Brain-on-a-dish: Innovative human disease modeling for fundamental research and personalized medicine

Hans van Bokhoven, 4 November 2021

Human Genetics Nijmegen

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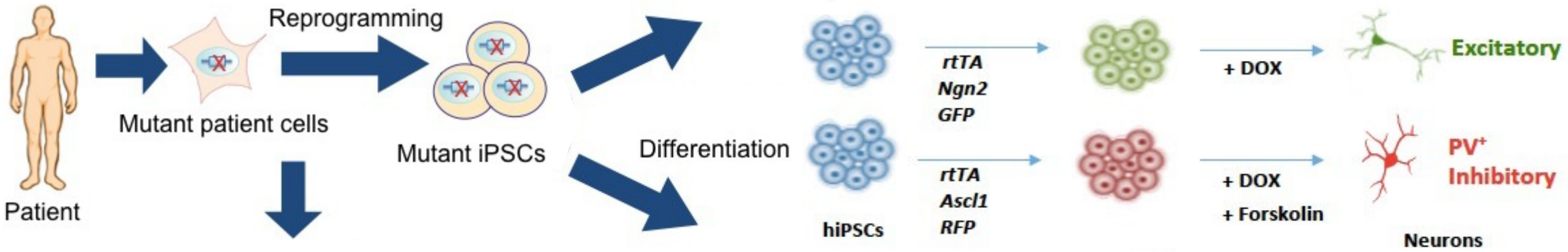
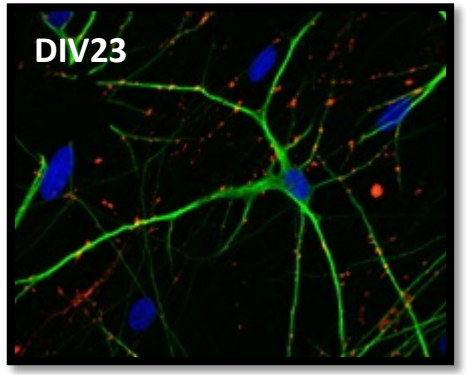
Brain-on-a-dish: Innovations

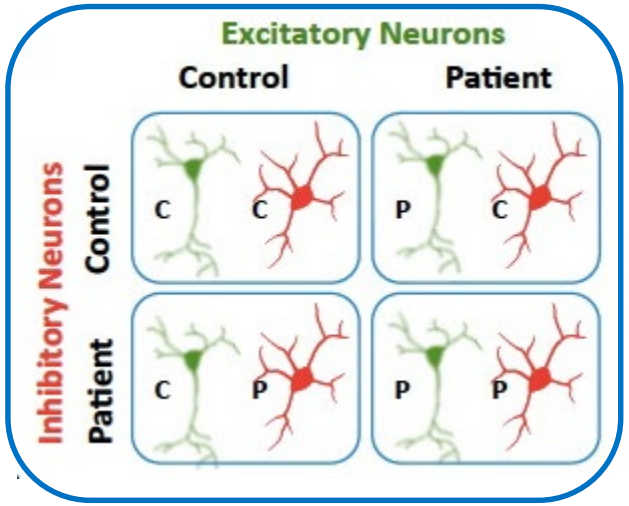
Stem Cell Biology

Established protocols for neural differention



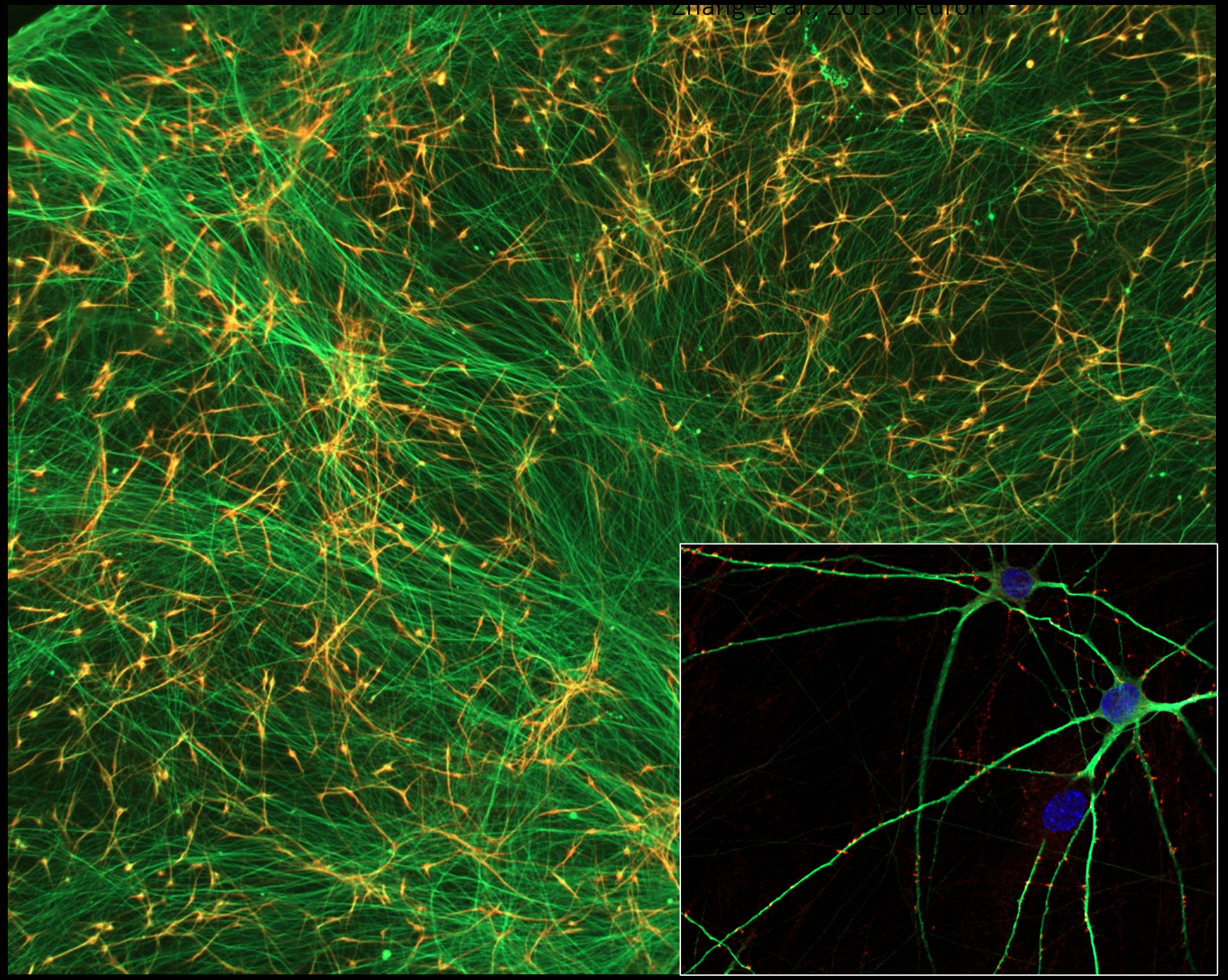
Neurons with the genetic background of the patient





Zhang et al., 2013 Neuron

- Fast protocol ± 3 weeks
- High efficiency
- Mature neurons
- Homogeneous population
- Glia dependent

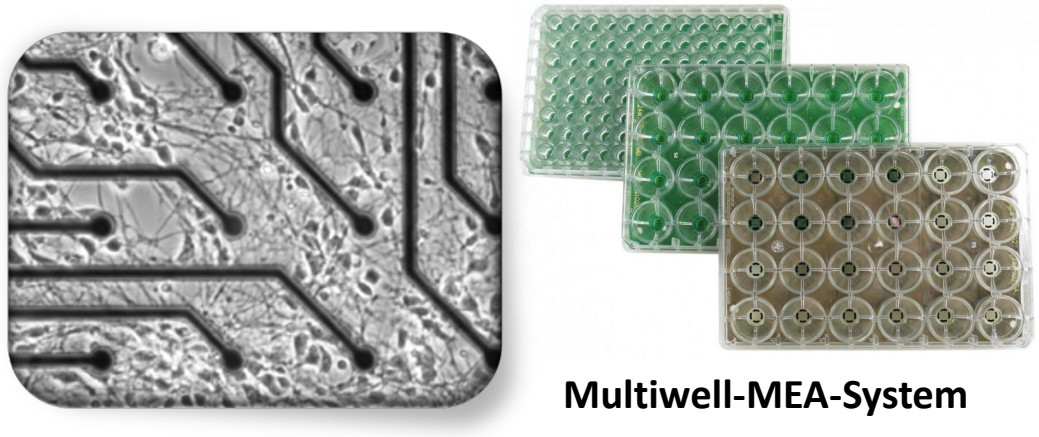


MAP2Axon

Organ-on-Chip
Technology

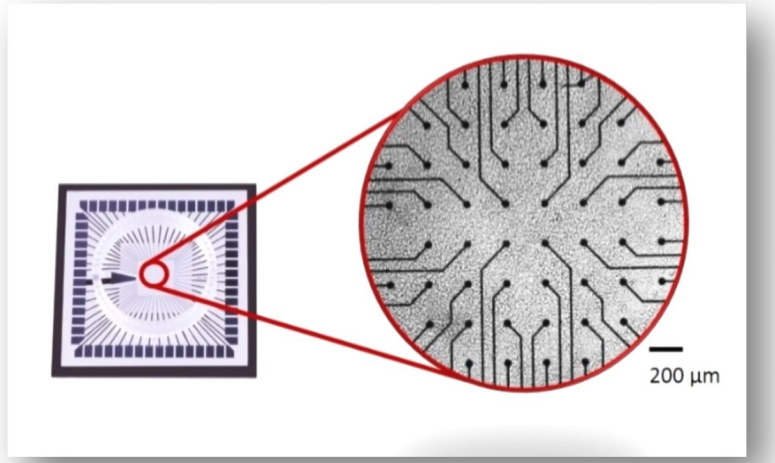
Brain-on-a-dish: Innovations Micro-Electrode Arrays (MEA)

- **Studying neuronal network activity in vitro**
  - They can survive for long period (weeks, months)
  - Density of the culture can be controlled
  - Non-invasive
- **High throughput experiments**
  - Genetic screening
  - neurotoxicity-neuropharmacology



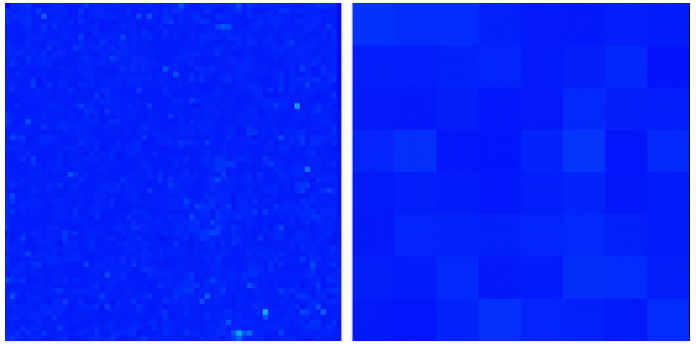
Multiwell-MEA-System

24-72-96 wells



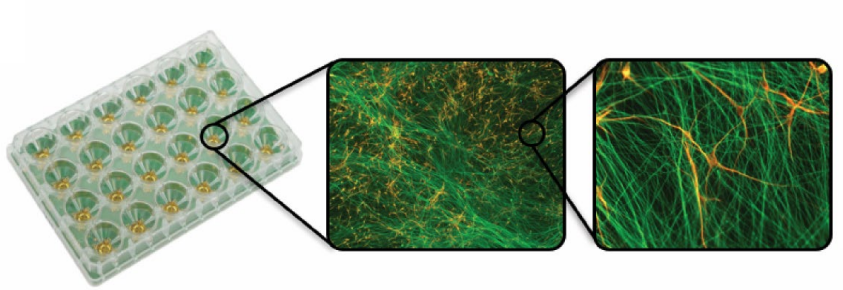
APS MEA (4096 electrodes)

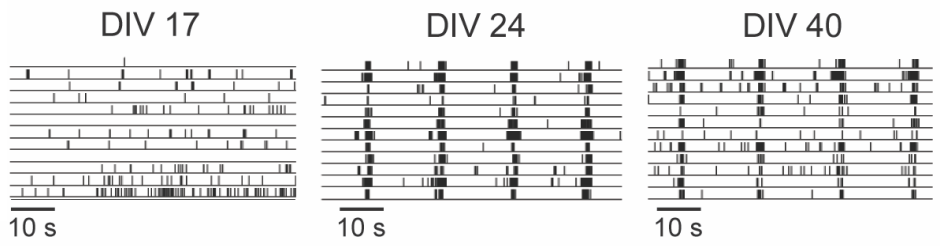
MEA (64 electrodes)

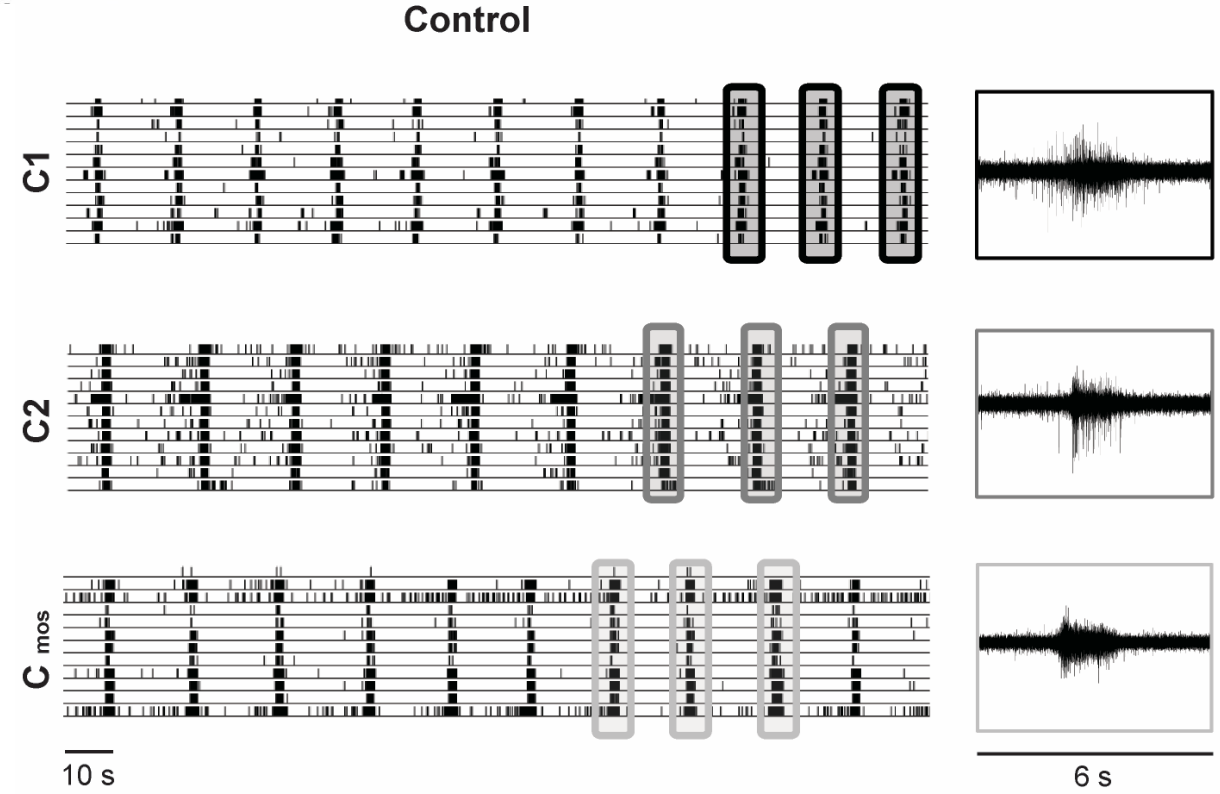


Frega et al. J Vis Exp. 2017

Excitatory iNeuron networks







Applications of iPSC-derived neurons

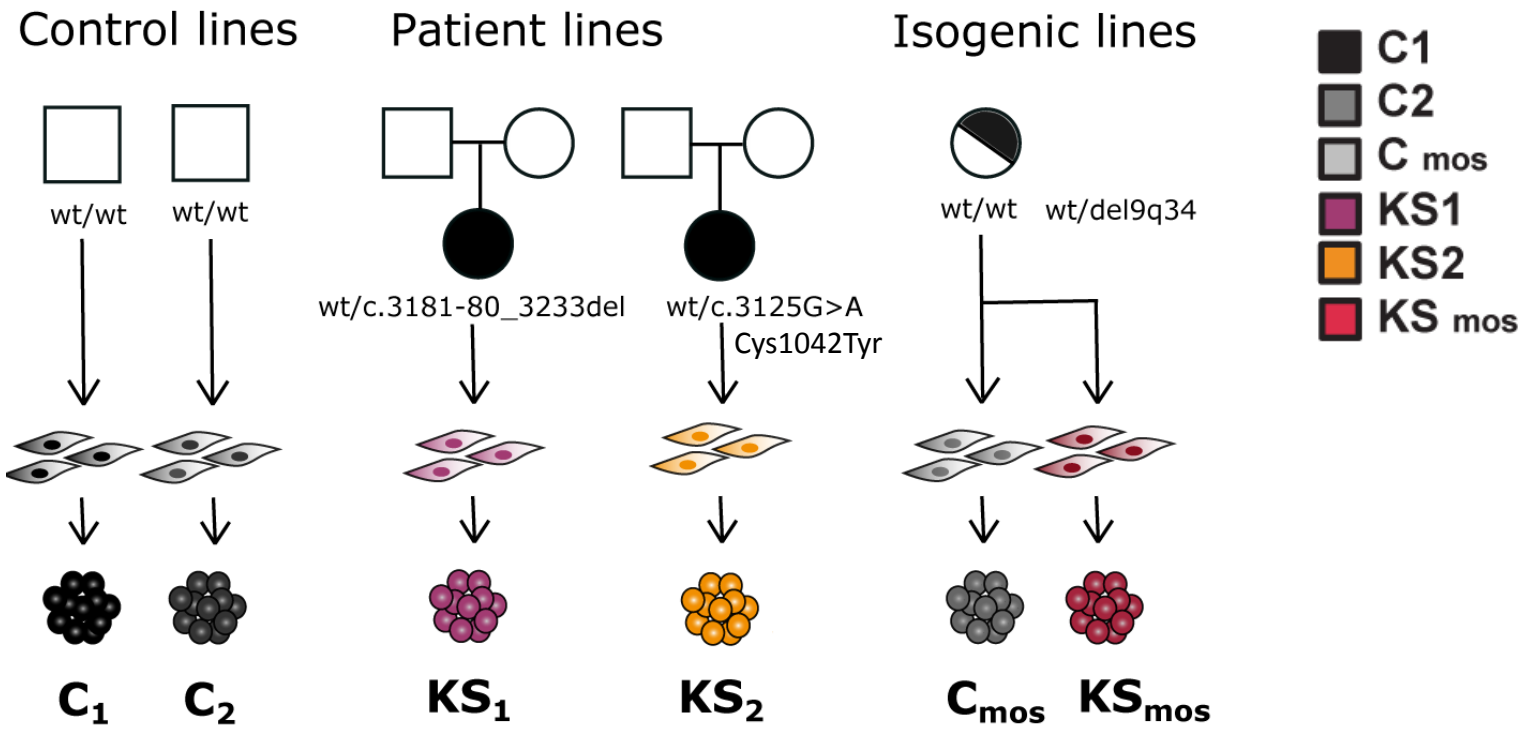
Studying mechanisms of disease

Diagnostic:
Interpretation of DNA variants

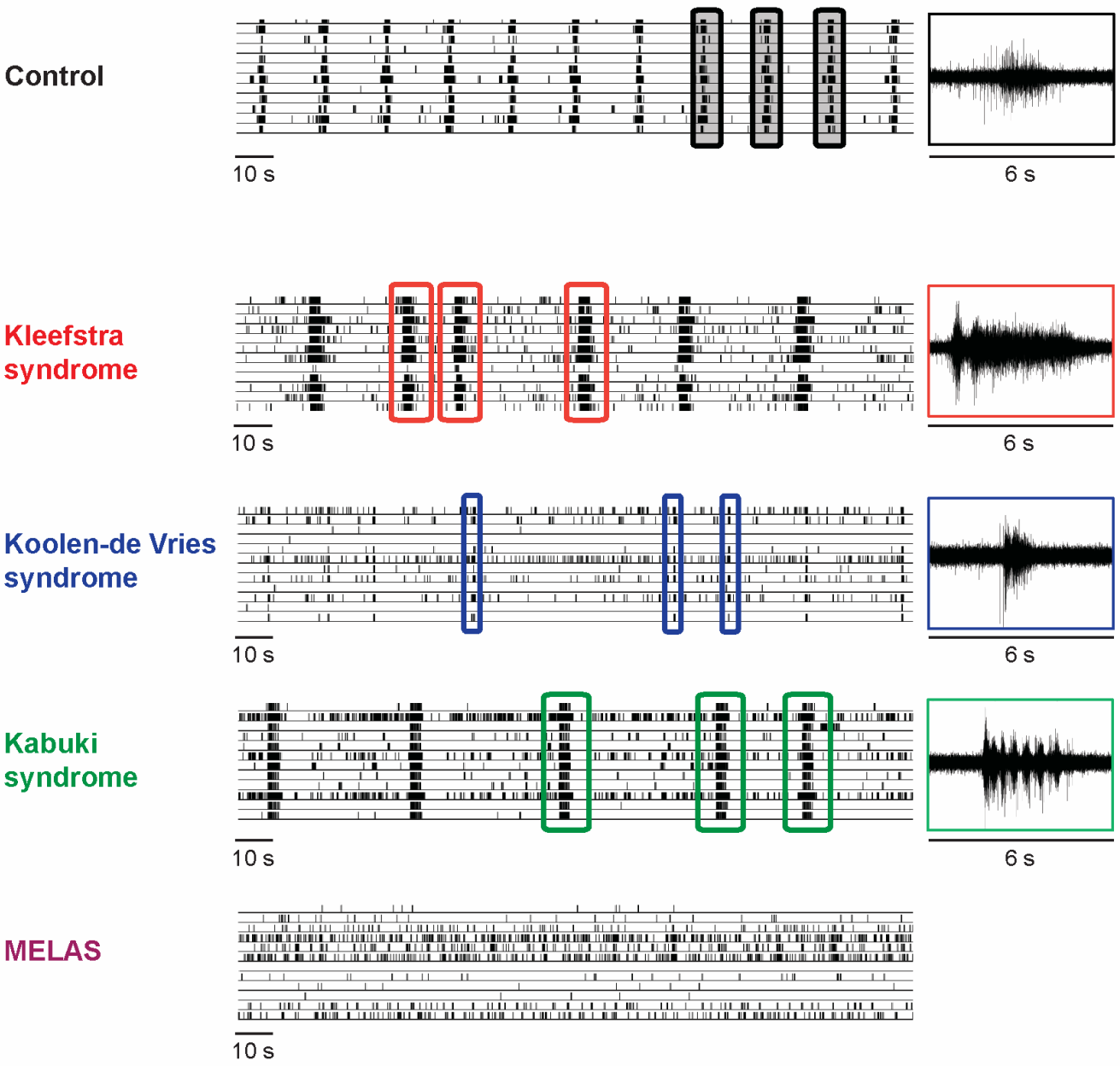
Finding therapeutics

Personalized medicine

1. Studying Mechanisms of disease: Control and Kleefstra iPSC lines



Disease-specific neuronal network phenotypes



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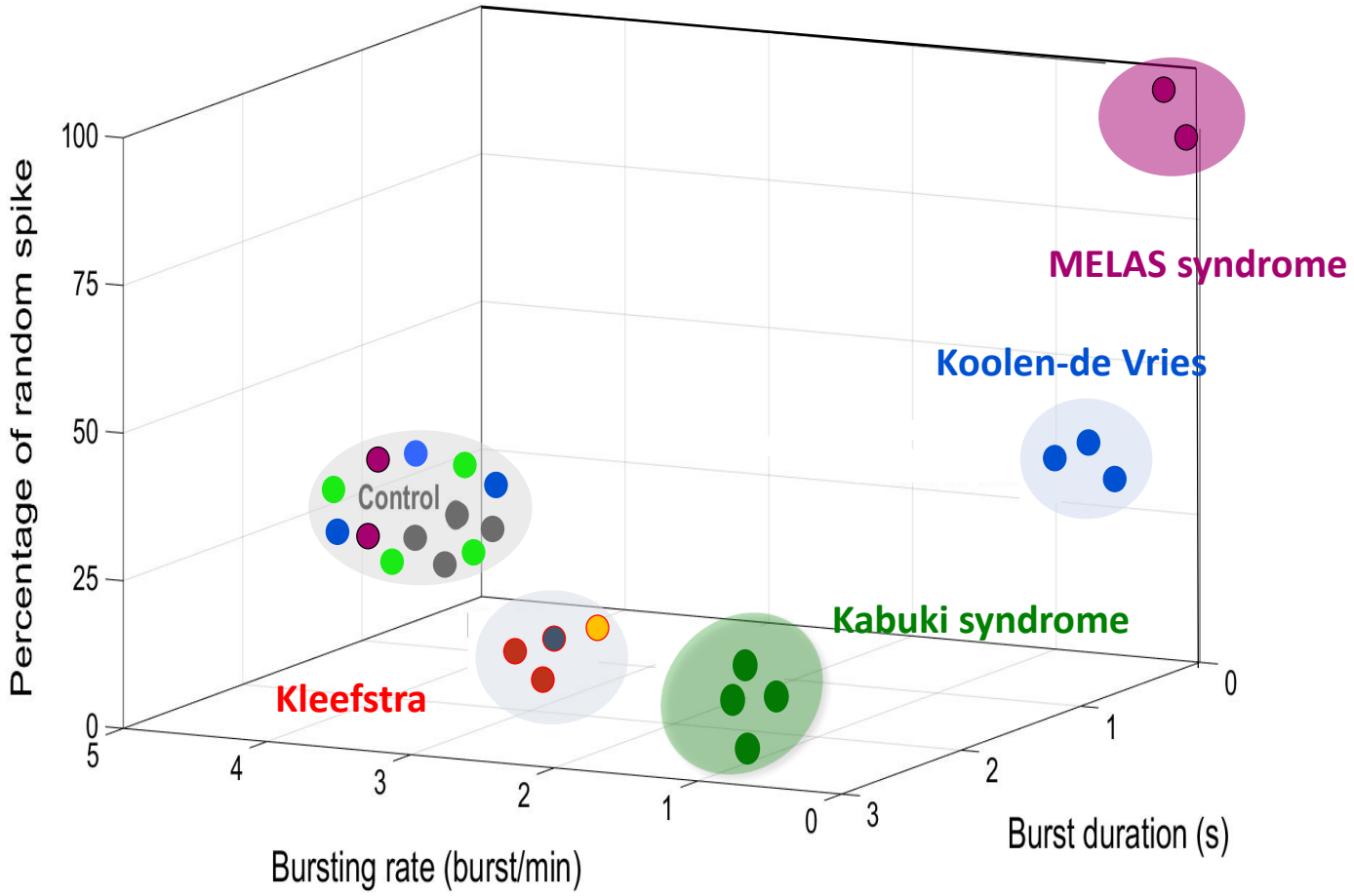
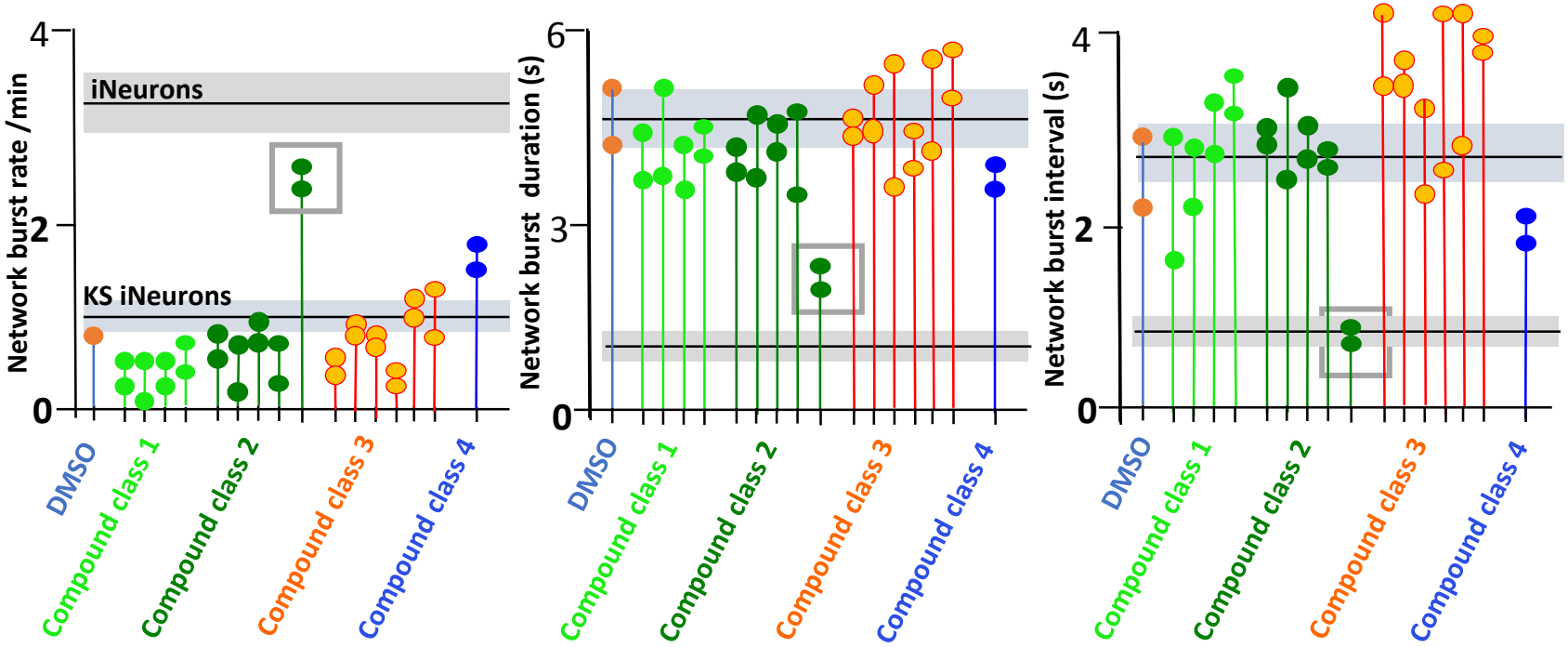
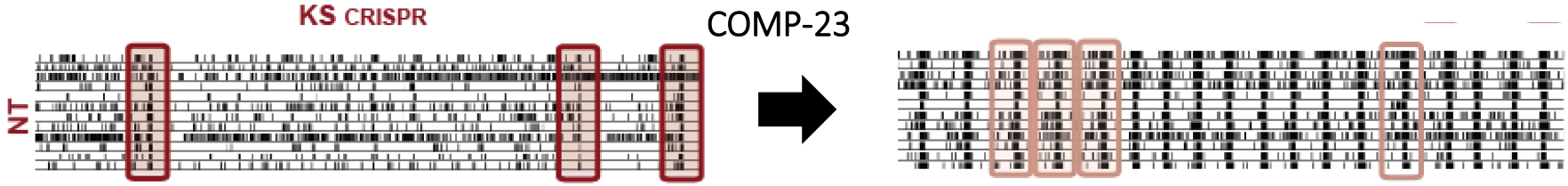


2. Diagnostics: classification of variants of unknown significance

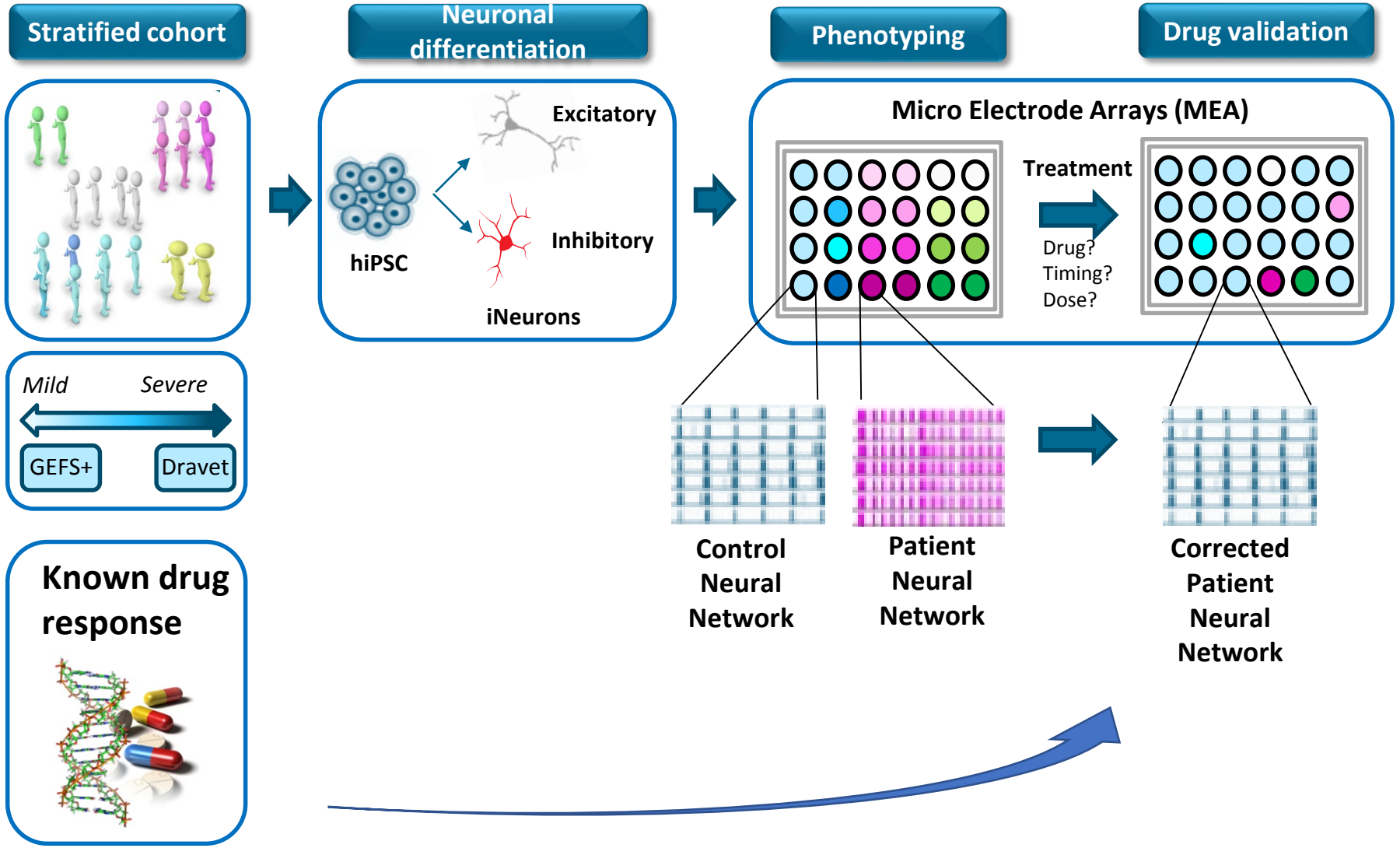
3. Personalized medicine: drug testing

- Testing >200 compounds: different classes of compounds that ”modify” the epigenome
- 1 dose/compound tested on 1 patient line and CRISPR line





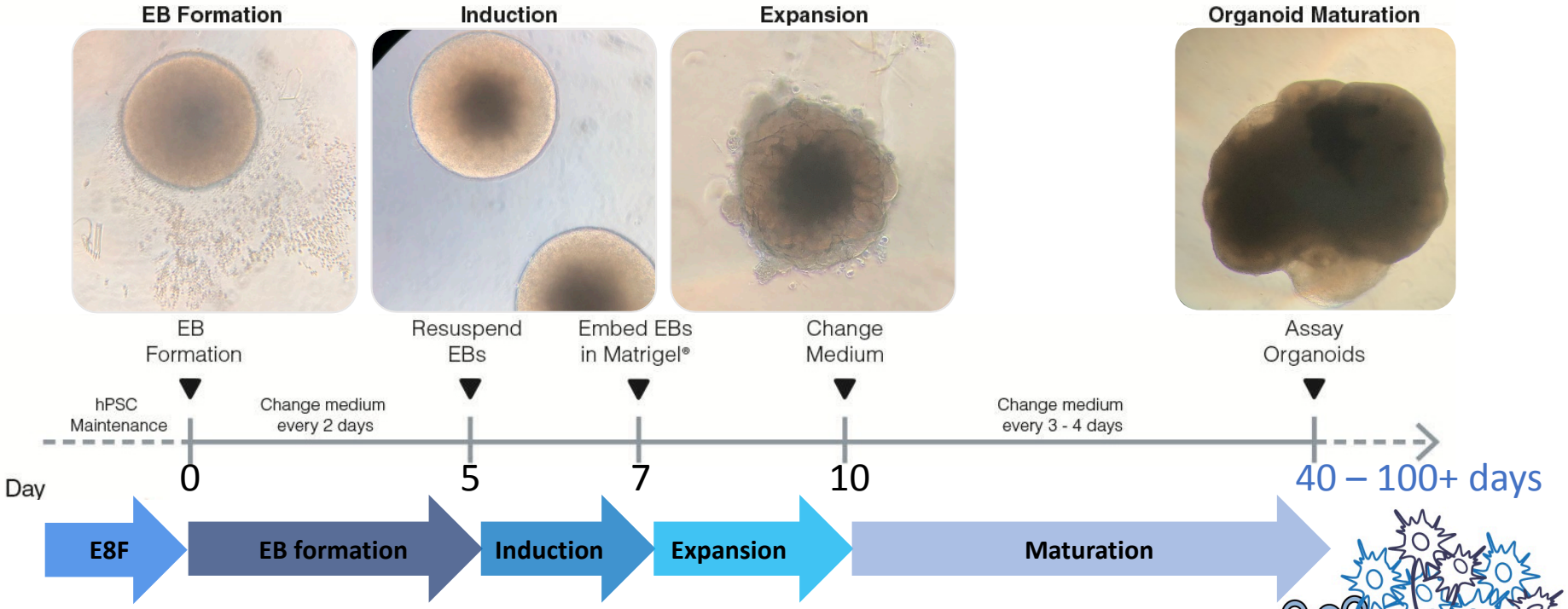
4. Personalized medicine: in vitro testing of optimal medication – example epilepsy -

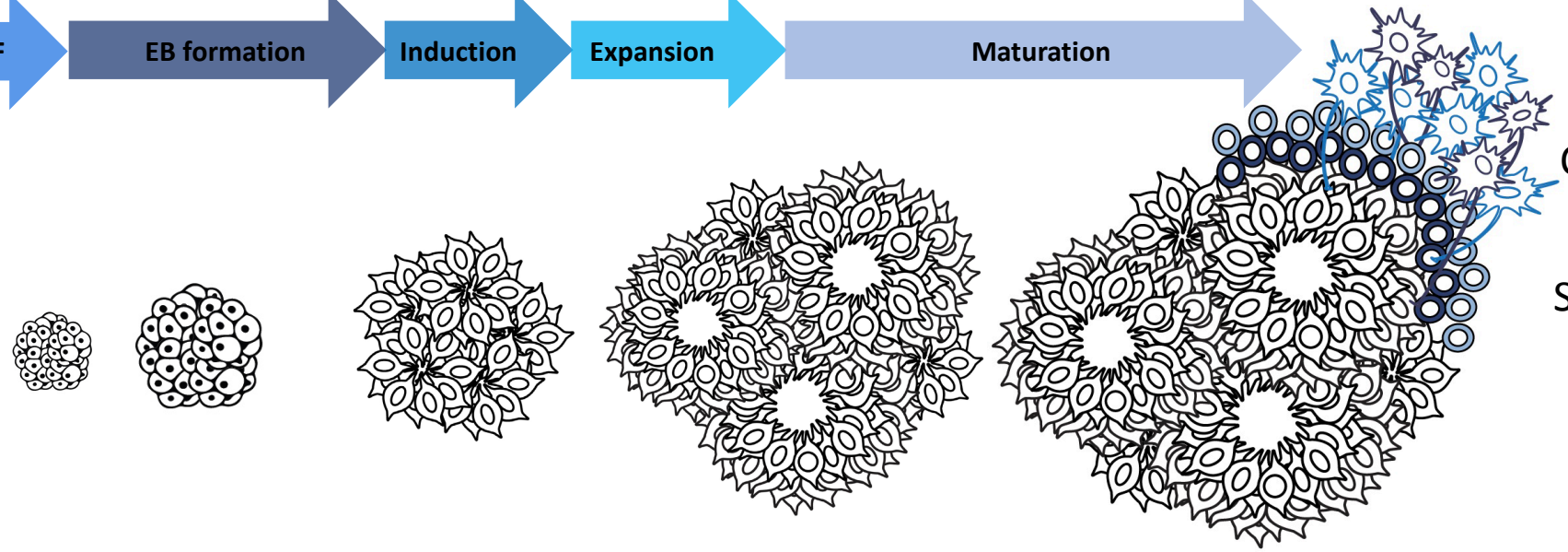


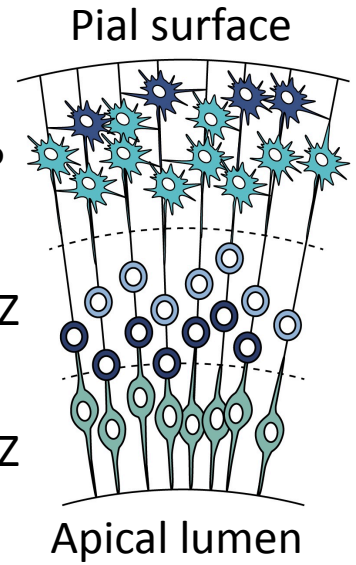
Applications of iPSC-derived neurons

- ✓ Studying mechanisms of disease
- ✓ Diagnostic: Interpretation of DNA variants
- ✓ Finding therapeutics
- ✓ Personalized medicine

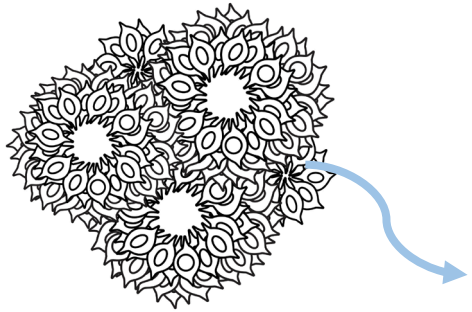
Novel applications: Cerebral organoid differentiation

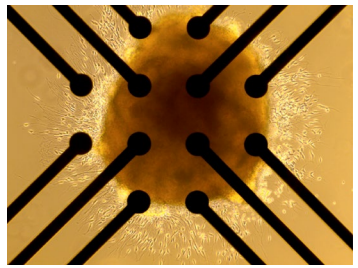


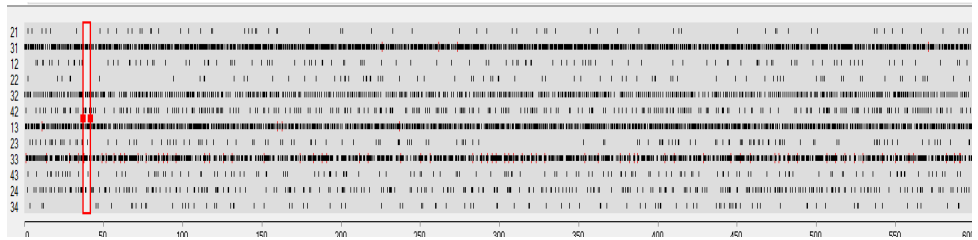




Network activity of iPSC-derived Organoids on MEAs

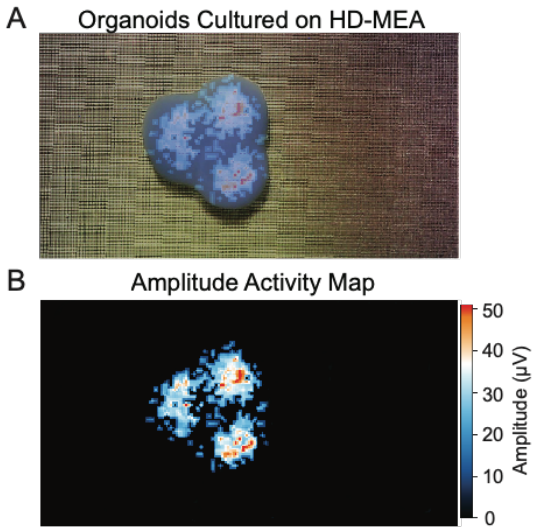




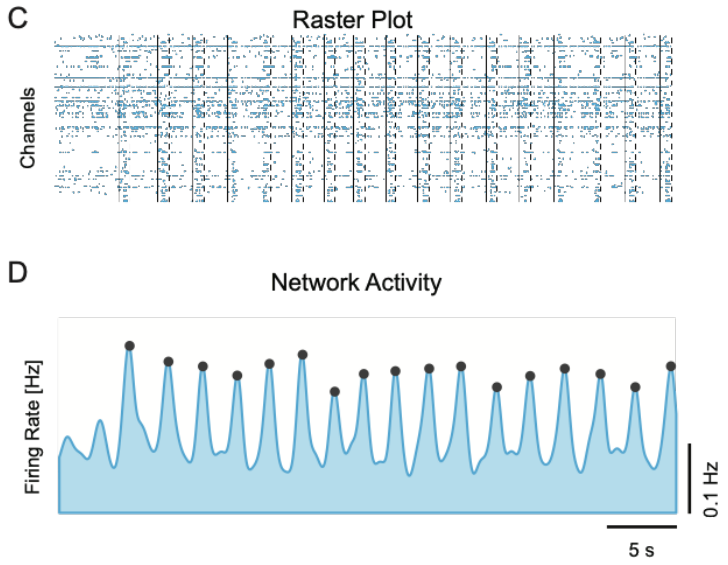


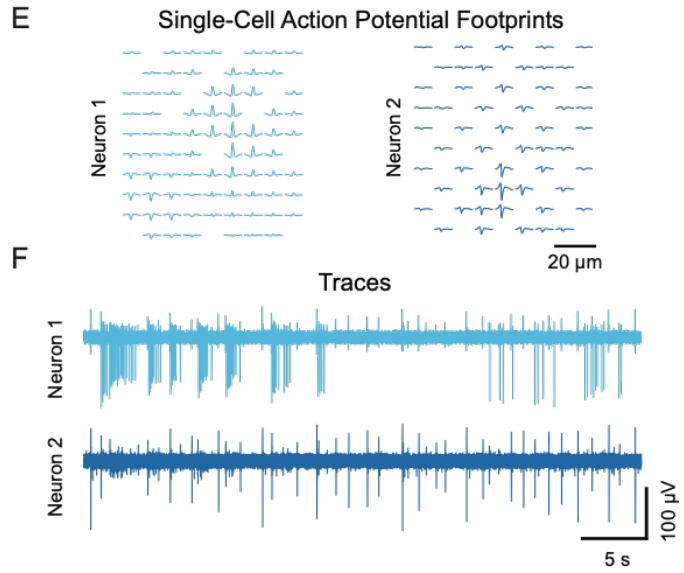
After 50 days

High-Density MEAs (courtesy of MaxWell Biosytems)



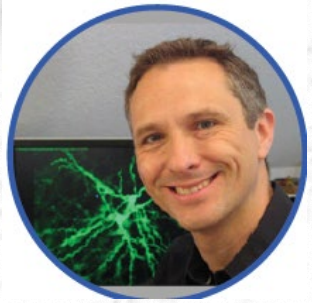
4096 electrodes





Acknowledgments

Nael Nadif Kasri



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SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

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