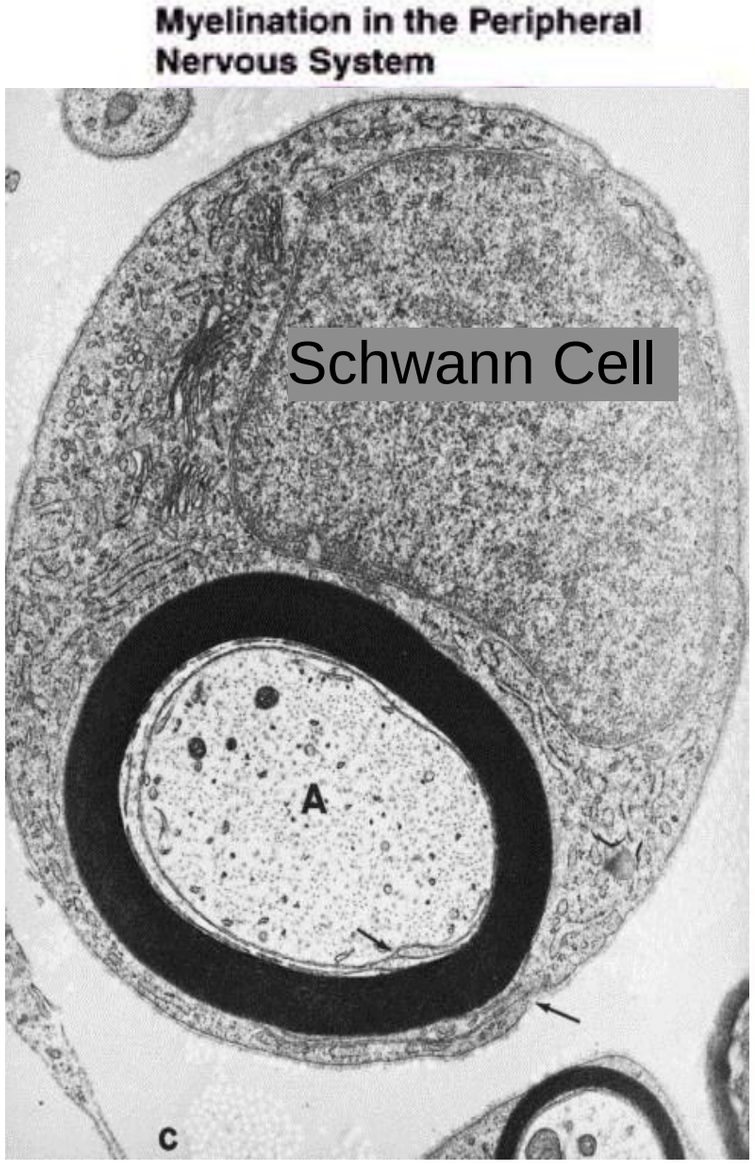
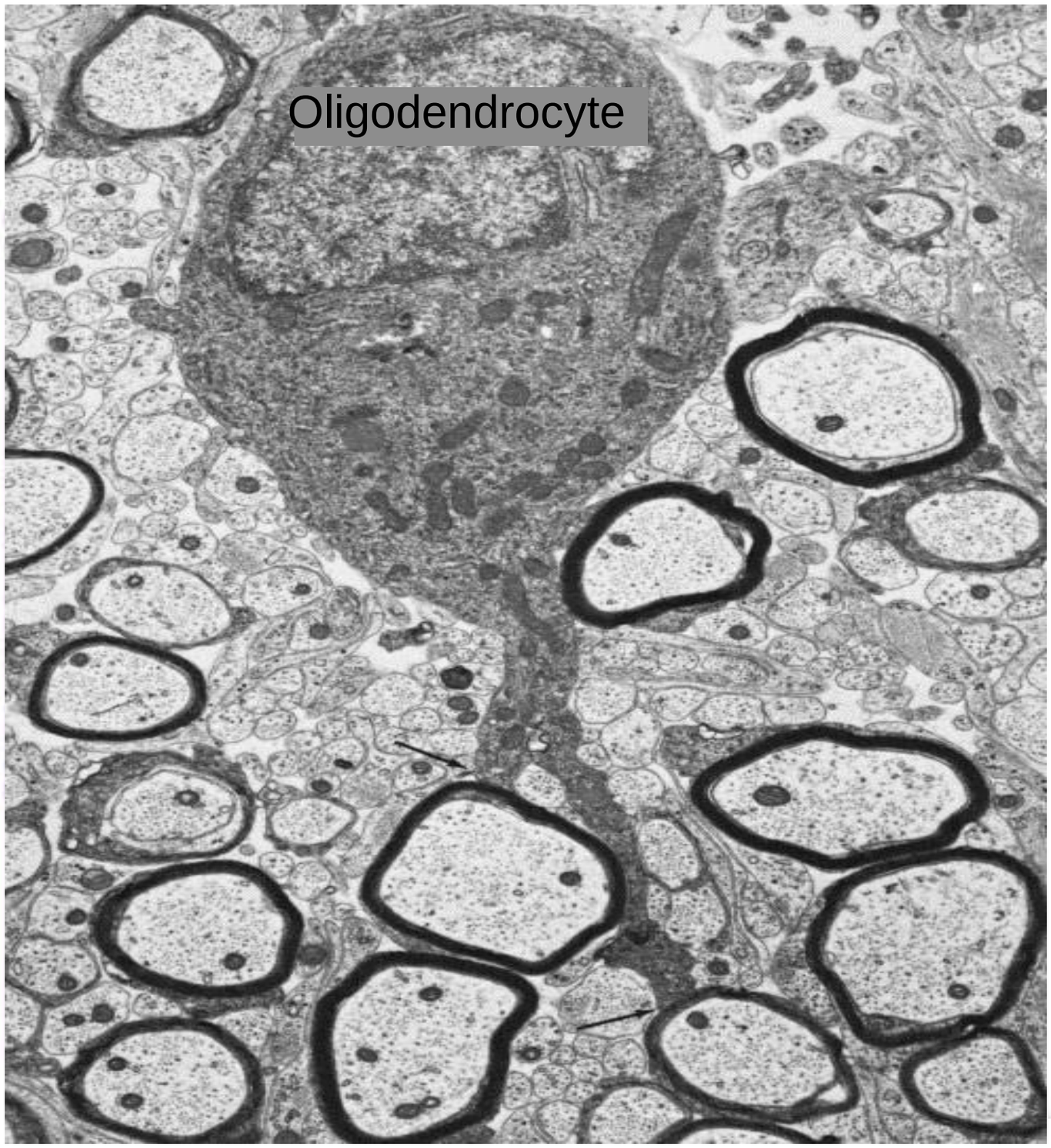
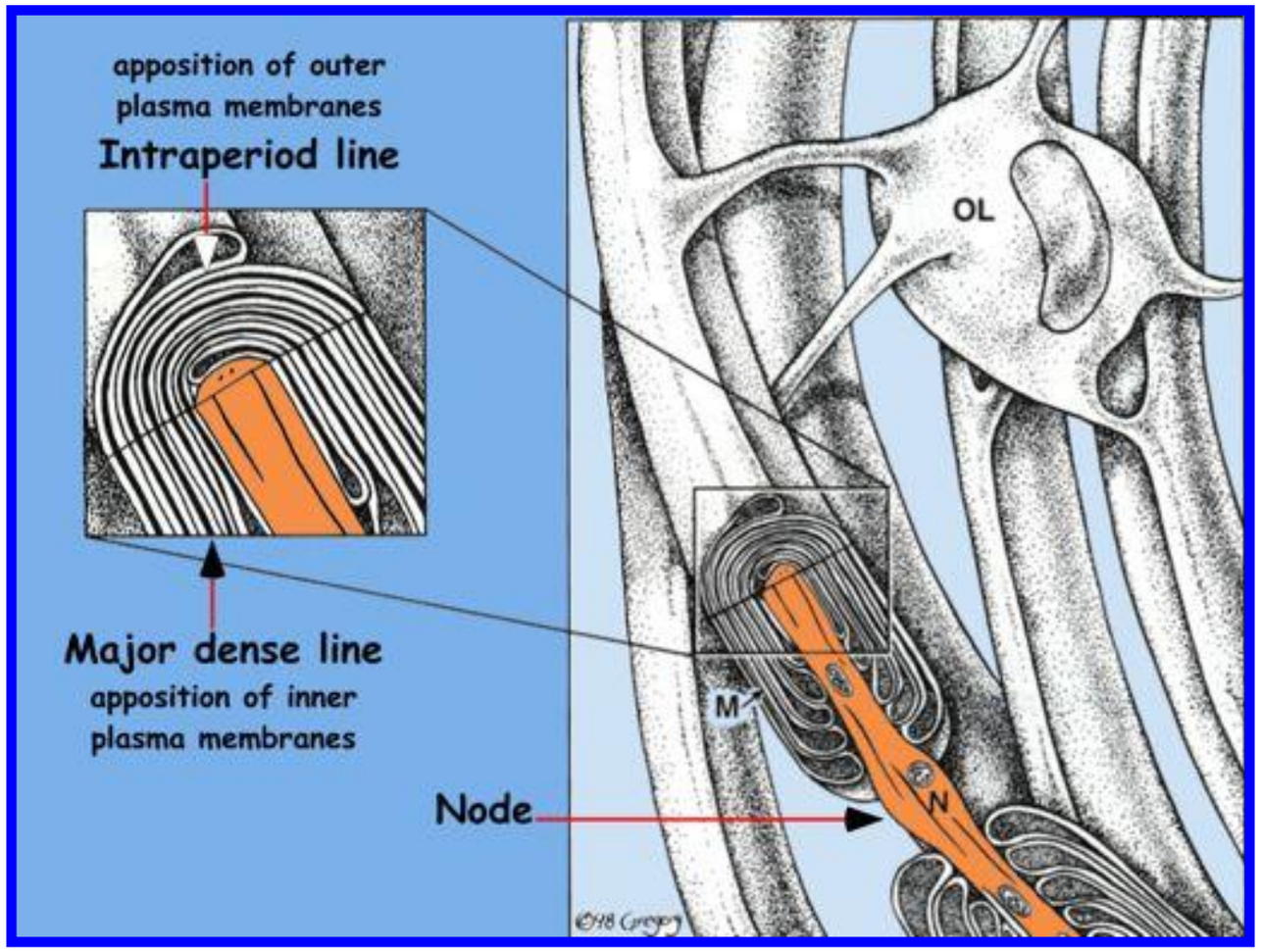
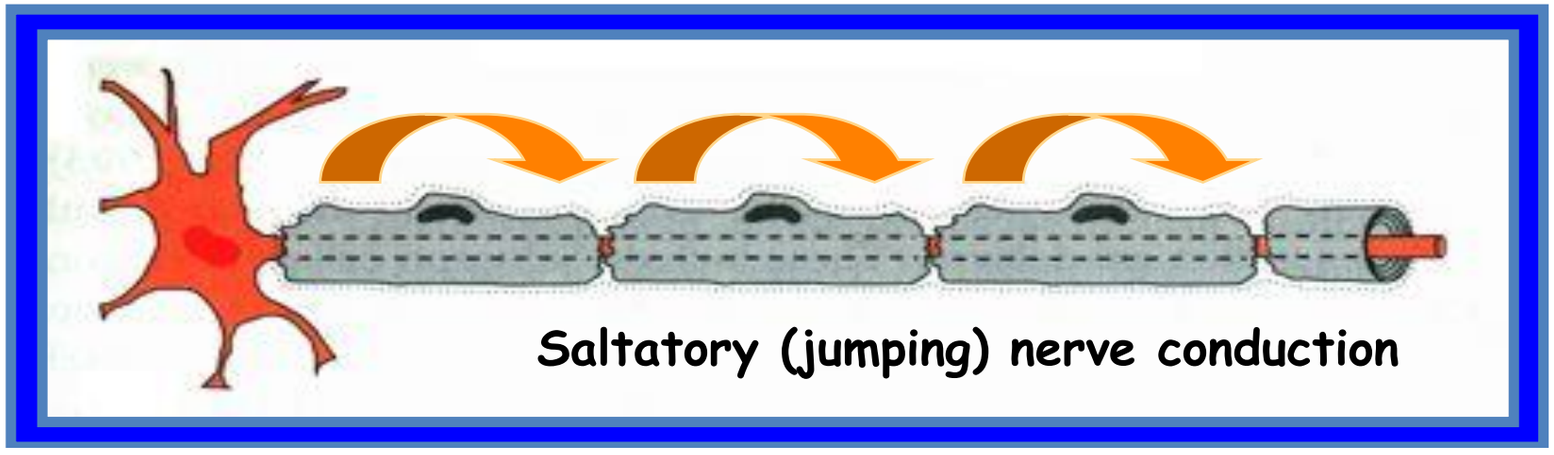
The Myelin-Forming Cells of the Nervous System (oligodendrocytes and Schwann cells)

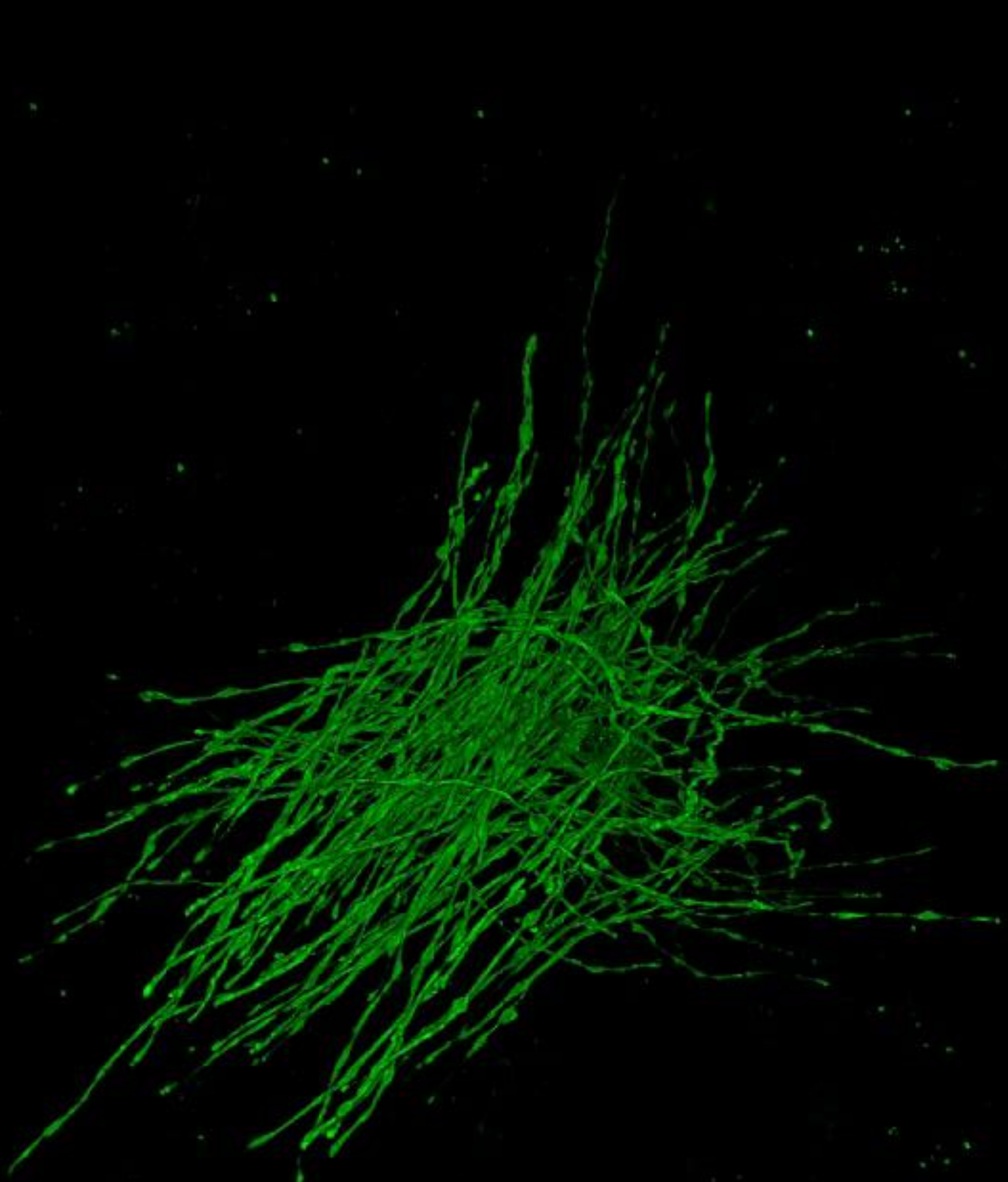




Oligodendrocyte function

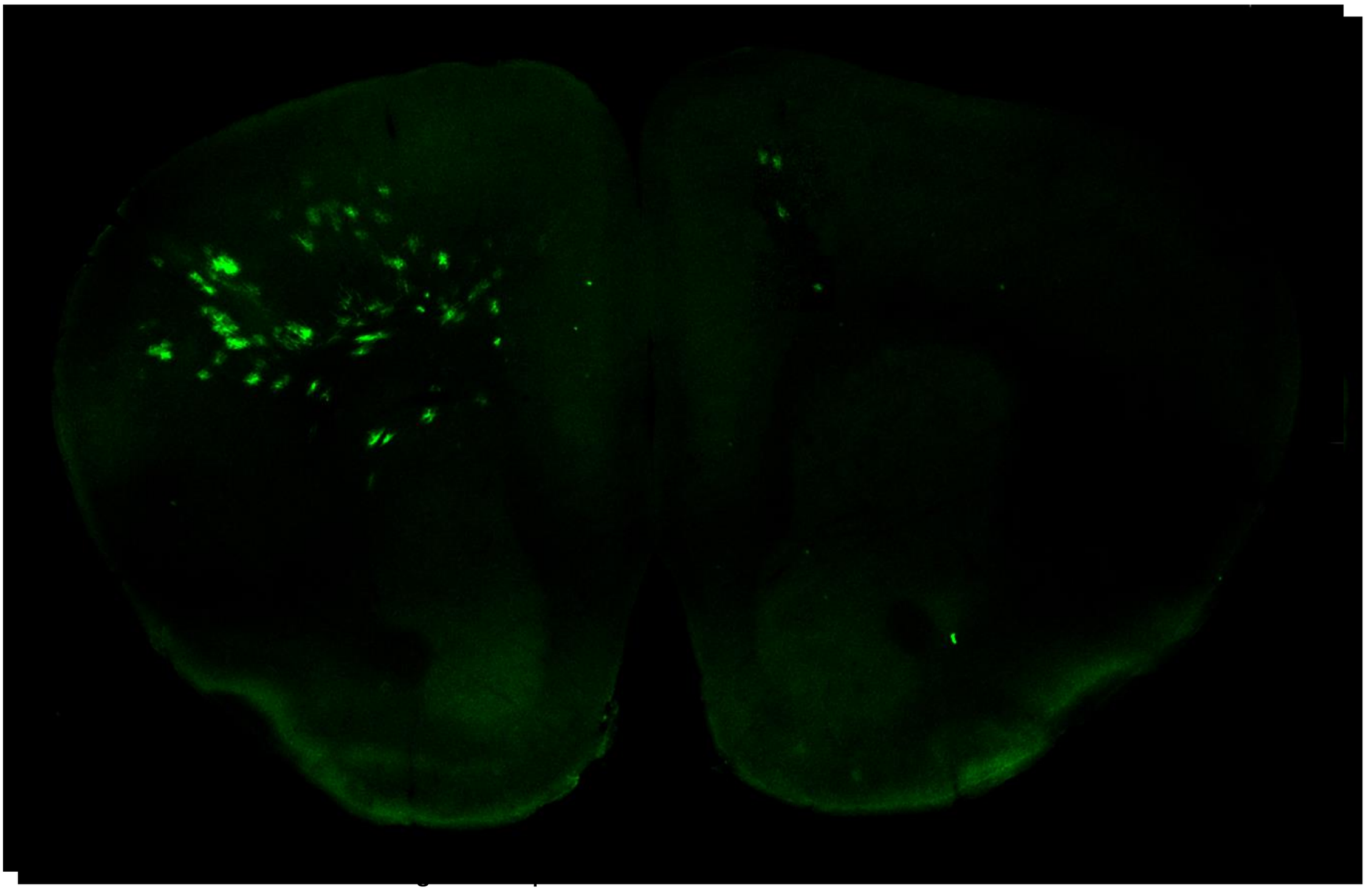


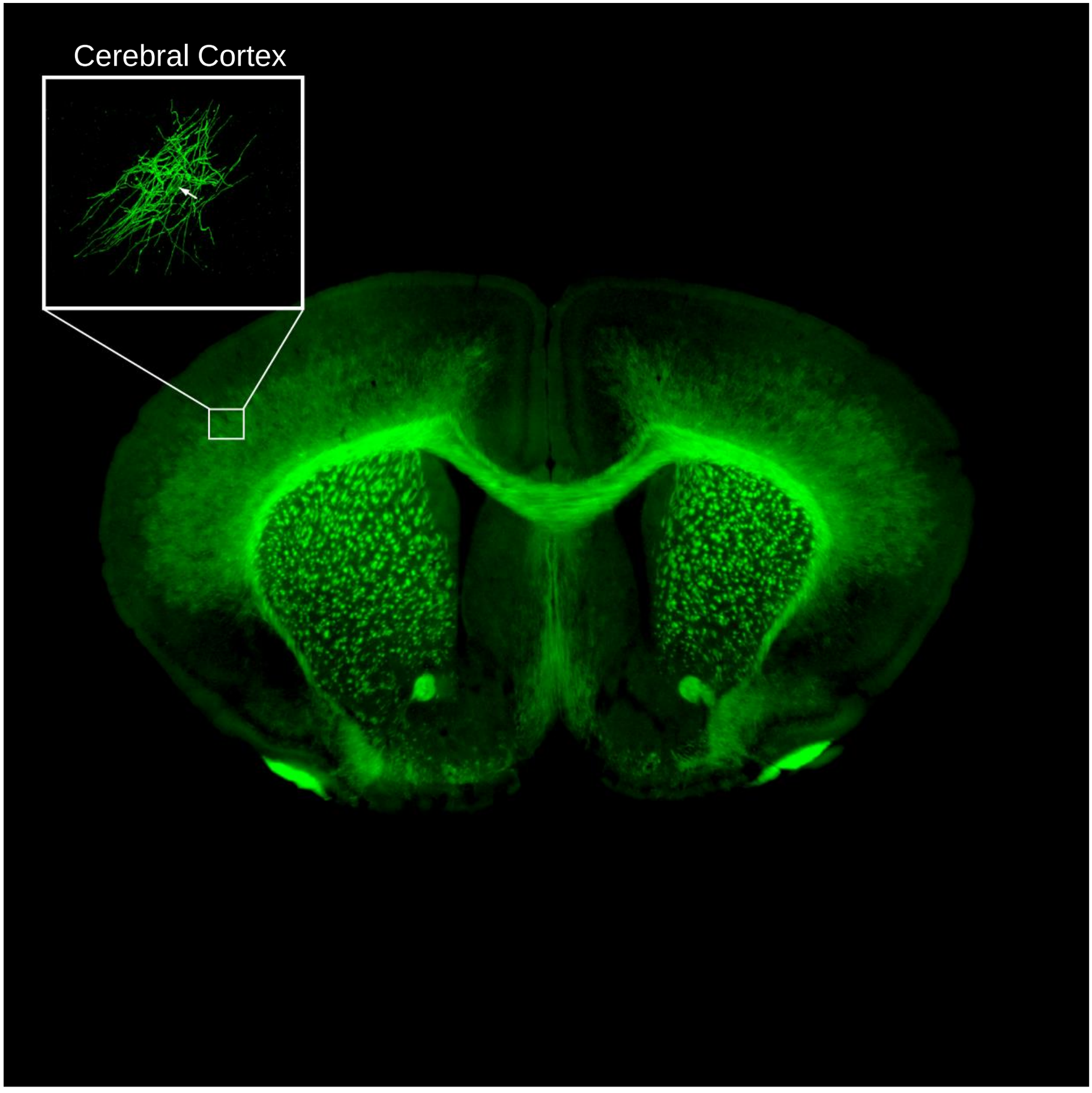


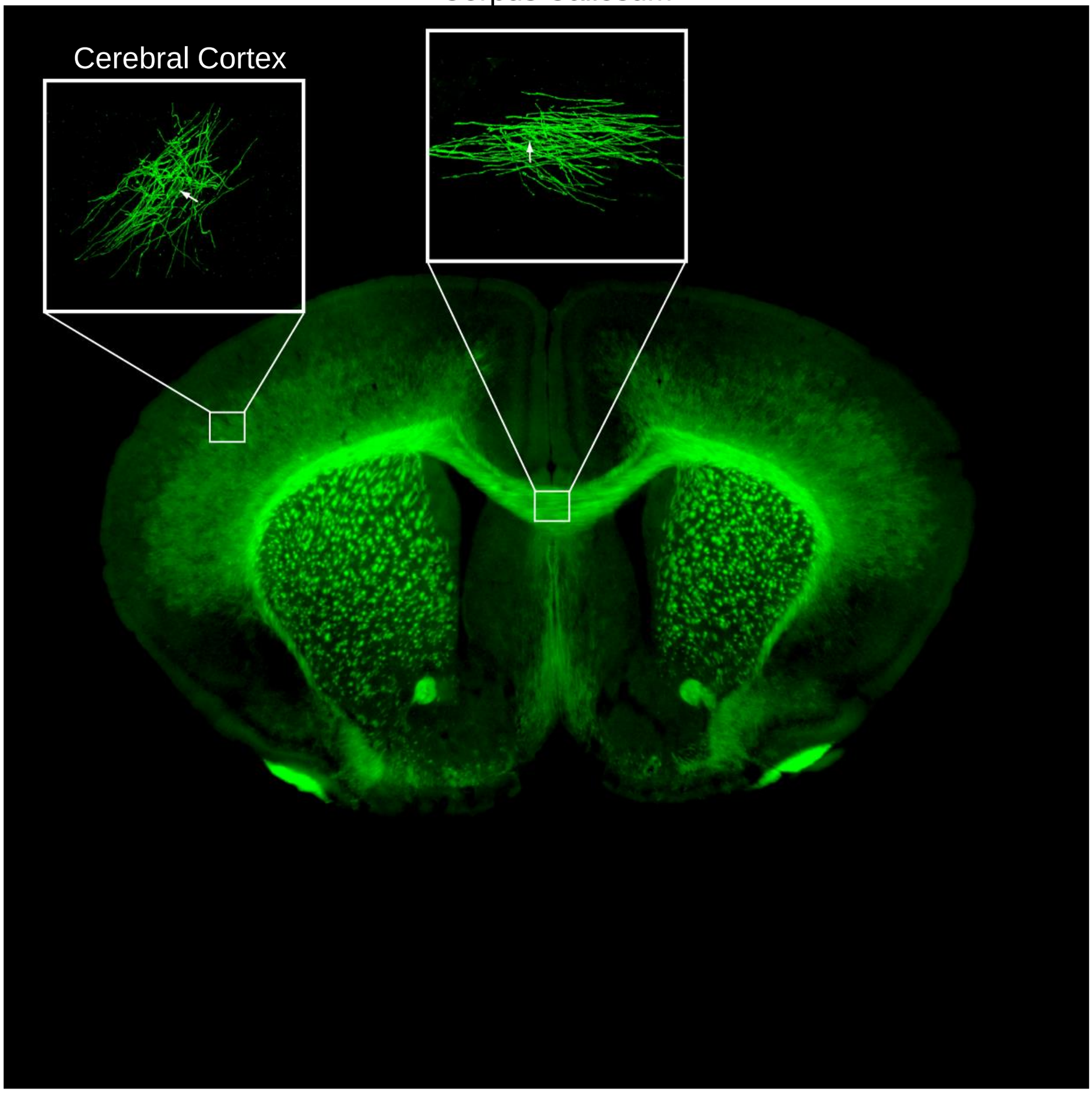


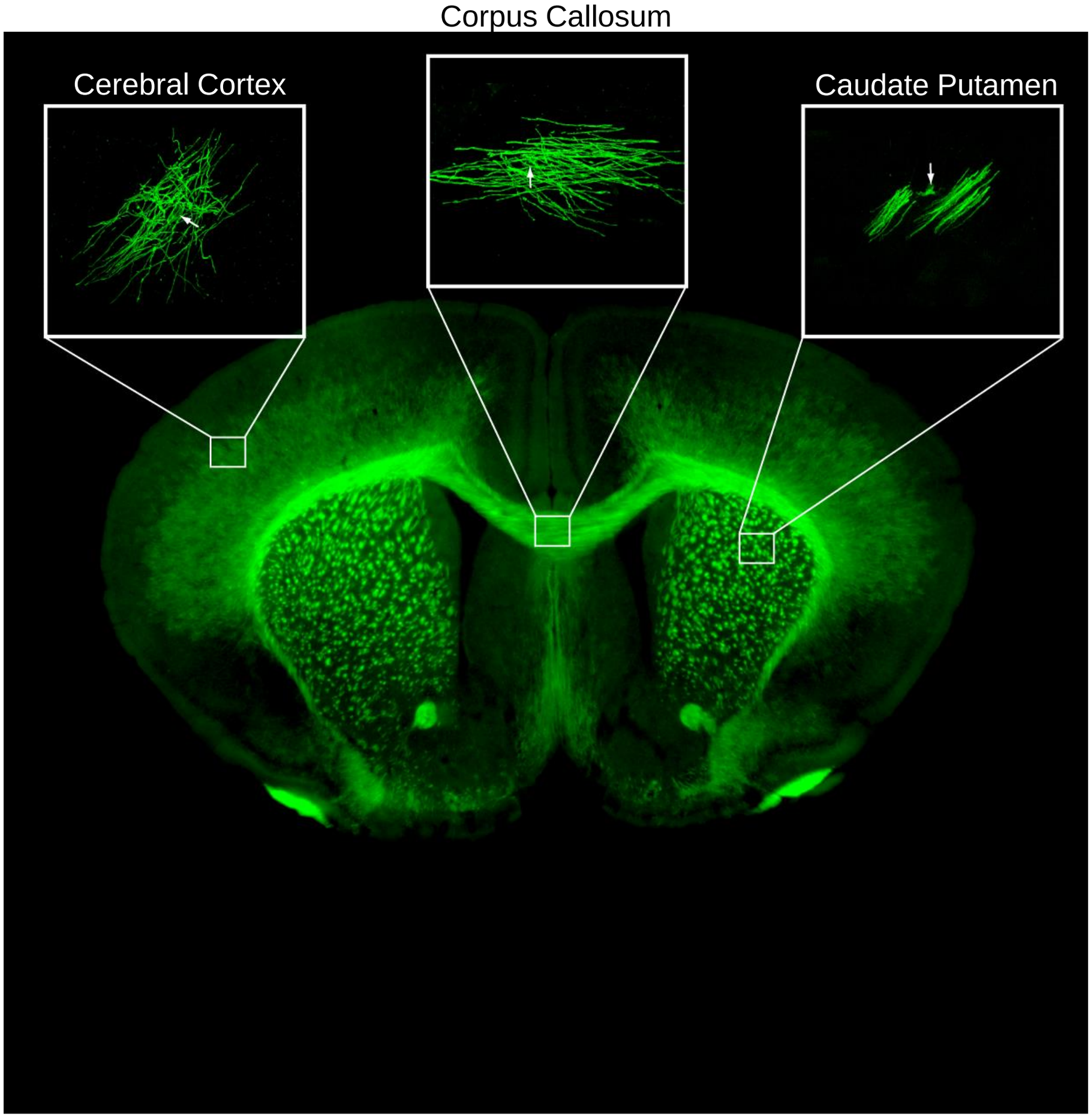
Investigating the Myelinogenic Potential of Individual Oligodendrocytes In Vivo

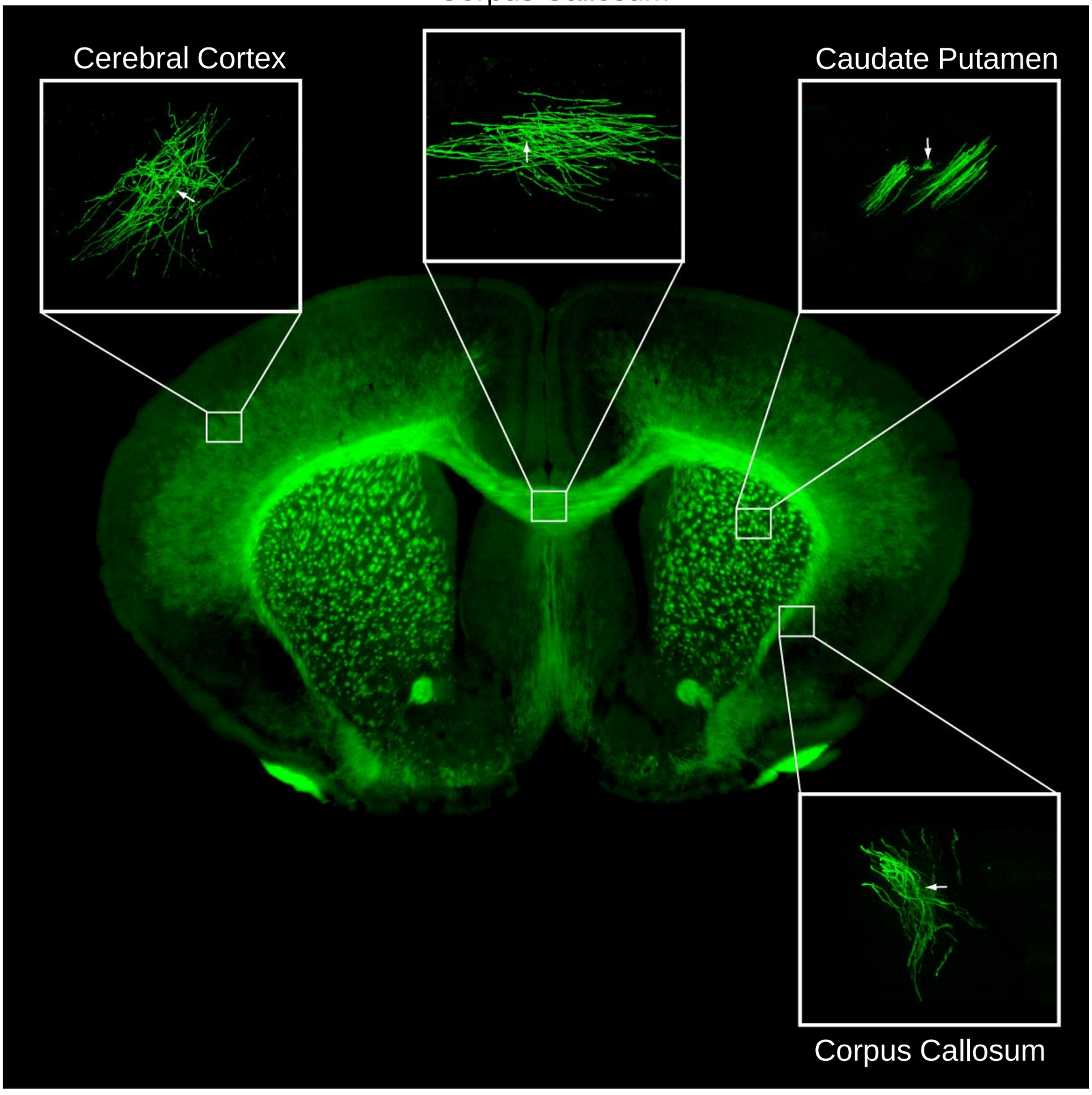
Sparse Labeling of Oligodendrocytes

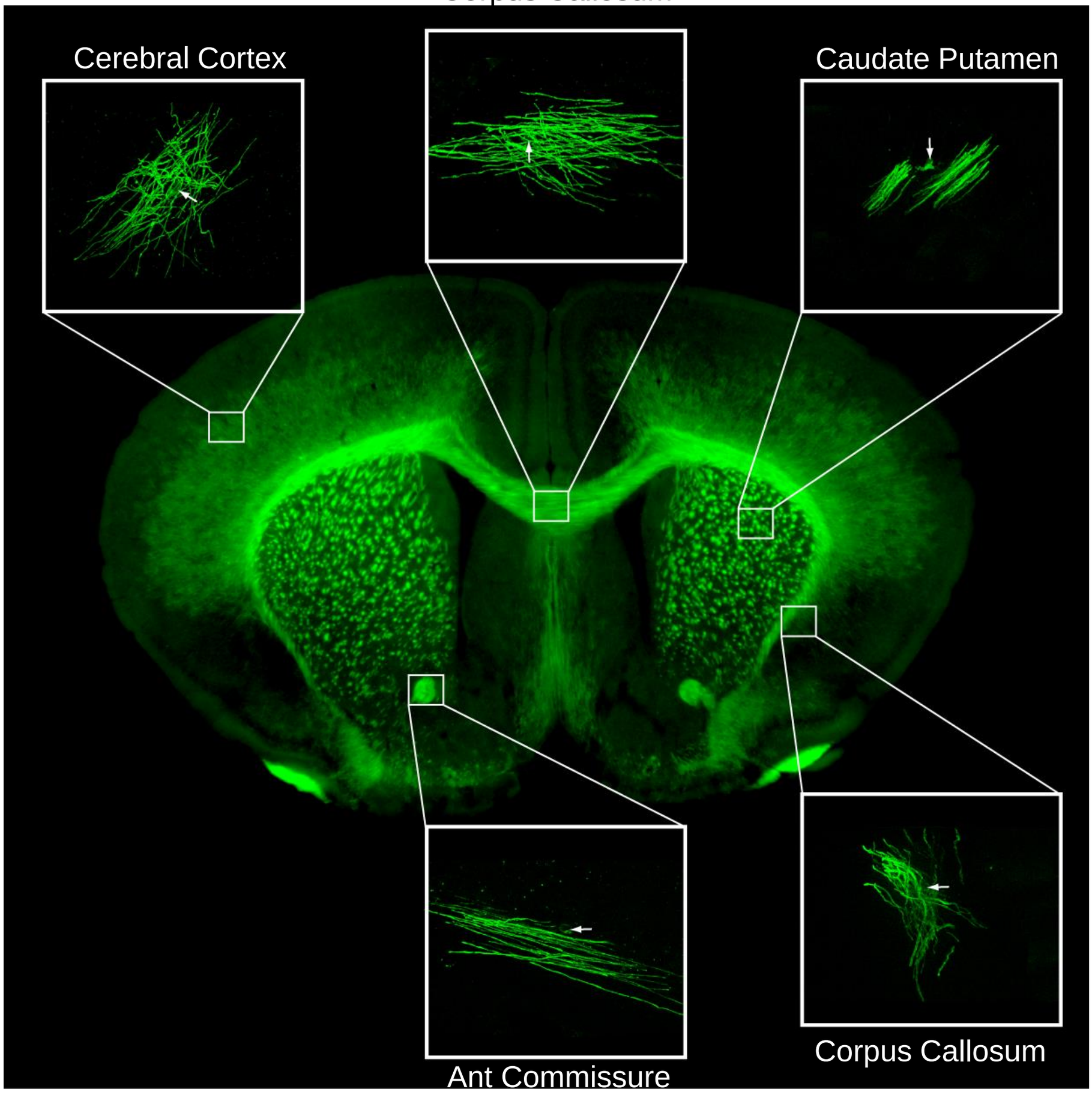


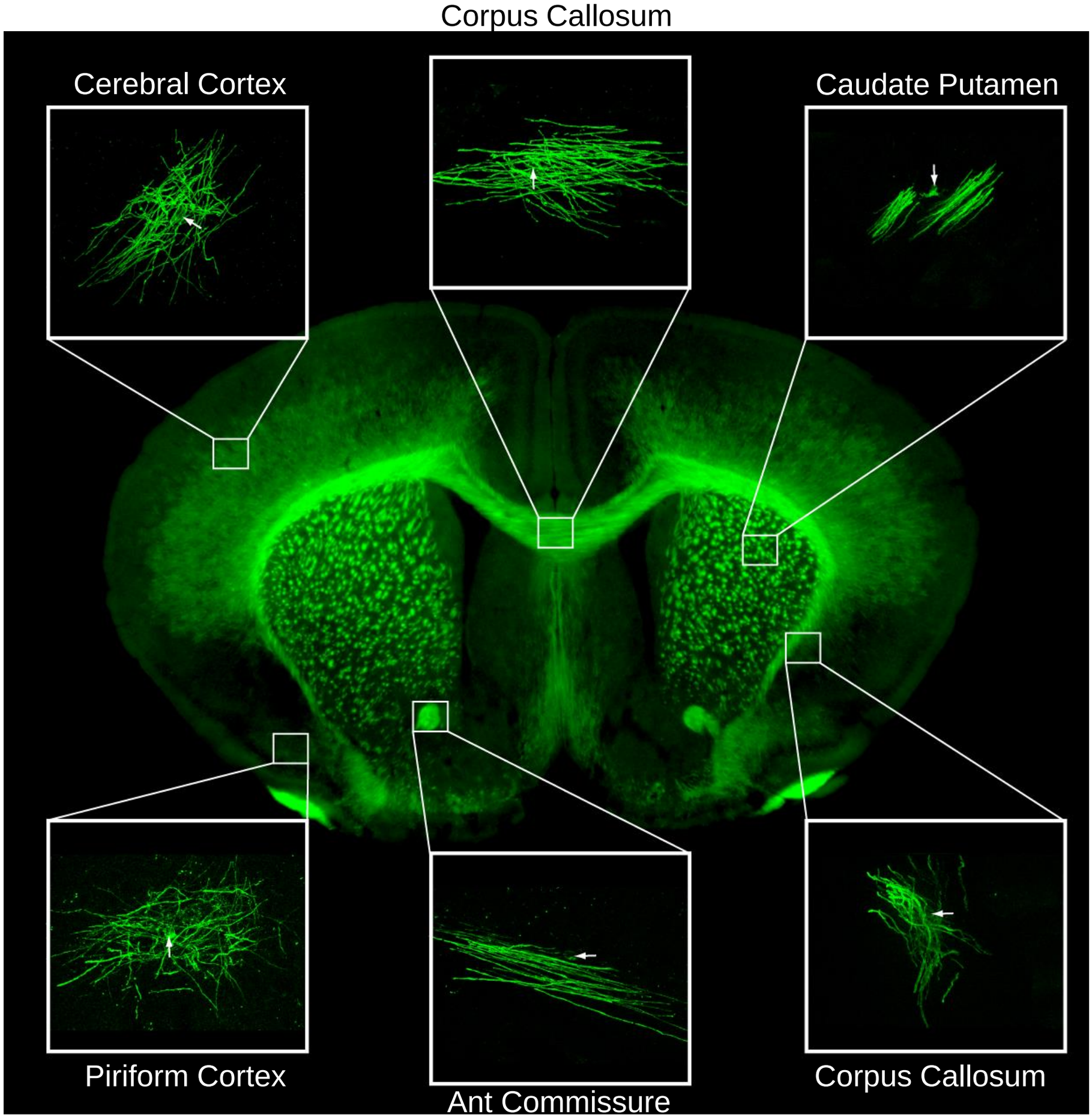

Cerebral Cortex


Corpus Callosum
Cerebral Cortex


Corpus Callosum
Cerebral Cortex
Caudate Putamen


Corpus Callosum
Cerebral Cortex
Caudate Putamen
Corpus Callosum


Corpus Callosum
Cerebral Cortex
Caudate Putamen
Ant Commissure
Corpus Callosum


Corpus Callosum
Cerebral Cortex
Caudate Putamen
Piriform Cortex
Ant Commissure
Corpus Callosum

Characterization of Oligodendrocyte Morphology

Cerebral Cortex

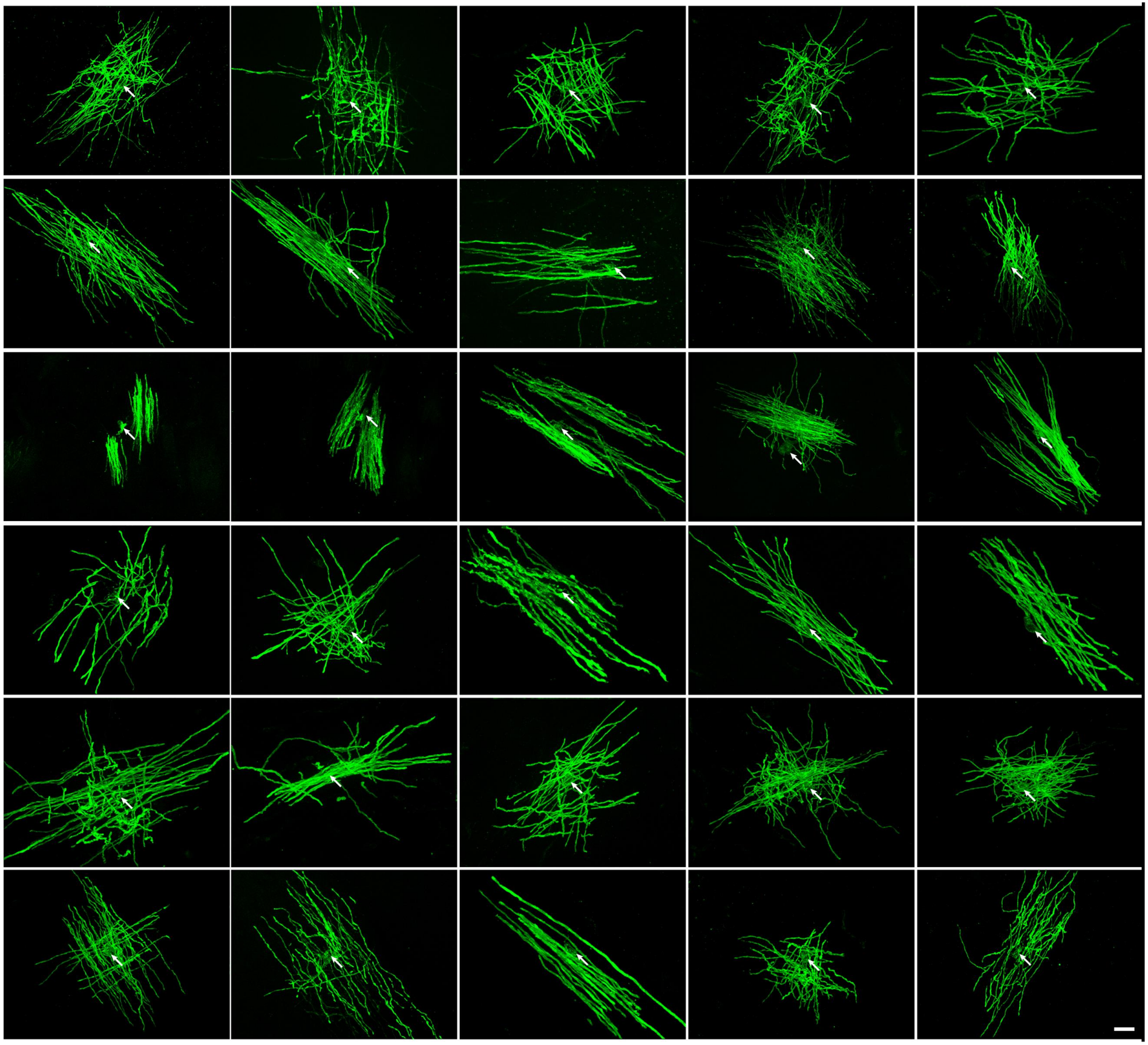
Corpus Callosum

Caudate Putamen

Cerebellum

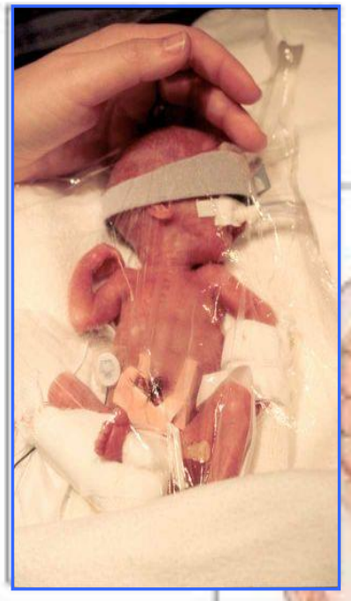
Brain Stem

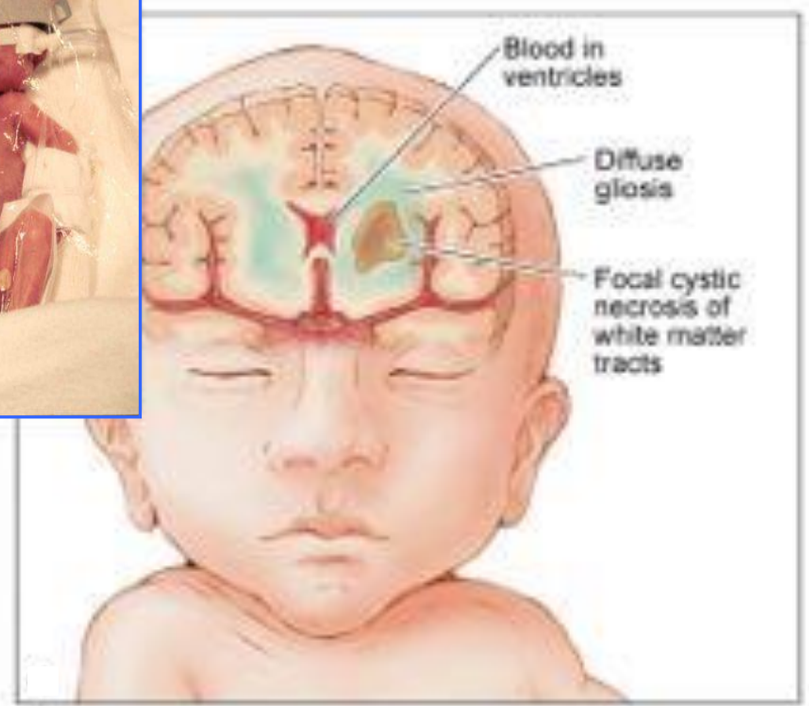
Spinal Cord

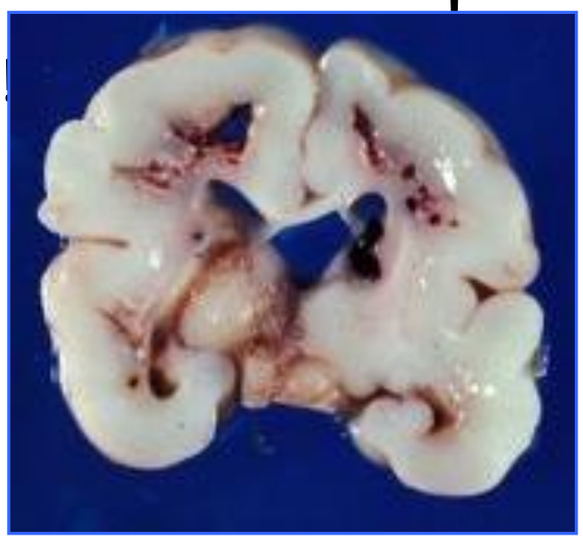


Oligodendrocytes in disease: Cerebral Palsy

- CP major cause of chronic neurological morbidity and mortality in children
- CP incidence now about 3/1000 live births compared to 1/1000 in 1980 when we started intervening for ELBW
- Of all ELBW {gestation 6 mo, Wt. 0.5kg} , 10-15% develop CP
- Prematurely born children prone to white matter injury {WMI}, principle reason for the increase in incidence of CP

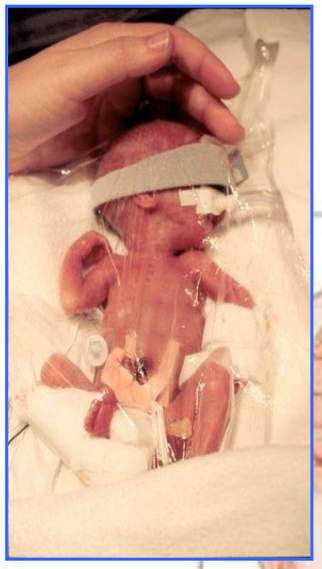


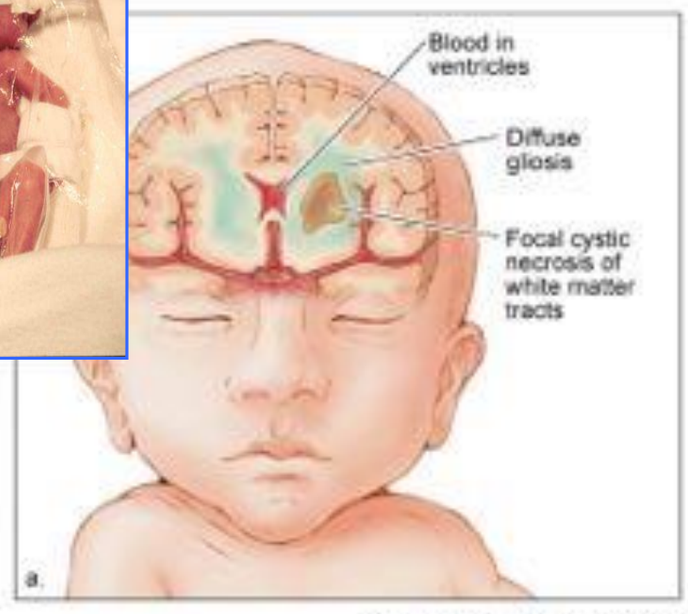


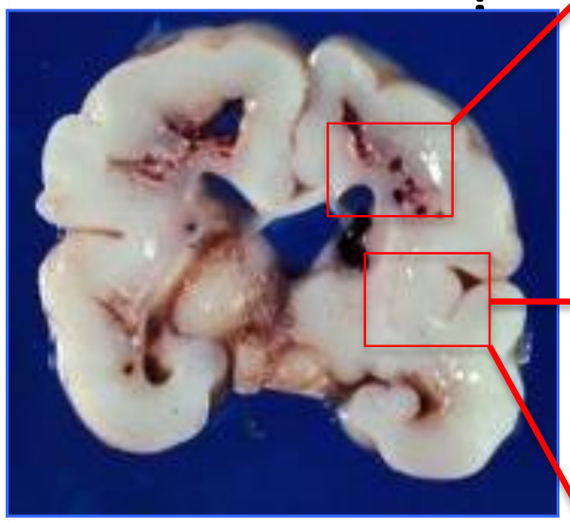


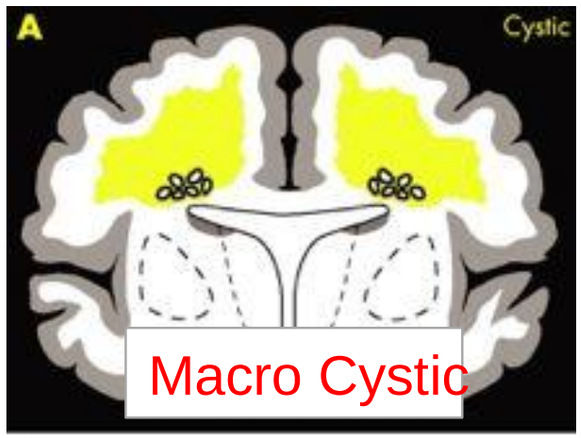
Cerebral Palsy

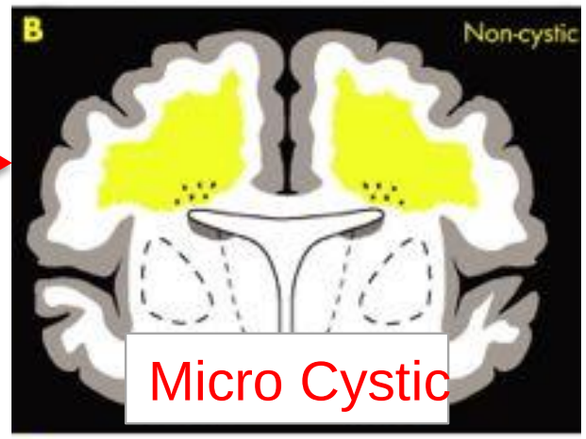
Spectrum of white matter injury

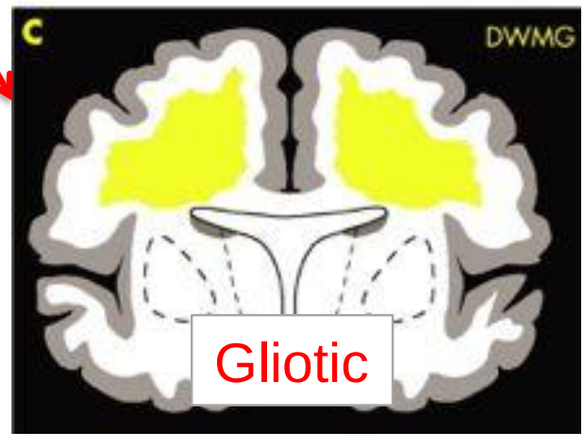






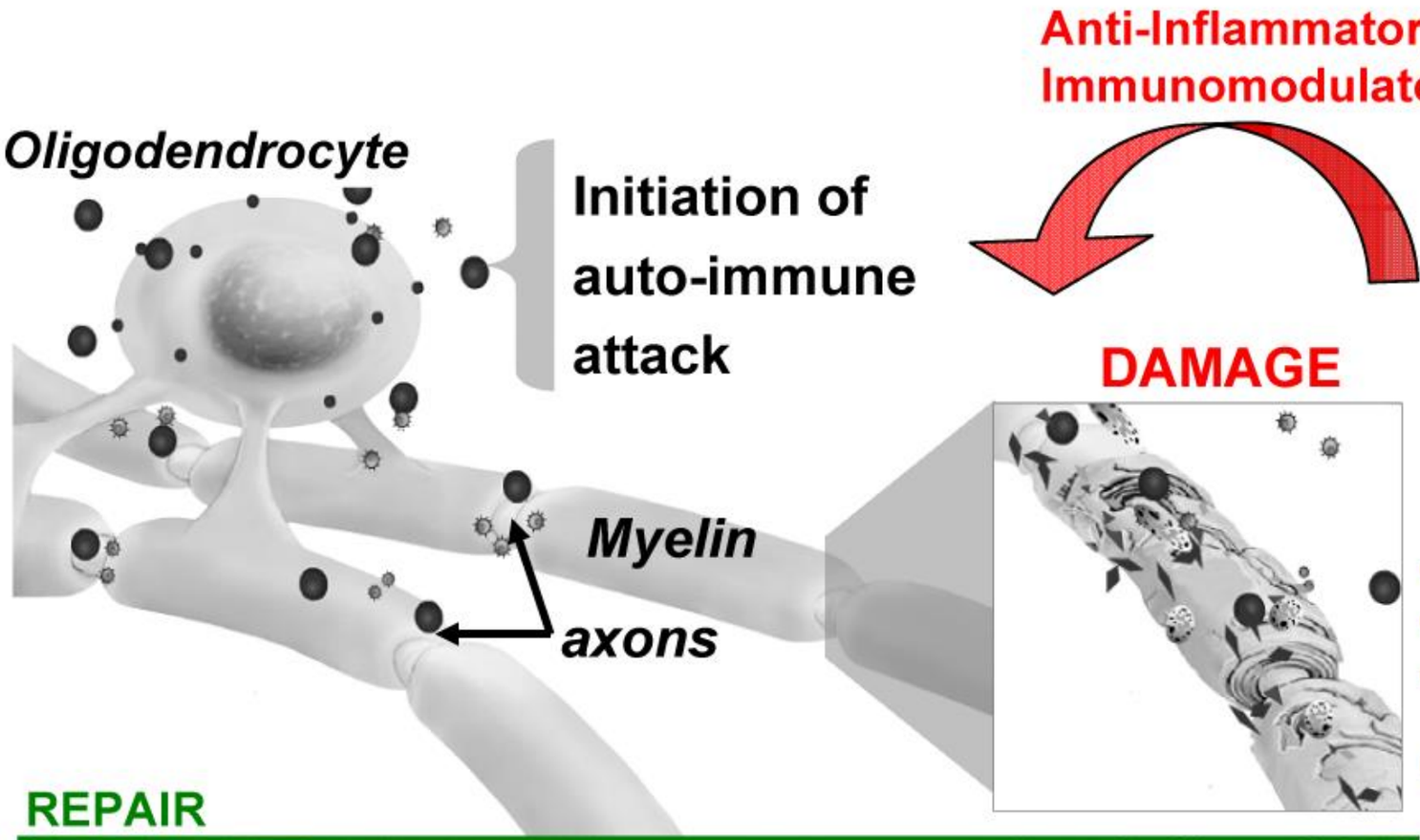






Khwaja and Volpe 2009

Rationale for Repair/Remyelination in Multiple Sclerosis



Anti-Inflammatory, Immunomodulatory

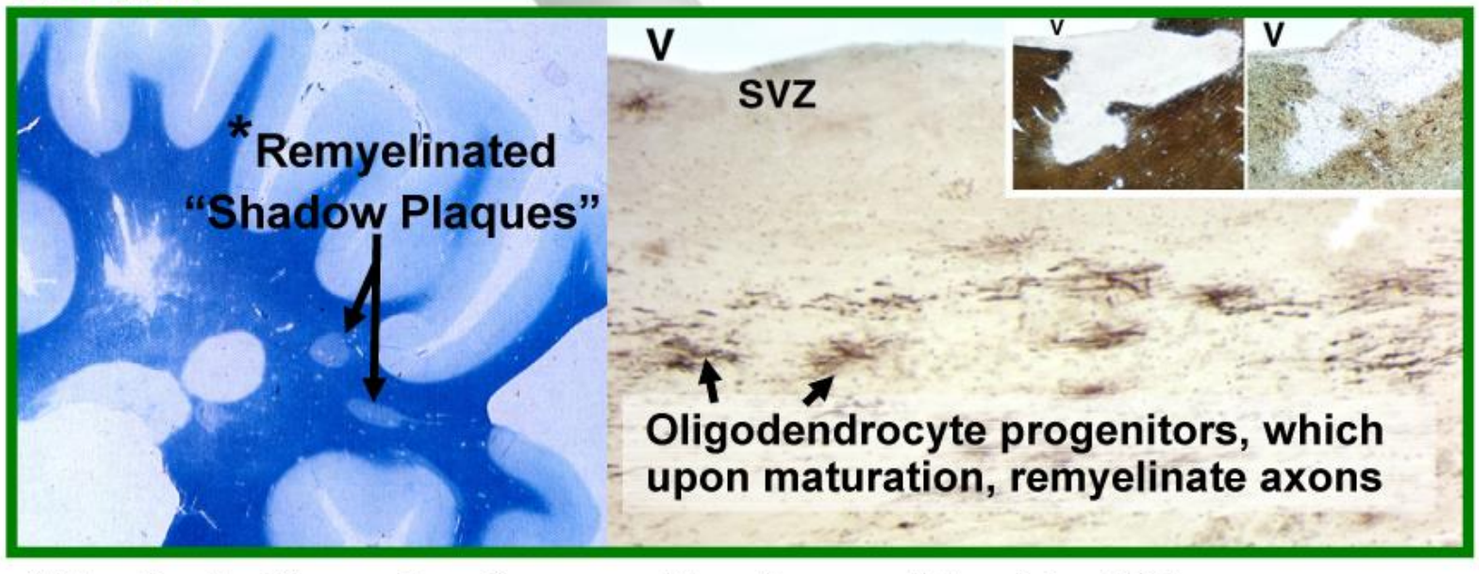
DAMAGE

- myelin destruction
- axonal damage
- disruption of neuronal signaling
- cell death

Small Molecules

Unmet need

REPAIR



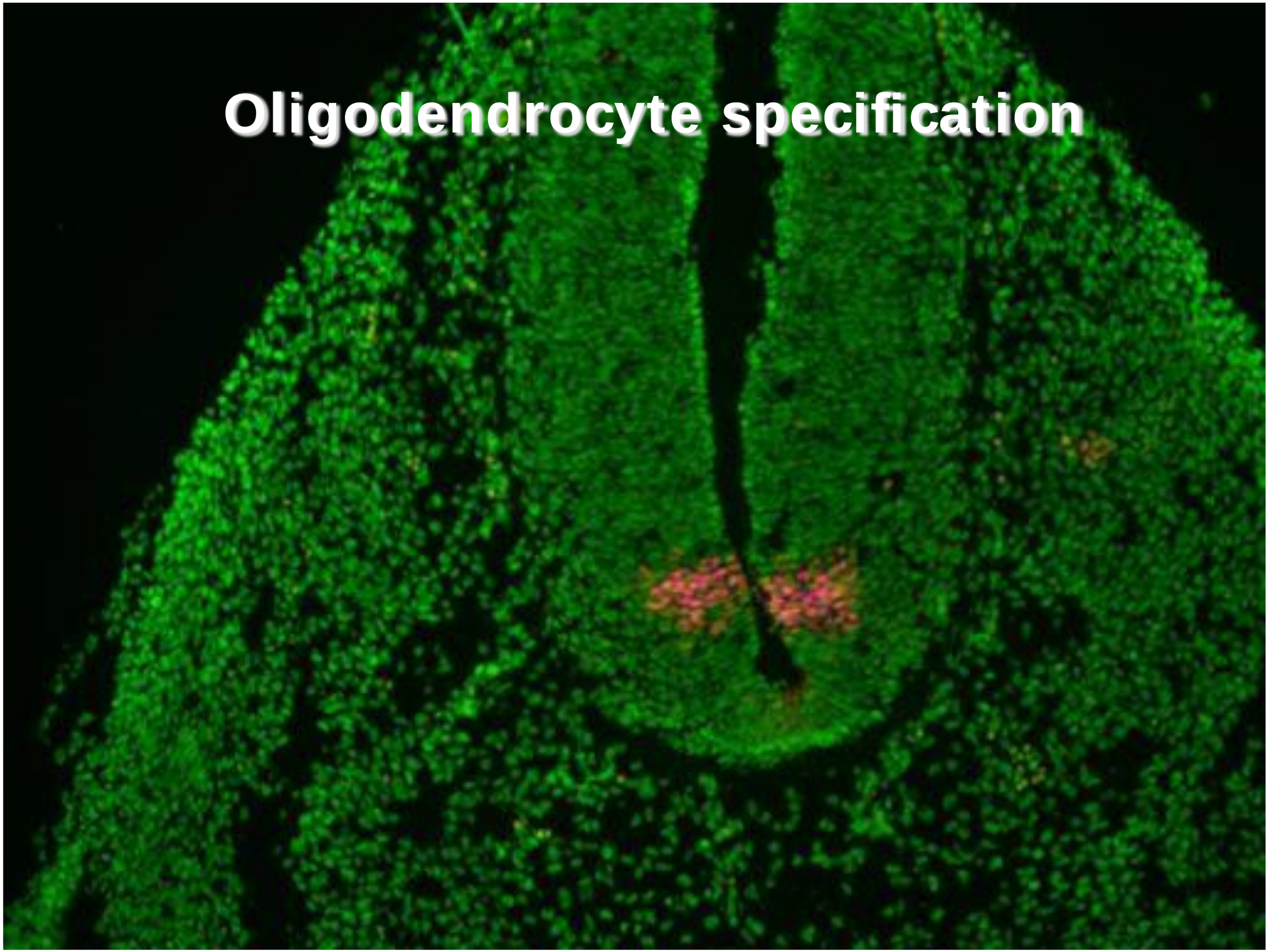
***Limited attempts at remyelination evident in MS**

Protect and Remyelinate Axons

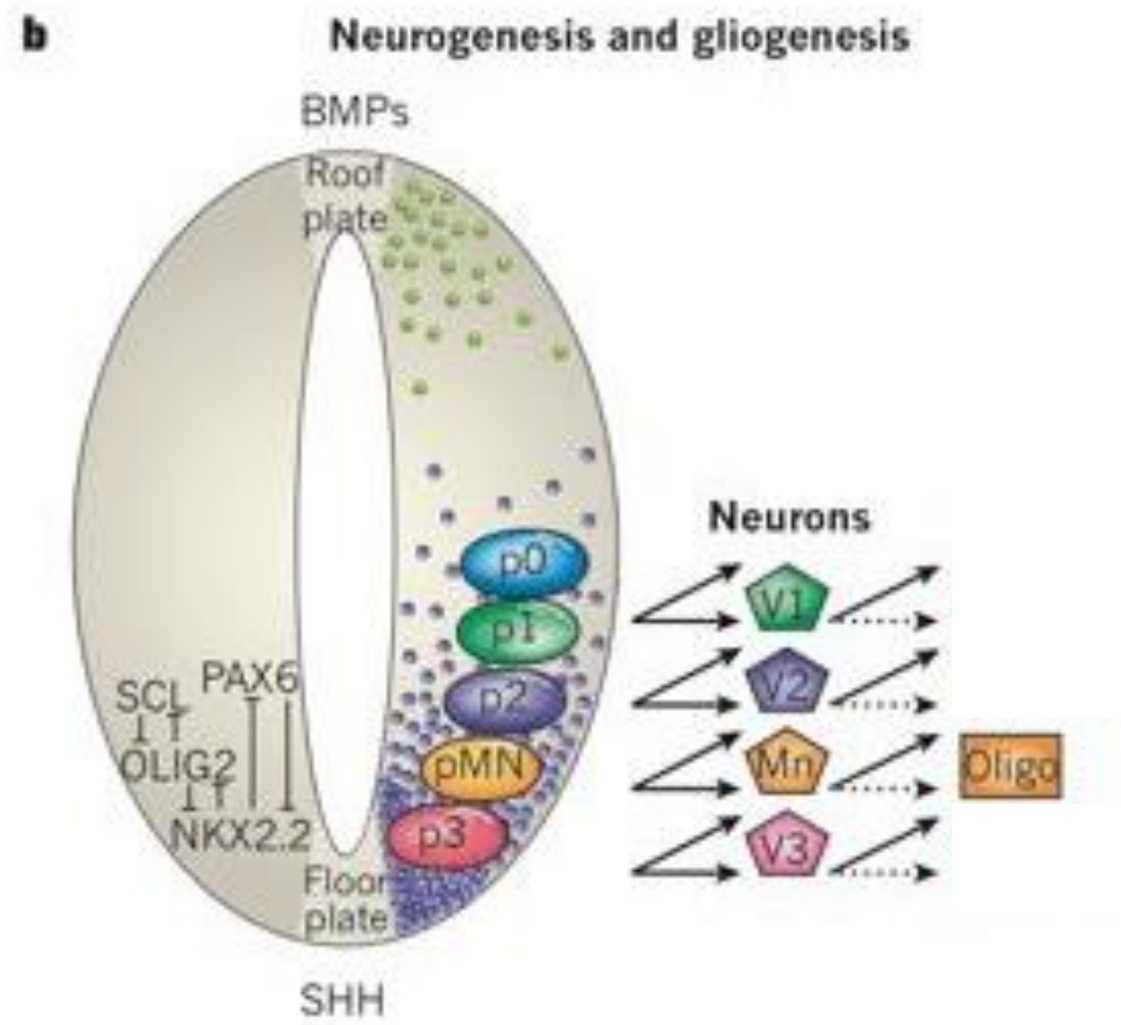
progenitor cell differentiation

Color Atlas of MS and other Myelin Disorders, Colin Adams, 1989, Sheridan Medical Books; J Neurosci 2000 20:6404; Prog Brain Res 2001 132:165

Oligodendrocyte specification



oligodendrocytes specified from the pMN after MNs - a ventral source of oligodendrocytes



•OLPs arise from the pMN in restricted domain, after the time of MN generation

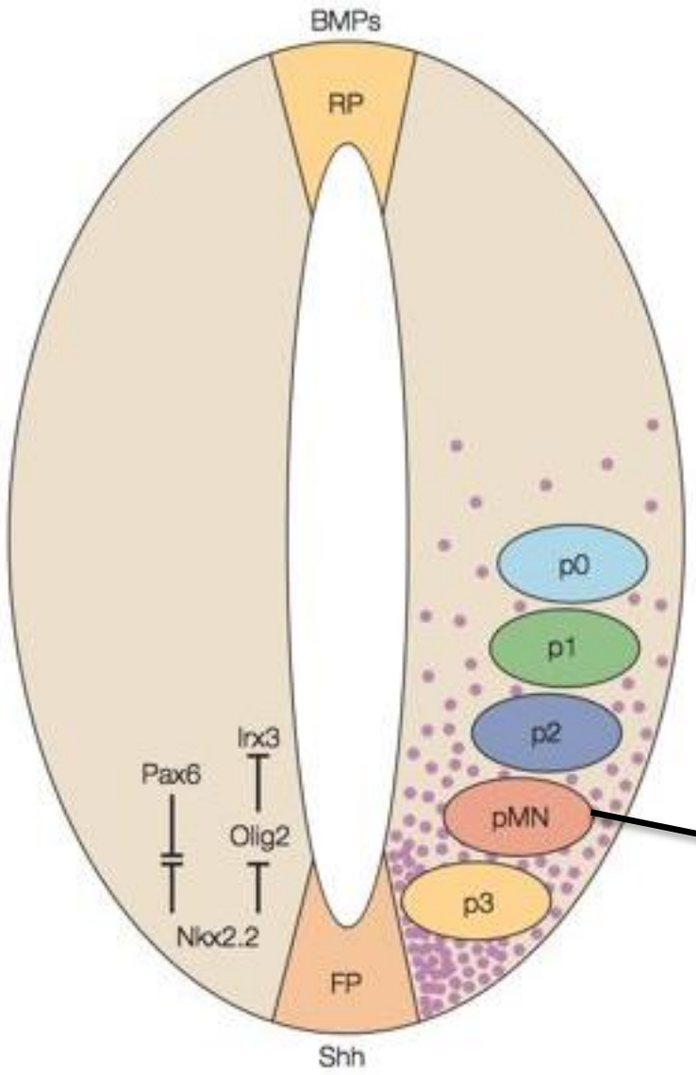
•Restricted domain surprising considering OL found abundantly in white matter and grey matter

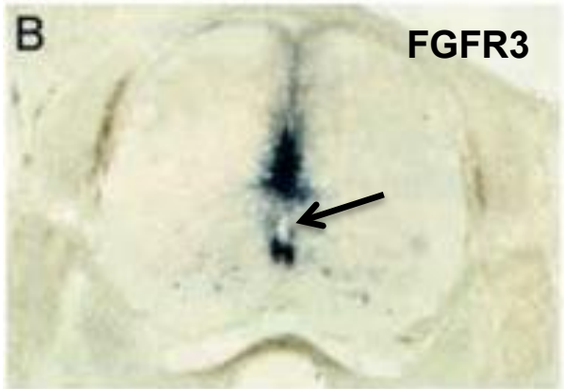
•Link between MN and OLP??

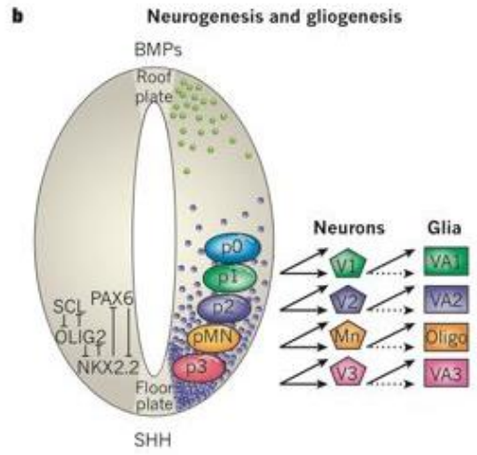
•Evolutionary relic? Advantage of myelinating motor circuits?

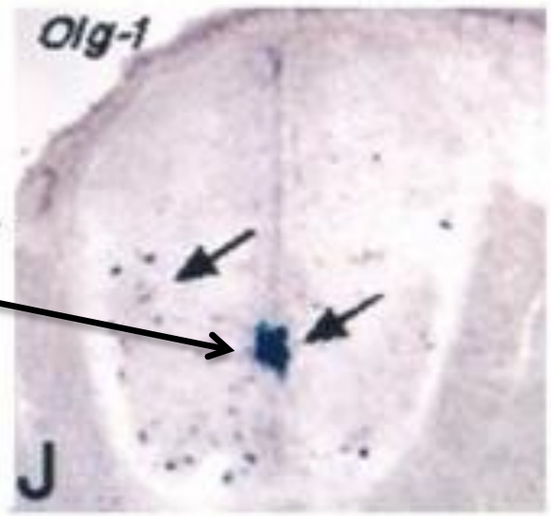
•Restricted domain of specification also suggests may fall under same cues as earlier patterning of neurons?

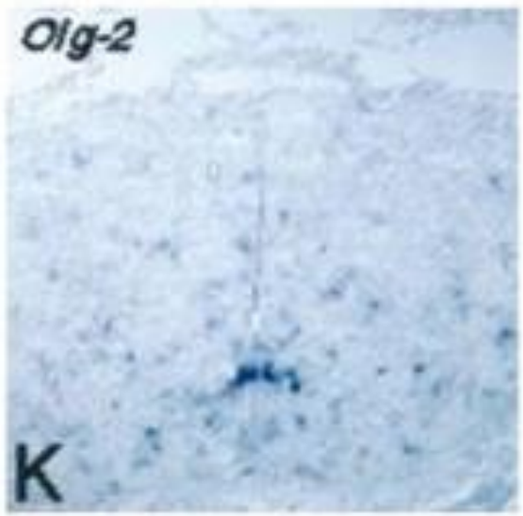
Astrocytes and oligodendrocytes from dif erent domains



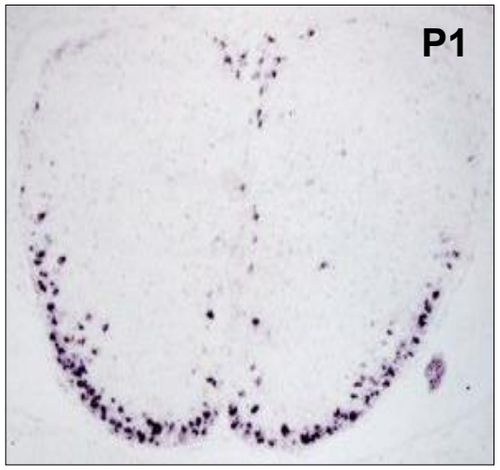


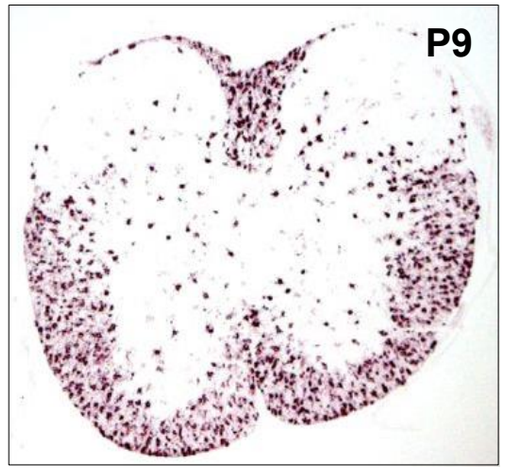


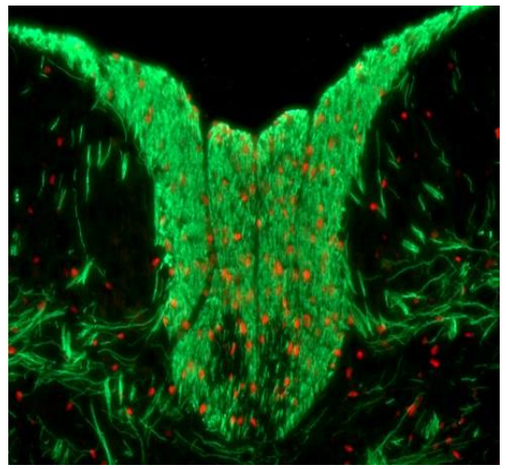


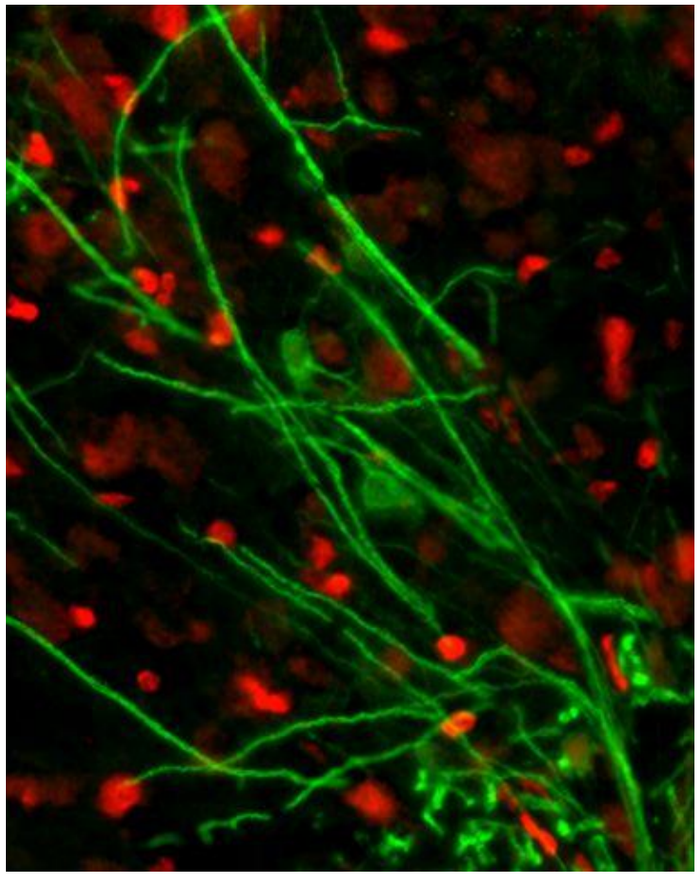


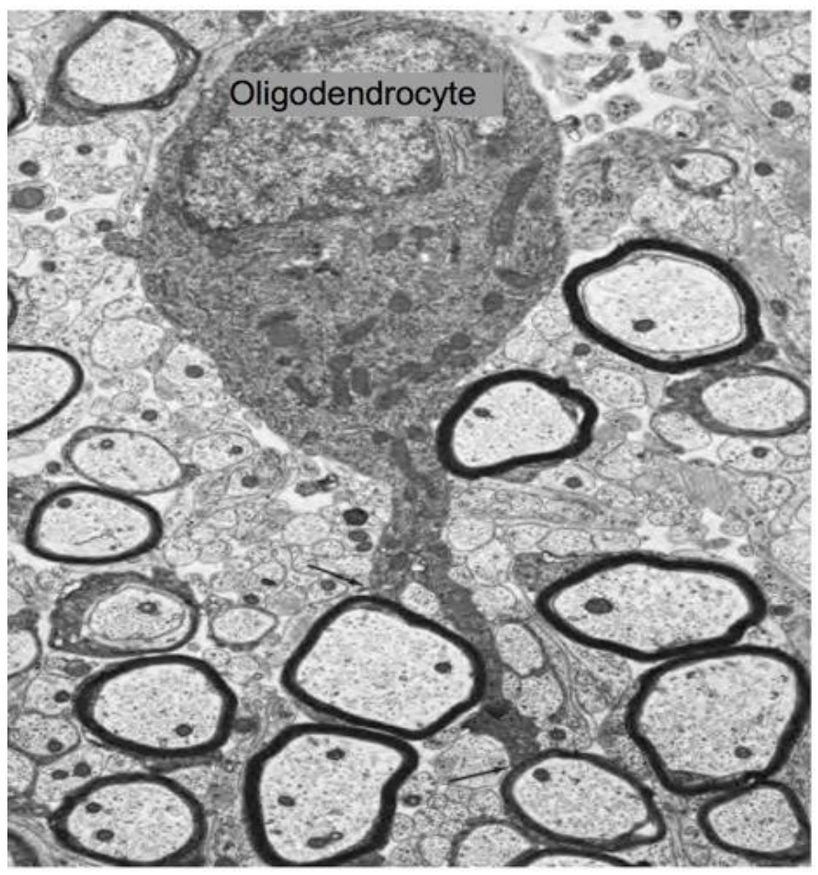
Dif erentiation and myelination following specification and migration



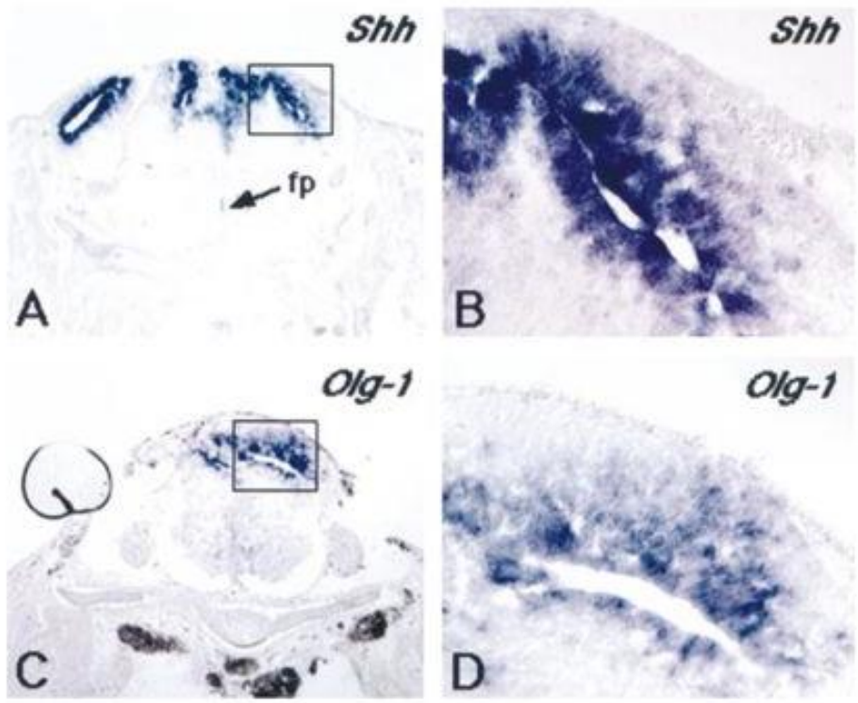








Shh is necessary and sufficient for Olig gene expression



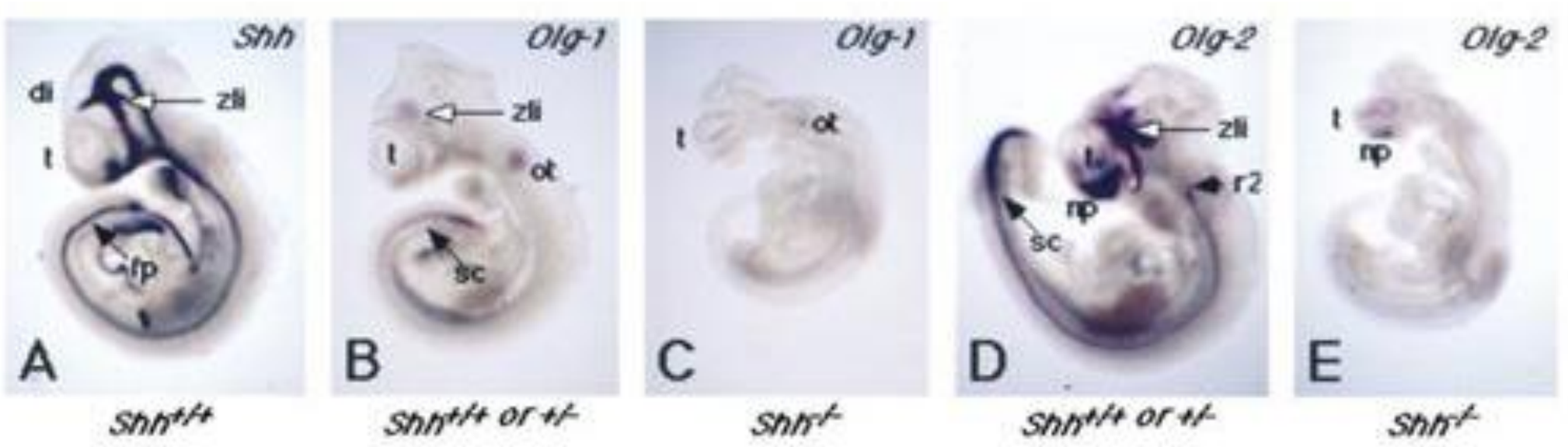
•Shh patterns the spinal cord via regulation of TF expression, as discussed earlier

•Do Olig genes fall under its regulation?

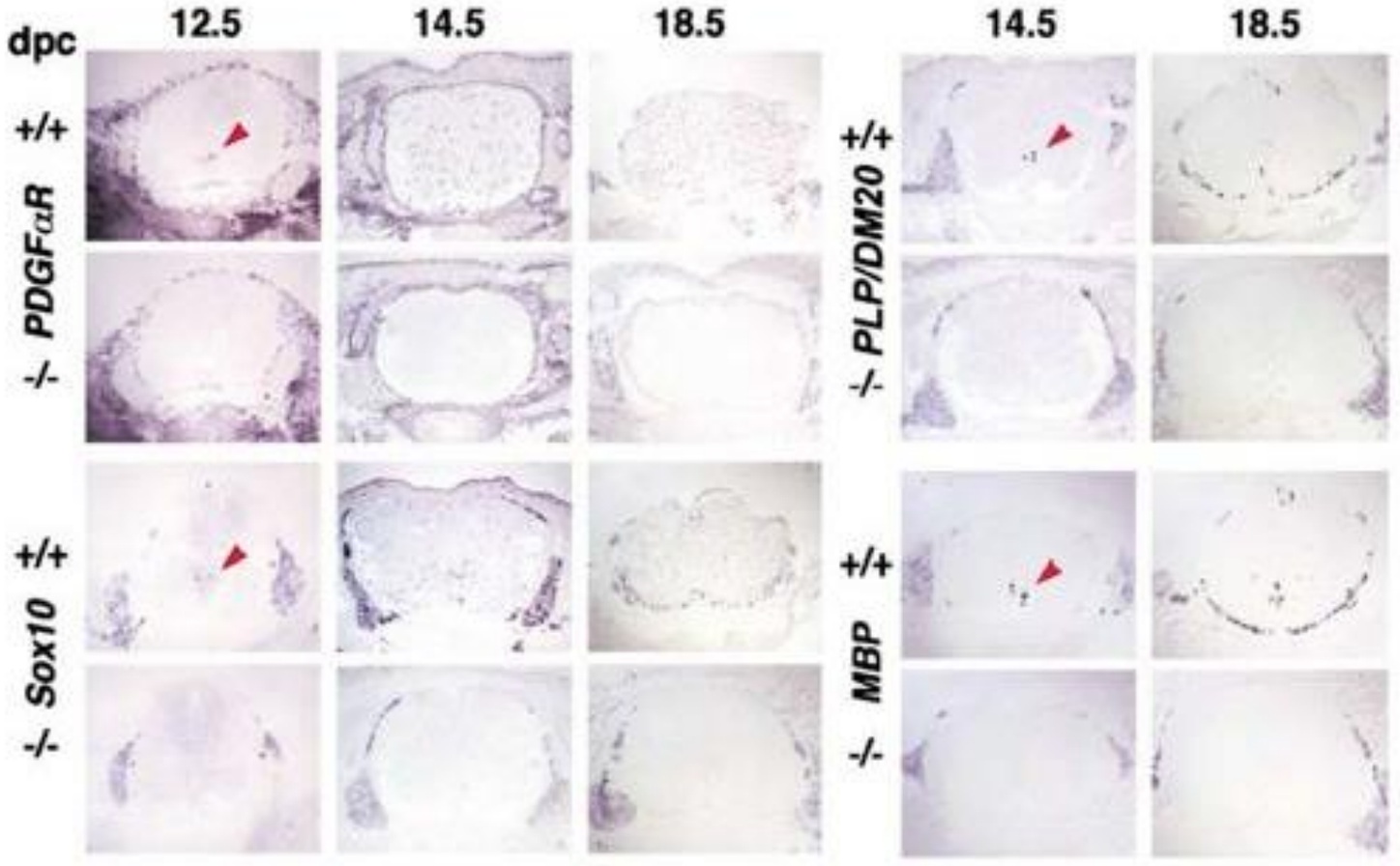
•Olig1 and 2 ectopically induced under action of Shh

•Failure of Olig1 and 2 expression in animals lacking Shh

•Olig genes ***under same patterning influence as TF genes of neuronal patterning***



Olig2 required for all oligodendrocyte specification

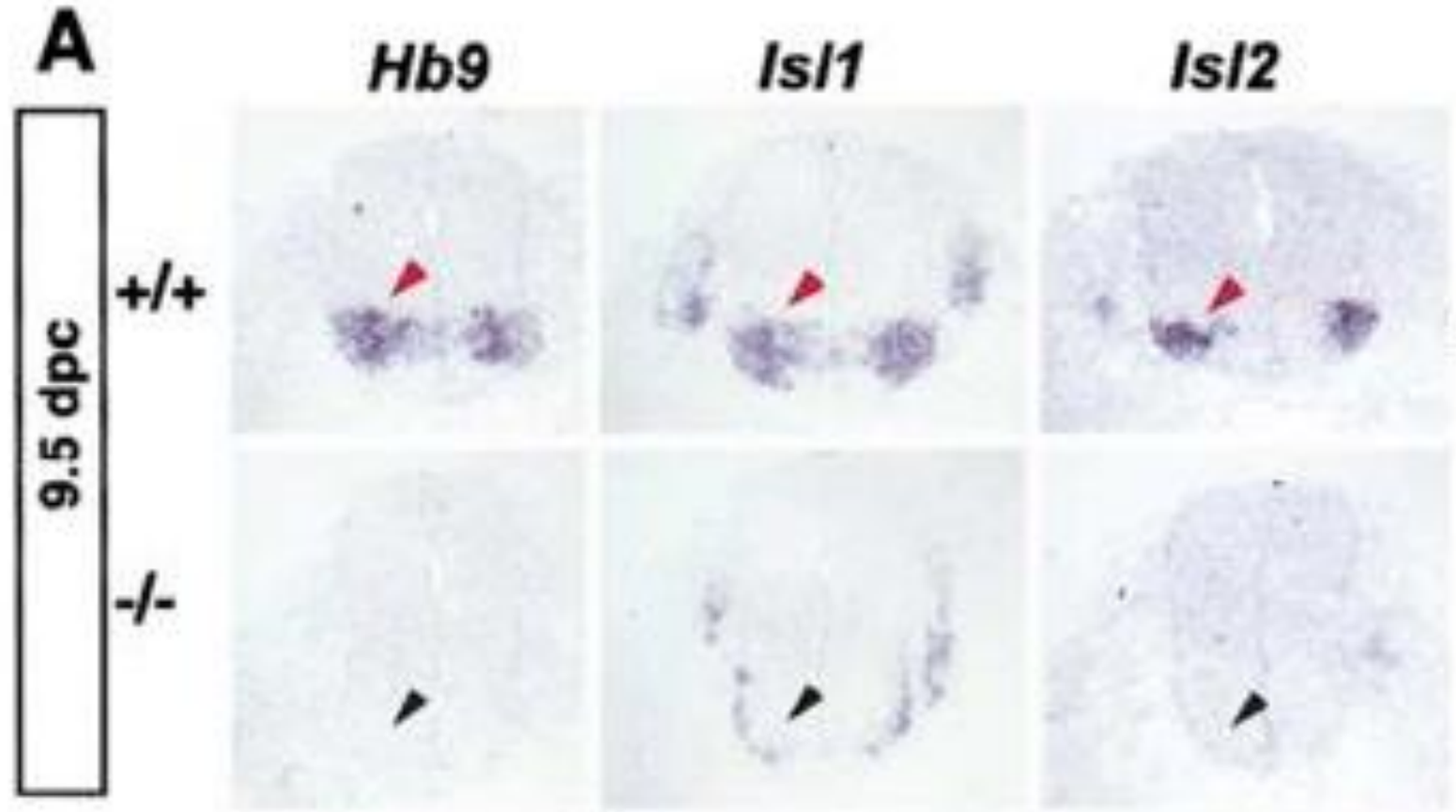


•Olig proteins essential for development of all OL in CNS

•Olig2 null lack all OLPs in spinal cord. Generate small pockets of OLPs in forebrain, and near-normal in midbrain and hindbrain…compensation by Olig1

•Compound mutant lack all OLPs throughout CNS. Overlapping functions of two Olig genes, in highly context dependent manner

Olig2 required for all motor neuron specification.. The link between OL and MN deepens



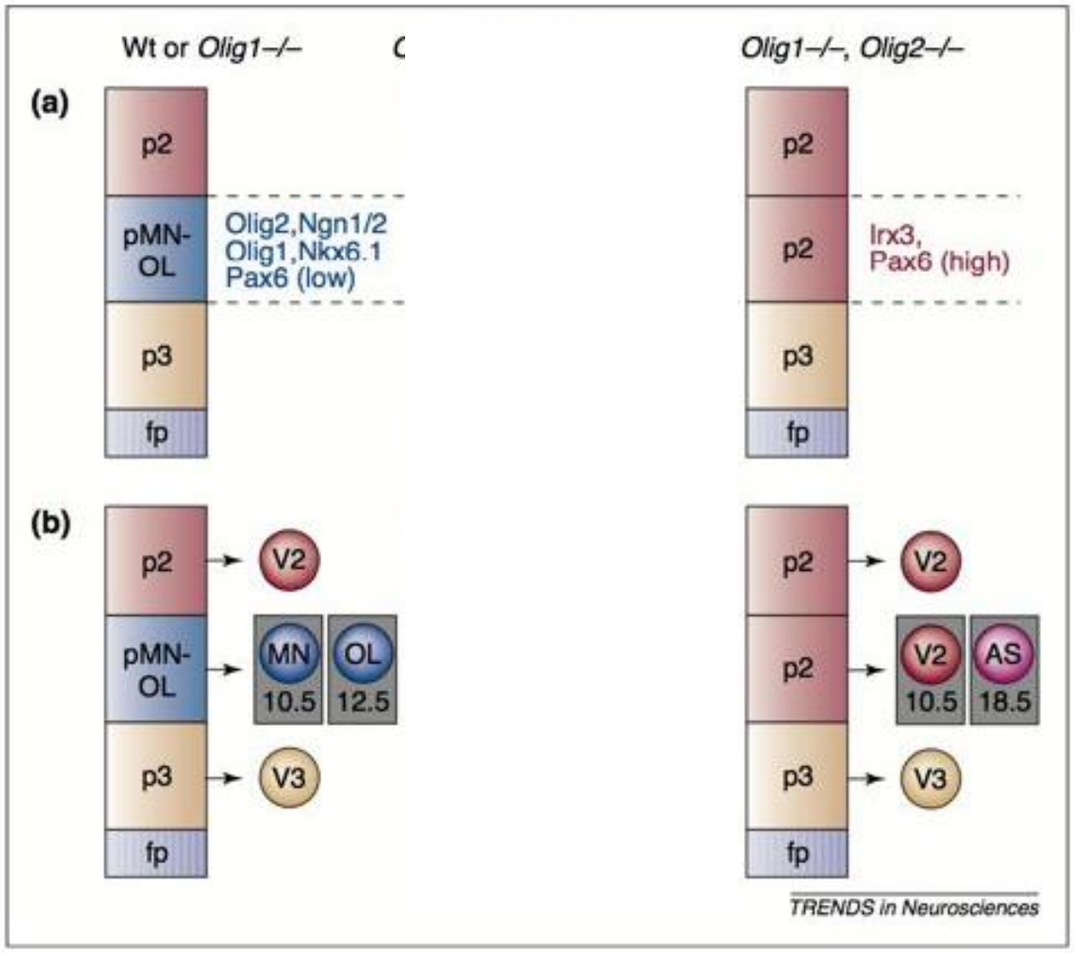
•Olig proteins also expressed in pMN at time of motor neuron production.

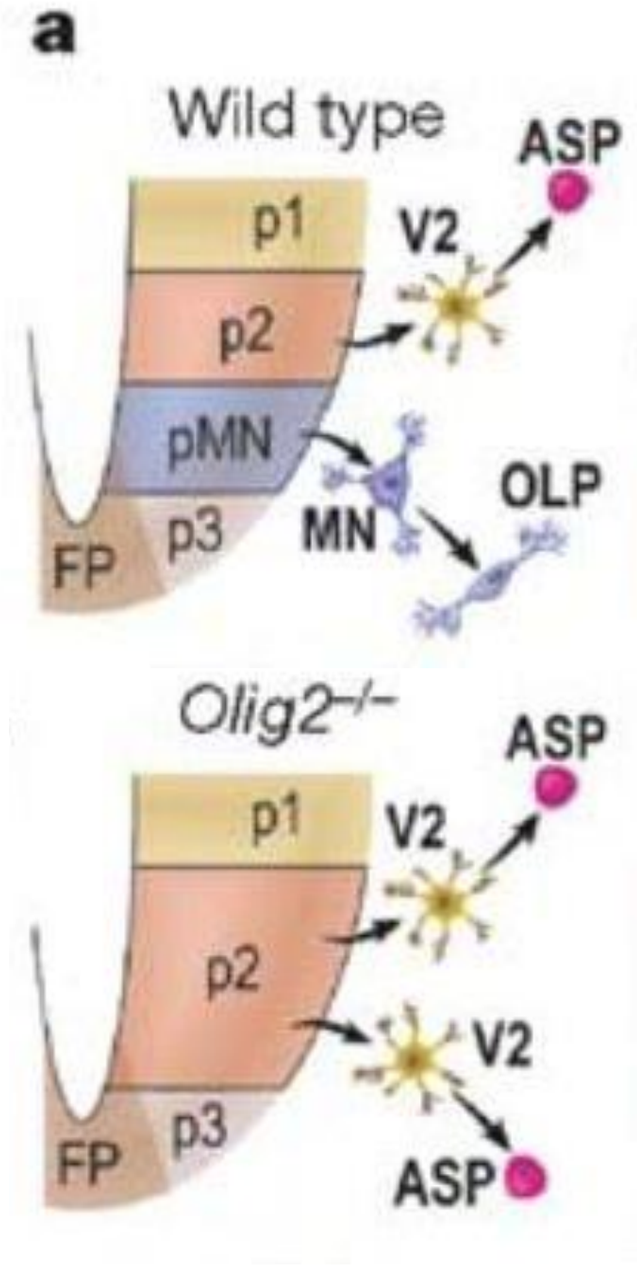
•Olig2 null animals have total lack of motor neurons , and Olig1 cannot compensate for this

•Olig2 ectopic expression can alter dorsal expansion of pMN domain

•Olig2 alone expressed ectopically in dorsal spinal cord cannot induce motor neurons, but can along with Ngn2 expression. Thus Olig proteins act in concert with other TFs to promote motor neuron fate.

motor neuron/ oligodendrocyte connection

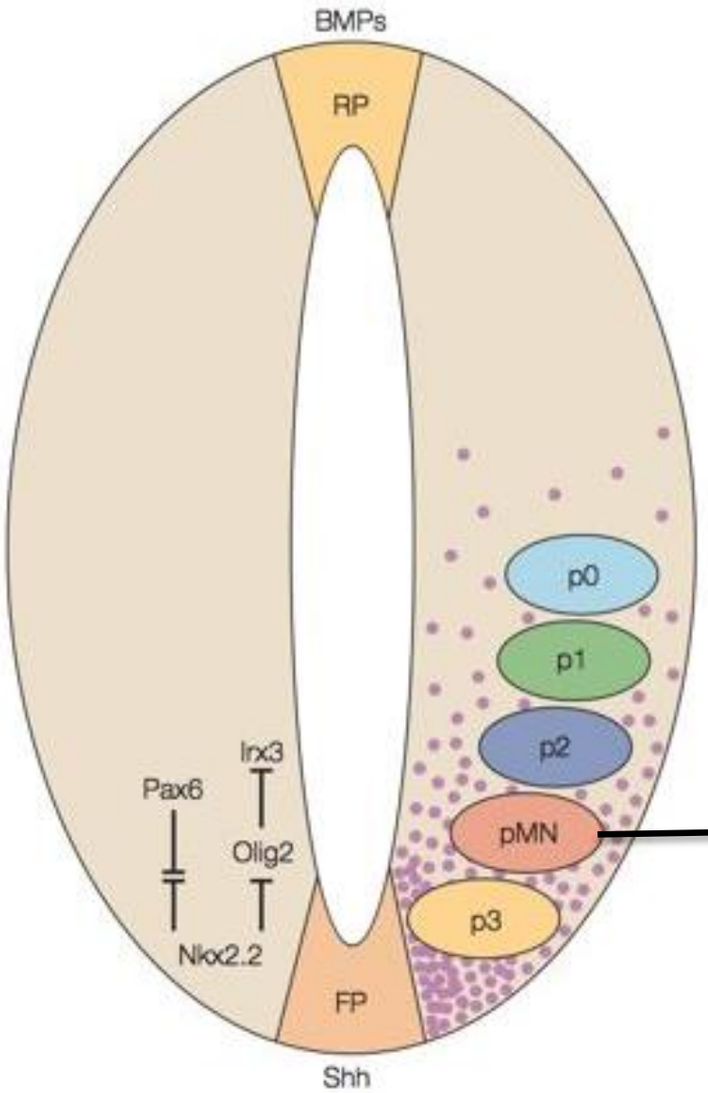




Astrocytes not af ected by loss of Olig2

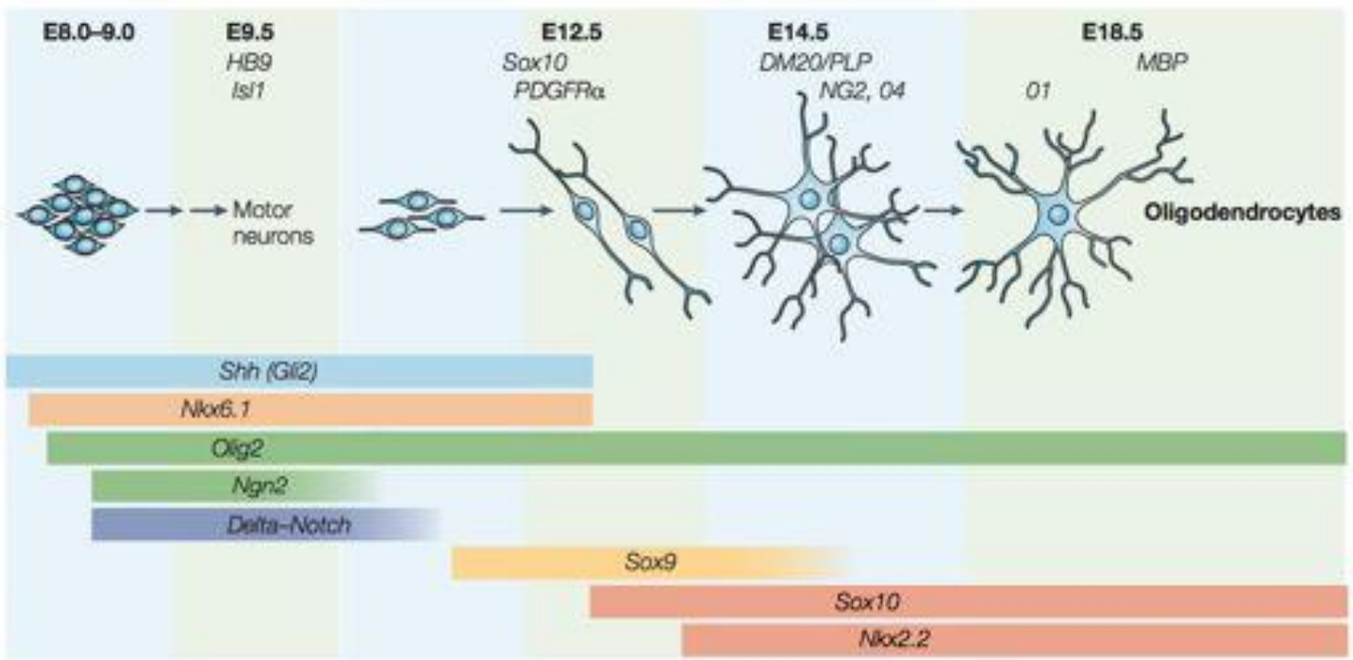
- Olig functions also necessary for appropriate pattern formation
- Compound mutants leads to pMN to P2 conversion.
- Olig repression of Irx3 in patterning

The Neuron- glial switch in the pMN

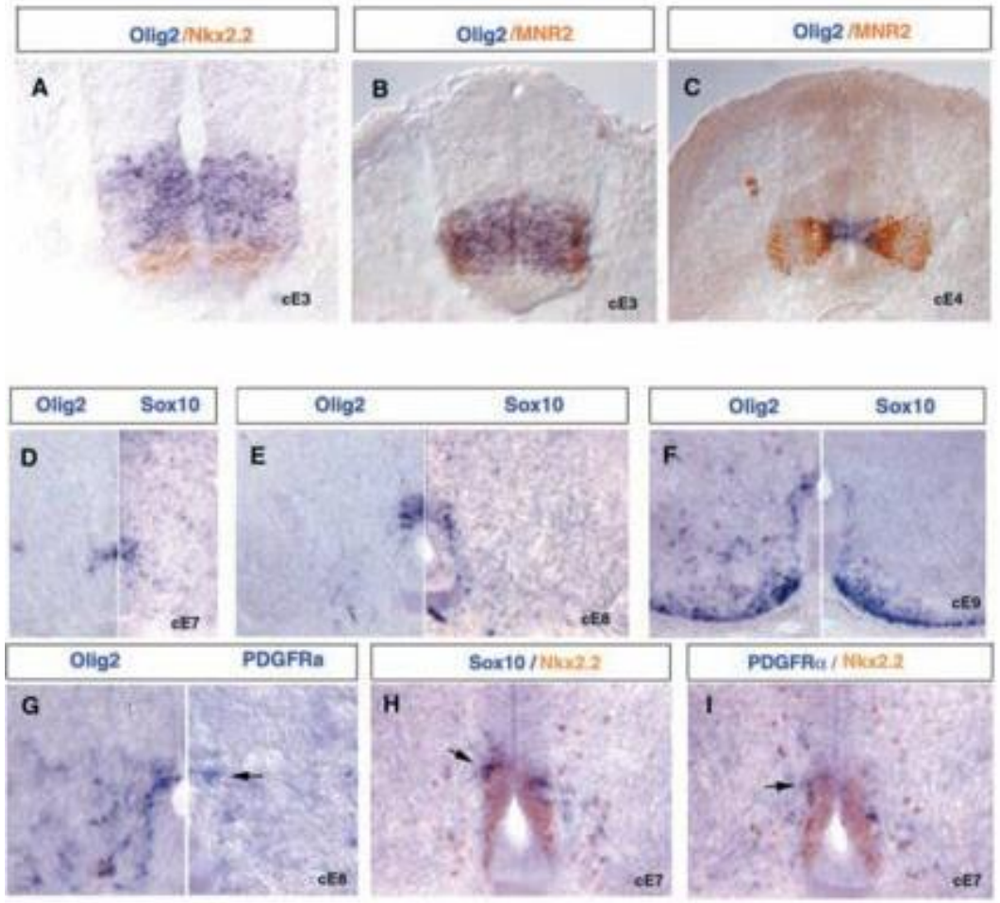


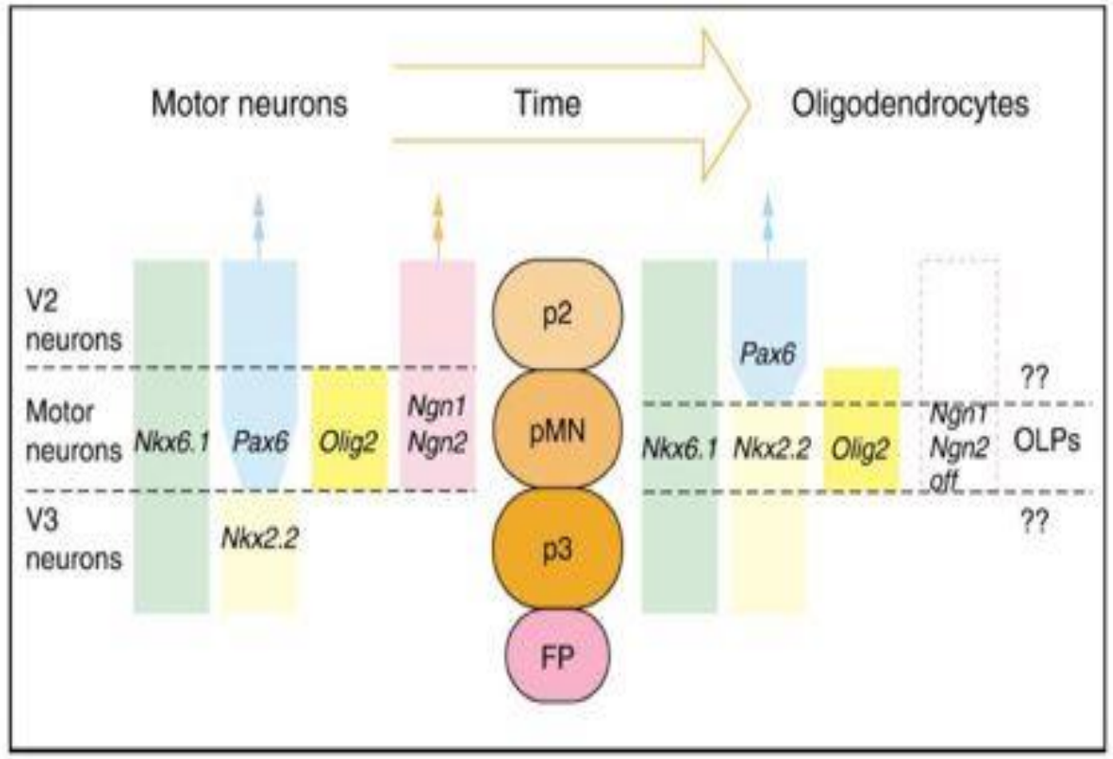
•Successive outputs of MN and OLP. Shh and Oligs required throughout. Additional factors must therefore be evoked for switch

•Switch very complex. Downregulation of pro-neural, such as Ngn2, maintenance of glial precusor potential requires Delta-Notch signaling. Switch also requires pro-glial expression of eg. Sox9. Later phases OLP maturation are Shh independent and require Sox10 and Nkx2.2



The Neuron- glial switch in the pMN

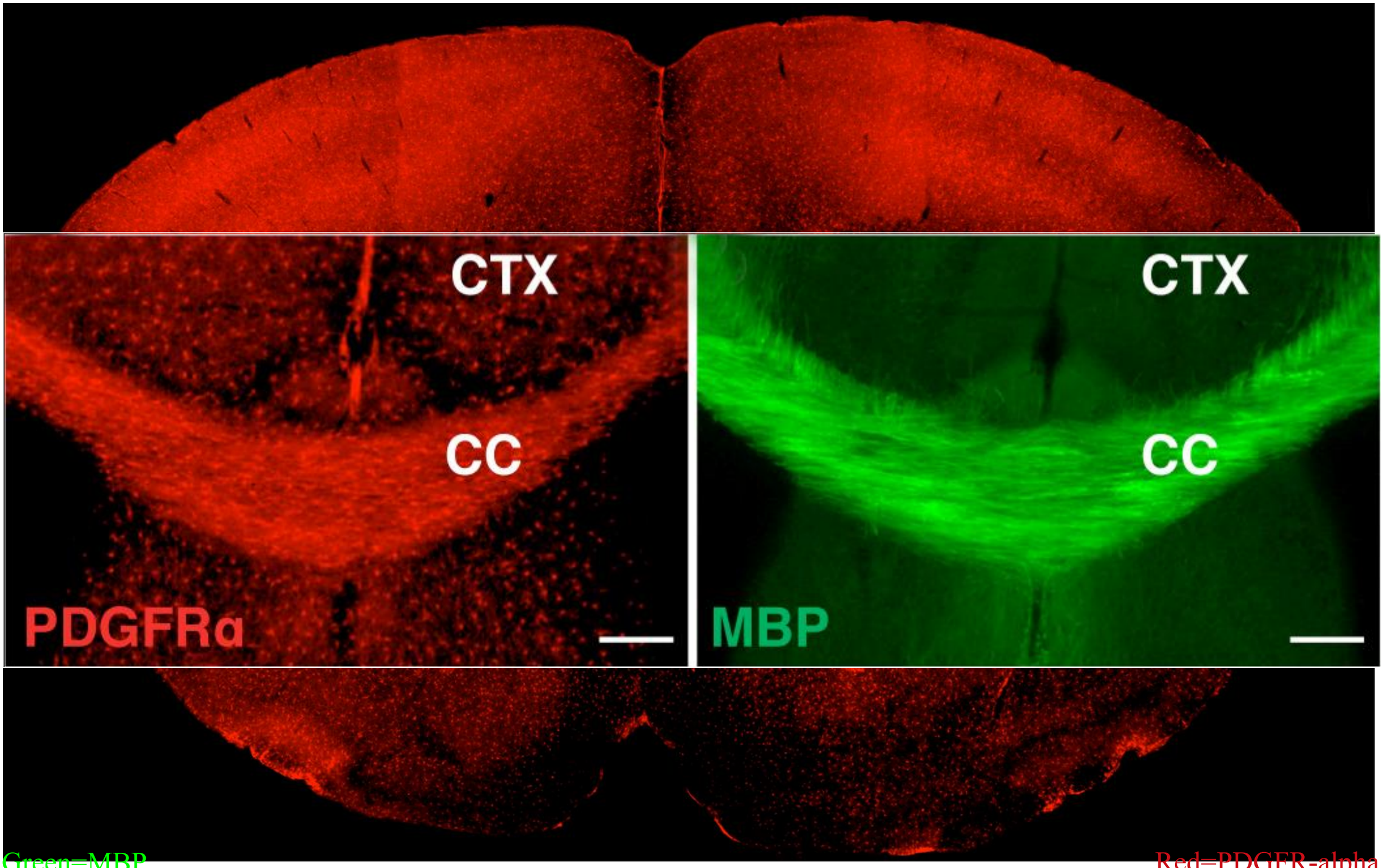




Nkx2.2 co- operates with Olig2 in OL maturation

The Adult Oligodendrocyte Precursor Cell

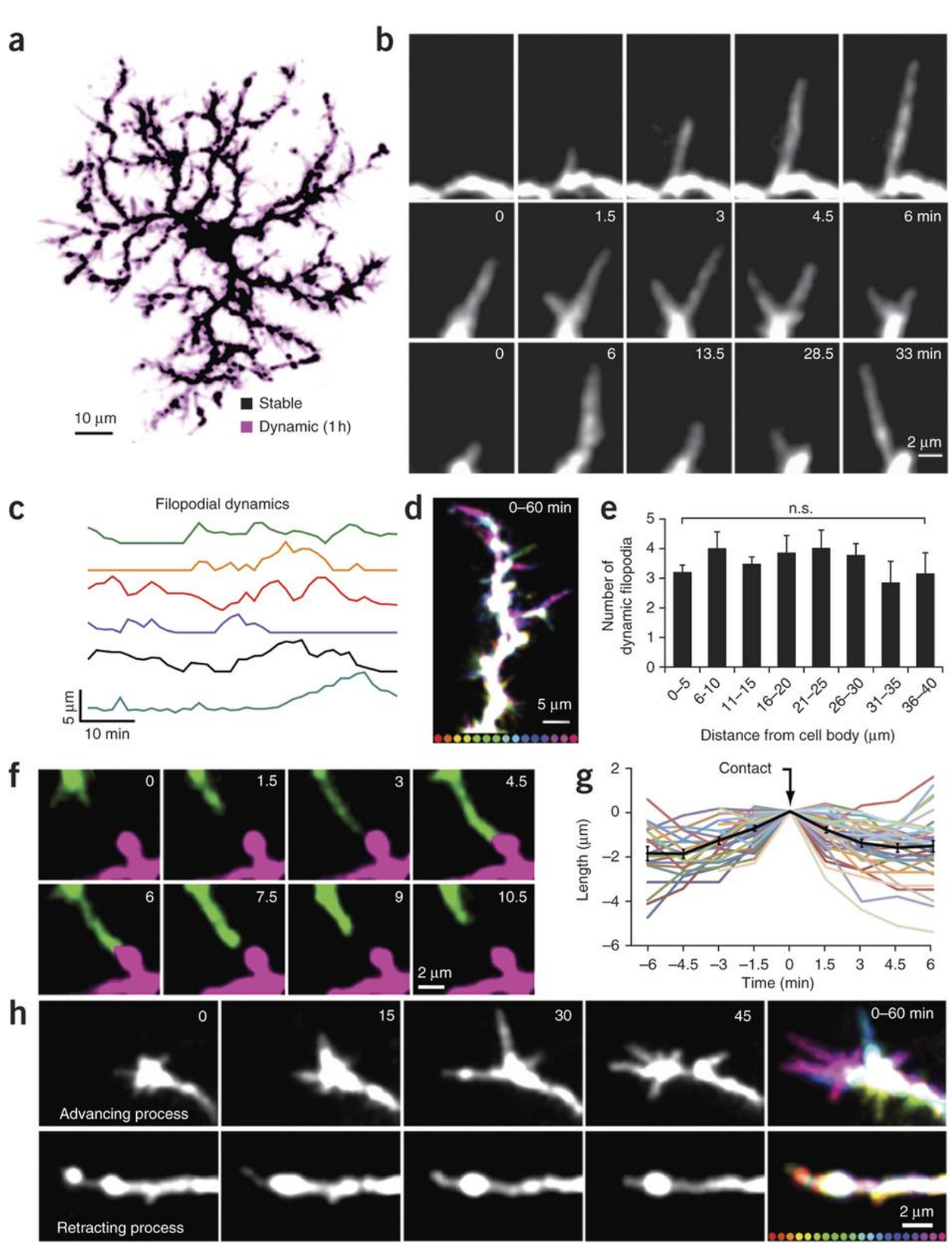
What function do they serve?

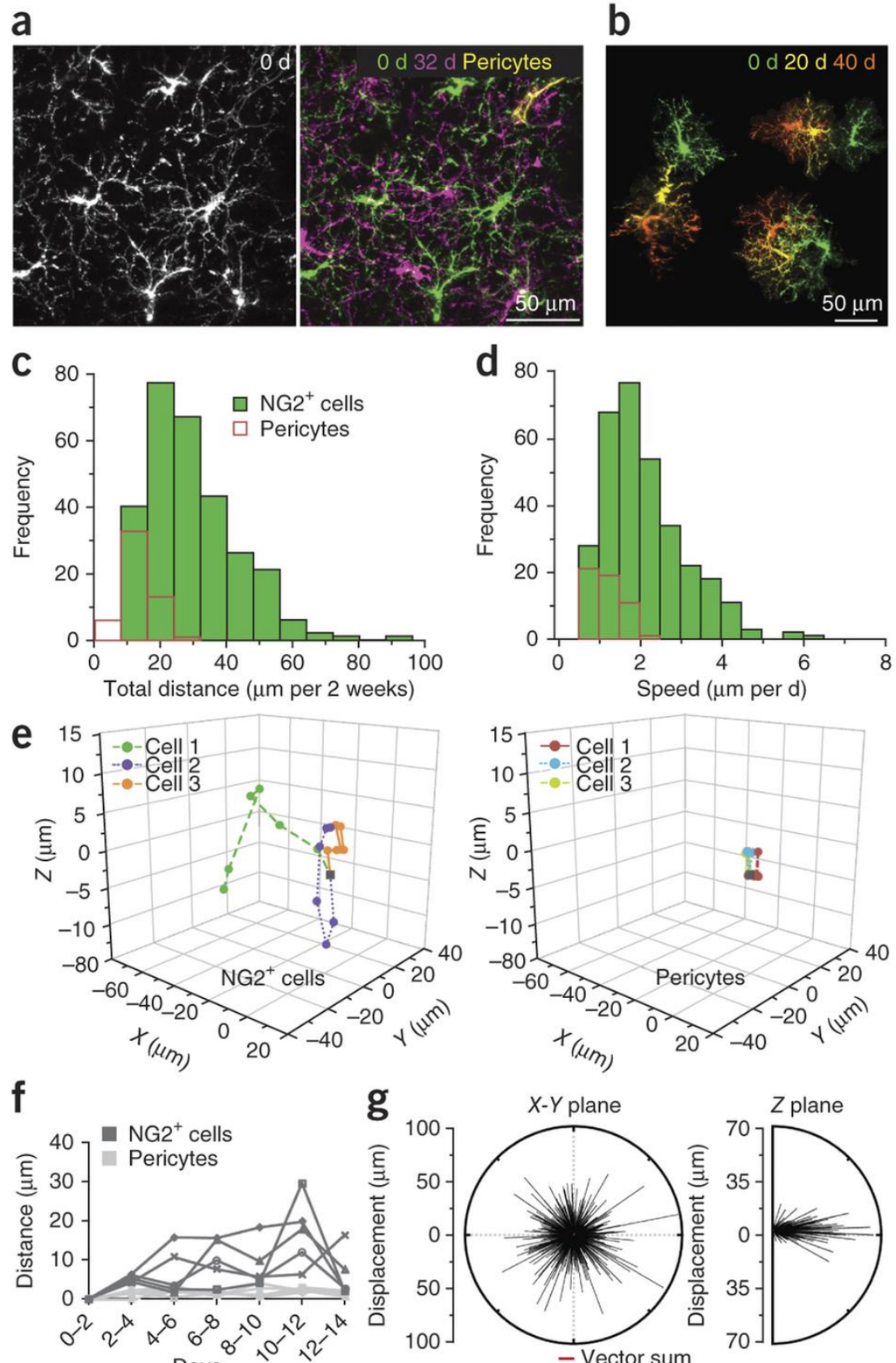


Green=MBP

Red=PDGFR-alpha

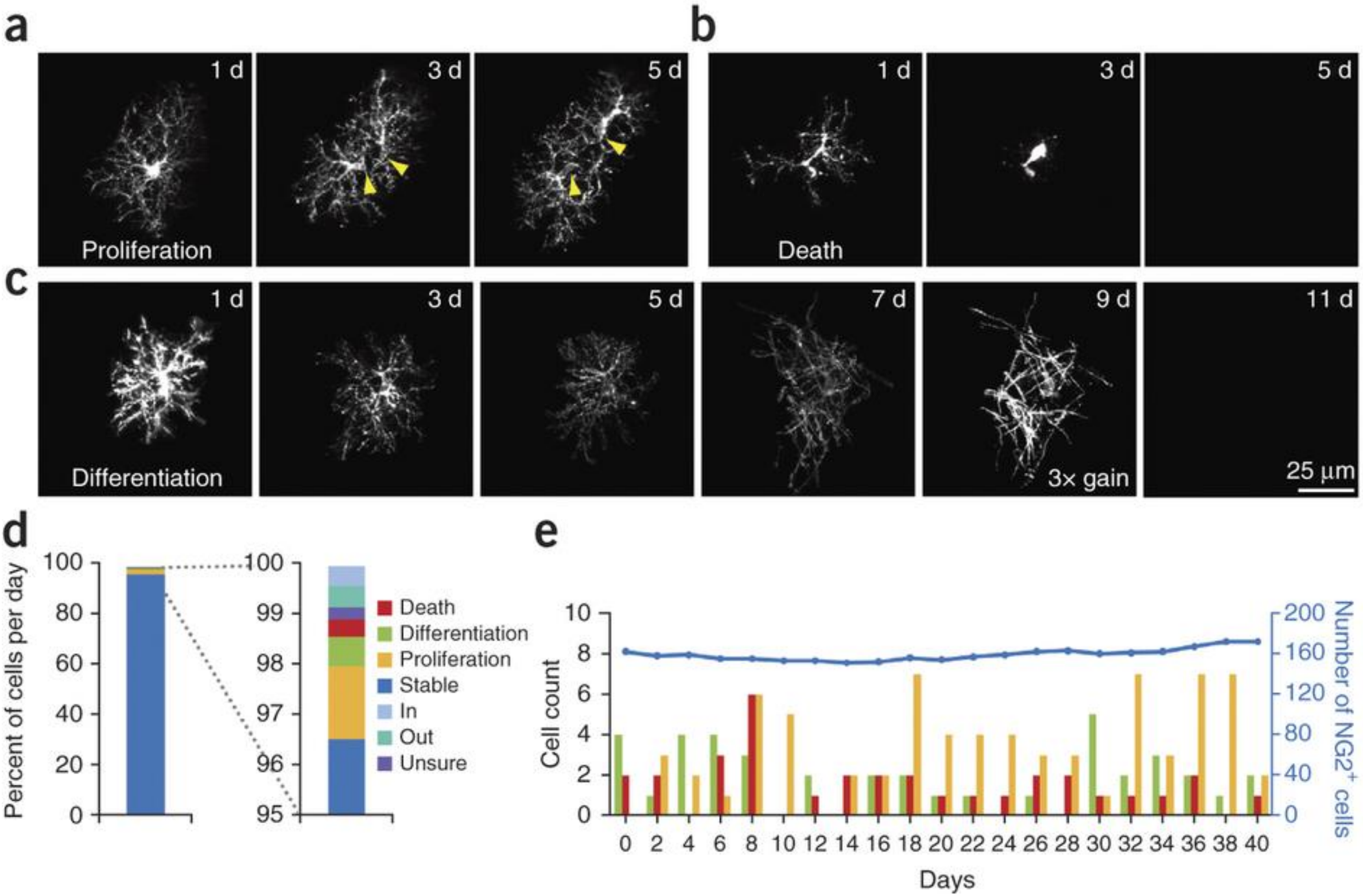
OPCs continually change their position in the adult cortex, extend dynamic filopodia and exhibit self-repulsion in the adult cortex.





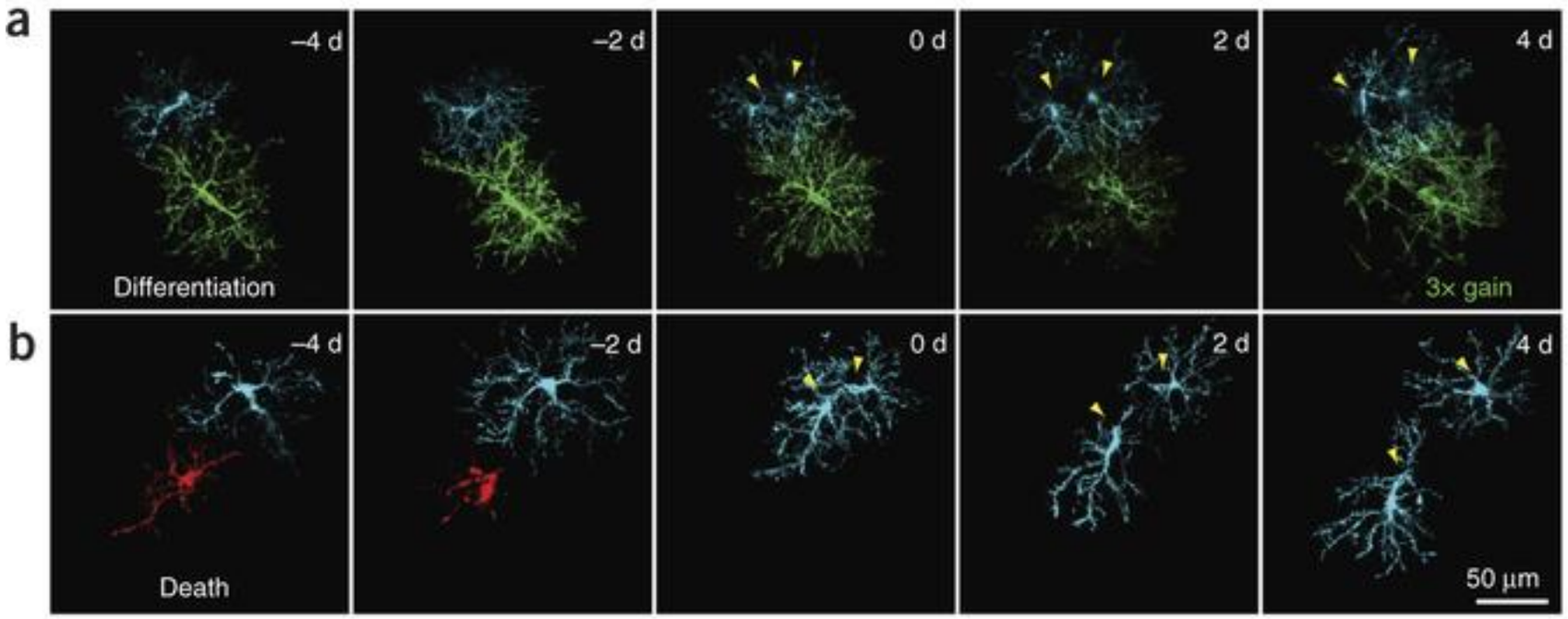
Hughes et al., 2013

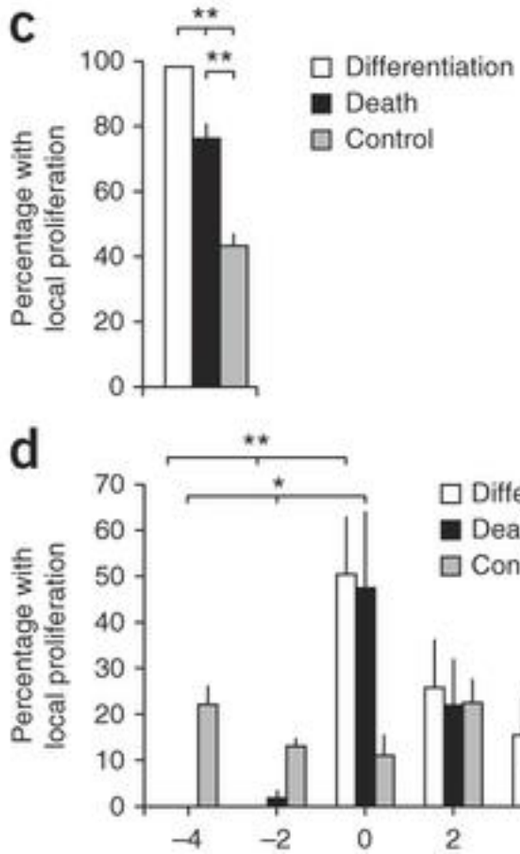
OPC density is maintained despite proliferation, differentiation, and death



Hughes et al., 2013

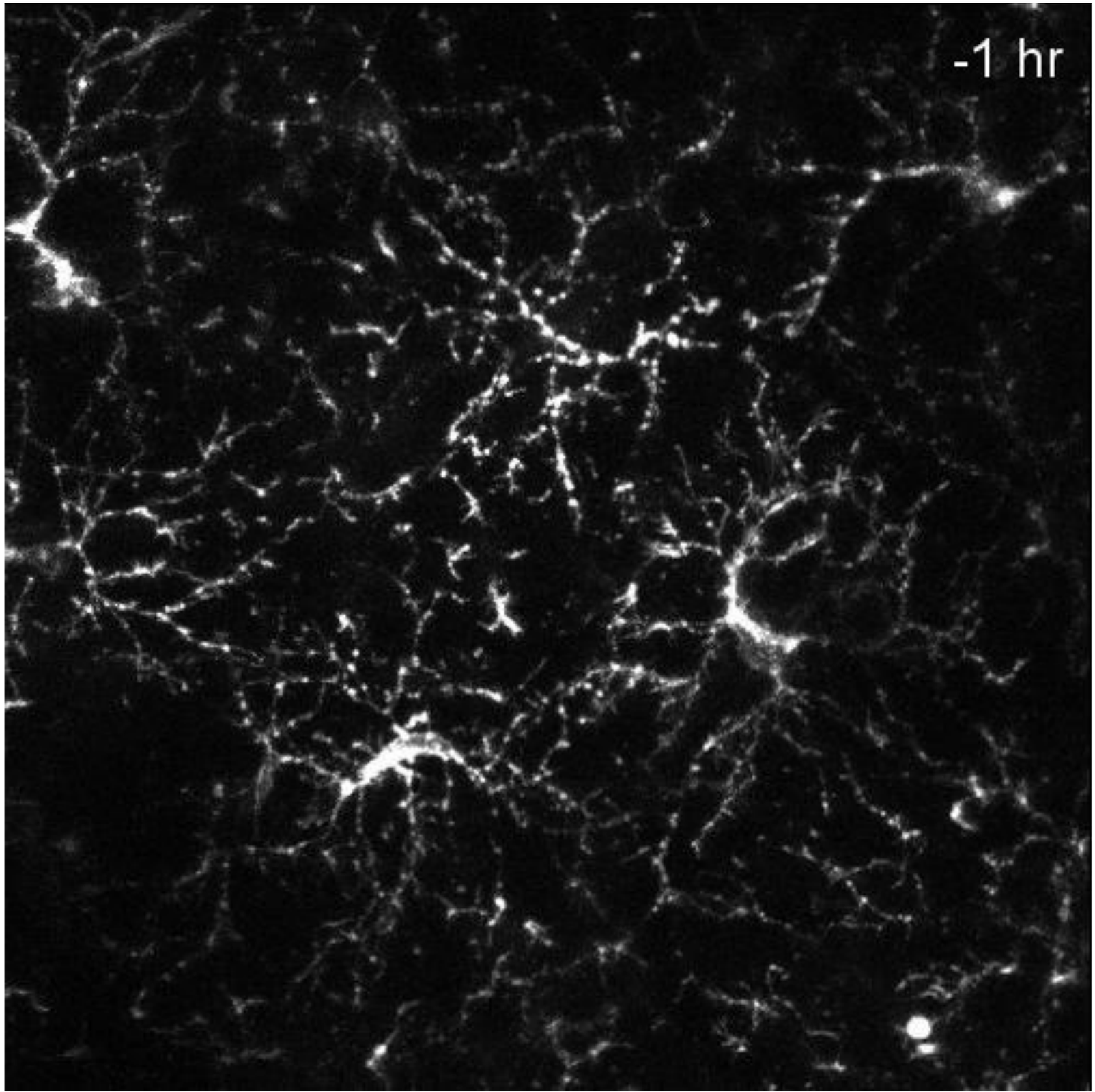
NG2⁺ cell density is maintained through local proliferation





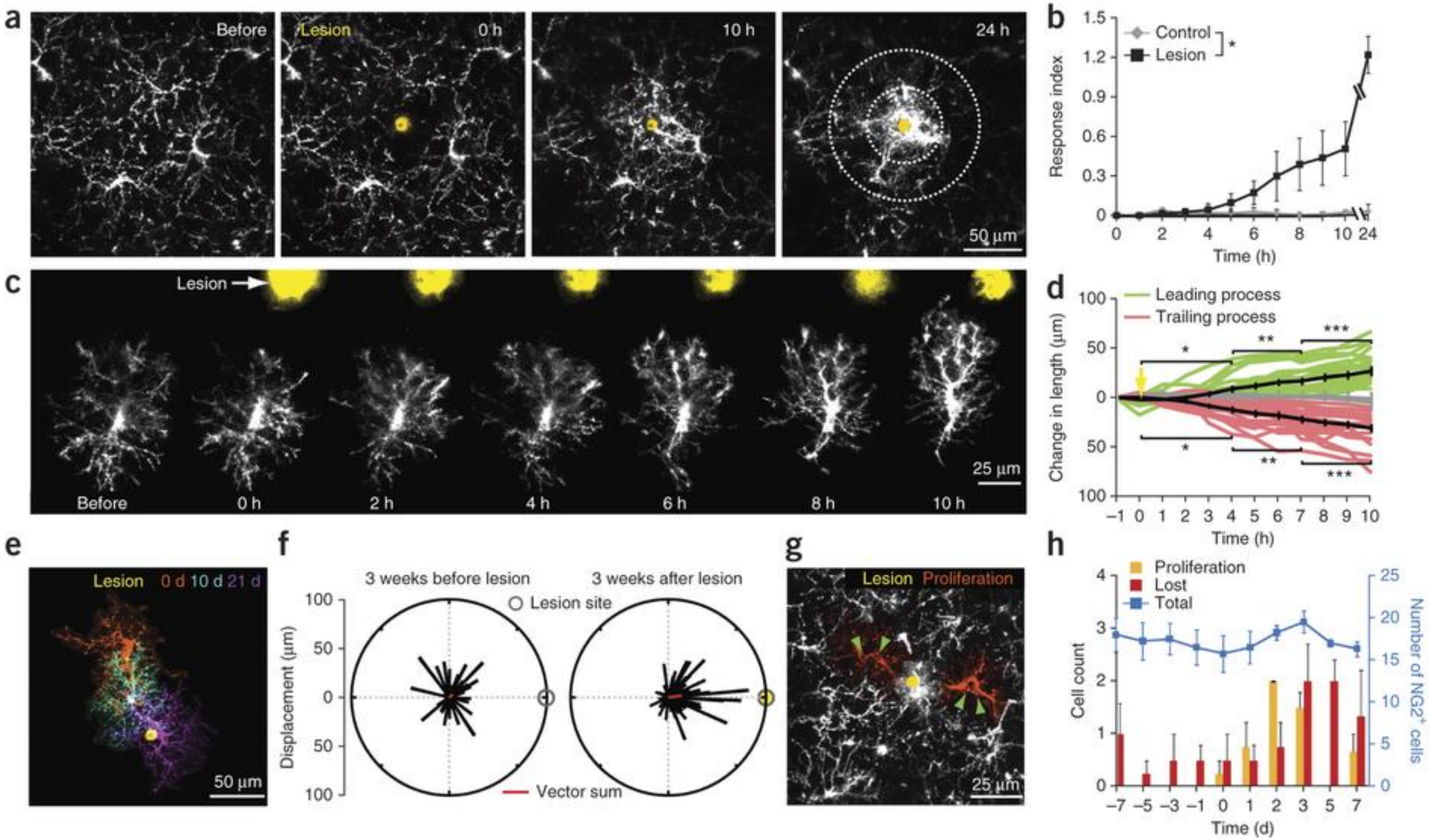
Hughes et al., 2013

OPCs extend processes and encapsulate regions of tissue injury



Hughes et al., 2013

NG2^{+} cells surround areas of CNS damage and proliferate to maintain their density



Hughes et al., 2013

Oligodendroglia metabolically support axons and contribute to neurodegeneration

Youngjin Lee[1]*, Brett M. Morrison[1]*, Yun Li[1], Sylvain Lengacher[2], Mohamed H. Farah[1], Paul N. Hoffman[1], Yiting Liu[1], Akivaga Tsingalia[1], Lin Jin[1], Ping-Wu Zhang[1], Luc Pellerin[3], Pierre J. Magistretti[2] & Jeffrey D. Rothstein[1,4,5]

Oligodendroglia support axon survival and function through mechanisms independent of myelination, and their dysfunction leads to axon degeneration in several diseases. The cause of this degeneration has not been determined, but lack of energy metabolites such as glucose or lactate has been proposed. Lactate is transported exclusively by monocarboxylate transporters, and changes to these transporters alter lactate production and use. Here we show that the most abundant lactate transporter in the central nervous system, monocarboxylate transporter 1 (MCT1, also known as SLC16A1), is highly enriched within oligodendroglia and that disruption of this transporter produces axon damage and neuron loss in animal and cell culture models. In addition, this same transporter is reduced in patients with, and in mouse models of, amyotrophic lateral sclerosis, suggesting a role for oligodendroglial MCT1 in pathogenesis. The role of oligodendroglia in axon function and neuron survival has been elusive; this study defines a new fundamental mechanism by which oligodendroglia support neurons and axons.

26 JULY 2012 | VOL 487 | NATURE | 443

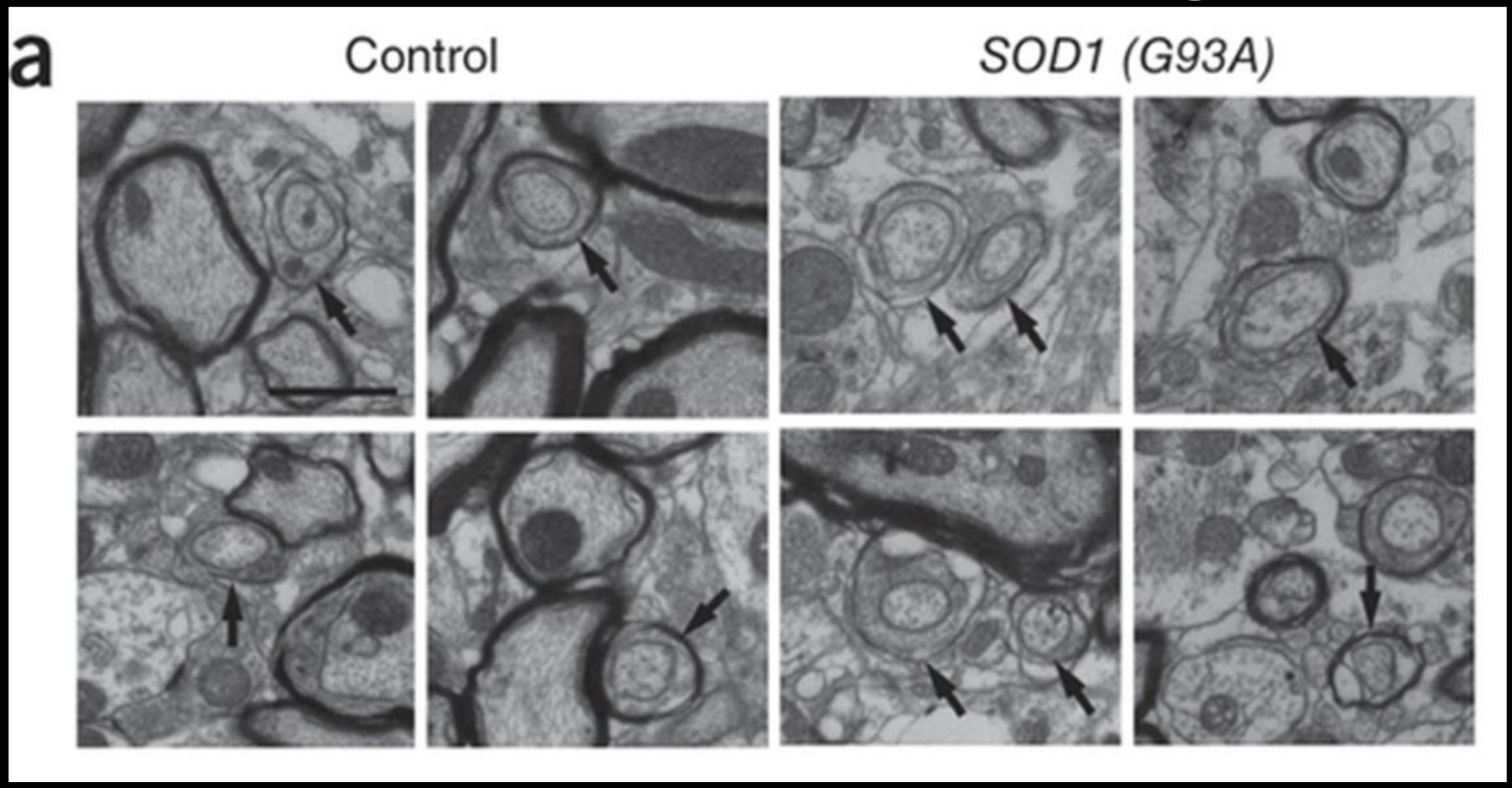
Degeneration and impaired regeneration of gray matter oligodendrocytes in amyotrophic lateral sclerosis

Shin H Kang[1,6,7], Ying Li[2,7], Masahiro Fukaya[3], Ileana Lorenzini[1,4], Don W Cleveland[5], Lyle W Ostrow[2,4], Jeffrey D Rothstein[1,2,4] & Dwight E Bergles[1]

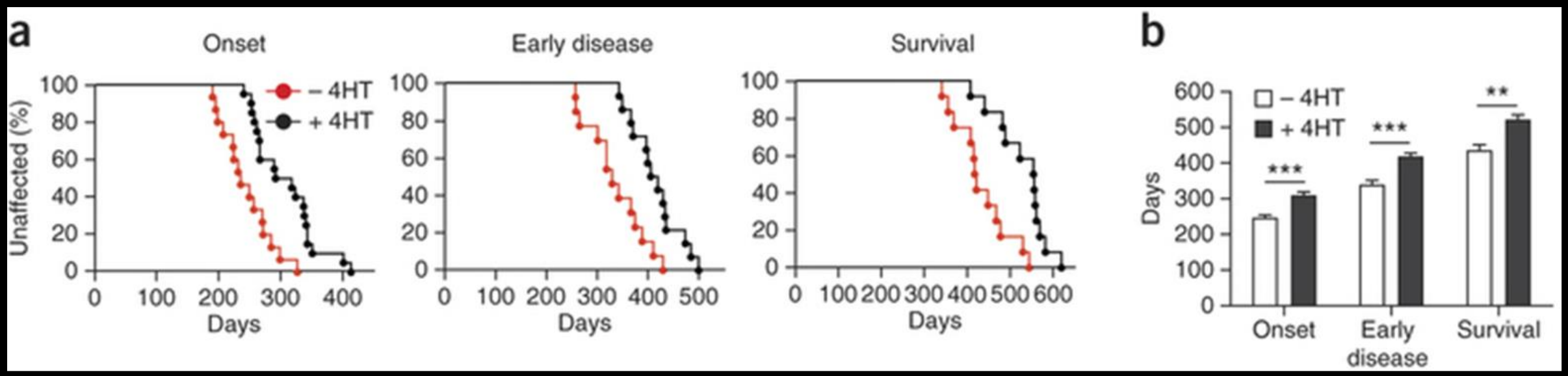
Oligodendrocytes associate with axons to establish myelin and provide metabolic support to neurons. In the spinal cord of amyotrophic lateral sclerosis (ALS) mice, oligodendrocytes downregulate transporters that transfer glycolytic substrates to neurons and oligodendrocyte progenitors (NG2$^+$ cells) exhibit enhanced proliferation and differentiation, although the cause of these changes in oligodendroglia is unknown. We found extensive degeneration of gray matter oligodendrocytes in the spinal cord of SOD1 (G93A) ALS mice prior to disease onset. Although new oligodendrocytes were formed, they failed to mature, resulting in progressive demyelination. Oligodendrocyte dysfunction was also prevalent in human ALS, as gray matter demyelination and reactive changes in NG2$^+$ cells were observed in motor cortex and spinal cord of ALS patients. Selective removal of mutant SOD1 from oligodendroglia substantially delayed disease onset and prolonged survival in ALS mice, suggesting that ALS-linked genes enhance the vulnerability of motor neurons and accelerate disease by directly impairing the function of oligodendrocytes.

NATURE NEUROSCIENCE VOLUME 16 | NUMBER 5 | MAY 2013

Myelin Abnormalities and Demyelination in Gray Matter of ALS Mice Prior to Degeneration



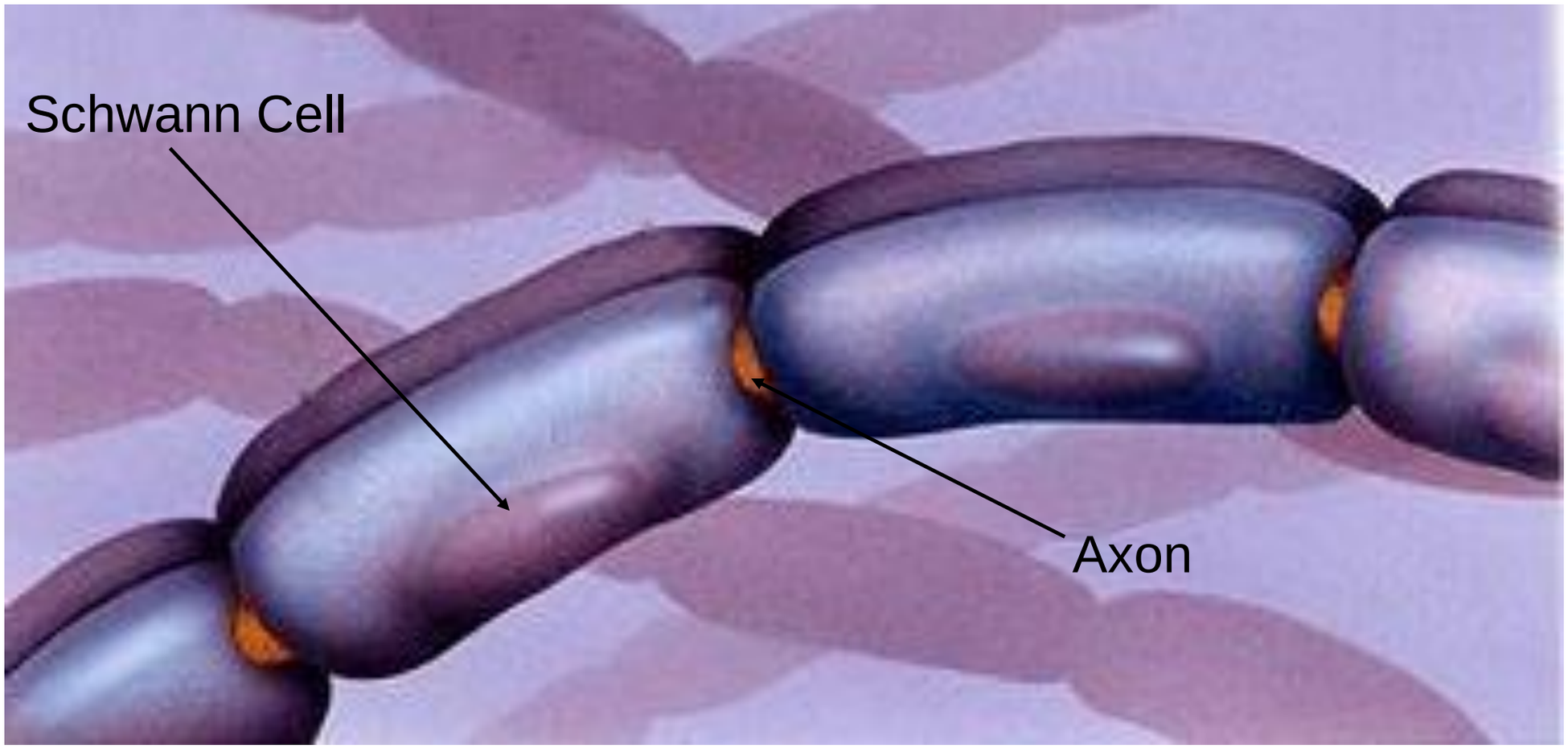
Excision of mutant SOD1 (G37R) from OPCs delays disease onset and prolongs survival in ALS mice



The Cells of Schwann

(Theodor Schwann 1810-1882)

Schwann Cell Myelin Internodes



Three Kinds of Schwann Cells?

1. Perisynaptic SCs
2. Non-myelinating
3. Myelinating

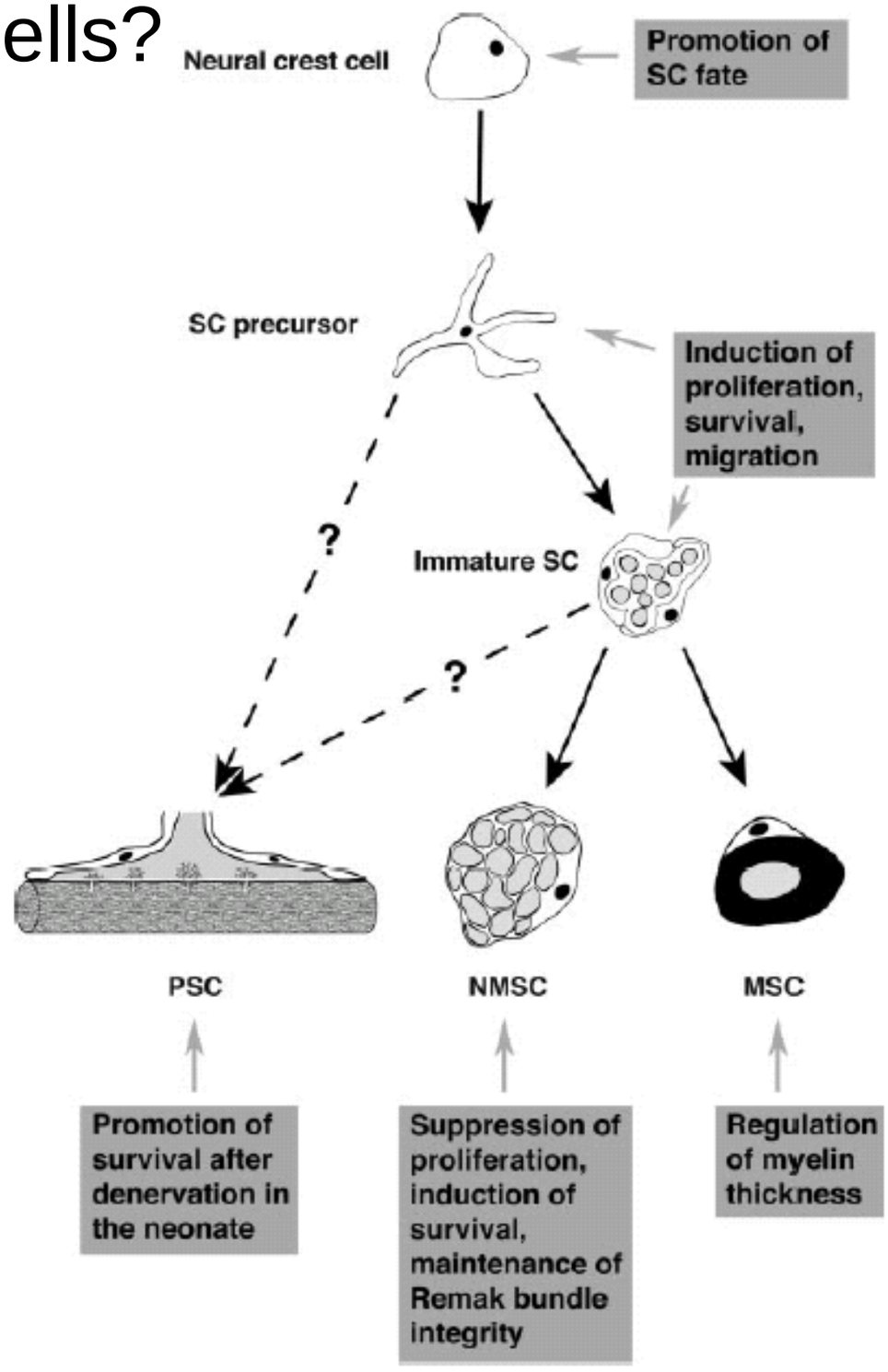


Figure 2. NRG1–erbB signaling and Schwann cell development. During development, neural crest cells give rise to Schwann cell precursors, which then develop into the three adult phenotypes: PSCs, NMSCs, or MSCs. Whereas, during their differentiation into MSCs and NMSCs, the precursors proceed through a stage called immature Schwann cell, the direct precursor of PSCs remains unknown. NRG1–erbB signaling regulates important aspects of Schwann cell biology at each step of their development (see boxed text).

Corfas et al., (2004) Mechanisms and roles of axon-Schwann cell interactions. J Neurosci. 24(42):9250-60

Schwann Cell Origin

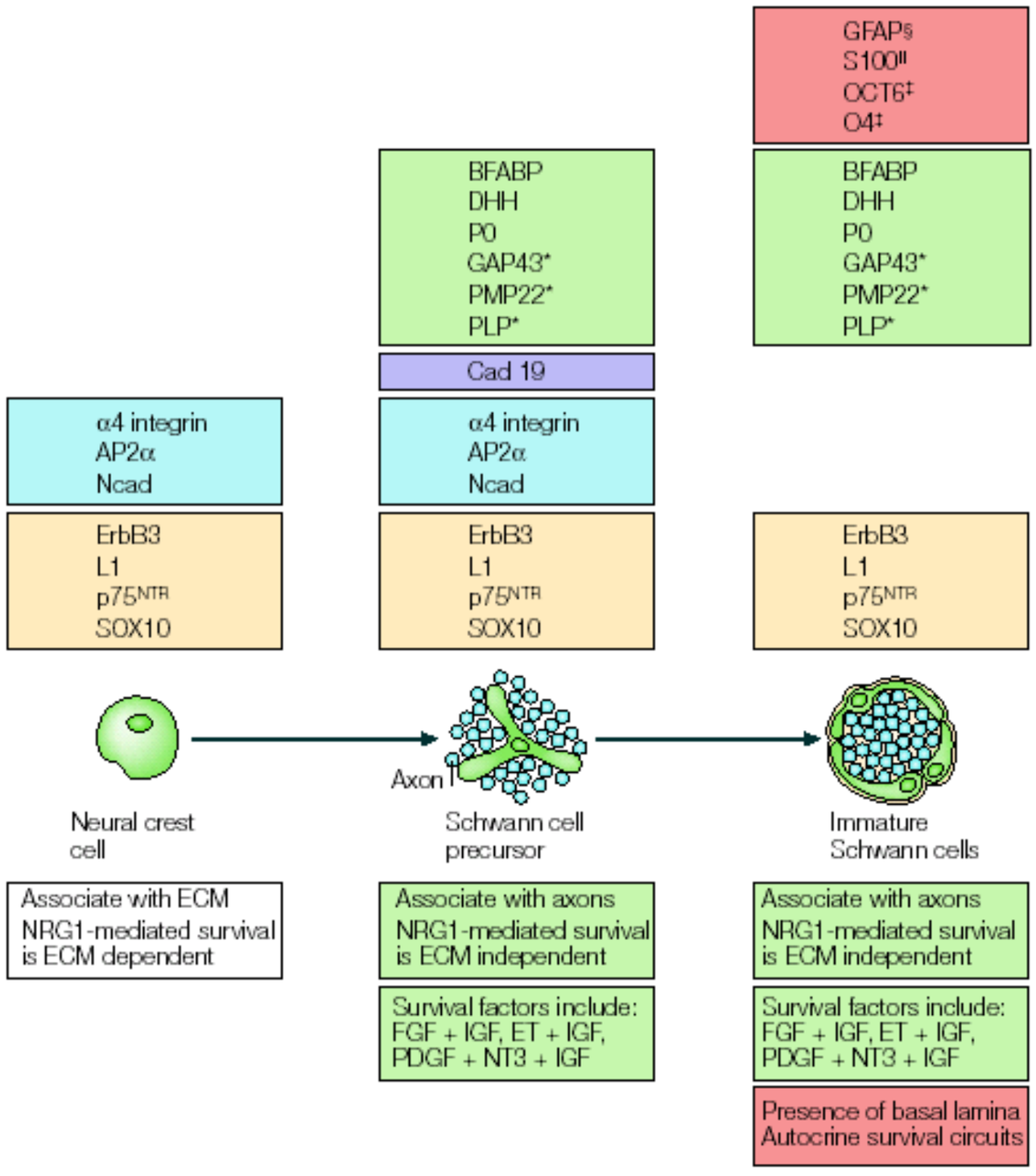
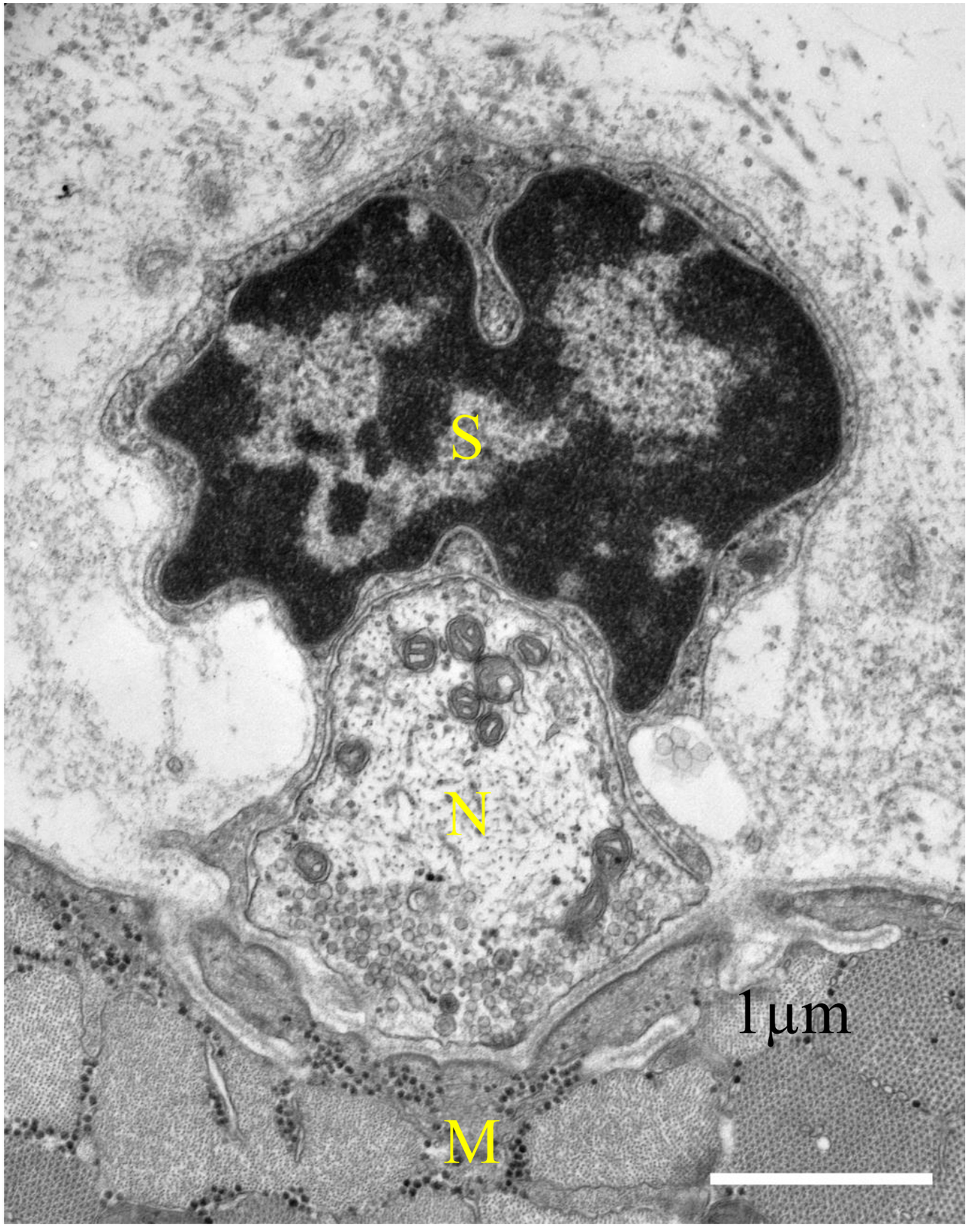


Figure 4 | **Changes in phenotypic profile as cells progress through the embryonic Schwann cell lineage.** Shared profiles are indicated by distinct colours. The boxes above

Jessen and Mirsky (2005) Nature Reviews Neuroscience. 6:671-682

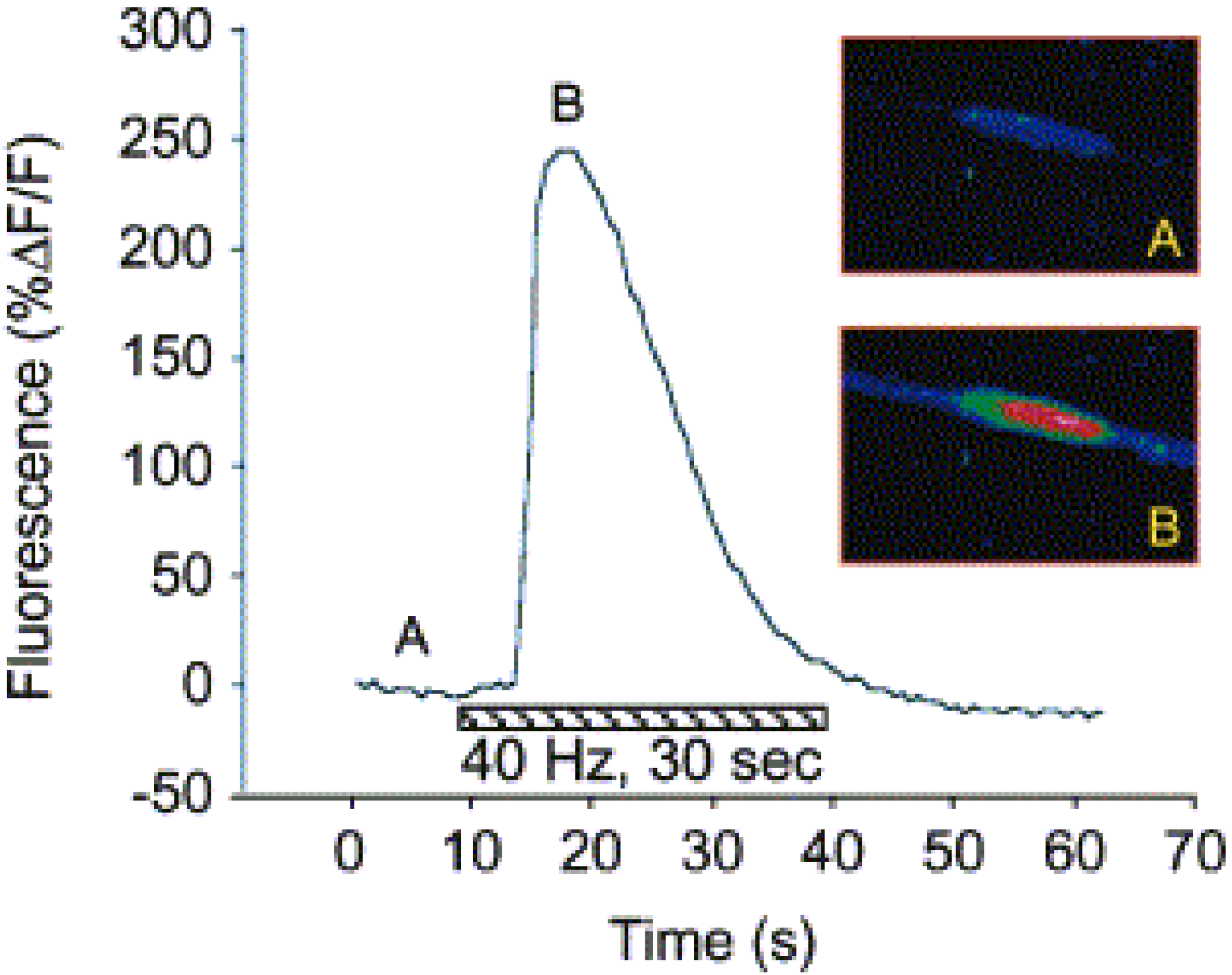
What do PSCs Do?

TEM of the Frog Neuromuscular Junction Cross-section



Micrograph by Dr. Yoshie Sugiura, USC

A PSC at the Frog NMJ Responds to Synaptic Activity with Increases in Ca^{2+}

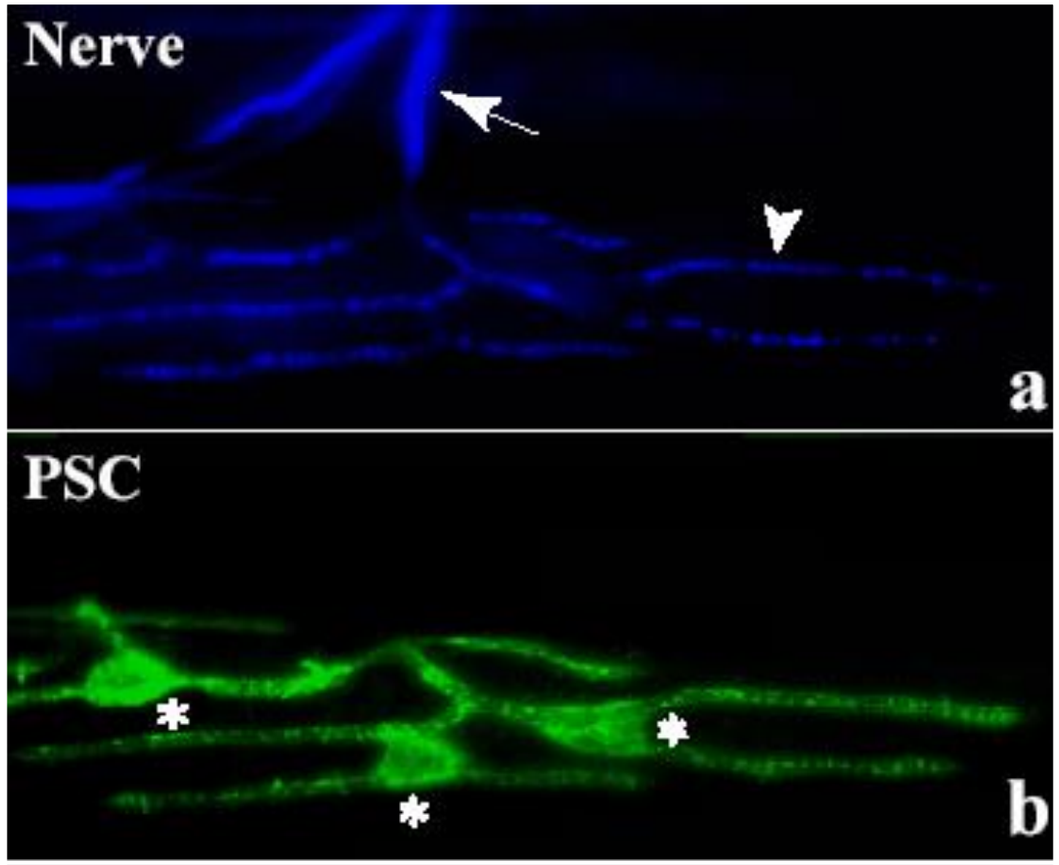


(From Auld & Robitaille, 2003, *Neuron* 40:389-400)

Anti-neurofilament & anti-synapsin

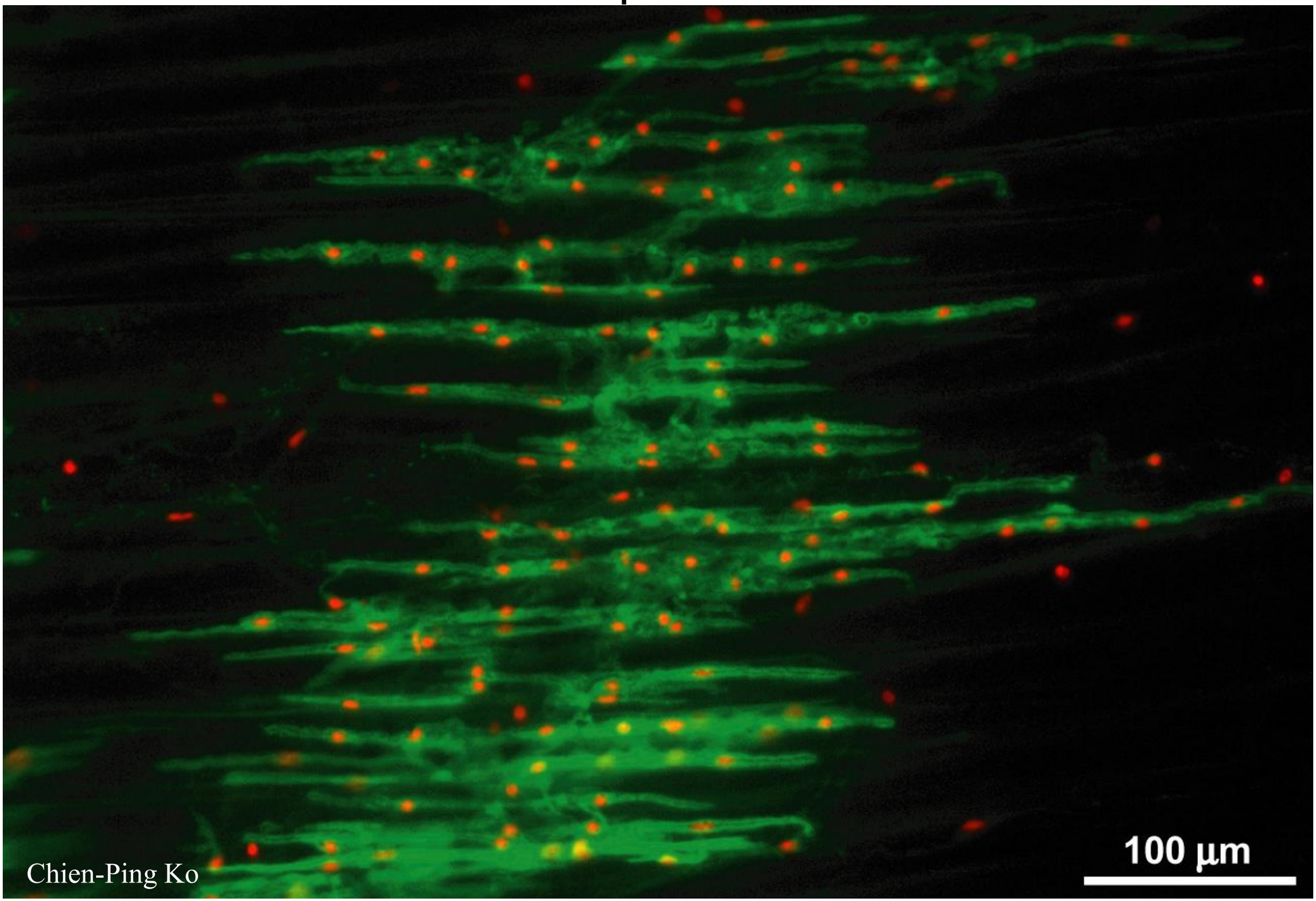
MAb 2A12

α-bungarotoxin

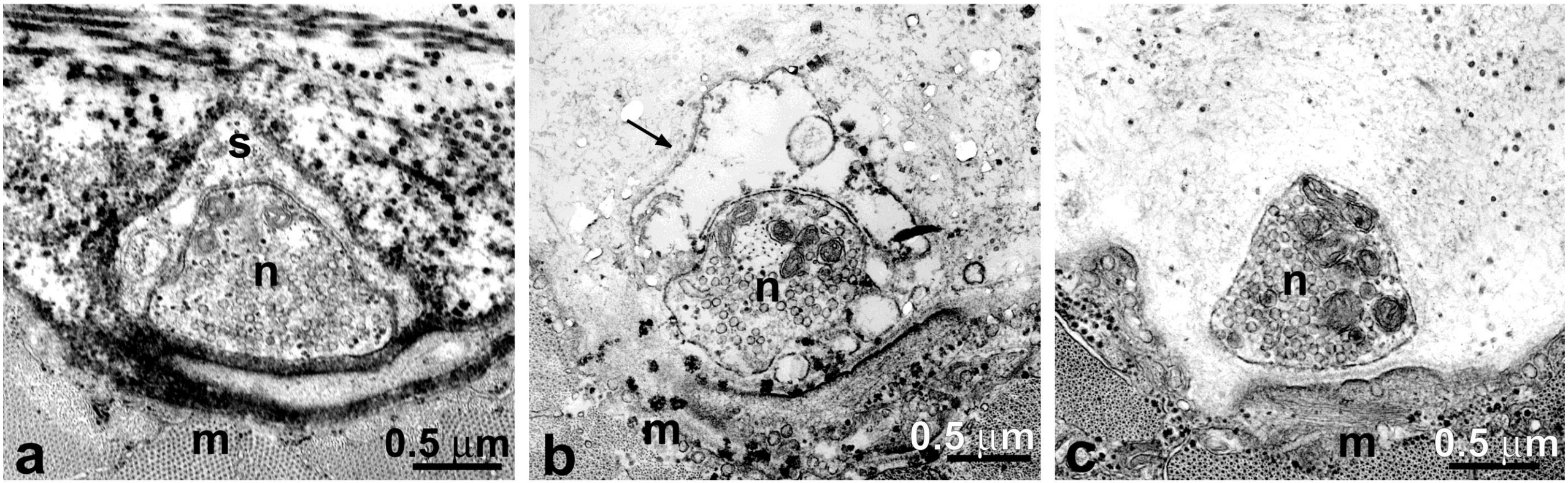


Chien-Ping Ko and Zhihua Feng

Labeling with PNA (*green*) and EthD-1 (*red*) shows the *en masse* ablation of PSCs on treating muscle with mAb 2A12 and complement

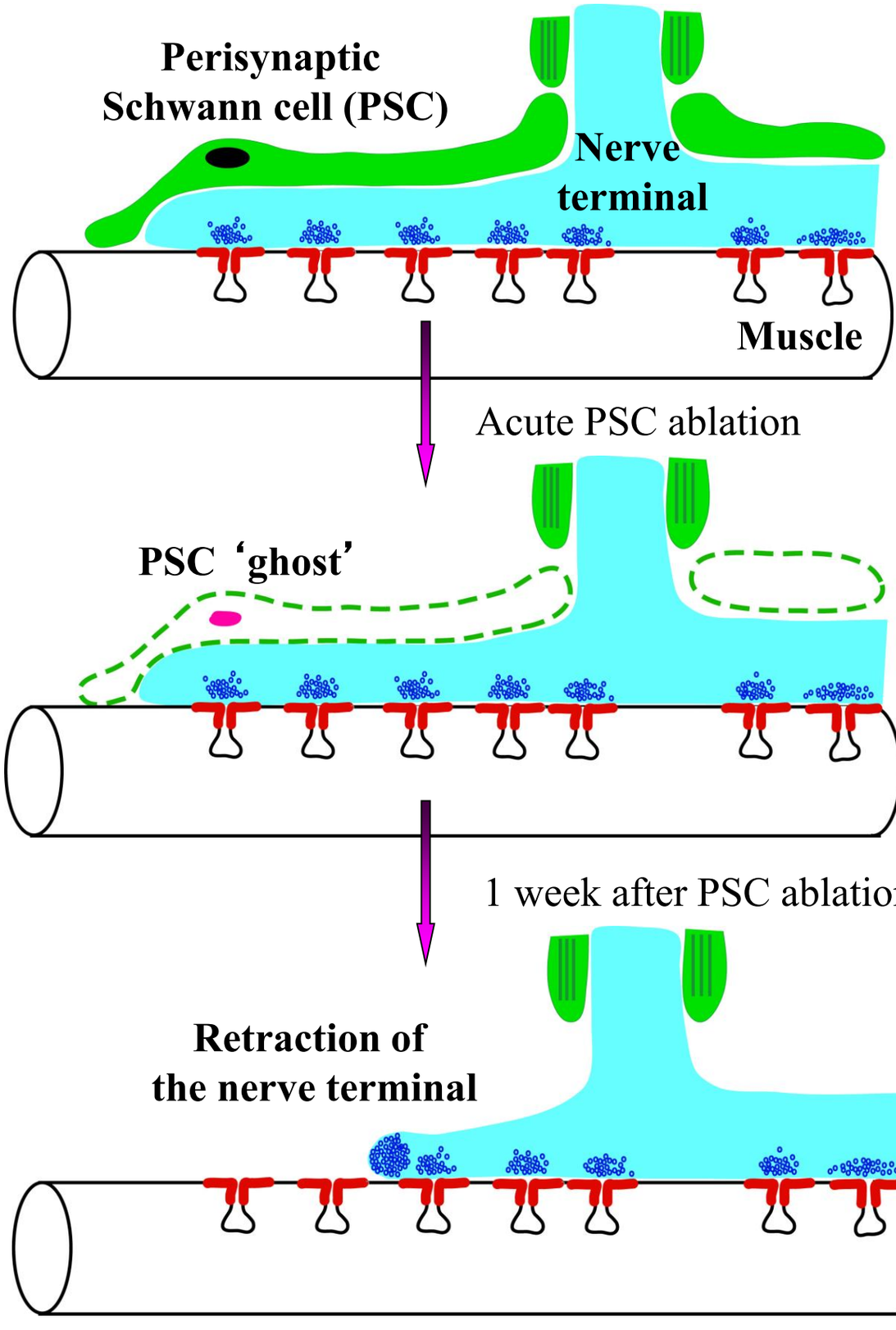


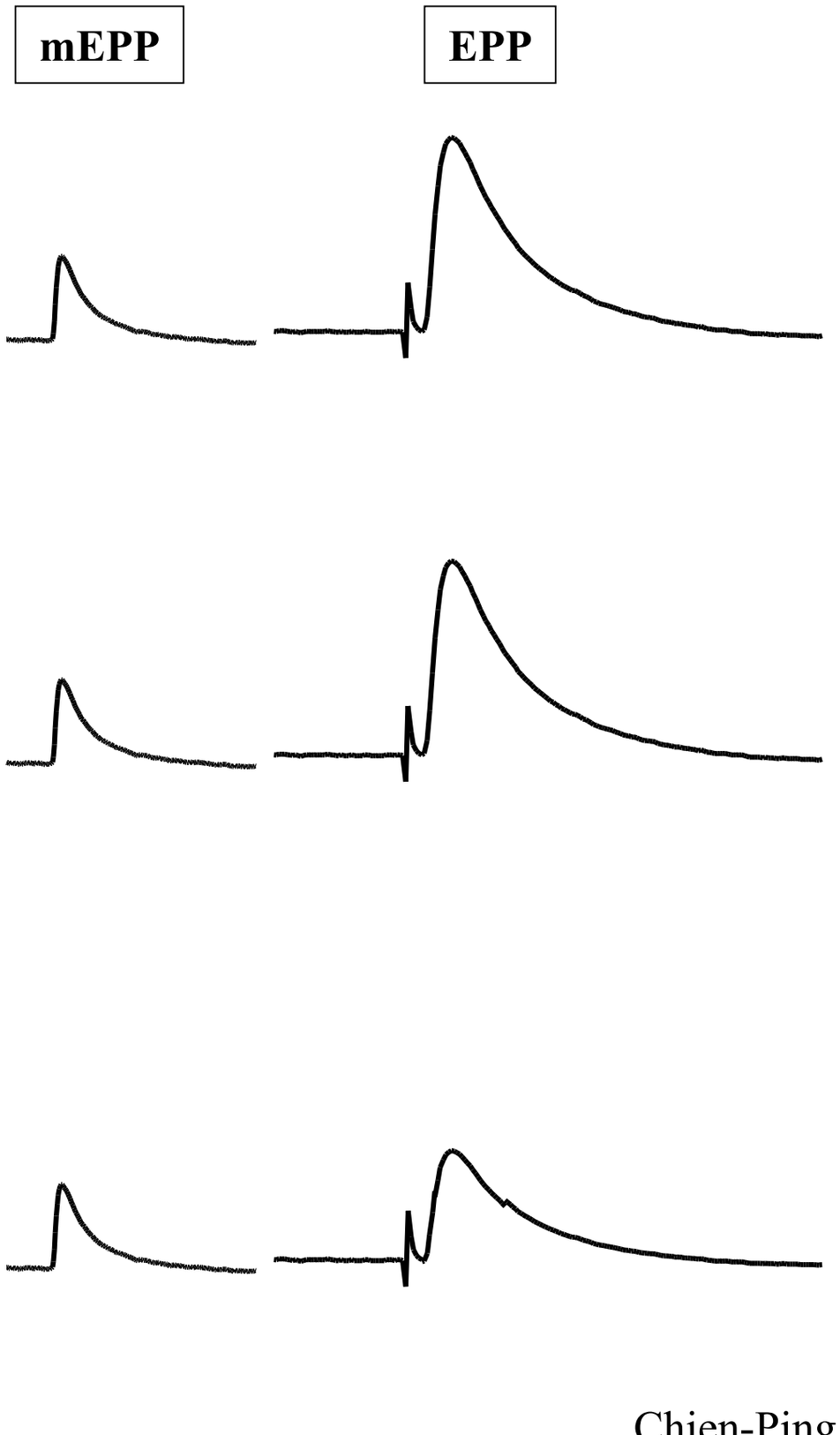
Electron Micrographs of the NMJ Following PSC Ablation



Chien-Ping Ko

PSCs do not play an acute role, but play a long-term maintenance role, in the presynaptic function and structure.

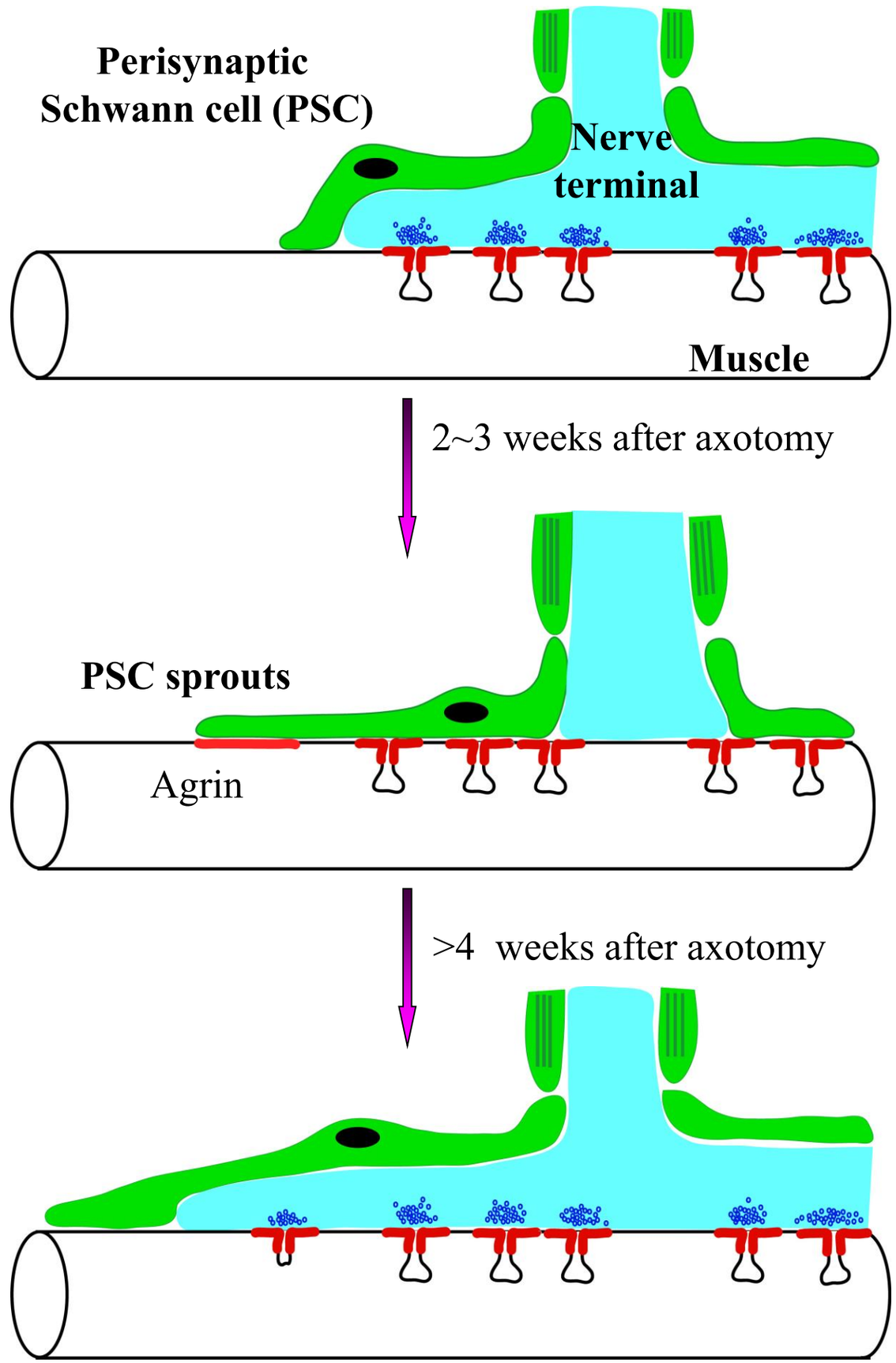




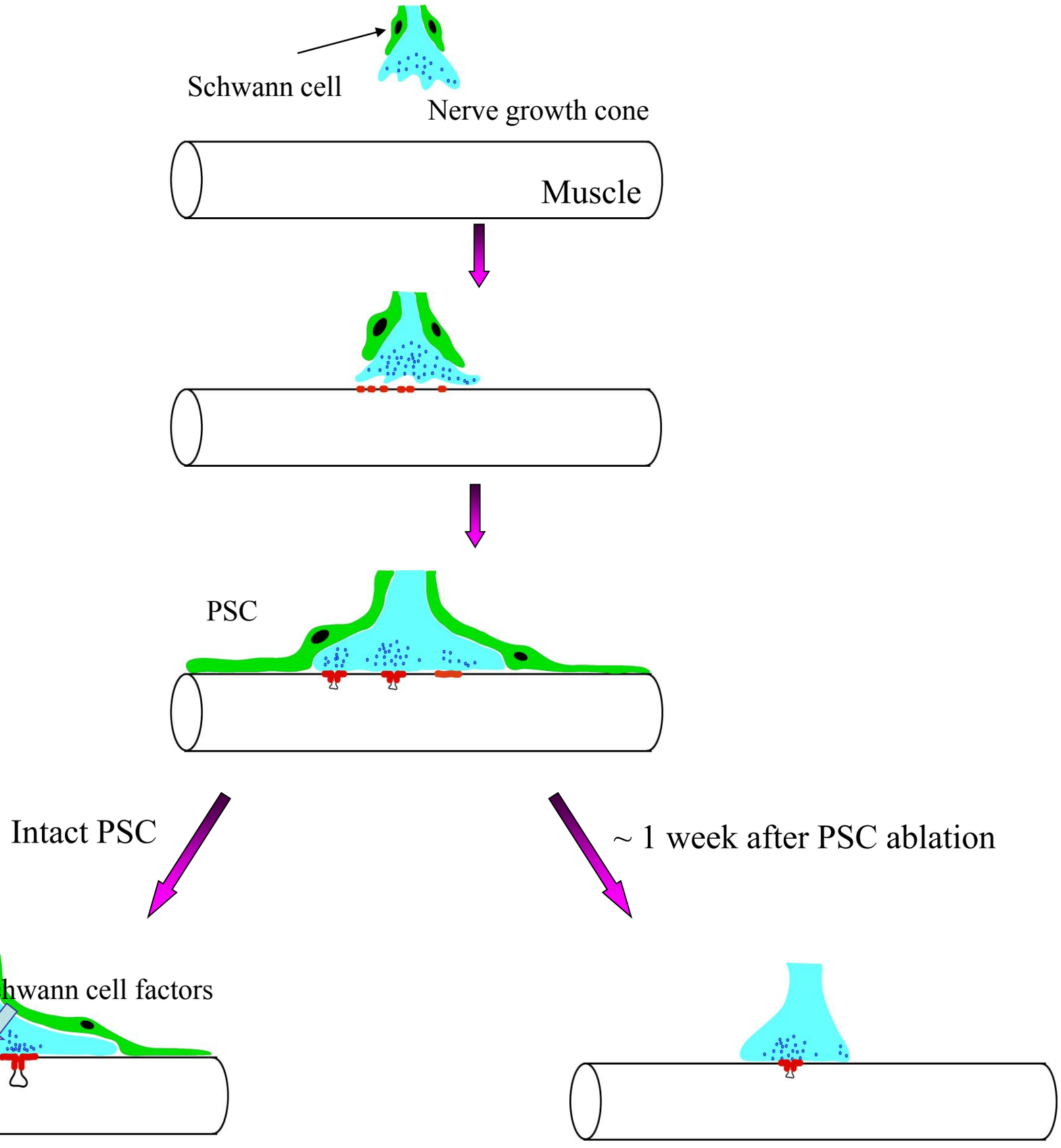
Chien-Ping Ko

•Regenerating nerve terminals induce PSCs to sprout, and PSC sprouts, in turn, lead and guide nerve terminal sprouts.

•Schwann cells express active agrin, and play a role in postsynaptic AChR aggregation.

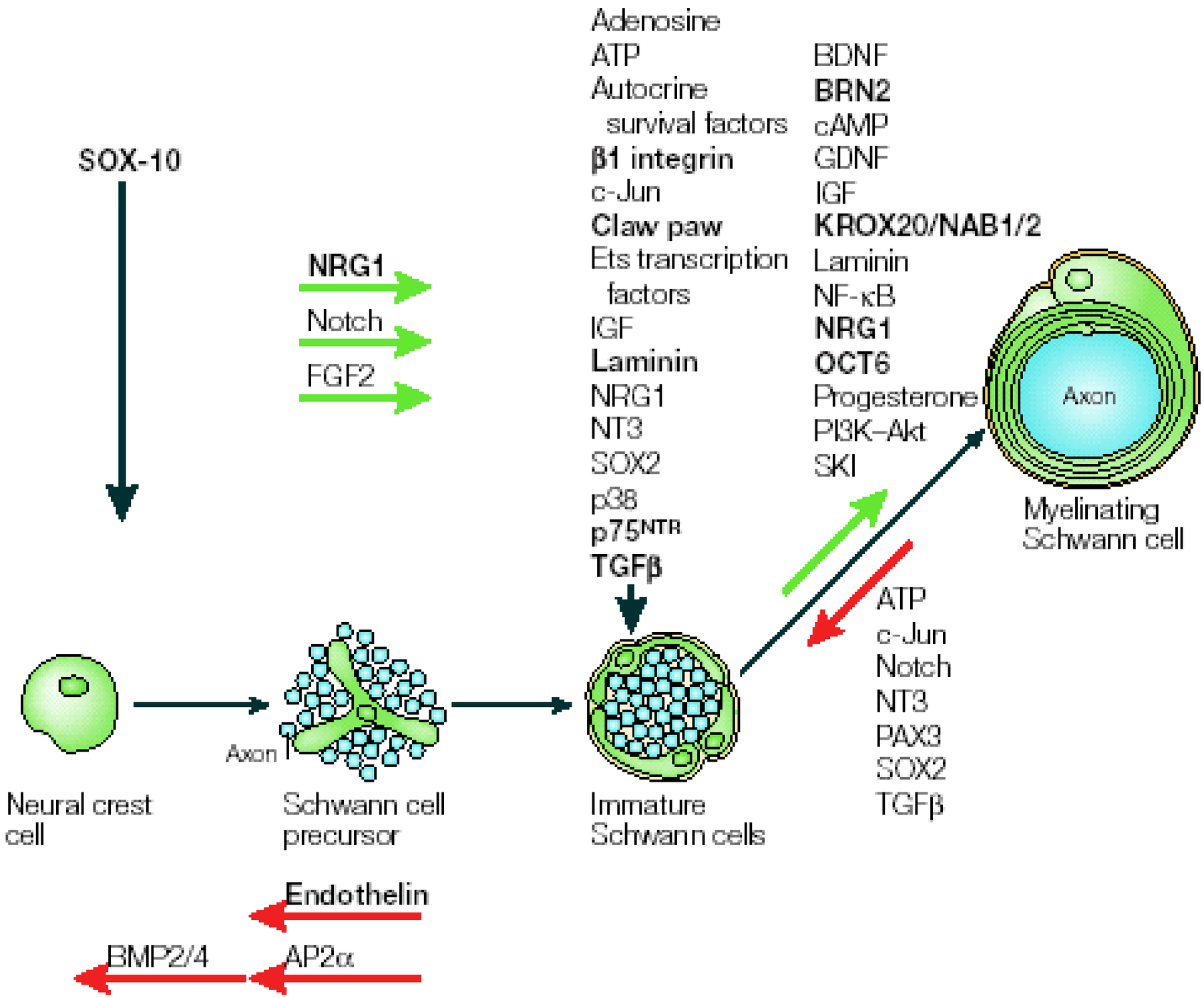


- PSCs lead nerve terminal extension and play a role in the growth and maintenance of developing NMJs.
- Schwann cell-derived factors promote synaptogenesis, and TGF-β1 may mediate the Schwann cell-induced synaptogenesis.
- Schwann cell-derived factors potentiate spontaneous, but inhibit evoked, transmitter release at developing NMJs *in vitro*.



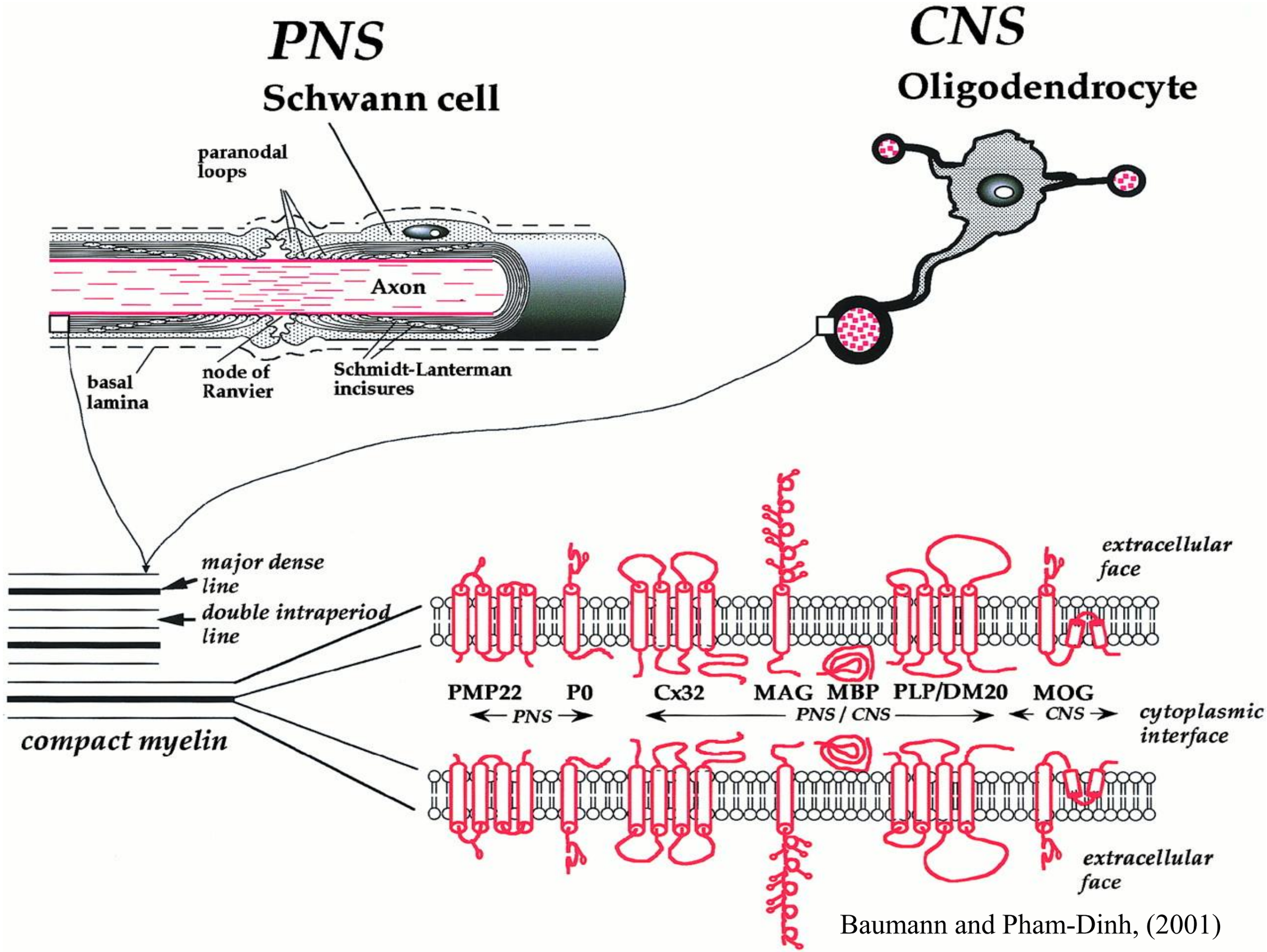
Chien-Ping Ko

Schwann Cell Development and Myelination



Jessen and Mirsky (2005) Nature Reviews Neuroscience. 6:671-682

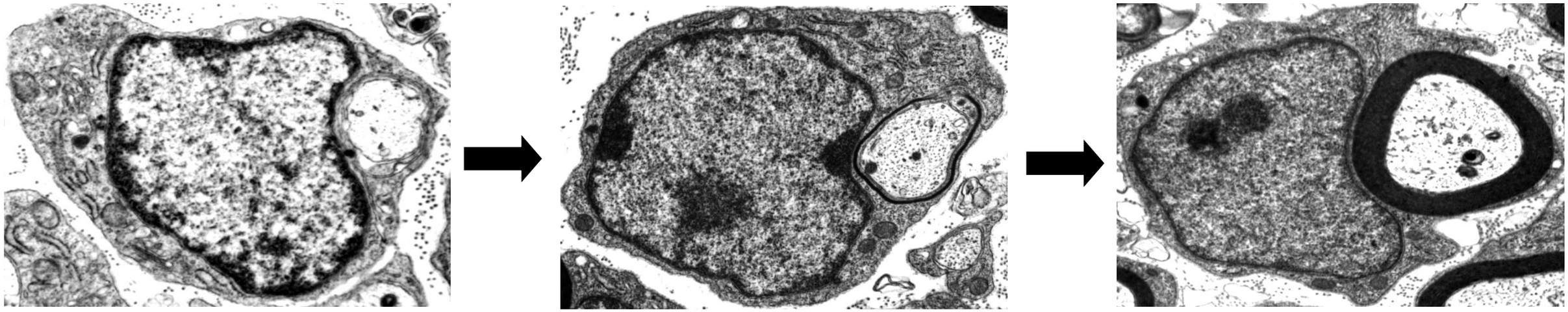
The Ultrastructure of Myelin



Baumann and Pham-Dinh, (2001)

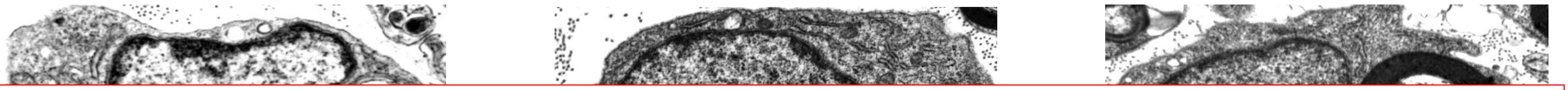
Mechanism of Myelination

Mechanism of myelin wrapping

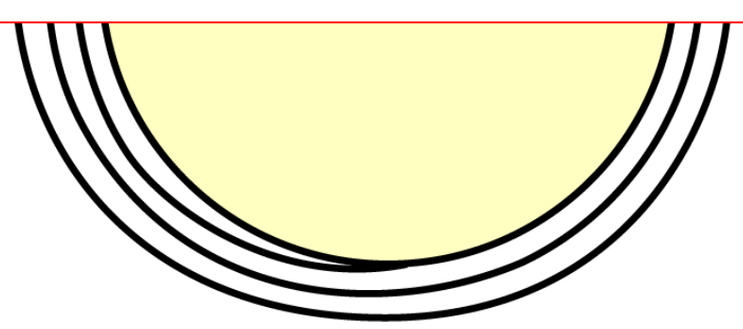


Mechanism of Myelination

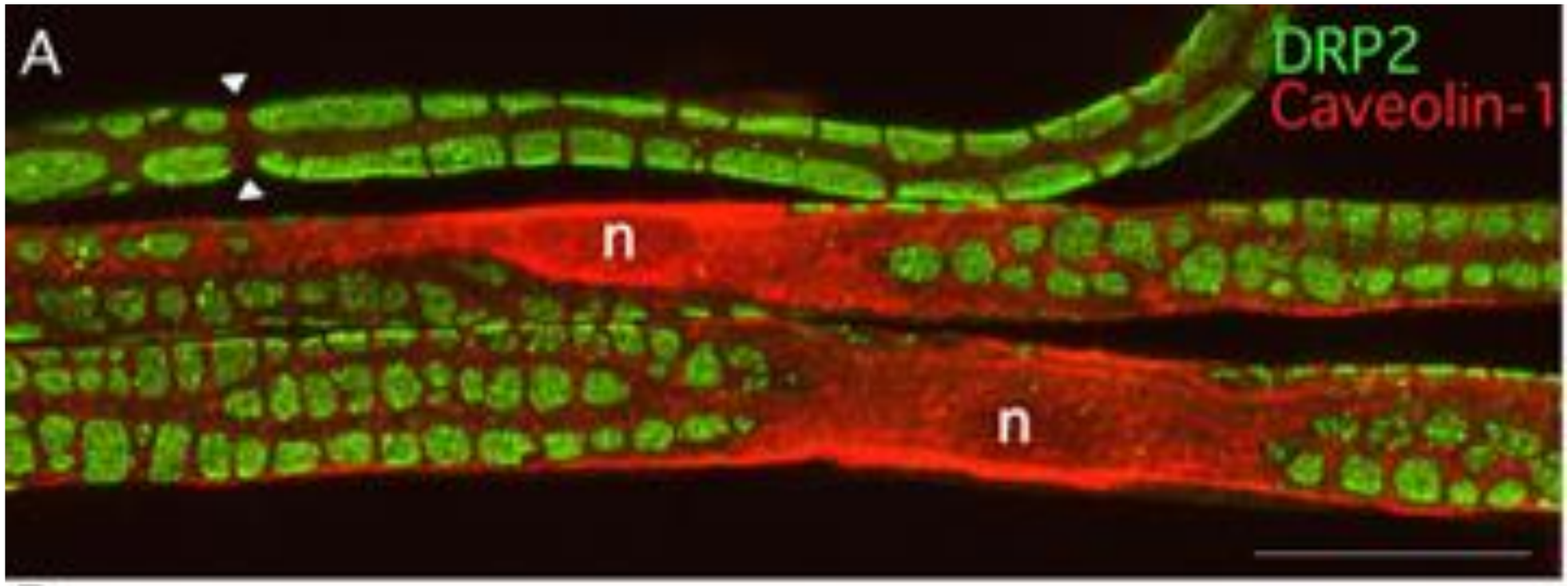
Mechanism of myelin wrapping



1. Recognition with axon/inductive cue
2. Mechanisms of polarity
3. Molecular motor



Myelin was Identified 200 Years Ago…What Do We Really Know?



Article

Cell

Macrophage-Induced Blood Vessels Guide Schwann Cell-Mediated Regeneration of Peripheral Nerves

Anne-Laure Cattin,[1] Jemima J. Burden,[1] Lucie Van Emmenis,[1] Francesca E. Mackenzie,[3] Julian J.A. Hoving,[1] Noelia Garcia Calavia,[1] Yanping Guo,[2] Maeve McLaughlin,[1] Laura H. Rosenberg,[1] Victor Quereda,[1] Denisa Jamecna,[1] Ilaria Napoli,[1] Simona Parrinello,[1] Tariq Enver,[2] Christiana Ruhrberg,[3] and Alison C. Lloyd[1,2,*]

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http://dx.doi.org/10.1016/j.cell.2015.07.021

SUMMARY

The peripheral nervous system has remarkable regenerative capacities in that it can repair a fully cut nerve. This requires Schwann cells to migrate collectively to guide regrowing axons across a 'bridge' of new tissue, which forms to reconnect a severed nerve. Here we show that blood vessels direct the migrating cords of Schwann cells. This multicellular process is initiated by hypoxia, selectively sensed by macrophages within the bridge, which via VEGF-A secretion induce a polarized vasculature that relieves the hypoxia. Schwann cells then use the blood vessels as "tracks" to cross the bridge taking regrowing axons with them. Importantly, disrupting the organization of the newly formed blood vessels in vivo, either by inhibiting the angiogenic signal or by re-orienting them, compromises Schwann cell directionality resulting in defective nerve repair. This study provides important insights into how the choreography of multiple cell-types is required for the regeneration of an adult tissue.

cell types over long distances within the architecture of the adult tissue (Zochodne, 2008).

Peripheral nerves consist of bundles of axons, with each axon associated and enveloped by Schwann cells (SCs), the main glial cell of the PNS. SCs either exist in a 1:1 ratio with larger diameter axons, which they myelinate, or group together smaller axons in structures known as Remak bundles. Groups of these axons are further organized into a fascicle, enclosed by the perineurium, which is made-up of layers of specialized, fibroblast-like cells. Several fascicles can be further enclosed within the epineurial sheath that surrounds each nerve. The axons exist in a specialized, privileged compartment, known as the endoneurium, protected by the blood/nerve barrier, which is maintained by both the perineurium and by specialized blood vessels that run throughout the nerve. Fibroblasts and macrophages also reside within the matrix of this compartment (Zochodne, 2008).

Remarkably, in contrast to nerves in the CNS, peripheral nerves can regenerate even following a complete transection. Following a transection, the stumps retract and in the distal part of the nerve, the axons, separated from their cell bodies, rapidly degenerate by an active process known as Wallerian degeneration (Zochodne, 2008). The major aim of the regeneration process is for the axons to regrow back to their targets, which requires guidance signals distinct from those that originally directed the axons during development (Dudanova and

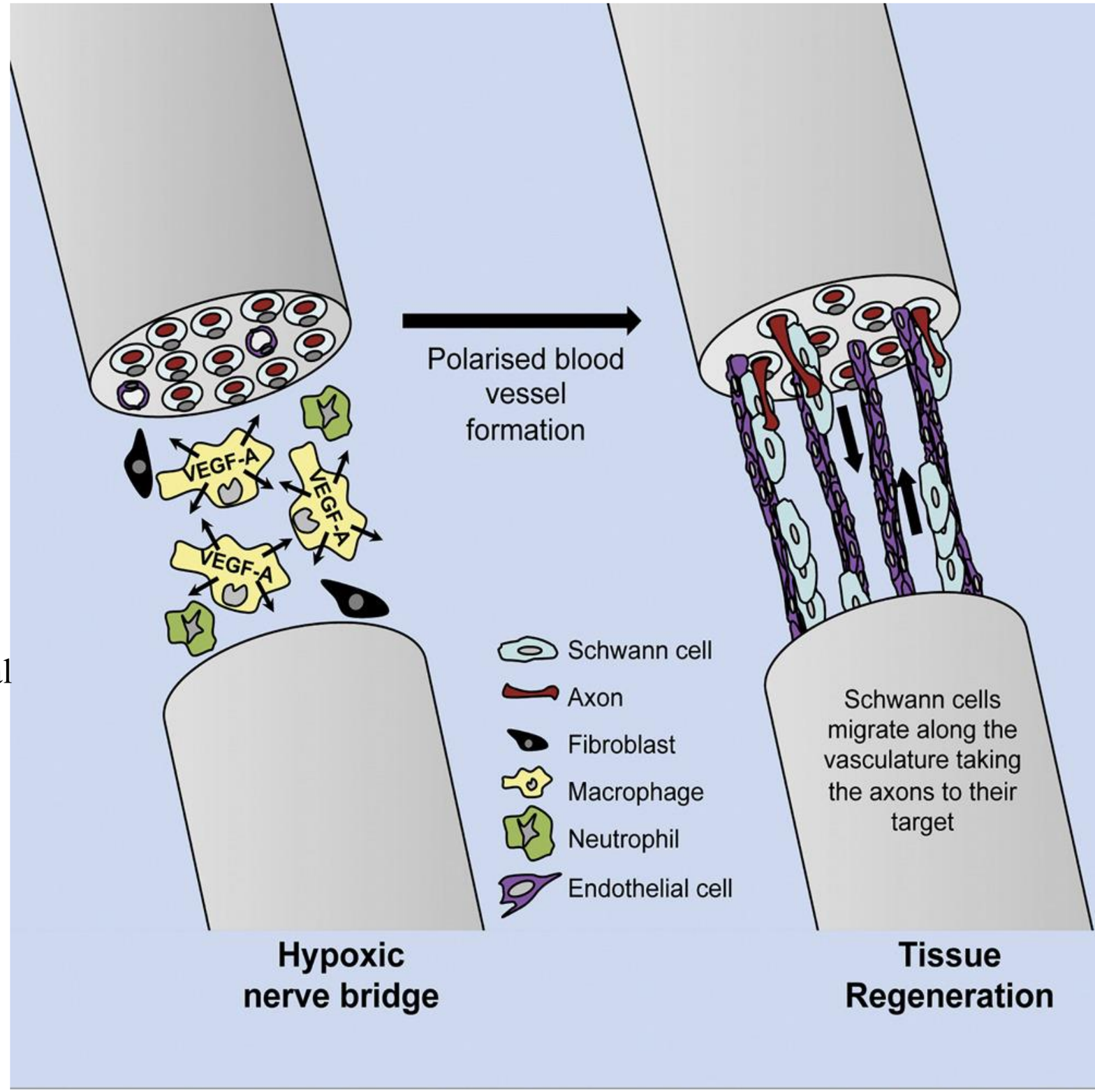
Highlights

-Hypoxia within the nerve bridge is selectively Sensed by macrophages

-Macrophage-derived VEGF-A induces a Polarized vasculature within the bridge

-Blood vessels are used as tracks to direct Schwann cell migration across the wound

-Macrophage-induced blood vessels are essential for nerve regeneration



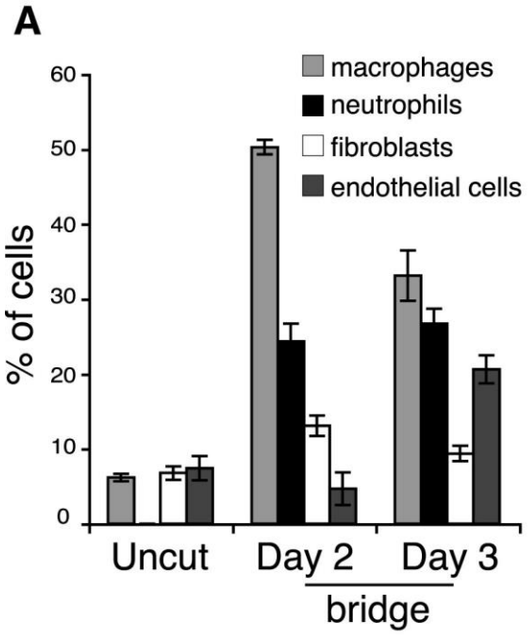
1

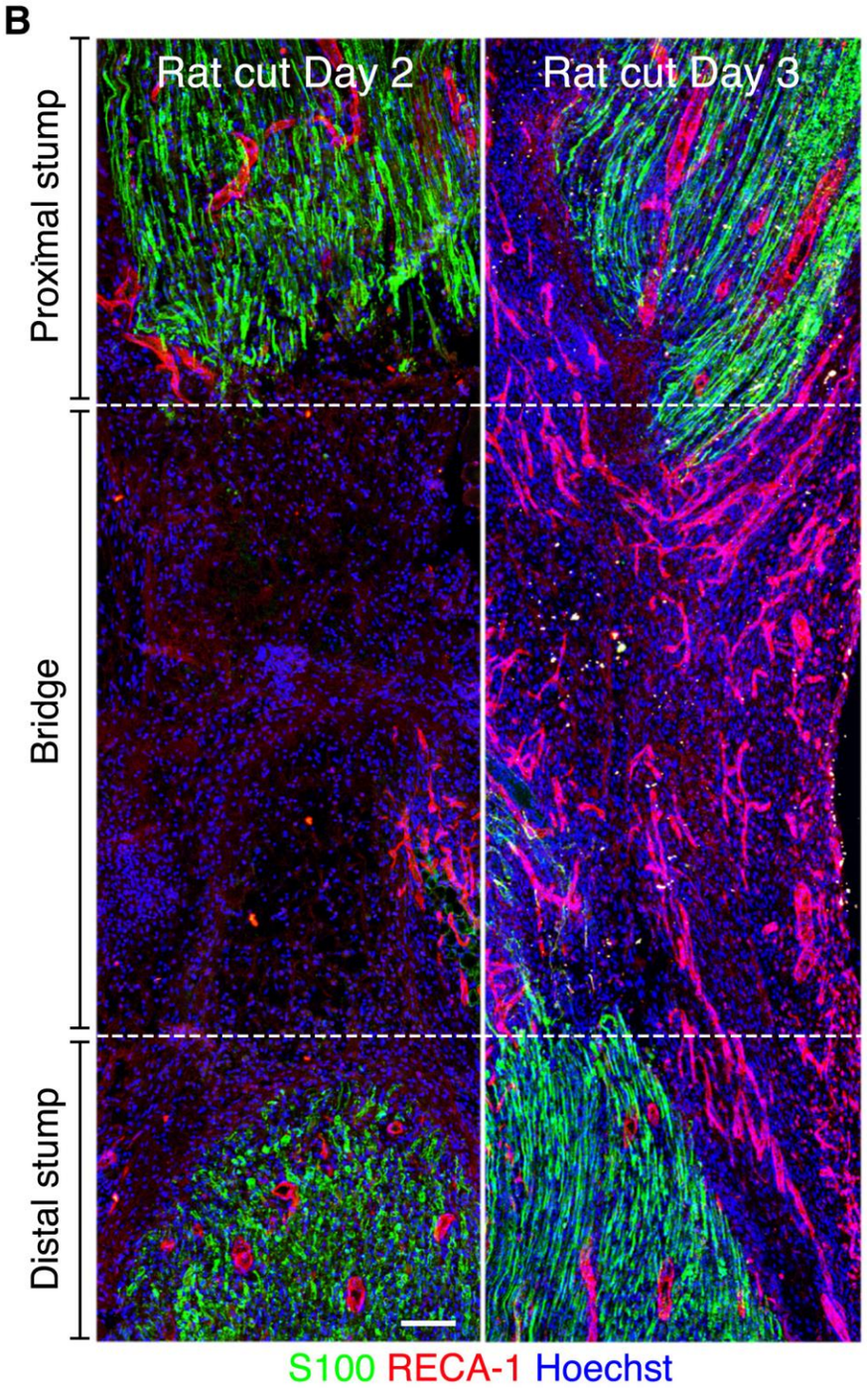
Blood vessels permeate the bridge prior to SC migration

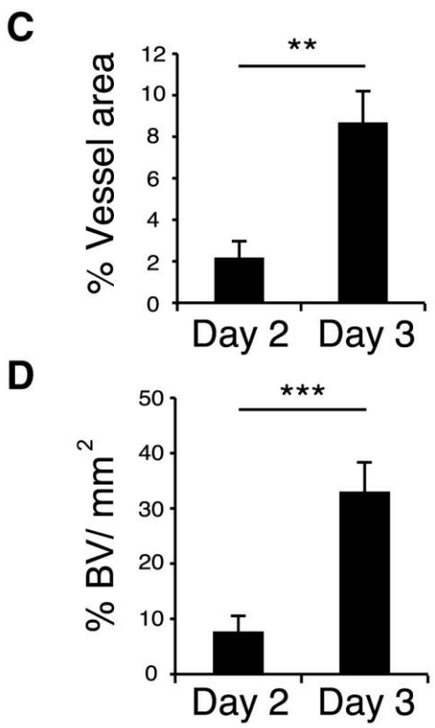
>95% of rats a bridge was formed in 2 days

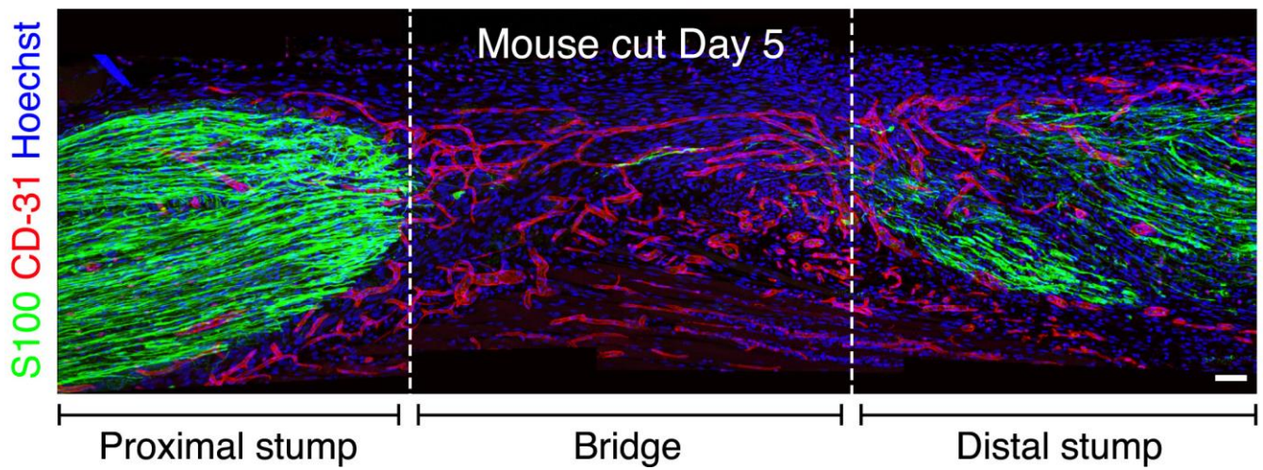
Bridge was composed of macrophages, neutrophils, fibroblasts, and endothelial cells

Mouse regeneration is slower, but with the identical innervation of cells.







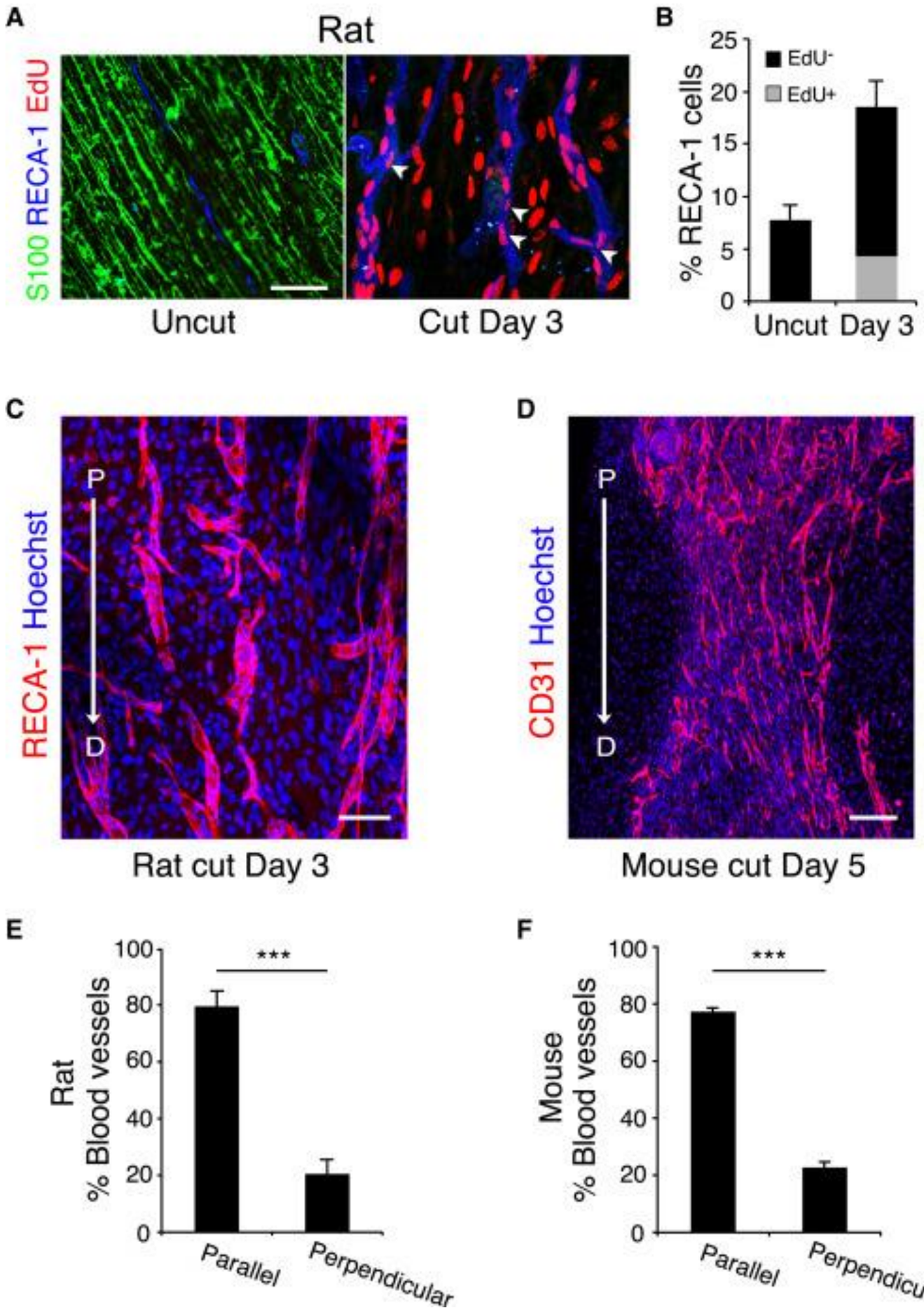


2

Newly formed blood vessels in the bridge are polarized in the Direction of SC migration

EdU incorporation of ECs in bridge

Polarized Ecs, aligned in the orientation and direction of SC migration.



A

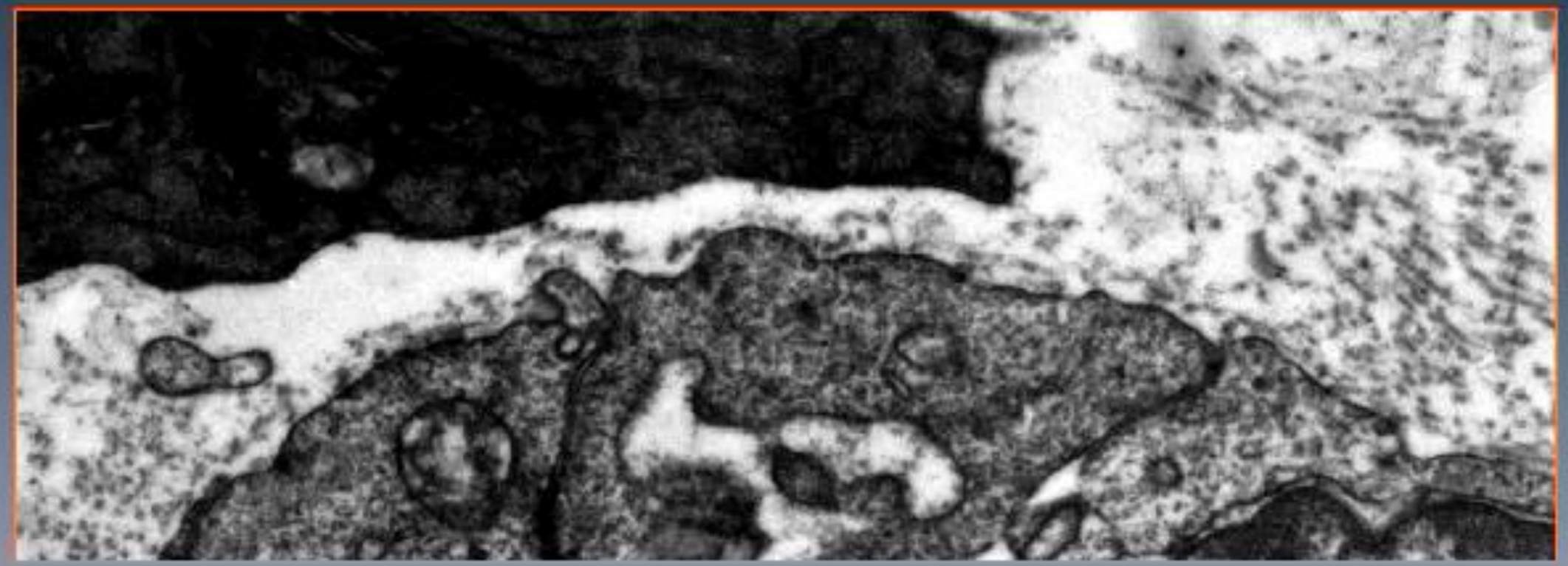
B

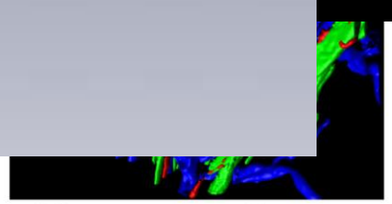
C

70

Schwann cells

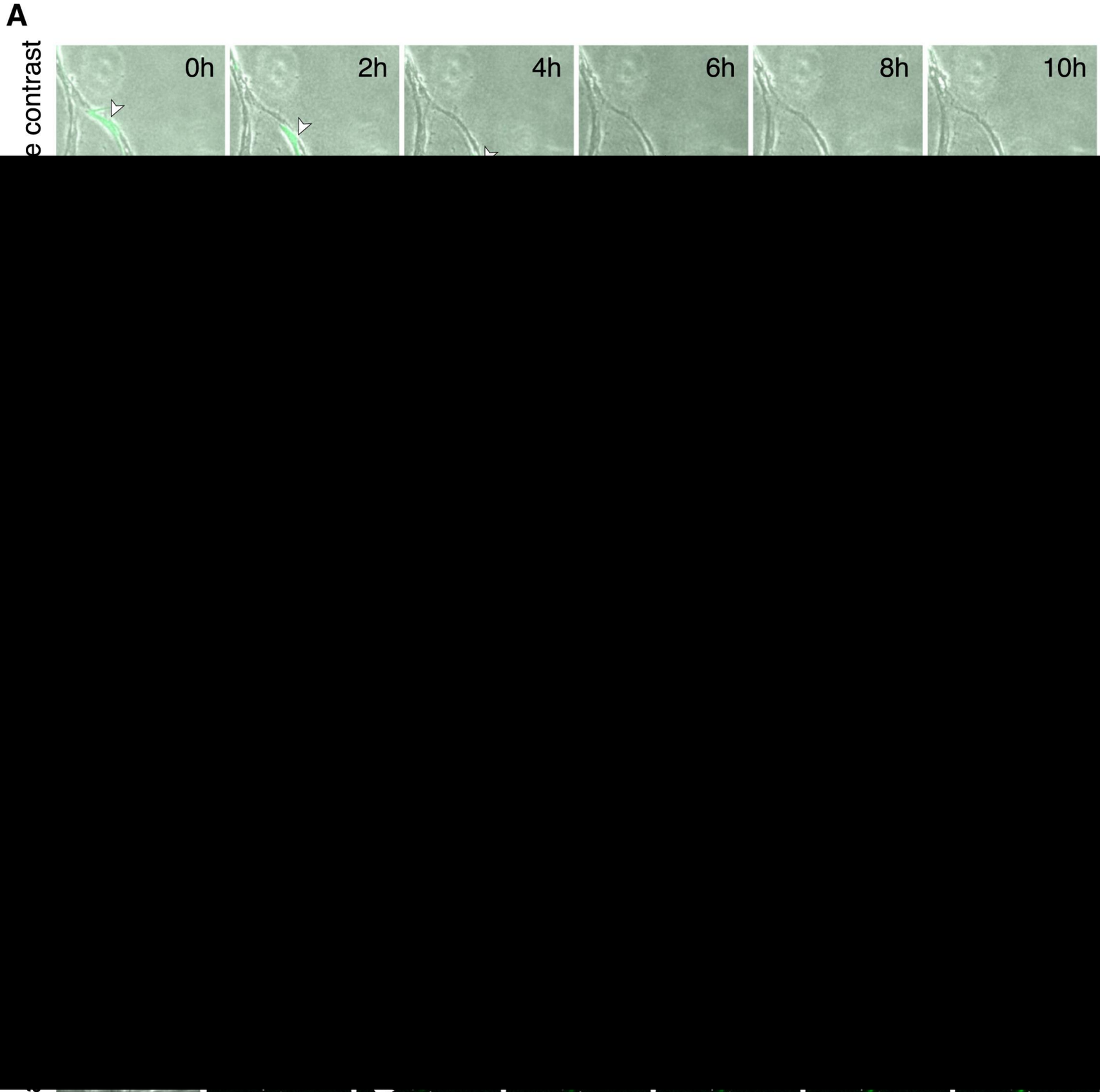
cells





Mouse cut Day 5

4


A
e contrast
0h
2h
4h
6h
8h
10h
GFP Ph
protrusion extension
rear contraction

5

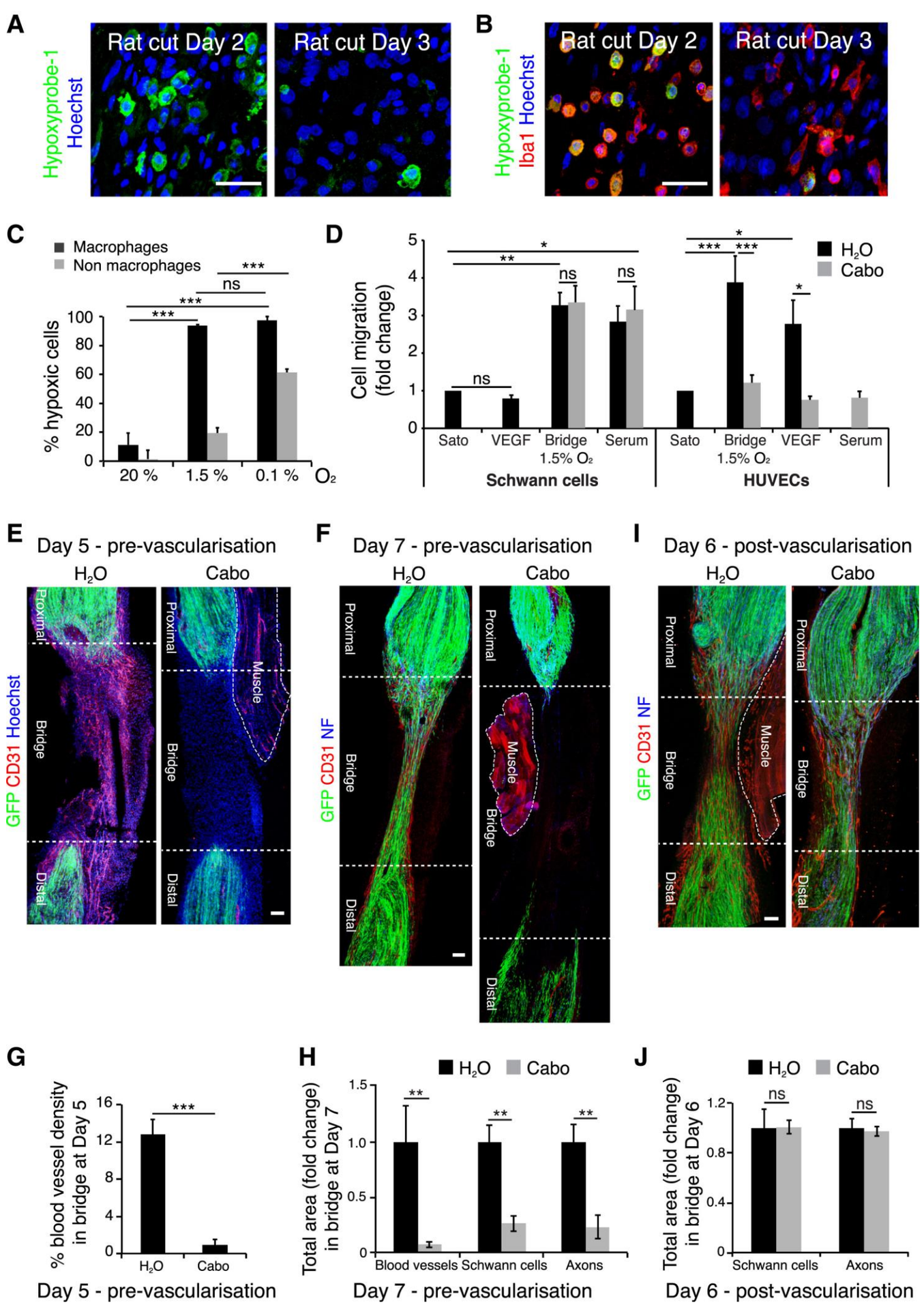
Hypoxia drives angiogenesis by a microphage-generated gradient of VEGF-A

New blood vessels form in response to low O2 levels—HIF-1 is stabilized and upregulates pro-angiogenic factors like VEGF

Hypoxyprobe-1 detects hypoxic cells—mostly macrophages

Macrophages highly express VEGF—tested to see if this could promote vascularization using a migration assay

Cabozantinib is a VEGFR2 inhibitor



6

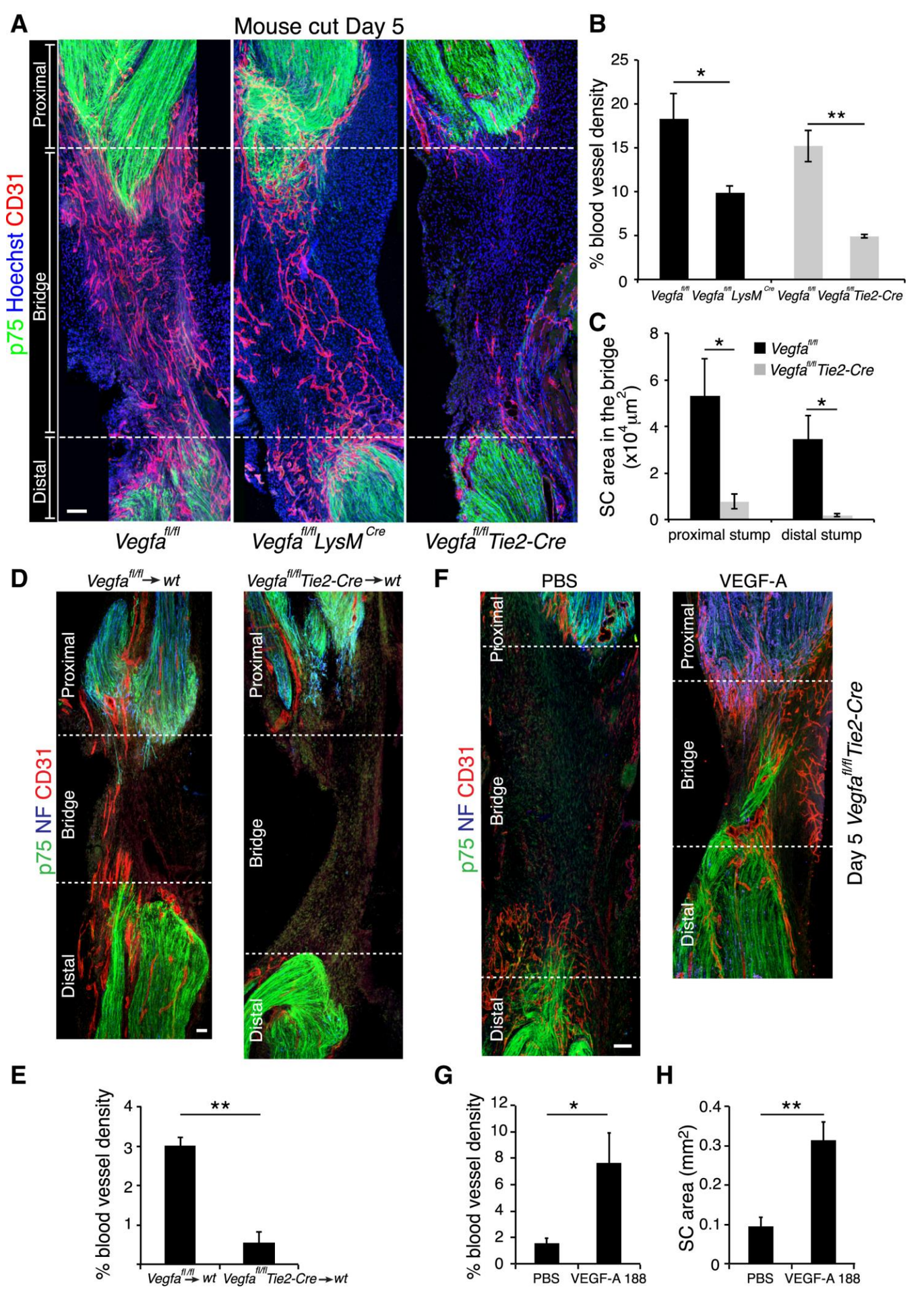
Inactivation of Vegfa in macrophages inhibits vascularization of the nerve bridge after nerve transection

Vegfa fl/fl Lysm Cre—macrophages and granulocytes—26% recombination

Vegfa fl/fl Tie2 Cre—hematopoietic cells and macrophages—82% recombination

Eliminate possibility of effects on ECs—performed bone marrow transplants in WT mice

Gain of function by injecting VEGF-A in the Vegfa fl/fl Tie2 Cre mice

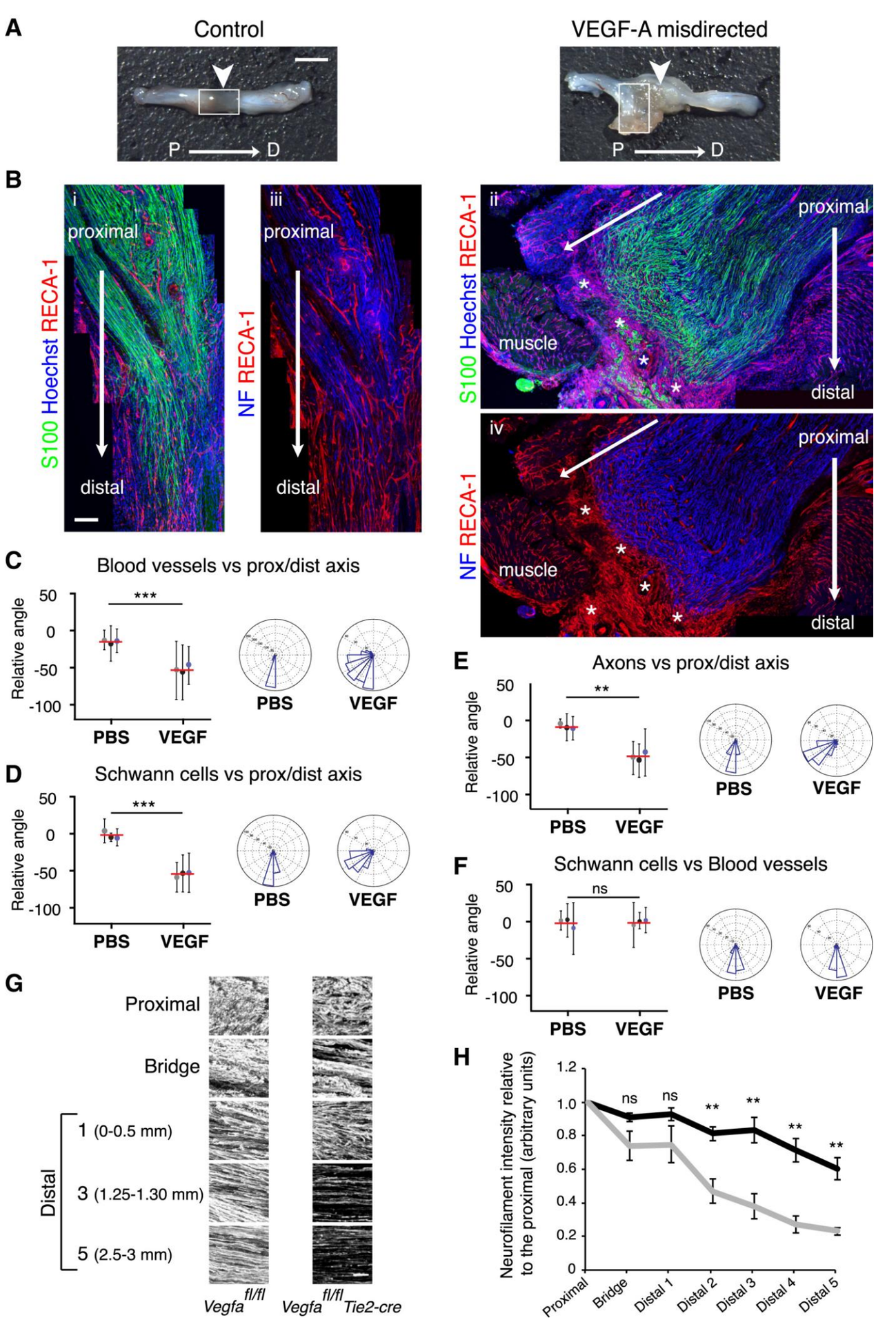


7

Redirection of the blood vessels leads to the misdirection of migrating SCs

VEGF-loaded hepain beads to the side of injury results in aberrant regeneration

Vegfa fl/fl Tie2 Cre mice—analyzed 14 days after lesion

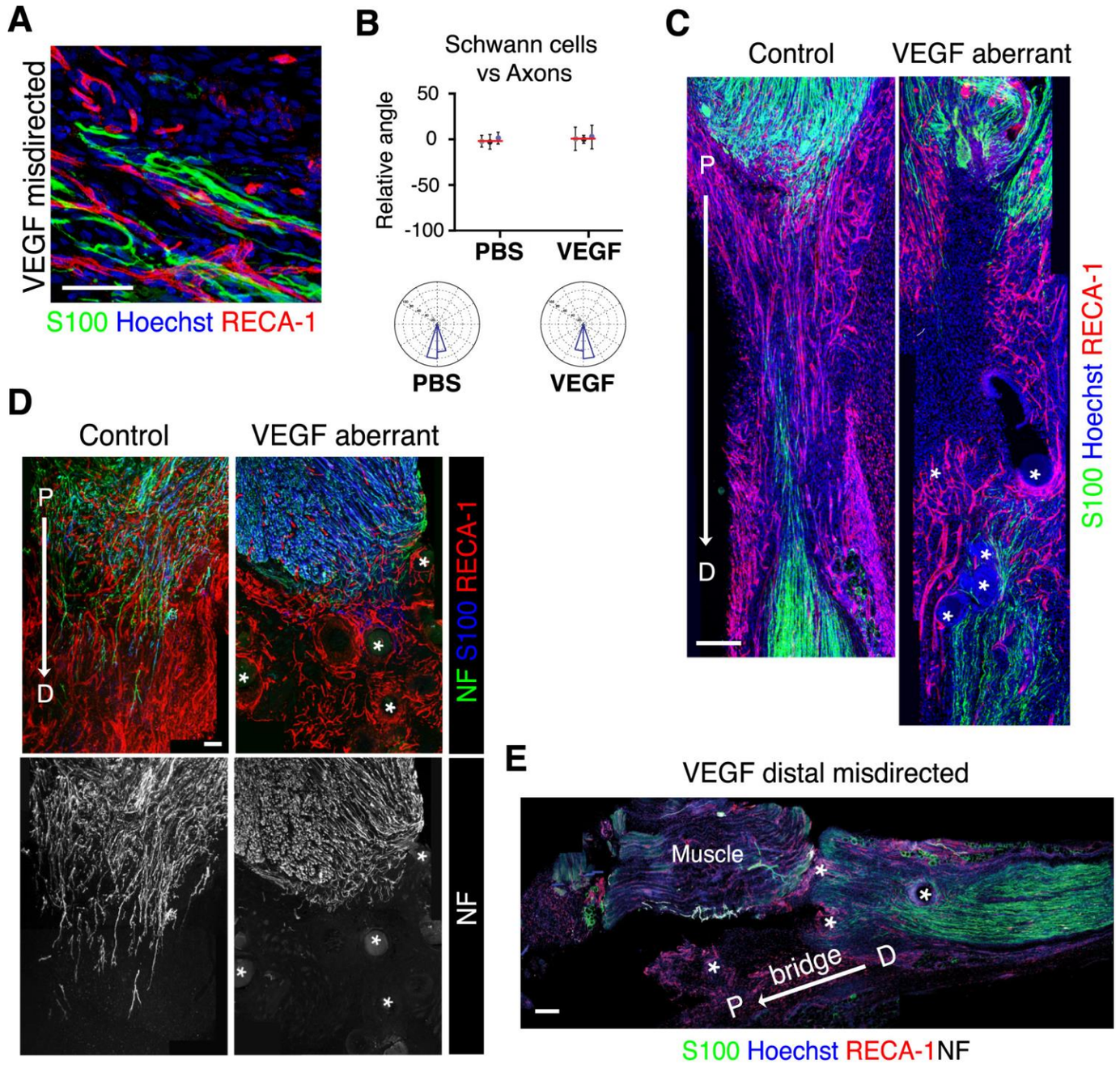


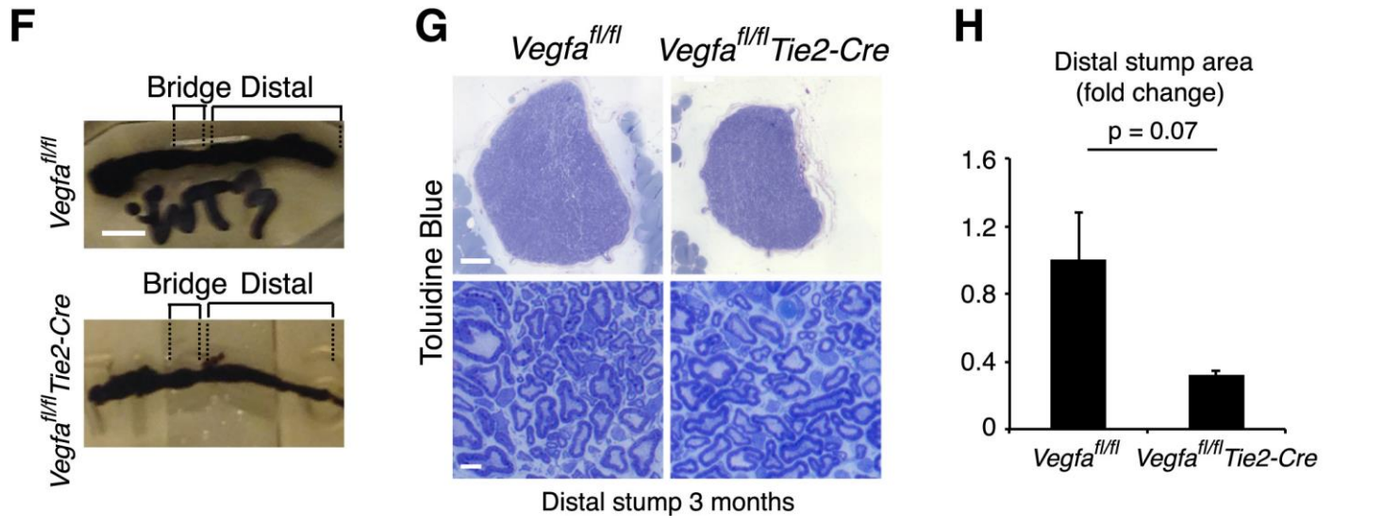
S7

Disorganization of blood vessels leads to disrupted Schwann cell migration and axonal regrowth

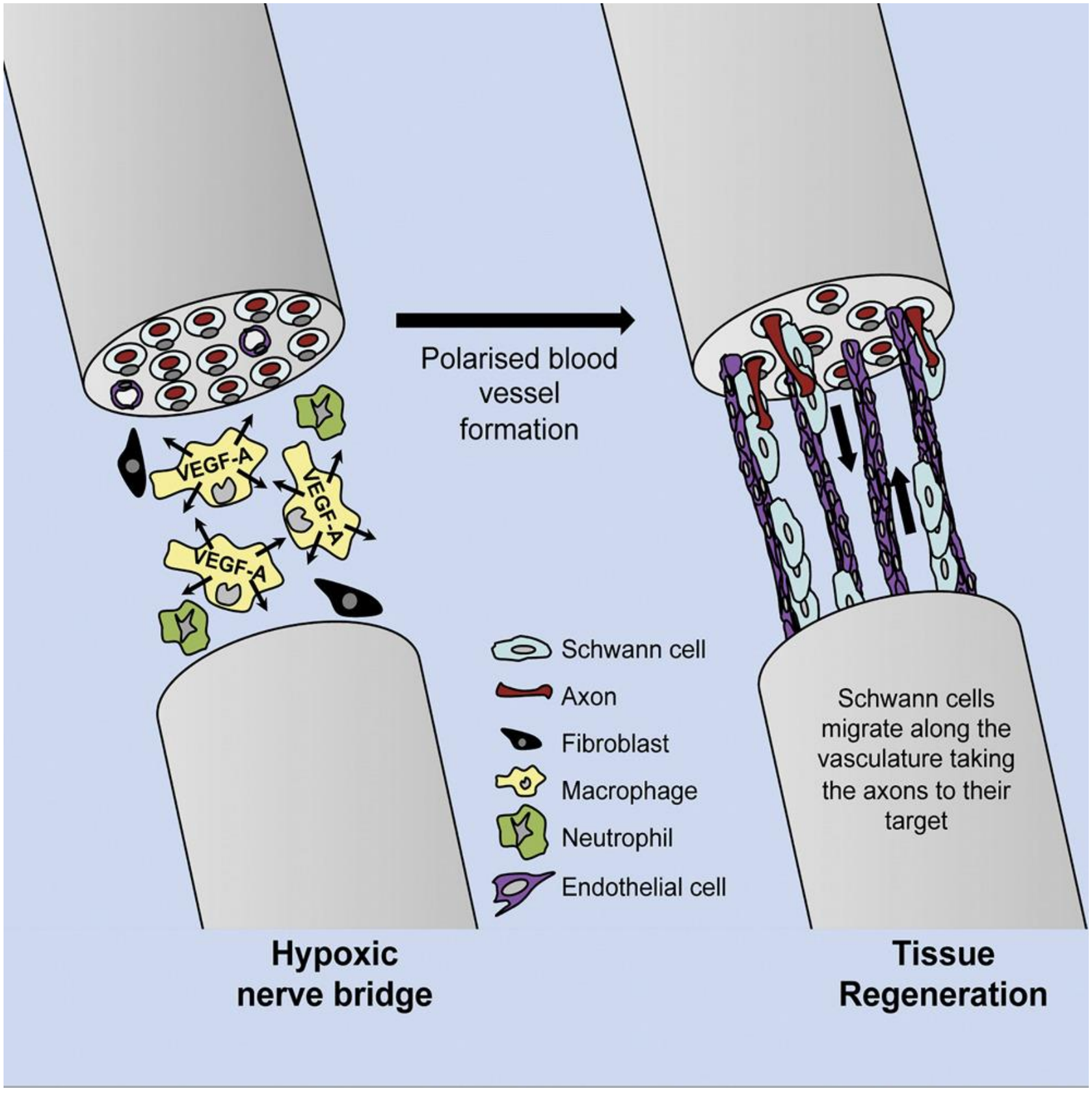
VEGF-loaded hepain beads to the side of injury results in aberrant regeneration

Vegfa fl/fl Tie2 Cre mice—analyzed 6 months after lesion



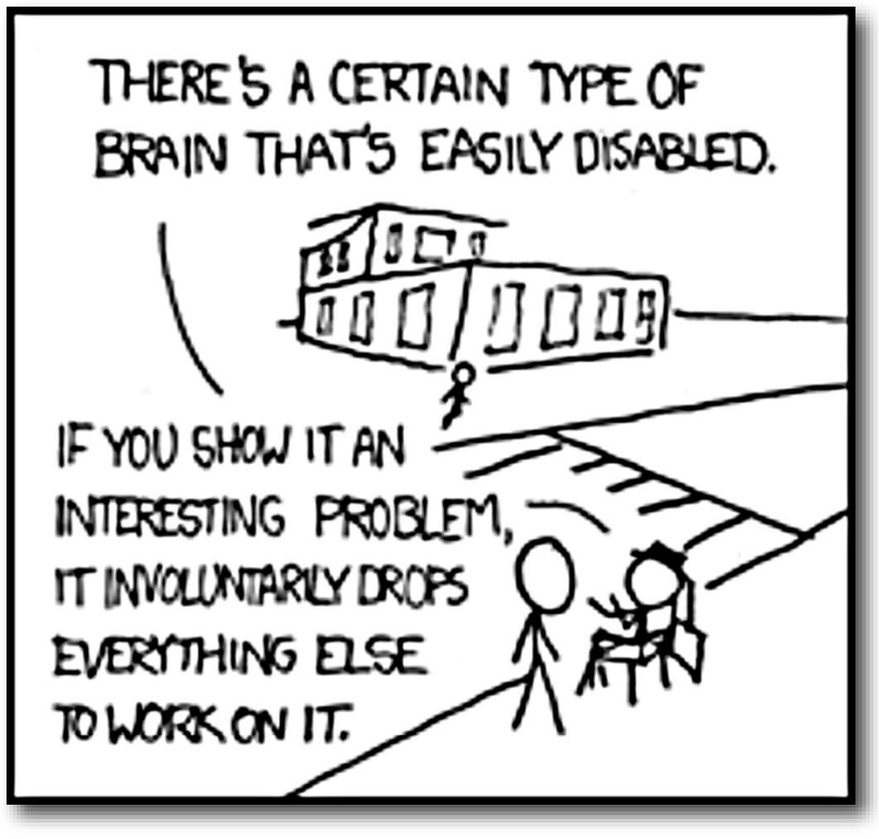


Summary


VEGF-A
VEGF-A
VEGF-A
Polarised blood vessel formation
Schwann cell
Axon
Fibroblast
Macrophage
Neutrophil
Endothelial cell
Schwann cells migrate along the vasculature taking the axons to their target
Hypoxic nerve bridge
Tissue Regeneration

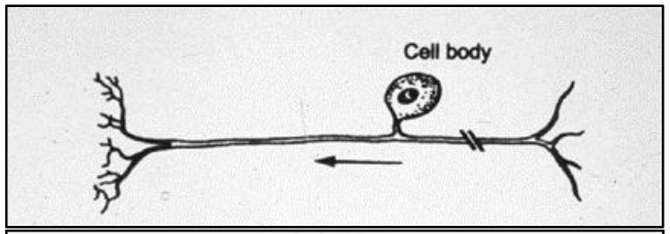
AXON-GLIA INTERACTIONS IN MYELINATED NERVES

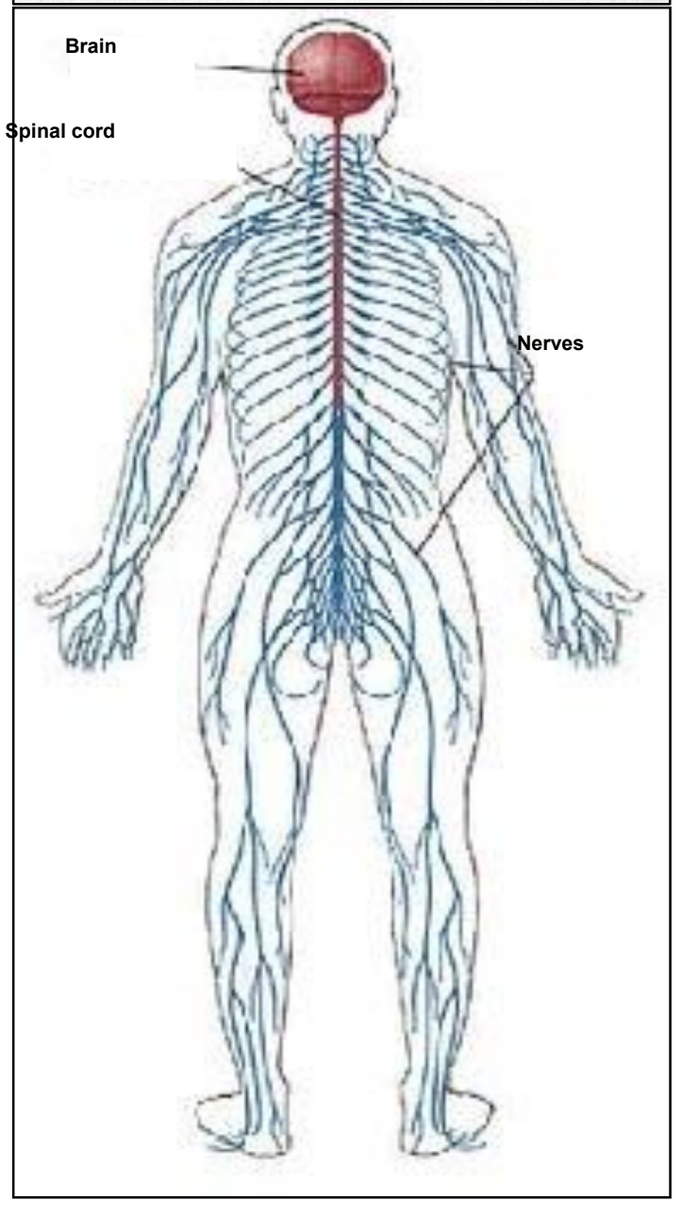
Peles, Elior
Chairman and Professor
Department for Molecular Cell Biology, Weizmann Institute of Science, Israel

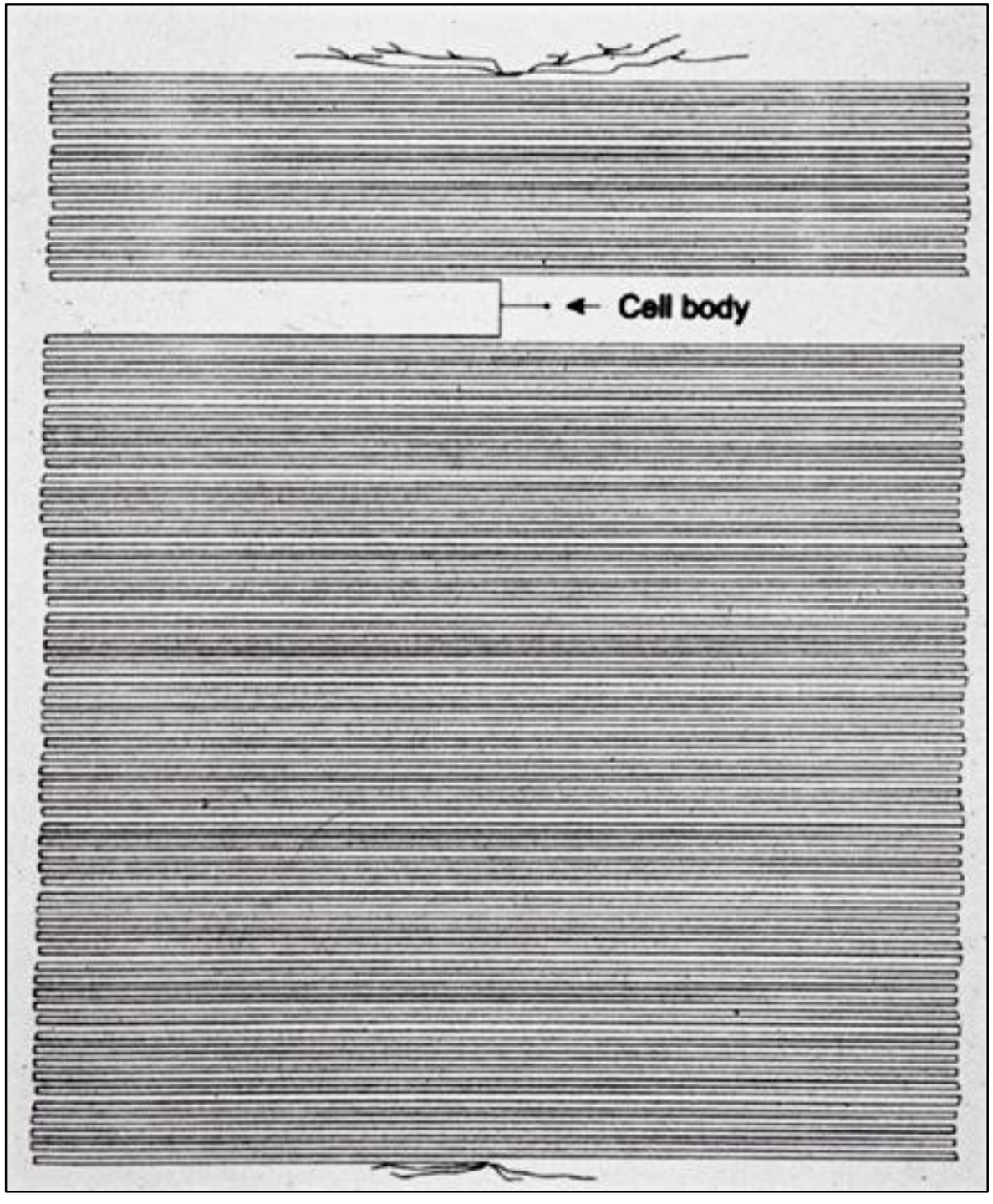


Role of glia in clustering of ion channels at nodes of Ranvier

The need for speed

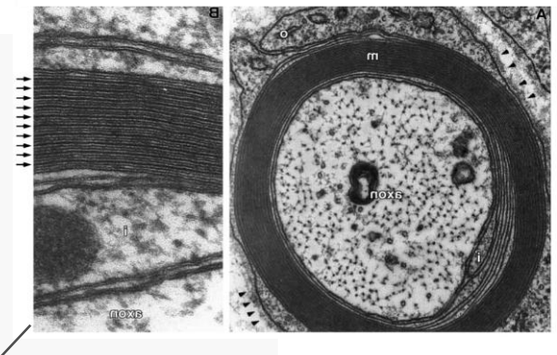


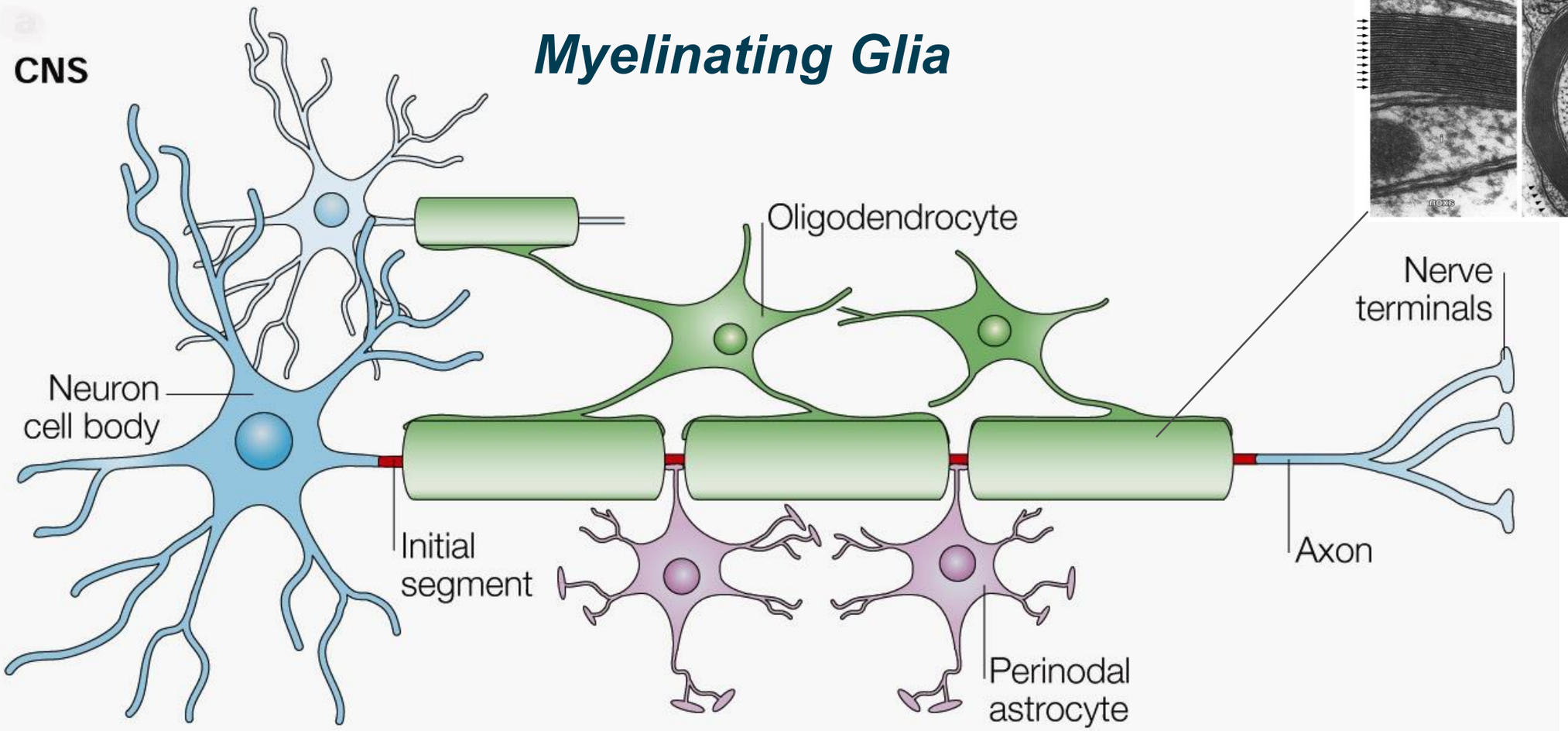




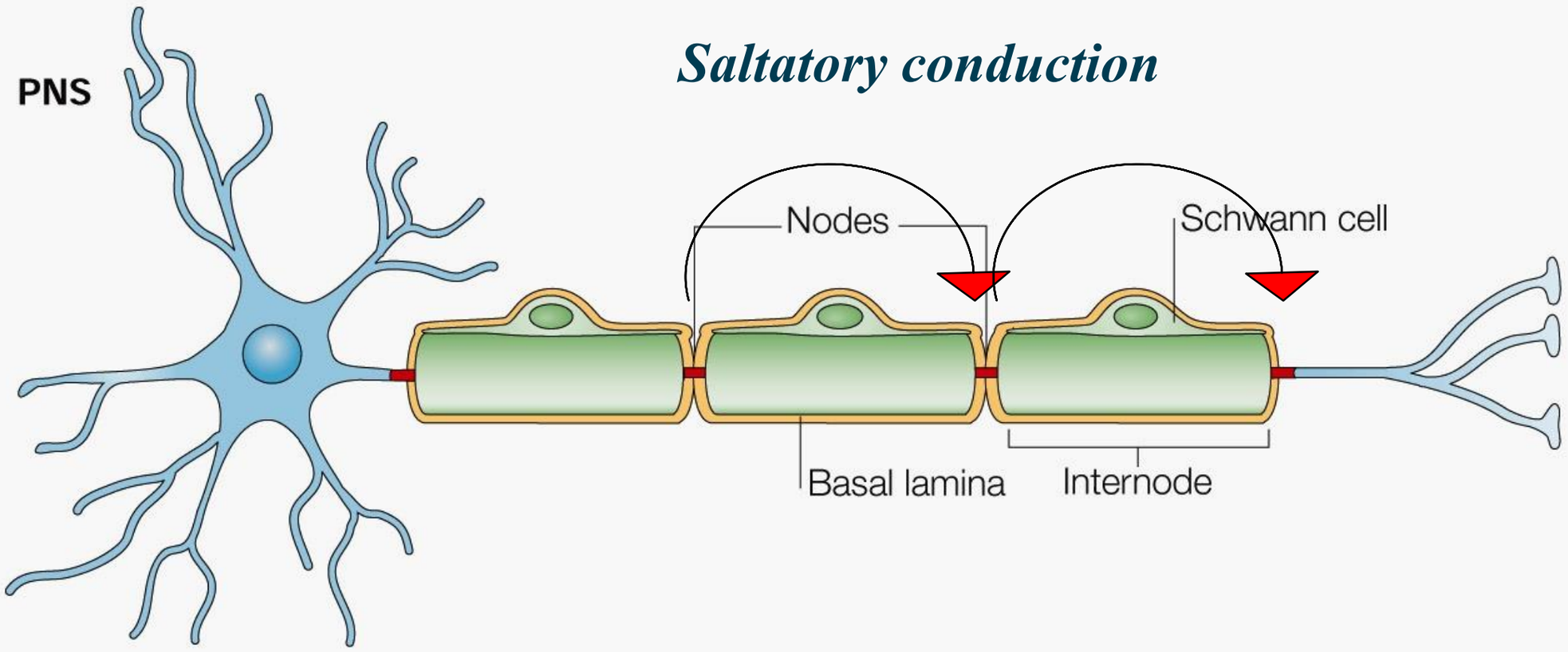
DRG neuron

Myelinating Glia

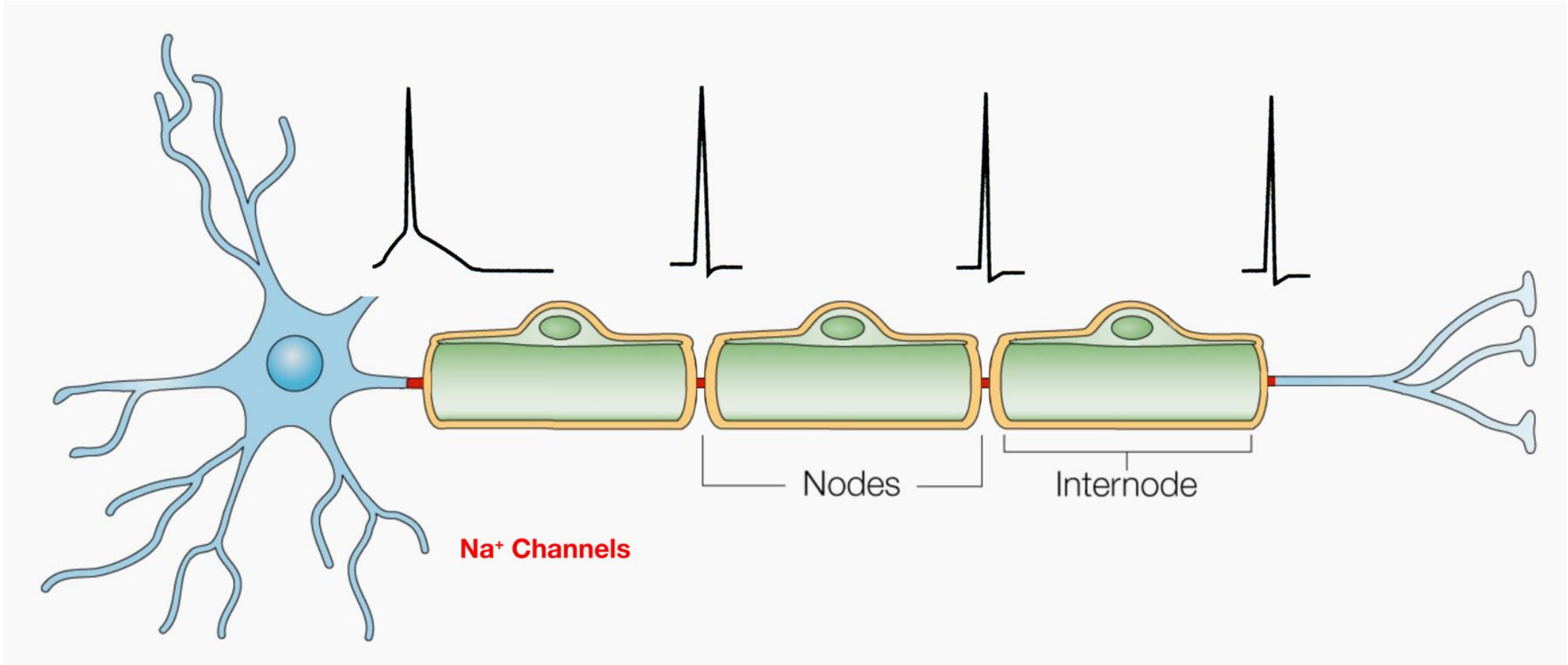


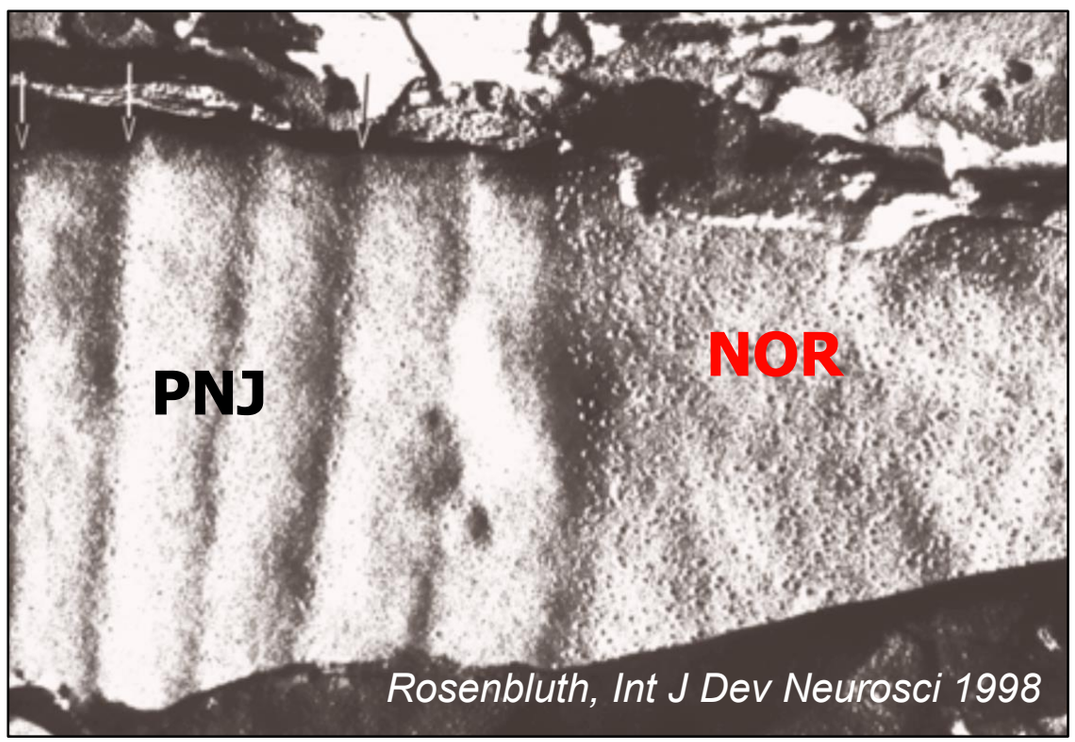


Saltatory conduction

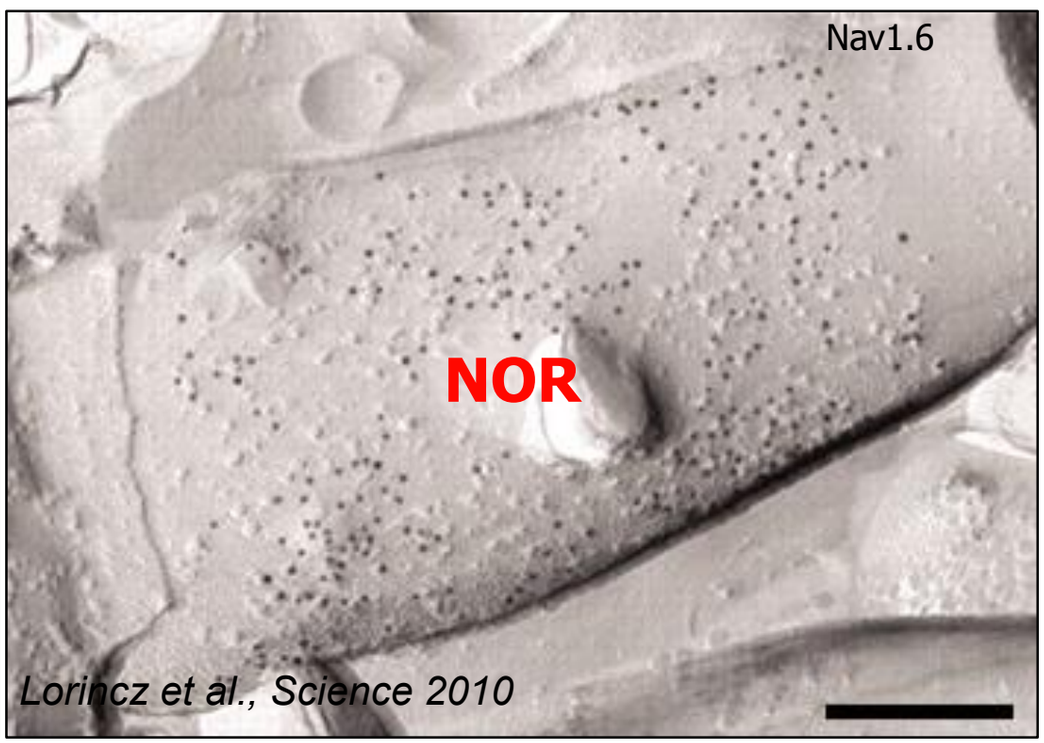


Conduction in myelinated axons requires high concentration of Na^+ channels at node of Ranvier



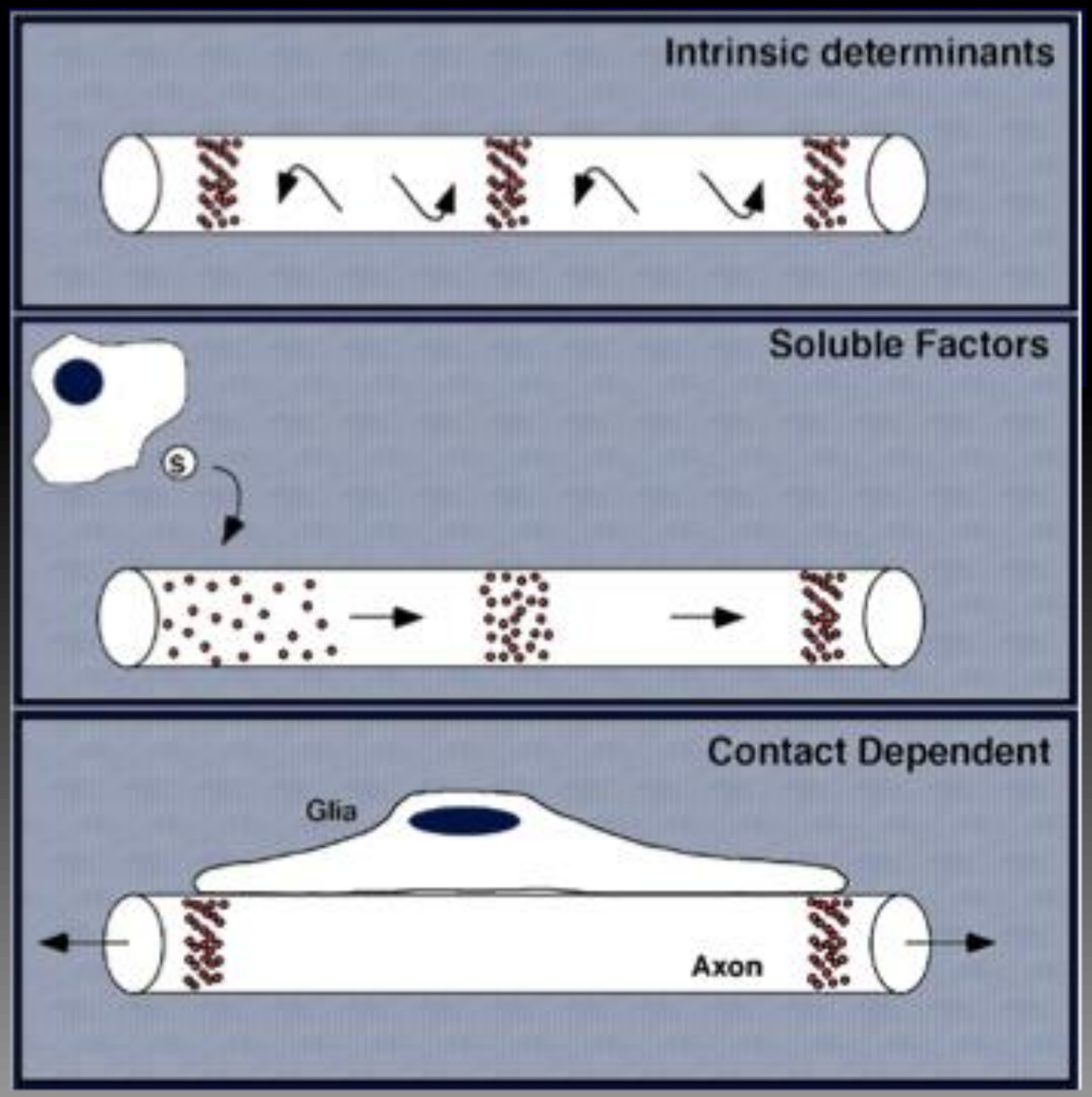


Rosenbluth, Int J Dev Neurosci 1998

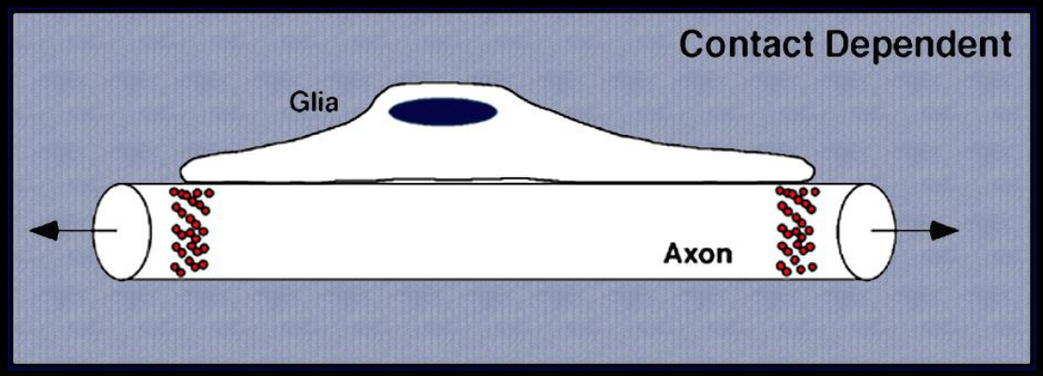


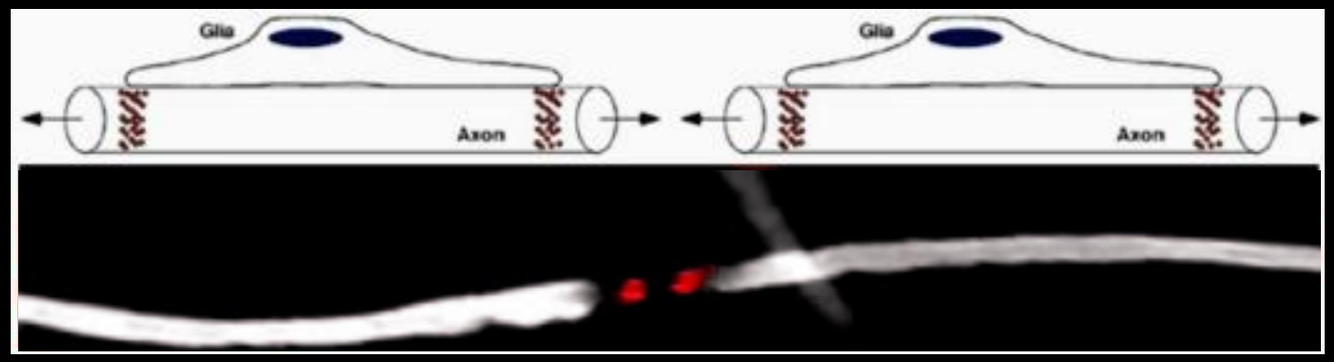
Lorincz et al., Science 2010

Intrinsic vs extrinsic models for Na^+ Channel clustering

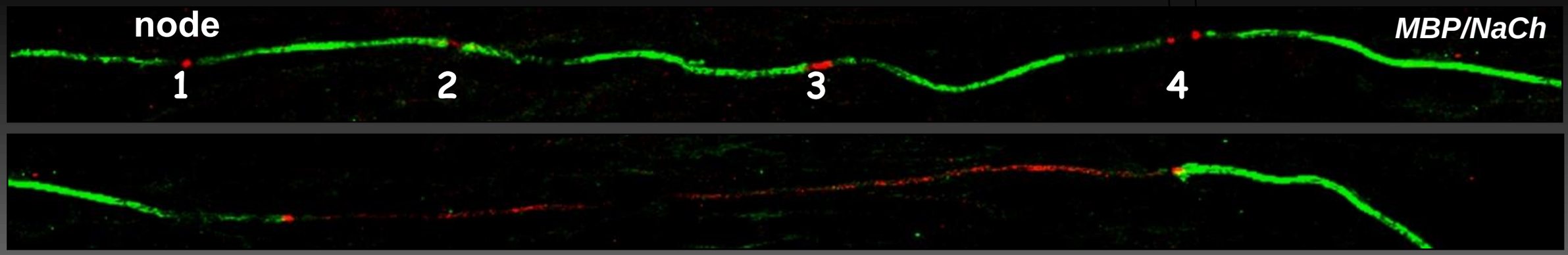


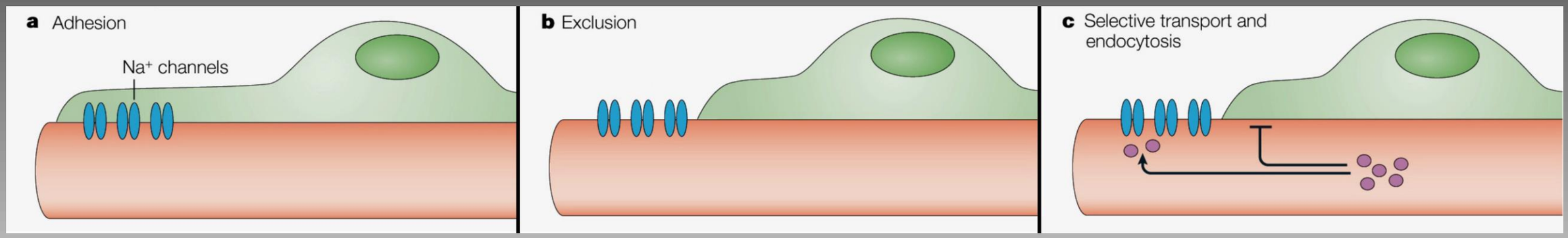
Na⁺ Channel clustering in the PNS requires glial contact





heminodes

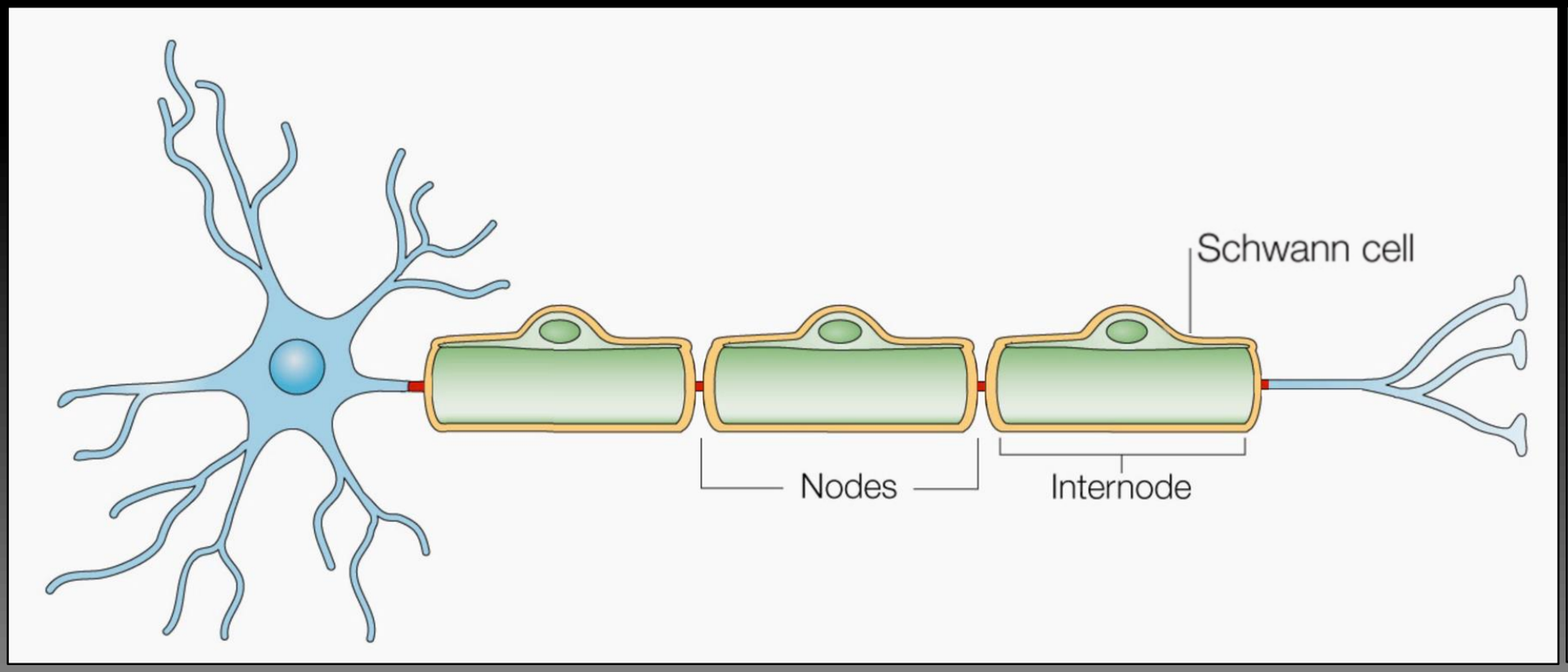


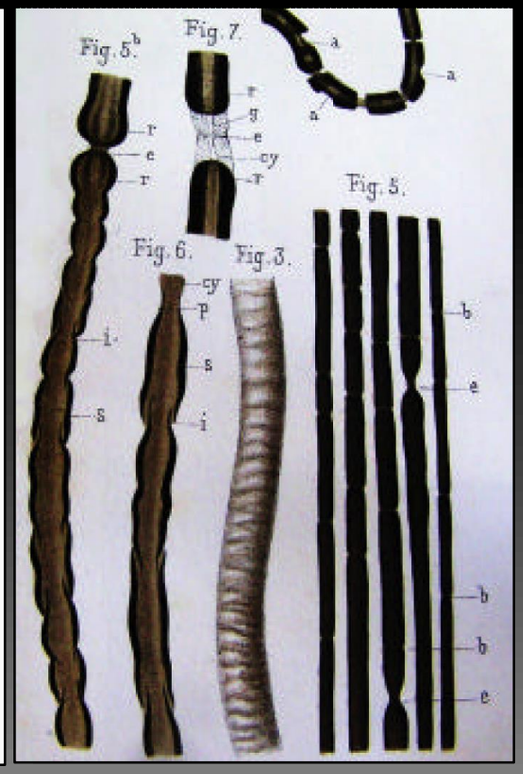


Poliak & Peles, Nat Rev Neurosci 2003

How do Schwann cells cluster Na^+ Channels at nodes of Ranvier?

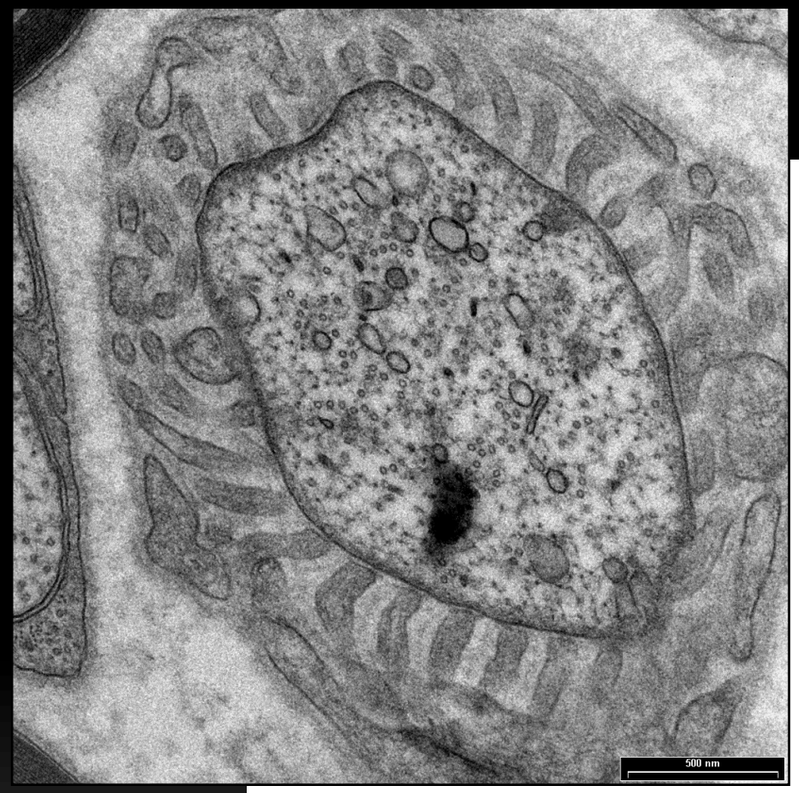
"étranglement annulaire"





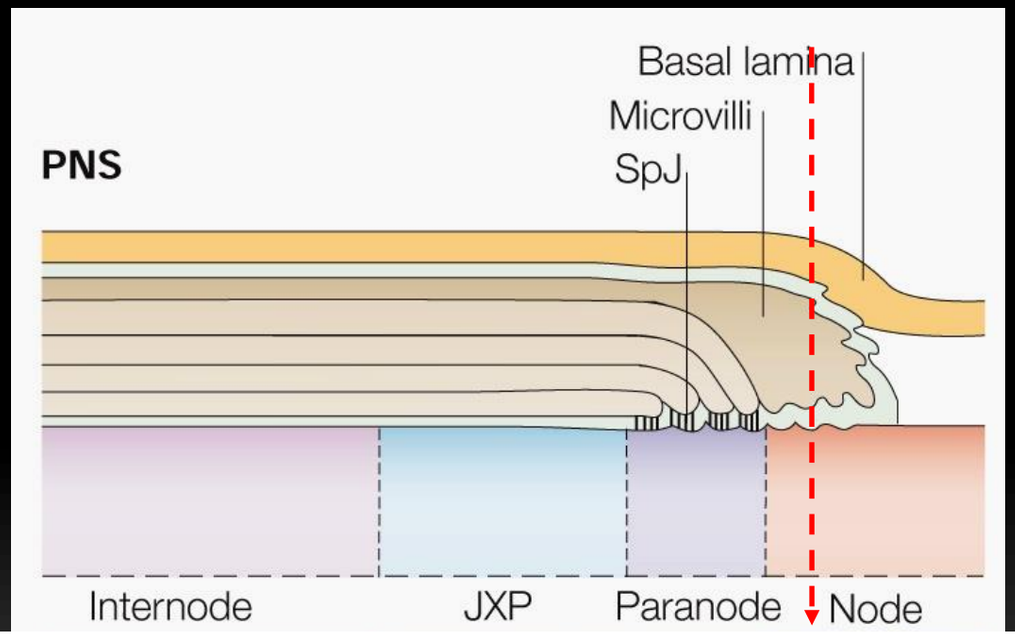
Louis-Antoine Ranvier
(1835-1922)

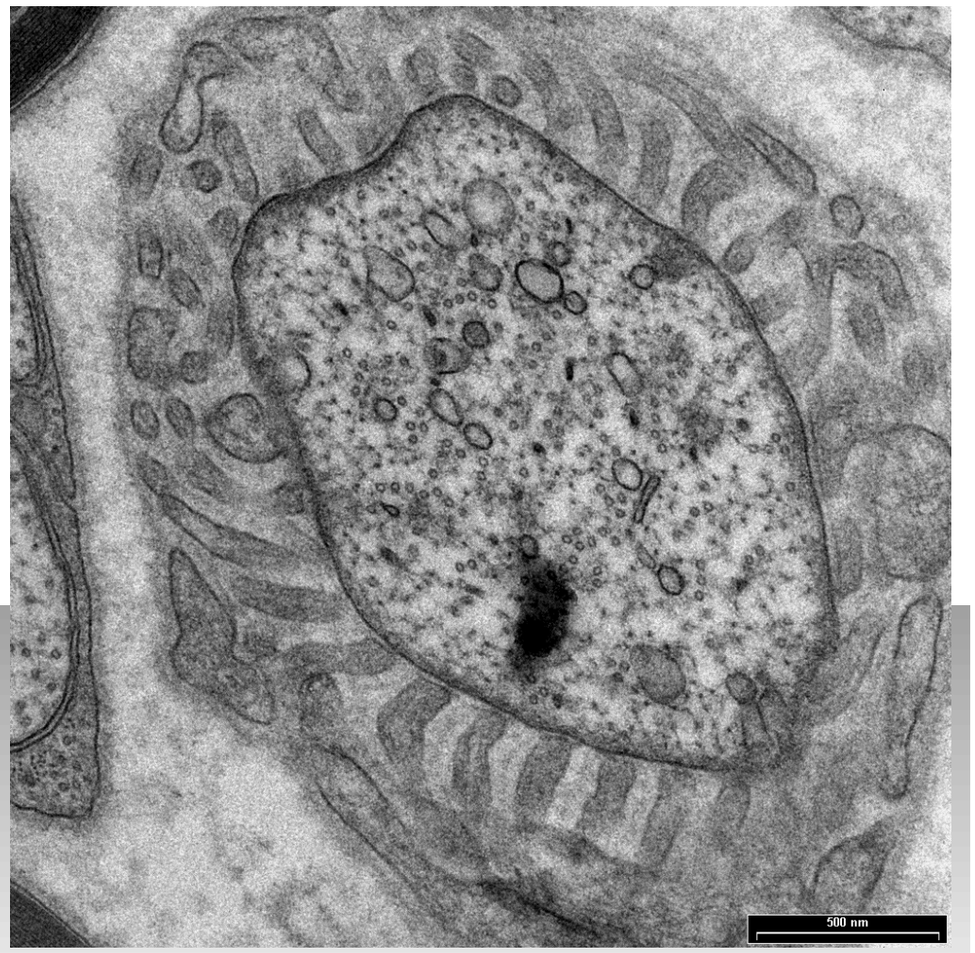
PNS myelin

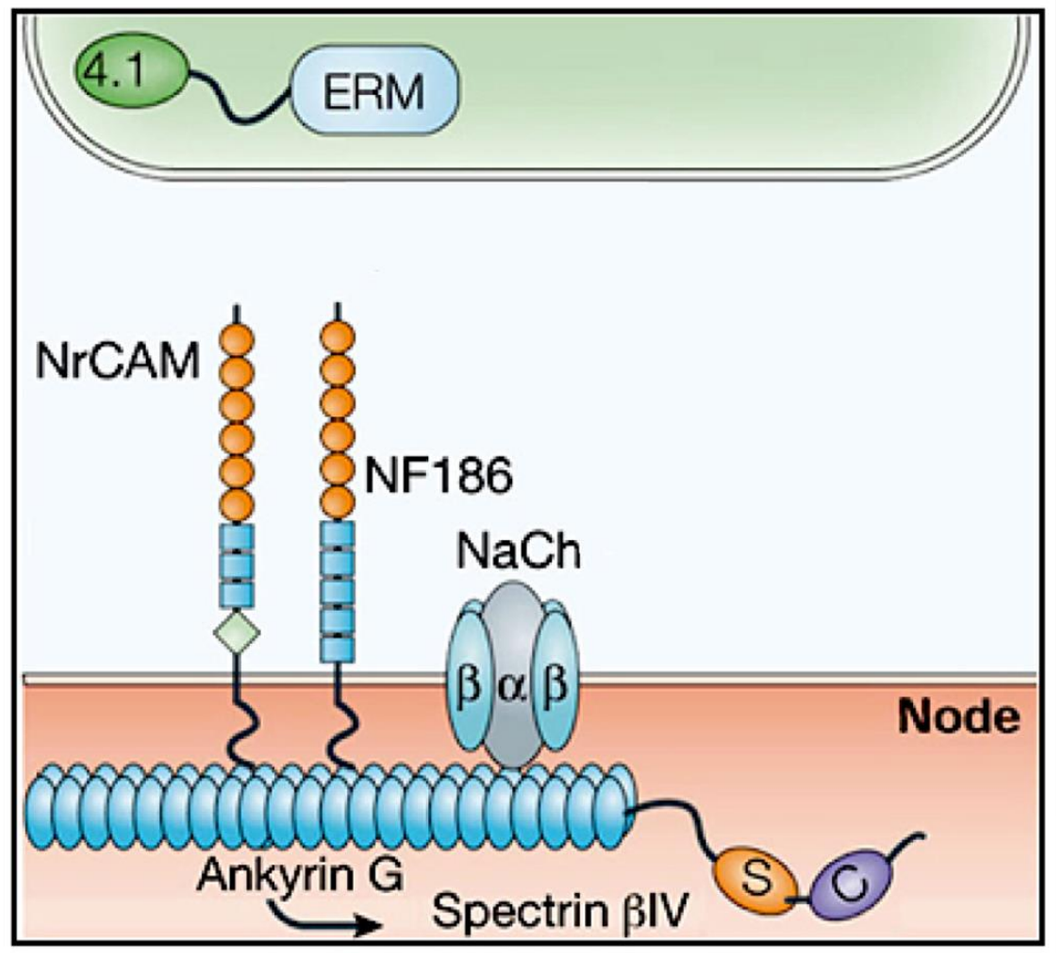

500 nm

Compact myelin
Paranodal loops
B
PNJ
NOR
A
Microvilli-Axon contact
Axon
Nodes of Ranvier
Microvilli
Paranodal junction

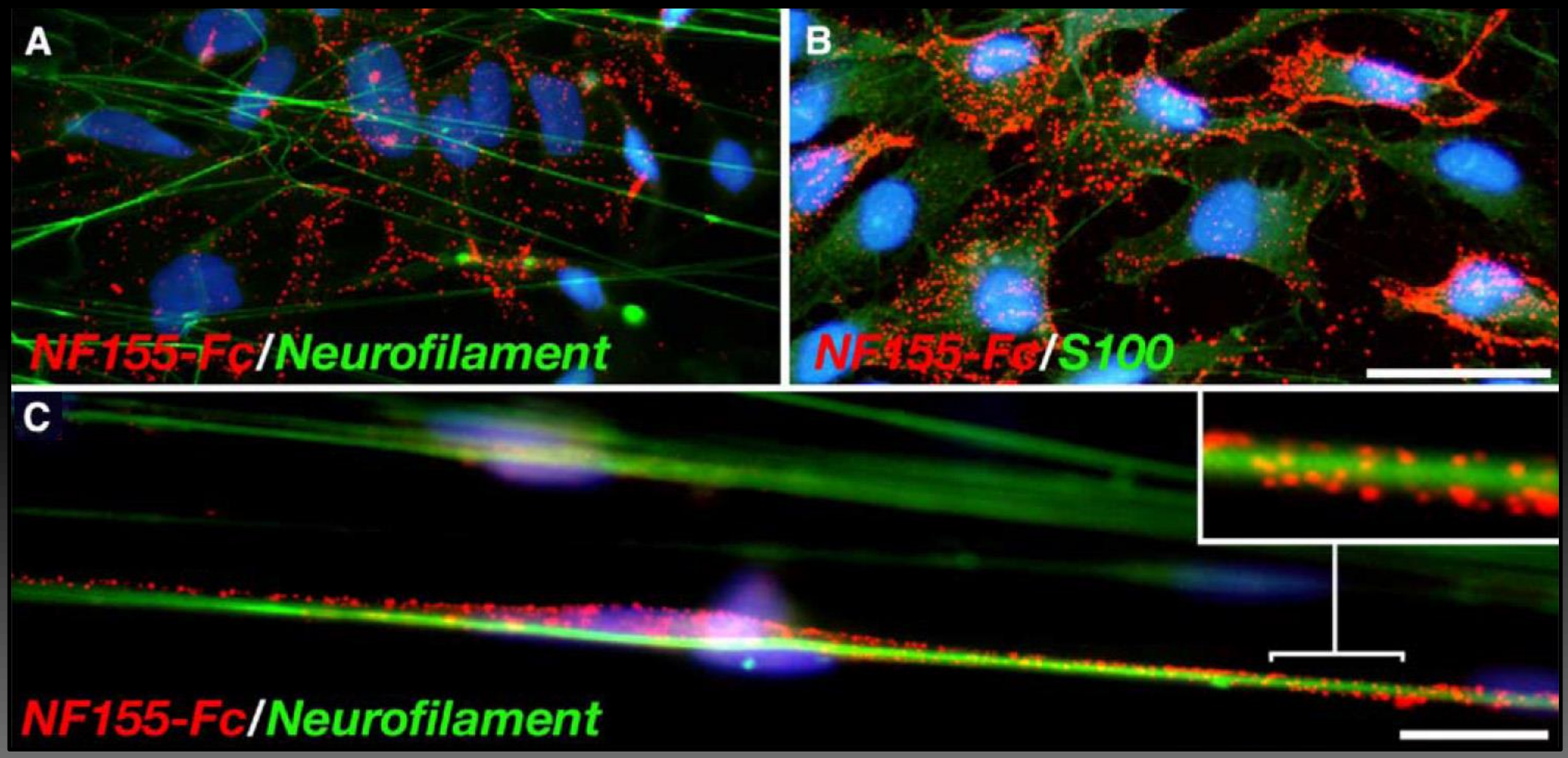
PNS nodes of Ranvier



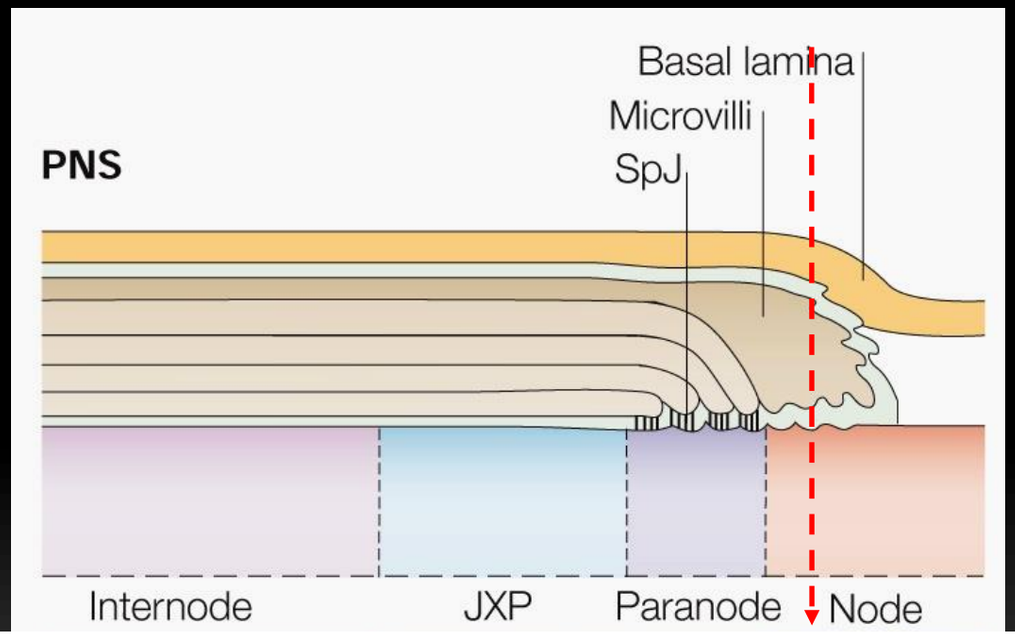




Schwann cells bind Neurofascin ECD



PNS nodes of Ranvier

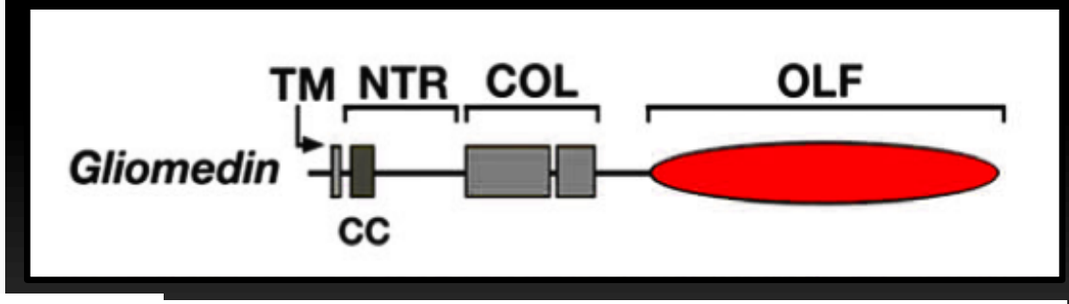


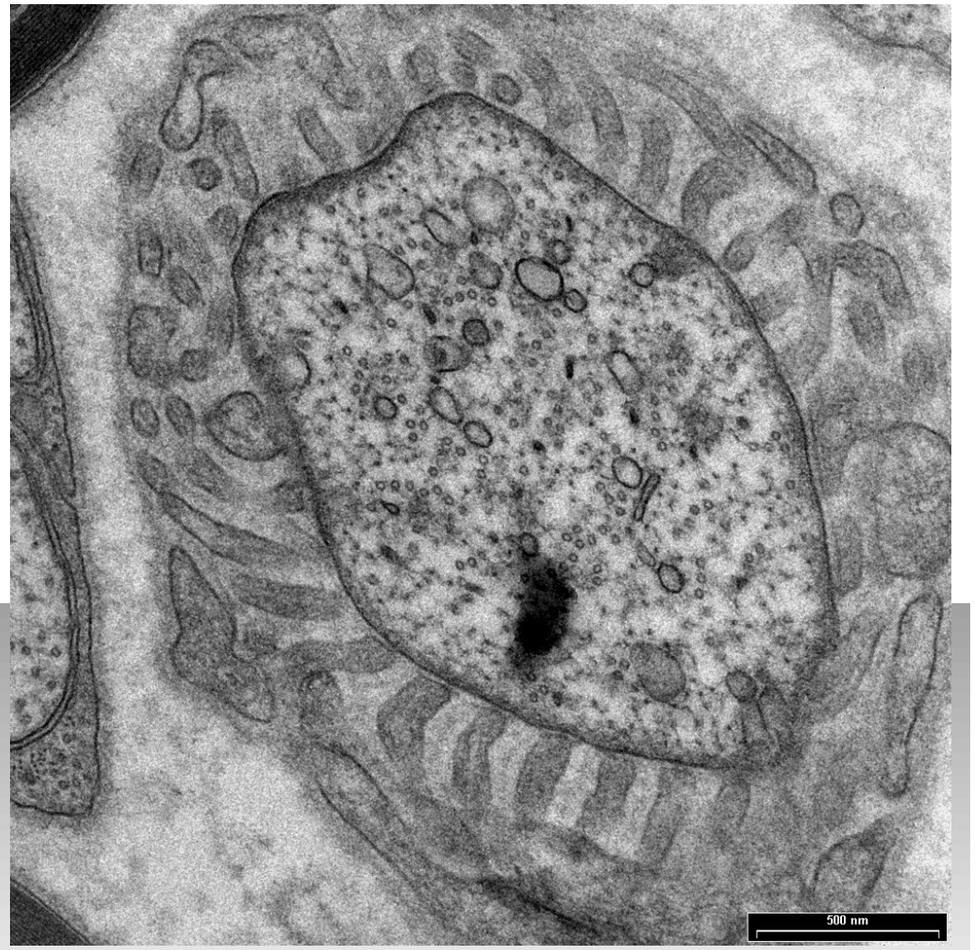
Axonodal:

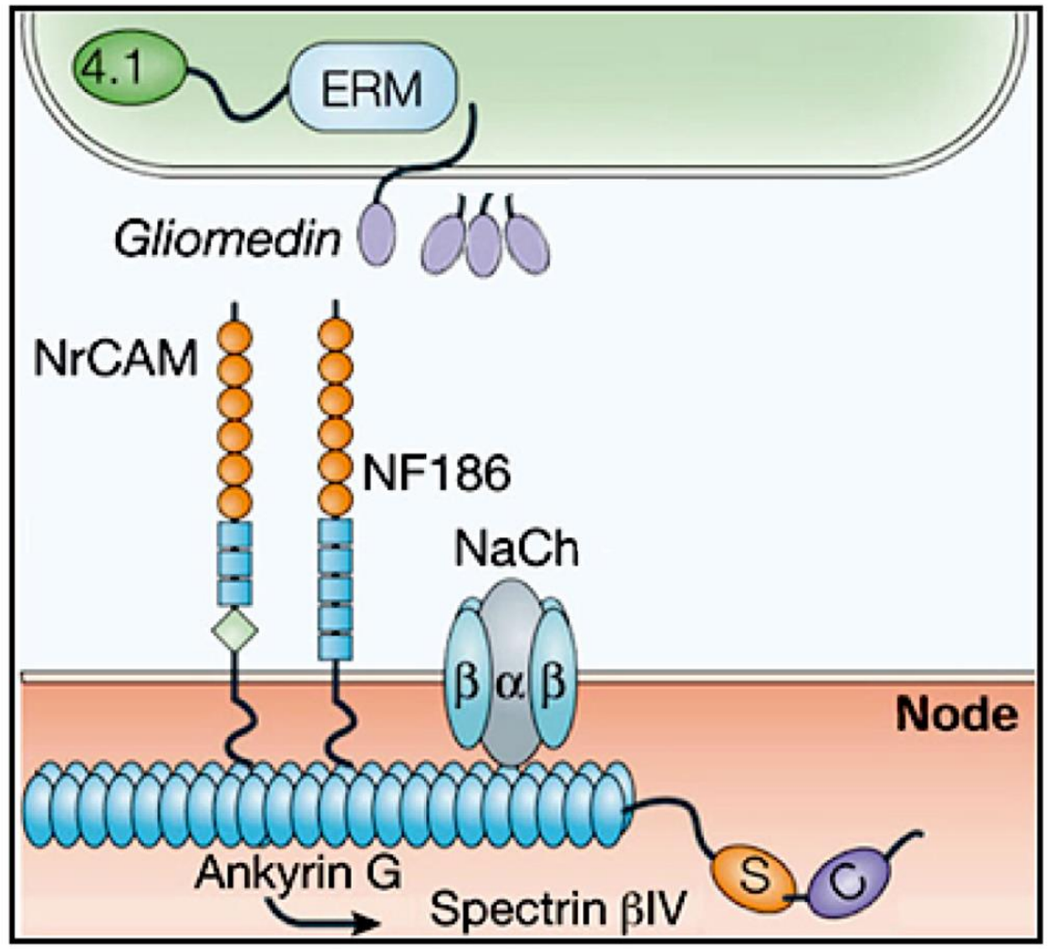
Channels - Nav1.6, KCNQ2,3

CAMs - Neurofascin 186 and NrCAM

Cytoskeletal - Ankyrin G and βIV Spectrin



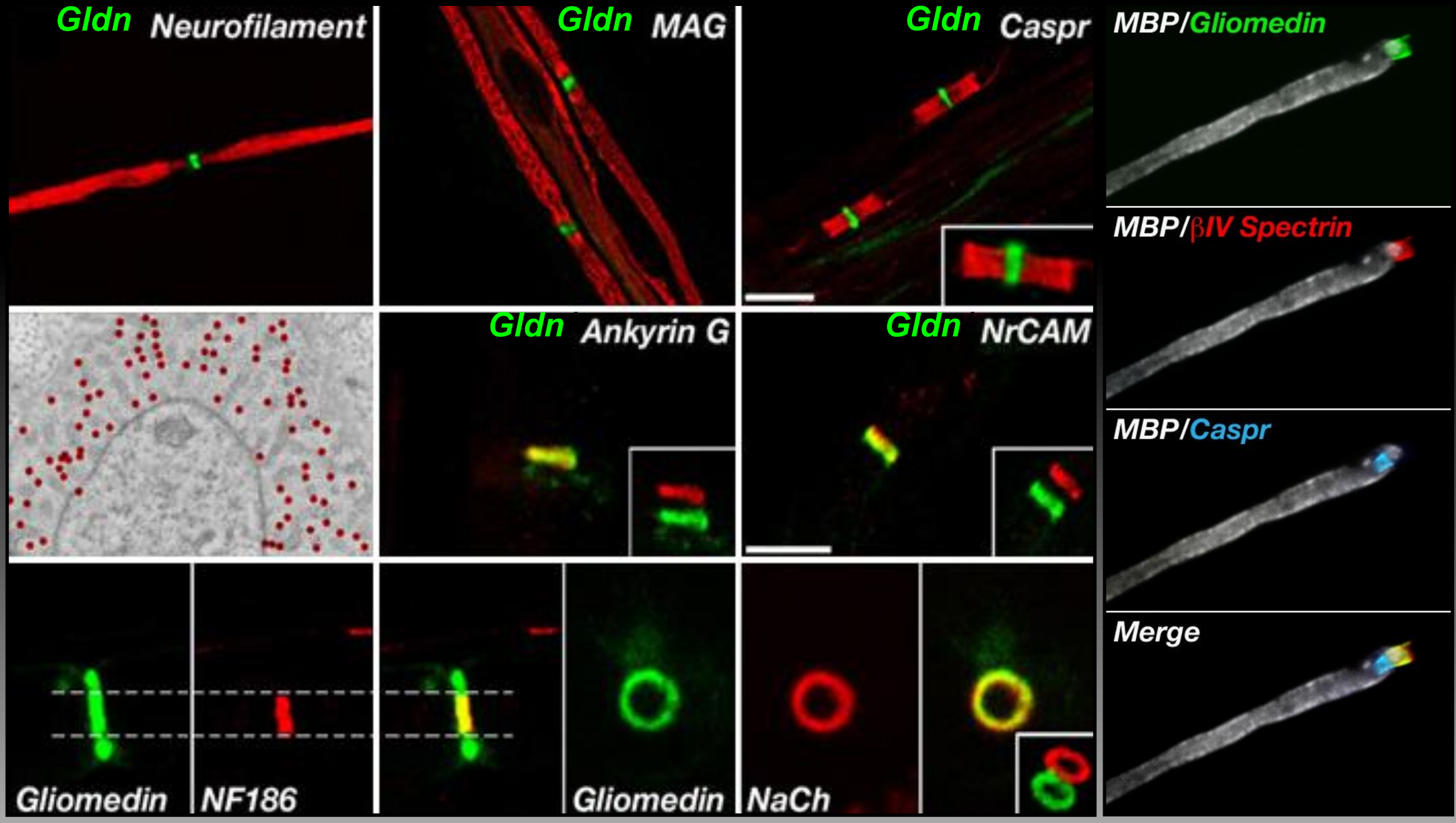




Gliomedin is localized at the Schwann microvilli that contact NOR

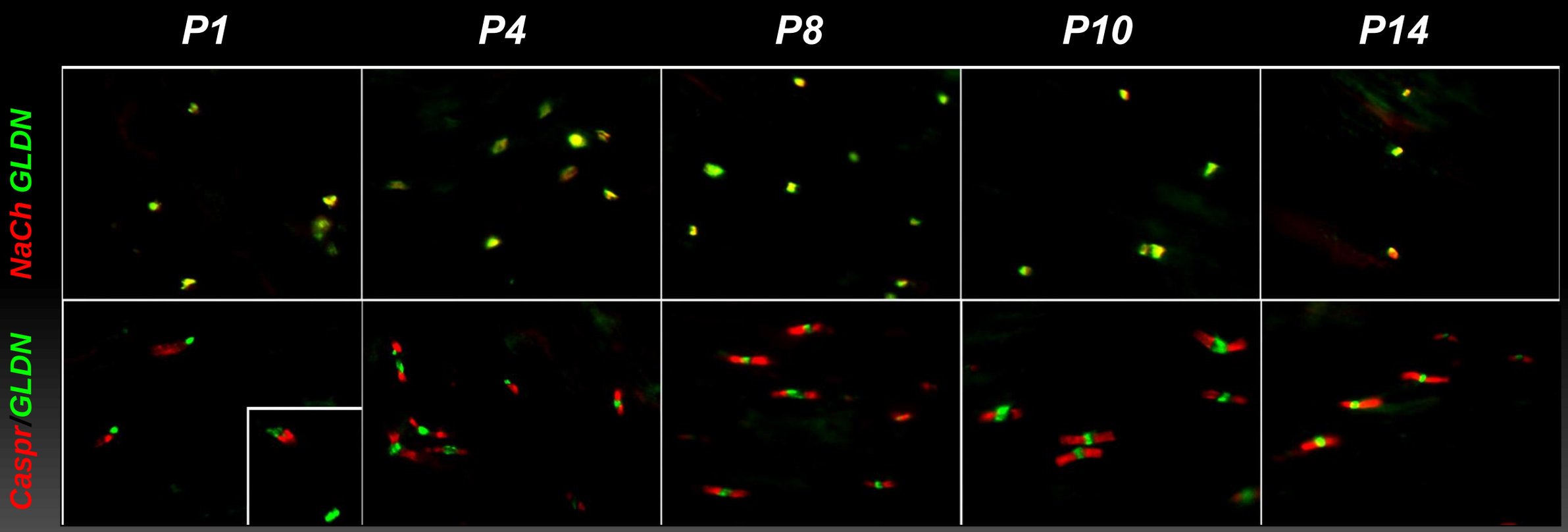
Sciatic nerve

Myelinated Culture

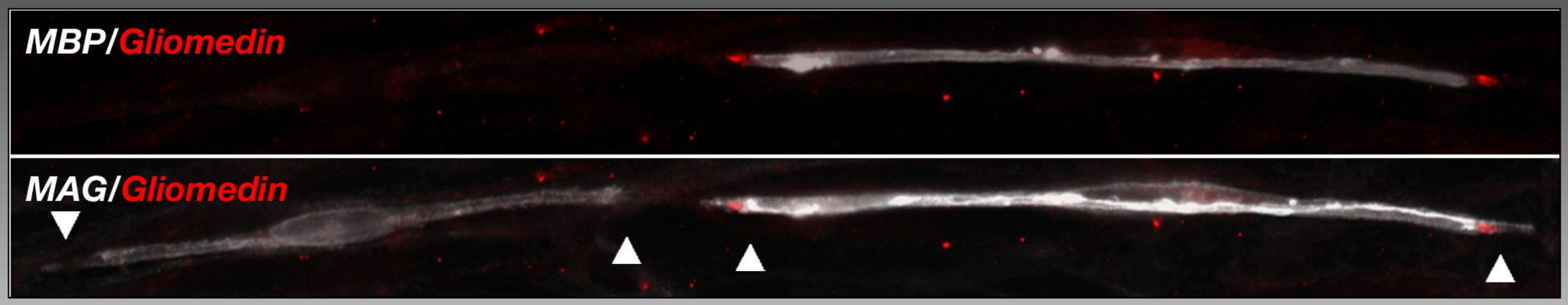


Eshed et al., Neuron 2005

Gliomedin co-localizes with NaCh during development

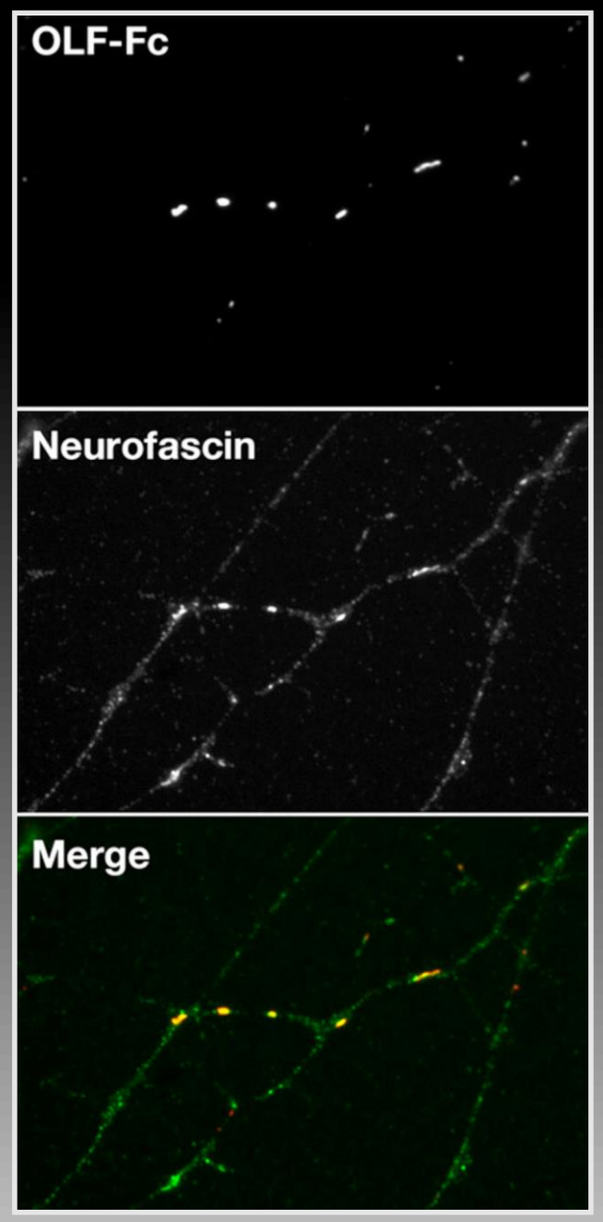


Sciatic nerve



Myelinated Culture

Gliomedin induces nodal clusters in DRG neurons



DRG neurons

Neurofascin

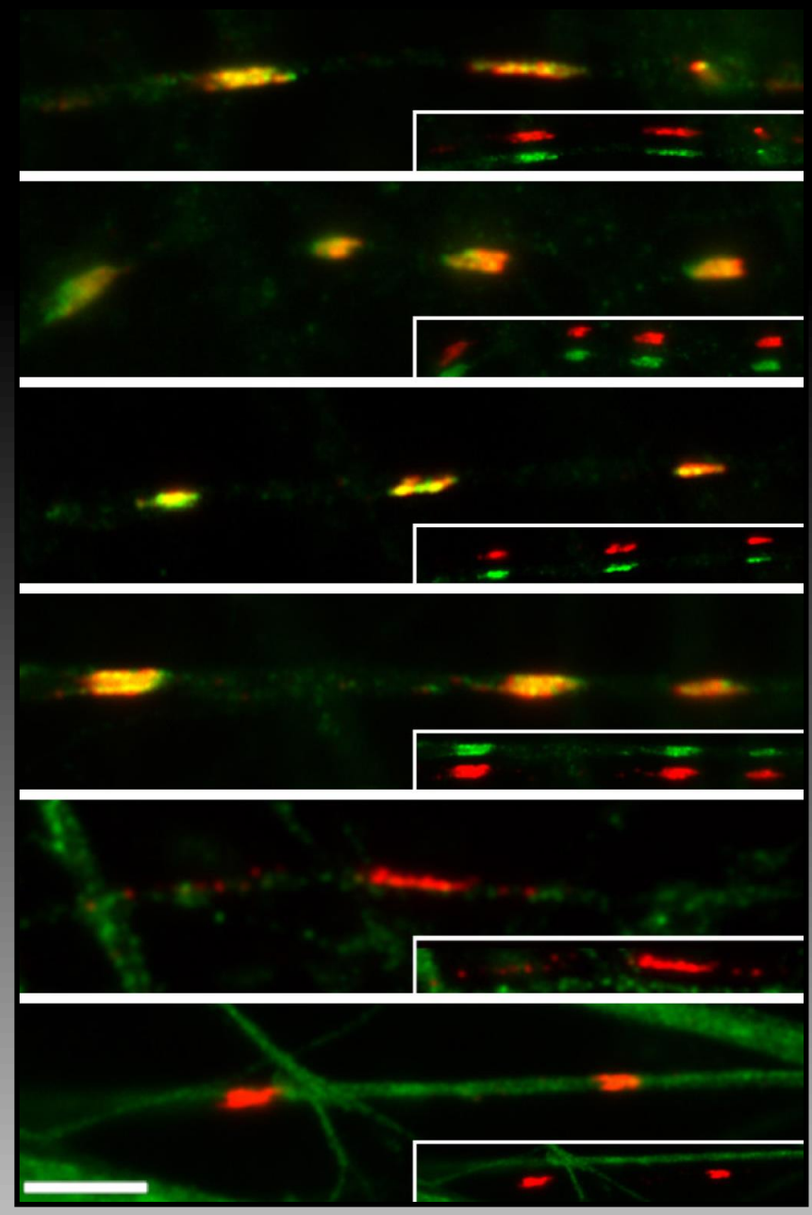
Ankyrin G

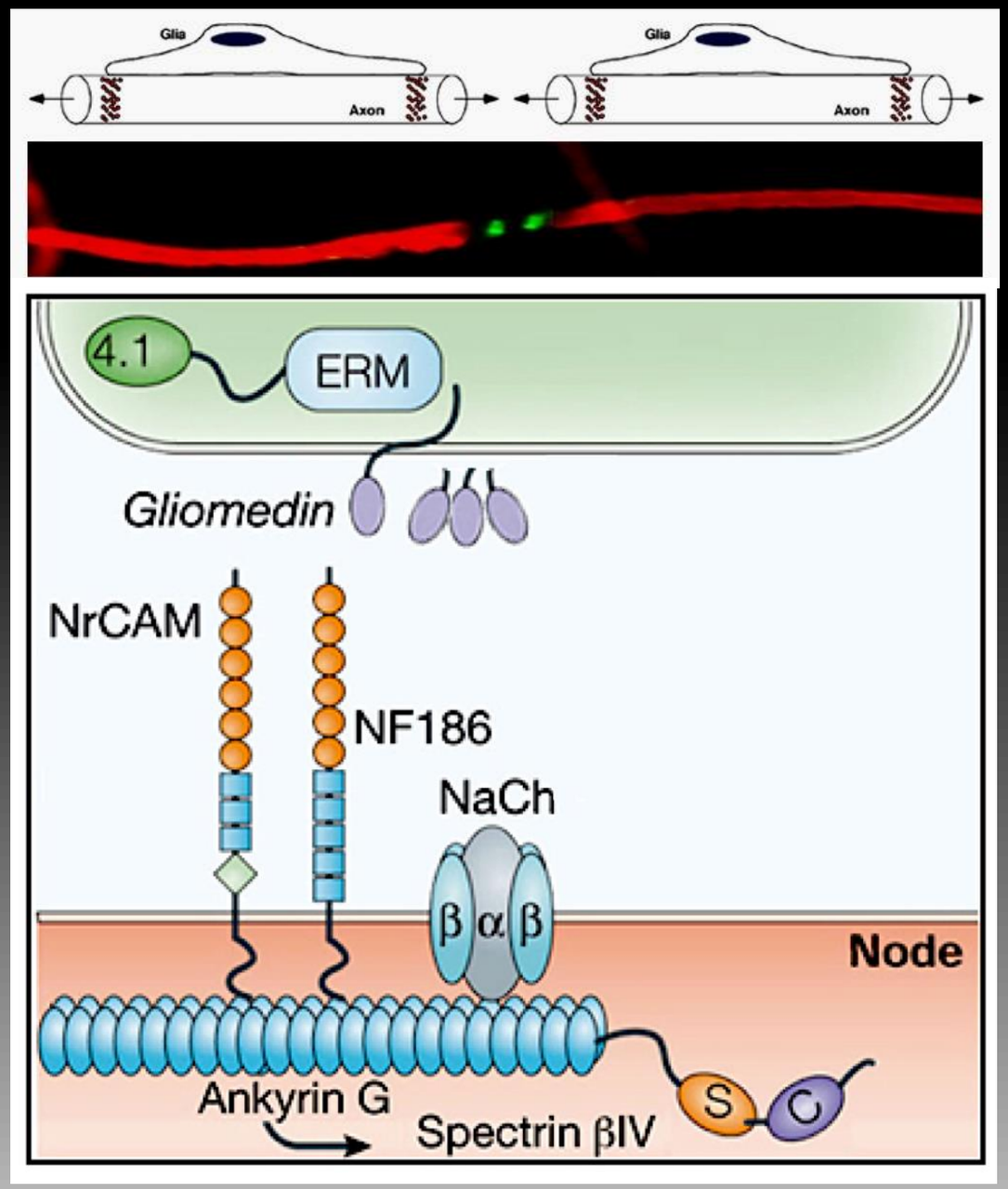
Spectrin

NaV1.2

Caspr

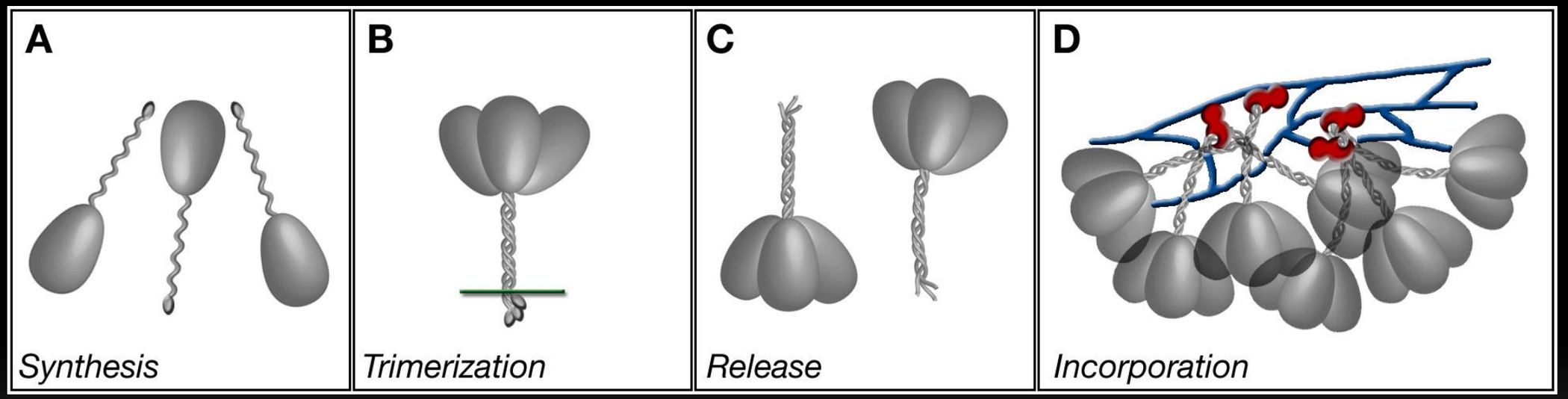
4.1B





- *Gliomedin is a glial ligand for both neurofascin and NrCAM.*
- *Gliomedin is localized to the Schwann cell microvilli that contact the node of Ranvier in the PNS*
- *Gliomedin accumulates at the edges of myelinating Schwann cells early during node formation.*
- *Gliomedin induces nodal clusters in DRG neurons*

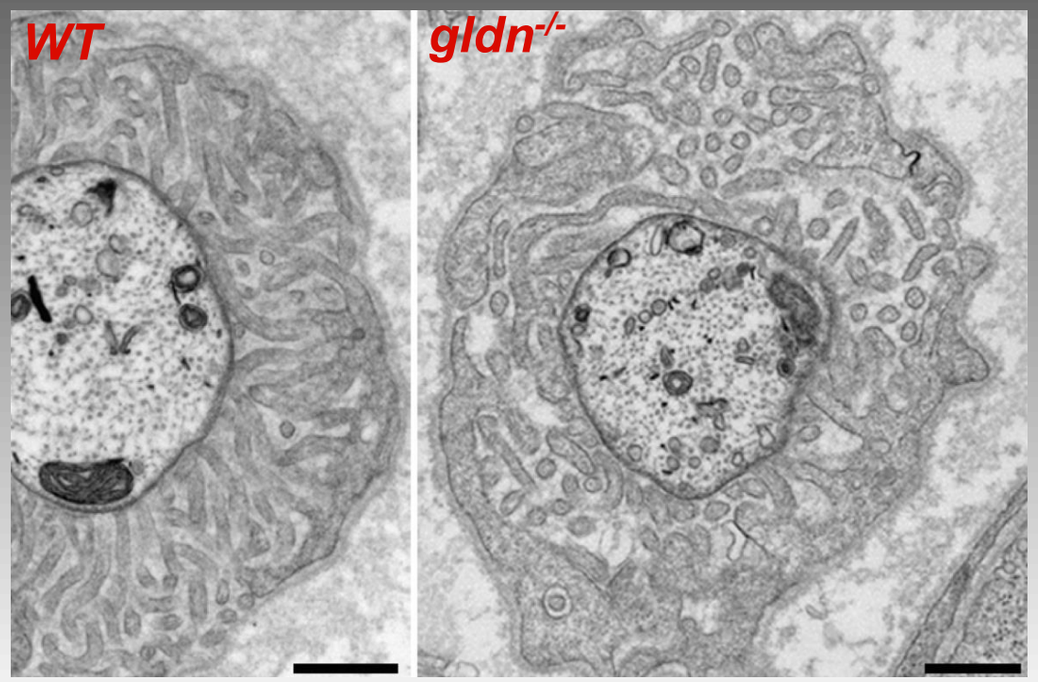
Gliomedin is a perinodal matrix component of PNS nodes

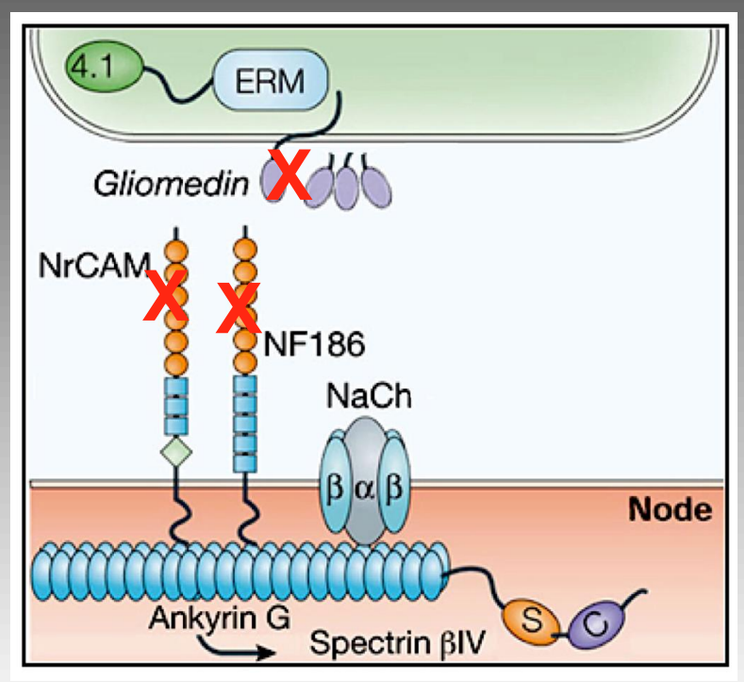


Eshed et al., JCB 2007

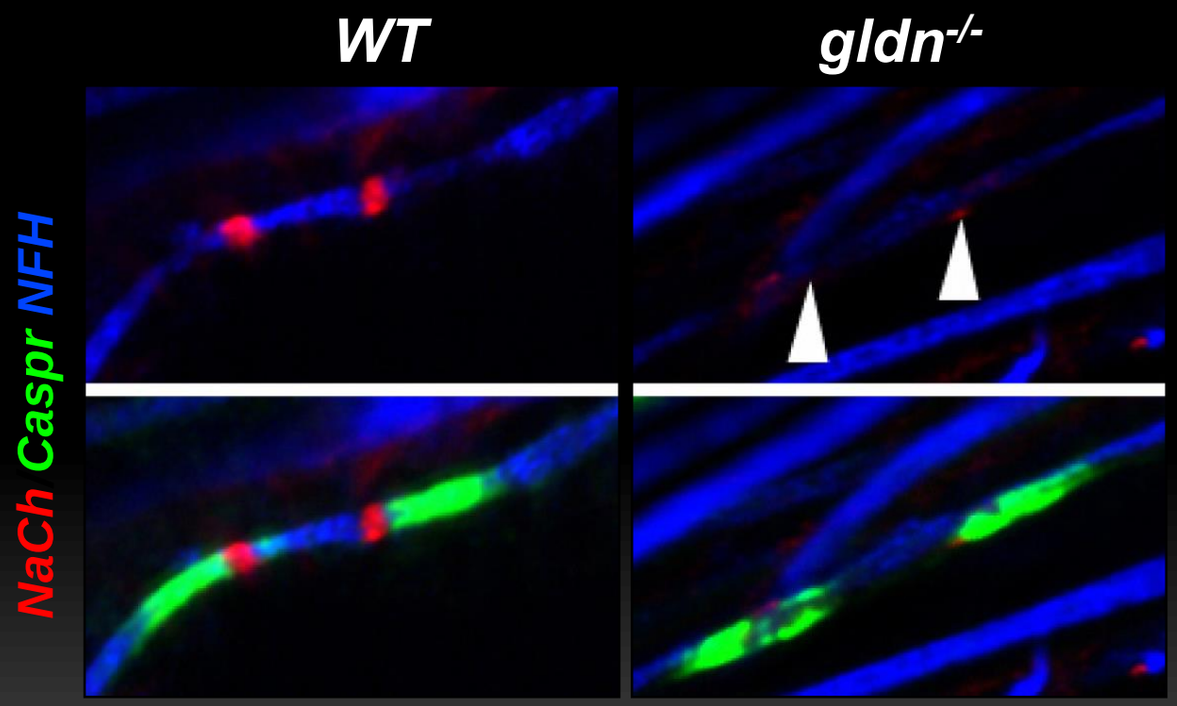
High-avidity gliomedin complexes at the forming node

Clustering of NF186 and ankyrin G on the axolemma

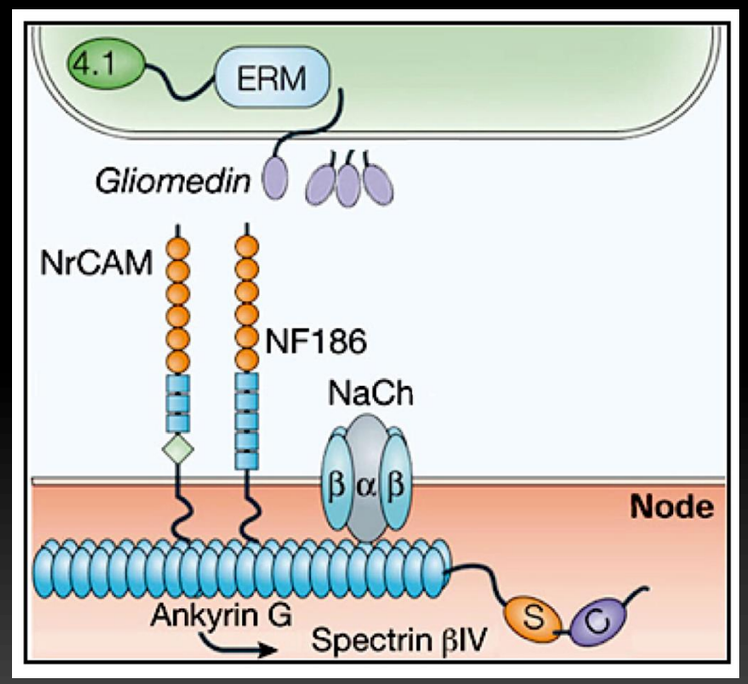


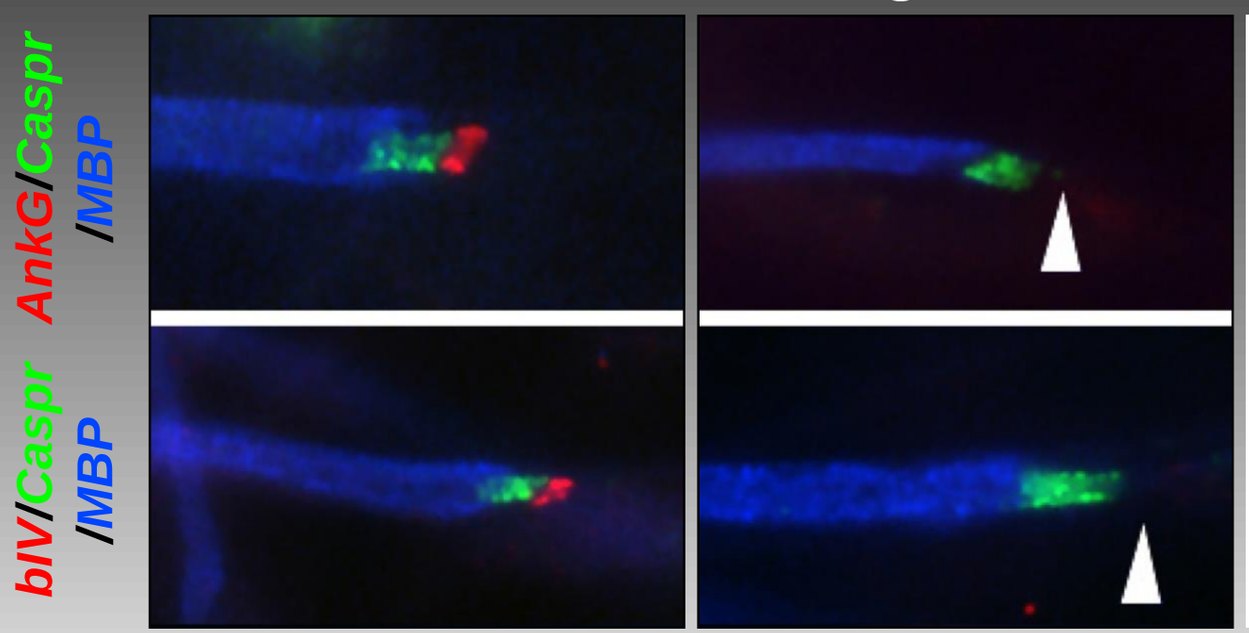


Gliomedin is required for clustering of Na^+ channels at heminodes

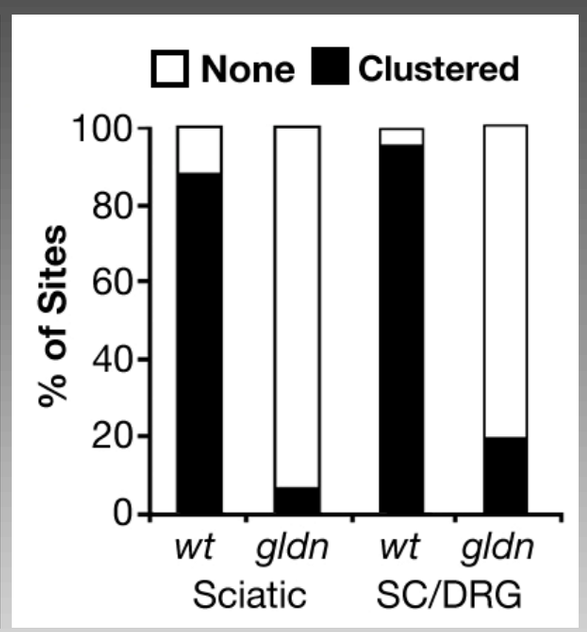


Sciatic nerve





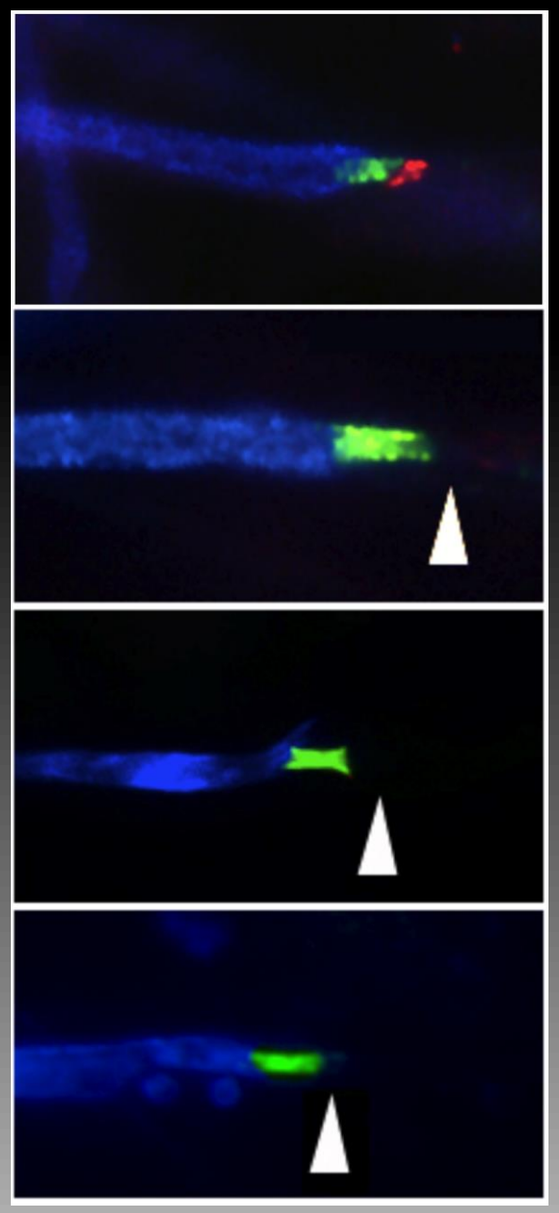
SC/DRG



Feinberg et al., Neuron 2010

Gliomedin, NrCAM and NF186 (nodal adhesion) are required for clustering of Na^+ channels at heminodes

MBP Caspr NaCh



wt

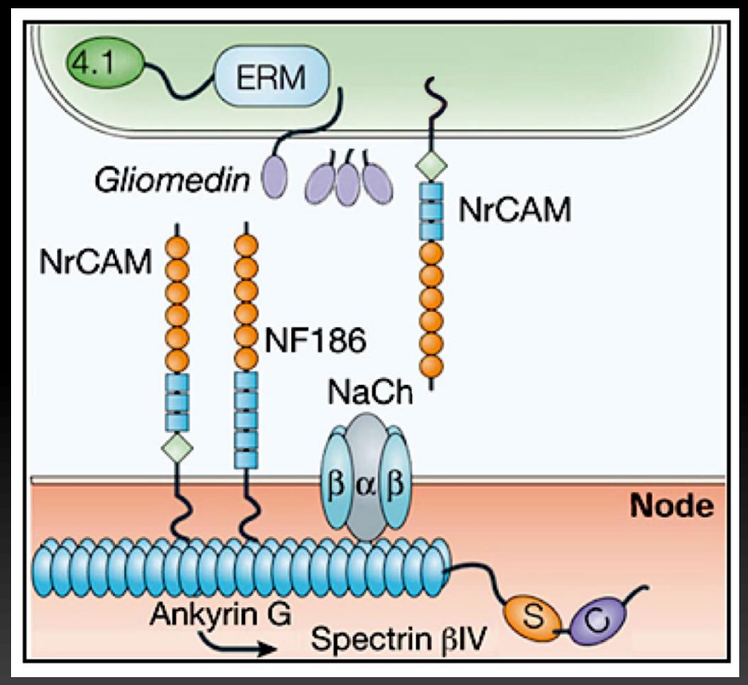
$gldn^{-/-}$

$nrcam^{-/-}$

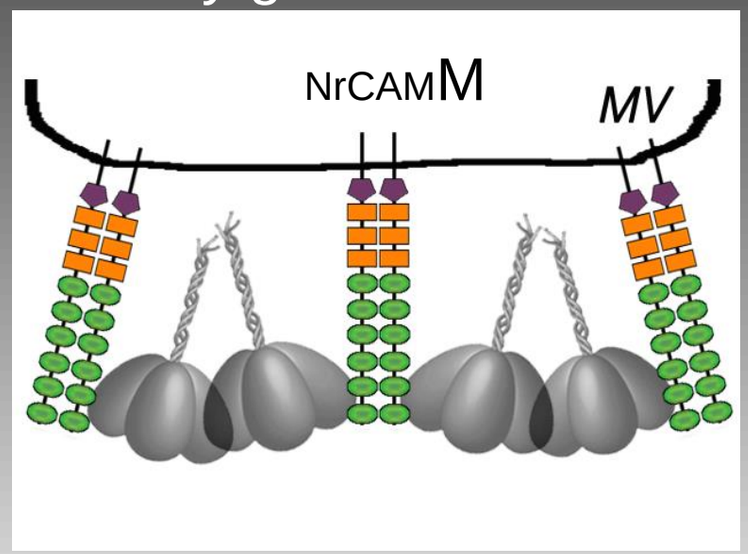
$nf186^{-/-}$

Heminode

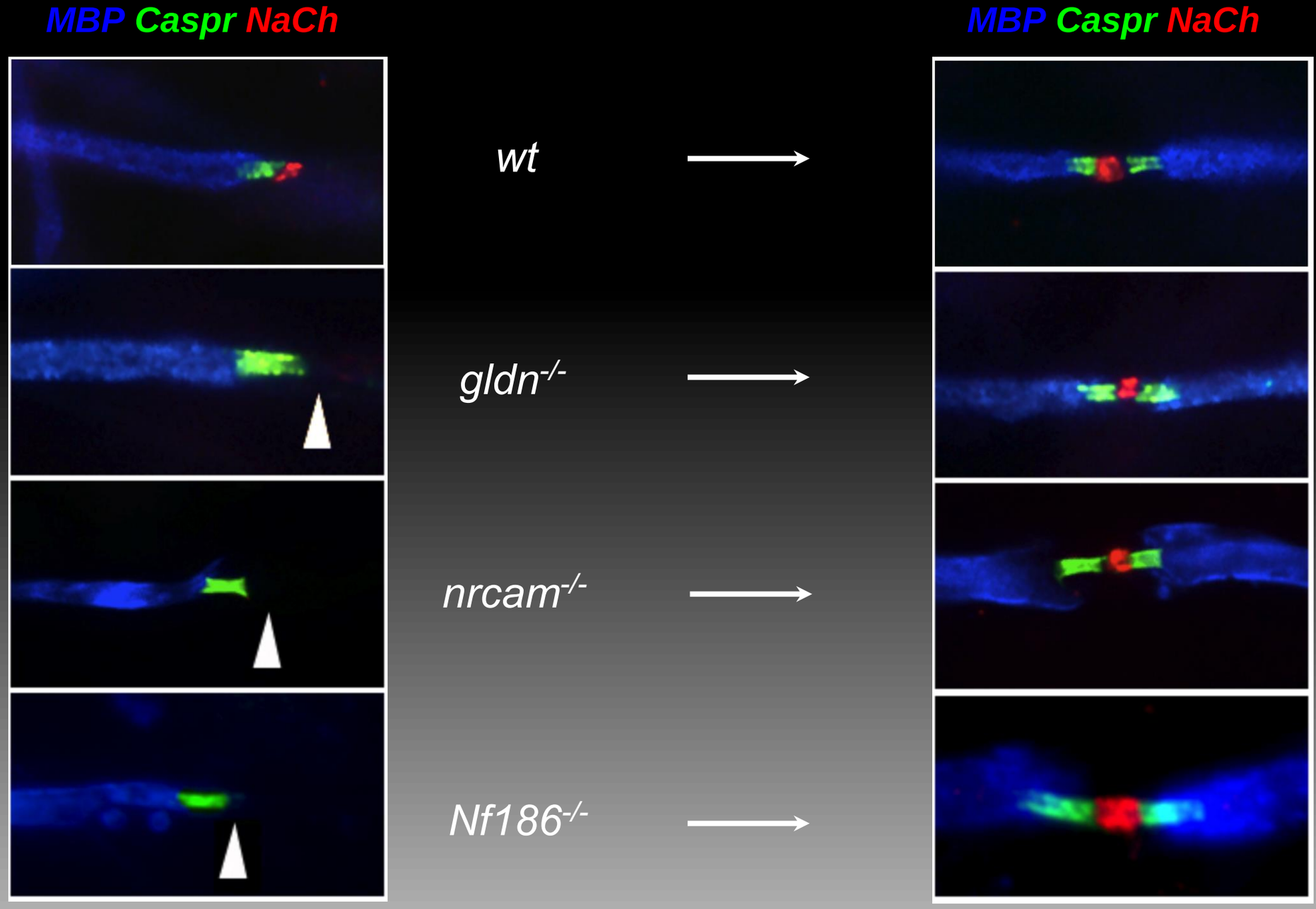
Glial clustering



Immobilization of gliomedin by glial NrCAM



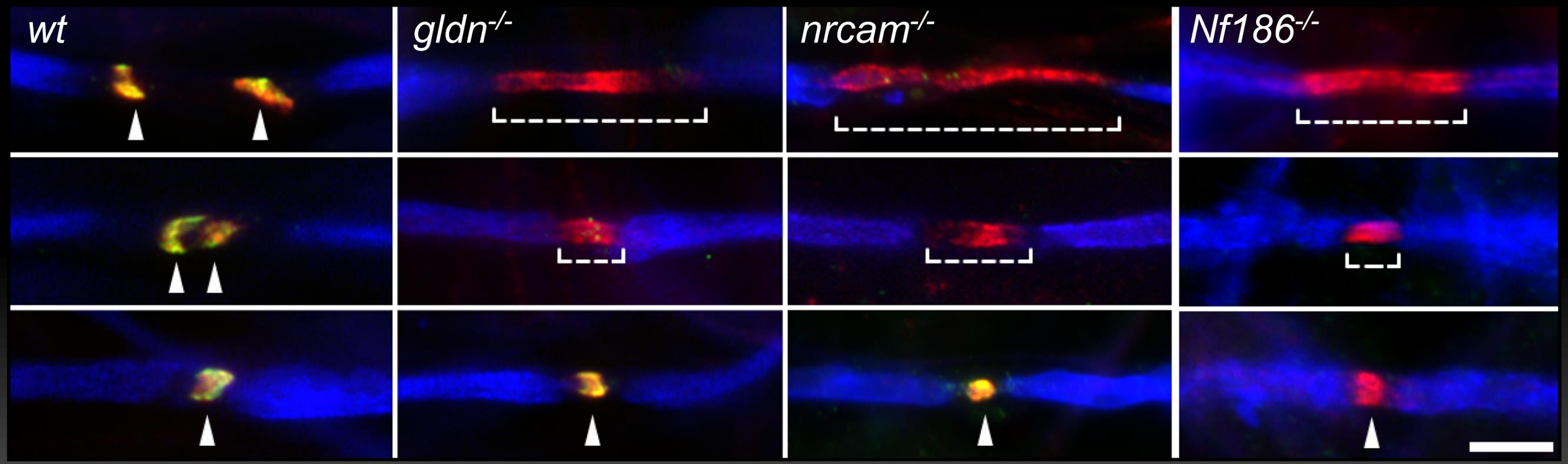
In the absence of nodal adhesion NaCh do not cluster at heminodes but accumulate later at mature nodes

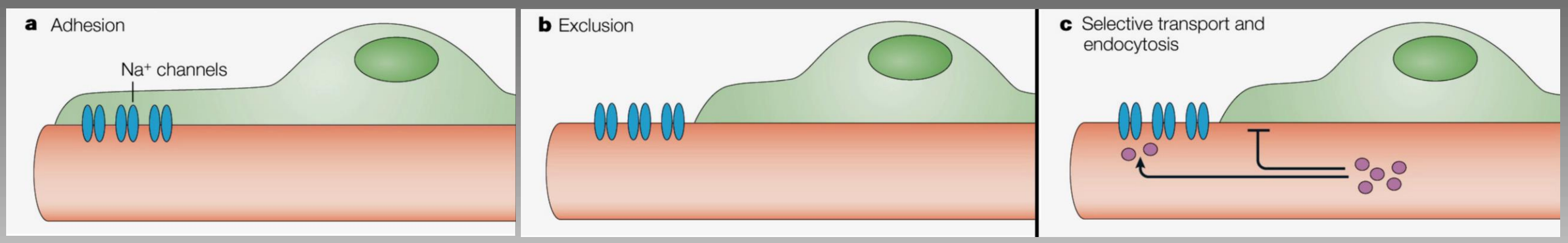


Glial clustering

Additional mechanism?

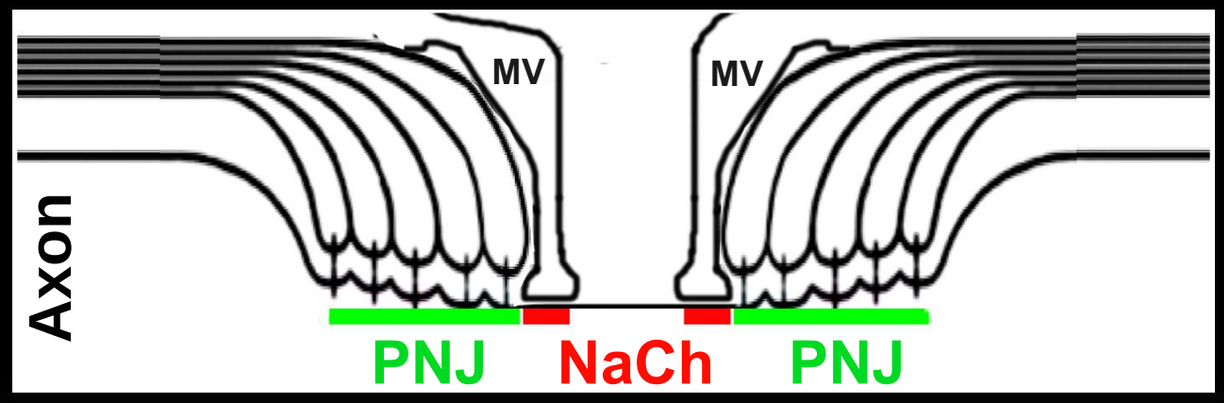
Accumulation of NaCh at mature nodes in the absence of heminodal clustering



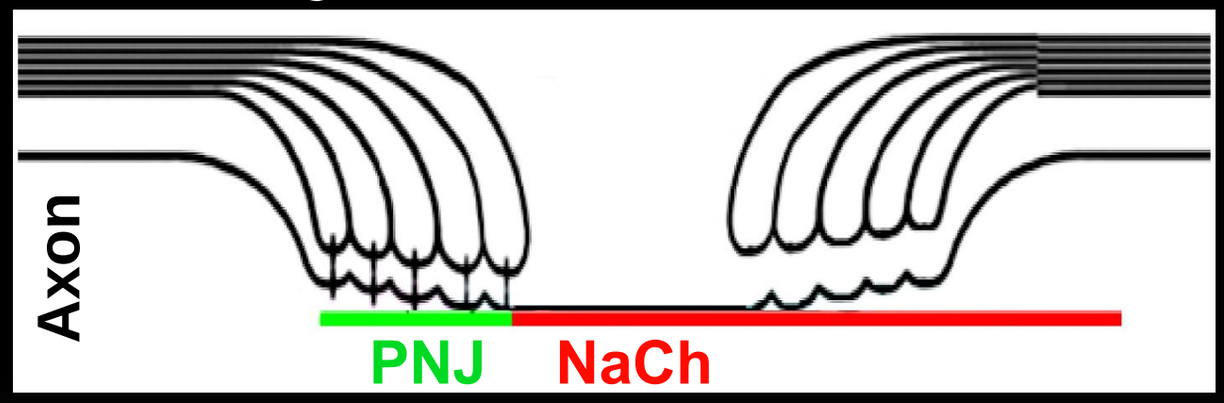


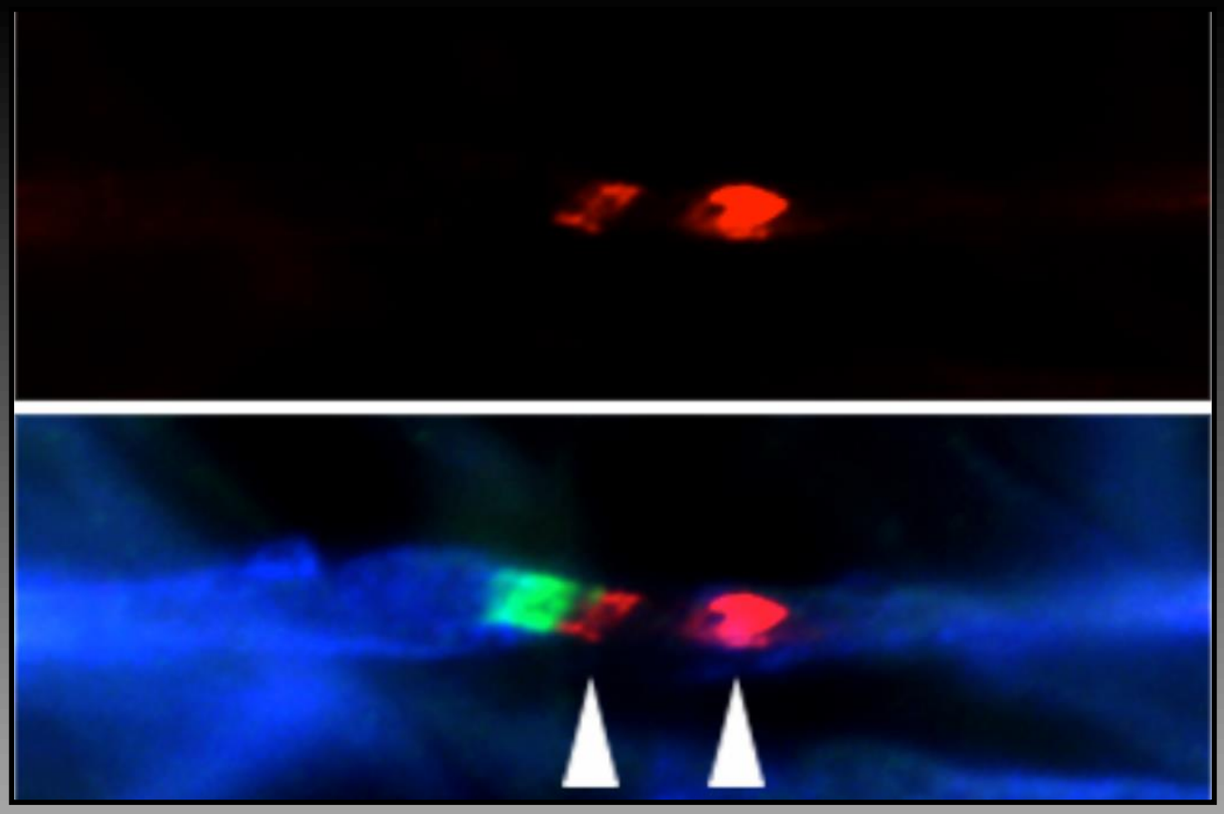
PNJ restrict the area occupied by Na⁺ channels

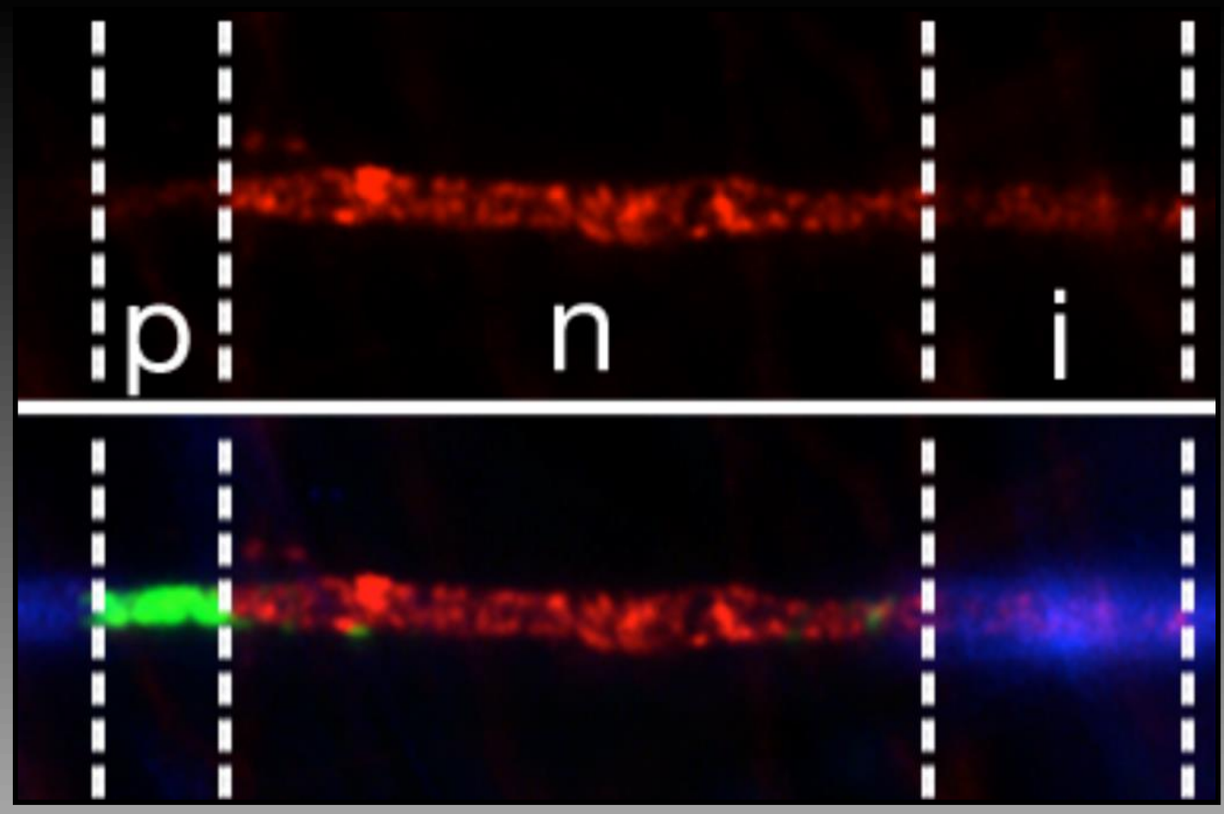
wt



gldn$^{-/-}$ *nrcam$^{-/-}$* *Nf186$^{-/-}$*

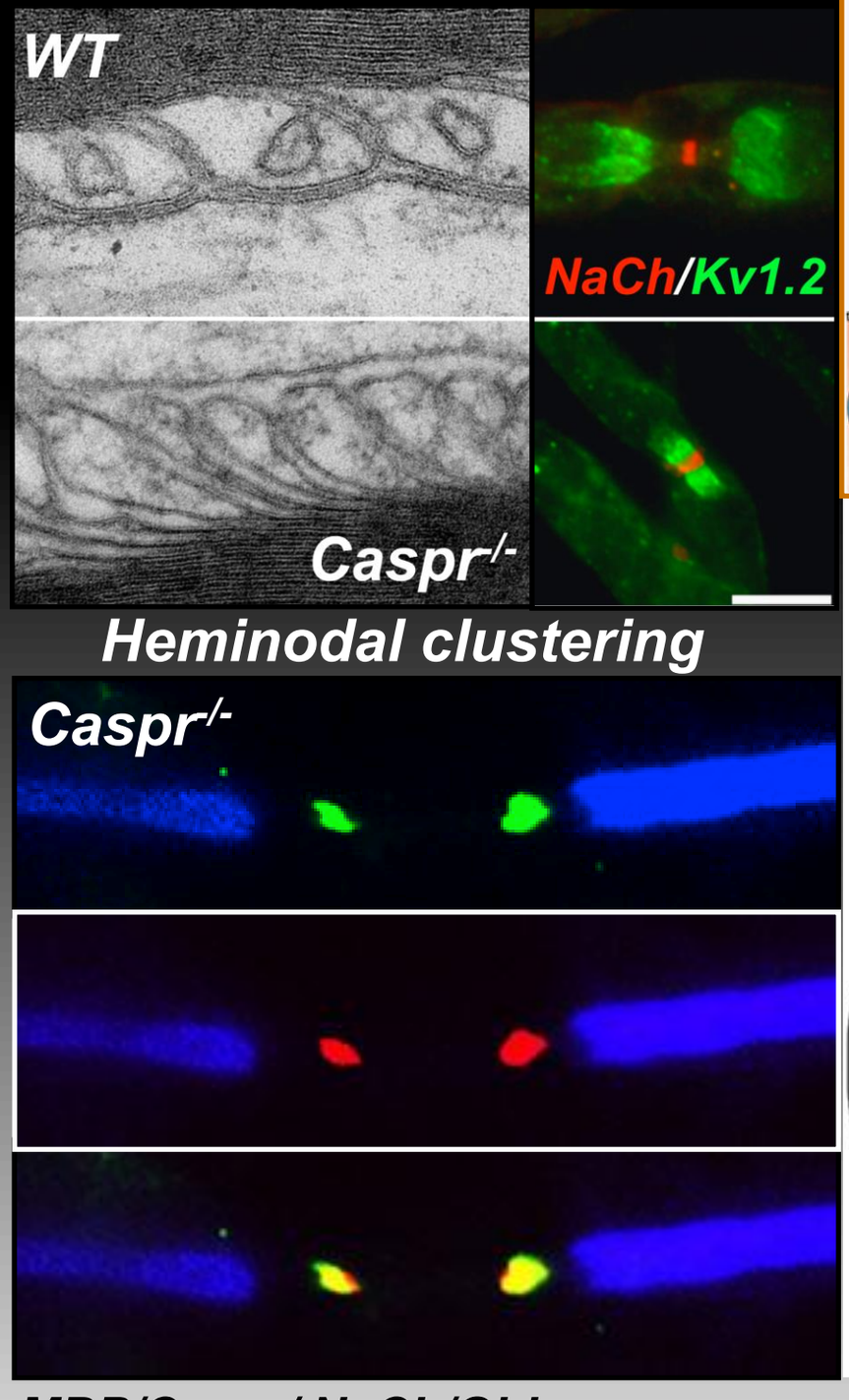


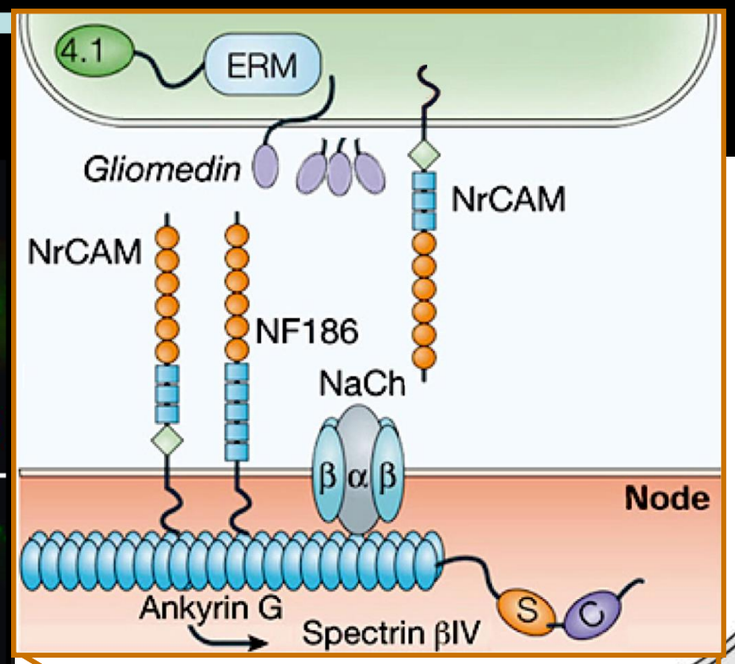


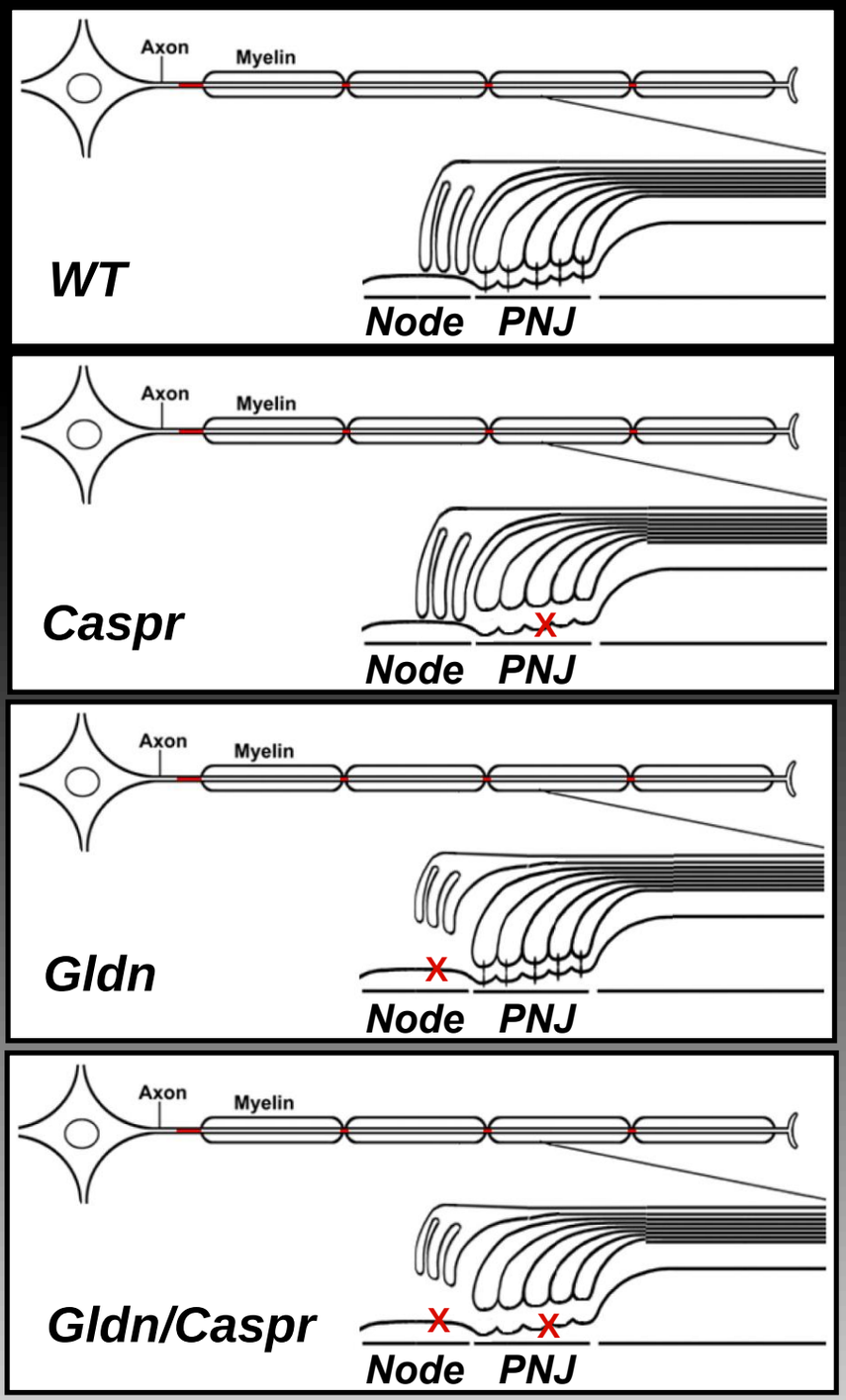


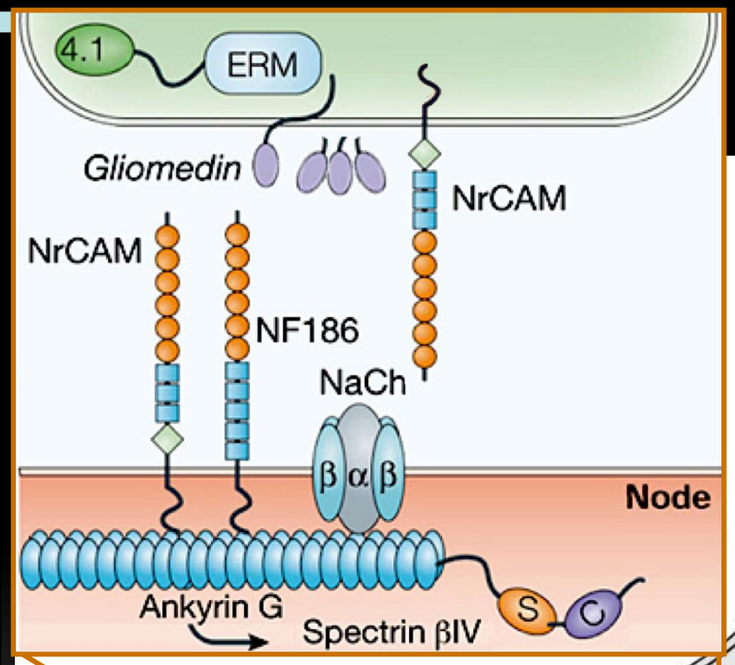
MBP/Caspr/NaCh

Nodes are assembled in the absence of PNJ by heminodal clustering





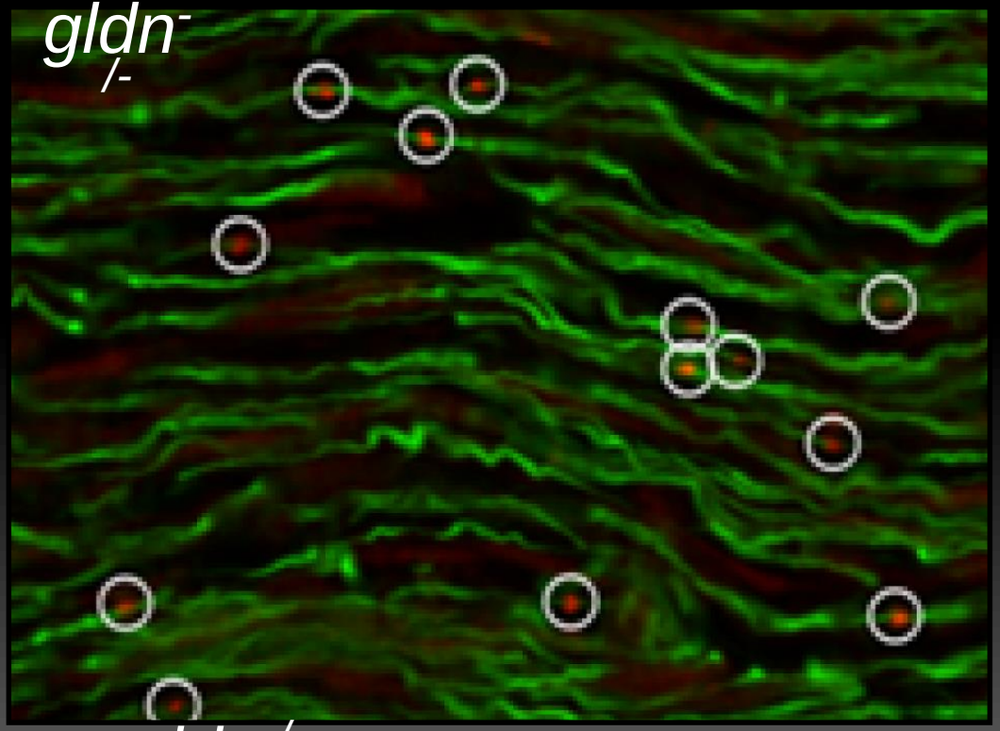

Axon
Myelin
WT
Node PNJ
Axon
Myelin
Caspr
Node PNJ
Axon
Myelin
Gldn
Node PNJ
Axon
Myelin
Gldn/Caspr
Node PNJ

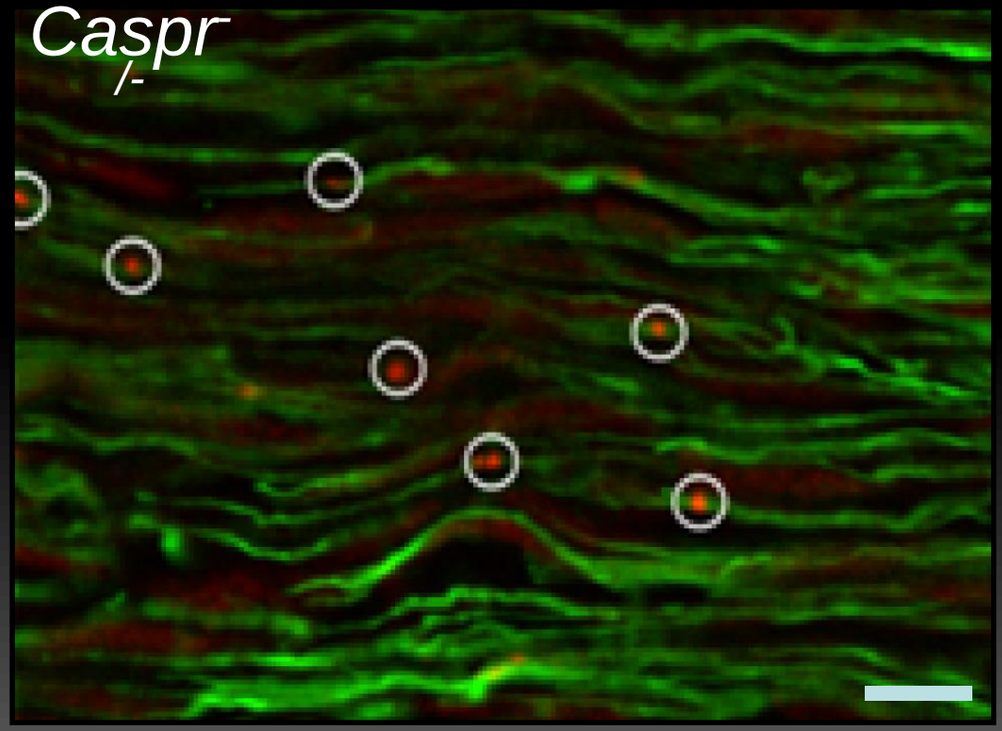

4.1
ERM
Gliomedin
NrCAM
NrCAM
NF186
NaCh
β α β
Node
Ankyrin G
Spectrin βIV
S
C

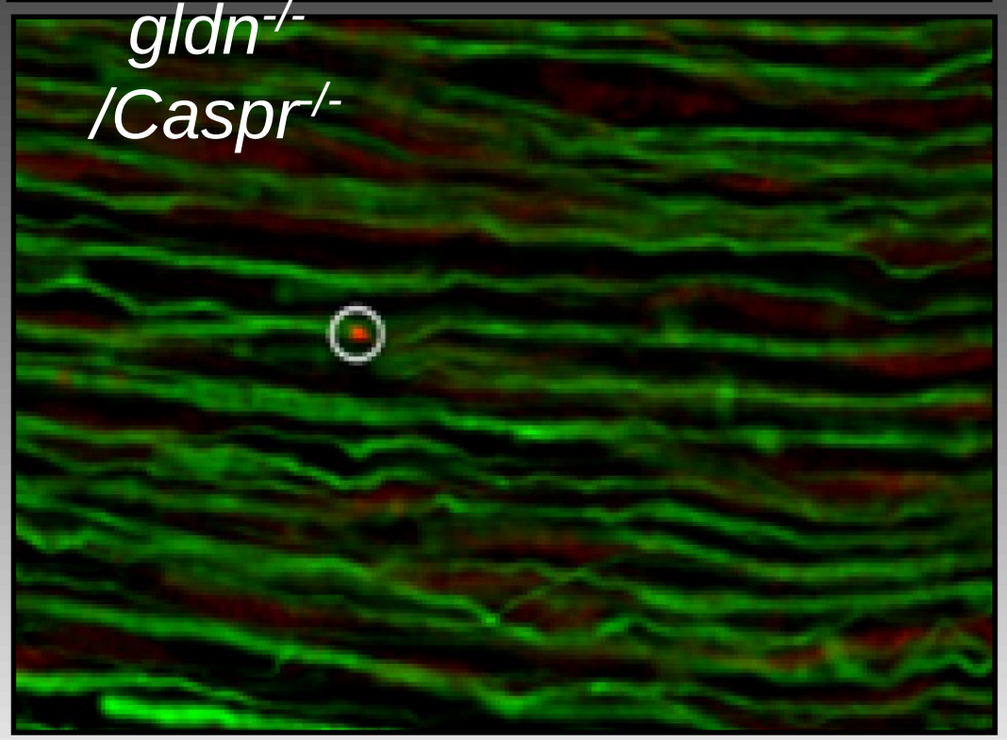
JXP
PNJ
NOR

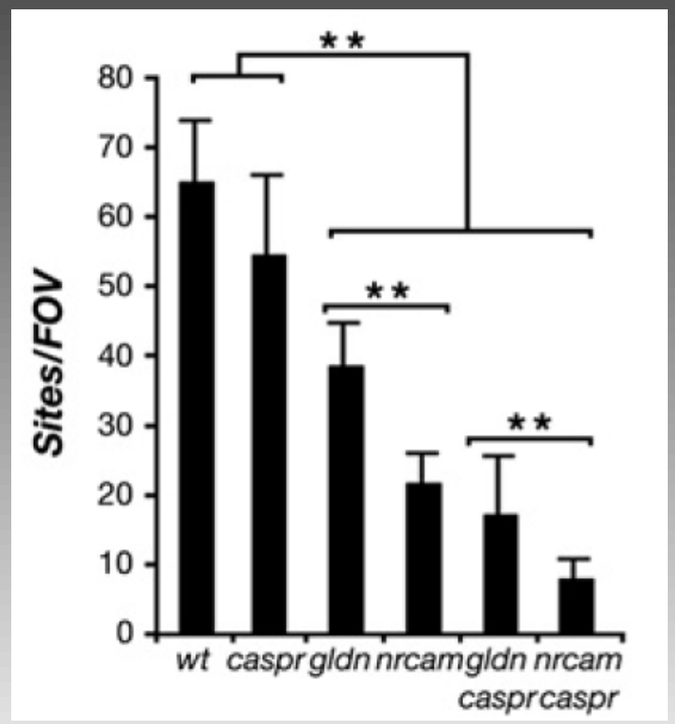
Glia
Caspr
NF155
Contactin
Axon
MBD
4.1B
S
C
α/βII Spectrin
Ankyrin B

Assembly of the nodes of Ranvier requires axoglial contacts at nodes and paranodes



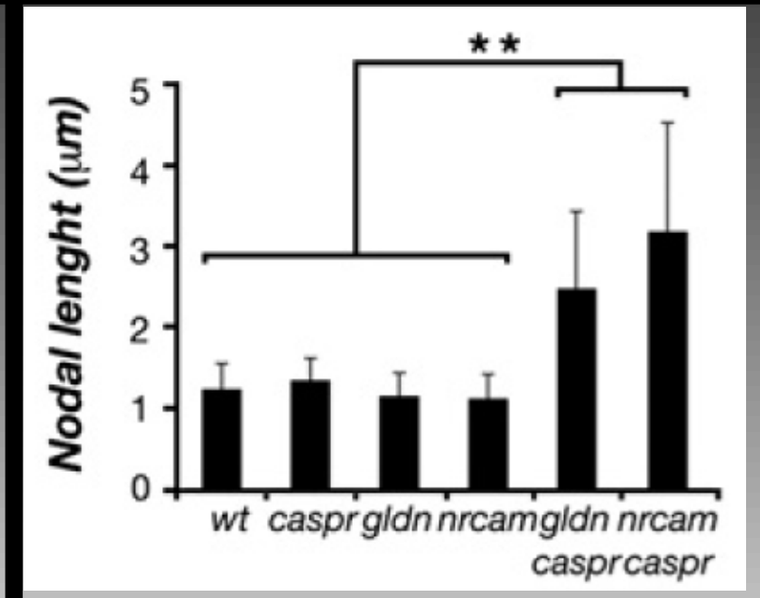




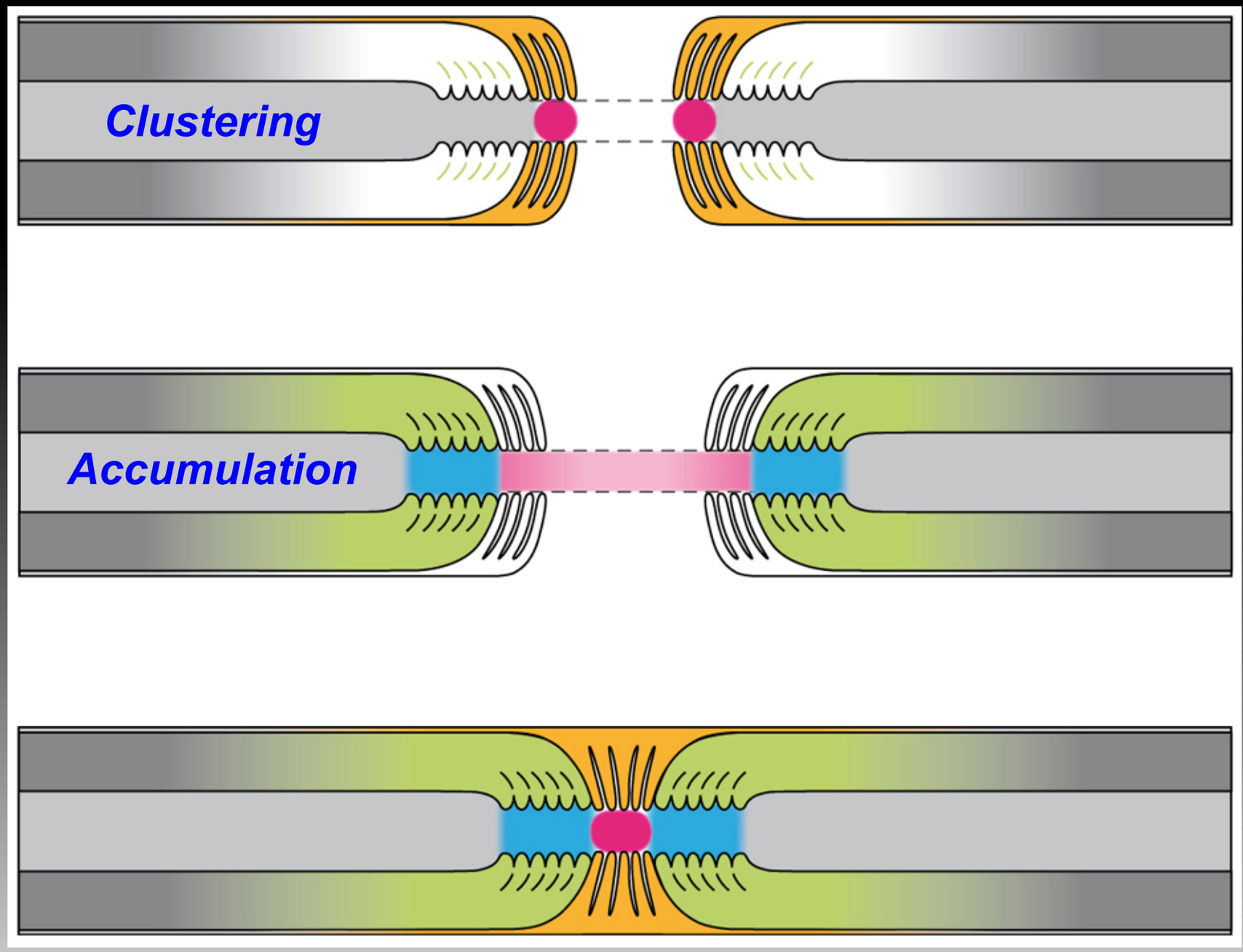


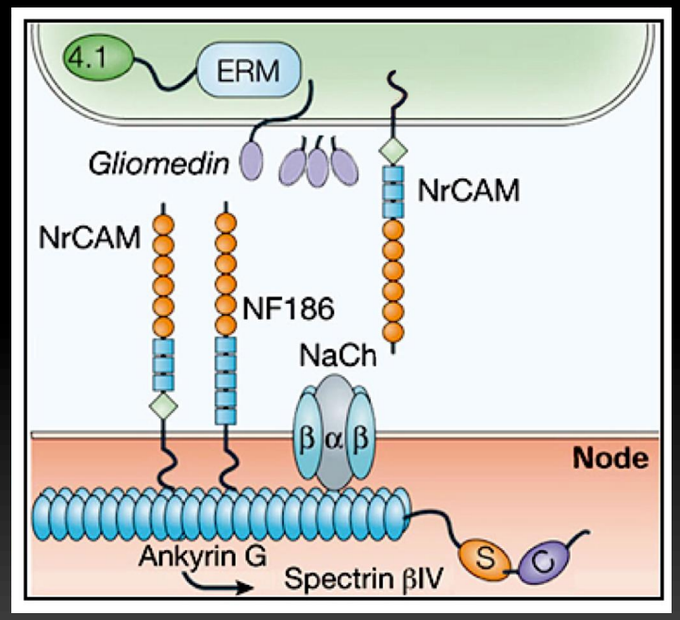
Assembly of the nodes of Ranvier requires axoglial contacts at nodes and paranodes

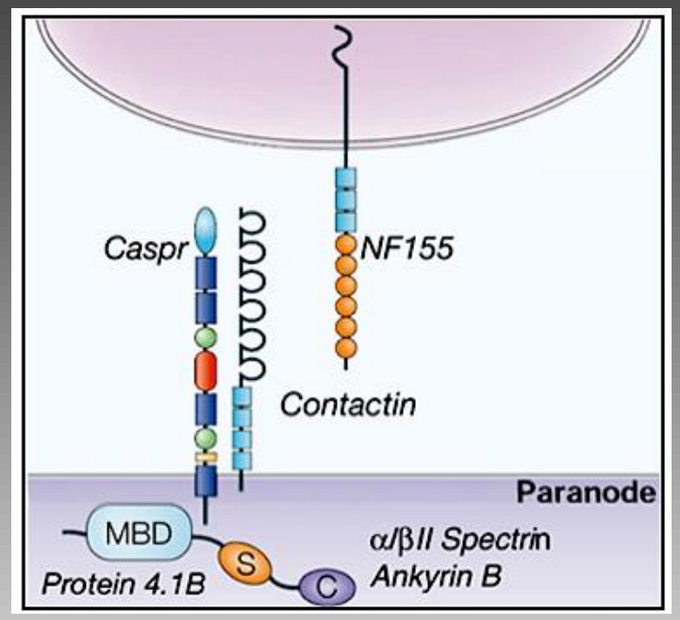
wt *gldn$^{-/-}$/caspr$^{-/-}$* *nrcam$^{-/-}$/caspr$^{-/-}$*



Two distinct axoglial contacts cooperate during the assembly of PNS nodes of Ranvier

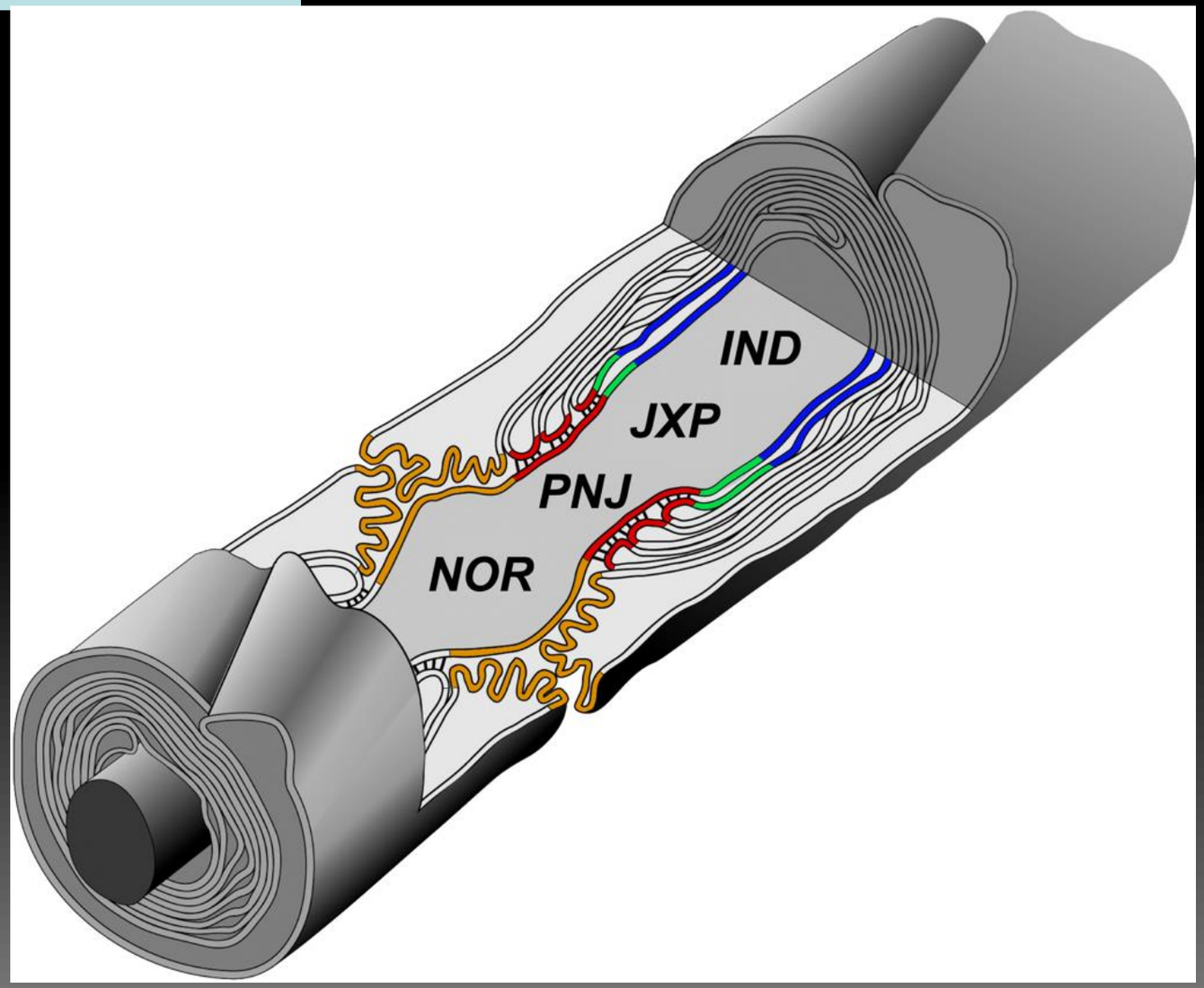


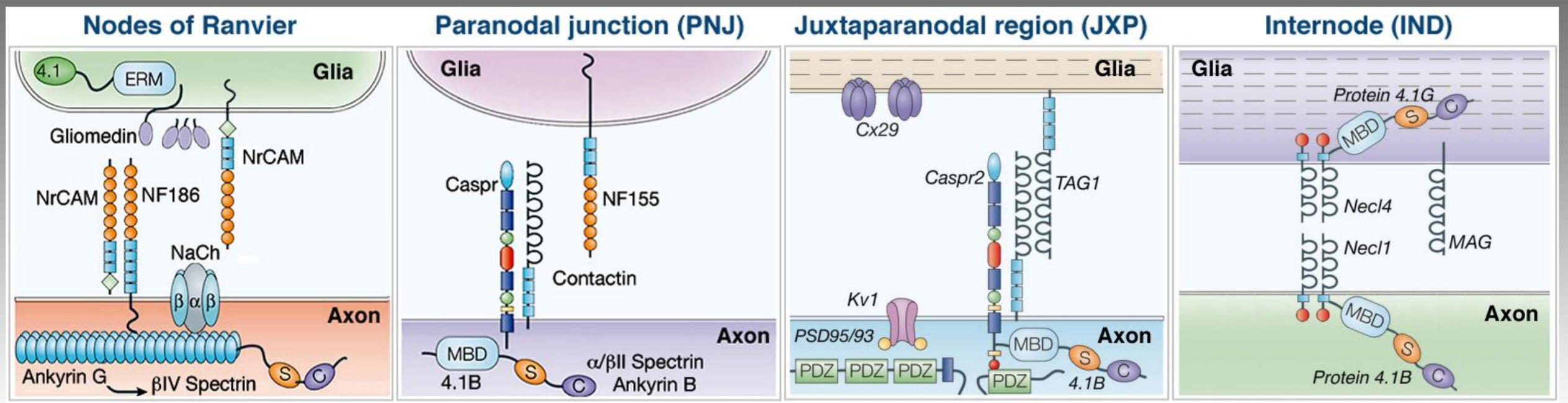




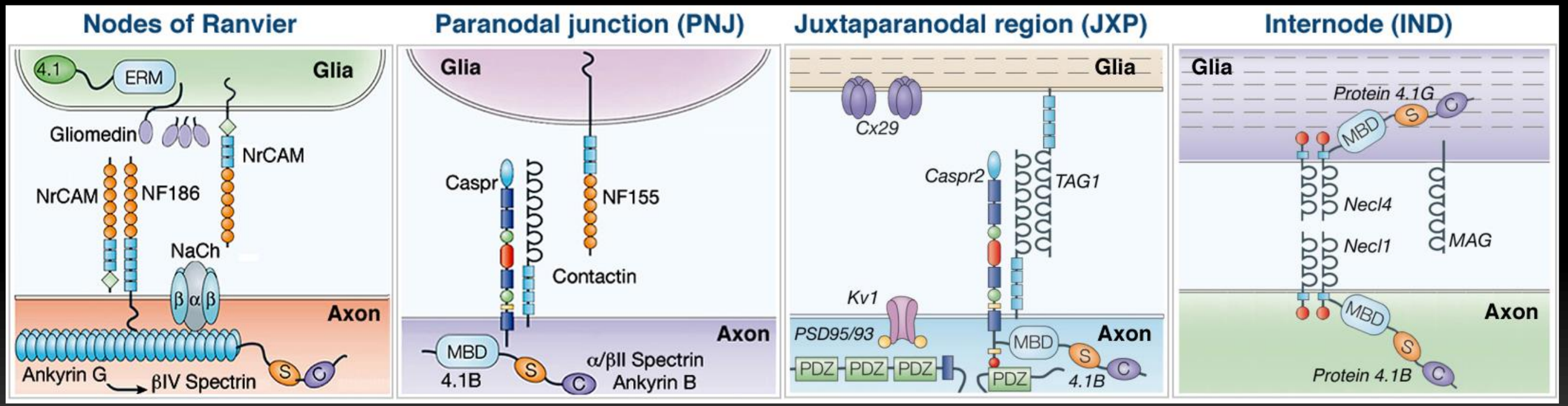
Feinberg et al., Neuron 2010

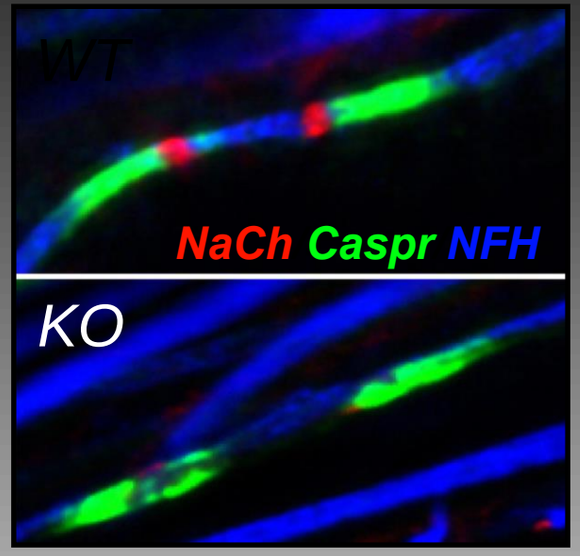
Specialization of the axonal membrane (axolemma)



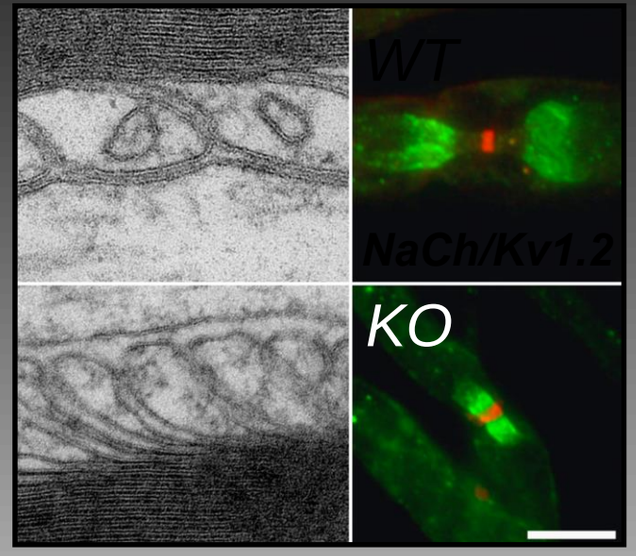


Distinct axoglial adhesion complexes control the functional organization of myelinated axons

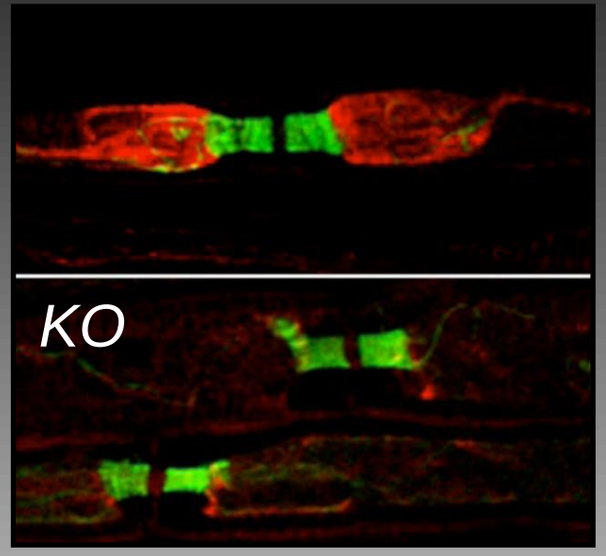




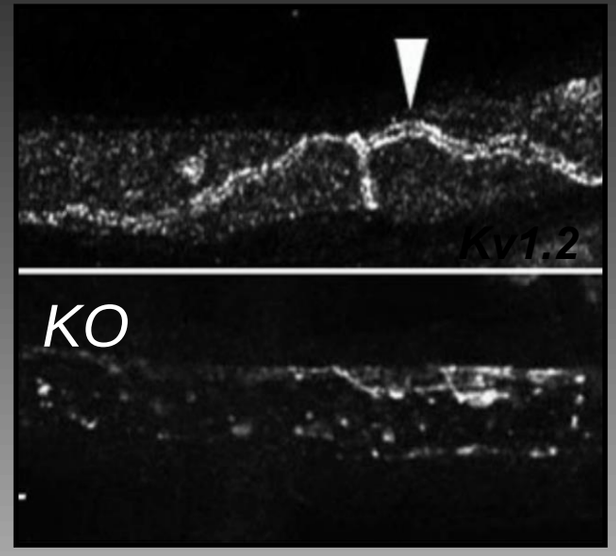
Clustering



Membrane barrier

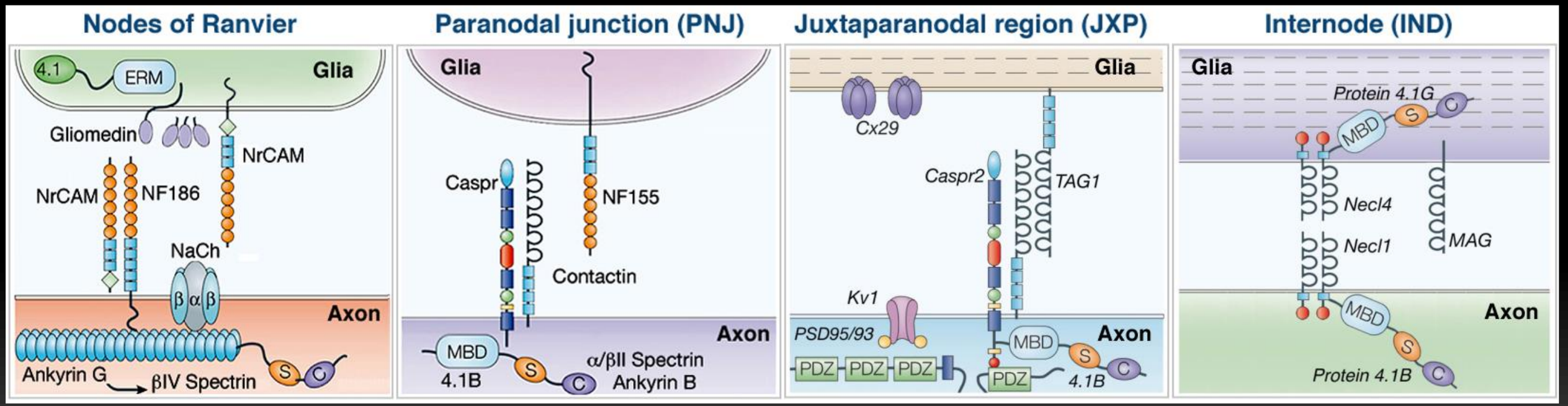


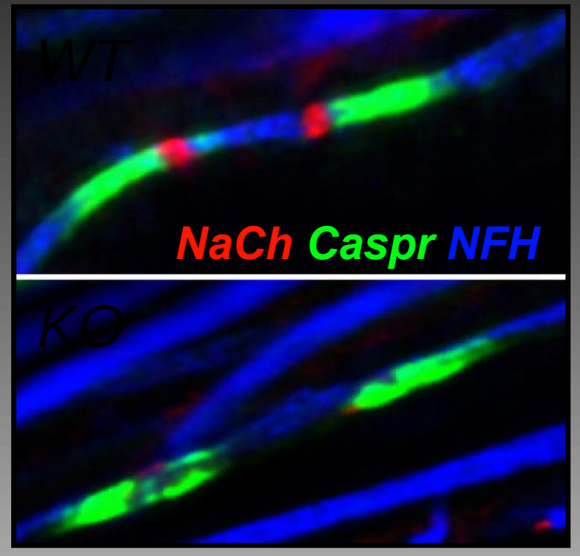
Scaffold



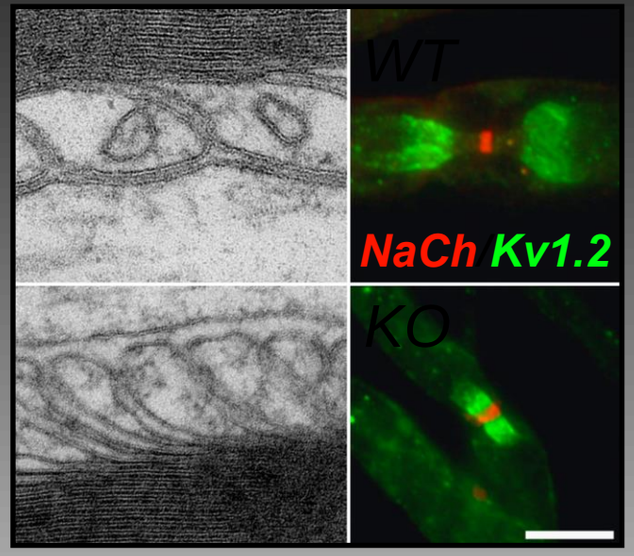
Polarization

Distinct axoglial adhesion complexes control the functional organization of myelinated axons

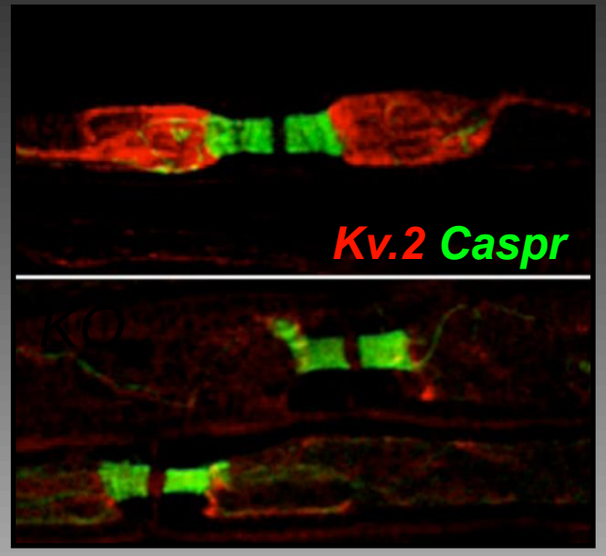




Clustering



Membrane barrier



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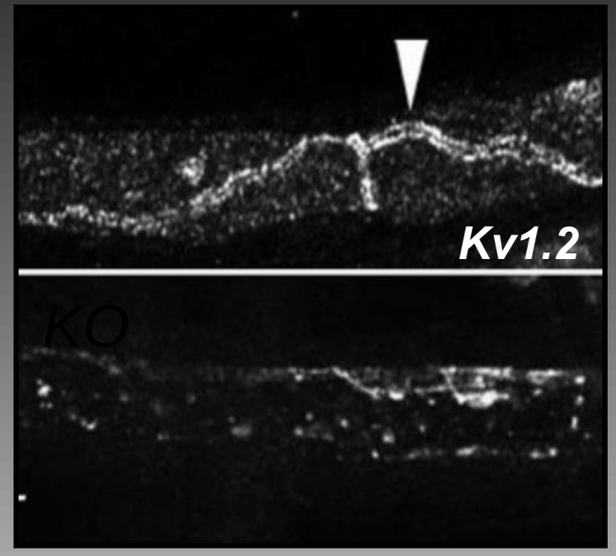
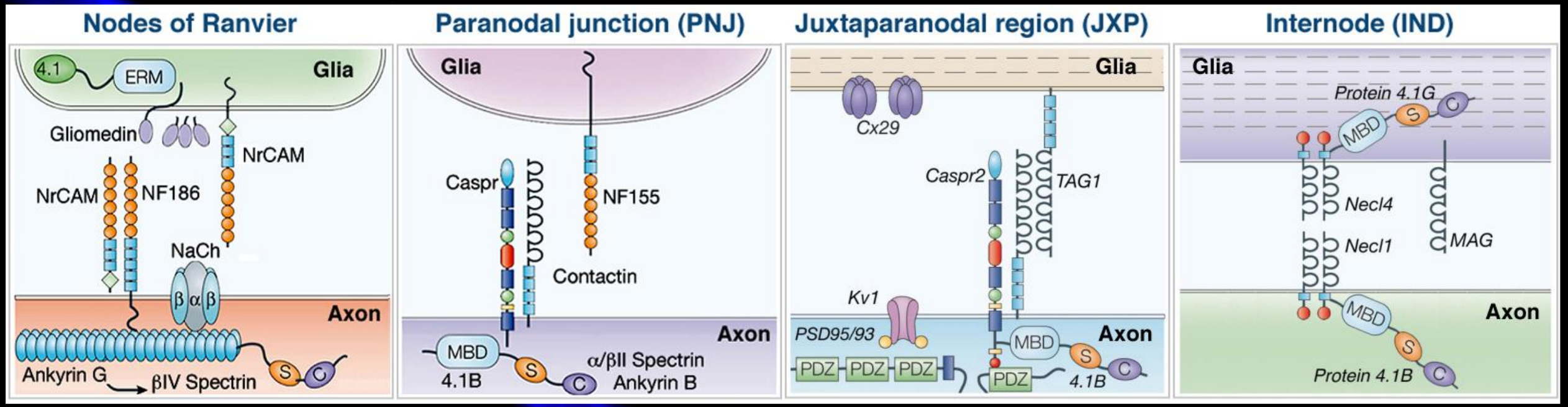


Polarization

Distinct axoglial adhesion complexes control the functional organization of myelinated axons



Nodes of Ranvier

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