Challenges in aging and immunosenescence

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Sepsis & Immuno-compromised Hosts: Challenges in 2024

Pr Virginie Prendki,
Division of Internal Medicine for the Aged,
Division of Infectious Diseases,
Geneva, Switzerland

virginie.prendki@hug.ch

UNIVERSITÉ DE GENÈVE

HUG Hôpitaux Universitaires Genève

Conflicts of interest

I am only a clinician, not an immunologist!

I am an internist and infectious diseases specialist, working part-time in geriatrics, but not a gerontologist!

ESGIE
ESCMID STUDY GROUP FOR INFECTIONS IN THE ELDERLY
European Society of Clinical Microbiology and Infectious Diseases

Survey

- Who takes care of elderly patients?
- Who works with geriatricians?

Clinical case 1: a 90-year-old woman

- Hospitalized for an acute fall
- Lives at home with her husband, independent for her activities of daily living
- Comorbidities/history: arterial hypertension
- Vaccinations: influenza, SARS-CoV-2, VZV, *Streptococcus pneumoniae*

Clinical case 1: a 90-year-old woman

- Fever 38.2, acute cough, dyspnea, crackles on the right lung base
- Concording infiltrate on the CXR
- PCR for influenza, SARS-CoV-2 and RSV, blood cultures and pneumococcal and *Legionella pneumophila* urinary antigens: negative
- Treated for a suspicion of pneumonia with co-amoxicillin IV with rapid oral relay
- Respiratory physiotherapy, mobilization and re-nutrition
- Dysphagia screening and oral examination
- Transfered to rehabilitation for a short duration
- Discharged home

Clinical case 2: a-90 year-old man

- Hospitalized for dypsnea and fever
- Lives in a nursing-home: cachexia/wasting, chronic falls, bedridden
- Comorbidities/history:
  - Chronic heart failure
  - Atrial fibrillations
  - Ischemic stroke
  - COPD
  - Cognitive disorders
  - Prostate cancer

Clinical case 2: a-93 year-old man

- Suspicion of pneumonia treated with co-amoxicillin IV
- Complication:
  - delirium -> neuroleptics
  - acute heart failure and urinary retention: IV diuretics and indwelling urinary catheter
- Day 10:
  - pulls out the IV line -> hematuria
  - CRP 305 mg/l, acute renal failure (creatinin 216 µmol/l)
  - blood cultures: *Escherichia coli* bacteremia
  - MOF
- Palliative care treatment

Outline

Part 1. Epidemiology of aging, definitions and concepts

Part 2. Immunosenescence and inflammaging

Part 3. Infection, host response and aging

Part 4. Impact in clinical practice and perspectives

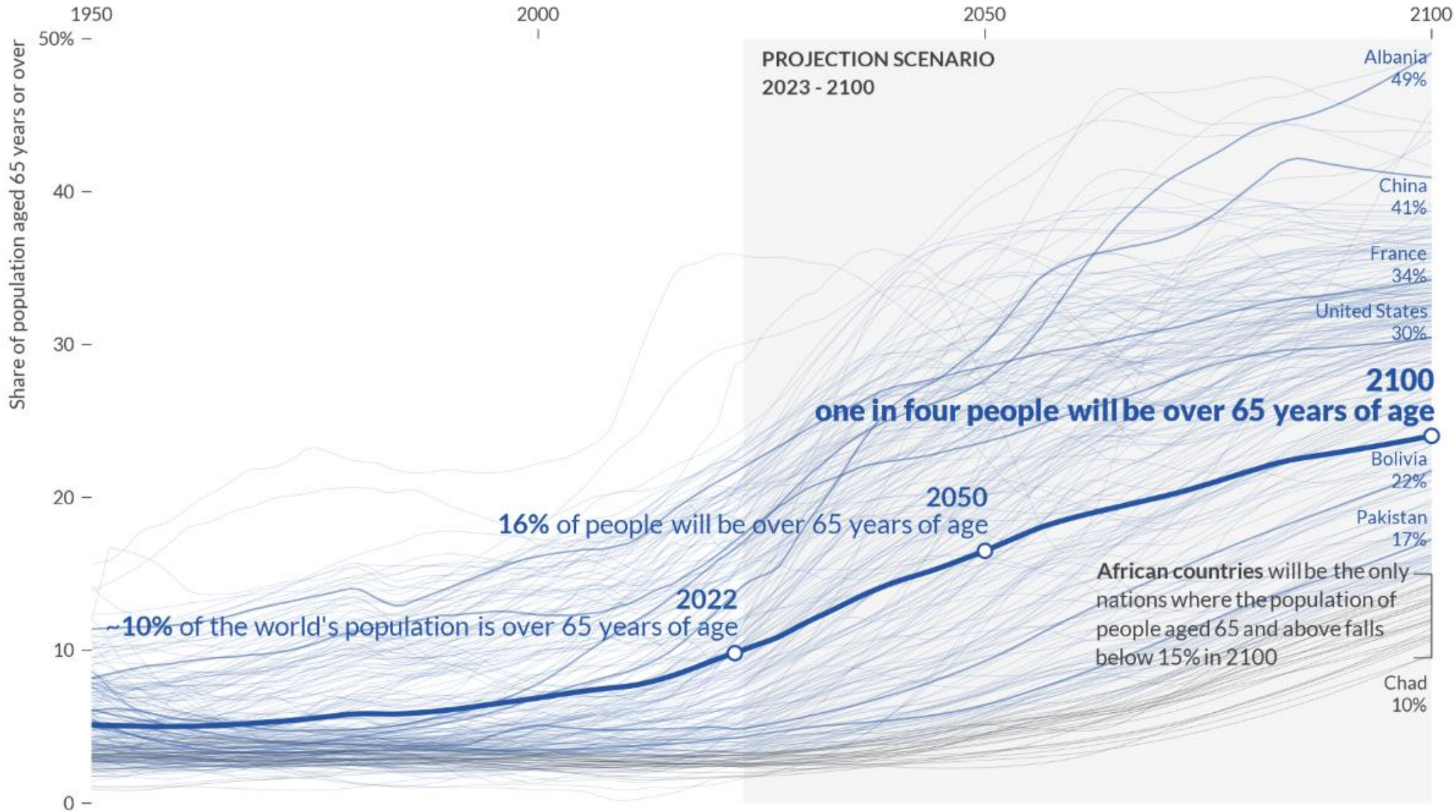
Part 1. Epidemiology, definitions and concepts

AVOID

Schedule your
free 30-minute

The world's population is aging

The population of people aged 65 and above is rising in every country, and will continue to do so in the future



Visualization: Pablo Alvarez | Source: United Nations World Population Prospects (2022) (via OurWorldInData.org)

Aging worldwide population: Europe has largest elderly population

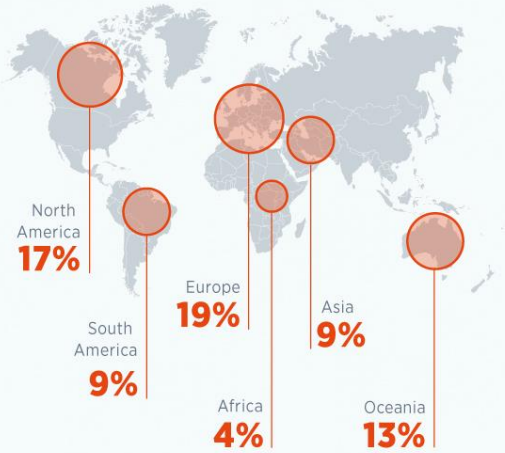
While elderly populations continue to grow worldwide, Europe is the continent with the world's oldest population

2021

WORLD POPULATION
7.9 BILLION

ELDERLY POPULATION
10%

Elderly population by continent



Countries with highest elderly populations

	%
Monaco	34.3
Japan	28.8
Italy	22.8
Greece	22.7
Puerto Rico	22.7
Finland	22.6
Germany	22.6
Slovenia	21.7
Croatia	21.6
Romania	21.5

22.03.2022 Source: Statista, Turkstat

Definitions

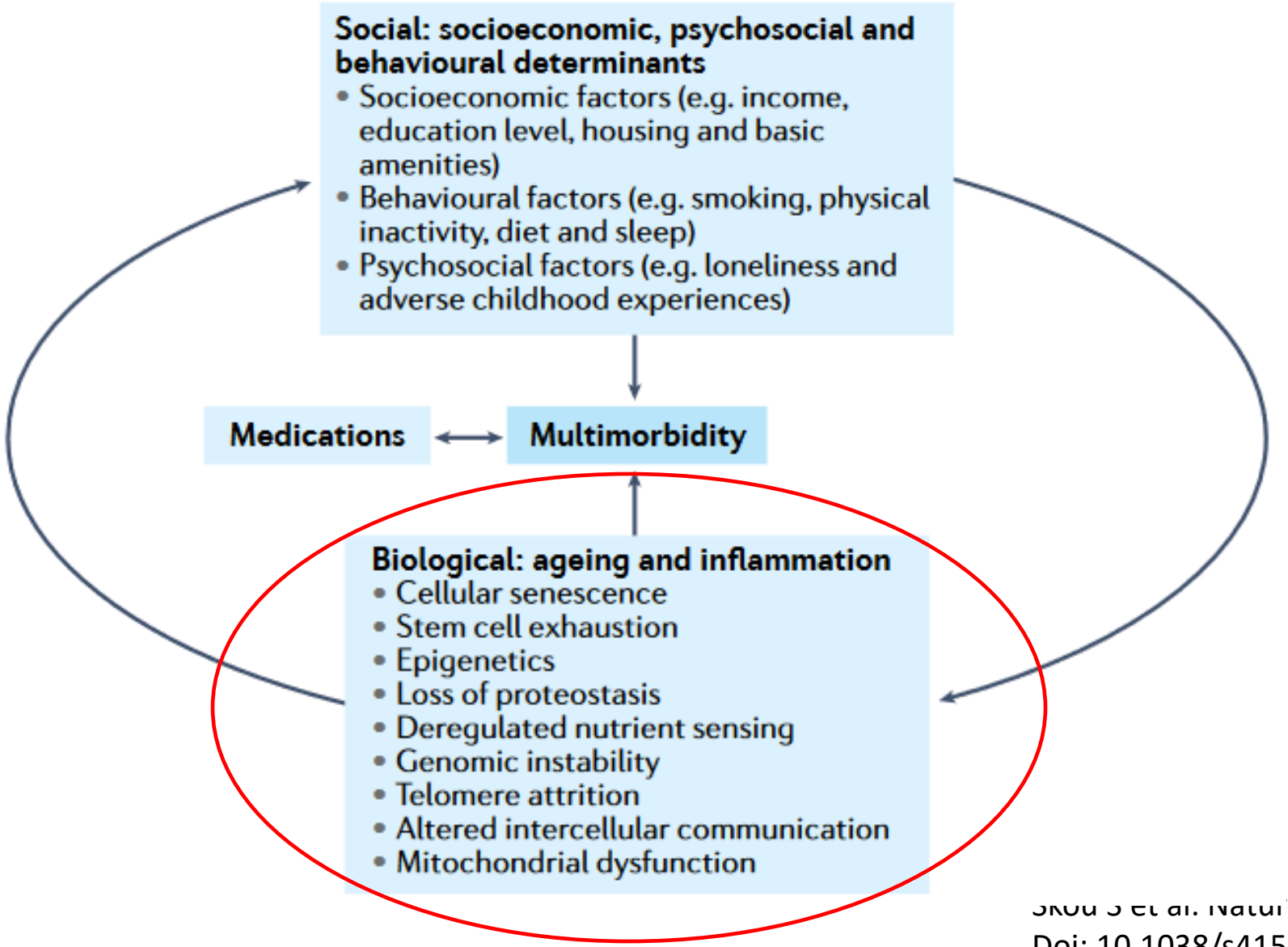
- **Aging** is a progressive **loss of function and structure of cells, tissues, and organs** resulting in **impaired immune response to stress and increasing vulnerability to death**
- With **aging** of the global population, there is increasing prevalence of **multimorbidity**, **disability** and **frailty**
- **Multimorbidity:** 2 or more coexisting conditions
- **Disability**: a physical or mental condition that limits a person's movements, senses, or activities

Healthy aging

WHO promotes the concept of **healthy aging** (WHO, 2015):

- process of developing and maintaining functional ability that enables wellbeing in older age
- it should be the focus of all modern societies
- pillars of healthy aging: physical exercise, healthy diet, immunization

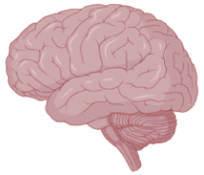
Determinants of multimorbidity



Skou S et al. Nature Reviews Disease Primers 2022
Doi: 10.1038/s41572-022-00376-4

Aging of the major organ systems

Brain



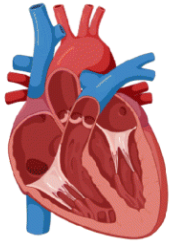
- Brain Volume [5]
- Deterioration of Myelin Sheath [12]
- Temporal Lobe [9]
- Hippocampus Volume [9]

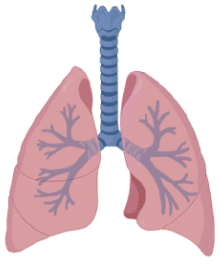
Degenerating Myelin Sheath

Healthy Myelin Sheath

Heart

- Reduced cell number of cardioyocytes and sinoatrial pacemaker [53,54]
- Decreased Strength and Elasticity of Cardiac walls [53,54]





Lungs

- Reduced Cough Strength [35,36]
- Reduced ability of cilia lining (upper and lower) [37]
- Decrease in Alveolus Elasticity [38-39]
- Increase in Alveolus size [38-39]

Common Features across Organs

Decreased Cell Number and Function

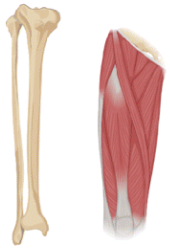
Change in Tissue Structure

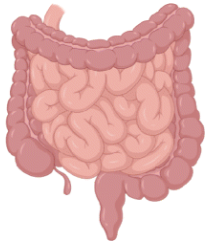
Increased Chronic Inflammation

Musculoskeletal

- Increased Brittleness: change in bone mineral density and protein matrix ([20-22]
- Decline in Muscle mass and formation [24-25]
- Decrease of fast myosin fibres

Accumulation of fat tissues [27-29]





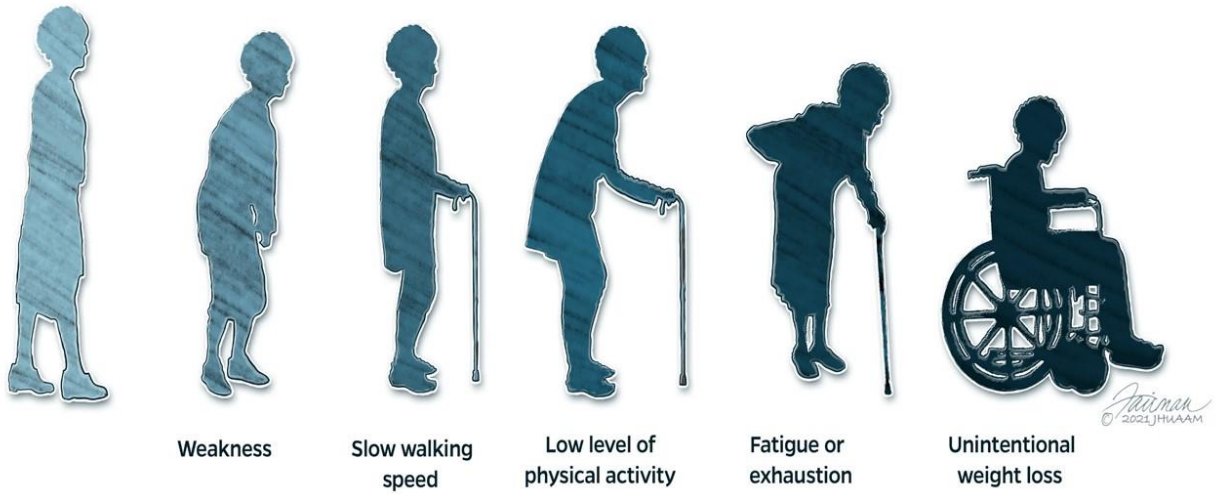
Gastrointestinal

- Decreased Microbiome Diversity [46,47]
- Reduced Gut Motility [48]
- Loss of Intestinal Barrier Integrity [48]

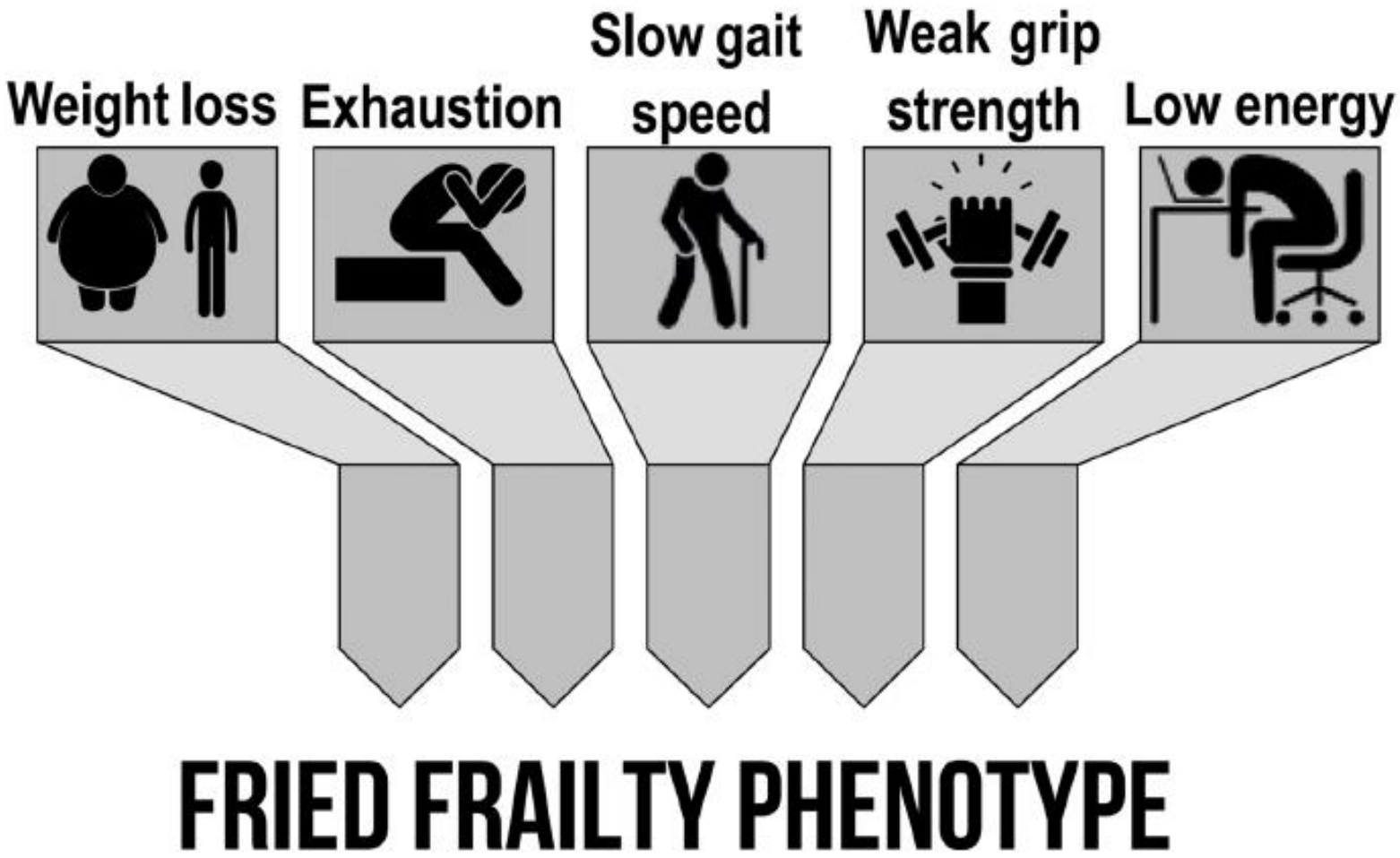
Xu W et al. Seminars in Immunopathology 2020
Doi: 10.1007/s00281-020-00824-x

What is frailty?

- A condition of **susceptibility and loss of resilience to stress**
- Highly prevalent in older ages (4-17% of the general population is frail, 28-44% is pre-frail)
- Associated with **increased risk of disability and mortality**
- Two conceptual models:
  - **Fried**'s physical frailty phenotype
  - **Rockwood**'s cumulative deficiency approach



Damiano C et al. Aging Clin Exp Res 2022
doi: 10.1007/s40520-022-02269-8



Fried L et al, Frailty in Older Adults: Evidence for a Phenotype. Journal of Gerontology 2001. Doi: 10.1093/gerona/56.3.m146

CLINICAL FRAILTY SCALE

Fit

Vulnerable, but not frail

Initial signs of frailty

1 VERY FIT — People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.

2 FIT — People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g., seasonally.

3 MANAGING WELL — People whose **medical problems are well controlled**, even if occasionally symptomatic, but often are **not regularly active** beyond routine walking.

4 LIVING WITH VERY MILD FRAILTY — Previously "vulnerable," this category marks early transition from complete independence. While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being "slowed up" and/or being tired during the day.

5 LIVING WITH MILD FRAILTY — People who often have **more evident slowing**, and need help with **high order instrumental activities of daily living** (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.

6 LIVING WITH MODERATE FRAILTY — People who need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 LIVING WITH SEVERE FRAILTY — **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).

8 LIVING WITH VERY SEVERE FRAILTY — Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.

9 TERMINALLY ILL — Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise living with severe frailty.** (Many terminally ill people can still exercise until very close to death.)

Initial signs of frailty

Severe or very severe frailty

SCORING FRAILTY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

In **very severe dementia** they are often bedfast. Many are virtually mute.

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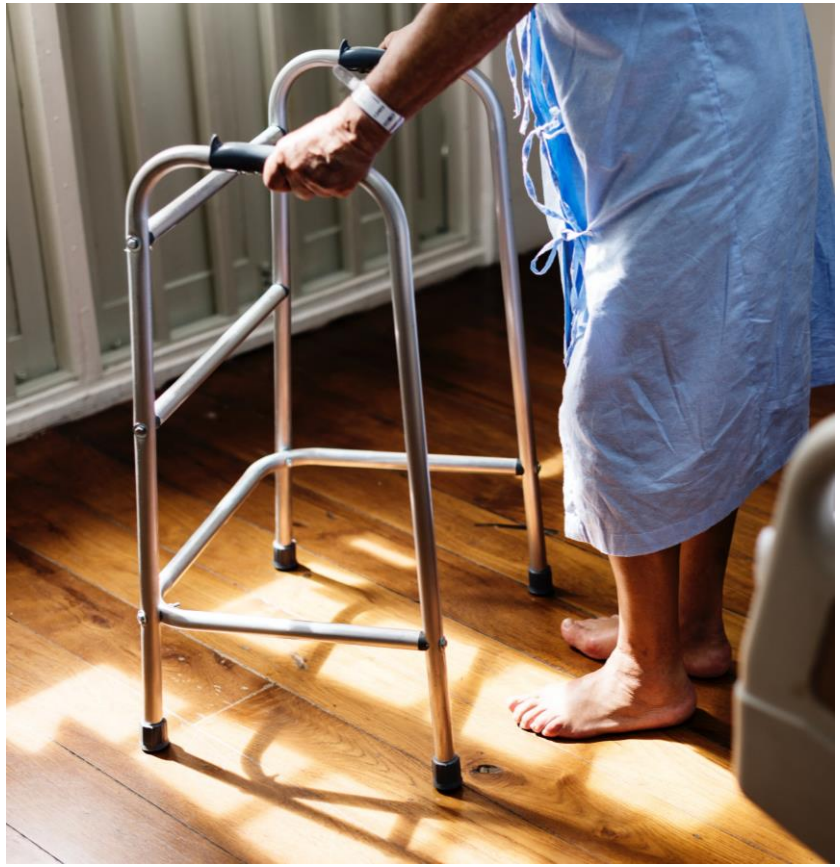
Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

Frailty and infections

- Frail older people with multimorbidity and disability, and those living in long-term care facilities, are **much more likely to be infected** and to experience **a higher case-fatality rate** than the general population

- Example of pneumonia, one of the most frequent diagnoses in hospitalized older persons affected by disability and frailty
  - ➢ It may trigger a vicious cycle where pneumonia increases the severity of frailty and vice versa, leading to accelerated functional decline and mortality



The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study

	Crude HR (95% CI)*	p value	Adjusted HR† (95% CI)‡	p value
Age, years				
<65	1 (ref)	..	1 (ref)	..
65–79	3·30 (2·40–4·55)	<0·0001	2·58 (1·82–3·64)	<0·0001
≥80	4·05 (2·95–5·57)	<0·0001	2·92 (2·02–4·22)	<0·0001
Sex				
Female	1 (ref)	..	1 (ref)	..
Male	0·99 (0·81–1·21)	0·93	1·07 (0·85–1·32)	0·56
Smoking status				
Never	1 (ref)	..	1 (ref)	..
Ex-smokers	1·20 (0·98–1·47)	0·079	0·95 (0·77–1·18)	0·67
Current smokers	0·84 (0·55–1·29)	0·43	0·91 (0·59–1·42)	0·69
Increased C-reactive protein (>40 mg/dL)	2·22 (1·69–2·92)	<0·0001	2·61 (1·97–3·45)	<0·0001
Patients with diabetes	1·12 (0·90–1·39)	0·30	1·03 (0·82–1·29)	0·83
Patients with coronary artery disease	1·57 (1·26–1·95)	<0·0001	1·19 (0·94–1·49)	0·83
Patients with hypertension	1·24 (1·01–1·51)	0·036	0·95 (0·77–1·18)	0·66
Impaired renal function (eGFR <60 mL/min per 1·73 m²)	1·93 (1·58–2·35)	<0·0001	1·43 (1·16–1·77)	0·0007
Clinical frailty scale				
1–2	1 (ref)	..	1 (ref)	..
3–4	2·25 (1·47–3·45)	<0·0002	1·55 (1·00–2·41)	0·052
5–6	3·12 (2·05–4·76)	<0·0001	1·83 (1·15–2·91)	0·011
7–9	4·41 (2·90–6·71)	<0·0001	2·39 (1·50–3·81)	<0·0002

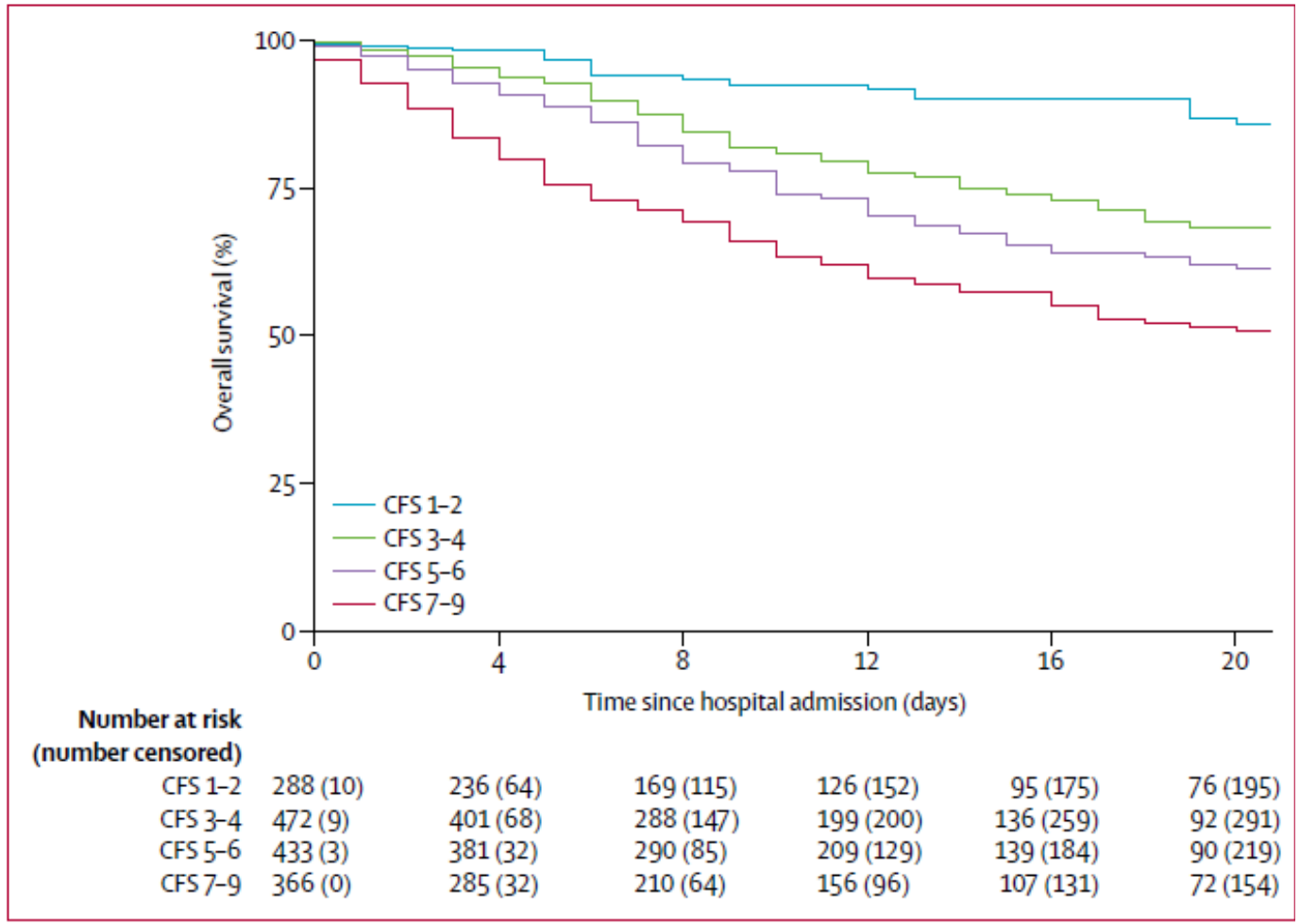


Figure 1: **Overall survival by CFS category**
CFS=clinical frailty score.

Compared with CFS 1-2, the adjusted HR for time from hospital admission to death was 2·39 (1·50-3·81) for CFS 7-9

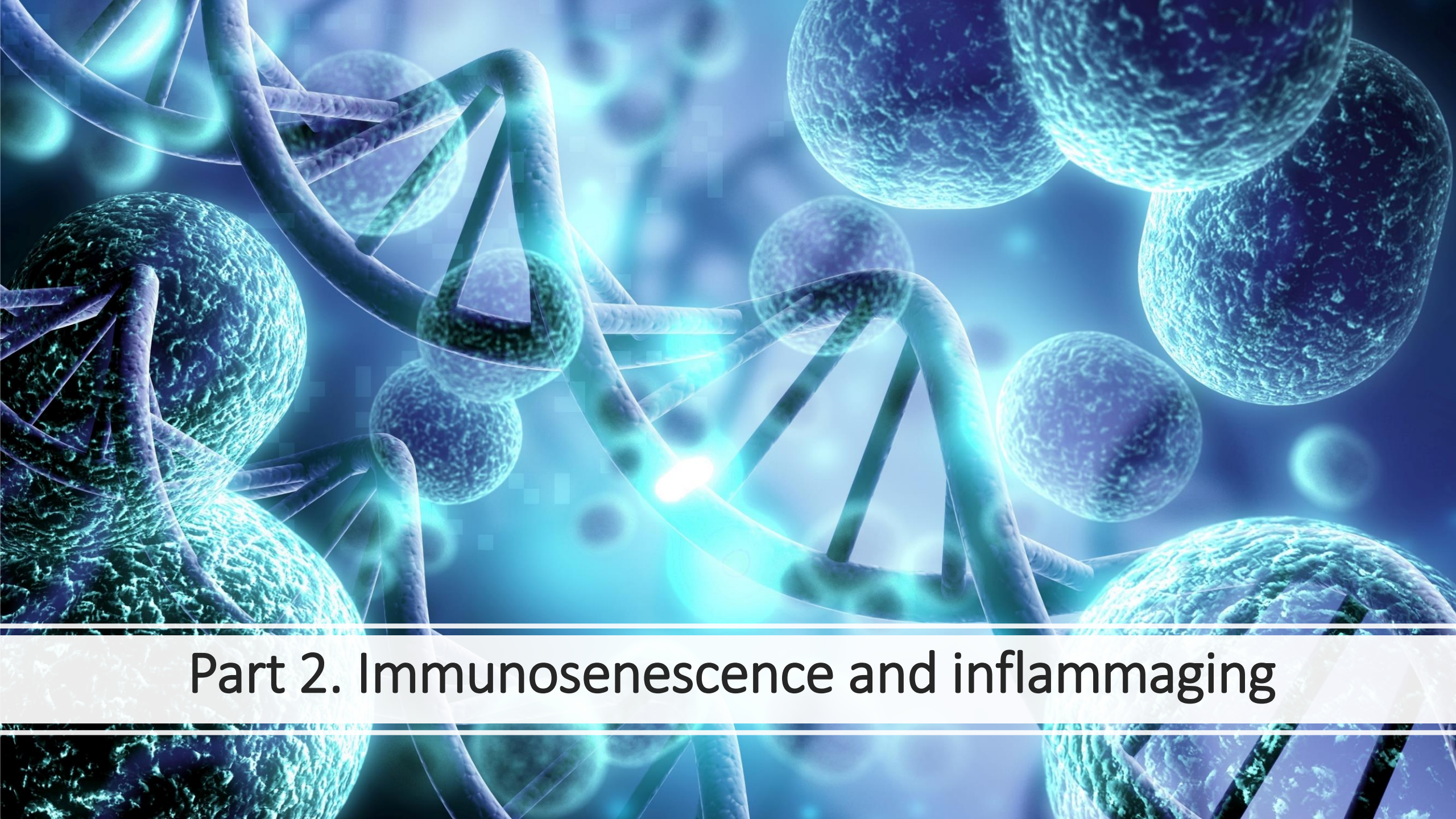
Hewitt J et al, Lancet Public Health 2020
10.1016/s2468-2667(20)30146-8

Frailty and hospitalization-associated disability after pneumonia: A prospective cohort study

Table 2 Frailty and Outcomes in Older Patients Hospitalized with Pneumonia

Outcomes	Number of Outcome Events (%) and OR (95% CI)[a]					*P* value
	Total	Robust	Pre-frailty	Mild-to-moderate frailty	Severe frailty	
Primary Outcome						
Death or functional decline at 30 days[b]	99 (67.4)	21 (46.7)	22 (61.1)	31 (83.8)	25 (86.2)	<0.001
	NA	Reference	1.46 (0.58-3.69)	3.95 (1.31-11.89)	5.34 (1.54-18.49)	0.014
Secondary patient outcomes						
Death at 30 days	19 (10.8)	3 (6.7)	1 (2.8)	6 (16.2)	9 (15.5)	0.129
	NA	Reference	0.38 (0.37-3.84)	2.36 (0.51-10.94)	2.27 (0.54-9.62)	0.281
Functional decline at 30 days[b]	84 (63.6)	18 (42.9)	21 (60.0)	25 (80.7)	20 (83.3)	0.001
	NA	Reference	1.63 (0.63-4.20)	3.84 (1.24-11.86)	5.33 (1.50-19.02)	0.022
Secondary process outcomes						
Intensive care unit stay	38 (21.8)	4 (8.9)	8 (22.2)	9 (24.3)	17 (30.4)	0.074
	NA	Reference	2.51 (0.67-9.44)	2.44 (0.64-9.27)	3.15 (0.92-10.73)	0.336
Psychoactive drug use[c]	41 (26.5)	10 (22.2)	7 (22.6)	13 (41.9)	11 (22.9)	0.189
	NA	Reference	0.88 (0.28-2.78)	1.92 (0.64-5.78)	0.66 (0.22-1.96)	0.236
Nasogastric tube feeding	50 (28.4)	3 (6.7)	5 (13.9)	7 (18.9)	35 (60.3)	<0.001
	NA	Reference	1.97 (0.42-9.22)	2.50 (0.56-11.22)	17.08 (4.49-64.99)	<0.001
Prolonged hospitalization (≥15 days)	62 (35.6)	8 (18.2)	14 (38.9)	11 (29.7)	29 (50.9)	0.006
	NA	Reference	2.72 (0.95-7.82)	1.58 (0.52-4.80)	3.72 (1.38-9.98)	0.039
Discharge to a long-term care institution[d]	39 (27.7)	2 (4.4)	7 (20.0)	14 (41.2)	16 (59.3)	<0.001
	NA	Reference	4.56 (0.83-24.87)	9.79 (1.88-51.00)	25.11 (4.70-134.07)	<0.001

Park C et al, BMC Geriatr 2021
Doi: 10.1186/s12877-021-02049-5



Part 2. Immunosenescence and inflammaging

What is immunosenescence?

- Aging is accompanied by **remodeling of the immune system**, called **immunosenescence**

- This provokes a decline in immune efficacy, resulting in:
  - **increased vulnerability to infectious diseases**
  - **diminished responses to vaccination**
  - **susceptibility to age-related inflammatory diseases**

Aiello A et al. Front Immunol 2019
Doi: 10.3389/fimmu.2019.02247

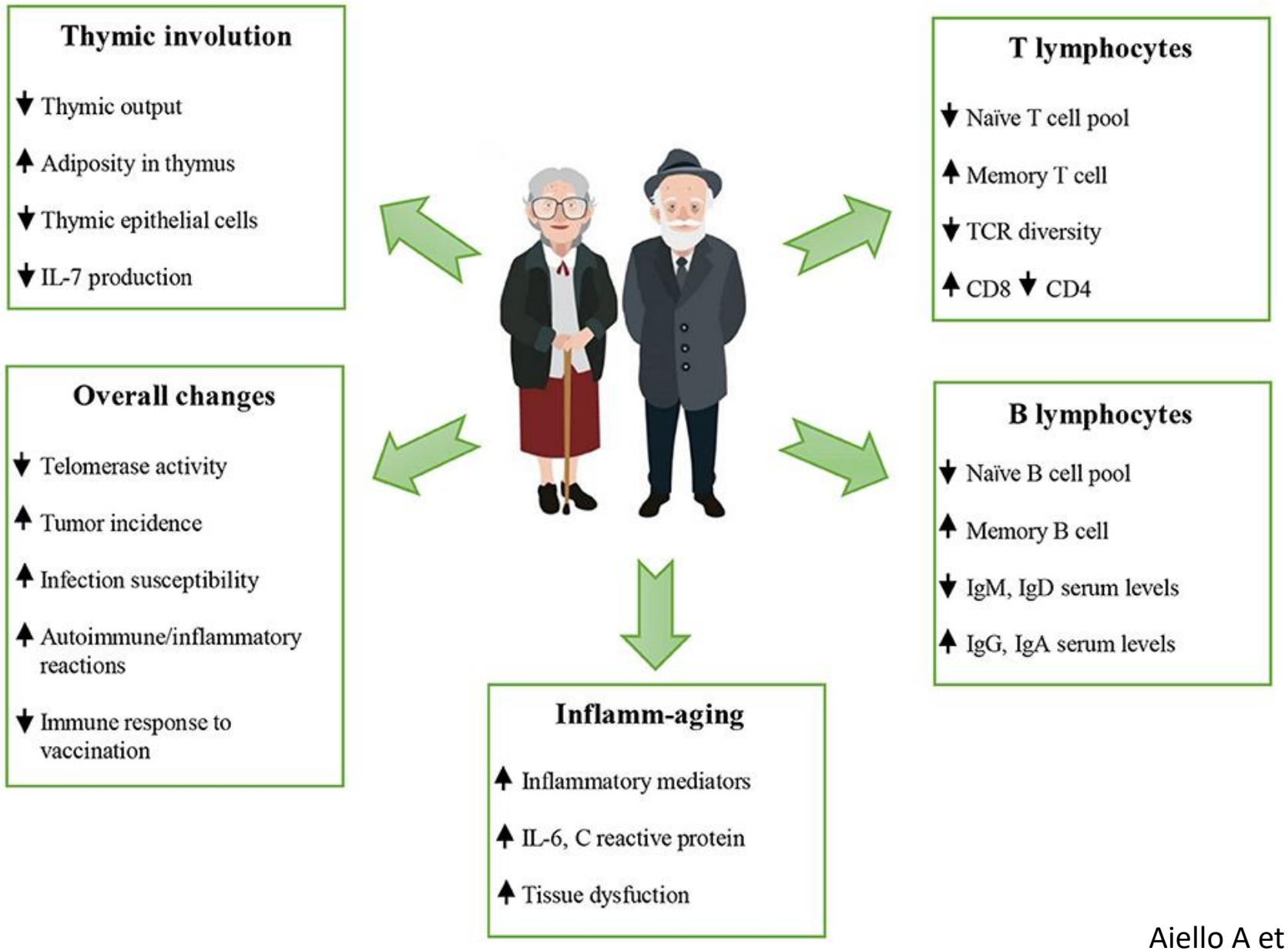
What is immunosenescence?

Immunosenescence is characterized by changes in different immune components, **both innate and adaptative**:

- **thymic involution** and **loss of diversity of adaptive immunity**
- increase in the number of memory T cells, loss of ability to respond to antigen and phenotypic changes in multiple immune cell types
- may lead to a persistent level of **low-grade inflammation called "inflamm-aging**"

Latent and chronic viral infection (CMV, EBV) also affect the immune system and contribute to immunosenescence

Aiello A et al. Front Immunol 2019
Doi: 10.3389/fimmu.2019.02247



Aiello A et al. Front Immunol 2019
Doi: 10.3389/fimmu.2019.02247

What is inflammaging?

- **Acute inflammation** is a physiological response to injury or infection, leading to the recruitment of immune cells to clear pathogens.
- However, **chronic inflammation**, or the dysfunction of signalling and/or effector pathways, is harmful.
- **Inflammaging** is a sterile, non-resolving, low-grade and chronic inflammation that increases with age.
- It can be considered an adaptive process because it can trigger an anti-inflammatory response to counteract the age-related pro-inflammatory environment.

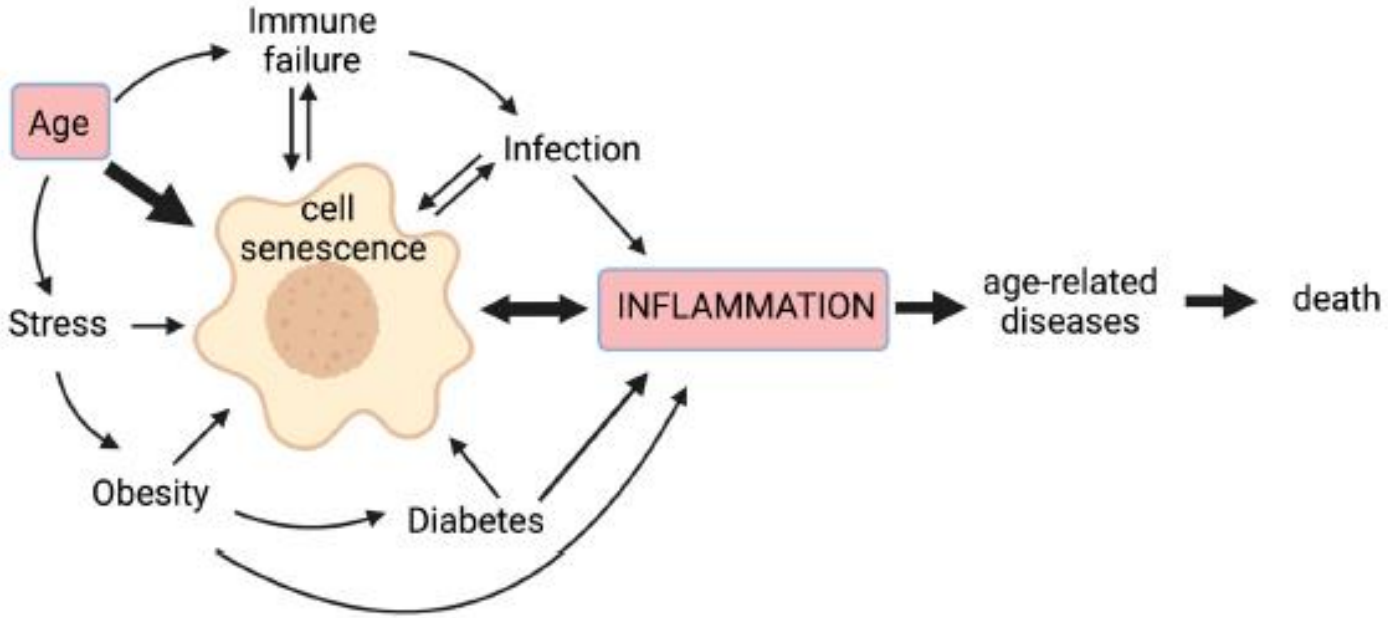
Franceschi C et al. Ann. N. Y. Acad. Sci. 2000
Teissier T et al. Cells 2022. Doi: 10.3390/cells11030359

What is inflammaging?

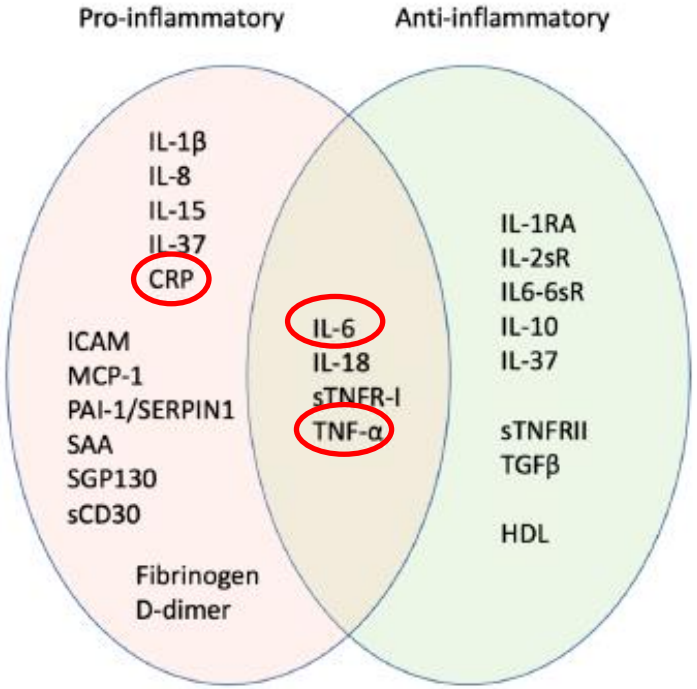
- But it **may contribute to diminishing health, age-related diseases and frailty**.
- The underlying causes of inflammaging are still unclear with several models postulated, including **accumulation of cellular debris (garb-aging)**
- **Failure of repair and autophagy** leads to increasing levels of cellular ‘garbage’, which can trigger inflammation via innate immune signalling

Franceschi C et al. Ann. N. Y. Acad. Sci. 2000
Teissier T et al. Cells 2022. Doi: 10.3390/cells11030359

Senescent cells and proinflammatory signature



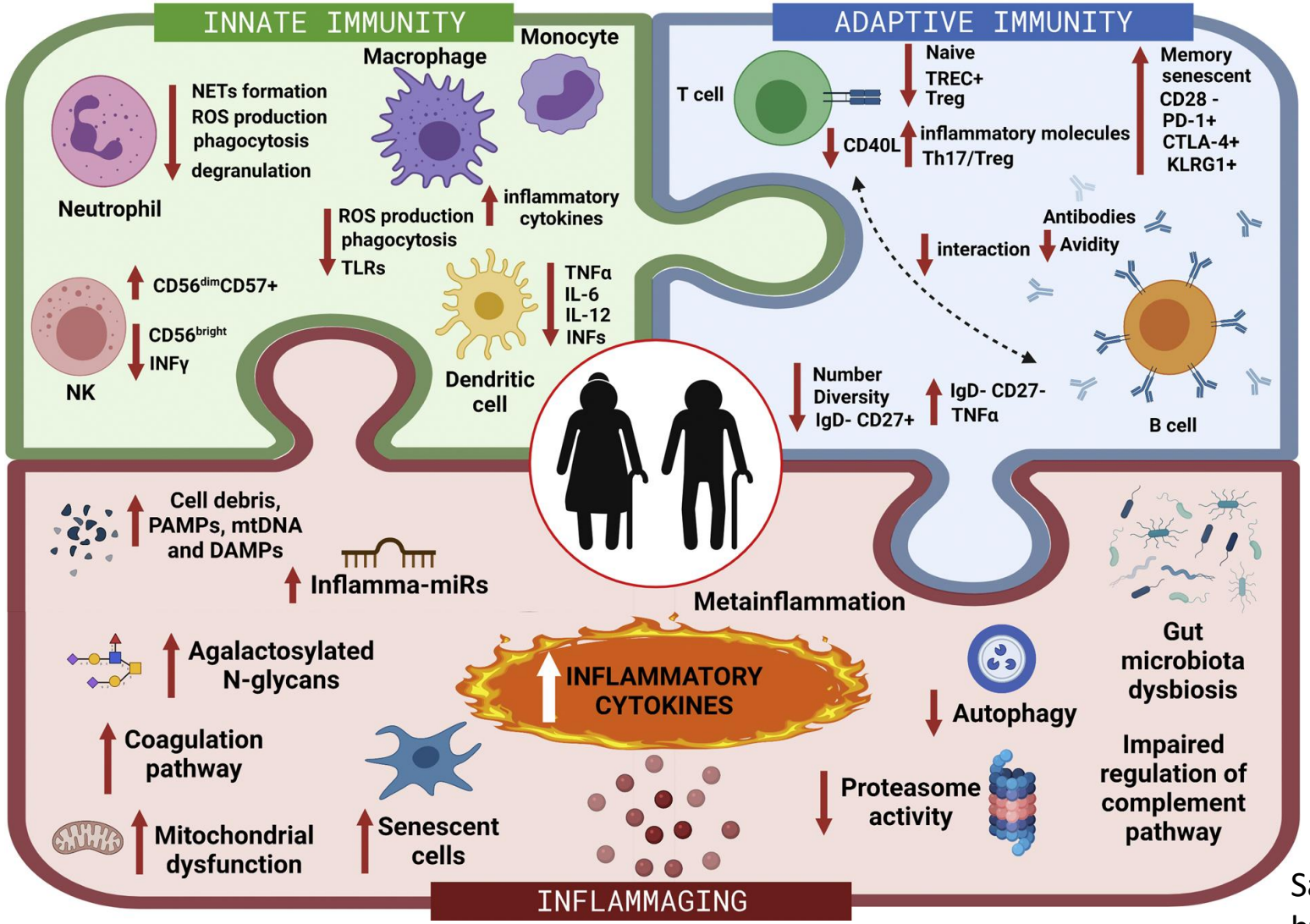
Cell senescence play a central role in inflammaging, producing large amounts of pro-inflammatory cytokines (called **senescence-associated secretory phenotype, SASP**)



Pro-inflammatory signatures

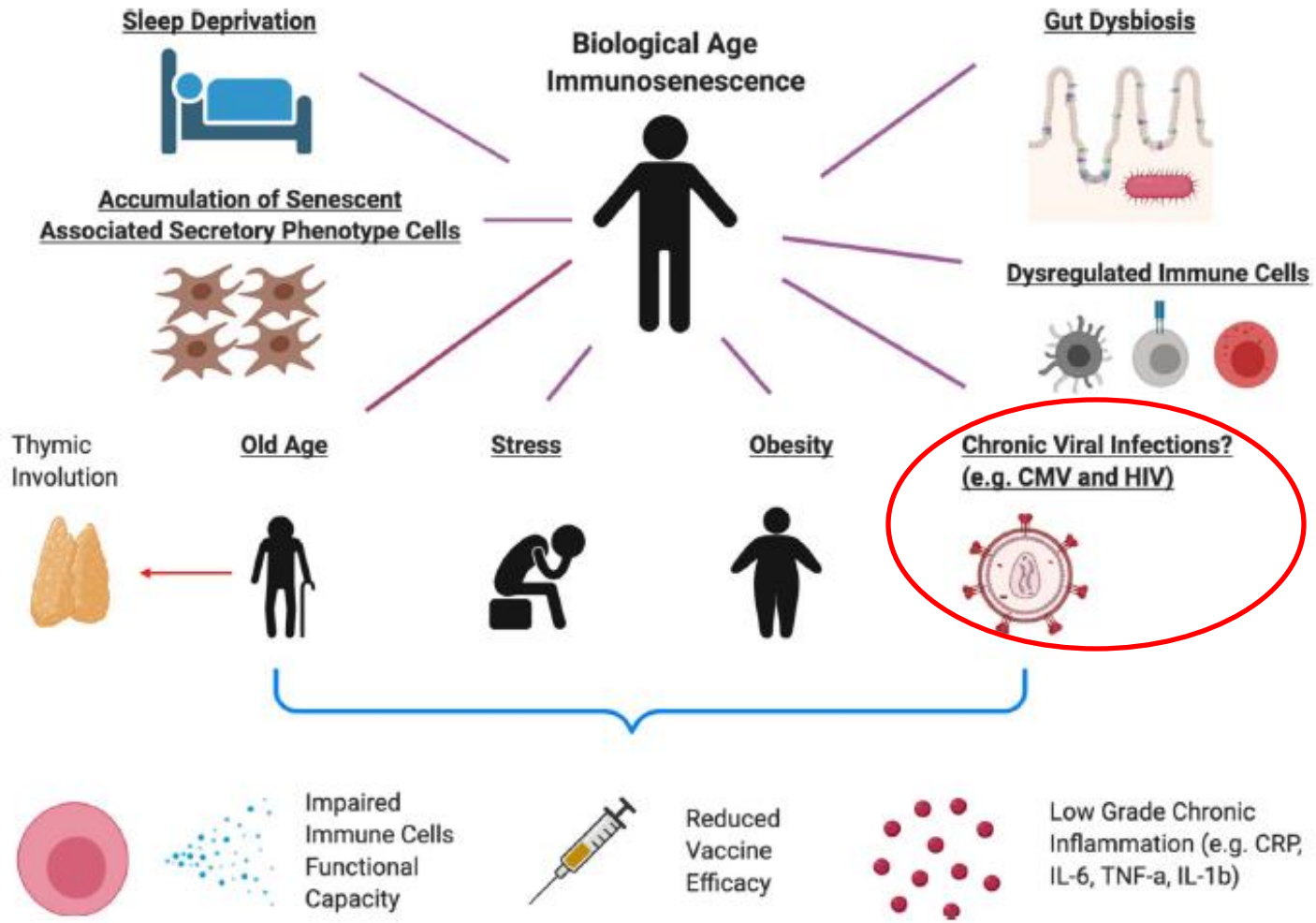
Teissier T et al. Cells 2022.
Doi: 10.3390/cells11030359

Age-related changes in innate and adaptive immunity and their contribution in inflammaging



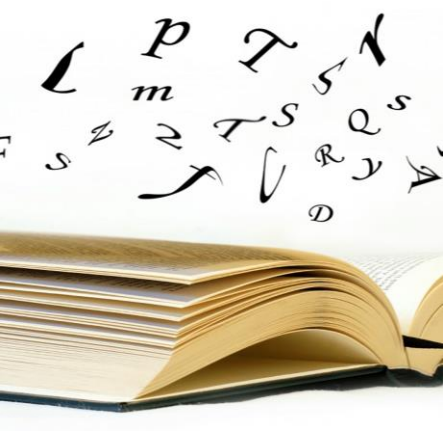
Santoro A et al. Ageing Research Reviews 2021
https://doi.org/10.1016/j.arr.2021.101422

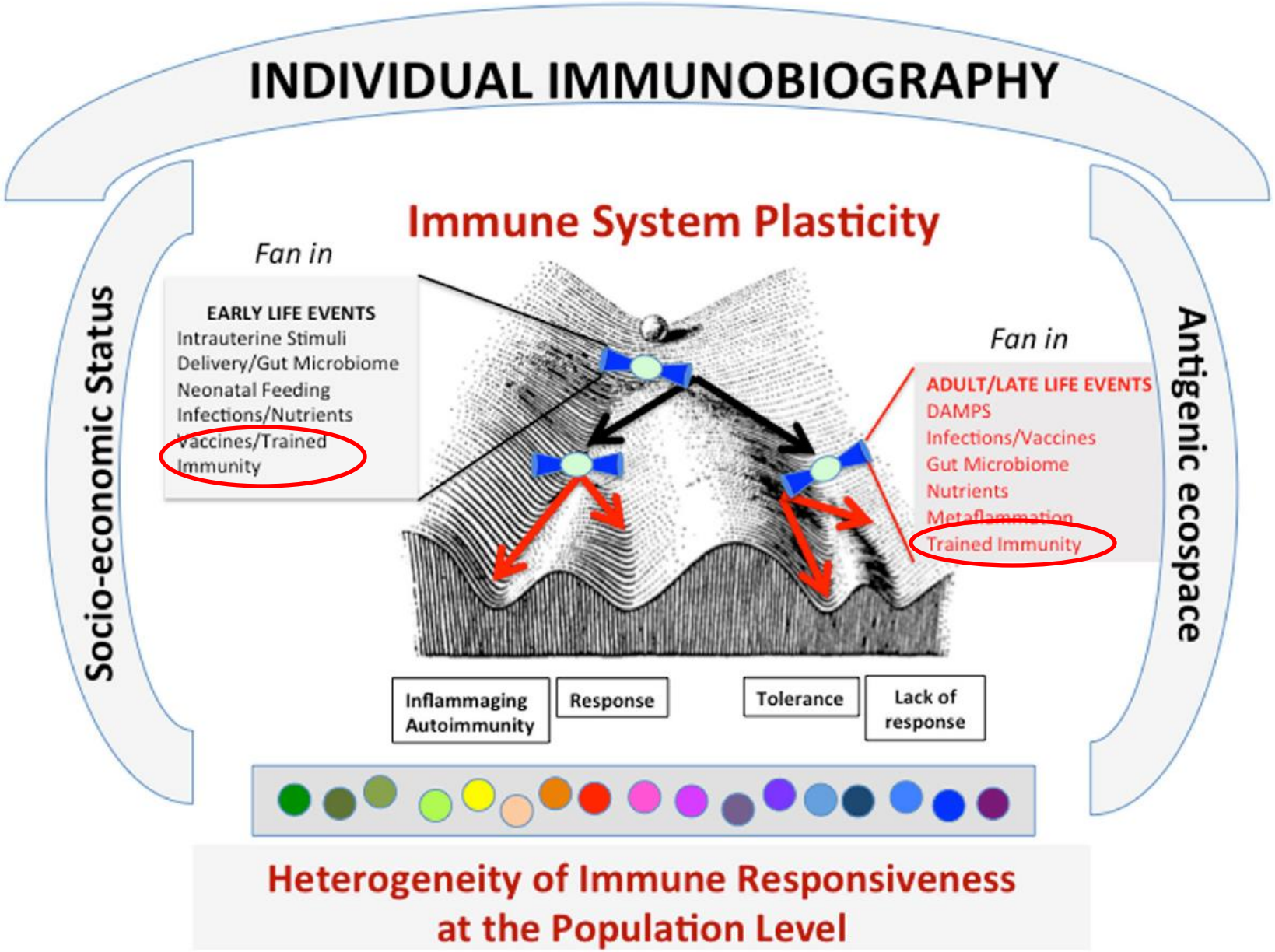
External stressors resulting in biological age-related immunosenescence



Xu W et al. Seminars in Immunopathology 2020
Doi: 10.1007/s00281-020-00824-x

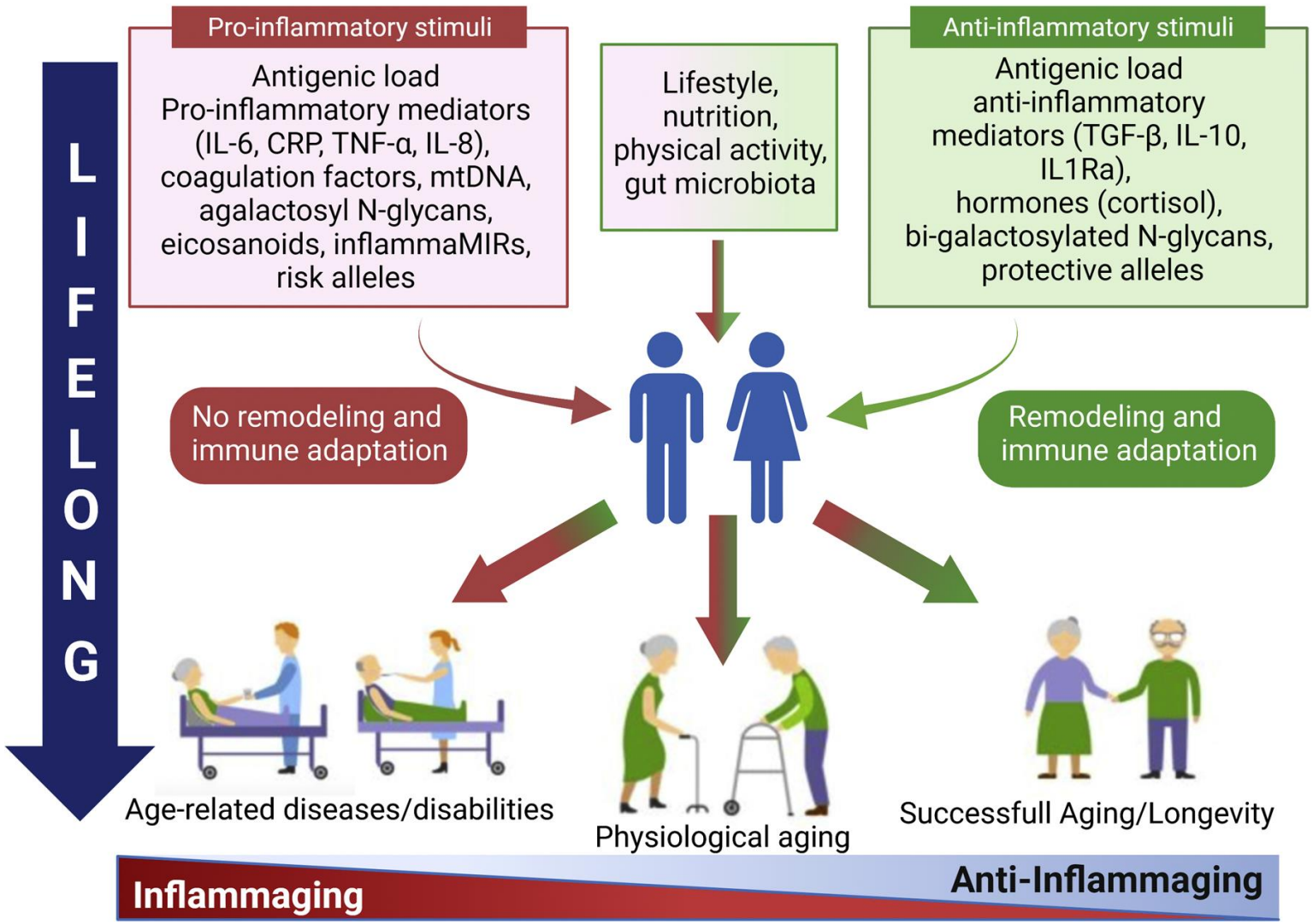

Product
COMPANY
Creative





Franceschi C et al. Front Immunol 2017
Doi 10.3389/fimmu.2017.00982

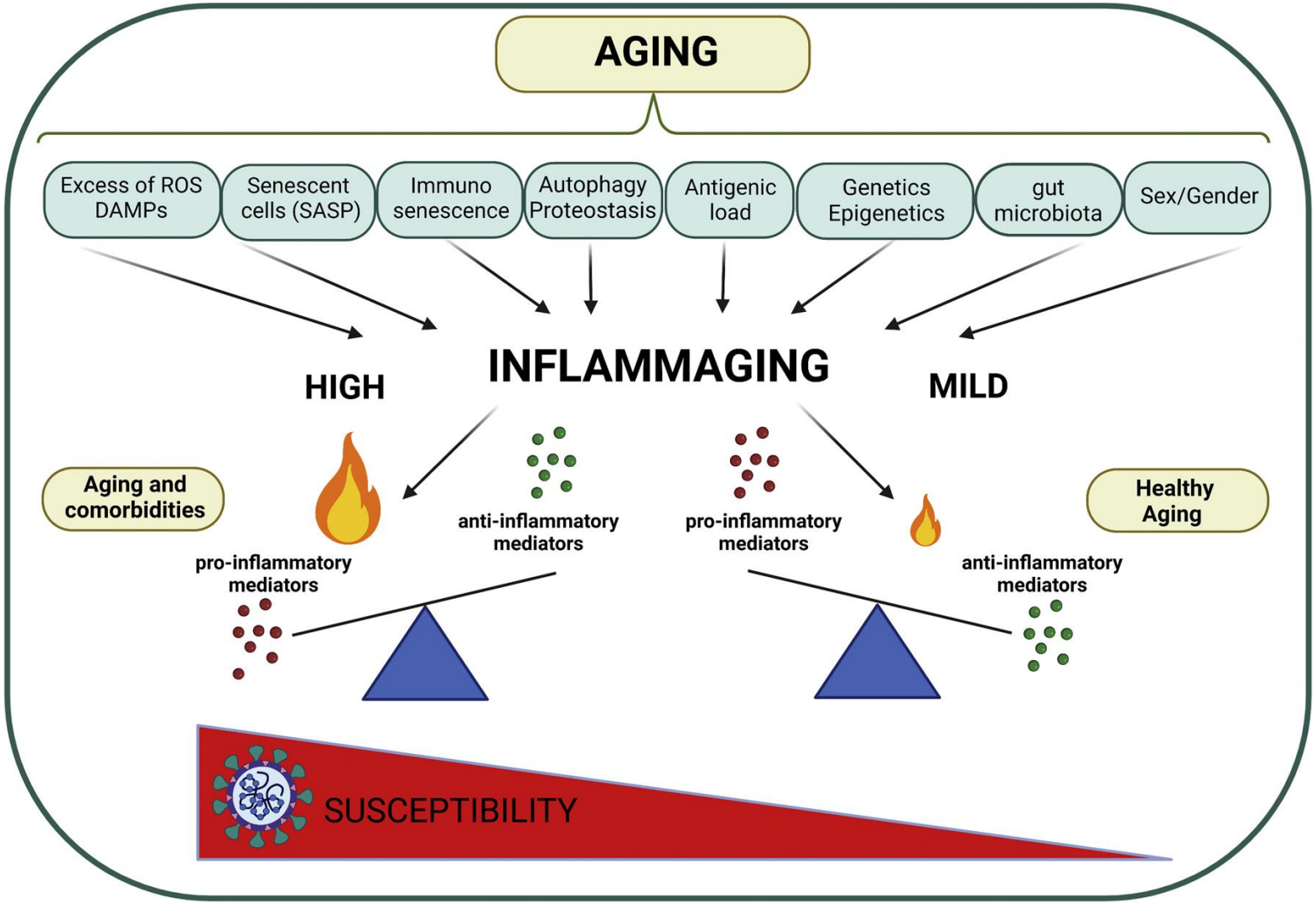
Adaptation or maladaptation to lifelong pro- and anti-inflammatory stimuli leads to longevity or diseases



Santoro A, Ageing Research Reviews 2021
https://doi.org/10.1016/j.arr.2021.101422

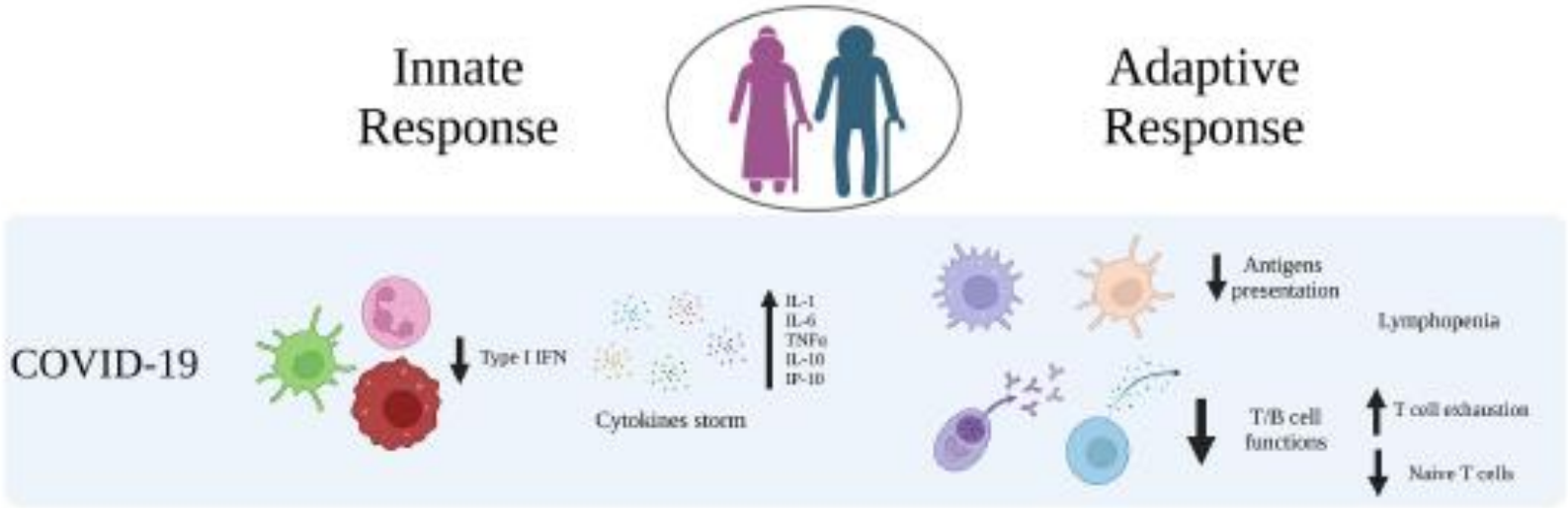
Part 3. Infection, host response and aging

Inflammaging and susceptibility to infections: the COVID-19 case



Santoro A, Ageing Research Reviews 2021
https://doi.org/10.1016/j.arr.2021.101422

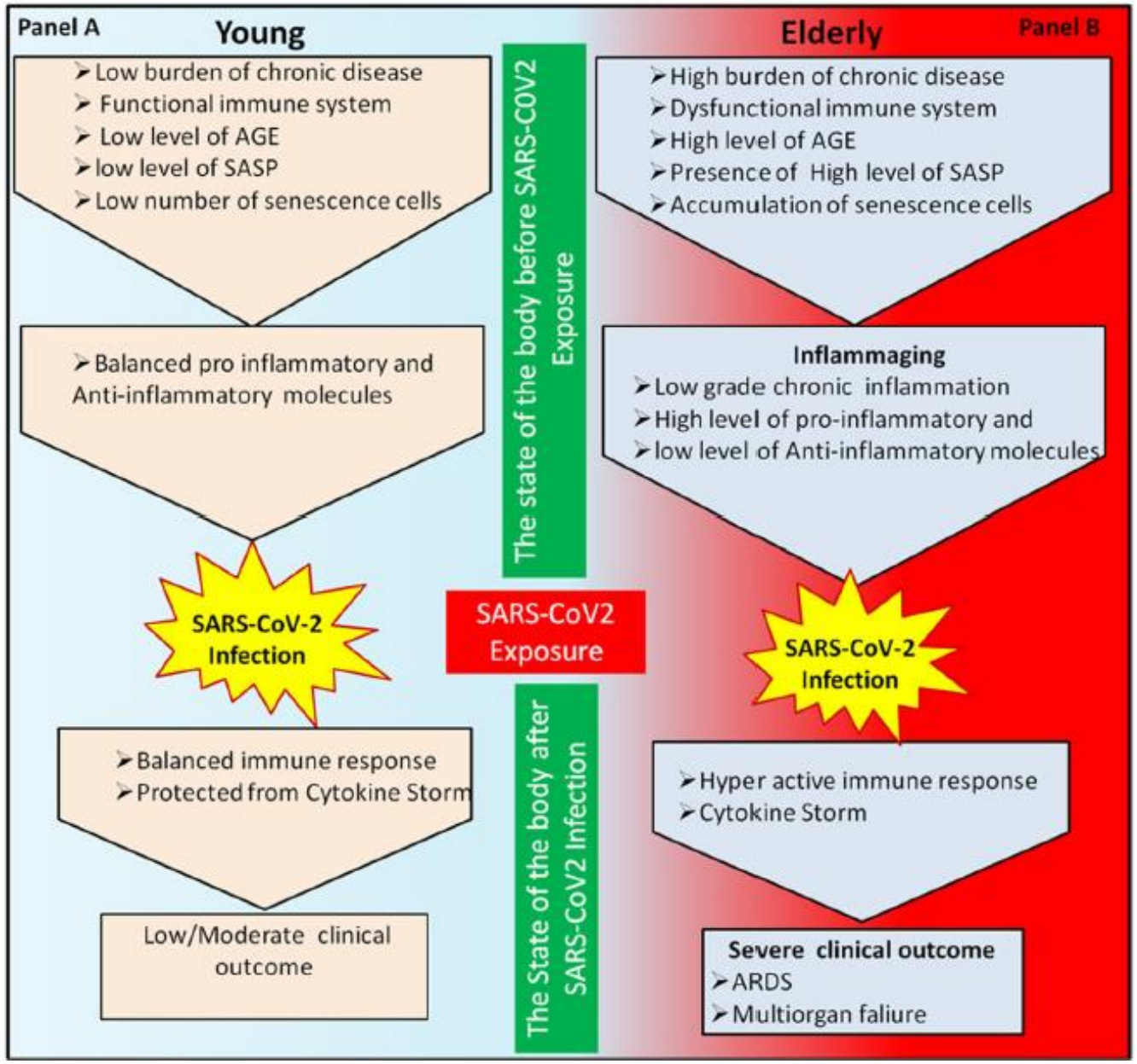
Age-related immune alterations in COVID-19



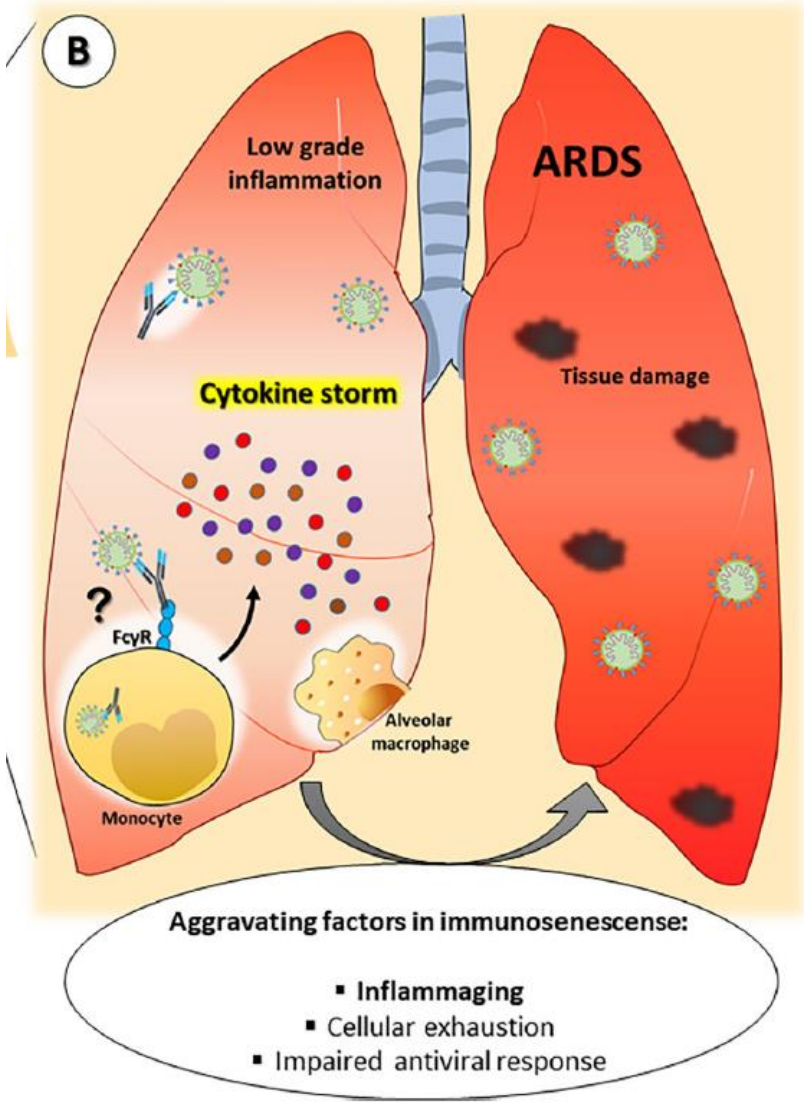
Aging may lead to modifications of both innate and adaptive immunity arms that induce a dysfunctional immune response against infections, which includes increased cytokines release, downregulation of APCs, T and B cell functions, upregulation of T-reg cells.

Elderly people are an at-risk group for a more aggressive organ damage and the development of secondary diseases.

Grifoni A et al. Frontiers in Immunology 2023
Doi: 10.3389/fimmu.2023.1146704



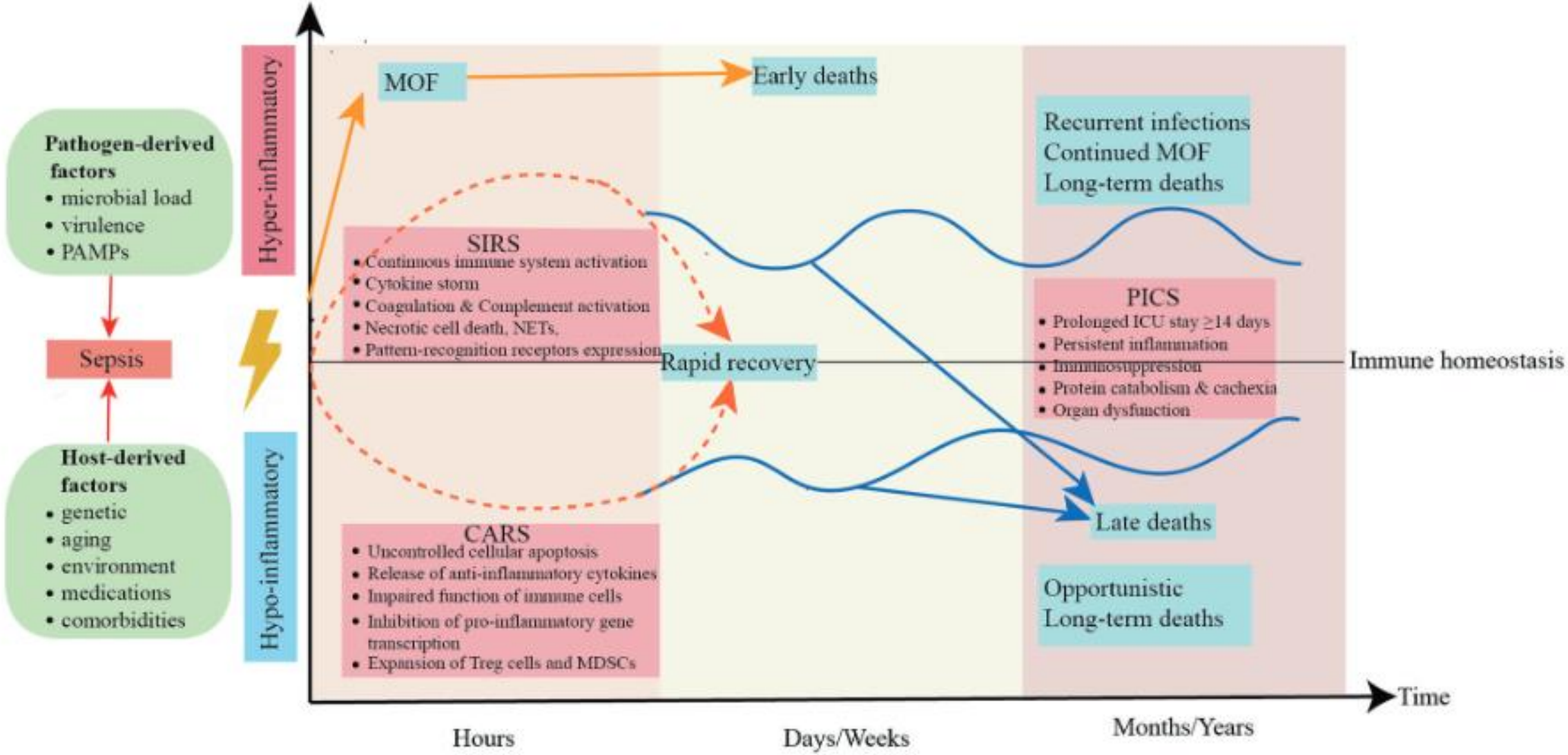
AGE: advanced glycation end-products, SASP: senescence associated secretory phenotype



Tizazu A et al. Immunity and Aging 2022
Doi: 10.1186/s12979-022-00309-5
Pietrobon A et al. Front Immunol 2020
Doi: 10.3389/fimmu.2020.579220

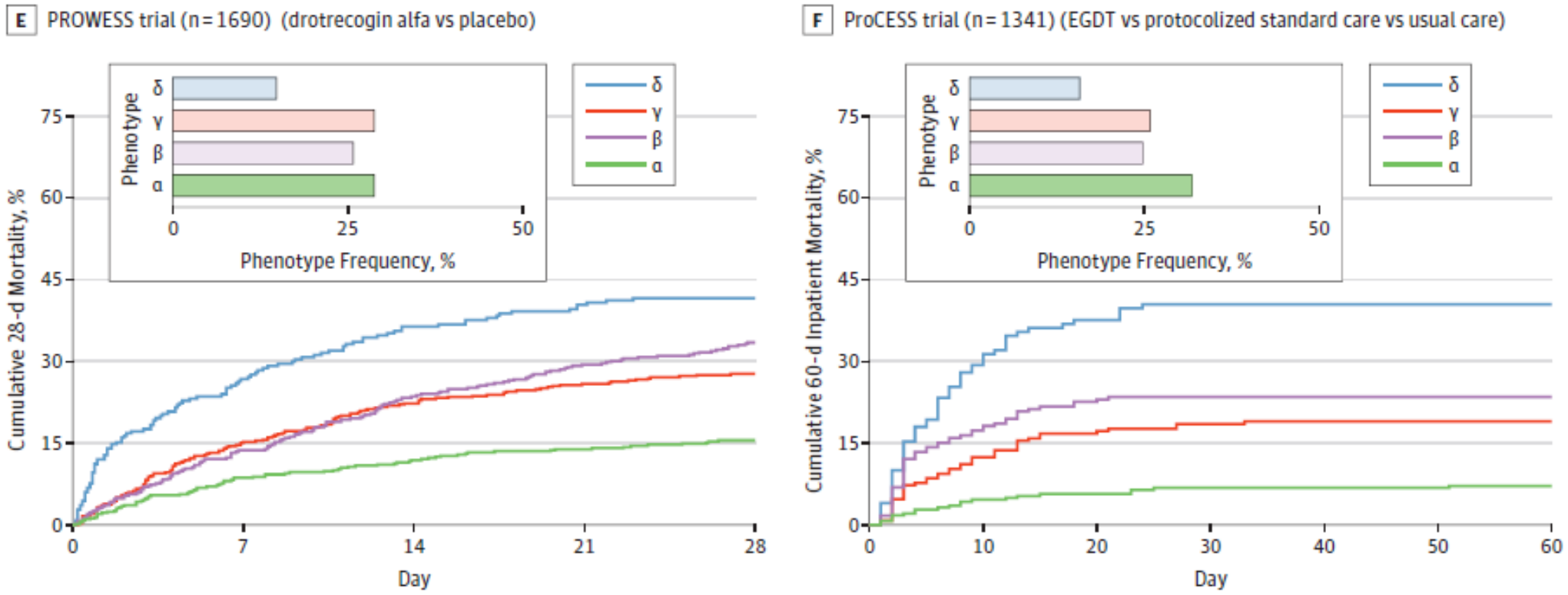
New challenges in sepsis treatment?

Host response to severe sepsis



Cao M et al. Cell Death Discov 2023
Doi: 10.1038/s41420-023-01766-7

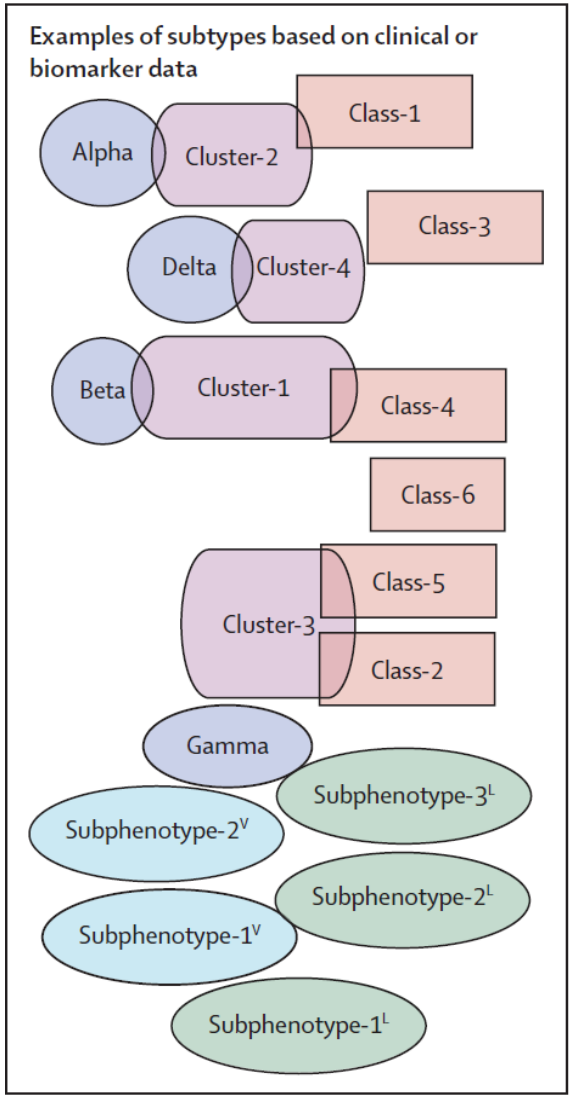
Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis



In a retrospective analysis of data sets from patients with sepsis,
4 clinical phenotypes were identified that correlated with host-response patterns and clinical outcomes

Seymour C et al. JAMA 2019
Doi: 10.1001/jama.2019.5791

Examples of phenotypes based on clinical or biomarker data



Subtyping based on clinical or biomarker data

Cluster-1: shock with elevated creatinine
Cluster-2: minimal MODS
Cluster-3: shock with hypoxaemia and altered mental state
Cluster-4: hepatic dysfunction

Alpha: few abnormal laboratory values, few markers of organ dysfunction
Beta: older age, more comorbidities, and higher renal dysfunction
Gamma: more inflammation with pulmonary dysfunction
Delta: liver dysfunction with septic shock

Class-1: uncomplicated septic shock with few markers of organ dysfunction
Class-2: pneumonia with ARDS requiring mechanical ventilation with few other markers of organ dysfunction
Class-3: postoperative abdominal sepsis in patients with older age and relatively low SOFA scores
Class-4: severe septic shock with high severity scores, high positive blood culture, high lactate levels, and low platelet concentrations
Class-5: pneumonia with ARDS and MODS, similar to class-2 but with higher SOFA scores and more nosocomial infections
Class-6: late septic shock (eg, increased time between ICU admission and start of vasopressors for septic shock)

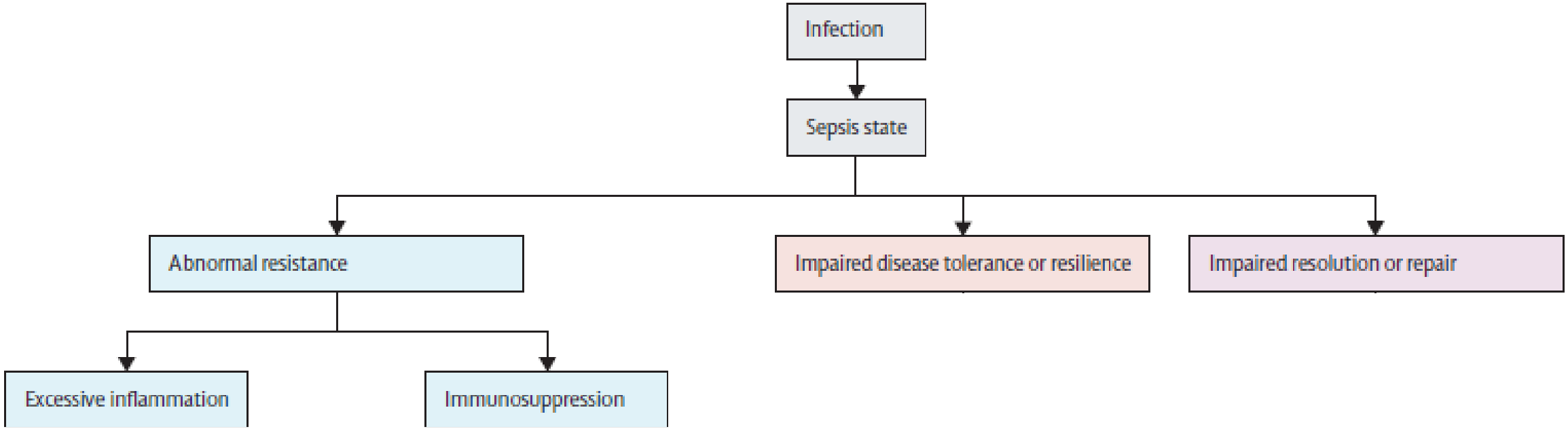
Subphenotype-1^{V}: reference subphenotype
Subphenotype-2^{V}: higher levels of inflammation, endothelial injury, and mortality

Subphenotype-1^{L}: reference subphenotype
Subphenotype-2^{L}: intermediate
Subphenotype-3^{L}: highest levels of inflammation, endothelial injury, and mortality

Shankar-Hari M et al. Lancet Respir Med 2024
Doi: 10.1016/s2213-2600(23)00468-x

Part 4. Impact in clinical practice and perspectives

Reframing sepsis immunobiology for translation: towards informative subtyping and targeted immunomodulatory therapies



Shankar-Hari M et al. Lancet Respir Med 2024
Doi: 10.1016/s2213-2600(23)00468-x

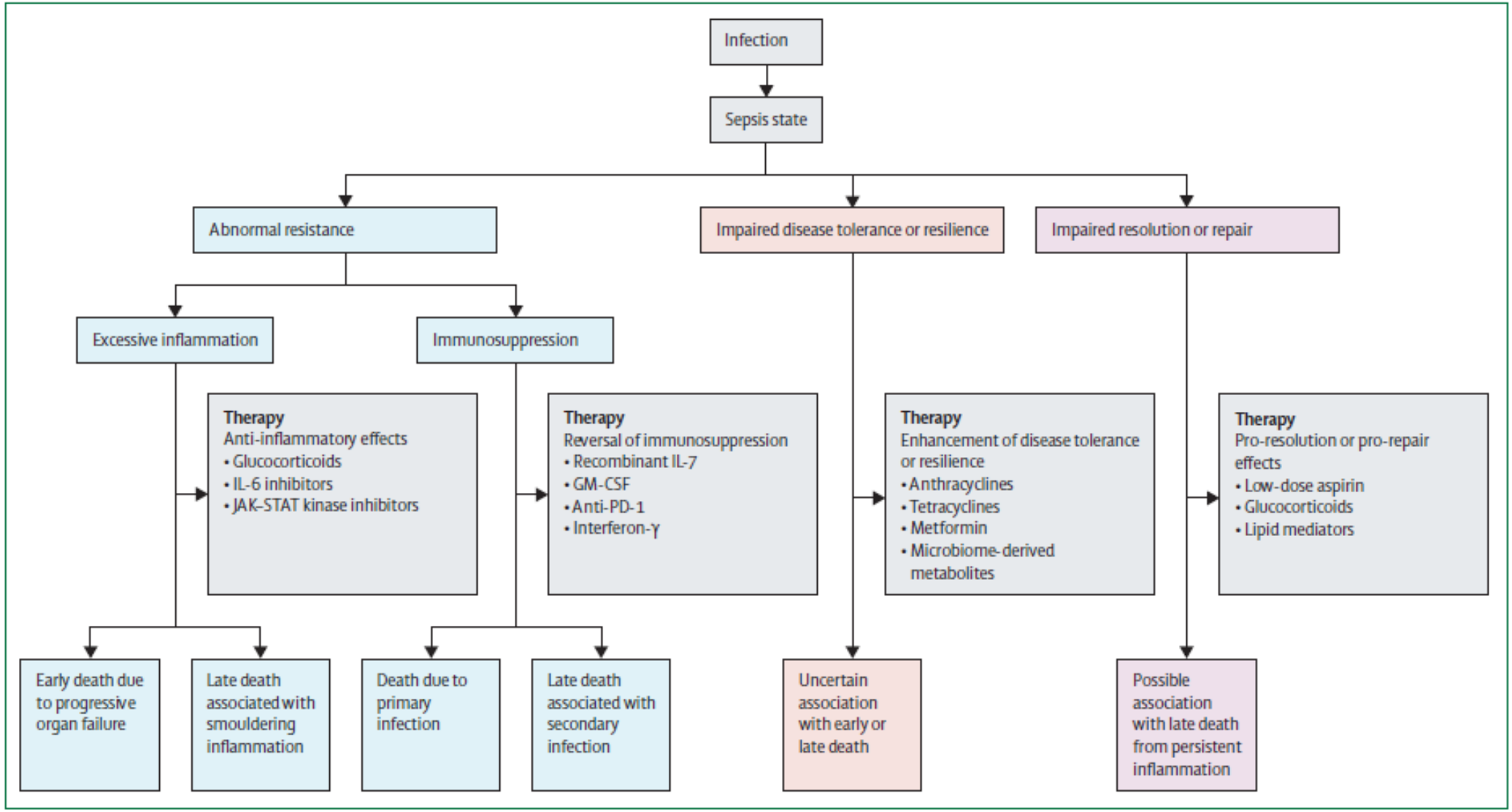
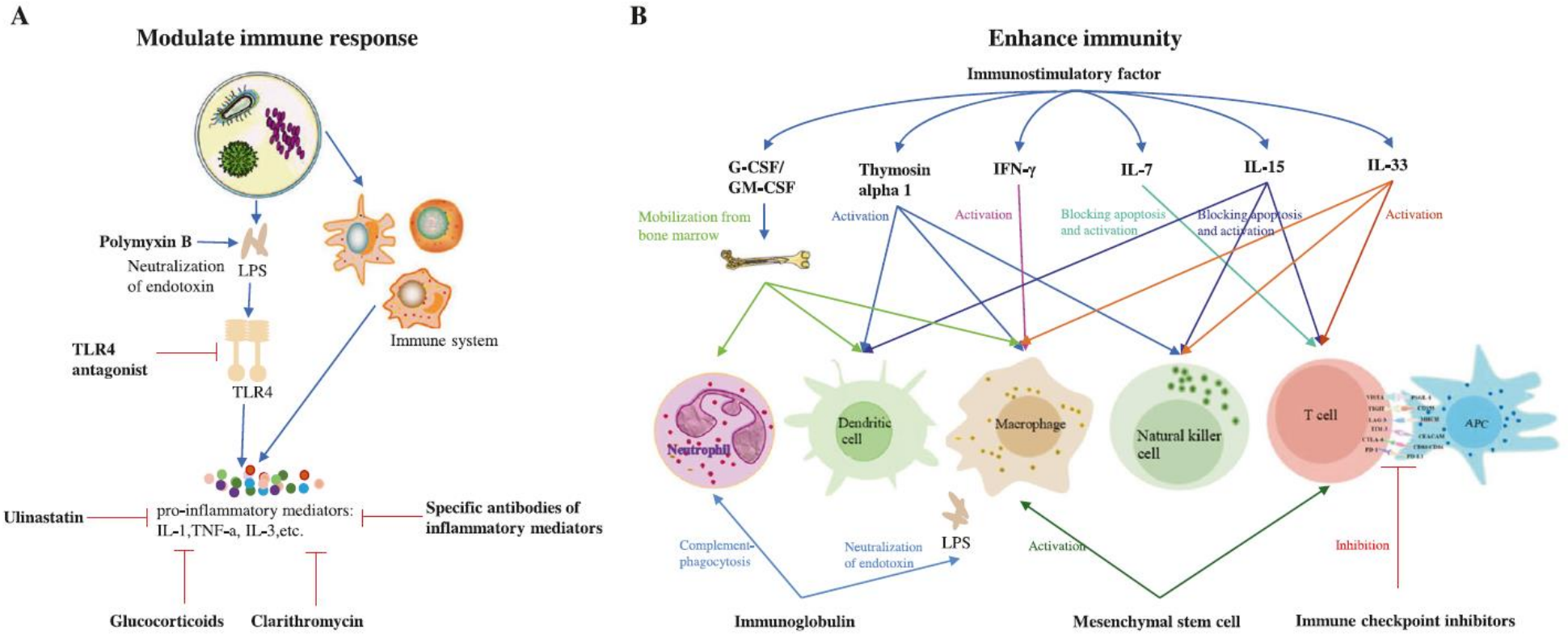


***Figure 3*: Reframing of dysregulated immune responses in sepsis to inform potential treatments**

The degree of immunopathology in sepsis is related to the magnitude and duration of abnormalities in resistance, disease tolerance, resilience, resolution, and repair mechanisms. If future studies could identify patients with one or more dominant mechanisms that explain the sepsis state, then these mechanisms could be targeted with specific treatments in clinical trials. The proposed treatments are examples and do not represent an exhaustive list. A patient might require more than one treatment based on their dominant mechanism(s). These dominant mechanisms might vary over time when assessed with longitudinal sampling. The dominant mechanism could also differ between blood and one or more tissue compartments and is likely to vary by sepsis subtype. GM-CSF=granulocyte-macrophage colony-stimulating factor. IL=interleukin. JAK=Janus kinase. PD-1=programmed cell death 1. STAT=signal transducer and activator of transcription.

Shankar-Hari M et al. Lancet Respir Med 2024

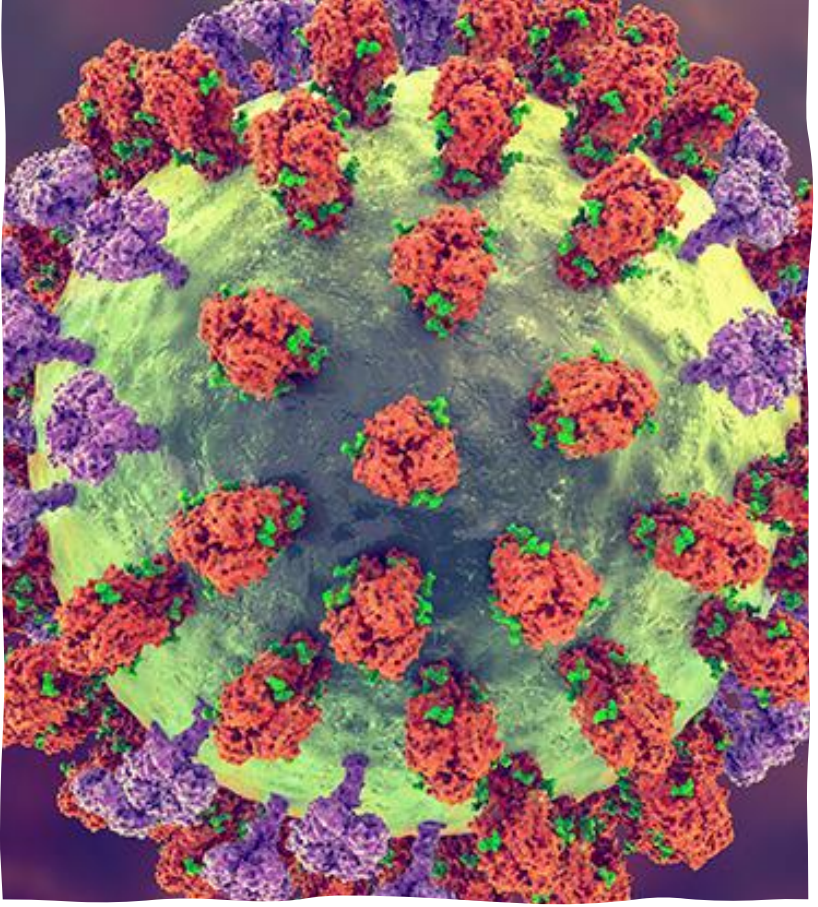
Potential immunotherapy for patients with sepsis: the importance of an individualized therapy

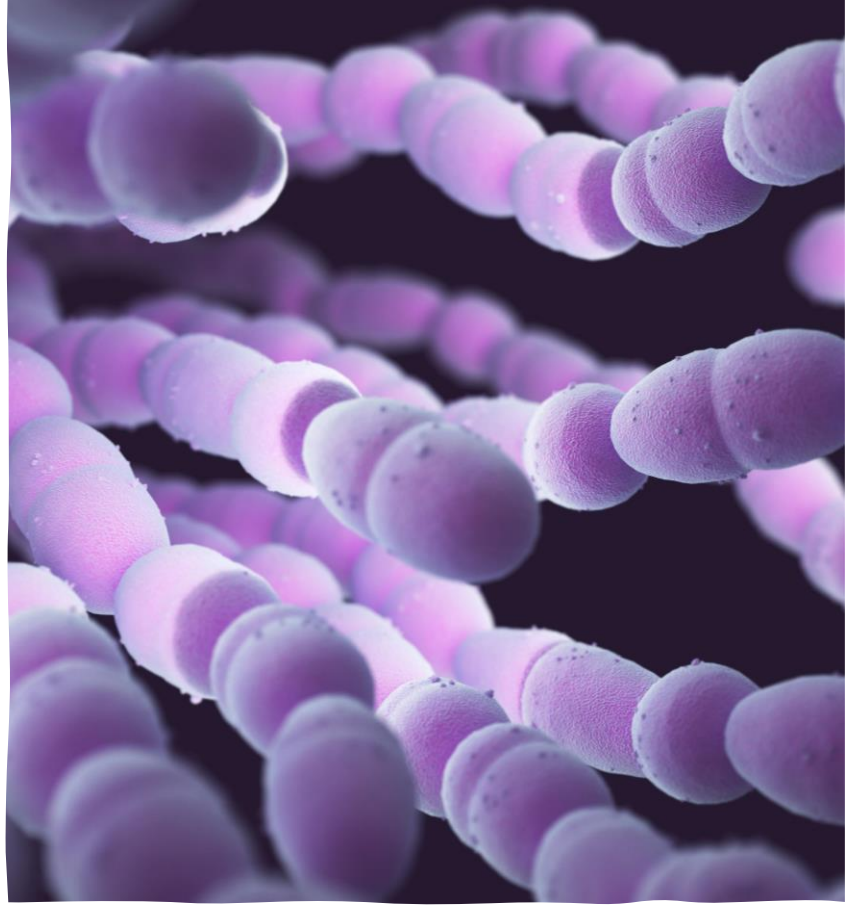


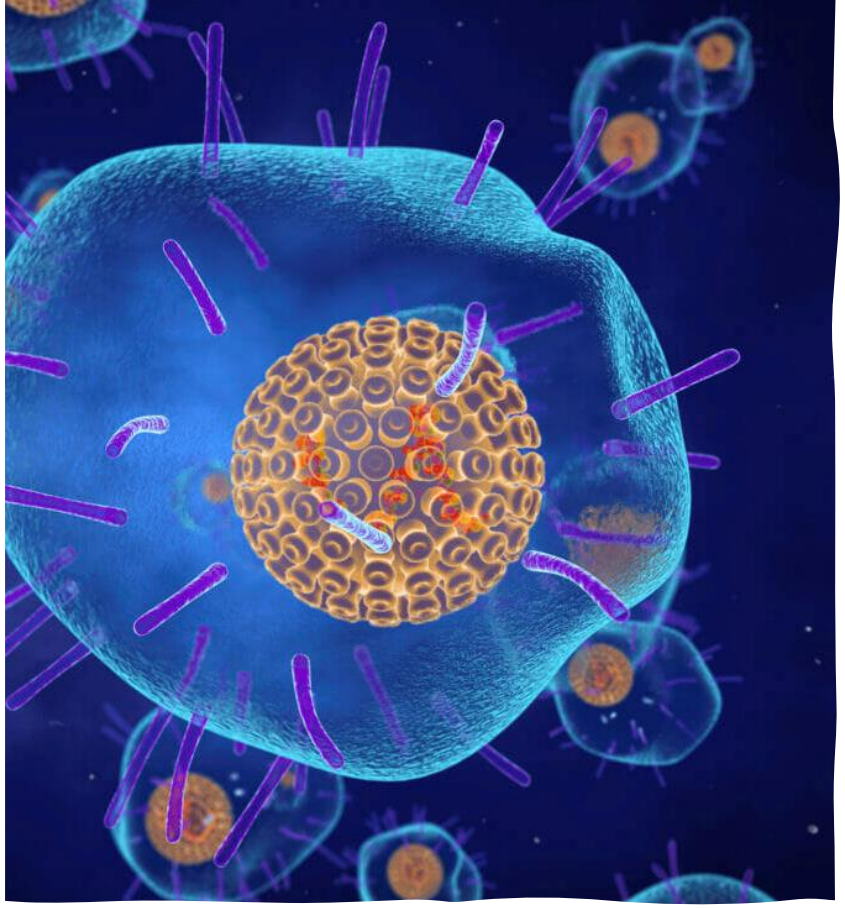
LPS: lipopolysaccharide, TLR4: toll-like receptor 4, G-CSF: granulocyte colony-stimulating factor, GM-CSF: granulocyte marcophage colony-stimulating factor, APC: antigen-presenting cell

Cao M et al. Cell Death Discov 2023
Doi: 10.1038/s41420-023-01766-7

What about elderly people?

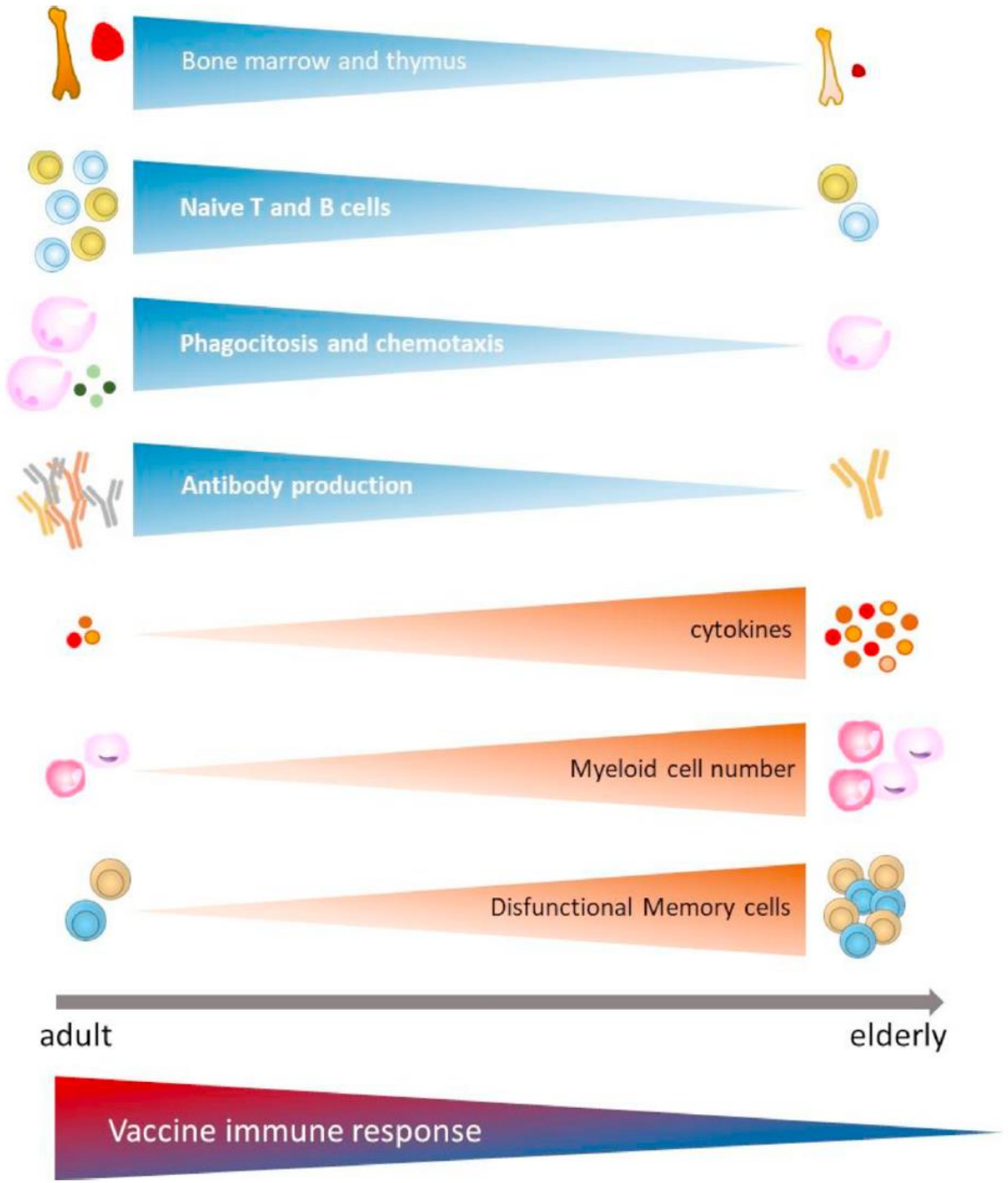






Influenza, *Streptococcus pneumoniae* and reactivation of varicella zoster virus : significant morbidity and mortality in old people

They are preventable diseases!!!



Ciabattini A et al.
Seminars in Immunology 2018
Doi: 10.1016/j.smim.2018.10.010

Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults

Table 2. Vaccine Efficacy against the First or Only Episode of Herpes Zoster Infection.*

Cohort and Age Group	HZ/su Group				Placebo Group				Vaccine Efficacy†
	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period ‡	Rate of Herpes Zoster	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period‡	Rate of Herpes Zoster	
			person-yr	*no./1000 person-yr*			*person-yr*	*no./1000 person-yr*	*% (95% CI)*
Modified vaccinated cohort									
All participants in cohort	7344	6	23,297.0	0.3	7415	210	23,170.5	9.1	97.2 (93.7–99.0)
50–59 yr	3492	3	11,161.3	0.3	3525	87	11,134.7	7.8	96.6 (89.6–99.3)
60–69 yr	2141	2	7,007.9	0.3	2166	75	6,952.7	10.8	97.4 (90.1–99.7)
70 yr or older	1711	1	5,127.9	0.2	1724	48	5,083.0	9.4	97.9 (87.9–100.0)
Total vaccinated cohort									
All participants in cohort	7698	9	25,584.5	0.4	7713	235	25,359.9	9.3	96.2 (92.7–98.3)
50–59 yr	3645	3	12,244.9	0.2	3644	95	12,162.5	7.8	96.9 (90.6–99.4)
60–69 yr	2244	5	7,674.1	0.7	2246	83	7,581.8	10.9	94.1 (85.6–98.1)
70 yr or older	1809	1	5,665.5	0.2	1823	57	5,615.6	10.2	98.3 (89.9–100.0)

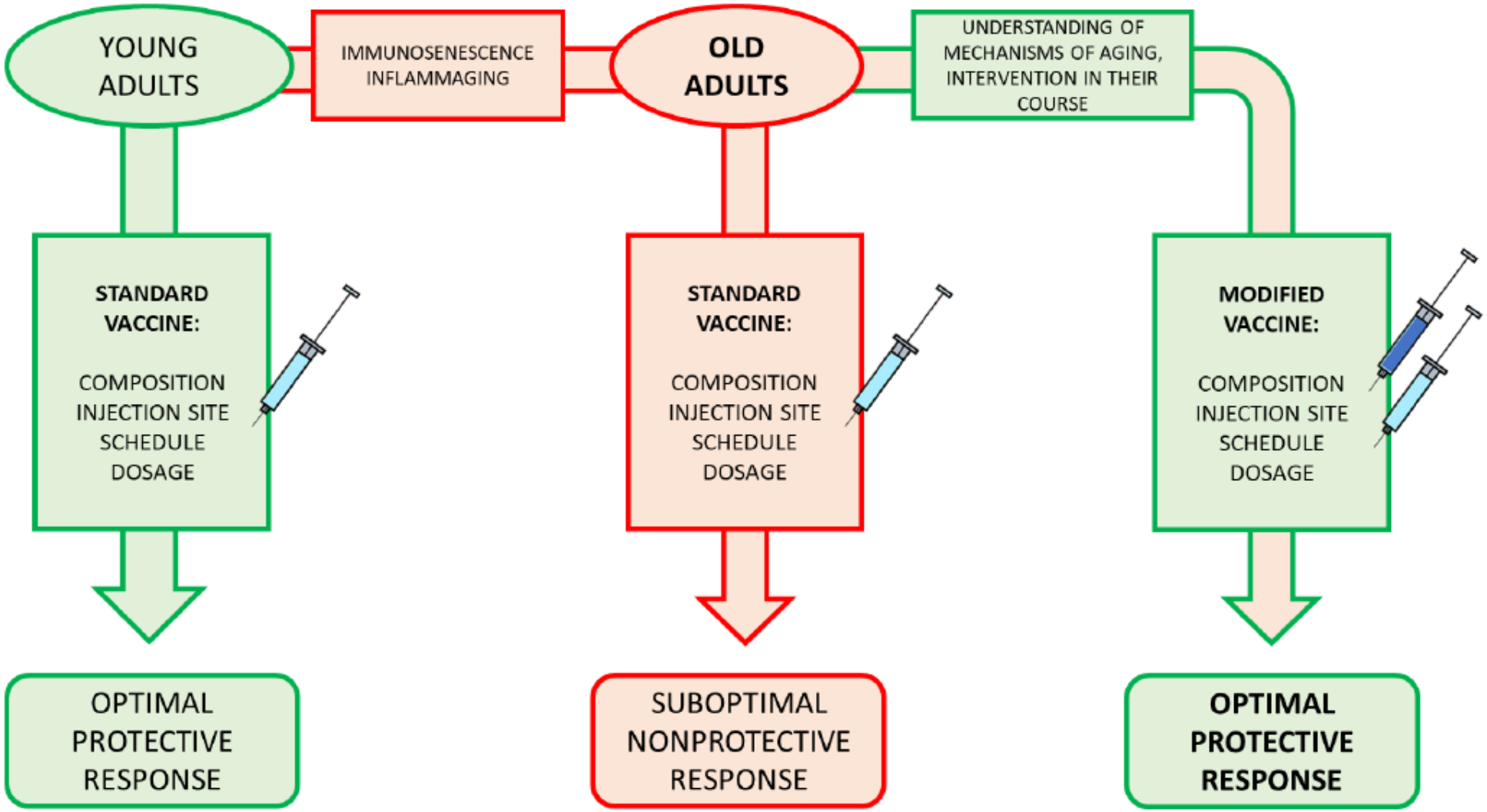
Vaccine efficacy was between 96.6% and 97.9% for all age groups

Both cell mediated and humoral immunity remained above prevaccination levels up to year 9 regardless of age

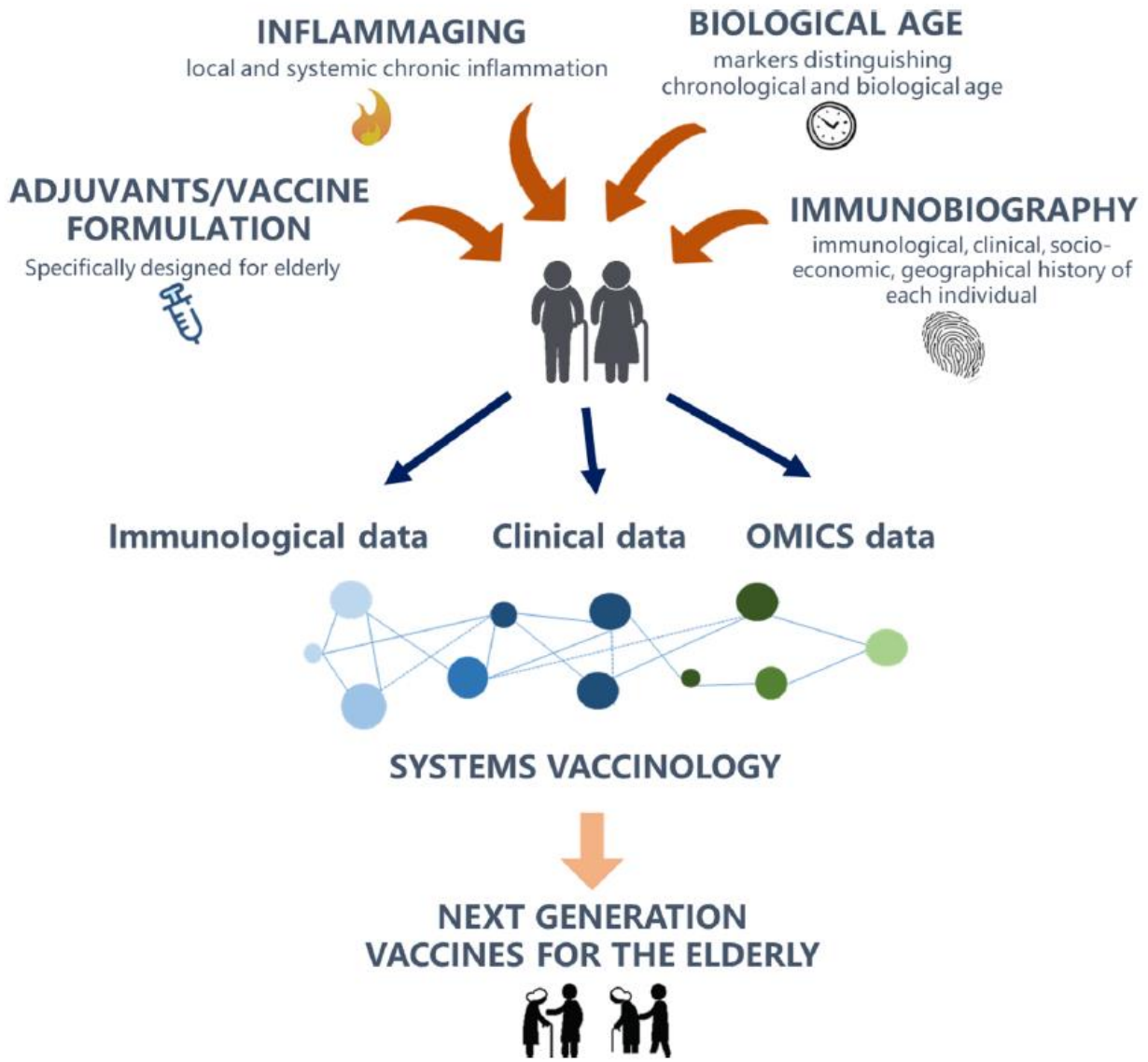
Lal H et al, doi: 10.1056/NEJMoa1501184
Schwarz TF et al, doi: 10.1080/21645515.2018.1442162

Review

Immunosenescence and Altered Vaccine Efficiency in Older Subjects: A Myth Difficult to Change



Fulop T et al. Vaccines 2022.
Doi: 10.3390/vaccines10040607



Ciabattini A et al.
Seminars in Immunology 2018
Doi: 10.1016/j.smim.2018.10.010

Dietary strategies currently being investigated in the context of immunosenescence

- Close connection between nutrition, intake of bioactive nutrients and supplements, immune function, and inflammation

  - > key role of dietary strategi[illegible]mune response and inflammatory status, AND possi[illegible]e rate of immunosenescence

- Under investigation:
  - Mediterranean diet
  - Caloric restriction or mimetics such as metformin (CAVE denutrition!)
  - Micronutrients: zinc, vitamins (E, C)
  - Symbiotics (combination of pro and prebiotics)
  - Nutraceuticals: Omega 3

Aiello A et al. Front Immunol 2019
Doi: 10.3389/fimmu.2019.02247

Therapeutic strategies currently being investigated in the context of immunosenescence

- Interleukin-7 as growth factor for naïve T cells
- Checkpoint inhibitors in impr during aging
- Drugs that inhibit mitogen-ac s and their interaction with nutrient signaling pathways
- Appropriate combinations of toll-like receptor agonists may enhance the efficacy of vaccination in older adults.

Aiello A et al. Front Immunol 2019
Doi: 10.3389/fimmu.2019.02247

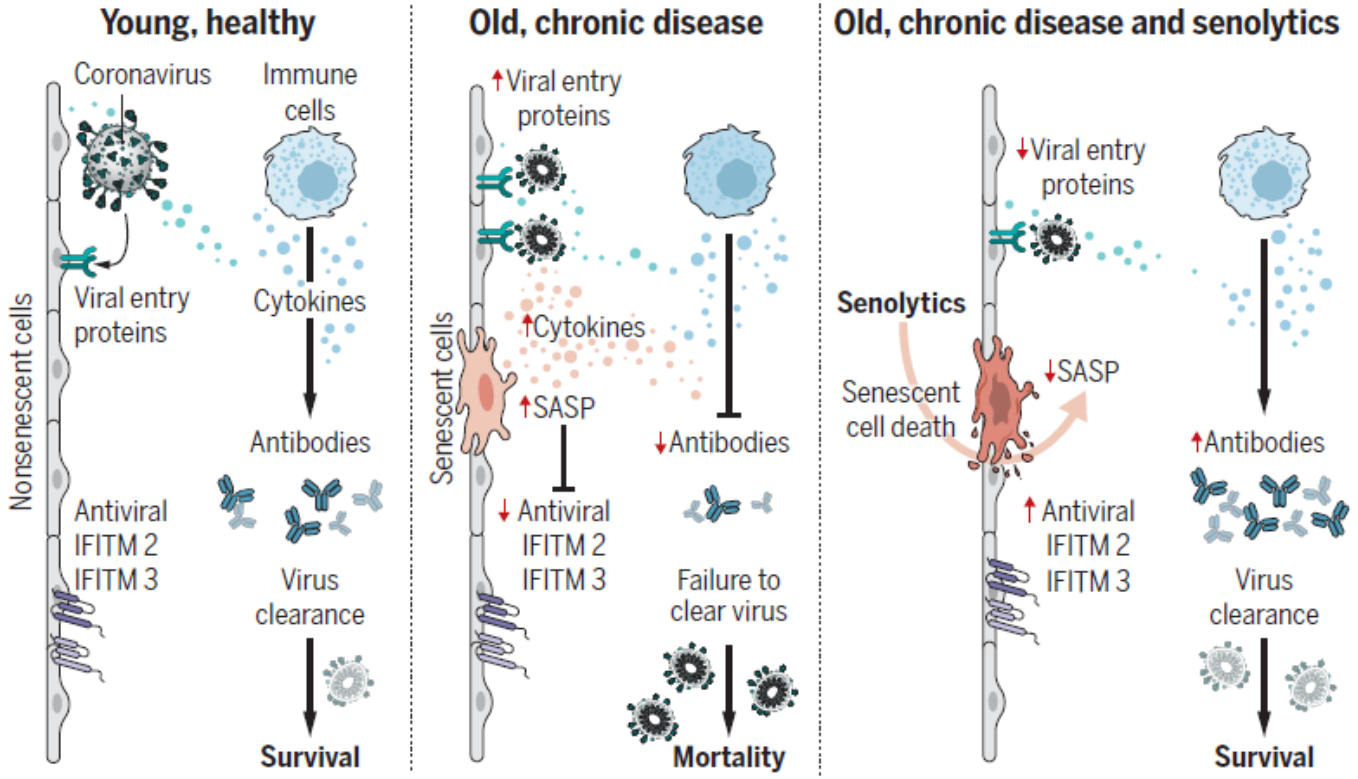
Immunosenescence and therapeutic interventions

- **Physical exercise and diet interventions** delayed the onset of frailty and improved vaccine response
- **Episodic exercise** showed to be a potential adjuvant to vaccination (Edwards and Booy, Hum Vaccin Immunother 2013. doi: 10.4161/hv.23365)
- **Reducing the senescent cell burden** and the inflammatory SASP by treatment with **senolytic compounds** improved the immune response and reduced mortality (Camell C et al, Science 2021. doi: 10.1126/science.abe4832)

RESEARCH ARTICLE SUMMARY

CORONAVIRUS

Senolytics reduce coronavirus-related mortality in old mice



SnCs that accumulate with age or chronic disease react to PAMPs such as SARS-CoV-2 S1 by amplifying the SASP, which increases viral entry protein expression and decreases viral defense IFITMs in normal cells. Old mice exposed to pathogens such as the β-coronavirus MHV have increased inflammation and higher mortality. Treatment with a senolytic decreased SnCs, inflammation, and mortality and increased the antiviral antibody response.

Camell C et al. Science 2021. doi: 10.1126/science.abe4832

Perspectives in sepsis

- The one-size-fits-all approach treatment plan is unlikely to be effective for sepsis in adults -> even more true in older patients
- The future in treating sepsis is to :
  - ➢ Make an early and personalized sepsis diagnostic, classifying patient's immune status in phenotypes
  - ➢ Develop a panel of biomarkers to target immunomodulatory interventions

Perspectives in older patients
The future is here!

- Screen for frailty and immunosenescence
- Vaccination
  - ➢Vaccinate older patients!
  - ➢Develop biomarkers to identify individuals likely to respond poorly to vaccines
  - ➢Develop better vaccines (new adjuvants, higher doses, different routes, schedule…)
- Investigate the efficacy of multimodal interventions jointly on frailty and immunosenescence including RTC studies on elderly population
- Promote healthy aging (physical exercise, healthy diet, immunization


merci
thank you
gracias
obrigado
danke
go raibh maith agat
спасибо
grazie
bedankt
sukriya
dakujem
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terima kasih
dank je
arigatô
ngiyabonga
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kia ora
ありがとう
мерси
grazzi
tanemirt
mersi
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dhanyavad
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bayarlalaa
děkuji
rahmat
tenki
chnorakaloutioun
enkosi



Childhood

Post-puberty and Adulthood

Old age

INNATE IMMUNITY

♂
- ↑ Inflammation
- ↑ NK cells
- ↑ Monocytes and Basophils

♀
- ↑ Inflammation, IL-6, IL-1β, IL-12, IL-8
- ↑ TLR4, phagocytic activity
- ↑ IFNγ killer DC, pDC INFα/β
- ↓ cytotoxic activity and chemotaxis

♂
- ↑ NK cells, Type 2 ILC count
- ↑ IL-10
- ↓ TLR4

♀
- ↑ IL-1β, IL-6, TNF-α, IL-10
- ↑ NK cells and cytotoxicity

♂
- ↑ IFNγ, IL-17, IL-15
- ↑ non-classical monocytes

ADAPTIVE IMMUNITY

♀
- ↑ CD4/CD8 ratio
- ↑ CD4 T cells
- ↓ CD8 T cells

♂
- ↑ IgA, IgM, IgE
- ↑ T_{reg} number

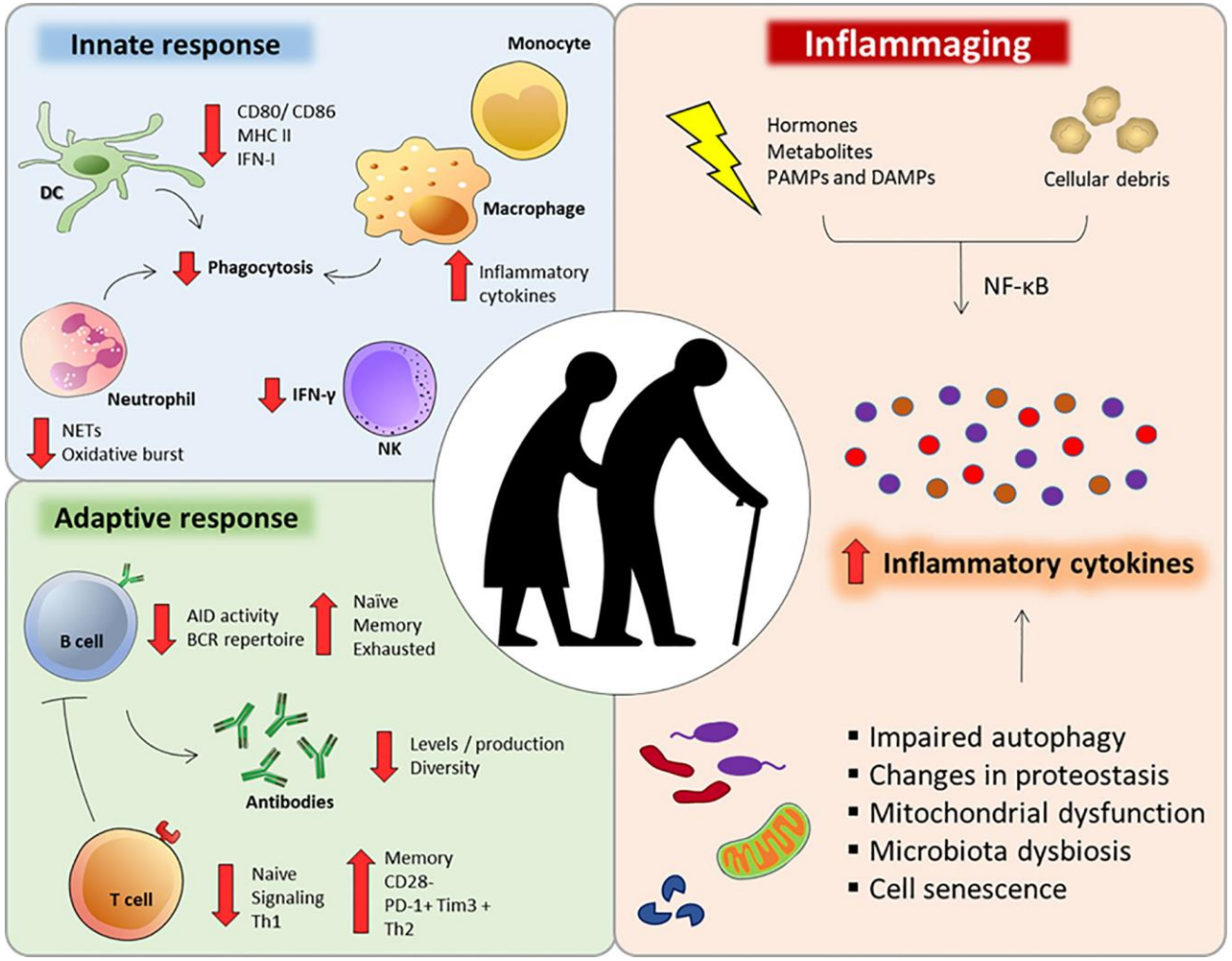
♀
- ↑ Antibodies, Ig class switch, somatic mutation
- ↑ CD4/CD8 ratio, CD4 T cells, Th2
- ↑ Th2 type cytokines
- ↑ B cells and autoreactive B cells
- ↑ T cell activation/proliferation
- ↓ apoptosis

♂
- ↑ T_{reg} cells, CD8 T cells and Th1
- ↑ apoptosis
- ↓ CD4/CD8 ratio
- ↓ autoreactive B cells

♀
- ↑ Inflammaging, IL-10
- ↑ CD4/CD8 ratio, CD4 cells
- ↑ antibodies

♂
- ↑ Inflammaging
- ↑ CD8 effector memory
- ↓ naive CD4 and B cells
- ↓ IFNγ and IL-17
- Faster immunosenescence

Major immunological alterations observed during immunosenescence, intensifying inflammaging



Pietrobon A, Immunosenescence and Inflammaging: Risk Factors of Severe COVID-19 in Older People, Front Immunol 2020

Healthy aging

- Centenarians show a complex and heterogeneous phenotype determined by an improved ability to adapt and remodel in response to harmful stimuli.
- This review aims to point out the intimate relationship between immunosenescence and inflammaging and how these processes impact unsuccessful aging rather than longevity.
- We also describe the **gut microbiota age-related changes as one of the significant triggers of inflammaging** and the sex/gender differences in the immune system of the elderly, contributing to the sex/gender disparity in terms of epidemiology, pathophysiology, symptoms and severity of age-related diseases.
- How these phenomena could influence the susceptibility to COVID-19 infection.

Santoro A, Ageing Research Reviews 2021
https://doi.org/10.1016/j.arr.2021.101422