16th COLOURS of SEPSIS

(BEFORE AS PG COURSE ON SEPSIS AND MODS)

Ostrava, 21.- 24. leden 2014

Damage-associated molecular patterns (DAMPs)

Prof. Jérôme Pugin, MD

Intensive Care
University Hospitals
Geneva, Switzerland

Ostrava,
January 22, 2014

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HUG
Hôpitaux Universitaires de Genève

Immunology dogma (1950 - ...)

The immune system has evolved to discriminate self from nonself

Sir F. McFarlane Burnet
1899-1985
Nobel prize 1960 Immune tolerance

C.A. Janeway, Jr.
1943–2003
(Immunol Today 1992)

OK, but how to explain:

- That pregnant women do not reject their fetus?
- That lactating women do not reject their breasts?
- That cancer cells expressing new antigens are not killed?
- That none dies after suffering from bacteremia following tooth brushing?
- The development of autoimmune diseases?

The danger model

"The immune system does not care about self and nonself; its force is to detect and protect against danger"

Polly Matzinger, Annu Rev Immunol 1994

Playboy bunny, jazz musician, carpenter, waitress in a bar, dogtrainer

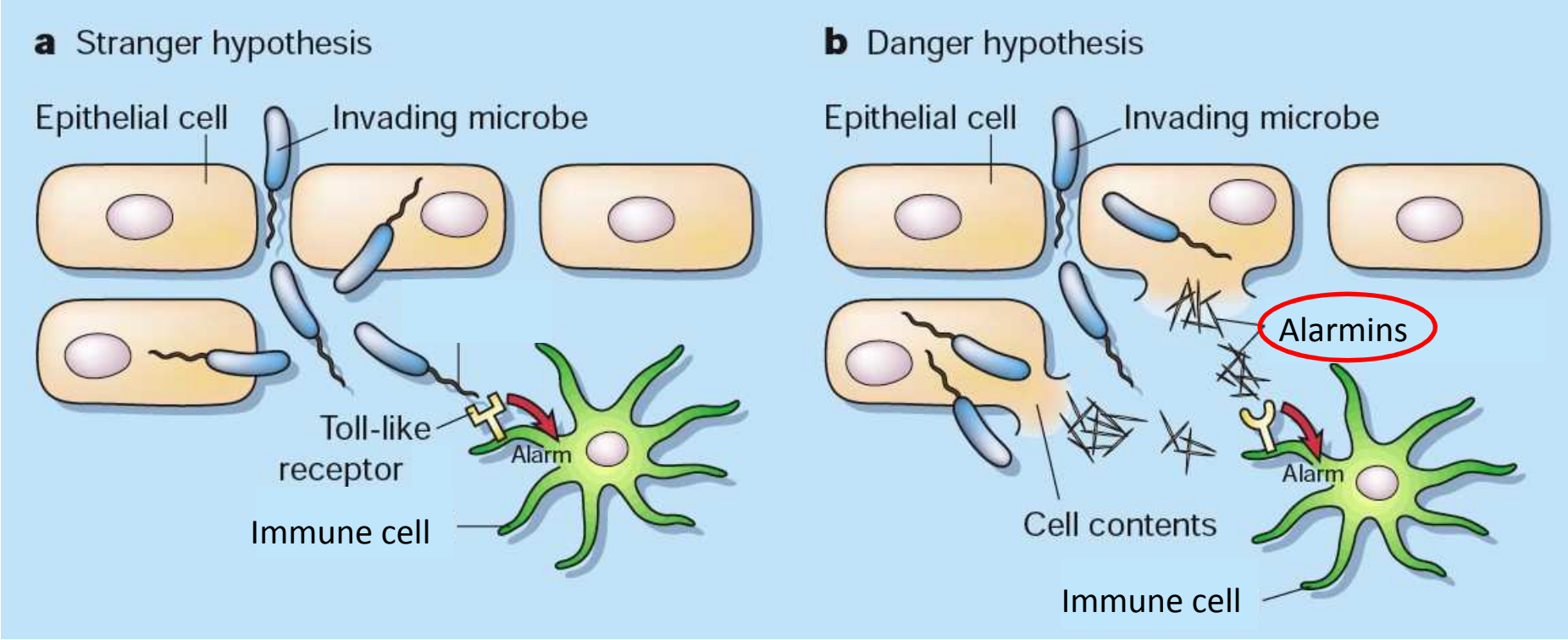
IN A FULLY H-2 INCOMPATIBLE CHIMERA, T CELLS OF DONOR ORIGIN CAN RESPOND TO MINOR HISTOCOMPATIBILITY ANTIGENS IN ASSOCIATION WITH EITHER DONOR OR HOST H-2 TYPE*

By POLLY MATZINGER AND GALADRIEL MIRKWOOD

(From the Department of Biology, University of California San Diego, La Jolla, California 92093)

J Exp Med 1978

Stranger vs. danger ?



Heath, Nature 2003

Intensive Care Med
DOI 10.1007/s00134-007-0888-4

EDITORIAL

Jérôme Pugin

Dear SIRS, the concept of "alarmins" makes a lot of sense!

"In critically ill patients, one observes an inflammatory response after bacterial infection/sepsis, but also in "non-infectious SIRS", such as pancreatitis, burns, multiple trauma, chemical lesions, major surgery

Common feature = tissue injury

Intensive Care Med 2008

Tissue lesions/necrosis
-
Shock/ischemia

DAMPs

Uric acid → **NALP3**

ATP_{ec} → **$P2X_7R$**

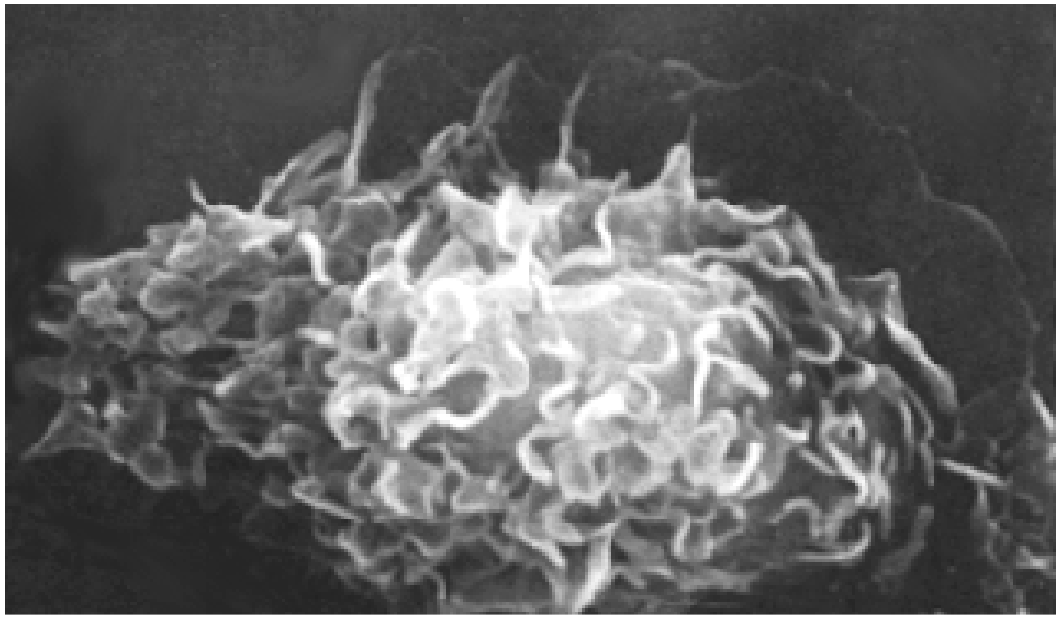
osmolality → **p38**

hypoxia → **ORE**

HSPs
HMGB-1 → **TLR2/4**
RAGE

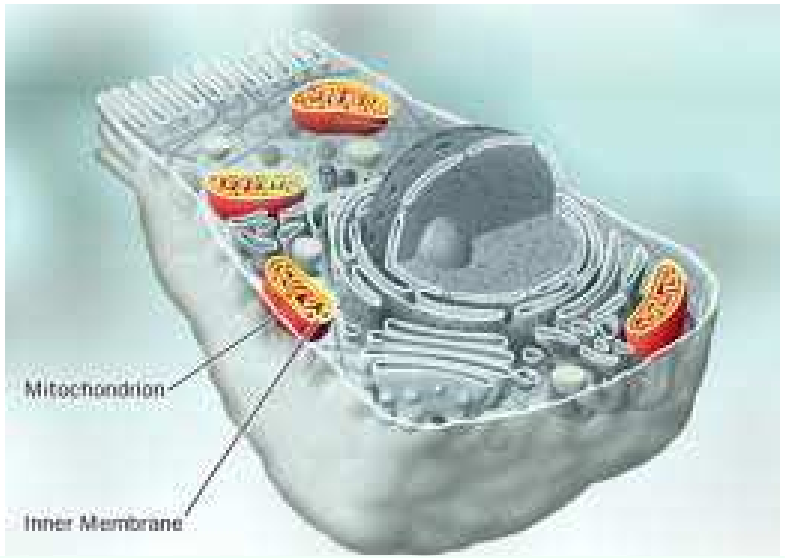
substance P → **Receptor NK-1**

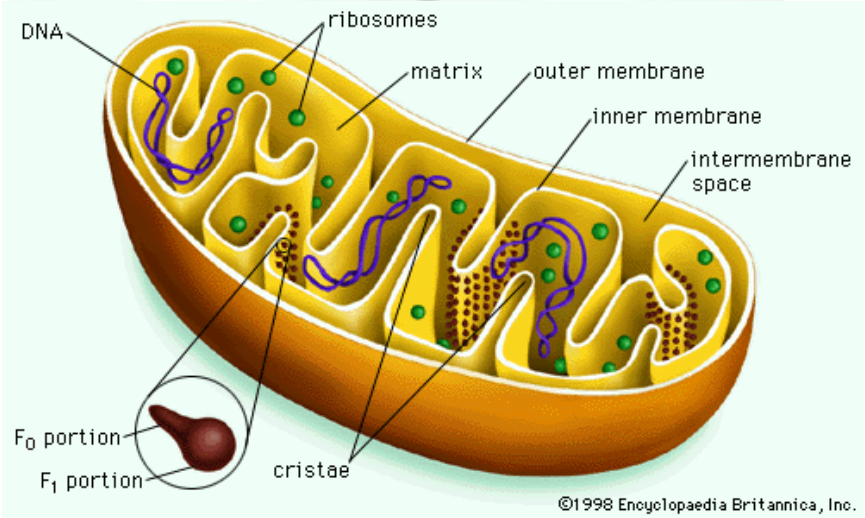
stretch → **Integrins**
FAK, MAPK
NF-κB



thrombin → **PAR**

What is inside of a cell that could become an danger signal when outside?





The mitochondria !

Ancient GN bacteria

Double membrane

Its own DNA (of bacterial origin!)

Cellular respiration

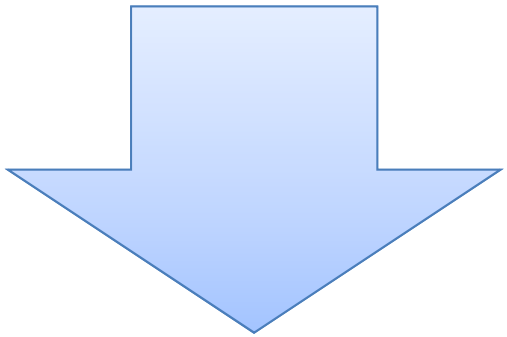
Respiratory chain

ATP production

Tissue injury, cells death

Mitochondrial alarmins (mtDNA, fMLP), ATP
IL-1ß

Immune cells activated



Pro-inflammatory cytokines
Neutrophil recruitment and activation

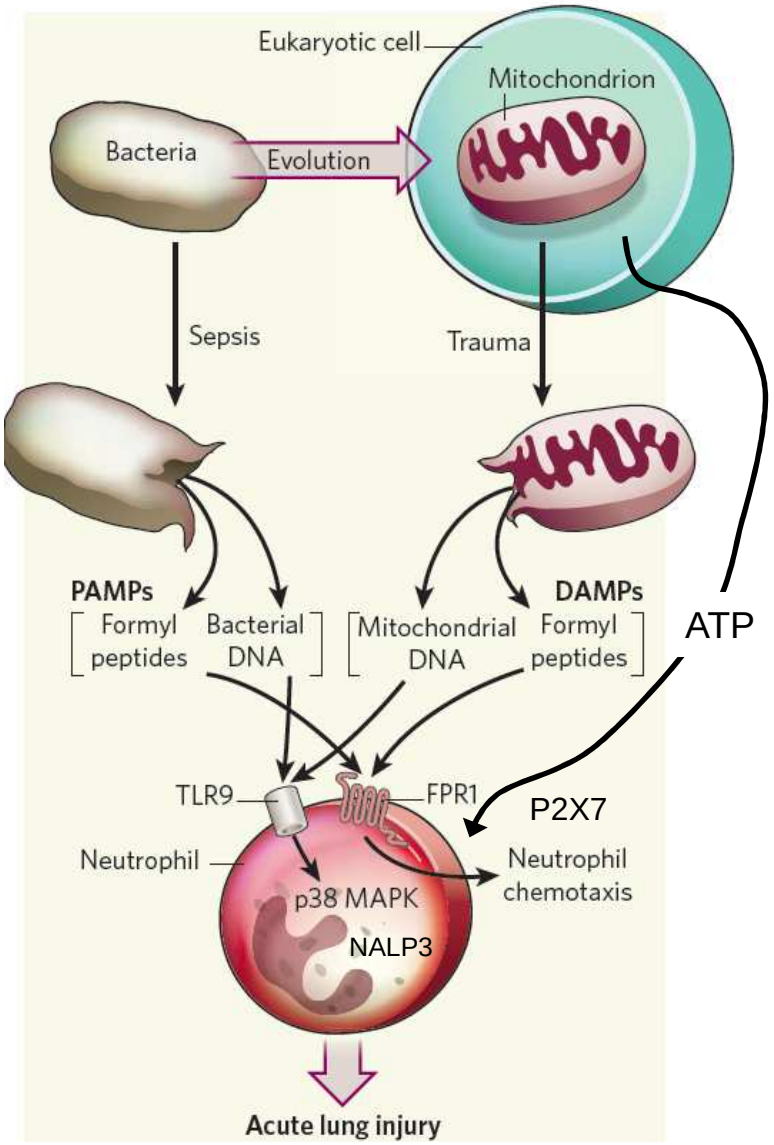
CLINICAL IMMUNOLOGY

Culprits with evolutionary ties

Carolyn S. Calfee and Michael A. Matthay

Newly recognized DAMPs (alarmins):

- **Mitochondrial DNA**
- **Mitochondrial fMLP**
- **ATP_{ec}**



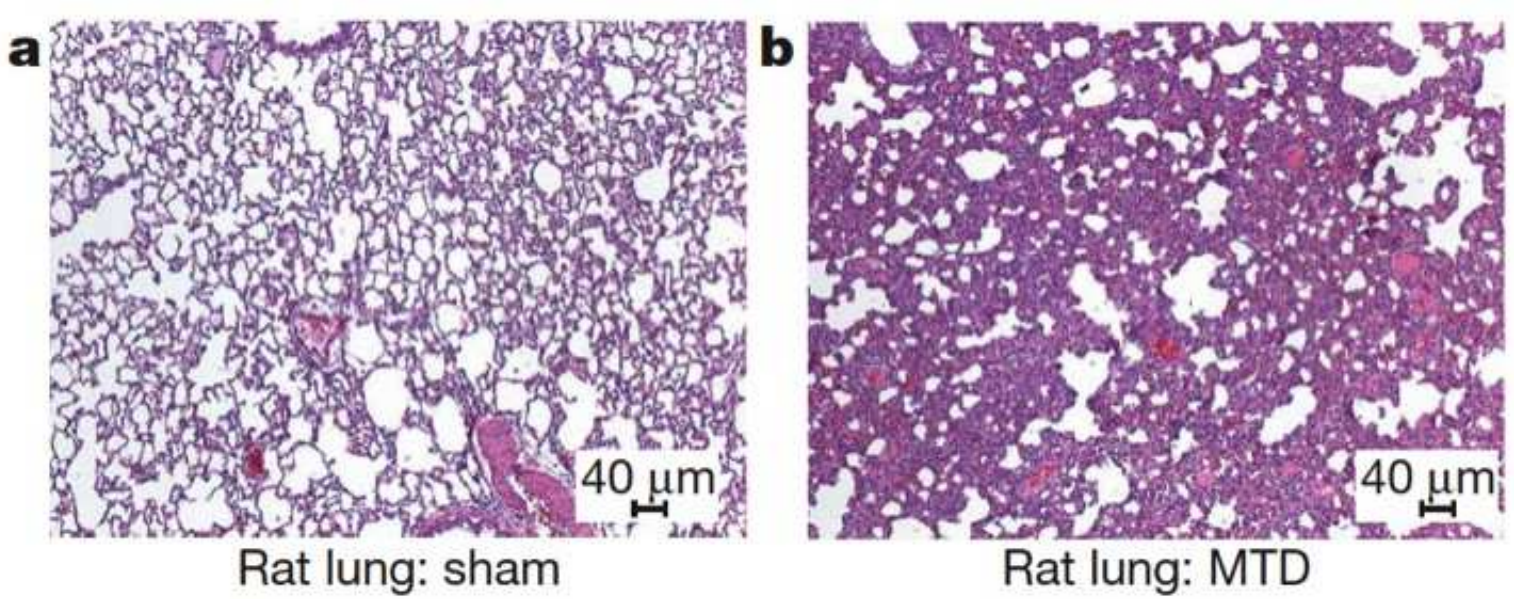
PAMPs = pathogen-associated molecular pattern

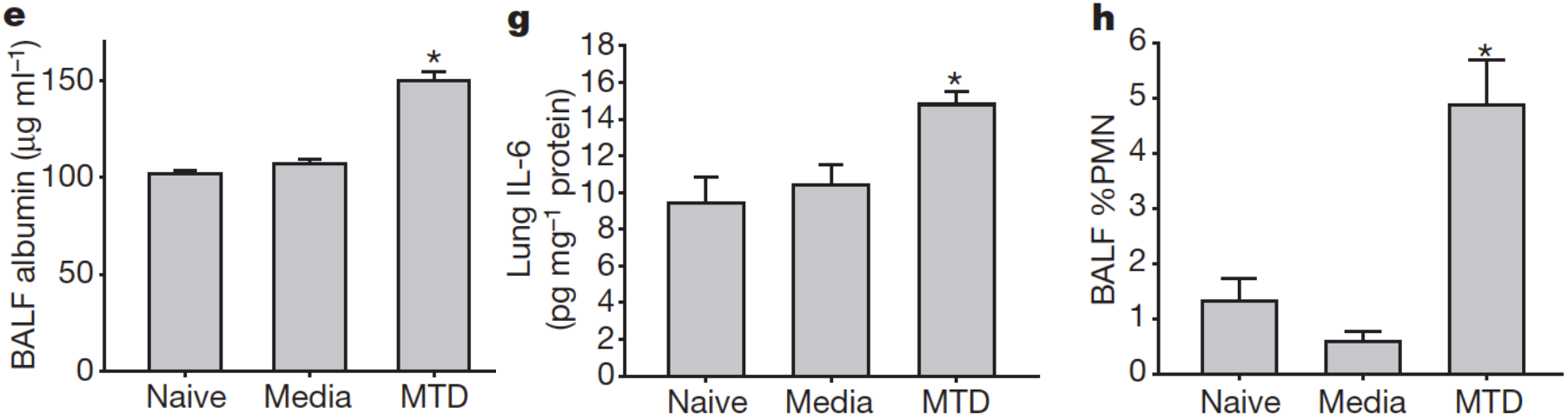
DAMPs = danger-associated molecular pattern

PRR = pattern-recognition receptors

Editorial. Nature, March 2010

IV injection of mitochondrial preparations induces an acute lung injury in rats

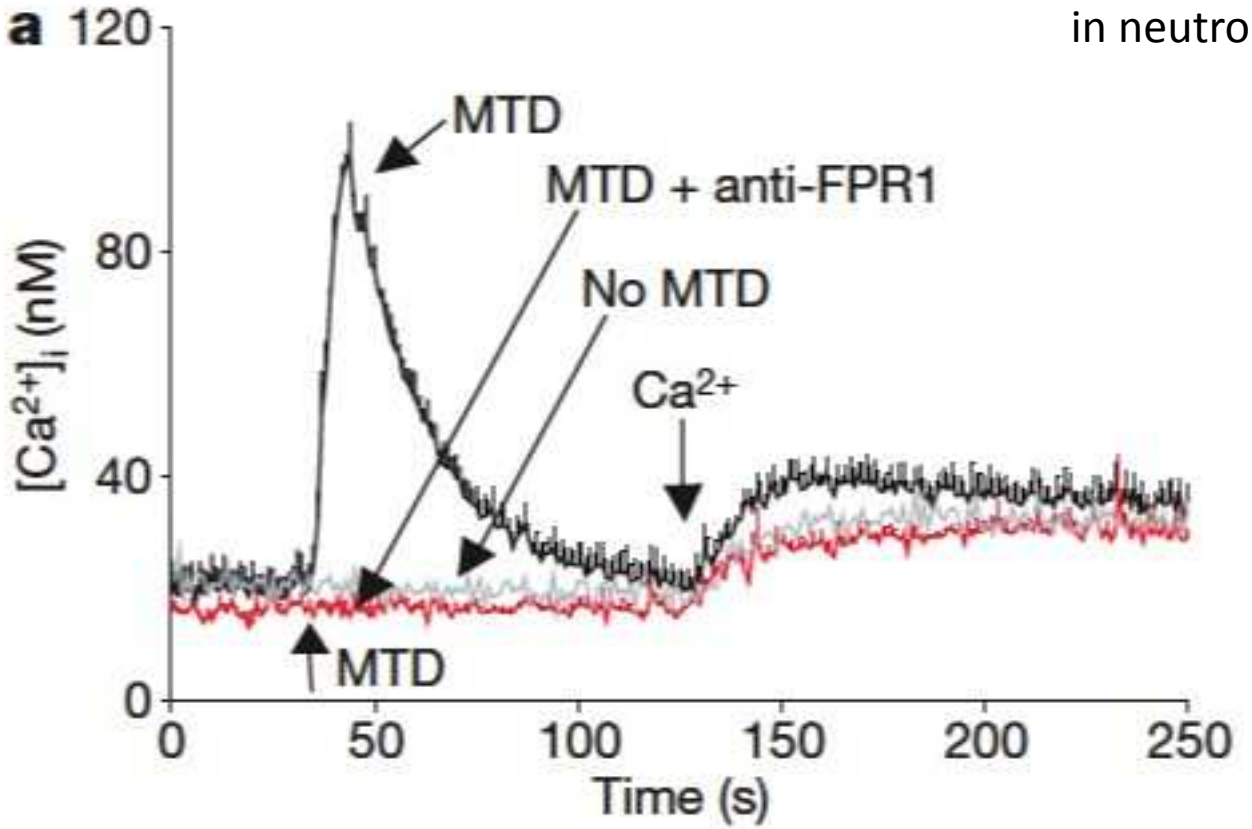




Zhang et al. Nature, March 2010

“fMLP activity” in mitochondrial preparations

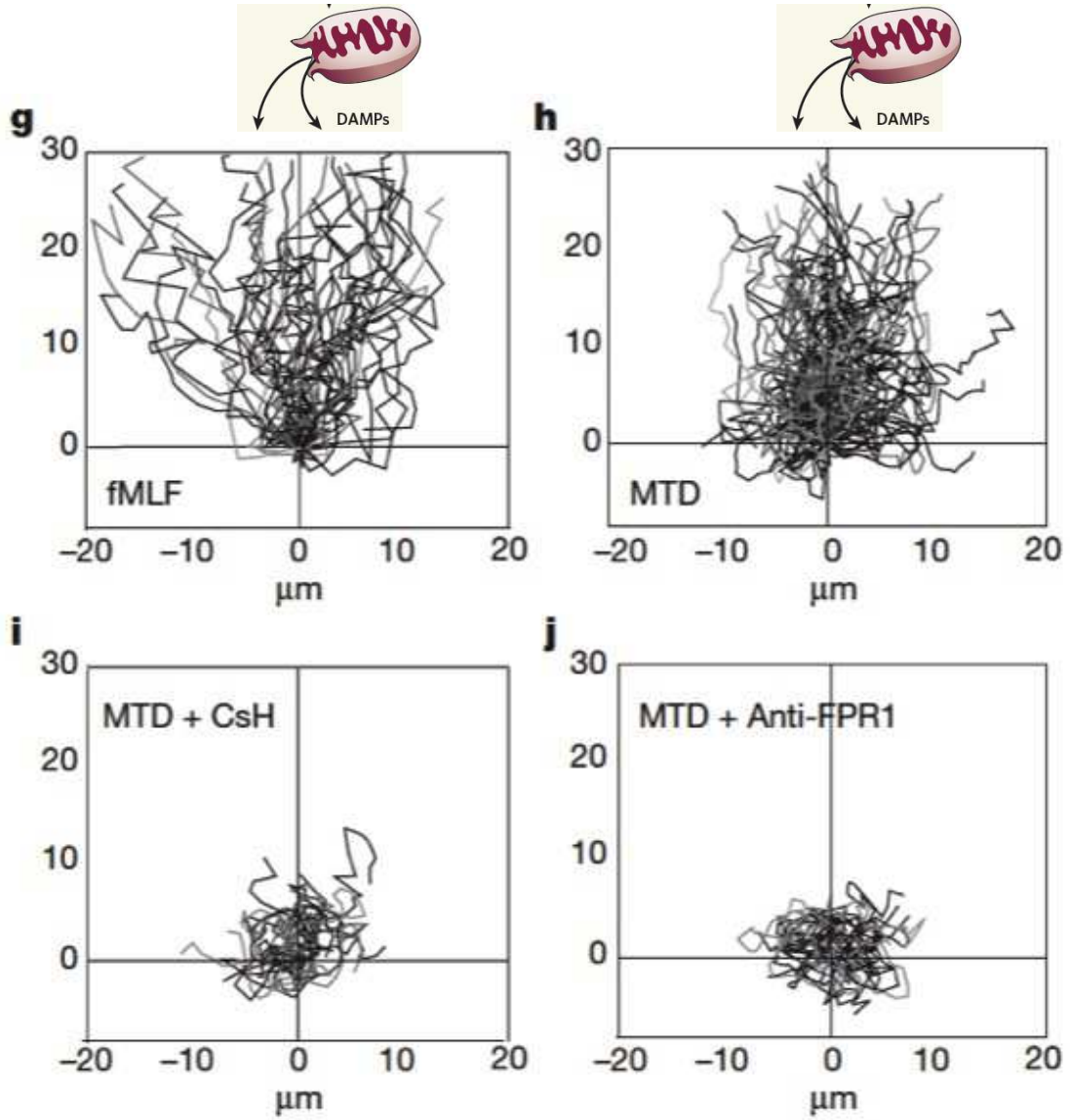
Calcium moblization
in neutrophils



MTD, Mitochondrial preparations from human monocytes
FPR1, fMLP recepotor-1

Zhang et al. Nature, March 2010

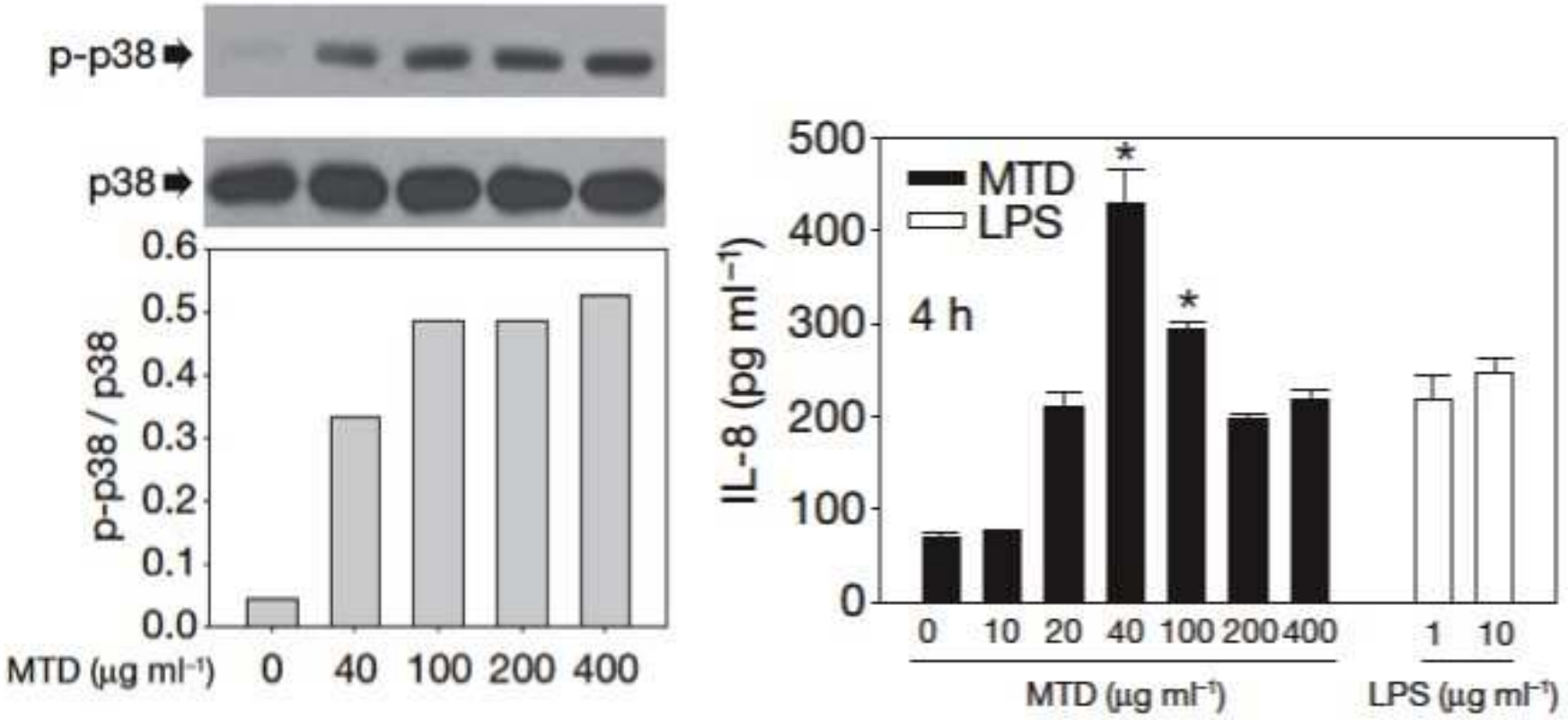
Chemotactic activity of mitochondrial preparations



CsH, cyclosporin H, FPR1 blocker

Zhang et al. Nature, March 2010

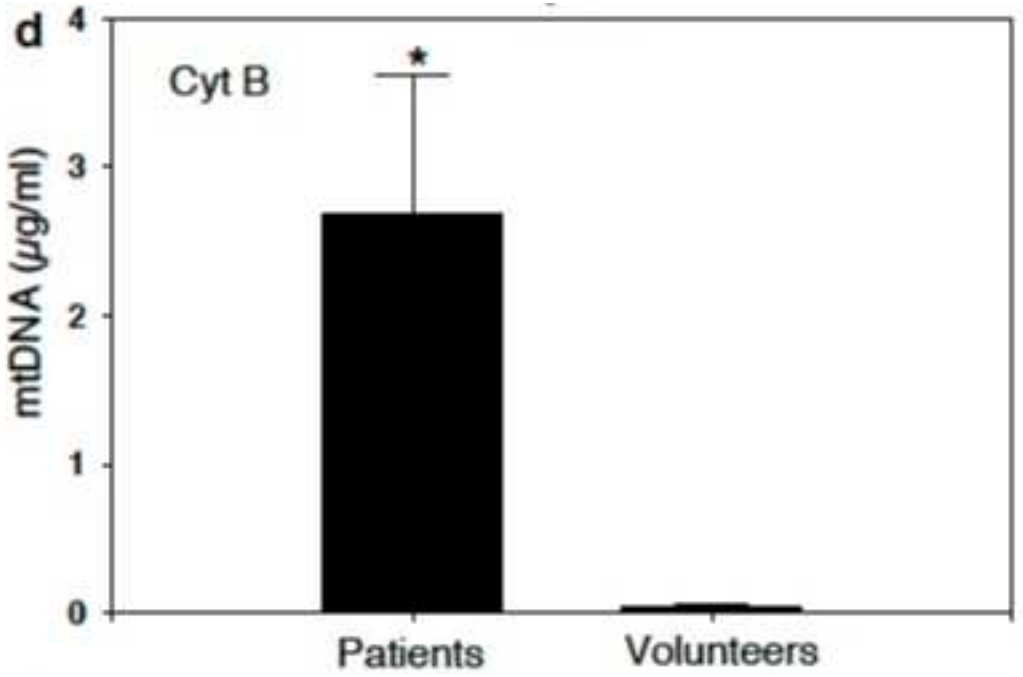
Mitochondrial preparations activate neutrophils (mtDNA)



MTD, mitochondrial preparations from human monocytes

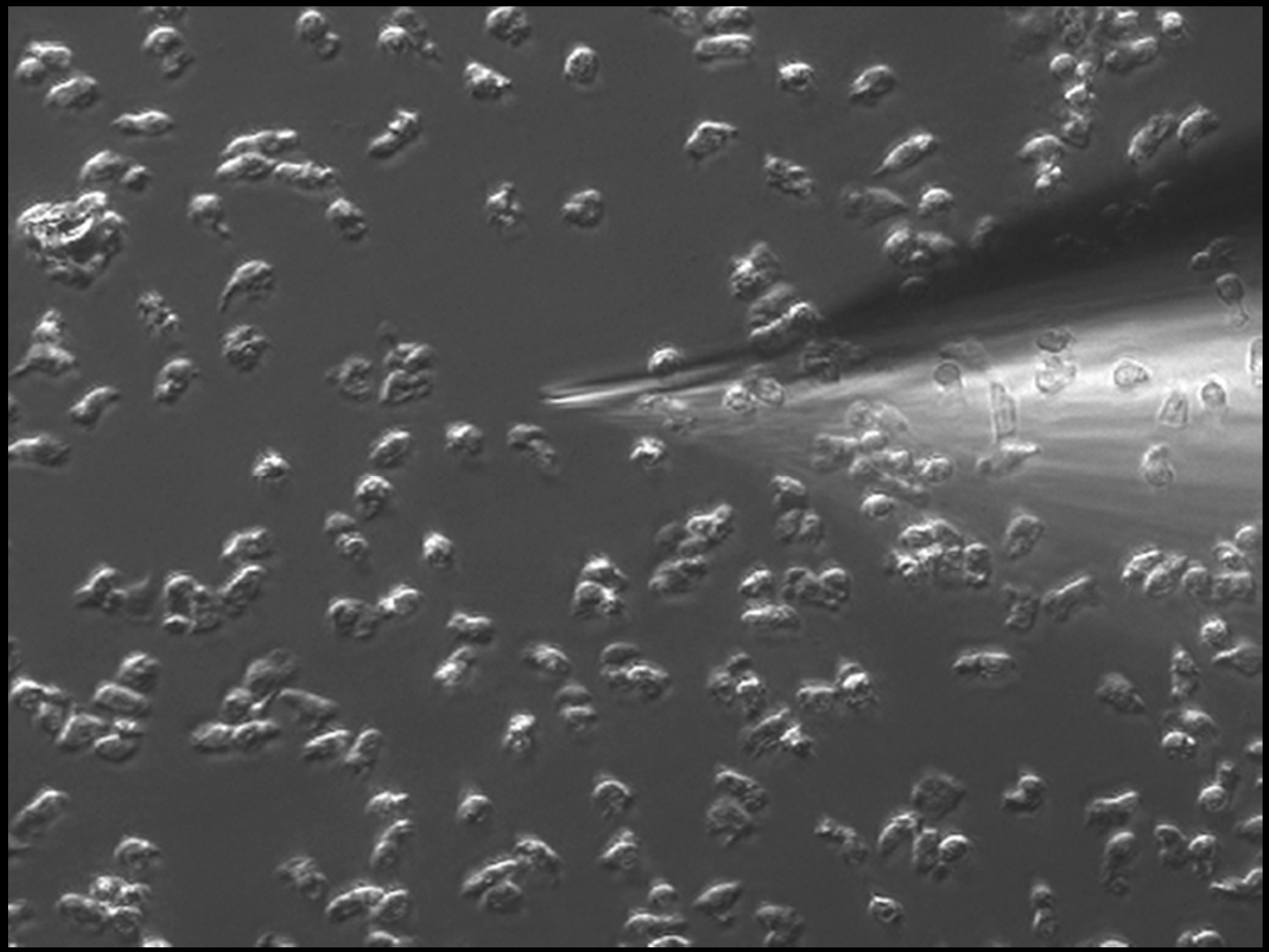
Zhang et al. Nature, March 2010

Plasma mtDNA 1,000x higher in trauma patients



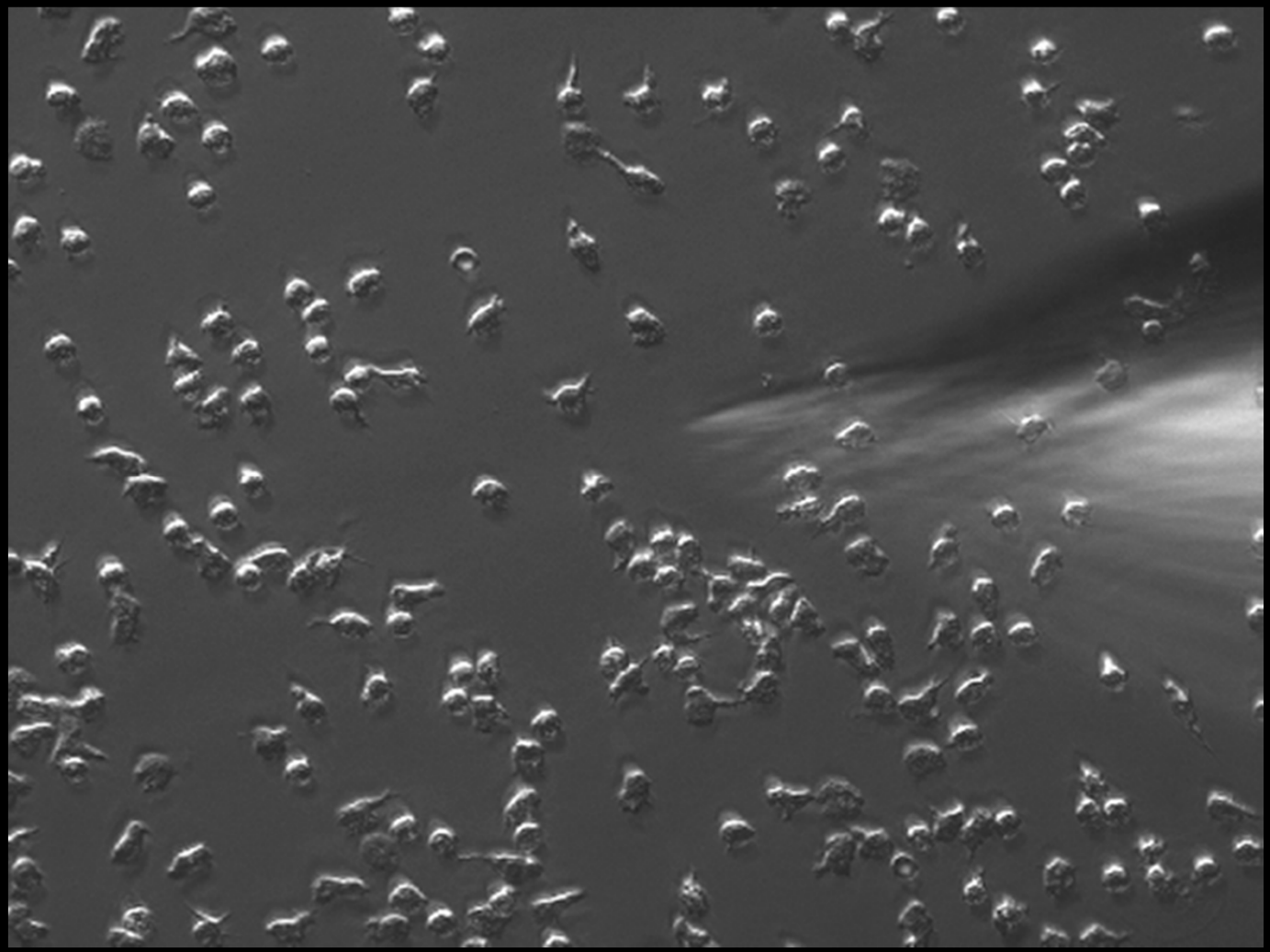
Zhang et al. Nature, March 2010

Neutrophil migration towards femur fracture



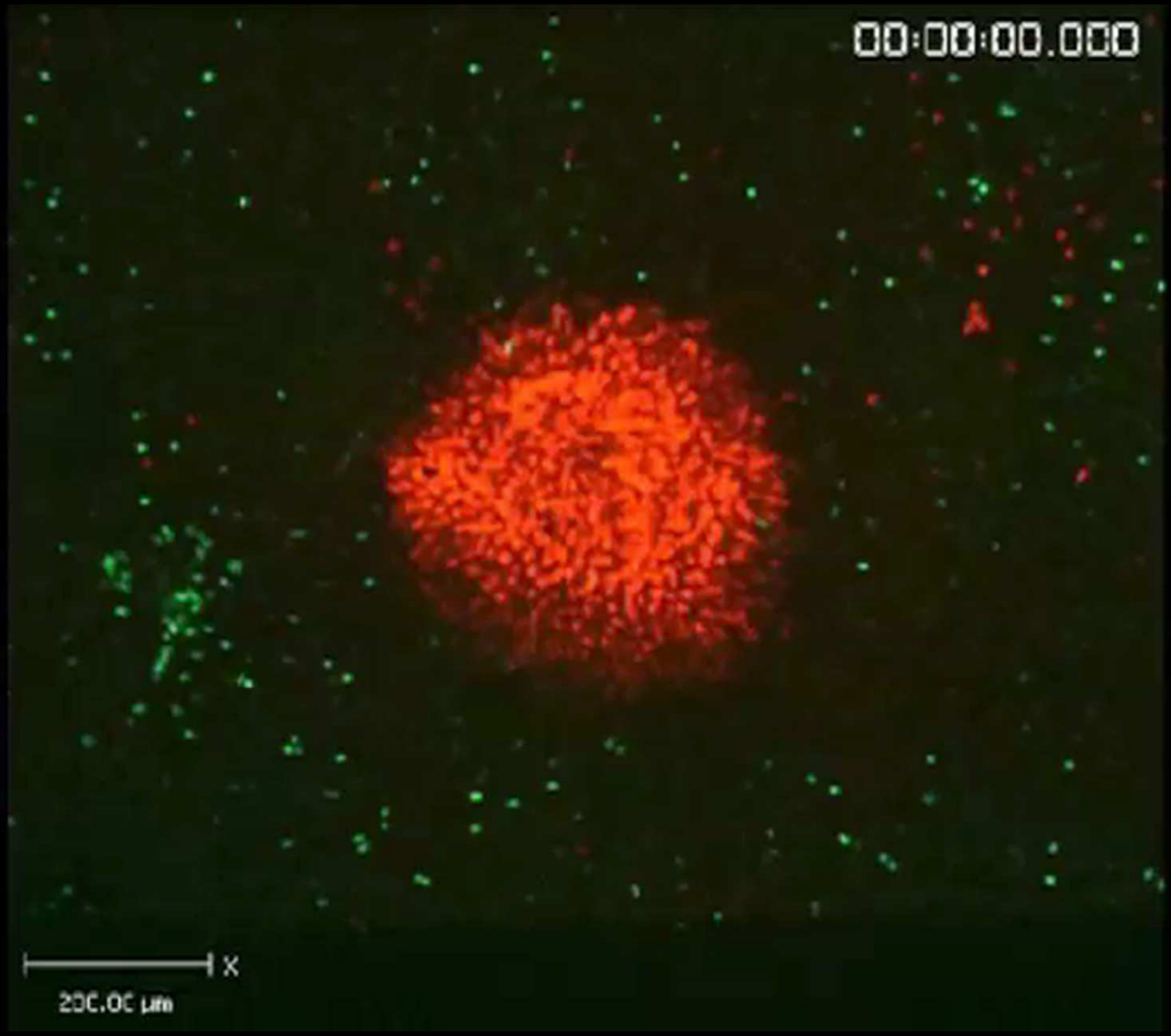
Zhang et al. Nature, March 2010

Neutrophil migration inhibited by anti-fMLP receptor MAb



Zhang et al. Nature, March 2010

Neutrophils migrate towards focal hepatic necrosis

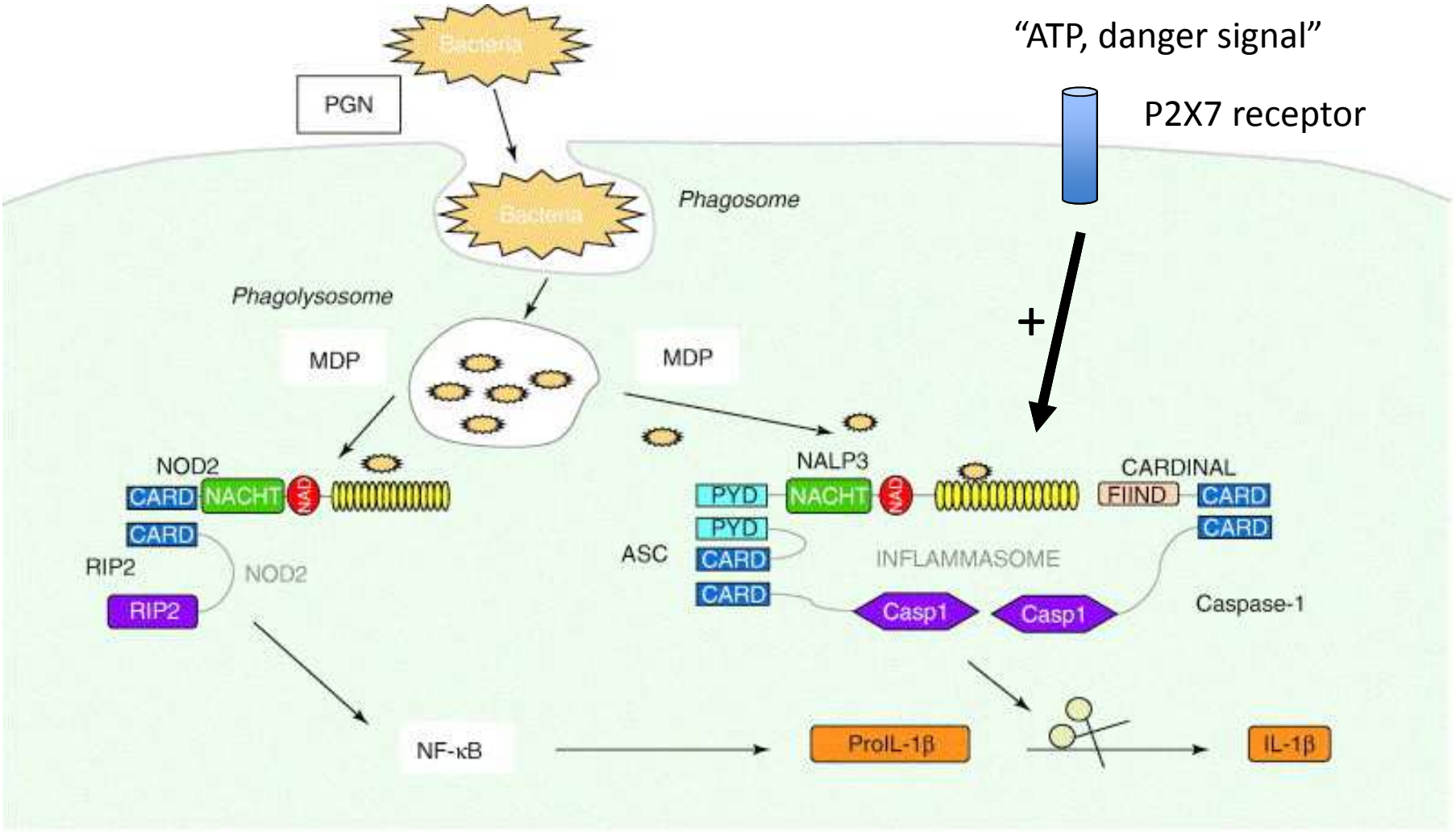


Spinning disk confocal intravital microscopy
Thermal injury on the surface of the liver

McDonald et al. Science, Octobre 2010

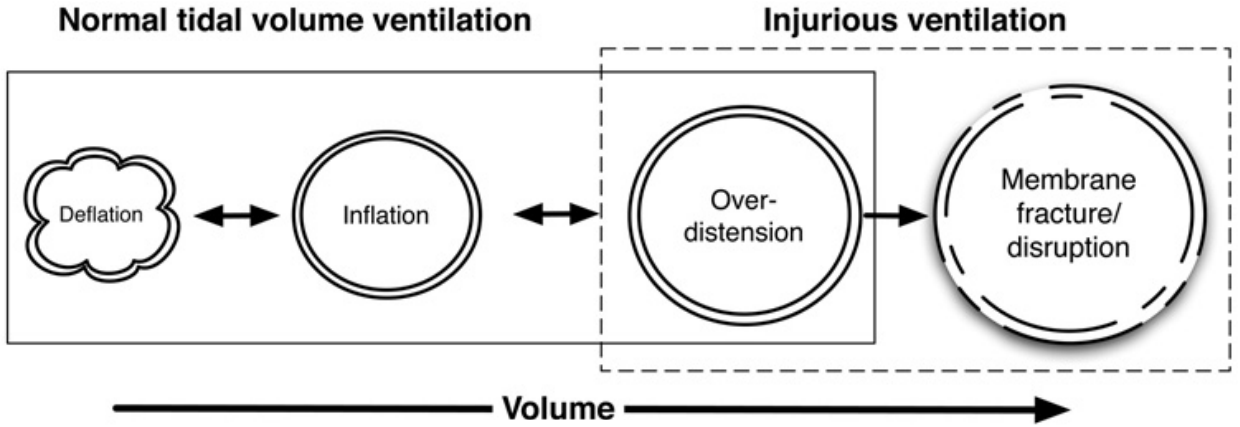
ATP hydrolysis (apyrase) blocks neutrophils migration

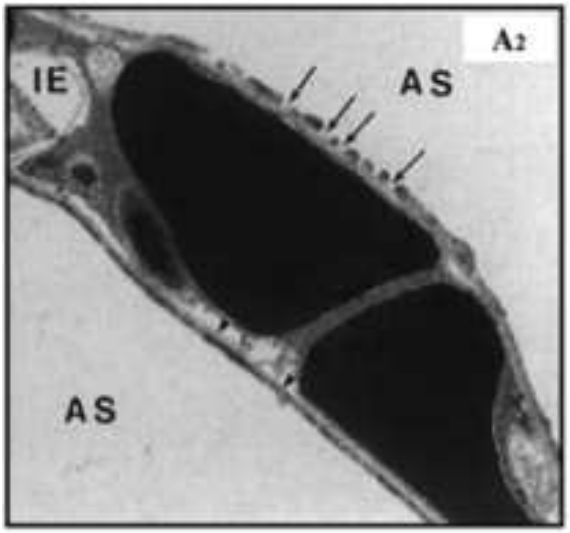
Extracellular ATP activates the NALP3 inflammasome

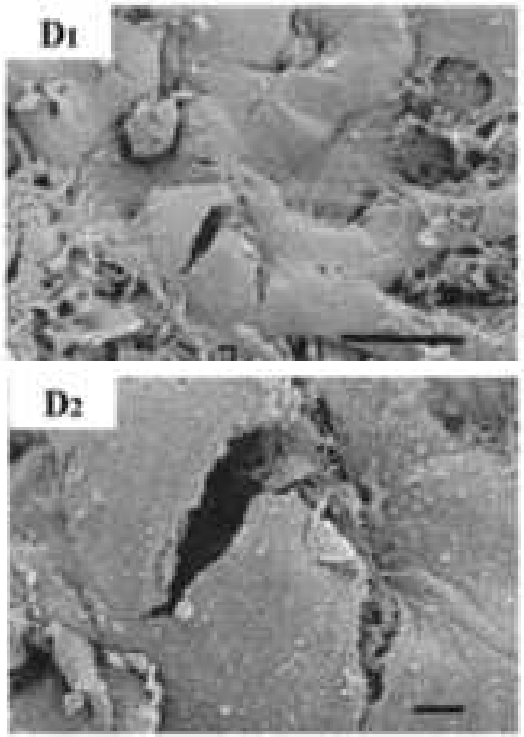


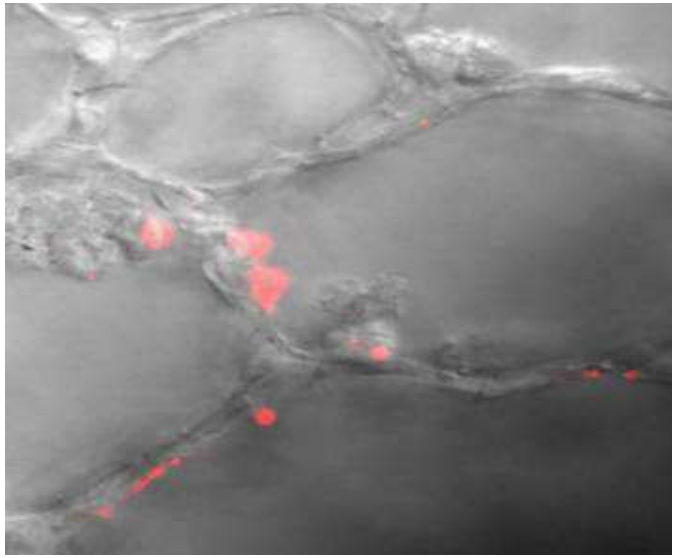
Adapted from Martinon & Tschopp Trends Immunol 2005

Cell wounding in ventilator injured lungs



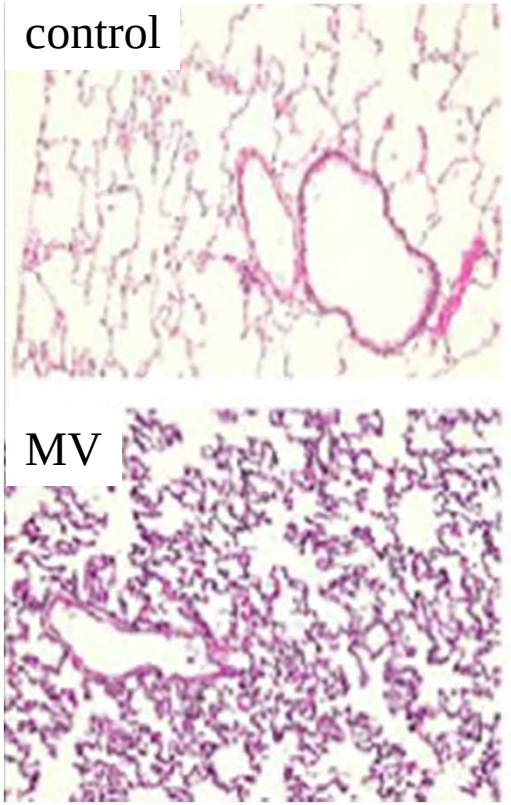


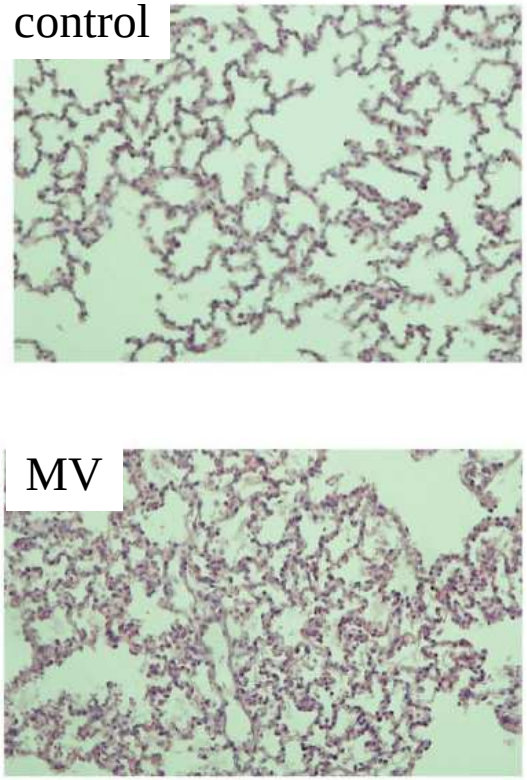




Vlahakis & Hubmayr AJRCCM 2005; Oeckler & Hubmayr, Respir Physiol Neurobiol 2008

Mechanical ventilation induces a neutrophil alveolitis

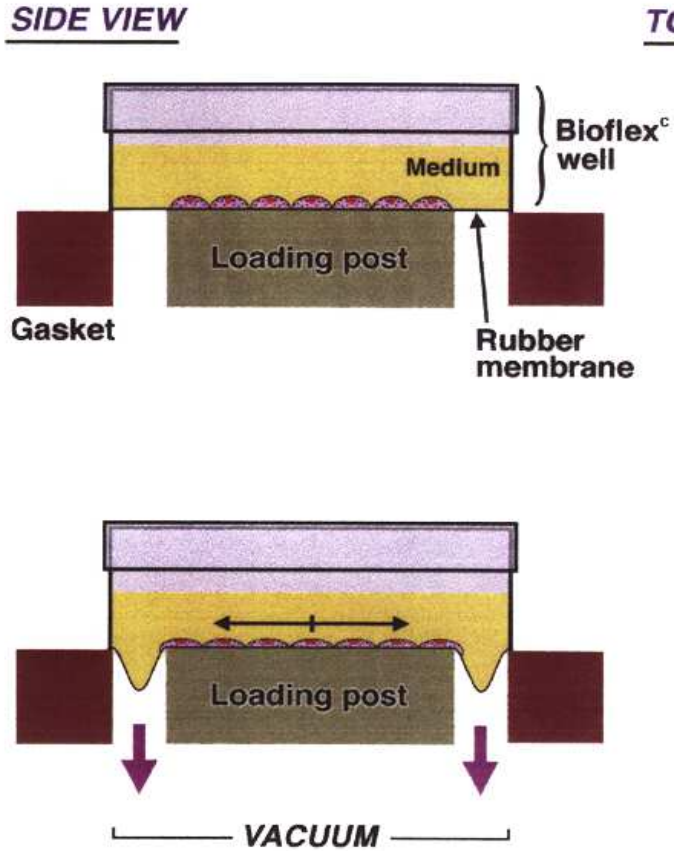




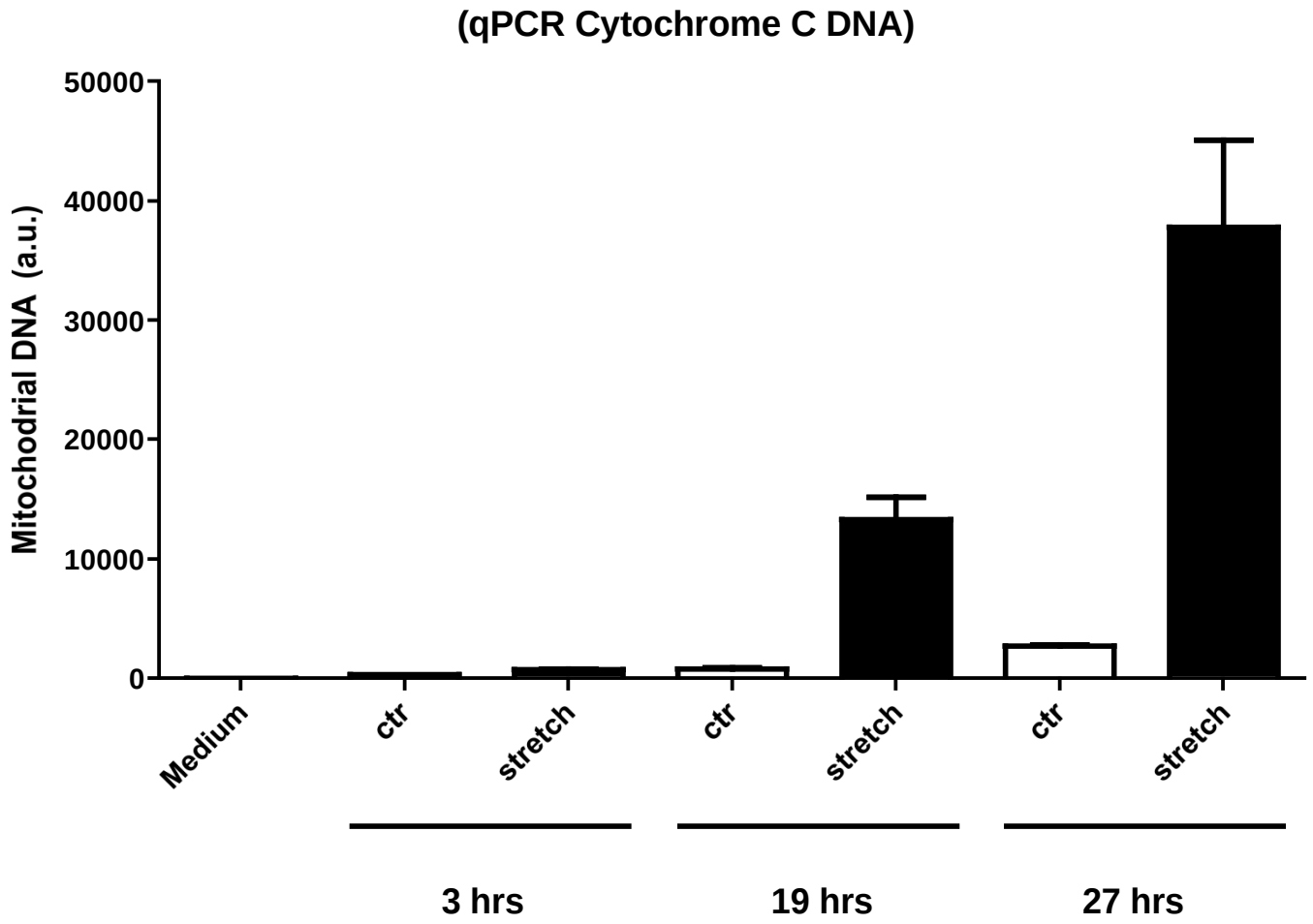
Brégeon, Pugin et al.
Anesthesiology 2005

Charles, Pugin et al.
Crit Care 2011

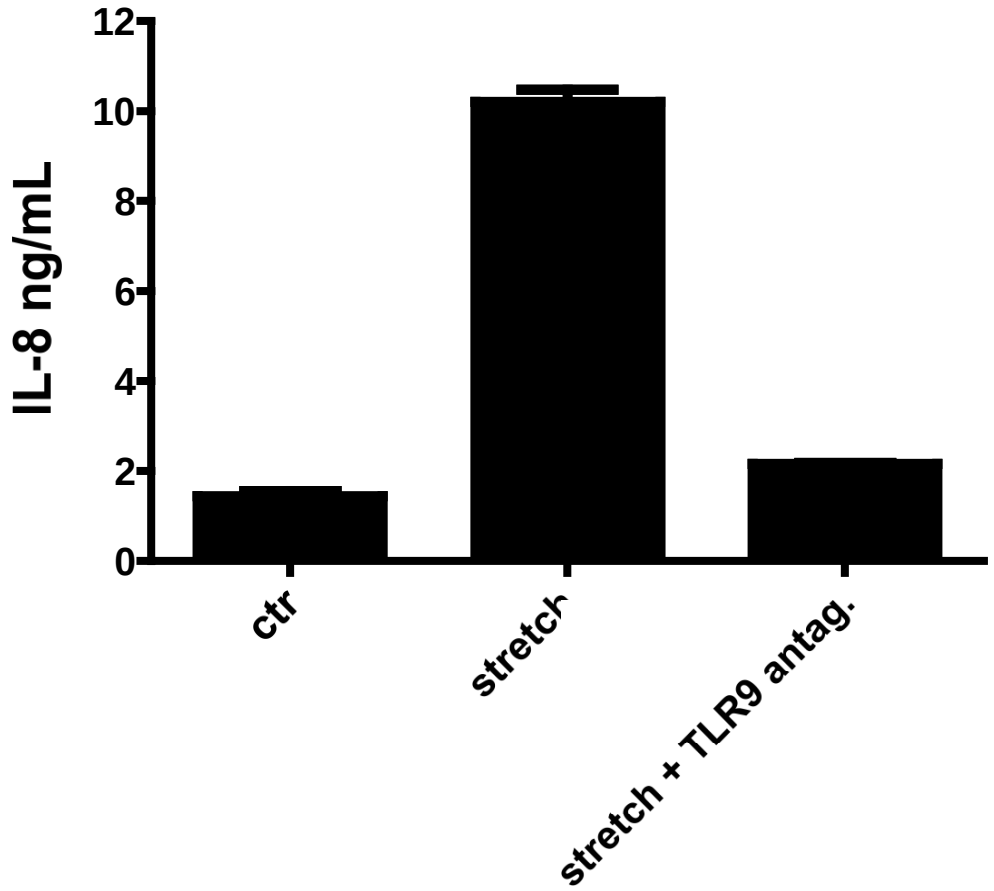
Stretching cells *in vitro* to simulate VILI



Stretching lung cells releases mitochondial DNA

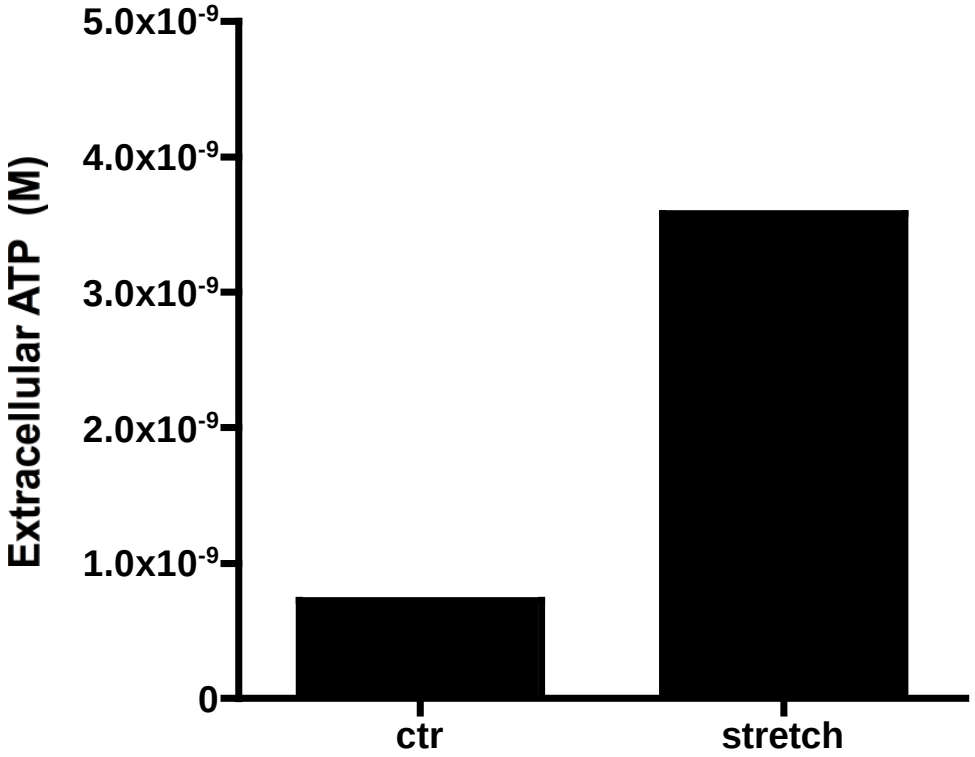


Blocking TLR9 decreases IL-8 induced by cell stretch

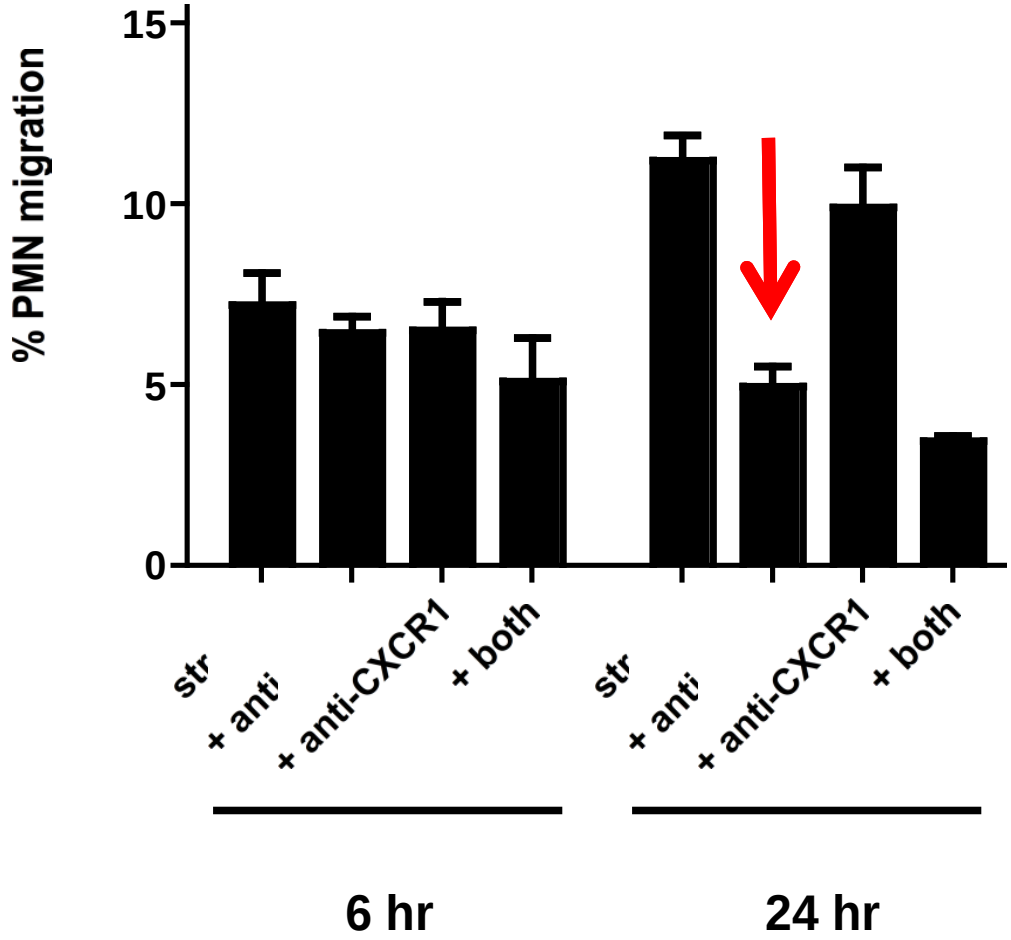


TLR9 = receptor for bacterial (mtDNA,…)

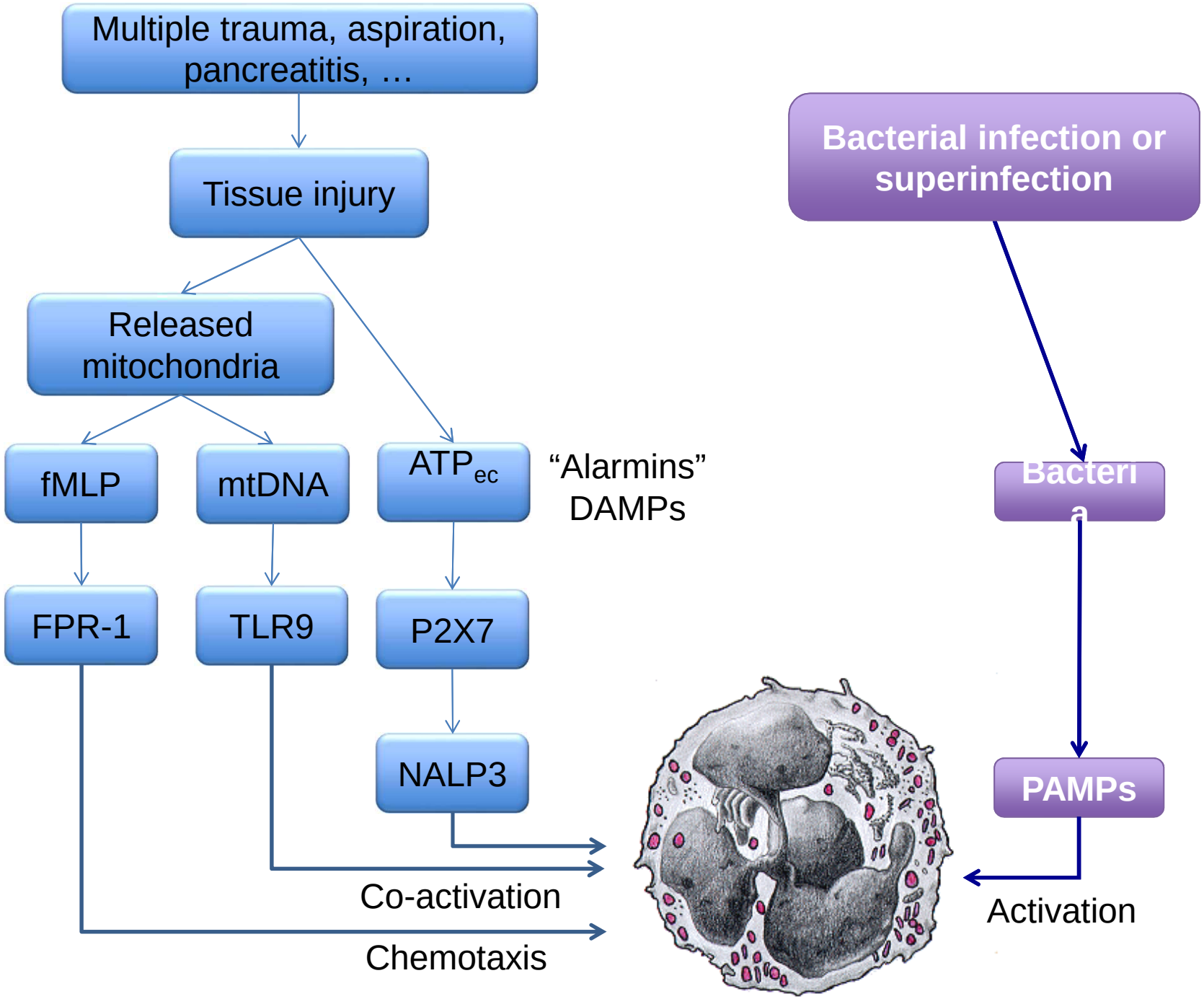
Stretching lung cells releases ATP



Stretching lung cells releases fMLP



Neutrophil chemotaxis in dual chamber
Chemotaxix by supernatants from stretched cells


Multiple trauma, aspiration, pancreatitis, …
Tissue injury
Released mitochondria
fMLP
mtDNA
ATPec
"Alarmins" DAMPs
FPR-1
TLR9
P2X7
NALP3
Co-activation
Chemotaxis
Bacterial infection or superinfection
Bacteri a
PAMPs
Activation

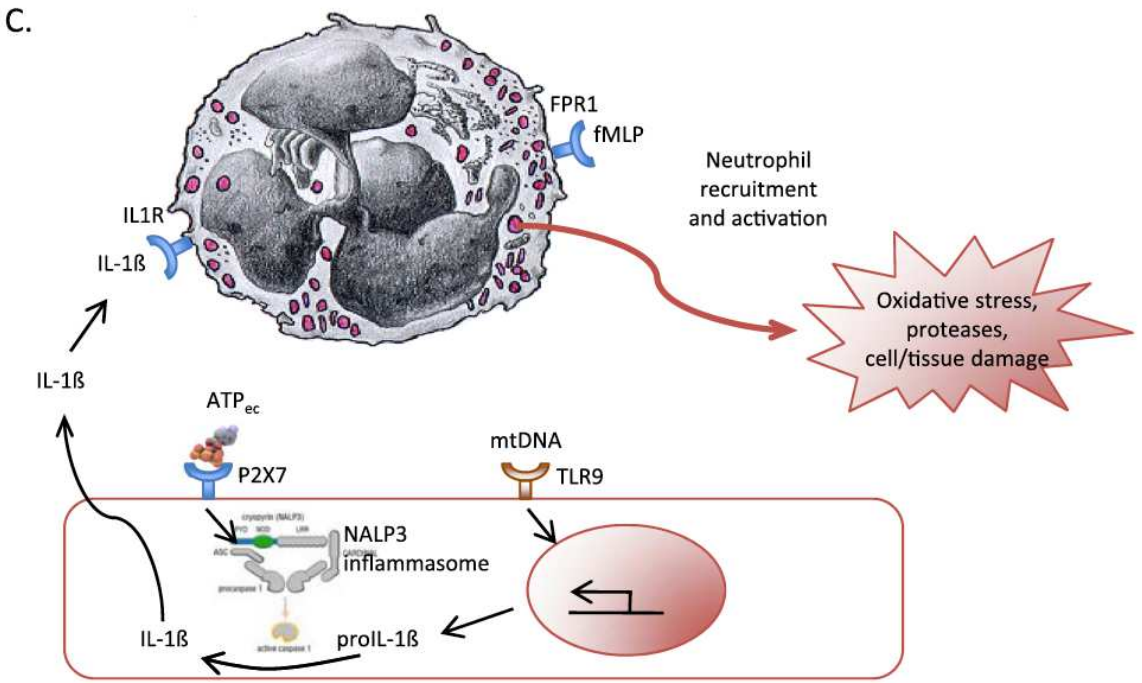
Pugin *Annals of Intensive Care* 2012, **2**:27
http://www.annalsofintensivecare.com/content/2/1/27

Annals of Intensive Care
a SpringerOpen Journal

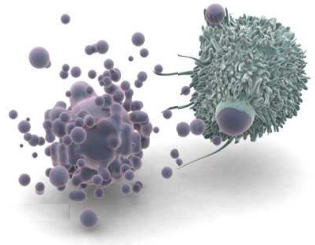
REVIEW Open Access

How tissue injury alarms the immune system and causes a systemic inflammatory response syndrome

Jérôme Pugin*



Conclusions



SIRS is the consequence of tissue injury/cell deatn

Mitochondrial alarmins and ATP released extracellularly mediate the activation of immune cells (macrophages) to produce pro-inflammatory mediators (such as IL-1ß)

These tissue alarmins (DAMPs) are responsible for the recruitment of neutrophils and represent the proximal mediators of tissue inflammation in aseptic SIRS

Tissue alarmins (DAMPs) act synergistically with cytokines

The blockade of these mediators/pathways offer novel therapeutic avenues

Semifinal Australian Open Grand Slam tournement

Stan Wawrinka vs. Tomáš Berdych

Thank you for your attention!

“Imagine a community in which the police accept anyone they met during elementary school and kill any new migrant. That's the Self/Nonself Model.

In the Danger Model, tourists and immigrants are accepted, until they start breaking windows. Only then, do the police move to eliminate them. In fact, it doesn't matter if the window breaker is a foreigner or a member of the community.”

Entretien avec Polly Matzinger The New York Times *1998*