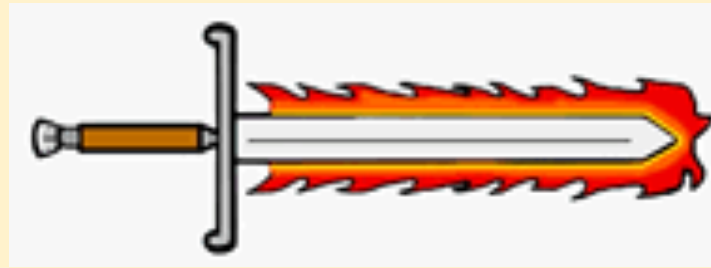


# Host heterogeneity in susceptibility to infectious & inflammatory diseases across the lifespan

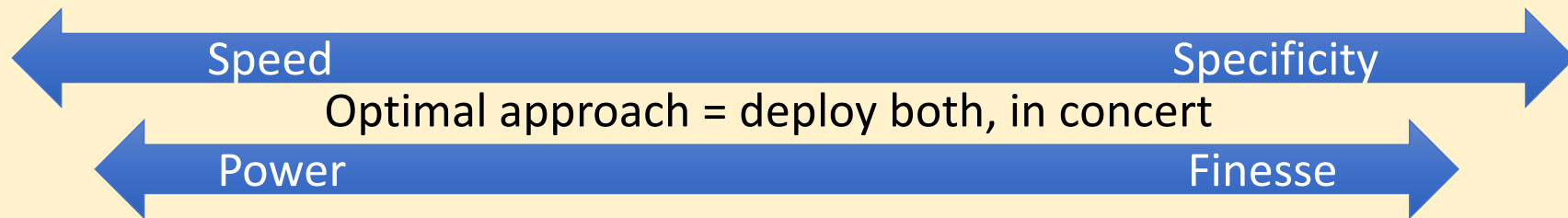
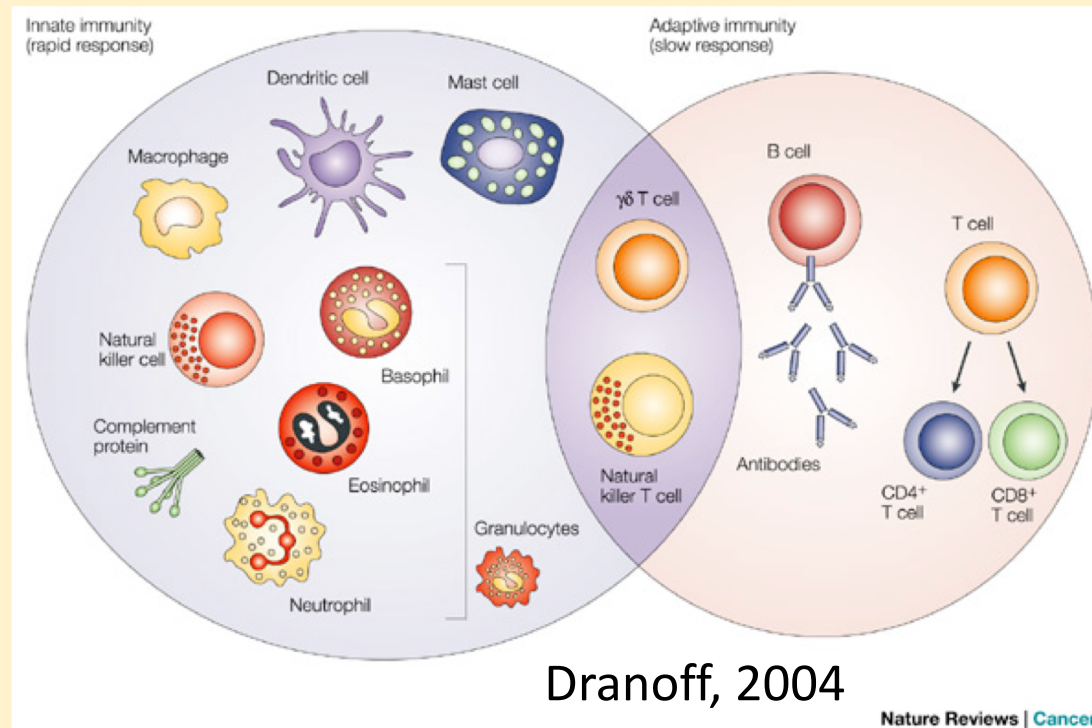


**Andrea L. Graham**

**Department of Ecology & Evolutionary Biology**



# Innate & adaptive immunity: distinctions are not so absolute as people once thought



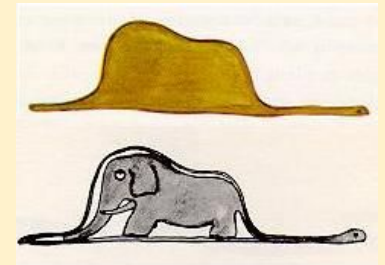
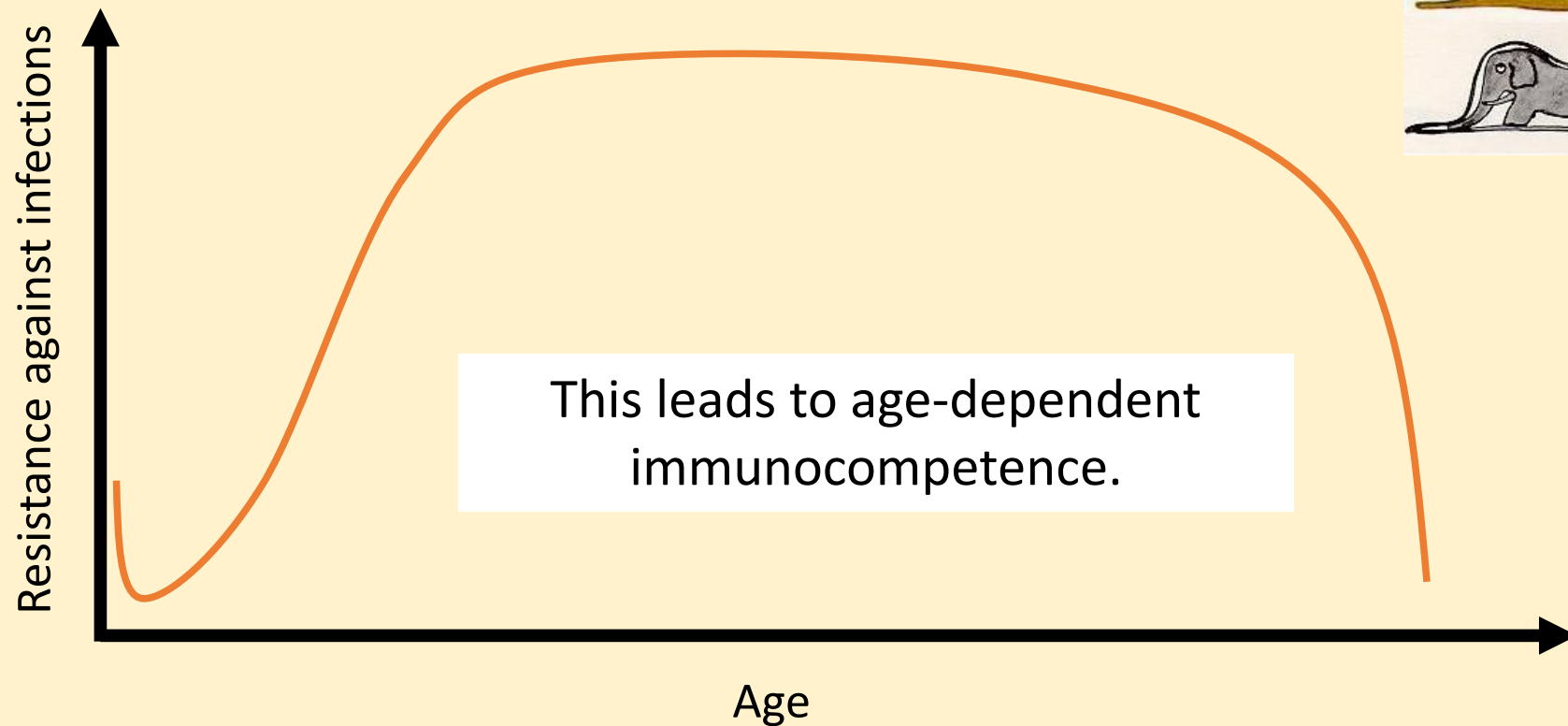
# Optimal mammalian immunology in a nutshell:

- “Clever clogs” adaptive immunity has long been appreciated.
- Innate immunity is increasingly admired.

## THE KEY IS COLLABORATION:

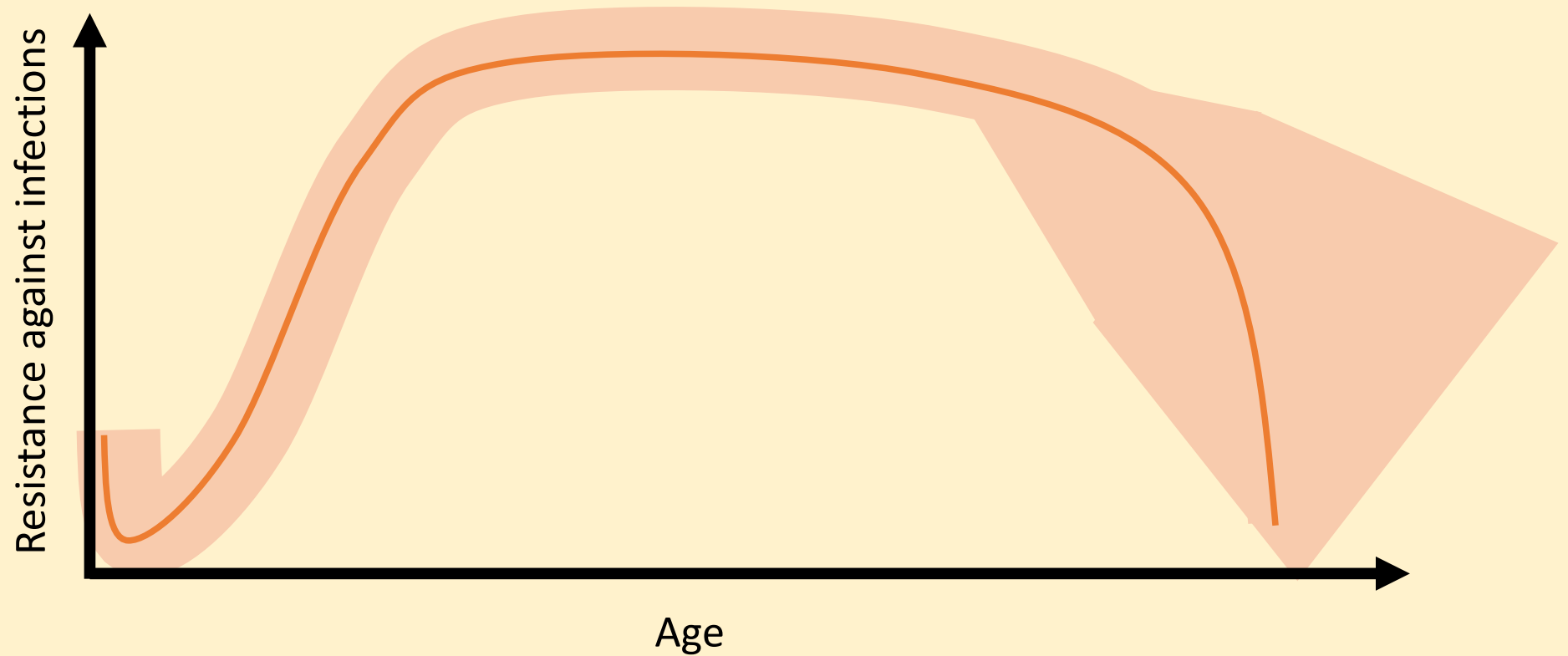
- Innate immune cells (during/via inflammation) instruct the adaptive.
- Adaptive immune cells rein in the damaging excesses of the innate.
  - Immunosuppression to a “Goldilocks optimum” (Germain 2001 Science)?
- Damage repair → disease tolerance &/or somatic maintenance

# Instruction & suppression are dynamic processes

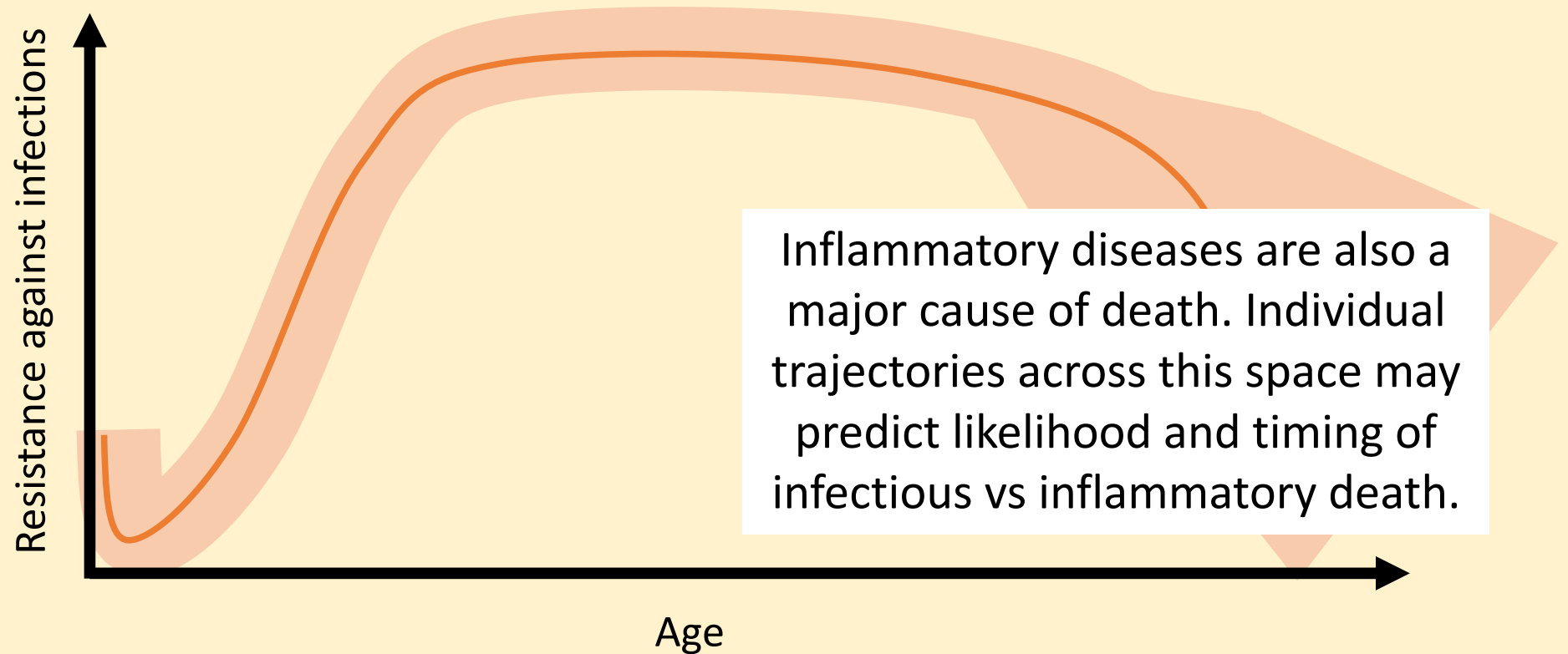




# Instruction & suppression are dynamic processes



# Instruction & suppression are dynamic processes

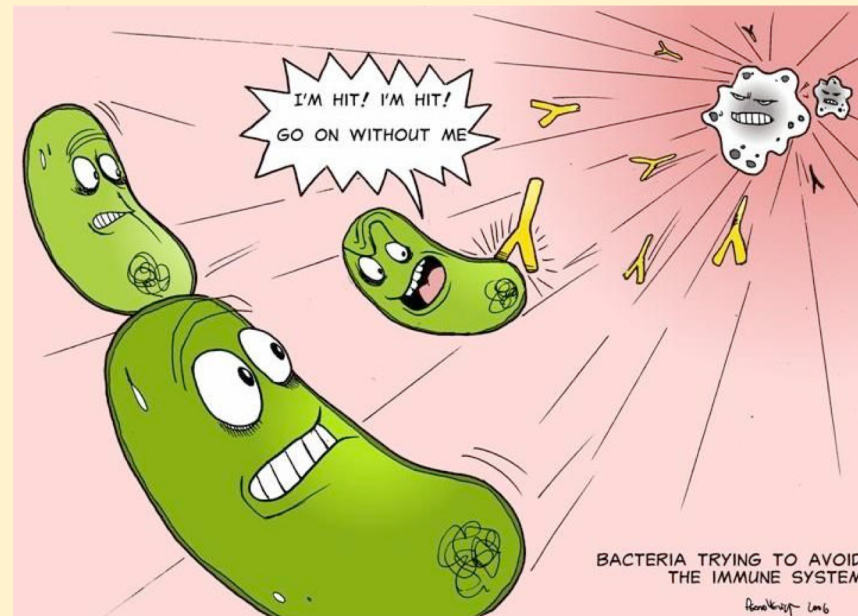


In parallel, evolutionary demographers & rheumatologists seem to have discovered a previously-unappreciated contribution of innate-adaptive immune collaboration to somatic maintenance:

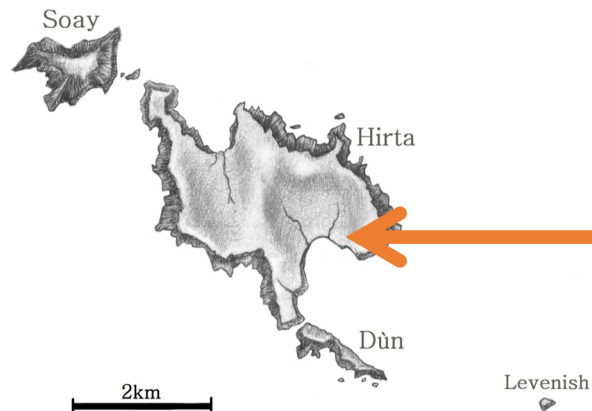
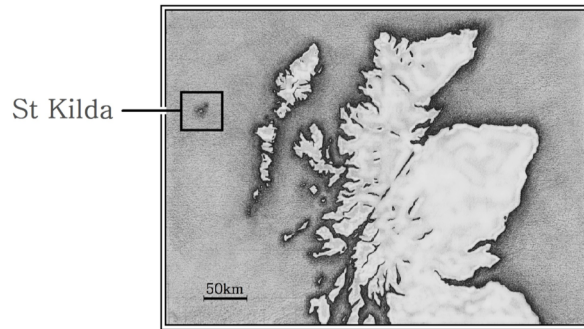
- **The key mechanism: self-reactive opsonizing antibodies?**

**Self-reactive antibodies** aid clearance of apoptotic & necrotic cells!

Just as bacteria-reactive antibodies do for bacteria:



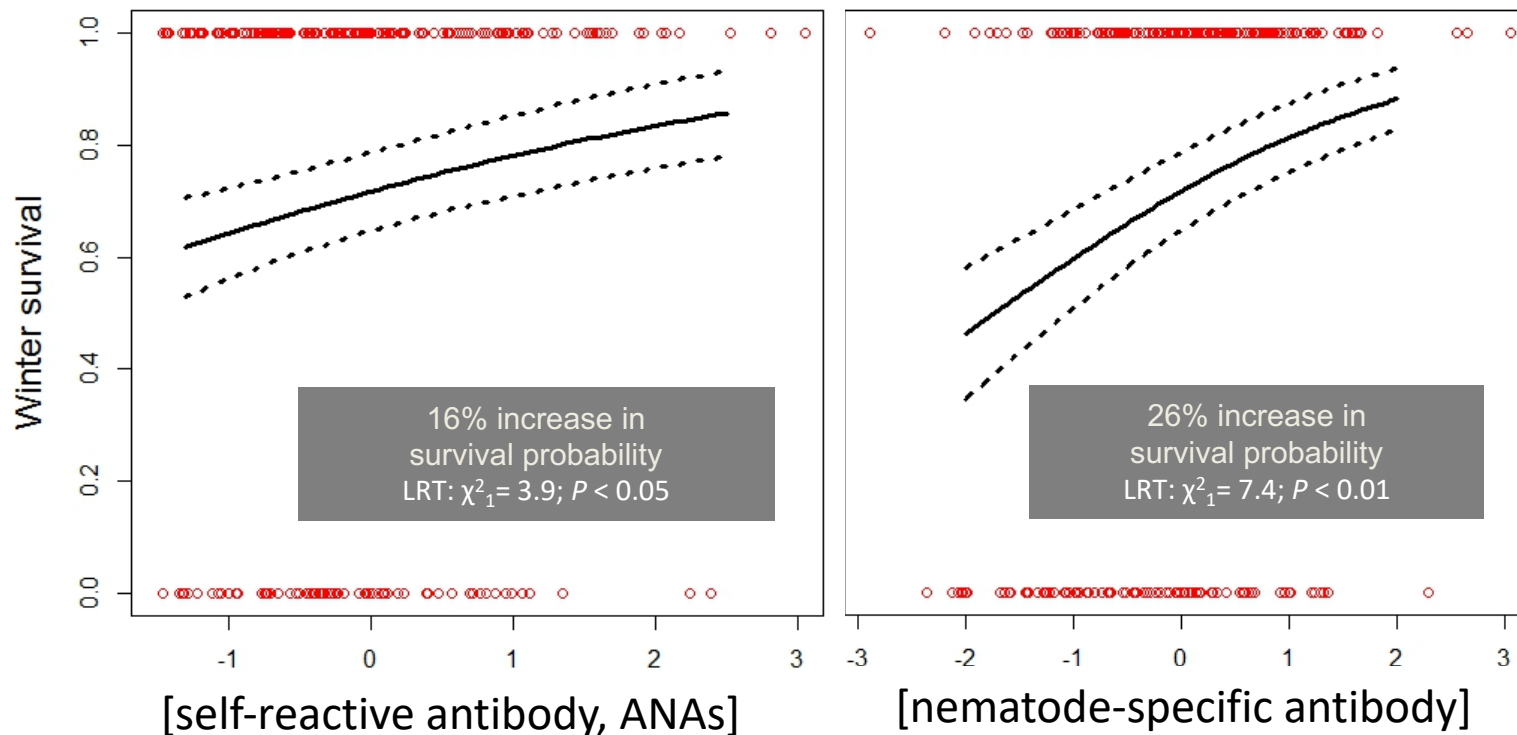
e.g., Catania et al. 2018 *EMPH*; Avrameas et al. 2013, *J Autoimm*; Zhou et al. 2013, *Sci Rep*



**For Soay sheep (*Ovis aries*) in the Outer Hebrides,  
nematodes are the main natural enemies.  
Exposure rate: up to 2400/day/sheep**

Clutton-Brock & Pemberton 2004, *Soay Sheep: Dynamics & Selection in an Island Population*

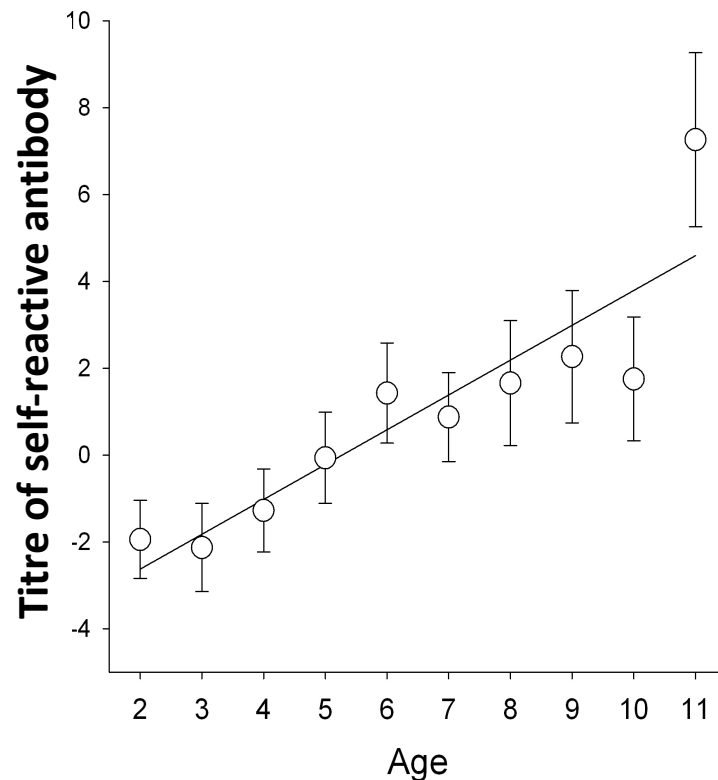
Positive associations between survival & antibodies:  
Nematode-specific and self-reactive antibody titres  
independently predicted ewe survival & lifespan



Nussey et al. 2014, *PRSB*

**Both associations are independent of age and weight** Graham et al. 2010, *Science*

# Rethinking how to interpret self-reactivity:



- **Cross-sectionally, self-reactive titre increased with age in sheep.** Similar patterns in people in Cameroon, Taiwan & Sweden,
- in baboons, chickens & pythons!

e.g., Njemini 2002; Nilsson 2006;  
Attanasio 2001; Sun 2011; Ujvari 2011

- Longitudinal analysis revealed that, in the sheep, this was due to **selective disappearance (early death) of sheep with consistently low titres.**

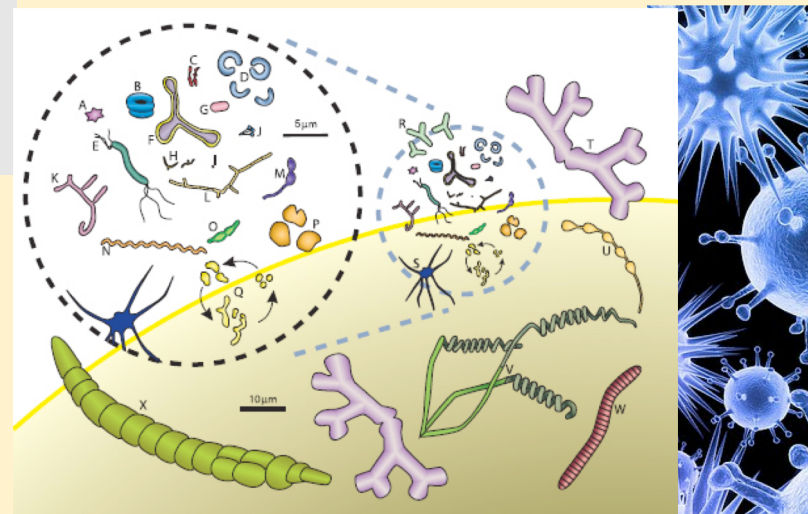
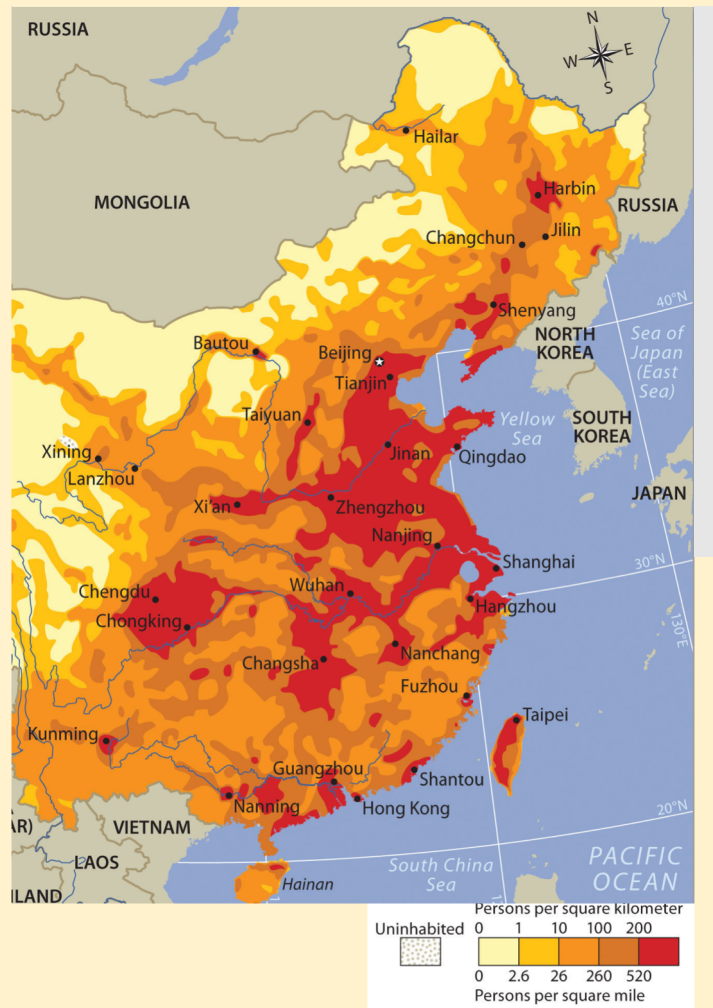


**How special are these sheep, their survival-promoting self-reactivity & their nematodes, on this rarely-sunny island?**



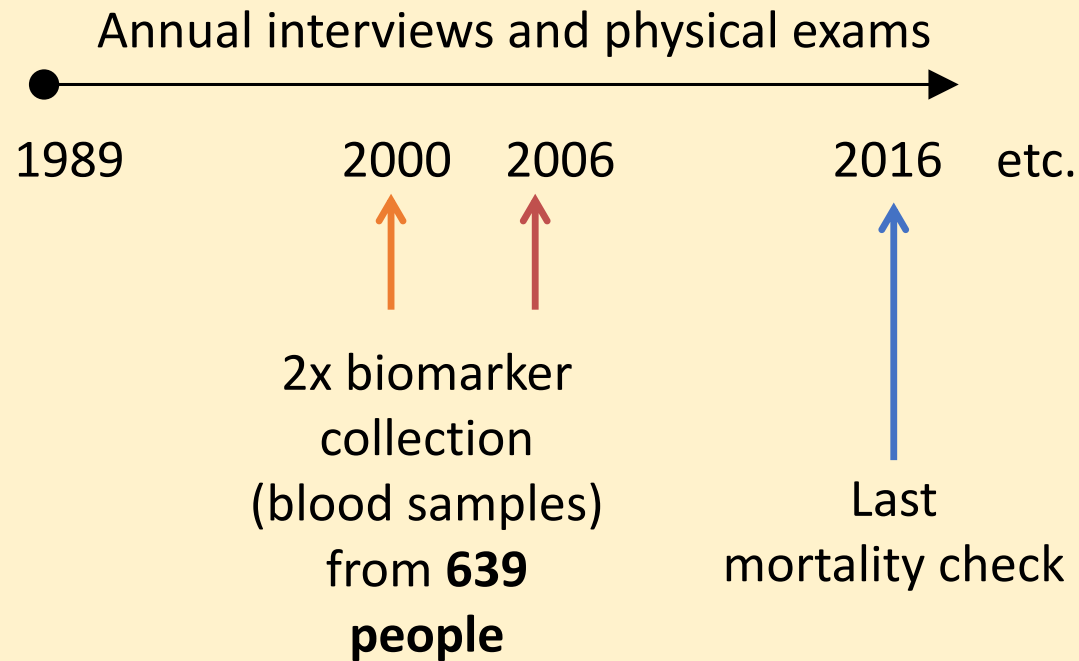


A generality test is underway: people in Taiwan, in collaboration with Ministry of Health, Noreen Goldman, Maxine Weinstein & Dana Gleit



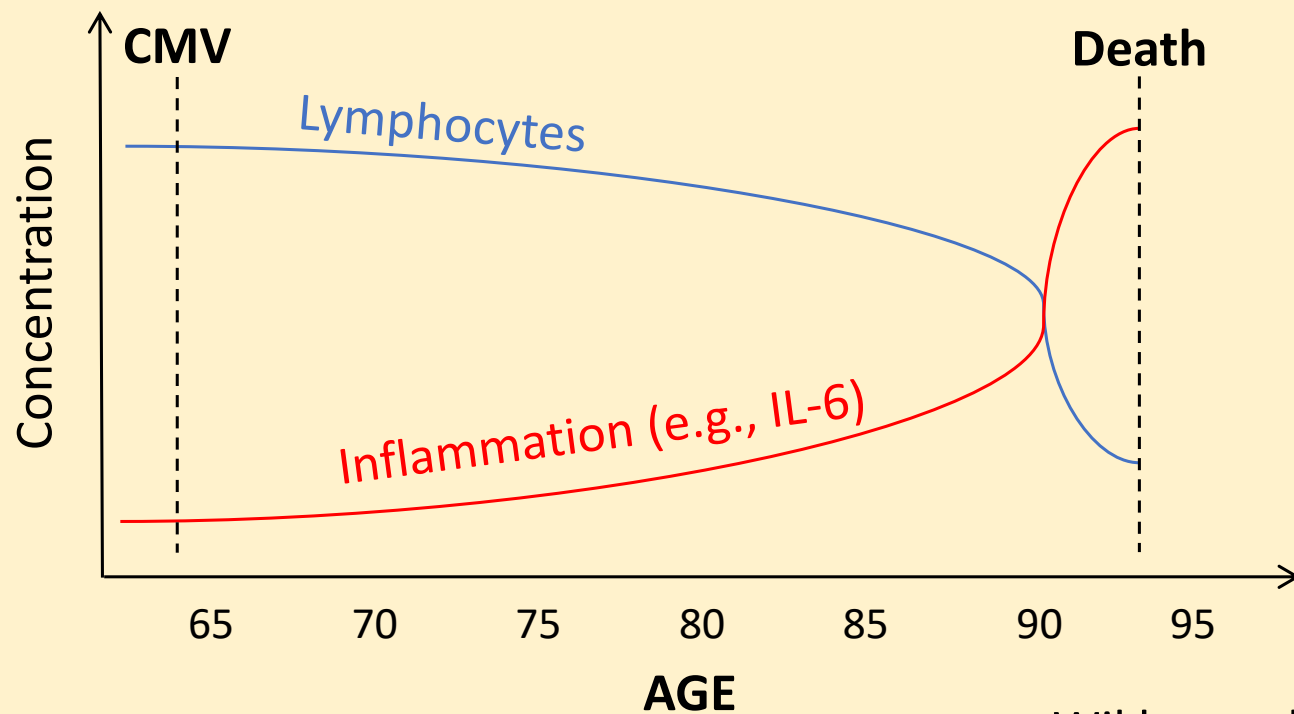


# Social Environment and Biomarkers of Aging Study (SEBAS) timeline, for ~1400 people born between 1892 & 1953



# Cytomegalovirus induces lethal breakdown of innate-adaptive collaboration in elderly humans?

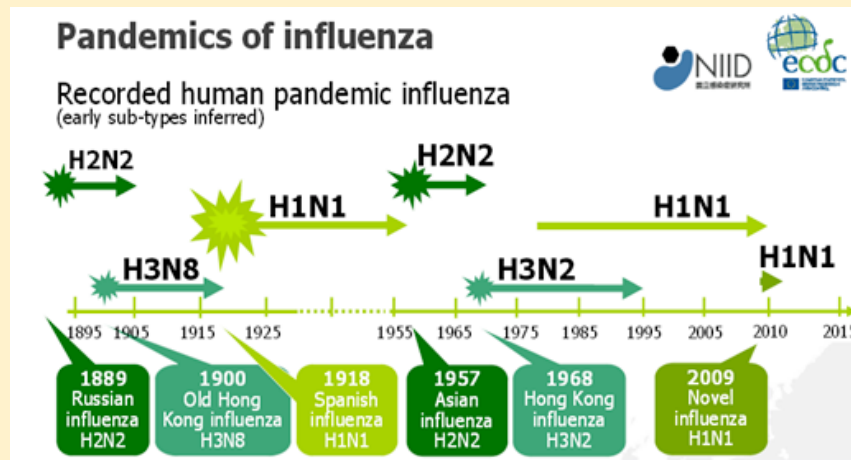
For example, the Immune Risk Profile:



e.g., Wikby et al. 2006 *Mech Age Dev*

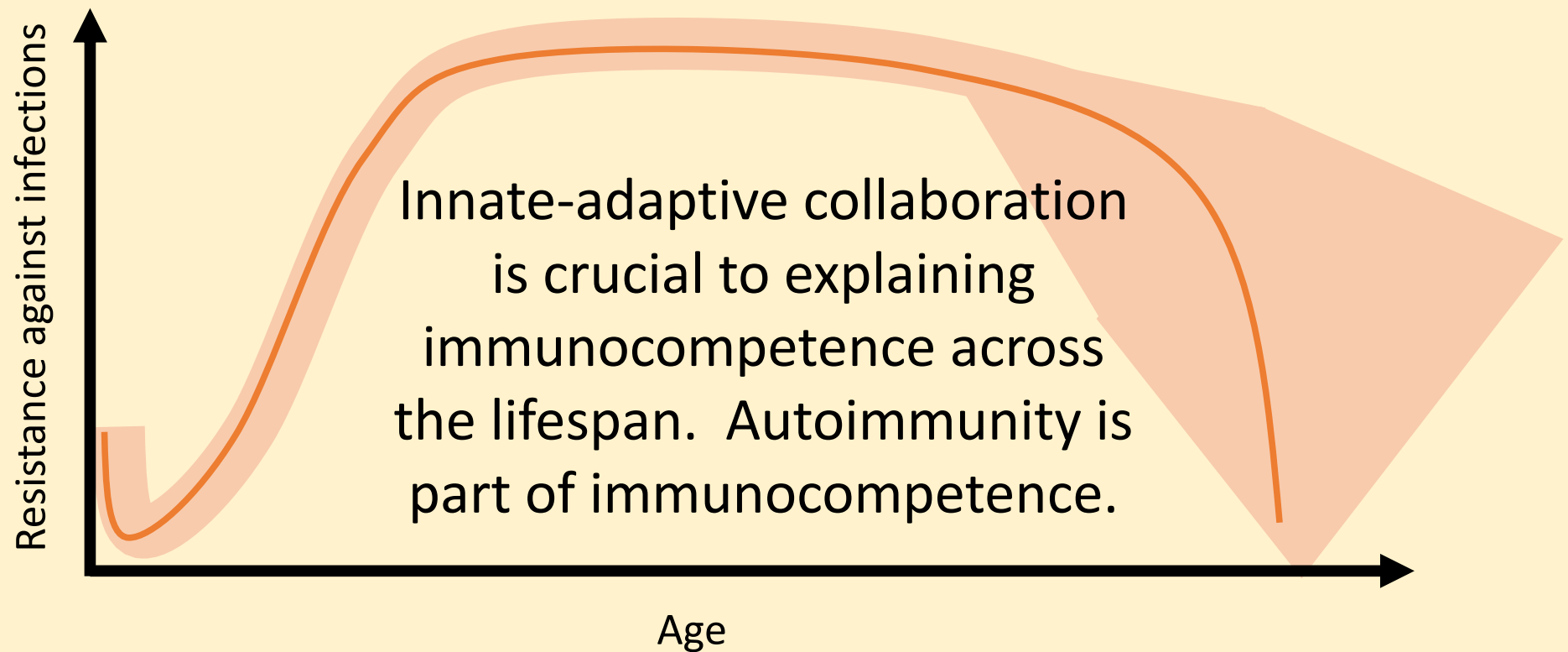
# Taiwanese elderly: Work in progress

- How similar are late-life survival predictors in people vs sheep? So far, quite similar...
  - Self-reactivity is positively associated with:
    - Survival, independent of cytomegalovirus
  - Flu virus resistance?



Graham, Gleib et al., in prep

# Instruction & suppression are dynamic processes



# Synopsis/outlook:

- We understand early life better than late life. We must balance that.
- We must better understand relationships between infectious & inflammatory diseases. Does Immune Risk Profile hold globally?
- We must better understand immune system contributions to tolerance & somatic maintenance (beyond defense against infections).
- There's a stereotypical age trajectory of immune defense capacity.
- But there's amazing heterogeneity in realized trajectories.
- **WHY?**