

ENGINEERING APPROACHES TO CONTROL BIOLOGICAL RESPONSES *‘ENGINEERING NEURAL CIRCUITRY’*

Eric Hill, Paul Roach, Willow Hall, Dan Merryweather

www.neuchip.eu

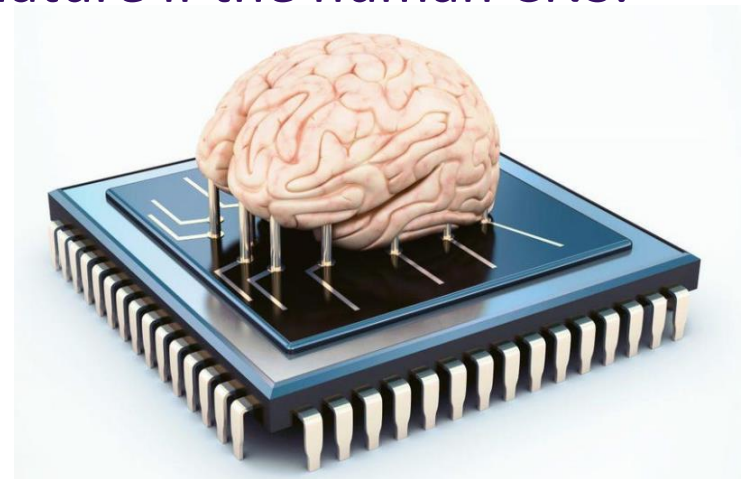
Dr Eric Hill

Department of Chemistry

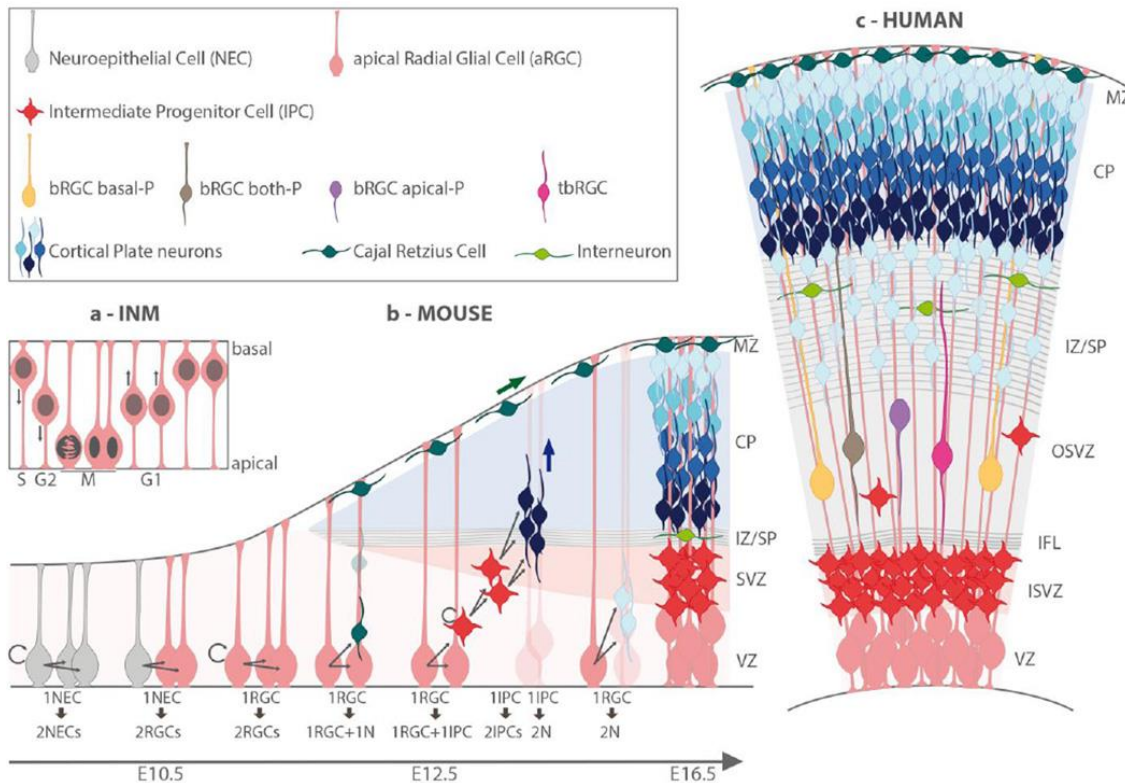
e.j.hill@lboro.ac.uk

‘Brain’ on chip devices

- Emergent organ-on-a-chip technologies could transform R&D efficiency by bridging the **gap between preclinical testing and human trials** through better predictive models, significantly impacting R&D costs.
- Human ‘Brain on a chip models’ for drug screening present a **huge challenge**, due to the complex nature of the human CNS.

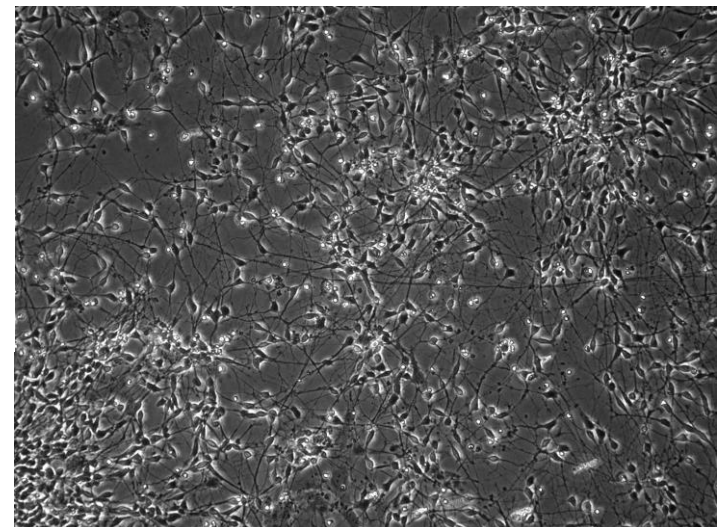
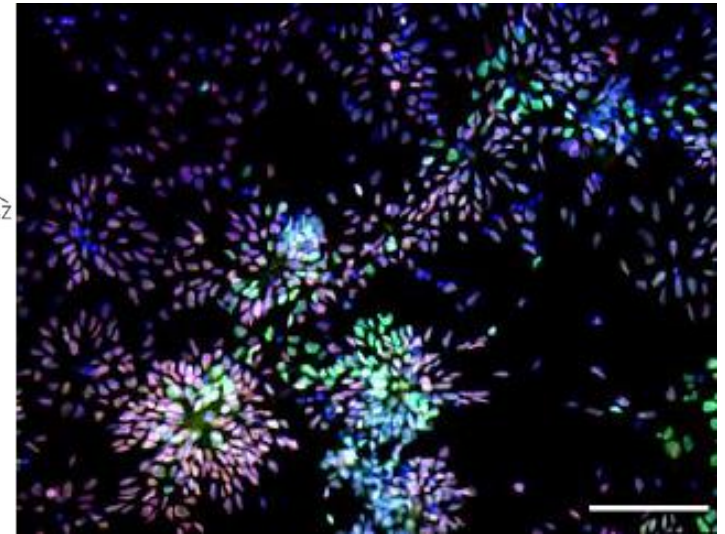


Generating neurons from iPSC

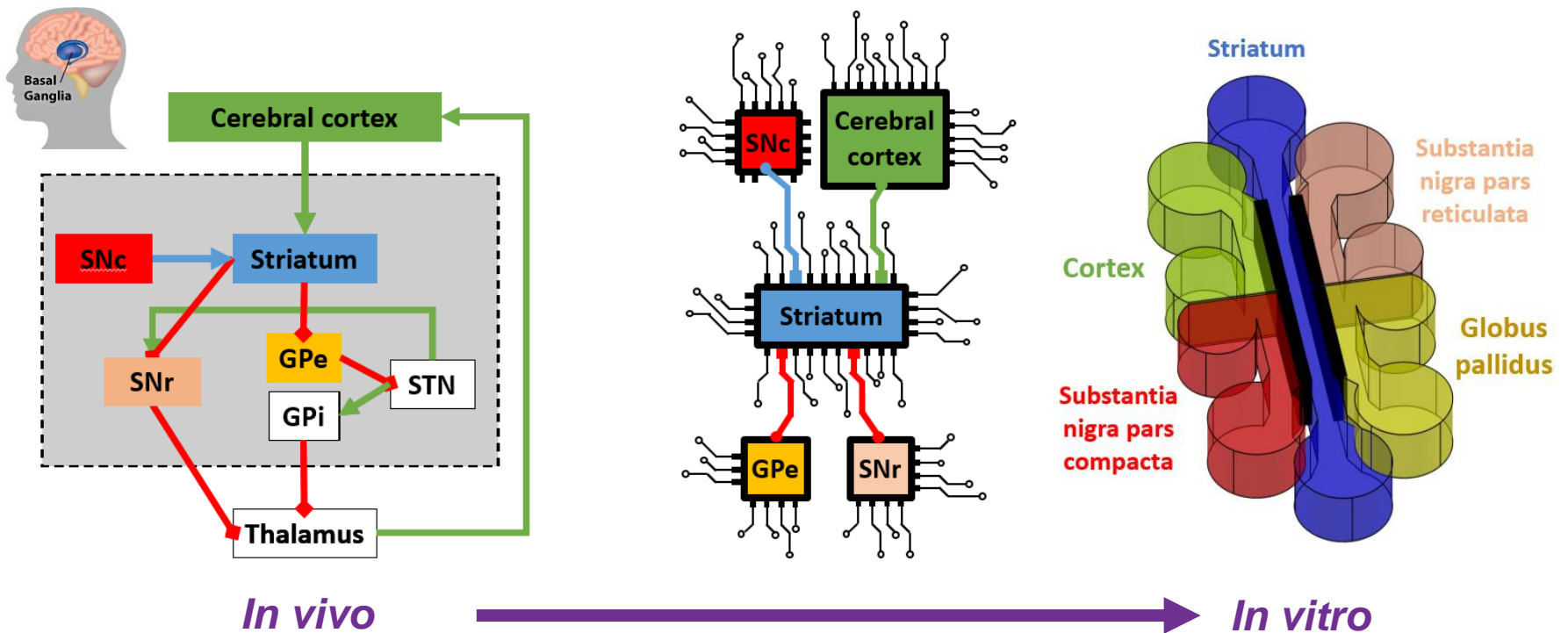


Jiang and Nardelli 2016

Issues with network architecture in 2D

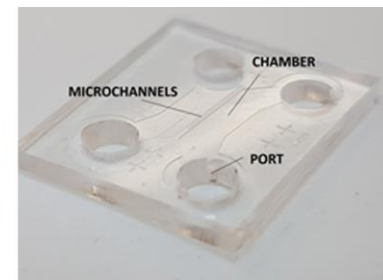
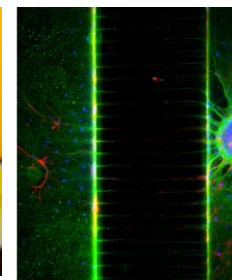
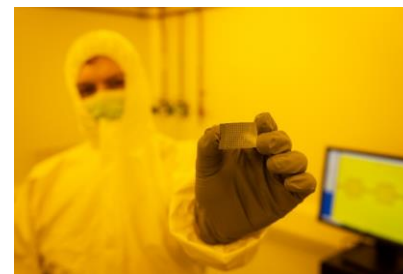
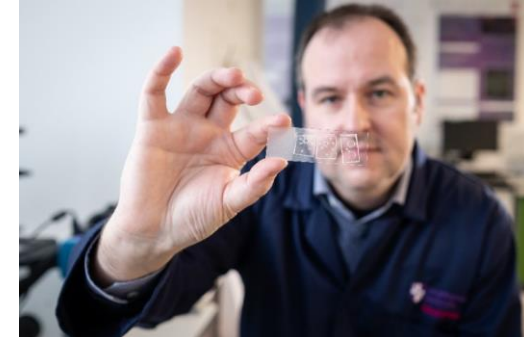
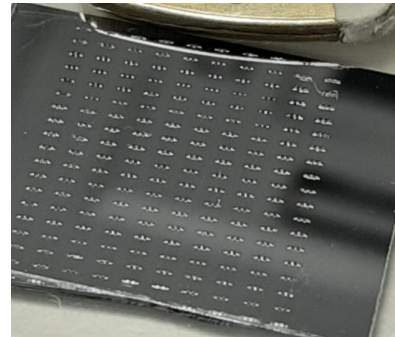
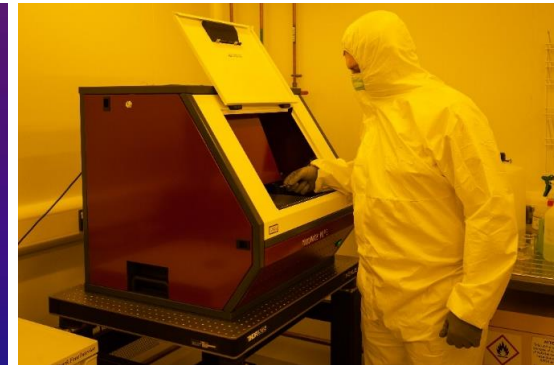
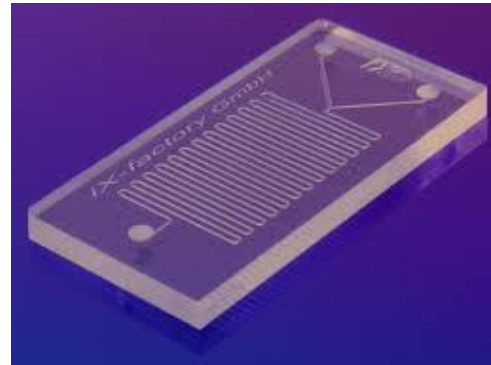


Neural Circuit Model



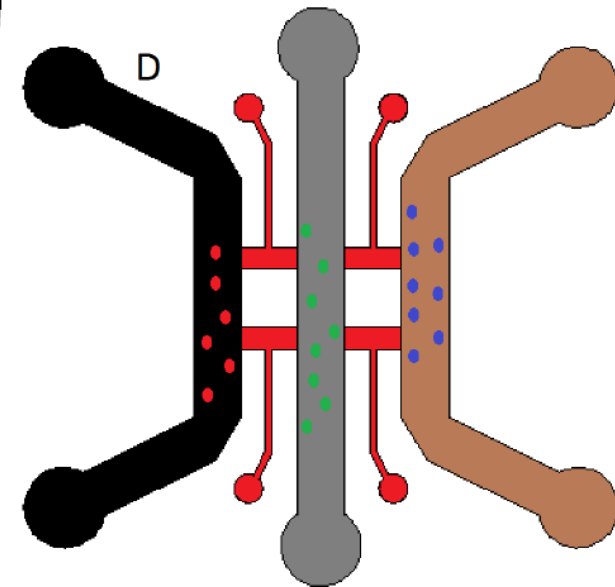
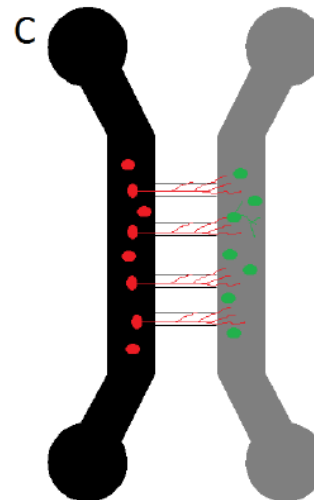
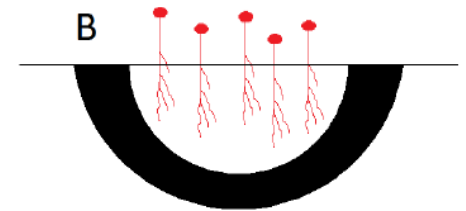
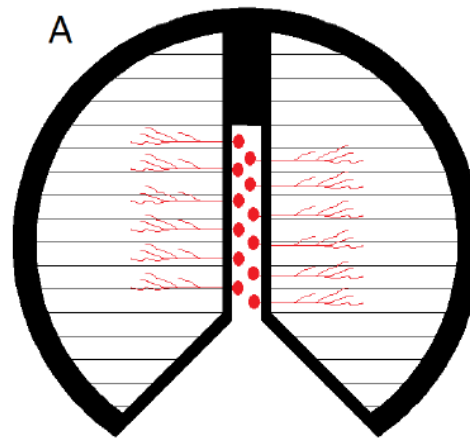
Microfluidic devices

- Microfluidic (microfabricated) *organ-on-a-chip* devices
- *The design to device process*
- *Considerations: features, chemistry...*

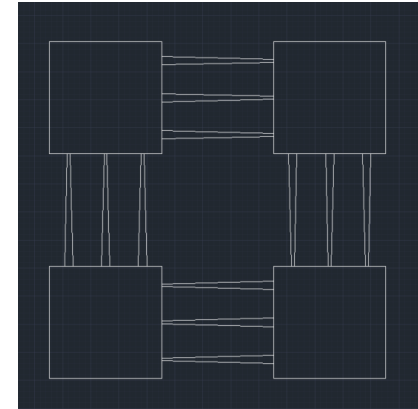
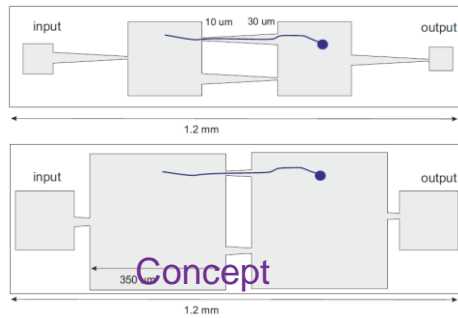


Micro-device Designs for Neural Engineering

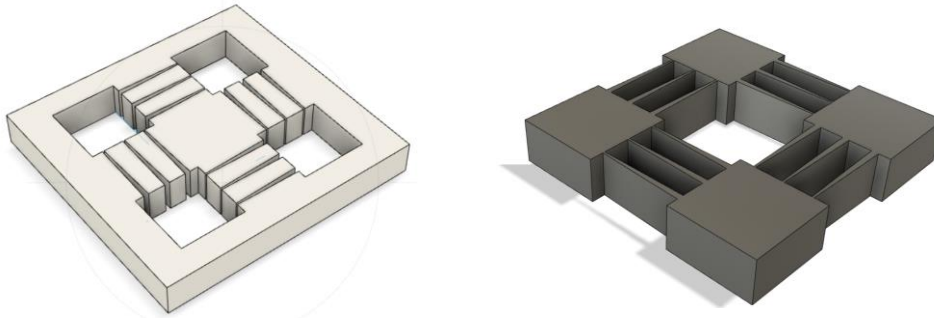
- Separation of multiple cell populations
- Directed growth
- Directed connectivity
- Transport of cellular components/ biological fluids/ disease progression...
- Drug testing '*normal*' '*tissue*' function



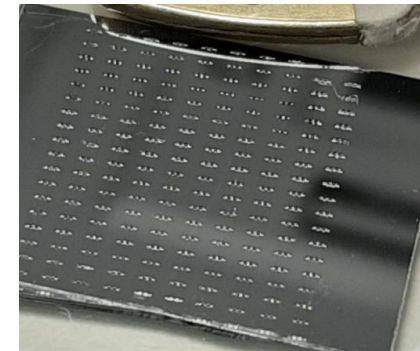
The Design Process



CAD



3D CAD Template

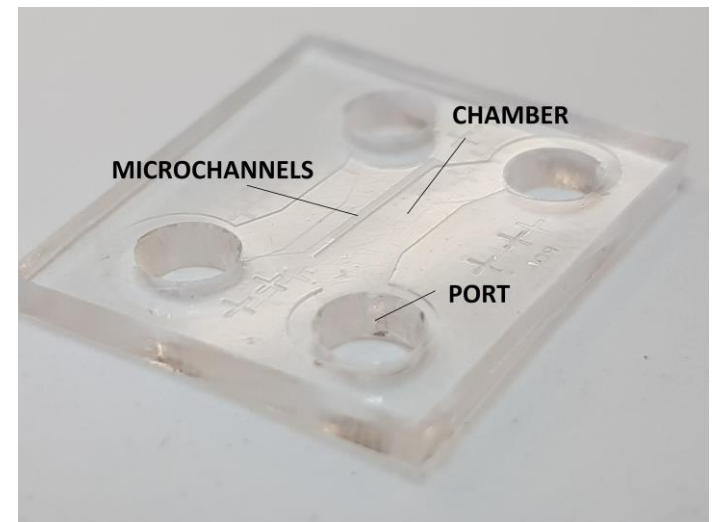
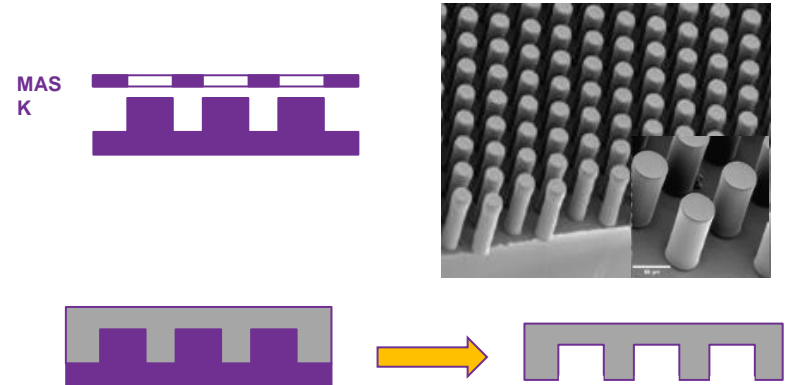
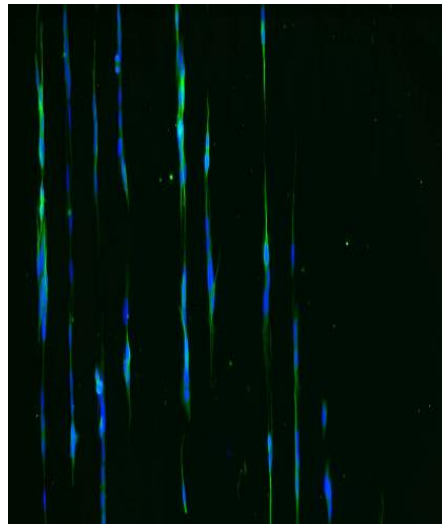
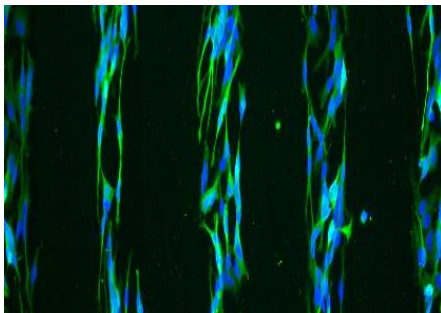
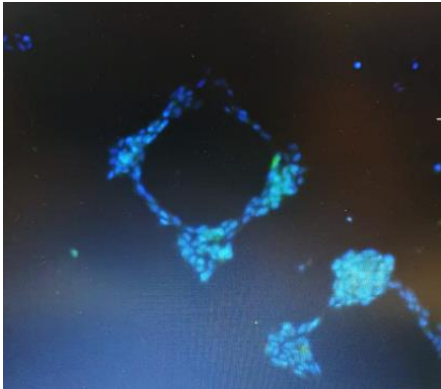


Device

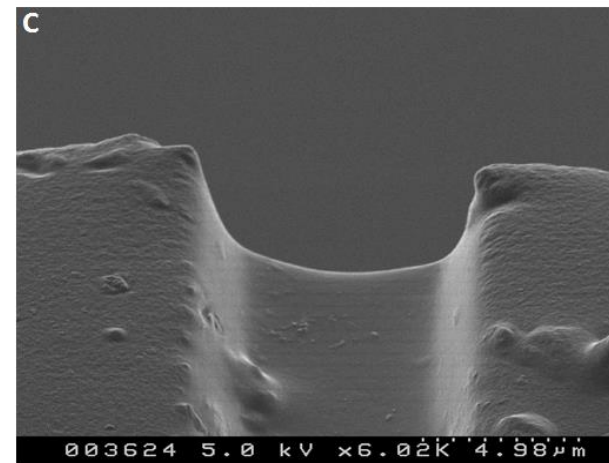
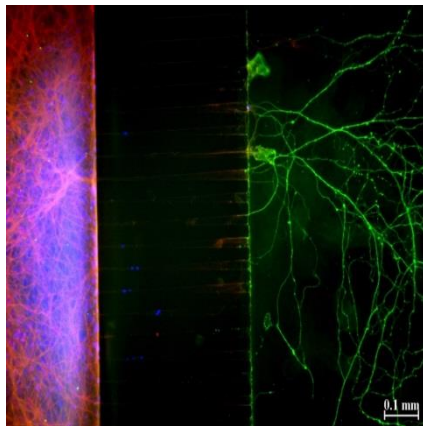
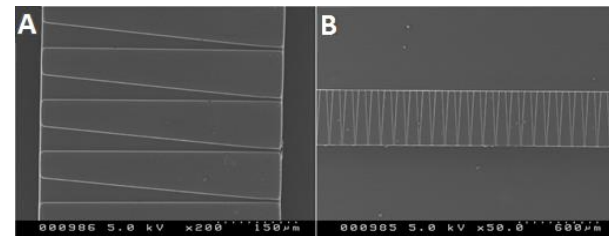
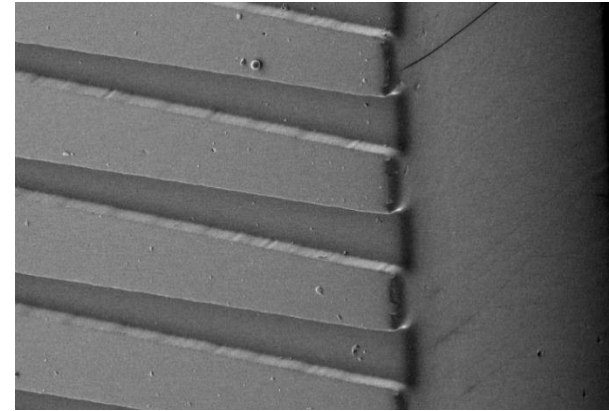
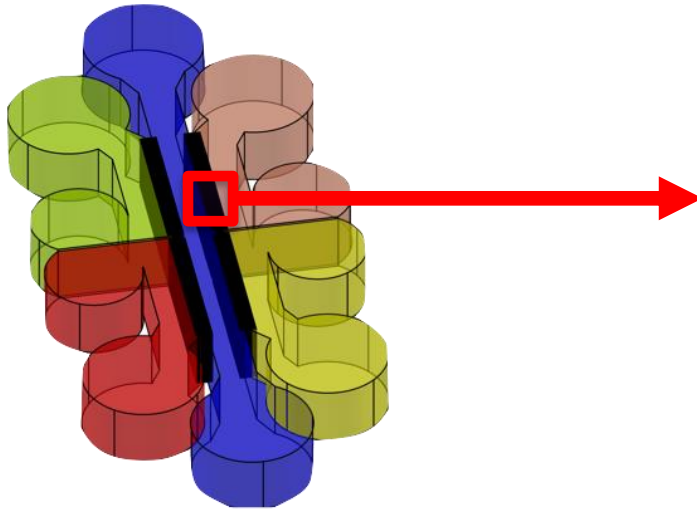
Directing cell attachment

Facilities

- Cannon PLA500 Photolith (~5 μm resolution)
- DMO ML3 Direct Write Photolithography (< 1 μm)
- Nano Frazer Thermal AFM lithography (nm)

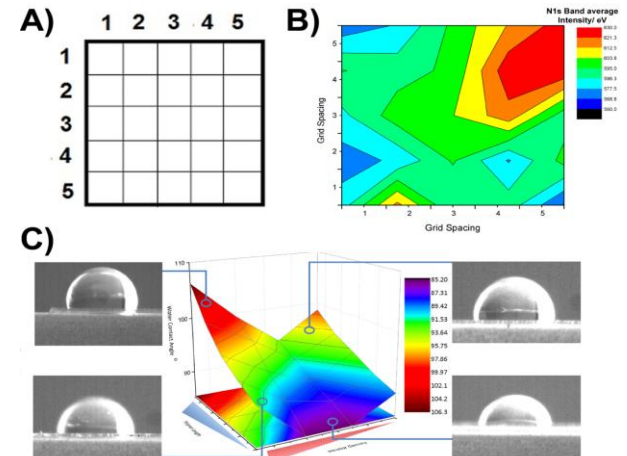
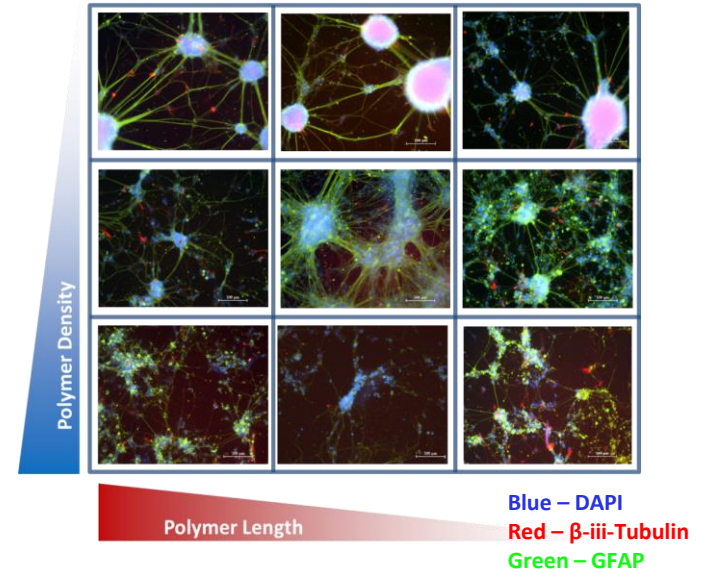
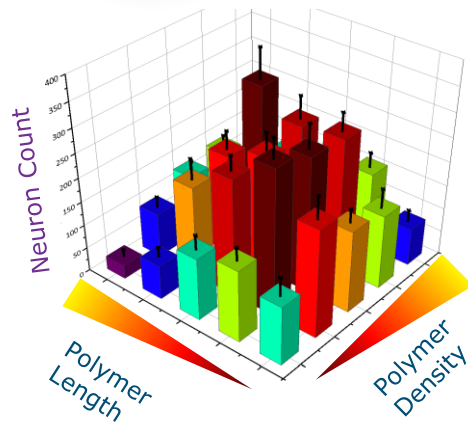
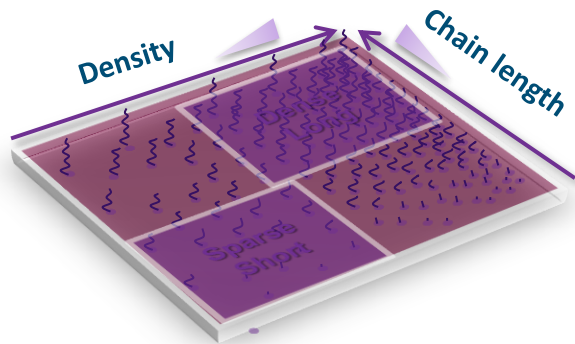


Physical design

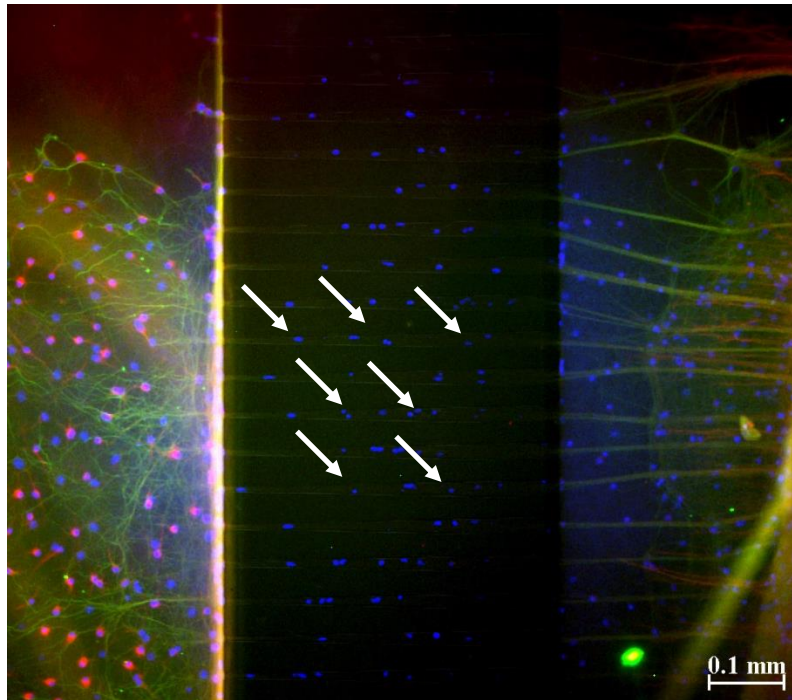


Combinatorial Platforms

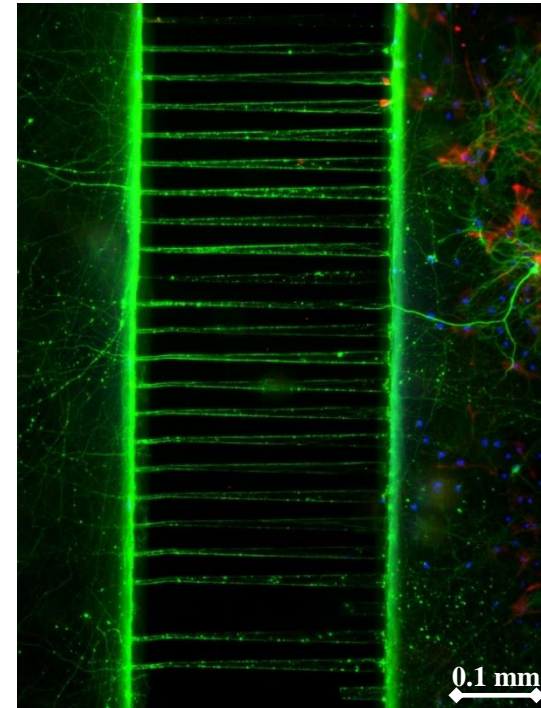
- High-throughput screening
- Chemically dictate response
- Spatially control differentiation



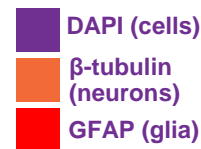
Surface chemical coatings



PDL

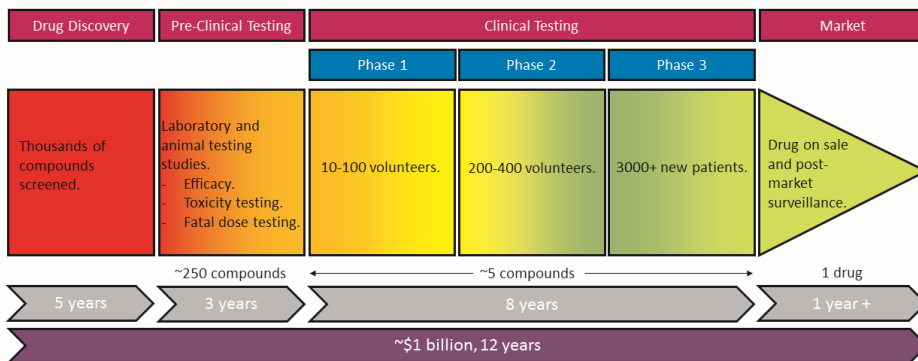
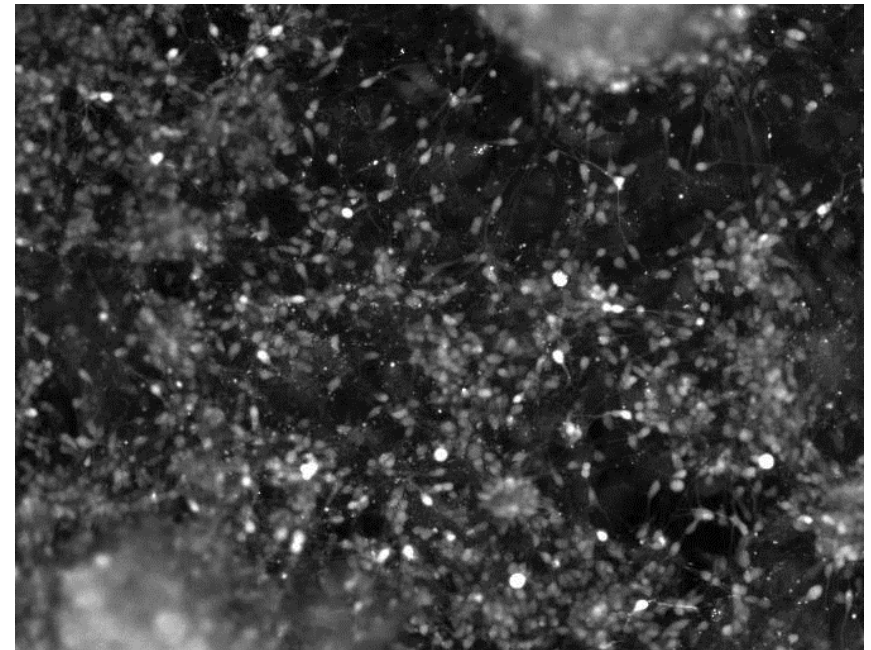
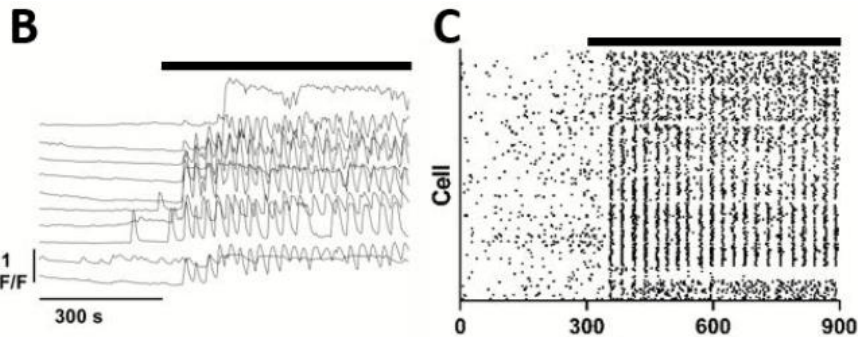


PEI/PDL



PEI reduces cell migration

Drug toxicity testing: Seizure like events



In vitro Models for Seizure- Liability Testing Using Induced Pluripotent Stem Cells

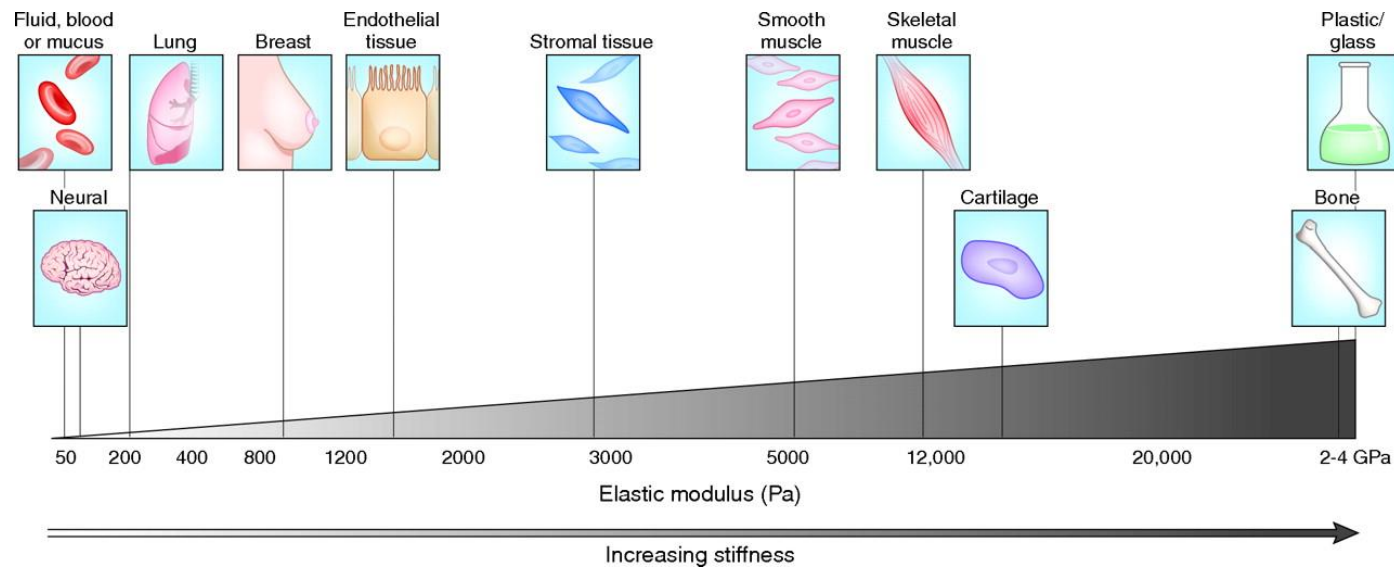
Alastair I. Grainger, Marianne C. King, David A. Nagel, H. Rheinallt Parri, Michael D. Coleman and Eric J. Hill*

3D cell culture: Challenges

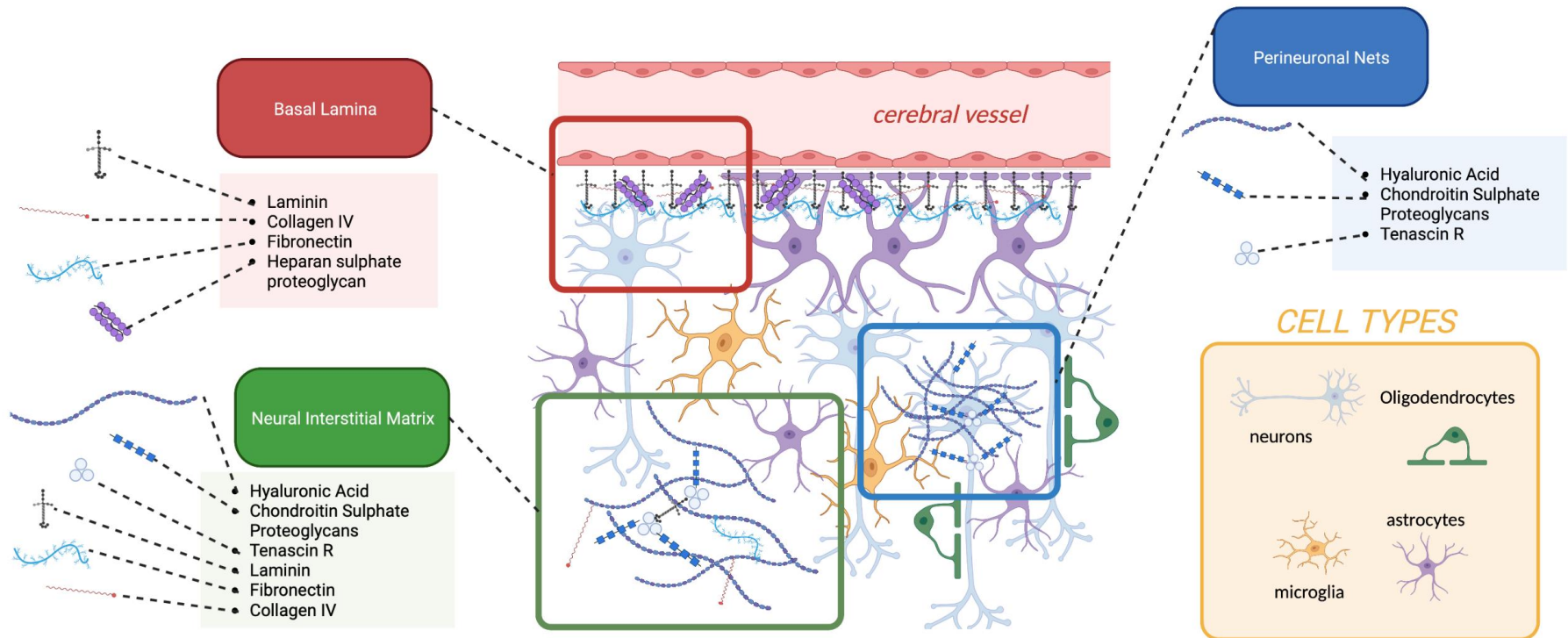
The brain is soft

Tissue culture plastic is stiff

How does that impact cellular behaviour?



The Brain Extracellular Matrix



Gallagher et al in preparation

Tissue engineering: Hydrogel choice and impact of crosslinker



Basement membrane matrix secreted by Engelbreth-Holm-Swarm mouse sarcoma cells

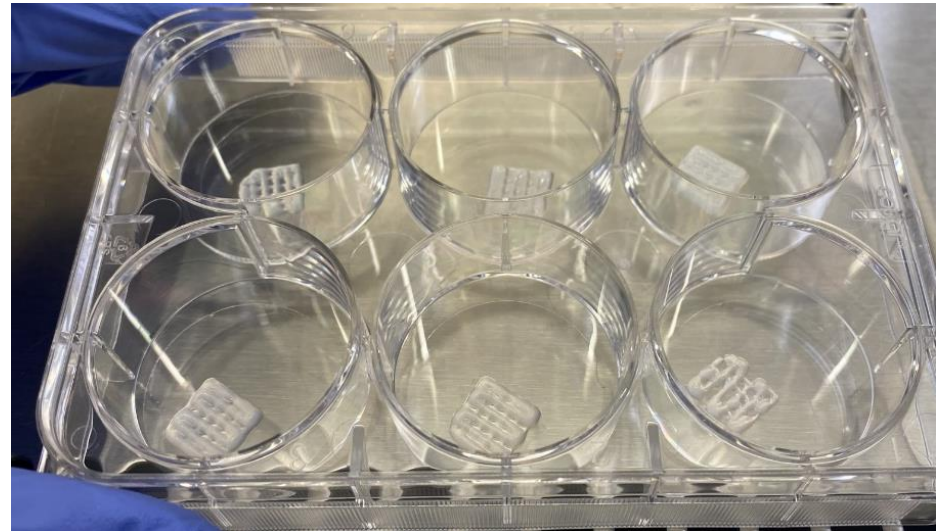


Gelatin turns to a transparent elastic hydrogel upon cooling below $\sim 35\text{ }^{\circ}\text{C}$,

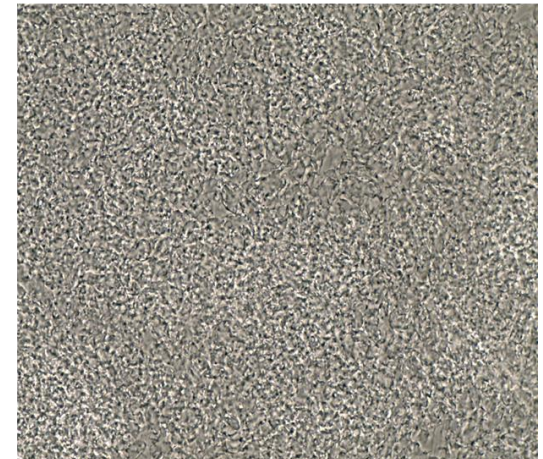
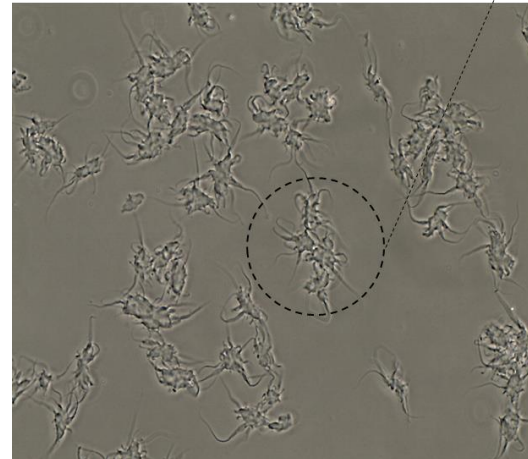
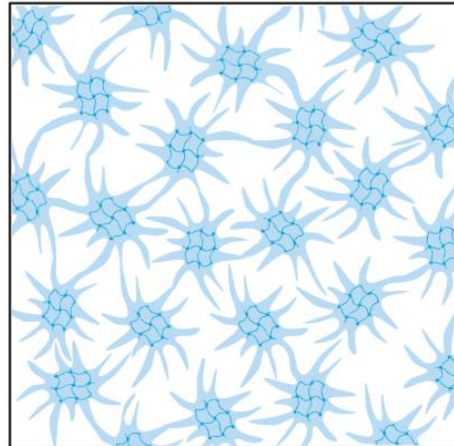
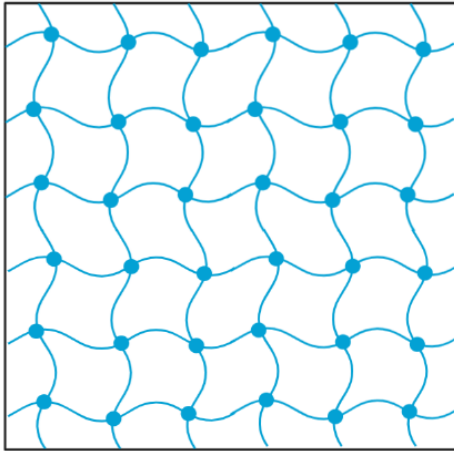


Aqueous solution of alginate can be cross-linked by various divalent and trivalent cations such as Ca^{2+}

BIO X extrusion printer



Bulk gel vs Shear thinning gel

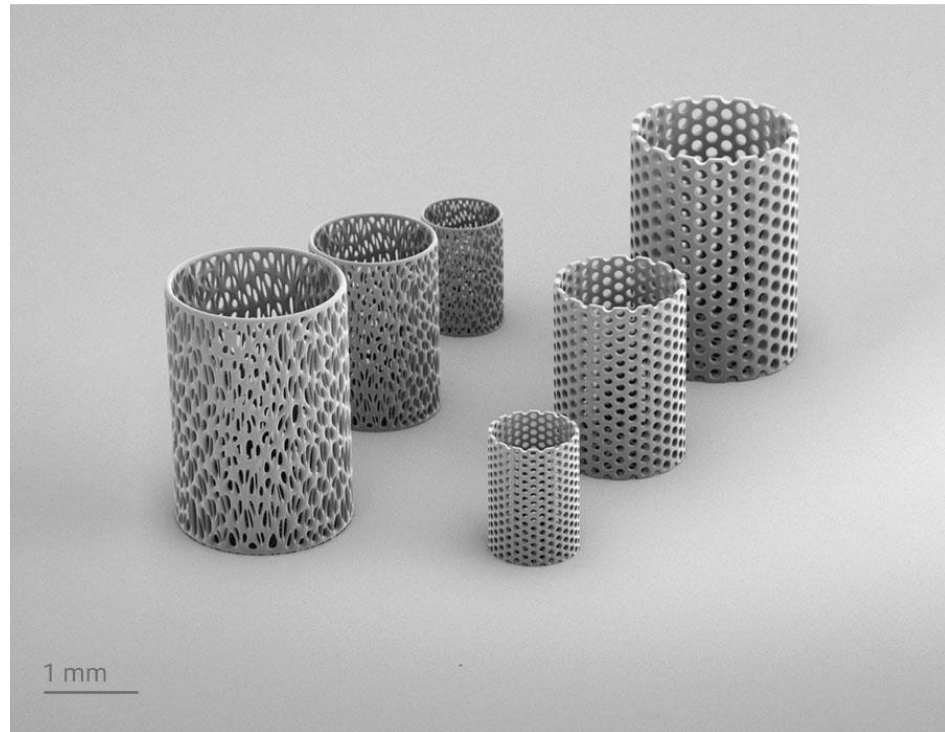


Light based printing: BIONOVA X



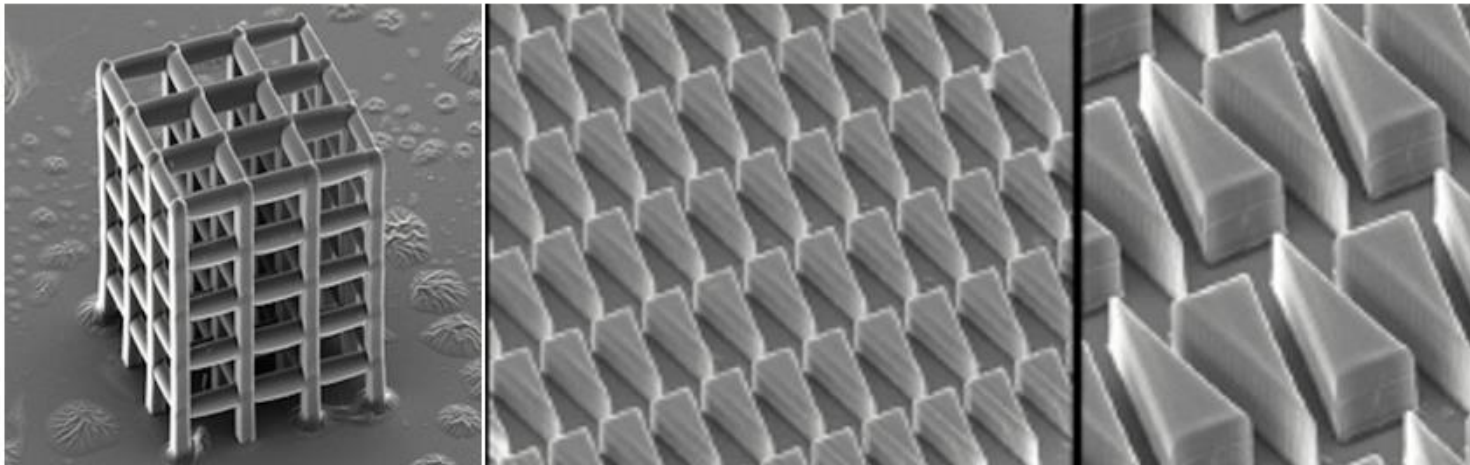
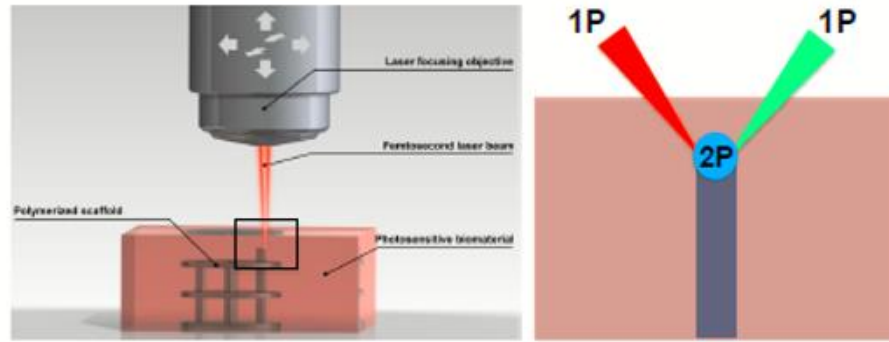
DLP bioprinting

Quantum X Bio



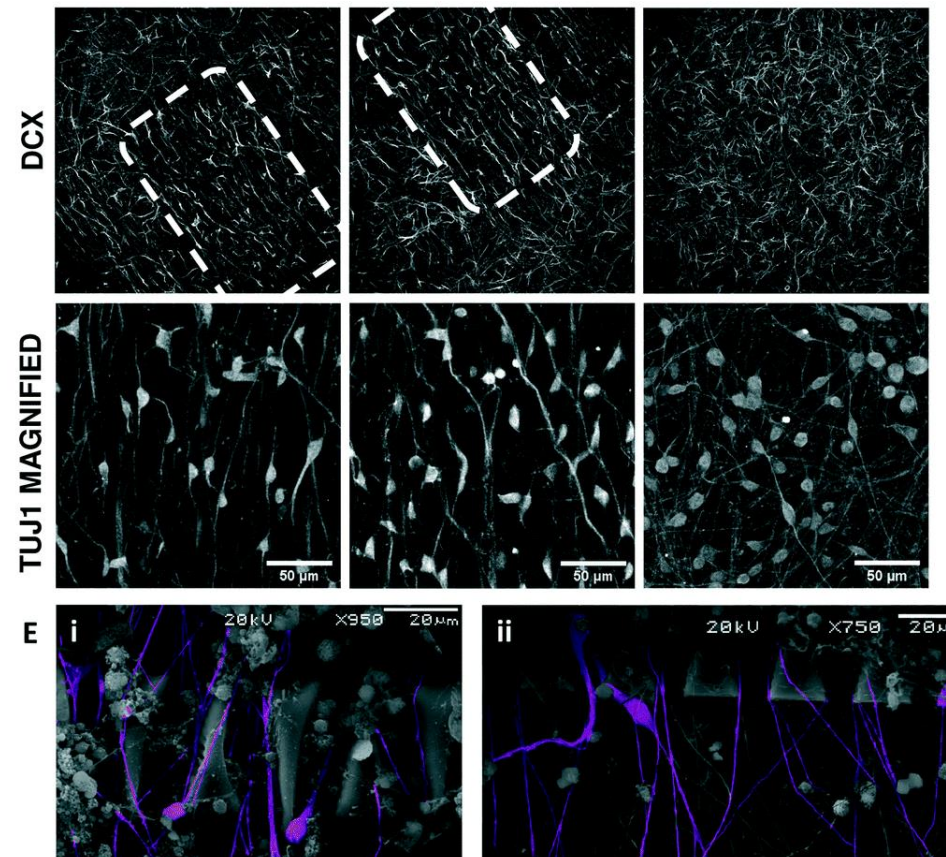
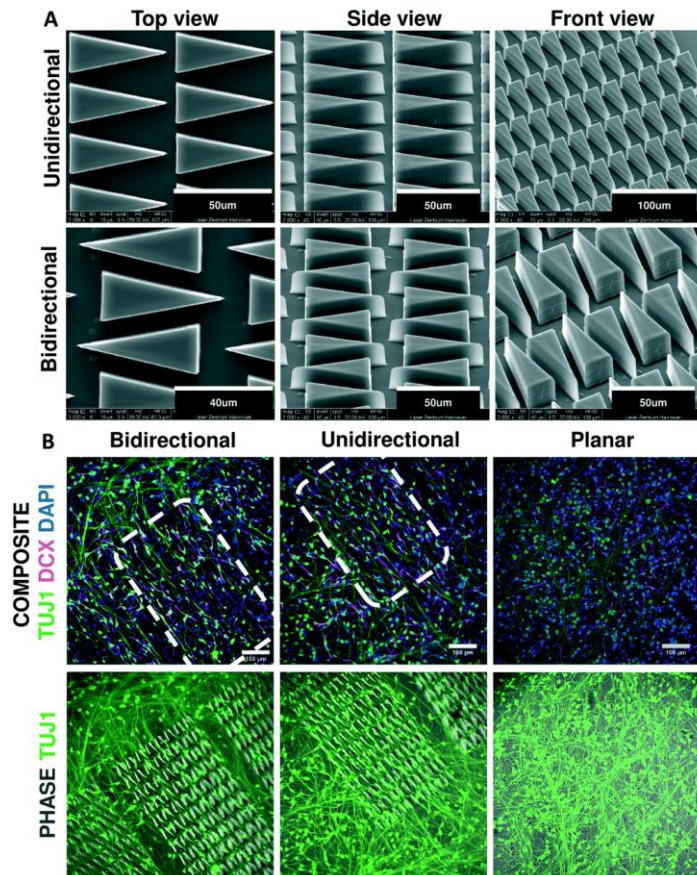
Layer-by-layer 3D printing based on Two-Photon Polymerization 2PP

Topographical features

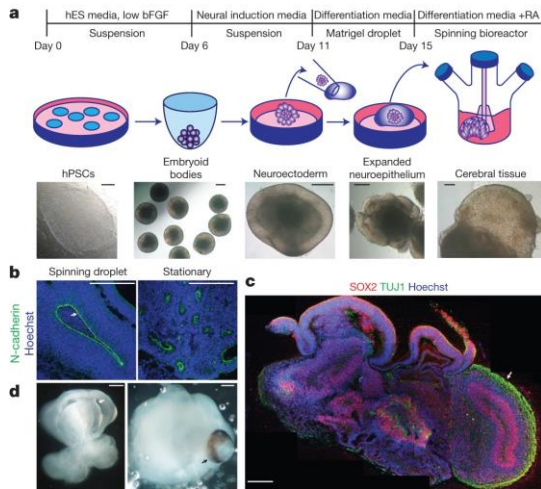


Crowe, J. A., El-Tamer, A., Nagel, D., Koroleva, A. V., Madrid-Wolff, J., Olarte, O. E., Sokolovsky, S., Estevez-Priego, E., Ludl, A.-A., Soriano, J., Loza-Alvarez, P., Chichkov, B. N., Hill, E. J., Parri, H. R., & Rafailov, E. U. (2020). Development of two photon polymerised scaffolds for optical interrogation and neurite guidance of human iPSC-derived cortical neuronal networks. *Lab on a Chip*, 20(10), 1791-1806.

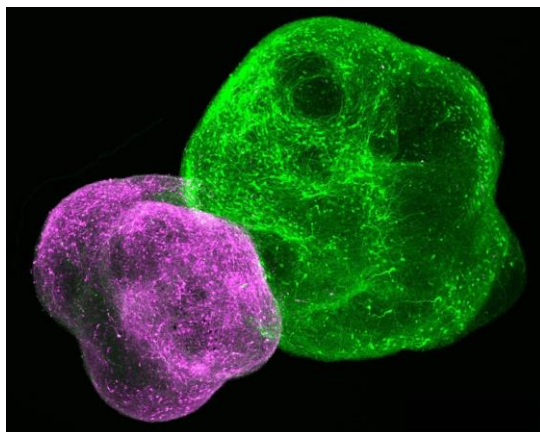
Influence of topography on neuronal growth



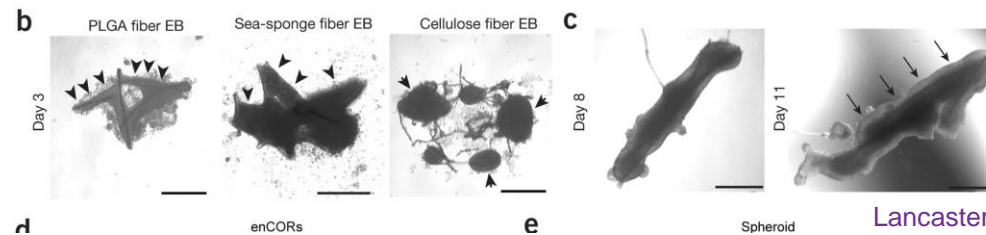
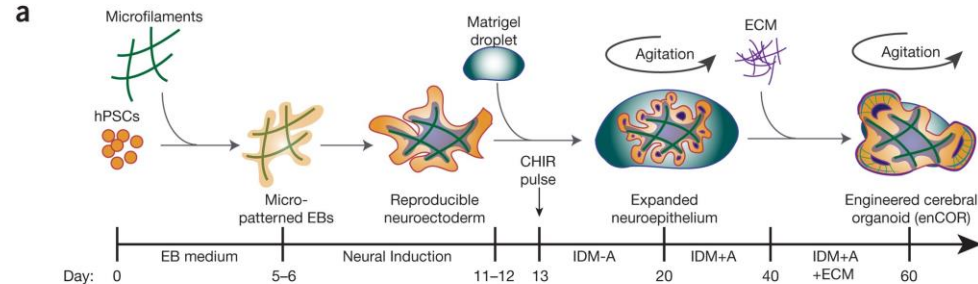
Engineering organoids (Challenges)



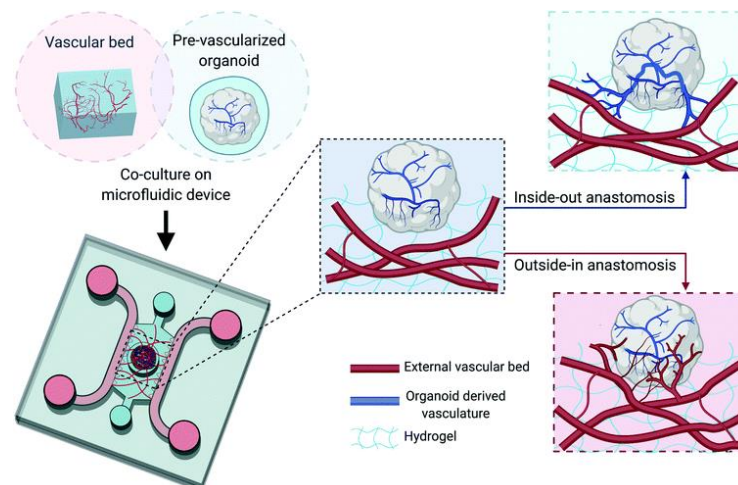
Lancaster et al 2013



Miura et al 2020

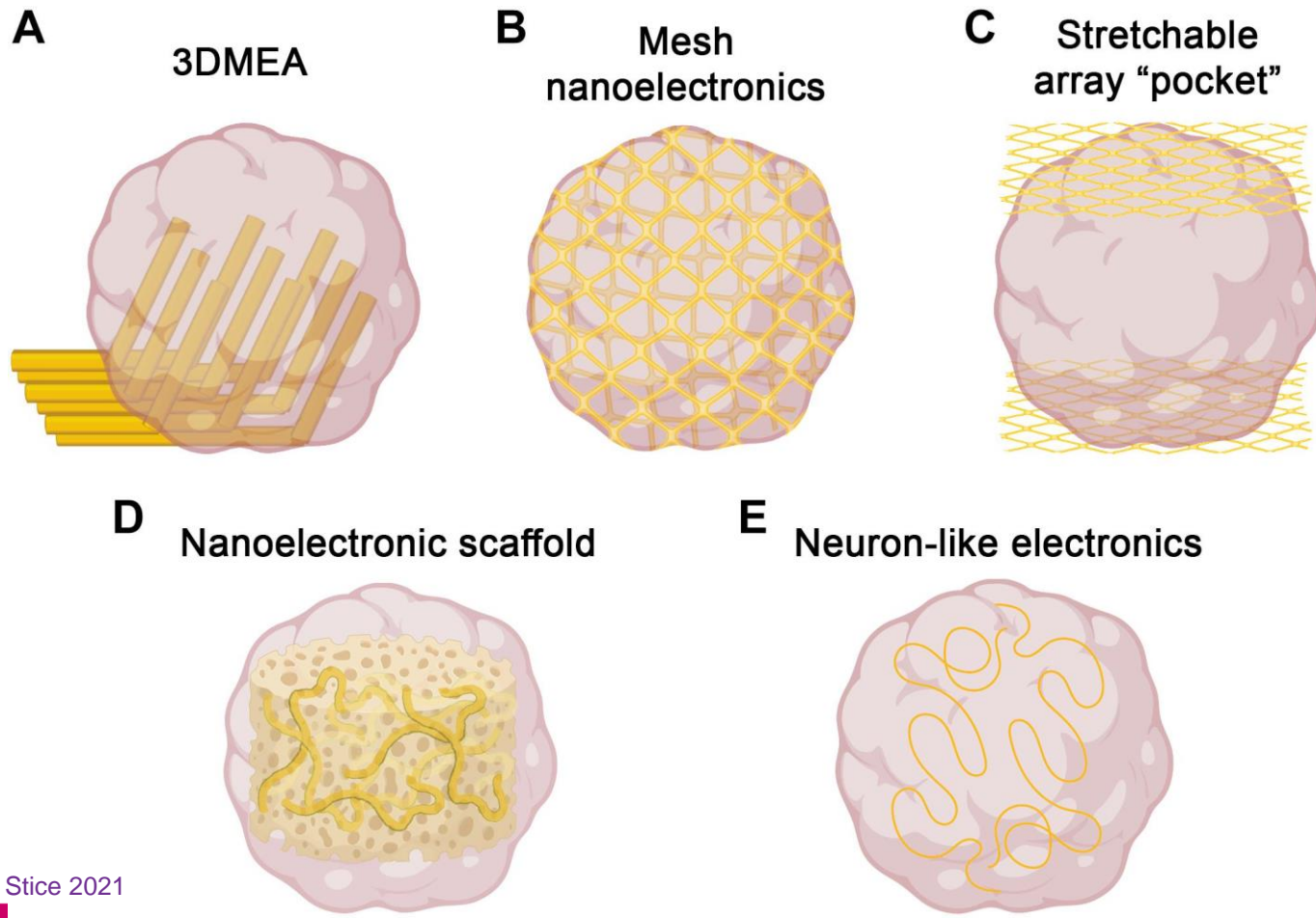


Lancaster et al 2017

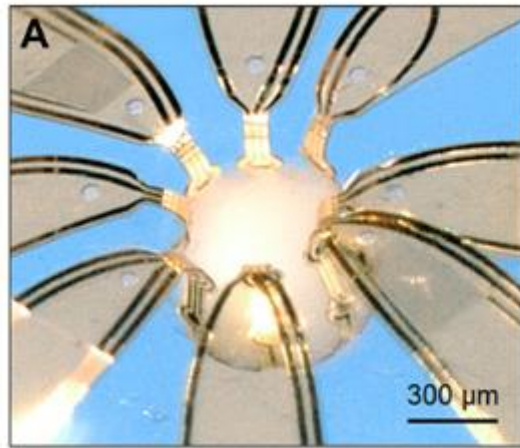


Zhang et al 2021

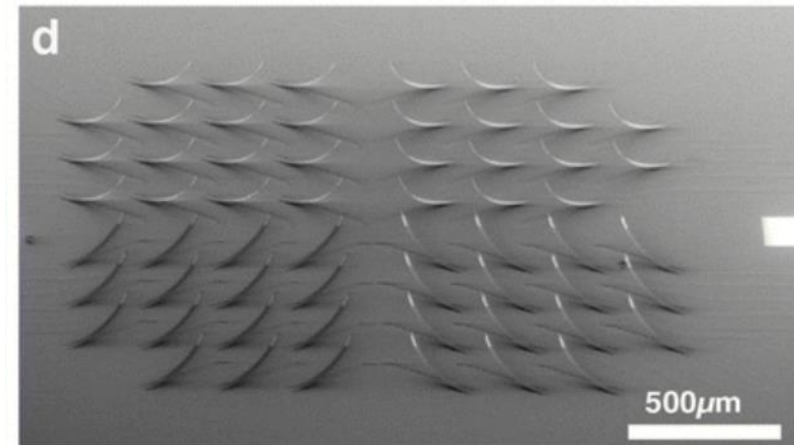
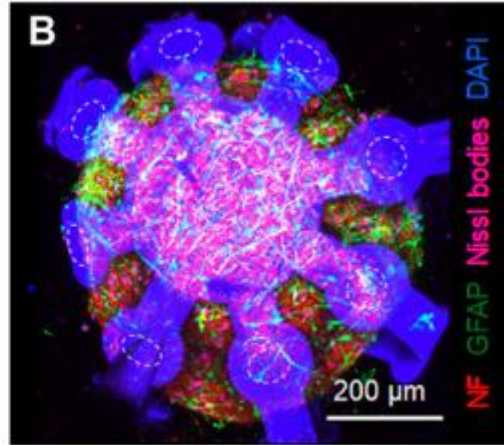
Electronic interface



3D Neural interfaces

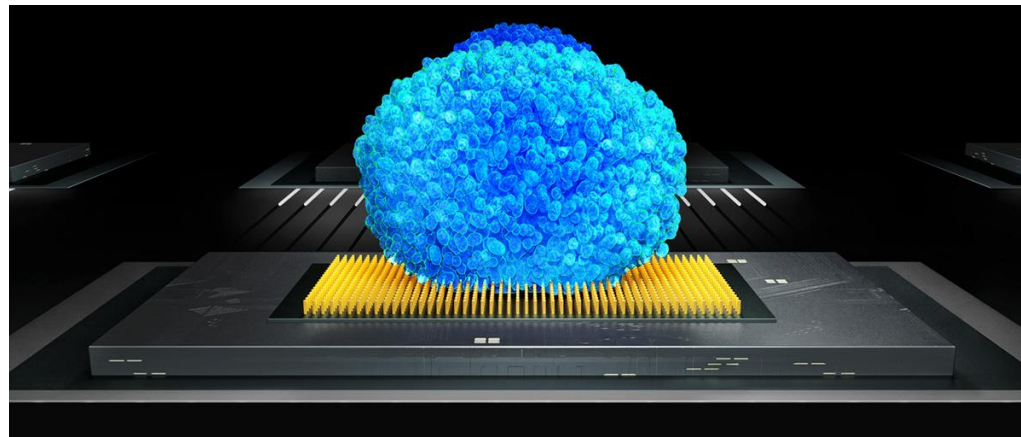


Yoonseok Park *et al.* 2021

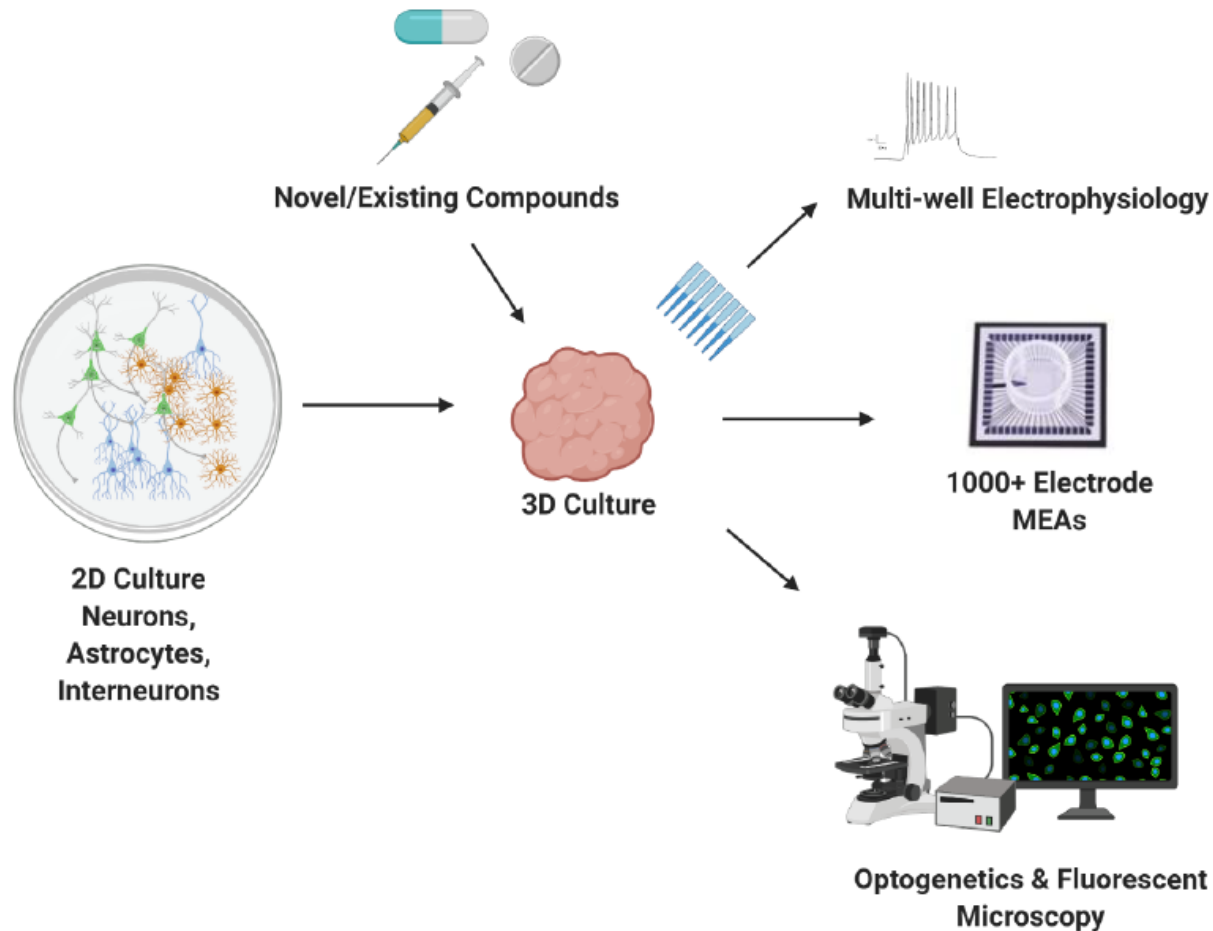


Phouphetlinthong *et al.* 2023

3Brain



The challenge of modelling neuronal systems





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- Professor Paul Roach