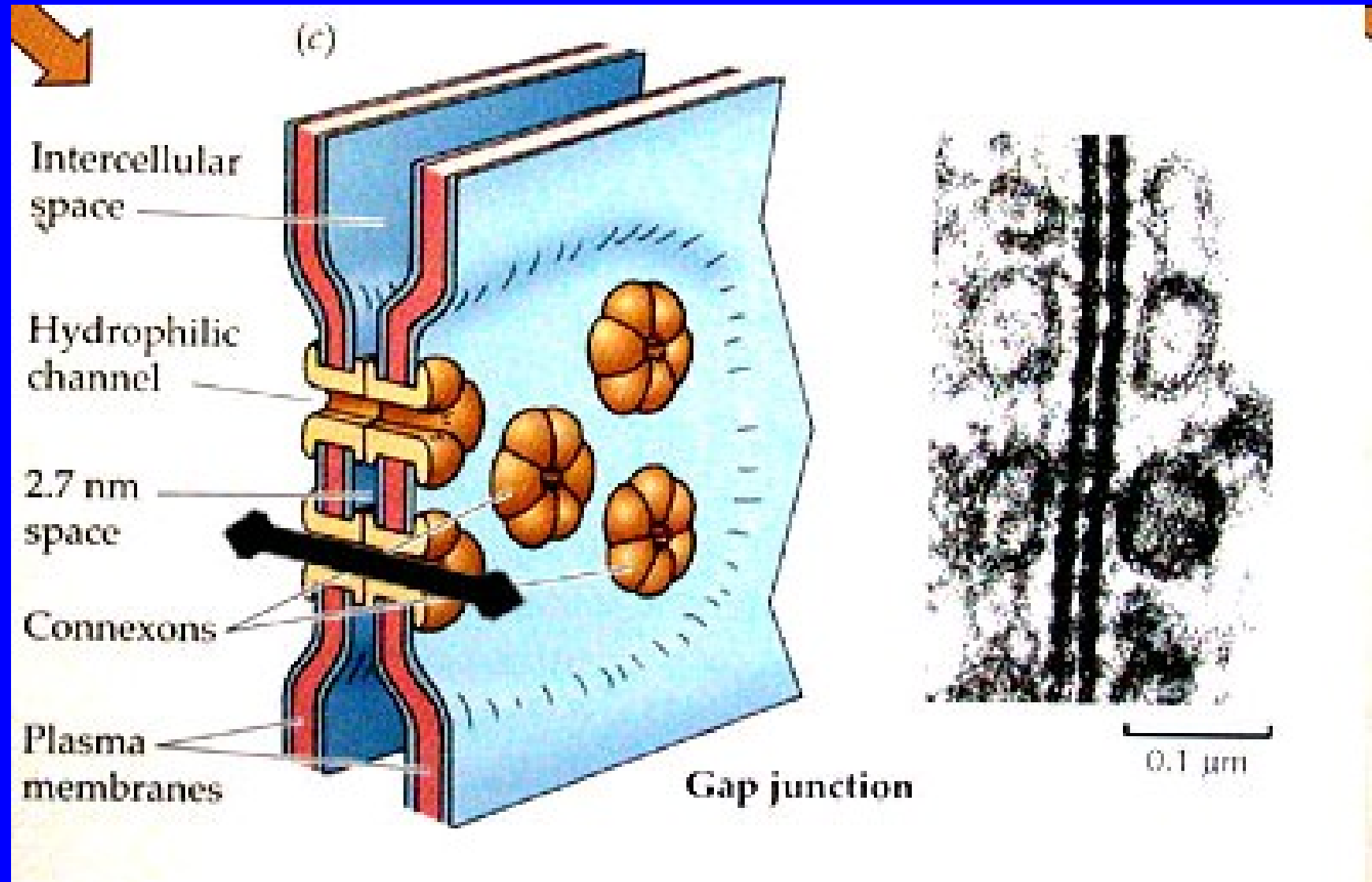
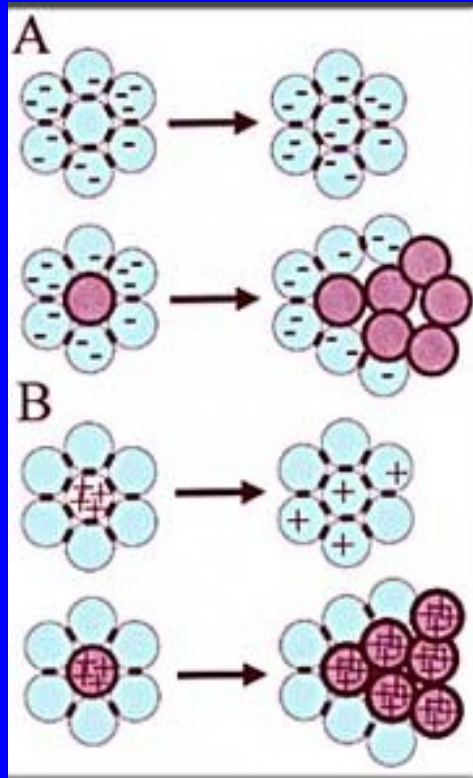


Gap junctions and cellular continuum

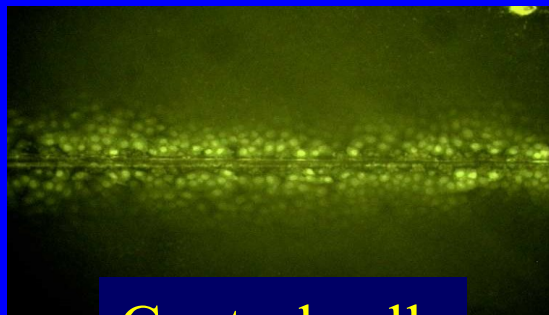
(Gap Junctional Intercellular Communication - GJIC)



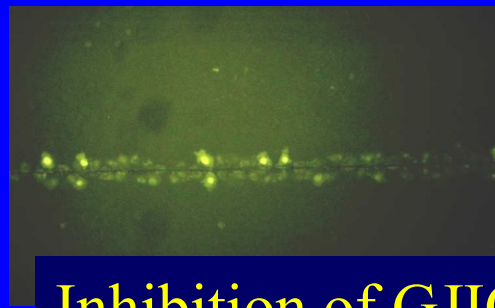
Inhibition of GJIC - mechanism of tumor promotion



- gap-junctional intercellular communication (GJIC)
- transfer of small signalling molecules via protein channels (*gap junctions*)
- regulation of proliferation, differentiation, apoptosis
- inhibition of GJIC -> proliferation ~ tumor promotion
- **relevance: tumors *in vivo* have inhibited gap-junctions**

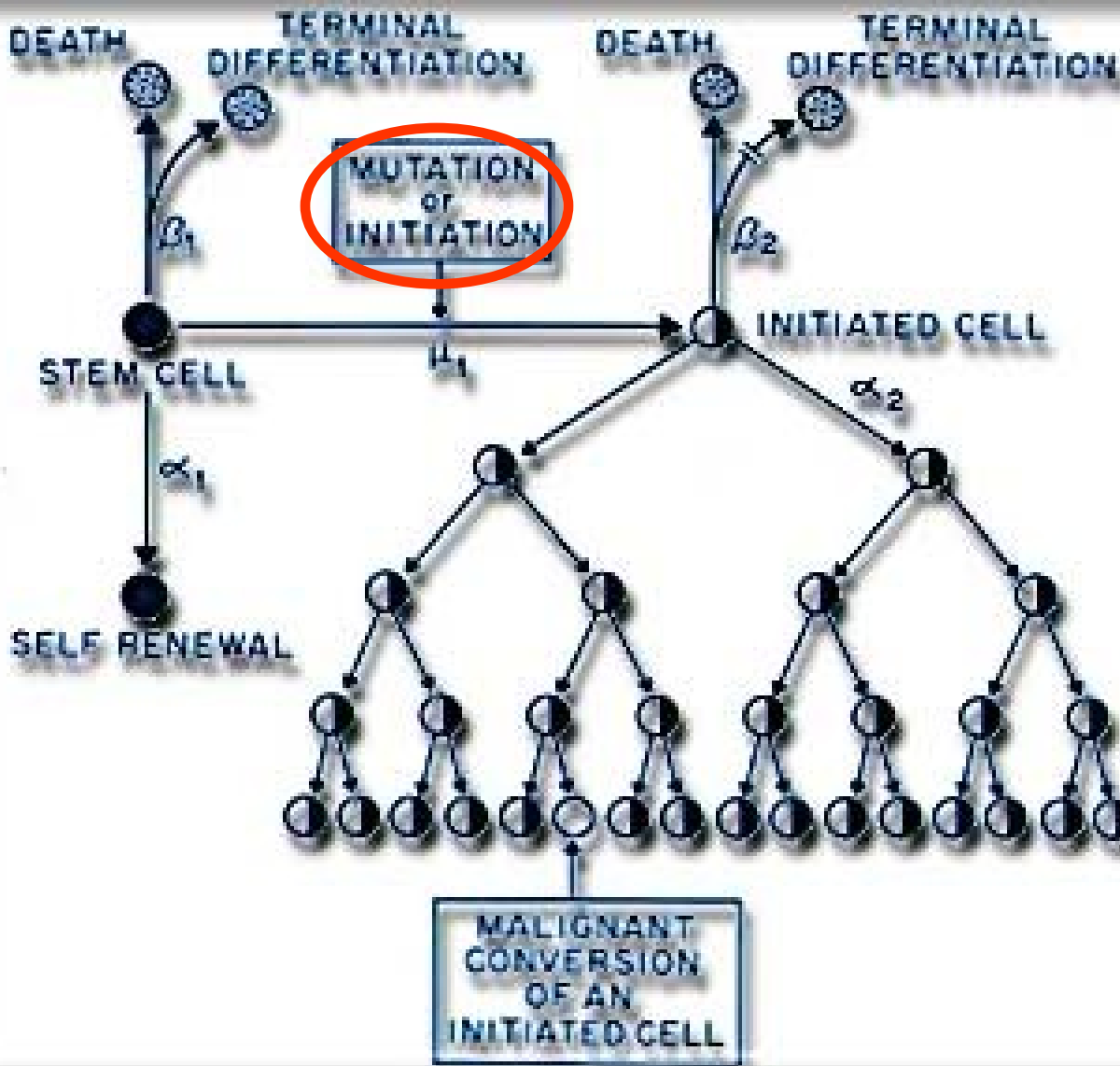


Control cells



Inhibition of GJIC

from Trosko and Ruch 1998,
Frontiers in Bioscience 3:d208

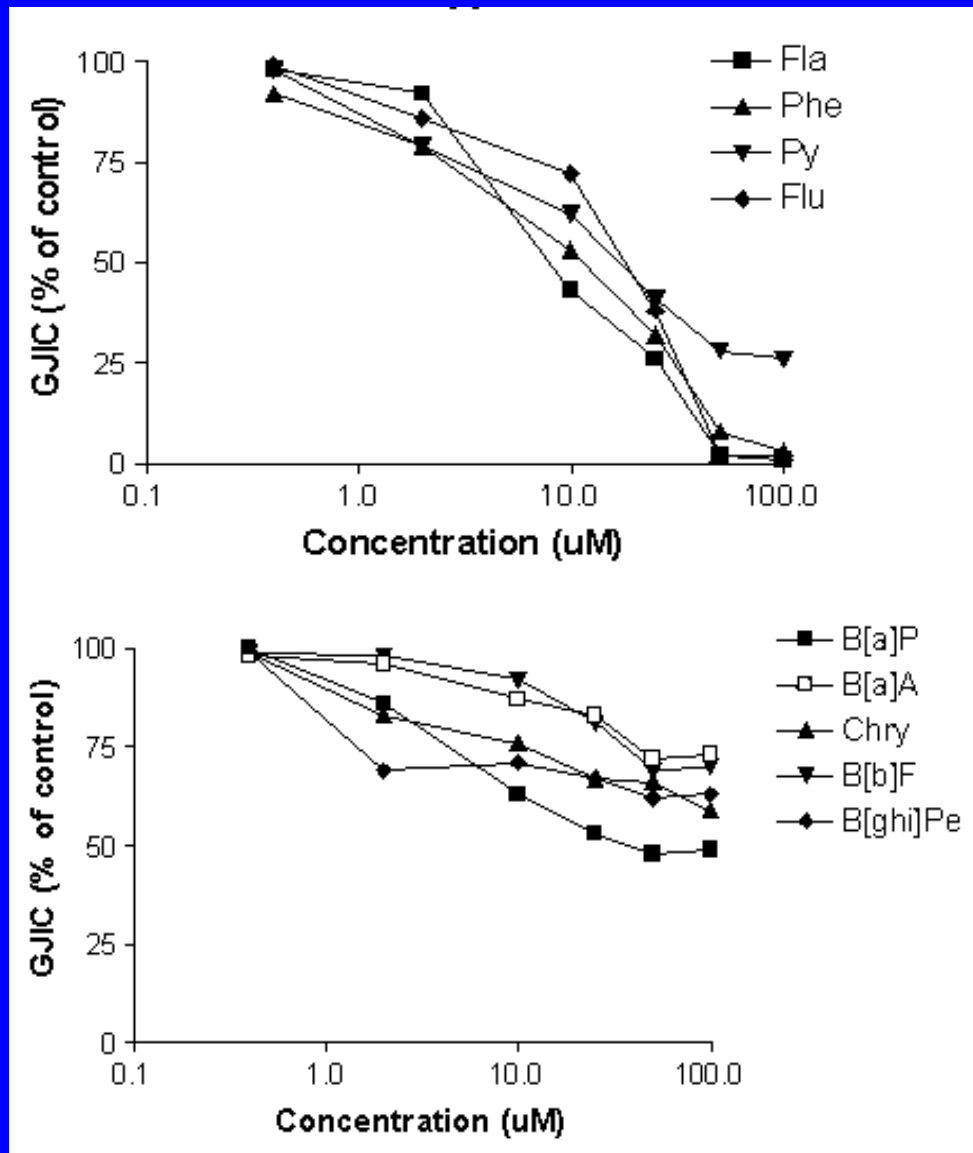


GJIC
AhR
ER
Oxidative Stress

SELECTIVE CLONAL EXPANSION OF INITIATED CELLS or PROMOTION

MUTATION 2--n or PROGRESSION

PAHs as tumor promoters - inhibition of GJIC -



- Several PAHs inhibits GJIC
within 30 min exposure
(IC₅₀ ~ 10-40 μM)

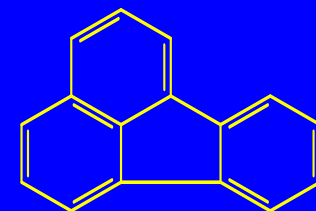
- Low MW and bay/bay-like
regions promotes the effect

-Fluoranthene

:non-mutagenic

:non-AhR-inducing

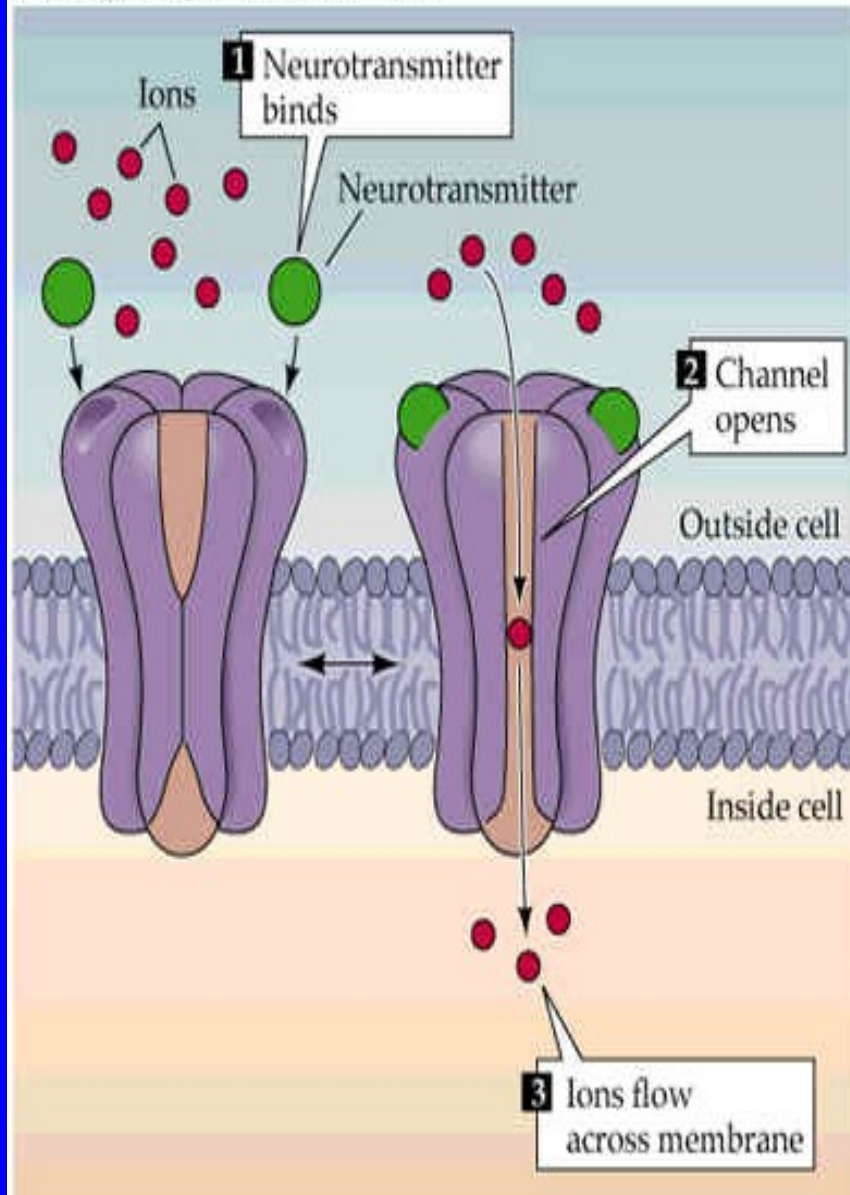
:tumor promoter *in vivo* (!)



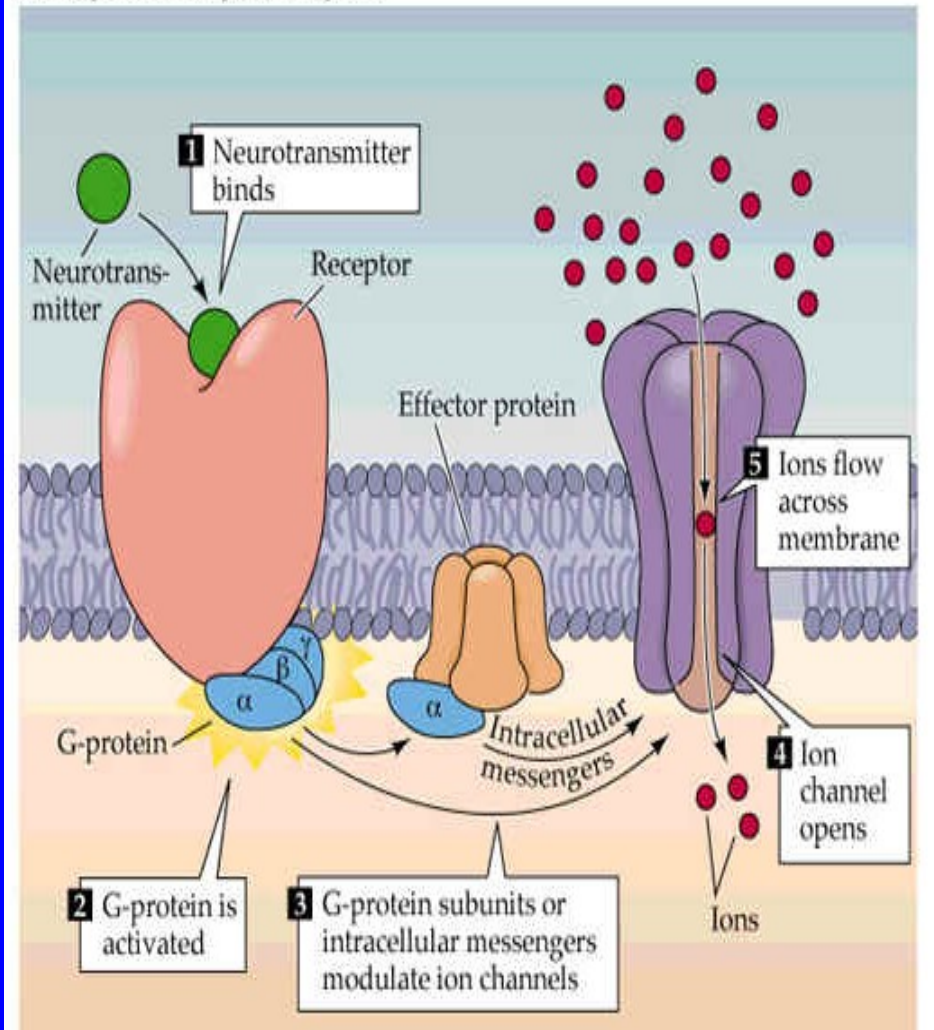
Toxicity to membrane gradients and transport

- **Semipermeability of membranes:**
several key functions
 - **cytoplasmic membrane:**
signalling, neural cells Na^+/K^+ gradient
 - **mitochondrial membrane:**
electron flow \rightarrow ATP synthesis
 - **endoplasmic reticulum**
 Ca^{2+} signalling
- **Membrane fusion / transport**
neurotransmitter release

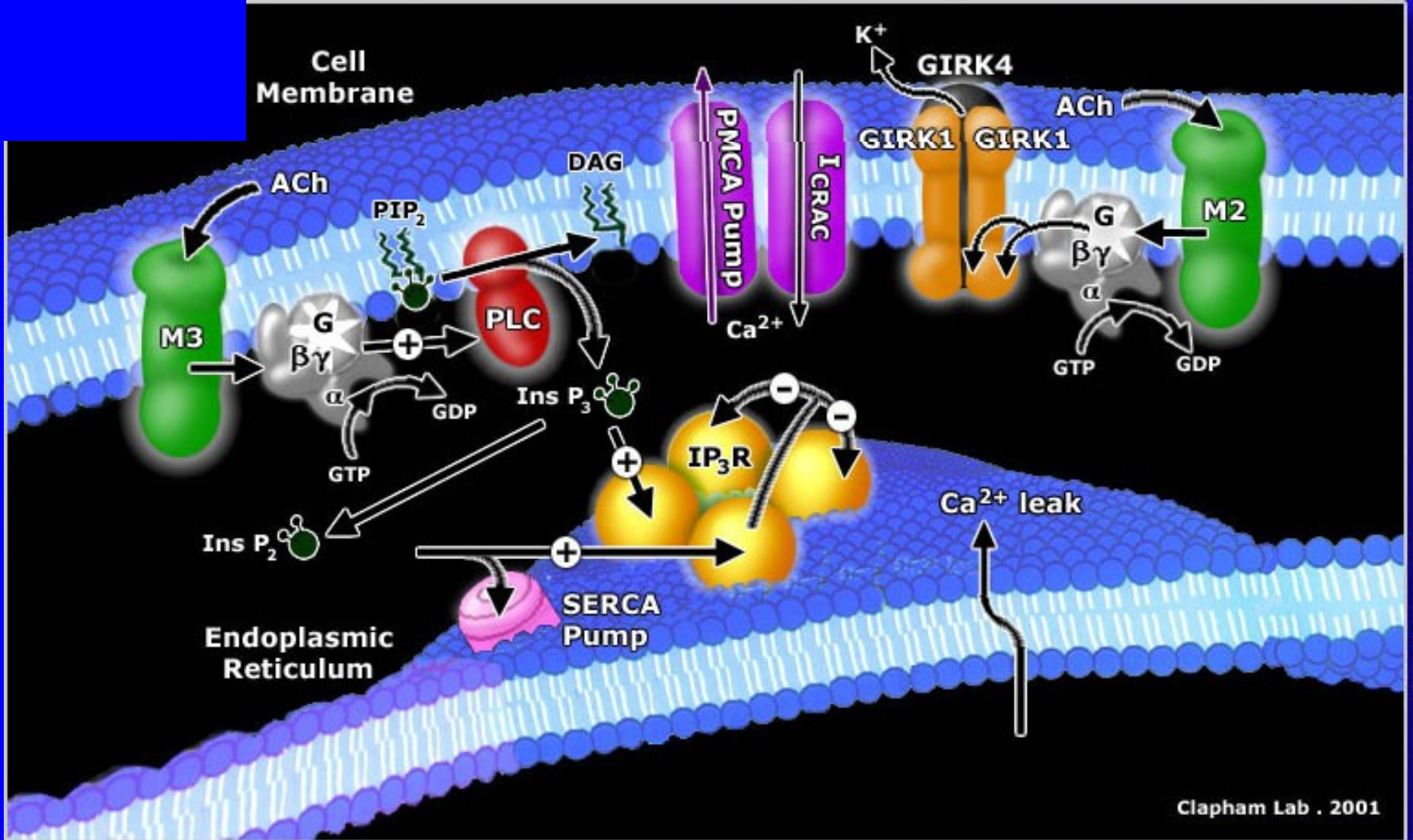
(A) Ligand-gated ion channels



(B) G-protein-coupled receptors

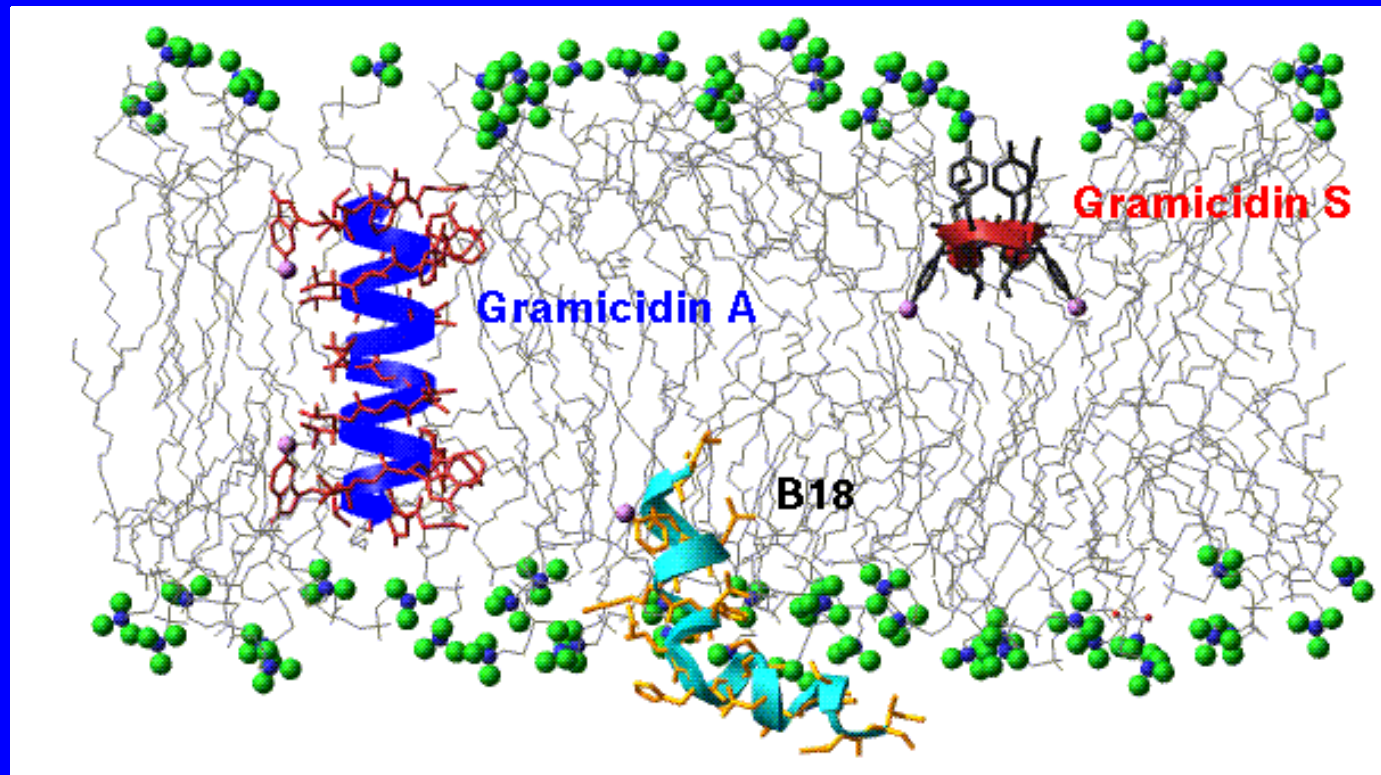
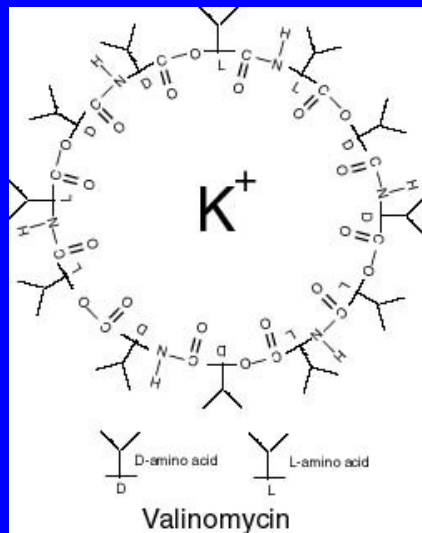
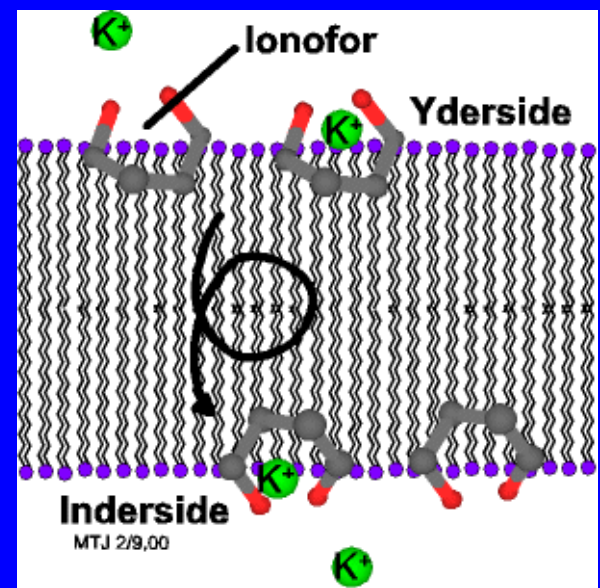


Cell Membrane



Membrane gradient disruption

Ion transfer ("ionofors")
antibiotics
(K^+ , Ca^{2+} , Mg^{2+})

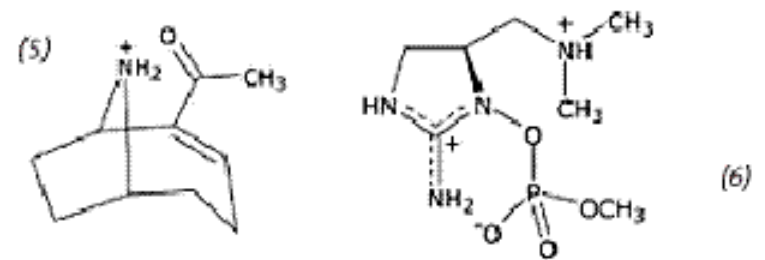
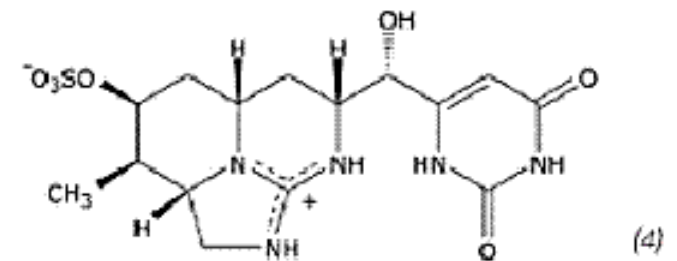
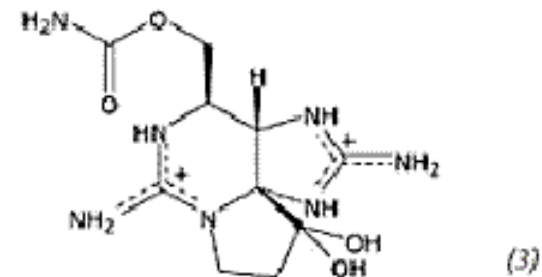
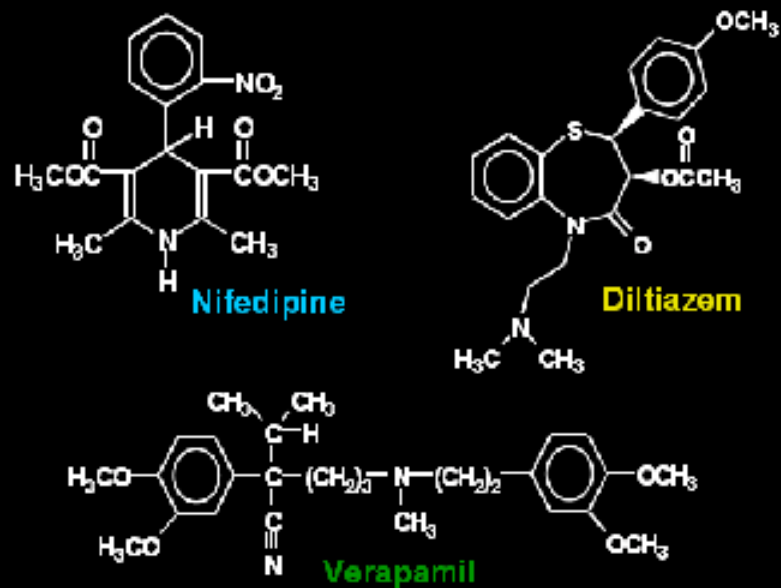


Ion Channel BLOCKERS / ACTIVATORS

Neuromodulators (drugs)

Neurotoxins (cyanobacterial)

Voltage-Gated L-Type Calcium Channel Blockers



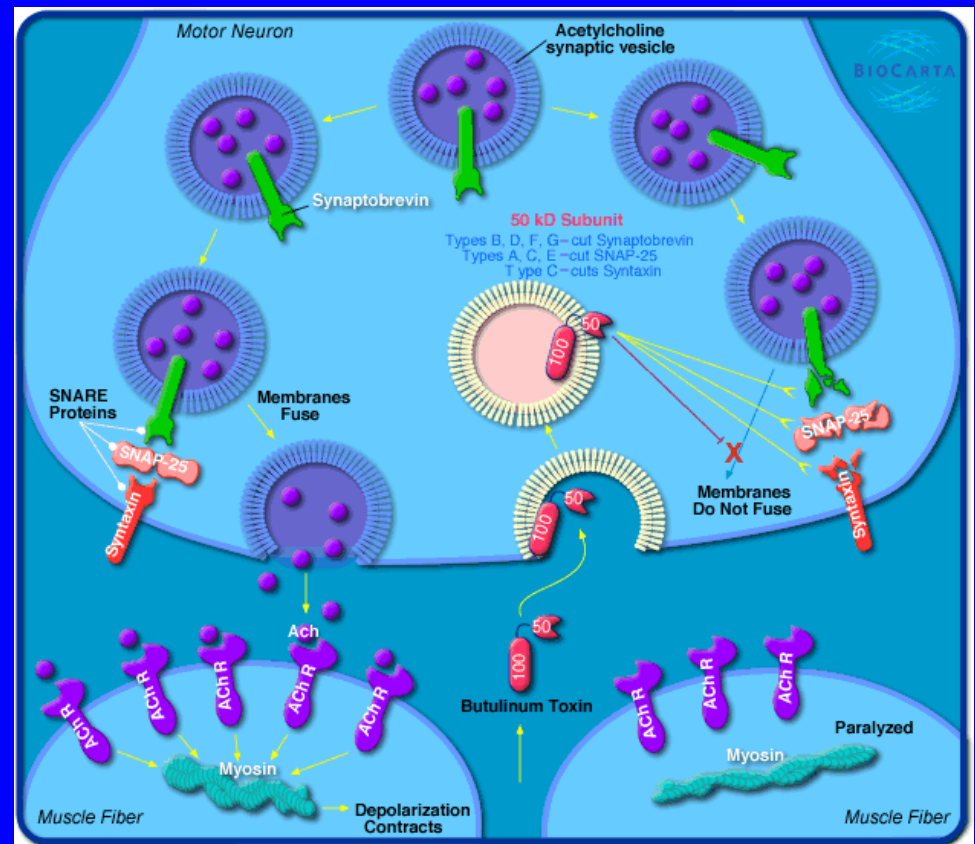
Botulinum and Tetanus toxins

(Clostridium botulinum, Clostridium tetani)

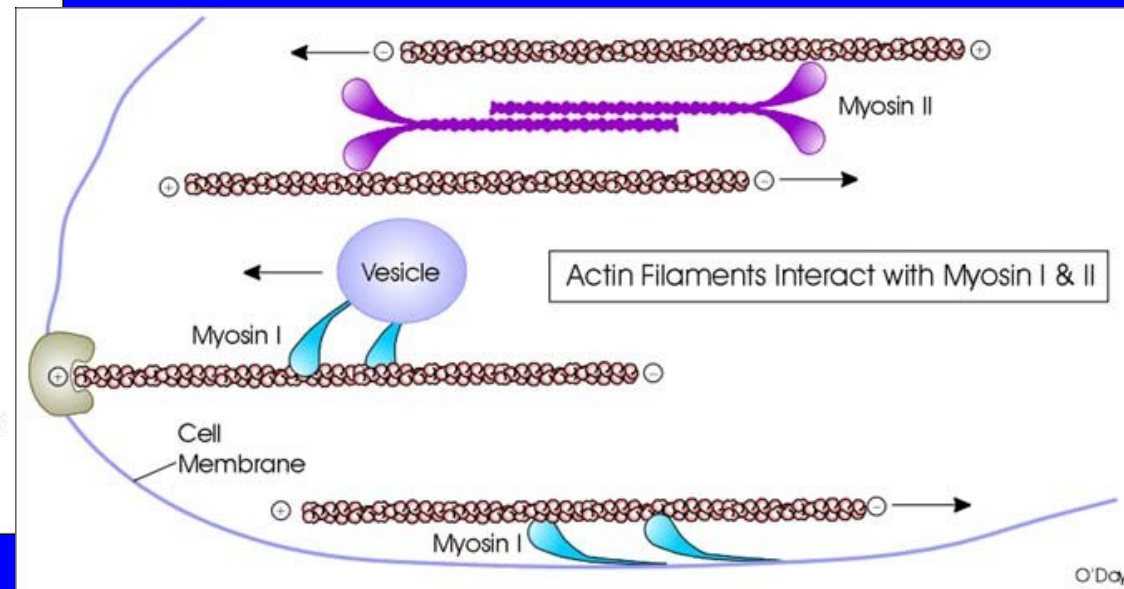
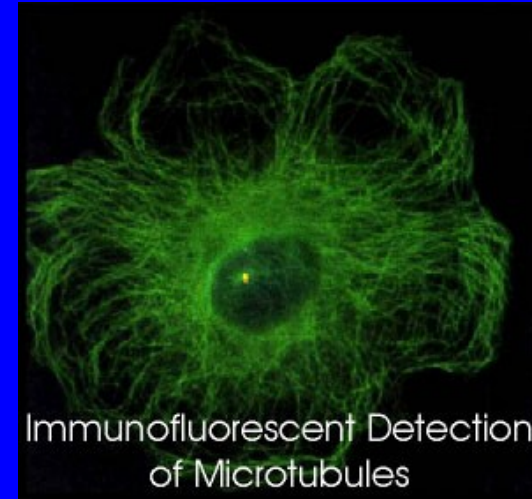
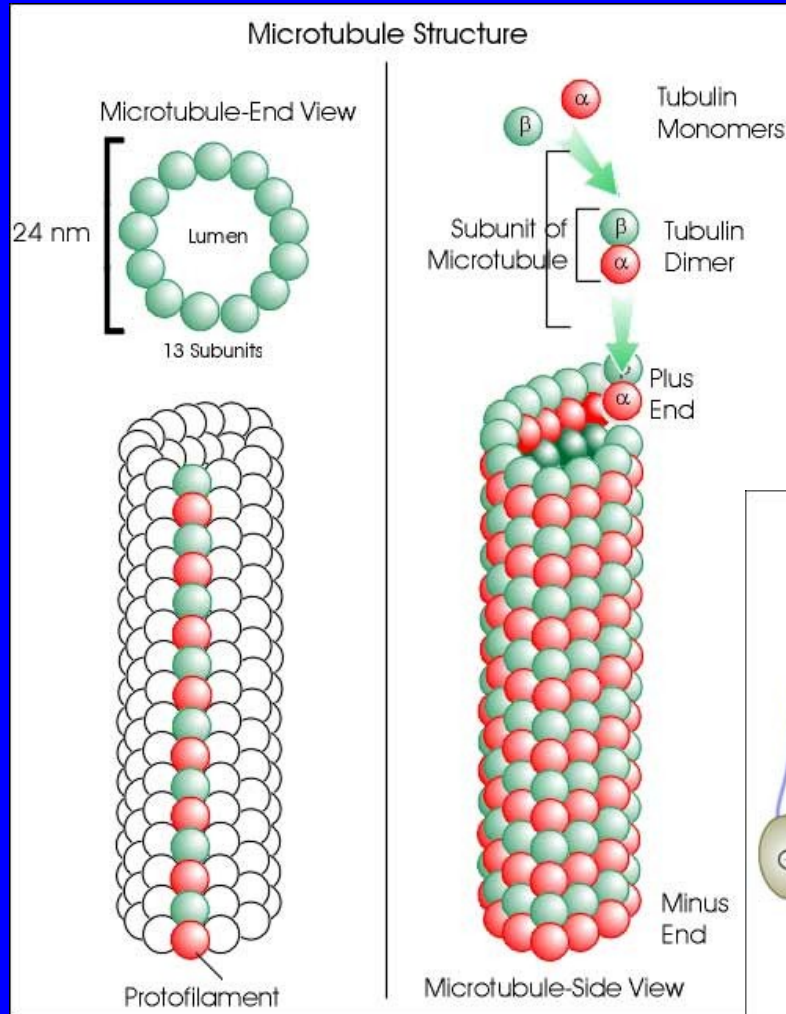
Toxins = enzymes - proteases (!)

- cleavage of proteins involved in vesicle formation
- selective inhibition of neurotransmitter release

neurotoxicity

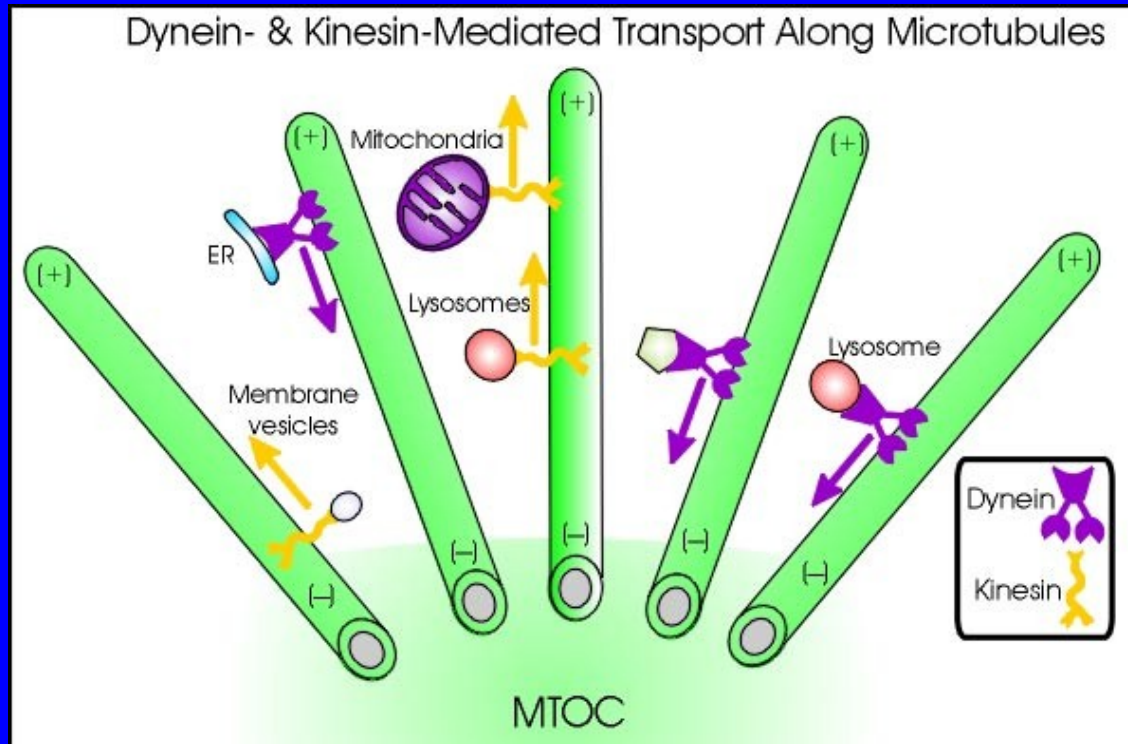


Cytoskeleton as target of toxicants microtubules / actin-myosin



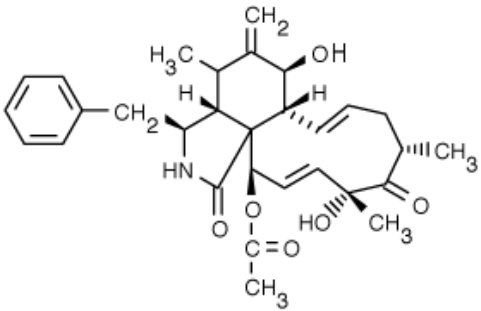
Cytoskeleton – function

- intracellular transport
- cell replication and division (mitosis:chromosomes)
- muscle movement
- membrane (vesicles) fusion

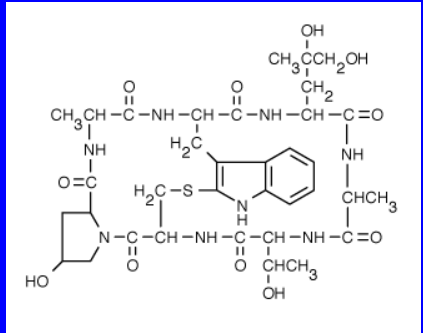


TOXINS: effects on (DE)POLYMERIZATION

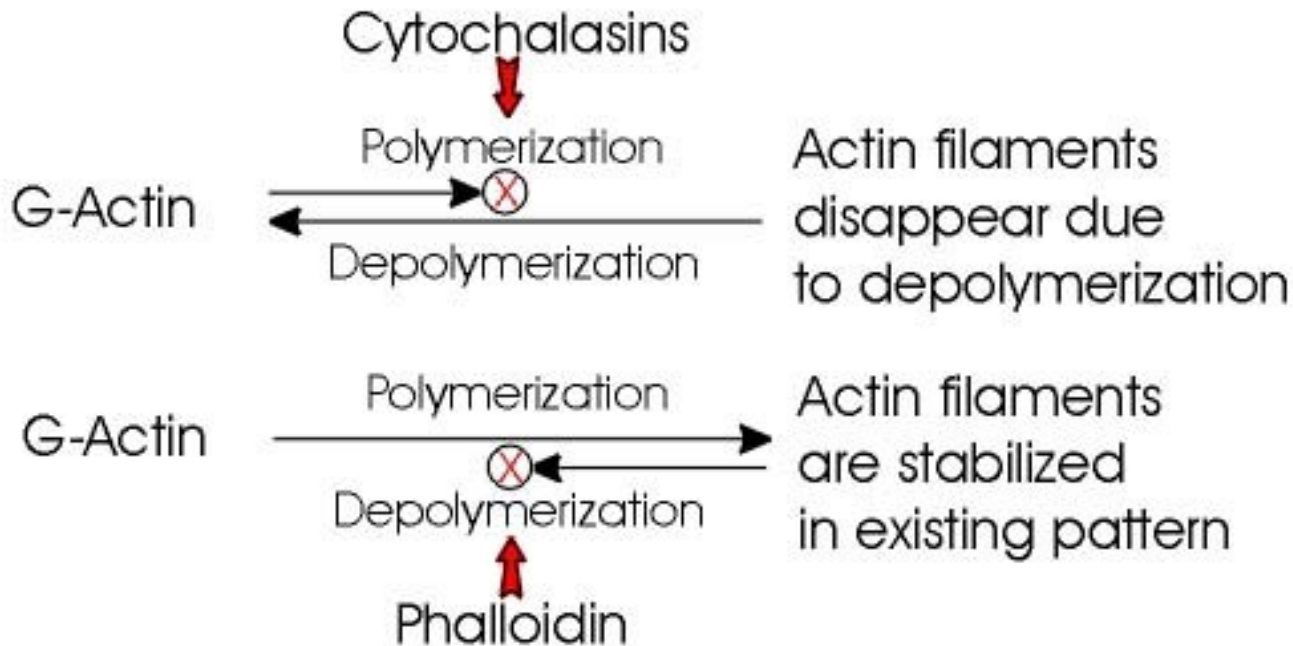
cytochalasin D
(fungal toxin)



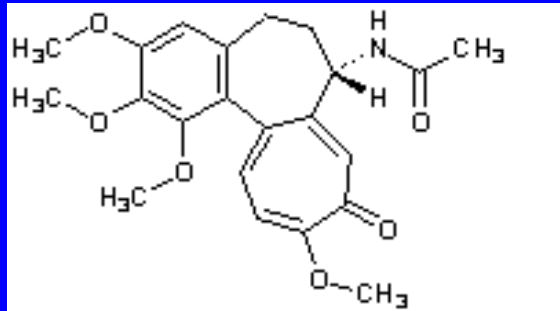
Phalloidin
(death cap - *Amanita phalloides*)



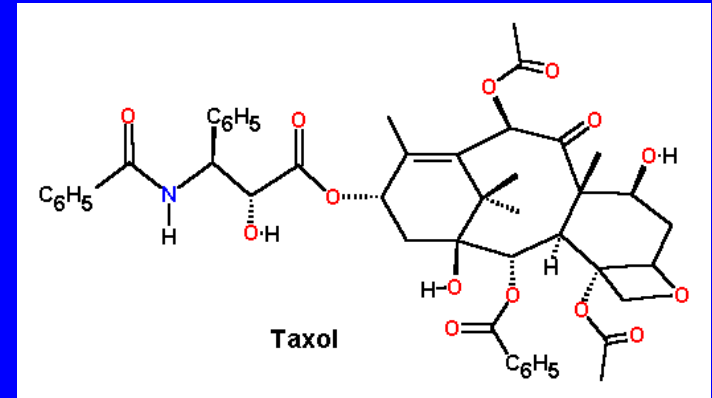
Effects of Inhibitors on Actin Filaments



TOXINS: effects on (DE)POLYMERIZATION

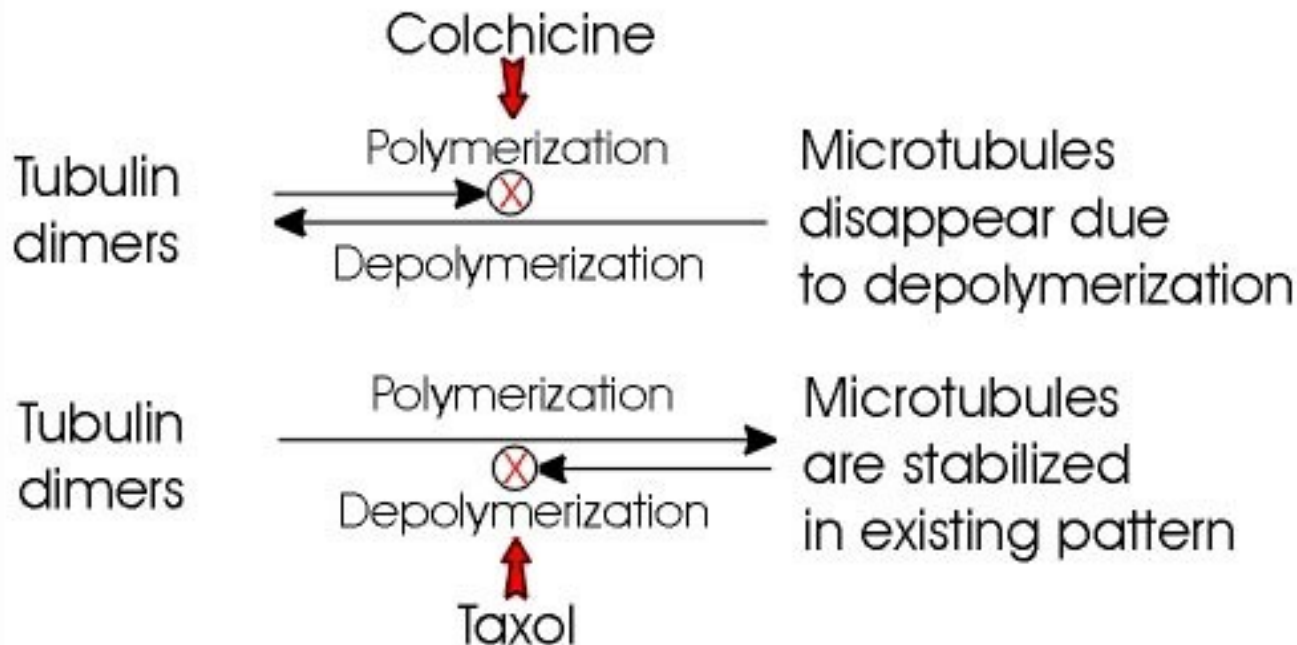


Colchicine



Taxol

Effects of Inhibitors on Microtubules



taxol

