PM CENTER DIRECTORS' MEETING

September, 2004

Washington, D.C.

In Search of Mechanisms for Ultrafine/Fine PM Induced Extrapulmonary Effects

The Rochester PM Center Team

Outline

- **Introductory remarks on ultrafine/fine PM**
- **Examples of integrated Rochester PM Center research**
  - ***ambient PM characterization***
  - ***epidemiological panel studies***
  - ***controlled clinical studies***
  - ***Animal models***
  - ***In vitro studies***

  PM – ROS; source apportionment

  Deposition/disposition

  Endothelial cell/platelet function

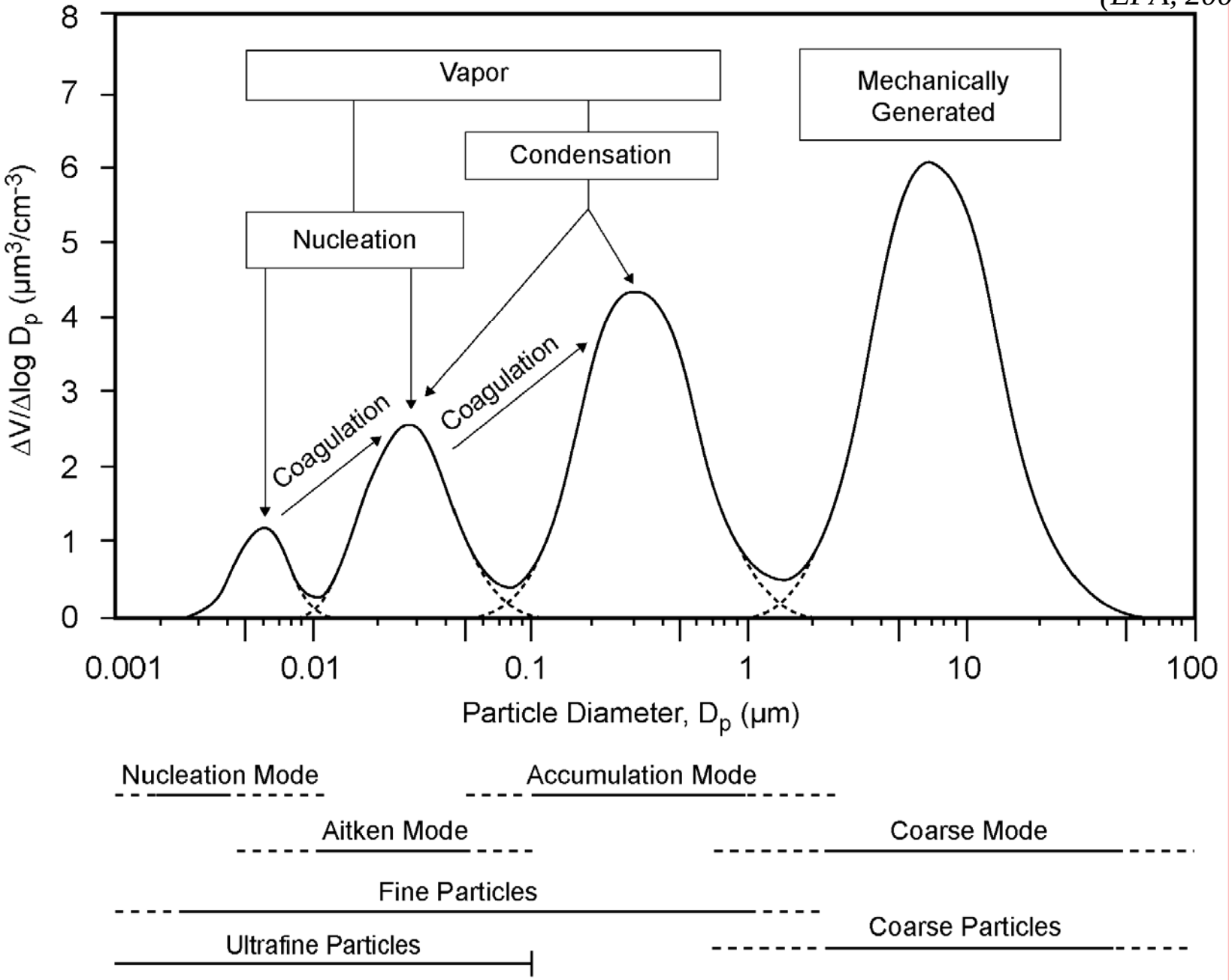
  Cardiac events

- **Connecting the available information:**

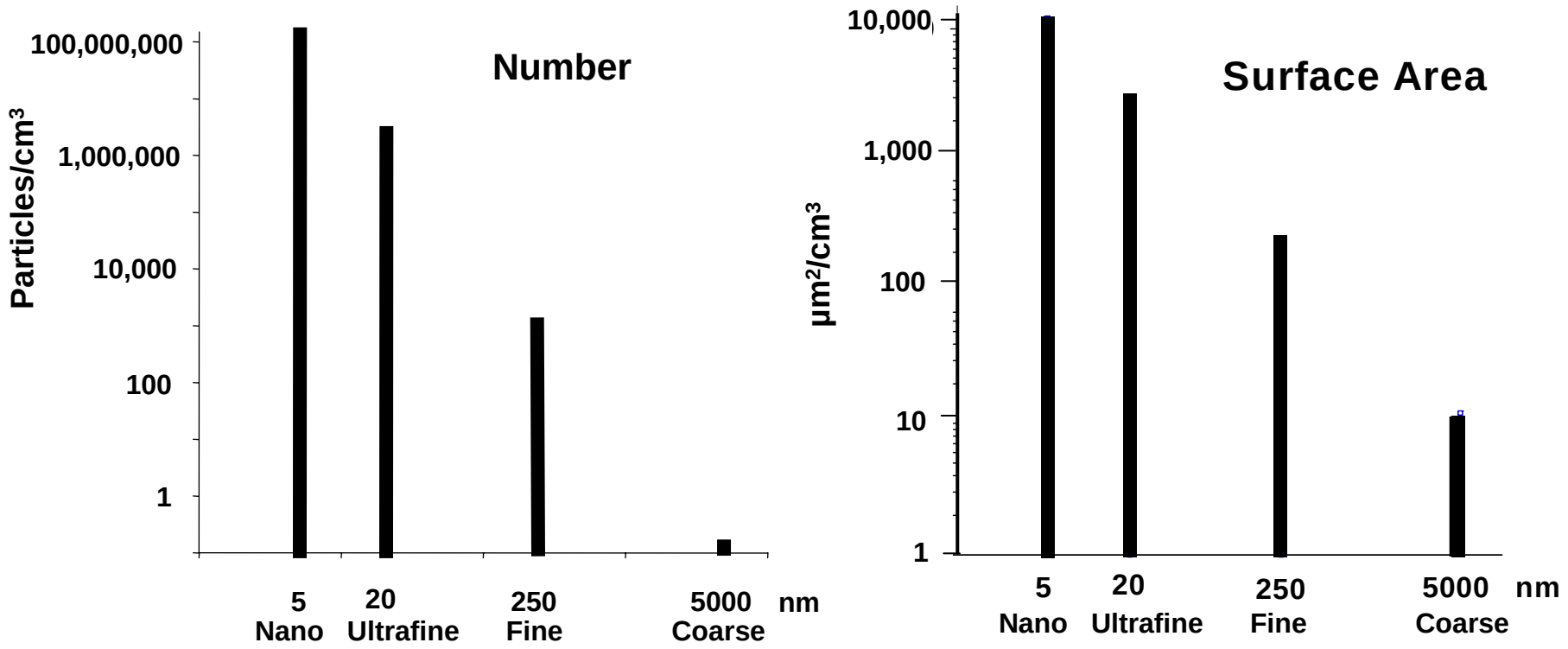
  Scheme of suggested sequence of extrapulmonary effects/mechanisms

Idealized Size Distribution of Traffic-Related Particulate Matter

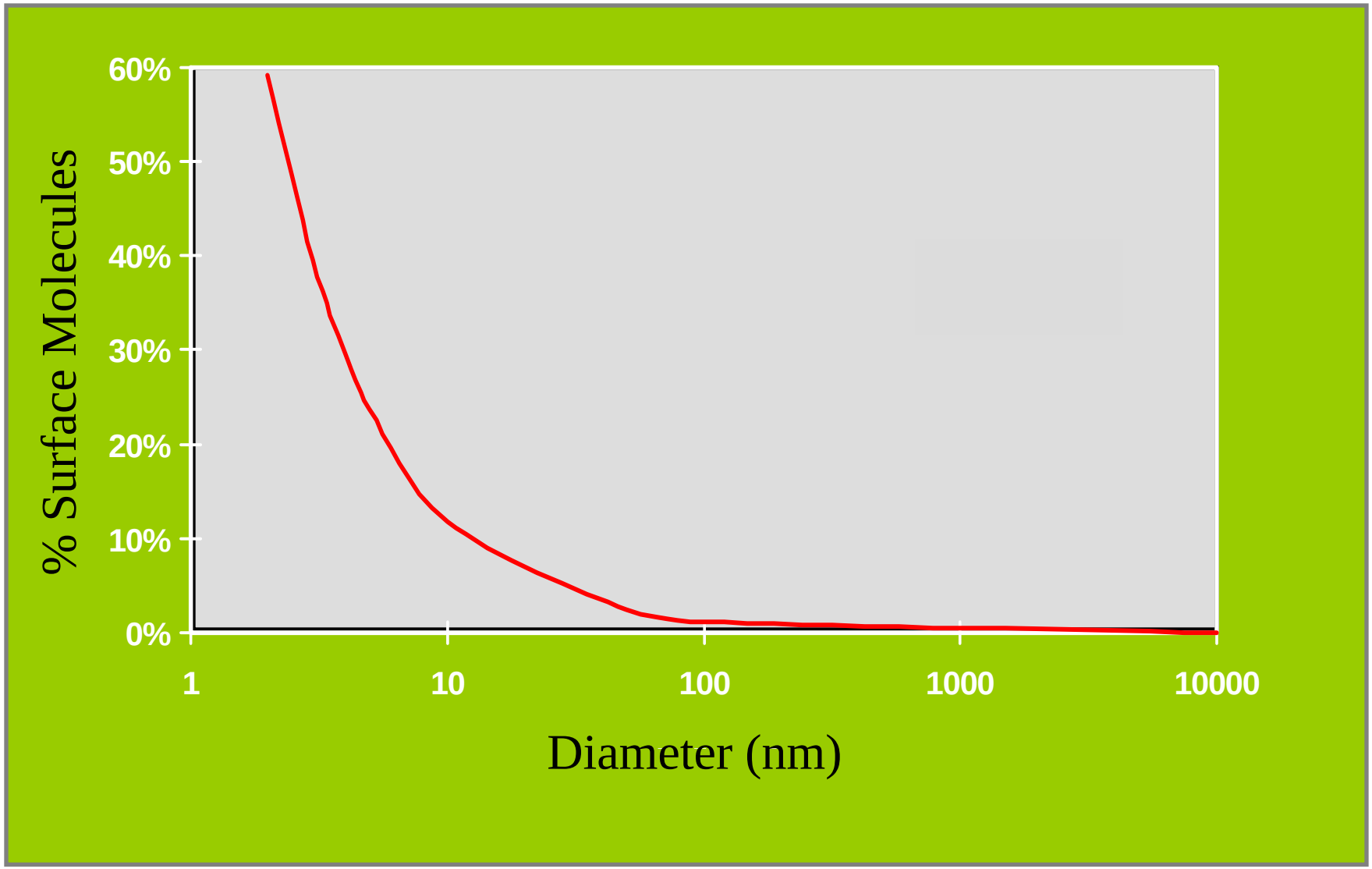
(EPA, 2004)



Number and surface area per 10 µg/m^3

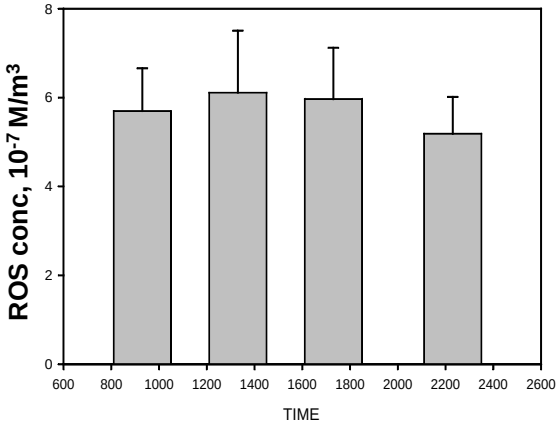


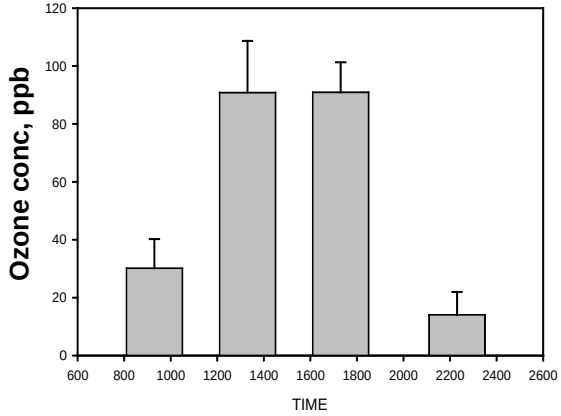
Surface Molecules as Function of Particle Size



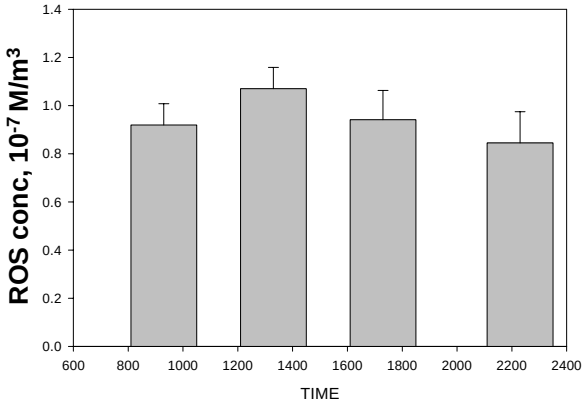
From Fissan, 2003

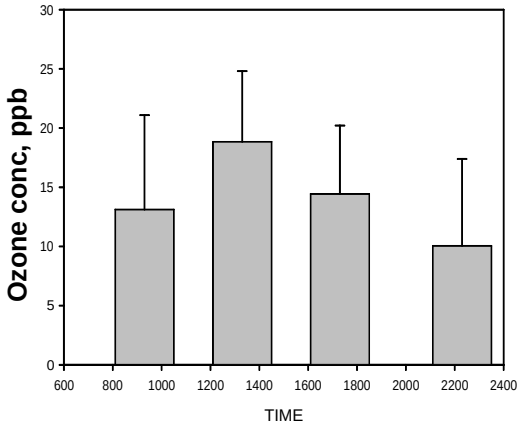
Reactive Oxygen Species





Measurements in Rubidoux, CA, July 2003





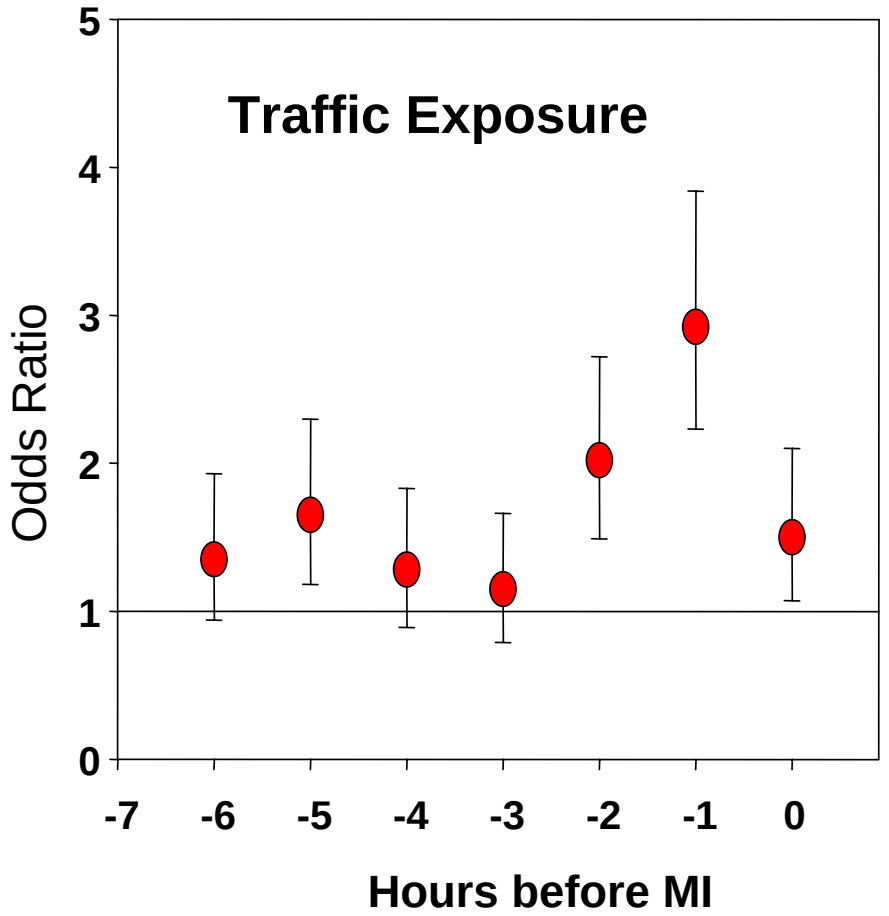
Measurements in New York City, February 2004

Particle bound reactive oxygen species (ROS) on $PM_{2.5}$ were found in both locations. The contribution of these ROS to adverse health effects will be evaluated in future studies.

Venkatachari et al., 2004

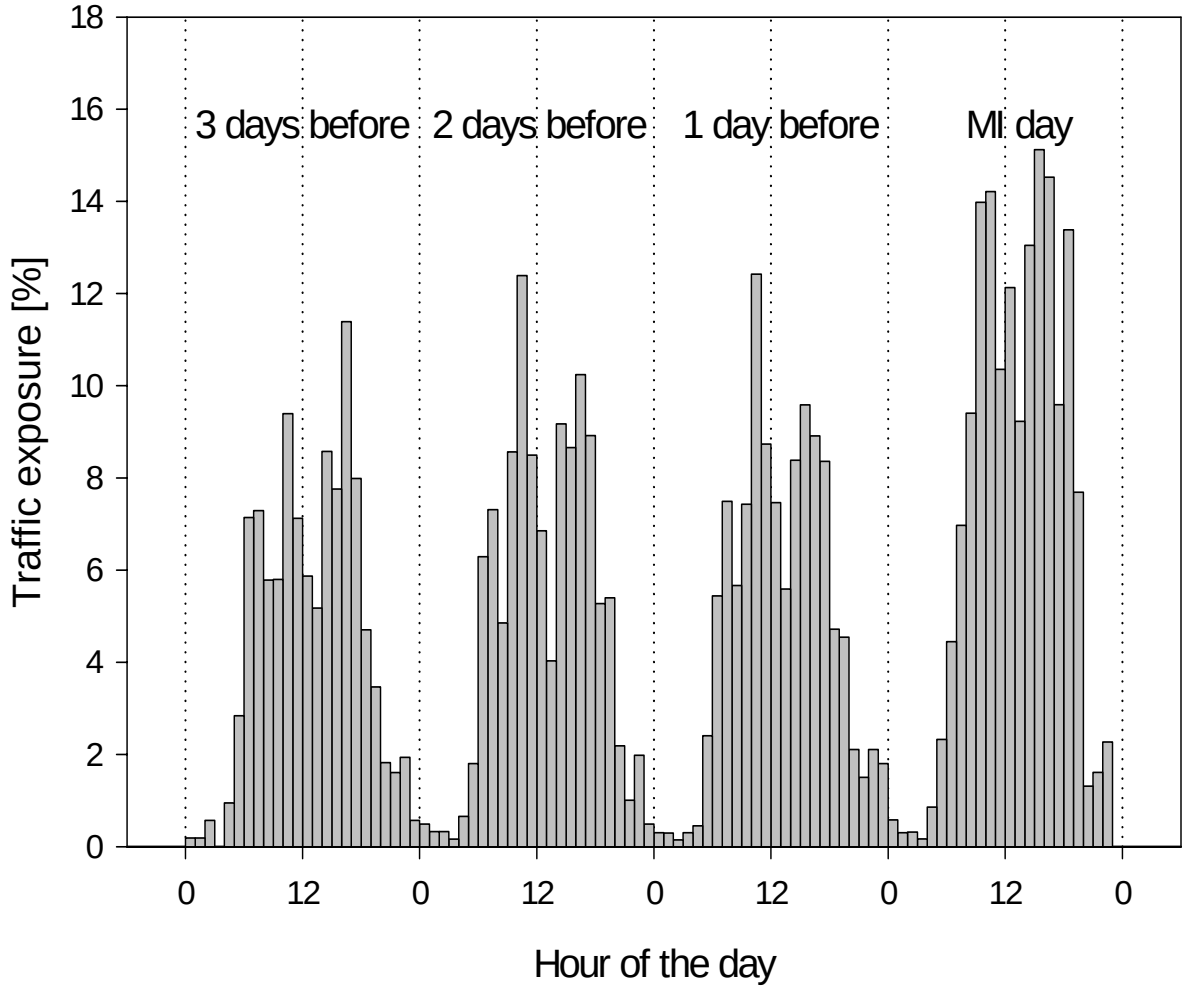
Traffic Exposure and MI Onset

- Activities on the four days before MI onset were recorded.
- Times spent in a car, public transportation, or on bicycles or motorcycles were associated with MI onset.



Peters et al., 2004

Traffic exposure in 691 myocardial infarction survivors



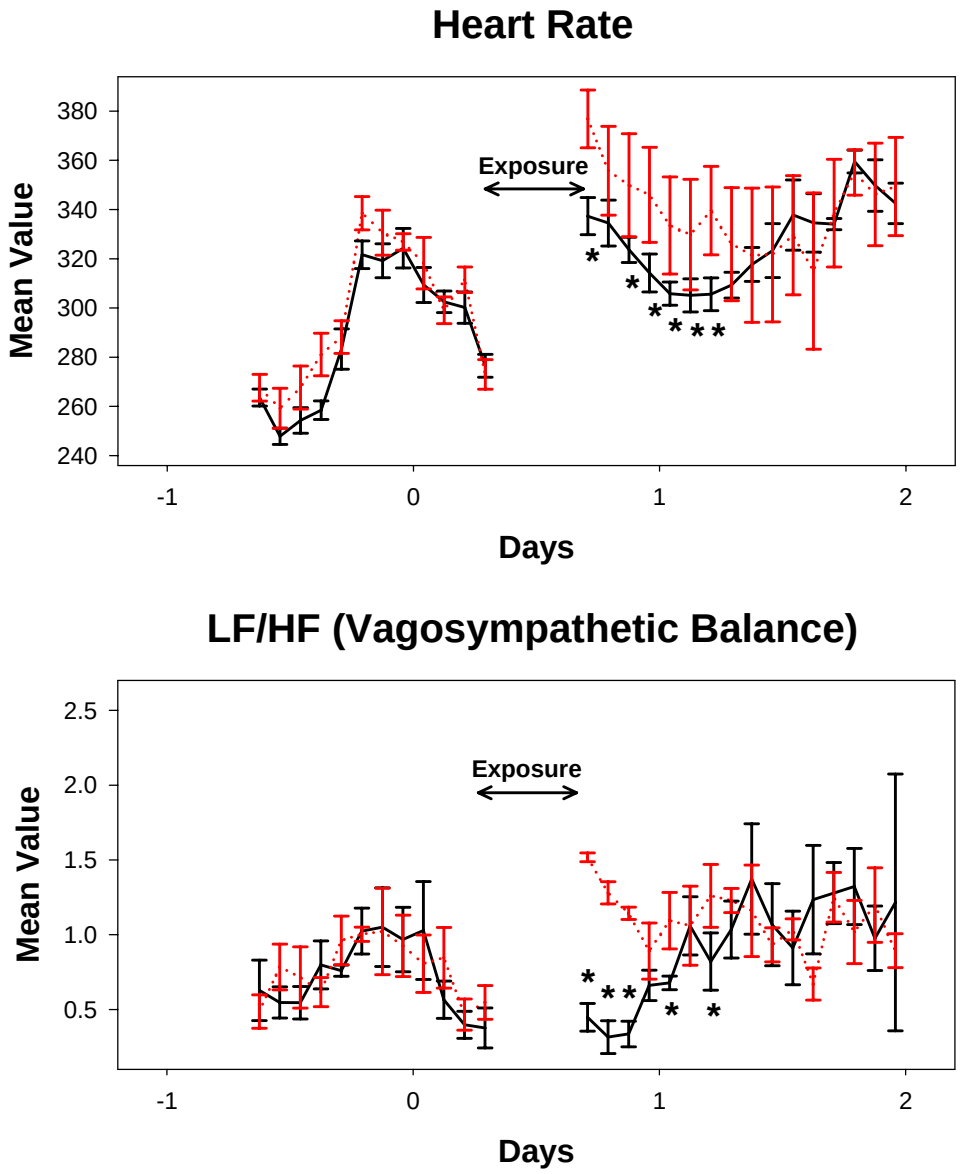
Peters et al., 2004

U of Minnesota Mobile Laboratory *(D. Kittelson)*

D. Kittelson, U. Minnesota

6-hr On-Road Exposure, Hypertensive ip LPS-primed Rats (*15 months*)

(number conc. ~ 2.0-5.6 x 10^5/cm^3; CMD = 15-20 nm; est. mass conc. ~ 37-106 $\mu g/m^3$)

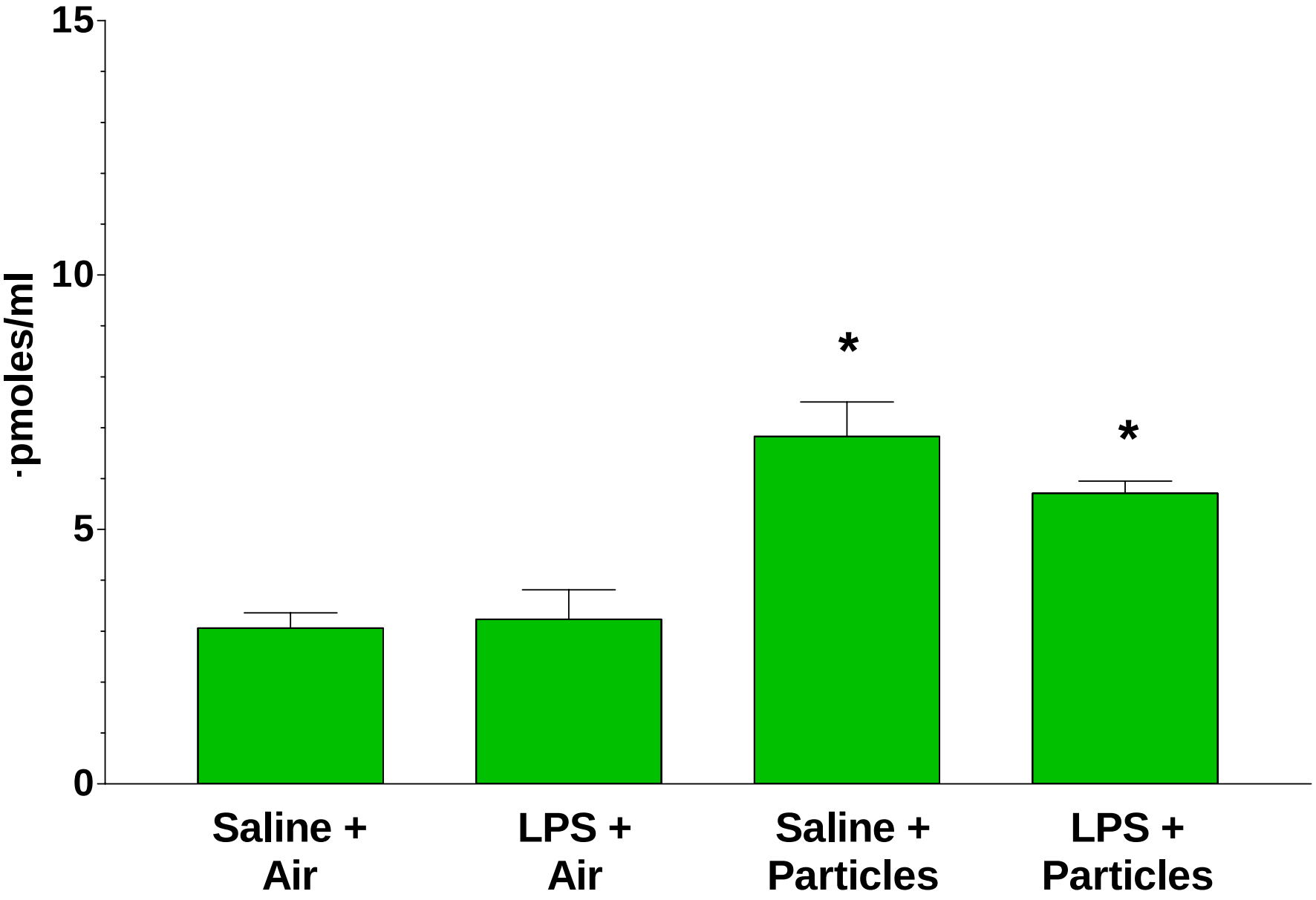


Clean air

On-road aerosol

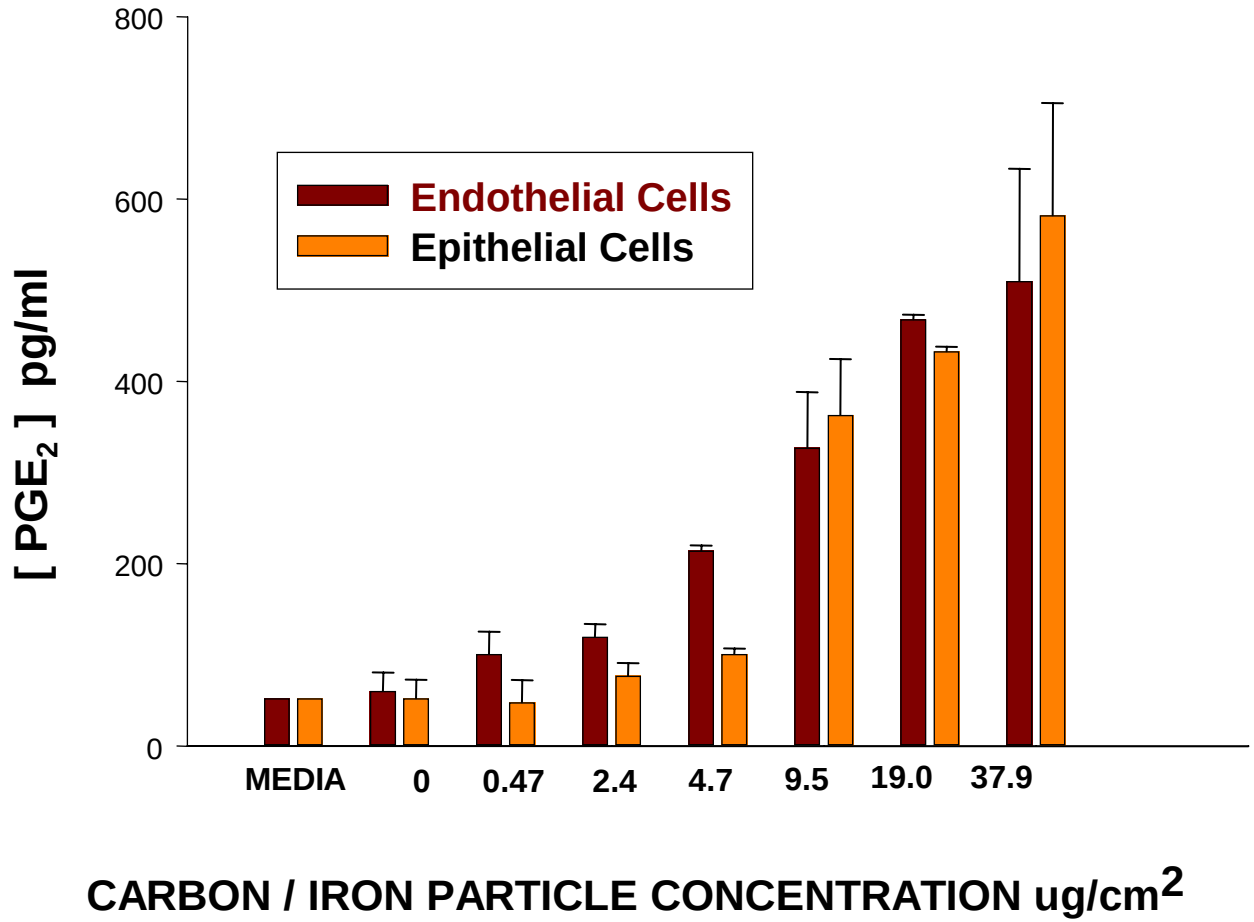
Elder et al., 2004

Plasma Endothelin-2 Levels from Old Rats Exposed to On-Road Ultrafine Particles or Filtered Air with and without LPS Priming



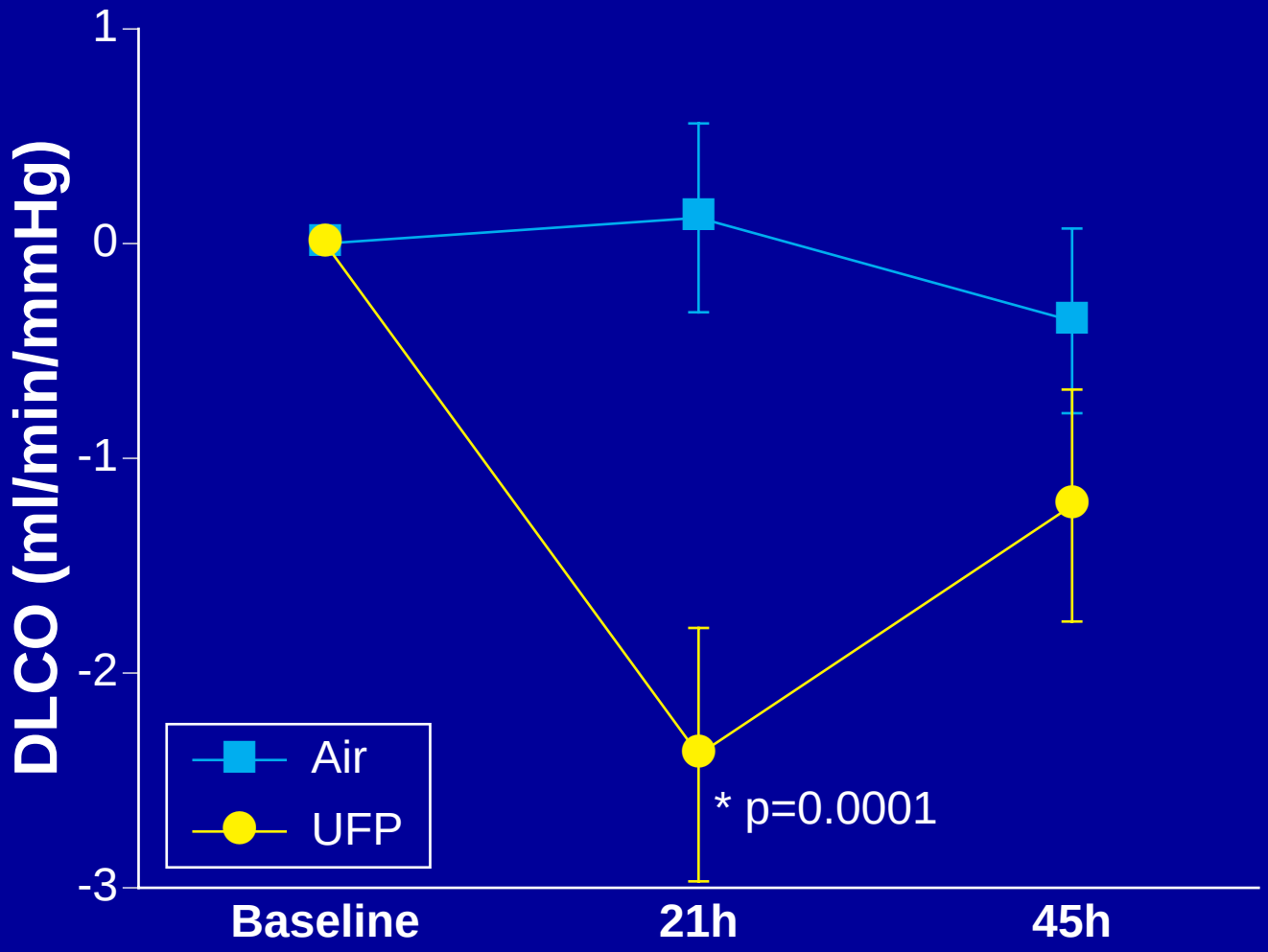
Elder et al., 2003

Response of Cells to Ultrafine Particles in vitro: Comparison of Human Epithelial and Endothelial Cells



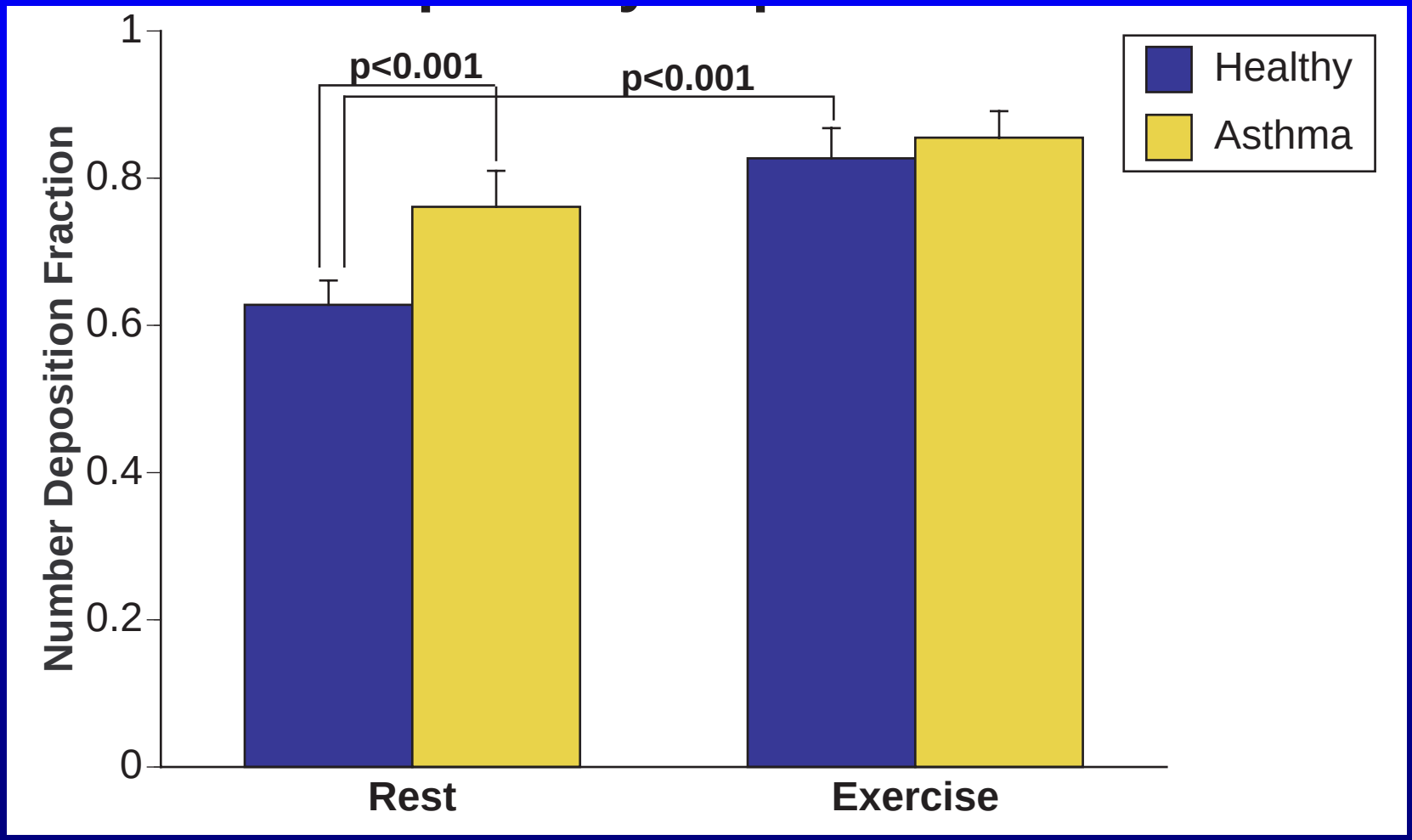
Finkelstein et al., 2004

Inhalation of 50 µg/m^3 carbon UFP by healthy subjects Decreases the Pulmonary Diffusing Capacity



Pietropaoli et al, 2004

Respiratory Deposition of UFP

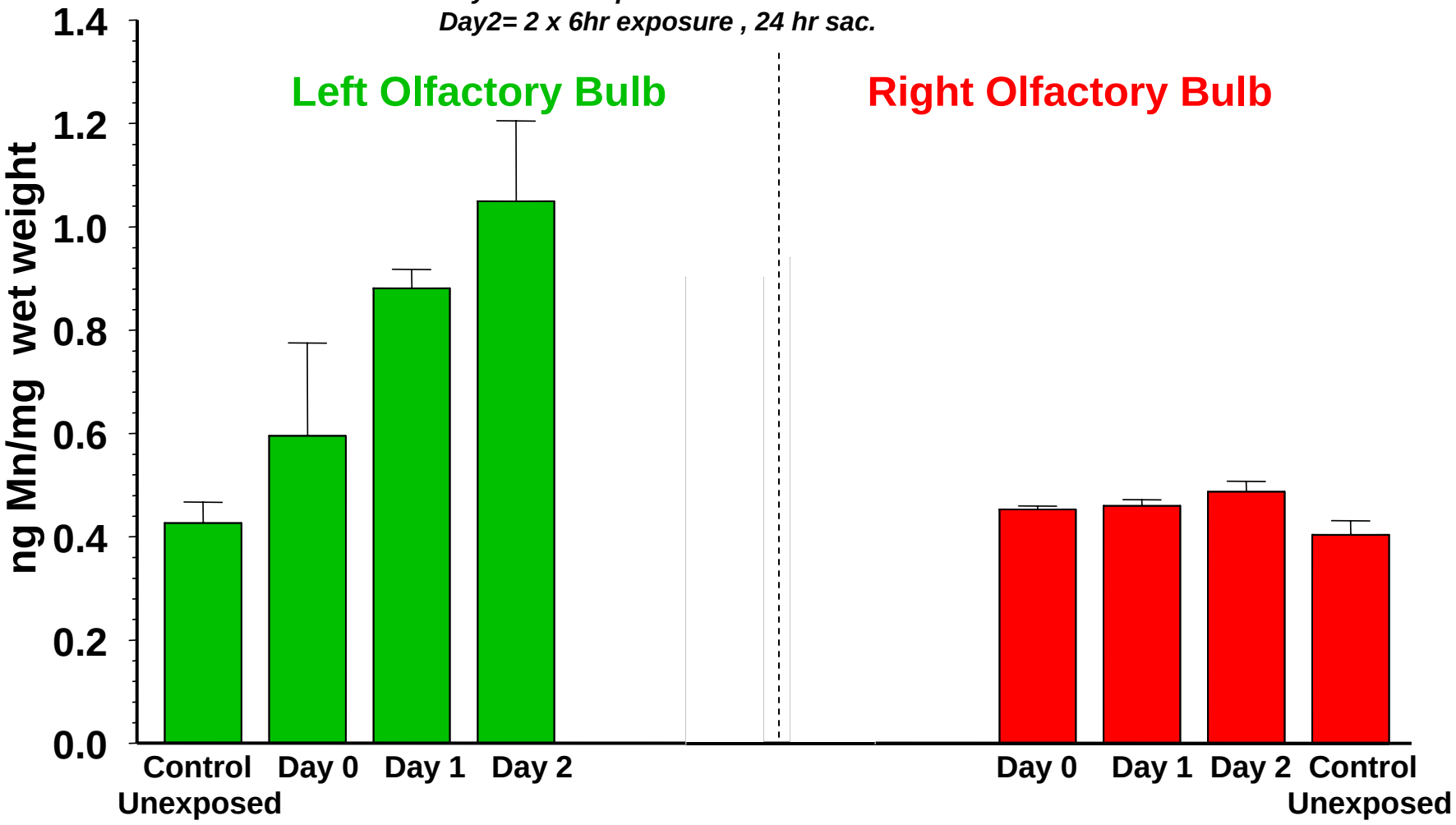


Chalupa et al., 2004

Rat, Right Nostril Occlusion Model:

Accumulation of Mn in Right and Left Olfactory Bulb Following Exposure to Ultrafine (~30 nm) ***Mn Oxide Particles*** (n = 3 - 5, mean +/- SD)

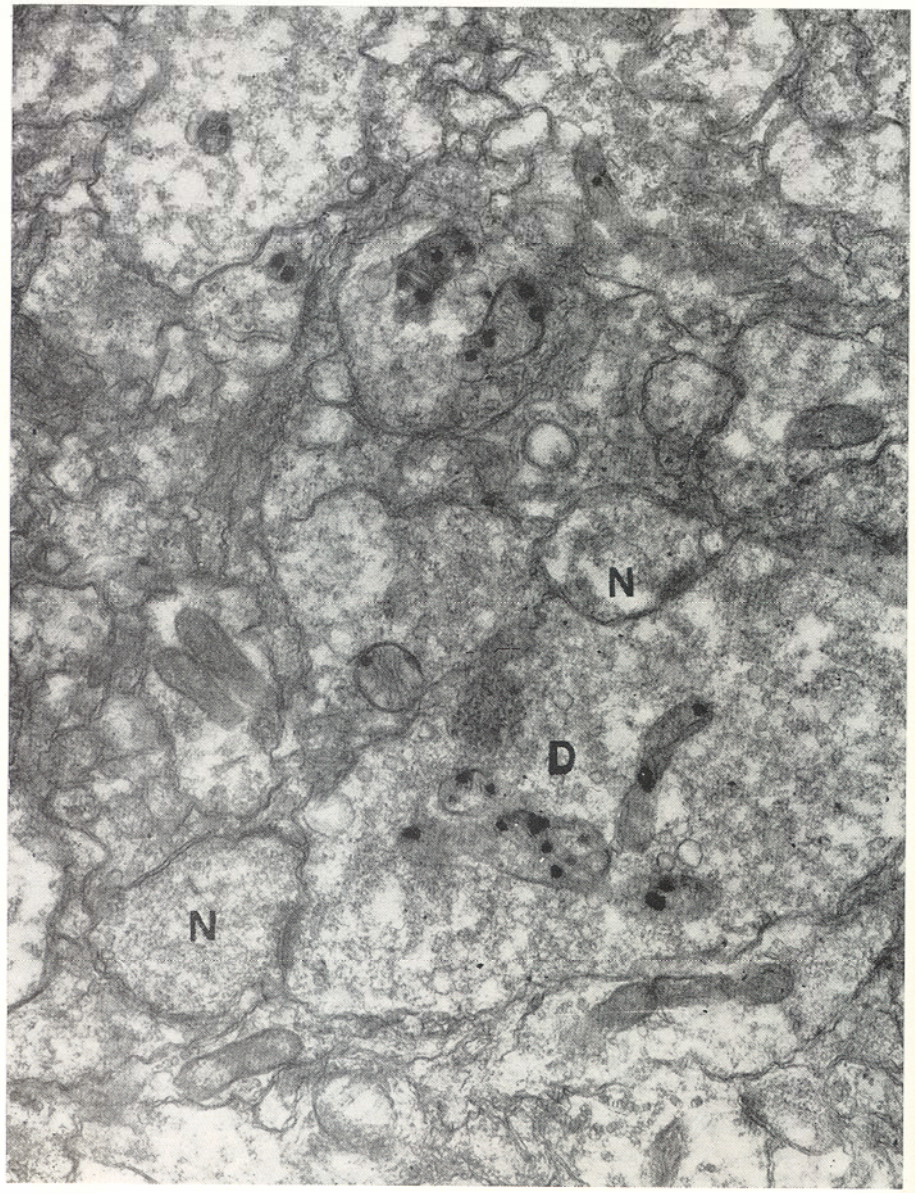
Day 0= 6 hr exposure, immediate sac.
Day 1= 6 hr exposure 24 hr sac.
Day2= 2 x 6hr exposure , 24 hr sac.



Squirrel monkey, intranasal colloidal gold particles (50 nm):

Translocation to mitochondria of dendrites in mitral cells (D) of olfactory bulb after crossing the olfactory nerve (N)/mitral cell synapse.

(de Lorenzo, 1970)



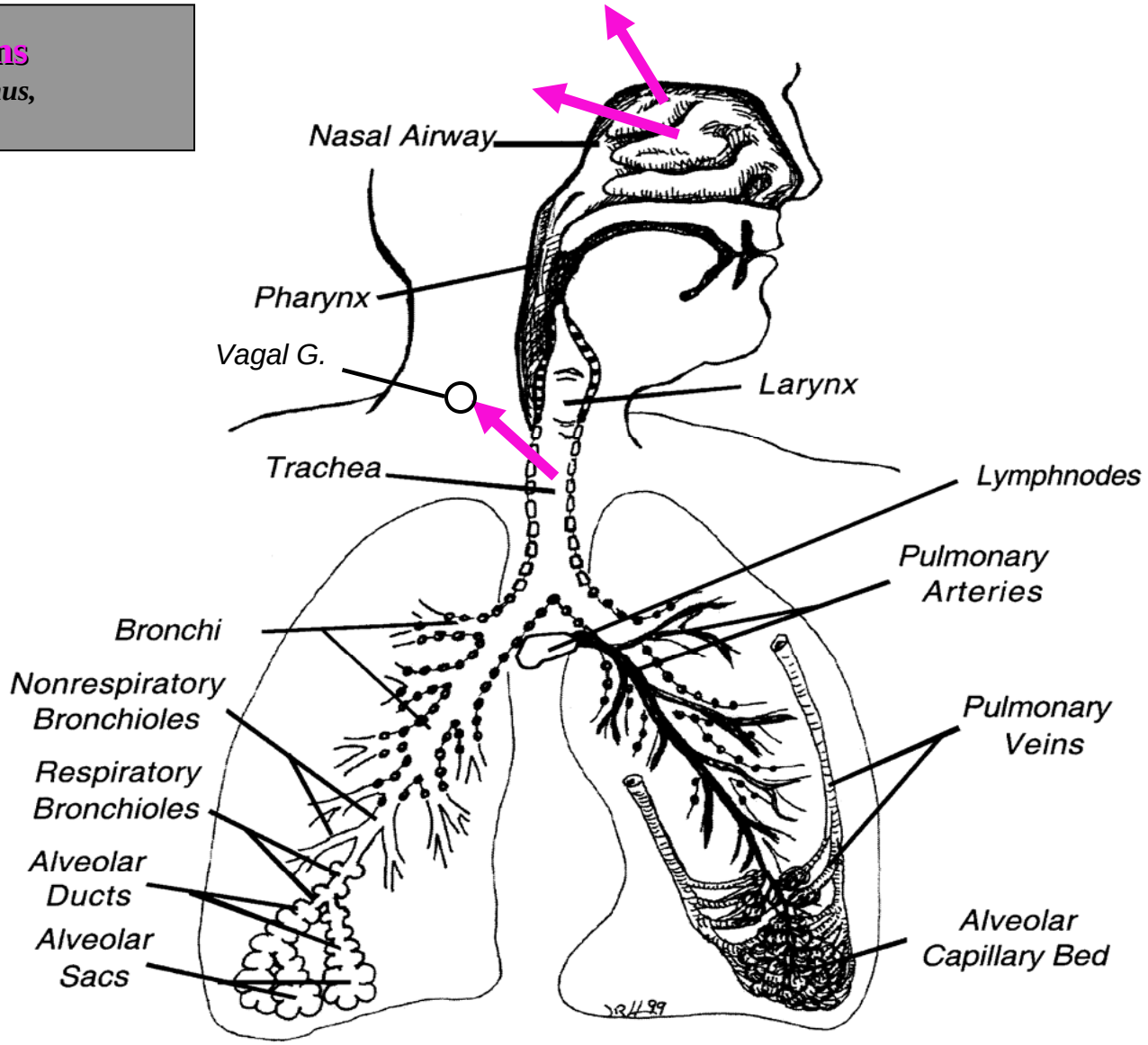
Oxidative stress?

Mitochondrial Localization after Dosing with Nano-sized Particles

Material and Cell Type	***Reference***
Gold nanoparticles, squirrel monkey mitral cells of olfactory bulb	***DeLorenzo (1970)***
Colloidal gold, Rhesus monkey, sustentacular cells of olfactory mucosa	***Gopinath et al. (1978)***
Fullerene derivative, *in vitro*, fibroblast cell line	***Foley et al. (2002)***
Ambient UFP, *in vitro*, macrophage cell line	***Li et al. (2003)***
Micellar nanocontainers (*Block copolymer micelles*), ***in vitro*, pheochromocytoma cells**	***Radoslav et al. (2003)***

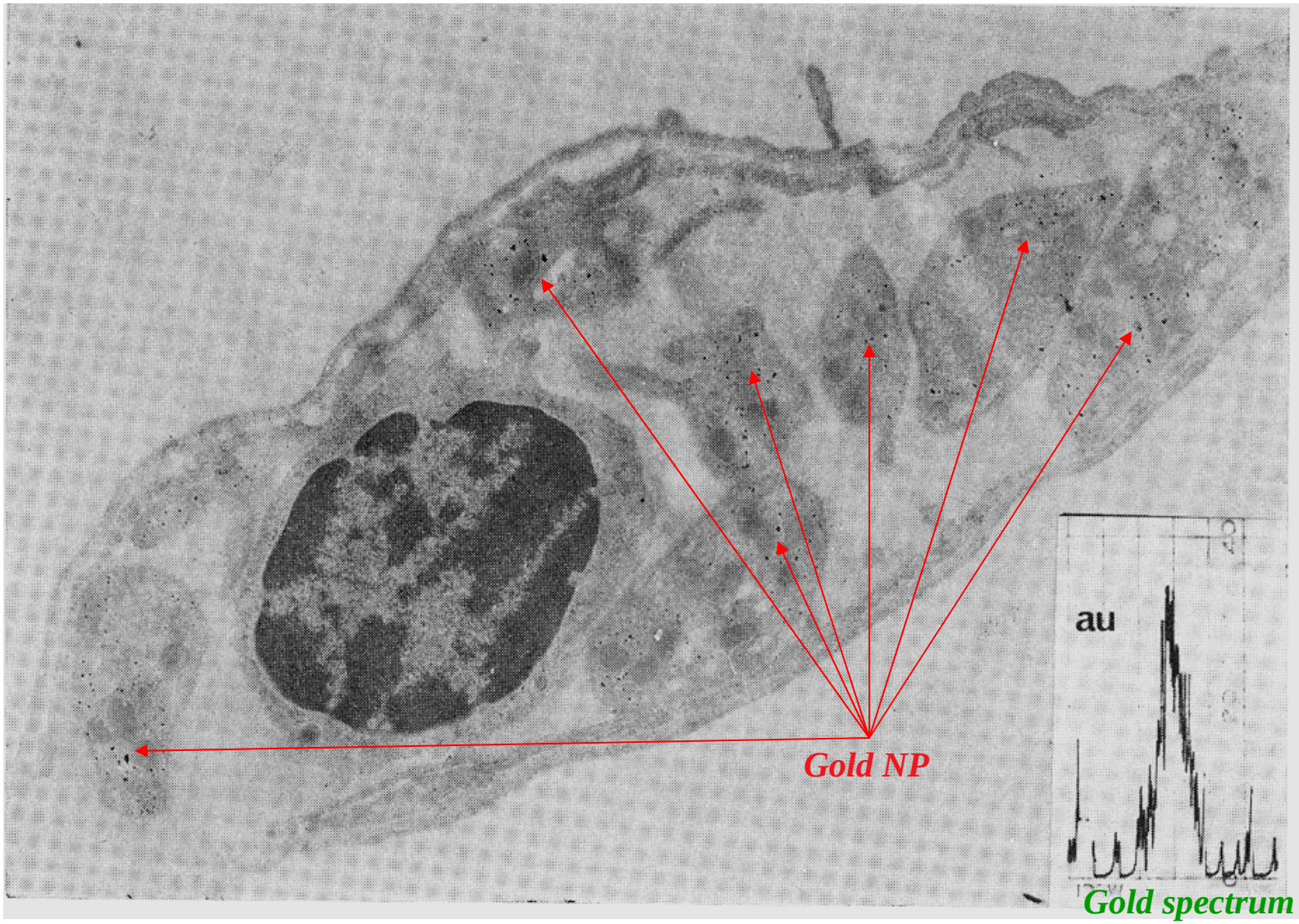
Pathways of Particle Translocation Within and Outside Respiratory Tract

Sensory Neurons
(olfactory, trigeminus, T.- bronchial)

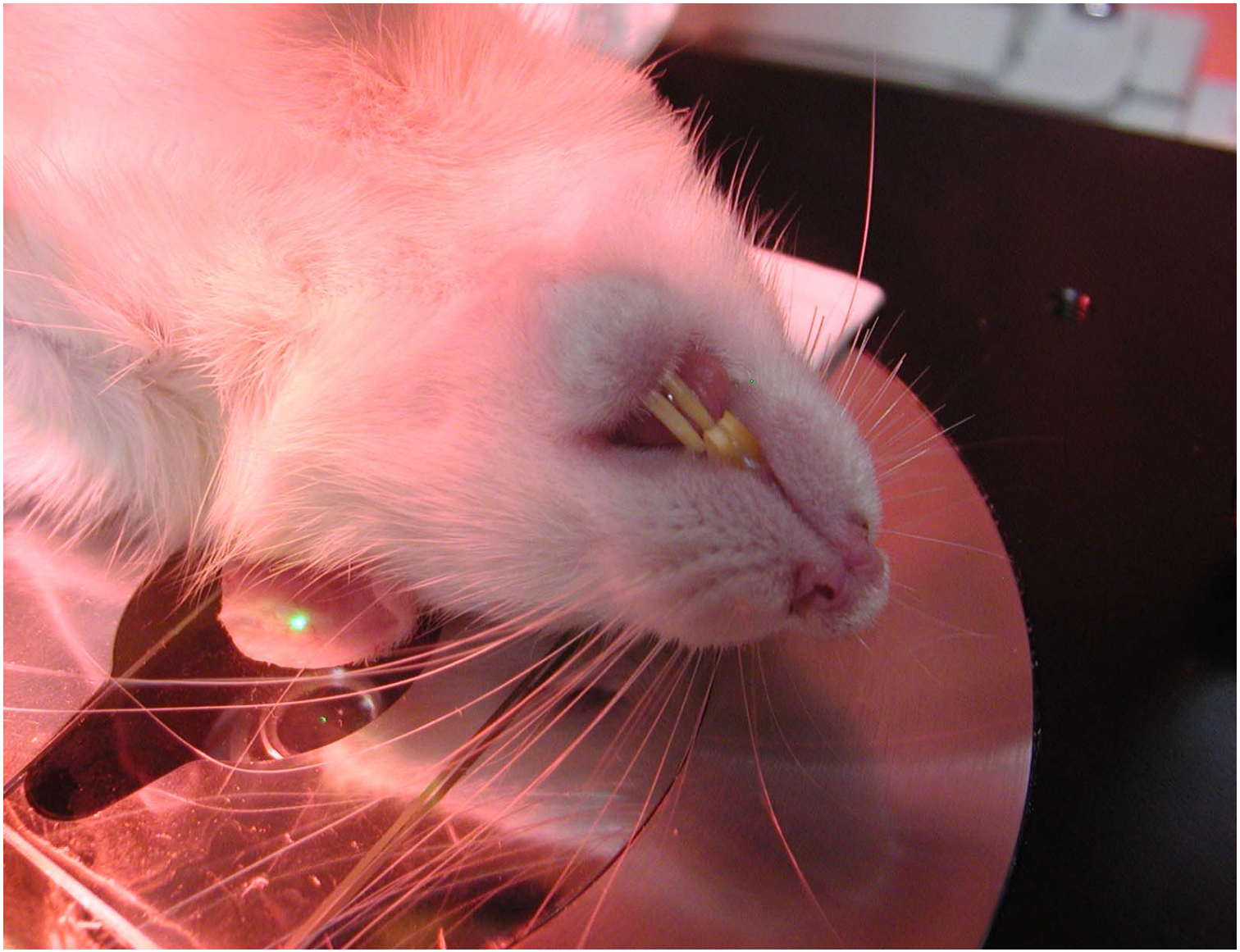


Gold nanoparticles (30 nm) in platelets of pulmonary capillary 30 mins. after intratracheal instillation into rats

(Berry et al., 1977)



Rat Ear Vein Model to Determine Particle Induced Thrombus Using Green Laser *(Silva et al, 2004)*



Alternative to femoral vein Rosebengal (RB) model:

Rat Ear Vein Model *(~ 100 um vessel)*

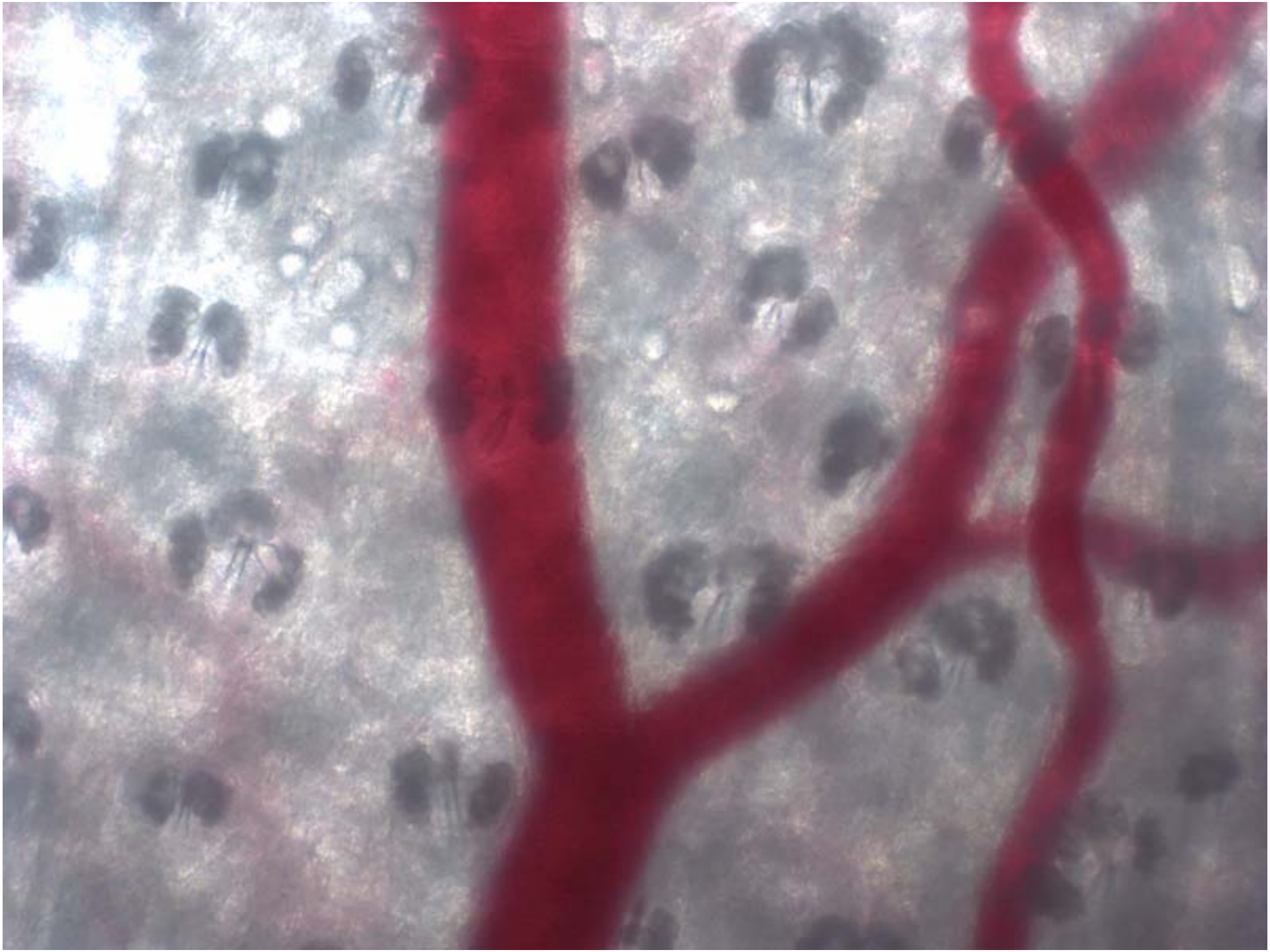
Advantages:

Noninvasive

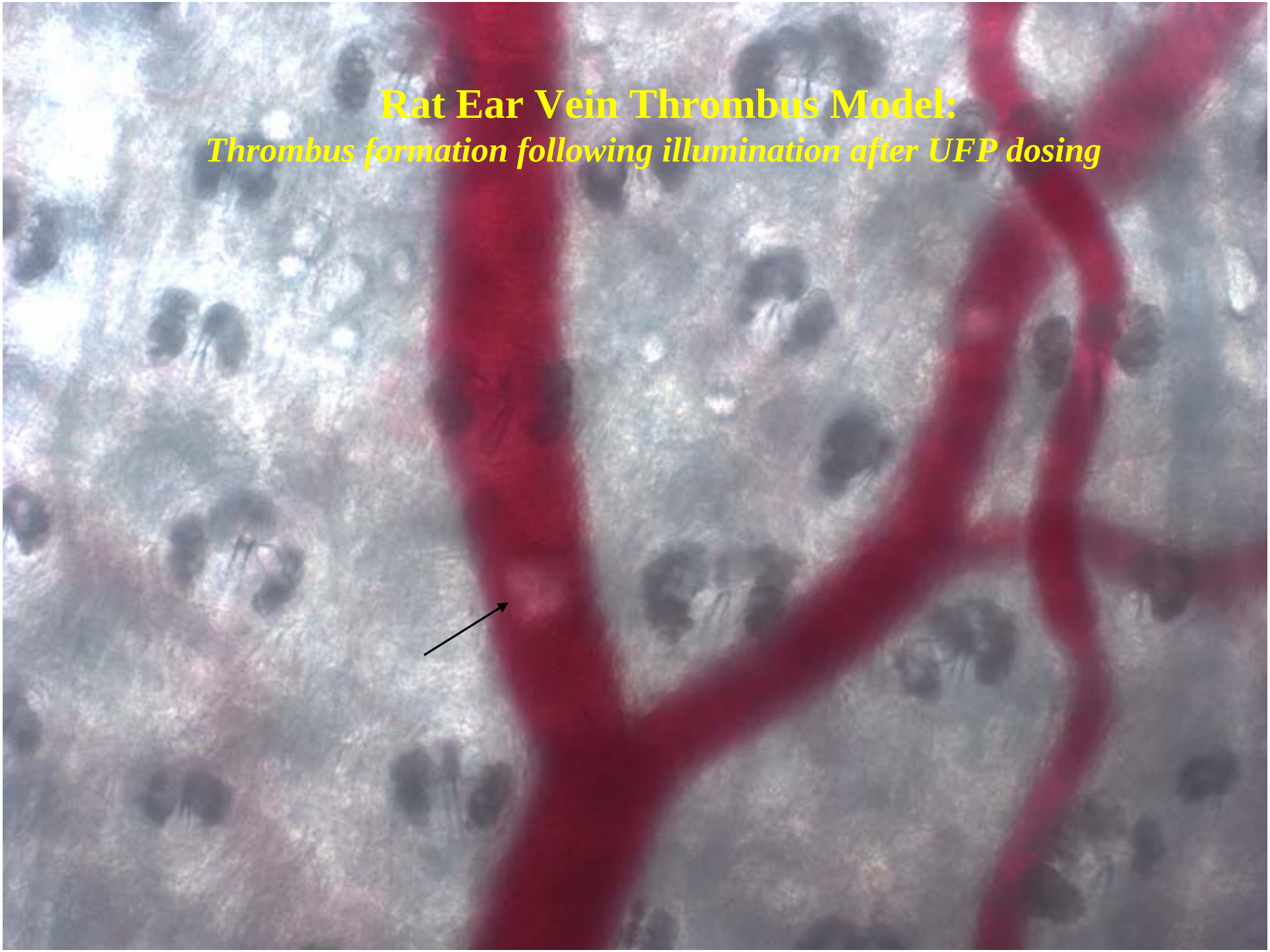
No RB, green laser only

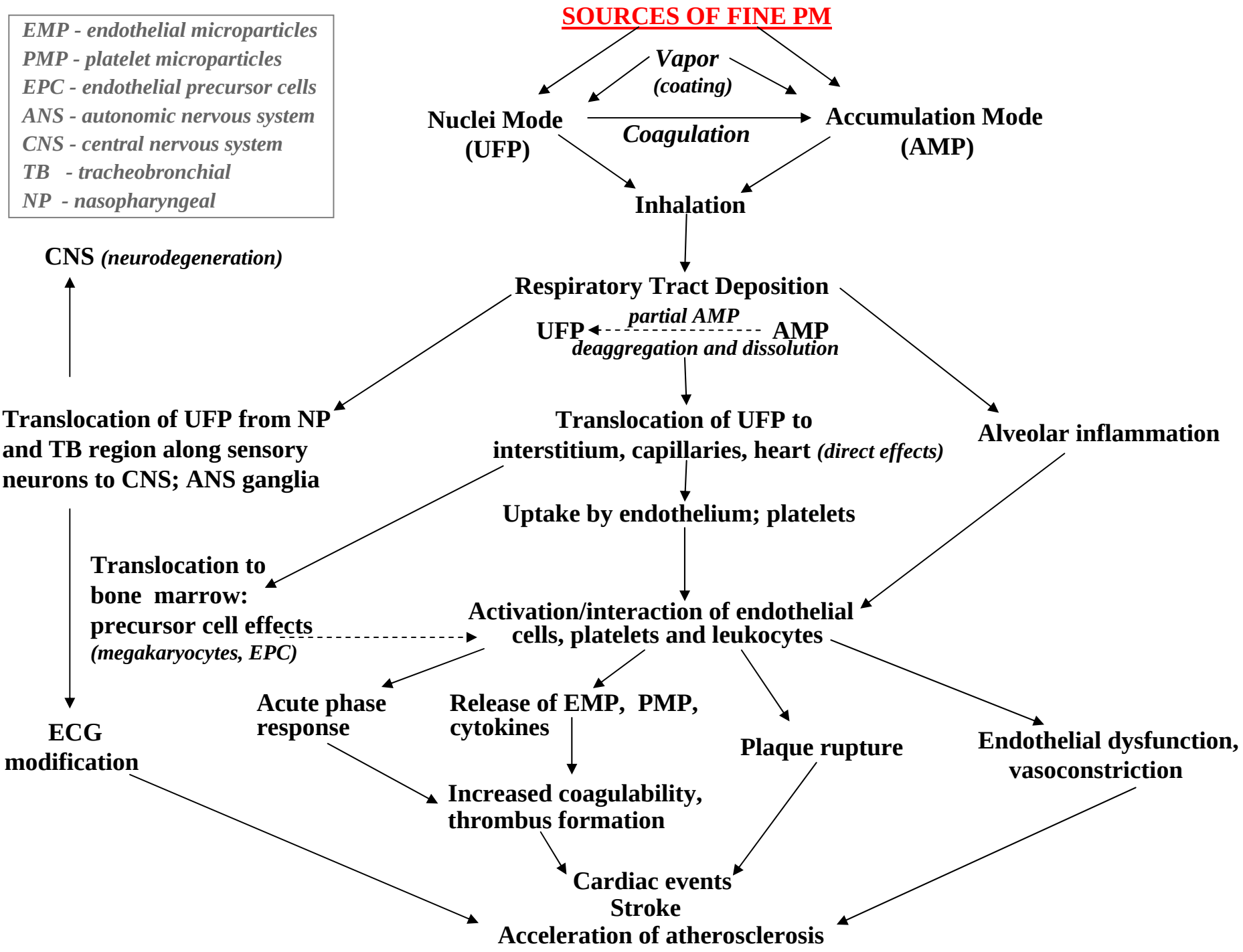
Same animal to be used as control and during and post PM exposure

Histological and histochemical examination of affected area




Rat Ear Vein Thrombus Model:
Placement of green laser for 30 sec


Rat Ear Vein Thrombus Model:
Thrombus formation following illumination after UFP dosing


EMP - endothelial microparticles
PMP - platelet microparticles
EPC - endothelial precursor cells
ANS - autonomic nervous system
CNS - central nervous system
TB - tracheobronchial
NP - nasopharyngeal
SOURCES OF FINE PM
Vapor
(coating)
Nuclei Mode
(UFP)
Coagulation
Accumulation Mode
(AMP)
Inhalation
CNS (neurodegeneration)
Respiratory Tract Deposition
partial AMP
UFP
AMP
deaggregation and dissolution
Translocation of UFP from NP and TB region along sensory neurons to CNS; ANS ganglia
Translocation of UFP to interstitium, capillaries, heart (direct effects)
Alveolar inflammation
Uptake by endothelium; platelets
Translocation to bone marrow: precursor cell effects
(megakaryocytes, EPC)
Activation/interaction of endothelial cells, platelets and leukocytes
Acute phase response
Release of EMP, PMP, cytokines
ECG modification
Plaque rupture
Endothelial dysfunction, vasoconstriction
Increased coagulability, thrombus formation
Cardiac events
Stroke
Acceleration of atherosclerosis