

Life Science Seen from Molecular Motor

Functions of brain and nerves, and molecular motor

2006.11.13.

Graduate School of Medicine, the University of Tokyo

Nobutaka Hirokawa

The figures, photos and moving images with ‡marks attached belong to their copyright holders. Reusing or reproducing them is prohibited unless permission is obtained directly from such copyright holders.

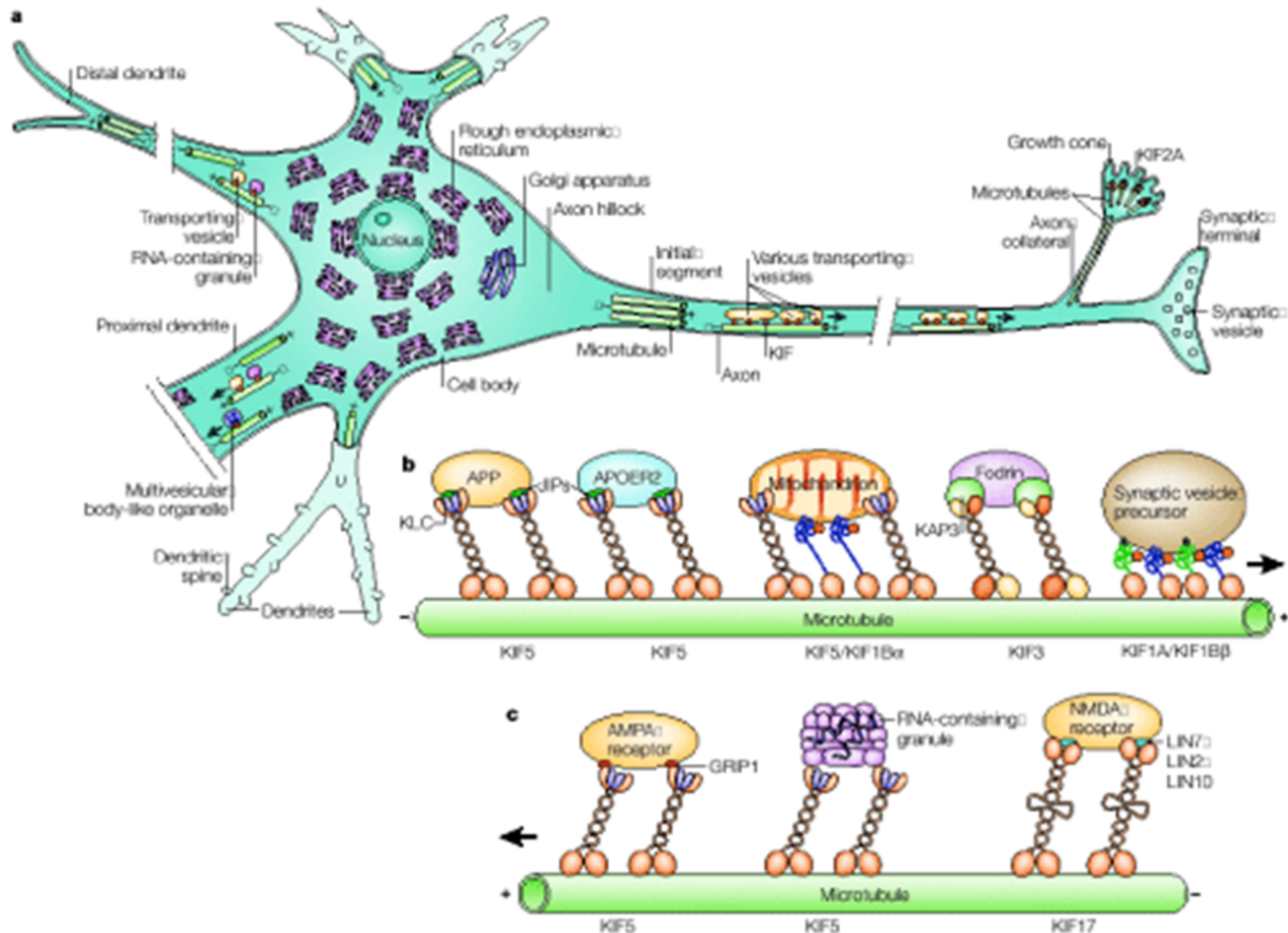
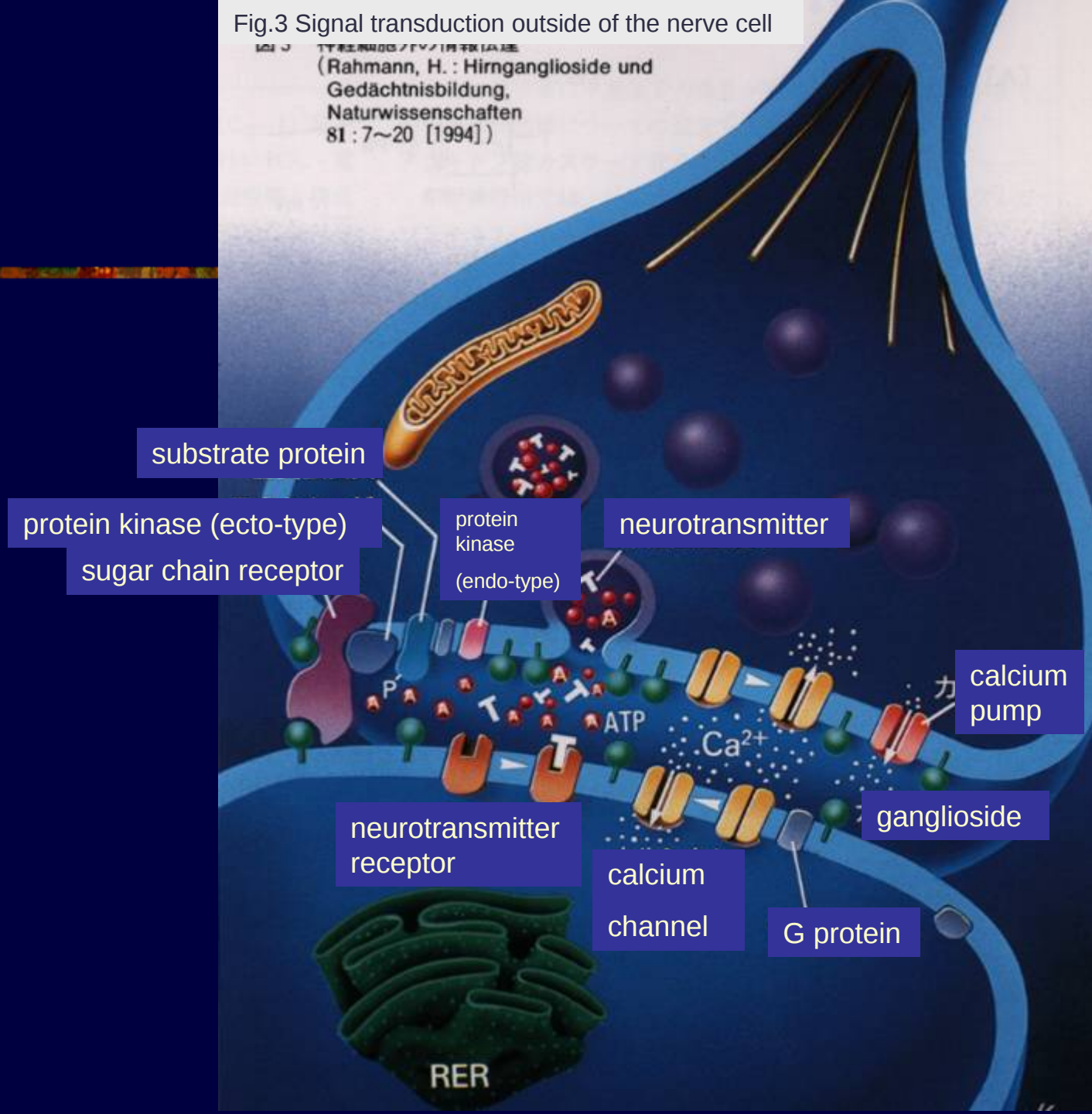
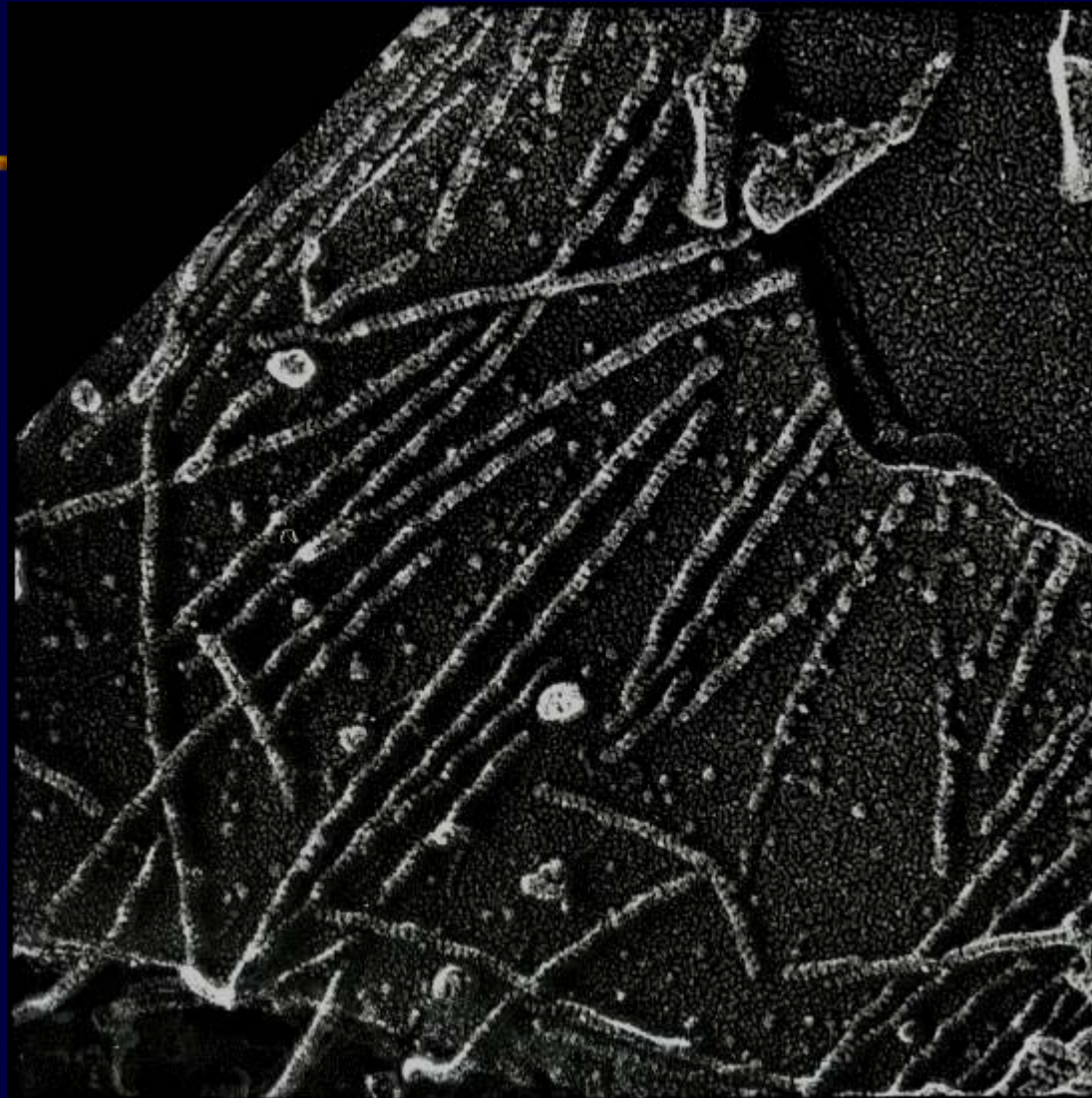


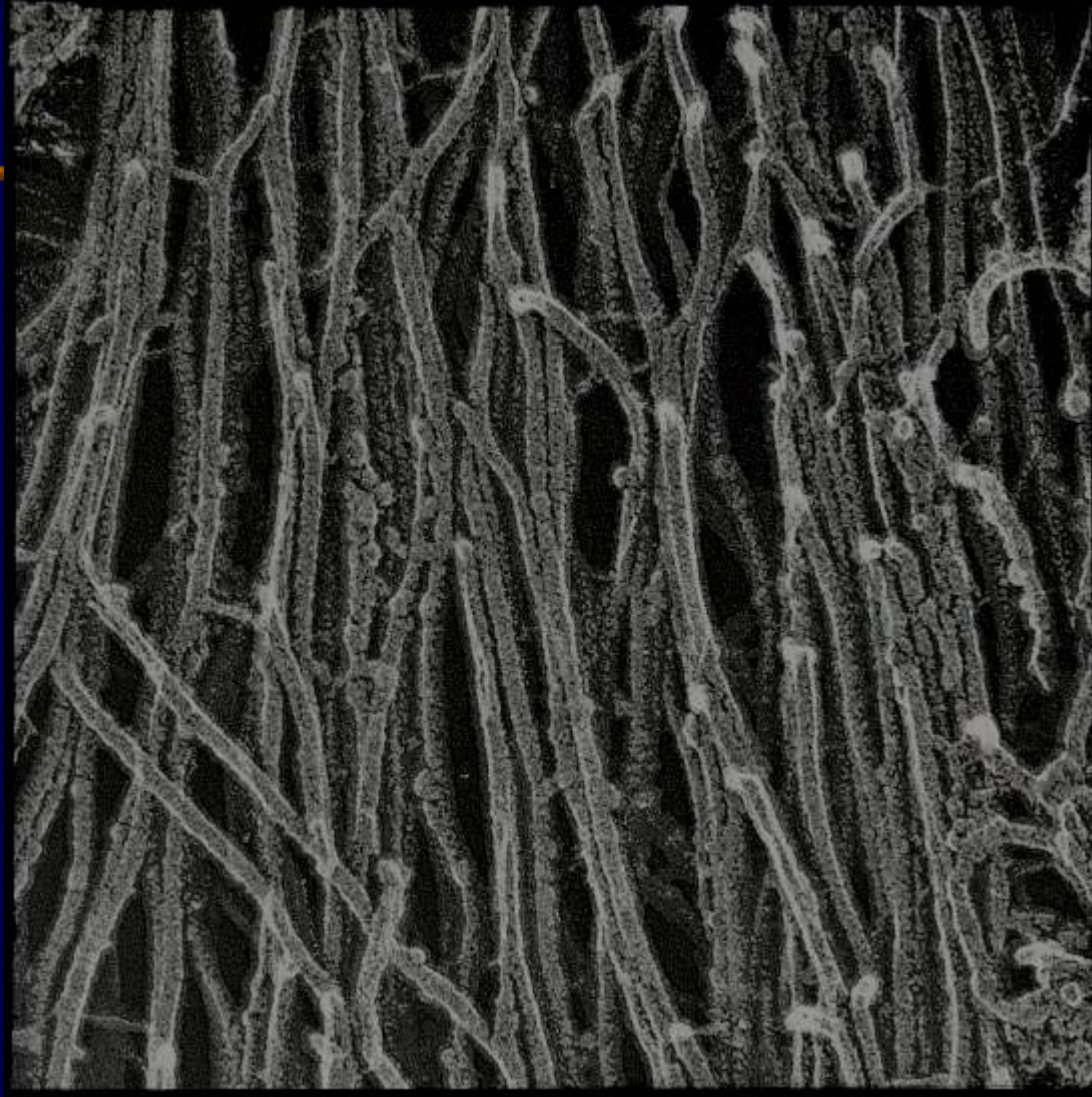
Fig.3 Signal transduction outside of the nerve cell

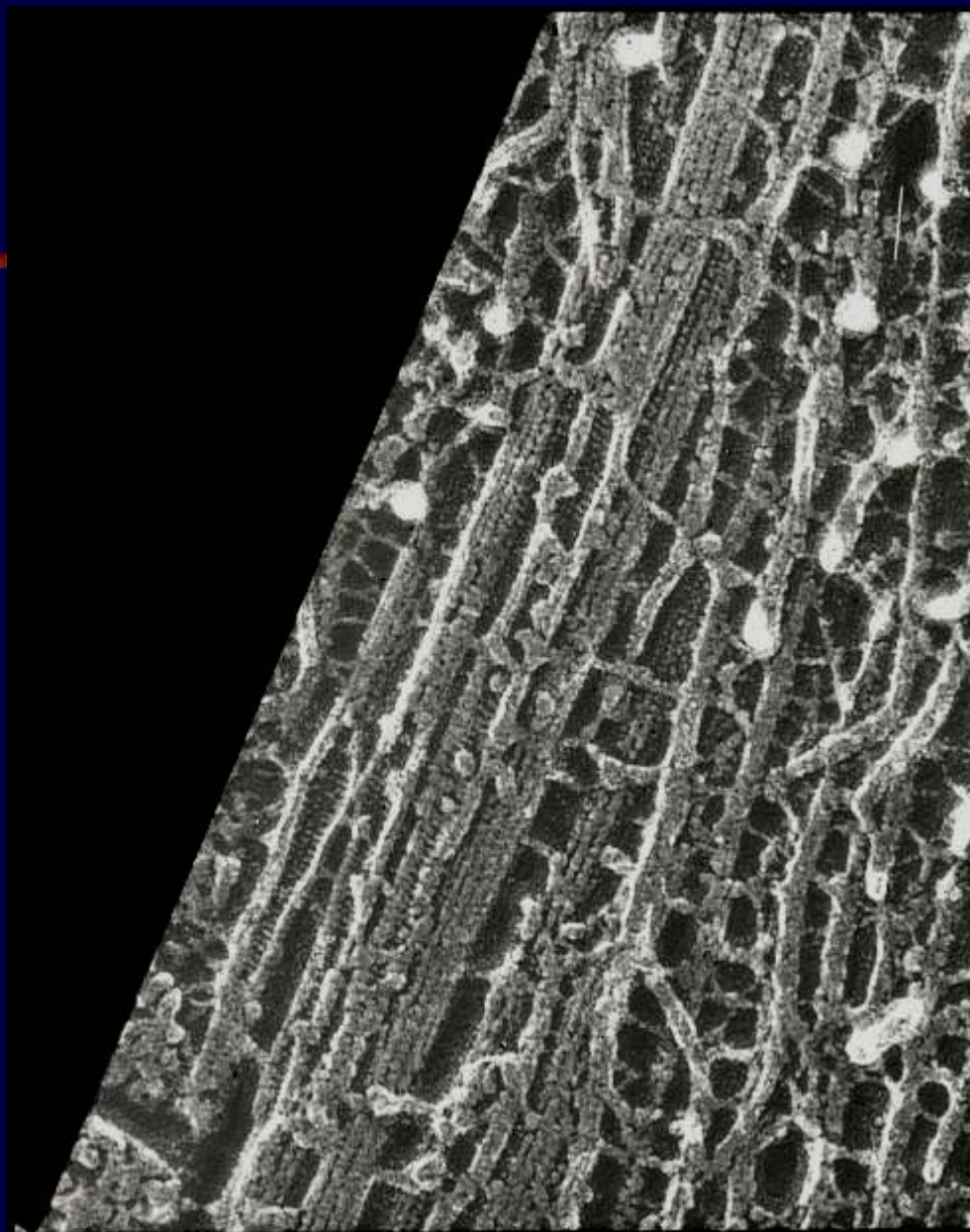
(Rahmann, H. : Hirnganglioside und
Gedächtnisbildung,
Naturwissenschaften
81 : 7~20 [1994])

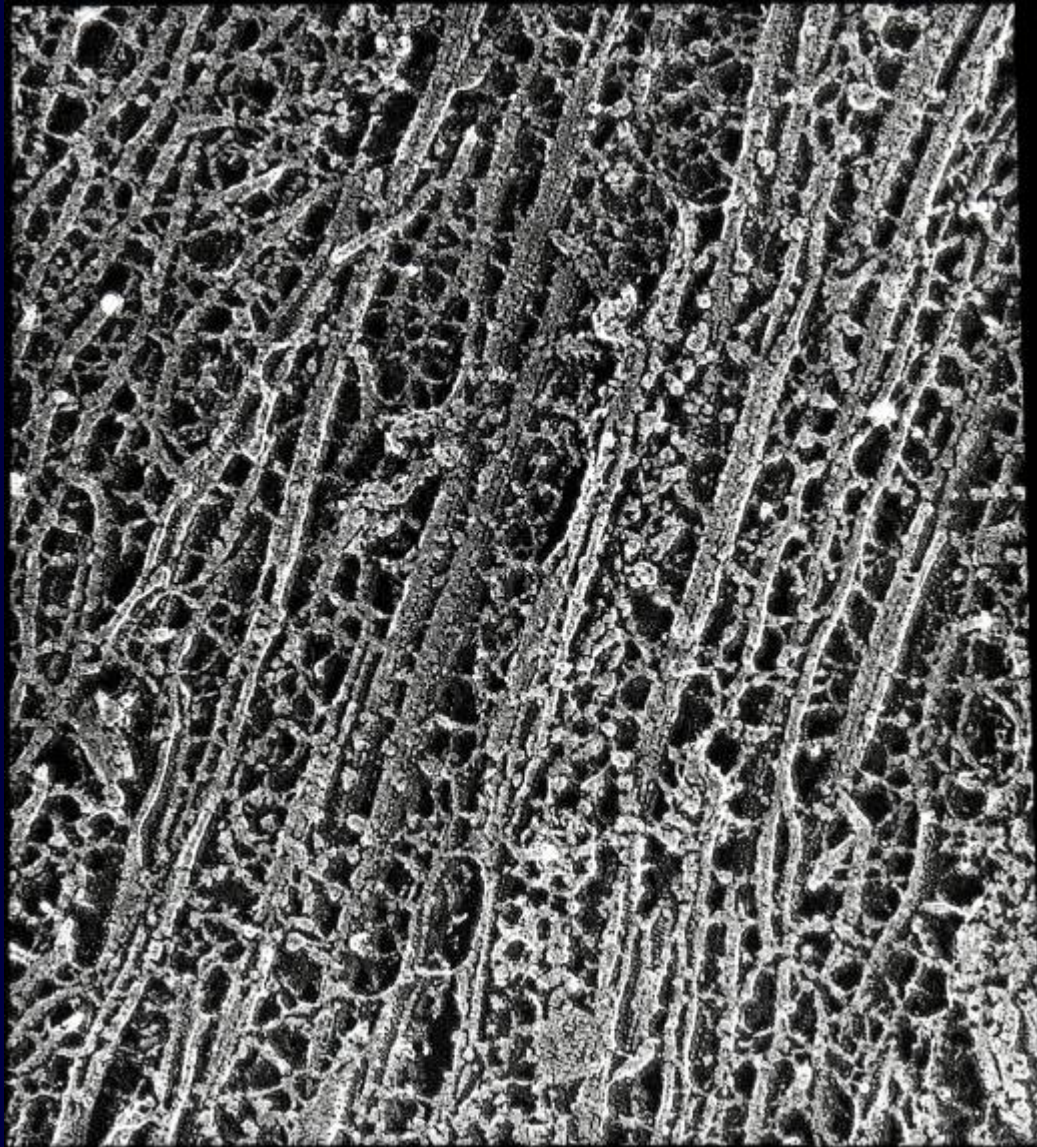


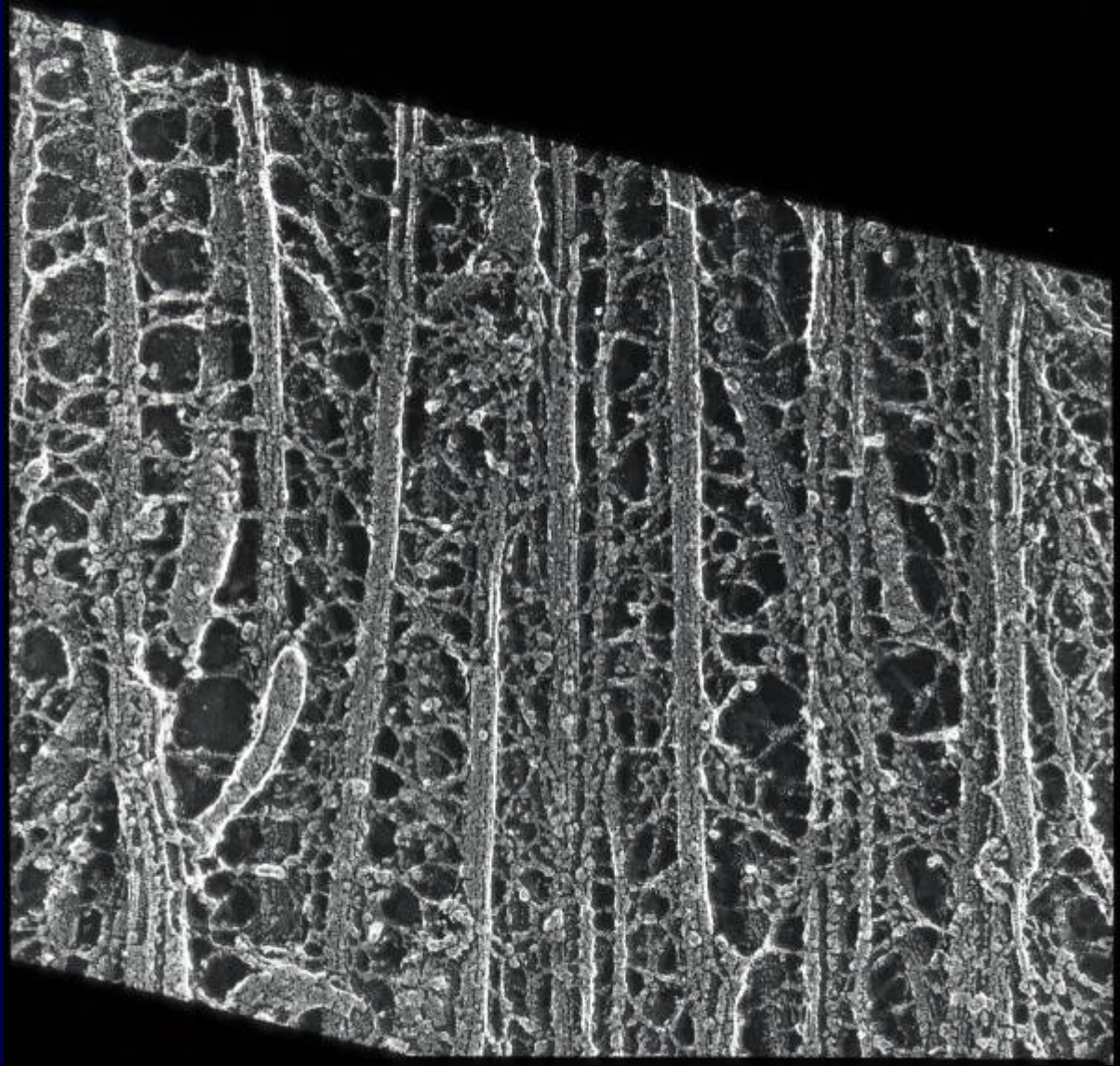
Cytoskeleton

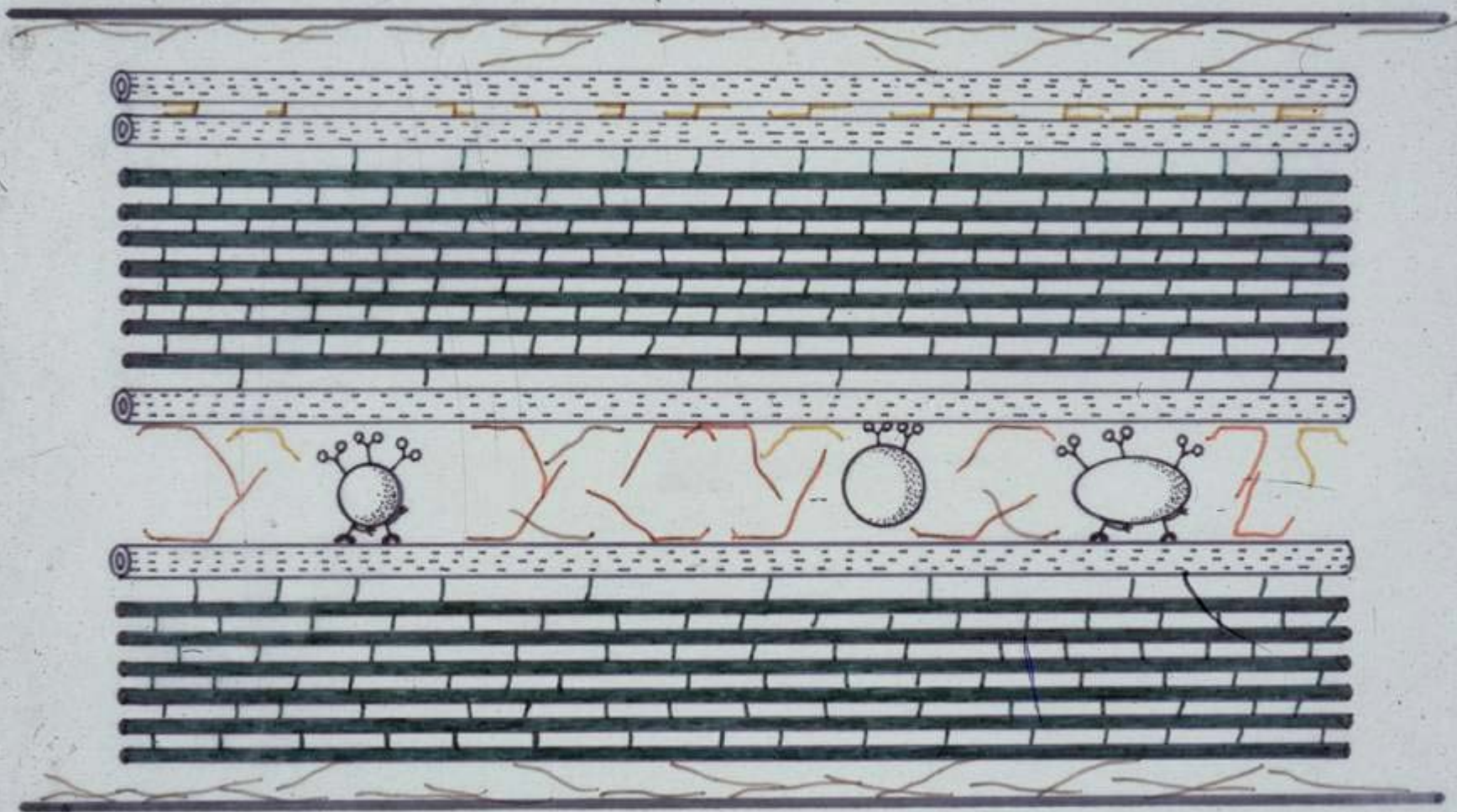




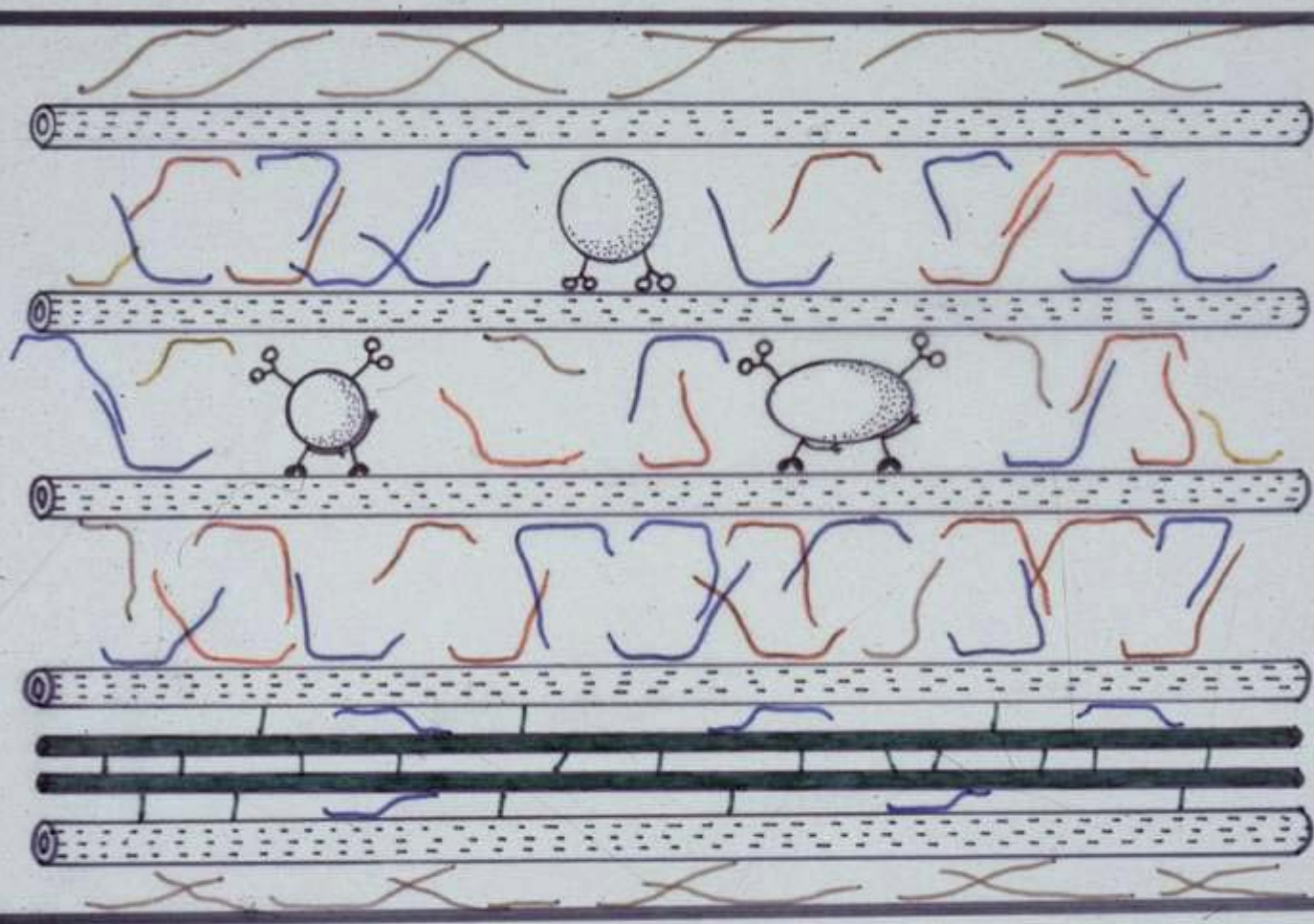








AXON



DENDRITE

Location of MAPs

Dendrite

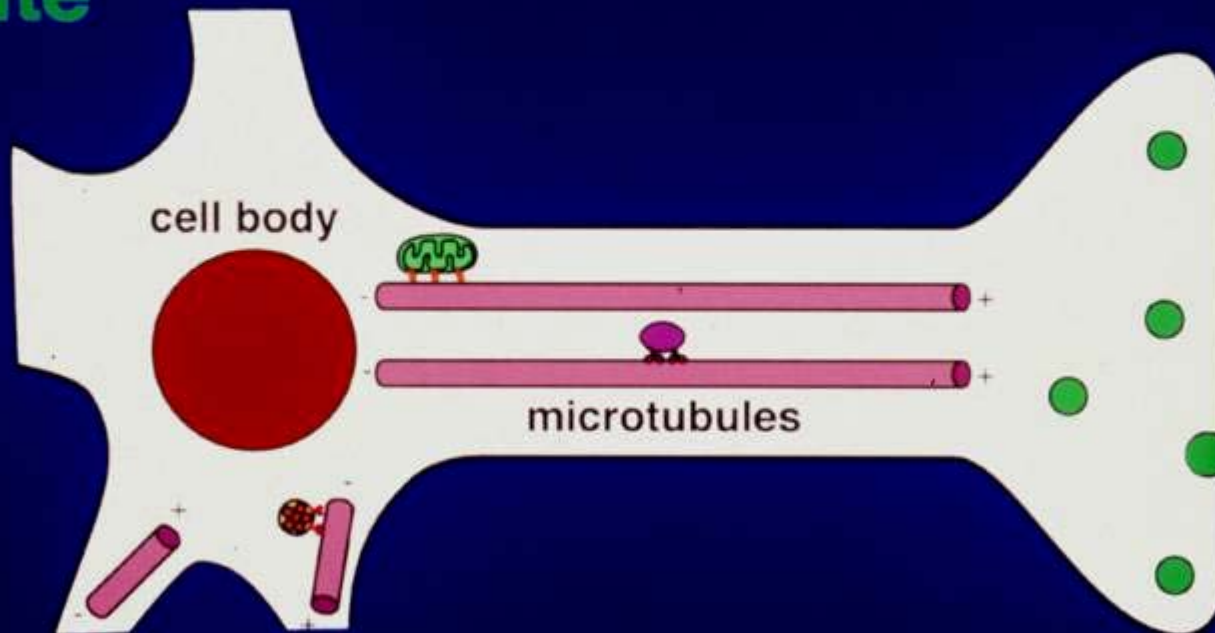
MAP1A

MAP1B

MAP2A

MAP2B

(Tau)



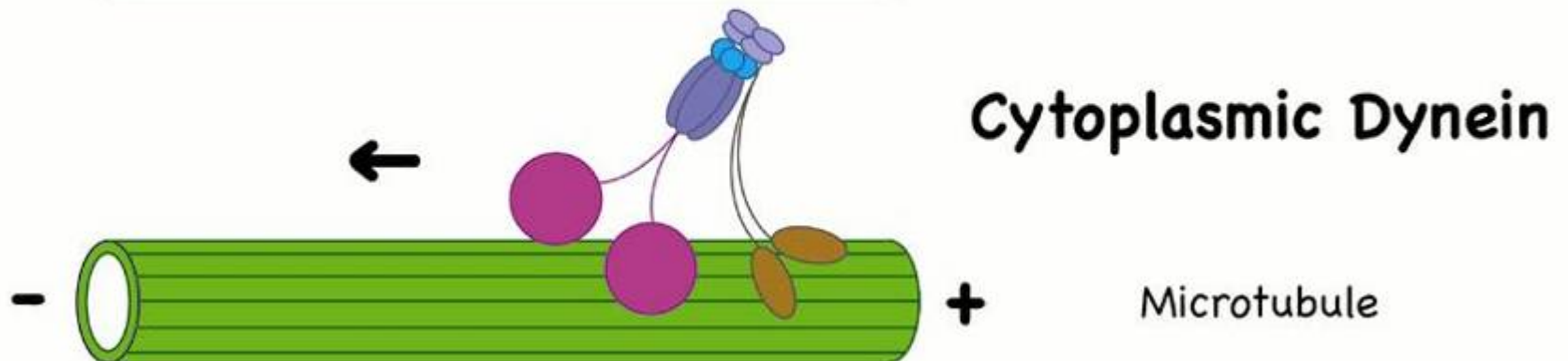
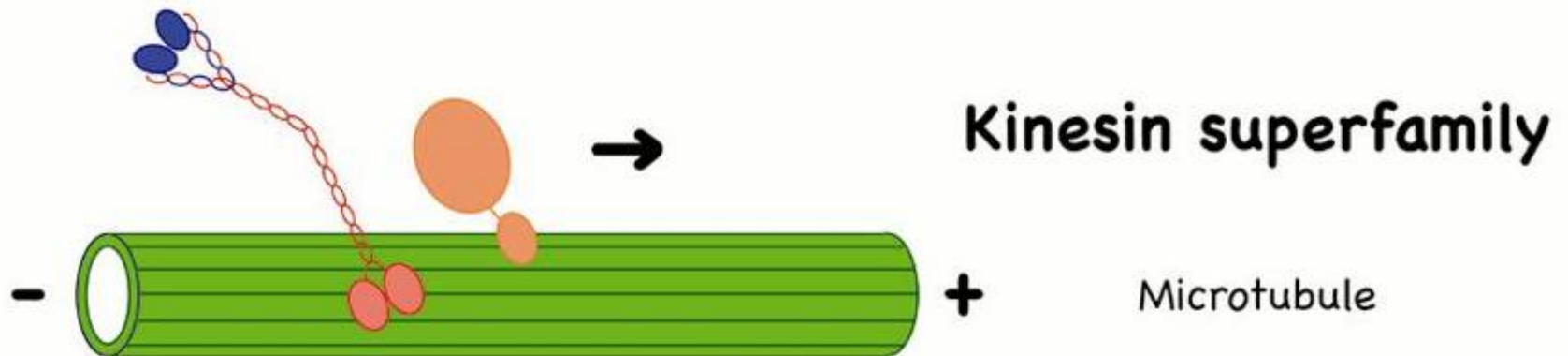
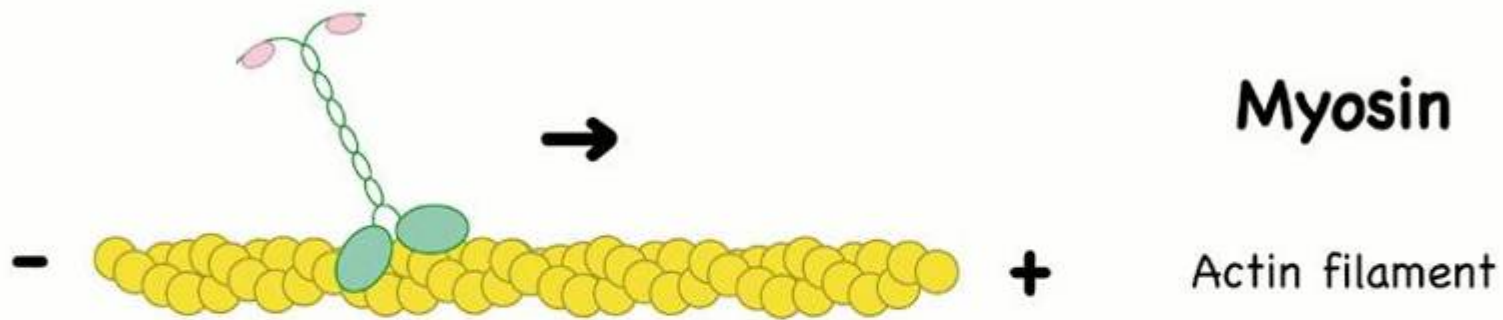
Axon

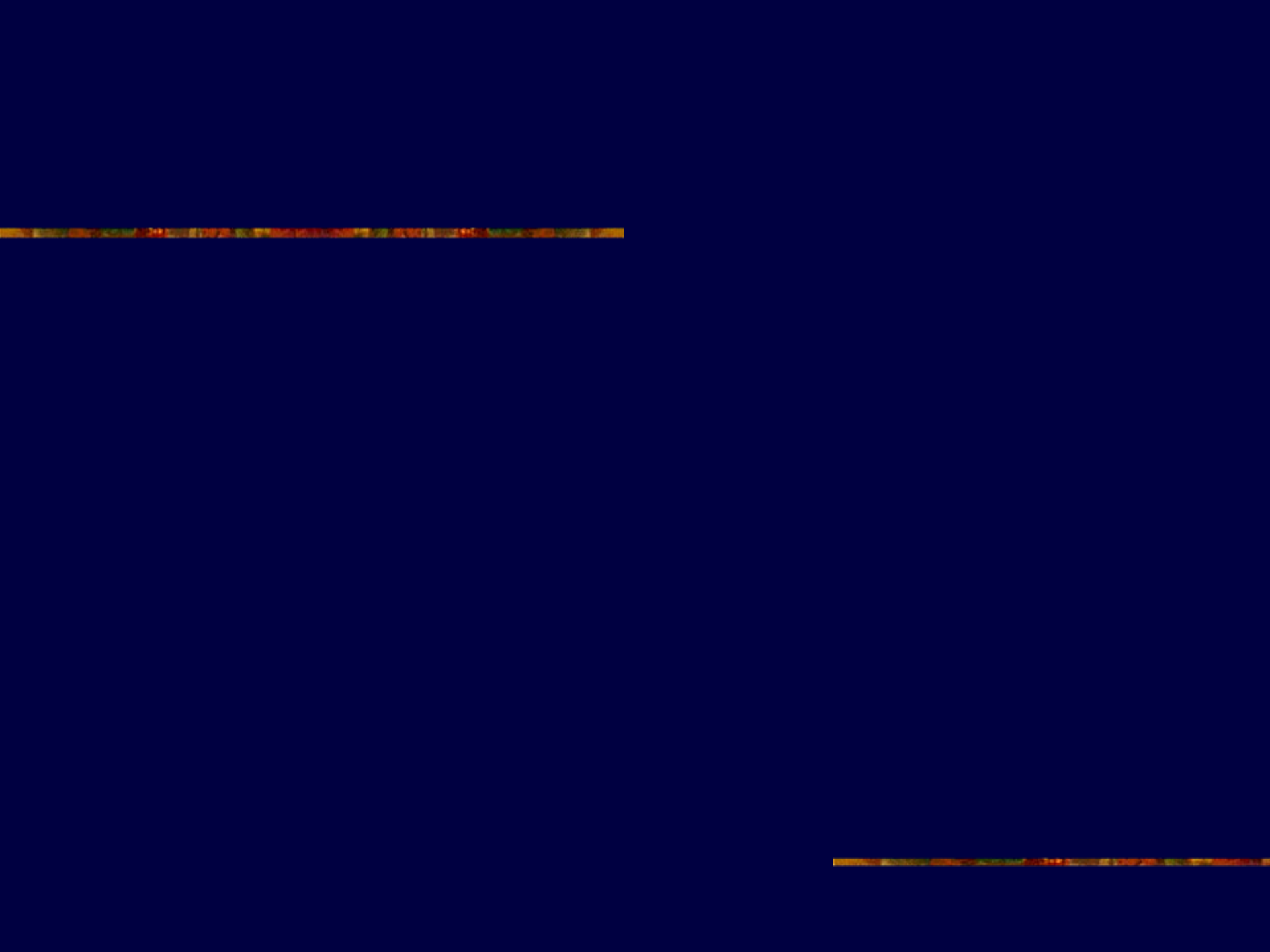
MAP1A

MAP1B

MAP2C

Tau







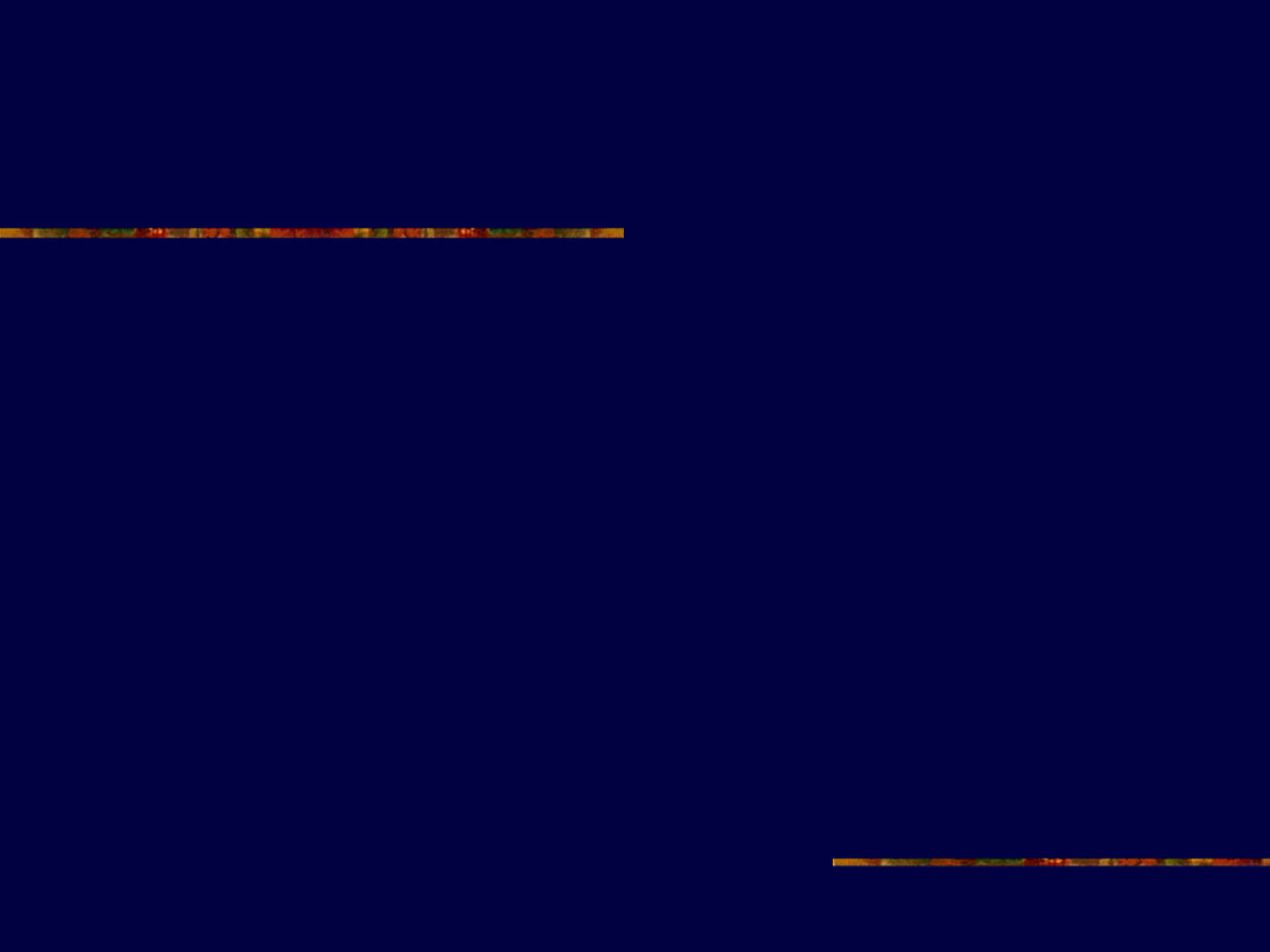
Intracellular Transport and Molecular Motors

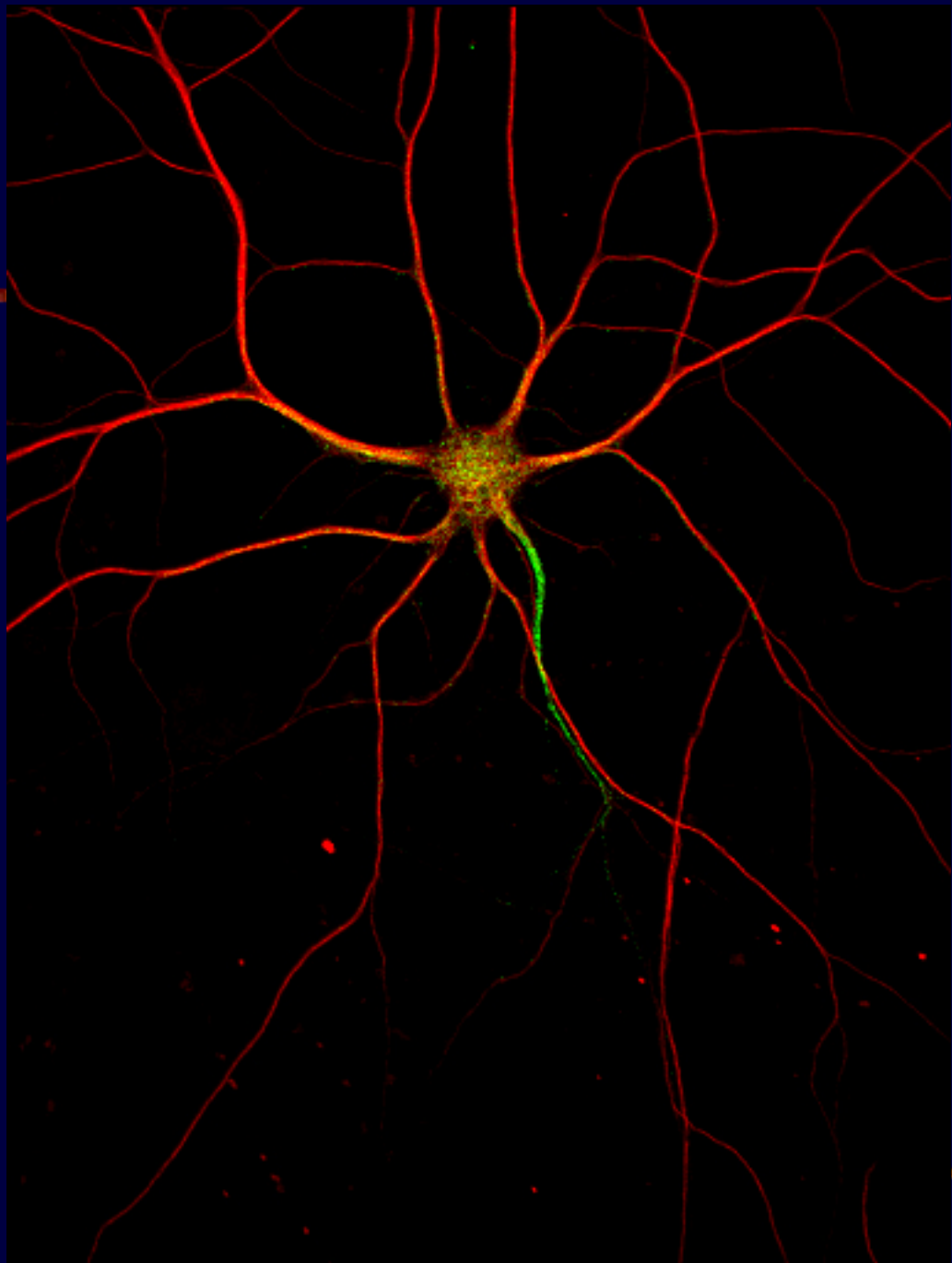


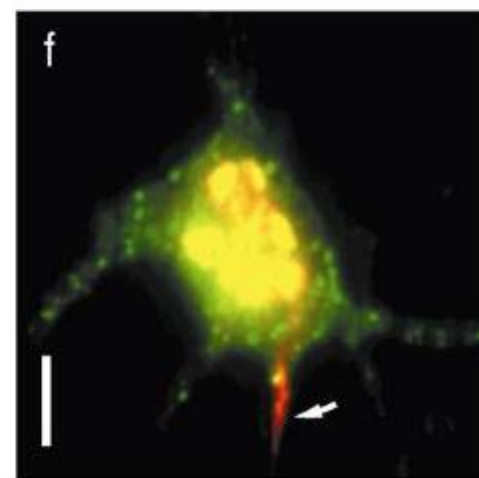
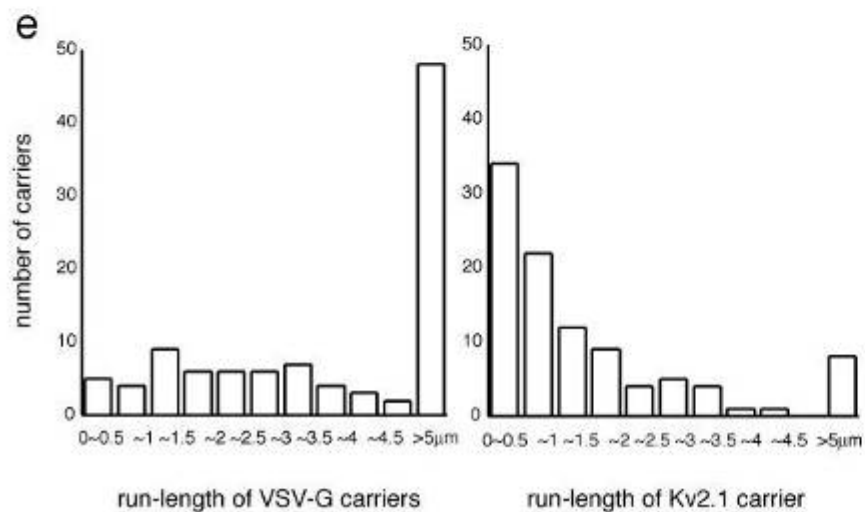
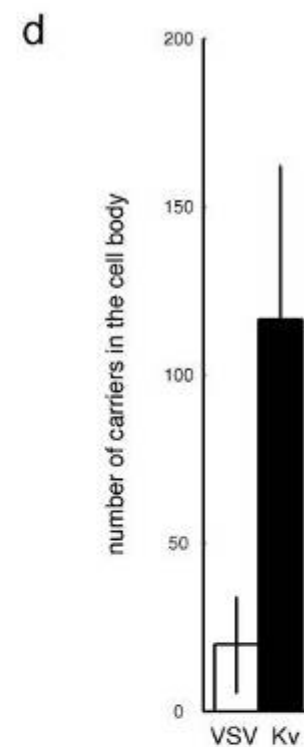
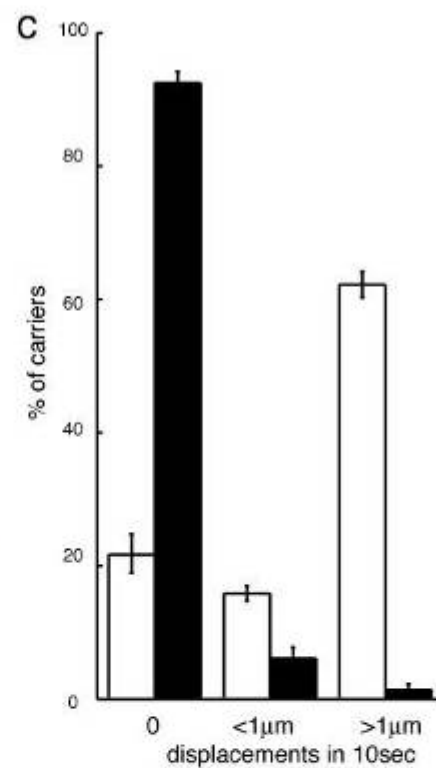
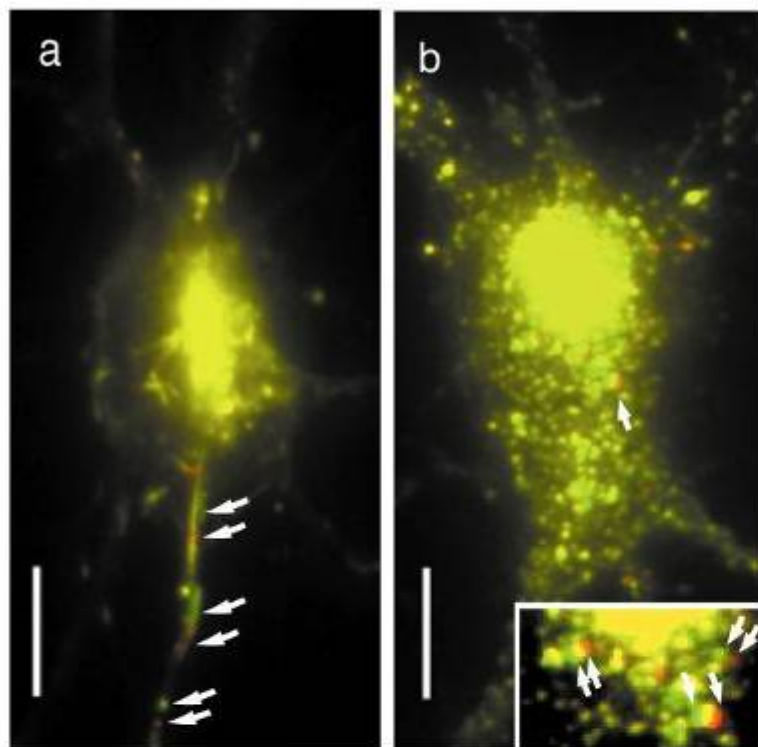
The Mechanism of Organelle Transport

Axonal Transport

	Group	Velocity mm/day	composition
Fast	I	240	membrane organella
	II	60	membrane organella
	III	6	myosin like actin binding protein
Slow	IV (SCb)	2	actin, clathrin calmodulin
	V (SCa)	1	tubulin, neurofilament triplet proteins









Hirokawa N. JCB 94: 425- ,1982, Hirokawa N. et al. Cell 56: 867- ,1989
Hirokawa N. Science 279: 519- ,1998

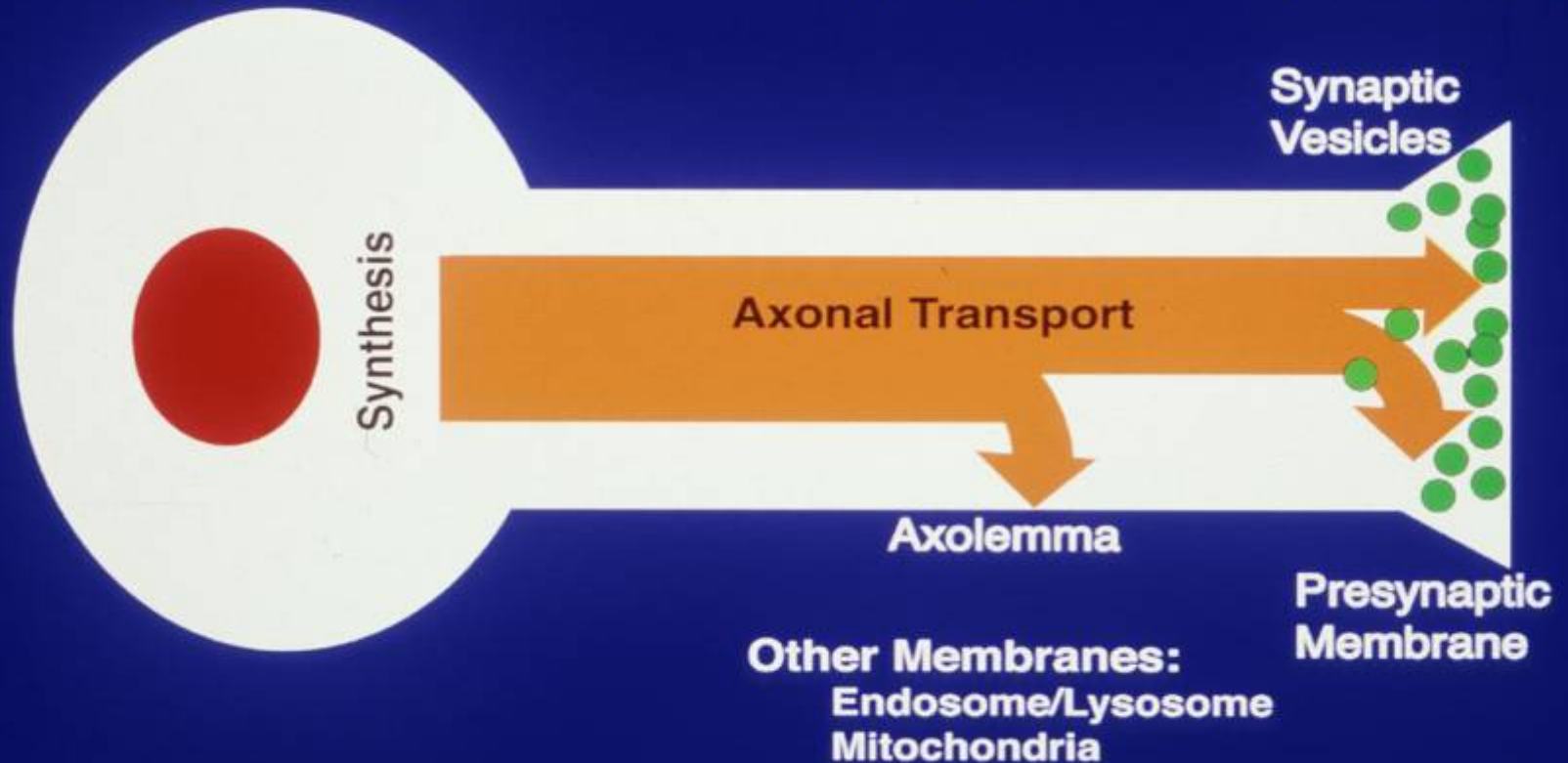


Hirokawa JCB 94:129—,1982; Hirokawa et al. Cell 56:867—,1989
Hirokawa Trends Cell Biol. 132:667—,1996

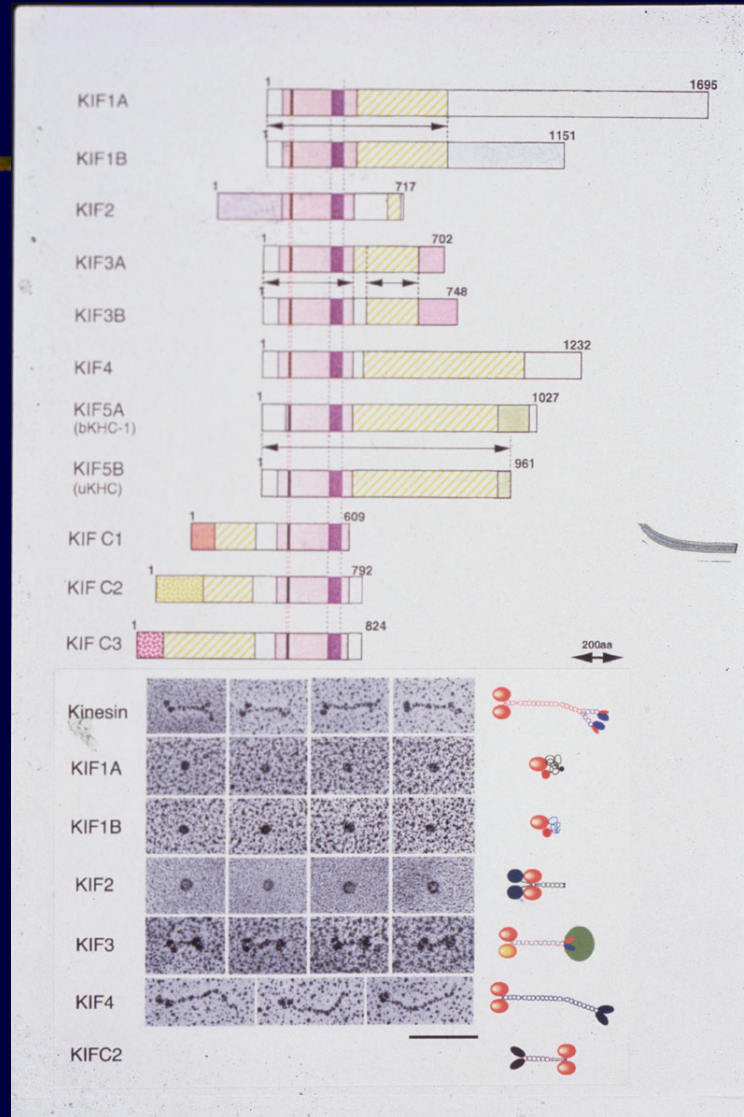
Cell Body

Axon

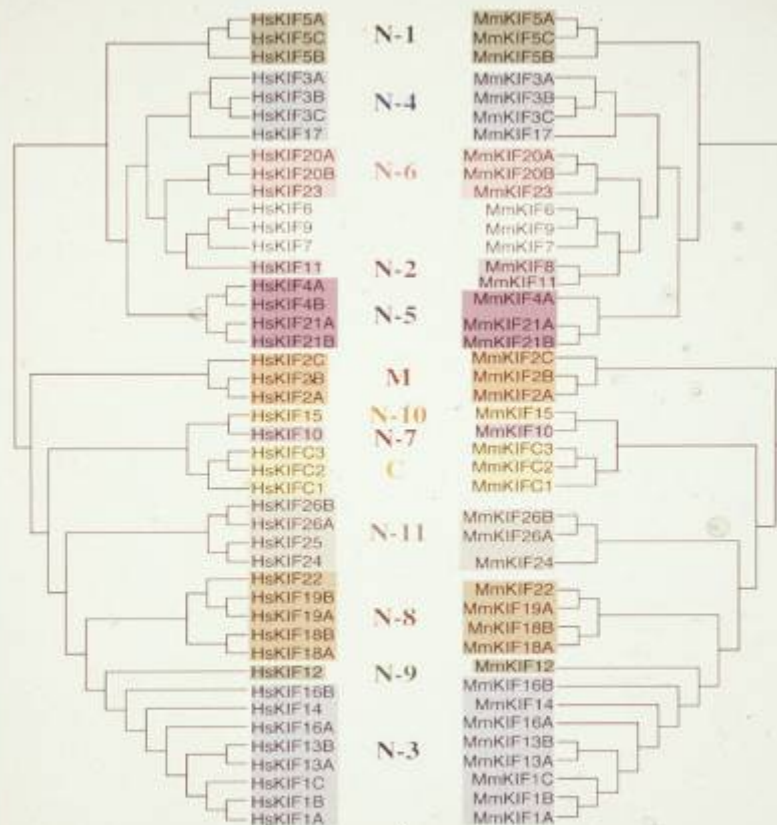
Synapse



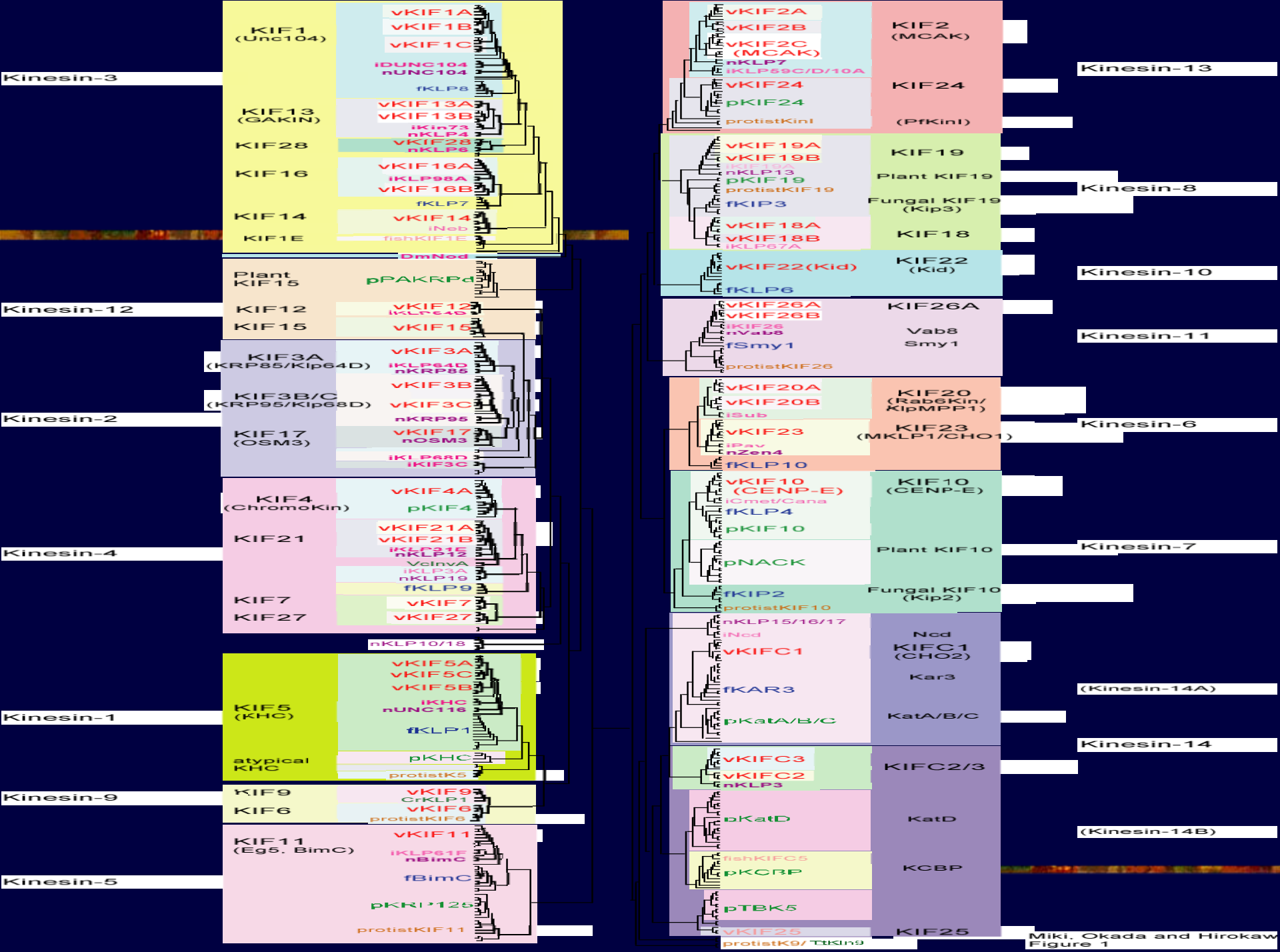
Kinesin Superfamily Proteins KIFs



Hirokawa et al.	Cell	56:867—,1989	Noda et al.,	JCB	155:77—,2001
Hirokawa et al.	JCB	114:295—,1991	Setou et al.	Nature	417:83—,2002
Aizawa et al.	JCB	119:1287—,1992	Xu et al.	JCB	158:293—,2002
Kondo et al.	JCB	125:1095—,1994	Wong et al.	PNAS	99:14500—,2002
Sekine et al.	JCB	127:187—,1994	Macho et al.	Science	298:2388—,2002
Nangaku et al.	Cell	79:1209—,1994	Guillaud et al.	J.Neurosci	23:131—,2003
Noda et al.	JCB	129:157—,1995	Homma et al.	Cell	114:229—,2003
Okada et al.	Cell	81:769—,1995	Okada et al.	Nature	424:574—,2003
Kikkawa et al.	Nature	376:274—,1995	Nakata & Hirokawa	JCB	162:1045—,2003
Yamazaki et al.	JCB	130:1387—,1995	Ogawa et al.	Cell	116:591—,2004
Nakata & Hirokawa	JCB	131:1039—,1995	Nitta et al.	Science	30:678—,2004
Hirokawa	Trends Cell Biol.	132:667—,1996	Kanai et al.	Neuron	43:513—,2004
Yamazaki et al.	PNAS	93:8443—,1996	Tanaka et al.	Nature	in press, 2005
Saito et al.	Neuron	18:425—,1997	Teng et al.	Nature Cell Biol.,	in press
Nakagawa et al.	PNAS	94:9654—,1997	Okada et al.	Cell	in press, 2005
Hirokawa	Science	279:519—,1998			
Yonekawa et al.	JCB	141:431—,1998			
Tanaka et al.	Cell	93:1147—,1998			
Nonaka et al.	Cell	95:829—,1998			
Okada & Hirokawa	Science	283:—,1999			
Takeda et al.	JCB	145:825—,1999			
Kikkawa et al.	Cell	100:241—,2000			
Takeda et al.	JCB	148:1255—,2000			
Setou et al.	Science	288:1796—,2000			
Kanai et al.	J.Neurosci	20:6374—,2000			
Terada et al.	Cell	103:141—,2000			
Nakagawa et al.	Cell	103:569—,2000			
Kikkawa et al.	Nature	411:439—,2001			
Zhao et al.	Cell	105:587—,2001			
Miki et al.	PNAS	98:7004—,2001			

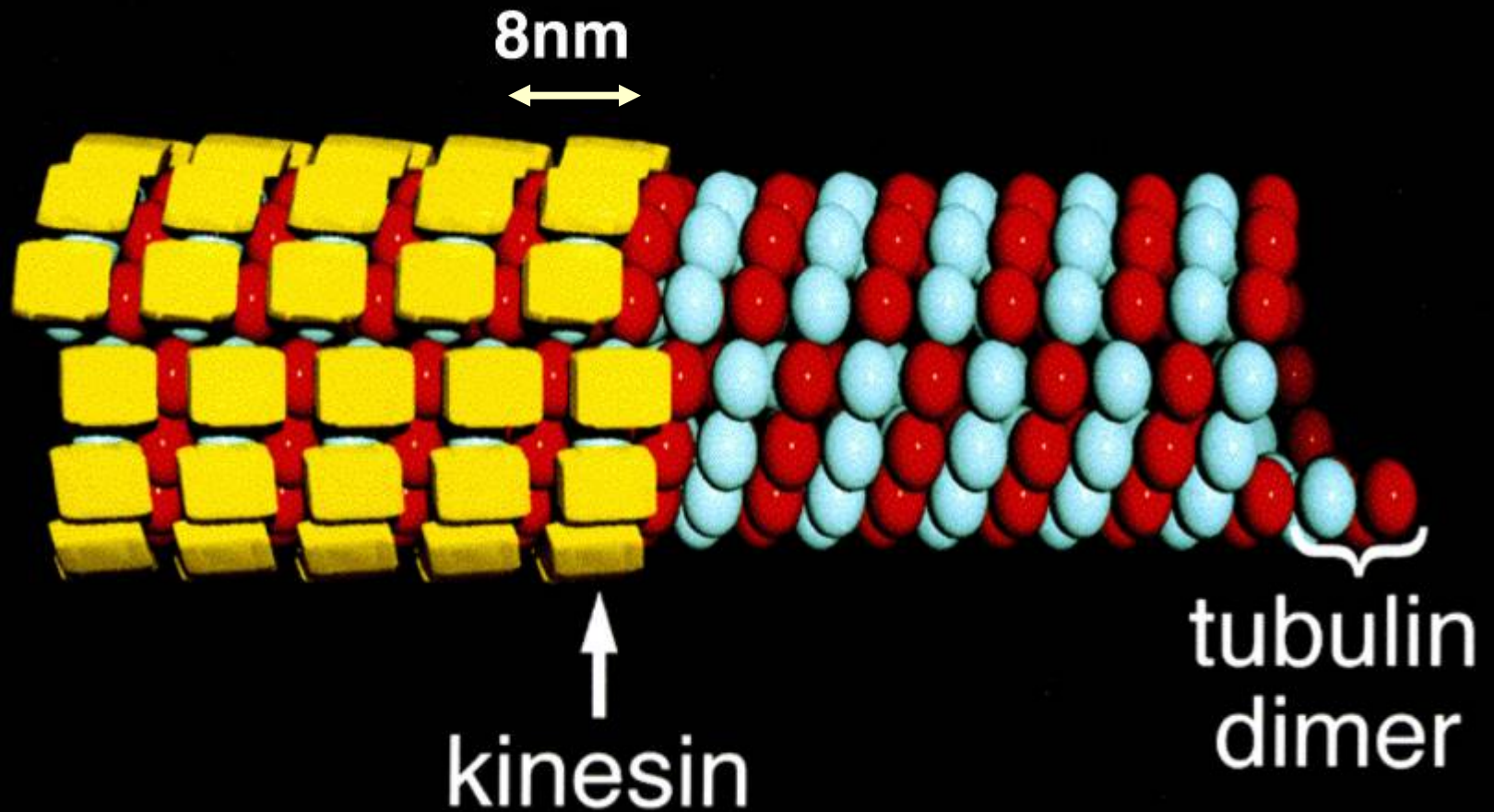


Phylogenetic Comparison of Mouse and Human KIFs



Name	Type	Cargo & Function	Reference
KIF1A	N-KIF Monomer	Synaptic vesicle precursor Essential for neuronal function and survival	Aizawa et al. JCB 1992 Yonekawa et al. JCB 1998 Kikkawa et al. Cell 2000 Okada et al. Nature 2003 Okada et al. Cell 1995 Okada et al. Science 1999 Kikkawa et al. Nature 2001 Nitta et. al. Science 2004
KIF1Bα	N-KIF Monomer	Mitochondria	Nangaku et al. Cell 1994
KIF1Bβ	N-KIF Monomer	Synaptic vesicle precursor Responsible gene of Charcot-Marie Tooth Type IIA Neuropathy	Zhao et al. Cell 2001
KIF2A KIF2C	M-KIF Homodimer	Expressed abundantly in Juvenile neurons Suppression of axon collateral branch extension Microtubule Destabilizer	Aizawa et al. JCB 1992 Homma et al. Cell 2003 Ogawa et al. Cell 2004 Noda et al. JCB 1995
KIF3A KIF3B	N-KIF Heterodimer	Form heterotrimer composed of KIF3A, KIF3B, and KAP3 Vesicles associated with α -fodrin important for neurite extension Protein complexes to form cilia > Nodal flow > Left / Right determination, Transport of N cadherin and β catenin to suppress tumorigenesis	Aizawa et al. JCB 1992 Yamazaki et al JCB 1995 Nonaka et al. Cell 1999 Takeda et al. JCB 2000 Teng et al. NCB 2005 Hirokawa et al. Cell 2006 Kondo et al. JCB 1994 Yamazaki et al. PNAS 1996 Takeda et al. JCB 1999 Tanaka et al. Nature 2005 Okada et al. Cell 2005
KIF4	N-KIF Homodimer	Expressed abundantly in Juvenile neurons Regulation of activity dependent neuronal survival through binding to PARP	Aizawa et al. JCB 1992 Sekine et al. JCB 1994 Midorikawa et al. Cell 2006
KIF5A KIF5B KIF5C	N-KIF Homodimer	Mitochondria, Lysosome, Tubulin oligomer GRIP1- AMPA type - glutamate receptor transport in dendrites RNA transport in dendrites	Hirokawa et al. Cell 1989 Aizawa et al. JCB 1992 Tanaka et al. Cell 1998 Terada et al. Cell 2000 Kanai et. Al. Neuron 2004 Hirokawa et al. JCB 1991 Nakata et al. JCB 1995 Kanai et al. J.Neurosci. 2000 Setou et al. Nature 2003
KIF13A	N-KIF Homodimer	Adaptin - AP1 adaptor complex - Mannose 6 phosphate receptor vesicle	Nakagawa et al. Cell 2000
KIF17	N-KIF Homodimer	Transport of Mint1 - NMDA type glutamate receptor in dendrites Learning & Memory	Setou et al. Science 2000 Macho et al. Science 2002 Guillaud et al. J.Neurosci. 2003 Wong et al. PNAS 2002
KIFC2	C-KIF Homodimer	Transport of multivesicular body like organella in dendrites	Saito et al. Neuron 1997
KIFC3	C-KIF Homodimer	Apical transportor of cholesterol, Annexin III enriched vesicles Golgi complex integration and positioning	Noda et al. JCB 2001 Xu et al. JCB 2002

Kinesin rail: structure of microtubule



Neuron



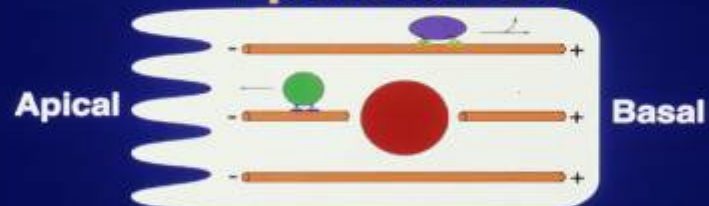
Dendrite

MAP2
MAP2C(Juvenile Neuron)
MAP1A
MAP1B

Axon

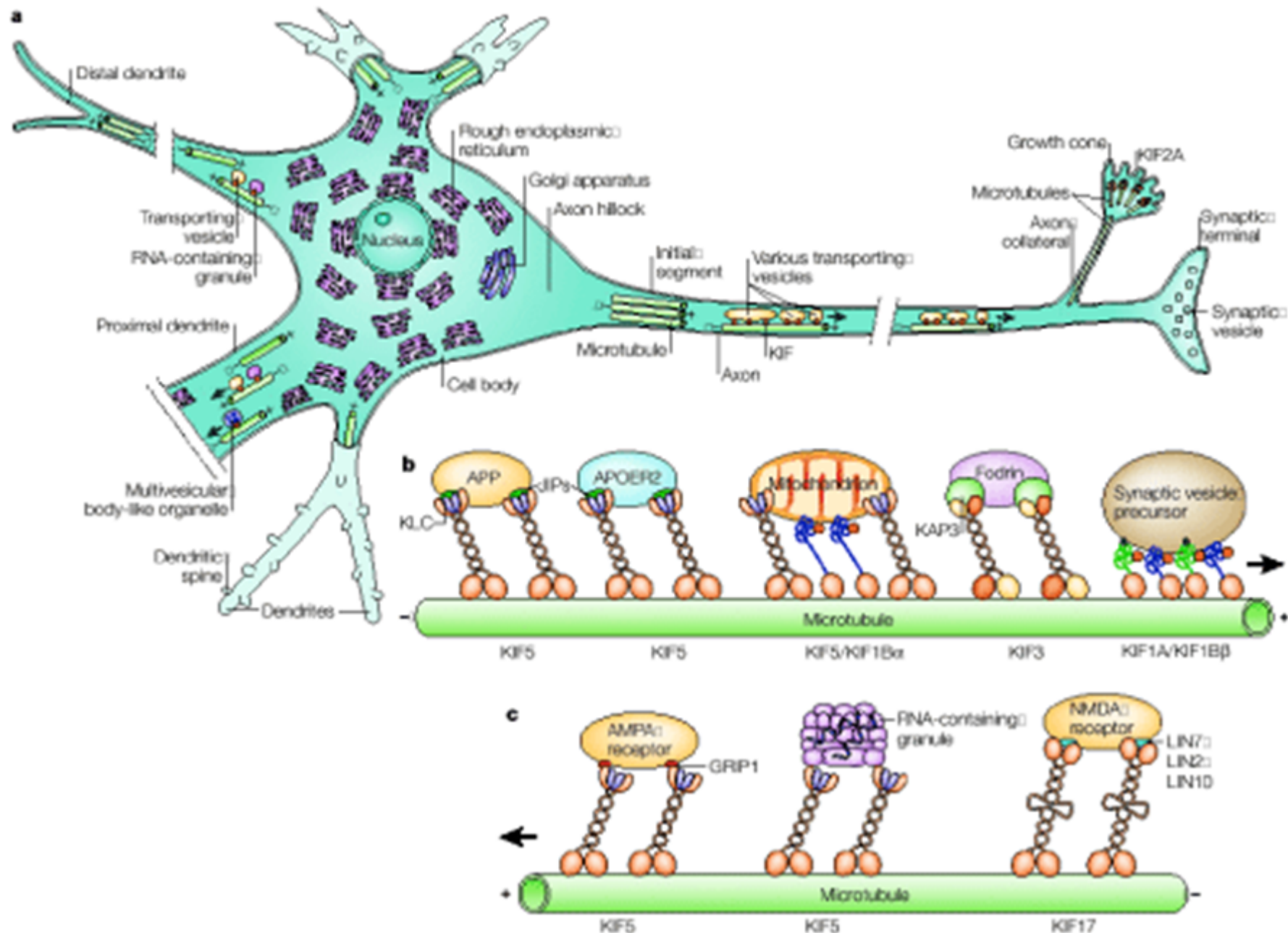
Tau
MAP2C(Juvenile Neuron)
MAP1A
MAP1B

Epithelial Cell



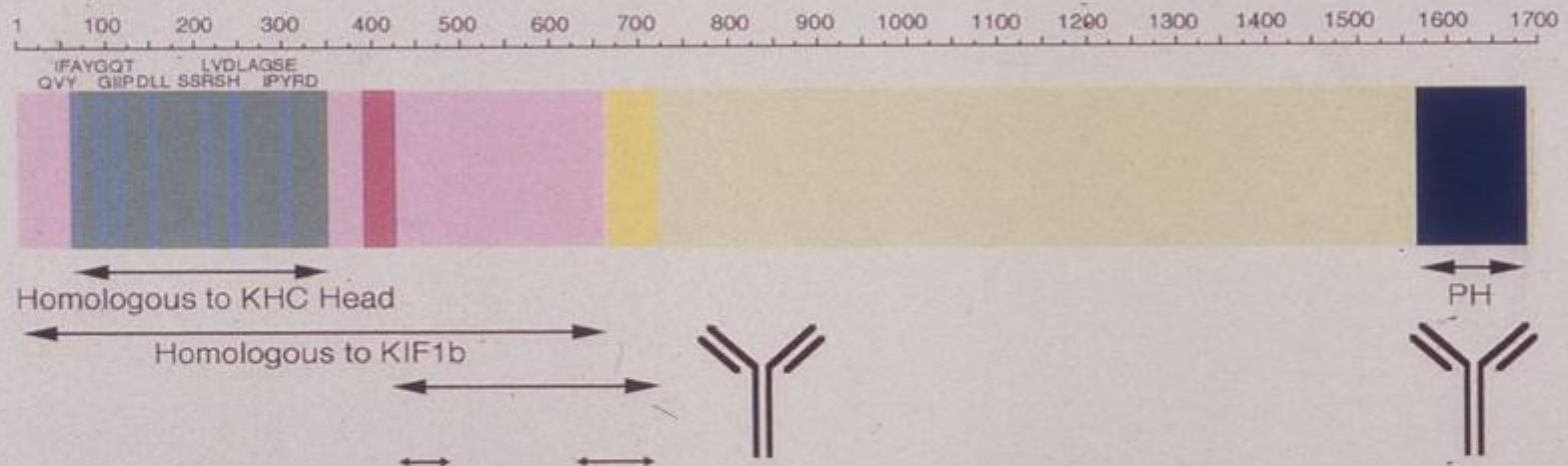
Fibroblast





KIF1A

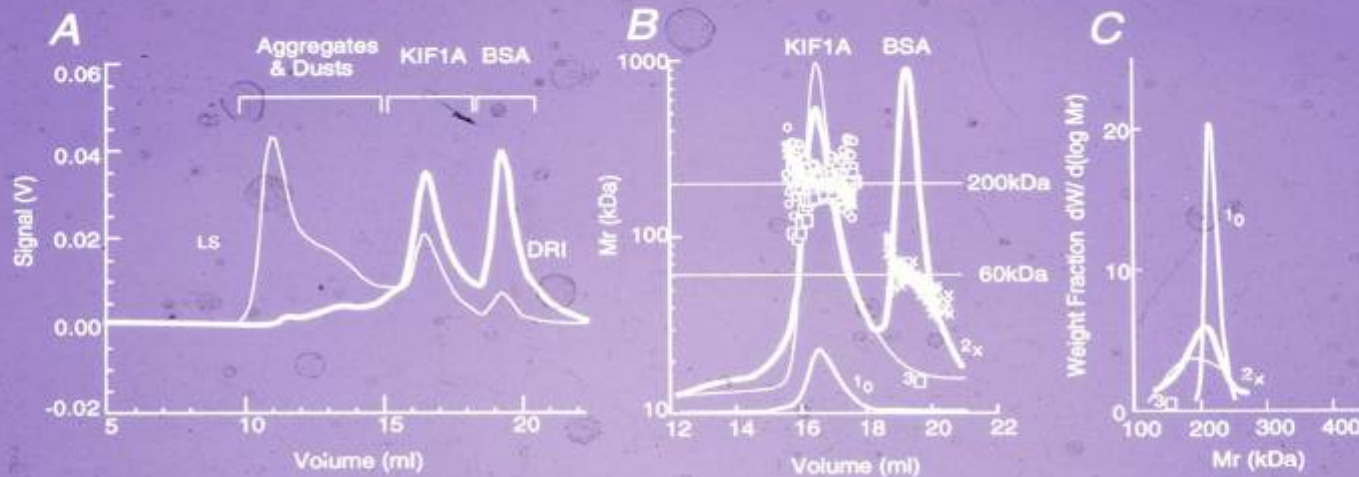
1695aa.
Mr 191710.84
pI 5.78



Aizawa et al. JCB 119:1287—, 1992

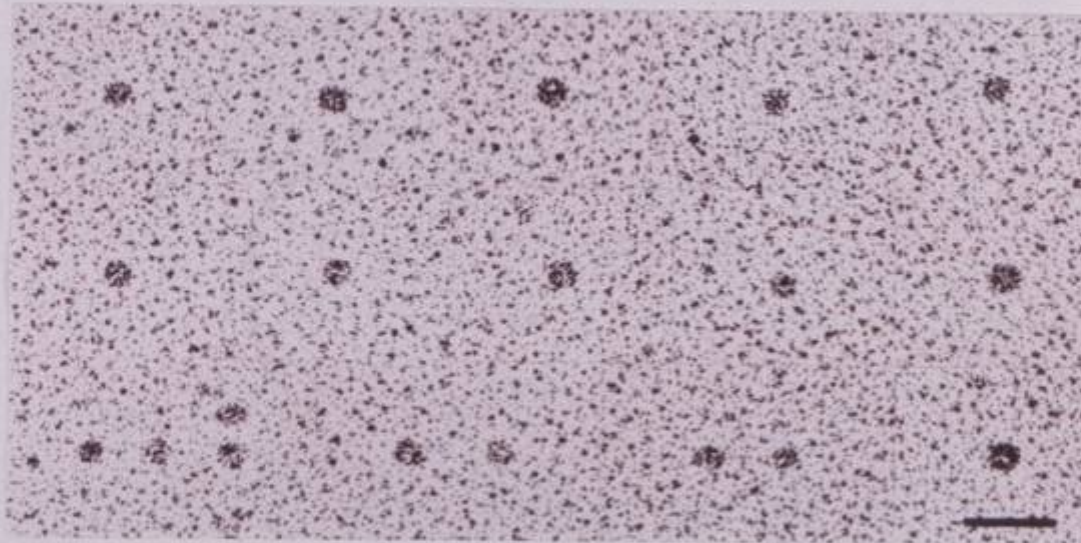
Okada et al. Cell 81:769—, 1995

Molecular Weight Determination by GPC-DLS



Molecular weight (M_r) of recombinant KIF1A protein was determined by gel permeation chromatography-differential laser light scattering (GPC-DLS), because this method absolutely determines M_r of polymer unbiased by its shape or other physical or chemical properties. **A** shows typical light scattering chromatogram at 90° (LS) contrasted with differential refractive index (DRI). **B** shows calculated M_r overlaid on DRI chromatogram. Results from three experiments are shown. These data were converted into differential M_r distribution (**C**). Thus, M_r of recombinant KIF1A was determined as 180-220 kDa, indicating that KIF1A is a monomer.

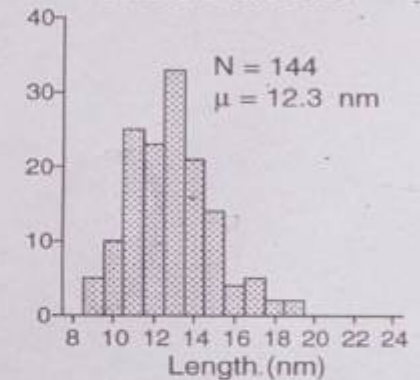
Single Molecule Structure of Recombinant KIF1A Revealed by Low-Angle Rotary-Shadowing EM



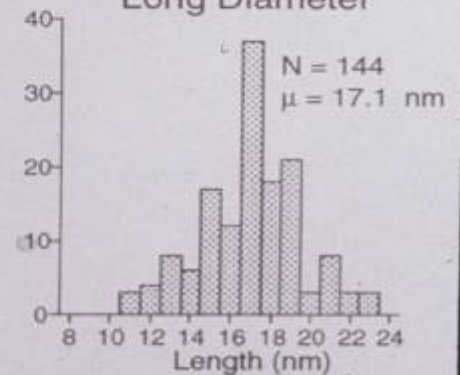
Bar: 50nm

Unlike other KRMPs, KIF1A was a globular molecule. No clearly discernable tails were observed.,

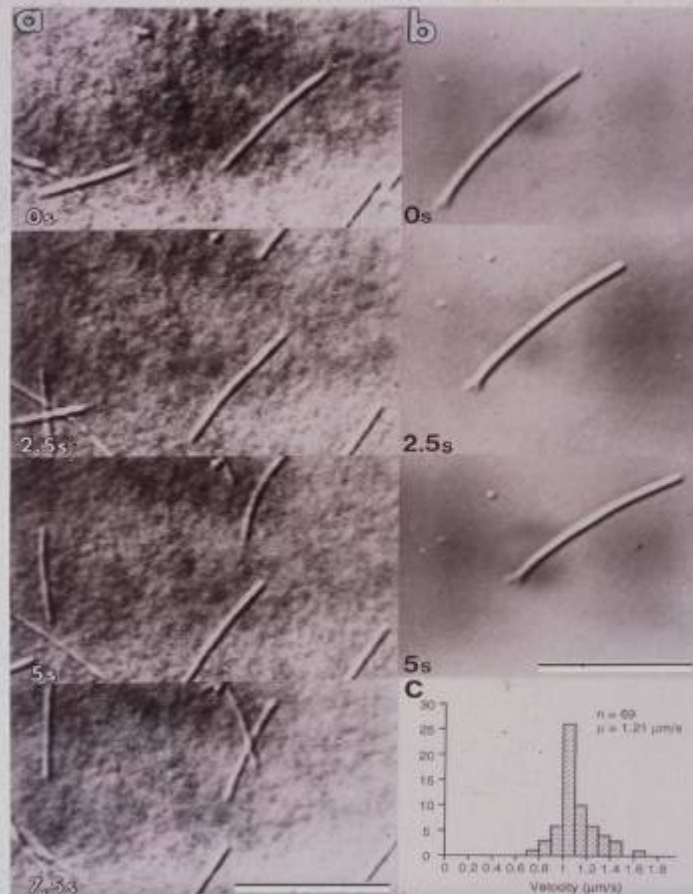
Short Diameter

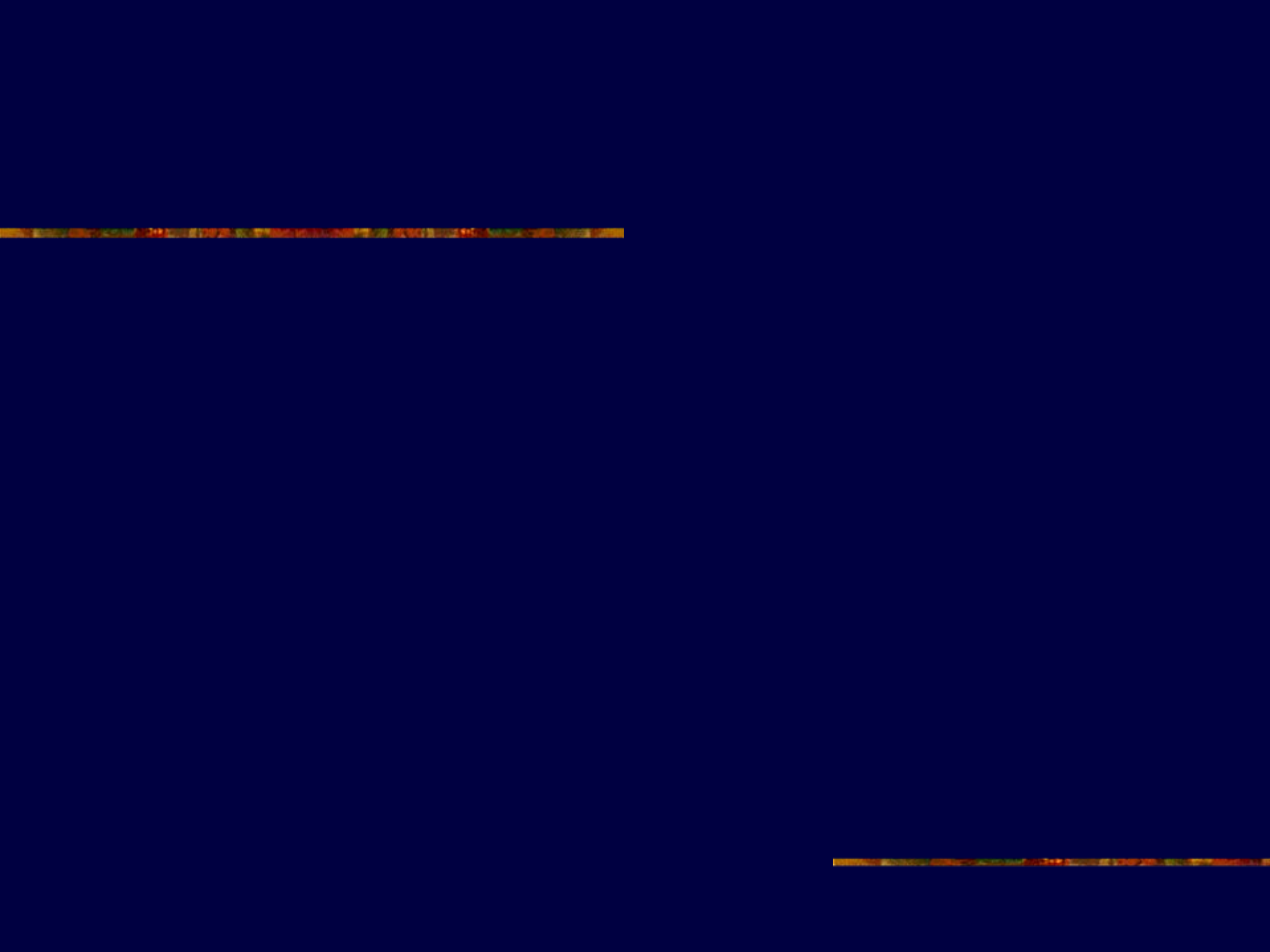


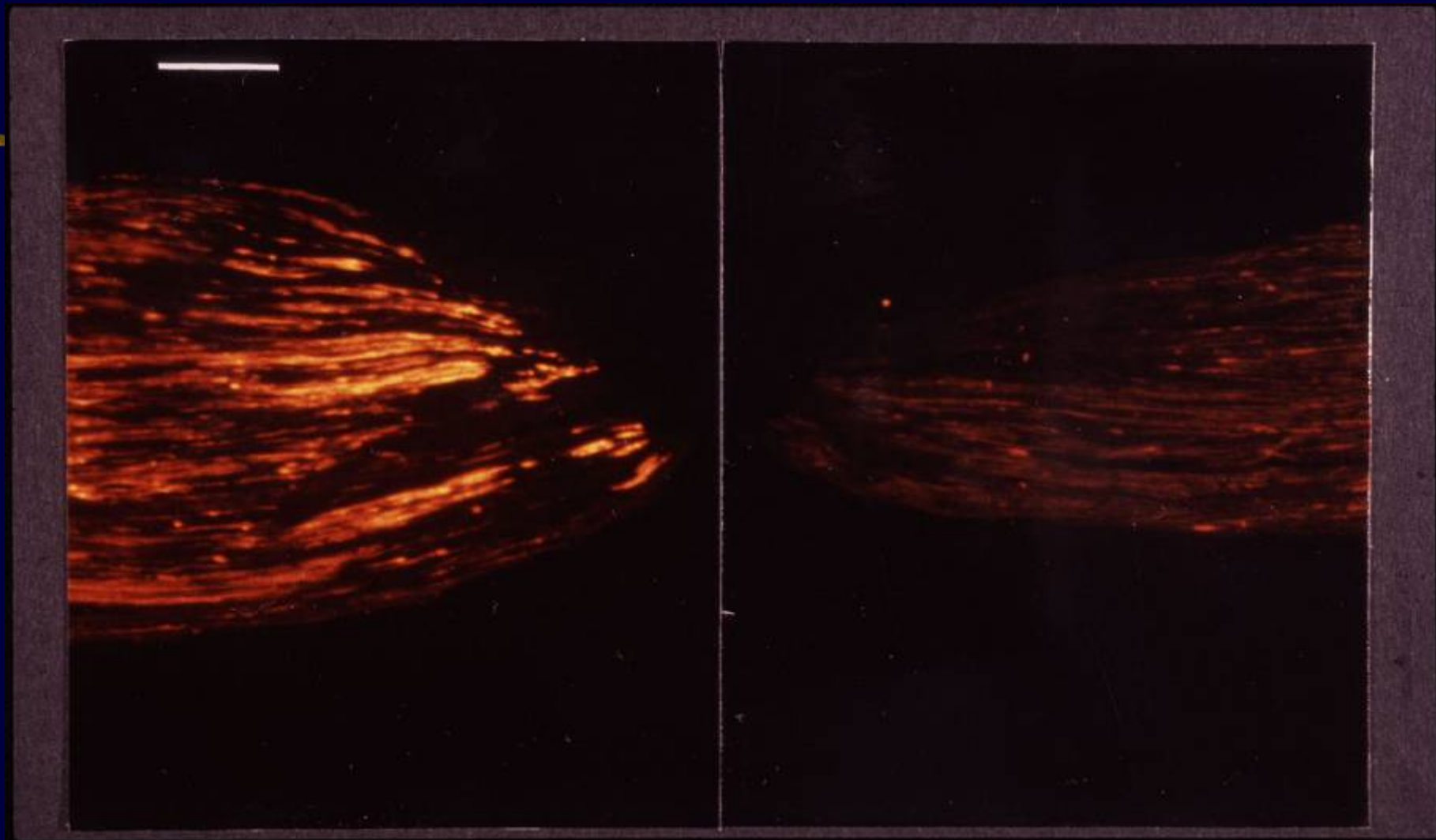
Long Diameter



In vitro Motility Assay of Recombinant KIF1A
 (~100 KIF1A monomers / μm^2)









KIF1A



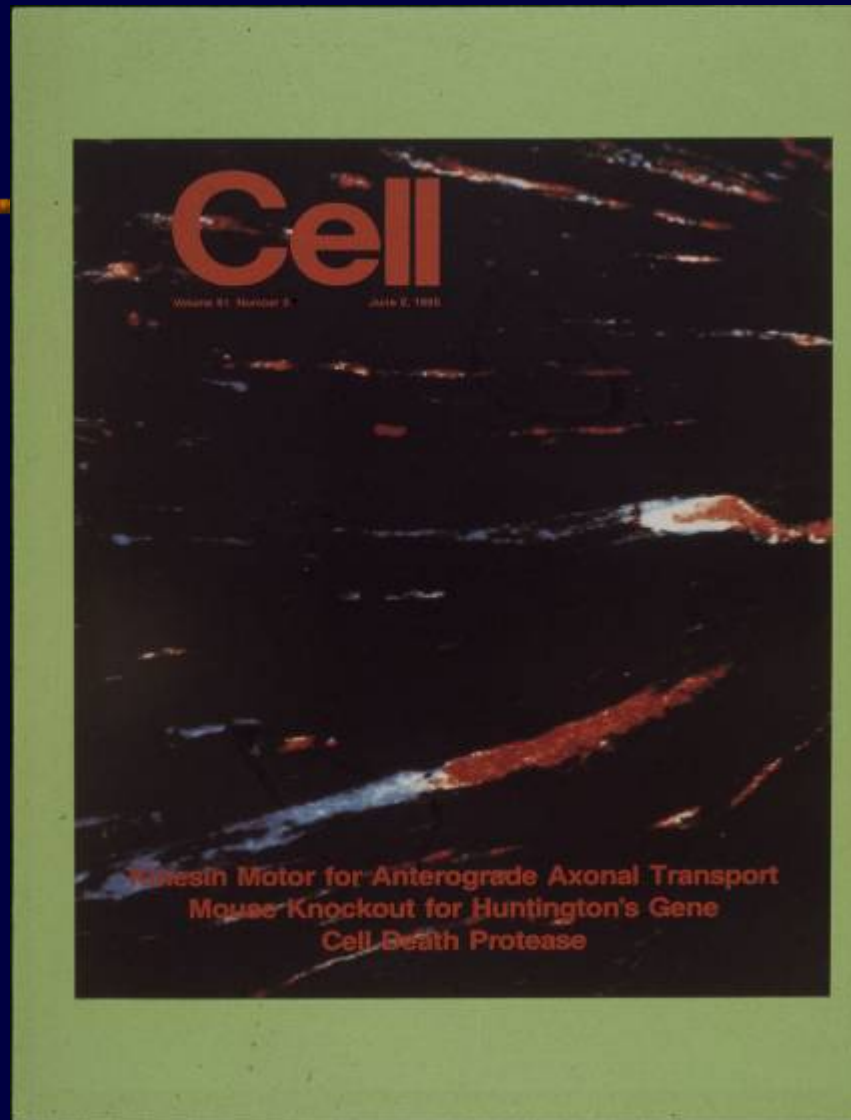
Synaptophysin



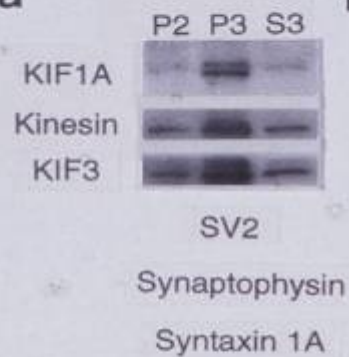
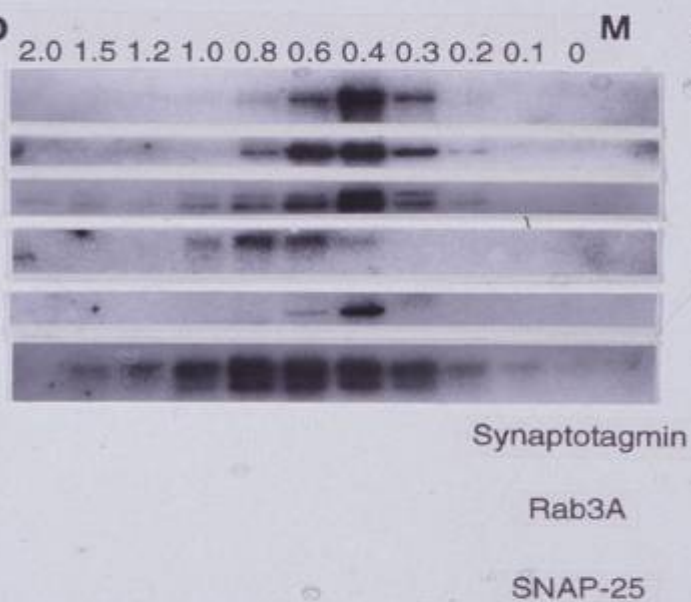
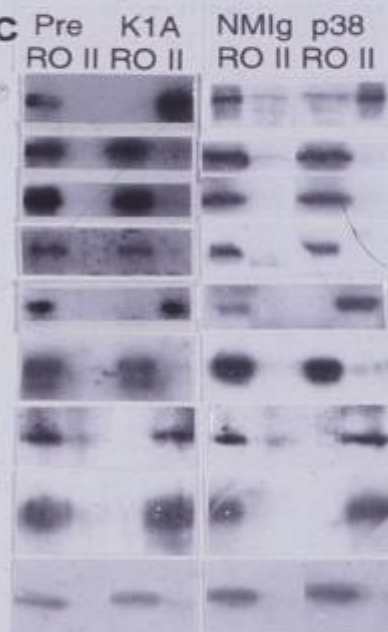
KIF1A

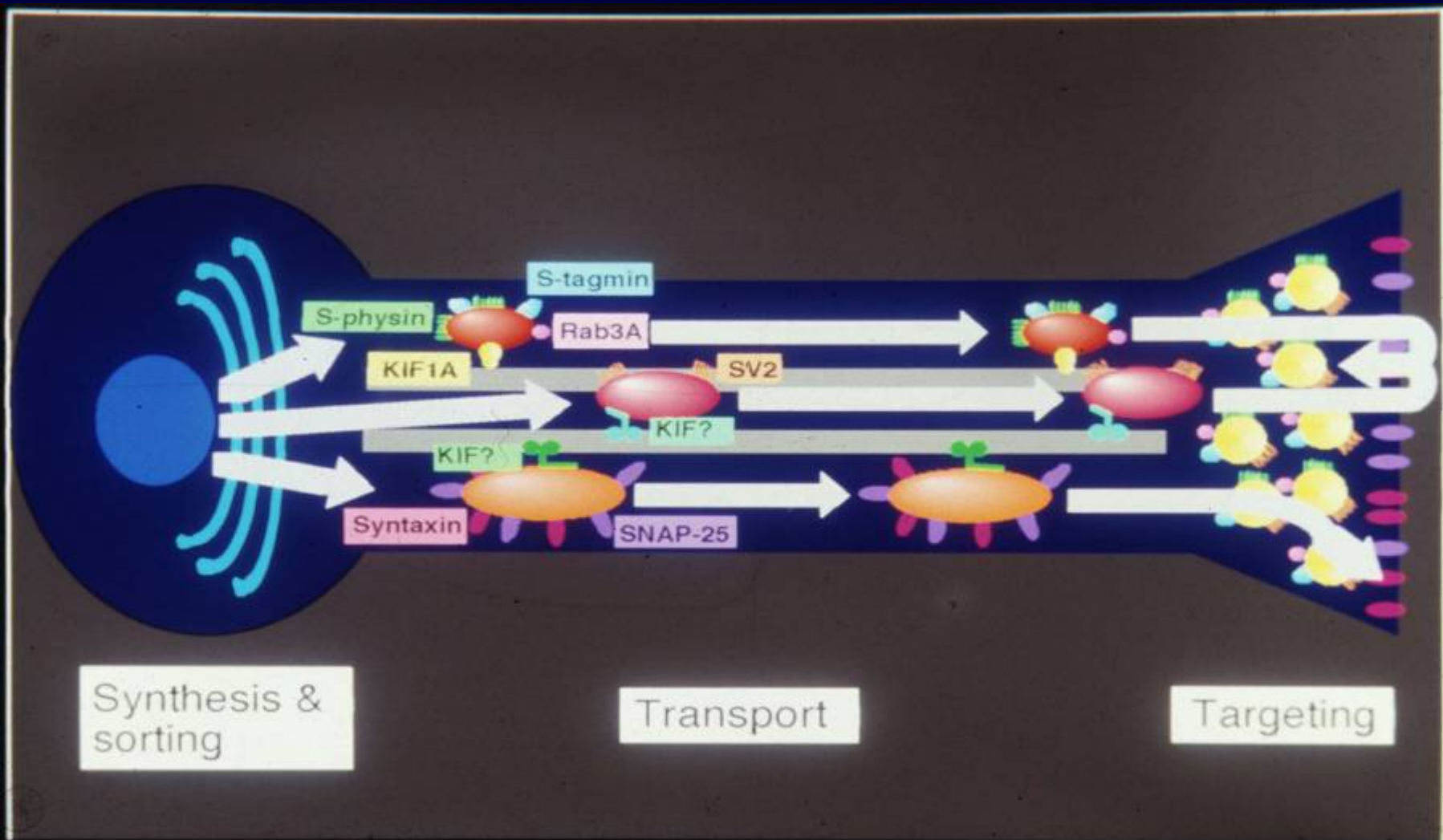


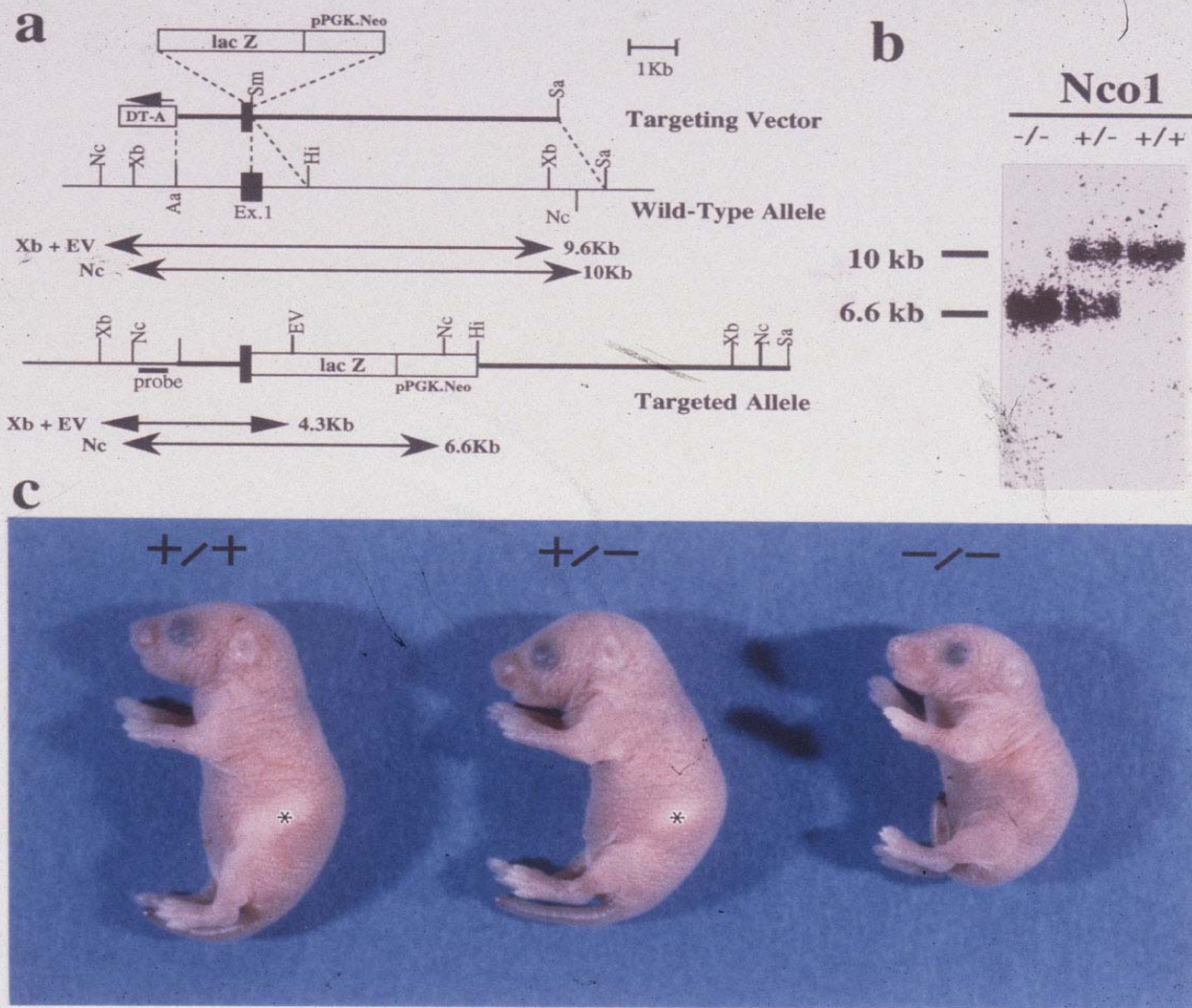
Syntaxin 1A



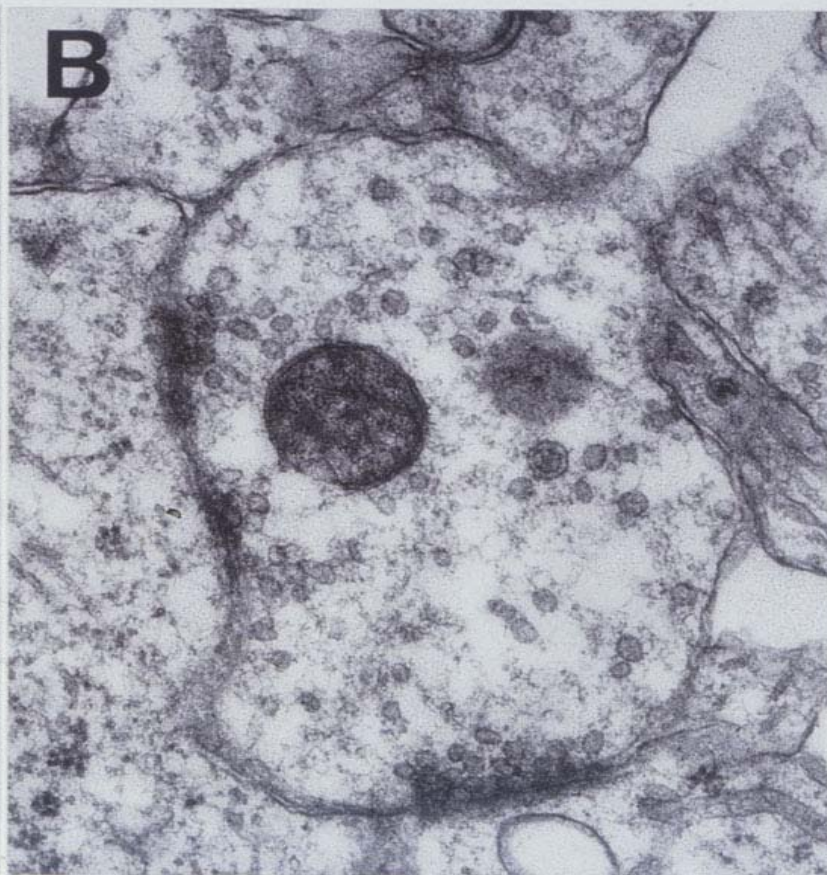
Okada et al. Cell 81:769-780, 1995

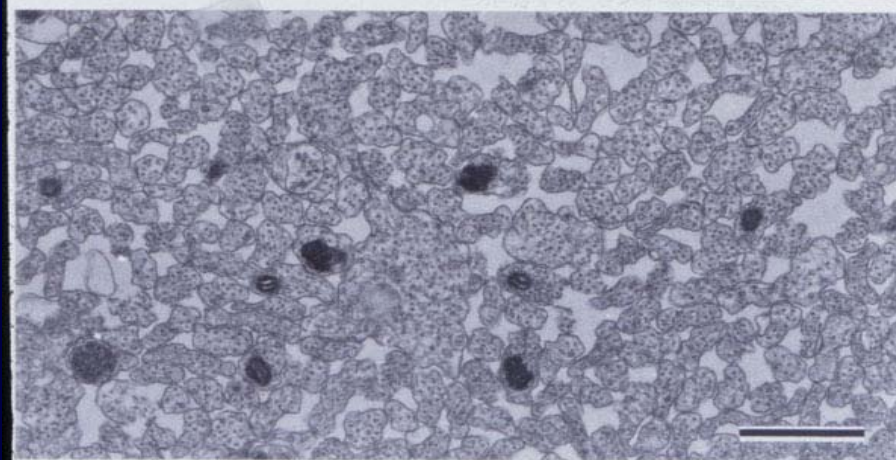
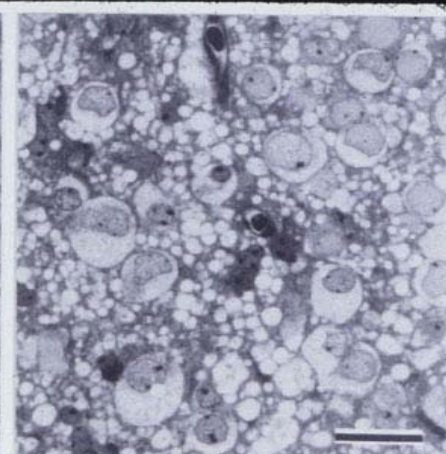
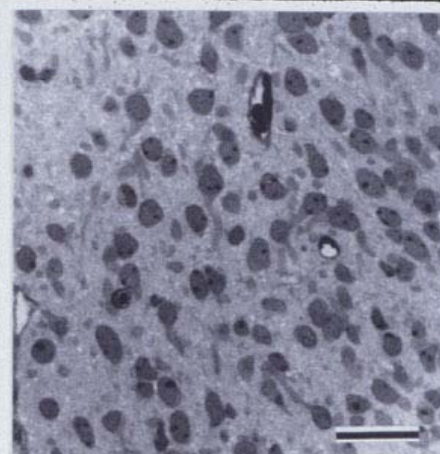
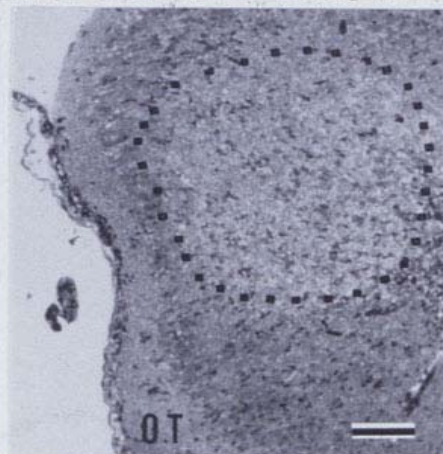
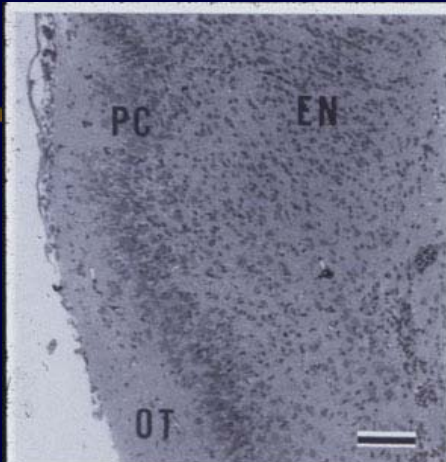
a**b****c**

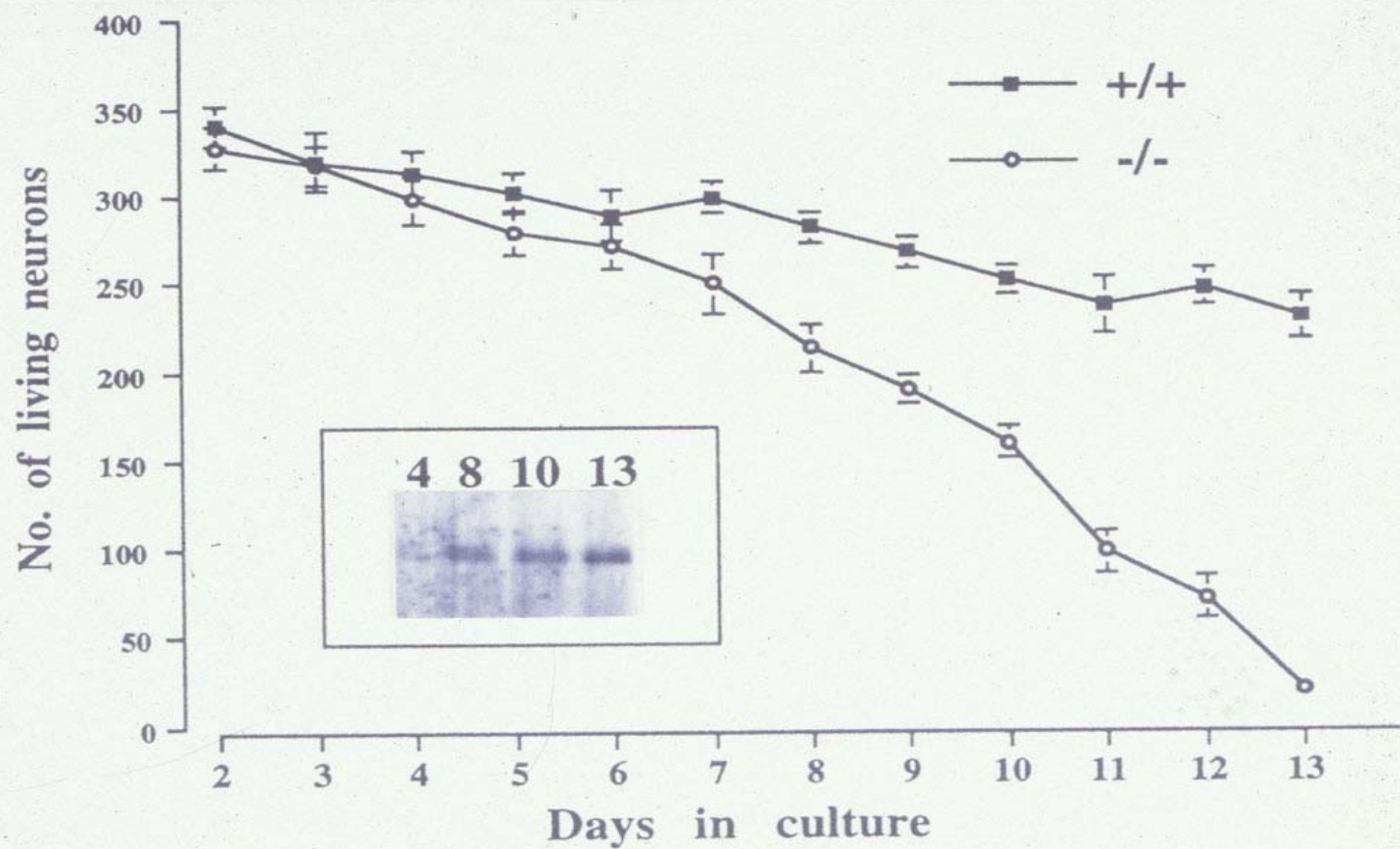


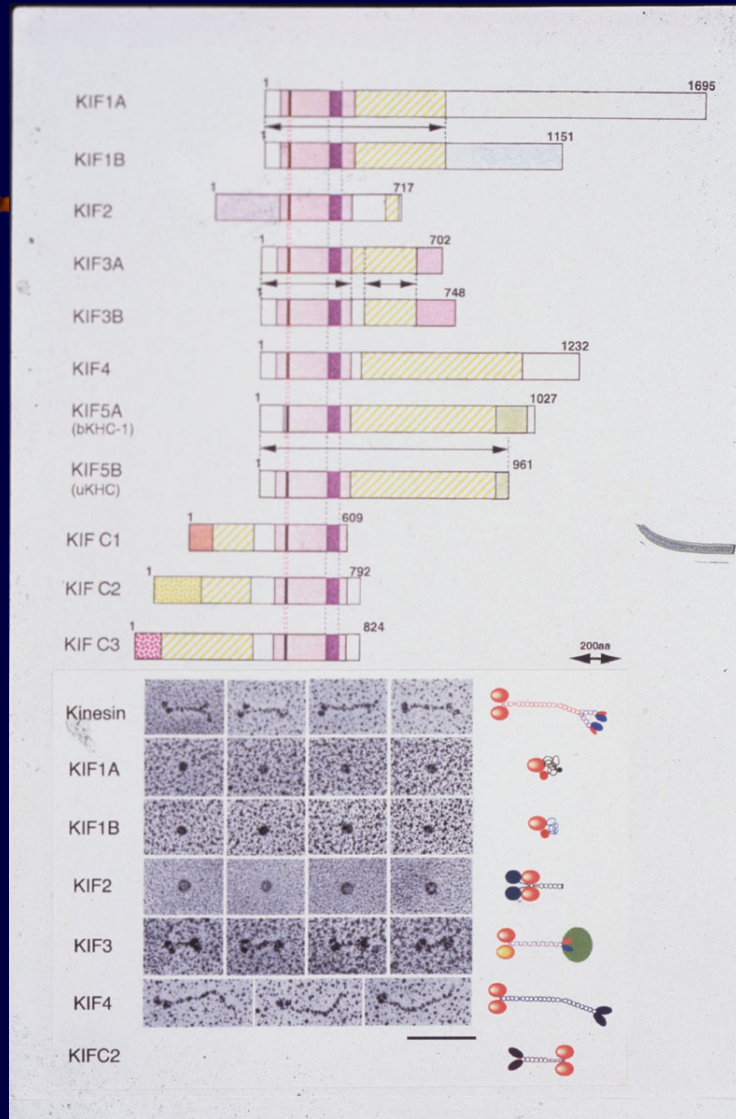


Yonekawa et al. JCB 141:431-, 1998







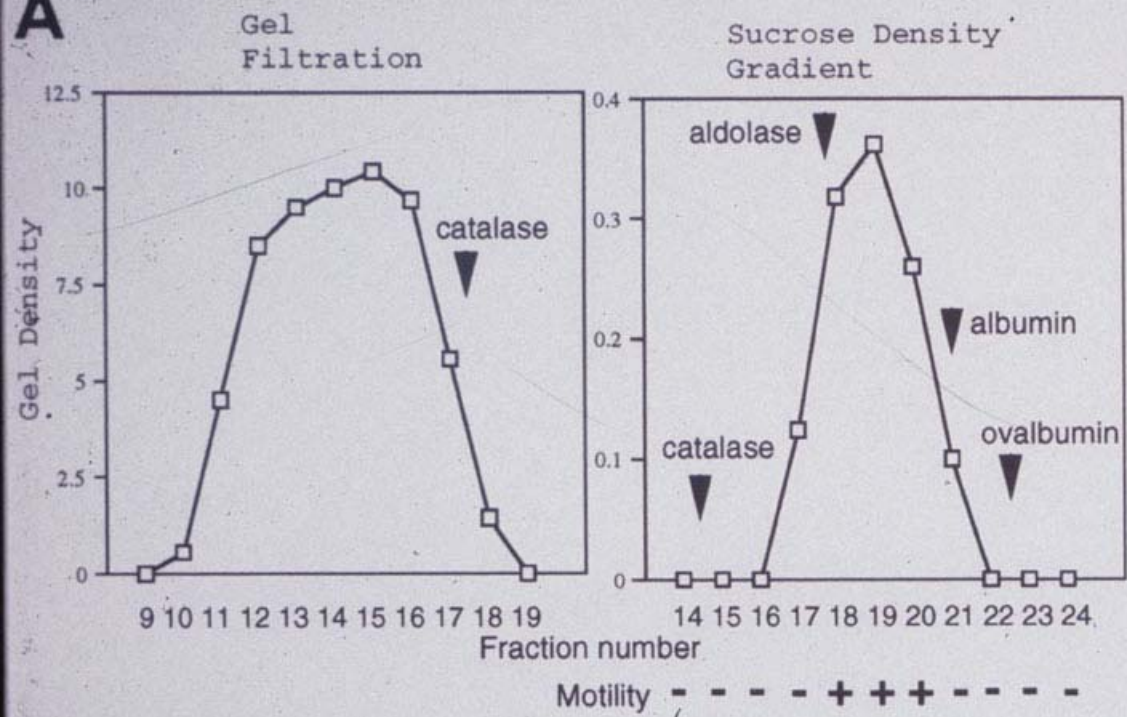
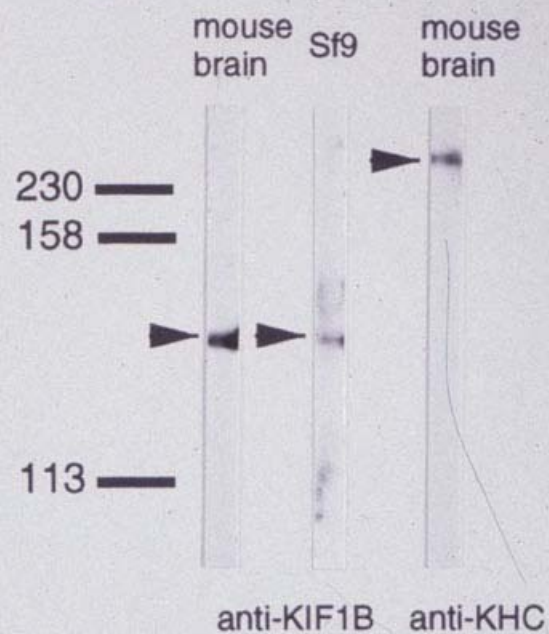
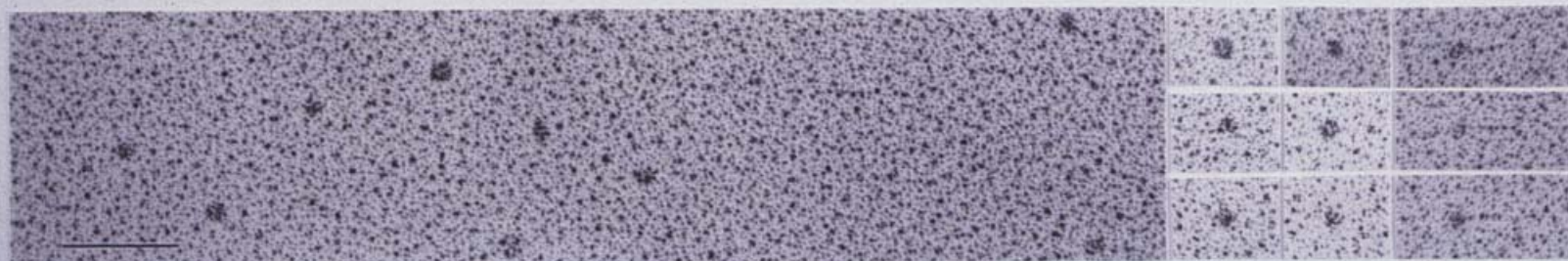


Nangaku, M. et al. Cell 79: 1209- , 1994

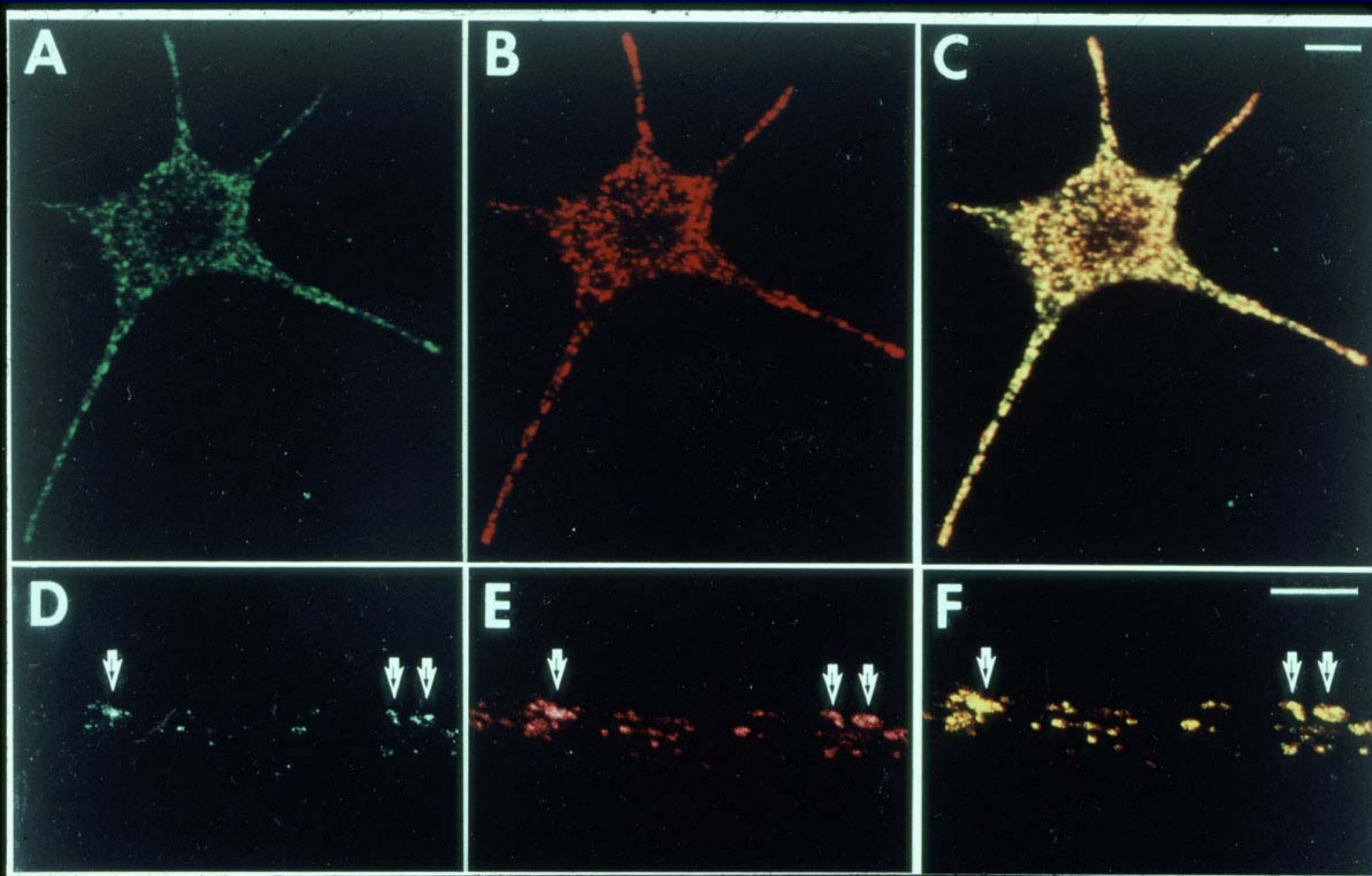
A

ACGTTTAAACACGCGCAATGTTGCGCGCTCCCGCGCTCCCGCAATCTCGATGAGAGCTGGCGCGCTCGATGGGCTGGGAGCGCGCTCGCGCTCGC
 181
 -1
 180
 60
 360
 120
 540
 180
 720
 240
 900
 300
 1080
 360
 1260
 420
 1440
 480
 1620
 540
 1800
 600
 1980
 660
 2160
 720
 2340
 780
 2520
 840
 2700
 900
 2880
 960
 3060
 1020
 3240
 1080
 3420
 1140
 3600
 1150
 3780
 3960
 4140
 4320
 4500
 4570

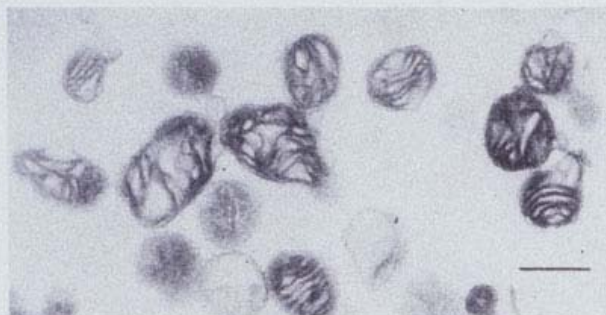
ACGTTTAAACACGCGCAATGTTGCGCGCTCCCGCGCTCCCGCAATCTCGATGAGAGCTGGCGCGCTCGATGGGCTGGGAGCGCGCTCGCGCTCGC
 181
 -1
 180
 60
 360
 120
 540
 180
 720
 240
 900
 300
 1080
 360
 1260
 420
 1440
 480
 1620
 540
 1800
 600
 1980
 660
 2160
 720
 2340
 780
 2520
 840
 2700
 900
 2880
 960
 3060
 1020
 3240
 1080
 3420
 1140
 3600
 1150
 3780
 3960
 4140
 4320
 4500
 4570

A**B****C**





L



M

