University of Glasgow | Institute of Infection, Immunity & Inflammation

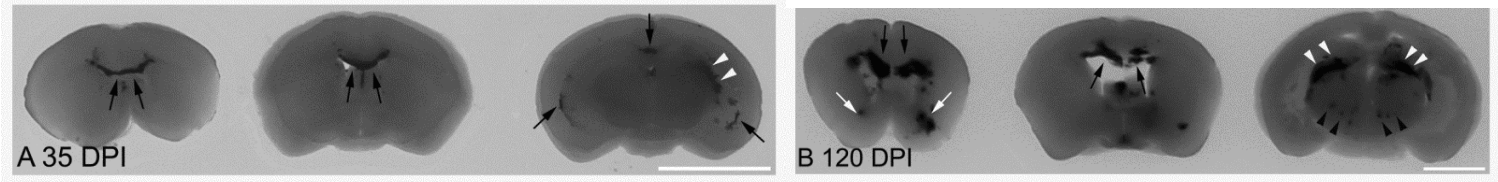
Max Planck Institut für Experimentelle Medizin

Oligodendroglial-axonal interaction

Julia M. Edgar

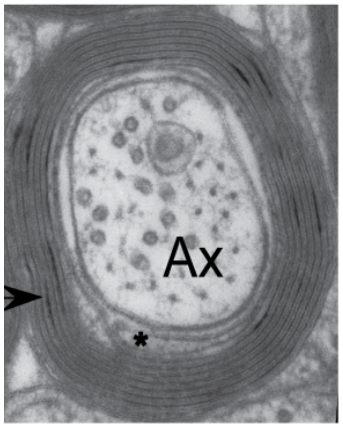
Techniques

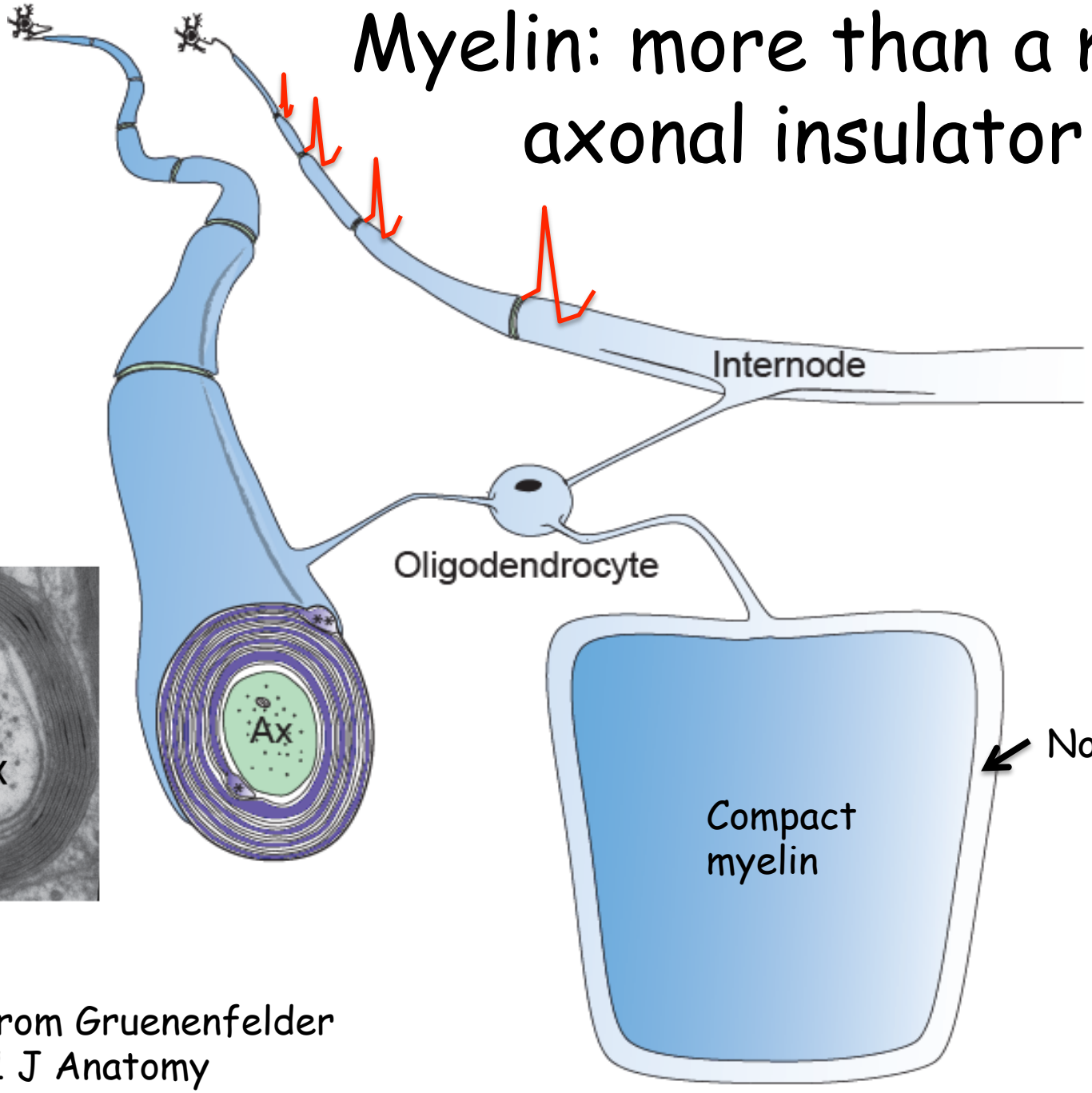
- **General**:
  - Immunocyto/histochemisty; histology; western blotting (phosphorylation assays); breeding mutant/transgenic mice; PCR genotyping; qRT-PCR; BrdU assays
- **Specfic**:
  - **In vivo:** cell transplantation brain/spinal cord/retina; stereotactic injection; optic nerve/sciatic nerve crush/transection; intra-uterine transplantation
  - **Morphometry:** EMs of white matter
  - **Cell culture:** neurospheres; myelinating cultures; mixed oligodendroglial cultures; embryonic brain slice cultures
  - **Imaging:** time-lapse; confocal; FRAP
  - **Molecular biology:** cloning; transgenic mice; lenti viral production



Mbp-LacZ neurospheres form myelinating oligodendrocytes after transplantation into P1 brains

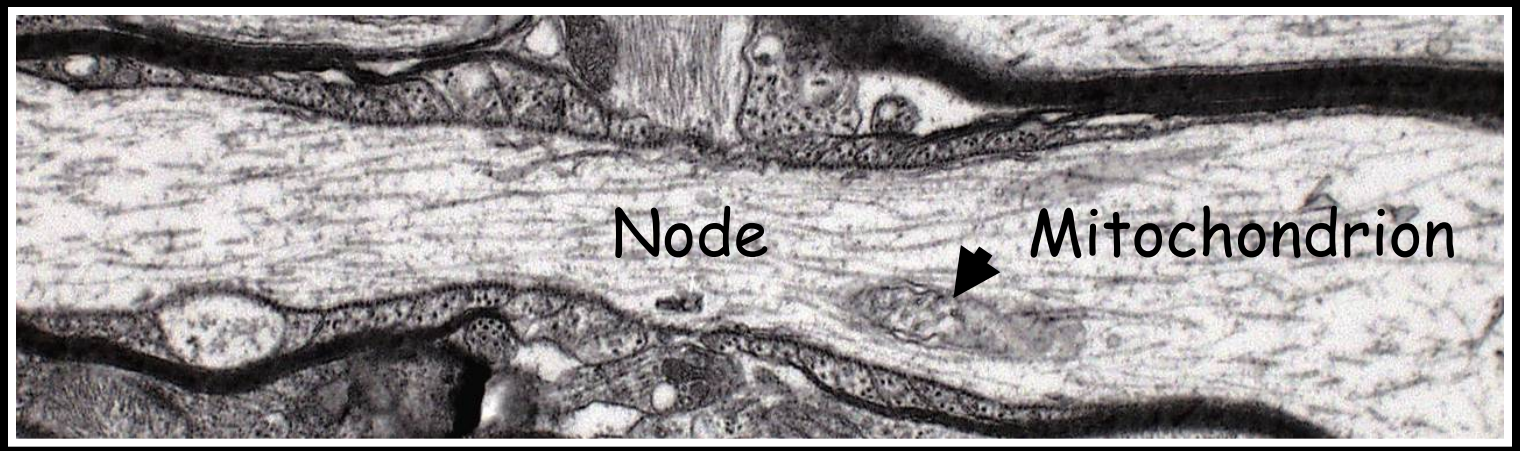
Myelin: more than a mere axonal insulator



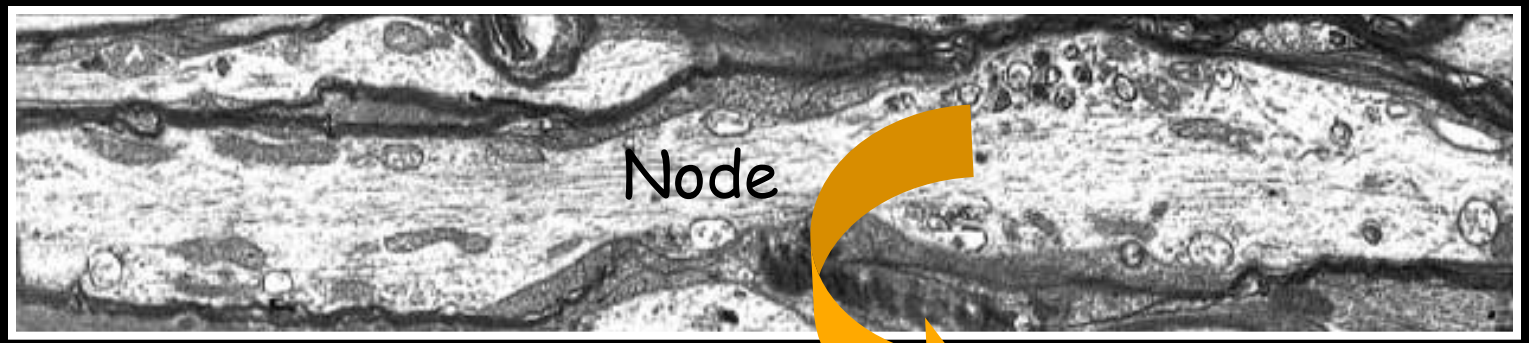


Adapted from Gruenenfelder et al., 2011 J Anatomy

Plp1 ko mouse synthesises relatively normal myelin but develops an axonal pathology



Wild-type



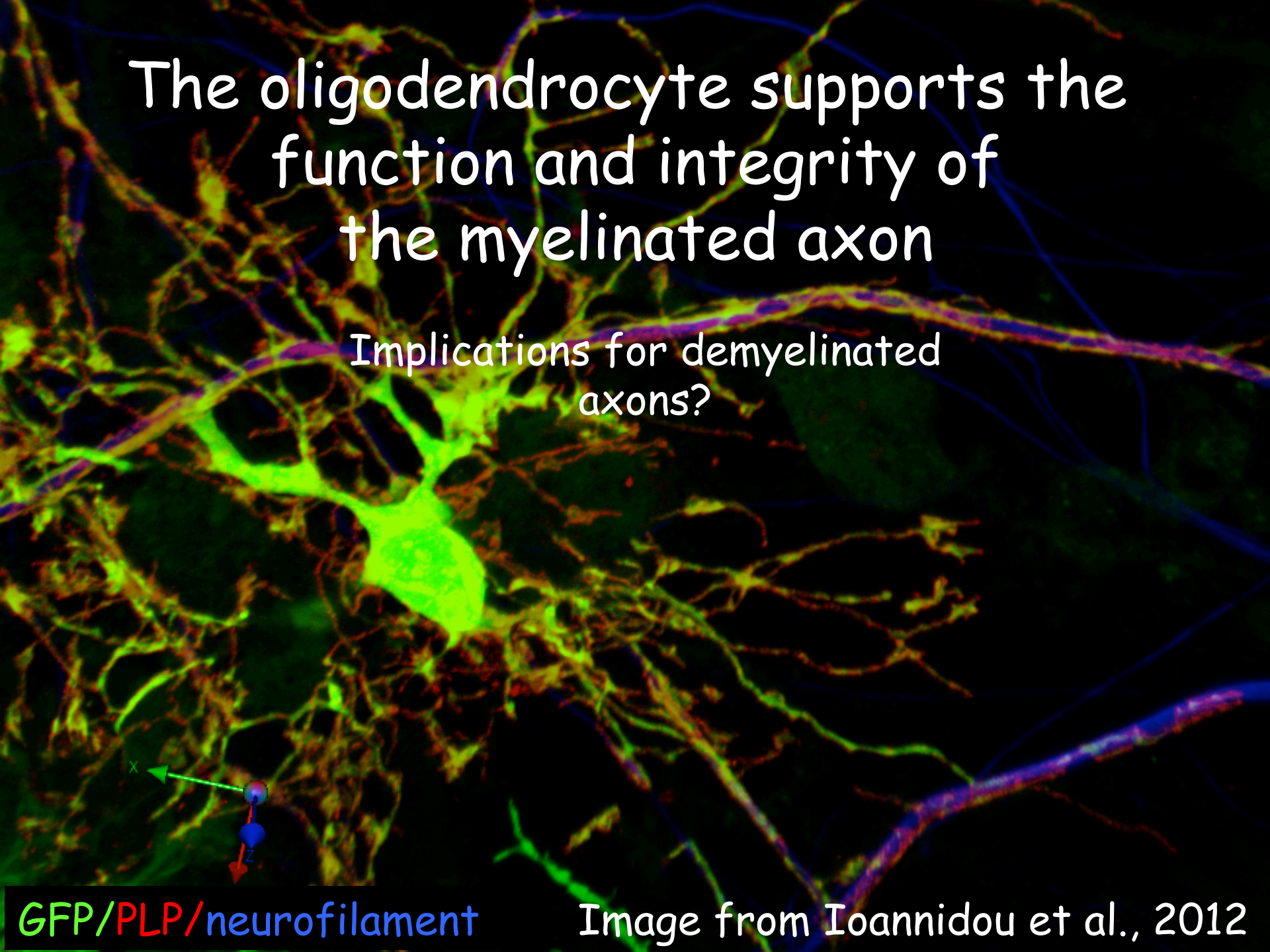
Plp1 null

Axonal 'traffic-jam'

Griffiths et al., 1998 Science; Edgar et al., 2004 JCB

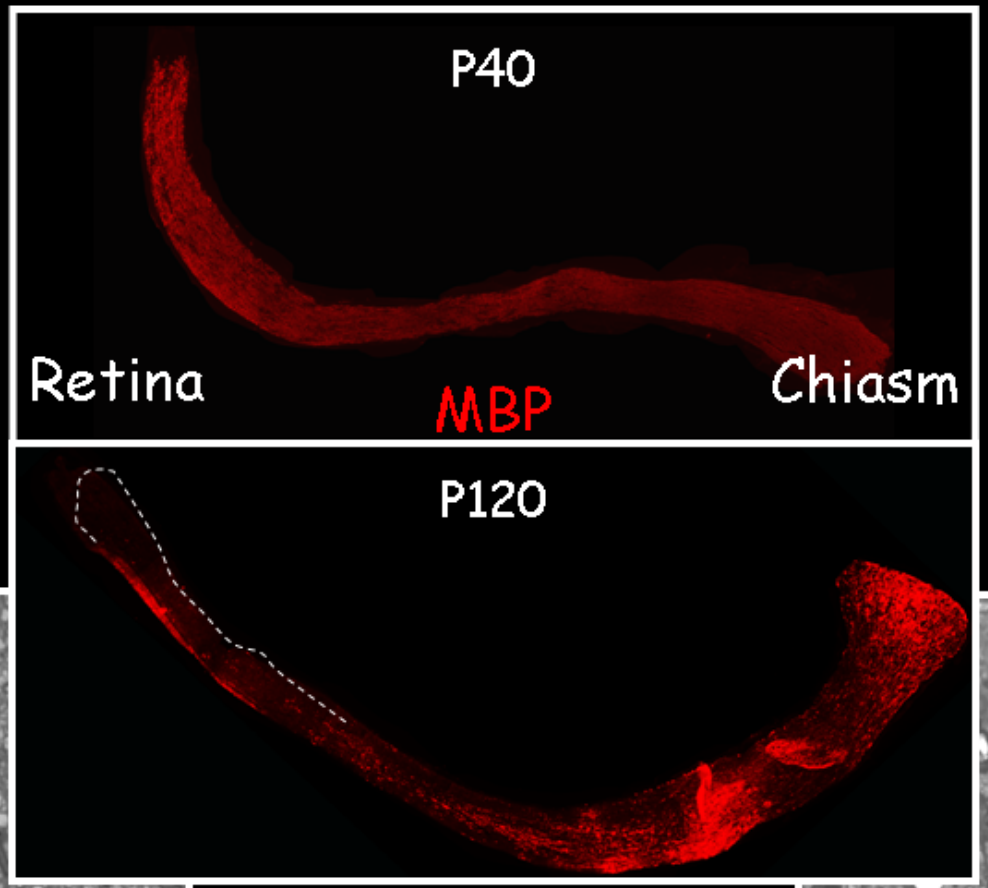
The oligodendrocyte supports the function and integrity of the myelinated axon

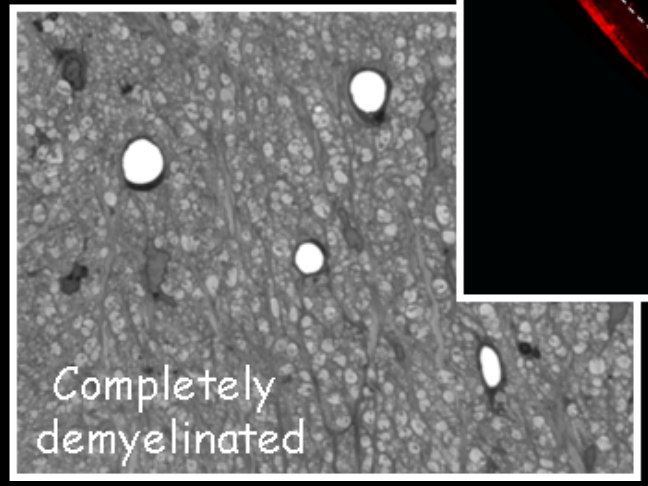
Implications for demyelinated axons?

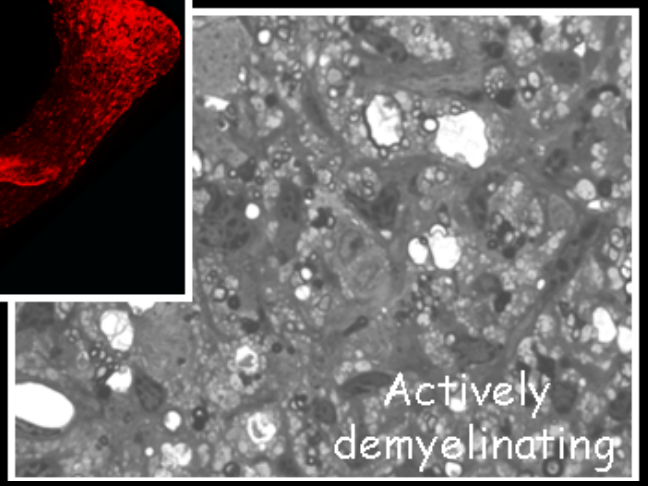


Demyelination and axonal preservation in the *Plp1* overexpressing mouse

Edgar et al., EMBO Mol Med 2010

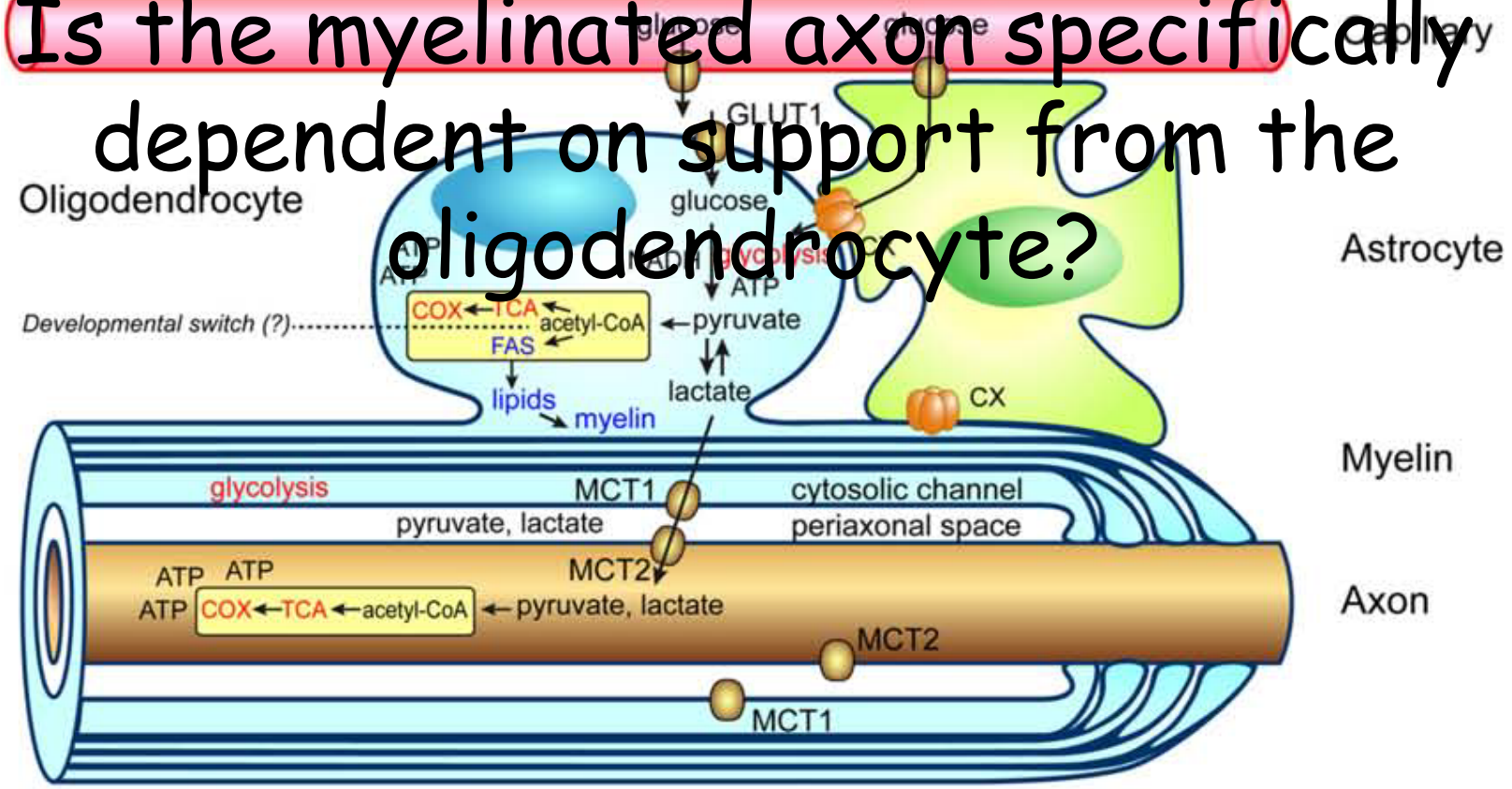




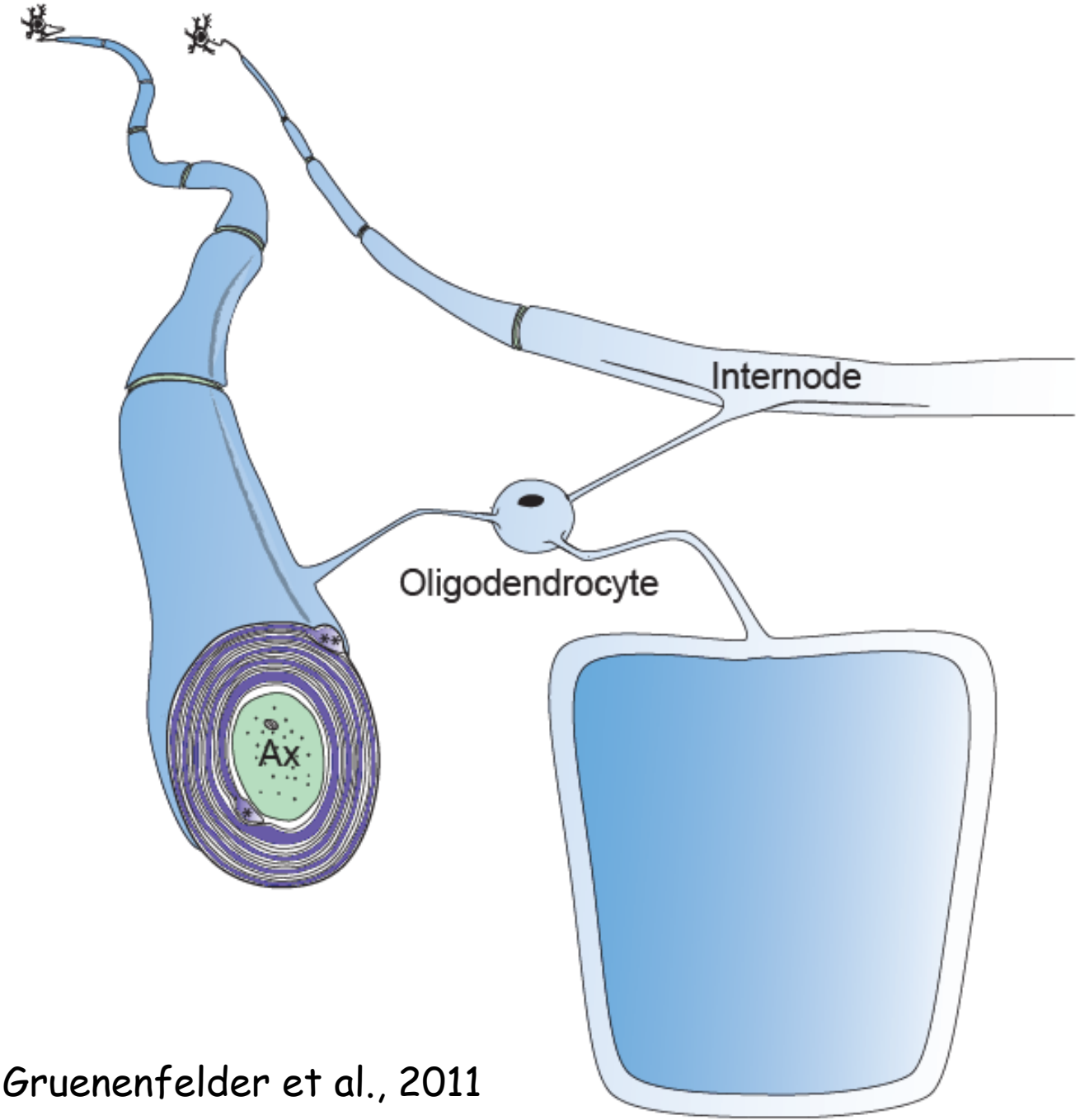


Hypothesis: glycolytic oligodendrocytes fuel axonal mitochondrial oxidative phosphorylation

Is the myelinated axon specifically dependent on support from the oligodendrocyte?



Fünfschilling et al., 2012 Nature



Adapted from Gruenenfelder et al., 2011

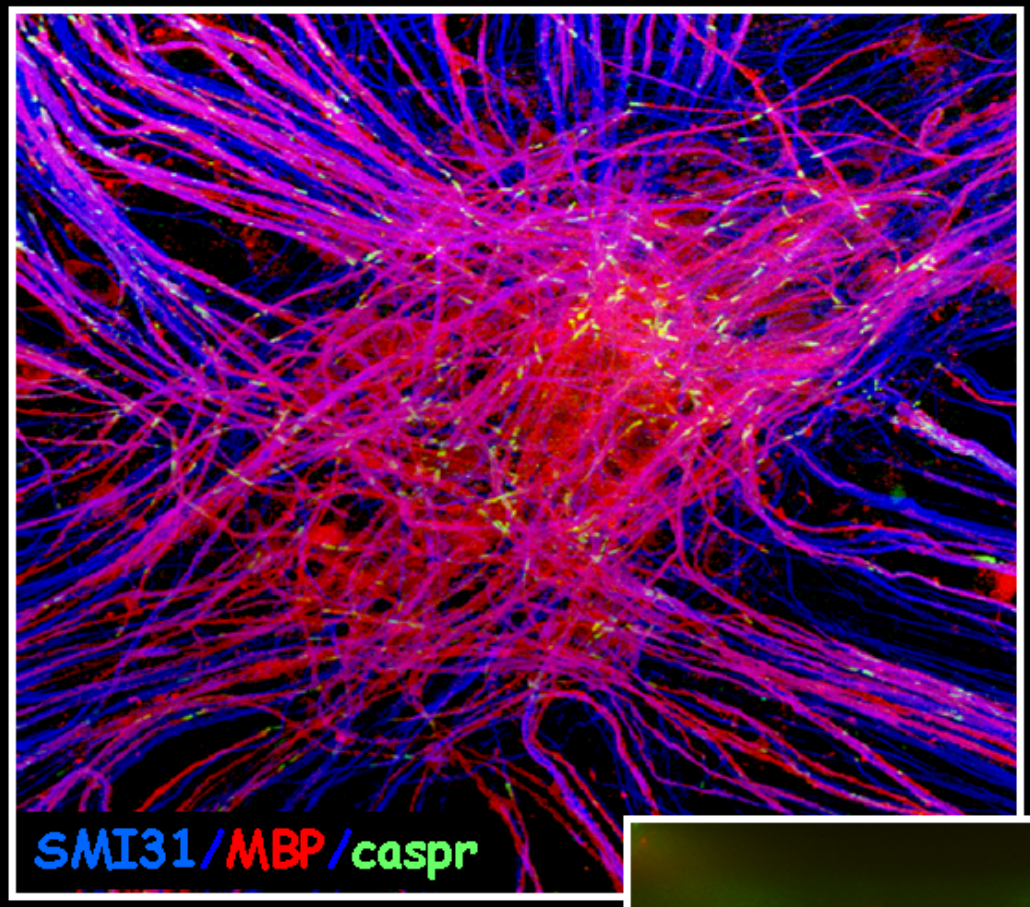
Hypothesis: Myelinic channel

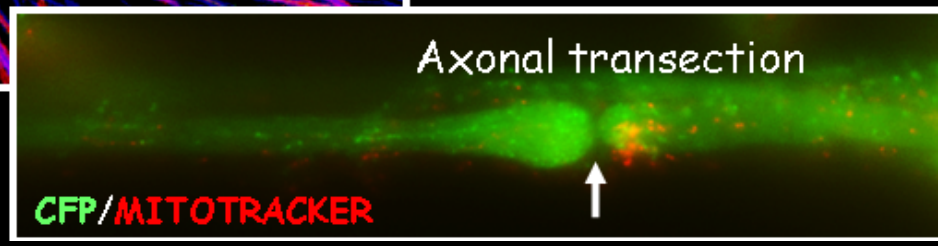
(i) a route through which the oligodendrocyte transports axono-protective materials and proteins involved in mediating metabolic support to the glial-axonal junction

(ii) inflammatory factors perturb transport through this channel system.

(iii) normal myelinic transport is a prerequisite for normal axonal structure and function

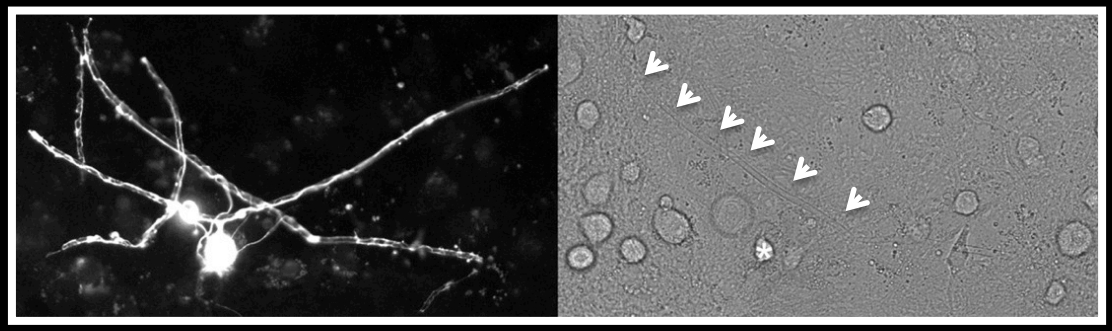
An in vitro model of CNS myelination



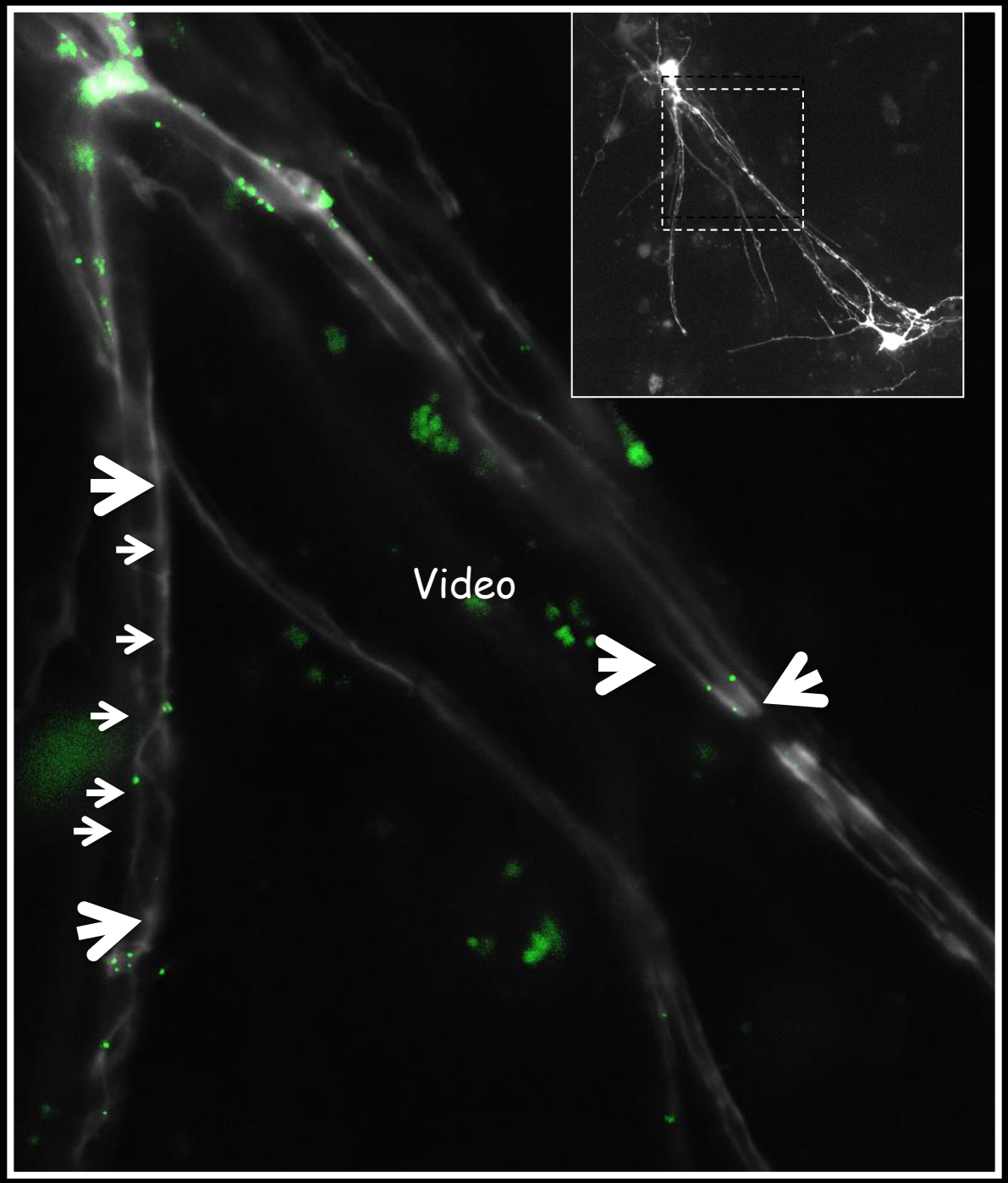


Protocol Thomson et al., 2006 J Neurosci Res; 2008 E J Neurosci; Edgar et al., 2008 J Neurosci Res; Sorensen et al., 2008 Glia

Myelinating cultures from *PLP CreERT2*Td tomato mice*



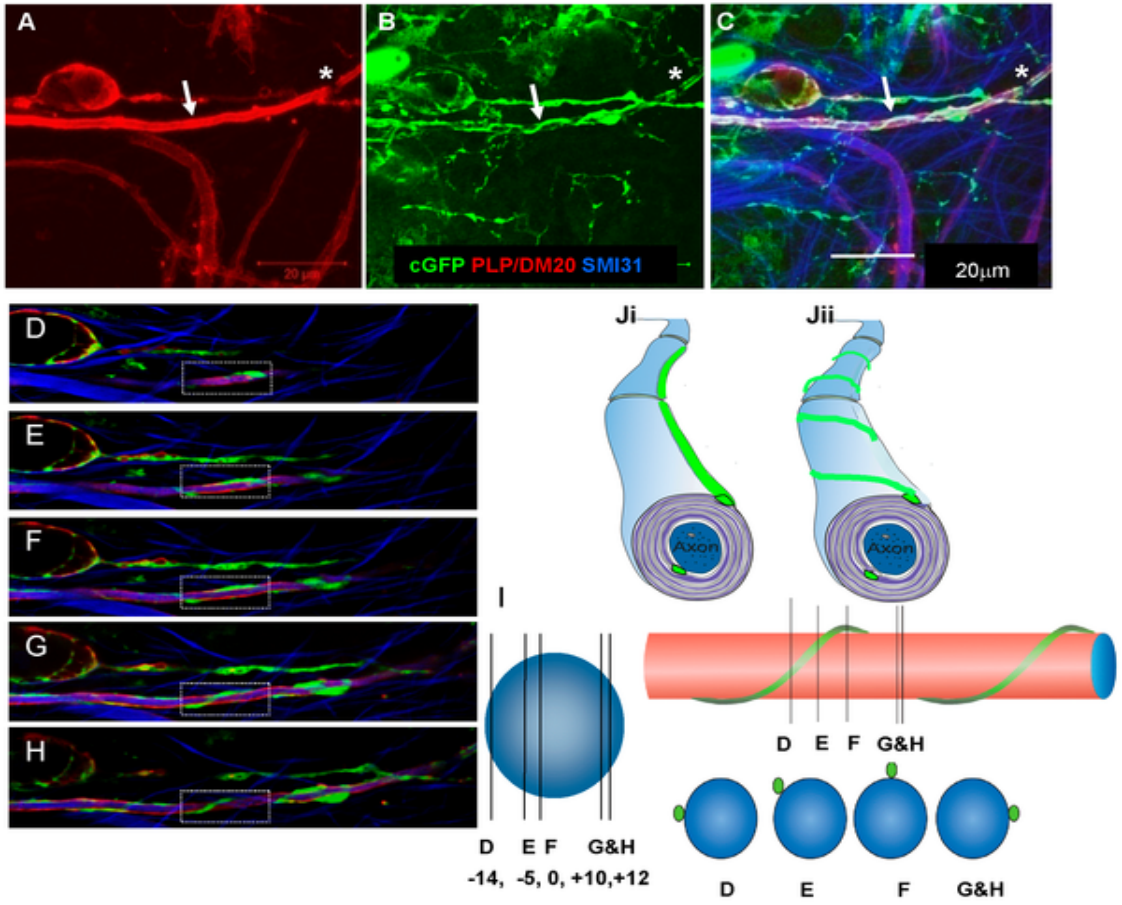
Video



Td-tomato
Pex1-EOS2

How CNS myelination happens

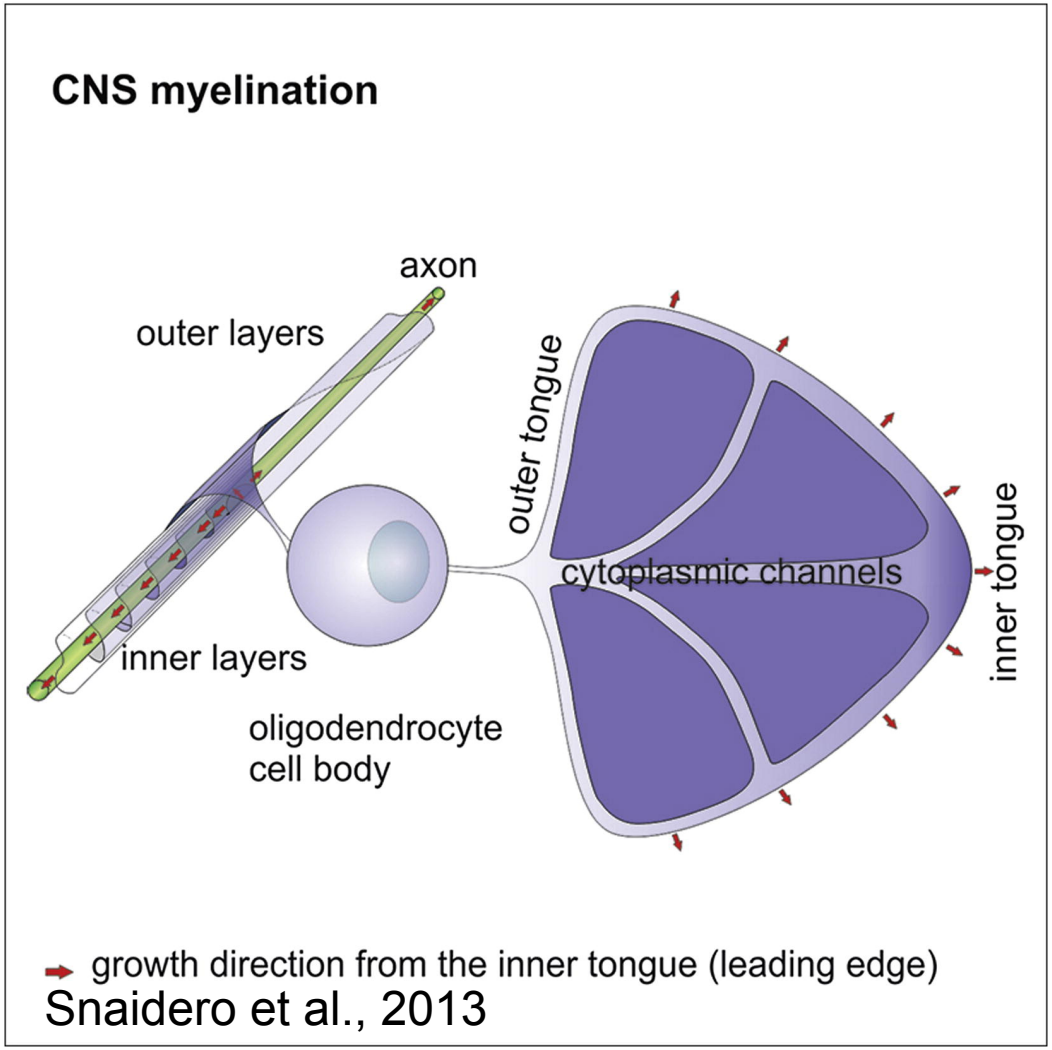
Figure 5. Evidence that oligodendrocytes form spiral processes around neurites.



Ioannidou K, Anderson KI, Strachan D, Edgar JM, Barnett SC (2012) Time-Lapse Imaging of the Dynamics of CNS Glial-Axonal Interactions In Vitro and Ex Vivo. PLoS ONE 7(1): e30775. doi:10.1371/journal.pone.0030775
http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0030775

PLOS | ONE

How CNS myelination happens



Snaidero et al., 2013

Cell PRESS

'Unusual collaborations'

- Christoph Schmidt - Carbon nanotubes to image motor protein movement in oligodendrocytes
- Clive McKimmie and Chris Linington - Semliki forest virus to assay functionality of antibody-mediated type 1 interferon response in myelinating cultures

'What I need'

- Funding!!!
- A method to specifically perturb the myelinic channel *in vivo* that won't also cause primary injury to axons
- Inflammatory factors that specifically perturb the myelinic channel
- Time-lapse imaging that does not cost £50/hour

Collaborators

- **Ian Griffiths**, Paul Montague, Mark McLaughlin, Jim Anderson, Christine Thomson, Jacques Penderis, Mailis McCulloch, Jennifer Barrie, Fredrik Gruenenfelder, Gemma Thomson, Silvia Bijland
- Susan Barnett and Kalliopi Ioannidou
- Debbie Dewar and Torsten Ruest
- Chris Linington, Clive McKimmie and Tiia Semenoff and Verena Schultz
- Hugh Willison
- Stuart Cobb and Kamal Gadalla
- **Klaus Armin-Nave** and members Dept of Neurogenetics (MPI), Goettingen, Germany
- Mickael Simons and Nicolas Snaidero,MPI, Goettingen, Germany
- Ian Duncan, Madison, Wisconsin, USA
- Rudolf Martini, University Hospital Würzburg, Würzburg, Germany

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