UNIVERSITY OF BIRMINGHAM

INSTITUTE OF INFLAMMATION AND AGEING

The Aged Immune System: A Central Driver of Ageing.

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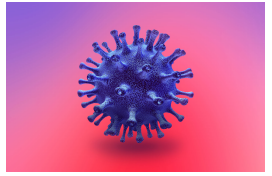
A Biological Definition of Ageing

Ageing = Increasing frailty of an organism with time that reduces the ability to deal with stress, resulting in increased chance of disease and death.

The Role of the Immune System

- Detect and kill pathogens
- Improve response with repeat exposure (Immune memory)
- Kill or remove damaged, senescent or transformed cells
- Not to damage self

SARS-Cov-2 Infection: Age and Sex differences



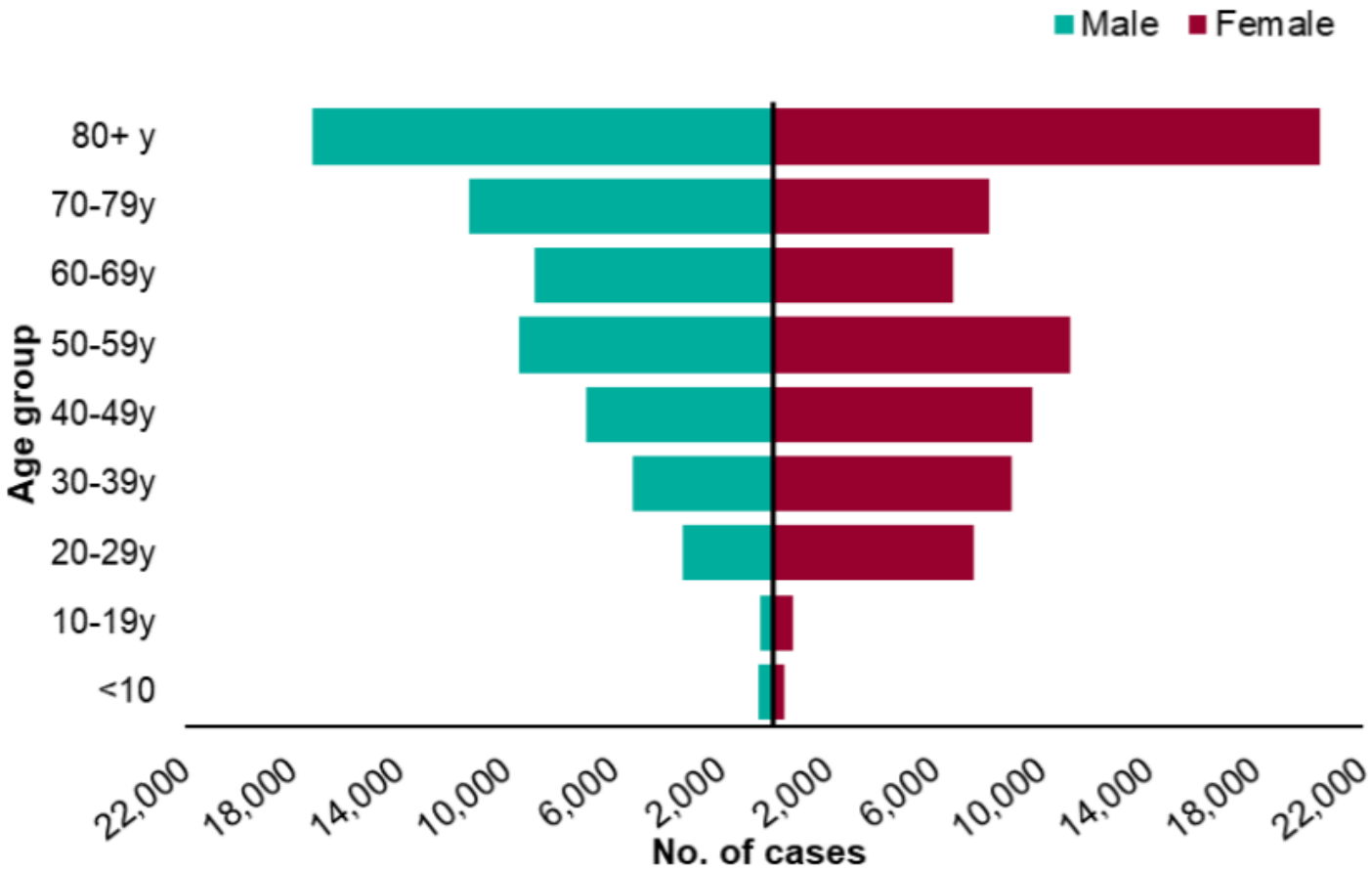
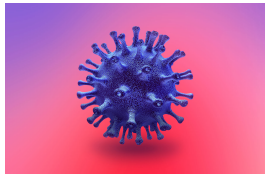


Figure 1.1. Age sex pyramid of laboratory confirmed COVID-19 cases as of 13 May 2020, England. Source: Public Health England Second Generation Surveillance System.

PHE: Disparities in the risk and outcomes of Covid-19

COVID19 Severity: Age and Sex differences



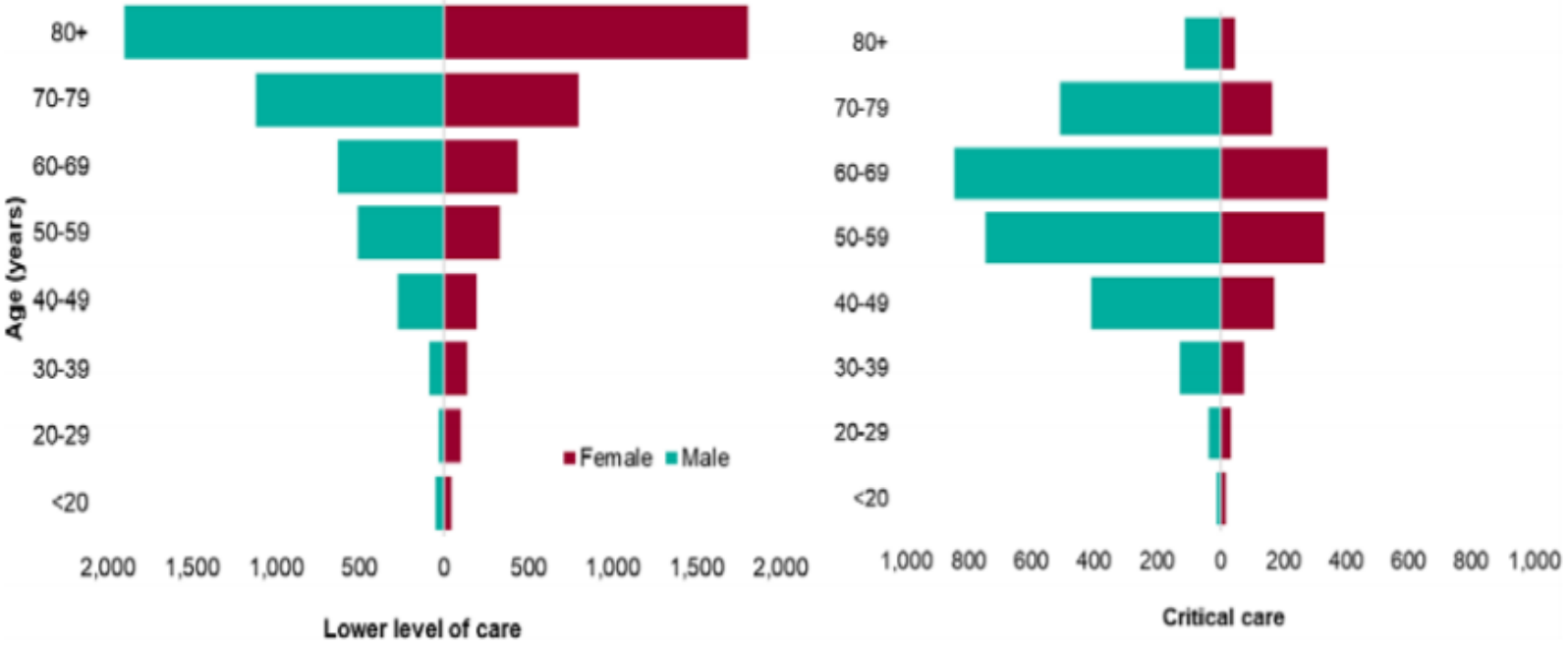
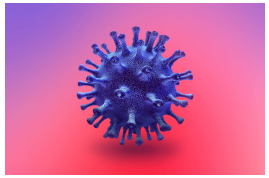


Figure 1.3. Age sex pyramids of admissions for laboratory confirmed COVID-19 to acute trusts, for lower level of care and critical care, as of 19 May 2020, England. Source: Public Health England COVID-19 Hospitalisations in England surveillance system (CHESS).

PHE: Disparities in the risk and outcomes of Covid-19

COVID19 Mortality: Age and Sex differences



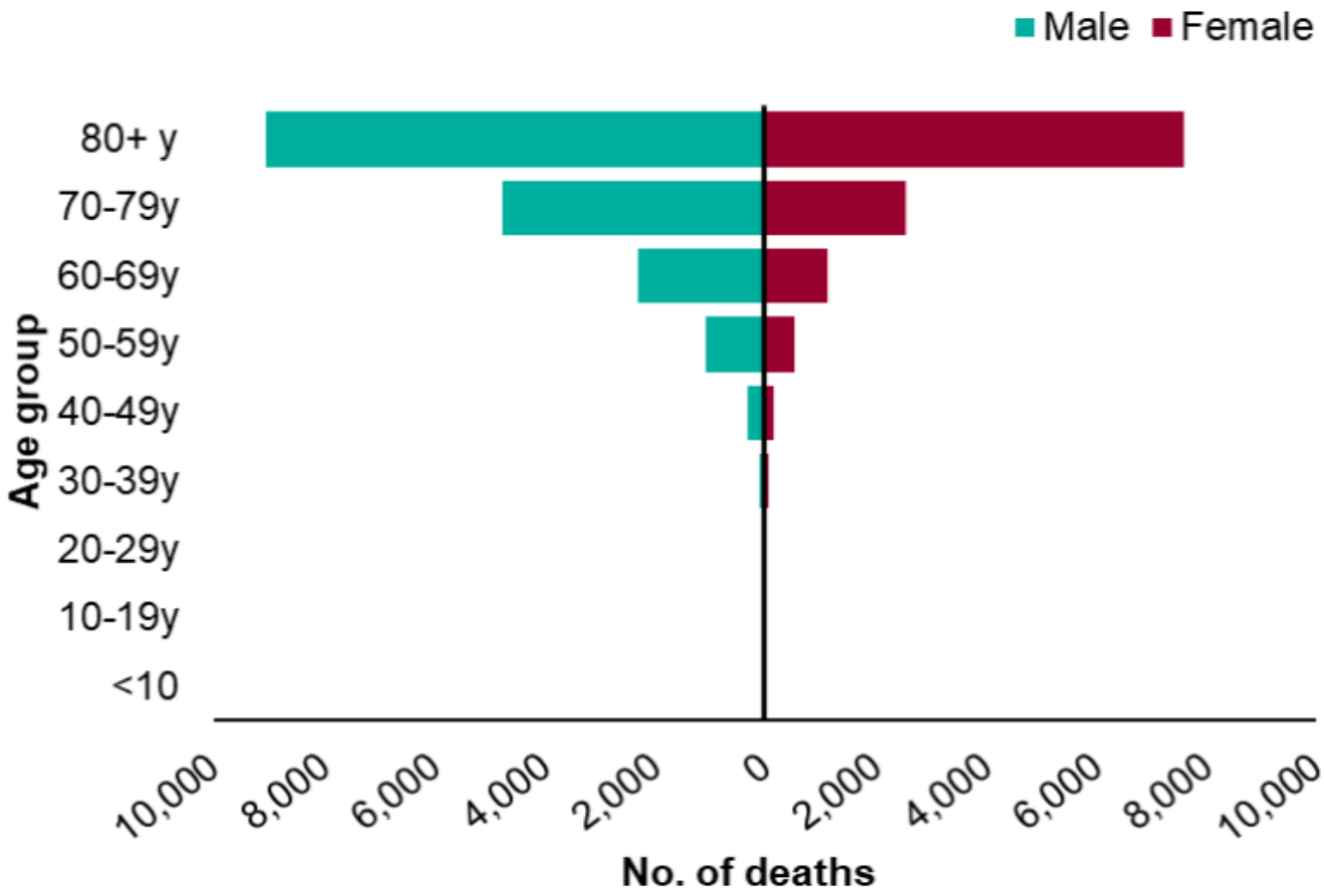


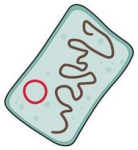
Figure 1.4. Age sex pyramid of laboratory confirmed COVID-19 deaths as of 13 May 2020, England. Source: Public Health England COVID-19 Specific Mortality Surveillance System.

PHE: Disparities in the risk and outcomes of Covid-19

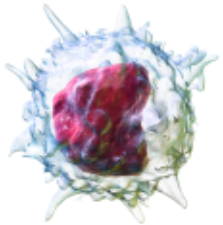
CELLS OF THE IMMUNE SYSTEM

Innate

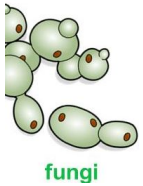
Neutrophil



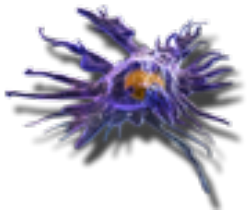
Bacteria



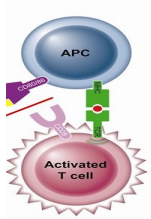
Monocyte



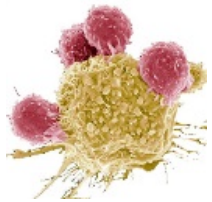
Sentinel cell
Removes dead cells
Cytokine production



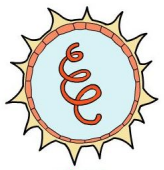
Dendritic cell



Antigen presentation

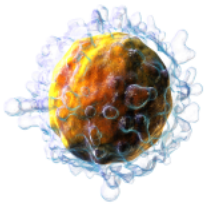


NK cell

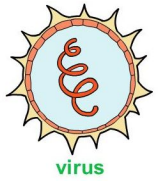


Viruses, tumor cells, senescent cells

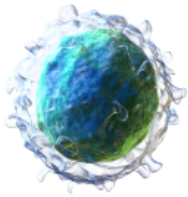
Adaptive



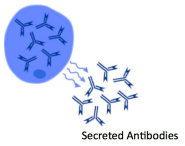
T cell



Viruses, tumor cells, senescent cells

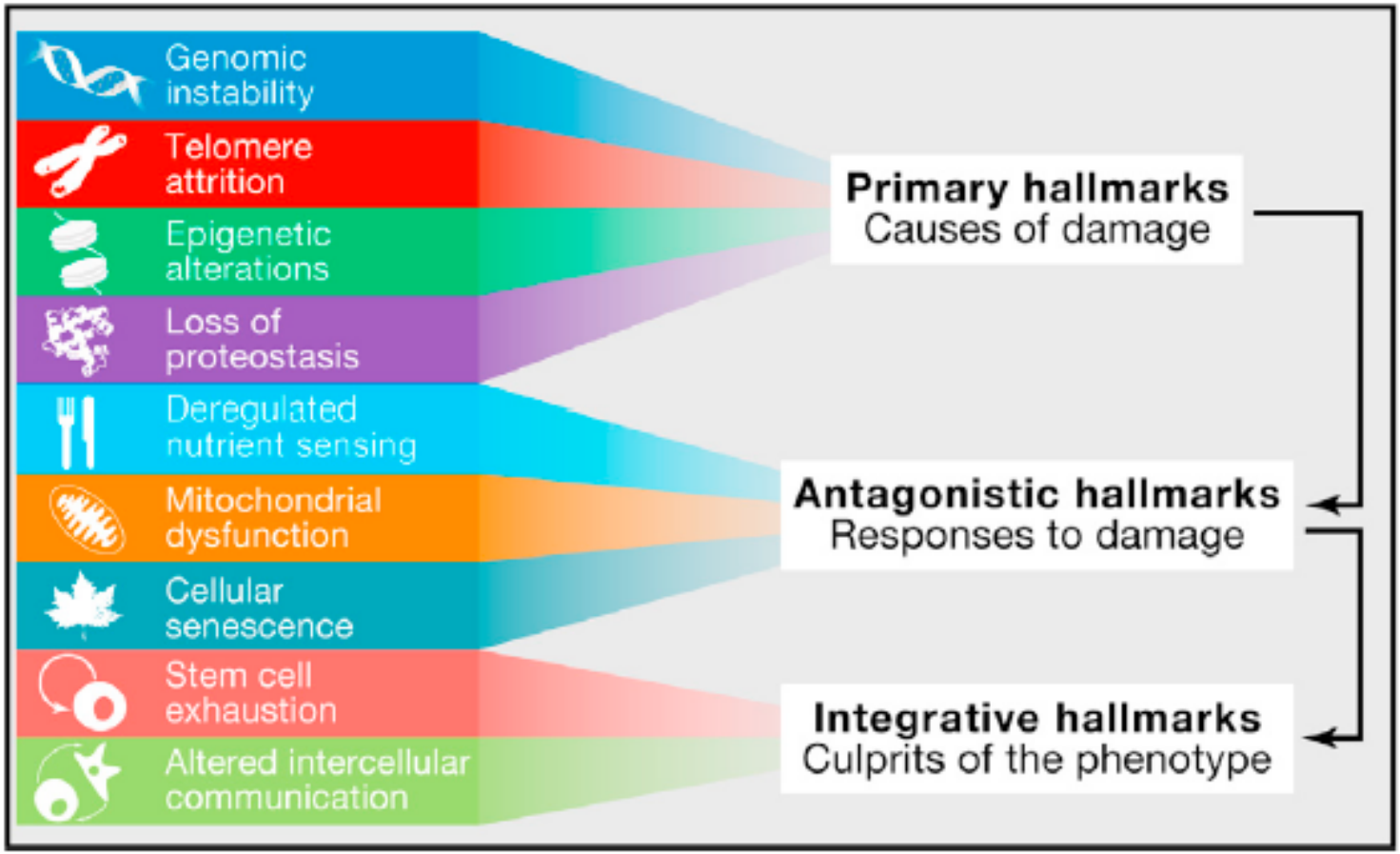


B cell



Antibody production

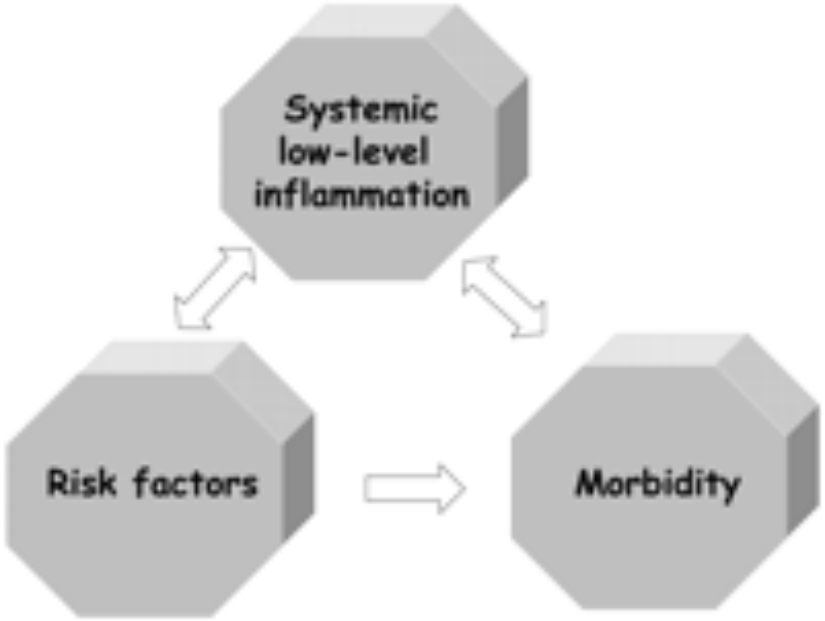
Hierarchy of Ageing mechanisms



Lopez-Otin C et al 2013 *Cell*

INFLAMMAGEING - iAGE

A universal feature of physiological ageing is an increase in circulating levels of pro-inflammatory cytokines termed "Inflammageing"



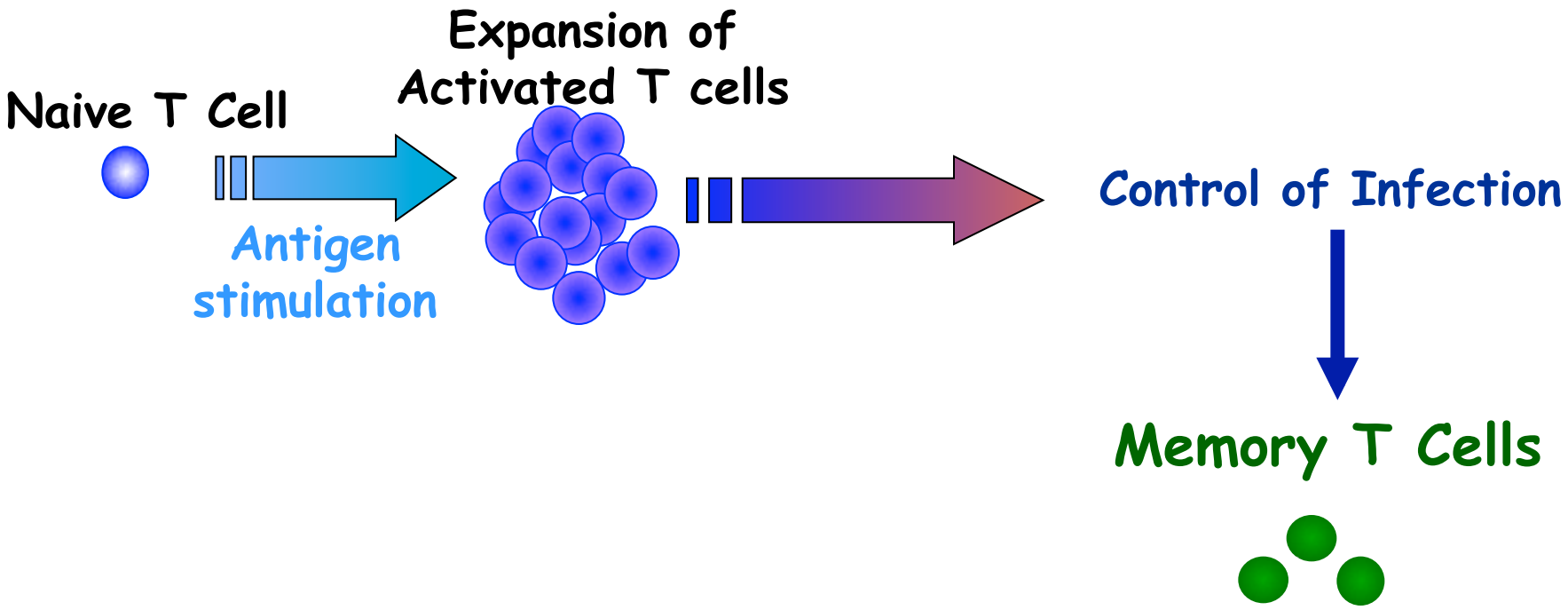
↑ TNFα

↑ IL-6

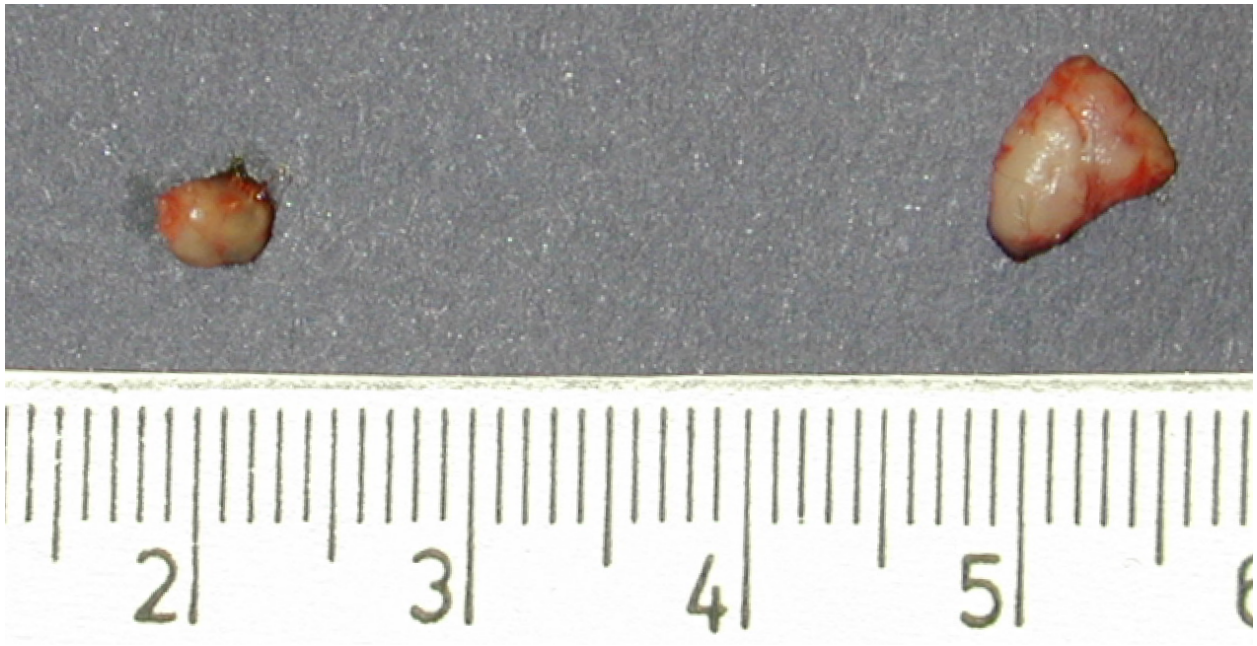
↑ CRP

↓IL10

Adaptive Immunity



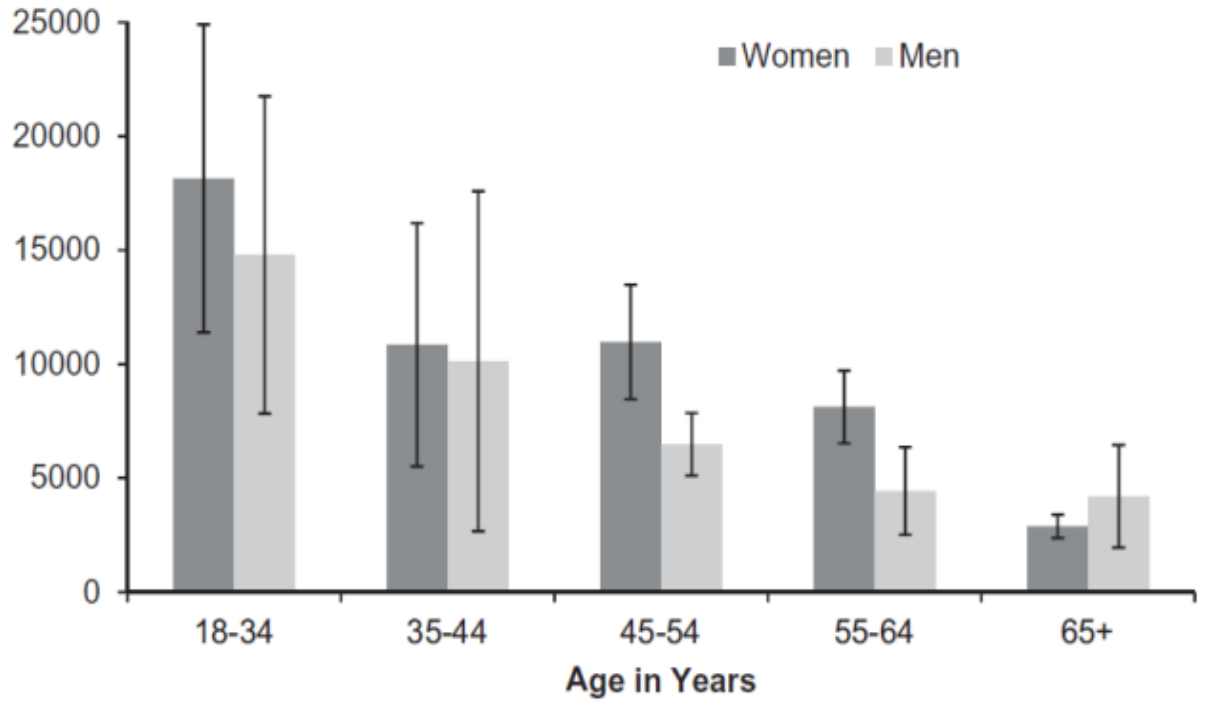
The thymus atrophies with age



Old **Young**

Thymic output decline in Humans

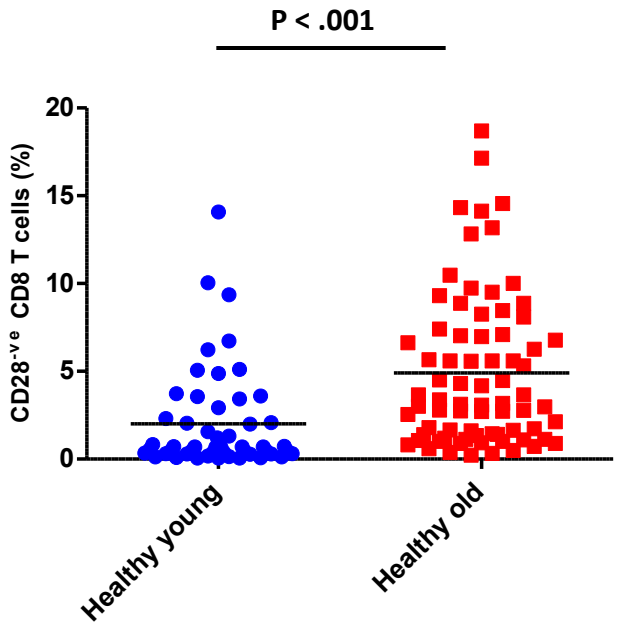
Detroit Neighbourhood Health study (n=263)

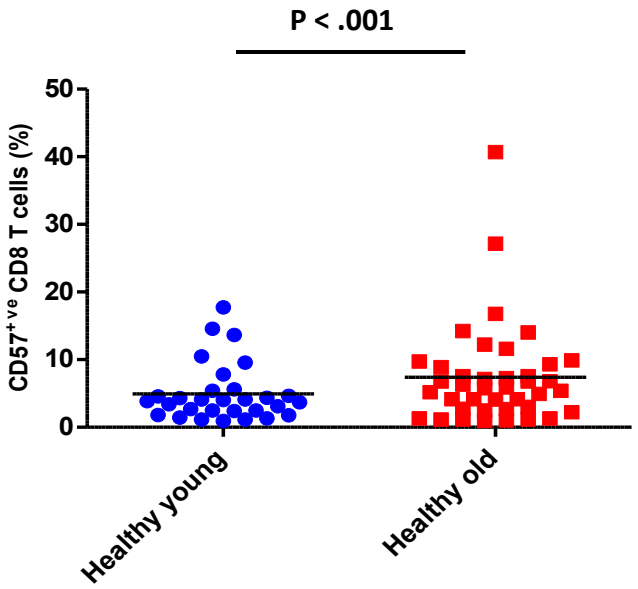


Feinstein L et al (2016) *Biodem Social Biol*

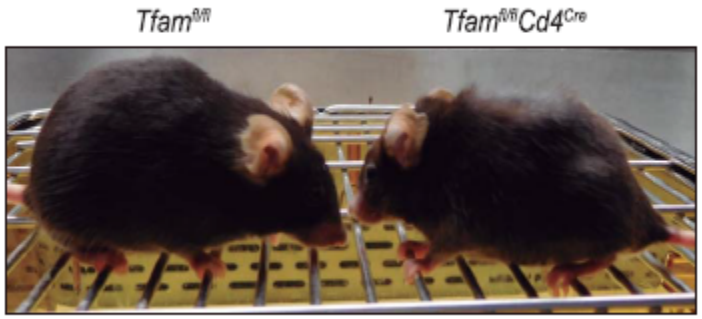
Increased Senescent T Cells with age (IMM-AGE)

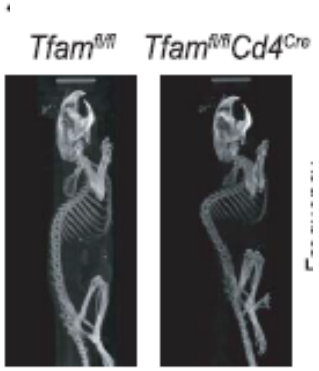
- Loss of CD28 and /or gain of CD57 expression
- Reduced proliferation
- Produce pro-inflammatory cytokines (TNFα , IFNγ)

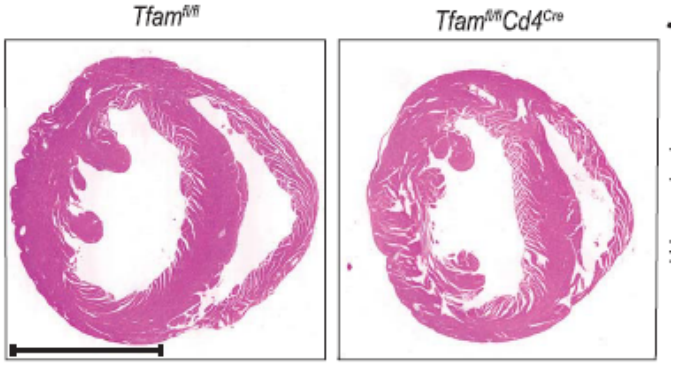


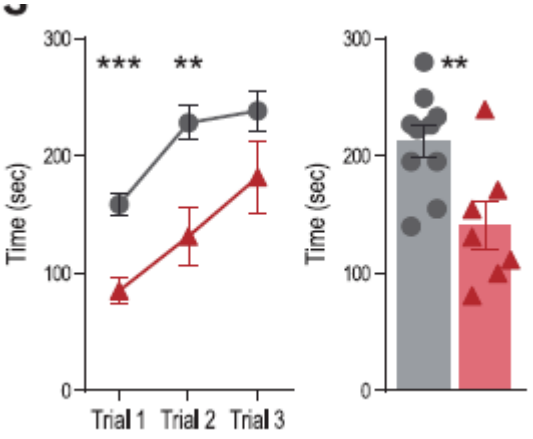


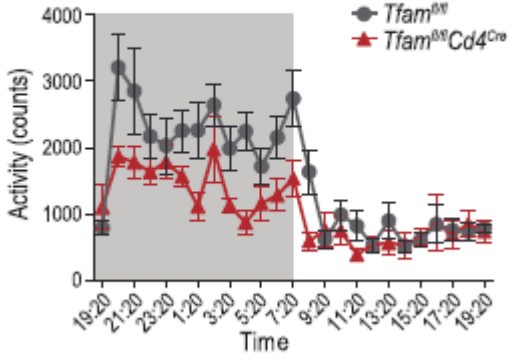
Senescent T cells are sufficient to induce an Aged phenotype

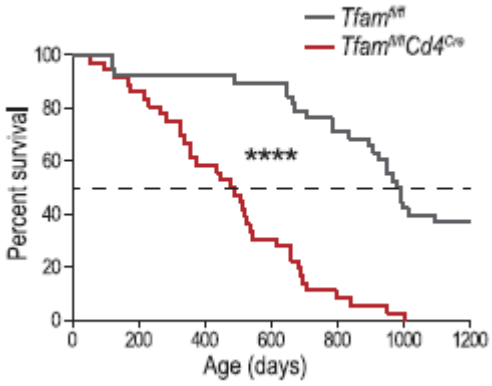






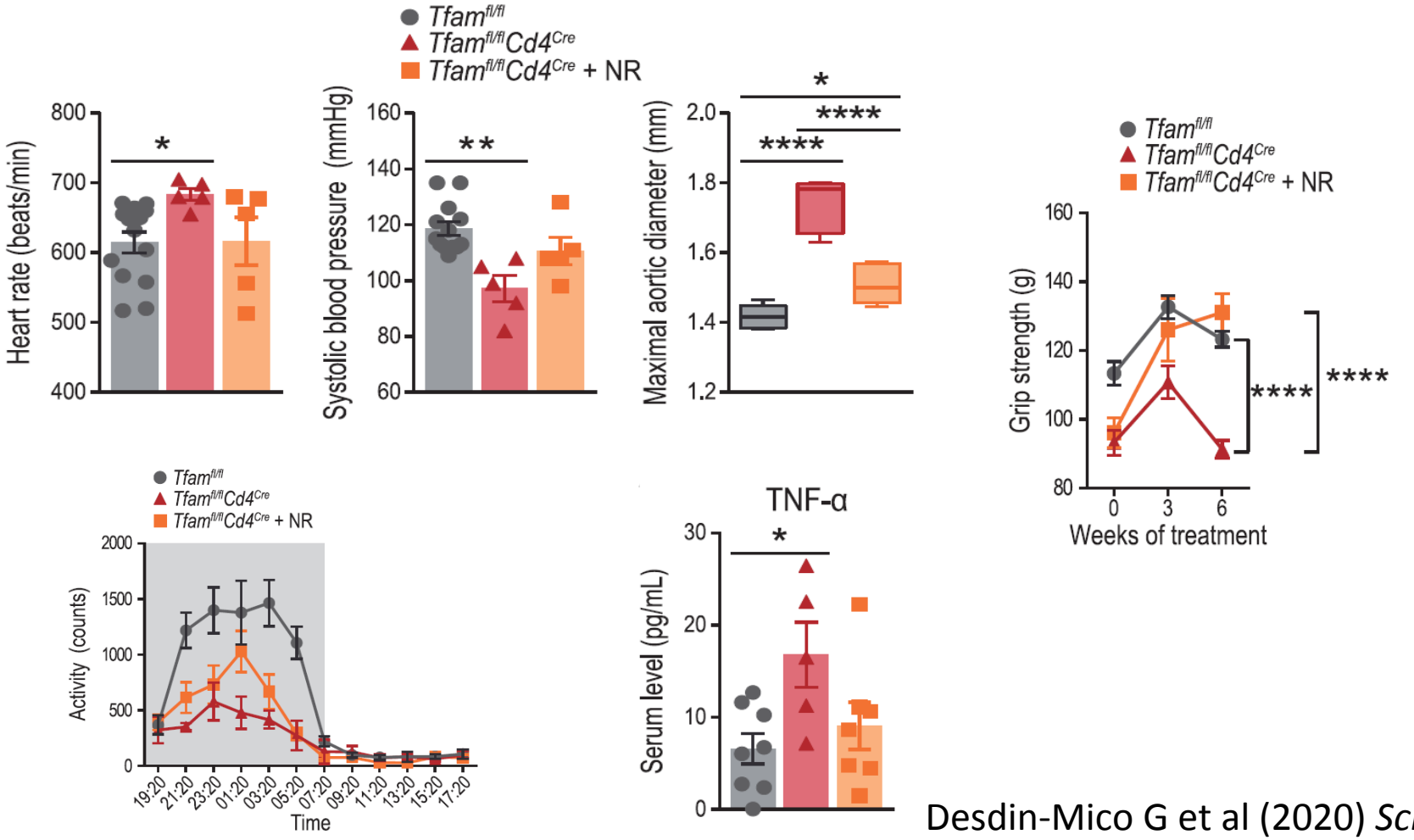






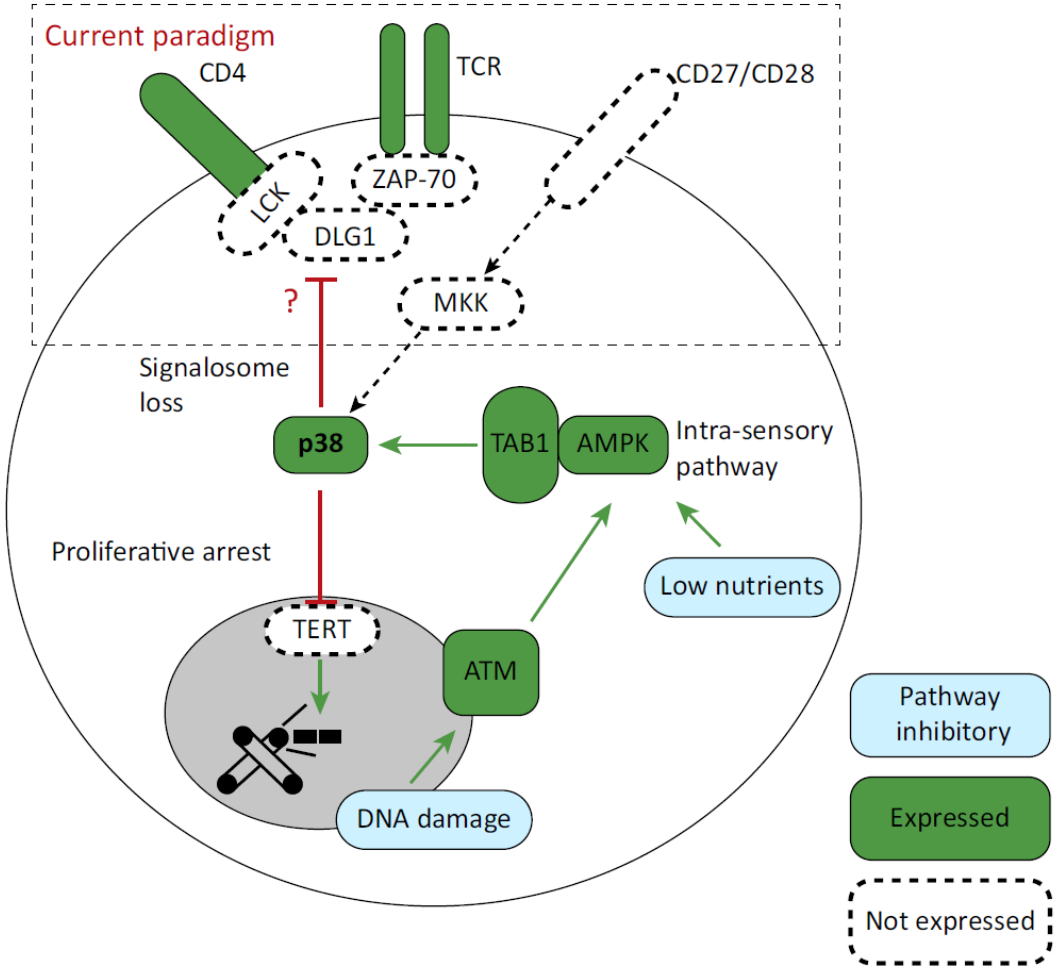
Desdin-Mico G et al (2020) *Science*

Restoring NAD levels reduces T cell induced Ageing



Desdin-Mico G et al (2020) *Science*

Overcoming T cell ageing in Humans

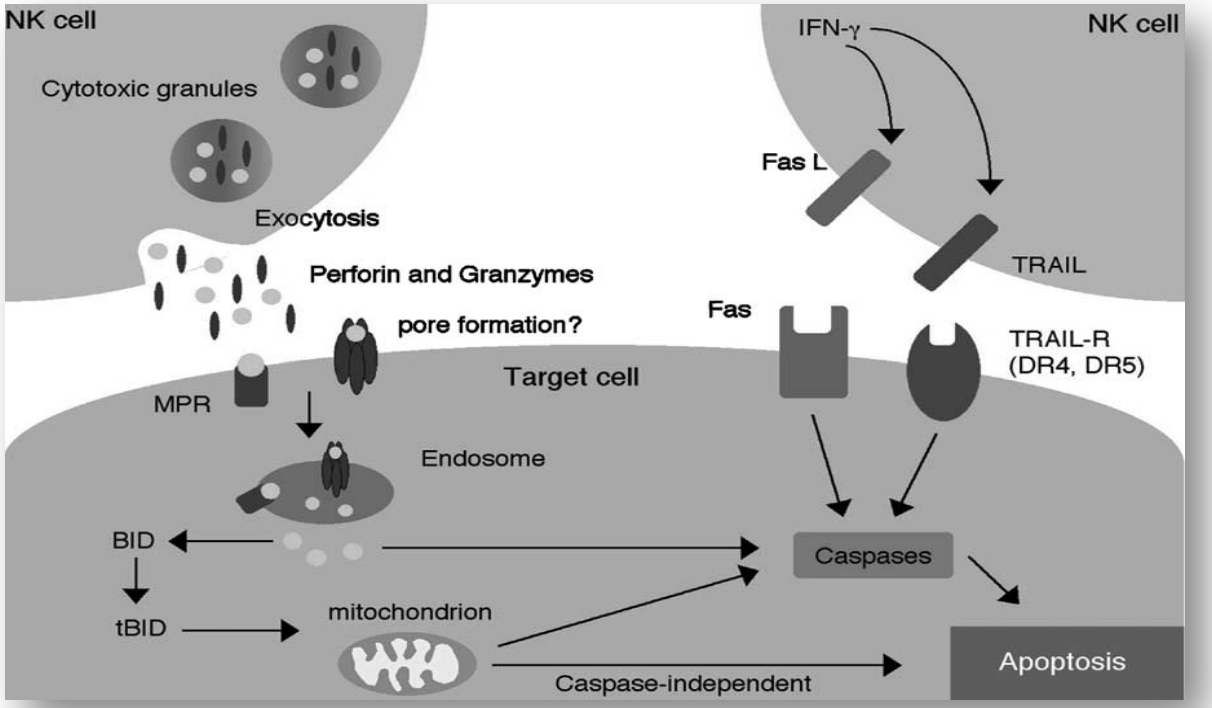


Akbar et al (2016) *Trends Immunol*

Why do Senescent cells accumulate with age - NK cells

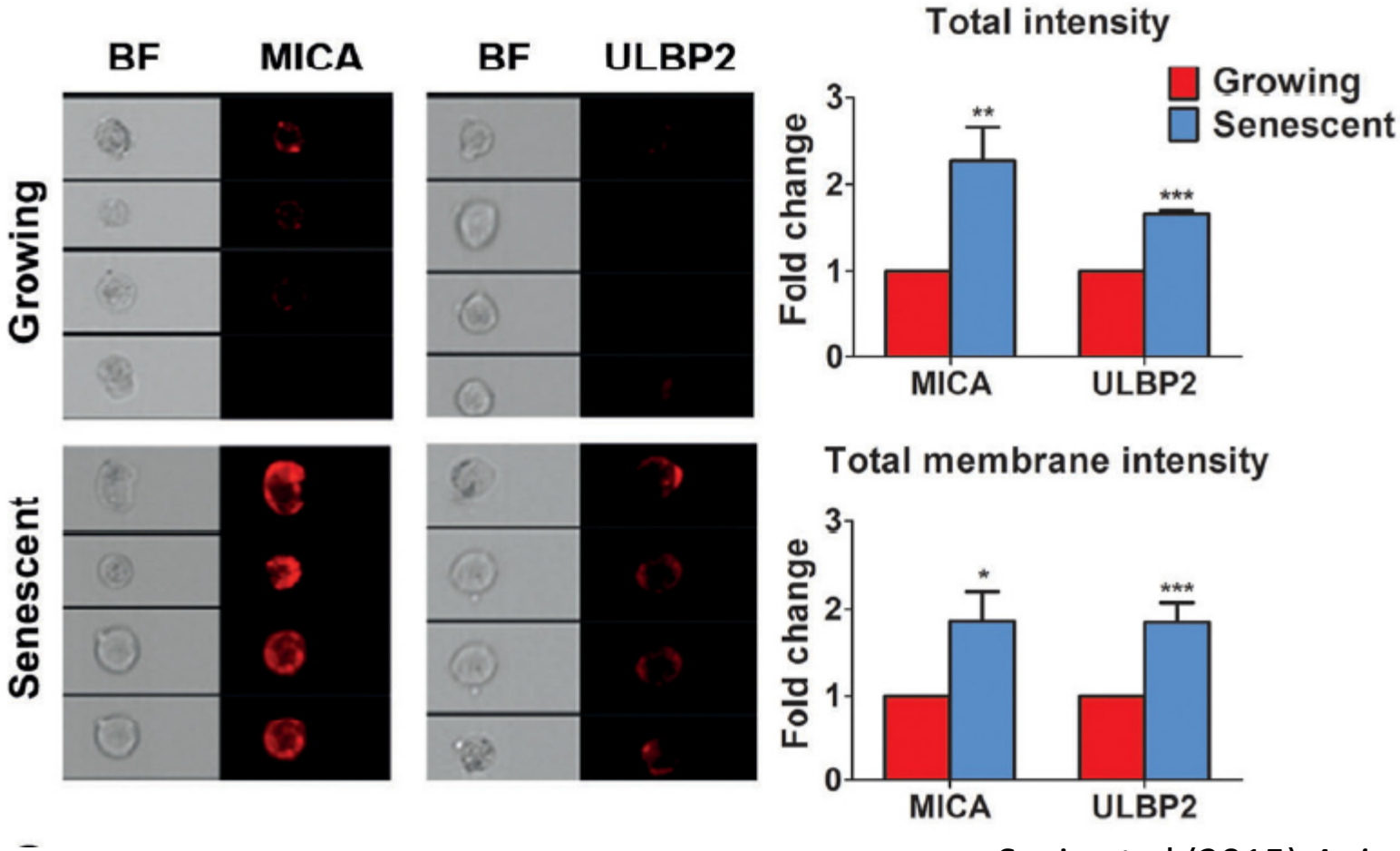
- **High cytotoxic activity**; governed through an array of germline encoded activatory and inhibitory receptors; e.g. **NKG2D** and KIR family members

- Induce apoptosis in infected, transformed and senescent cells through one of two **contact-dependent** mechanisms;



Smyth et al. 2005

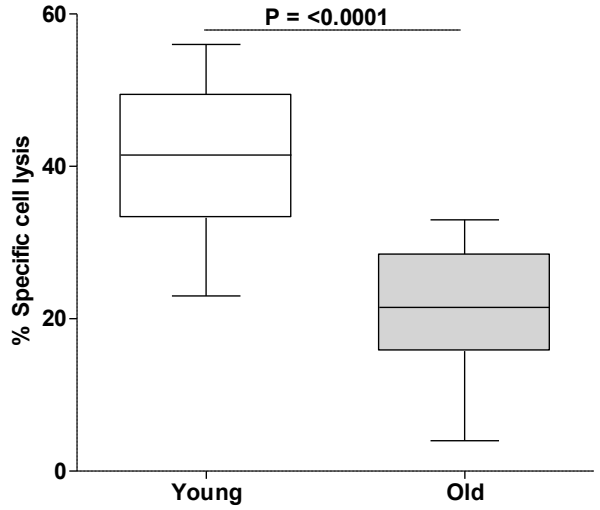
Senescent cells upegulate NKG2D ligands



Sagiv et al (2015) *Aging*

NK killing ability decreases with age

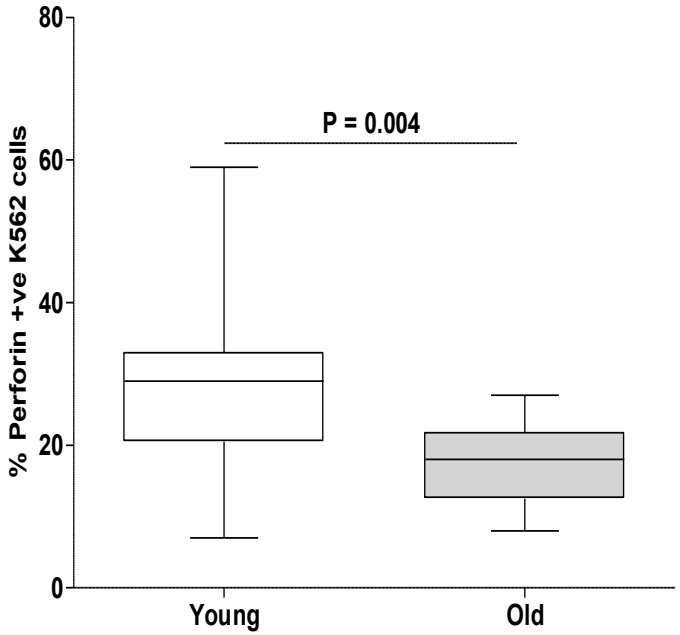
	Young (n = 21)	Old (n = 21)	p Value
CD56DIM:BRIGHT	23:1±3.54	51:1±5.72	**0.0001**



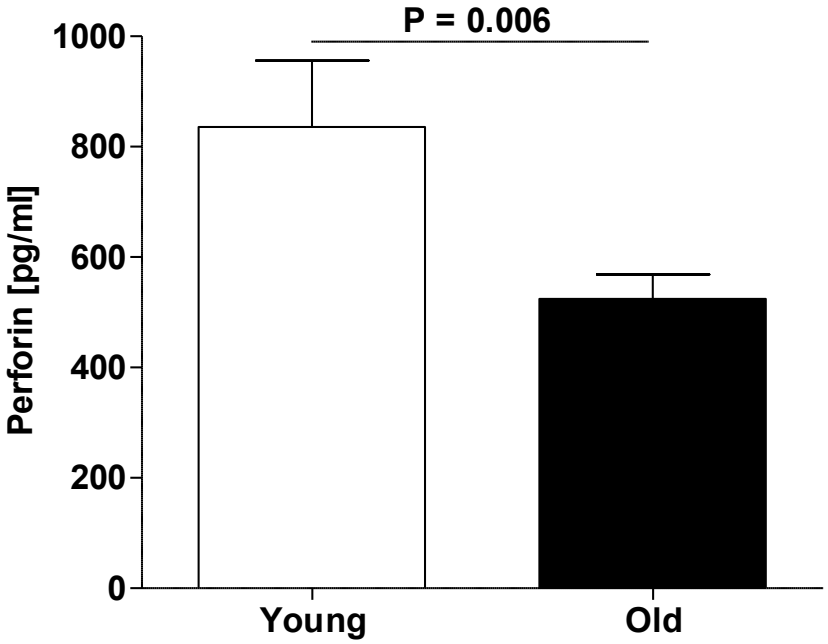
Hazeldine J et al (2012)

Mechanism of functional decline

Perforin binding to Target



Perforin release

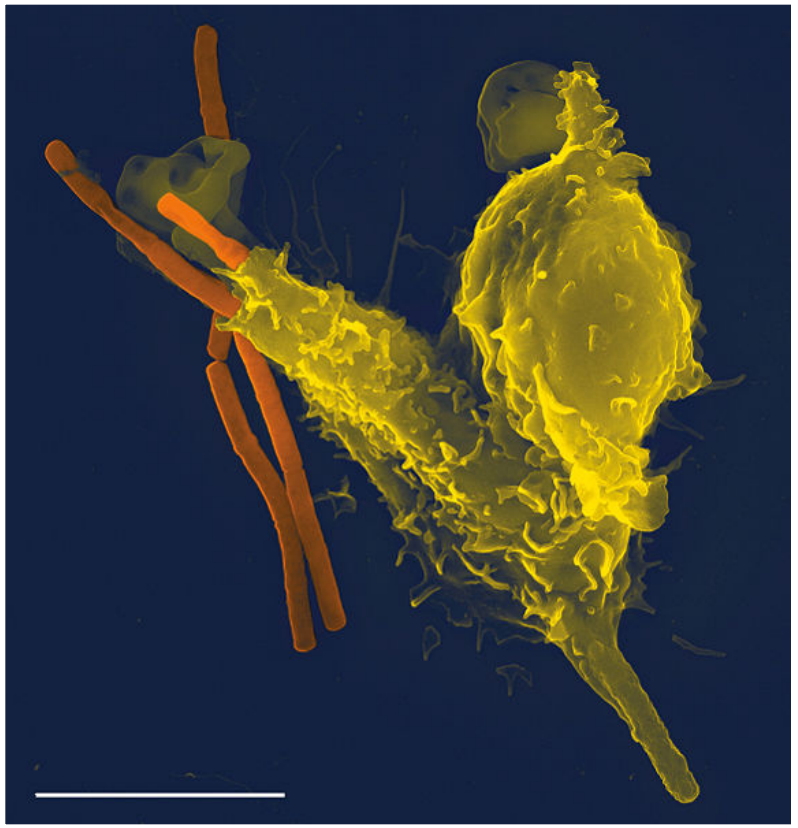


Hazeldine J et al (2012) Aging Cell

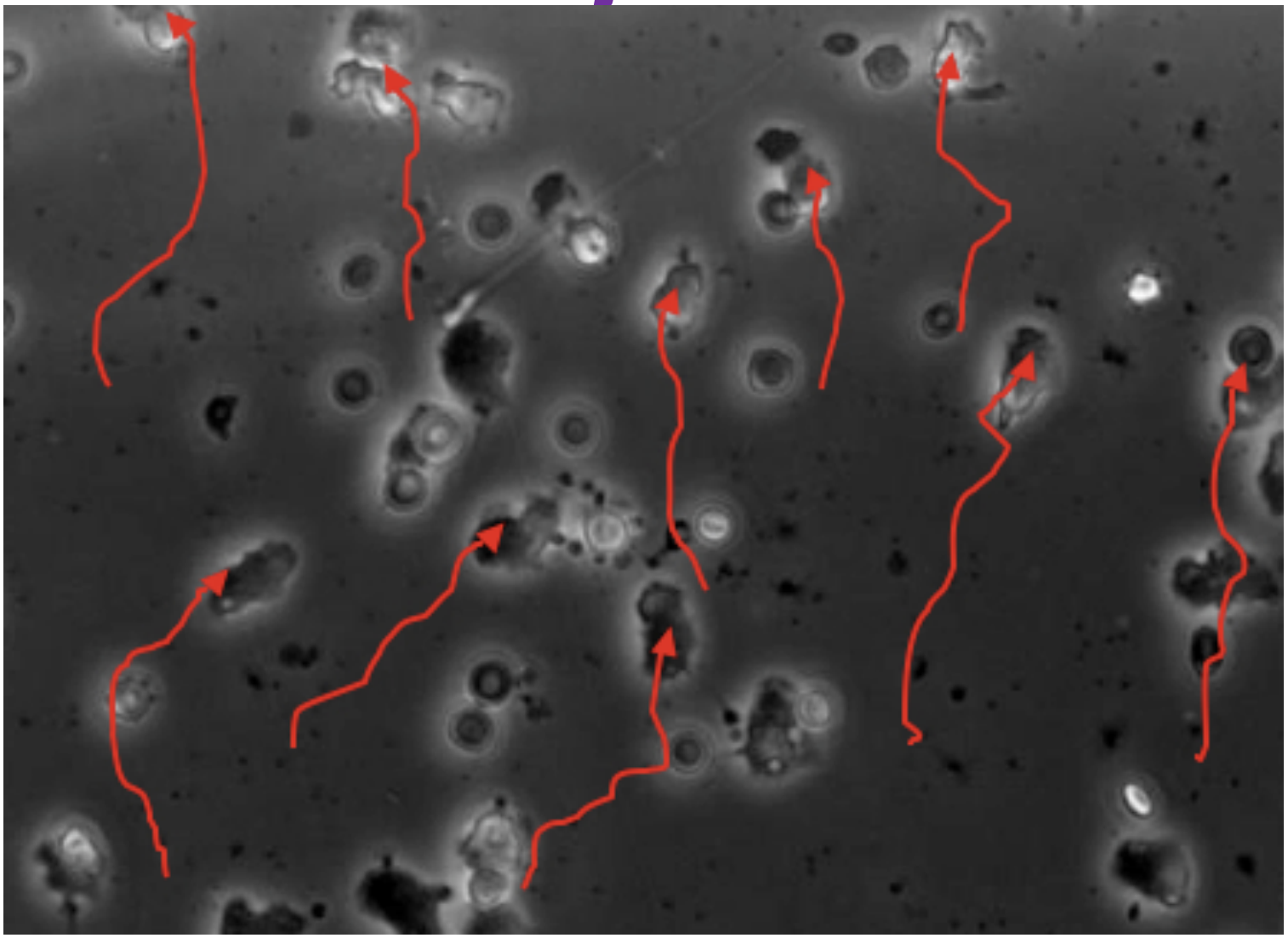
Inflammageing and Neutrophils

- **Chemotaxis**
- Phagocytosis
- Bacterial killing:

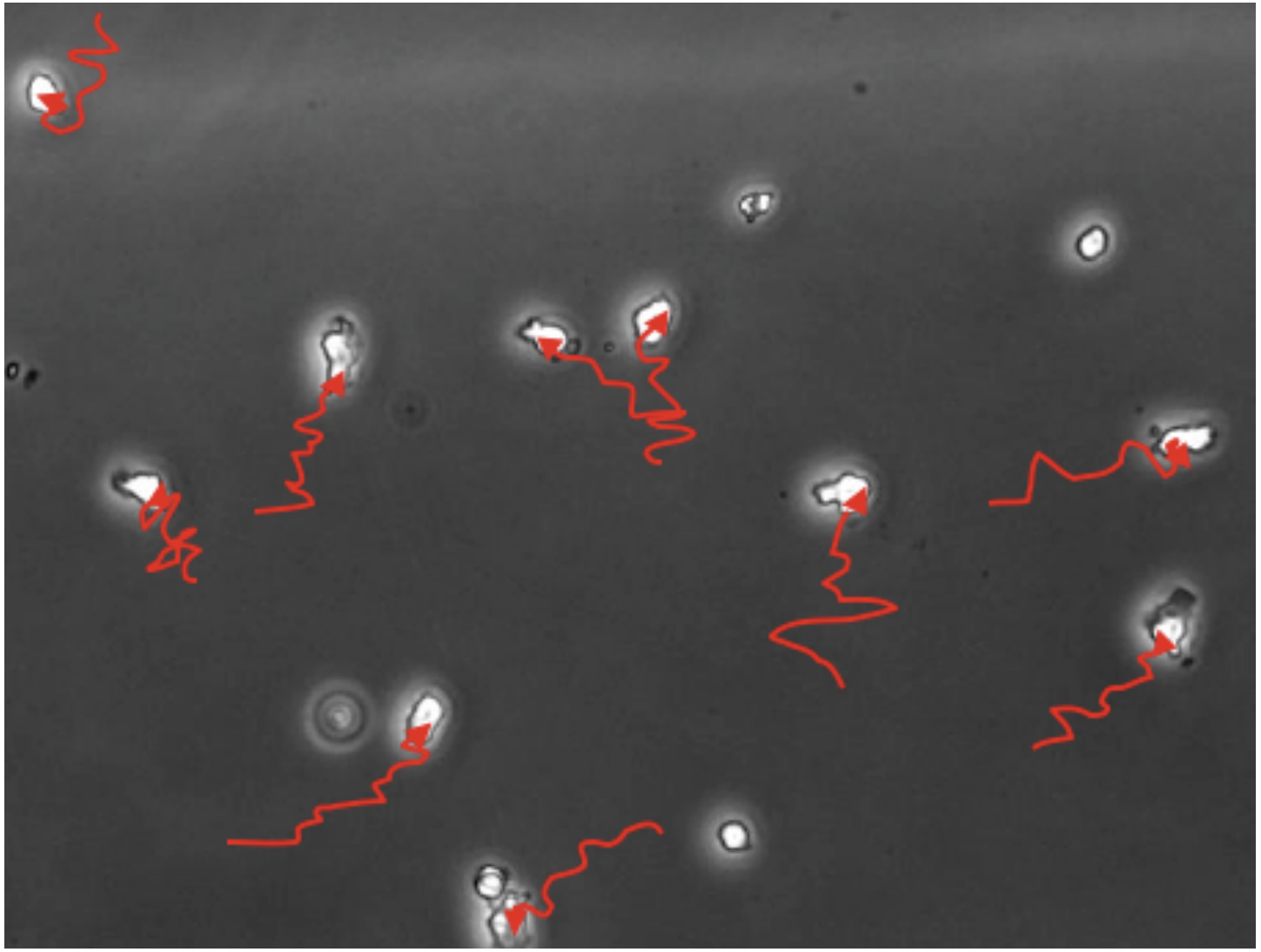
ROS generation



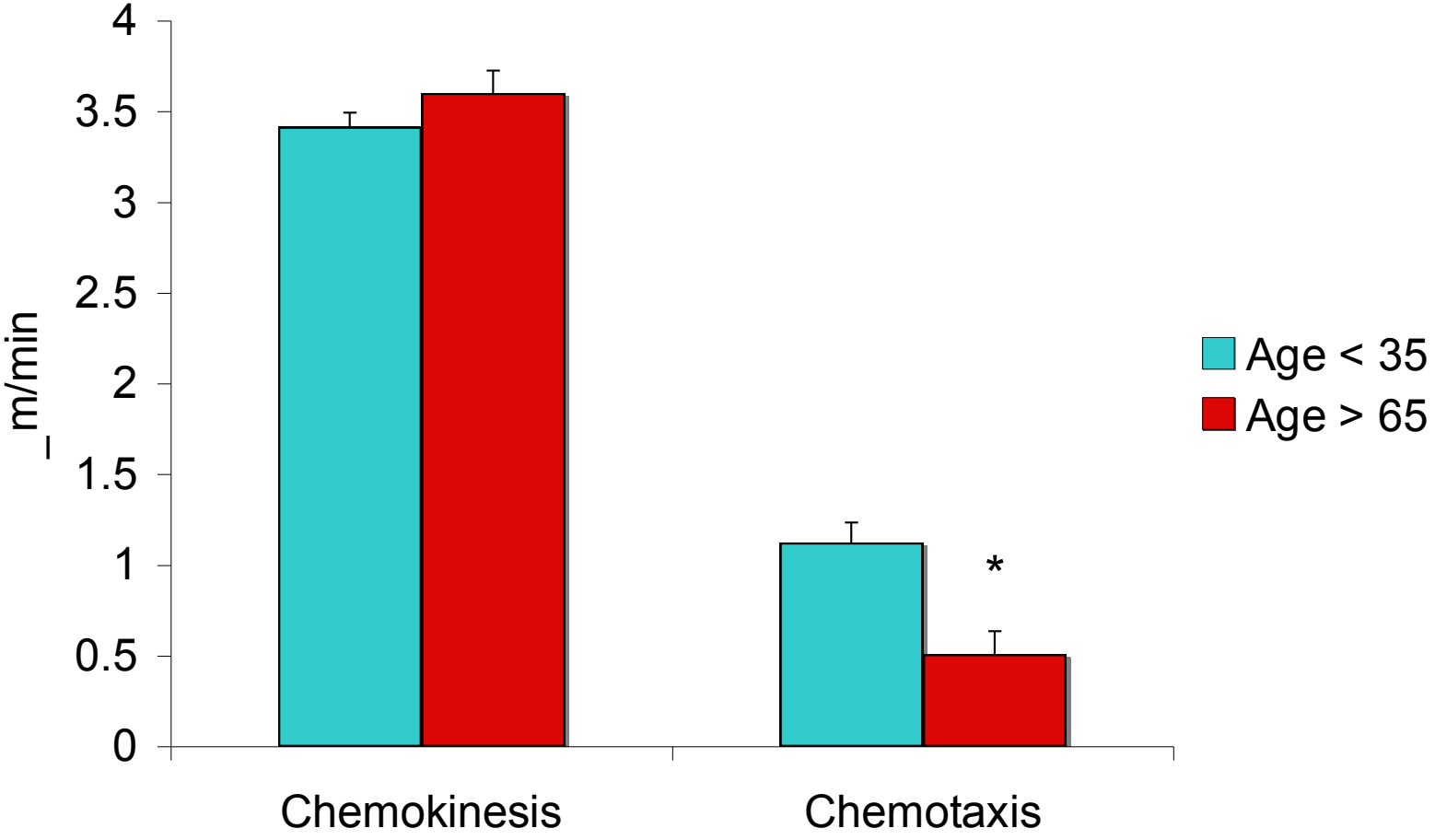
Neutrophil migration - young subjects



Neutrophil migration - old subjects

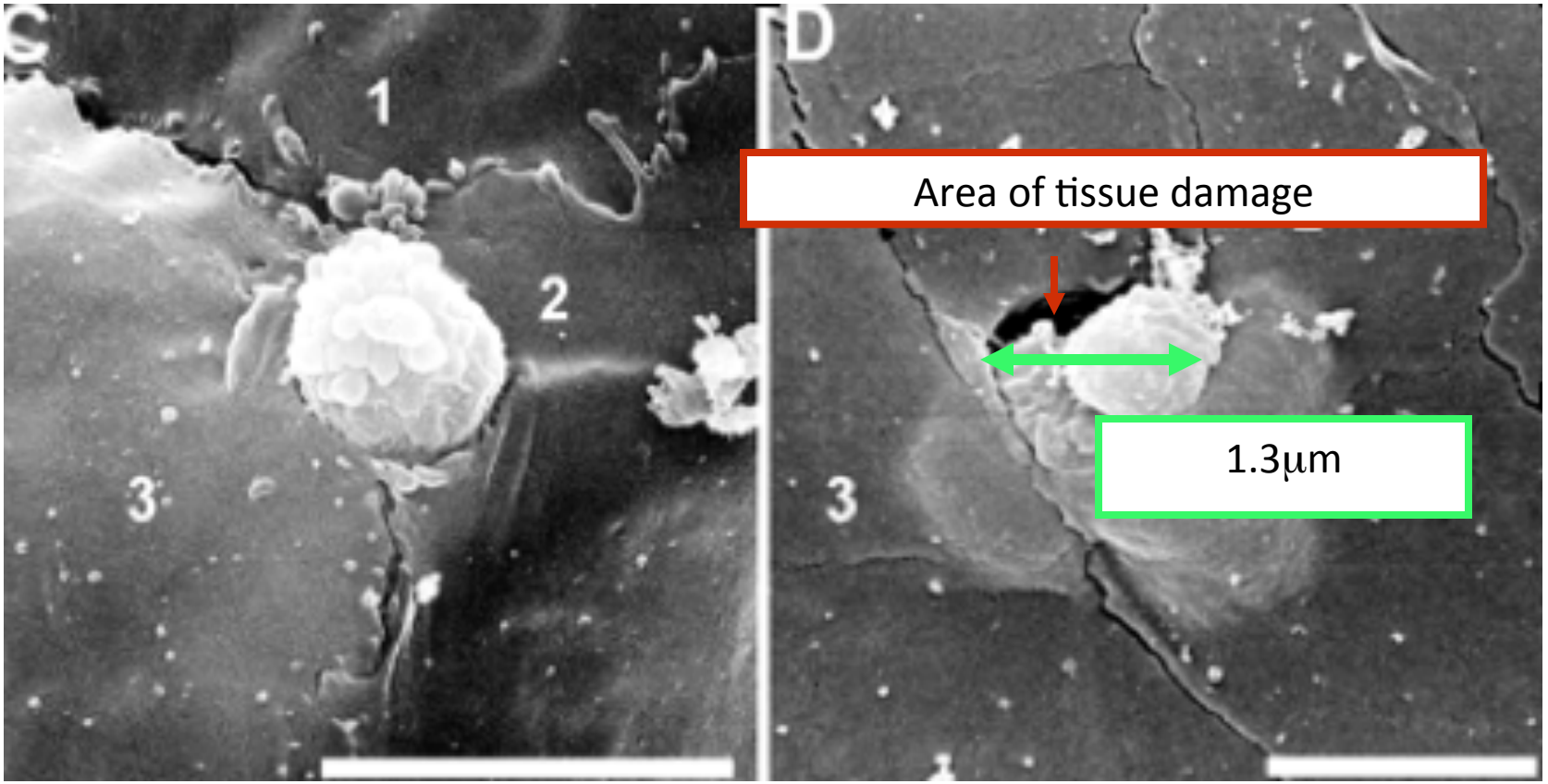


Chemokinesis and chemotaxis with Age



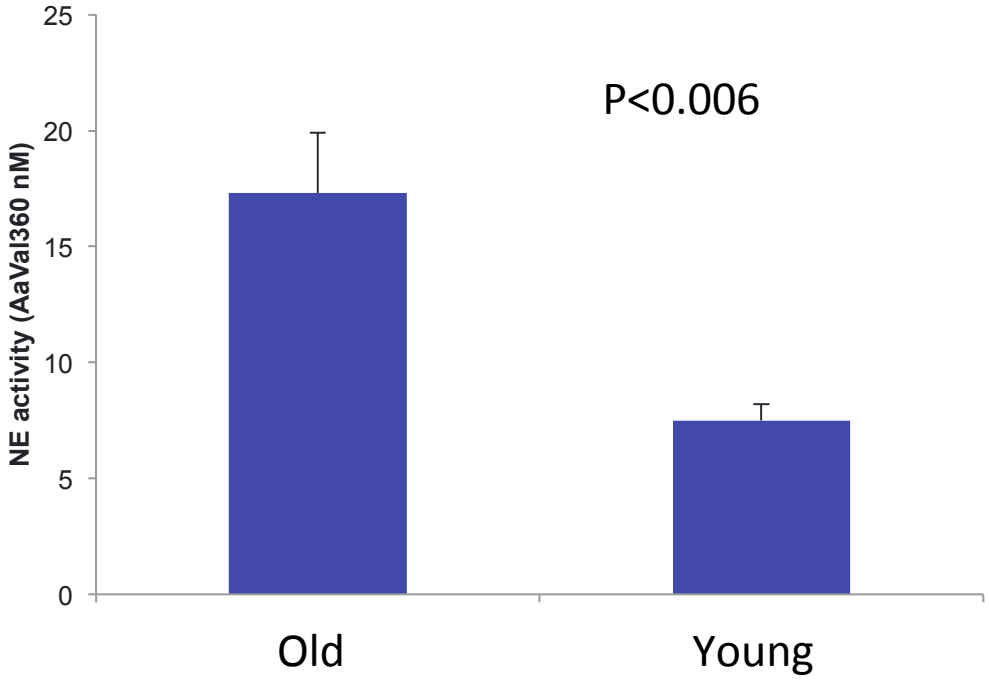
Sapey E et al, (2014) *Blood*

Increased tissue damage during migration – increased inflammation



Burns et al, Physiol Rev (2003)

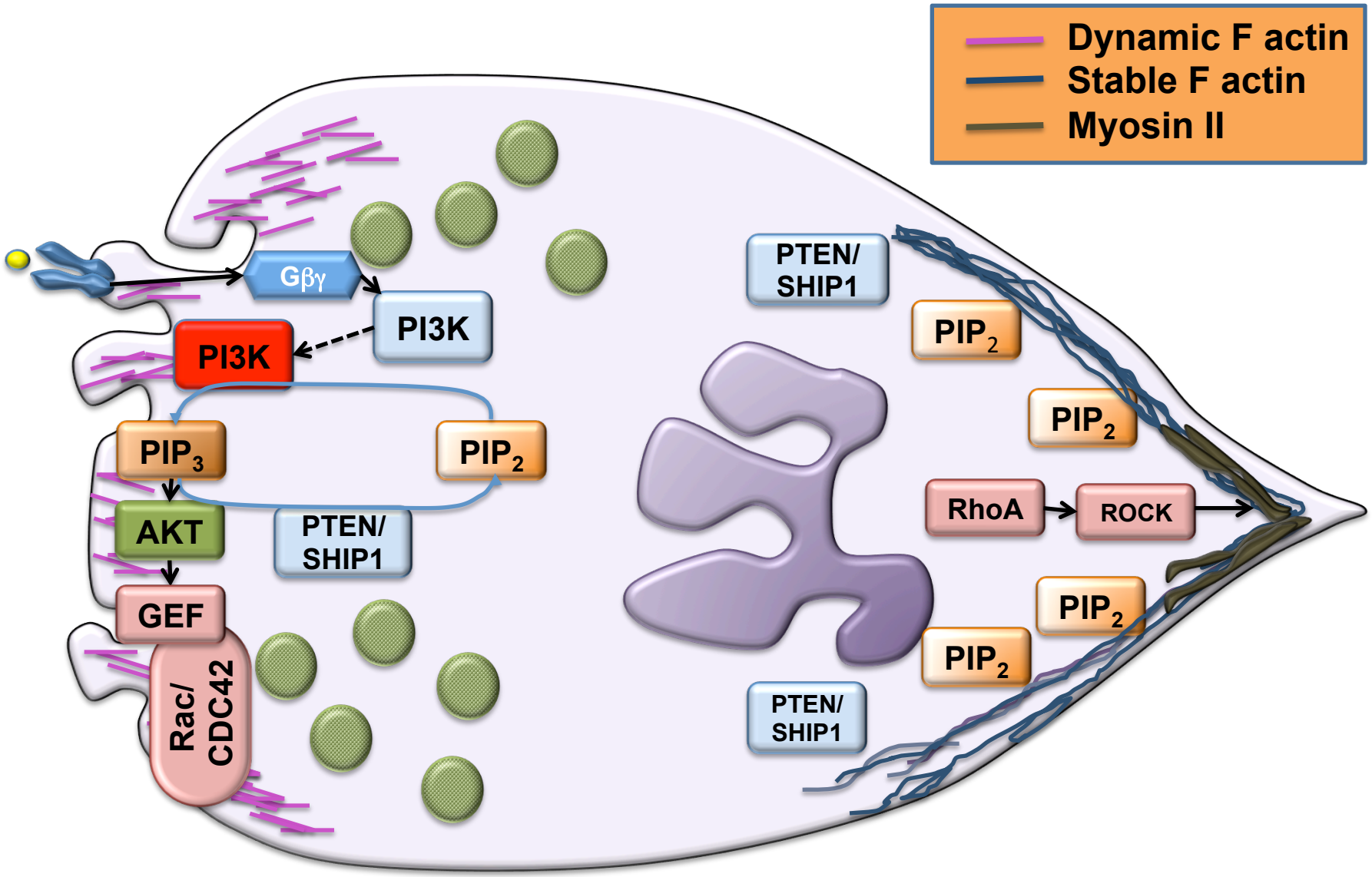
Increased tissue damage and inflammation in Healthy Elders



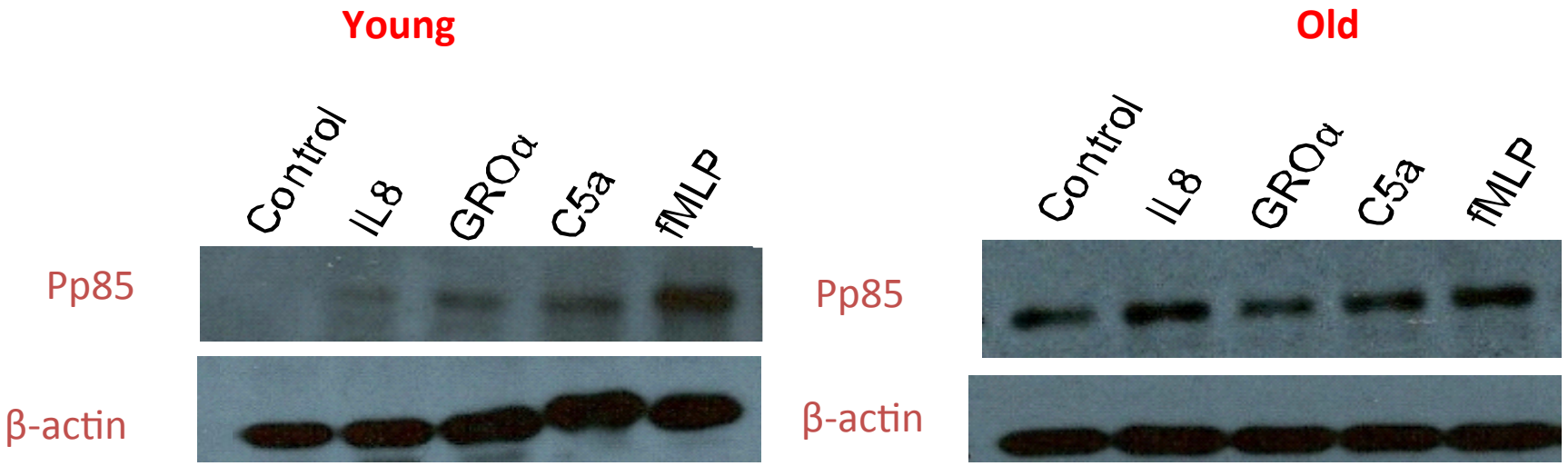
TNF (nM)	1.6	0.56	p<0.03
hsCRP (mg/dl)	3.4	1.1	p<0.01

Sapey E et al 2014 *Blood*

Signalling for Neutrophil migration

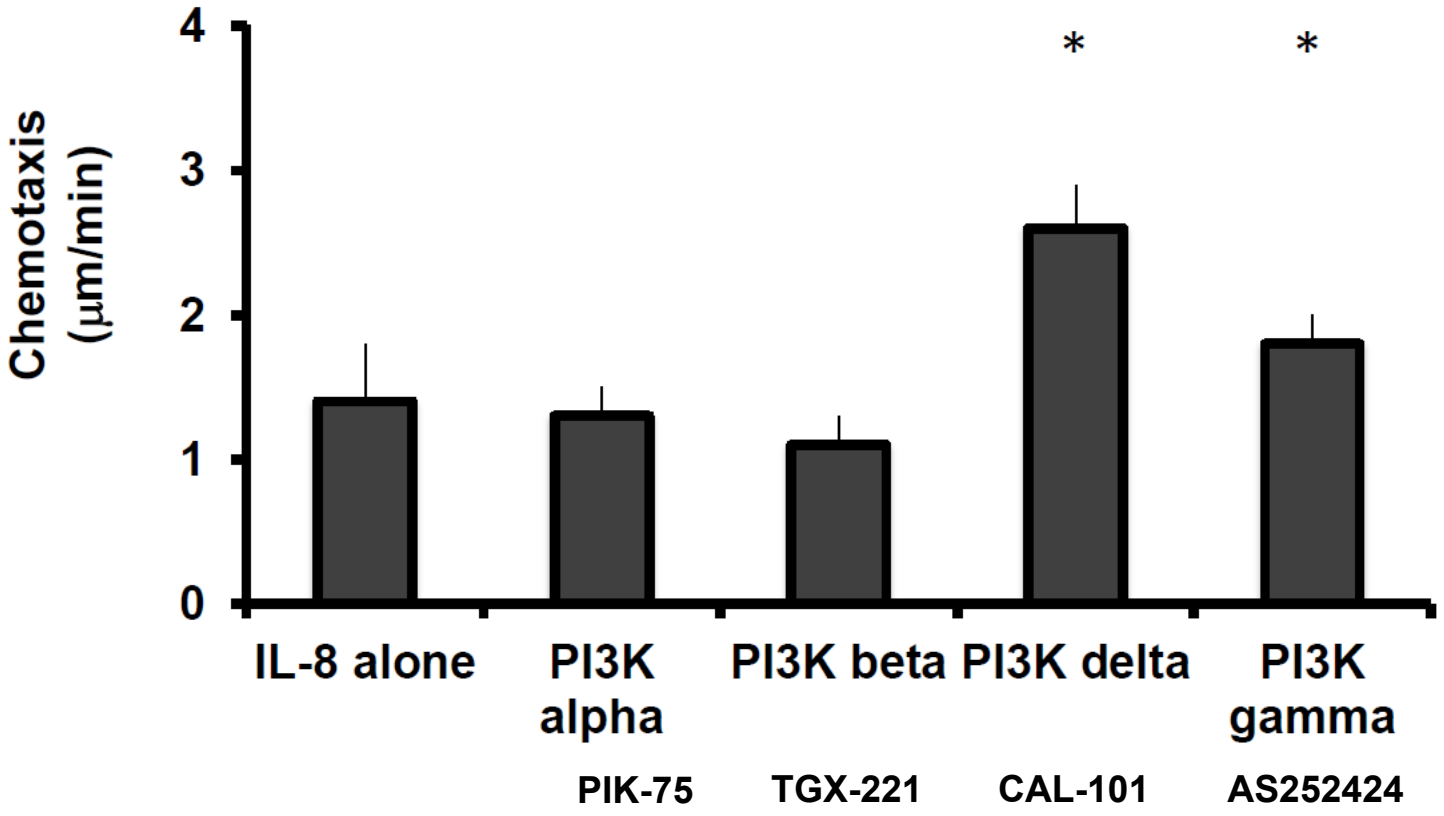


PI3K signalling in Neutrophils from young and old donors



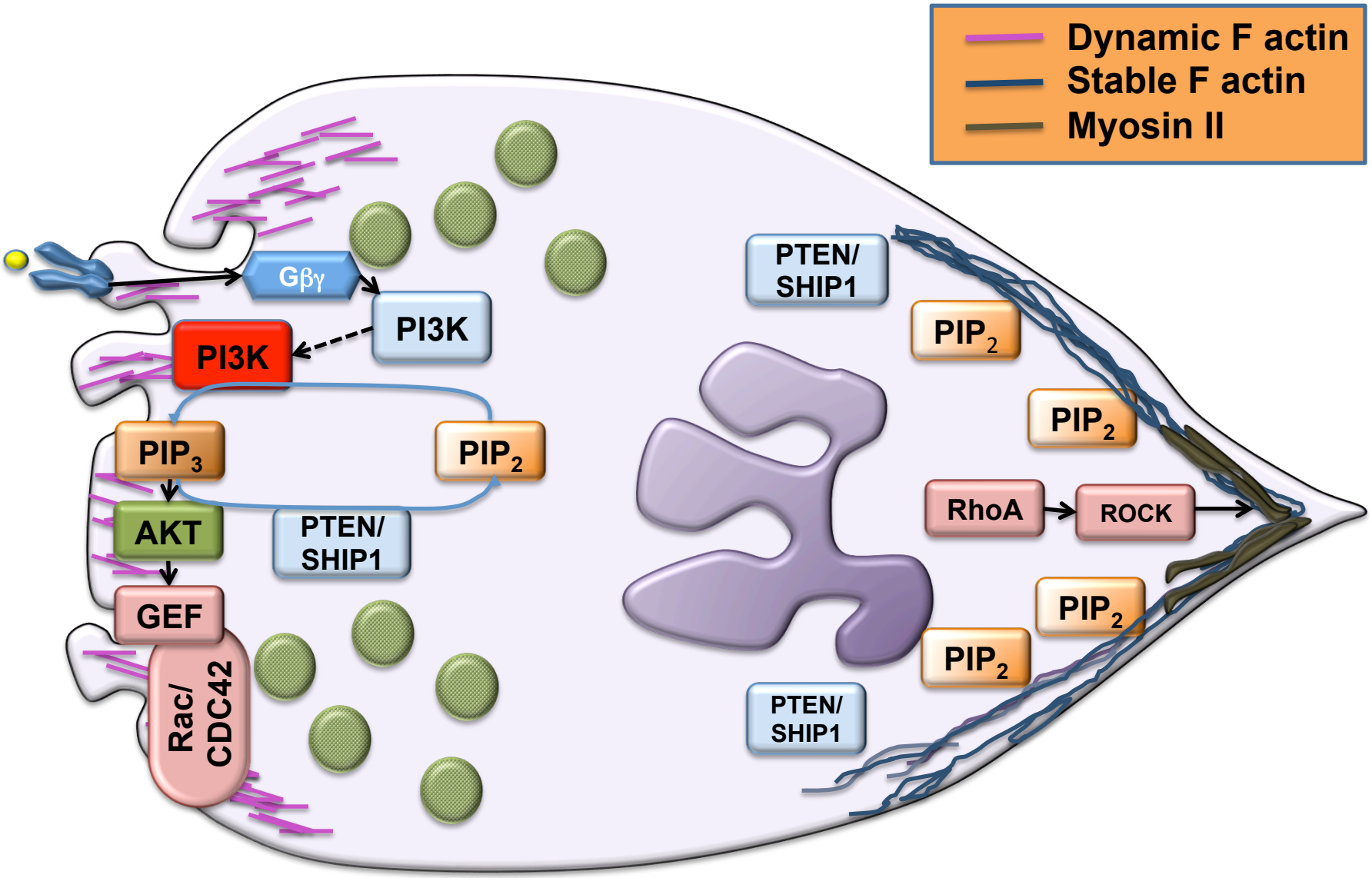
Sapey E et al (2014) *Blood*

PI3kδ inhibition corrects chemotactic defect

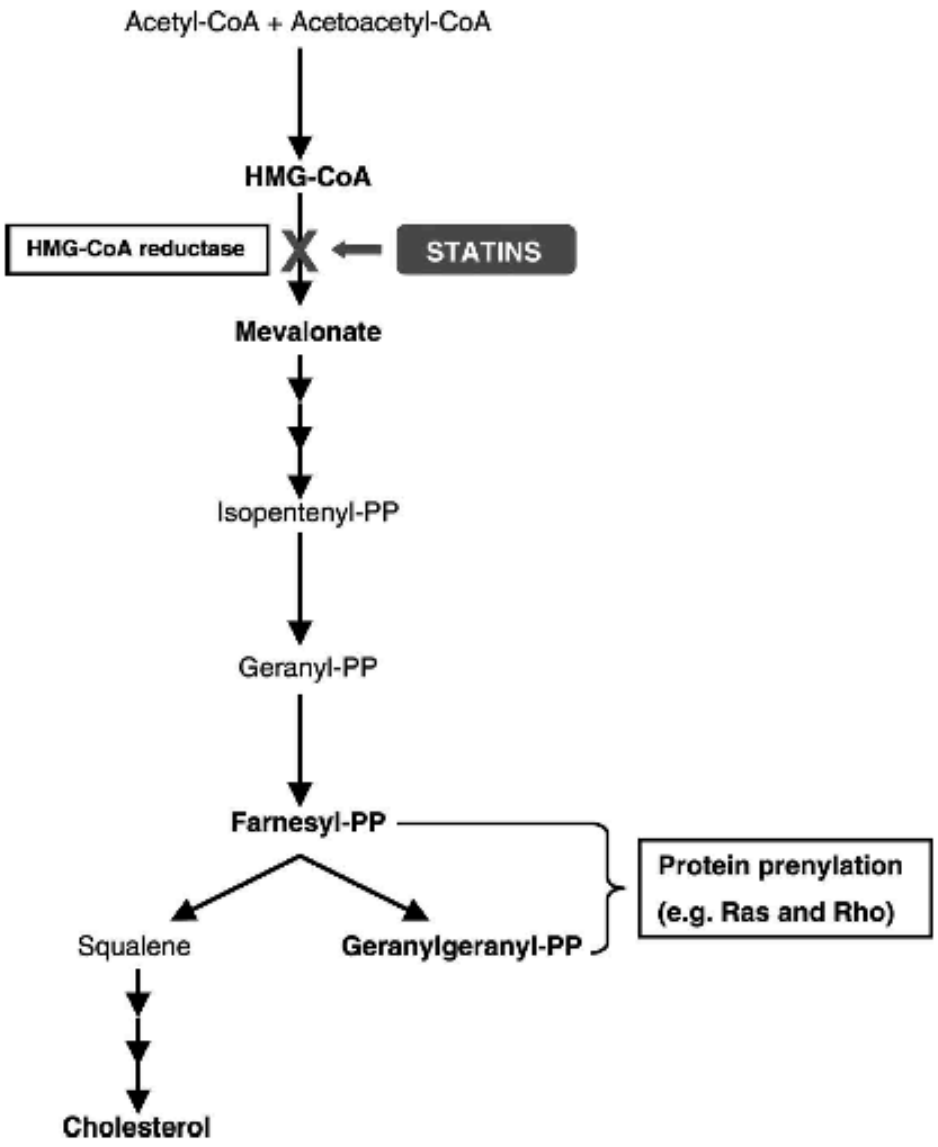


Sapey et al (2014) *Blood*

Signalling for Neutrophil migration

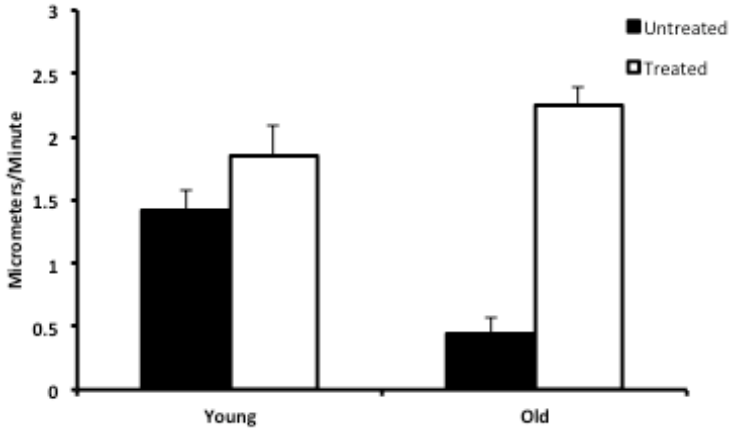


Statins reduce GTPase activation

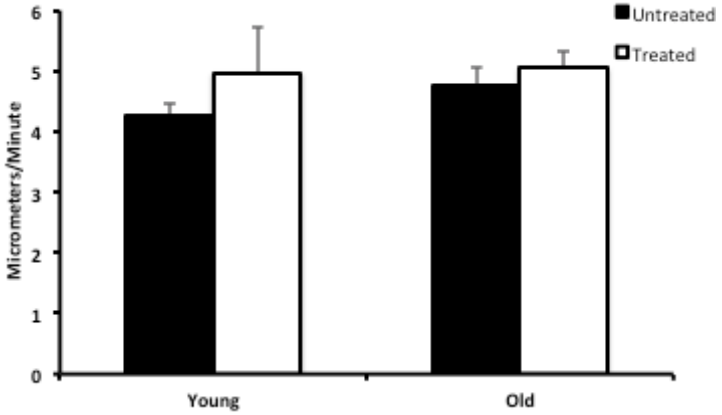


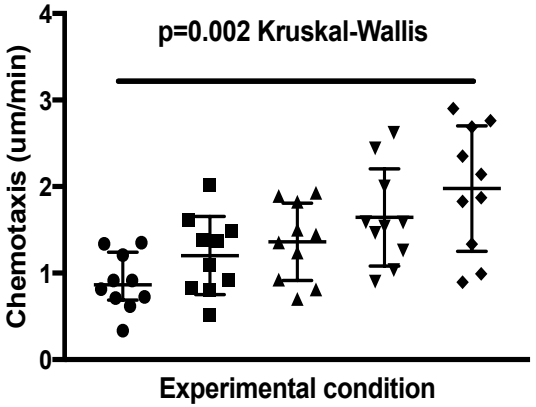
Statins improve Neutrophil migration *in vitro*

Chemotaxis



Chemokinesis





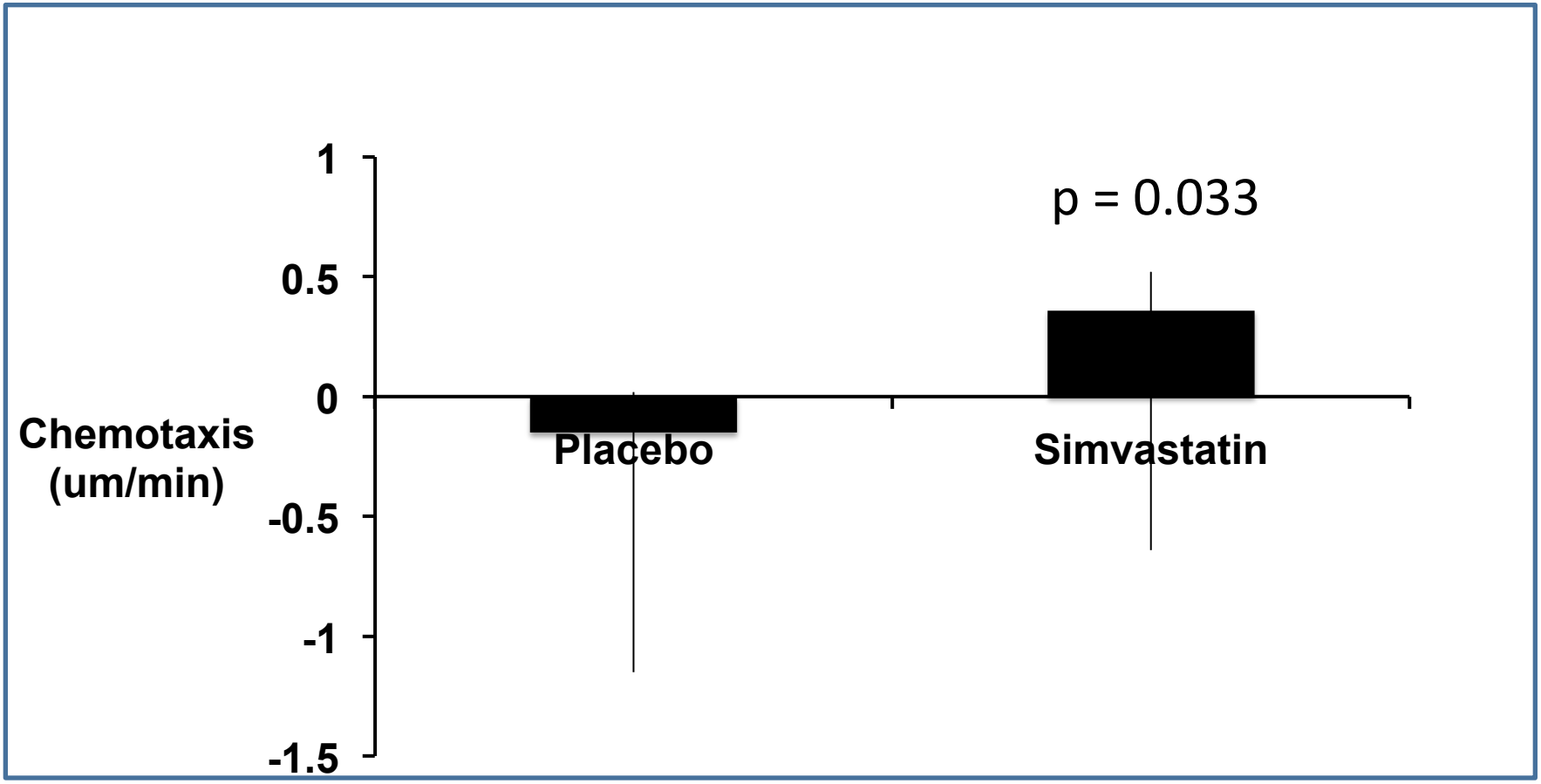
- VC
- Sim 1nM
- Sim 10nM
- Sim 100nM
- Sim 1uM

Sapey E et al (2017) AJRCCM

Simvastatin to modify **N**eutrophil functi**O**n in **O**lder patients with **P**neumon**I**a (SNOOPI)

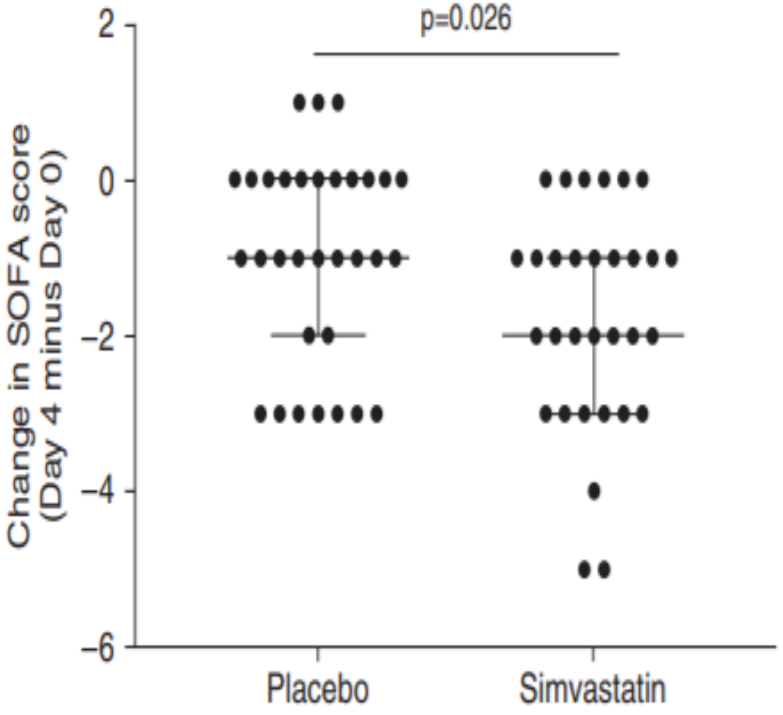
- Patients with CAP
- Simvastatin 80mg daily or placebo for 7 days
- Primary endpoint – Neutrophil functions
- Secondary endpoints
  - Tolerability, Safety,
  - Survival, time to readmission

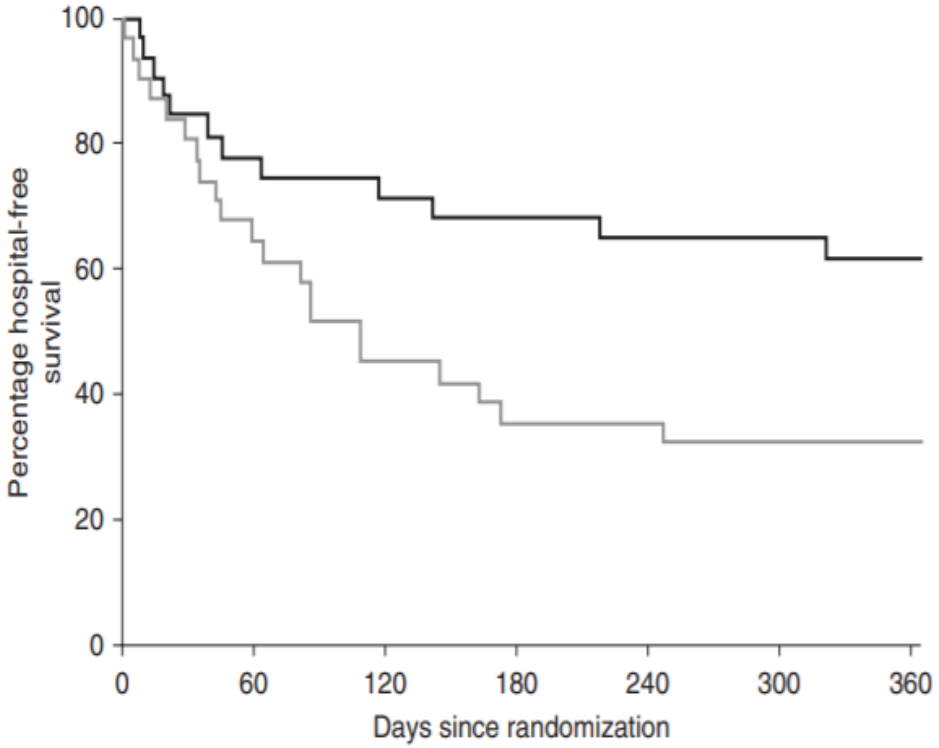
Statin improved neutrophil migration



Sapey E et al (2019) AJRCCM

Statin reduced SOFA score and 12 month mortality





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Art is me, Science is we!

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