

**NEUROSCIENCE**



**RESEARCH ARTICLE**

*Mari Paz Serrano-Regal et al. / Neuroscience xxx (xxxx) xxx–xxx*

# Oligodendrocyte Differentiation and Myelination Is Potentiated via GABA<sub>B</sub> Receptor Activation

Mari Paz Serrano-Regal,<sup>a,b,c</sup> Irene Luengas-Escuza,<sup>a</sup> Laura Bayón-Cordero,<sup>a</sup> Naroa Ibarra-Aizpurua,<sup>a</sup> Elena Alberdi,<sup>a,b,c</sup> Alberto Pérez-Samartín,<sup>a,b,c</sup> Carlos Matute<sup>a,b,c,\*</sup> and María Victoria Sánchez-Gómez<sup>a,b,c,\*</sup>

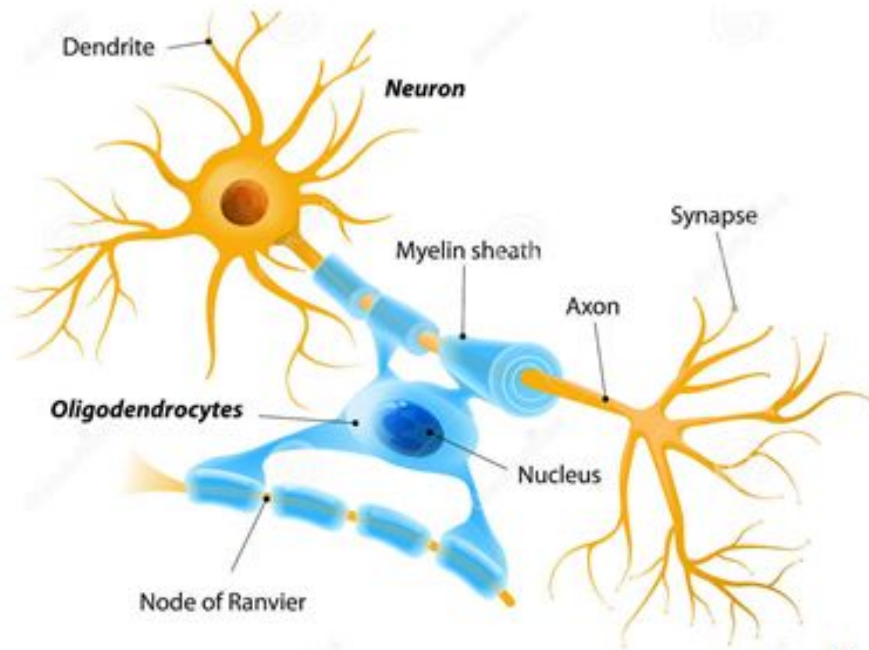


Adriana Chiabotto  
Marialaura Ostuni



UNIVERSITÀ  
DEGLI STUDI  
DI TORINO

# Oligodendrocytes (OLs)



[1]

- **Neuroglia**
- **Central nervous system** of vertebrates
- **Axonal myelination** → saltatory conduction  
→ metabolic support
- **Oligodendrocyte precursor cells (OPCs):**
  - DIFFERENTIATION during development
  - REMYELINATION in demyelinating diseases

Myelination: mediated by neuron–glia interactions

requires the participation of several regulators

**Very immature OLs express a range of neurotransmitter receptors:**

they may be involved in the regulation of OL development



ATP, adenosine, glutamate or **GABA** can modulate

OPCs proliferation, differentiation and migration

OLs survival and myelination

# Scientific question



**What is the role of GABA Receptors in OLs differentiation and myelination?**

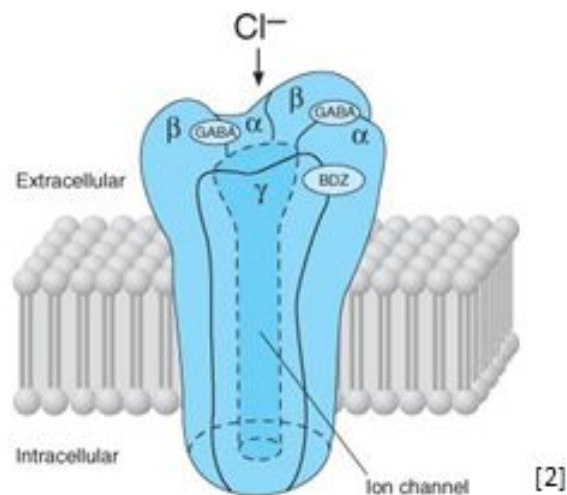
# GABA

- $\gamma$ -aminobutyric acid
- Major neurotransmitter in neonatal brain
- Recognized by receptors on plasma membrane (**GABAR**)

# GABAR

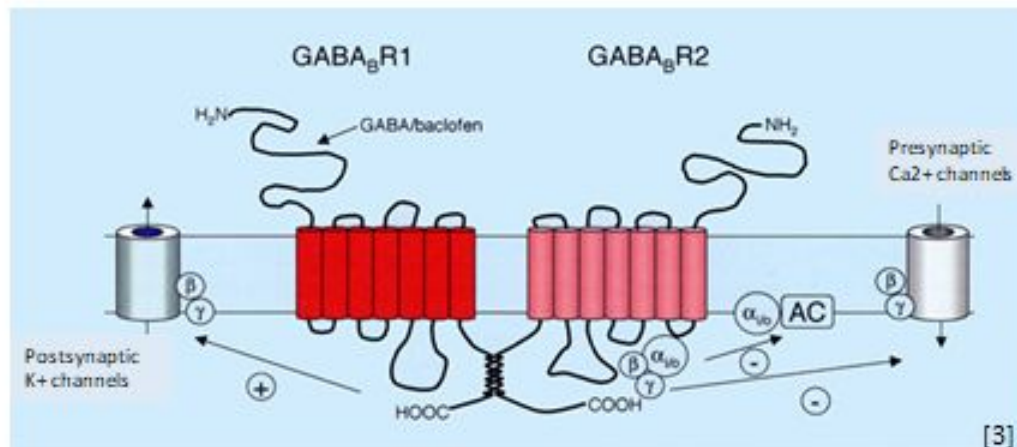
## GABA<sub>A</sub> Rs

- Ligand-gated ionotropic (Cl<sup>-</sup>) → fast inhibitory transmission
- in OPCs
- Agonist: muscimol



## GABA<sub>B</sub> Rs

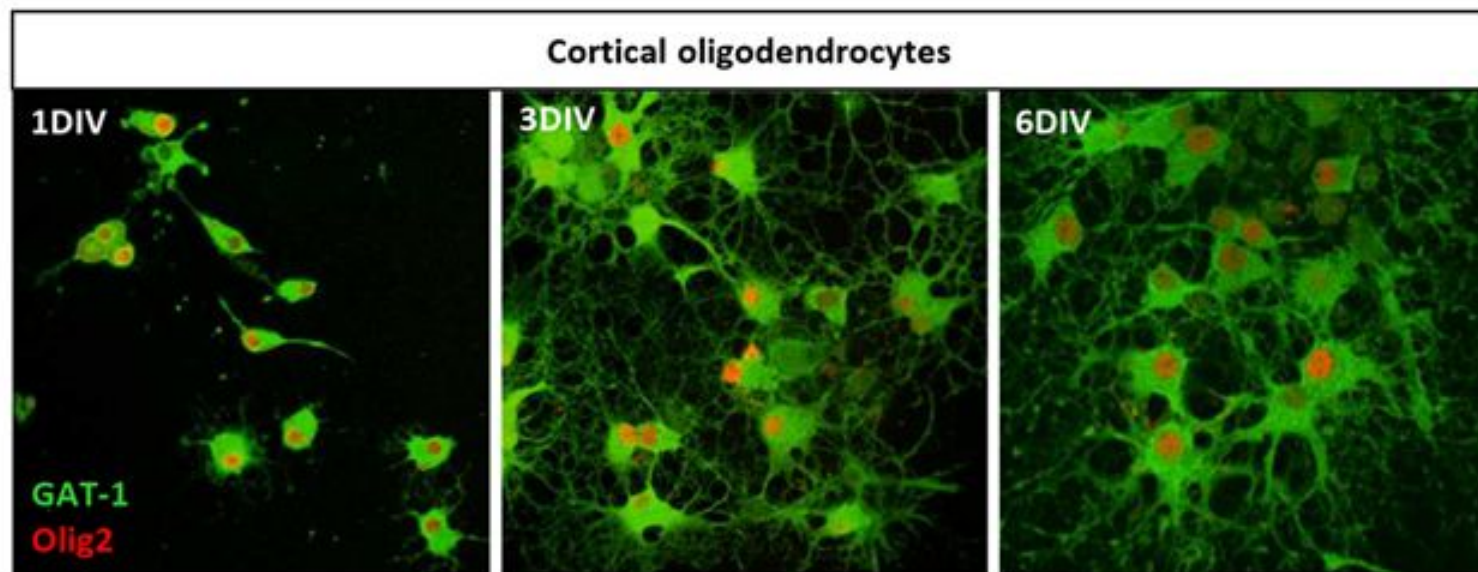
- Heterodimeric
- G protein-coupled metabotropic → slow and prolonged inhibitory transmission
- in developing OLs
- Agonist: baclofen
- Antagonist: CGP55845



Mature and immature OLs → GABA transporter GAT-1



May communicate with each other and with neurons through GABAergic pathways → specific role for GABA signaling in the oligodendroglial lineage development



# Signaling mechanism

## The tyrosine kinase Src-family:

- Involved in **OLs** and Schwann cells **differentiation** and myelination
- Related to **GABAergic system**



# Scientific questions



## **What is the role of GABAR in OLs differentiation and myelination?**

Which GABAR is involved?

How does GABA neurotransmitter affect the process?

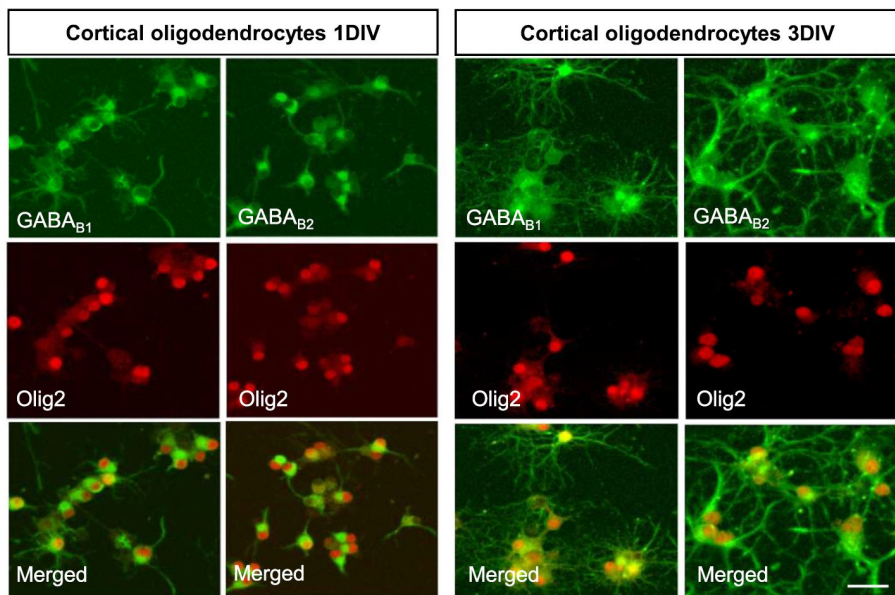
# Methods overview

## In vitro

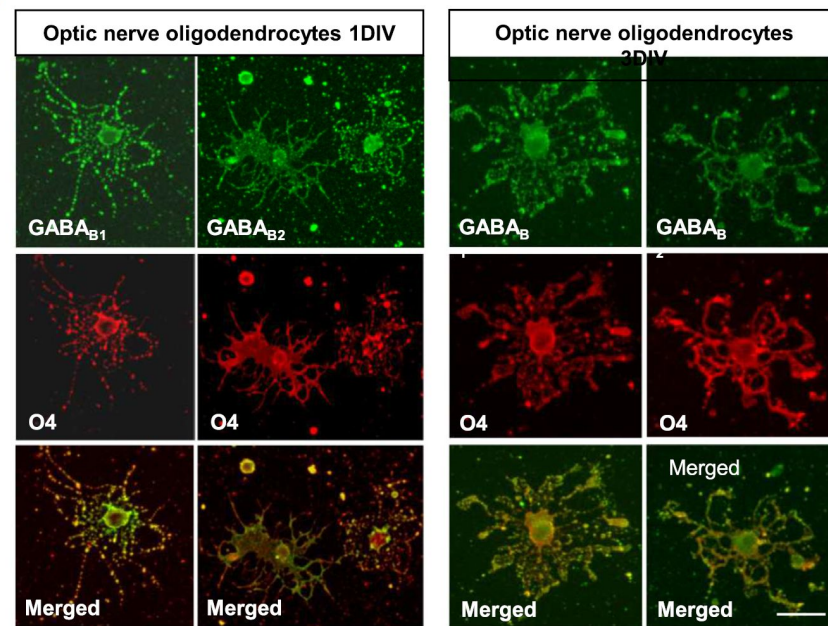
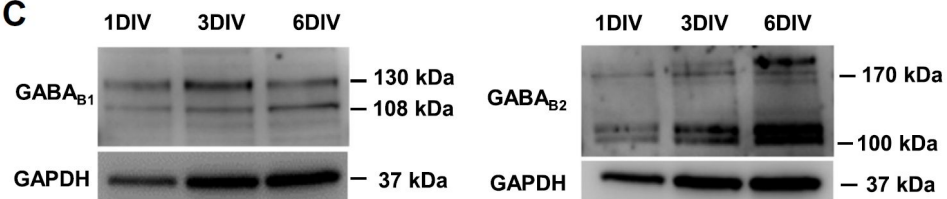
- 1) Purified OPCs from rat forebrain (P0-P2)
- 2) OLs: rat optic nerve (P11)
- 3) DRG-OPCs cocultures: 1) or 2) with E15 rat dorsal root ganglia

## In vivo

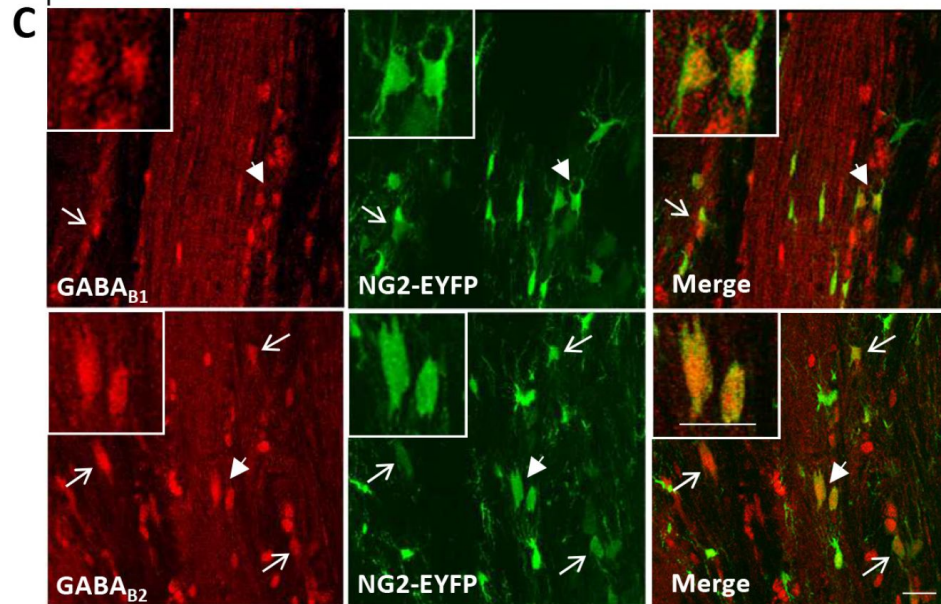
- Localizations: Transgenic rats
  - ➔ express EYFP under NG2 control (OPC marker)

**A**

## Cultured oligodendrocytes express GABA<sub>B</sub>R *in vitro*

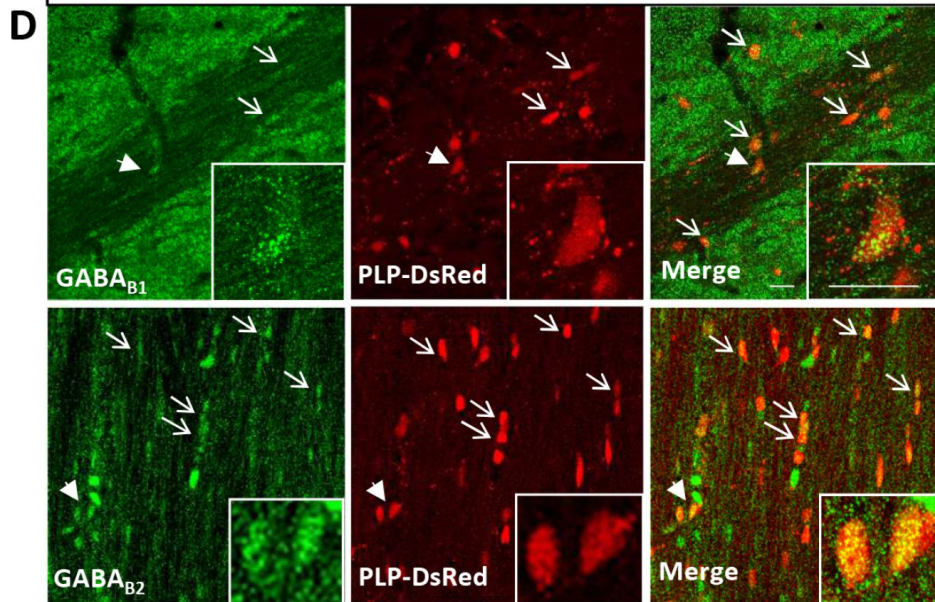
**B****C**

NG2-EYFP mice brain slices

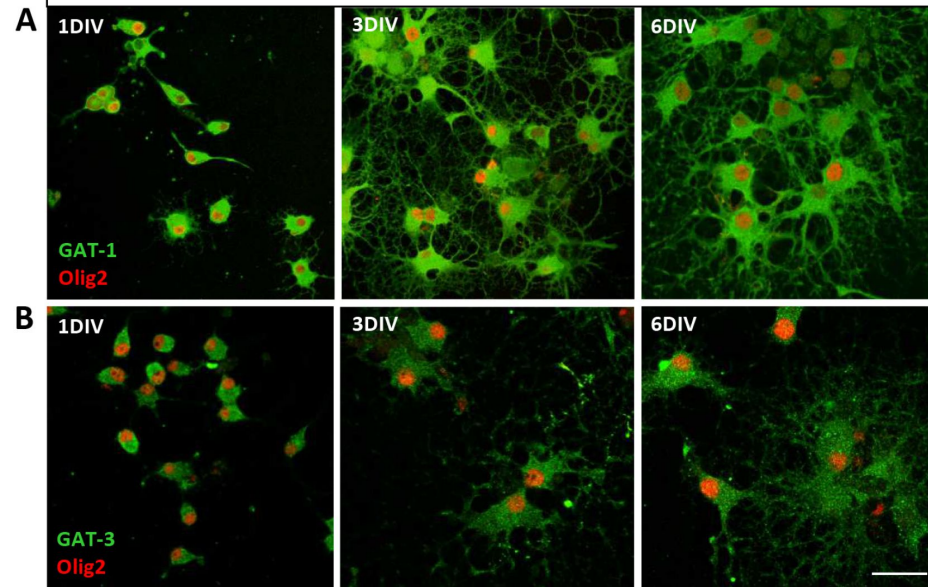


Expression of GABA<sub>B</sub>R in  
OLs *in vitro* and *in vivo*

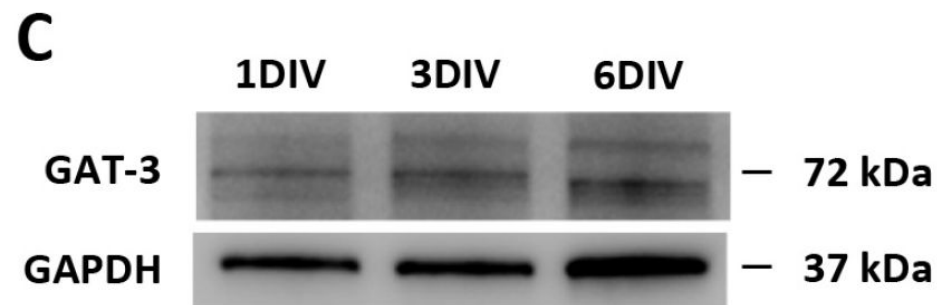
PLP-DsRed mice brain slices



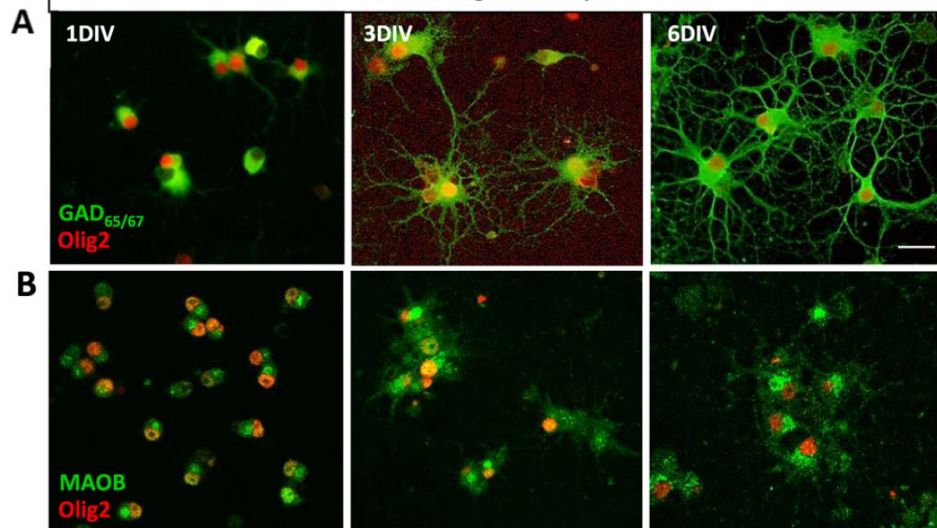
Cortical oligodendrocytes



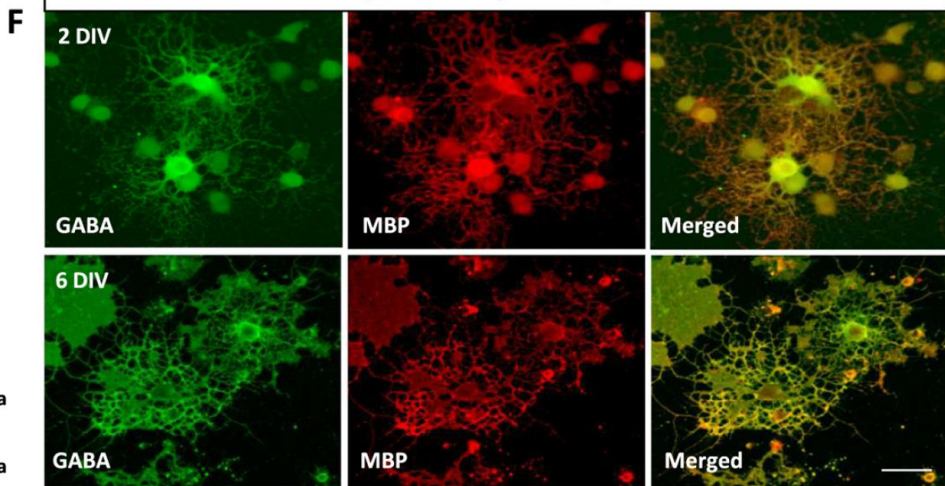
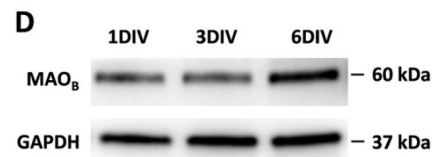
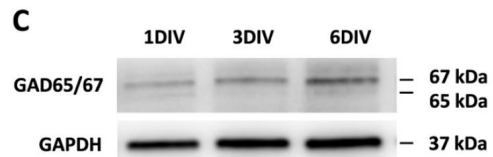
**Expression of GABA transporters  
in oligodendroglial cells *in vitro*  
and *in vivo***

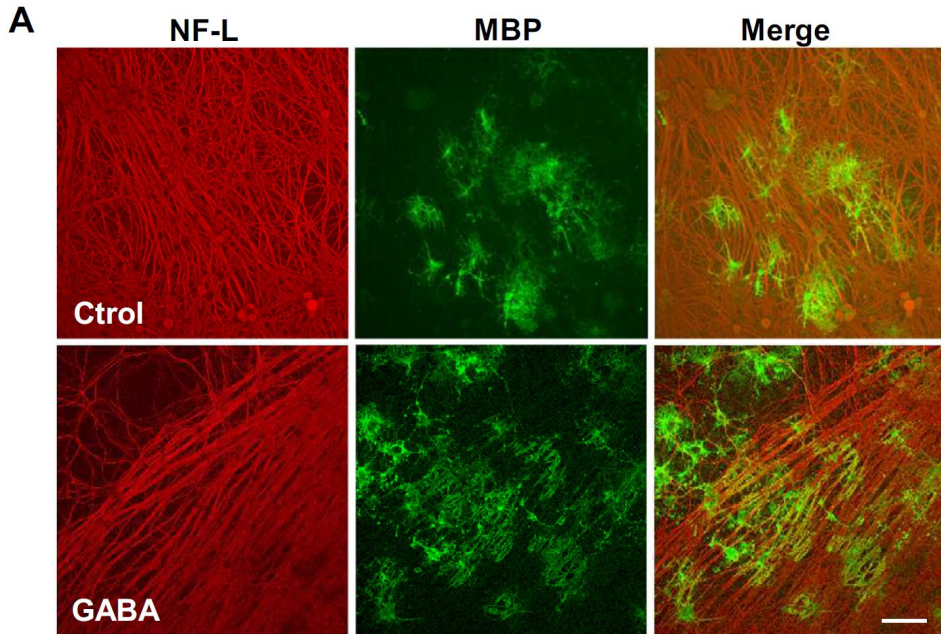


Cortical oligodendrocytes

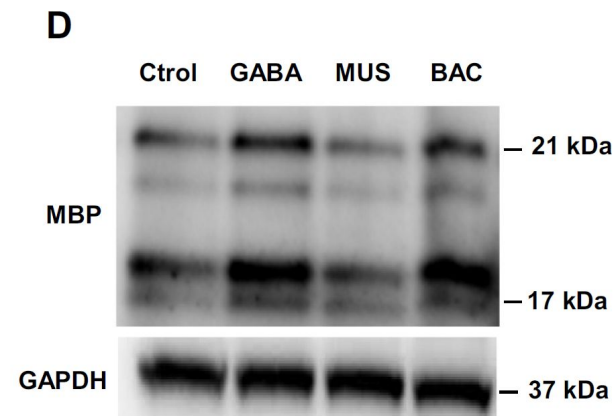
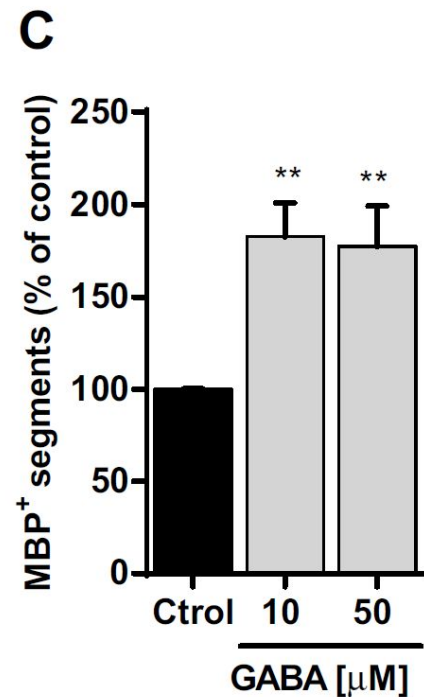
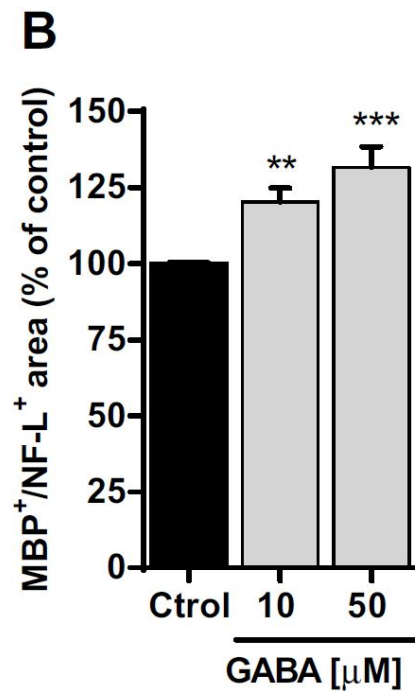


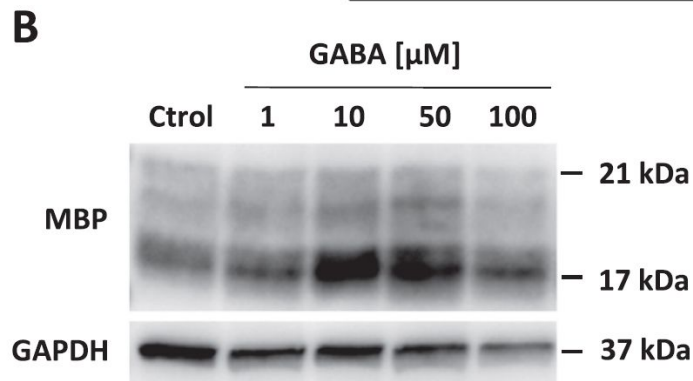
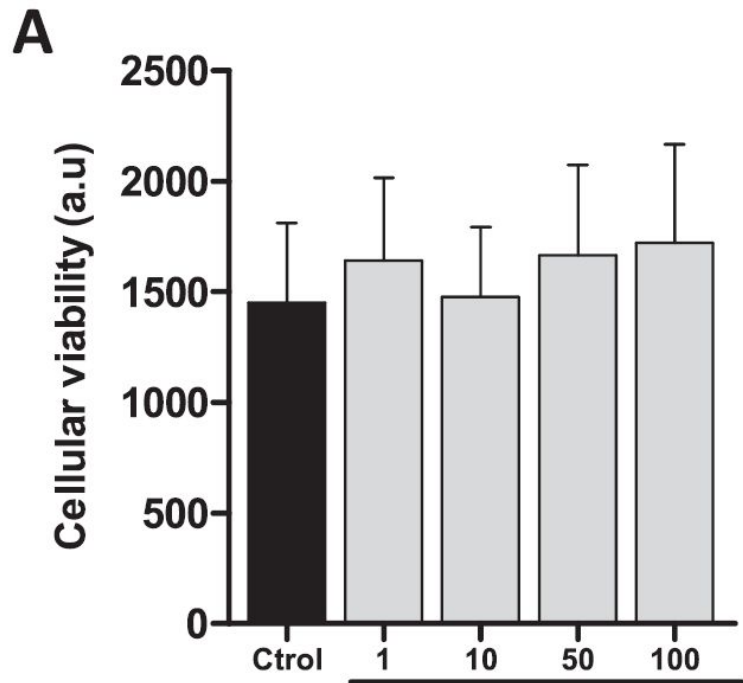
OLs synthesize GABA *in vitro*





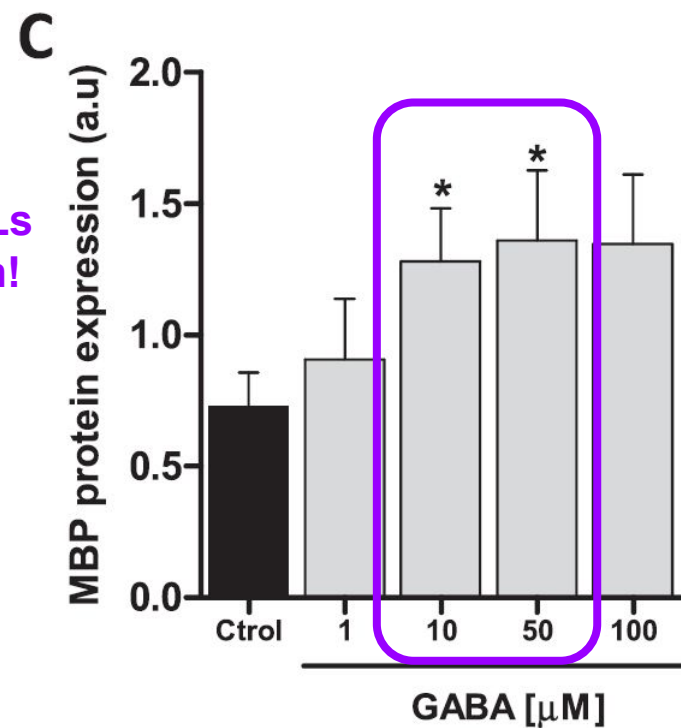
## GABA regulates myelination in DRG-OPC coculture system



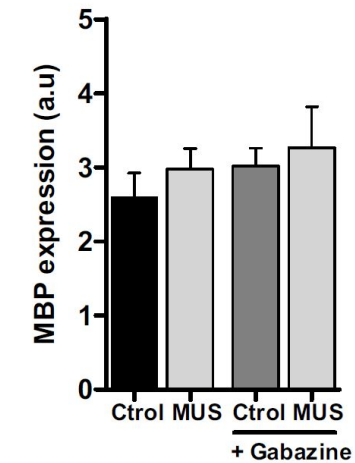
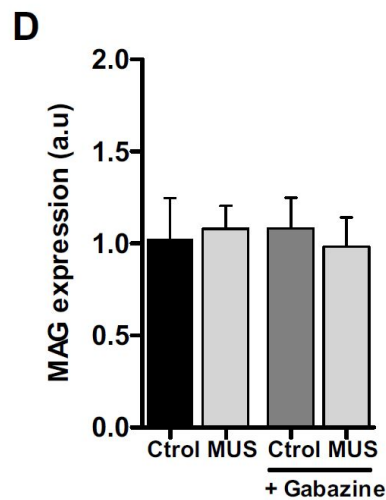
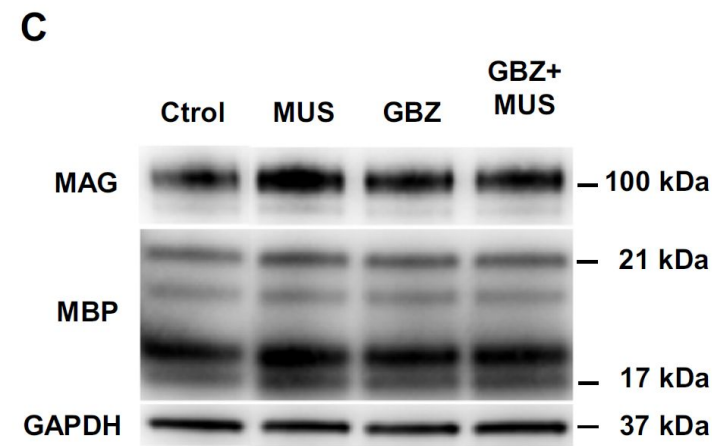
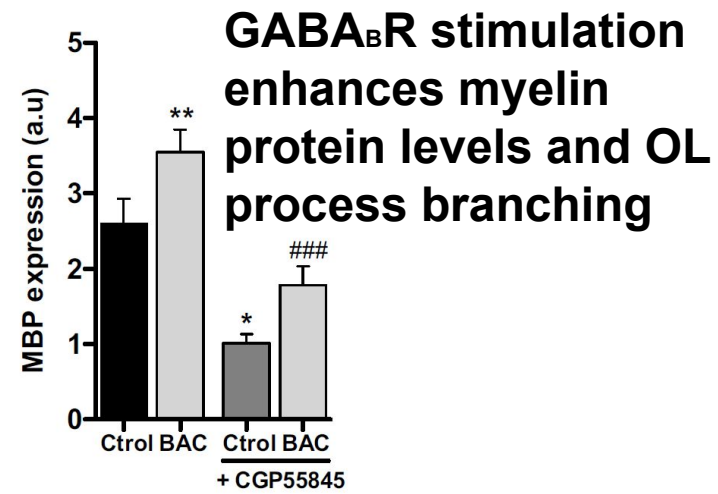
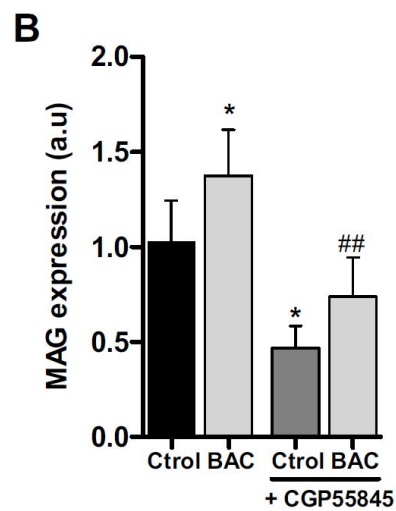
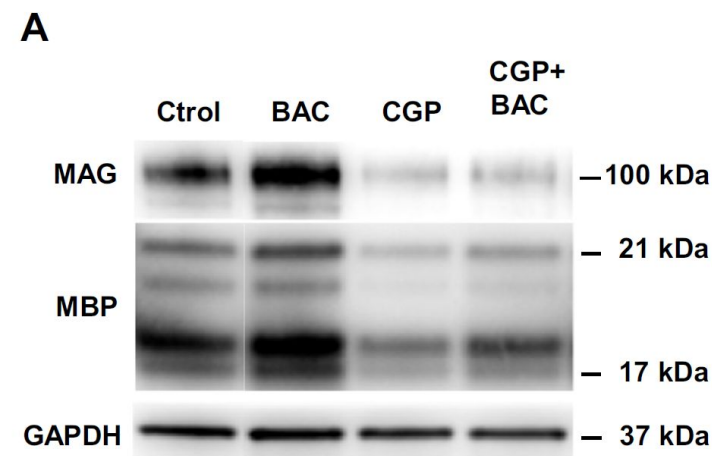


**GABA upregulates MBP expression in OL cultures**

**GABA promotes directly OLs maturation!**







# Conclusions

- Oligodendrocytes synthesize GABA and express the major components of the GABAergic system
- Oligodendroglial cells express both GABA<sub>A</sub> and GABA<sub>B</sub> receptors
- Oligodendrocytes express both GAT-1 and GAT-3
- OLs express both GAD<sub>65/67</sub> and MAO<sub>B</sub>
- GABA has been postulated as one of the modulators of oligodendroglial cell proliferation, differentiation and myelination

The present study introduces an important role for the GABAergic system

**It will be relevant to study the role of GABA in demyelinating diseases**

# Bibliography

- G Fattorini, M Melone, MV Sánchez-Gómez, RO Arellano, S Bassi, C Matute, F Conti, *GAT-1 mediated GABA uptake in rat oligodendrocytes*, *Glia*, 2017
- Mari Paz Serrano-Regal, Irene Luengas-Escuza, Laura Bayón-Cordero, Naroa Ibarra-Aizpurua, Elena Alberdi, Alberto Pérez-Samartín, Carlos Matute, María Victoria Sánchez-Gómez, *Oligodendrocyte Differentiation and Myelination Is Potentiated via GABA<sub>B</sub> Receptor Activation*, *Neuroscience*, 2019
- [1] google research «oligodendrocytes»/images
- [2] [cellularscale.blogspot.com/2013/02/gaba-how-exciting.html](http://cellularscale.blogspot.com/2013/02/gaba-how-exciting.html)
- [3] translated and modified from <https://www.medicinapertutti.it/argomento/recettore-gabaergico-b/>

**Thank you for  
your attention**



UNIVERSITÀ  
DEGLI STUDI  
DI TORINO