

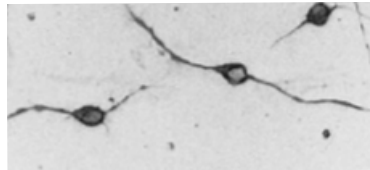
Cell number control

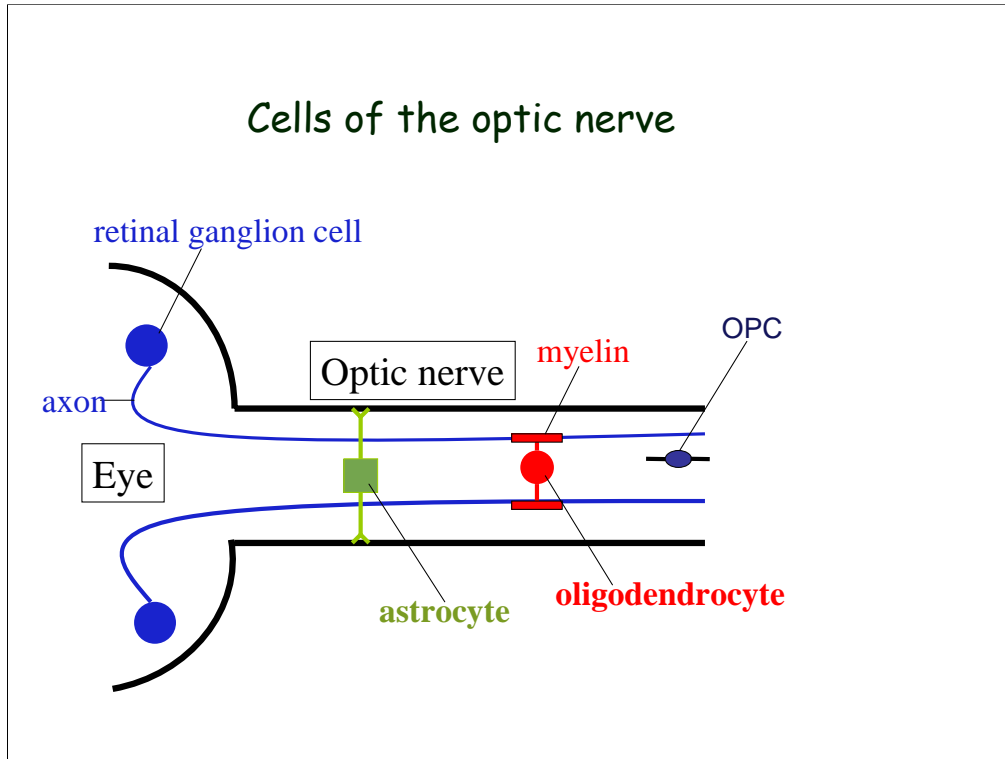
1. Cell division
2. Cell death

Oligodendrocytes and their precursors

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

oligodendrocyte
precursor cells
(OPCs)



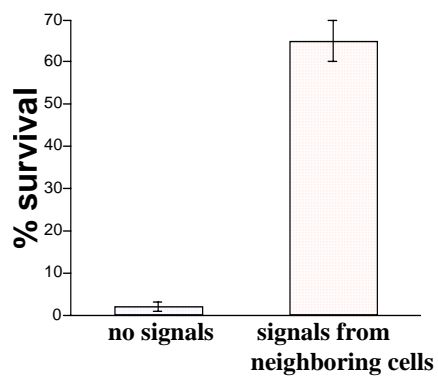


What determines the final number
of oligodendrocytes in the adult rat
optic nerve?

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

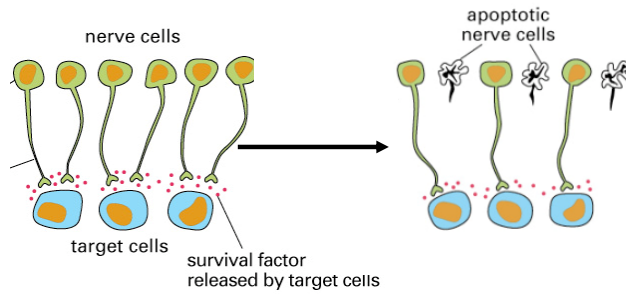


Ian Hart

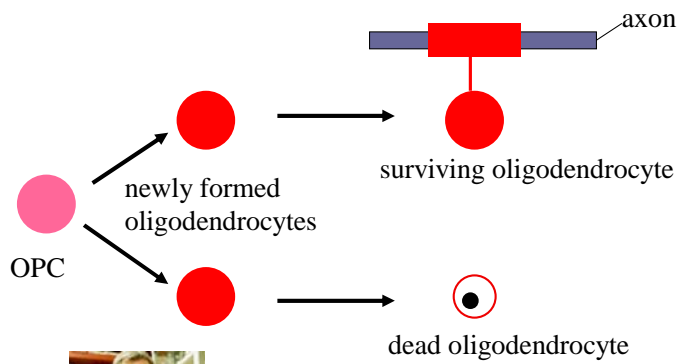
Most animal cells die by
apoptosis if deprived of signals
from their neighbors

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)



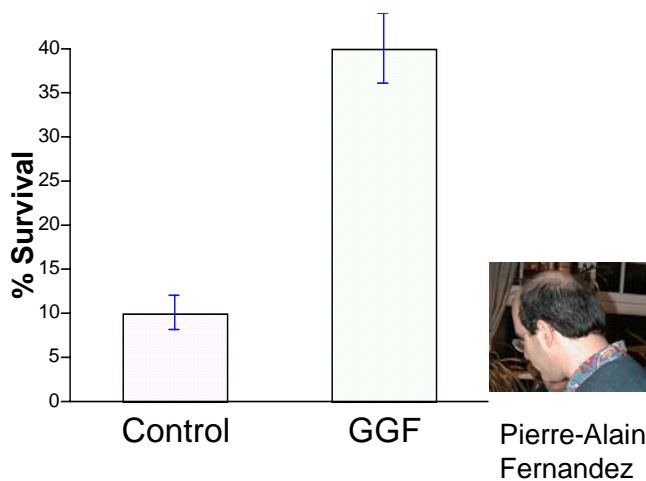
3. Increase oligodendrocyte production (Bill Richardson)

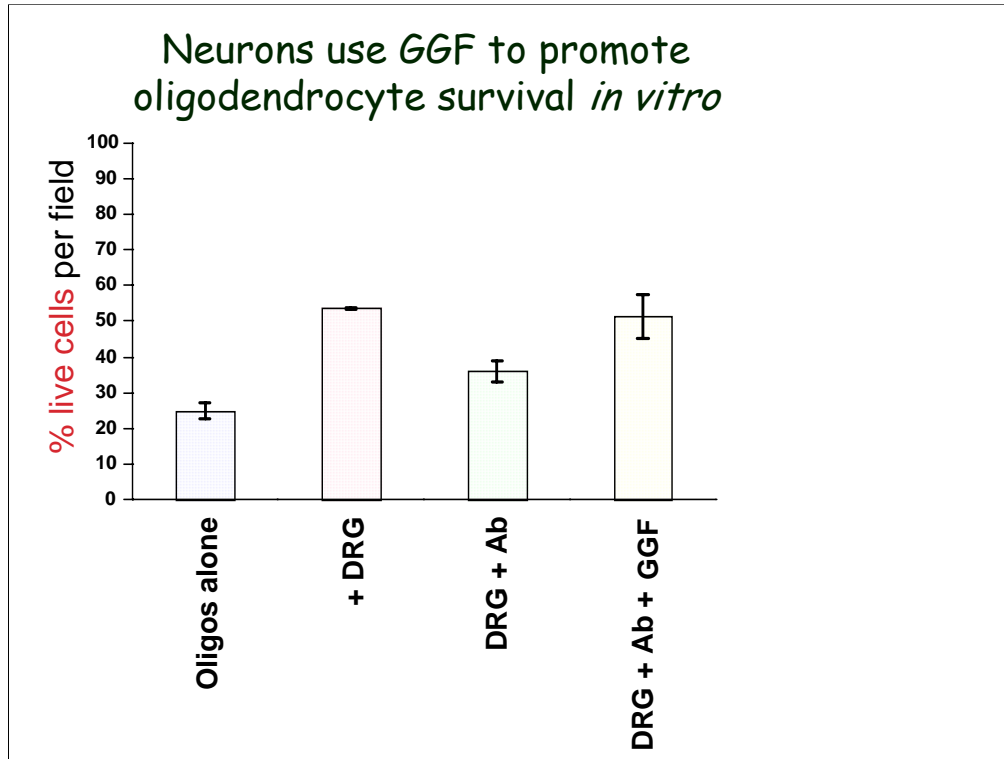


4. Decrease oligodendrocyte production (Charles French-Constant)

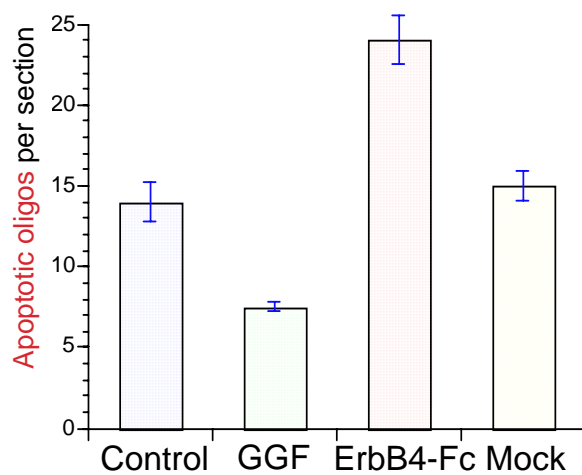


The neuregulin GGF promotes the survival of oligodendrocytes in vitro

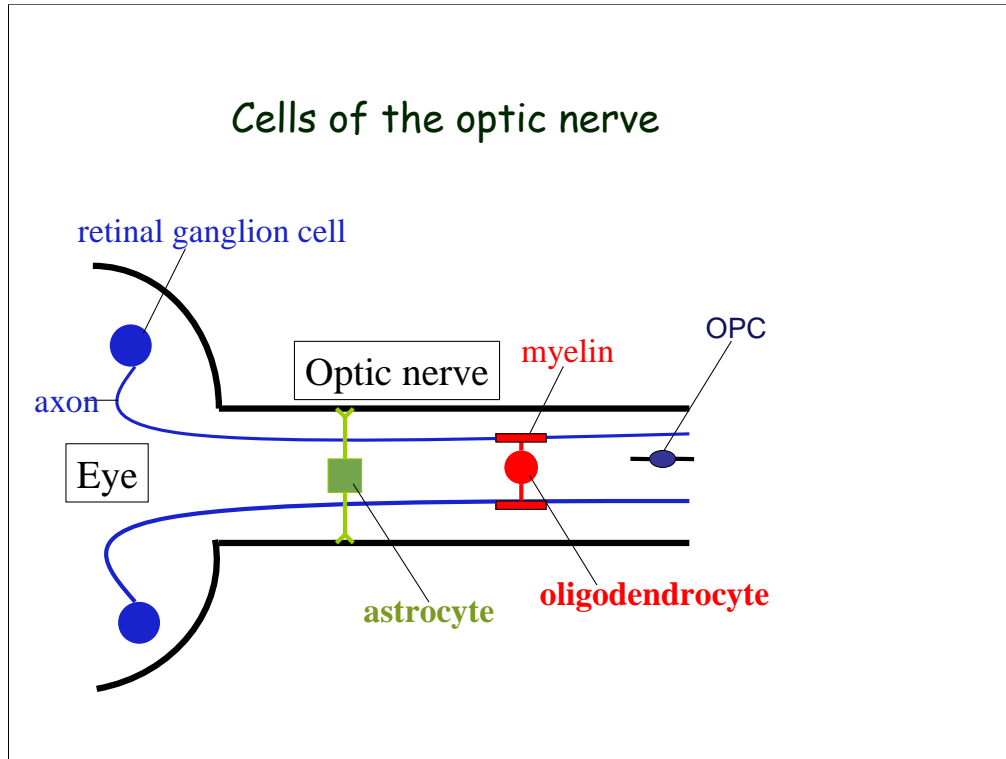




Transplanting transfected *COS-7* cells into the brain to show that *GGF* is required for oligodendrocyte survival *in vivo*

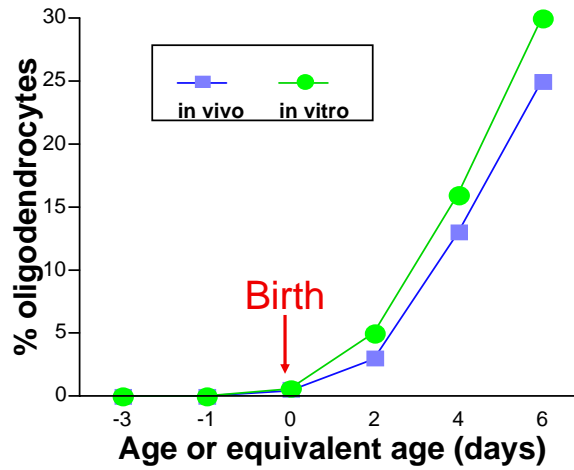


Control of *OPC* proliferation

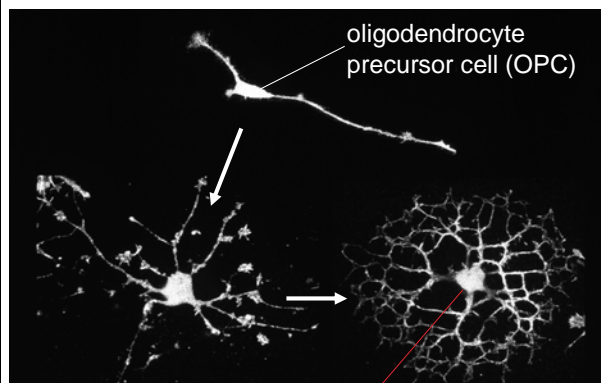


Why do OPCs stop dividing and
differentiate?

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



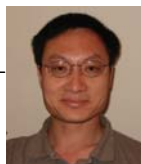
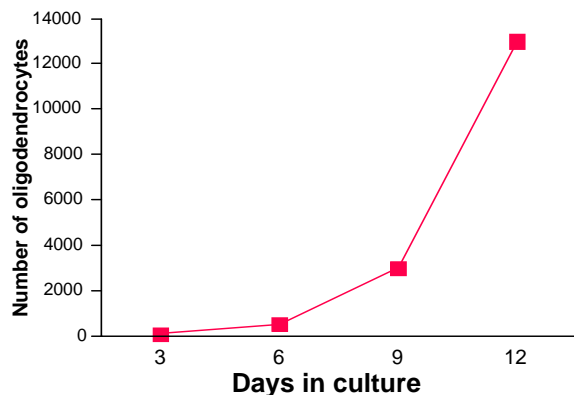
Ben Barres

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



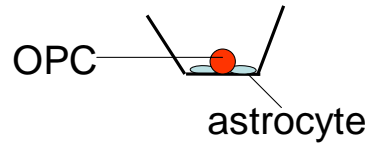
Nathalie Billon

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



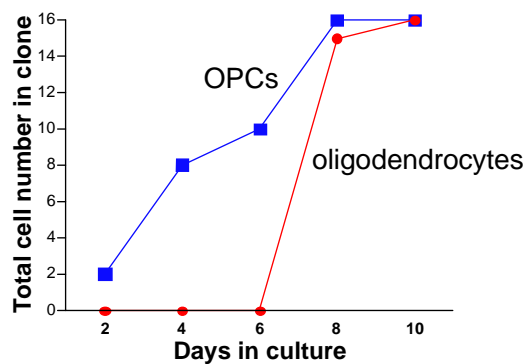
Fen-Biao Gao

A *single OPC* proliferates and
differentiates on an astrocyte
monolayer



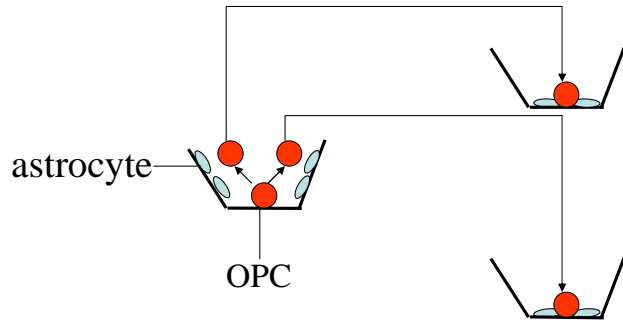
Sally Temple

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

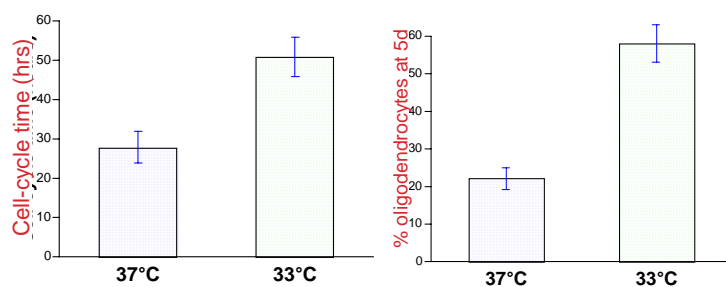


Sally Temple

Sibling OPCs behave similarly even
when cultured on separate
monolayers

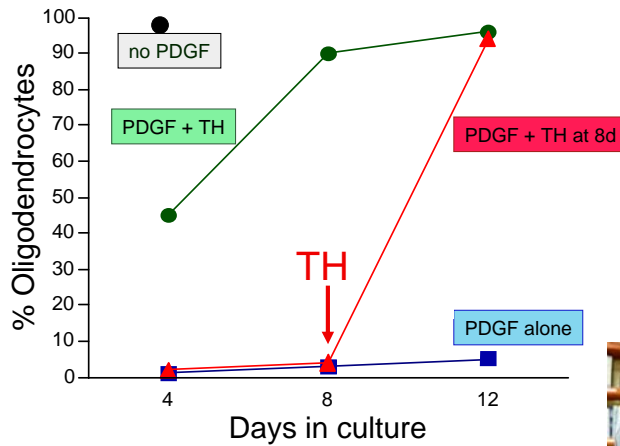


OPCs divide more slowly but
differentiate sooner at 33°C than
at 37°C



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

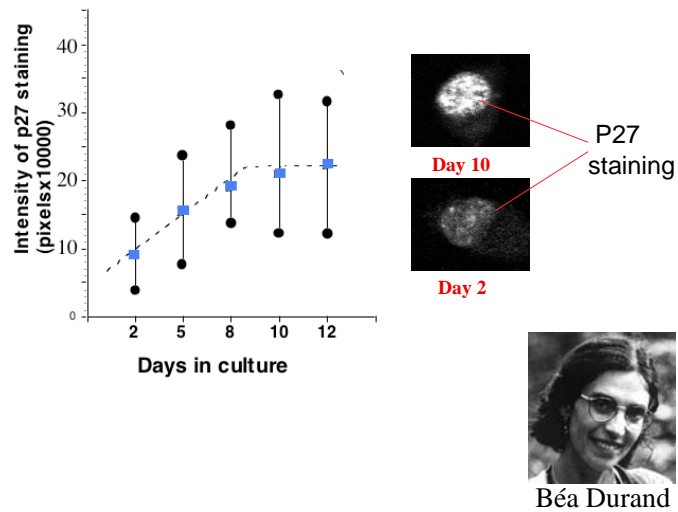
CIP/KIPs

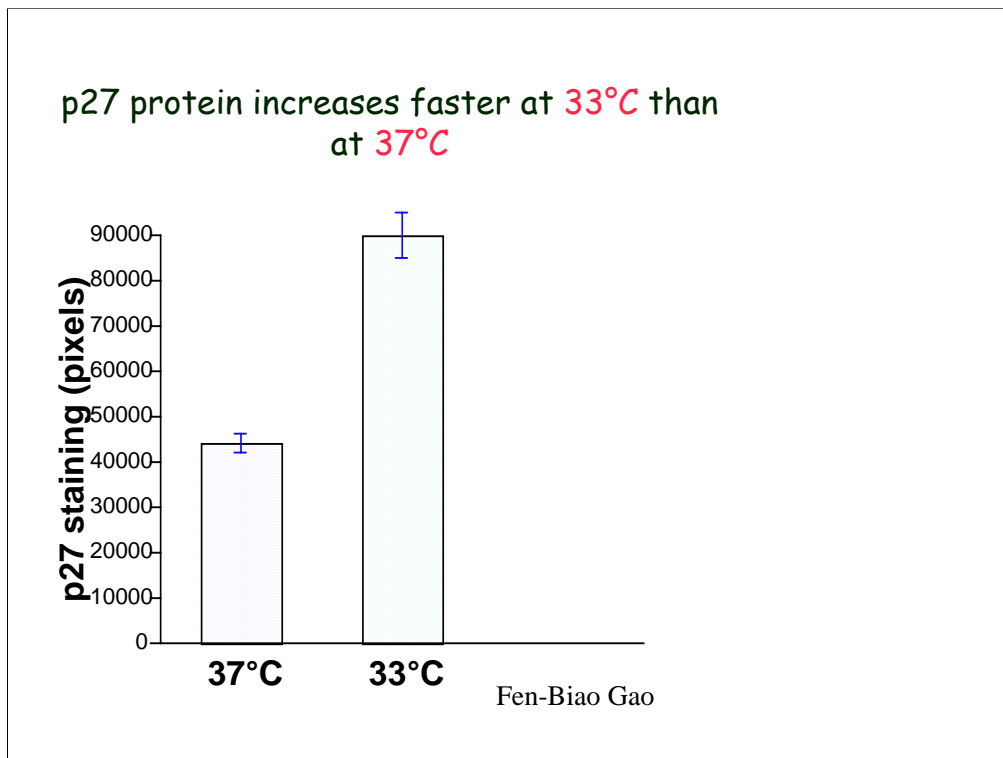
(P21, P27, P57)



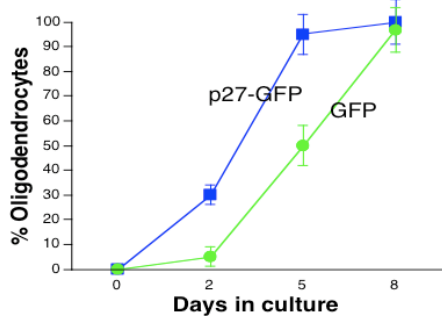
Cyclin E or A /Cdk2

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



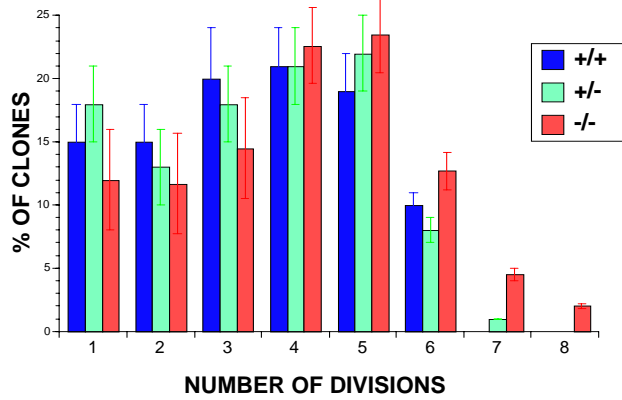


**P27 over-expression accelerates P7
OPC differentiation in presence of
PDGF and TH**



Jim Apperly

**P27 deficiency delays P7 OPC
differentiation in PDGF and TH**

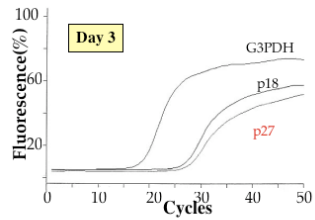


Béa Durand
and Jim Roberts

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

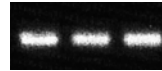
1. p27^{-/-} mice are about 30% larger
than normal
2. p27 homologs in worms and flies

p27 mRNA does not increase in OPCs over time

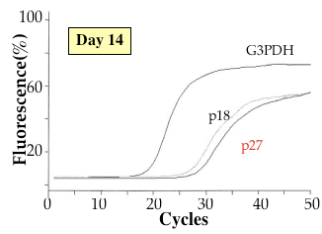
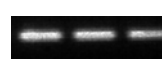


Days in culture 3 6 14

p27



G3PDH



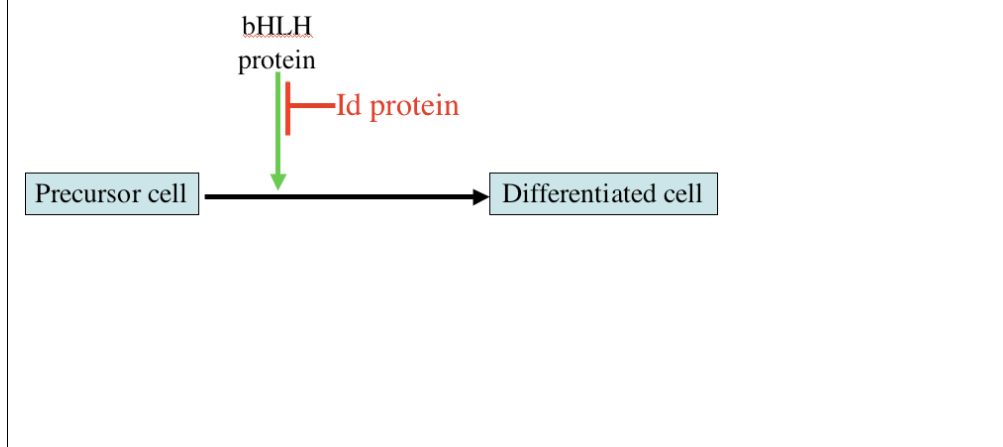
Yasu Tokumoto

p57 is also a component of the timer

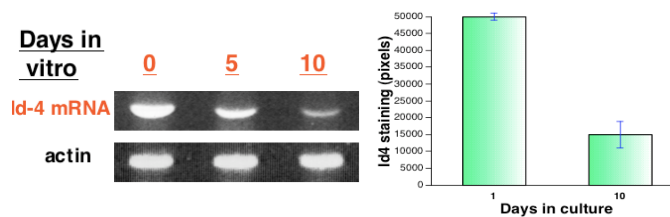


Jason Dugan

Id proteins inhibit differentiation and
promote proliferation by inhibiting
bHLH proteins

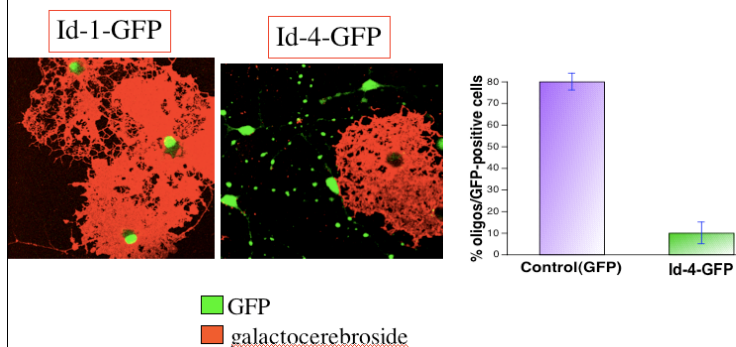


Id-4 mRNA and protein decrease as purified P7 rat OPCs proliferate in culture

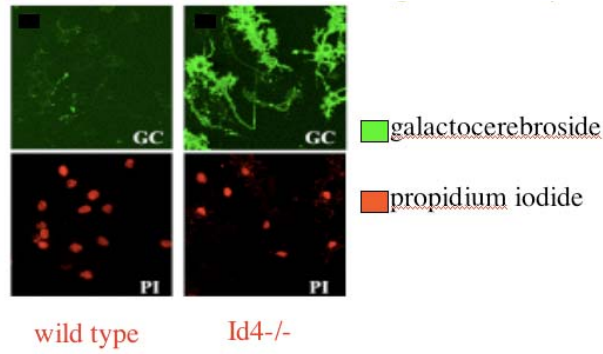


Toru Kondo

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

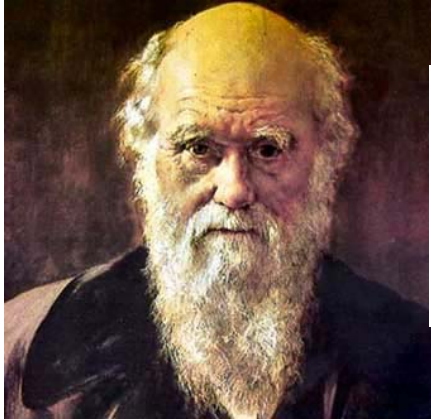


Toru Kondo
Fred Zablitsky

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



Why do most of us not look like
mice?



THANKS TO...

Jim Apperly
Ben Barres
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Ian Conlon
Béa Durand
Pierre-Alain Fernandez
Kay Fields
Fen-Biao Gao
Ian Hart
Toru Kondo
Sally Temple
Yasu Tokumoto