoids exhibit progressively dynamic functional neural activity increasing over time, resembling aspects of embryonic brain development. Notably, we identified rhythmic firing patterns, high synchrony, and coordinated activity across electrodes, highlighting the presence of robust neural interactions within the organoids. These findings provide valuable insights into neural network development, highlighting the evolution of neural activity during organoid maturation and setting the stage for using brain organoids to investigate changes in neuronal activity under neurodegenerative conditions.

19. AXIAL STEM CELL DERIVED HUMAN DORSAL ROOT GANGLION MODEL RECAPITULATES CELLULAR DIVERSITY AND SOMATOSENSORY FUNCTIONALITY

R. de Vries, F. Teichert, N. Schulten, K. van Gent, C. Schröter, M. Drukker

Leiden University

Dorsal root ganglia (DRG) play central roles in somatosensory signalling and neuropathic pain. DRG function critically relies on interactions between sensory neurons, Schwann cells, and satellite glia, but human in vitro DRG models that capture this cellular diversity have not been reported. We use human axial stem cells (AxSCs), a new type of multipotent stem cell that harbors the developmental potential of DRG precursors, to generate self-organizing DRG-like structures. Single-cell RNA sequencing and high-content imaging demonstrate that the DRG-like structures recapitulate all major cell types of the human DRG. We observe heterogeneous neuronal populations including developing nociceptors and mechanoreceptors, which show characteristic pseudo-unipolar morphology of DRG neurons. Schwann cells and satellite glia aligned with axon tracts and cell bodies, respectively. Longitudinal high-density microelectrode array (HD-MEA) recordings demonstrate progressive sensory neuron maturation and functional responses to sensory stimuli. Altogether, AxSC-derived DRG-like structures provide a scalable platform to investigate neuron-glia interactions and model human somatosensory disorders.

20. DISSECTING NEURONAL CONTRIBUTIONS TO NETWORK HYPEREXCITABILITY IN HUMAN IPSC MODELS OF NEURONOPATHIC GAUCHER DISEASE USING HIGH-DENSITY MICROELECTRODE ARRAYS

J. Crowe, D. Colameo, Z. Matúšová, A. Girard, O. Zetterdahl, L. Oburoglu, L. Valihrach, H. Ahlenius, I. Canals

University of Zurich

Neuronopathic Gaucher disease (nGD) is a severe lysosomal disorder caused by pathogenic variants in GBA1, with neurological manifestations that remain poorly understood at the cellular and network level. Using human induced pluripotent stem cell (iPSC)-derived models, we are investigating altered neuronal activity and network hyperexcitability in both forward-programmed neuronal cultures and three-dimensional brain organoids. Here, we present recent progress using high-density microelectrode array (HD-MEA) recordings to dissect the cellular basis of this network phenotype. Isogenic GBA1 mutant and corrected iPSC lines are forward programmed into glutamatergic and GABAergic neurons and combined in defined co-cultures, enabling systematic manipulation of neuronal genotype and excitatory–inhibitory composition. By comparing network activity across these configurations, we aim to determine the relative contributions of glutamatergic and GABAergic neuronal dysfunction to the hyperexcitable phenotype and distinguish cell-autonomous effects from dysfunction emerging through interactions between neuronal populations. This approach combines genetically controlled human iPSC models with high-resolution functional interrogation of neuronal networks, providing a framework to connect GBA1-associated cellular dysfunction with emergent circuit-level phenotypes in neuronopathic Gaucher disease

21. HD-MEA VALIDATION OF HUMAN IPSC-DERIVED NEURON – GLIA MODELS FOR 2D AND 3D NEURAL NAMS

A. Othman, S. Schachtele, R. Fiene, D. Majewski, C. Carlson

Fujifilm Cellular Dynamics

Limited translation from animal models to human clinical outcomes remains a major challenge in neuroscience drug development, motivating the adoption of human-relevant New Approach Methodologies (NAMs). Human induced pluripotent stem cell (hiPSC)-derived neurons and glia provide renewable, defined, and scalable cellular inputs that can establish reproducible baseline models of human neural function. Rigorous characterization of these cells in reductionist monocultures is therefore essential for interpreting how cellular composition, culture conditions, and model architecture alter function as NAMs advance to multicellular 2D and 3D systems. In this study, we established baseline electrophysiological profiles for hiPSC-derived neuronal monocultures and 2D neuron–astrocyte co-cultures using FUJIFILM Cellular Dynamics iCell neurons and glia paired with high-density microelectrode array (HD-MEAs) recordings using Maxwell Biosystems platforms. Reproducibility was assessed across cell lots and independent experiments, and spike activity and network bursting were compared across neuronal subtypes, cell densities, neuron-to-astrocyte ratios, and media formulations. To determine how increasing model complexity affects network function, matched neural cultures were evaluated in 2D and 3D formats. Culture conditions were further optimized for complementary calcium-imaging and neurite-degeneration assays, and model utility was extended to patient-derived or engineered hiPSC neurons and to incorporation of hiPSC-derived microglia for modeling central neuroinflammation. Together, these studies define the baseline performance, reproducibility, and experimental boundaries of hiPSC-derived neurons and glia as foundational components of neural NAMs. Establishing these reference profiles enables systematic interpretation of functional changes introduced by added cell types, disease backgrounds, and 3D architecture, supporting scalable, fit-for-purpose platforms for seizure-liability assessment, neurodegeneration, pain, inflammation, and neuroscience drug discovery.

22. GENERATION OF A GLIA-ENRICHED HUMAN CEREBELLAR ORGANOID MODEL TO INVESTIGATE DEVELOPMENTAL GLIA-NEURON INTERACTIONS

O. Bianciotto, S. Diana, F. Ceccarelli, N. Hosseini, S. Lafon, C. Concordano, M. Lorenzati, G. Quadrato, A. Genovesio, A. Buffo

Department of Neuroscience Rita Levi Montalcini, University of Torino, Torino, Italy

Neuroscience Institute Cavalieri Ottolenghi, University of Torino, Orbassano, Italy

Department of Physiology, Sapienza University of Rome, Rome, Italy

Keck School of Medicine of USC, Development, Stem Cell and Regenerative Medicine, Los Angeles, CA, USA

Department of Pharmaceutical Sciences, University of Piemonte Orientale, Novara, Italy

Across the development of the cerebellum, its definite compartmentalization allows for the generation of morphologically and molecularly distinct glial subtypes, which carry out fundamental roles in the establishment of correct functional connectivity and cytoarchitectural organization. While recent cerebellar organoid models represent an advanced system to address open questions regarding human-specific features of neuronal development and pathology of the region, the under-representation of astrocytes and oligodendrocytes poses a limit for modelling gliogenesis, developmental glia-neuron interactions and the pathological consequences of their dysfunction. To address this, we generated a glia-enriched organoid model of the developing human cerebellum through integration of hiPSC-derived glial progenitors to the system and altered culture conditions to favor oligodendroglial maturation. We observe the emergence of oligodendroglia and show that exogenously added glial progenitors give rise to morphologically heterogeneous astrocytes, together with the organization of a scaffold-like structure of GFAP+ processes at the organoid surface. To assess whether enriched glial populations support neuronal maturation and the establishment of a defined circuitry as occurs in vivo, we are evaluating their influence on endogenous neuronal populations through analysis of their morphology, molecular profile, cytoarchitectural organization and electrophysiological properties. Extracellular recordings of neuronal activity show that glia-enriched conditions favor faster firing dynamics and the inhibition of synchronized activity. We are now assessing whether these functional phenotypes are related to an increased maturation of specific neuronal subtypes. This glia-enriched cerebellar organoid model provides a platform to investigate cerebellar gliogenesis, while also enabling deeper analyses of developmental and pathological events involving glia-neuron interactions in this region. This work was funded by the PNC project D3 4 Health - Digital Driven Diagnostics, prognostics and therapeutics for sustainable Health care.

23. ADAPTIVE ELECTRODE SELECTION FOR LONGITUDINAL TRACKING OF EARLY NETWORK DYNAMICS IN CORTICAL CULTURES

K. Takehana, D. Akita, H. Takahashi

The University of Tokyo

High-density CMOS microelectrode arrays (HD-MEAs) enable large-scale extracellular recordings from cultured neuronal networks at single-cell resolution. Their switch-matrix architecture provides flexible access to tens of thousands of electrodes, while allowing only a subset to be routed to recording channels at any given time. For longitudinal recordings, this turns electrode selection into a time-dependent problem: configurations optimized at one time point may become less representative as spatial activity patterns evolve. Here, we established stable culture-recording conditions for prolonged HD-MEA measurements and evaluated adaptive electrode selection as a strategy for tracking non-stationary network activity. Dissociated cortical neurons from embryonic Wistar rats (E18) were cultured on an HD-MEA containing 26,400 electrodes, of which 1,024 could be routed simultaneously. We obtained 34-h densely routed recordings from local 529-electrode regions and characterized firing-rate maps, active-electrode distributions, synchronized network bursts, center-of-activity trajectories, and population-level coordination. Across nine recordings from eight cultures, the top-100 active-electrode set changed progressively, reaching 47.8% turnover at 34 h (95% CI, 34.4–61.2%). Thus, nearly half of the electrodes most representative of ongoing activity were replaced during a single recording. Under the same channel budget, adaptive selection captured more activity than static selection, outperforming it by 17.2 percentage points after normalization to a retrospectively optimal (oracle) configuration at 34 h (paired sign-flip test, $p = 0.004$). Longitudinal recordings also revealed the emergence of synchronized network bursts and evolving center-of-activity trajectories, demonstrating coordinated early network dynamics alongside spatial reorganization. Together, these results show that electrode selection is not a one-time setup decision but a time-dependent component of longitudinal functional phenotyping. Adaptive electrode selection can maintain sensitivity to evolving activity patterns and provides a practical strategy for robust HD-MEA assays of network development, disease phenotypes, drug responses, and biocomputing.

24. SELF-SUPERVISED DEEP LEARNING MODEL FOR UNDERSTANDING CIRCUIT DEVELOPMENT AT SCALE

H. Schweiger, A. Robbins, S. Hernandez, I. Cline, K. Doganyigit, M. Mouzaya, Z. Pang, J. Duan, D. Haussler, M. Teodorescu, M. Mostajo-Radji

University of California Santa Cruz

Every recording carries its own units, electrodes, and therefore dimensionality, so no two recordings share a common feature space. Analysis of cultured neural networks still rests on hand-chosen summary statistics that rarely transfer across chips, preparations, or species. We trained a self-supervised state-space model to predict each unit's next 20 ms of spiking from past activity, on approximately 900 hours of high-density microelectrode array recordings spanning human and mouse 3D organoids, 2D dissociated cultures, and ex vivo slices, without any biological labels. This created a unified high-dimensional space in which any two recordings become comparable, regardless of which units were sorted or which preparation produced them. In this embedding space, stimulation-evoked responses are far more discriminable than in raw firing rates, on chips never seen during pretraining, giving a zero-shot criterion for choosing stimulation sites for potential bio-computing tasks. In organoids playing a closed-loop cartpole task, the geometry separates sustained balance from failure independently of pole state and firing rate, and measures the network's latent set-point drift over hours as a confined random walk. The same geometry bears on a long-standing question about learning: whether a task recruits patterns already present in spontaneous activity or writes in new ones. Play moves the network outside its spontaneous repertoire, shifting both the location and the shape of its distribution. Finally, the same space recovers biological relationships across pharmacological perturbation, regional patterning, and autism-spectrum-disorder models.

25. DISTINCT PRESYNAPTIC HOMEOSTATIC ADAPTATIONS IN HUMAN SYNAPSES REVEAL A LINK TO TDP-43

M. Brasili, B. Gatta, K. Schmidt, B. Watmuff, B. Kagan, M. Polymenidou, M. Müller

University Of Zurich

Presynaptic forms of homeostatic plasticity stabilize synaptic transmission across diverse synapses and species. However, evidence for presynaptic homeostatic adaptations in human synapses is lacking. Here, we investigated homeostatic plasticity in human iPSC-derived, NGN2-induced excitatory cortical neurons co-cultured with human astrocytes. Chronic action potential blockade with tetrodotoxin (TTX, 24 h) increased both, miniature EPSC (mEPSC) amplitude and frequency, suggesting synaptic upscaling and presynaptic compensation. Furthermore, Synapsin-1 immunofluorescence was enhanced after TTX treatment, supporting presynaptic adaptation. We next perturbed synaptic transmission by partially blocking AMPA receptors. Acute GYKI-53655 treatment reduced both mEPSC and AP-evoked EPSC (eEPSC) amplitudes. After 24 h, mEPSC amplitudes remained reduced, whereas eEPSC amplitudes recovered toward baseline, indicating presynaptic compensation. In addition, paired-pulse ratio was decreased, and short-term depression enhanced, implying increased release probability. In contrast to TTX, Synapsin-1 levels were unchanged, suggesting mechanistically distinct presynaptic adaptations. Multi-electrode array recordings revealed stable firing rates during chronic GYKI exposure, followed by a 4-fold increase in mean firing rate upon washout after 24 h, consistent with network-level homeostatic adaptations. Loss of TDP-43 was previously shown to reduce UNC13A levels, which in turn disrupts presynaptic homeostatic plasticity in Drosophila. We therefore next investigated whether TDP-43 similarly regulates presynaptic homeostatic mechanisms in human neurons. TDP-43 knockdown reduced Unc13A protein levels, mEPSC frequency, and eEPSC amplitude, suggesting impaired baseline synaptic transmission. Intriguingly, TDP-43 knockdown disrupted presynaptic homeostatic compensation in response to chronic GYKI treatment. Together, our results demonstrate distinct presynaptic adaptations in human synapses and implicate TDP-43 in presynaptic homeostatic plasticity.

26. EXPANDING LIVING NEURONAL COMPUTING SYSTEMS BY VIRTUAL COUPLING ACROSS HD-MEAS

D. Akita, Y. Onuma, Y. Kawahara, H. Takahashi

The University of Tokyo

Living neuronal networks provide a promising substrate for biocomputing, but the limited size and controllability of a single culture constrain scalability. We developed a software-defined interface that connects two dissociated rat cortical cultures across separate high-density microelectrode arrays (HD-MEAs). Spikes detected at selected sites in the upstream culture were transmitted in real time and converted into electrical stimulation of the downstream culture. This architecture enables directed coupling without physically rewiring either biological network. We evaluated the information-processing capabilities of the combined system within the reservoir computing framework using information processing capacity (IPC), which quantifies how accurately various functions of the input history can be reconstructed from neuronal responses using a linear readout. Under virtual coupling, input-related information became decodable from the downstream culture, and the total IPC increased relative to both an isolated condition and a stimulation-count-matched random control. We then asked which upstream sites should be used to create an effective connection. For this purpose, we introduced nodeIPC, an IPC measure computed from a single recording site and decomposed into instantaneous, delayed, and nonlinear components. The nodeIPC of a trigger site strongly predicted the IPC induced in the downstream culture, while the fraction of nodeIPC attributable to delayed and nonlinear components predicted the gain obtained by combining the two cultures. These relationships were reproduced in echo state network simulations. Our results demonstrate that virtual coupling can expand the computational repertoire of living neuronal networks and that IPC provides a practical basis for designing modular biocomputing systems.

27. BRIDGING FUNCTIONAL DYNAMICS AND SPATIAL TRANSCRIPTOMICS IN BIOLOGICAL NEURONAL NETWORKS

N. Kido, Y. Miyahara, Y. Yamagishi, Y. Inoue, M. Sugino, K. Shimba, K. Kotani

The University of Tokyo

Animals adapt to environments via continuous perception-action cycles. Biological neuronal networks (BNNs), cultured on microelectrode arrays and coupled with embodied agents, are promising in vitro constructive models for elucidating these mechanisms, demonstrating autonomous optimization of neuronal activities [1]. However, functional dynamics alone are insufficient to fully uncover the underlying mechanisms driving this adaptation, requiring the evaluation of interacting cellular properties, such as transcriptomic states. To address this, we established a framework seamlessly connecting high-density microelectrode array (HD-MEA) electrophysiology with in situ spatial transcriptomics. Rat cortical cells were cultured on MaxOne HD-MEA chips for over a month. After a five-minute baseline activity recording, 4-Aminopyridine was applied via an automated fluid delivery system to record 70-minute response dynamics. Cell positions were estimated from spike waveforms, and temporal connectivity changes were calculated with spike-time cross-correlation. Using the same fluidic system ensured immediate post-recording tissue fixation for on-chip spatial transcriptomics [2], enabling the detection of nine marker genes. Following spatial alignment, hierarchical clustering was performed using a complementary linear combination of distance matrices constructed from the temporal connectivity changes and the marker gene expression. Specifically, this multimodal distance matrix maximized the mean silhouette coefficient at 85% functional and 15% transcriptomic contributions, outperforming single-modality clustering. In summary, this framework demonstrates the utility of jointly assessing network functions and molecular properties. Given its single-cell resolution, this HD-MEA system is highly compatible with closed-loop paradigms, providing a robust foundation to evaluate multifaceted network internal states of embodied BNNs during environmental adaptation.

References
[1] Kagan BJ, et al. In vitro neurons learn and exhibit sentience when embodied in a simulated game-world. Neuron, 110(23): 3952-3969.e8 (2022).
[2] Gyllborg D, et al. Hybridization-based in situ sequencing (HybISS) for spatially resolved transcriptomics in human and mouse brain tissue. Nucleic Acids Res, 48(19): e112 (2020).

28. IMPACT OF COP-ID DYSFUNCTION ON BRAIN DEVELOPMENT IN HUMAN

T. Lahoud, A. Albert, G. Le Guilloux, M. Moussay, S. Lebon, S. Passemard, M. El Ghouzzi

INSERM U1141 - NEURODIDEROT

Genetic primary microcephaly is a rare neurodevelopmental disorder that affects cerebral cortex size at birth and cognitive function, representing a societal problem in hundreds of families worldwide (1). It is typically inherited in an autosomal recessive manner, but some microcephaly are autosomal dominant such as that associated with haploinsufficiency in the ARCN1 gene, encoding the δ subunit (COPI-D) of the COPI (coat protein complex I). COPI complex mediates retrograde transport of proteins from the Golgi apparatus to the endoplasmic reticulum (ER), and its disruption impairs protein trafficking and ER stress (2). Interestingly, ER stress is an essential physiological response during the early stages of corticogenesis, and its forced prolongation induces congenital microcephaly in mice due to a loss of basal progenitors (3). In this study, we generated hiPS cells from patients with truncating ARCN1 mutations, as well as an isogenic cell line carrying a patient's mutation, and investigated the impact of haploinsufficiency on the fate of neural progenitors and on endoplasmic reticulum stress. Our preliminary results suggest a decrease in the number of basal progenitors, while the number of apical progenitors appears unaffected in 50-day-old organoids. We also detected an increase in the chaperone protein BiP/Grp78 and an activation of the ATF4 protein, which mediates one of the three branches of the unfolded protein response. Finally, inducing endoplasmic reticulum stress in organoids using thapsigargin, a specific non-competitive inhibitor of the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), leads to a depletion of progenitor cells, resulting in a phenotype consistent with microcephaly. These findings suggest that the microcephaly associated with COP-ID deficiency is caused by a dysregulation of ER stress that is potentially deleterious to basal progenitors in humans. 1. Farcy S., et al. Genetic Primary Microcephalies. Cells, 2023, 12, 1807 2. Izumi K., et al. ARCN1 mutations cause a recognizable craniofacial syndrome due to COPI-mediated transport defects. Am. J. Hum. Genet., 2016, 99, 451-459 3. Godin JD., et al. Emerging roles of the unfolded protein response in the developing nervous system. Trends Neurosci. 2016, 39, 394-404

29. INFERRING EFFECTIVE NETWORKS OF EXCITATORY-INHIBITORY NETWORKS IN VITRO USING TRANSFER ENTROPY

G. Amos, J. Ondris, L. Cornelisse, J. Vörös, V. Vasiliauskaite

ETH Zurich

Biological neural circuits operate in a finely tuned balance between excitation and inhibition (E/I) that underlies stable yet flexible dynamics. Understanding how this balance shapes computation requires knowing the network of connections and discerning excitatory neurons from inhibitory. Transfer entropy (TE) is a widely used tool to extract effective connectivity from spike trains, yet it detects inhibitory connections unreliably for finite recordings and for low source or target activity. TE also conflates a connection's sign with the predictive information it carries: at equal synaptic strength an excitatory source carries far more information about its target than an inhibitory one, especially at low firing rates, where the target is likely silent regardless of inhibition. Excitatory links are therefore intrinsically easier to detect. Standard estimators further ignore Dale's principle, a biological constraint that single-unit recordings enforce. Because inhibition shapes network dynamics and computation, this detection asymmetry distorts the inferred E/I balance and analysis built on it. Here we characterise the failure modes of TE-based inference from neuron-resolved spiking data. On simulated finite spike trains with varied statistics (memoryless, history-dependent, bursty), we compare model-free and model-based TE estimators at recovering pairwise connectivity, measuring the true-positive rate (the fraction of real connections detected) separately for excitatory and inhibitory links of equal strength. We also quantify how the resulting detection gap between them depends on firing rate, coupling strength, and recording duration. For validation on real data, we use random cultures as well as a compartmentalised in vitro platform, both cultured on high-density microelectrode arrays for simultaneous network-wide recording. In the compartmentalised platform, iPSC-derived neurons occupy multiple wells connected by axon-guiding microchannels, and the connectivity between wells imposes a small-world topology. Because the E/I composition is known and varied, we relate inferred to imposed balance directly. We also apply selective synaptic blockers to test whether the inference responds correctly, removing the targeted class of inferred links. With a validated method, we then apply network analysis to the inferred connectomes, characterising the signed structure and recurring motifs (feedforward, feedback, lateral inhibition) that emerge under each imposed E/I composition and topology.

30. KETAMINE DOSE-DEPENDENTLY SUPPRESSES PVN SINGLE-UNIT FIRING AND LEAVES A REORGANISED NETWORK STATE AFTER WASHOUT

F. Bin

The Chinese University of Hong Kong

Ketamine is an NMDA-receptor antagonist with rapid antidepressant action, and the paraventricular nucleus of the hypothalamus (PVN) is a plausible locus for part of that action given its role in the stress axis. Most electrophysiological characterisation of ketamine has been performed either in cortical tissue or with small numbers of simultaneously recorded neurons, which limits the ability to ask whether the drug acts uniformly on a local network or selectively on subsets of neurons. High-density microelectrode arrays make a different question tractable: within a single slice, hundreds of units can be followed continuously across drug application and washout, so each neuron serves as its own control and the heterogeneity of the response becomes measurable rather than averaged away. Three questions follow naturally. First, is the suppression dose-dependent and reversible at the level of individual units? Second, does any measurable property of a neuron — its spike waveform, its position, its baseline discharge, its functional coupling — predict how strongly ketamine affects it? Third, does the network return to its starting configuration after the drug is washed out, or does it settle into a different state? A single PVN slice was recorded on a MaxWell MaxOne array for 82.7 min through a two-dose ketamine protocol (ACSF baseline, 100 µM, washout, 300 µM, washout). Kilosort4 yielded 1004 units, of which 393 passed curation and manual waveform review. Ketamine suppressed firing dose-dependently and partially reversibly: the population rate fell to 80% of baseline at 100 µM and 63% at 300 µM, while the median unit fell by 1.65 log2 units at 300 µM. Waveform class, array position and baseline firing rate all failed to predict which units were suppressed; baseline discharge irregularity and weak functional coupling did. After washout the firing-rate rank order did not return to baseline, whereas pairwise coupling did — a dissociation between how activity is distributed and how it is synchronised. All results come from one slice and are descriptive.

31. KCNQ2 VARIANT-SPECIFIC SIGNATURES IN CHANNEL FUNCTION, NEURONAL EXCITABILITY AND GENE EXPRESSION

A. Kapnulina, G. Siegel, A. Frei, L. Heinrich, K. Schmidt, A. Rauch, M. Müller

University of Zurich, Department of Molecular Life Sciences, Zurich, Switzerland

University of Zurich, Institute of Medical Genetics, Zurich, Switzerland

Variants in KCNQ2, a gene encoding a subunit of neuronal voltage-gated K+ channels, are linked to benign familial neonatal epilepsy (BFNE), developmental and epileptic encephalopathy (DEE) and intellectual disability (ID). While most studies have examined the effects of KCNQ2 variants on channel function in heterologous systems, their impact on neuronal function remains poorly understood. Here, we assessed the effects of de novo KCNQ2 variants on channel function in CHO cells using patch-clamp electrophysiology and compared them with channel function, neuronal excitability, and gene expression in CRISPR/Cas9-edited human iPSC-derived neurons. In CHO cells, most variants resulted in loss-of-function (LOF) phenotypes impacting ion channel function and/or functional channel density. DEE variants produced more pronounced LOF phenotypes than BFNE variants, whereas the ID variant resulted in a GOF at the level of channel conductance. In neurons, the effects of a BFNE variant resembled those of an acute pharmacological M-current block, including decreased neuronal K+-current density and action potential frequency. Despite their link to a more severe clinical phenotype, two DEE variants displayed milder or no detectable phenotypes at the level of neuronal currents and excitability. Bulk RNA-sequencing revealed variant-specific changes in gene expression, including synaptic and ion channel-encoding genes. Electrophysiological phenotypes correlated with the number of differentially expressed genes. Together, our data suggest variant-specific phenotypes in KCNQ2-channel function and density that correlate with patient phenotype, which may not be discernible in neurons owing to potential compensatory mechanisms.

32. POST-RECORDING SPATIAL GENE DETECTION FOR CELL-TYPE-RESOLVED HD-MEA NETWORK ANALYSIS

K. Shimba, N. Kido, M. Yagishita, Y. Miyahara, K. Kotani

The University of Tokyo

High-density microelectrode arrays (HD-MEAs) enable label-free, high-resolution recording of cultured neuronal networks, capturing spontaneous firing, network bursts, spike waveforms, and spatial activity patterns. However, extracellular recordings alone do not reveal the molecular identity of recorded cells, limiting interpretation of network dynamics in heterogeneous cultures. Here, we present a workflow that combines HD-MEA recording with post-recording spatial gene detection to link network activity with cell-type-related marker expression. Dissociated neuronal cultures were grown on CMOS-based HD-MEAs and recorded during spontaneous activity. Network bursts were detected from population firing, and recorded units were characterized by firing rate, burst participation, waveform features, and firing timing during bursts. After recording, the same cultures were fixed and subjected to HybISS-based spatial gene detection. Marker-gene spots were detected across the recorded area and assigned to individual cells, allowing gene-defined populations to be mapped onto the HD-MEA recording field. This workflow confirmed that multiple marker genes can be detected after HD-MEA recording and spatially aligned with activity maps. We are currently applying the analysis to new samples to examine how gene-defined populations relate to burst-related activity. This approach provides a route toward cell-type-resolved HD-MEA analysis and should be applicable to heterogeneous neuronal cultures, engineered networks, and disease models.

33. HD-MEA PLATFORM FOR DRUG DISCOVERY IN PATIENT-DERIVED MODELS OF NEURODEVELOPMENTAL DISORDERS

J. Cortinhas, R. Van Acker, C. Bosone, K. Froussios, K. Stecher, F. Salaris, M. Pires, J. Schaden, C. Pfeffer

Neurolentech

Epilepsy and associated neurodevelopmental disorders (NDDs) affect an estimated 2–4% of the global population, yet effective therapies targeting core symptoms remain limited. This gap reflects the lack of relevant, scalable preclinical models that capture human physiology and patient heterogeneity. Neurolentech has established an optimized patient-derived neuronal platform supported by a biobank of >180 patients and parental controls. Donor PBMCs are reprogrammed in-house into iPSCs, with disease-associated mutations genetically corrected by CRISPR-Cas9 to generate isogenic controls. Using our optimized pipeline, cells are differentiated into mature glutamatergic and GABAergic neurons and co-cultured with rat astrocytes directly on HD-MEA plates, enabling reproducible functional characterization of patient-derived neuronal networks for drug discovery. Using MaxTwo HD-MEA technology, we characterized spontaneous network activity in patient-derived models of GRIN2A-associated monogenic epilepsy, including five lines carrying Loss-of-Function (LOF) mutations and one Gain-of-Function (GOF) mutation. GRIN2A patient networks showed altered activity dynamics, with reduced temporal organization, decreased interspike interval (ISI) outside bursts, and increased ISI within bursts. Notably, the GOF line uniquely showed increased median burst peak firing rate and shorter ISI within bursts compared with its isogenic control, contrasting with the pattern observed across all LOF lines and supporting distinct LOF- and GOF-associated electrophysiological phenotypes. As part of our CRO offering, we developed validated assays for assessing the seizure-protective effects of antiseizure medications (ASMs) in human neuronal networks. Chemoconvulsants commonly used in in vivo and in vitro preclinical seizure models, such as kainate, 4-aminopyridine and GABAzine, induced recurrent epileptiform discharges (REDs), enabling the assessment of pharmacological counteraction of pathological network activity. Reference ASMs such as Retigabine, Perampanel and Valrpoic Acid effectively counteracted REDs, while drugs that failed clinical trials in phase II-III fail to do so, demonstrating the platform’s ability to recapitulate pharmacological responses to established therapies. By integrating patient-specific disease phenotyping with mechanism-relevant drug testing, we are advancing toward a “clinical trial in a dish” for NDD drug development and functional patient stratification.

34. HUMAN IPSC-DERIVED NEURAL ORGANOIDS REVEAL EARLY DEVELOPMENTAL PATHWAY DYSREGULATION IN PCH2A

D. Andreeva, L. Branco, P. Collignon, F. Castagnetti, T. Kagermeier, I. Potthof, Z. Yentuer, S. Mayer

Karlsruhe Institut fur Technologie

Pontocerebellar hypoplasia type 2a (PCH2a) is a rare neurodevelopmental disorder caused by single nucleotide pathogenic variant p.TSEN54 A307S. TSEN54 is a core subunit of the tRNA-splicing endonuclease complex. Although tRNA splicing is a ubiquitous process, the mutation affects predominantly the cerebellum and pons, and the basis for this region-specific vulnerability remains unknown. Previous work in patient-derived neural organoids demonstrated altered proliferation and maturation, suggesting disturbed early developmental programs (Kagermeier et al., 2024). Building on these findings, transcriptomic analysis of PCH2A and control organoids identified WNT-associated pathways among the most strongly dysregulated developmental processes. Because WNT signalling regulates the balance between progenitor maintenance and differentiation, we hypothesized that PCH2A cells exhibit altered developmental responses to WNT pathway modulation. To test this hypothesis, we are now pharmacologically perturbating WNT signalling in neural organoids generated from an isogenic pair of TSEN54 wild-type and p.TSEN54 Ala307Ser induced pluripotent stem cell lines and quantified organoid growth longitudinally. These experiments establish a framework for determining how altered WNT signalling contributes to early PCH2A pathology and open a window of opportunity to assess pharmacological perturbation that could provide a specific treatment for PCH2a patients.

35. DISSECTING THE CELLULAR MECHANISM OF TEMPORAL INTERFERENCE STIMULATION IN HUMAN IPSC-DERIVED NEURONS

F. Karimi, T. Ruff, L. Balle, N. Kuster, J. Voros, E. Neufeld, T. Newton

ETH Zurich

Temporal interference stimulation (TIS) applies two kilohertz fields with a small offset frequency, creating a low-frequency amplitude-modulated (AM) envelope for non-invasive deep targeting [1]. Whether and if so, how human neurons demodulate the AM envelope is unclear, complicating parameter choice. To address this question, we grew 9 independent networks of human iPSC-derived excitatory neurons in a PDMS microstructure platform, extending existent rodent-culture work [2]. A cap with 2 electrode pairs applied two HF fields where the driving-current ratio steered the location of the AM envelope maximum. As fields interfered with the CMOS MEA readout, we measured suprathreshold responses by calcium imaging. We varied carrier (2–90 kHz) and beat frequency (0–5 Hz), field strength and current ratio, and assessed response threshold, magnitude, temporal dynamics, beat locking and spatial organization. Our results show that TIS and unmodulated HF stimulation (HFS) activated cultures at comparable thresholds, consistent with existing in vitro work [3]. Carrier frequency affected excitability more than beat frequency and at matched peak amplitude HFS evoked larger responses, though TIS reached threshold at lower time-averaged power. TIS synchronized activity at the beat frequency, but entrainment declined as carrier frequency rose and responses became HFS-like. Yet human in vivo TIS reports effects at carriers up to 20 kHz [4–8], where our entrainment was already weak. Under steering, overall activity followed the stronger carrier, while beat-locked activity peaked where fields were balanced. Thus, in excitatory human microcircuits suprathreshold TIS is driven mainly by the carriers, while AM shapes when and where activation occurs, consistent with carrier-driven rectification up to 100 kHz in peripheral locust nerve [9]. One limitation is that our circuits consist mainly of excitatory neurons whereas brain circuits comprise excitatory and inhibitory neurons. This and the suprathreshold regime may explain the discrepancy with existing human in vivo results [4,5].

References

[1] Grossman N et al., Cell 2017.
[2] Ahtiainen A et al., Lab Chip 2024.
[3] Semenov I et al., Cell Rep Phys Sci 2025.
[4] Wessel MJ et al., Nat Neurosci 2023.
[5] Lamoš M et al., Mov Disord 2025.
[6] Missey F et al., Brain Stimul 2026.
[7] Schaeffer EL et al., medRxiv 2025.
[8] Wang Y et al., Front Hum Neurosci 2024.
[9] Opančar A et al., Nat Commun 2025.

36. EXPLORING GENE NETWORK EXPRESSION DYNAMICS USING INTEGRATED SPATIAL TRANSCRIPTOMICS AND LARGE-SCALE ELECTROPHYSIOLOGY IN CELLULAR MODELS OF HUMAN NEURODEVELOPMENTAL DISORDERS

Y. Yang Cao, A. Marishi, L. Sadiraj, S. Kumar, Y. Chen, S. Adivarahan, S. Chamberlain, S. Alber, A. Hierlemann, A. Moor, M. Schröter

Department of Biosystems Science and Engineering (D-BSSE), ETH Zurich, Basel, Switzerland

Roche Pharma Research and Early Development (pRED), Roche, Basel, Switzerland

Duplication of the imprinted chromosome 15q11-13 region (Dup15q) is a neurodevelopmental disorder caused by maternal duplication of this locus and is strongly associated with autism spectrum disorder (ASD) and severe epilepsy. Dup15q is characterized by network hyperexcitability and co-occurs with neuronal circuit dysfunction. UBE3A, a ubiquitin ligase encoded within the duplicated region, is likely a primary driver of Dup15q syndrome and has been implicated in the hyperexcitable phenotype. However, UBE3A overexpression alone fails to account for all observed synaptic defects, suggesting that other genes and inter-gene interactions may also contribute to disease pathogenesis. Furthermore, the interplay between transcriptional regulation and neural function during disease progression remains poorly defined. To identify the involved mechanisms, we developed a patient-derived induced pluripotent stem cell (iPSC) tri-culture model comprising excitatory neurons (iGLUTA), inhibitory neurons (iGABA), and human astrocytes. Functional characterization using high-density microelectrode arrays (HD-MEAs) showed that Dup15q neurons exhibit pronounced hyperexcitability compared to isogenic controls. To evaluate whether these functional differences are associated with differential regulation of ASD- and epilepsy-related genes, we performed targeted single-molecule fluorescence in situ hybridization (smFISH). We designed a 40 gene panel based on disease-associated genes and cell type markers to visualize their spatial distribution in both conditions. smFISH confirmed established transcriptional alterations, such as UBE3A up-regulation in Dup15q neurons, and revealed different gene expression trajectories during development and between disease and control cultures. Isogenic controls displayed lower expression of UBE3A and ATP10A expression relative to Dup15q cultures and recapitulated expected shifts in N-methyl-D-aspartate (NMDA) subunit dynamics (GRIN2B decreased expression, GRIN2D increased expression), mirroring findings of previous studies. Comparable expression levels of hallmark neurodevelopmental markers (GAD1, LHX6, MAP1B, MAP2) across both conditions provide evidence of similar neurodevelopmental state and that observed differences reflect disease-specific phenotypic pathology. Future studies aim to utilize this platform to gain a multimodal understanding of the correlation between distinct patterns of electrical activity and gene expression across neuronal subtypes in disease and isogenic models, providing deeper insights into functional phenotypes in ASD and epilepsy.

37. A SINGLE-CELL MICROFLUIDIC MODEL FOR INVESTIGATING SYNAPTIC SPREAD OF AMYLOID-B AND TAU IN ALZHEIMER'S DISEASE

D. Balallo, A. Viol, A. van Grunsven, M. Aramesh, J. Vörös, N. Winter-Hjelm

ETH Zurich

Alzheimer's disease (AD) is characterized by the accumulation of amyloid-β (Aβ) and tau pathology. Aβ pathology first develops diffusely throughout the cortex, whereas tau pathology first emerges in the entorhinal cortex and hippocampus. This temporal and spatial separation has led to an unresolved question in the field: How do Aβ and tau interact during disease progression, and is the presence of both pathologies required to drive neurodegeneration? Understanding how these pathological processes disrupt synaptic function and neuronal communication, ultimately leading to network dysfunction and cognitive decline, is critical for elucidating the mechanisms of AD progression. Building on our group's work [1], we are developing a compartmentalized microfluidic platform interfaced with a high-density microelectrode array (HD-MEA). Each chip comprises up to 100 parallel neuronal networks, each consisting of three sequential neuronal chambers that isolate individual neurons. Microchannels connect adjacent chambers, permitting neurite outgrowth while restricting neuronal somas to chambers, with channel geometries optimized to enforce unidirectional axonal growth. A customized flow compartment system maintains fluidic isolation between neuronal chamber layers, enabling layer-specific exposure to Aβ or tau. As an initial step, individual system components including the flow compartment system and Aβ and pathological protein perturbation conditions were optimized separately. Human iPSC-derived neuronal cultures were used to establish experimental conditions that reproducibly induced pathological protein aggregation while preserving neuronal morphology for longitudinal imaging and electrophysiological studies. The next step is to integrate these validated components by selectively exposing two neuronal layers with Aβ or tau while monitoring downstream effects into an untreated third neuronal layer. Combined with confocal imaging and HD-MEA electrophysiology, this approach can be used to visualize pathological protein aggregation and propagation at single-neuron resolution and quantify associated changes in neuronal network function. Beyond AD, this platform provides a broadly applicable in vitro system for studying toxic protein propagation across neurodegenerative diseases.

References

[1] Amos, G., et al., iScience, 2026. doi: 10.1016/j.isci.2026.115488

38. FULLY ON-CHIP BIO-PLAUSIBLE LEARNING AND INFERENCE FOR MEMRISTIVE NEUROMORPHIC SYSTEMS

N. Olalla, M. Dober, L. Chérix, J. Leuthold, P. Aceituno, N. Jimenez

ETH Zurich

With the increasing demand for artificial intelligence applications, the differences between AI systems and biological brains are becoming more evident. One major distinction is that the brain uses its biological architecture to perform computation and store memory simultaneously. It is from this premise that the field of Neuromorphic Computing was born, seeking to emulate the human brain in hardware based on the inherent dynamics of physical components [1]. Among various technologies, memristors have emerged as leading candidates for building artificial synapses due to their close resemblance to their biological counterparts [2,3]. However, most memristor-based neuromorphic systems focus on inference, relying on energy- intensive offline training [4]. In contrast, the biological brain co-integrates learning within its physical architecture, enabling efficient, continual adaptation at the edge. Predictive coding (PC) suggests that the brain minimizes errors between internal predictive models and sensory inputs [5]. Furthermore, PC occurs at the cellular level within cortical pyramidal neurons. These neurons receive learning signals through their apical dendrites, which then modulate basal synapses to correct network-wide prediction errors [3]. In this work, we present the simulation of a standalone memristive-based circuit that realizes PC-based on-chip learning and inference [2]. We exploit the analogy between biological synaptic potentiation and the voltage-dependent conductance changes in filament-based memristors. Our system utilizes a 2-2-1 neural network in which memristors serve as synaptic weights and learning signals SL are delivered through the non-inverting inputs of operational amplifiers. A feedback loop compares the output signal Sout to a reference Sref (the prediction model) using a control system. The resulting learning signal SL adjusts neuronal activity until the network converges to the desired response. We demonstrate that this circuit autonomously learns the XOR operation without external software intervention. This architecture provides a scalable path for integrating bio-plausible learning directly into memristive hardware.

References

[1] Indiveri G., et al. Proceedings of the IEEE, 103(8), 1379-1397, 2015.
[2] Nadia Jimenez Olalla et al 2026 Neuromorph. Comput. Eng (in press).
[3] Aceituno P. V., et al., bioRxiv 2024.04.10.588837, 2025.
[4] Aguirre, F., et al. Nat Commun 15, 1974, 2024.
[5] Bastos A. M., et al., Neuron 76 695–711, 2012.

39. TOWARDS MODEL PREDICTIVE CONTROL OF ENGINEERED IN VITRO NEURAL CULTURES

J. Löhle, T. Newton, E. Neufeld, J. Vörös

Laboratory of Biosensors and Bioelectronics, Eidgenössische Technische Hochschule (ETH) Zurich, Zurich, Switzerland

IT'IS Foundation for Research on Information Technologies in Society, Zurich, Switzerland

Integrated Systems Laboratory, Eidgenössische Technische Hochschule (ETH) Zurich, Zurich, Switzerland

Neural population activity is commonly described by low-dimensional trajectories [1], but such descriptions capture only the dynamics a network produces unprompted, leaving open how it responds when driven by stimulation and which states it can be brought to on demand. Answering both questions requires closed-loop control: steering activity along a desired manifold. This requires a perturbational model of how stimulation propagates through the network that maps the current activity and a candidate stimulus onto the resulting trajectory. In vivo, building such a model is limited by partial observability and imprecise input control. We culture human induced pluripotent stem cell (hiPSC)-derived NGN2 neurons on high-density CMOS microelectrode arrays, where growth is spatially constrained by polydimethylsiloxane (PDMS) microstructures. This addresses both limitations: activity can be read out at near-cellular resolution across the whole network and stimulation can be delivered at precise network locations on the same chip. We aim to establish model-predictive control [2] of such networks, where a model of the perturbation response is used to compute the stimulation that drives activity toward a specific target. Here, we present our progress towards reaching this goal in three steps. First, characterizing how the network responds to stimulation, using systematic perturbation to map input-output relations that spontaneous activity alone does not reveal. Second, fitting dynamical models to these responses and testing how far they generalize to stimuli they were not fit on. Third, using such models as forward predictors in an model-predictive control loop, initially in simulation and subsequently on live cultures. References: [1] Cunningham, John P., and Byron M. Yu. "Dimensionality reduction for large-scale neural recordings." Nature neuroscience 17.11 (2014): 1500-1509. [2] Rawlings, James B., David Q. Mayne, and Moritz M. Diehl. "Model predictive control: theory, computation, and design." (2020).

40. TOWARDS BIOLOGICAL NEURAL NETWORKS AS INTELLIGENT AGENTS: INVESTIGATING THE EFFECT OF NETWORK SIZE

F. Willi, D. Tanneberg, J. Vörös

ETH Zurich

Biological neural networks (BNNs) offer a fundamentally different computational substrate from silicon-based, artificial neural networks: computation emerges from the dynamics of living neuronal populations whose activity and connectivity continuously change through activity-dependent plasticity. These properties make BNNs particularly interesting for embodied control, where neural activity, actions and sensory input can form a continuous, closed feedback loop because the controller can fundamentally reorganize as its interaction with the environment changes. This setup promises advantageous properties like learning from limited data, continuous adaptation, robustness to noise, and recovery from damage. However, it remains poorly understood how such self-organizing neural dynamics can be created and trained to produce reliable goal-directed behaviour. The overarching goal of this project is to answer this question by using a BNN as the controlling agent for a minimal robotic task in real time. The first step in this larger project is to investigate the dependency of the computational potential of BNNs on the number of neurons that constitute them. To this end, neurons derived from human iPSCs are cultivated on a high-density CMOS-MEA. Further, the networks are topologically constrained using PDMS microstructures that physically and functionally separate an input and an output compartment in a unidirectional way. This ensures biological processing of the input rather than the network possibly acting as a simple noisy channel. These microstructures are populated with different, but specific amounts of neurons. Their computational potential is then analysed in three ways: (1) Calculation of complexity metrics based on spontaneous activity; (2) calculation of information processing capacity based on open-loop stimulation; and (3) quantification of performance in a closed-loop simulated game environment. The goal is to relate the BNN size to both the task performance and the calculated computational potential metrics, as well as to assess whether these metrics can serve as predictive indicators of a culture's task performance prior to training.

41. TOWARDS A COMPARTMENTALIZED IN VITRO MODEL OF NOCICEPTION USING MICROFLUIDICS FOR DRUG SCREENING TARGETED AT CHRONIC PAIN

F. Konnerth, B. Clément, B. Maurer, Y. Zeng, J. Vörös

ETH Zurich

Chronic pain affects more than 20% of the global population and remains difficult to treat effectively, with current pharmacological therapies often providing insufficient pain relief or causing severe side effects [1]. Human-induced pluripotent stem cell (hiPSC)-derived sensory neurons have emerged as a promising alternative to animal models, enabling the investigation of human-specific pain mechanisms in vitro. Although several microphysiological models have been developed to recreate individual components of the nociceptive pathway [2,3], these platforms typically rely on static culture systems that fail to reproduce key physiological features of the peripheral nervous system, including compartment-specific microenvironments, dynamic chemical stimulation, and controlled cell–cell interactions. To address these limitations, we are developing a compartmentalized in vitro model of the nociceptive pathway combining hiPSC-derived neuronal cultures, microfluidic perfusion, and high-density microelectrode array (HD-MEA) recordings. Independent perfusion will enable culture conditions to be tailored to individual cell types and allows localized delivery of inflammatory mediators, pharmacological compounds, and growth factors. HD-MEA integration will enable electrophysiological investigation of neuronal activity and axonal signal propagation in response to these controlled perturbations. Combined with automated liquid handling, the platform aims to provide a reproducible human in vitro model to investigate peripheral nociception and enable scalable drug screening for chronic pain.

References
[1] Thouaye and Yalcin, “Neuropathic Pain,” Pharmacology & Therapeutics, 251 (2023).
[2] Kimourtzis and Raouf, “Microfluidic model of the first sensory synapse”, Molecular Pain, 20 (2024).
[3] Clément et al., “Axonal Electrophysiology of Human Nociceptors,” Biosensors & Bioelectronics 281 (2025)

42. A PROOF-OF-CONCEPT AUTOMATED PLATFORM FOR SYNAPTIC ASSAYS ON HD-MEA

S. Ramon-Carrasco, B. Maurer, K. Vulic, G. Amos, F. Konnerth, J. Vörös, L. Cornelisse

Vrije Universitet Amsterdam

Monogenic neurodevelopmental disorders (mNDDs) often lack effective treatments due to their complexity and the limitations of current drug-screening techniques. Traditional methods such as patch-clamp electrophysiology and low-density microelectrode arrays are time-consuming or fail to capture network-level neuronal behavior essential for understanding synaptic dysfunction. Within the context of the BRAINmodel consortium, we aim to advance the development of a high-throughput drug-screening platform for patient-specific induced pluripotent stem cell (iPSC)-derived neurons on high-density microelectrode arrays (HD-MEAs) to evaluate disease dynamics and identify off-label therapeutic candidates for mNDD patients. The proposed platform integrates four components to enable high-resolution electrophysiological screening: i) PDMS single-pair neuron microstructures, which enable directional neuronal connectivity and isolate individual iPSC-derived neuronal pairs cultured on top of HD-MEAs to measure synaptic transmission [1], ii) a custom incubator chamber which provides precise environmental control and stability during extended electrophysiological recordings, iii) a custom water-compartment lid to prevent media evaporation, designed with two inlet and one outlet syringe for fluidic access [2], and iv) a custom automated perfusion system designed in collaboration with Bronkhorst High-Tech, enabling hands-free compound administration and media replacement. This ongoing project uses the platform to precisely quantify baseline synaptic transmission and neuronal excitability. Once these baseline parameters are established, the platform can be used to induce specific phenotypes in excitatory neurons cultured within the microstructures. Ultimately, by systematically screening compounds to test if they can rescue these induced phenotypes, the platform aims to provide a robust, scalable framework for validating disease mechanisms and accelerating personalized drug treatments.

References

[1] Amos, G., Vasiliauskaite, V., Duru, J., Saramago, M. L. A., Schmid, T., Suter, A., Cid Torren, F., Küchler, J., Ruff, T., Vörös, J., & Vulić, K. (2026). An integrated in vitro platform and biophysical modeling approach for studying synaptic transmission in isolated neuronal pairs. iScience, 29(5), 115488. https://doi.org/10.1016/j.isci.2026.115488

[2] Maurer, B., Fischer, F., Amos, G., Vasiliauskaitė, V., & Vörös, J. (2026). A water compartment cell culture lid enables stable longitudinal recording of neuronal networks in vitro. bioRxiv. https://doi.org/10.64898/2026.04.01.713917

43. CRISPR-CAS9 KNOCKOUT OF ASD-ASSOCIATED GENES DIFFERENTIALLY ALTERS NEURONAL EXCITABILITY

N. Dusan, A. Marishi, A. Brunecker, A. Hierlemann, M. Schröter

ETH Zurich

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder associated with alterations in a range of genes. From the hundreds of genes listed in the SFARI database (https://gene.sfari.org/), we selected a subset of seven high-confidence candidates. Previous studies indicated that these genes have been strongly implicated in electrophysiological dysfunction of excitatory neurons. All seven genes have a SFARI gene score of 1, indicating high-confidence evidence for an association with ASD; several of them are further implicated with syndromic forms of ASD. To investigate the individual contributions of each gene to electrophysiological phenotypes at the cellular and network level, we performed CRISPR-Cas9 knockouts and screened for functional phenotypes. As cellular model system we used human CRISPRko-Ready ioGlutamatergic Neurons (bit.bio, Cambridge, UK), which carry an integrated CRISPR-Cas9 system, co-cultured with human astrocytes. Gene-specific guide RNAs (gRNAs) were designed for each target and delivered using lentiviral vectors. Immunocytochemistry was used to assess morphological alterations following transduction. Electrophysiological development and network activity were then monitored over six weeks using high-density microelectrode array (HD-MEA) recordings, followed by spike sorting and a standardized feature-extraction pipeline. Knockouts lead to gene-specific differences in neuronal morphology and electrophysiological activity. Relative to control neurons, we found robust alterations in firing and burst dynamics as well as network synchrony measures: While some knockouts showed decreased neuronal excitability, others resulted in increased excitability and early network maturation. This proof-of-principle study demonstrates that ASD knockouts result in distinct electrophysiological phenotypes in excitatory neurons - highlighting heterogeneous cellular mechanisms, which may – in the future - help to link specific genetic alterations to define neuronal phenotypes.

44. HUMAN BRAIN ORGANOIDS AS PLATFORMS FOR STUDYING REACTIVE ASTROGLIOSIS AND COMPLEX DISEASE MECHANISMS

M. Faria Pereira, A. Matos, V. Mylka, A. Cornil, G. Mairet-Coello, P. Downey, D. Moreno, M. Geraerts

UCB, Braine l'Alleud, Belgium

For decades, neuroscience has relied heavily on transgenic and induced rodent models, which have been instrumental in defining the cellular and molecular mechanisms of glial activation, where reactive astrocytes often exhibit morphological hypertrophy, activation of inflammatory pathways, and impaired homeostatic functions such as potassium buffering, glutamate uptake, gap-junction coupling. Collectively, these findings have shifted the perception of astrocytes from passive responders to active contributors to neuronal hyperexcitability and neurodegeneration. With this mechanistic framework in place, human iPSC-derived models and brain organoids, now provide an opportunity to reduce in vivo testing and interrogate these pathways directly in human genetic and developmental contexts. Through multimodal characterization integrating single-cell transcriptomics, spatial transcriptomics, imaging, and electrophysiology, we demonstrate that organoids recapitulate key features of human brain maturation, including the emergence of diverse neuronal and glial populations and the progressive development of functional neuronal networks. Functional profiling was performed using multielectrode arrays (MEAs) and showed increasing neuronal activity and network complexity with maturation, supporting the establishment of physiologically relevant neuronal and glial interactions. Upon exposure to inflammatory stimuli, cortical and cerebellar organoids exhibited molecular signatures consistent with reactive astrogliosis, including activation of inflammatory pathways and induction of astrocyte-associated markers. Together, these results demonstrate that human brain organoids provide scalable and translationally relevant models to investigate astrocyte-mediated mechanisms in health and disease. The integration of cellular, spatial, and functional phenotyping establishes a versatile framework for studying complex brain pathologies and for enabling target identification and therapeutic discovery in neurological disorders.

45. ARE BIOLOGICAL NEURAL NETWORKS USEFUL FOR TASK-SPECIFIC COMPUTATION? A BIOLOGICAL-ARTIFICIAL NEURAL NETWORK CLASSIFIER

J. Küchler, A. Lebedenko, J. Schulz, B. Maurer, K. Vulić, S. Ihle, J. Vörös

Laboratory of Biosensors and Bioelectronics, Institute for Biomedical Engineering, ETH Zürich, Zurich, Switzerland

Department of Neurobiology and Department of Physics, University of Chicago

Artificial neural networks (ANNs) excel at solving complex problems across various domains, but biological neural networks (BNNs) surpass them in energy efficiency and parallel processing, motivating growing interest in biological computation. In bio-computation, BNNs are cultured in vitro, stimulated, and recorded predominantly via microelectrode arrays (MEAs). Recent approaches like "organoid intelligence" aim to train BNNs on specific tasks using biological learning paradigms. However, such systems often overlook fundamental limitations or risk overinterpreting the underlying electrical signals. Our goal is to engineer a BNN with a defined architecture and controlled stimulation to investigate task-solving behavior in interpretable, well-defined conditions. Human induced pluripotent stem cell-derived NGN2 neurons are seeded on high-density MEAs, with neuronal growth spatially confined and directed by polydimethylsiloxane (PDMS) microstructures. This setup enables precise investigation of stimulation-induced network activity. We observe nonlinear neuronal responses, such as changes in firing rates or latency, depending on stimulation intensity or frequency, analogous to activation functions in ANNs. Utilizing this insight, we construct a feed-forward hybrid network in which BNNs are artificially interconnected in silico. Stimulation-induced responses are represented either by scalar features or by spike trains, with the latter formulation additionally incorporating in silico spiking neurons. These representations are linearly combined to define the input for downstream computational units. The non-differentiable nature of neurons is accommodated by a sub-differentiable mapping of the input-output relation. A multistage training strategy gradually transitions the model towards increasingly realistic conditions. Using this framework, we create a hybrid network with a single hidden layer of 16 nodes that achieves ∼80% accuracy on the Yin-Yang dataset, with performance remaining stable over 24h. This hybrid network illustrates an initial step toward practical supervised biological computation.

46. FROM NEURONAL NETWORKS TO SEIZURE MODELS: INTEGRATING FUNCTIONAL AND CELLULAR PROFILING TO INFORM CANDIDATE PRIORITIZATION

M. Tollenaere, L. Schneider, M. Elliott, S. Illes, M. Klett, K. Russ, T. Stummann, A. Martinez, X. Sun, I. Klewe, M. Ambjørn

H. Lundbeck ApS

Epilepsy drug discovery relies on a range of in vitro and in vivo models with differing levels of biological and translational relevance1,2. While in vivo models remain essential for assessing efficacy, early-stage research requires scalable in vitro systems that enable efficient hit validation and support structure–activity relationship studies. Cell-based functional assays provide an important bridge between molecular pharmacology and in vivo models by providing a model of neuronal network activity under controlled conditions. Here, we describe a complementary panel of neuronal activity assays spanning distinct species, cellular compositions, recording modalities and network states. Together, these assays provide orthogonal phenotypic and pharmacological information to support compound characterization and prioritization in drug discovery projects.

47. TOWARDS UNDERSTANDING THE ROLE OF TDP-43-G3BP1 AXIS IN MATURATION DEPENDENT FUNCTIONAL DEFECTS IN ALS

R. Guruswamy, C. Fauchon, H. Fakim, C. Vande Velde

University of Montreal

Amyotrophic lateral sclerosis (ALS) is increasingly recognised to involve neuronal dysfunction before overt neurodegeneration, with cortical hyperexcitability emerging as an early feature. TDP-43 pathology, characterised by nuclear loss and cytoplasmic accumulation, disrupts RNA stability and splicing. Recent work shows TDP-43-dependent mis-splicing of KCNQ2 produces non-functional Kv7.2 and intrinsic hyperexcitability in iPSC-derived cortical and spinal motor neurons. This adds to mis-splicing of UNC13A, and other genes involved in synaptic function and neuronal excitability. Our previous work identified G3BP1, a regulator of stress-granule formation and RNA metabolism, as a downstream TDP-43 target. TDP-43 loss reduces canonical G3BP1 and generates CRYPTIC-G3BP1, a dominant-negative isoform that impairs stress -granule formation. CRYPTIC-G3BP1 is detected in ALS/FTD patient neurons and motor cortex with TDP-43 pathology. G3BP1 localises to synapses, dendritic spines and axons, where it is proposed to regulate local RNA translation, synaptic plasticity and calcium homeostasis. Taken together, we hypothesize that canonical G3BP1 loss and/or CRYPTIC-G3BP1 expression may contribute to altered neuronal excitability and vulnerability in ALS. We are investigating whether G3BP1 depletion or CRYPTIC-G3BP1 expression produces distinct, maturation-dependent electrophysiological phenotypes in iPSC-derived cortical neurons. Longitudinal high-density microelectrode array recordings will quantify extracellular action potentials, network maturation, and axonal action-potential propagation. G3BP1 knockdown and CRYPTIC-G3BP1 expression in neurons will be compared with controls and TDP-43 models to test whether disruption of the TDP-43-G3BP1 axis produces progressive axonal conduction defects and altered network phenotype. Acute pharmacological challenges will assess neuronal firing and network recovery from depolarising stress. This work will determine whether TDP-43-dependent G3BP1 loss/dysfunction links aberrant RNA processing to altered neuronal network activity and axonal action-potential propagation, and whether these phenotypes evolve over time. Defining this connection may identify an early functional stage linking TDP-43 molecular pathology to neuronal dysfunction in ALS.

48. INPUT ENCODING IN HUMAN BRAIN ORGANOIDS UNDER RESOURCE-LIMITED NETWORK BURSTS

A. Chinn, D. El Din, T. Hartung, E. Johnson, L. Smirnova

Johns Hopkins University

Spontaneous network bursts are ubiquitous across neuronal cultures and have become trademarks of culture health and maturation; however, what drives bursting and what role it plays in organoid network dynamics remain elusive. Separately, organoids have yet to surpass simpler artificial systems in computing performance despite their biological complexity. We hypothesize that bursts and biocomputing capacity are inversely linked features of the brain organoid substrate. To address this hypothesis, we analyzed spontaneous and evoked activity in MaxTwo HD-MEA recordings of brain organoids. As previously demonstrated, spontaneous bursts arrived in clusters flanked by quiescent periods. Within a cluster, successive bursts decremented in magnitude (pooled $p < 0.0001$); between clusters, the preceding quiescent interval predicted the magnitude of the next cluster ($p < 0.001$), while cluster magnitude did not predict subsequent quiescent duration ($p = 0.95$). This predictive asymmetry is typical of a system discharging to a common floor: quiescent recovery time sets the size of the event, and the event itself resets activity to the same state. These results motivated a depletion-recovery model fit, which resolved two dynamic timescales, 1-2 s and 40-120 s, corresponding to population rate relaxation between bursts and recovery of network excitability between clusters, respectively. A neuronal network governed by a single resource-driven dynamic should support few distinguishable response states. We tested this with electrical stimulation of 32 unique spatial patterns and found evoked responses inseparable from a label-shuffled null under multiple decoders. Stimulation also failed to evoke bursts. Together, these results suggest that organoid connectivity is shaped for synchronous bursting, which leaves the network a single dimension for evoked responses and absorbs input structure. This organization is consistent with a deafferented preparation, where surgically isolated cortex adopts a similar clustered burst pattern once afferent input is removed. Prolonged organoid bursting may therefore reflect absent afferent drive rather than culture immaturity. Ongoing experiments supplement biologically relevant afferent input to developing brain organoids to alleviate hypersynchronous bursting and improve biocomputing performance. This work aims to enhance the development of human-relevant brain models for disease, toxicological, and biocomputing applications.

49. NEXT-GENERATION ELECTROPHYSIOLOGY FOR FUNCTIONAL CHARACTERIZATION OF HUMAN NEURAL ORGANOIDS AND ASSEMBLOIDS

Marilina Douloudi, Elvira Guella, Simon Sennhauser, Laura D'Ignazio, Praveena Manogaran, Marie Engelene Obien

MaxWell Biosystems

Human-induced pluripotent stem cell (hiPSC)-derived 3D neural models (e.g. organoids, assembloids, etc.) are crucial tools for replicating human brain development and studying neurological disorders like Alzheimer's and Parkinson's disease. High-density microelectrode arrays (HD-MEAs) offer a label-free, non-invasive approach to real-time, high-resolution electrophysiological recordings from neural organoids, assembloids, and tissue explants.
We used the MaxOne and MaxTwo HD-MEA platforms, each featuring 26.400 electrodes per well, to record extracellular action potentials from various 3D neural models across different scales, ranging from cell population networks down to single-cell and subcellular levels. We showcased the flexible selection of recording electrodes, enhancing the data's reproducibility and statistical power. Key parameters, including firing rate, spike amplitude, and network burst profile, were extrapolated. The AxonTracking Assay was employed to trace action potential propagation along axonal branches and analyze conduction velocity, latency, and axonal morphology. This breakthrough assay enables high-resolution analysis of disease models targeting axon initial segment, development, and conduction. The here presented HD-MEA platforms' capability for targeted electrode selection improves data consistency and enables more comprehensive statistical insights. Furthermore, automated data visualization and metric extraction make these systems a robust and user-friendly choice for in-vitro disease modeling and drug testing in both acute and longitudinal studies.

50. VIRTUAL REALITY GAMES AND GAMERS' WELL-BEING

M. Eshaghzey

Medineth

Previous research has shown that virtual reality games are playing an increasingly important role in the digital lives of adolescents and young adults. However, the relationship between VR gaming and the subjective well-being of Generations Z and Y remains underexplored. Both positive effects, such as relaxation and social connectedness, and potential risks, including overstimulation and isolation, are examined. Using a literature review and a quantitative survey (N = 101), this master's thesis analyses the relationships between gaming experience, gaming time, positive messages, microtransactions, and mental well-being. The study is based on the hypothesis that VR gaming can contribute to users' quality of life. The results provide relevant insights for game developers, policymakers, and healthcare professionals seeking to use VR responsibly. Notably, gamers who play for more than five hours per week report a more positive effect on their mental health, although there appears to be a threshold beyond which the effect becomes negative. The findings also indicate that microtransactions may reduce enjoyment, particularly among gamers who do not belong to Generation Z. Furthermore, less frequent gamers appear to be more receptive to positive messages than frequent gamers. This study focused on the impact of VR gaming on the well-being of Generations Z and Y. However, respondents from Generation X and the Baby Boomer generation were not excluded from the analysis. Based on the sample, variables such as gaming time, microtransactions, and game content have a significant impact on well-being. Microtransactions negatively affect well-being, whereas the influence of positive messages appears to be less conclusive. Given the relatively small number of respondents, these findings highlight the importance of further research into VR gaming experiences and their effects on well-being.

51. TOWARDS ADAPTIVE, SELF-ASSESSING AGENTIC TOOLS FOR ELECTROPHYSIOLOGY ANALYSIS

A. Forni, A. Marishi, M. Zabolocki, L. Sadiraj, O. Kim, S. Kumar, J. Themann, A. Hierlemann, J. Knoblich, M. Schröter

ETH Zurich

Recent agentic frameworks for electrophysiology analysis, such as the Spike Sorting AI Agent [1] or SpikeLab [2], improve the reliability of large language model (LLM)-assisted analysis by constraining agent autonomy to expert-defined workflows. While these approaches reduce methodological errors and unreported decisions, they remain largely modality-specific and lack a quantitative assessment of intermediate-output reliability. This shortcoming leaves orchestrating agents and human users without a principled means of determining whether a result should be trusted or revised. Here, we present EphysAgent, a modular LLM-driven framework for adaptive electrophysiology analysis across different modalities, including low-density and high-density microelectrode arrays (LD- and HD-MEAs), silicon probes, patch-clamp, and EEG. A key contribution is a set of lightweight deterministic scoring modules that evaluate intermediate outputs at important processing stages, assigning confidence scores, detecting signal anomalies, and generating recommendations for subsequent stages. The current pipeline is embedded into a SQLite database framework allowing it to keep track of each processing step and providing a standardized basis for provenance tracking, cross-experiment comparison and detection of systematic errors. The scoring modules enable the orchestrating LLM-agent to determine whether to proceed, adjust parameters, or request human review, replacing the reliance on fixed heuristic thresholds or manual intervention with more autonomous data-driven decision-making. We demonstrate this architecture on HD-MEA recordings, implementing scoring modules for spike-sorting outputs and inferred features such as burst statistics and functional connectivity. Confidence scores agreed with expert ratings in the majority of cases – and improved the feature inference quality compared to a fixed analysis pipeline. Our implementation represents the first step toward extending this architecture across a variety of electrophysiological modalities and processing stages.

References

[1] Lin Z, et al., Spike sorting AI agent. bioRxiv. 2025. doi: 10.1101/2025.02.11.637754

[2] Van der Molen T, et al., SpikeLab: Agentic tools for spike data analysis. bioRxiv. 2026. doi:10.64898/2026.04.25.720833.

52. CORE FACILITY FOR INDUCED PLURIPOTENT STEM CELLS - IPSCORE ZURICH

D. Meier, D. Zorndt, A. Migenda Herranz, T. Picozzi, M. Generali

iPSCore (University of Zurich)

The iPSC Core Facility (iPSCore) at the University of Zurich is a centralized technology platform dedicated to advancing research through induced pluripotent stem cell (iPSC) technologies. Established to support the life science community in Zurich and beyond, the facility provides comprehensive services including somatic cell reprogramming, directed differentiation, hands-on training, experimental design support, and strategic project planning. iPSCore has established robust and reproducible differentiation protocols for a broad spectrum of clinically relevant cell types, including cardiomyocytes, smooth muscle cells, endothelial cells, neural progenitor cells, neurons, and macrophages. Additional lineage-specific protocols can be developed upon request to meet emerging scientific needs. All workflows are implemented under stringent quality control standards, including molecular characterization, functional validation, and genomic integrity assessment. The mission of iPSCore is to democratize access to cutting-edge stem cell technologies and to accelerate translational research by enabling the generation of tailored human in vitro models. By supporting projects from initial concept development through to validated cellular products, the facility empowers researchers to create disease models, perform mechanistic studies, and establish patient-specific platforms for therapeutic development. Through its integrated and collaborative approach, iPSCore serves as a critical infrastructure hub for innovative and reproducible stem cell research.

54. PHYSIOLOGICALLY RELEVANT MEDIA UNMASKS SEVERE MITOCHONDRIAL DYSFUNCTION IN A DETERMINISTICALLY PROGRAMMED IPSC-DERIVED MODEL OF HUNTINGTON'S DISEASE

R. Northeast

bit.bio

Huntington's disease (HD) is characterised by degeneration of the medium spiny neurons (MSNs) in the striatum. Patients suffer from uncontrollable movements and severe mental problems and currently no disease modifying treatments are available. HD is caused by a CAG repeat expansion encoding an elongated polyglutamine stretch in the Huntingtin (HTT) protein. The mutant HTT protein has been reported to affect cellular processes, including mitochondrial biogenesis, fission, transport and respiration. HTT is ubiquitously expressed in the brain and, albeit MSNs are the most susceptible to the toxic effects of mutant HTT, other neuronal subtypes such as cortical glutamatergic neurons are affected during later disease stages. We developed a novel iPSC-derived HD model based on our ioGlutamatergic Neurons that have been generated utilising opti-ox™ deterministic cell programming. ioGlutamatergic Neurons HTT 50CAG/WT contain a heterozygous 50 CAG repeat expansion in exon 1 of Huntingtin. To investigate mitochondrial function, a Seahorse analysis was performed on cells cultured in either Neurobasal medium or a medium that has a more physiologically relevant concentration of glucose. The HD model showed a significant but modest reduction in basal and ATP-linked respiration relative to the wild type control. Unexpectedly, at day 25 oxygen consumption rates in both genotypes were highly similar as neurons switched from mitochondrial respiration to glycolysis. Culturing cells in a more physiologically relevant medium supported mitochondrial respiration at day 25 and unmasked a significant mitochondrial dysfunction in the HD model. Functional assessment by HD-MEA showed a significantly decreased firing amplitude in the HD model independent of the medium. Overall, we have developed a scalable and consistent human HD model that recapitulates critical disease aspects and enables disease mechanistic and drug discovery studies.

55. SCALABLE HUMAN IPSC-DERIVED TRIGEMINAL NEURONS FOR MIGRAINE AND PAIN THERAPEUTIC DISCOVERY

V. Truong, T. Strassmaier, I. Lu, M. Gray, H. Moeller, T. Knox, D. Arora, R. Haedo, P. Walsh

Anatomic Incorporated Minneapolis, MN

Nanion Technologies Livingston, NJ

Human trigeminal ganglion neurons (TGNs) mediate craniofacial pain, migraine, thermosensation, and other sensory modalities unique to the trigeminal system. However, studies of human trigeminal biology remain limited by the scarcity of primary tissue. Given the central role of ion channels in nociceptor excitability and therapeutic response, defining the molecular and functional properties of human TGNs is critical for advancing migraine and craniofacial pain research. To address this need, we generated TGNs from human induced pluripotent stem cells (hiPSCs) through an anterior cranial neural crest lineage using a rapid, small molecule and growth factor-based differentiation protocol. TGNs were produced within 7 days without genetic manipulation or mitotic inhibitors and evaluated across three independent manufacturing batches following maturation in a fully defined maturation media. Immunocytochemical analysis demonstrated a highly enriched sensory neuron population expressing ISL1, BRN3A, TUJ1, and the trigeminal lineage marker SIX1, with consistent marker expression observed across differentiations. Transcriptomic characterization by bulk RNA sequencing and qPCR confirmed reproducible sensory neuron identity and revealed elevated expression of trigeminal-relevant ion channels including SCN10A (NaV1.8) and TRPM8 compared with primary human DRG controls. Functional maturation assessed using multielectrode array (MEA) recordings demonstrated spontaneous neuronal activity within two weeks post-thaw. By week four, cultures displayed widespread electrode activity and reproducible responses to the TRPV1 agonist capsaicin (100 nM) and PACAP (1 uM) across independent batches, confirming functional nociceptor phenotypes. To further evaluate ion channel function in a high throughput screening format, TGNs were analyzed using the SyncroPatch 384 automated patch clamp platform. Recordings identified robust TTX-resistant sodium currents consistent with NaV1.8 activity that were inhibited by 30 nM Suzetrigine. These findings establish compatibility with high-throughput automated electrophysiology workflows and demonstrate the utility of TGNs for scalable NaV1.8 pharmacology studies. Together, these results establish a reproducible human trigeminal neuron platform with consistent molecular identity, robust TRPV1 responsiveness, and functional NaV1.8 activity across independent manufacturing batches. This system provides a scalable tool for investigating trigeminal biology, migraine mechanisms, ion channel pharmacology, and pain therapeutic discovery.

56. LABEL-FREE FUNCTIONAL CHARACTERIZATION OF HUMAN IPSC-DERIVED NEURONS AT SUBCELLULAR LEVEL

Elvira Guella, Silvia Ronchi, Luna Alvarado Añón, Francesco Modena, Zhuoliang Li, Praveena Manogaran, Marie Engelene Obien

MaxWell Biosystems

The use of brain models derived from induced pluripotent stem cells (iPSCs) has revolutionized the study of neurological diseases such as frontotemporal dementia (FTD), Alzheimer's and Huntington's disease. Gaining real-time and label-free access to the electrical activity of human iPSC-derived neurons can offer valuable insights into the complexity of their neuronal networks.
High-density microelectrode arrays (HD-MEAs) provide a powerful, non-invasive platform for high-resolution electrical imaging, enabling in vitro extracellular recordings of action potentials across multiple levels of resolution, spanning entire networks to individual cells and subcellular structures.
In this study, the MaxTwo HD-MEA platform, featuring 26.400 electrodes per well, was employed to record extracellular action potentials from both healthy and disease iPSC-derived neurons over multiple days/weeks, to functionally characterize them. Additionally, electrophysiological metrics including firing rate, spike amplitude and network burst profile were extracted and analyzed.
To further assess subcellular dynamics, the AxonTracking Assay was used to trace the propagation of action potentials along axonal branches, enabling precise investigation of axonal properties, such as conduction velocity, latency, axonal length and branching patterns. This revolutionary assay offers a high-resolution approach for studying disease models focusing on axon initial segment, axonal development, branching and conduction.
The HD-MEA platform's flexible electrode selection for recording neural activity enhances the statistical robustness of the collected data while ensuring higher reproducibility. Combined with integrated tools for automated data visualization and metric extraction, the system presented here provides a user-friendly and reliable platform for in vitro disease modeling and drug testing, suitable for both acute and long-term electrophysiological studies

57. iPSC-DERIVED DRG-LIKE MODEL FOR INVESTIGATING NEURONAL DYSFUNCTION IN FABRY DISEASE

Ferdinand Teichert[1,2], Ruben de Vries[1], Maria Ferraz[3], Marta Artola[3], Rafaella Buzatu[1],

Christian Schröter[1], Andreas Leffler[4], Robert Zweigerdt[2] & Micha Drukker[1]

Division of Cell Systems and Drug Safety, LACDR, Leiden University

Department of Cardiac, Thoracic, Transplantation and Vascular Surgery (HTTG), LEBAO, Medizinische Hochschule Hannover

Department of Bio-Organic Synthesis, Leiden Institute of Chemistry (LIC), Leiden University

Department of Anesthesiology and Intensive Care Medicine, Pain Management Service, Medizinische Hochschule Hannover

Fabry disease is a lysosomal storage disorder characterized by a genetic deficiency of α-galactosidase A, resulting in the accumulation of globotriaosylceramide (Gb3). A hallmark of the disease is severe neuropathic pain, yet the molecular mechanisms by which Gb3 accumulation leads to nociceptor dysfunction is poorly understood. Here, we establish an iPSC-based dorsal root ganglion (DRG) -like culture as a Fabry disease model. We differentiated iPSCs from two Fabry patients and genetically corrected controls via an axial stem cell intermediate into mixtures of DRG sensory neurons and supporting glia. Our model demonstrates functionality and the relevant DRG markers (e.g. TRPV1, TUJ1, POU4F1, SOX10). Recordings of neuronal activity with High-density multi-electrode arrays (HD-MEA) uncovered patient-specific network dysfunctions such as hyperactivity and recruitment-driven burst remodeling. Transcriptomic comparison revealed a cohort of shared downregulated genes that point to a Fabry-specific stress state. More generally, we are providing an integrated Fabry disease DRG-like culture model linking organellar dysfunction changes with cellular electrophysiology and currently testing how these potential pain-relevant modulatory factors can reverse the hyperactivity phenotype.

List of Posters

Poster Number	Presenting Author	Title of the Poster	Day of Presentation
1	Flora Brozzi	An Open, Remotely Accessible Neuroplatform for Long-Term Closed-Loop Electrophysiology of Human iPSC-Derived Biological Neural Networks	Day 1
2	Sreedevi Raghu	Delayed Maturation of GABAergic Interneurons and Pathological Mitochondrial Dynamics as Key Driving Factors of Epileptic Seizures in hiPSC Derived Cortical Organoid Models of Rett Syndrome	Day 2
3	Michele Bertacchi	High-Density MEA Analysis of Neural Network Activity, Maturation and Plasticity in Region-Specific Human Brain Organoids	Day 1
4	Gregorio Rebecchi	SpikeTrain Spotting: How to Infer Synaptic Connectivity in Brain Organoids	Day 2
5	Scott Erickson	A Bioelectronic Platform for Modeling Functional Connections Between Neural Organoids	Day 1
6	Marcus Kaji	Driving with the Parking Brake On. Repairing KCNQ2 Gain-of-Function Neuronal Hypo-excitability with an Antisense Oligonucleotide tune-up	Day 2
7	Nina Doorn	Beyond Phenotyping: From MEA Data to Mechanistic Insight Using Computational Modeling	Day 1
8	Ferenc Deak	Prevention of Cognitive Impairment and Synaptic Dysfunction in Alzheimer's Disease	Day 2
9	Michal Liput	Physioxia Regulates Mitochondrial Dynamics and Protects Developing Cortical Neurons from Hypoxia-Induced Cell Death in Human Brain Organoids	Day 1
10	Zofia Knapinska	Selective Modulation of the Senescence-Associated Transcriptome in Human Dorsal Forebrain Organoids Cultured Under Physiological Oxygen Tension	Day 2
11	Aidan Loehde-Woolard	Functional Pharmacology of Brain Organoids Enabled by Automated Microfluidic Electrophysiology	Day 1
12	Benedikt Maurer	A System for Unperturbed Longitudinal Recording of Neuronal Networks Through Constant Culturing Conditions	Day 2
13	Aline Girard	Human iPSC-Derived Models to Unravel the Role of Glypicans in Synaptic Alterations in Sanfilippo Syndrome	Day 1

Poster Number	Presenting Author	Title of the Poster	Day of Presentation
14	Yoko Uwate	Effects of Time-Series Length and Noise on Recurrence Plot Analysis of Developmental Neural Dynamics in iPS Cell-Derived Networks	Day 2
15	Veronica Astro	Dosage-Dependent Disruption of Neural Stem Cell Proliferation and Neuronal Network Activity in X-Chromosome Aneuploidies Is Mediated by the Cell-Autonomous ZFX–SOX2 axis	Day 1
16	Rebecca Bonrath	Human Adherent Cortical Organoids Derived from Individuals with Grey Matter Heterotopia	Day 2
17	Pablo Carbajal Martin	Unmasking Energetic and Intracellular Dysregulation in HK1-Associated Neurological Disorders Using iPSC-Based Neural Models	Day 1
18	Moran-Adel Khamaisi	Studying Functional Neural Activity in iPSC-derived Brain Organoids Using Microelectrode Arrays	Day 2
19	Ruben de Vries	Axial Stem Cell Derived Human Dorsal Root Ganglion Model Recapitulates Cellular Diversity and Somatosensory Functionality	Day 1
20	James Crowe	Dissecting Neuronal Contributions to Network Hyperexcitability in Human iPSC Models of Neuronopathic Gaucher Disease Using High-Density Microelectrode Arrays	Day 2
21	Amr Othman	HD-MEA Validation of Human iPSC-Derived Neuron – Glia Models for 2D and 3D Neural NAMs	Day 1
22	Olga Teresa Bianciotto	Generation of a Glia-Enriched Human Cerebellar Organoid Model to Investigate Developmental Glia-Neuron Interactions	Day 2
23	Kazushi Takehana	Adaptive Electrode Selection for Longitudinal Tracking of Early Network Dynamics in Cortical Cultures	Day 1
24	Hunter Schweiger	Self-Supervised Deep Learning Model for Understanding Circuit Development at scale	Day 2
25	Marta Brasili	Distinct Presynaptic Homeostatic Adaptations in Human Synapses Reveal a Link to TDP-43	Day 1
26	Dai Akita	Expanding Living Neuronal Computing Systems by Virtual Coupling across HD-MEAs	Day 2
27	Nobuyuki Kido	Bridging Functional Dynamics and Spatial Transcriptomics in Biological Neuronal Networks	Day 1

Poster Number	Presenting Author	Title of the Poster	Day of Presentation
28	Theresa Lahoud	Impact of COP-ID Dysfunction on Brain Development in Human	Day 2
29	Vaiva Vasiliauskaite	Inferring Effective Networks of Excitatory-Inhibitory Networks in Vitro Using Transfer Entropy	Day 1
30	Feng Bin	Ketamine Dose-Dependently Suppresses PVN Single-Unit Firing and Leaves a Reorganised Network State After Washout	Day 2
31	Alena Kapnulina	KCNQ2 Variant-Specific Signatures in Channel Function, Neuronal Excitability and Gene Expression	Day 1
32	Kenta Shimba	Post-Recording Spatial Gene Detection for Cell-Type-Resolved HD-MEA Network Analysis	Day 2
33	Romy Van Acker	HD-MEA Platform for Drug Discovery in patient-derived models of Neurodevelopmental Disorders	Day 1
34	Daria Andreeva	Human iPSC-Derived Neural Organoids Reveal Early Developmental Pathway Dysregulation in PCH2A	Day 2
35	Faribi Karimi	Dissecting the Cellular Mechanism of Temporal Interference Stimulation in Human iPSC-Derived Neurons	Day 1
36	Yue Yang Cao	Exploring Gene Network Expression Dynamics Using Integrated Spatial Transcriptomics and Large-scale Electrophysiology in Cellular Models of Human Neurodevelopmental Disorders	Day 2
37	Diane Balallo	A Single-Cell Microfluidic Model for Investigating Synaptic Spread of Amyloid-β and Tau in Alzheimer's Disease	Day 1
38	Nadia Jimenez	Fully On-Chip Bio-Plausible Learning and Inference for Memristive Neuromorphic Systems	Day 2
39	Josephine Loehle	Towards Model Predictive Control of Engineered in Vitro Neural Cultures	Day 1
40	Florian Willi	Towards Biological Neural Networks as Intelligent Agents: Investigating the Effect of Network Size	Day 2
41	Fiona Konnerth	Towards a Compartmentalized in Vitro Model of Nociception Using Microfluidics for Drug Screening Targeted at Chronic Pain	Day 1
42	Salma Marselha Ramon-Carrasco	A Proof-of-Concept Automated Platform for Synaptic Assays on HD-MEA	Day 2

Poster Number	Presenting Author	Title of the Poster	Day of Presentation
43	Nicol Dusan	CRISPR-Cas9 Knockout of ASD-Associated Genes Differentially Alters Neuronal Excitability	Day 1
44	Marlene Faria Pereira	Human Brain Organoids as Platforms for Studying Reactive Astrogliosis and Complex Disease Mechanisms	Day 2
45	Joel Kuchler	Are Biological Neural Networks Useful for Task-Specific Computation? A Biological-Artificial Neural Network Classifier	Day 1
46	Lennart Valentin Schneider	From Neuronal Networks to Seizure Models: Integrating Functional and Cellular Profiling to Inform Candidate Prioritization	Day 2
47	Revathy Guruswamy	Towards Understanding the Role of TDP-43-G3BP1 Axis in Maturation Dependent Functional Defects in ALS	Day 1
48	Andrew Chinn	Input Encoding in Human Brain Organoids Under Resource-Limited Network Bursts	Day 2
49	Marilina Douloudi	Next-Generation Electrophysiology for Functional Characterization of Human Neural Organoids and Assembloids	Day 1
50	Monika Eshaghzey	Virtual Reality Games and Gamers' Well-Being	Day 2
51	Arianna Forni	Towards Adaptive, Self-Assessing Agentic Tools for Electrophysiology Analysis	Day 1
52	Anabel Migenda Herranz	Core Facility for induced Pluripotent Stem Cells - iPSCore Zurich	Day 2
53	Tjitse van der Molen	AI-Native Provenance from Recordings to Conclusions with the Open Culture Science Knowledge Graph	Day 1
54	Rebecca Northeast	Physiologically Relevant Media Unmasks Severe Mitochondrial Dysfunction in a Deterministically Programmed iPSC-Derived Model of Huntington's Disease	Day 2
55	Vince Truong	Scalable Human iPSC-Derived Trigeminal Neurons for Migraine and Pain Therapeutic Discovery	Day 1
56	Elvira Guella	Label-Free Functional Characterization of Human iPSC-Derived Neurons at Subcellular Resolution	Day 2

Poster Number	Presenting Author	Title of the Poster	Day of Presentation
57	Ferdinand Teichert	iPSC-Derived DRG-Like Model for Investigating Neuronal Dysfunction in Fabry Disease	Day 1

Conference Venue

Ambassador House - Thurgauerstrasse 101, 8152 - Zürich, Switzerland

Unique Venue History

Originally built at the end of the 1980s, the Ambassador House has been part of Zürich North's transformation for more than three decades. Long before today's Glattpark took shape, the building stood as a distinctive landmark between Zürich's city center and the airport.

Following an extensive architectural transformation completed in 2017, the Ambassador House was reinvented as a modern business and conference destination while retaining the core structure of the original building.

Today, it is one of Switzerland's largest office complexes and brings together contemporary architecture, light-filled spaces and modern conference facilities - providing a fitting setting for NeuMoS and for bringing our scientific community together.

Conference Dinner

17 September 2026 | 19:30
Zunfthaus zur Meisen, Zürich

The conference dinner will provide the perfect opportunity to connect and network with fellow NeuMoS 2026 attendees, including speakers, members of the Scientific Committee, and the MaxWell Biosystems team.

Enjoy an evening of Swiss cuisine in the historic Zunfthaus zur Meisen, located in the heart of Zürich's Old Town and overlooking the Limmat - a beautiful setting to continue conversations and connect beyond the conference.

Zurich City | Key Information

Zurich is the largest city in Switzerland and is a fascinating destination that offers something for everyone.

Visitors should be aware that Switzerland uses Swiss Franc (CHF) as their currency, and that Zurich is a German-speaking city, although English is widely spoken.

Public Transport

Getting around Zurich is easy thanks to the city's efficient public transportation system. The system consists of trams, buses, and trains, all of which are operated by the Zurich Transport Network (ZVV). Passengers must purchase a ticket before boarding the transport at the ticket machines located at each stop or online, but there are no ticket barriers or inspectors on board. However, ticket checks are conducted randomly, and passengers caught without a valid ticket face a hefty fine.

Top Things to Do

Explore the Old Town: The Old Town of Zurich is a charming area with narrow cobblestone streets, medieval houses, and charming squares. It is a great place to explore on foot and soak up the atmosphere of the city. The area is also home to several museums, churches, and galleries.

Take a Boat Ride: Another great way to experience the beauty of Zurich is by taking a boat ride on the Limmat River or Lake Zurich. There are several boat tours available that provide stunning views of the city's skyline, including the iconic Zurich Opera House and Grossmünster Church.

The Uetliberg Viewpoint: The viewpoint is a popular attraction in Zurich, offering stunning panoramic views of the city and surrounding countryside from the top of Uetliberg mountain. Easily accessible by train from the city center, the viewing platform provides unobstructed views of Zurich, Lake Zurich, and the Alps. Visitors can climb the observation tower for a 360-degree view of the area.

Useful Swiss German Phrases

"Grüezi" (pronounced "grew-tzi"). This is a common Swiss German greeting that means "hello" or "good day." It's a polite and friendly way to greet someone.

"En Schöne Tag no" (pronounced "en shö-neh tahg no"). This phrase means "have a nice day" and is a friendly way to say goodbye.

“Merci vilmal" (pronounced "mehr-see feel-mahl"). This phrase is a typical way to say "thank you".

About the Host | MaxWell Biosystems

MaxWell Biosystems is a global technology leader in high-content electrophysiology. Headquartered in Switzerland, we unite world-class engineering and biological insight to help scientists capture and understand the intricate electrical activity of living systems.

As recognized experts in High-Density Microelectrode Array (HD-MEA) technology, we provide advanced solutions that reveal the dynamic behavior of cells, uncover the mechanisms of complex neuronal systems, and accelerate the development of new therapies in in-vitro 2D and 3D models. Our HD-MEA platforms deliver unmatched resolution and reproducibility, setting the standard for *in-vitro* electrophysiology, and allowing to capture neuronal activity across multiple scales, from sub-cellular to single cells, up to full networks in unprecedented detail.

Trusted by scientists in academia, biotech, and pharma, MaxWell Biosystems is committed strengthening the global scientific community. Together, we advance research, innovation, and discov across neuroscience, disease modeling, and bio-inspired computing to transform cellular data ir progress for science and human health.

The MaxWell Biosystems Team, April 2025

Stay in Touch

Visit our Website

Book a Discovery Call

Social Media, Contact Information and WiFi Details

We'd love to see NeuMoS 2026 through your eyes! Share your favorite moments, scientific highlights, and conversations from the symposium, and connect with fellow attendees online.
Follow MaxWell Biosystems on LinkedIn and join the conversation using #NeuMoS2026. Feel free to tag MaxWell Biosystems, our speakers, sponsors, and fellow attendees in your posts.

Follow us on X @mxwbio

Follow us on LinkedIn @MaxWell Biosystems

Share Your NeuMoS Experience

Not sure what to post? Here are a few ideas:

1. Arriving at NeuMoS
   Excited to be at #NeuMoS2026 in Zurich! Looking forward to two days of discussions around organoids, NAMs, neural circuit assays, disease modeling, and drug discovery.

2. Inspired by a talk
   Great insights from [speaker name] at #NeuMoS2026 on [topic]. Lots to think about and take back to the lab!

3. Sharing your research
   Excited to present our work on [topic] at #NeuMoS2026 and connect with researchers working across human neural models, electrophysiology, disease modeling, and neurotechnology.

WiFi Details

Name: AMBASSADOR-PUBLIC

Instructions:
You'll be redirected to a browser page automatically - tap CONNECT.
Enter your mobile number and tap REGISTER.
You'll receive a 4-digit code via SMS - enter it and tap CONNECT again.
You're now connected to AMBASSADOR-PUBLIC Wi-Fi.

Contact Information

Need help during NeuMoS? The MaxWell Biosystems team will be happy to assist.
For questions related to the symposium, please speak with a member of the organizing team on site or contact us at marketing@mxwbio.com.

maxwell BIOSYSTEMS

10 Years. Beyond Every Well.

Neuronal Model Symposium (NeuMoS) 2026
Organoids, NAMs, and Neural Circuit Assays for Disease and Drug Discovery

16-18 September 2026

Zurich, Switzerland

Visit our website to stay up to date with the latest news, publications, and products.

Scan the QR code to visit our website.

www.mxwbio.com