Société Belge d'infectiologie et de microbiologie clinique
Belgische verenigging voor infectiologieen klinische microbiologie

Symposium:
Micro-organisms bridging ages!
Mutual benefits of vaccination
Musée de la Médecine, Brussels, 4th April 2019

Immunosenescence

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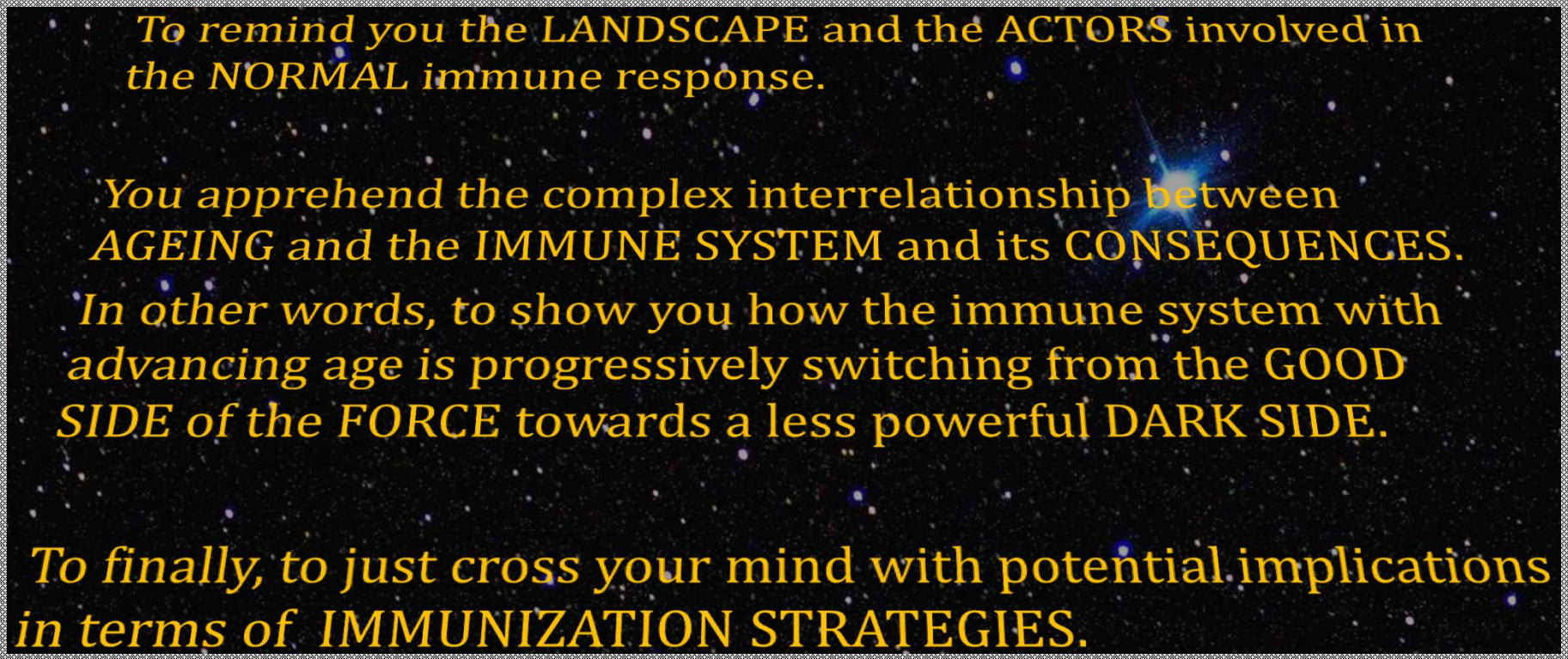
I have no conflict of interest to declare for this symposium

Pierre Olivier Lang

MY OBJECTIVES FOR TODAY



THE IMMUNE SYSTEM

PREAMBLE

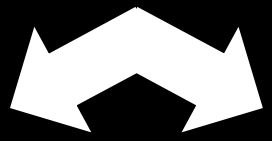
« ... *The art of war* ... »

Aspinall R & Lang PO. Expert Rev Vaccines. 2014;13:885-94

Our immune system is ...

A COMPLEX BIOLOGICAL SYSTEM

- Composed by coordinated elements



OF DEFENSE **OF RECONNAISSANCE**

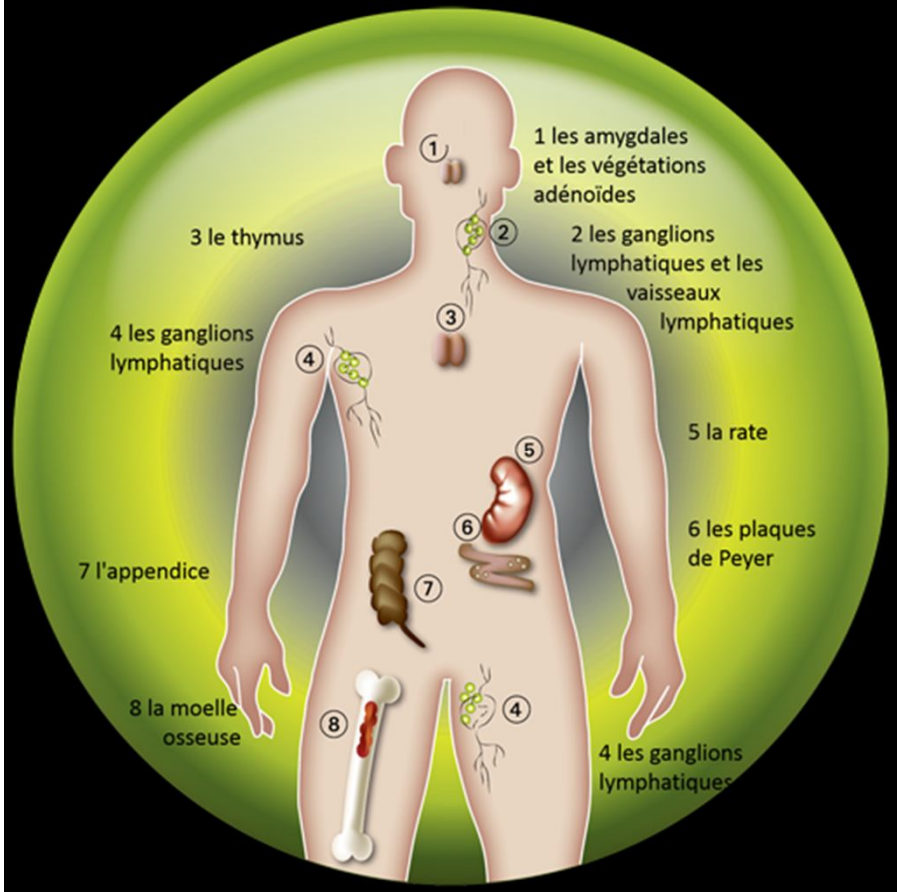
- For which the main goal is to differentiate « **SELF** » from « **NON-SELF** ».

- And, what is recognized as **« non-self »** is immediately and properly destroyed.

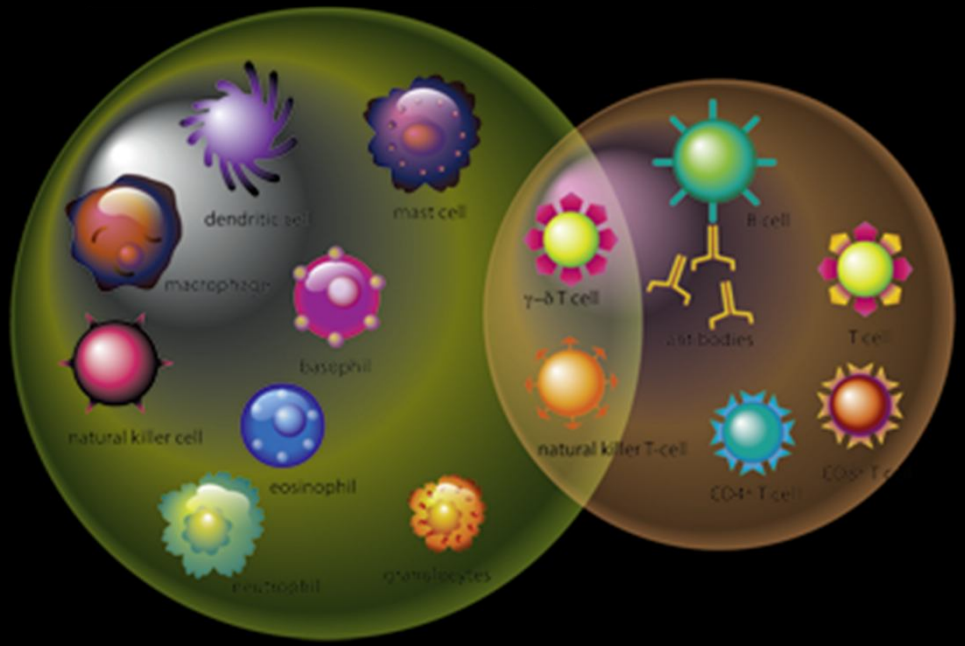
The immune system is composed

...

By ORGANS



And CELLS



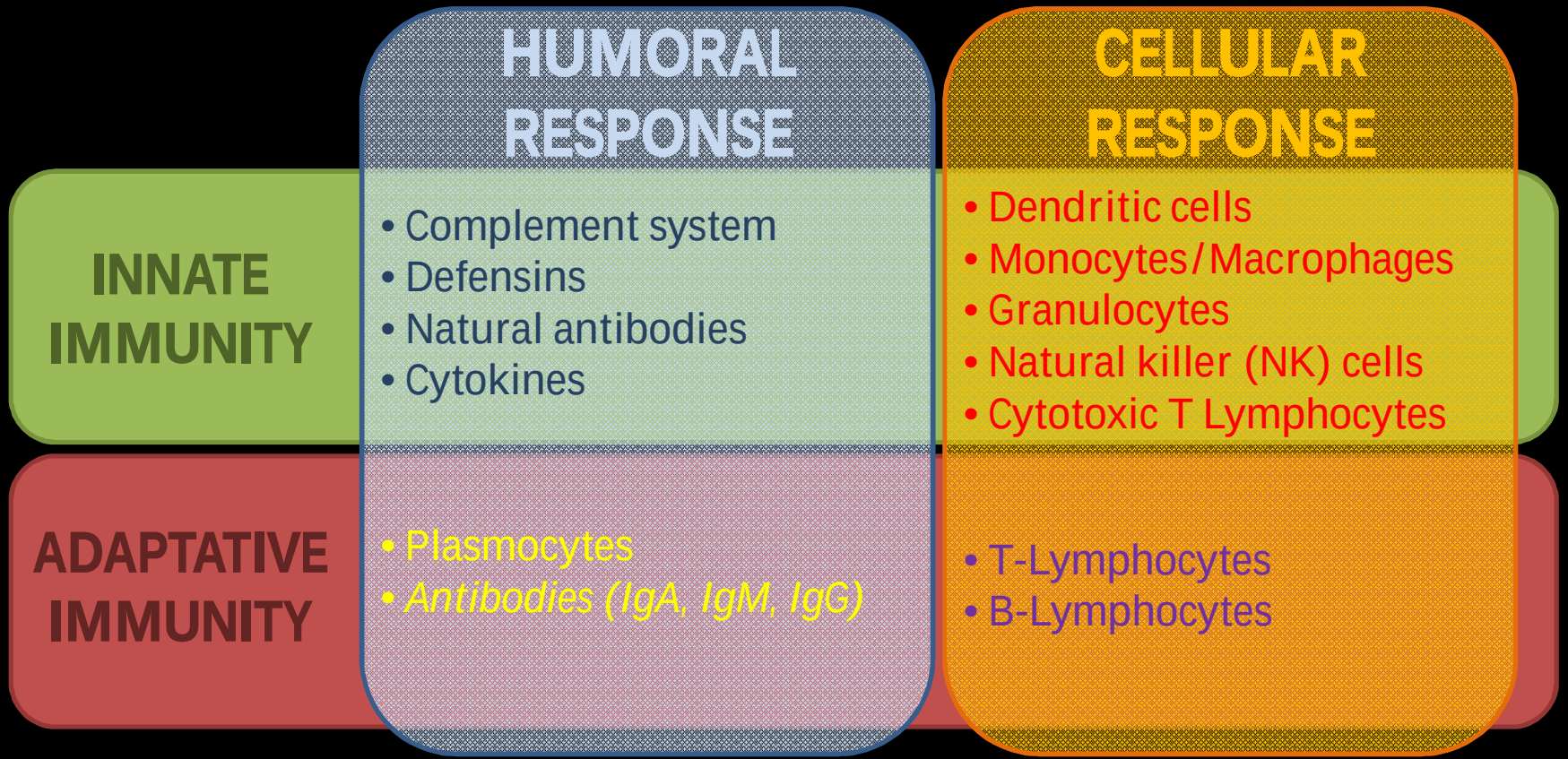
That communicate
and interact together *via*

SOLUBLE MEDIATORS

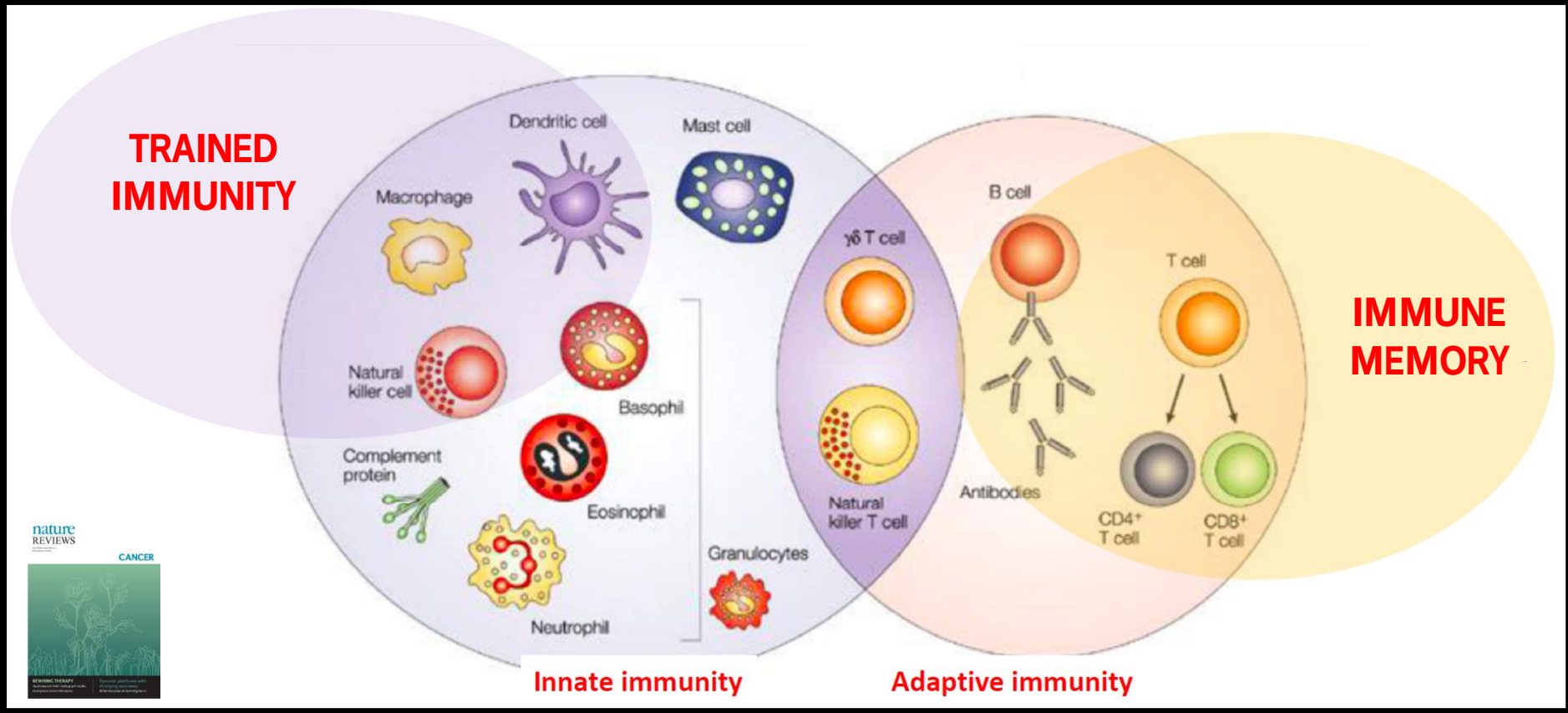
cytokines, interleukines, ...

The immune system is devided…

into 2 entities with 2 modalities of response

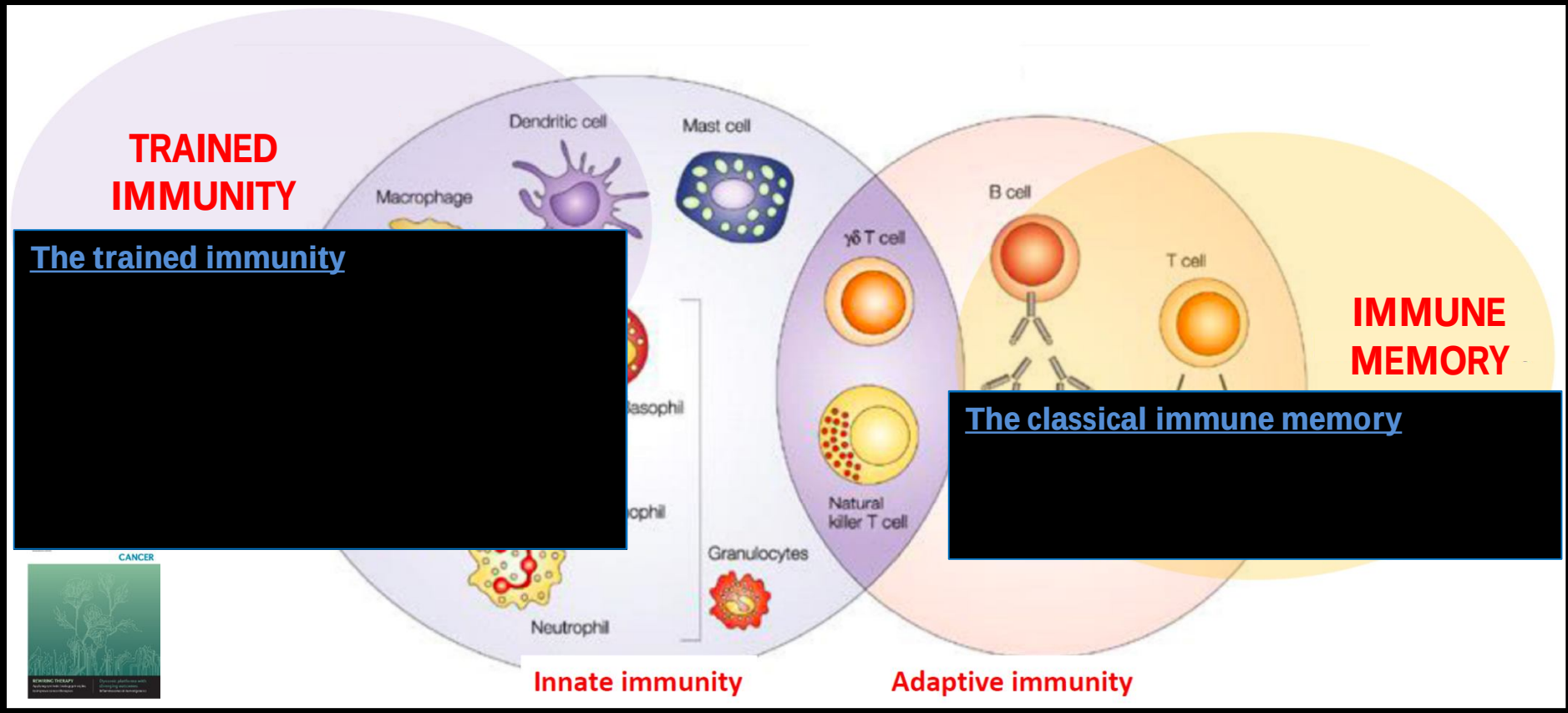


These 4 squadrons are interconnected



IN ORDER TO BETTER PROTECT US AGAINST ANY PATHOGENS AND FOREING ANTIGENS

These 4 squadrons are interconnected



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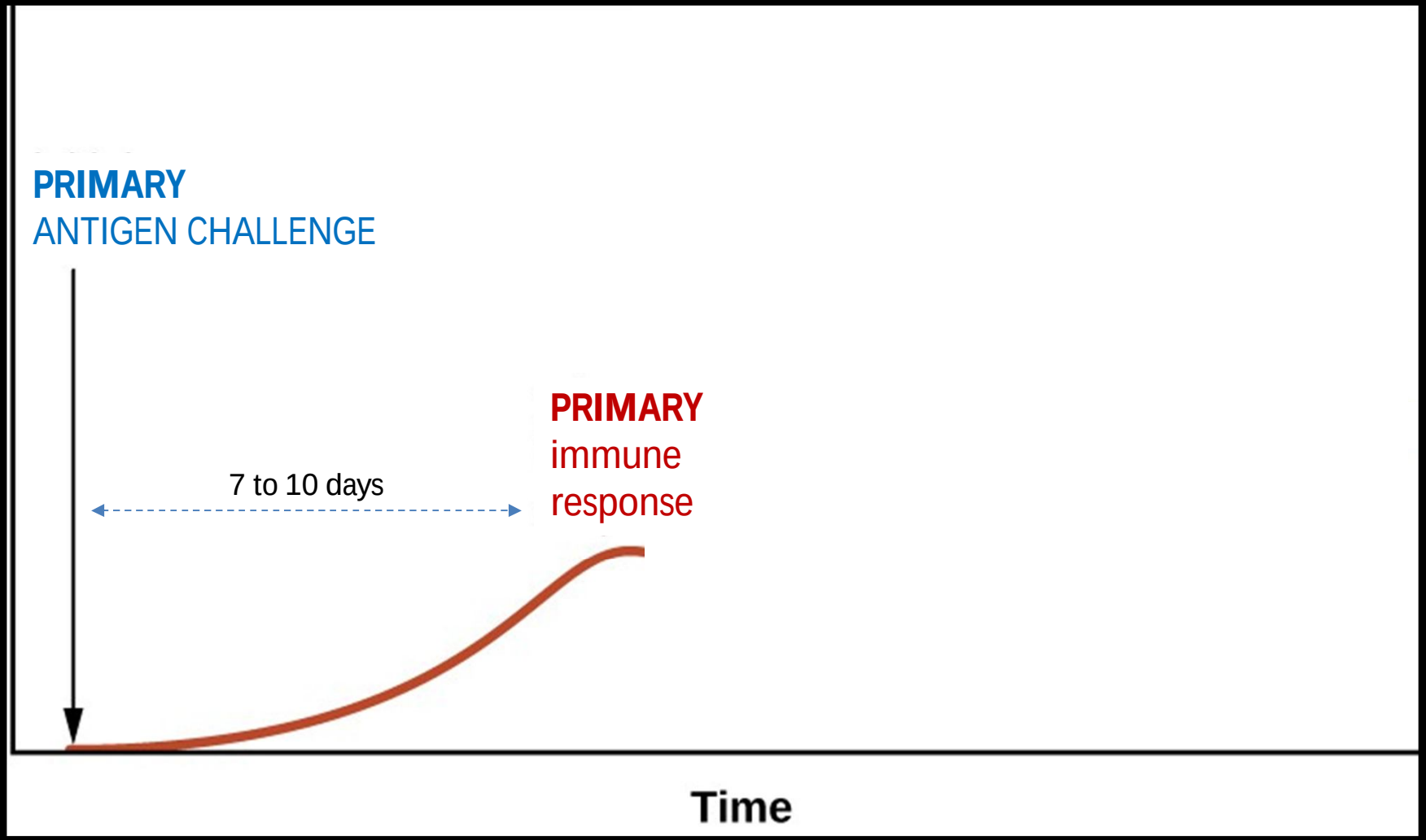

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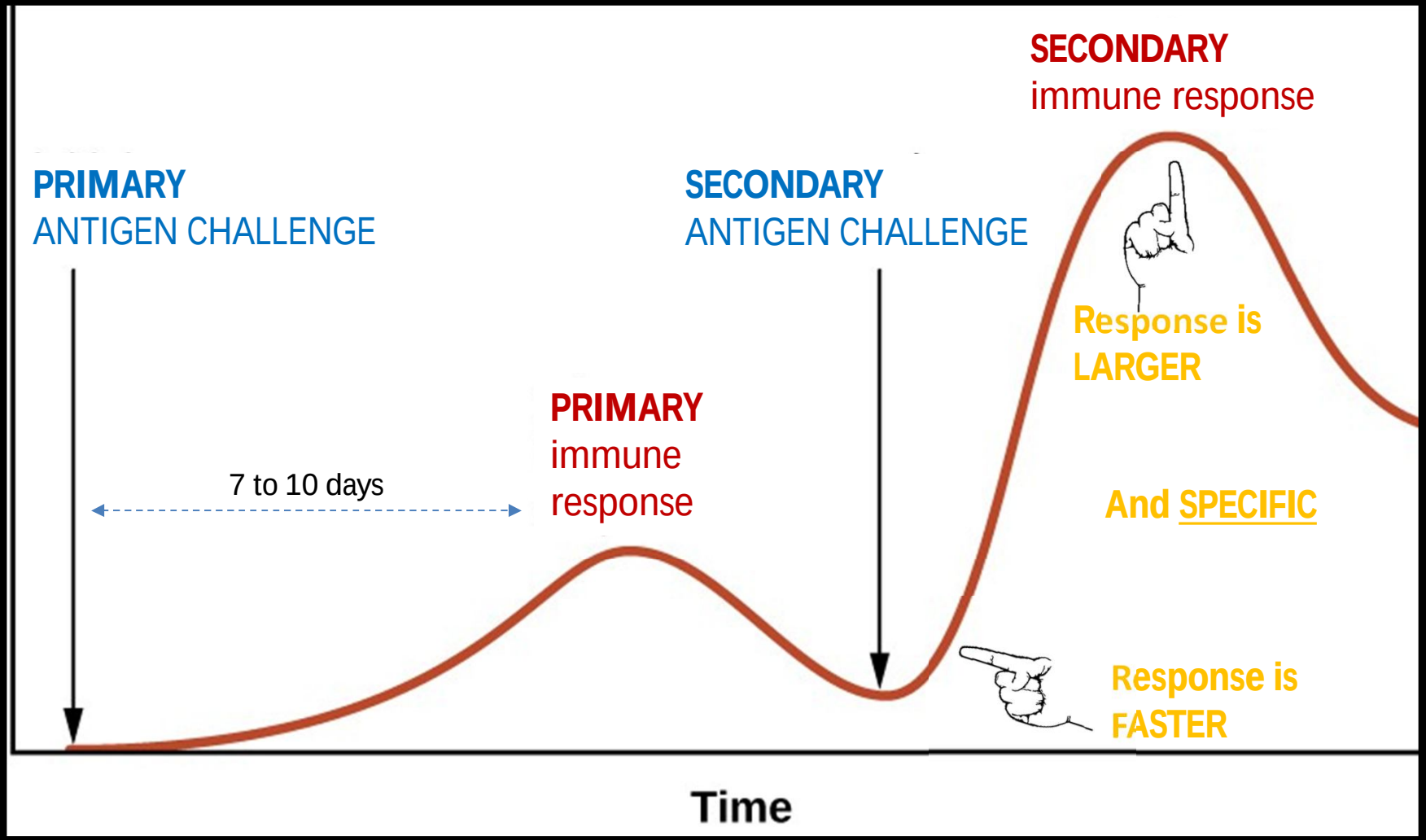


IN ORDER TO BETTER PROTECT US AGAINST ANY PATHOGENS AND FOREING ANTIGENS

IMMUNOSENESCENCE
EPISODE I

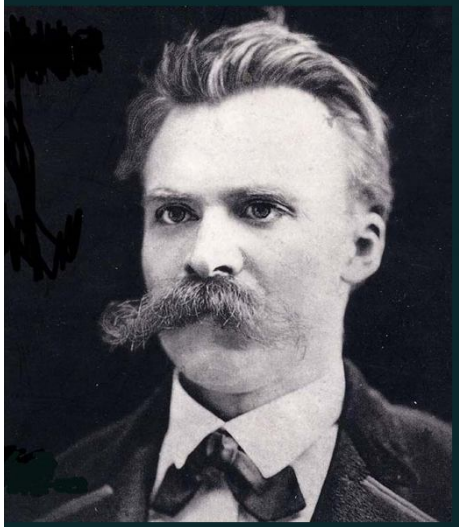
« … *The decoding of an at-risk phenotype…* »

Lang PO & Aspinall R. Immunosenescence and herd immunity. Expert Rev Vaccines. 2012;11:167-76

Nowhere on earth, you will find a sterile environment ...

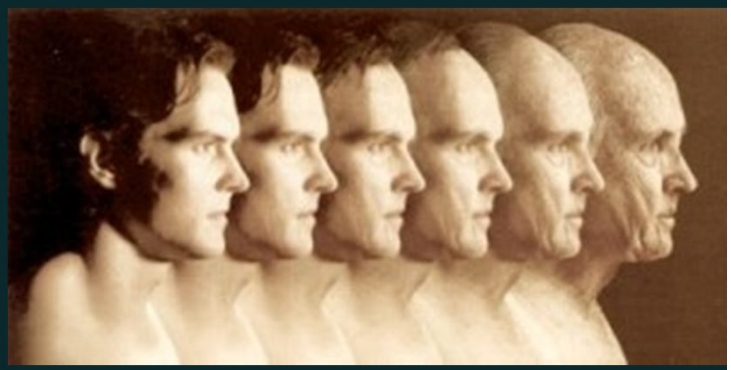
Thus, we can easily perceive that for surviving longer,

- ✓ People have had to deal with **many pathogens**
- ✓People have had to build a **powerful immunity** against diverse pathogens
- ✓People have had to acquire an **strong and large immune repertoire**



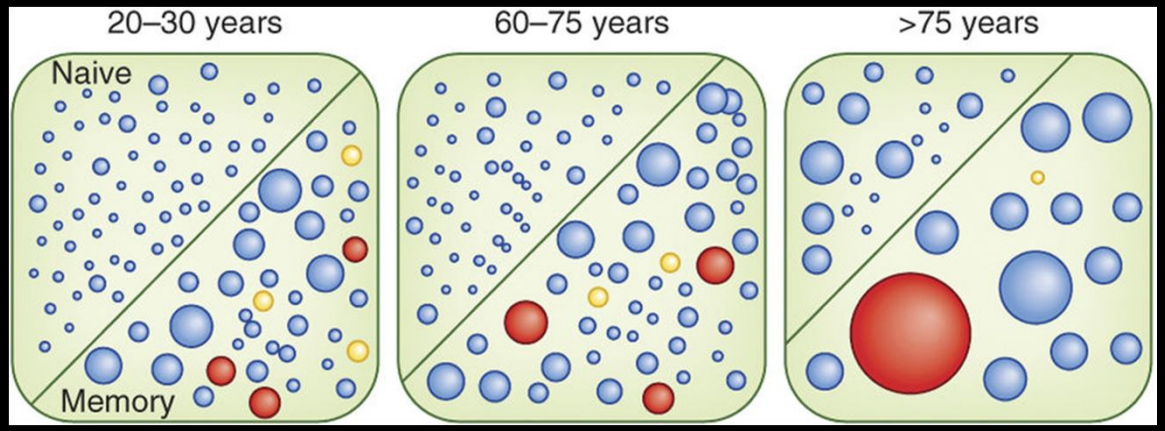
Whatever does not destroy me makes ME stronger

Friedrich Wilhelm Nietzsche



With advancing in age…

There is effectively an accumulation of memory T-cells



… **but these cells**…

Which originally defined the “Immune Risk Profile”

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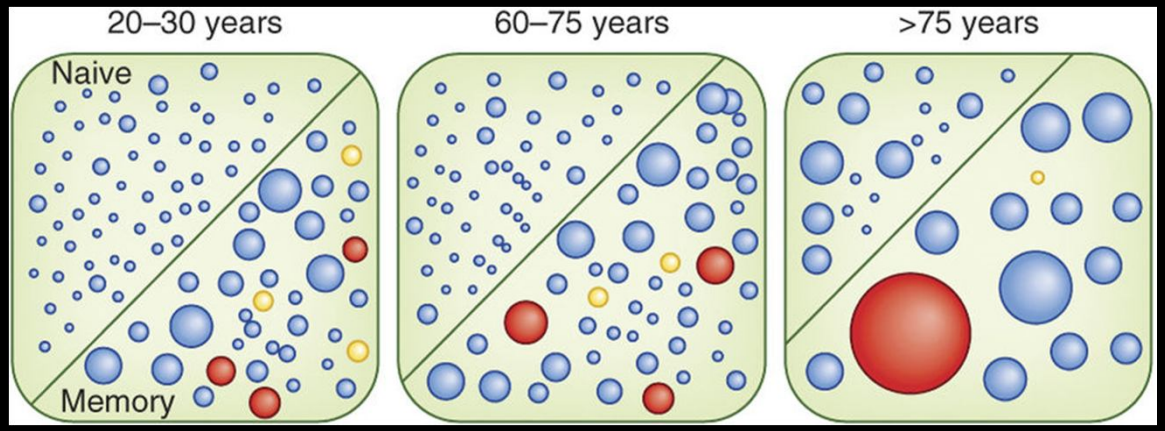


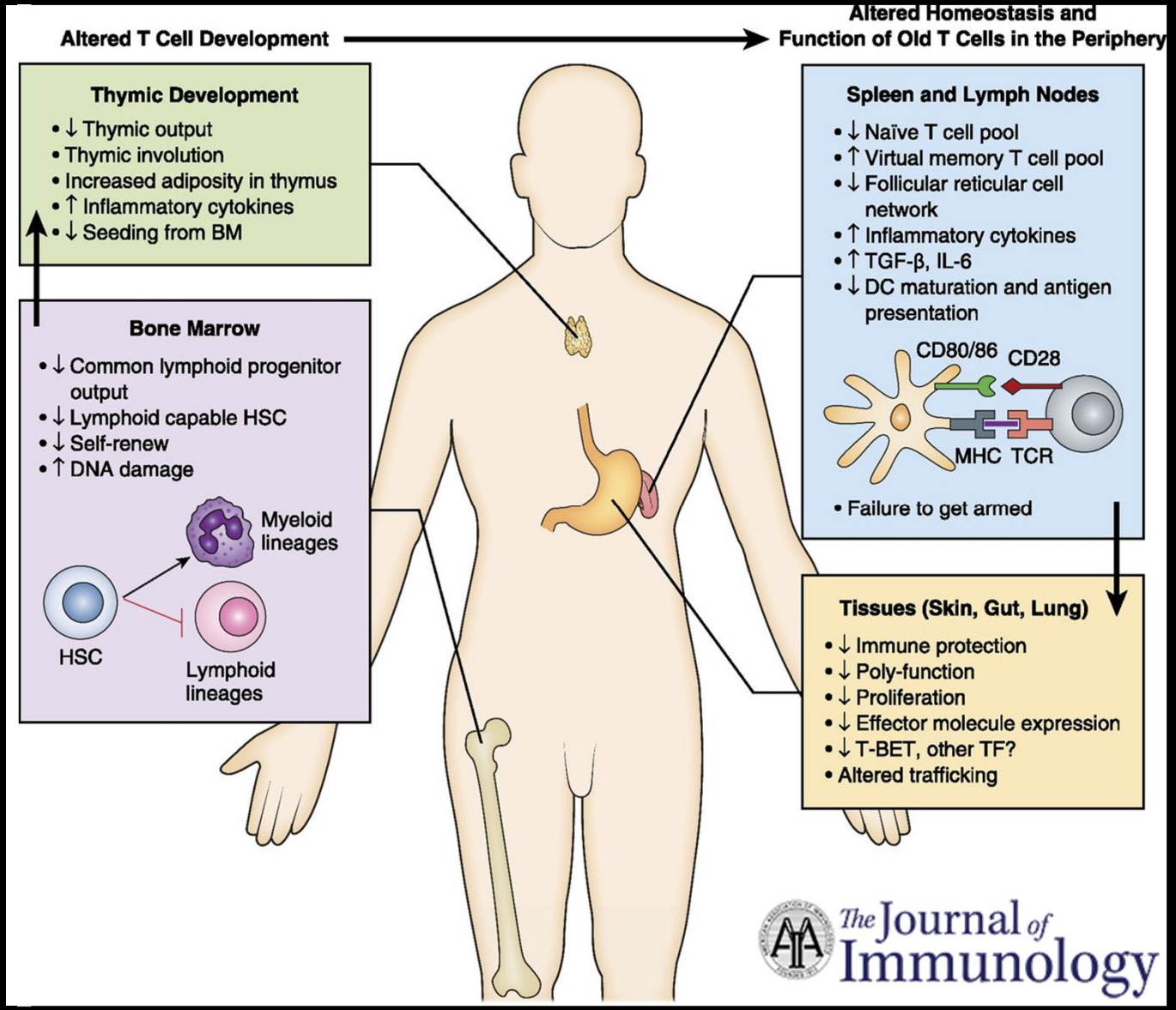
… **but these cells**…

Result from the clonal expansion of :

- T-cells with shortened memory repertoire (CMV specific)
- T-cells which become resistant to apoptosis
- Preferentially with cytotoxic phenotype (inverted CD4+/CD8+ ratio)
- Which produce pro-inflammatory cytokines (*Inflamm-aging)*

Which originally defined the “Immune Risk Profile”

More specifically at the cellular and molecular level…



Janko Nikolich-Žugich J Immunol 2014;193:2622-2629

It occurs multiple defects in the T-cell compartment

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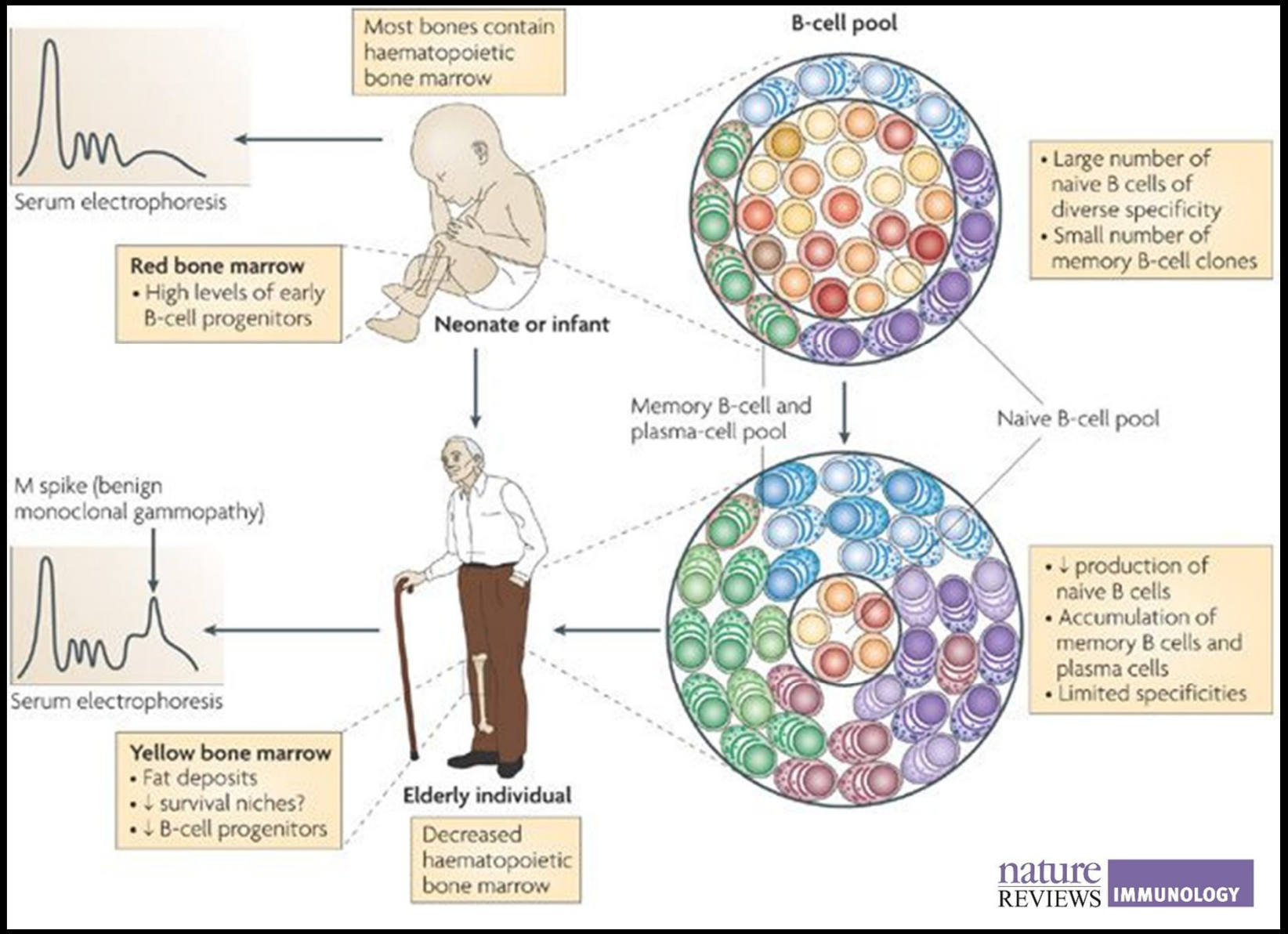

Siegrist AC, Aspinall R Nature Rev Immunol 2009;9:185-194

It occurs multiple defects in the B-cell compartment

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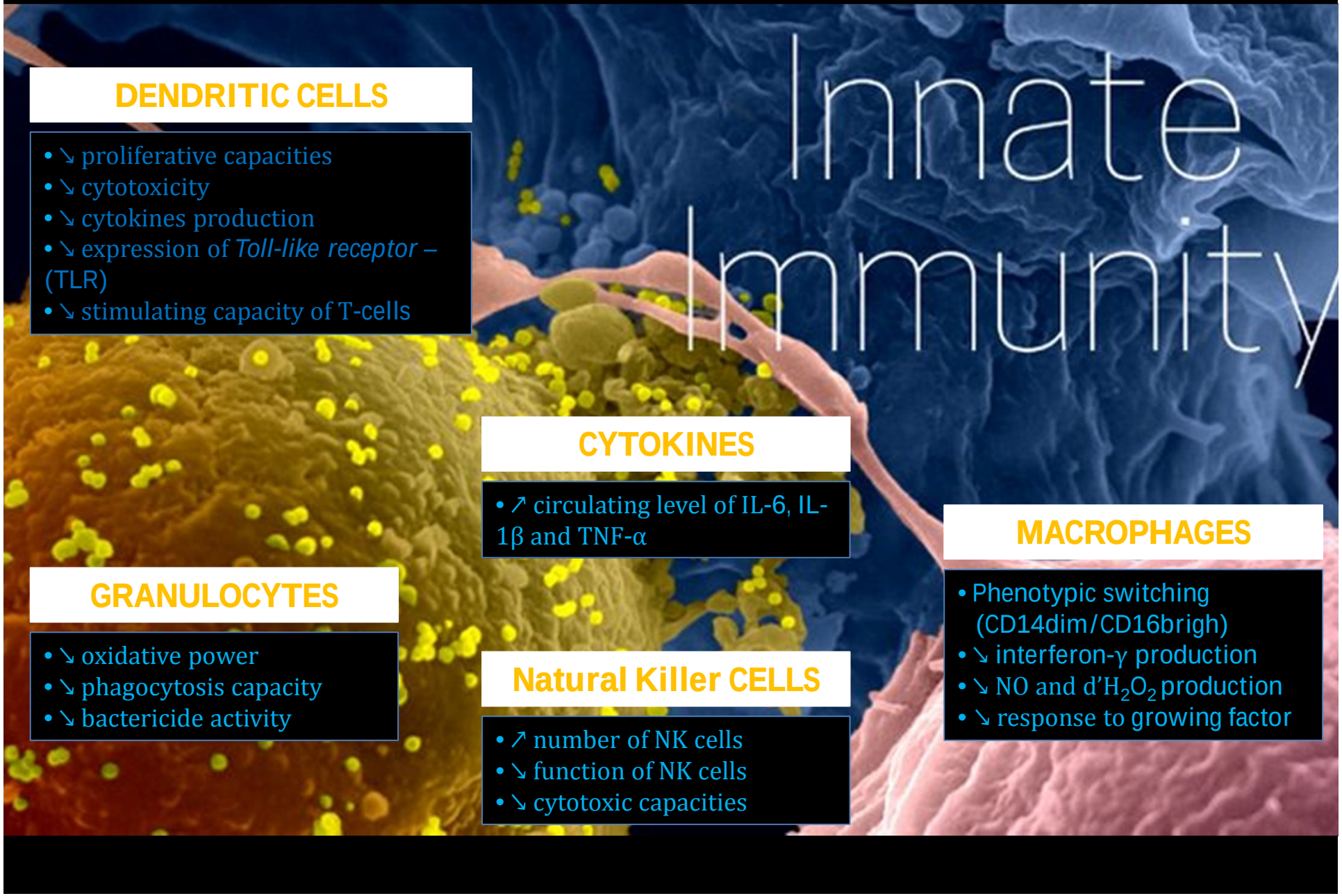

DENDRITIC CELLS

- ↘ proliferative capacities
- ↘ cytotoxicity
- ↘ cytokines production
- ↘ expression of *Toll-like receptor* – (TLR)
- ↘ stimulating capacity of T-cells

CYTOKINES

- ↗ circulating level of IL-6, IL-1β and TNF-α

GRANULOCYTES

- ↘ oxidative power
- ↘ phagocytosis capacity
- ↘ bactericide activity

Natural Killer CELLS

- ↗ number of NK cells
- ↘ function of NK cells
- ↘ cytotoxic capacities

MACROPHAGES

- Phenotypic switching (CD14dim/CD16brigh)
- ↘ interferon-γ production
- ↘ NO and d'H_2O_2 production
- ↘ response to growing factor

IMMUNOSENESCENCE
EPISODE II

« … *The possible consequence…* »

or

« … *The attack of the clones …* »

Lang PO & Aspinall R. Immunosenescence and herd immunity. Expert Rev Vaccines. 2012;11:167-76

Immunosenescence it is...

AT THE INDIVIDUAL LEVEL

- A chronic state of low-grade inflammation

(commonly nammed *Inflamm-aging*)

- ↗ intensity of inflammatory reaction

Lang PO et al. Immunological pathogenesis of main age-related disease and frailty: role of immunosenescence. Eur Geriatr Med 2010;1:112-21

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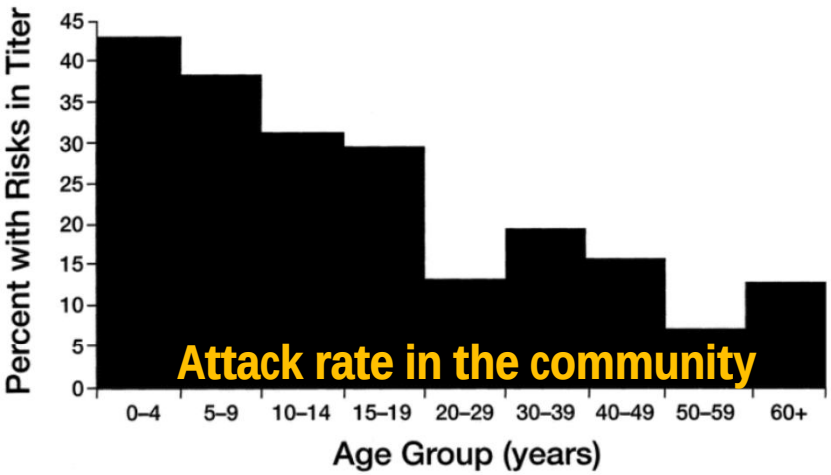
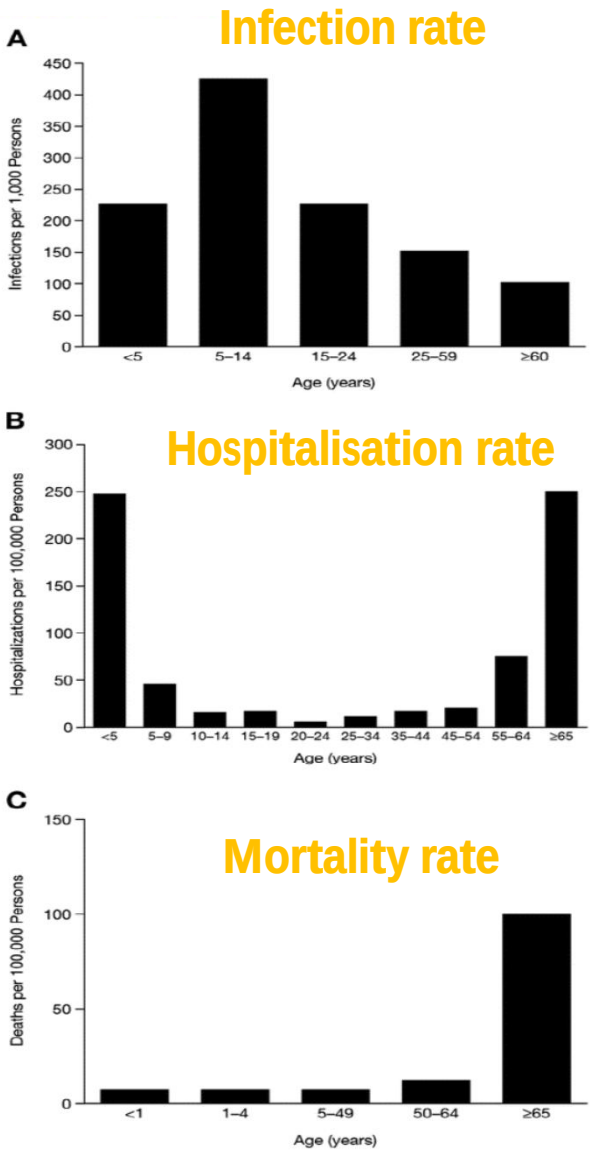
INFLUENZA

Into statistics…

Community influenza attack rates and complication by age



Monto, et al. *Epidemiol Infect*. 1993;110:145-60.



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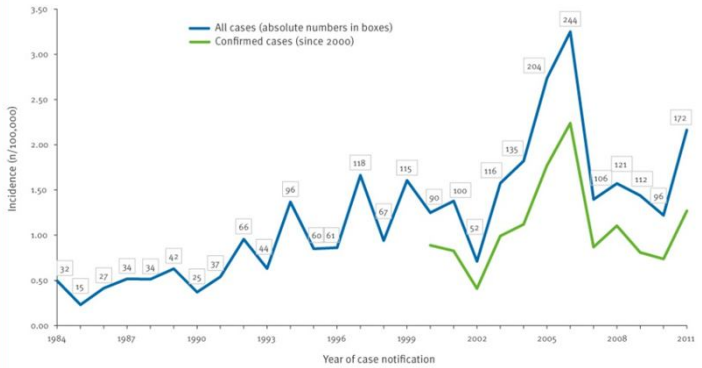
TICK-BORN ENCEPHALITIS

Small bites – Big problems

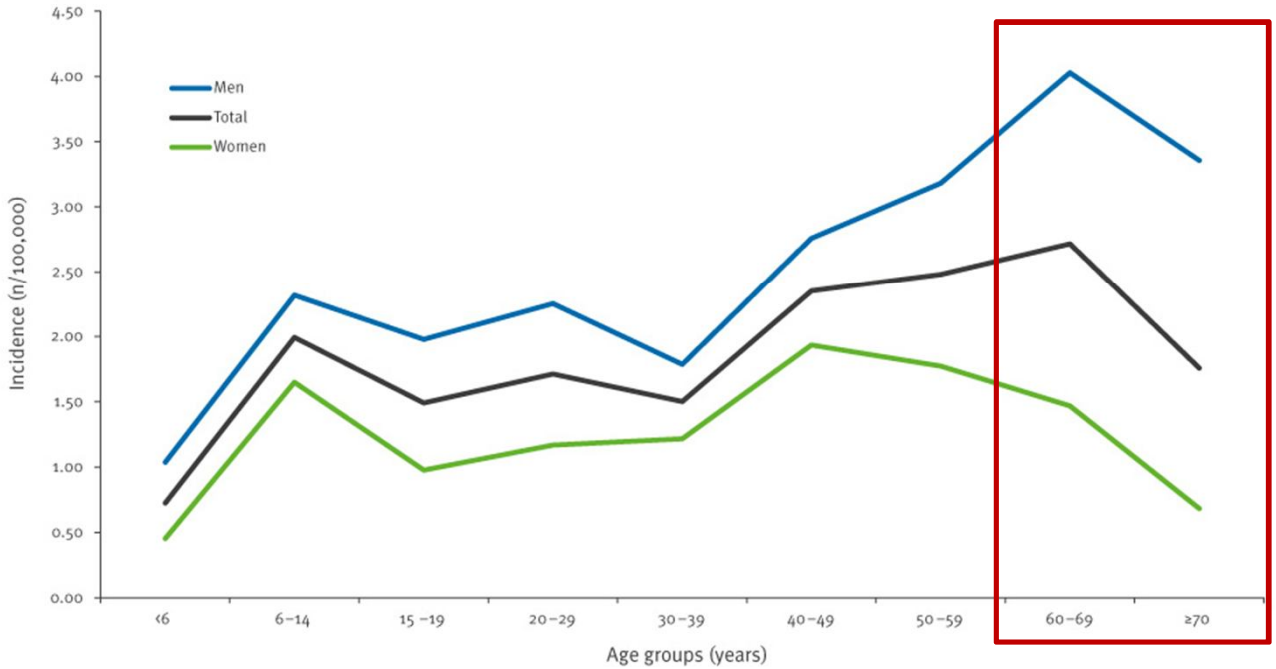
The love story of *Ixodes ricinus* and one of the encephalitogenic flaviviruses

FIGURE 1
Annual incidence of tick-norne encephalitis in Switzerland, 1984 to 2011 (n=2,421)



Epidemiology of Tick-borne encephalitis in Switzerland, 2005 to 2011.
M. Schuler, et al, Eurosurveillance, 2014;19

FIGURE 2
Incidence of tick-born encephalitis by age and sex, Switzerland, 2005 to 2011 (n=1,053)



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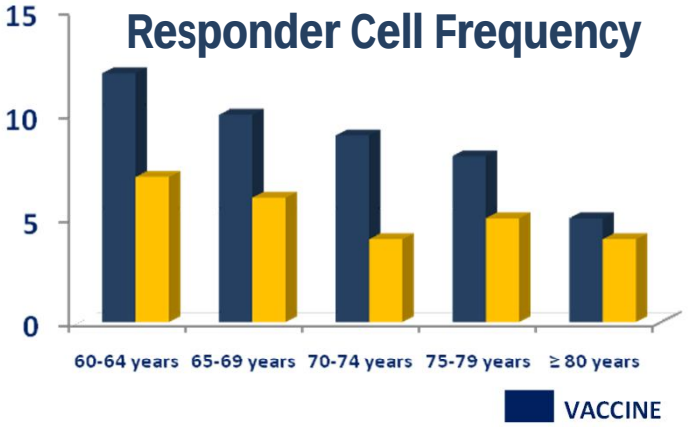
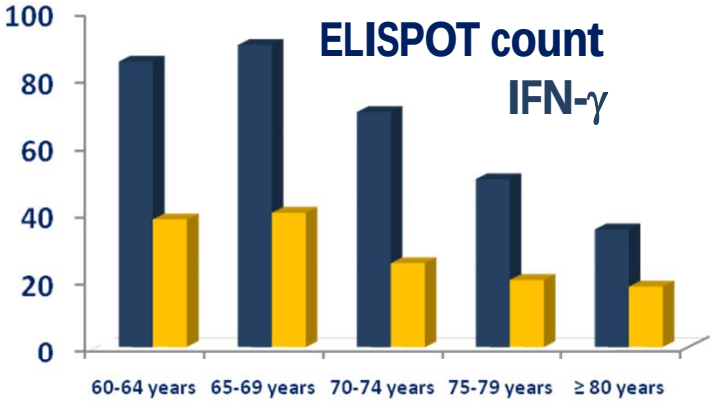
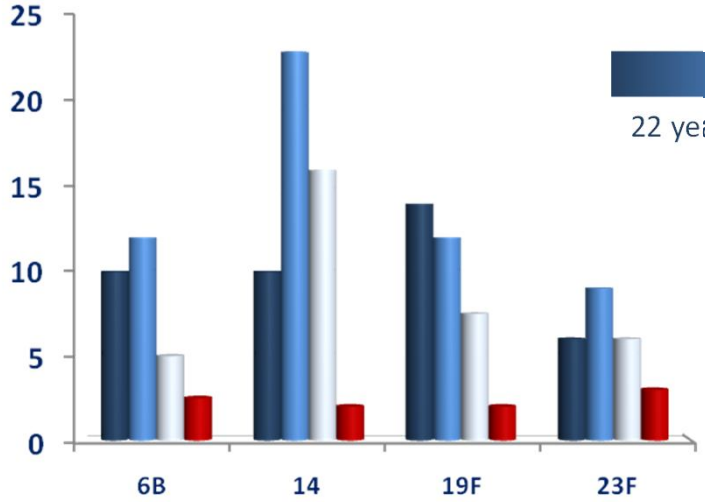
Herpes zoster vaccine





Levin MJ *et al*, J Infect Dis 2009

Pneumococcal vaccine



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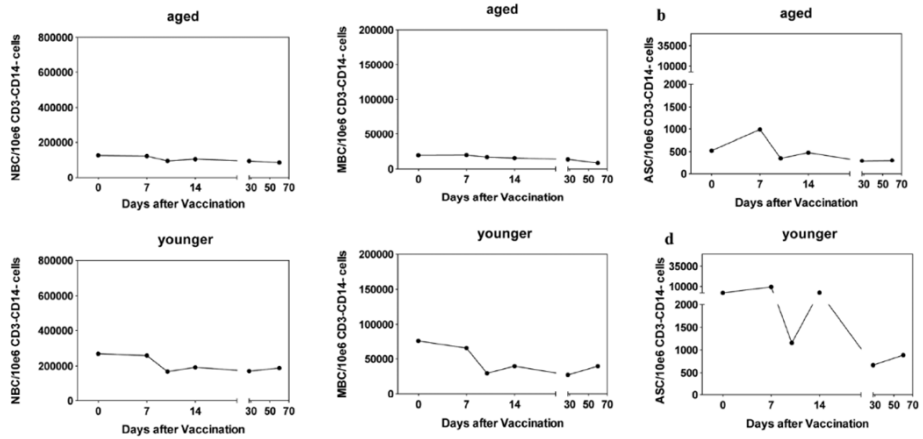
- **This reduction is also observed with the new PCV-13**

Vila-Corcoles A *et al*, Drugs Aging, 2013

Influenza vaccine



N = 74 individuals ranging in age from 65 to 87 year

Kurupati RK *et al*, Aging 2013

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- ↗ intensity of inflammatory reaction

- ↗ susceptibility to common pathogens
- ↗ susceptibility to emerging pathogens
- ↘ vaccine immunogenicity and efficacy
- ↗ incidence of auto-immune disorders
- ↗ incidence of cancers
- ↗ incidence of main age-related diseases

Lang PO et al. Immunological pathogenesis of main age-related disease and frailty: role of immunosenescence. Eur Geriatr Med 2010;1:112-21

IMMUNOSENESCENCE

EPISODE III

« A complex reality that is not fully understood»

Aspinall R & Lang PO. Vaccination choices for older people: looking beyond age specific approaches. Expert Rev Vaccines. 2018;17:23-30

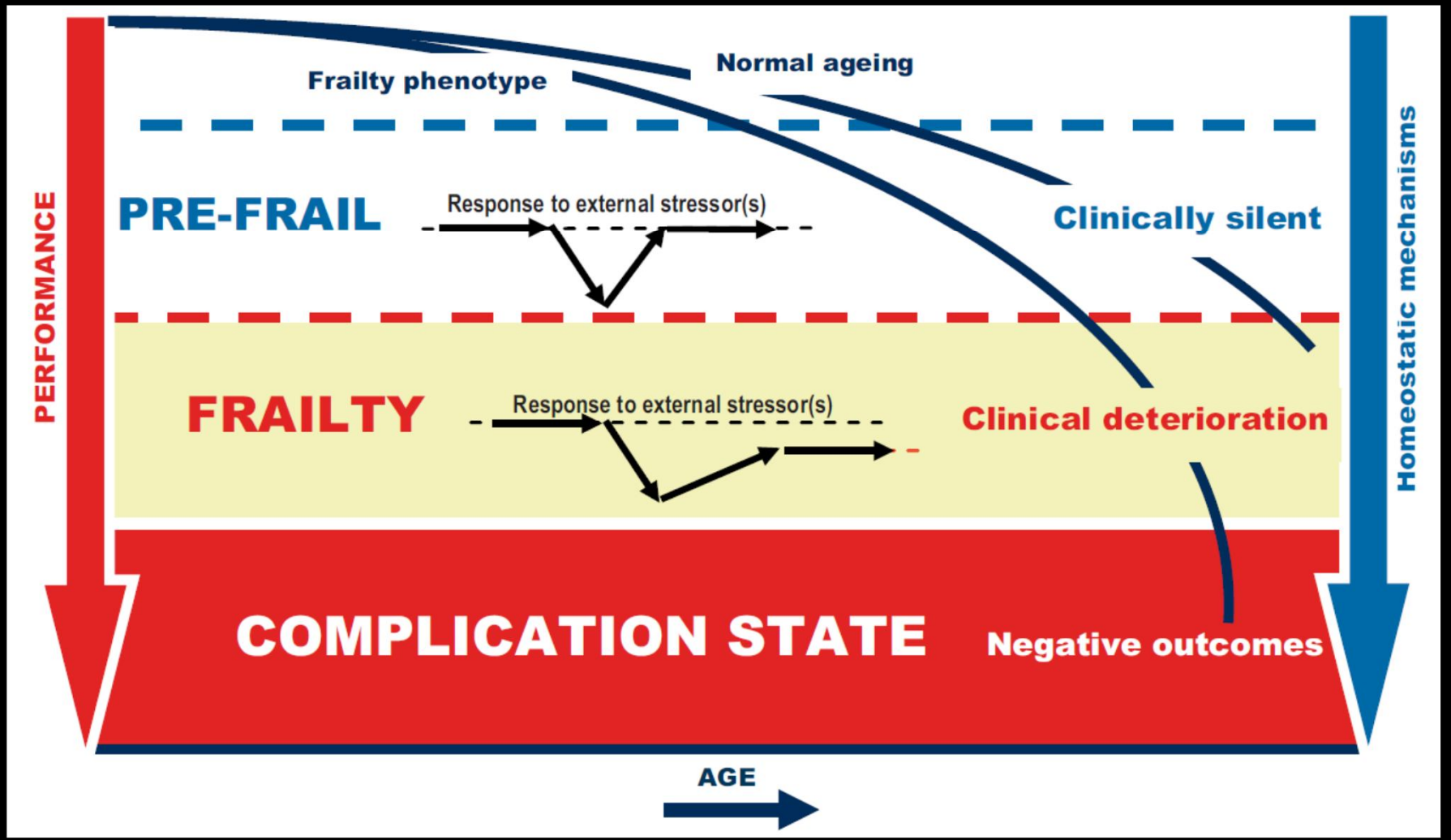
If Ageing is Universal, Intrinsec, Progressive and somehow Deleterious

Ageing is

Environment (comorbidites) → **HETEROGENEOUS** ← Genetic Epigenetic

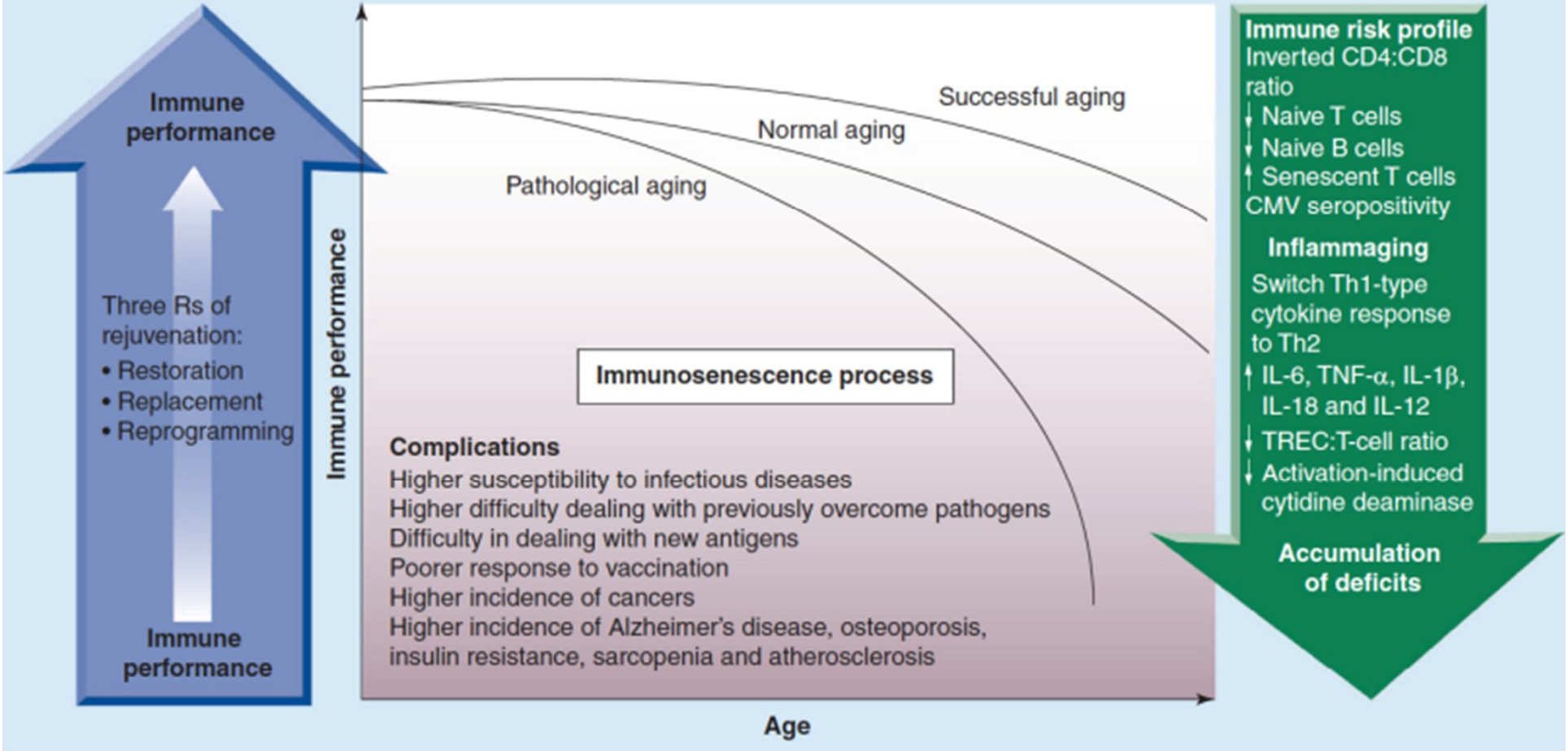
80% OF >80 Y POP. AT HOME WITHOUT ANY DISABILITY

AGEING is heterogeneous...



Performance and homeostatic reserve are gradually getting WEAKER with advancing age

AGEING is heterogeneous…

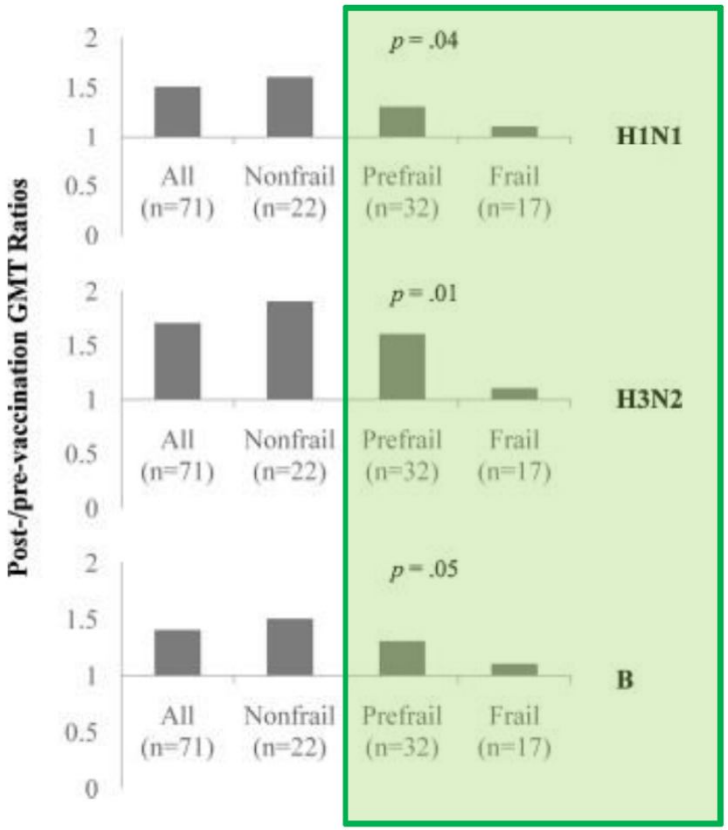


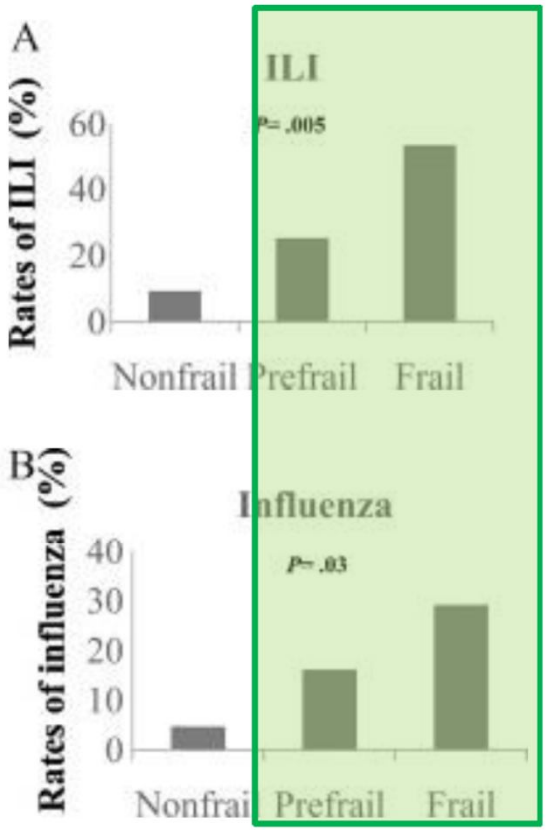
The immune system is also gradually getting WEAKER

INFLUENZA

From a clinical point of view…

IMMUNOSENESCENCE & VACCINE RESPONSE





Vaccine 2011; 29: 5015-5021

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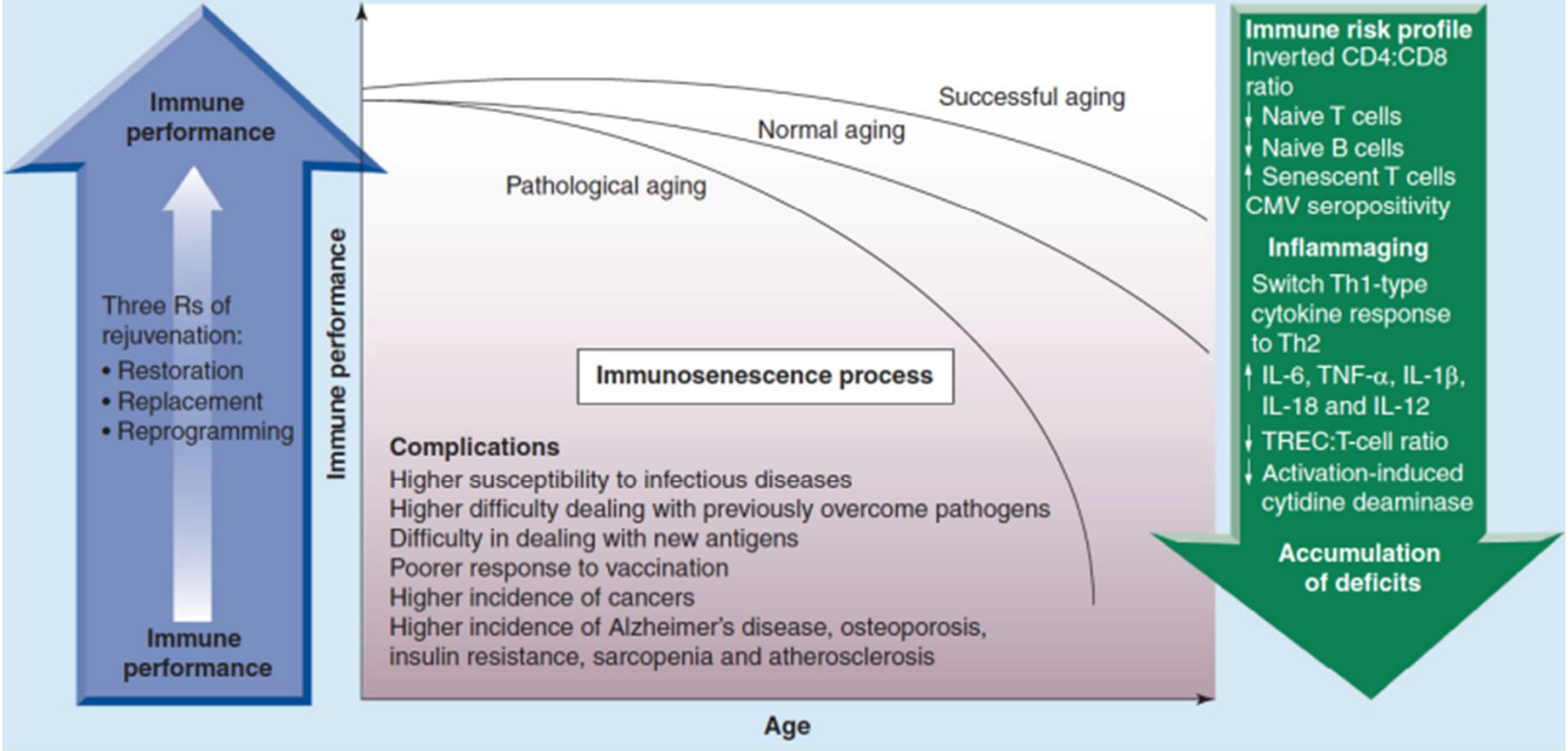


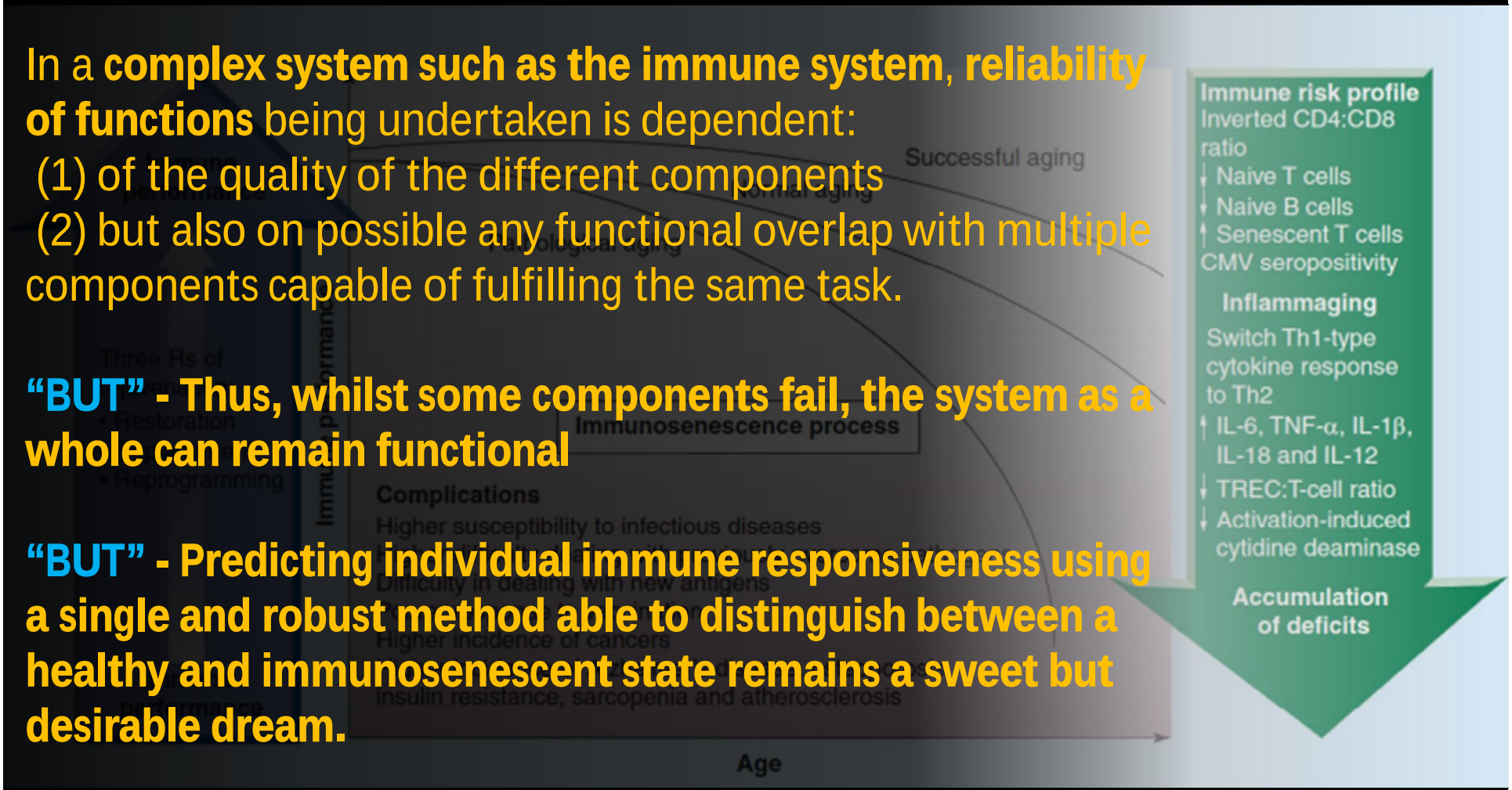
BUT the immune system is also gradually getting WEAKER

BUT… because there always is a “but”

In a **complex system such as the immune system**, **reliability of functions** being undertaken is dependent:
(1) of the quality of the different components
(2) but also on possible any functional overlap with multiple components capable of fulfilling the same task.

“BUT” - Thus, whilst some components fail, the system as a whole can remain functional

“BUT” - Predicting individual immune responsiveness using a single and robust method able to distinguish between a healthy and immunosenescent state remains a sweet but desirable dream.

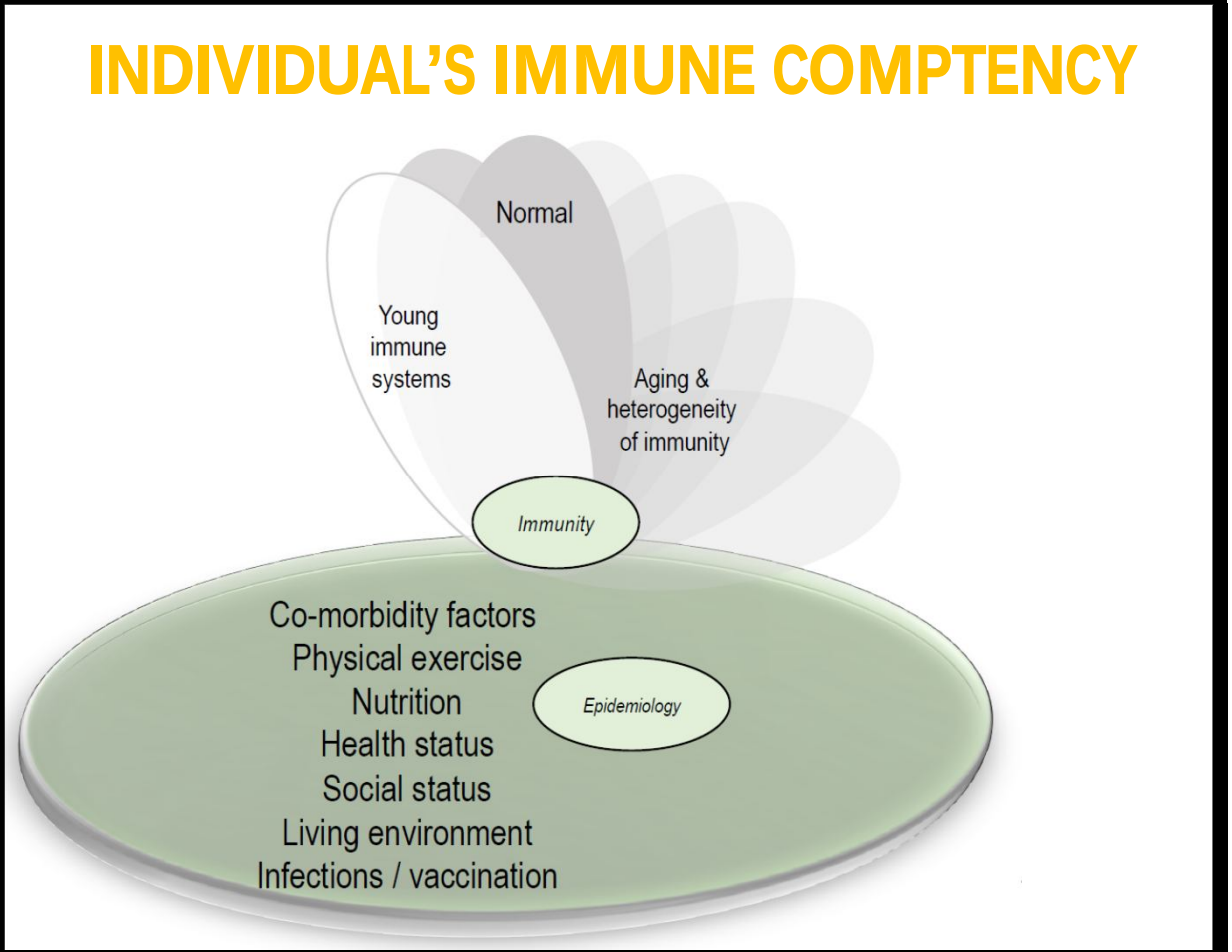


AND with immunosenescence, there are many “BUT”

Age-associated immune remodelling

Although an individual's age is a major contributor, there is no single cause of immunosenescence.

Rather, it is the consequence of a complication of events including ...



...is a complex reality that is far to be fully understood yet

BUT... because there always is a “but”

Healthy
and
normally effective
immune system

Non-functional
immune system

WE STILL HAVE TO MAP THIS ROAD

TO IDENTIFY SPECIFIC TARGETS AND DIFINE THE OPTIMAL TIMING FOR NOVEL THERAPEUTIC APPROACHES

The immune system is gradually getting WEAKER

IMMUNOSENESCENCE: EPISODE IV

THE PARADOX

« ... It is commonly believe that immunosenescence reduces vaccine responsiveness, but we advocate for immunization programmes in this population ... »

Lang PO & Aspinall R. Vaccination in the elderly: What can be recommended? Drugs Aging. 2014;31:581-99

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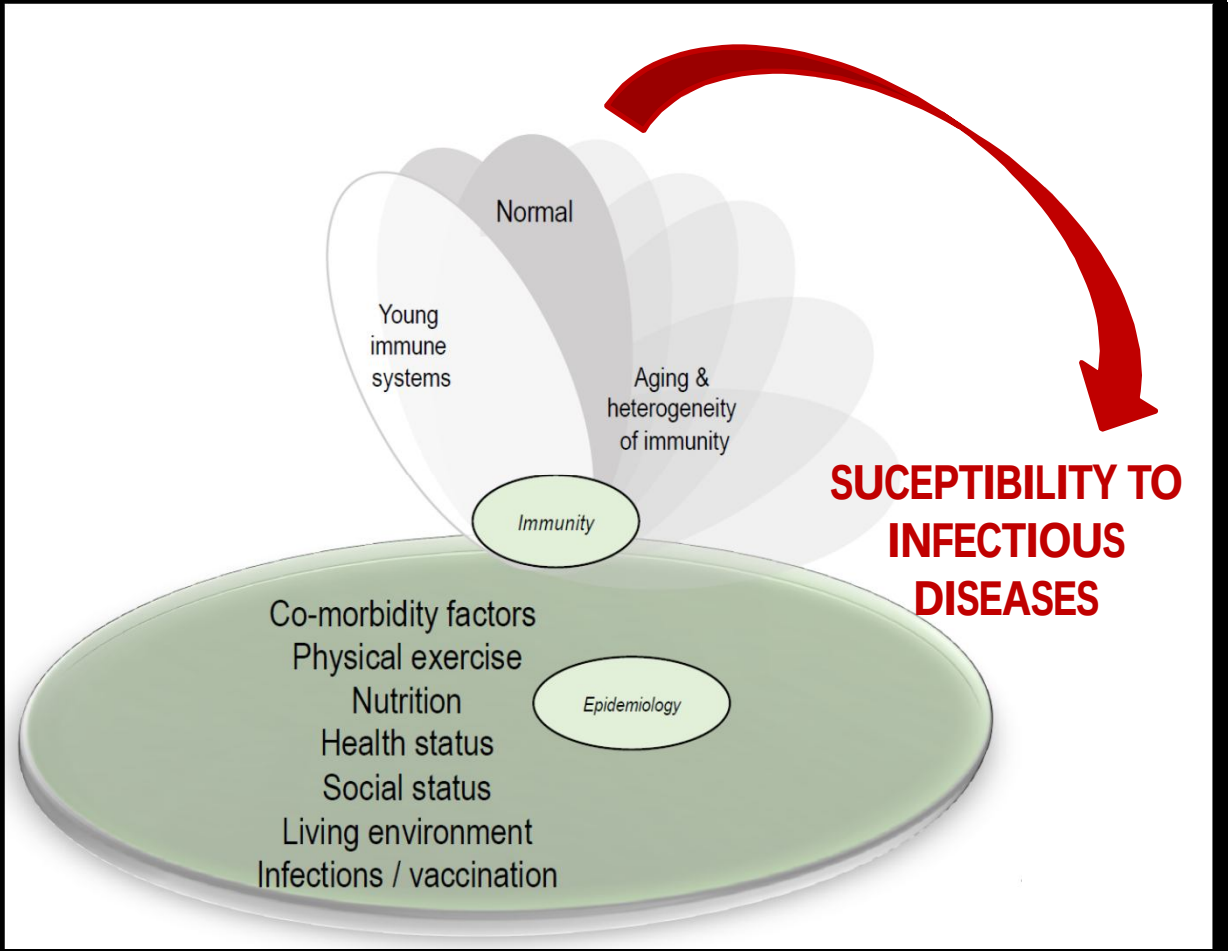

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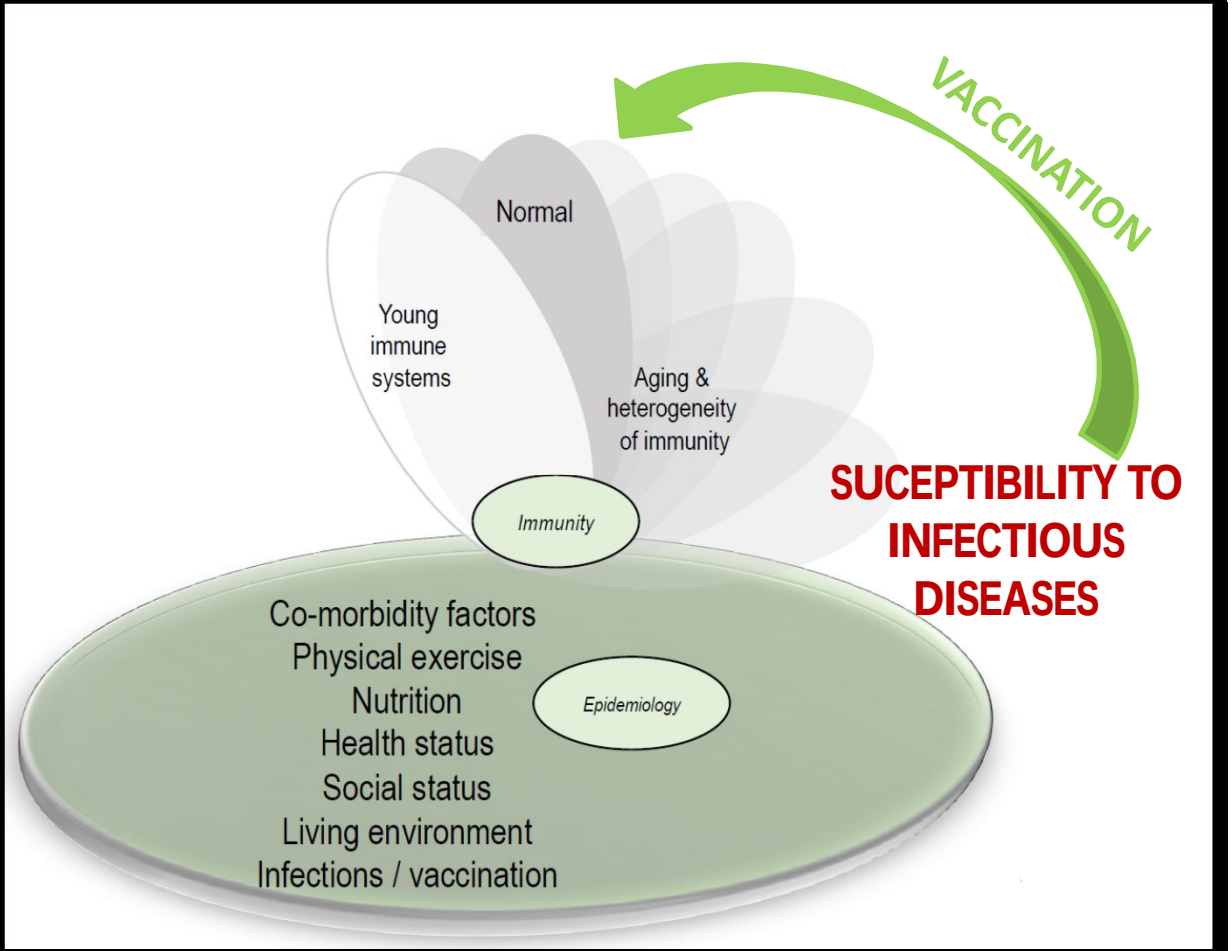

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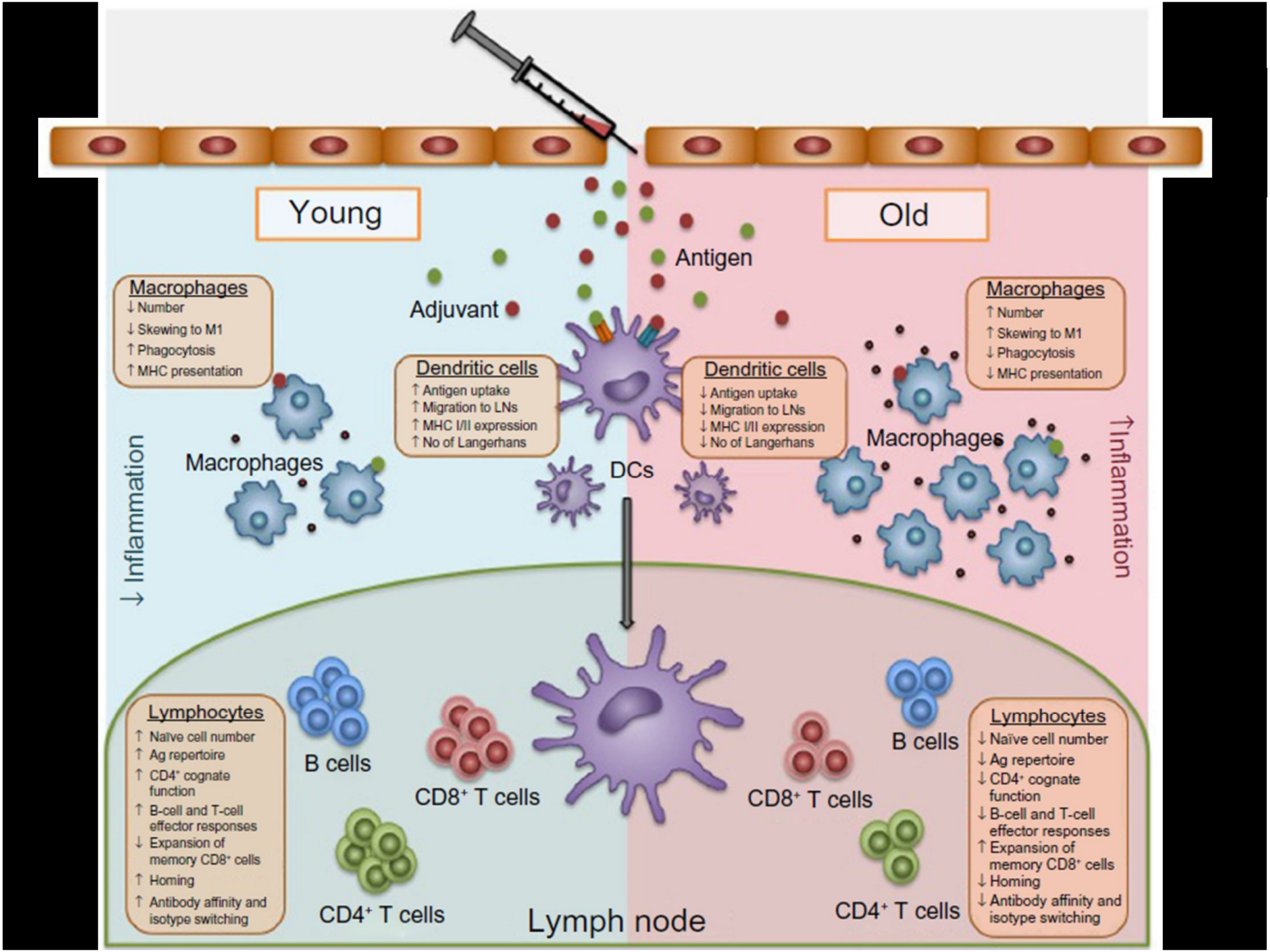
Young
Old
Antigen
Adjuvant
Macrophages
↓ Number
↓ Skewing to M1
↑ Phagocytosis
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Dendritic cells
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Lymphocytes
↑ Naïve cell number
↑ Ag repertoire
↑ CD4+ cognate function
↑ B-cell and T-cell effector responses
↓ Expansion of memory CD8+ cells
↑ Homing
↑ Antibody affinity and isotype switching
B cells
CD8+ T cells
CD4+ T cells
Lymph node
B cells
CD8+ T cells
CD4+ T cells
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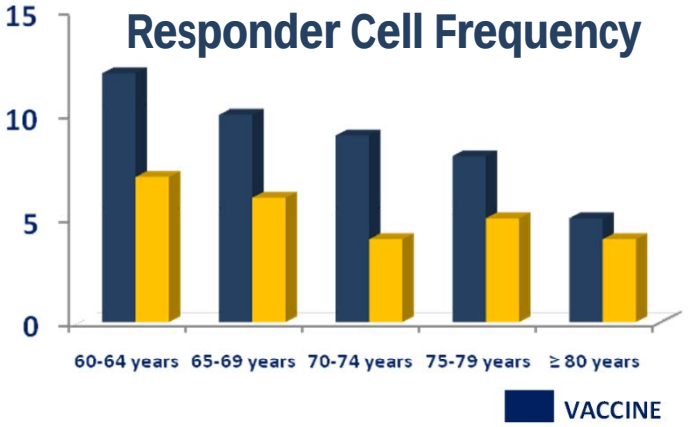
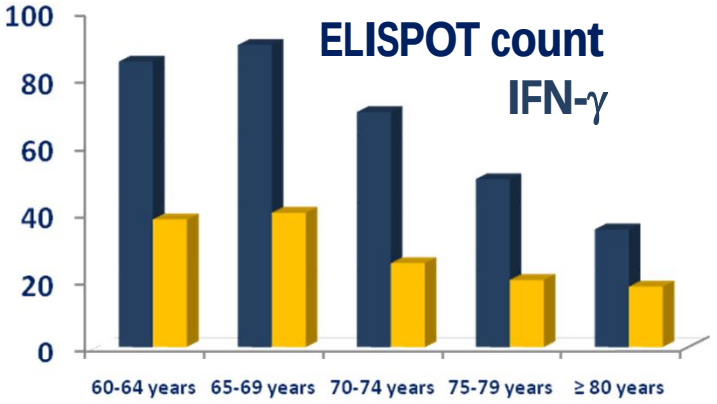
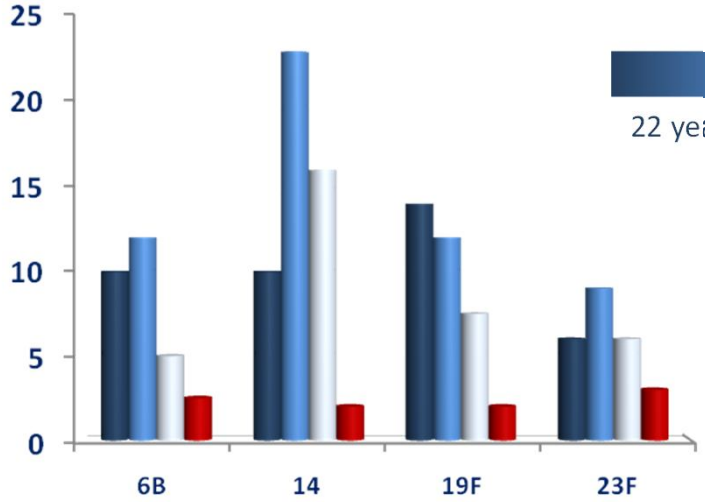
Herpes zoster vaccine





Levin MJ *et al*, J Infect Dis 2009

PPSV23 vaccine



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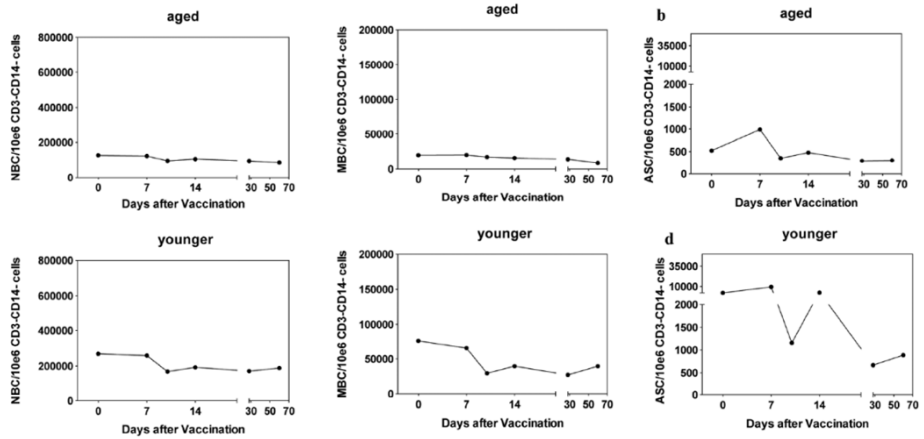
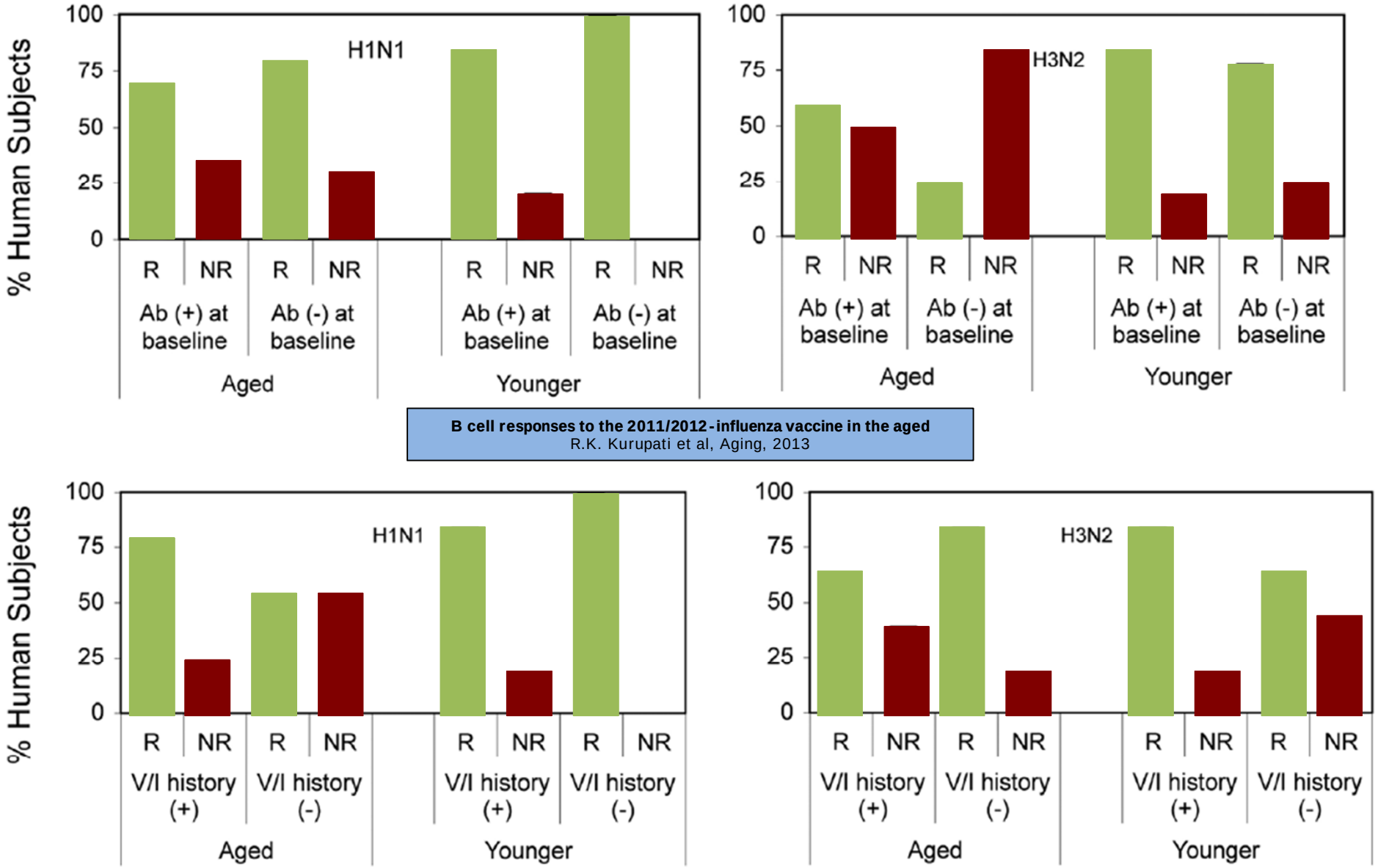


N = 74 individuals ranging in age from 65 to 87 year

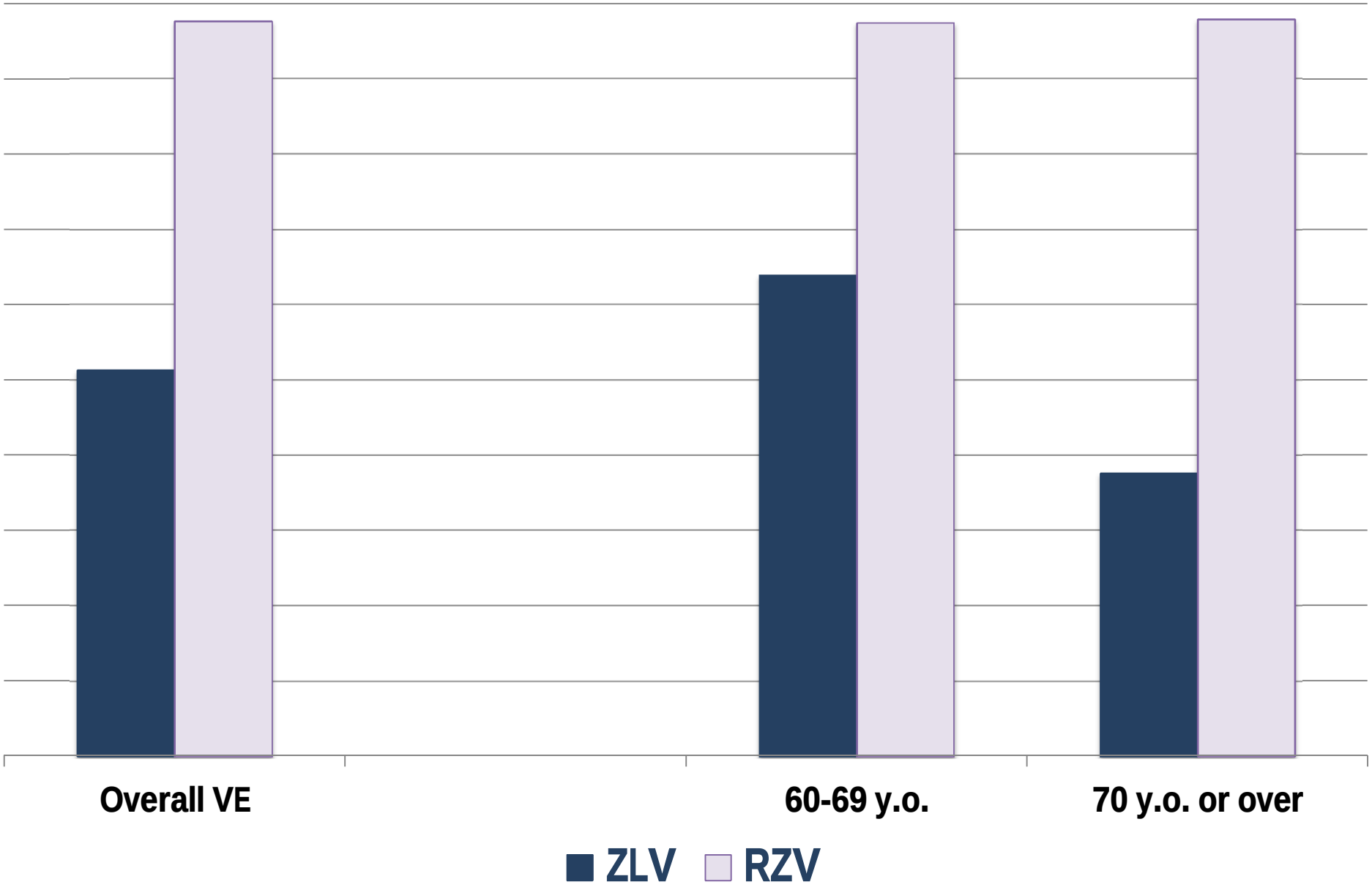
Kurupati RK *et al*, Aging 2013

BUT, the story can change because of …



B cell responses to the 2011/2012-influenza vaccine in the aged
R.K. Kurupati et al, Aging, 2013

BUT, the story can change because of …

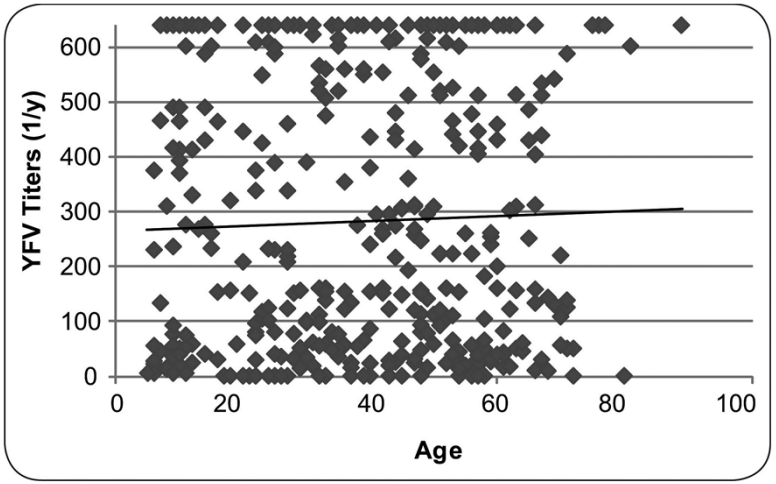


Yellow fever

FSME

Pertussis

TdaP



Effect of AGE on AB titer

OR = 1.054 ; 95% CI 1.009-1.099

p = 0.016

N = 383 adults in Brazil

Wolff Machado V *et al*, Rev Soc Bras Med Trop 2013

- **Studies have revealed a significantly lower antibody response in people more than 50 years of age compared to that of younger individuals (< 30 years).**
- **Pre- and post-booster antibody concentrations as well as neutralizing antibody titers are significantly lower among those over 50 years of age in response to TBE vaccination.**

- **BUT no age-related differences are found in the avidity and functional activity of antibodies induced by vaccination.**

Lang PO *et al*, Curr Top Med Chem 2013

Stiasny K *et al*, PLos ONE 2012

- **A single dose of aP vaccine induced good and effective immune response in most older individuals (89% pertussis toxoid – 96% filamentus hemagglutinin, and 94% pertactin).**

Theeten H *et al*, Curr Med Res Opin 2007

Grimpel *et al*, Vaccine 2005

- **A single dose of TdaP (Boostrix®) is immunogenic in adults aged 65 years or older. BUT long-lasting immunity is only provided by repetitive booster doses**

Van Damme P *et al*, Vaccine 2011

Weinberger B *et al*, PLos ONE 2013

Age-associated immune remodelling

- #1: Lower vaccine responsiveness is a trend not observed with all the vaccines.
- #2: **The vaccine efficacy and effectiveness do not only depend of the quality of the vaccinee (*age, comorbidities, nutrition and etc*) but also of the vaccine type:**
  - *in terms of antigenic contents (sub-unit, live attenuated, etc..)*
  - *in term of the pathogen targeted (epidemiology, way of infectivity)*
  - *in terms of presence or not of an adjuvant*
  - *and, in terms of route of administration*
- #3: The link between immunogenicity and protection is not direct and this because:
  - *While antibody level is important, the quality of the antibodies produced is also of high importance (avidity and affinity)*
  - *Is the immune component(s) that effectively induce(s) the protection really the readout considered?*
- #4: The vaccine responsiveness can be influenced by prior contact(s) with pathogen antigen(s) and/or prior vaccination.

...and vaccine responsiveness. Who has said easy?

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EPILOGUE

Aspinall R & Lang PO. Vaccine choice for older people, looking byond age specific approaches. Expert Rev Vaccines. 2018;17:23-30

Despite the mass of information generated, neither the cross-sectional nor the longitudinal studies has provided a clear mapping of the age-associated remodeling processes that impact the immune system.

Despite the mass of information generated, neither the cross-sectional nor the longitudinal studies approach has provided a clearly identifiable strategy for manufacturers to design specific vaccines for older individuals.

Consequently, vaccine companies have taken a more pragmatic view in making changes in order to improve the immunogenicity of the vaccine by considering the immune system to be gradually getting weaker in older individuals and just providing a stronger stimulus.

To improve the ability of vaccines to protect older individuals we can no longer consider those over 65 years of age to be an homogenous population termed the 'elderly' displaying a condition termed immunosenescence.

TO BE CONTINUED ...

MAY THE FORCE BE WITH YOU!

PLang@montchoisi.ch

IMMUNOSENESCENCE

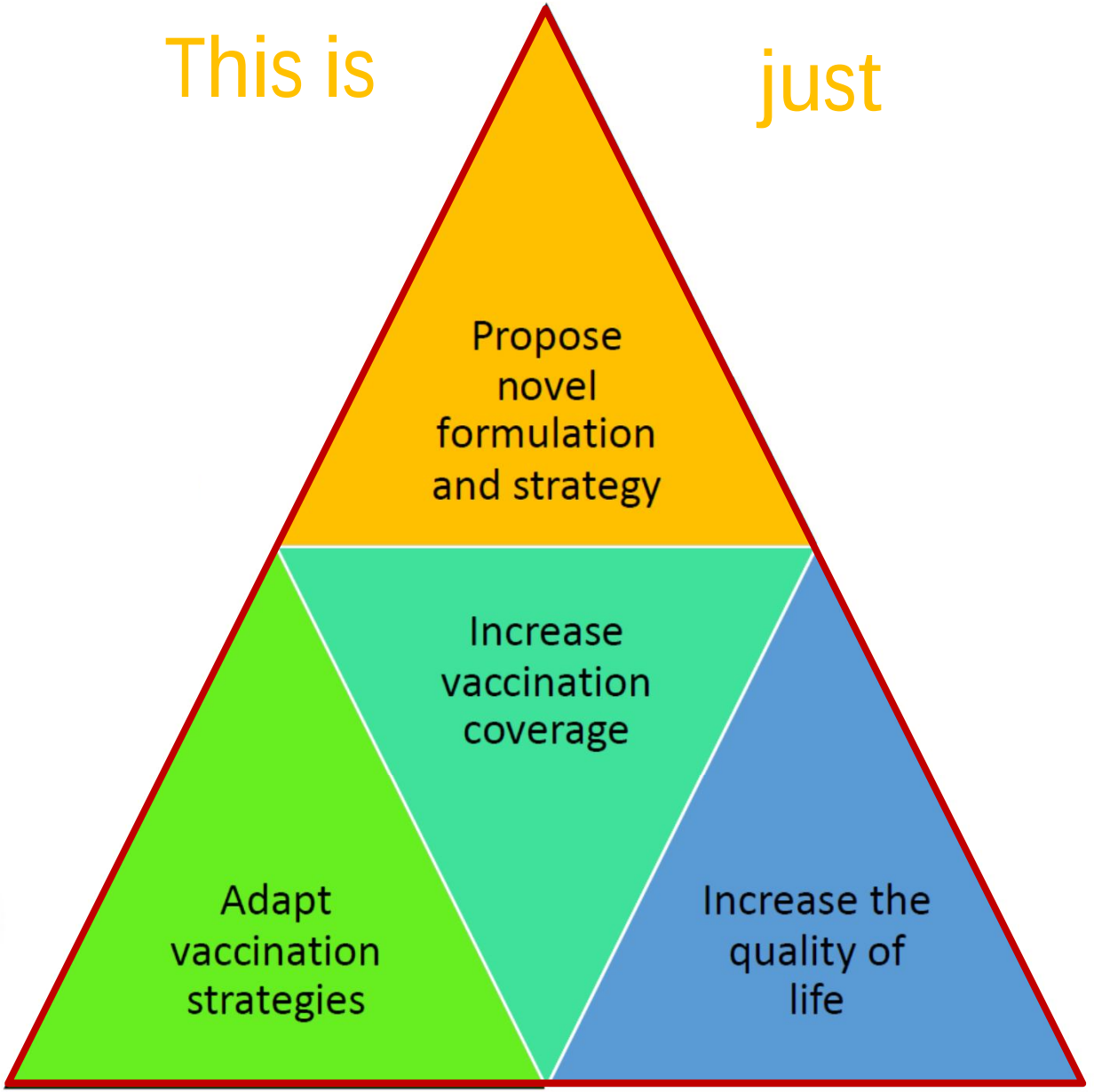
EPISODE V

Strategies to strike back

Lang PO & al. Reversing T-cell immunosenescence: Why, who, and how. Age 2013;35:609-20

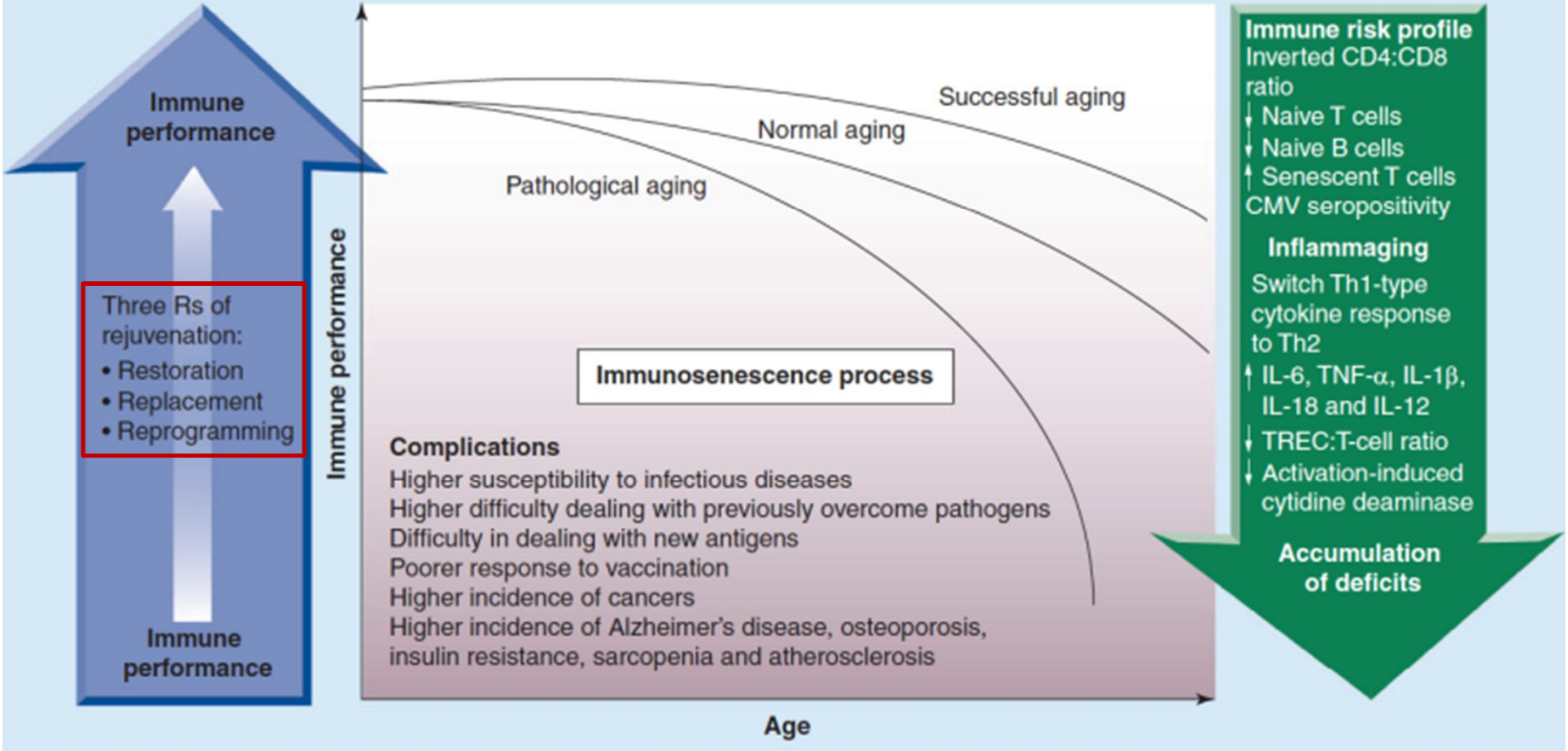
Aspinall R & Lang PO. Intervention to restore appropriate immune function in the elderly. Immun Aging. 2018;15:5

This is just



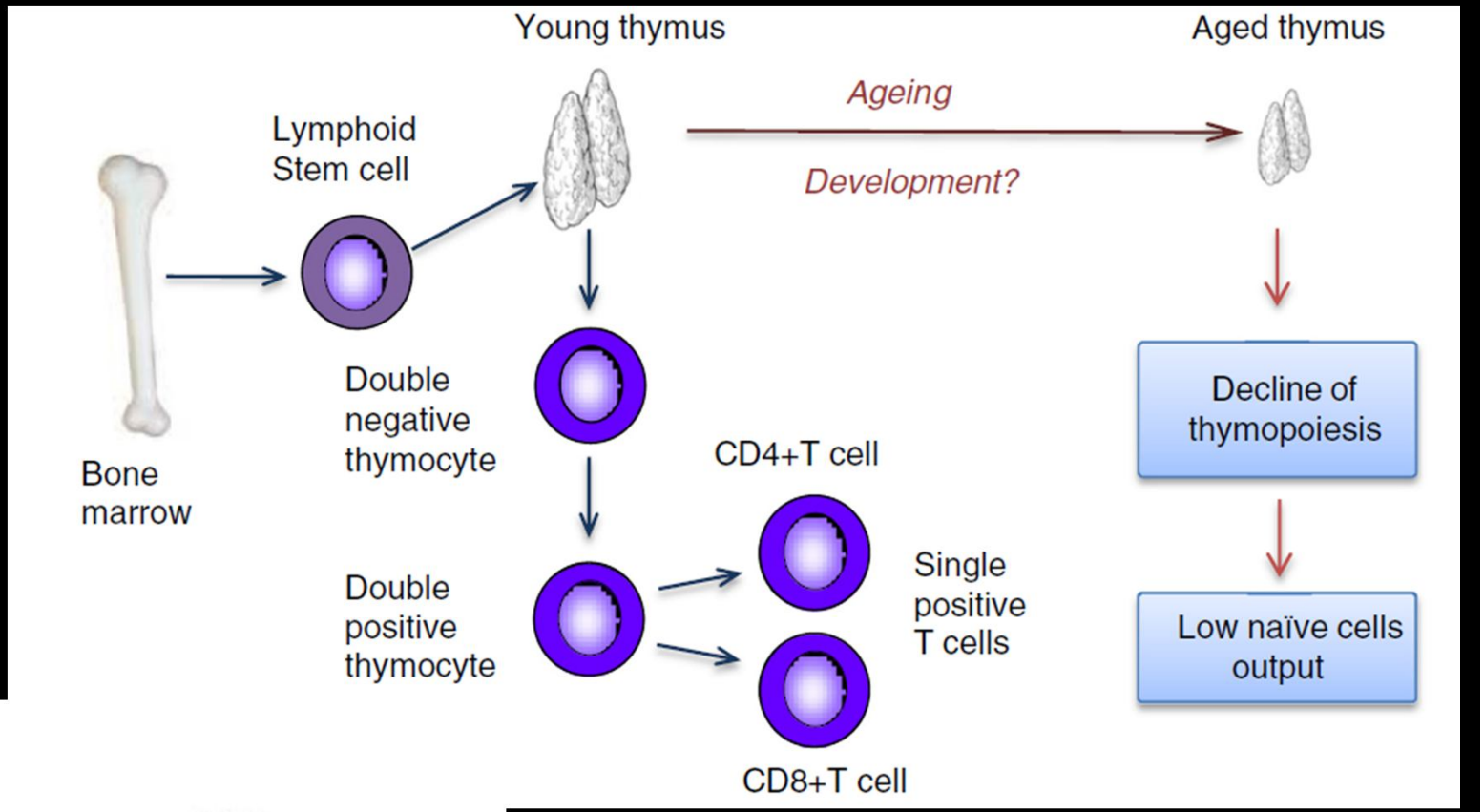
A focus on what it is already possible to do now

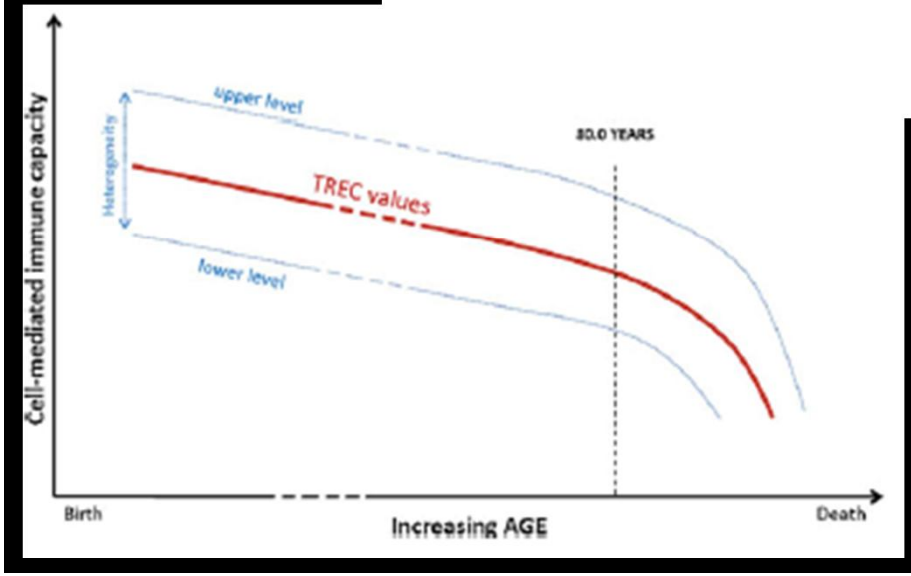
More complicated things are also possible…



To enhance the immune system more in depth

More specifically at the cellular and molecular level…





Clinical and Experimental Immunology ORIGINAL ARTICLE

Tracing thymic output in older individuals

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