

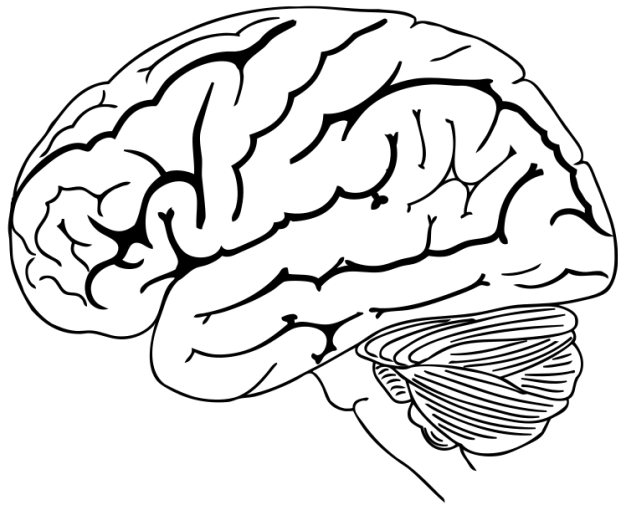
# Patient-specific modelling of Helsmoortel-Van der Aa Syndrome: what are we learning from cellular models?

Ludovico Rizzuti

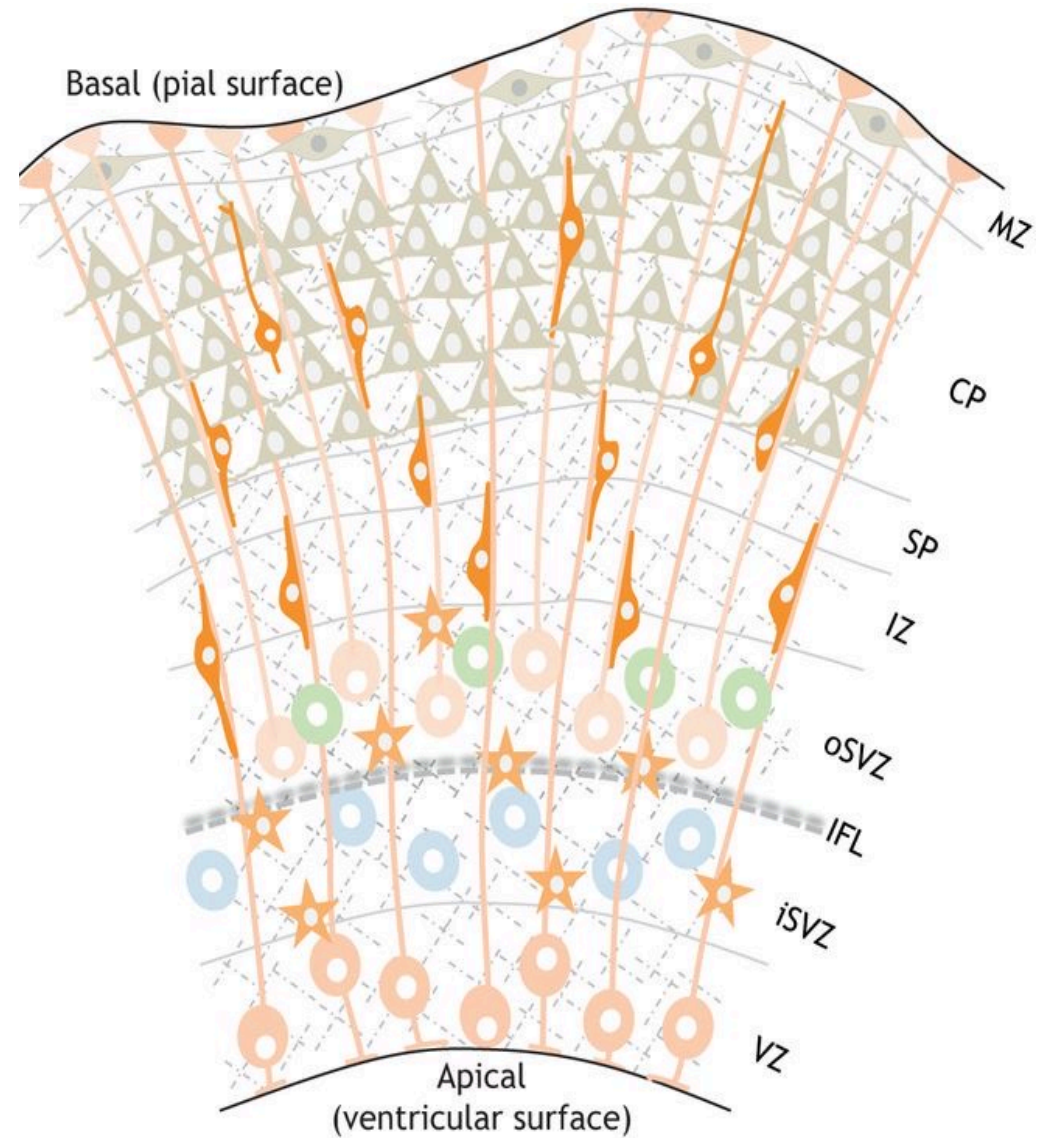
Giuseppe Testa Lab

Patient Community Day

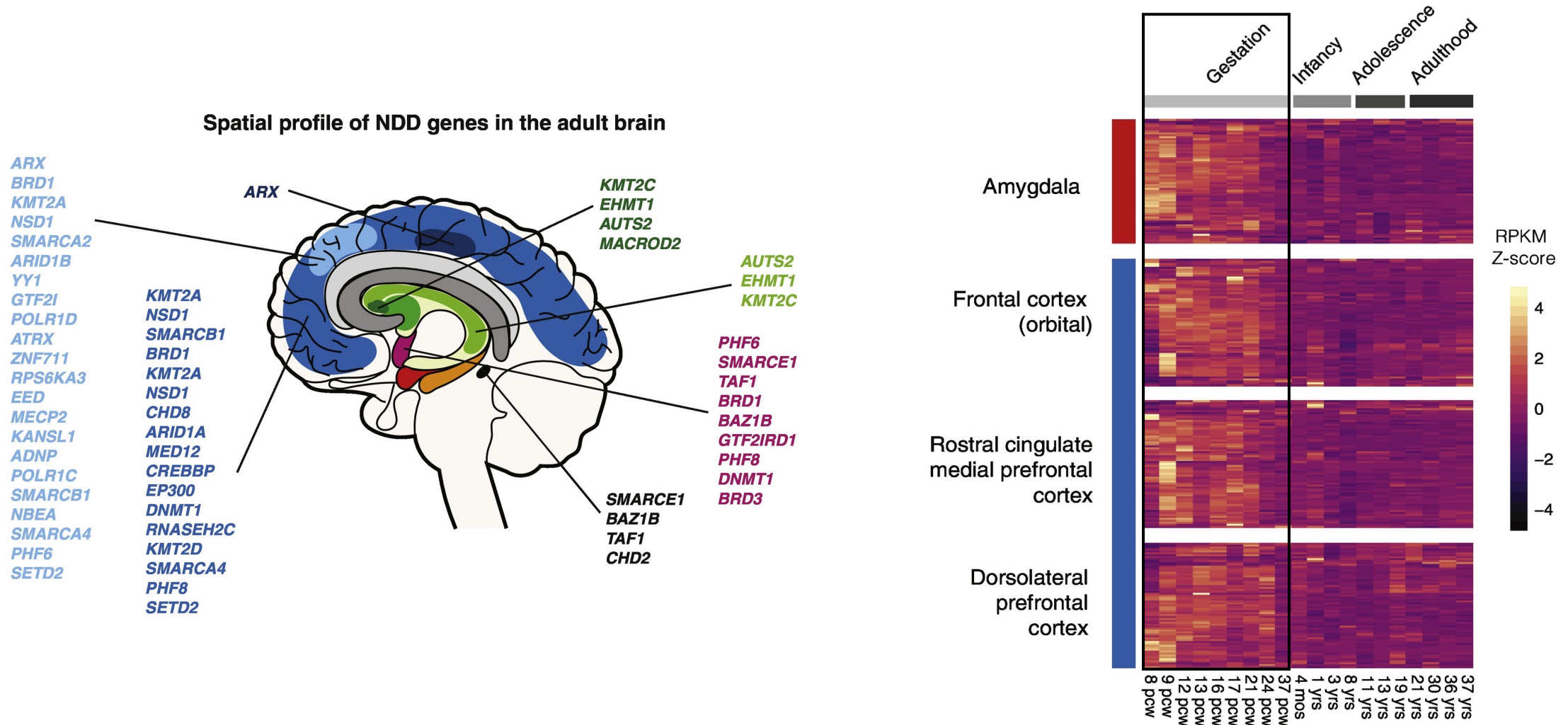
# Spatio-temporal profile of Neurodevelopmental Disorders



The **cortex** is involved in higher cognitive functions often disrupted in multiple NDDs



# Spatio-temporal profile of Neurodevelopmental Disorders



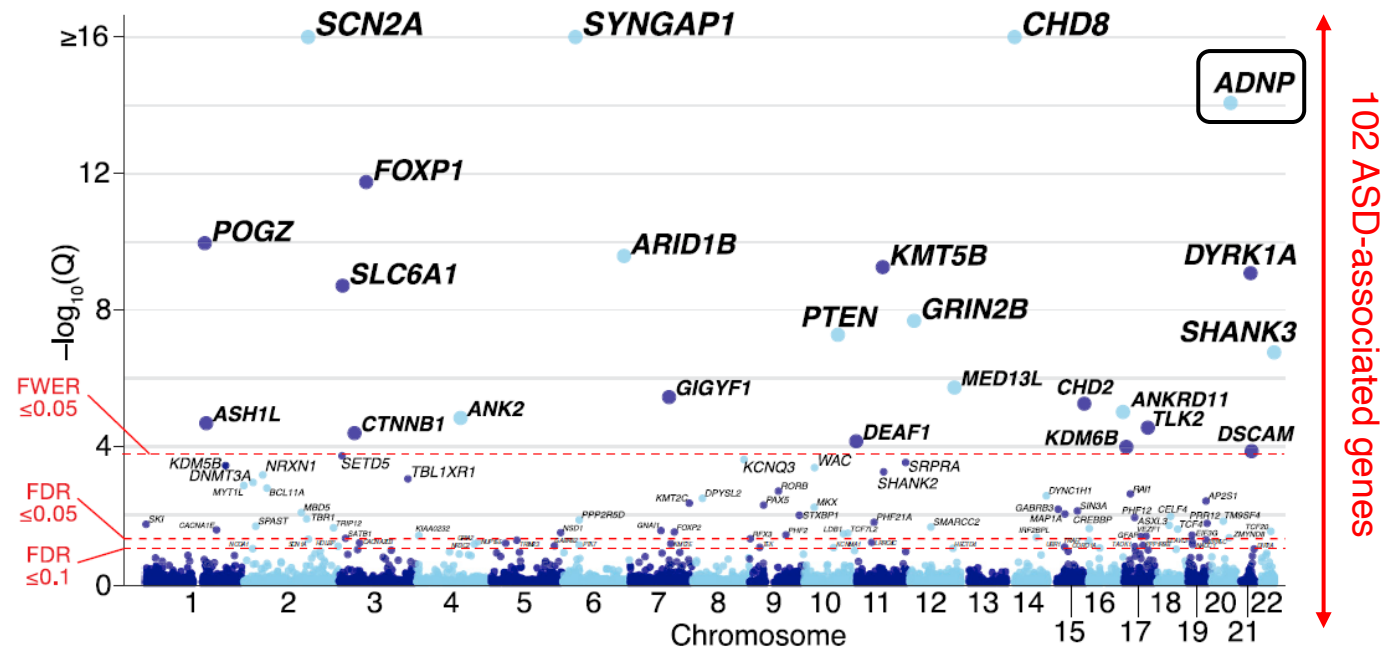
**Early development** is a particularly susceptible window in which gene mutations can result in their **highest phenotypical impact**

# ADNP in the genetic architecture of Autism Spectrum Disorder

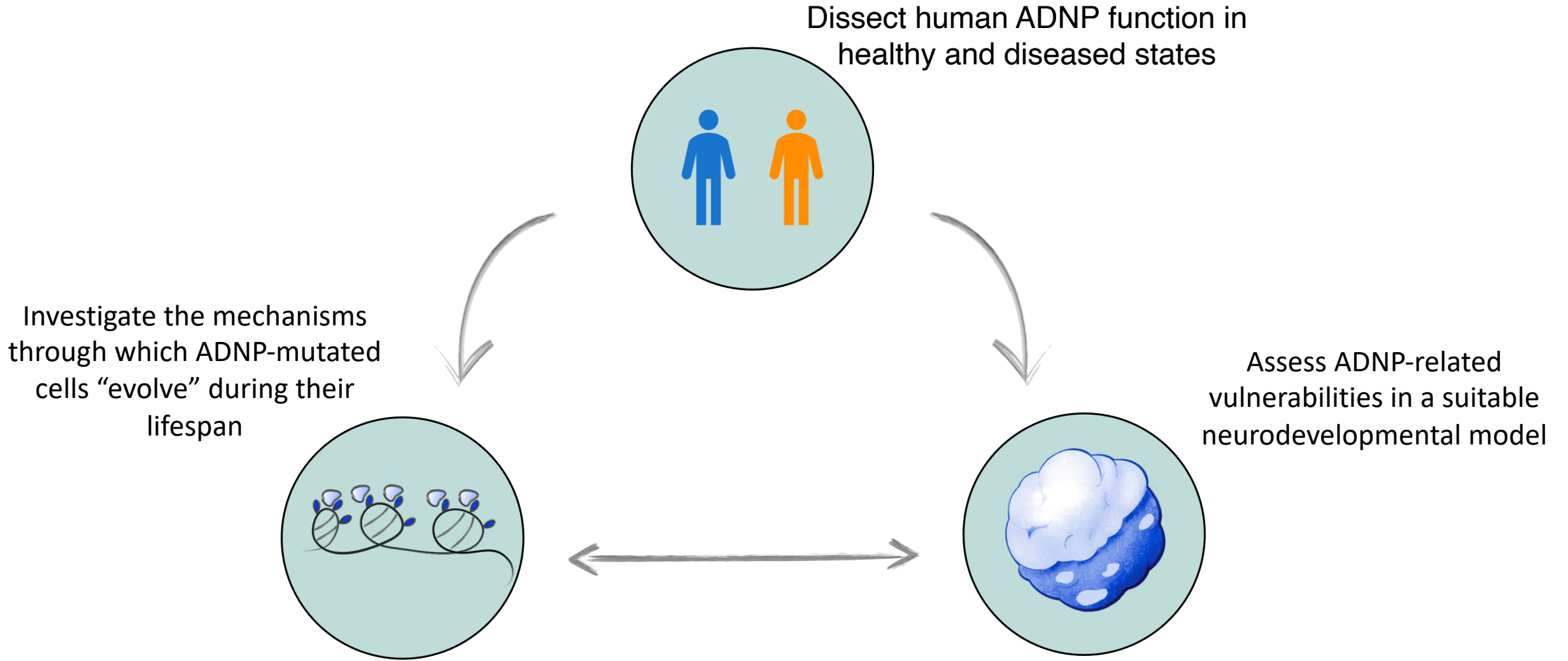
## A SWI/SNF-related autism syndrome caused by *de novo* mutations in *ADNP*

[Céline Helsmoortel](#), [Anneke T Vulto-van Silfhout](#), [Bradley P Coe](#), [Geert Vandeweyer](#), [Liesbeth Rooms](#), [Jenneke van den Ende](#), [Janneke H M Schuurs-Hoeijmakers](#), [Carlo L Marcelis](#), [Marjolein H Willemsen](#), [Lisenka E L M Vissers](#), [Helger G Yntema](#), [Madhura Bakshi](#), [Meredith Wilson](#), [Kali T Witherspoon](#), [Helena Malmgren](#), [Ann Nordgren](#), [Göran Annerén](#), [Marco Fichera](#), [Paolo Bosco](#), [Corrado Romano](#), [Bert B A de Vries](#), [Tijtske Kleefstra](#), [R Frank Kooy](#) ✉, [Evan E Eichler](#) & [Nathalie Van der Aa](#) ✉

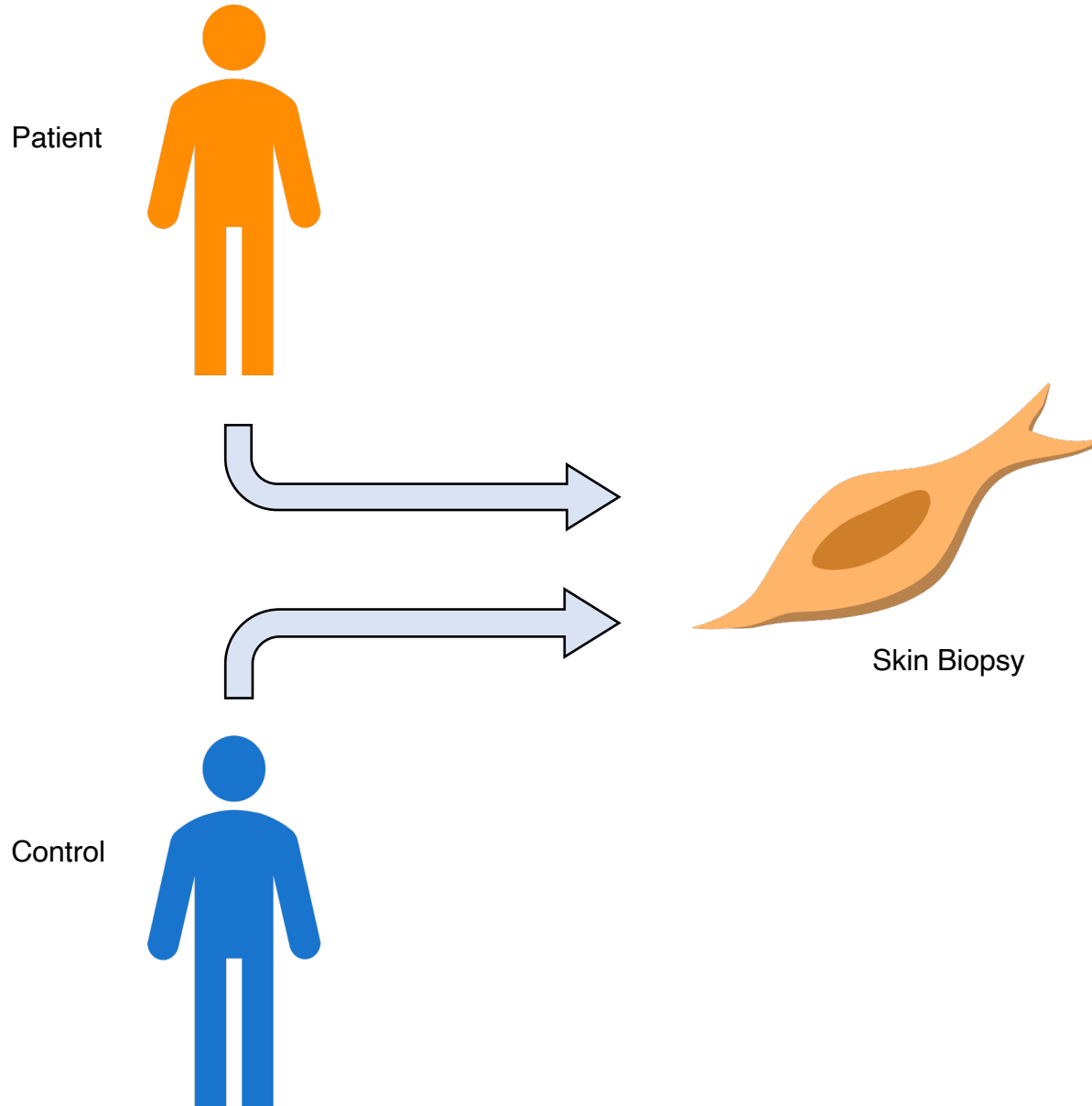
### Large-scale exome-seq identifies high-risk ASD-associated genes



# Objectives

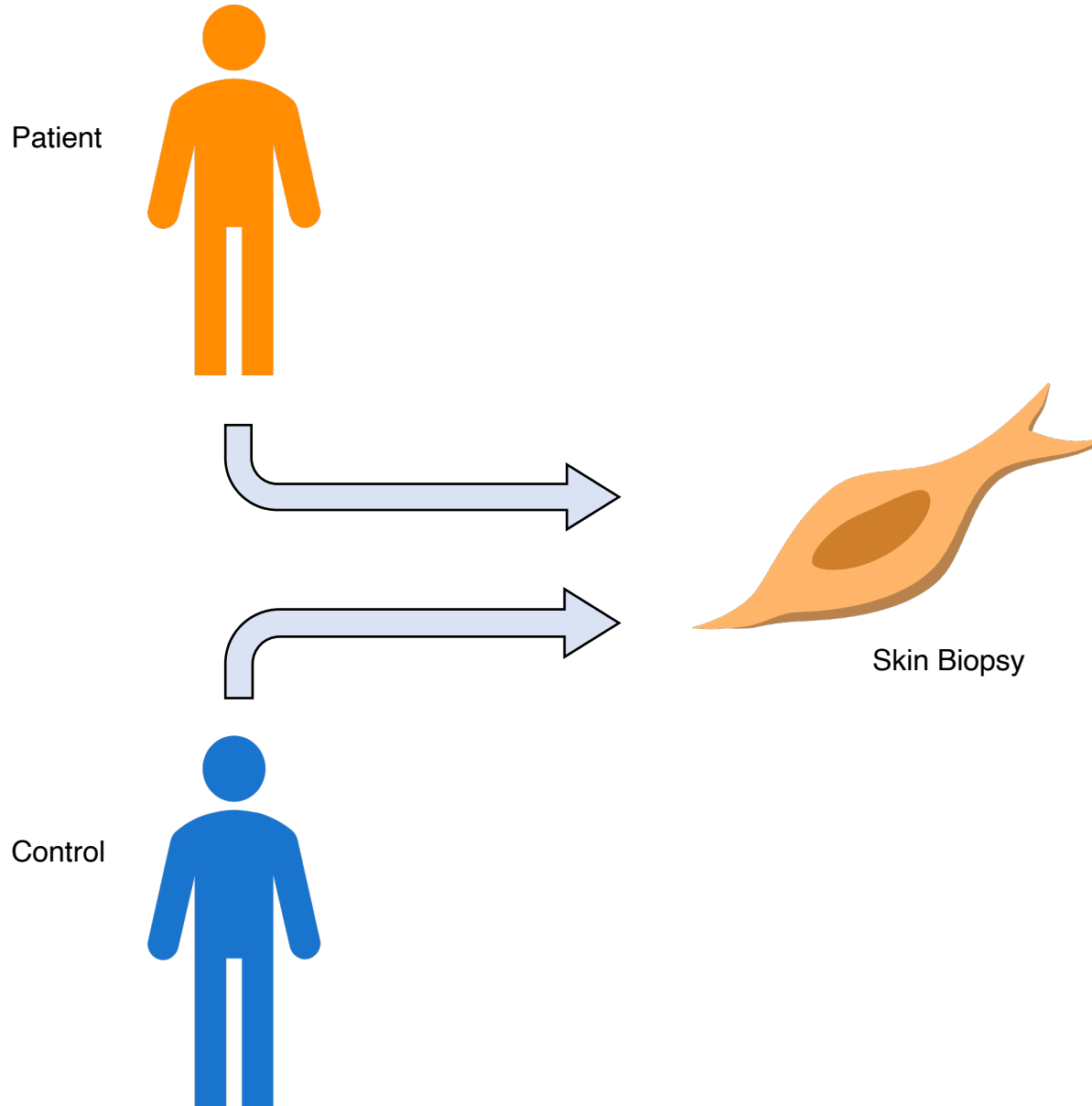


# Where do we start to study HVDAS?



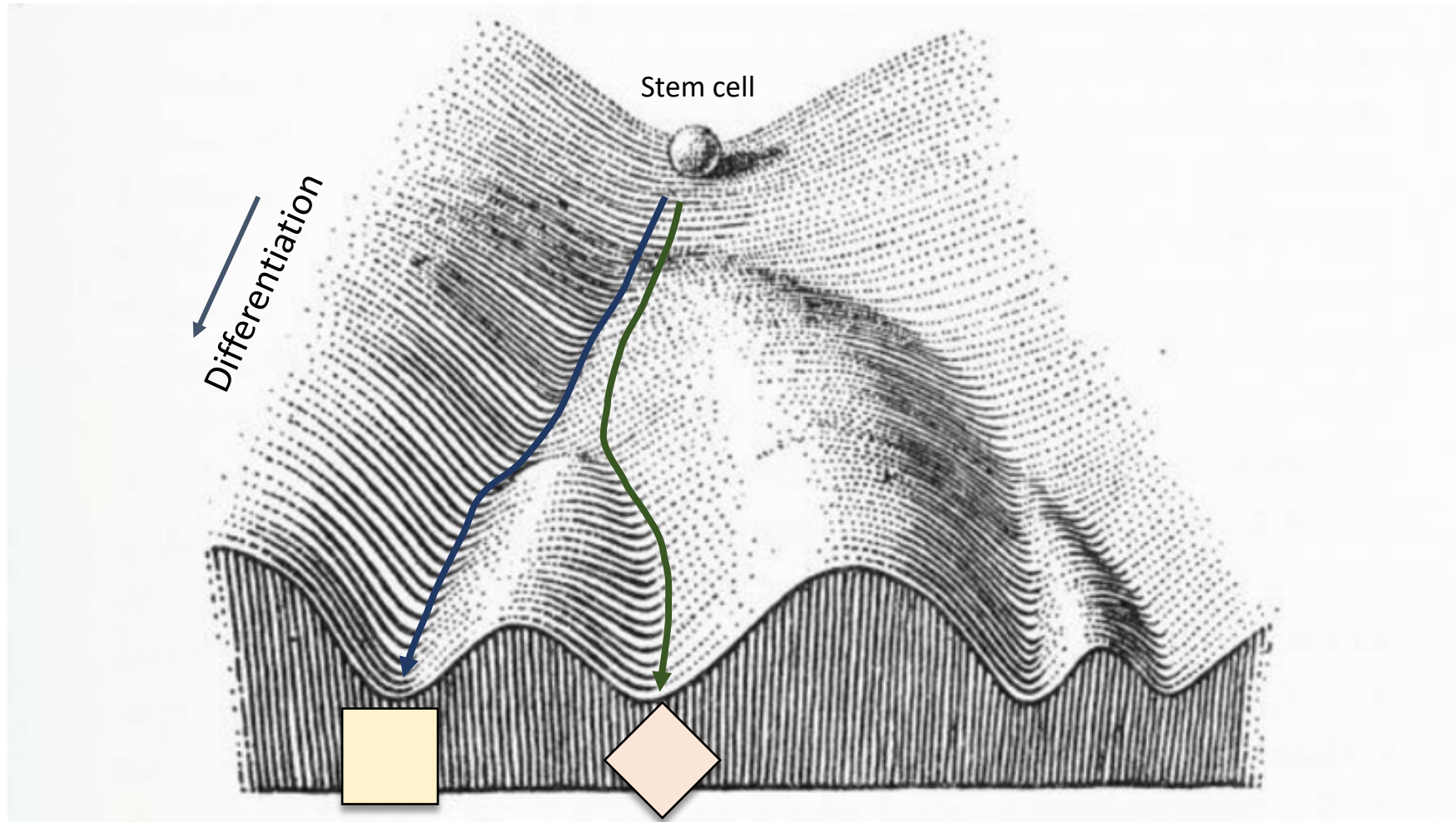
- Not relevant for the study of the pathology
- Not suitable for long term culture *in vitro*
- No differentiation potential

# Where do we start to study HVDAS?



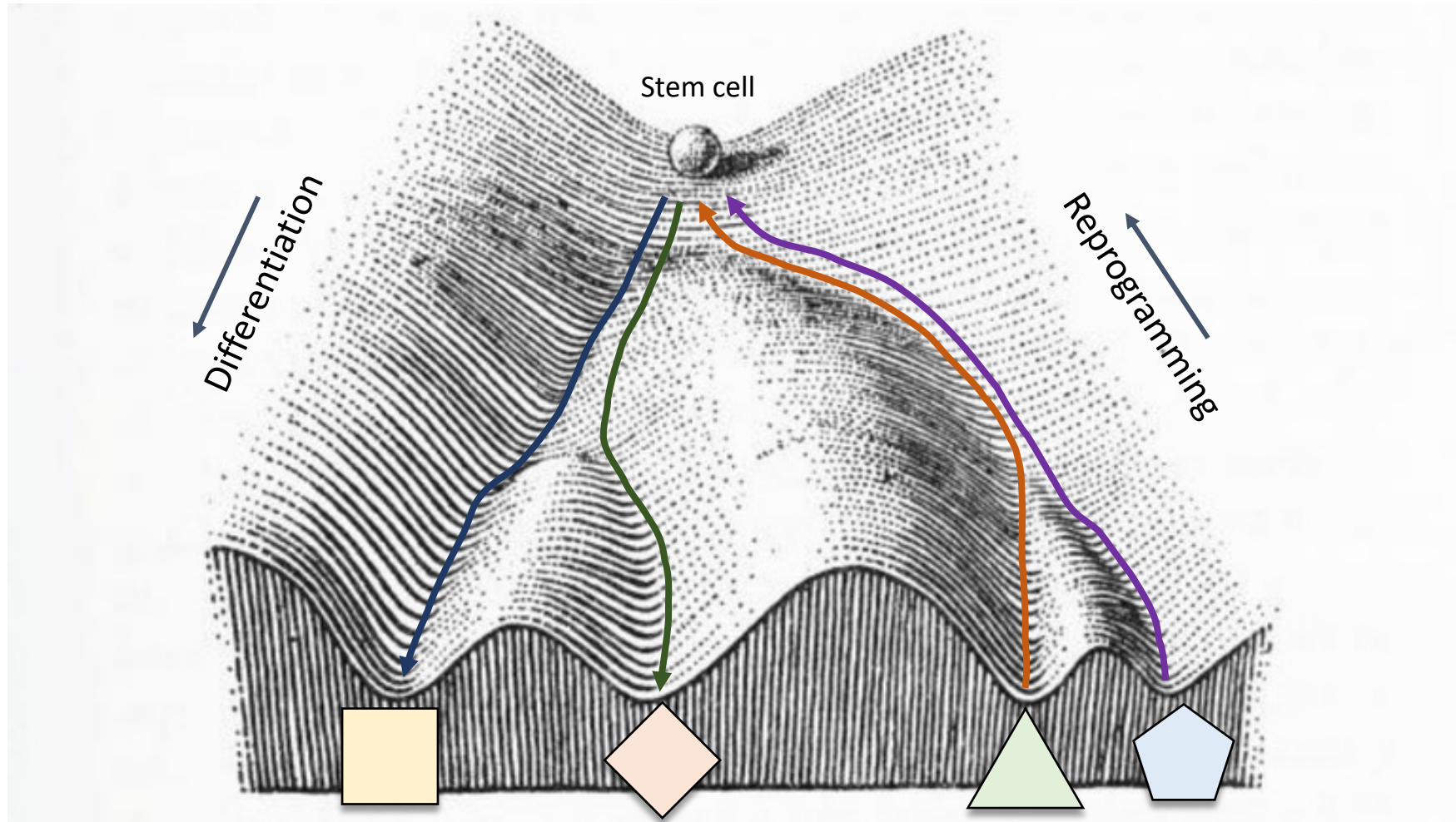
- Not relevant for the study of the pathology
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What is a pluripotent stem cell, and why is that important?

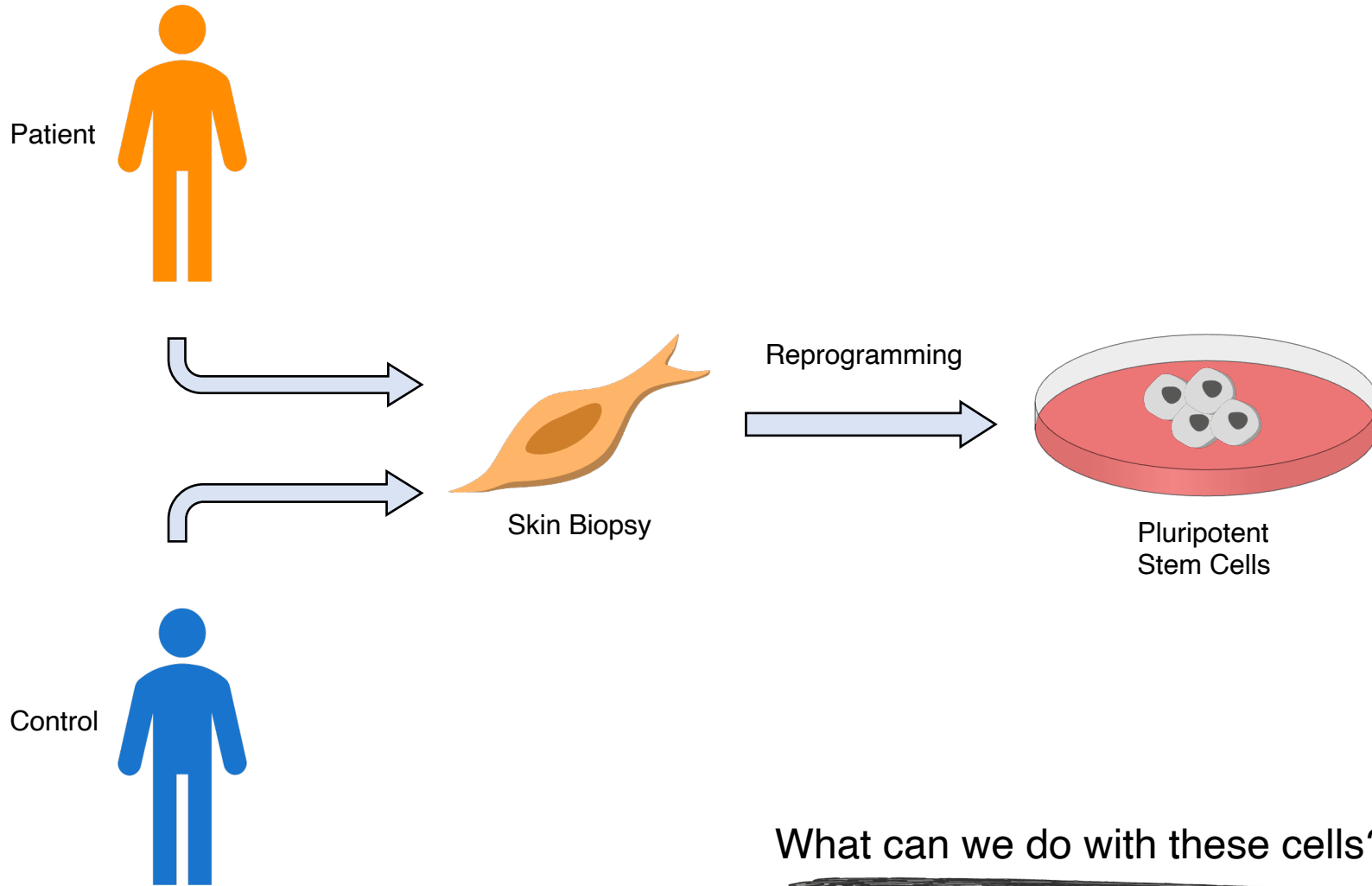




# What is a pluripotent stem cell, and why is that important?



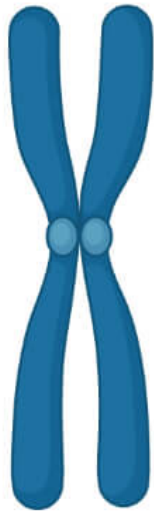
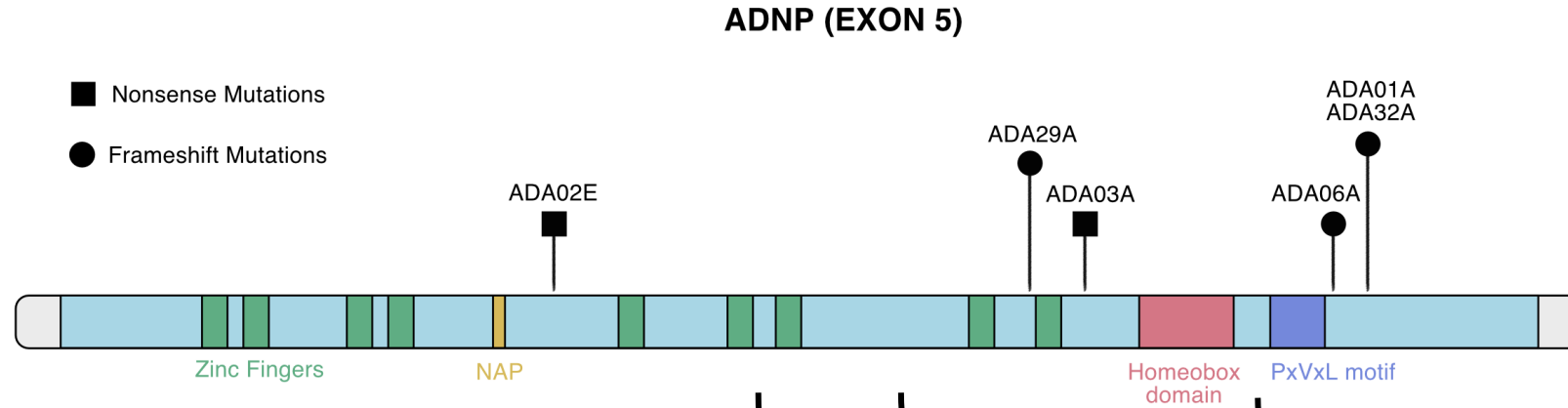
# What is a pluripotent stem cell, and why is that important?



- Representative of the embryonic-like patient-specific cell behaviour
- Suitable for long term culture *in vitro*
- Ability to differentiate into every organism tissue

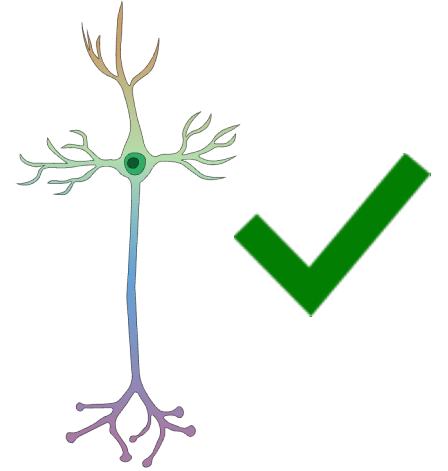
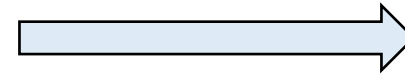
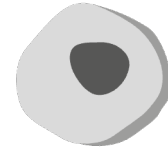
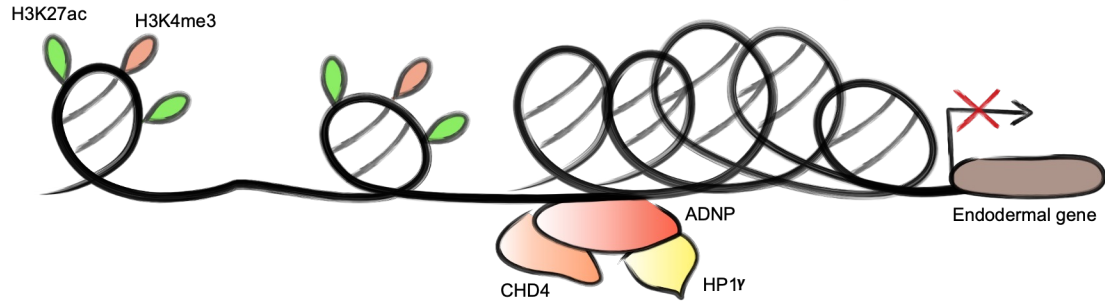
What can we do with these cells?

# Where does ADNP act on a molecular level, and why is that important?

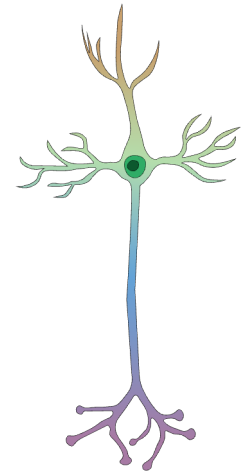
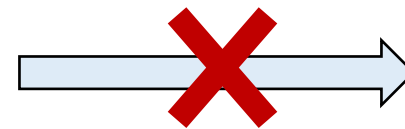
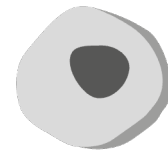
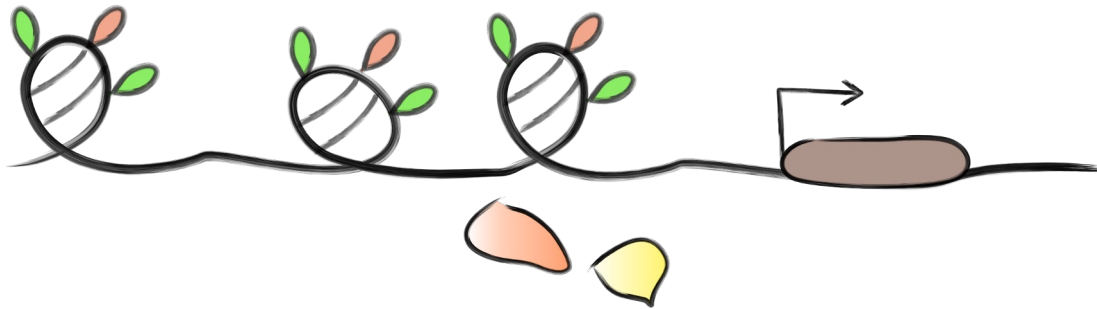


# Where does ADNP act on a molecular level, and why is that important?

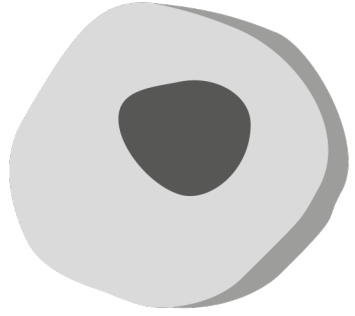
ADNP properly functioning



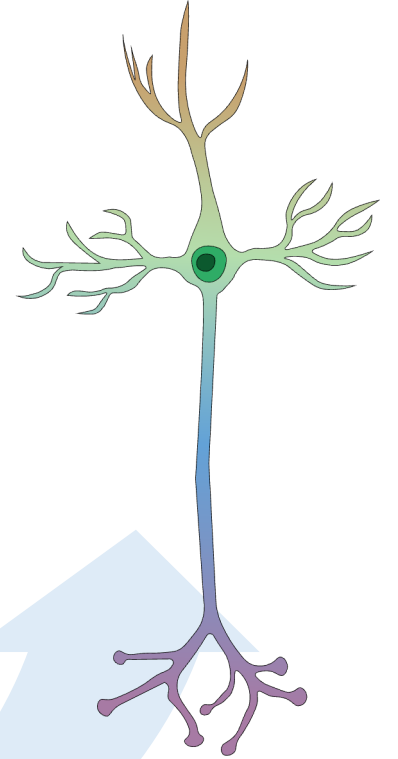
ADNP missing



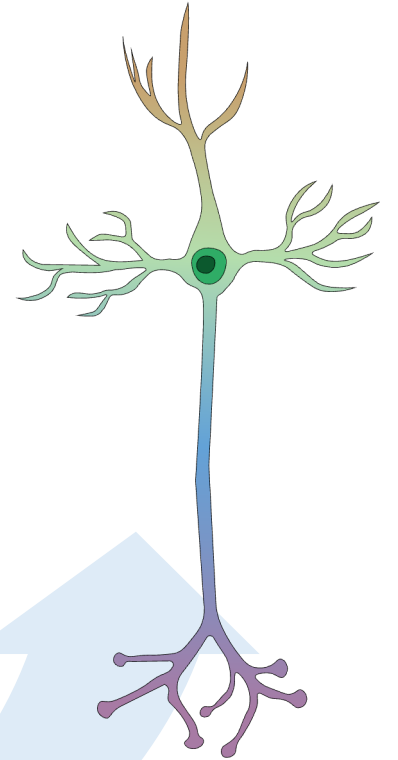
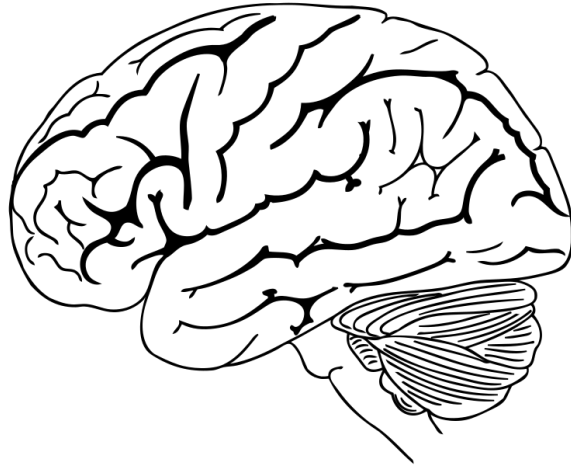
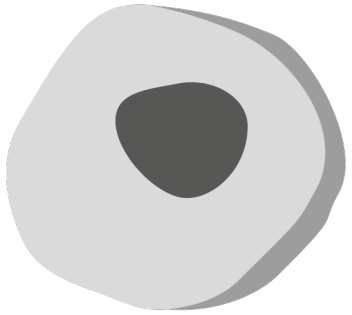
What is a pluripotent stem cell, and why is that important?



Investigate the function of ADNP in genomic regulation during neurogenesis

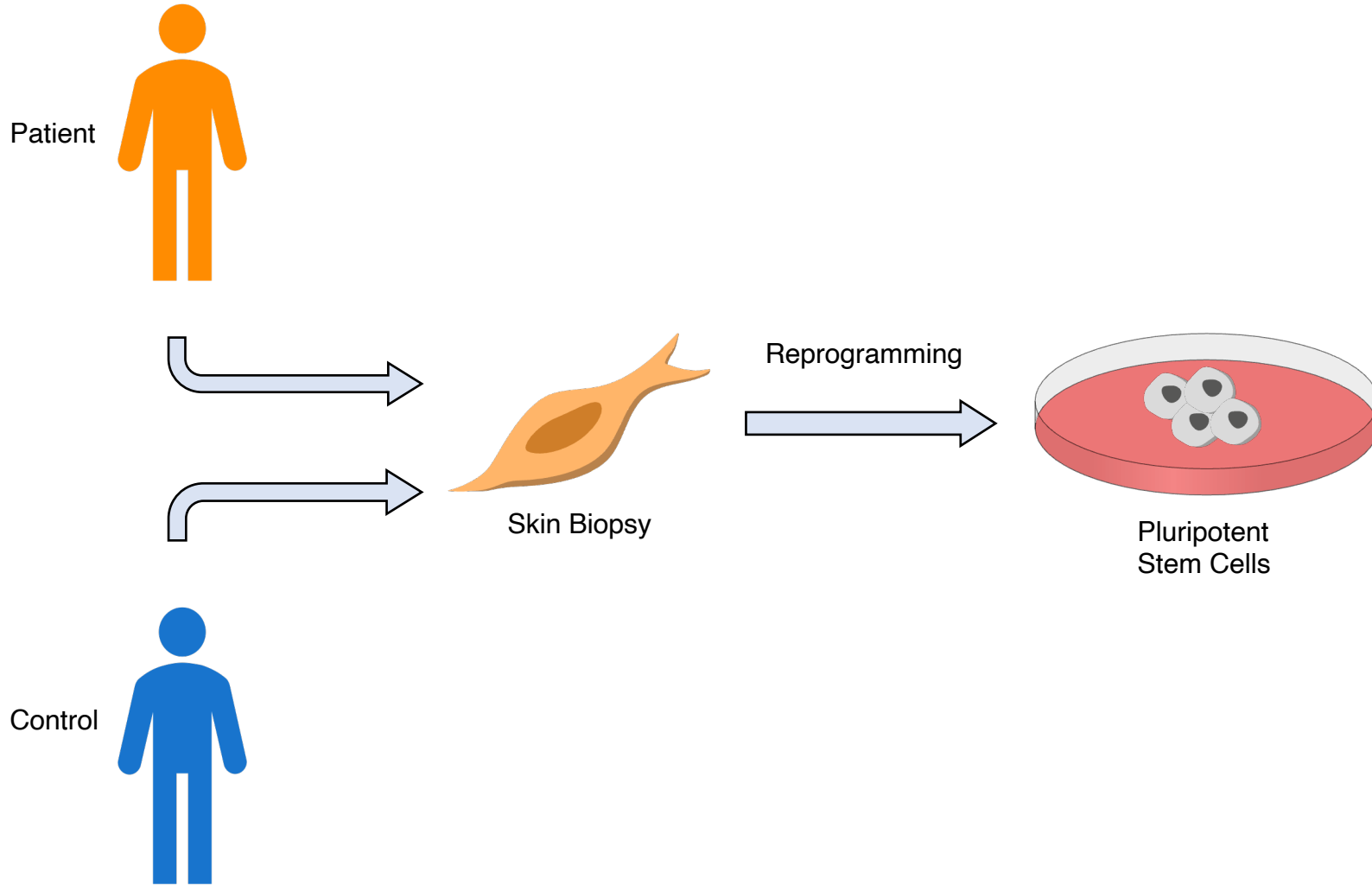


# What is a pluripotent stem cell, and why is that important?



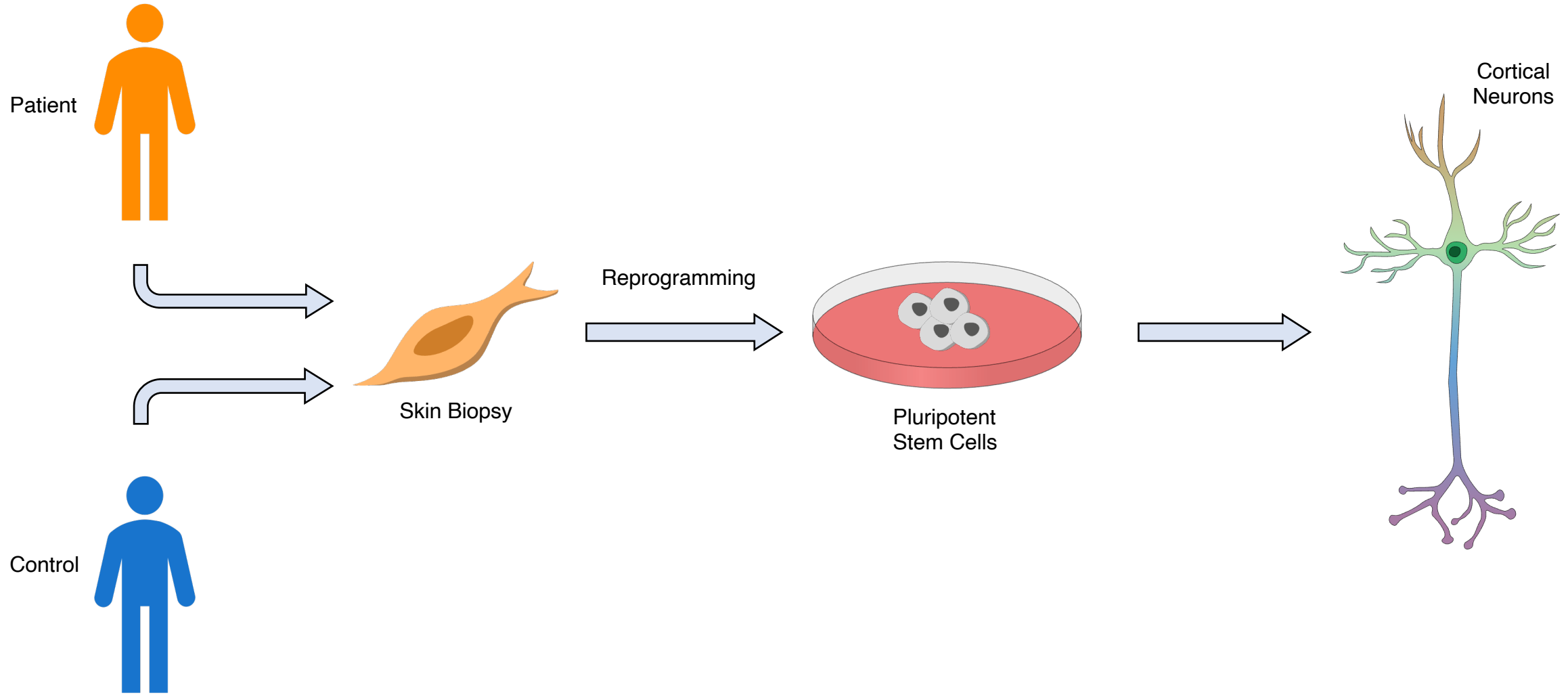
- Inaccessible tissue
- Post-mortem samples do not recapitulate developmental features of human brain

# What is a pluripotent stem cell, and why is that important?



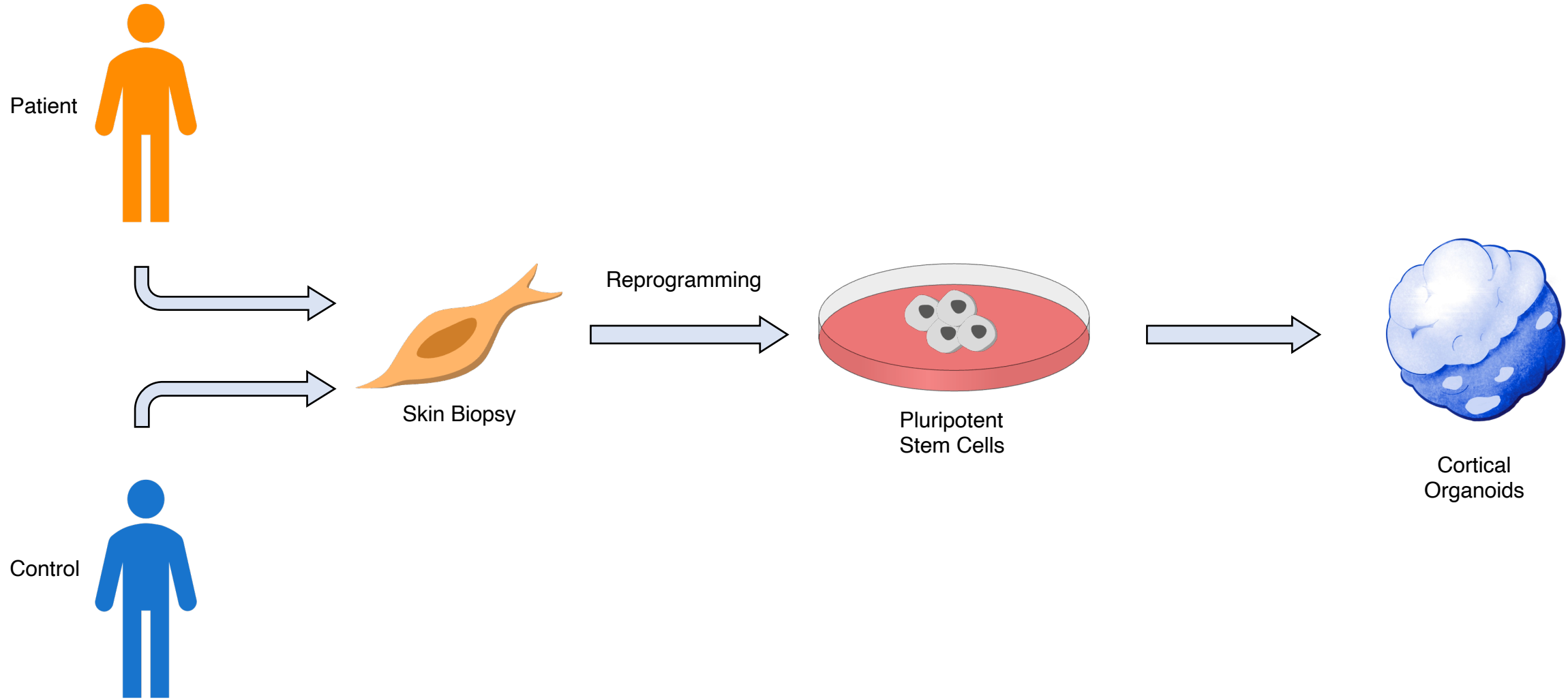
- Representative of the embryonic-like patient-specific cell behaviour
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# What is a pluripotent stem cell, and why is that important?

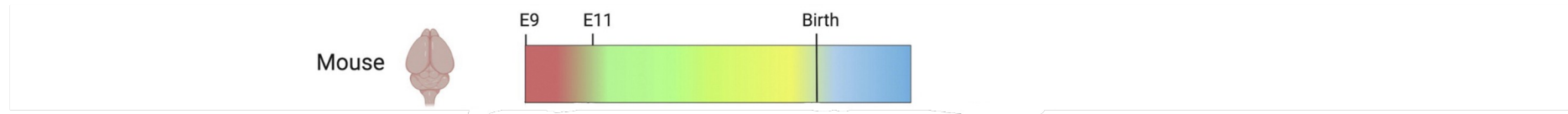




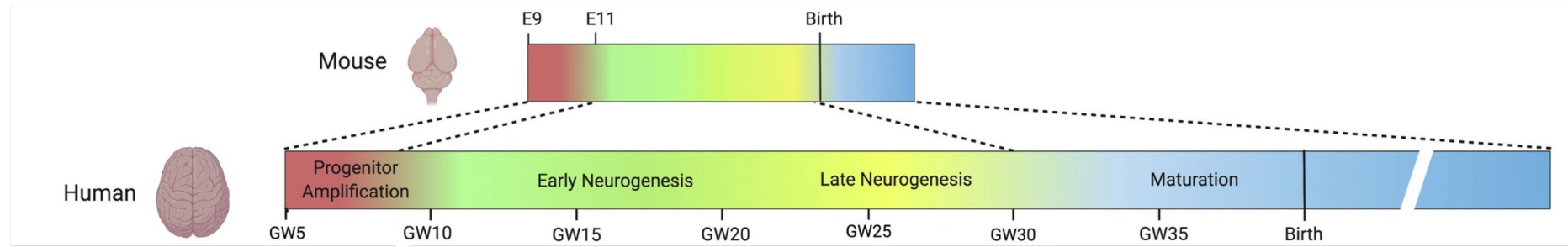
# What is a pluripotent stem cell, and why is that important?



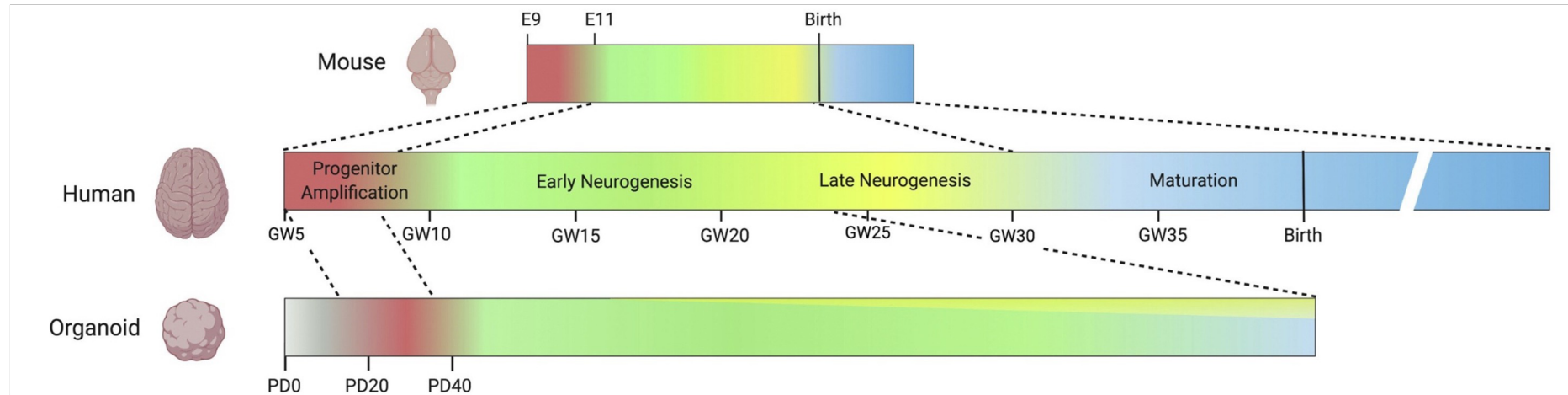
# Neurodevelopmental range of experimental models



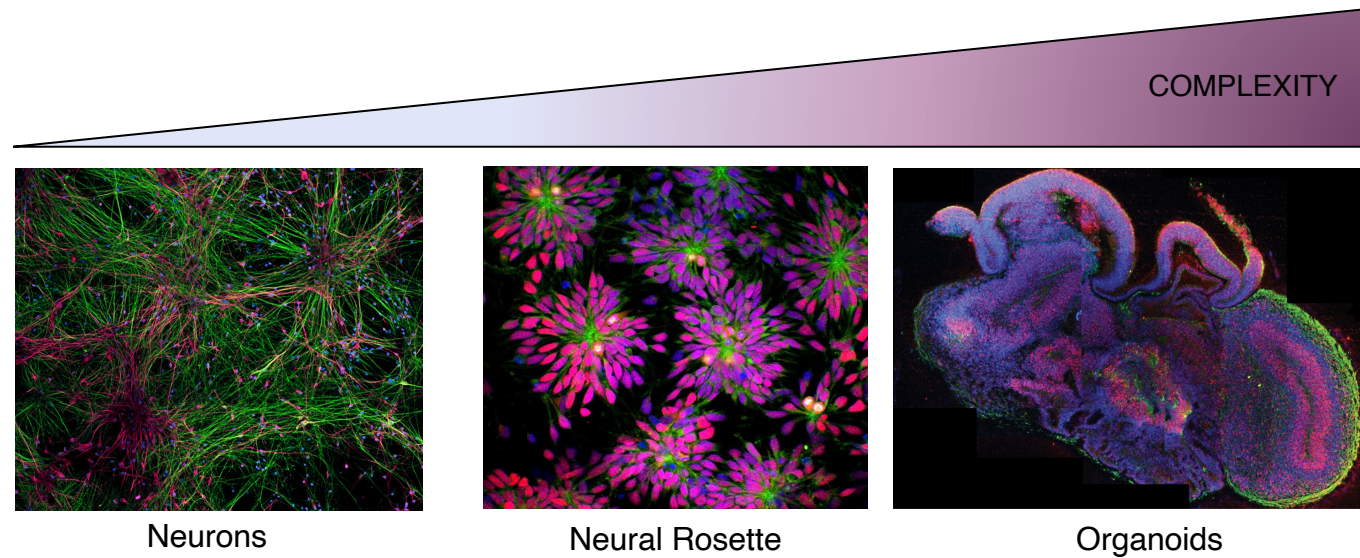
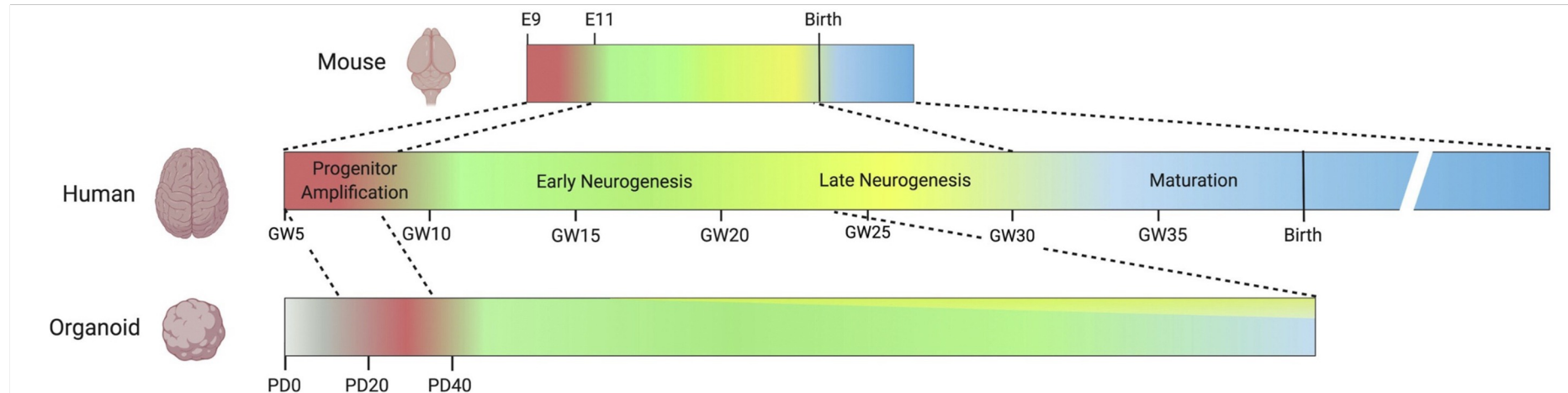
# Neurodevelopmental range of experimental models



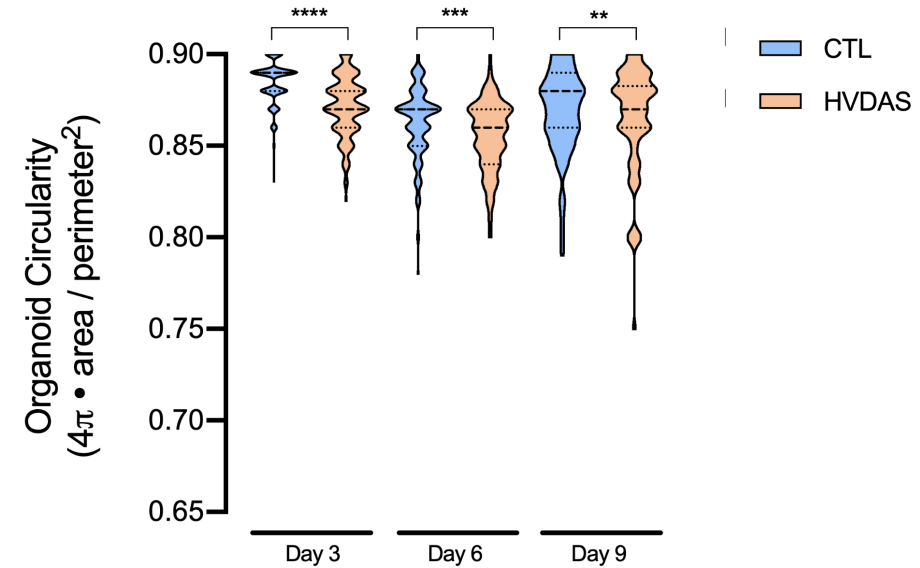
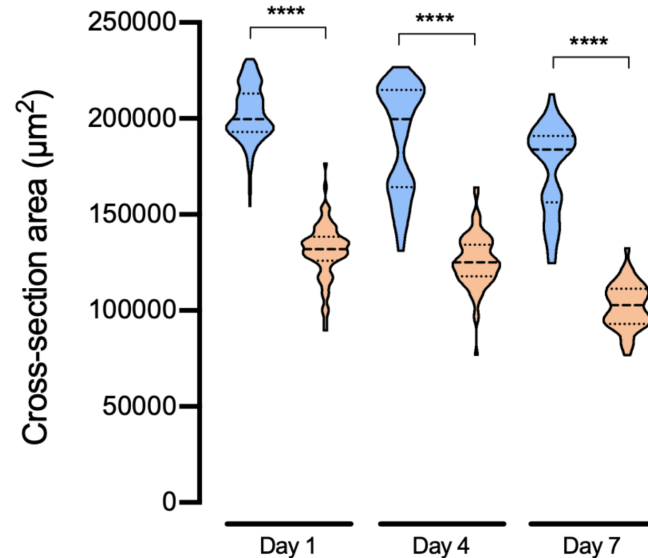
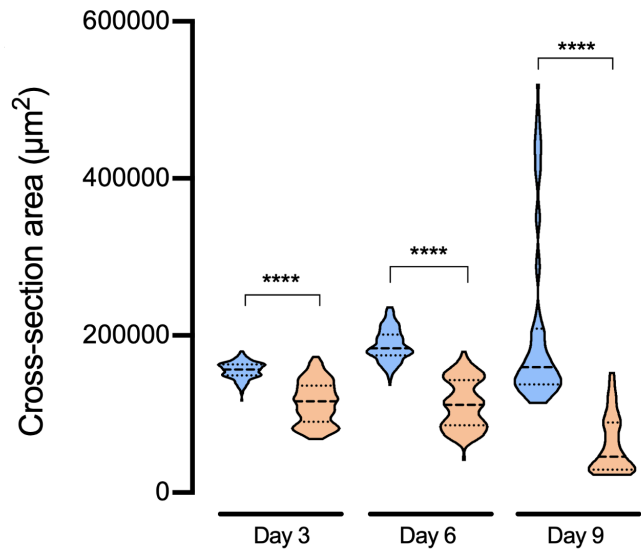
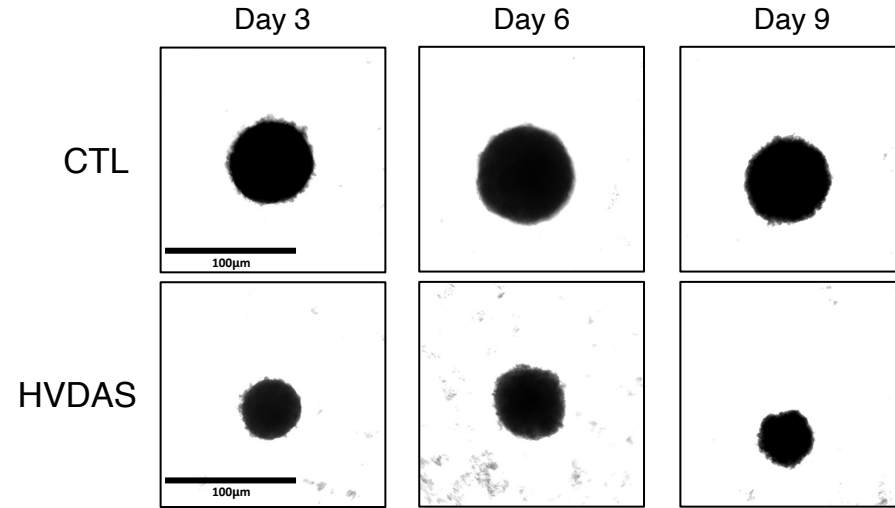
# Neurodevelopmental range of experimental models



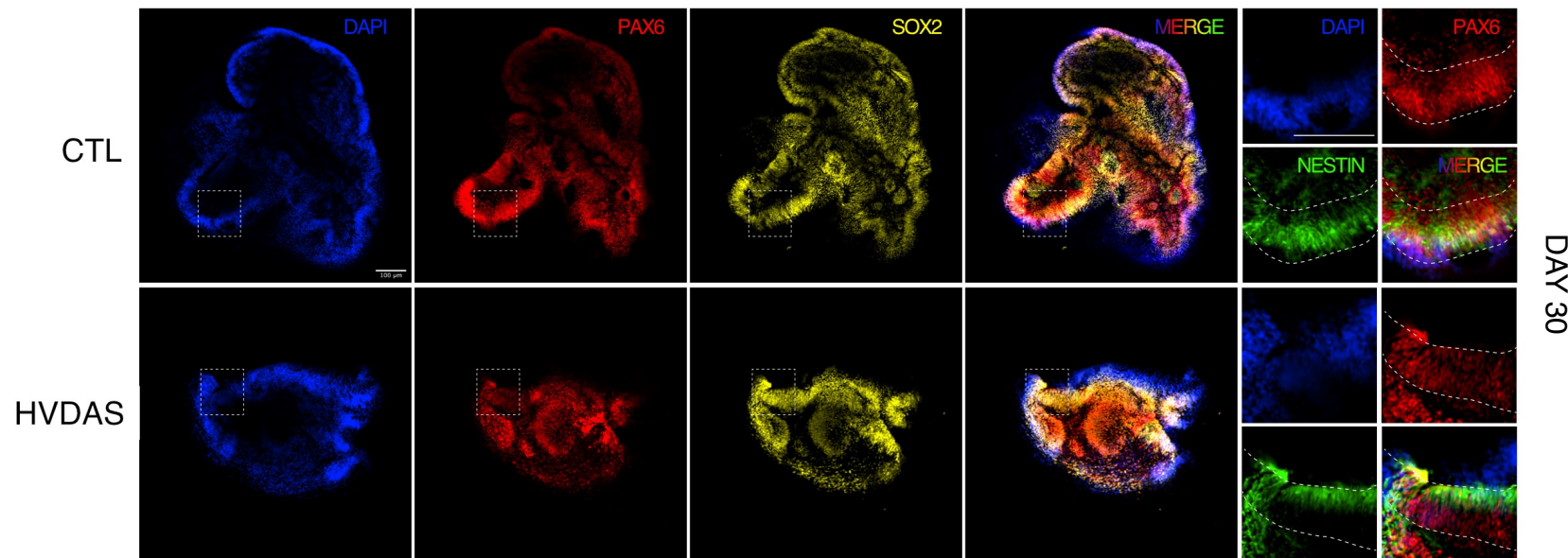
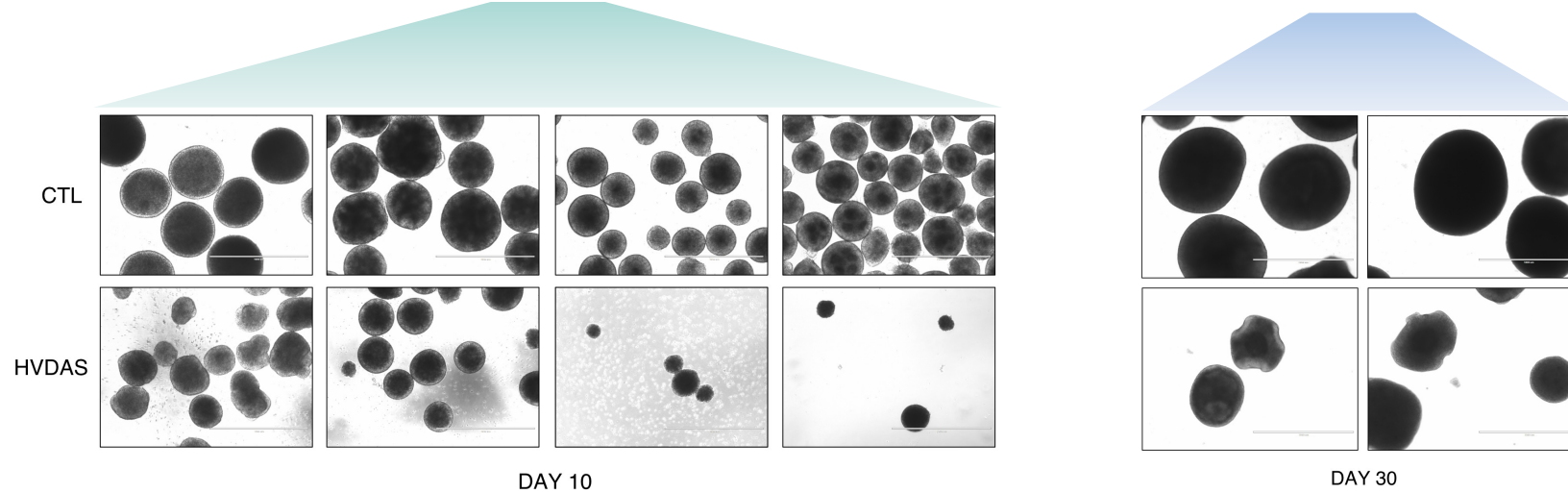
# Neurodevelopmental range of experimental models



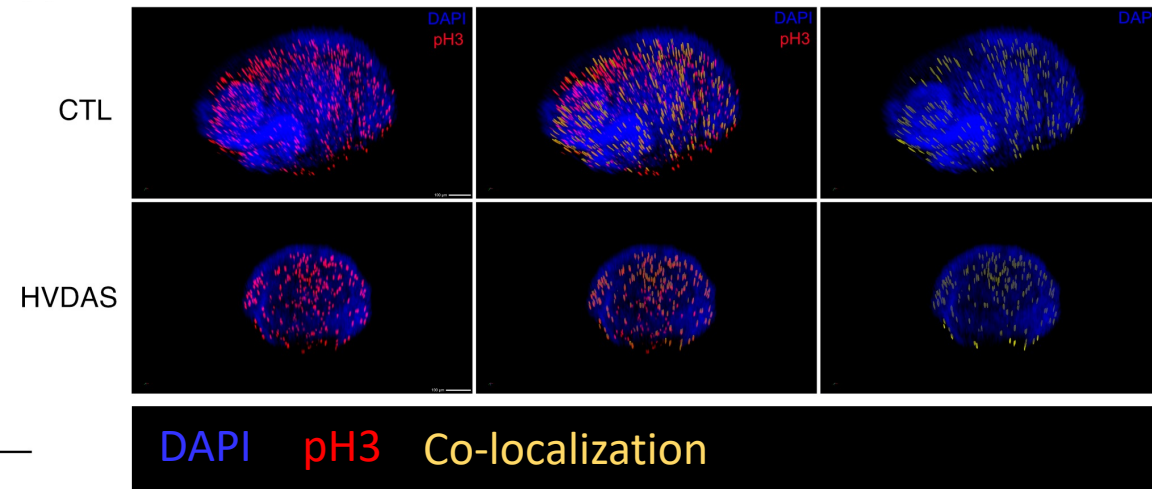
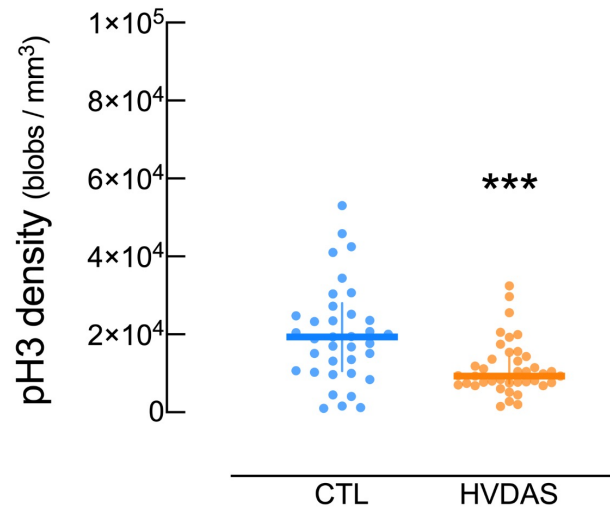
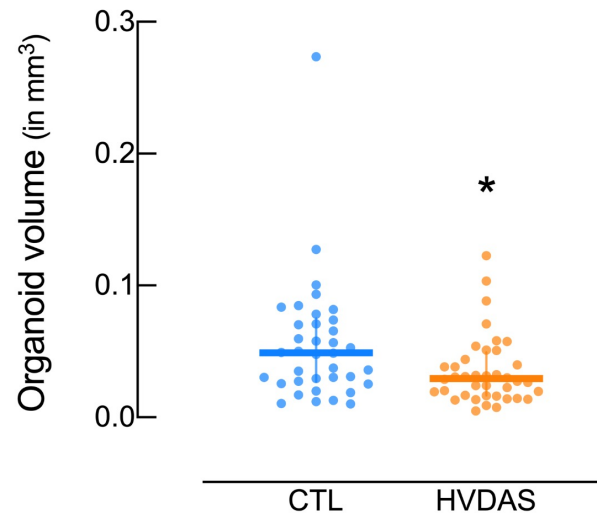
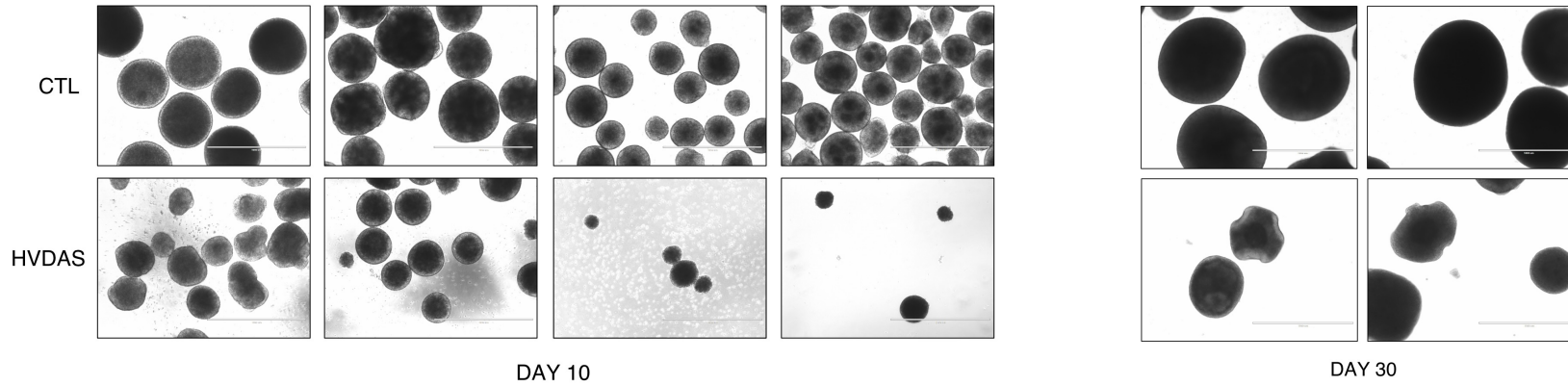
# HVDAS cortical spheroids show morphological alterations



# HVDAS cortical organoids show morphological alterations with proliferation defects

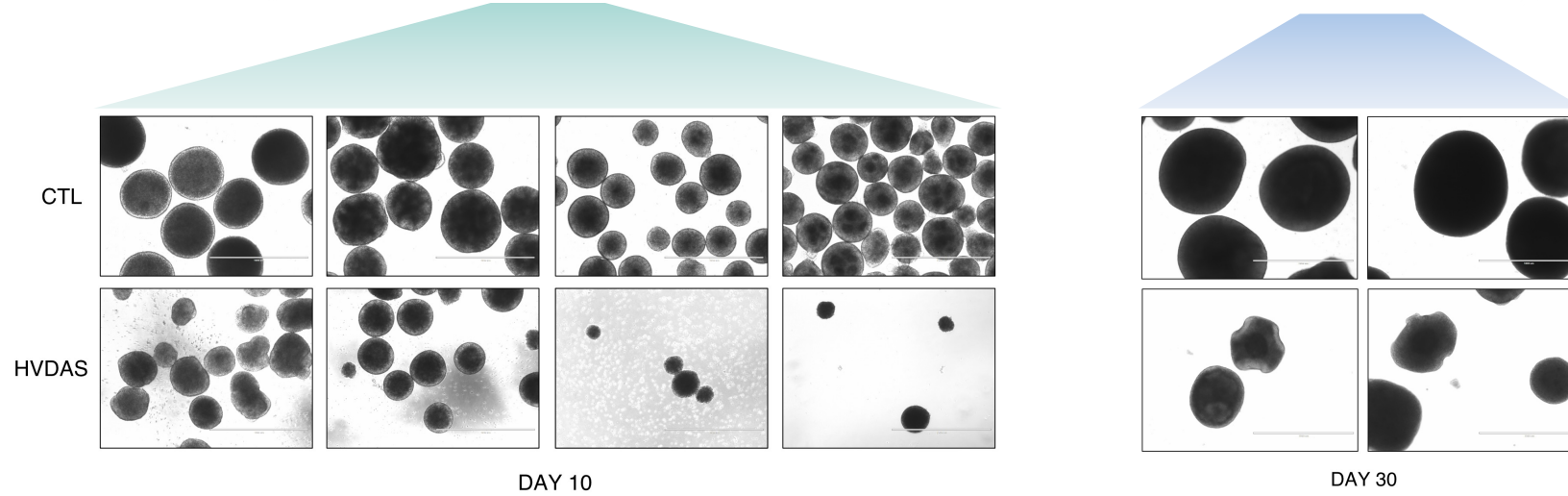


# HVDAS cortical organoids show morphological alterations with proliferation defects

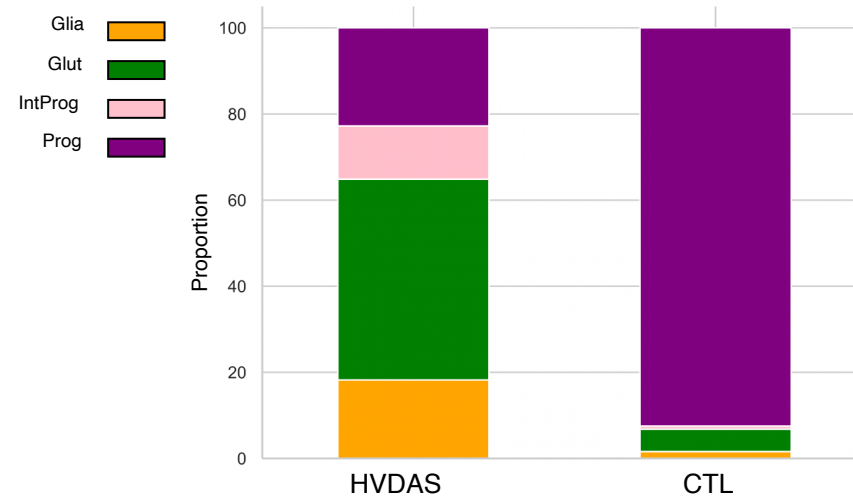




# HVDAS cortical organoids show accelerated maturation phenotype



1-month-old organoids



## Future perspectives:

- Identify actionable targets among ADNP-sensitive effectors: if a gene is deregulated, can we restore its function and ameliorate the phenotype?
- Drug intervention on selective pathways: once we identify a neuronal-related abnormal chain of molecular events, can we effectively modulate it to properly activate/repress it?

# Future perspectives: an example of therapeutic approach

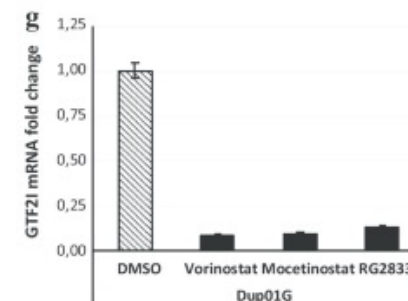
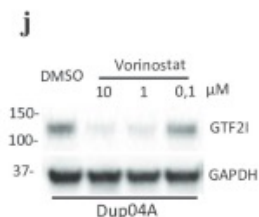
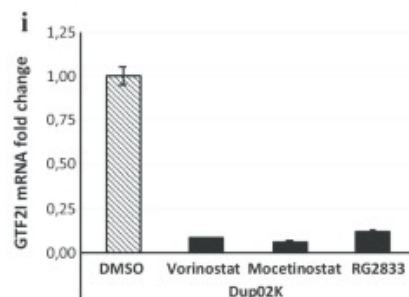
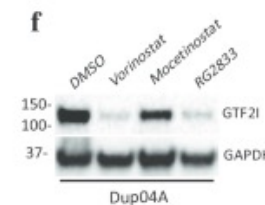
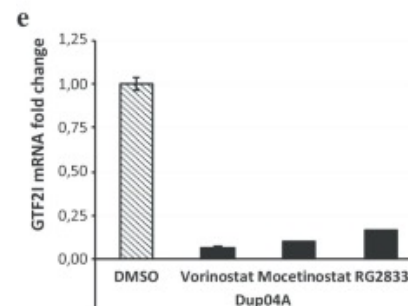
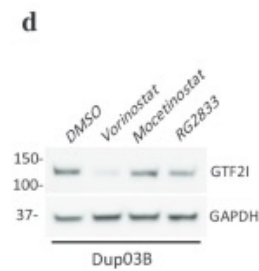
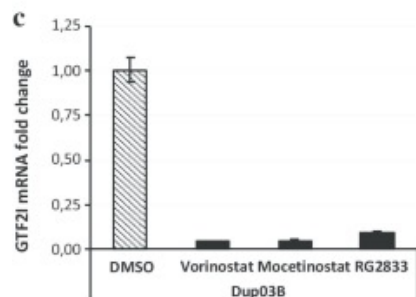
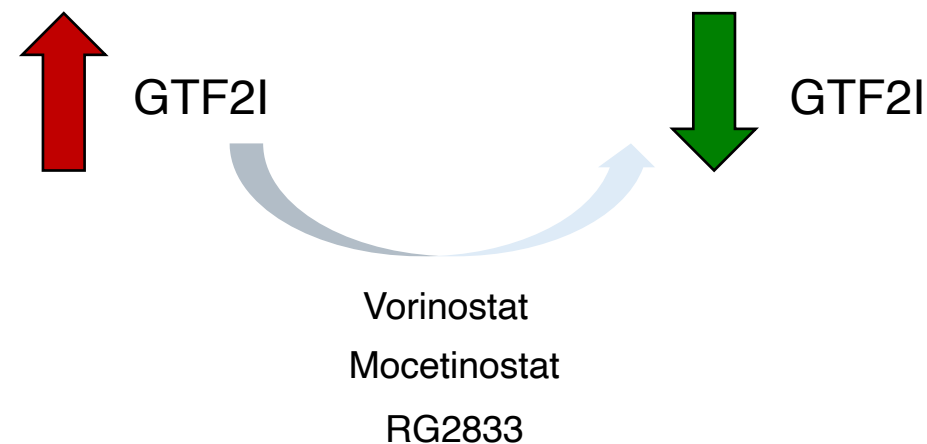
Research | [Open Access](#) | [Published: 19 November 2020](#)

## High-throughput screening identifies histone deacetylase inhibitors that modulate GTF2I expression in 7q11.23 microduplication autism spectrum disorder patient-derived cortical neurons

[Francesca Cavallo](#), [Flavia Troglio](#), [Giovanni Fagà](#), [Daniele Fancelli](#), [Reinald Shyti](#), [Sebastiano Trattaro](#), [Matteo Zanella](#), [Giuseppe D'Agostino](#), [James M. Hughes](#), [Maria Rosaria Cera](#), [Maurizio Pasi](#), [Michele Gabriele](#), [Maddalena Lazzarin](#), [Marija Mihailovich](#), [Frank Kooy](#), [Alessandro Rosa](#), [Ciro Mercurio](#), [Mario Varasi](#) & [Giuseppe Testa](#) ✉

[Molecular Autism](#) **11**, Article number: 88 (2020) | [Cite this article](#)

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# Summary

- We can model HVDAS by taking cellular material (skin cells) from the patients and reprogram them to a pluripotent stage (embryonic-like stage) to understand the behaviour of patients' cells, when compared to healthy controls.
- We can learn molecular mechanisms of ADNP action by looking into patient-derived pluripotent stem cells.
- We can use patient-derived pluripotent stem cells to produce cortical organoids (3D structure resembling human cortex) in order to investigate the alterations of neurodevelopmental processes when ADNP is mutated.
- Patient-derived cortical organoids have morphological deficits compared to healthy control ones.
- We observe an acceleration of neuronal maturation in patient-derived cortical organoids; it means that when ADNP is mutated stem cells and progenitor cells seem to differentiate faster into mature neurons. This could represent a strong imbalance during neurodevelopment, and needs to be further investigated to understand the precise molecular events leading to this phenotype.

# Thank You

**Giuseppe Testa**

## Testa Lab

**Alessandro Vitriolo**  
**Marlene Cristina Faria Pereira**  
**Francesco Dossena**  
**Michele Gabriele**  
**Sebastiano Trattaro**  
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Erika Tenderini  
Lorenza Culotta  
Reinald Shyti  
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Raffaele Luongo  
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Flavia Troglio  
Marco Tullio Rigoli  
Emanuele Villa  
Cristina Cheroni



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## Imaging Unit

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**IEO Units and Cogentech**



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