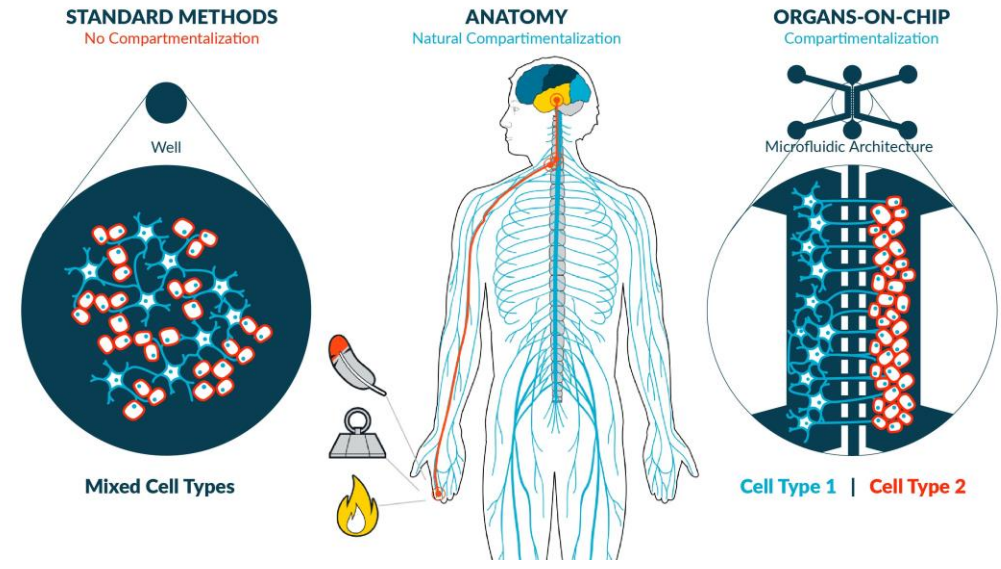




Bio-Diamond Project: Translational Brain-on-a-Chip Models for Alzheimer's Disease Drug Discovery ETAP-Lab www.etap-lab.com

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BACKGROUND



Over the past decade, few molecules brought to market slowed memory and cognitive decline of Alzheimer's patients. We present here an essential first step towards the development of innovative **organs-on-chip** (OoC) models of Alzheimer's disease.

This innovative medium-throughput brain-on-chip platform uses:

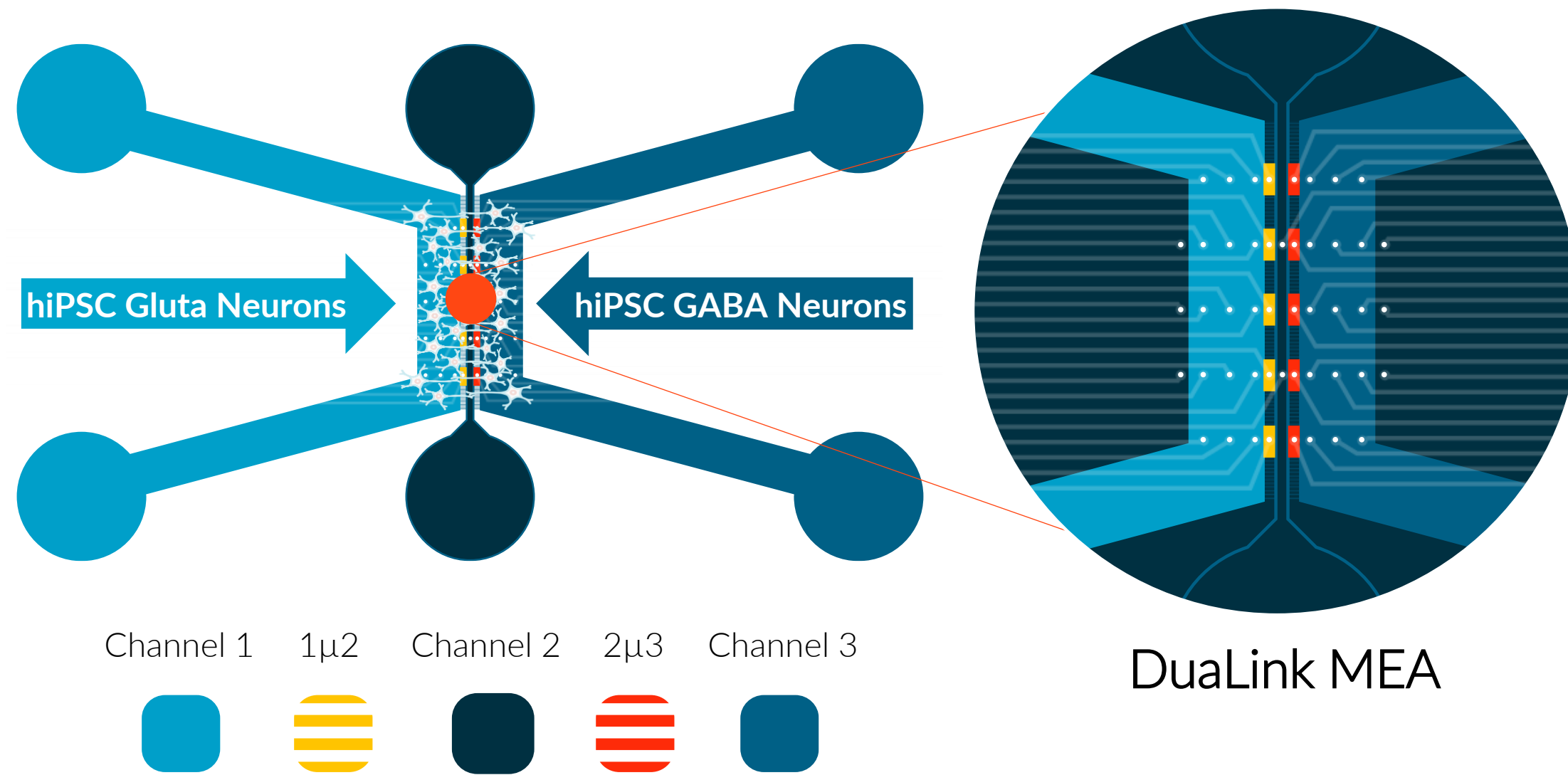
- Compartmentalized co-culture of hiPSC derived glutamatergic and GABAergic neurons in NETRI's DuaLink MEA device,
- The addition of ETAP-Lab's oligomeric forms of amyloid- β oligomers ($A\beta_{1-42}$) or Tau Oligomers (TauO).

EXPERIMENTAL DESIGN

COMPARTMENTALIZED MEA-CAPABLE OoC DEVICES.

Co-culture of hiPSCs neurons:

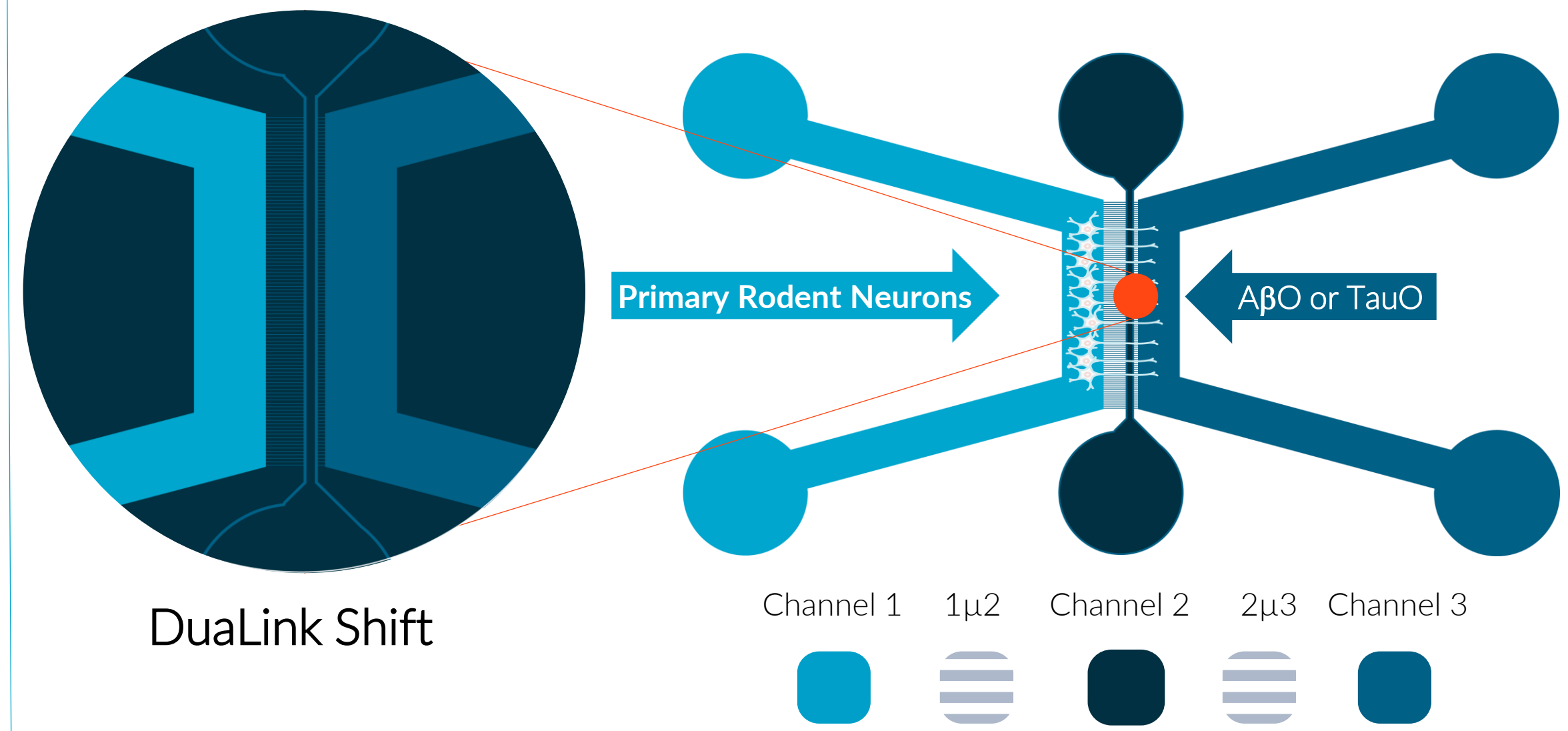
- hiPSC-derived glutamatergic neurons (BX-0300) in Channel 1
- hiPSC-derived GABAergic neurons (BX-0400) in Channel 3
- Oligomers and/or compounds applied in Channels 1, 2, or 3
- Response recorded in all channels and microchannels



A β O-INDUCED NEURODEGENERATION

Culture of primary rodent neurons:

- Primary cortical neurons in Channel 1
- At Day 21, $A\beta$ O or TauO challenge for 4 days in Channel 3
- Response analysed in Channel 1 and Channel 3: staining β -tubulin/DAPI and imaging with Operetta CLS High Content Analysis System from REVVITY

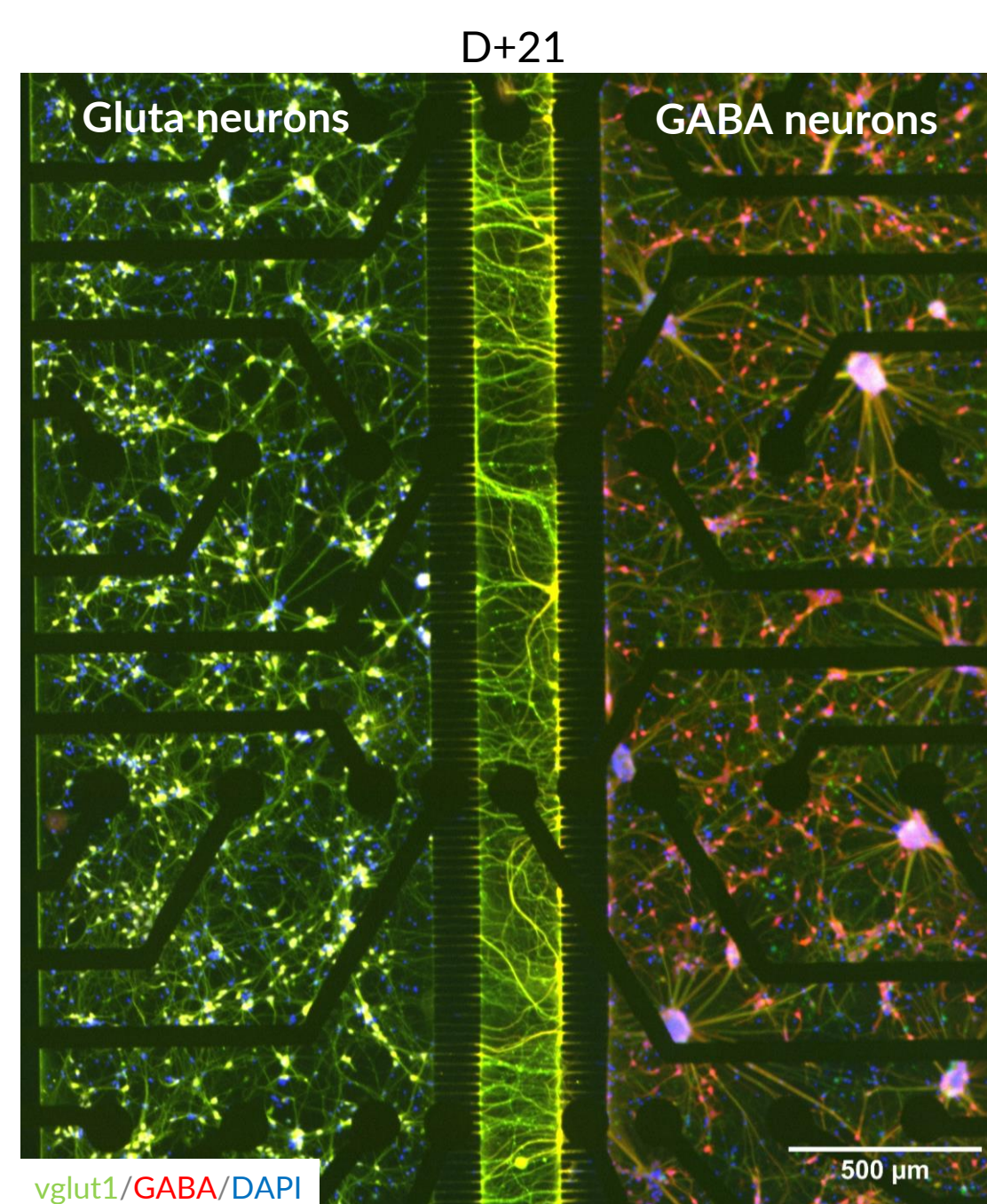
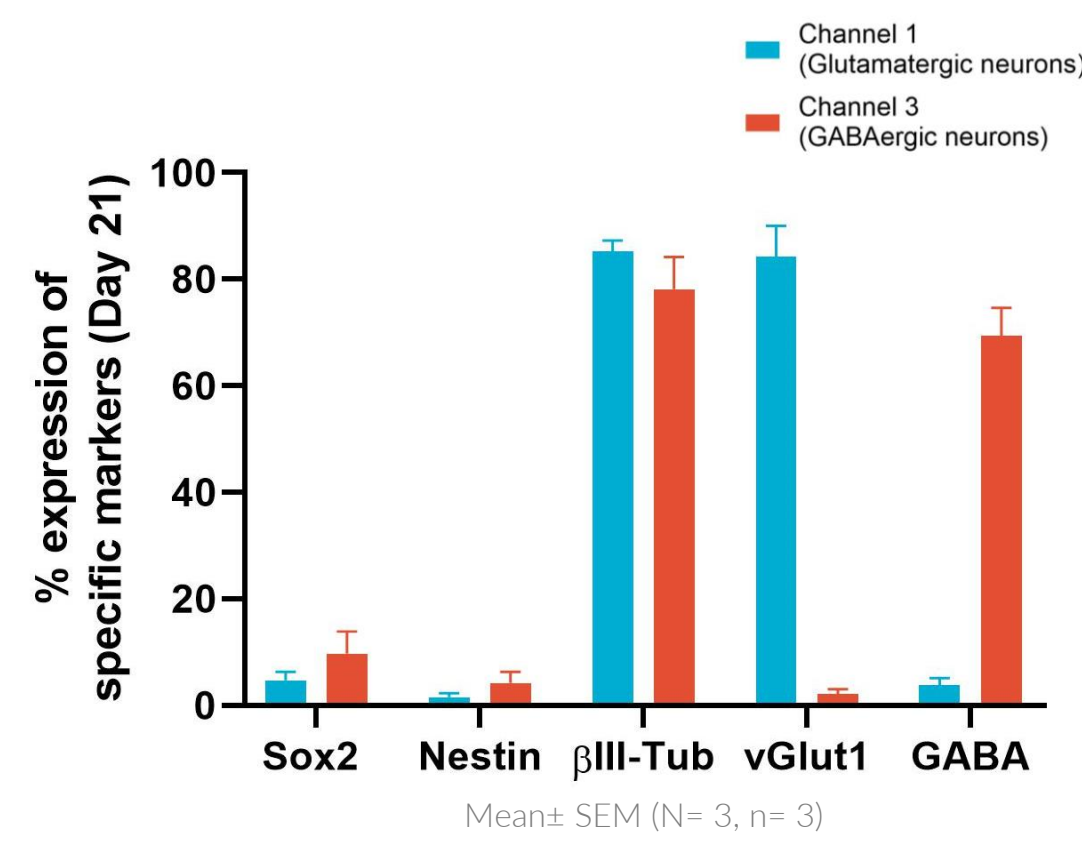


RESULTS

RELEVANT CELLULAR MODEL

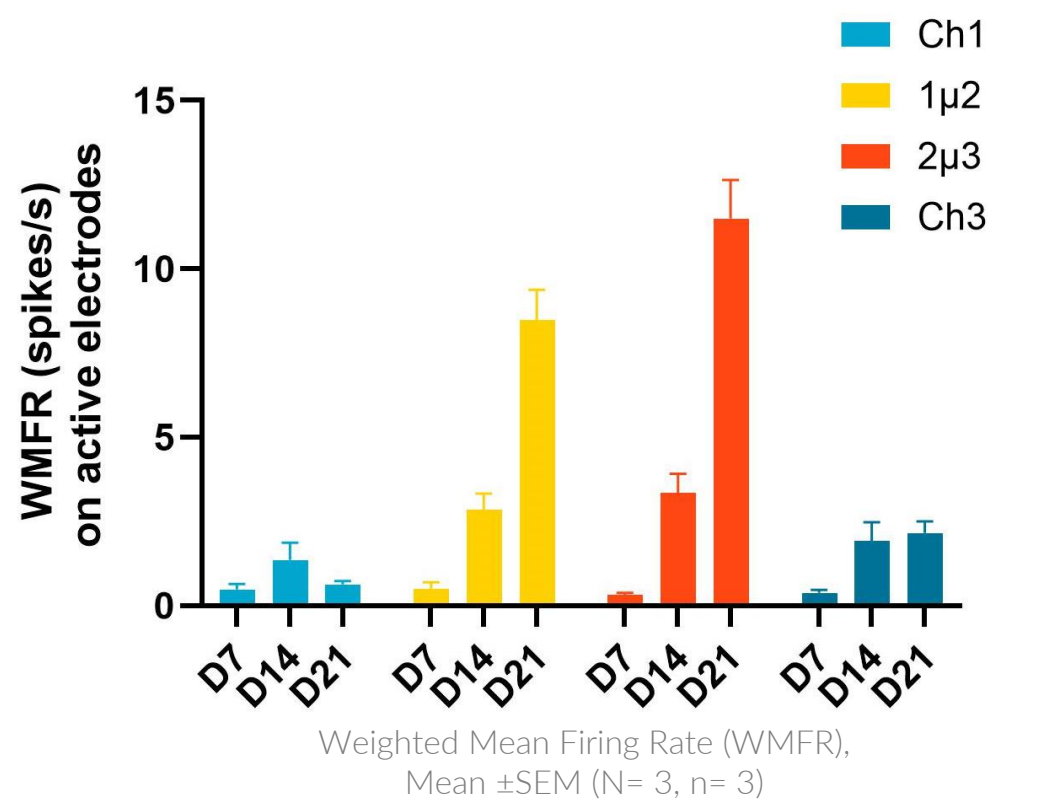
Semi-automatic quantification of marker expression using NETRI's proprietary software

- >70% phenotypic markers (D+21)
- <10% pluripotency markers (D+21)



Increase of firing rate in the neuronal networks-on-chip:

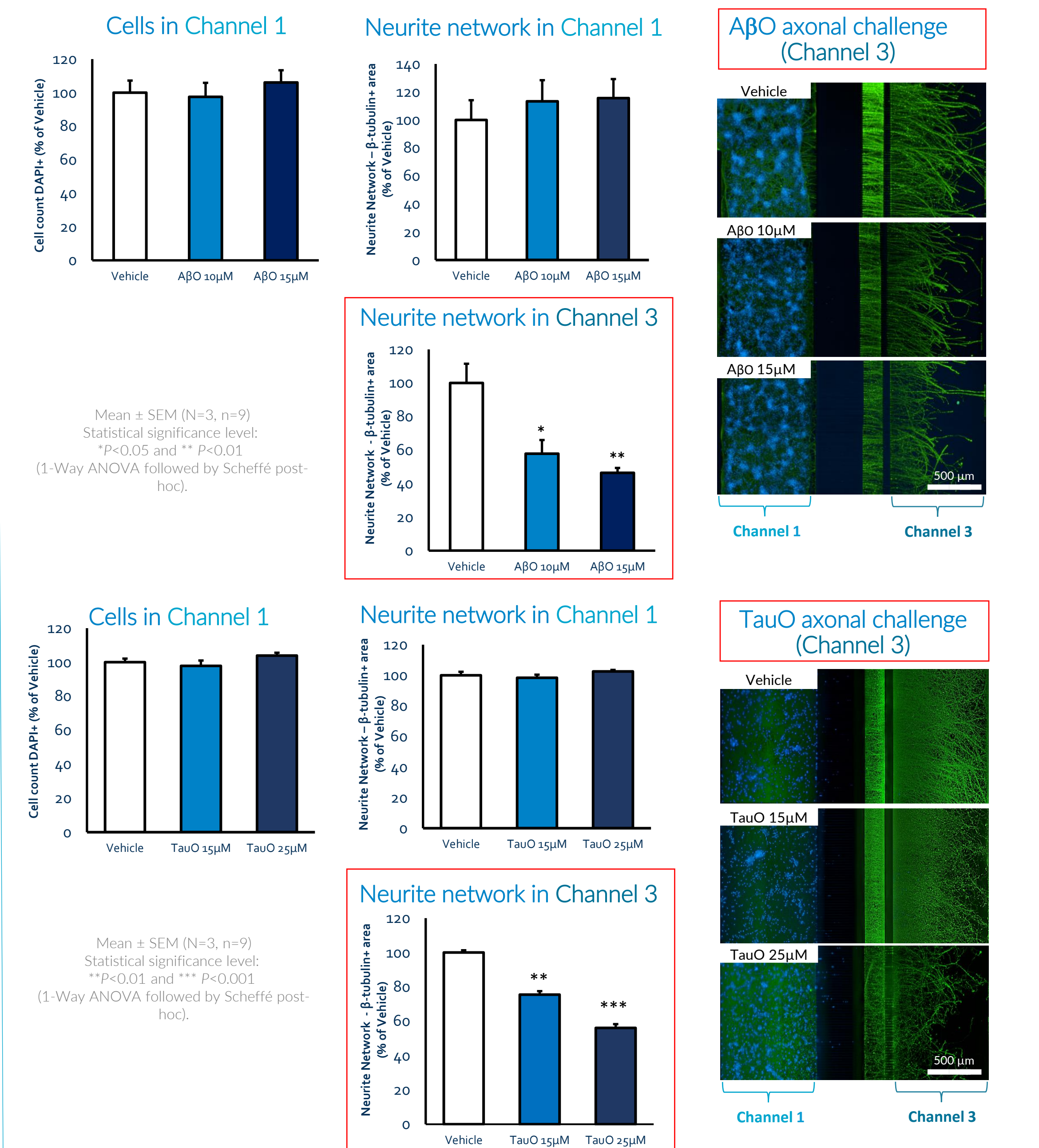
- No cell damages after three recordings (up to D+21)
- Stable recordings of electrophysiological activity from D+14



RELEVANT INJURY ALZHEIMER'S MODEL

Localized axonal degeneration

- Axonal challenge with oligomers (i.e., $A\beta$ O or TauO) induced axonal degeneration in dose-dependent manner
- Soma challenge with oligomers (same doses) did not induce neurodegeneration (*data not shown*)
- Axons are more vulnerable for $A\beta$ O/TauO-induced neurodegeneration than soma



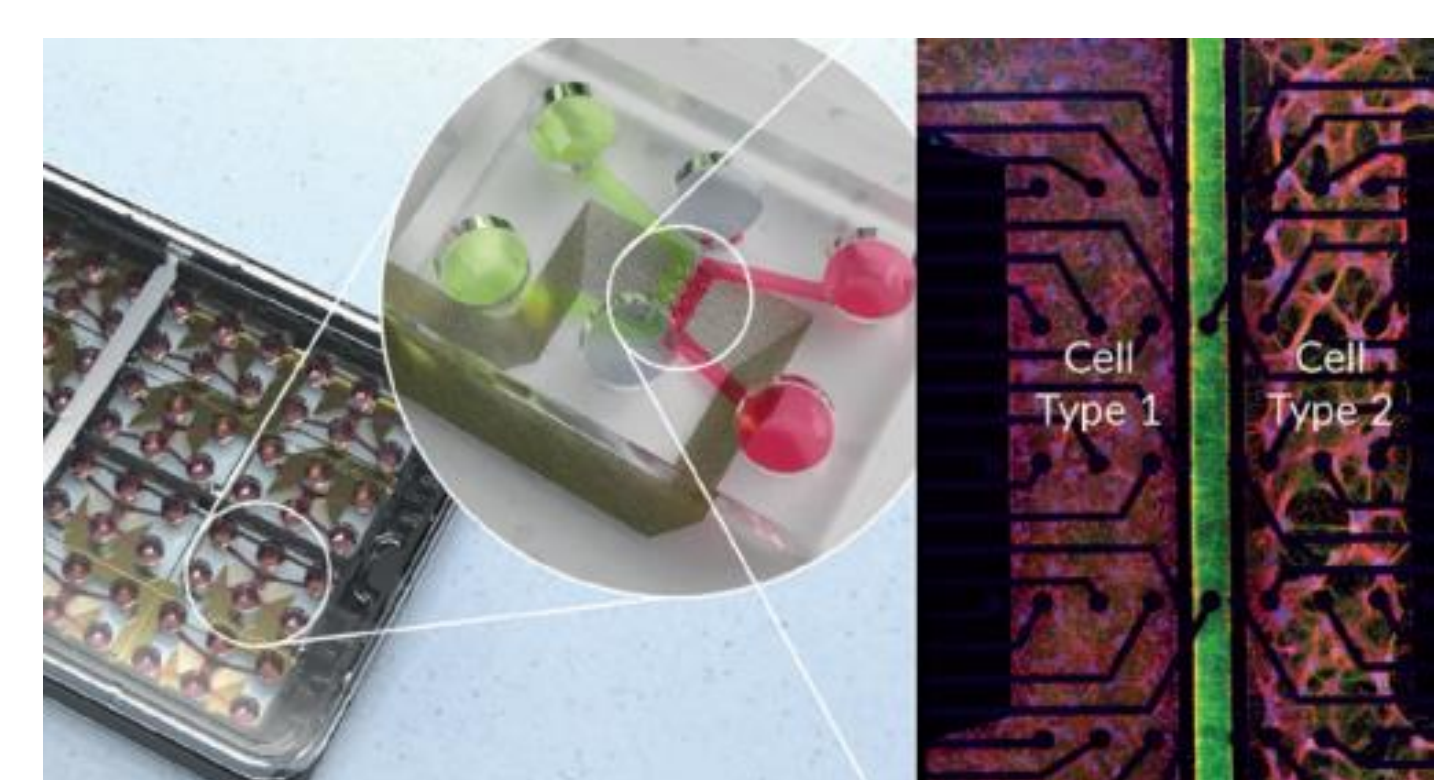
CONCLUSION & PERSPECTIVES

By combining NETRI's engineering, biological, and digital expertise with ETAP-Lab's expertise in the modeling of neurological diseases on rodent cells and hiPSCs and in the development and manufacture of neurotoxic oligomers, we have set up a model of Alzheimer's disease-on-chip:

- Standard Operating Protocol of human glutamatergic and GABAergic neurons co-culture
- Fully differentiation and maturation of human neurons on-chip
- Protocol to induce $A\beta$ O or TauO injuries on-chip with rodent cells and hiPSC-derived neurons

Then, we will focus on the injury model on hiPSCs and the extraction of digital signatures, using our UpLink™ utility software, to finally add reference compounds and compounds of interest.

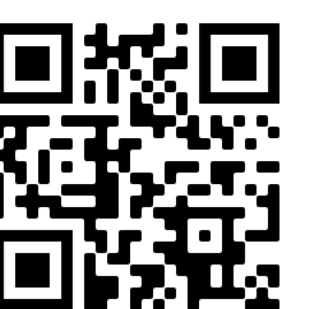
Our Brain-on-Chip platform will offer pharmaceutical companies and researchers a new model for preclinical studies, enabling them to reproduce complex neuropathological phenomena finely.



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