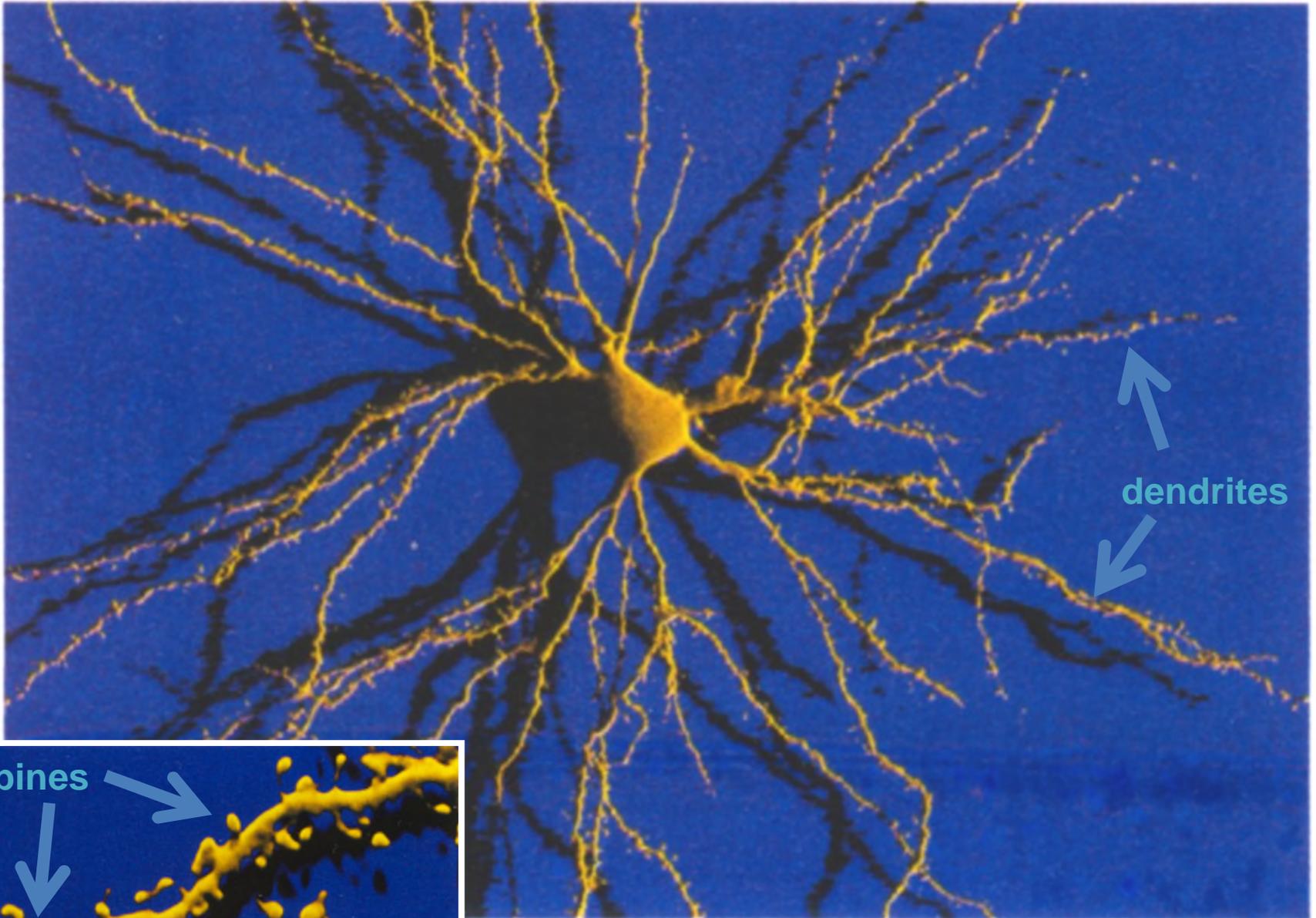


Lesson 12

Localization of mRNAs in neuronal dendrites
and axons

Dendrites can represent up to 90% of the entire cellular volume of a neuron



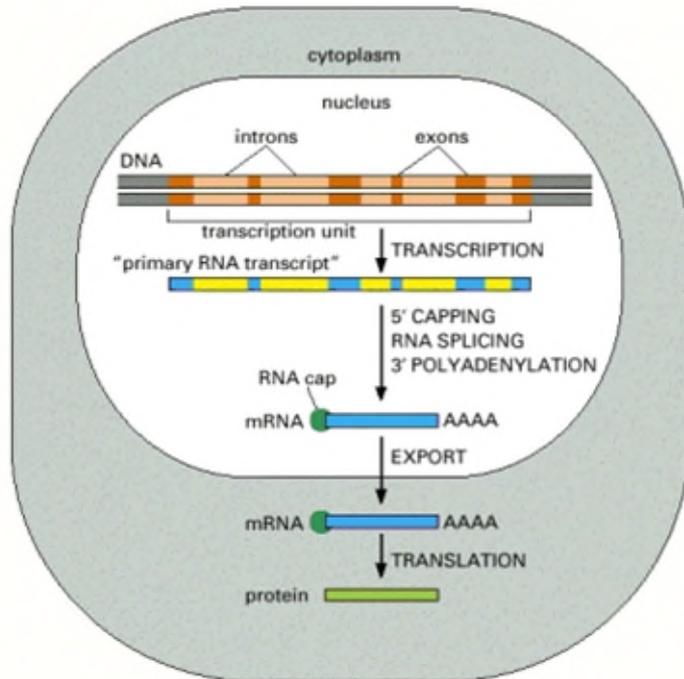
Katharina Braun - Magdeburg

How common is mRNA localization in nature?

A general introduction

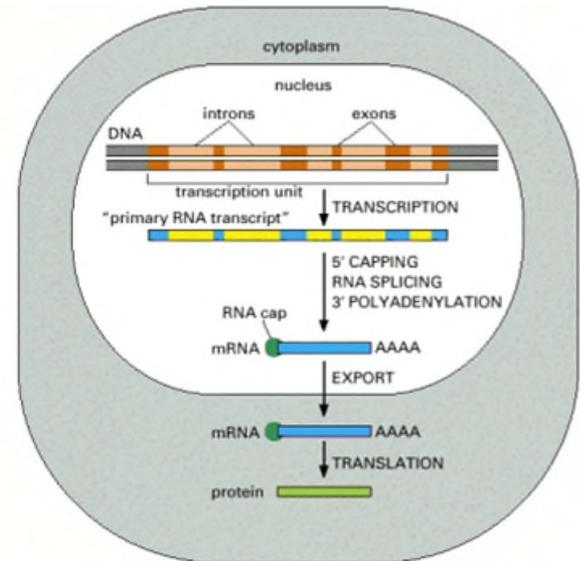
Post-transcriptional gene regulation in eukaryotic cells

mRNAs are synthesized in the nucleus and undergo a series of regulatory steps each of which is tightly regulated



- transcription
- splicing
- mRNA stability (5'Cap 3'polyA)
- mRNA transport
- translation
- degradation

Once exit from nucleus,
mRNAs have two possible
fates:



- 1) mRNAs are generally readily translated in the cytoplasm.
- 2) Certain classes of mRNAs are transported to specific cellular regions and are not translated until they reach their final destination.

RNA localization

Localization of mRNAs to restricted subcellular domains is an evolutionary conserved mechanism
(from fungi to plants and animals)

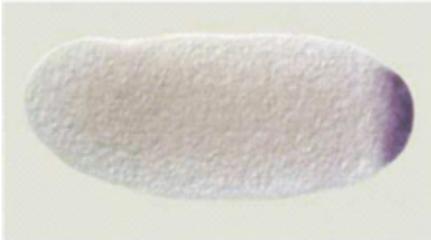
local high-level production of the encoded protein at the site of mRNA localization

prevents production of the encoded protein in a region where it might have deleterious effects

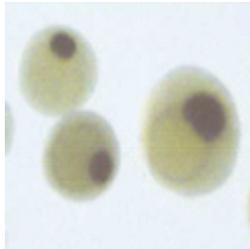
The spatial regulation of protein translation is an efficient way to create functional and structural asymmetries in cells.

Buxbaum et al. Nat Rev Mol Cell Biol. 2015 - <http://doi:10.1038/nrm3918>

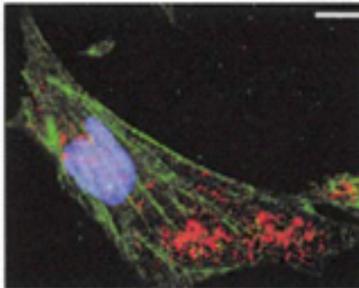
Localized RNAs in Different Organisms and Cell Types



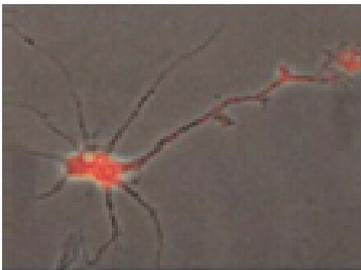
The localization of maternal *nanos* mRNA at the posterior of an activated, unfertilized *Drosophila* egg is the result of two different mechanisms: generalized degradation and local protection.



Xpat mRNA localized in the mitochondrial clouds of stage I *Xenopus* oocytes, whole mount in situ hybridization. Xpat mRNA is associated with the germ plasm and is localized through the METRO pathway.



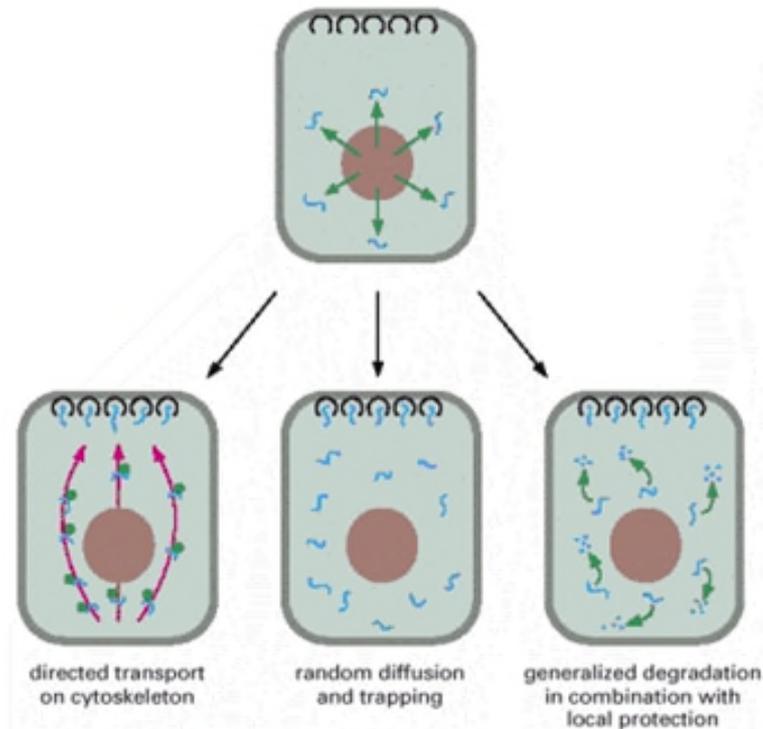
Colocalization of β -actin mRNA (red) in the leading lamellae of chicken fibroblast with phosphorylated myosin (green immunofluorescence). Nucleus stained blue with DAPI.



β -actin mRNA localization in the neurite and growth cones.

Mechanisms by which RNAs can be localized

1. random cytoplasmic diffusion and trapping
2. general degradation and localized RNA stability
3. vectorial transport from the nucleus to a specific target
4. active directional transport on cytoskeletal elements

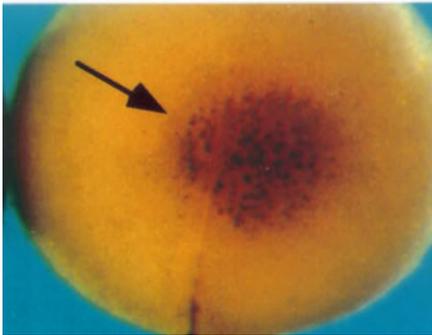


Examples of mechanisms of RNAs localization in Different Organisms and Cell types



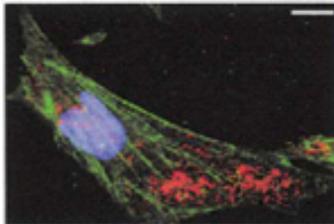
Mechanisms 1 & 2 (combined):

The localization of maternal *nanos* mRNA at the posterior of an activated, unfertilized *Drosophila* egg is the result of two different mechanisms: **generalized degradation and local protection**.



Mechanism 3:

Xpat mRNA is localized to the vegetal cortex of stage I *Xenopus* oocytes through a region of the mitochondrial cloud called the messenger transport organizer (METRO) that also contains the nuage or germ plasm. This represents an example of **vectorial transport to a specific target**



Mechanism 4:

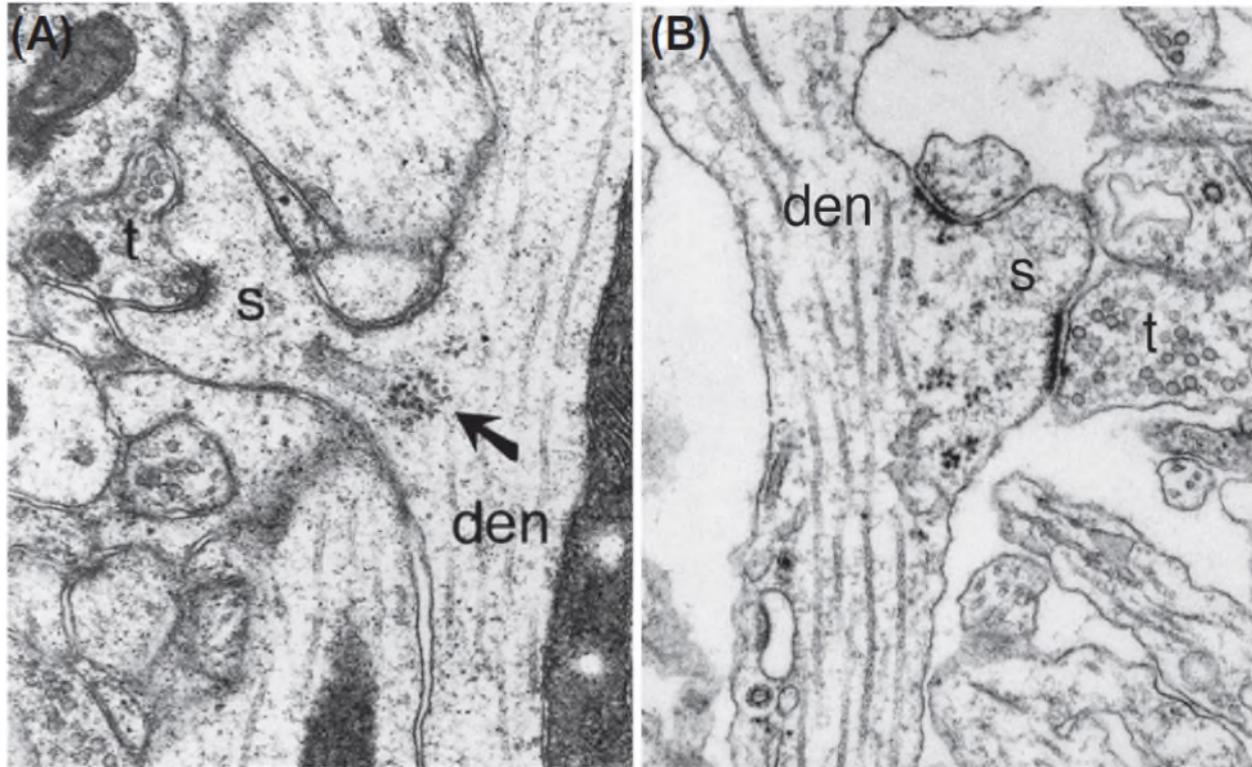
Localization of β -actin mRNA (red) in the leading lamellae of chicken fibroblast (myosin = green immunofluorescence) or in in the neurite and growth cones of a neuron. These are examples of **active directional transport on cytoskeletal elements**



How did researchers discover the localization of mRNAs in axons and dendrites?

A brief historical perspective

Detection of ribosomes at the base of dendritic spines



Electron microscopy of ribosomes (polysomes) in mature dendrites from mouse brains.

History of the techniques for visualization of mRNAs

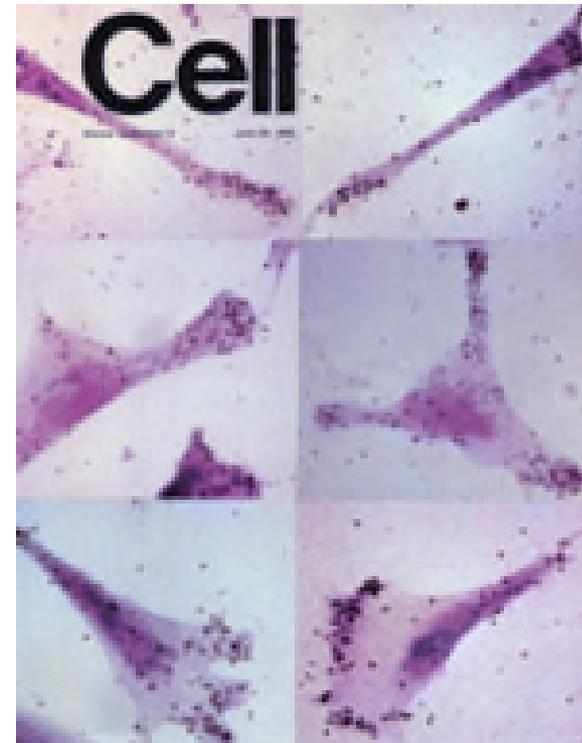
IN SITU HYBRIDIZATION

1986 till 1990's. *In situ* hybridization studies using digoxigenin or radioactive (~10-20 mRNAs)

Late 1990's. RNA- fluorescent *in situ* hybridization studies (FISH, ~50 mRNAs)

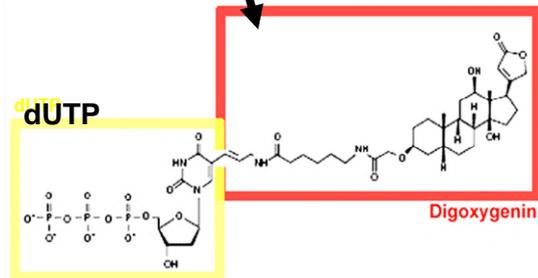
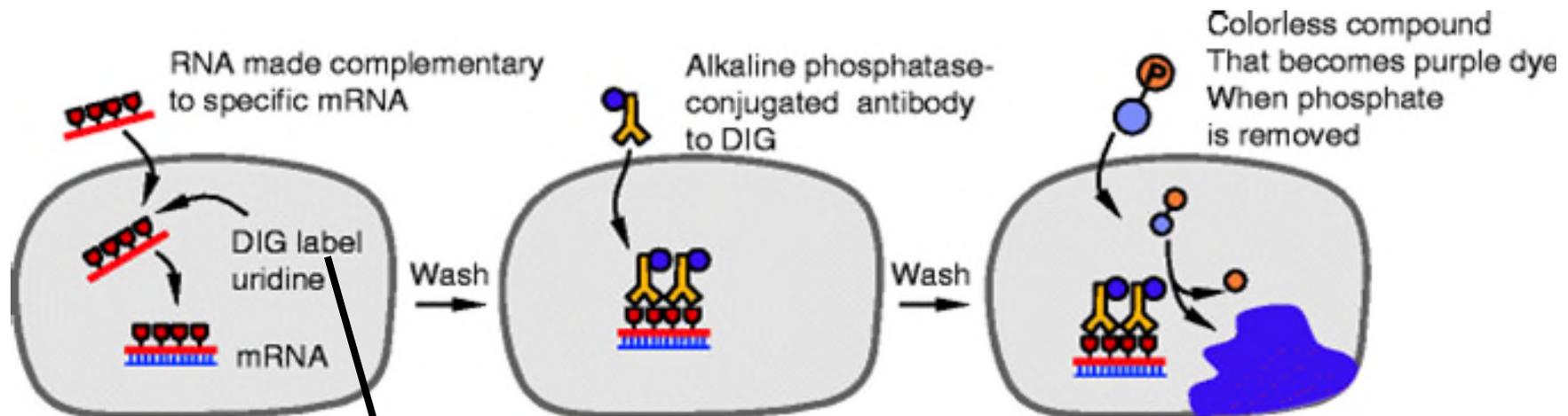
2007. Allen Brain Atlas project – FISH not optimized for dendritic mRNAs (65 mRNAs)

Lawrence & Singer 1986



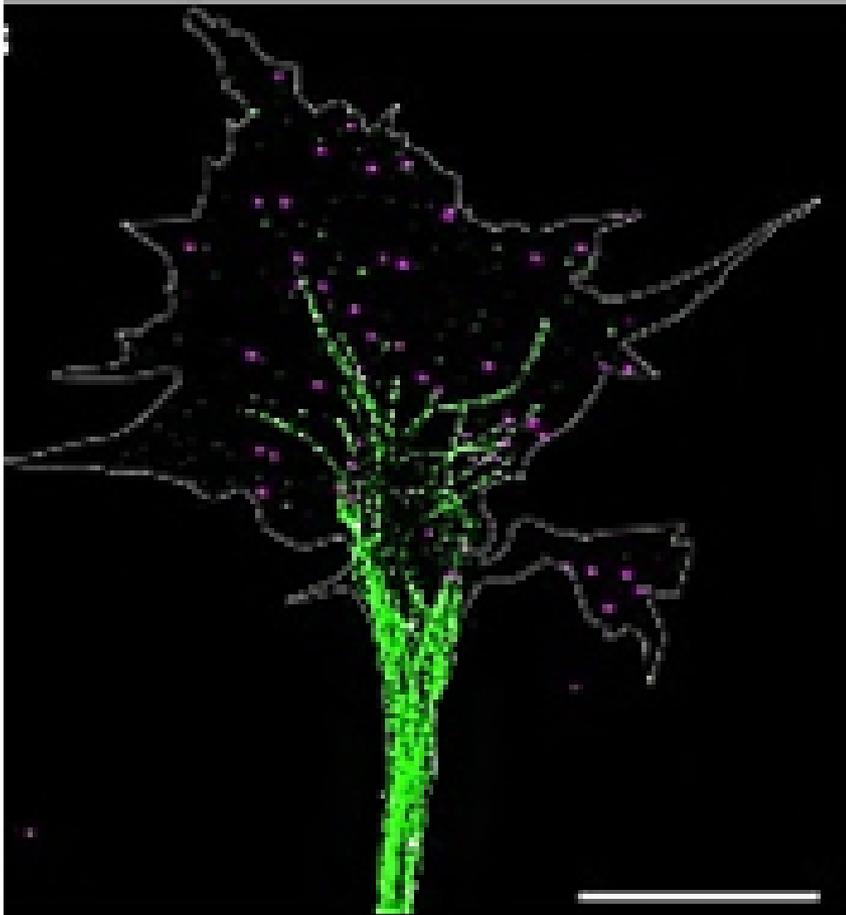
First localized mRNA:
actin mRNA in fibroblasts' lamellipodia
(vimentin, tubulin mRNA)

In situ Hybridization-based methods for RNA imaging

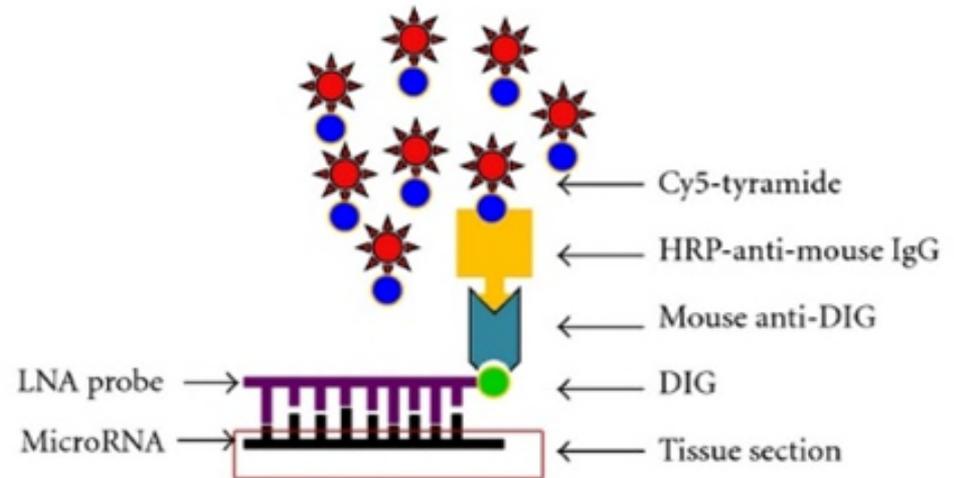


Digoxigenin-labeled probes coupled to alkaline-phosphatase

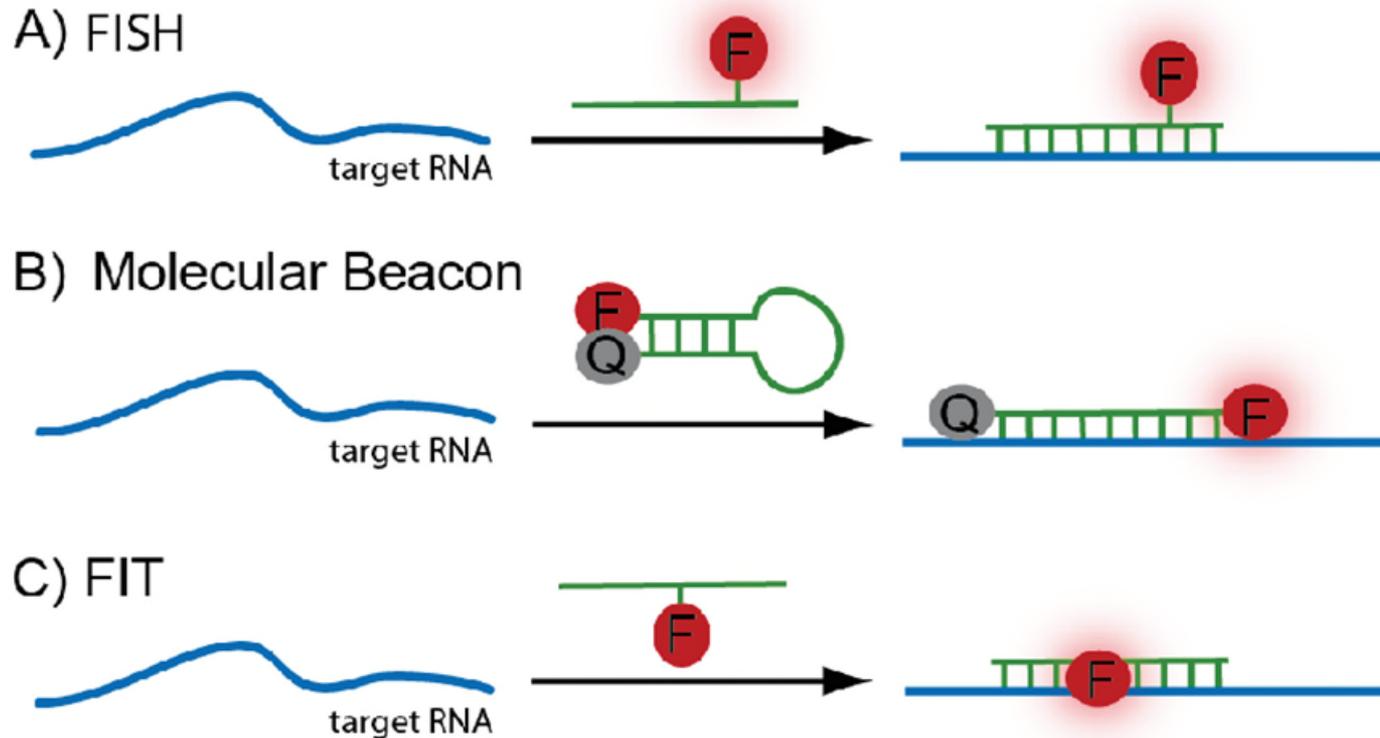
In situ Hybridization-based methods for RNA imaging



FISH with tyramide enhancement

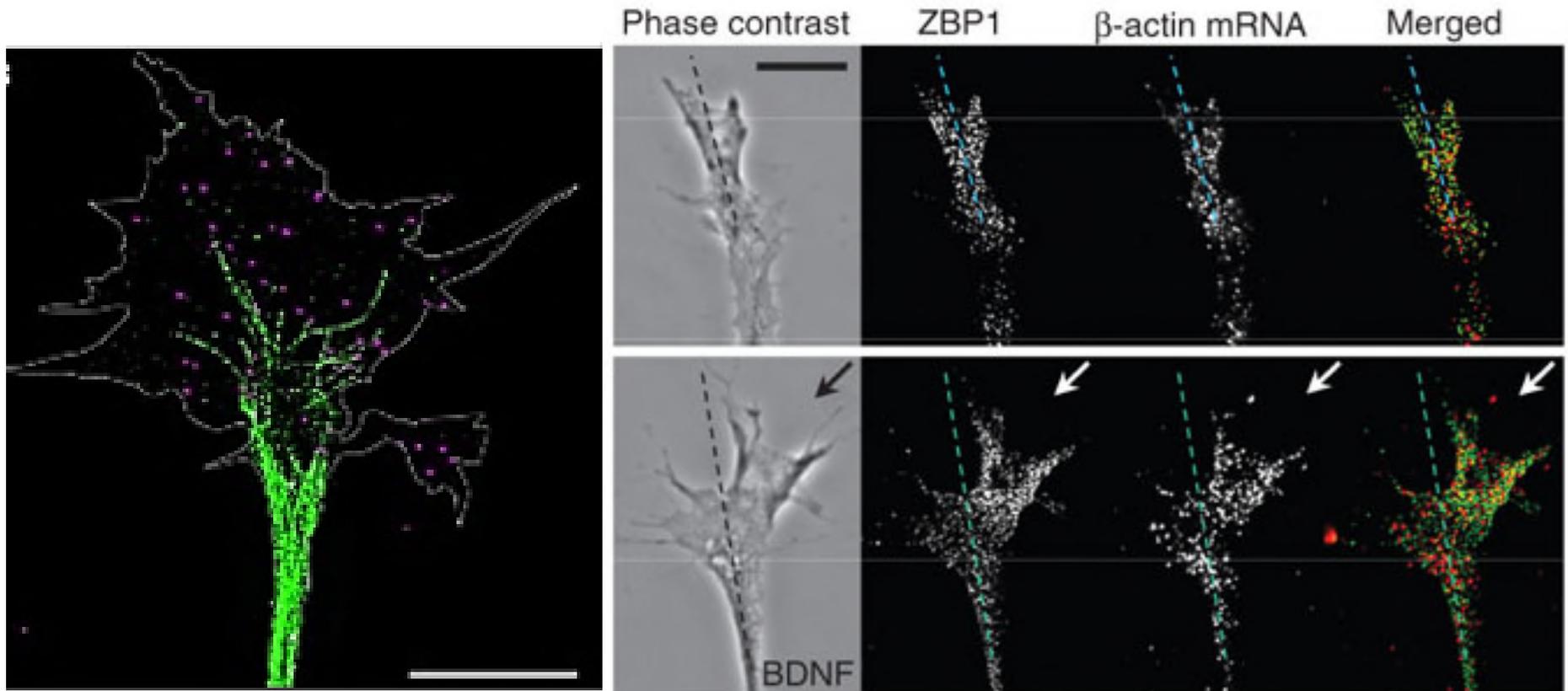


In situ Hybridization-based methods for RNA imaging



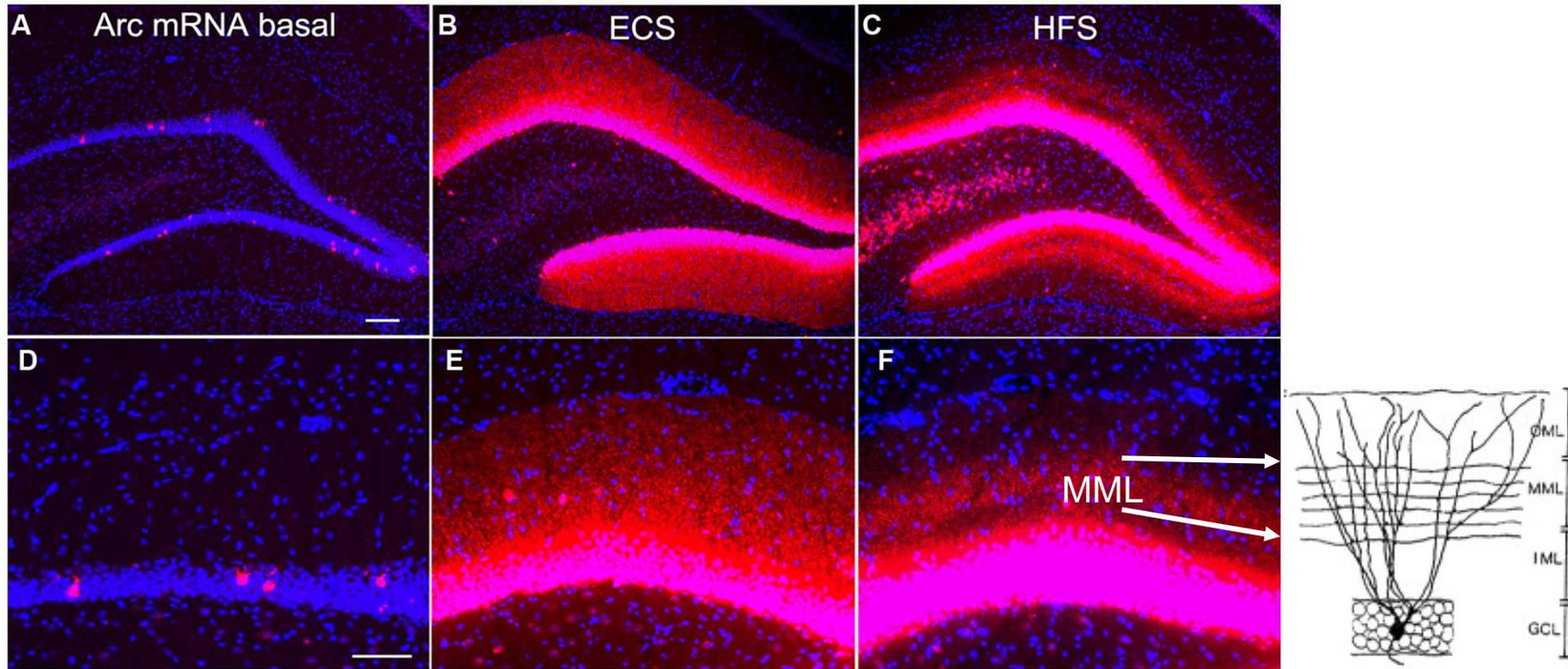
(A) Standard fluorescence in situ hybridization (FISH): a fluorophore-linked RNA probe binds the target RNA sequence. (B) Molecular beacon: signal to noise is improved relative to a standard FISH probe because the fluorescence signal of the reporter probe is quenched when unbound. (C) Forced intercalation (FIT) probes: binding enforces intercalation of the dye molecule into the probe-target duplex, resulting in a strong turn-on effect of the fluorophore.

B-Actin mRNA is localized in axonal growth cones



Yao et al. Nature Neuroscience (2006)

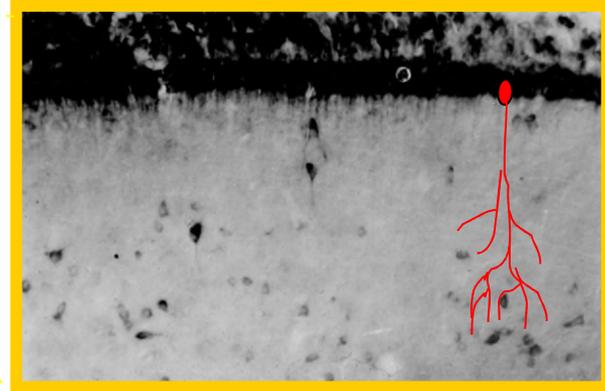
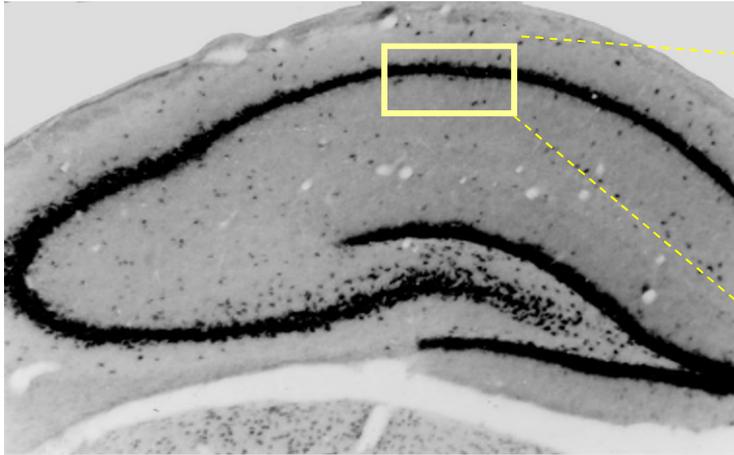
ARC (activity-regulated cytoskeleton) mRNA localizes to active synapses



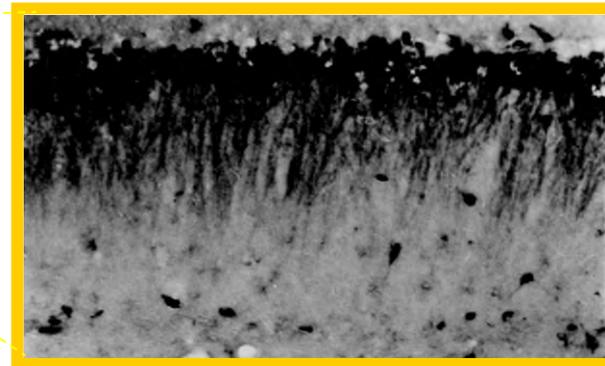
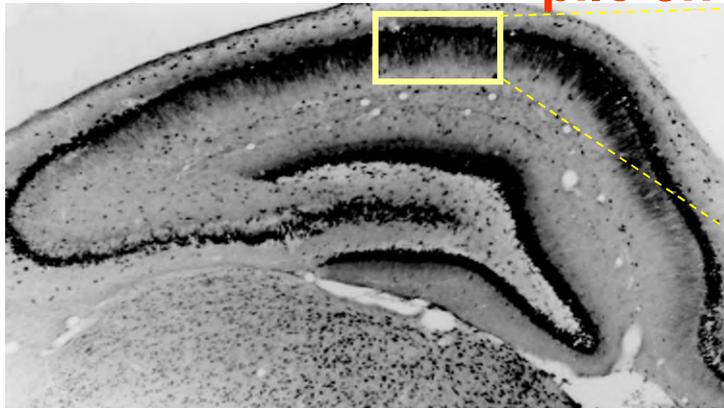
- ARC is an 'immediate early gene' - transcriptionally regulated by neuronal activity
- After transcription, ARC mRNA is transported into dendrites.
- In hippocampal slice preparations, ARC is transported to activated laminae (synapses) but not to adjacent silent laminae (synapses)

Epileptogenic seizures induce in vivo accumulation of BDNF mRNA in dendrites

control



pilo 3h



Sequencing methods for RNA analysis

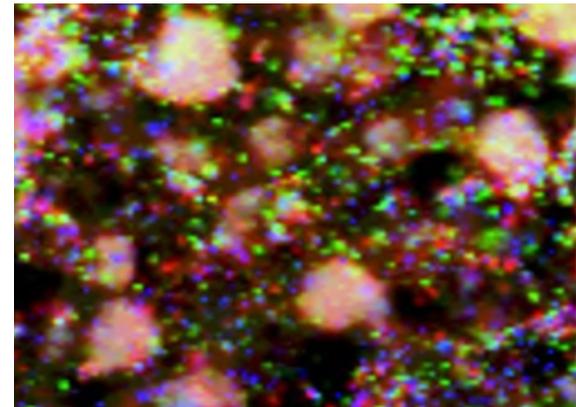
2006-7. RNA microarray analysis of neurites mechanically separated from somata (**150-400 mRNAs**)

2012. RNA deep sequencing/NanoString analysis and high-resolution FISH (**2.550 mRNAs**)*

2015. Fluorescent in situ sequencing (FISSEQ) using multiple hexamer probes.**



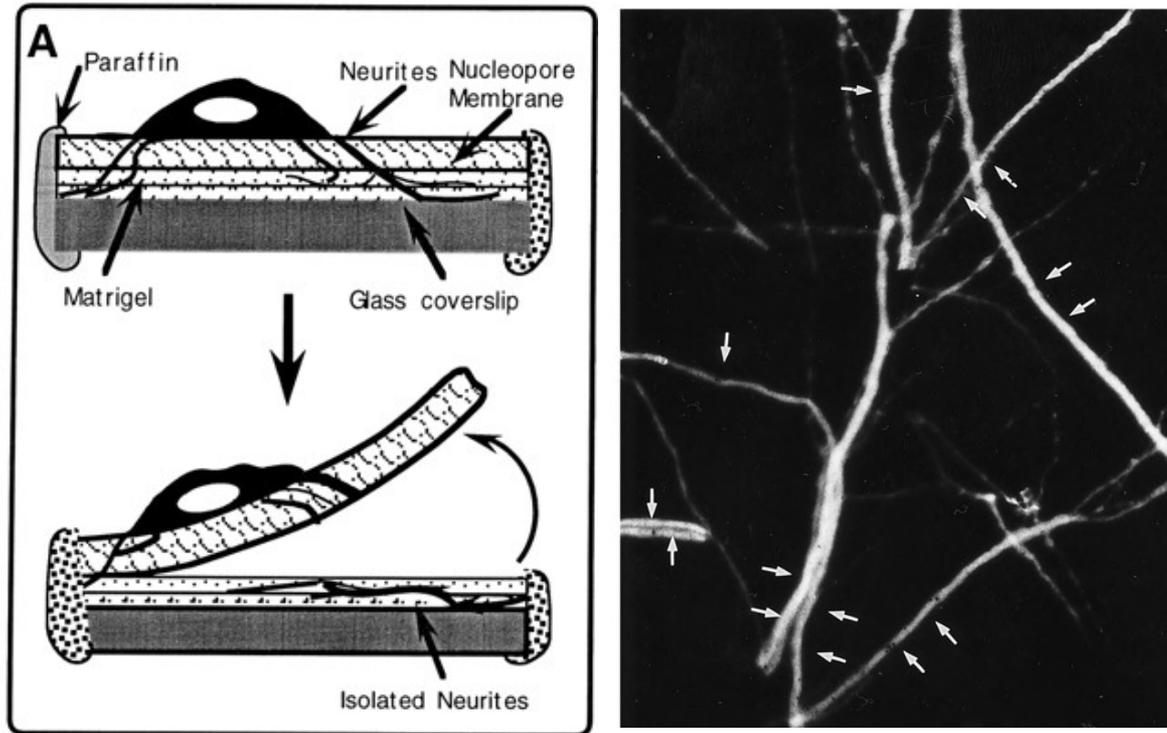
*Erin Schuman MAX PLANK
INSTITUT Frankfurt am Main (D)



**FISSEQ: Each spot is one base of an RNA transcript localized in 3D in the tissue. The color of the spot identifies the base (A, T, G or C). The spots change color over time, building up to image a full RNA sequence, up to 30 bases.

Which mRNAs are localized in dendrites of mature neurons?

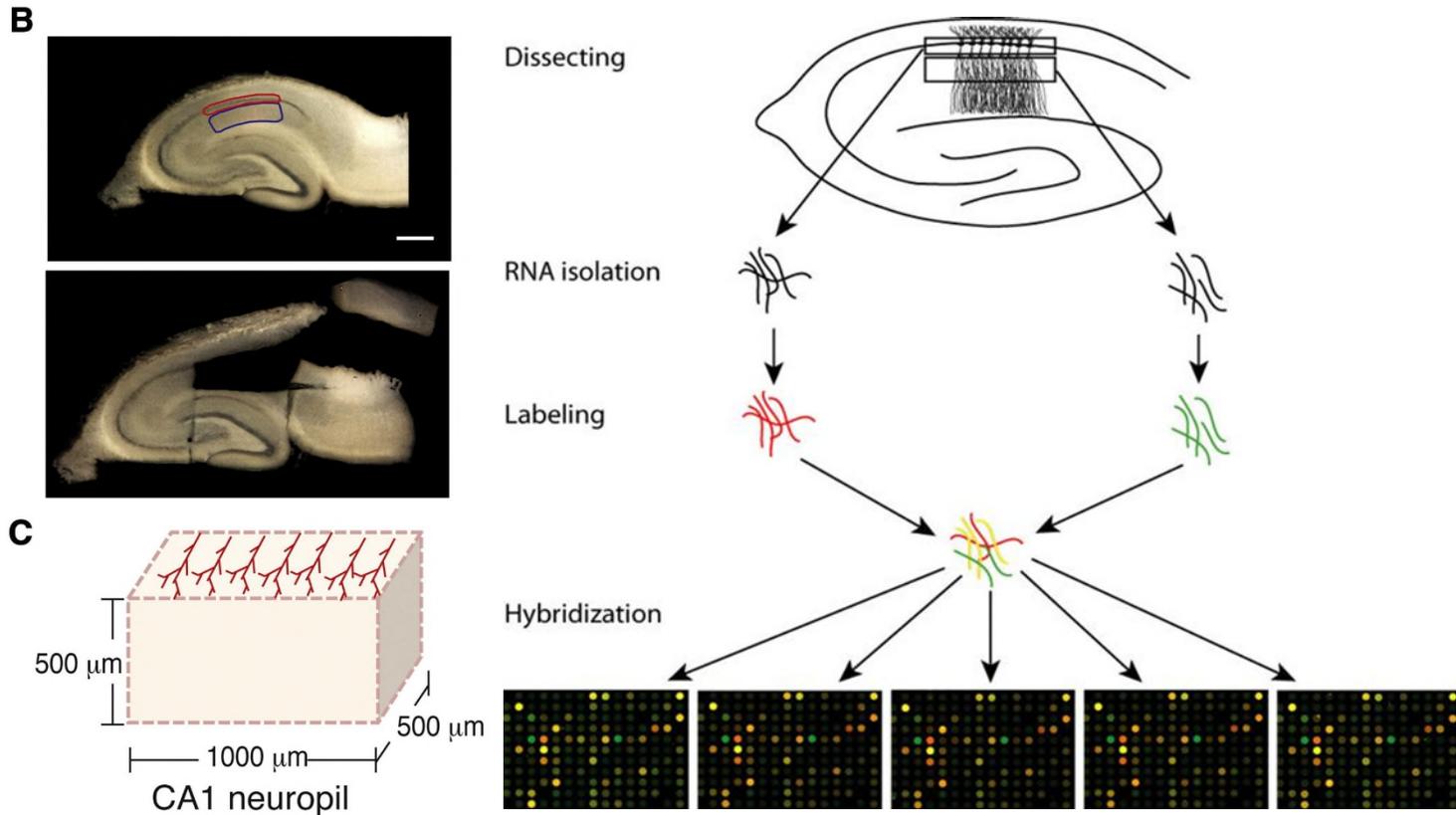
Analysis of mRNAs isolated from neurites in sandwich-hippocampal cultures



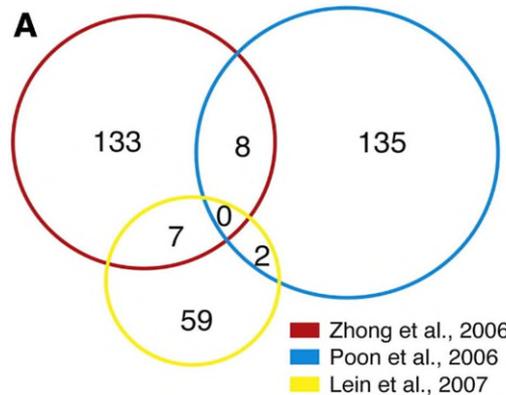
Method developed by Torre & Steward, JNeurosci1992
mRNA analysis Eberwine et al, 2002

Which mRNAs are localized in dendrites of mature neurons?

Microrray analysis of mRNAs isolated from CA1 hippocampal **neuropil**



Which mRNAs are localized in neurites of mature neurons?



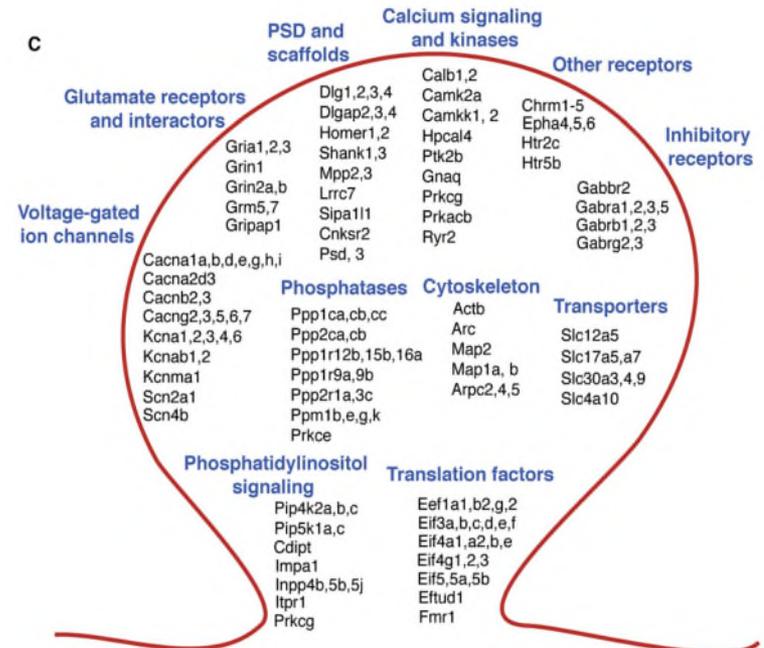
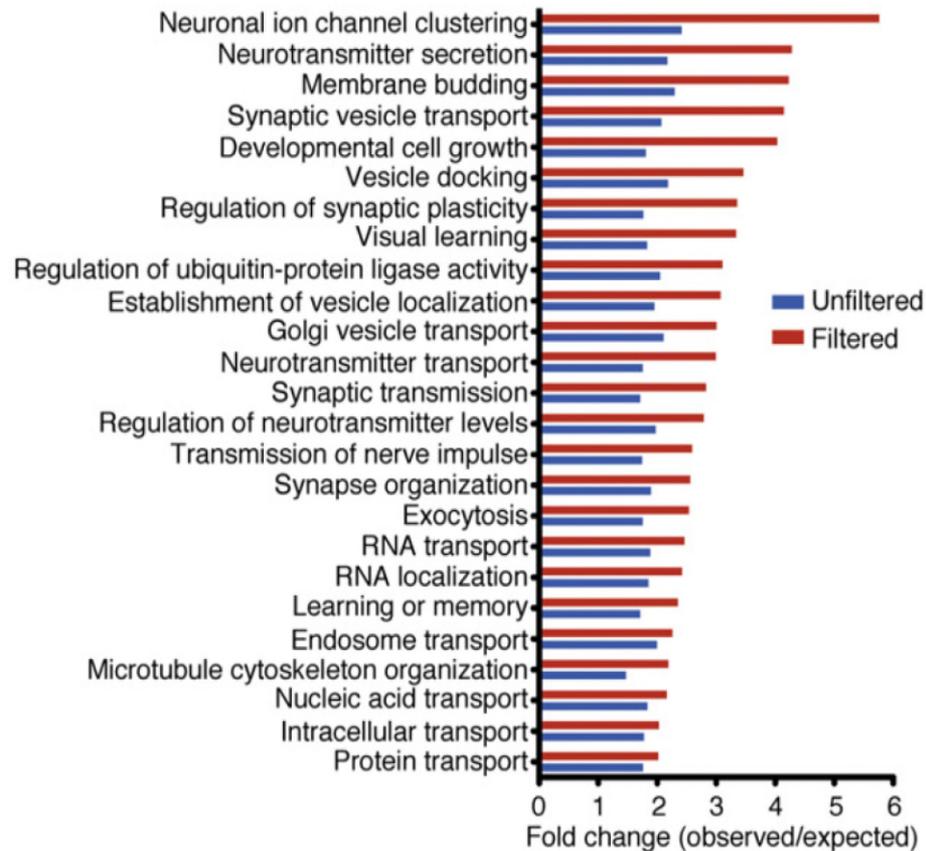
Based on 150-400 different mRNAs
(~5% expressed genes)

Category of mRNAs in CA1 dendrites	percentage
Receptors, ion channels, and postsynaptic molecules	7.8%
Cytoskeleton	7.8%
Extracellular matrix, cell adhesion, and immuno-molecules	20.1%
Signal transduction and Protein modification	16.9%
Translation factors and RNA-binding proteins	4.5%
Ribosomal proteins	16.2%
Peptide processing and degradation	7.8%
Protein transport, membrane trafficking, endocytosis, and exocytosis	6.5%
Molecular motor	0.6%
Growth factors	2.6%
Other	9.1%

Zhong, Zhang and Bloch, 2006 BMC Neuroscience

Local Transcriptome in the Synaptic Neuropil

(2550 mRNAs)



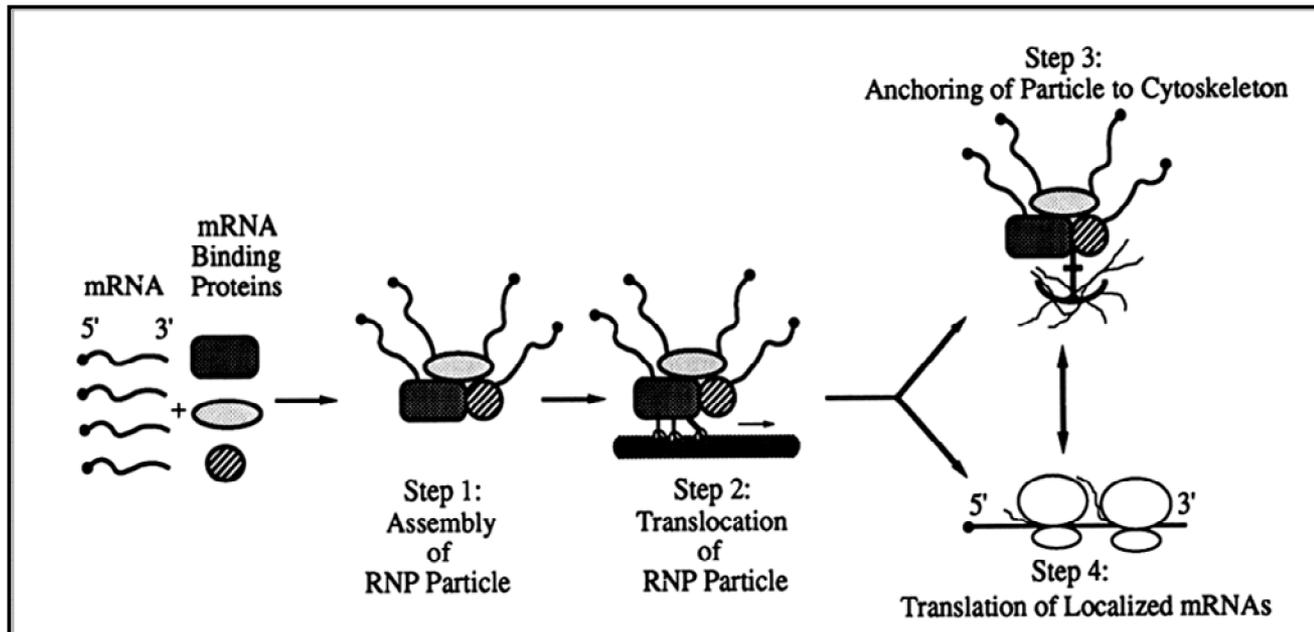
How are mRNAs transported in axons and dendrites?

Multiple and complex molecular mechanisms

How are mRNAs transported?

Wilhem & Vale (1993) proposed that mRNAs transport consists of 4 consecutive steps:

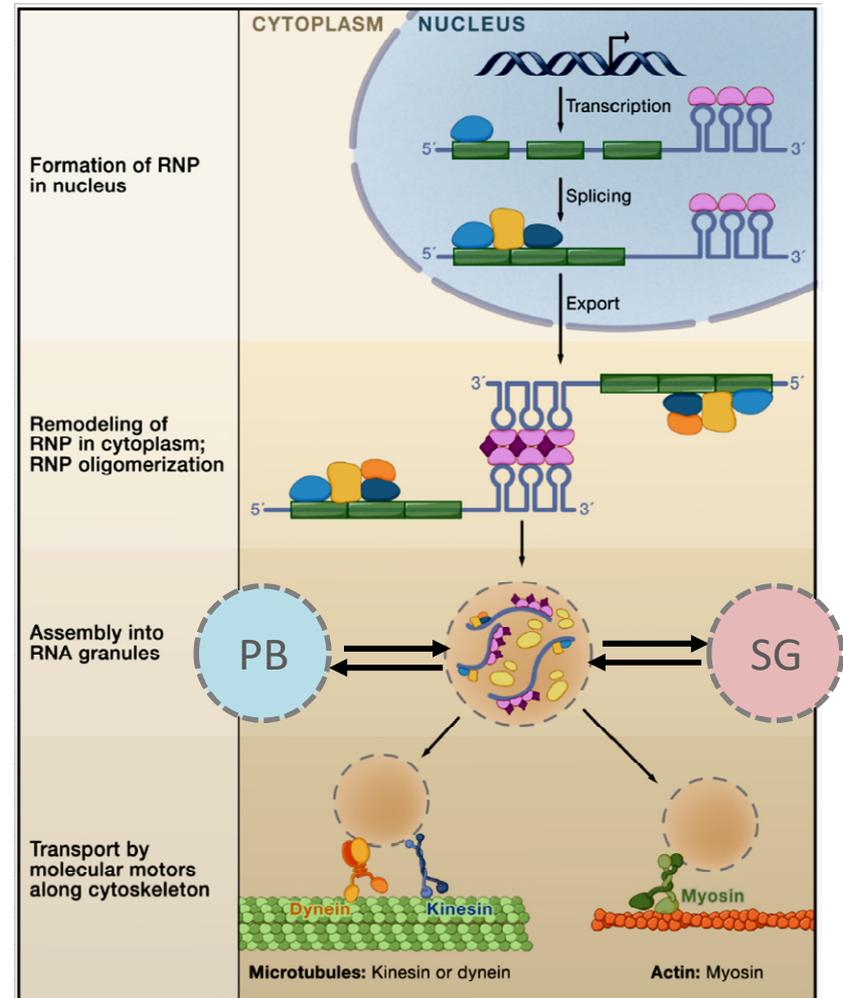
- 1) Formation of large ribonuclear particles (mRNPs, transporting granules) by interaction of mRNA with RNA-binding proteins (RBPs);
- 2) Transport of mRNPs to their destination site;
- 3) Anchoring of mRNPs at the destination site;
- 4) Local translation of delivered mRNAs



Revision of the initial model of mRNP transport

Original Wihlhem & Vale model +revisions

1. (A) Formation of mRNPs in the nucleus;
(B) Cytoplasmic mRNP remodeling, oligomerization and assembly (possible exchanges with P-Bodies, Stress Granules)
2. Transport of mRNPs to their destination with bi-directional movements (sushi-belt model);
3. Anchoring of mRNPs at the destination with involvement of actin-myosin system;
4. Local translation of delivered mRNAs and local degradation



Modified from Martin KC, Ephrussi A. *mRNA localization: gene expression in the spatial dimension*. Cell. 2009 doi: 10.1016/j.cell.2009.01.044

Trans-factors bind to the cis-elements of the mRNA in various cellular districts

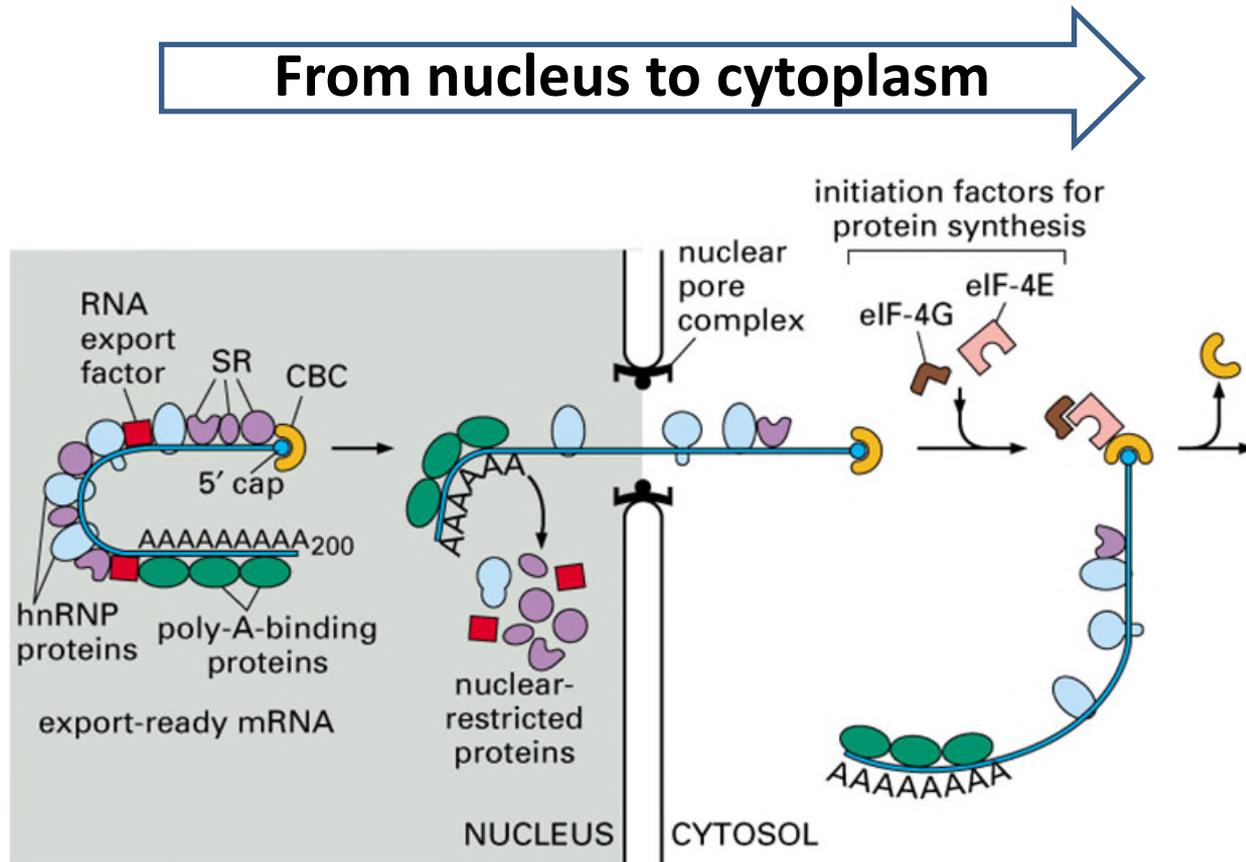
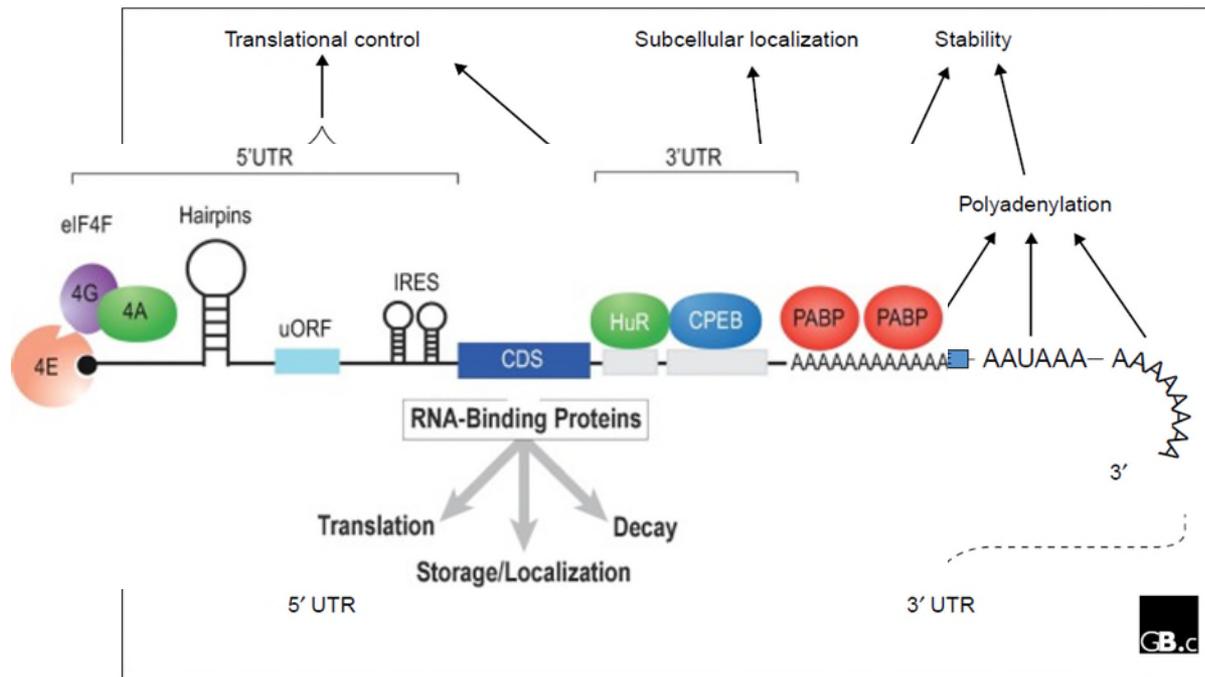


Figure 6-40 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

The subcellular destination of an mRNA is determined by the presence of cis-acting elements within its sequence.

- **Cis-elements** = signals (either linear sequences or 3D structures) that are mainly, but not exclusively, located within the 3' UTR and direct the binding of **trans-acting factors** to the RNA.
- **Trans-acting factors** = RNA binding proteins (RBPs).



Box 1: RNA-binding proteins acquired in the nucleus affect the cytoplasmic fate of mRNAs

Many proteins that bind to mRNAs in the nucleus have been shown to remain bound in the cytoplasm and to regulate mRNA localization and translation. Such proteins include heterogeneous nuclear ribonucleoproteins (hnRNPs), exon junction complexes (EJC) and a number of other nuclear RNA binding proteins.

hnRNP A2 binds an RNA element, called the A2 response element (A2RE) within the 3'-untranslated region (UTR) of the mRNA encoding myelin basic protein (MBP) and localizes MBP mRNA to the distal processes of oligodendrocytes [96]. In neurons, A2REs mediate dendritic localization of reporter transcripts, and a subset of dendritically-localized mRNAs contain A2REs, indicating a role for hnRNP A2 in dendritic mRNA targeting [97].

The EJC consists of a set of nuclear proteins that bind to pre-mRNA transcripts during splicing and that have been shown to be required for the cytoplasmic localization of *oskar* mRNA in *Drosophila* oocytes [98]. Many EJC components are present in neuronal dendrites, where they have also been shown to bind localized mRNAs [99]. When EJC components are bound within coding regions, they may recruit ribosomes to promote translation; when they are deposited downstream of coding regions, the transcripts are usually targeted for degradation *via* the Nonsense-Mediated Decay (NMD) pathway after the first round of translation. The mRNA encoding *Arc* contains two conserved introns within its 3'-UTR and thus may be rapidly degraded by NMD after the first round of translation [100]. Such regulation may ensure tight temporal control and a 'burst' of *Arc* protein synthesis at stimulated synapses.

The zip-code binding proteins ZBP1 and ZBP2 associate with β -actin mRNA during transcription and are required for both export and dendritic targeting of β -actin mRNA [99].

ELAV/HuD proteins, neuron-specific nuclear RNA binding proteins known to regulate mRNA stability, have been shown to associate with many localized mRNAs, including those encoding GAP43, Homer 1a, neuritin and CamKII α . [101].

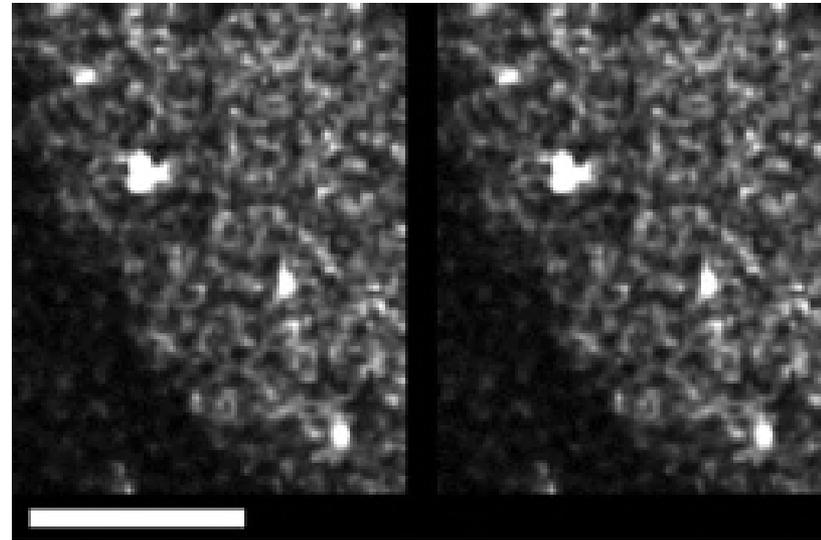
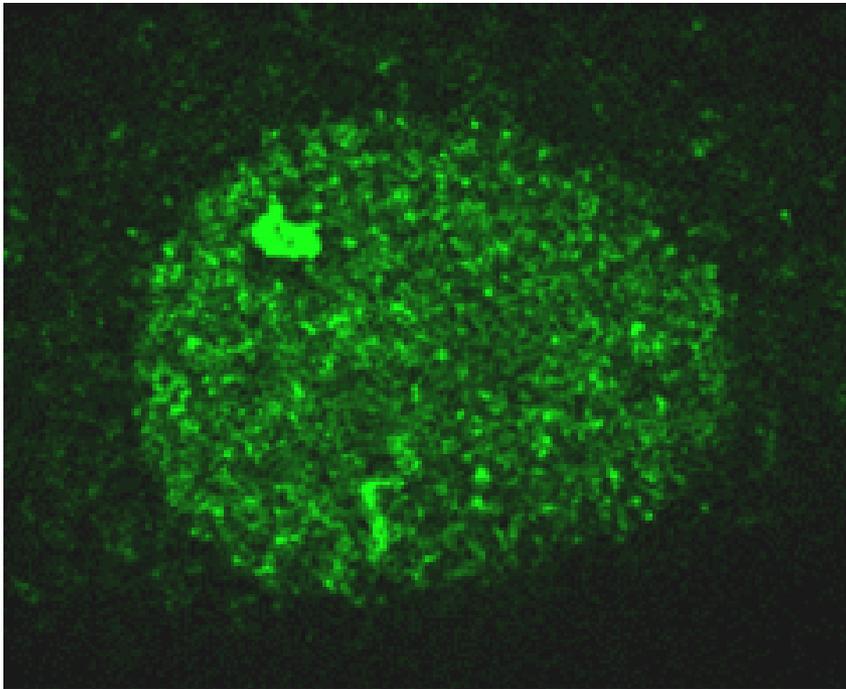
LSm1, an auxiliary factor for RNA degradation, and CBP80, a (pre)mRNA binding protein have been shown to bind to dendritically localized mRNAs β -actin, eEF1 α , and the IP3 receptor [102].

STEP 1 = mRNP formation, A) in the nucleus

How are mRNAs transported?

Let's follow a single mRNA from birth to death in a neuron

STEP 1) Formation of large ribonuclear particles (mRNPs, transporting granules) by interaction of mRNA with RNA-binding proteins (RBPs) in nucleus

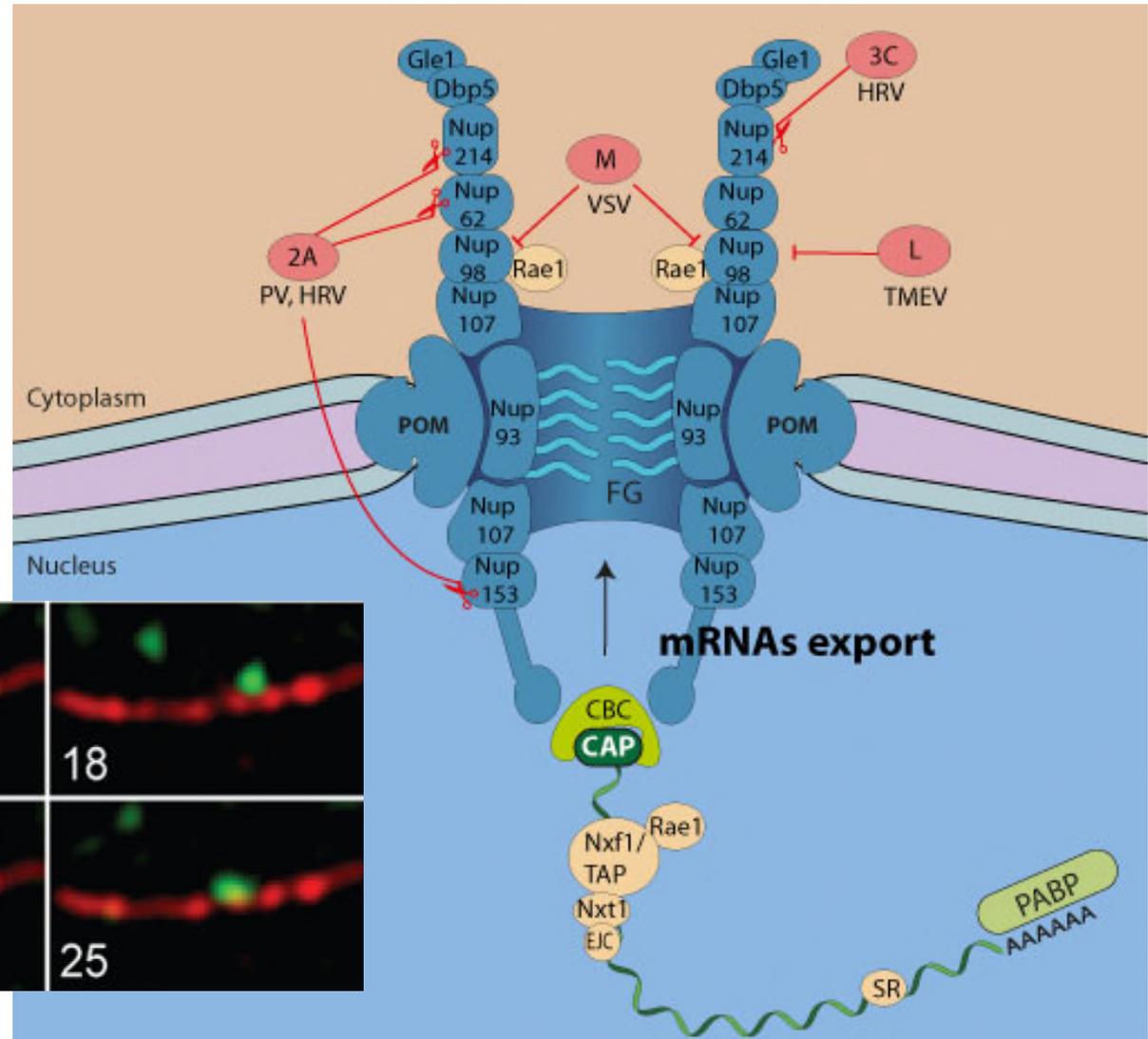
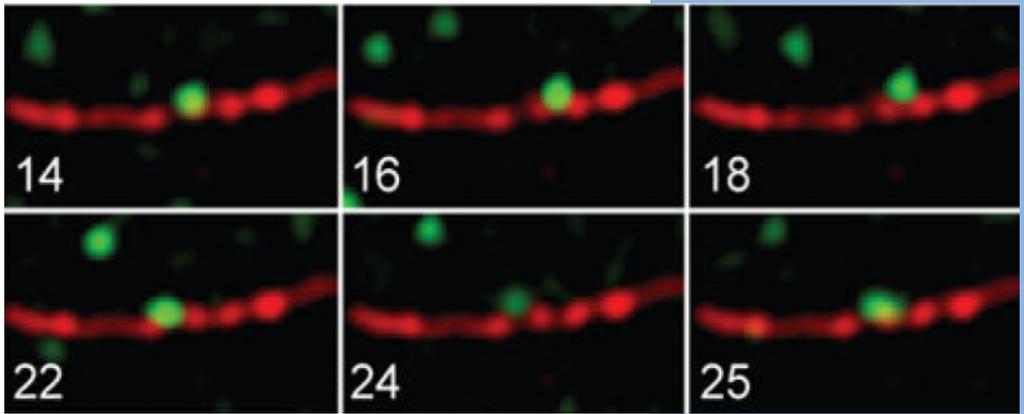


Dynamics of Single mRNPs in Nuclei of Living Cells
Yaron Shav-Tal et al. Science. 2004

STEP 1 = mRNP formation, A) in the nucleus

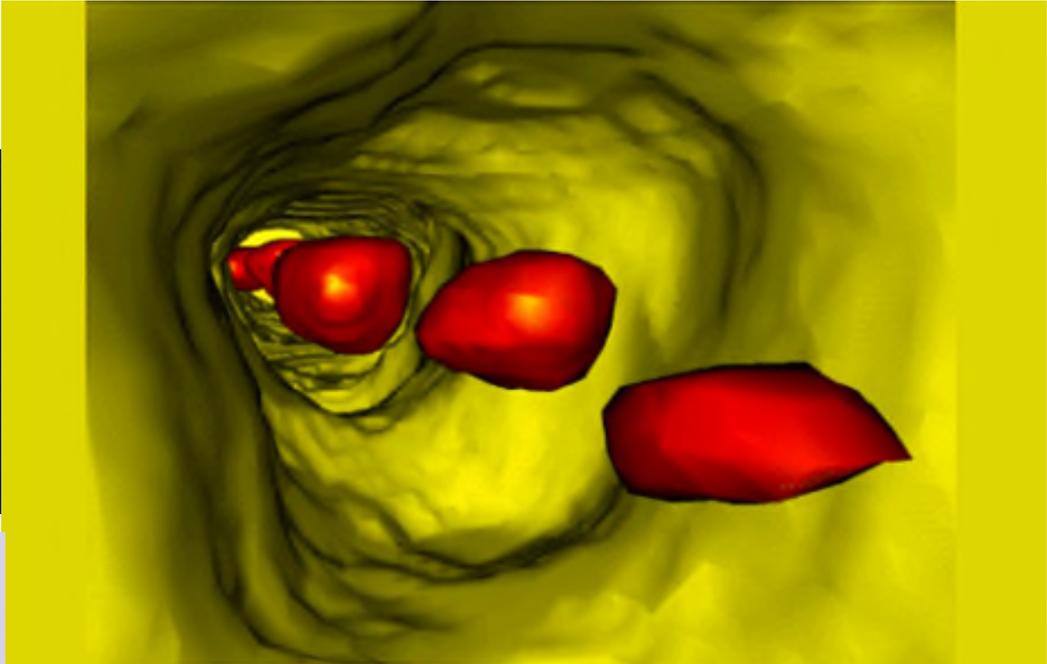
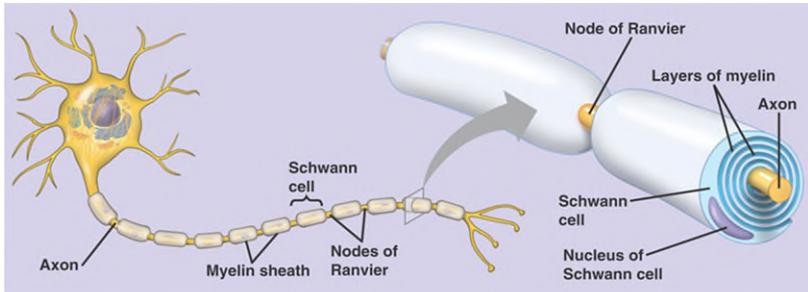
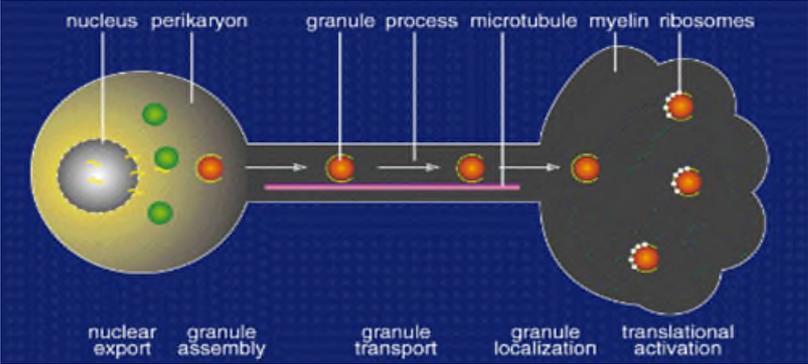
Exit of an mRNA from the nuclear pore

Around 3.000 nuclear pores in a nuclear envelope: only 48 sec for an mRNA to exit



STEP 1 = mRNP formation, B) in the cytoplasm

Visualization of mRNA granules in oligodendrocytes by fluorescence microscopy

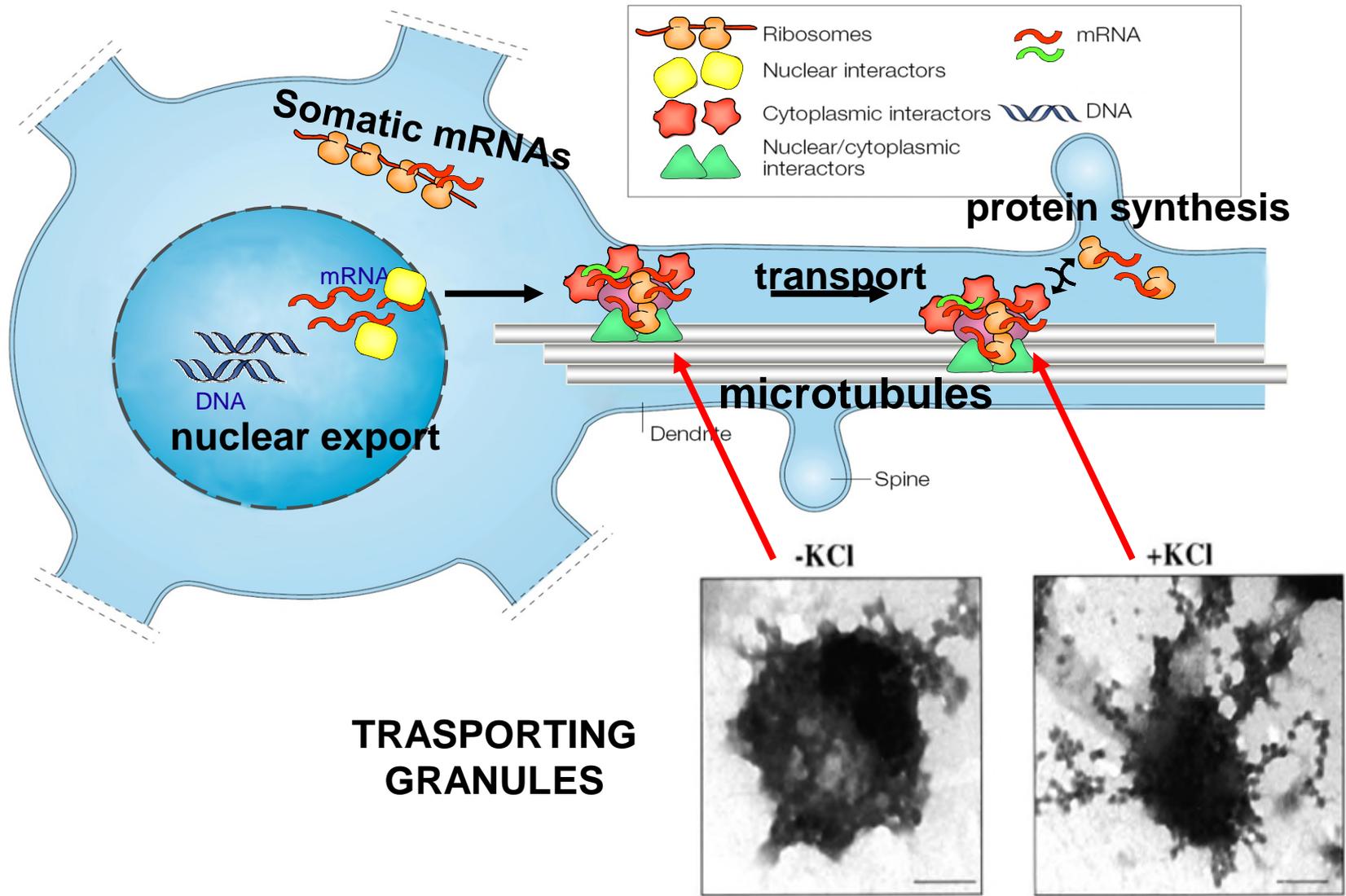


Interior view of RNA granules transported within an oligodendrocyte process.

Fluorescent RNA was microinjected into an oligodendrocyte in culture. The microinjected cell was optically sectioned by confocal microscopy. Two different isosurfaces were generated - one delineating the plasma membrane (shown in yellow) and one delineating the RNA granules (shown in red). Experimental details are described in Ainger et al., (1993).

STEP 1 = mRNP formation, B) in the cytoplasm

mRNAs granules visualized by electron microscopy



Anna M. Krichevsky and Kenneth S. Kosik, Neuron 2001

Approximate size of neuronal mRNA granules

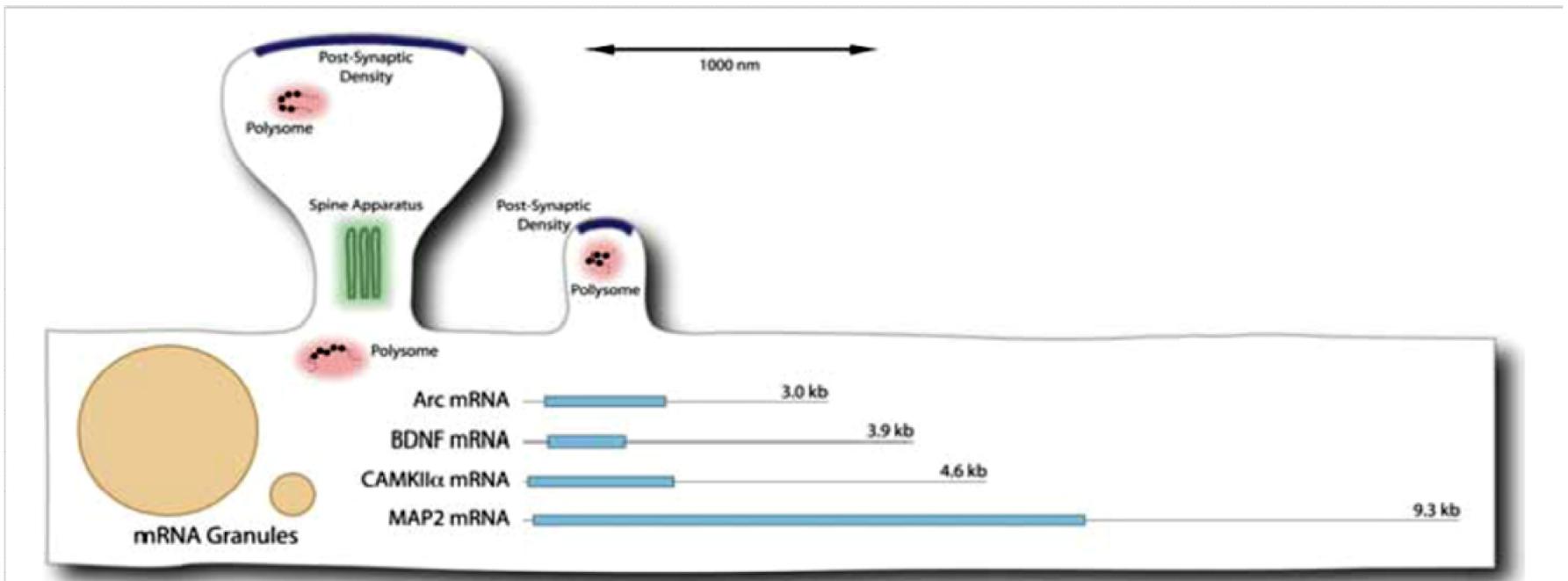


Figure 1. Approximate sizes of representative dendritic mRNAs and translational elements at synaptic sites on dendrites. The drawing illustrates the approximate size range of spine synapses that would be found in rat forebrain structures such as the hippocampus and cerebral cortex. The lines represent the approximate length of representative dendritic mRNAs if they were straightened out. Shading indicates the length and position of the coding region.

Different RBPs in different transporting mRNA granules

Kanai et al. (2002) immunoprecipitated RNA granules using an antibody against KIF5

(42 RBPs identified from granules containing CamKII- α mRNA – NO Ribosomes!)

Table 1. Identified Proteins in the RNA-Transporting Granules

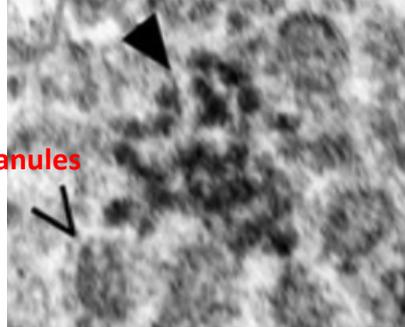
Function/Type (Number)	Protein Name
RNA transport (6)	FMR1, FXR1, FXR2, Pur α, Pur β, staufen
Protein synthesis (6)	EF-1α, eIF2α, eIF2β, eIF2γ, Hsp70, ribosomal protein L3
RNA helicases (3)	DDX1, DDX3, DDX5
hnRNPs (5)	hnRNP-A/B, hnRNP-A0, hnRNP-A1, hnRNP-D, hnRNP-U,
Other RNA associated (12)	ADP-ribosylation factor guanine nucleotide factor 6, ALY, cold inducible RNA binding protein, EWS, NonO, Nucleolin, paraspeckle protein 1, PSF, RNA 3'-terminal phosphate cyclase, RNA binding motif protein 3, SYNCRIP, TLS
Other known proteins (3)	Ser/Thr kinase receptor associated protein, TRIM2, TRIM3
Hypothetical proteins (7)	CGI-99, FLJ38426, HSPC-117, zfp385, 2610528C06Rik, 5730436H21Rik, 6720458F09Rik

A total of 42 proteins were identified. Proteins that were investigated in this work are shown in bold. See also Supplemental Figure S4 for their accession numbers [<http://www.neuron.org/cgi/content/full/43/4/513/DC1>].

STEP 1 = mRNP formation, B) in the cytoplasm

Elvira et al. (2005) purified RNA granules by sucrose density gradient centrifugation

(205 RBPs identified from granules containing β -actin mRNA – Include Ribosomes!)



RNA-Binding Proteins previously identified in RNA granules

- hnRNPs
- hnRNP D (Auf 1) (16)
- **hnRNP A1** (16)
- **SYNCRIP/hnRNP Q1/Gry-RBP** (16, 37)
- hnRNP R1 (16)
- hnRNP A/B (16)
- hnRNP A2/B1 (20)
- hnRNP A0 (16)
- hnRNP U(16)
- DEAD box helicases
- **DEAD box 3** (16)
- DEAD box 1/DDX1 (16)
- DEAD box 5/17 (16)
- Other RNA-binding proteins
- ZCBP/IMP-2 (19)
- Nucleolin (16)
- **Staufen 2** (14, 16)
- RNA granule protein 105 (45)

RNA-binding proteins not previously identified in RNA granules

- hnRNPs
- hnRNP K
- **hnRNP C**
- TAR DNA binding
- hnRNP L
- hnRNP X (E2)
- hnRNP H
- hnRNPA3
- hnRNP M
- DEAD box helicases
- DEAD box 6
- DEAD box 9
- NORP1 (regulator of nonsense)
- eIF4A
- DEAD box BAT-1

Other RNA-binding proteins

- Zip code-binding protein 2/MARTA1
- **G3BP1**
- Nucleophosmin
- Activator of dsRNA kinase
- **Interleukin enhancer-binding factor 2**
- Interleukin enhancer-binding factor 3
- G3BP2
- PTB
- Poly(A)-binding protein
- Matrin-3
- PAI-1 RNA binding
- **Y box-binding protein 1 (mYB-1b)**
- CYFIP2
- ELAV-like proteins
- ELAV-like 2 (Hu-B)
- **ELAV-like 4 (Hu-D)**
- ELAV-like 3 (Hu-C)
- ETR-R3B

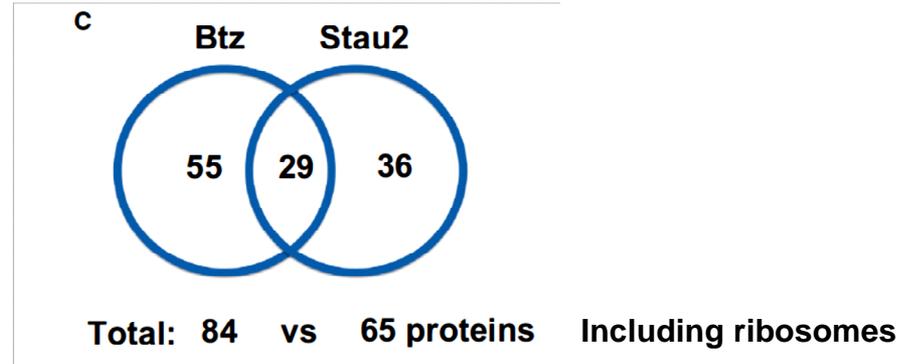
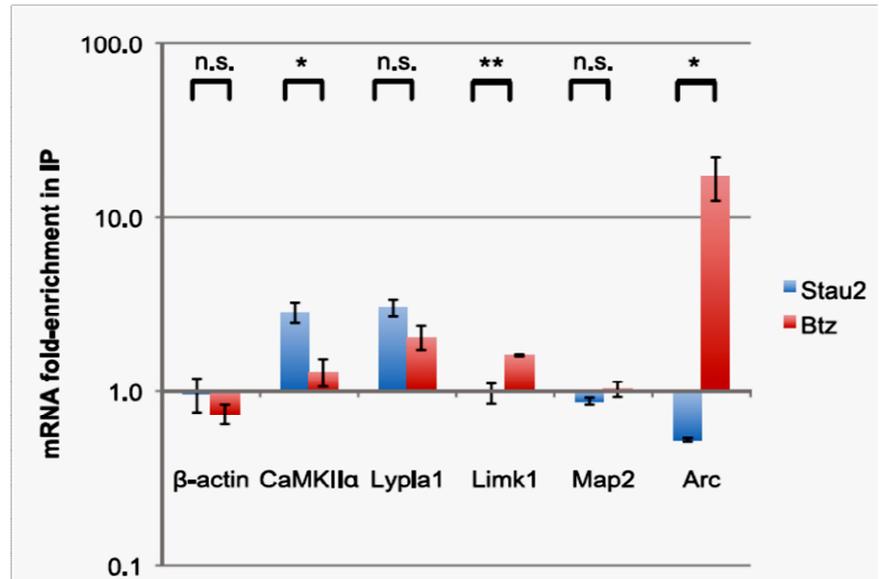
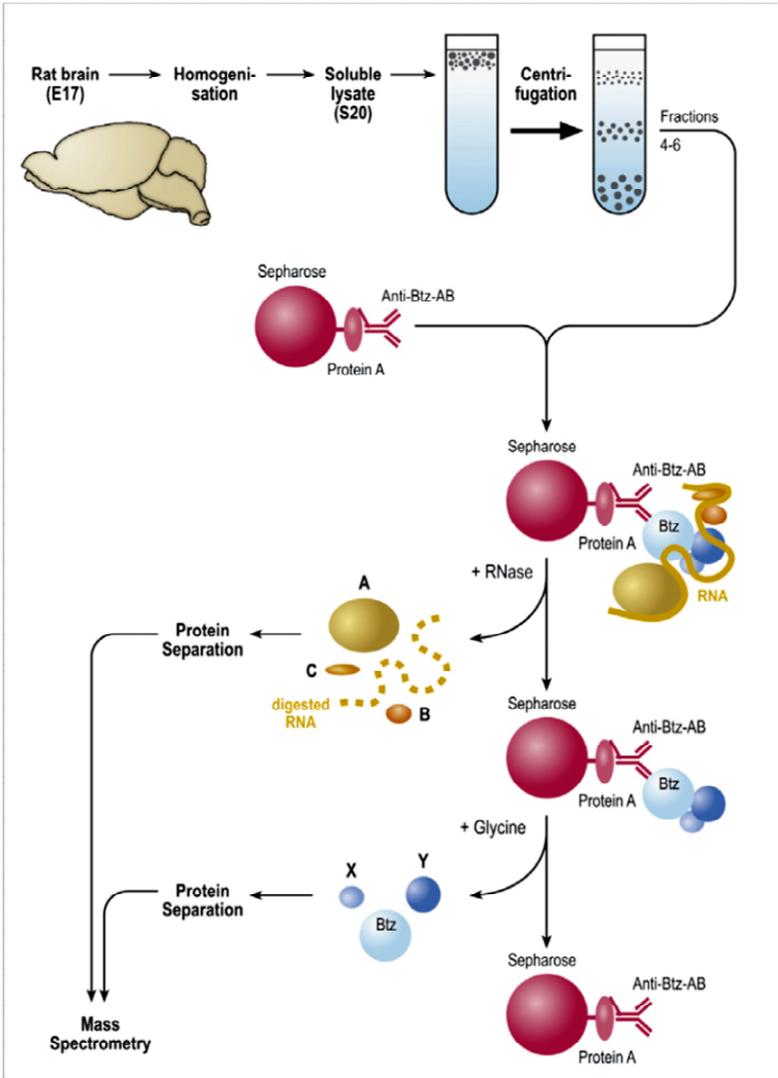
No FMRP
No Pur- α

Isolated 61 of 64 total ribosomal proteins

Ribosomal Proteins
Ribosome chaperons
Traslation Factors

STEP 1 = mRNP formation, B) in the cytoplasm

Analysis of trans-factors revealed heterogeneity in neuronal mRNPs composition



How is an mRNAs transported?

1. (A) Formation of mRNPs in the nucleus;
(B) Cytoplasmic mRNP remodeling, oligo-merization and assembly (possible exchanges with P-Bodies, Stress Granules)
2. Transport of mRNPs to their destination with bi-directional movements (sushi-belt model);
3. Anchoring of mRNPs at the destination with involvement of actin-myosin system;
4. Local translation of delivered mRNAs and local degradation

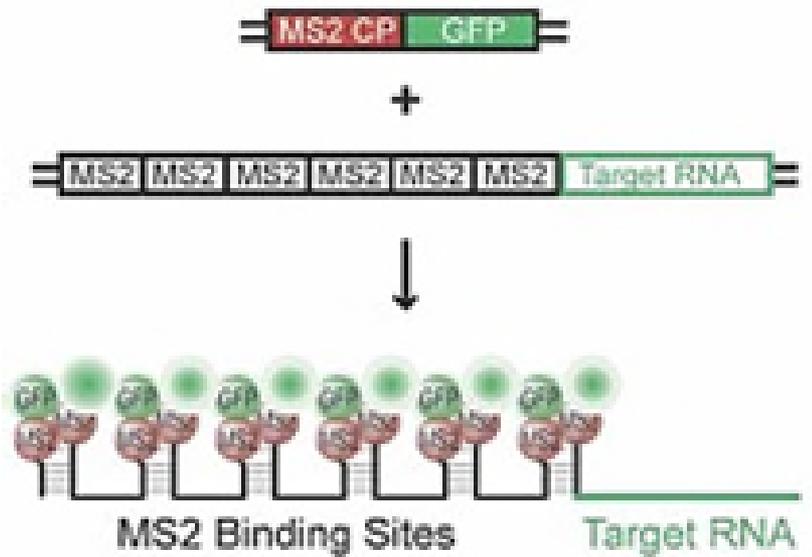
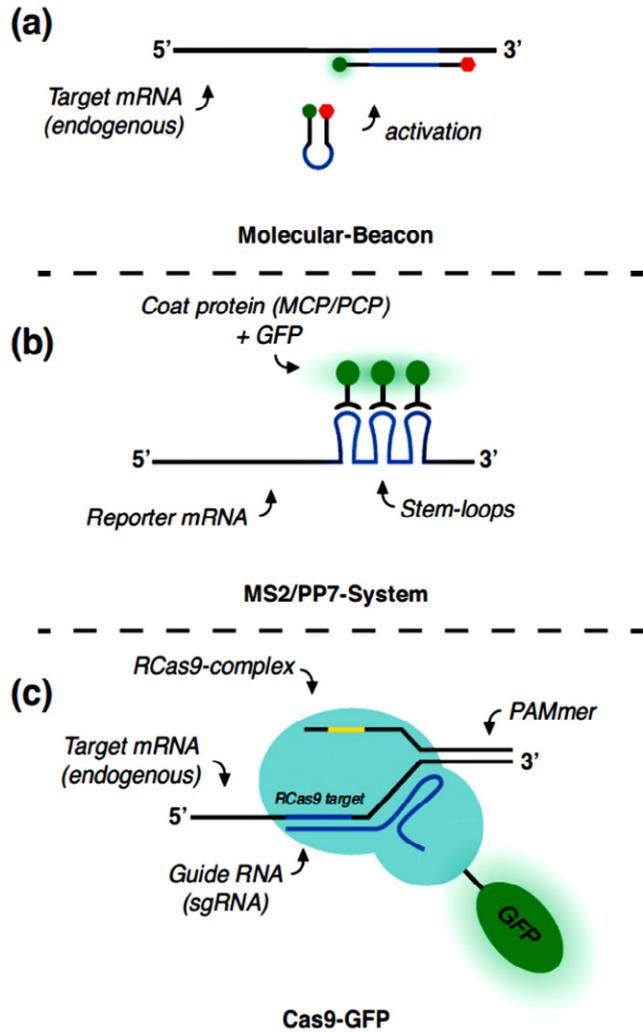
Two basic principles are evolutionary conserved:

1. mRNAs are translational repressed during transport
2. Repression is relieved at specific cellular locations

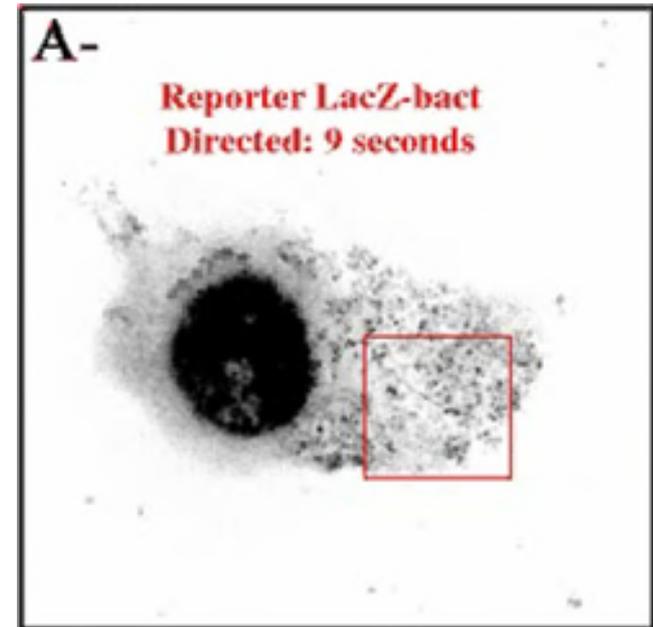
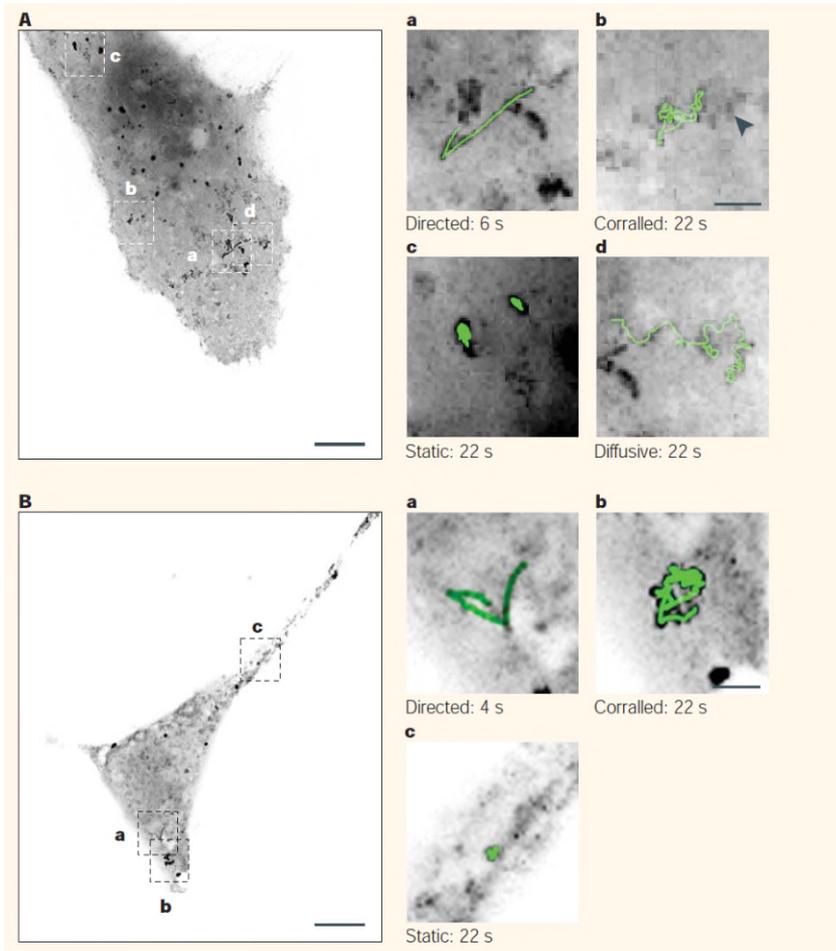
Additional principles apply specifically to dendrites:

1. Different mRNAs are in different granules
2. Distally localized RNA granules contain 1 or 2 transcripts, while soma and proximal region display higher numbers of RNAs per particle
3. mRNA transport in dendrites is a motor-based traffic along cytoskeletal structures (microtubules and actin microfilaments)

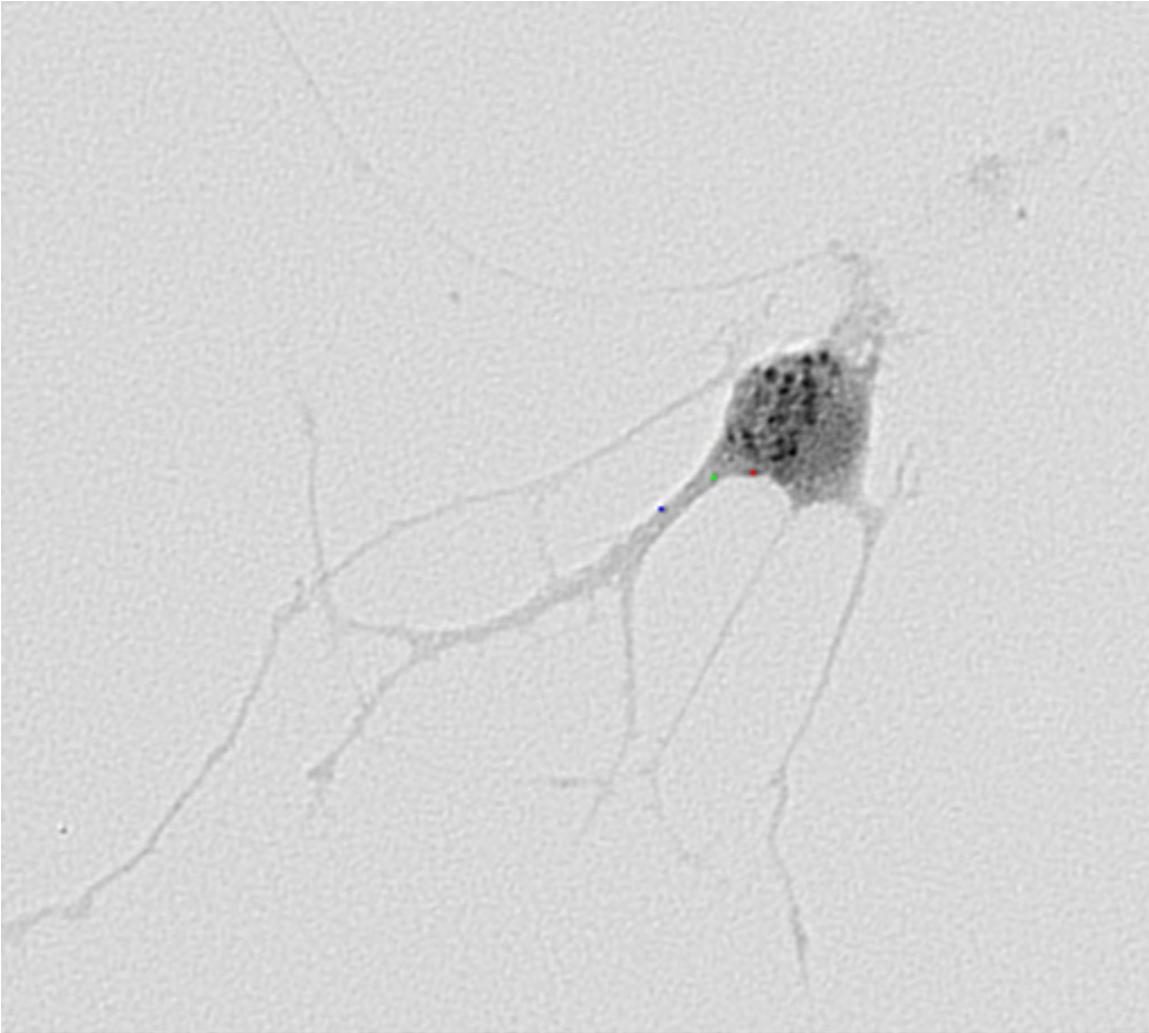
How is mRNAs transport visualized?



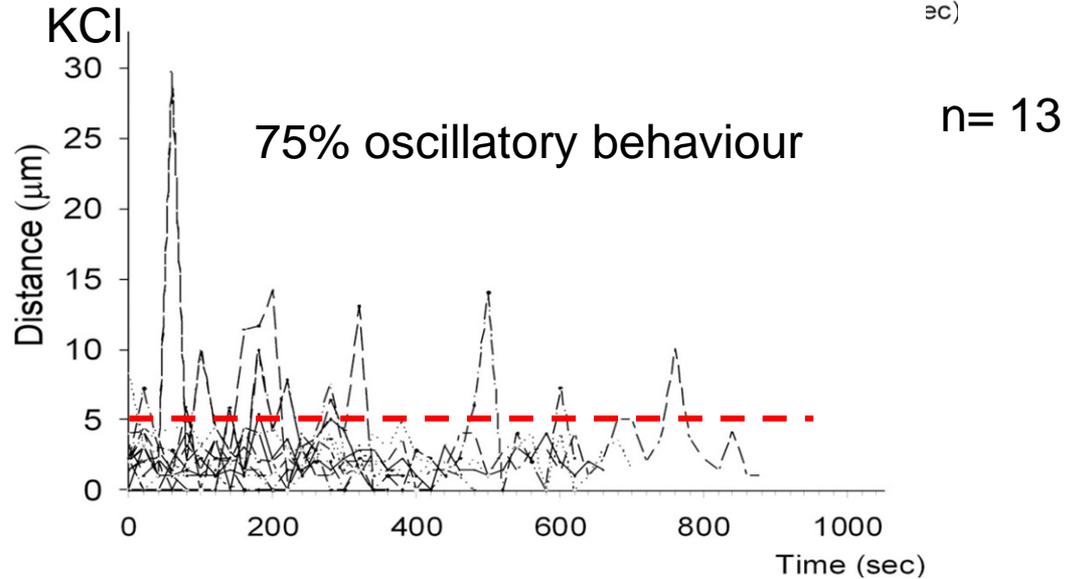
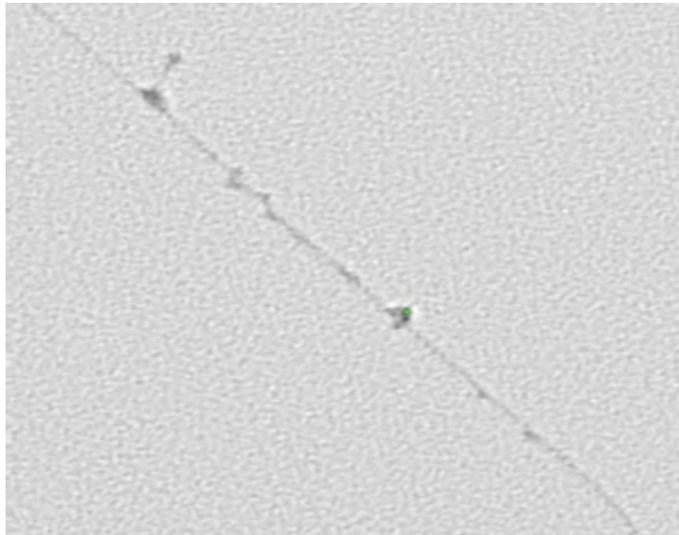
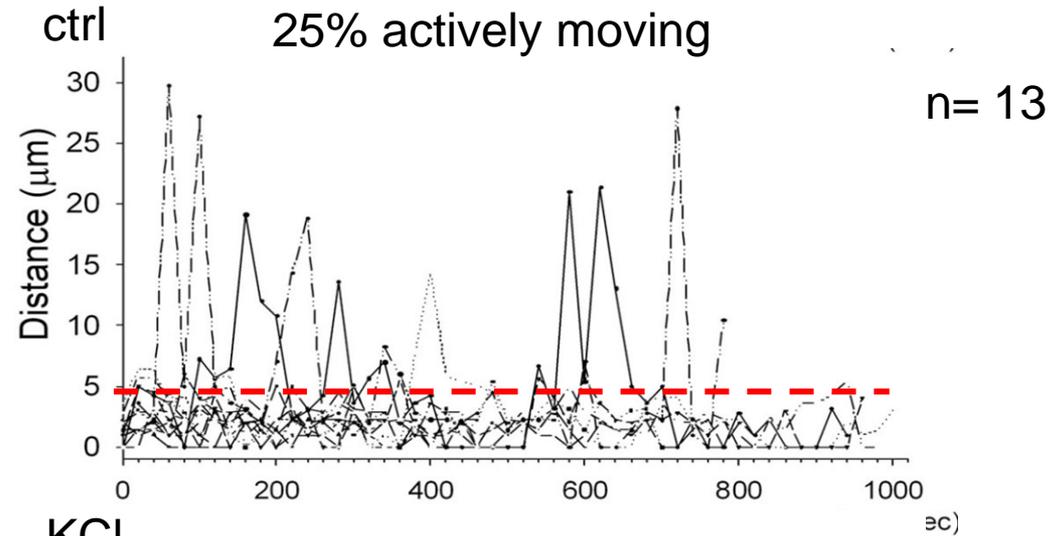
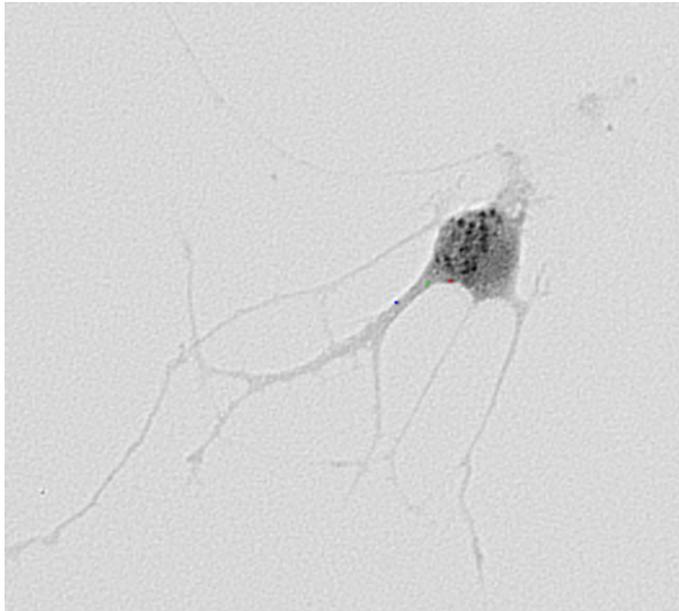
Dynamics of mRNA molecules in the cytoplasm of mammalian cells



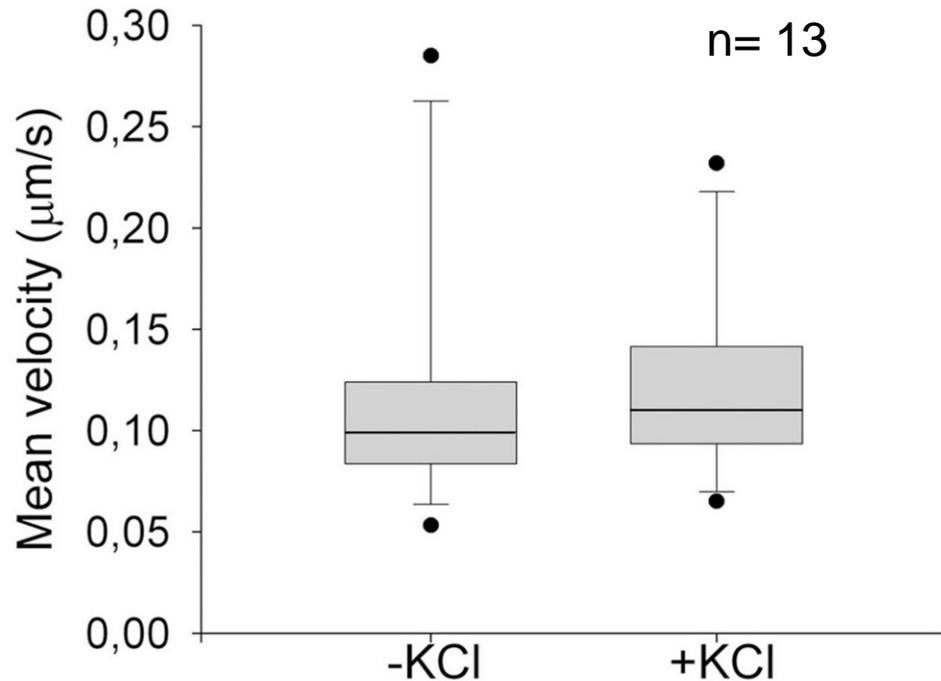
Dynamics of BDNF mRNA granules (MS2 system)



Dynamics of BDNF mRNA transport



Dynamics of BDNF mRNA transport



Max velocity 0.26 $\mu\text{m}/\text{sec}^*$

Min. velocity 0.07 $\mu\text{m}/\text{sec}$

GRANULES containing Arc mRNA

Mean max velocity 0.22 $\mu\text{m}/\text{sec}$

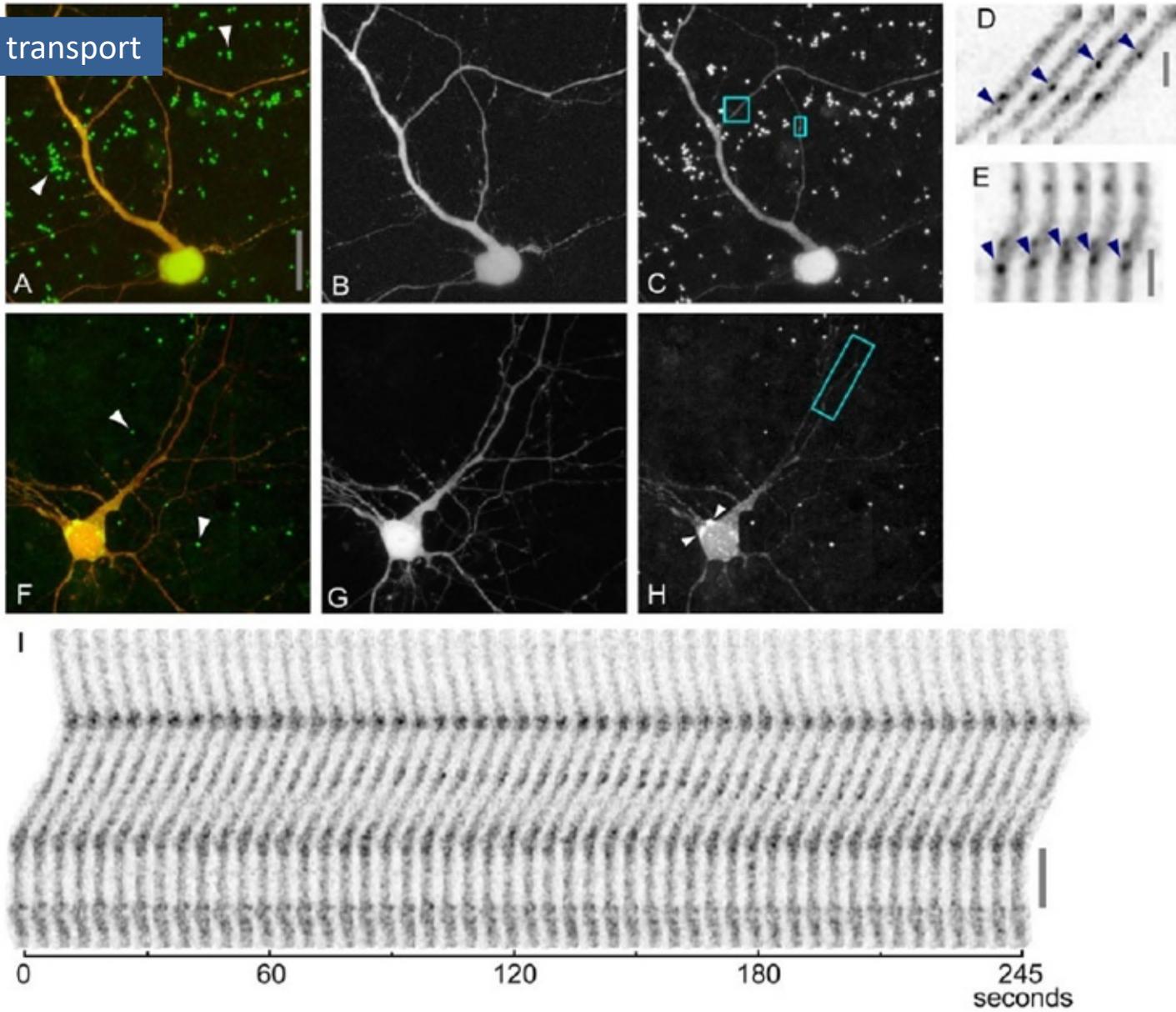
Mean min. velocity 0.15 $\mu\text{m}/\text{sec}$

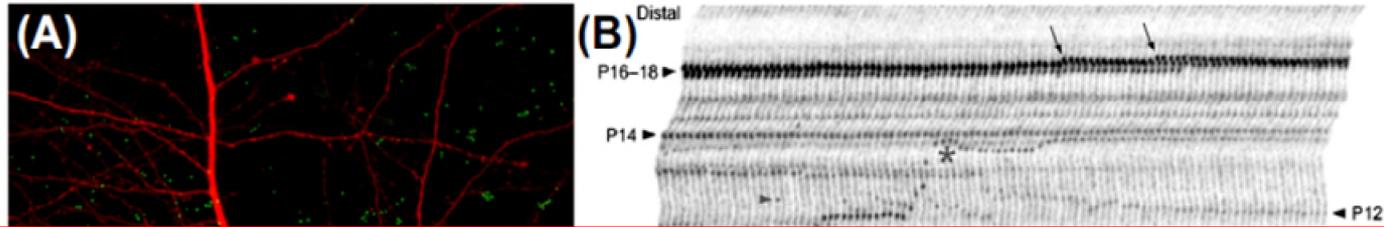
(Dynes and Steward, 2007)

* approx 15 $\mu\text{m}/\text{min}$ = 0.9 mm/h
between fast (1-2 $\mu\text{m}/\text{sec}$) and slow (0.001-0.07 $\mu\text{m}/\text{sec}$) axonal transport

DYNAMICS OF *ARC* mRNA TRANSPORT

STEP 2 = mRNP transport



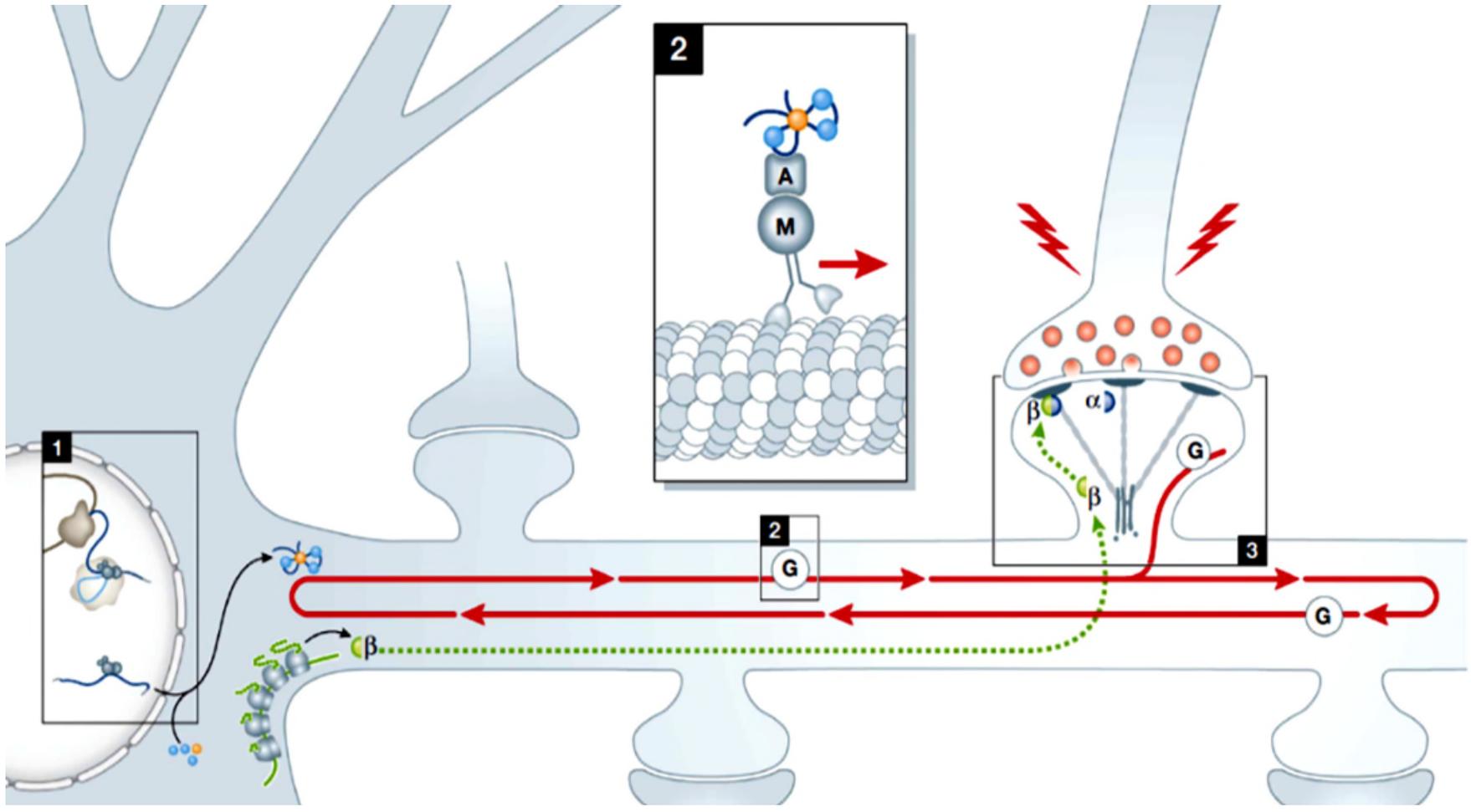


Particle Splitting

P01

ture that had been biolistically transfected with constructs containing the 3'-UTR of Arc mRNA and a sequence that binds the bacterial protein MS2 (Arc/MS2 mRNA) and transcripts encoding fusion proteins of MS2 and GFP. The Arc/MS2 construct also contained the coding sequence for dsRed. Red fluorescence is present throughout the cell body, axons, and dendrites of transfected neurons. Arc/MS2 mRNA tagged with MS2/GFP protein is present in particles in the cell body and dendrites (yellow fluorescence). Larger green particles are the beads that were biolistically delivered to the cultures. (B) The image illustrates a kymograph of a single dendritic segment that was imaged for 500 s in which particles can be seen to move at different rates. Particles are numbered from 01 to 18. Particle #3 exhibits the fastest rate of movement approaching $70 \mu\text{m/s}$. Particle number 09 exhibits slow movements just before stopping completely (asterisk). Large arrow head illustrates a particle that undergoes fragmentation. *From Dyne and Steward (2007).*

The sushi-belt model of mRNA transport



Myelin basic protein mRNA granules move along microtubules

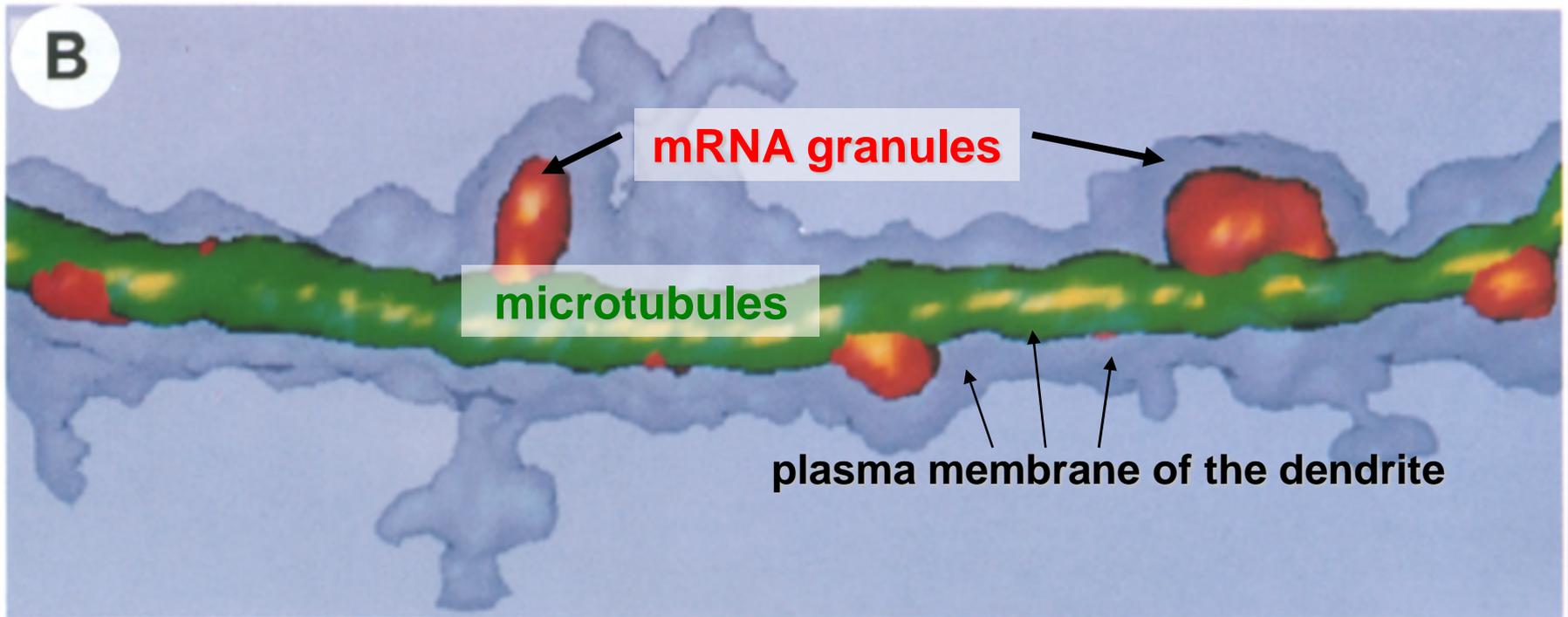
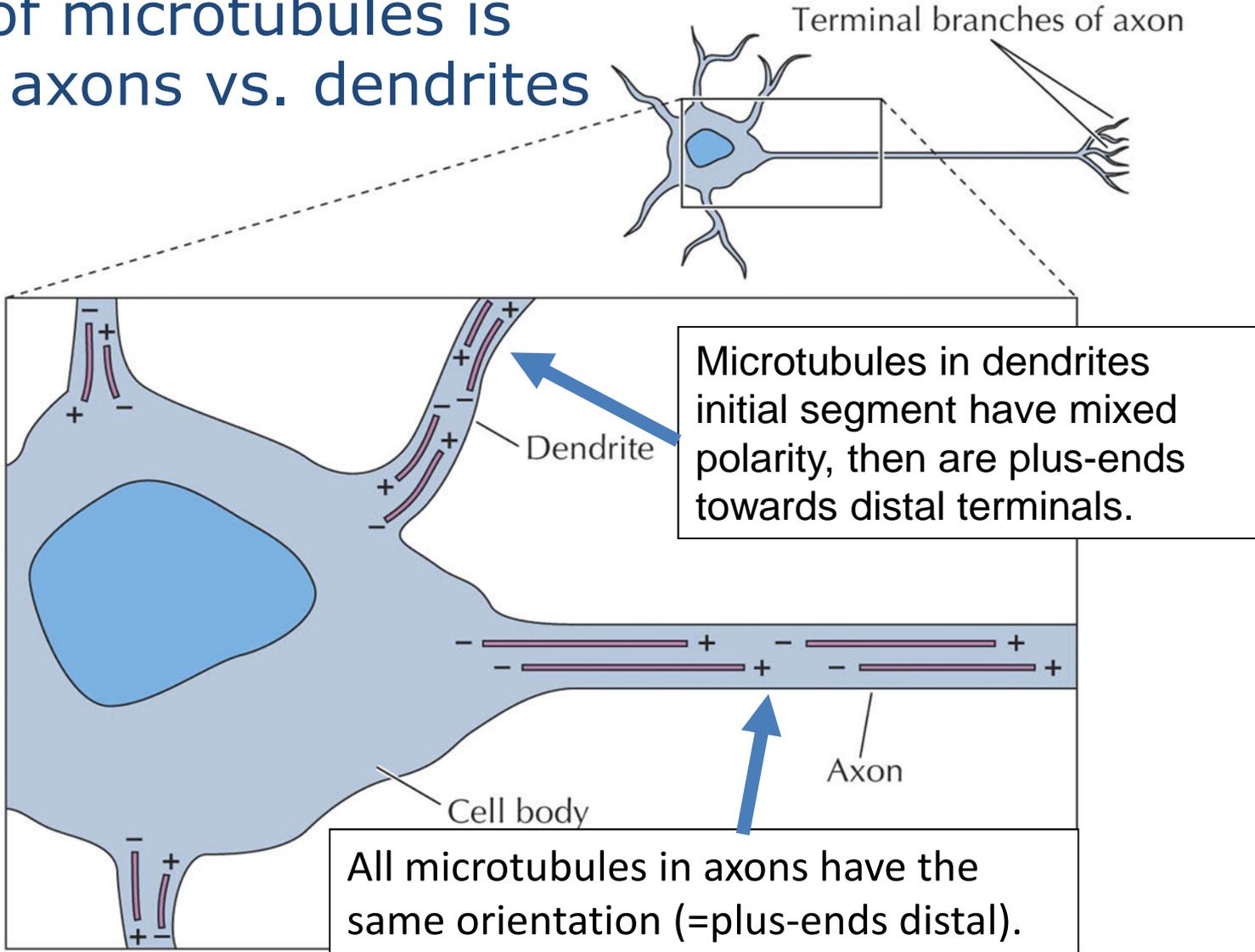
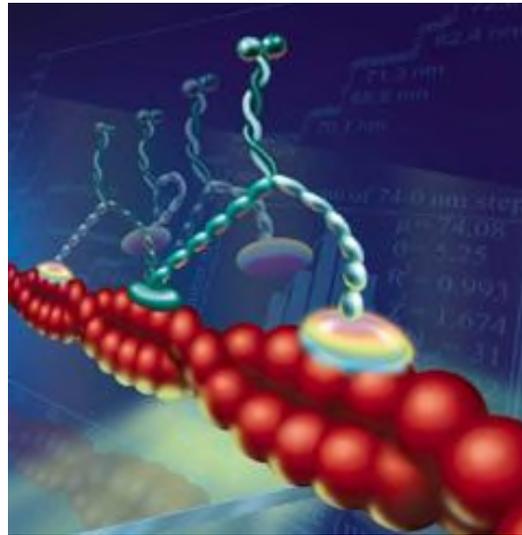
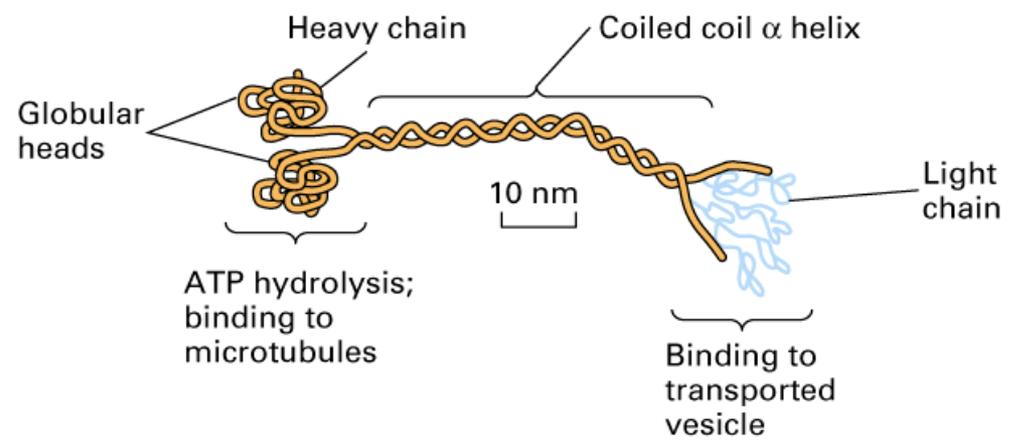
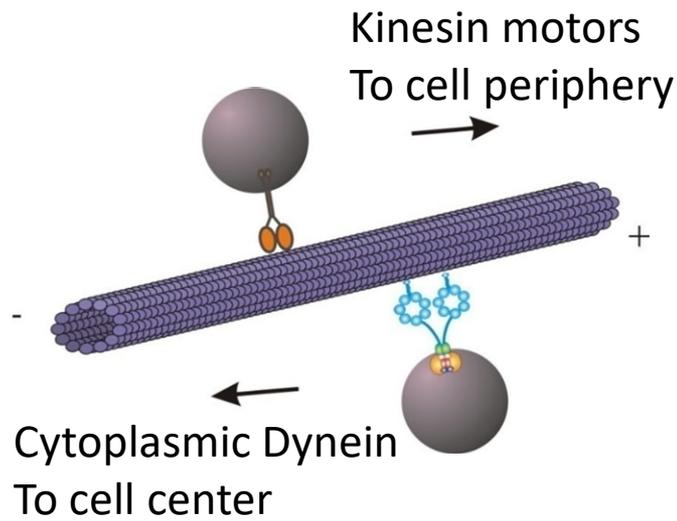


Figure 3. Three dimensional visualization of digoxigenin-labeled MBP mRNA microinjected into oligodendrocytes. Digoxigenin-labeled MBP mRNA was microinjected into mouse oligodendrocytes and visualized as described in Fig. 1 A. A series of 20 optical sections was collected at 0.5- μm intervals through the cell. The data was reconstructed in three dimensions and displayed using volume rendering (A).

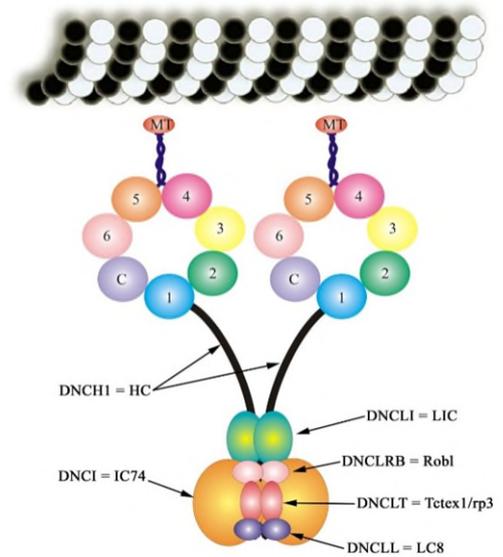
Polarity of microtubules is different in axons vs. dendrites



Motor proteins Walk Along Filaments



Yildiz *et al.* Science 2003.



Kinesins: a family of ~45 members in mammals

Conserved motor domain fused to variable domains
almost more kinesin proteins than cargo – and redundancy

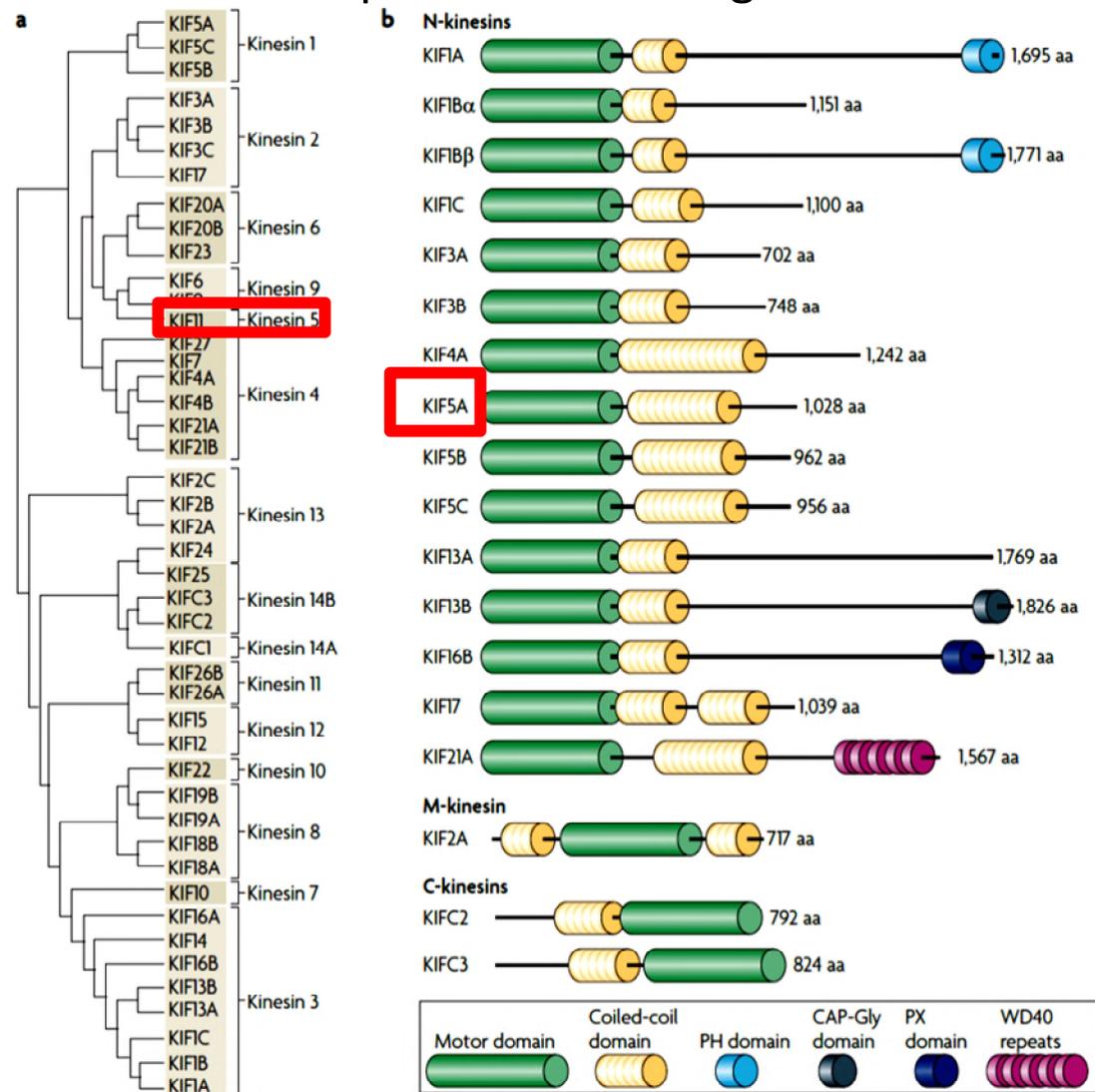
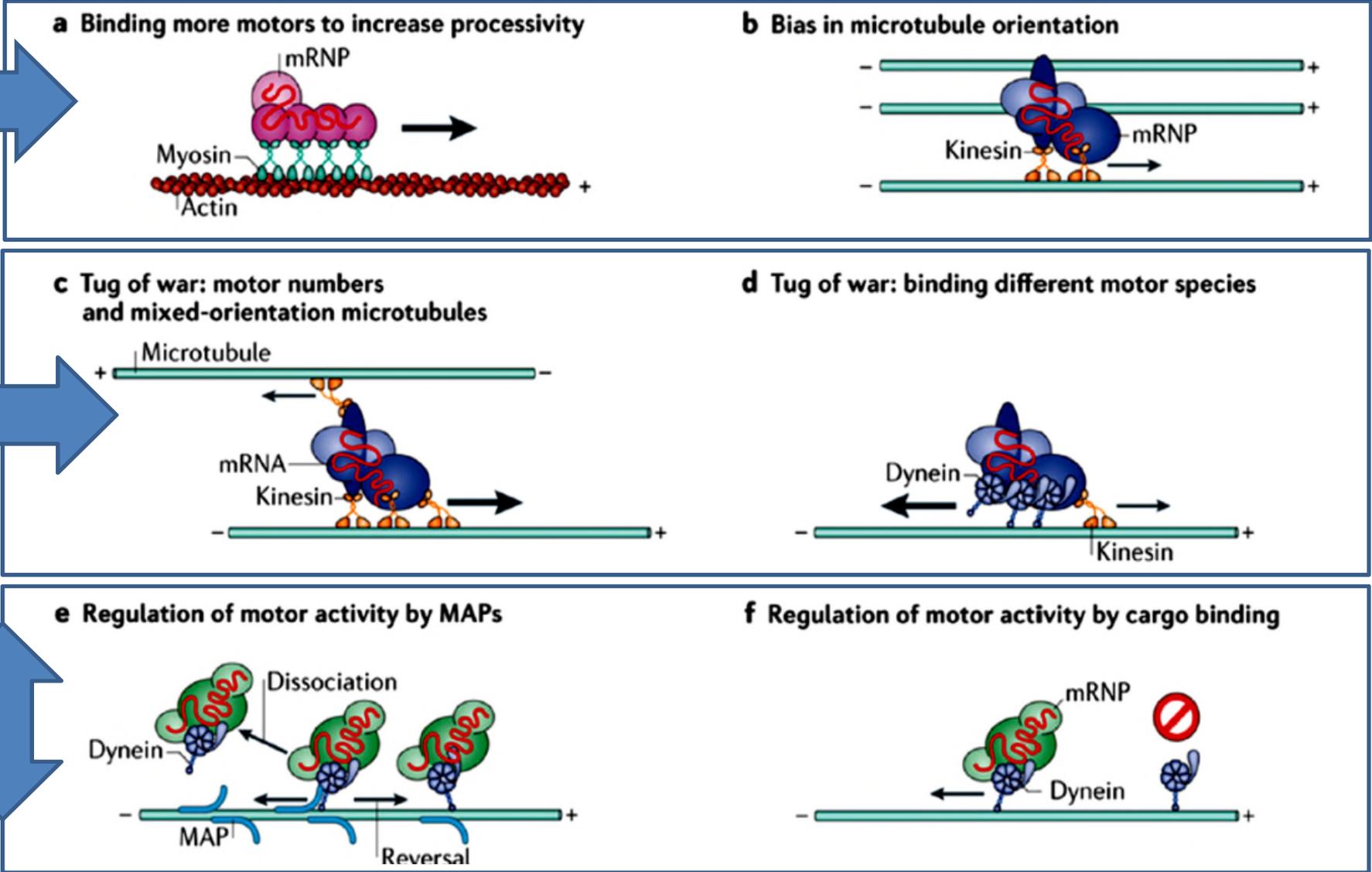


Figure 1 | **The structure and phylogeny of major mouse kinesins.** **a** | A phylogenetic tree of all 45 kinesin superfamily (also known as KIF) genes in the mouse genome², which are classified into 15 families^{8,9,15,152-154}. **b** | The domain structure of

Cellular determinants of motored mRNA transport

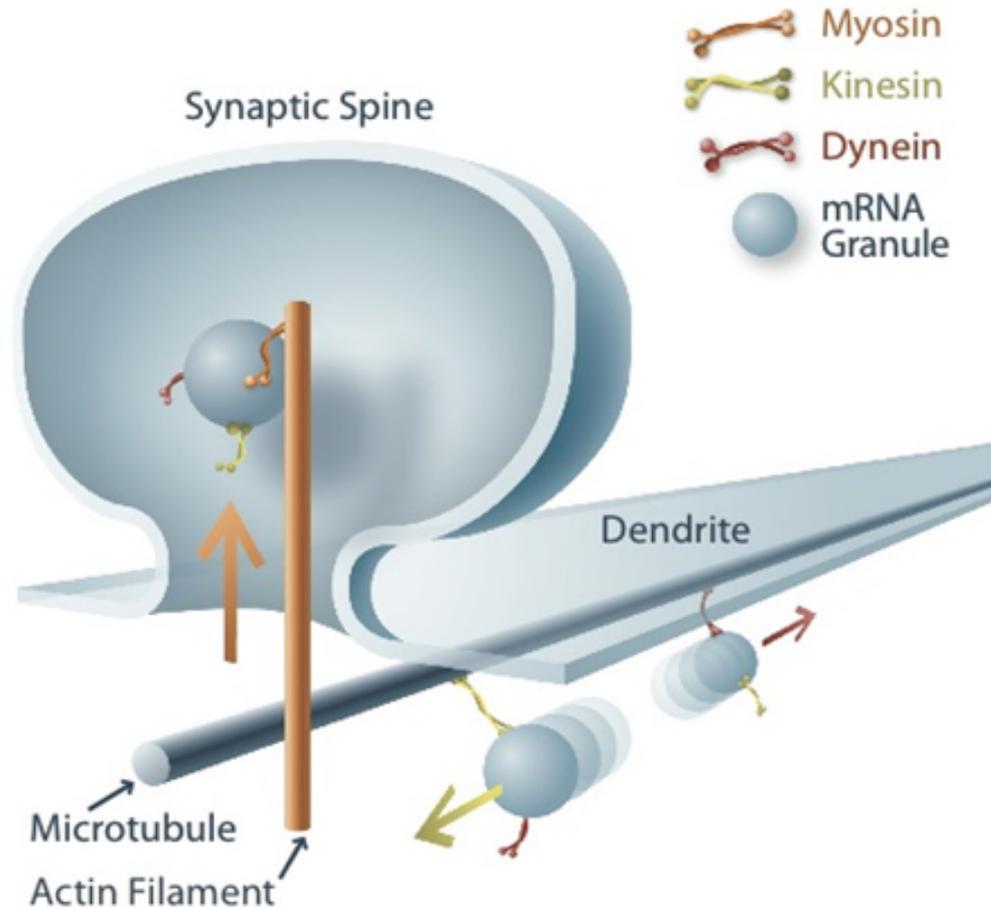


How is an mRNA anchored at its destination?

1. (A) Formation of mRNPs in the nucleus;
(B) Cytoplasmic mRNP remodeling, oligo-merization and assembly (possible exchanges with P-Bodies, Stress Granules)
2. Transport of mRNPs to their destination;
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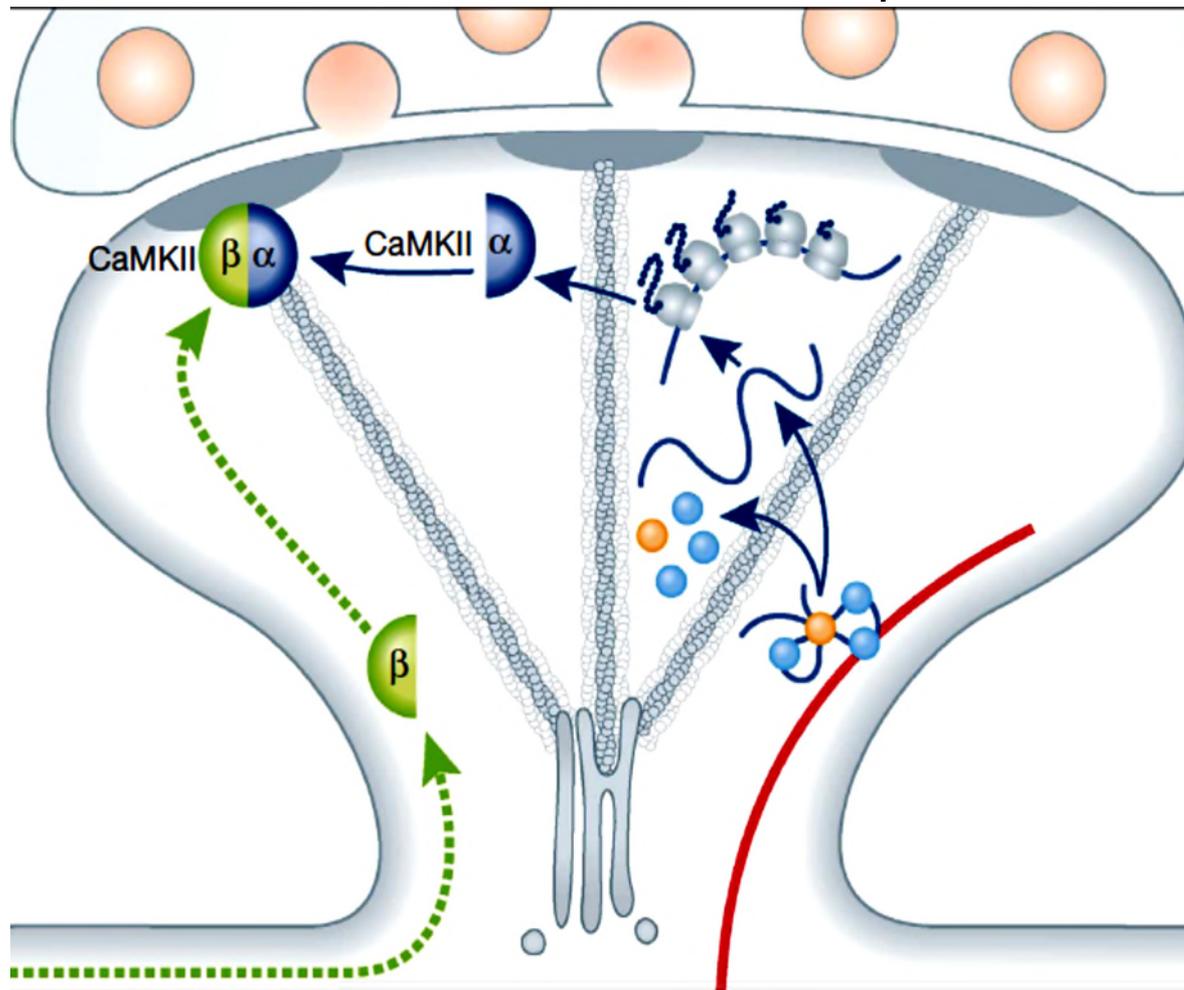
How are dendritic mRNAs anchored at synapses?

Role of the cytoskeleton (A): the actin-myosin pass-over

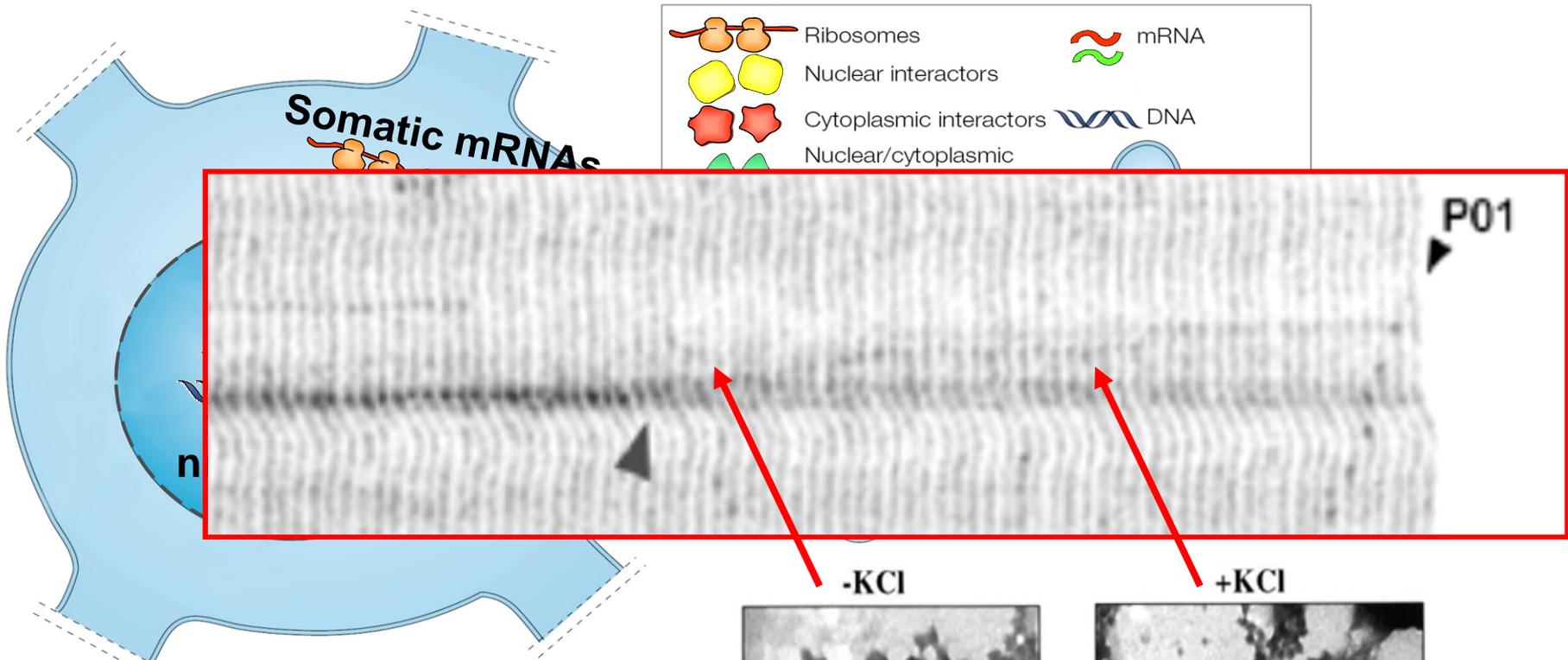


How are dendritic mRNAs anchored at synapses?

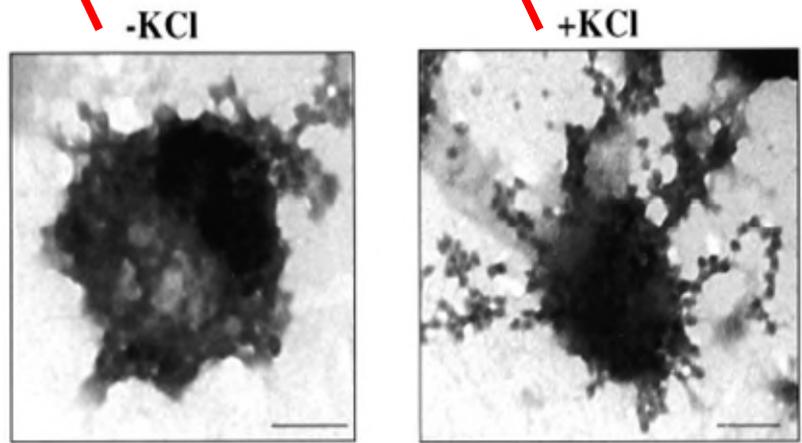
Role of the cytoskeleton (B): growing microtubules extend into the head of dendritic spines



mRNA splitting in distal dendrites?



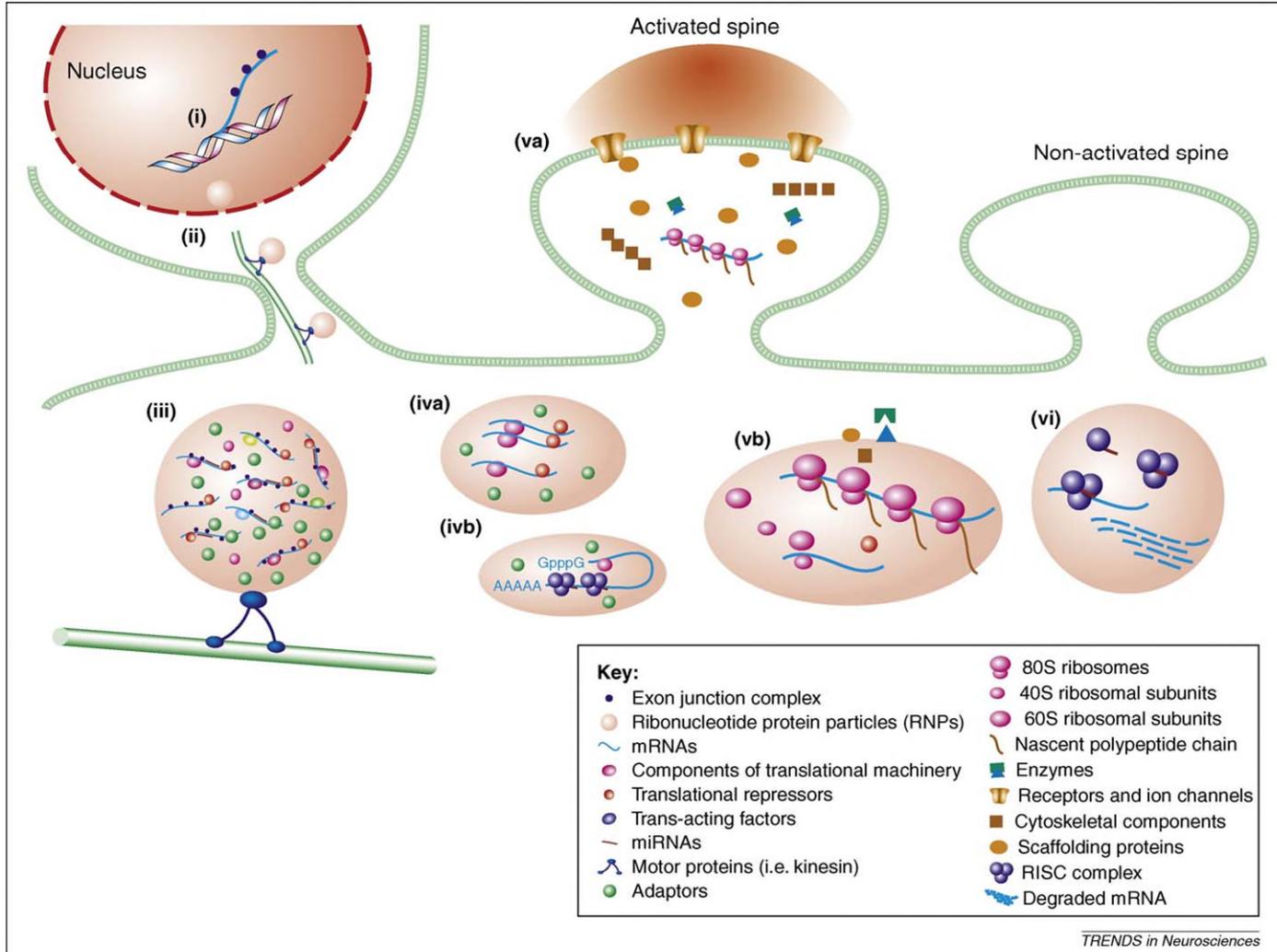
Distally localized RNA granules contain 1 or 2 transcripts, while soma and proximal region display higher numbers of RNAs per particle.
RNA granules splitting?



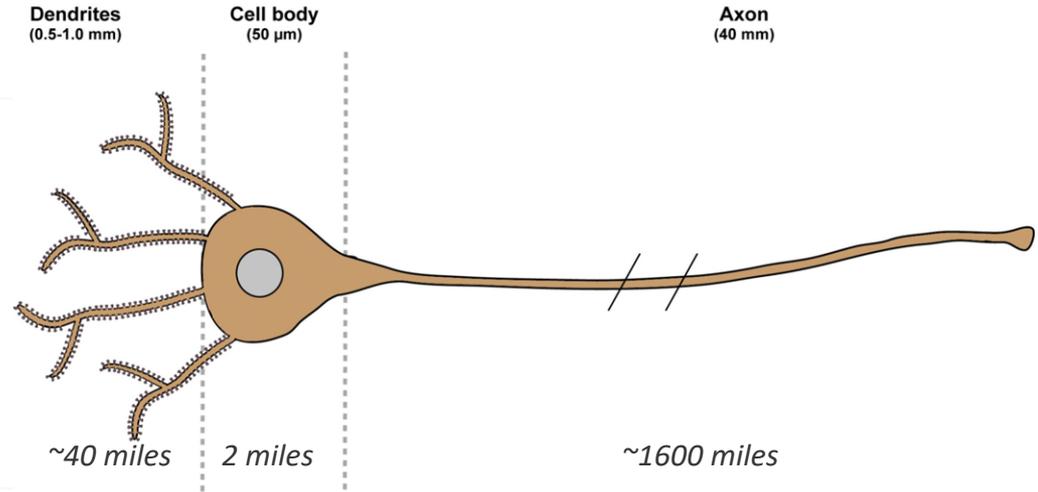
How is an mRNA translated at its destination?

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Local translation of delivered mRNAs and local degradation



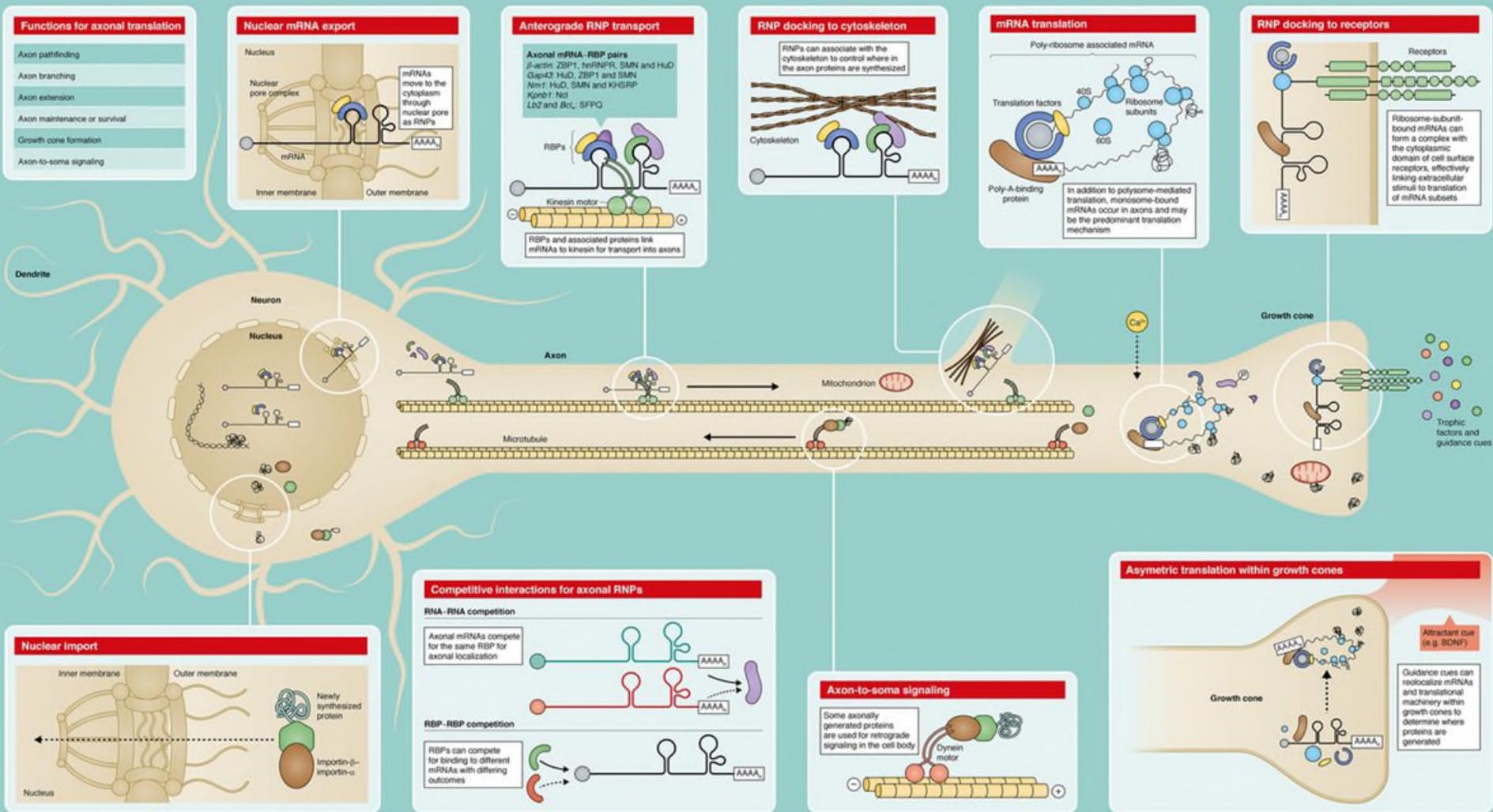
What about the axonal compartment ?



- Axons of invertebrate neurons - mRNAs & ribosomes (1970's)
- Axons of vertebrate hypothalamic neurons and retinal neurons (1990's) - but no ribosomes by EM.
- Developing axons of embryonic vertebrate (chick) neurons (1998) – ribosomes & mRNAs.
- Adult mammalian neurons (since 2001) - mRNAs, ribosomes, & translation factors.

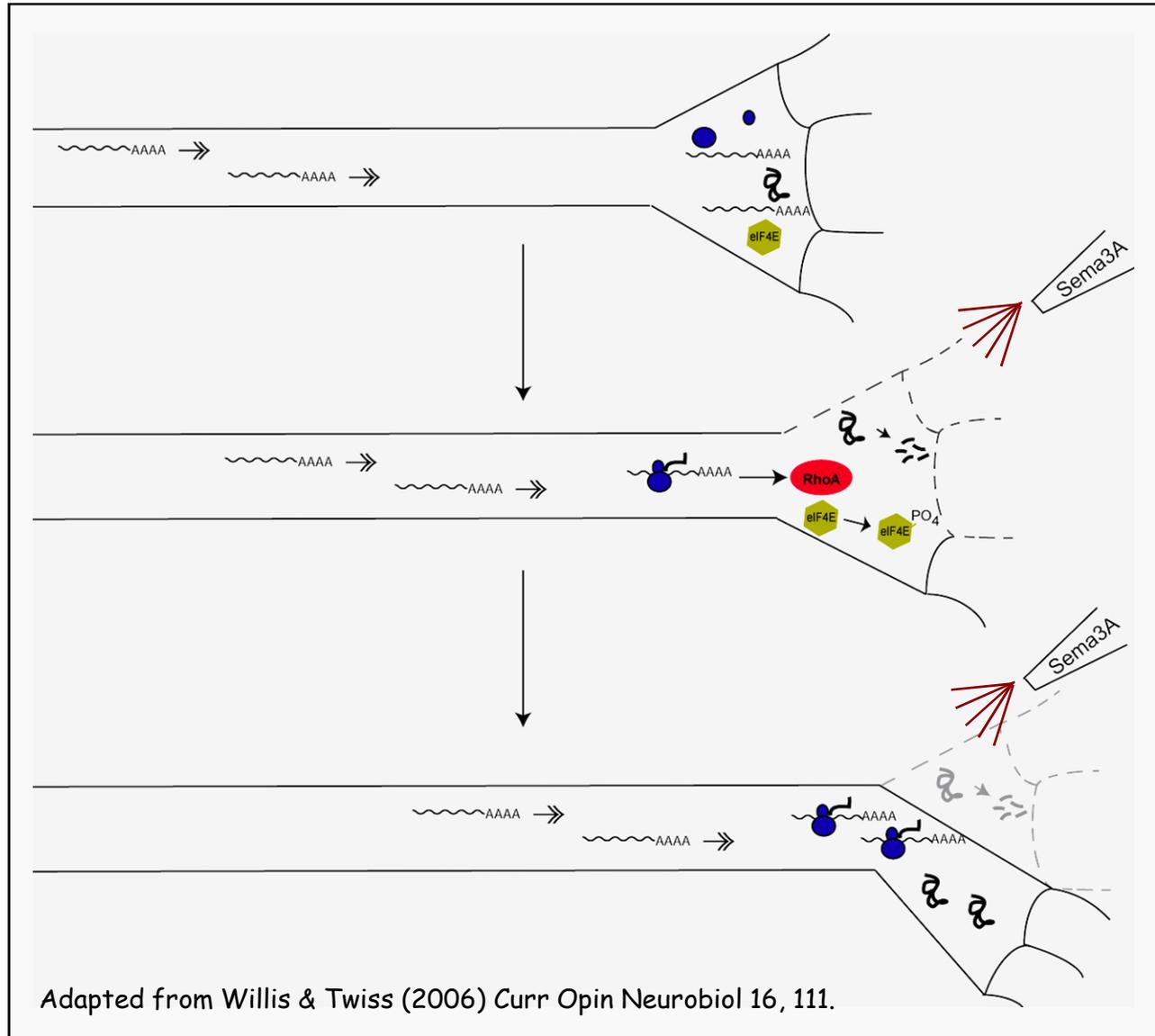
Historical view: mRNA profiles of axons

- Willis et al. (2005) used proteomics with metabolically labeled (35S-methionine) to demonstrate local synthesis of 35 proteins in axons.
- Low density arrays showed > 200 mRNAs in sensory axons (Willis et al., 2007).
- Taylor et al. (2009) used microfluidic chambers to isolate axons from cultured hippocampal neurons; with high density arrays detected ~ 800 mRNAs.
- Andreassi et al (2009) used compartmentalized cultures to detect mRNAs enriched in axons of sympathetic neurons – similarly complex populations.
- Gumy et al. (2011) used isolated axons from developing and adult sensory neurons with arrays for RNA profiling --> >1000 different mRNAs.



Abbreviations: Bcr, B-Cell CLL/Lymphoma W protein mRNA; Gap43, Growth-associated 43 kDa protein mRNA; HuD, Hu-antigen-D protein; hnRNP B, heterogeneous nuclear ribonucleoprotein B; KIF19A, kinesin-like regulatory protein; Kozak1, transcription initiation site 1 mRNA (encodes importin β 1 protein); Lnc, lariat 82 mRNA; Ncl, nucleolin; RBP, RNA binding protein; RBP1, ribonucleoprotein; SFPQ, splicing factor protein and guanine rib-protein; SMN, spinal motor neuron protein; ZBP1, zip code binding protein 1.

Guidance cues trigger protein synthesis in developing axons



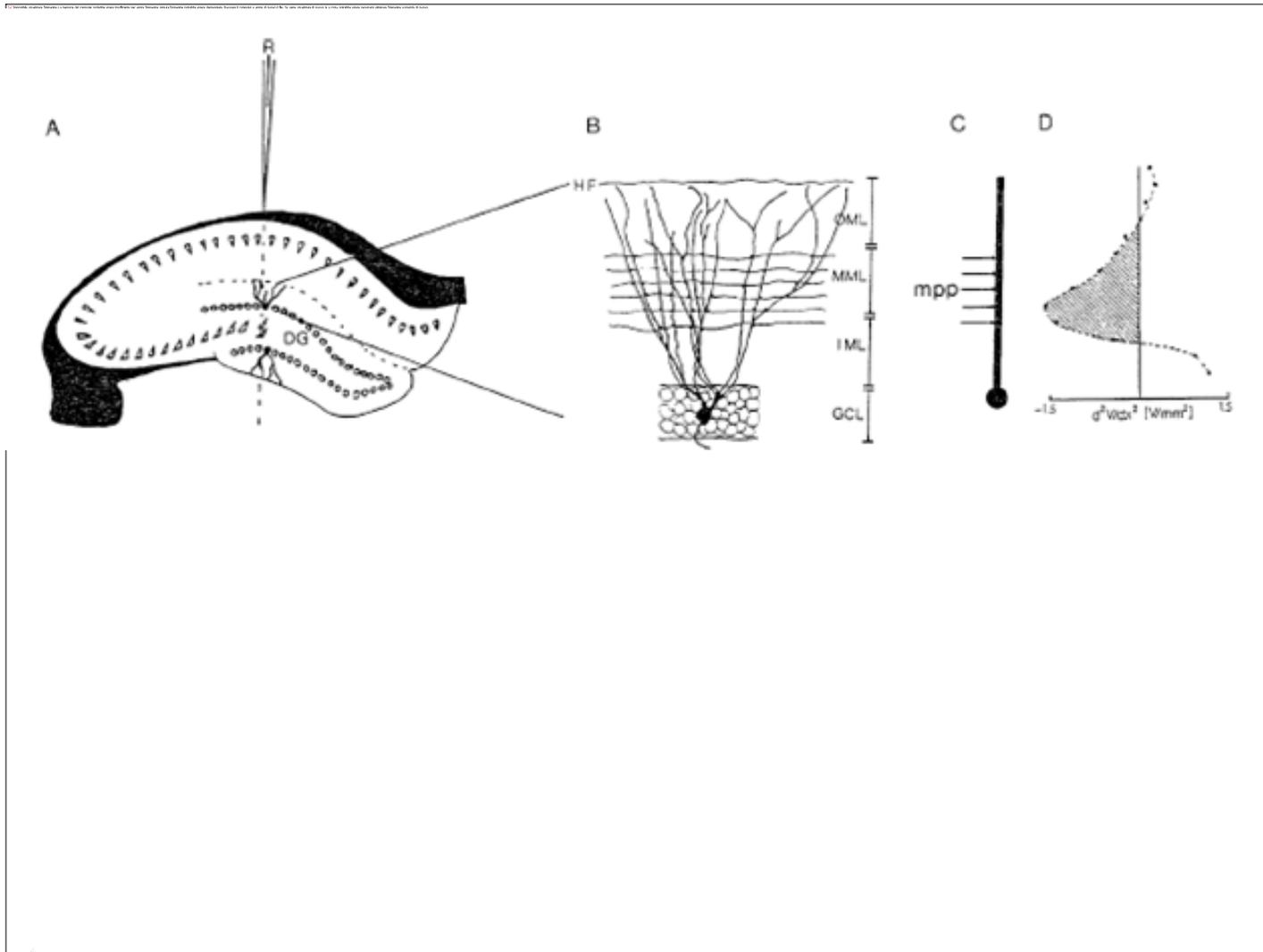
Take-Home Message

- **Both dendrites (post-synaptic) and axons (pre-synaptic) processes contain components needed to synthesize proteins:**
 - Templates (mRNAs)
 - Machinery (ribosomes, translation factors, P-bodies, stress granules)
- **Complex population of mRNAs are transported into dendrites and axons (1000's of 'transcripts').**
- **Regulation of 'localized' neuronal protein synthesis occurs through at least two separate mechanisms:**
 - Transport of templates (i.e., targeting)
 - Regulation of the machinery (i.e., translational control)
- **The regulation is driven by RNA-protein interactions.**

Synaptic Activation Causes the mRNA for the IEG *Arc* to Localize Selectively near Activated Postsynaptic Sites on Dendrites



Oswald Steward



Synaptic Activation Causes the mRNA for the IEG *Arc* to Localize Selectively near Activated Postsynaptic Sites on Dendrites

