Pro-Inflammatory Cytokine Responses to Exposure to Diesel Soot

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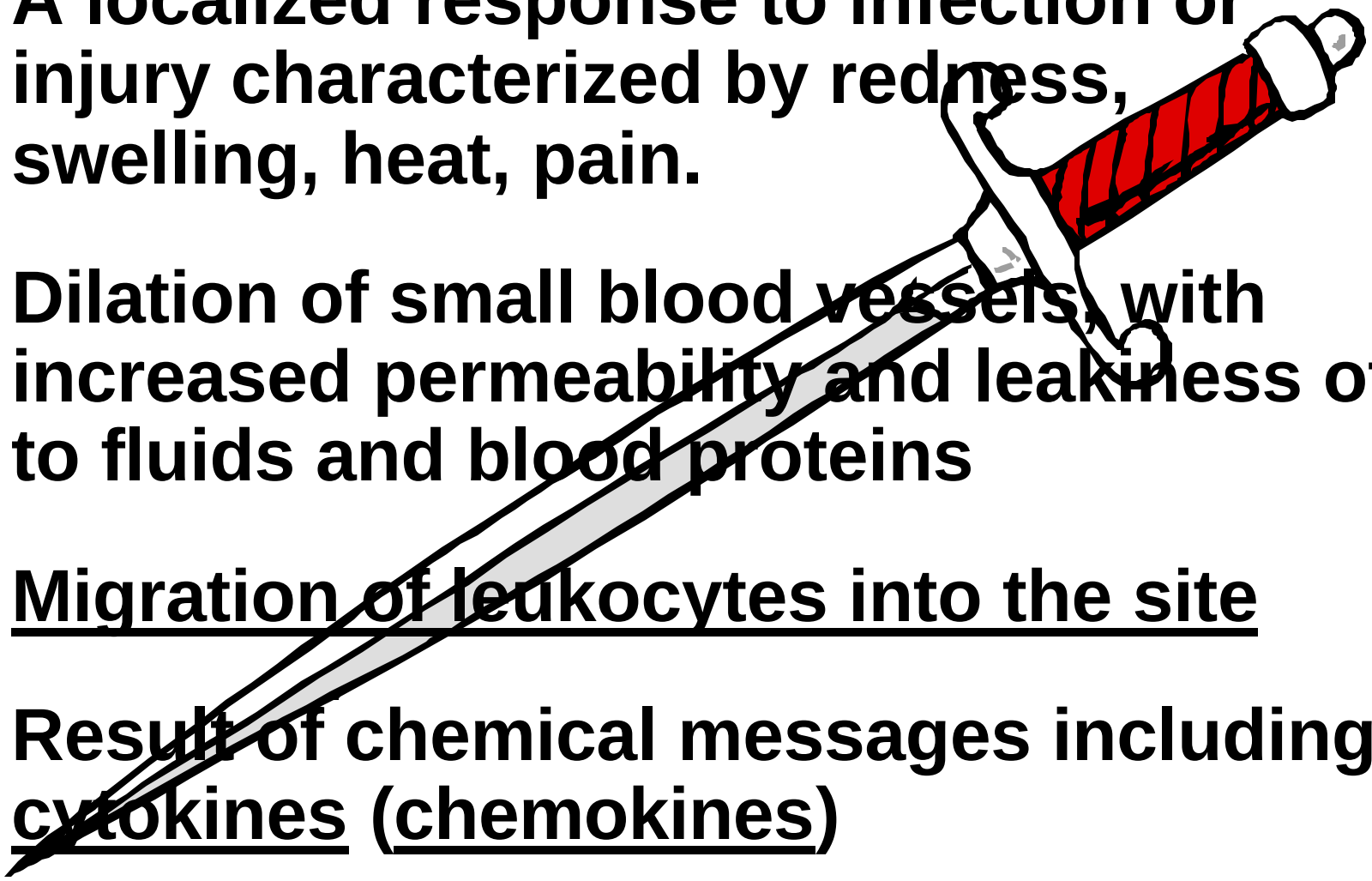
Inflammation

- **A localized response to infection or injury characterized by redness, swelling, heat, pain.**
- **Dilation of small blood vessels, with increased permeability and leakiness of to fluids and blood proteins**
- **<u>Migration of leukocytes into the site</u>**
- **Result of chemical messages including <u>cytokines</u> (<u>chemokines</u>)**

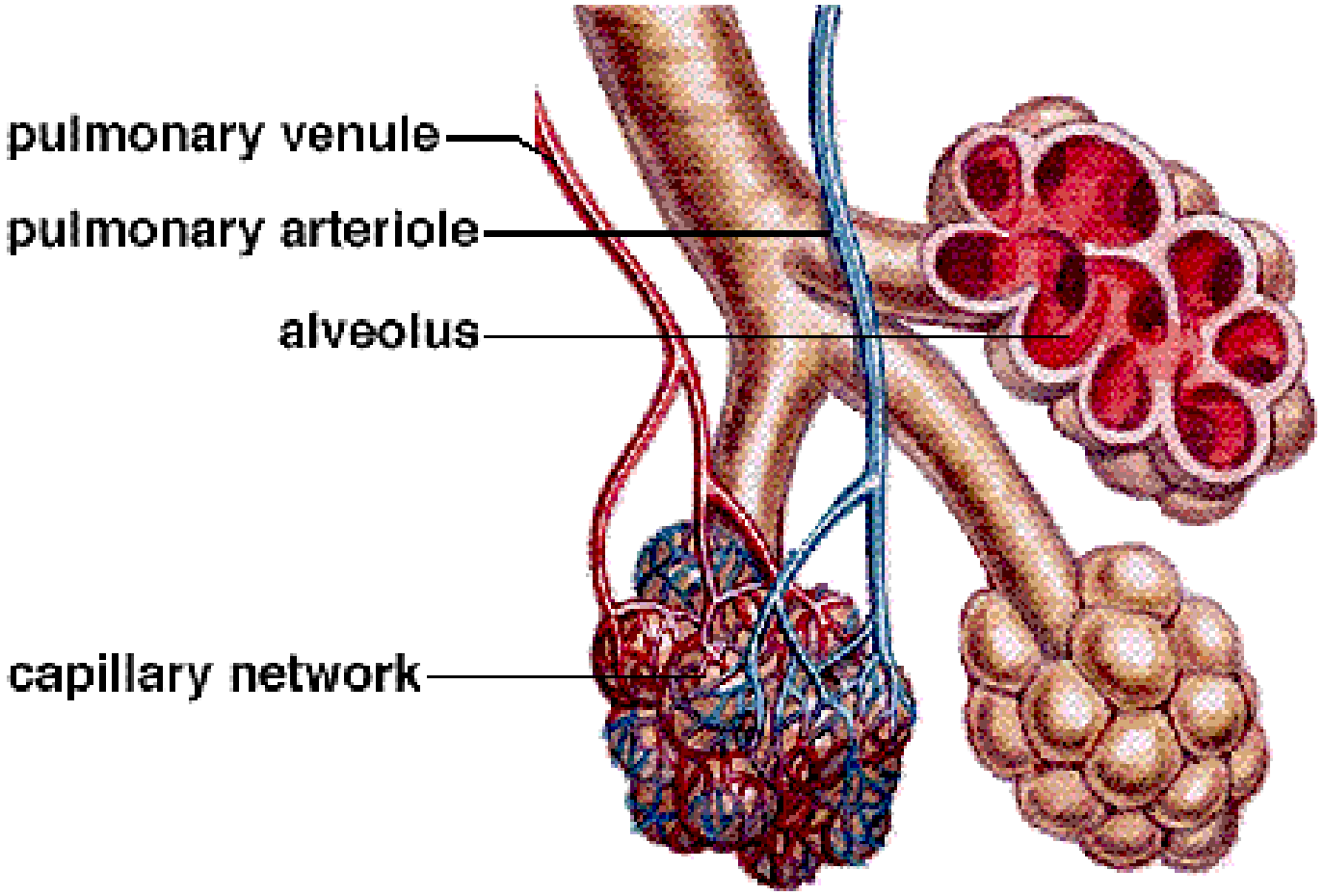


Rationale

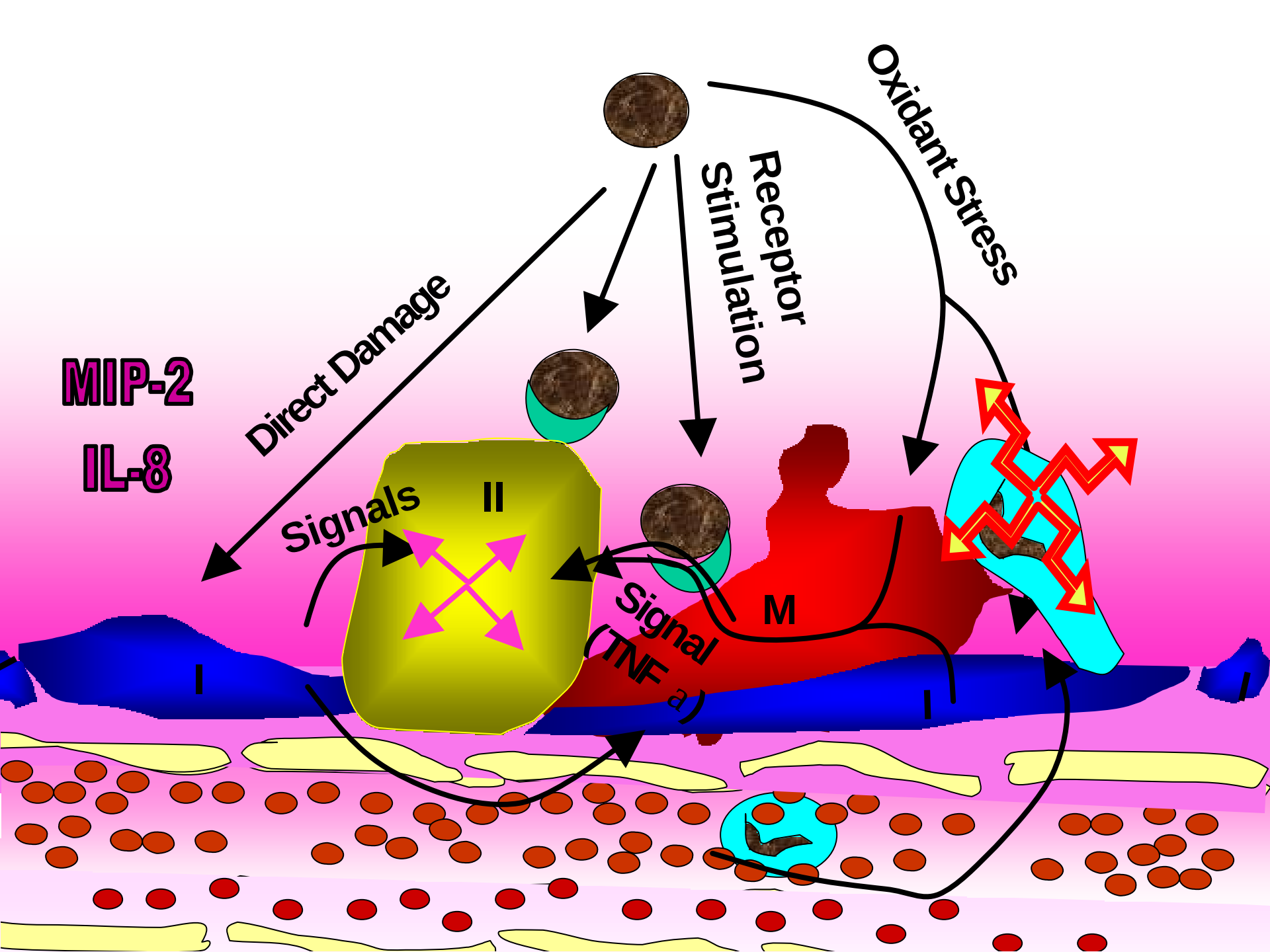
Diesel exhaust causes lung inflammation.

- Little known about mechanisms
- What metric should be used to assess value of changes in technology?
  - Mass
  - Number
  - Size
  - Chemistry
  - Surface area
- Understanding the biological effects can focus future engineering/regulatory efforts

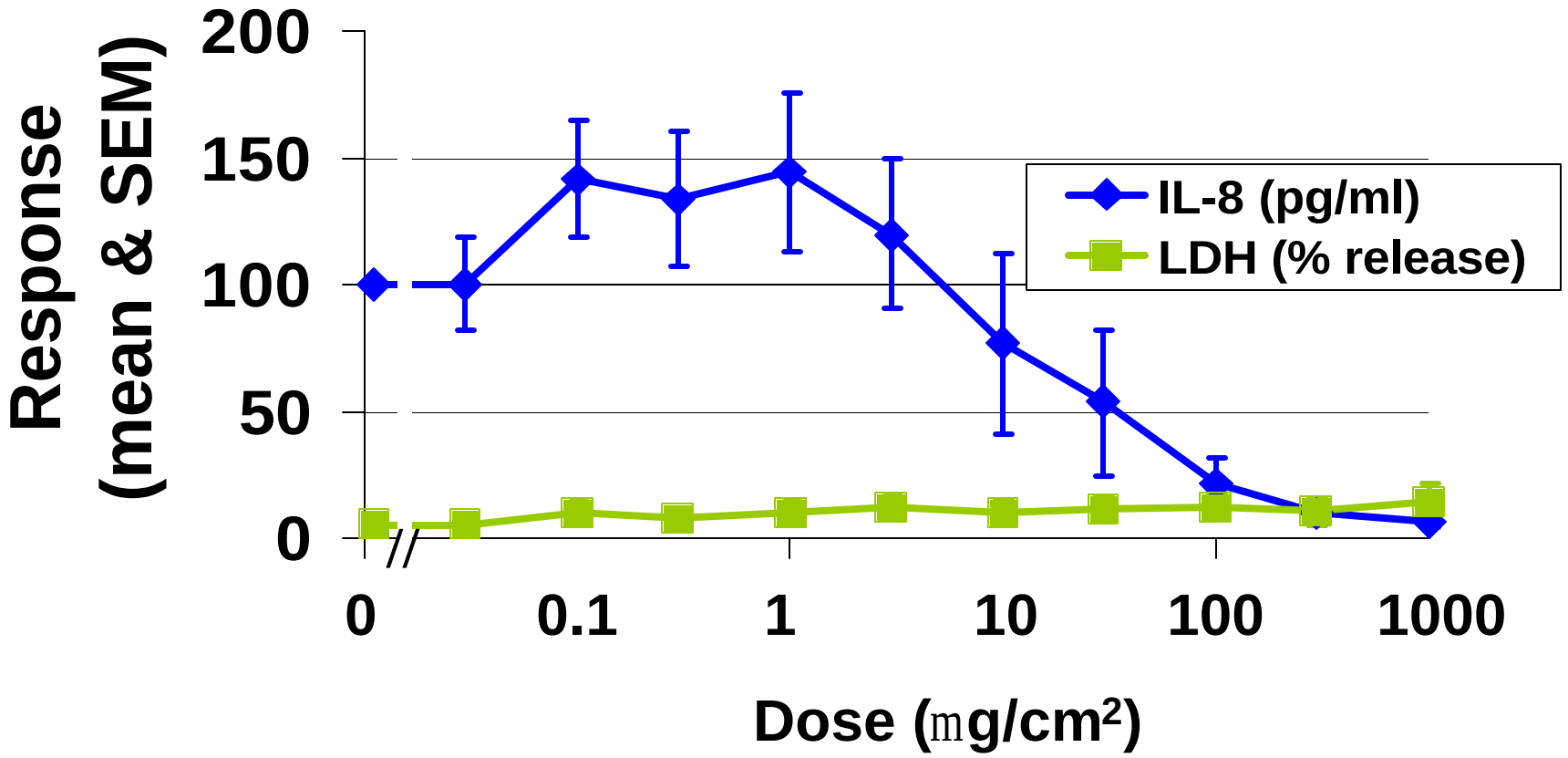
Closeup of the Alveoli



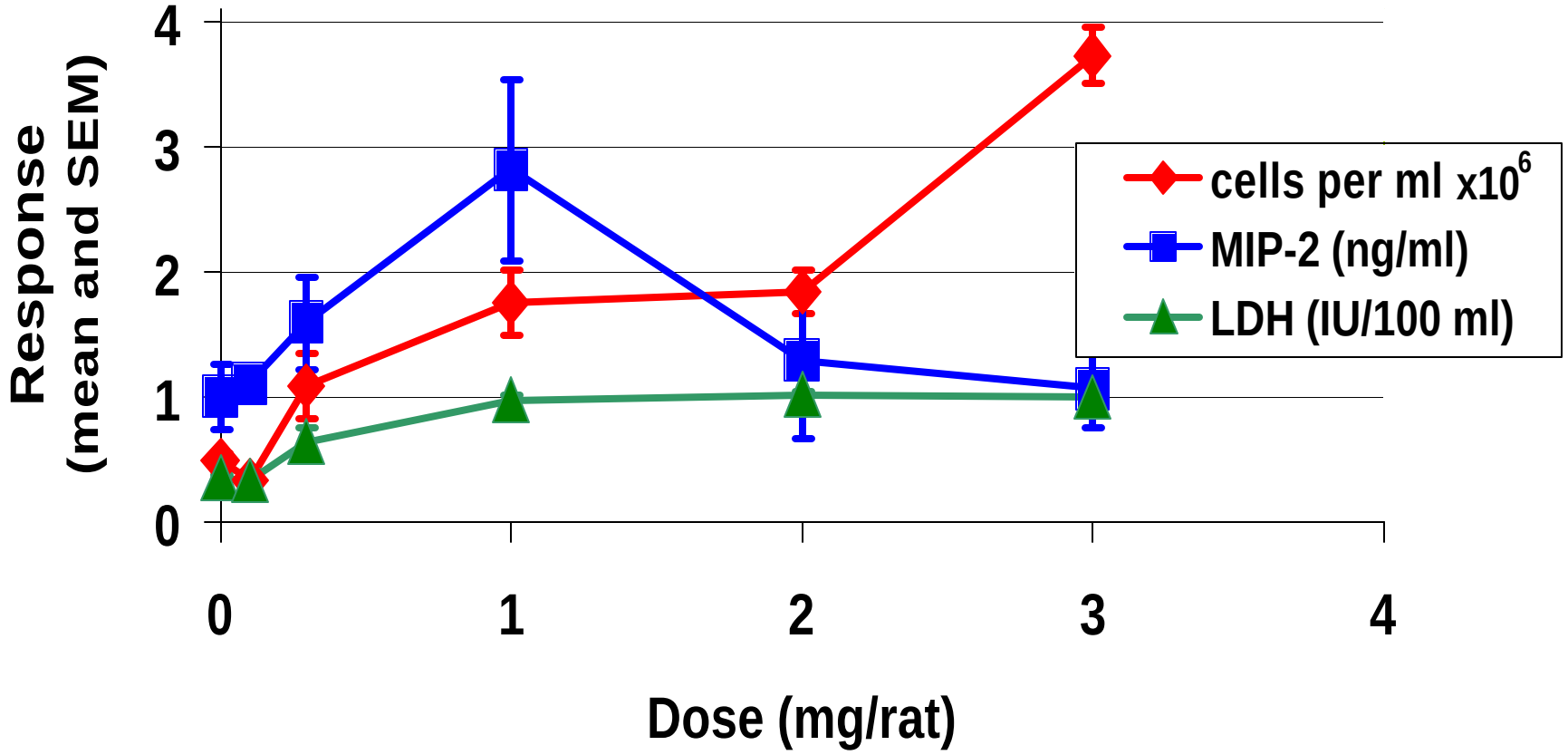
http://www.sinc.sunysb.edu/Class/bio101/Lecture9/sld010.htm


Oxidant Stress
Receptor Stimulation
Direct Damage
MIP-2
IL-8
Signals
II
M
Signal (TNF α)
I
I
I

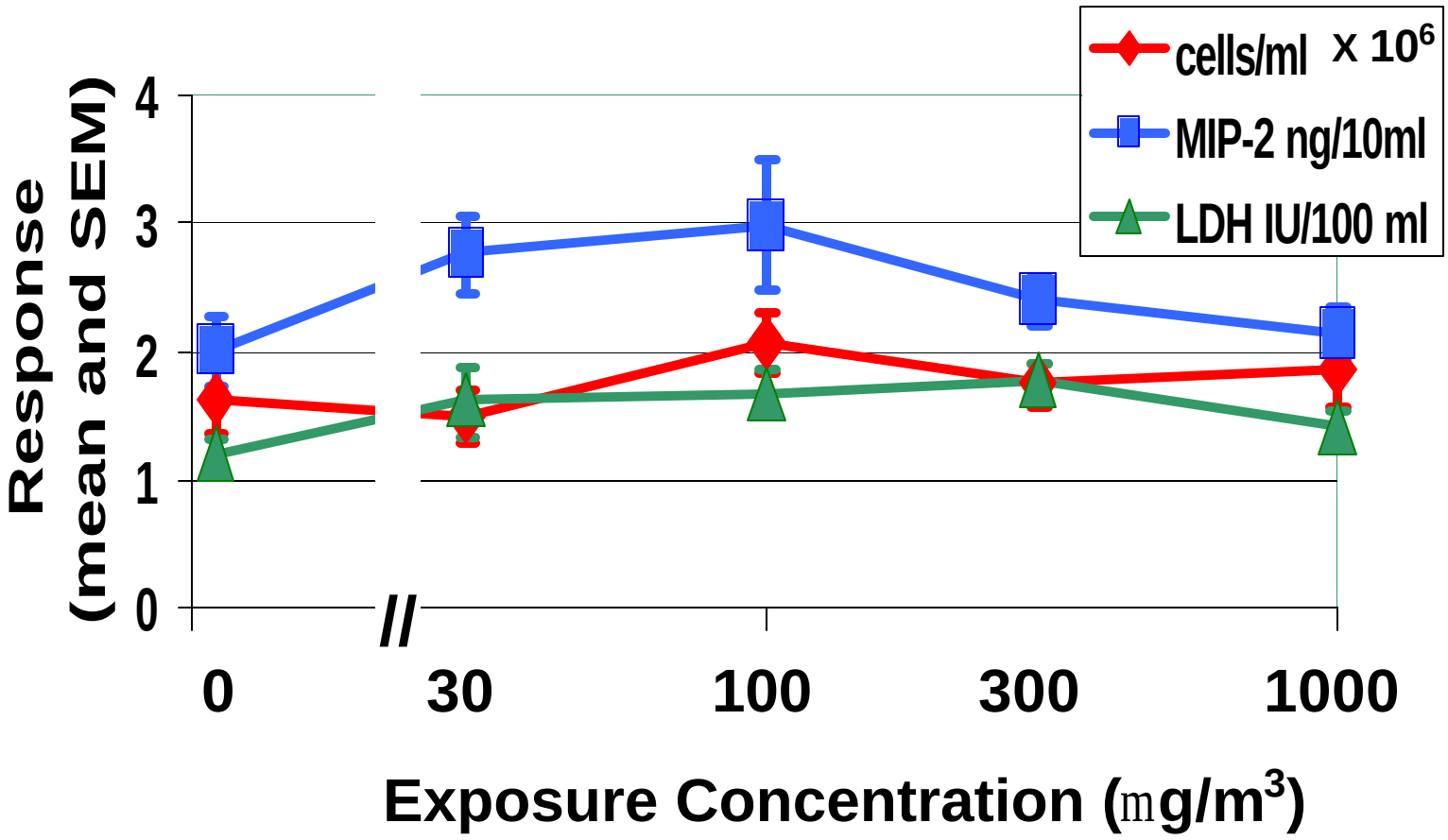
Response of Epithelial Cells in Culture to Diesel PM (SRM2975)



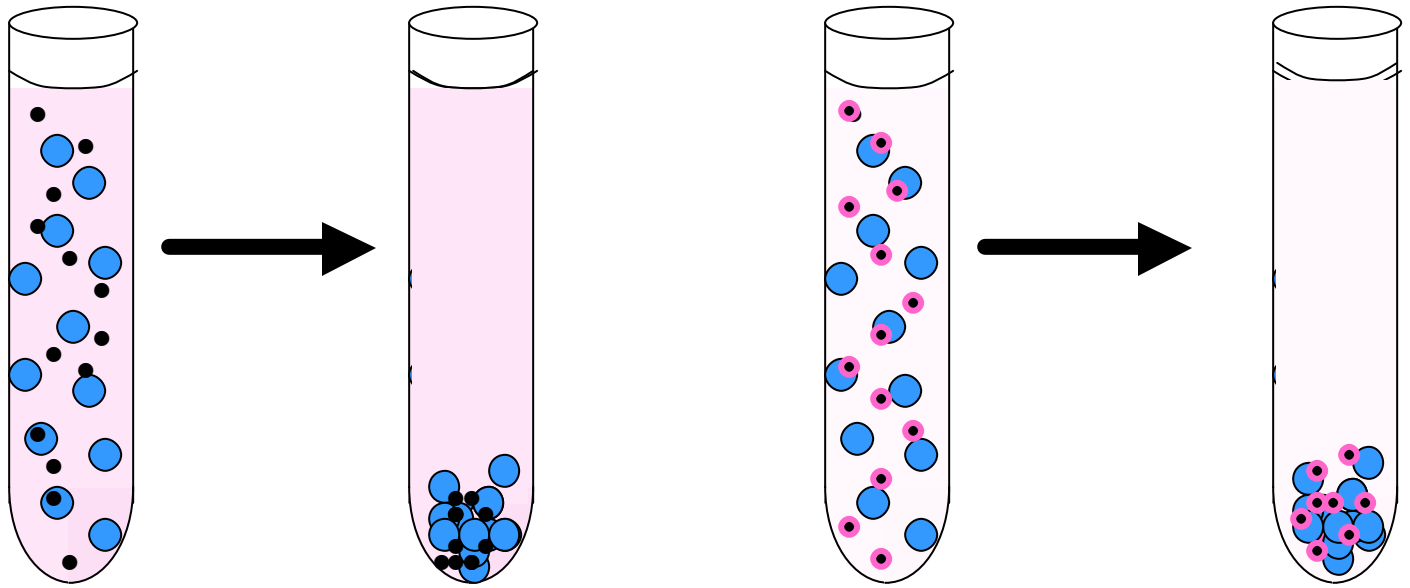
Response to Intratracheal Instillation of Diesel PM (SRM2975)



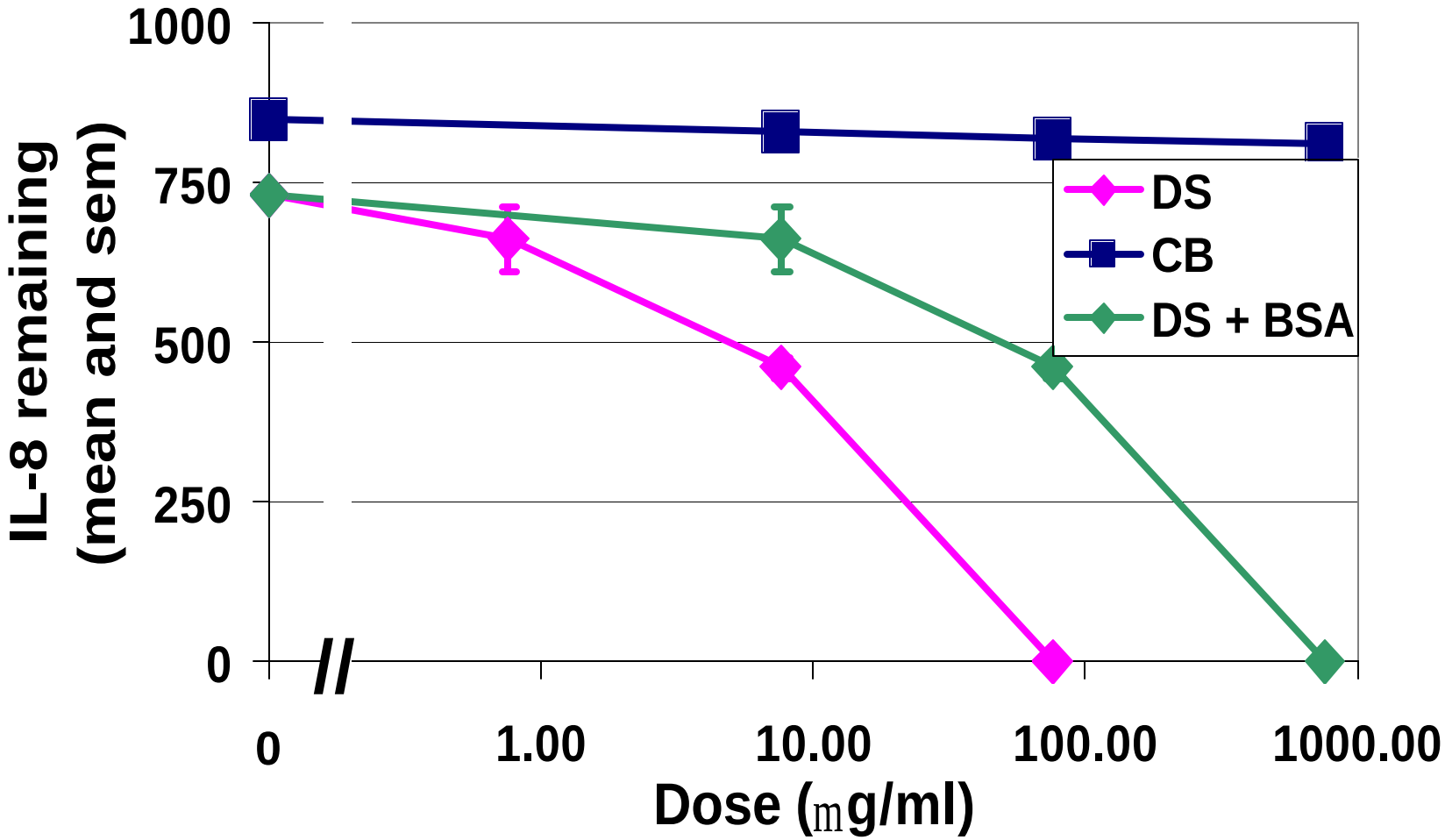
Response to 6 mo Inhalation of Diesel Exhaust



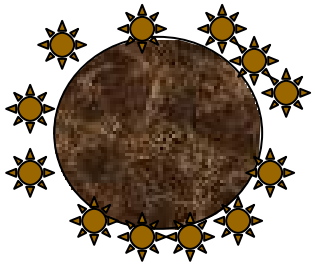
Cytokines and PM in Suspension

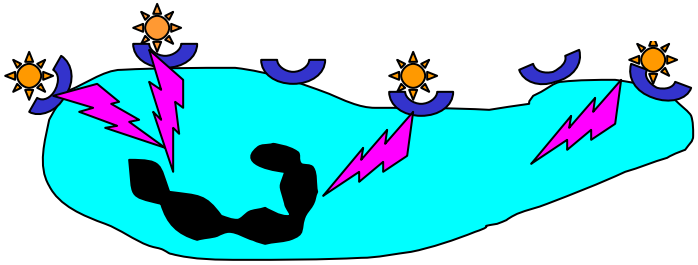


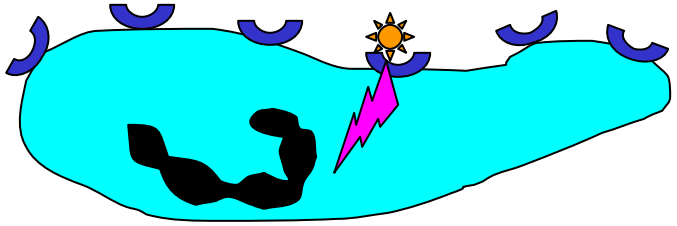
Diesel PM (SRM2975) Binds IL-8



Biological Implications?

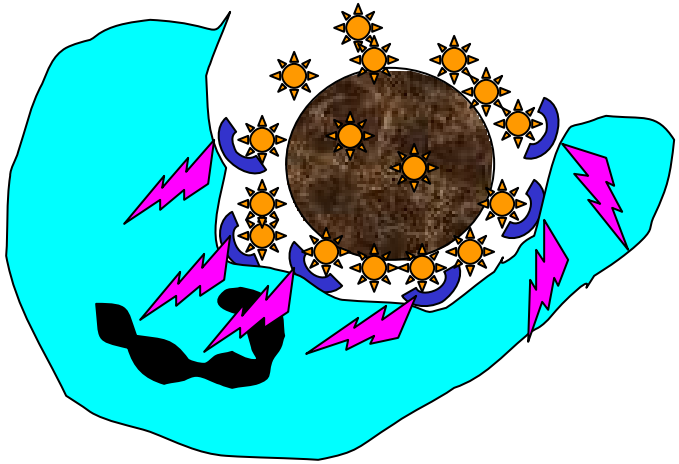




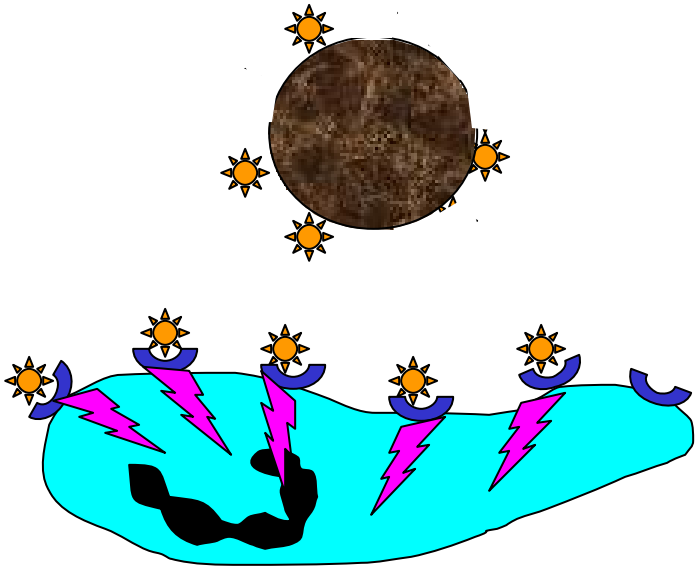


Normal: Free IL-8 diffuses to receptors, eventually cleared.

IL-8 Bound and inactive: Less available for receptor binding and neutrophil recruitment



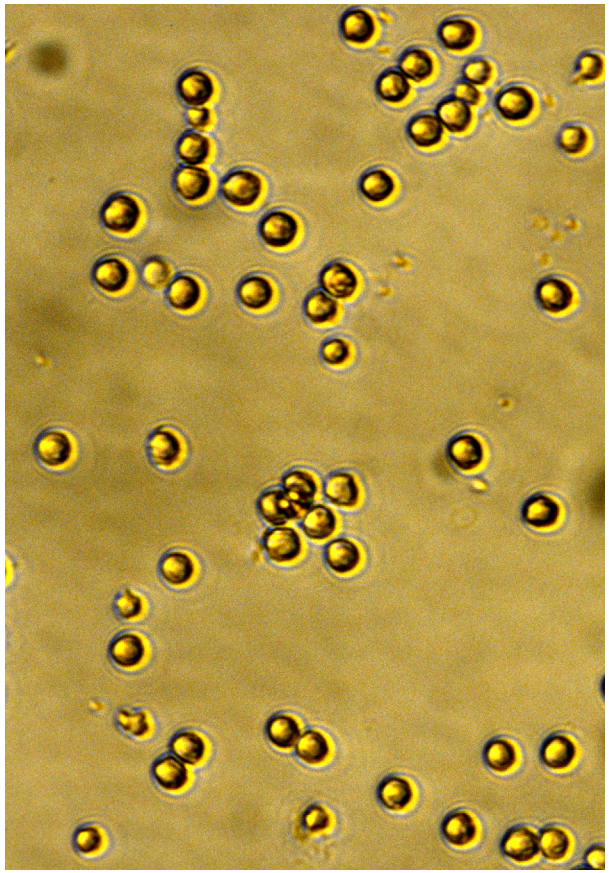
IL-8 tightly bound but active: Possible concentrated presentation to neutrophils and increased activation.



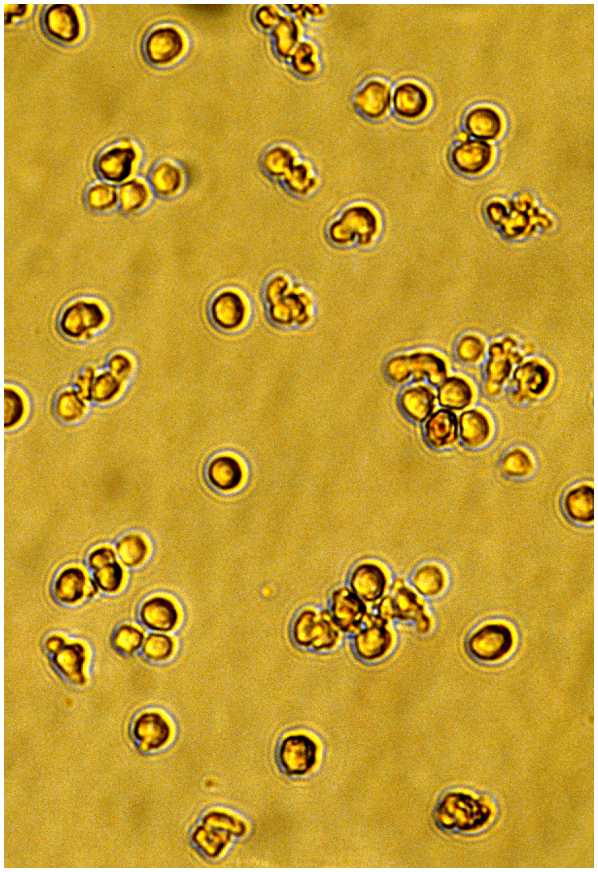
IL-8 weakly bound but active: may serve as reservoir for sustained release.

Neutrophils Change Shape in Response to IL-8, not to DS

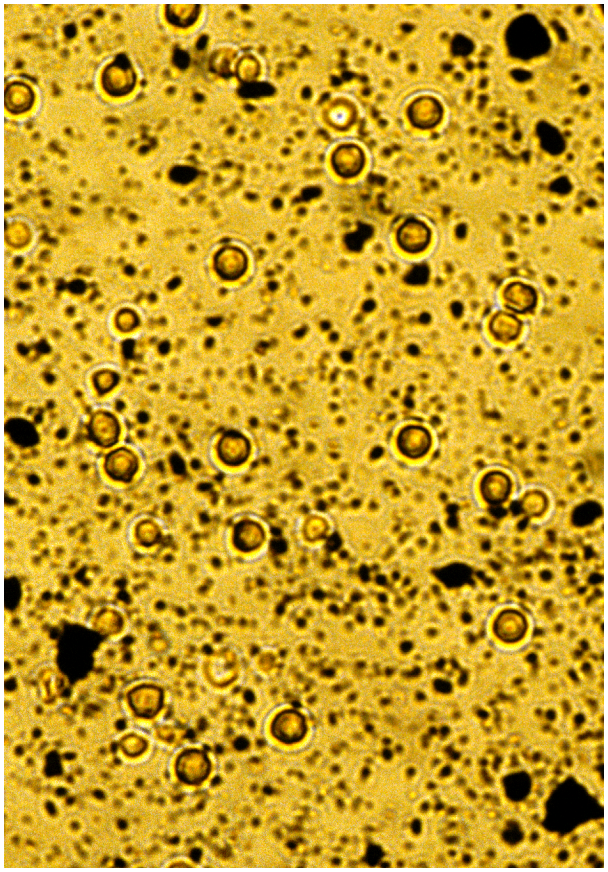
Control neutrophils



+ 500 ng/ml IL-8

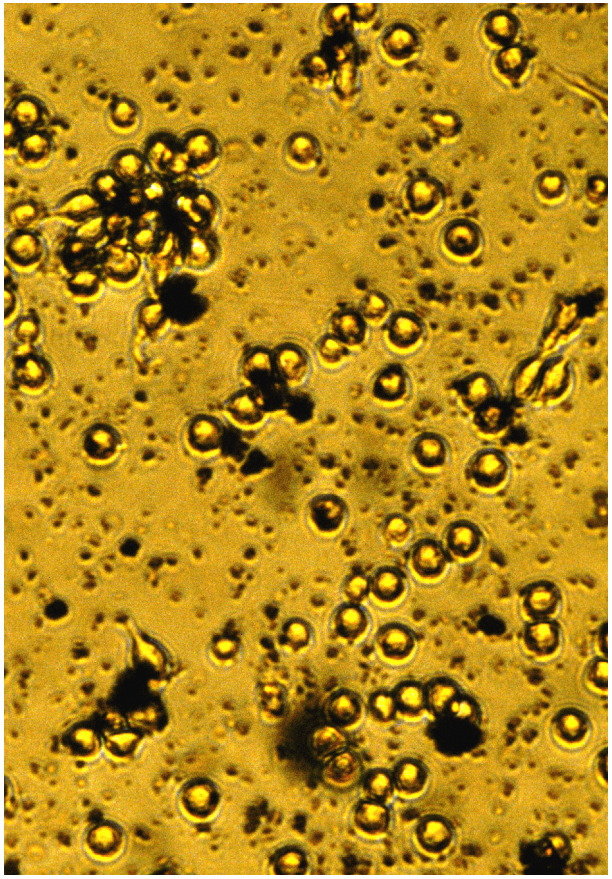


+ 150 μg/ml DS

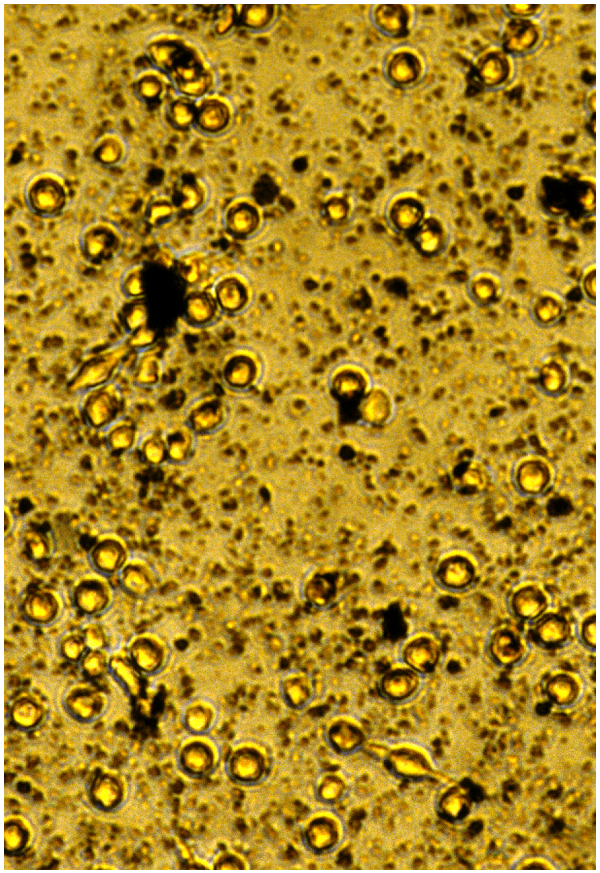


Neutrophils Respond to DS-Bound IL-8

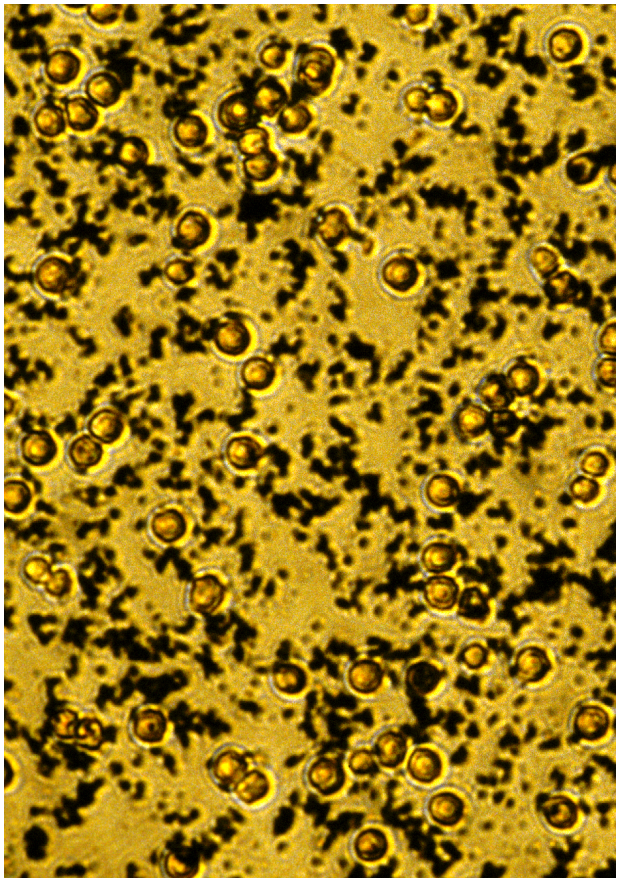
DS pre-treated with 250 ng/ml IL-8



DS + BSA + 250 ng/ml IL-8



CB pre-treated with 250 ng/ml IL-8



Summary

- **Diesel PM binds IL-8 (and MIP-2)**
  - **Diesel PM >>CB**
  - **High affinity/specific**
    - **not simple non-specific binding of proteins**
  - **Biologically active**
- **Surface chemistry may be an important factor in emissions-associated inflammation.**