Centre for
Inflammation
Research

Inflammatory Pathways in Humans – A Broader Perspective.

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Inflammation

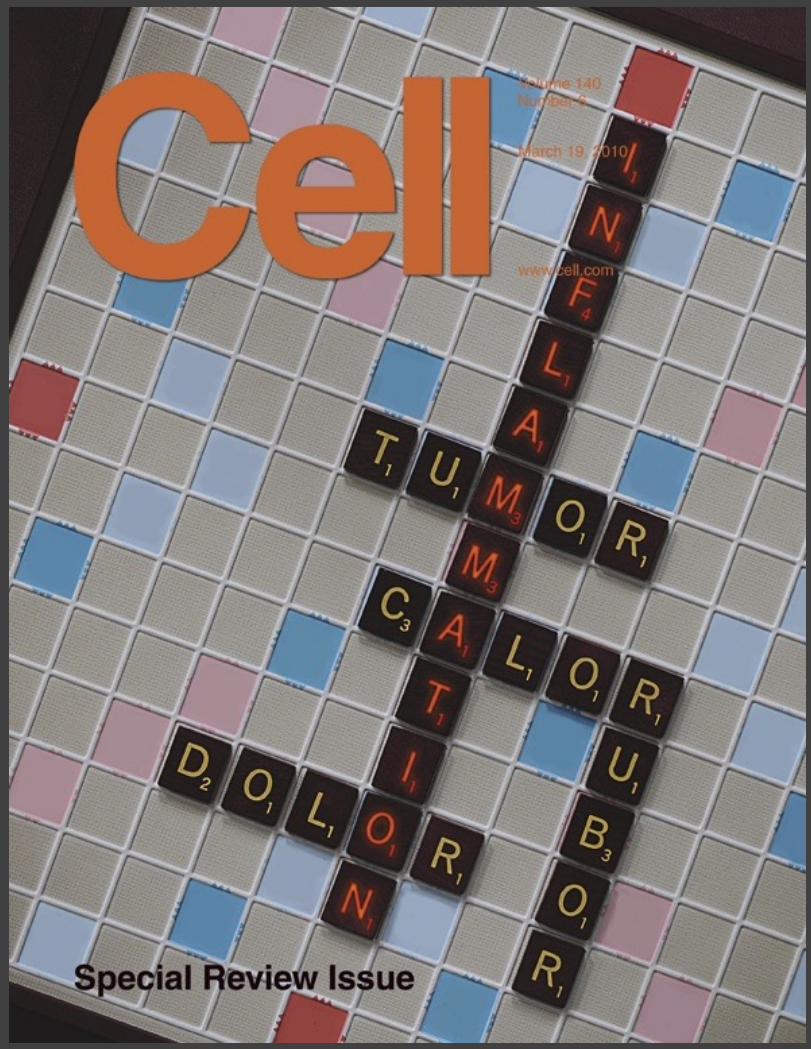
Inflammation:
the response of living tissue to damage.

The acute inflammatory response

1. Inflammatory Mediators and Cells:
- delivered to inflamed site

2. Causative agent removed
- destruction and elimination

3. Repair of Damage:
- tissue degradation and clearance



We still don't fully understand why inflammatory processes PERSIST and cause DISEASE

Key features of inflammation?

Function:

Host defence against micro-organisms

Control of tumour growth and metastasis

Tissue repair and restoration of organ function

Controlled by inflammatory mediators:

Cytokines, chemokines, lipid mediators, peptides

Collaboration between tissue and inflammatory cells

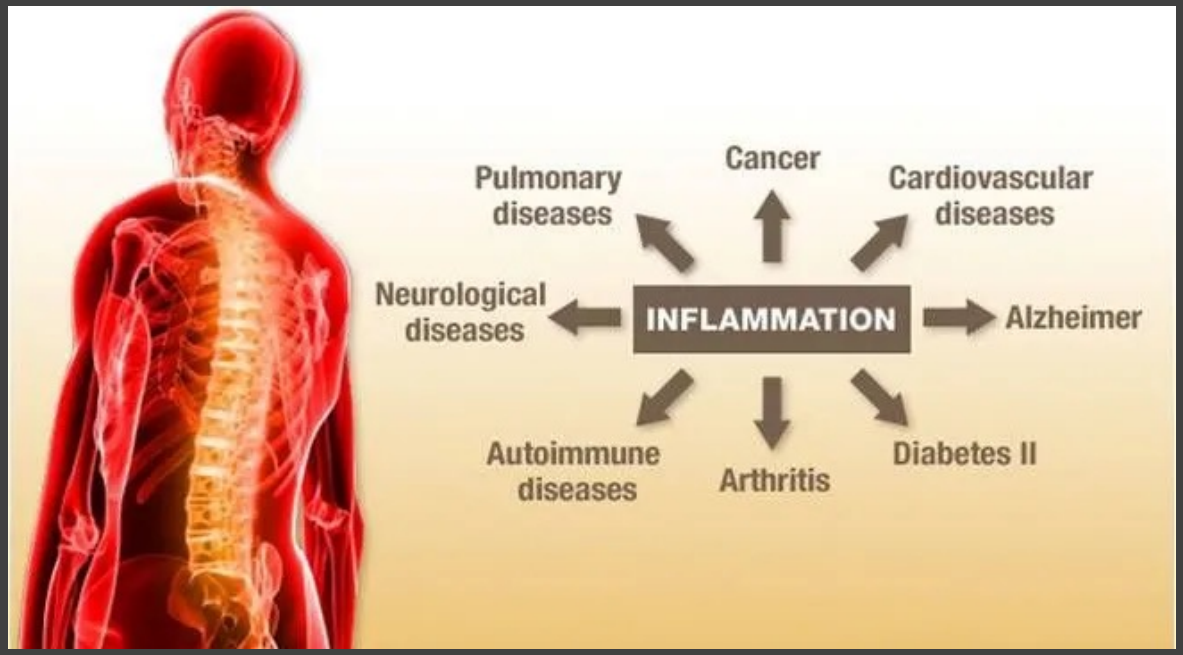
Granulocytes, Monocytes/macrophages, Mast Cells

Epithelial, Fibroblasts, Endothelial and Stem cells

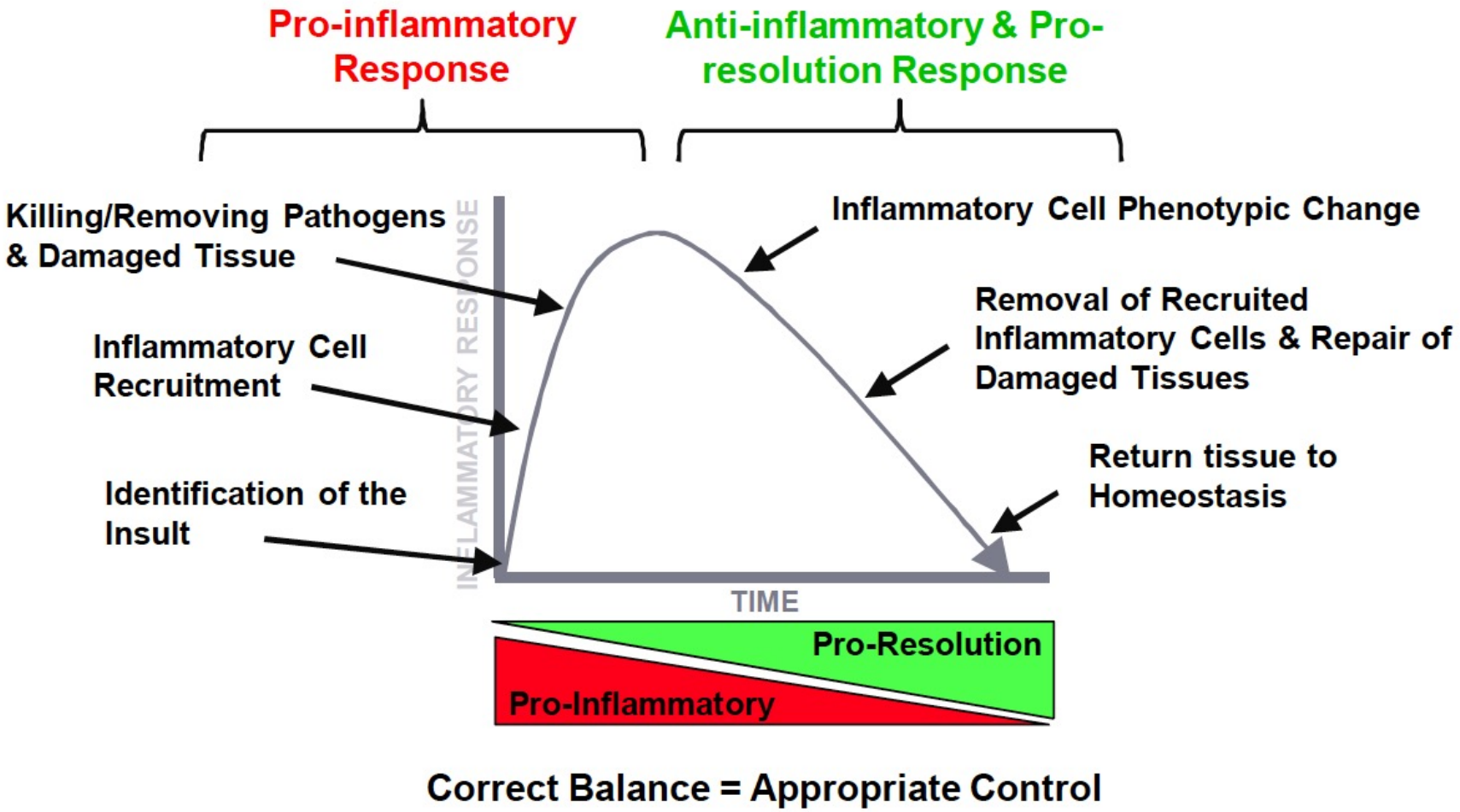
Inflammatory diseases

Inappropriate host response leading to disease:

- Some common mechanisms
- Affect virtually every organ in the body:

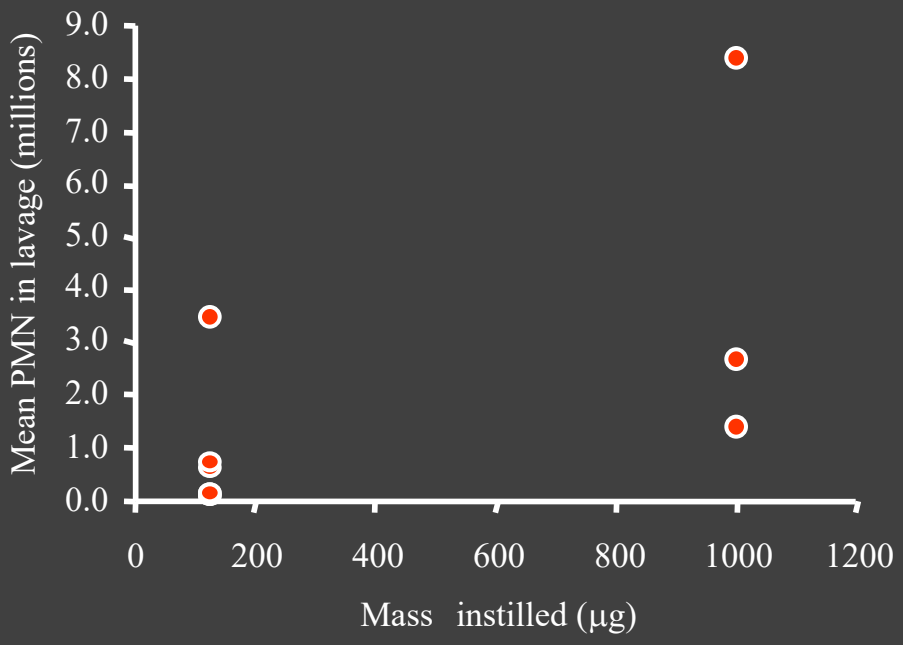


Inflammation: how should it be orchestrated?

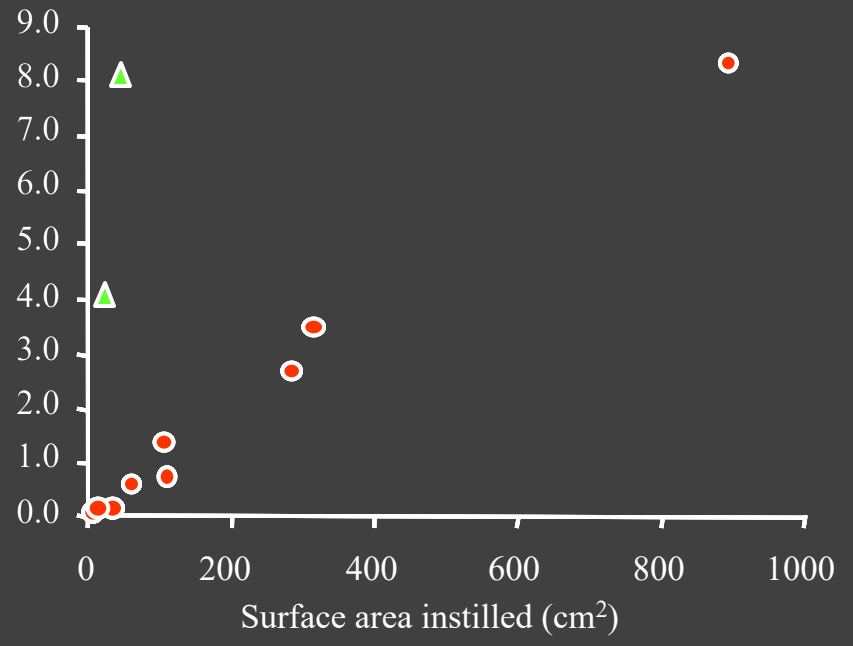


A range of fine and nanoparticle-sized PSLTs cause inflammation in relation to surface area dose, not mass dose

Dose expressed as mass instilled

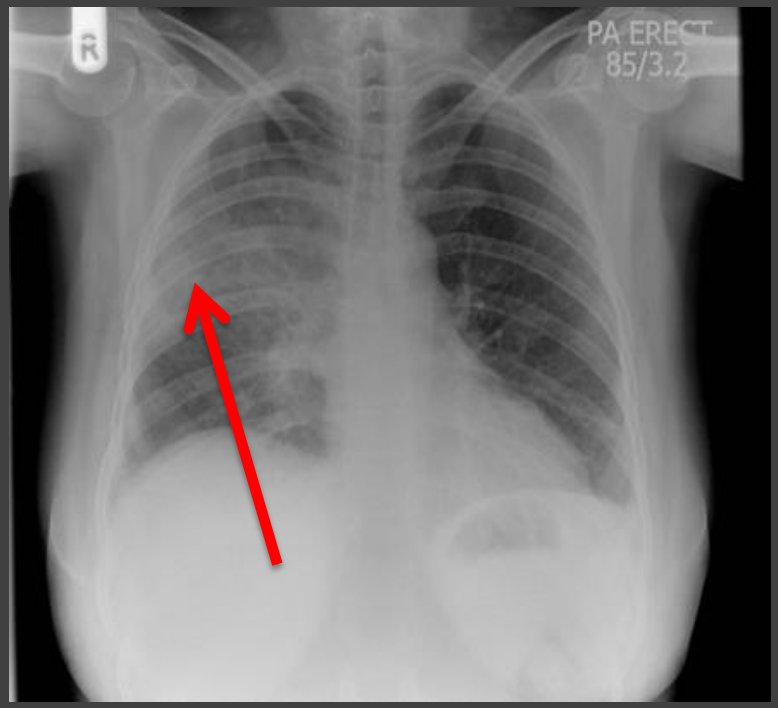


Dose expressed as surface area instilled



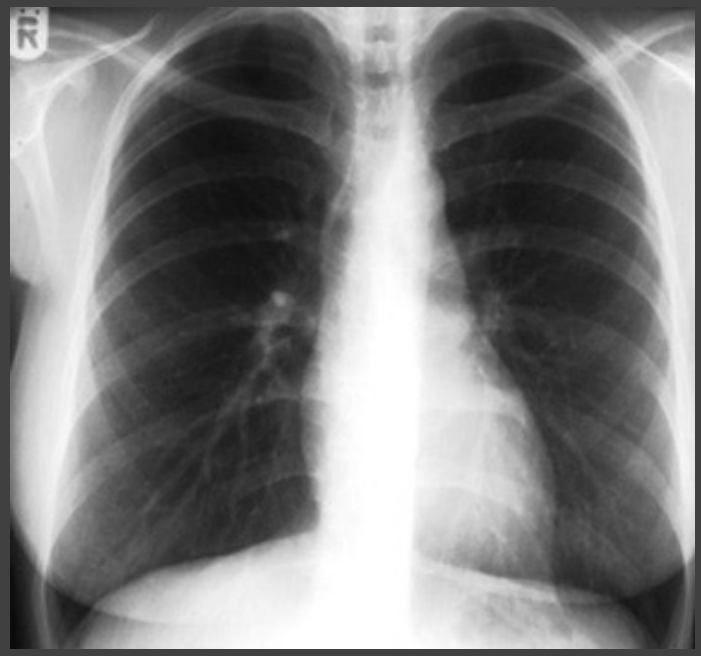
Duffin R, Clouter A, Brown DM, C. L. Tran, MacNee W, Stone V, and Donaldson K. 2002. The importance of surface area and specific reactivity in the acute pulmonary inflammatory response to particles. *Ann Occup.Hyg* 46 Suppl 1:242-245.

Pneumonia: a common medical problem



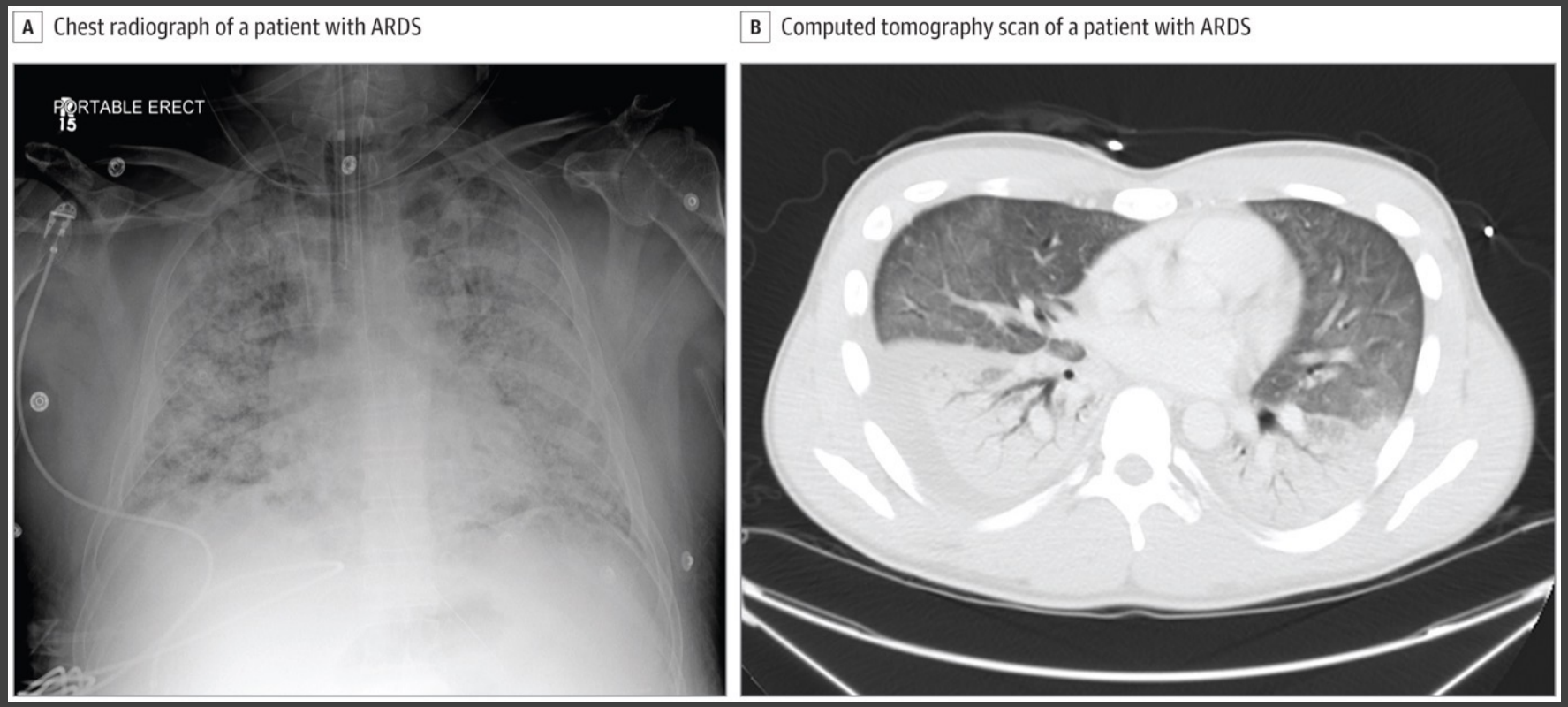
Pneumonia

Treatment



Recovery

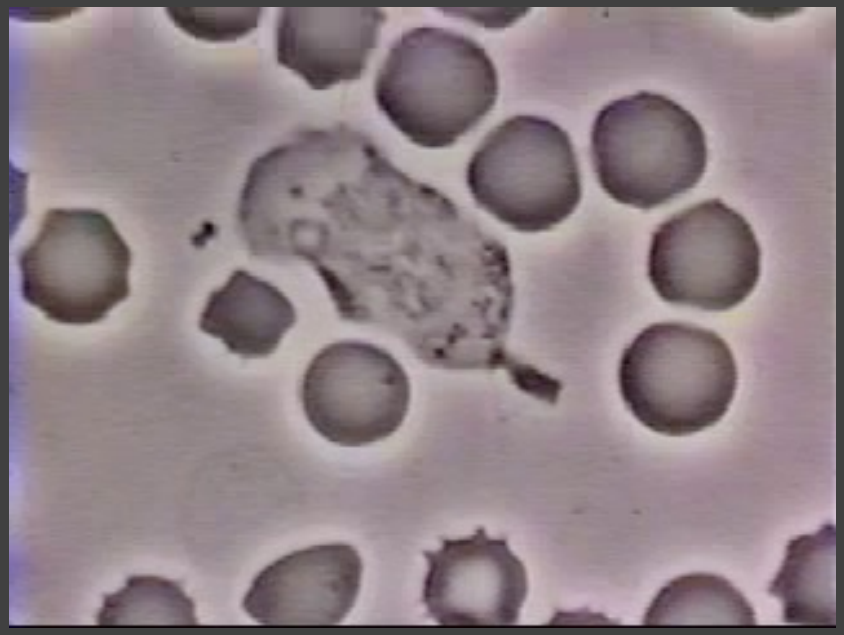
ARDS: when lung inflammation goes rogue



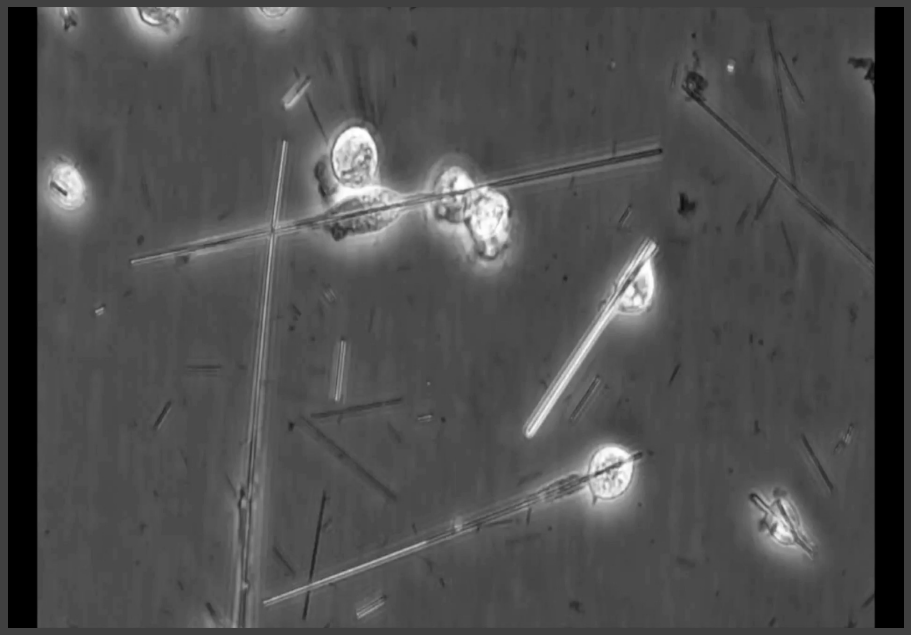
JAMA 2018

Inflammation - to kill or to clear?

neutrophil



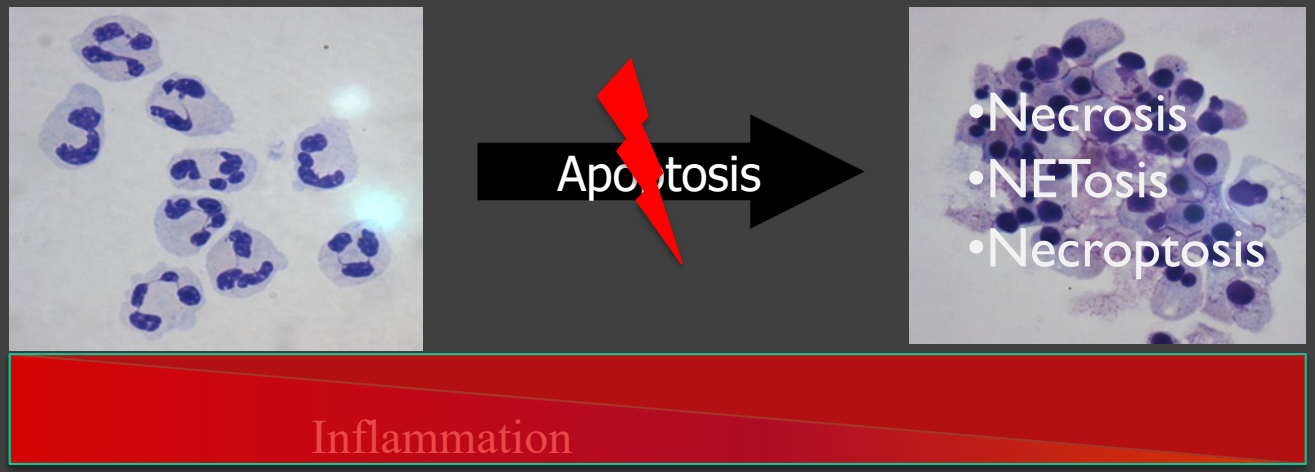
macrophage



….whichever, the ultimate goal is resolution with a return to tissue homeostasis

Neutrophil Apoptosis and Resolution of Inflammation

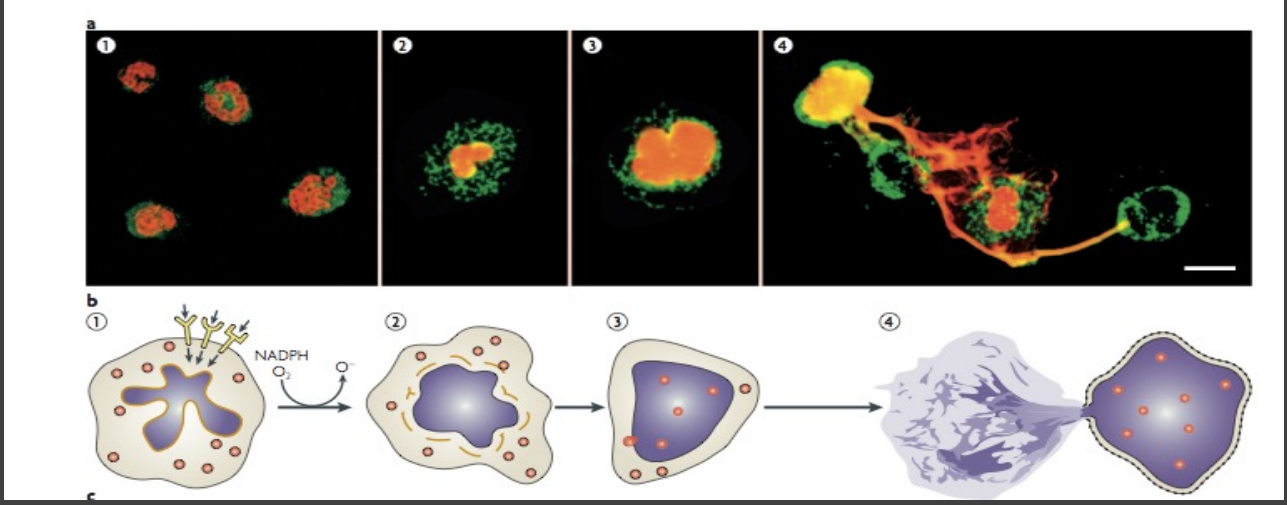
- Neutrophil apoptosis is a key process in inflammation resolution



Neutrophil Extracellular Traps (NETs)

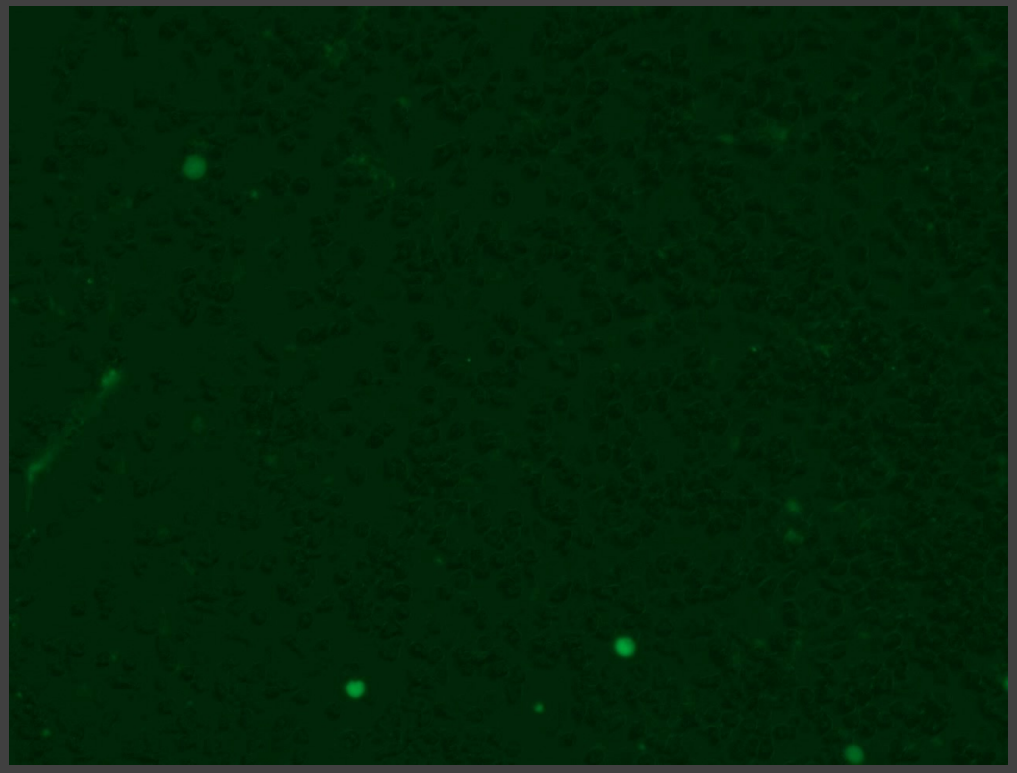
- NETs are a conserved anti-microbial defence mechanism, releasing DNA complexed to neutrophil proteins

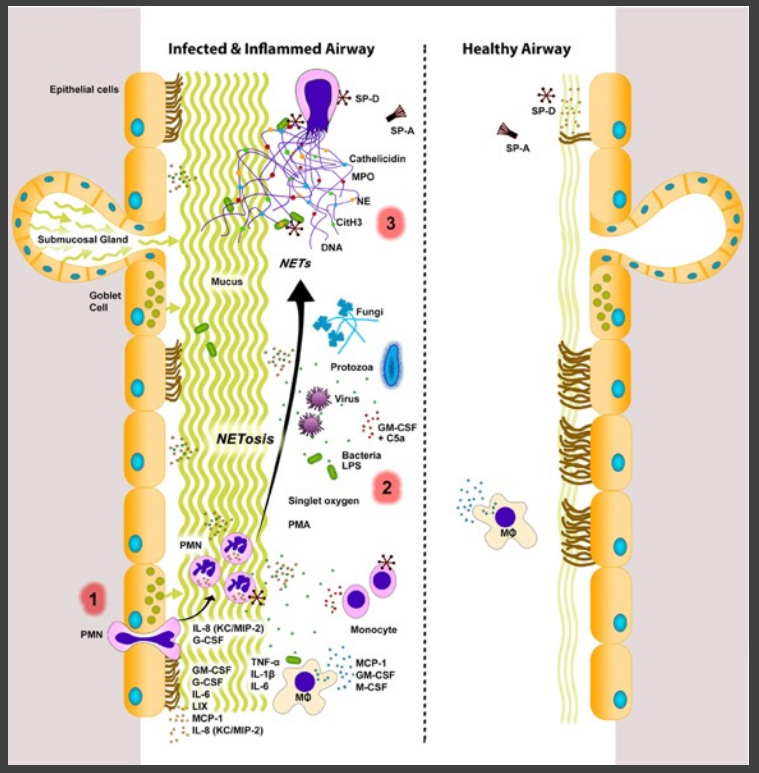
- NETs implicated in tissue damage and inflammation in a number of inflammatory and autoimmune conditions



Brinkman and Zychlinsky, Nat Rev Microbiol, 2007 vol. 5 (8) pp. 577-82

NET formation is a dynamic process

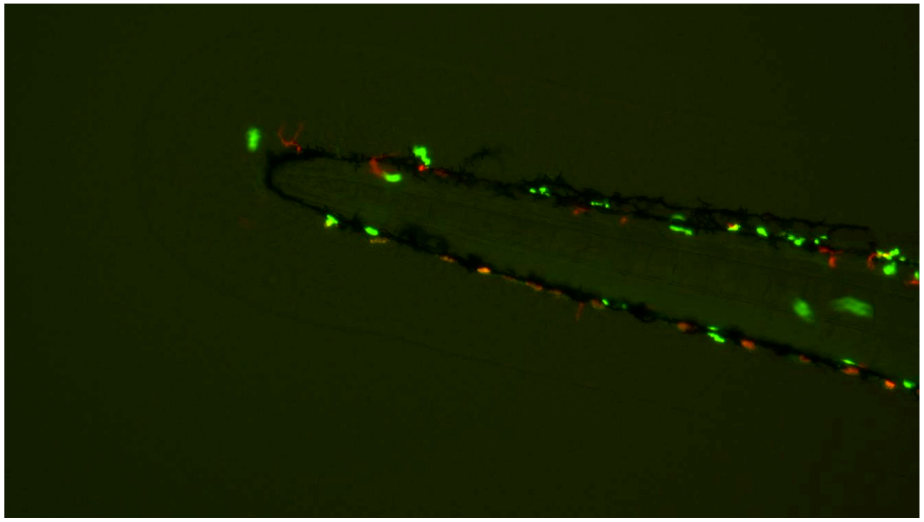




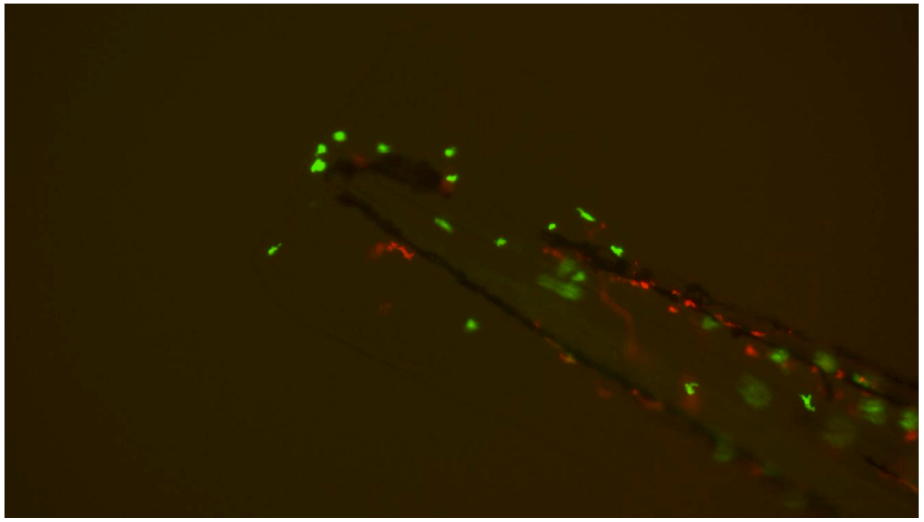
Cheng, Front. Immunol., 24 January 2013

Immune response to tissue injury (Zebrafish)

Uninjured



Injured



RFP – Macrophages (Tg(mpeg:RFP))
GFP – Neutrophils (Tg(mpx:GFP))

Oremek, Lucas, Rossi & Duffin, unpublished

Summary: acute lung inflammation

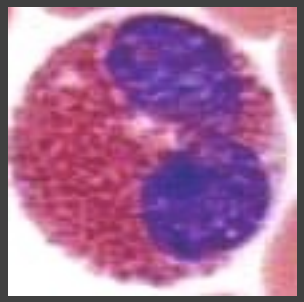
- Inflammation is essential for normal host defence.
- A switch from inflammation to resolution is essential to limit host damage.
- The therapeutic potential for manipulating this process is huge.

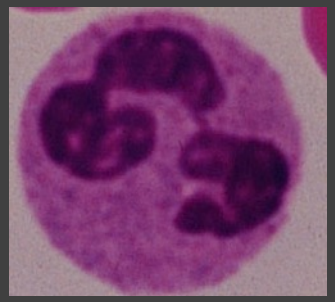
Asthma and COPD: chronic inflammation of the airways

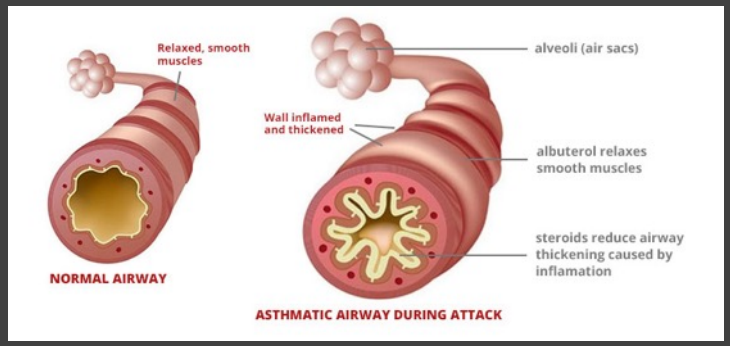
- Both processes lead to airflow limitation in the lung
- This obstruction is reversible in Asthma but not in COPD
- Asthma and COPD behave in a similar way, are treated with similar drugs but are two separate conditions
- Confusing?

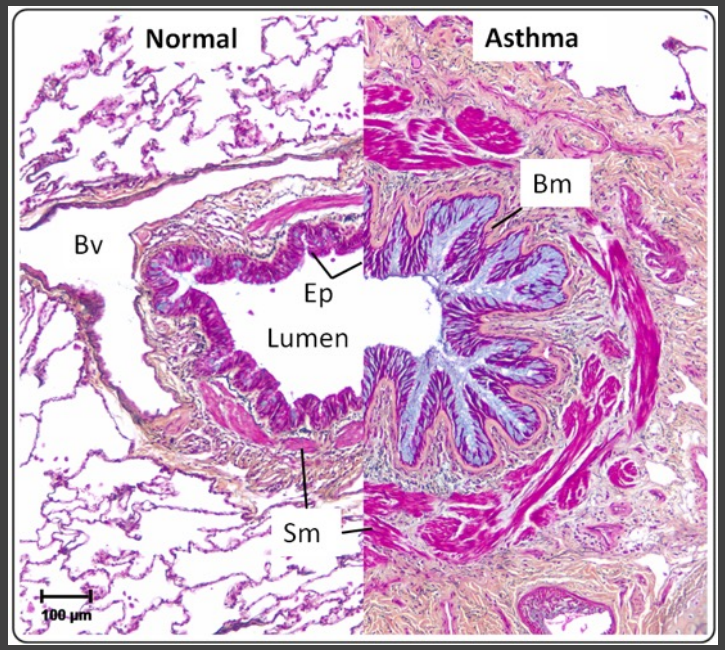
Is Asthma the same as COPD?

- Not really
- Asthma:
  - Reversible airways obstruction
  - Airways inflammation
  - Airways hyperresponsiveness
- Eosinophil vs neutrophil







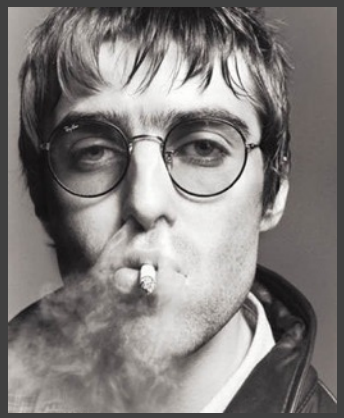


Why does the type of inflammation matter?

- Some patients don't respond to steroid therapy: either partially or at all
- New drugs have been developed to target aspects of the TH2 pathway
- Different inflammatory phenotypes are emerging in asthma that might allow for a personalized therapy approach

Inflammation in COPD less well defined and harder to treat (unless you focus on the cause…)

- COPD can be associated with a chronic bronchitis phenotype or emphysema phenotype or both
- Protease/anti-protease problem
- The best treatment is to remove the stimulus to inflammation: smoking cessation and bronchodilators



…….so what does this all mean for PSLTs?

- inflammation is a great marker of particle exposure
- but inflammation isn't always a straightforward response – its dynamic, highly orchestrated and at times complex – acute vs chronic, innate vs adaptive?
- timing is key
- inflammatory response in an already diseased system?

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