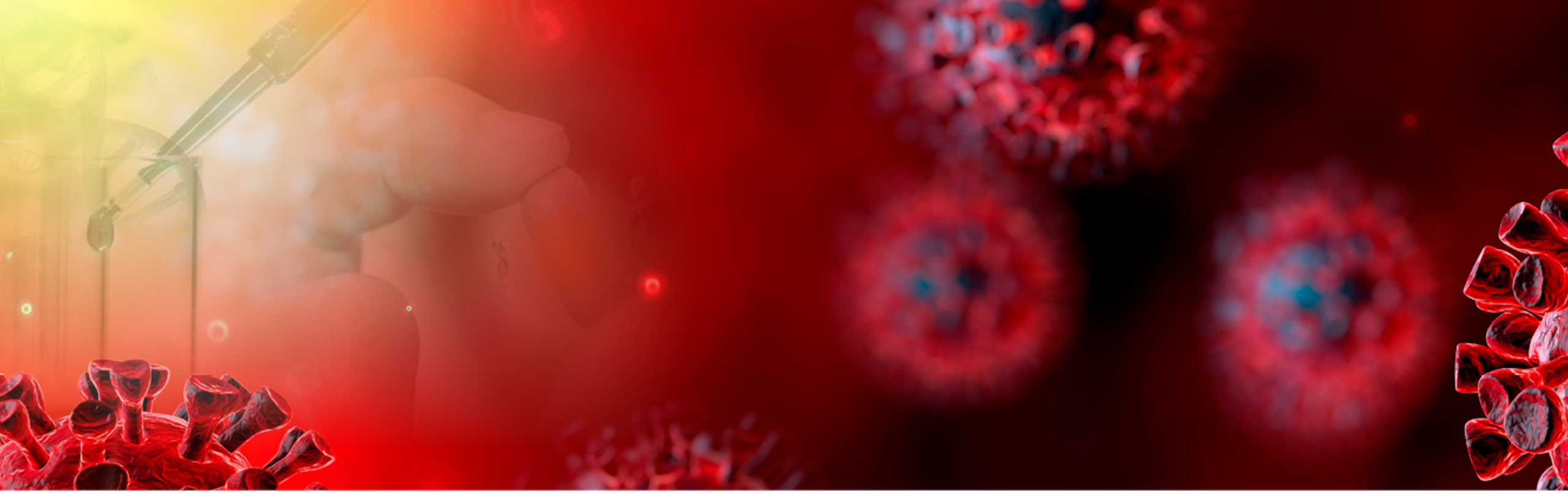

Presentation by George Kuchel, MD, FRCP, AGSF

WEBINAR: *COVID-19: Can the Science of Aging move us Forward?*

March 24,2020

afar american federation for aging research

Vulnerability of Older Adults to COVID-19:

Importance of frailty, biological aging and geroscience-guided therapies

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Vulnerability of Older Adults to COVID-19:

Importance of frailty, biological aging and geroscience-guided therapies

According to CDC highest Risk Populations for COVID-19 deaths include:

- Older adults
- All individuals (but especially older adults) with chronic diseases
- These may include heart and lung disease, diabetes and others
- Older men are at greater risk than older women
- What does this all mean?

Is date of birth (chronological aging) the best measure?

Frailty, chronic diseases, physiology, social factors and biology add essential clinical information

Acknowledgements to J McElhaney

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Vulnerability of Older Adults to COVID-19:

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Experience from influenza (flu) vaccination:

- All older adults should be vaccinated
- Older adults represent over 90% of all flu-related deaths in most years
- Vaccine is 80% effective in preventing flu-related hospitalization in non-frail older adults, yet it is less effective in those who are frail (Andrew MK *et al. J of Infectious Diseases* 2017)
- Declines in antibody and cell-mediated responses seen with aging (Nikolich-Zugich, *Nature Imm* 2018)
- These are augmented by frailty, chronic diseases, physiological aging (McElhaney *et al*, *Front Imm* 2016)

Potential lessons for COVID-19 and future pandemics involving novel pathogens:

- Inevitable delays in vaccine and drug development impact mostly the most vulnerable
- A geroscience-guided approach designed to target biological drivers shared by aging and common chronic conditions could improve clinical outcomes against varied novel pathogens long before pathogen-specific vaccines and drugs become available (J. Mannick)
- COVID-19 vaccine will most likely be less effective in older adults with chronic conditions

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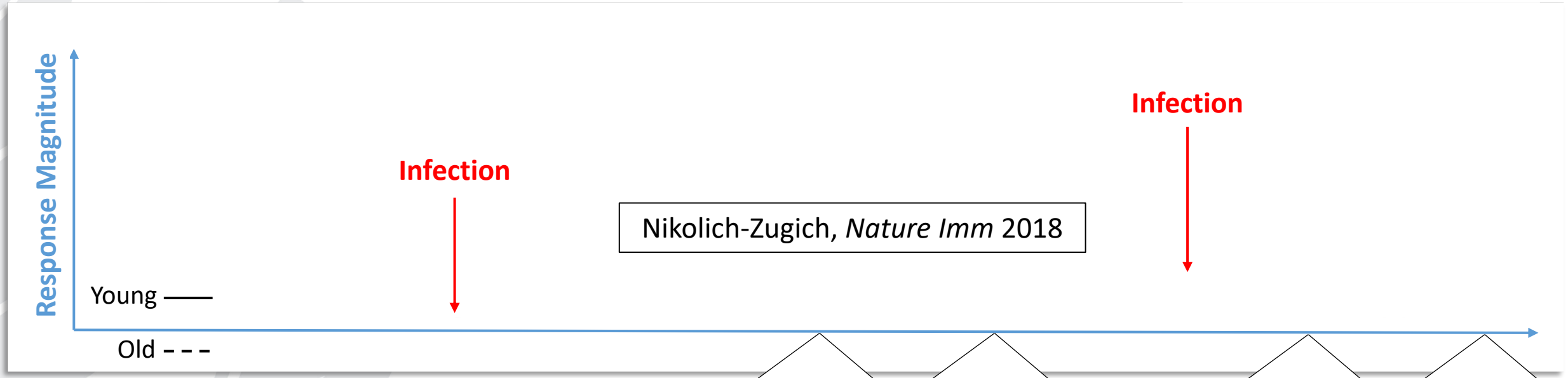
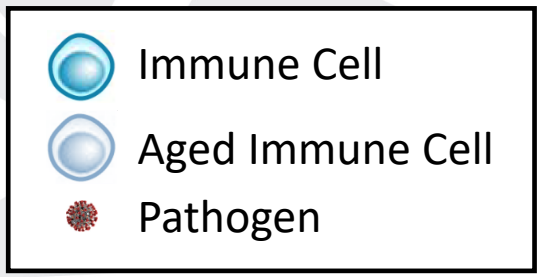
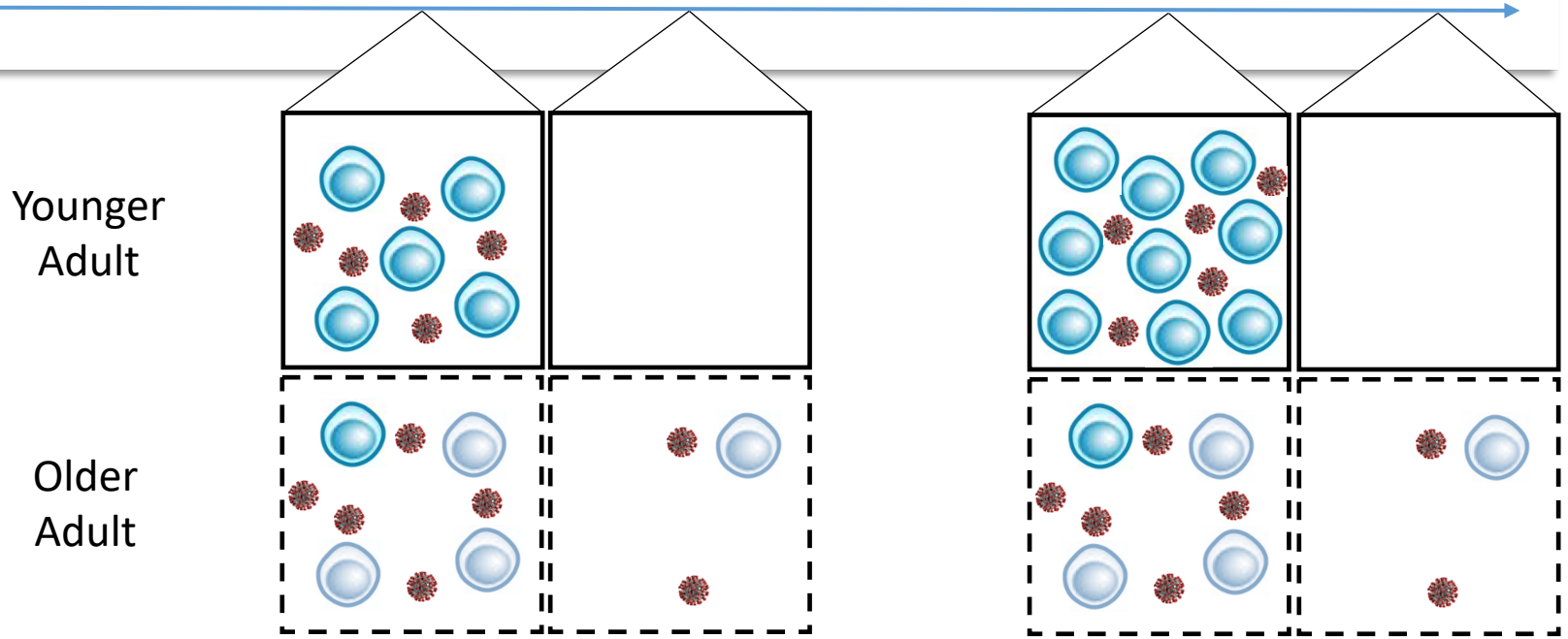
Vulnerability of Older Adults to COVID-19:

Impact of Immune Aging on Ability to Handle Familiar and Unfamiliar Pathogens



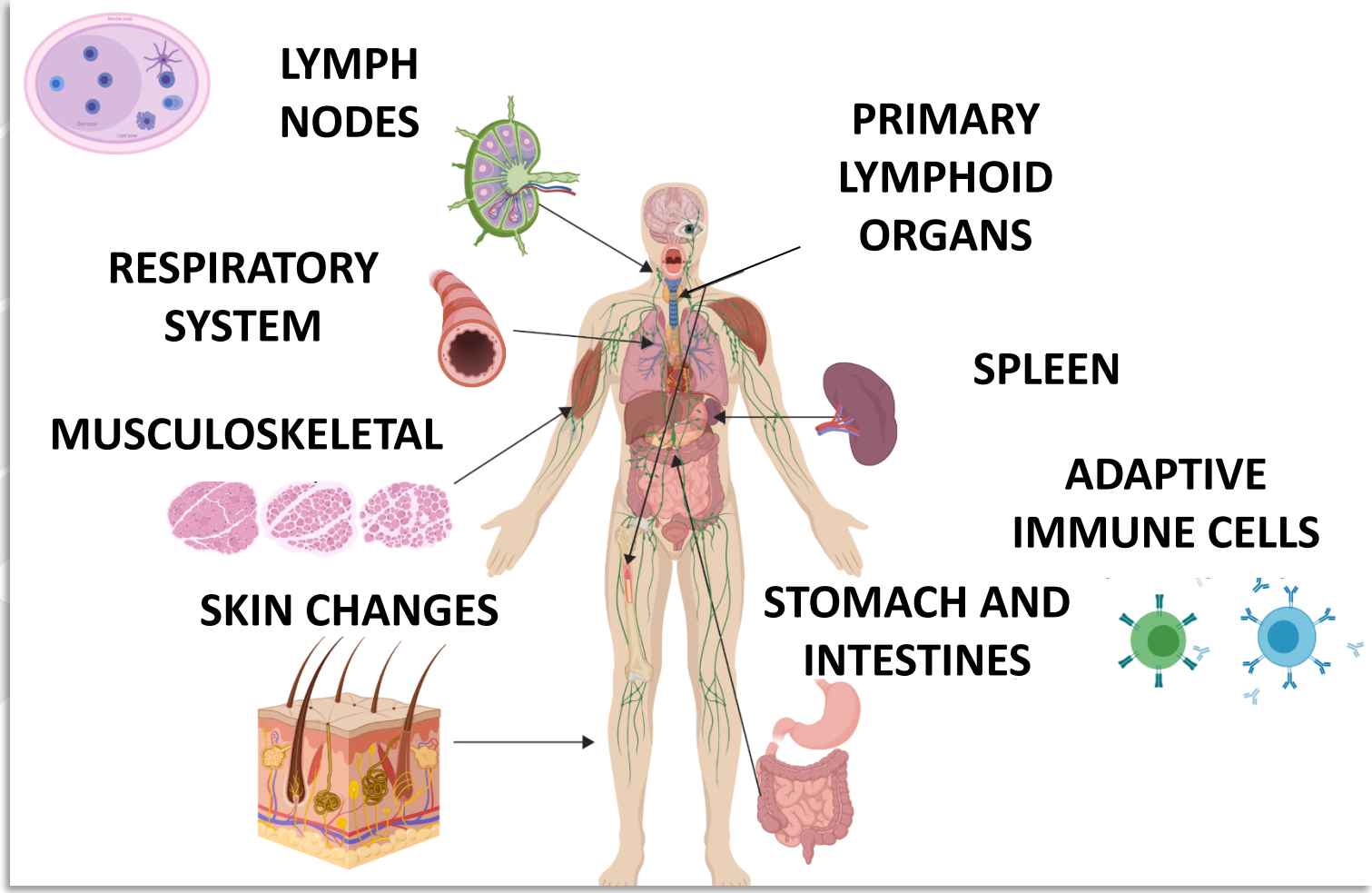
Acknowledgements to G Hargis & C Bonin





Vulnerability of Older Adults to COVID-19:

Nearly all aspects of immune response and host defense are impacted by aging



Acknowledgements to A Masters & S Keilich

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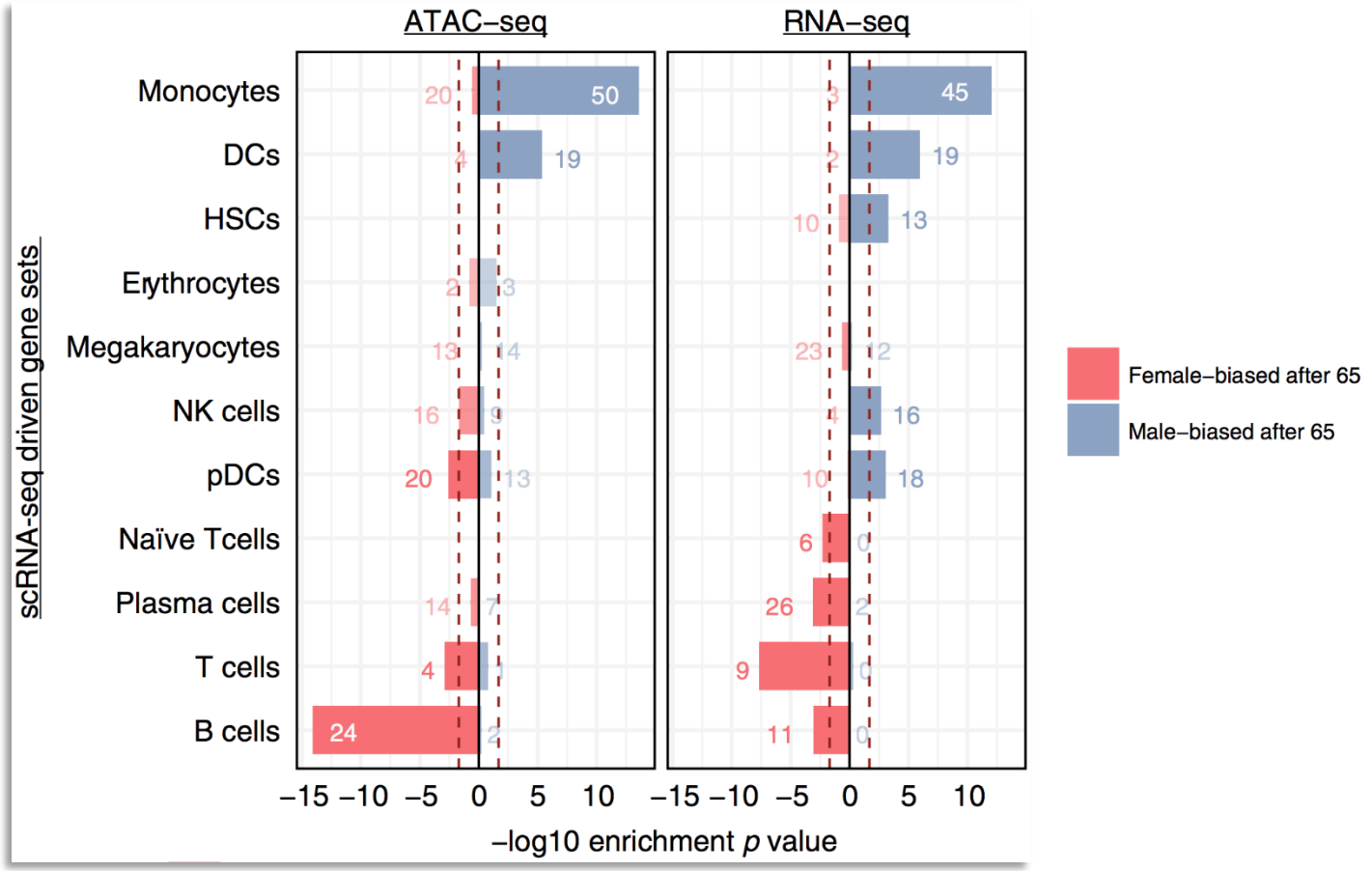
Vulnerability of Older Adults to COVID-19:

Older men have more innate cell activity (inflammation)
but less adaptive cell activity (T and B cell function) compared to older women



Marquez …Kuchel, Banchereau, Ucar *Nature Communications* Feb 6;11(1):751, 2020

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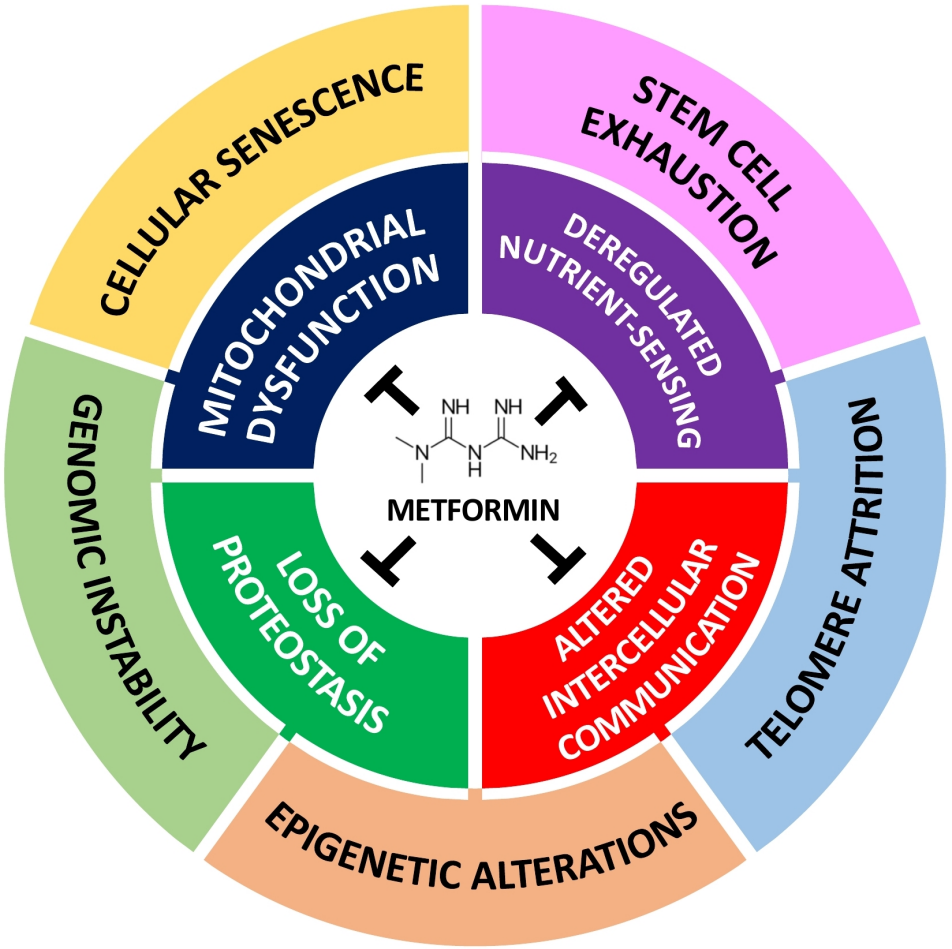
Vulnerability of Older Adults to COVID-19:

Metformin and Emergence of Geroscience-Guided Therapies



Kulkarni *et al Cell Metabolism* (In Press)

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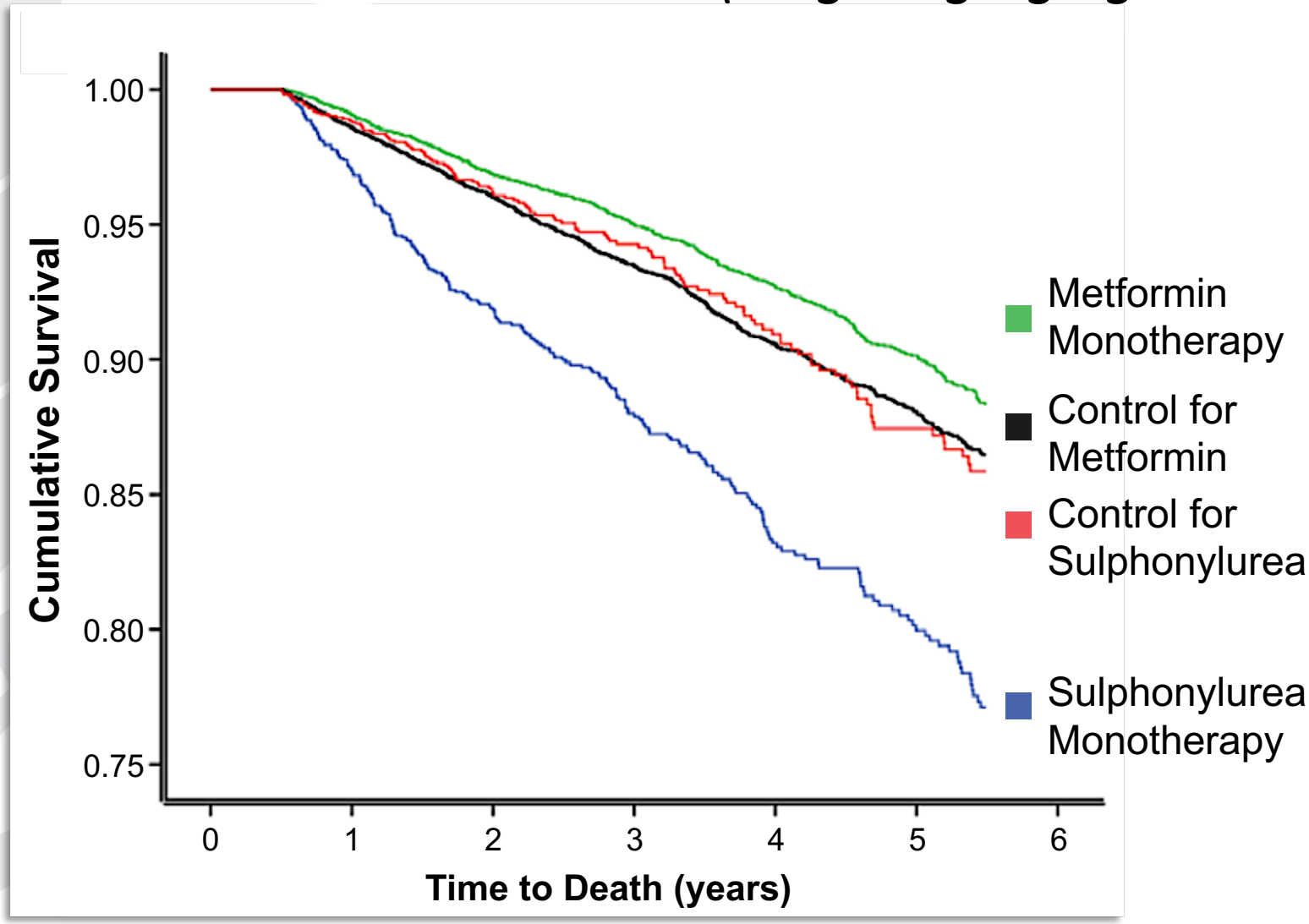
Vulnerability of Older Adults to COVID-19:

TAME Trial (Targeting Aging with Metformin)



Bannister et *al Diabetes, Obesity & Met* 2014.

- **Metformin extends health span and life span in animals**
- **It is a first-line, generic drug to treat diabetes**
- **>60 year experience and outstanding safety record**

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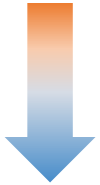
Vulnerability of Older Adults to COVID-19:

TAME Trial (Targeting Aging with Metformin)

Inclusion Criteria: Age 65-80, nondiabetic, some comorbidities allowed; n = 3,000

Double blind placebo-controlled trial



Primary Outcome: **TIME TO MAJOR DISEASES (FDA)**

Secondary Outcome: **FUNCTIONAL AGING**

Tertiary Outcomes: **BIOMARKERS (NIA)**

Impact of Metformin on Flu Vaccine Responses (VEME-AFAR/NIA, Jenna Bartley, PhD - UConn)

Gordon *et al.* A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing.

- Not yet peer-reviewed but posted on bioRxiv (3/22) https://www.biorxiv.org/content/10.1101/2020.03.22.002386v1
- AP-MS identification of 66 “druggable” human proteins or host factors targeted by 69 existing FDA-approved drugs, drugs in clinical trials and/or preclinical compounds. These include metformin and rapamycin.
- CAUTION!!..Mechanism?; Effects in cell infection assays?; Dose?; *In vivo* effects in animal models?; Human studies?

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