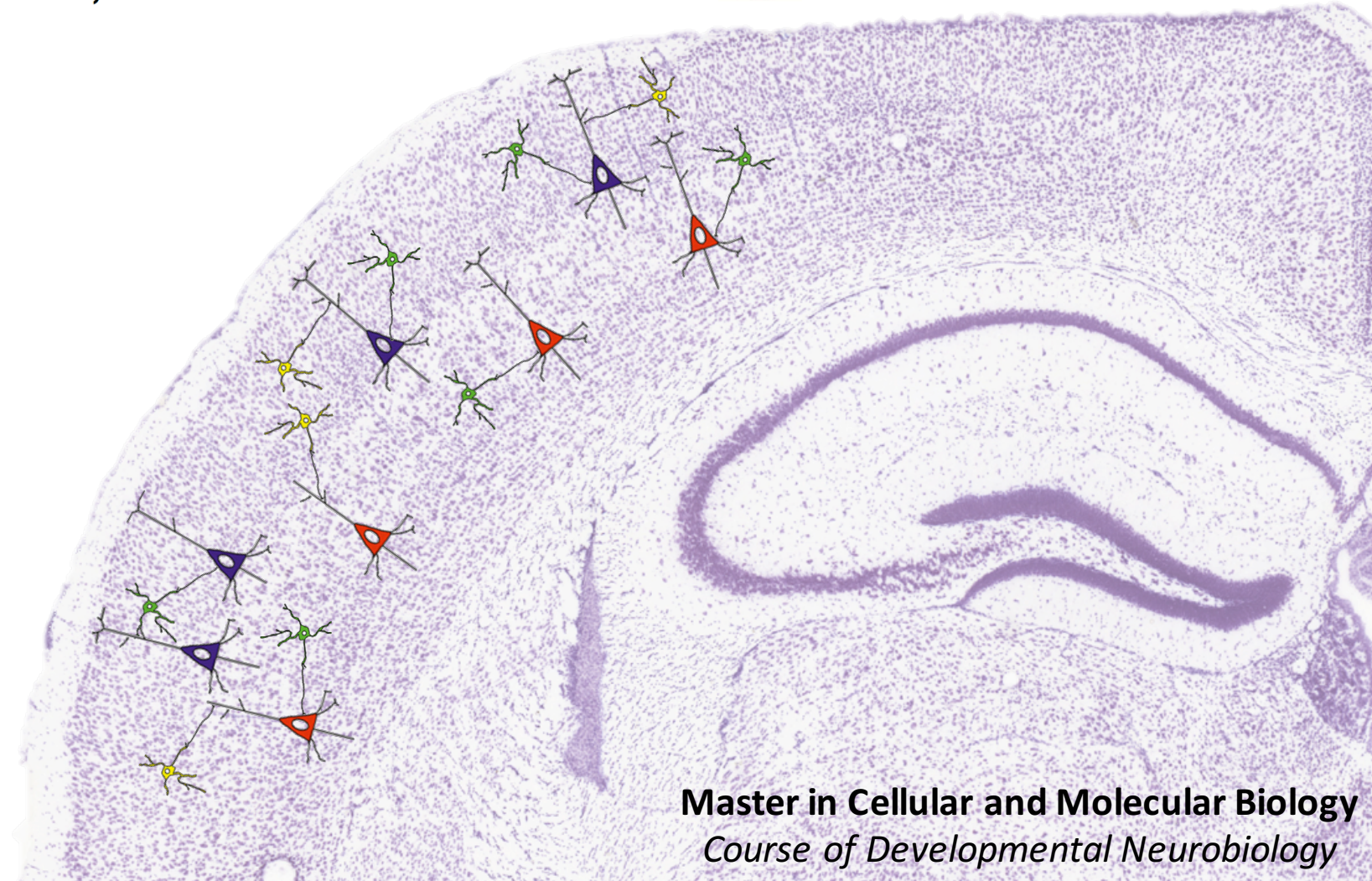
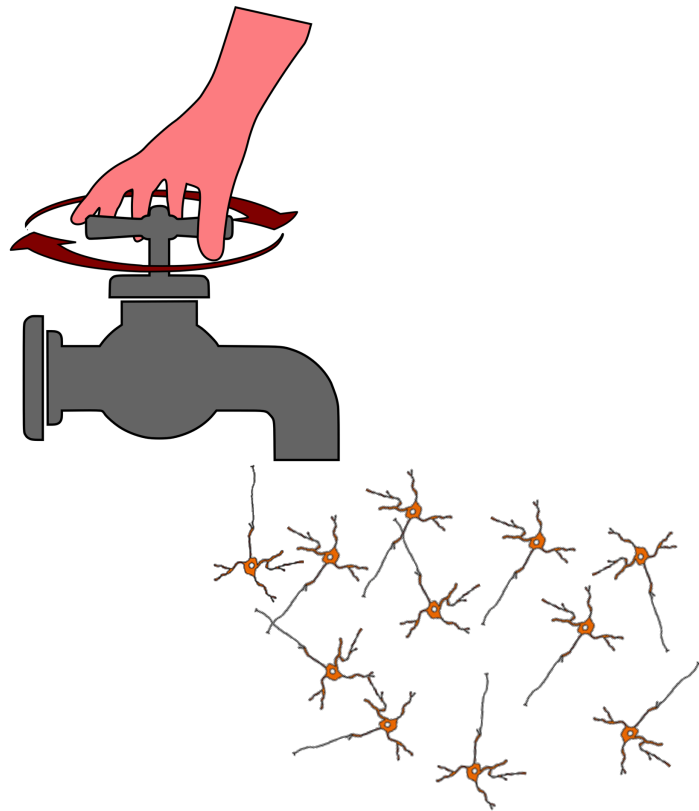


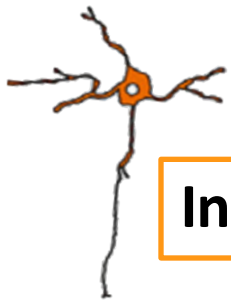
# Tuning neural circuits by turning the interneuron knob

Nathalie Dehorter<sup>1</sup>, Nicolás Marichal<sup>3</sup>, Oscar Marín<sup>1,2</sup> and  
Benedikt Berninger<sup>3</sup>

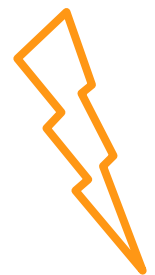
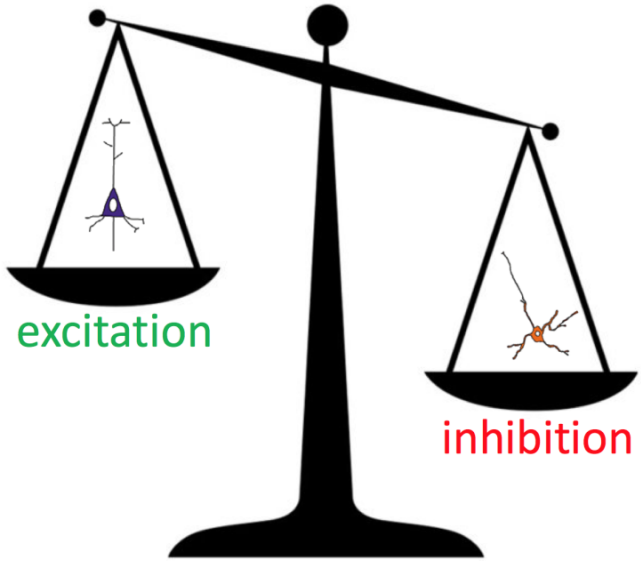
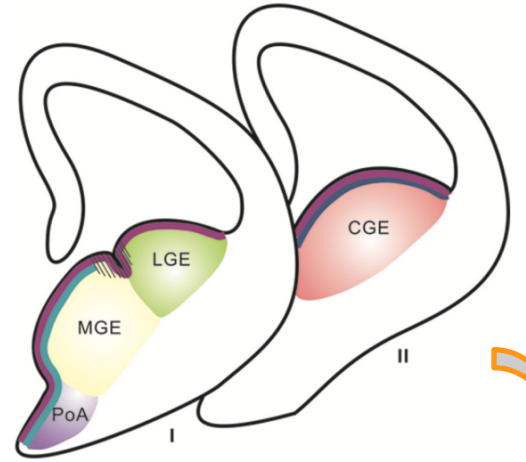
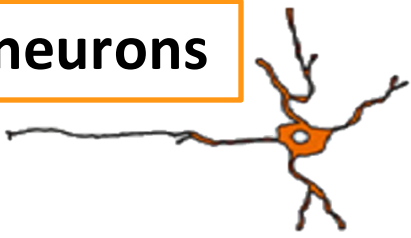




# Introduction



**Interneurons**



Neurological and neuropsychiatric disorders

PV (~40%)	SOM (~30%)	5HT <sub>3A</sub> R (~30%)
<p>Basket cells (FS)      Chandelier cells (FS)</p>	<p>Martinotti cells (NFS, IB)</p>	<p>VIP+ Bipolar cells, Bitufted cells (IS)</p>
	<p>NPY</p>	<p>CR+ Bipolar cells, Double-bouquet cells (AD)</p>
		<p>Reelin+ Neurogliaform cells, Multipolar cells (LS)</p>

- Soma- and proximal dendrite-targeting
- Axon initial segment-targeting
- Dendrite- and tuft-targeting
- Dendrite-targeting



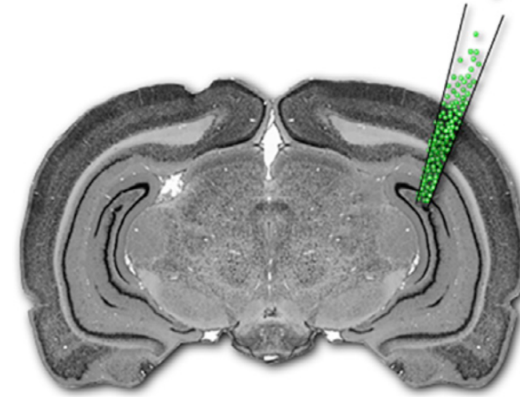


# Aim of the review

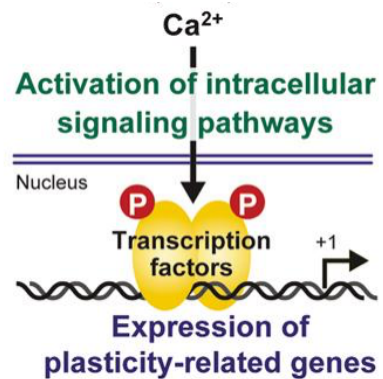
→ Modulation of neuronal plasticity



→ Interneuron grafting



→ Molecular mechanisms



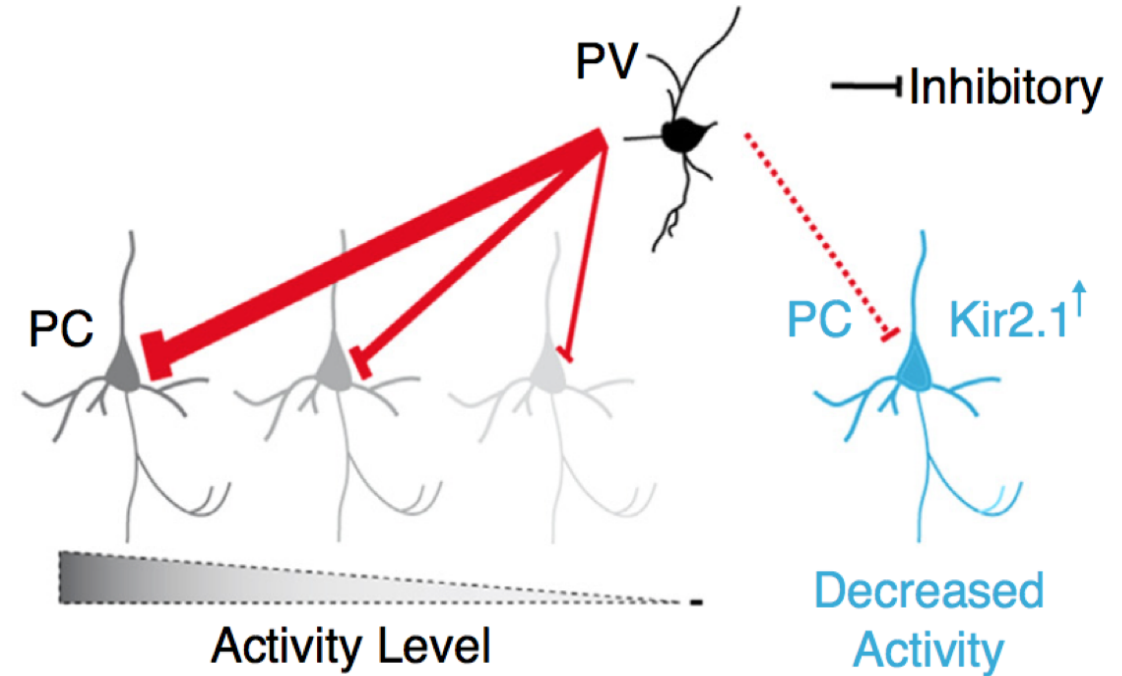
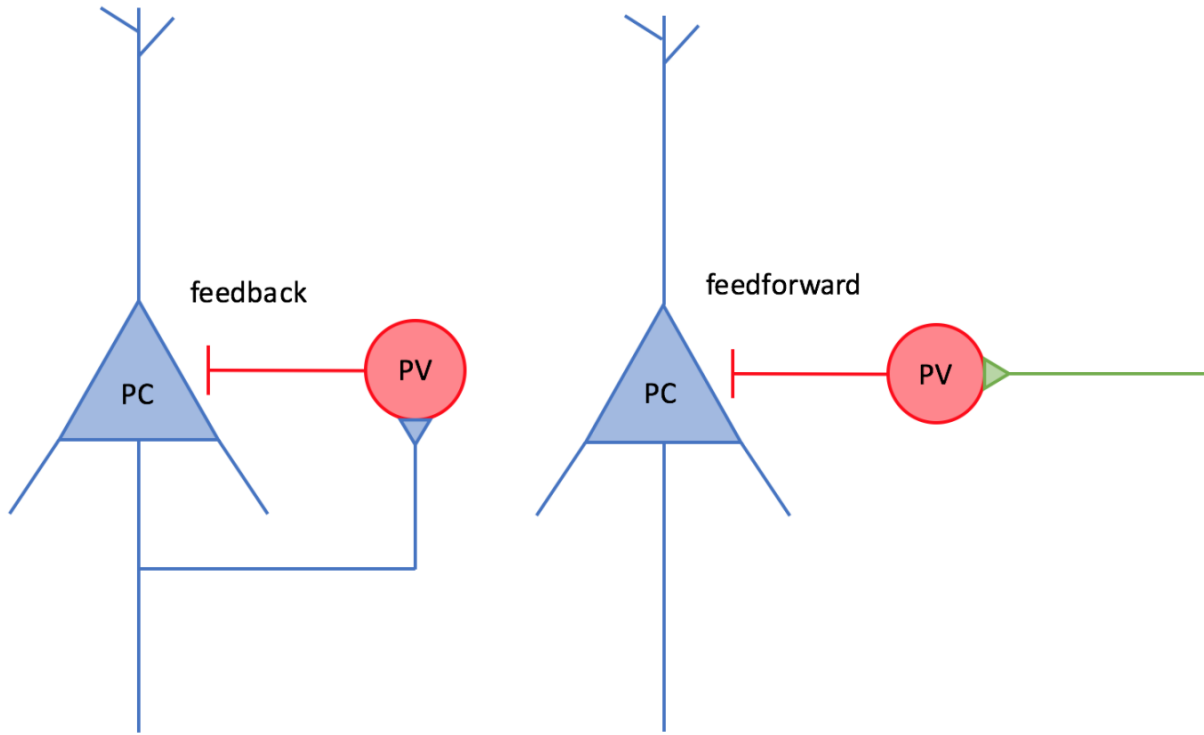
→ Lineage reprogramming *in vivo*



...using TFs cocktails



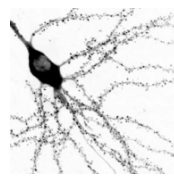
E224G Y242F Kir2.1 *in utero electroporation*



**Equalizing Excitation-Inhibition Ratios across Visual Cortical Neurons**

Mingshan Xue<sup>1</sup>, Bassam V Atallah<sup>2</sup>, and Massimo Scanziani<sup>1,3</sup> 2014

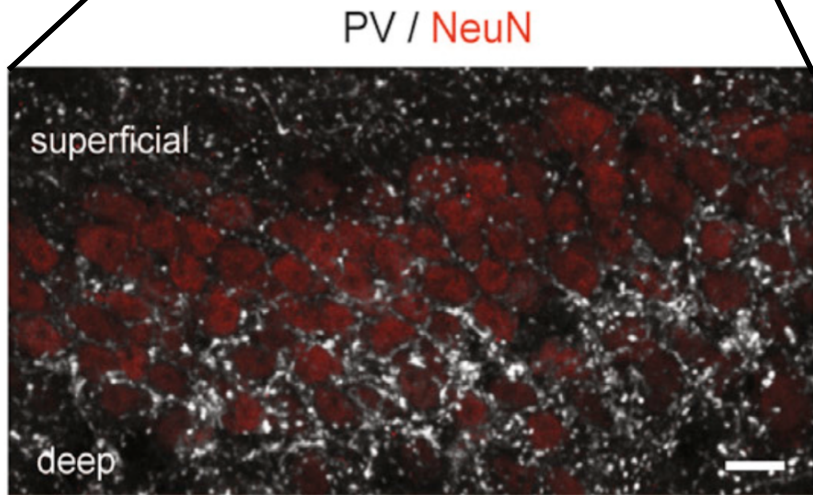
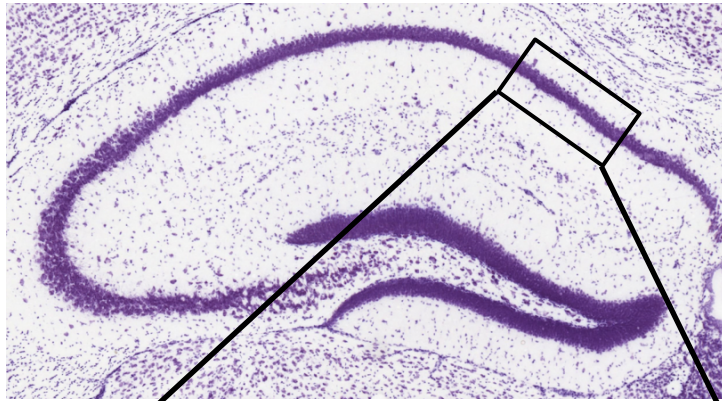
$$\frac{Excitation}{Inhibition} = constant$$



## Early- and Late-Born Parvalbumin Basket Cell Subpopulations Exhibiting Distinct Regulation and Roles in Learning

Flavio Donato,<sup>1,2,3</sup> Ananya Chowdhury,<sup>1,2</sup> Maria Lahr,<sup>1</sup> and Pico Caroni<sup>1,\*</sup>

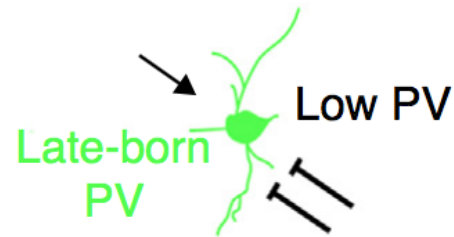
2015



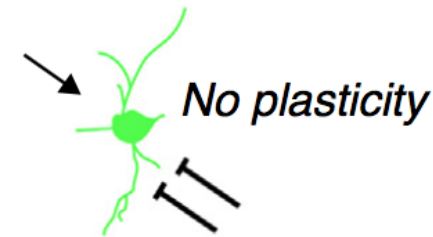
Hippocampal CA1

Scale bar 30µm

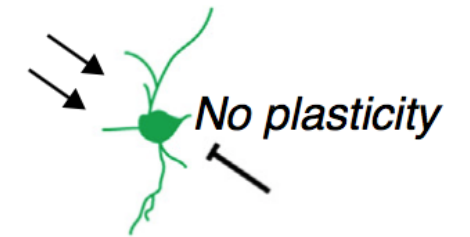
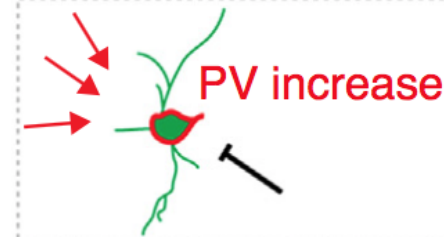
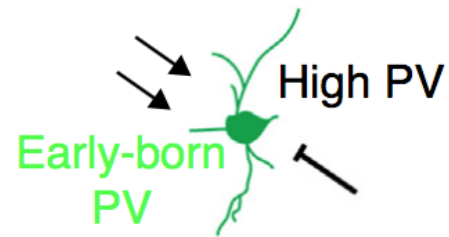
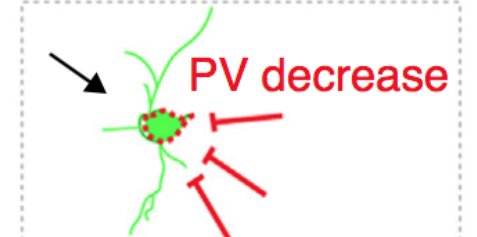
→ Excitatory  
→ Inhibitory



Synaptic excitation



Synaptic inhibition



New information acquisition

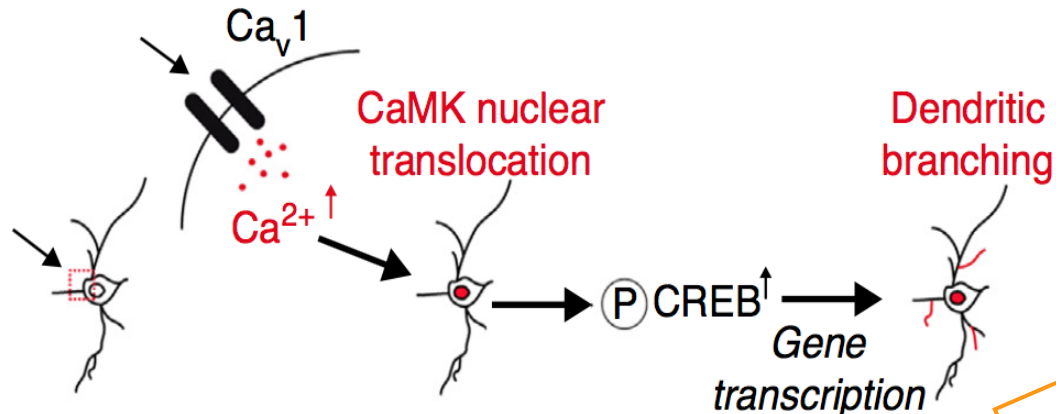
Rule consolidation



# Molecular mechanisms underlying plasticity

## SPECIFIC GENE EXPRESSION PATTERNS

Synaptic excitation



*Pvalb, Gad1, Er81*

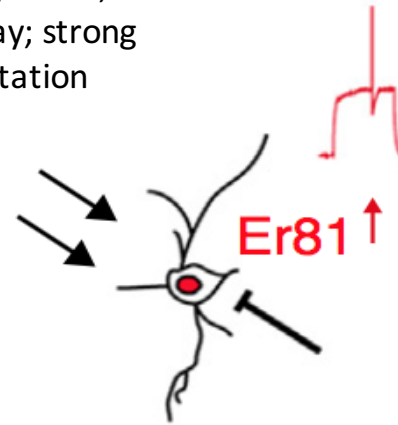
## Tuning of fast-spiking interneuron properties by an activity-dependent transcriptional switch

2016

Nathalie Dehorter,<sup>1,2</sup> Gabriele Cicceri,<sup>2\*</sup> Giorgia Bartolini,<sup>1,2</sup> Lynette Lim,<sup>1,2</sup> Isabel del Pino,<sup>1,2†</sup> Oscar Marín<sup>1,2‡</sup>



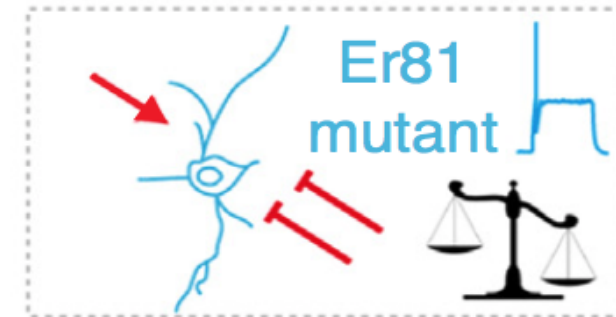
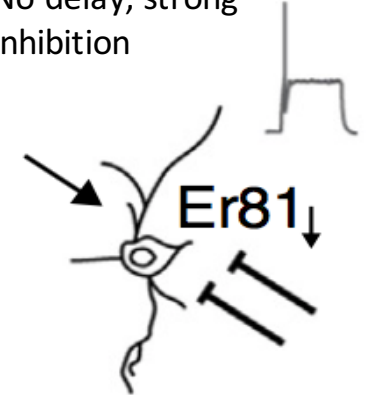
PV+/Er81+;  
Delay; strong excitation



PV+/Er81-;  
No delay; strong inhibition



- ↔ +  
Activity



Activity-induced transcriptional response

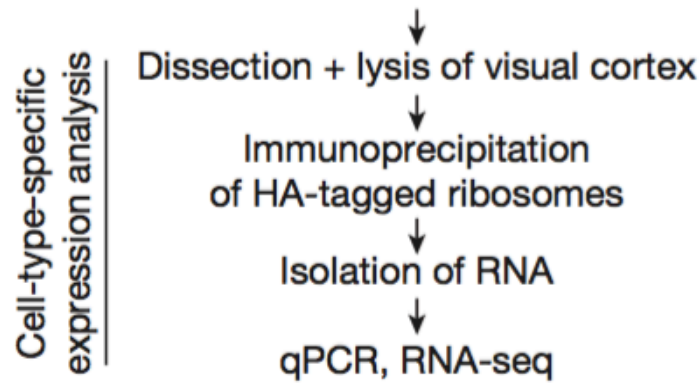
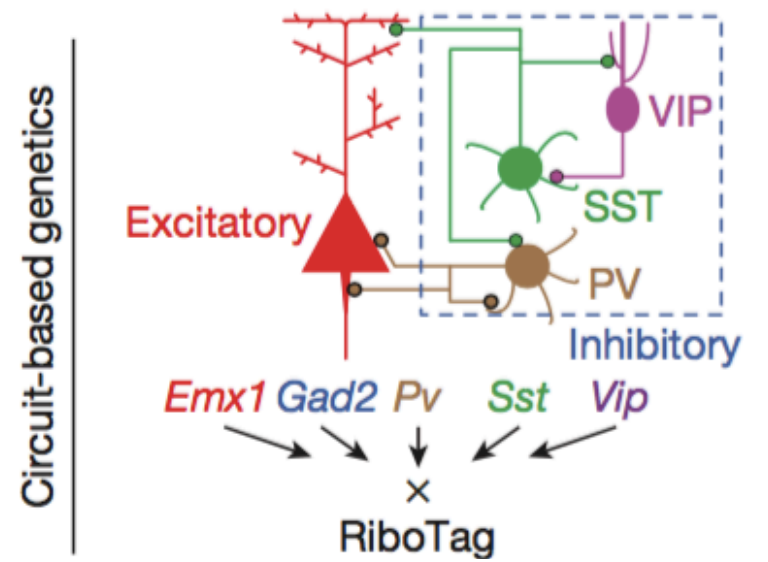


# Sensory experience regulates cortical inhibition by inducing IGF1 in VIP neurons

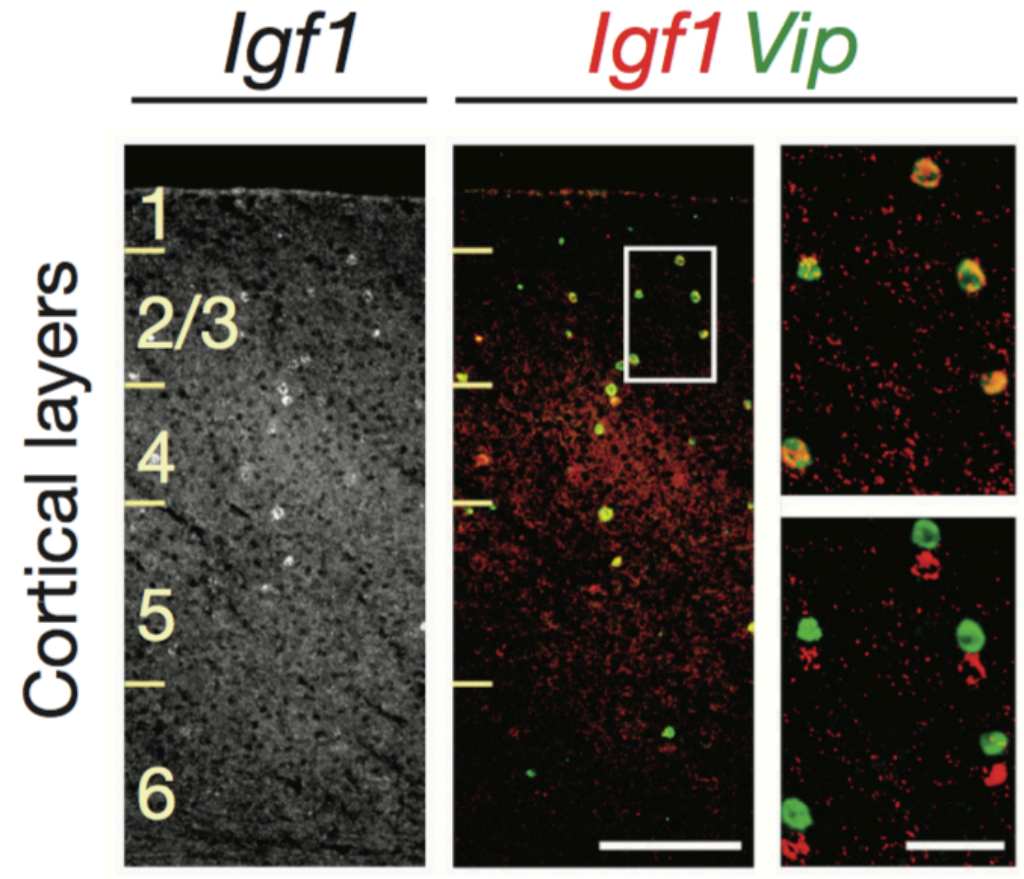
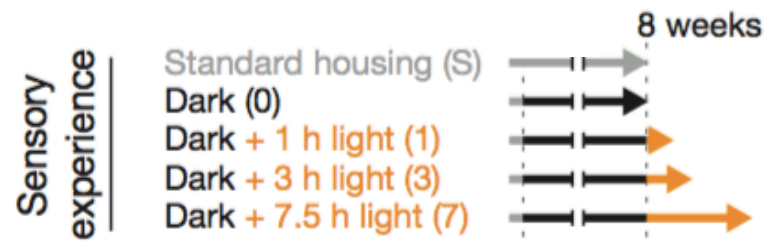
2016

A. R. Mardinly<sup>1\*</sup>, I. Spiegel<sup>2\*</sup>, A. Patrizi<sup>3</sup>, E. Centofante<sup>3</sup>, J. E. Bazinet<sup>2</sup>, C. P. Tzeng<sup>2</sup>, C. Mandel-Brehm<sup>2</sup>, D. A. Harmin<sup>2</sup>, H. Adesnik<sup>1</sup>, M. Fagiolini<sup>3</sup> & M. E. Greenberg<sup>2</sup>

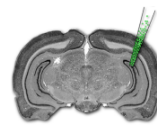
IGF1 enhances inhibitory inputs



High expression of sensory experience-regulated genes in VIP+ neurons



expression of *Igf1* in VIP+ neurons



## NEW FIELD

### *Cell Based Therapy*

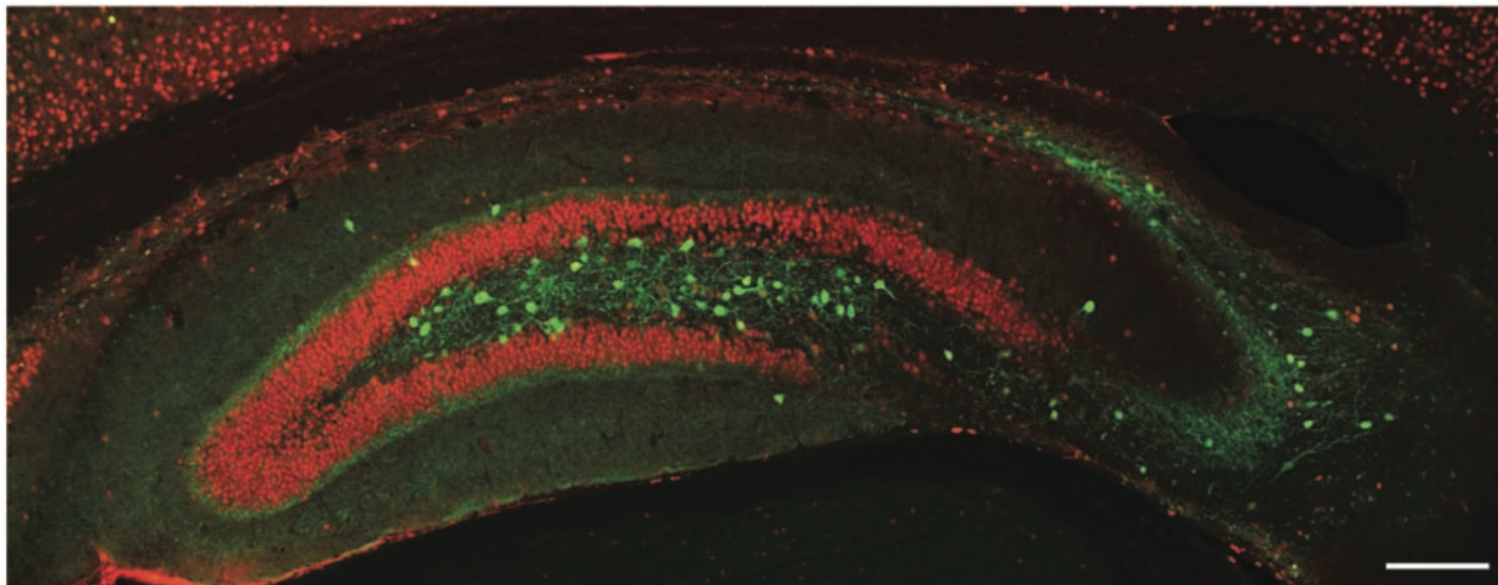


## GABA progenitors grafted into the adult epileptic brain control seizures and abnormal behavior

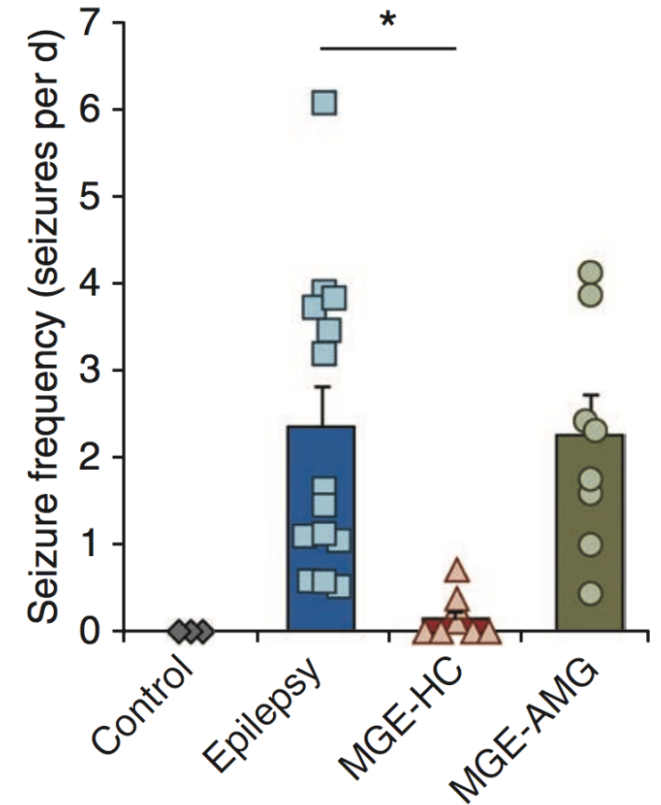
Robert F Hunt<sup>1,2</sup>, Kelly M Girsakis<sup>1,2</sup>, John L Rubenstein<sup>3</sup>, Arturo Alvarez-Buylla<sup>2</sup> & Scott C Baraban<sup>1,2</sup> 2013

**!** Functional consequences of interneurons addition to neuronal circuits

GFP NeuN



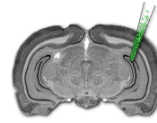
Scale bar 1,000 μm







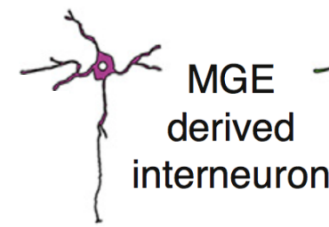
# Consequences of interneuron grafting



## Inhibitory Neuron Transplantation into Adult Visual Cortex Creates a New Critical Period that Rescues Impaired Vision

2015

Melissa F. Davis,<sup>1</sup> Dario X. Figueroa Velez,<sup>1</sup> Roblen P. Guevarra,<sup>1</sup> Michael C. Yang,<sup>1</sup> Mariyam Habeeb,<sup>1</sup> Mathew C. Carathedathu,<sup>1</sup> and Sunil P. Gandhi<sup>1,\*</sup>



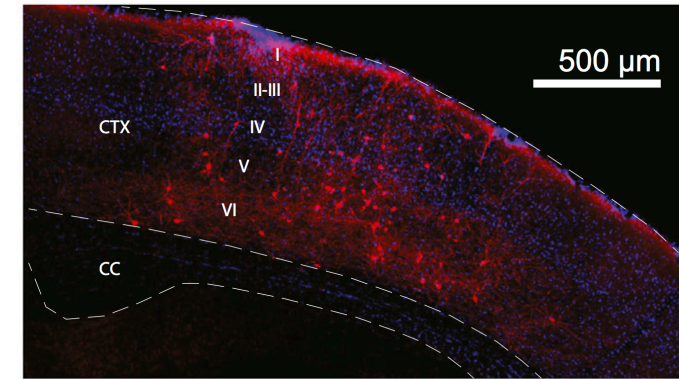
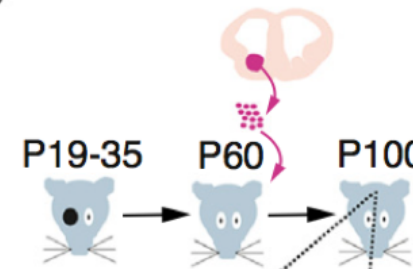
MGE derived interneuron



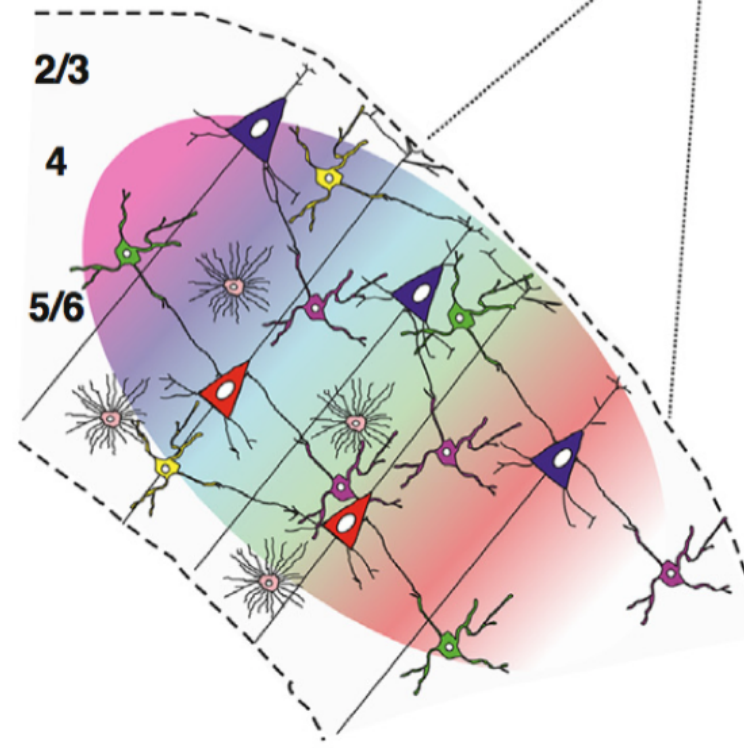
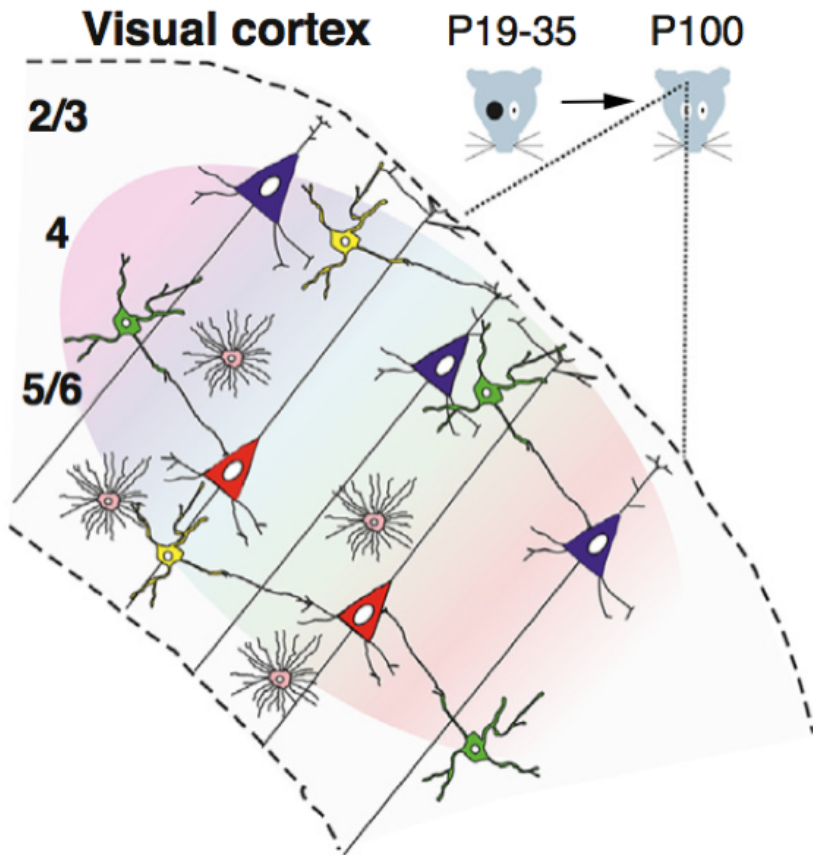
PV+interneuron



SST+interneuron



VGAT (vesicular GABA transporter)



### Other Interesting Studies:

*hESCs* → *MGE-like precursors*

When grafted in mouse correctly differentiate into PV+ and SST+

Also graft in injured mouse spinal cord lead to relieve of symptoms

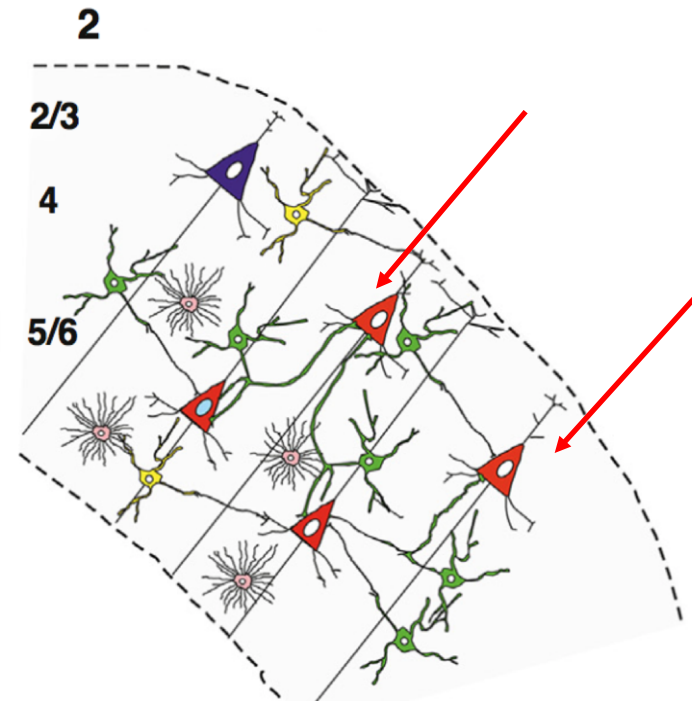
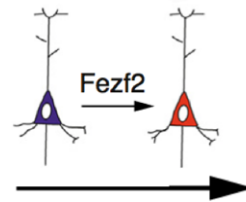
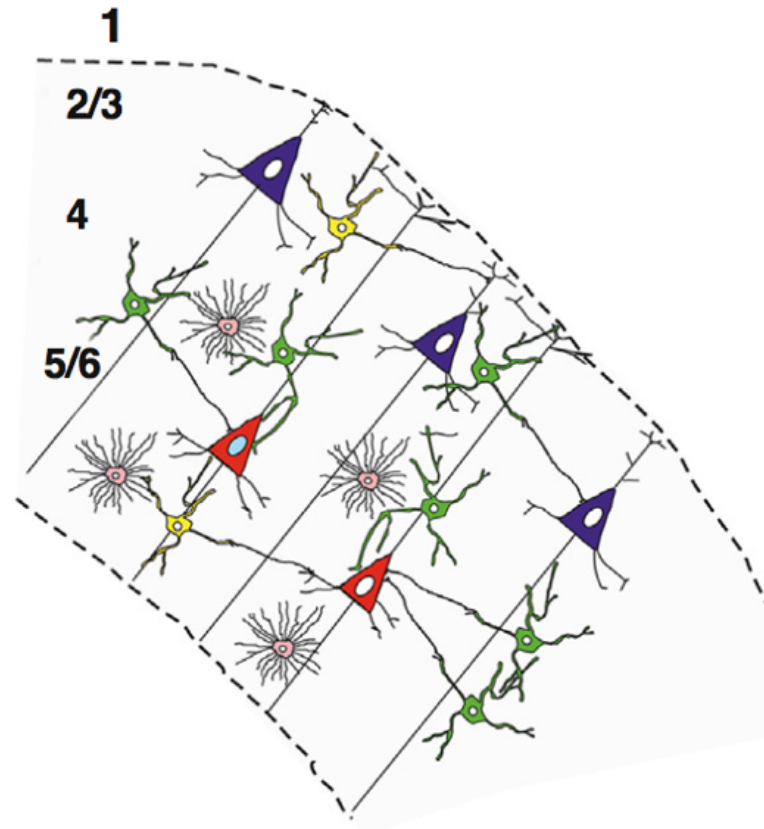
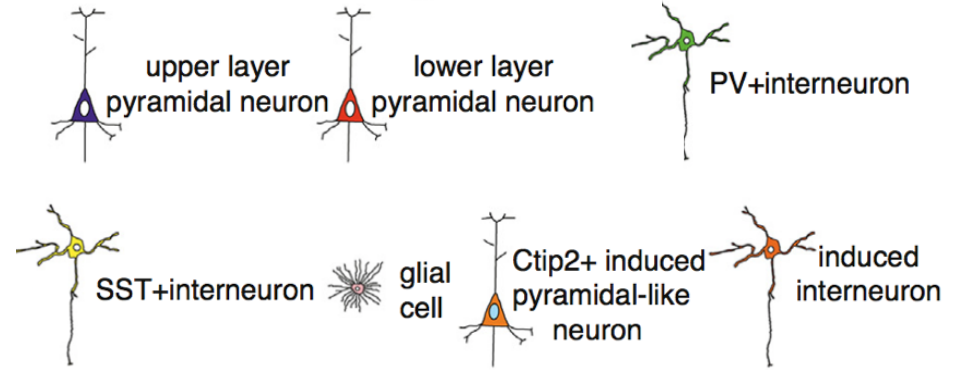


# Inhibitory circuits remodelling by lineage reprogramming



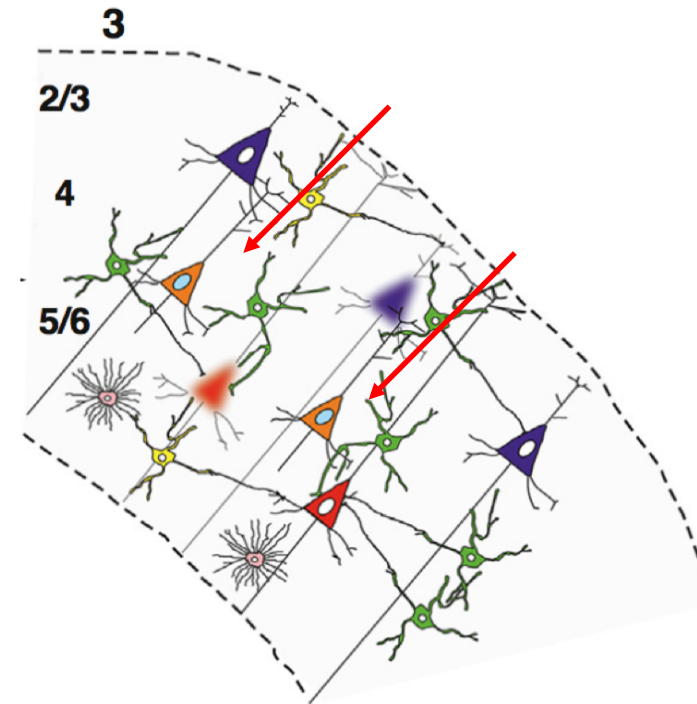
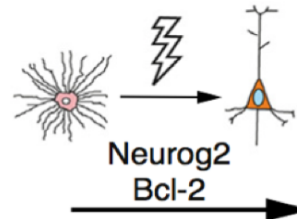
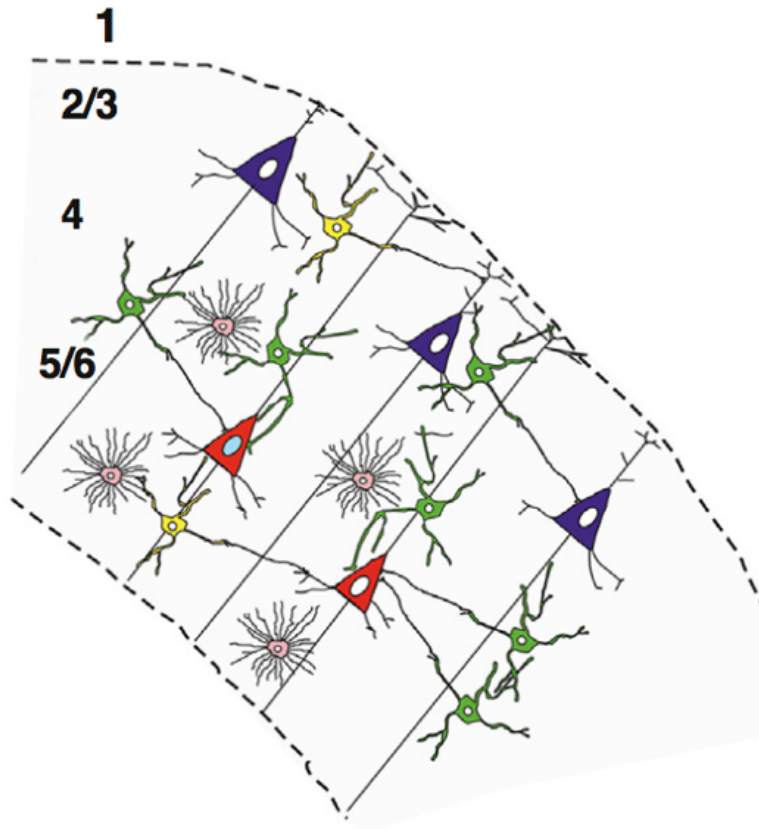
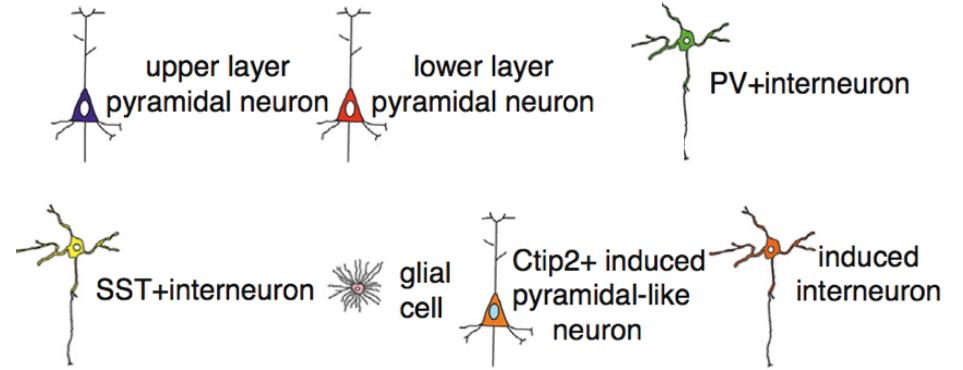
## Instructing Perisomatic Inhibition by Direct Lineage Reprogramming of Neocortical Projection Neurons 2015

Zhanlei Ye,<sup>1,2,5</sup> Mohammed A. Mostajo-Radji,<sup>1,3,5</sup> Juliana R. Brown,<sup>3</sup> Caroline Rouaux,<sup>3,4</sup> Takao K. Hensch,<sup>1,2,\*</sup> and Paola Arlotta<sup>3,\*</sup>



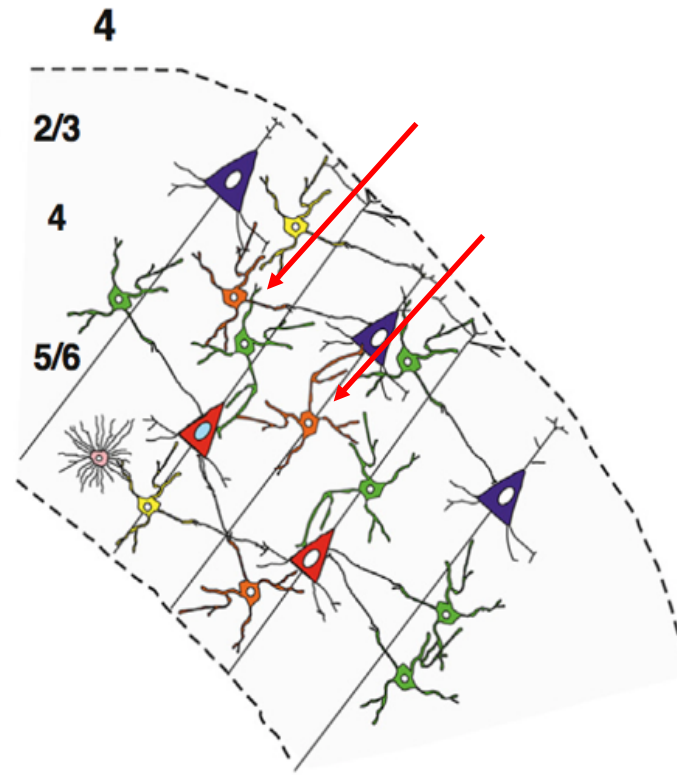
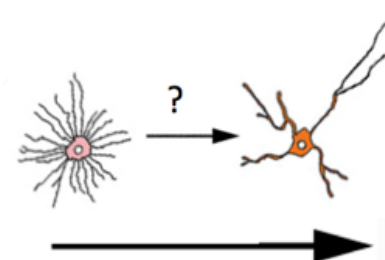
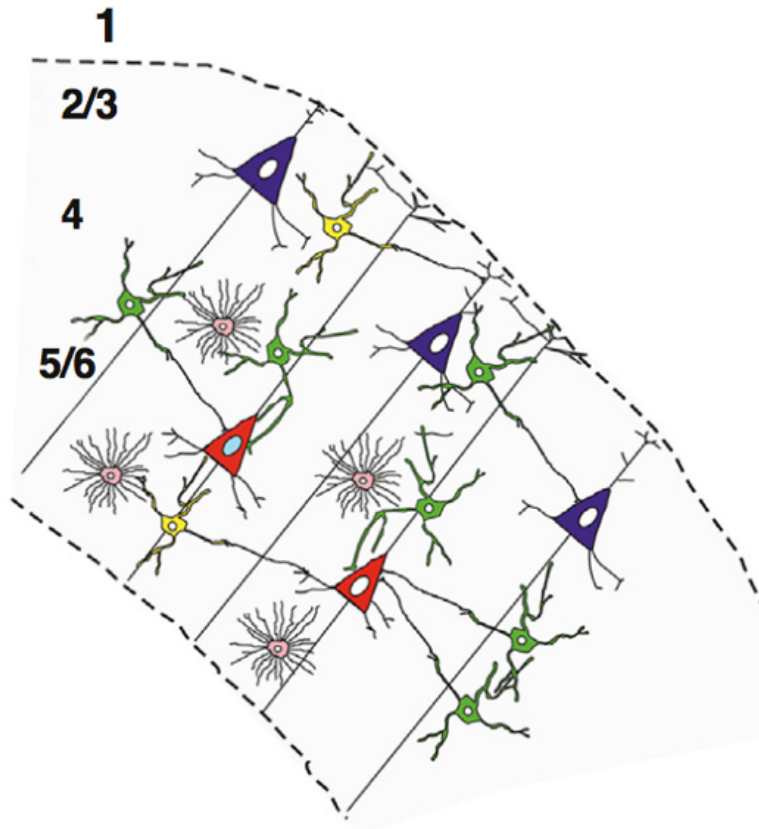
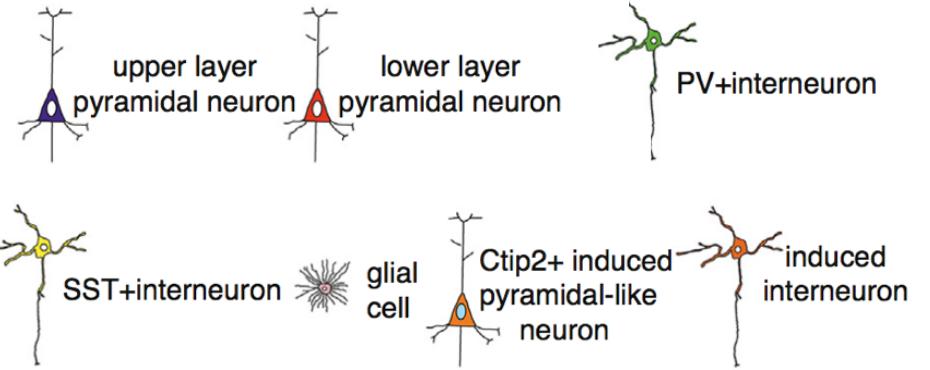


# Inhibitory circuits remodelling by lineage reprogramming





# Inhibitory circuits remodelling by lineage reprogramming





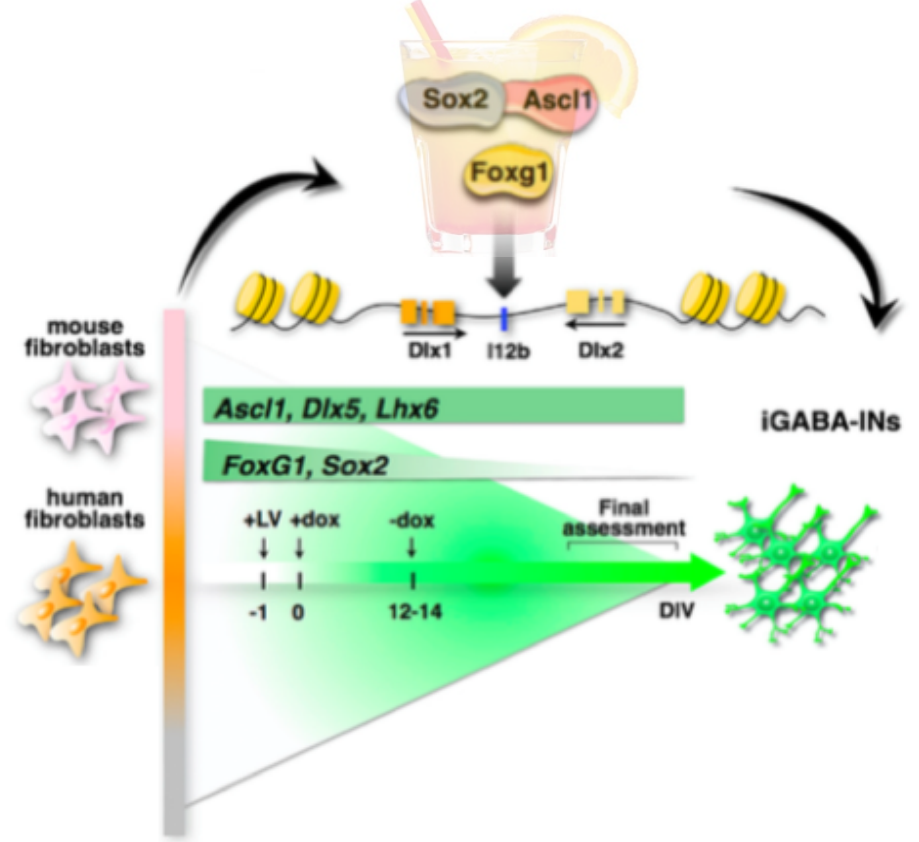
# Inhibitory circuits remodelling by lineage reprogramming



## Rapid Conversion of Fibroblasts into Functional Forebrain GABAergic Interneurons by Direct Genetic Reprogramming

Gaia Colasante,<sup>1</sup> Gabriele Lignani,<sup>2,9</sup> Alicia Rubio,<sup>1</sup> Lucian Medrihan,<sup>2,10</sup> Latefa Yekhlief,<sup>2,3</sup> Alessandro Sessa,<sup>1</sup> Luca Massimino,<sup>1</sup> Serena G. Giannelli,<sup>1</sup> Silvio Sacchetti,<sup>2</sup> Massimiliano Caiazzo,<sup>1,11</sup> Damiana Leo,<sup>2</sup> Dimitra Alexopoulou,<sup>4</sup> Maria Teresa Dell'Anno,<sup>1,12</sup> Ernesto Ciabatti,<sup>1,13</sup> Marta Orlando,<sup>2</sup> Michele Studer,<sup>5,6</sup> Andreas Dahl,<sup>4</sup> Raul R. Gainetdinov,<sup>2,7</sup> Stefano Taverna,<sup>2,3</sup> Fabio Benfenati,<sup>2</sup> and Vania Broccoli<sup>1,8,\*</sup>

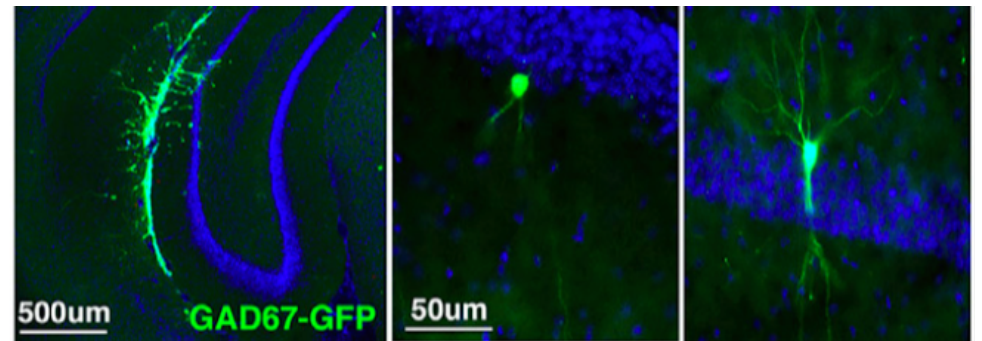
2015



Functional GABAergic-inhibitory behaviour



light stimulation of iGABA-INs



# 🎯 Conclusions and perspectives ✈️



## PV+ basket cells:

- Different types of memory
- E/I balance



## Molecular dynamics:

- Activity-induced transcriptional responses underlie plasticity

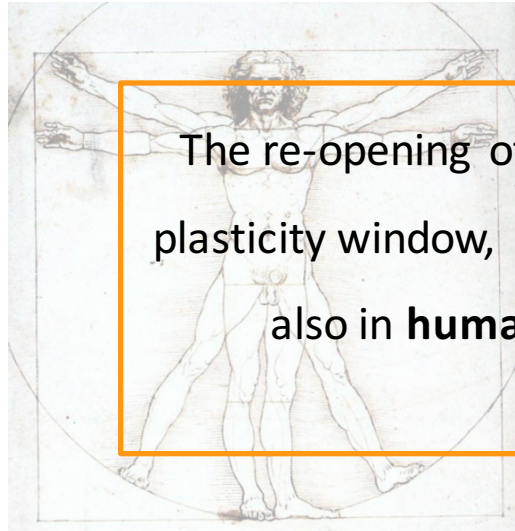
Role of neural activity in the specification of neuronal fate



## Interneuron grafting & Lineage reprogramming

- Therapeutic approach for the treatment of **neurological** and **neuropsychiatric diseases**

## 🎯 Conclusions and perspectives ✈️



The re-opening of cortical plasticity window, is possible also in **humans**?

What is the **right cocktail** of TFs for the interneurons conversion starting from glial cells?



*Thank you all!*

