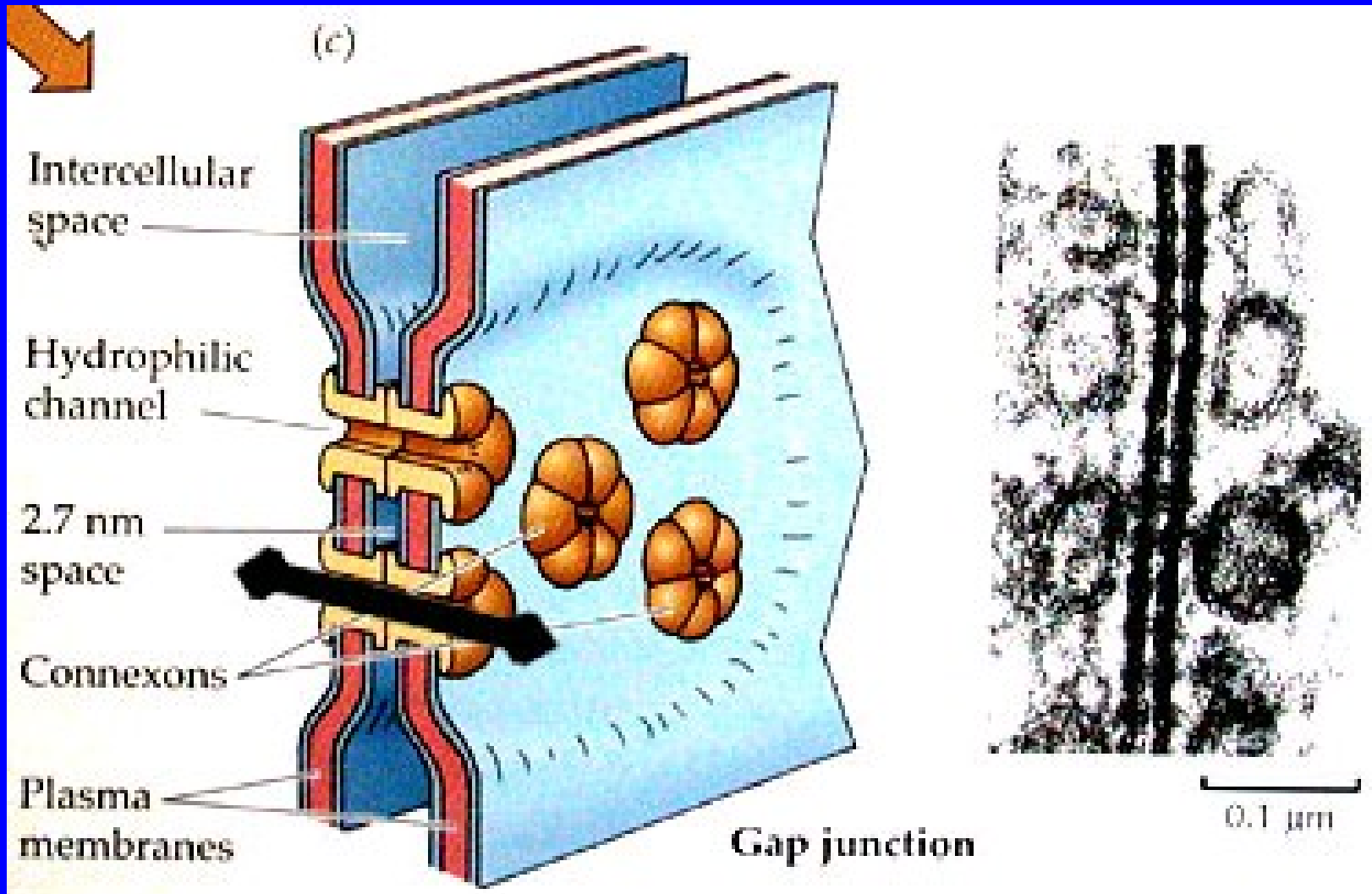
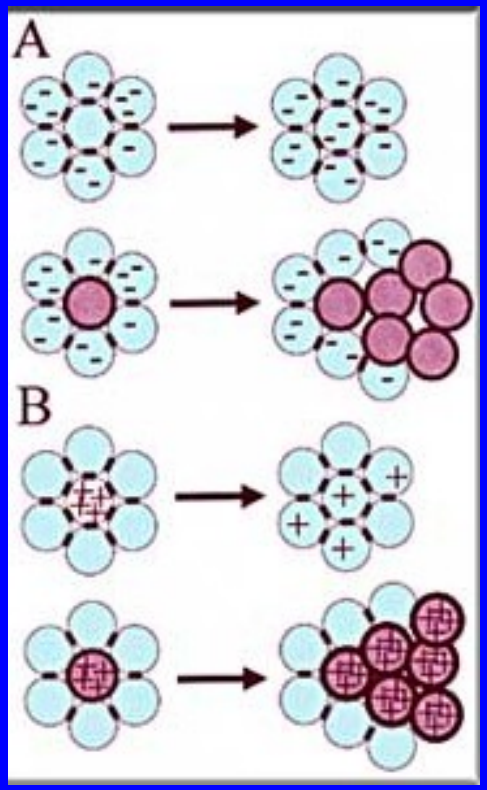
Gap junctions and cellular continuum

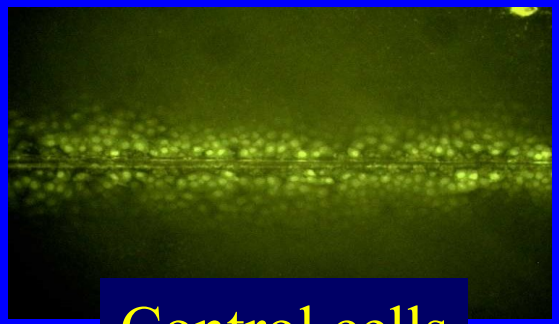
(Gap Junctional Intercellular Communication - GJIC)



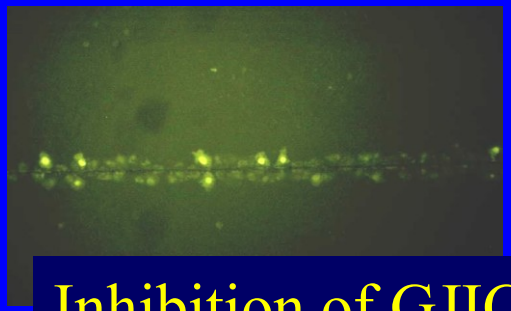
Inhibition of GJIC - mechanism of tumor promotion



- 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**

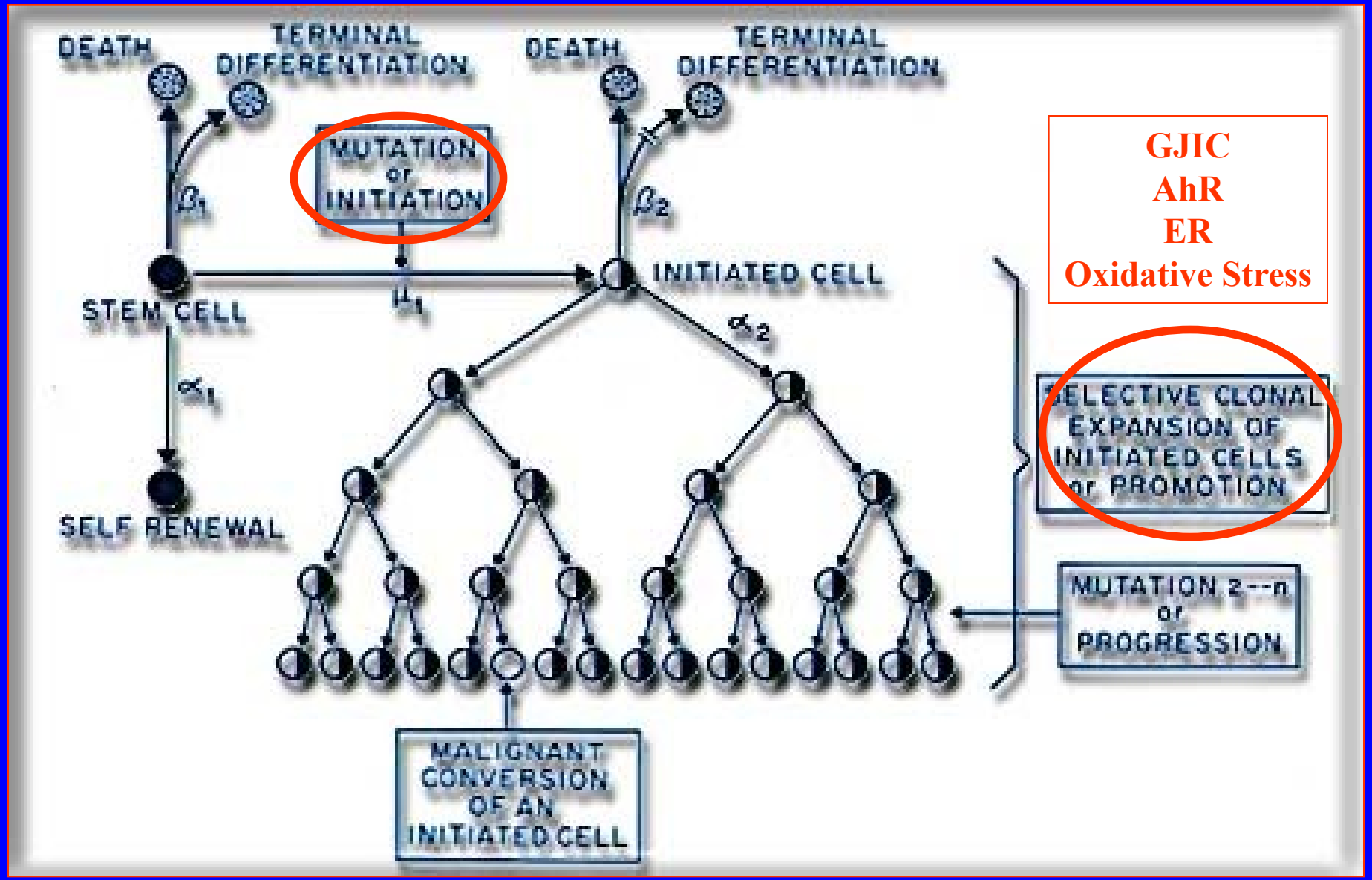


Control cells

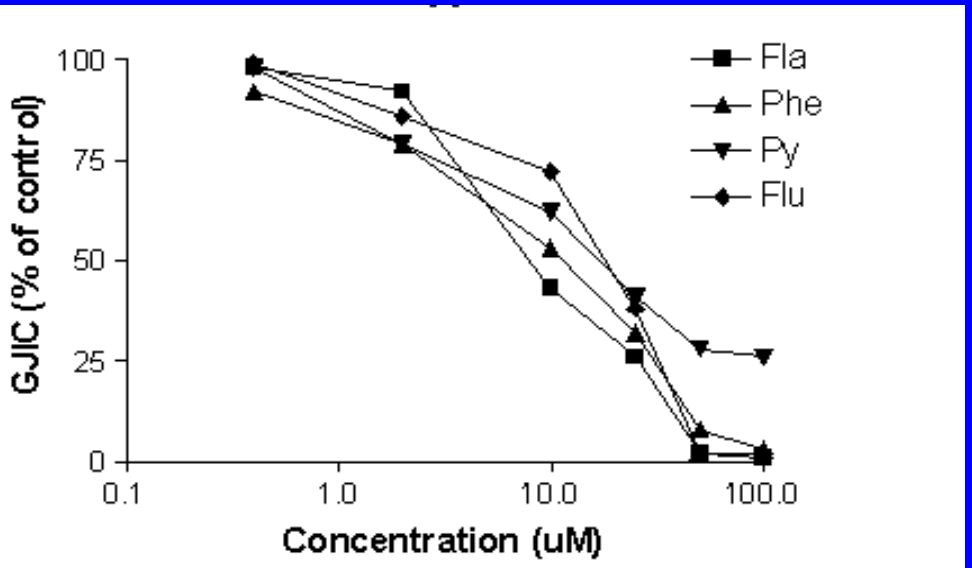


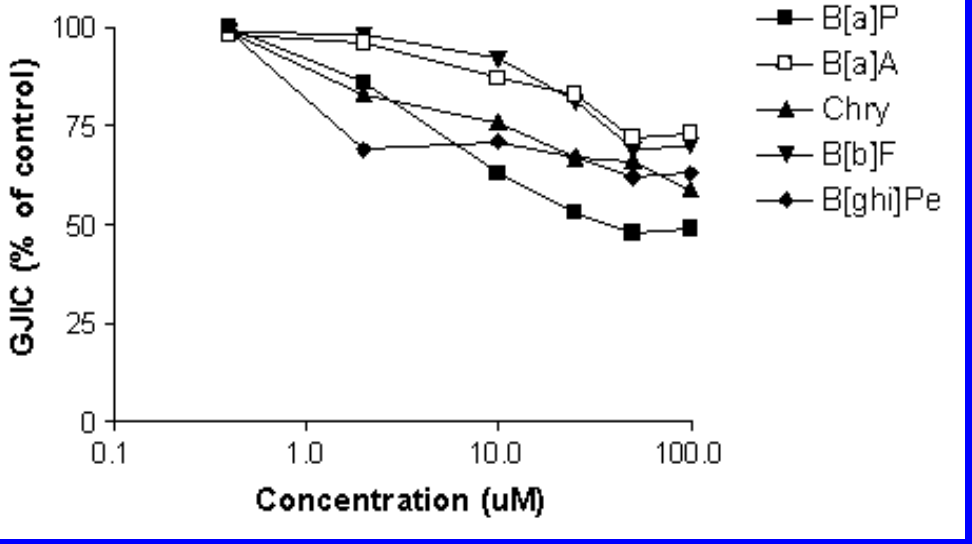
Inhibition of GJIC

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


DEATH
TERMINAL DIFFERENTIATION
DEATH
TERMINAL DIFFERENTIATION
MUTATION or INITIATION
β_1
β_2
STEM CELL
μ_1
INITIATED CELL
α_2
α_1
SELF RENEWAL
SELECTIVE CLONAL EXPANSION OF INITIATED CELLS or PROMOTION
MUTATION 2--n or PROGRESSION
MALIGNANT CONVERSION OF AN INITIATED CELL
GJIC
AhR
ER
Oxidative Stress

PAHs as tumor promoters
- inhibition of GJIC -



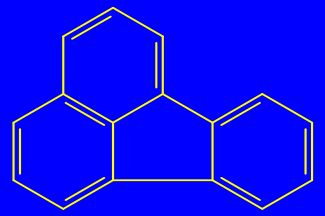


- Several PAHs inhibits GJIC within 30 min exposure (IC_{50} ~ 10-40 μM)

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

-Fluoranthene

:non-mutagenic
:non-AhR-inducing
:tumor promoter *in vivo* (!)



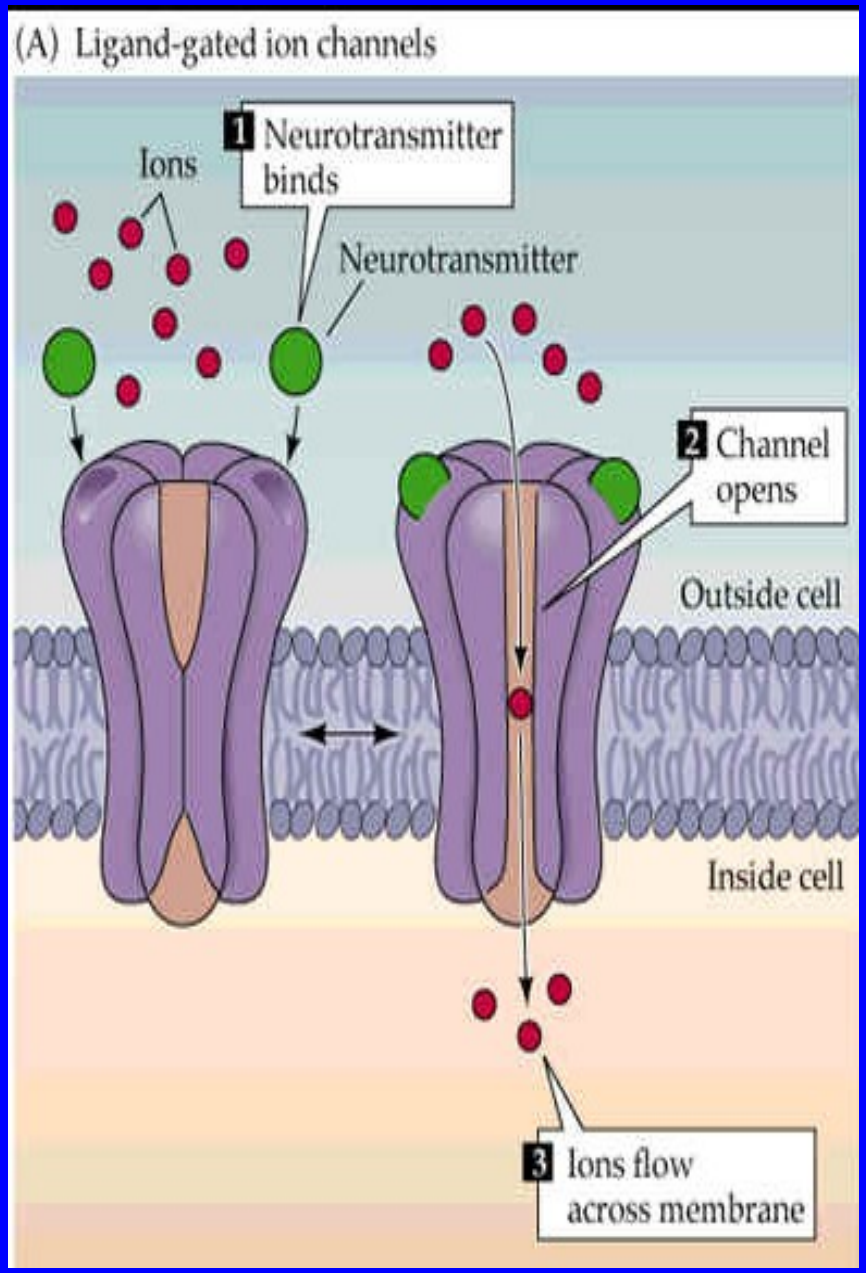
Bláha et al. 2002 Toxicol Sci 65: 43

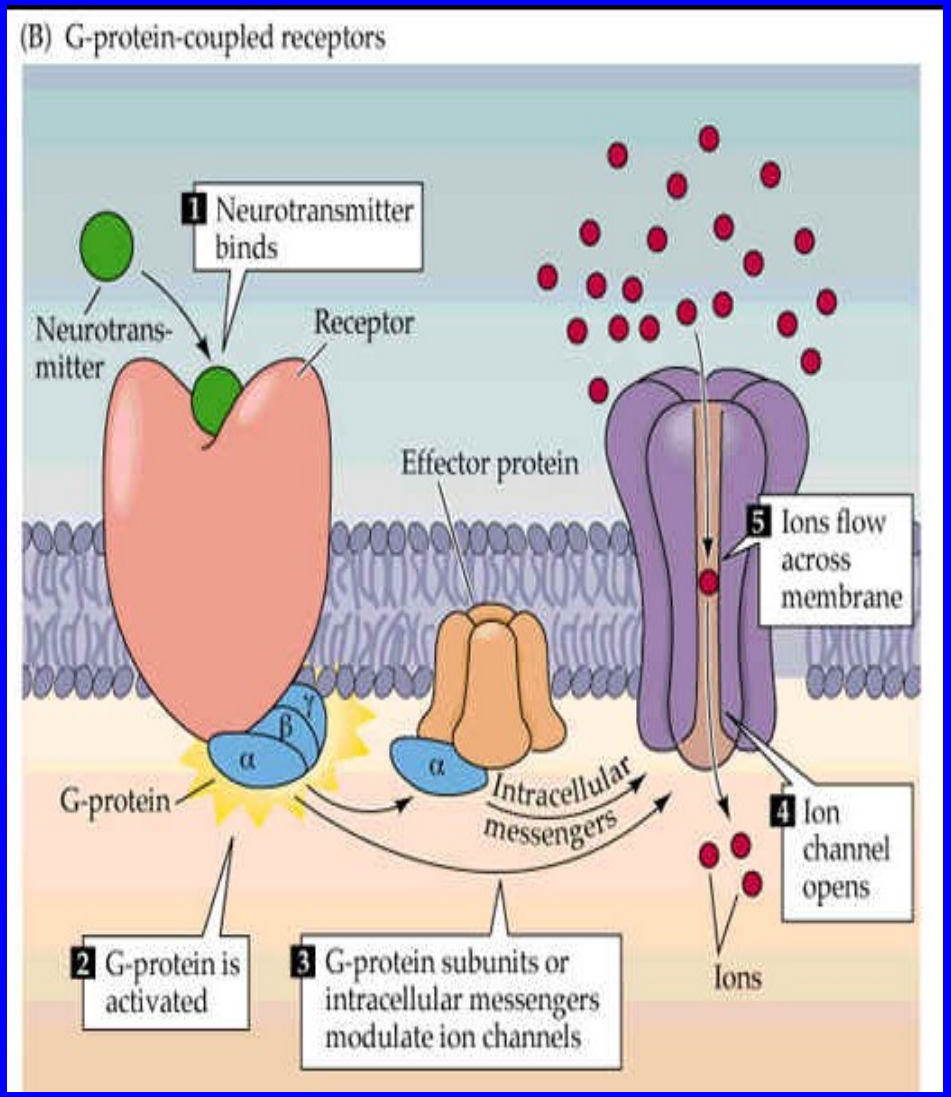
Toxicity to membrane gradients and transport

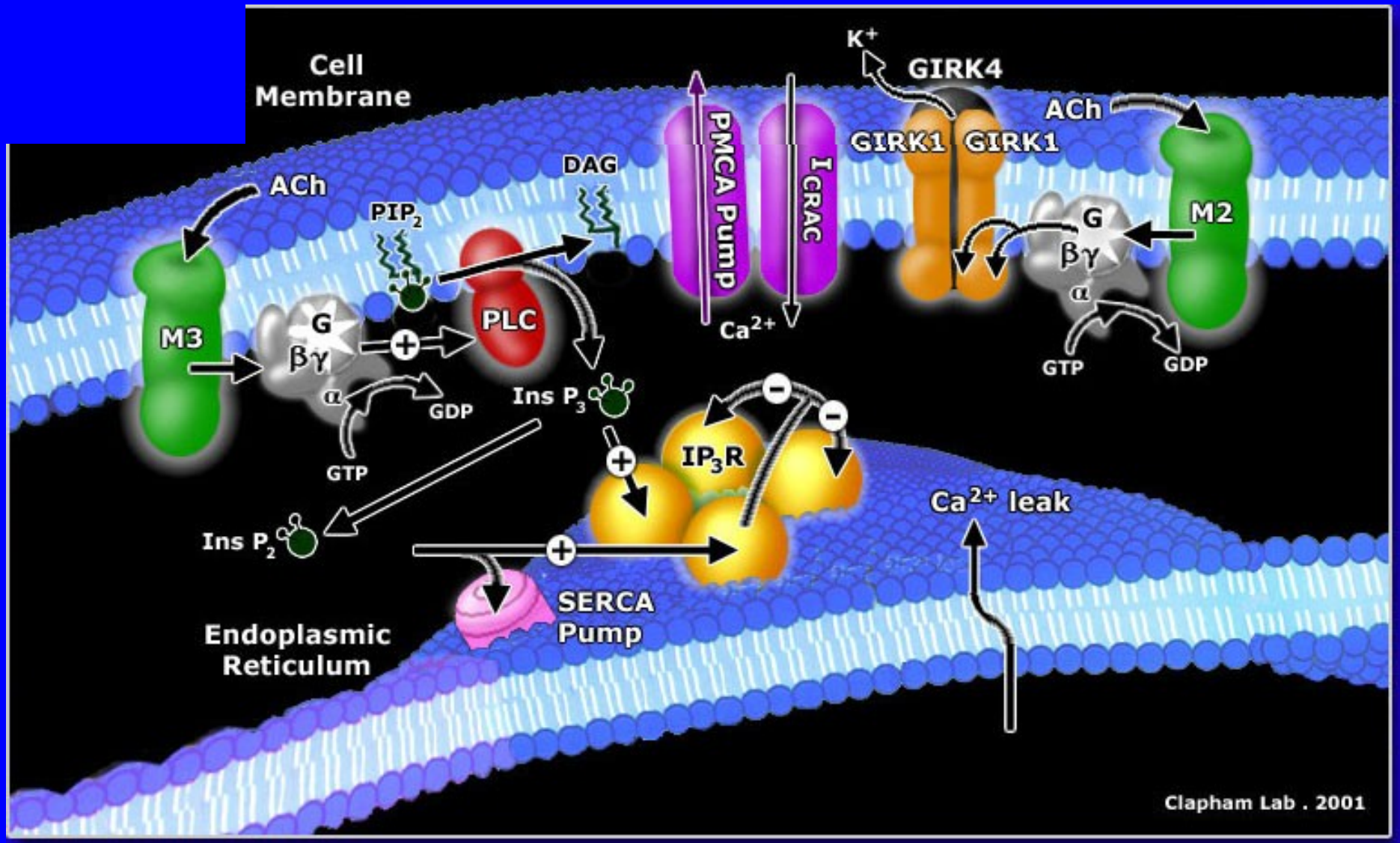
- Semipermeability of membranes:
several key functions

- cytoplasmic membrane:
signalling, neural cells Na+/K+ gradient
- mitochondrial membrane:
electrone flow -> ATP synthesis
- endoplasmatic reticulum
Ca^{2+} signalling

- Membrane fusion / transport
neurotransmitter release


(A) Ligand-gated ion channels
Ions
1 Neurotransmitter binds
Neurotransmitter
2 Channel opens
Outside cell
Inside cell
3 Ions flow across membrane

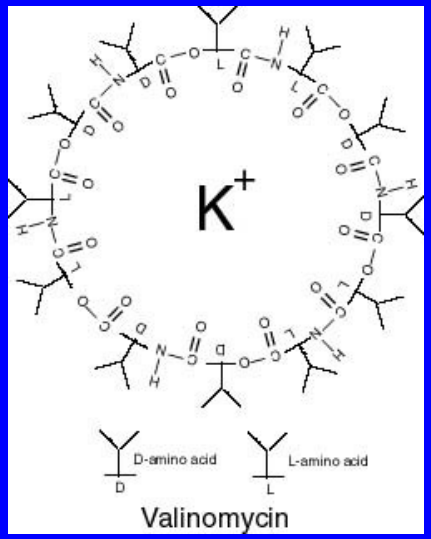

(B) G-protein-coupled receptors
1 Neurotransmitter binds
Neurotrans-mitter
Receptor
Effector protein
5 Ions flow across membrane
α
β
γ
G-protein
α
Intracellular messengers
4 Ion channel opens
2 G-protein is activated
3 G-protein subunits or intracellular messengers modulate ion channels
Ions

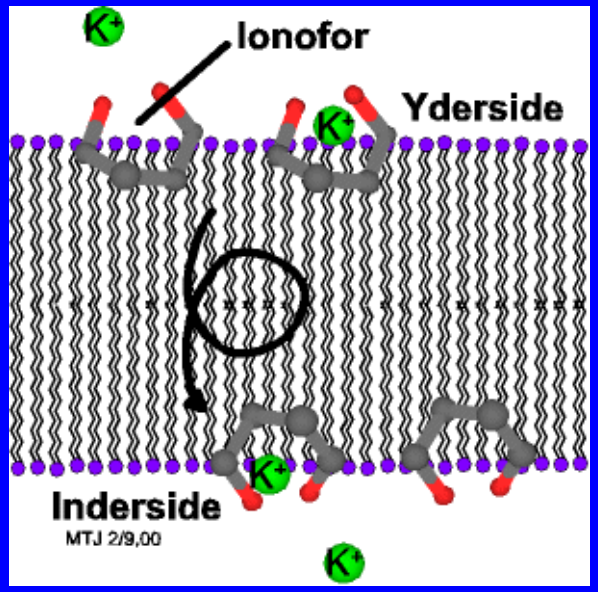

Cell Membrane
K+
GIRK4
ACh
GIRK1
GIRK1
ACh
DAG
PMCA Pump
ICRAC
PIP2
M2
M3
G
βγ
α
PLC
Ca2+
GTP
GDP
Ins P3
IP3R
Ca2+ leak
Ins P2
SERCA Pump
Endoplasmic Reticulum
Clapham Lab . 2001

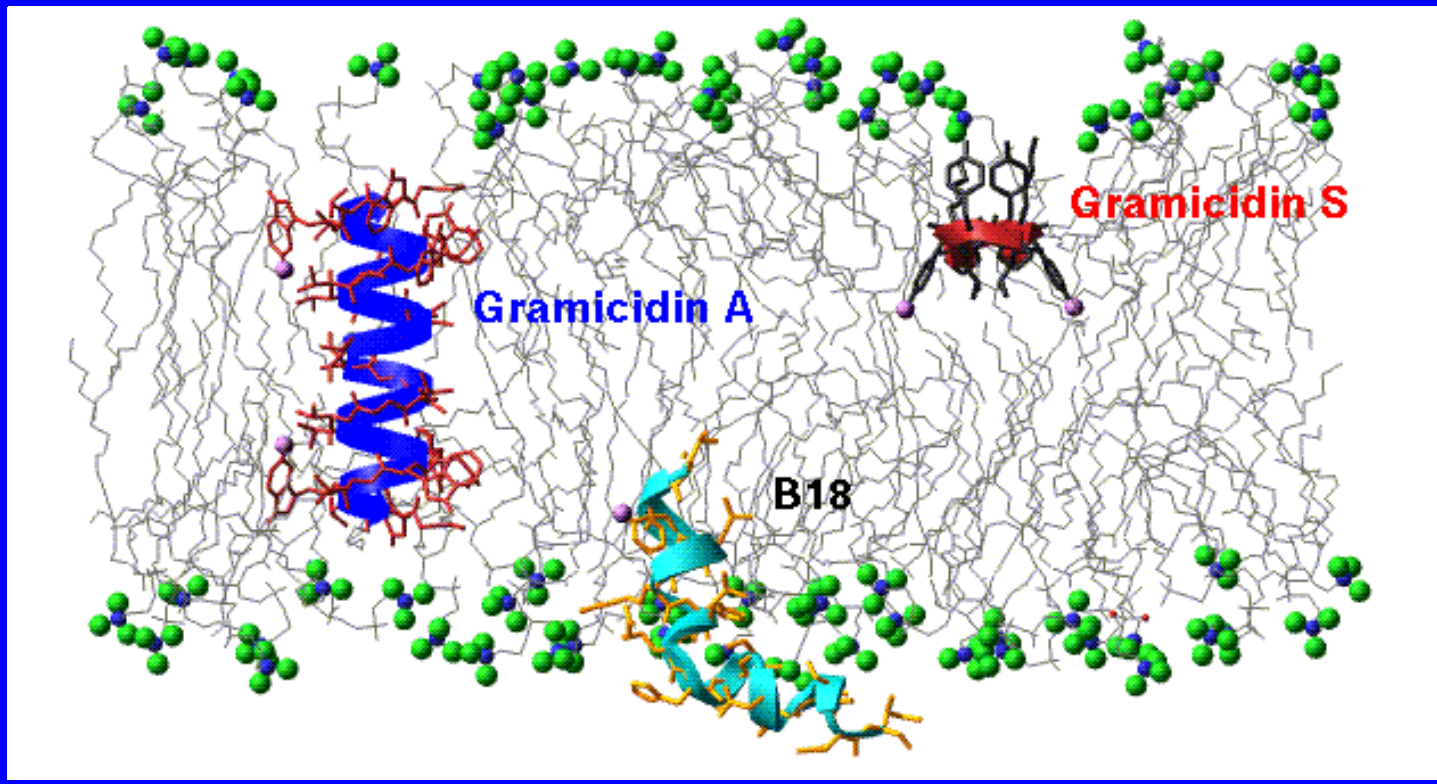
Membrane gradient disruption

Ion transfer ("ionofors")

antibiotics
(K+, Ca2+, Mg2+)

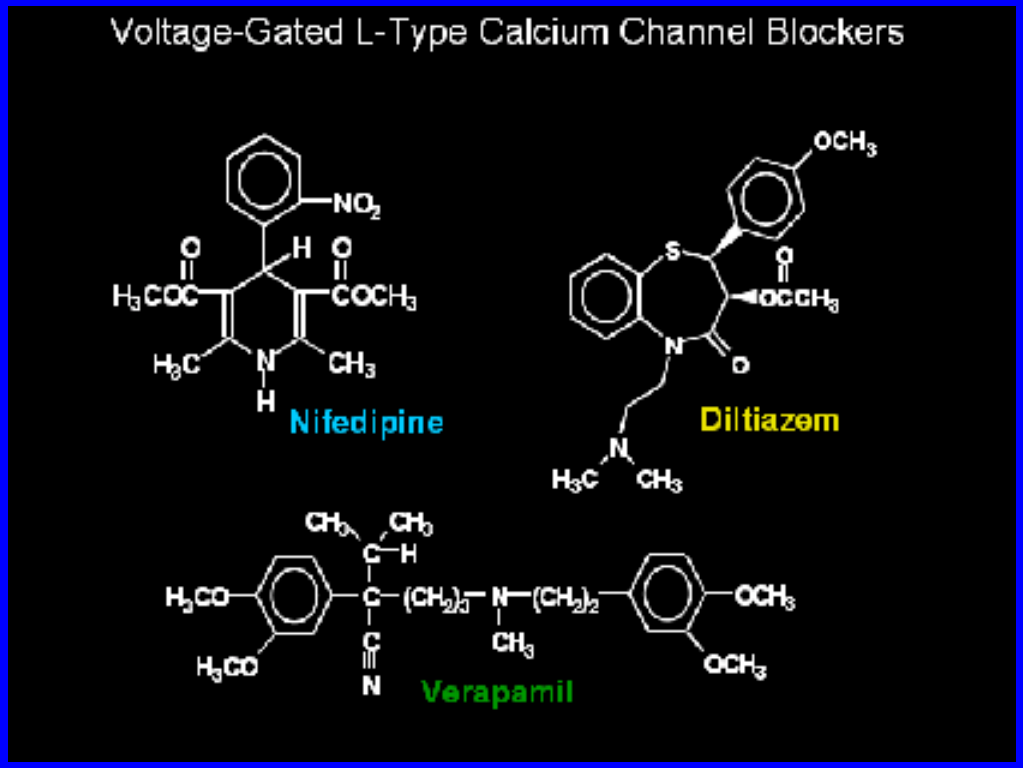




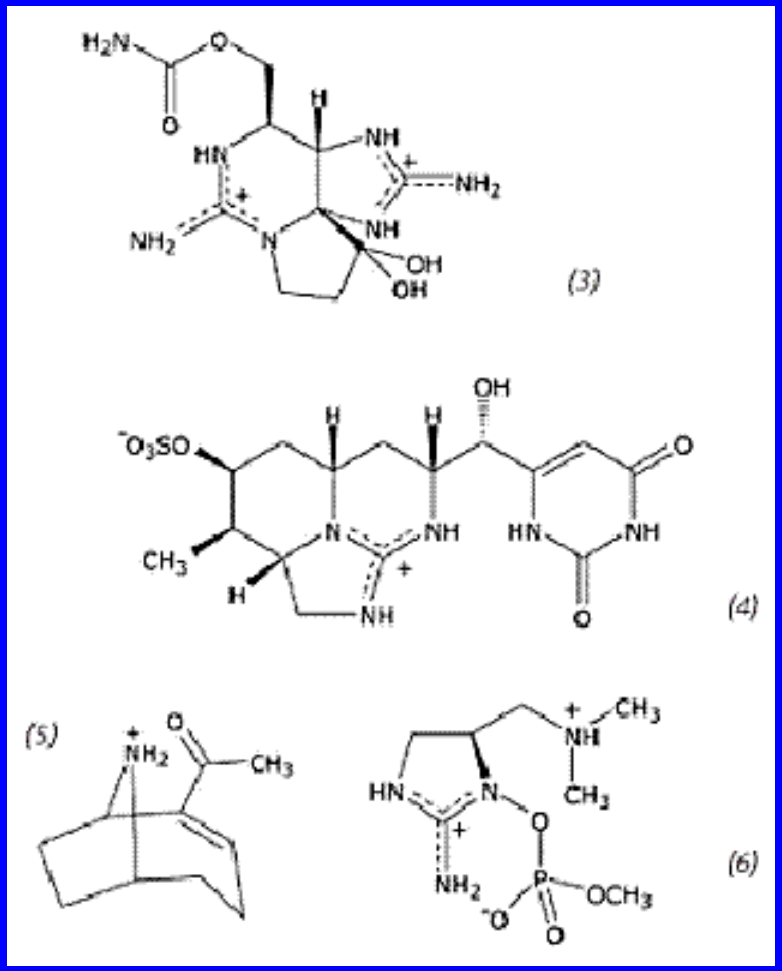


Ion Channel BLOCKERS / ACTIVATORS

Neuromodulators (drugs)



Neurotoxins (cyanobacterial)



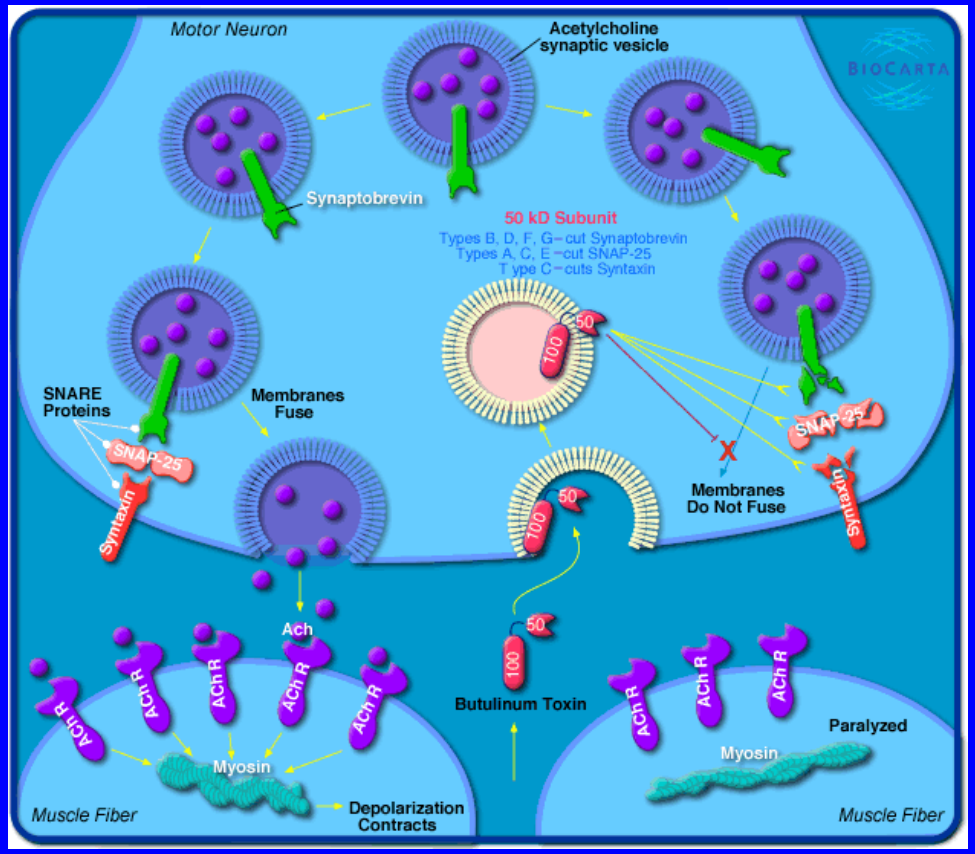
Botulinum and Tetanus toxins

(Clostridium botulinum, Clostridium tetani)

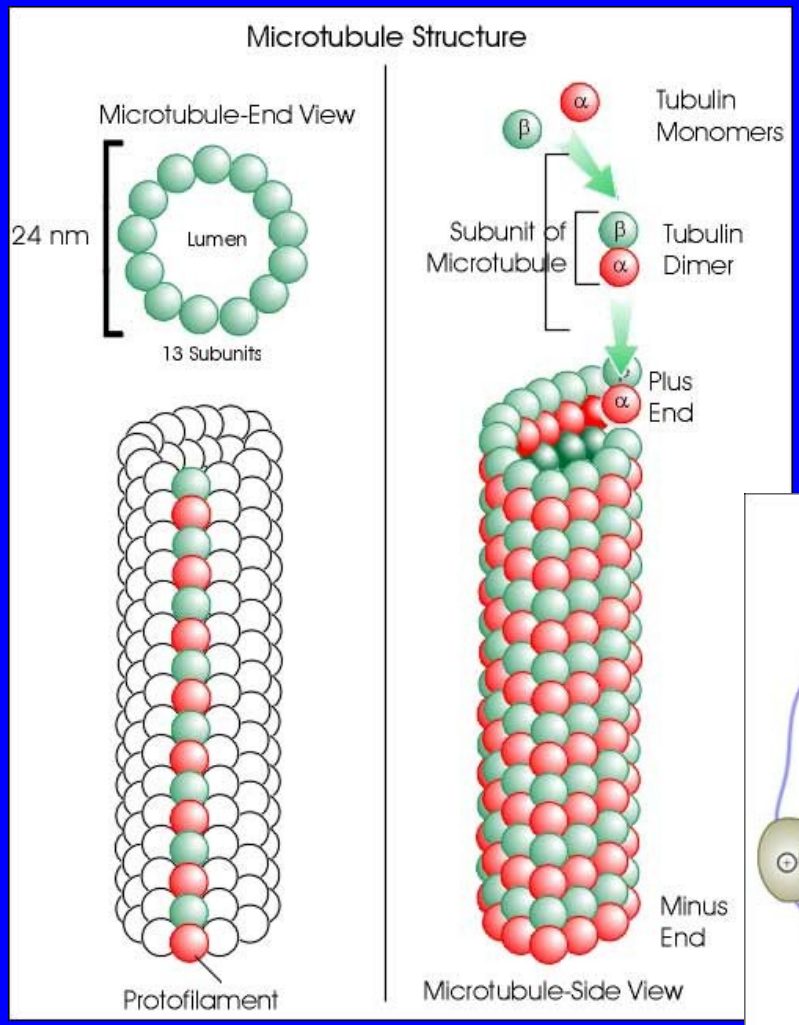
Toxins = enzymes - proteases (!)

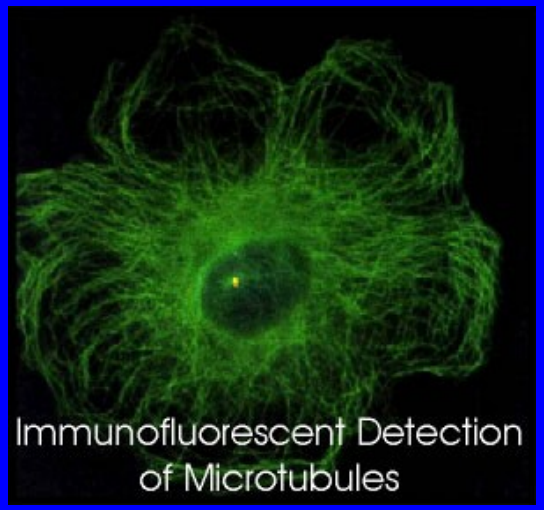
- cleavage of proteins involved in vesicle formation
- selective inhibition of neutrotransmitter release

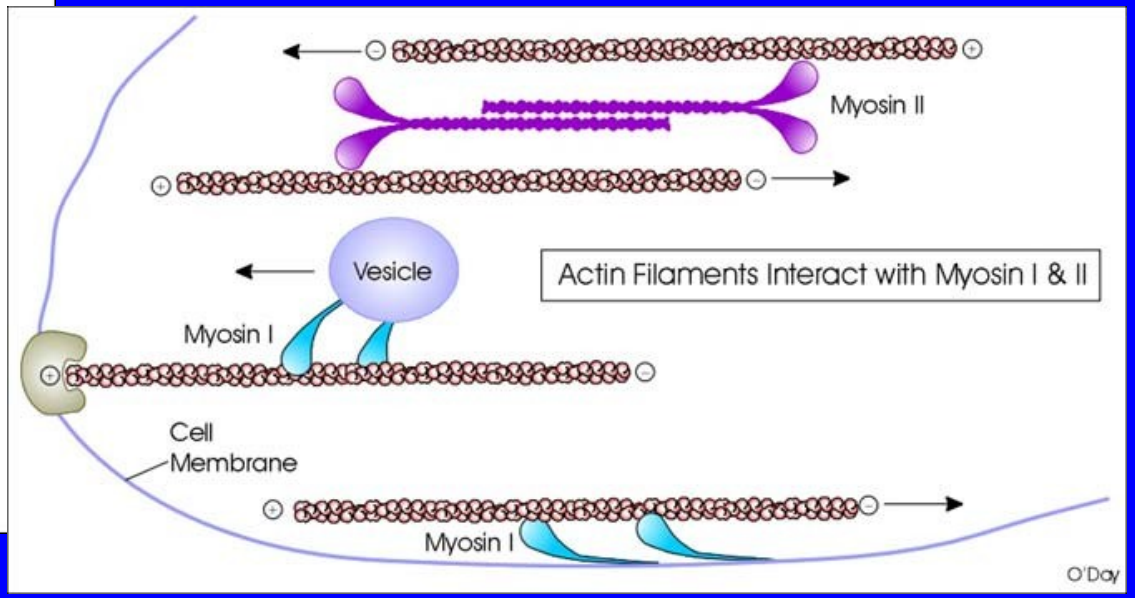
neurotoxicity



Cytoskeleton as target of toxicants
microtubules / actin-myosin

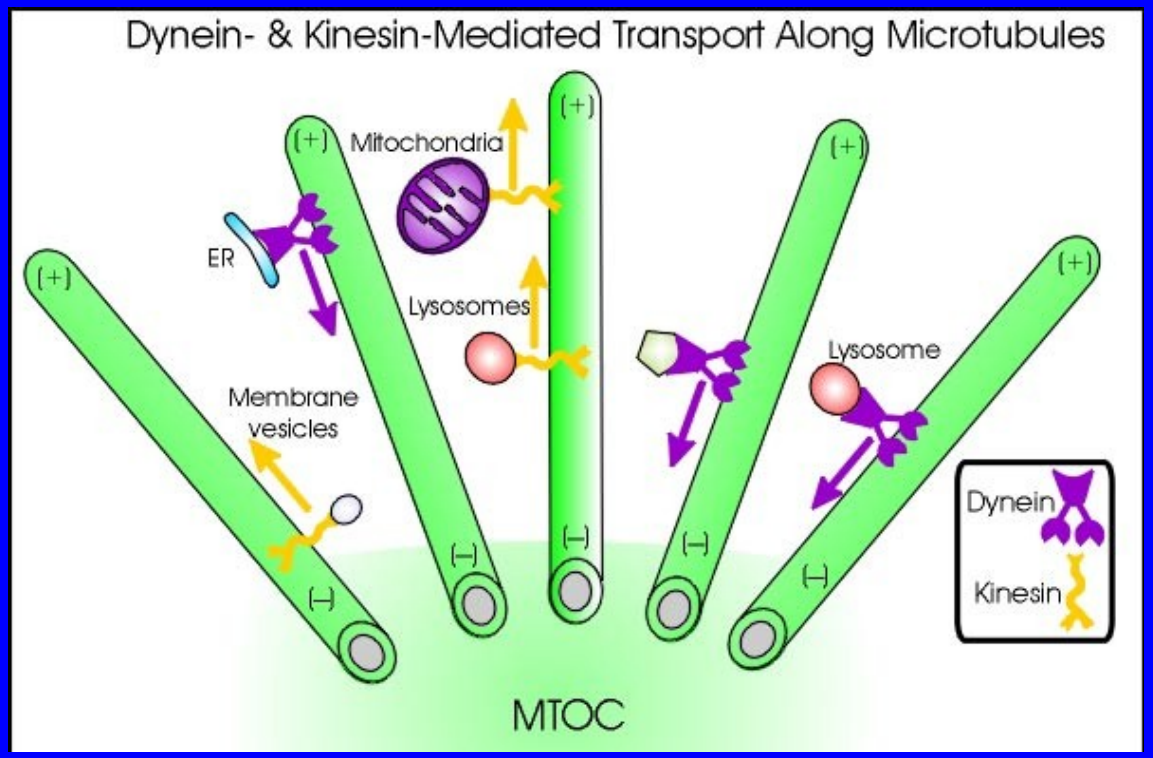




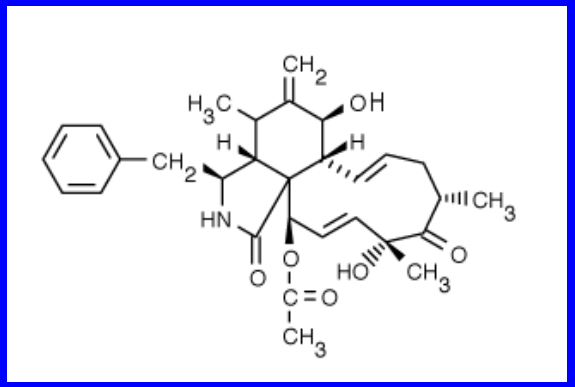


Cytoskeleton – function

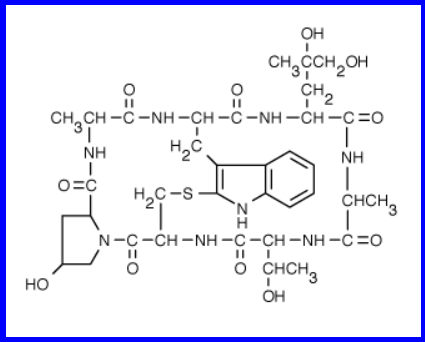
- intracellular transport
- cell replication and division (mitosis:chromosomes)
- muscle movement
- membrane (vesicles) fusion



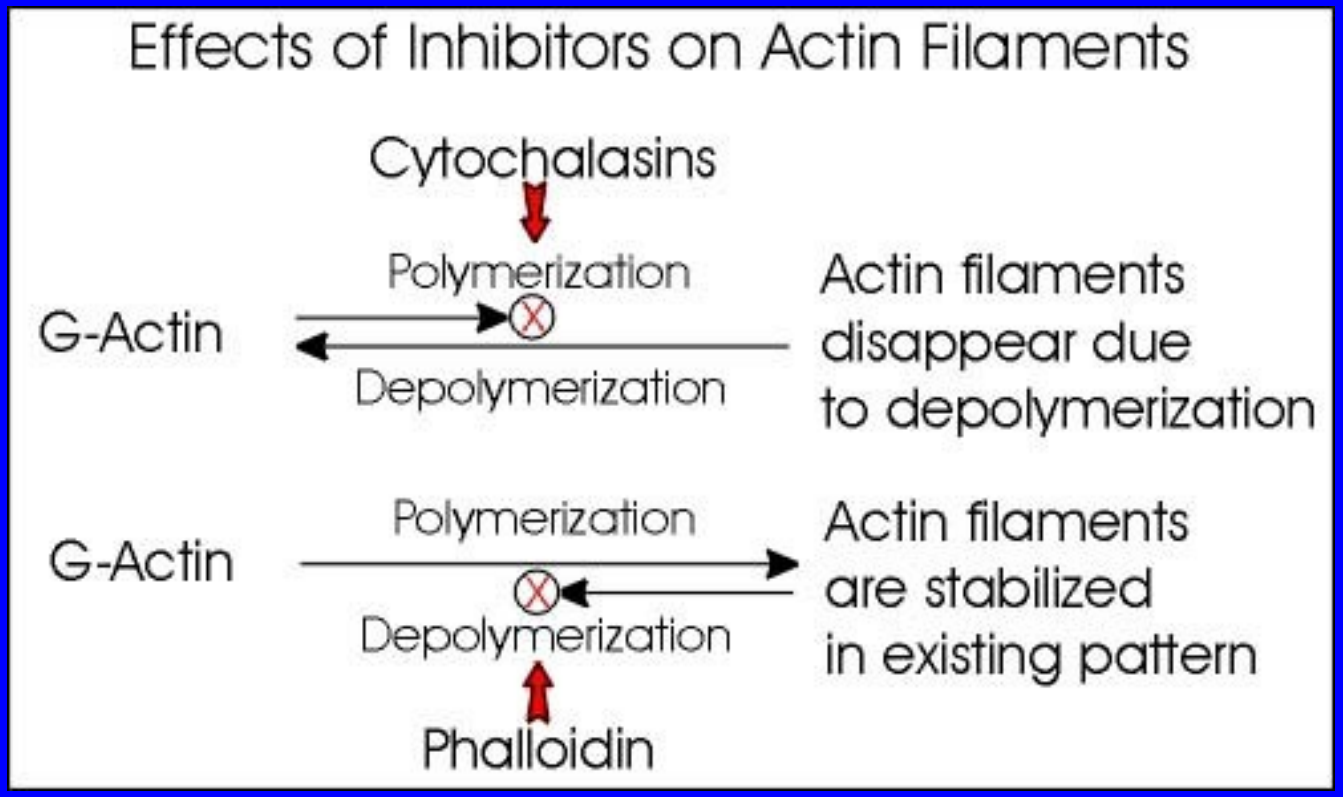
TOXINS: effects on (DE)POLYMERIZATION



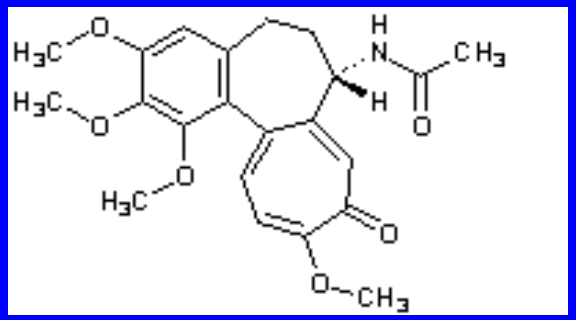
cytochalasin D
(fungal toxin)



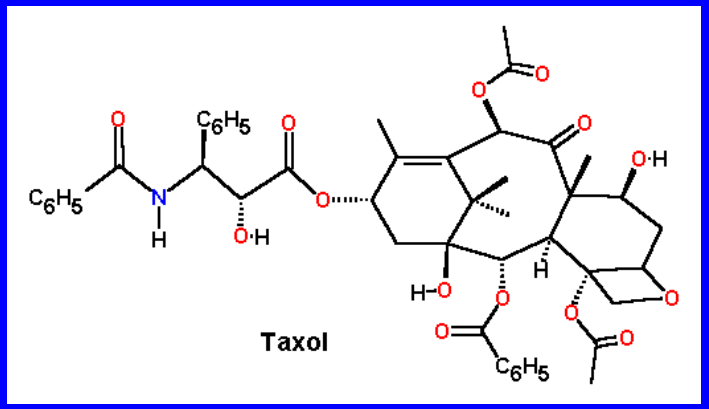
Phalloidin
(death cap - Amanita phalloides)

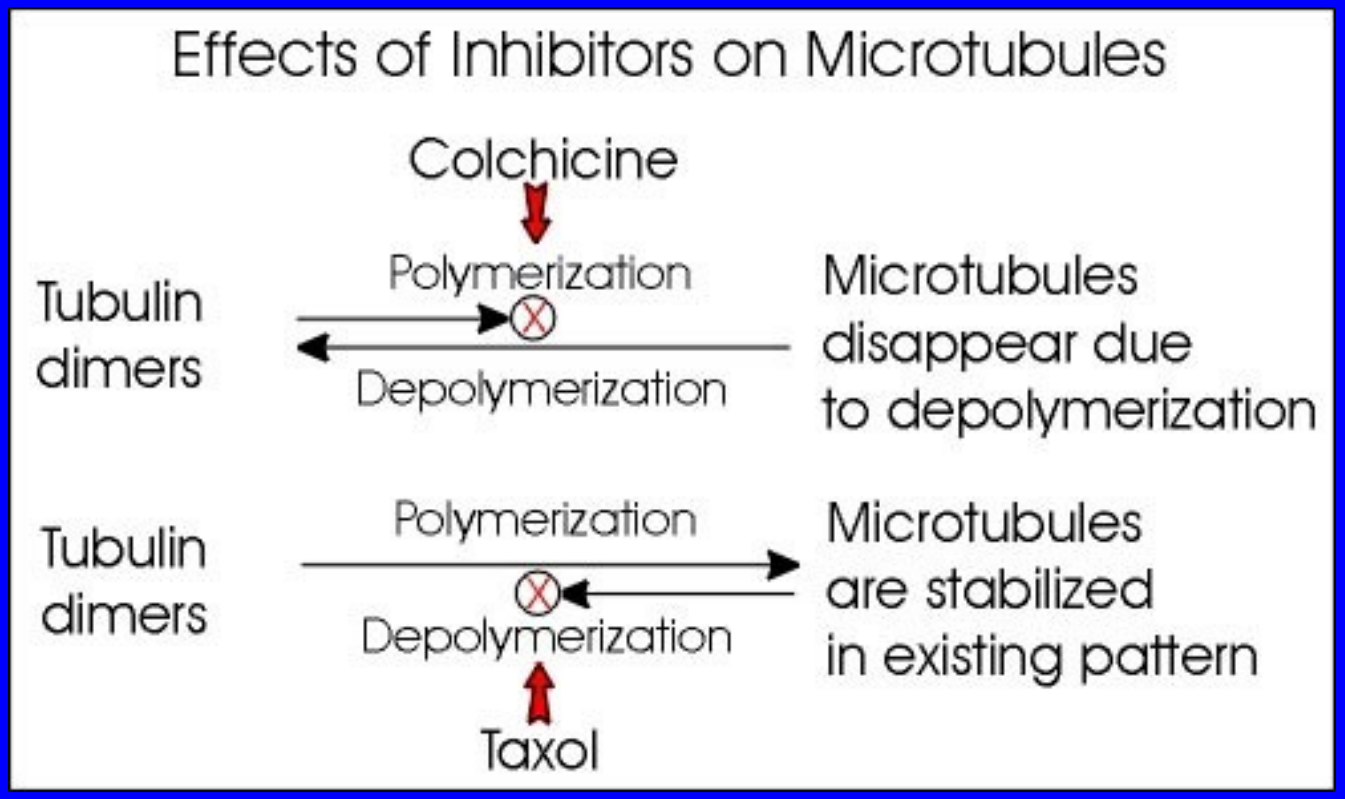


TOXINS: effects on (DE)POLYMERIZATION



Colchicine





taxol