The CNS response to axonal injury

A non-permissive environment
for regeneration is produced

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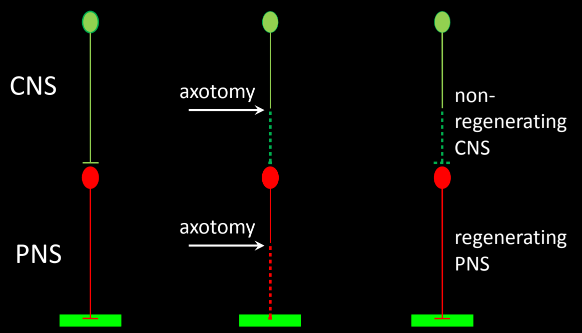
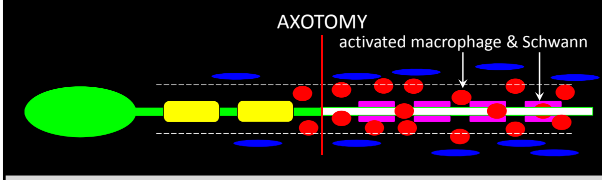
PNS is regenerating - CNS is not



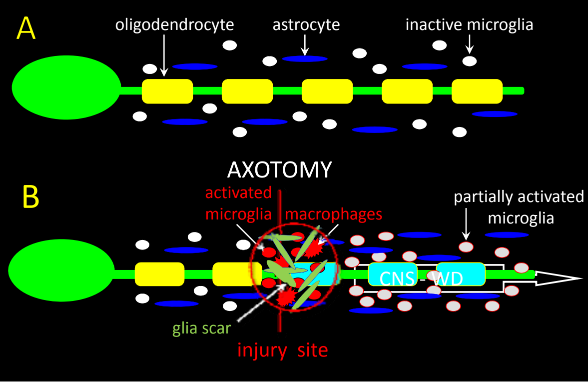
Normal PNS Wallerian degeneration



The PNS tissue is permissive for regeneration due to

- Removal of inhibitory myelin by macrophages and Schwann
- Production of nerve growth factors (e.g. NGF produced by Schwann and fibroblasts)
- Presence of extra-cellular matrix adhesive molecules (e.g. laminin, fibronectin and collagen produced by Schwann and fibroblasts)

CNS: (A) intact and (B) Wallerian degeneration



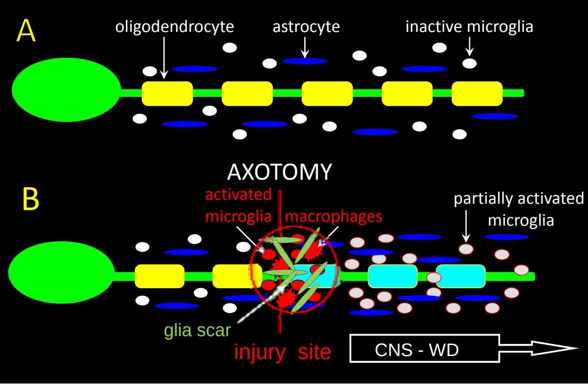
Glia scars form at the lesion site

A mature scar develops at the lesion in two to four weeks

- macrophage/microglia invasion – myelin clearance
- meningeal cells
- oligodendrocyte precursor cells
- reactive astrocytes produce inhibitory molecules (Semaphorins, CSPG)

There is a time window of opportunity

CNS: (A) intact and (B) Wallerian degeneration



How can regeneration be promoted?

- change the environment from non-permissive to permissive
  - remove inhibitory factors/molecules
  - provide growth promoting factors/molecules
  - transplant Schwann cells or olfactory ensheathing glia cells (OEG)
- change the response of growth-cones to inhibitory factors/molecules from collapse to growth
  - elevate cAMP levels
  - inhibit RhoA/ROCK signaling

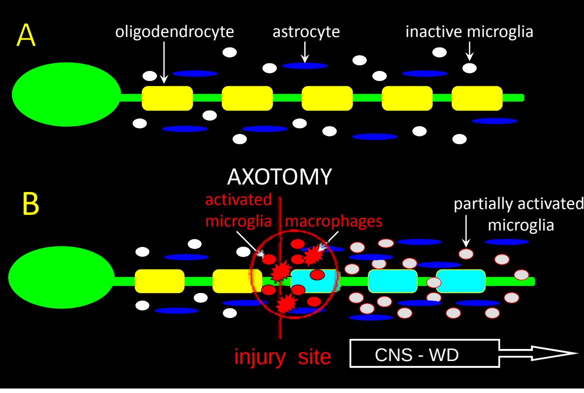
Changing the environment: the astrocytic scar

- neutralize chondroitin sulfate proteoglycans
  - enzymatic digestion by Chondroitinase ABC
- neutralize semaphorins
  - neutralize semaphorin by function blocking antibodies
  - neutralize semaphorin receptors on growth-cones by function blocking antibodies

Changing the environment: myelin

- remove myelin by phagocytosis
  - activate resident microglia
  - transplant activated macrophages

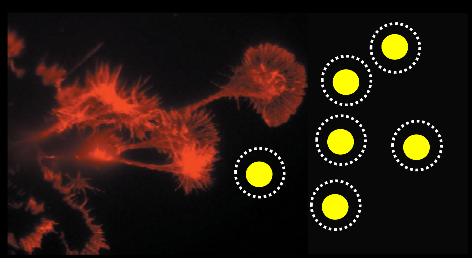
CNS: (A) intact and (B) Wallerian degeneration



Changing the environment: myelin

- remove myelin by phagocytosis
  - activate resident microglia
  - transplant activated macrophages
- neutralize inhibitory molecules on myelin
  - introduce anti-myelin antibodies
  - introduce Fc-NGR (decoy soluble receptor)

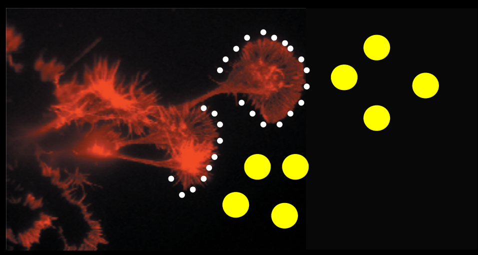
Neutralize myelin by anti-myelin Abs or Fc-NGR



Changing the environment: myelin

- remove myelin by phagocytosis
  - activate resident microglia
  - transplant activated macrophages
- neutralize inhibitory molecules on myelin
  - introduce anti-myelin antibodies
  - introduce Fc-NGR (decoy soluble receptor)
- neutralize myelin receptors on growth cones
  - introduce anti-NGR antibodies
  - introduce $NEP_{1\text{-}40}$

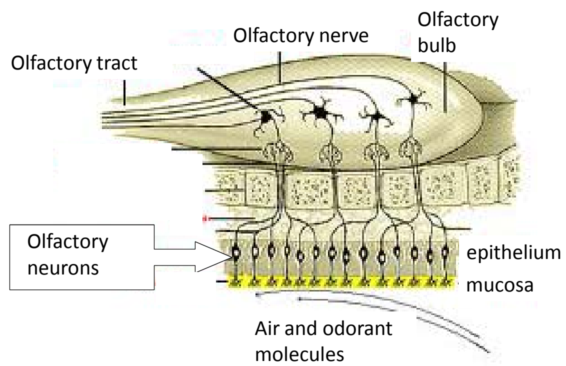
Neutralize NGR by anti-NGR Abs or $NEP_{1\text{-}40}$ peptide



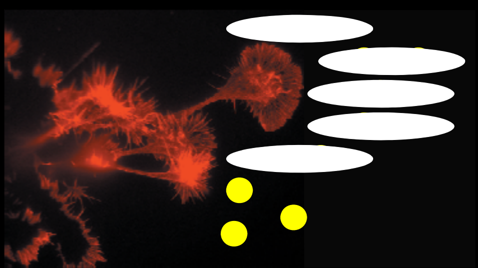
Change the environment

- transplant Schwann cells
- transplant olfactory ensheathing glia cells (OEG)

Olfactory pathway

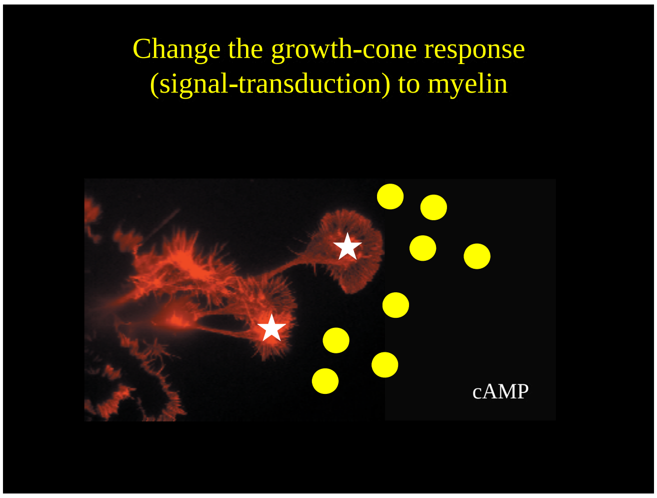


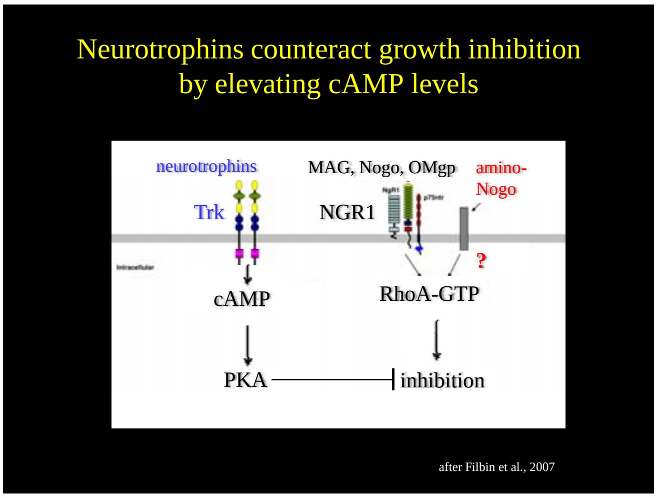
Transplant cells which promote regeneration (Schwann & olfactory ensheathing glia)

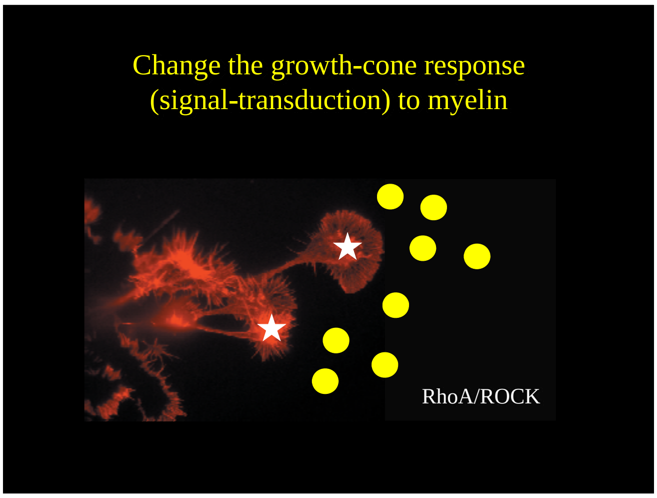


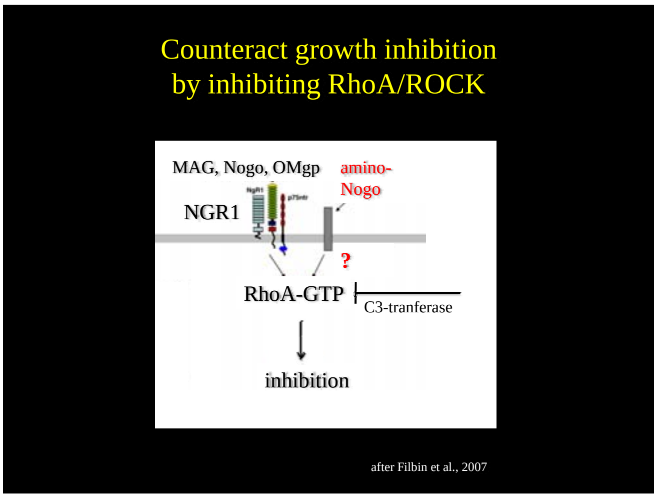
Change the response of growth-cones to inhibitory factors/molecules from collapse to growth

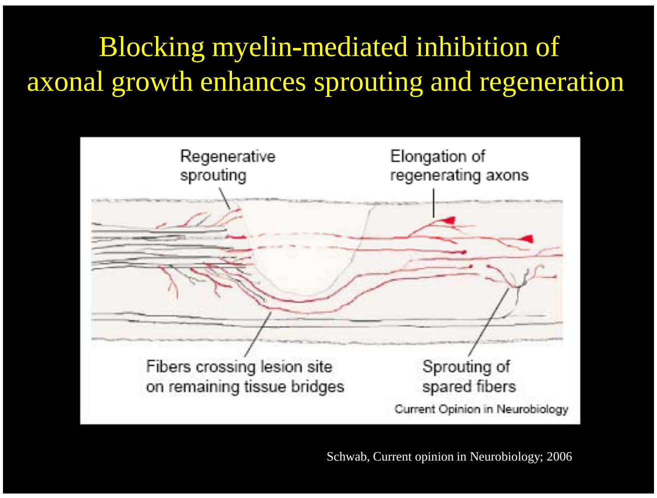
- elevate cAMP levels pharmacologically or by neurotrophins
- inhibit RhoA/ROCK signaling


Change the growth-cone response
(signal-transduction) to myelin
cAMP


Neurotrophins counteract growth inhibition
by elevating cAMP levels
neurotrophins
Trk
MAG, Nogo, OMgp
NGR1
amino-
Nogo
?
cAMP
RhoA-GTP
PKA
inhibition
after Filbin et al., 2007


Change the growth-cone response
(signal-transduction) to myelin
RhoA/ROCK


Counteract growth inhibition
by inhibiting RhoA/ROCK
MAG, Nogo, OMgp
NGR1
amino-
Nogo
?
RhoA-GTP
C3-tranferase
inhibition
after Filbin et al., 2007


Blocking myelin-mediated inhibition of
axonal growth enhances sprouting and regeneration
Regenerative
sprouting
Elongation of
regenerating axons
Fibers crossing lesion site
on remaining tissue bridges
Sprouting of
spared fibers
Current Opinion in Neurobiology
Schwab, Current opinion in Neurobiology; 2006