The Biology of Aging and Our Body's Readiness for COVID-19 Vaccines

How do we translate what we know from animal studies to improve vaccine responses in older adults?

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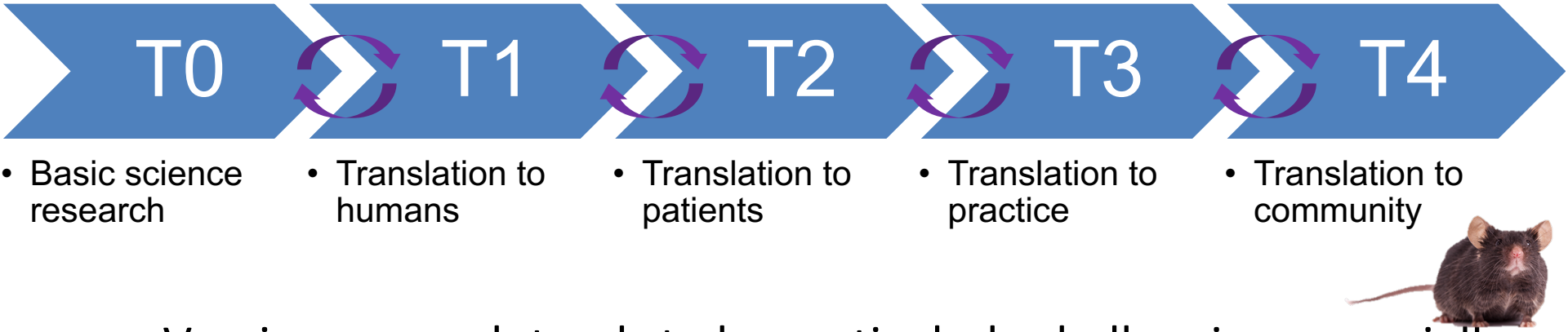
Challenges of Translational Studies

- The road from the **bench to the bedside** is not always straight forward



- Vaccine research tends to be particularly challenging, especially for novel pathogens that may not readily infect animal models
- This translational research is complicated with aging
  - Preclinical studies and early translational studies of vaccines are almost always tested in younger animals and people

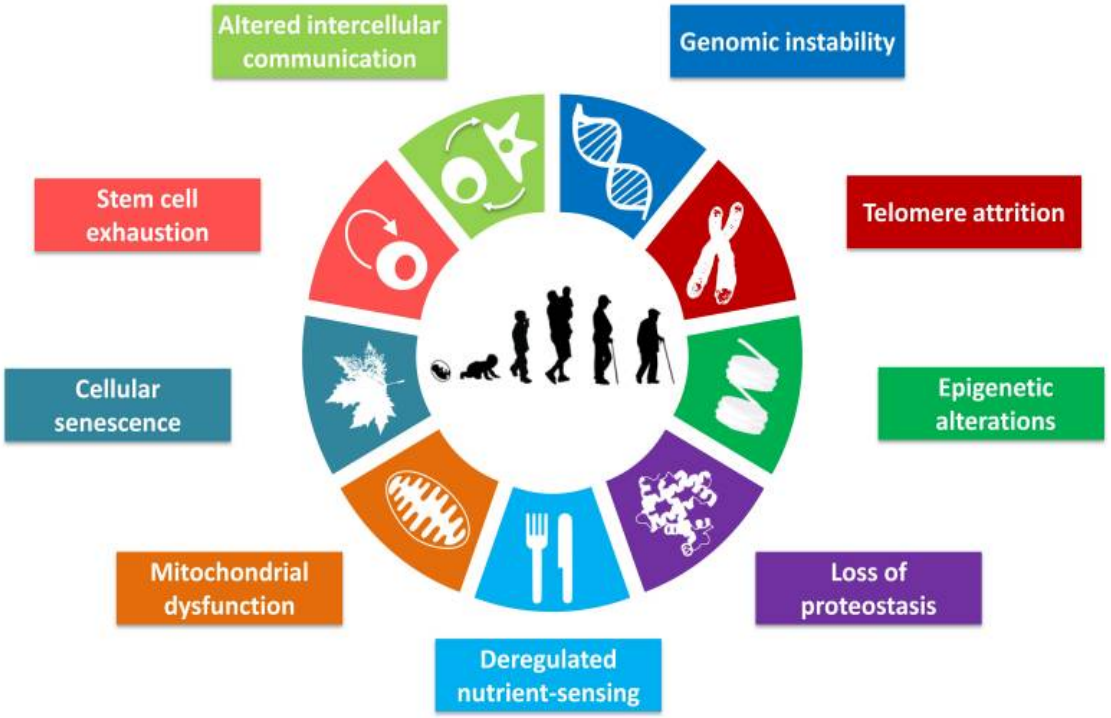
What do we know works in older adults?

- Experience from shingles vaccine
  - Improved adjuvanted recombinant vaccine (Shingrix) showed greater protection than the live attenuated vaccine (Zostavax)
- Experience from flu vaccine
  - Both the High-Dose flu vaccine (Fluzone HD) and Adjuvanted Flu Vaccine (Fluad- MF59 adjuvant) improve efficacy in older adults

We already have specific ways to improve immunogenicity of vaccines for older adults, but these methods require integration in vaccine development and may be different for different pathogens

Changing the paradigm: Geroscience-guided research

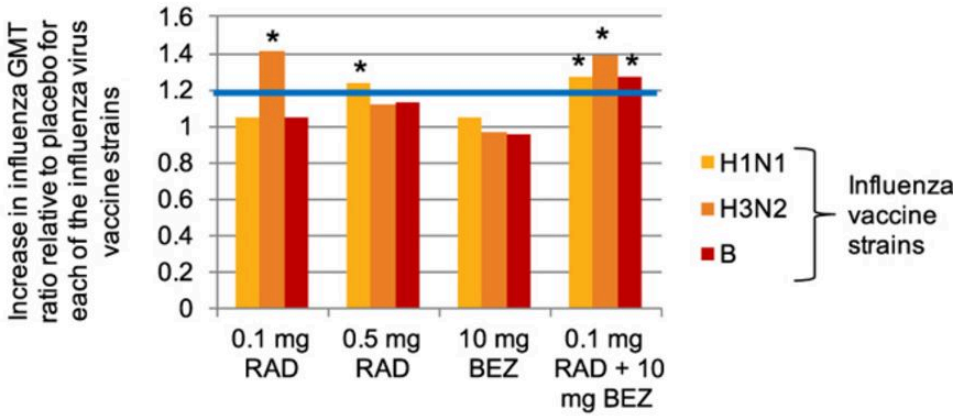
Rather than target specific deficits, geroscience approaches target biological drivers of aging, which may improve clinical outcomes against not only COVID, but a variety of pathogens

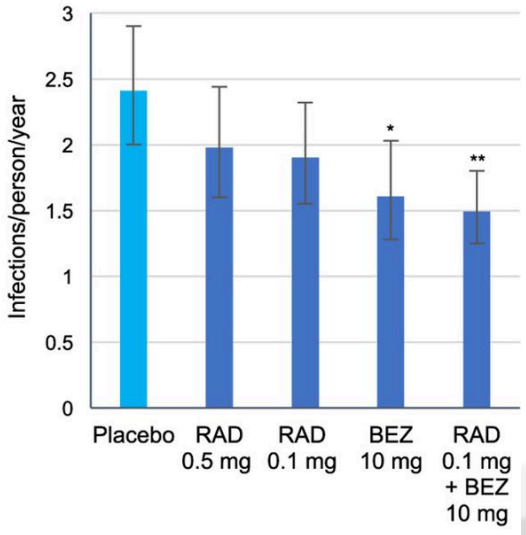


Otin et al. *Cell* 2013

There are completed and ongoing geroscience-guided clinical trials that show tremendous promise for vaccines

- Improved flu vaccine responses with mTORC1 inhibitor (RAD001 and BEZ235)
  - Improved post flu vaccine antibody titers
  - Decreased overall rate of infection in older adults for 1 year following treatment



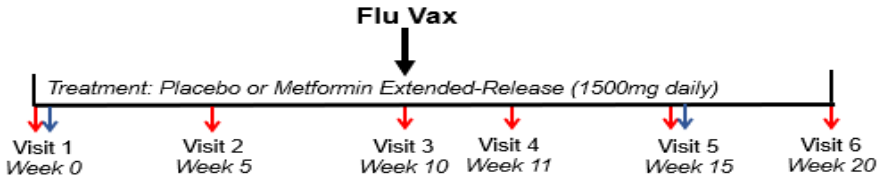


Mannick *Sci Trans Med* 2014
Mannick *Sci Trans Med* 2018

Metformin is also currently under investigation to improve vaccine responses in older adults

- Impact of metformin on Pneumococcal conjugate vaccine (PCV-13, Prevnar13) in older adults (NCT03713801)

- Impact of metformin on flu vaccine responses in older adults (NCT03996538)
  - Based on my preliminary studies showing altered T cell metabolism in aged mice
    - Metformin modulates metabolism among other targets and has been shown to improve CD8 T cell memory responses in young mice
  - Completed study visits right before COVID-19 shutdown
  - Analyses are still underway



These approaches may represent a gero-"adjuvant" that could be integrated into COVID-19 vaccination for older adults

Pearce *Nature* 2009
Diaz *Vaccine* 2017

What does this mean for a COVID-19 vaccine in older adults?

- ***Even though vaccine responses are reduced with aging, vaccination will still likely provide some level of protection for older adults***
- ***Geroscience approaches are promising to improve vaccine responses***
- ***In the mean time, while the COVID-19 vaccine is still under development, get your flu vaccine!***

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