

B Cells and Aging

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OUTLINE

Brief introduction of aging effects on the immune system and B cells

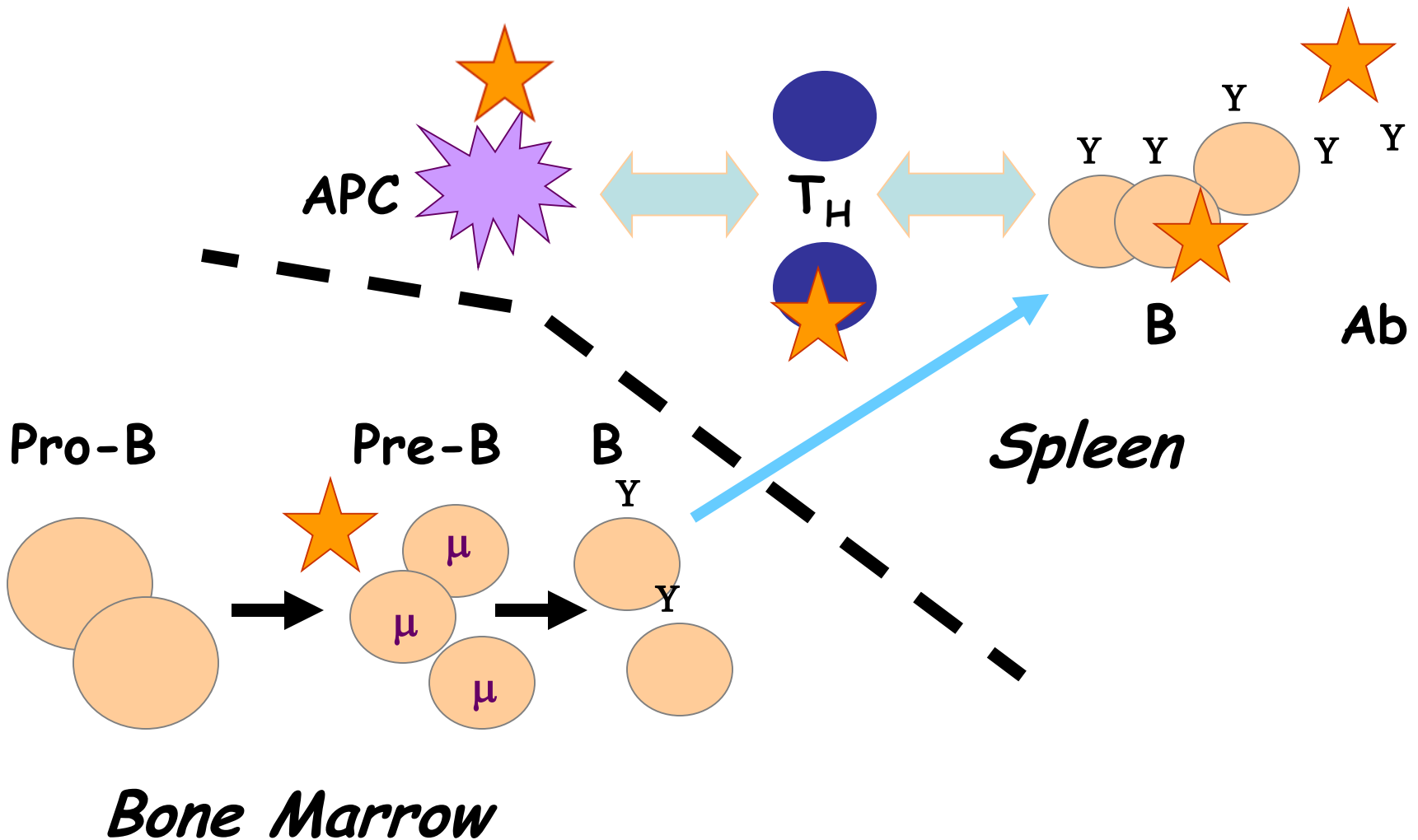
To address the issues - 1) **the need for reliable biomarkers – better diagnostic tools**: our contribution of biomarkers to predict as well as track an optimal (vaccine) response: Sw Mem B cells, AID, (low) TNF- α , (low) miRs (155 and 16) and CMV (**issue 3**)

2) our contribution to understanding **the cellular and molecular basis for immune senescence**: our results for influenza vaccine responses – regulated by inflammation due to e.g. viral seropositivity (CMV), increased miRs in aging and obesity (**issue 1**)

3) Reviewing our recent evidence that repeated vaccination in the elderly **“delays the transition between “young old” to “old old”**: B memory, plasma cells and inflammation in B cells in aging (**issue 2**).

4) For discussion – **how to translate** our knowledge into the development of vaccine strategies (especially for the poorest countries)

Immune Deficiencies in Senescence

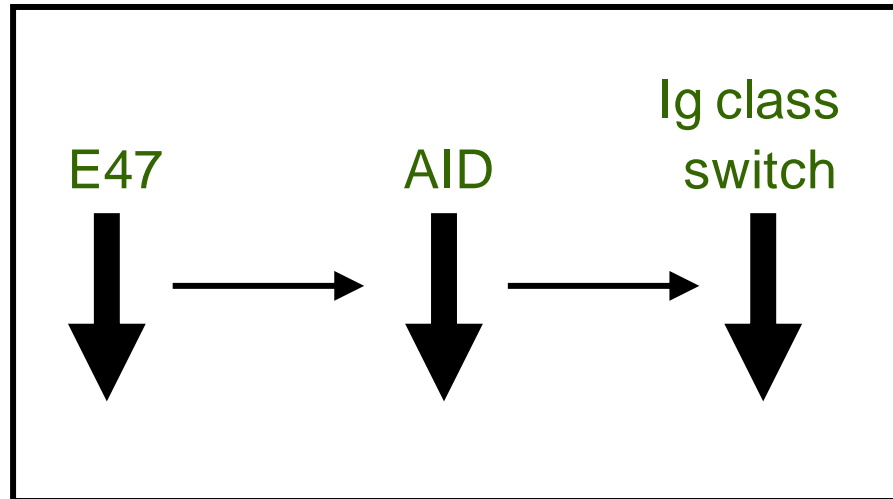


Aging and the Influenza Vaccination

- 1) The serologic response to influenza vaccine decreases with age
- 2) Successive annual vaccinations increase protection against influenza, suggesting that cellular and humoral immune mechanisms are important for protection in elderly individuals
- 3) Age-related decrease in antibody responses to influenza vaccination have previously been correlated with T cell function
- 4) *Objectives of our work were to determine if autonomous biomarkers of human B cell function could help to predict the in vivo response to the influenza vaccine*

EFFECT OF AGE ON Ig CLASS SWITCH

- Aging decreases E47 in activated B cells
- Aging decreases AID and CSR in activated B cells
- Aging decreases IgG antibody production by activated B cells



AID, activation-induced cytidine deaminase, regulates CSR and SHM, critical for high affinity antibodies

Frasca et al. J. Immunol.
2004, 2005, 2007, 2008, 2012
Frasca et al. Vaccine 2010
Frasca et al. Int Immunol 2012

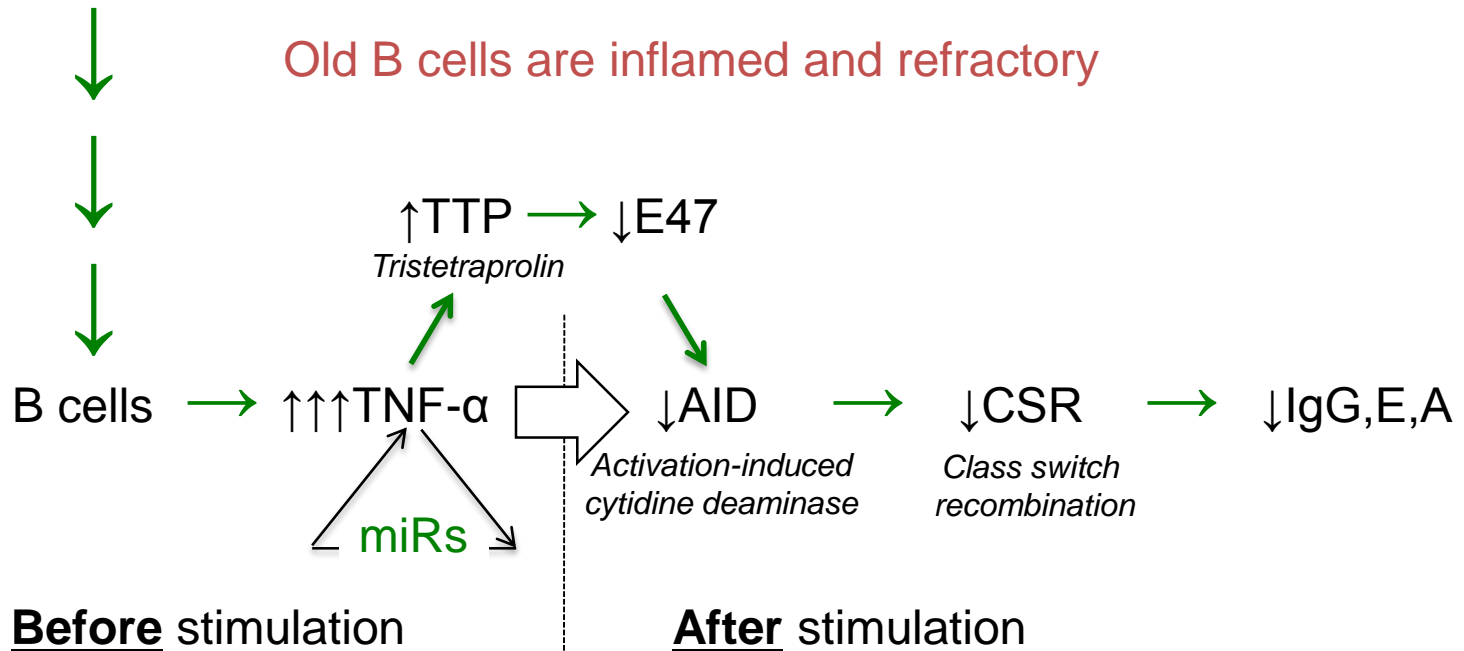
MOLECULAR PATHWAYS FOR REDUCED B CELL RESPONSES IN AGING

Inflammatory cytokines

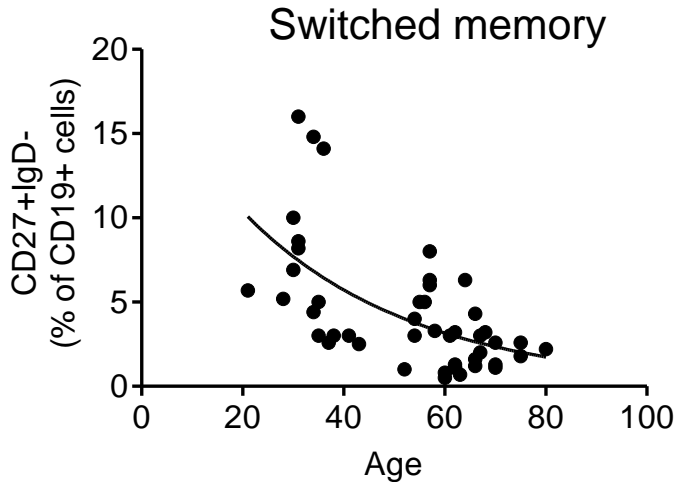
Microbiome

Fat

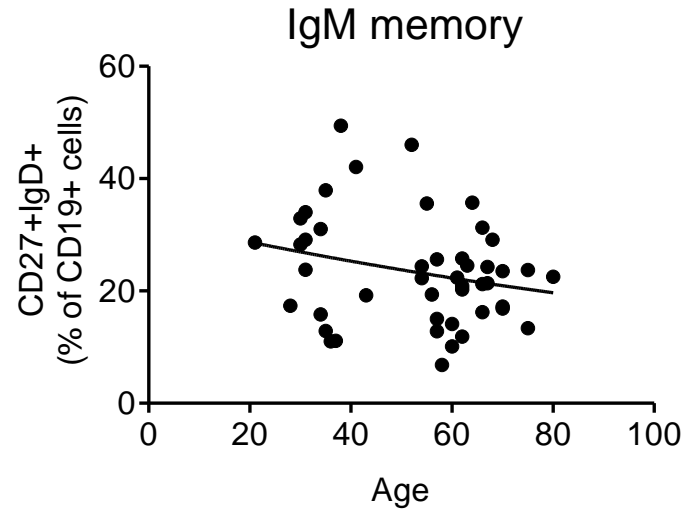
CMV



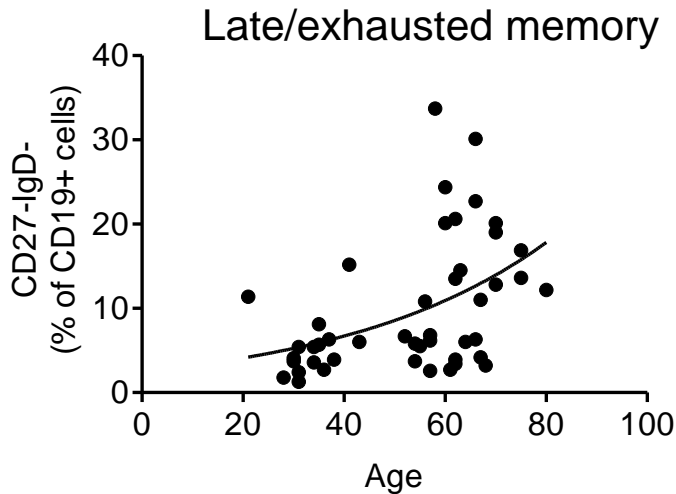
Age effects on B cell subsets



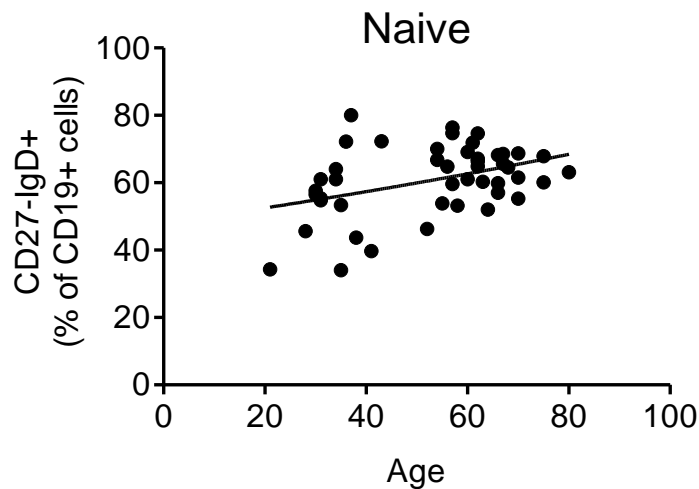
Spearman's rho= -0.61, $p < 0.0001$



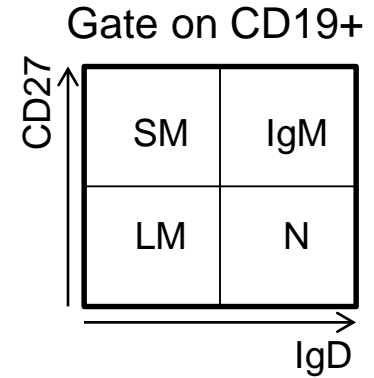
Spearman's rho= -0.20, $p = 0.17$



Spearman's rho= 0.51, $p = 0.0003$



Spearman's rho= 0.32, $p = 0.03$



Total #s and % of B cells decrease with age

We call our "elderly" those 60 and older (where we see the changes)

AGE DEFECTS IN B CELLS CONTRIBUTE TO THE REDUCED RESPONSE OF THE ELDERLY TO INFLUENZA VACCINATION

(summary of our published results)

1. At t0, CpG (a B cell mitogen which mimics B cell stimulation by antigen/T cells)-induced AID predicts serum response before vaccination → therefore AID is a biomarker to predict the immune response in both young and elderly
2. At t0, the percentages of switched memory B cells correlate with the serum antibody response to the vaccine and these are lower in the elderly therefore this is another biomarker to predict the response in both young and elderly

Frasca et al. Vaccine. 2010, 28:8077-84

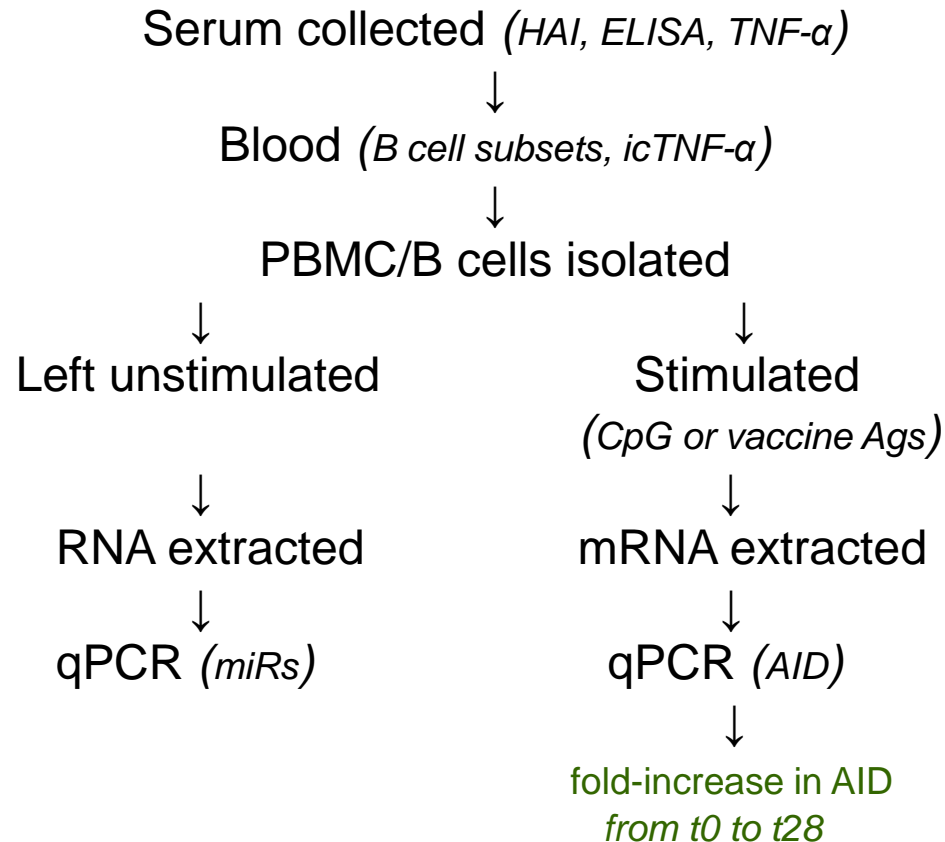
Frasca et al. Int Immunol. 2012, 24:175-82

Khurana et al. PLoS Pathog. 2012, Sep;8:e1002920

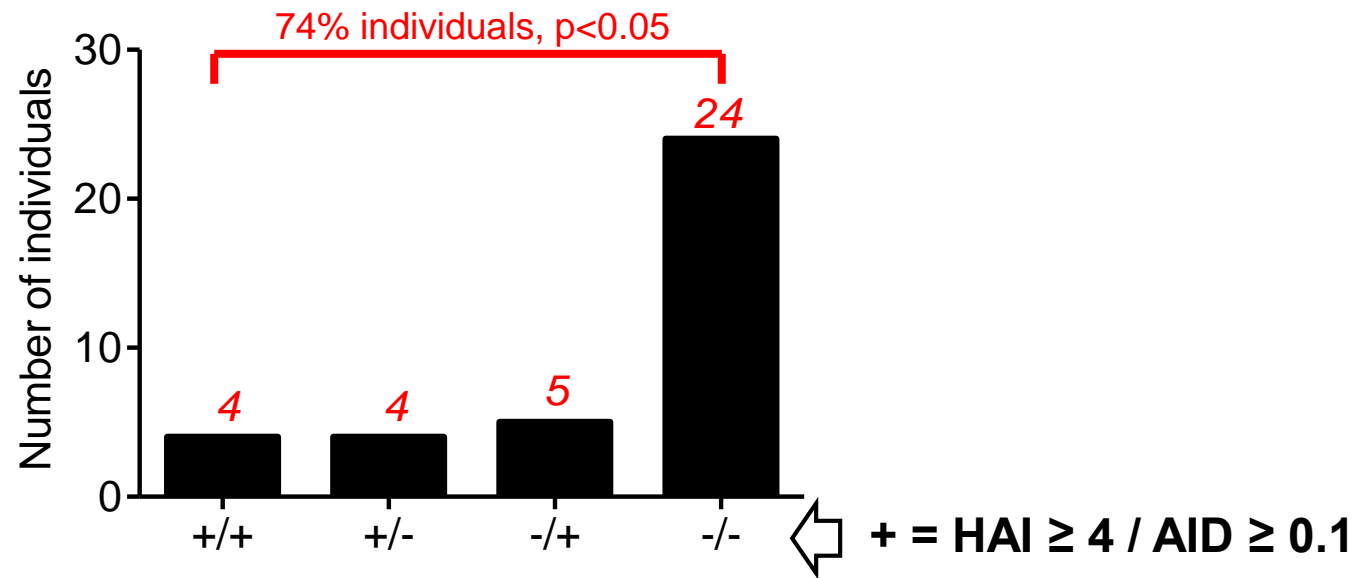
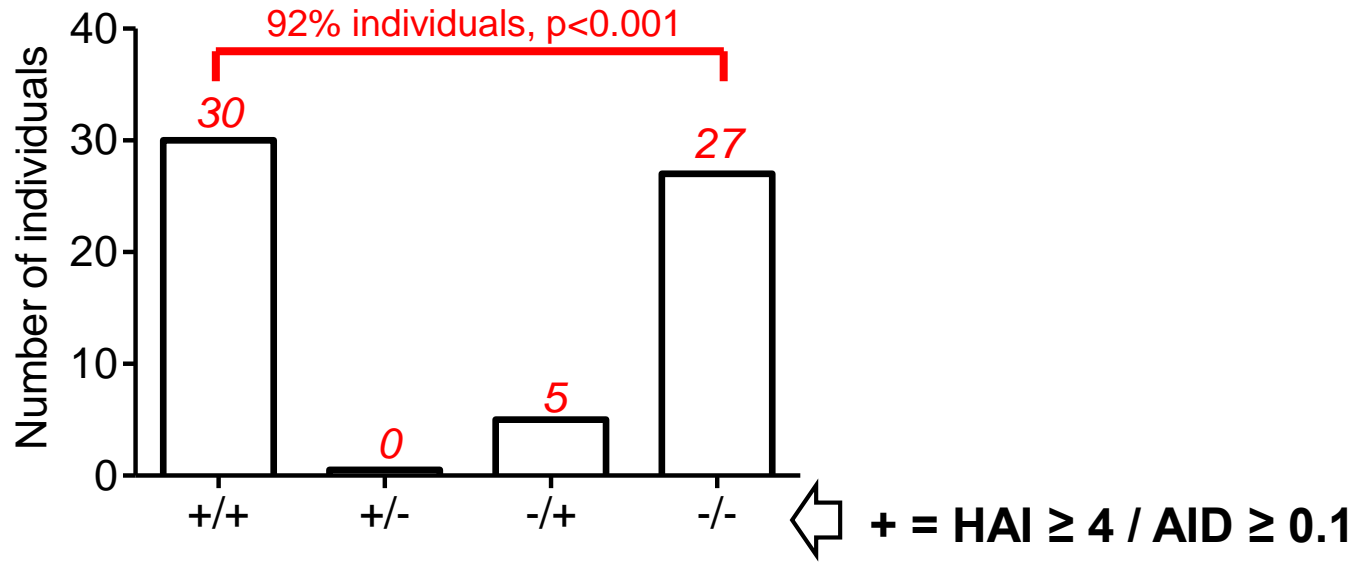
EXPERIMENTAL SCHEME

Seasonal influenza vaccine 2011-2012
(Novartis TIV Fluvirin and GSK TIV Fluarix)

Blood drawn at t_0 , t_7 and t_{28} :

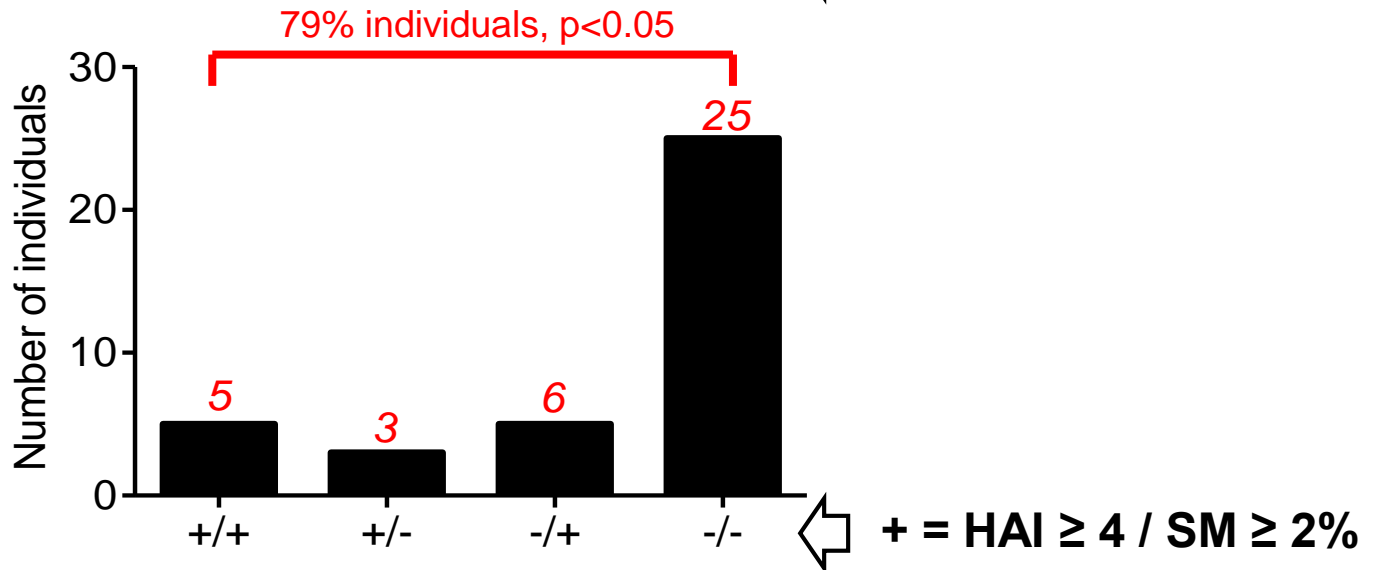
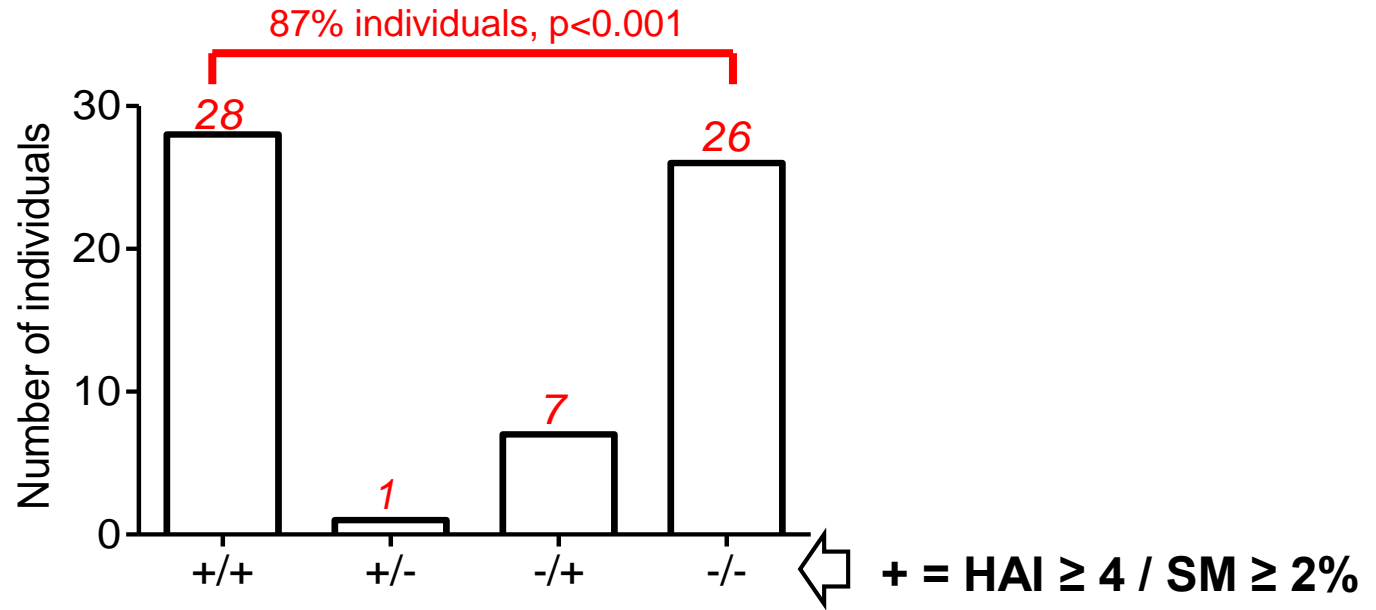


AID predicts the HAI response in 92% of young and 74% of elderly individuals



Season 2010-2011
and 2011-2012
62 young, 39 elderly

Switched memory B cells predict the HAI response in 87% of young and 79% of elderly individuals



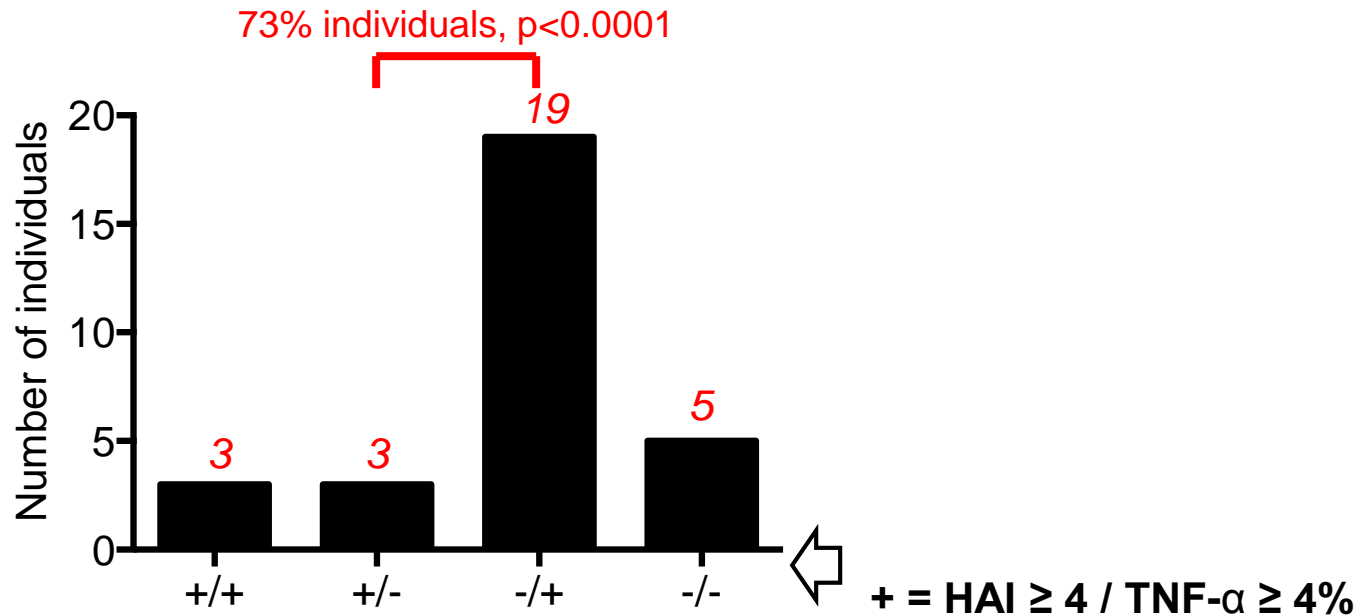
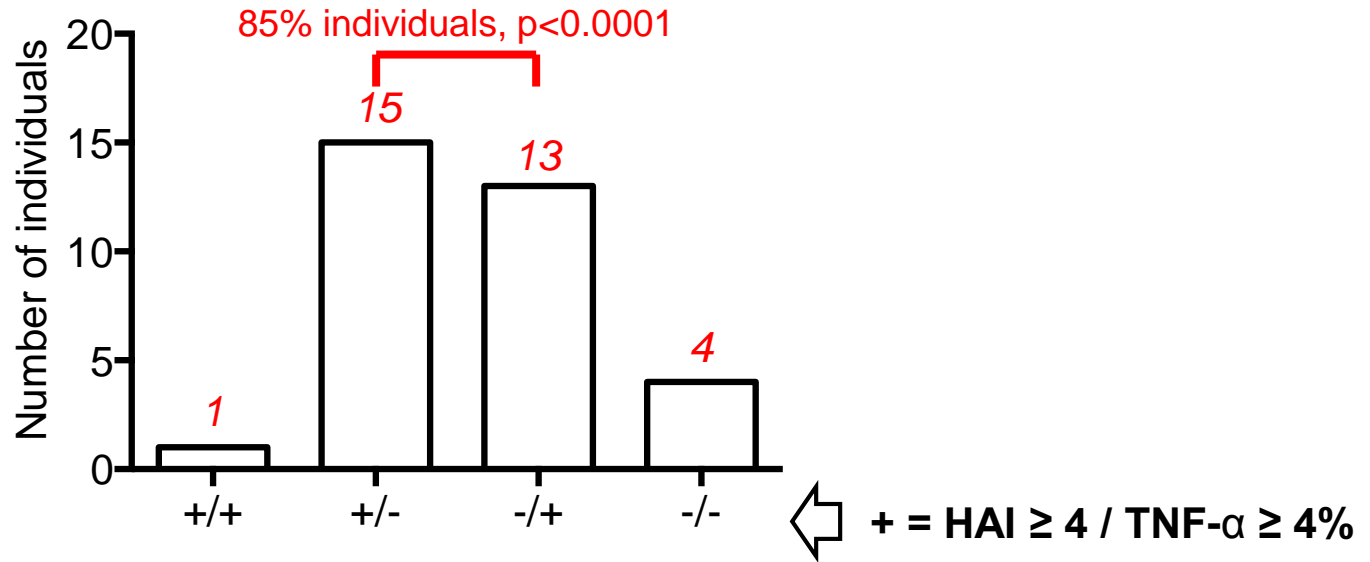
Season 2010-2011
and 2011-2012

62 young, 39 elderly

SUMMARY OF TNF- α DATA

- 1) Both serum and (unstimulated) B cell-derived TNF- α increase with age (they are “refractory”)**
- 2) Systemic (serum) and B cell-derived TNF- α are correlated**
- 3) AID in vaccine-stimulated B cells is negatively correlated with intracellular levels of B cell-derived TNF- α protein**
- 4) Anti-TNF- α antibody increases CpG-induced AID in aged B cell cultures (and in aged mice)**

icTNF- α in B cells at t0 predicts a low HAI response in 85% of young and 73% of elderly individuals



Season 2010-2011
and 2011-2012

62 young, 39 elderly

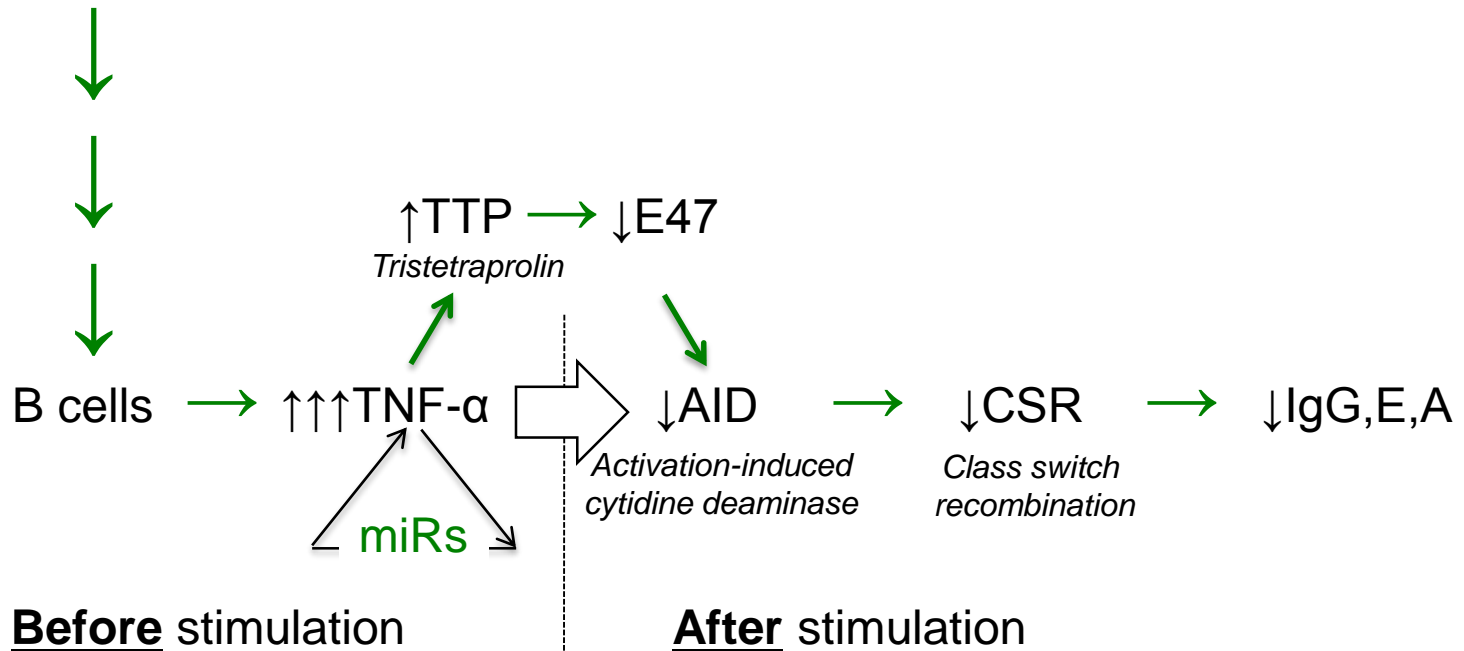
MOLECULAR PATHWAYS FOR REDUCED B CELL RESPONSES IN AGING

Inflammatory cytokines

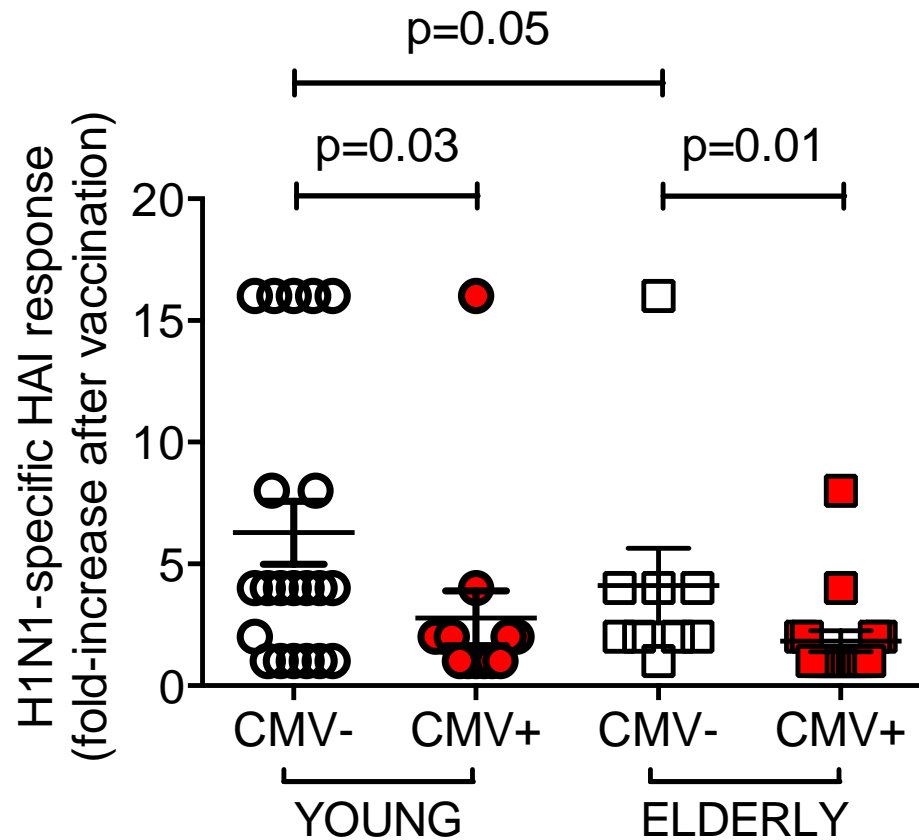
Microbiome

Fat

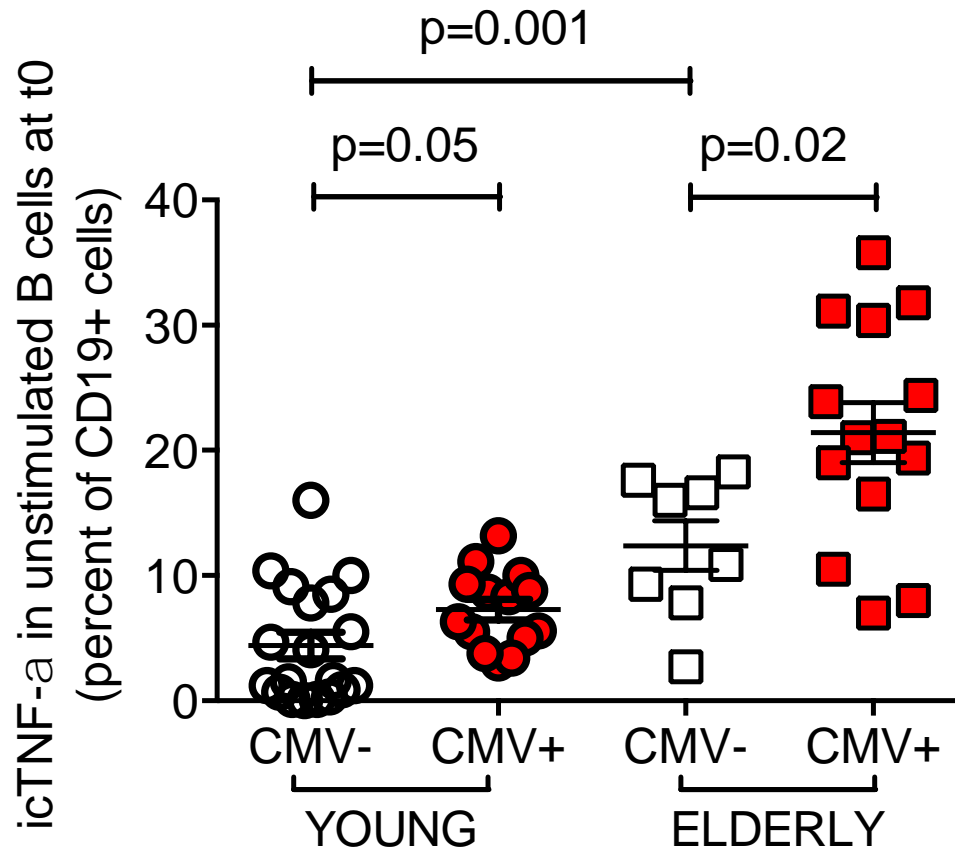
CMV



CMV SEROPOSITIVITY DECREASES THE IN VIVO RESPONSE TO THE VACCINE



LEVELS OF B CELL-DERIVED TNF- α ARE HIGHER IN ELDERLY CMV+ INDIVIDUALS



CONCLUSIONS

- 1) Intrinsic defects in human B cells affect their function with age
- 2) Molecular B cell signatures, such as AID, switched memory B cells and TNF- α can be used as “biomarkers” to predict functional B activity in potentially compromised immune conditions, e.g. aging
- 3) AID correlates with ability to generate a high affinity antibody to the influenza vaccine (published – PLoS Pathogens)
- 4) CMV seropositivity is
 - a) increased in the elderly and associated with lower influenza vaccine response
 - b) associated with higher serum and B cell TNF- α and negatively associated with AID and SW mem B cells

CONCLUSIONS (contd.)

5) a) AID (and E47) mRNA stability is lower in aged and CMV+

b) miRs

1) miR-155 is higher in unstimulated B cells from elderly as compared to young individuals and also higher in CMV-positive elderly individuals

2) miR-155 is positively correlated with B cell TNF- α and negatively correlated with AID

3) miR-155 and miR-16 are increased in unstimulated B cells from elderly

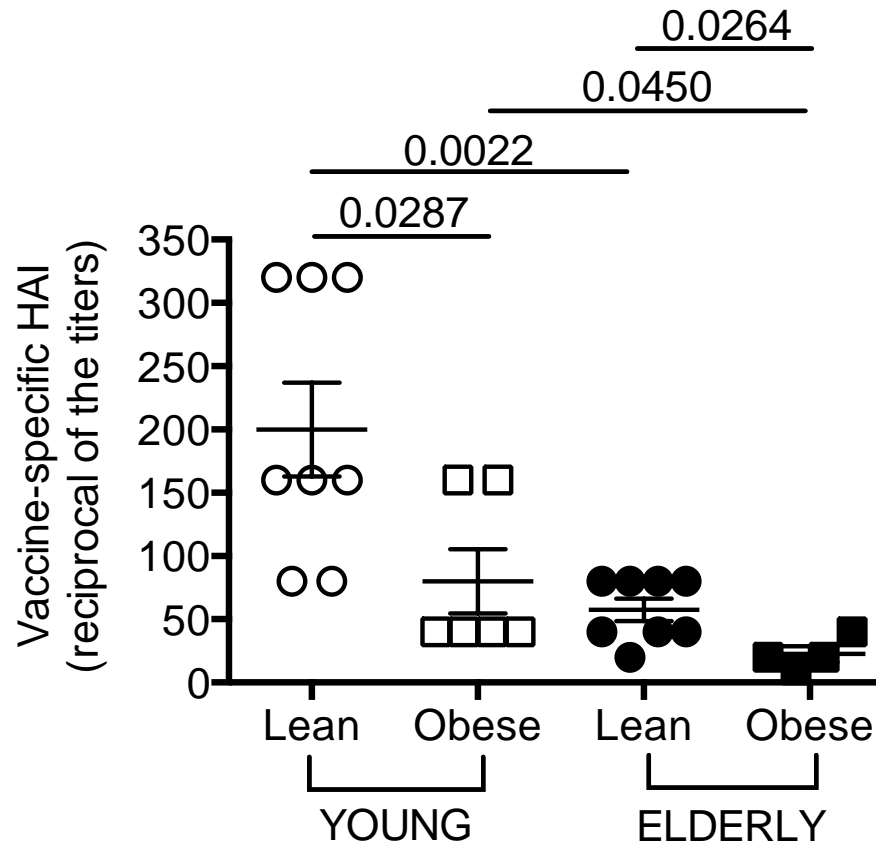
Most recent results

- Effects of obesity on B cell responses
- Effects of aging on B memory and plasma cell formation

OBESE INDIVIDUALS SHOW ATTENUATED INFLUENZA VACCINE RESPONSES AS COMPARED TO LEAN CONTROLS

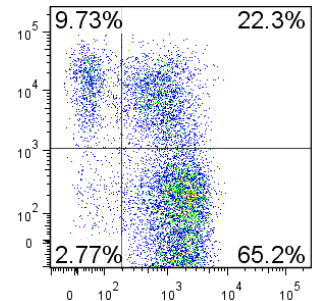
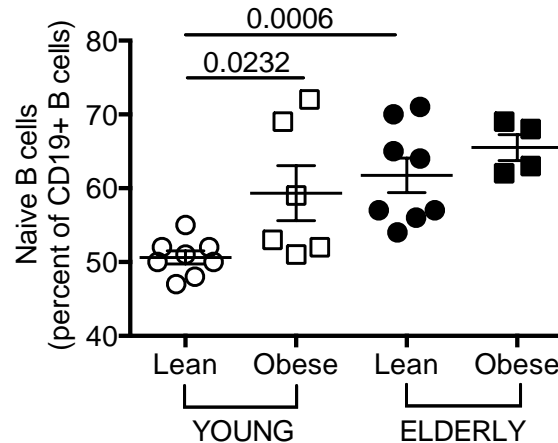
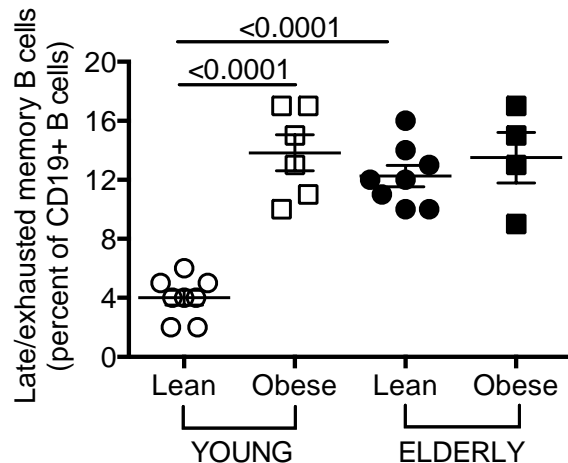
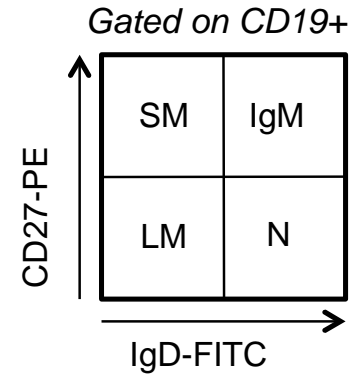
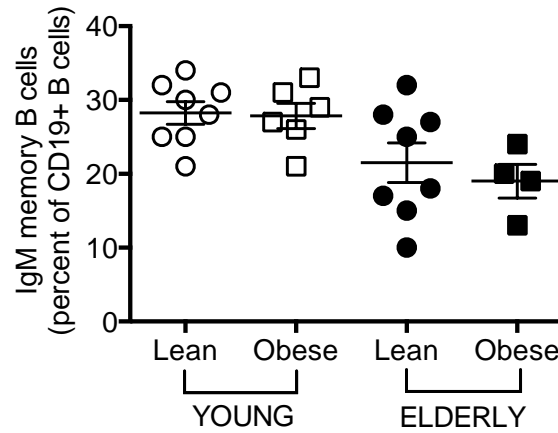
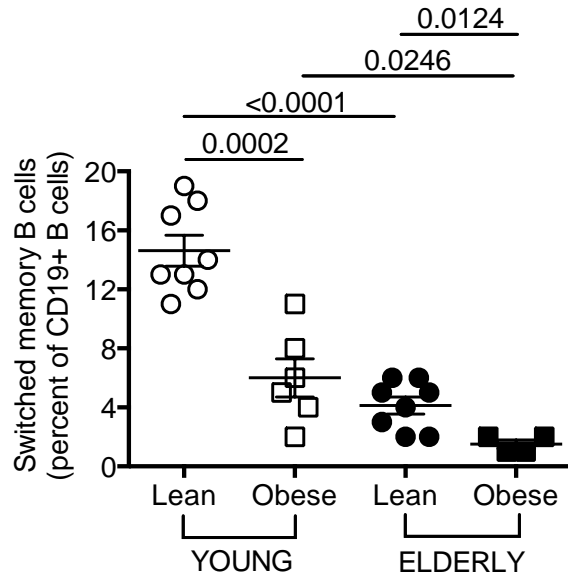
TIV (2011-2012):

A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2), B/Brisbane/60/2008 (B)

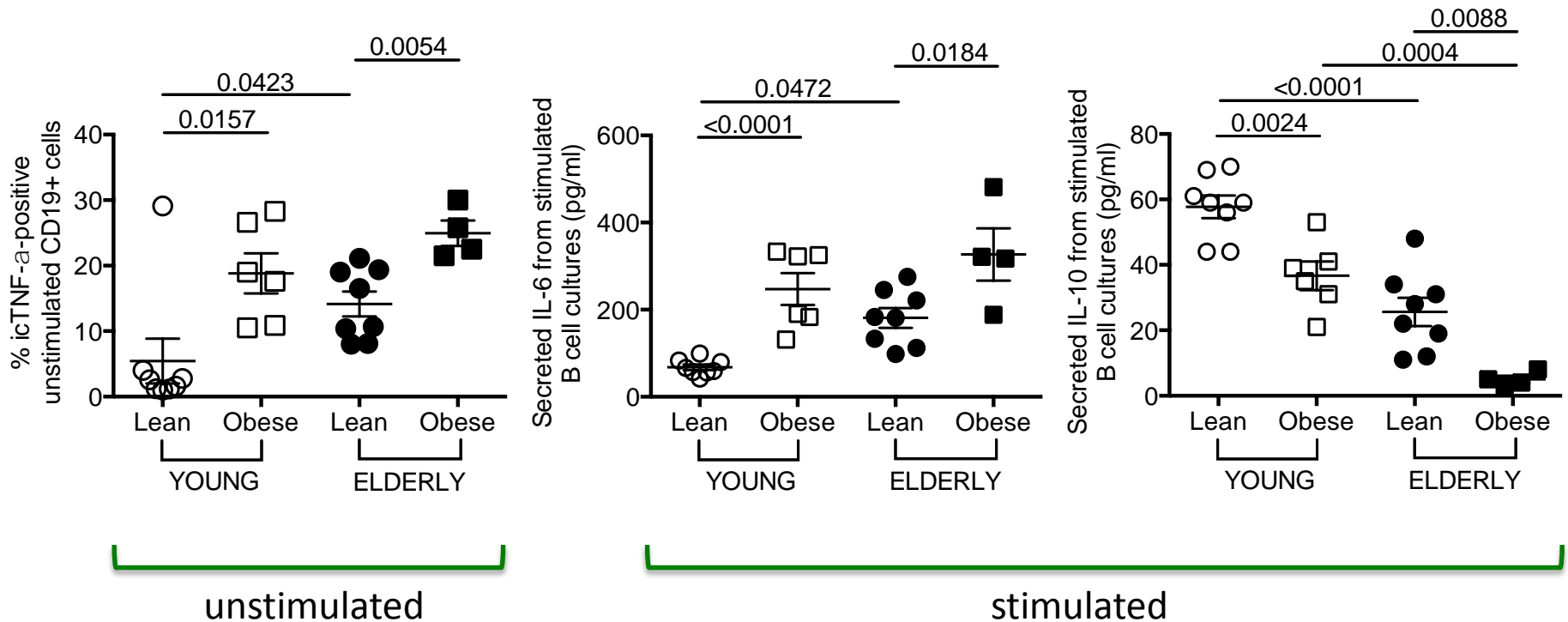


Accepted in
Obesity 2015

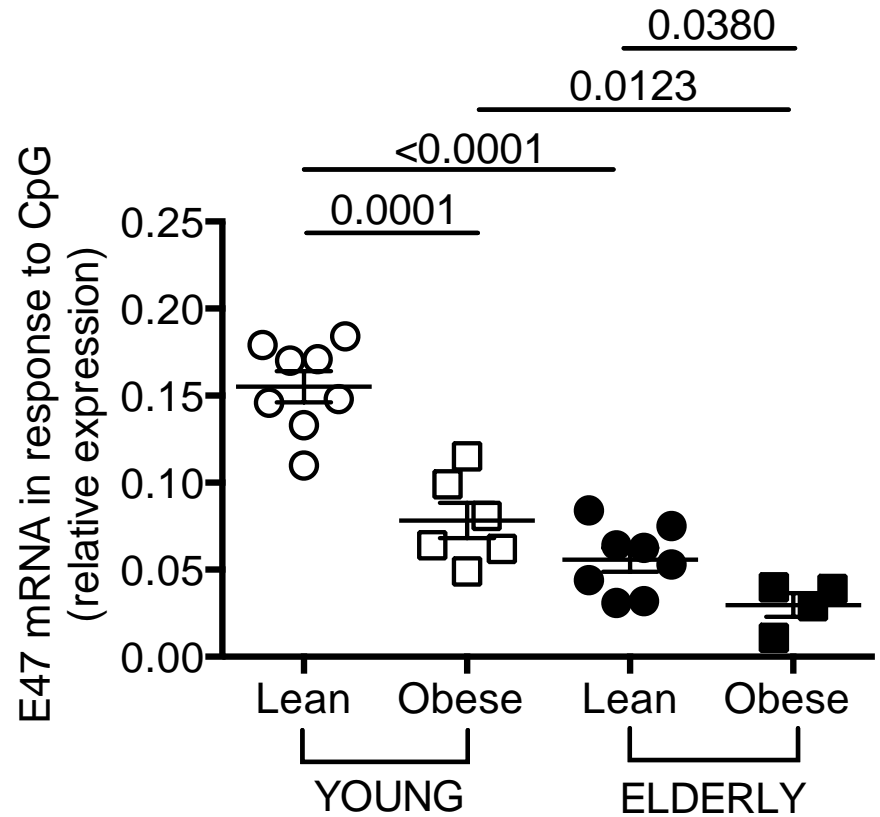
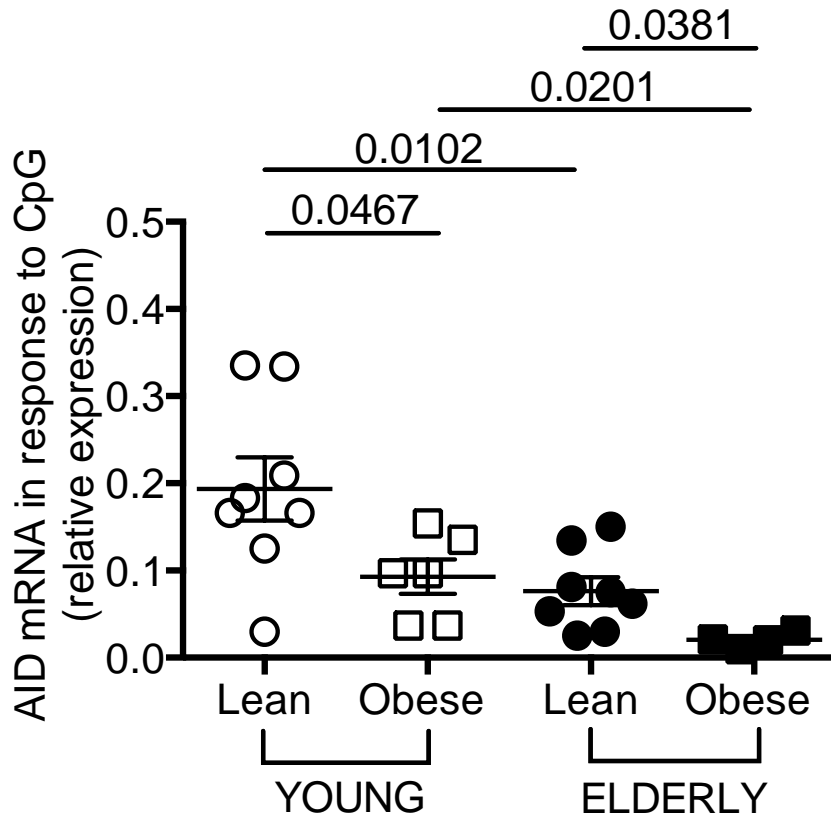
OBESITY IS ASSOCIATED WITH A DECREASED PERCENTAGE OF SWITCHED MEMORY B CELLS AND INCREASED PERCENTAGE OF LATE/EXHAUSTED MEMORY B CELLS



OBESITY IS ASSOCIATED WITH INCREASED PRODUCTION OF PRO-INFLAMMATORY CYTOKINES AND DECREASED PRODUCTION OF ANTI-INFLAMMATORY CYTOKINES BY B CELLS



OBESITY IS ASSOCIATED WITH DECREASED AID AND E47 IN CULTURED B CELLS



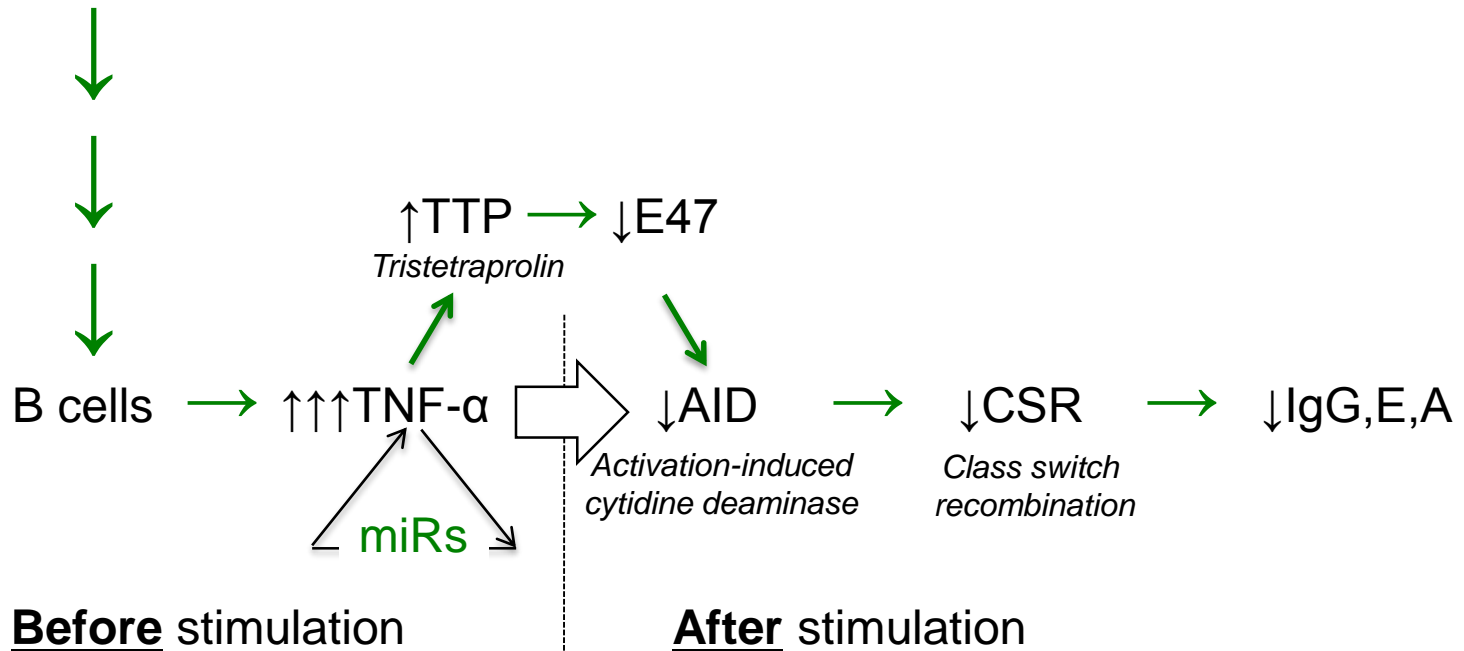
MOLECULAR PATHWAYS FOR REDUCED B CELL RESPONSES IN AGING

Inflammatory cytokines

Microbiome

Fat

CMV



CURRENT/FUTURE DIRECTIONS

- 1) Inflammation
- 2) CMV
- 3) Obesity/T2D
- 4) RA
- 5) Other vaccines (e.g. Pneumovax, Prevnar)
- 6) Small molecule screens and animal model testing, as possible new adjuvants for antigens/vaccines
- 7) Visceral fat as a contributor to inflammatory B cells



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BB

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All the subjects!