Therapeutic potential of neurotrophic factors on cellular and molecular alterations induced by Apnea of Prematurity in the murine cerebellum.

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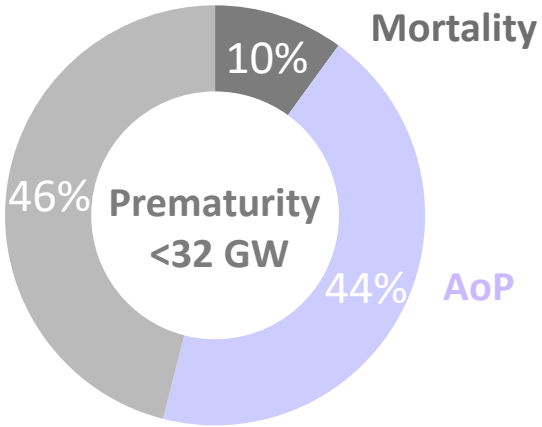
Thesis Advisor: Dr Delphine Burel

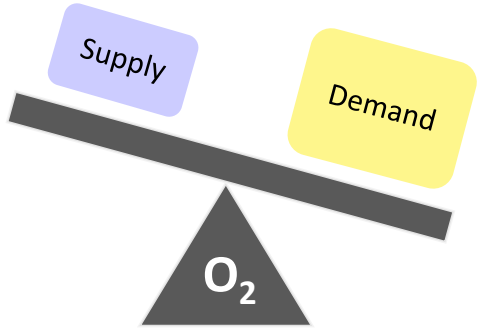
JED
May
2021

Apnea of Prematurity (AoP)

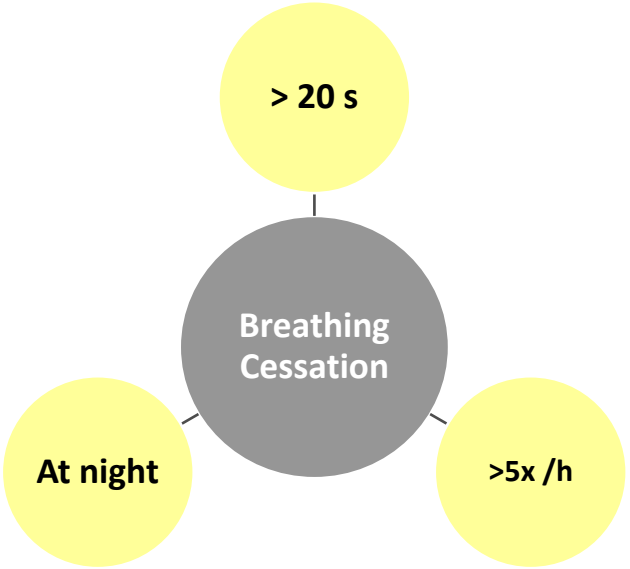
Epidemiology



(Zhao *et al.*, 2011)



Definition

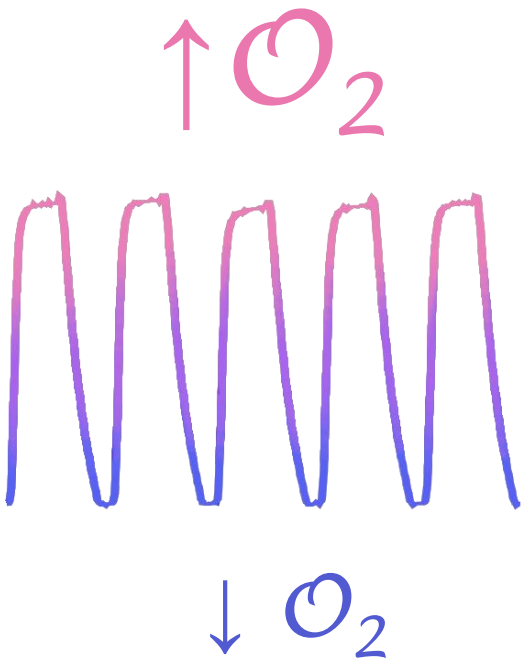


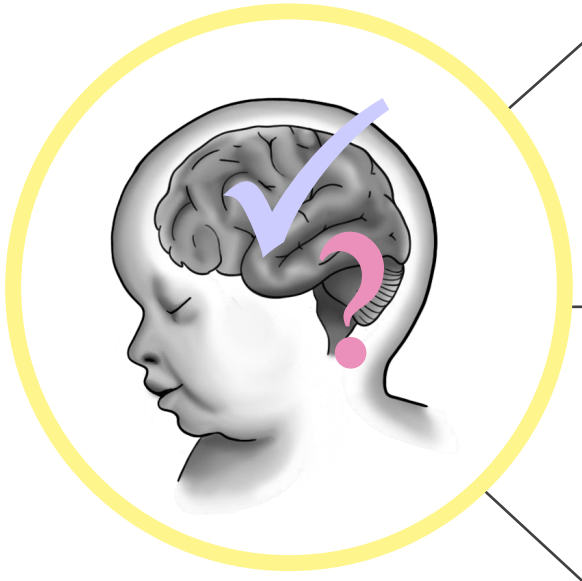
Consequences

Intermittent Hypoxia → Developmental Alterations → Neurological Deficits

(Janvier *et al.*, 2004 ; Pillekamp *et al.*, 2007)

Intermittent Hypoxia and the Brain





Cellular

- ↓synaptic plasticity
- Mouse

(Goussakov *et al.*, 2019)

Histological

- Hypomyelination
- Mouse

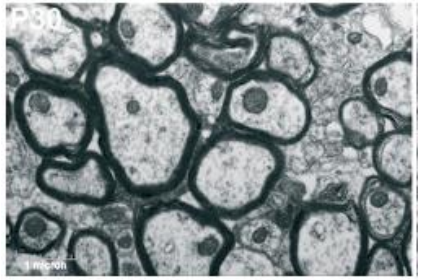
(Cai *et al.*, 2012)

Anatomical

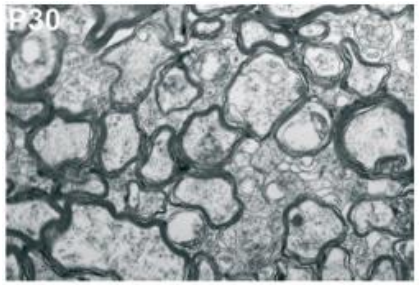
- Periventricular WM lesions
- Premature newborns

(Van Bel *et al.*, 2019)

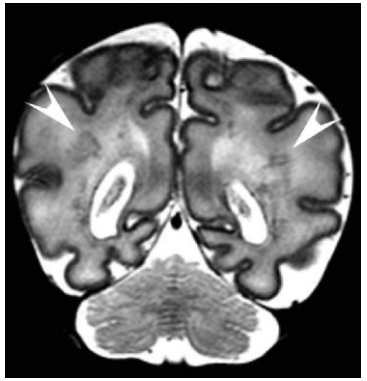
Control



Intermittent Hypoxia



(Striatum - Cai *et al.*, 2012)

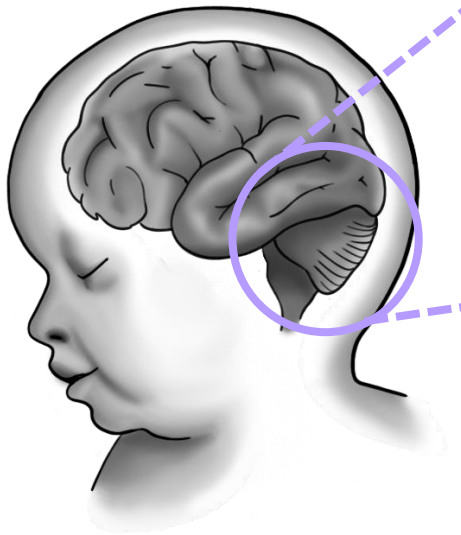


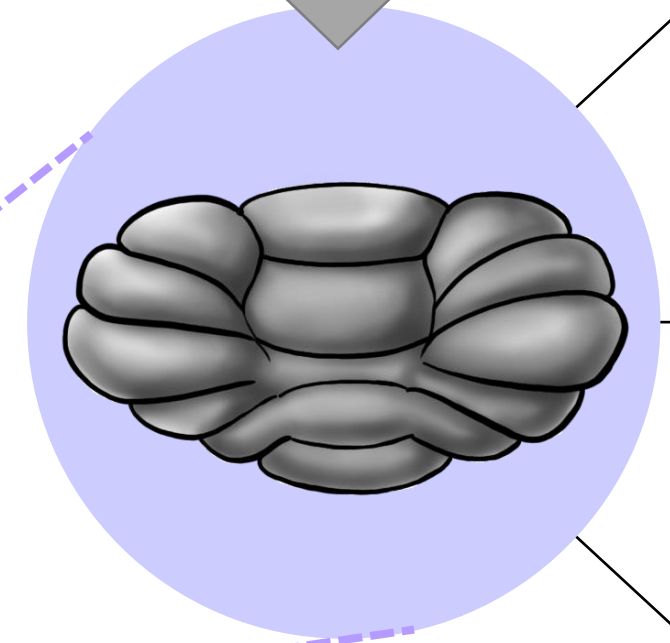
(Van Bel *et al.*, 2019)

Importance of the Cerebellum

Immaturity at birth

AoP





Motor Skills

- Balance
- Coordination

Cognition

- Attention
- Learning

Behavior

- Affect
- Conduct

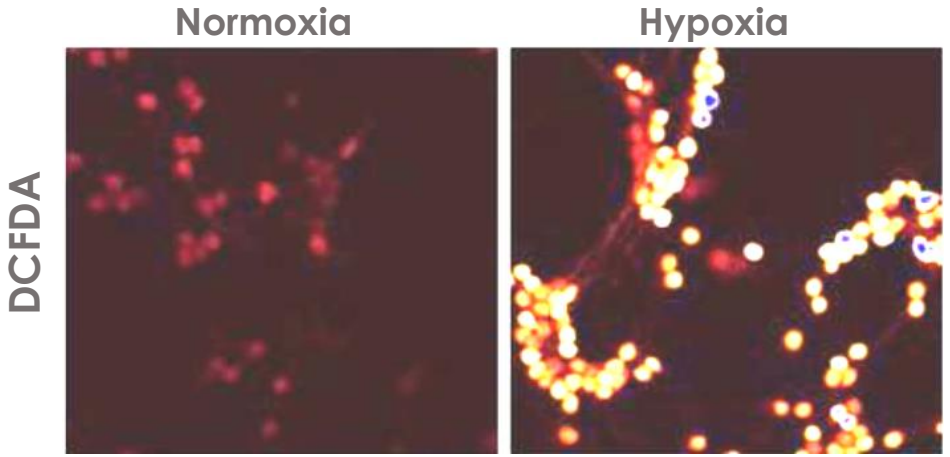
Intermittent Hypoxia and the Cerebellum

↑ROS

In vitro

- Granule cell culture
- Rat P7

(Chiu *et al*., 2012)



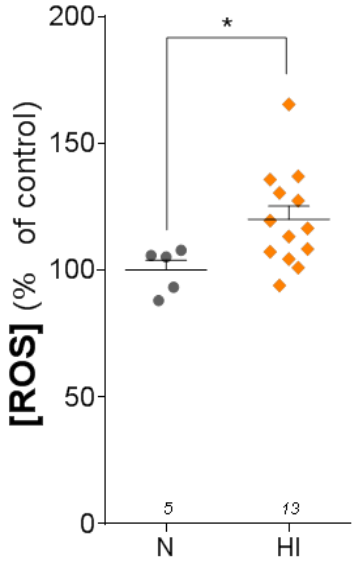
(Chiu *et al*., 2012)

↑ROS

In vivo

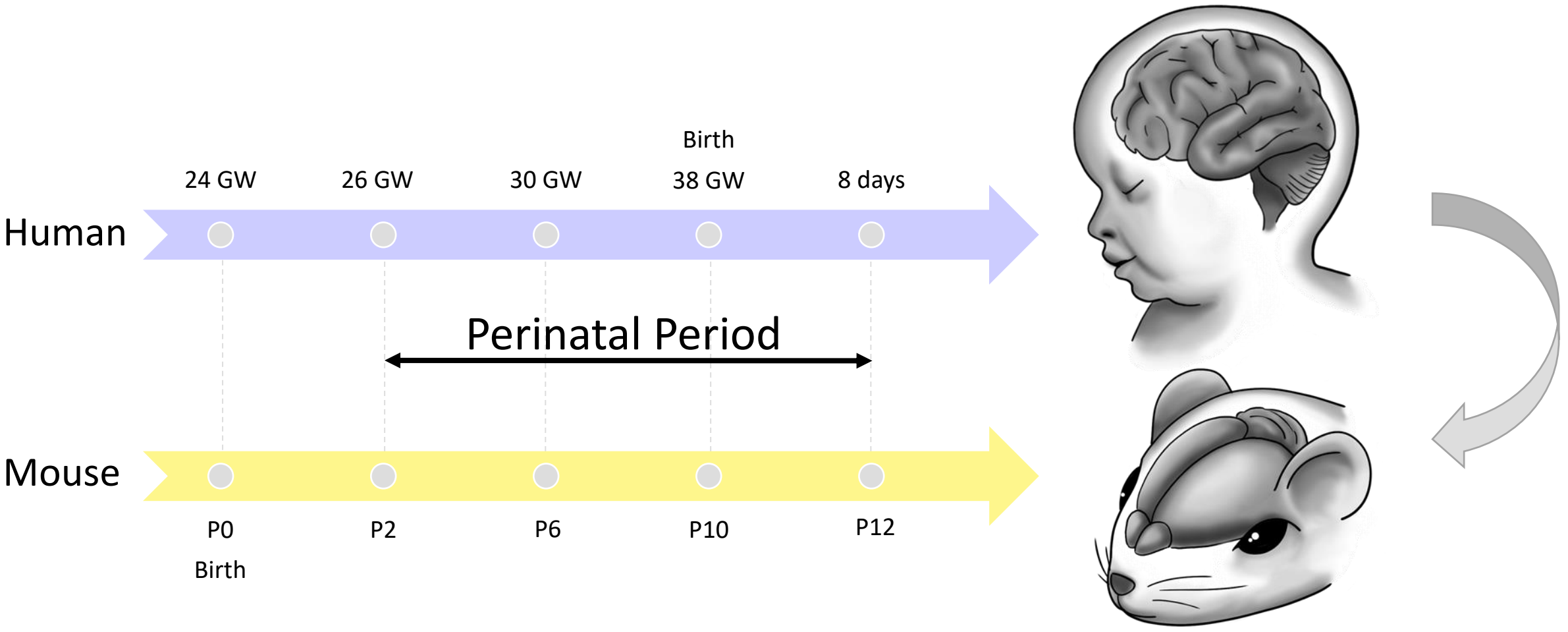
- Whole cerebellum
- Mouse P12

(Leroux *et al*., in preparation)

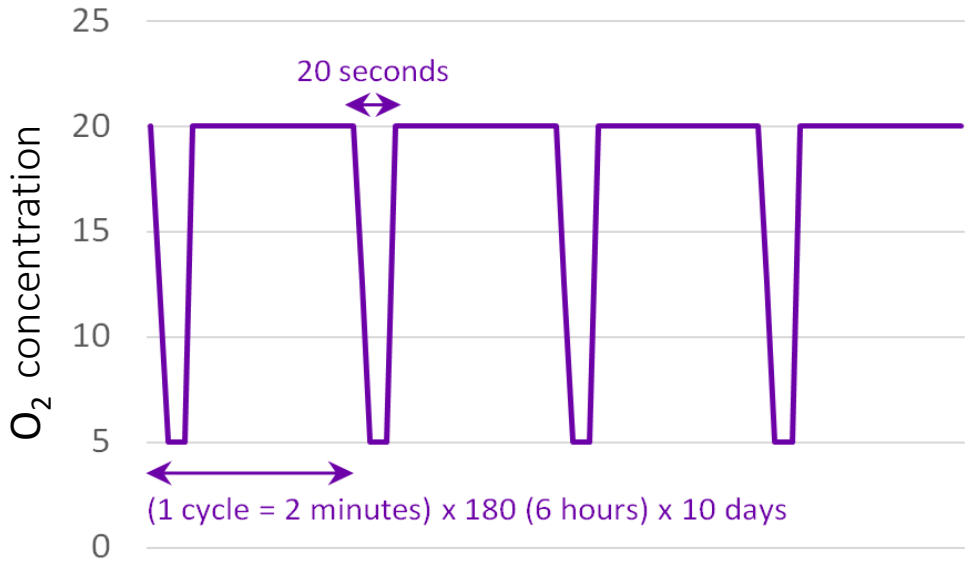


(Leroux *et al*., in preparation)

Model


Birth
24 GW
26 GW
30 GW
38 GW
8 days
Human
Perinatal Period
Mouse
P0
Birth
P2
P6
P10
P12

Intermittent Hypoxia



Model of Apnea of Prematurity

Hypoxia/reoxygenation

- 6 h/day, P2 → P12

1 cycle

- 2 min with 20 seconds at 5% O_2

Environment

- Same for controls

Immunohistochemistry

Immunohistochemical markers:

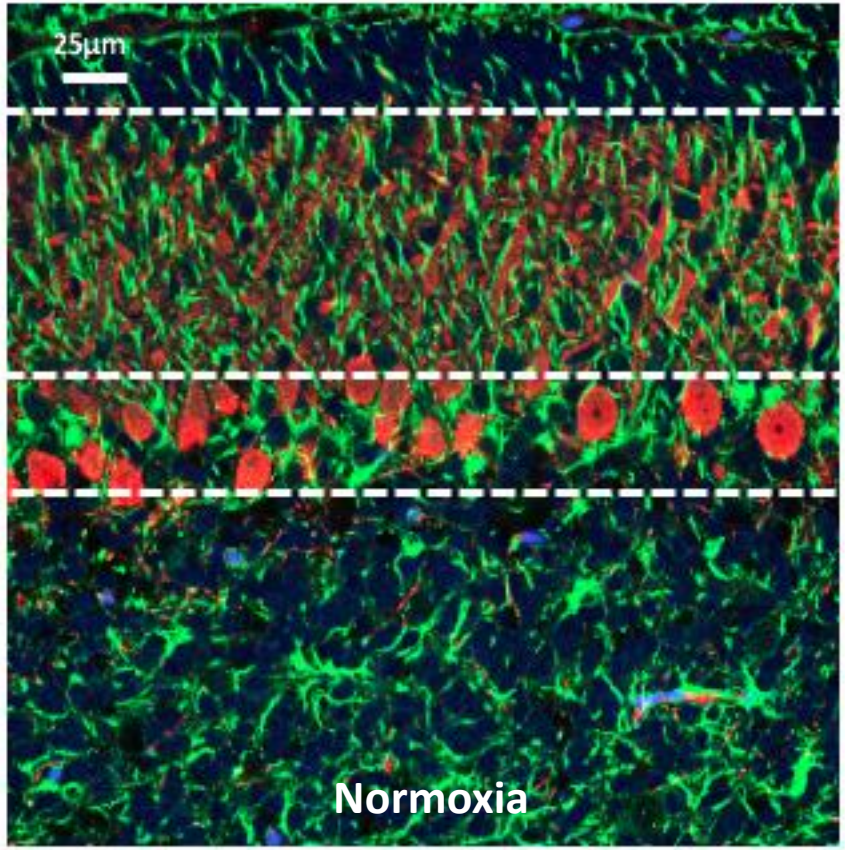
- GFAP → Astrocytes and Bergmann Glia
- Calbindin → Purkinje Cells
- DAPI → Granule Cells and Cerebellar Layers

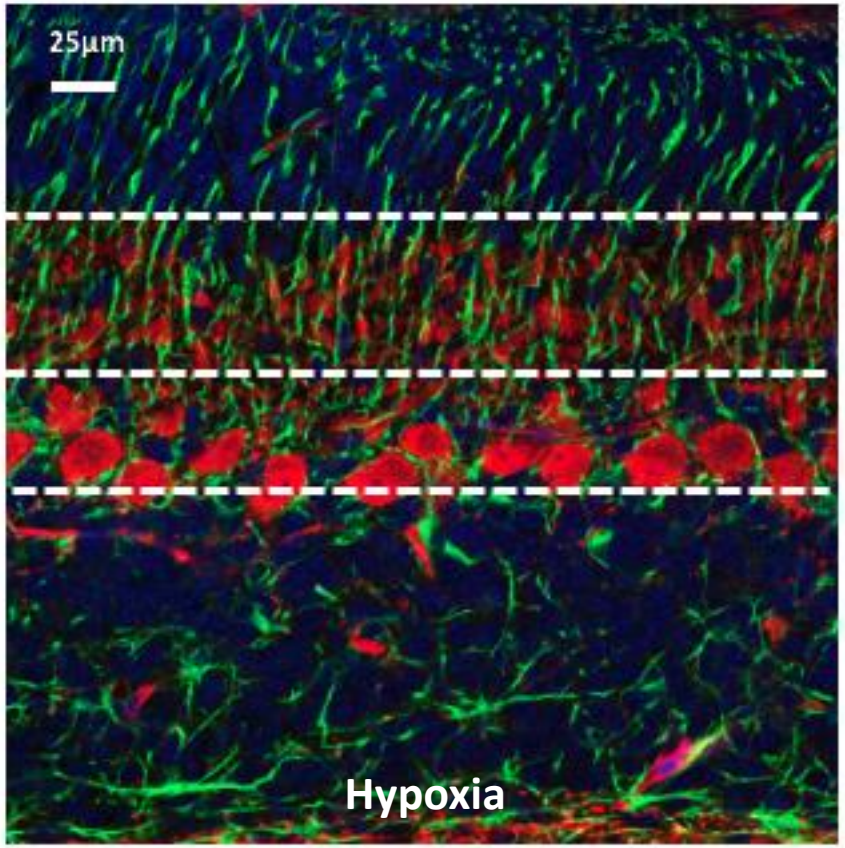
External Granular Layer — Proliferation

Molecular Layer — Migration

Purkinje Cell Layer — Differentiation

Internal Granular Layer





Hypoxia → Learning and motor skills → Long term behavioral deficits

(Leroux *et al.*, in preparation)

Oxidative Stress (OS)

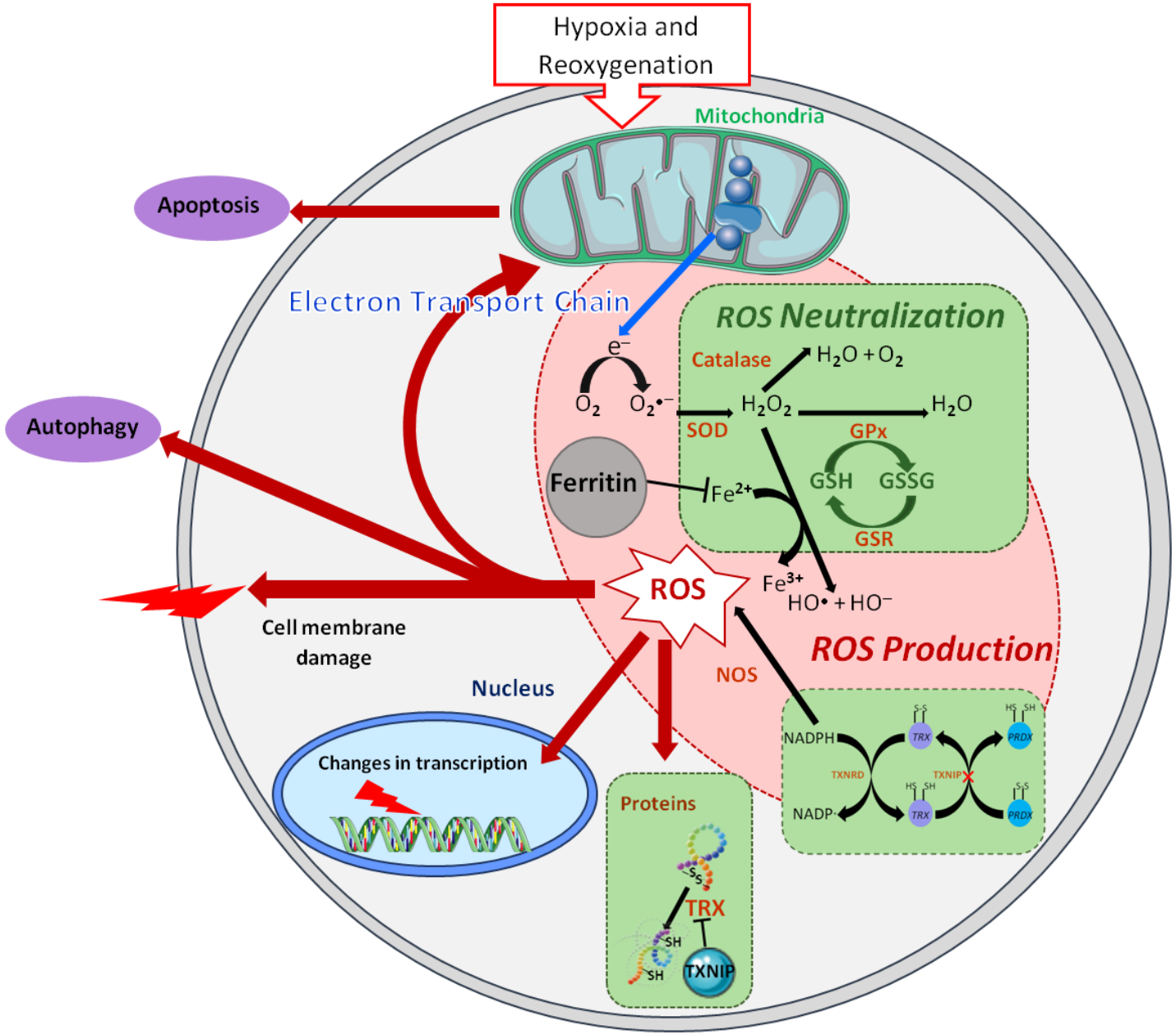
?

Pro-OS

- ↑O_2
- METC
- NOS

Anti-OS

- Ferritin
- Thioredoxin
- Gluthatione



Oxidative Stress (OS)

Pro-OS

Anti-OS

Cox4i1

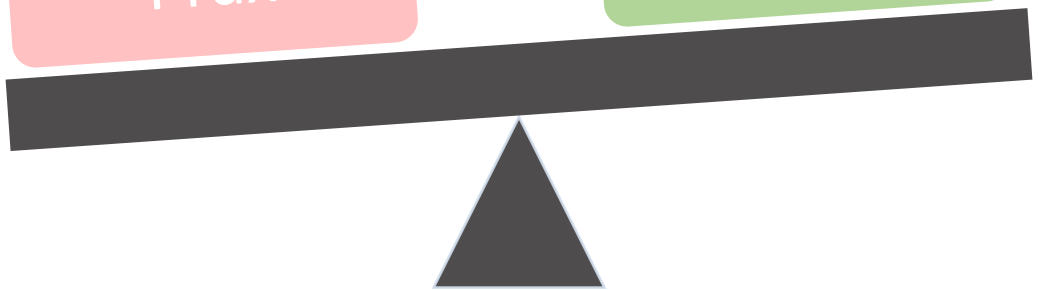
Fth1

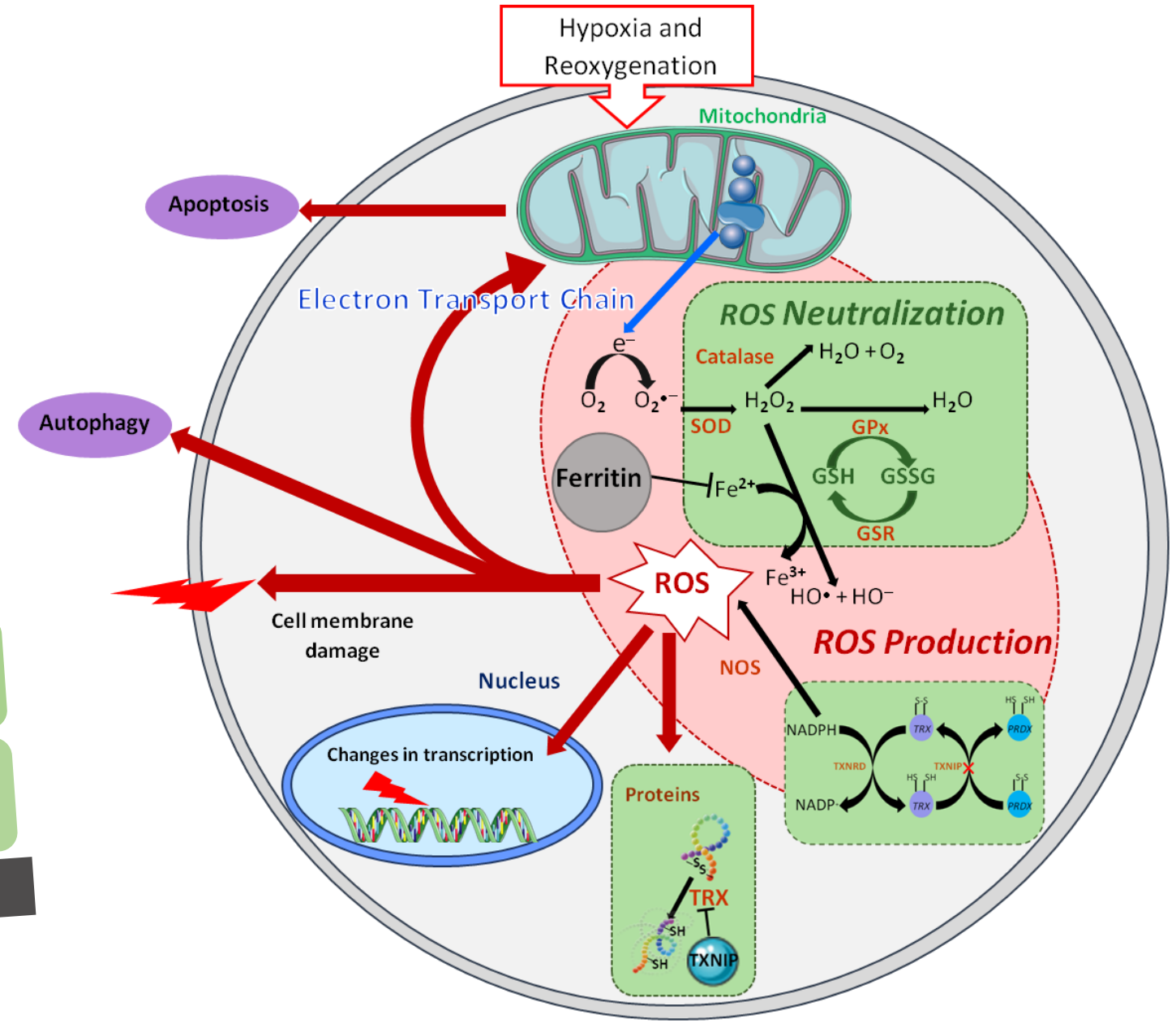
GSH

Prdx

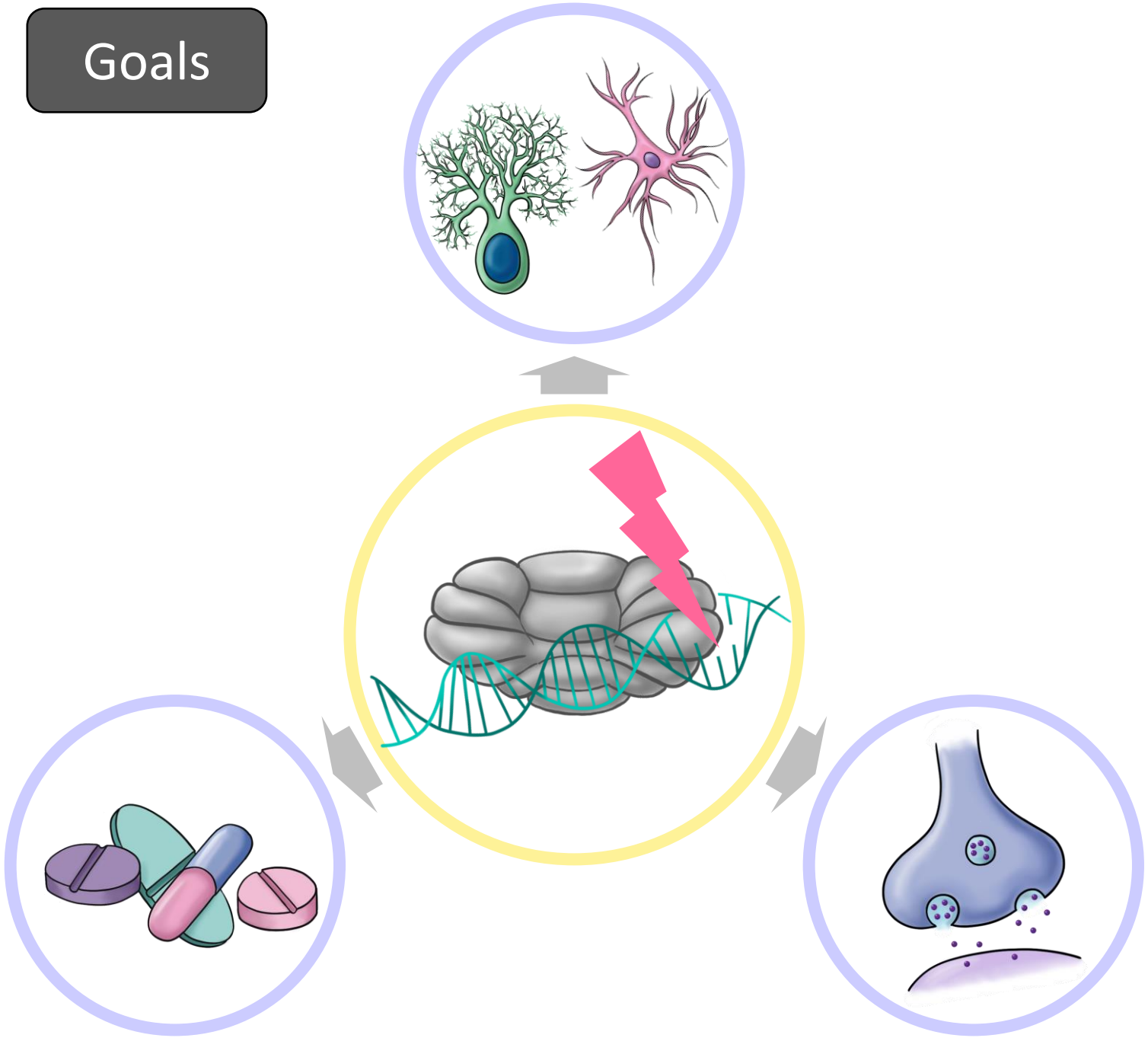
Nos

Trx

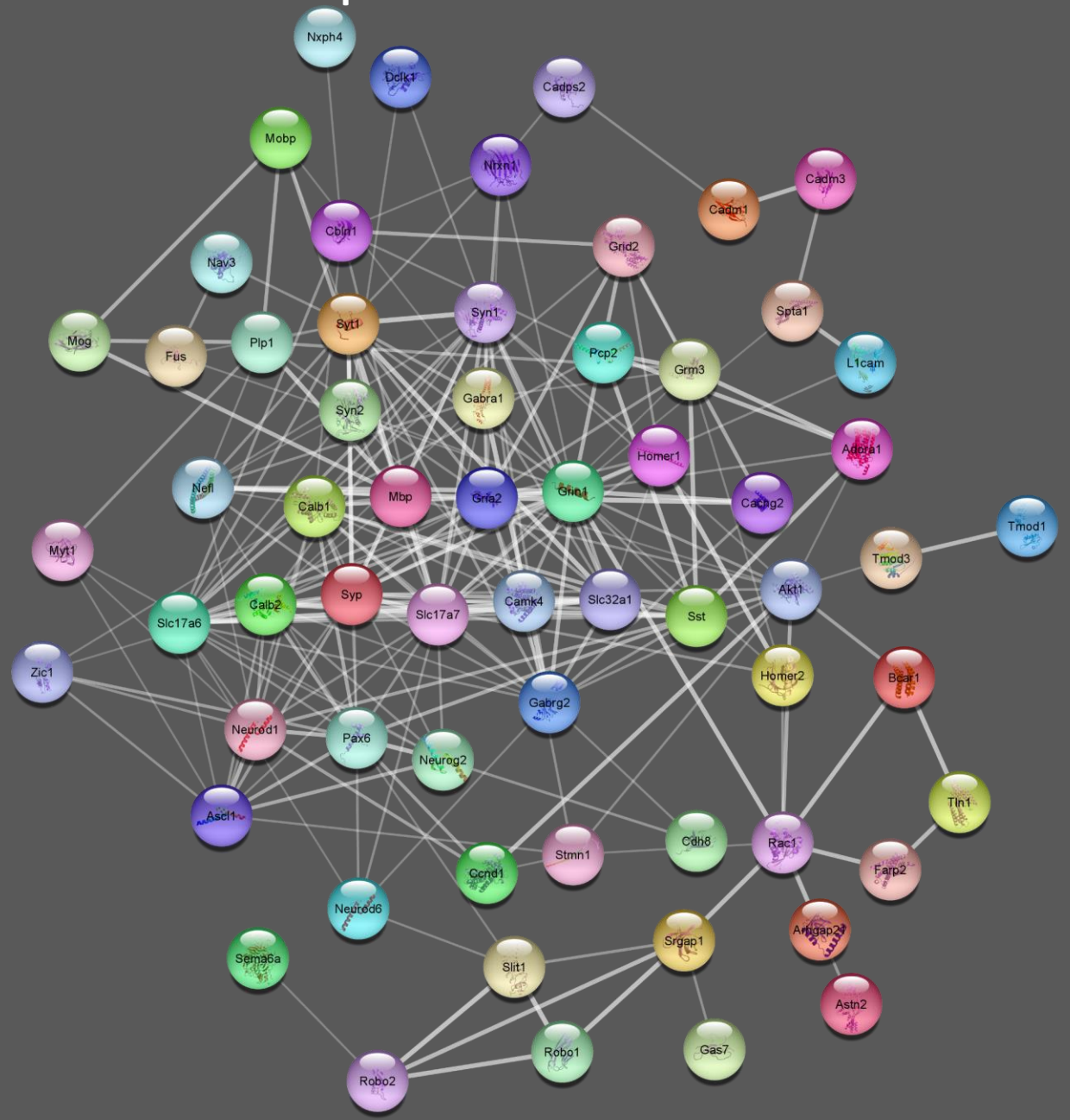




Goals



Development Gene Set



Methods

Hypoxia Protocol
Freezing of cerebella

↓

Laser Capture Microdissection
Separate layers

↓

Extraction
mRNA

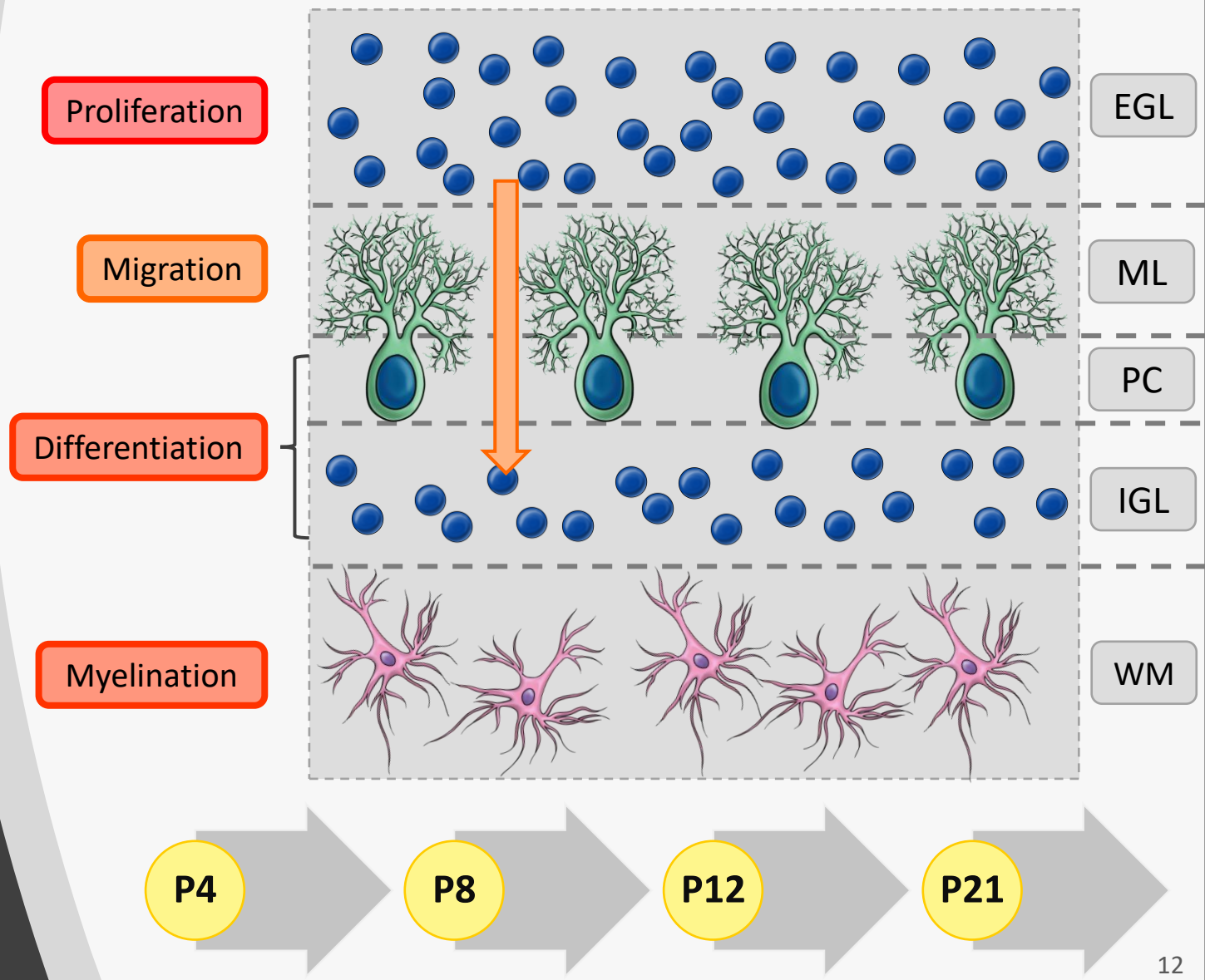
↓

Retrotranscription
cDNA

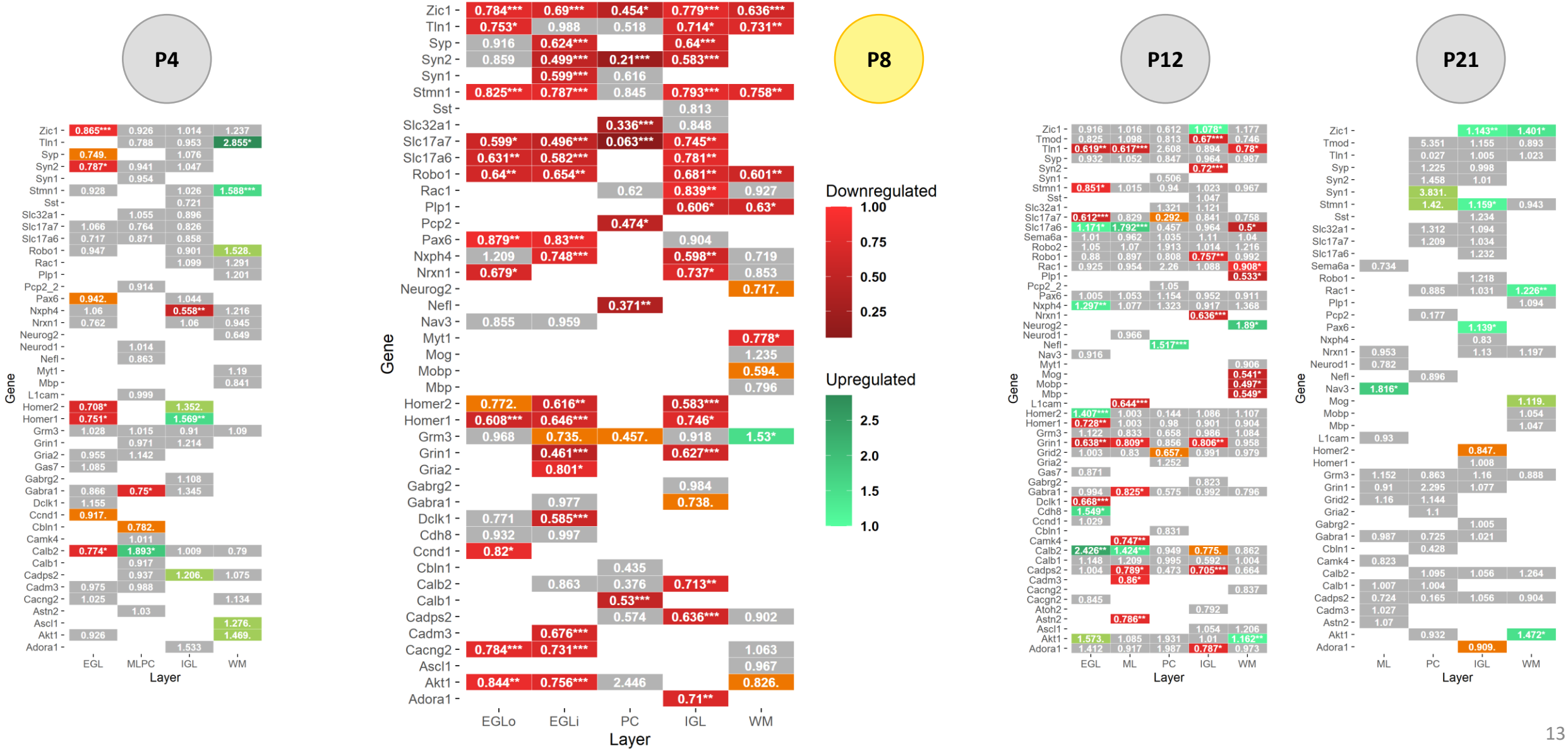
↓

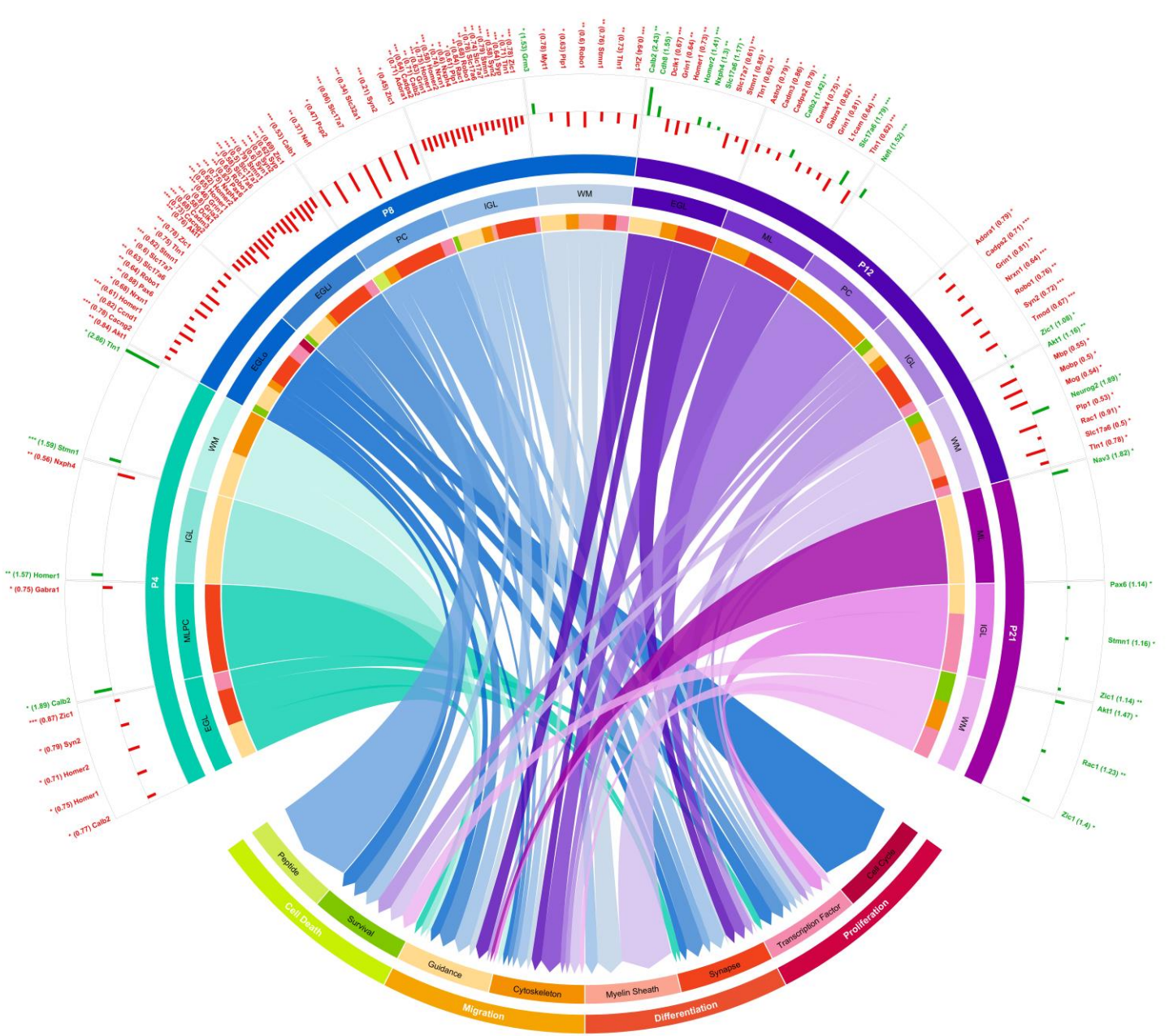
RT quantitative PCR
Differential expression

Layers and processes of the developing cerebellar cortex



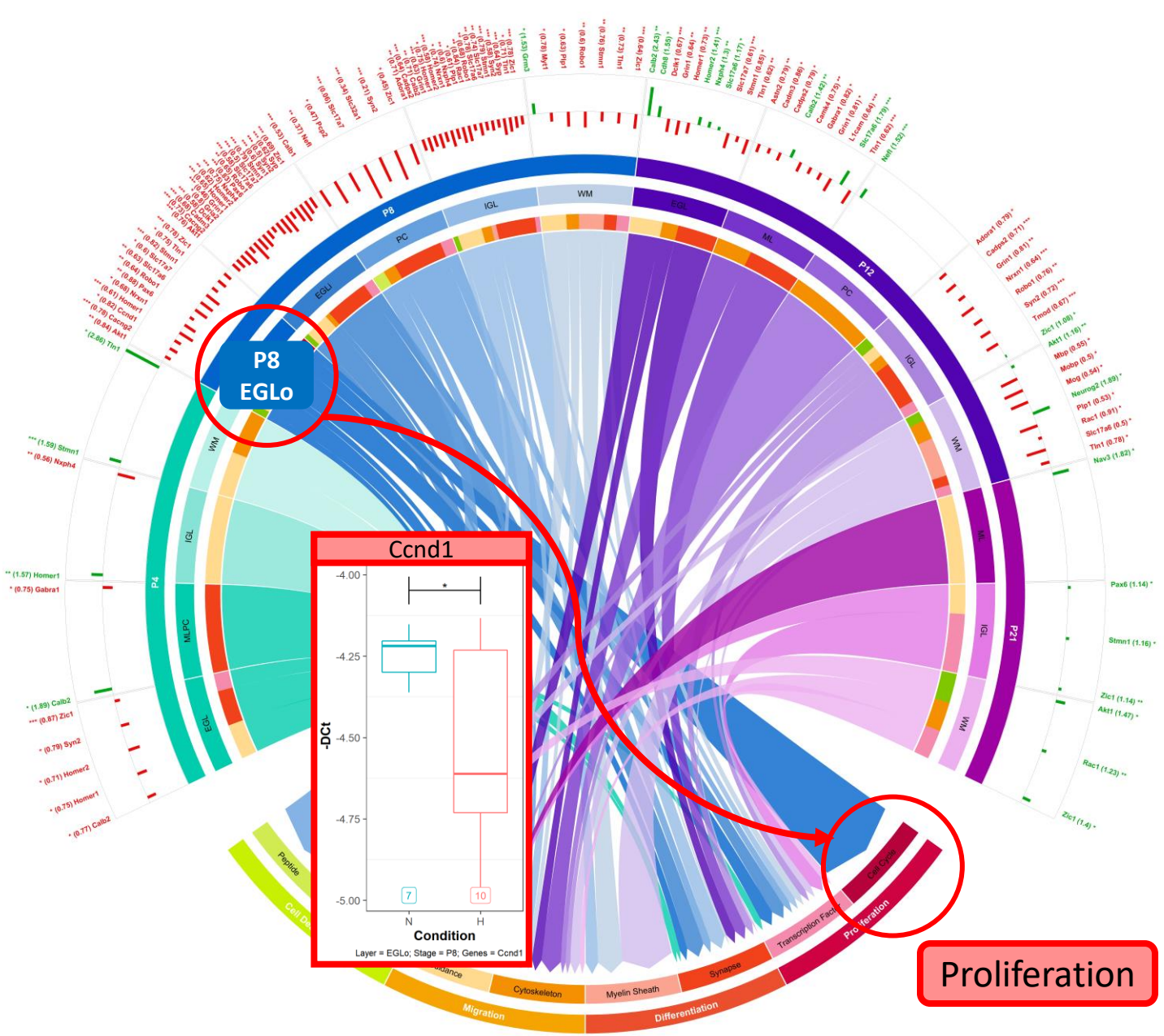
Regulation Timeline





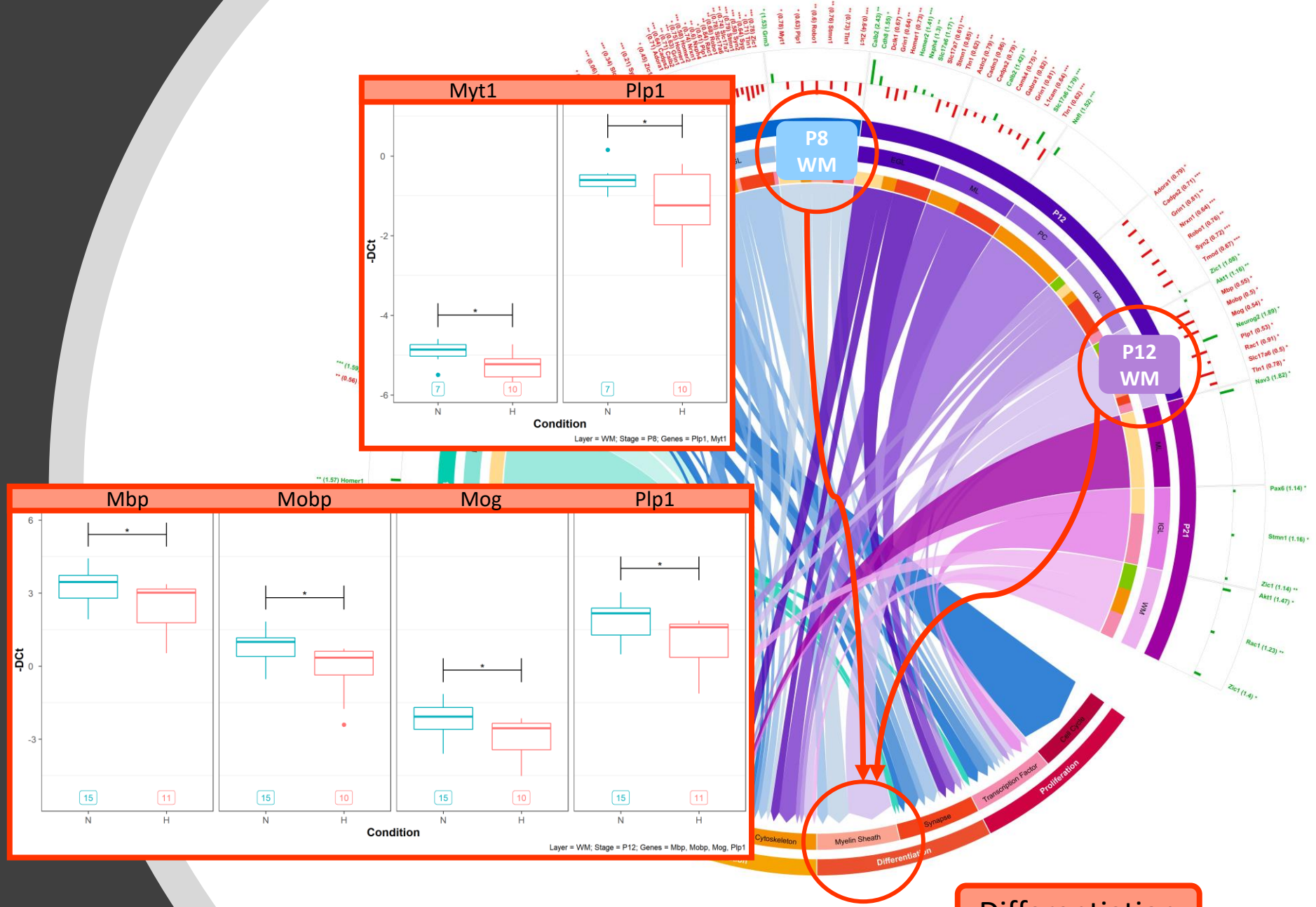
Hypoxia Influence on Gene Expression

(Rodriguez-Duboc *et al.*, in preparation)



(Rodriguez-Duboc *et al.*, in preparation)

Hypoxia influence on gene expression



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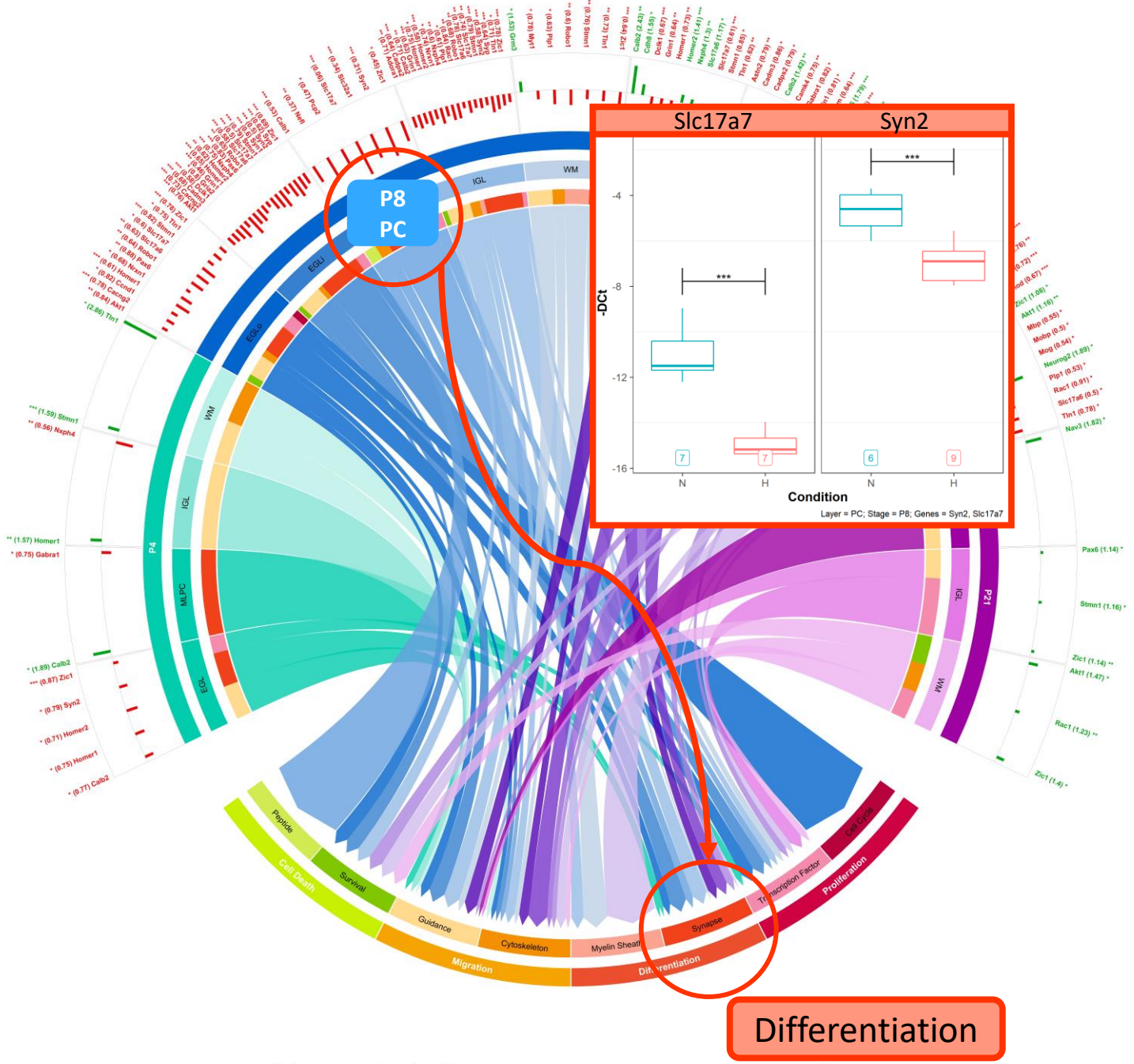
Hypoxia influence on gene expression



Hypoxia influence on gene expression

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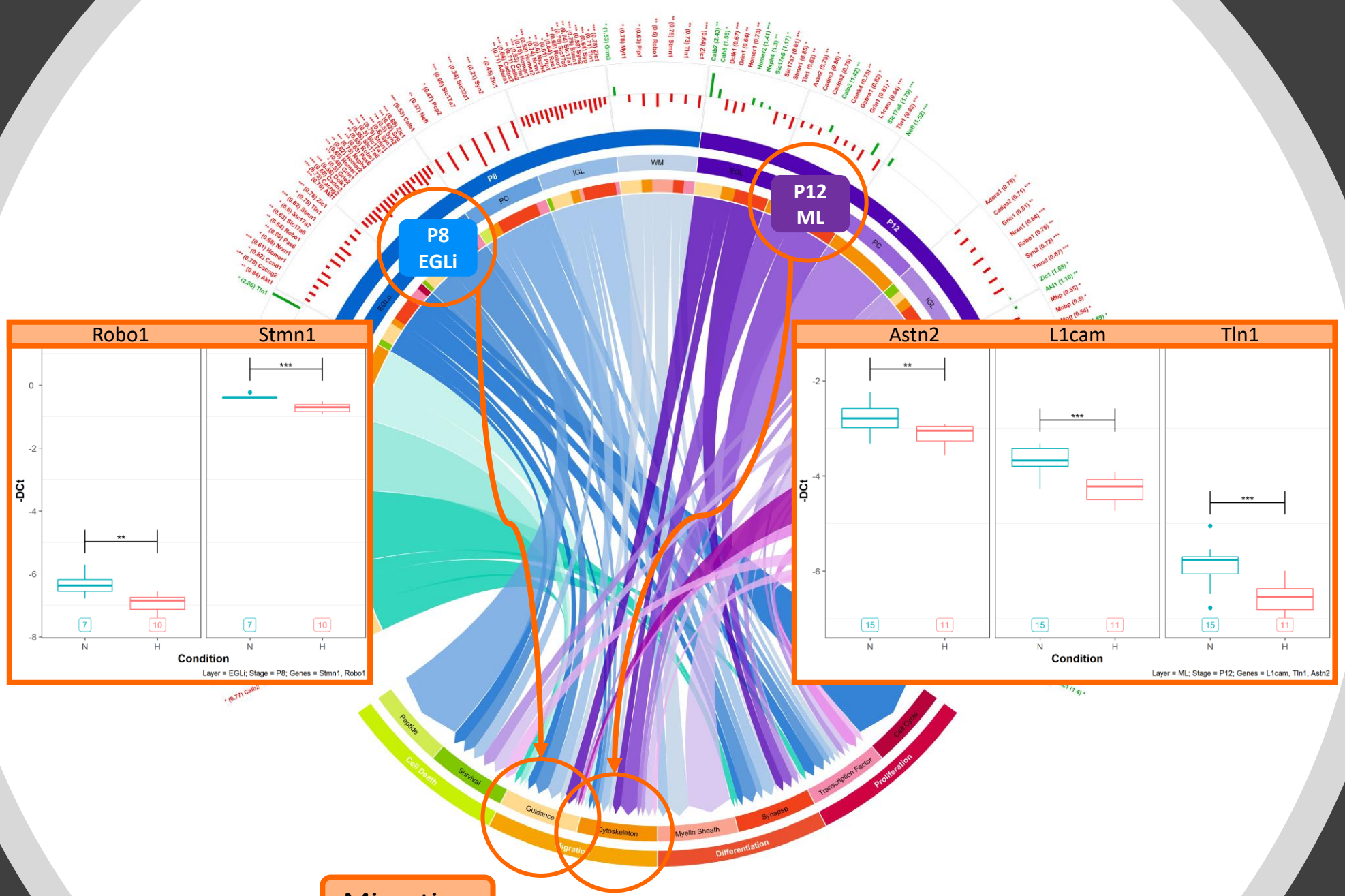

Hypoxia influence on gene expression

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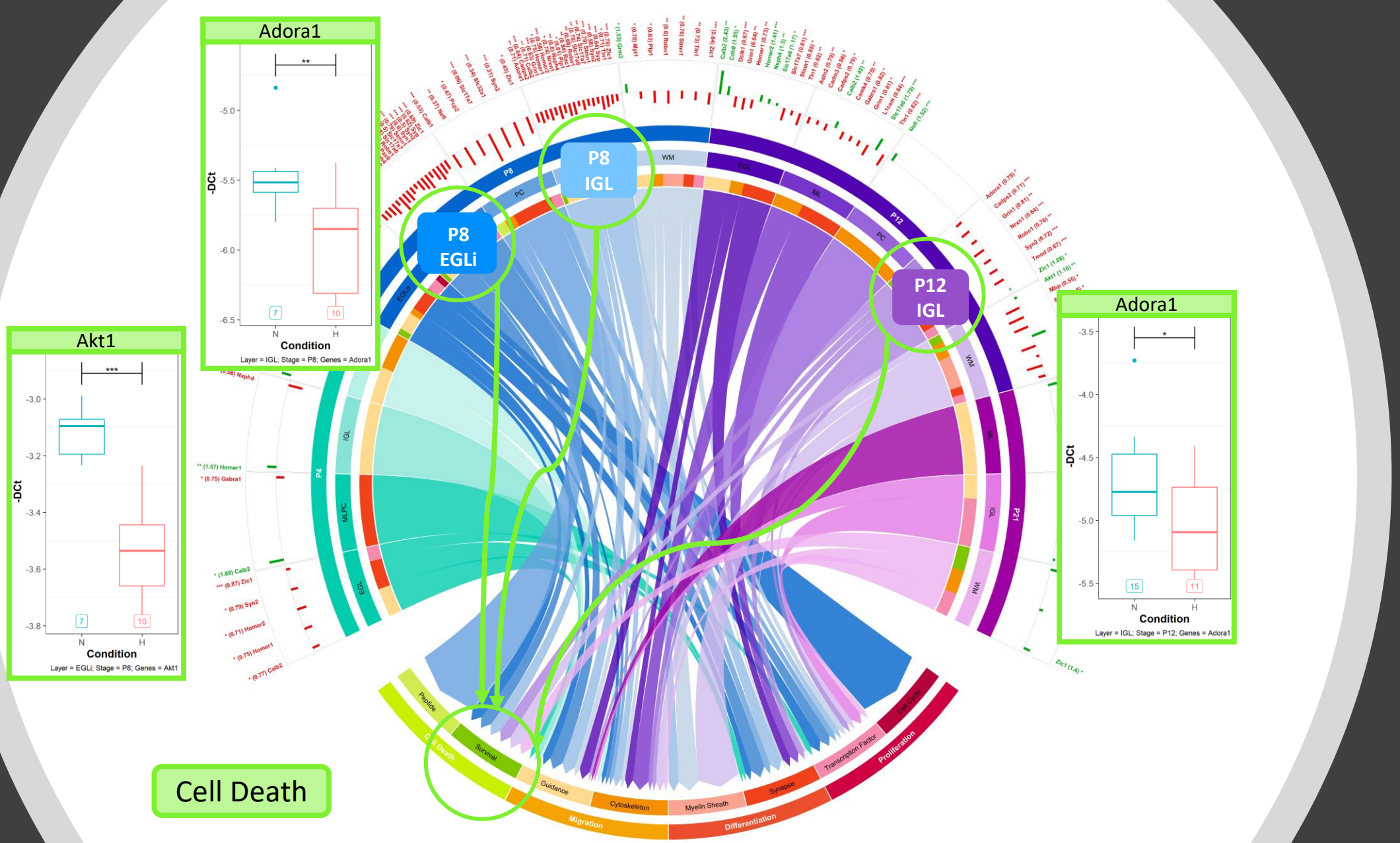
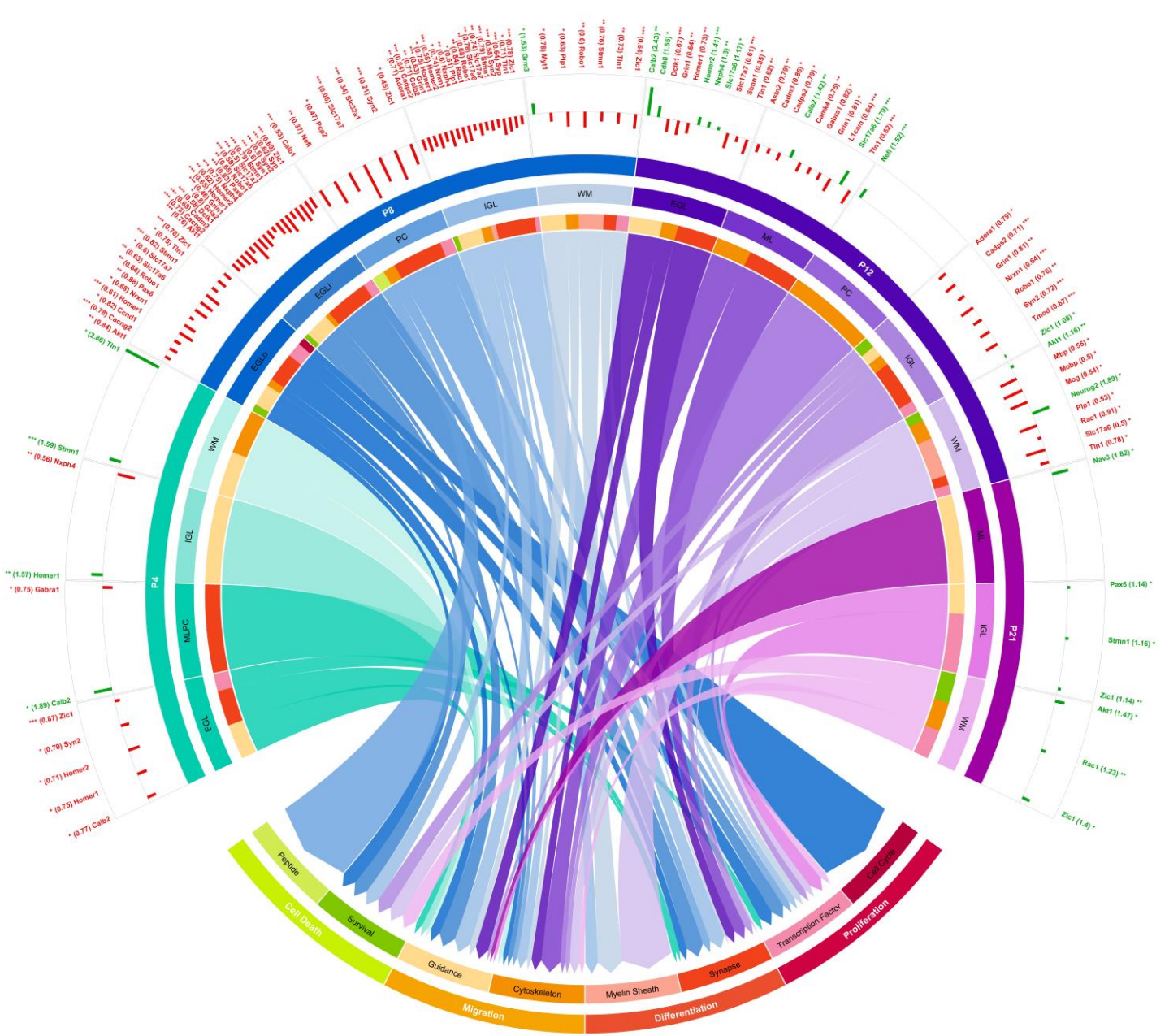


(Rodriguez-Duboc *et al.*, in preparation)

Hypoxia influence on gene expression

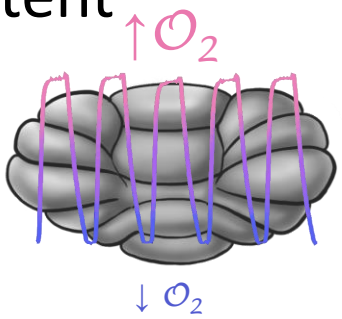


Hypoxia Influence on Gene Expression

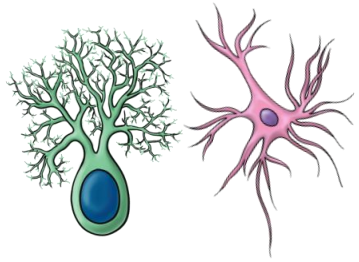
(Rodriguez-Duboc *et al.*, in preparation)

Consequences

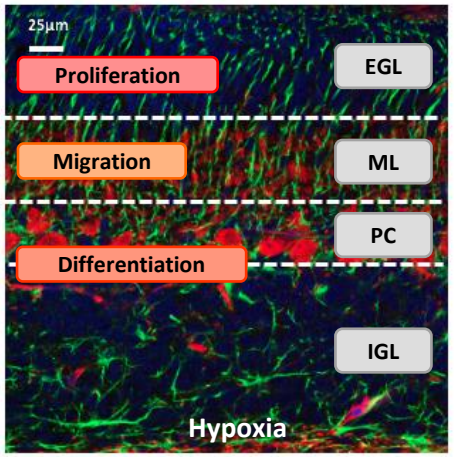
Intermittent Hypoxia



Cell Phenotype and Activity

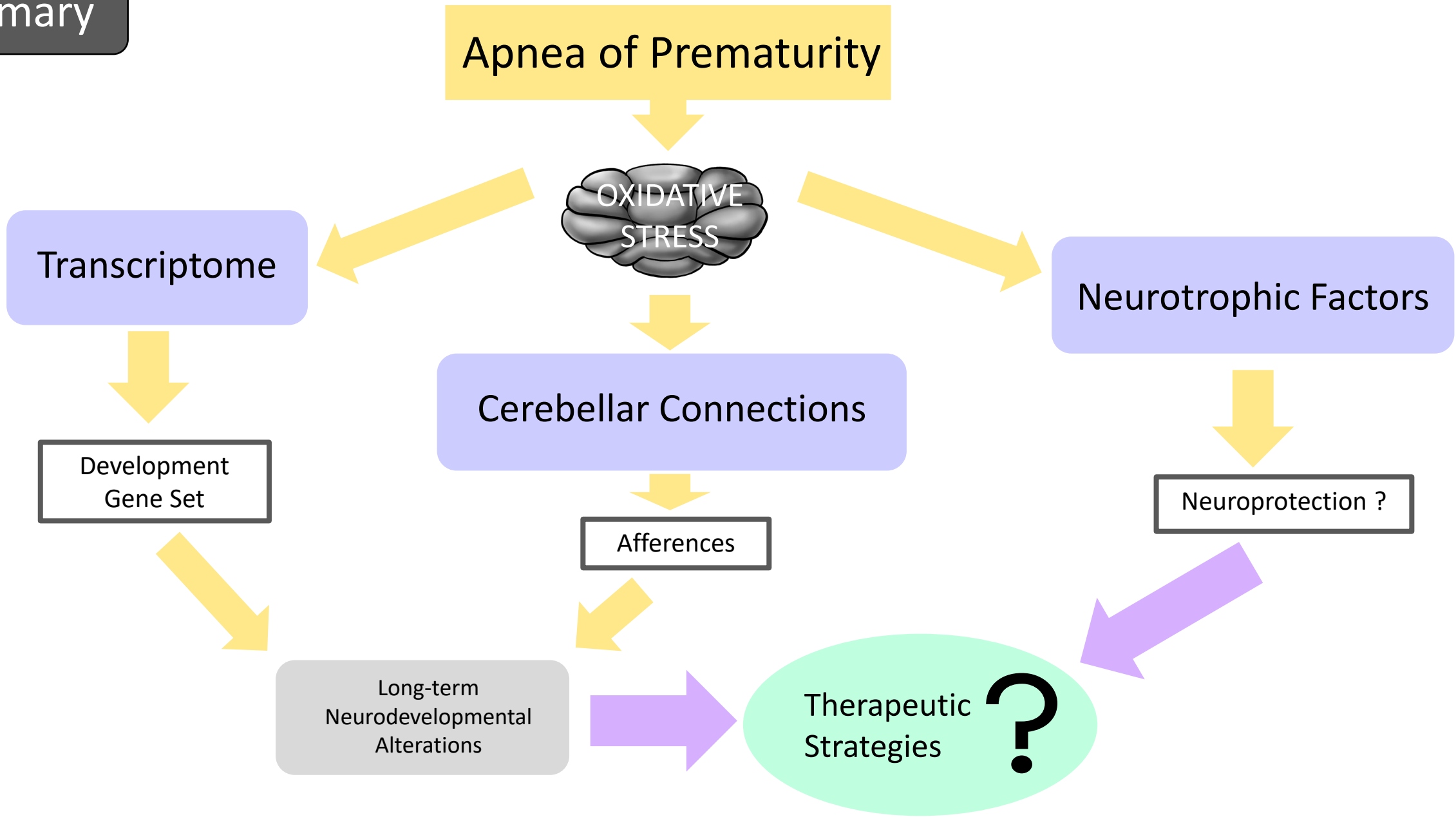


Histological Defects



Behavioral Deficits

Summary


Apnea of Prematurity
OXIDATIVE STRESS
Transcriptome
Development Gene Set
Cerebellar Connections
Afferences
Neurotrophic Factors
Neuroprotection ?
Long-term Neurodevelopmental Alterations
Therapeutic Strategies
?

Questions?

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Unité INSERM U1239, IRIB, Université de Rouen-Normandie
Director : Dr Youssef Anouar

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