

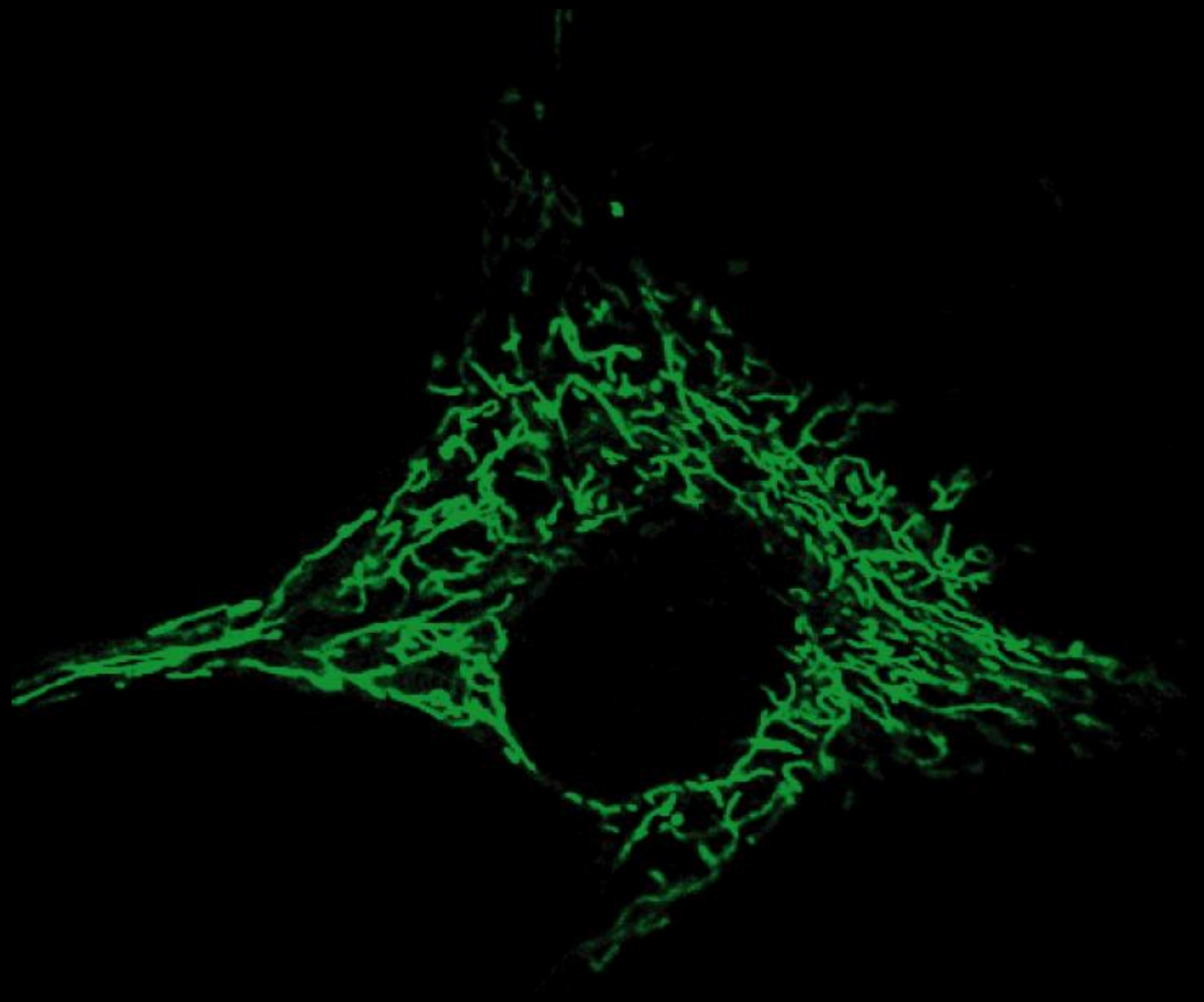
# Targeting therapeutic molecules to mitochondria

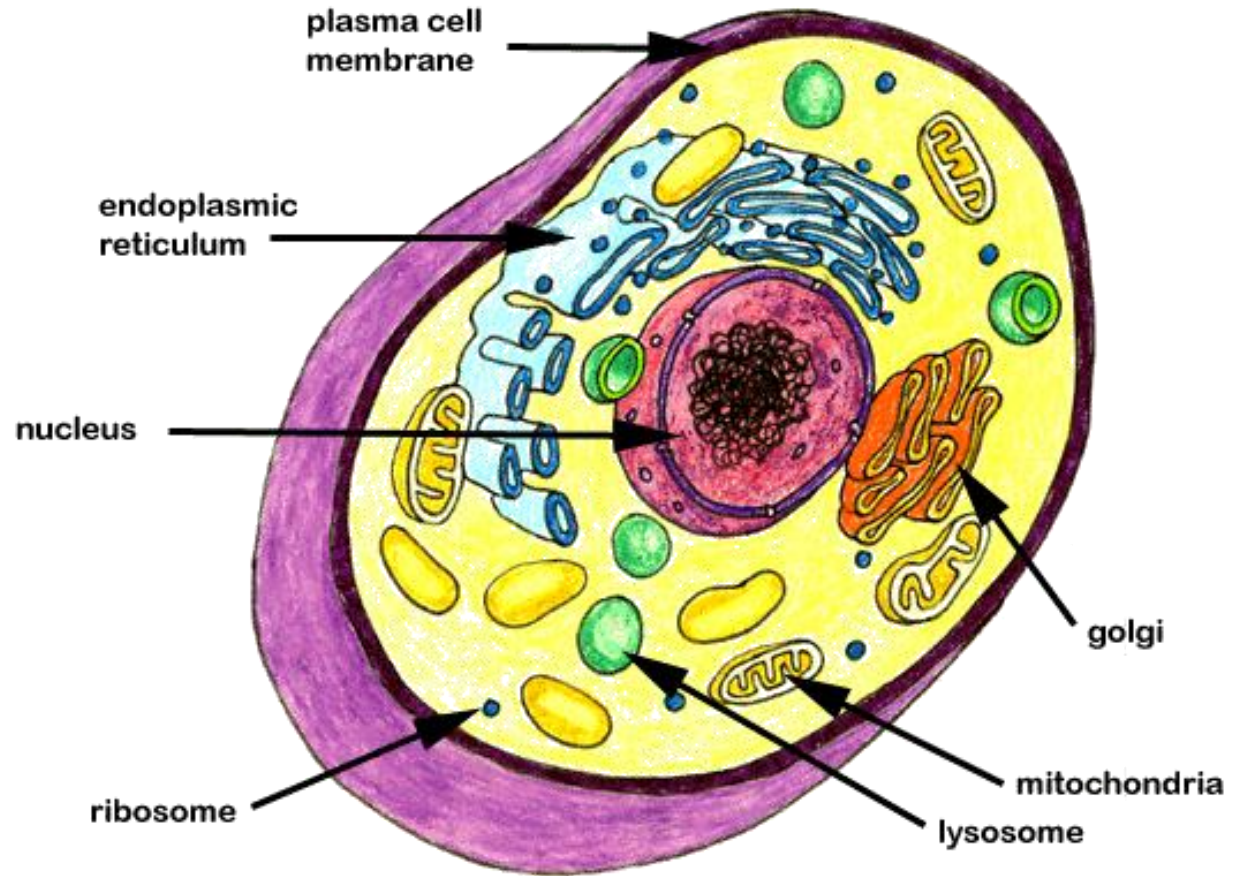
Mike Murphy

MRC Mitochondrial Biology Unit

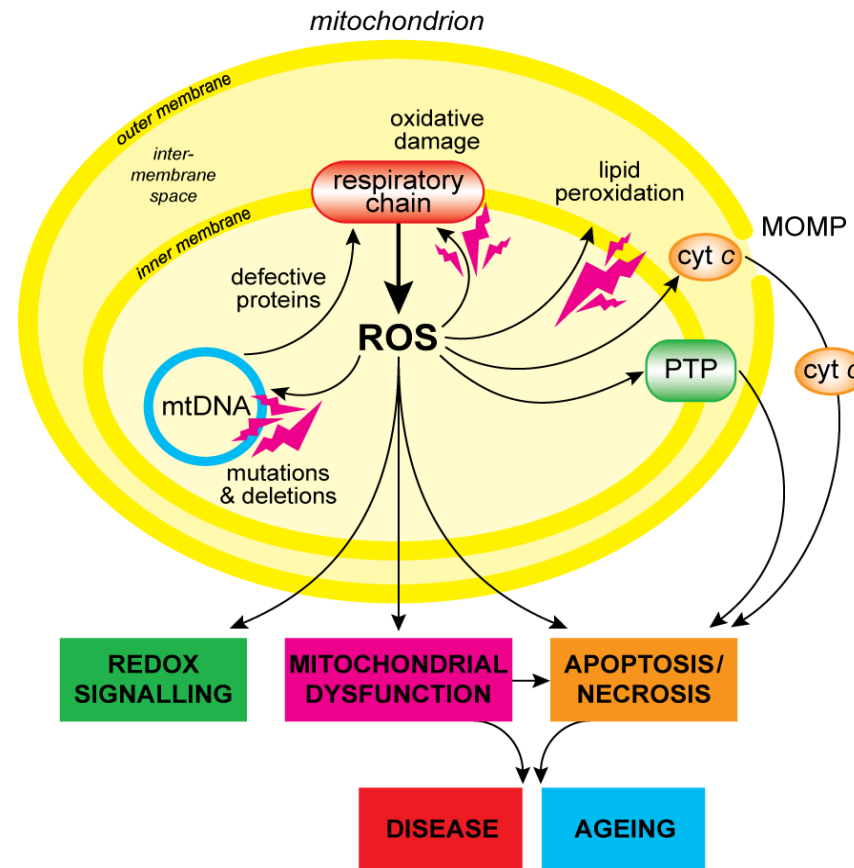
Cambridge

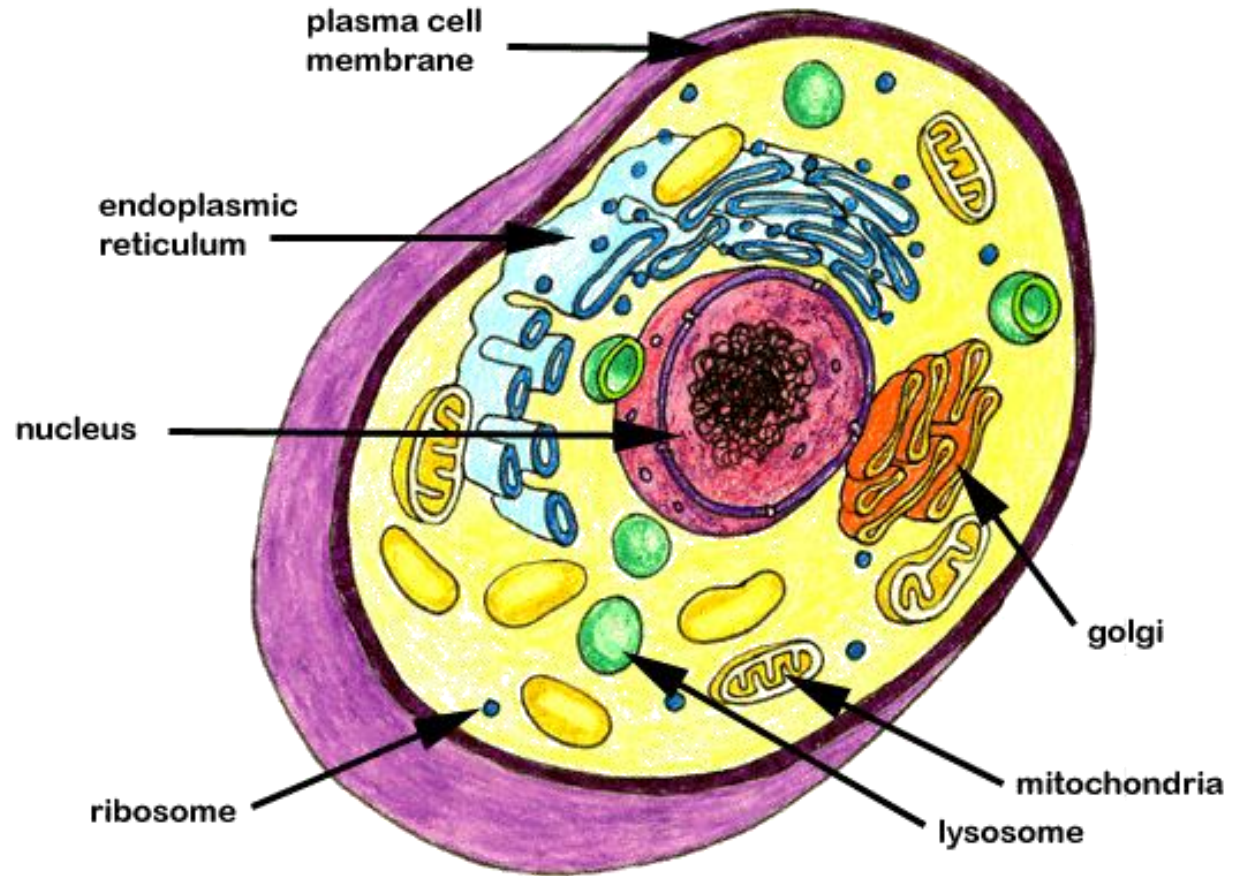


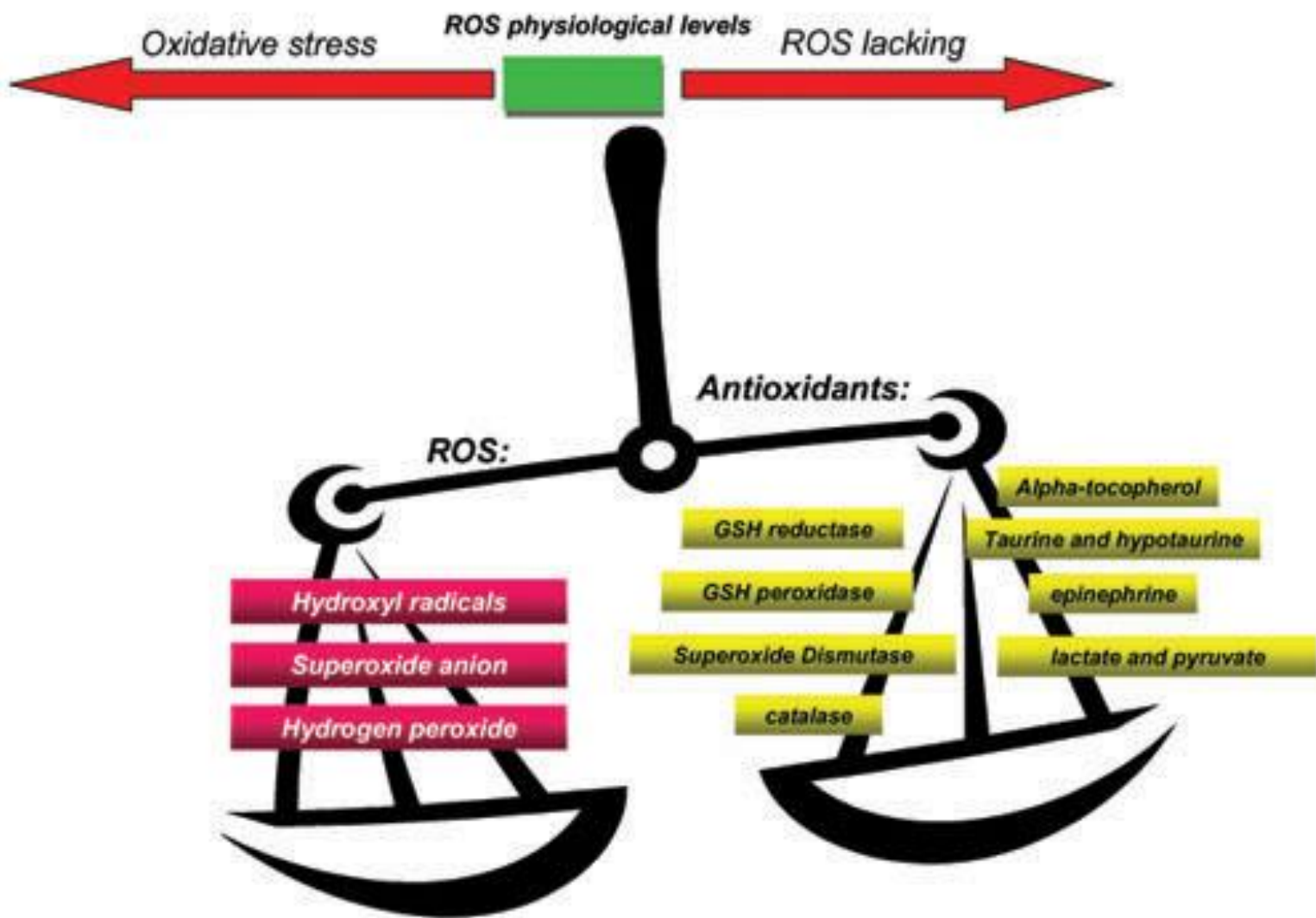




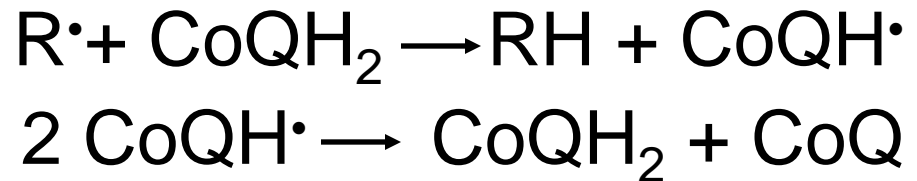
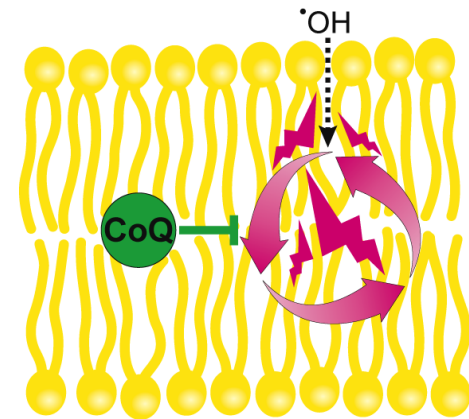
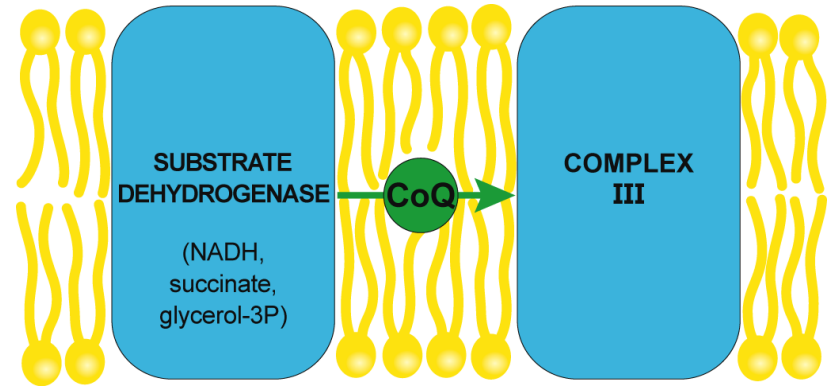
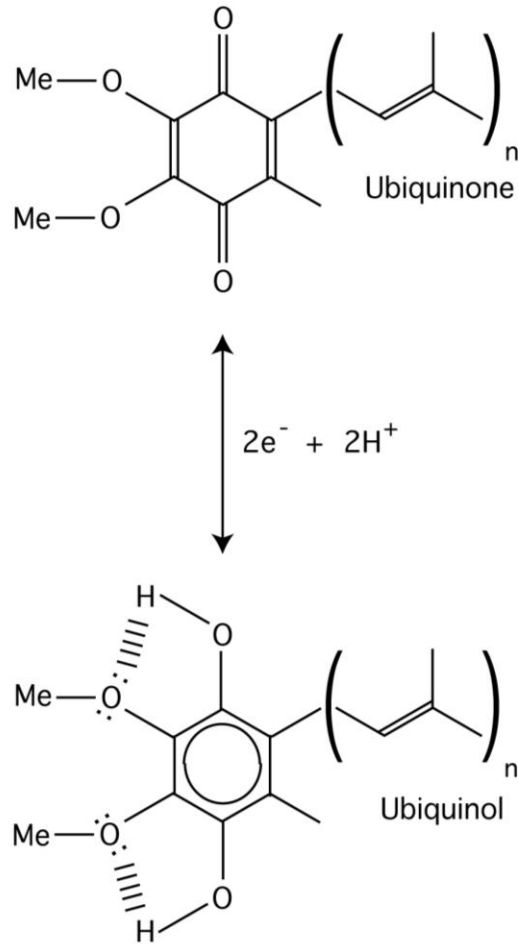
# mitochondrial ROS







# Functions of Coenzyme Q

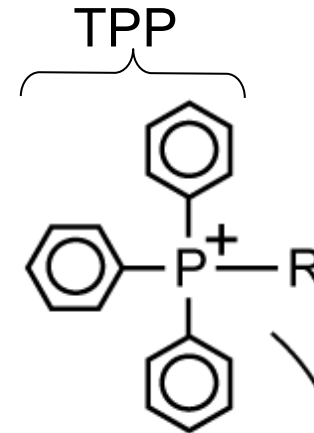


# Why aren't antioxidants effective therapies?

- **Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases.** Bjelakovic G, et al: ***Cochrane Database Syst Rev*** 2008:CD007176.
- **Can antioxidants be effective therapeutics?** Helena M Cochemé & Michael P Murphy ***Current Opinion in Investigational Drugs*** 2010 11:426-431

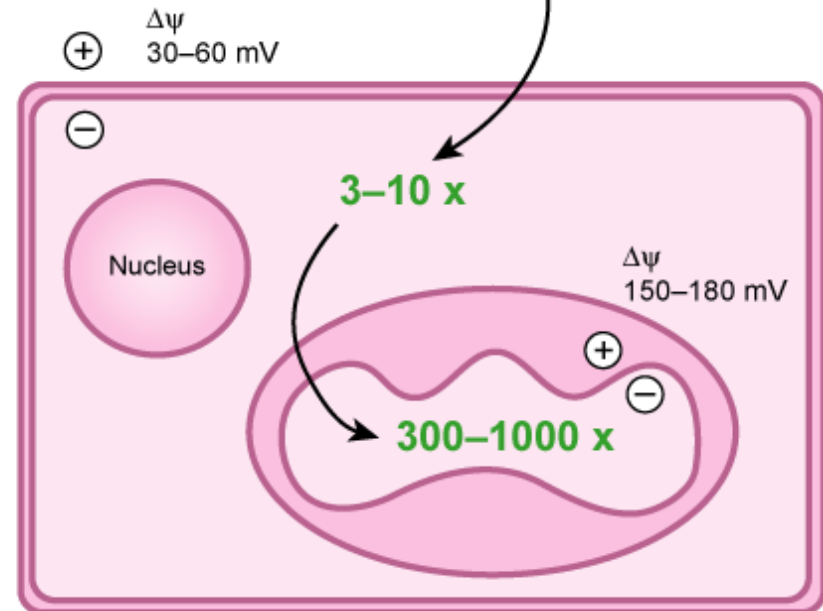
# Targeting to Mitochondria

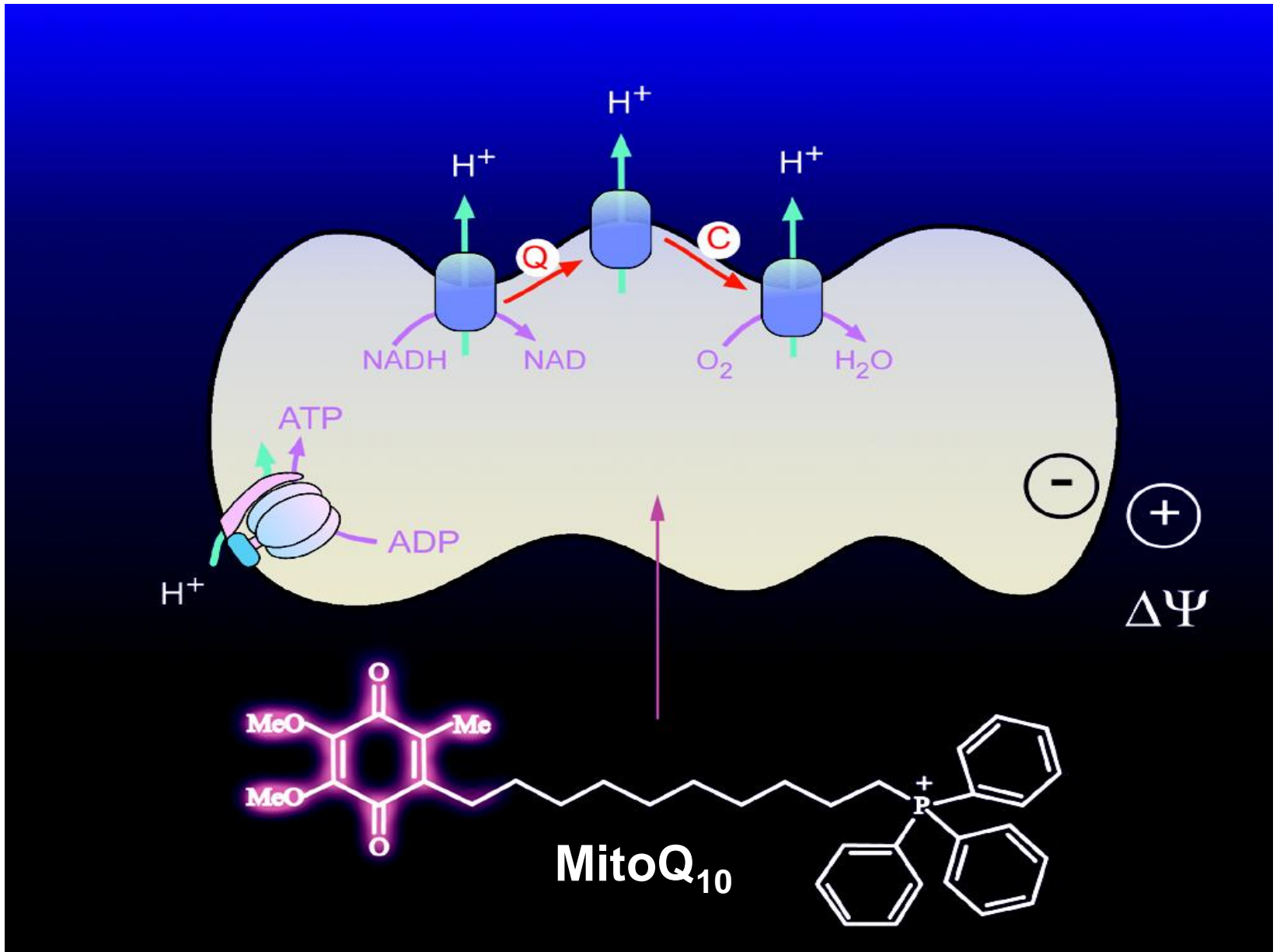
Triphenylphosphonium (TPP) moiety attached to antioxidant compound (R)



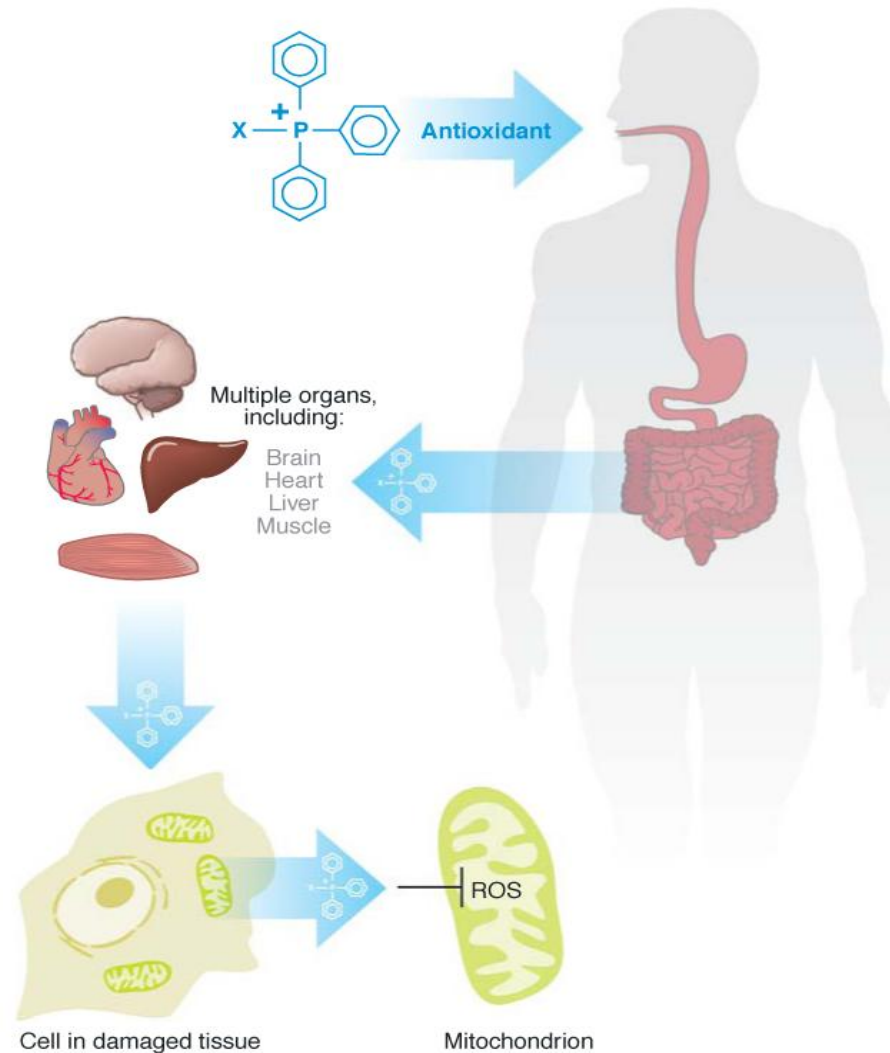
Nernst Equation:

$$\Delta\psi_m \sim 60 \log_{10} \frac{[\text{cation}]_{\text{in}}}{[\text{cation}]_{\text{out}}}$$

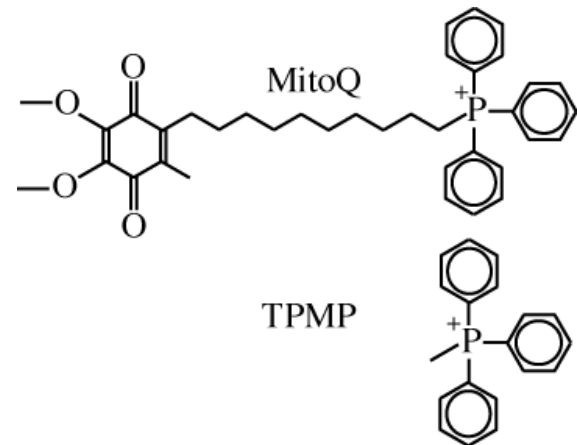
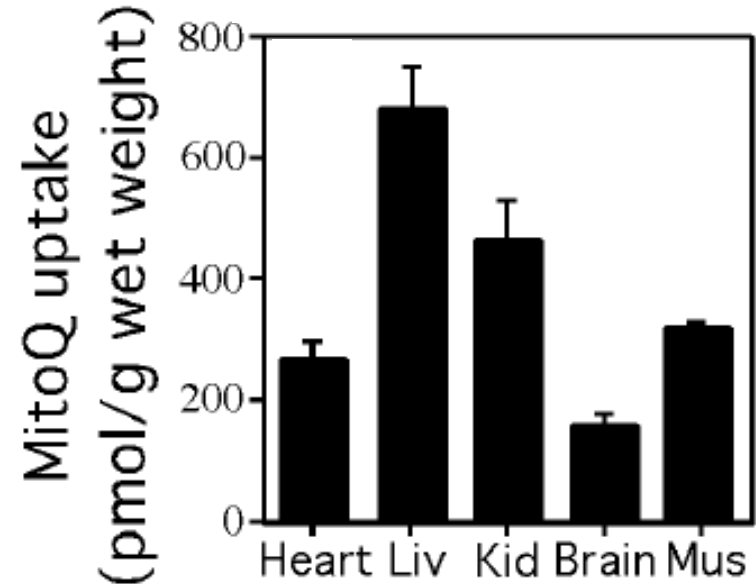
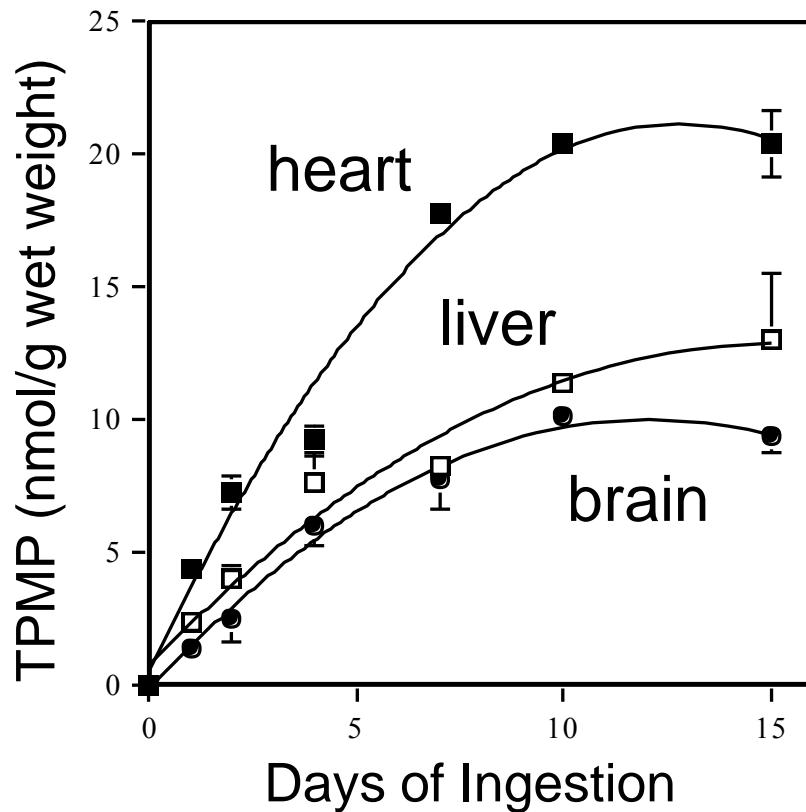




# Targeting Mitochondria *In Vivo*



# Distribution of TPP Compounds in Mice

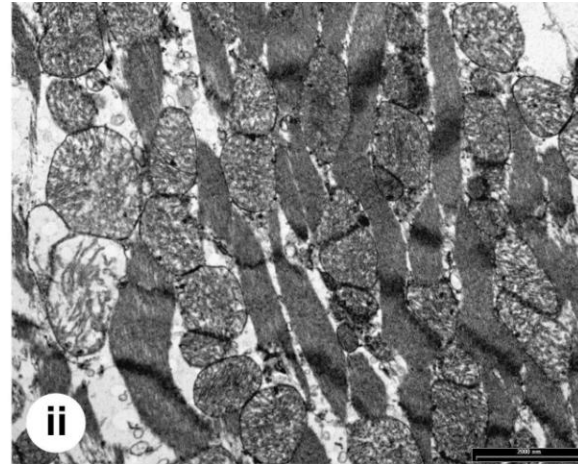
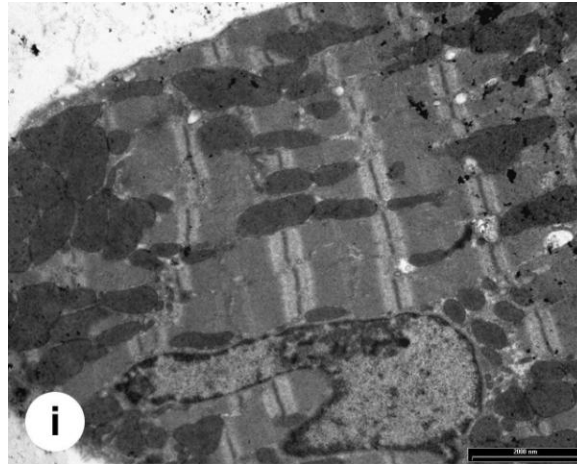


# MitoQ Decreases Heart Ischemia-Reperfusion Damage

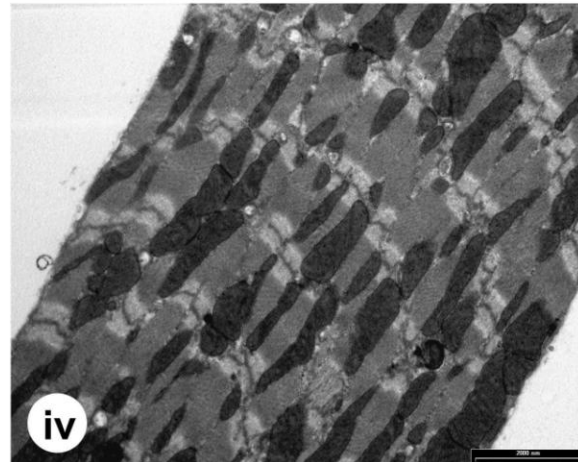
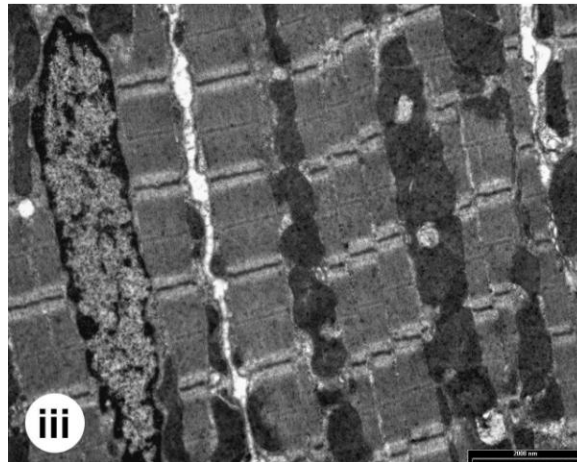
control

ischemia-reperfusion

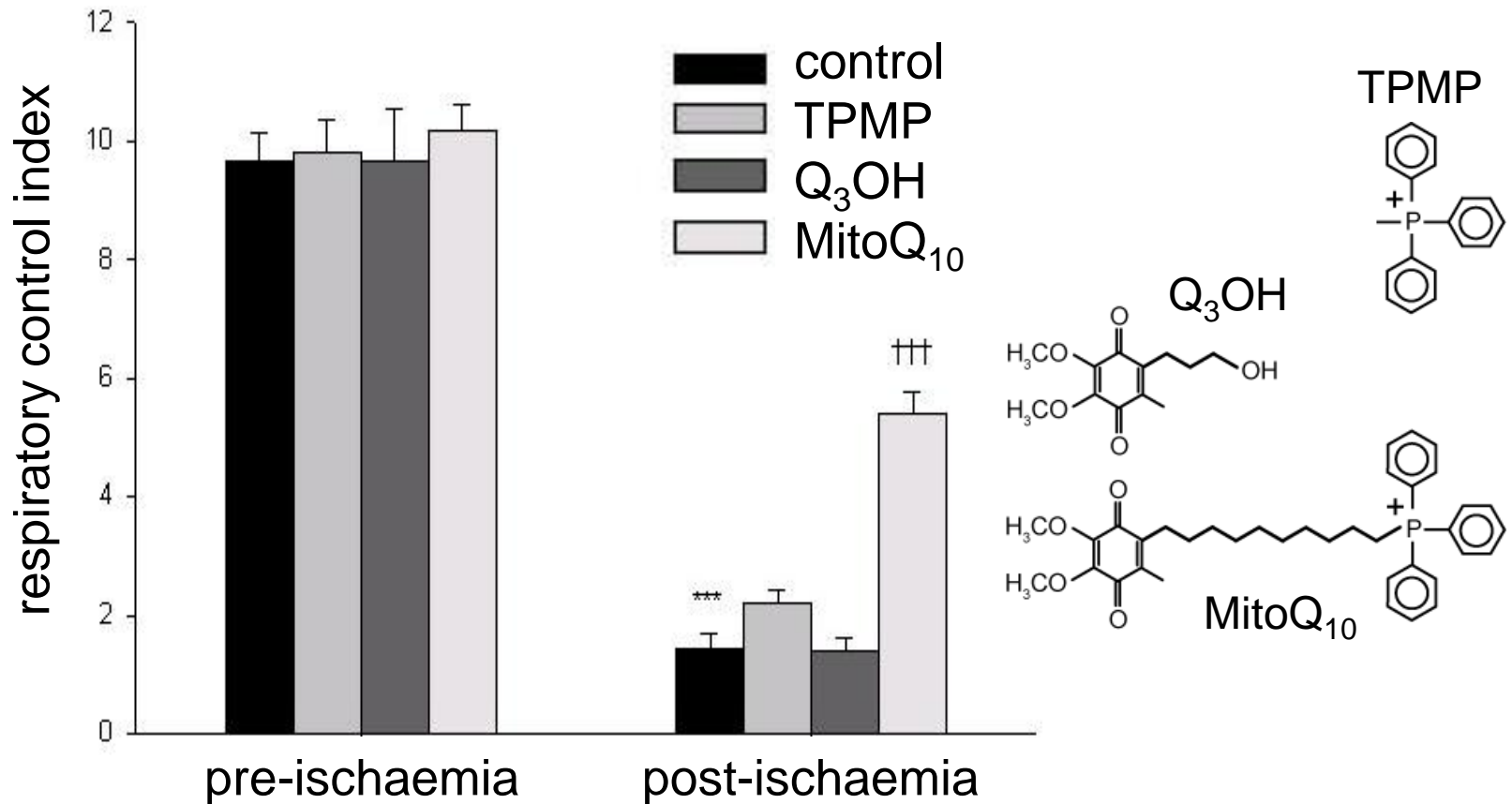
– MitoQ



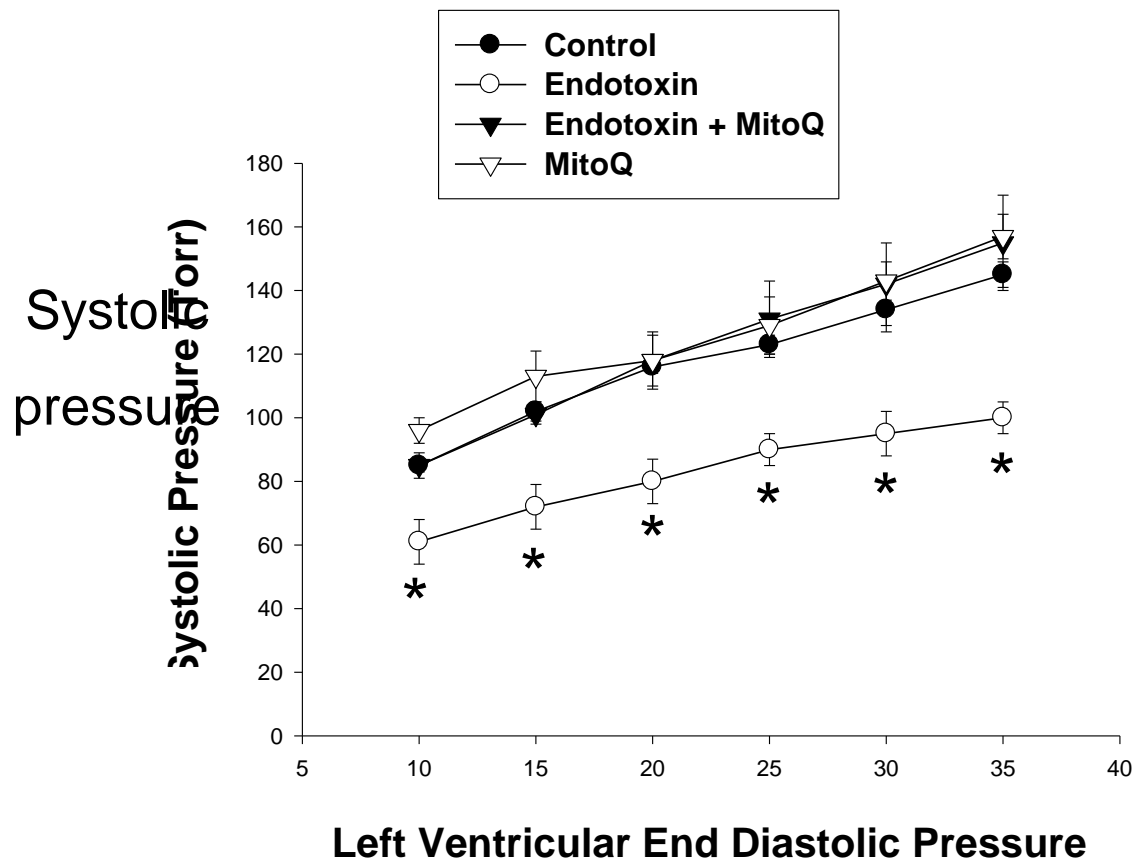
+ MitoQ



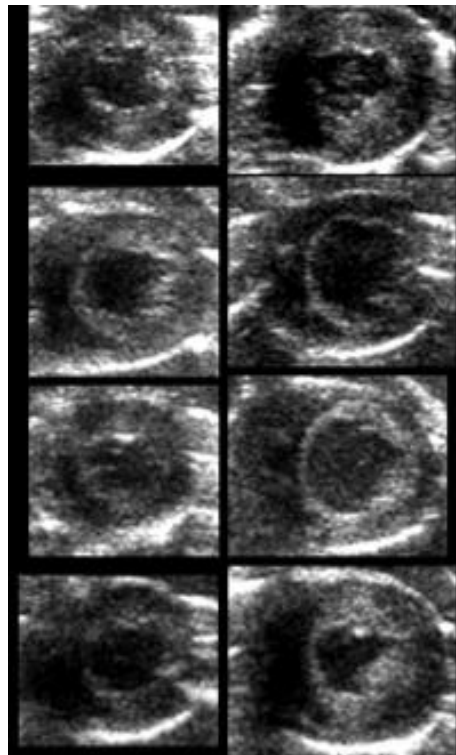
# MitoQ Protects Mitochondrial Function



# Protection against sepsis by MitoQ



# MitoQ protects against doxorubicin cardiotoxicity



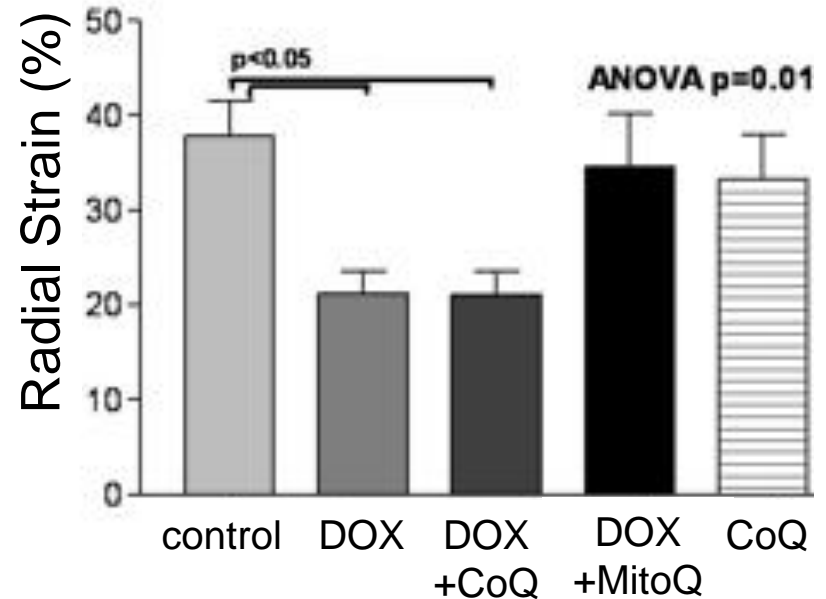
control

DOX

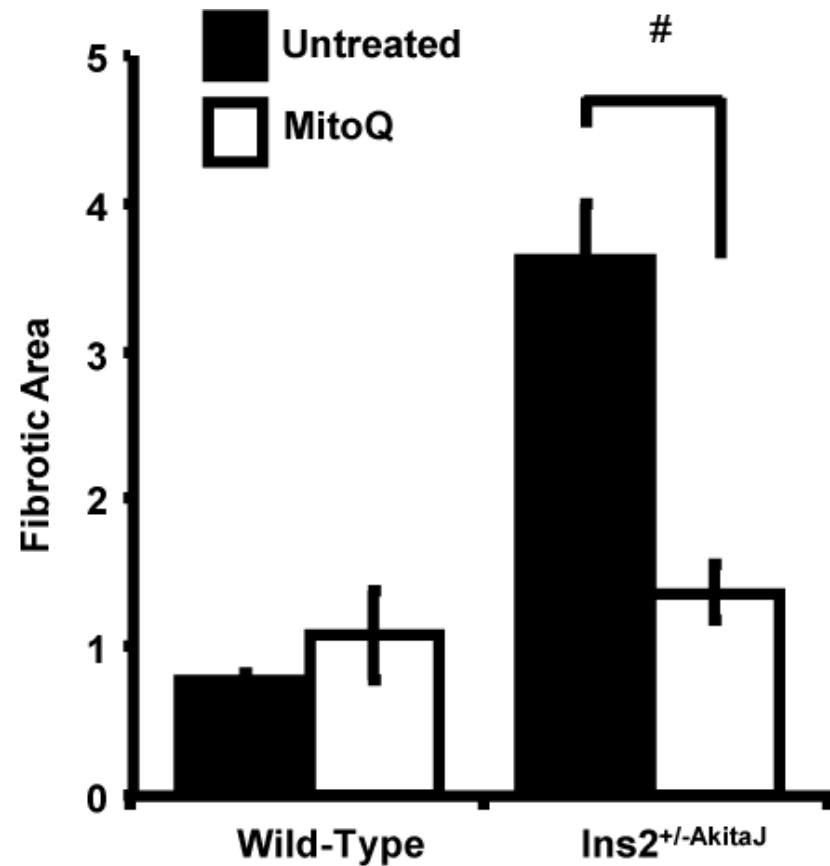
DOX + CoQ

DOX + MitoQ

## Global Radial Strain



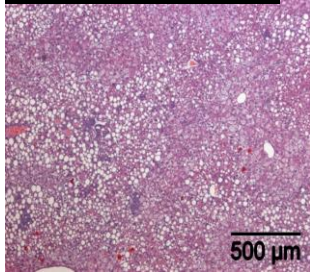
# Protection against diabetic nephropathy in Akita mouse model



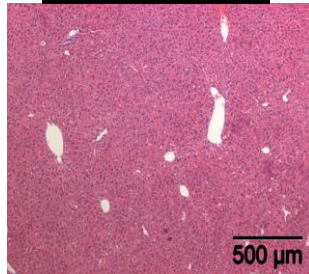
# Protection against fatty liver disease

ATM

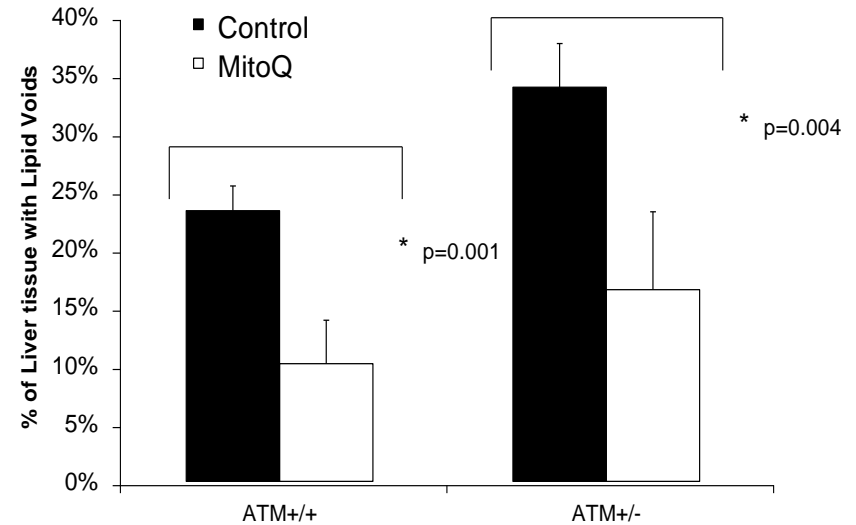
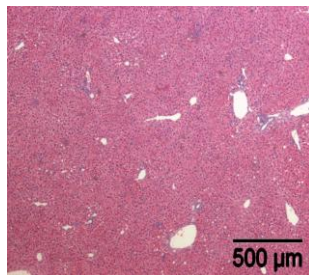
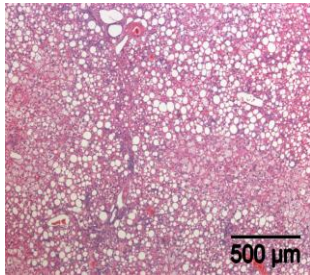
Control



MitoQ

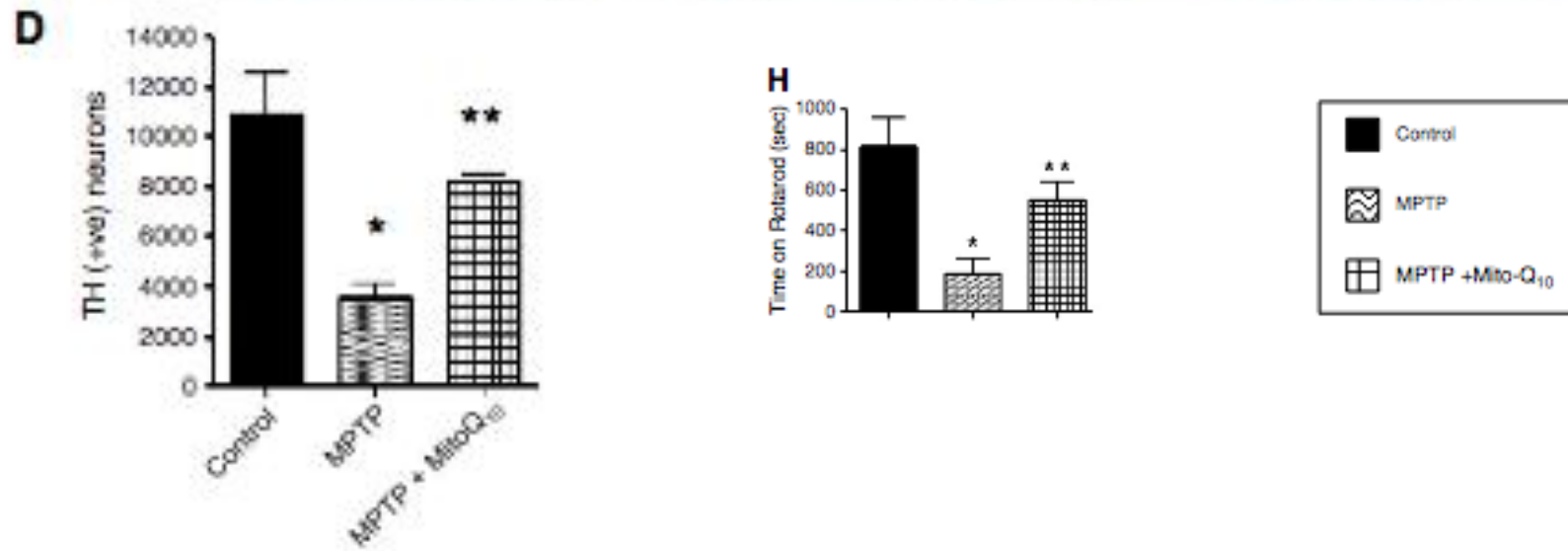
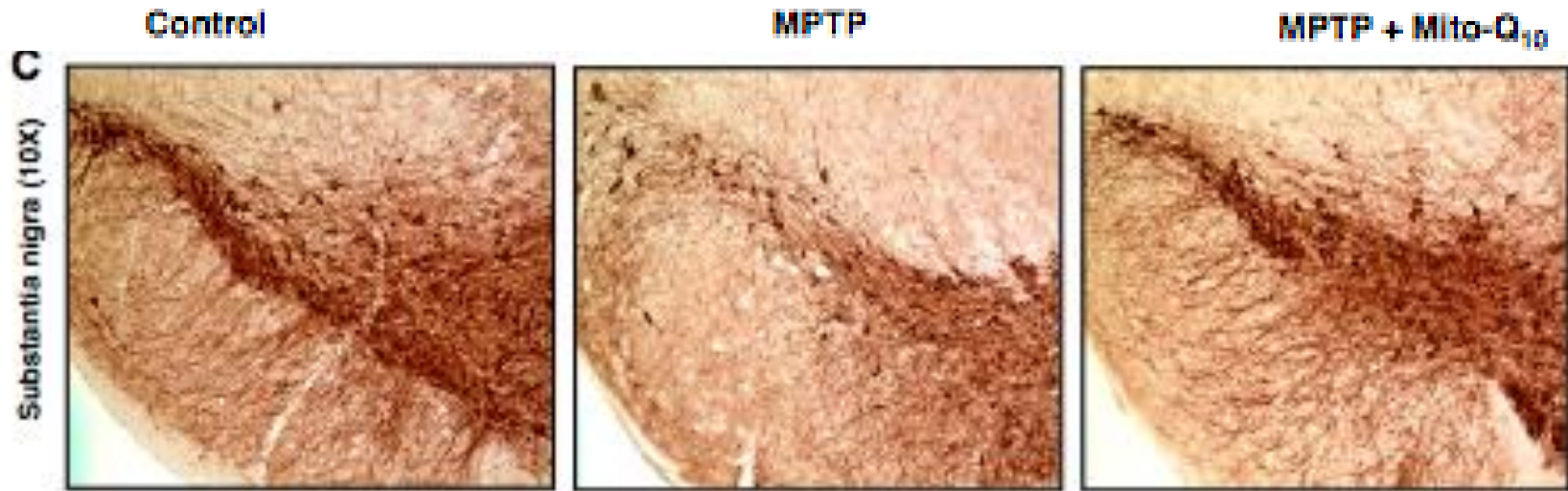


APOE

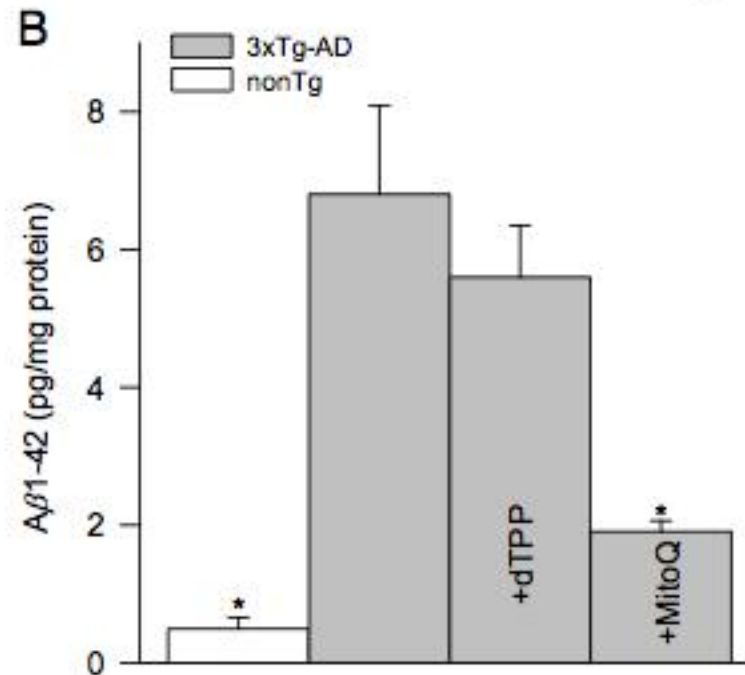
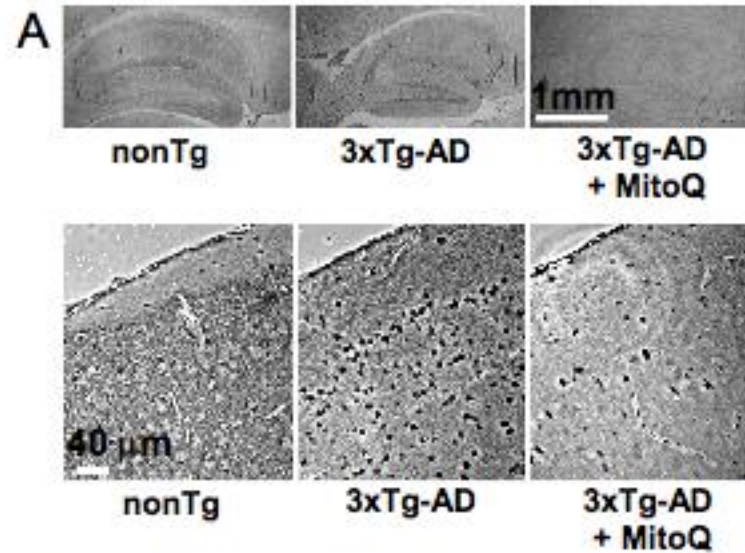


Mercer & Bennett, unpublished

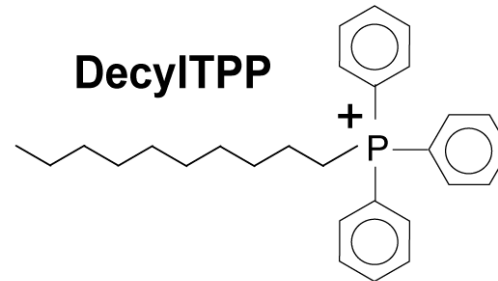
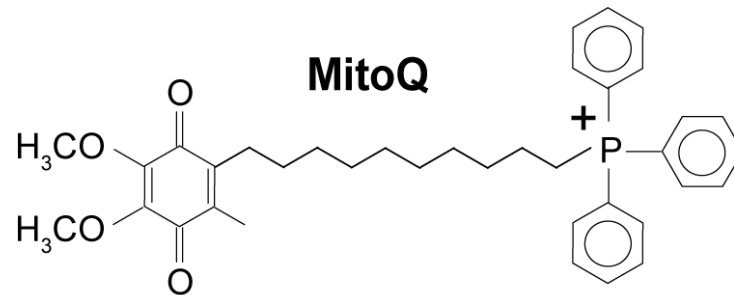
# MitoQ prevents loss of dopaminergic neurons in MPTP model of Parkinson Disease



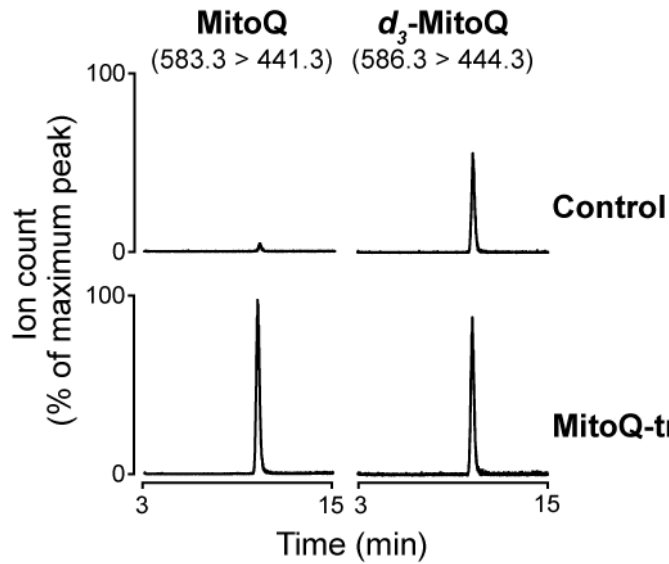
# MitoQ decreases A $\beta$ 1-42 in 3xTg Alzheimer mice



# Control compounds

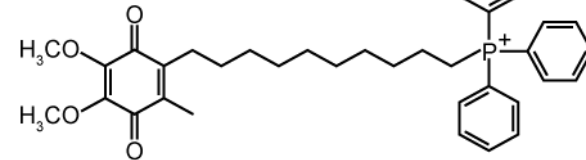


# Measure the compound *in situ*



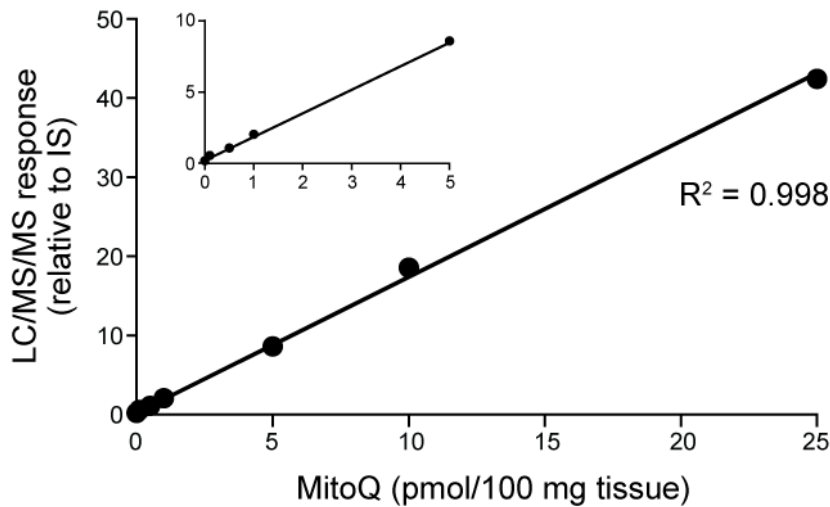
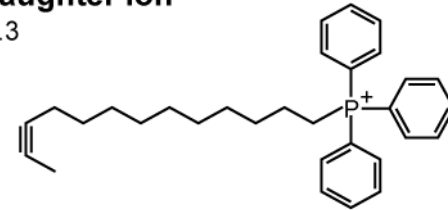
**MitoQ**

$m/z = 583.3$



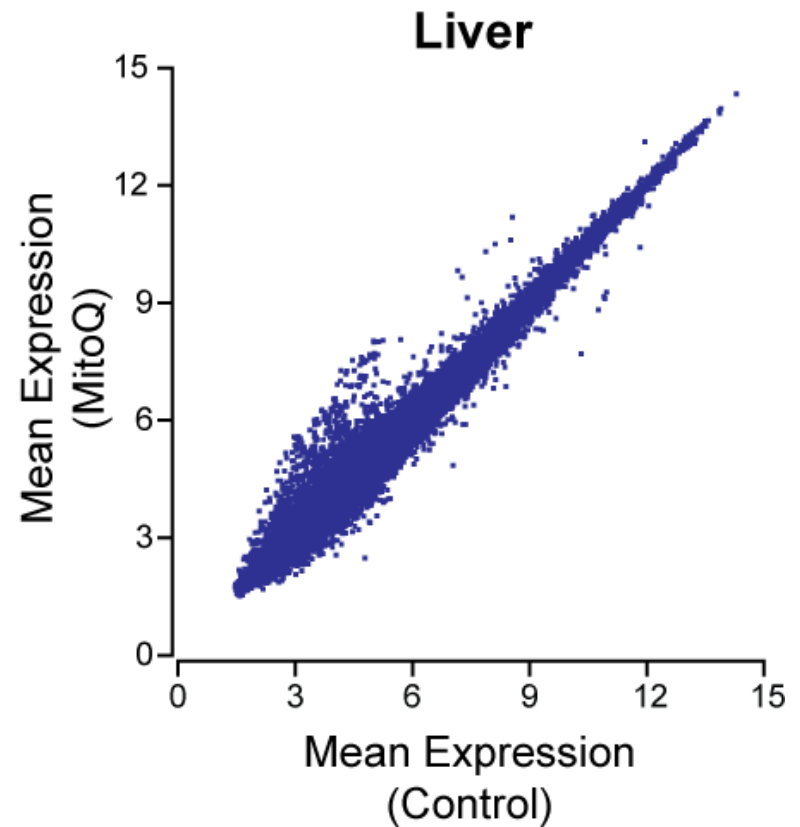
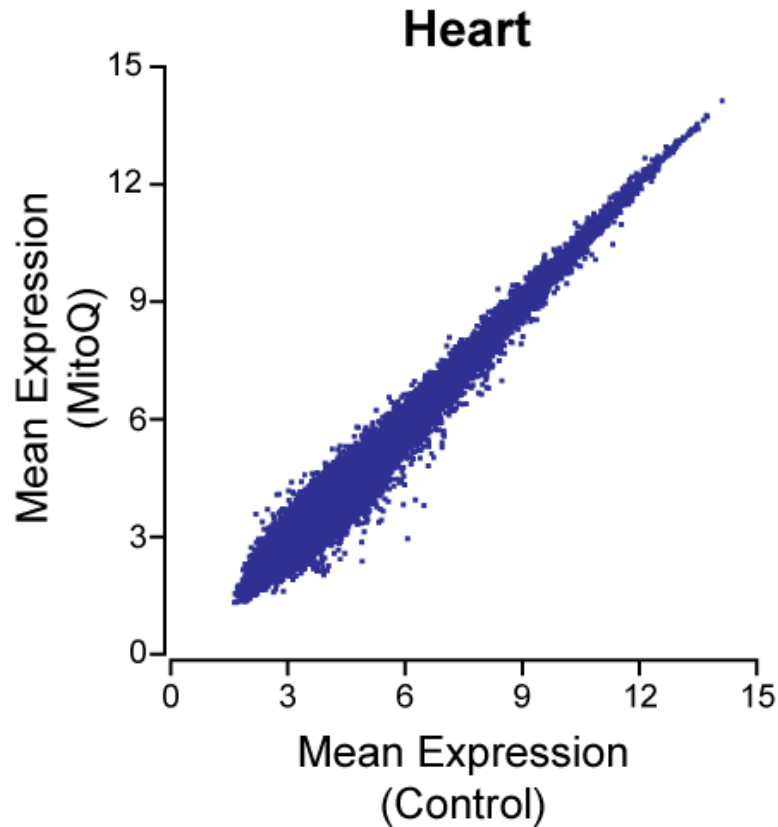
**MitoQ daughter ion**

$m/z = 441.3$



Tissue	MitoQ content (pmol/g)
Liver	20 ± 2
Heart	113 ± 42
Brain	2.3 ± 0.4

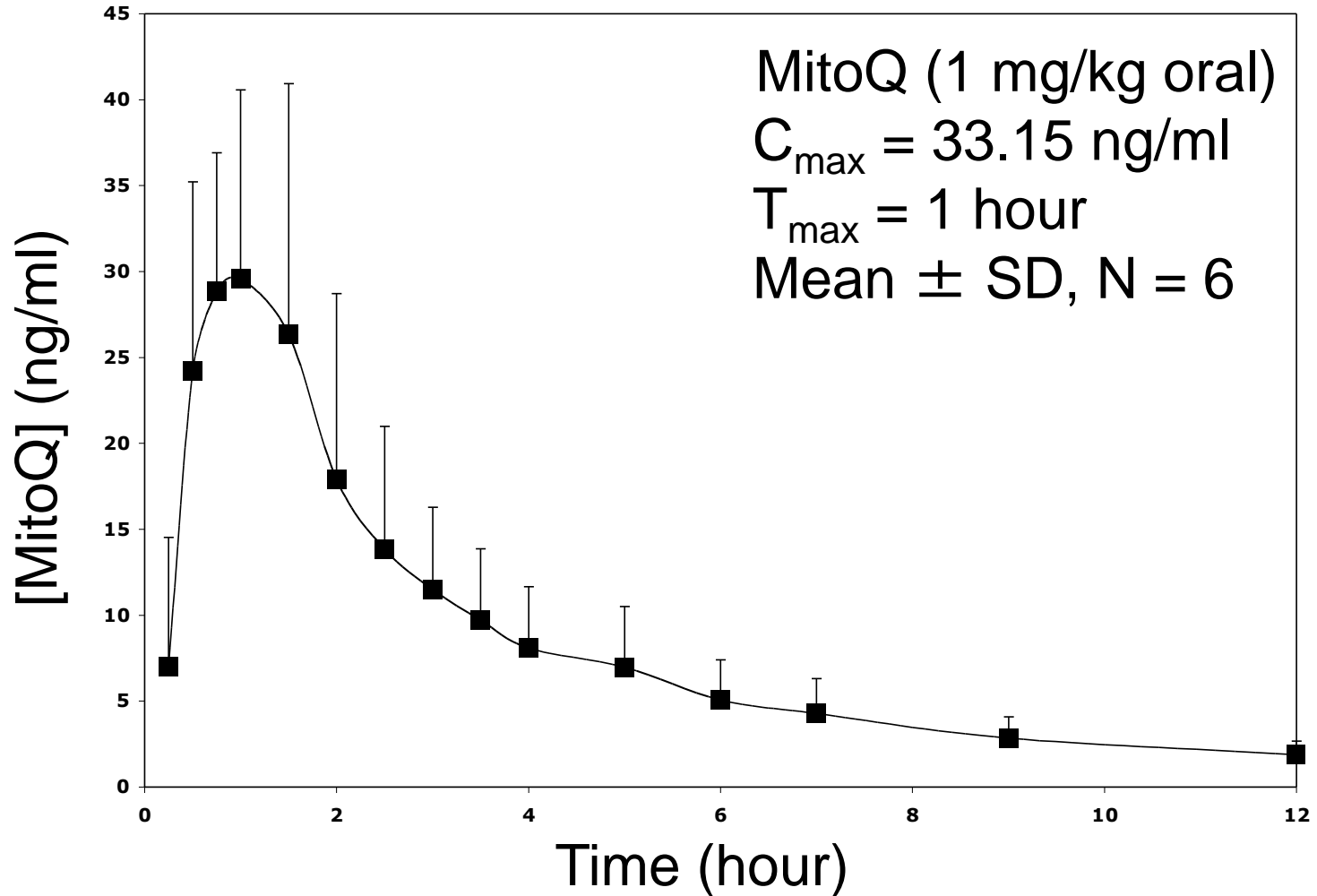
# Negligible effects on gene expression



FRBM (2010) **48** 161- 172

- Affymetrix chip – assessed expression of 28,853 genes  
Liver: 204 changes, heart 19 changes

# Plasma Levels of MitoQ in Human Phase I Study Following Oral Administration



# Phase 2 trials with MitoQ

## • Parkinson's Disease "Protect" trial

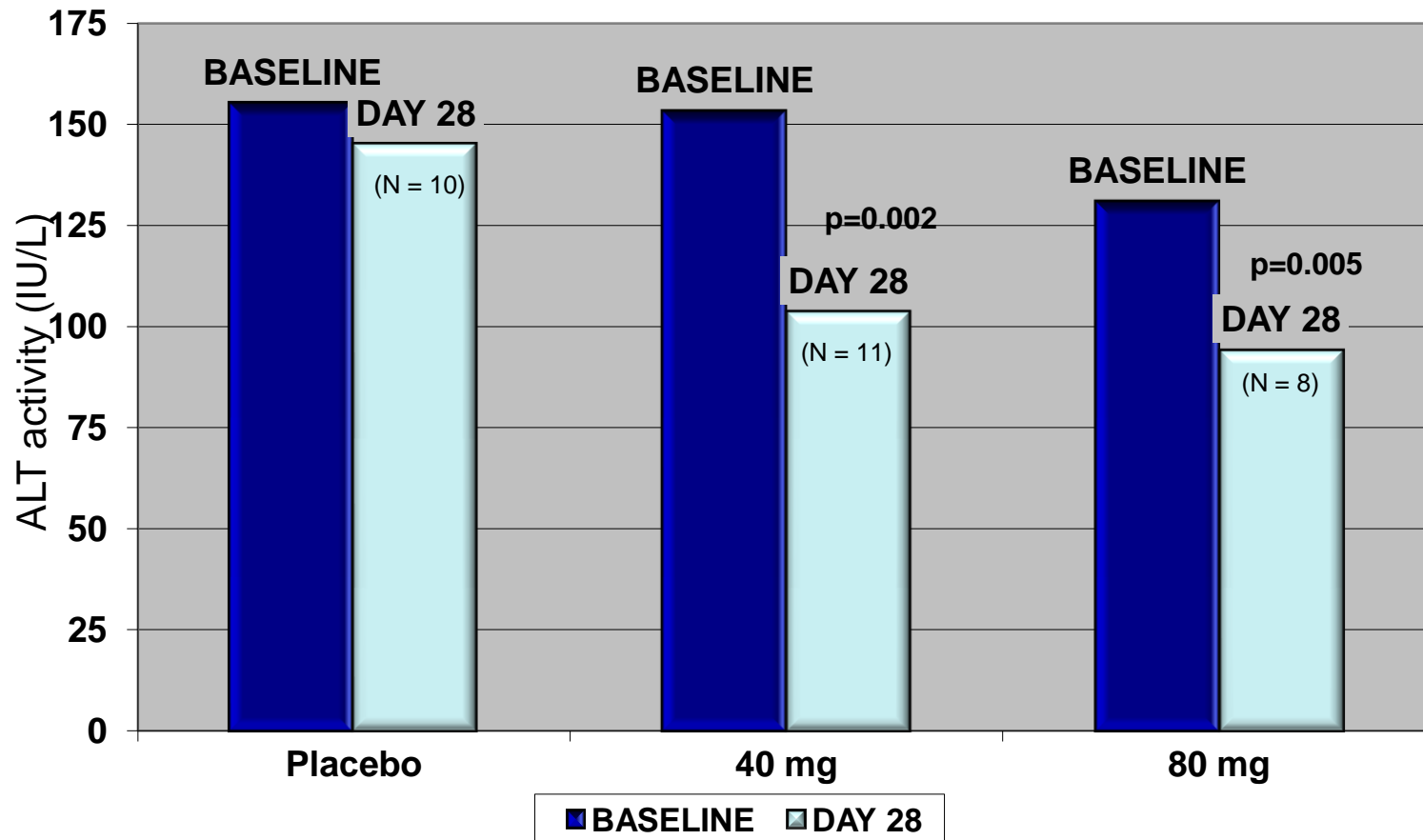
- A double-blind, prospective, randomized comparison of 2 doses of MitoQ
- (40 and 80 mg) and placebo for Parkinson's Disease
- Primary outcome: Unified Parkinson's Disease Rating Scale (UPDRS)
- Multi centre (New Zealand and Australia)

## • Hepatitis C "Clear" trial

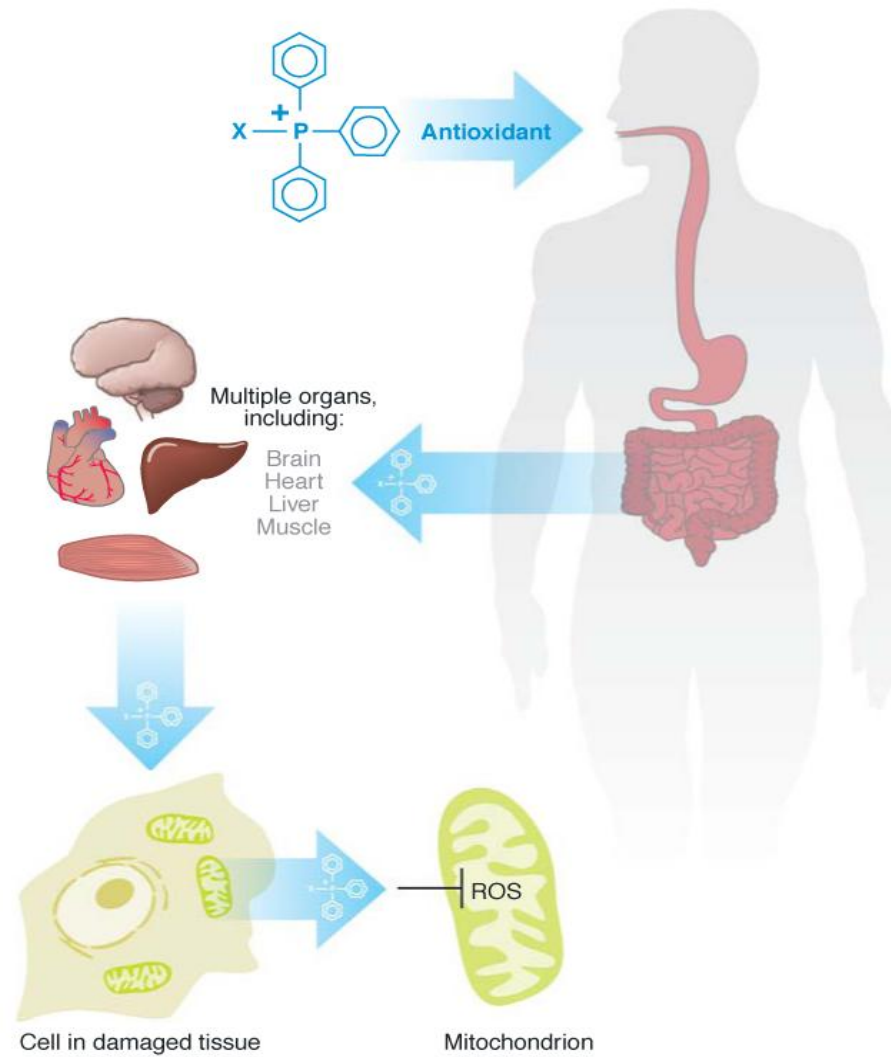
- Phase II clinical trial of MitoQ to reduce liver damage in patients with Hepatitis C virus
- Auckland, NZ.
- A double-blind, prospective, randomized comparison of 2 doses of MitoQ
- (40 and 80 mg) and placebo

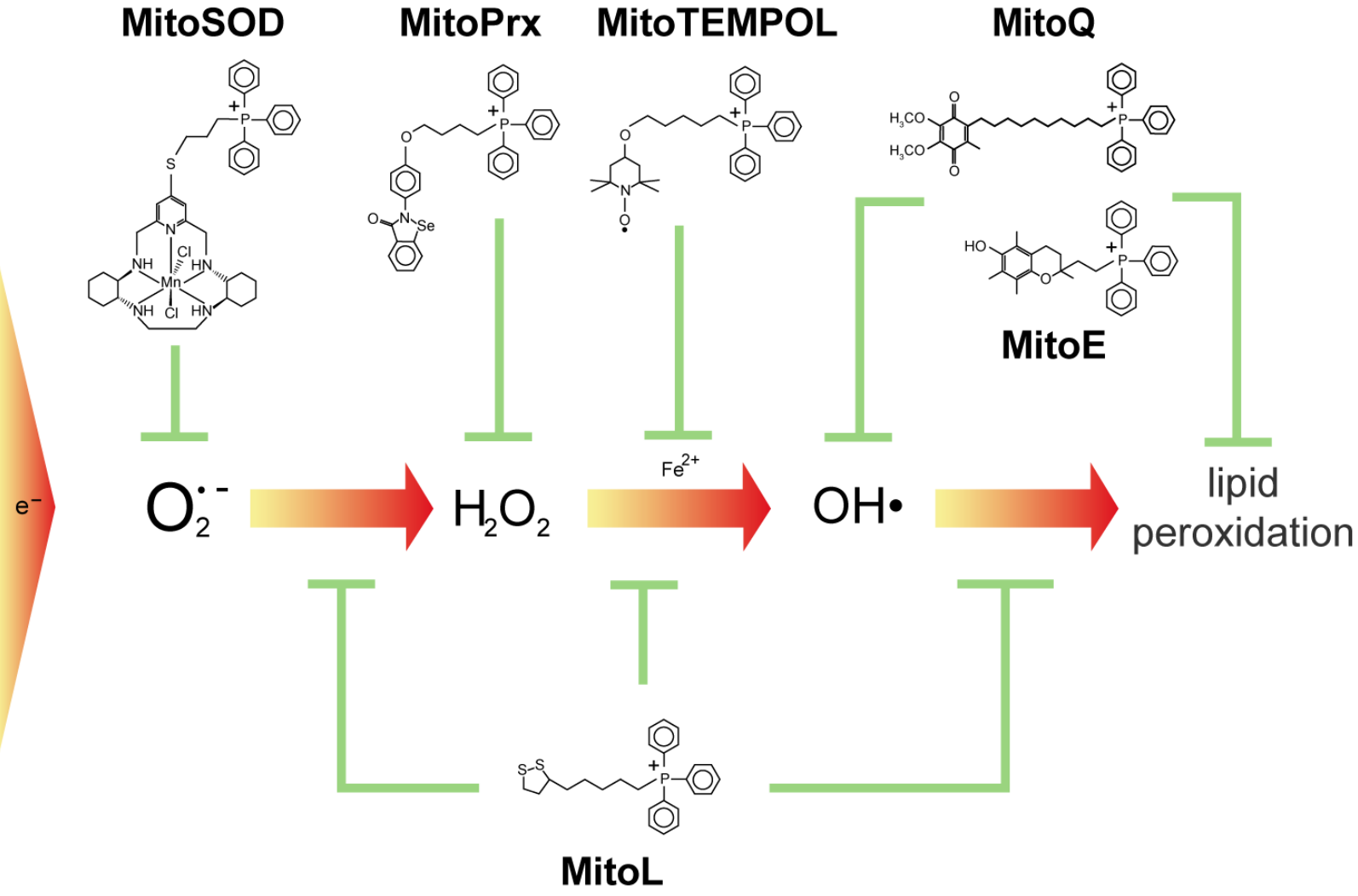
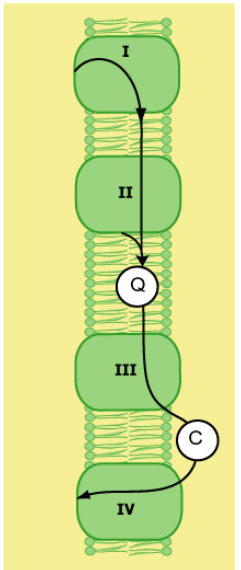
# MitoQ protects the liver in humans

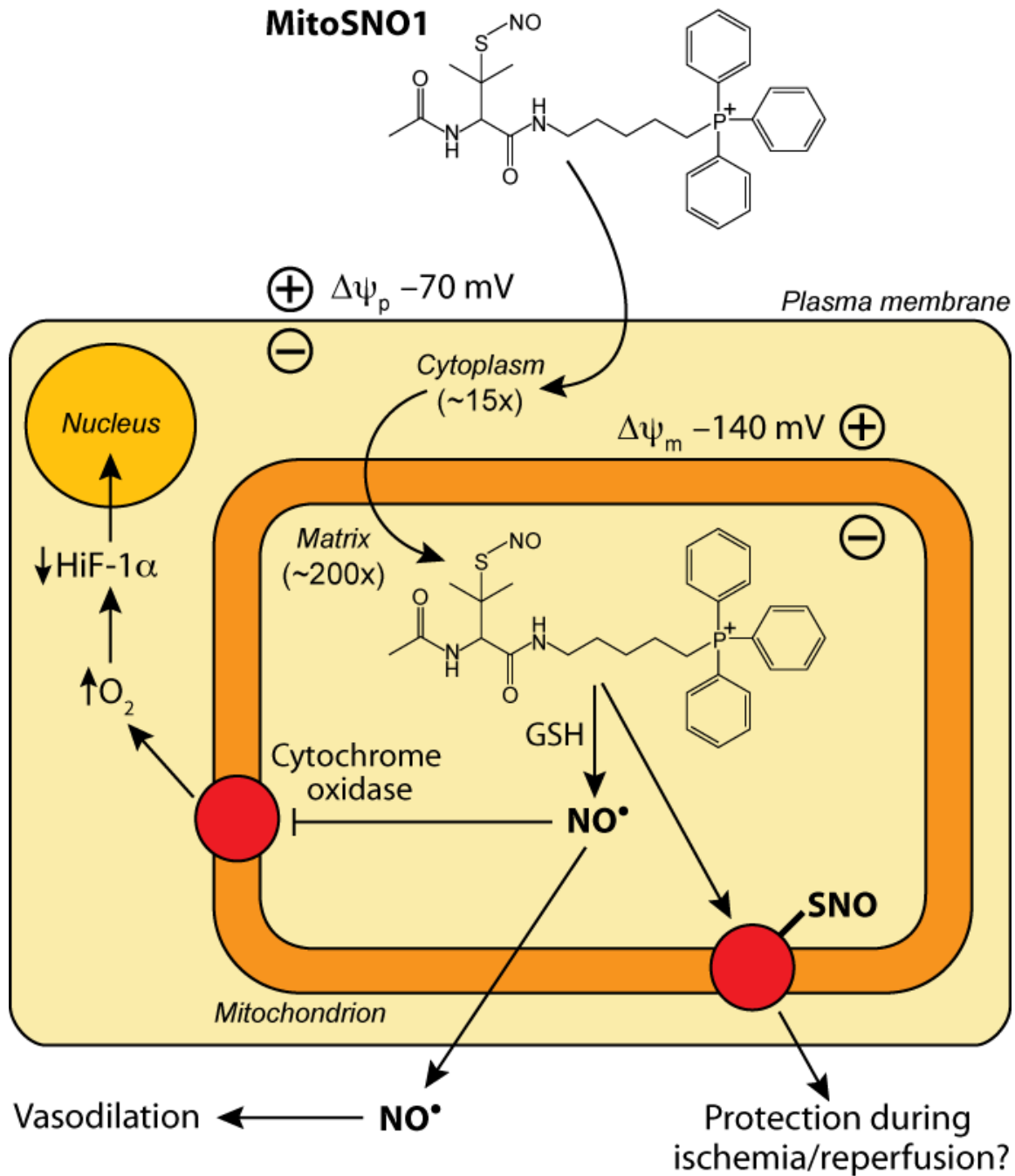
## Change of ALT From Baseline to Day 28



# Targeting Mitochondria *In Vivo*

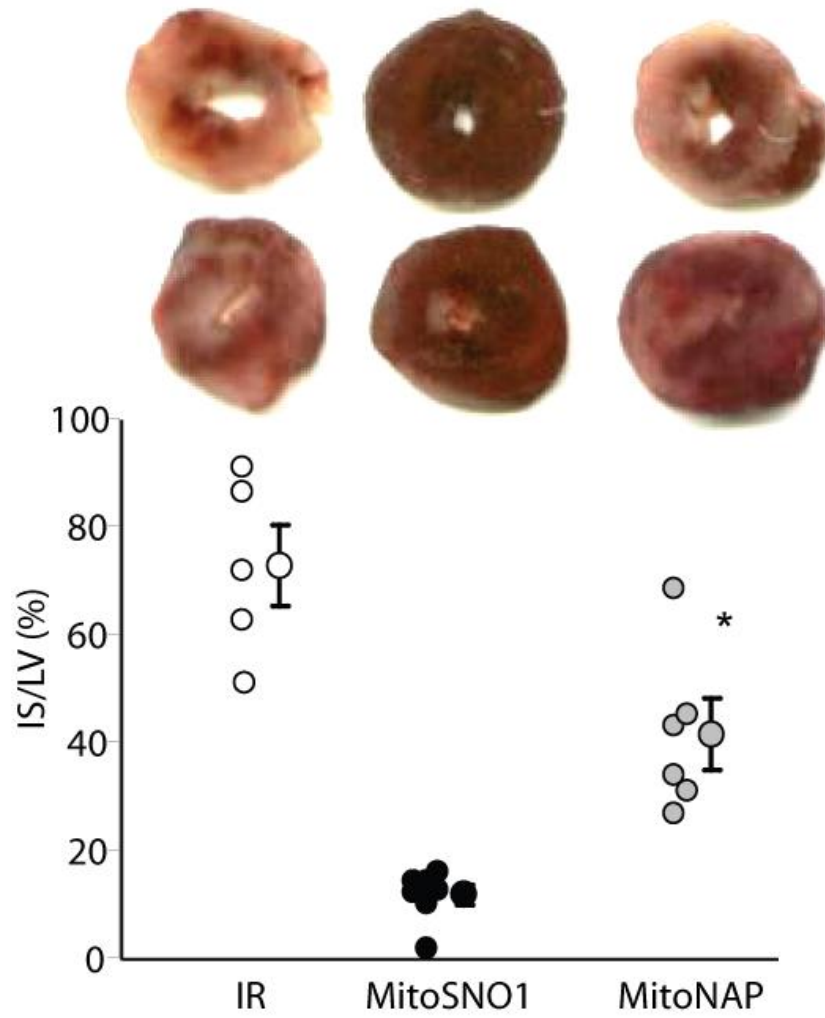




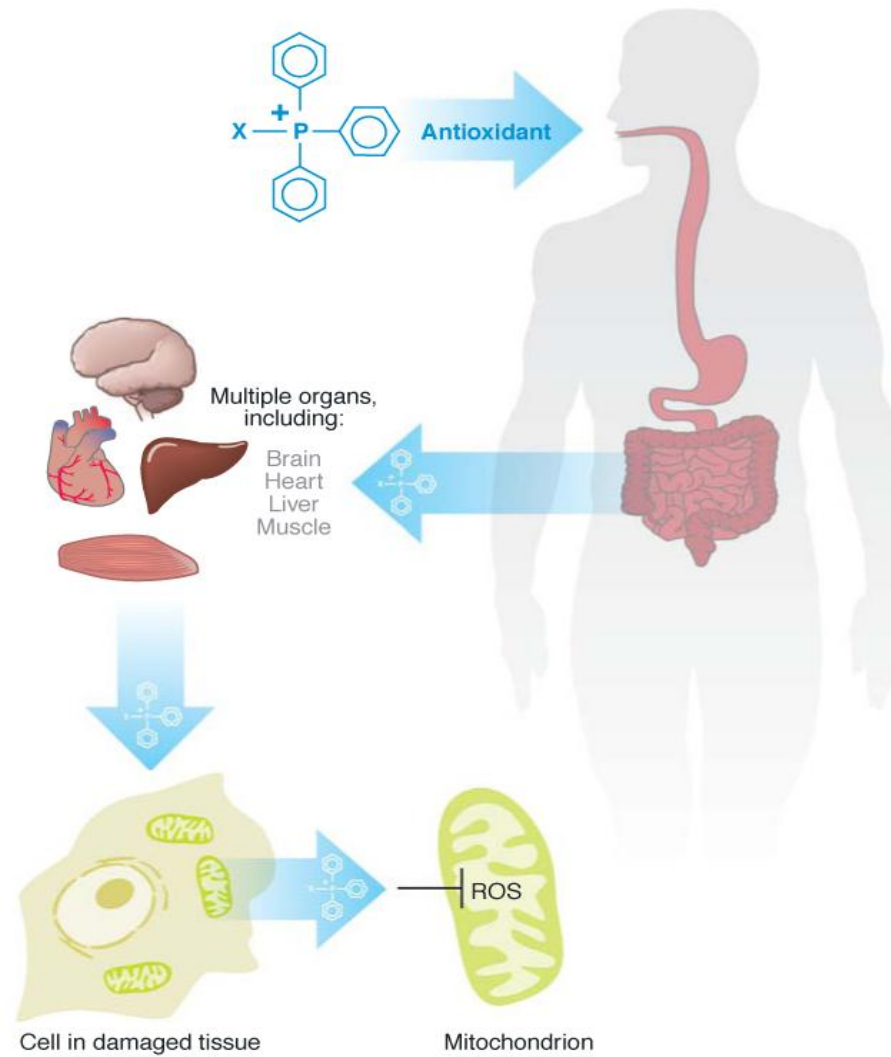


PNAS (2009) 106  
10764-10769

# MitoSNO1 prevents heart damage



# Targeting Mitochondria *In Vivo*



# Acknowledgements

- Otago, NZ
  - Rob Smith
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- London
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  - Linda Partridge
  - Jigna Patel
  - Mervyn Singer
  - Saima Saeed
  - Jane Carré
  - David Gems
  - Filipe Cabreiro

# Disclosure

*I consult for Antipodean Pharmaceuticals Inc and I hold stock in the company*