Neuropharmacology and Drug Design

Week 13

Fides Zenk

Learning Objectives of this week

Identifying drug targets in the CNS

Testing and predicting a drugs function

Mechanisms of CNS drugs targeting pain - pertubration screens, virtual cells

Delivery systems to the CNS and the Blood-Brain-Barrier

iPSC derived therapies and systems to model diseases

Cost of CNS diseases and drug development

European Brain Council estimate (2010): **798 billion Euro/per year** (mental and neurological disorders)

CNS drugs

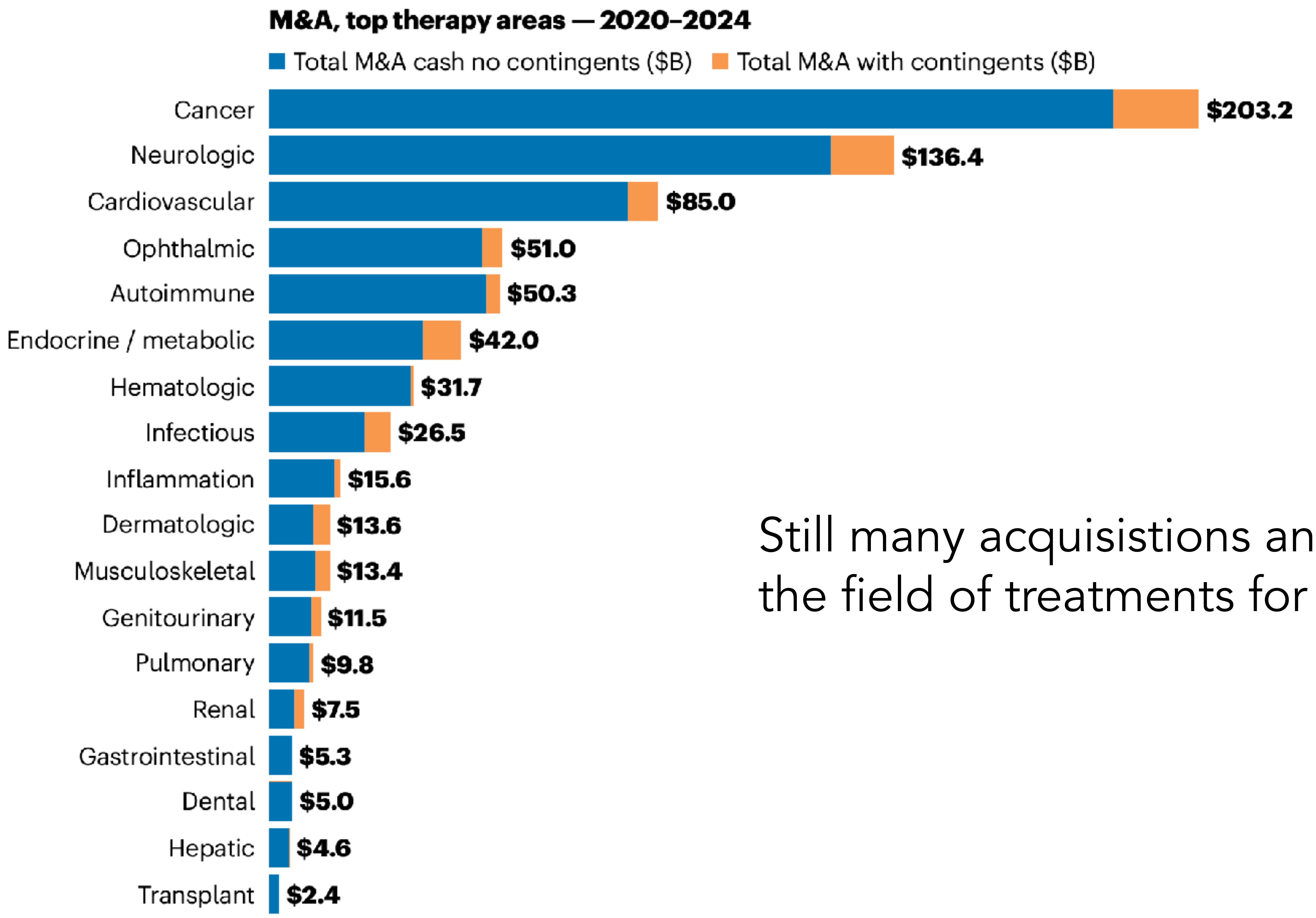
Probability of reaching the market: 7% (other therapeutics 15%)

Average time to develop: 12.5 years (6.3 cardiovascular)

Cost: about 2.5 Billion $

Not a very good business for Pharma companies

Cost of CNS diseases and drug development



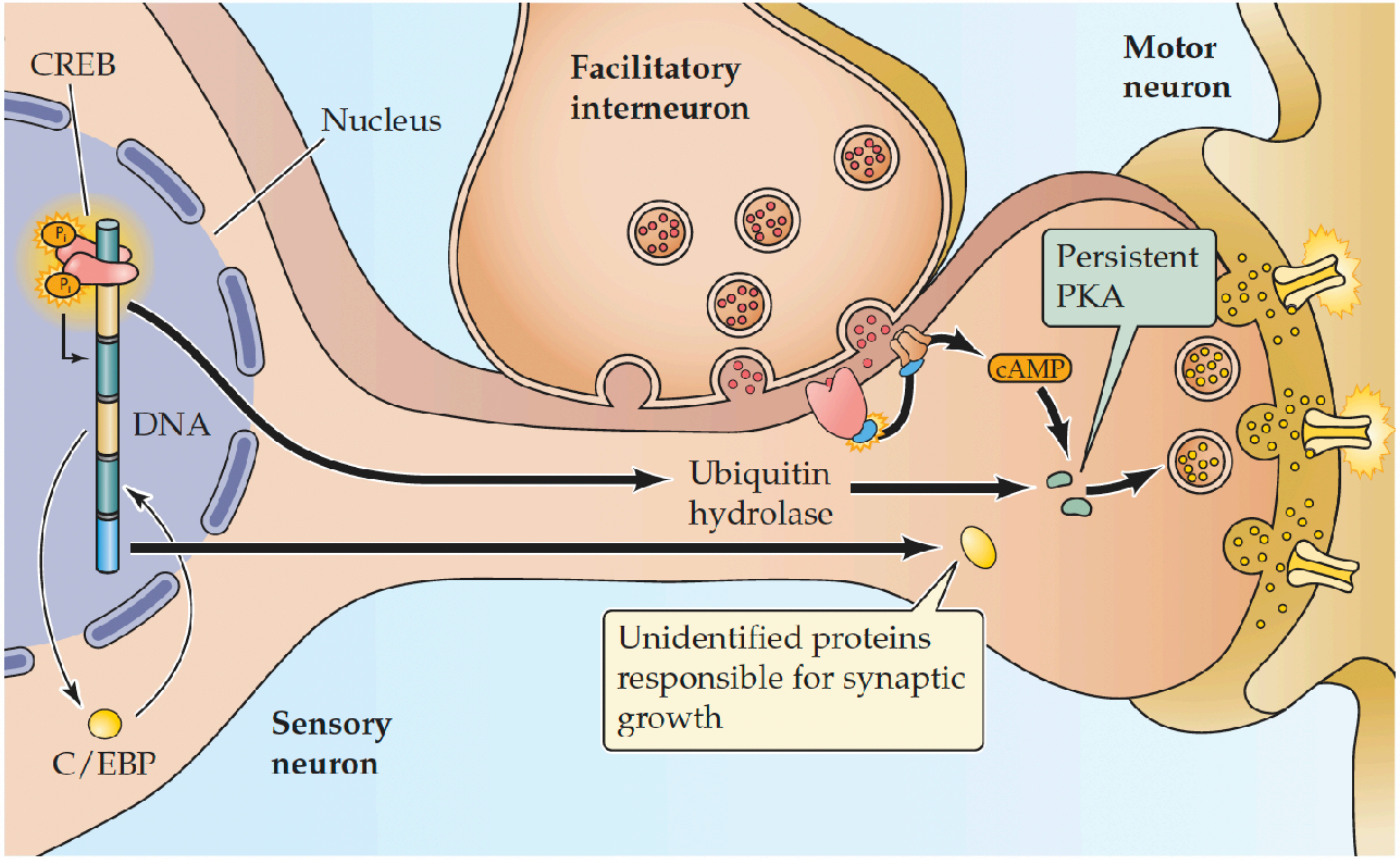
Still many acquisistions and mergers happen in the field of treatments for neurologic disorders.

Senior (2025) Nature Biotech.

Which pathways do you remember from the lecture that could be targets for drugs?

Which pathways do you remember from the lecture that could be targets for drugs?

(B)



Ion channels

Neurotransmitter receptors

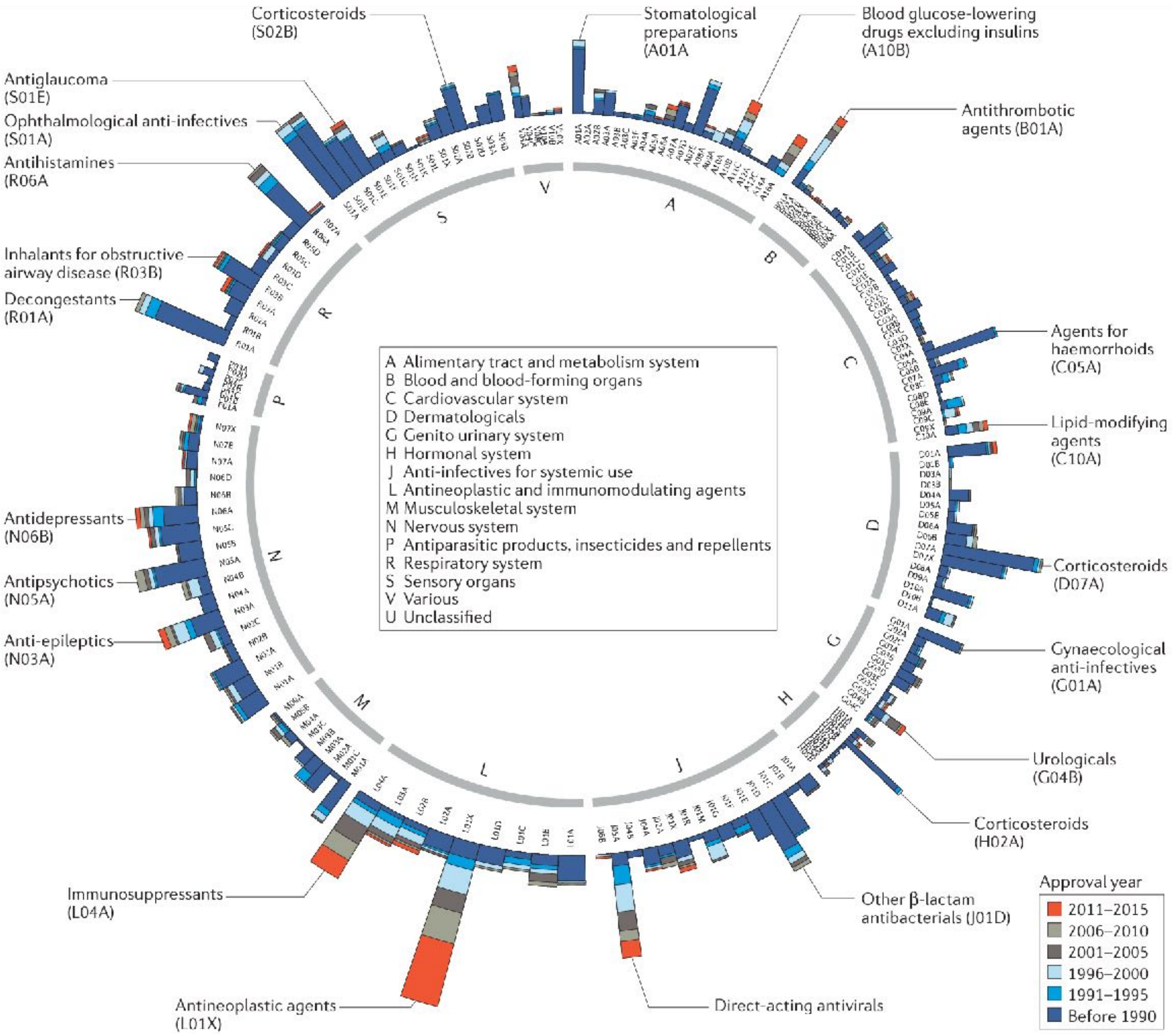
G-Protein coupled receptors

Kinases

Nuclear receptors

(many more…)

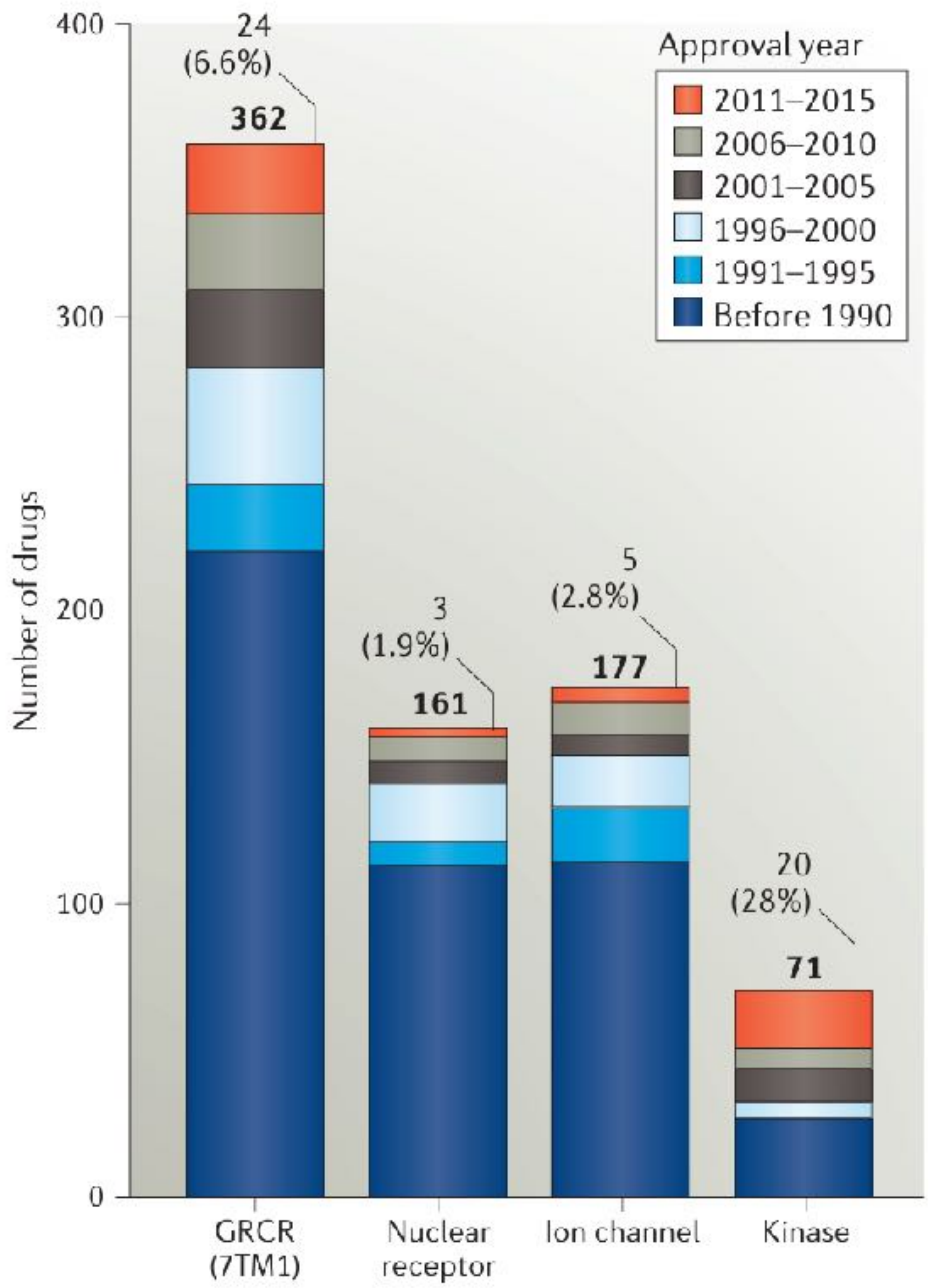
Popular drug targets

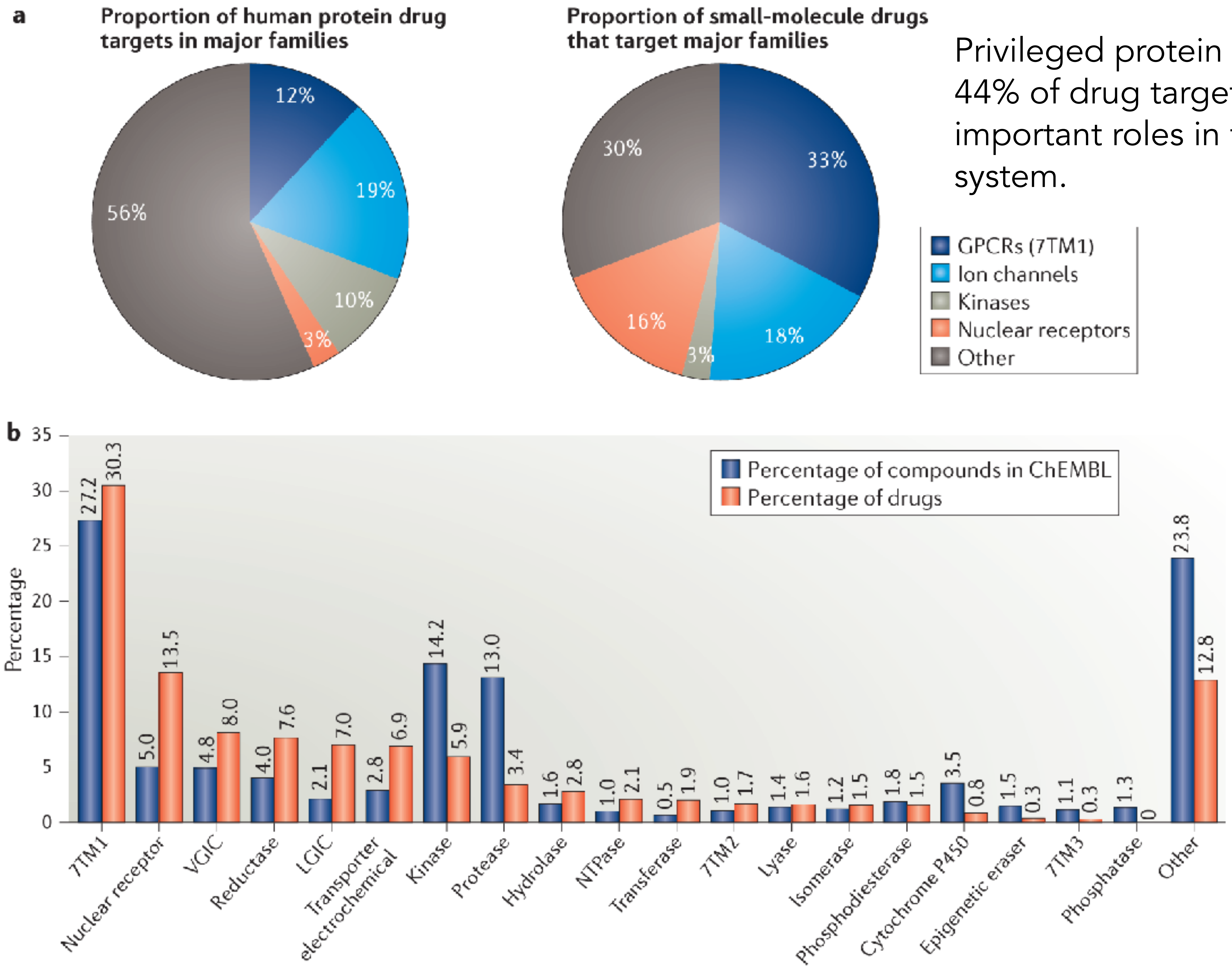


Santos et al. (2017) Nature Reviews Drug Discovery

Most recent drug developments (here only until 2015) in the nervous system focus on psychiatric and mental disorders but also neurodegenerative disorders.

Popular drug targets

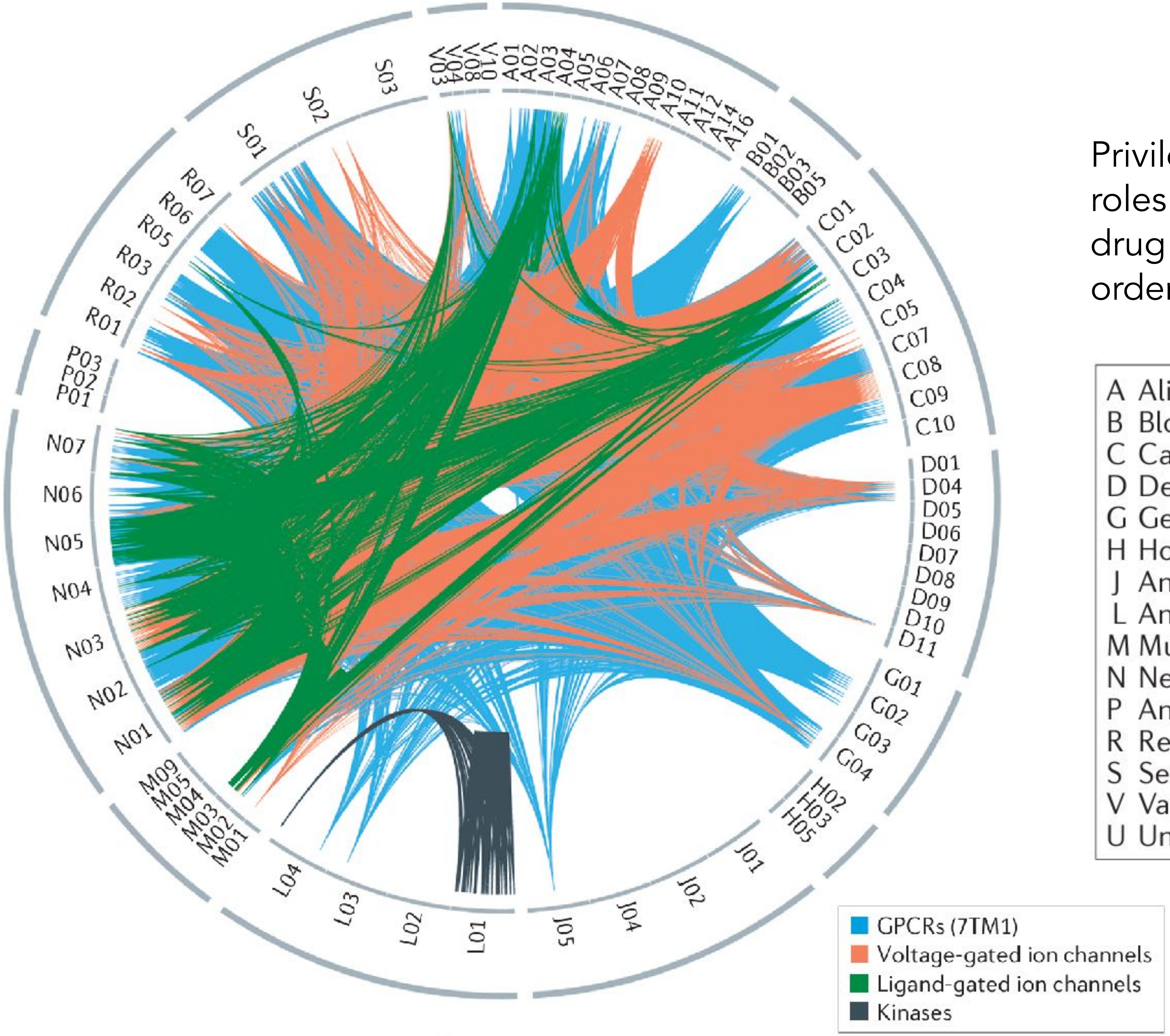




Privileged protein families make up 44% of drug targets. They play important roles in the nervous system.

Santos et al. (2017) Nature Reviews Drug Discovery

Popular drug targets

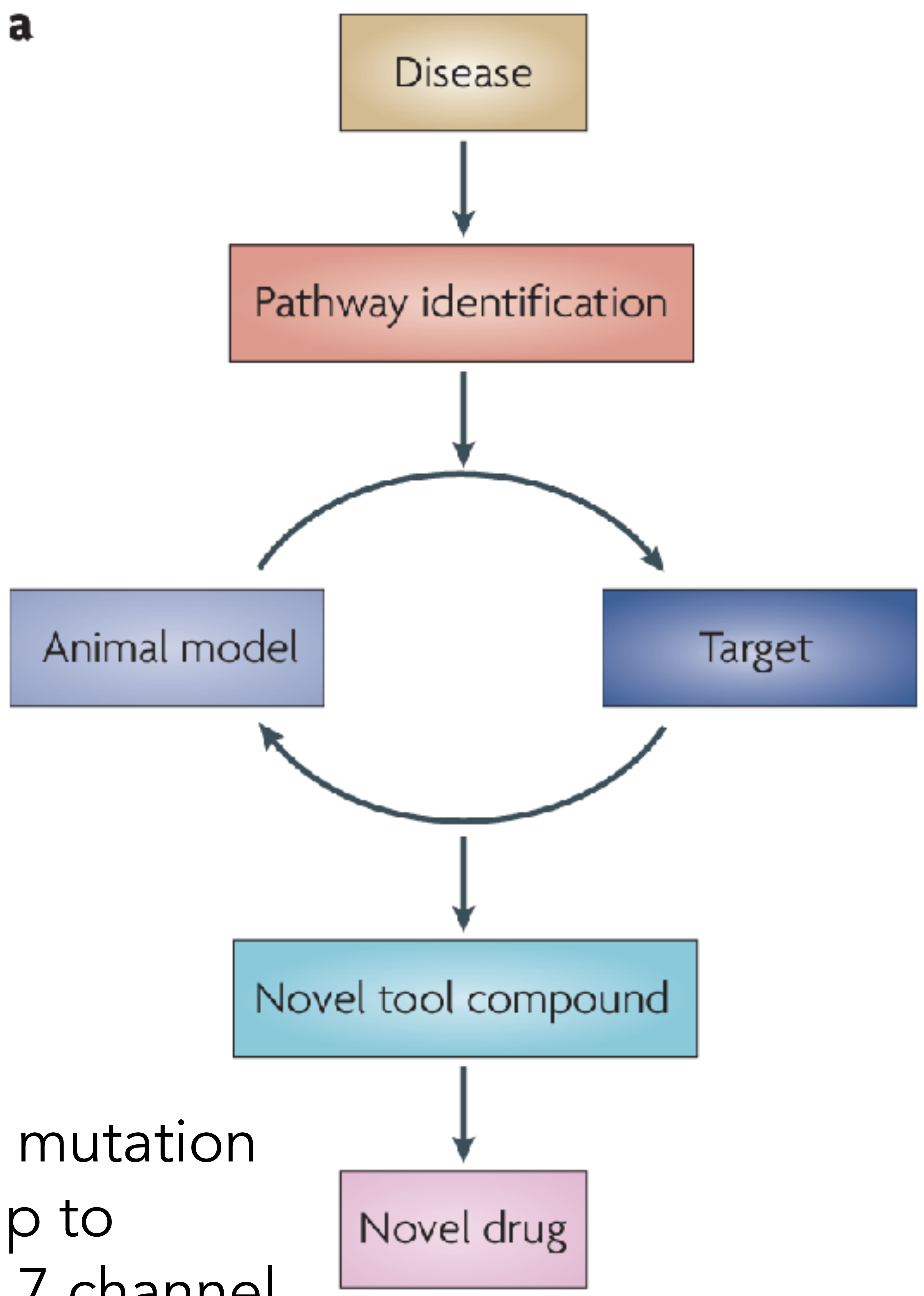


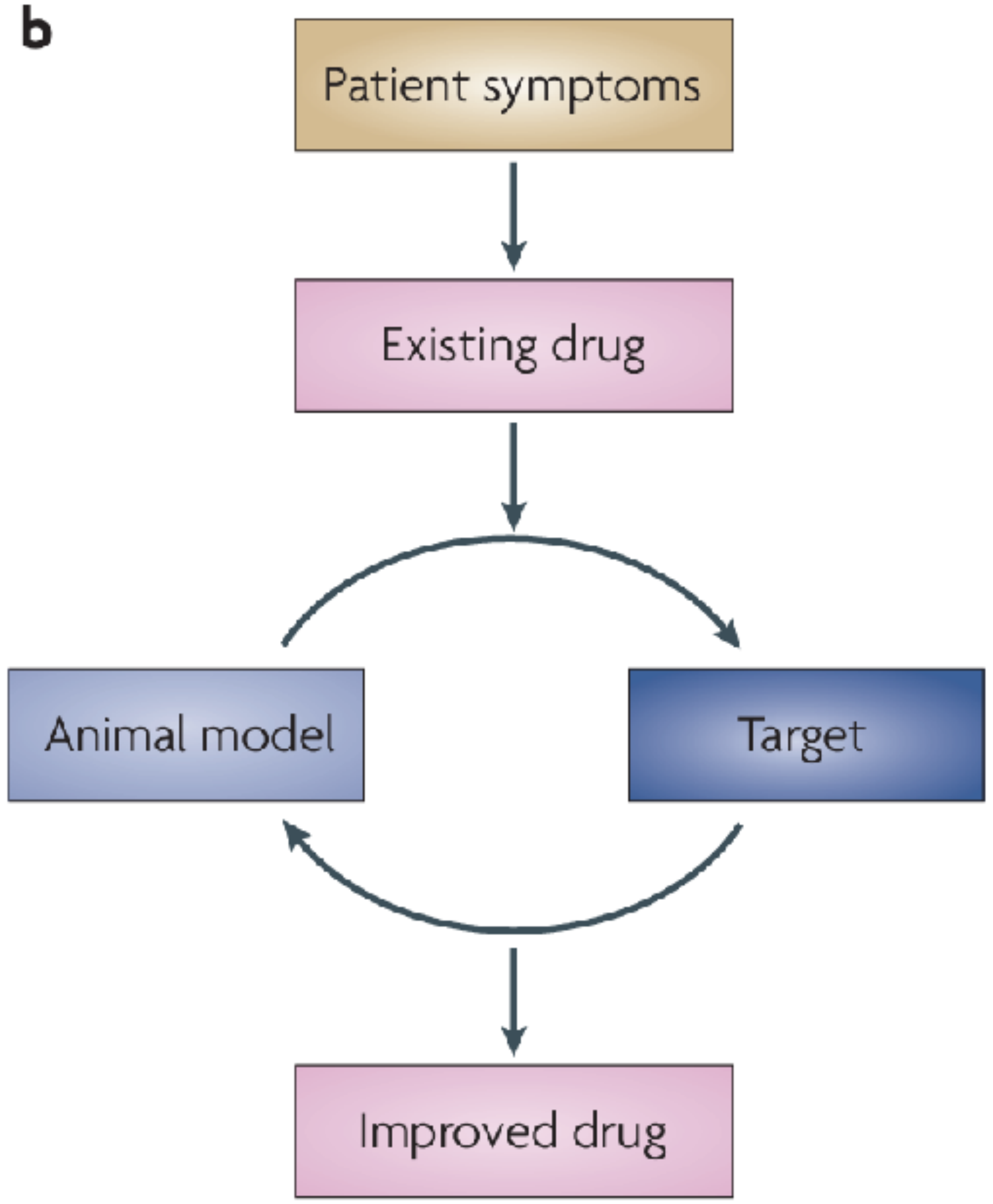
Privileged protein families also play important roles outside of the nervous system. Making drug development often more difficult in order to target a specific target or system.

A Alimentary tract and metabolism system
B Blood and blood-forming organs
C Cardiovascular system
D Dermatologicals
G Genito urinary system
H Hormonal system
J Anti-infectives for systemic use
L Antineoplastic and immunomodulating agents
M Musculoskeletal system
N Nervous system
P Antiparasitic products, insecticides and repellents
R Respiratory system
S Sensory organs
V Various
U Unclassified

Santos et al. (2017) Nature Reviews Drug Discovery

Process and approaches to drug development



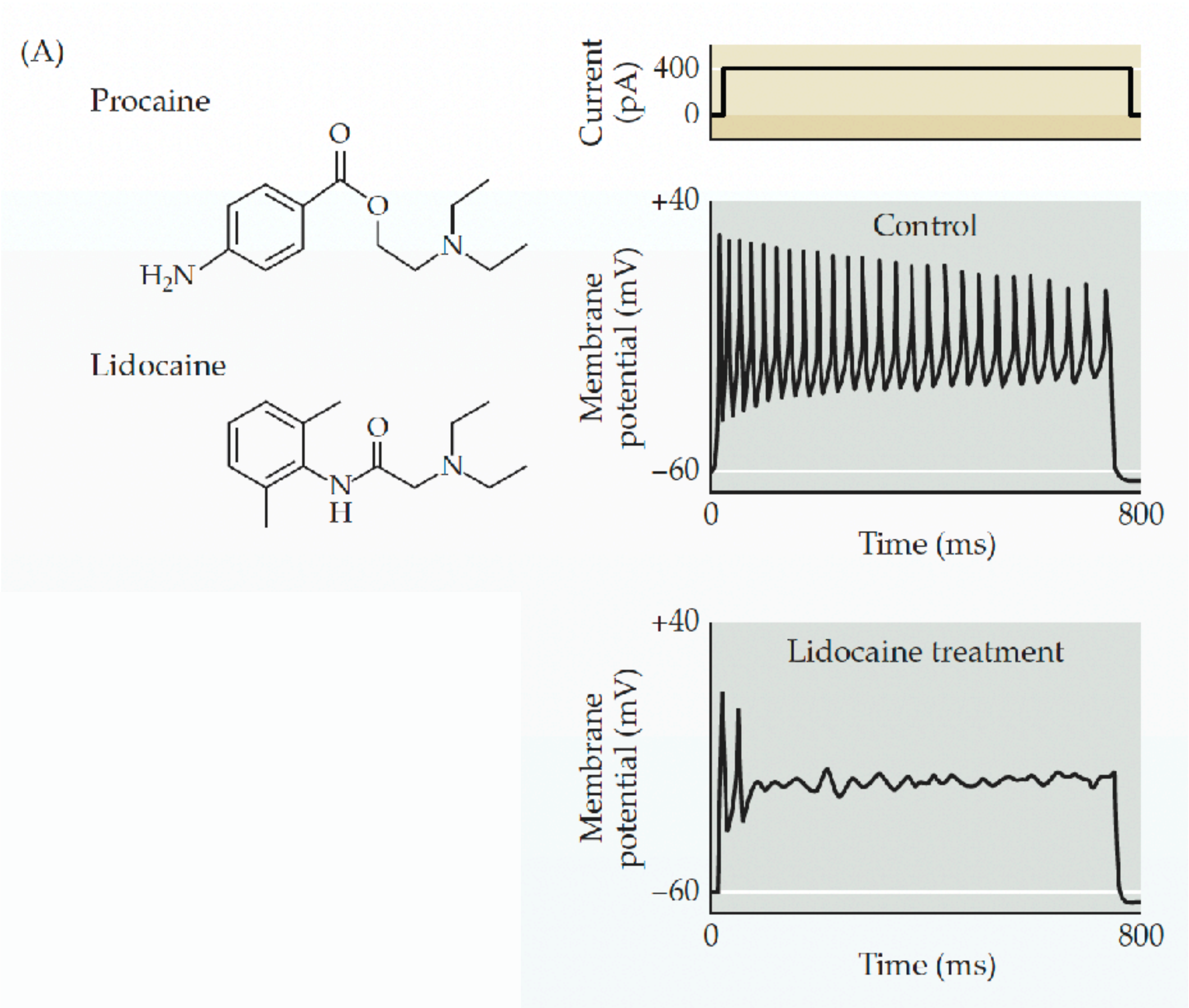


E.g. knowing a specific mutation and phenotype can help to identify a target. (Nav1.7 channel mutations in human lead to loss of pain sensation

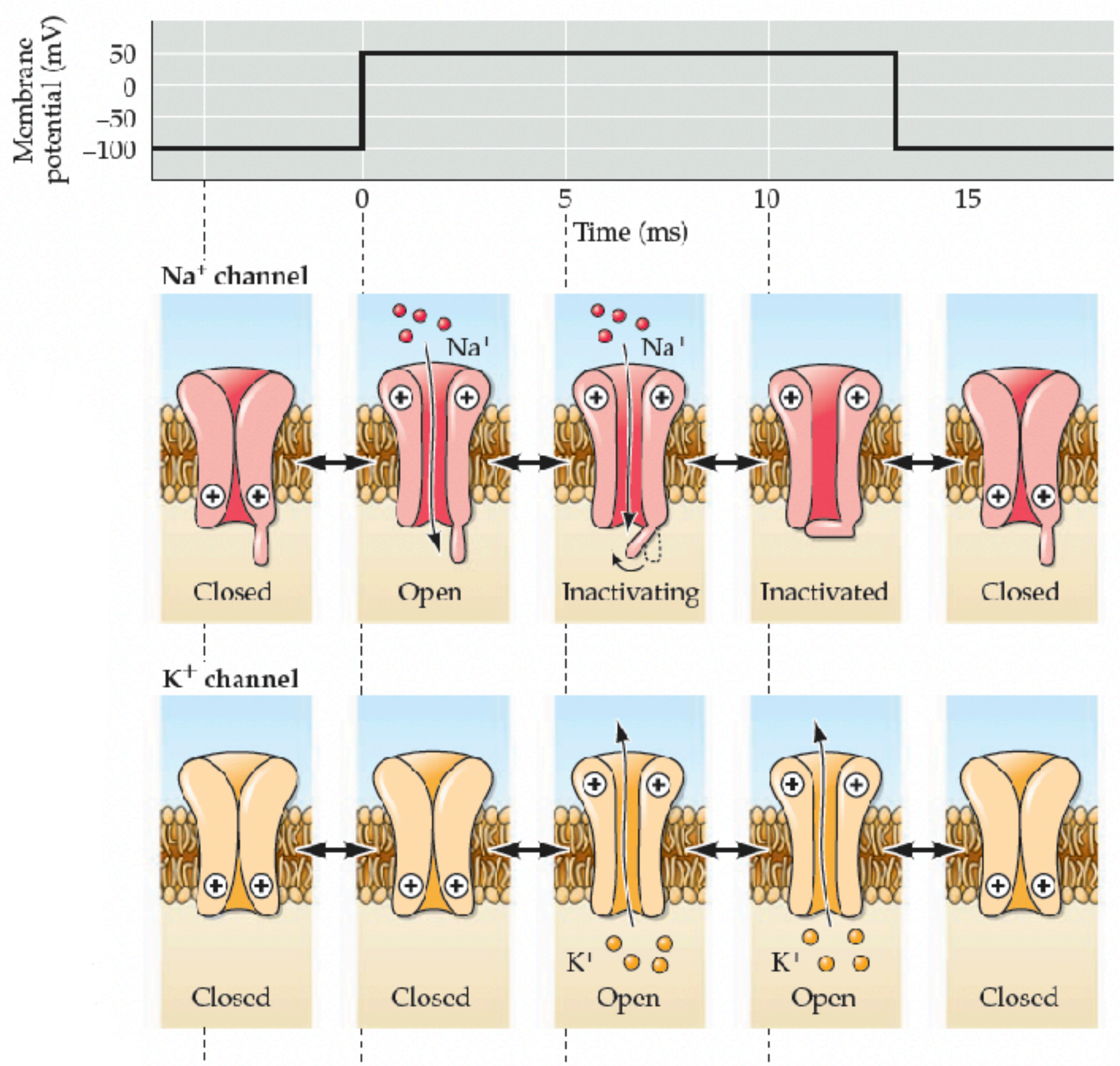
E.g. Cobenfy against schizophrenia combines Xanomeline muscarinic acetylacholine receptor agonist combined with trospium muscarinic antagonist in the enteric nervous system

Pangalos et al. (2007) Nature Reviews Drug Discovery

Typical drugs use in the CNS - most target pain

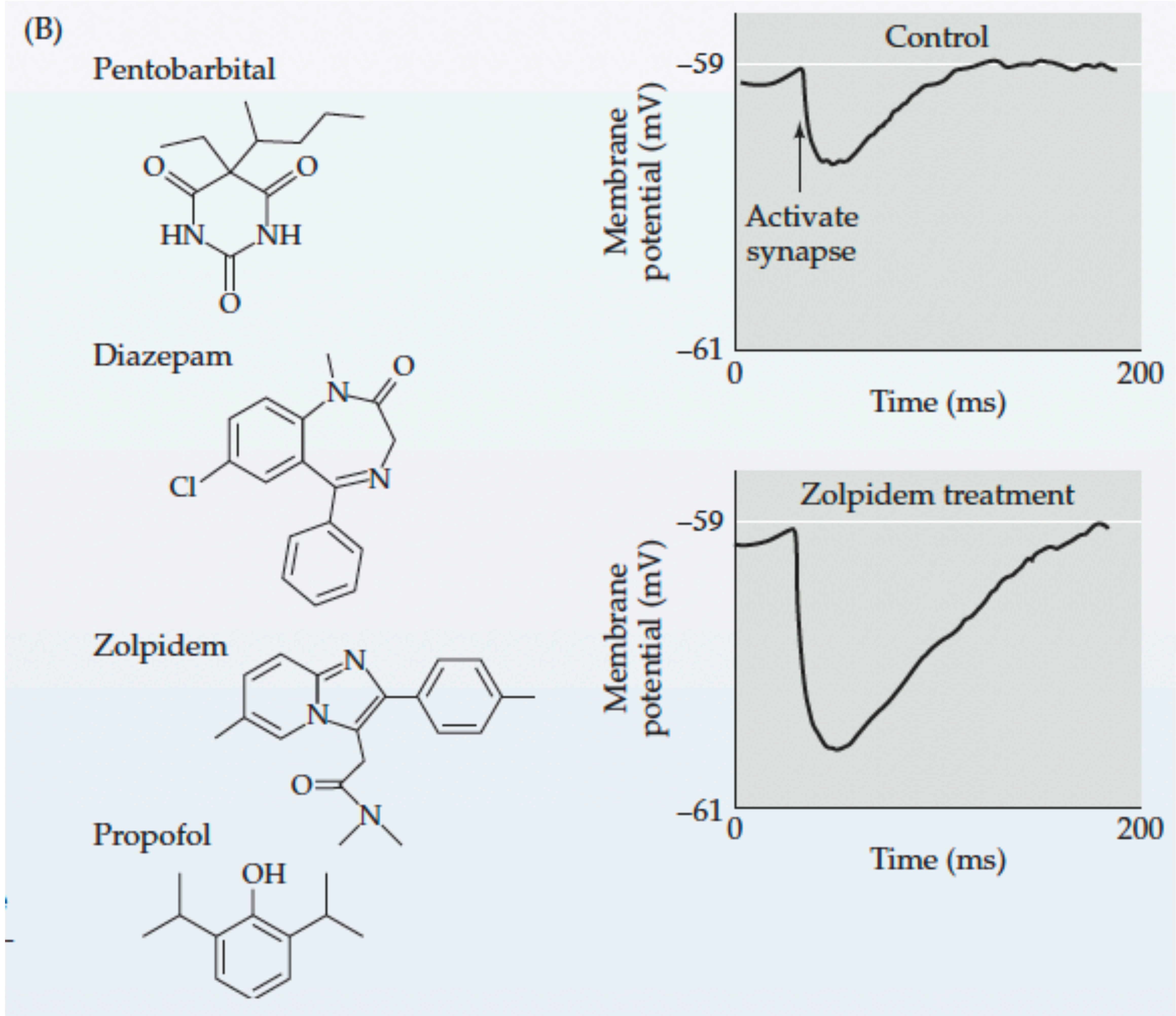


Lidocaine blocks voltage-gated sodium channels and prevents the generation and propagation of action potentials. Most commonly used as a local anaesthetic.

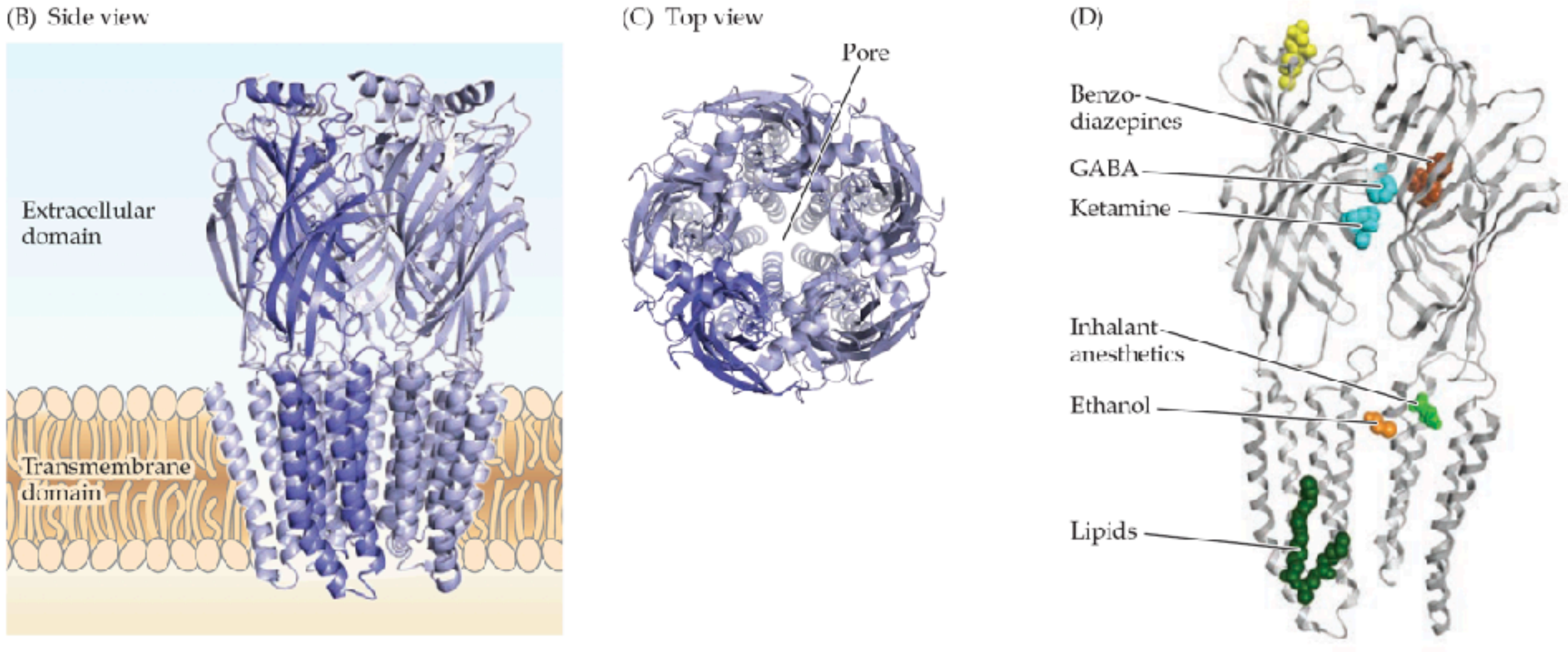


Purves et al. Neuroscience

Typical drugs use in the CNS - most target pain

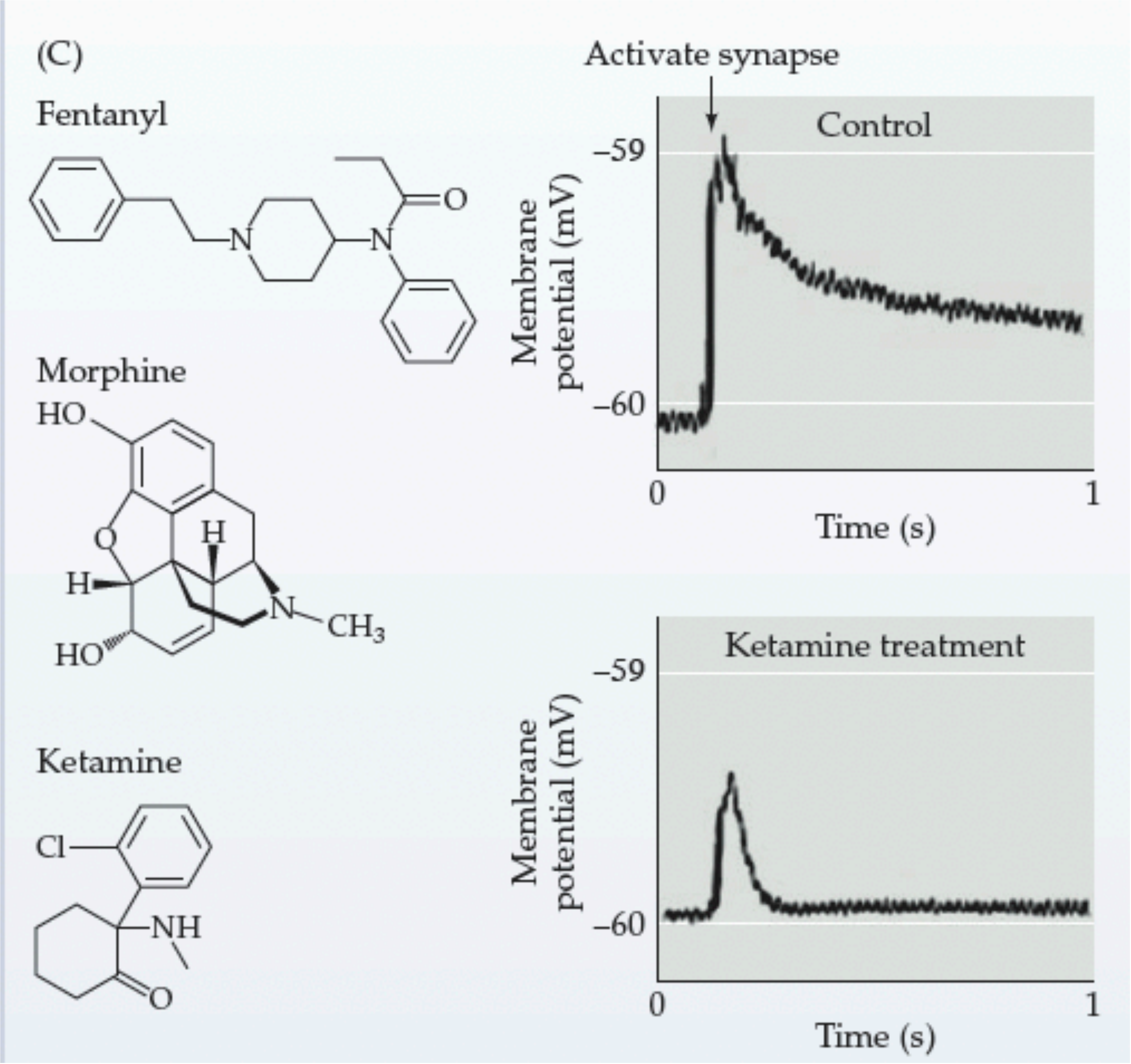


Sedatives enhance the activity of postsynatptic GABA receptors. Enhances inhibitory signalling and reduces neural activity. Barbiturates are used to treat anxiety and depression, today mostly benzodiazepines are used. They also block Sodium channels. Overdoses can be lethal.

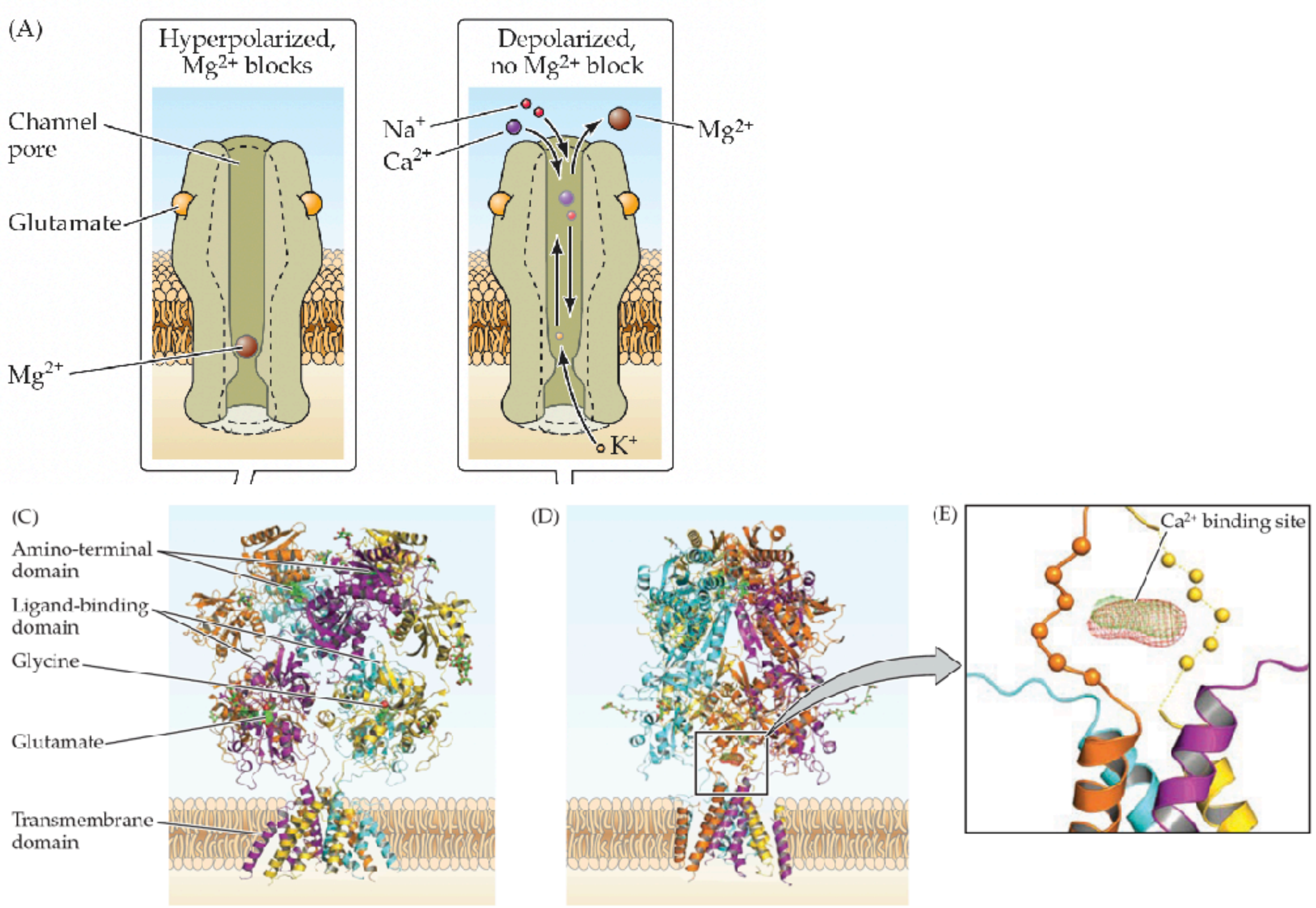


Purves et al. Neuroscience

Typical drugs use in the CNS - most target pain

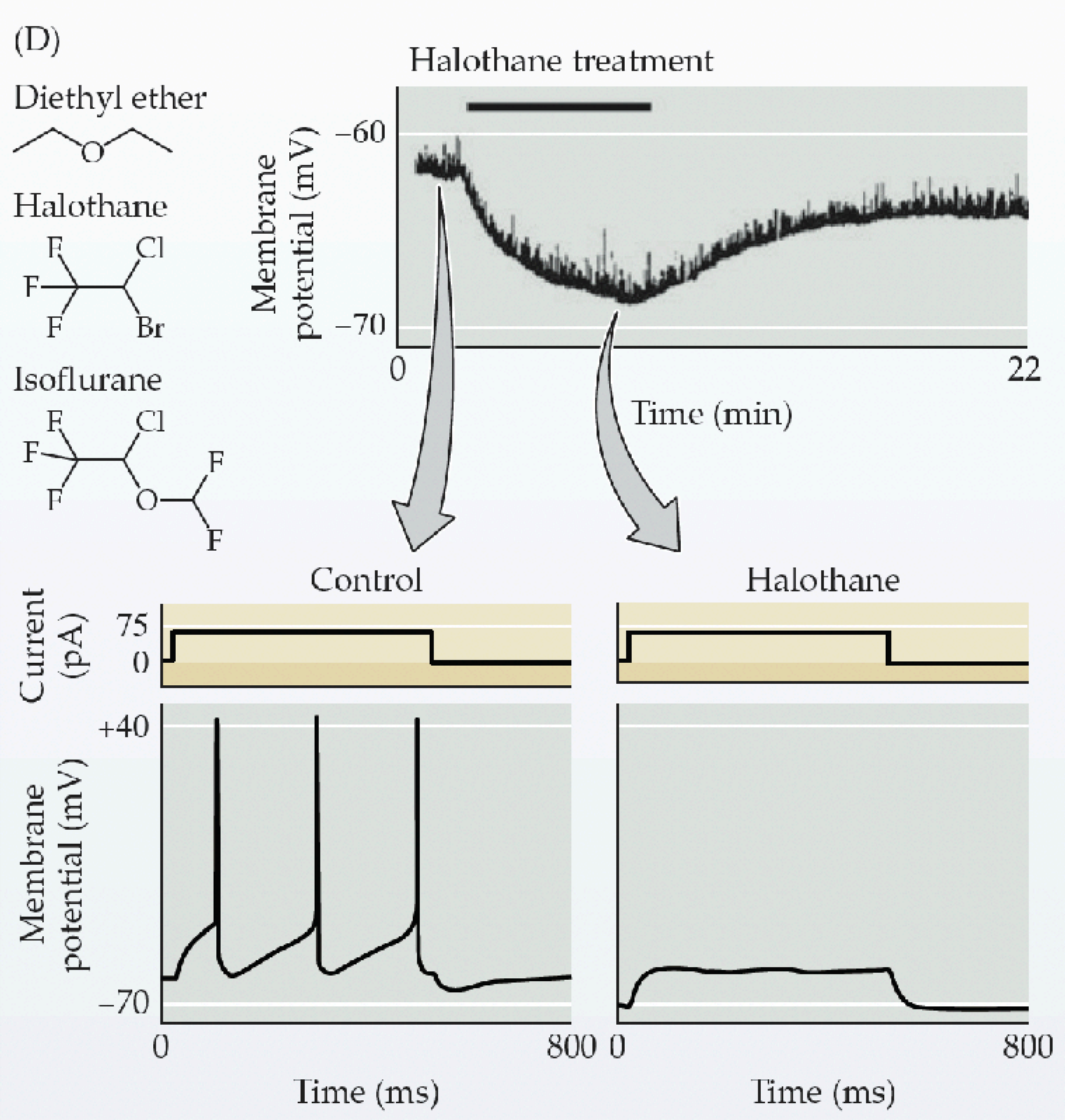


Analgesic agents prevent pain sensation by blocking NMDA-type glutamate receptors. These blocks excitatory transmission.



Purves et al. Neuroscience

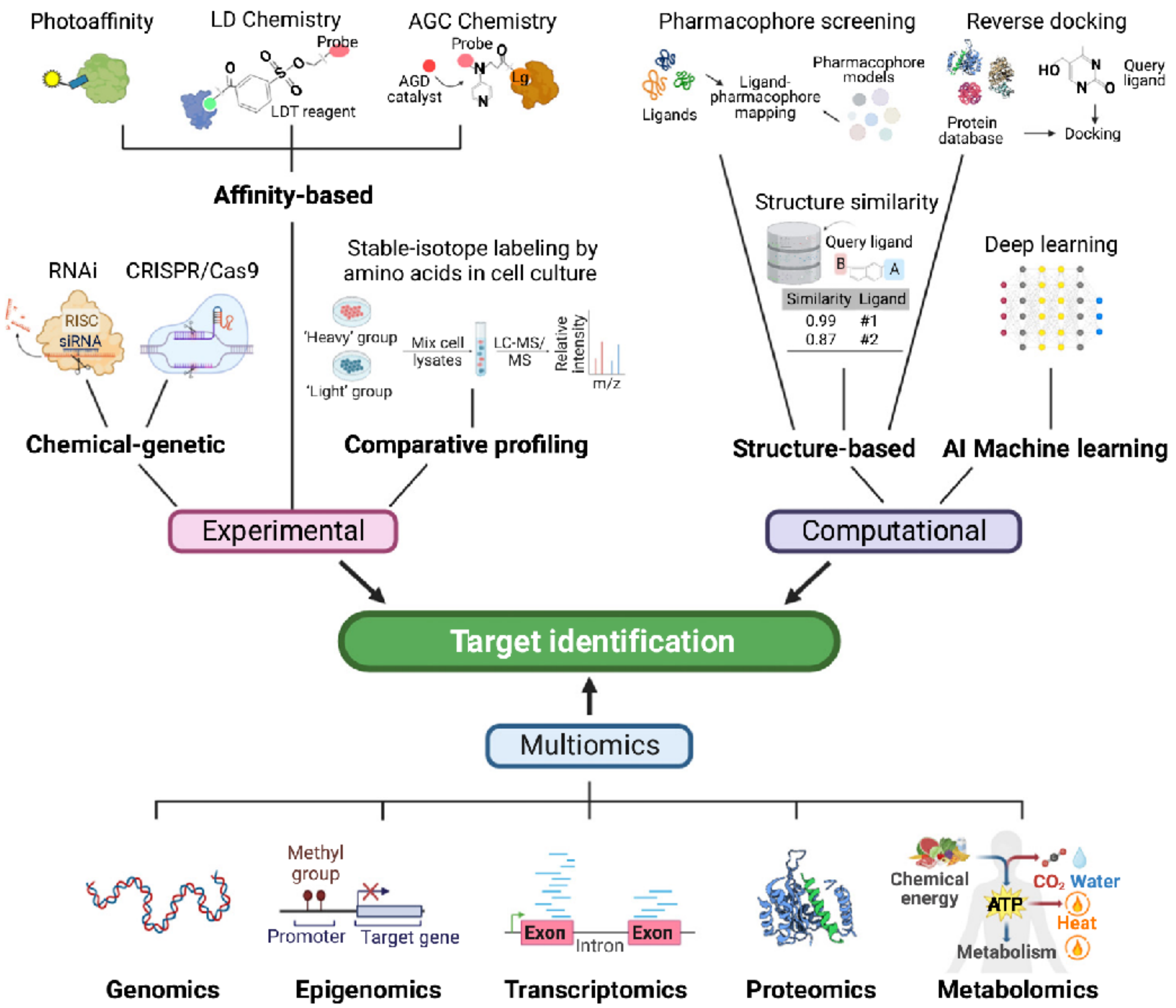
Typical drugs use in the CNS - most target pain



Inhalation anaesthetics hyperpolarise the membrane and block action potential propagation. The exact mechanisms have not been explained.

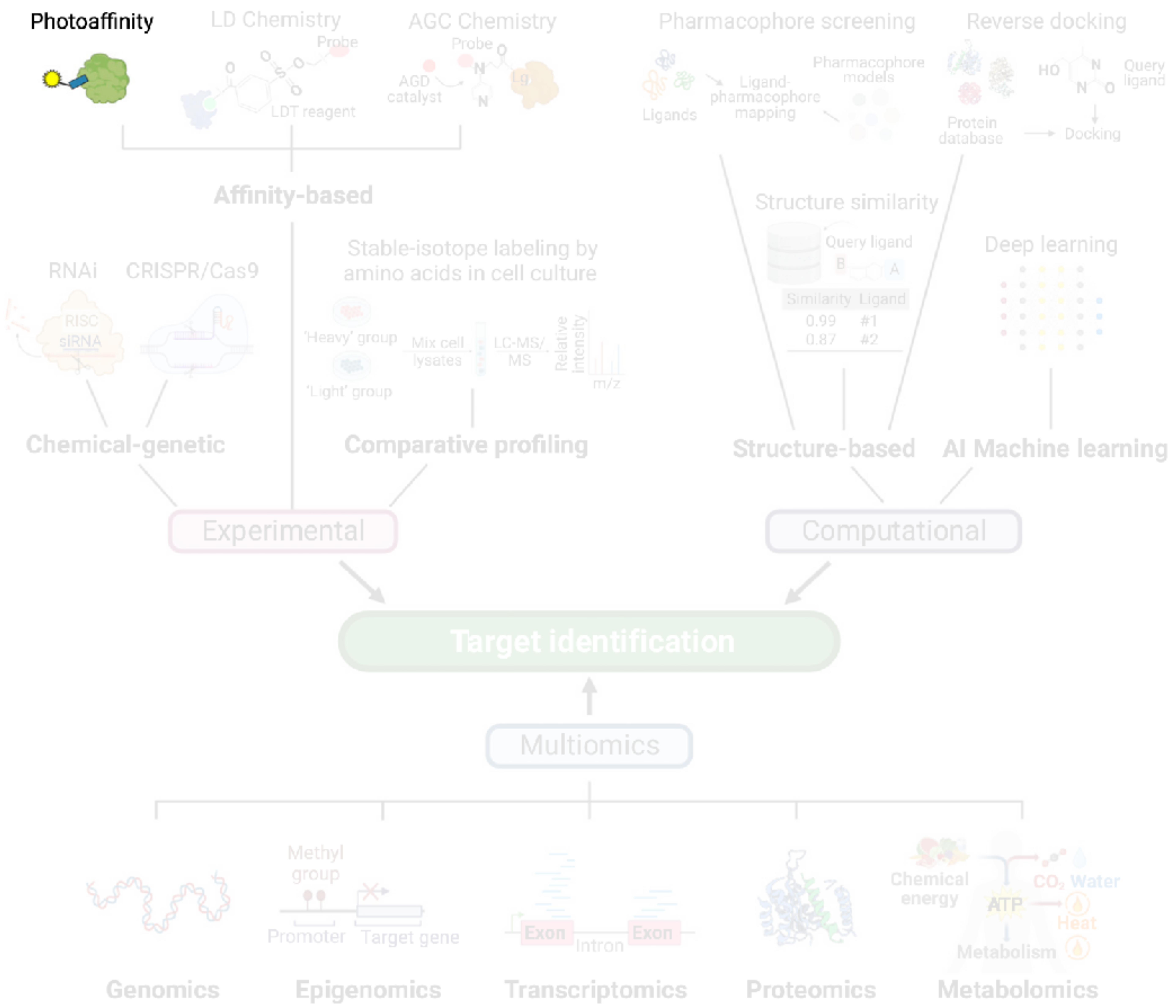
Purves et al. Neuroscience

How do you identify a drug target?



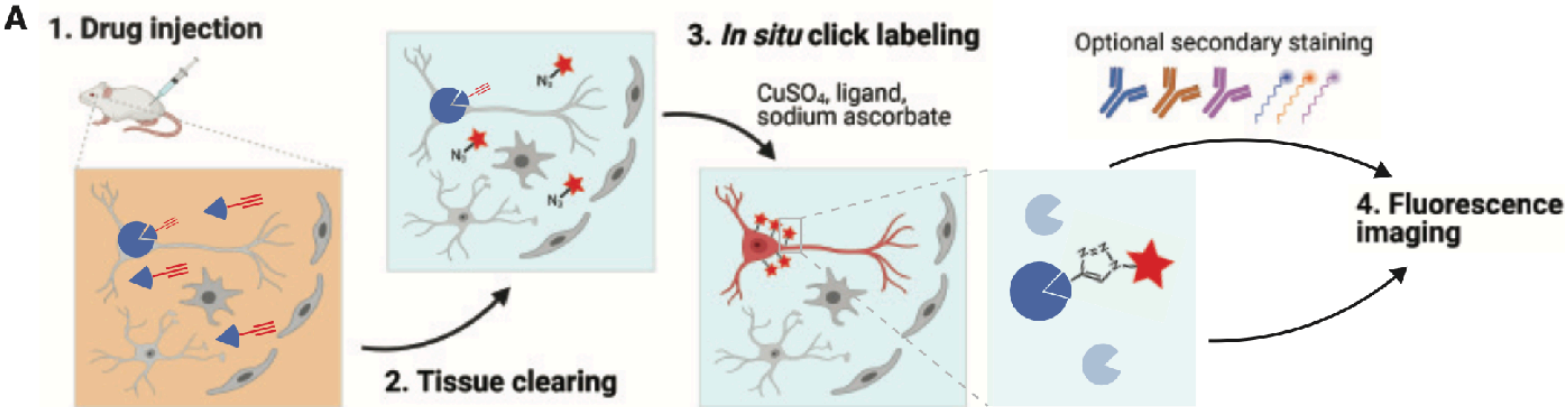
Pun et al. (2023) Trends in Pharmacological Sciences

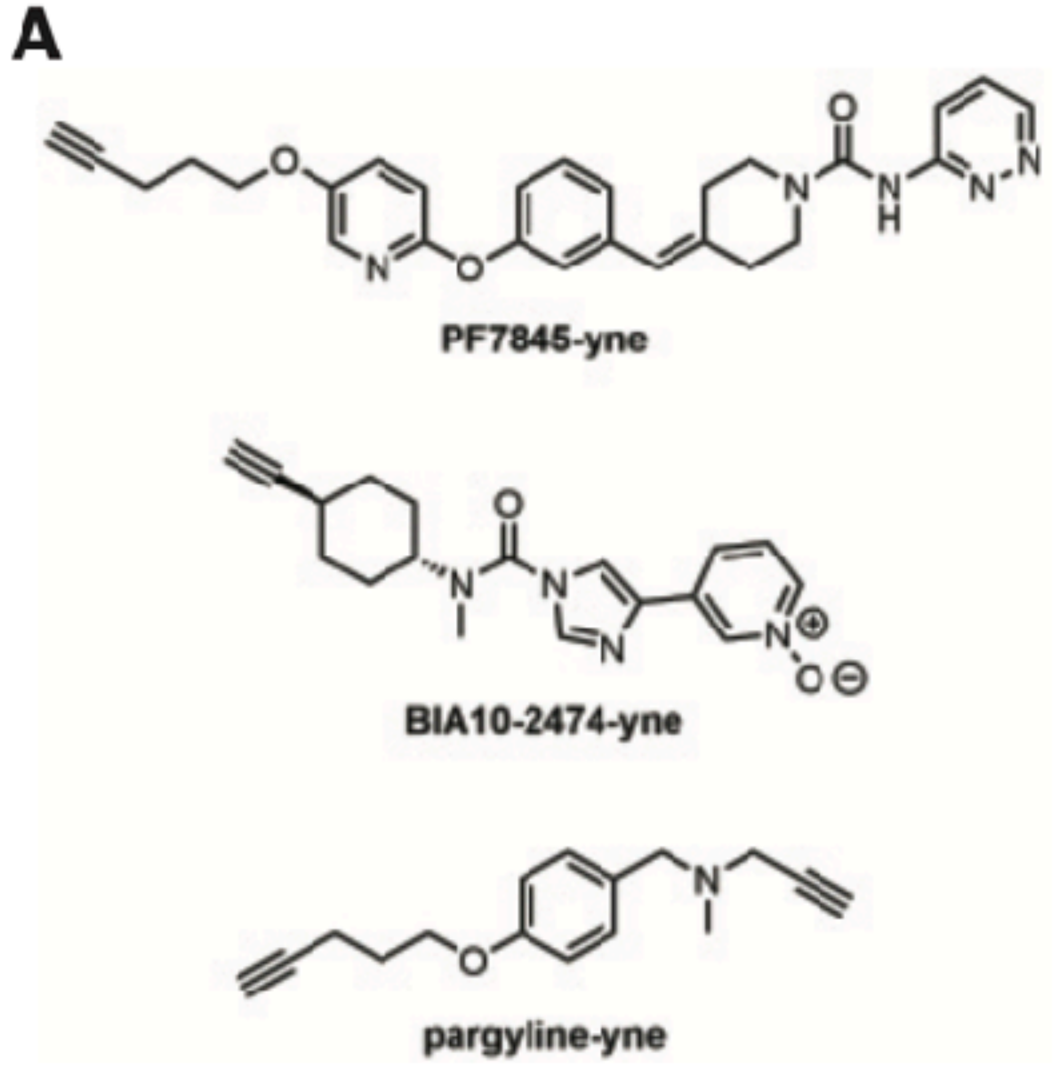
How do you identify a drug target?

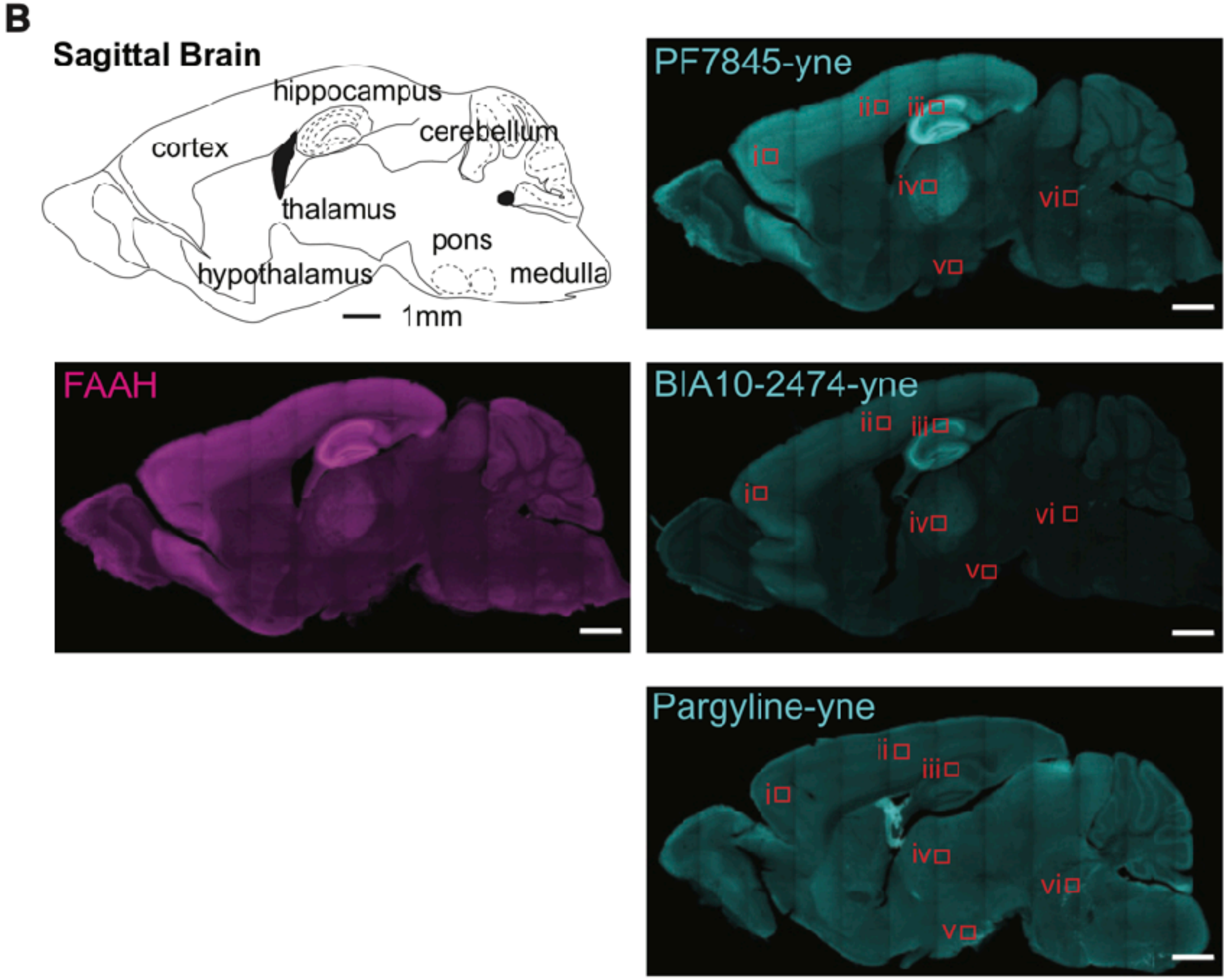


Pun et al. (2023) Trends in Pharmacological Sciences

Photoaffinity



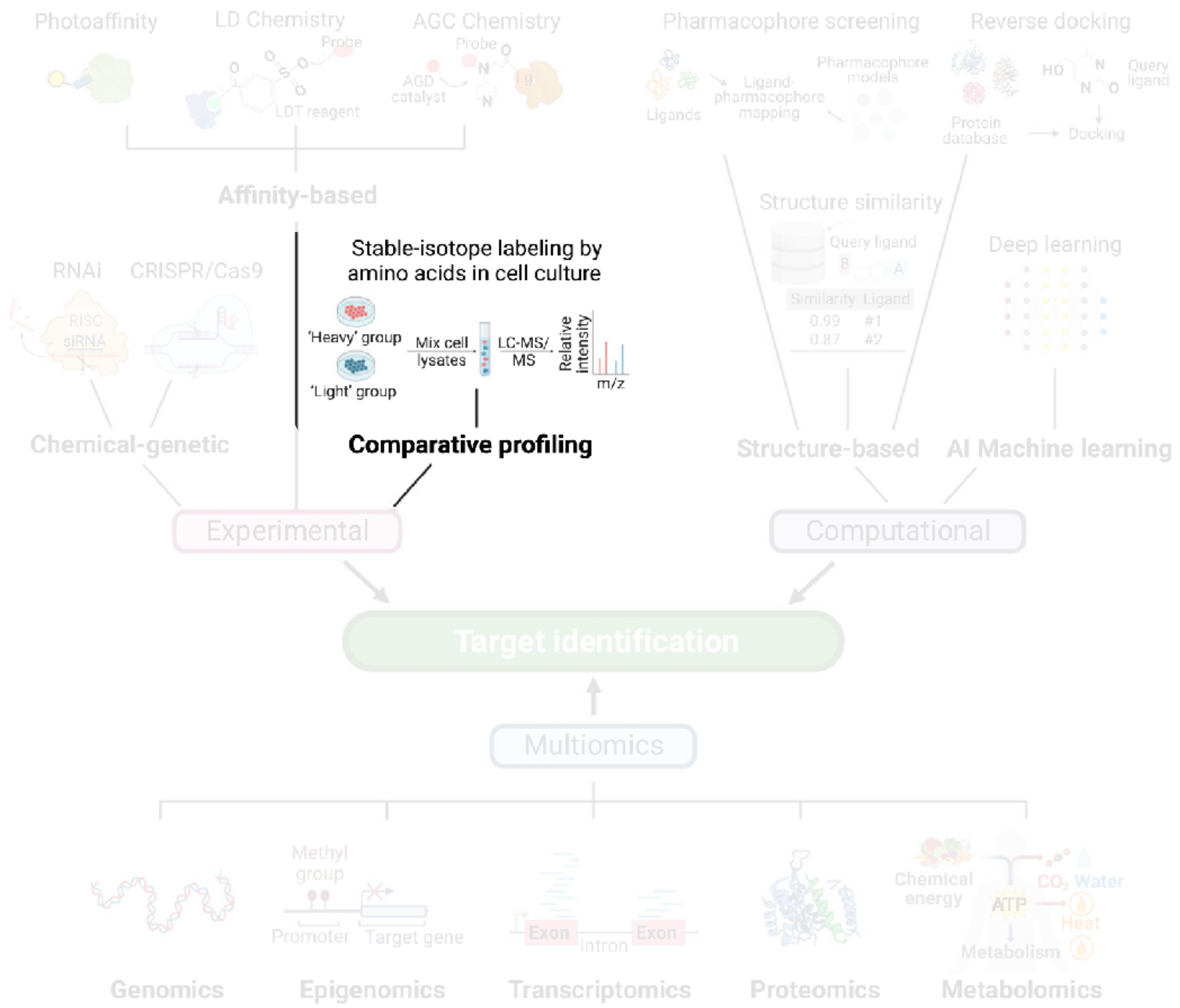




Fluorescent labelling of small molecules reveals that different molecules localize specifically to various brain regions potentially explaining differences in efficacy

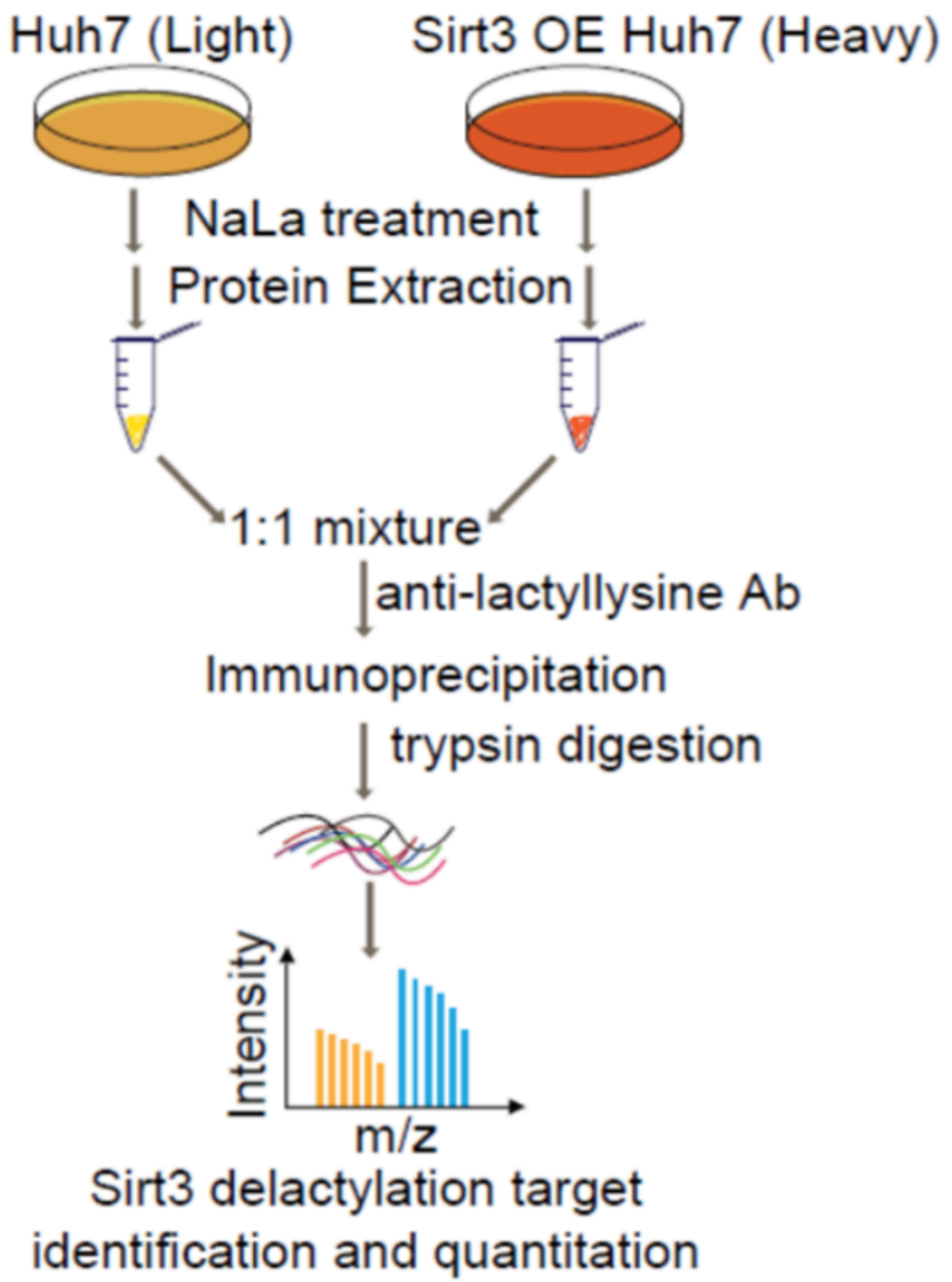
Pang et al. (2022) Cell

How do you identify a drug target?



Pun et al. (2023) Trends in Pharmacological Sciences

SILAC

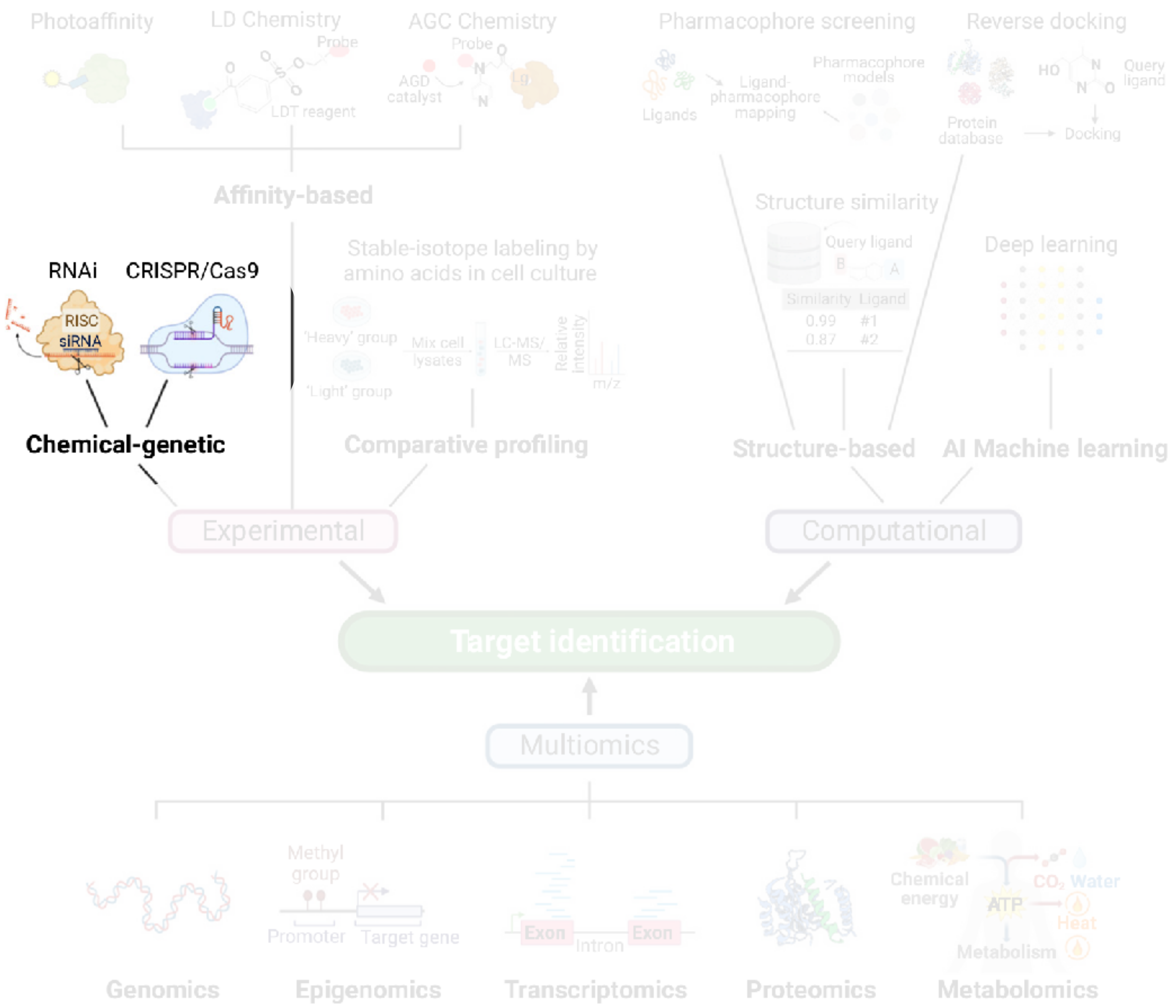


SILAC allows for the measurement of proteome changes in response to drug perturbations.

In this way proteins that changes their expression of modification can be identified.

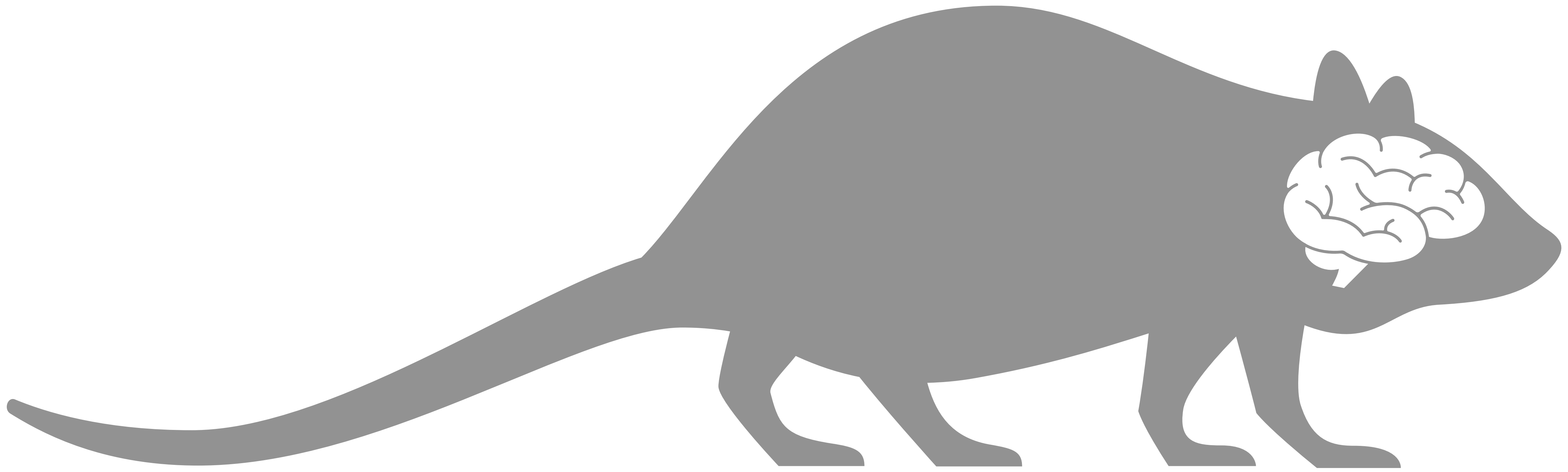
Jin et al. (2023) EMBO reports

How do you identify a drug target?

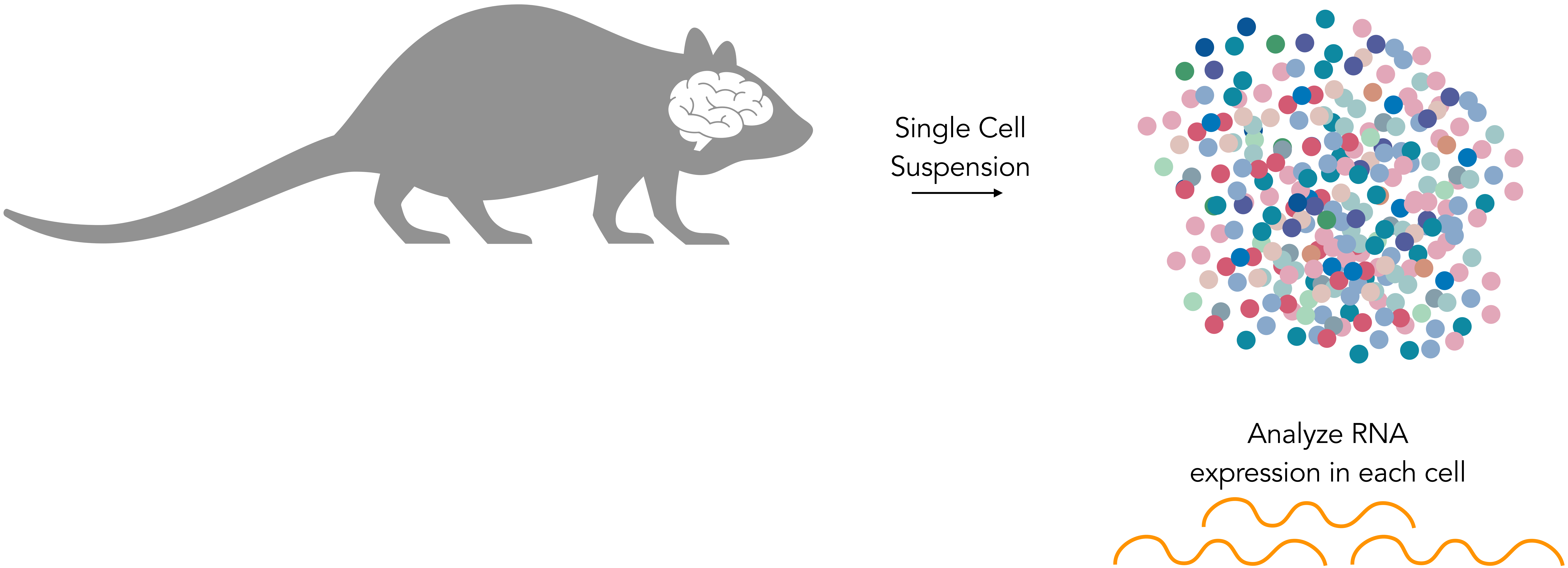


Pun et al. (2023) Trends in Pharmacological Sciences

Quantifying gene expression changes upon perturbation



Quantifying gene expression changes upon perturbation



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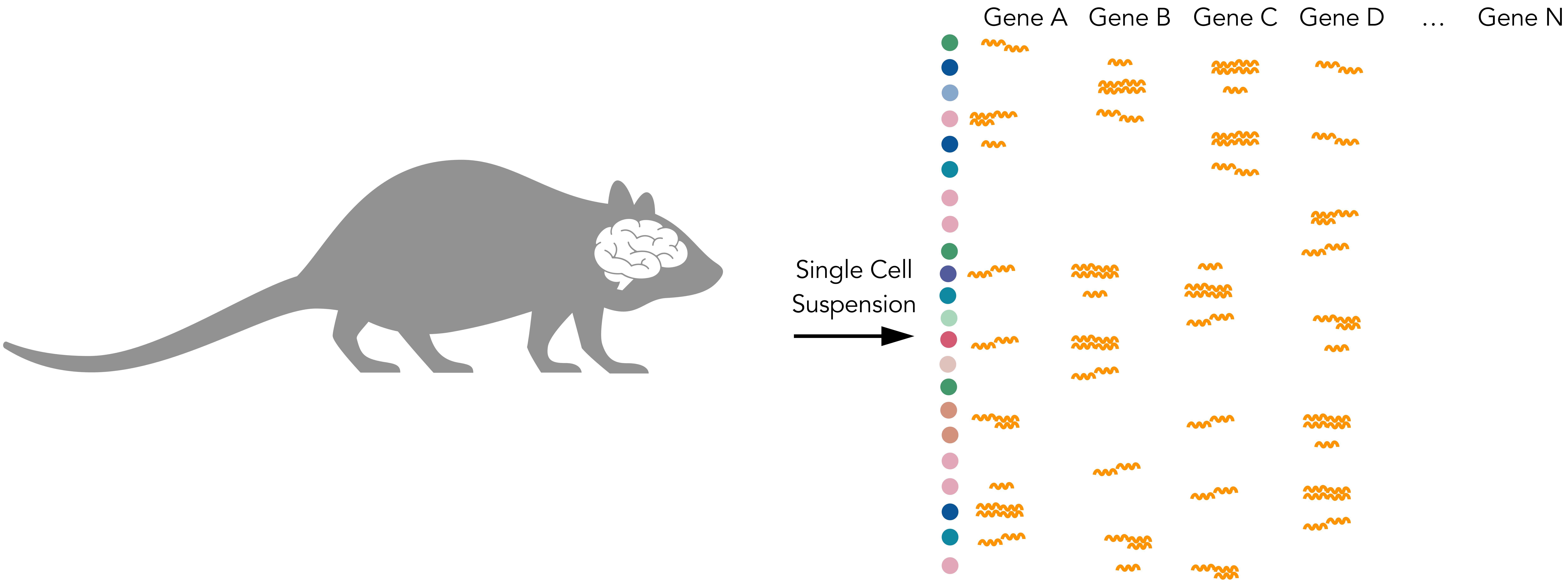
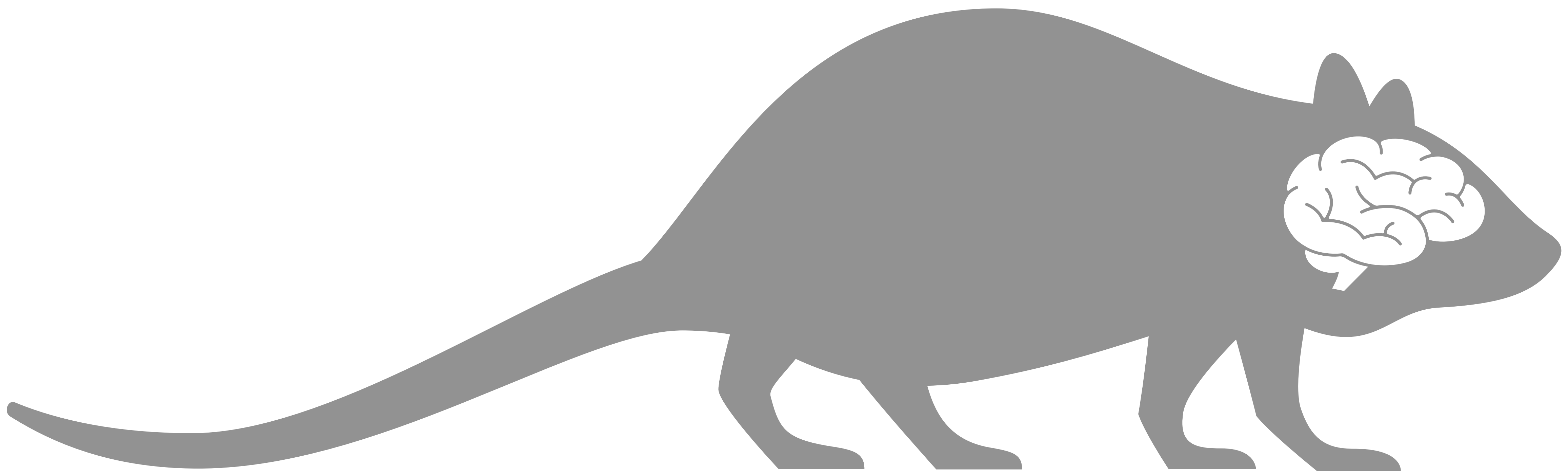
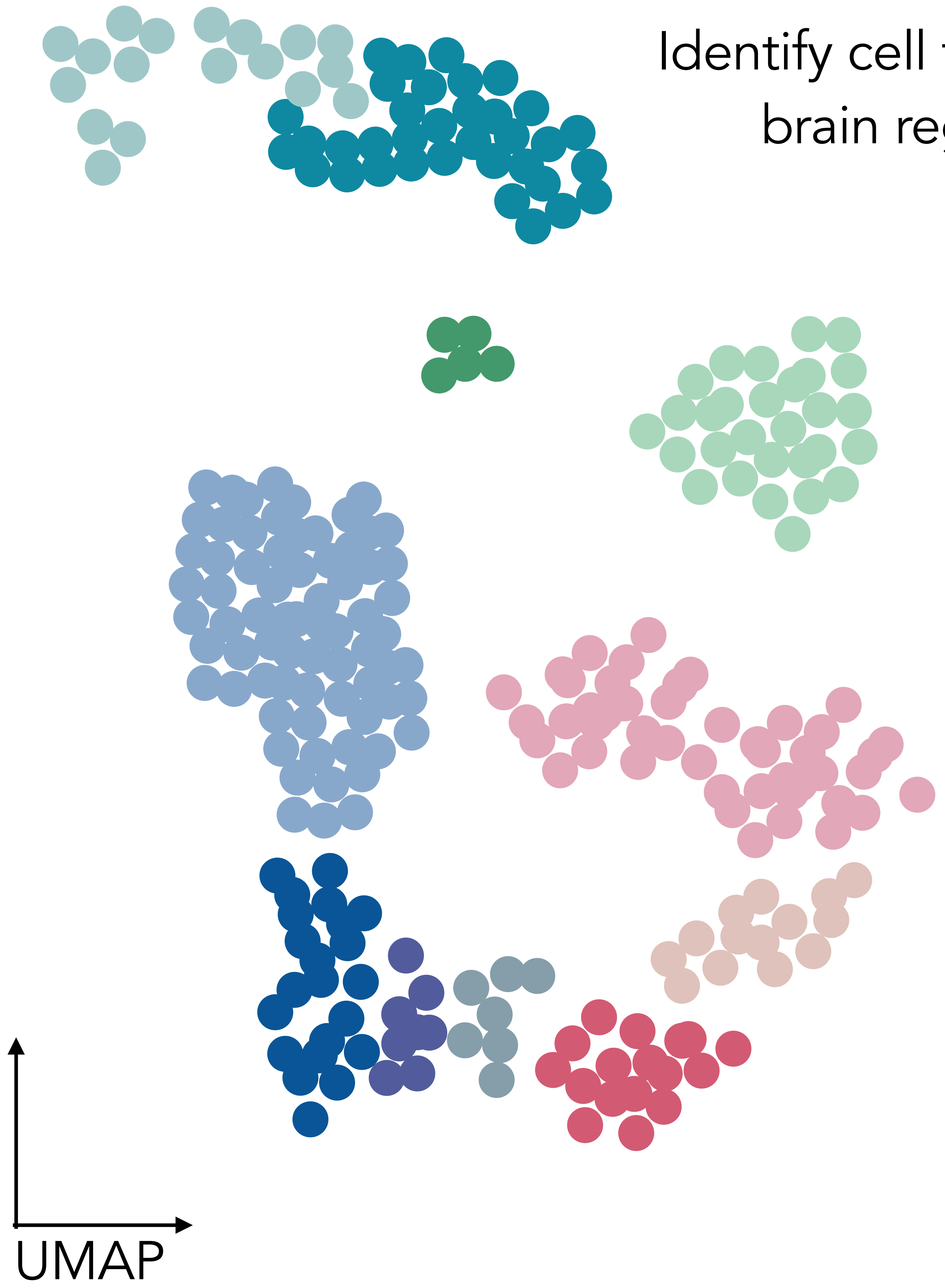


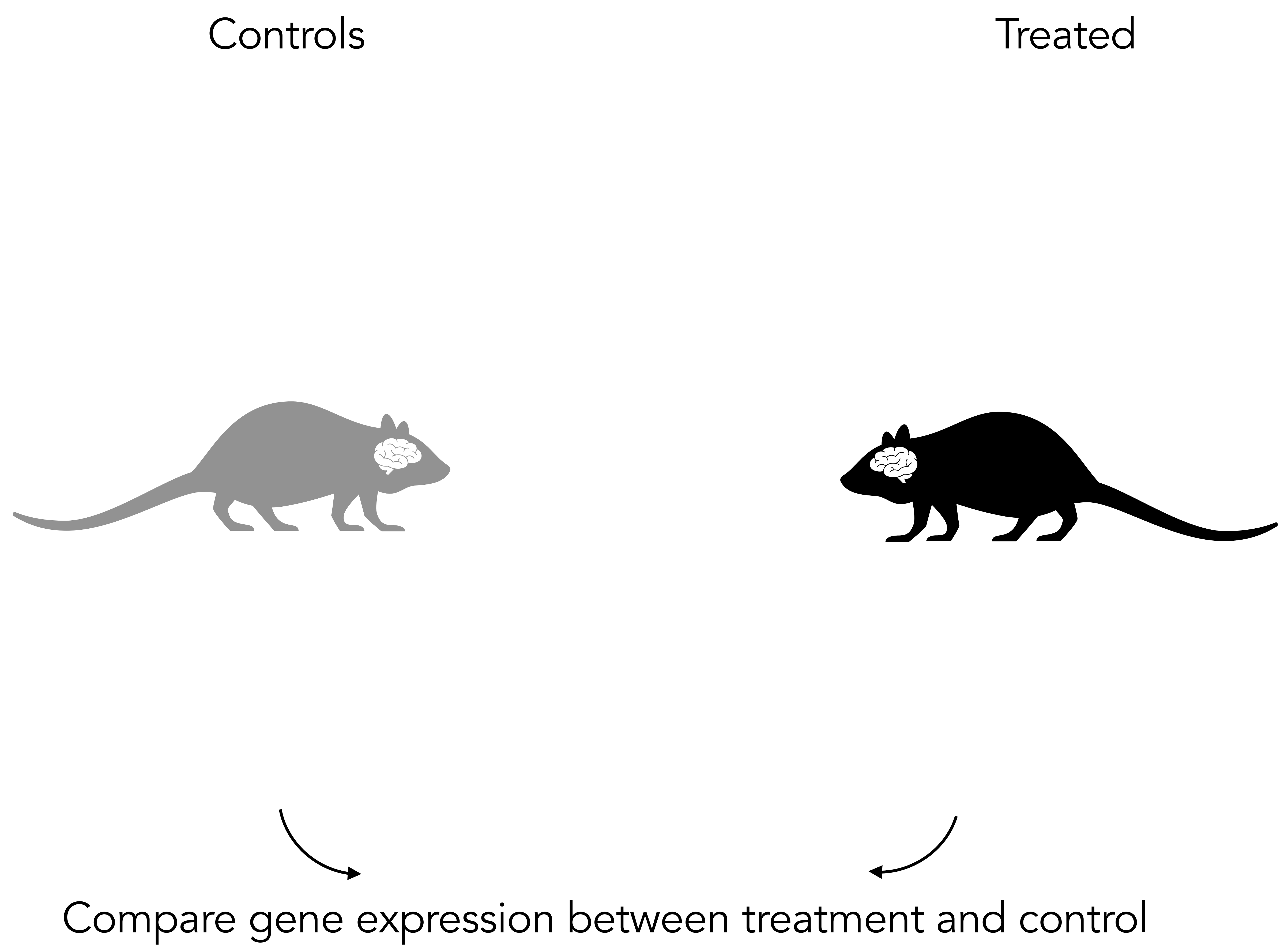
Quantifying gene expression changes upon perturbation

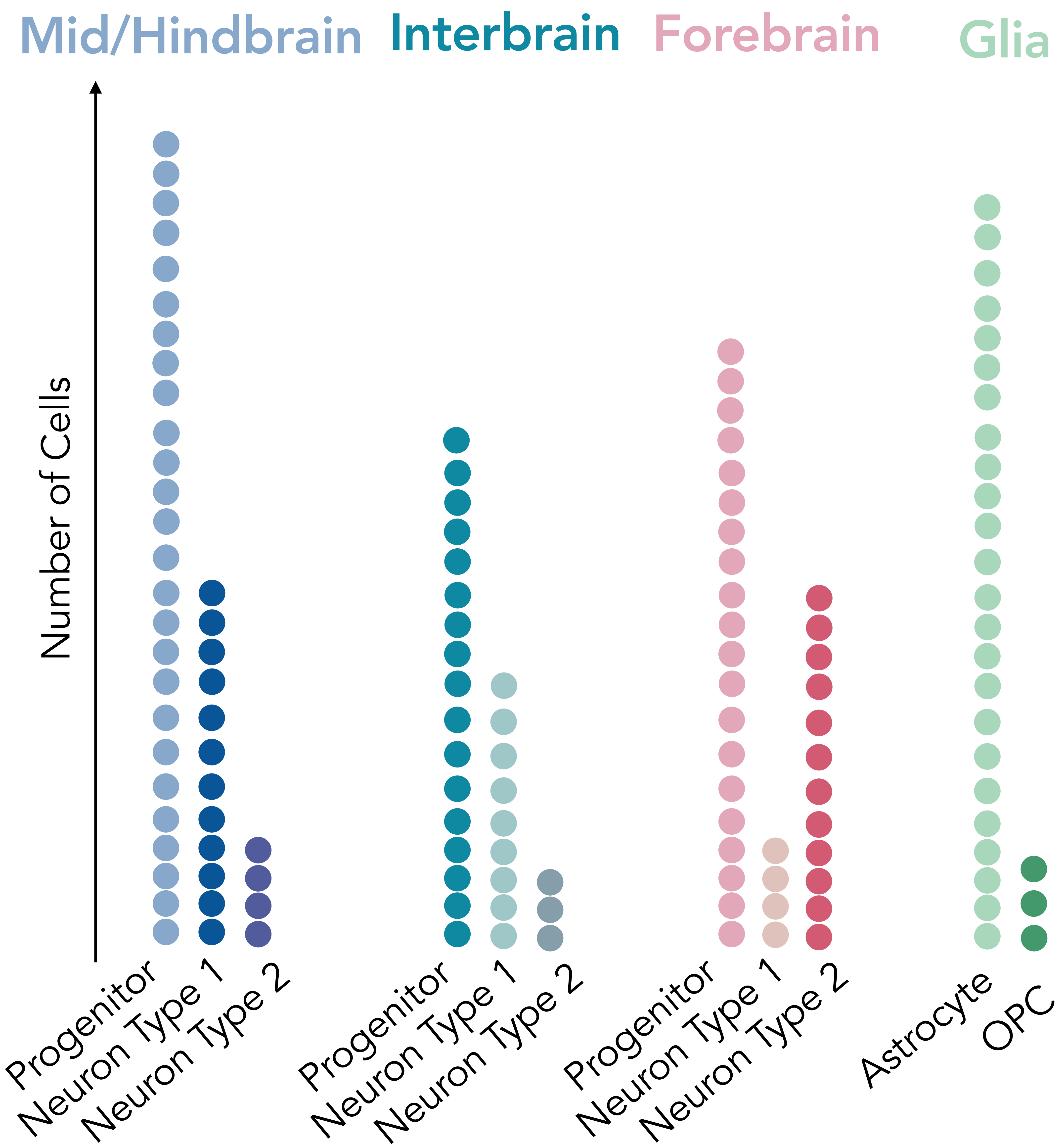




Identify cell types and brain regions

Quantifying gene expression changes upon perturbation

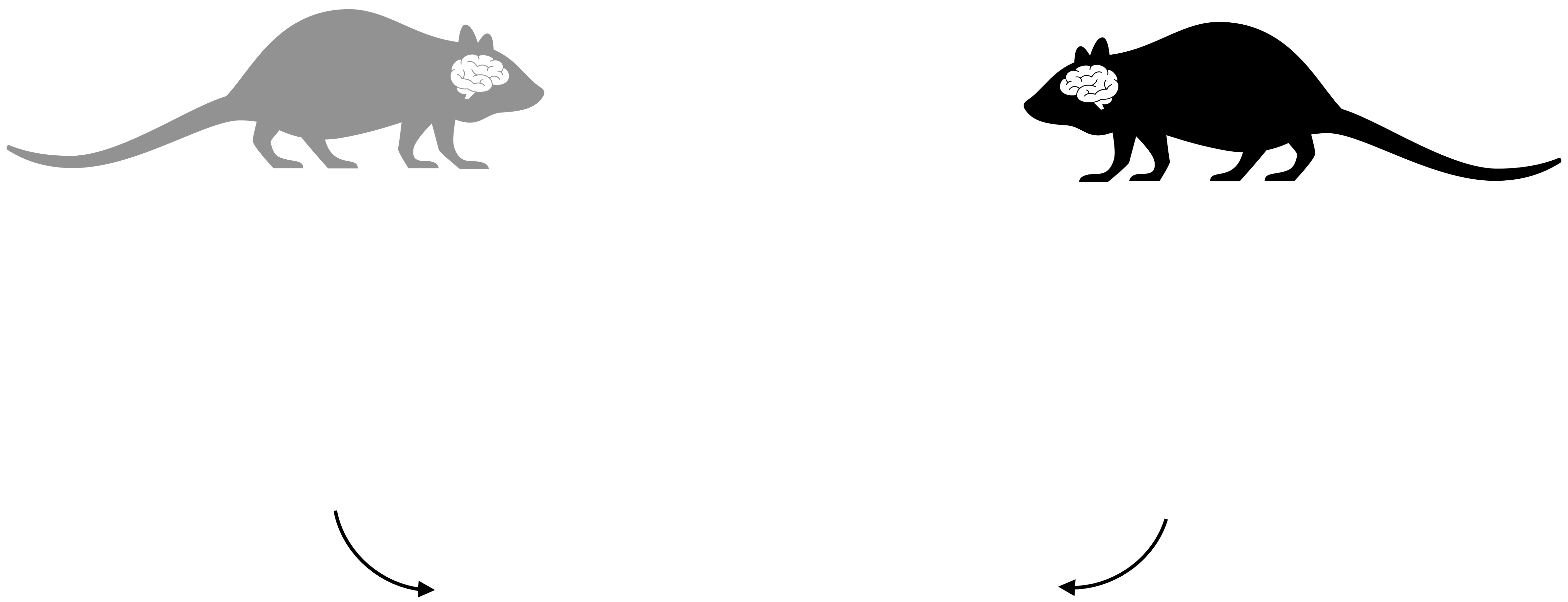




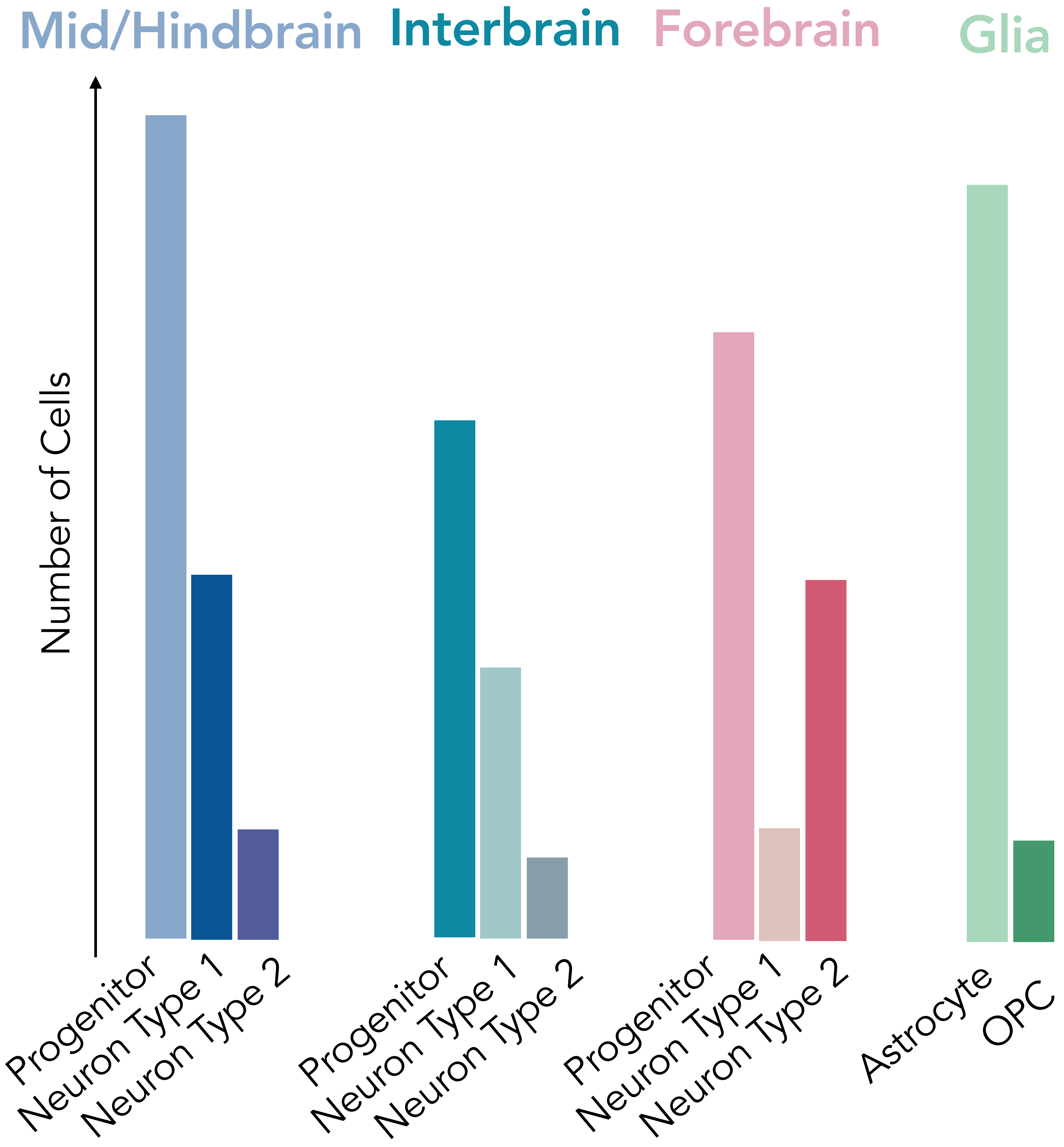
Quantifying gene expression changes upon perturbation

Controls

Treated



Compare gene expression between treatment and control



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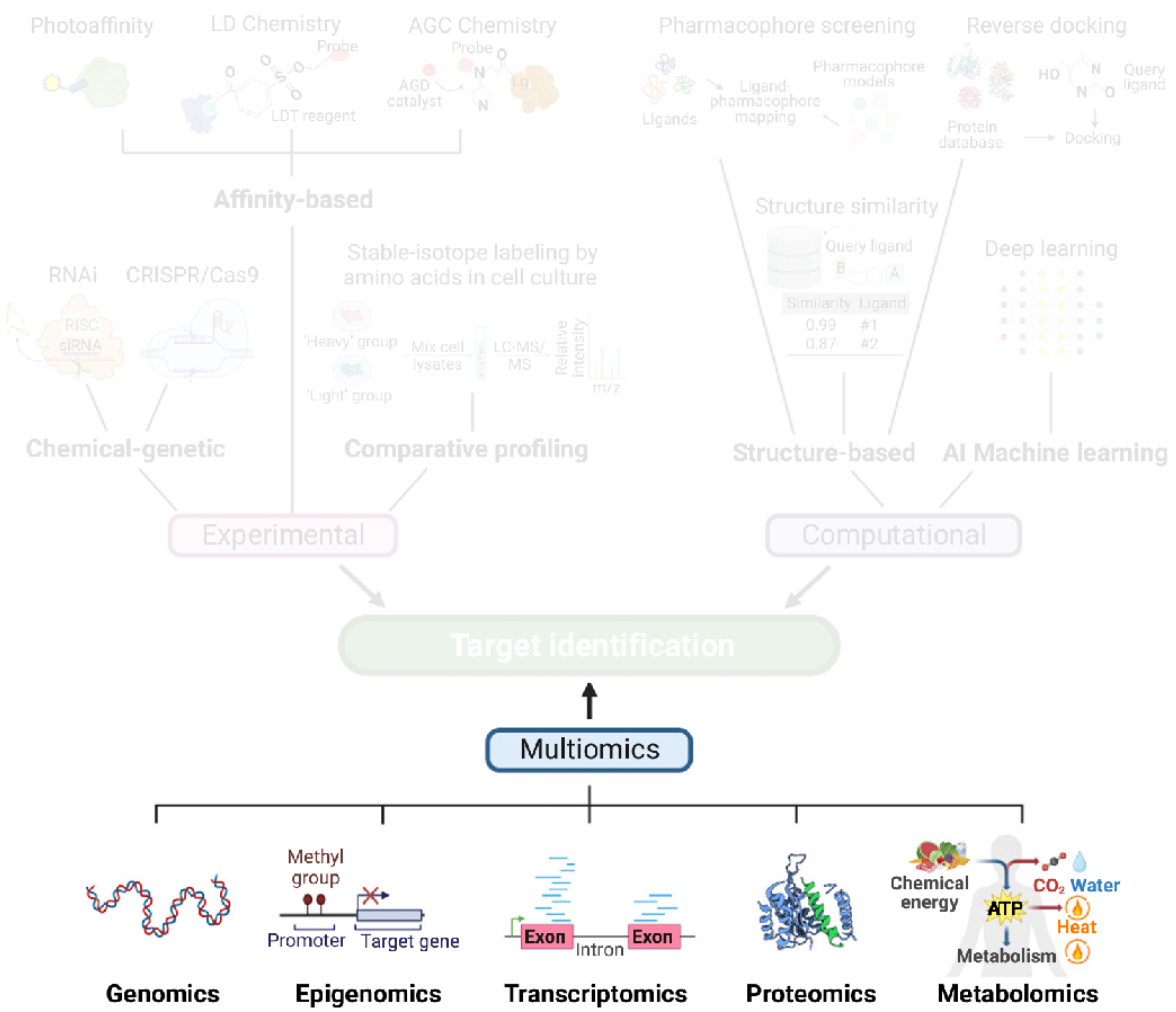
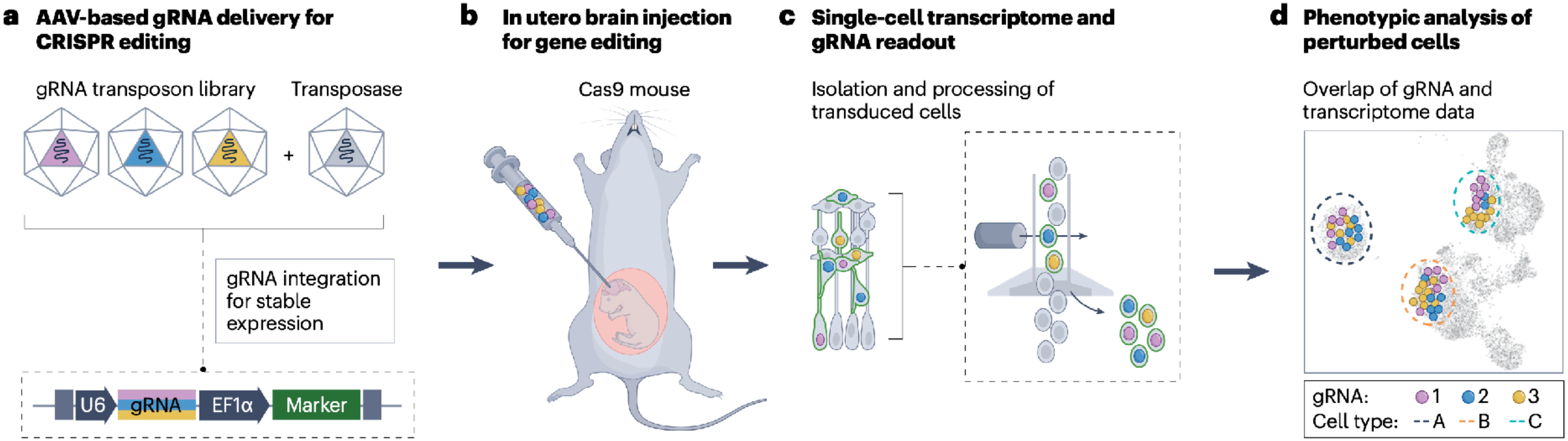


Pun et al. (2023) Trends in Pharmacological Sciences

Large scale CRISPR screens

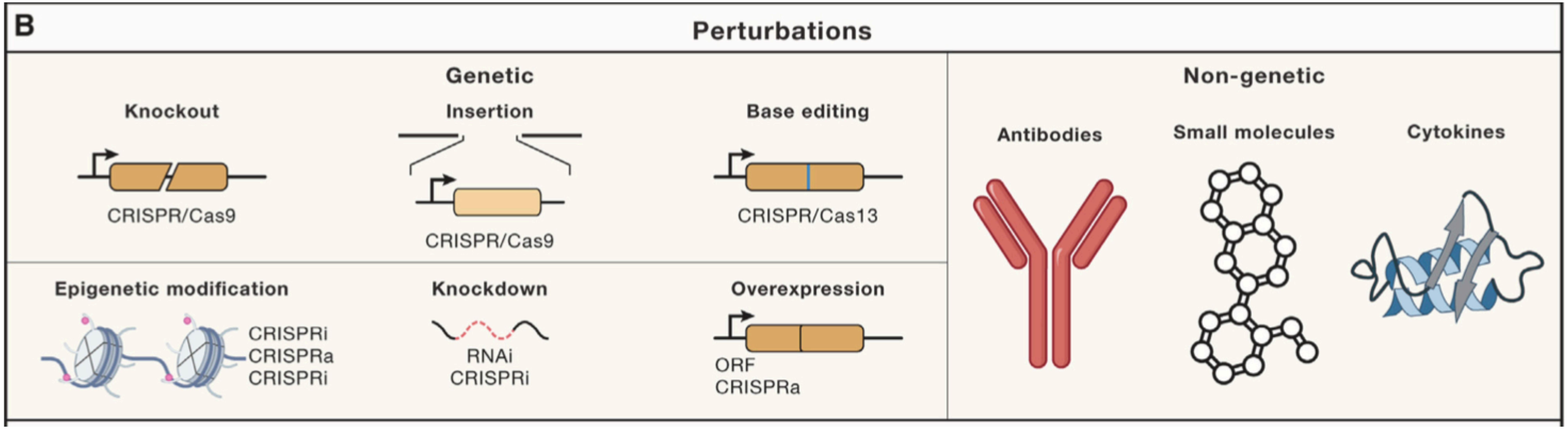


Large-scale CRISPR screens help identify the role of certain genes in different cellular processes.

The identification of growth regulators, for example, can help identify targets for cancer drugs.

Bock et al. (2022) Nature Reviews Method Primers

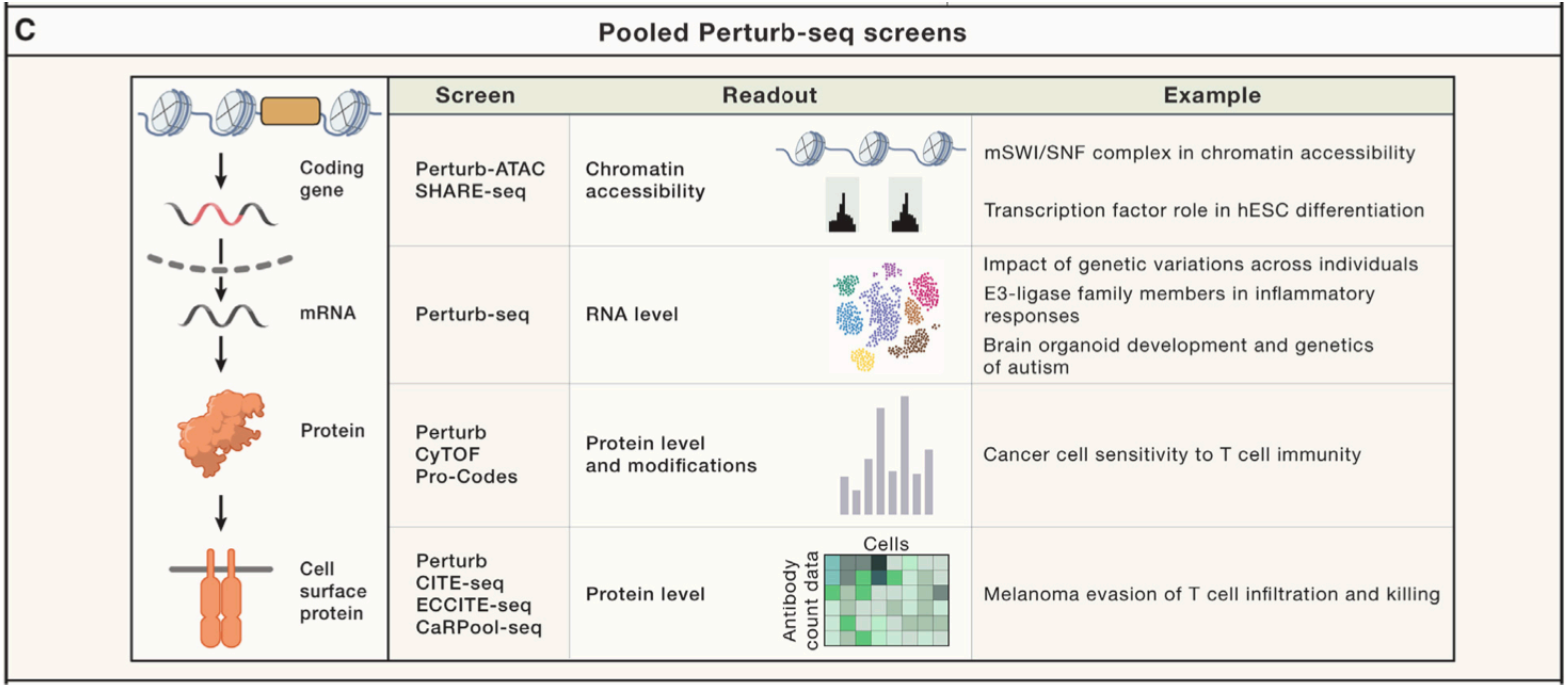
Large scale single cell perturbation screens



With different genetic and single-cell technologies we can perform many different perturbations to individual cells

Rood et al. (2024) Cell

Building virtual cells



C

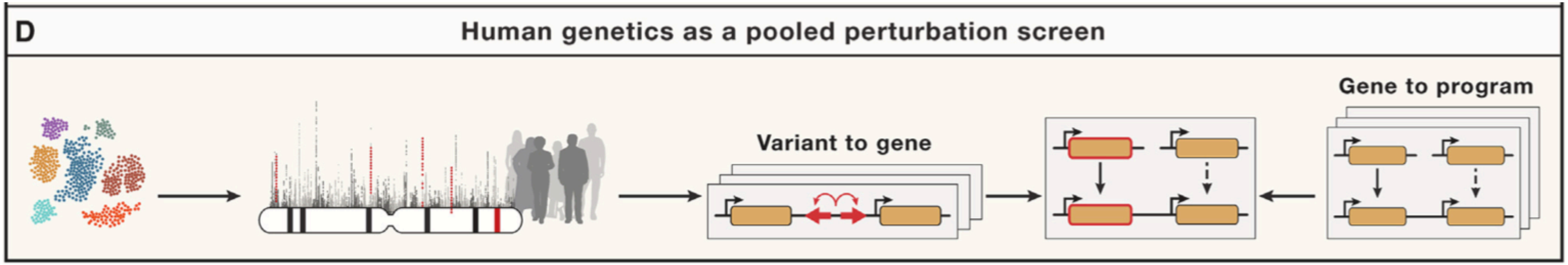
Pooled Perturb-seq screens

Screen	Readout	Example
Perturb-ATAC SHARE-seq	Chromatin accessibility	mSWI/SNF complex in chromatin accessibility Transcription factor role in hESC differentiation
Perturb-seq	RNA level	Impact of genetic variations across individuals E3-ligase family members in inflammatory responses Brain organoid development and genetics of autism
Perturb CyTOF Pro-Codes	Protein level and modifications	Cancer cell sensitivity to T cell immunity
Perturb CITE-seq ECCITE-seq CaRPool-seq	Protein level	Melanoma evasion of T cell infiltration and killing

The perturbations can be read out at many different levels (chromatin changes, transcription changes, protein changes..)

Rood et al. (2024) Cell

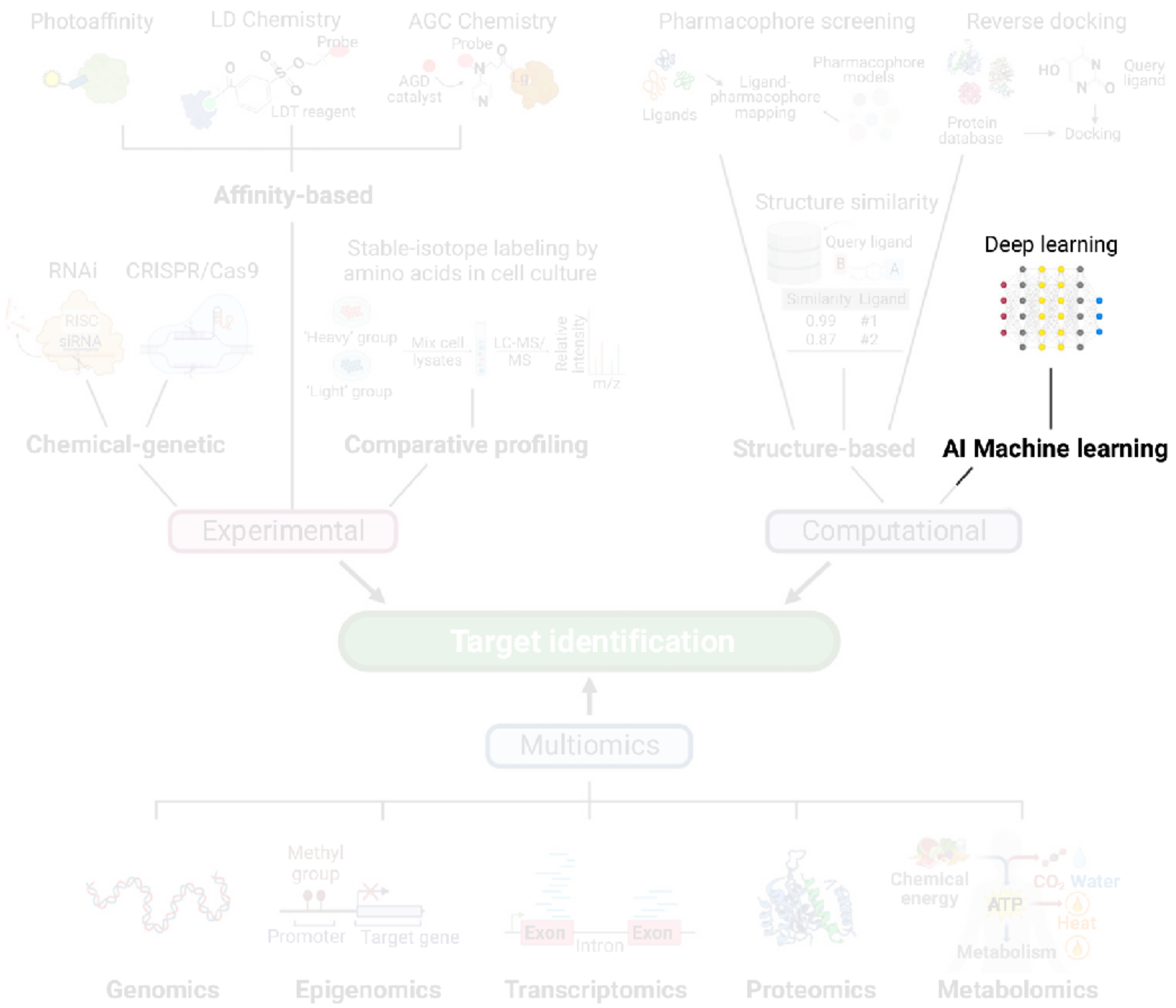
Building virtual cells



Also, variation in the human genome can used to associate gene expression changes.

Rood et al. (2024) Cell

How do you identify a drug target?



Pun et al. (2023) Trends in Pharmacological Sciences

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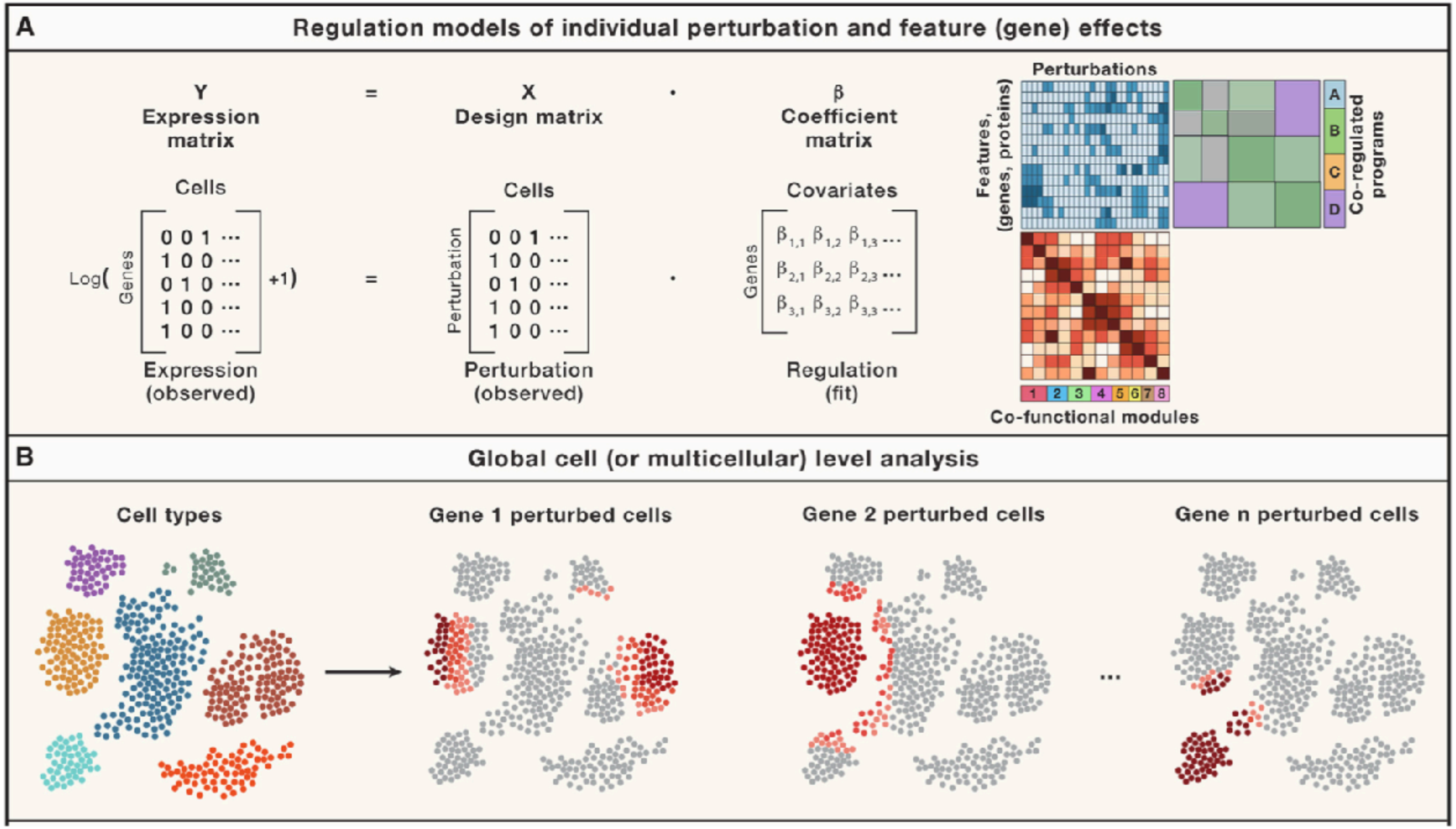
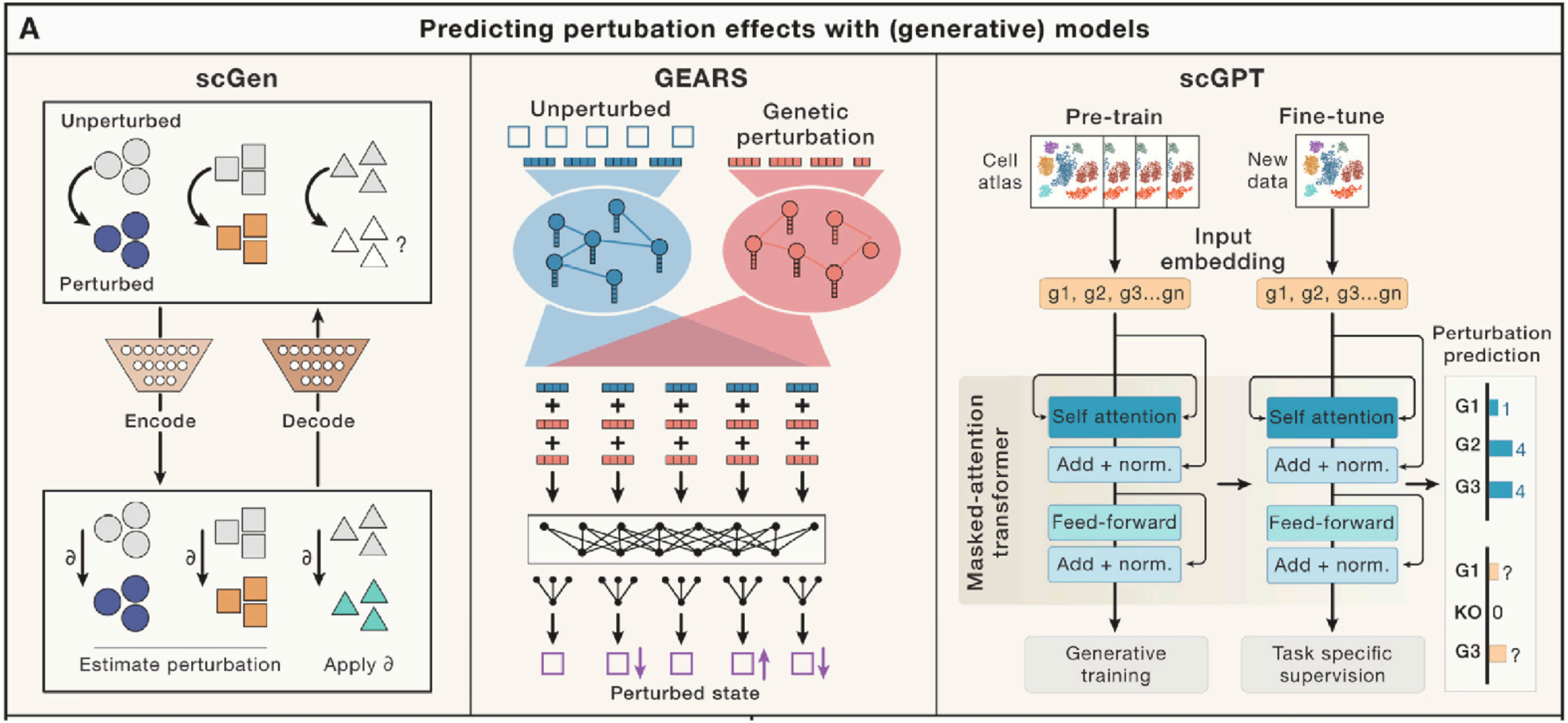


From large-scale screens, we can identify groups of genes or gene regulatory models that respond to the same perturbation. This will help to identify potential targets to drug.

Rood et al. (2024) Cell

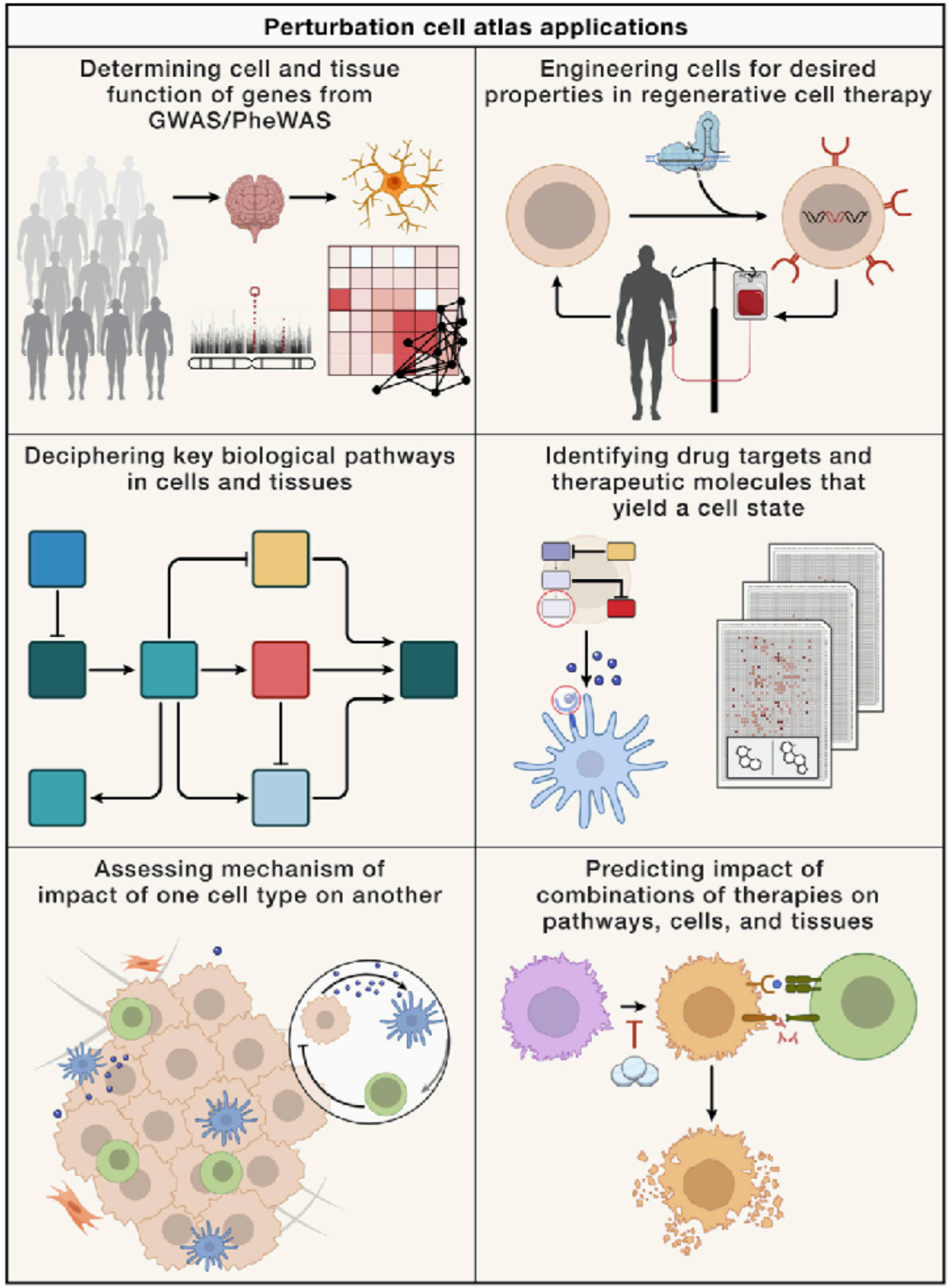
Building virtual cells



Many generative models have already been developed to predict the effect of unknown perturbation on different cell types. These foundation model can now be adapted to many other different cells types.

Rood et al. (2024) Cell

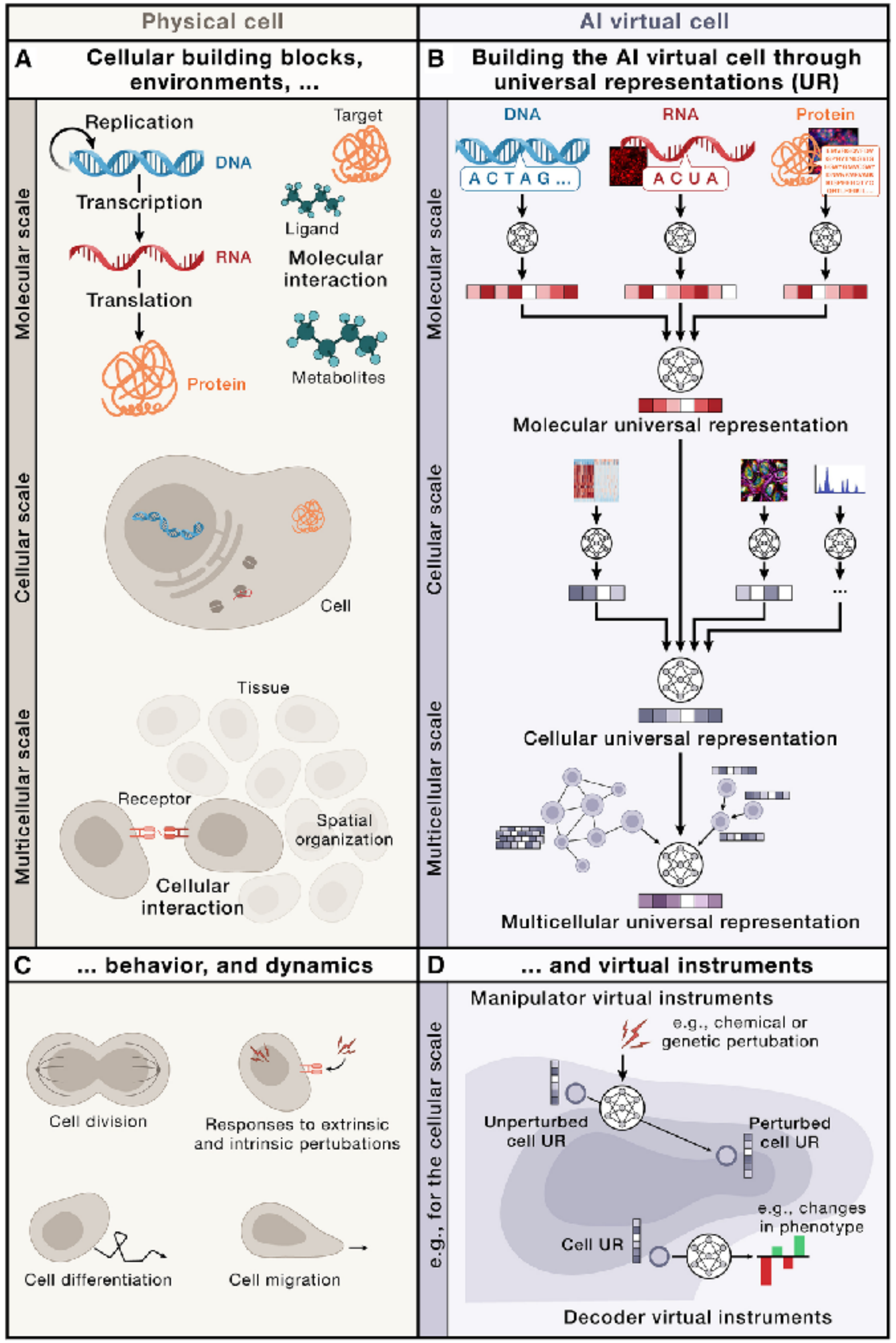
Perturbation Cell atlases



Perturbation cell atlases will be link genotype and phenotype, engineer cellular models (examples later), and understand biological pathways and drug targets.

Rood et al. (2024) Cell

Building virtual cells



Bunne et al. (2024) Cell

Virtual cells will help to predict the effect of unknown molecules/perturbations and patient mutations in the future

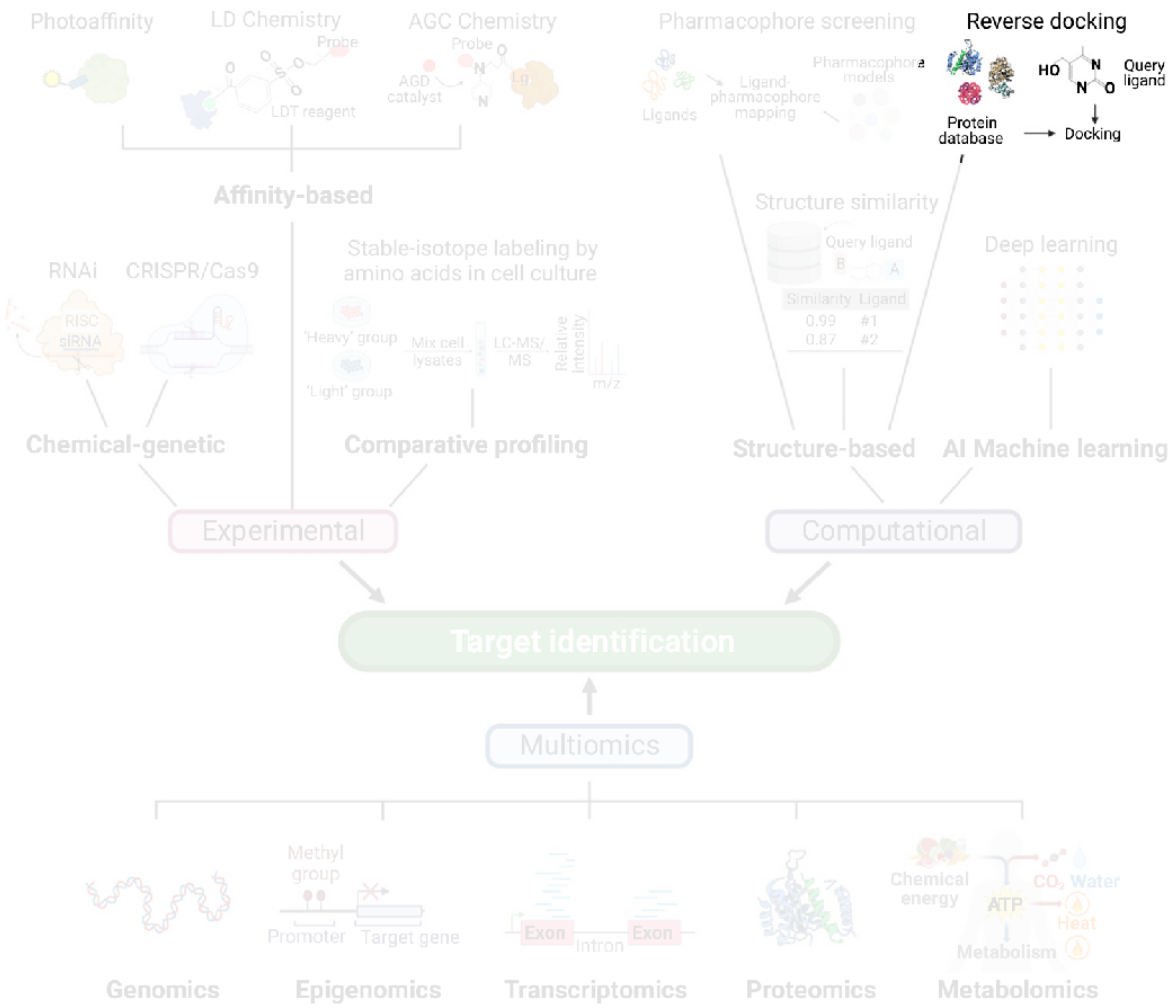
Professor at EPFL-IC: Artificial Intelligence in Molecular Medicine

Building virtual cells

HUMAN CELL ATLAS

The Human Cell Atlas and Chan Zuckerberg CellxGene are huge collaborative scientific initiatives that collect the transcriptomes of Millions of individual cells that can be used to build foundation models.

How do you identify a drug target?



Pun et al. (2023) Trends in Pharmacological Sciences

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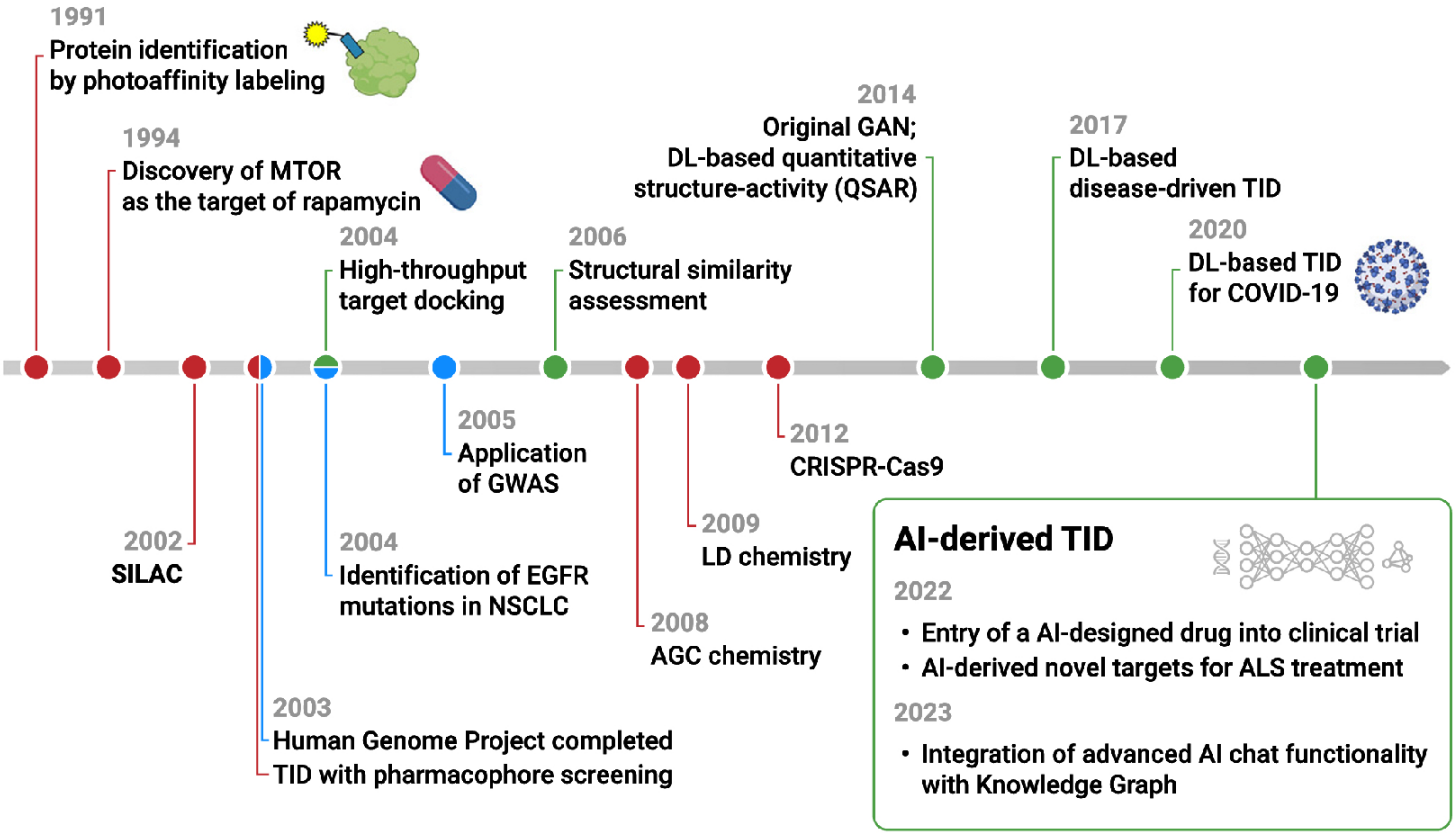
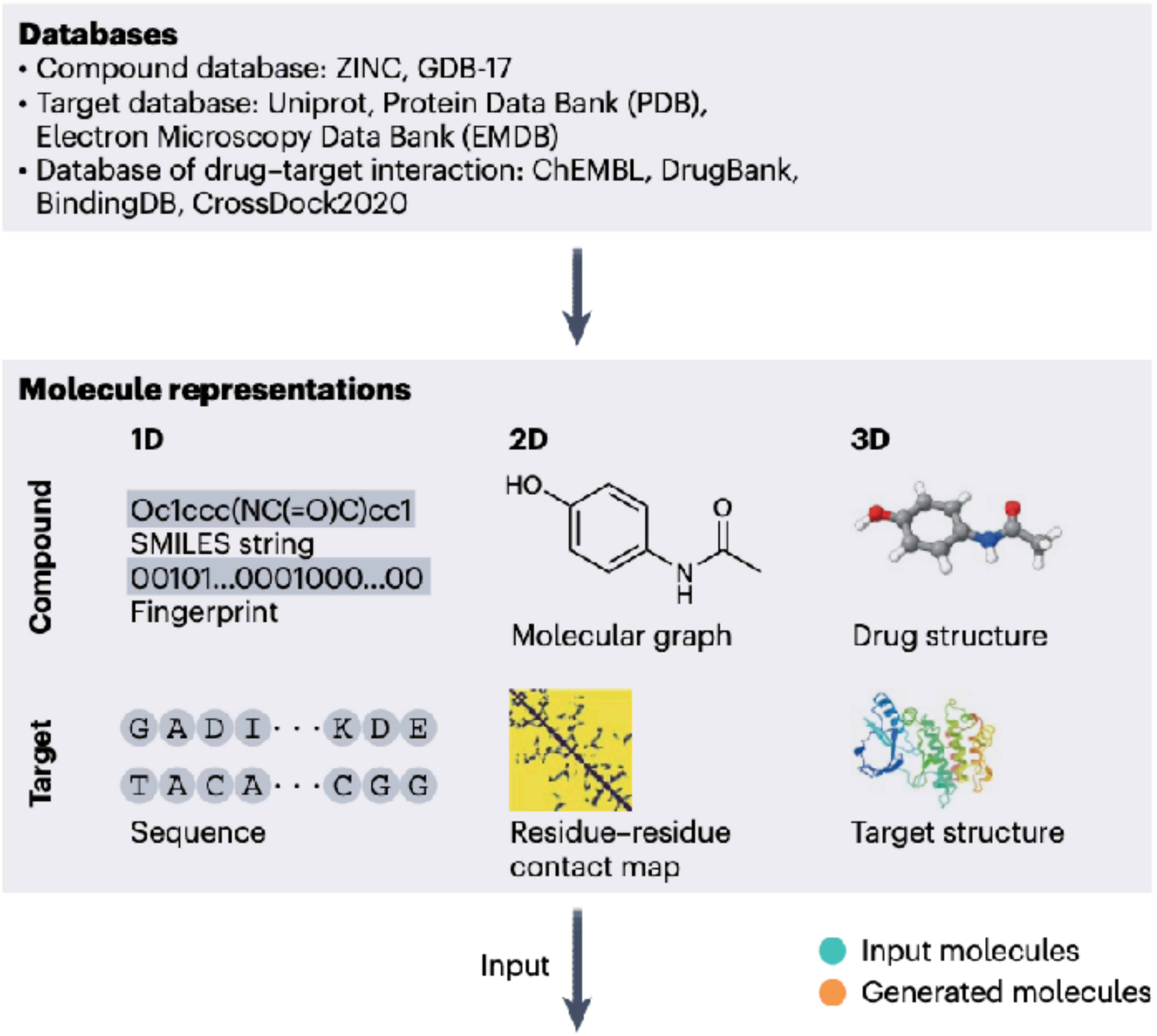
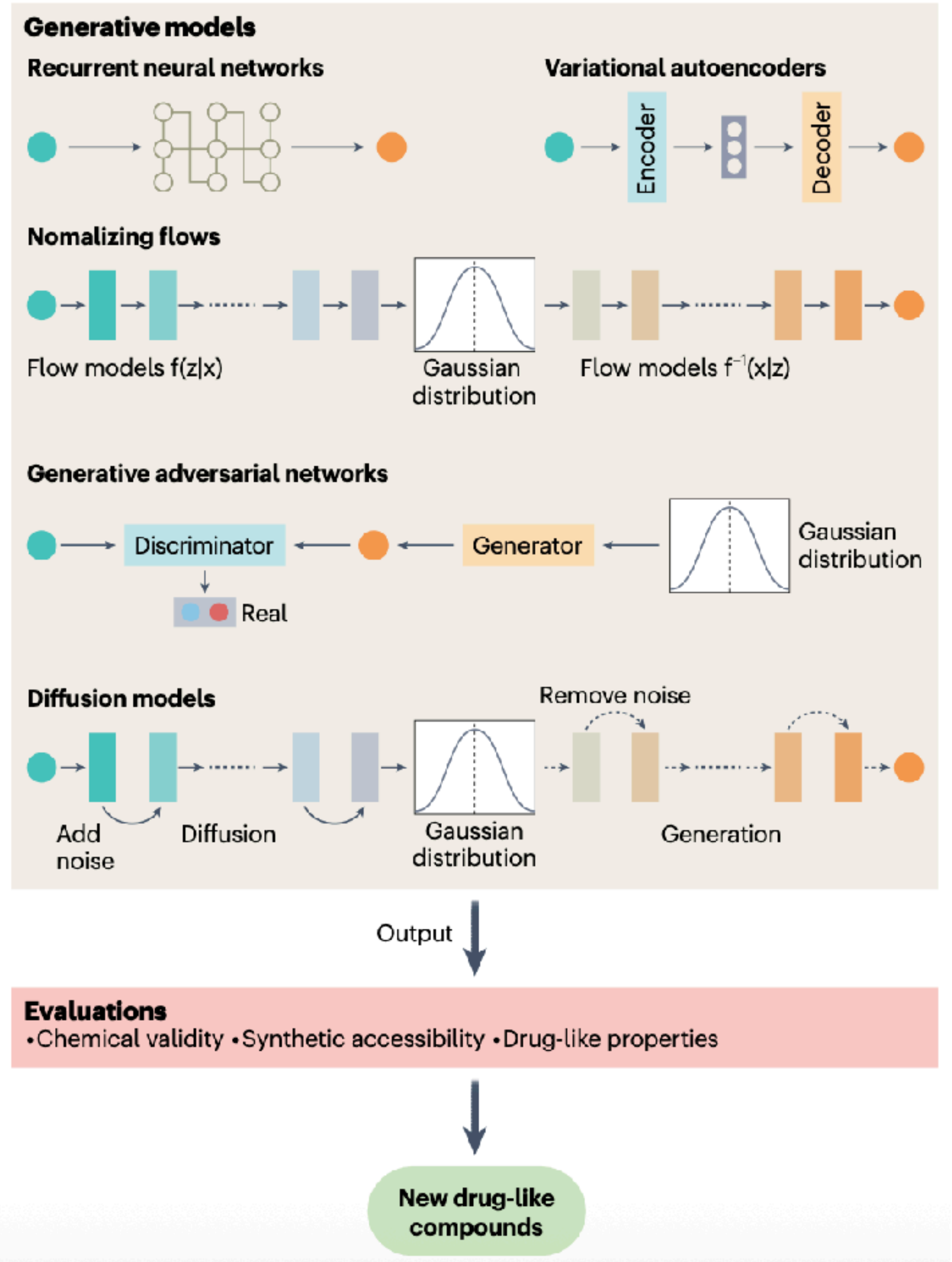


Pun et al. (2023) Trends in Pharmacological Sciences

Reverse Docking

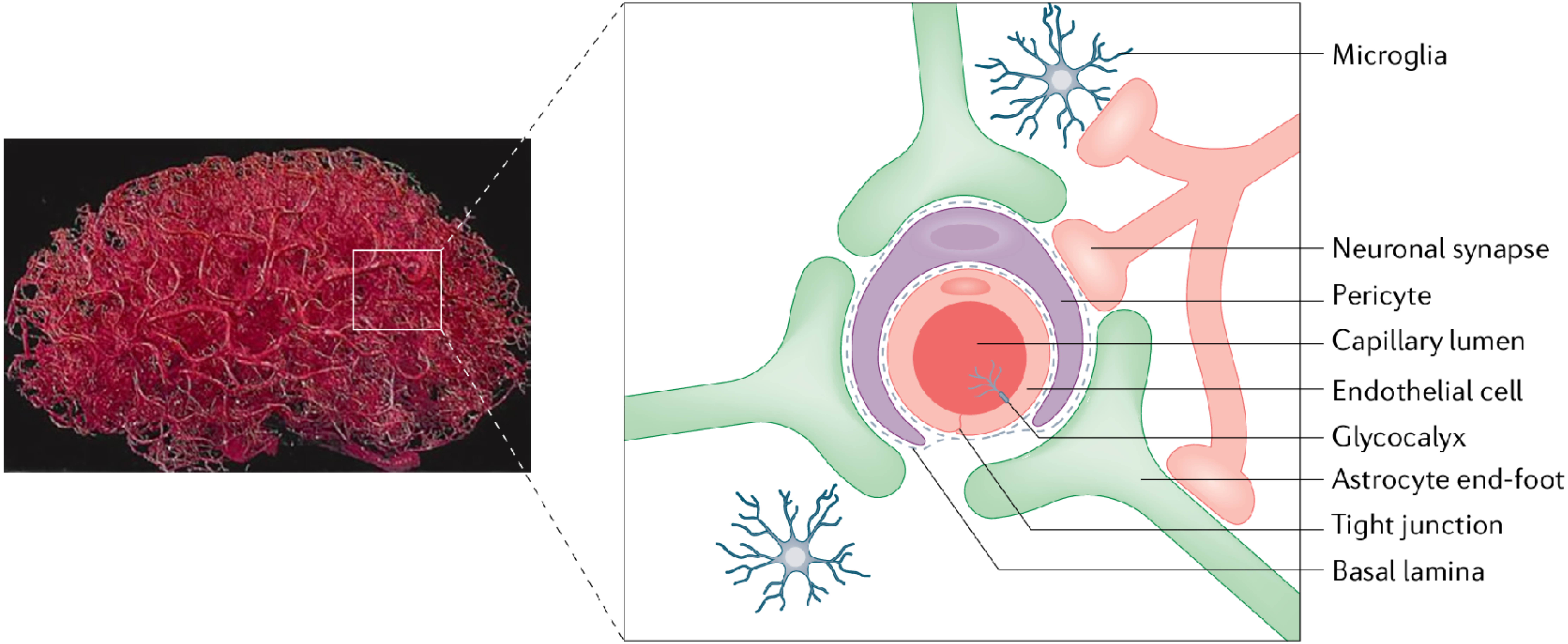




Generative models can also help to learn and predict which molecules might bind to which protein targets.

Zhang et al. (2024) Nature Medicine

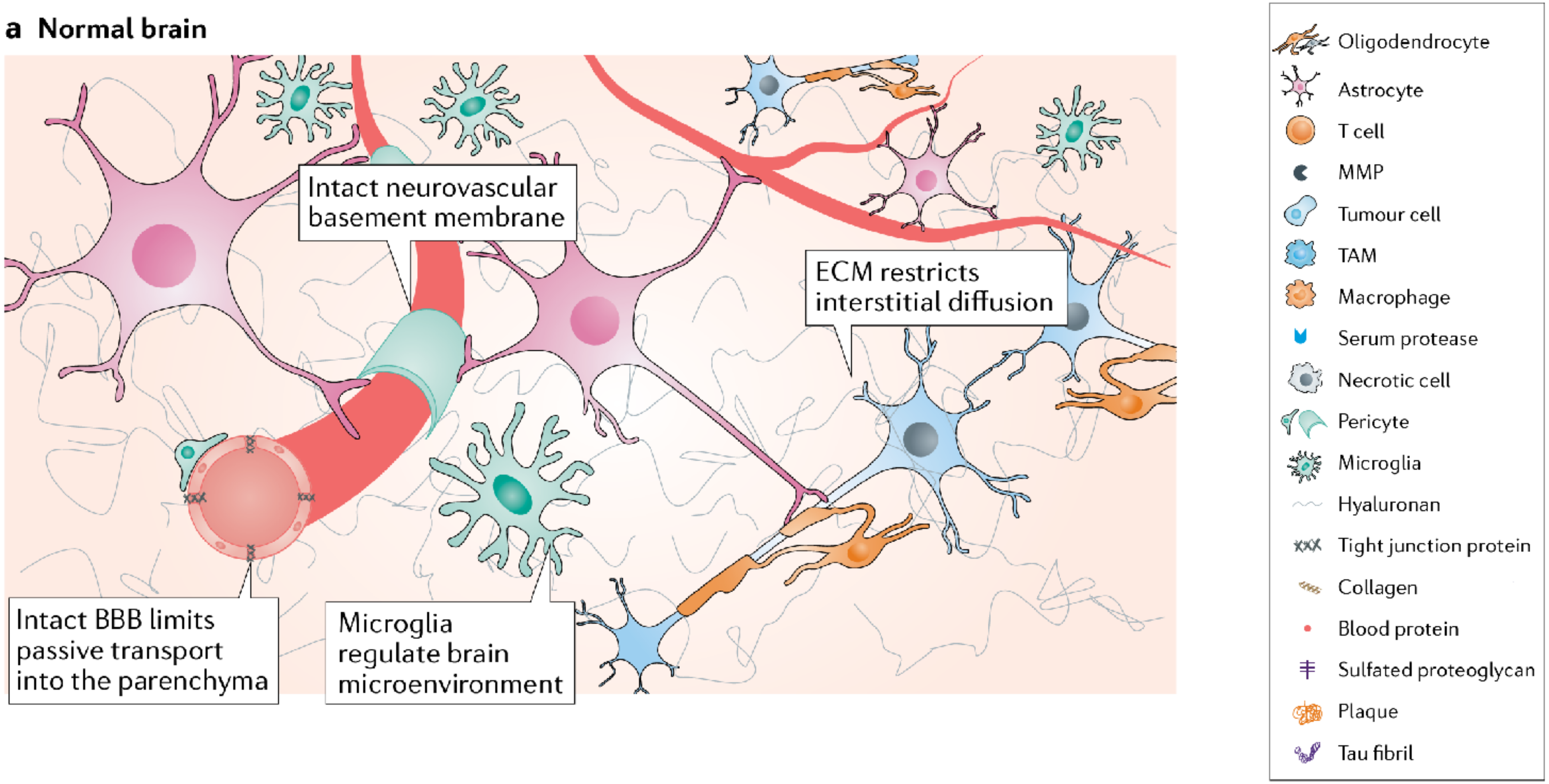
Blood Brain Barrier



The blood-brain barrier limits the diffusion of molecules from the blood system into the brain. It's one of the very few tight boundaries in the human boundaries in the human body.

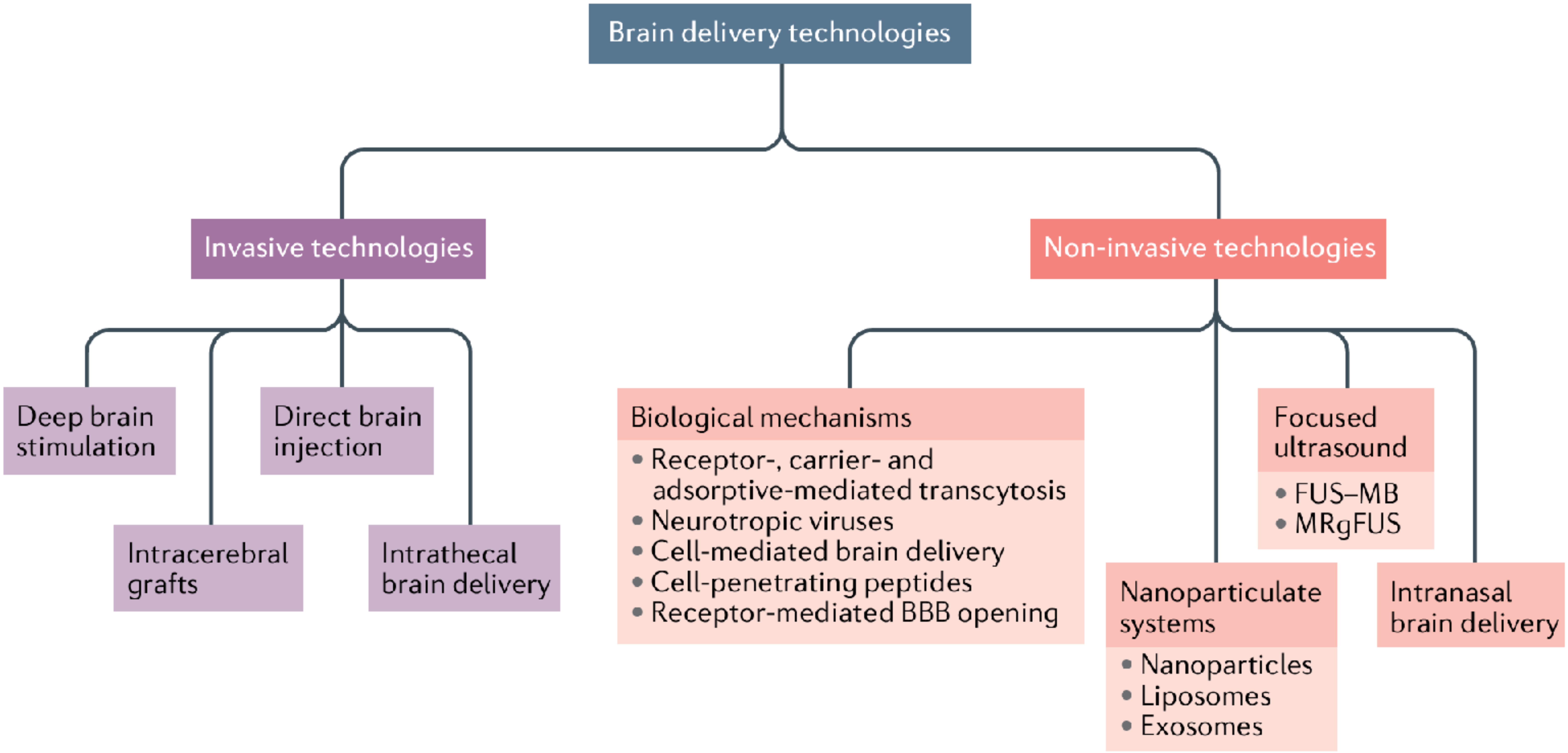
Terstappen et al. (2021) Nature Reviews Drug Discovery

Blood Brain Barrier



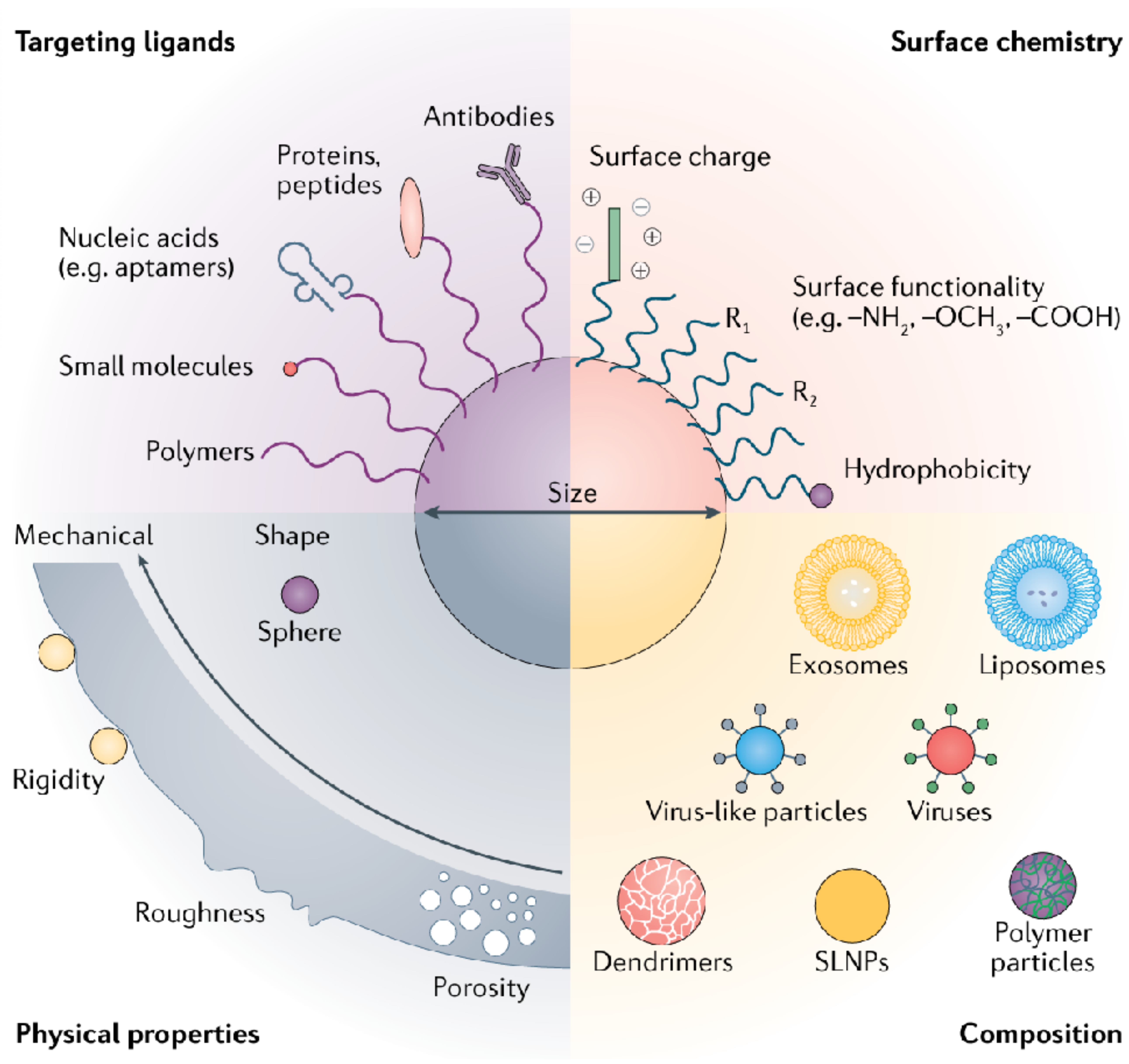
Nance et al. (2021) Nature Reviews Materials

Drug Delivery to the brain



Terstappen et al. (2021) Nature Reviews Drug Discovery

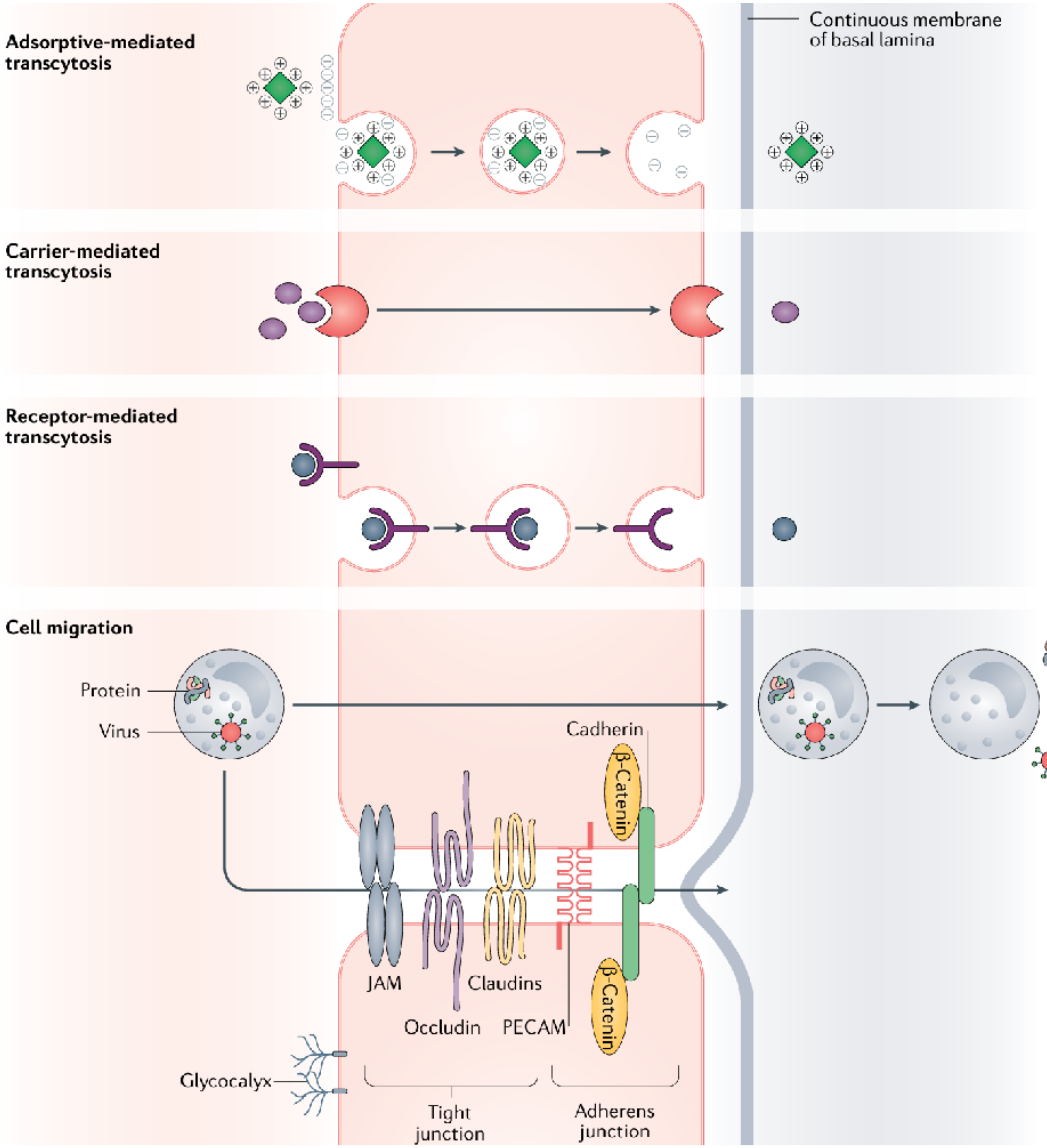
Blood Brain Barrier



Several factors influence the permeability of the BBB and novel tools try to effectively cross it.

Terstappen et al. (2021) Nature Reviews Drug Discovery

Blood Brain Barrier



Postitively charged molecules interact with the negatively charged glycocalyx

Target molecule binds to carrier and gets endocytosed

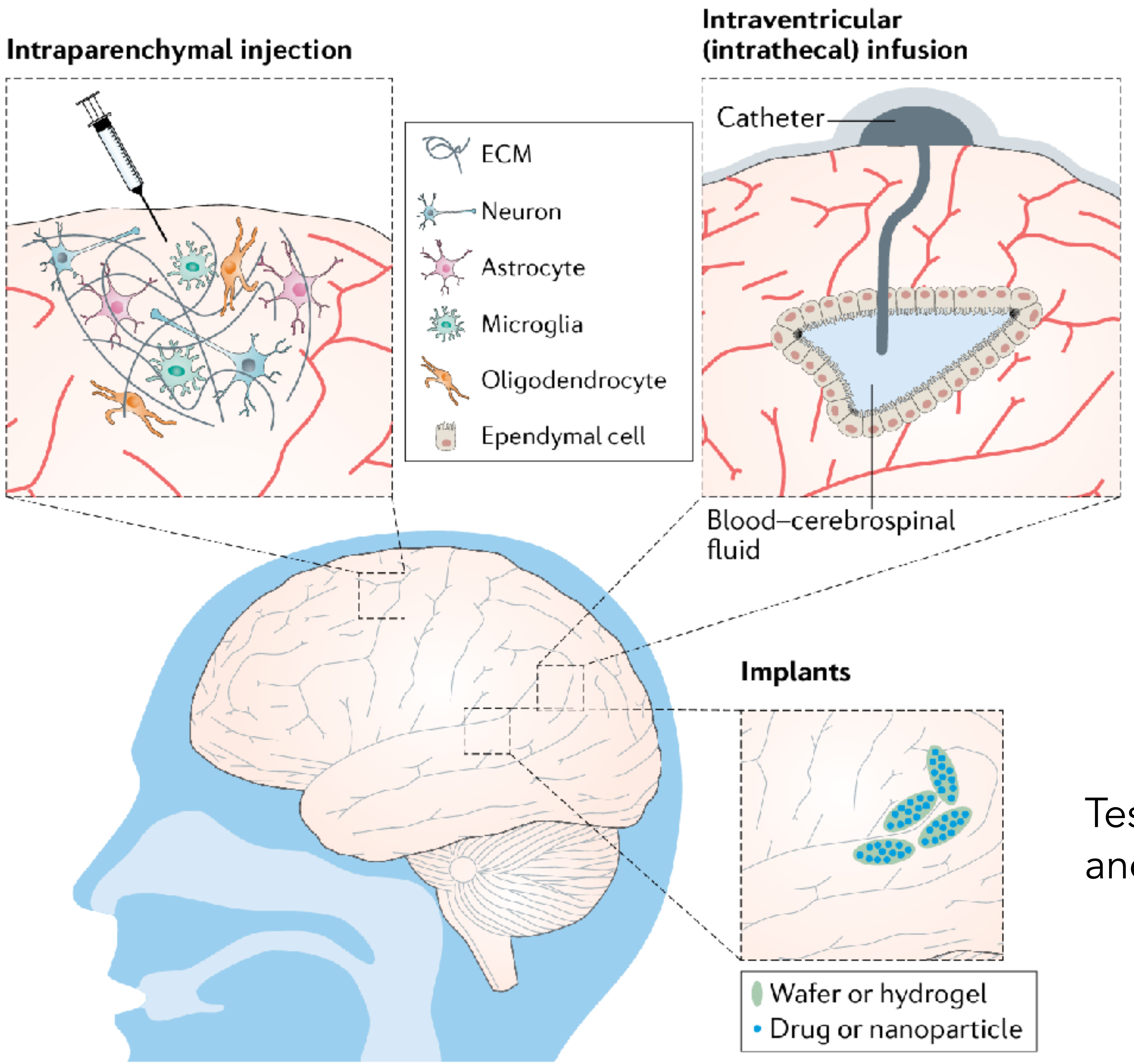
Receptor or antibody bind to target molecule and get endocytosed

Macrophages and monocytes (immune cells) can get endocytosed or travel through the pericellular space

Terstappen et al. (2021) Nature Reviews Drug Discovery

Drug Delivery to the brain

Drug coupled to polymers for longterm release

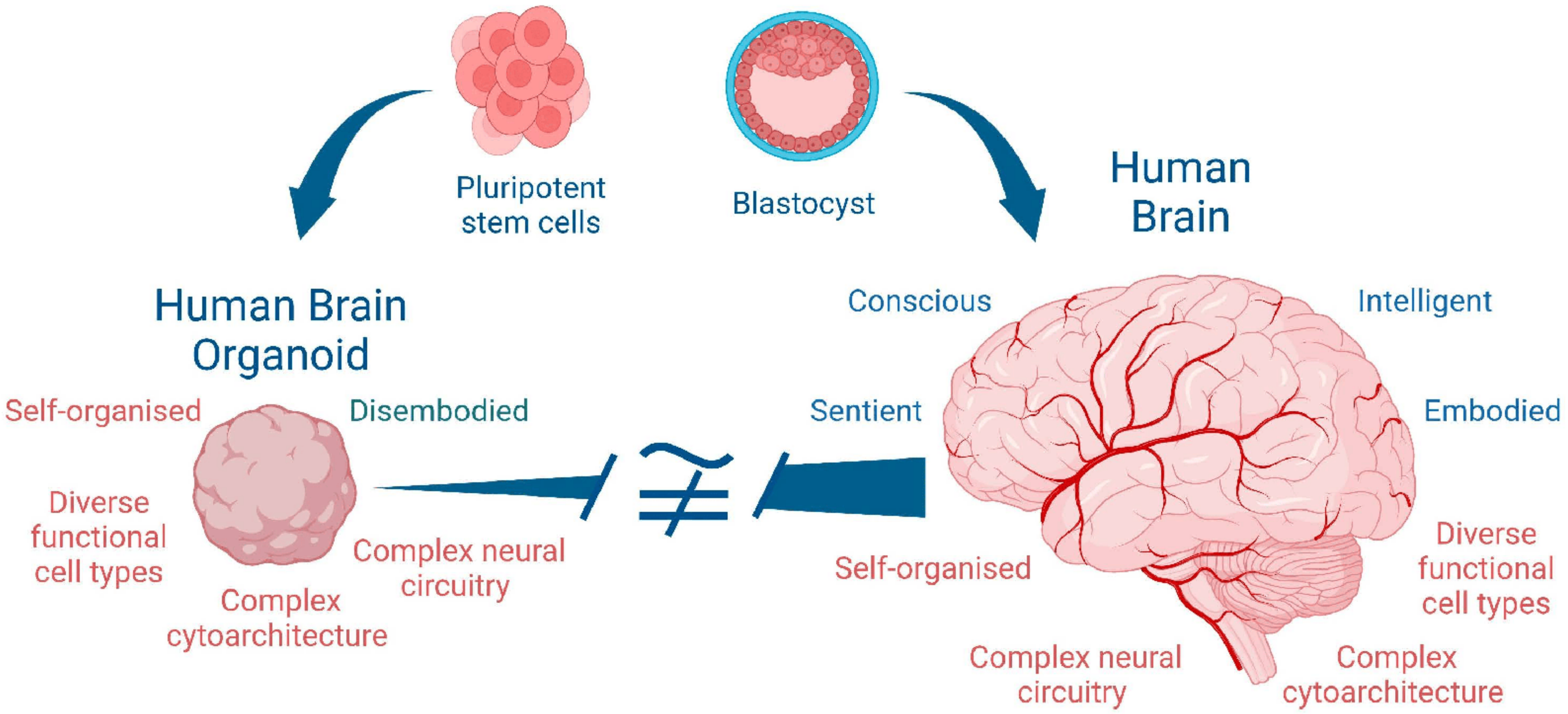


Cerebrospinal fluid boundary is more permeable

Tested in glioblastoma and inflammation

Nance et al. (2021) Nature Reviews Materials

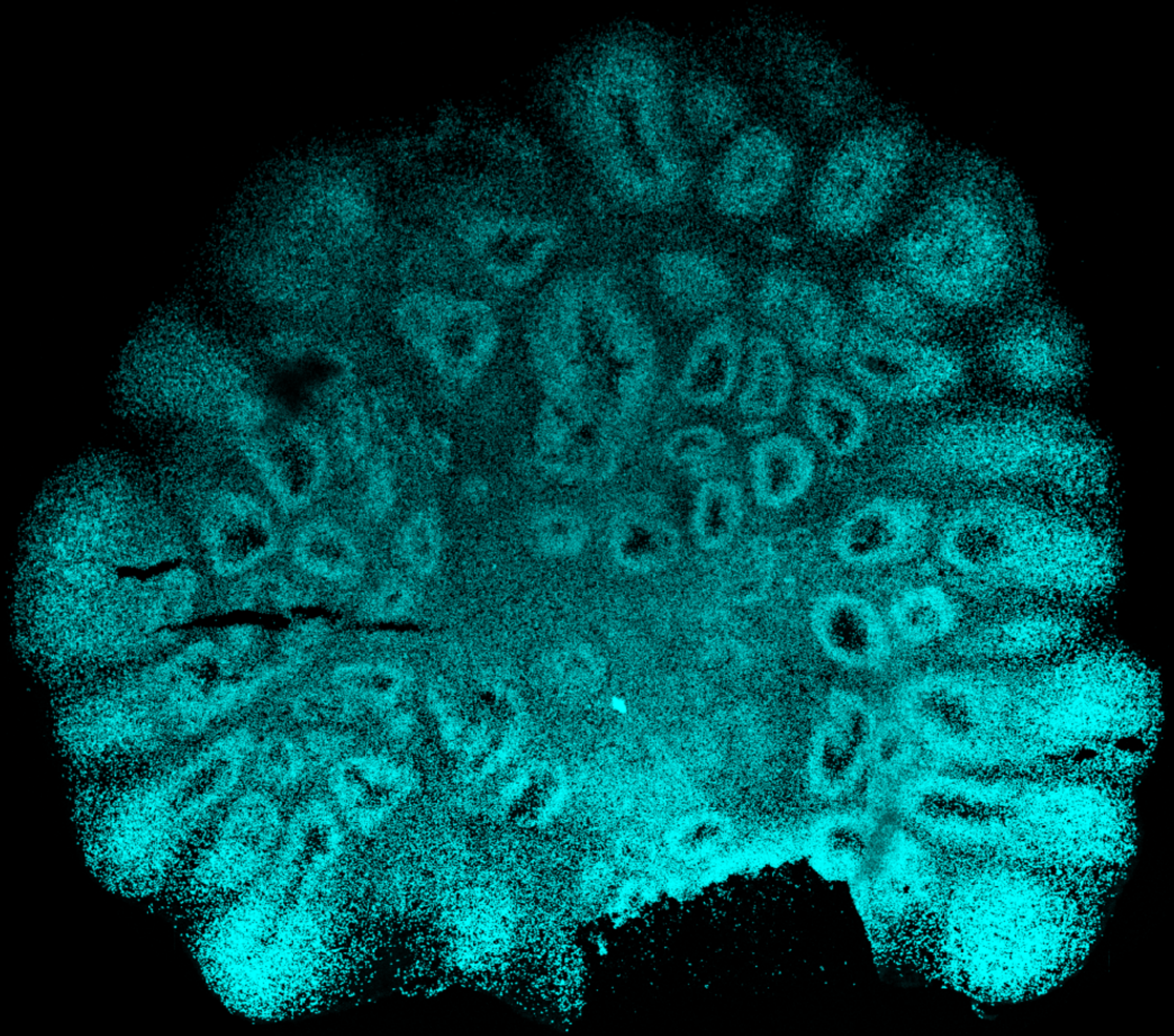
Building reliable in vitro models of the CNS



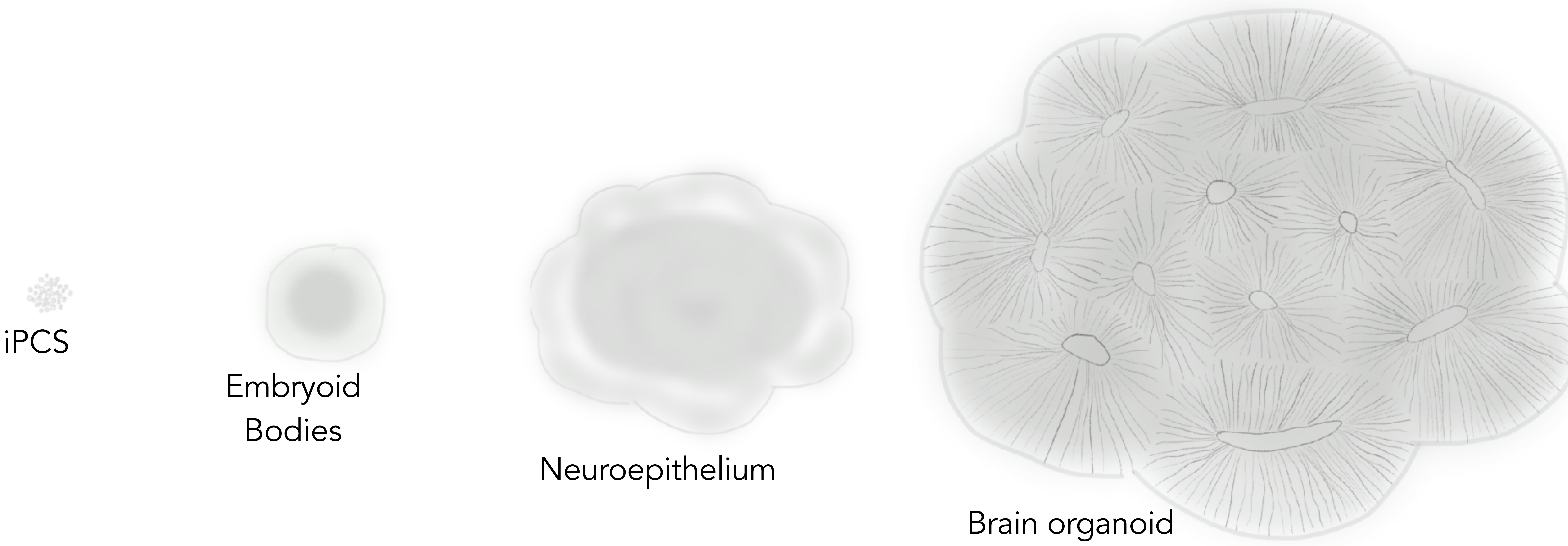
Molecular studies on human patient brains are almost impossible. Stem Cell models can help overcome this bottleneck.

Goddard et al. (2023) MDPI Organoids

Understanding Human Brain Development using Neural Organoids

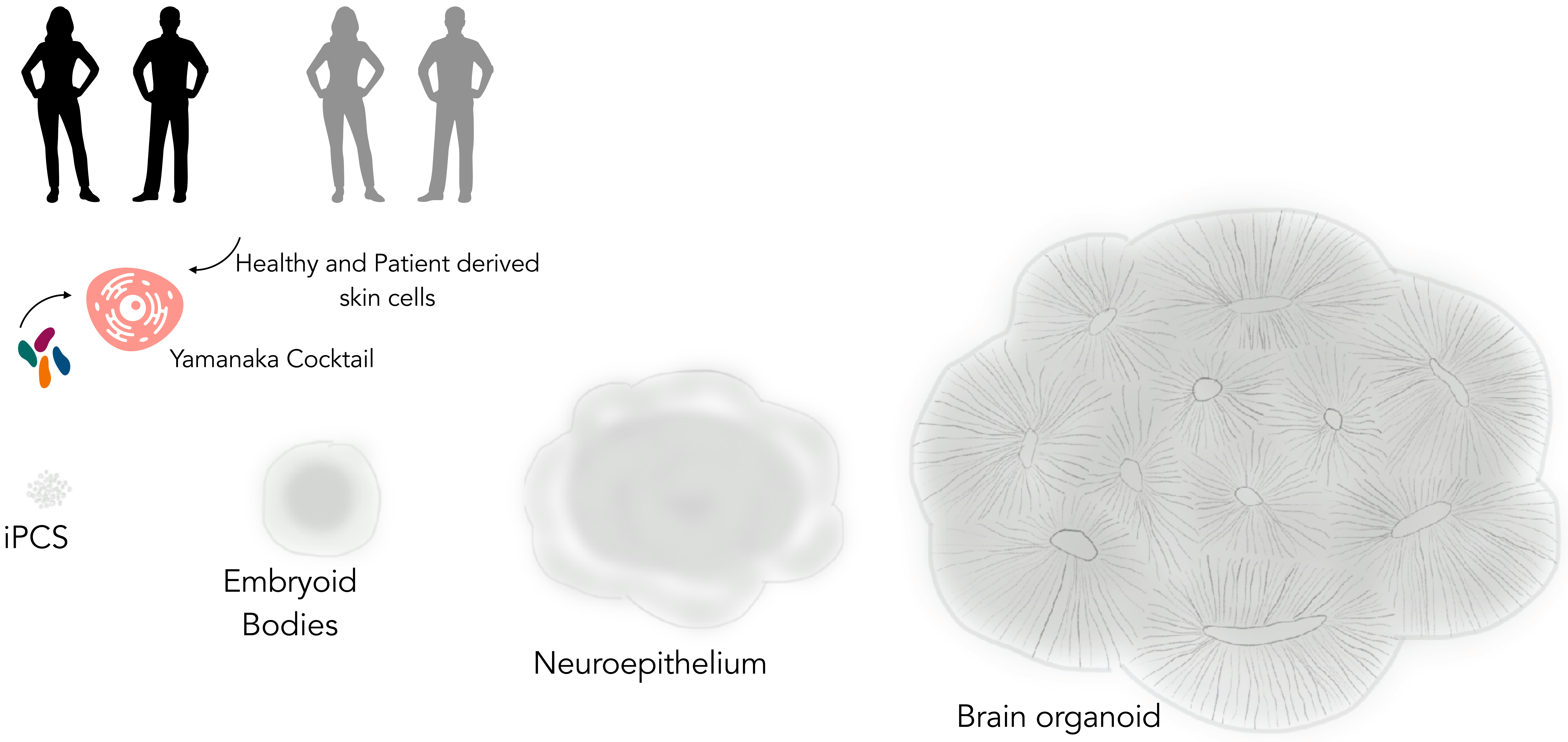


Human Neural Organoids recapitulate embryonic Development

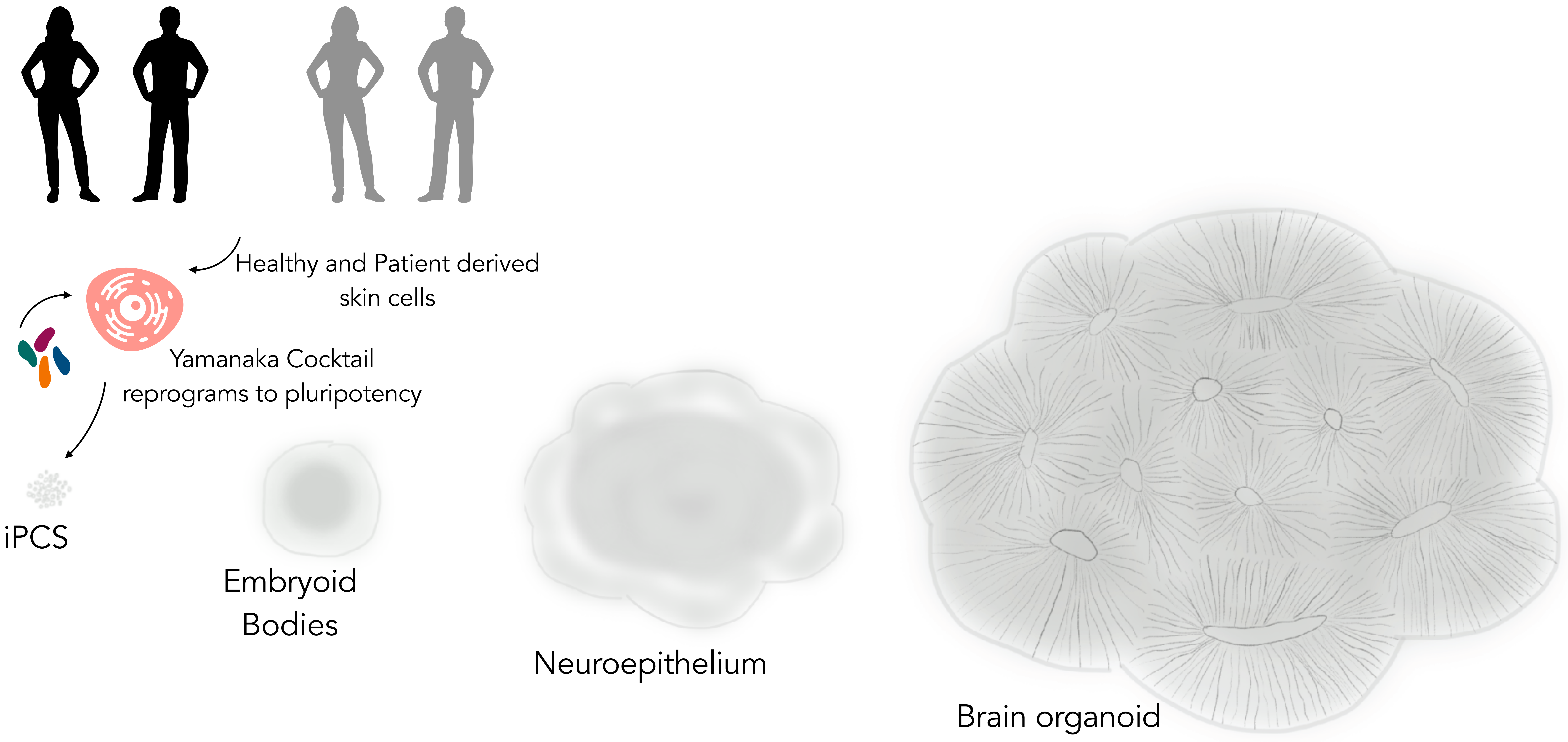


Human Neural Organoids are generated from iPSCs

Human Neural Organoids are generated from iPSCs



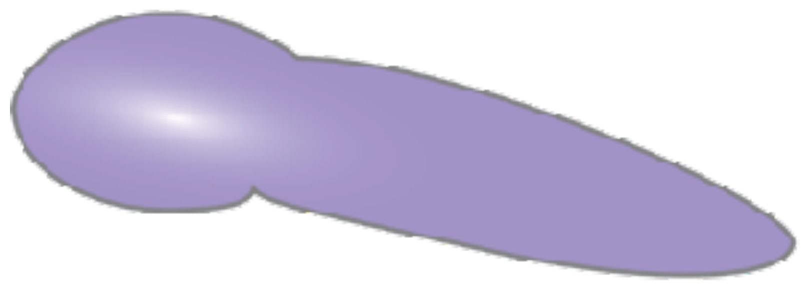
Human Neural Organoids are generated from iPSCs



Human Neural Organoids recapitulate embryonic Development

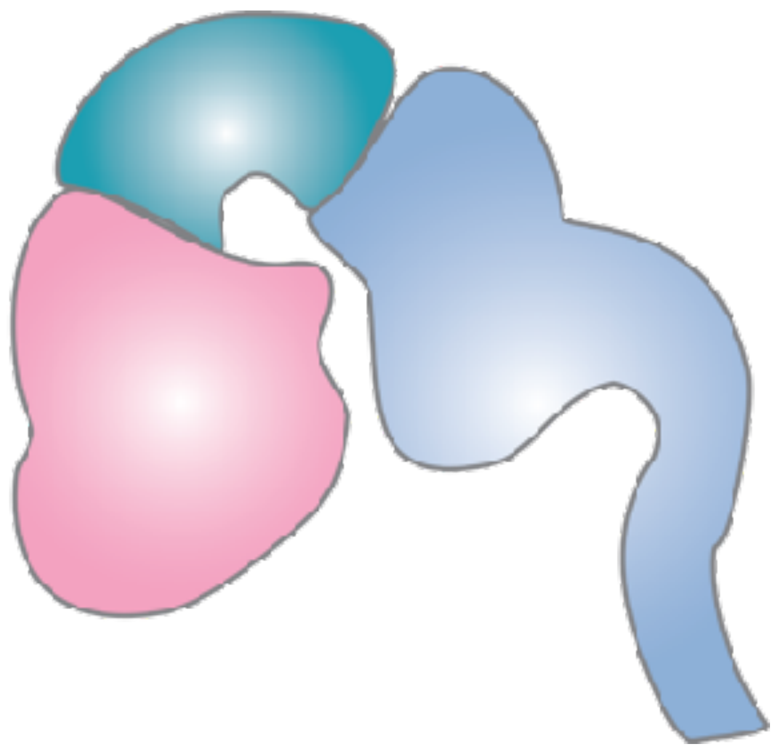
Understanding Human Brain Development

21 Days



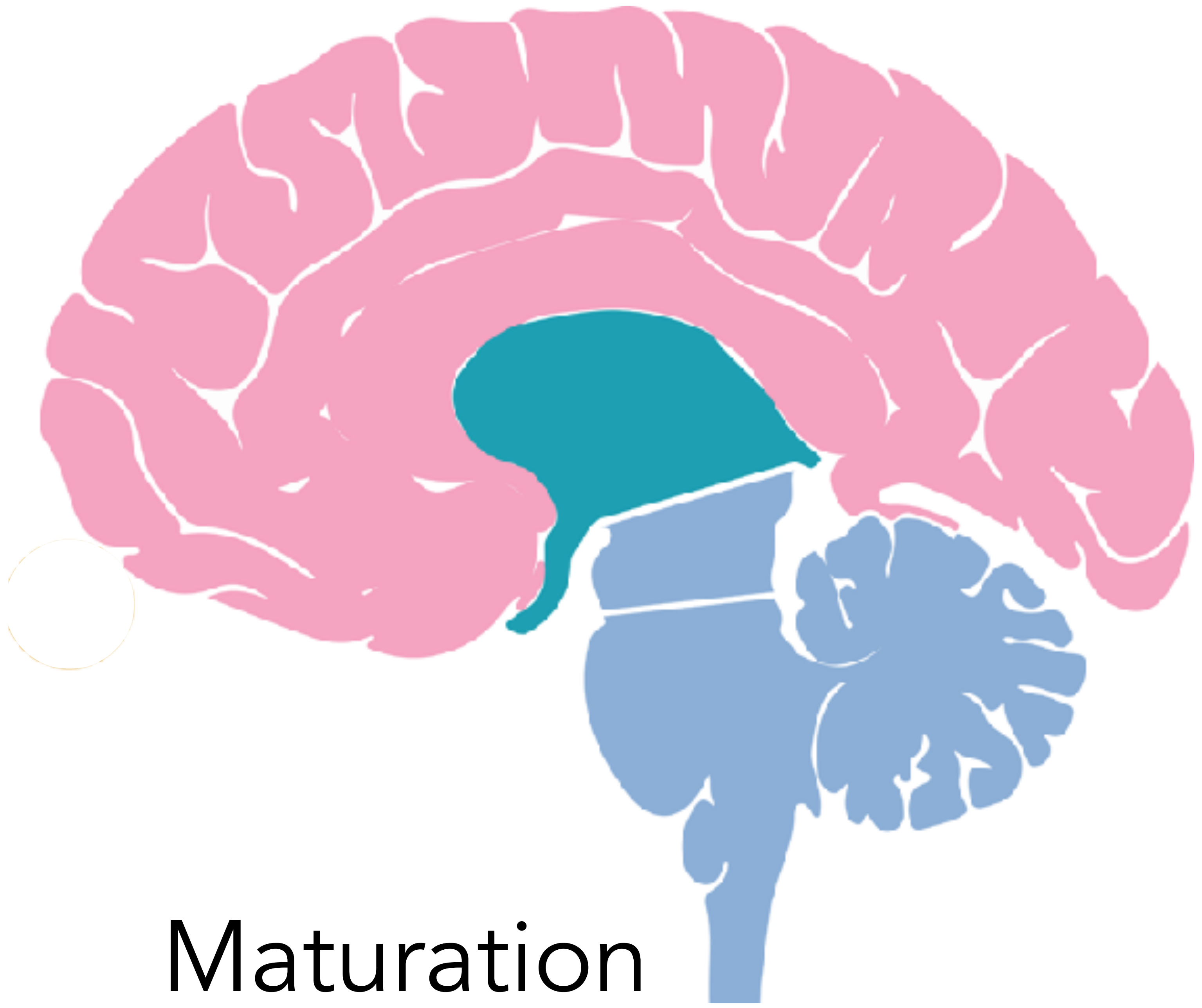
Formation of Neural Tube

35-40 Days



Regionalization

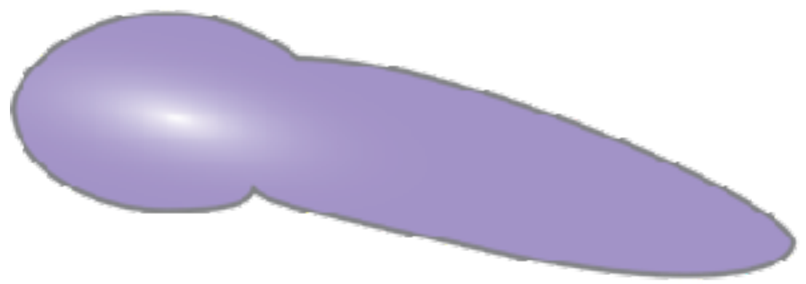
9 Months



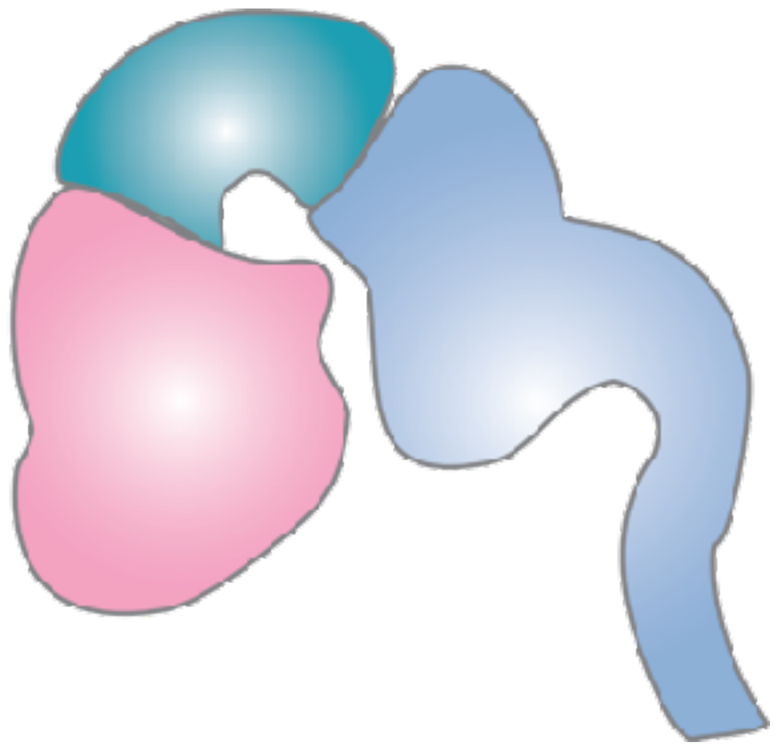
Maturation

Understanding Human Brain Development

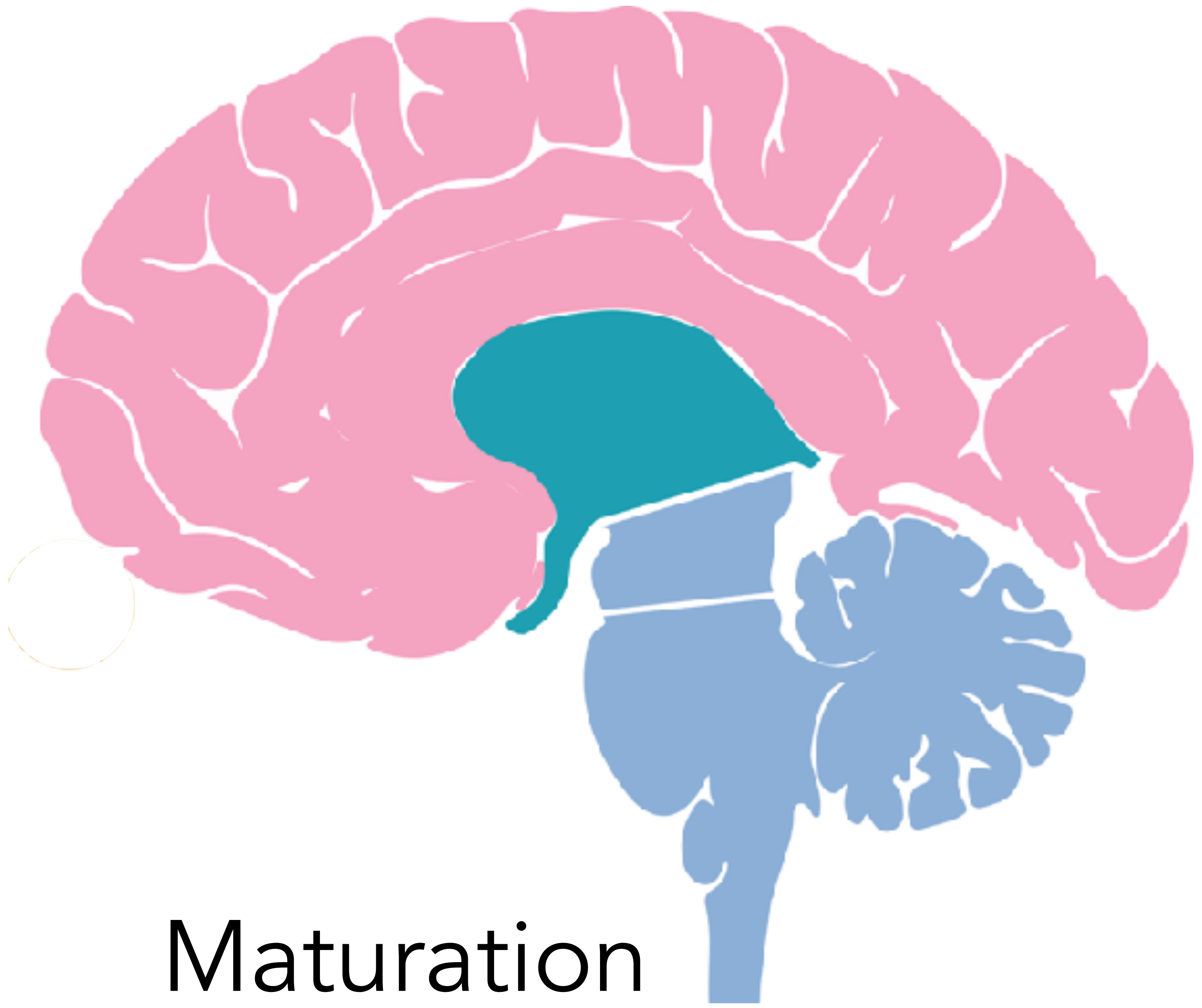
21 Days



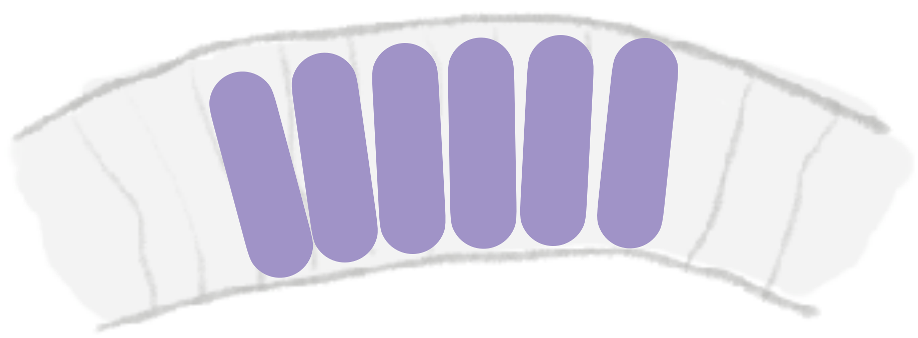
35-40 Days



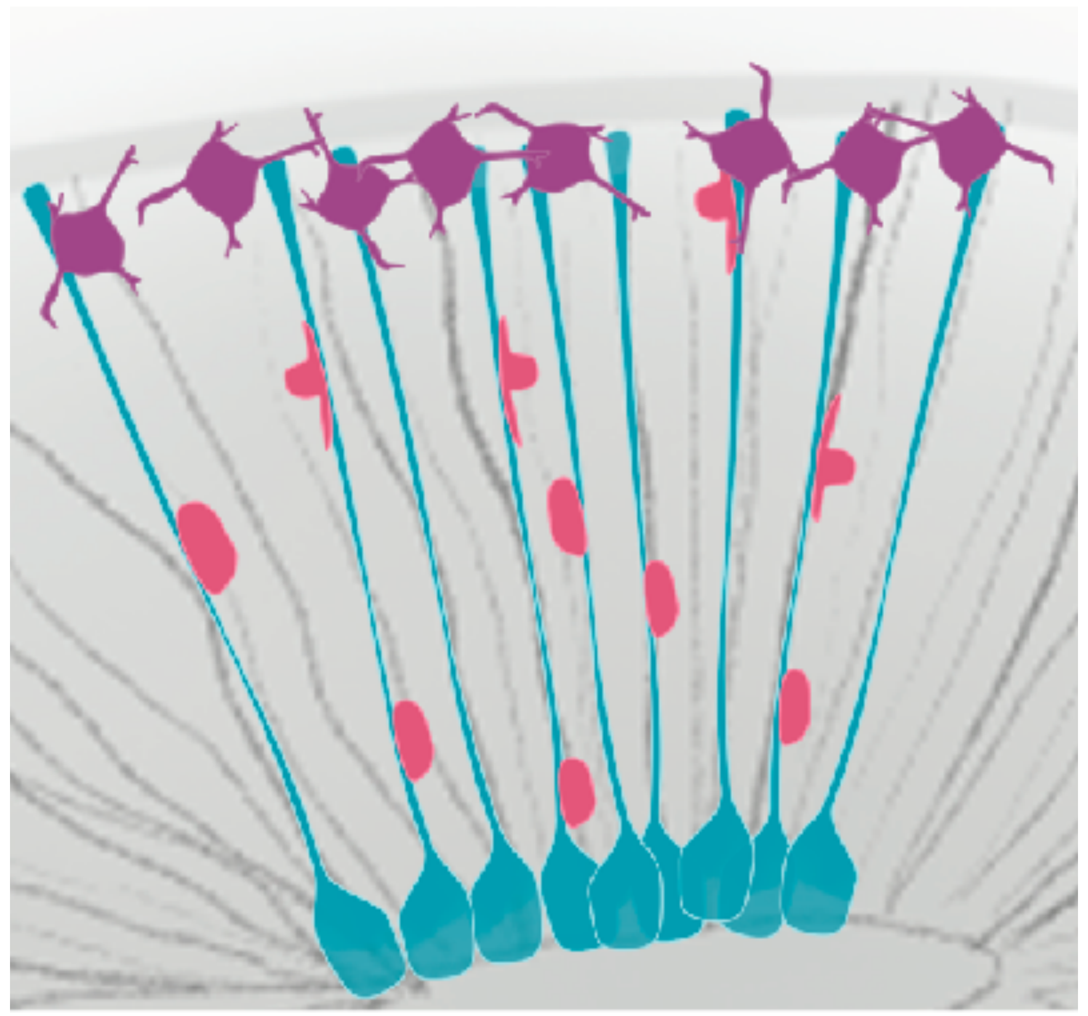
9 Months



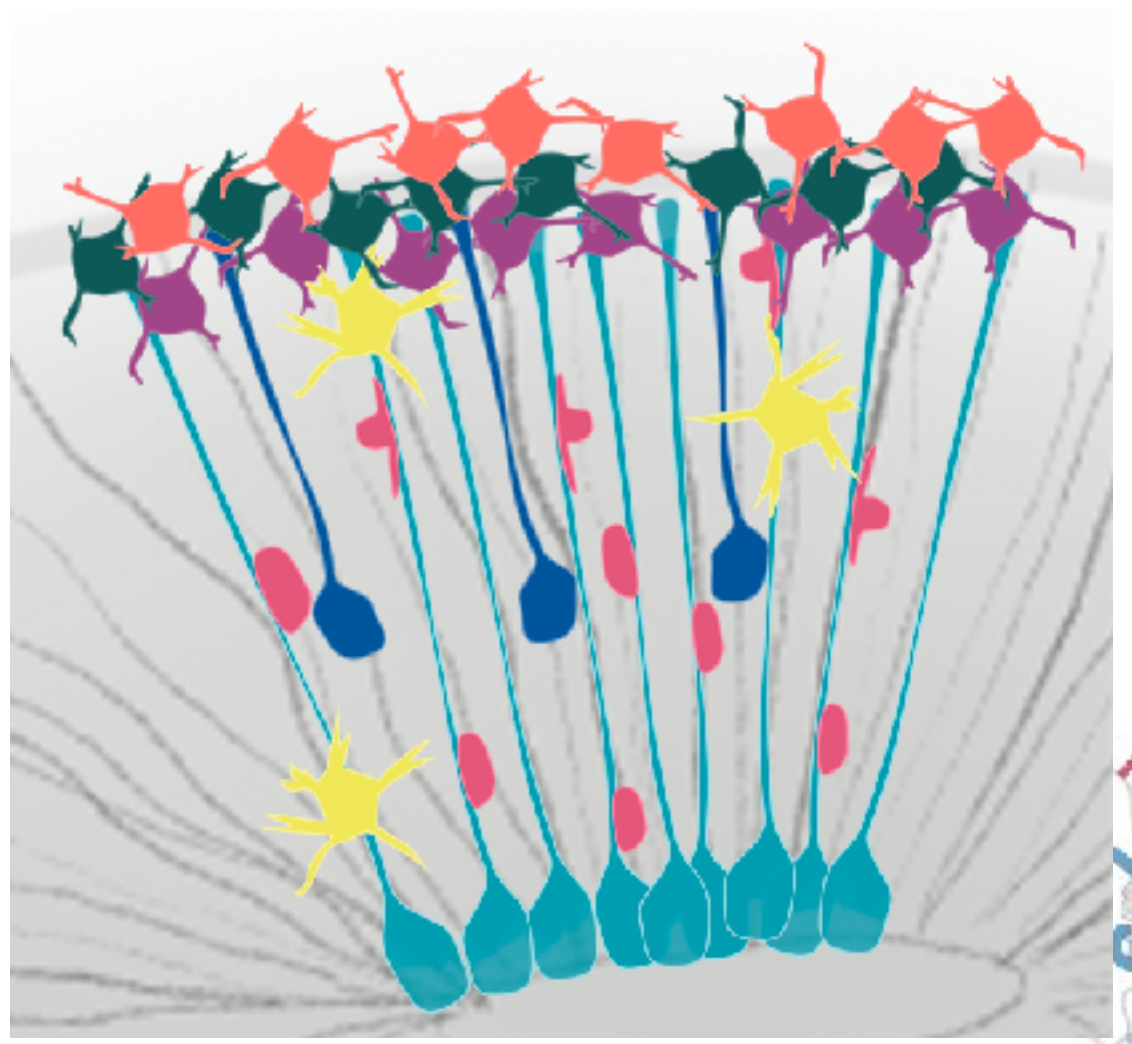
Formation of Neural Tube



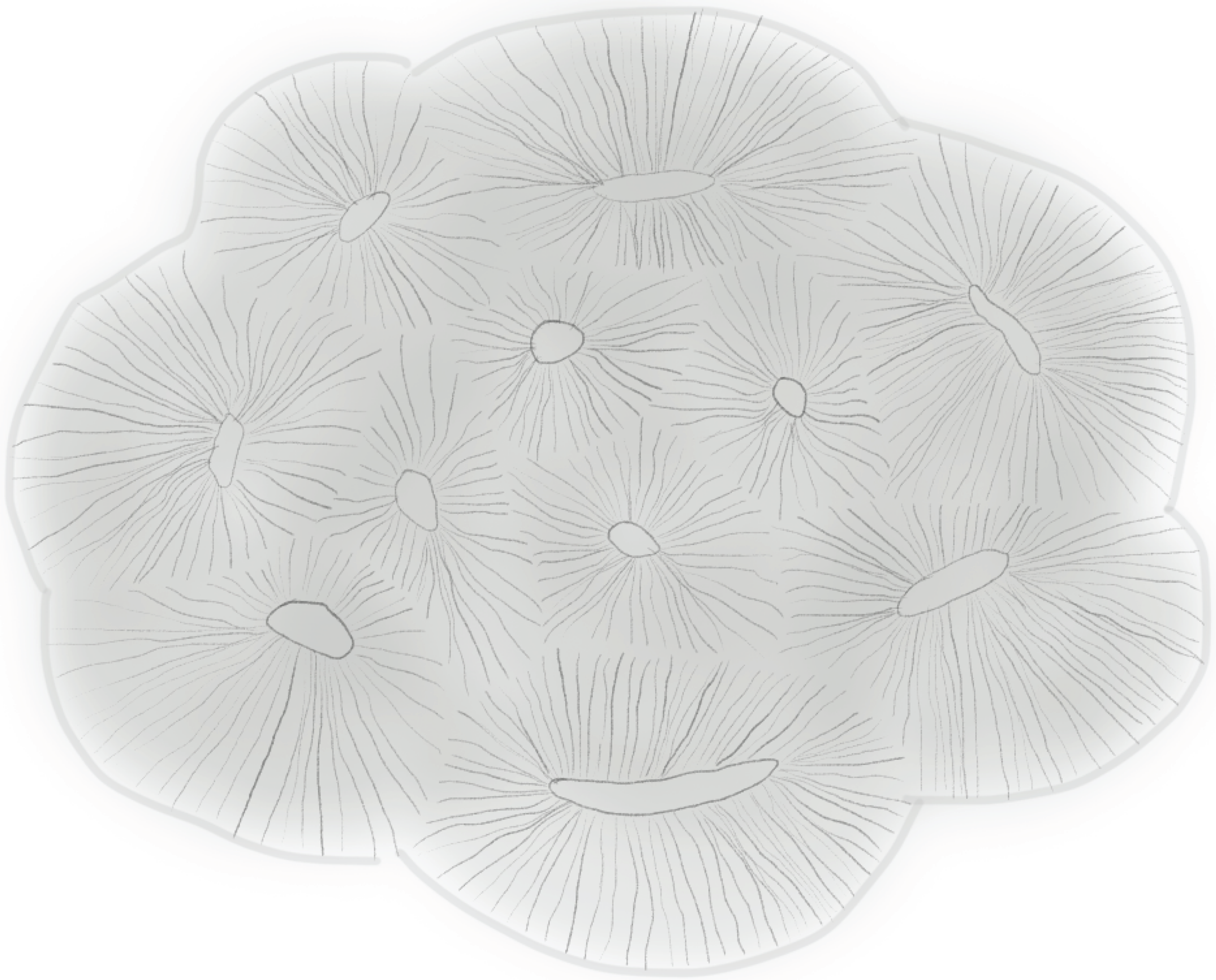
Regionalization



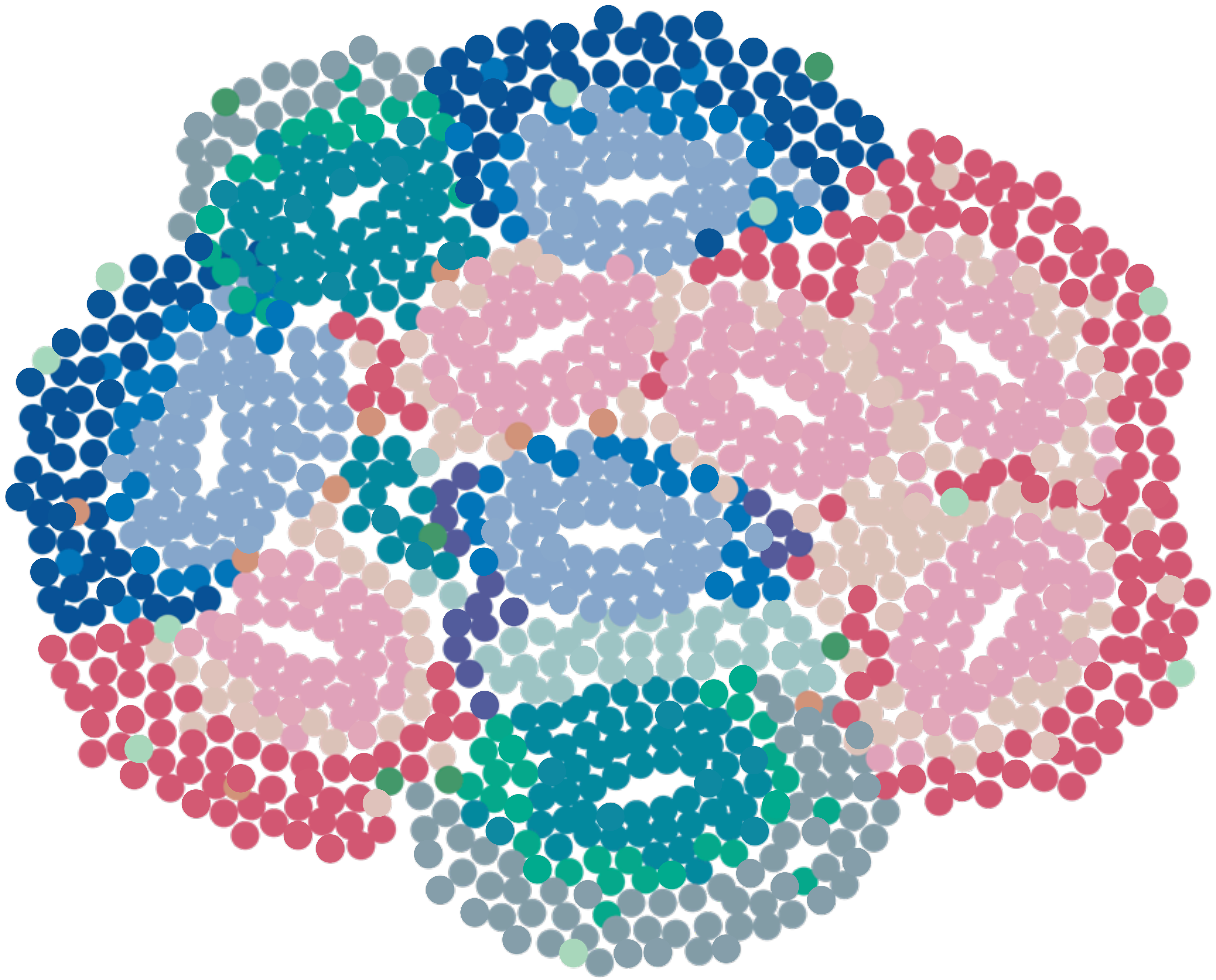
Maturation

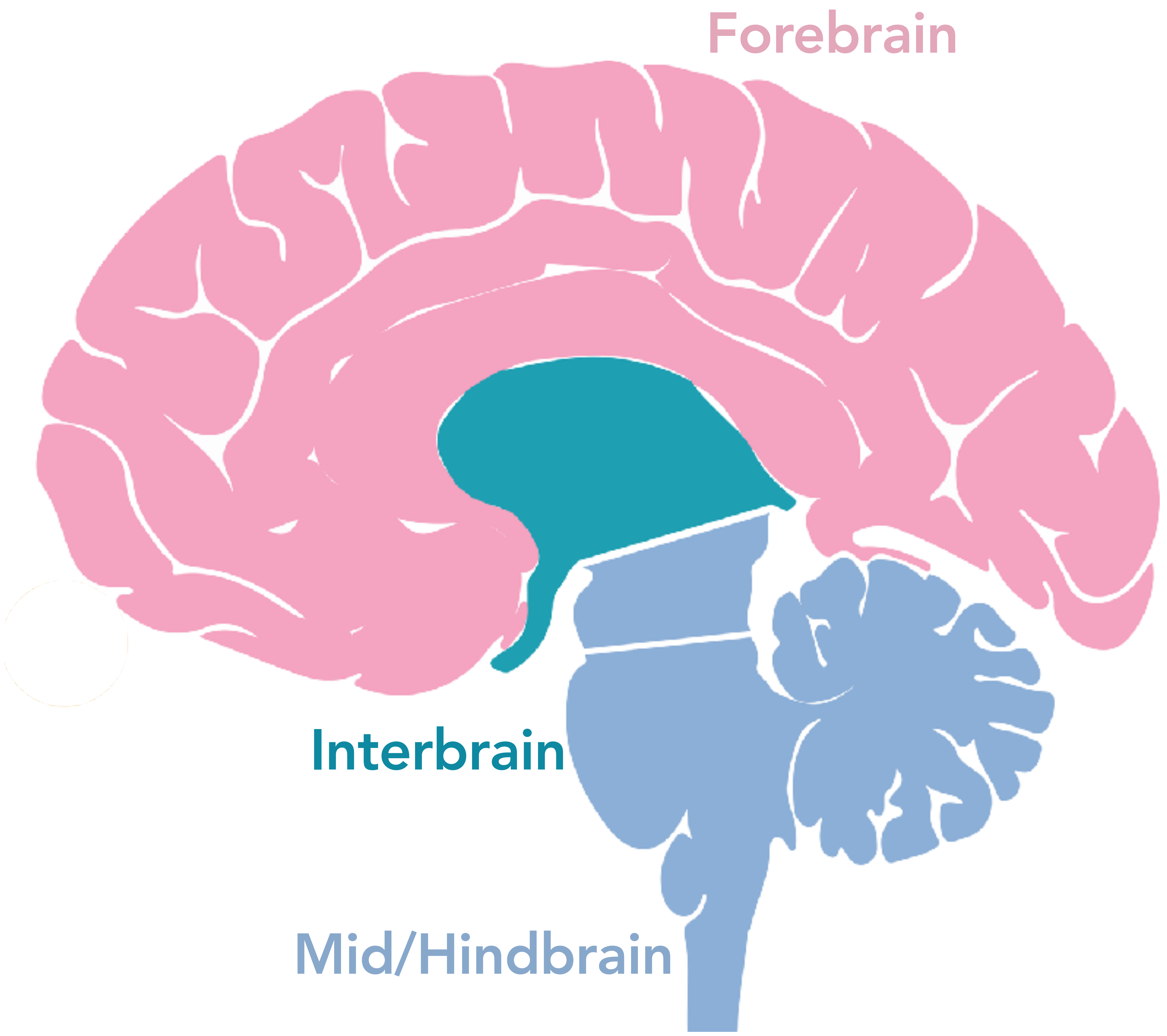


Quantifying differences in Organoid Development



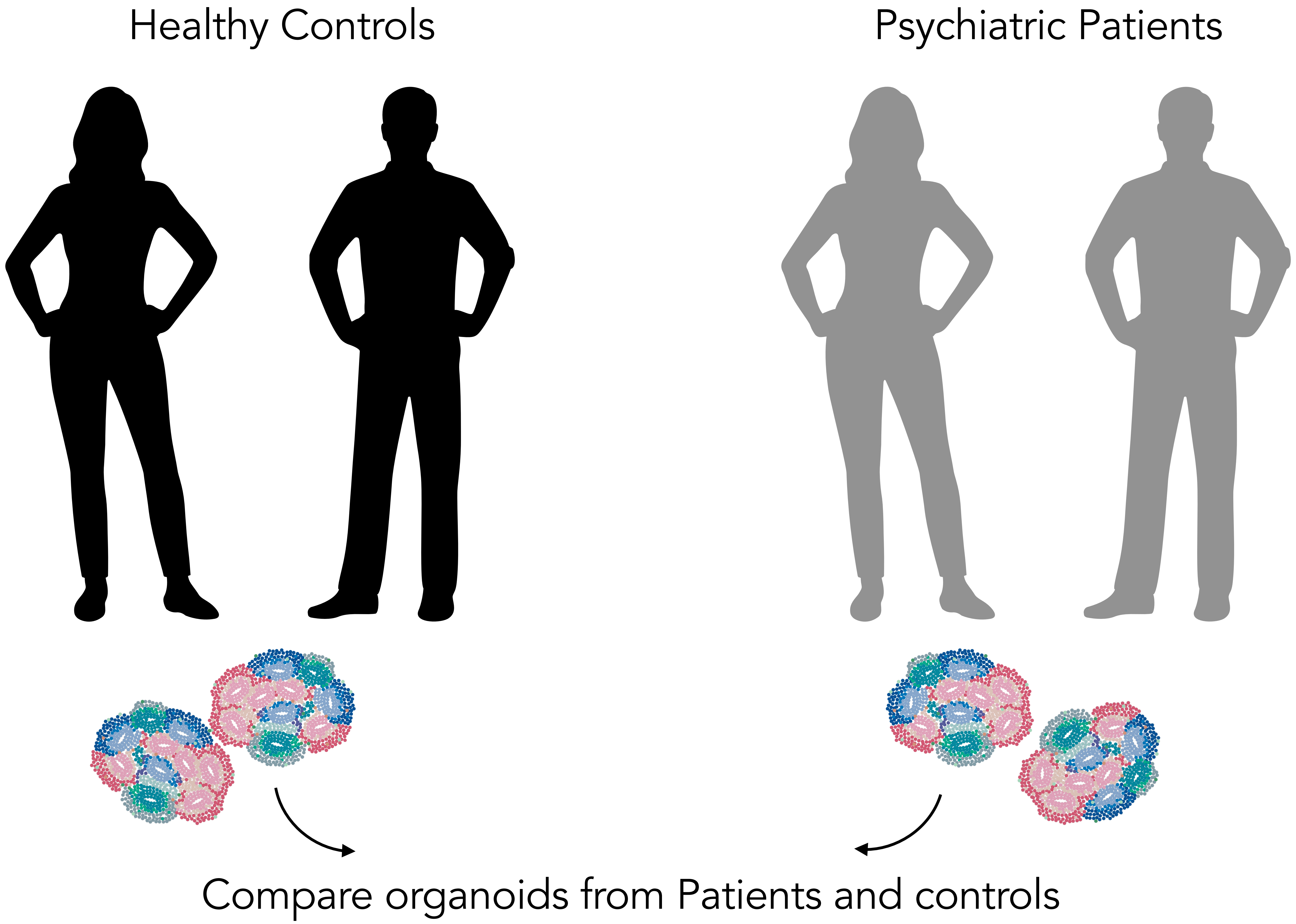
Quantifying differences in Organoid Development





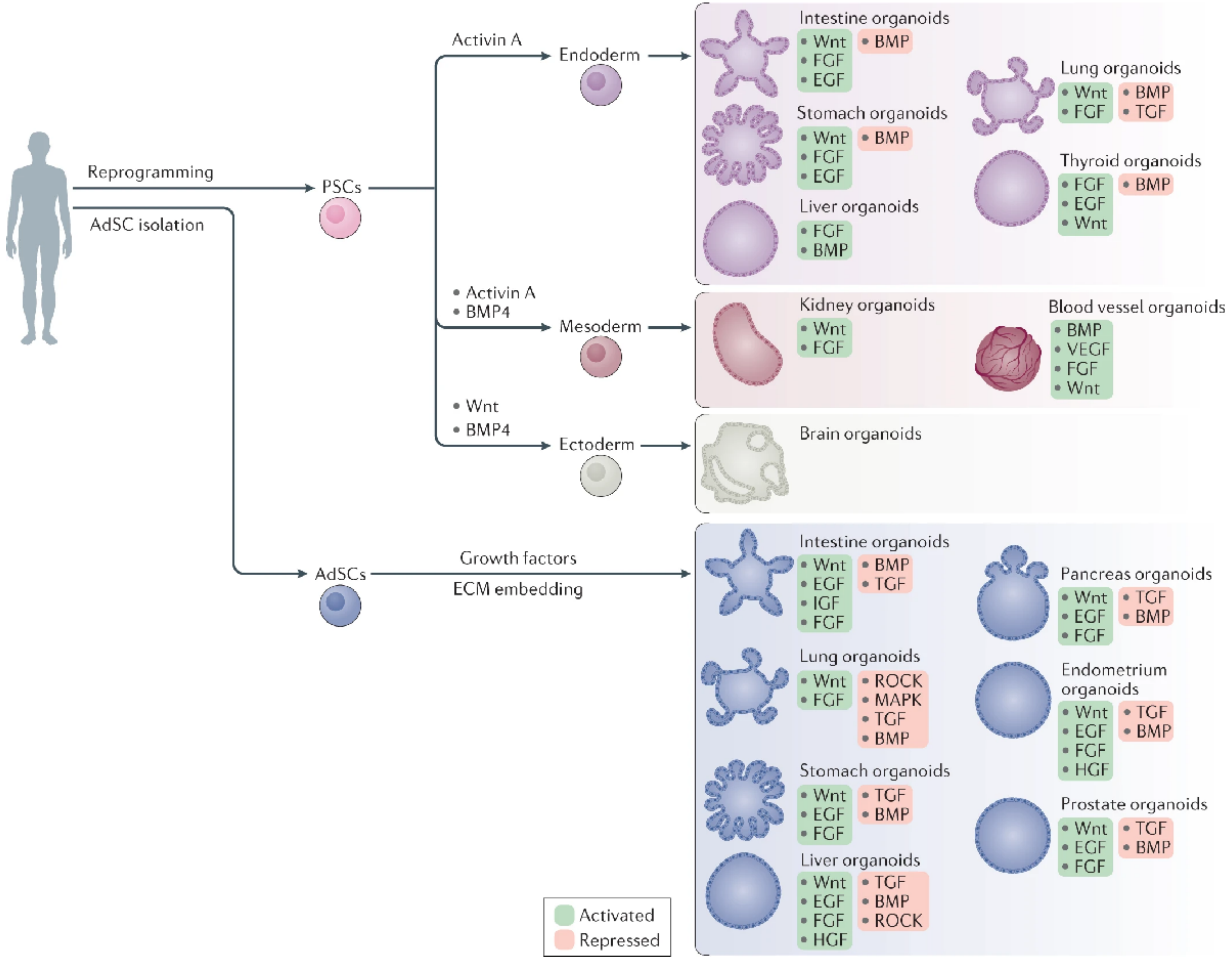
Combine brain organoids with single-cell sequencing studies to understand molecular mechanisms of diseases.

Quantifying differences in Organoid Development



Organoids can serve as patient surrogates, aiding in the development and testing of personalised medicine.

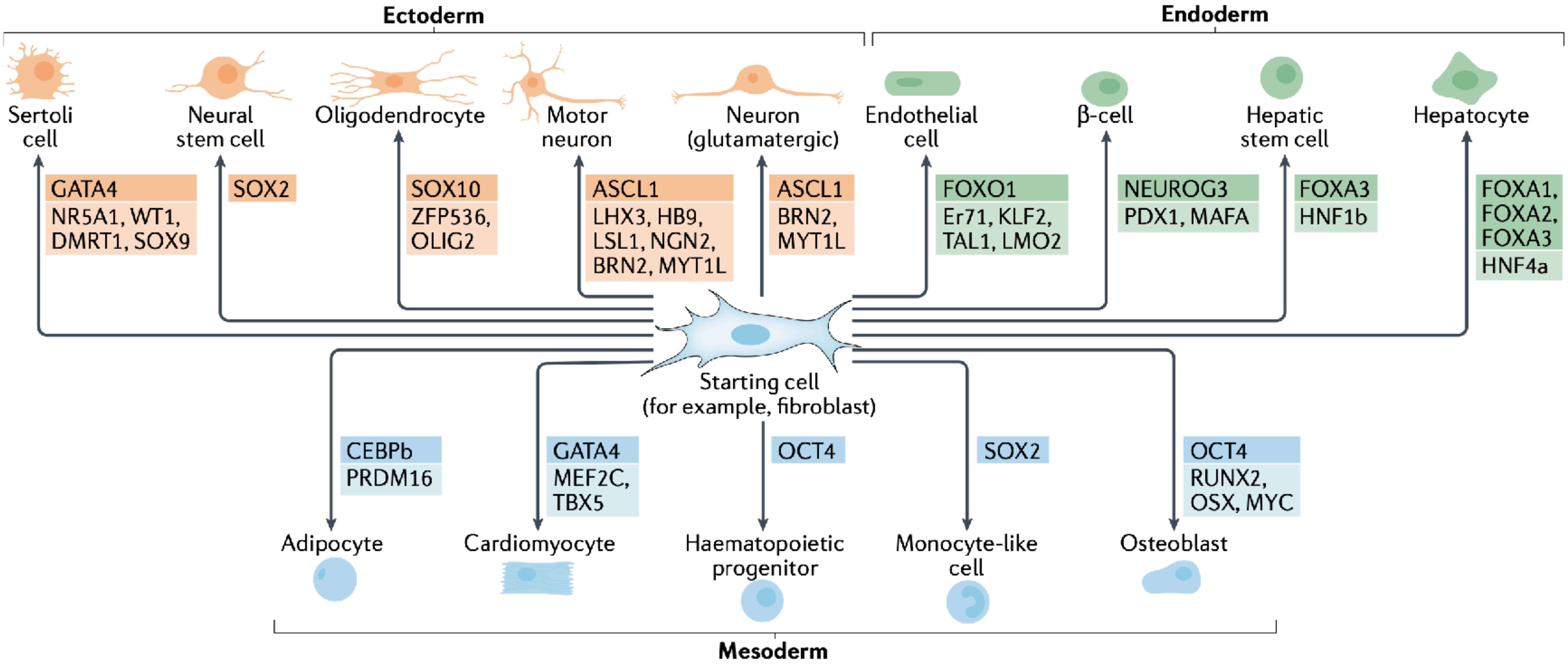
iPSCs can be used to derive organoids



Organoids are 3D aggregates of cells that recapitulate the organotypic functions and morphology

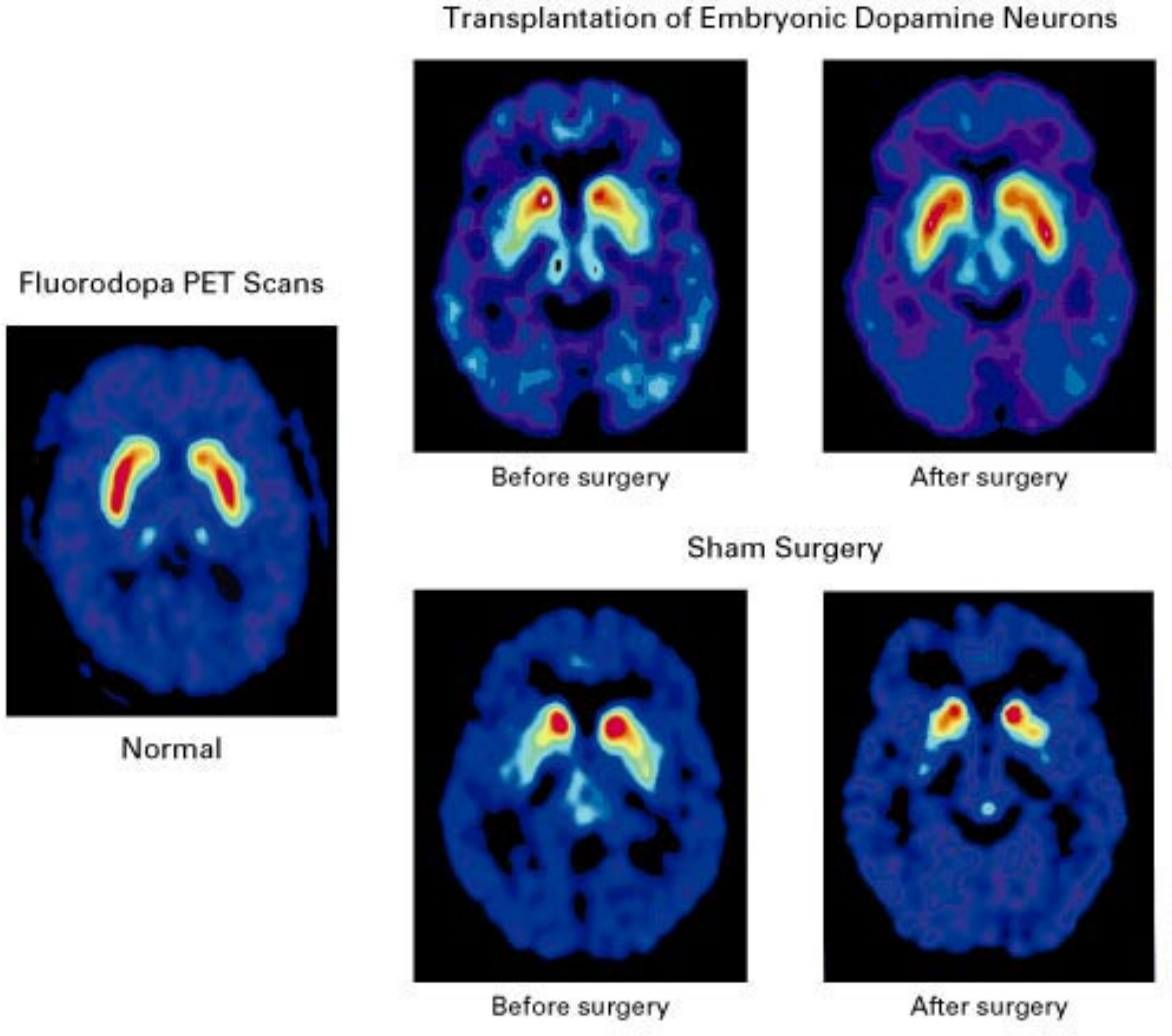
Kim,…, Knoblich (2020) Nature Reviews Molecular Cell Biology

Direct reprogramming can give rise to multiple cell types



Wang,…, Qian (2021) Nature Reviews Molecular Cell Biology

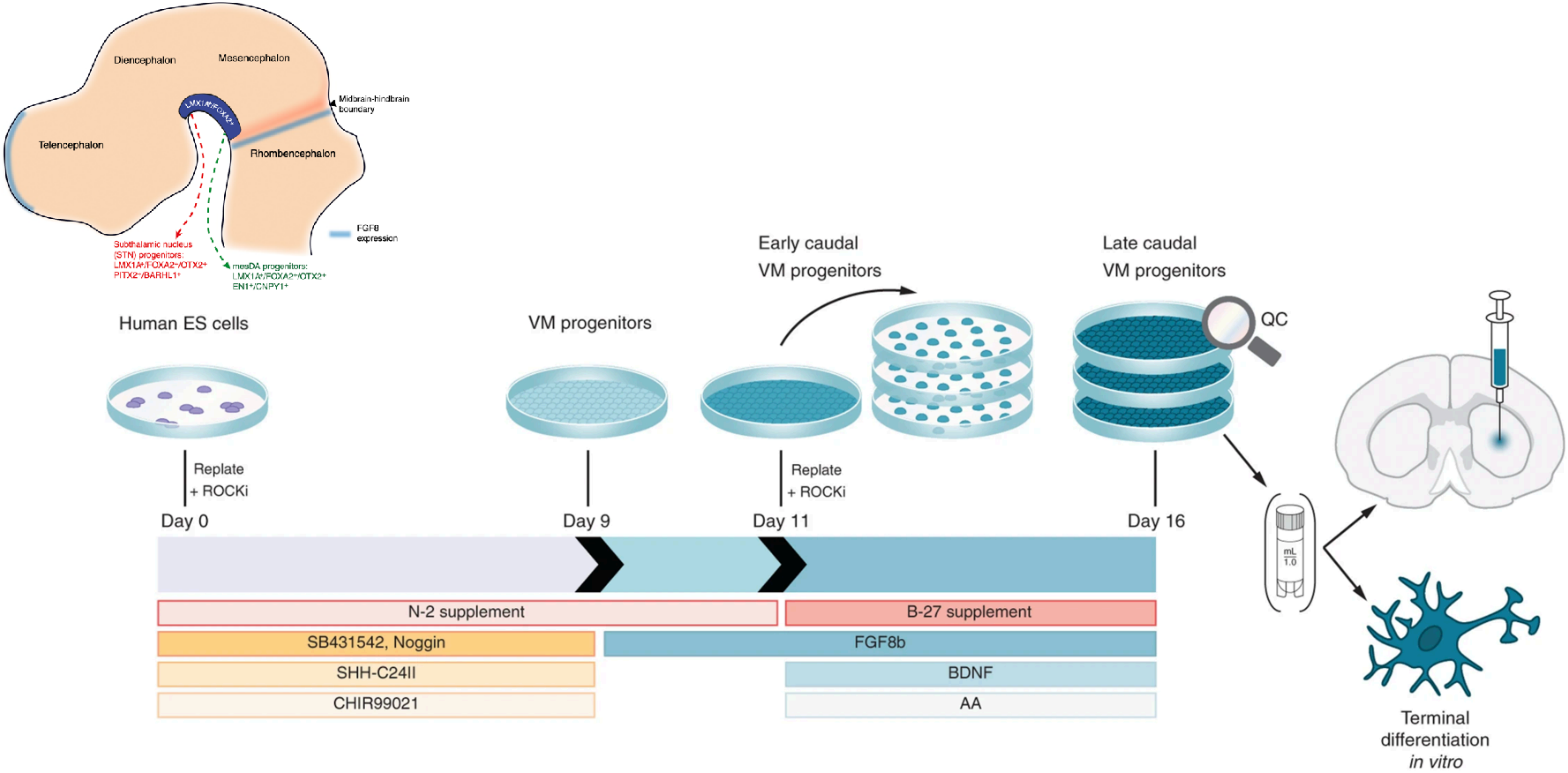
Stem Cell derived therapies



2001, first clinical trial to treat Parkinson’s disease by implanting dopaminergic neurons from abortion tissue

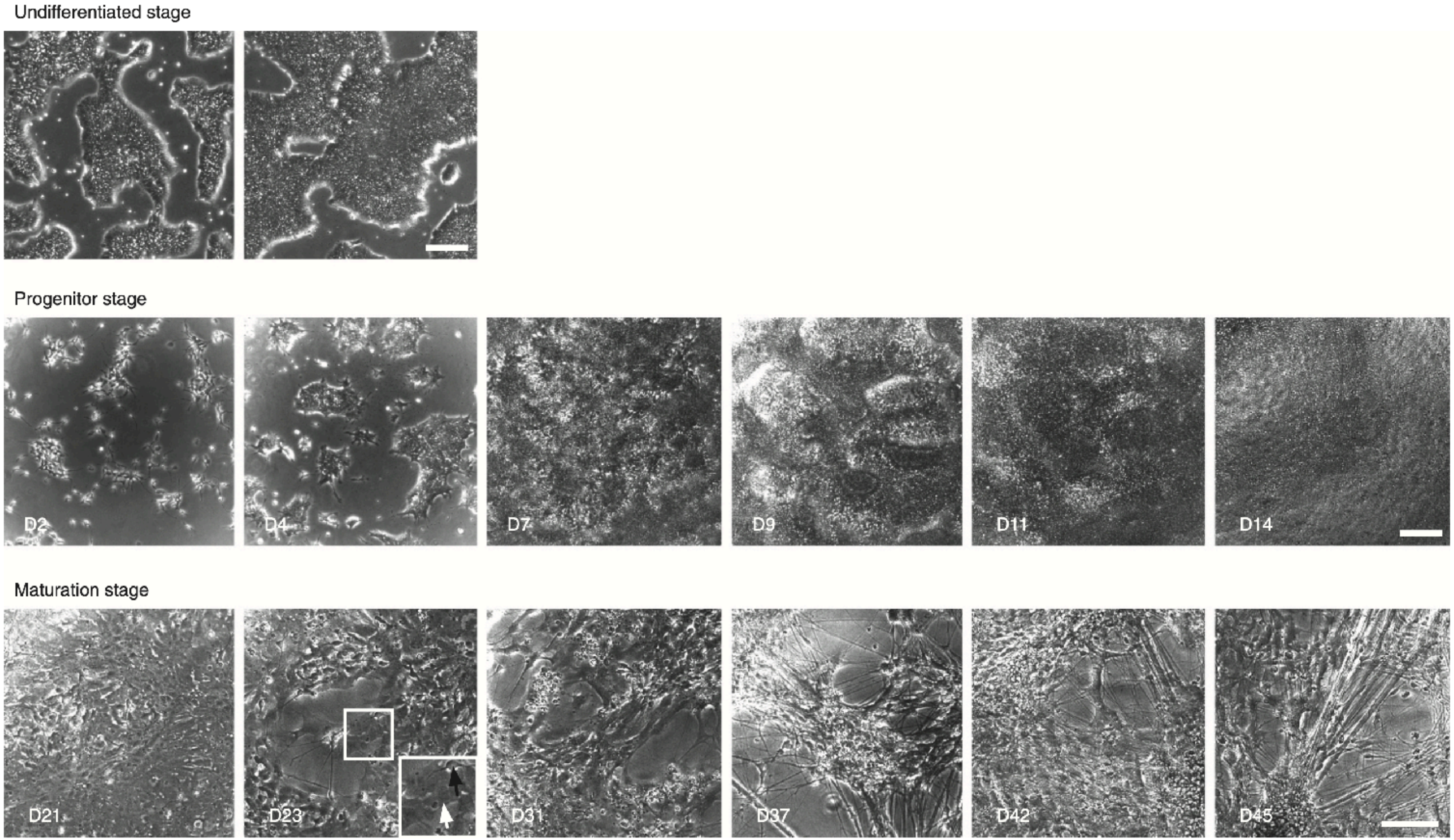
-low efficiency of the graft
-little material
-high variability
-effect too little

Generating mid-brain dopaminergic neurons in vitro



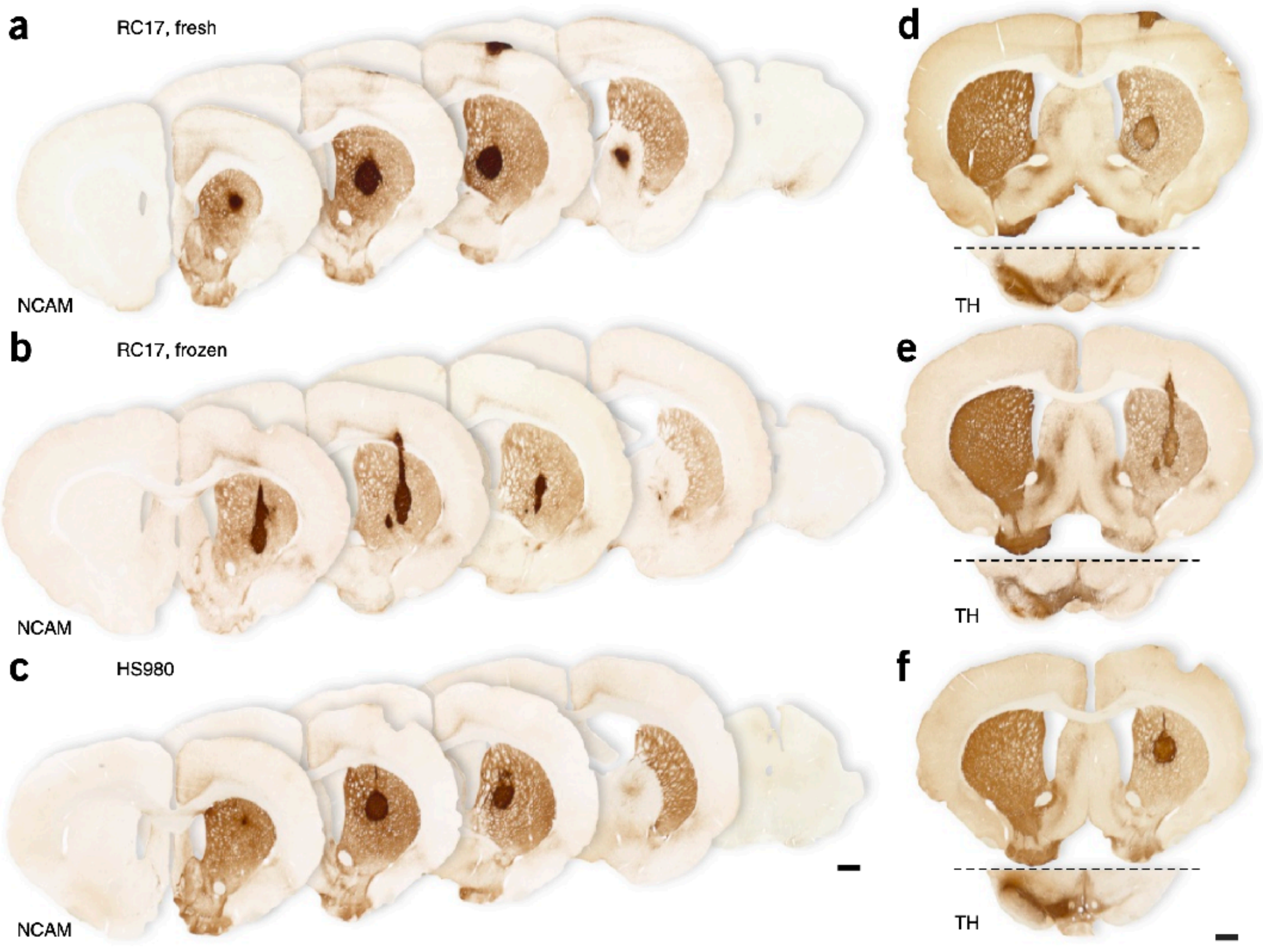
Nolbrant, …,Kirkeby (2017) Nature Protocols

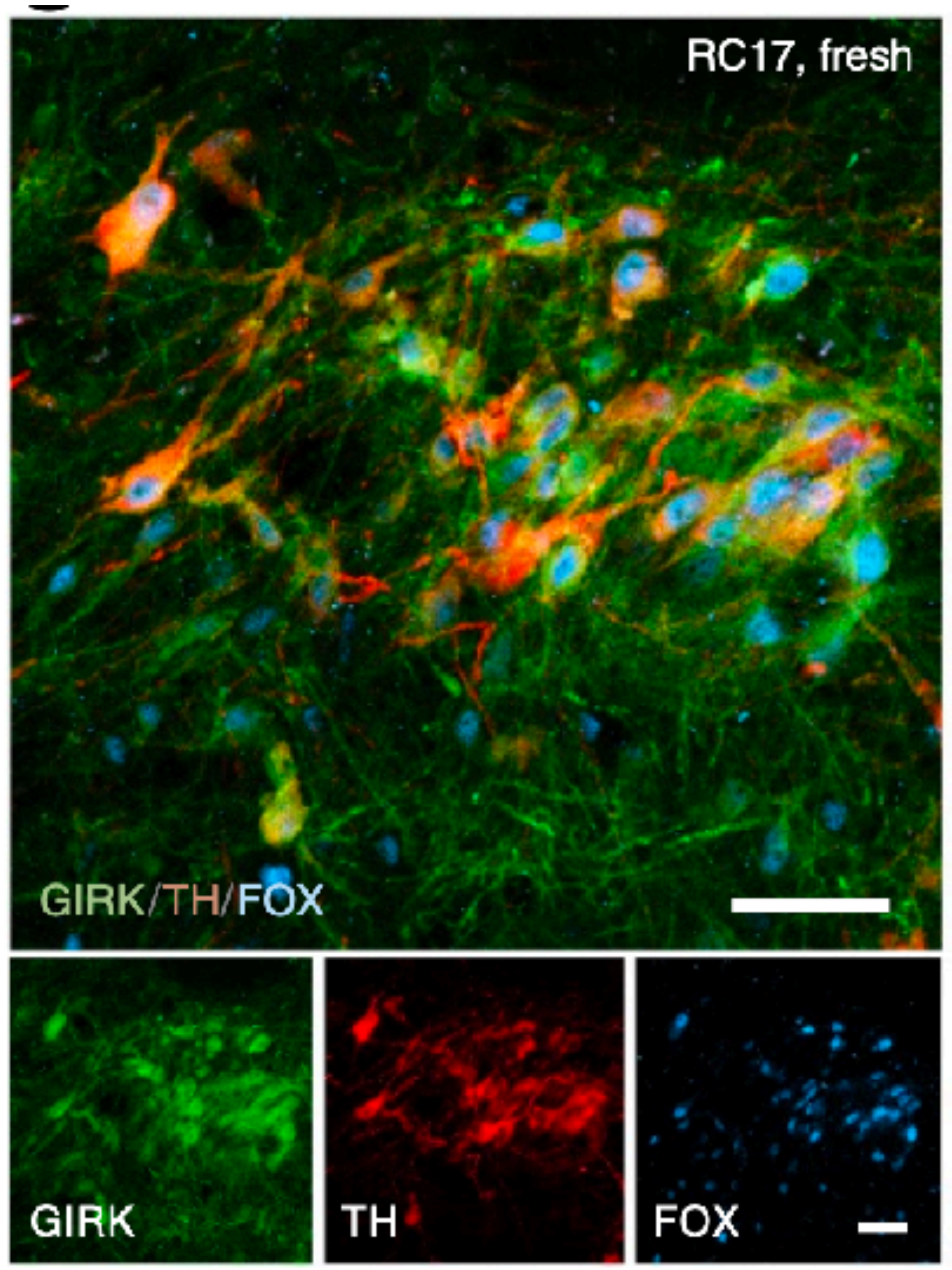
Generating mid-brain dopaminergic neurons in vitro

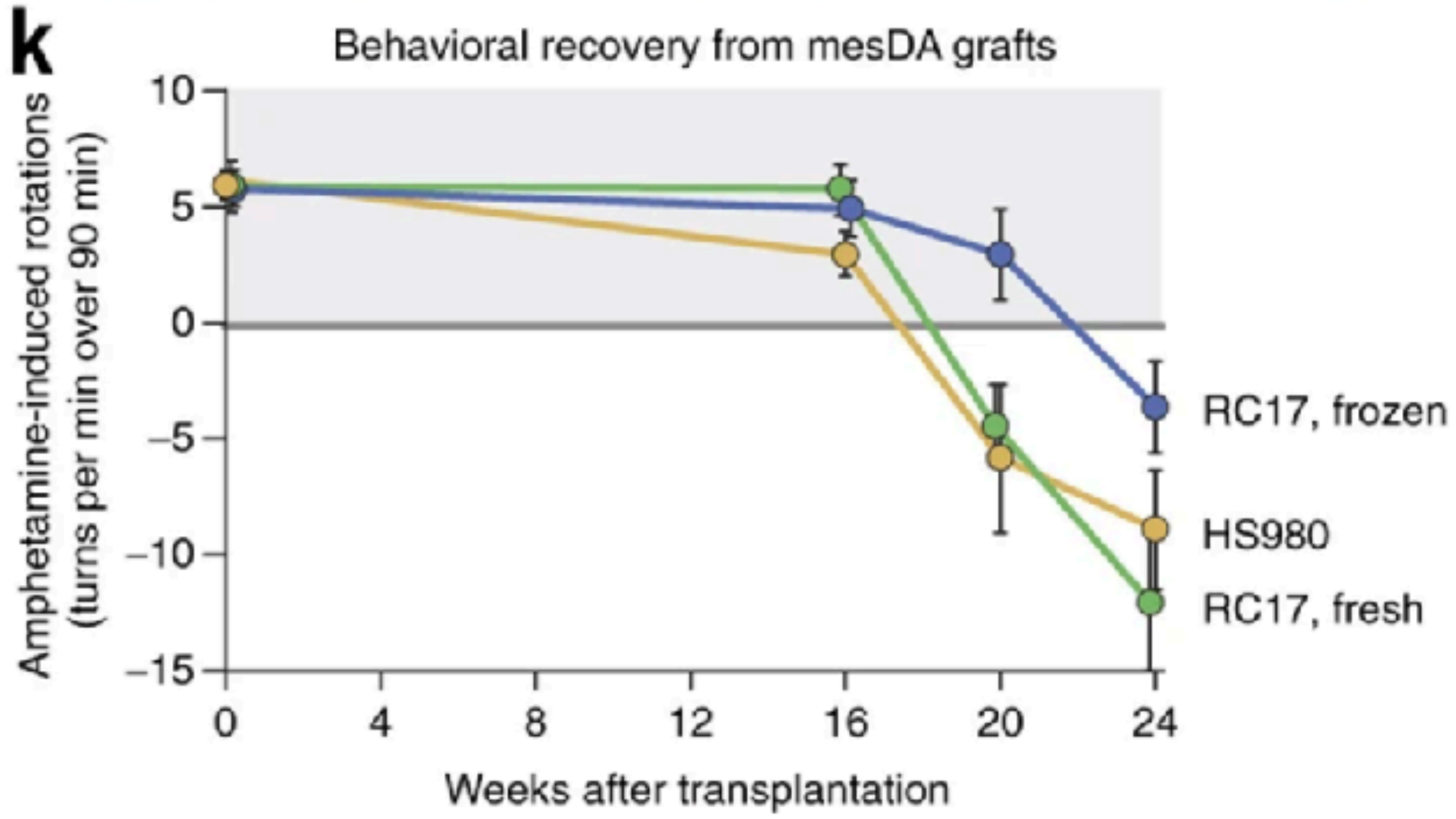


Nolbrant, …,Kirkeby (2017) Nature Protocols

Generating mid-brain dopaminergic neurons in vitro







Nolbrant, …,Kirkeby (2017) Nature Protocols

Stem Cell derived therapies

BlueRock THERAPEUTICS

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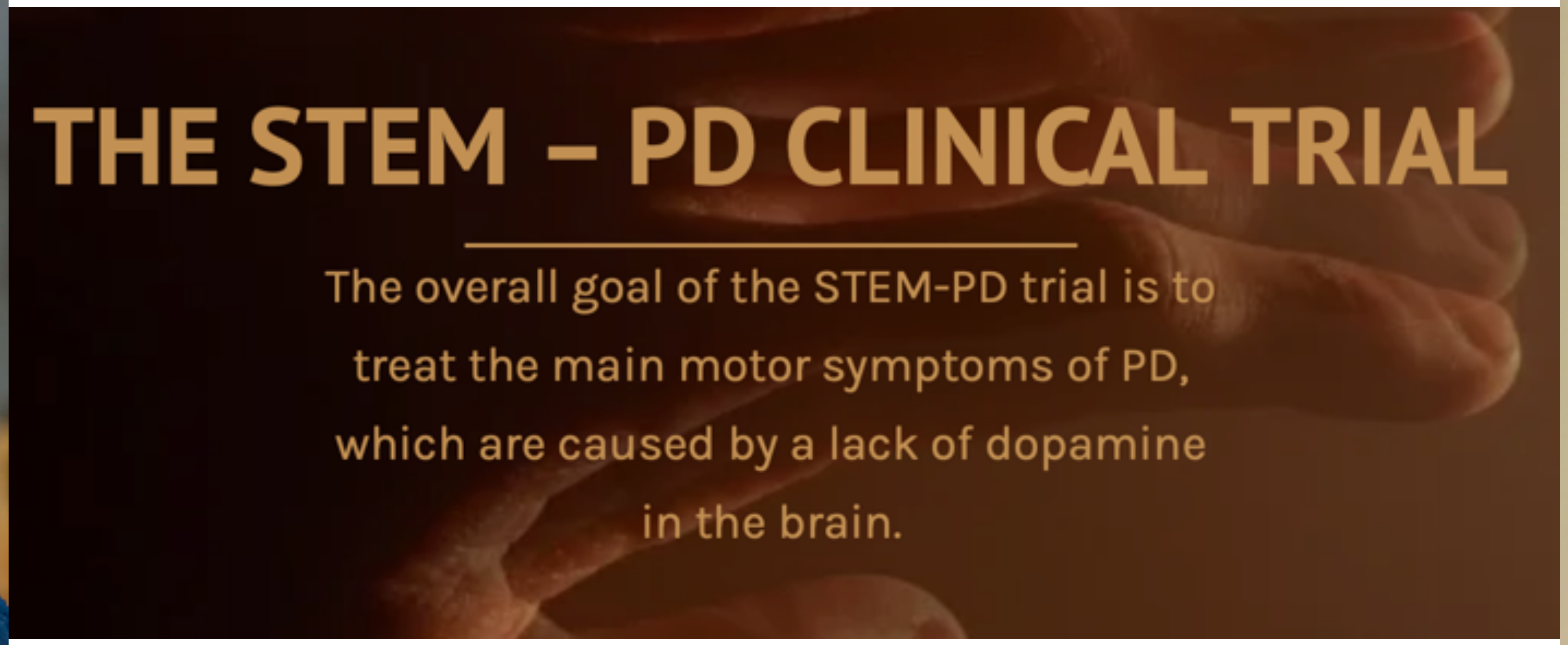
Pharmaceuticals

BlueRock Therapeutics' investigational cell therapy bemdaneprocel for Parkinson's disease shows positive data at 24-months

Viviane Tabar & Laurenz Studer

Agnete Kirkeby



Kirkeby, …,Parmar (2023) Cell Stem Cell

Malin Parmar

Exercise questions

How can you identify a drug target?

Name two different molecular examples of how to target pain sensation.

Explain broadly how single-cell methods work and how they can help to identify drug targets.

Why is it so difficult to target drugs to the brain?

What are the constituents of the BBB?

What determines if a molecule can cross the BBB?

What are iPSCs, and how are they generated?

Why are iPSCs useful in research and medicine (therapeutics and drug discovery)?

What are the limitations of iPSC-derived 3D systems?