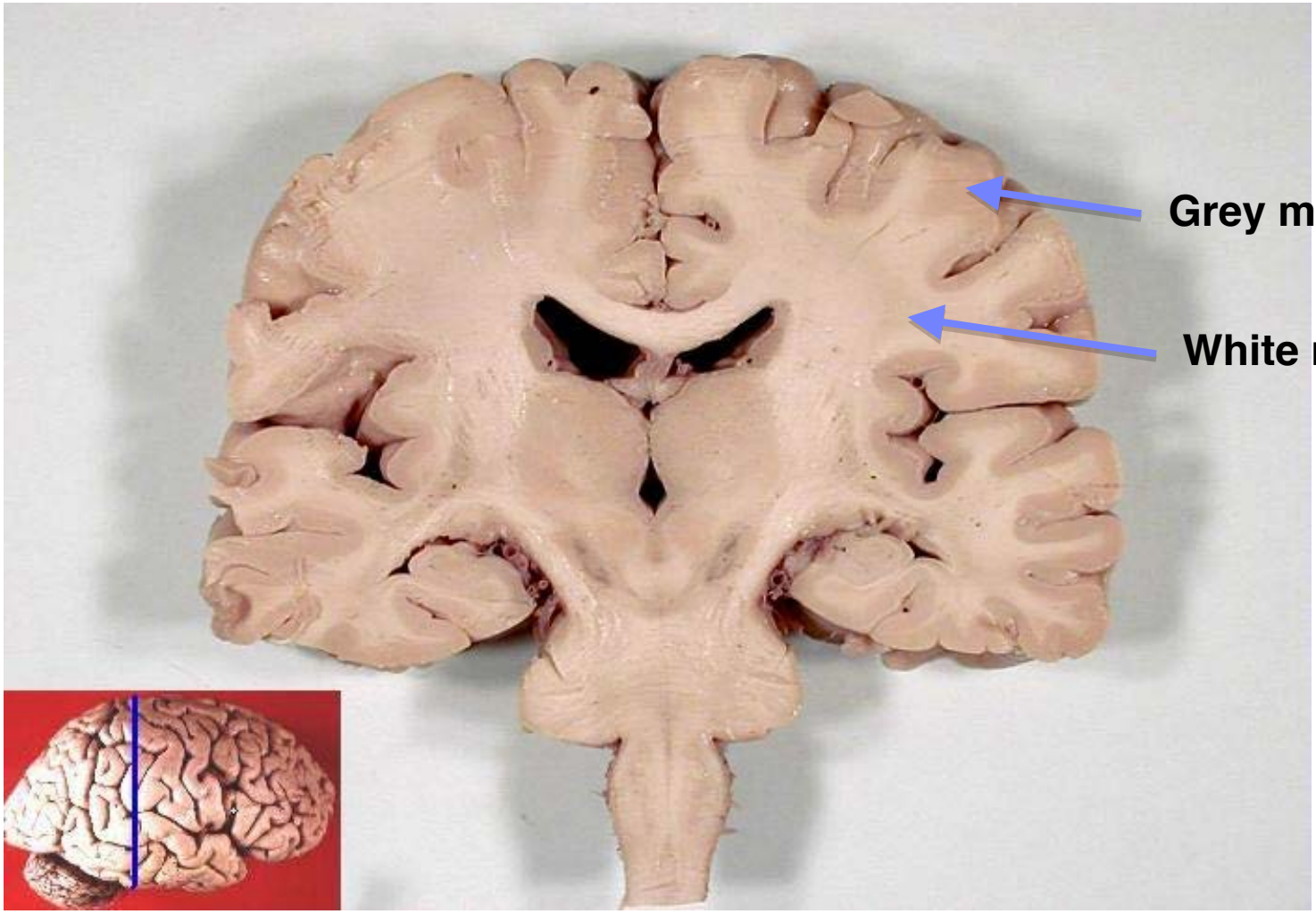
Neurons

(and glial cells)

Pietro De Camilli

October 11, 2012

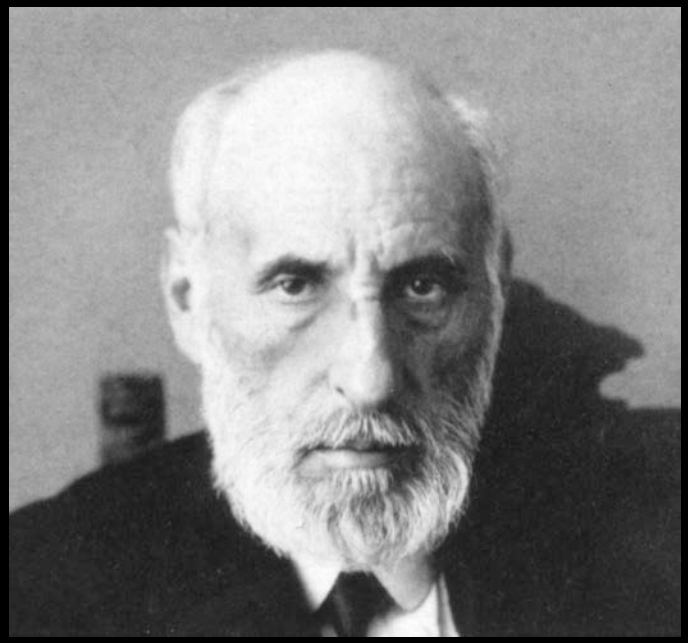
Human Brain



Camillo Golgi

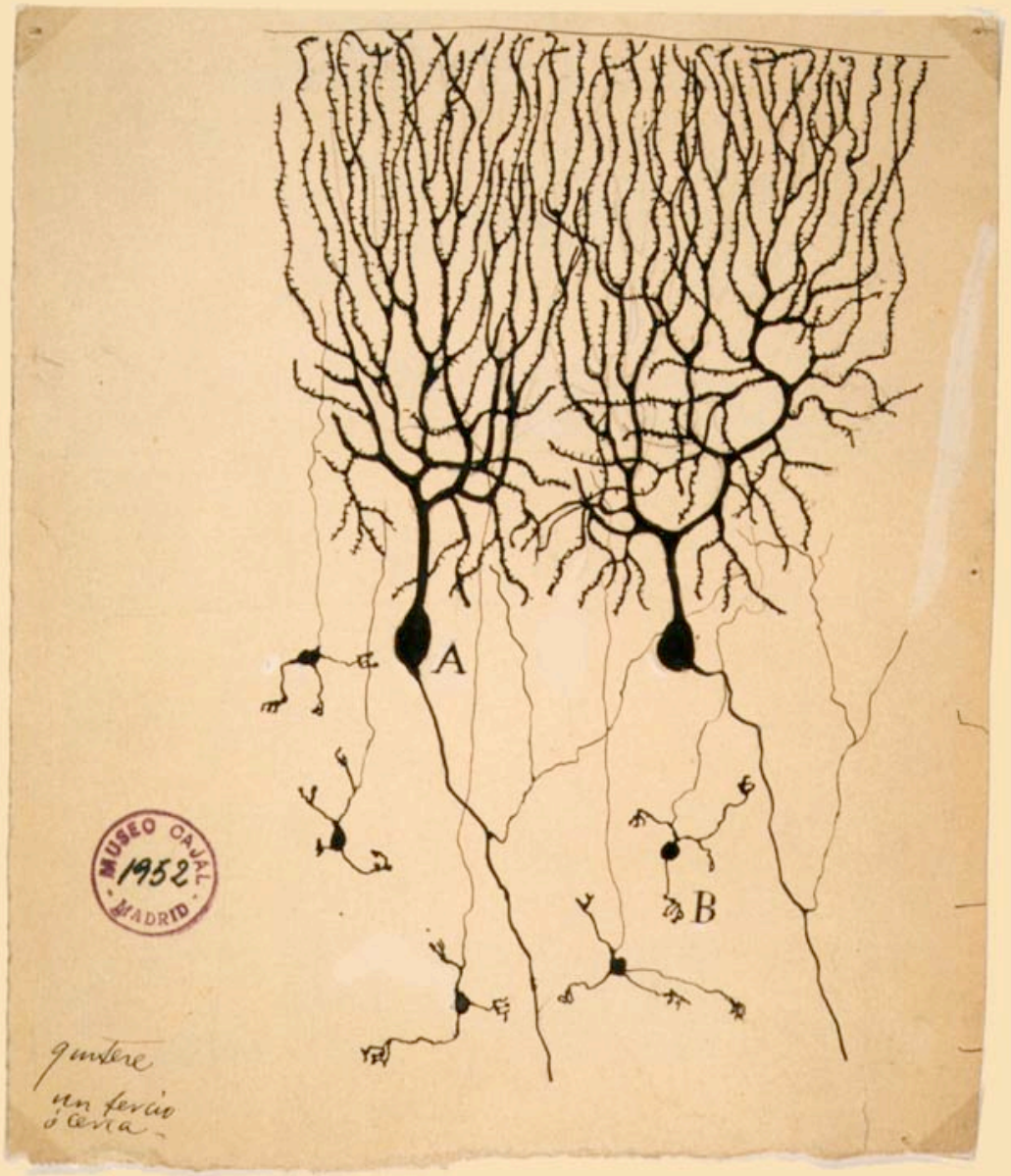
Golgi Stain

He mistakenly left brain sample in silver stain overnight. Next day he looked at slices of brain under a microscope and saw these cells which are neurons.



Cajal

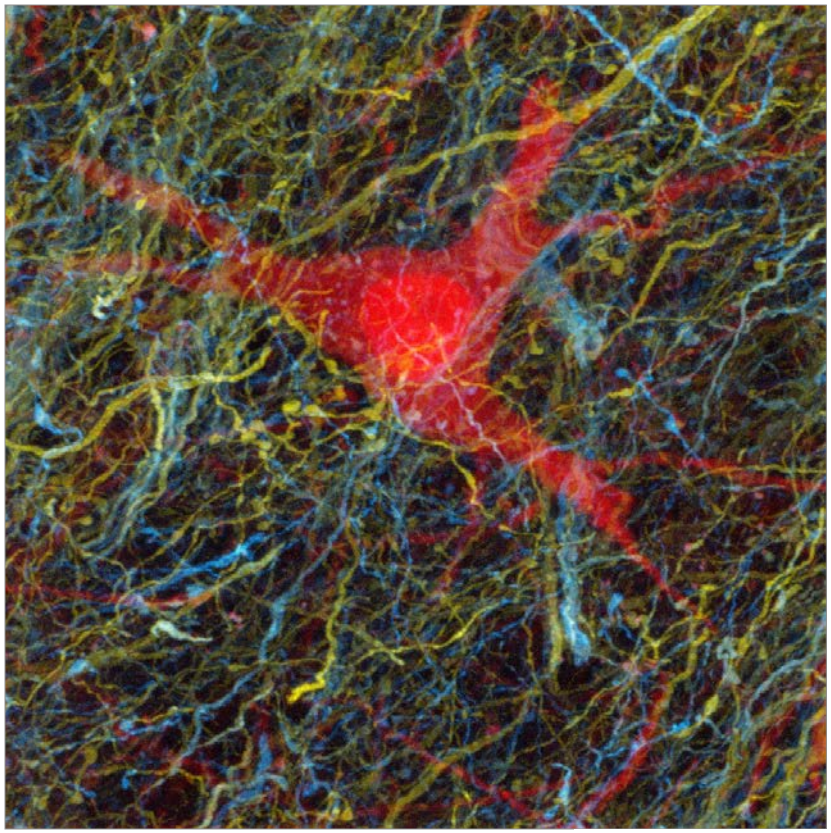
Cajal used Golgi stain to describe the structure of neurons and define axons and dendrites.



"Pigeon cerebellum. A, Purkinje cell, B, granule cell Modified from a photograph taken from the original (14X15.5 cm). Drawn on sheet/paper. P.Y. 1899. S.R. y Cajal Institute - CSIC - Madrid, Spain.

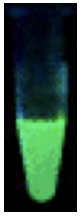
Genetically encoded dyes

Genetic dyes (GFP and variants) can be used to label individual neurons.

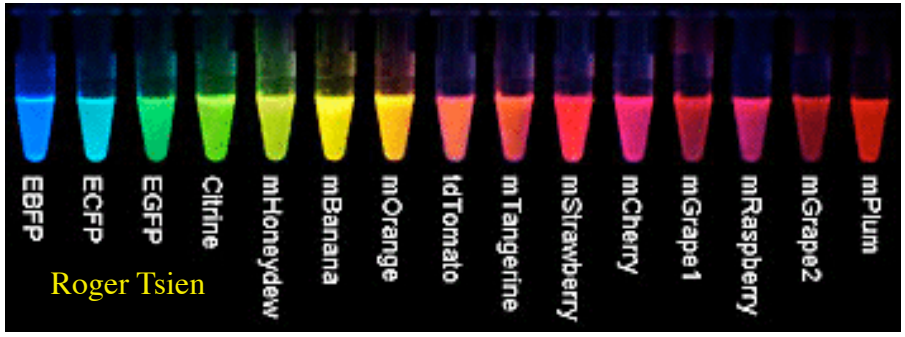


Jeff Lichtman

Martin Chalfie



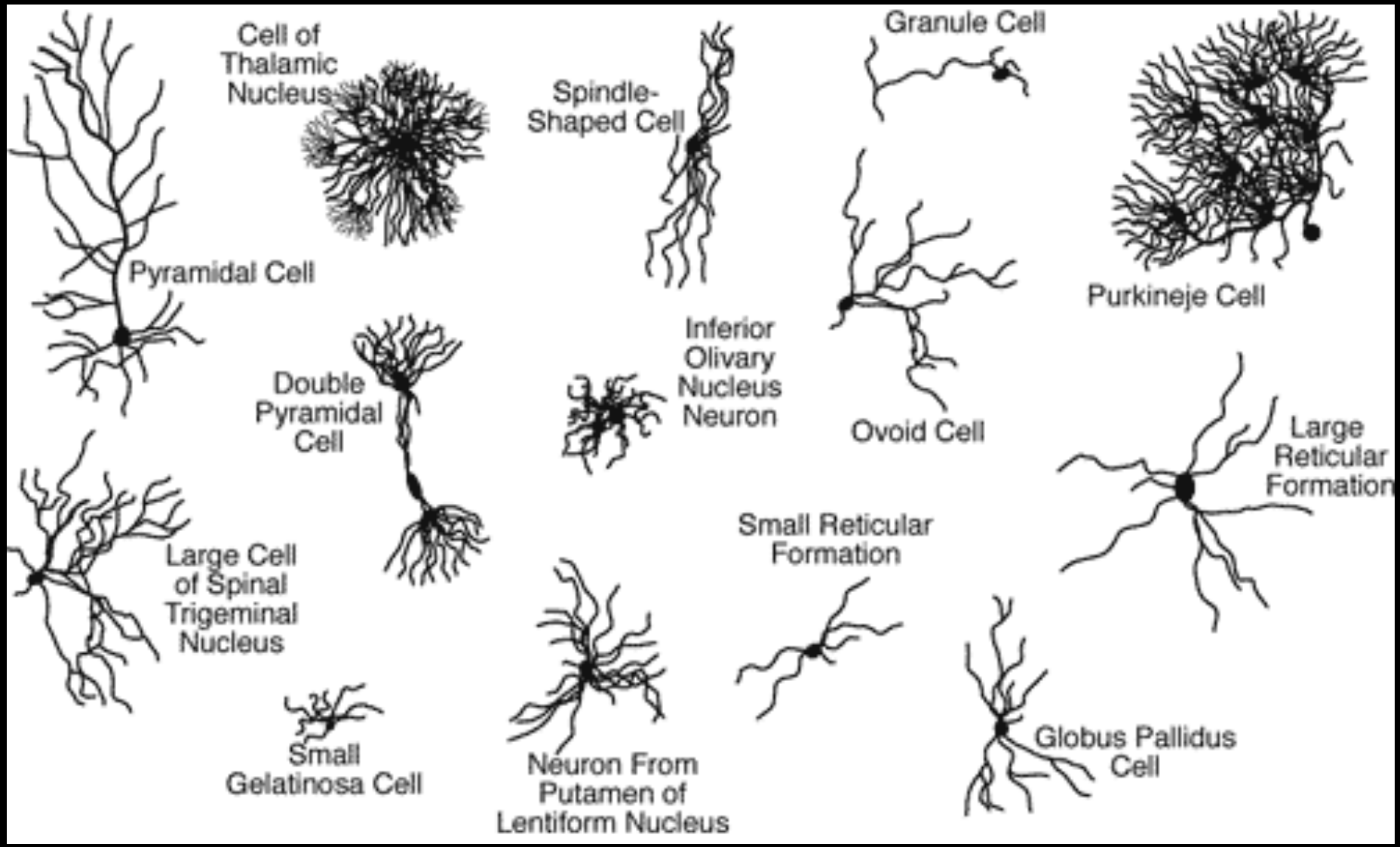
green fluorescent protein



Genetically encoded dyes

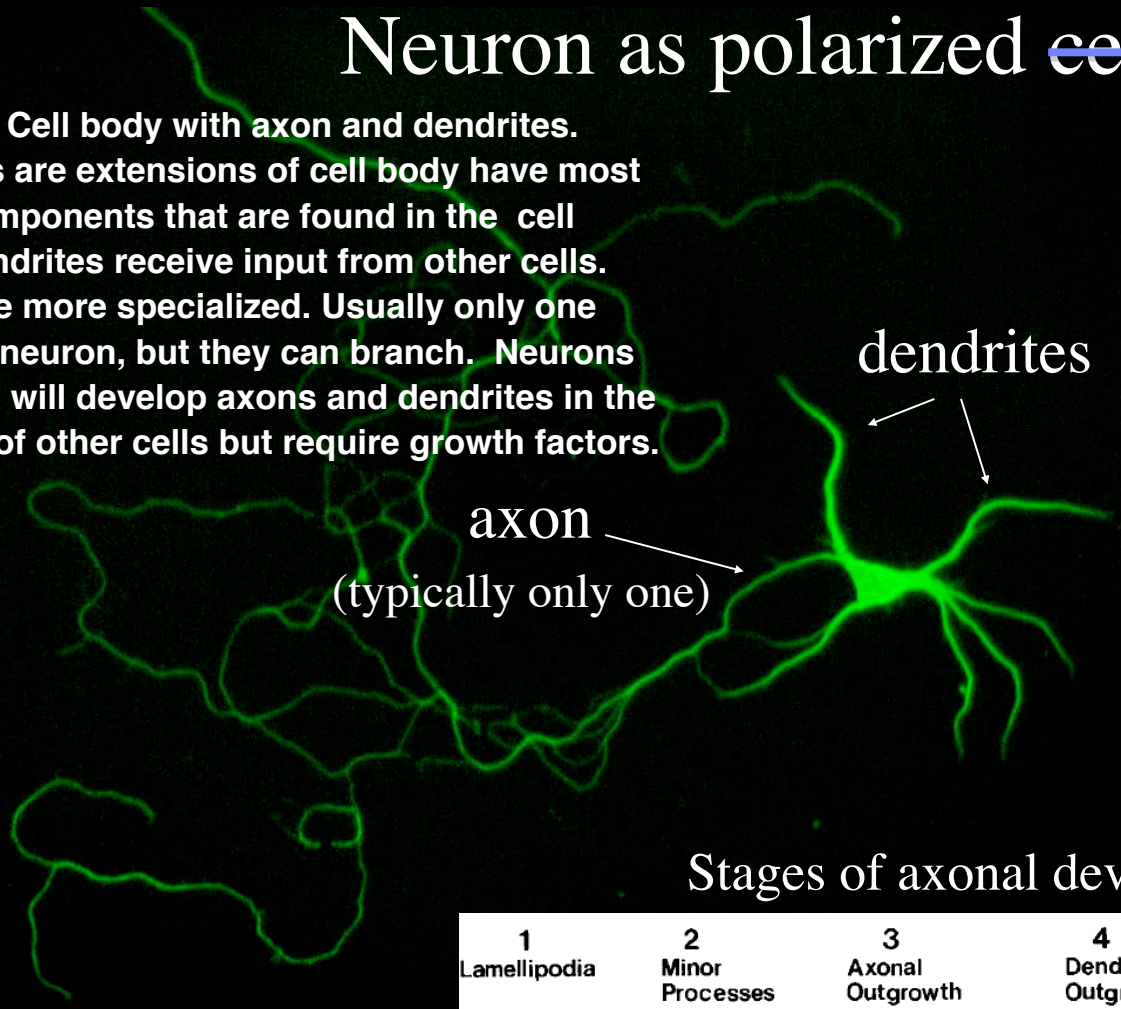
Neurons have a variety of shapes

Cajal found that neurons have a variety of shapes. Researchers are trying to determine how the expressions of different genes generate these unique cellular shapes.

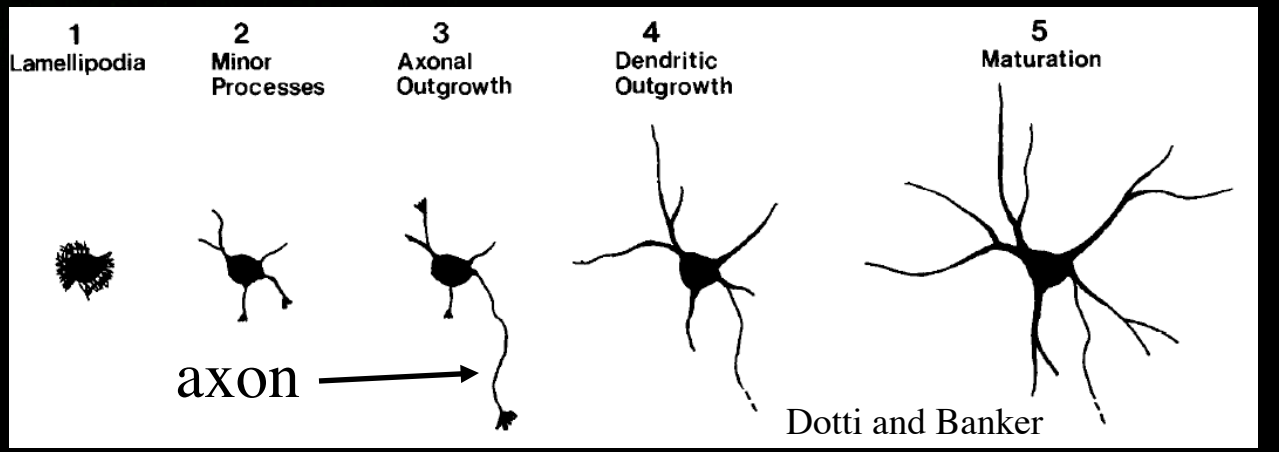


Neuron as polarized ~~cells~~

Neurons: Cell body with axon and dendrites. Dendrites are extensions of cell body have most of the components that are found in the cell body. Dendrites receive input from other cells. Axons are more specialized. Usually only one axon per neuron, but they can branch. Neurons in culture will develop axons and dendrites in the absence of other cells but require growth factors.

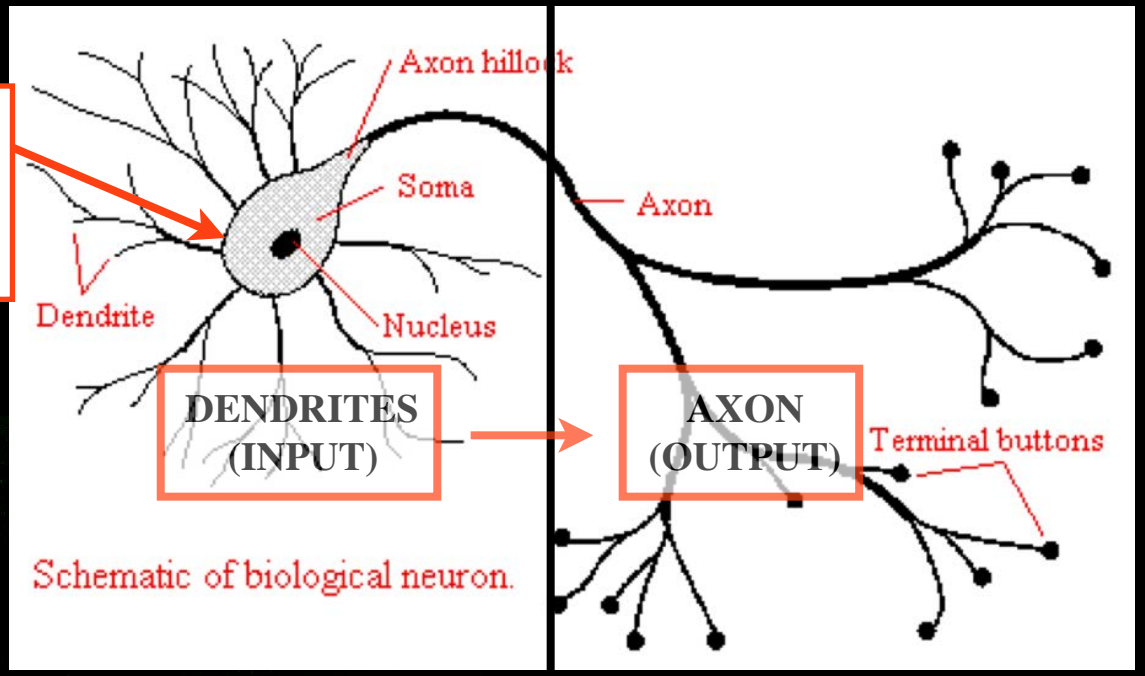


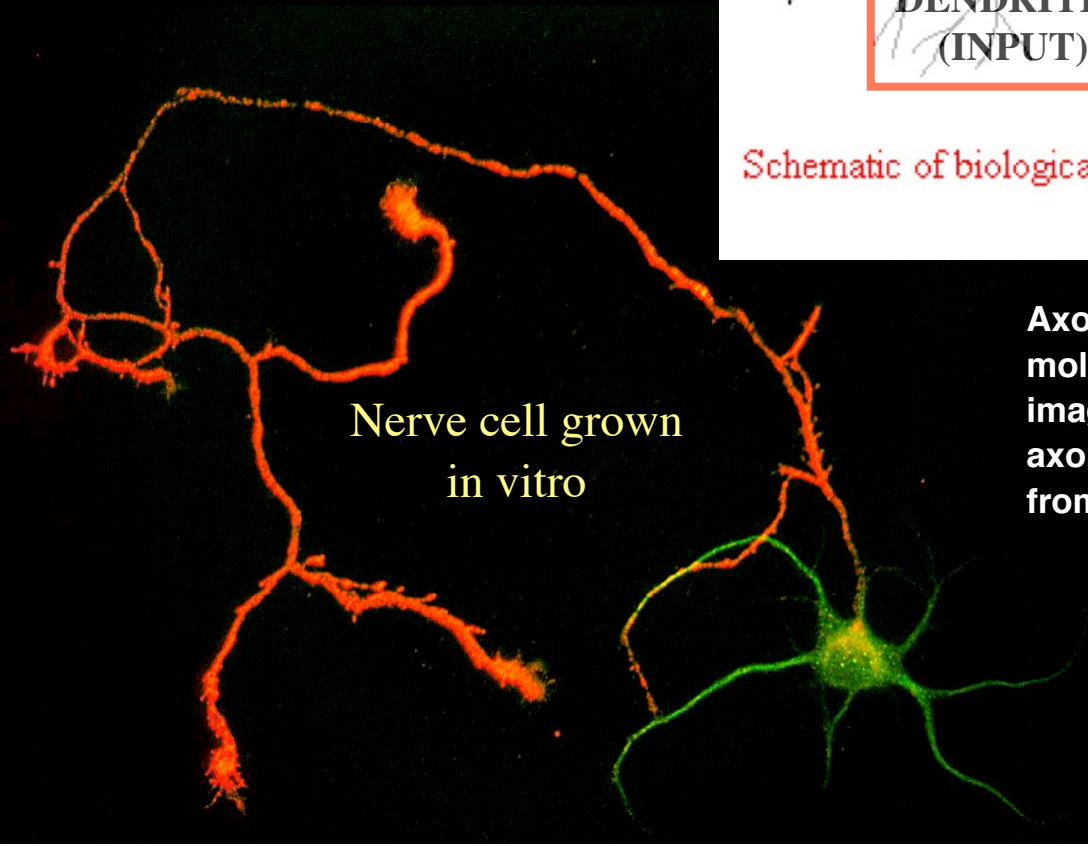
Stages of axonal development (in vitro)



Axon and dendrites have different properties

perikaryon
soma
cell body





Axons and dendrites have different molecular compositions as shown by this image of a neuron in culture. Note that the axon synapses onto one of the dendrites from the same cells.

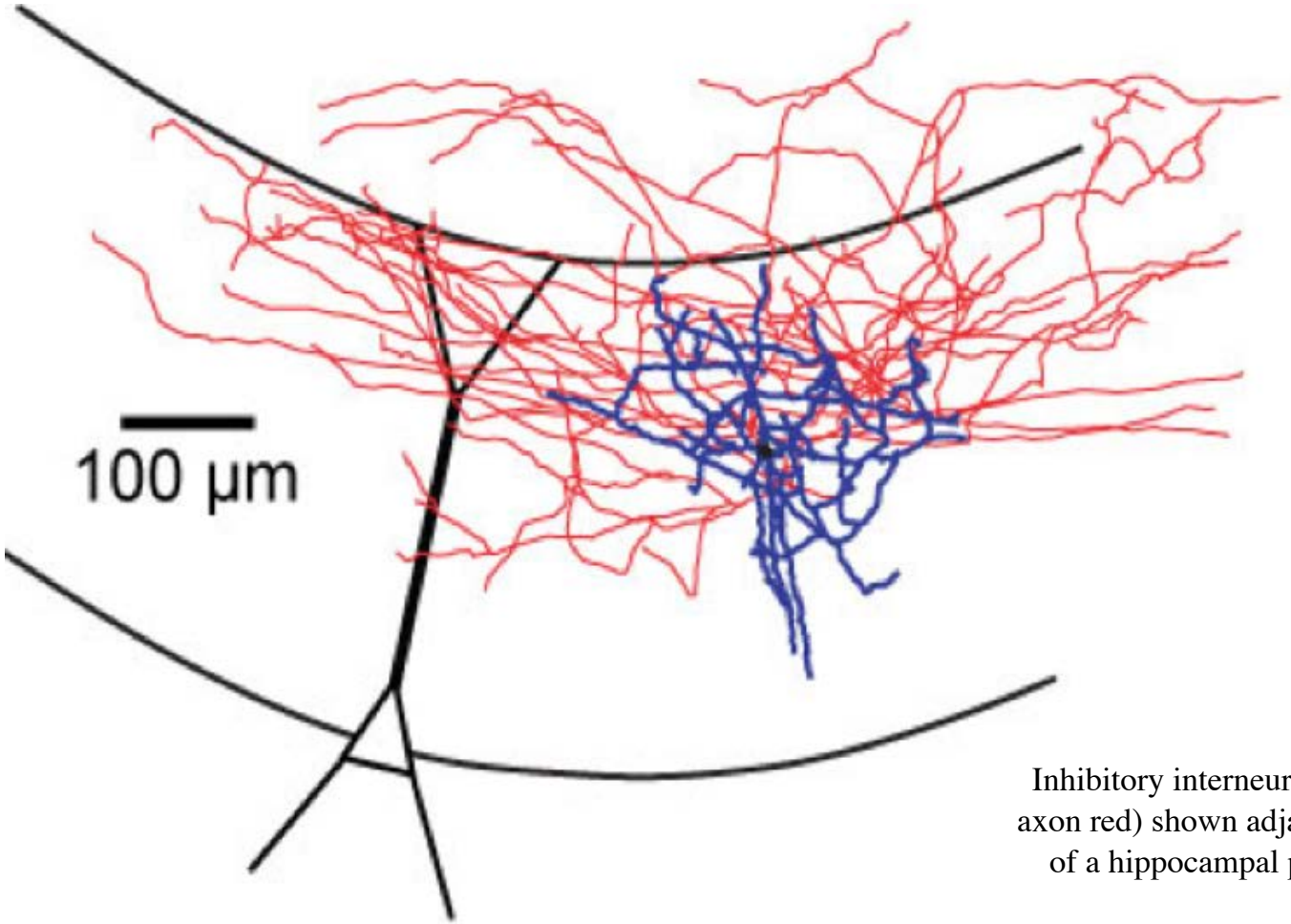
Red: axonal marker

Green: dendritic marker

Both dendrites and axons can be extremely branched

axons are typically longer (can be much longer)

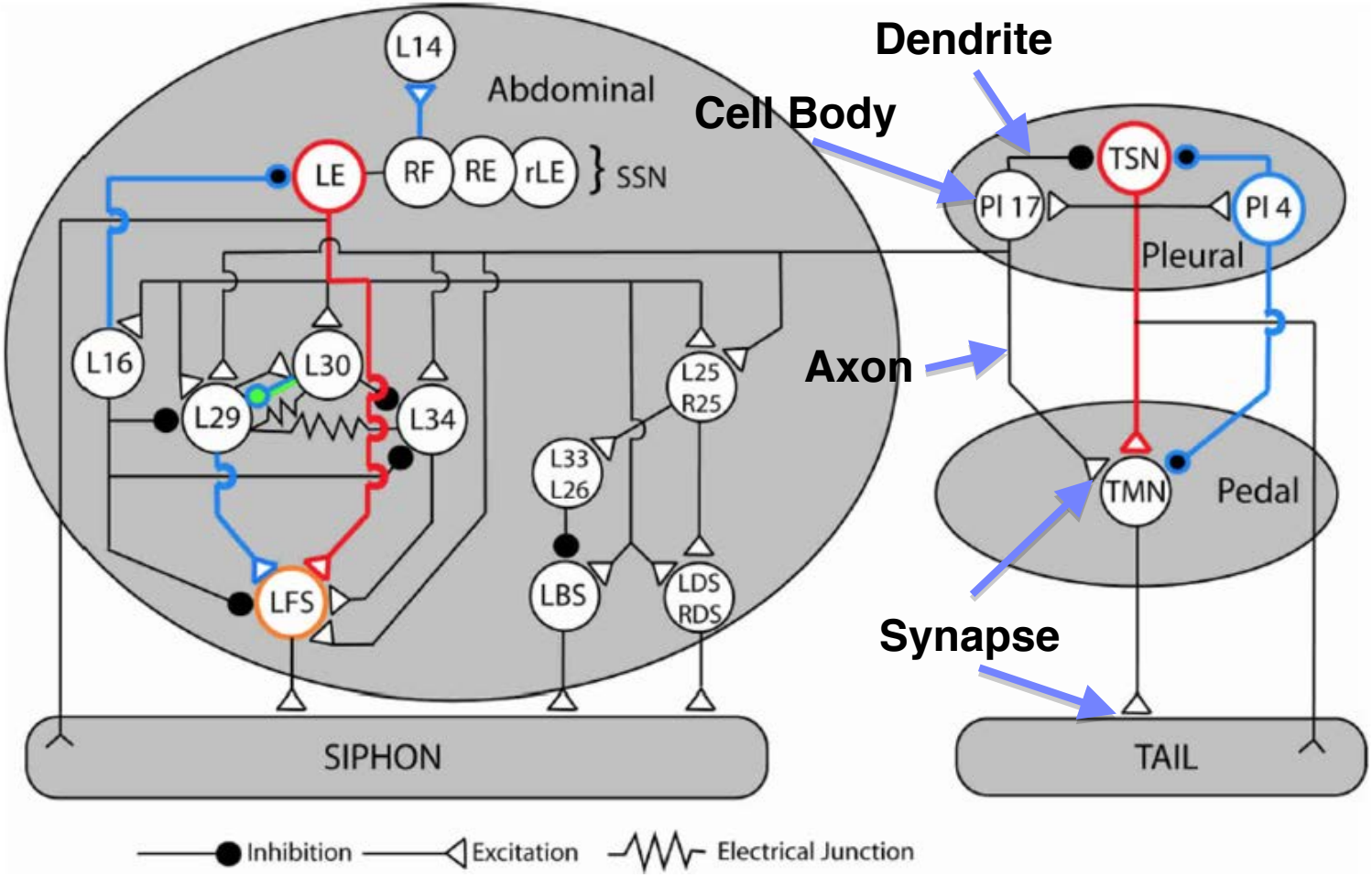
axon and dendrites of a single neuron



Inhibitory interneuron (dendrites blue, axon red) shown adjacent to a schematic of a hippocampal pyramidal neuron

http://www.clp.northwestern.edu/news/rewrite-textbooks-findings-challenge-conventional-wisdom-how-neurons-operate

Neurons are organized in neuronal circuits



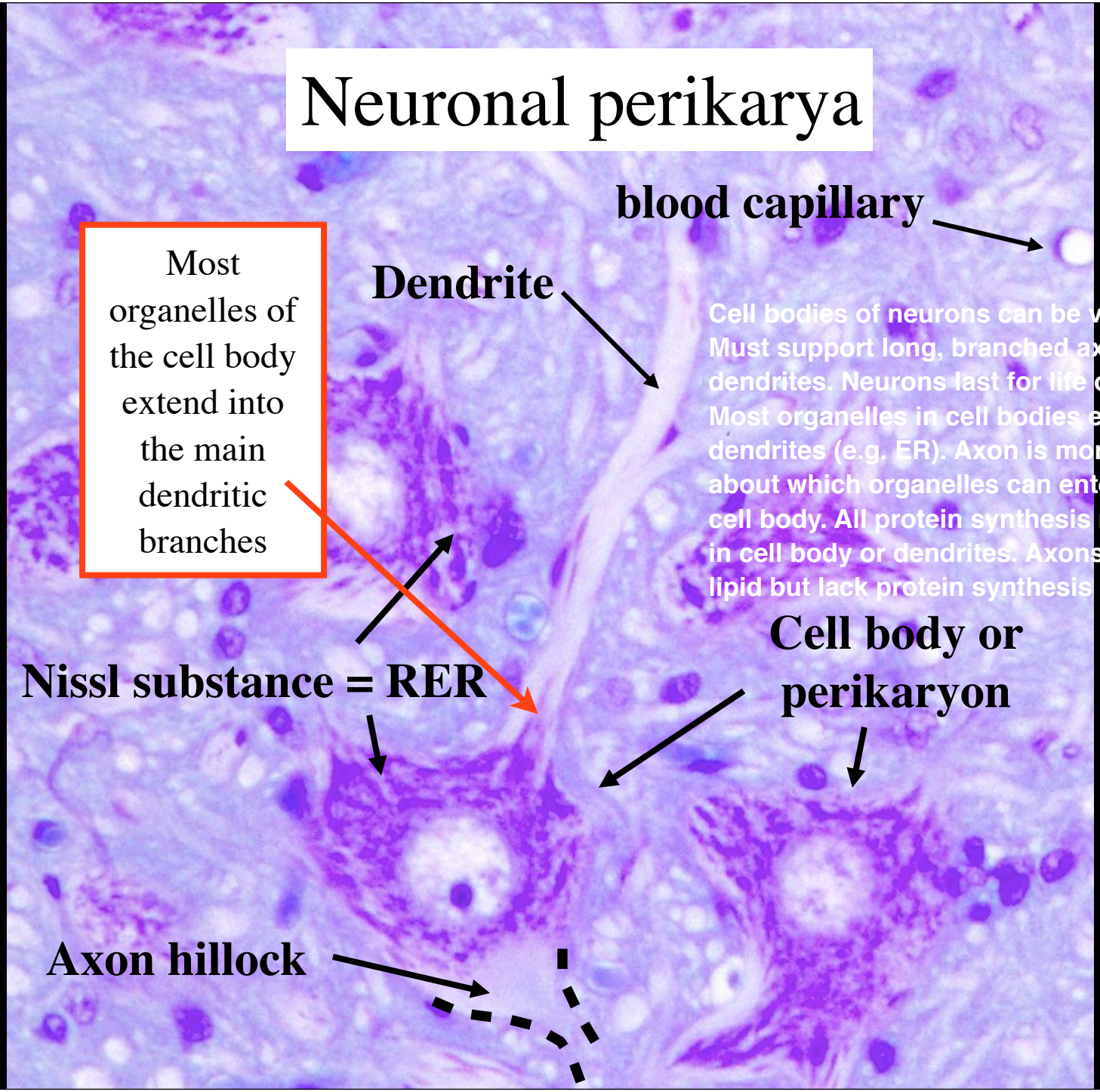
Schematic diagram of the neuronal circuit mediating tail and siphon withdrawal reflex in Aplysia (an invertebrate organism)

Demian Barbas, Luc DesGroseillers, Vincent F. Castellucci, et al. Learn. Mem. 10: 373, 2003

Key compartments of the neuron:

cell body (soma, perikaryon)
dendrites
axons

Neuronal perikarya



Neuronal perikarya

Entry of organlles in axons is selective. There are no rough endoplasmic reticulum or ribosomes (and thus no protein synthesis) and Golgi complex in mature axons

blood capillary

Dendrite

Nissl substance = RER

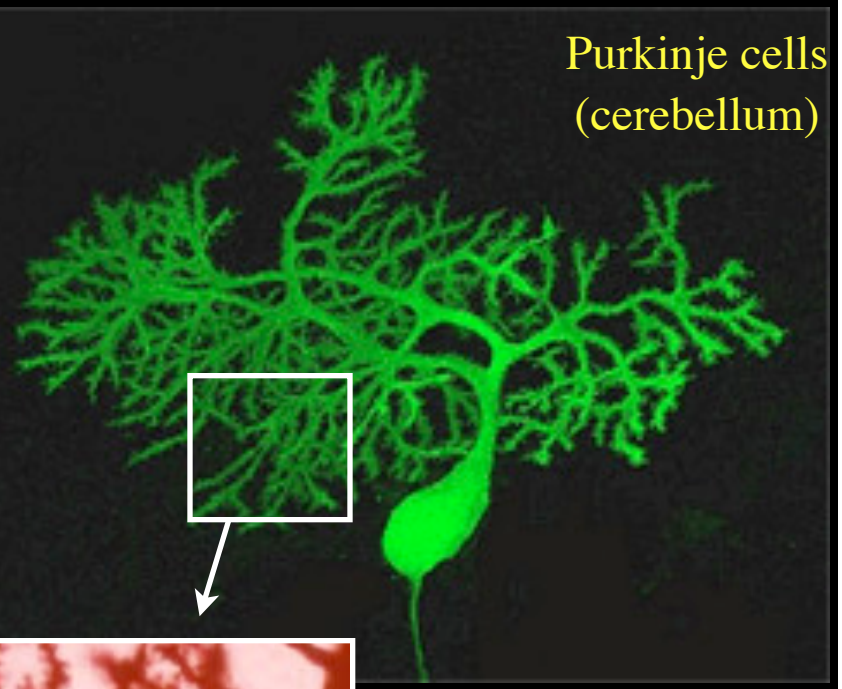
Axon hillock

Dendritic trees

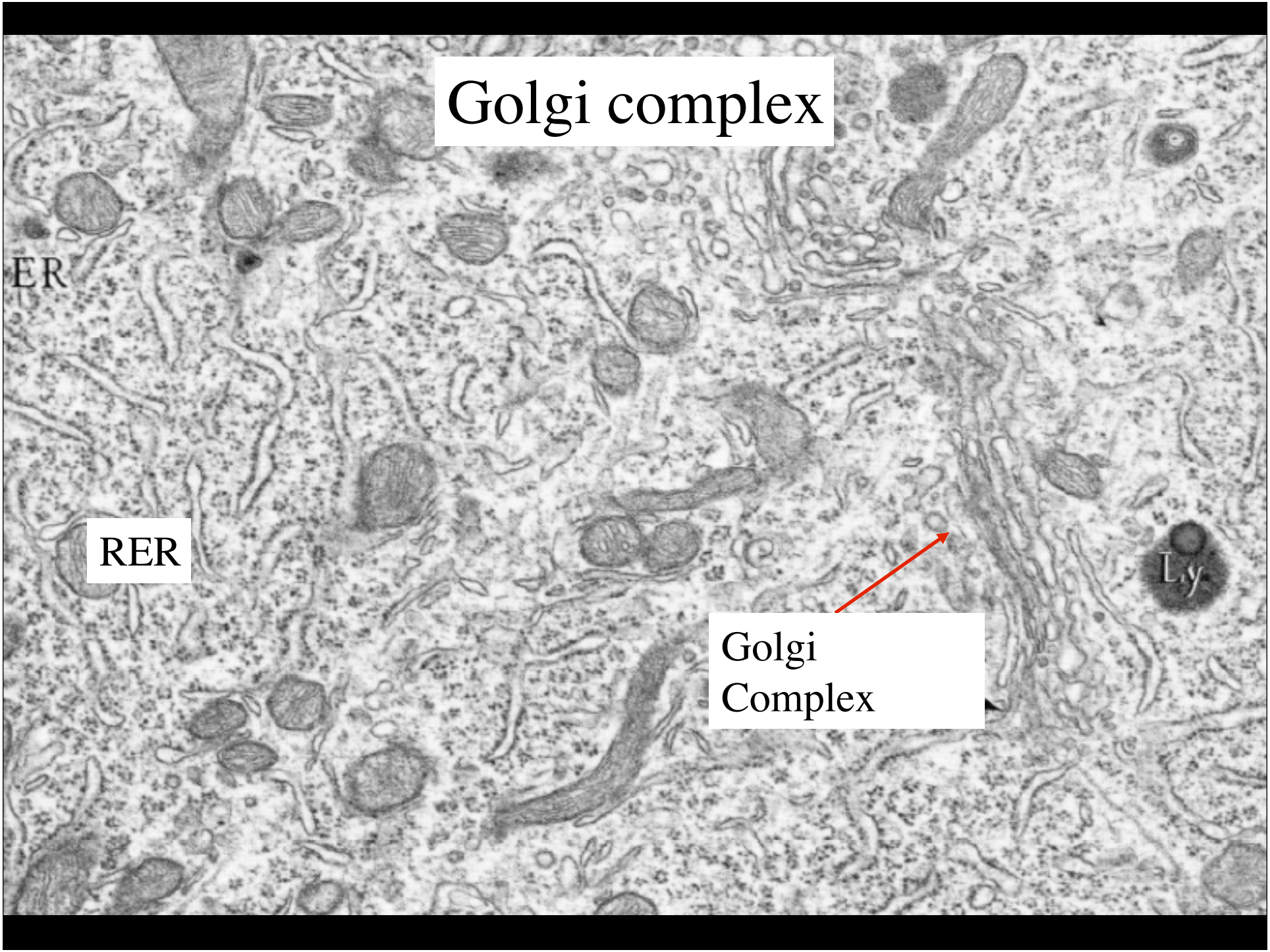
Purkinje cells (cerebellum)

Dendrites integrate inputs from many different axons (can receive 1000s of inputs). Each synapse contributes a small amount of depolarization of the neuron. If the sum of the signals is sufficient, an action potential will be triggered in the axon.

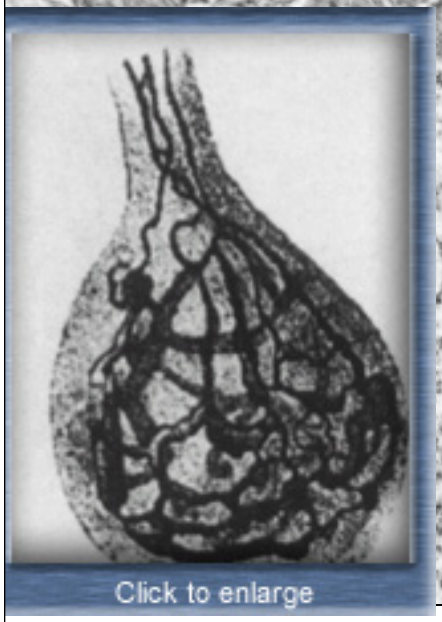
axons



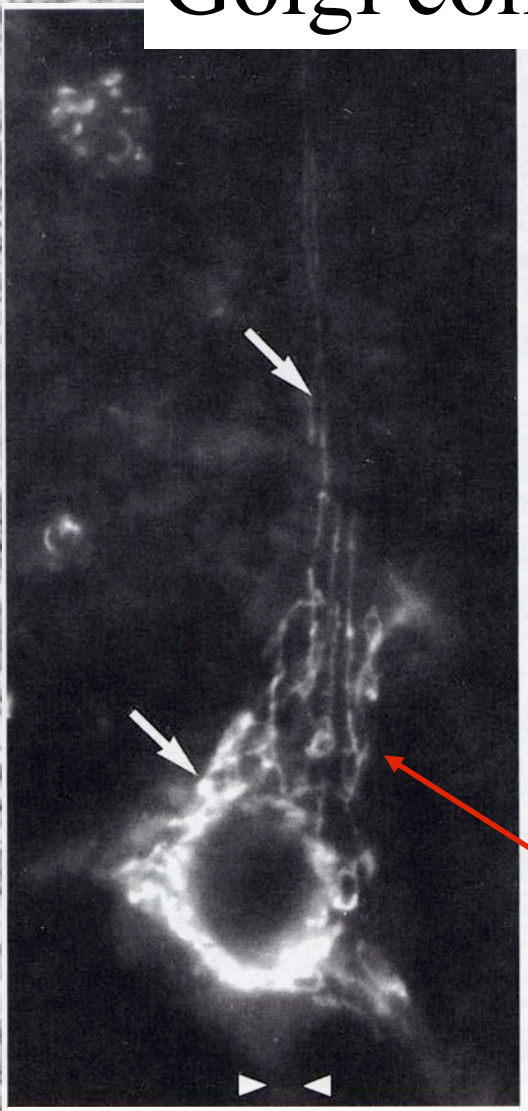
Dendritic spines


Golgi complex
ER
RER
Golgi
Complex
Ly

Golgi complex



Silver impregnation
(From Camillo Golgi)



immunofluorescence

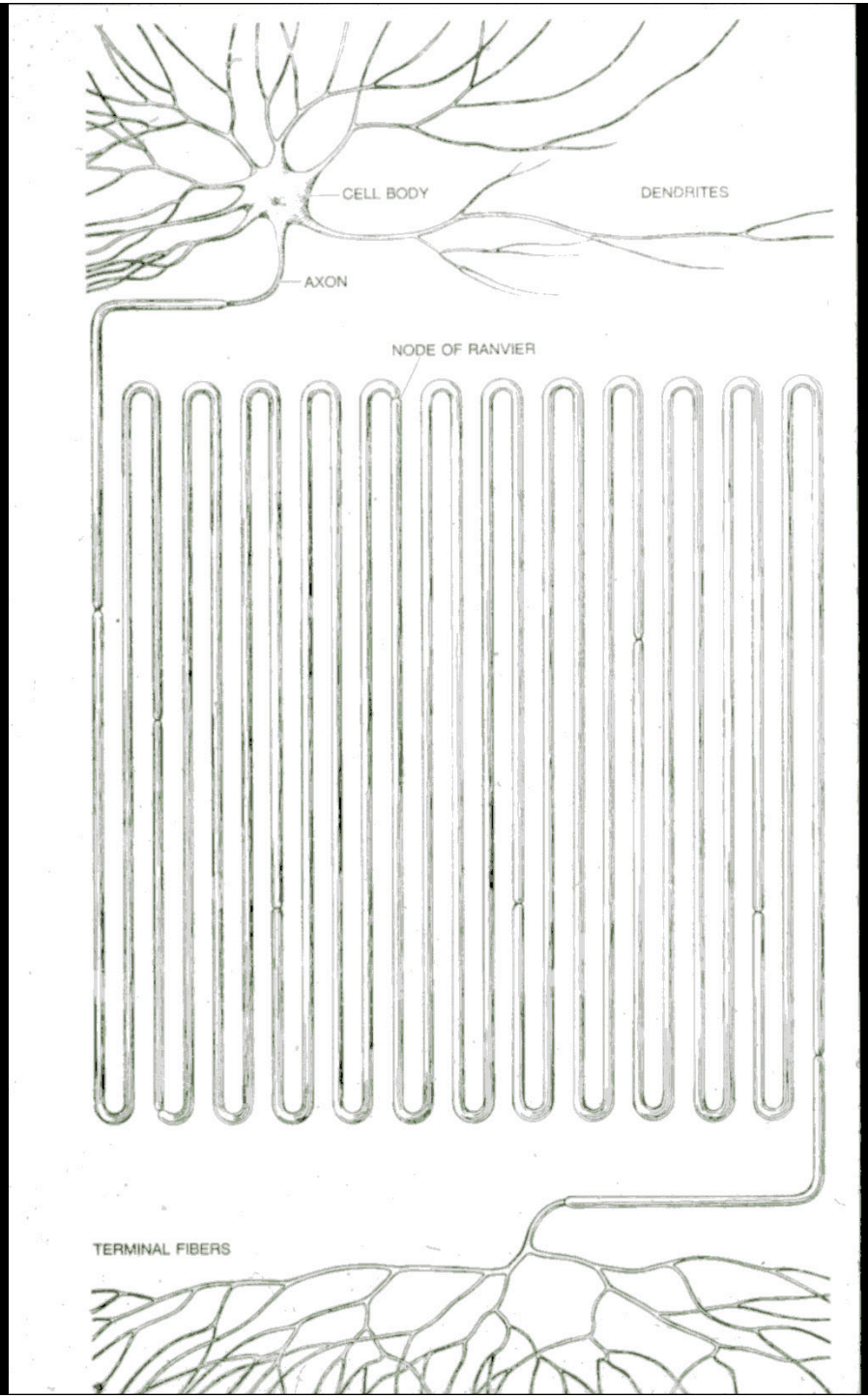
Golgi
Complex

Golgi complex extends into dendrites but not axons.

The length of the axons poses special needs:

-Structural support
-Assisted organelle transport
-Local synthesis and degradation of metabolites
-Signal propagation

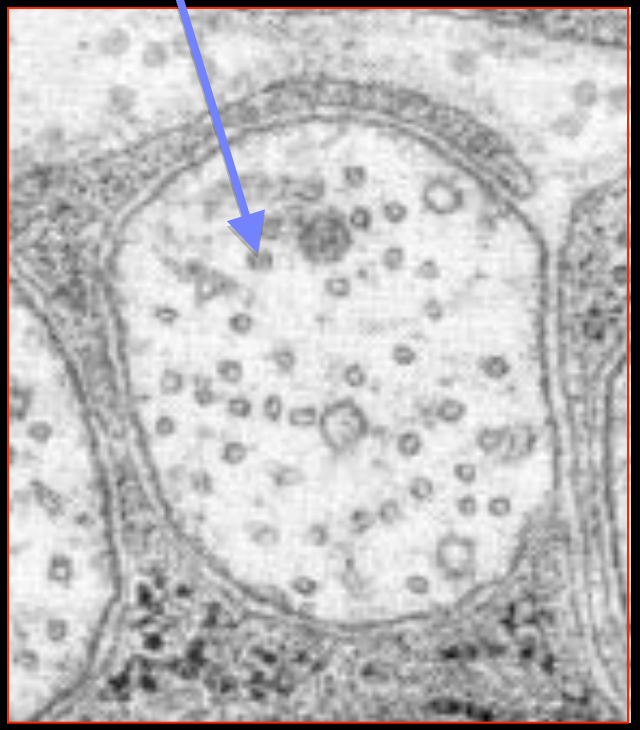
Axons can be extremely long compared to the cell body. Neurons need deliver machinery down the axon. Need structural support both internally (cytoskeleton) and externally. Neurons deliver signals via their axons to specific cells, similar to phone cables that make specific connections. Because axons make specific contacts, few different types of neurotransmitters are used.



Axons are surrounded by glial cells

Unmyelinated Axons

Microtubule



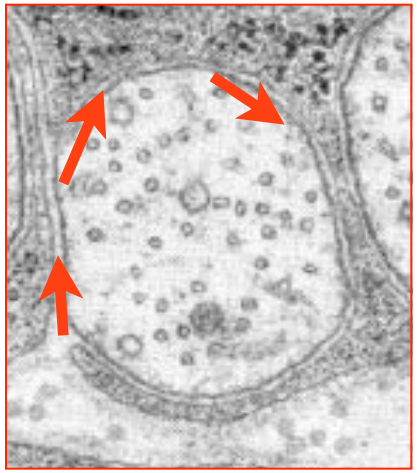
Axons are surrounded by glial cells

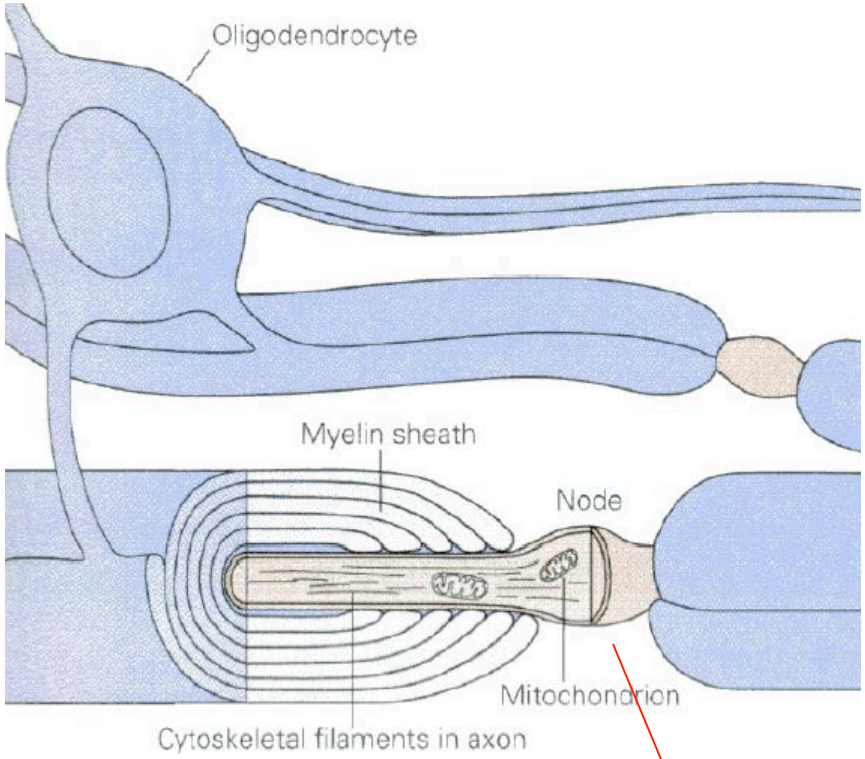
Myelinated
axon

Myelin sheath wraps axons

Schwann cells (PNS)
Oligodendrocytes (CNS)

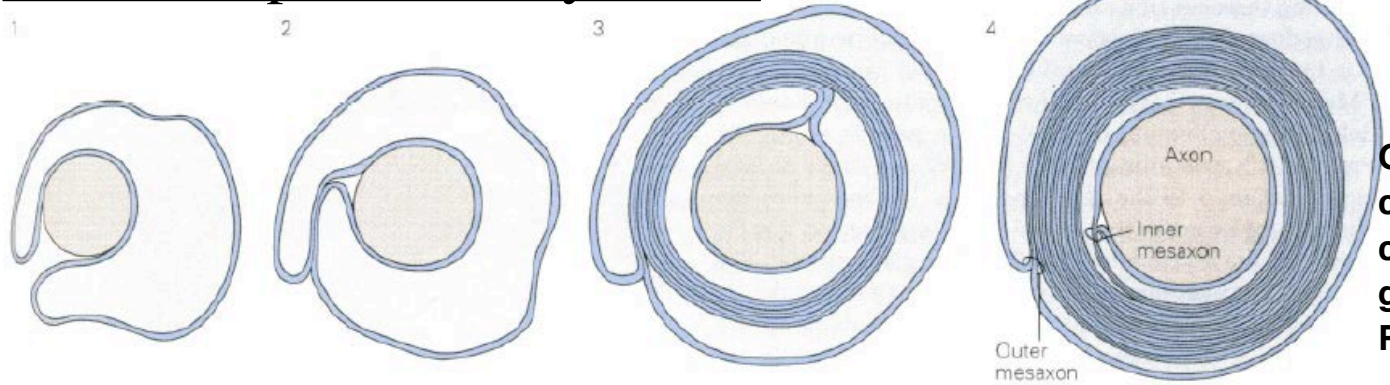
Myelin





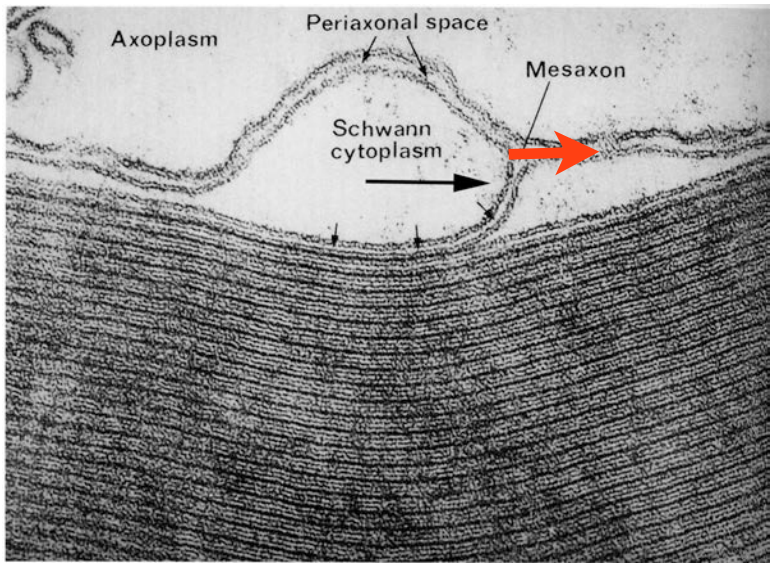
Node of Ranvier

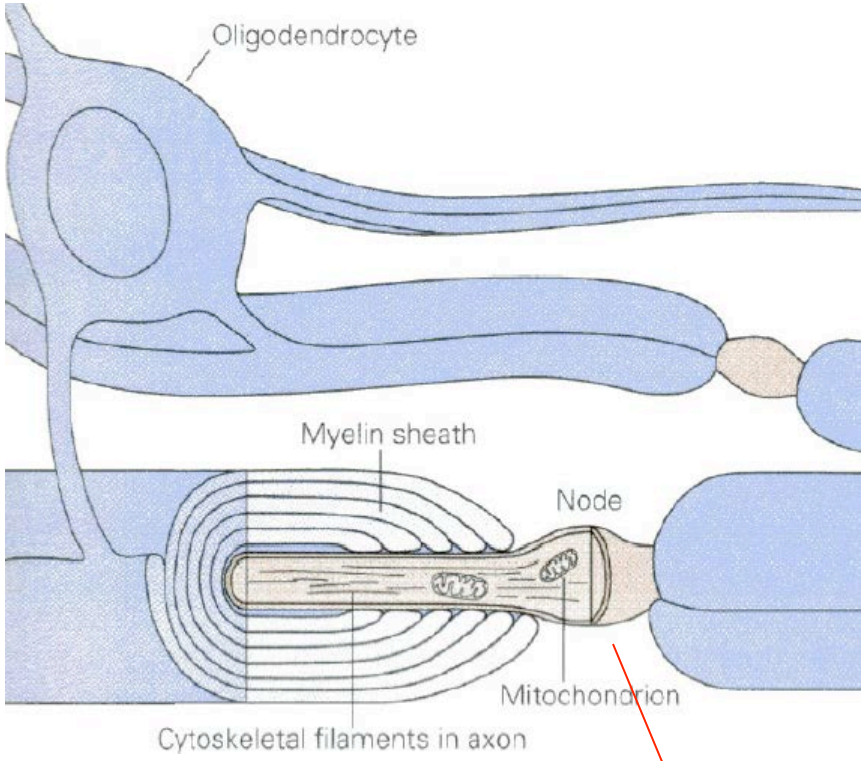
Development of myelin



Gaps in myelin sheath are created where adjacent glia cells meet on the axon. These gaps are called nodes of Ranvier.

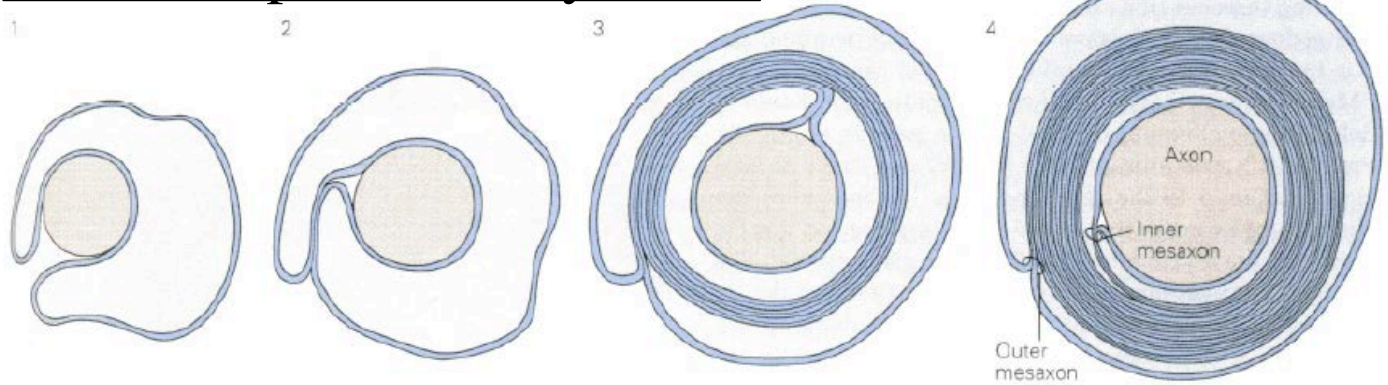
Myelin



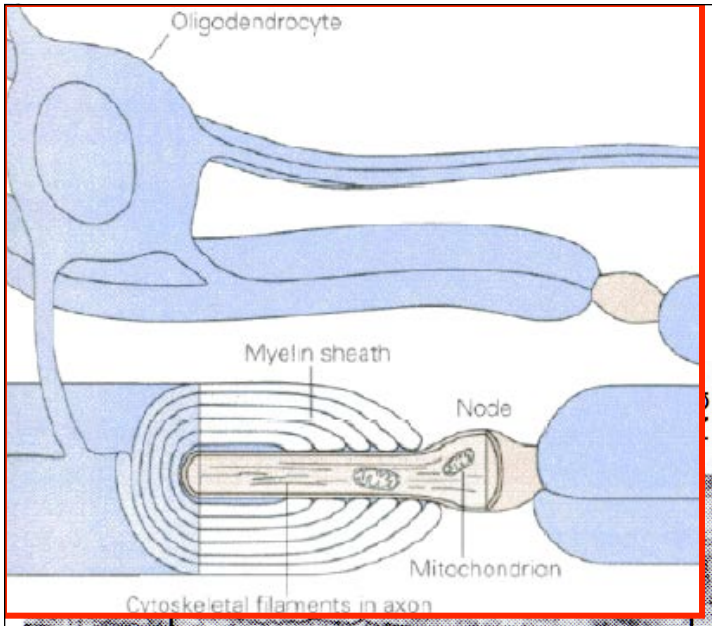


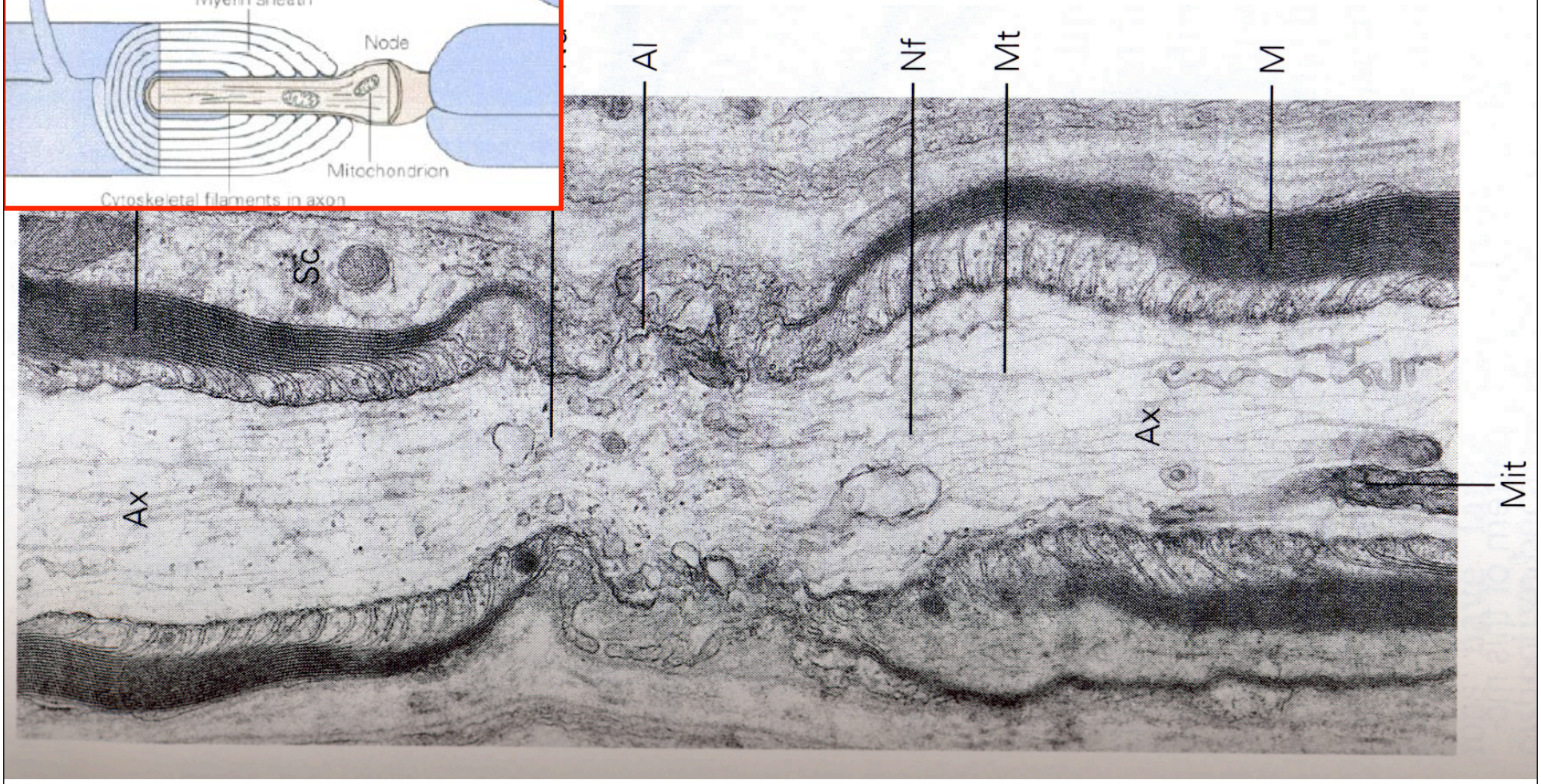
Node of Ranvier

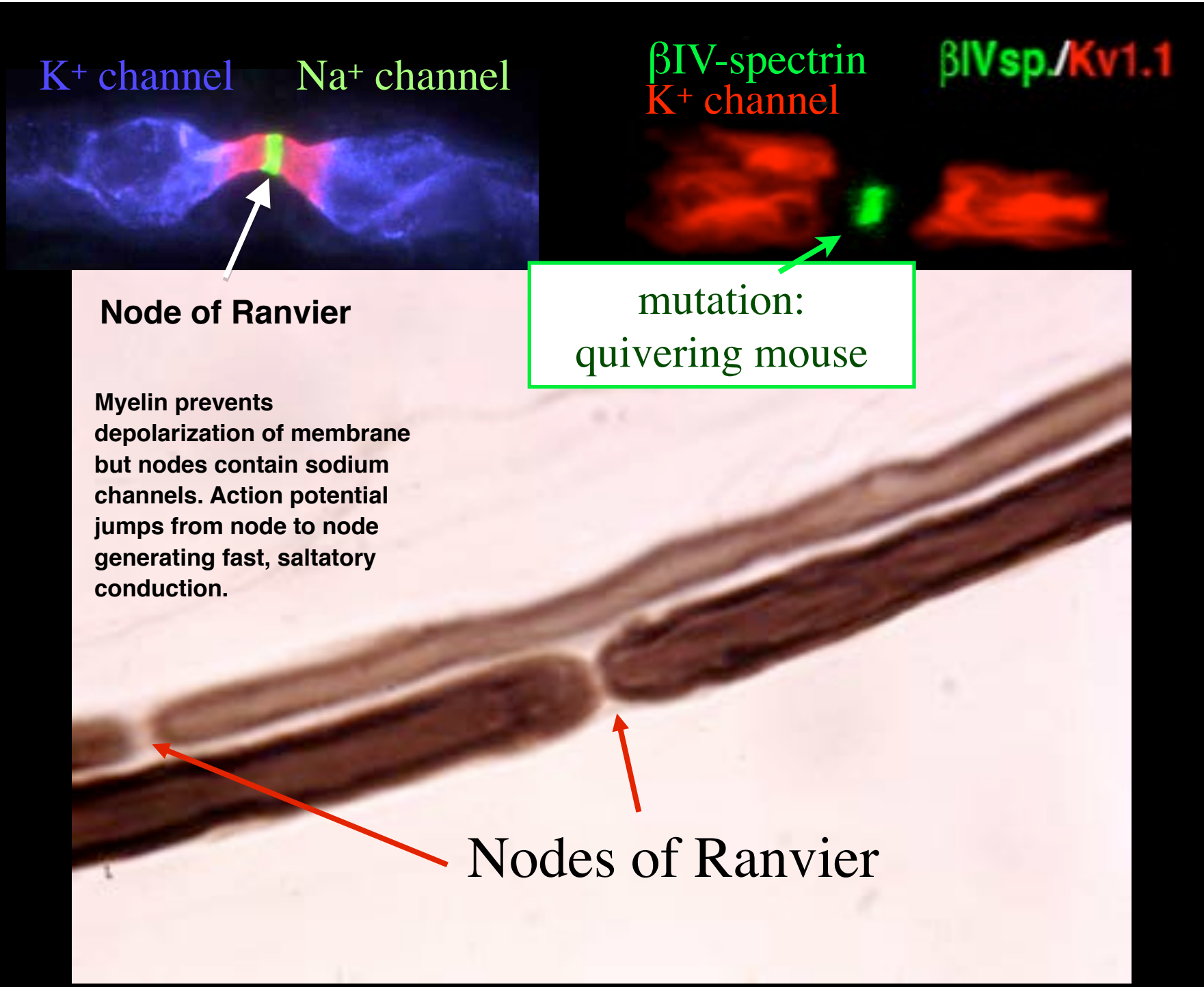
Development of myelin



Node of Ranvier, EM

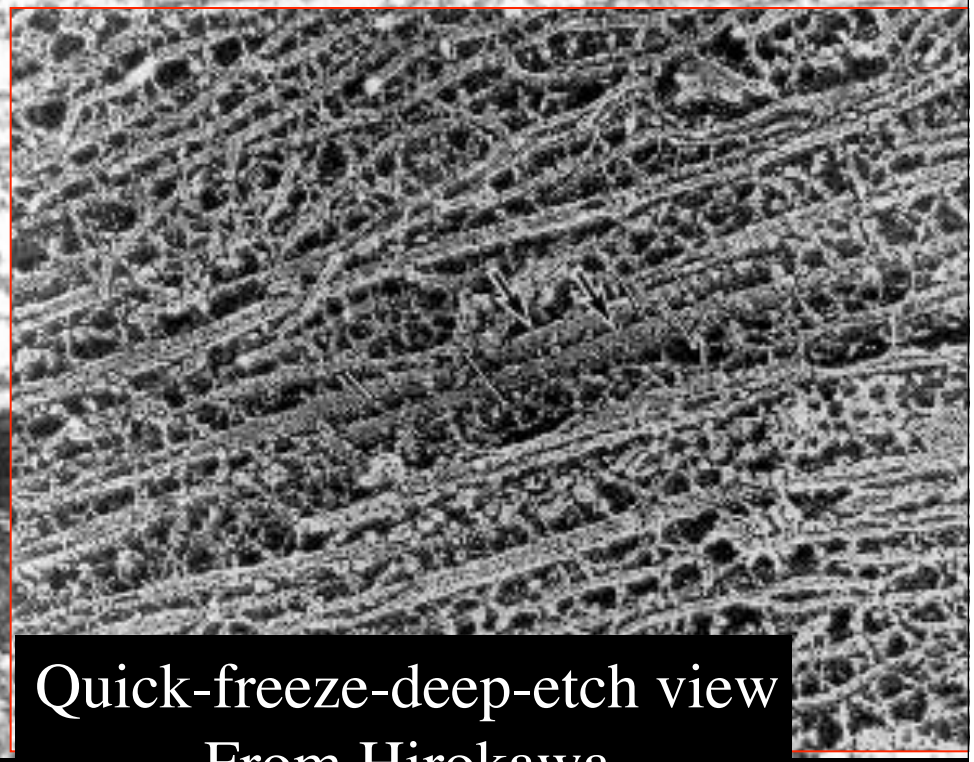





K+ channel
Na+ channel
βIV-spectrin
K+ channel
βIVsp./Kv1.1
Node of Ranvier
mutation:
quivering mouse
Myelin prevents depolarization of membrane but nodes contain sodium channels. Action potential jumps from node to node generating fast, saltatory conduction.
Nodes of Ranvier

A prominent cytoskeletal scaffold

Cytoskeleton provides structural support and creates tracks for transport of cellular material.



Quick-freeze-deep-etch view
From Hirokawa

Myelinated Axon longitudinal-section

Axonal transport

Toward axon terminus

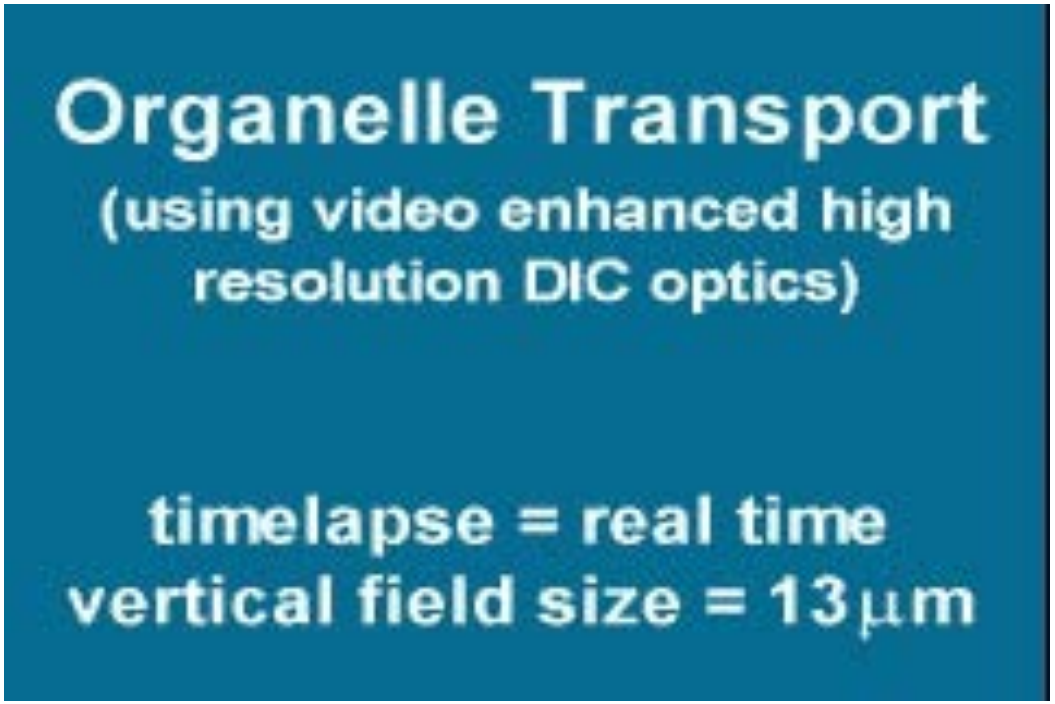
- Anterograde, slow 2-4 mm/day
  - cytosolic proteins, cytoskeletal elements…
- Anterograde, fast (kinesins) 100-400 mm/day
  - organelles, particles

Toward cell body

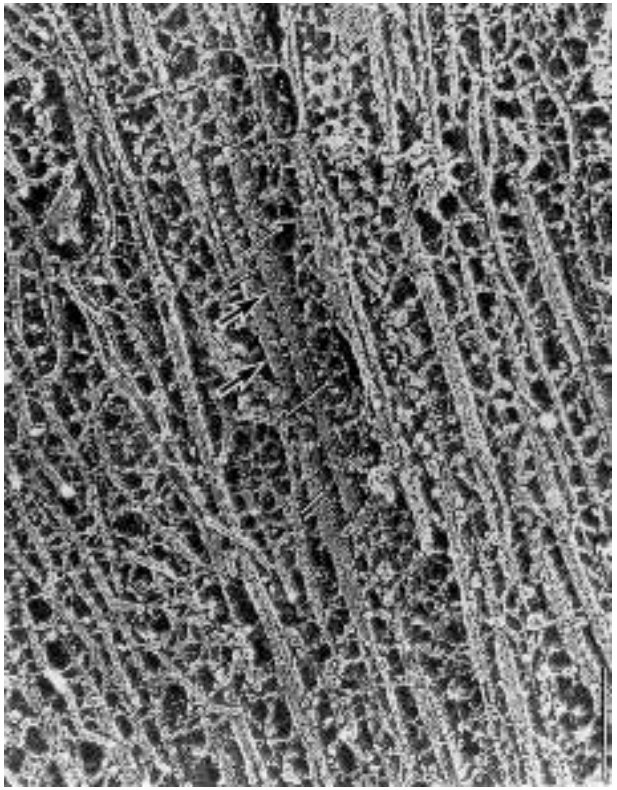
- Retrograde, fast (cytoplasmic dynein)
  - organelles, particles (retrograde signaling, targeting to lyososomes)

Organelle transport

(microtubular motors in axonal cytoplasm)

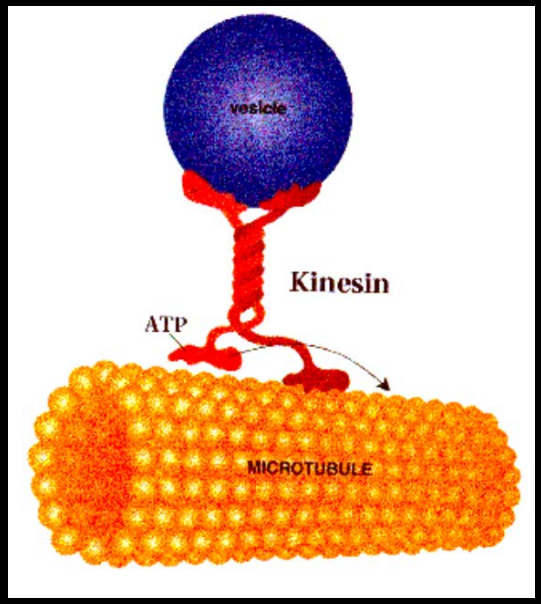


From Paul Forscher

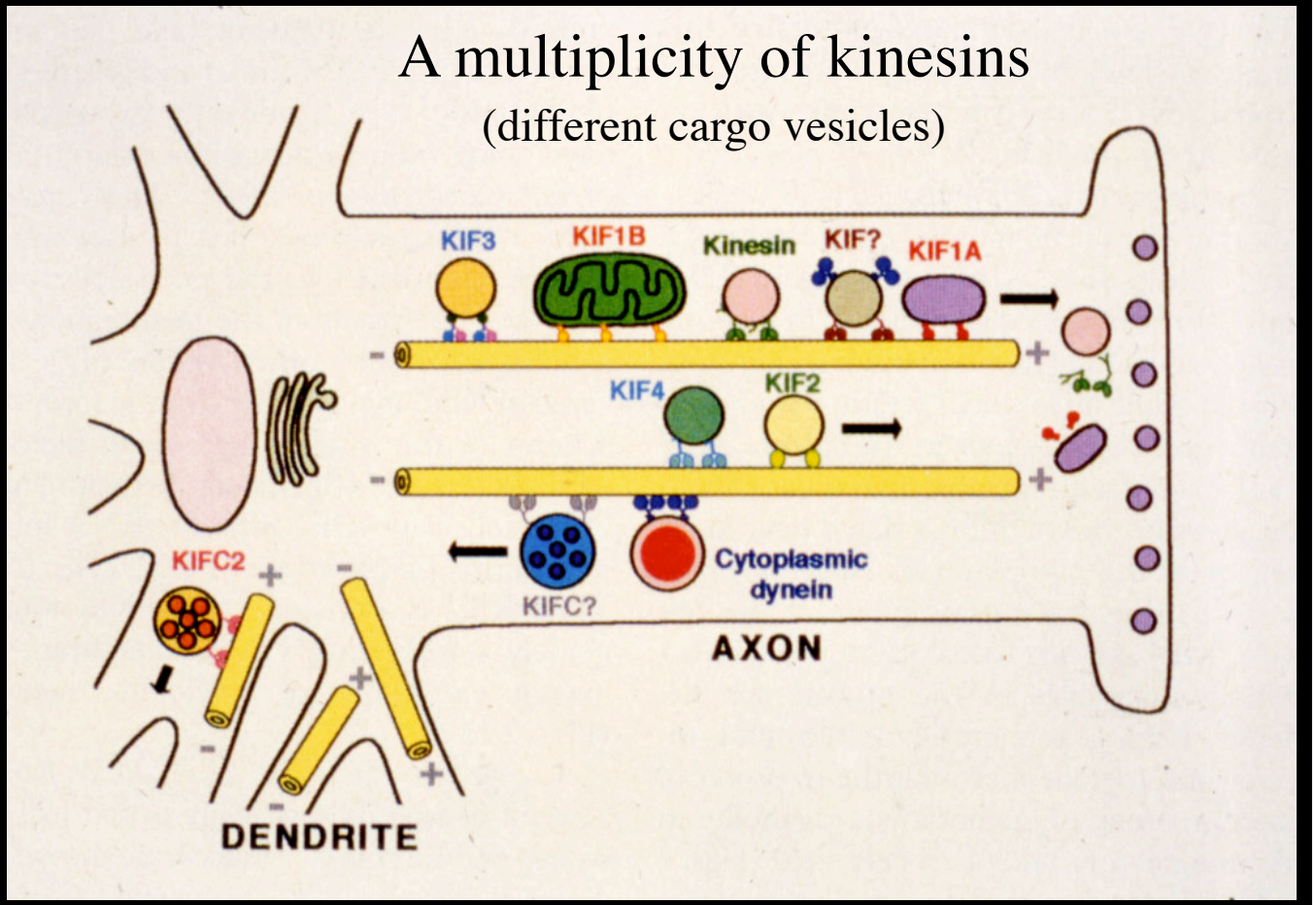


From Nabutaka Hirokawa

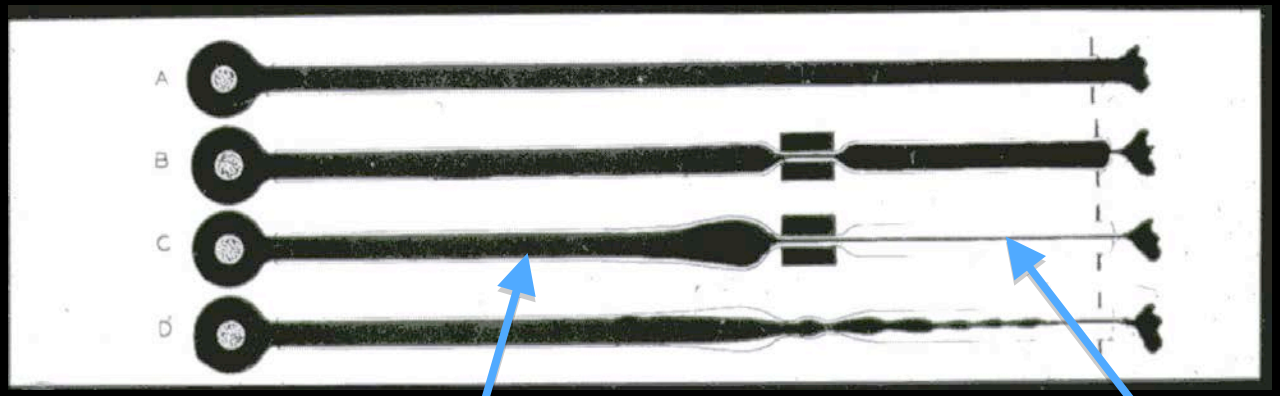
Microtubular motors: kinesin(s) and cytoplasmic dynein



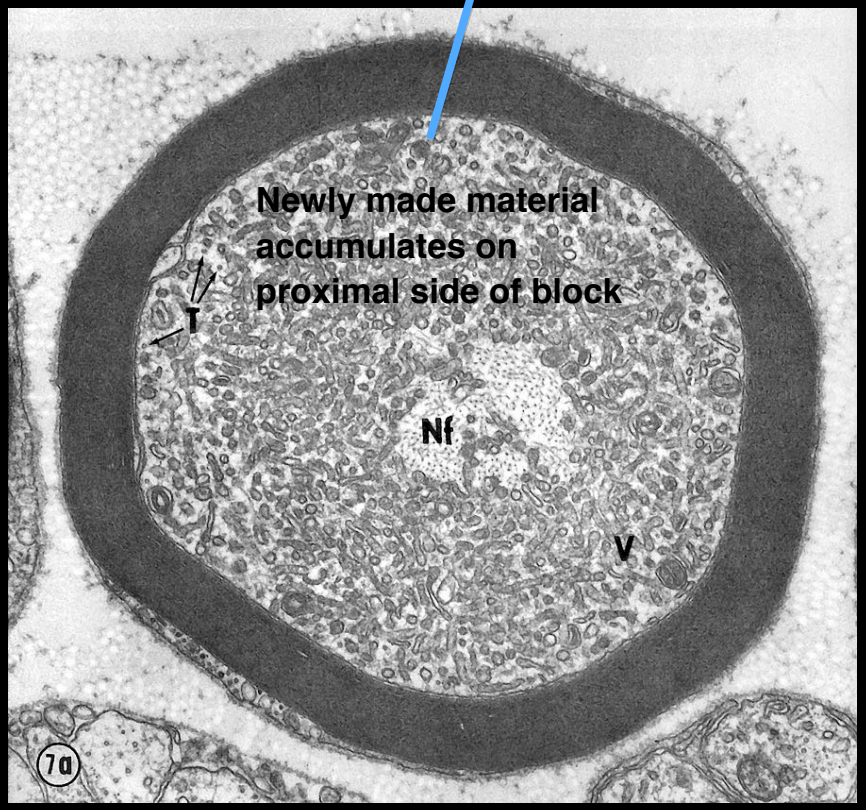
Different types of kinesin are responsible for transporting different kinds of cellular organelles.



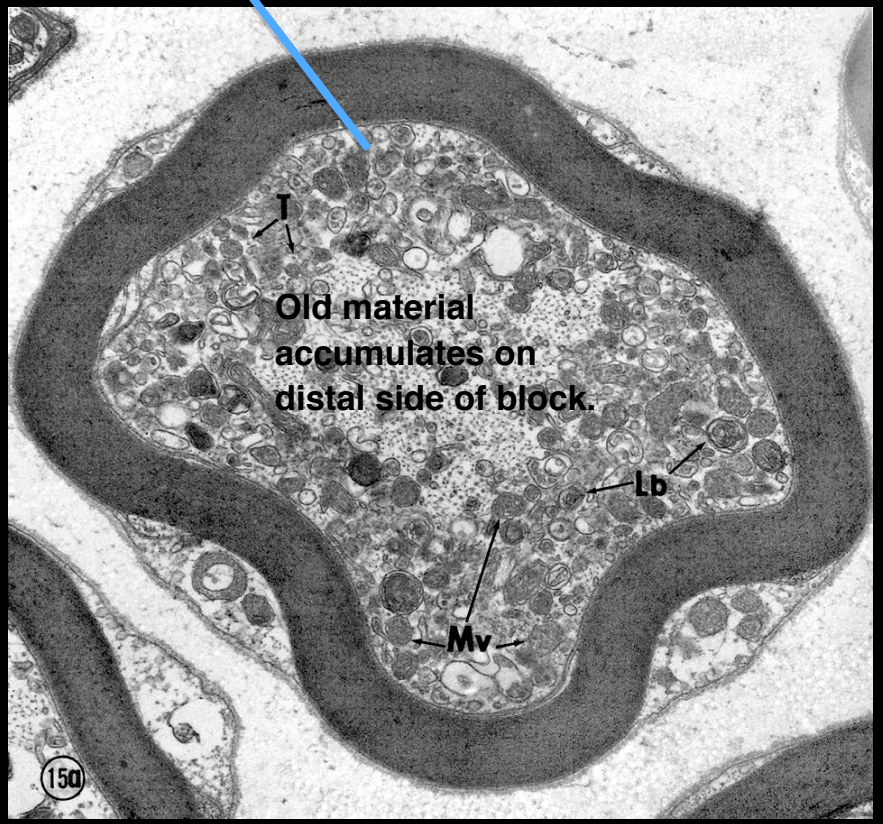
Axonal block



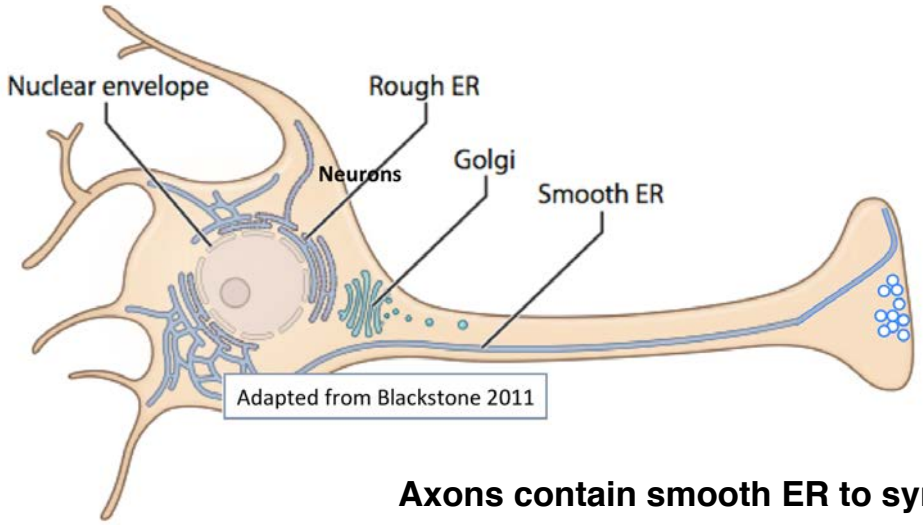
From Tsukita and Ishikawa



Proximal to axonal block

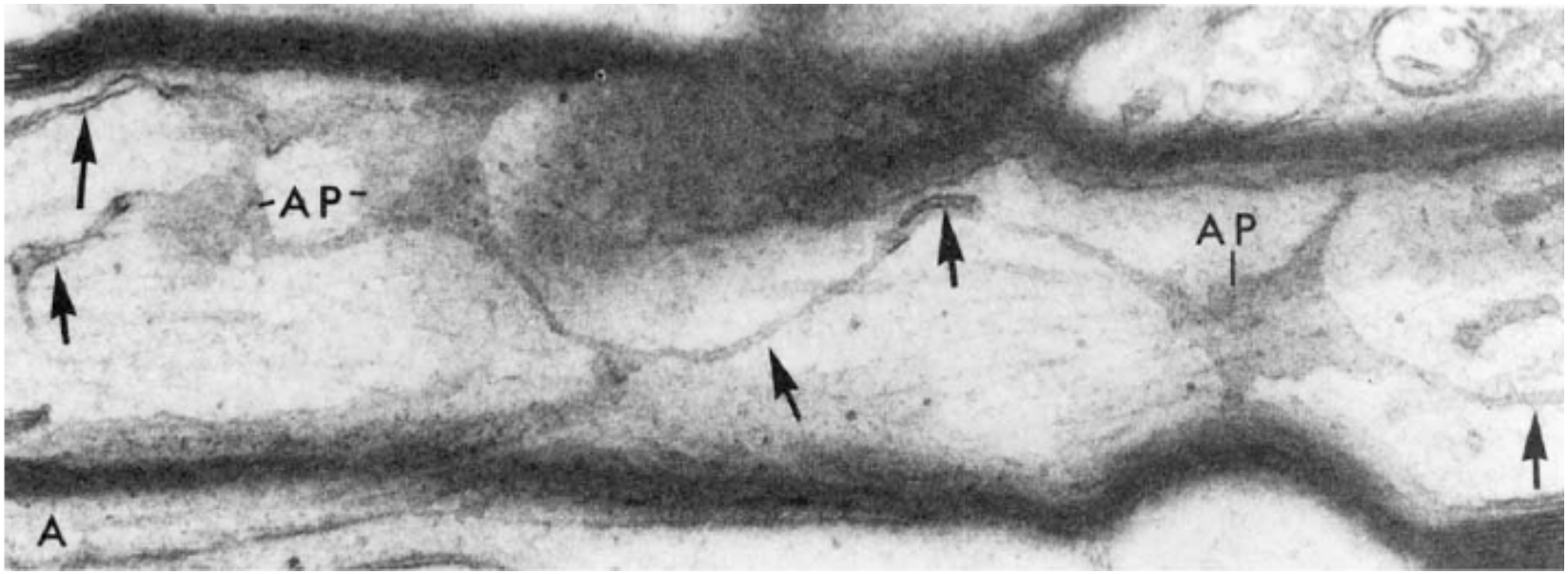


Distal to axonal block



A continuous smooth ER from the cell body to axon terminal

Axons contain smooth ER to synthesize lipids.



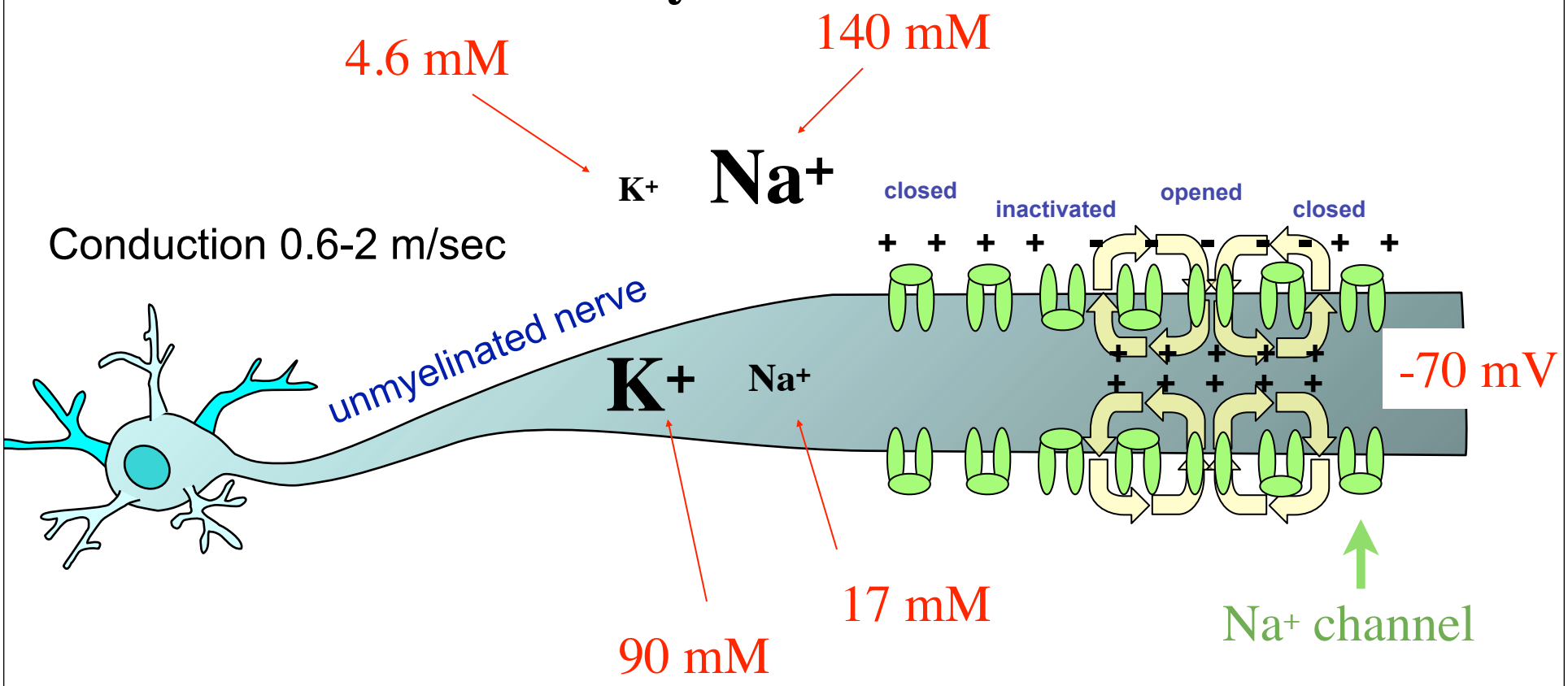
arrows = endoplasmic reticulum

From Broadwell and Cataldo, 1984

Several forms of hereditary spastic paraplegias are due to mutations in proteins that control the shape and the dynamics of the ER

Signal propagation in axons

Unmyelinated nerve



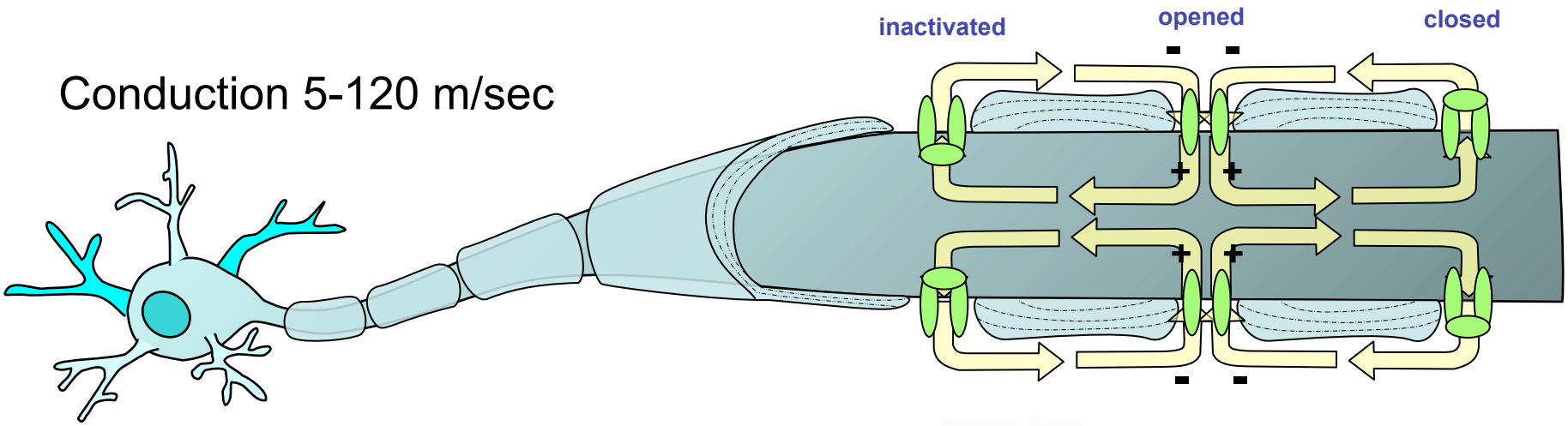
gradient of Na^+ and K^+ across the plasma membrane is mantained by Na^+/K^+ ATPase

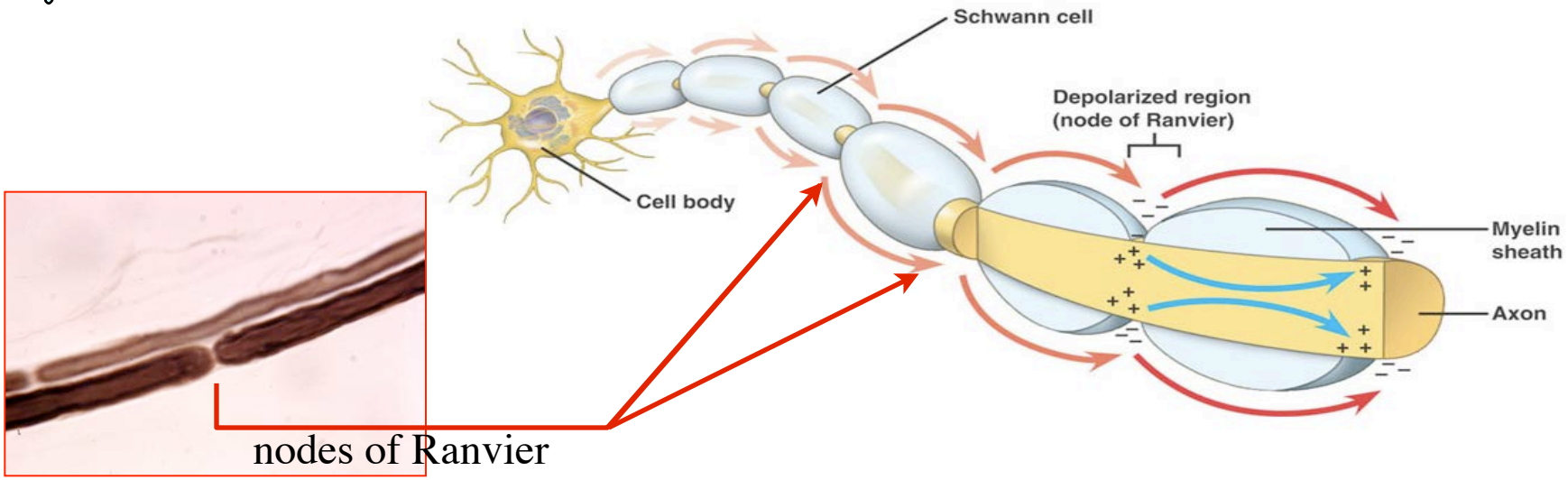
Signal propagation in axons

Myelinated nerve

Saltatory conduction

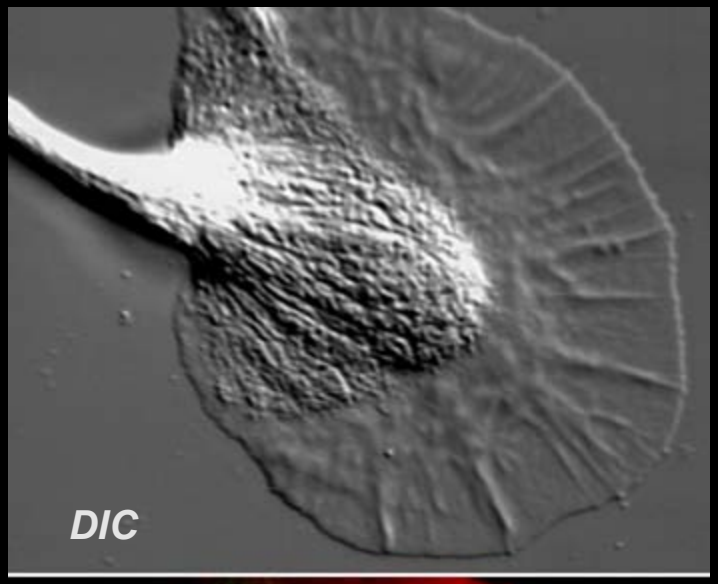
Conduction 5-120 m/sec

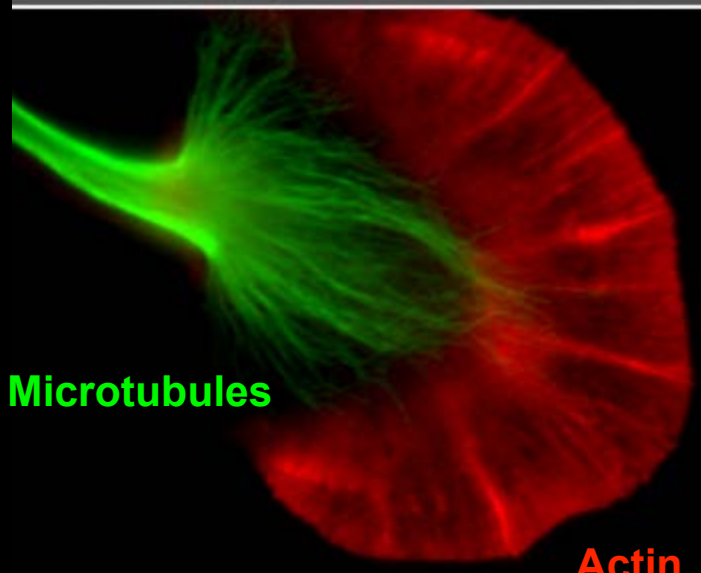




nodes of Ranvier

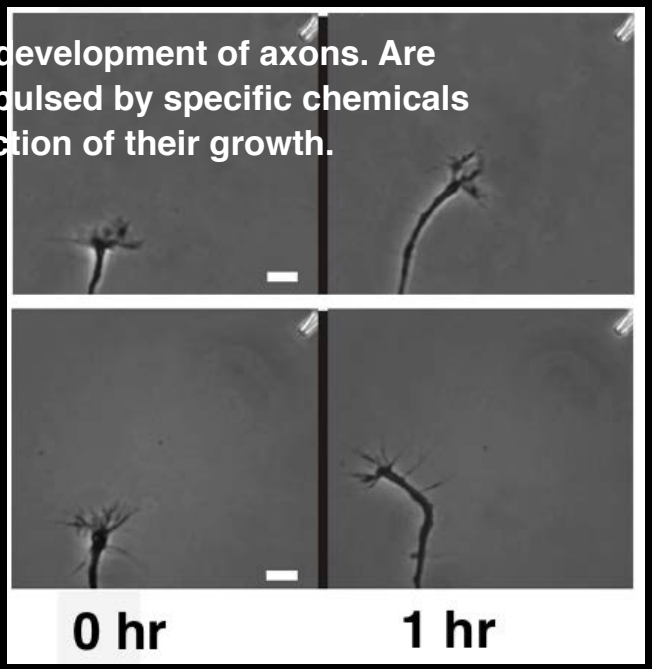
Growth cones



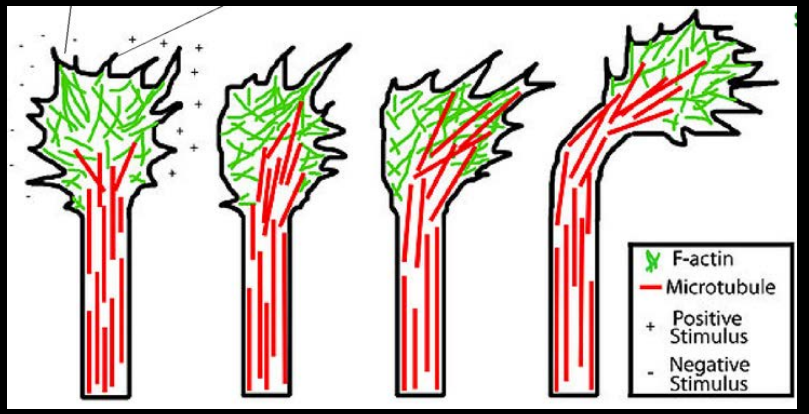


Lab of Paul Forscher

Guide growth and development of axons. Are attracted to and repulsed by specific chemicals that guide the direction of their growth.

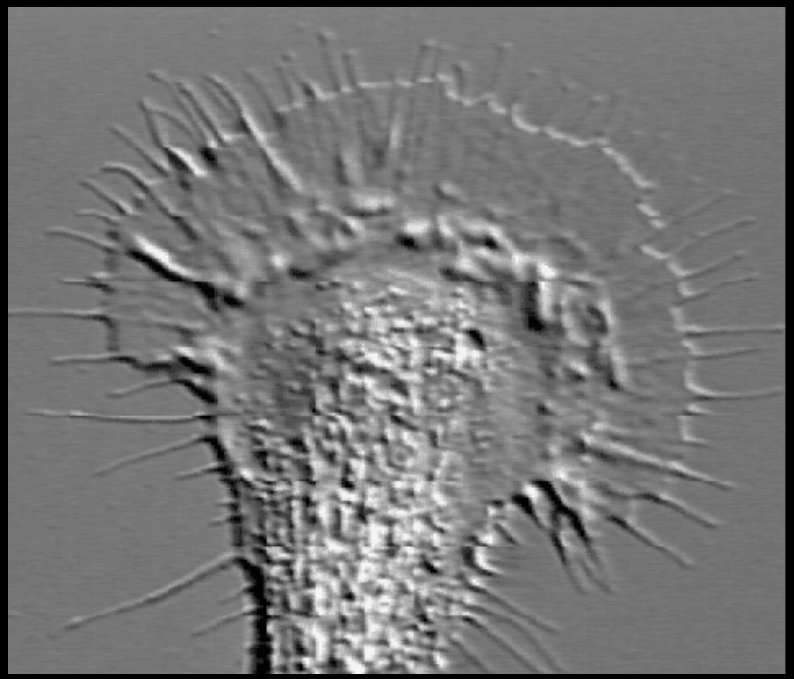


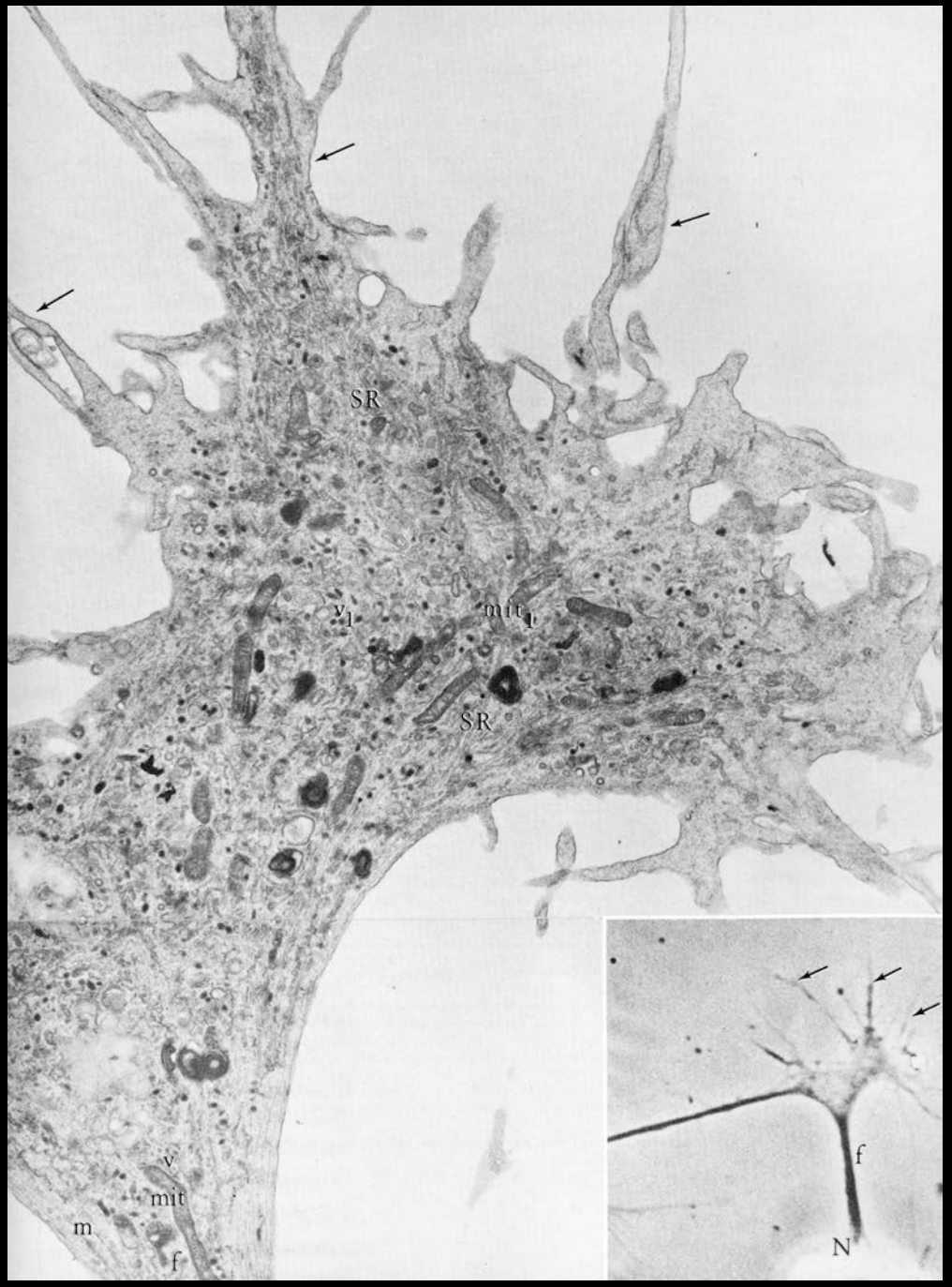
attraction/repulsion



Elke Stein

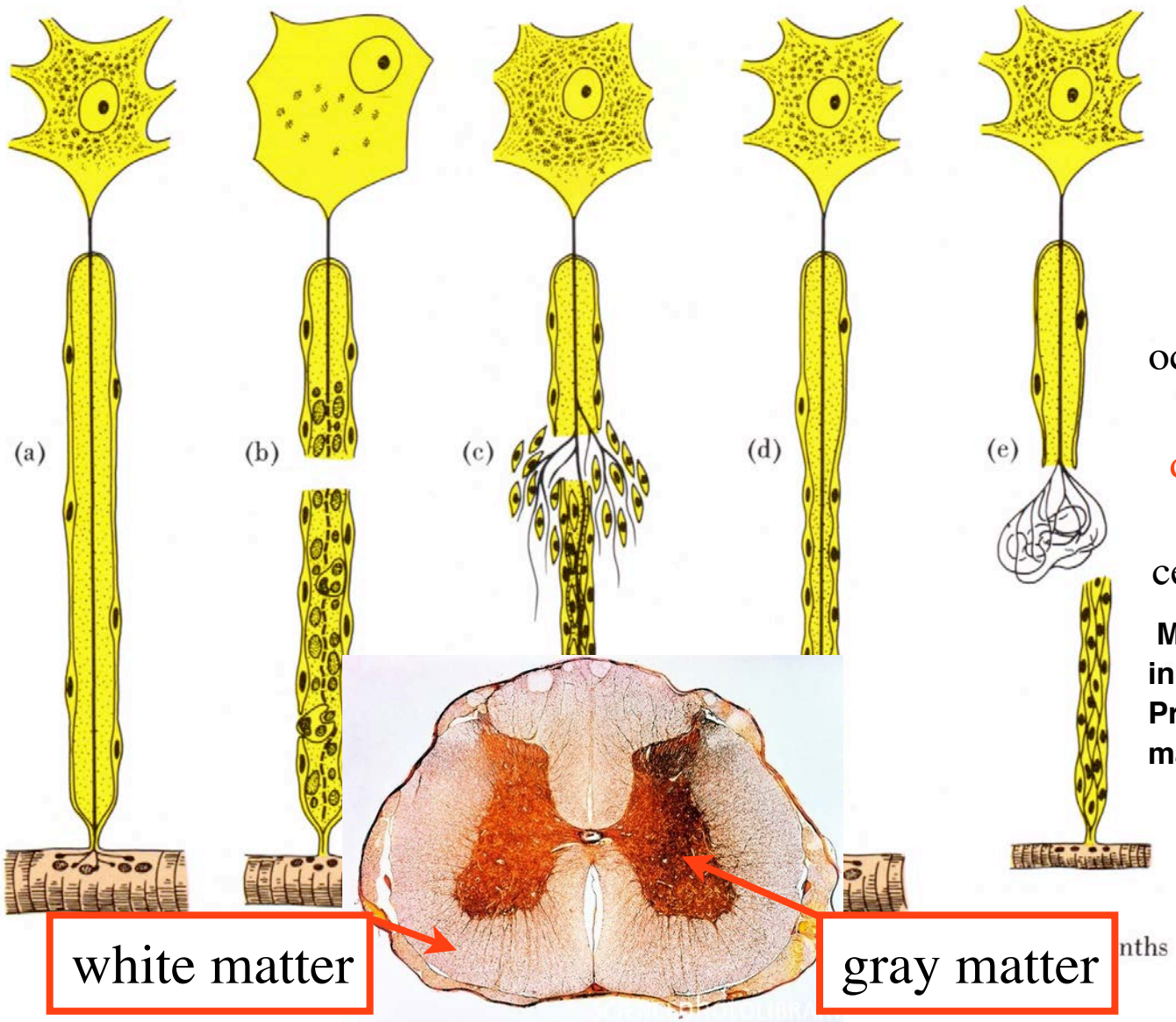
Growth Cone





Lab of Paul Forscher, Yale

Axonal Degeneration and Regeneration

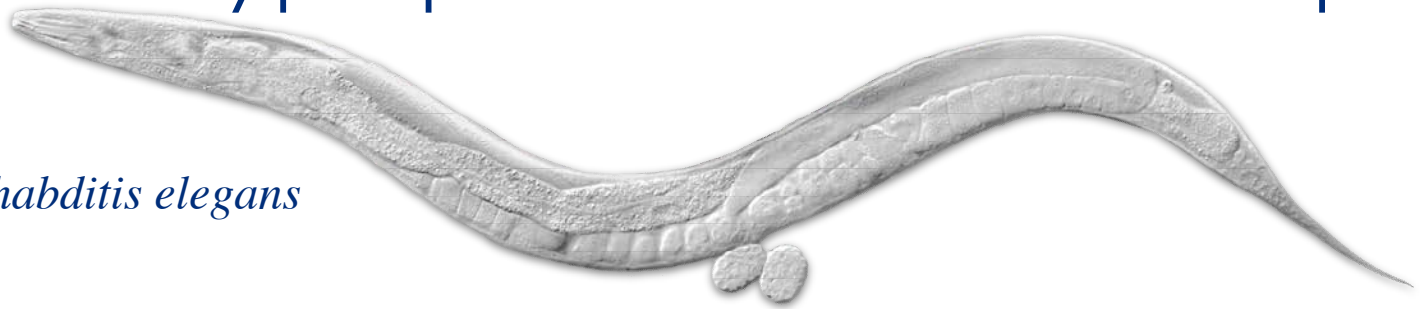


Axon regeneration occurs in the peripheral nervous system but does not occur in the white matter of the central nervous system

Myelin made by Schwann cells inhibit growth of axons in CNS. Prevents overgrowth of axons to maintain fidelity of connections.

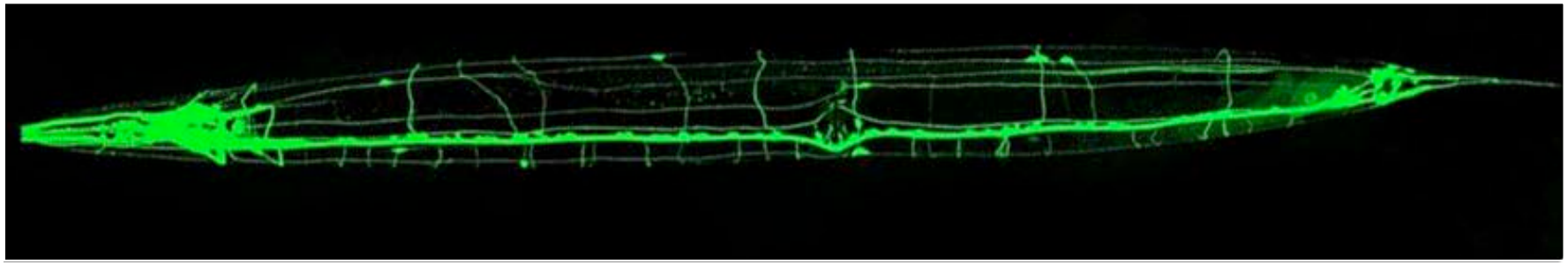
Model organisms

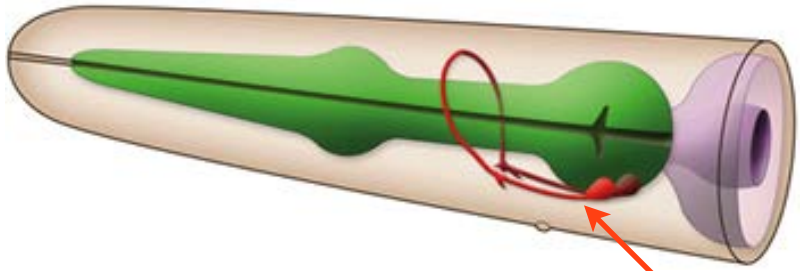
tools to study principles in neurons and circuits development

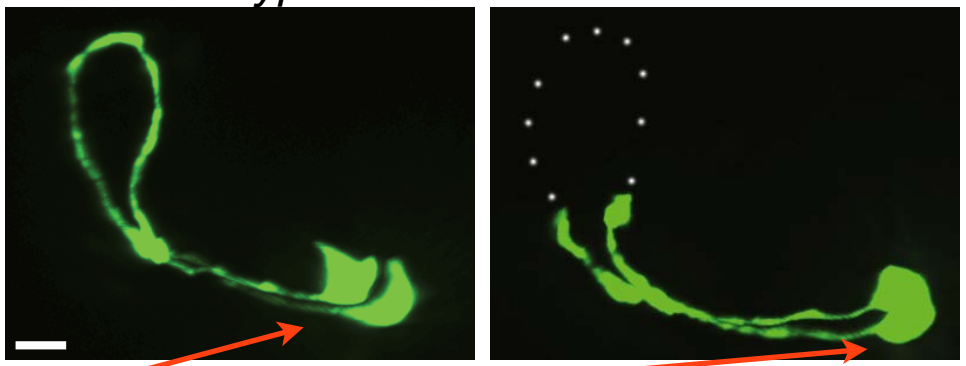


Caenorhabditis elegans

302 neurons (instead of billions as in the human brain)



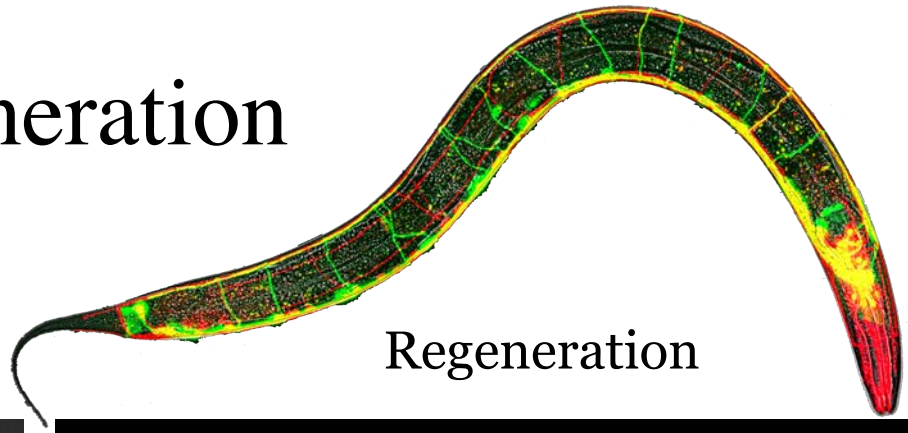




AIY neurons

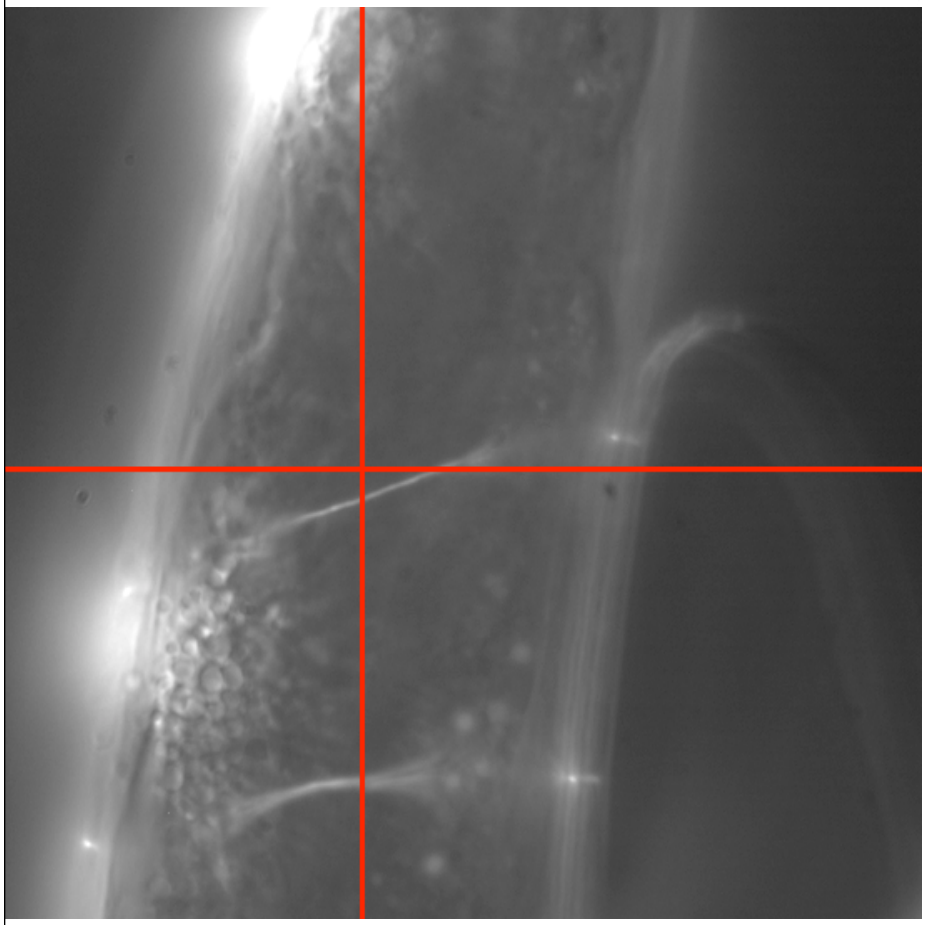
Colon Ramos lab

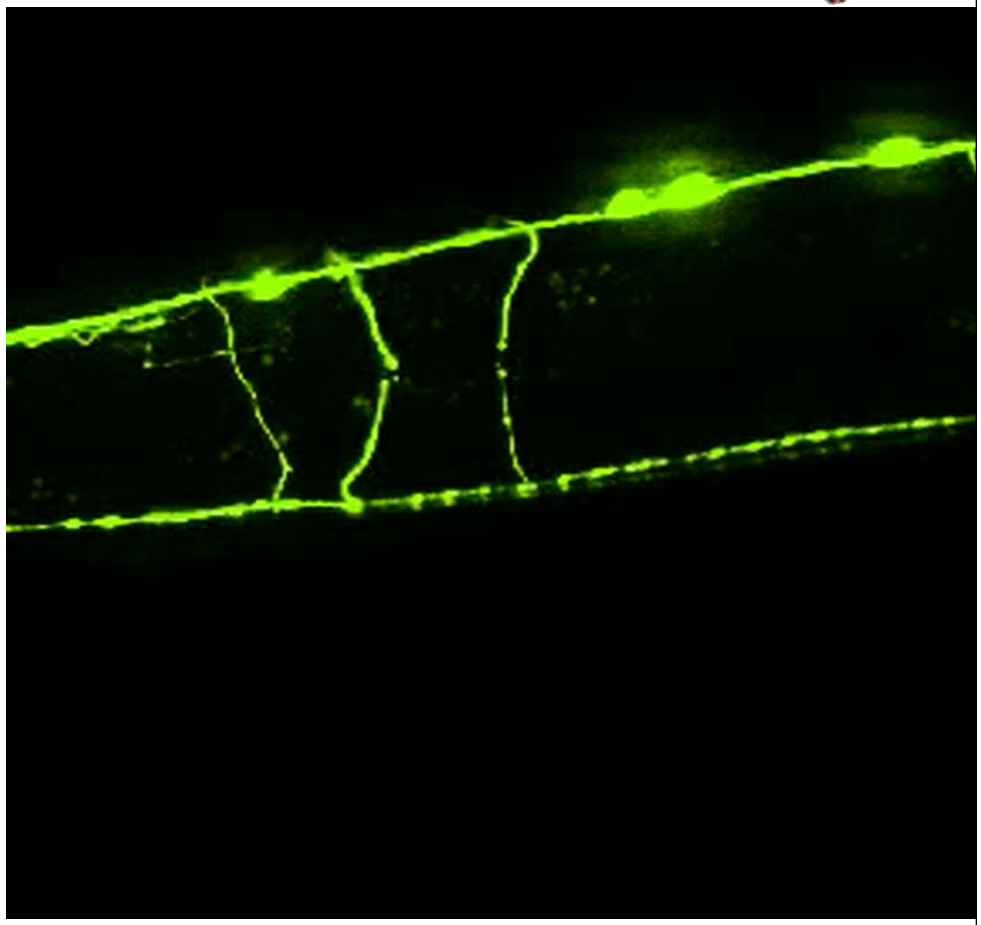
Axonal Regeneration



Axotomy

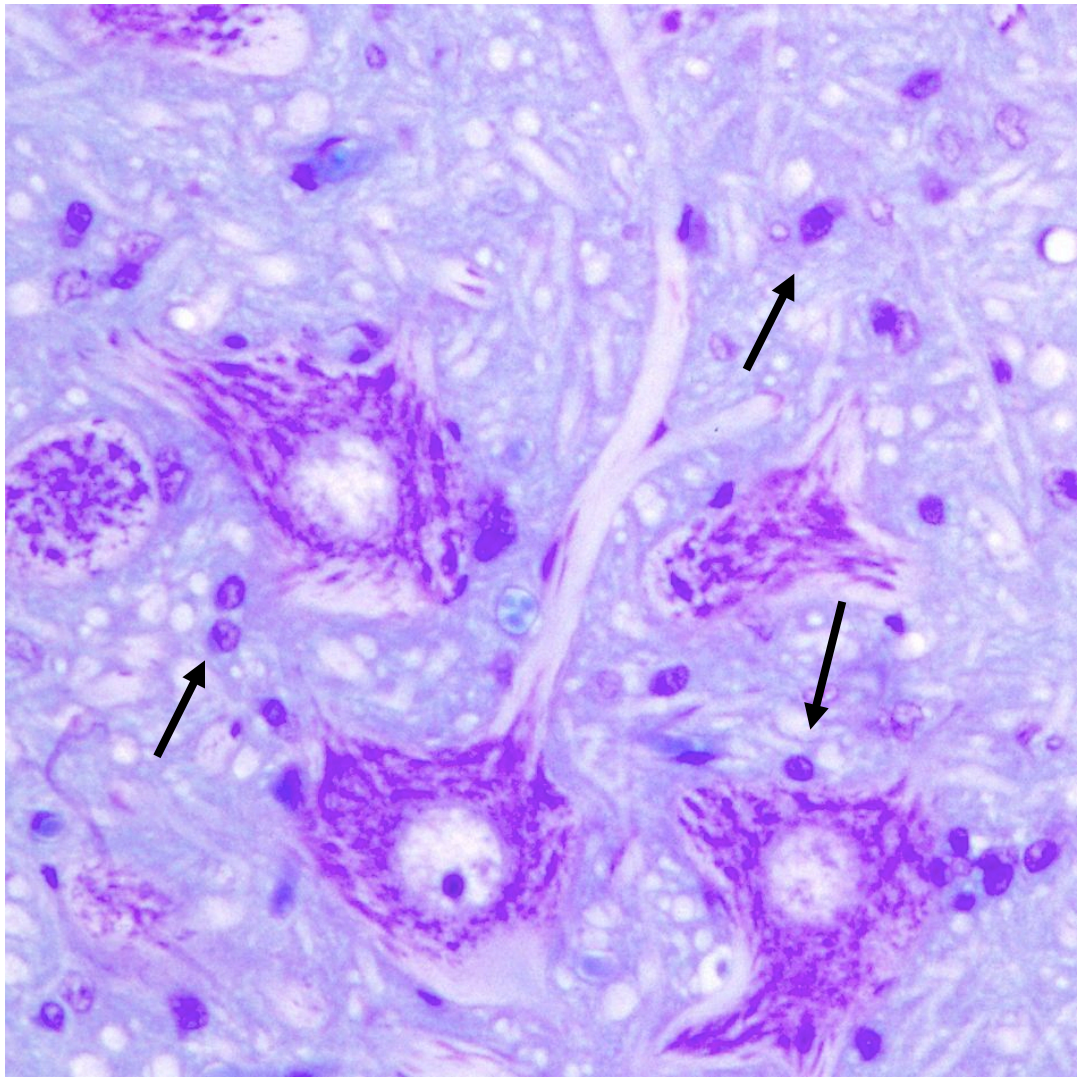
Regeneration



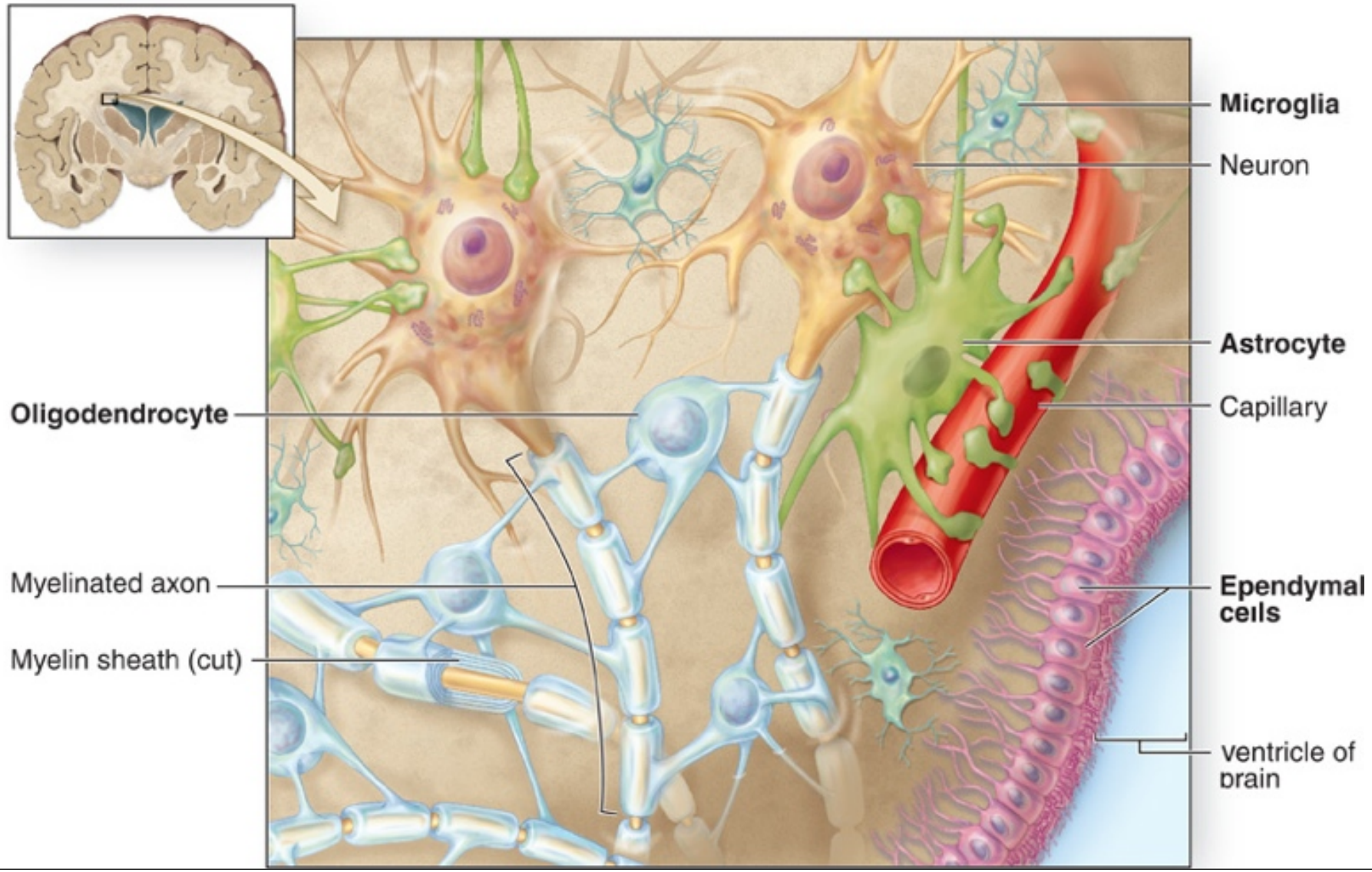


Lab of Marc Hammarlund, Yale CNNR

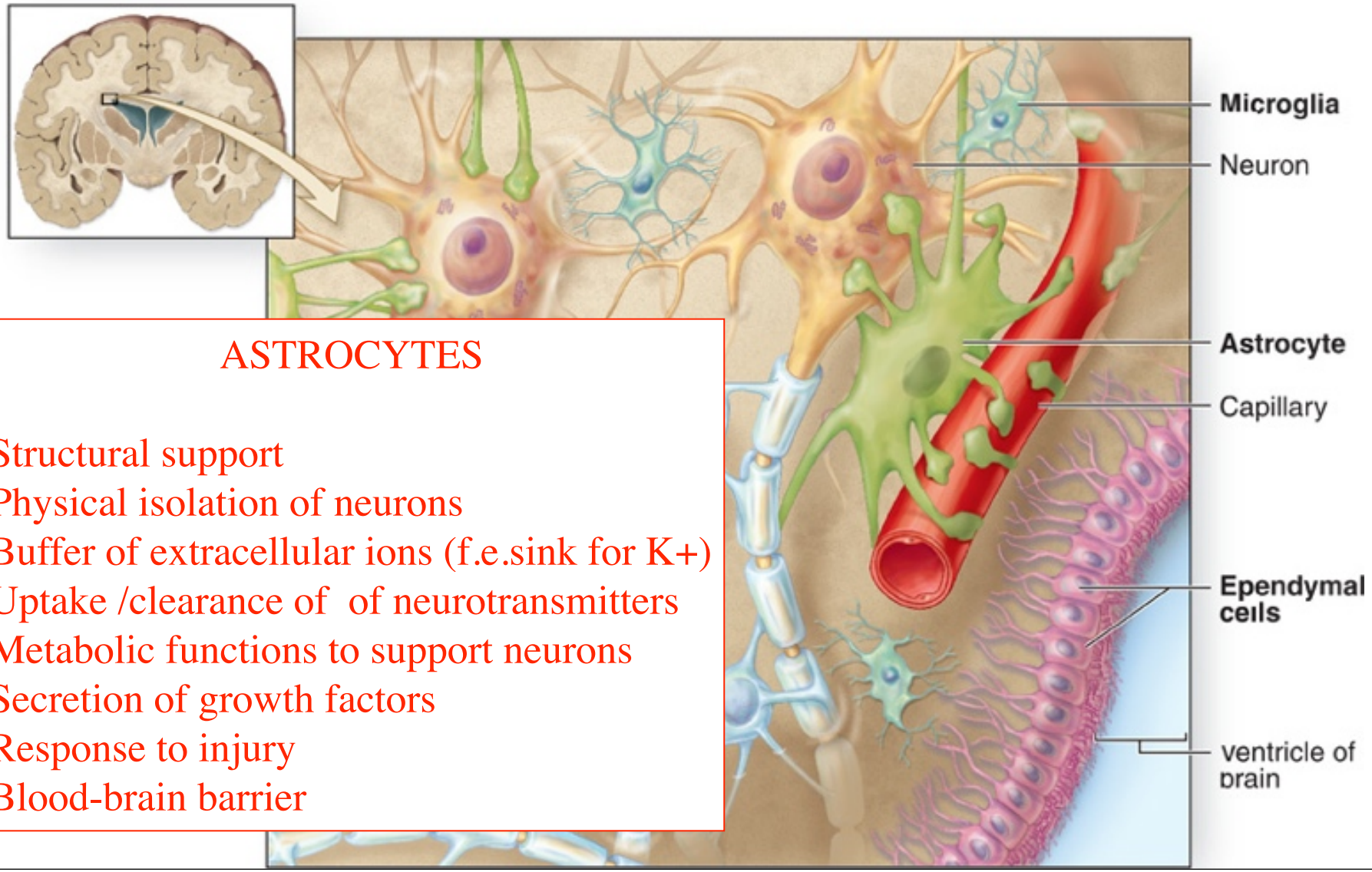
Glial cells



Glial cells

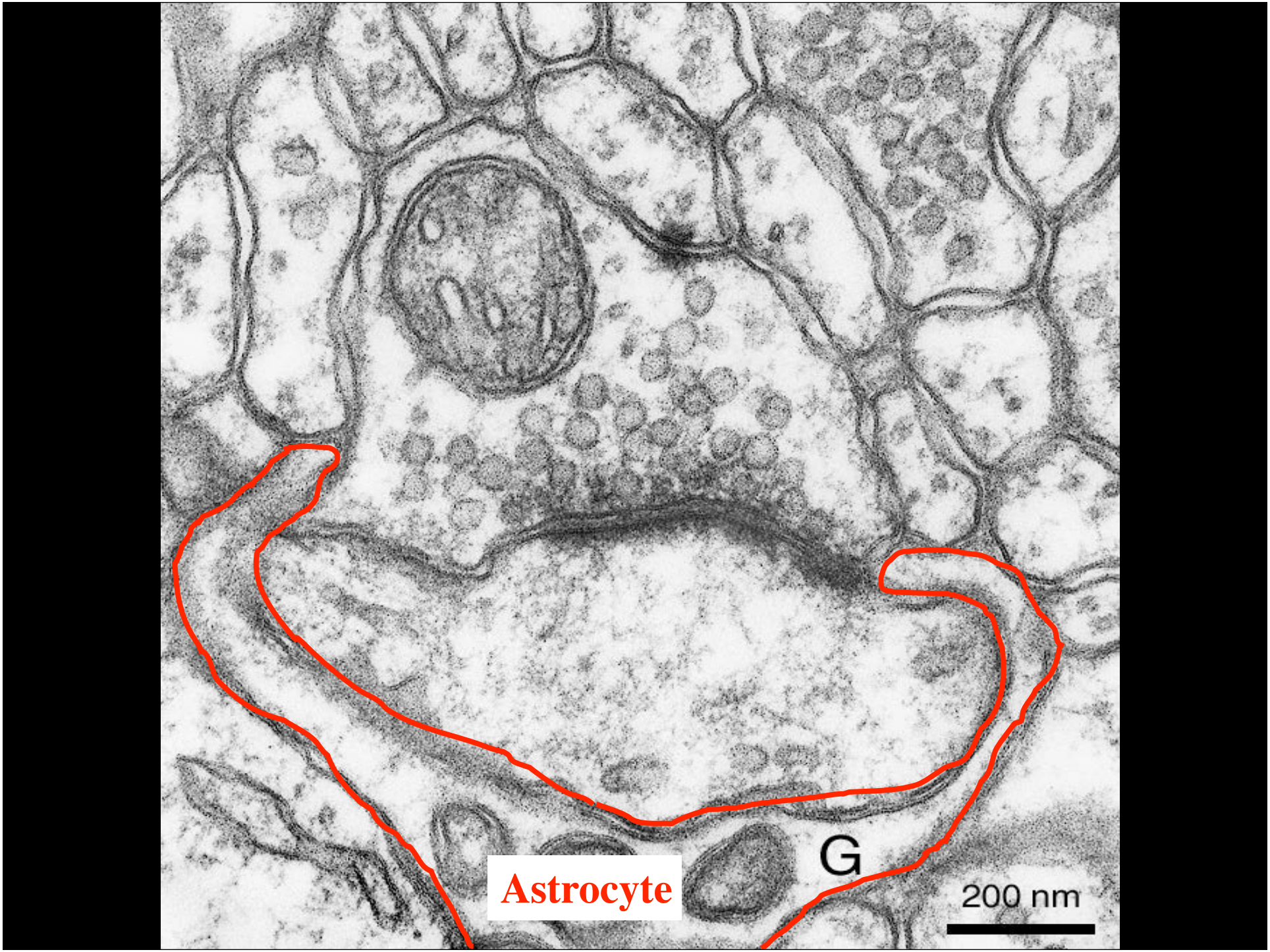


Glial cells



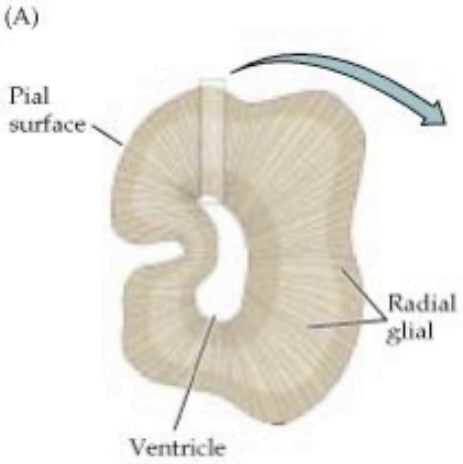
ASTROCYTES

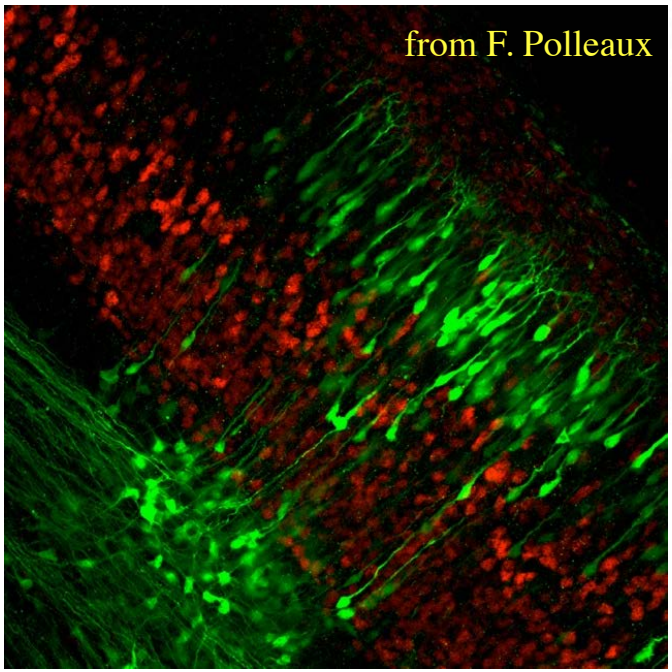
Structural support
Physical isolation of neurons
Buffer of extracellular ions (f.e.sink for K+)
Uptake /clearance of of neurotransmitters
Metabolic functions to support neurons
Secretion of growth factors
Response to injury
Blood-brain barrier


Astrocyte
G
200 nm

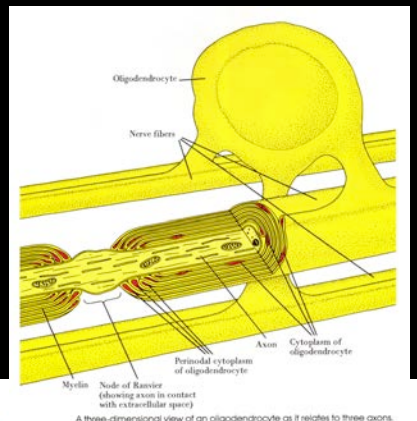
Radial glia

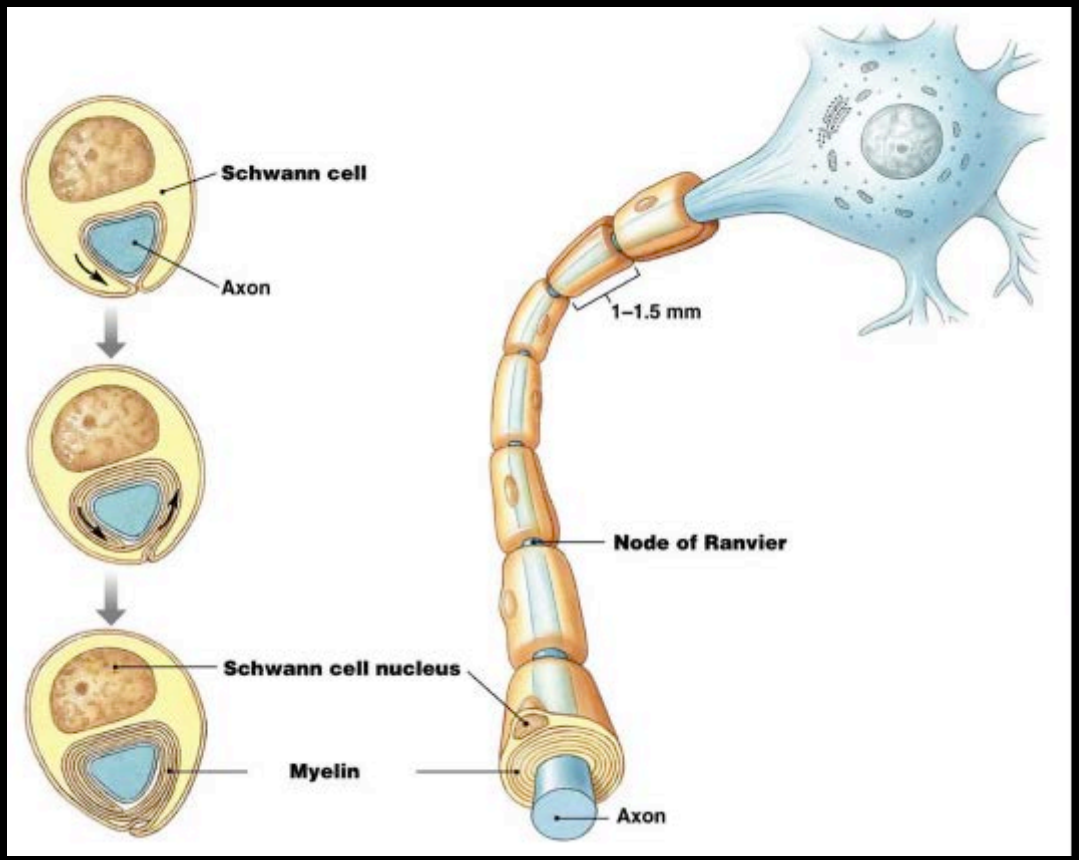
tracks for neuronal migration during brain development

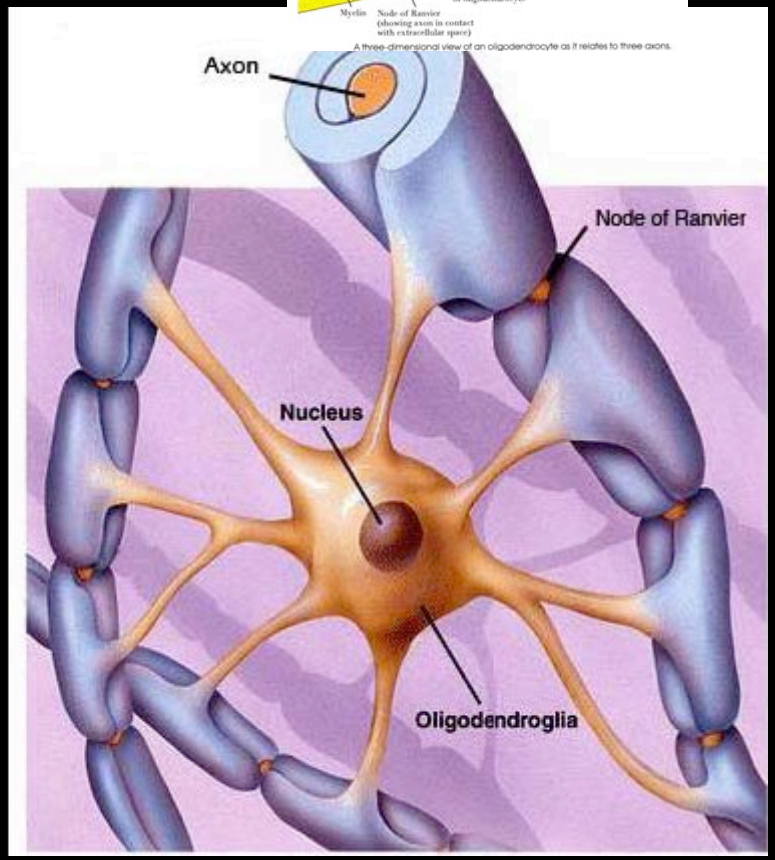




Myelin generating cells:
Oligodendrocytes (CNS)
& Schwann cells (PNS)





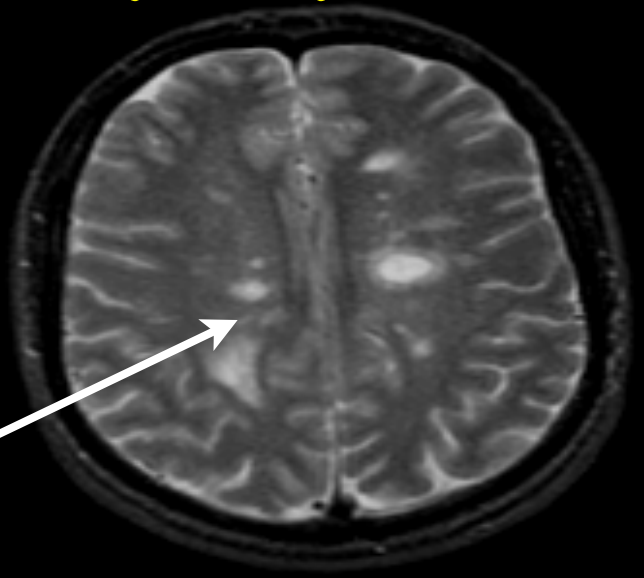


Schwann cells = peripheral nervous system

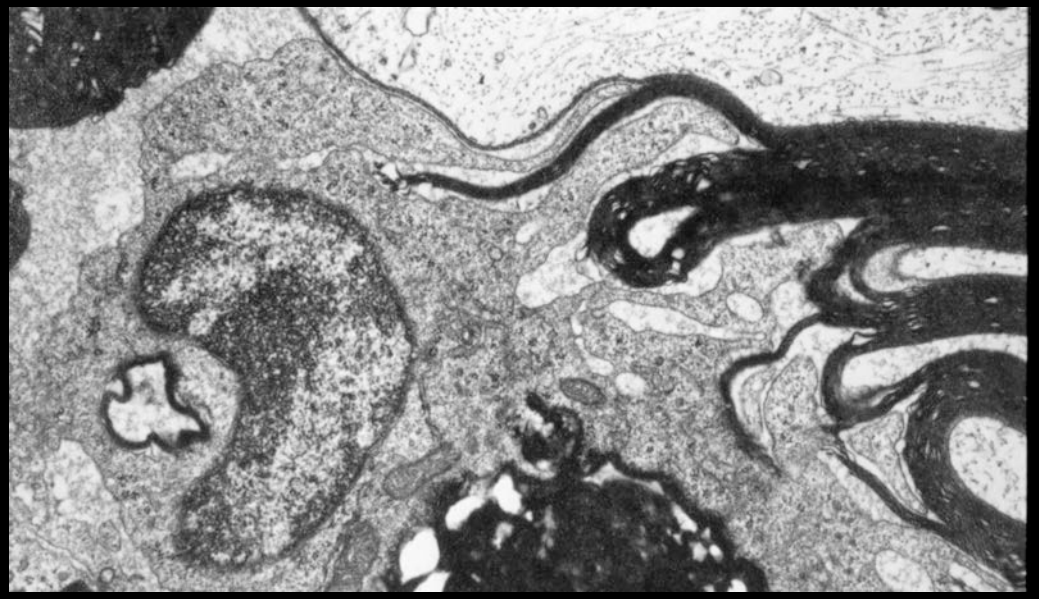
Oligodendrocytes = central nervous system

Multiple Sclerosis (MS)

1. **Inflammation**
2. **Demyelination**
3. **Impairment of nerve conduction**
4. **Neurological deficits**



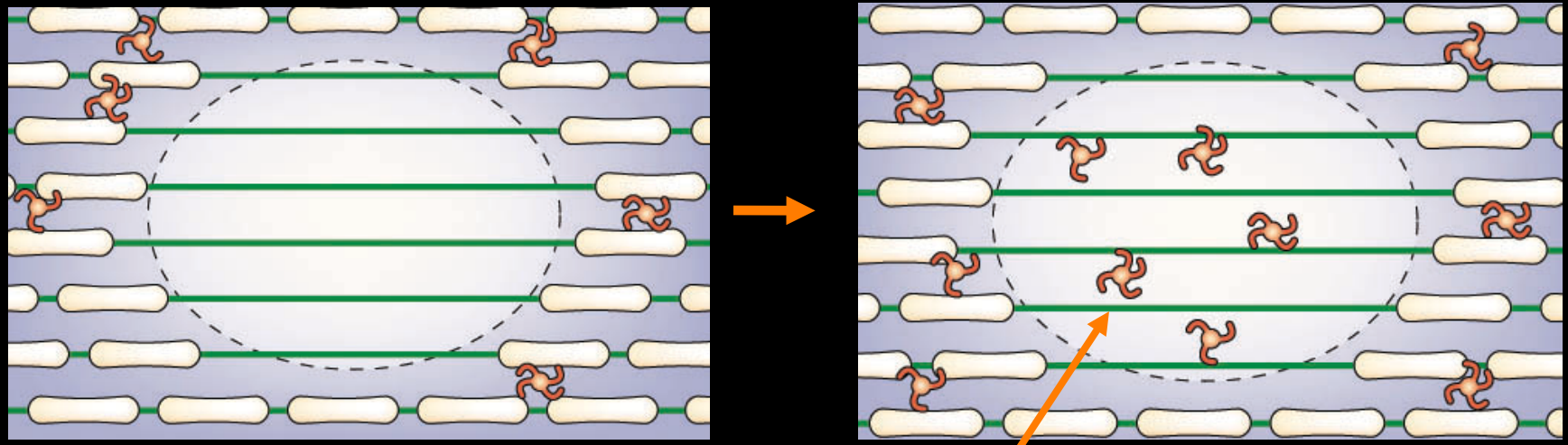
Macrophage engulfing myelin in experimental autoimmune encephalytis (EAE), a mouse model for MS



Remyelination

Acute lesion

Recruitment of OPCs

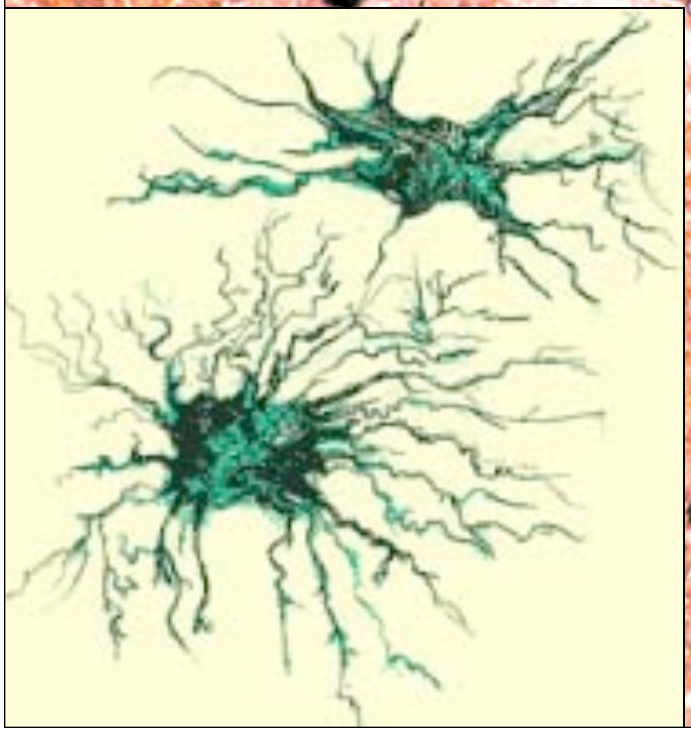


Oligodendrocyte progenitor cells (OPCs)

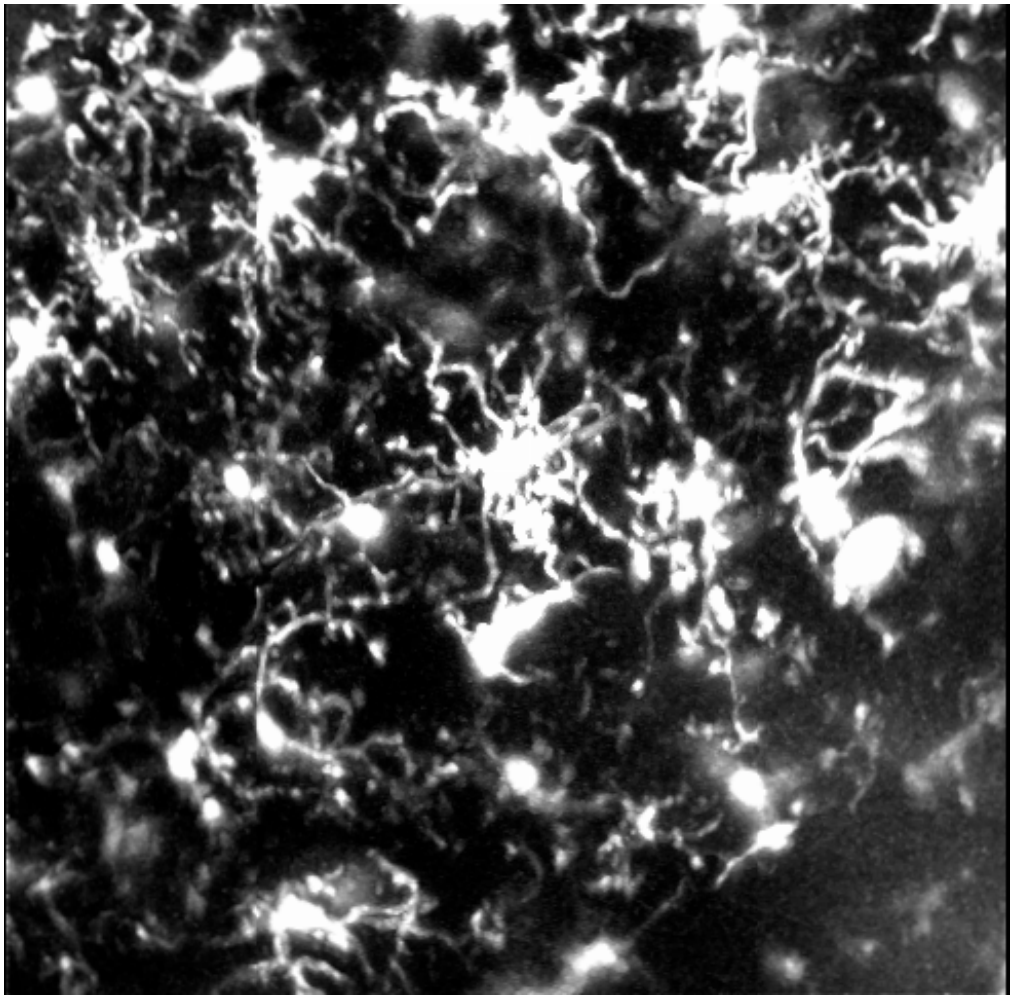
Franklin NatRevNeurosci 2002

Microglia

the macrophages of the brain

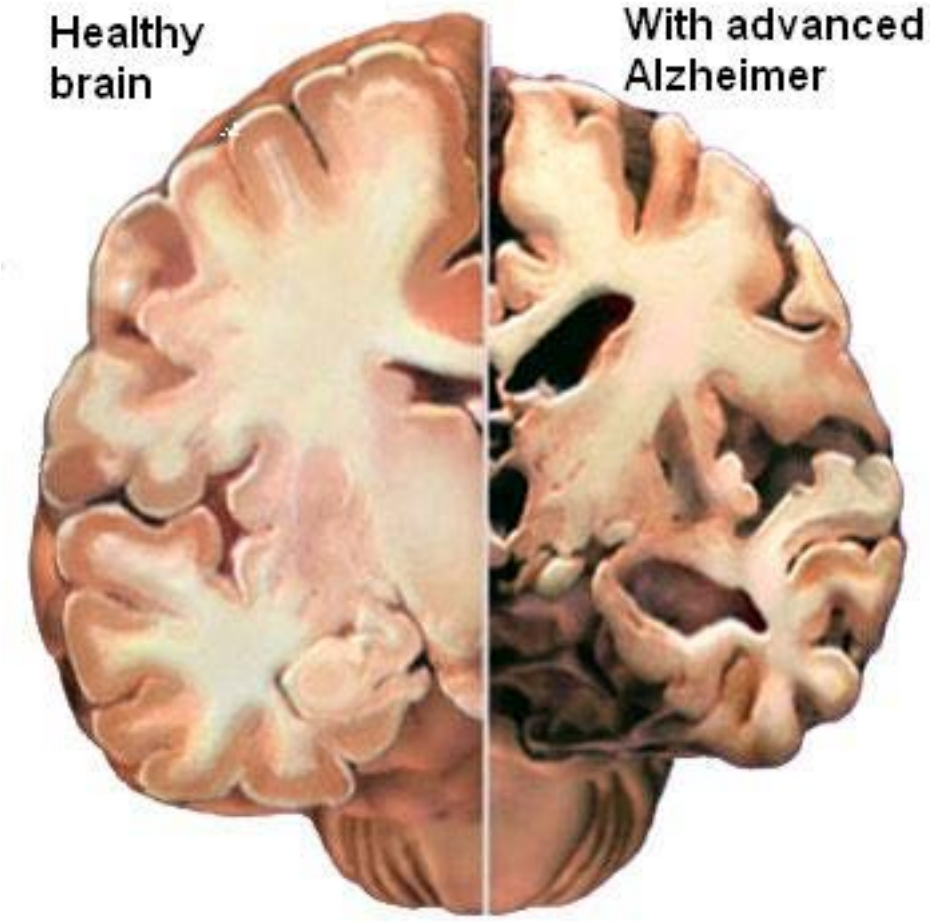


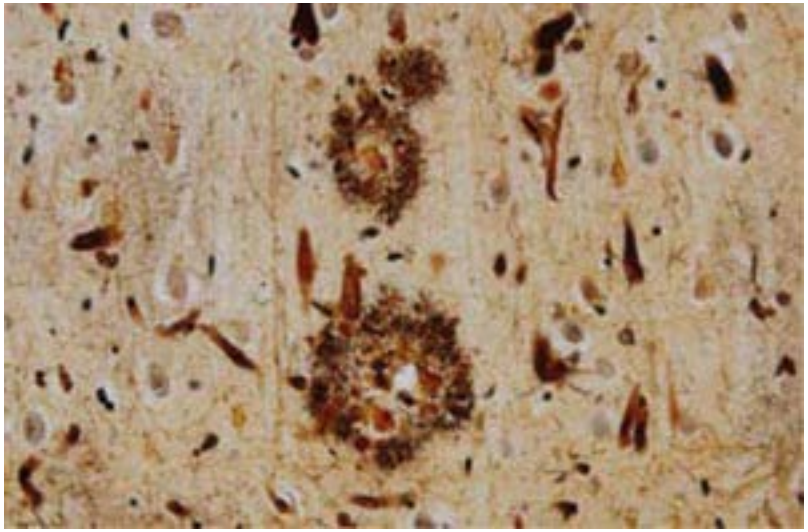
Microglia



Wenbiao Gan (NYU)

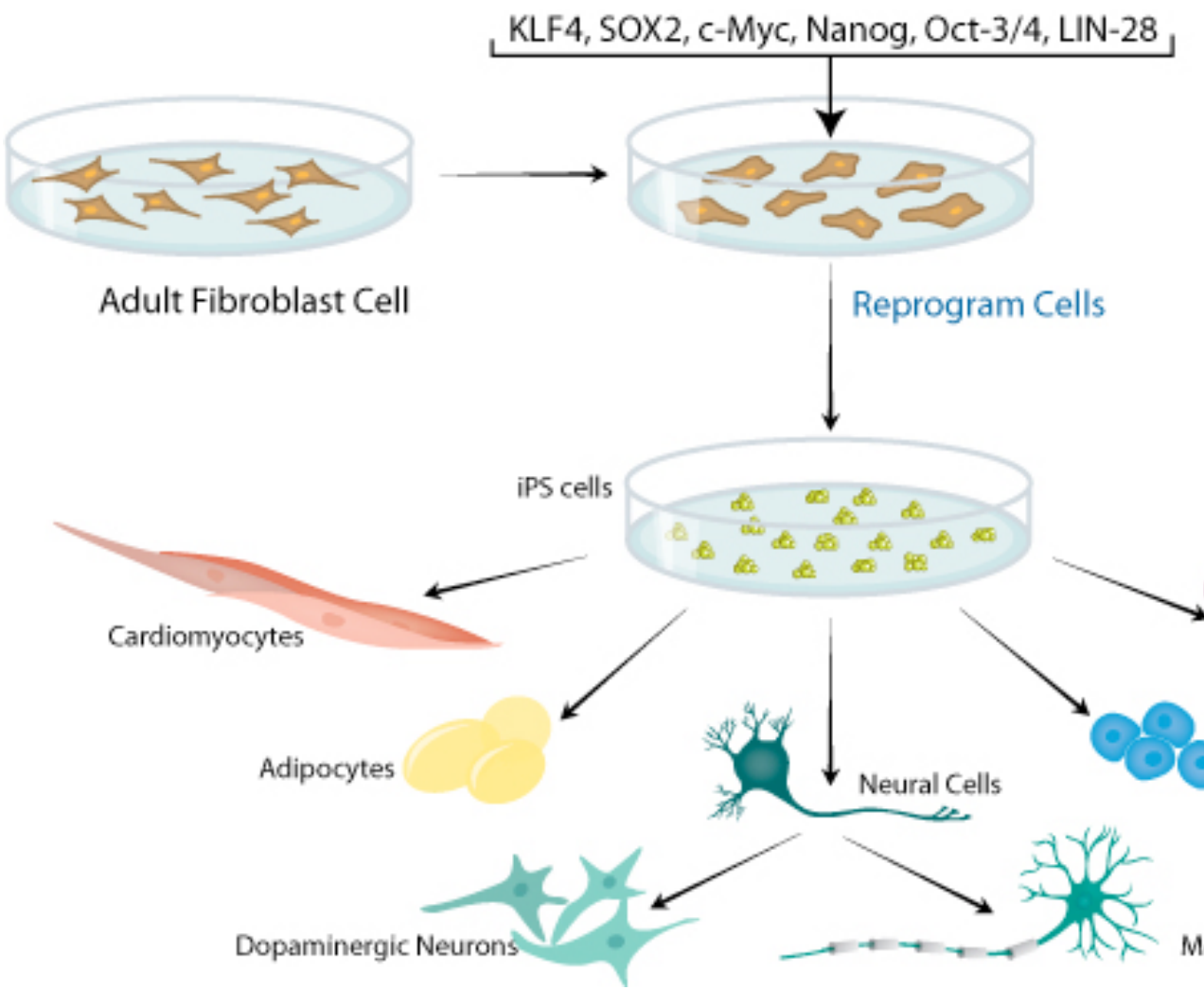
Neurodegeneration



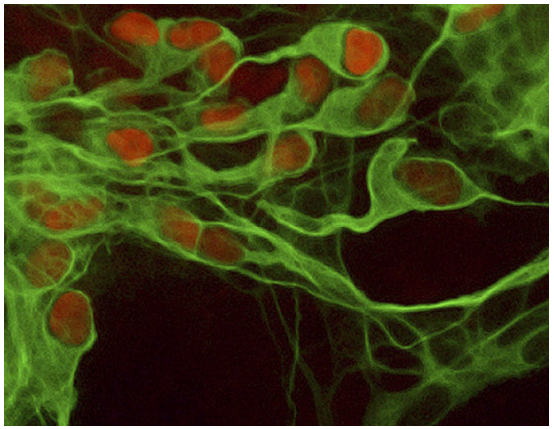


Alzheimer plaques

iPS cells



Motor neurons from patient with ALS



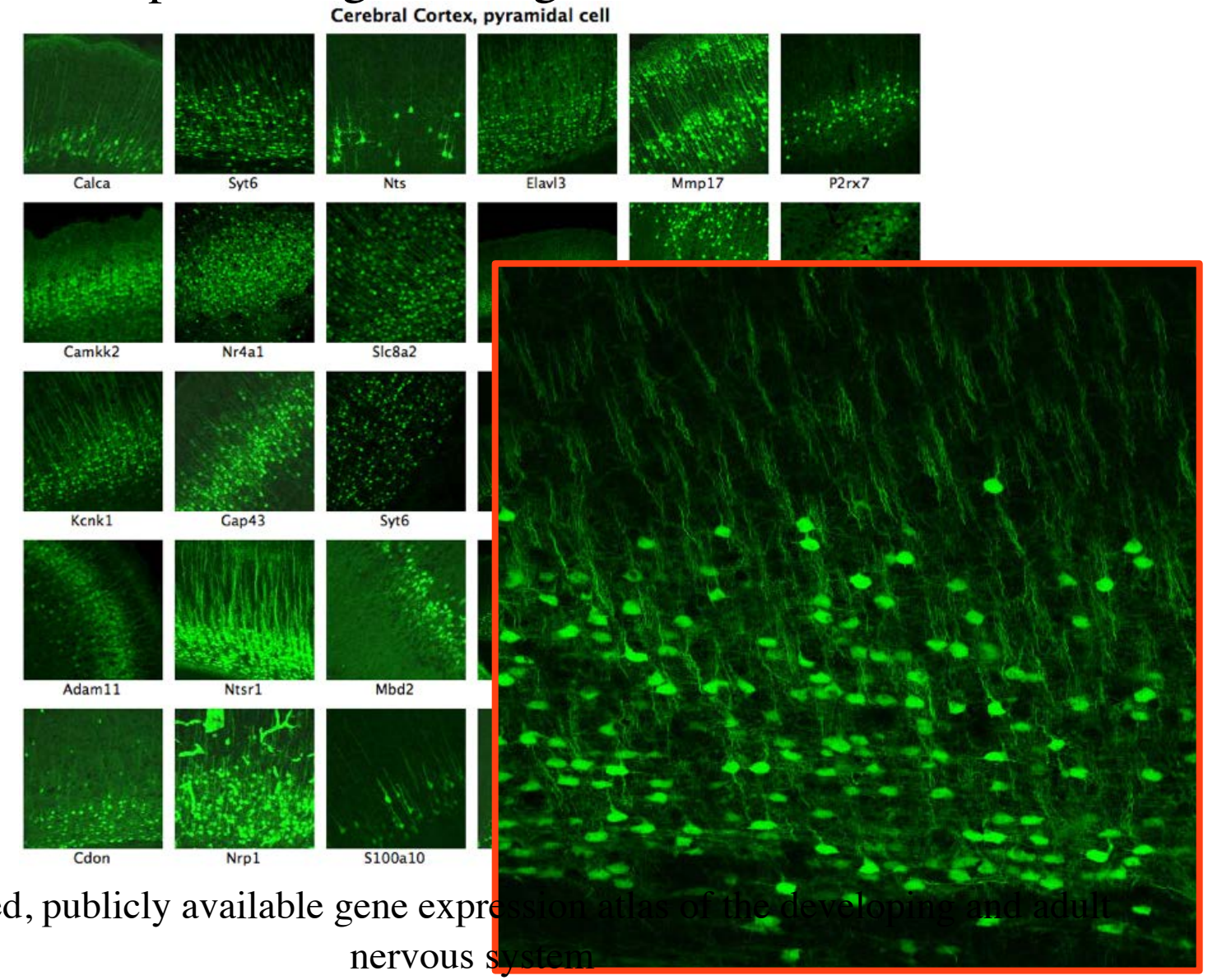
Dimos/Eggan Lab at HSCI.

John B. Gurdon, Shinya Yamanaka
2012 Physiology and Medicine Nobel Prize

Gensat project

http://www.gensat.org/index.html

different shapes and differential gene expression



NIH funded, publicly available gene expression atlas of the developing and adult nervous system