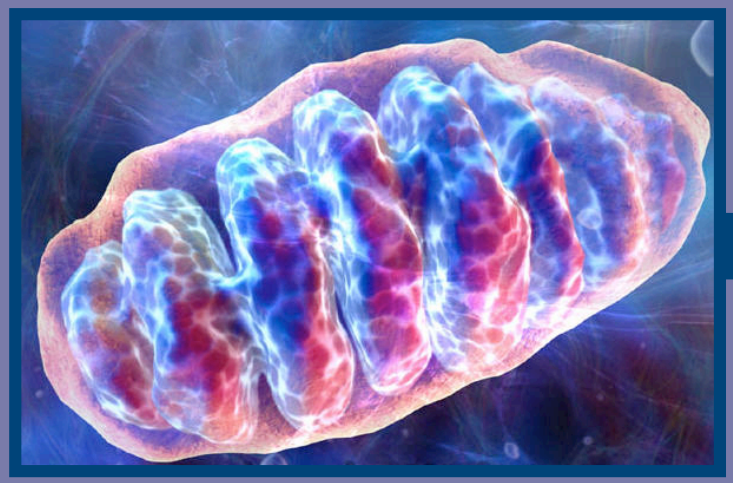
Targeting Antioxidants to Mitochondria



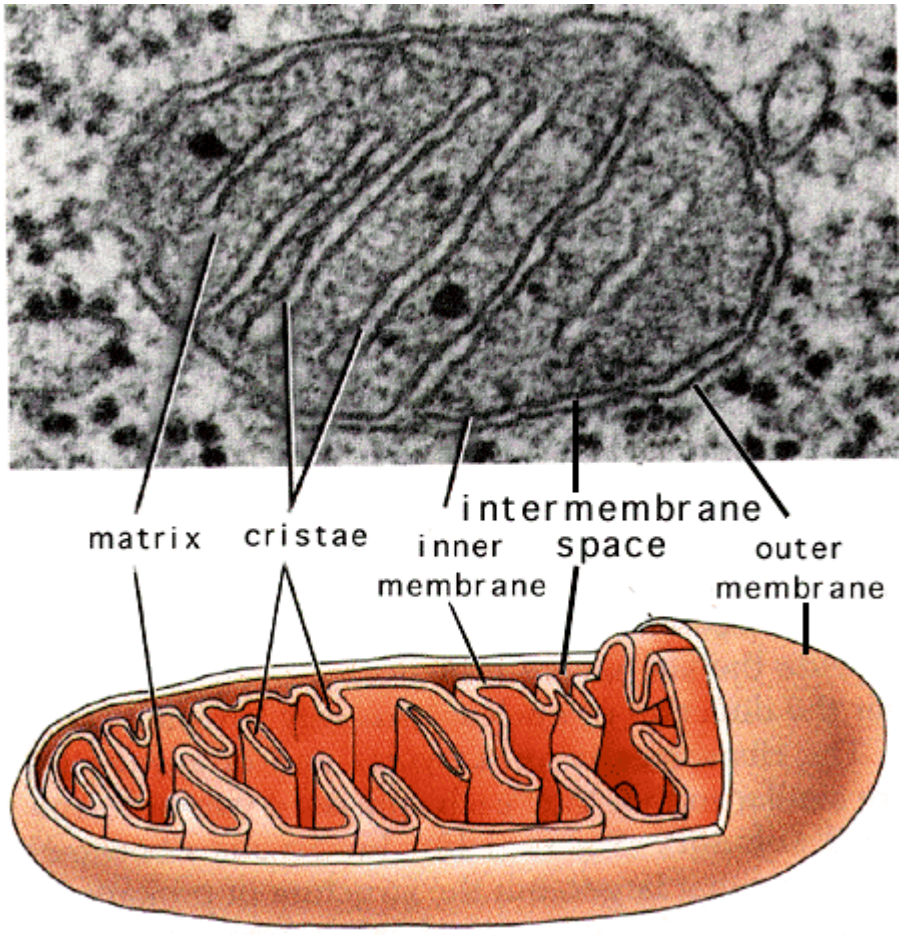
Amir H. Faraji

February 17, 2007

Schedule of Topics

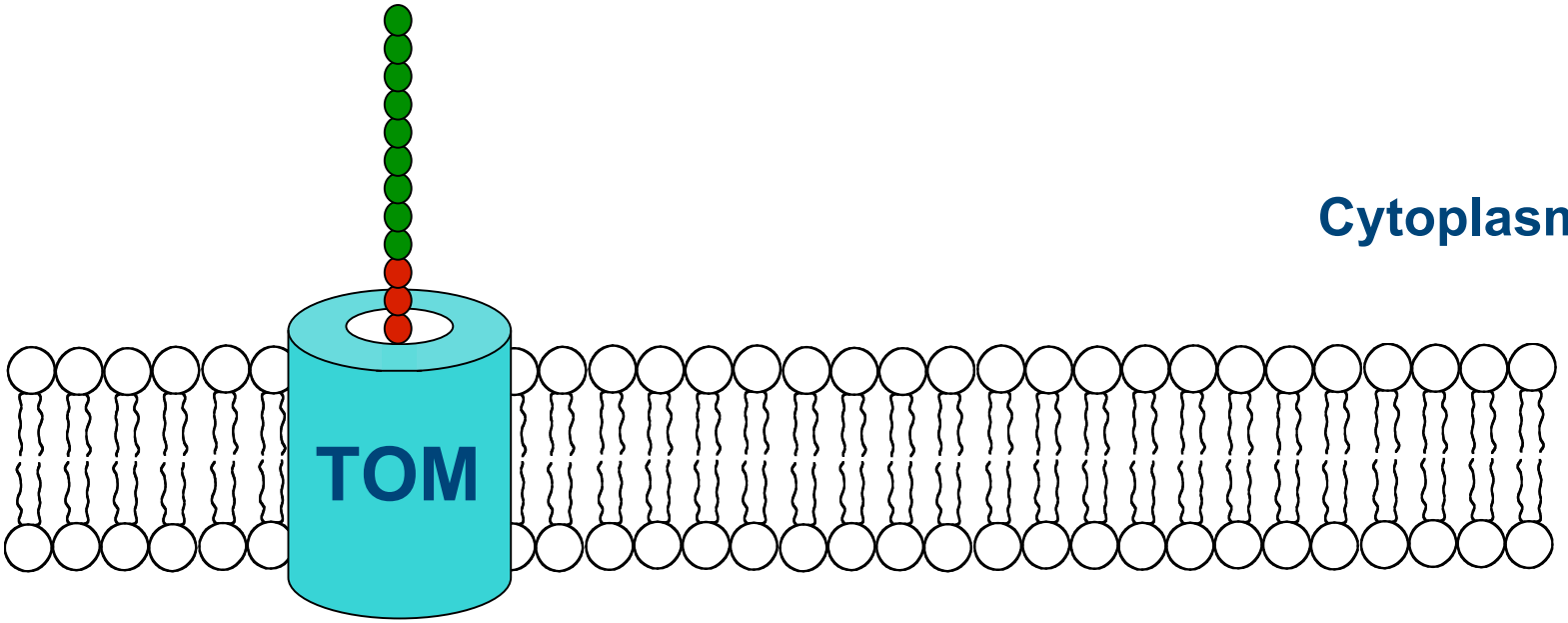
- Mitochondrial Structure & Function
- Triphenylphosphonium Targeting Strategy
- Clinical Correlation for Drug Design - Stroke

Mitochondrial Anatomy



http://www.life.uiuc.edu/crofts/bioph354/lect10.html

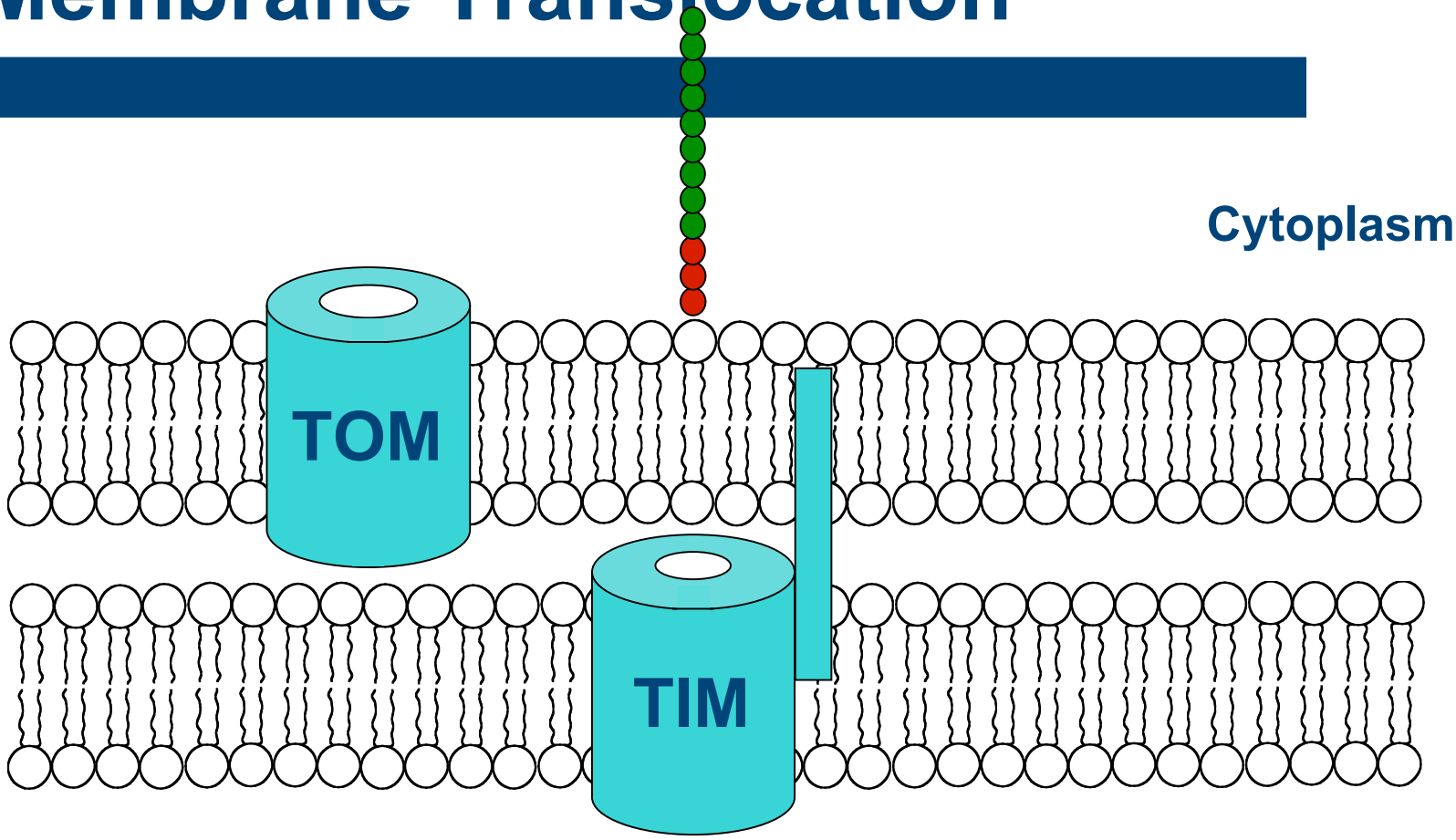
Membrane Translocation



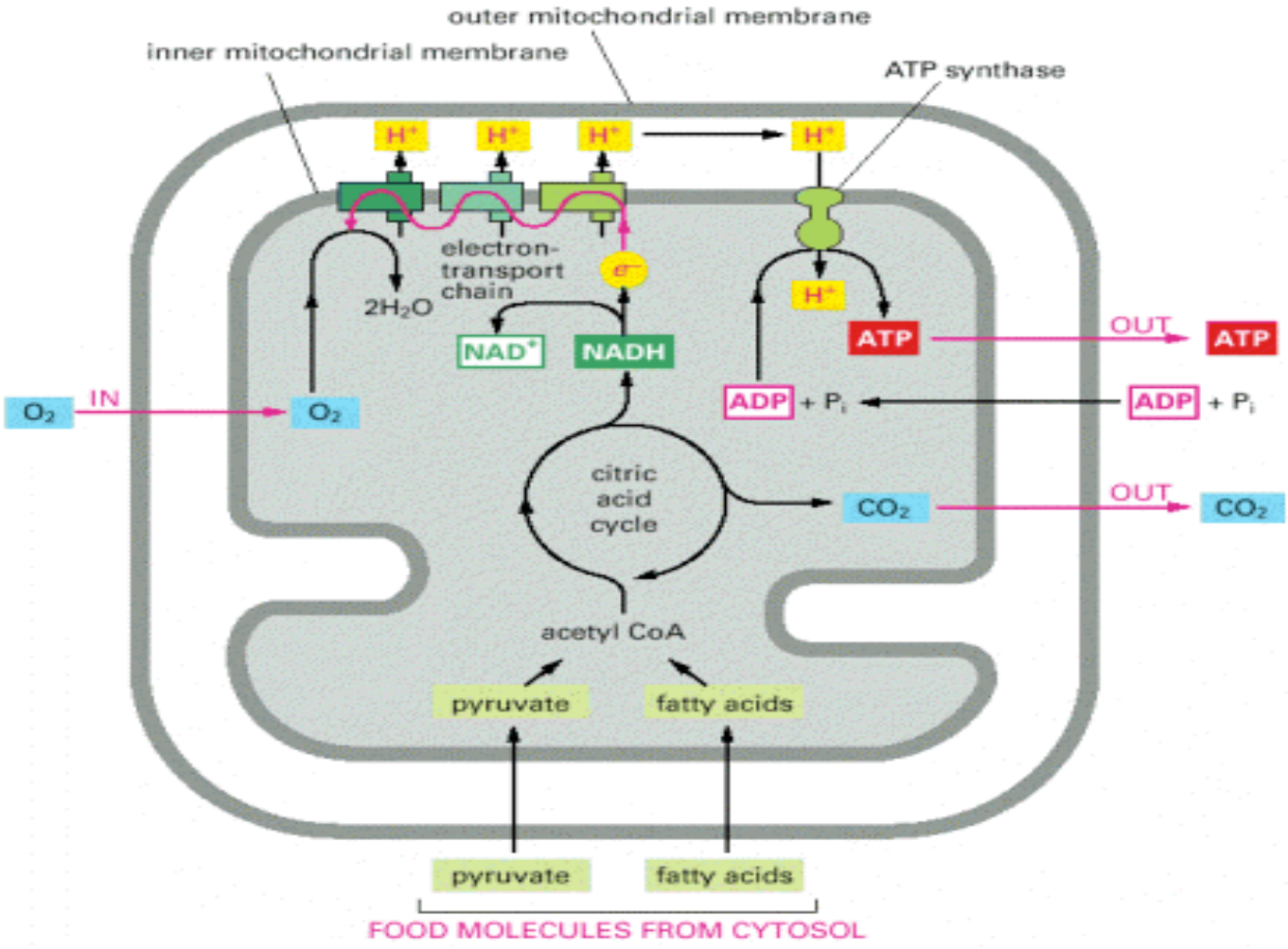
Cytoplasm

Intermembrane Space

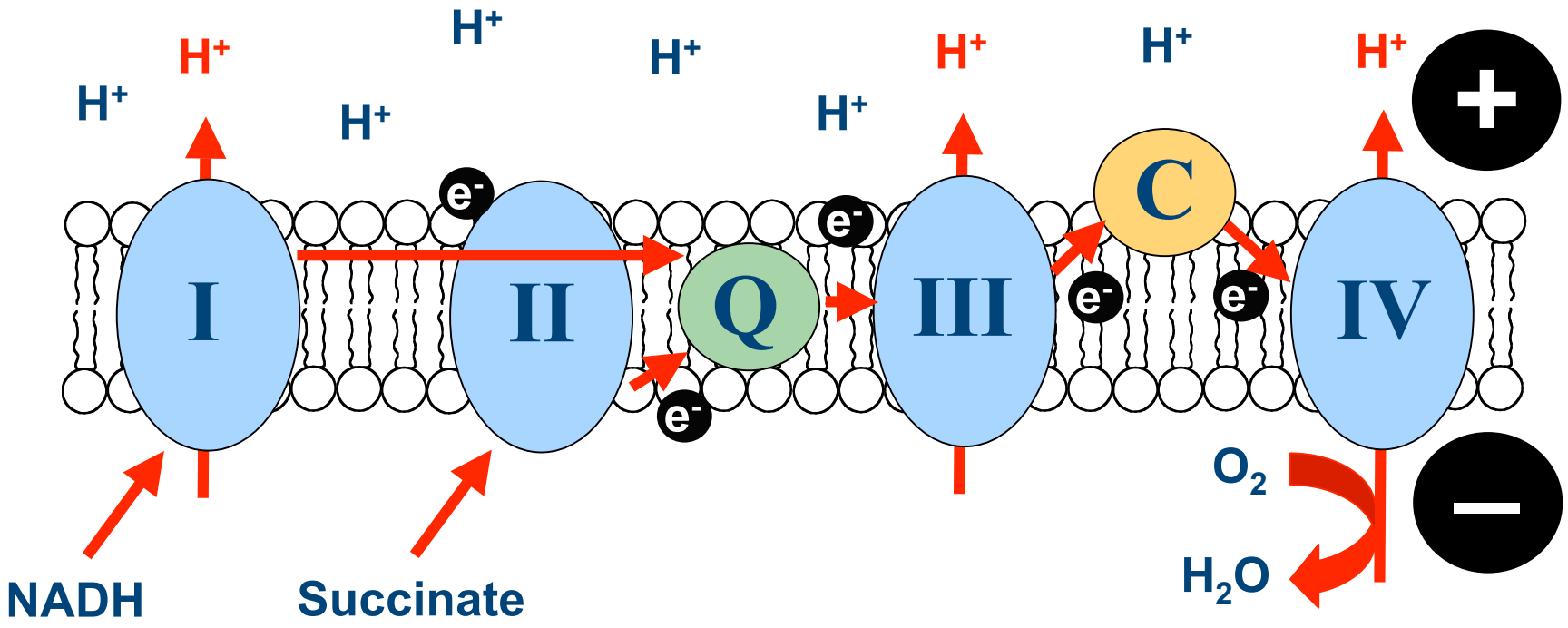
Membrane Translocation



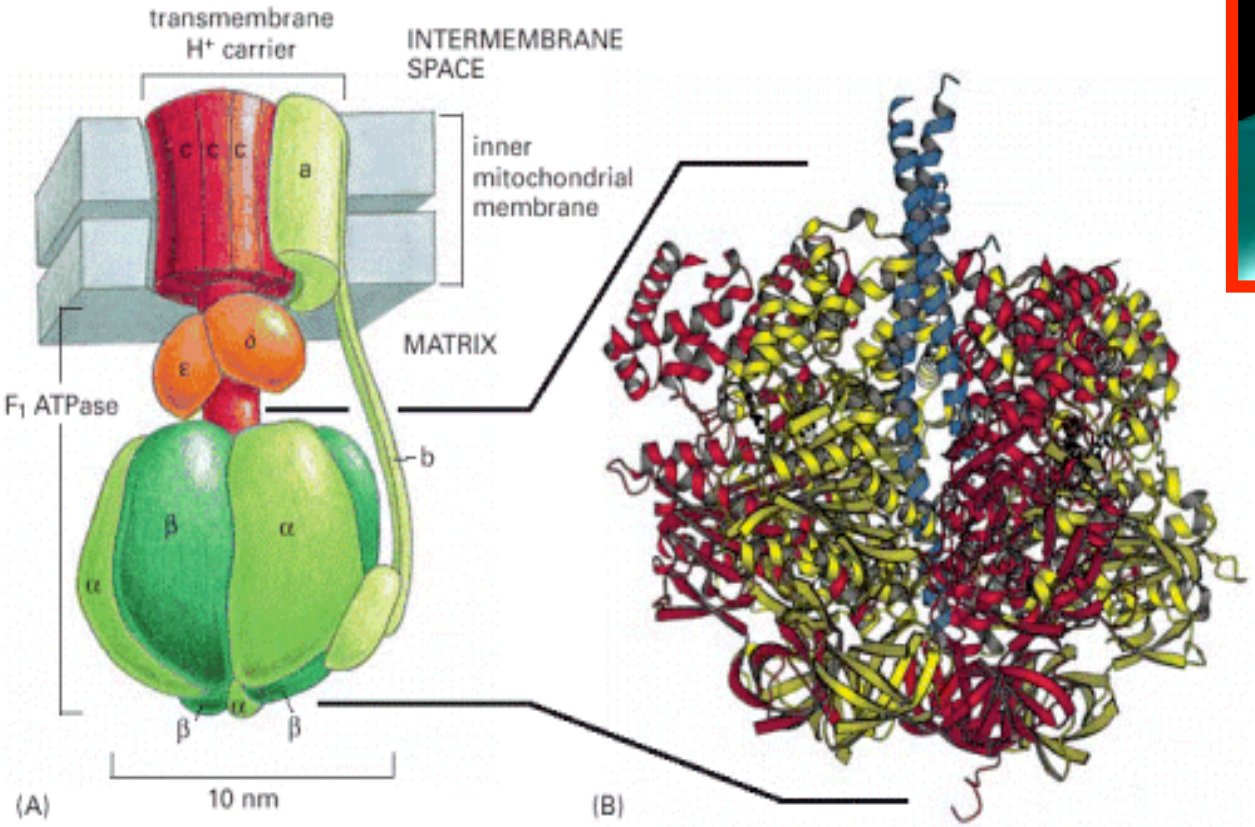
Mitochondrial Matrix



Electron Transport Chain



ATP Synthase



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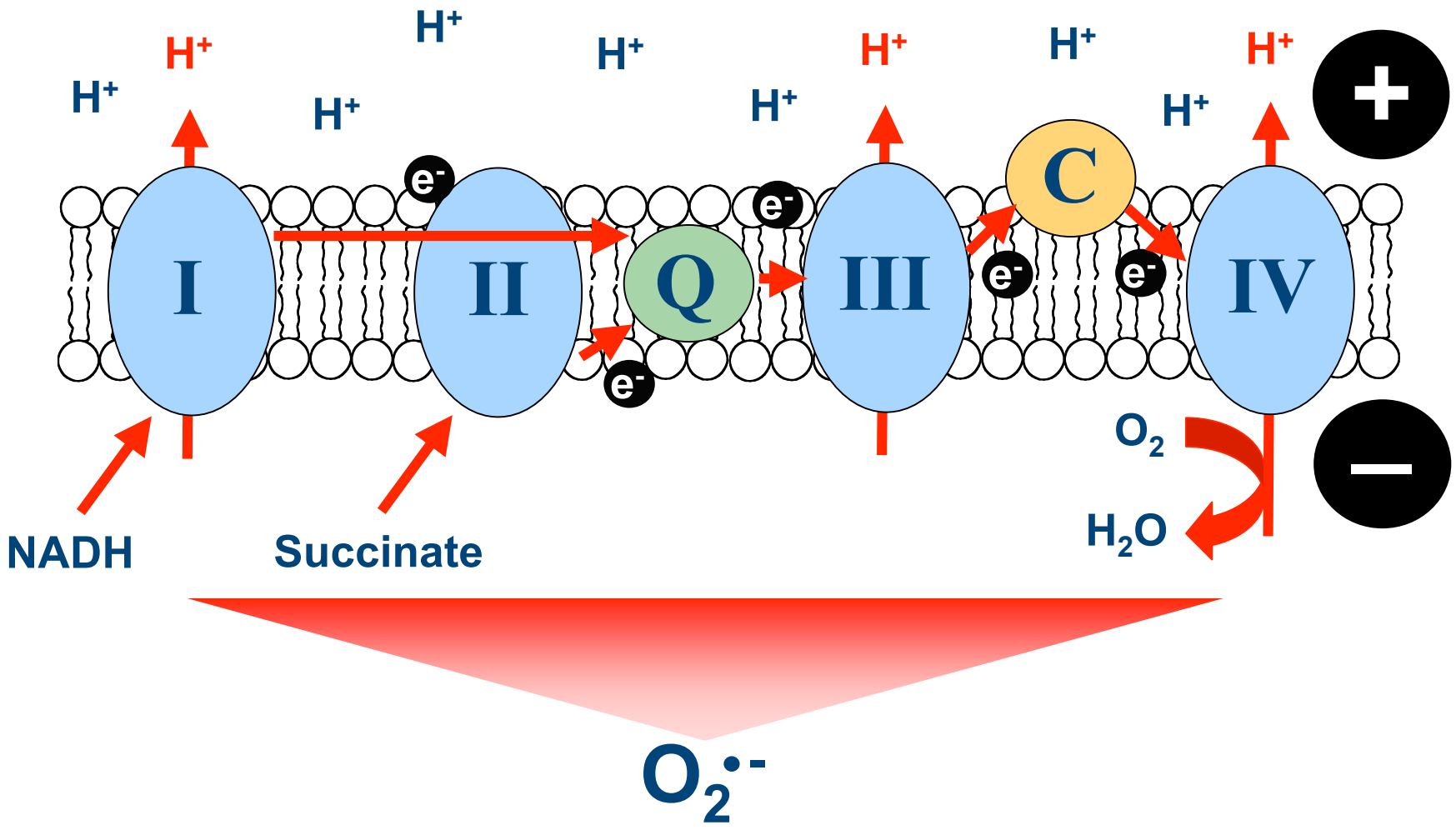
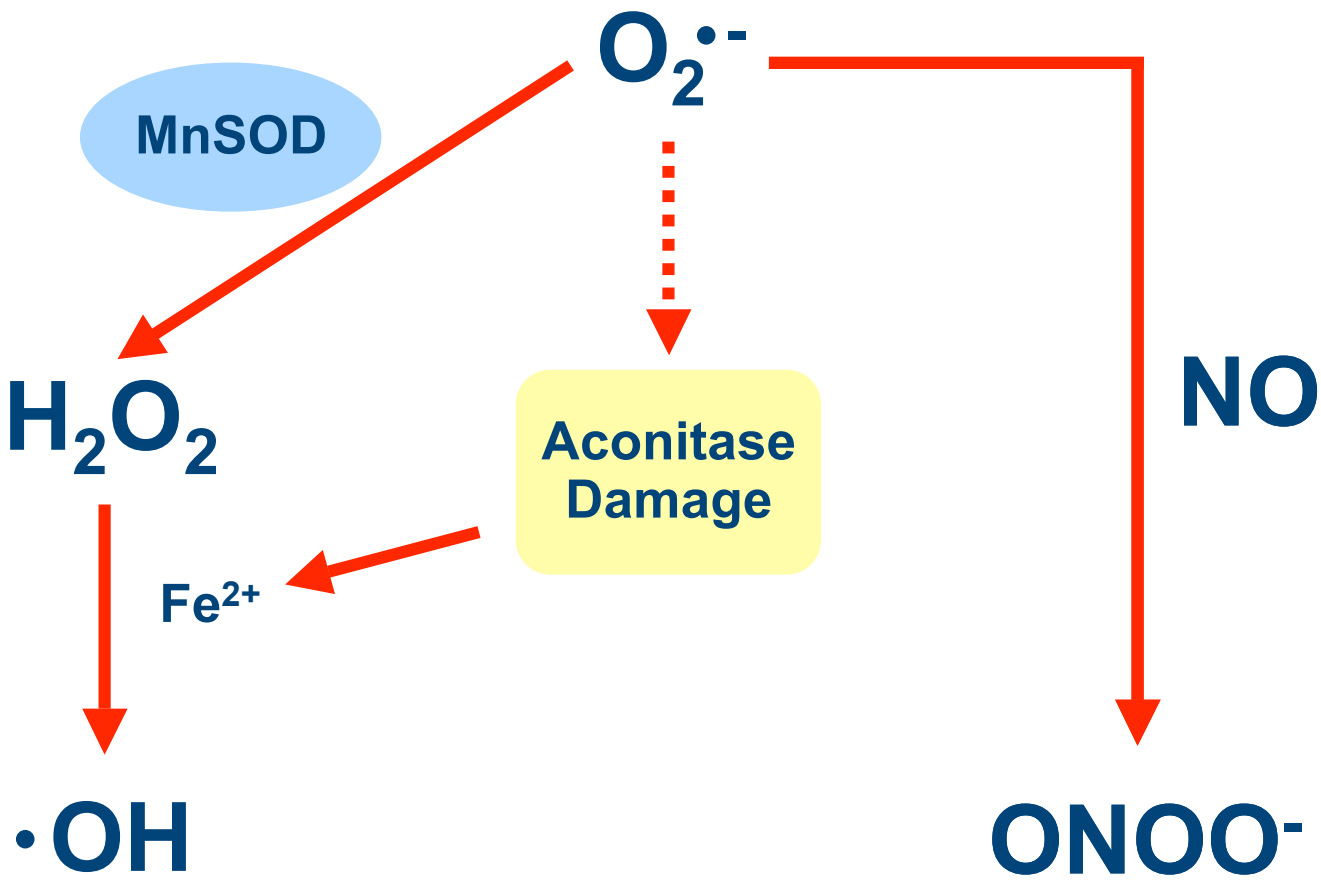
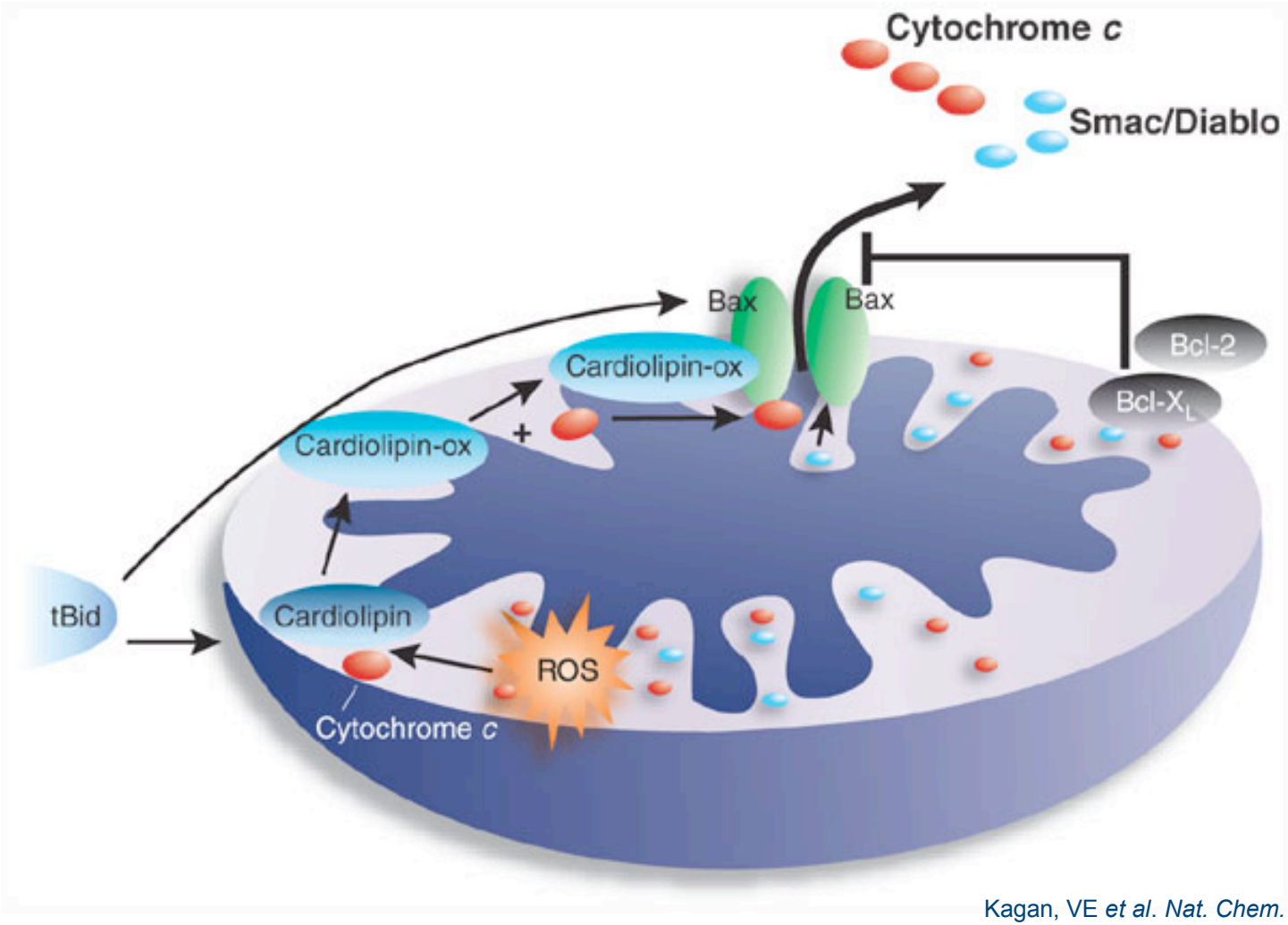
Sources of Free Radicals



Sources of Free Radicals



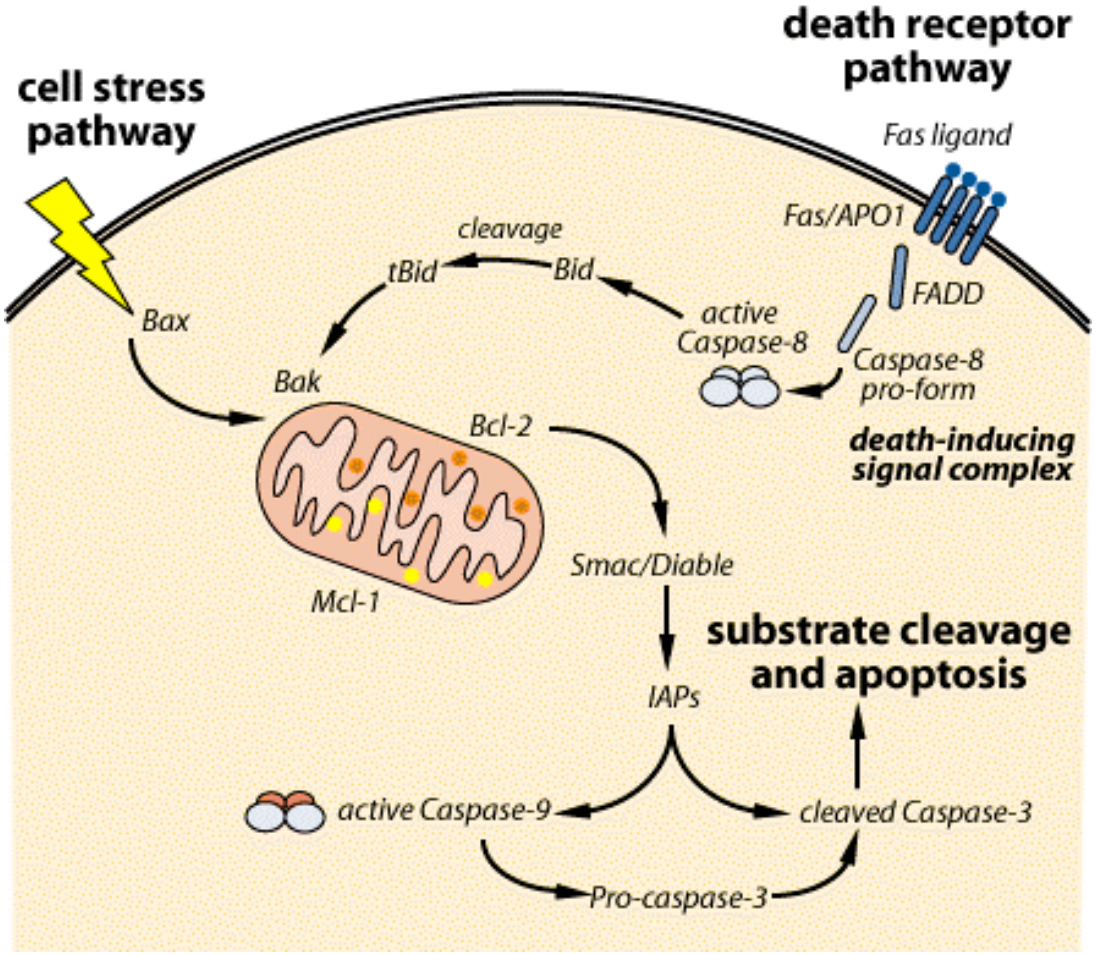
Initiation of Apoptosis



Kagan, VE *et al*. *Nat. Chem. Biol.* 1, 223-232. **2005**.

Intrinsic Pathway of Apoptosis

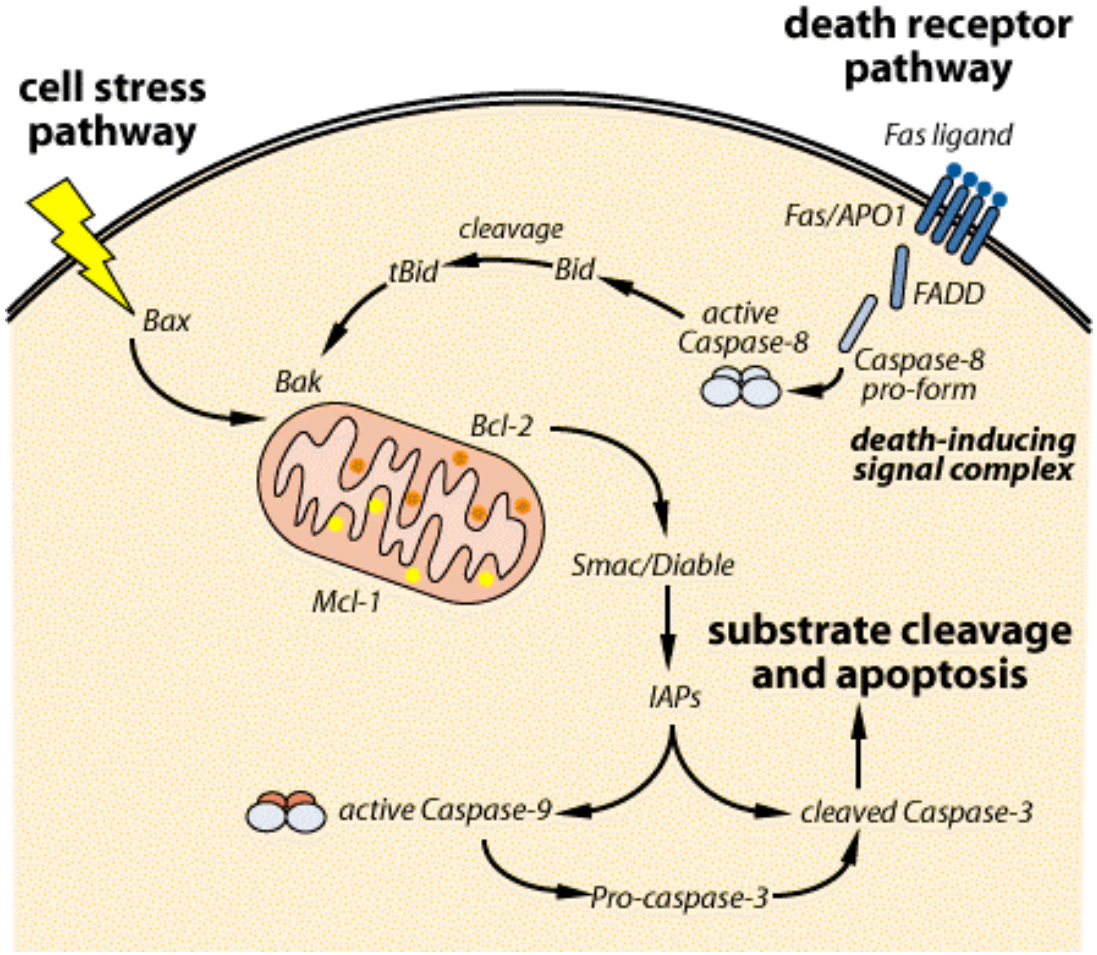
- Cellular stress
- Bax, Bid bind to outer mitochondrial membrane
- Bak required to release mitochondrial factors
- Cytochrome c released
- Cyt c, ATP, Apaf-1 form complex
- Caspase-9 & complex forms Apoptosome
- Apoptosome activates Caspase-3



http://www.bioteach.ubc.ca/CellBiology/Apoptosis/

Extrinsic Pathway of Apoptosis

- FasL binds to Fas
- Receptors aggregate
- Fas-Associated Death Domain (FADD) formed
- Caspase-8 recruited
- Death-Inducing Signal Complex (DISC) formed
- Caspase-8 activated
- Activated Caspase-8 activates Caspase-3
- Caspase-3 initiates degradation of cell



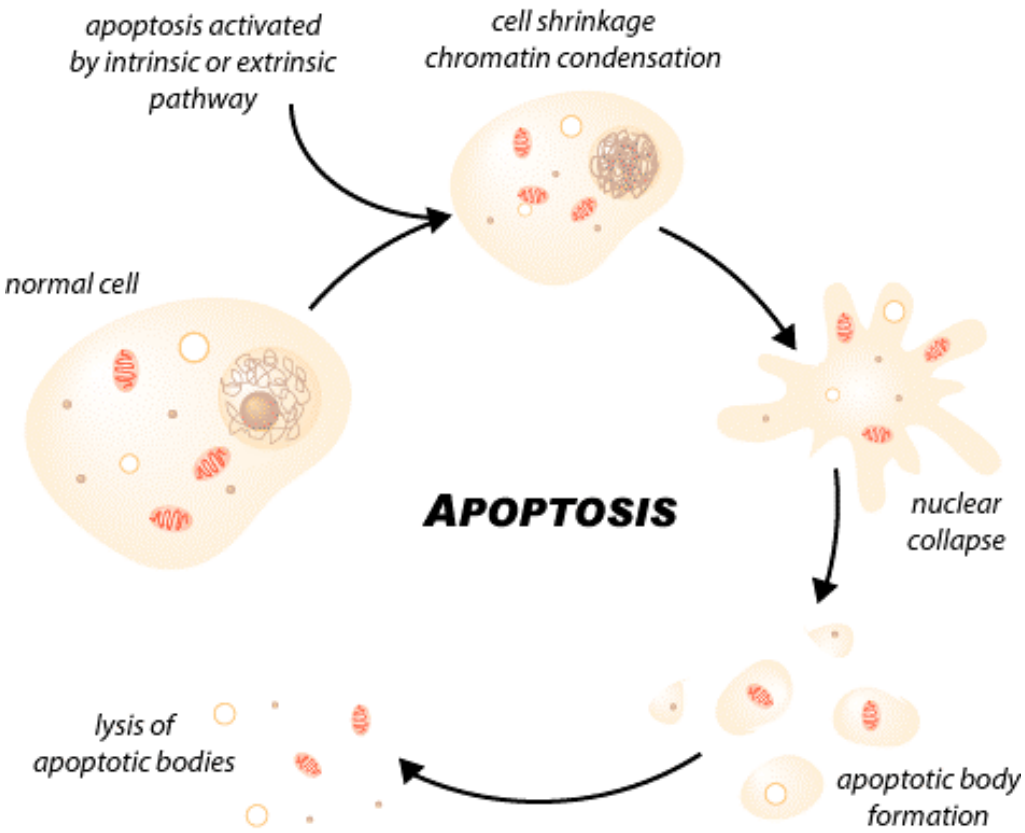
http://www.bioteach.ubc.ca/CellBiology/Apoptosis/

Programmed Cell Death: Apoptosis

Morphology of Apoptosis:

- Chromatin condensation
- Cell shrinkage
- Nuclear collapse
- Membrane blebbing
- Specific DNA Cleavage
- Cytoskeleton collapse
- Apoptotic bodies

http://www.biologie-lfhk.cz/files/apoptosis.mpg



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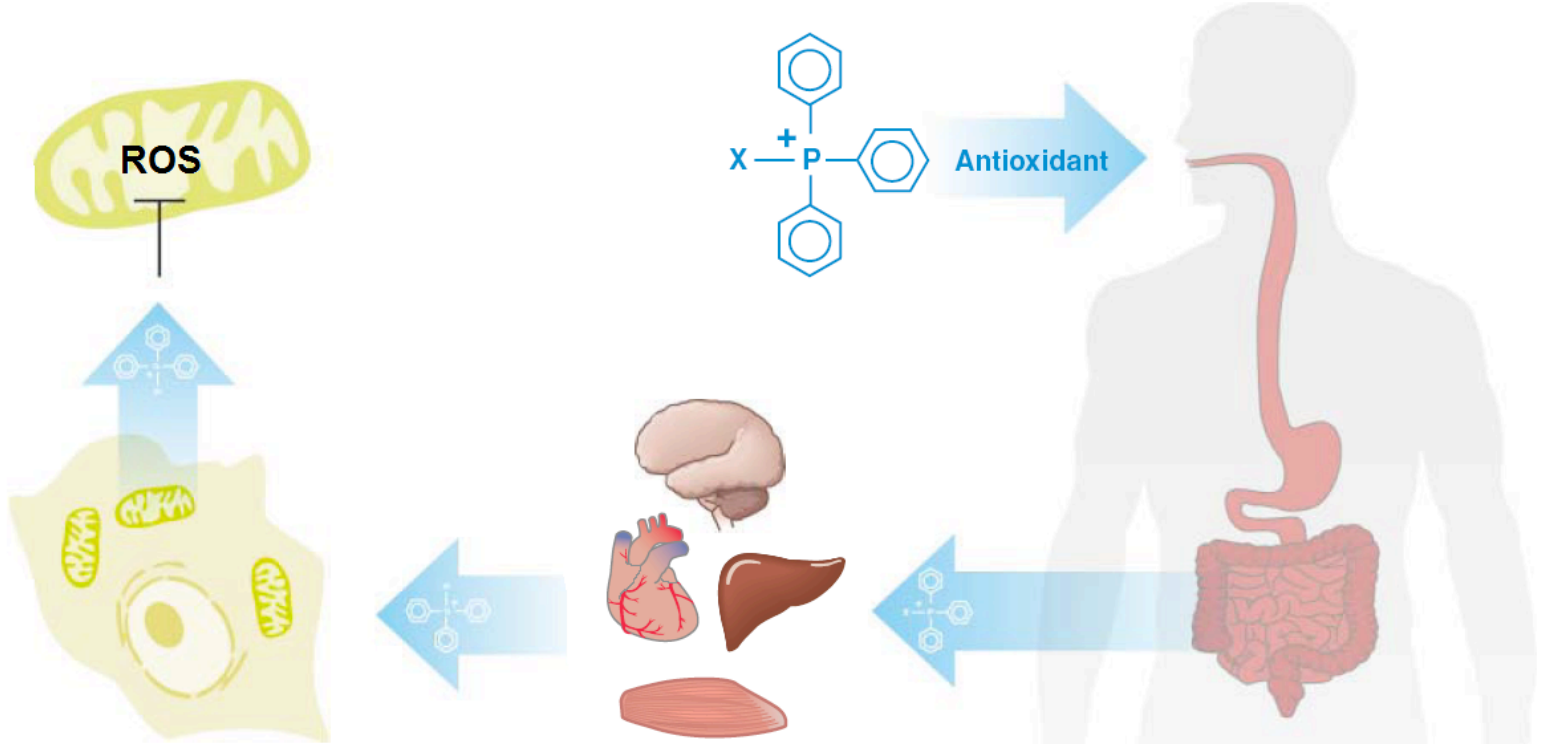
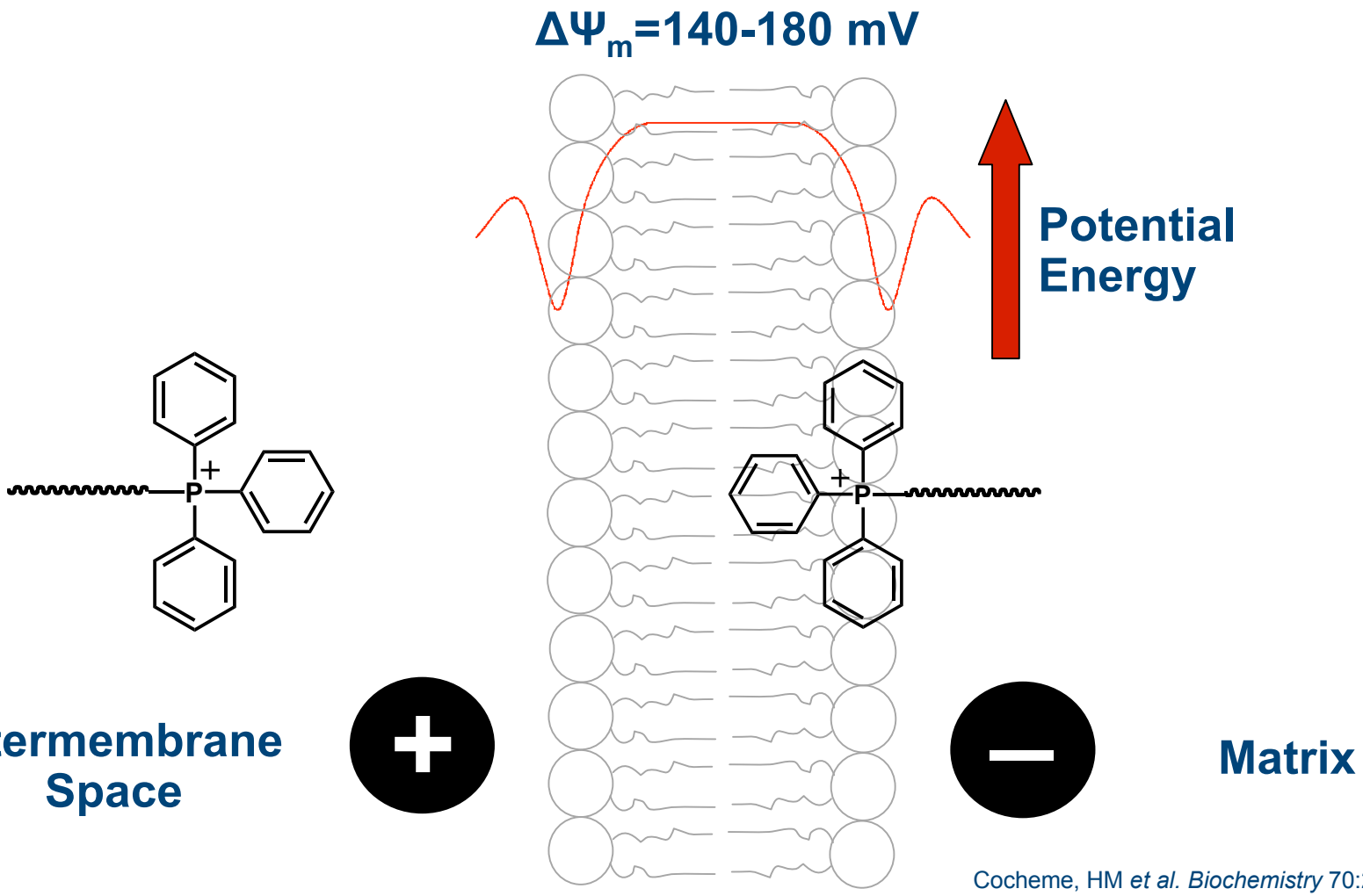
Triphenylphosphonium Targeting



Murphy, MP and Smith, R. *Annu. Rev. Pharmacol. Toxicol*. 47:629–56. **2007**.

Triphenylphosphonium Targeting

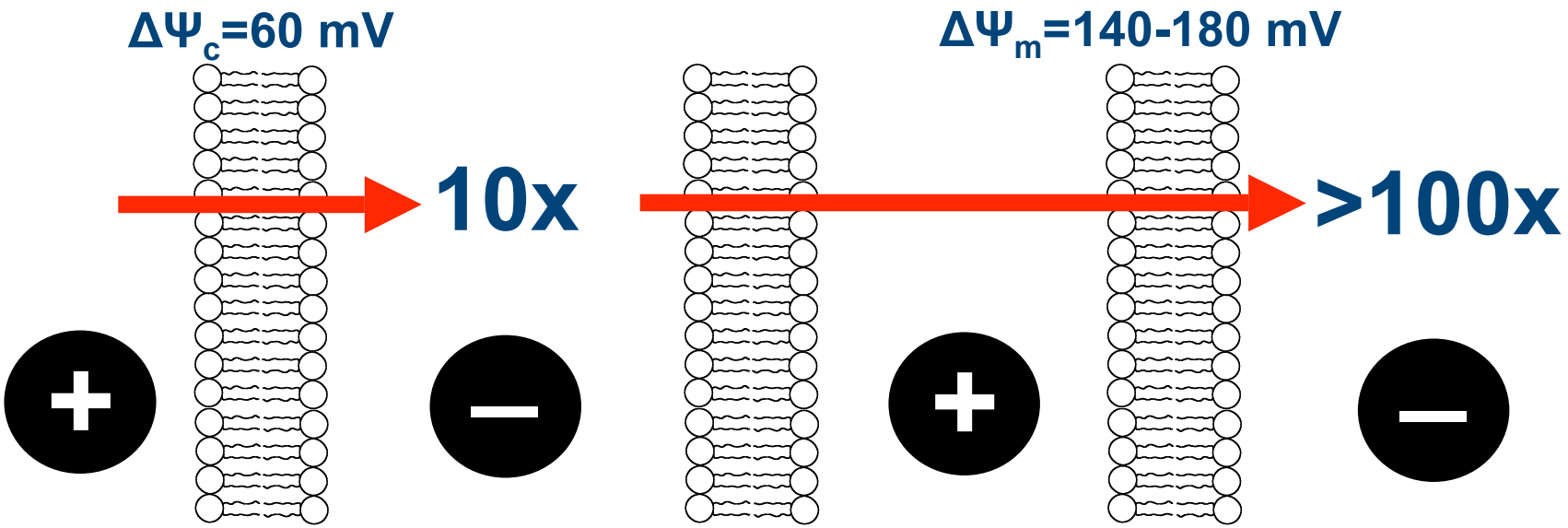


Cocheme, HM *et al. Biochemistry* 70:222–30. **2005.**

Triphenylphosphonium Targeting

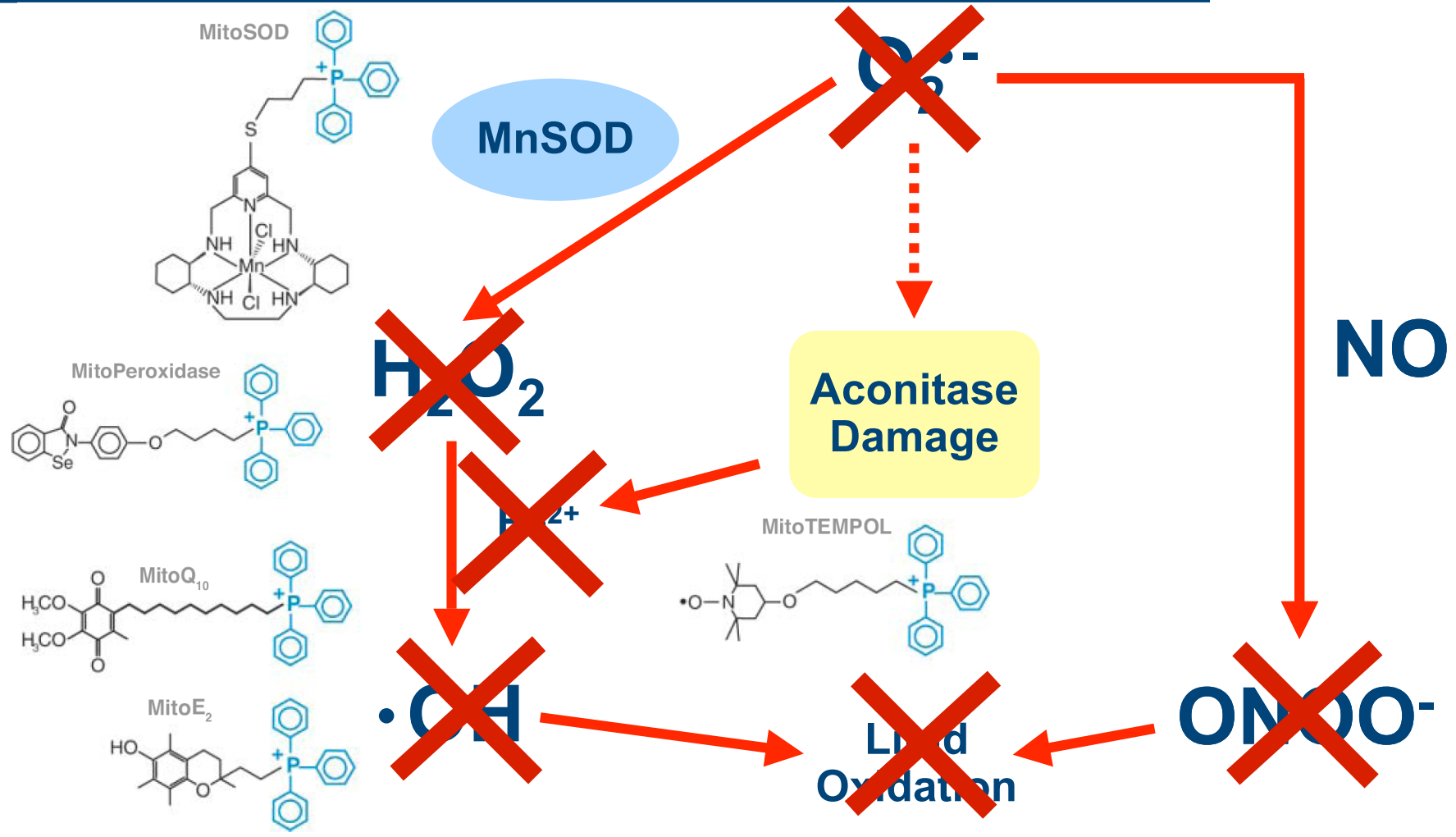
$$\Delta\psi = \frac{2.303\,RT}{F}\log_{10}\left(\frac{[cation_{in}]}{[cation_{out}]}\right)$$

Under biological temperatures and conditions, there will be approximately a tenfold accumulation per ~60 mV increase in ΔΨ



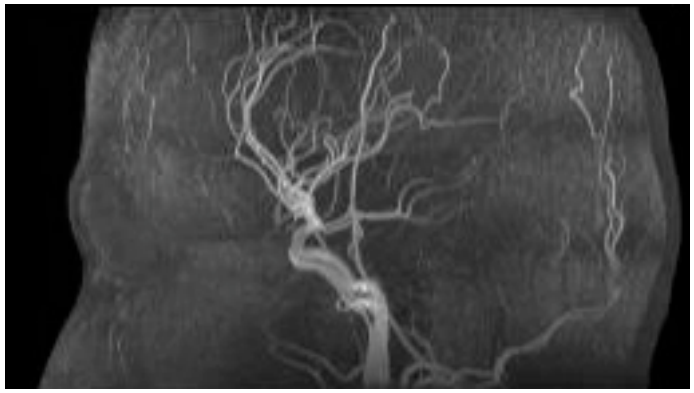
Skulachev, VP *et al. Nature* 222:1076–78. **1969**.

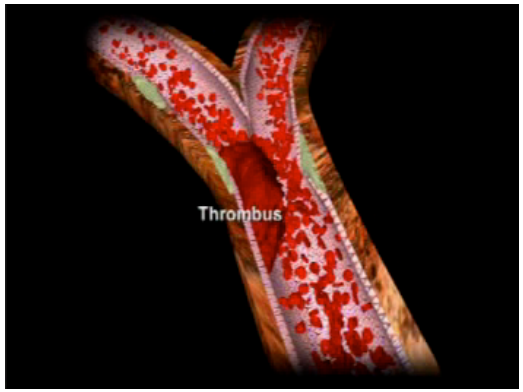
Triphenylphosphonium Targeting

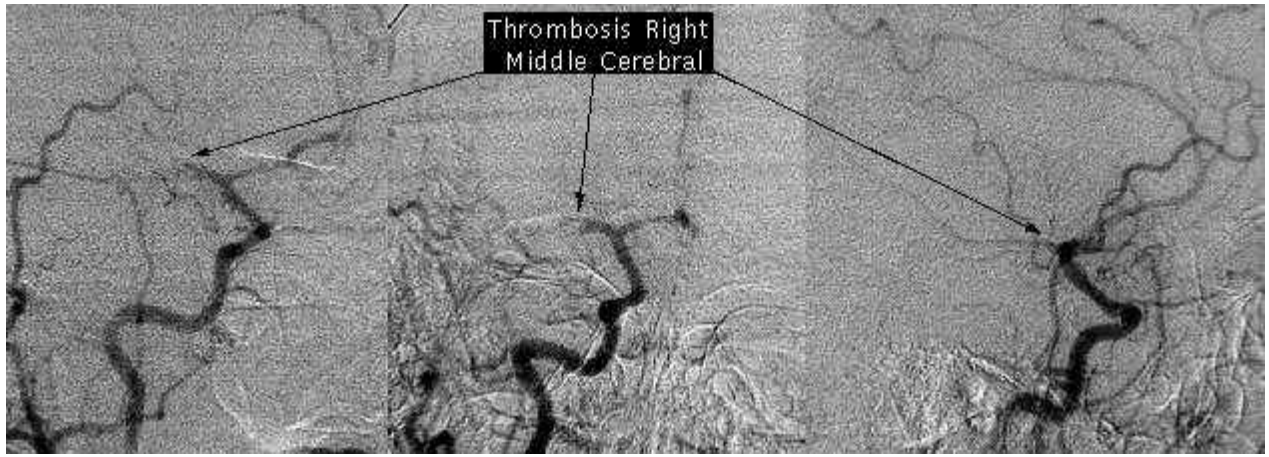


Murphy, MP and Smith, R. *Annu. Rev. Pharmacol. Toxicol*. 47:629–56. **2007**.

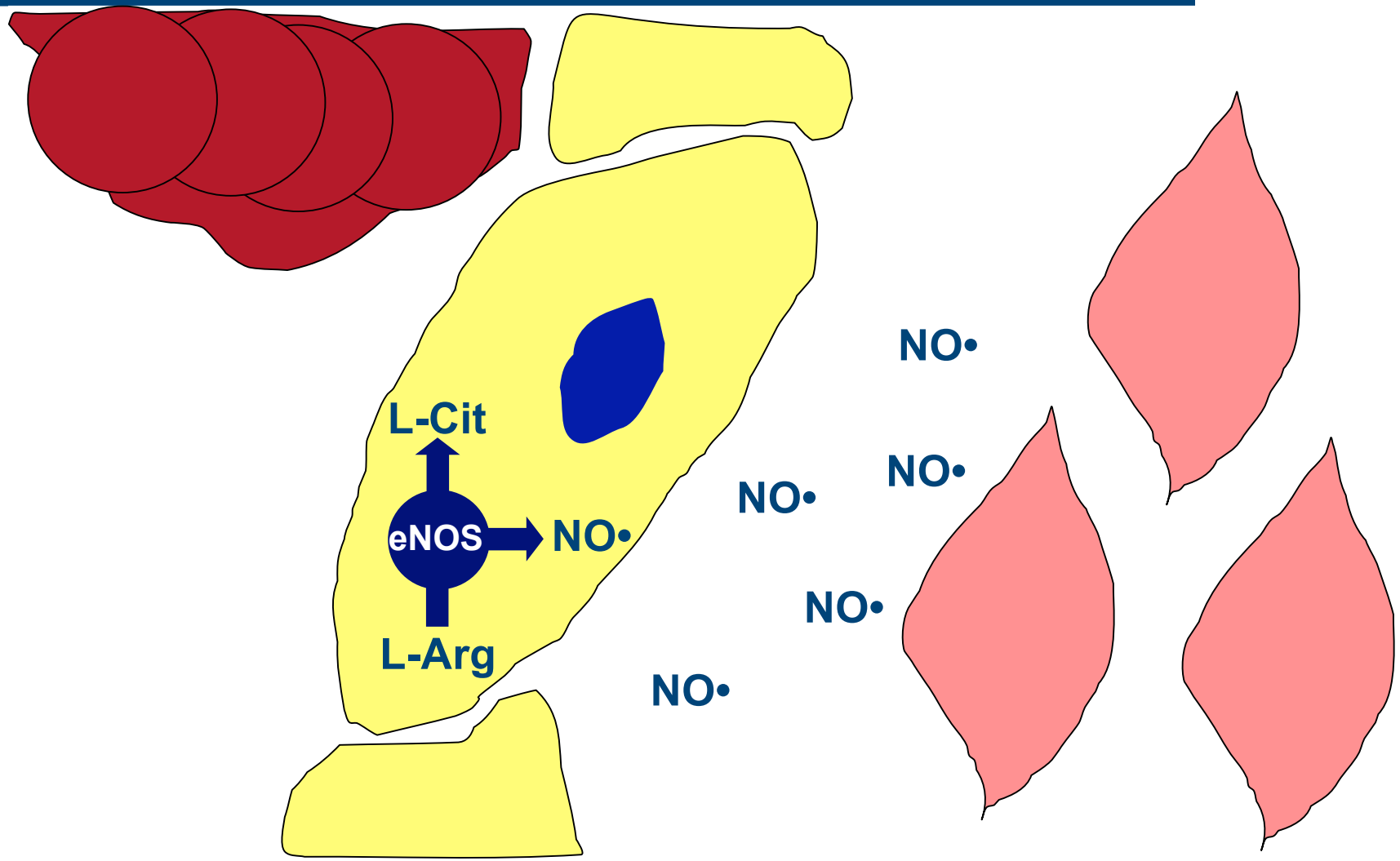
Neurological Stroke



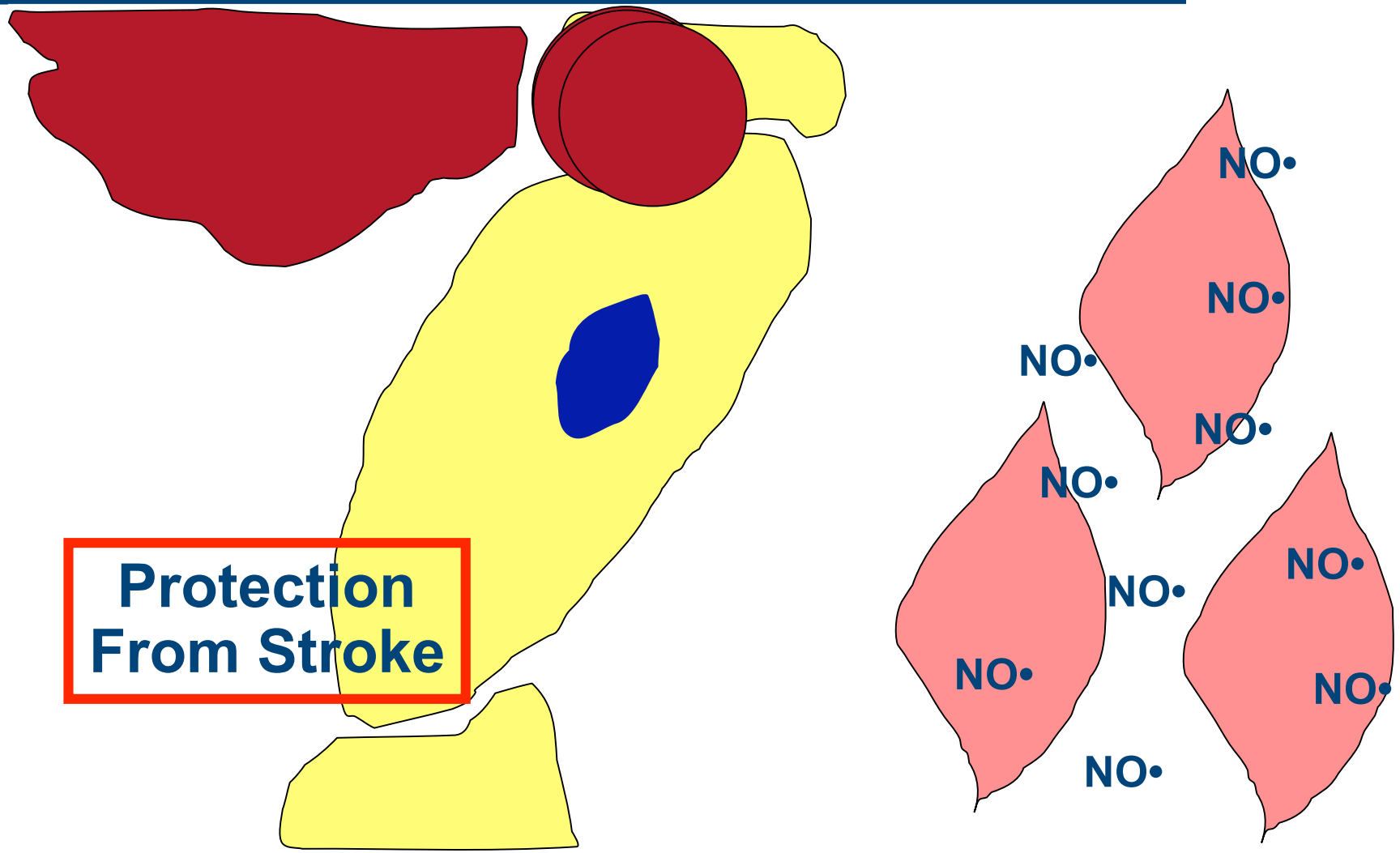




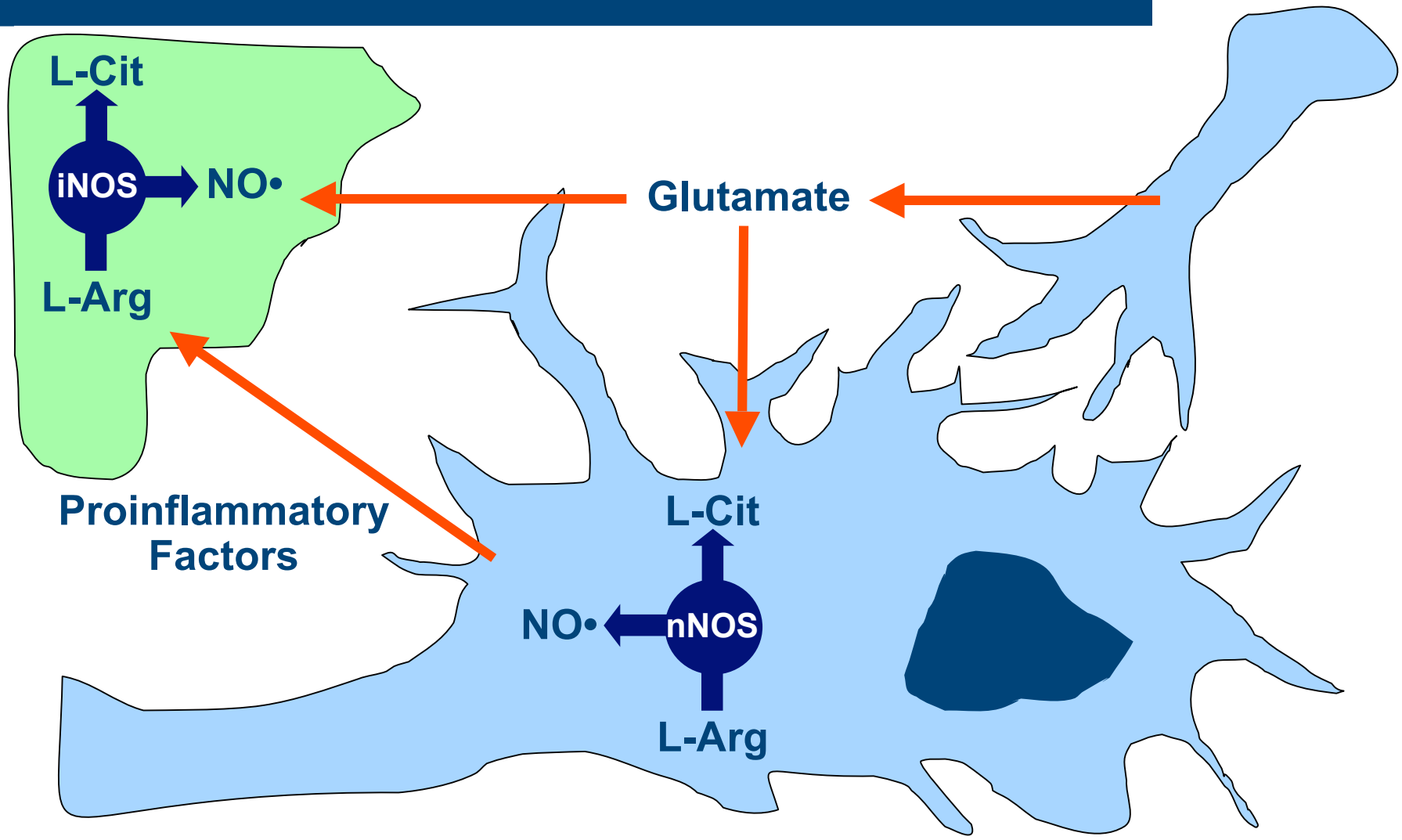
Neurological Stroke



Neurological Stroke



Neurological Stroke



Neurological Stroke

COX

$2O_2 + AA \rightarrow PGG + O_2^-$

Xanthine Oxidase

AMP ⋯▶ Hypoxanthine ⋯▶ O_2^-

NADPH Oxidase

Neutrophils ⋯▶ O_2^-

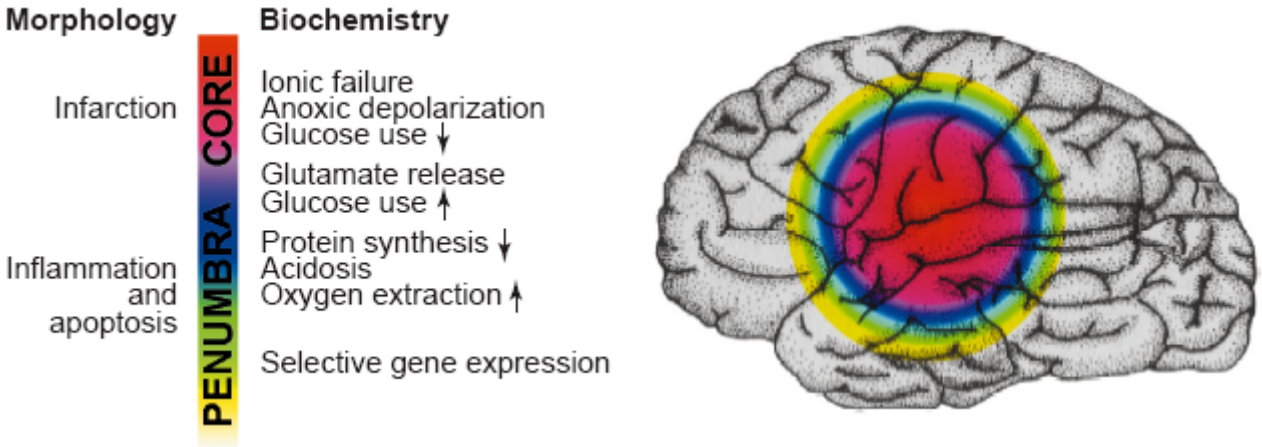
Mitochondria

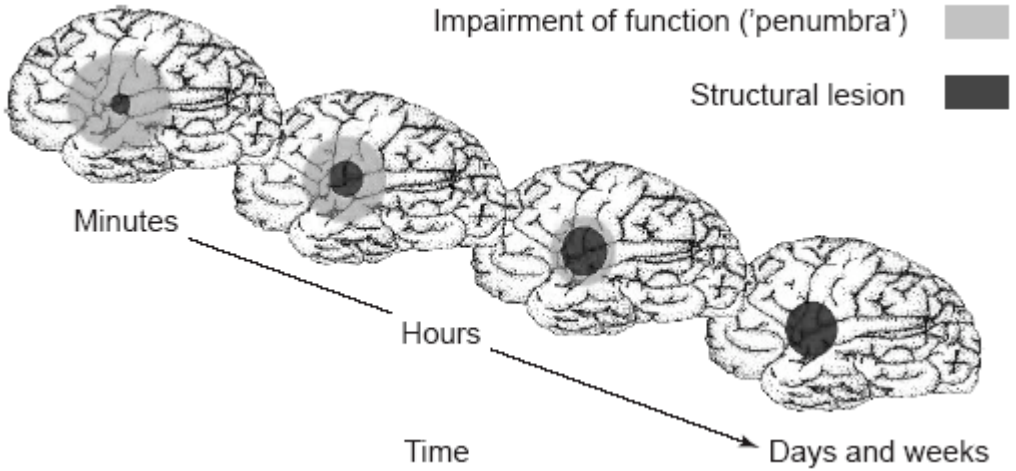
$O_2 + e^- \rightarrow O_2^-$

(and •OH)

Neurological Stroke

Neurological Stroke





Thanks For Your Attention!

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