VITALiTY
Vaccine Initiative To Add Life To Years

Health Sciences North Research Institute
Institut de recherches d'Horizon Santé-Nord

Elderly Immunisation and Immunosenescence

Strategies for developing new influenza vaccines with enhanced protection in older adults

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Presenter Disclosure

- I have relationships with commercial interests
  - Advisory Boards – GSK, Pfizer, Sanofi
  - Clinical Trials – GSK, Sanofi
  - Speaker Honoraria – Pfizer, Merck

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Overview:

1) Influenza as a barometer of health in older people is the single most vaccine preventable disease and vaccination programs are cost-saving. *Why is influenza still a serious illness?*

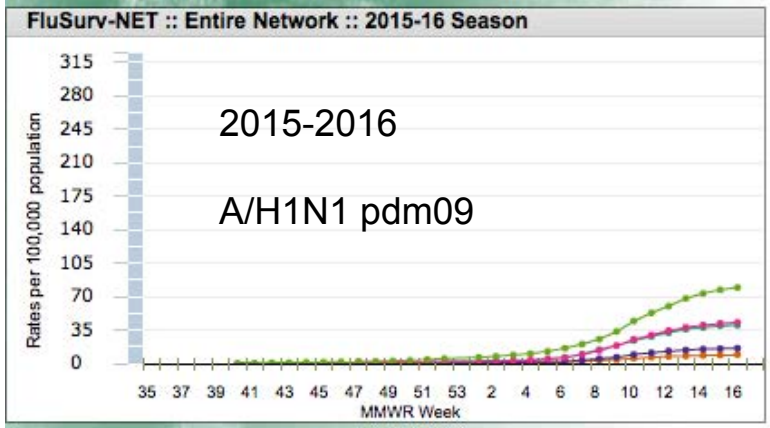
2) Strain-specific antibody titres become poor predictors of vaccine failure with aging. How do we account for the effects of frailty on humoral and cell meditated immune response to influenza vaccination?

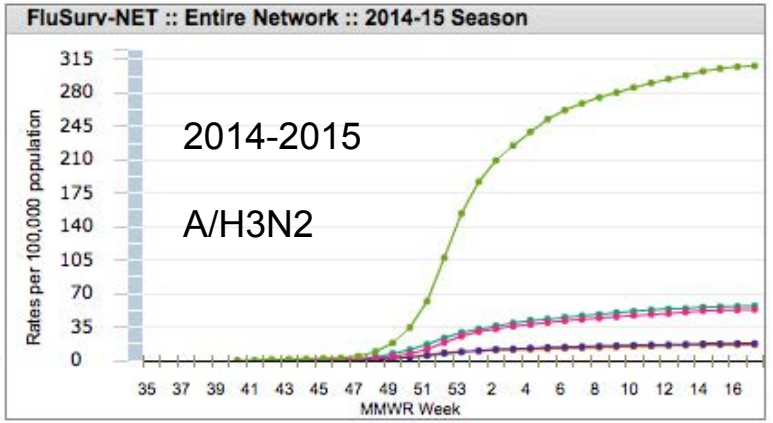
3) CD8 T cell responses show that greatest functional decline with aging. How can we recapitulate through vaccination, the ability of aged memory CD8 T cells to respond to natural influenza infection?

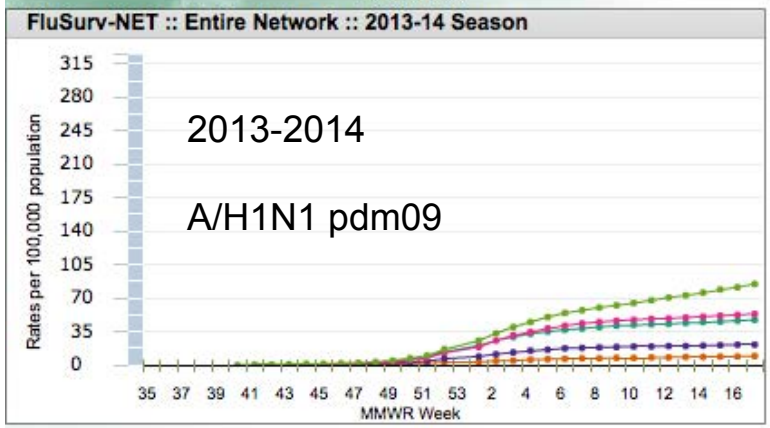
FLUVIEW

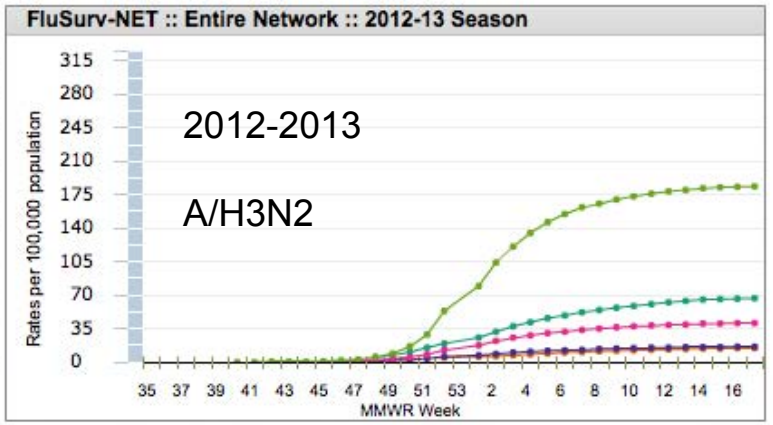
Laboratory-Confirmed Influenza Hospitalizations

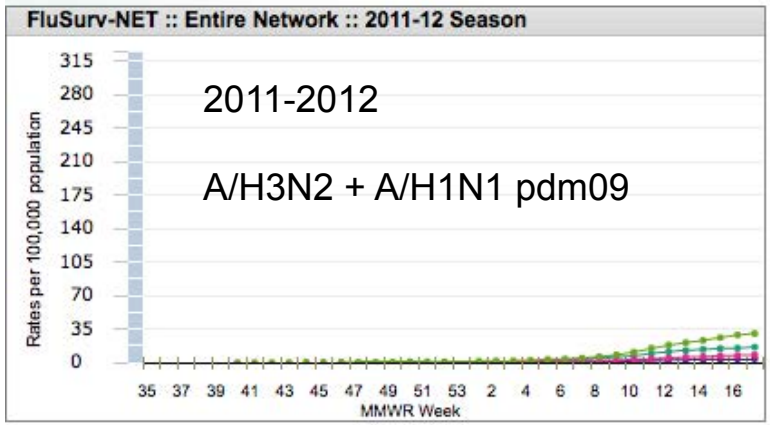
Preliminary cumulative rates as of Apr 23, 2016

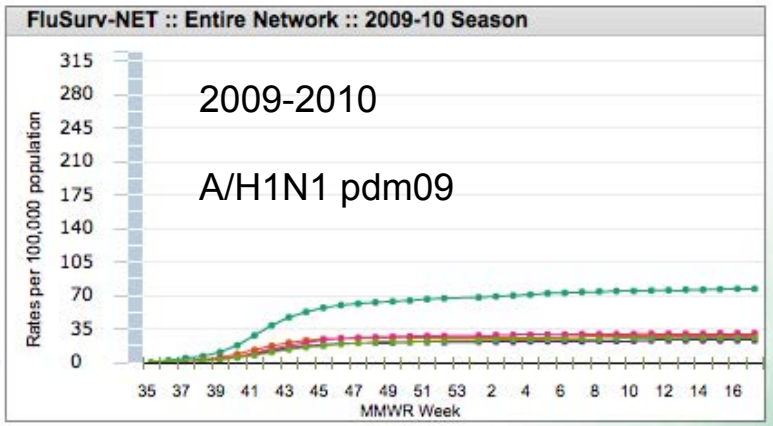








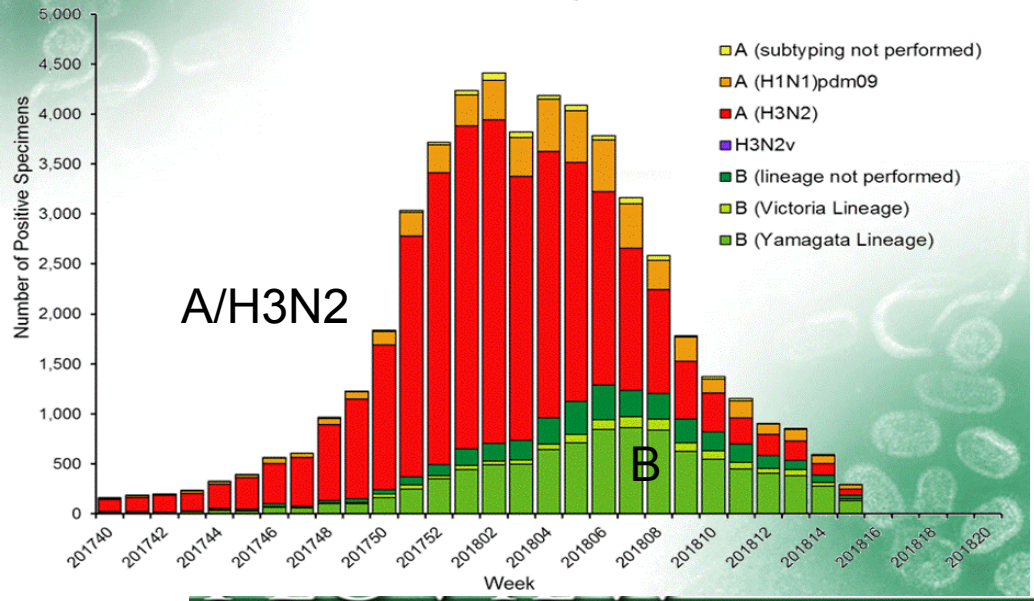




FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2017-2018 Season

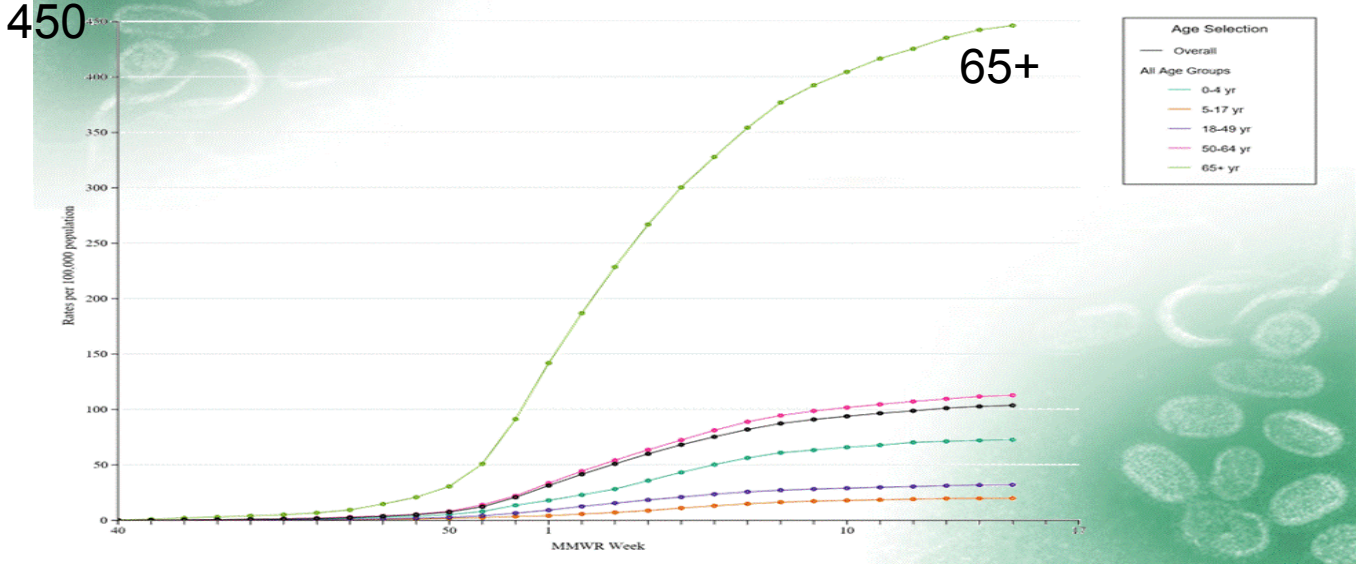


2017-18 Influenza Season

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

Laboratory-Confirmed Influenza Hospitalizations

Preliminary cumulative rates as of Apr 14, 2018



Influenza A/H3N2 remains the greatest challenge to developing more effective vaccines in older adults

Incidence of serious outcomes of influenza ↑

90% of influenza deaths occur in older people

For every influenza death, there are 3–4 influenza hospitalization

greatest impact when A/H3N2 strains circulate

Response to vaccination ↓

CURRENT INFLUENZA VACCINE

Efficacy is 70–90% in preventing respiratory illness in healthy adults and only 30–40% in older people **particularly for H3N2 strains**

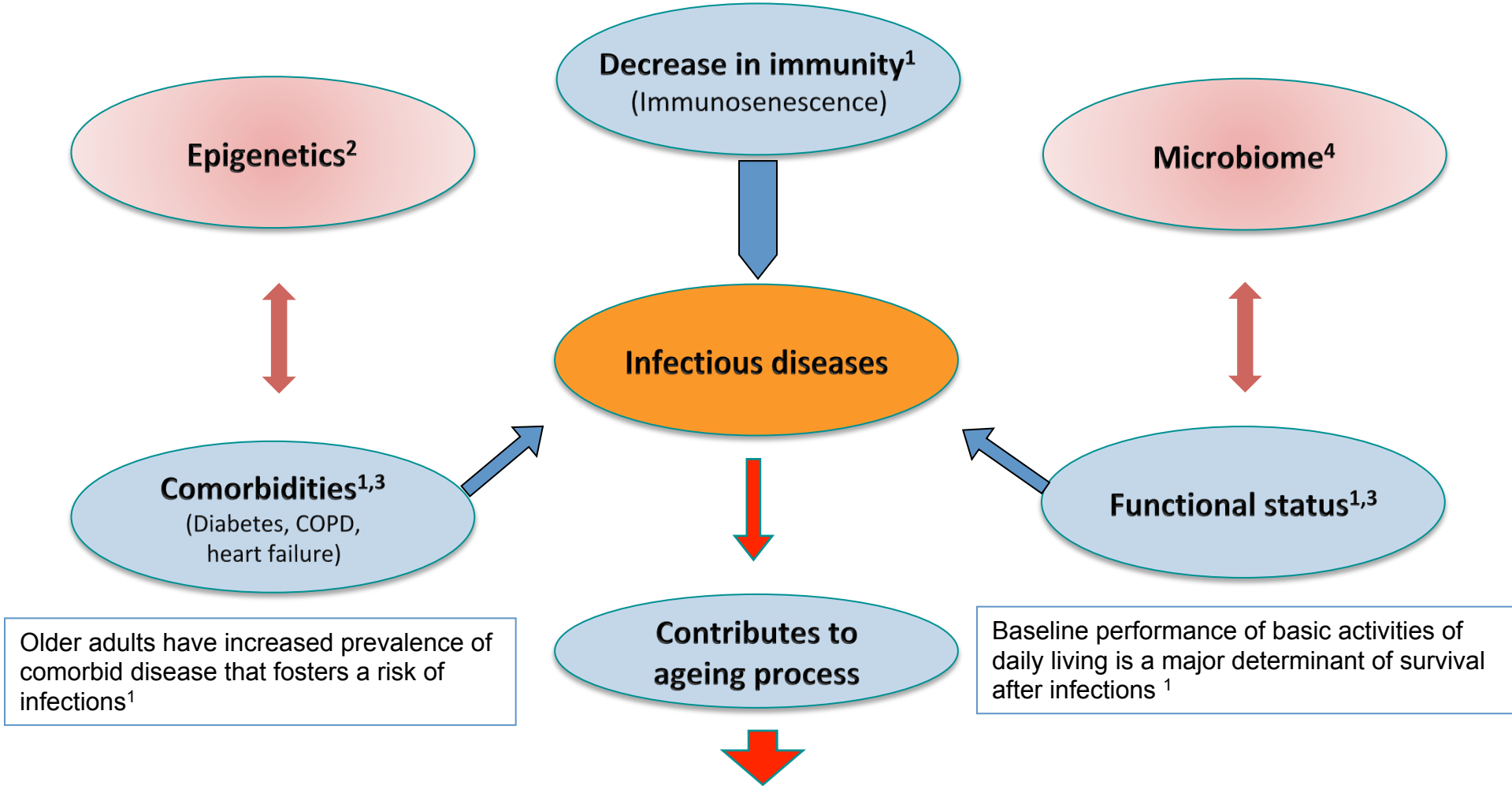
BUT are cost-saving –

mainly due to the prevention of A/H3N2 hospitalization

indicates a clear margin for improvement

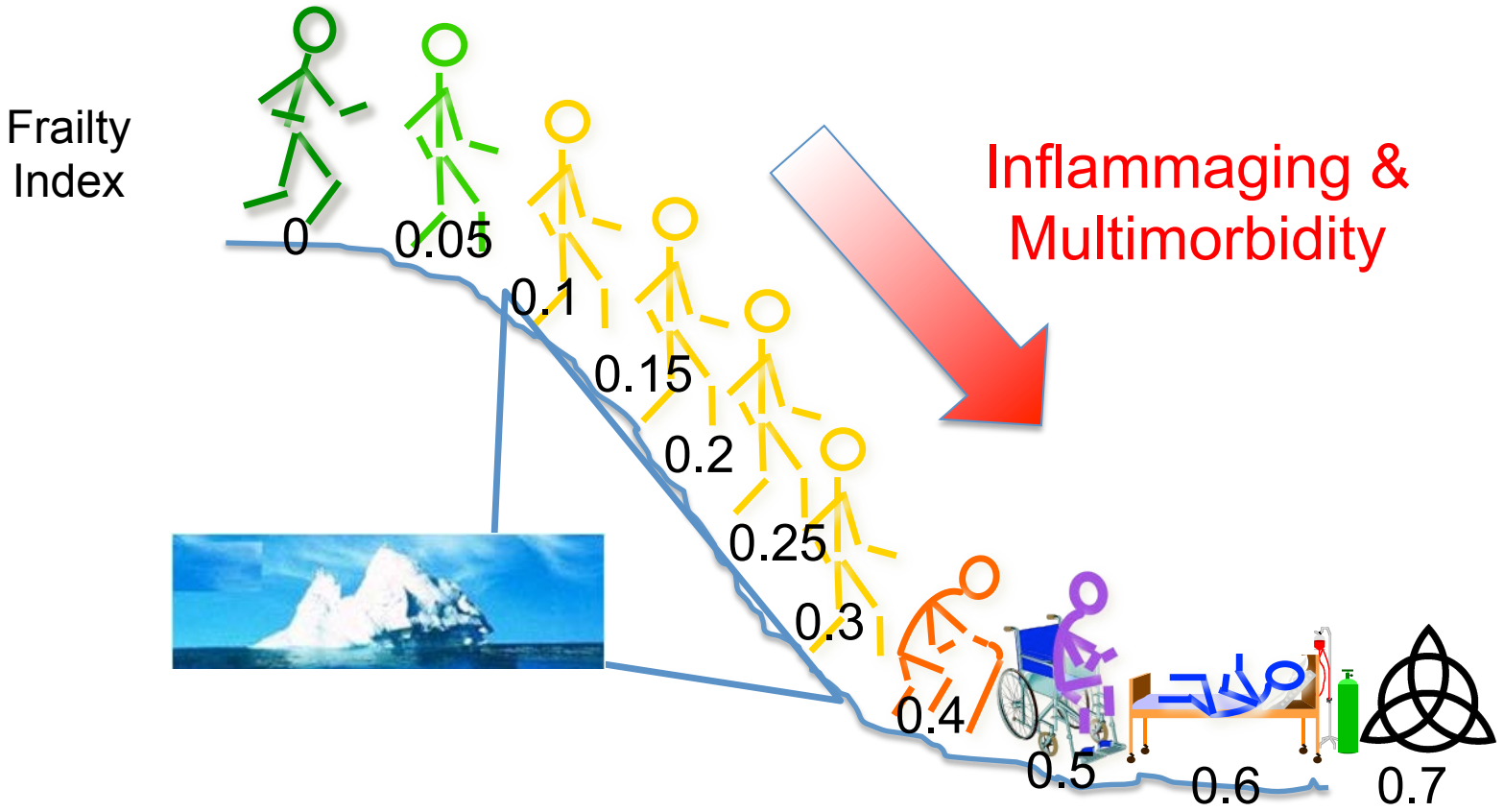
in protection against A/H3N2

Older adults have increasing susceptibility to pneumonia and influenza



1. High KP, Bradley S, Loeb M, et al. Clin Infect Dis. 2005; 40:114–22.
2. CMAJ August14;189:E1043-5, 2017 (Indian Residential School diets and current patterns of diabetes)
3. Rockwood et al., J Am Geriatr Soc. 2010 Feb;58(2):318-23
4. Meehan et al., Interdiscip Top Gerontol Geriatr. 2015;41:54-65..

Vaccine-mediated resilience to influenza with aging



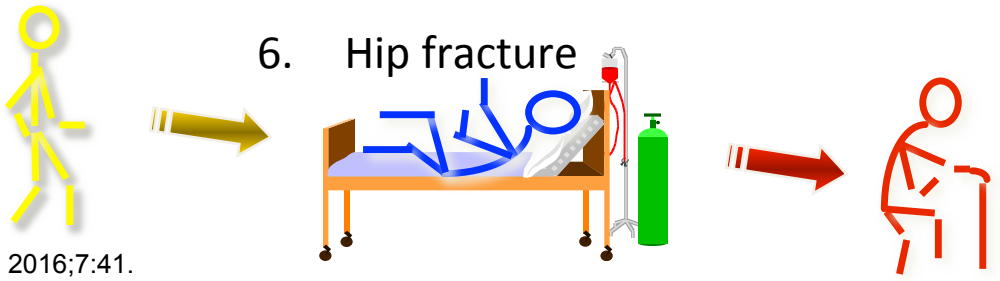
Andrew JID 2017

Vaccine Preventable Disability[1]

Catastrophic disability

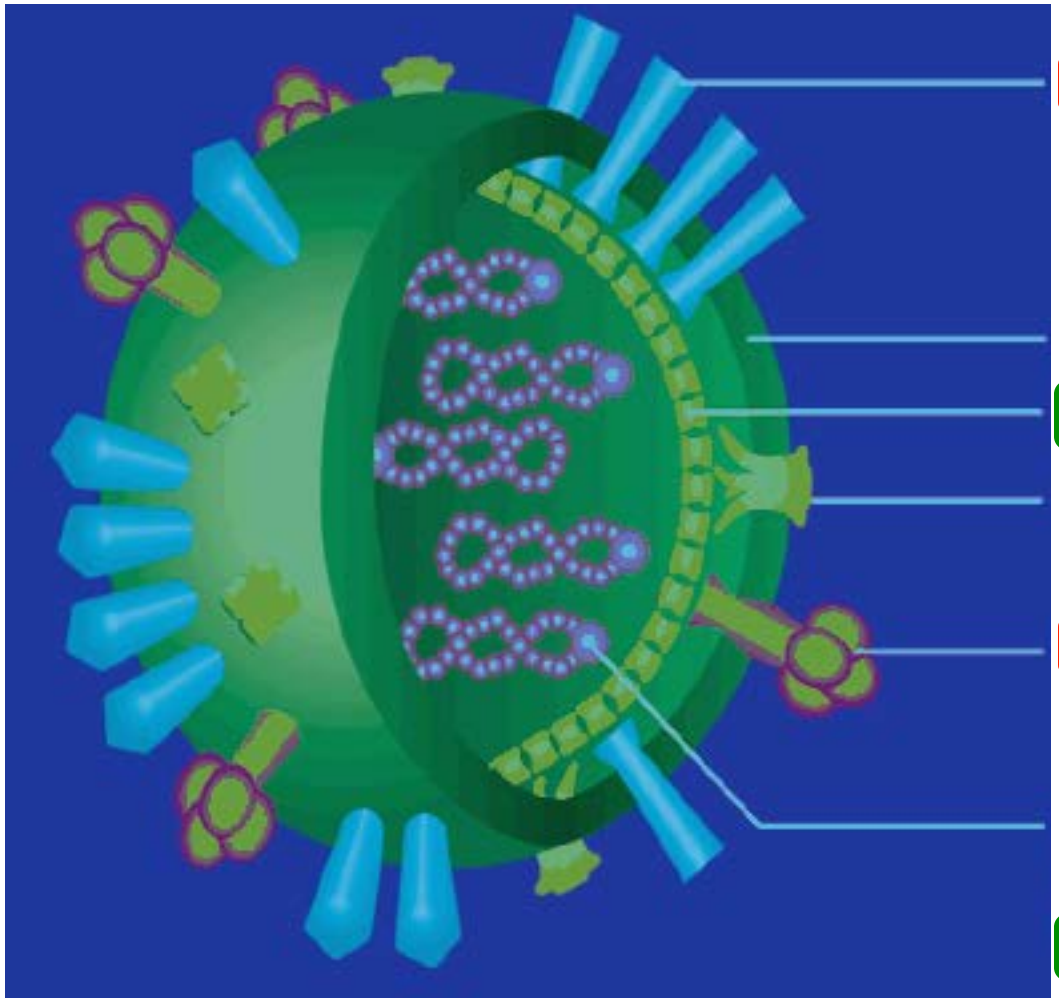
- Defined as a loss of independence in **≥ 3 basic** Activities of Daily Living[2]
- **15%** of older adults hospitalized with influenza **experience catastrophic disability**[3]
- Dysregulated immune responses are the 'geriatric giant' of chronic diseases: influenza wakes the giant **increasing the risk of catastrophic disability**[2] with:

1. Strokes
2. CHF
3. Pneumonia and influenza [4,5]
4. Ischemic heart disease
5. Cancer
6. Hip fracture



[1] McElhaney JE et al. Front Immunol. 2016;7:41.
[2] Ferrucci et al. JAMA 1997;277:728.
[3] Andrews MK et al. Canadian Immunization Conference. 12/7/2016.
[4] Barker et al. Arch Int Med 1998;158:645.
[5] Falsey et al. *N Engl J Med*. 2005;352:1749.

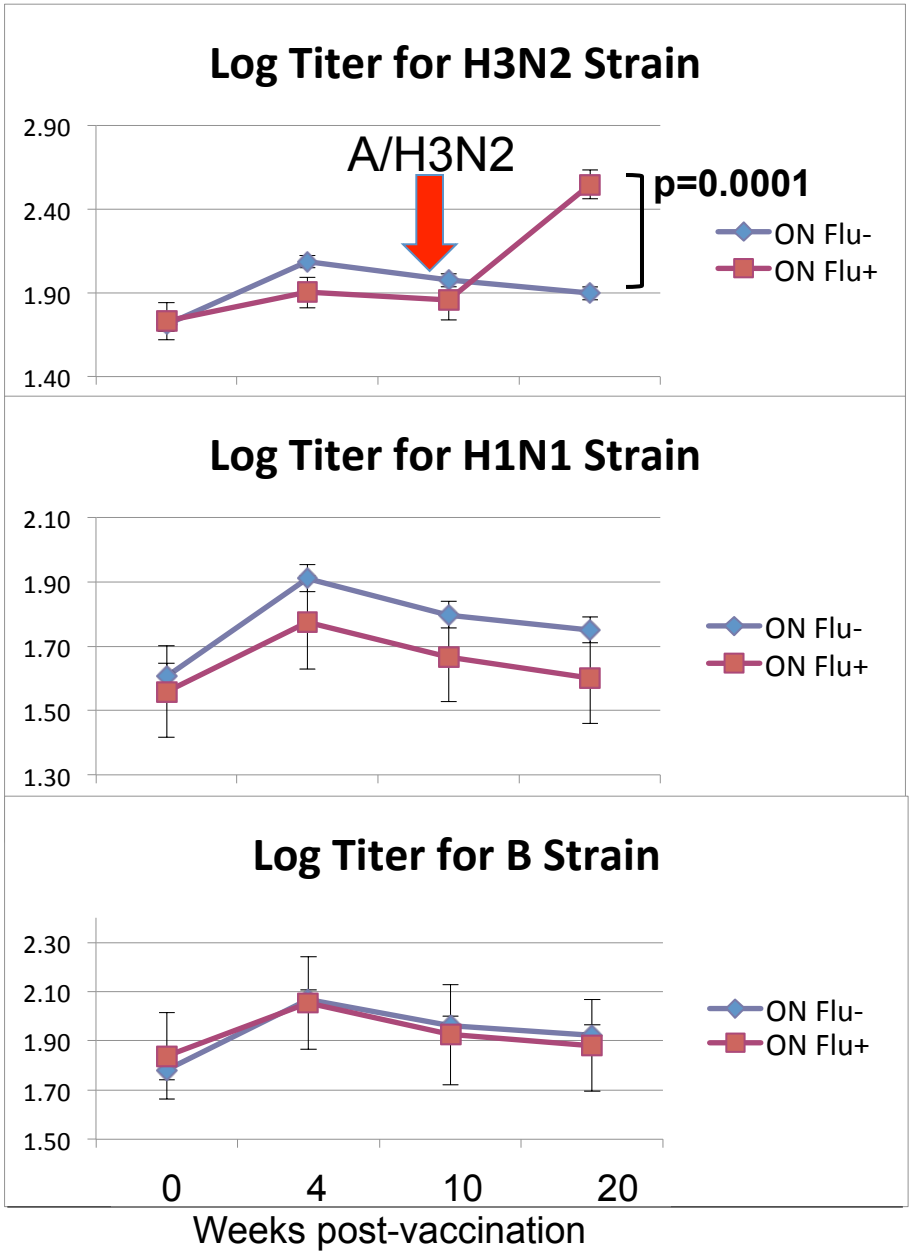
Why do A/H3N2 strains have greatest impact in older adults?



Opportunities for developing new Influenza vaccines for older adults

- Antibody titers against influenza (hemagglutination inhibition assay) measures protection through sterilizing immunity
- Childhood exposure to different subtypes of influenza alters the antibody response to influenza vaccination later in life
- Age-related decline in the antibody response to influenza vaccination is an effect of repeat vaccination (not age)
- Frailty increases with age as we accumulate social, physical and cognitive deficits and contributes to "inflammaging"
- Frailty indices predict survival better than age and can be used as a single variable to measure of overall health status

Antibody responses as correlates of protection

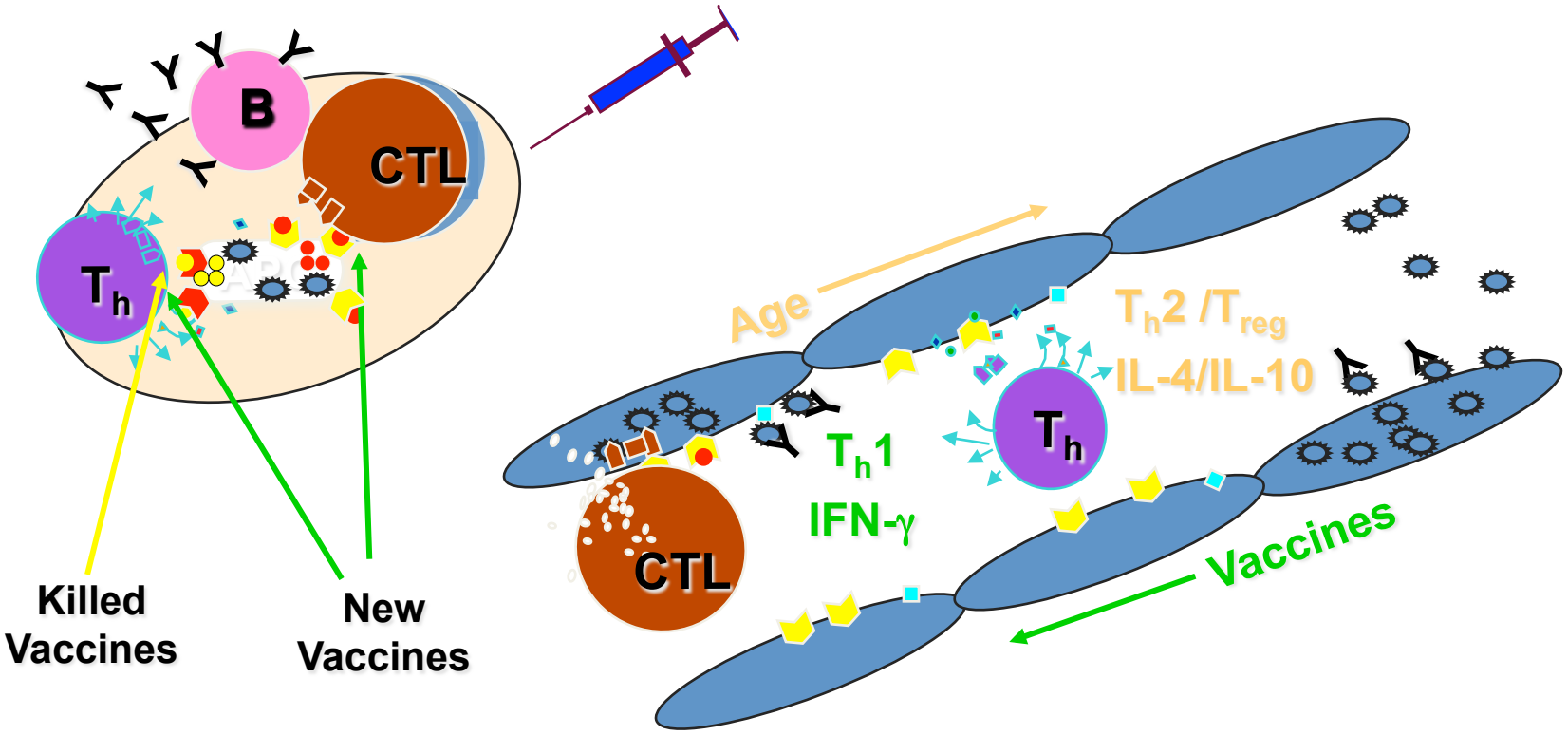


H3N2-specific antibody responses as correlates of protection in older adults ***may not predict vaccine failure***

H1N1-specific antibody responses as correlates of protection in older adults may be the ability to recall antibody responses from ***childhood priming***

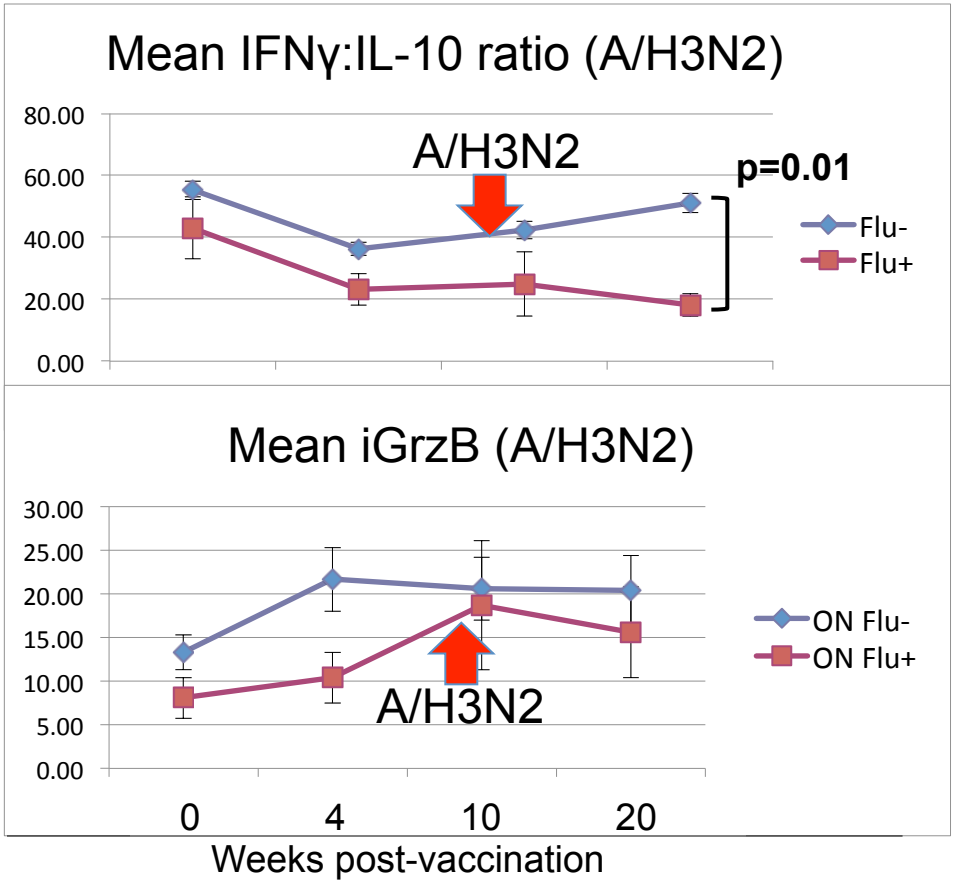
Flu B-specific immune responses as correlates of protection have ***no shared epitopes*** with Flu A

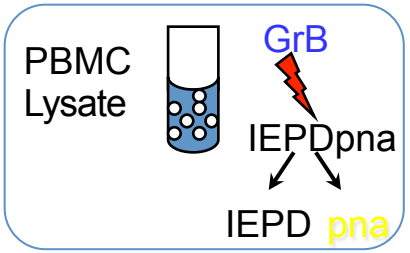
Targeting Immune Responses:
Developing more effective influenza vaccines for older adults



T cell correlates of protection: IFNγ:IL-10 ratio and iGrzB

Ex vivo challenge with A/H3N2

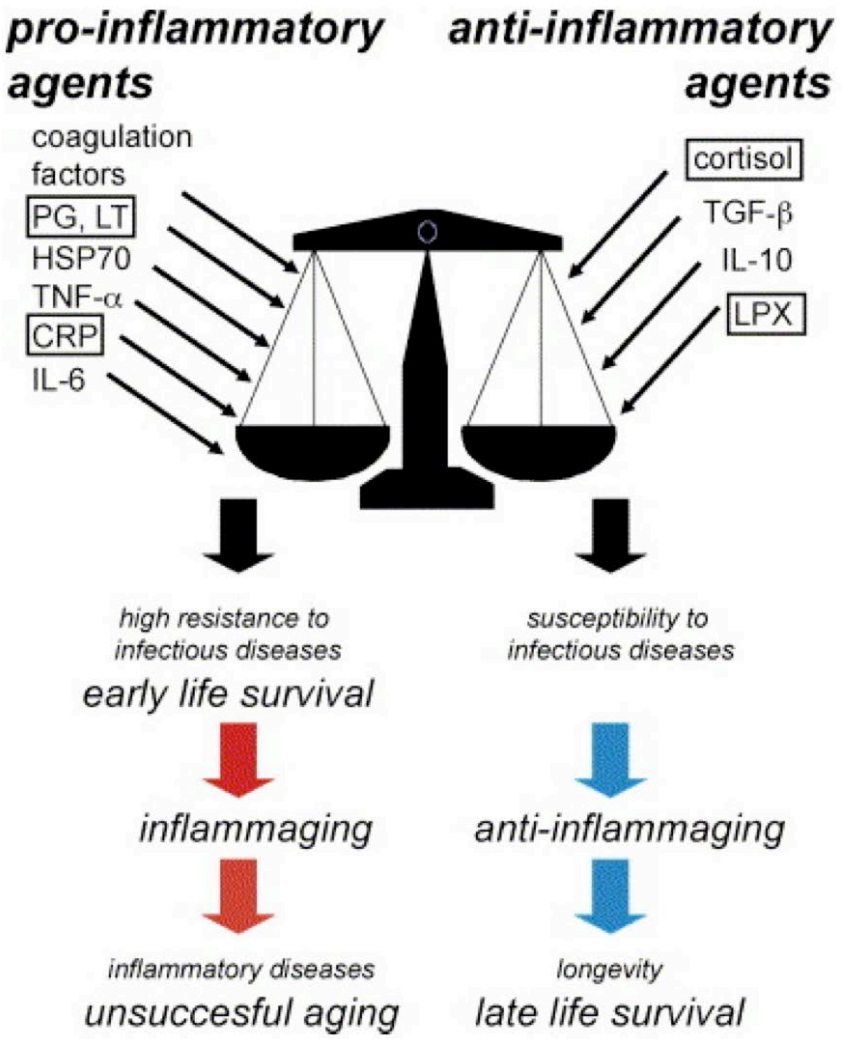




IFNγ:IL-10 ratio response to influenza predicts protection **NOT** IFNγ alone in older adults
(McElhaney et al. J Immunol 2006, McElhaney et al. Vaccine 2009)

Poor GrB responders to influenza vaccination predicts ⇧risk of influenza infection
(McElhaney et al. J Immunol 2006, McElhaney et al. Vaccine 2009)
AND
illness severity correlates with IFNγ:IL-10 ratio & GrB (r= -.99)
(Shahid et al. Vaccine 28:6145-51, 2010)
BUT
can respond to influenza infection

Healthy Aging: The Balance



Stimulates T cell responses

but

Do we press down on the gas pedal?

Suppresses T cell responses

or

Take our foot off the brake?

Franceschi C et al. Mech Age Dev 128: 92-105, 2007.

Figure 4 : Inverse correlation of crossreactive T cells and symptom score. Sridhar et al. Nat Med 19:1305-12, 2013.

IFNγ^+IL-2$^-$ CD8 T cells (NP/M1) inversely correlate with pH1N1 illness symptoms in young adults

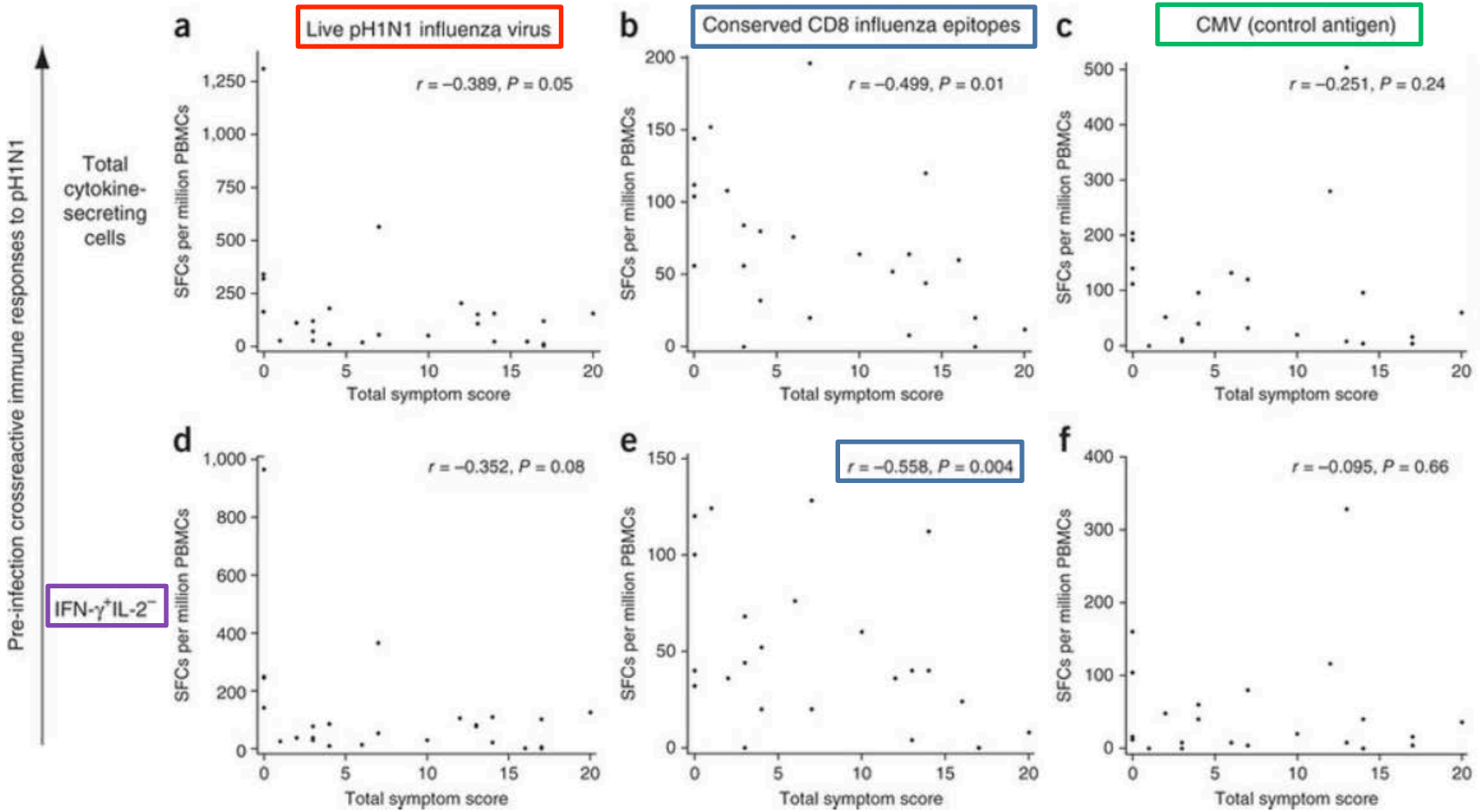
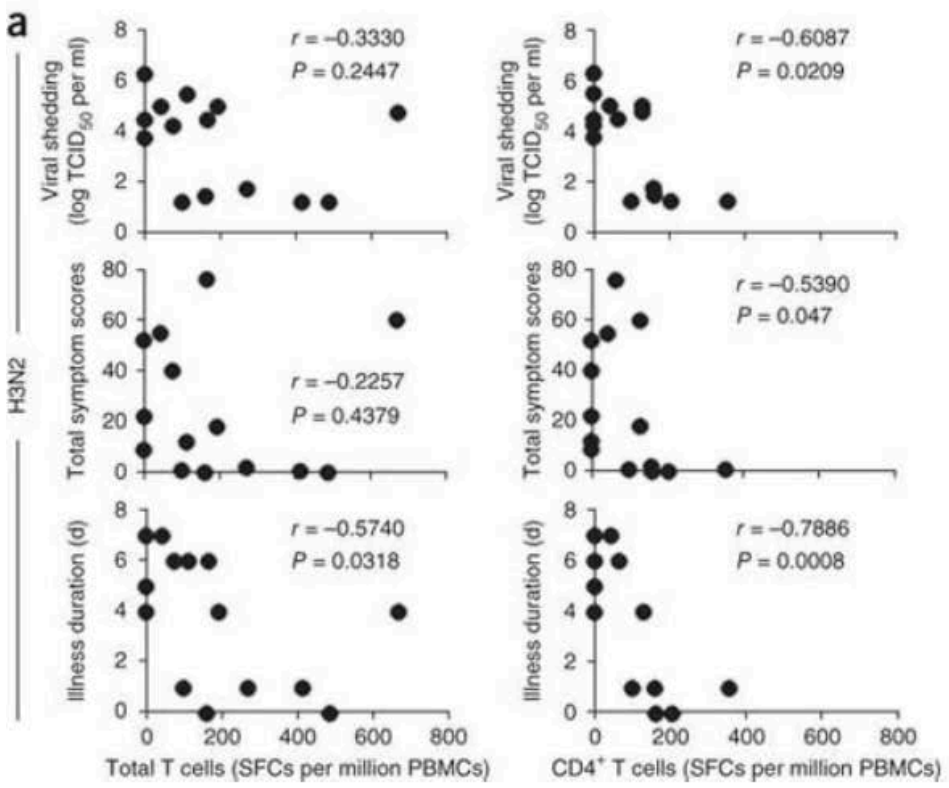
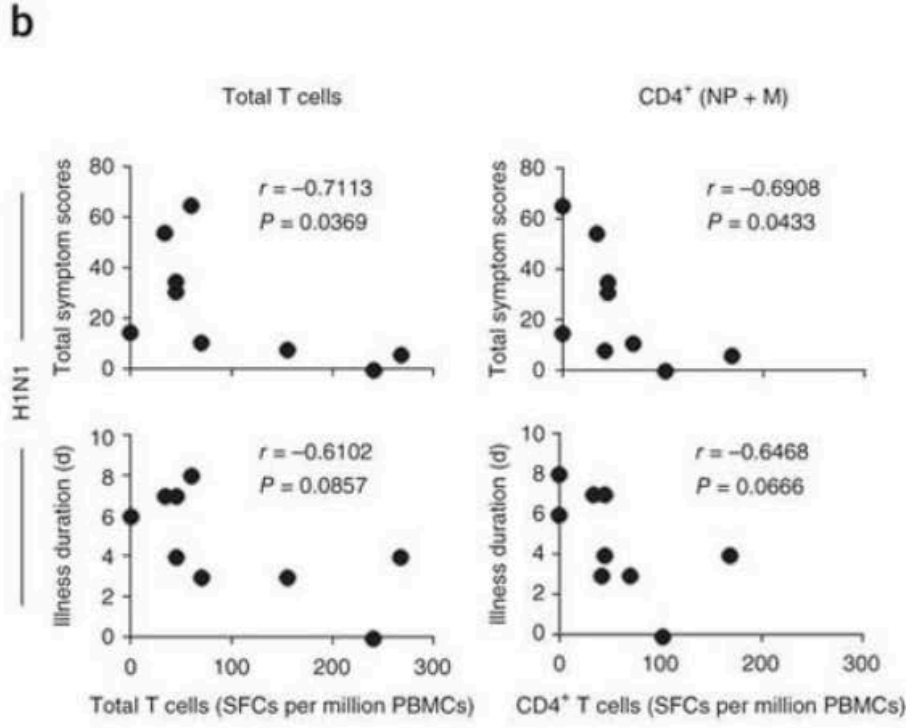


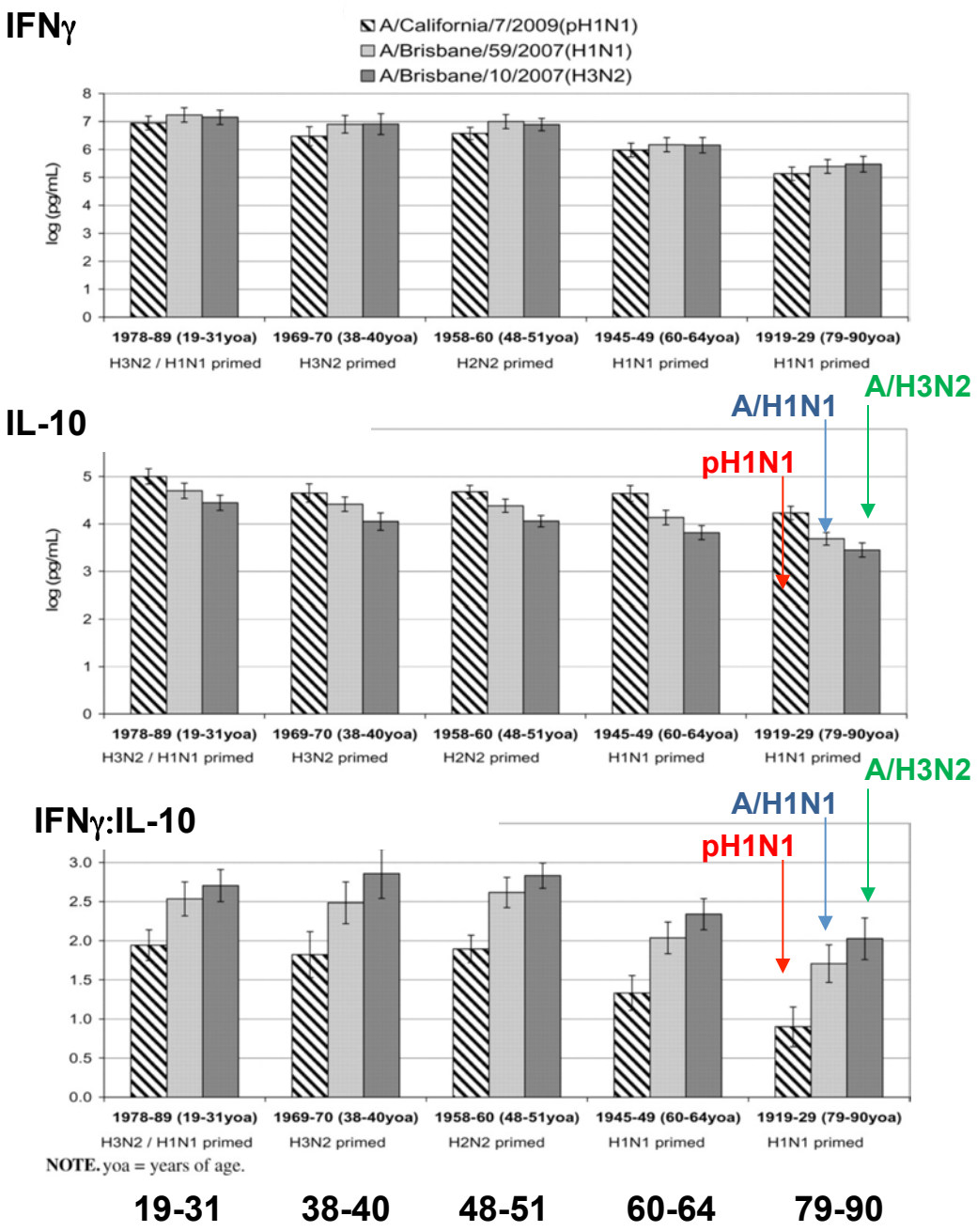
Figure 3 : T cell responses and illness severity.

IFNγ^+ CD4 T cells (NP/M1) inversely correlate with A/H1N1 & A/H3N2 illness symptoms in young adults





Wilkinson et al. Nat Med 19:1305-12, 2013.



Childhood priming does ***not*** affect **IFNγ** or **IL-10** responses to H1N1 or H3N2 challenge

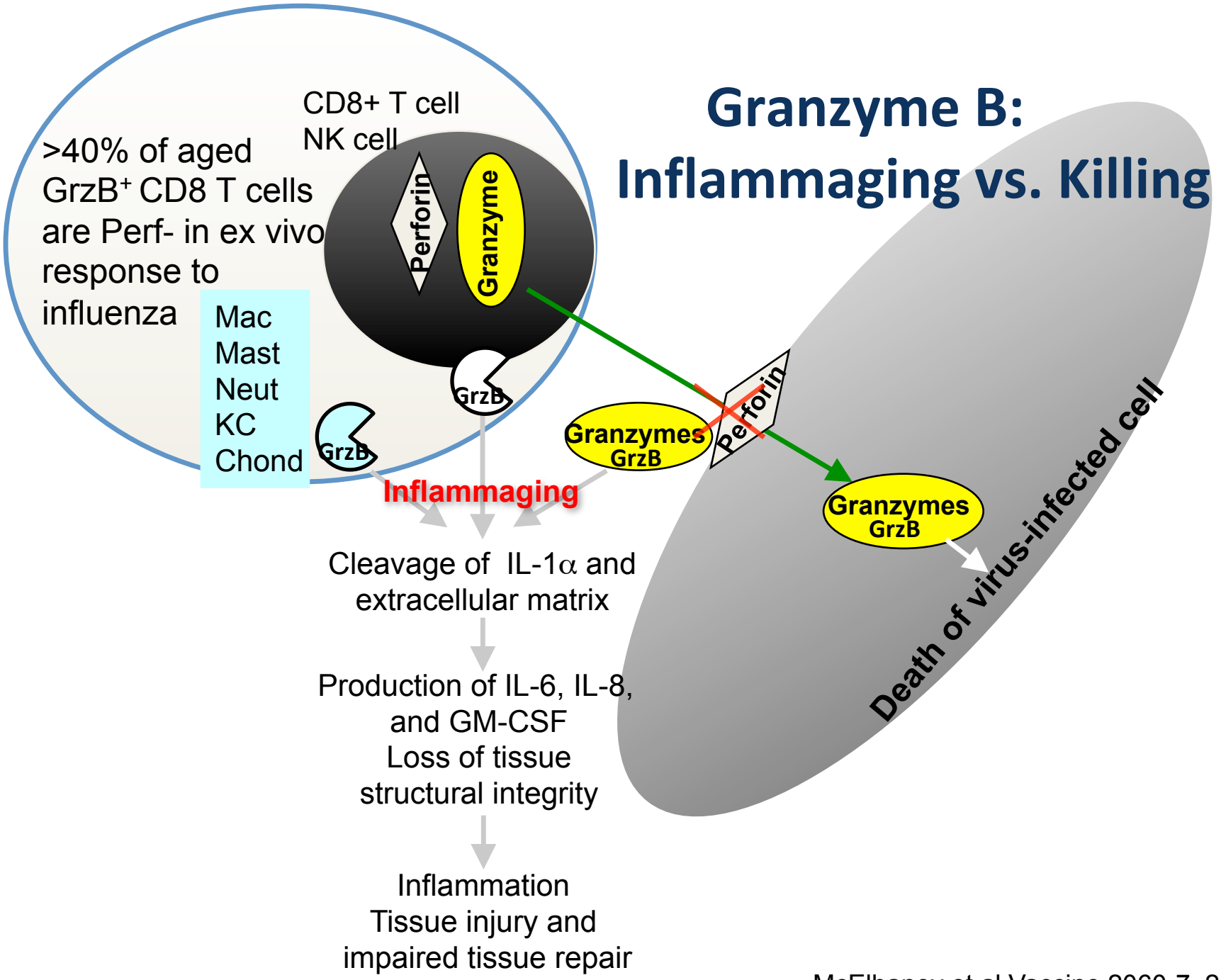
Aging effect is associated with a decline in **IFNγ** ***independent*** of H1N1 or H3N2 challenge

Aging effect on childhood priming is associated with an increase in **IL-10** response to H1N1 vs. H3N2 challenge

IFNγ:IL-10 ratio is a correlate of protection when antibodies fail to provide sterilizing immunity

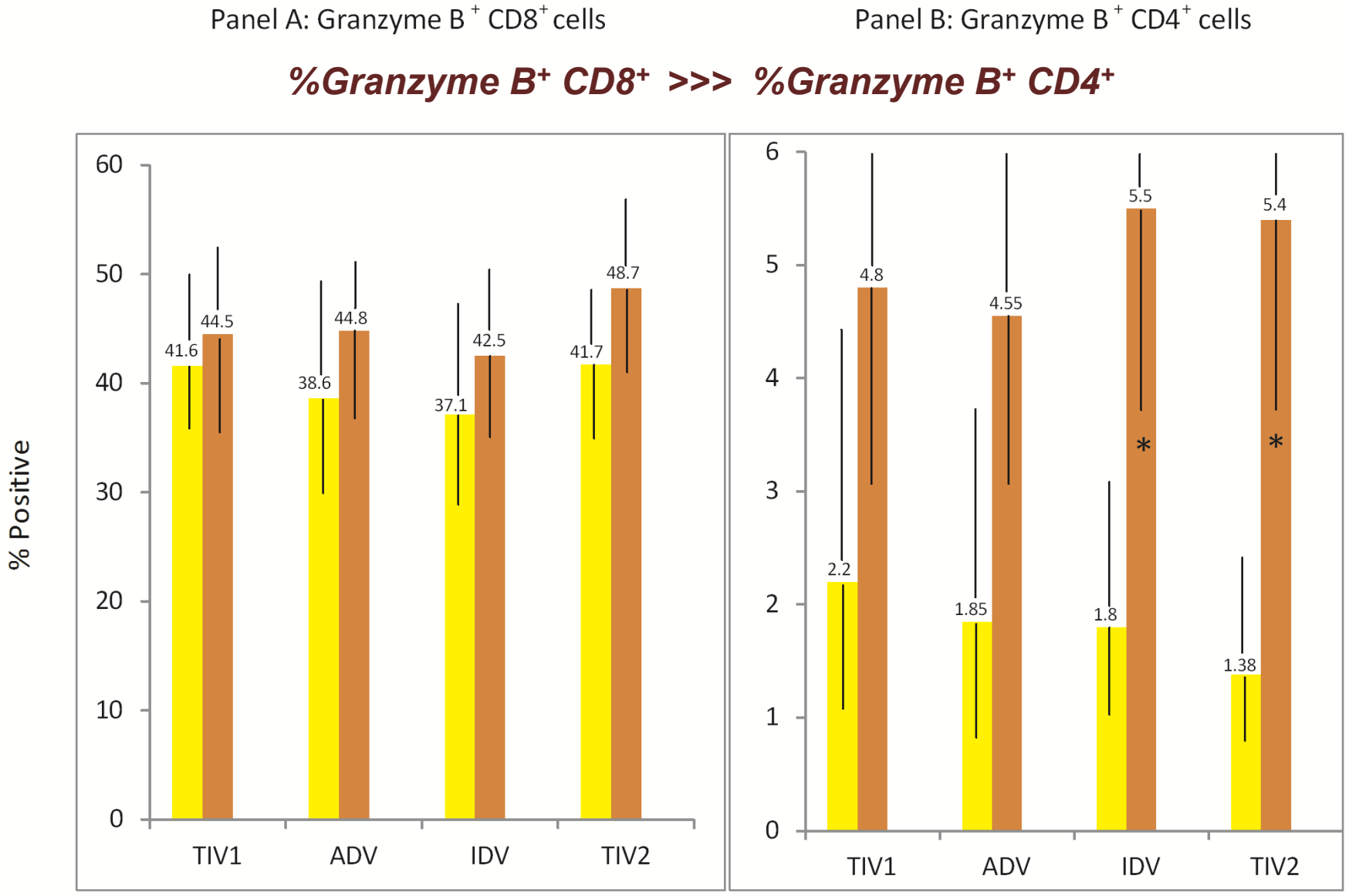
Skowronski et al. J Infect Dis. 2011;203(2):158-167.

Granzyme B: Inflammaging vs. Killing

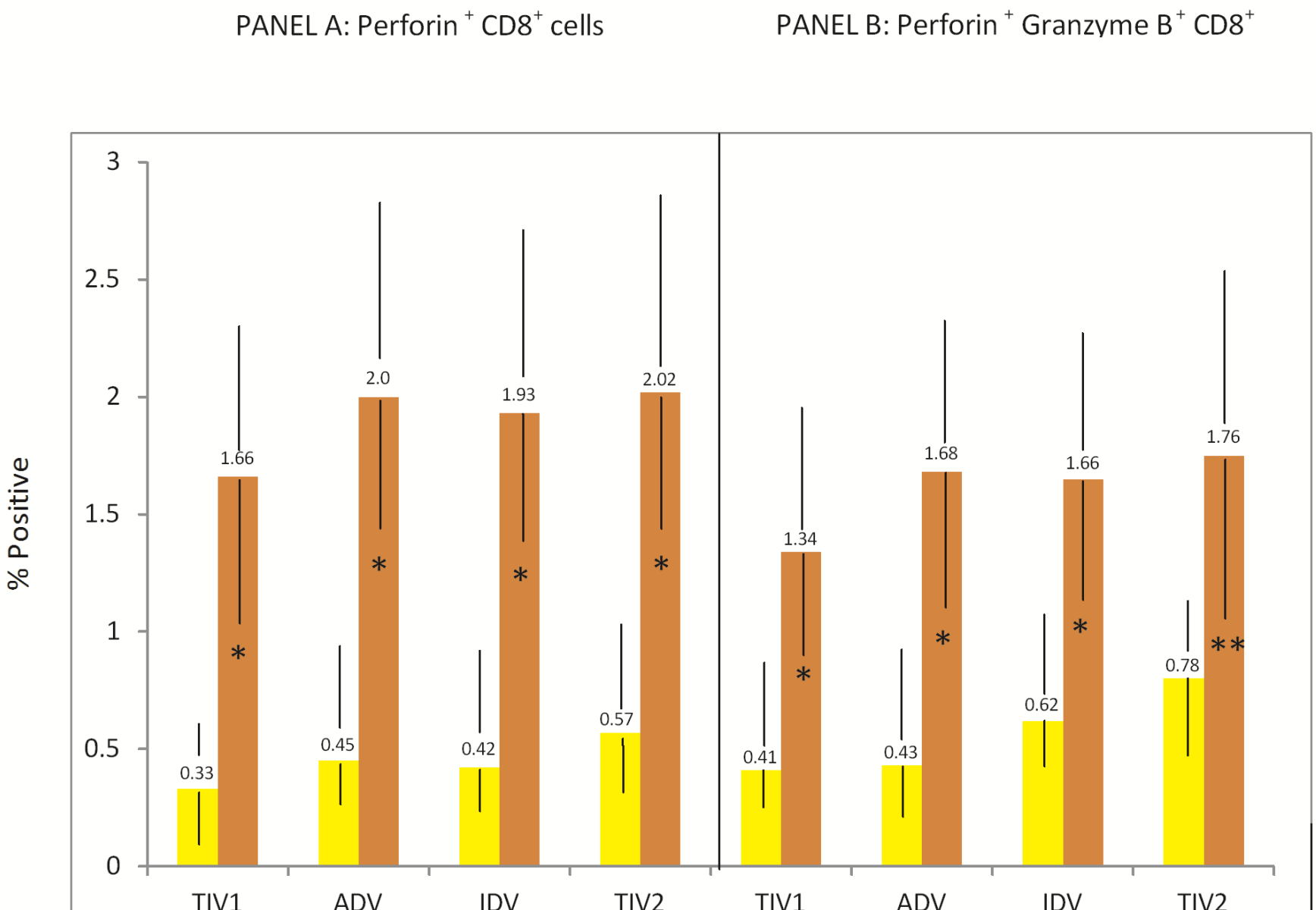


McElhaney et al Vaccine 2060-7, 2012

Randomized trial of 4 Subunit Influenza Vaccines



Randomized trial of 4 Subunit Influenza Vaccines: %Perforin$^+$ CD8$^+$ = %Perforin$^+$ Granzyme B$^+$ CD8$^+$

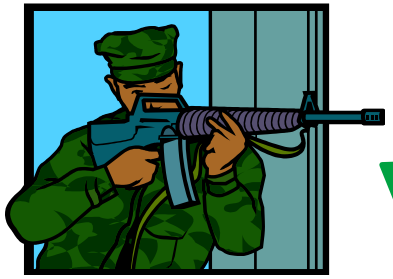


bGrB activity correlates with frequency of late differentiated $CD8^+$ T cell subsets

$CD8^+$ T cell subset	$CD8^+$ T cell phenotype	Pearson Correlation (r)	p value
Total $CD8^+$ T cells	$CD3^+CD8^+$	0.601	.001
Late or terminally differentiated $CD8^+$ T cells	$CD8^+CD57^+$	0.586	.001
	$CD8^+KLRG1^+$	0.555	.002
	$CD8^+/CD45RA^+CCR7^-CD27^-CD28^-$	0.553	.002
Memory T cells	$CD8^+/CD28^+$	-0.579	.001
	$CD8^+/CD45RA^-CCR7^+CD27^+CD28^+$	-0.476	.010
	$CD8^+/CD45RA^-CCR7^-CD27^+CD28^+$	-0.627	.0001

Haq et al. J Gerontol A Biol Sci Med Sci. 72:1163-70, 2017.

Granzymes – Beneficial, Pathogenic, or Both?

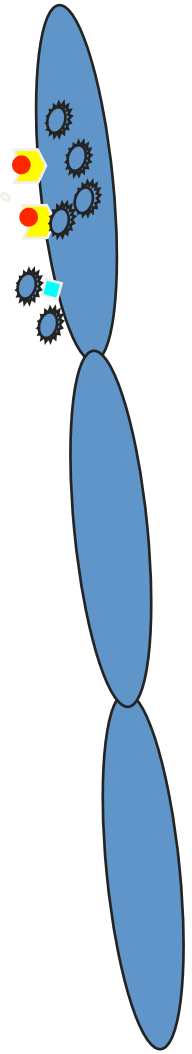


Good
(apoptosis)

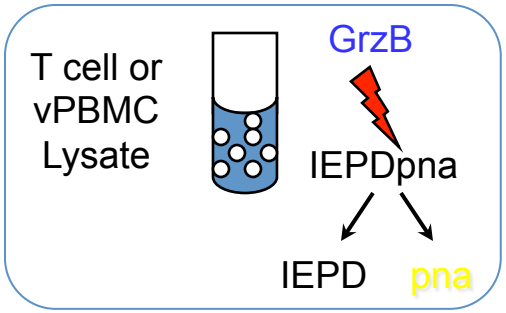
Adjuvanted NP+M1
Influenza Vaccines

Cytomegalovirus
Age
Chronic Conditions

Bad
(extracellular, inflammation, autoantigens, anoikis)

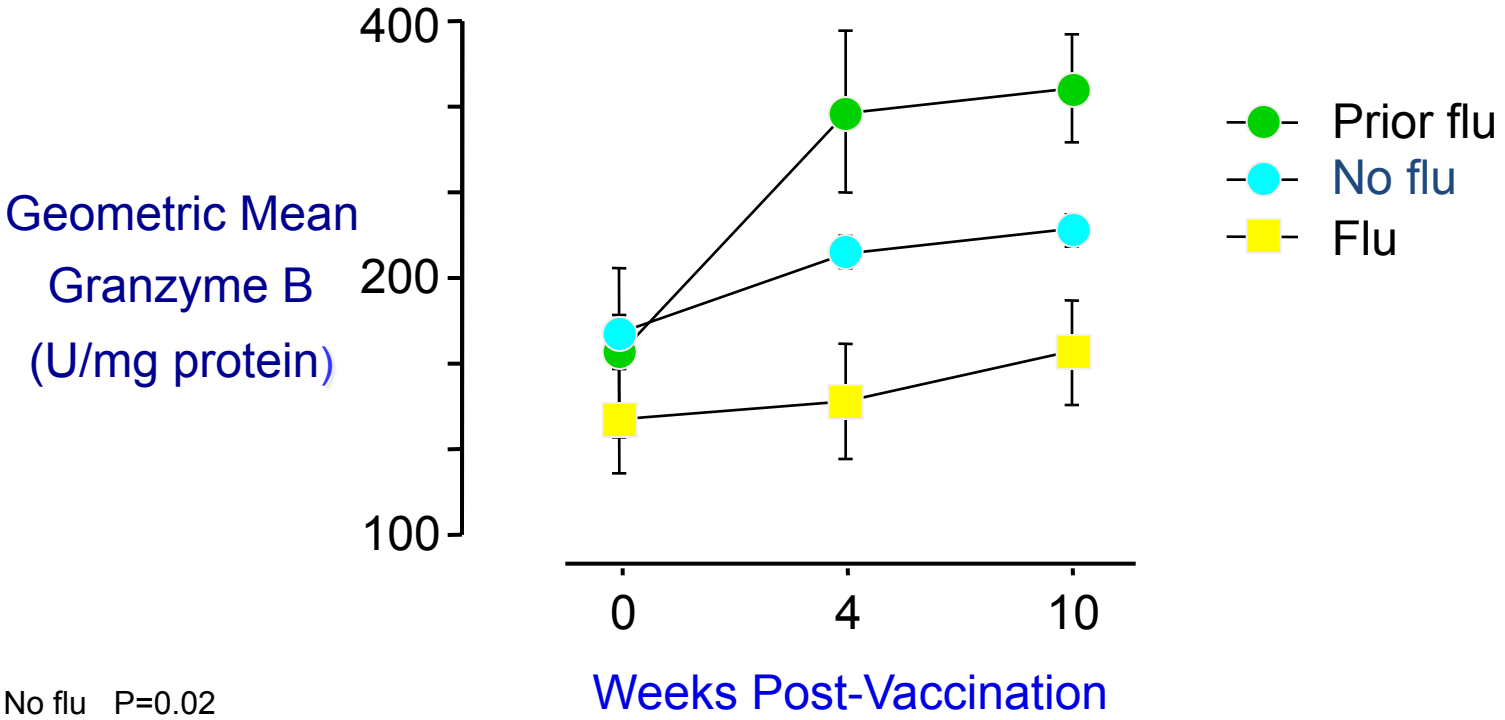


Correlate of protection: Granzyme B



Combined '03-'04 and '04-'05 Seasons

Influenza A/H3N2



Prior vs. No flu P=0.02
No flu vs. Flu P=0.004
SMWT, statins - significant at pre-vacc only
Error bar: std error

McElhaney et al. Vaccine 27:2418-2425, 2009

Relative Vaccine Efficacy of FLUZONE® High-Dose[1-3]

Benefit demonstrated across age groups, influenza types, comorbidities, and frailty-associated conditions

PRIMARY ENDPOINT[1]

24.2%
more efficacious*
HD (N=228) vs. SD (N=301)
(95% CI: 9.7; 36.5)

Demonstrated SUPERIOR EFFICACY against primary endpoint compared to FLUZONE® Standard Dose Vaccine[1]

Similar to Vaccine Strains[1]
35.4%
(95% CI: 12.5; 52.5)

Year 1[3]
45.3%
(95% CI: 6.9; 68.6)

Year 2[3]
20.7%
(95% CI: 4.4; 34.3)

65-74 Years of Age[2]
19.7%
(95% CI: 0.4; 35.4)

75+ Years of Age[2]
32.4%
(95% CI: 8.1; 50.6)

≥1 High-Risk Comorbidity[2]
22.1%
(95% CI: 3.9; 37.0)

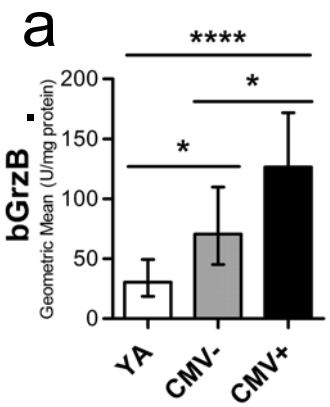
1 Frailty-Associated Condition[2]
27.5%
(95% CI: 0.4; 47.4)

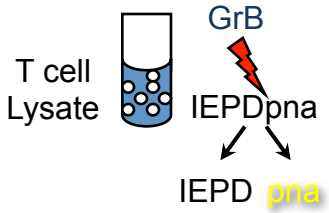
**against laboratory-confirmed influenza illness caused by any virus type or subtype in adults 65 years of age and older*

References:
1.DiazGranados CA, et al. (2014). N Engl J Med, 371, 635-645.
2.DiazGranados CA, et al. (2015). Vaccine, 33, 4565–4571.
3.DiazGranados CA, et al. (2014). N Engl J Med, 371, supplementary appendix

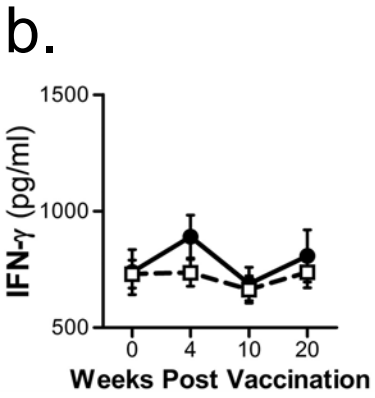
T-cell responses to H3N2 challenge following HD vs. SD influenza vaccination in older adults

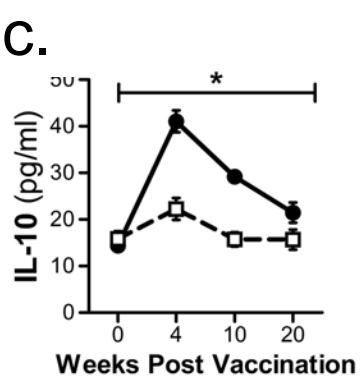
bGrB activity in resting T cells

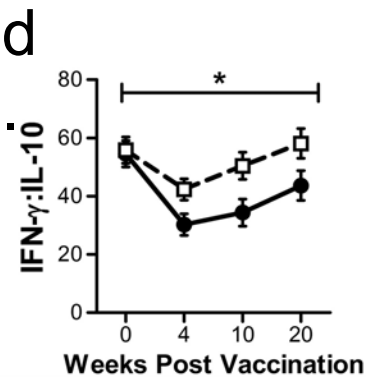




Dysregulated **IFNγ** and **IL-10** responses are vaccine dose dependent





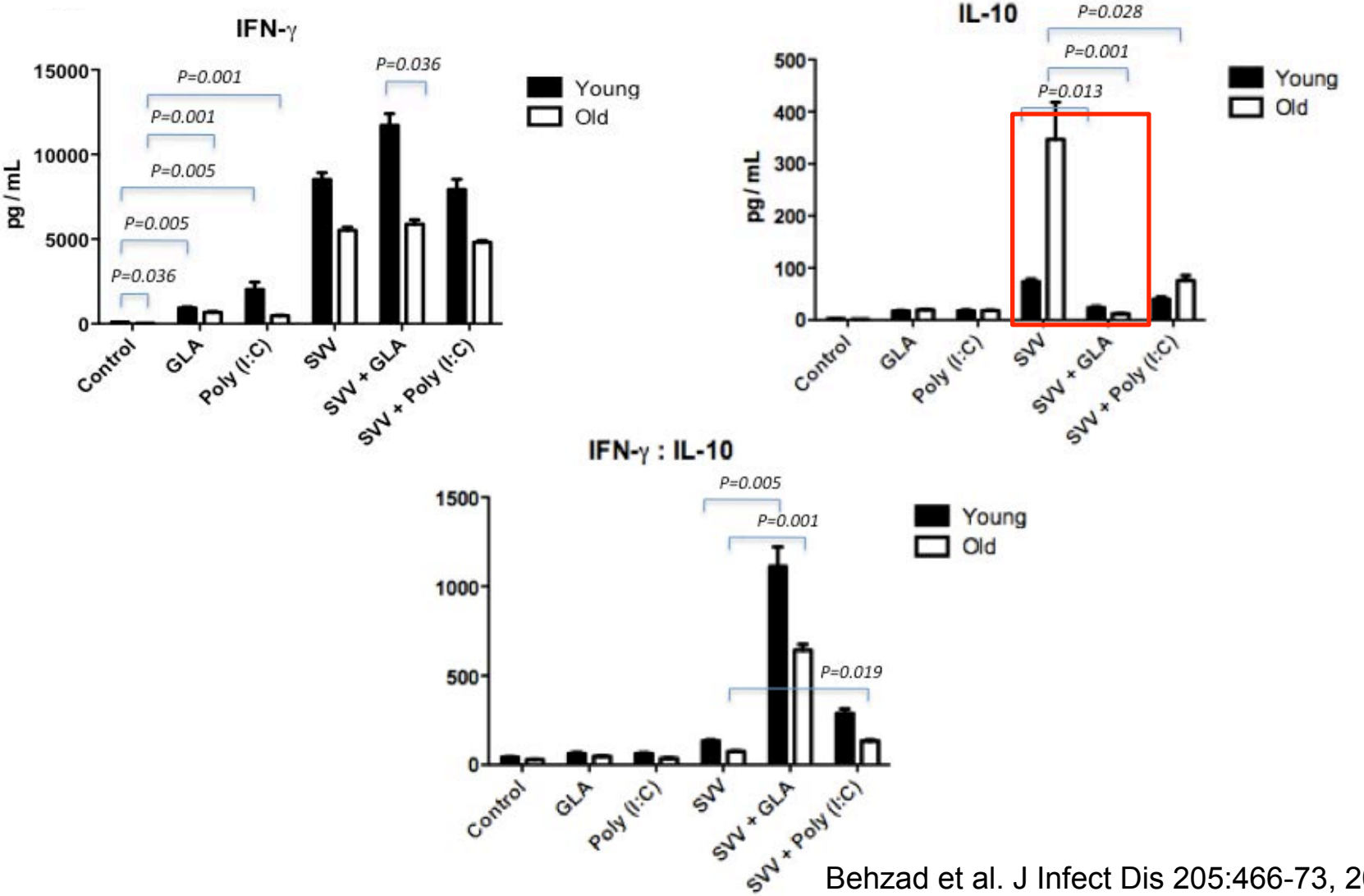


● High-dose SVV

□ Standard-dose SVV

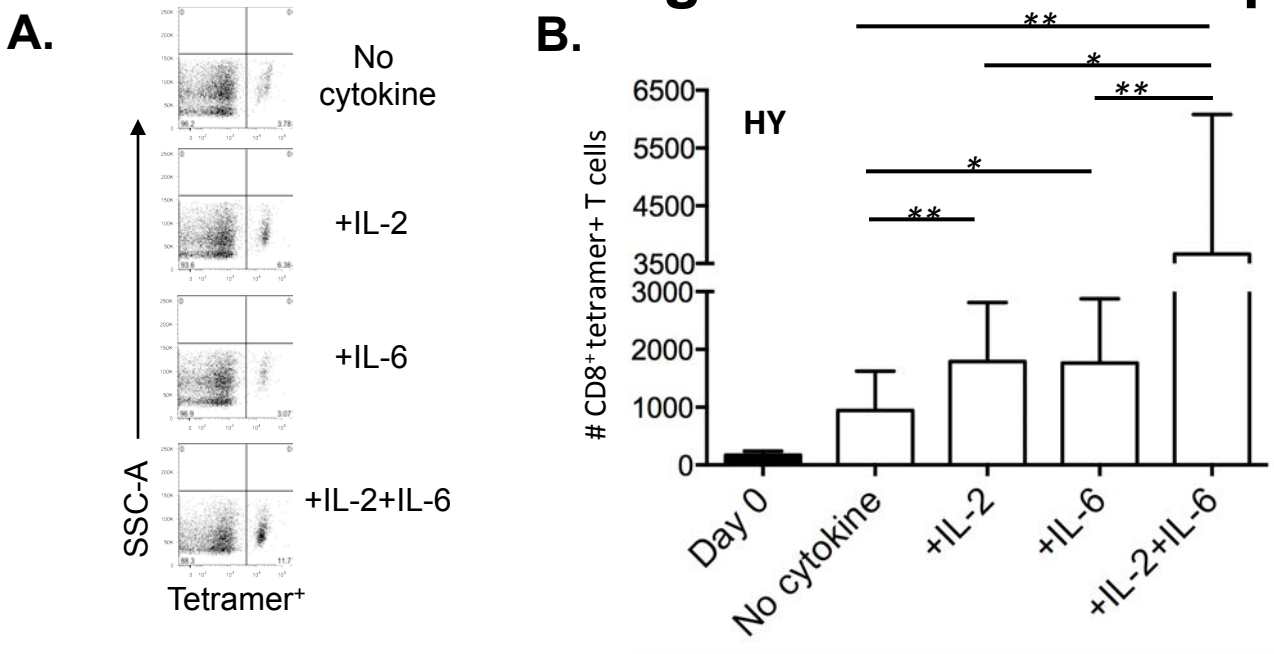
Merani et al. Exp Gerontol.107:116-125, 2018.

GLA-SE: Regulating Th1:Th2 response



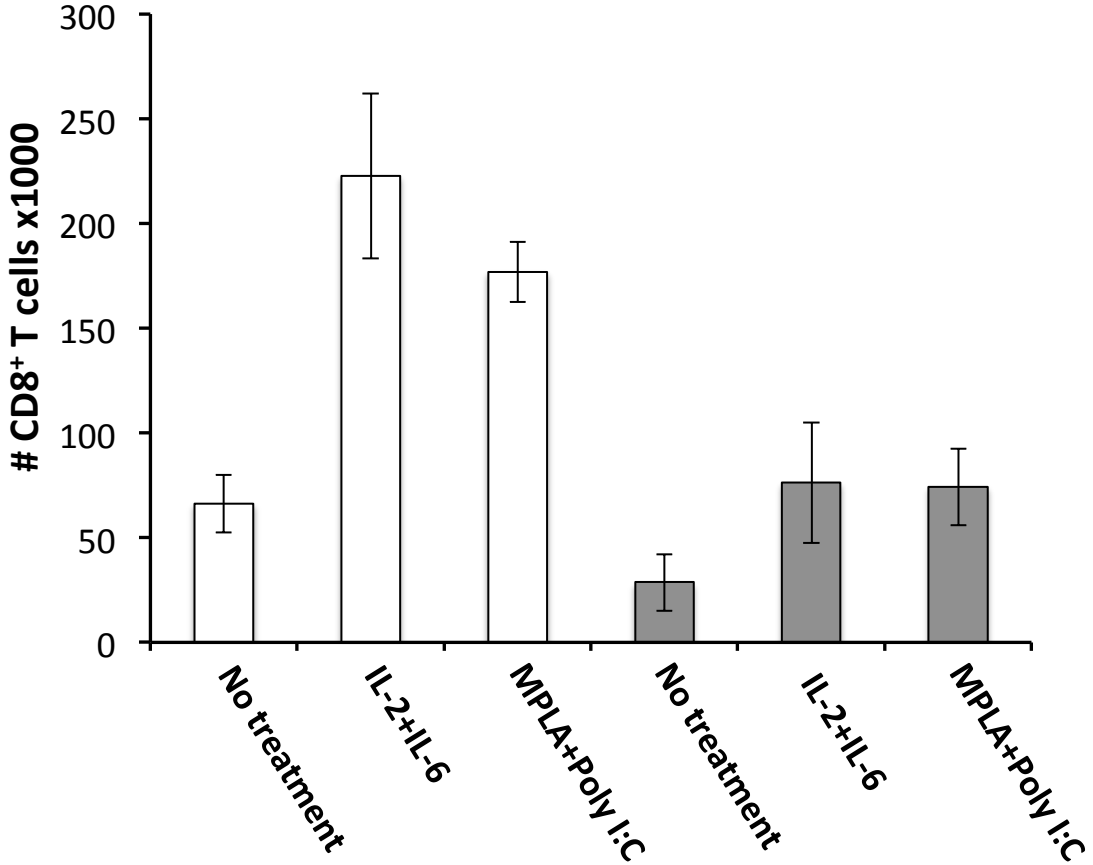
Behzad et al. J Infect Dis 205:466-73, 2012

IL-2/IL-6 restores the aged CD8+ T cell response to influenza



Zhou et al Oncotarget. 7:39171-83, 2016

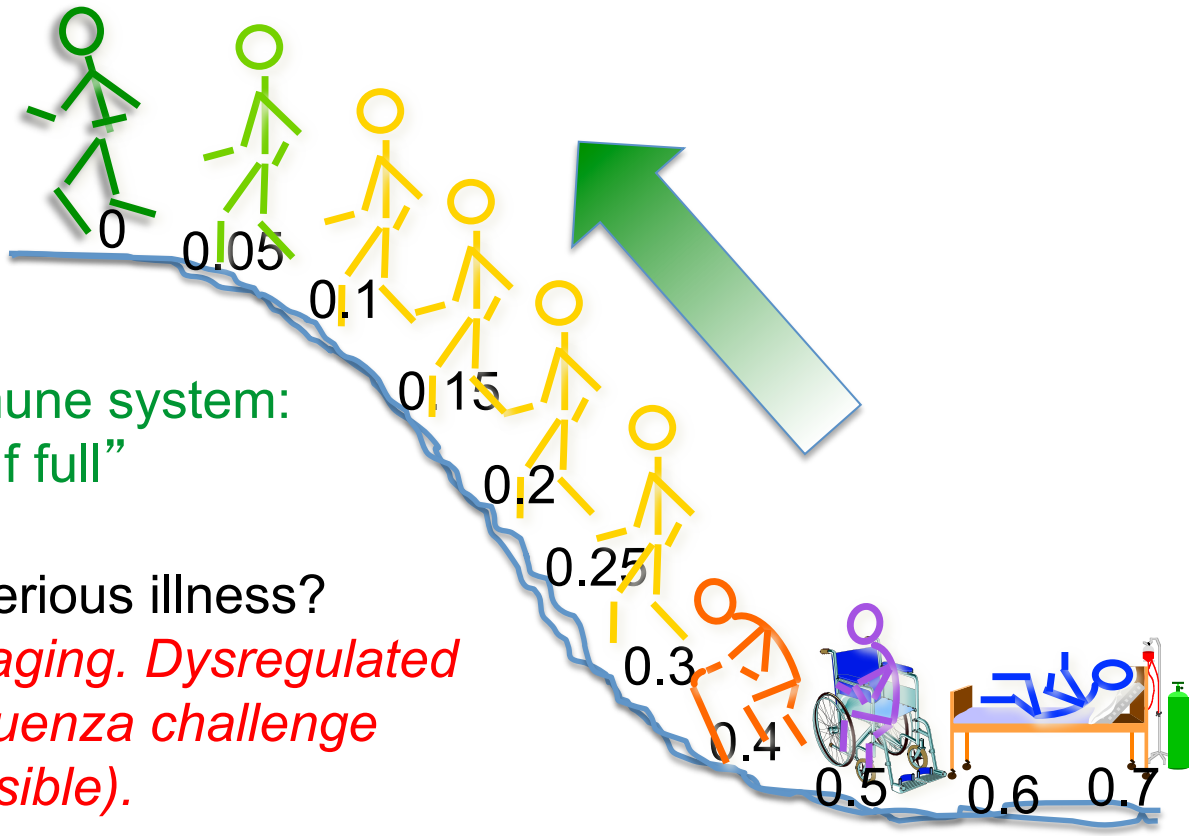
IL-2/IL-6 effect can be replicated with TLR3/4 ligand: CD8$^+$ T cell response to influenza virus*



*unpublished

Zhou et al Oncotarget. 7:39171-83, 2016

Summary



Resilience of aging immune system:
"Keeping your glass half full"

Why is influenza still a serious illness?
CD8+ CTL decline with aging. Dysregulated immune response to influenza challenge (but appears to be reversible).

How can we develop more effective influenza vaccines?

- *Vaccines that include M1 and NP*
- *TLR agonists stimulate mDC to produce IL-6, TNF-α, IL-1*
- *Suppress IL-10 production (?Treg) upon influenza challenge*