

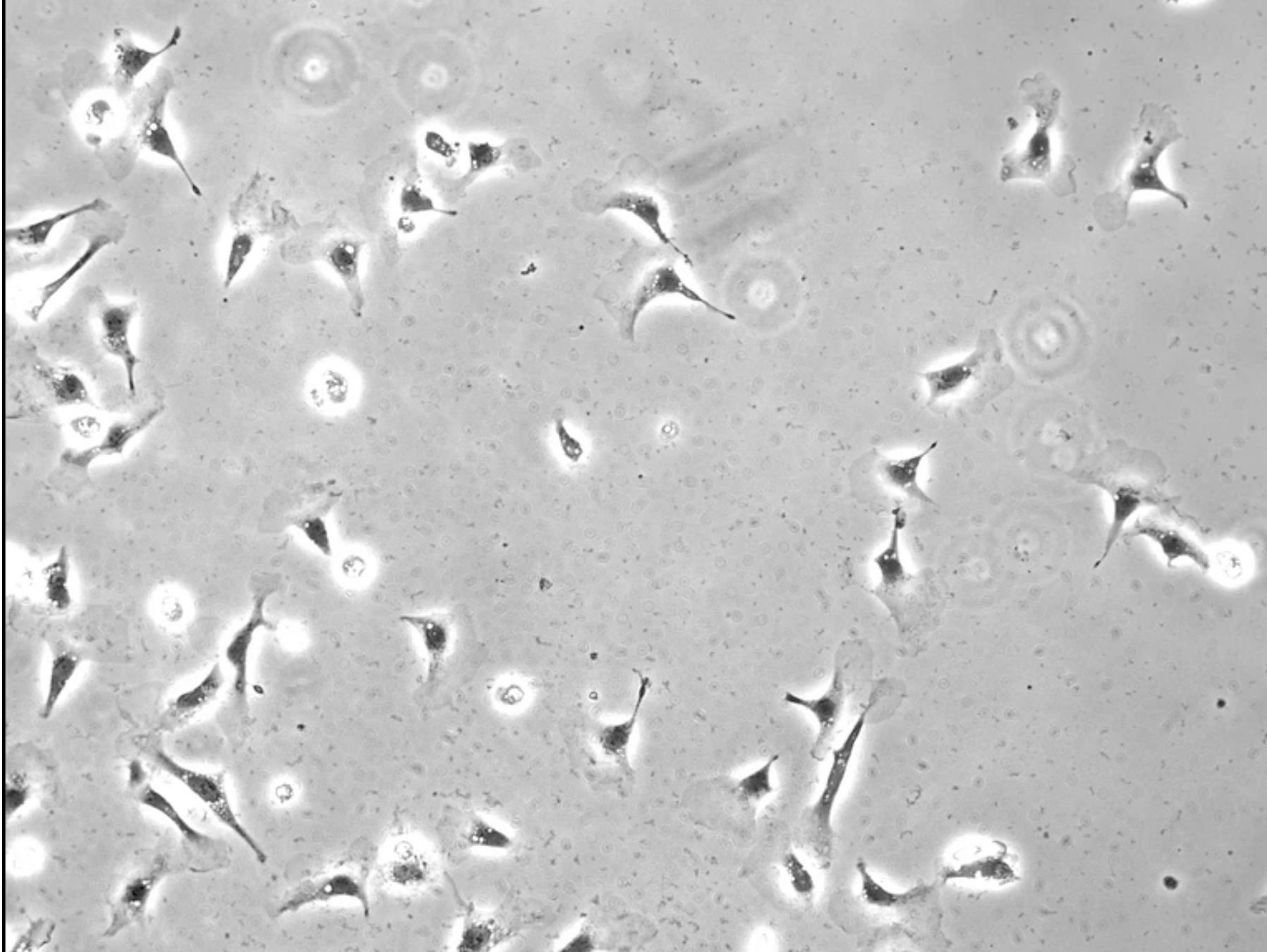
cell movement and neuronal migration

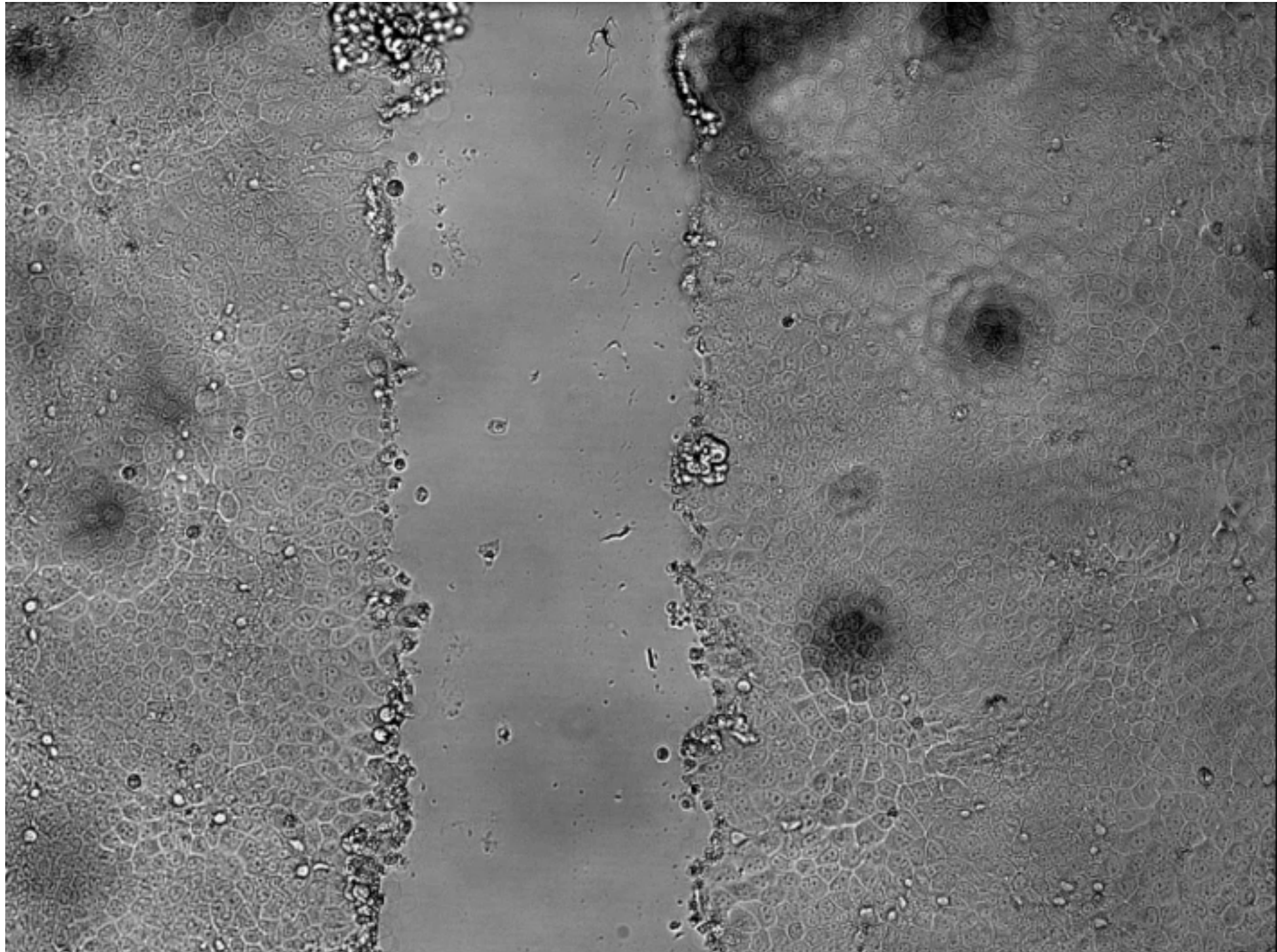
Paul Letourneau
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Cell migration

- Cell migration in 3 steps; protrusion, adhesion, traction
- What is the involvement of cytoskeletal and adhesion proteins?
 1. Actin filaments
 2. Actin binding proteins
 3. Microtubules
 4. Motor proteins
 5. Adhesion proteins

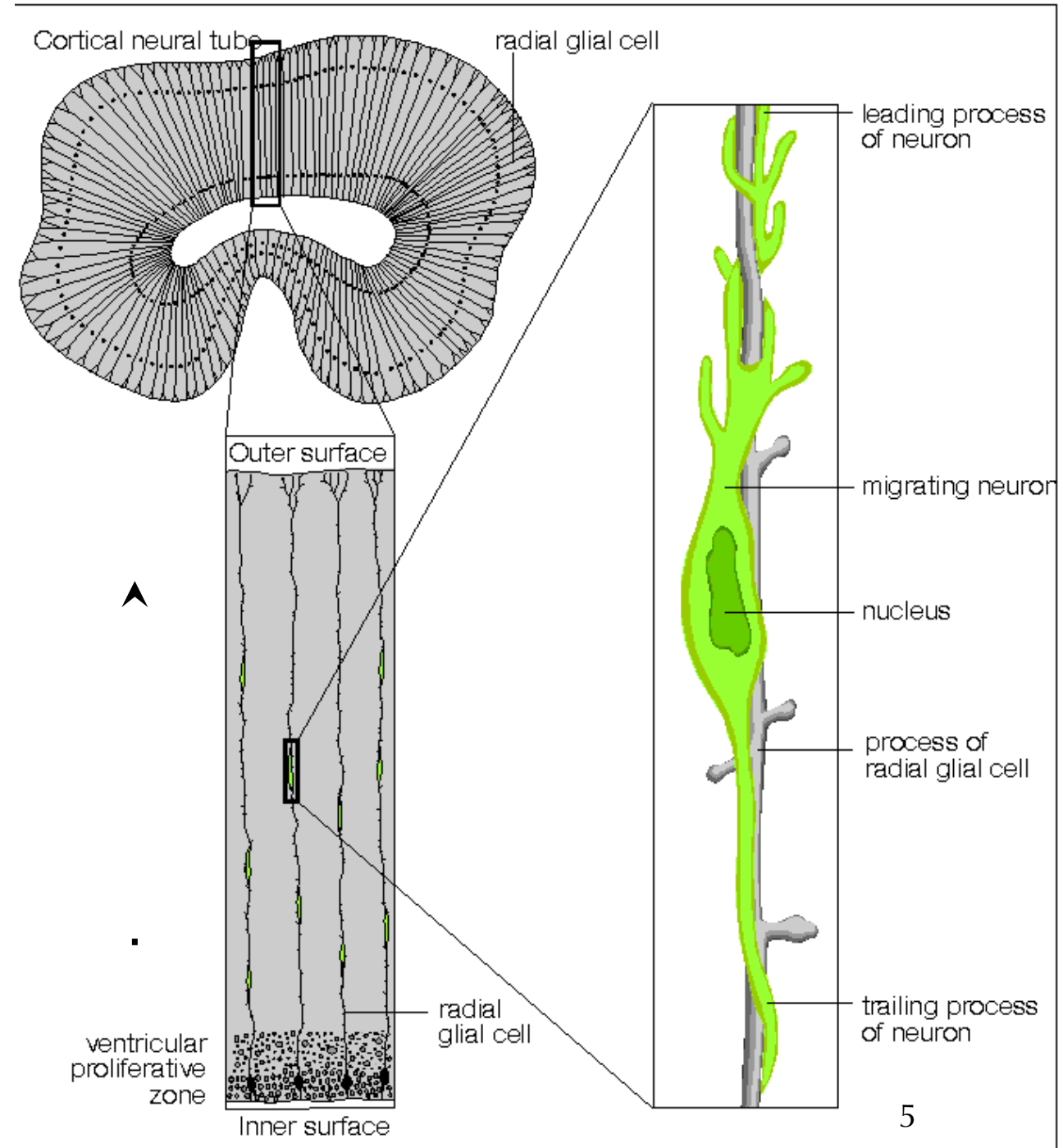
Cell migration is cells crawling along surfaces, as individual cells or in groups



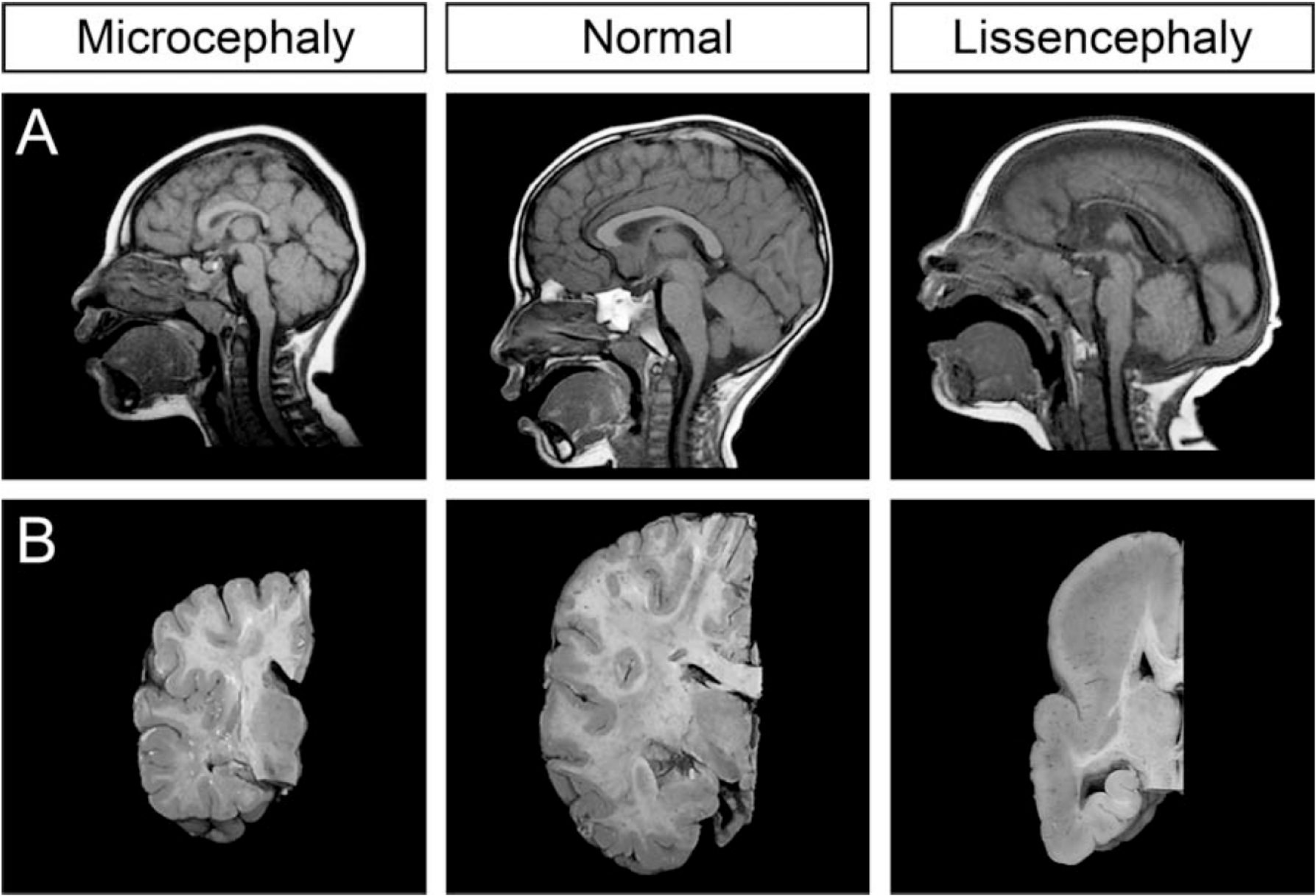


- Neuronal migration is important in neural development because neurons migrate from their birthplace to their adult location.

- Immature cortical neurons migrate along **radial glial cells** that span from the inner ventricular lining to the outer surface of the brain.

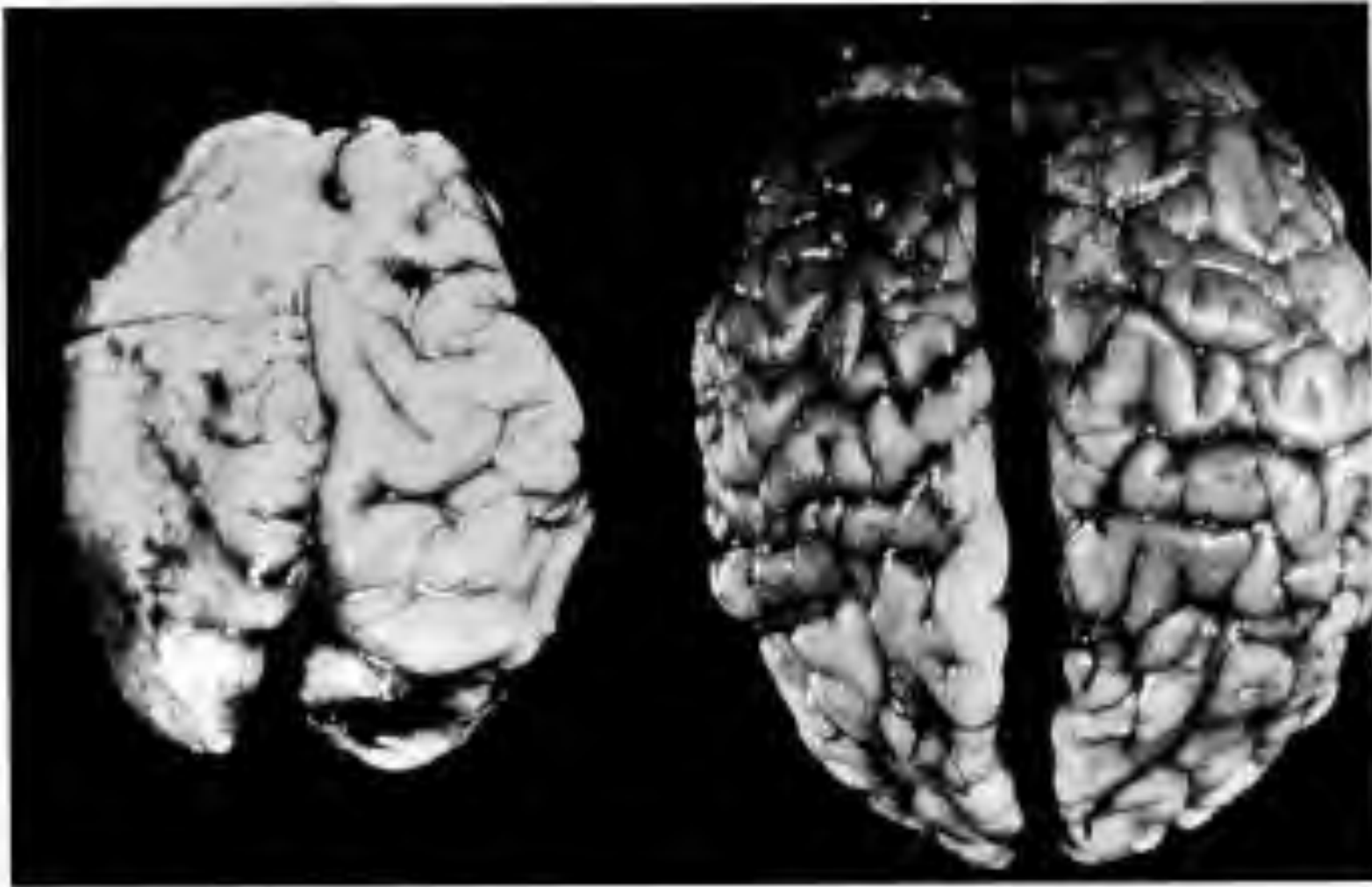


Congenital or environmental defects in neurogenesis and neuronal migration produce structural brain defects and mental retardation.



defective neurogenesis (Zika virus, e.g.)

defective neuronal migration

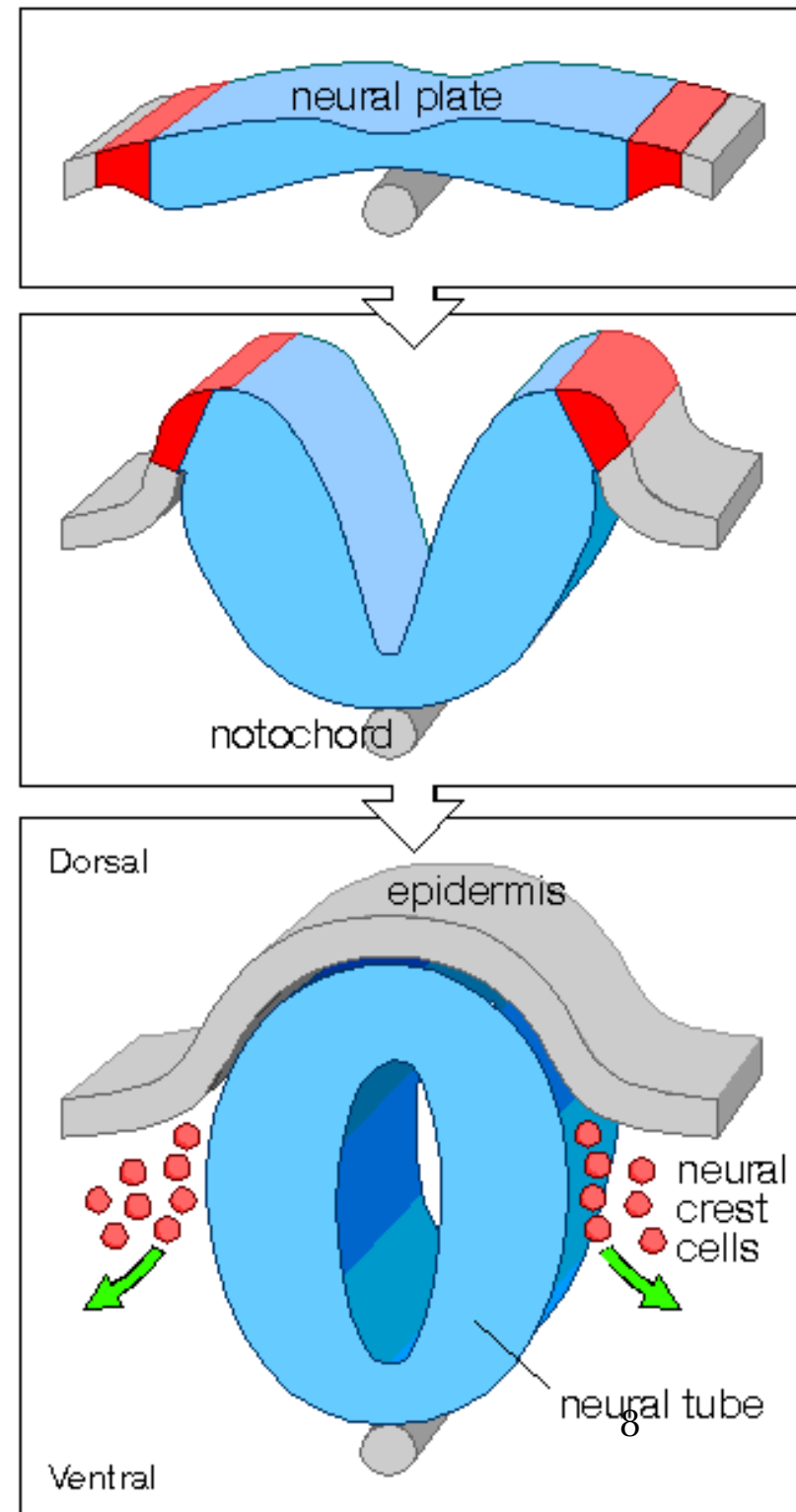


Fetal alcohol syndrome

normal

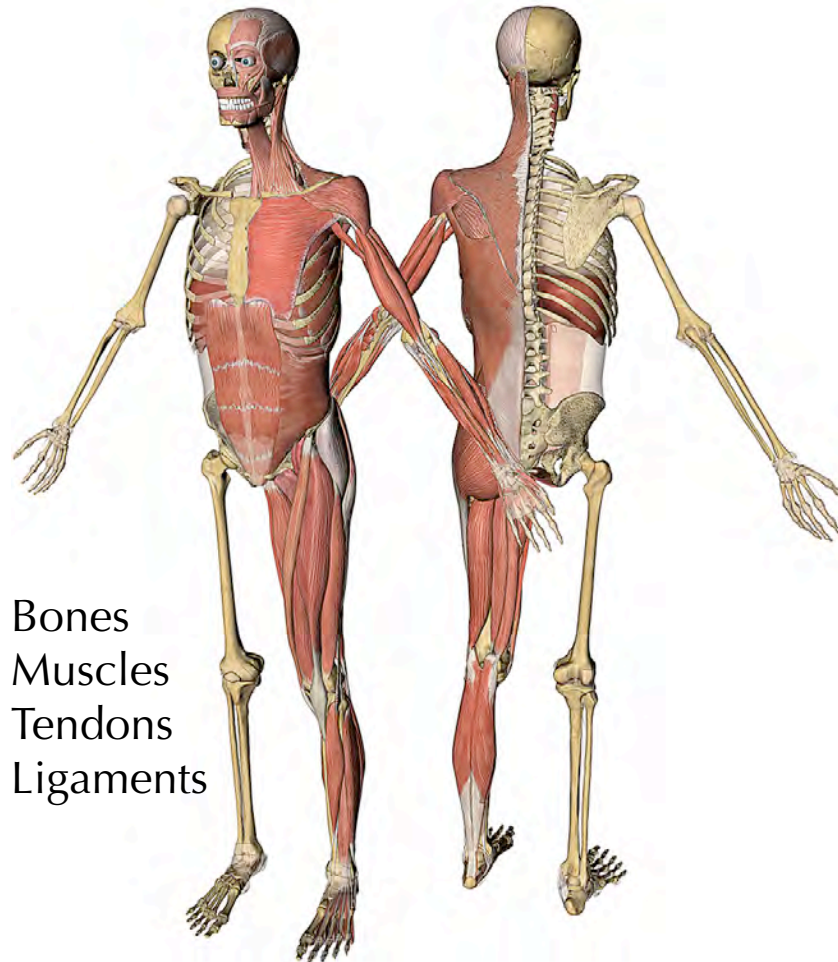
- The most common non-genetic cause of mental retardation is **fetal alcohol syndrome**. Alcohol consumption can impair neurogenesis and neuronal migration.

- Neural progenitors, called the **neural crest**, migrate extensively to produce the **sensory neurons, autonomic neurons, pigment cells** of the skin, and **connective tissue** of the head and heart.
- Defective neural crest migration causes Hirschprung's Disease, cranio-facial malformations, heart and adrenal malformations.
- Malignant melanoma arises from cells derived from the neural crest.



Cell movement involves the cell's cytoskeleton

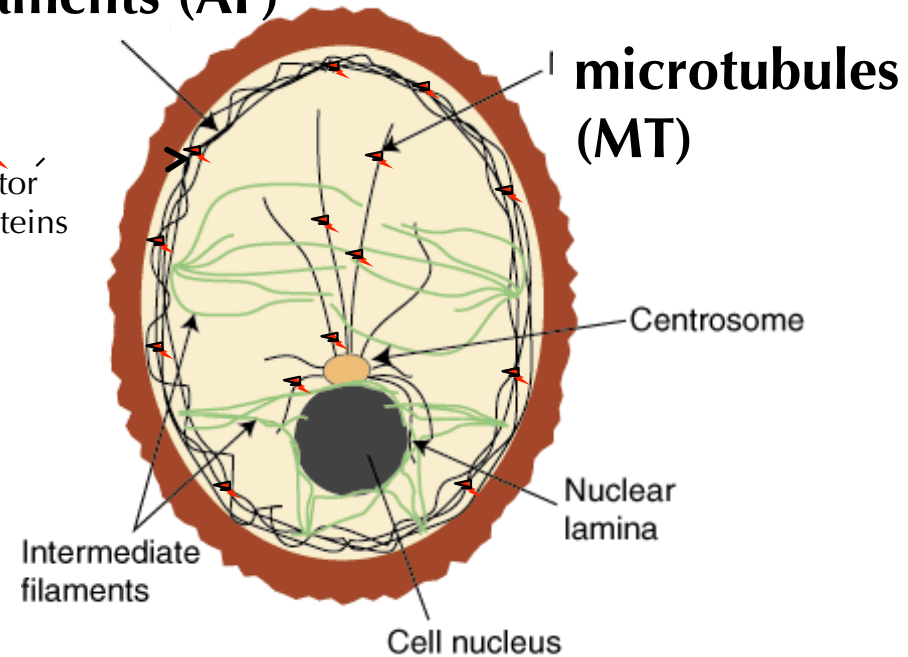
musculoskeleton



cytoskeleton

actin filaments (AF)

motor proteins



- The cytoskeleton supports and shapes a cell (AFs and MTs).
- Cytoskeletal motor proteins move cellular components and generate force to move cells.

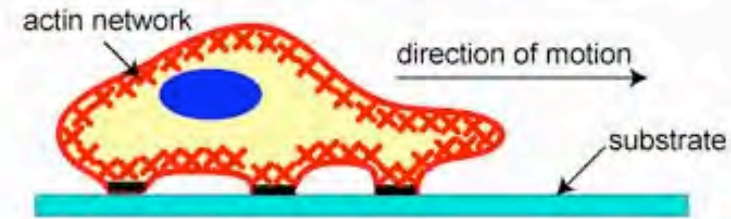
Cell movement occurs in three steps; protrusion, adhesion, and pulling forward

1. Protrusion of the leading edge

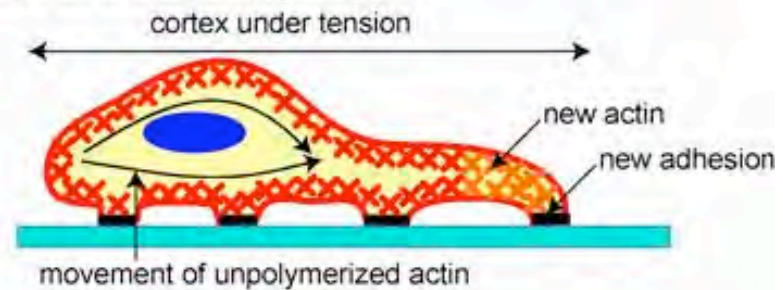
2. Adhesion at the leading edge

3. Traction to pull ahead

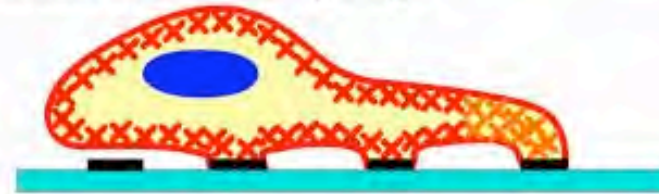
1) Protrusion of the Leading Edge



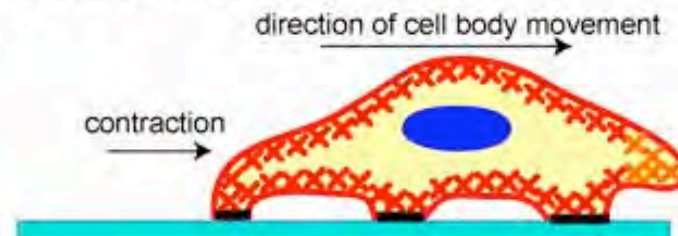
2) Adhesion at the Leading Edge

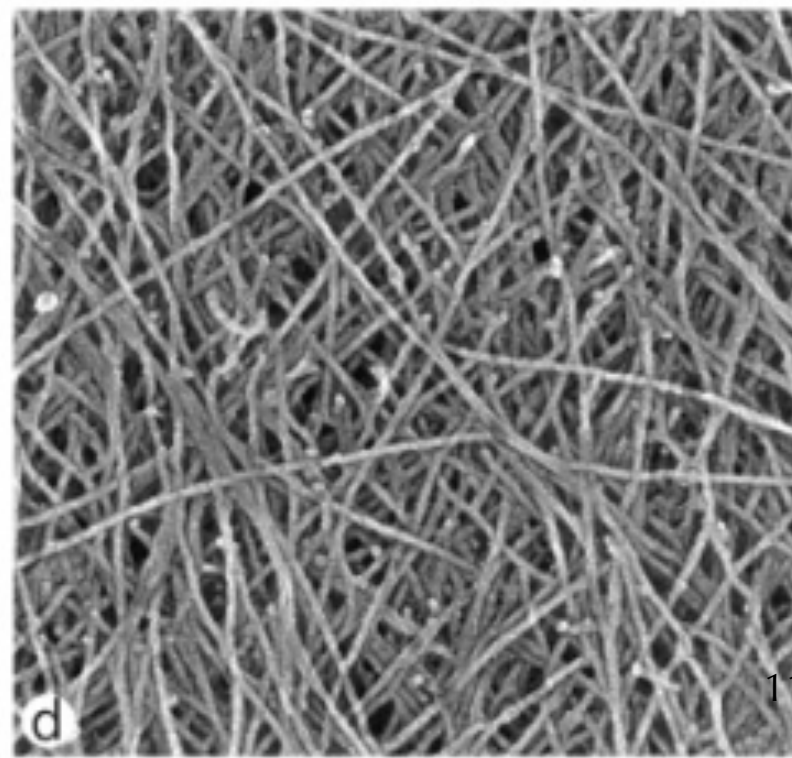
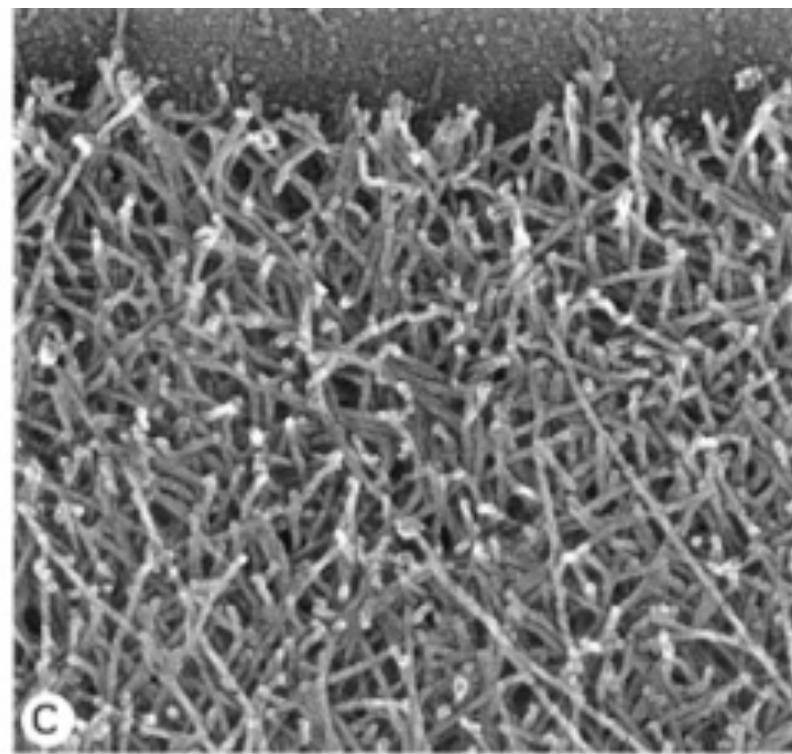
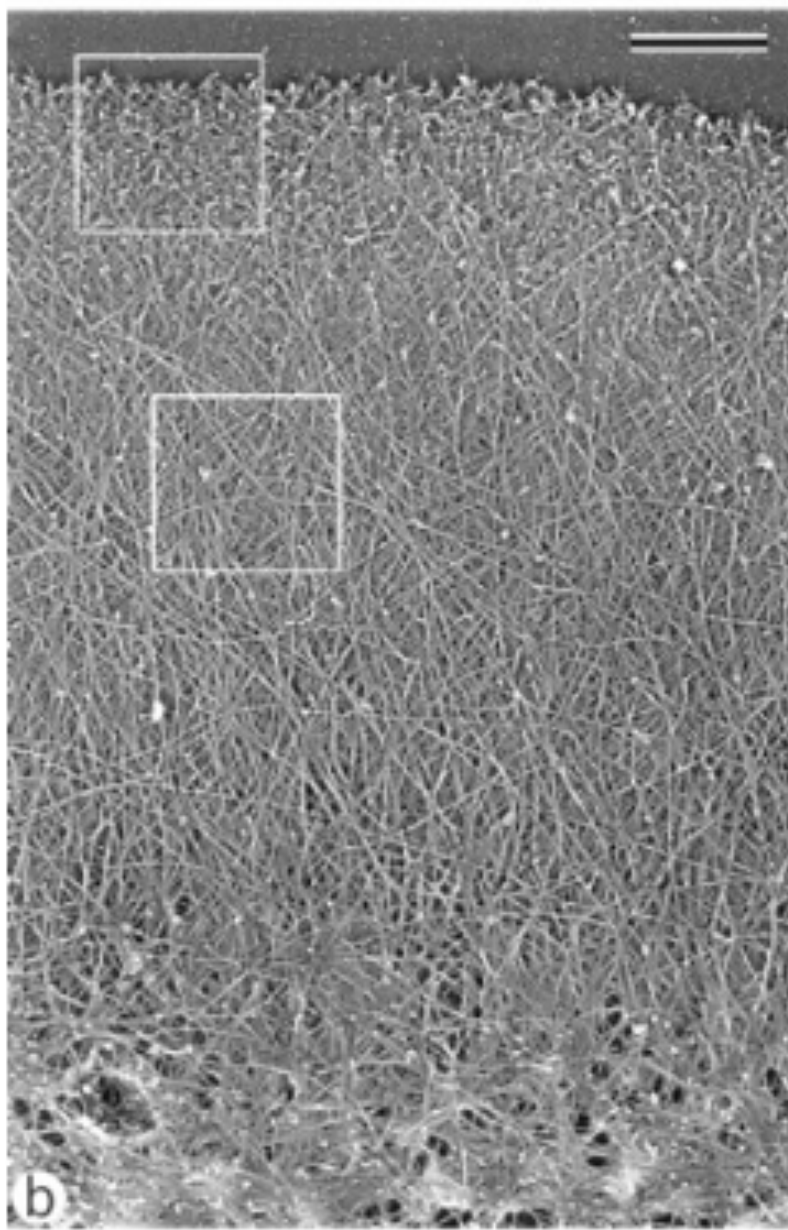
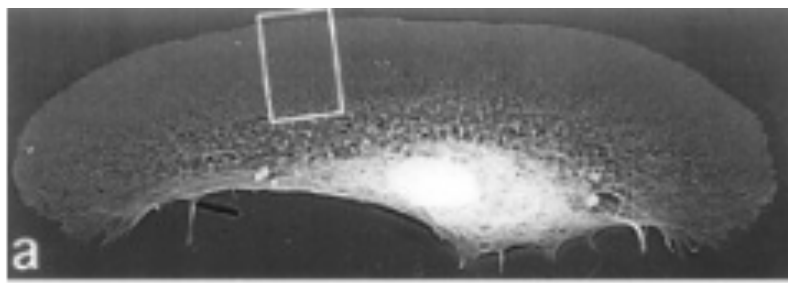


Deadhesion at the Trailing Edge



3) Movement of the Cell Body





Actin filaments are critical components of cell migration

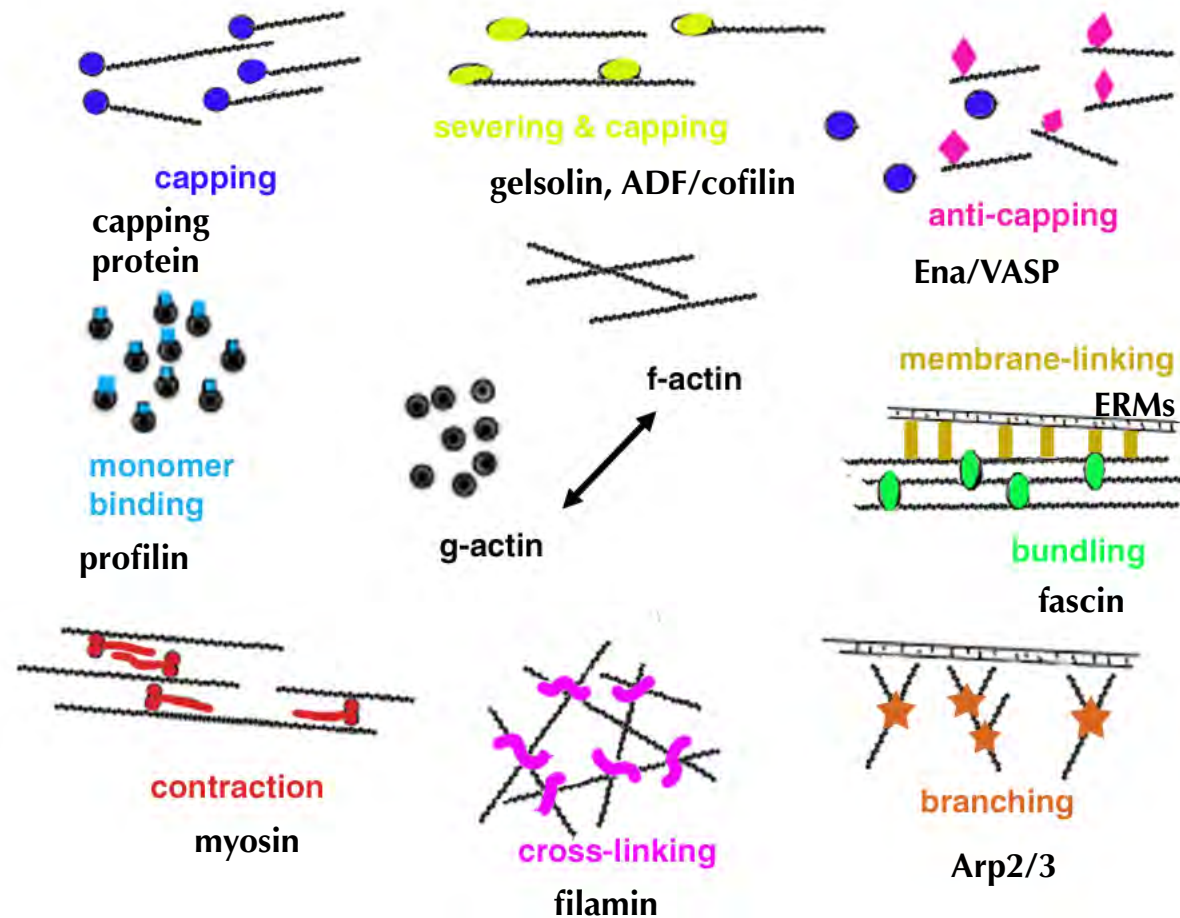
- Actin filaments are linear polymers of the globular protein actin.
- Actin polymerizes by subunit addition to a filament end, forming polarized F-actin filaments.
- Actin filaments (F-actin) form spontaneously in solution when the concentration of globular actin (G-actin) exceeds a critical concentration.
- The critical concentration of the barbed (plus) end ($0.1 \mu\text{M}$) is lower than that of the pointed (minus) end ($0.7 \mu\text{M}$), so actin polymerization is more rapid at barbed ends.



-
- ATP-Actin
 - ADP-P_i-Actin
 - ADP-Actin

Actin-binding proteins (ABPs)

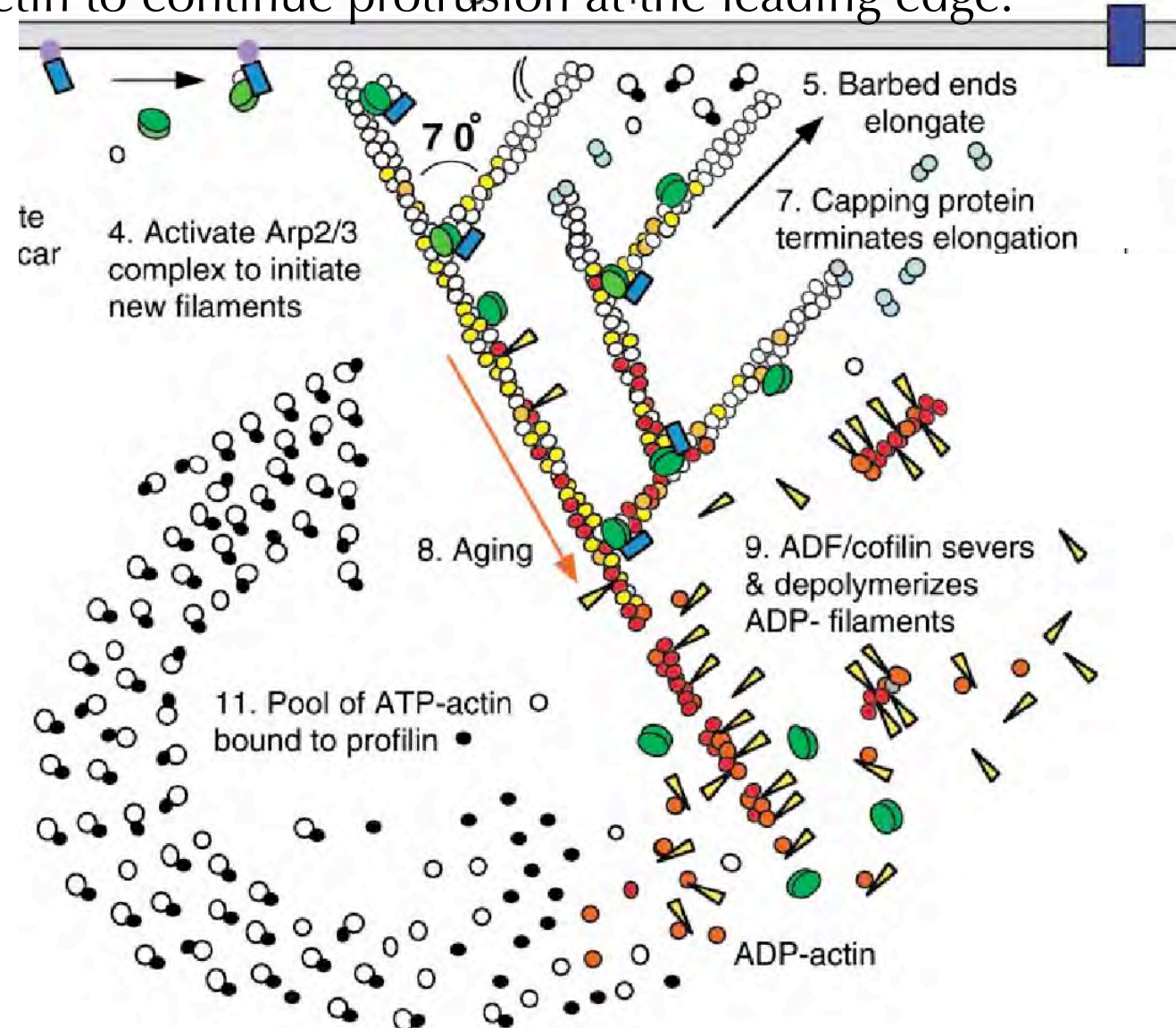
- The intracellular concentration of actin is high (20-100 μM), much above the critical concentration for polymerization of purified actin.
- Yet, <50% of cellular actin is in F-actin, instead of $\gg 90\%$.
- Intracellular actin polymerization and organization is regulated by about 200 actin-binding regulatory proteins (ABPs).



- Actin organization depends on:
 - localization
 - relative concentrations
 - activity levels of actin regulatory proteins (ABPs)

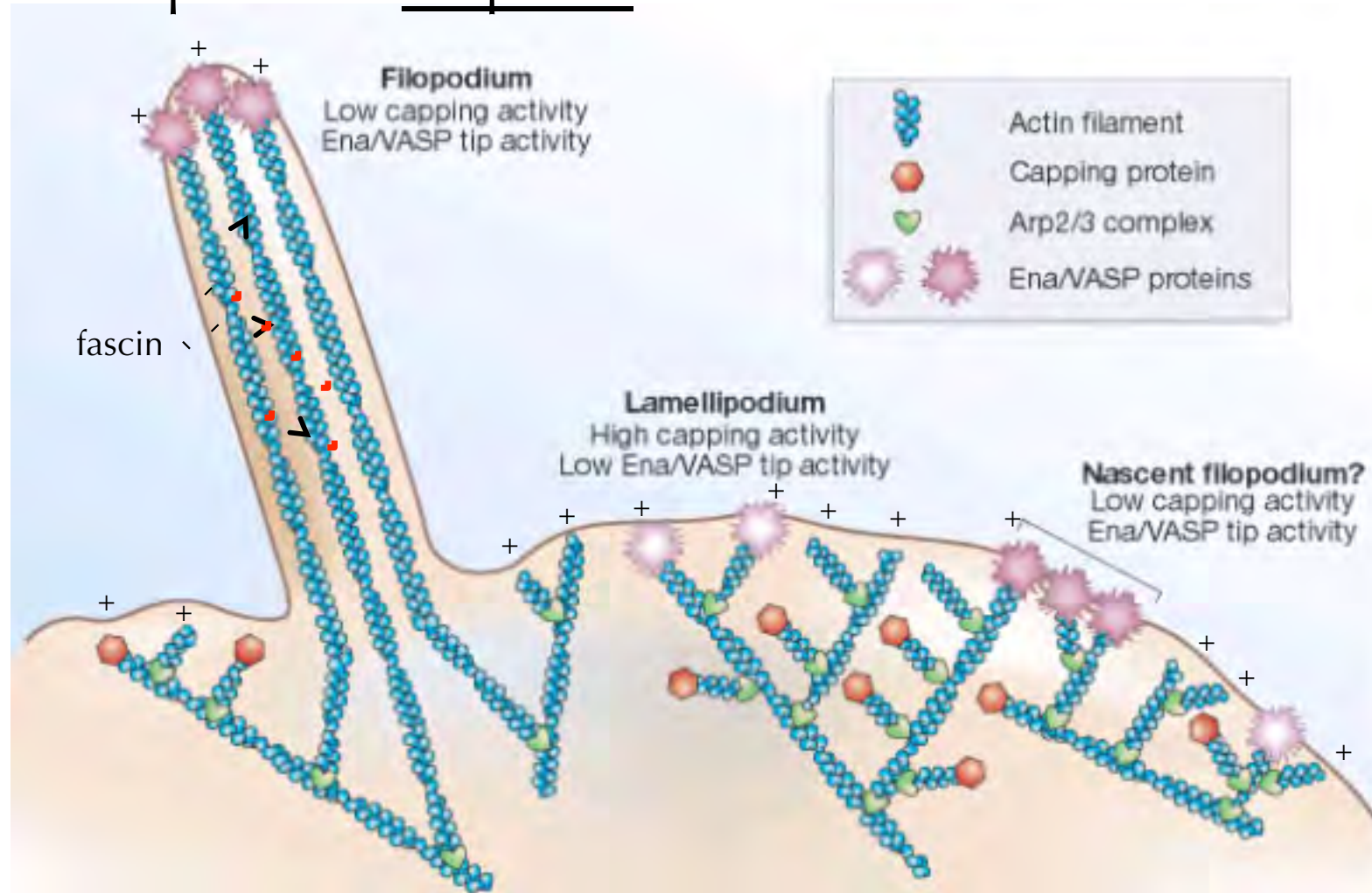
Protrusion

- Rapid actin polymerization at the plasma membrane pushes the membrane outward, driving the protrusion of the leading cell margin.
- The ABPs Arp2/3, capping protein, and ADF/cofilin promote rapid recycling of G-actin into F-actin to continue protrusion at the leading edge.

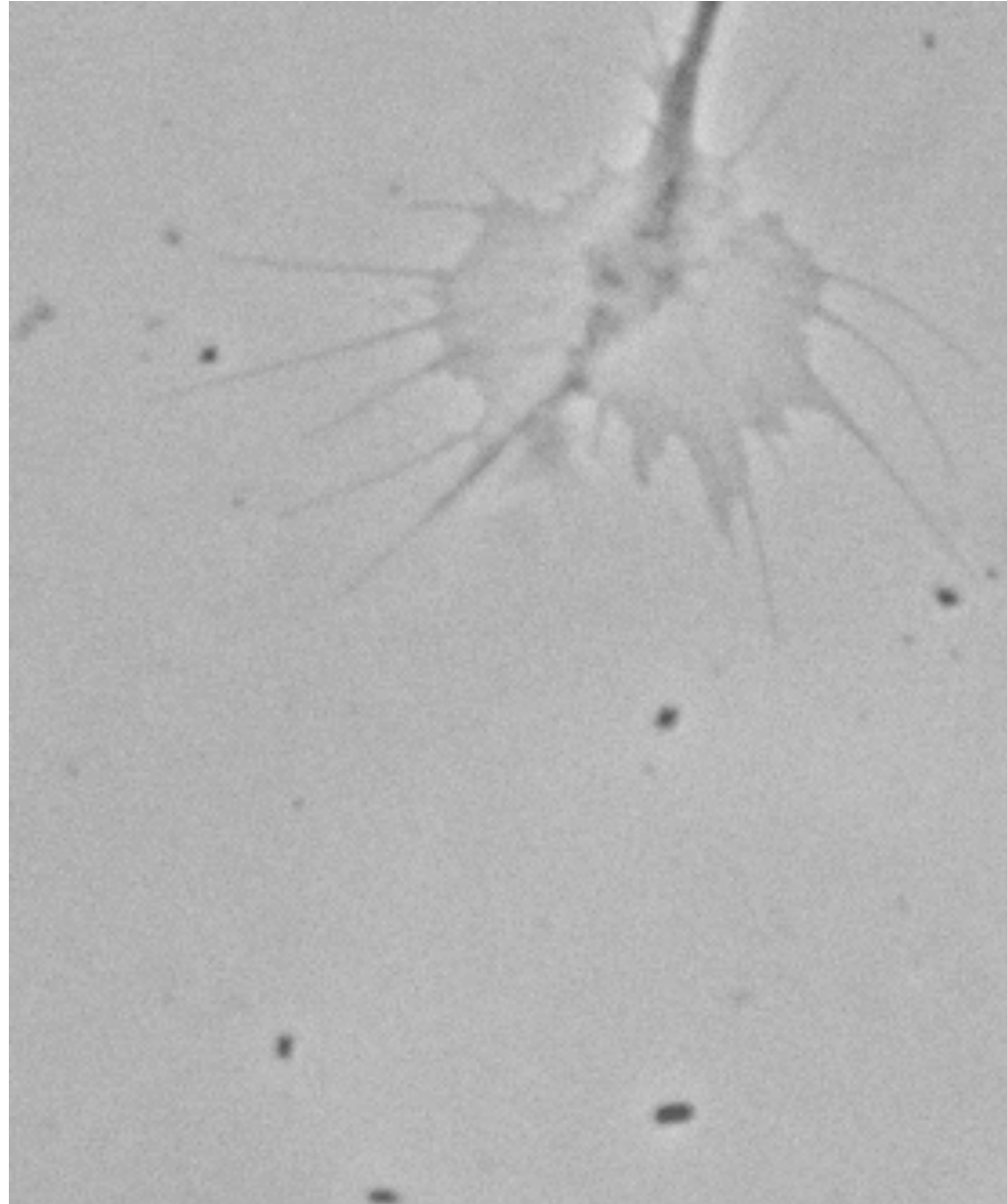


ABPs regulate the shapes of leading edge protrusions

- The Arp2/3 complex organizes actin polymerization into branched networks to form lamellipodia.
- ABPs Ena/VASP and fascin organize actin polymerization into bundles to protrude filopodia.



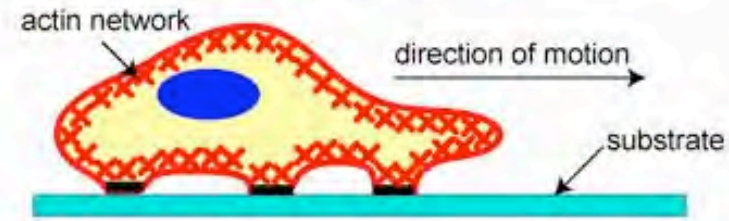
Dynamic protrusion of the leading margin of an axonal growth cone



Cell movement occurs in three steps; protrusion, adhesion, and pulling forward

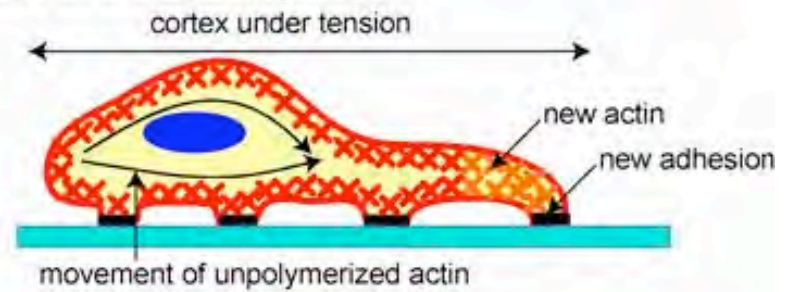
1. Protrusion of the leading edge

1) Protrusion of the Leading Edge



2. Adhesion at the leading edge

2) Adhesion at the Leading Edge

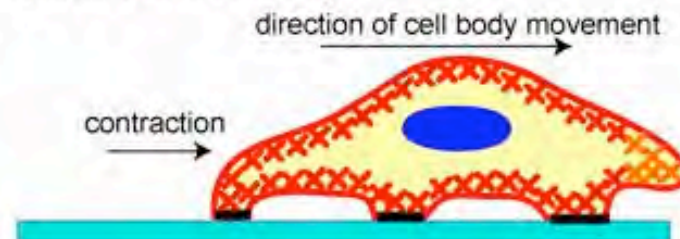


3. Traction to pull ahead

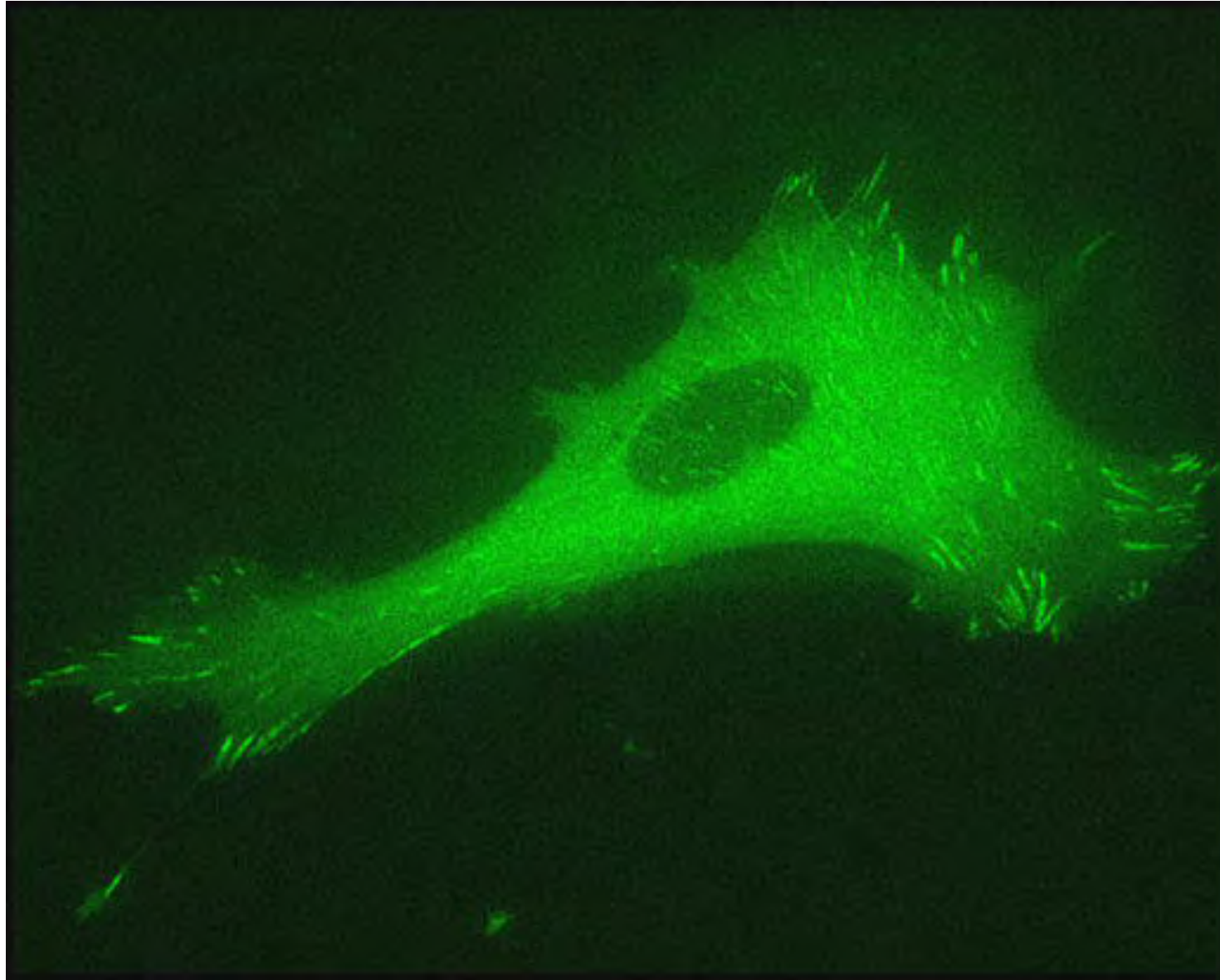
Deadhesion at the Trailing Edge



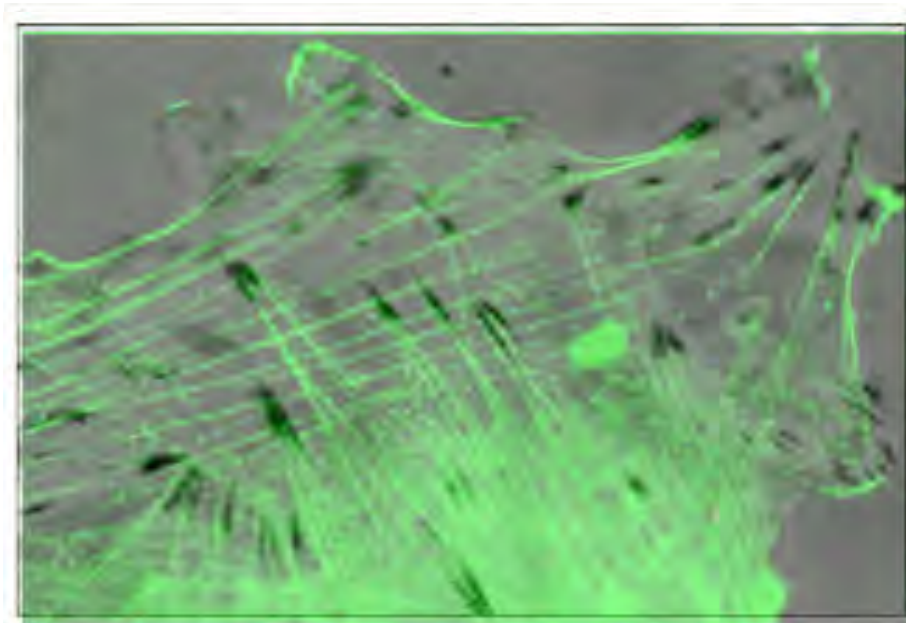
3) Movement of the Cell Body



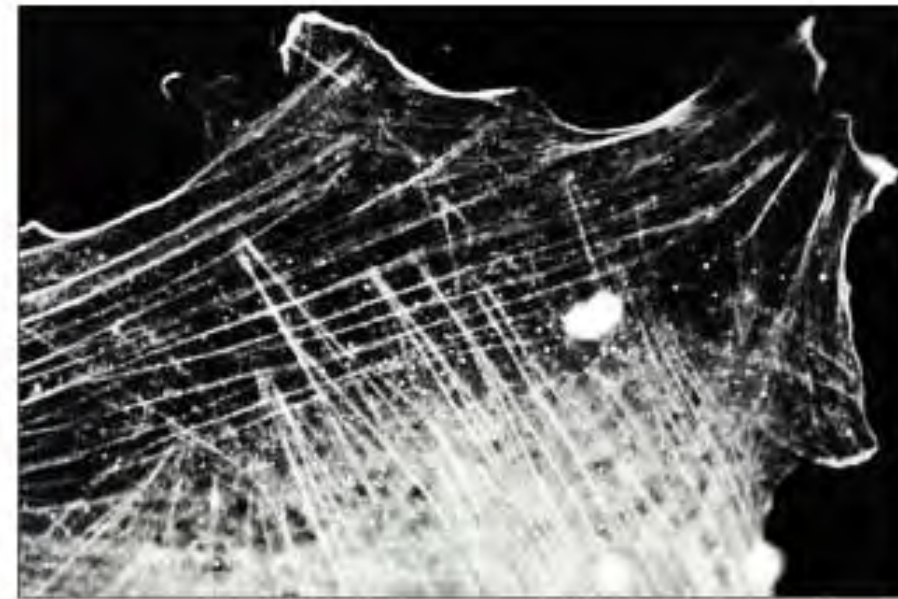
New adhesive sites appear beneath the leading margin



- In the left image cell-substratum adhesions are black patches.
- In the right image F-actin bundles are white streaks.
- Adhesive sites coincide with the ends of F-actin bundles.



(A)



(B)

10 μm

ABPs link F-actin bundles to adhesive sites

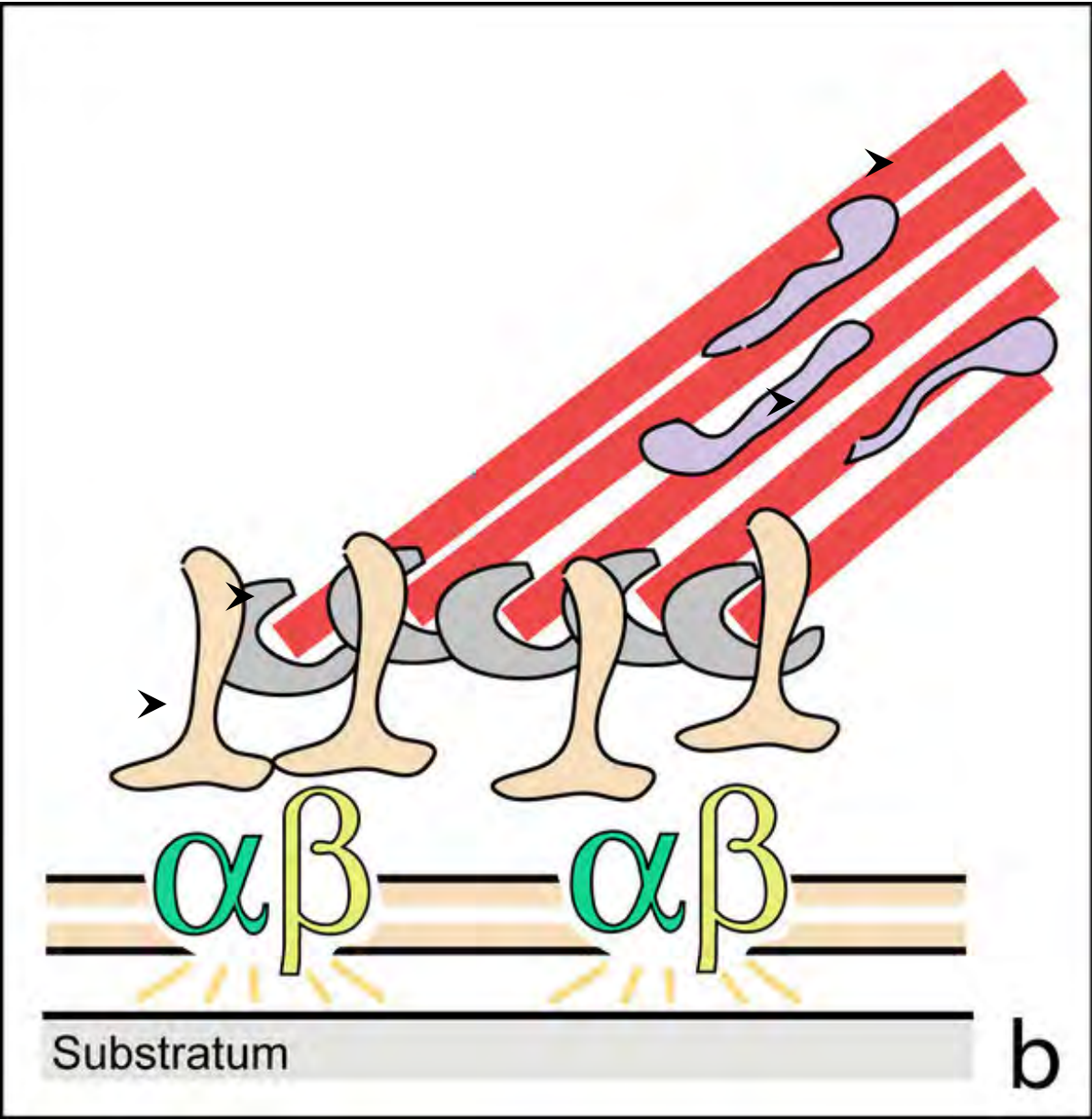
F-actin ◊

alpha-actinin = F-actin linker ◊

vinculin = actin-integrin linker ◊

talin = actin-integrin linker ◊

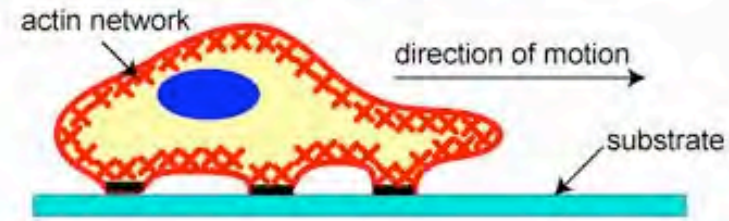
Integrin dimer = adhesion receptor



Cell movement occurs in three steps; protrusion, adhesion, and pulling forward

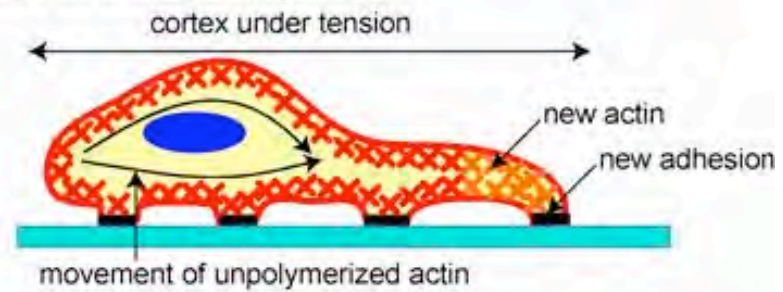
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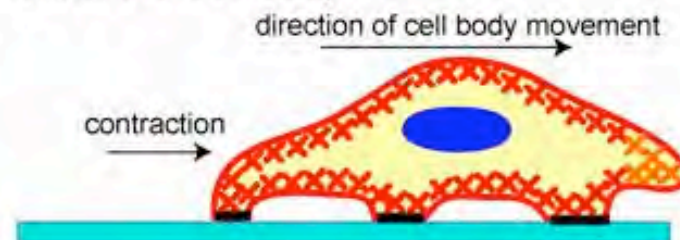


3. Traction to pull ahead

Deadhesion at the Trailing Edge



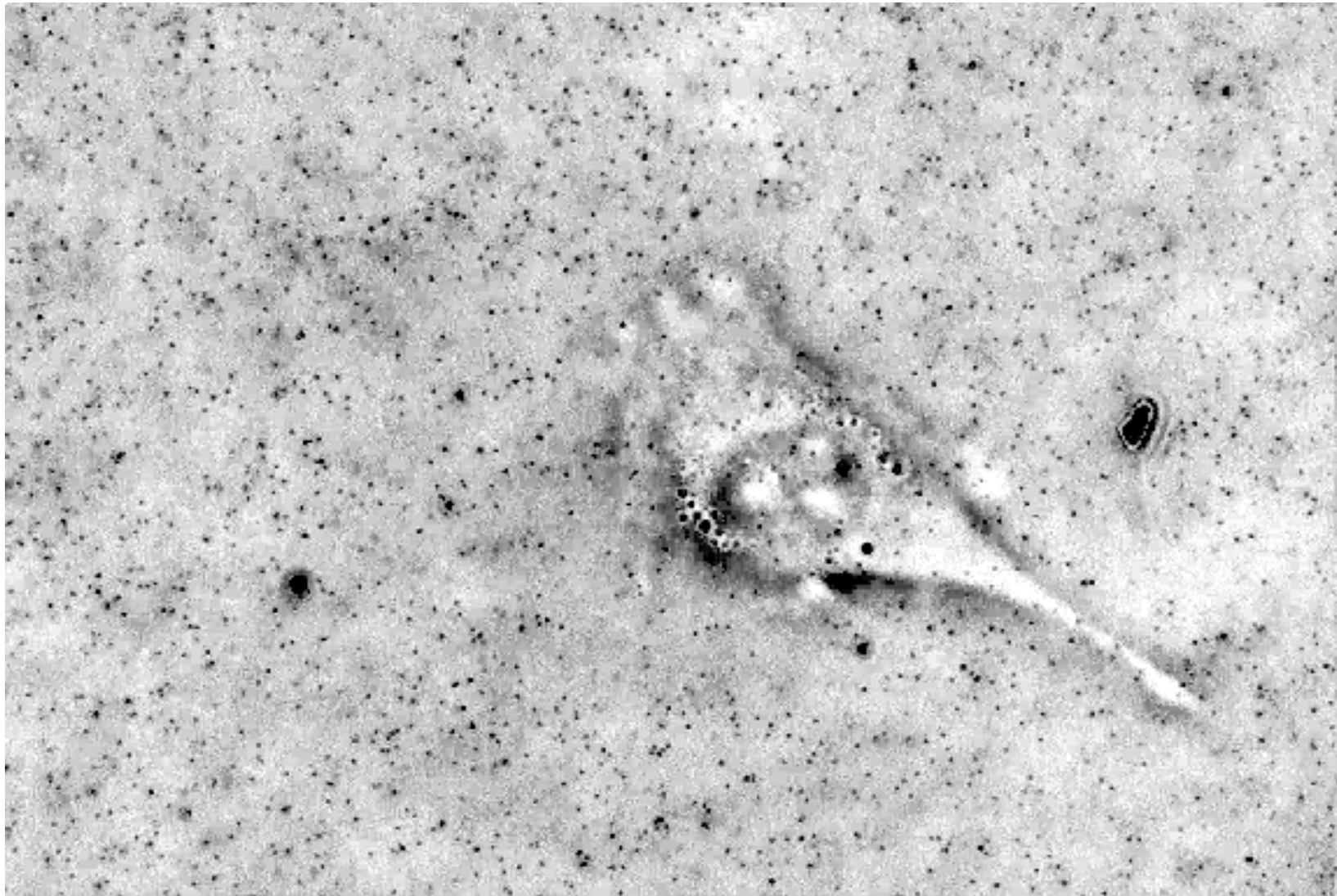
3) Movement of the Cell Body



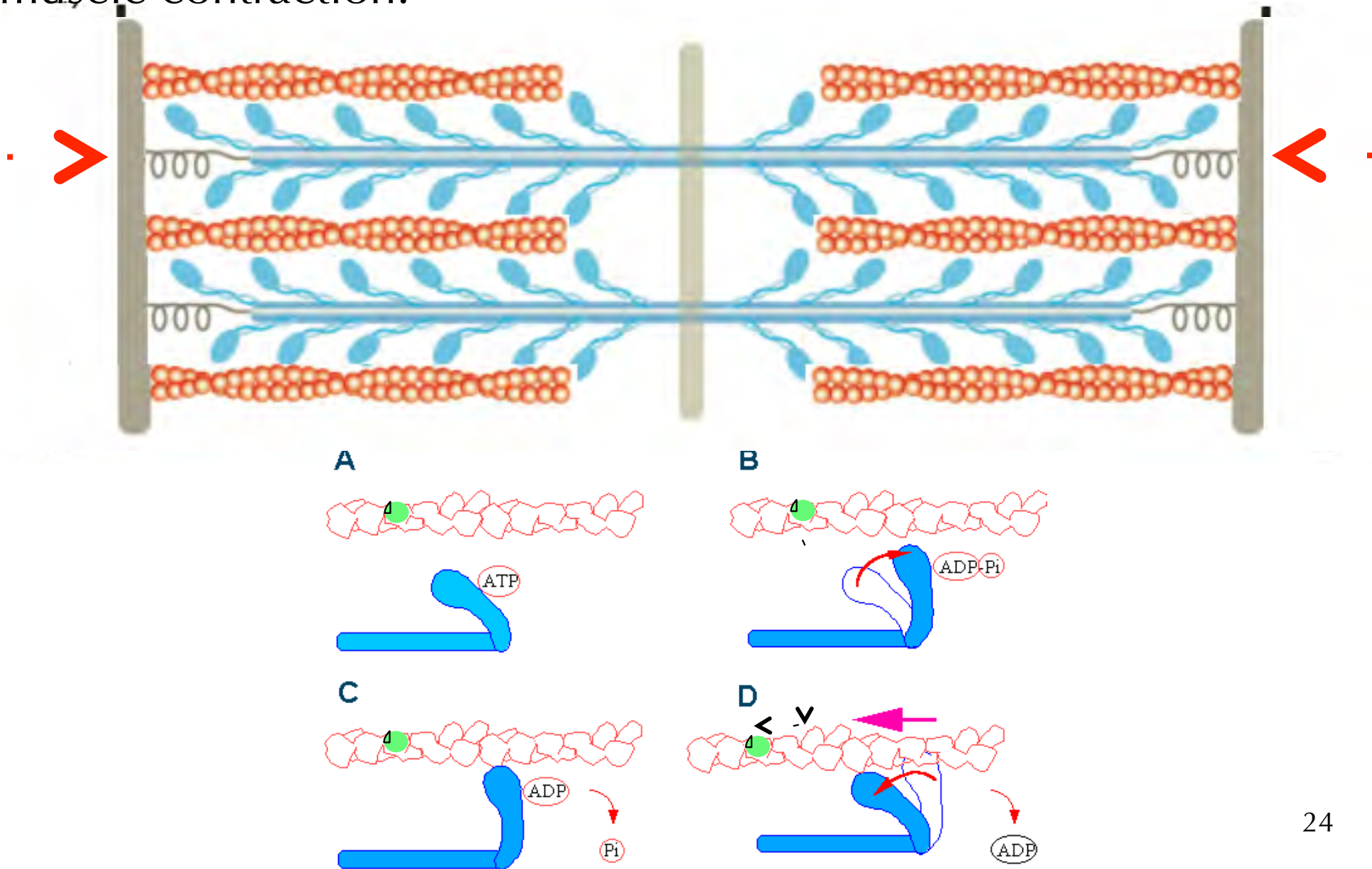
The third step of migration is to pull the cell forward.



This video shows the leading edge of a cell pulling on a deformable substratum

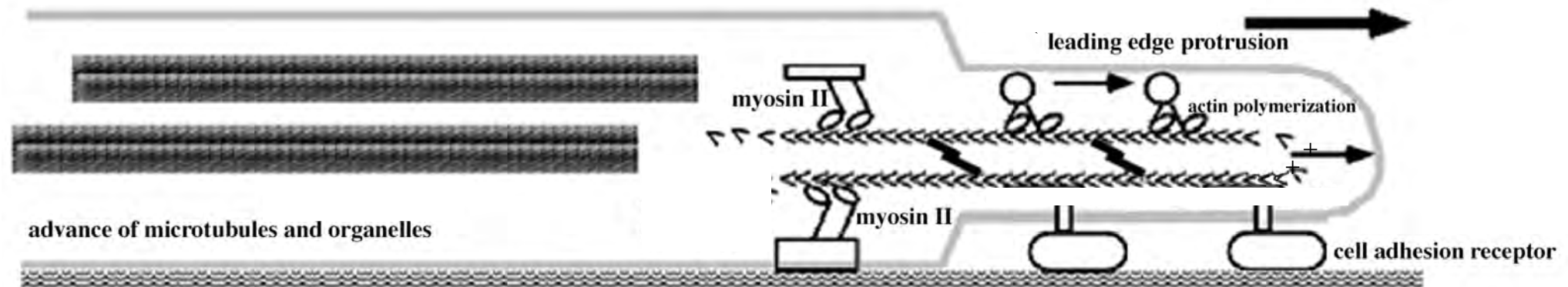


- Myosin II is the motor molecule that exerts tension to slide actin filaments.
- Myosin II uses energy of ATP to produce mechanical energy for muscle contraction.

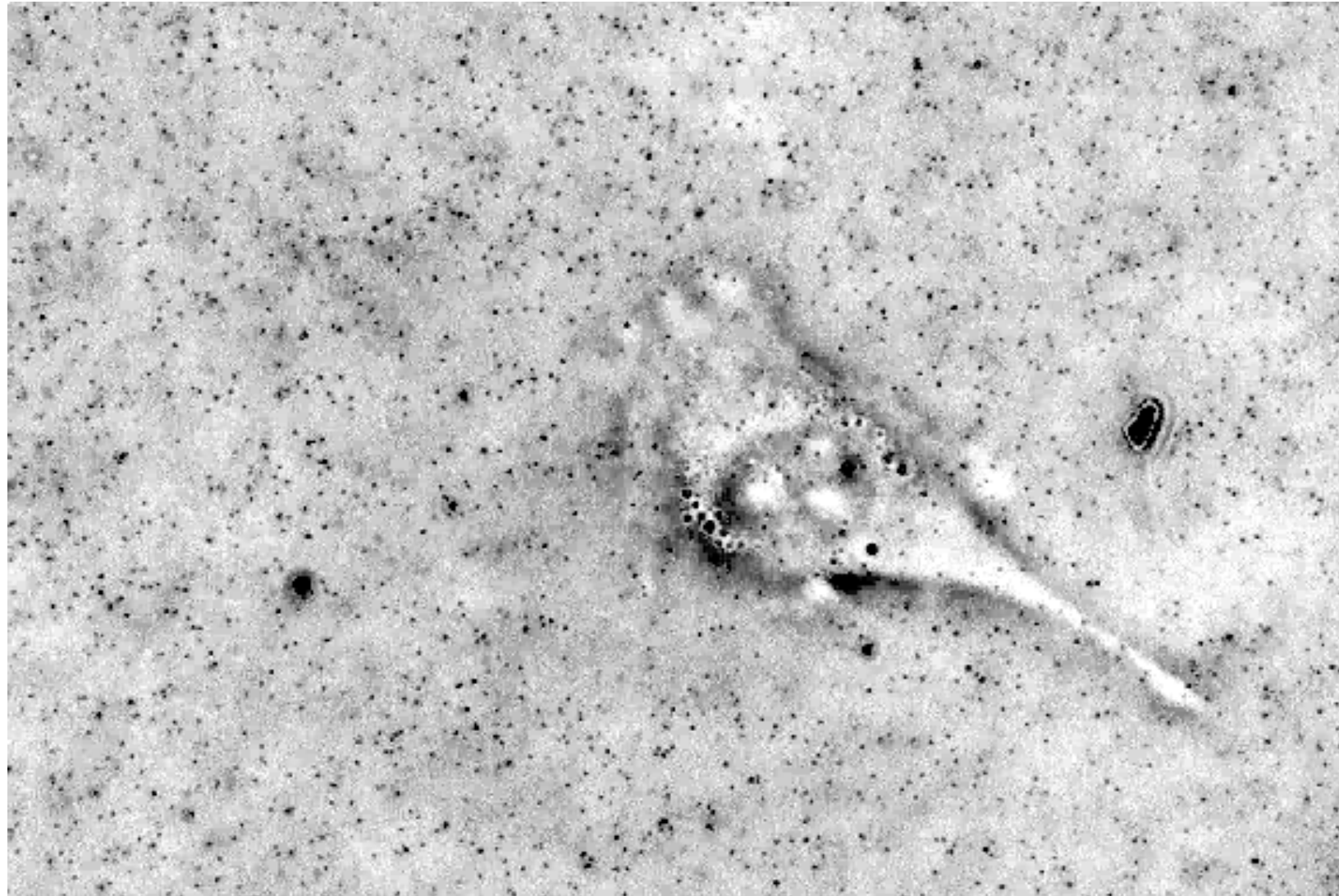


The clutch hypothesis of cell migration

- Assembly of F-actin at the leading edge protrudes filopodia and lamellipodia.
- Retrograde flow, powered by myosin II, pulls the F-actin backward, and actin is disassembled.
- When protrusions make adhesions, a clutch is engaged to link F-actin to the stable adhesive sites. This reduces retrograde flow.
- Forces exerted by motor molecules (myosin II, other myosins, dynein) pull, push organelles forward (microtubules, vesicles) to advance the cell.



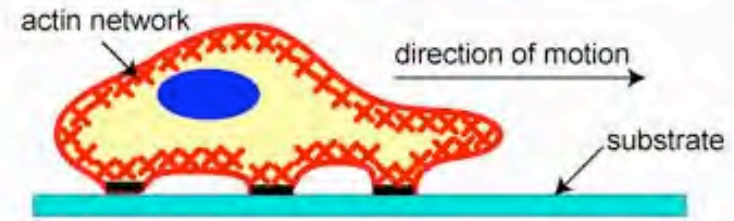
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Cell movement occurs in three steps; protrusion, adhesion, and pulling forward

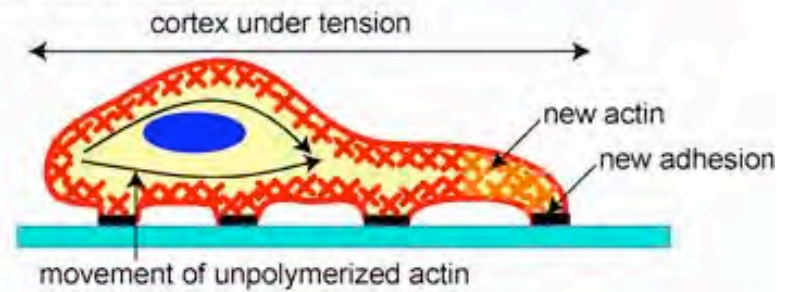
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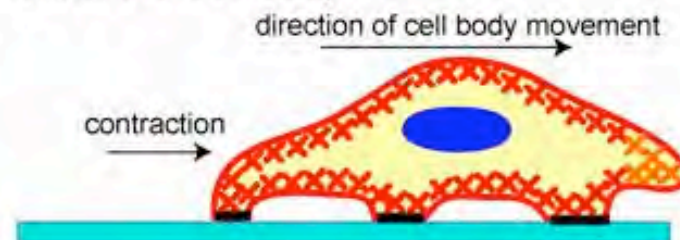


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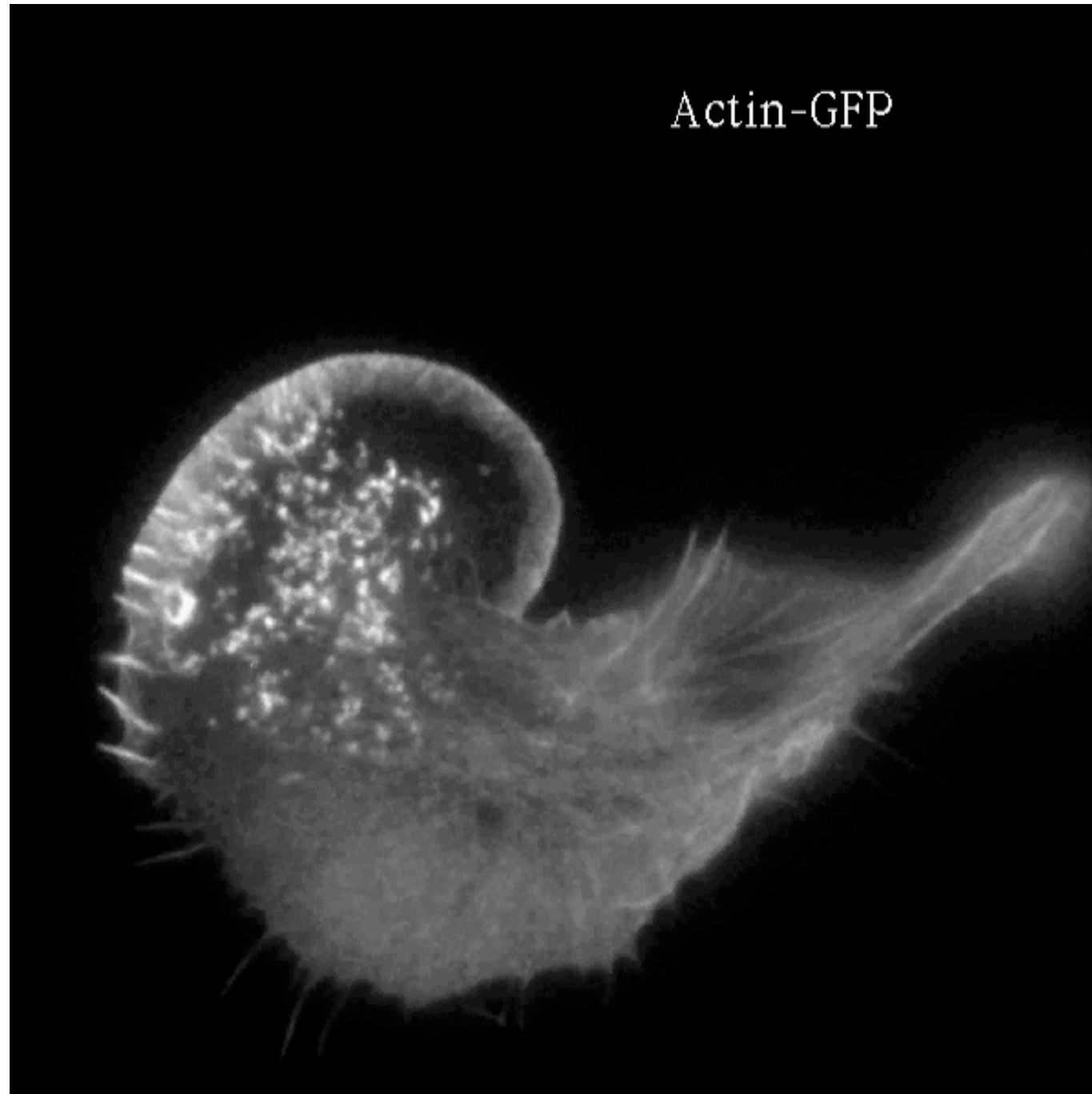
Deadhesion at the Trailing Edge



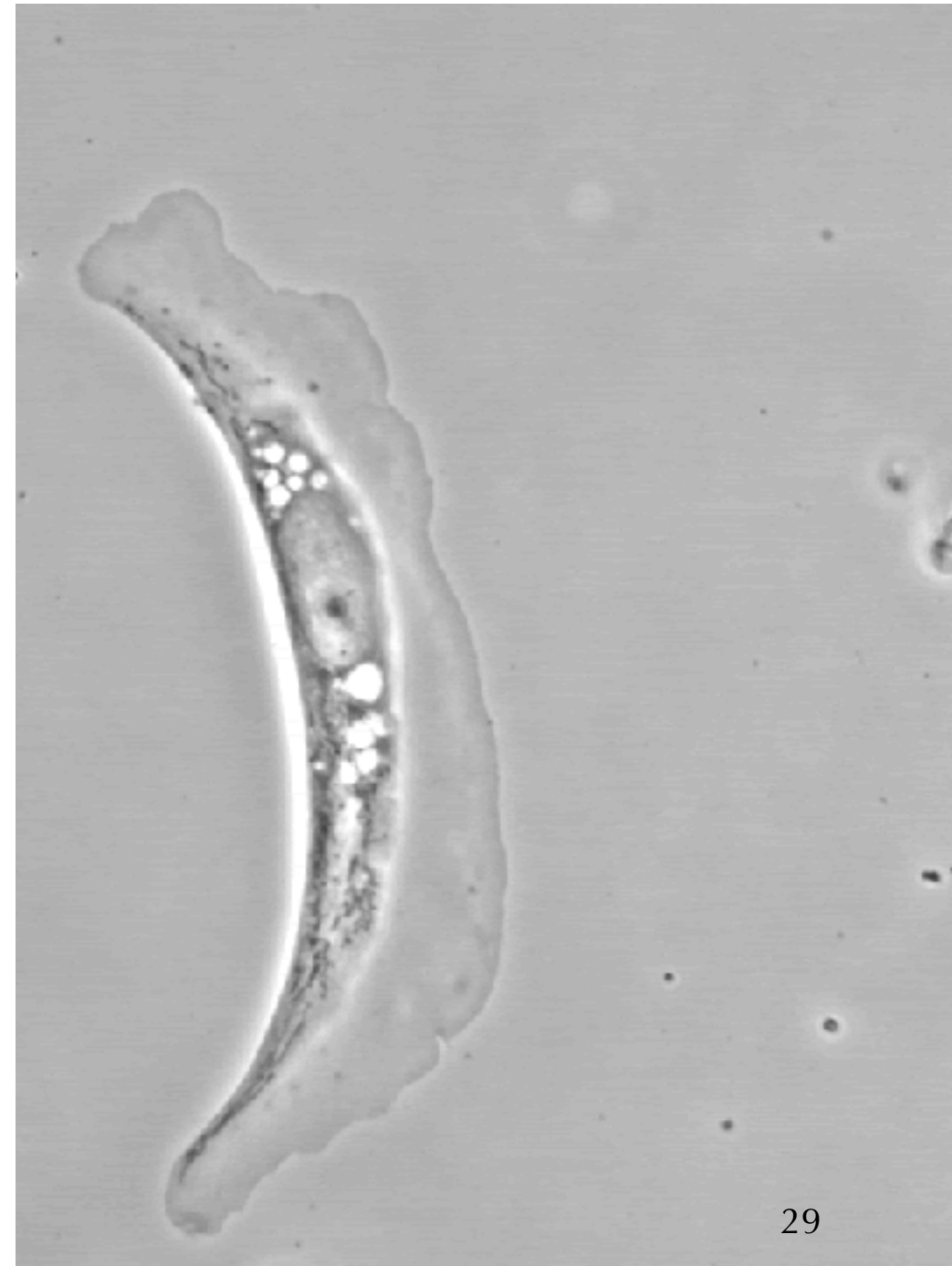
3) Movement of the Cell Body



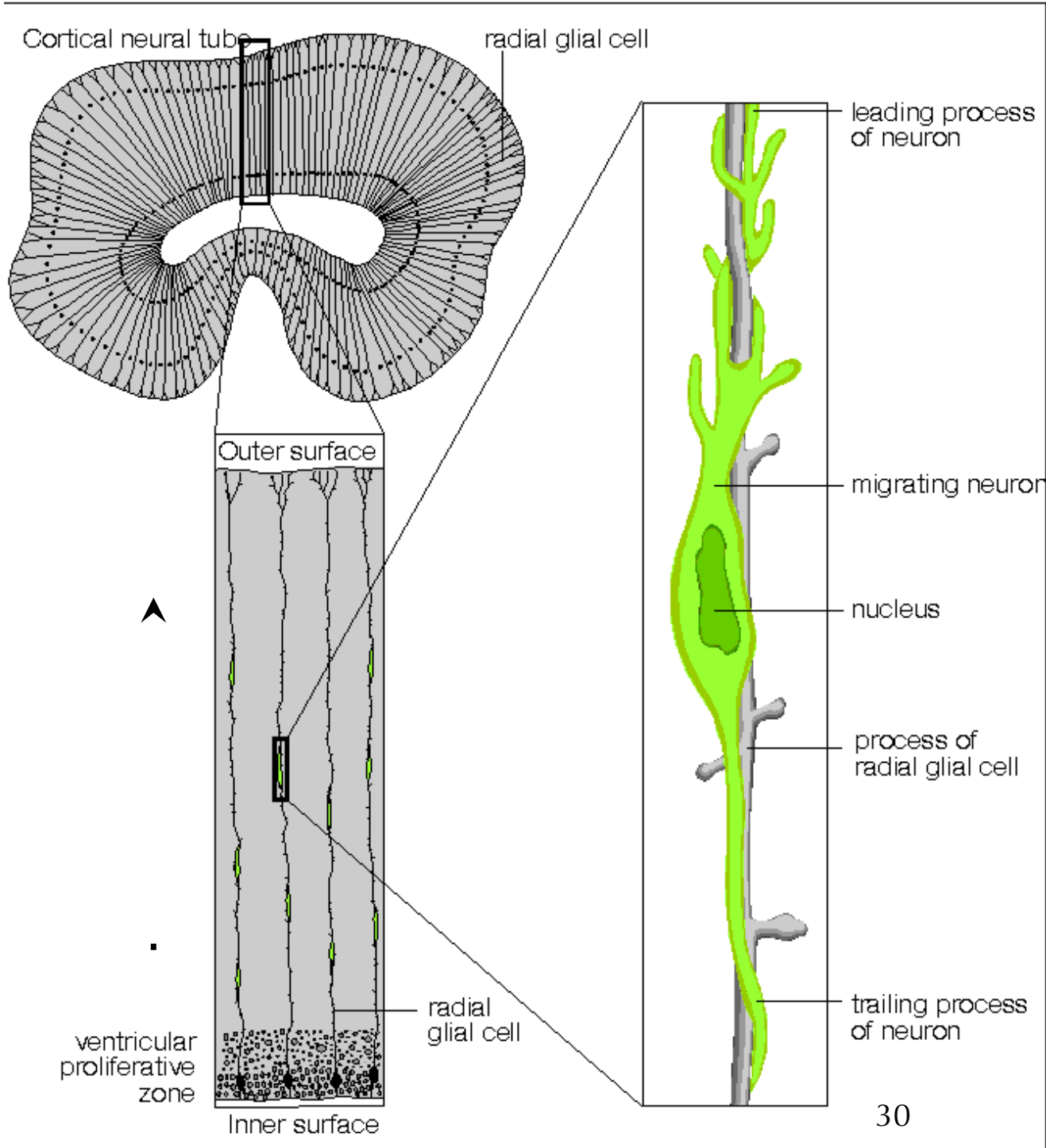
F-actin dynamics at the front of a migrating melanoma cell



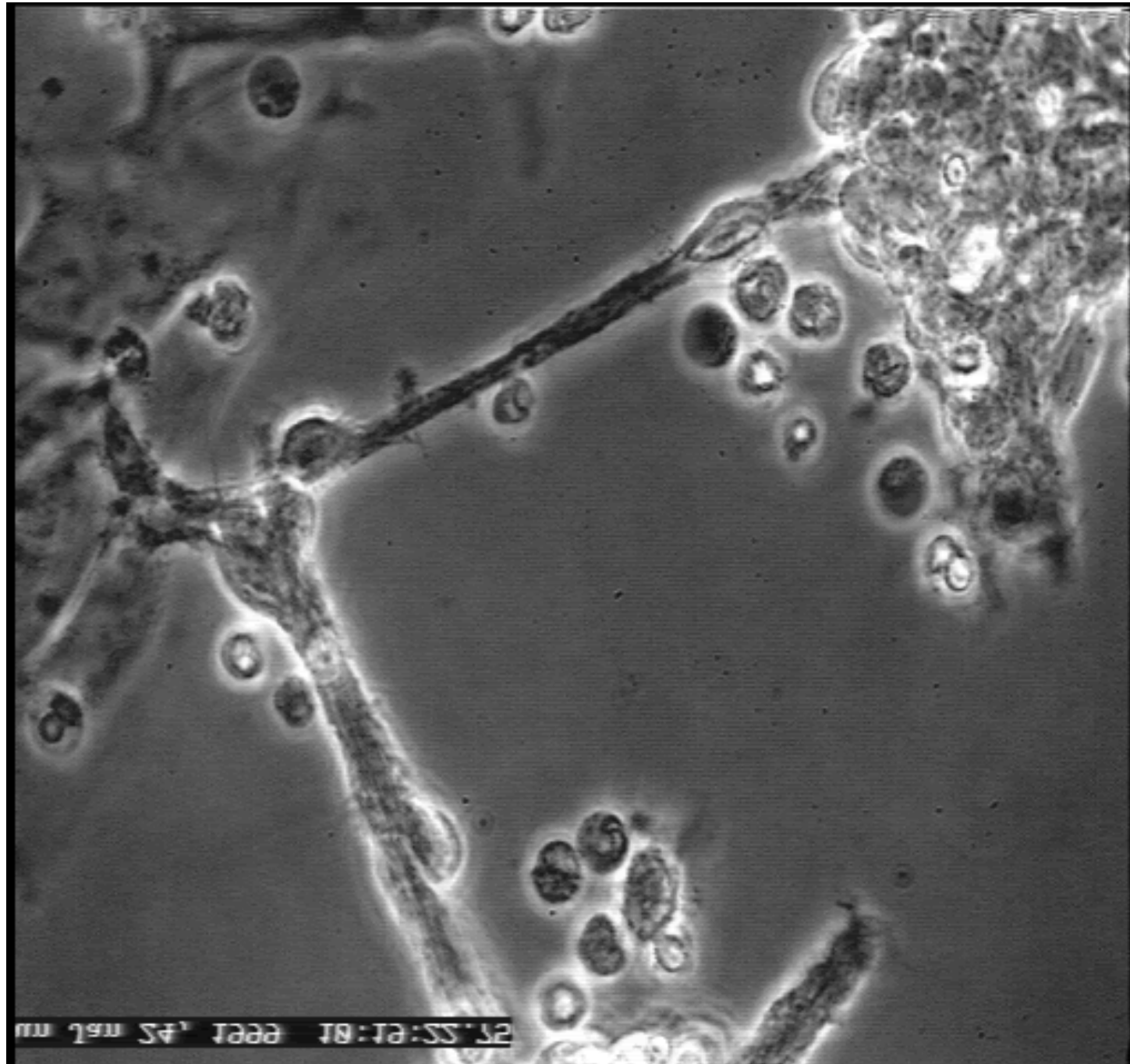
The third step of migration is to pull the cell forward.



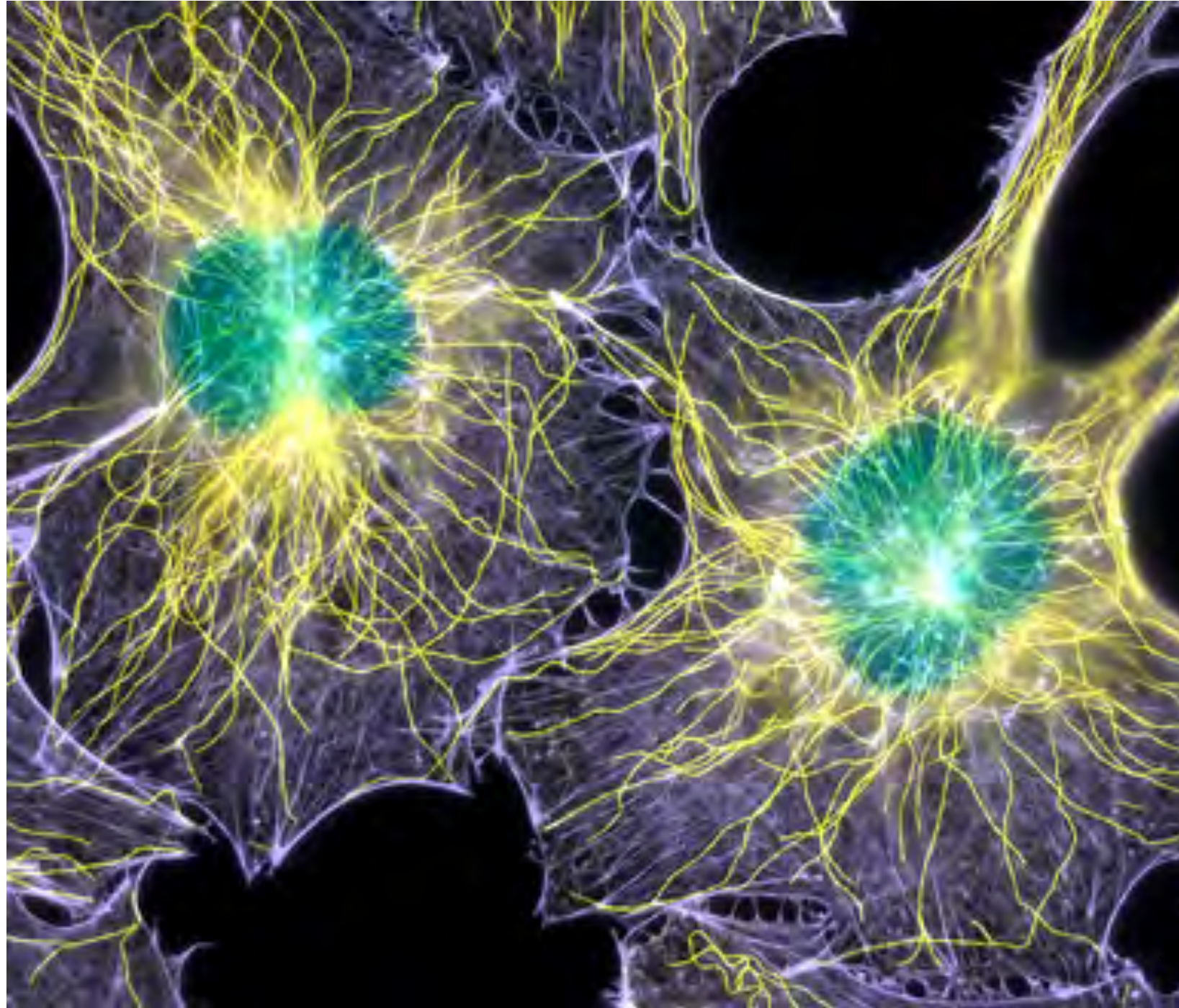
- Now look at another form of neural cell migration, when cells migrate along linear tracks, such as axons or long cell processes, such as radial glia.



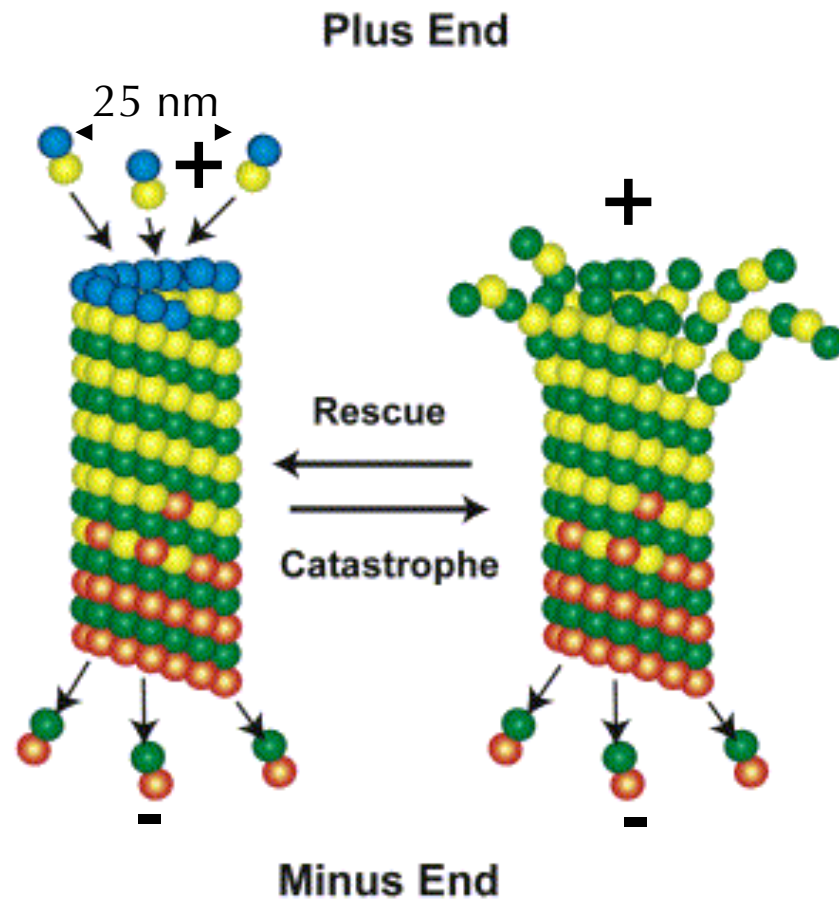
This video shows immature neurons migrating along a glial pathway



Microtubules are the other cytoskeletal component involved in cell migration



Microtubules support cell shape and elongation

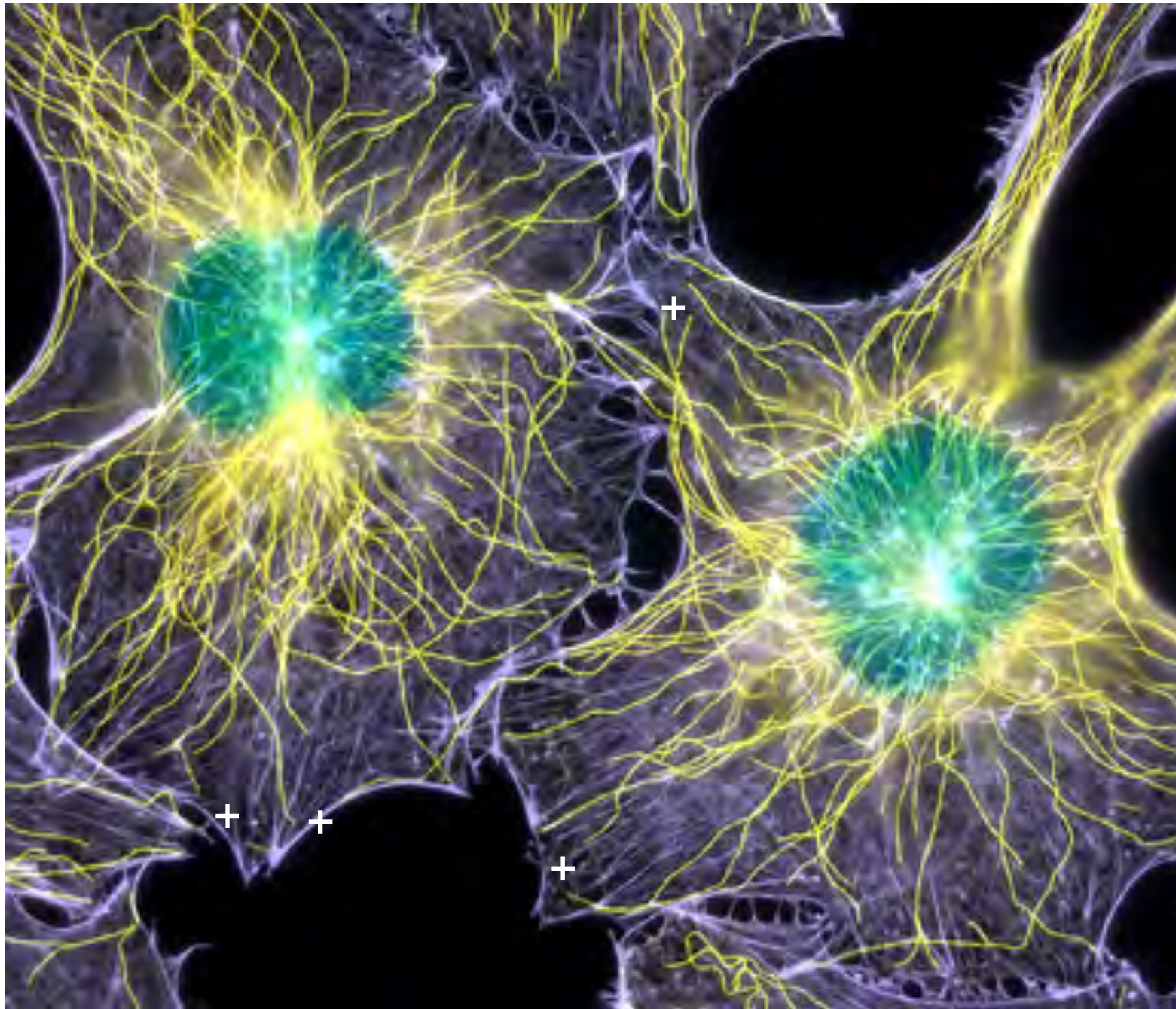


- | | |
|-----------------|---------------------------|
| ● GTP-β-Tubulin | ● Tyrosinated-α-Tubulin |
| ● GDP-β-Tubulin | ● deTyrosinated-α-Tubulin |

- Polymers of tubulin dimers. Diameter is 25 nm. Individual microtubules resist compression.
- Polymerization requires GTP bound to tubulin dimers
- have intrinsic polarity - important in transport
- plus ends alternate between states of growing, shrinking (catastrophe) and resting.

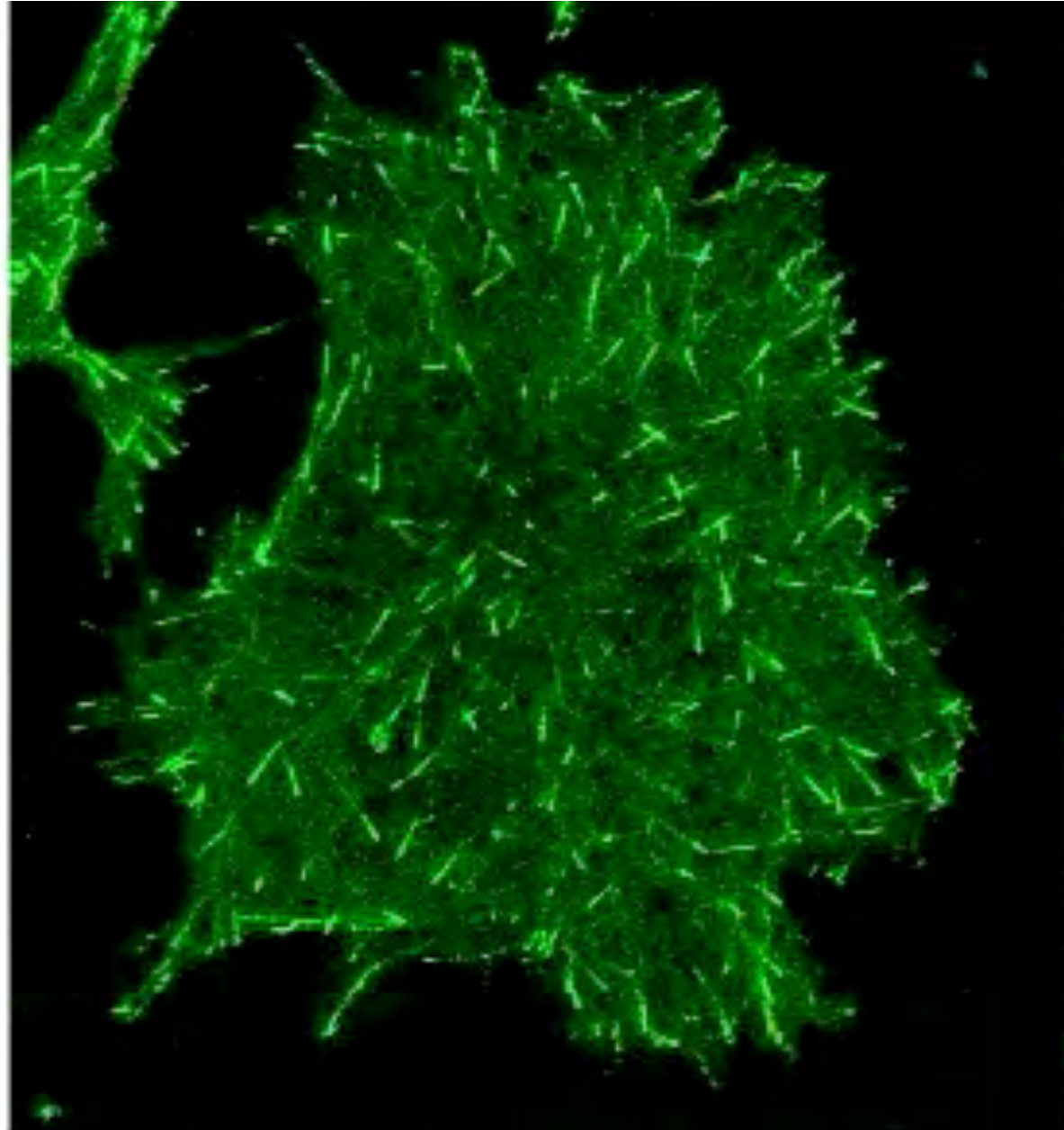
Microtubules alternate between growing and shrinking plus ends:
dynamic instability





Imaging of microtubule dynamics in live cells

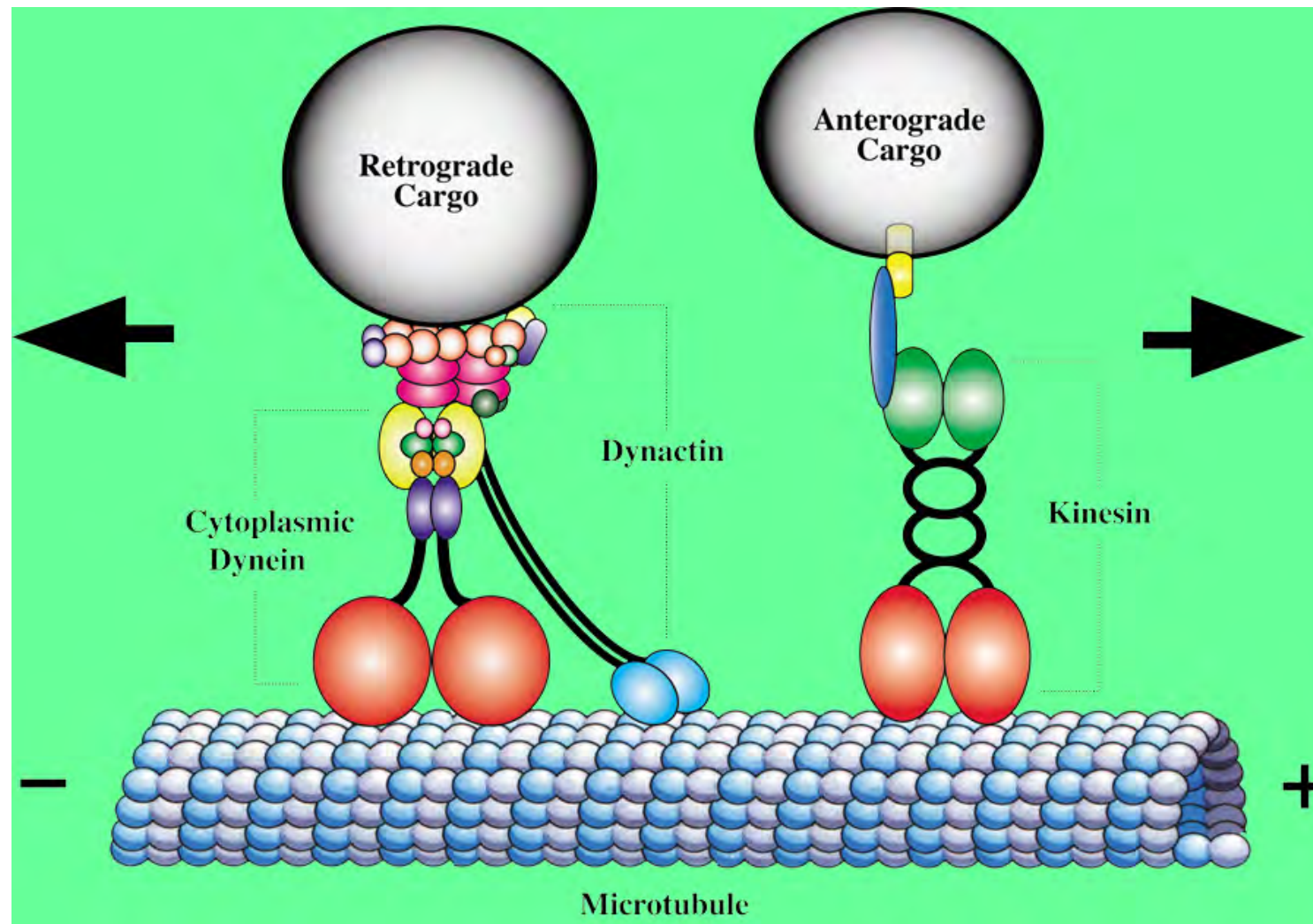
- GFP-EB1 binds to growing MT plus ends



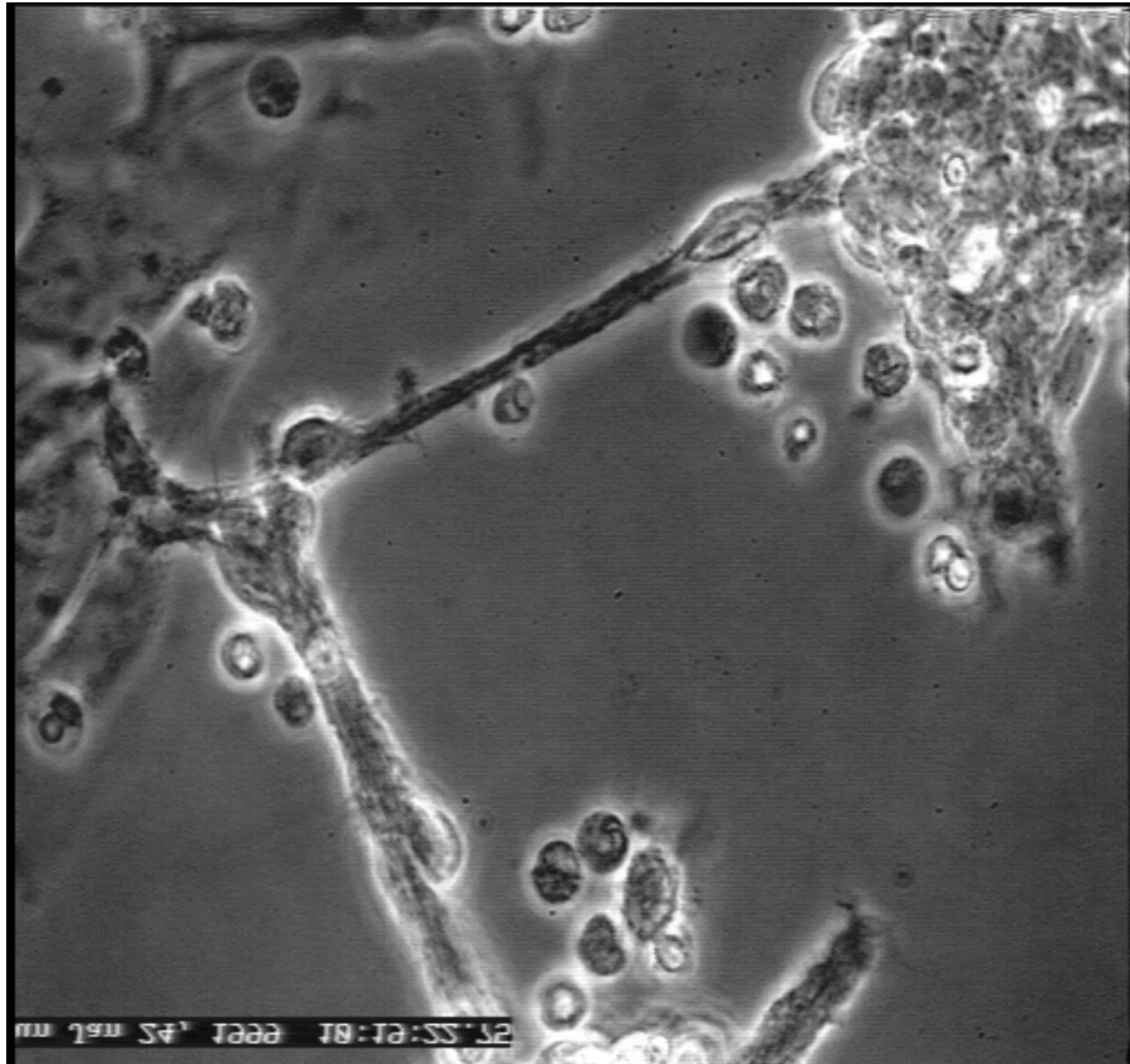
Microtubules are the tracks along which organelles are transported by molecular motors.



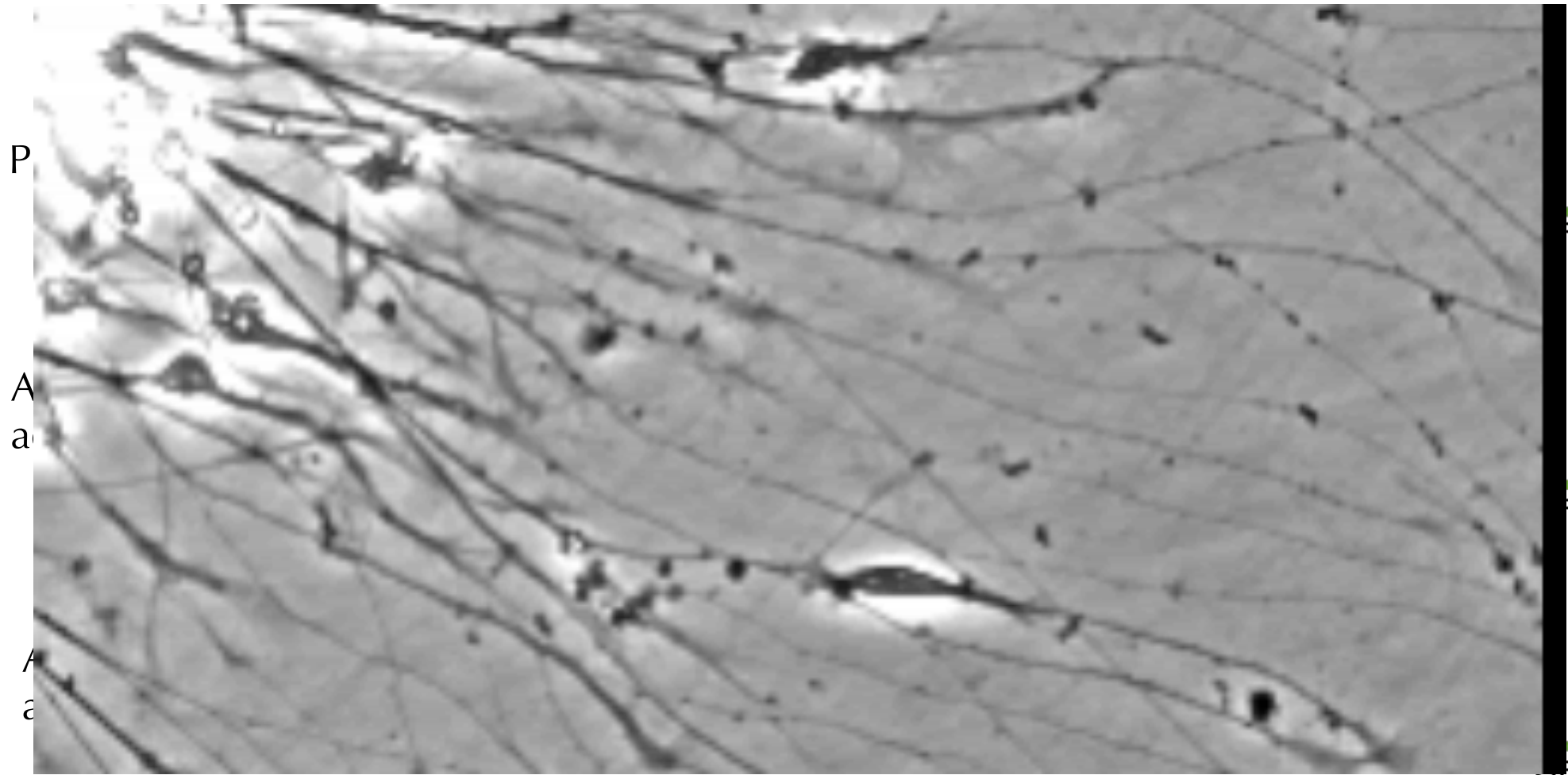
- Kinesin motors move cargo toward microtubule + ends
- Dynein motors move cargo toward microtubule - ends



This video shows immature neurons migrating along a glial pathway

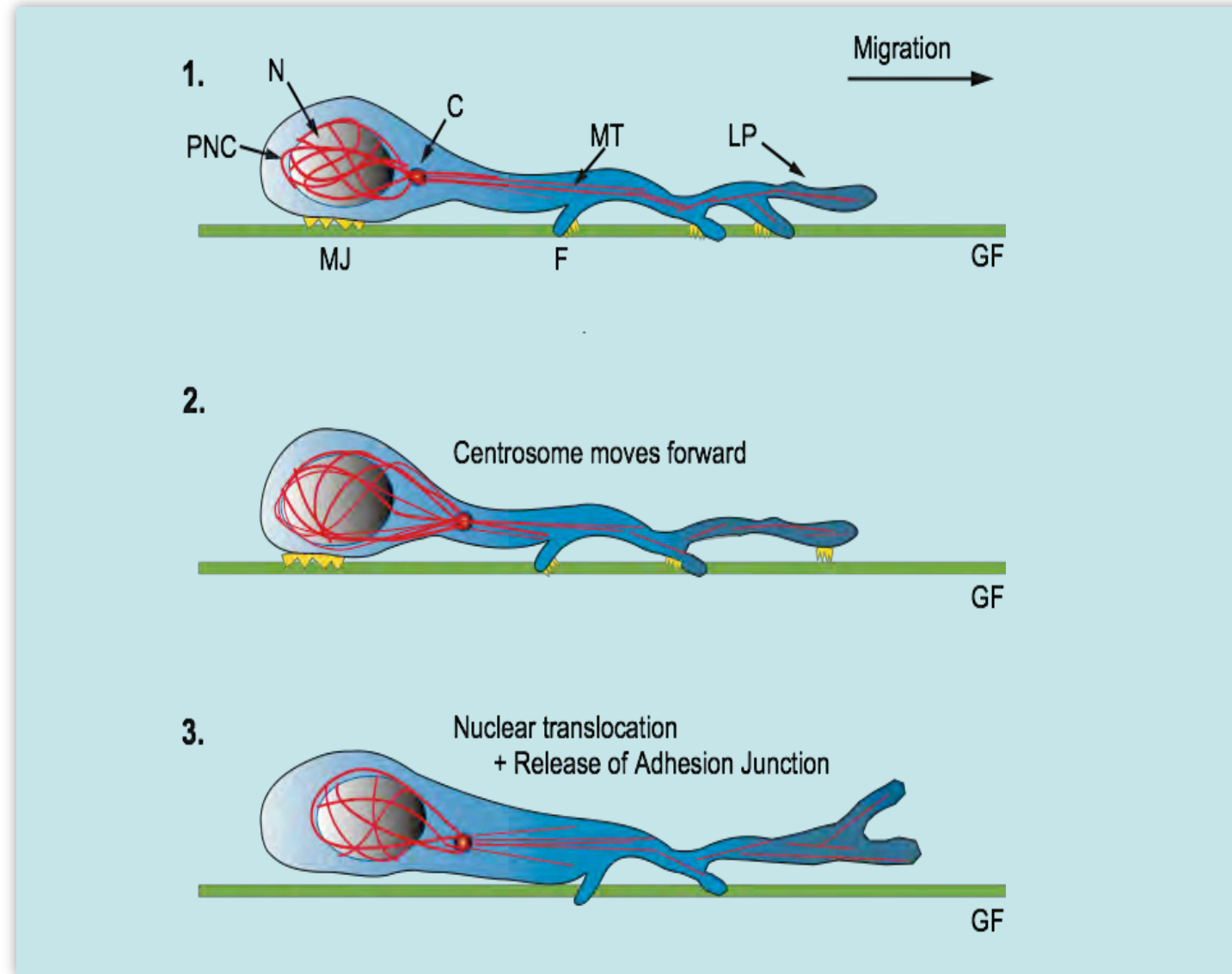


Steps in migration along axons or glial fibers



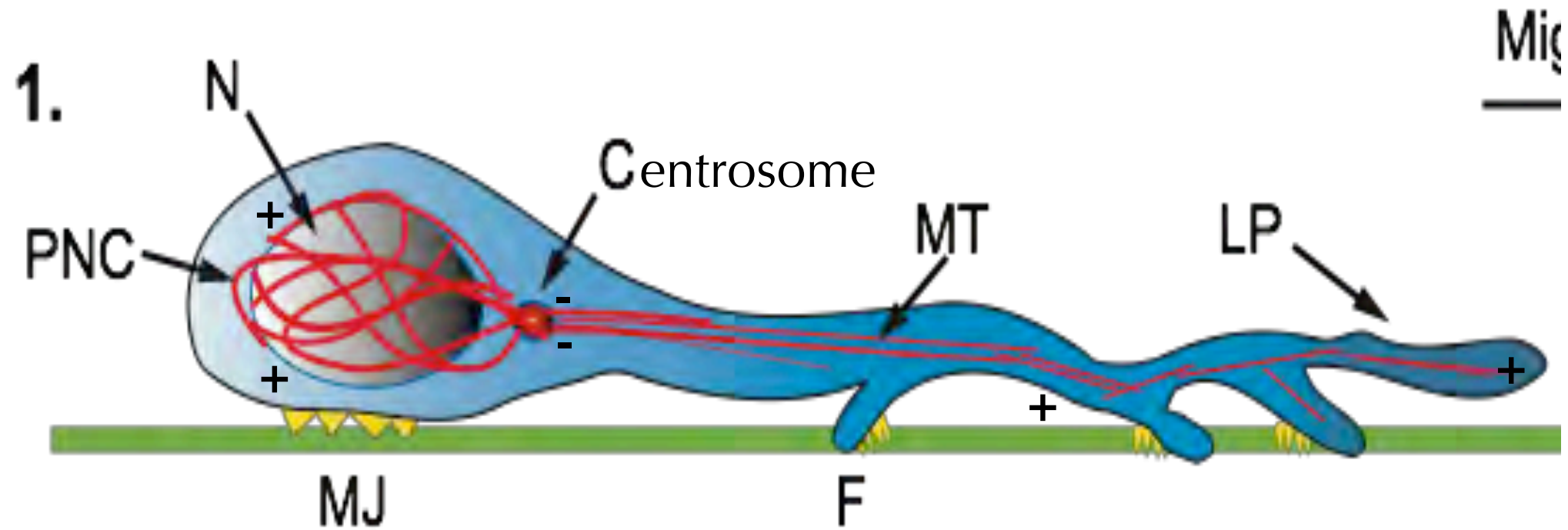
What motors power the advance of the nucleus and cell body?

Neuronal migration along glia involves 3 steps; 1. leading process extension and adhesion, 2. centrosome advance, 3. nuclear translocation

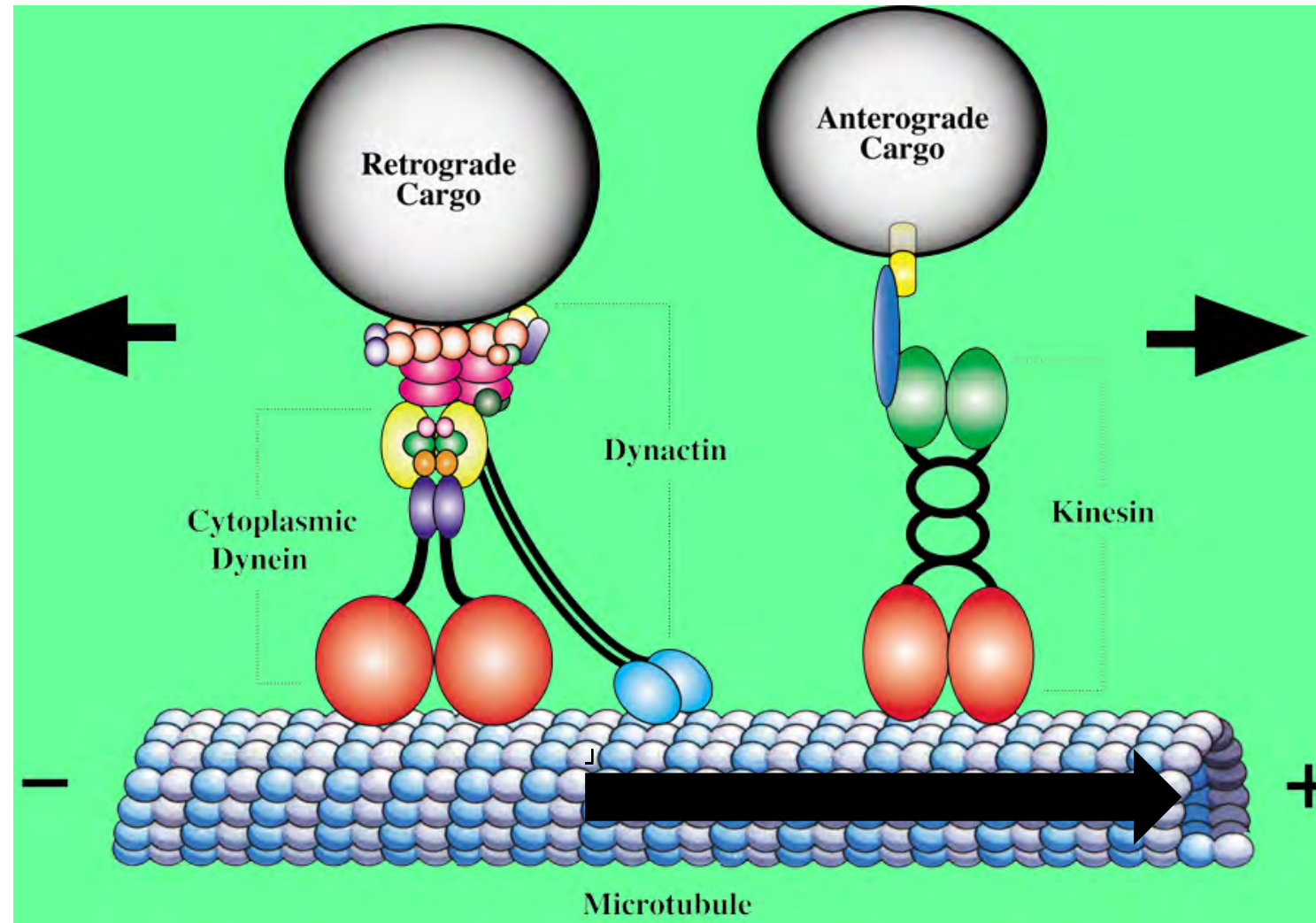


What are the roles of microtubule-linked and actin-linked motor proteins?⁴¹

Microtubule plus ends are oriented both toward the front (leading edge) and the rear (around the nucleus) of the cell

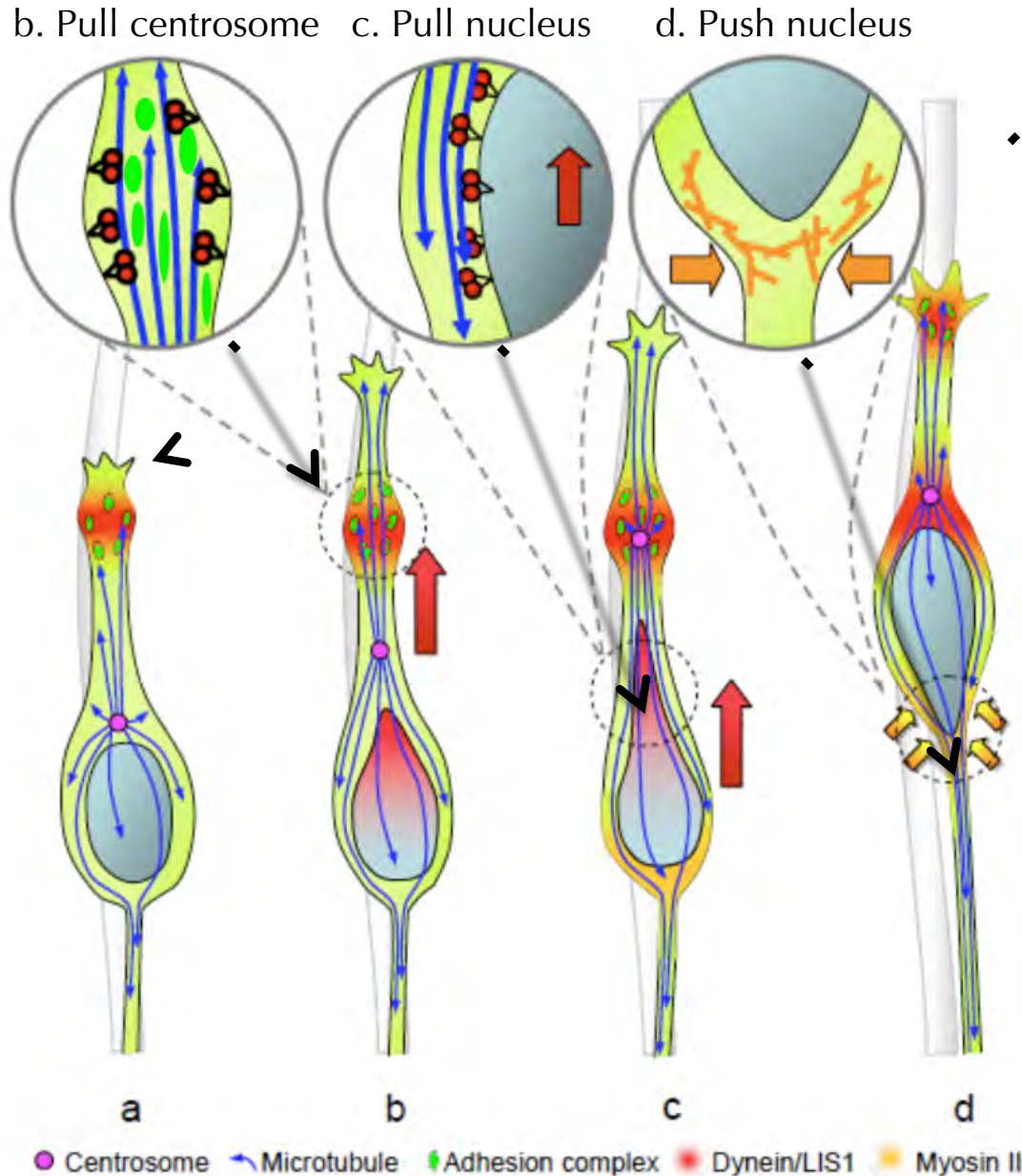


- Kinesin motors move cargo toward microtubule + ends
- Dynein motors move cargo toward microtubule – ends



- If dynein is linked to large immobile cargo, dynein motor activity can slide microtubules with plus end forward

- Dynein motors are a source of pulling power for advancing the centrosome and the nucleus



- a. Protrusion of leading edge; actin and microtubule polymerization

b. Dynein anchored to adhesion site pulls on MTs to move centrosome forward

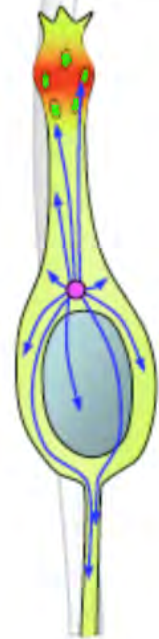
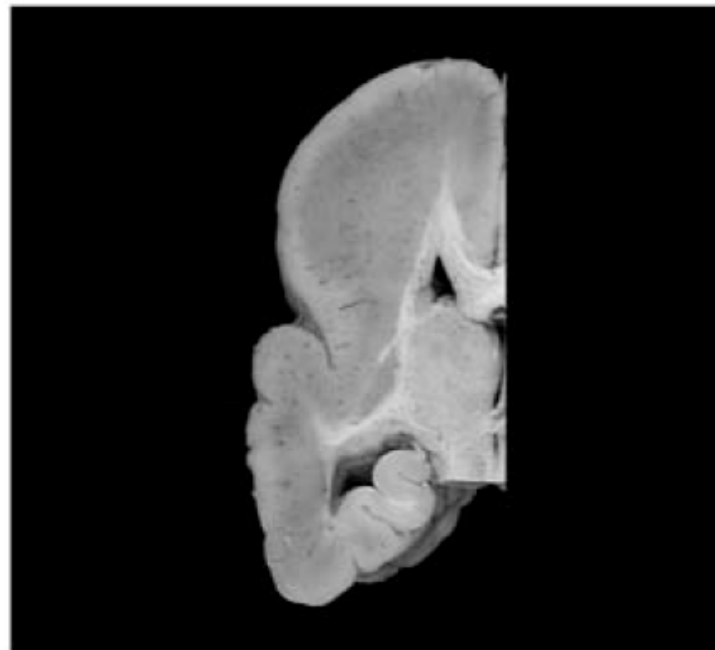
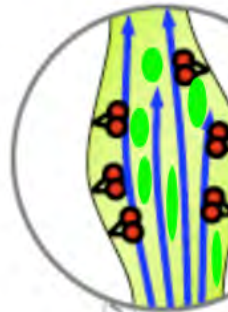
c. Dynein anchored to nucleus pulls nucleus forward toward centrosome

d. Myosin II contractility at rear pushes nucleus forward

Lissencephaly

Source of pulling power for the nucleus and the centrosome

b. Pull centrosome



a

● Centrosome

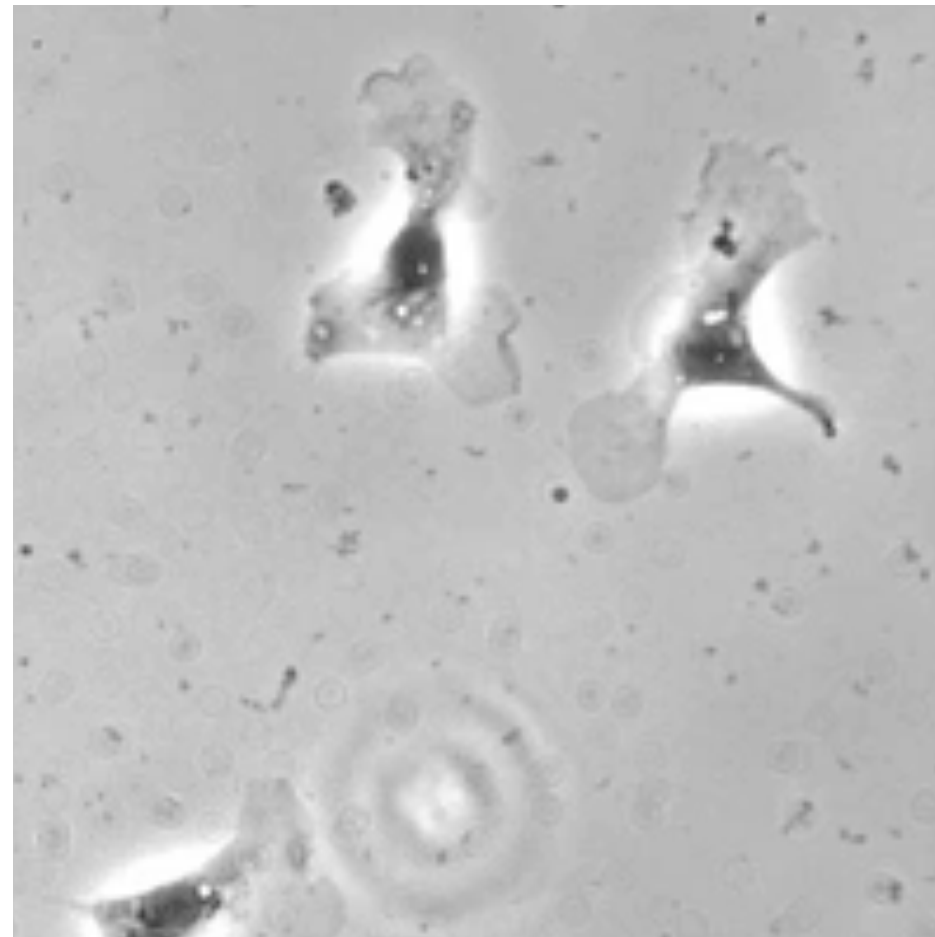
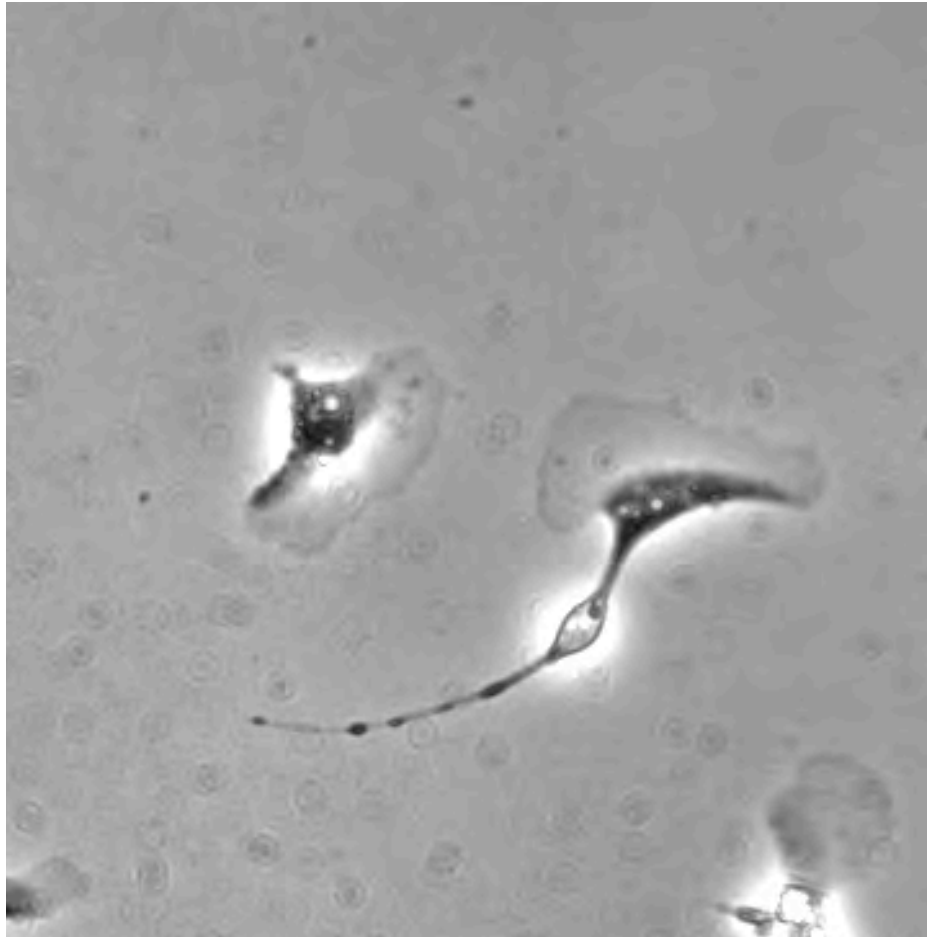


d

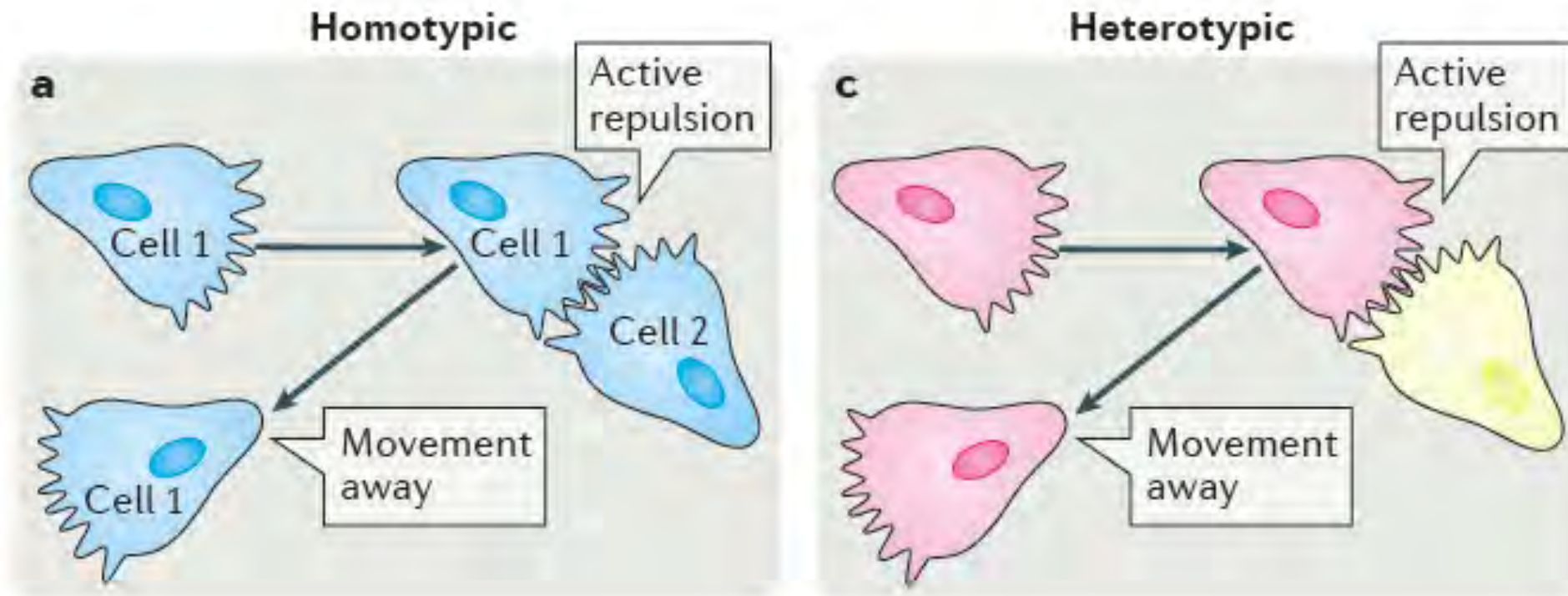
dynein II

- Lis1 was one of the first genes identified that causes neuronal migration defects.
- Lis1 is multifunctional, binding with many proteins.
- One key role of Lis1 is in regulating dynein activity during neuronal migration.

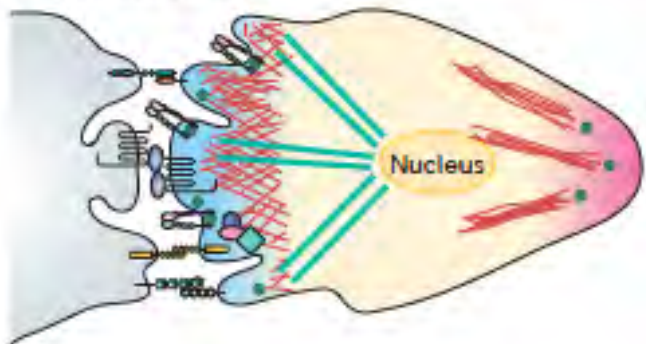
Contact inhibition of cell movement occurs when moving cells collide, and cease motility and/or change direction of movement.



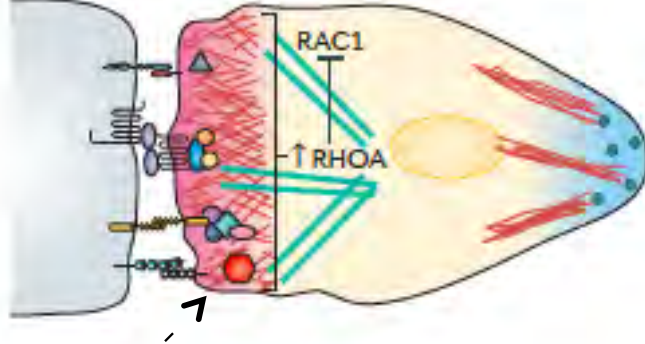
Contact inhibition can occur between cells of the same type or between cells of different types.



a Cell-cell contact

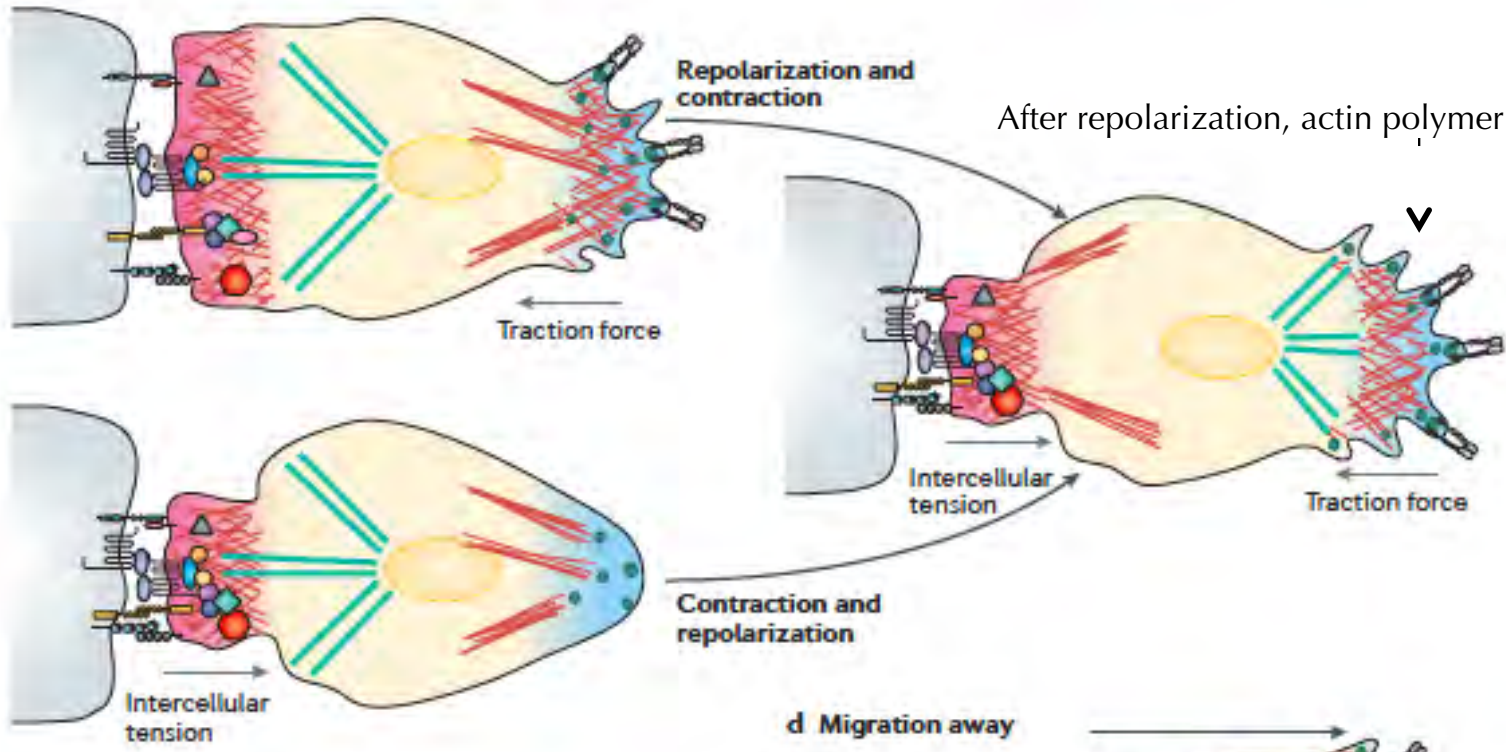


b Protrusion inhibition



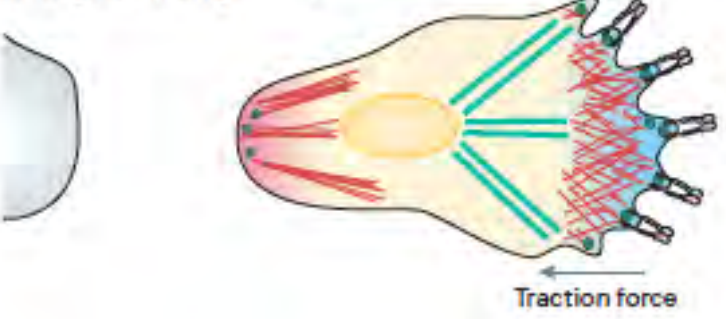
Actin polymerization stops here

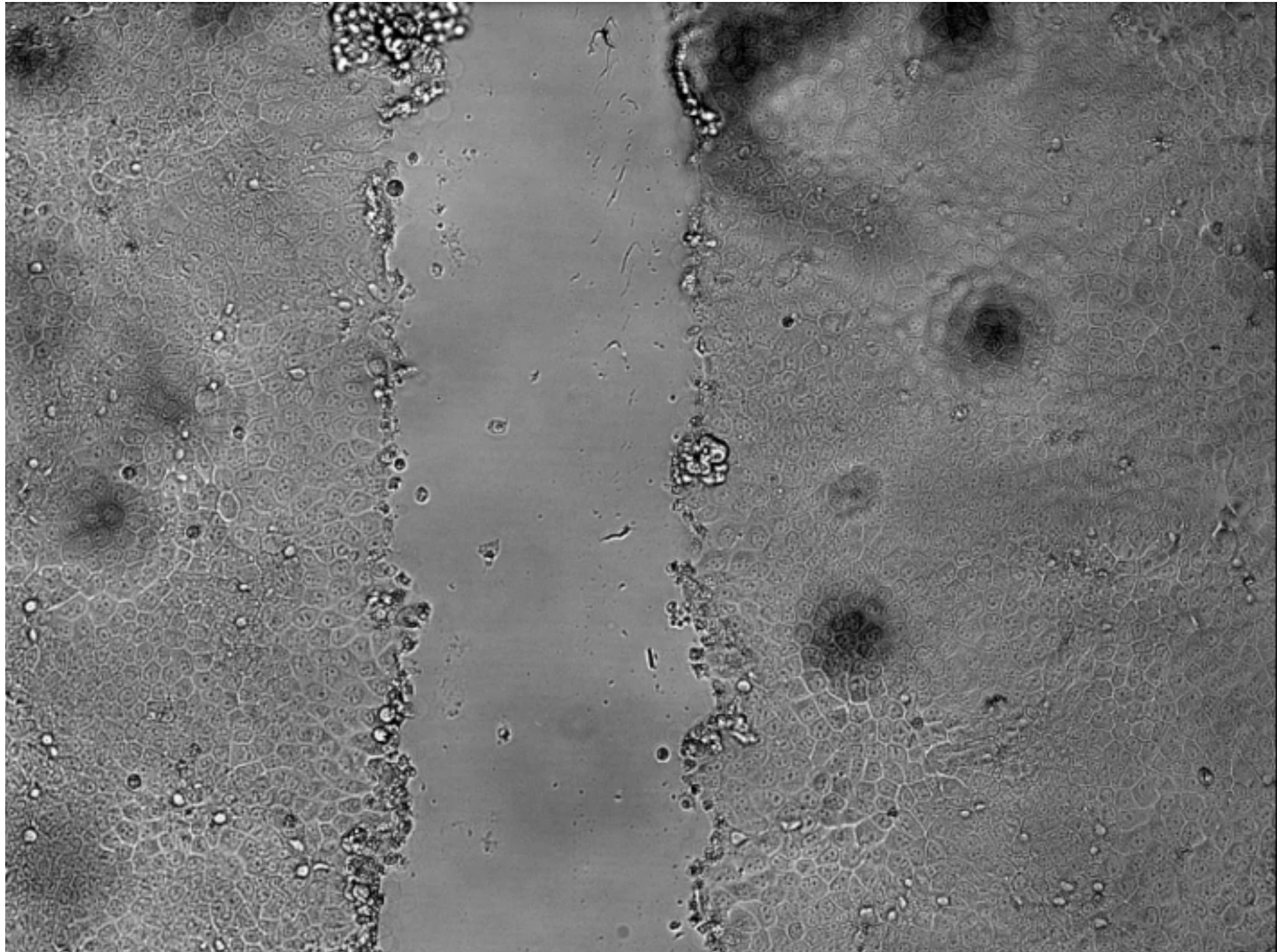
c



After repolarization, actin polymerization starts here

d Migration away





Cell migration

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- How is mechanical force used in cell migration?
- What is the involvement of cytoskeletal and adhesion proteins?
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