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PSYCHIATRY ACADEMY

Developmental Neuroscience:
Using patient-derived stem cells to study
psychiatric disease mechanisms

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Disclosures



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Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Psychiatric Disorders



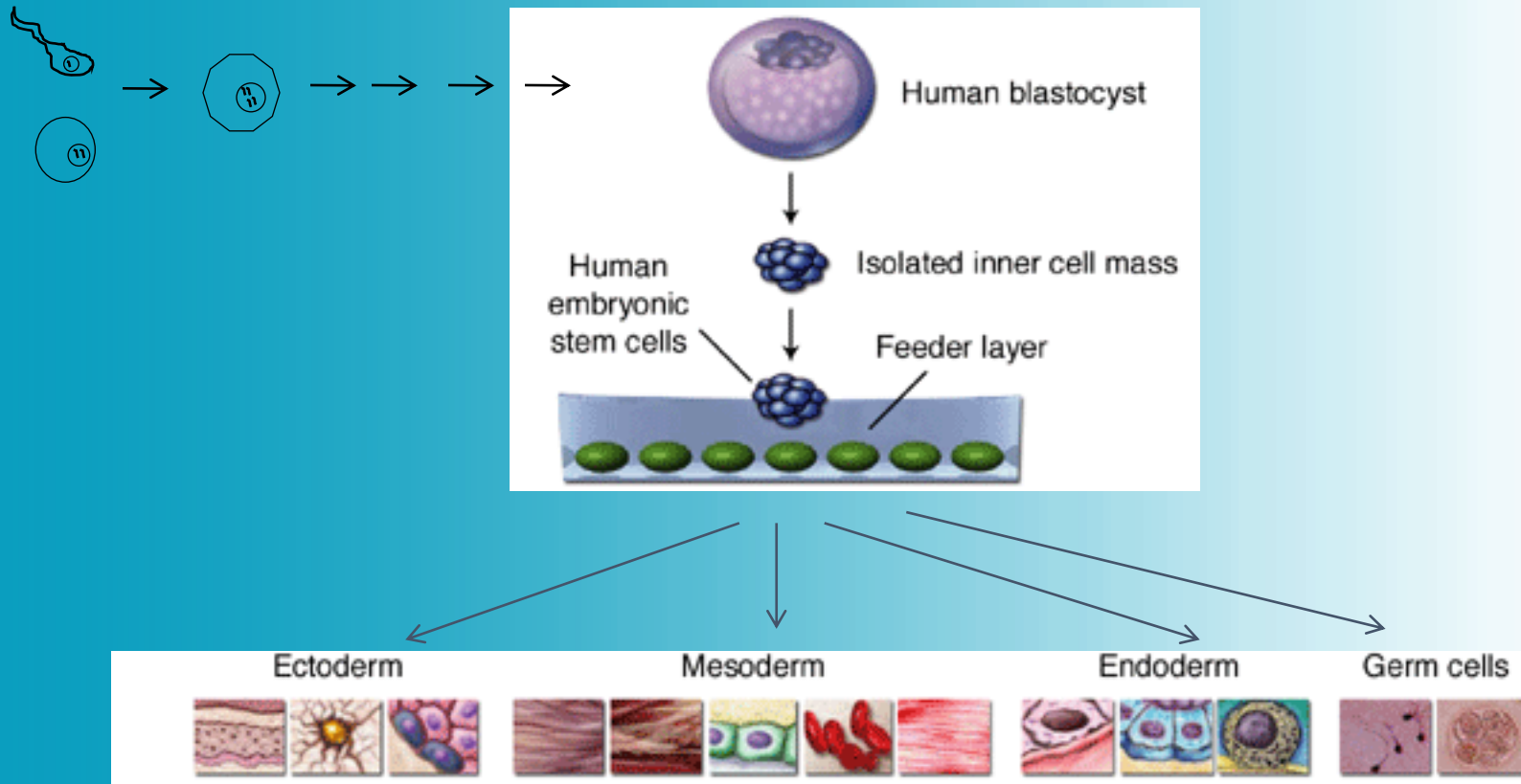
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- Major impediments to studying disease biology:
 - Lack of access to live neuronal tissue
 - Limited to postmortem brains, brain imaging

Using stem cells to make patient-specific neurons and brain organoids in the lab.

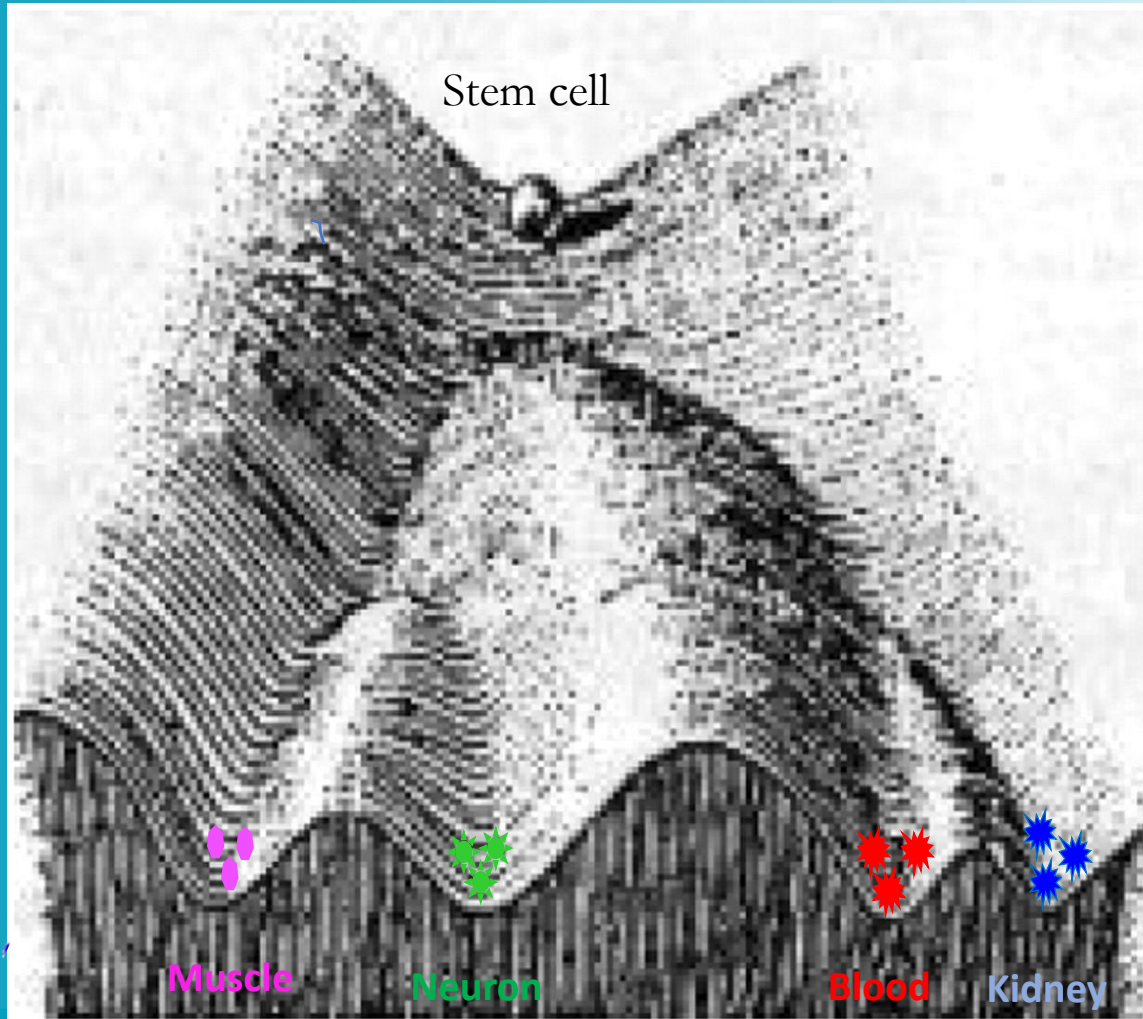
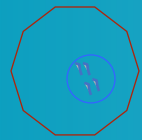
Embryonic stem cells



Adapted from Hyslop et al., Expert Rev Mol Med (2005), 17.



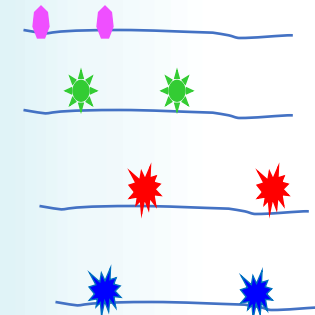
Stem Cell Differentiation



DNA



Epigenetic
changes



Summary



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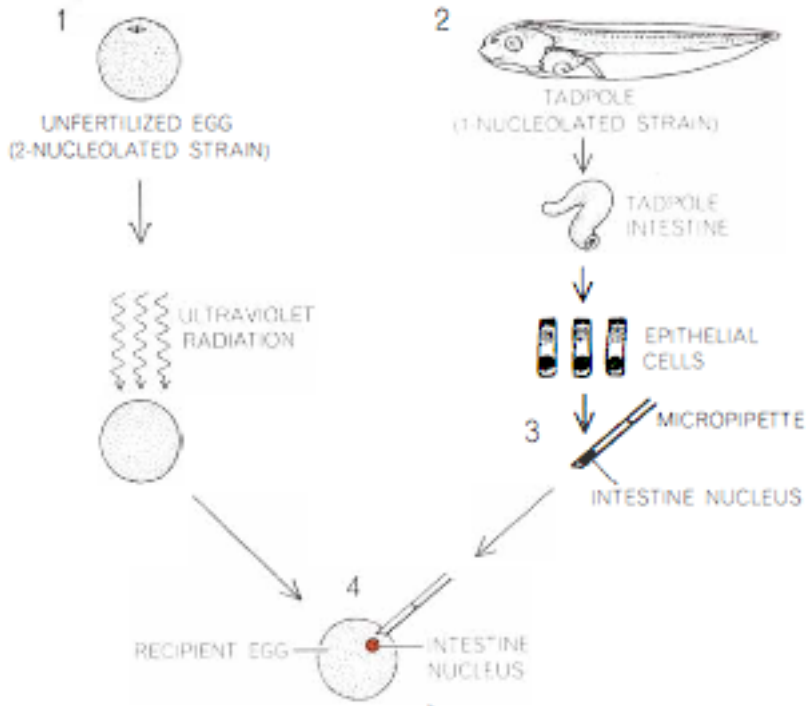
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Stem cell differentiation is a one way-ticket.

Once you become a skin cell, you are always a skin cell – there is no going back.

But...

Somatic Cell Nuclear Transfer – Early days



The Developmental Capacity of Nuclei taken from Intestinal Epithelium Cells of Feeding Tadpoles

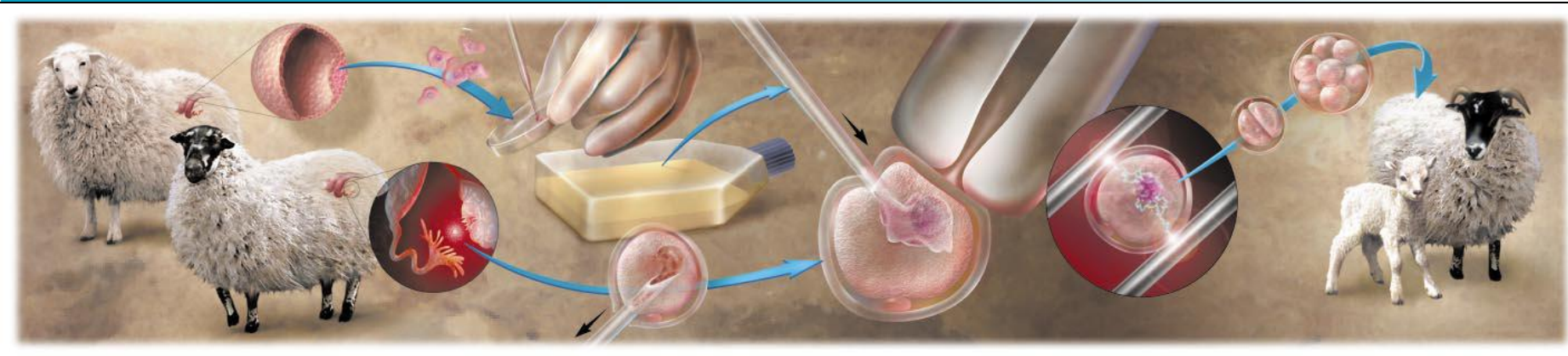
by J. B. GURDON¹

From the Embryology Laboratory, Department of Zoology, Oxford

[*J. Embryol. exp. Morph.*, Vol. 10, Part 4, pp. 622-40 December 1962]

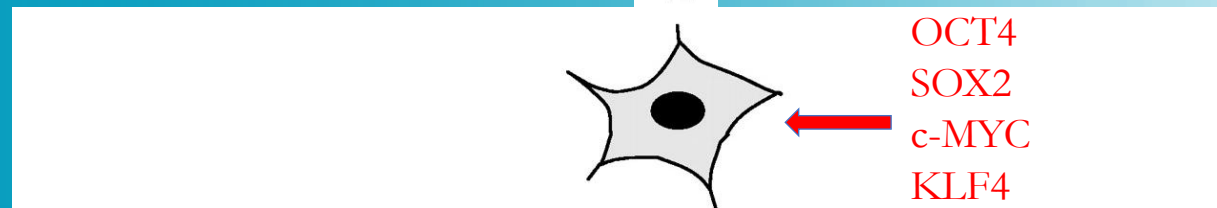
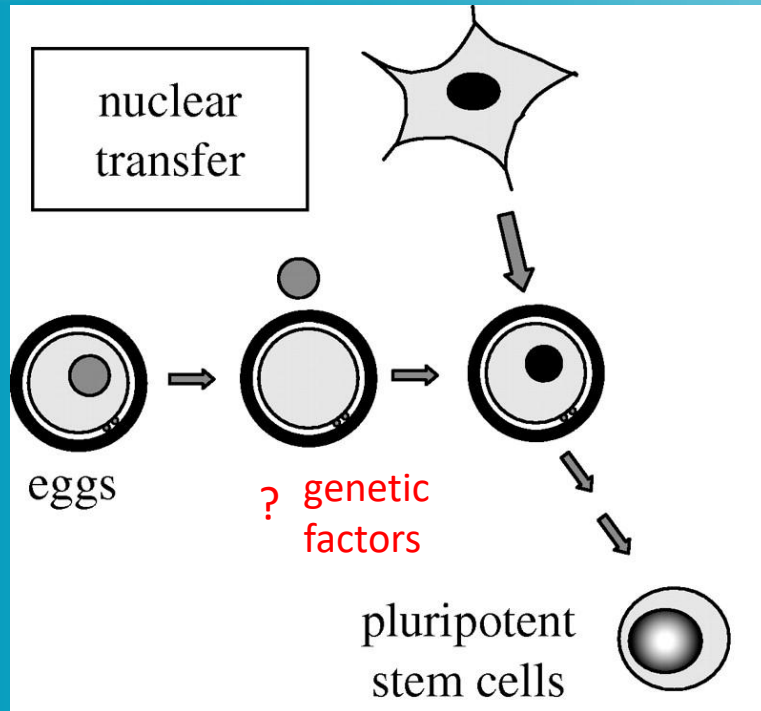


Somatic Cell Nuclear Transfer – Dolly



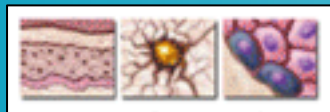
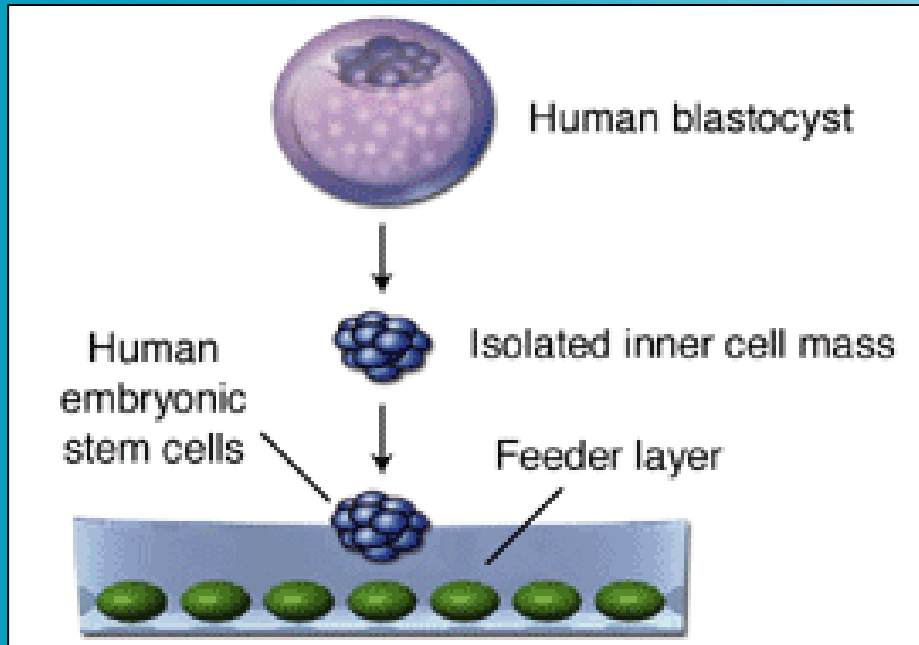
Adapted from I. Wilmut, Scientific American (1998), 269: 58-63

Induced pluripotent stem cells - Yamanaka

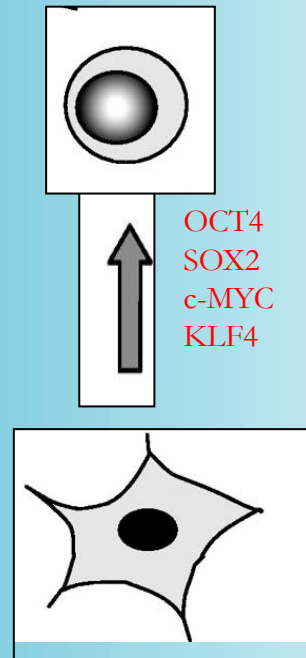


S. Yamanaka *Phil Trans R Soc B* 2008; 363:2079-87.

Induced pluripotent stem cells



Human induced pluripotent stem cell



Human skin cell

Induced pluripotent stem cells - iPSCs



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The Nobel Prize in Physiology or Medicine



Photo: U. Montan

Sir John B. Gurdon

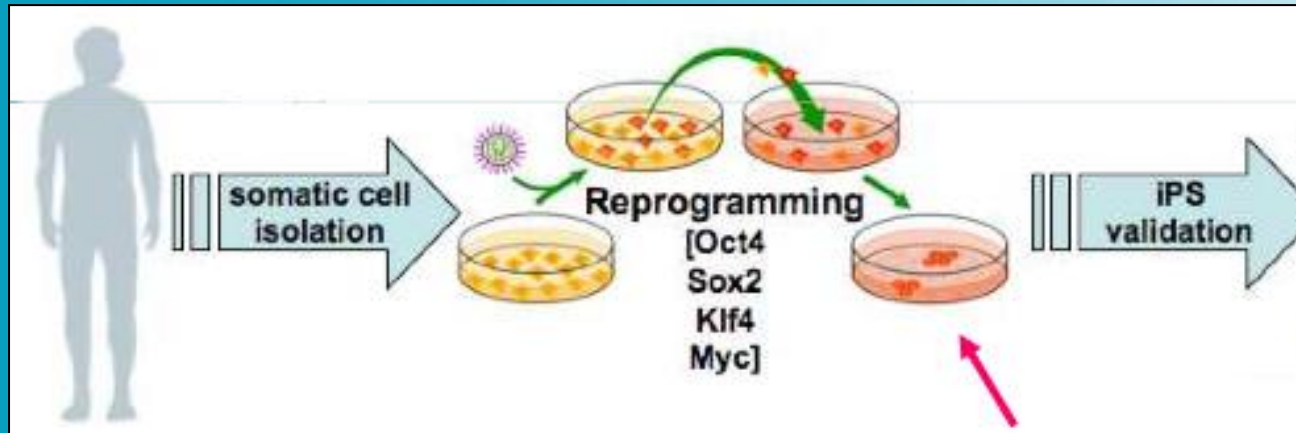


Photo: U. Montan

Shinya Yamanaka

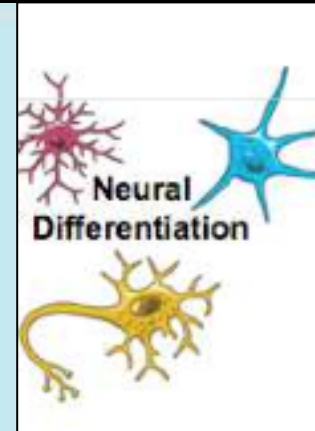
“for the discovery that mature cells can be reprogrammed to become pluripotent.”

Patient-derived stem cells

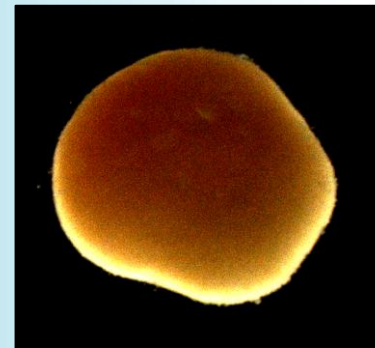


Patient blood

Patient-specific stem cells

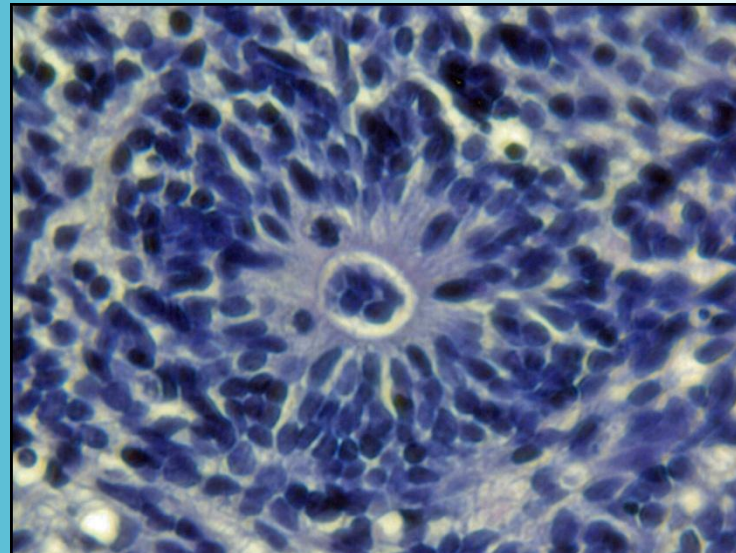
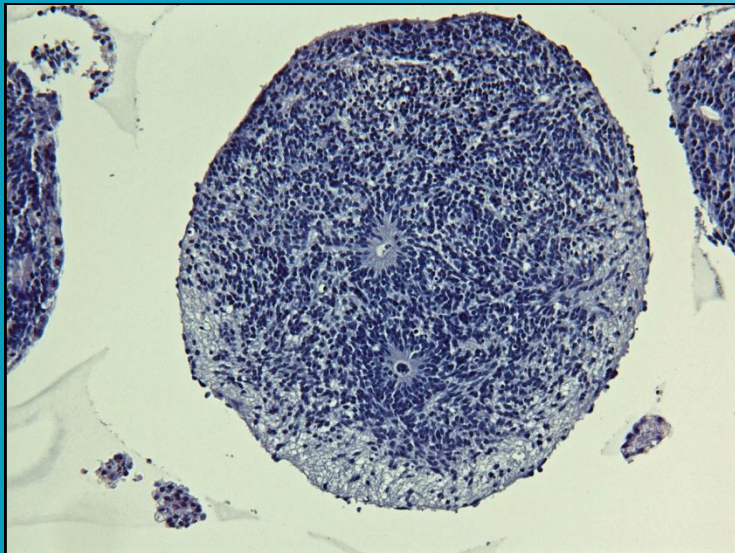
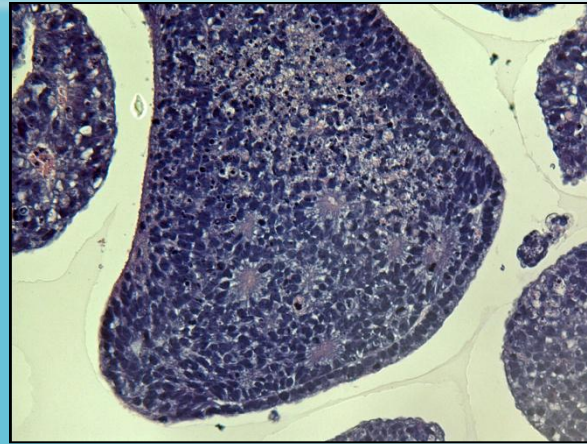
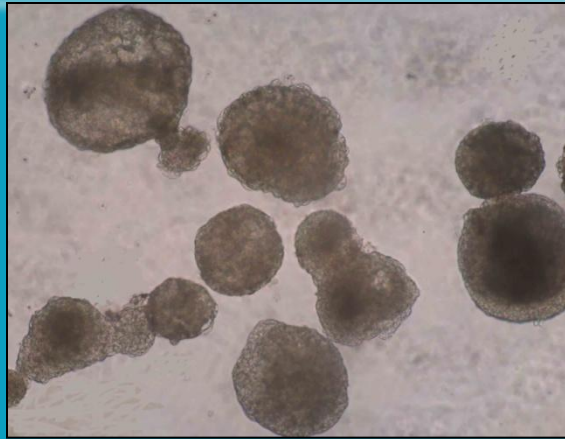


Neuronal and glial cells



Brain organoids

iPSC differentiation - embryoid bodies

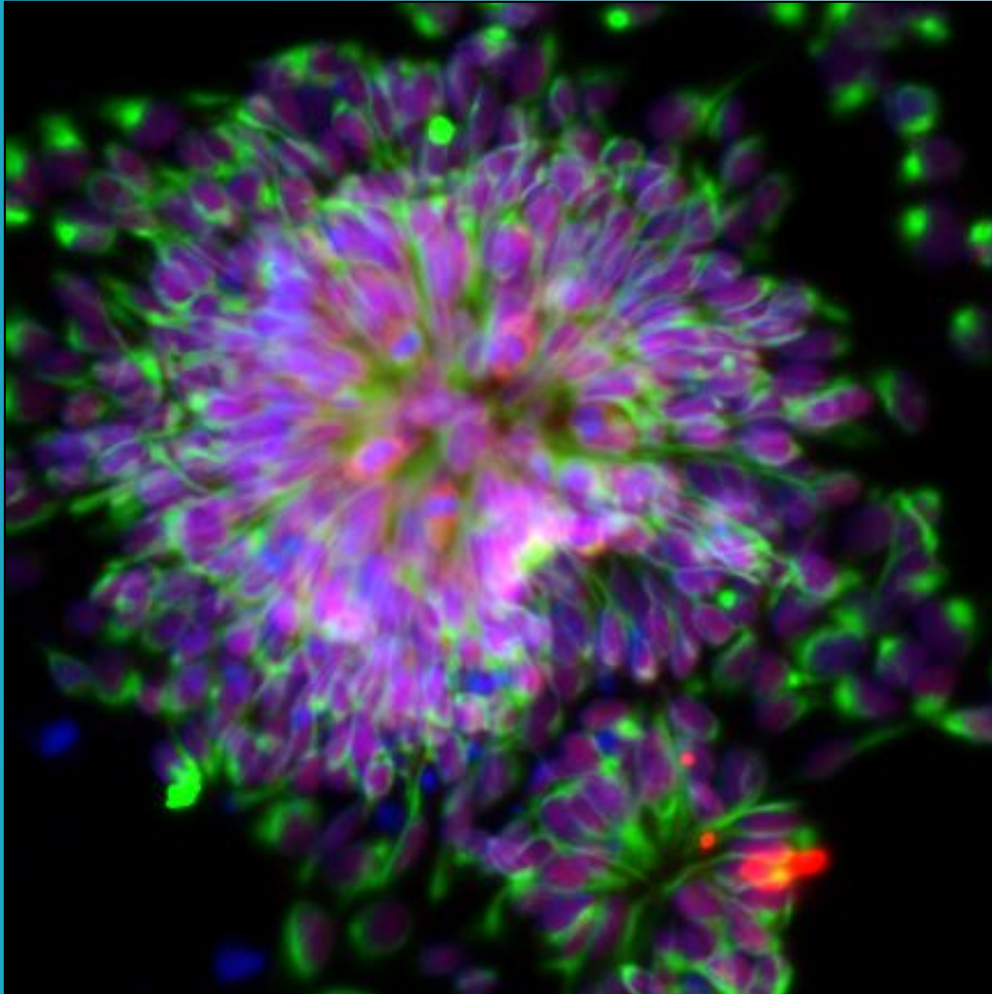


iPSC differentiation – neural rosettes



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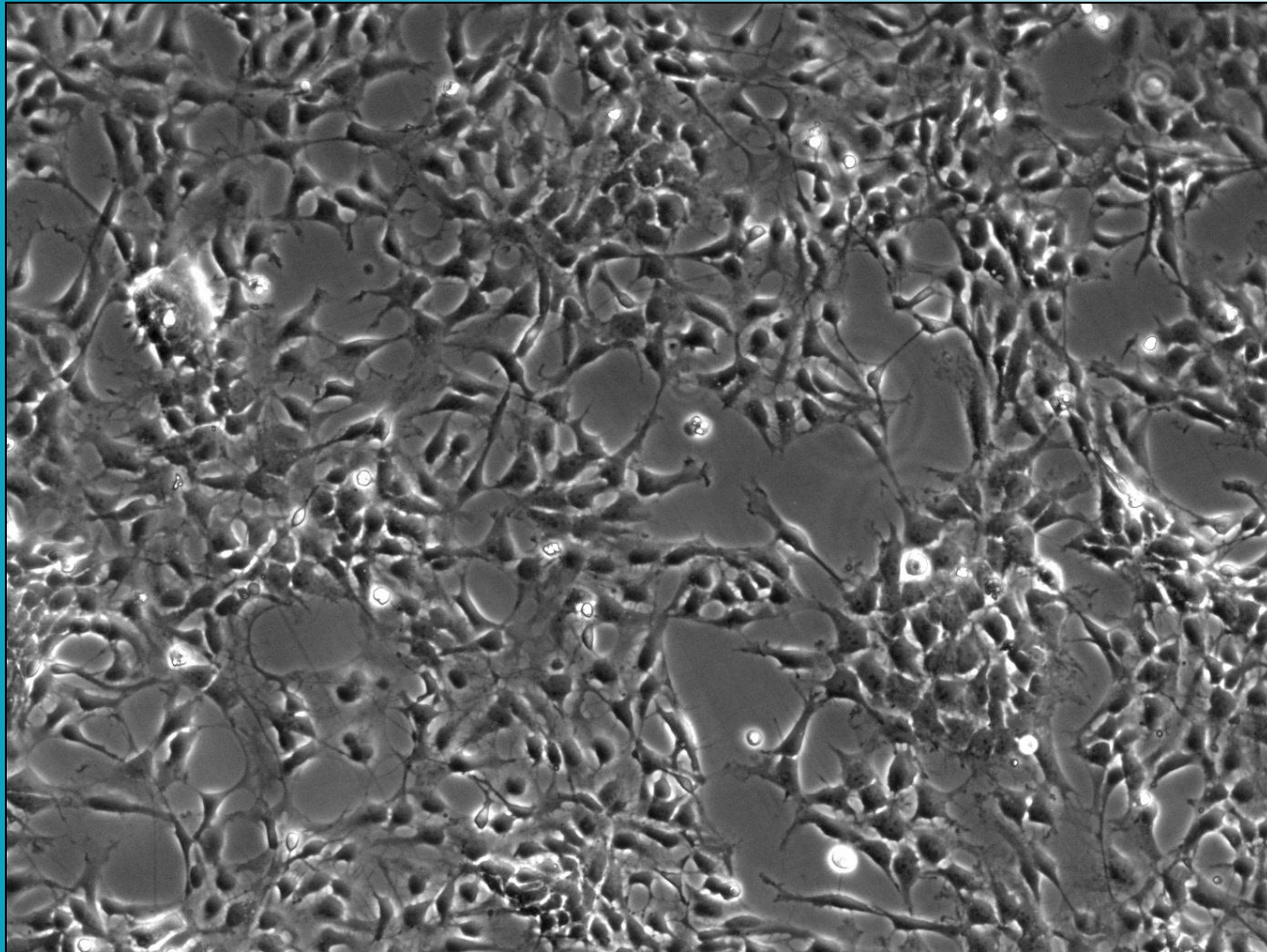


iPSC differentiation – neural stem cells

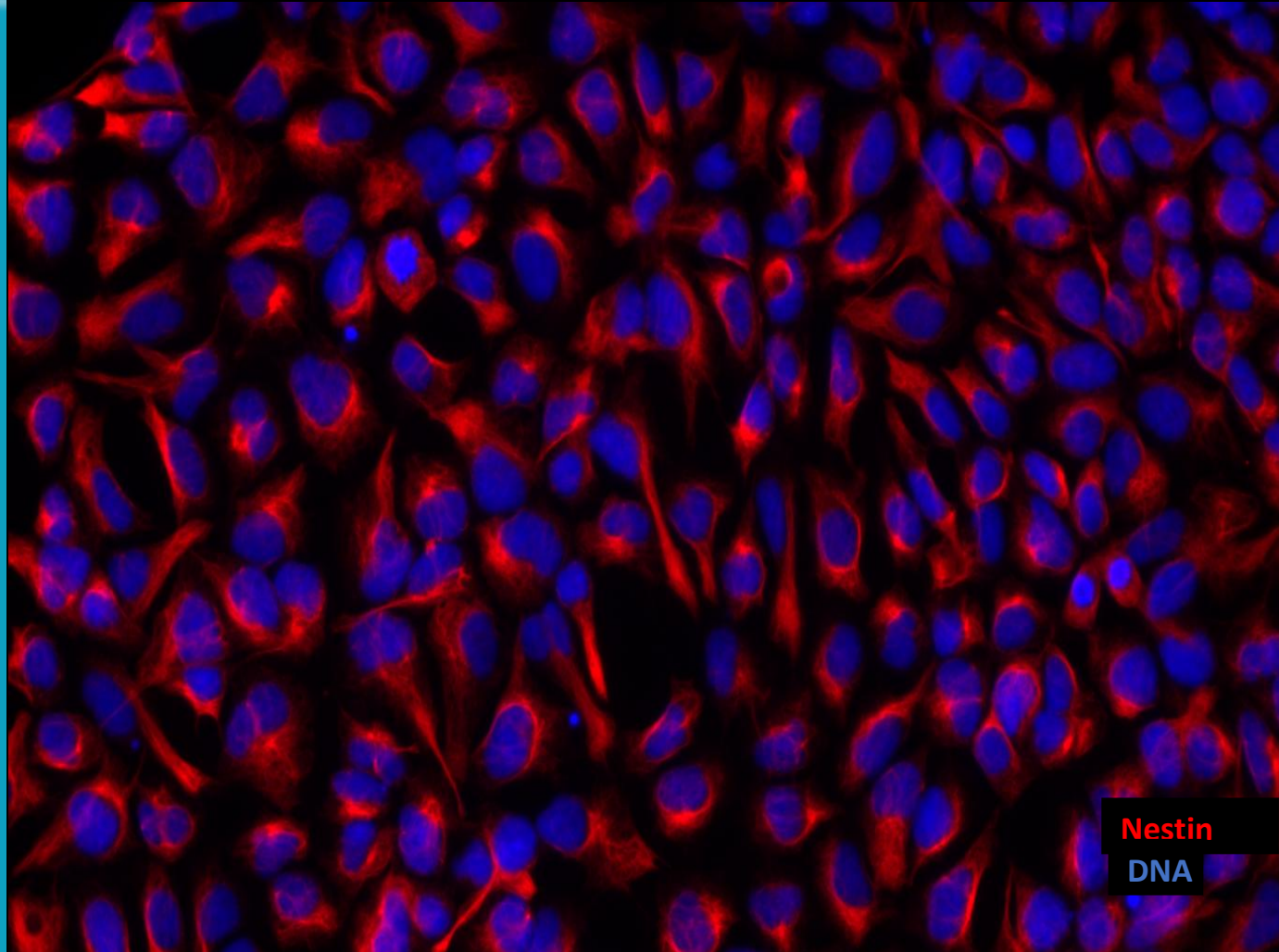


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iPSC-derived neural stem cells



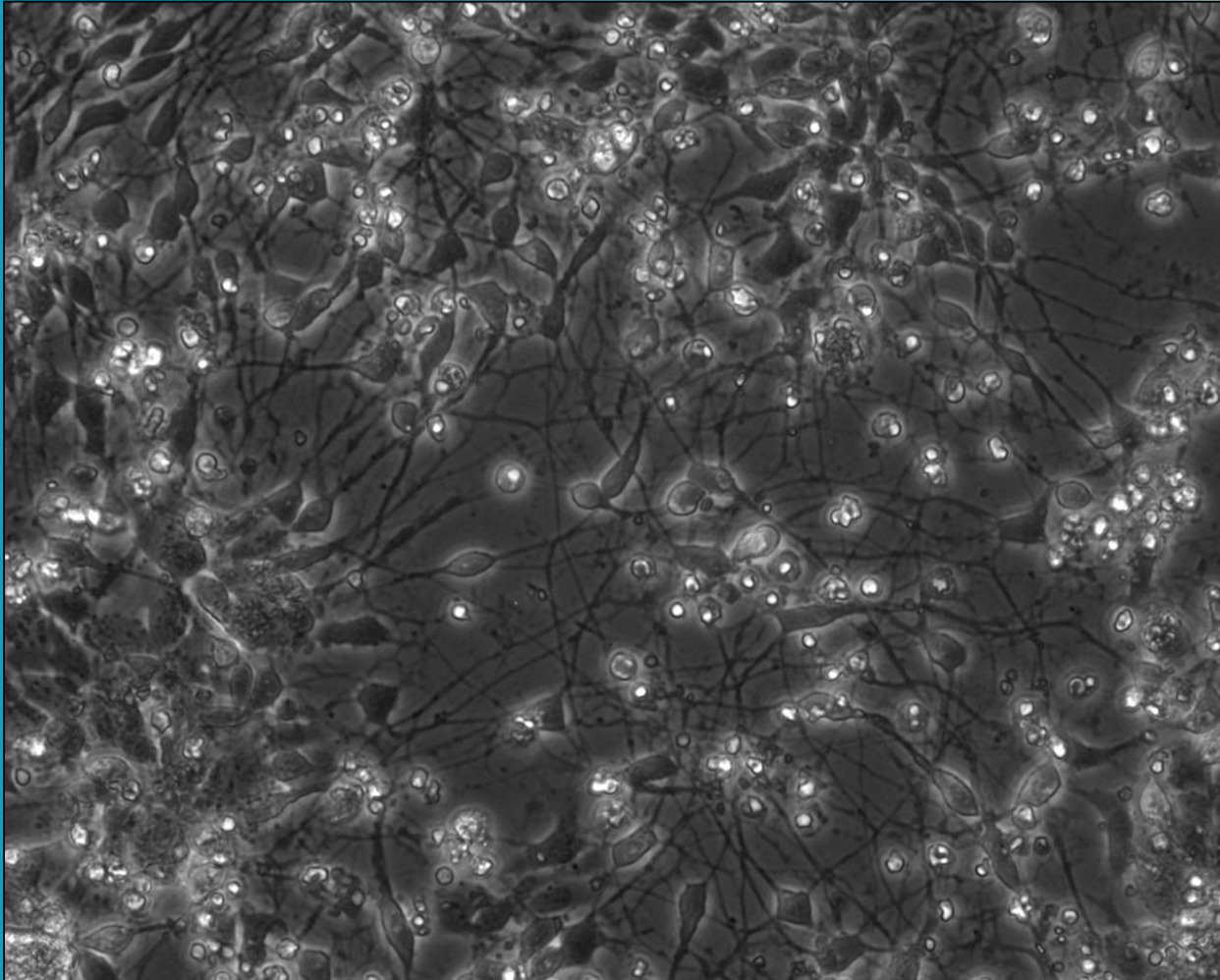
Nestin
DNA

iPSC-derived neurons



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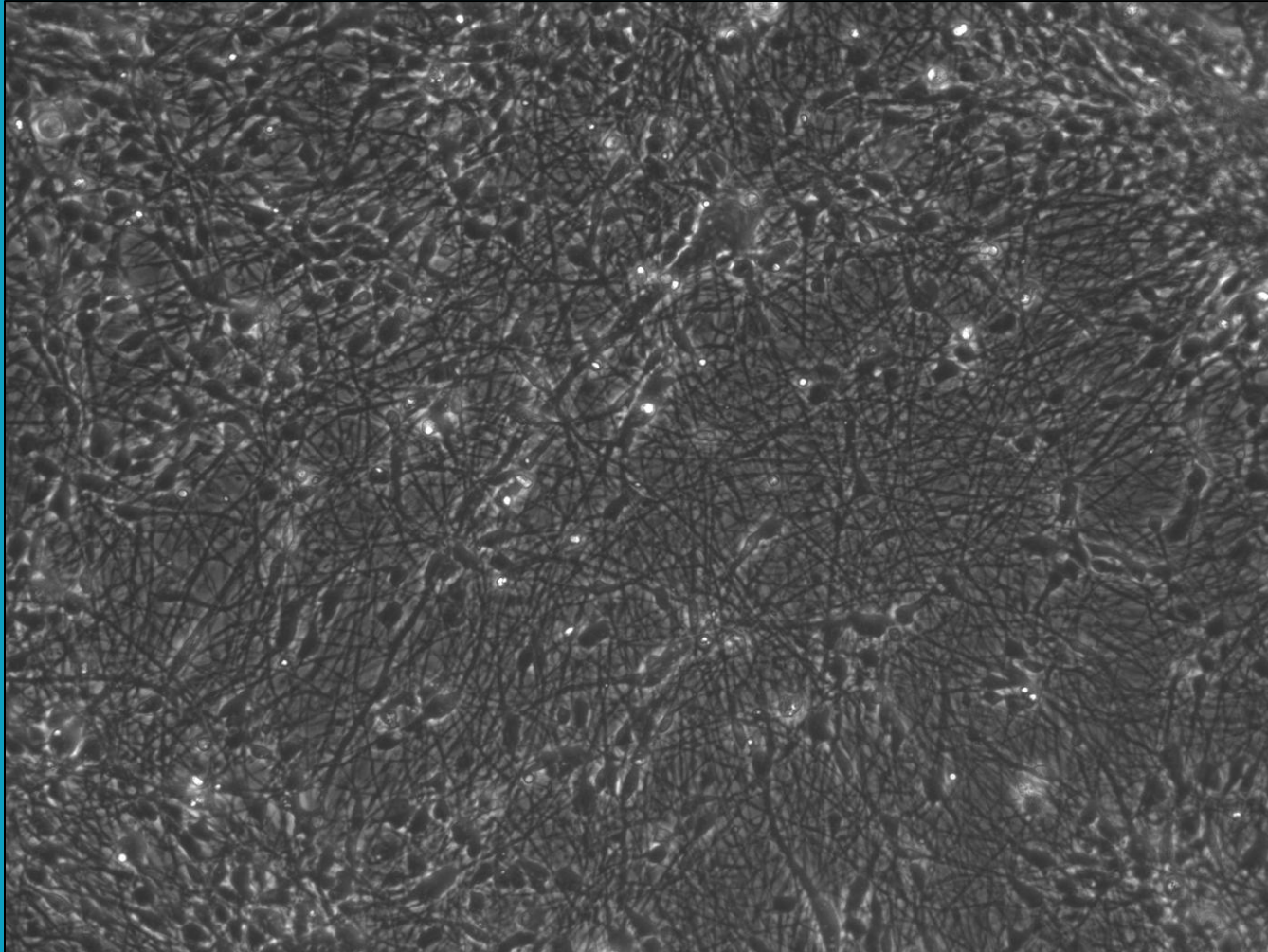


iPSC-derived neurons

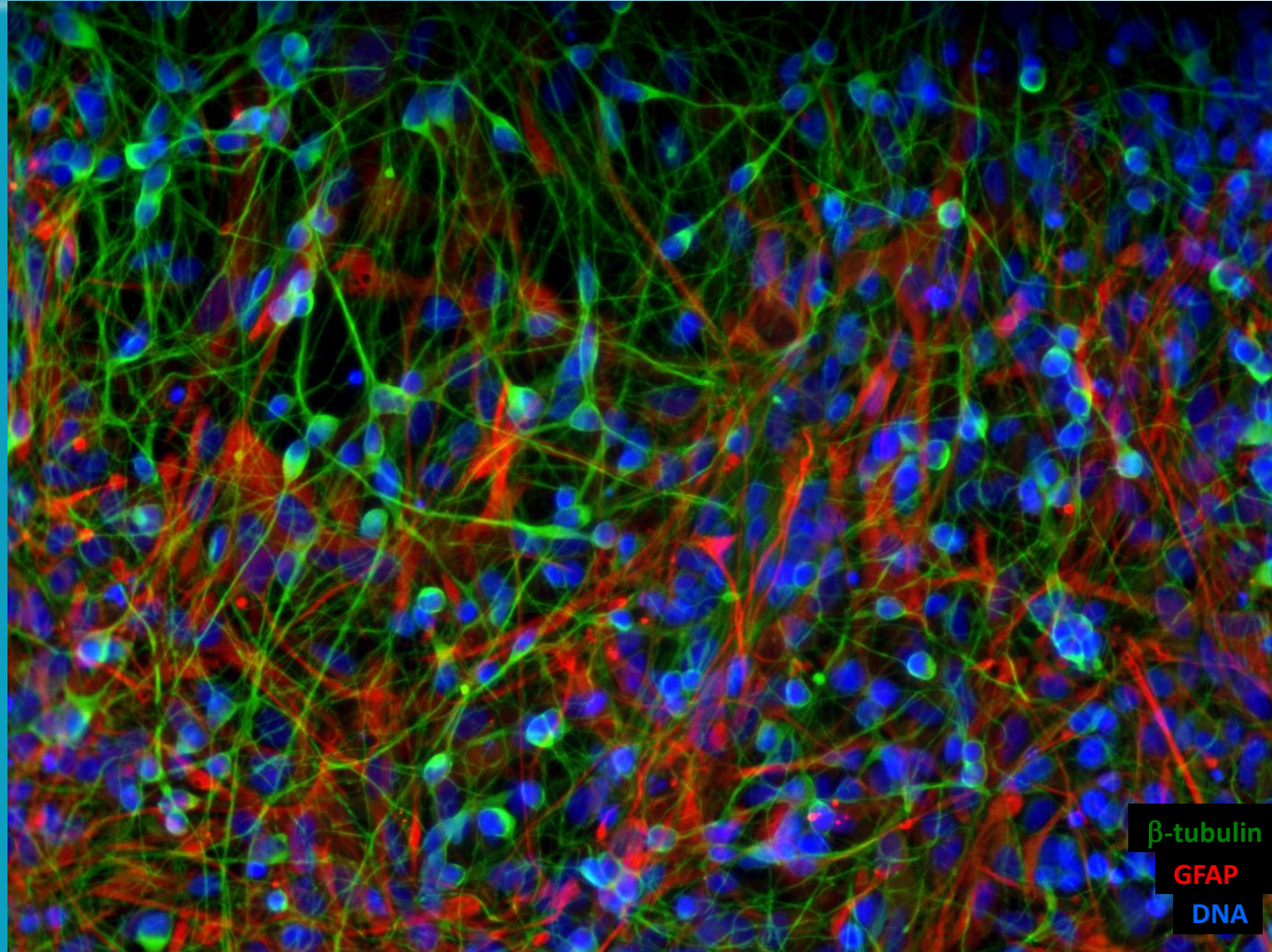


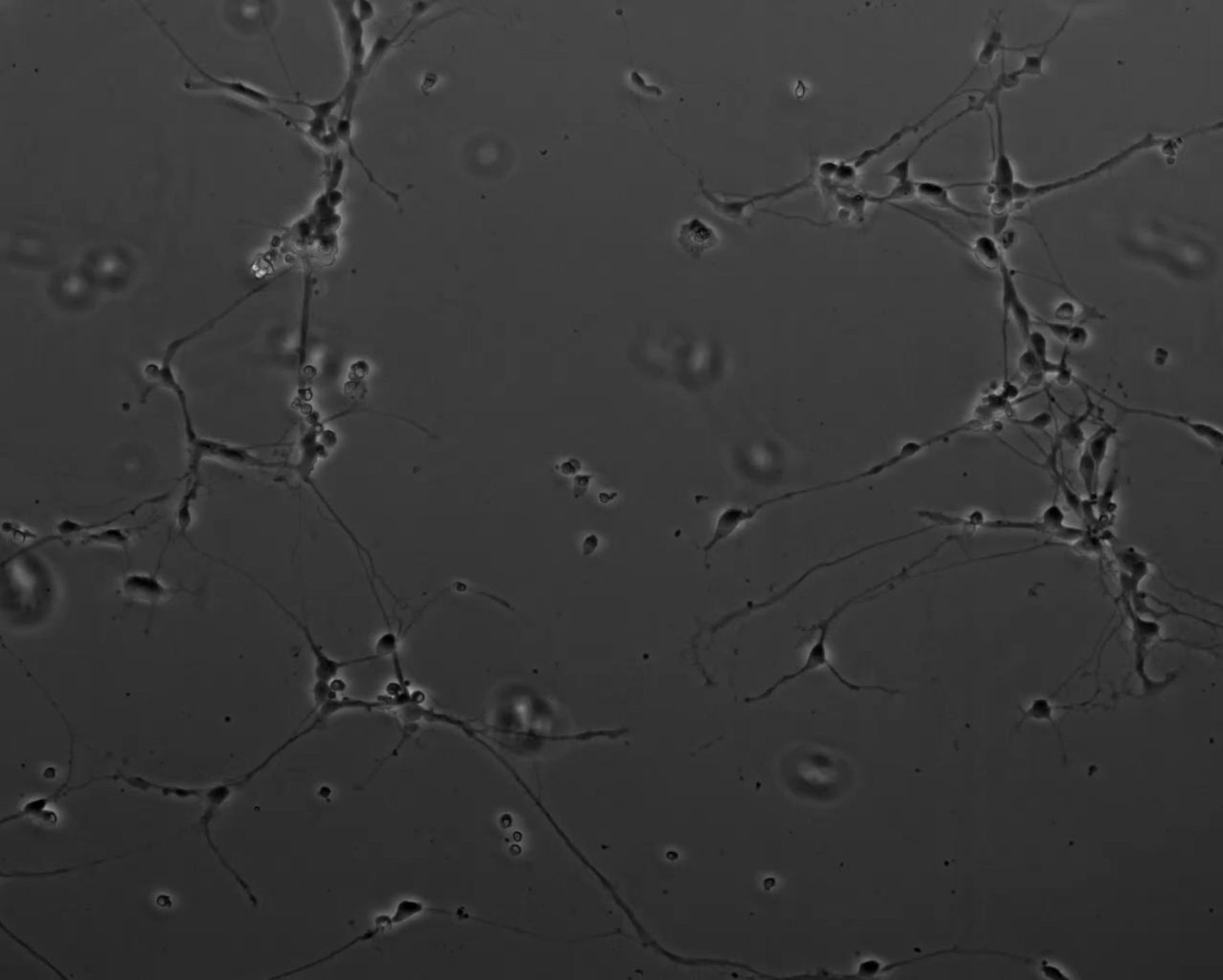
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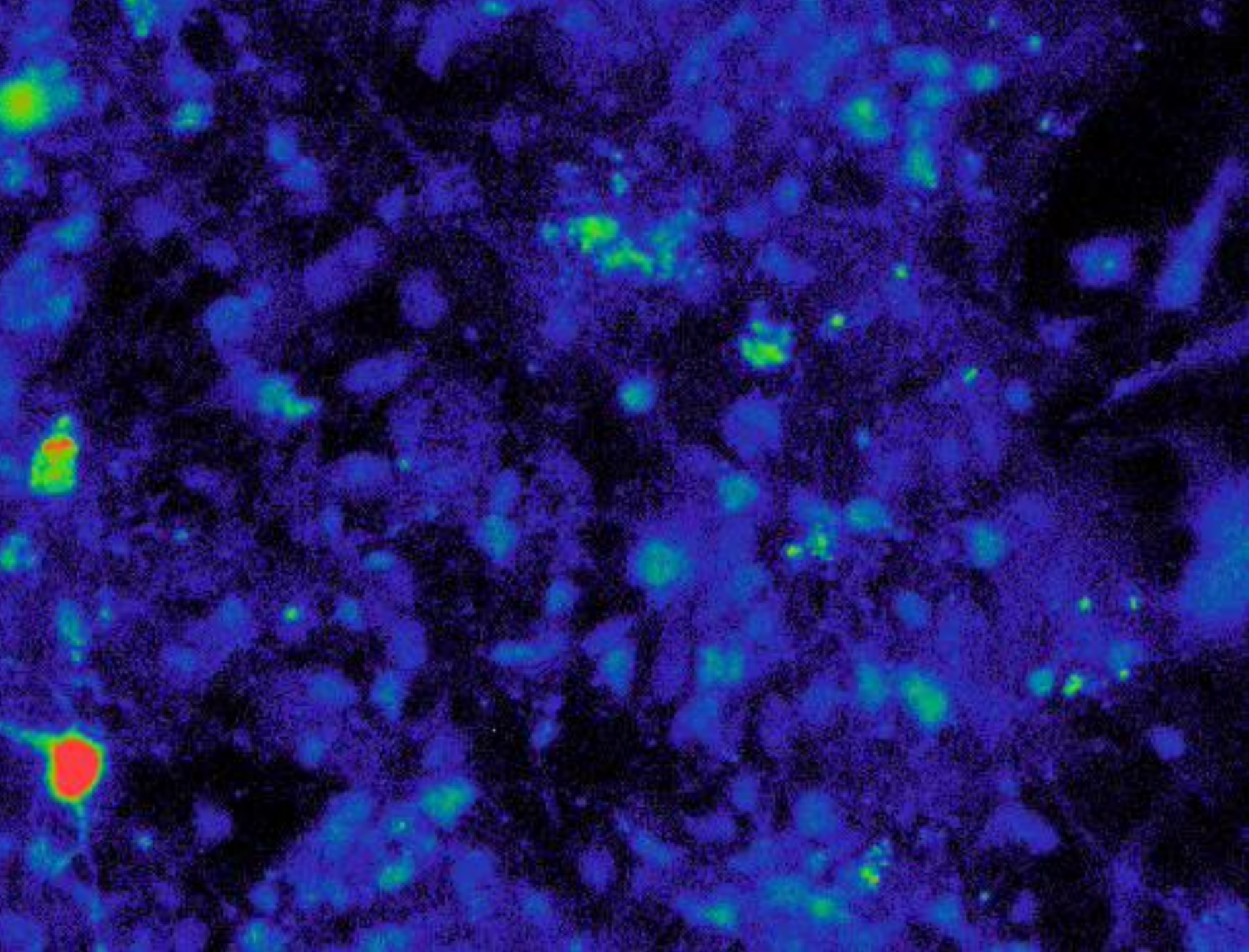
iPSC-derived neurons





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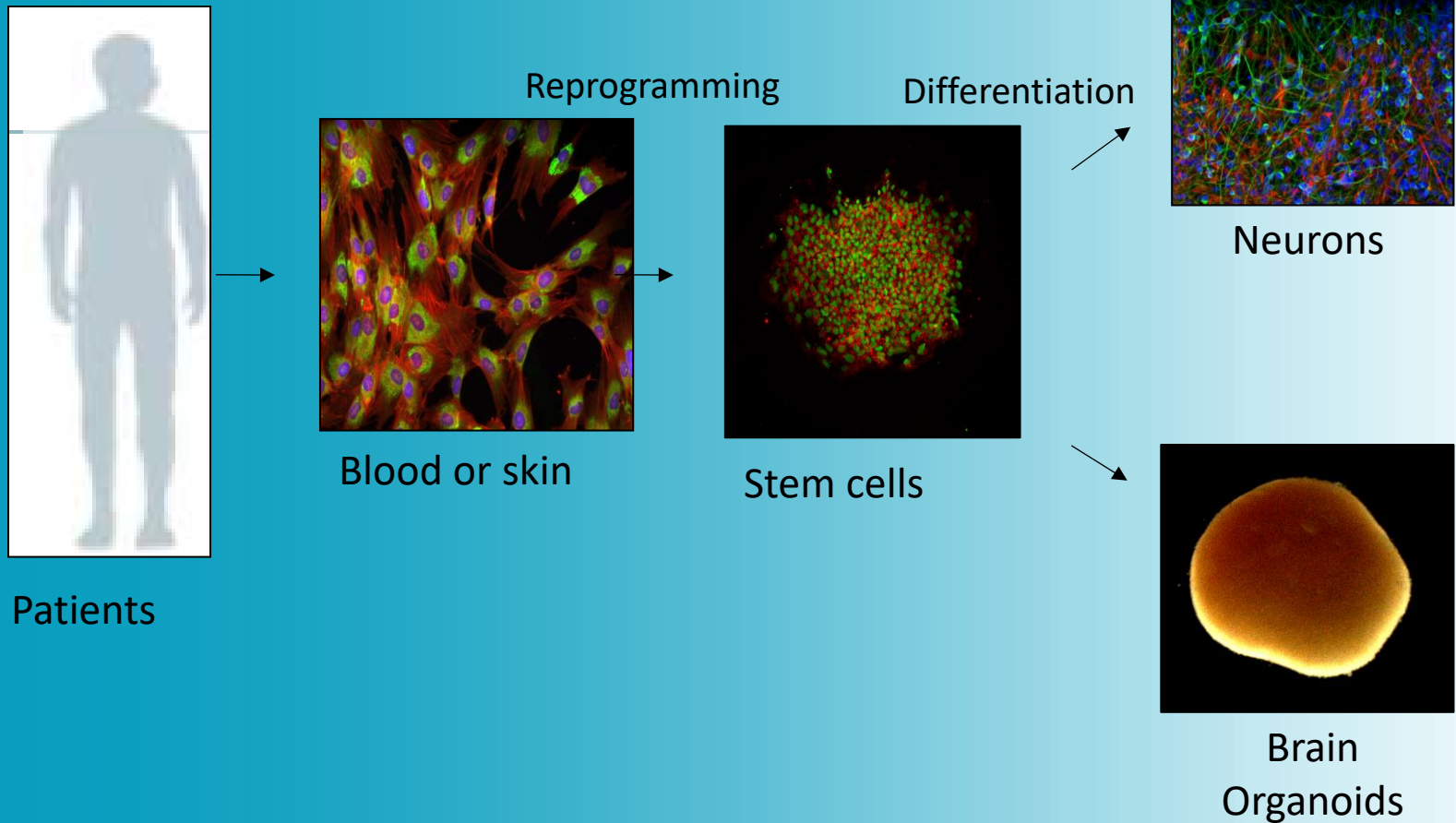
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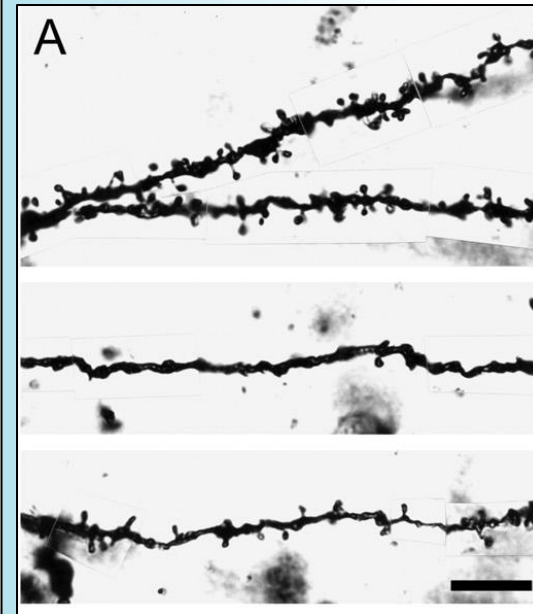
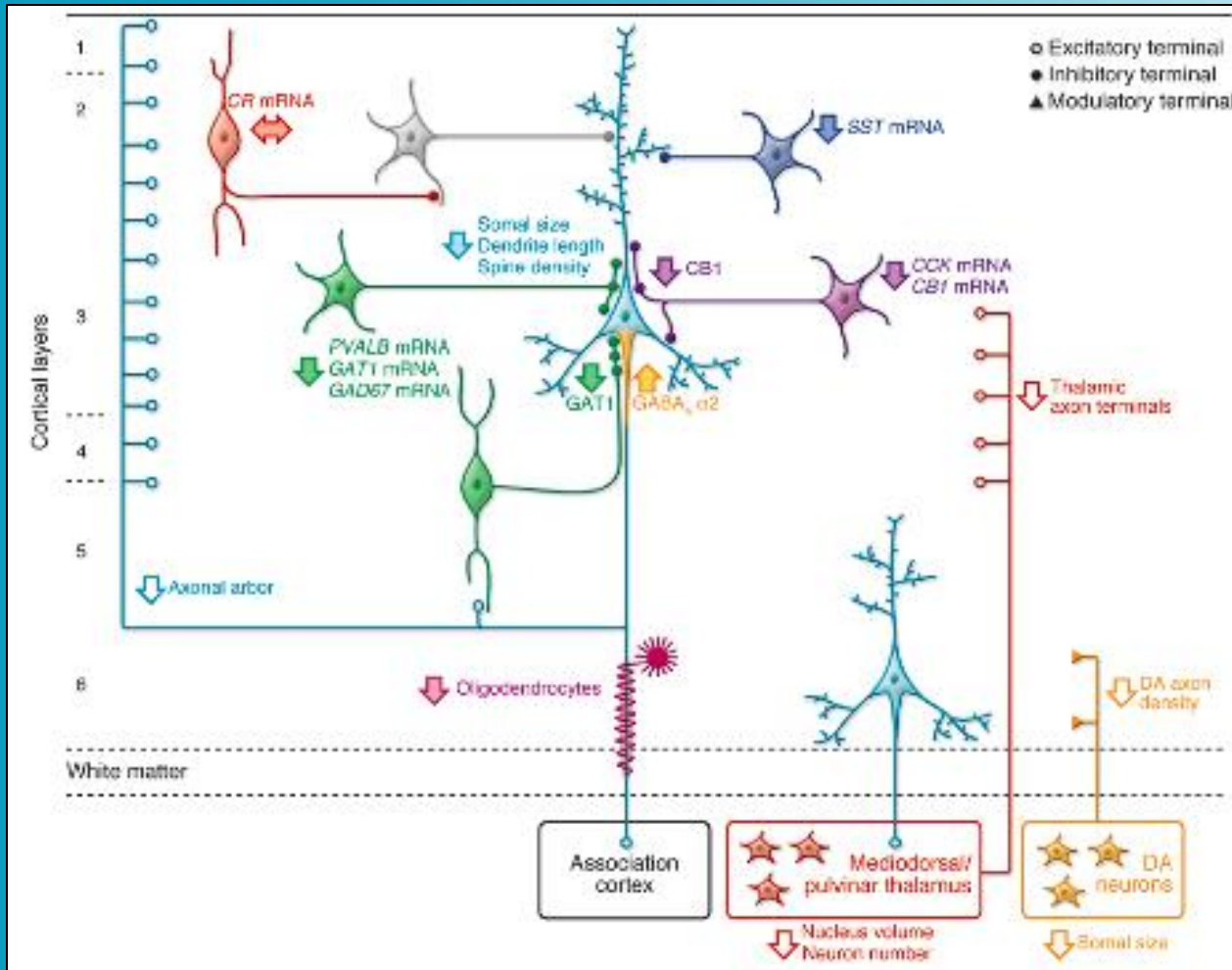
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Patient-specific stem cells



Postmortem studies in schizophrenia



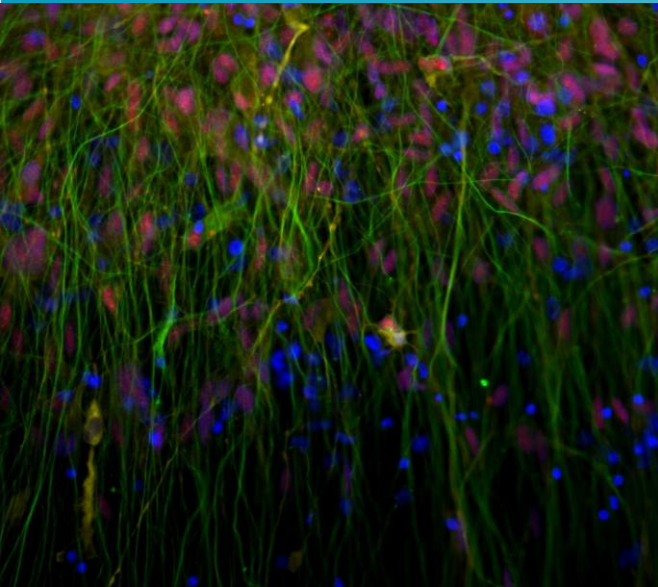
Lewis and Sweet, JCI (2009)
 Glausier et al., Neuroscience (2012)
 Konopaske et al., JAMA Psychiatry (2014)

Generating cortical neurons in the lab

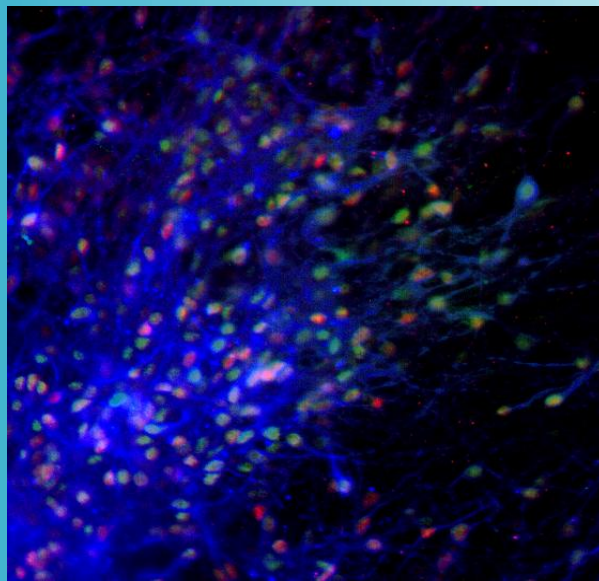


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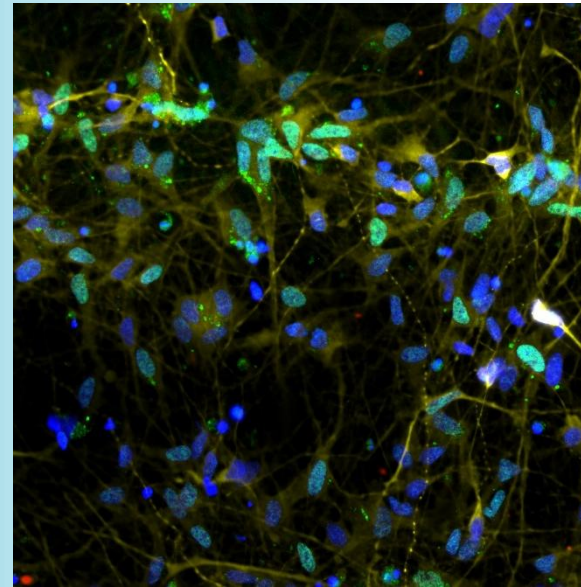
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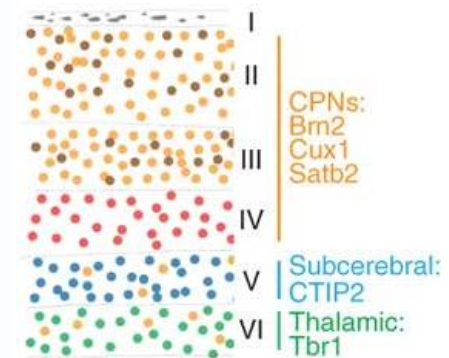
BRIN2



TBR1 CTIP2



SATB2

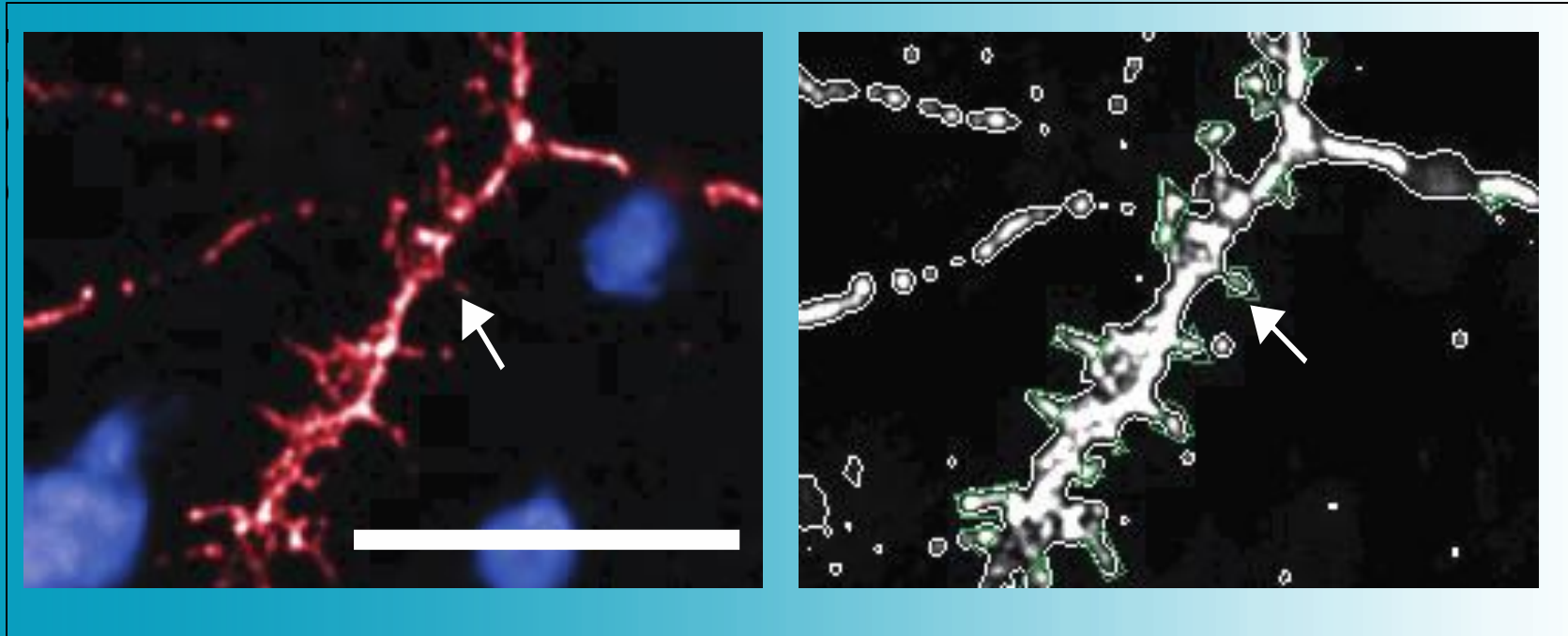


Human iPSC-derived cortical pyramidal neurons

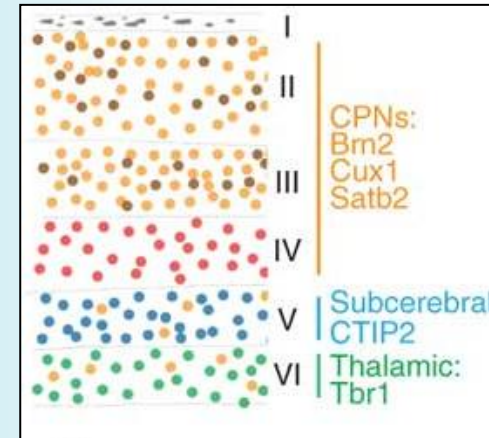
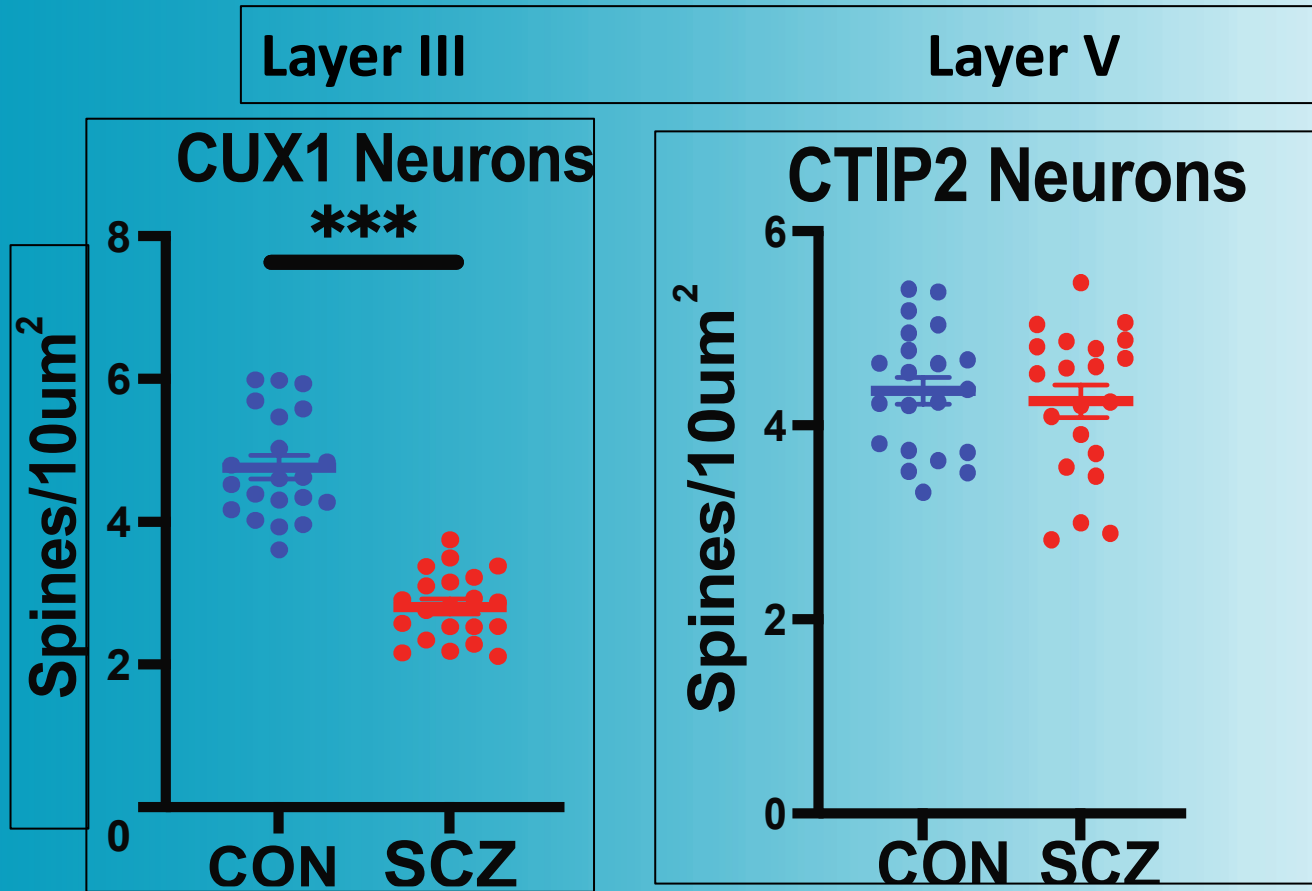


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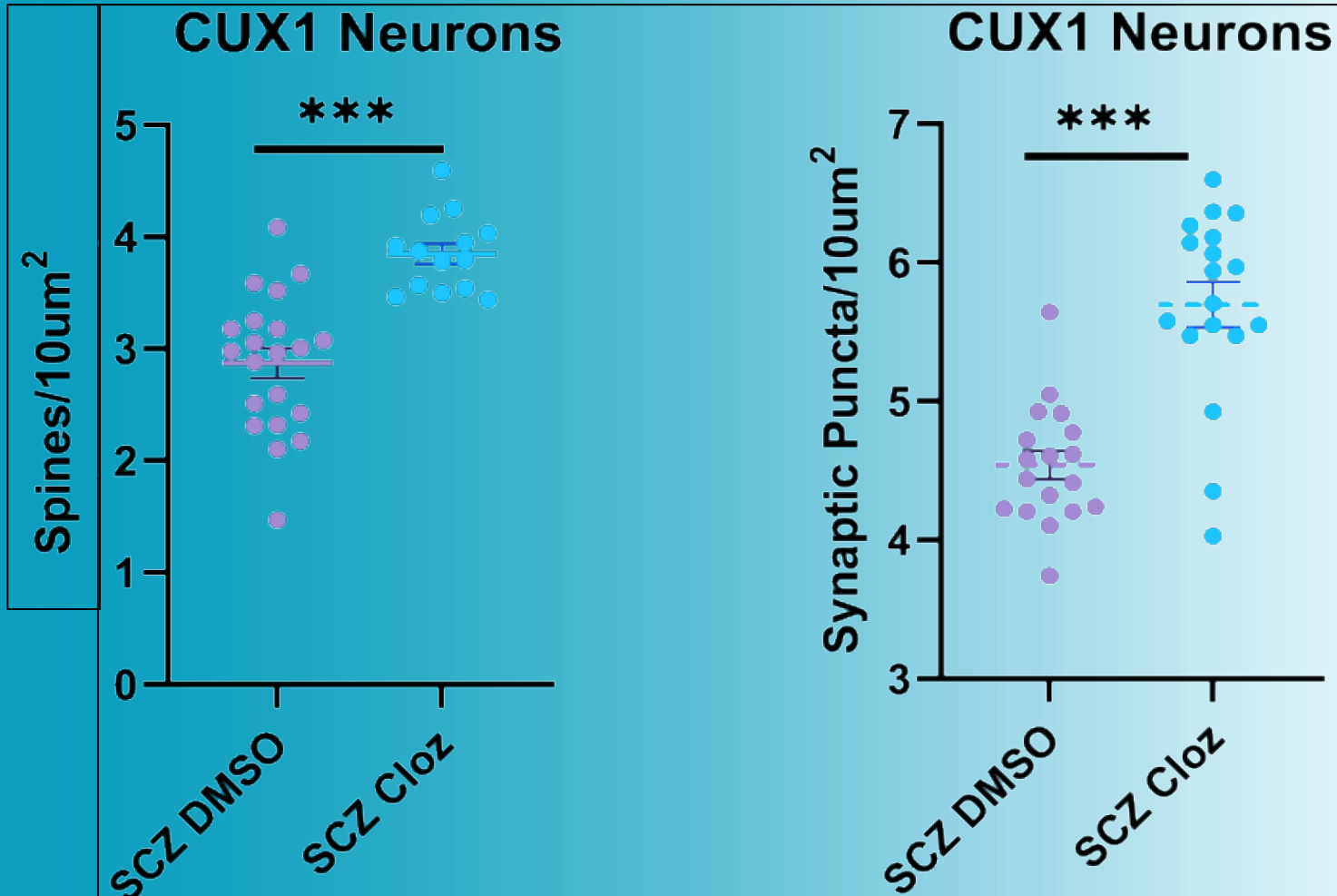


Human iPSC-derived cortical pyramidal neurons

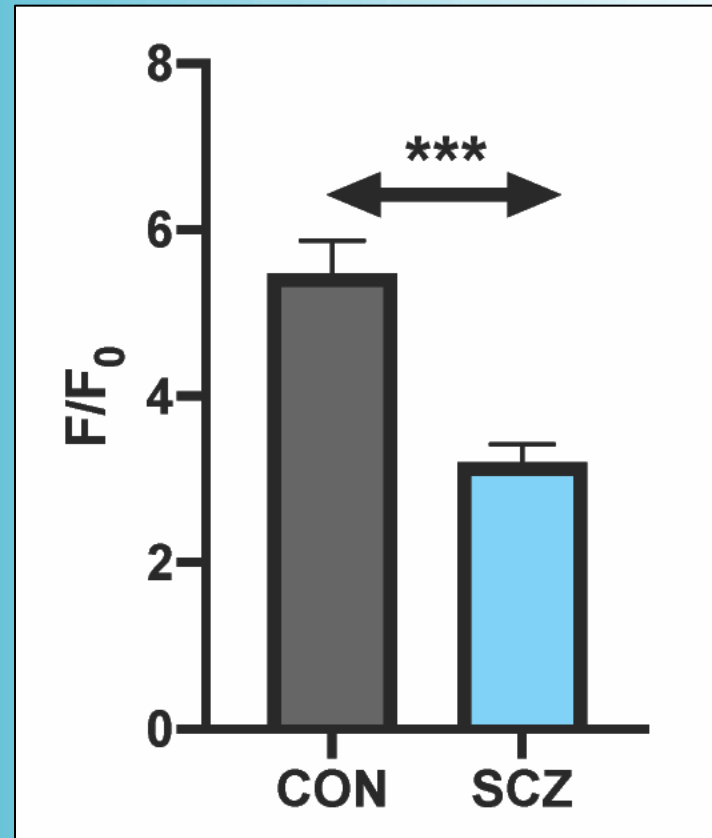
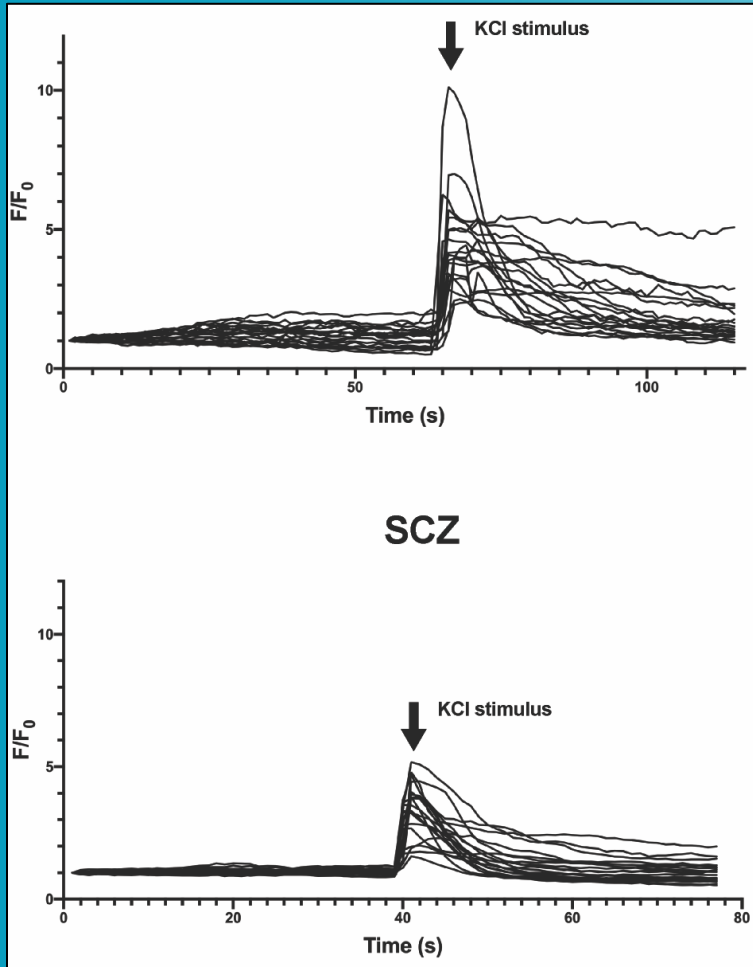




Effect of clozapine on cortical neurons

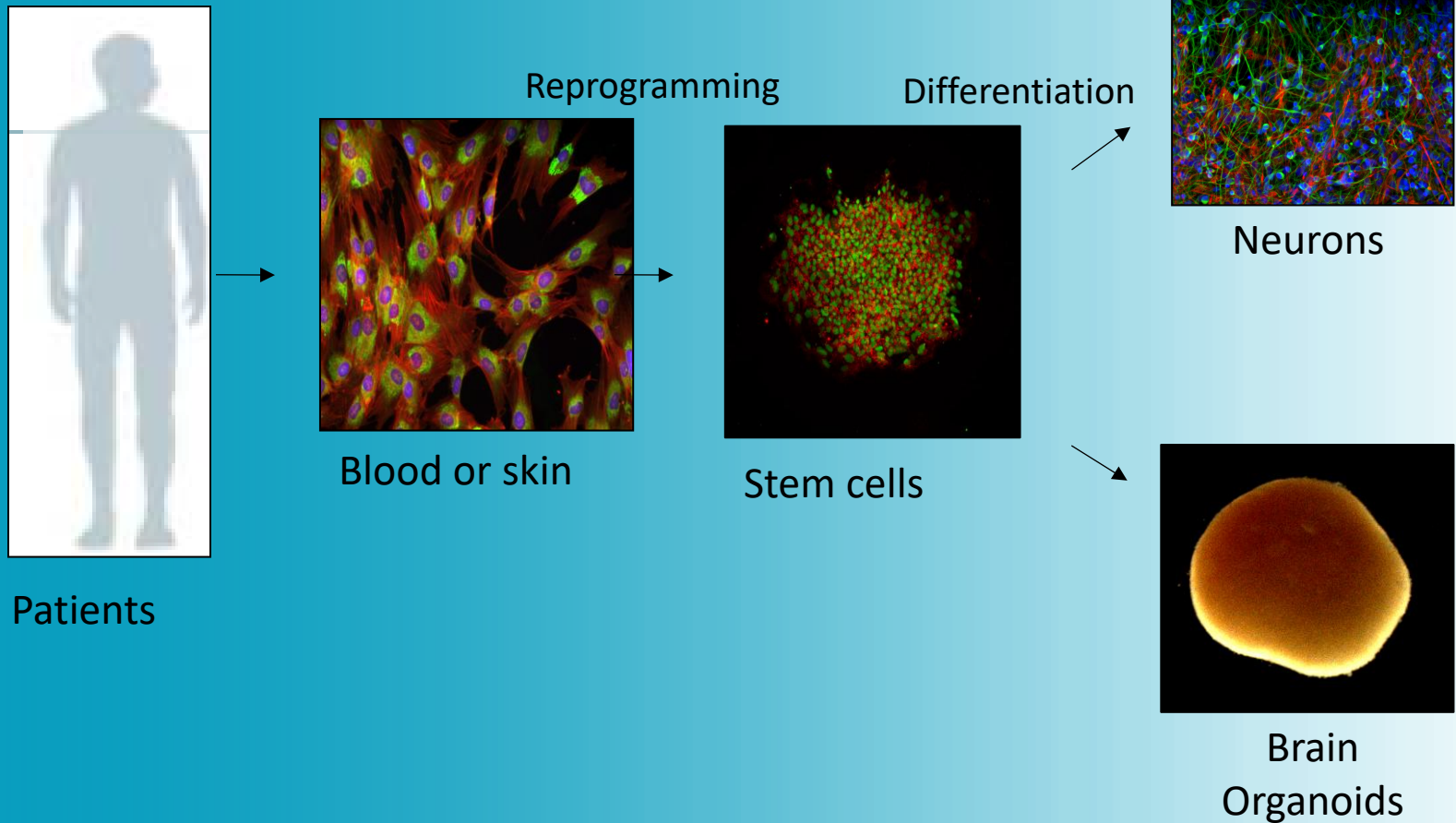


Functional activity in cortical neurons



- Disease-specific deficits in iPSC-derived cortical neurons:
 - Reduced dendritic spine density specifically in layer III neurons – as in postmortem studies
- Reduced neuronal firing with depolarization
- Clozapine rescues spine and synapse deficits

Patient-specific stem cells

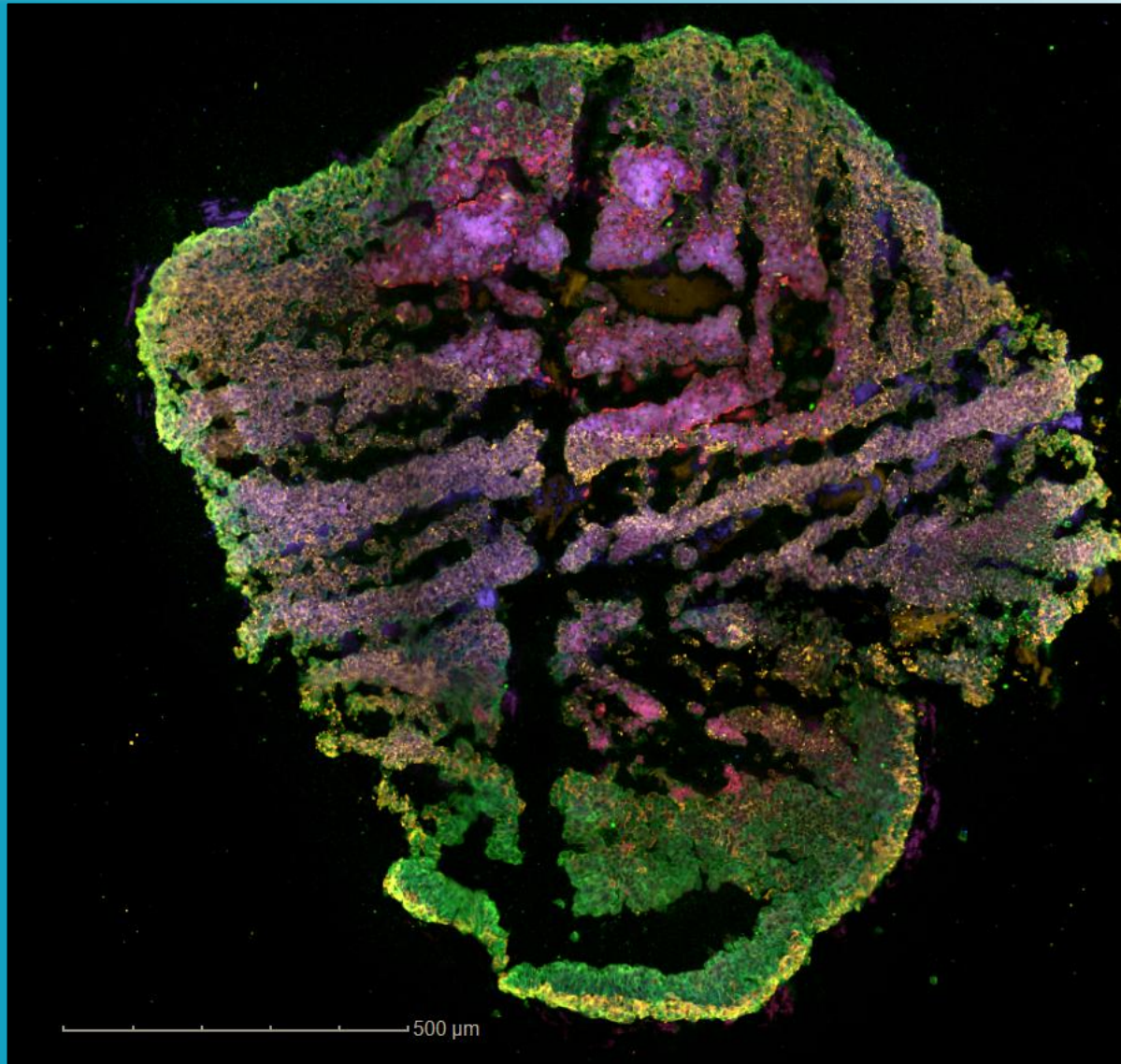


Brain organoids

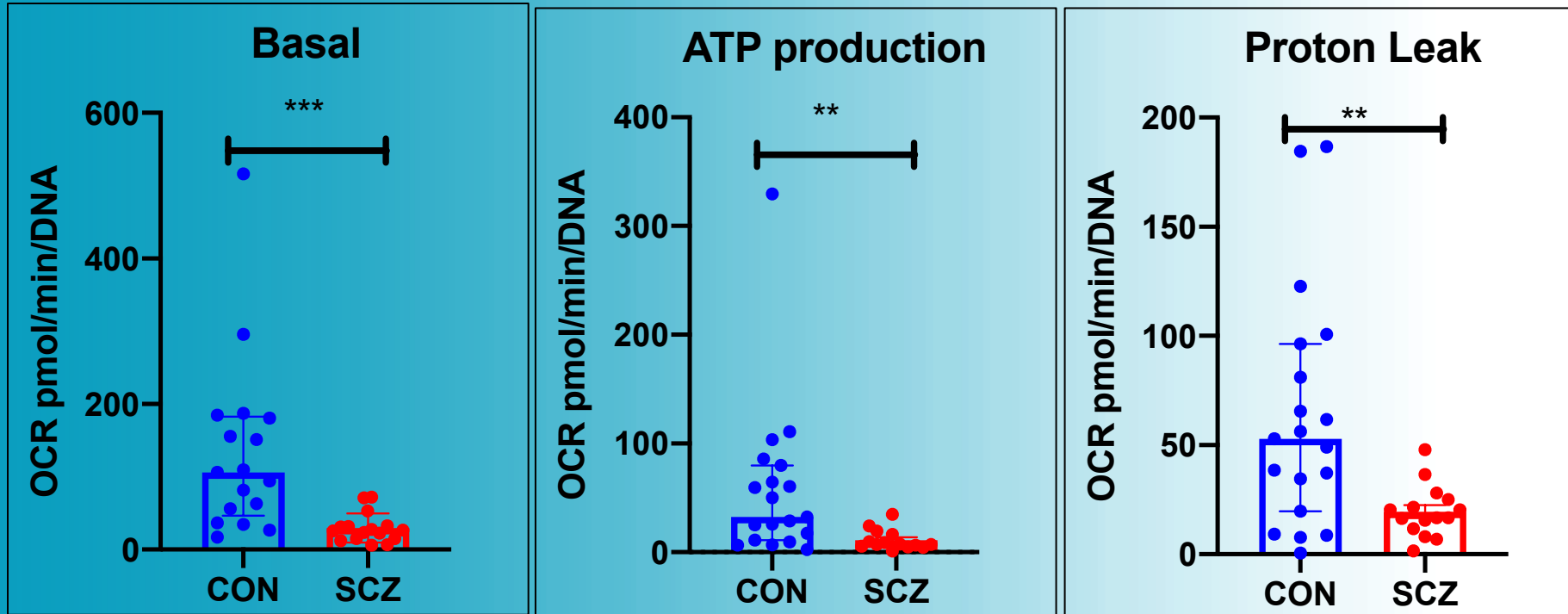


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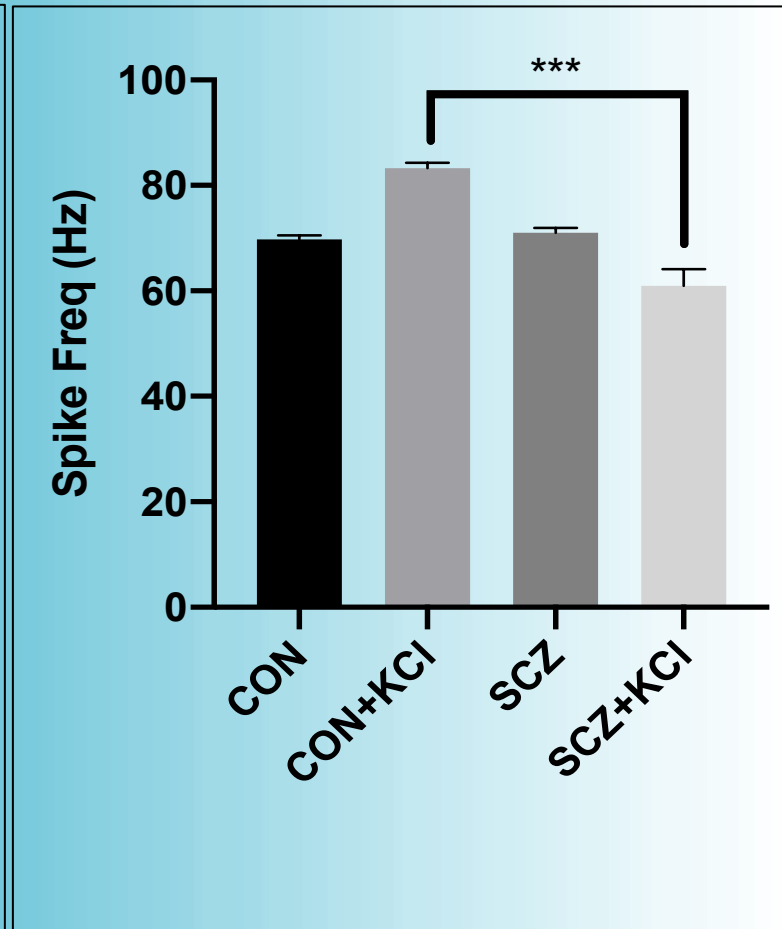
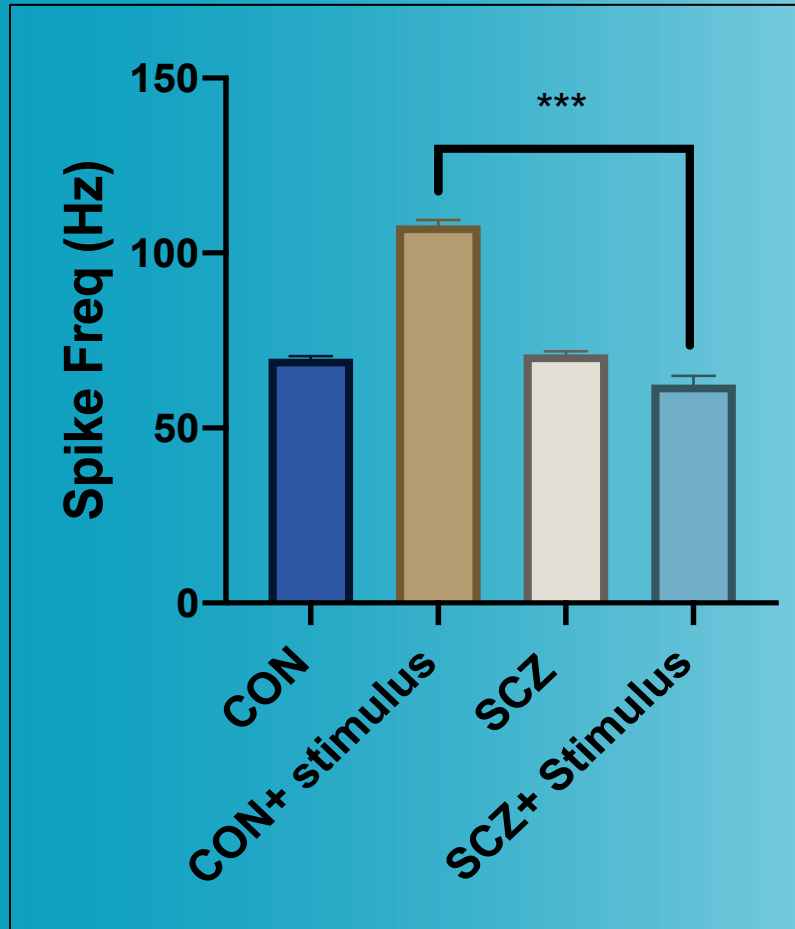
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Mitochondrial function in brain organoids



Neuronal activity in brain organoids



- Brain organoids from schizophrenia patients:
 - Transcriptomic profiling pointed to cellular processes related to mitochondrial function and excitation/inhibition balance
 - Functional studies show differences in mitochondrial biology and neuronal response to stimulation.



Future directions

- Cerebral organoids to study neurodevelopment
 - Single cell RNA-seq experiments
 - Interrogating neural network oscillations
- Gene-environment interactions in psychotic disorders
 - Focus on maternal immune activation
- Microglia-containing organoids and vascularized organoids
- Developing *in vivo* / *ex vivo* experimental paradigms
 - PET/MRI/MRS and cellular studies in same subjects

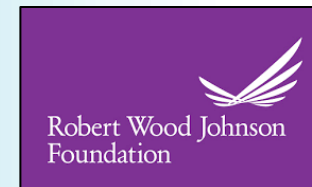
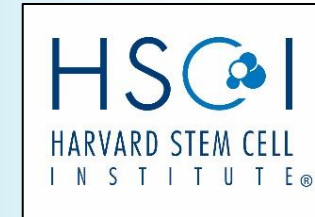
Funding

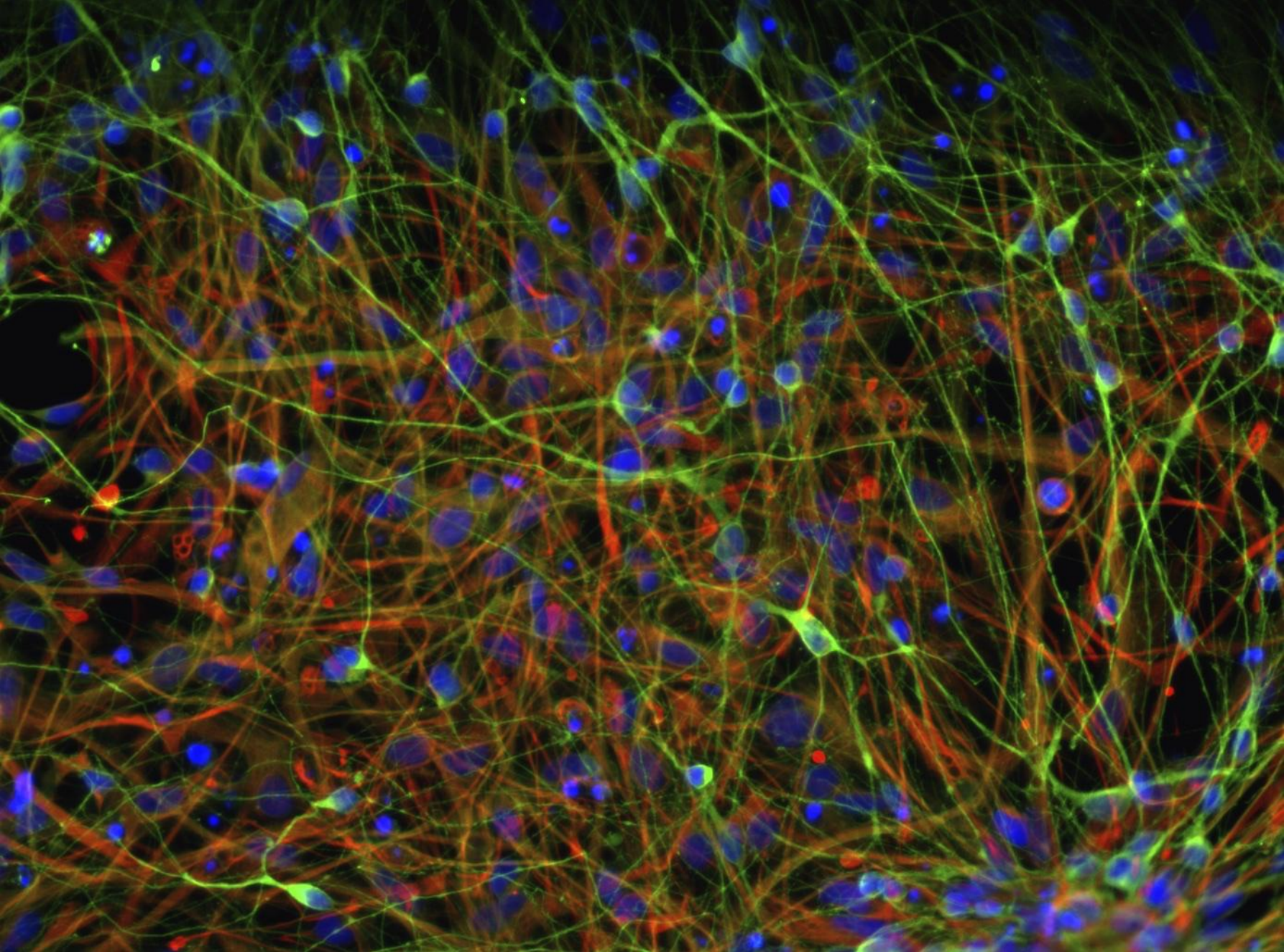


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- National Institute of Health BRAINS award
- Harvard Stem Cell Institute
- Doris Duke Charitable Foundation
- Robert Wood Johnson Foundation





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