Mechanism and modeling of particle-induced inflammation

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What's the bad stuff in the San Joaquin Valley?

"Ions" - Free Radicals, Ozone, Nitrogen Dioxide

What is a free radical?

Free radicals

- A free radical is a molecule that has an unpaired electron.
- This tends to make it more likely to react with other molecules.
- Nitrogen dioxide, the brown gas you see when you fly into LAX, is a free radical.

Free radicals

- Free radicals and other reactive molecules are produced by interactions of particles with compounds found in the lining fluid of the lung
- They are also produced by cells, particularly the cells that are supposed to protect us from infection.
- We will return to this later.

But not all the pollutants are free radicals

What's the bad stuff in the San Joaquin Valley?

"Ions" - Free Radicals, Ozone, Nitrogen Dioxide

"Tires" - Diesel Exhaust, Road Dust

What's the bad stuff in the San Joaquin Valley?

"Ions" - Free Radicals, Ozone, Nitrogen Dioxide

"Tires" - Diesel Exhaust, Road Dust

"Flares" - Fires

Research Goals

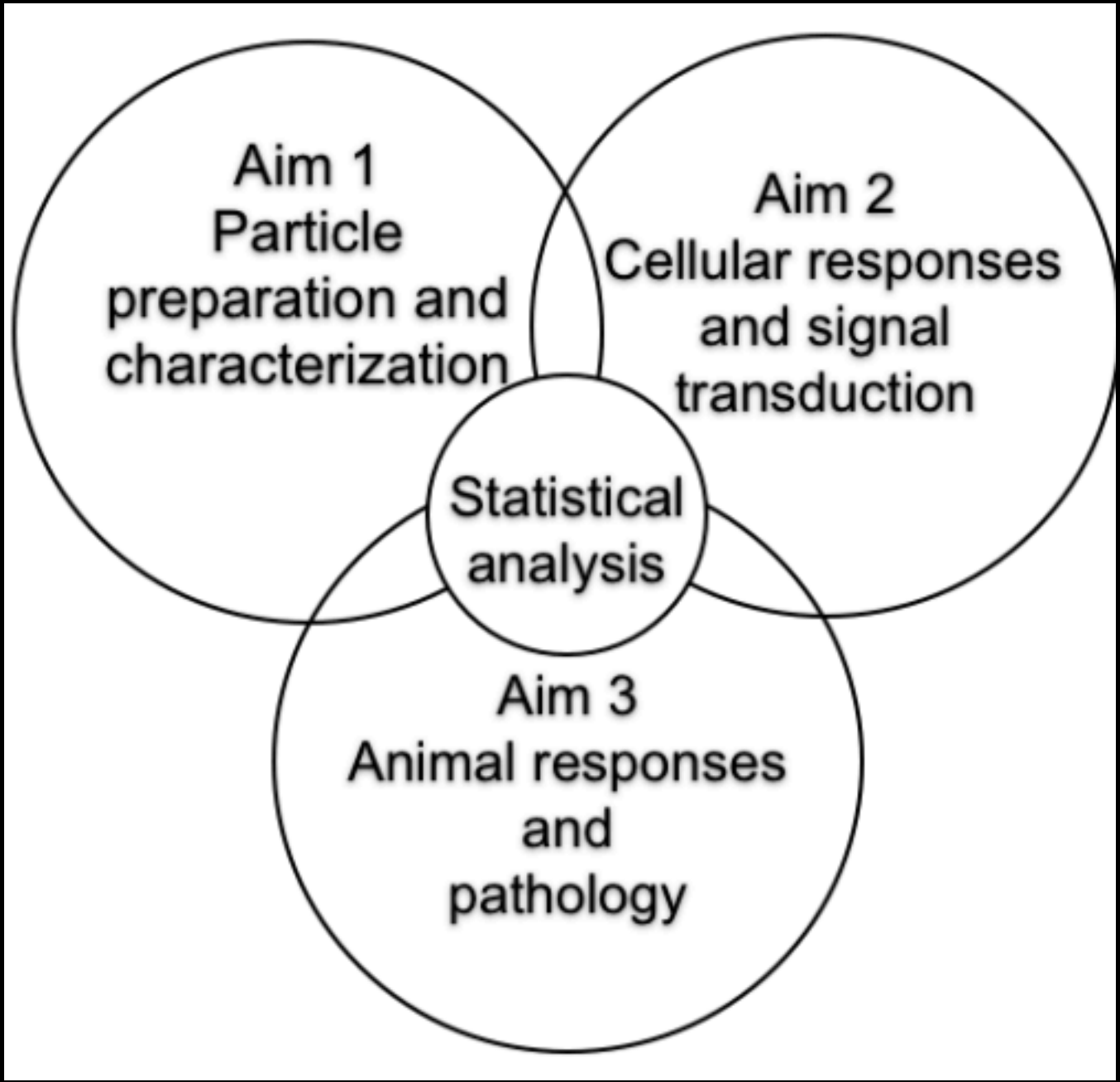
- Understanding how the toxic substances in the air we breathe damage lungs.

Mechanism and modeling of particle-induced inflammation

- Henry Jay Forman, Ph.D. - biochemist/ molecular biologist, UCM
- Peggy O'Day, Ph.D. - geochemist, UCM
- Valerie Leppert, Ph.D. - materials scientist, engineer, UCM
- Kent Pinkerton, Ph.D., pathologist, toxicologist, UCD

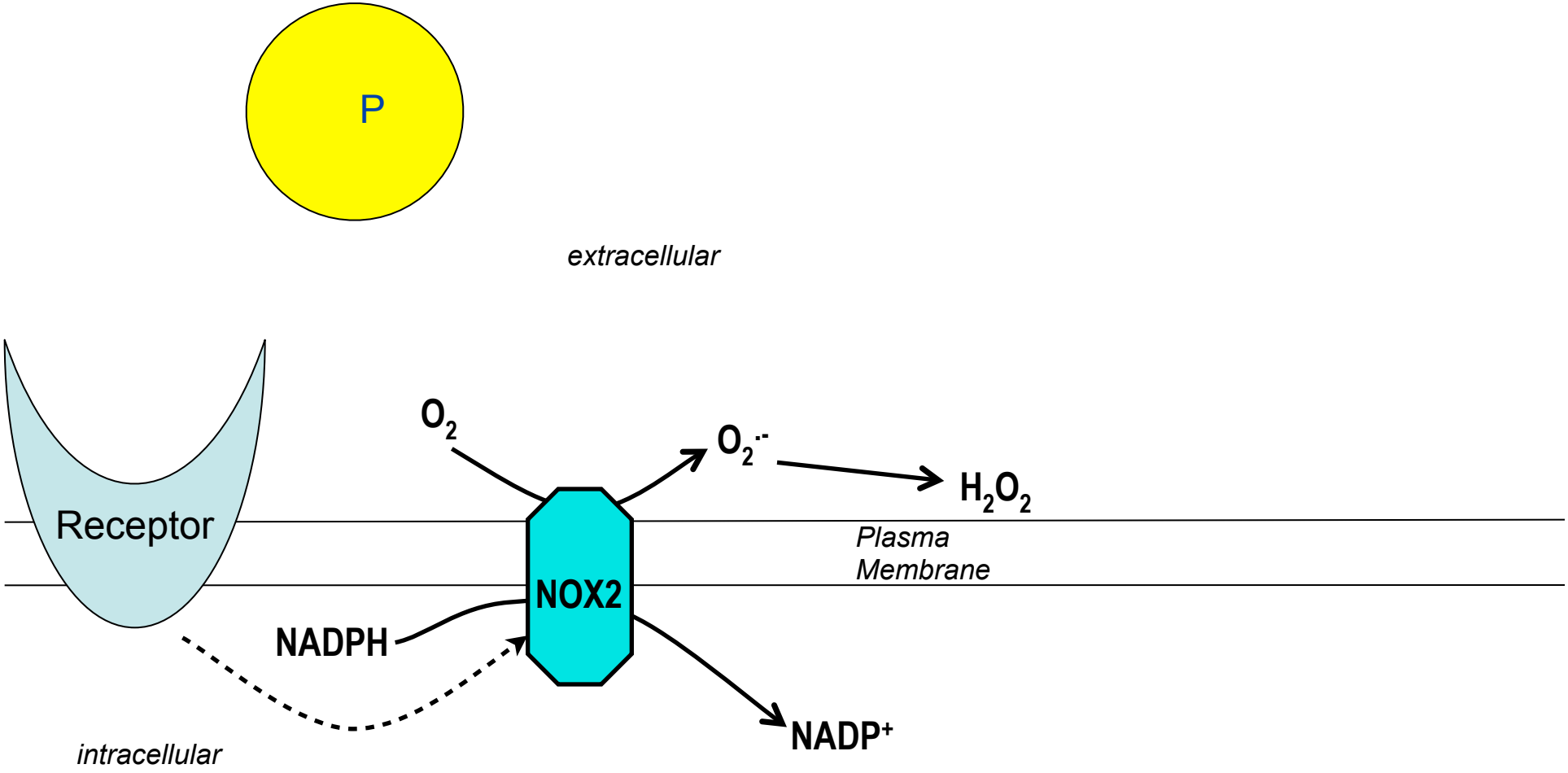
Specific studies

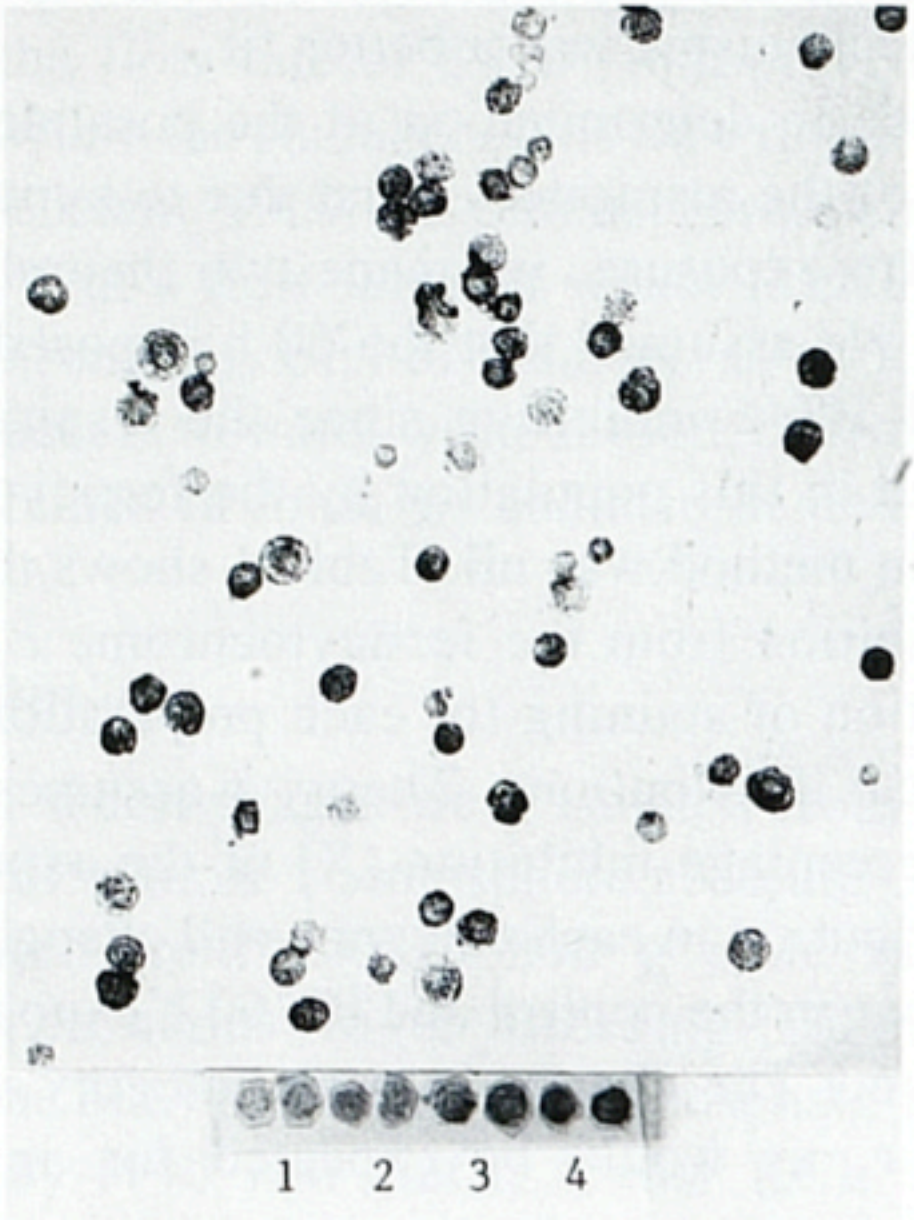
- To characterize airborne particulates collected from California's San Joaquin Valley.
- To test a mechanism for oxidative stress signaling for particle-induced cytokine expression in macrophages.
- To examine the hypothesis that the signaling pathway defined in Aim 2 is responsible for inducing or exacerbating early responses to low dose particles in mice.

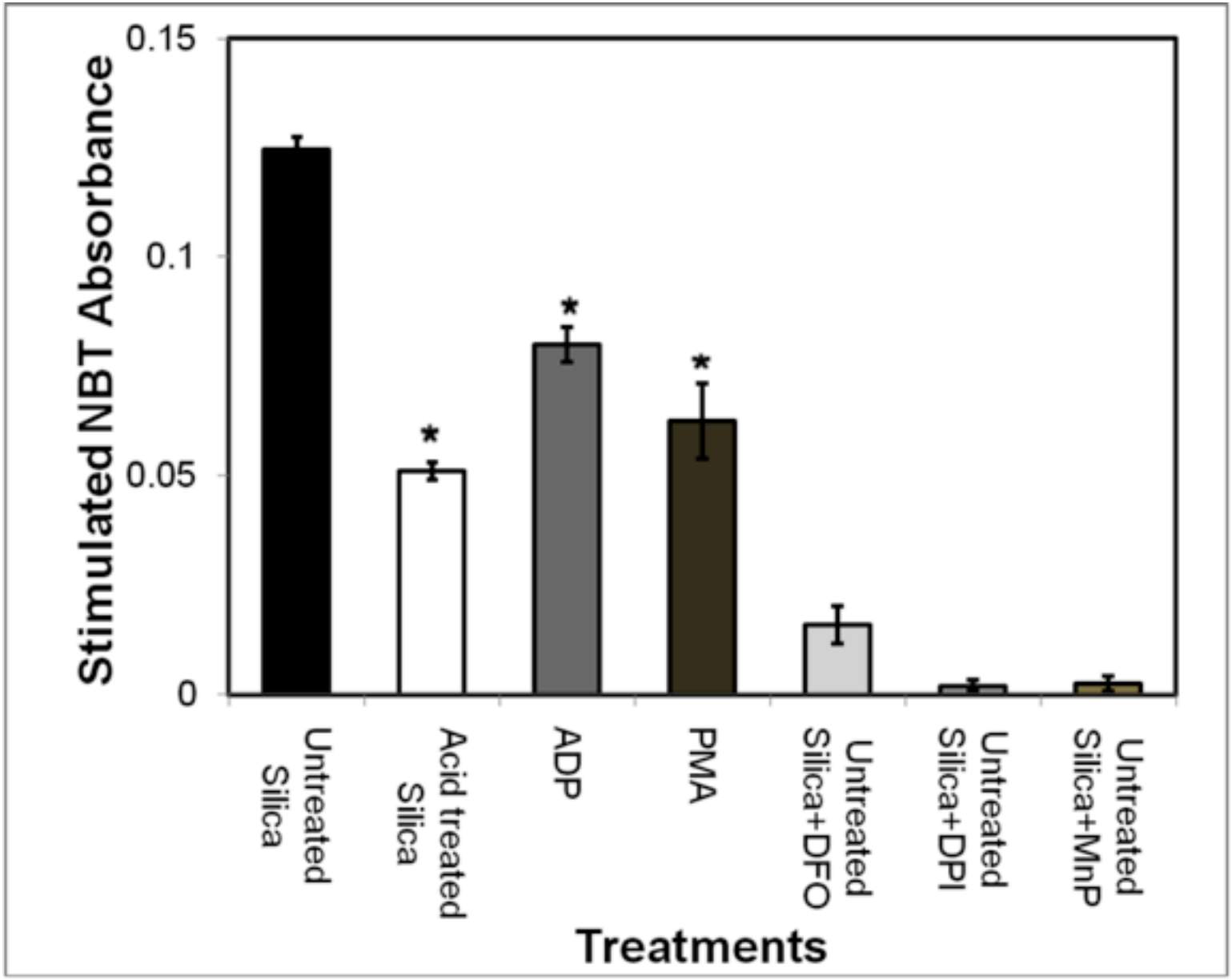

Aim 1
Particle
preparation and
characterization
Aim 2
Cellular responses
and signal
transduction
Statistical
analysis
Aim 3
Animal responses
and
pathology

Specific studies

- How do cells make reactive oxygen species?

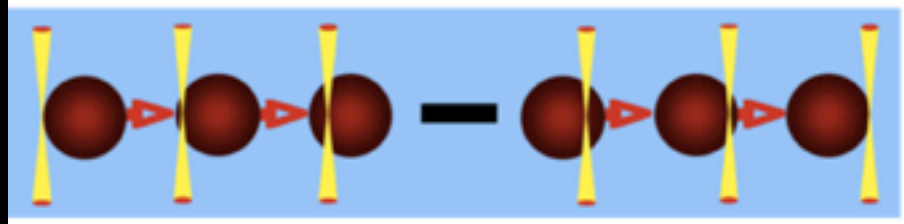

P
extracellular
Receptor
O_2
$O_2^{\cdot -}$
H_2O_2
Plasma
Membrane
NOX2
NADPH
$NADP^+$
intracellular

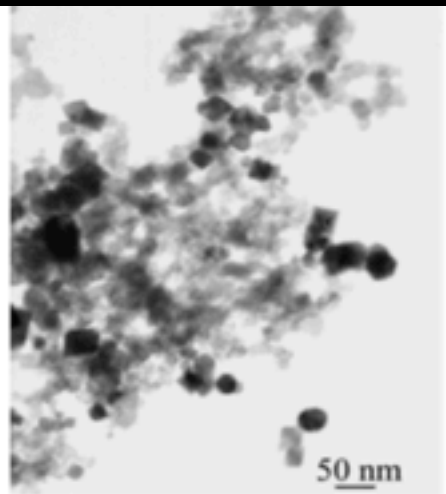

1
2
3
4

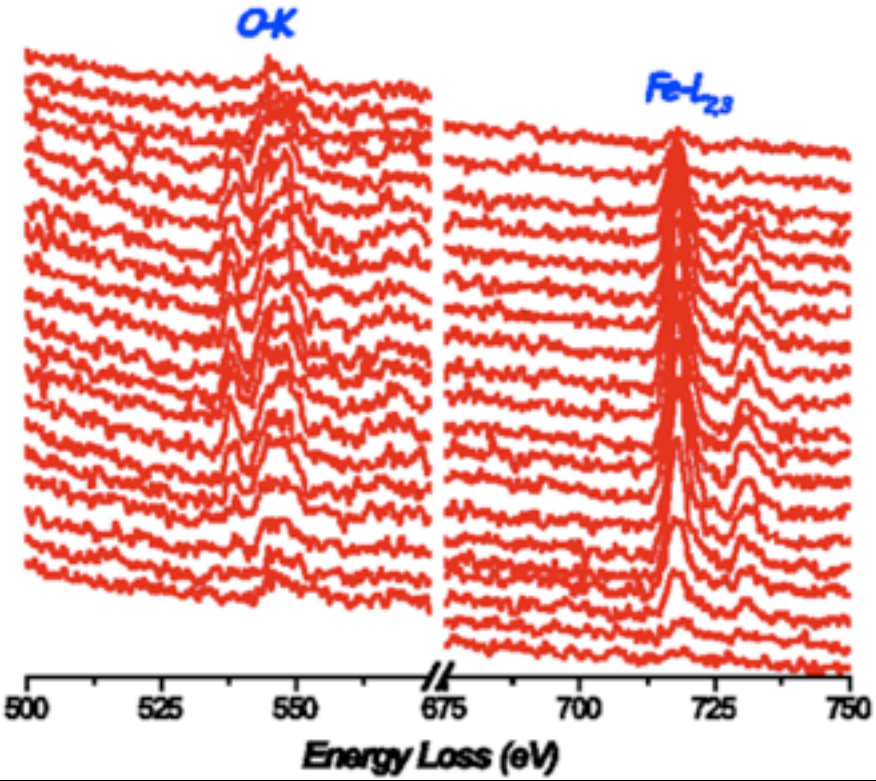

Stimulated NBT Absorbance
0.15
0.1
0.05
0
*
*
*
Untreated Silica
Acid treated Silica
ADP
PMA
Untreated Silica+DFO
Untreated Silica+DPI
Untreated Silica+MnP
Treatments

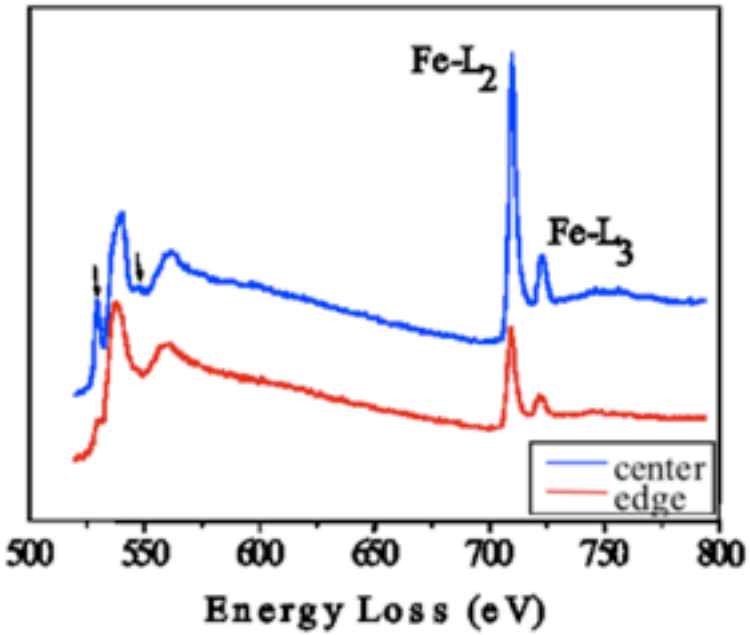
Specific studies

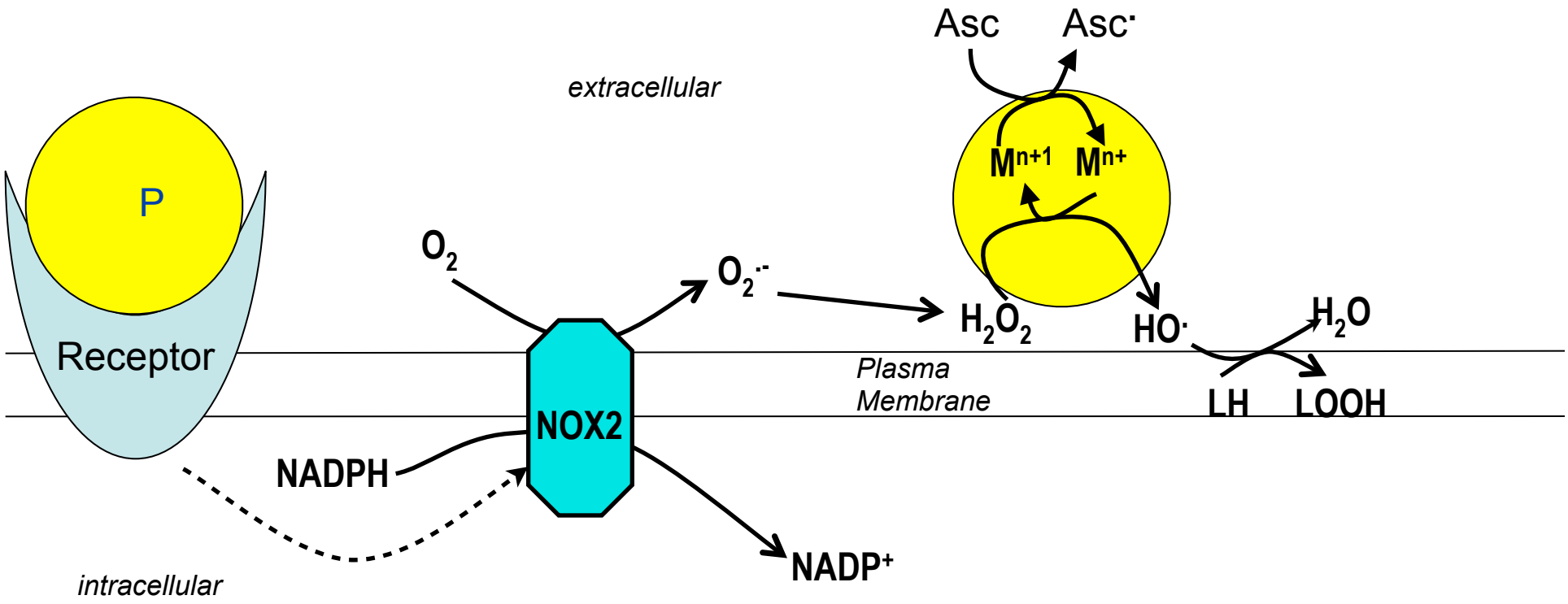
- How do cells make reactive oxygen species?
- What it is about particles that causes cells to make inflammatory mediators?

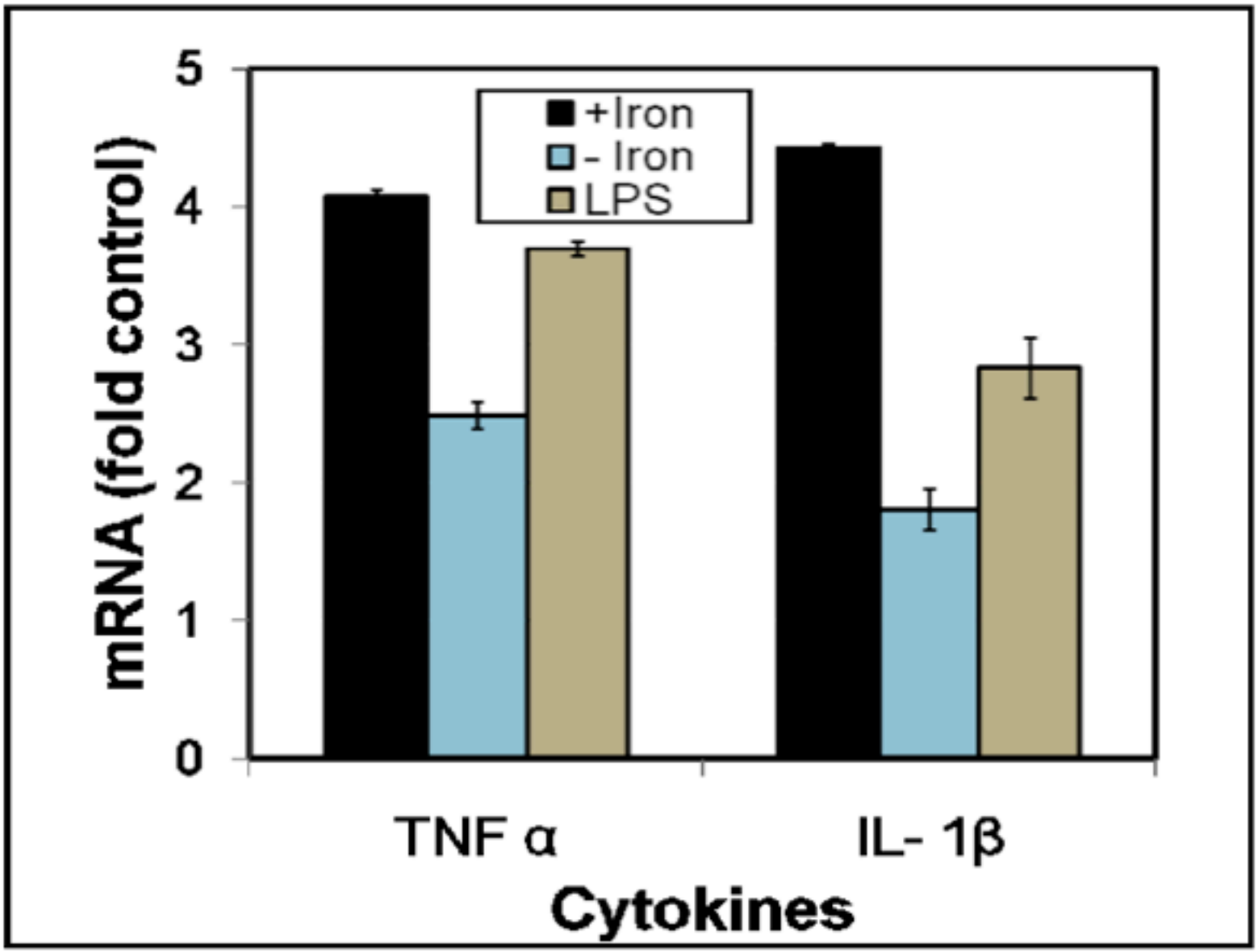



50 nm


O-K
Fe-L2,3
500
525
550
675
700
725
750
Energy Loss (eV)

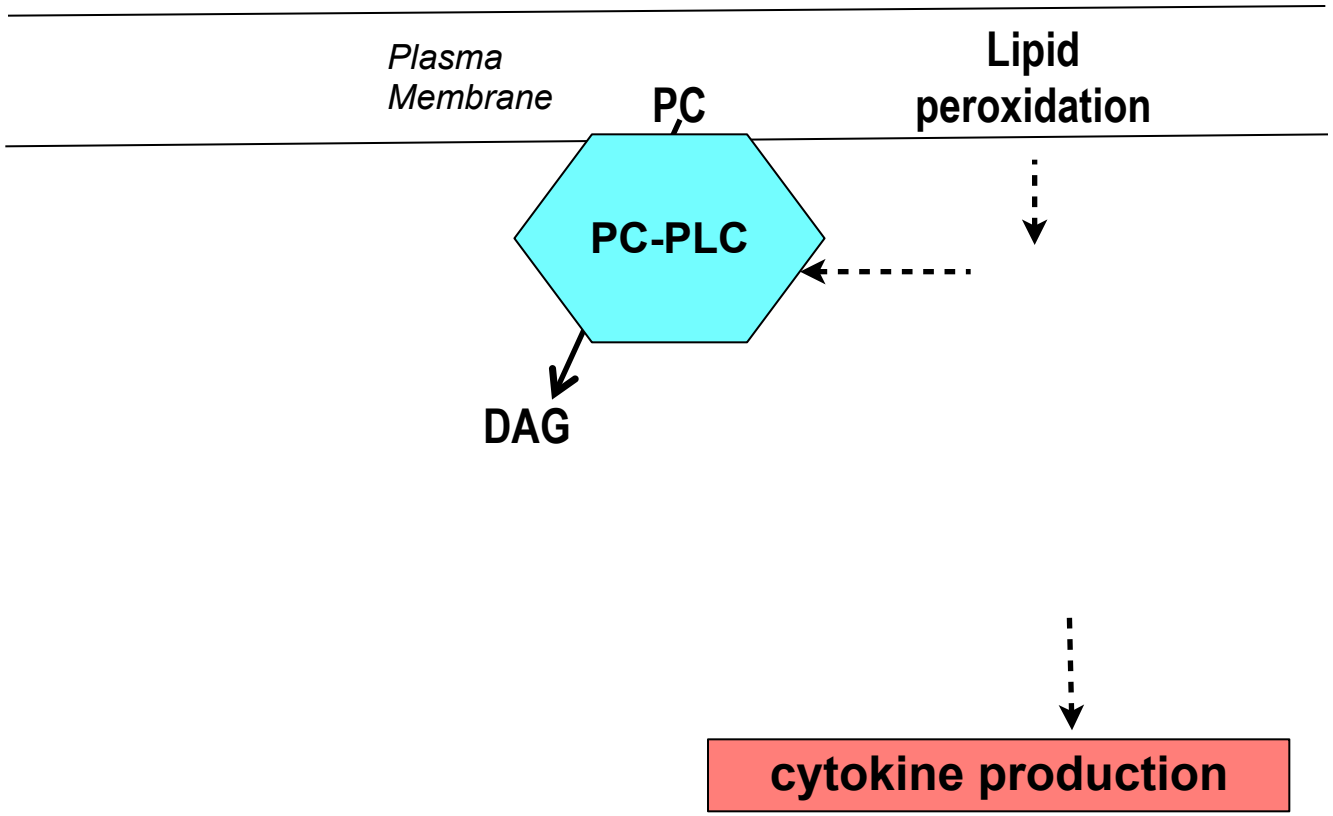

Fe-L2
Fe-L3
center
edge
500
550
600
650
700
750
800
Energy Loss (eV)

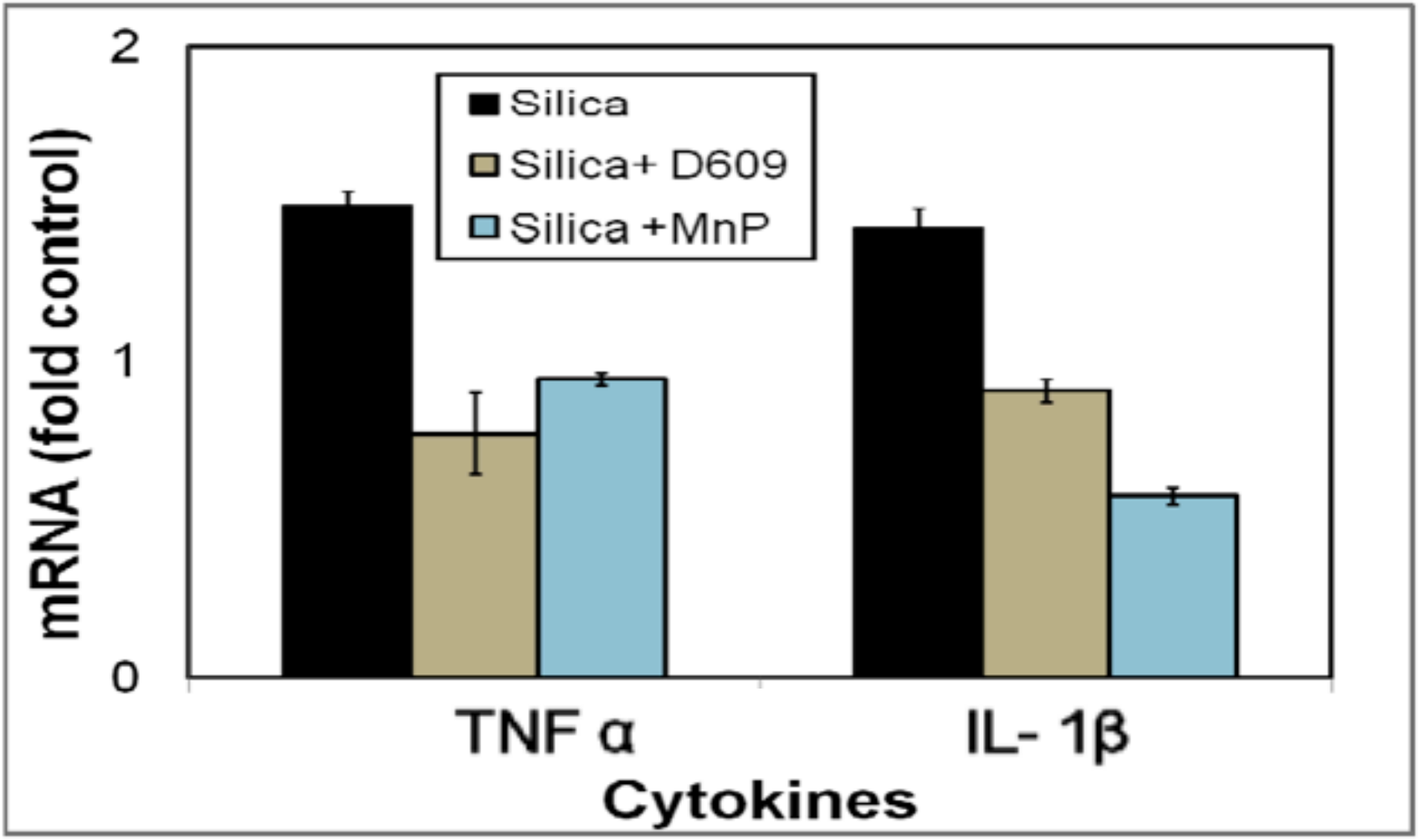

Asc
Asc·
extracellular
P
Mn+1
Mn+
O2
O2·-
Receptor
H2O2
HO·
H2O
Plasma
Membrane
LH
LOOH
NOX2
NADPH
NADP+
intracellular

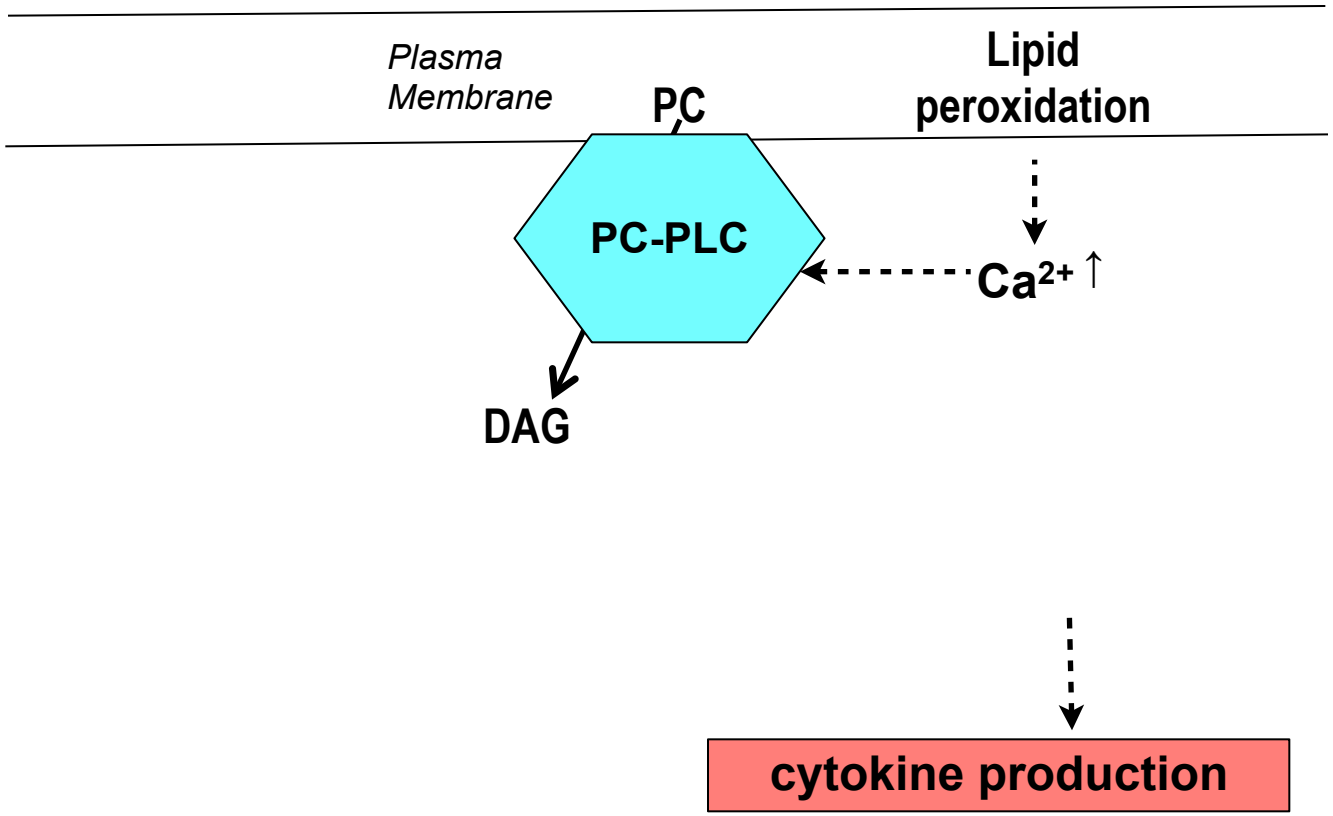

5
4
3
2
1
0
mRNA (fold control)
+Iron
- Iron
LPS
TNF α
IL- 1β
Cytokines

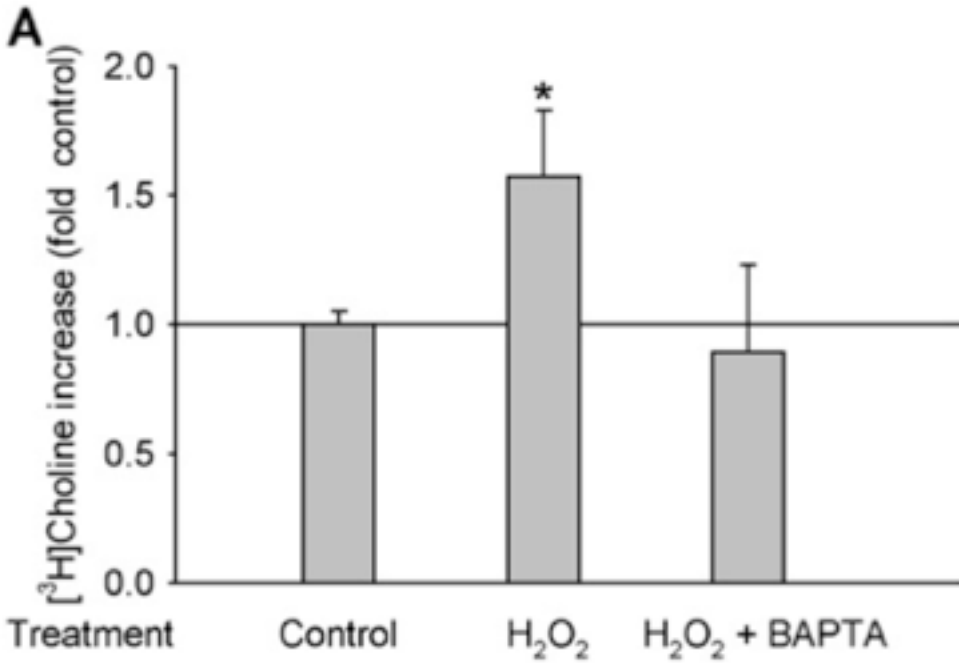
Specific studies

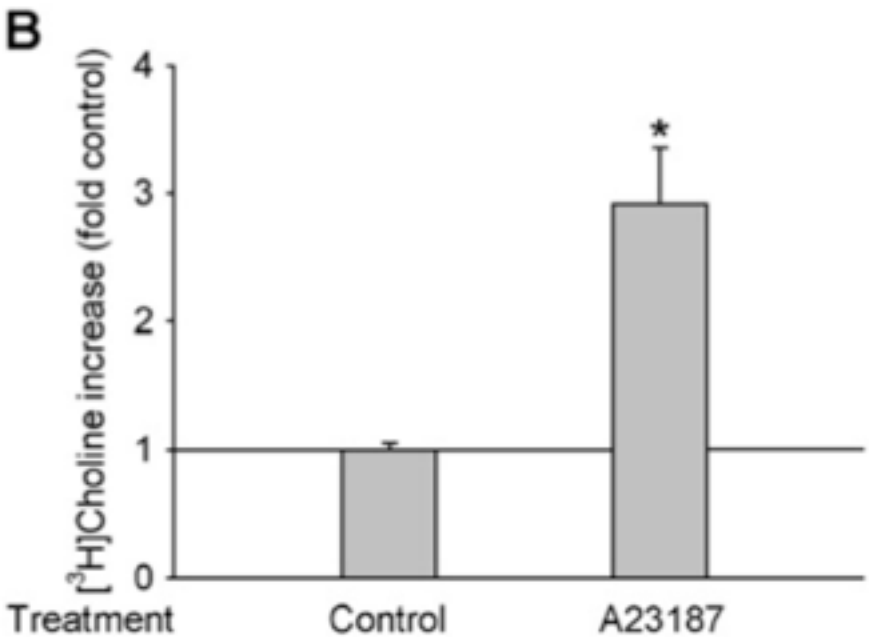
- How do cells make reactive oxygen species?
- What it is about particles that causes cells to make inflammatory mediators?
- How cells use lipid peroxidation to signal for production of inflammatory mediators?

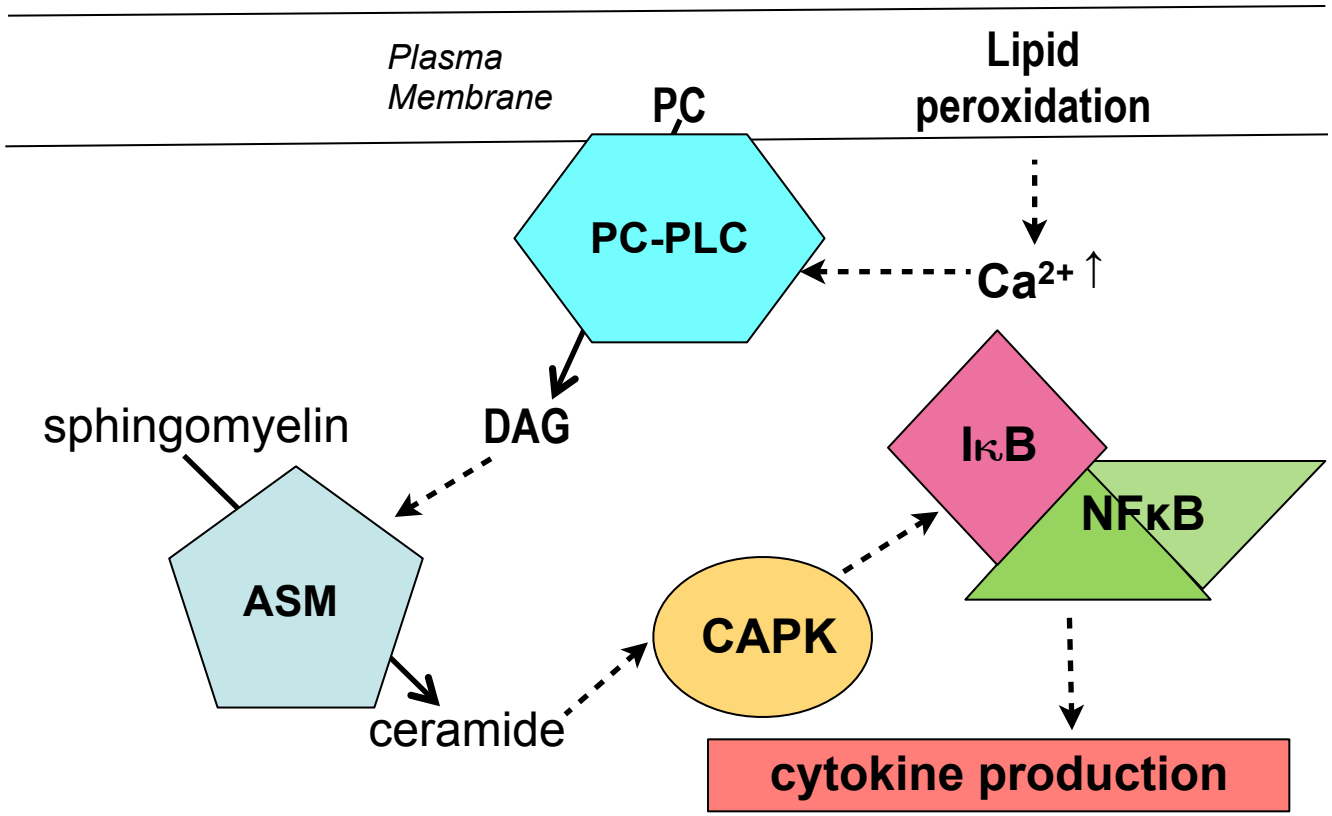

Plasma
Membrane
PC
Lipid
peroxidation
PC-PLC
DAG
cytokine production


2
1
0
mRNA (fold control)
Silica
Silica+ D609
Silica +MnP
TNF α
IL- 1β
Cytokines


Plasma
Membrane
PC
Lipid
peroxidation
PC-PLC
Ca2+ ↑
DAG
cytokine production

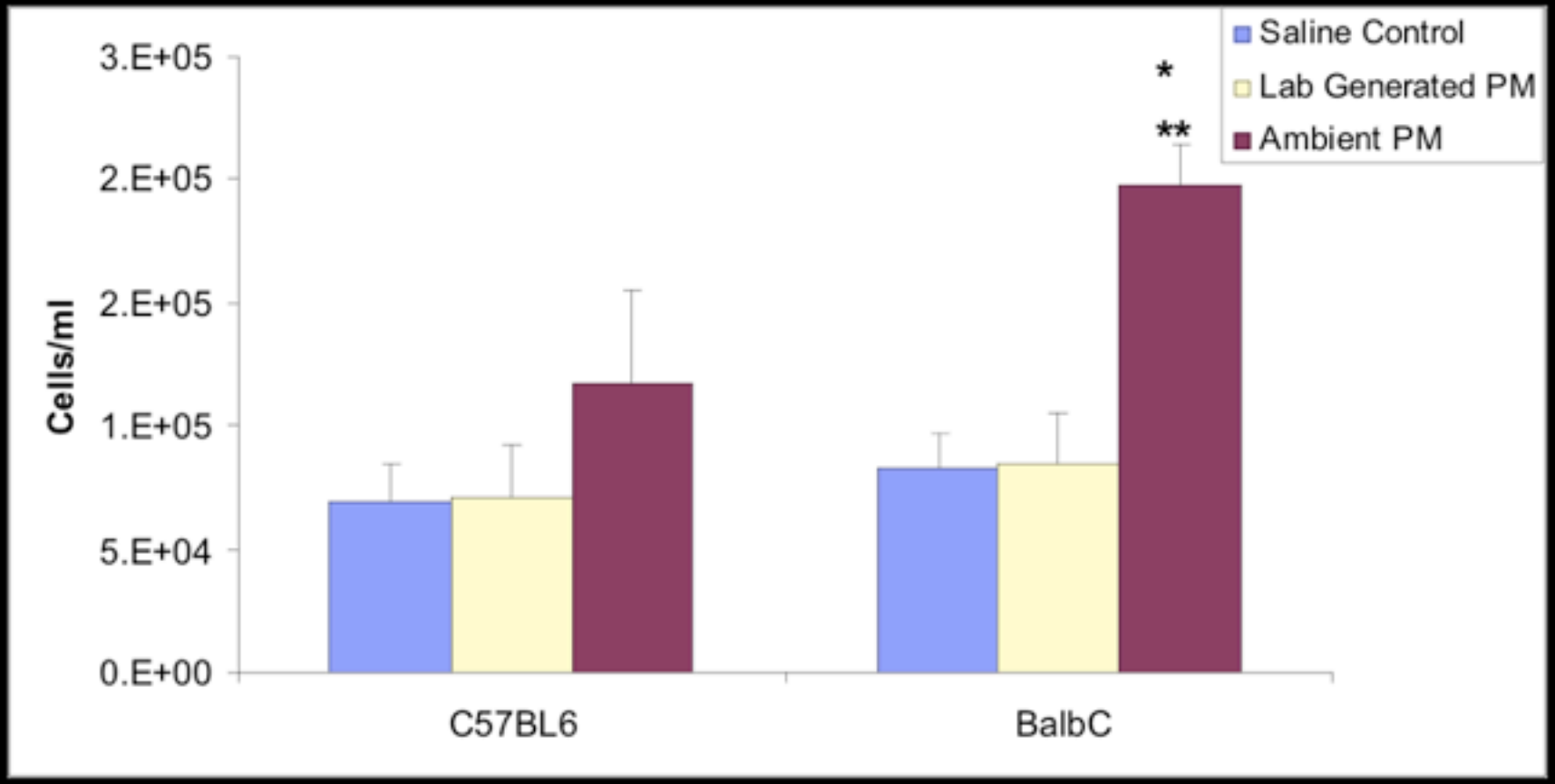

A
[3H]Choline increase (fold control)
2.0
1.5
1.0
0.5
0.0
*
Treatment
Control
H2O2
H2O2 + BAPTA


B
[3H]Choline increase (fold control)
4
3
2
1
0
*
Treatment
Control
A23187


Plasma
Membrane
PC
Lipid
peroxidation
PC-PLC
Ca2+ ↑
DAG
sphingomyelin
IκB
NFκB
ASM
CAPK
ceramide
cytokine production

Specific studies

- How do cells make reactive oxygen species?
- What it is about particles that causes cells to make inflammatory mediators?
- How cells use lipid peroxidation to signal for production of inflammatory mediators?
- Can we apply this information to an animal model?


Saline Control
Lab Generated PM
Ambient PM
Cells/ml
3.E+05
2.E+05
2.E+05
1.E+05
5.E+04
0.E+00
*
**
C57BL6
BalbC