

B cell selection events affecting immunoglobulin repertoire

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Rosetrees Trust



The Dunhill Medical Trust





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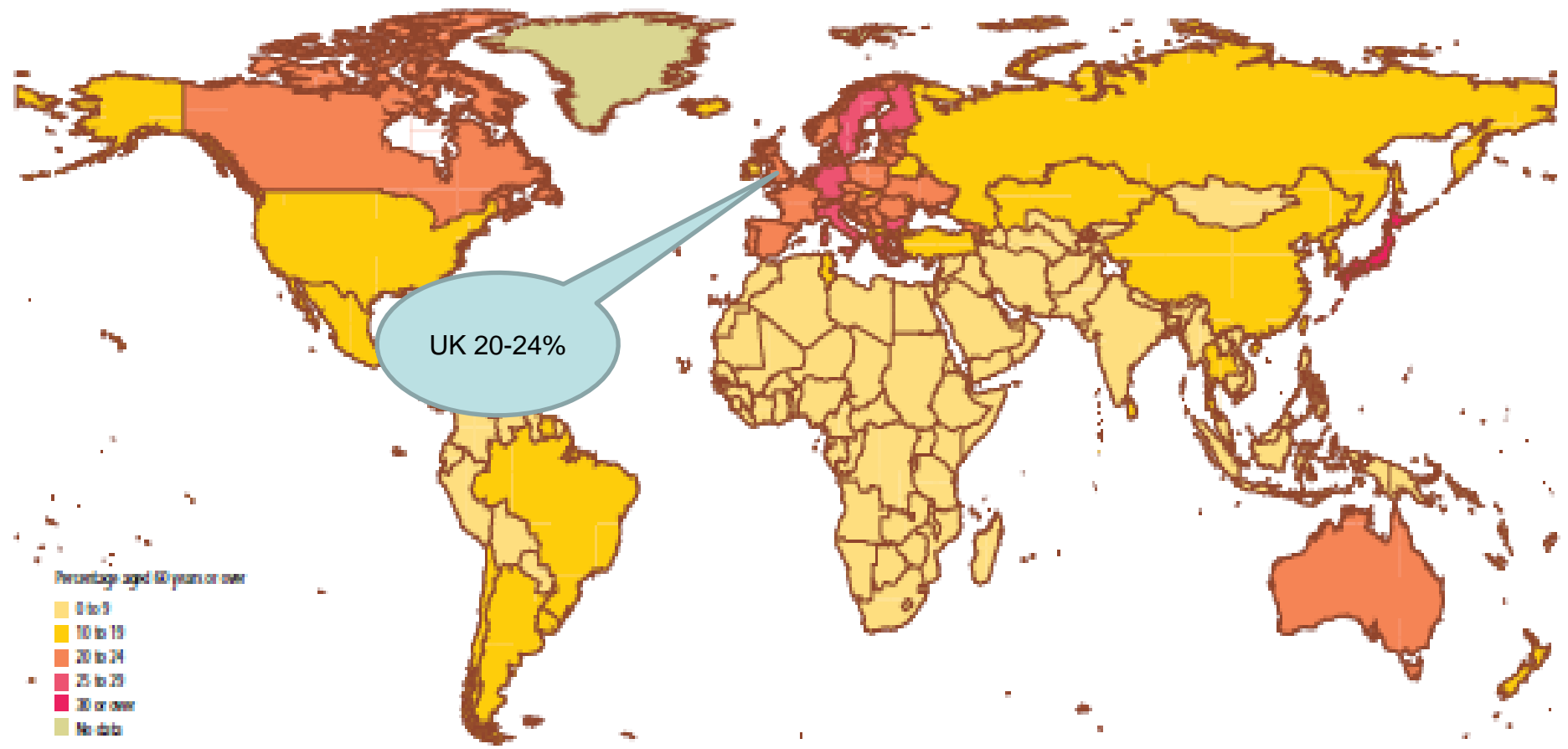
David Kipling



- Ageing and immunology
- Overview of B cell development and selection checkpoints
- Cell population changes – particularly IgM memory repertoire, subclasses of antibody
- Ig gene repertoire changes:
 - CDR3 after exogenous challenge
 - CDR3 and VDJ changes before exogenous antigen (tolerance selection?)

% of population over 60

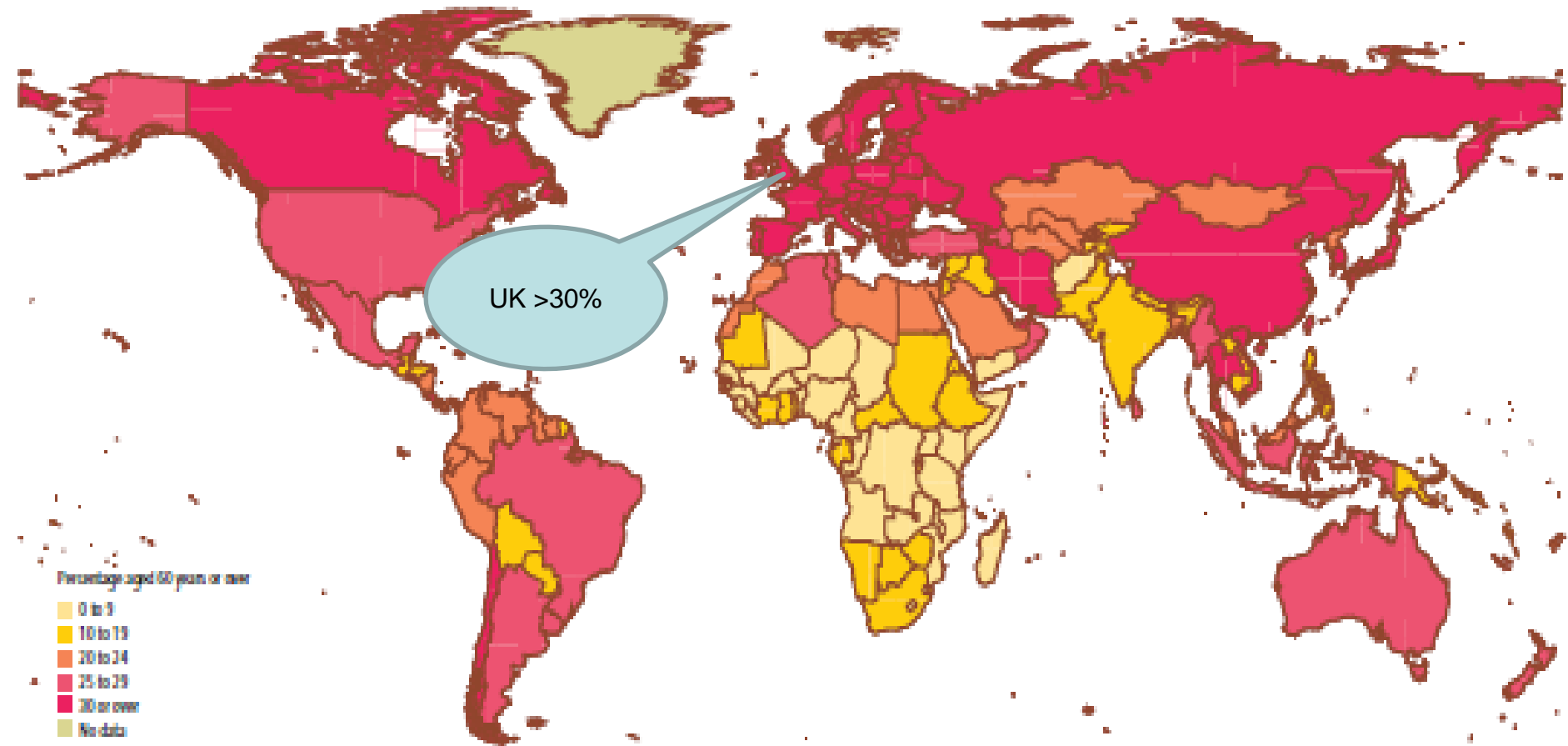
2012



343,000 centenarians
1.5% over 80

% of population over 60

2050

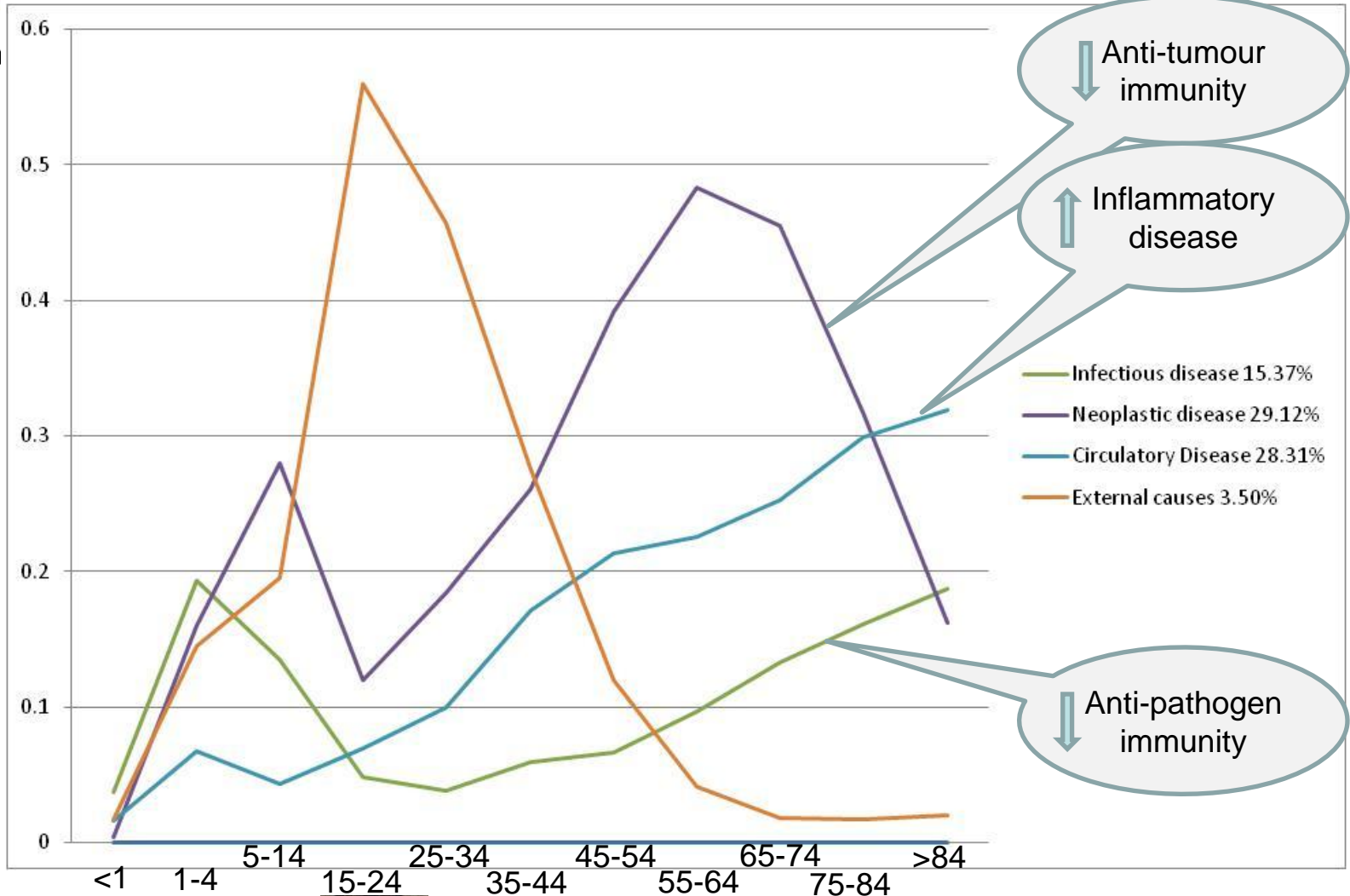


3.2 million centenarians (estimate revised up from 2.2 million in 2002)
4% over 80

Immune system and Mortality

(UK Office National Statistics July 2013 release)

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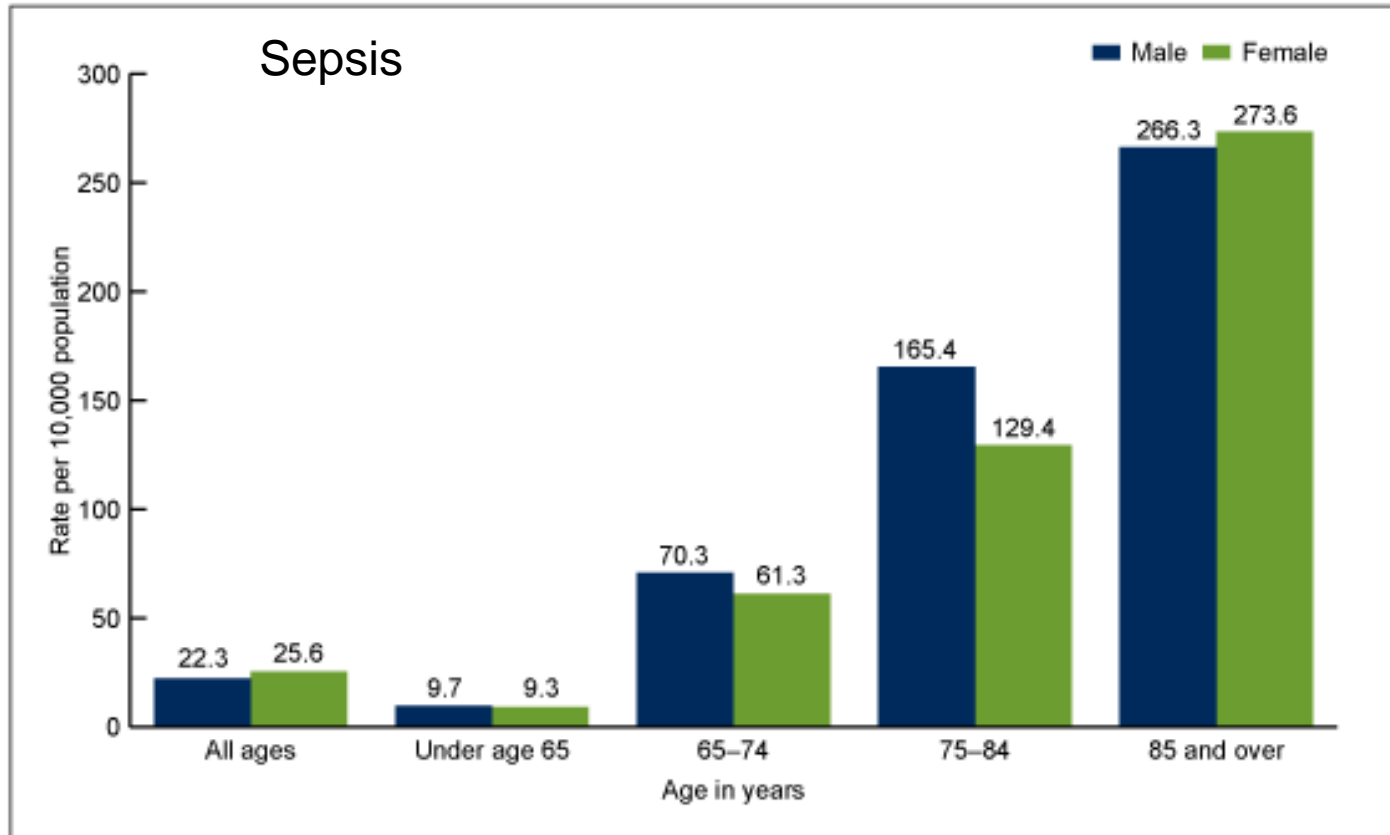


Age



Morbidity of infection changes with age

Figure 2. Rates of hospitalization for septicemia or sepsis, by sex and age, 2008



NOTES: Rates are significantly higher for males and females in each successive age group.

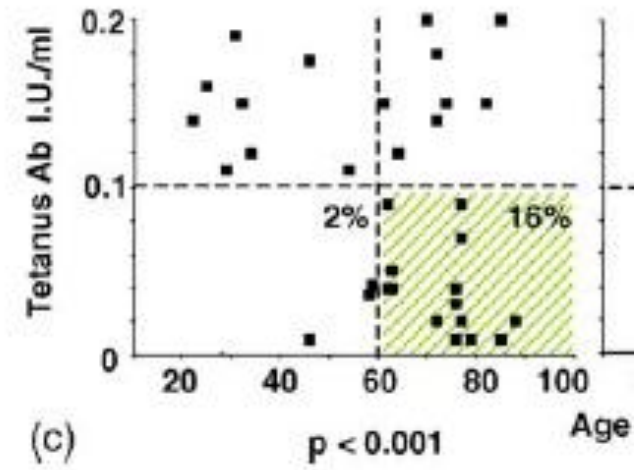
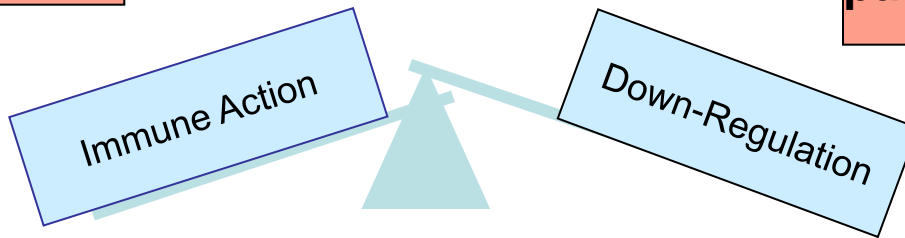
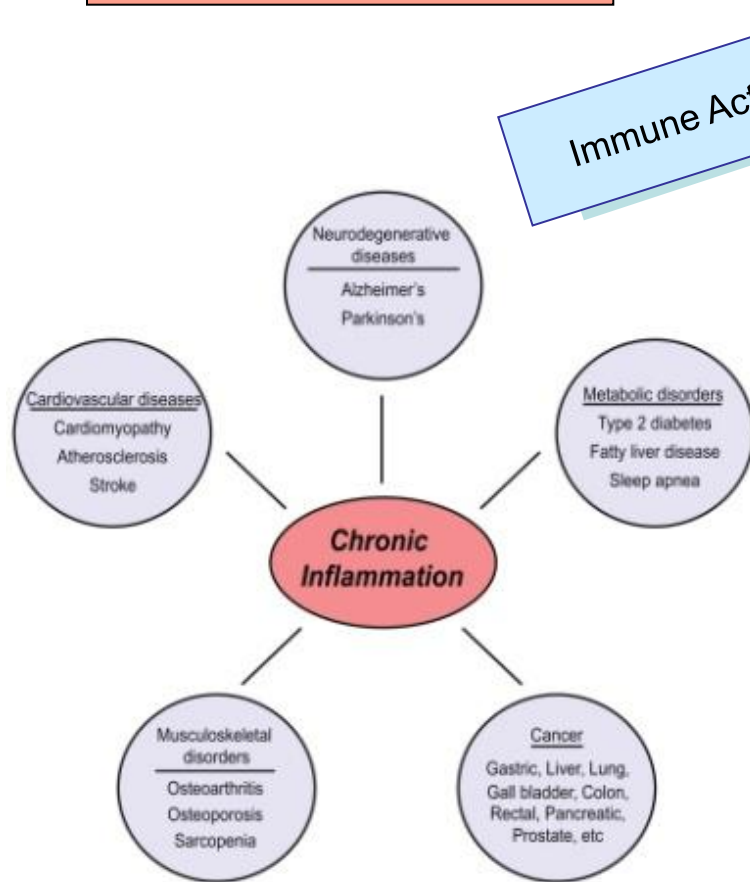
SOURCE: CDC/NCHS, National Hospital Discharge Survey, 2008.

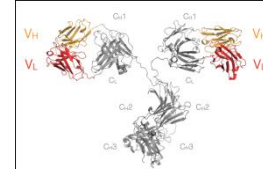
The older immune system fails on multiple levels

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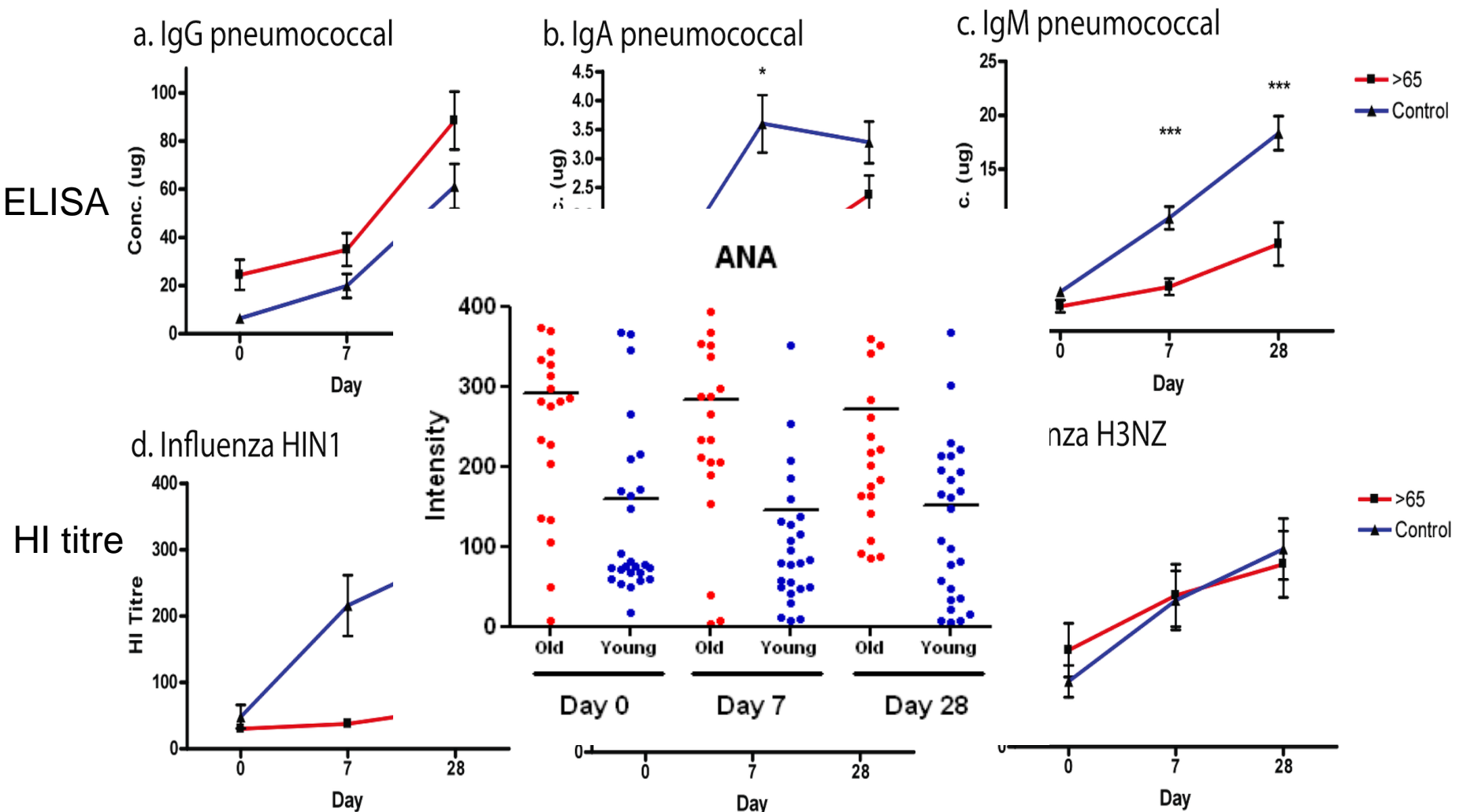
Inflammatory disease and autoimmunity

LOSS of protection against external pathogens and cancer

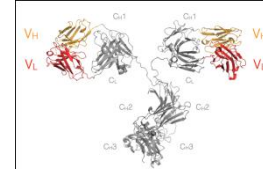




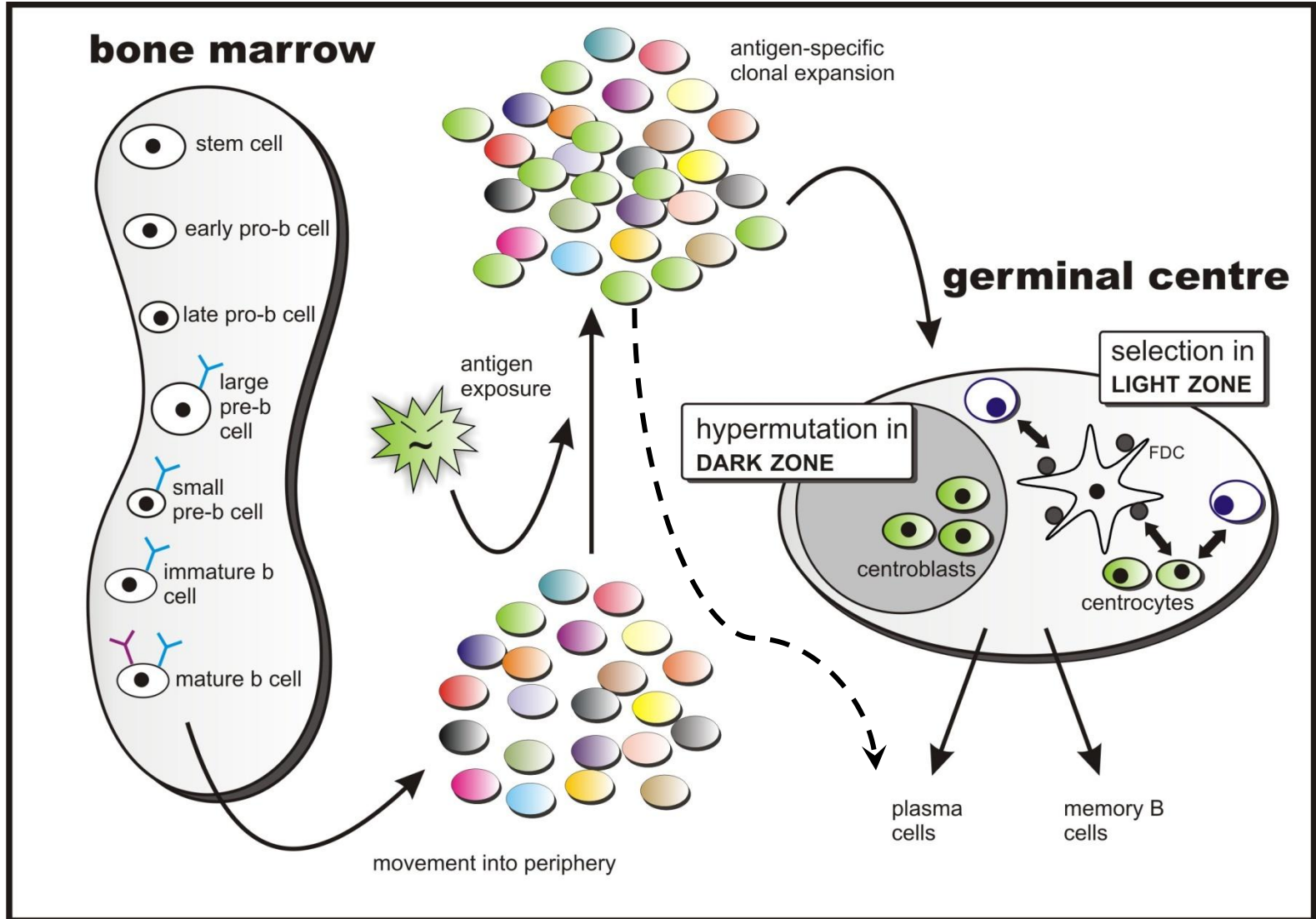
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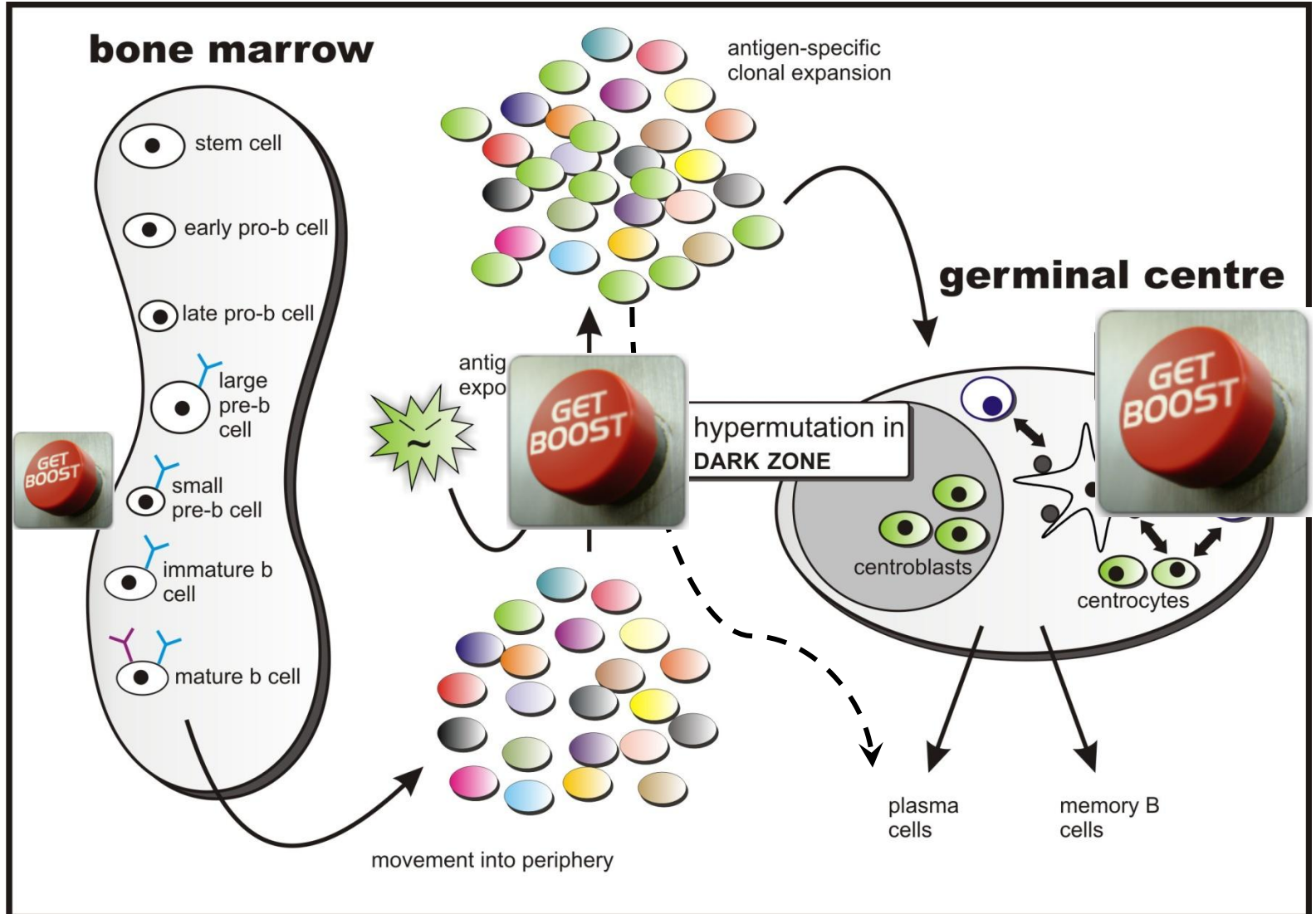
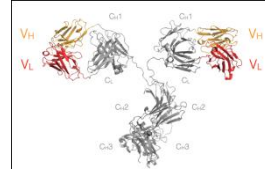
B cell development road map



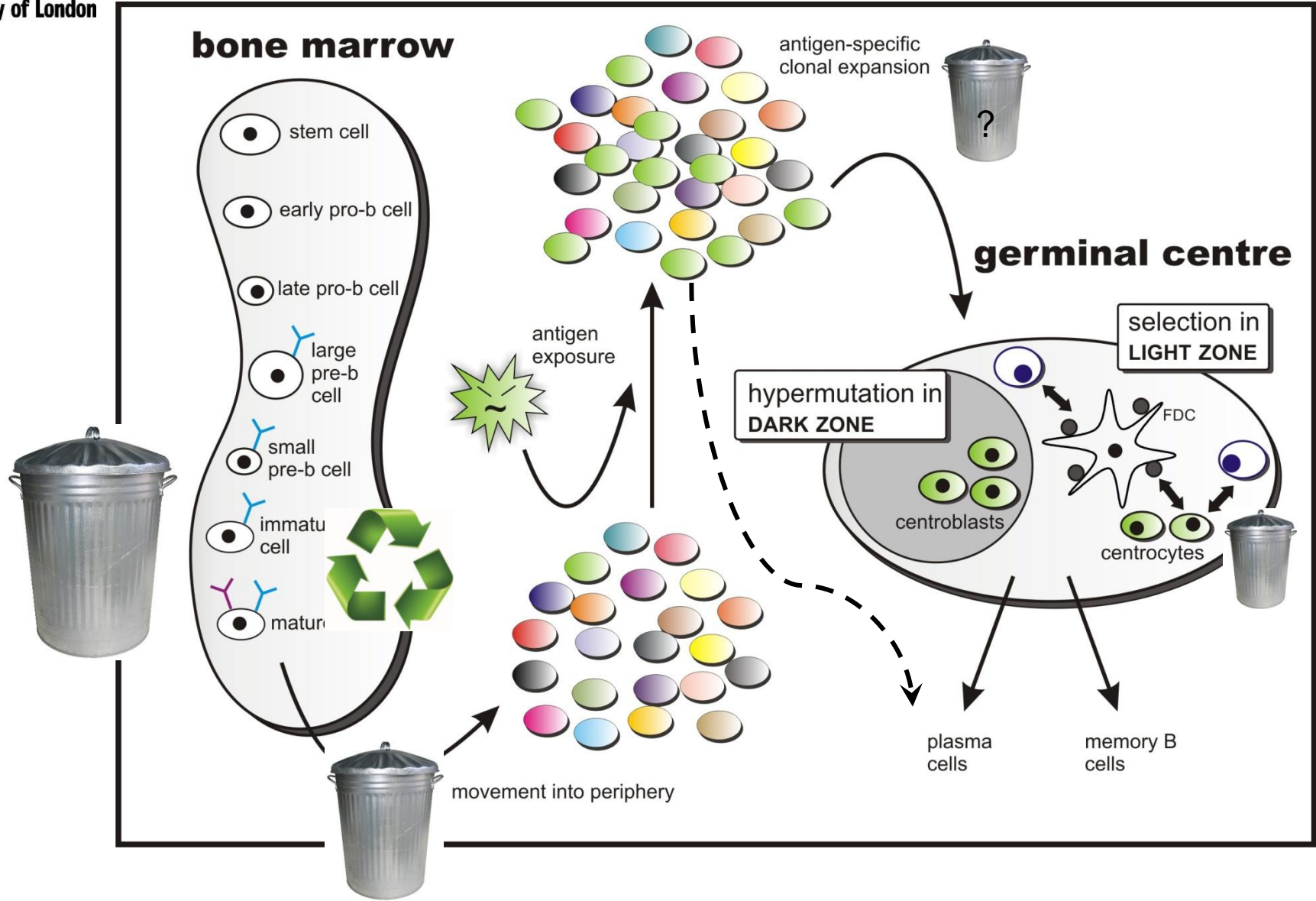
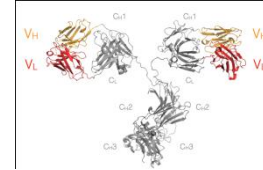
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Positive selection events to increase useful cells



Negative selection to remove potentially harmful B cells



Why look at repertoire?

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Poor negative selection = increased risk of autoimmune activation. Which B cells are more likely to be involved in autoimmune disease?

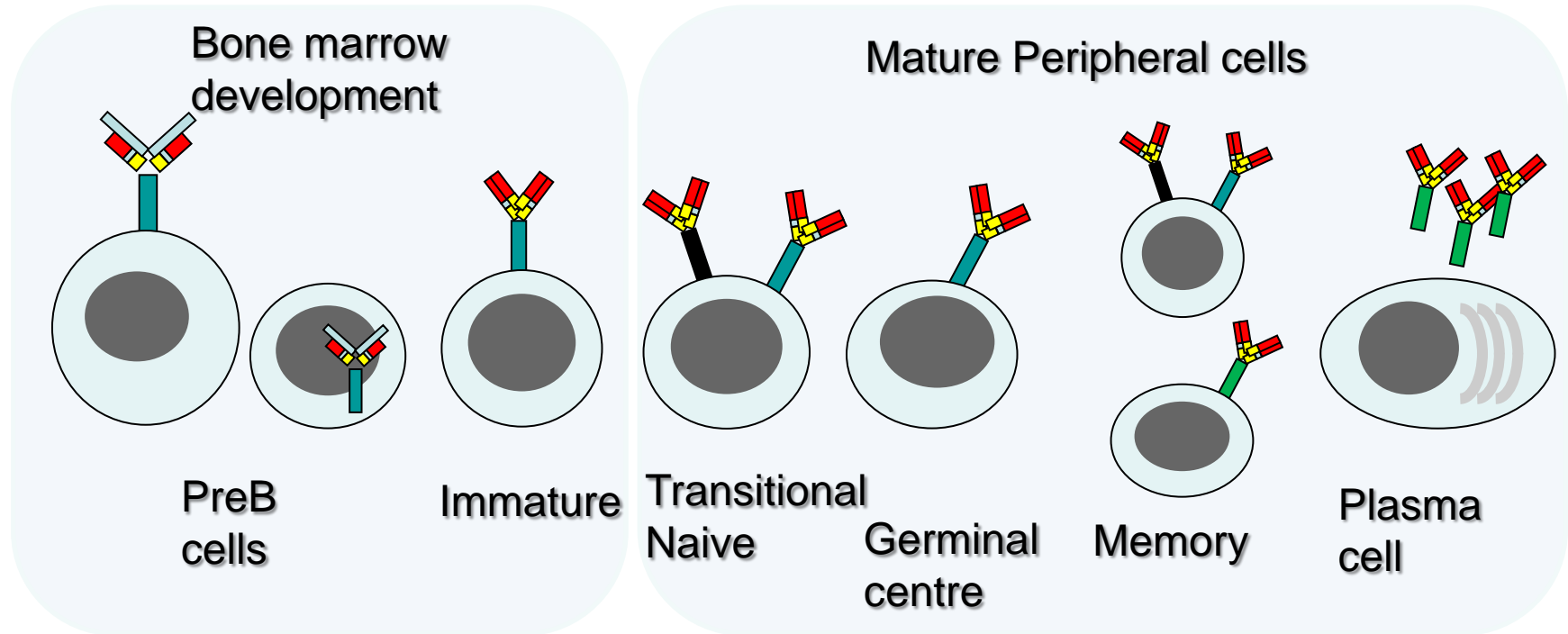
Poor positive selection = poor responses to vaccine and infectious challenge?

Different type of immune activation events = different repertoire of B cells?

Useful Ig genes in a response may be identifiable by their over expression in a population – antibody discovery for therapeutics

Changes in repertoire - cells

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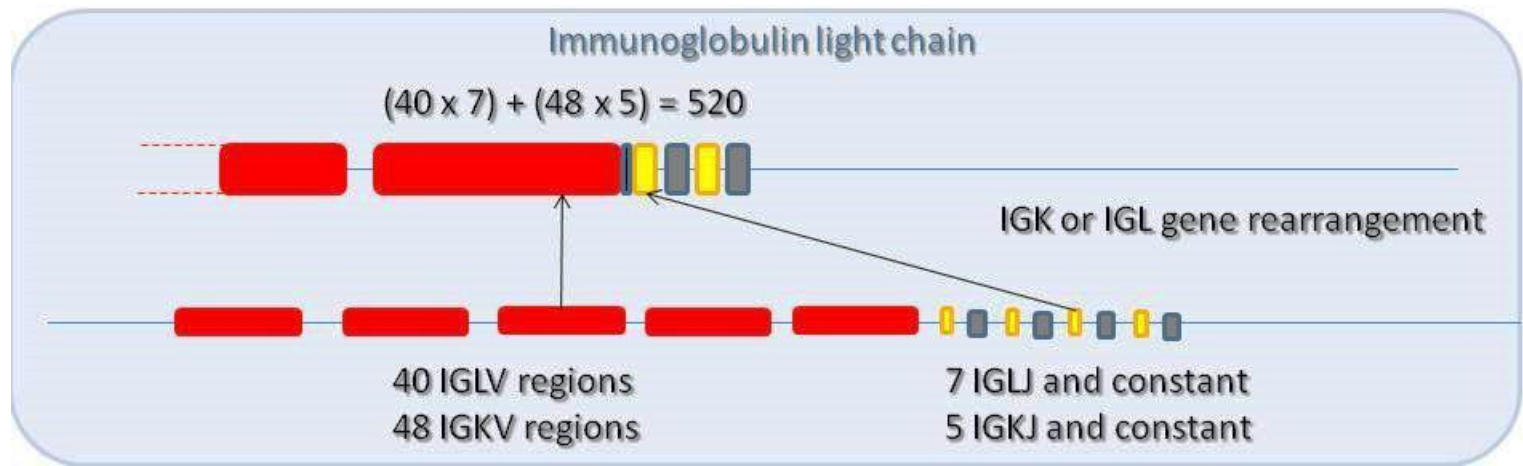
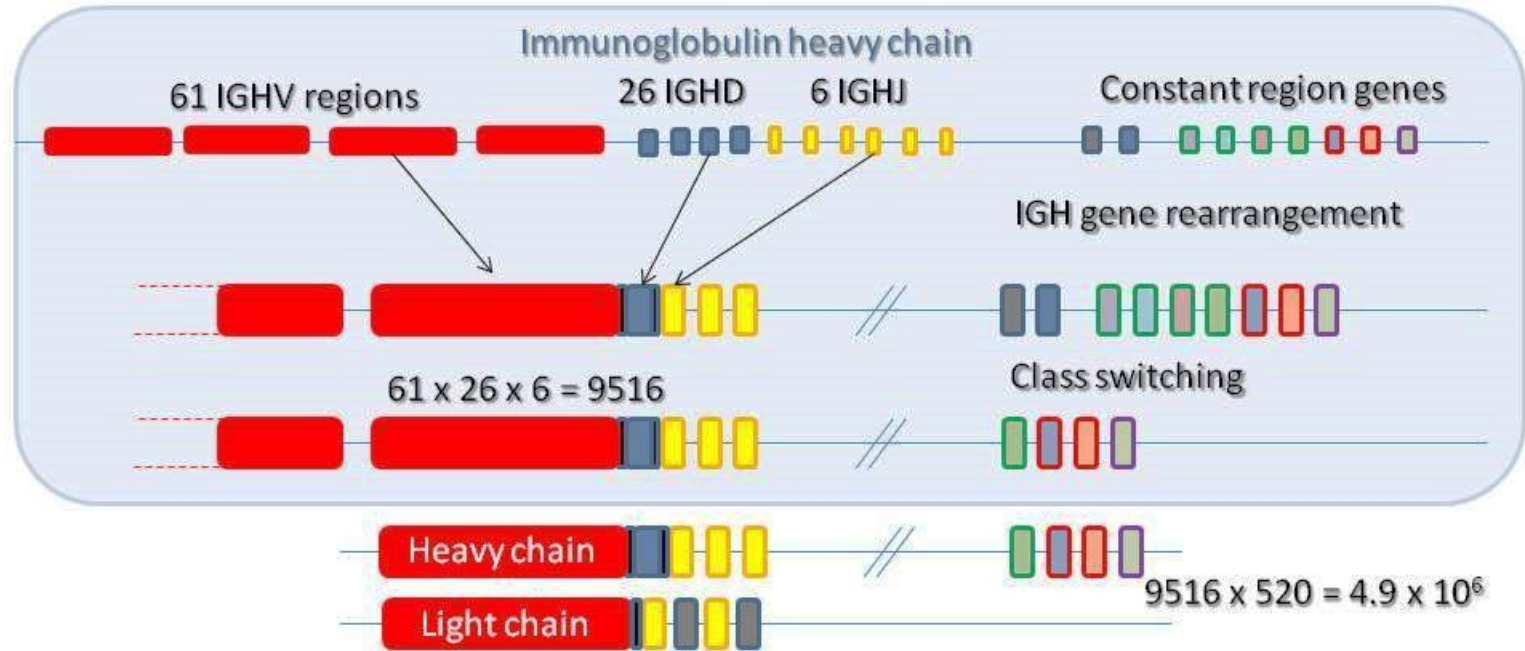
IgM

Class variation
IgM/IgG/IgA/IgE

Activation type –
CD27+ or CD27-

Changes in repertoire - genetic

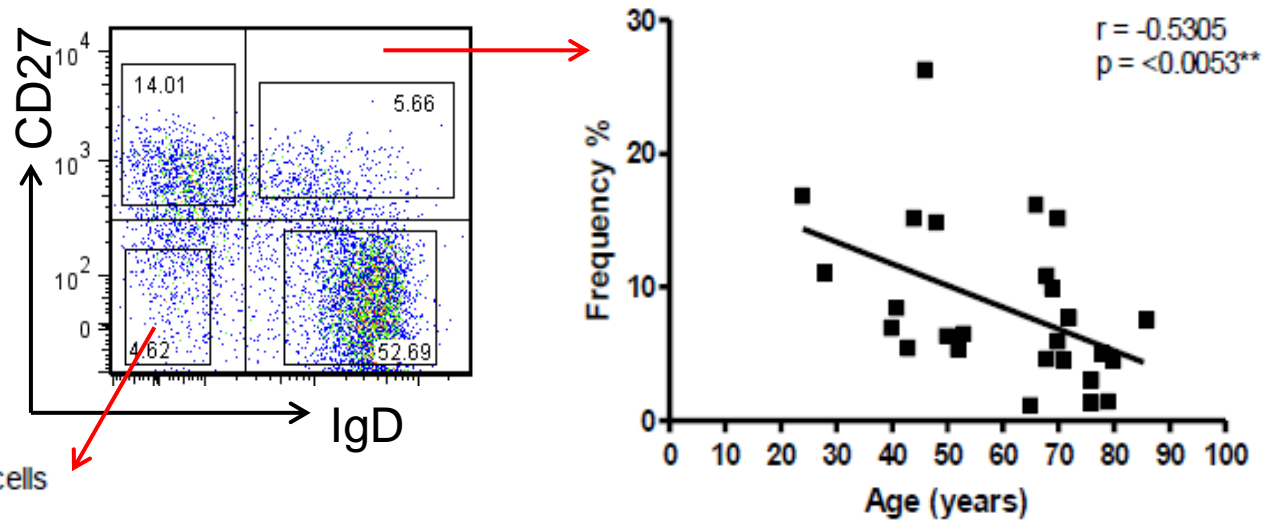
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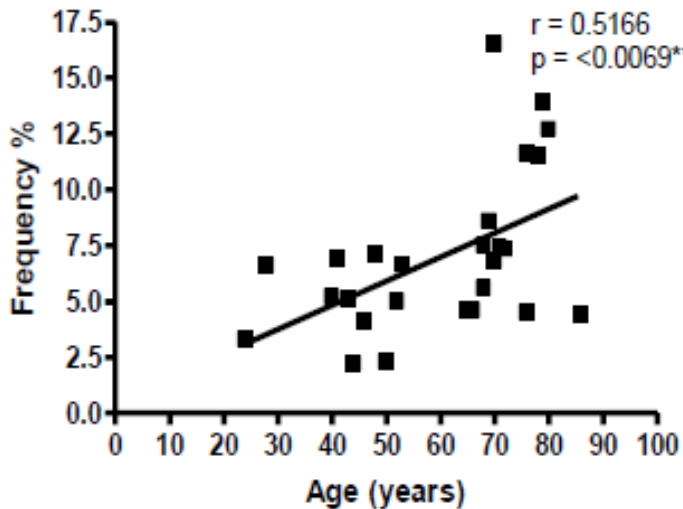
Changes in cell populations with age

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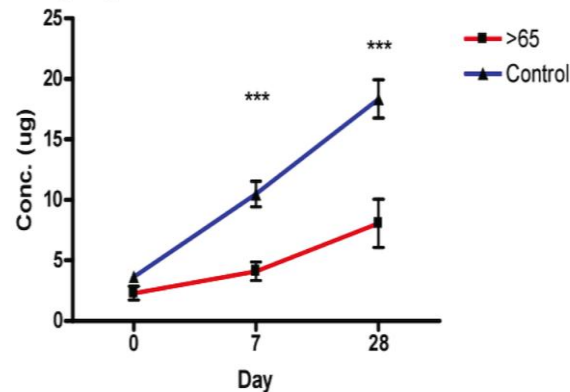
IgM Memory cells



Double Negative (CD27-IgD-) B cells



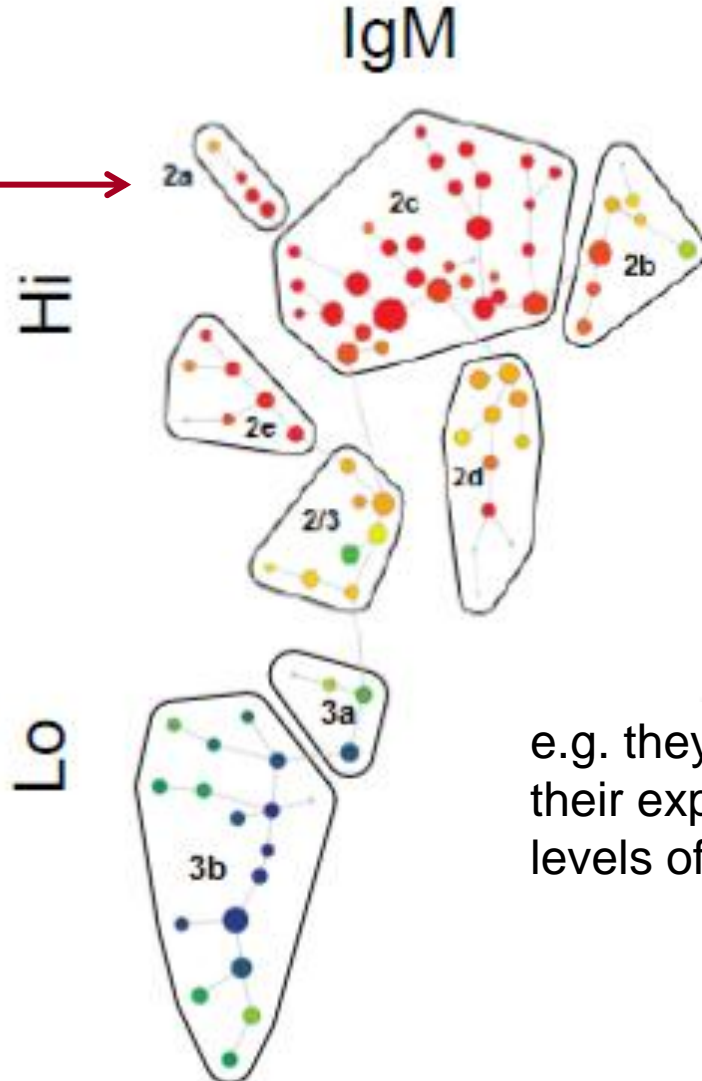
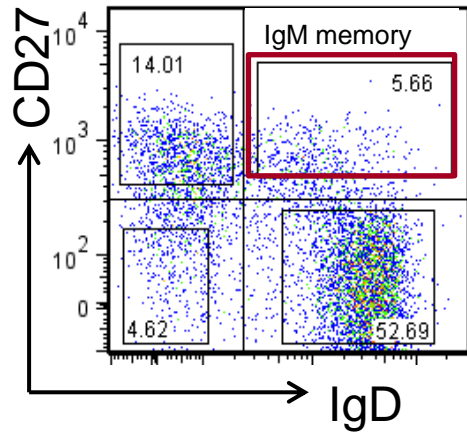
c. IgM pneumococcal



Yu-Chang Wu/Victoria Martin

IgM memory cells are heterogeneous:

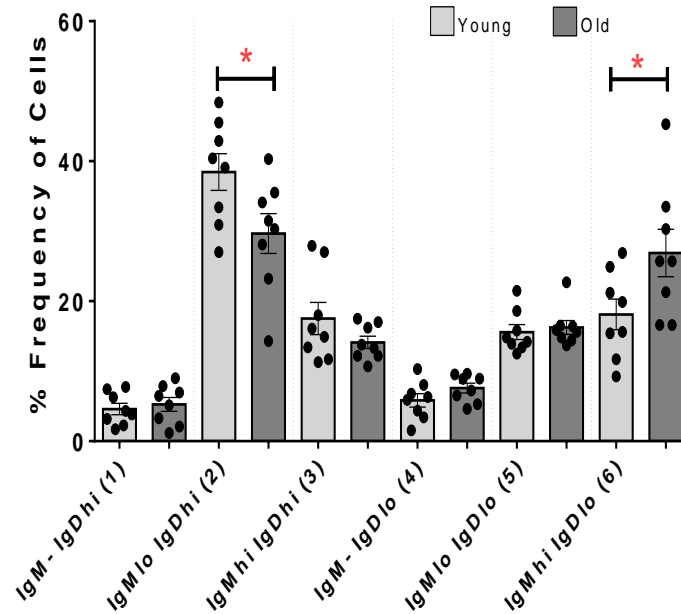
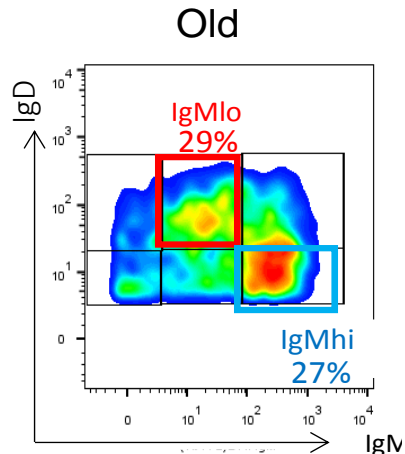
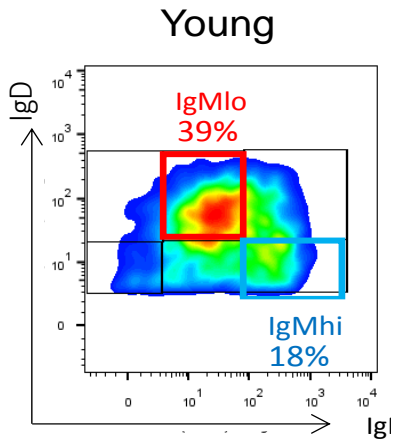
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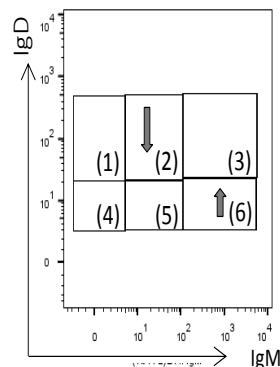
e.g. they differ in their expression levels of IgM

Populations of IgM memory cells, distinguished by levels of IgM expression, change with age.

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Change with Age



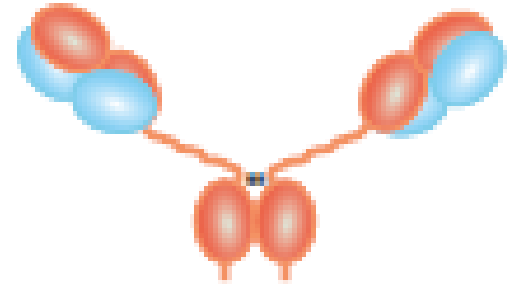
	IgM ^{hi}	IgM ^{lo}
CD35	Hi	lo
CD44	Hi	lo
CD74	Hi	lo
CD24	+	-
CD40	-	+
CD23	-	+
Beta7	-/lo	+
CD21	Lower	Higher
CD38	-	+
CD95	Lo	-
CXCR4	-	-/+
TNFa	Lo	-
CD69	-	Lo
CD27	Hi	Lo

Significance of IgD IgM changes?

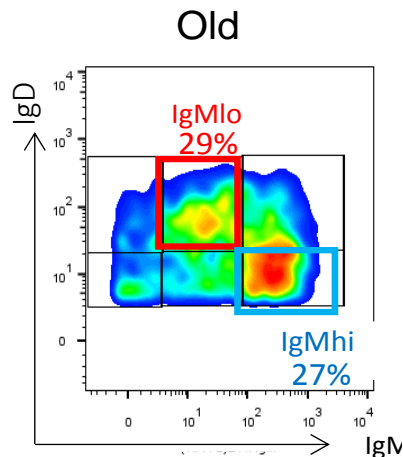
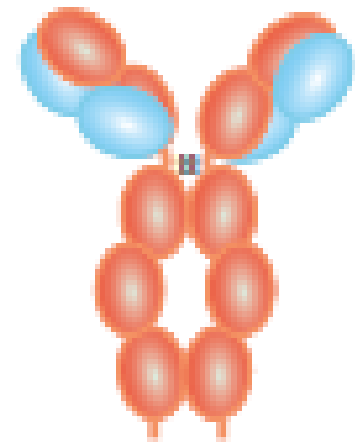
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IgD. Flexible Hinge region. Responds polyvalent antigens not monovalent

More important in T-independent responses to polyvalent polysaccharides?

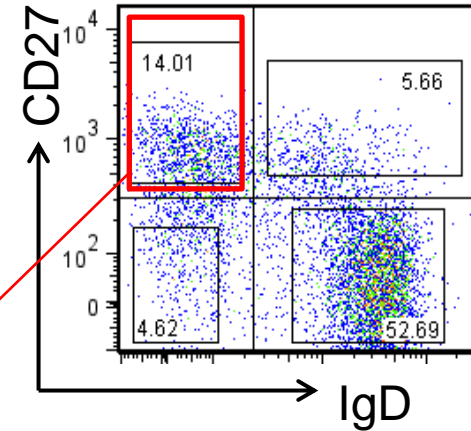
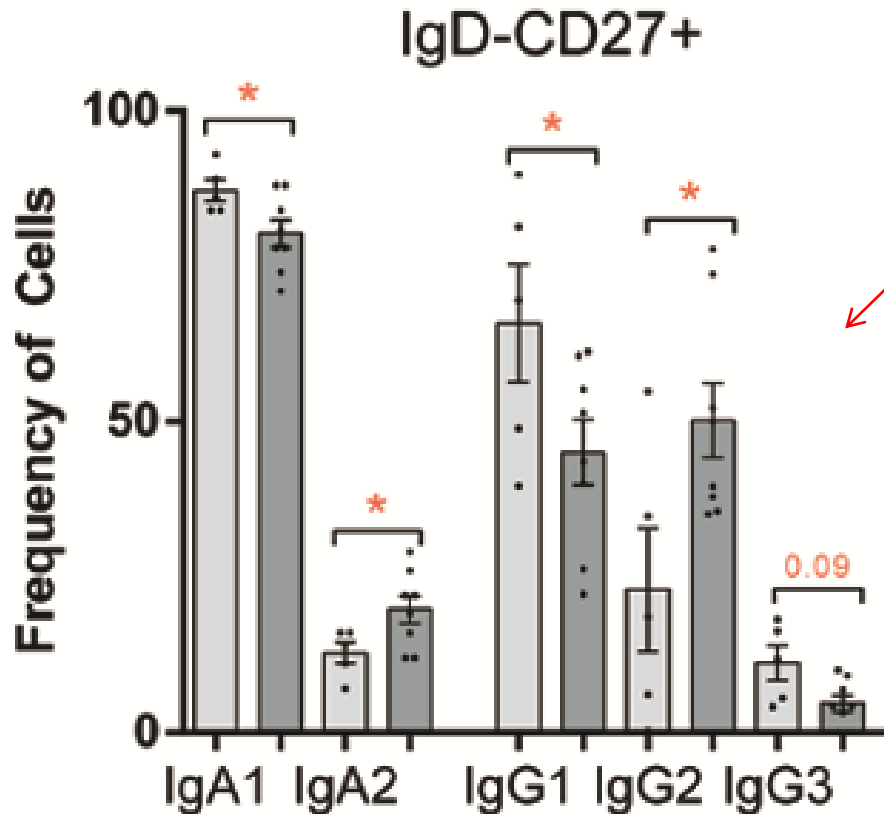


IgM responds both types of antigens



Age changes in class switched B cells

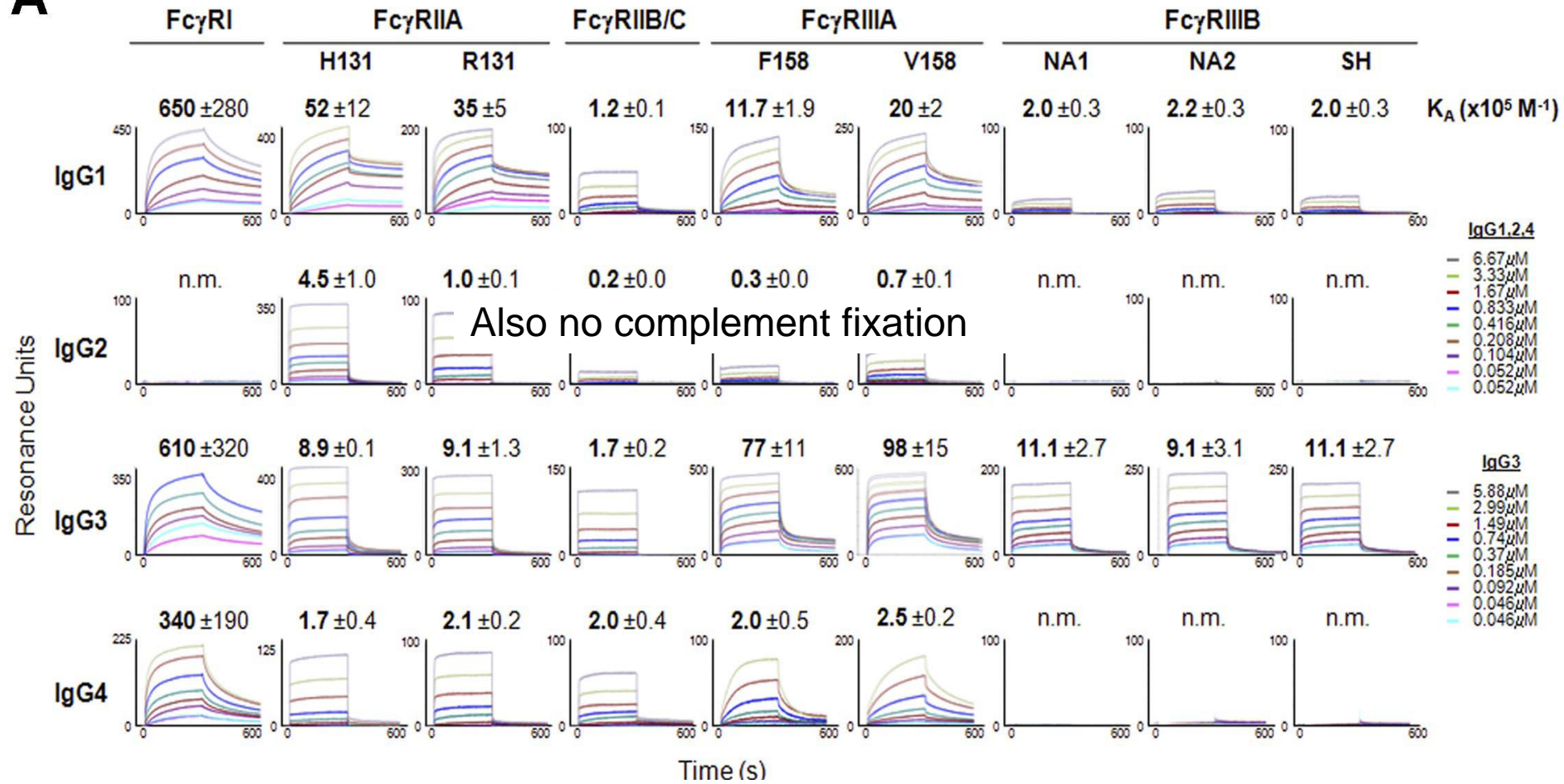
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IgG1/IgG2 ratio altered

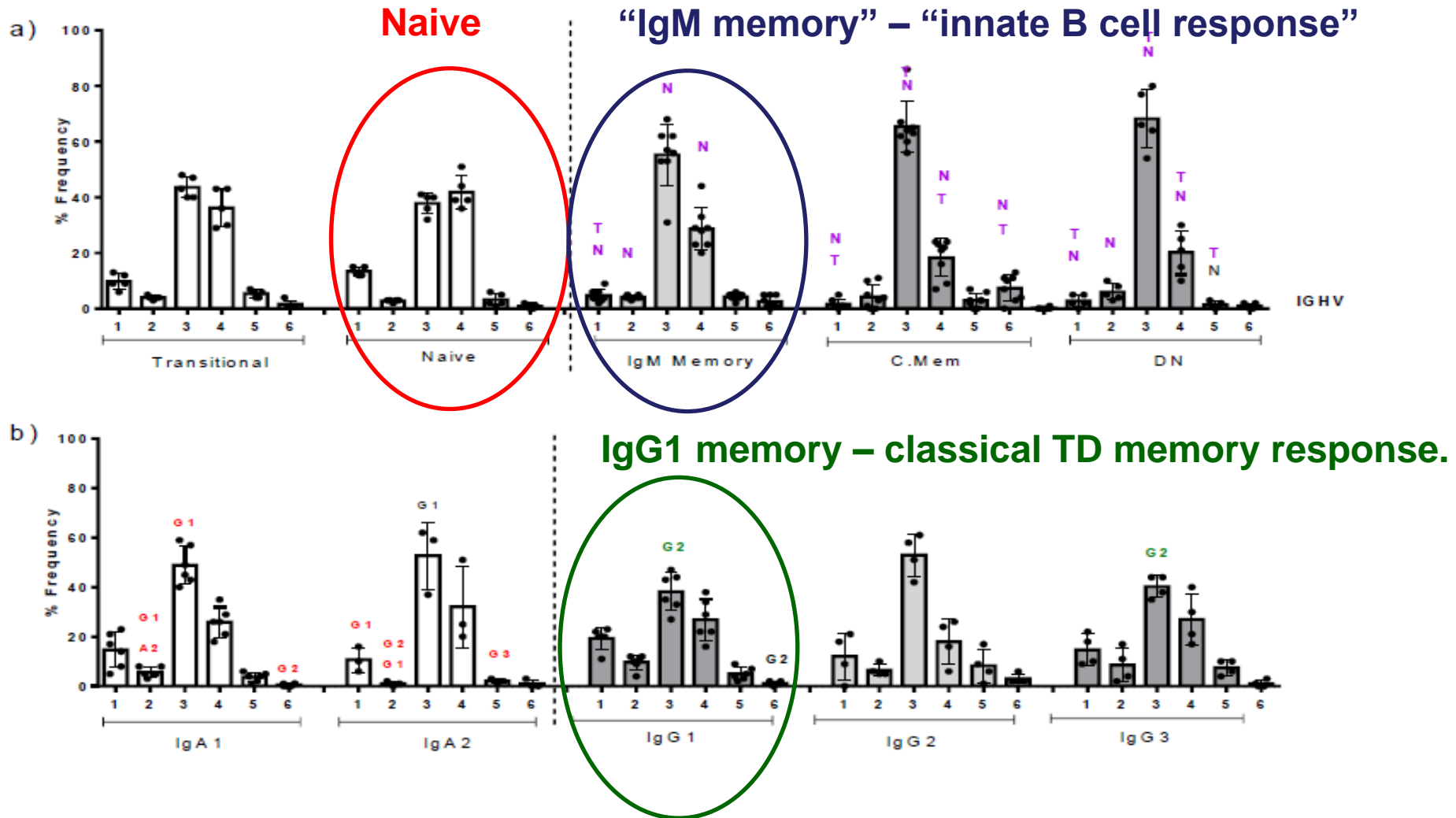
FcγR interactions: Real-time surface plasmon resonance sensorgrams

A

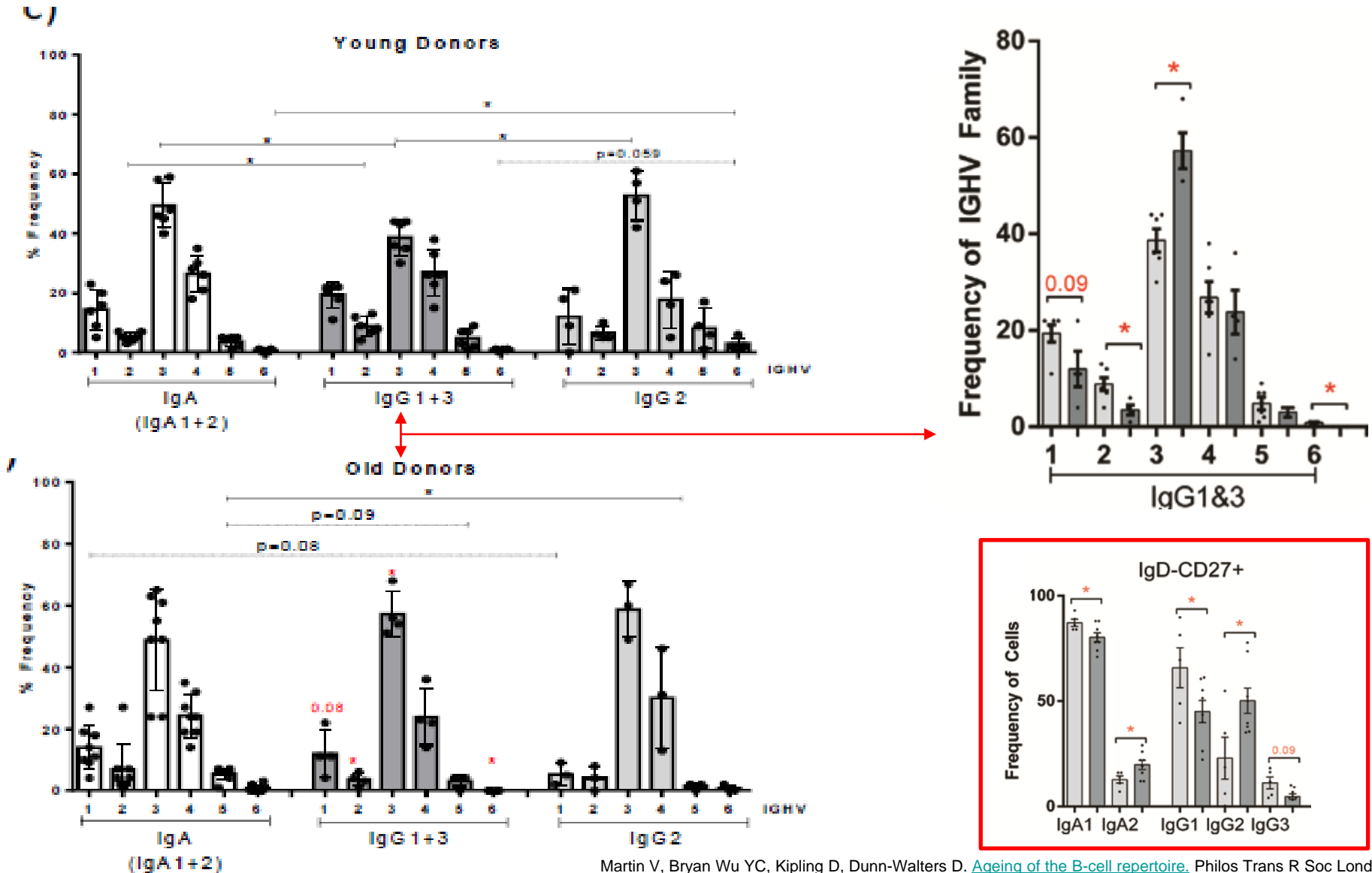


Different populations have different repertoire characteristics: *IGHV* family use

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IGHV family: IgG1+3 repertoire starts to look like IgG2 repertoire in the aged.



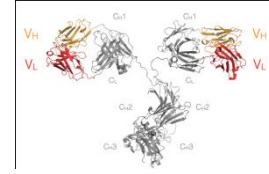
Class AND subclass antibody important:

- for IgG the IgG1/2 ratio
- also consider IgM, IgD and IgA contributions

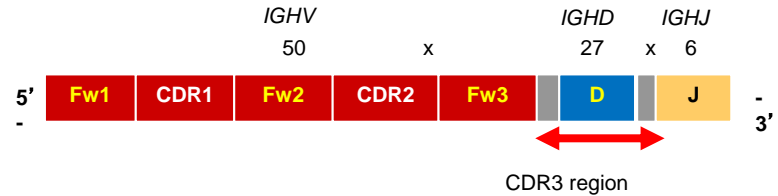
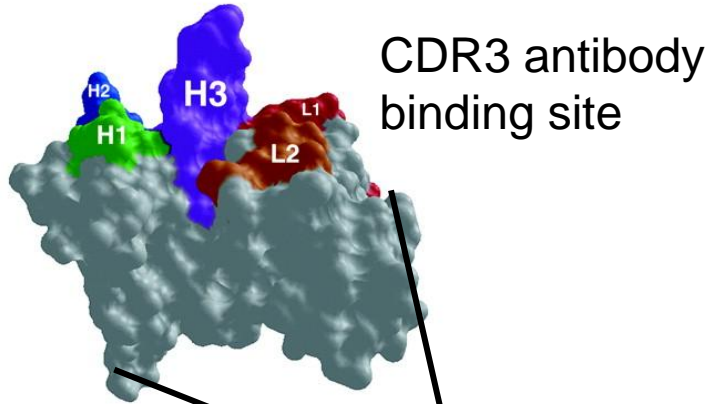
Different types of B cell activation favour different selection of repertoire

- Generally the relative contribution of IGHV1/IGHV3 family is a good distinguishing feature

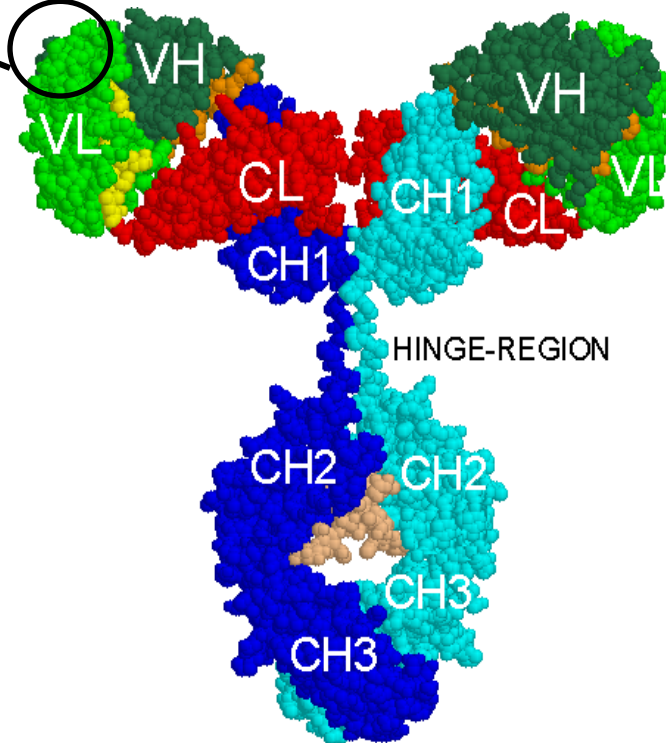
CDR3 binding site is largest contributor to antigen specificity (?)



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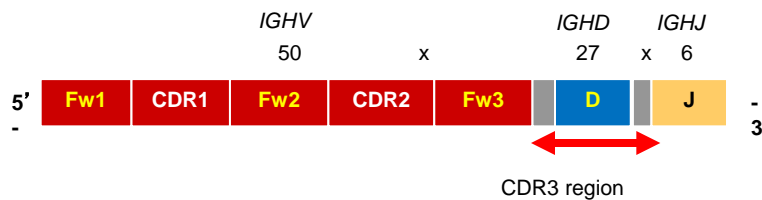
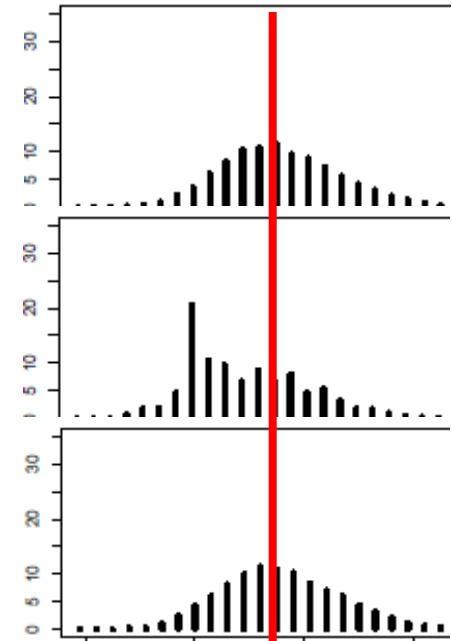
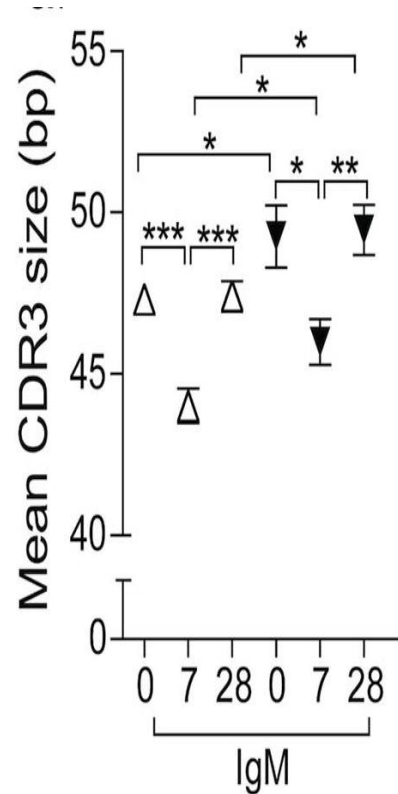


Variable region with two binding sites which determine the ANTIGEN SPECIFICITY

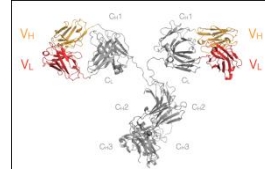


CDR-H3 size selection upon challenge

(Spectratype PBMCs)



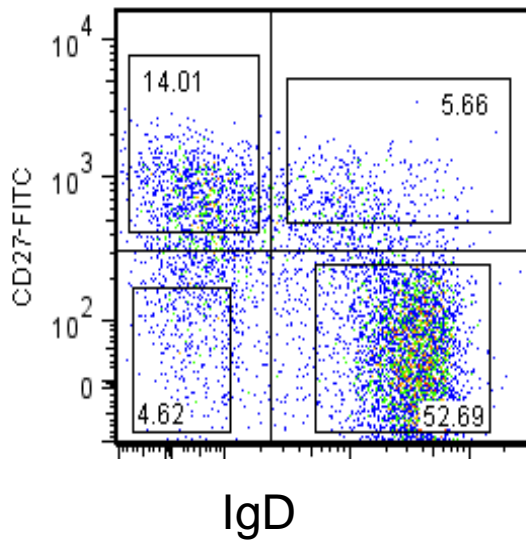
Smaller CDR-H3 size is a feature of all memory cells.



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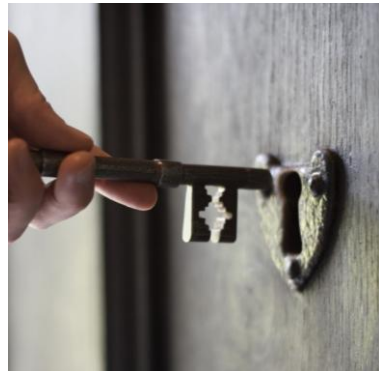
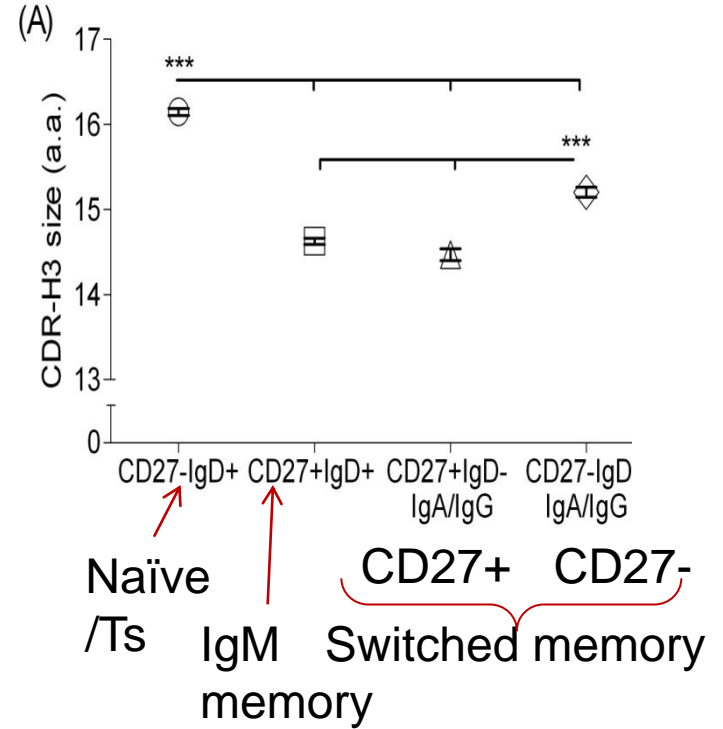
**CD27+
memory**

**CD27-
memory**

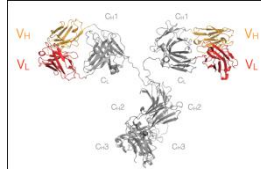


IgM memory

**Naïve &
Transitional**



What is the effect of CDR-H3 size?

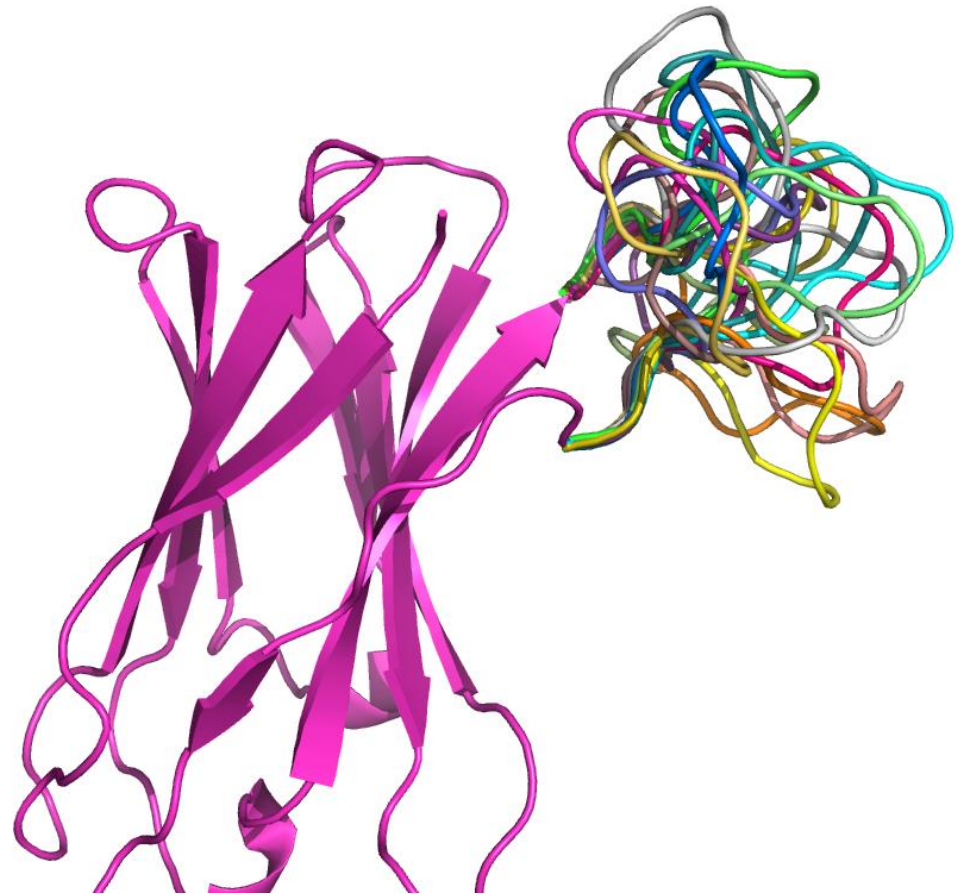


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Short CDRH3 sequence
AREGWQWLAPLDC



Long CDRH3 sequence
ARDSSYYDFYSESGEGGWFDSD

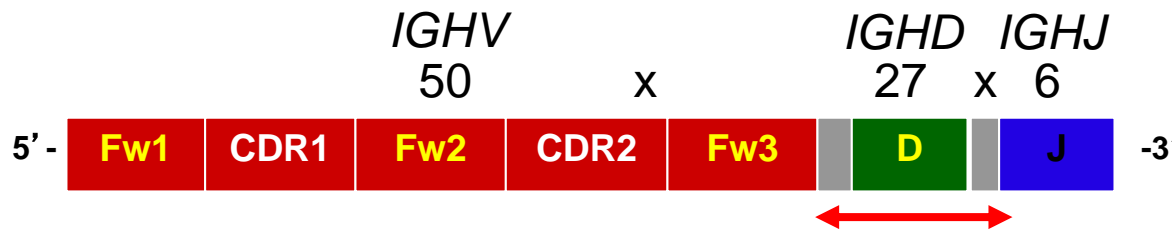
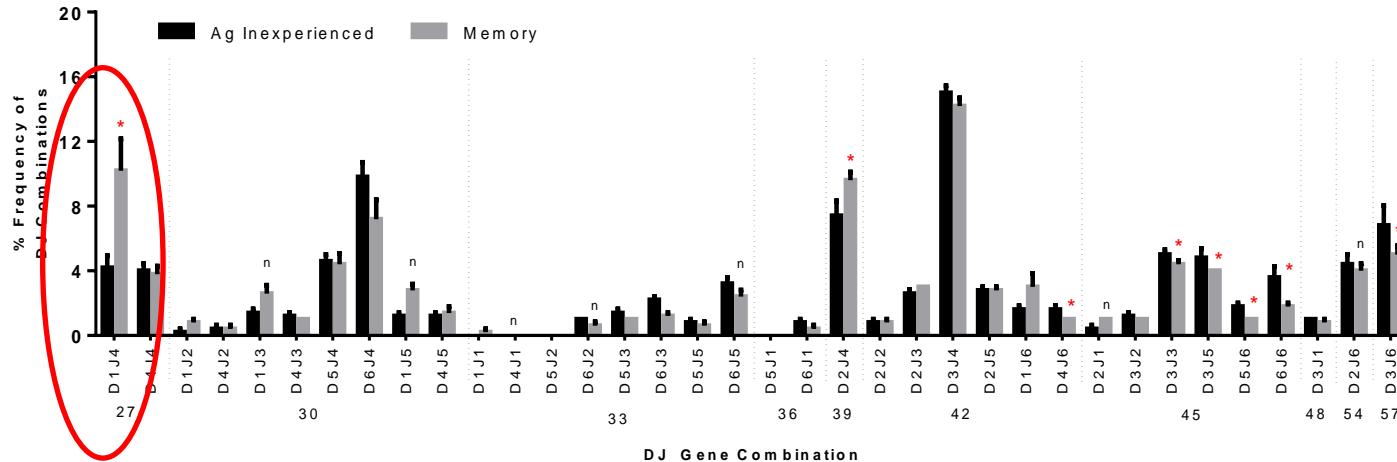


Franca Fraternali

IGHD/J gene selection of memory cells after antigen challenge

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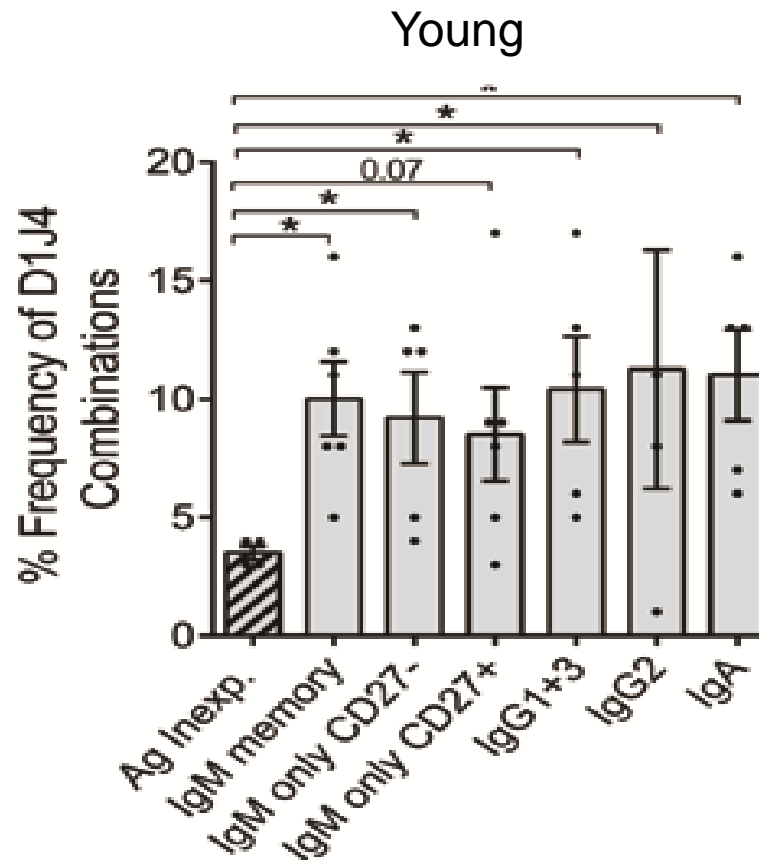
ie the CHANGE between naïve and memory cells = selection event



CDR3 selection of memory cells after antigen challenge

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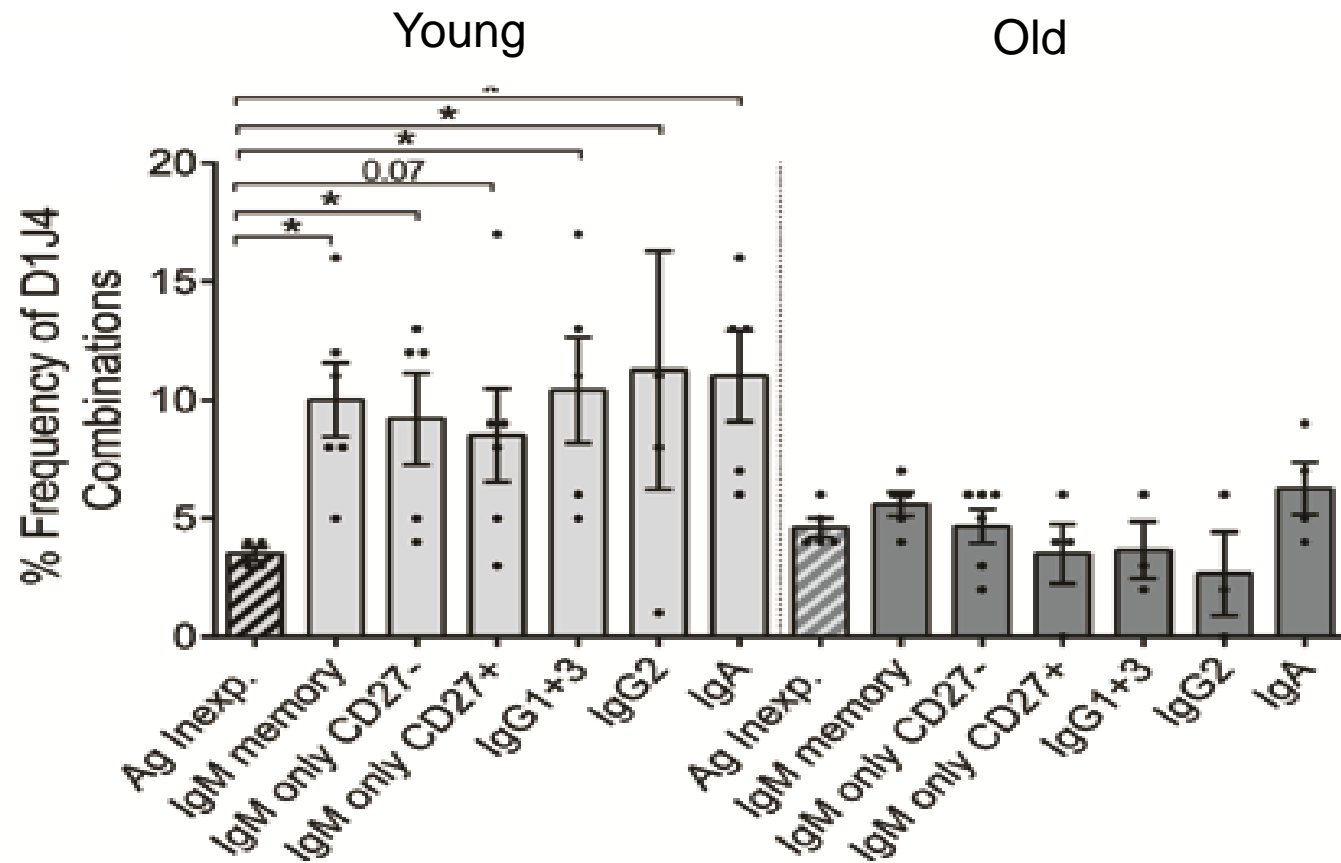
le the CHANGE between naïve and memory cells = positive selection event



CDR3 selection of memory cells after antigen challenge decreases with age

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le the CHANGE between naïve and memory cells = positive selection event

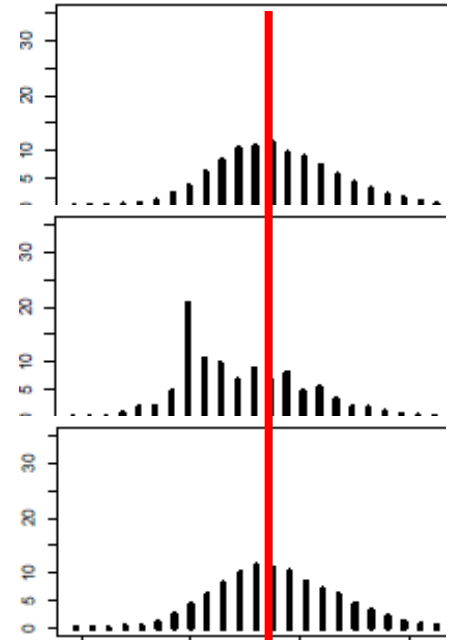
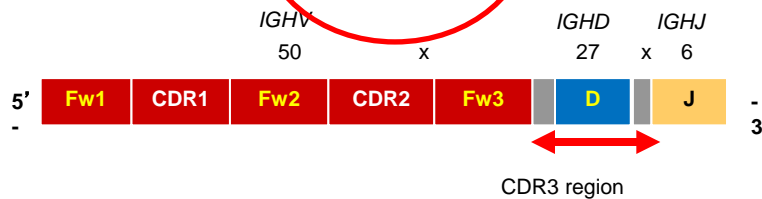
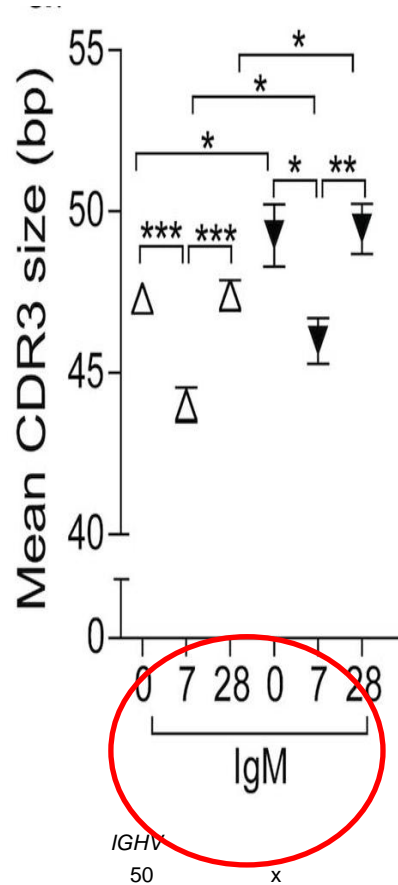


CDRH3 region undergoes selection in favour of smaller loops.

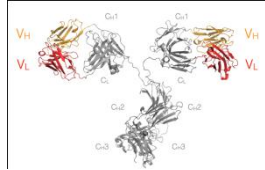
- This seems to be independent of the type of antigen challenge as is in all memory cells.
- Some of this size difference is related to selection of IGHD and IGHJ regions.
- This selection is not as strong in older people.

CDR3 size selection even before exogenous challenge????

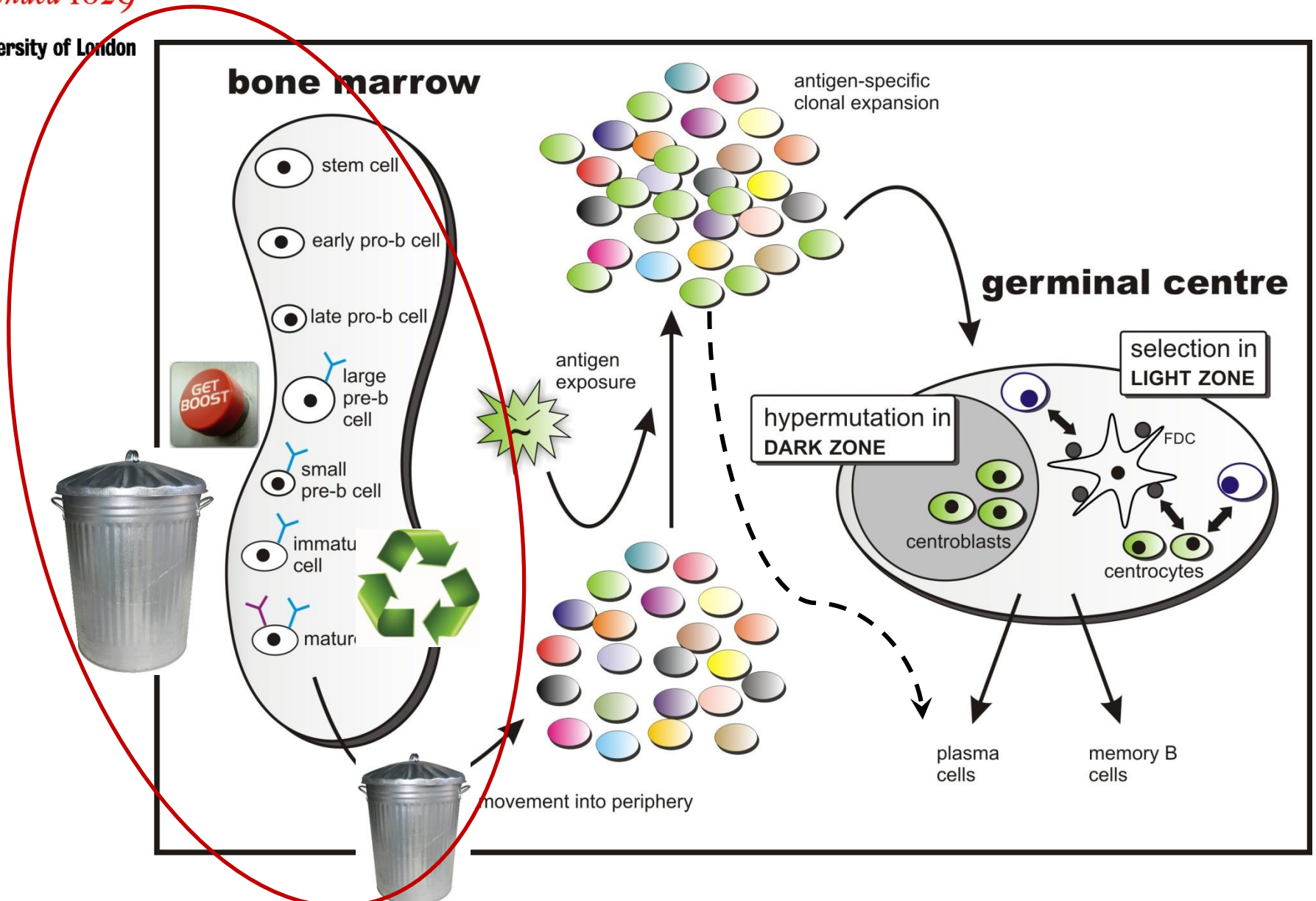
(Spectratype PBMCs)



Negative selection – central tolerance

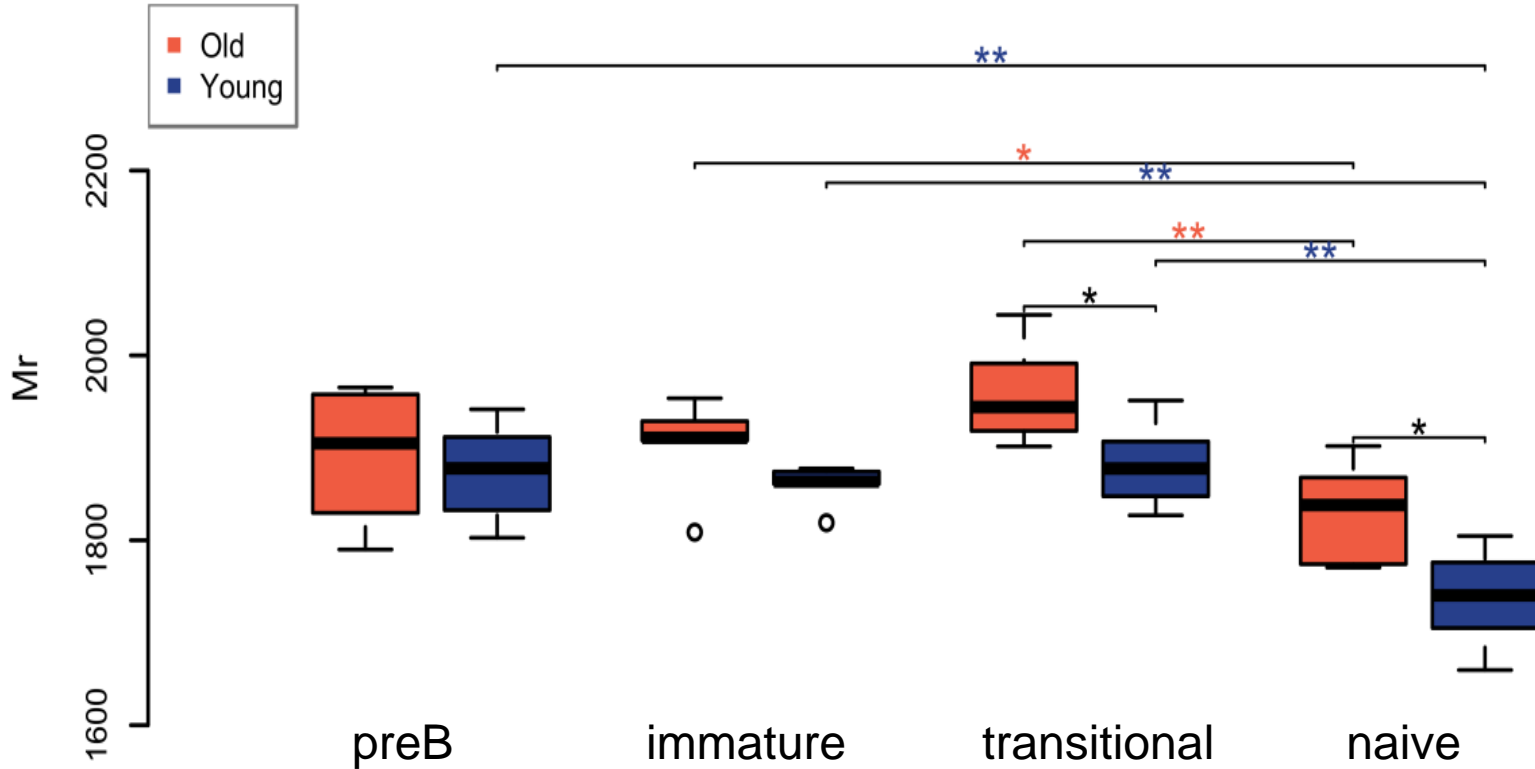


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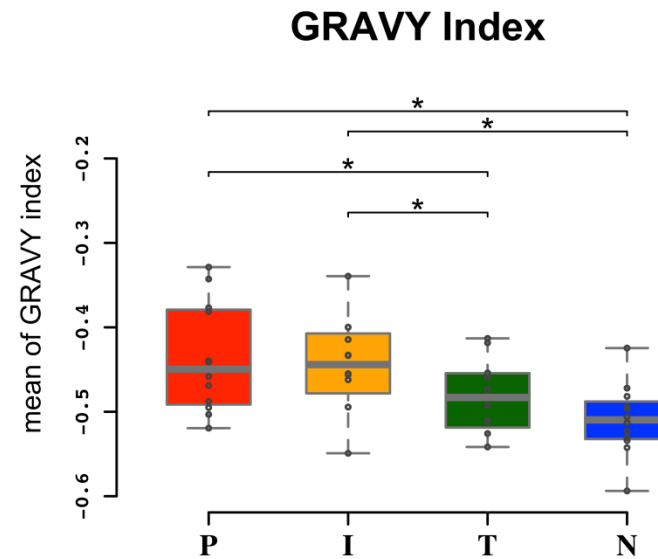
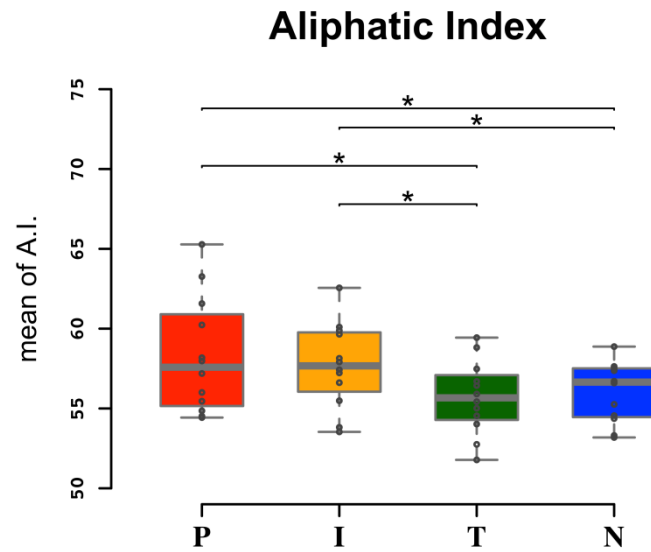


CDR3 is longer in old cells – even in early development

University of

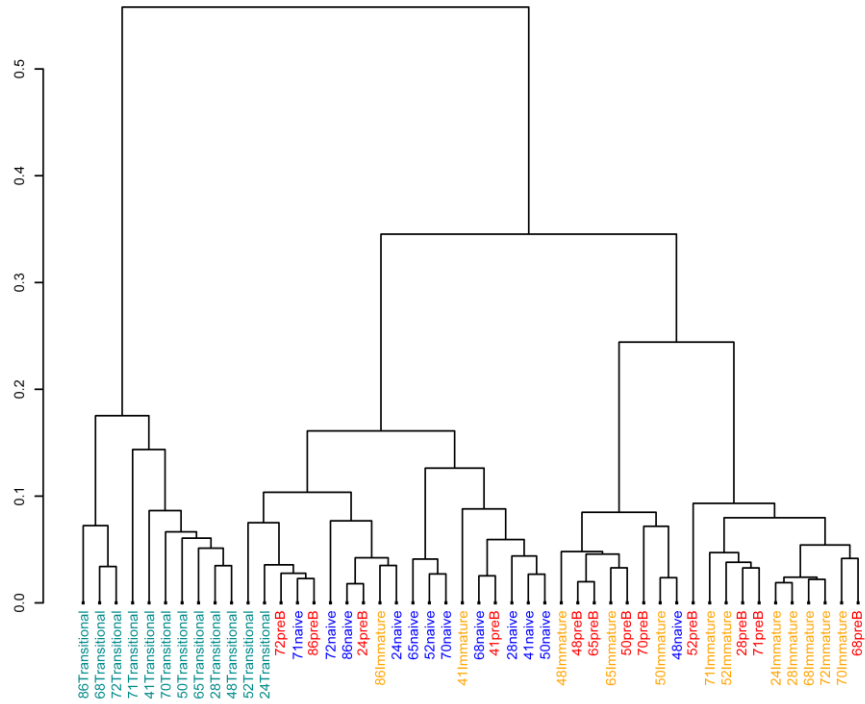


Biophysical properties of CDR3 change during repertoire development



Anova stats

All kidera factors



All kidera factors

