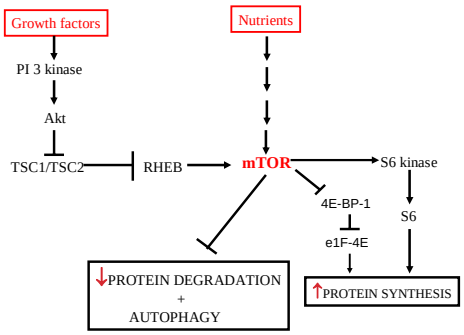
A current model for the role of mTOR in cell growth control



Cell number control

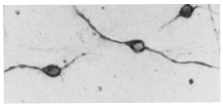
1. Cell division
2. Cell death

Oligodendrocytes and their precursors

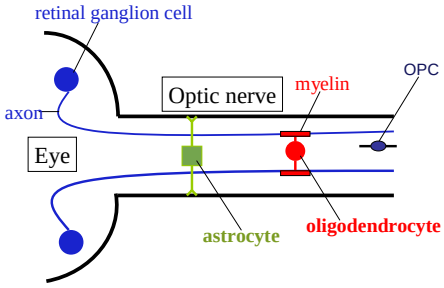
oligodendrocyte

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

oligodendrocyte precursor cells (OPCs)



Cells of the optic nerve

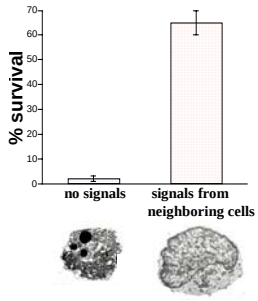


What determines the final number of oligodendrocytes in the adult rat optic nerve?

1. Number of OPCs that migrate into nerve
2. Amount of cell death in lineage
3. Number of OPC divisions before differentiation

Control of cell survival and death in the oligodendrocyte cell lineage

Single OPCs die by apoptosis after one day in culture without signals

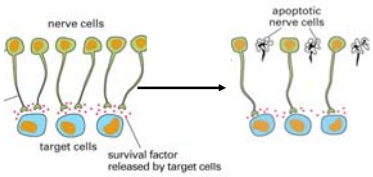


Ian Hart

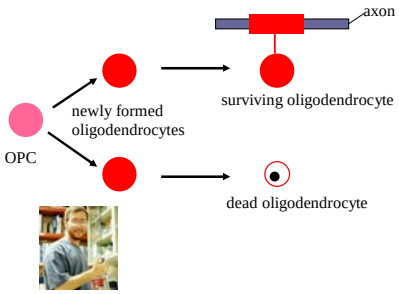
Most cells animal cells die by apoptosis if deprived of signals from their neighbors

This "death by default" mechanism ensures that animal cells survive only where and when they are needed

"Death by default" helps regulate cell numbers: the neurotrophic hypothesis



Model for how "death by default" helps regulate oligodendrocyte numbers in the optic nerve

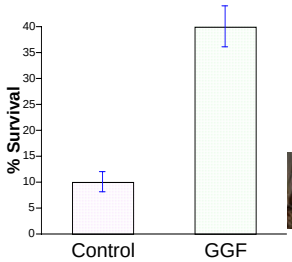


Ben Barres

Tests of the model

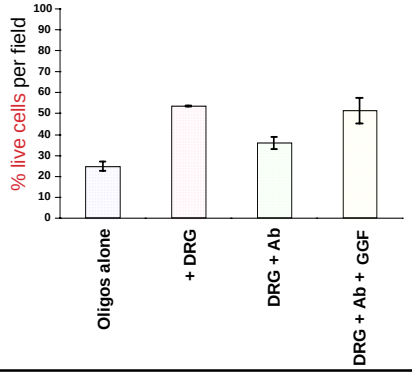
1. Decrease axons (Ben Barres) 
2. Increase axons (Julia Burne) 
3. Increase oligodendrocyte production (Bill Richardson) 
4. Decrease oligodendrocyte production (Charles ffrench-Constant) 

The neuregulin GGF promotes the survival of oligodendrocytes in vitro

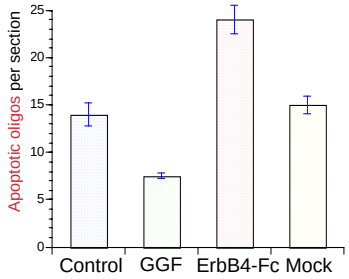


Pierre-Alain Fernandez

Neurons use GGF to promote oligodendrocyte survival *in vitro*

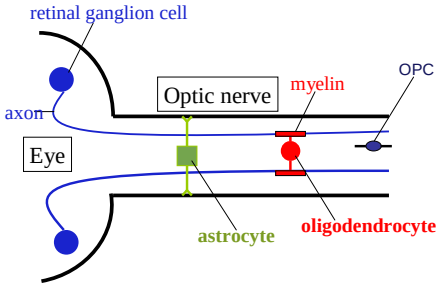


Transplanting transfected COS-7 cells into the brain to show that GGF is required for oligodendrocyte survival *in vivo*



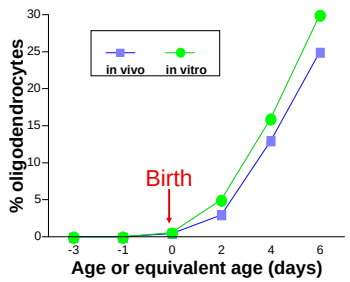
Control of *OPC* proliferation

Cells of the optic nerve

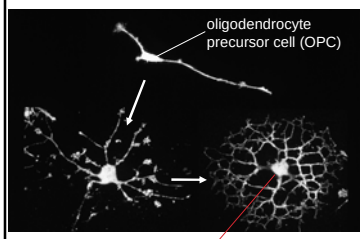


Why do OPCs stop dividing and differentiate?

OPCs differentiate on schedule in dissociated-cell cultures of embryonic rat optic nerve



Purified postnatal day 7 (P7) OPCs proliferate and differentiate in serum-free culture in PDGF

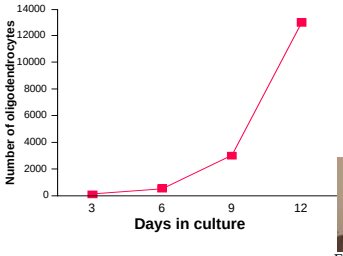


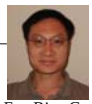
Ben Barres

Purified P7 OPCs migrate, proliferate, and differentiate in serum-free culture with PDGF

Nathalie Billon

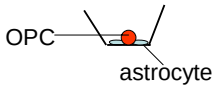
Purified embryonic day 18 (E18) OPCs differentiate on schedule in serum-free culture in PDGF





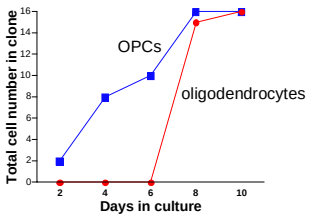
Fen-Biao Gao

A single OPC proliferates and differentiates on an astrocyte monolayer



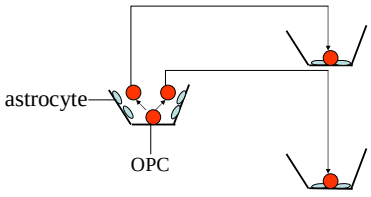
Sally Temple

The progeny cells of a single P7 OPC stop dividing and differentiate at the same time

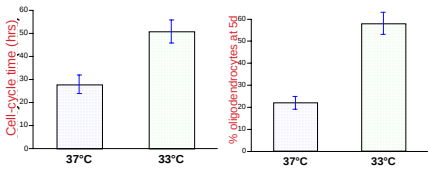


Sally Temple

Sibling OPCs behave similarly even when cultured on separate monolayers

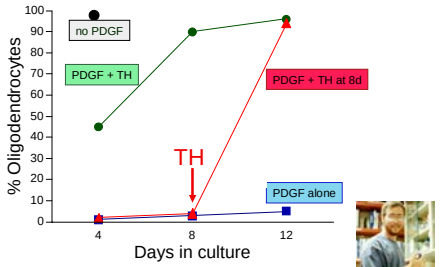


OPCs divide more slowly but differentiate sooner at 33°C than at 37°C



Fen-Biao Gao

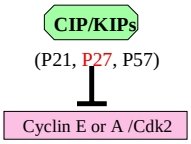
PDGF and thyroid hormone (TH) are required for the cell-intrinsic timer to operate normally



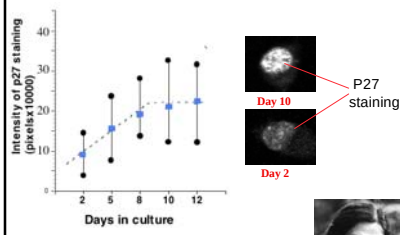
Ben Barres

What is the molecular mechanism underlying the cell-intrinsic timer in OPCs?

The Cip/Kip family of cyclin-dependent protein kinase inhibitors

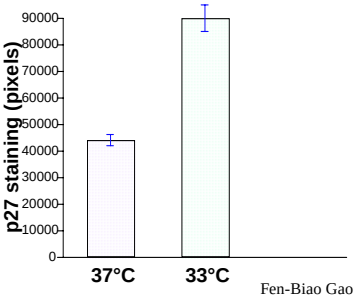


p27 increases as purified OPCs proliferate in culture in PDGF without TH



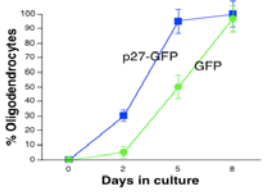
Béa Durand

p27 protein increases faster at 33°C than at 37°C



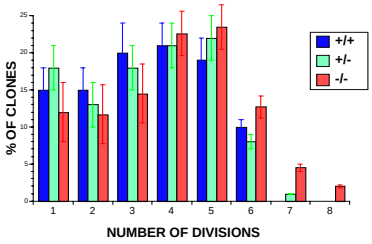
Fen-Biao Gao

P27 over-expression accelerates P7 OPC differentiation in presence of PDGF and TH



Jim Apperly

P27 deficiency delays P7 OPC differentiation in PDGF and TH

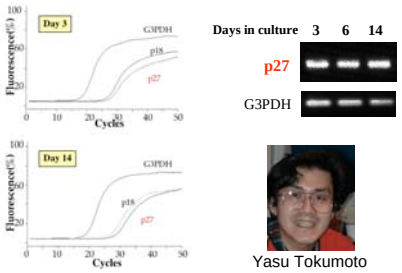


Béa Durand and Jim Roberts

p27 probably has a similar role in many cell lineages and animals

1. p27-/- mice are about 30% larger than normal
2. p27 homologs in worms and flies

p27 mRNA does not increase in OPCs over time

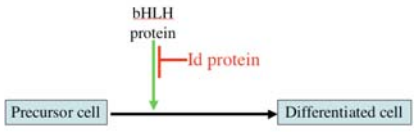


Yasu Tokumoto

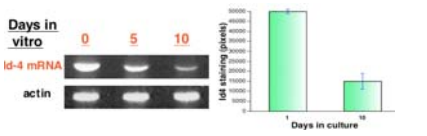
p57 is also a component of the timer

Jason Dugan

Id proteins inhibit differentiation and promote proliferation by inhibiting bHLH proteins

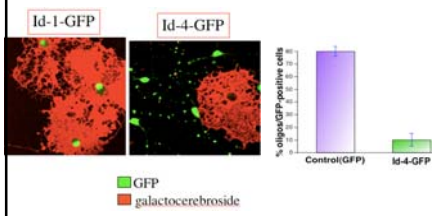


Id-4 mRNA and protein decrease as purified P7 rat OPCs proliferate in culture

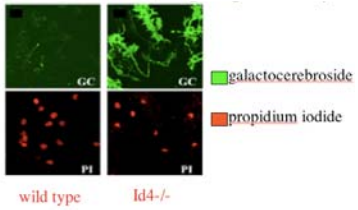


Toru Kondo

Over-expression of Id-4 inhibits OPC differentiation induced by PDGF withdrawal

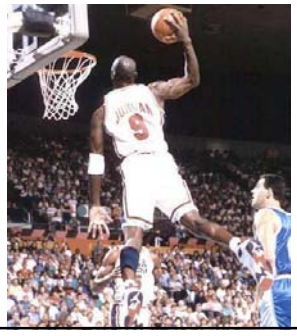


Accelerated oligodendrocyte development when embryonic Id4-/- brain neural stem cells are cultured in TH and sonic hedgehog for 3 days

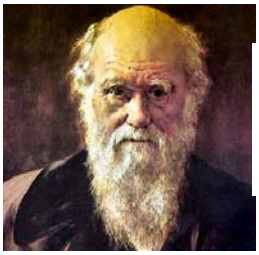


Toru Kondo
Fred Zablitsky

So, why do humans grow to be so much larger than mice?



Why do most of us not look like mice?



THANKS TO....

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Ian Hart
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Sally Temple
Yasu Tokumoto