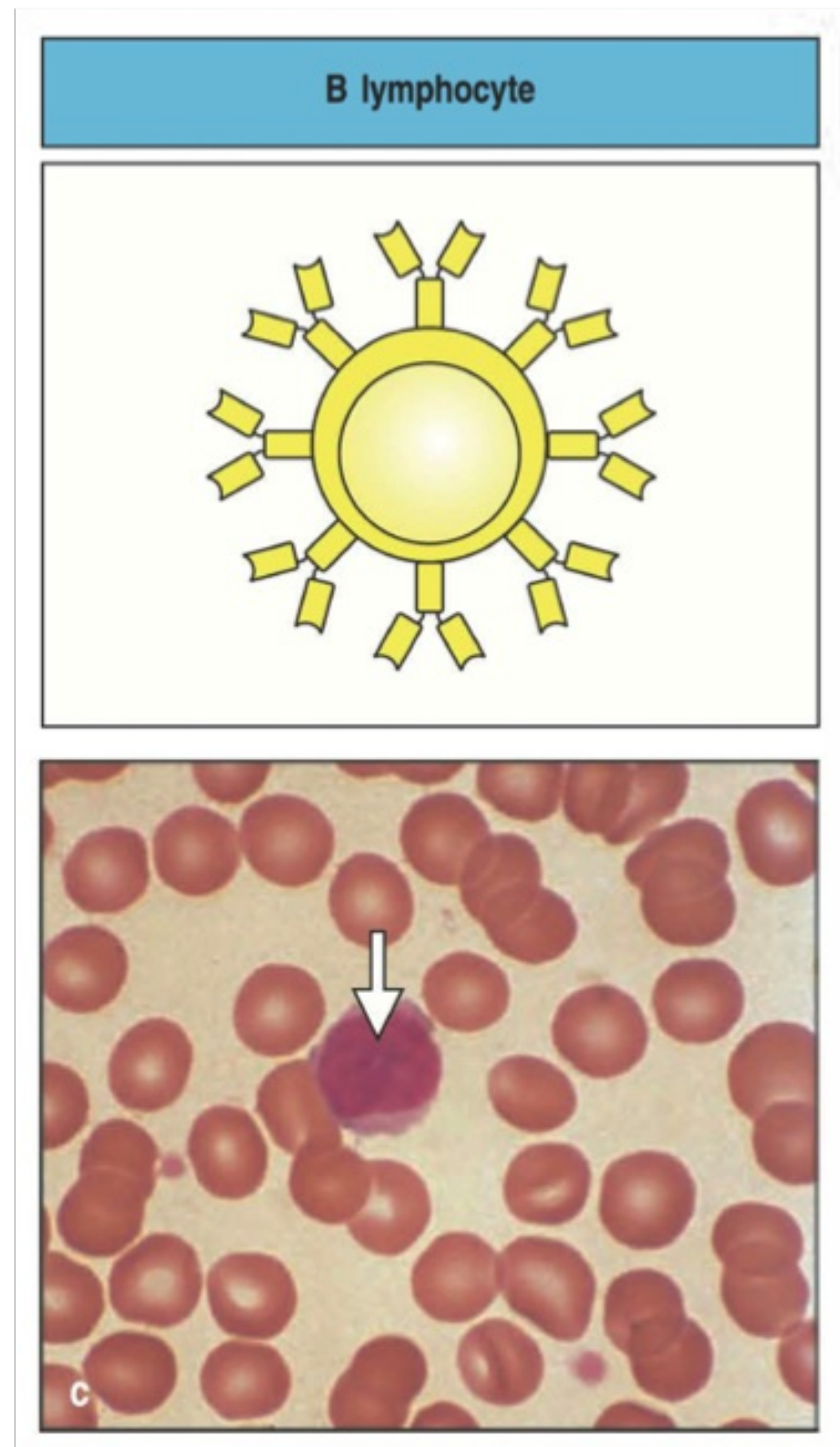




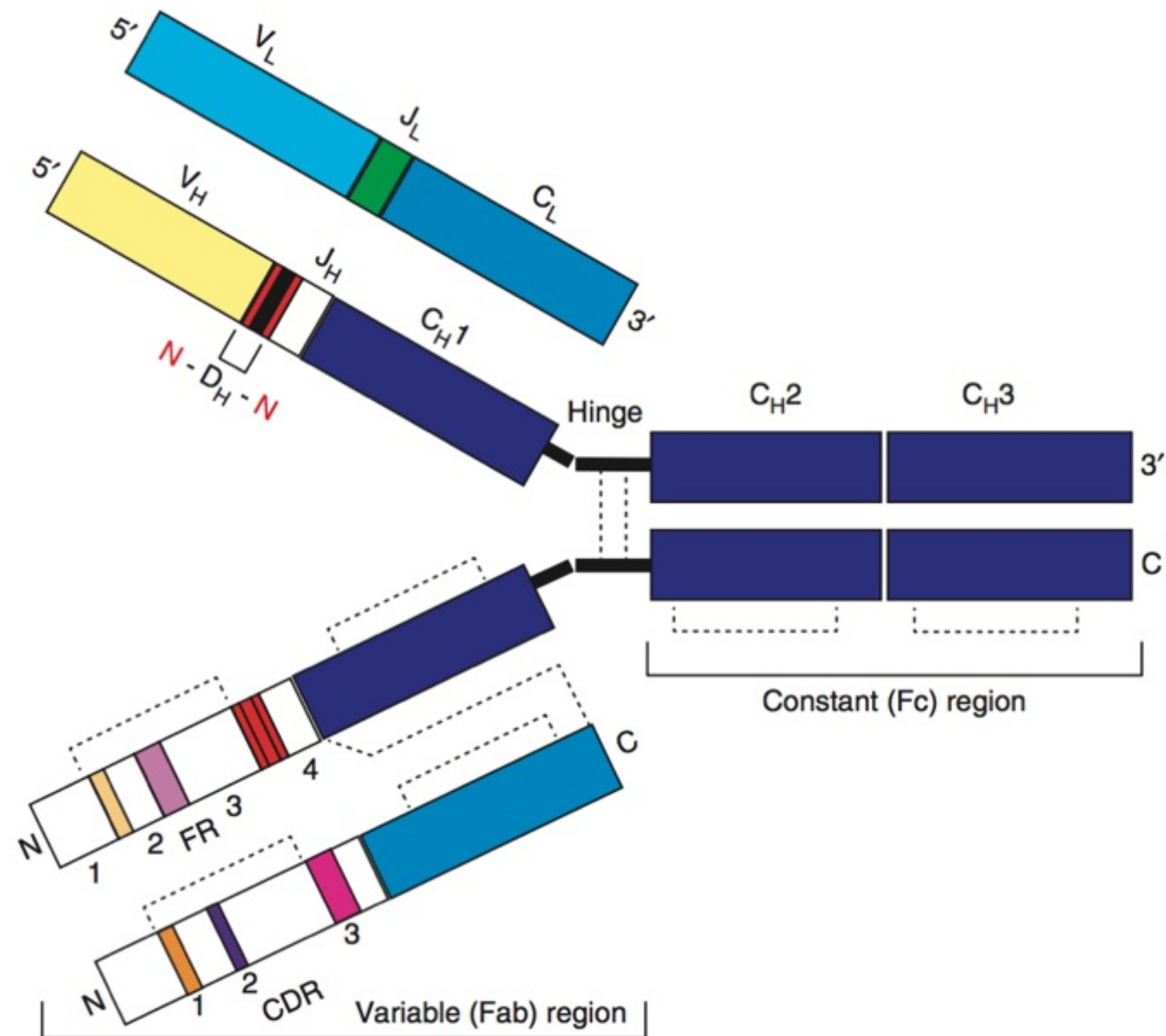
Selection and evolution in B cells



B cells determine antibody diversity



Structure of a B cell receptor





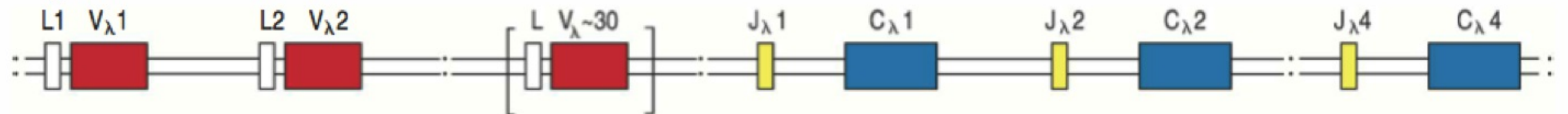
Origins of B cell receptor diversity

VDJ recombination

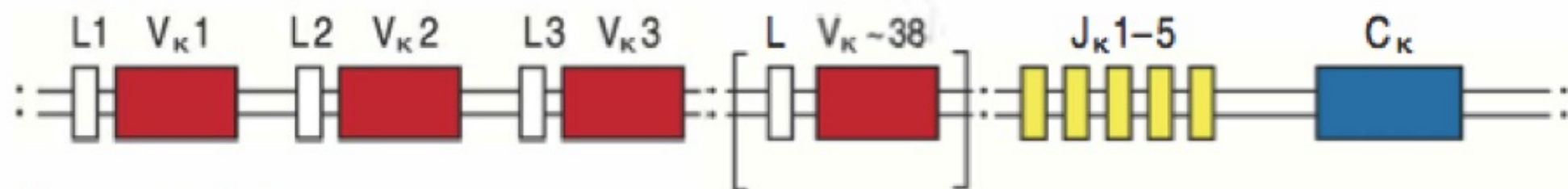
Affinity maturation

VDJ loci

λ light-chain locus



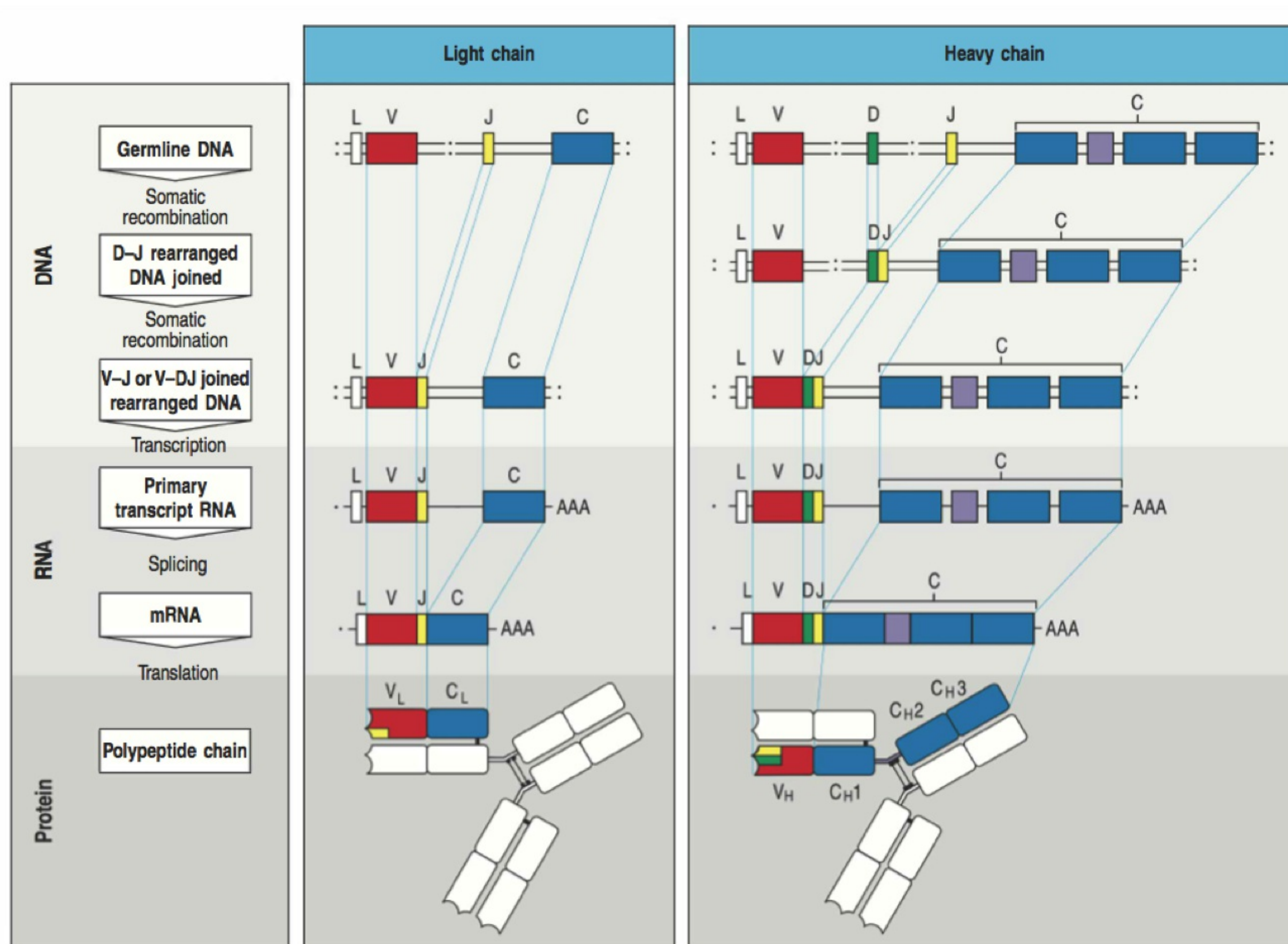
κ light-chain locus



Heavy-chain locus



VDJ recombination



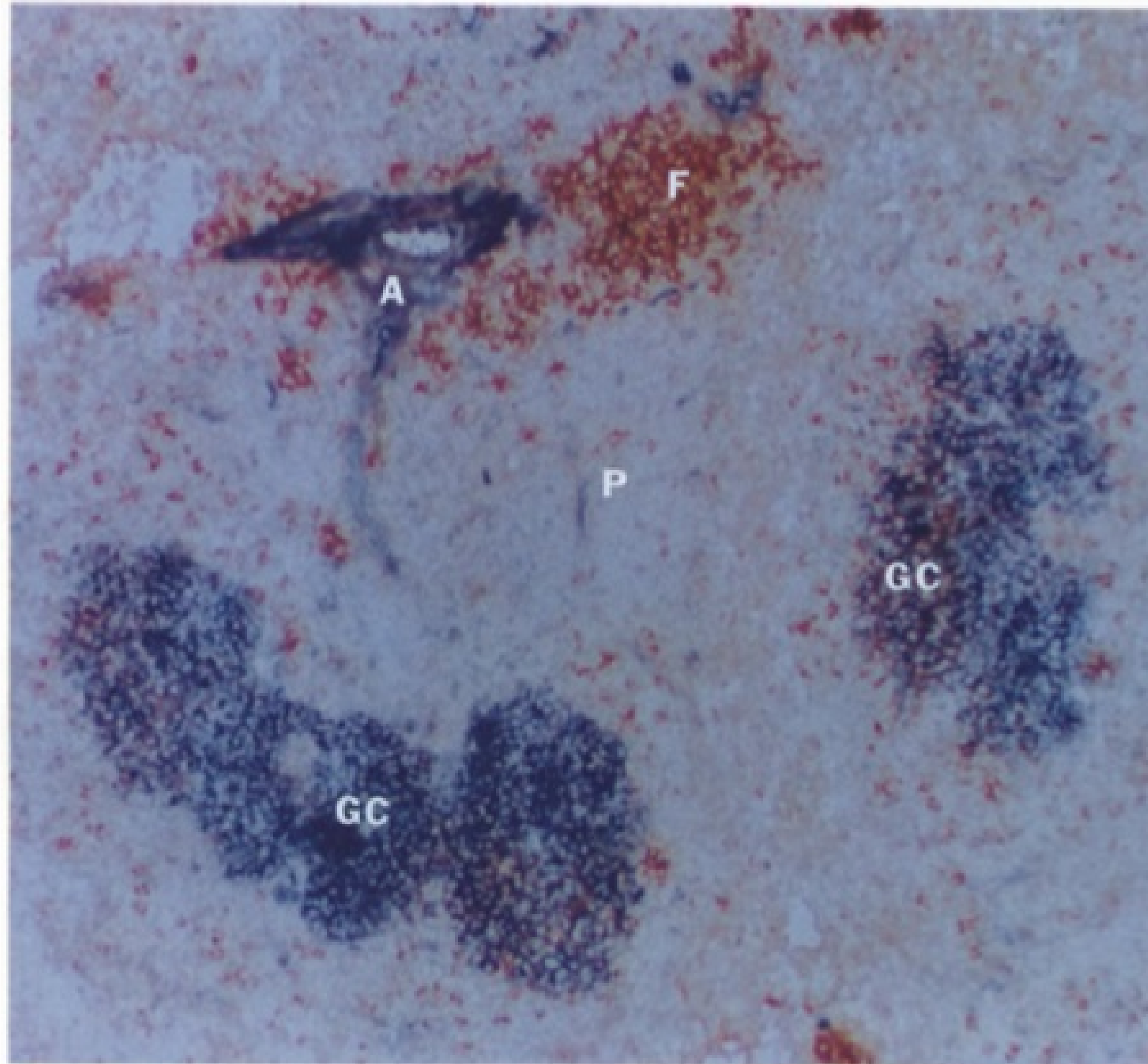


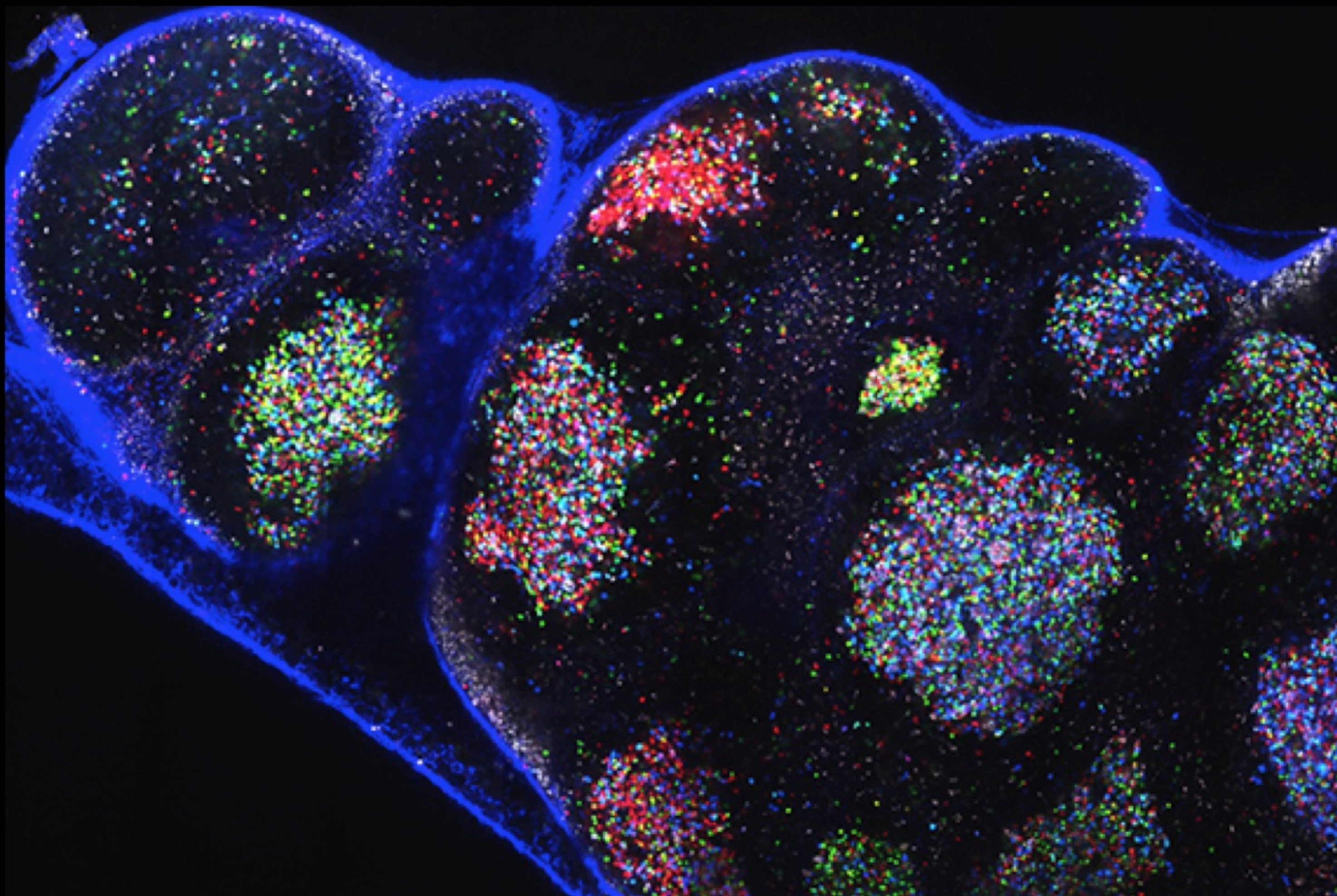
Selection on naive repertoire

Stability

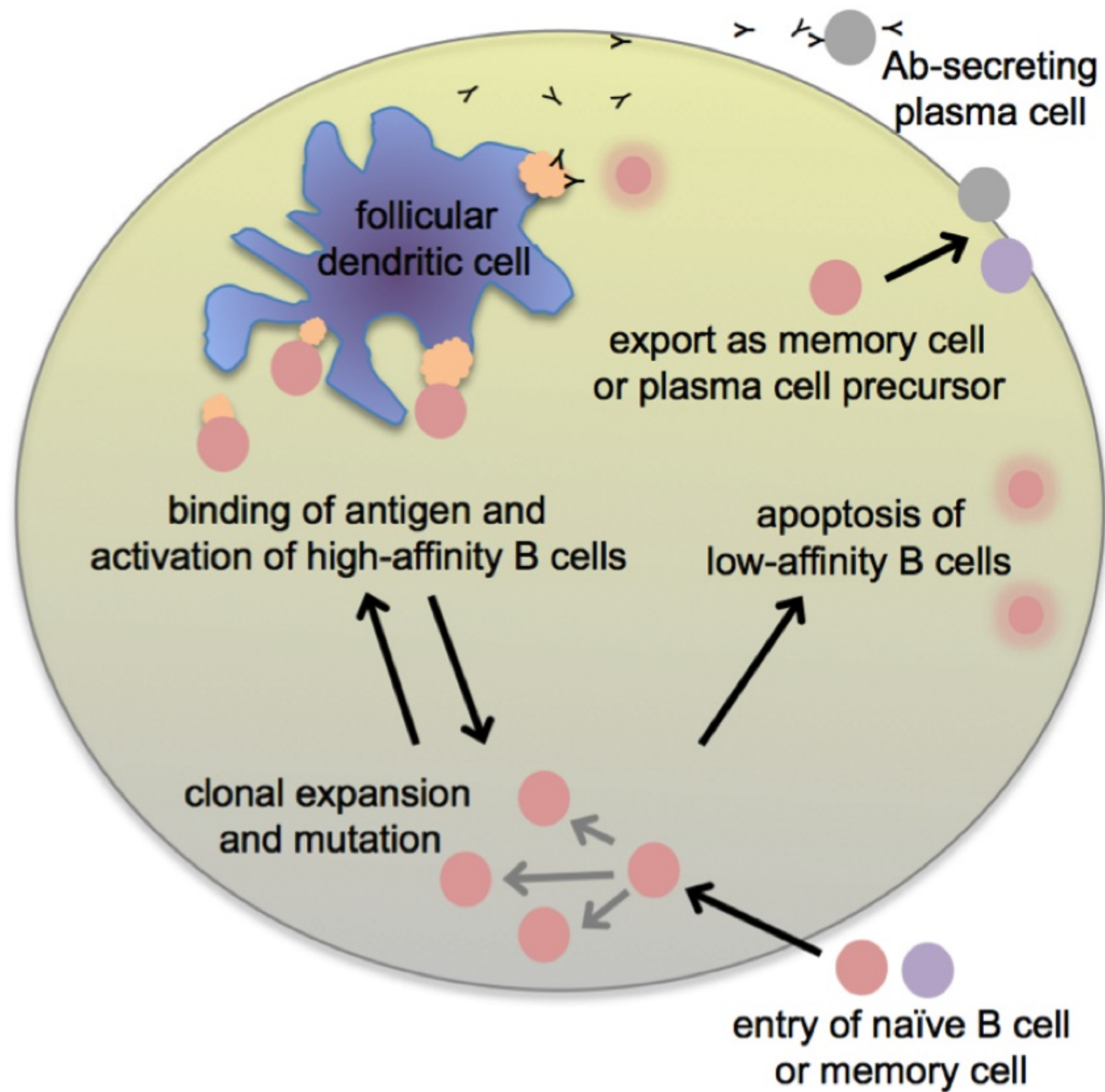
Autoreactivity

Germinal centers





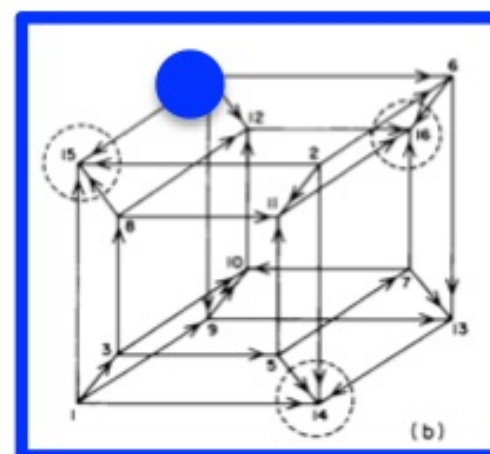
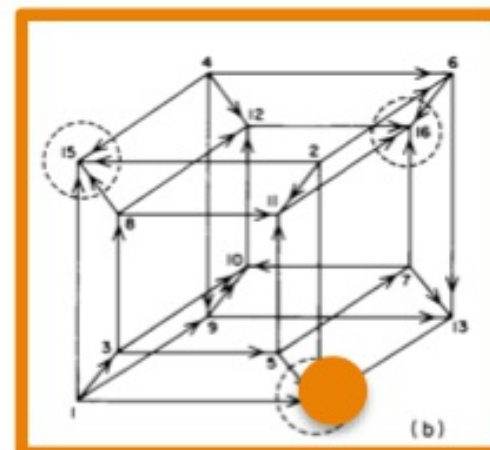
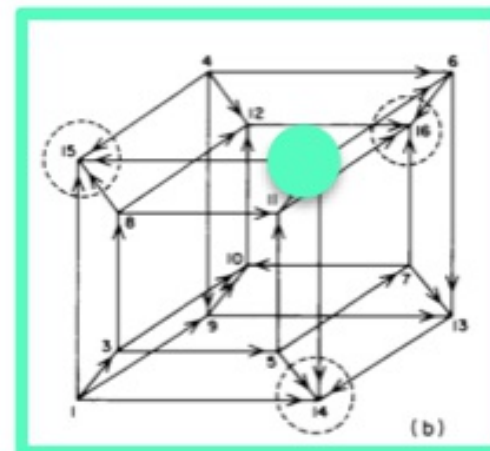
Affinity maturation



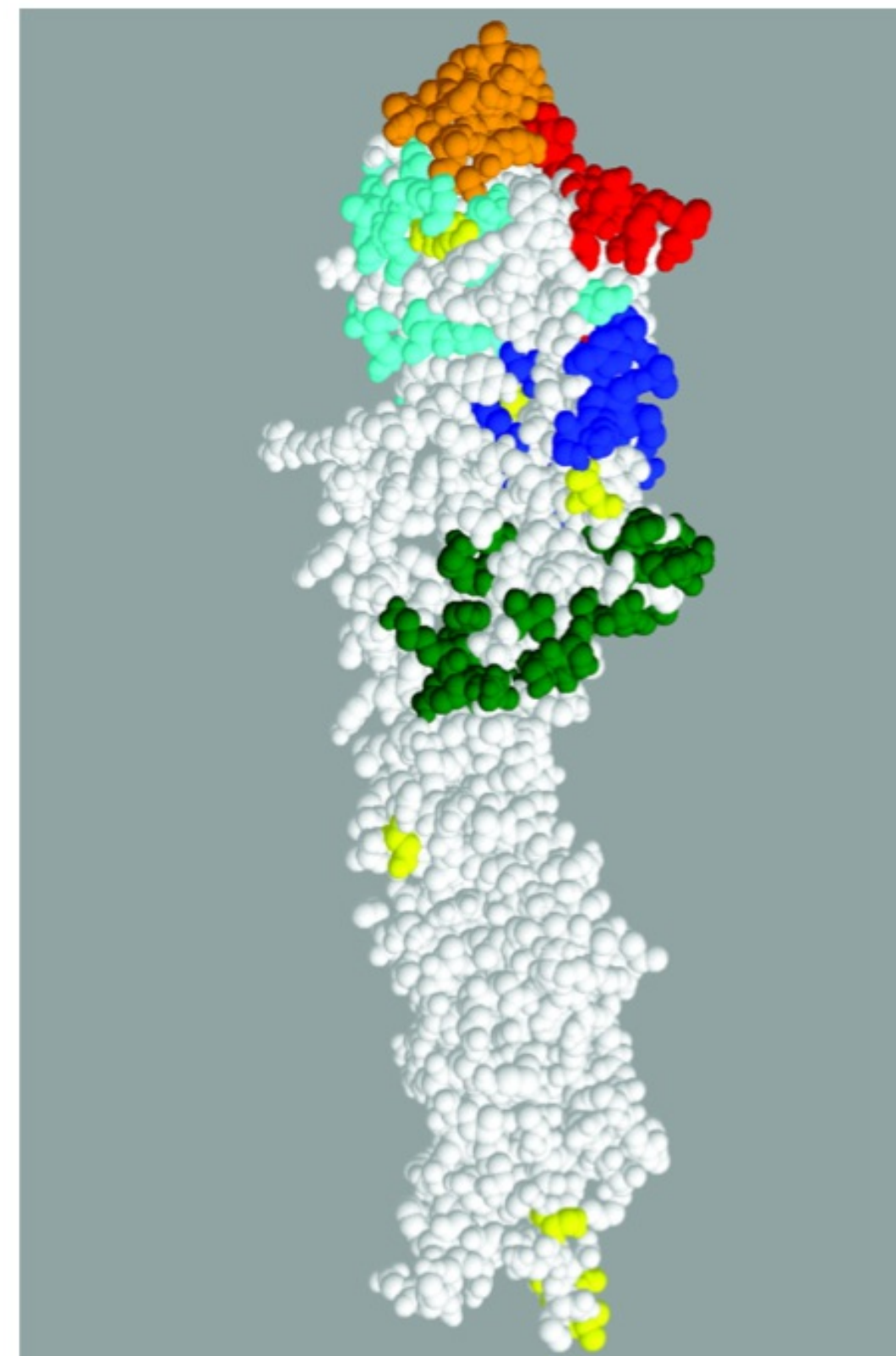
Affinity maturation

3002304214...

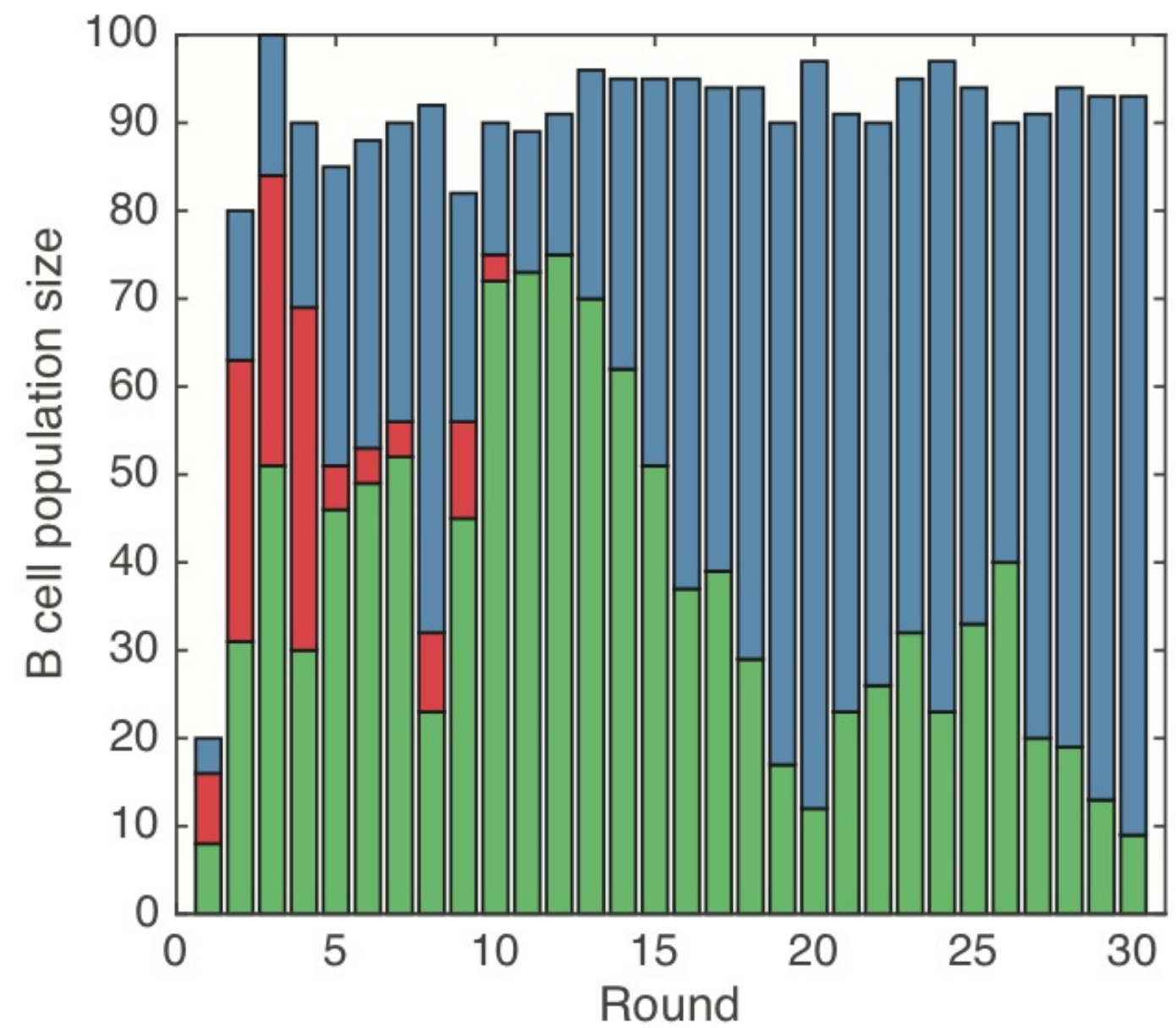
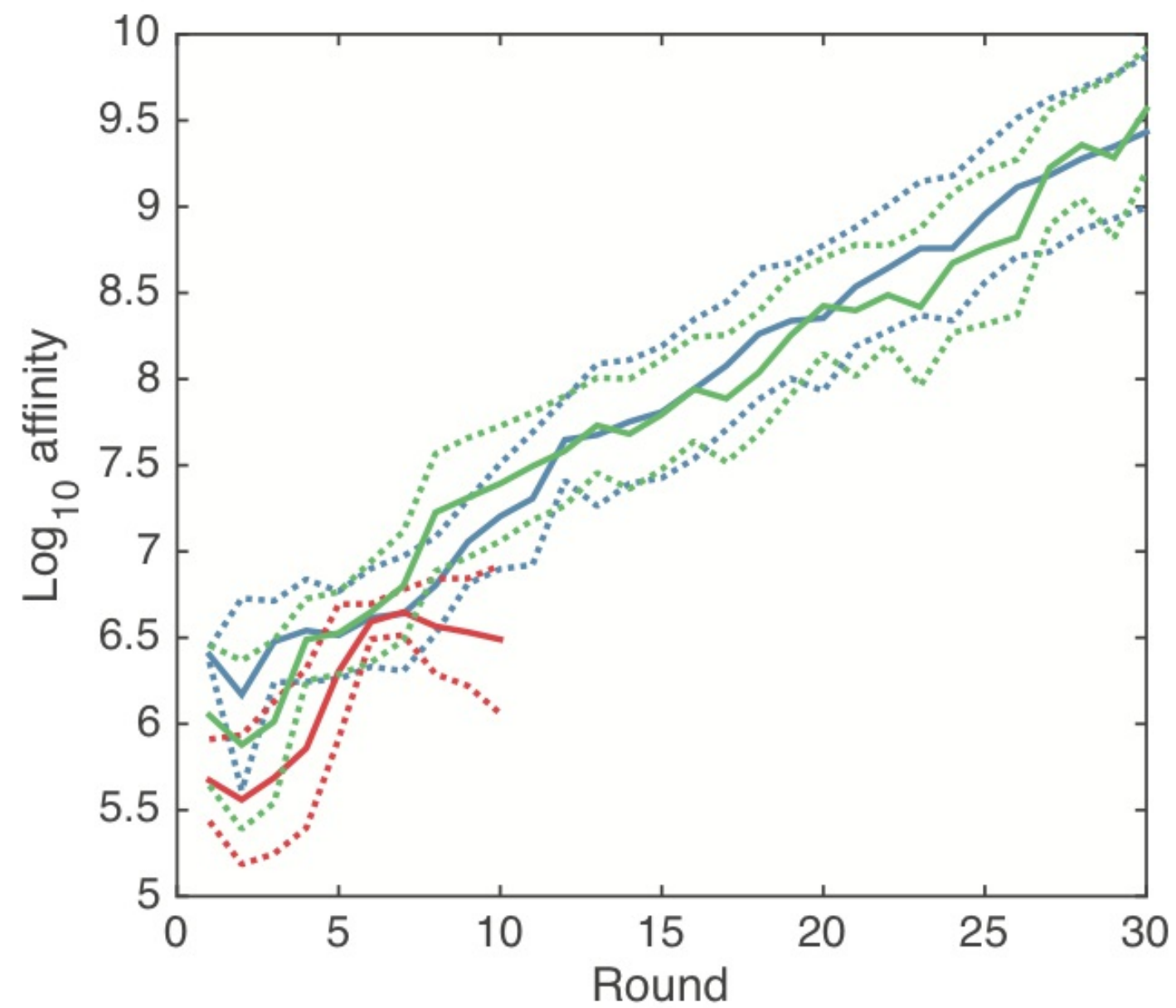
$\{10^4, 10^5, 10^4, \dots\}$



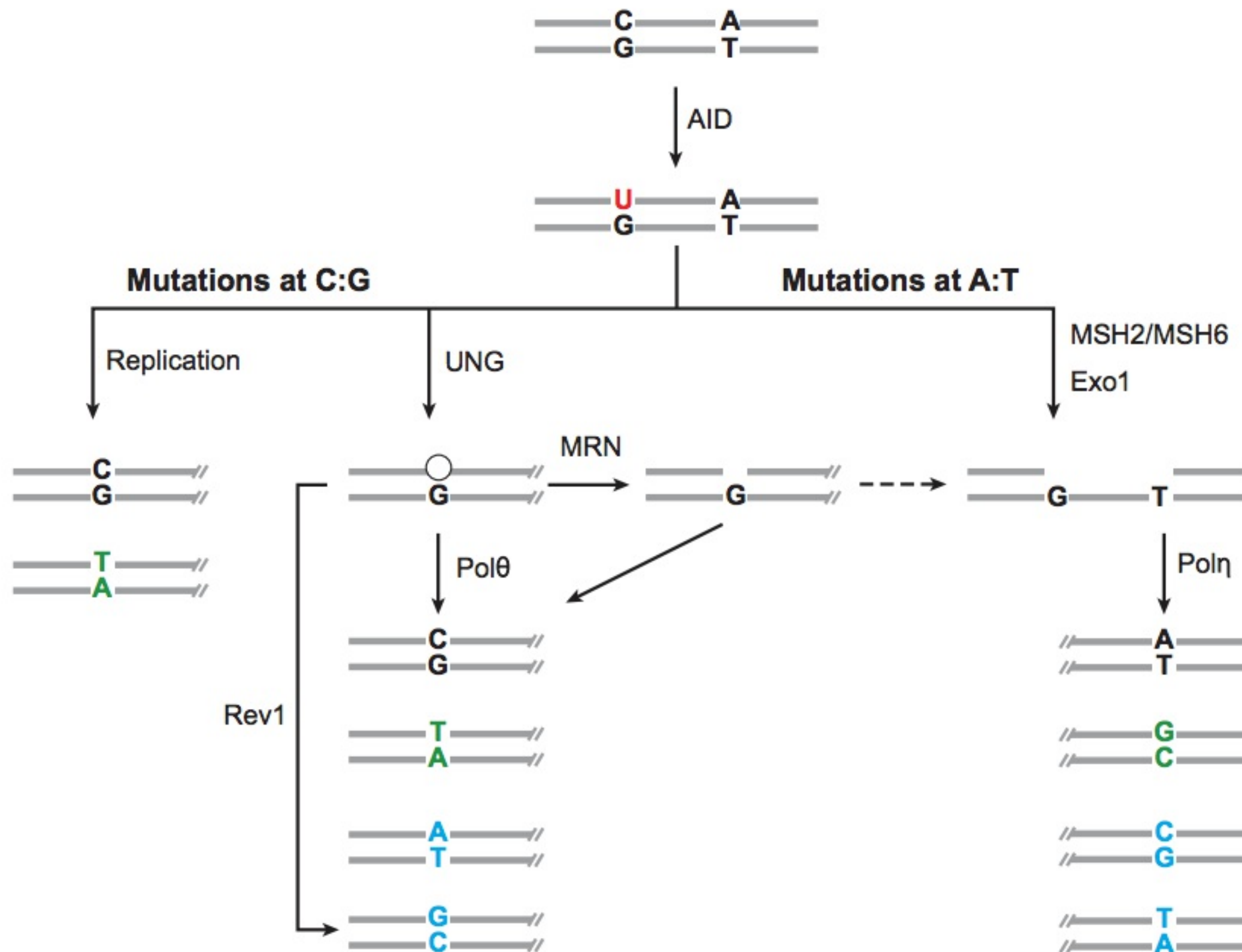
⋮



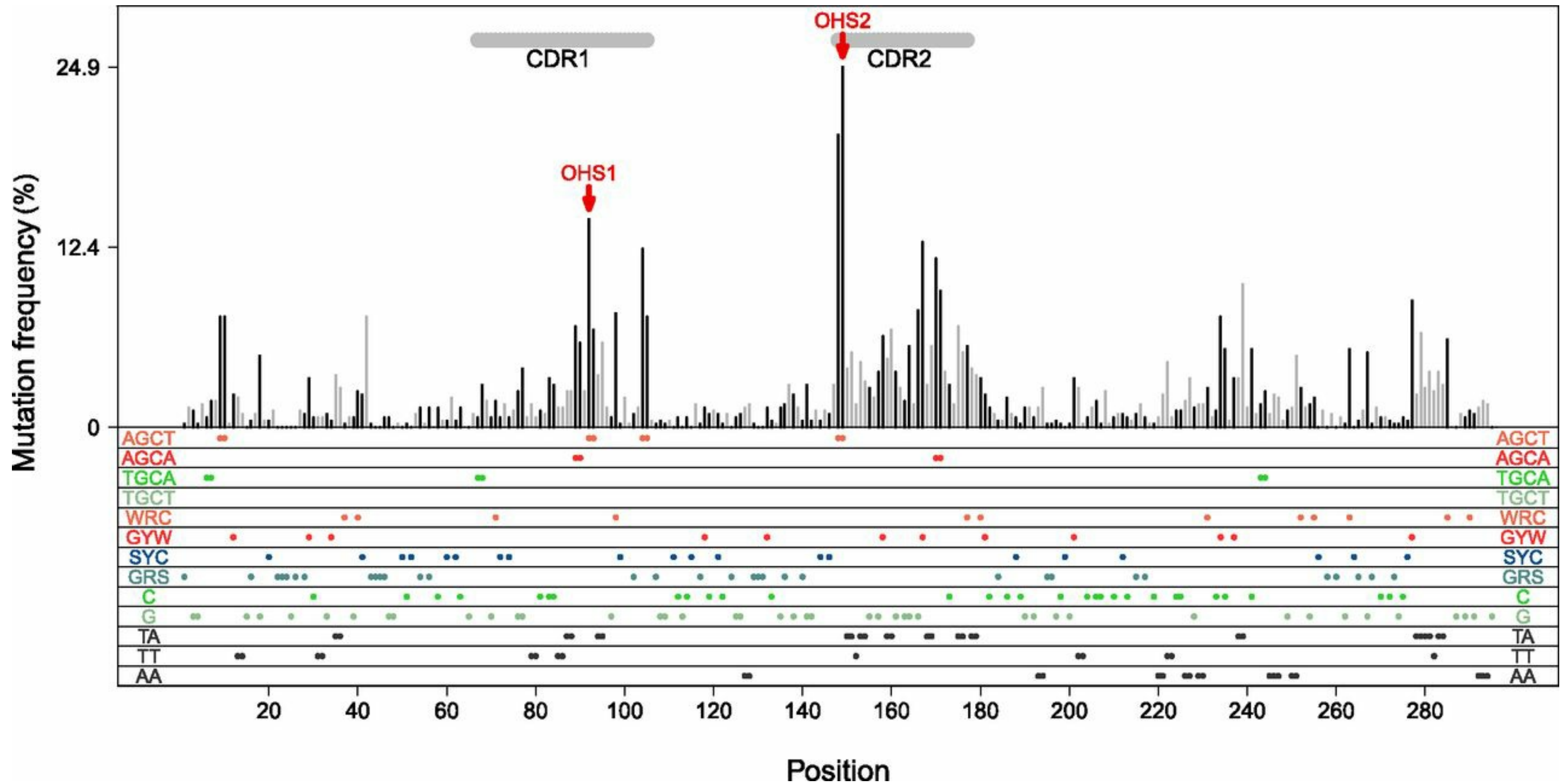
Dynamics in one GC



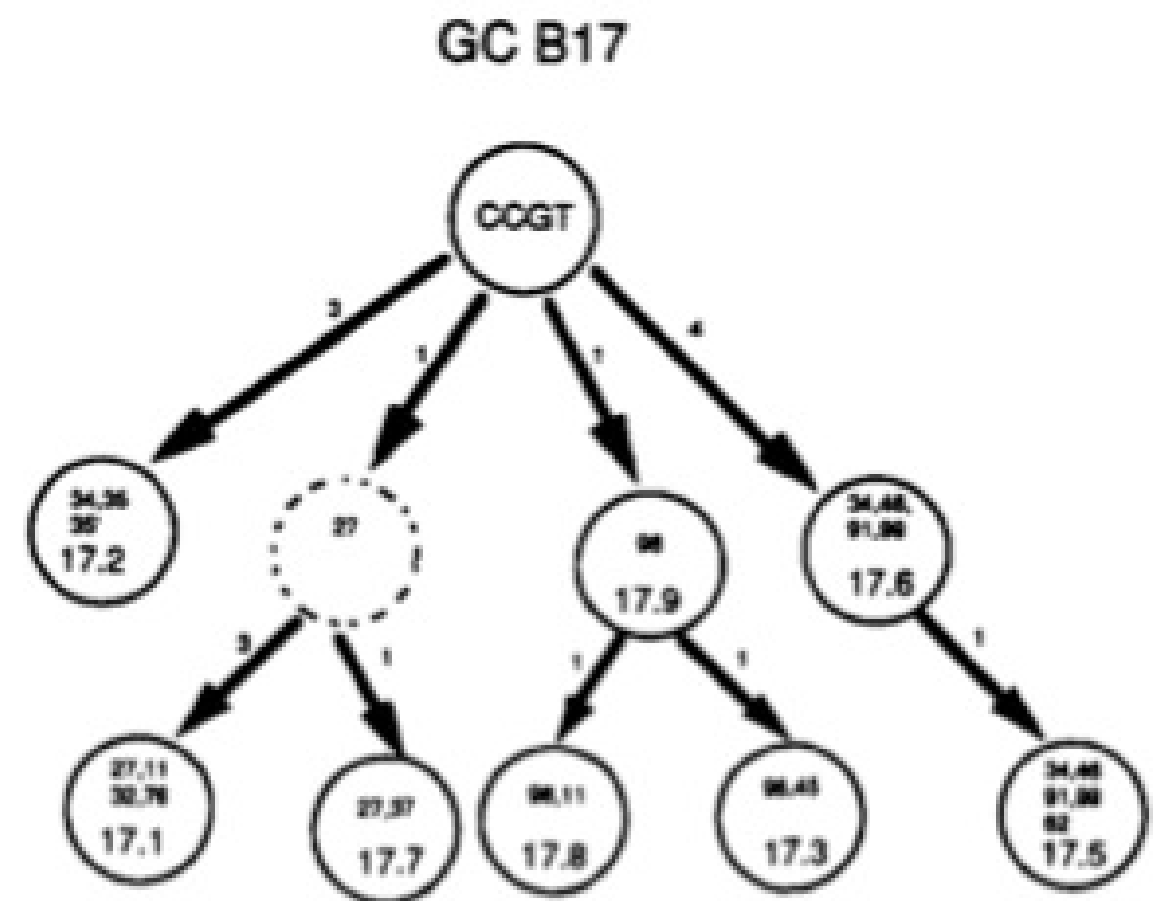
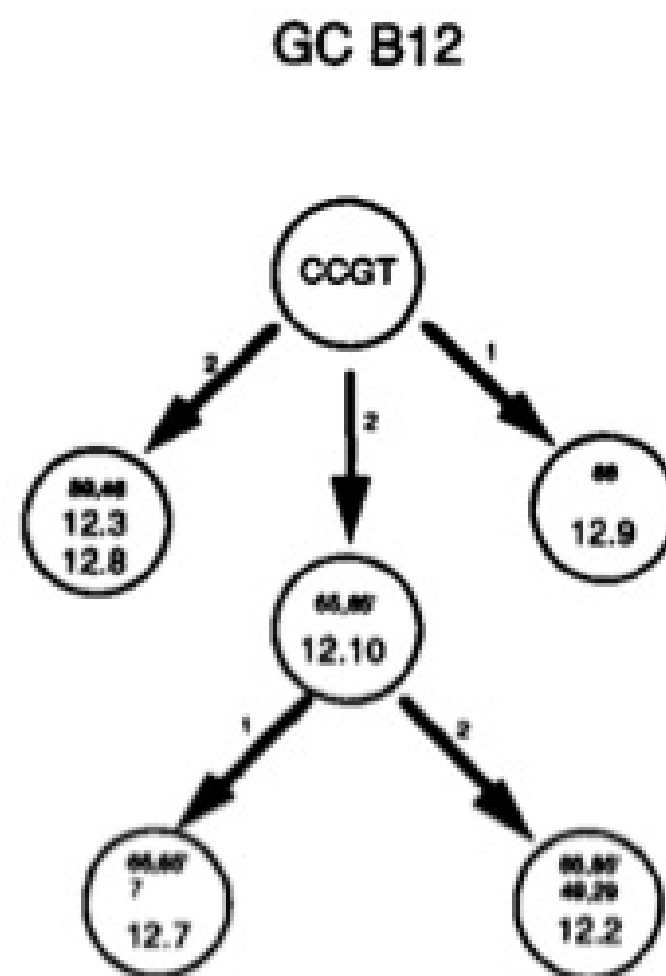
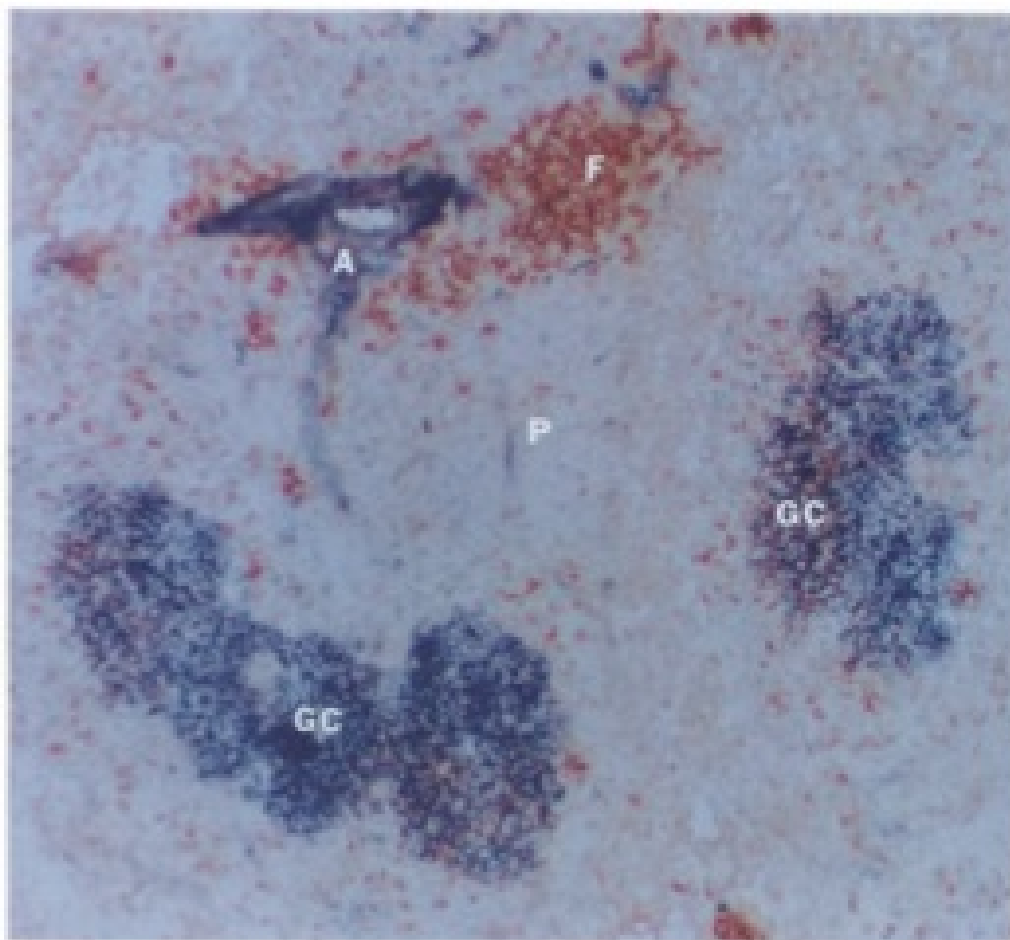
AID induces somatic hypermutation



Mutation rate varies over BCR

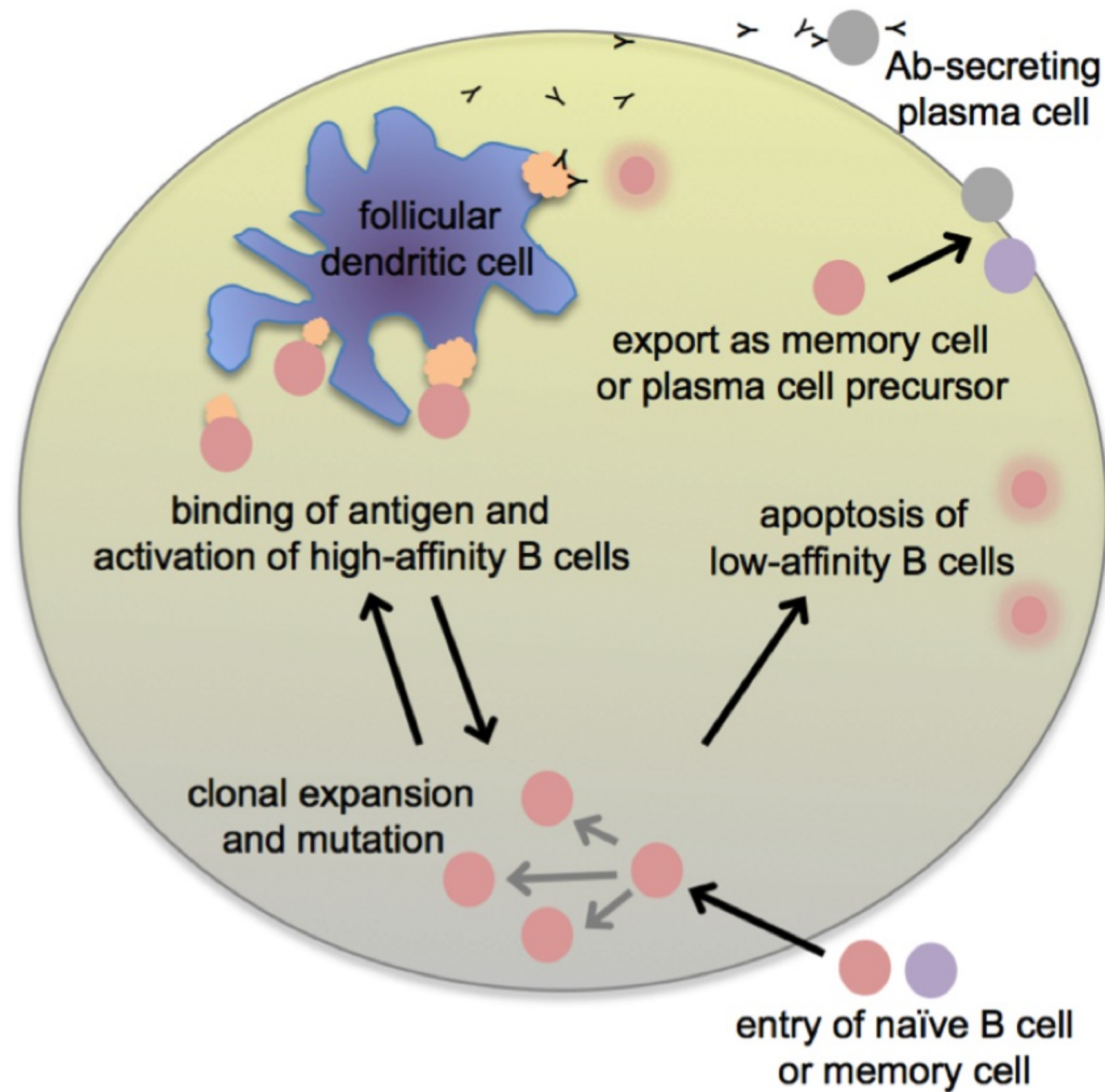


GC B cells evolve

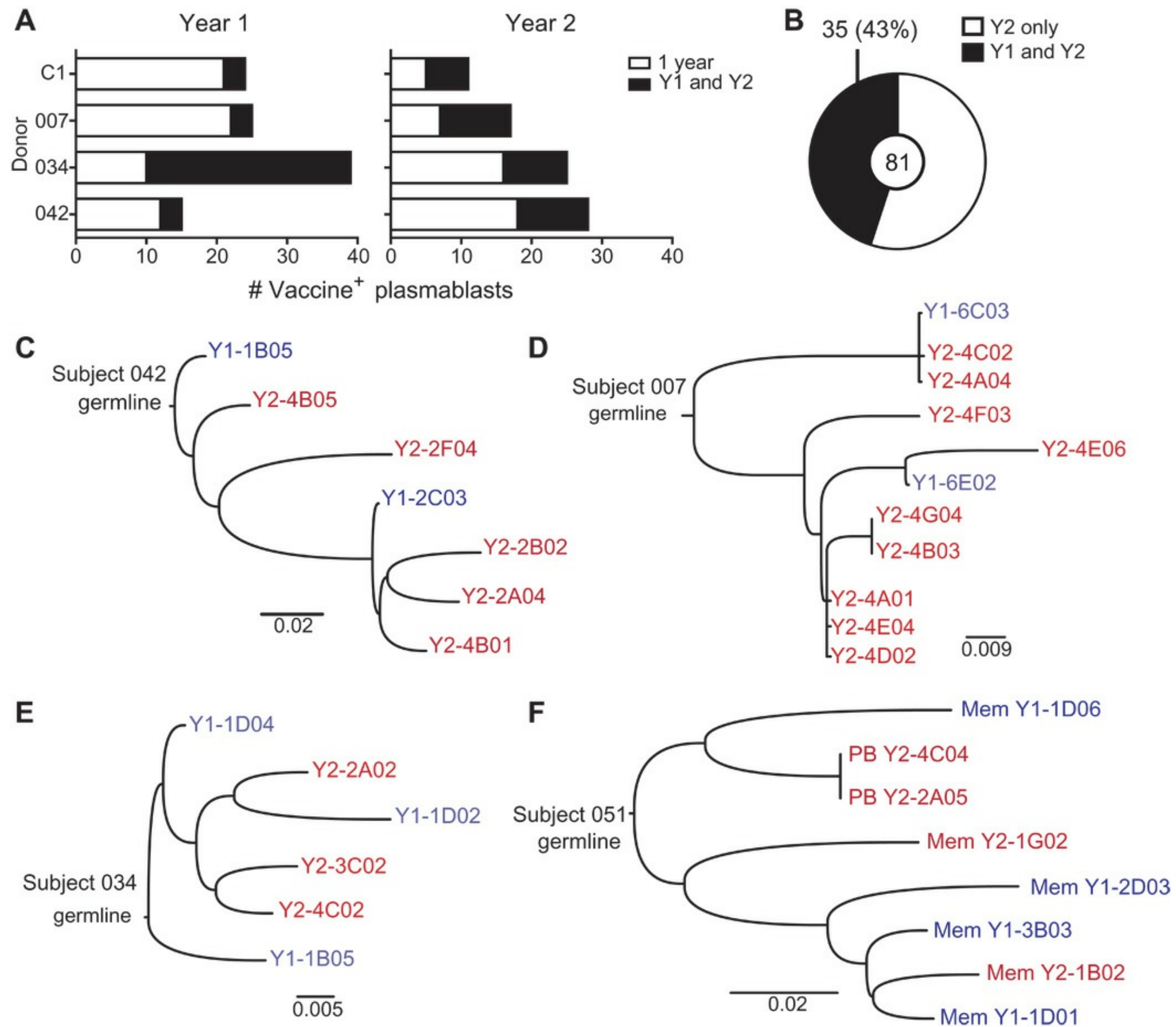


Jacob and Kelsoe 1992

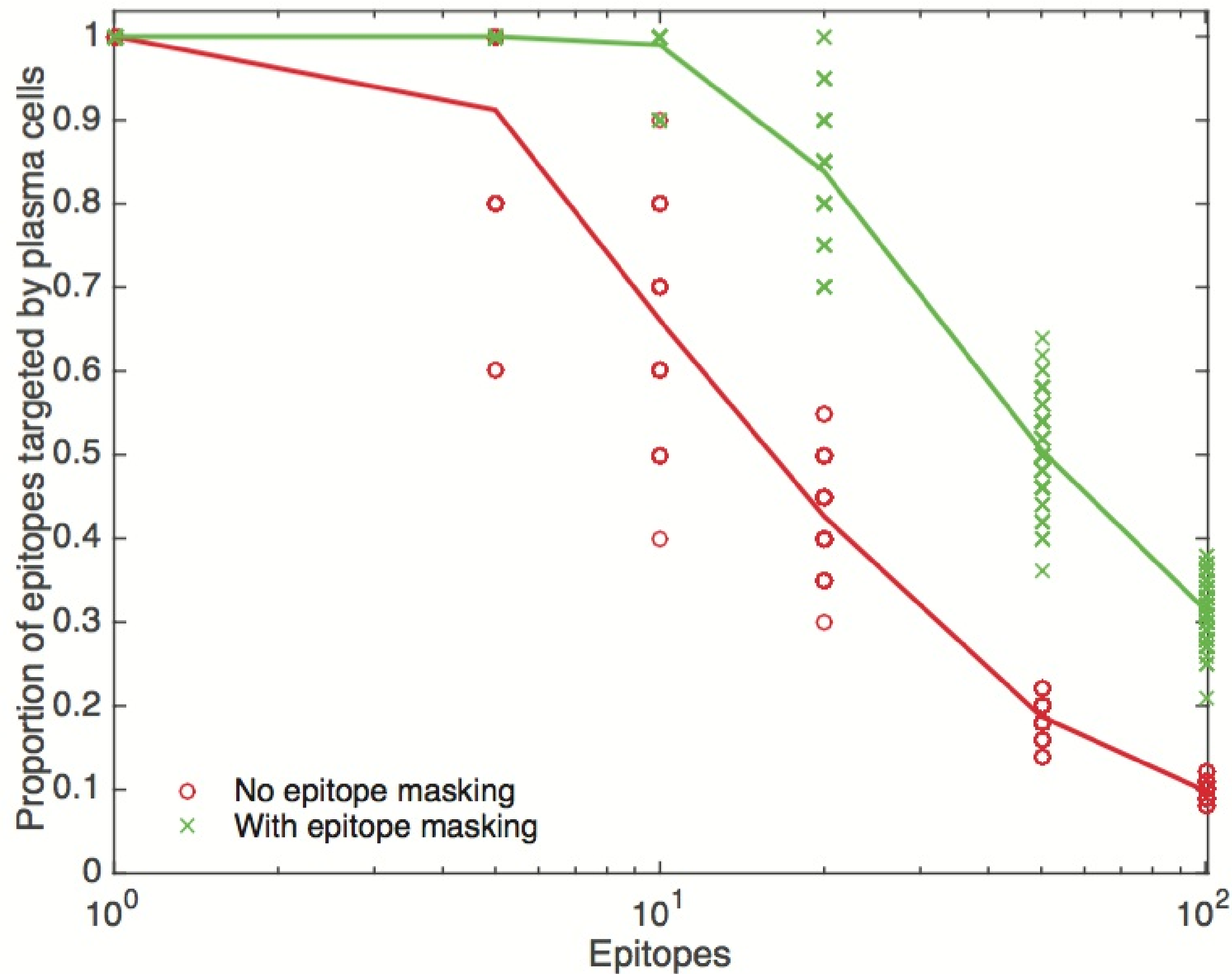
GCs produce plasma and memory cells



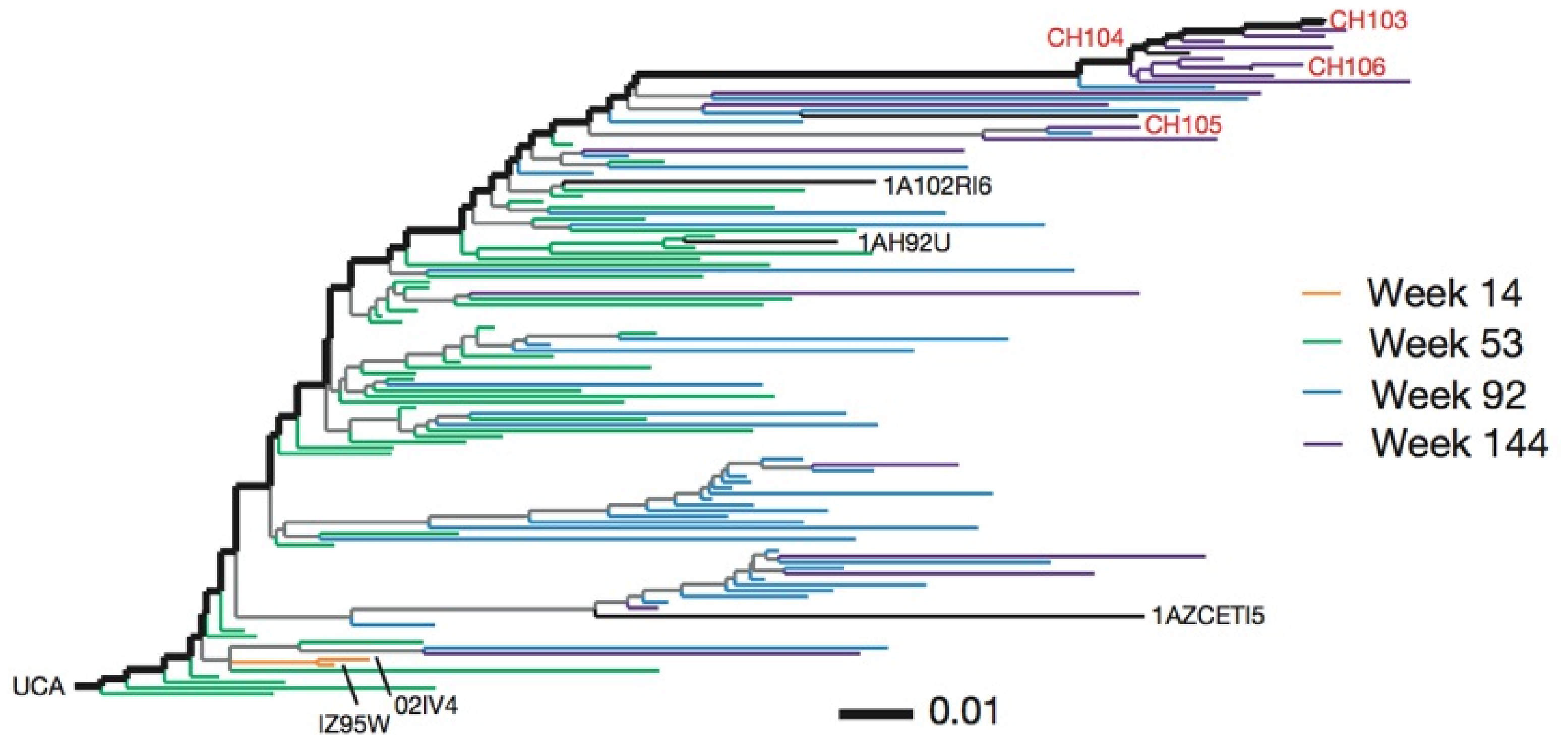
Memory cells can affinity mature



Ab feedback may diversify the repertoire

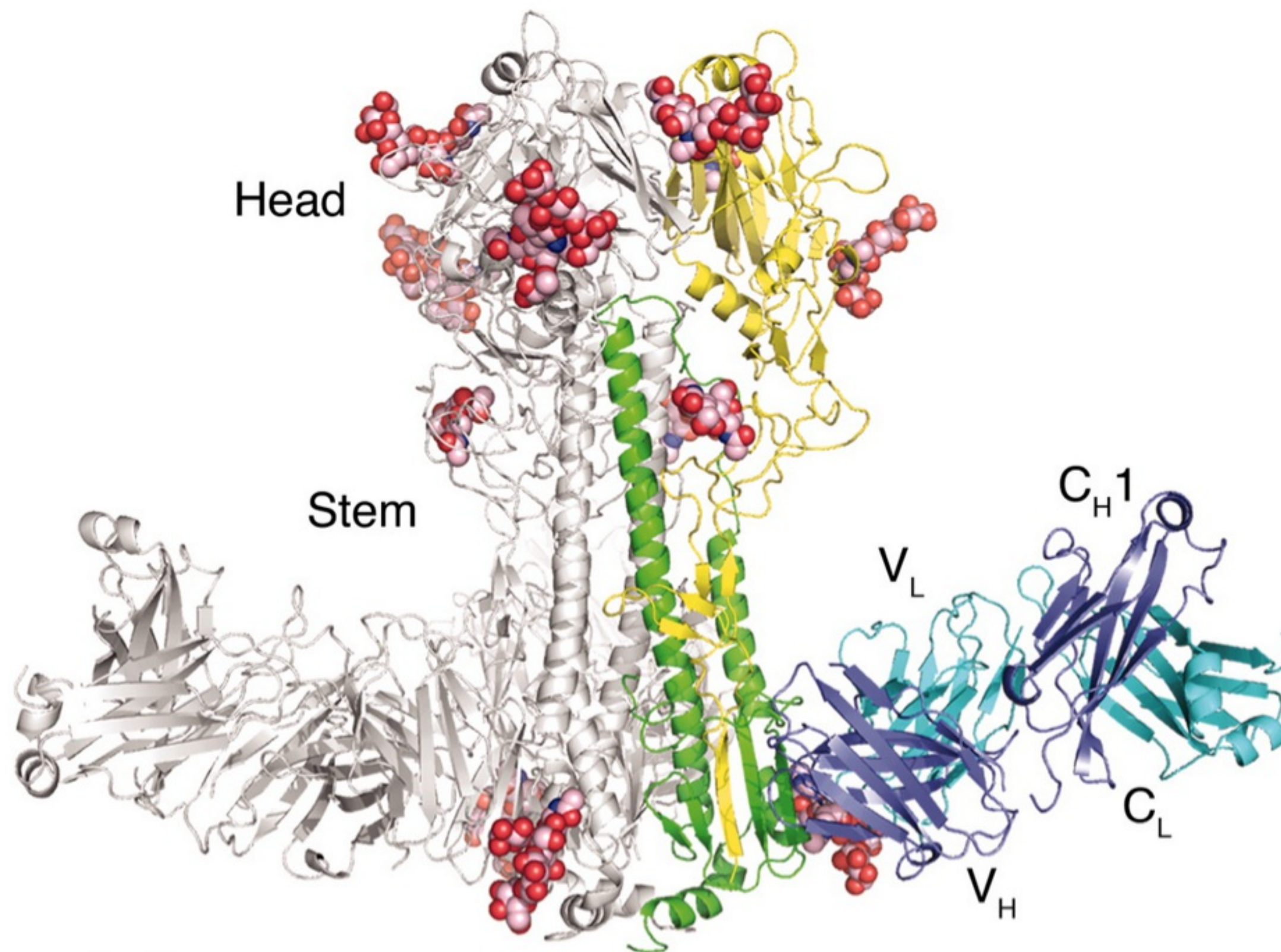


Clones can be long-lived





Broadly neutralizing antibodies to flu elusive



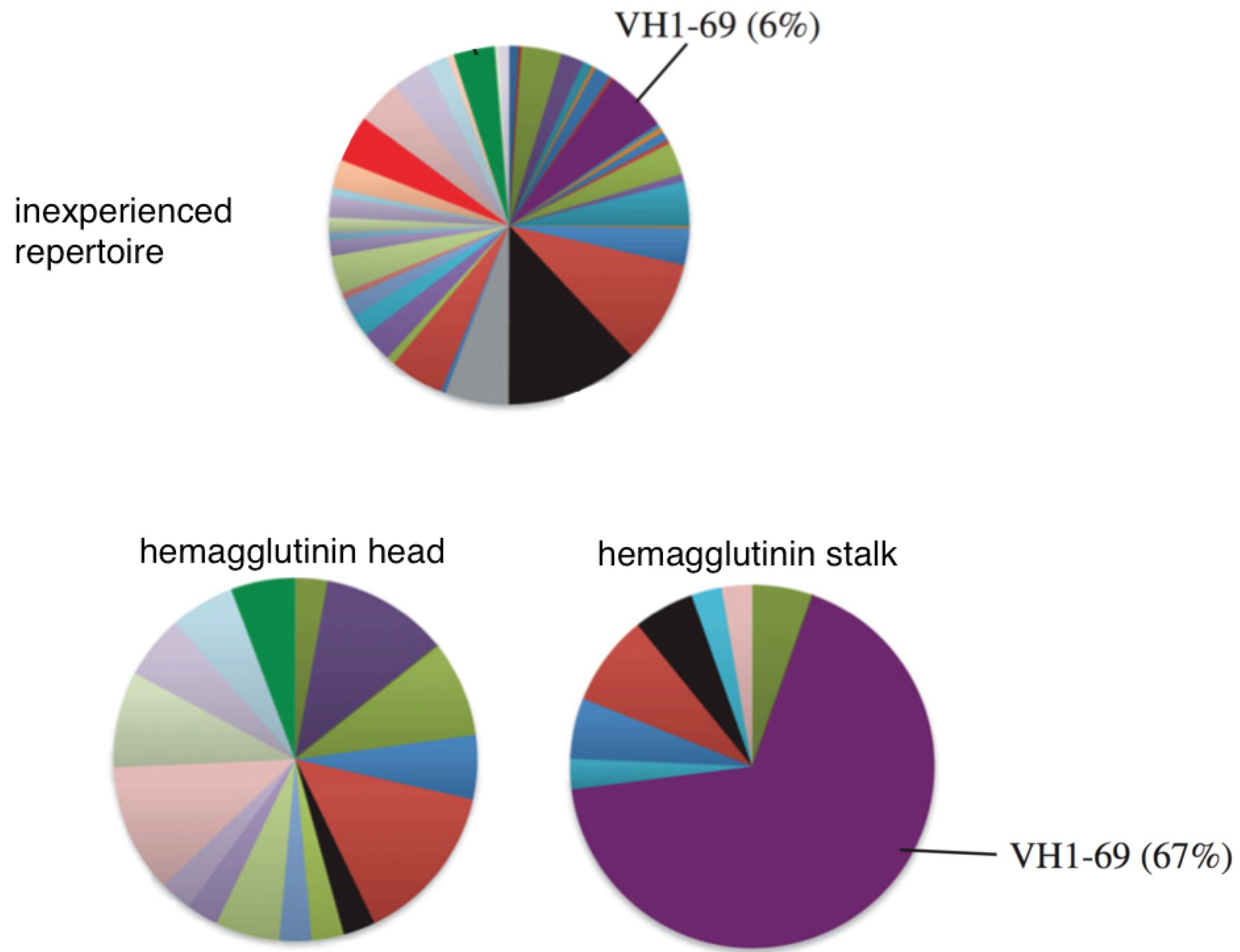


Why do some people develop broadly neutralizing antibodies?

Can we induce them in everyone?

Will they dominate?

"Restricted" responses to epitopes

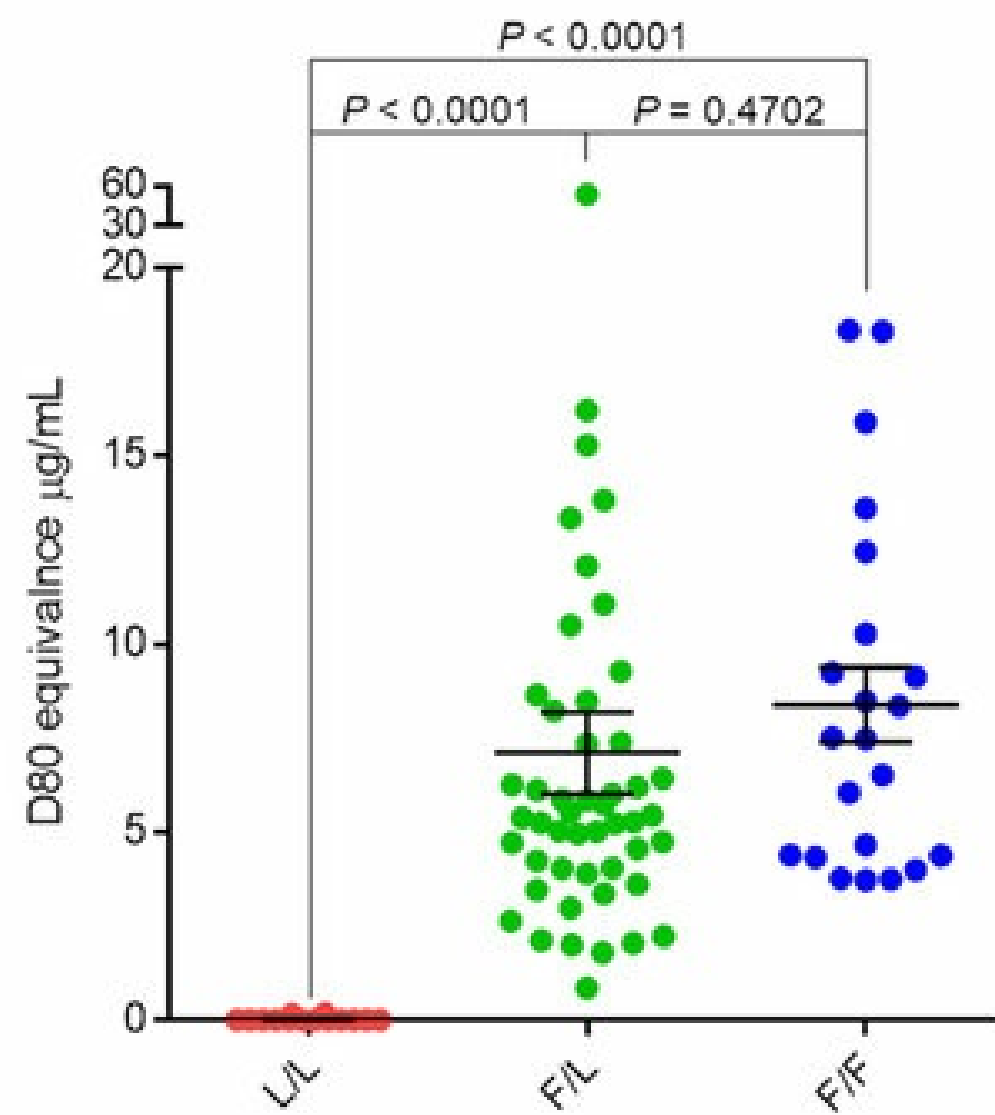


Genotype affects response to H5N1 vaccination

a

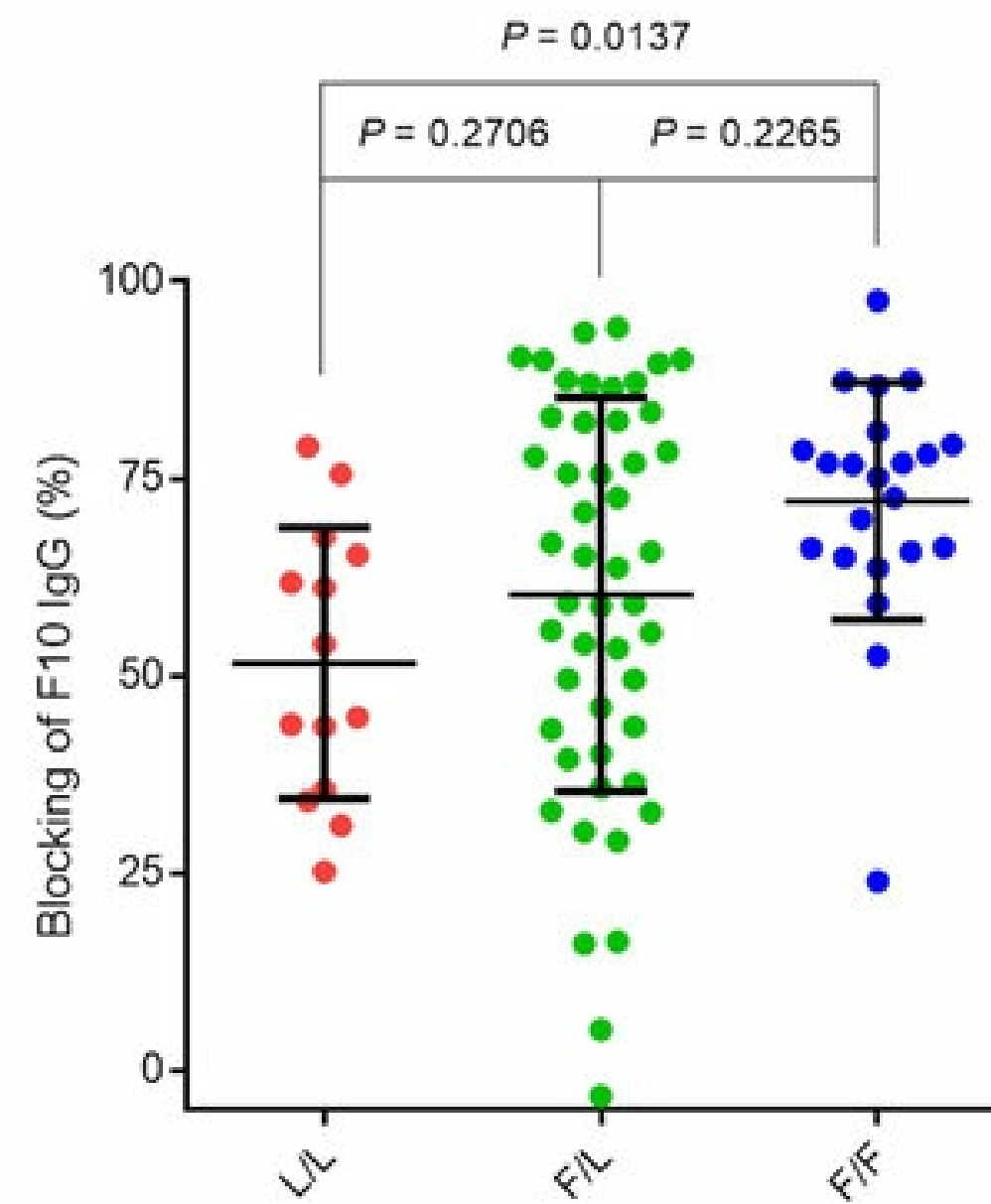
	Sample #	Mean	Std. Error of Mean	Minimum	Maximum
L/L	14	0.024	0.016	0.000	0.175
F/L	49	7.100	1.090	0.851	53.600
F/F	22	8.380	0.998	3.710	18.300

Kruskal-Wallis test $P < 0.0001$

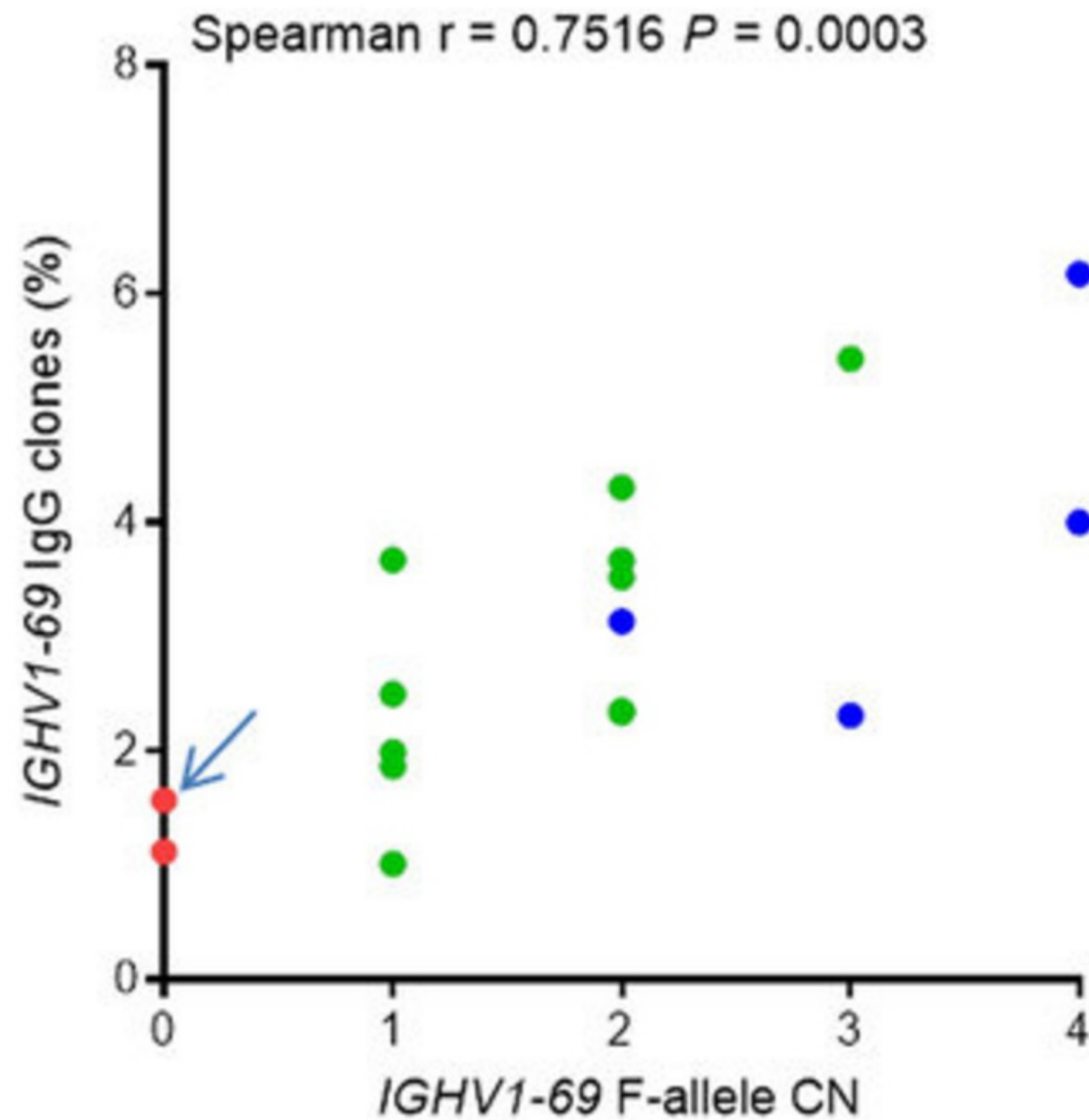


b

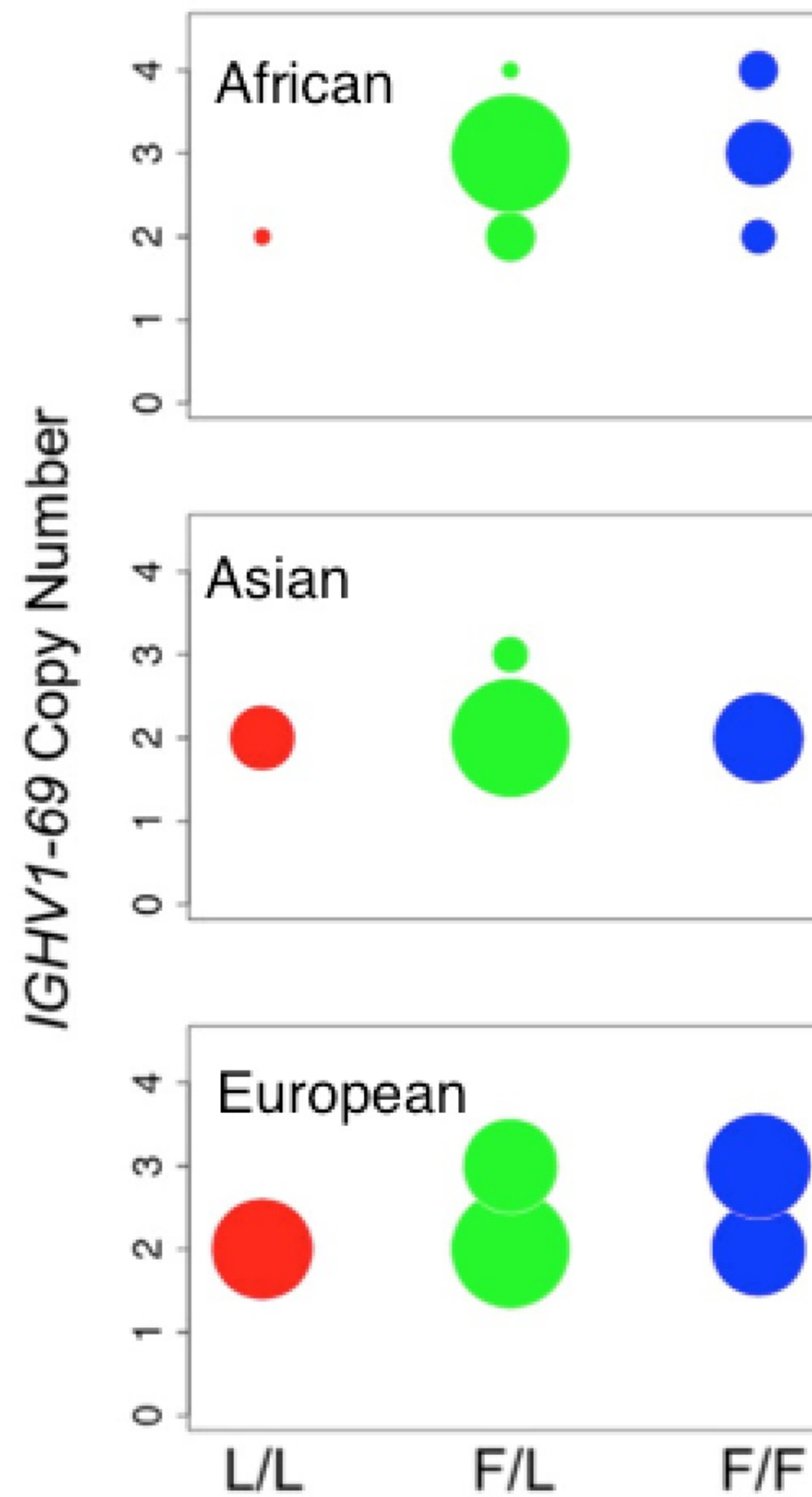
Kruskal-Wallis test $P = 0.0168$
Cuzick's trend test $z = 2.856$, $P = 0.004$



Allele copy number affects clone frequency



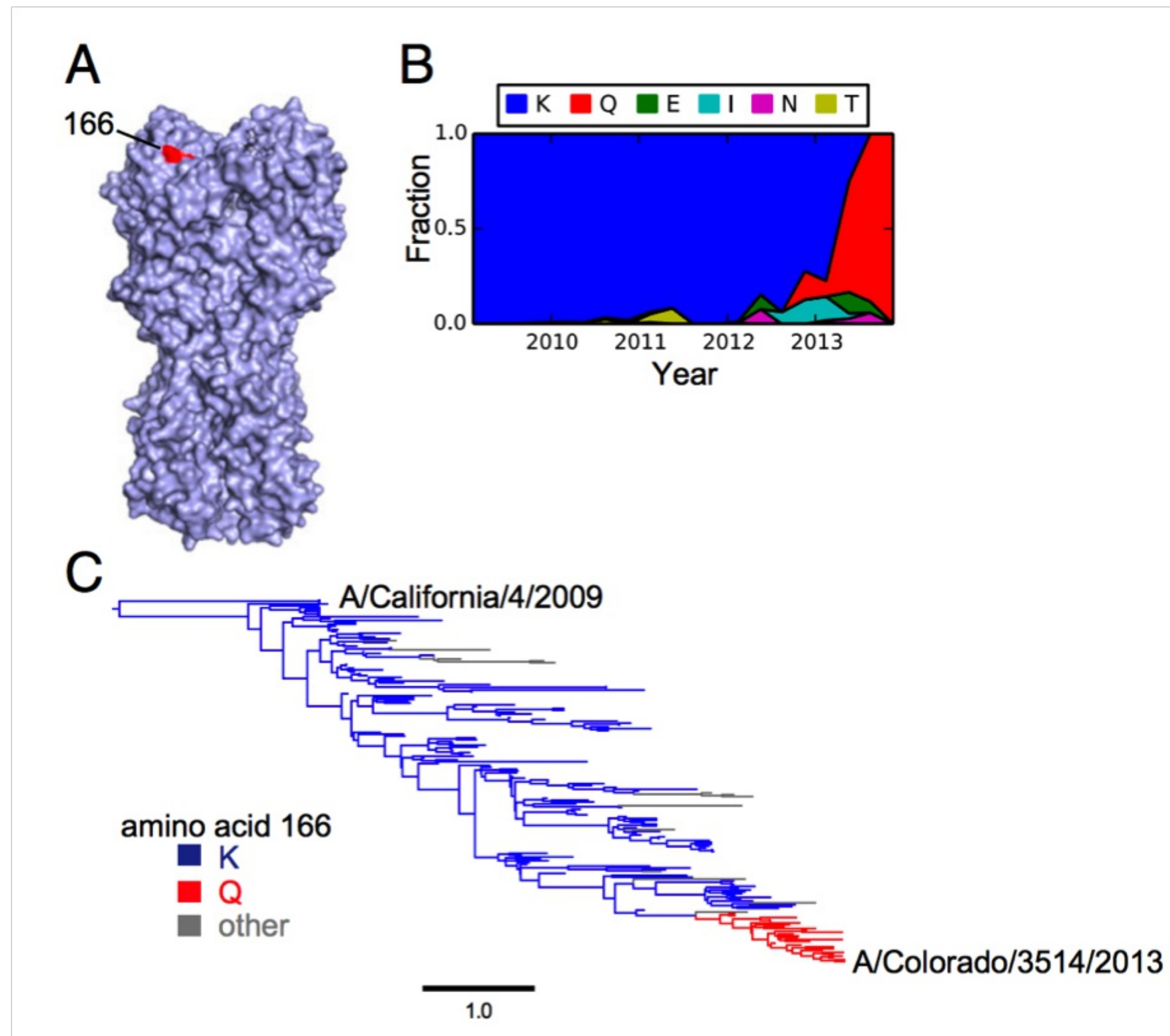
Ethnic differences in copy number



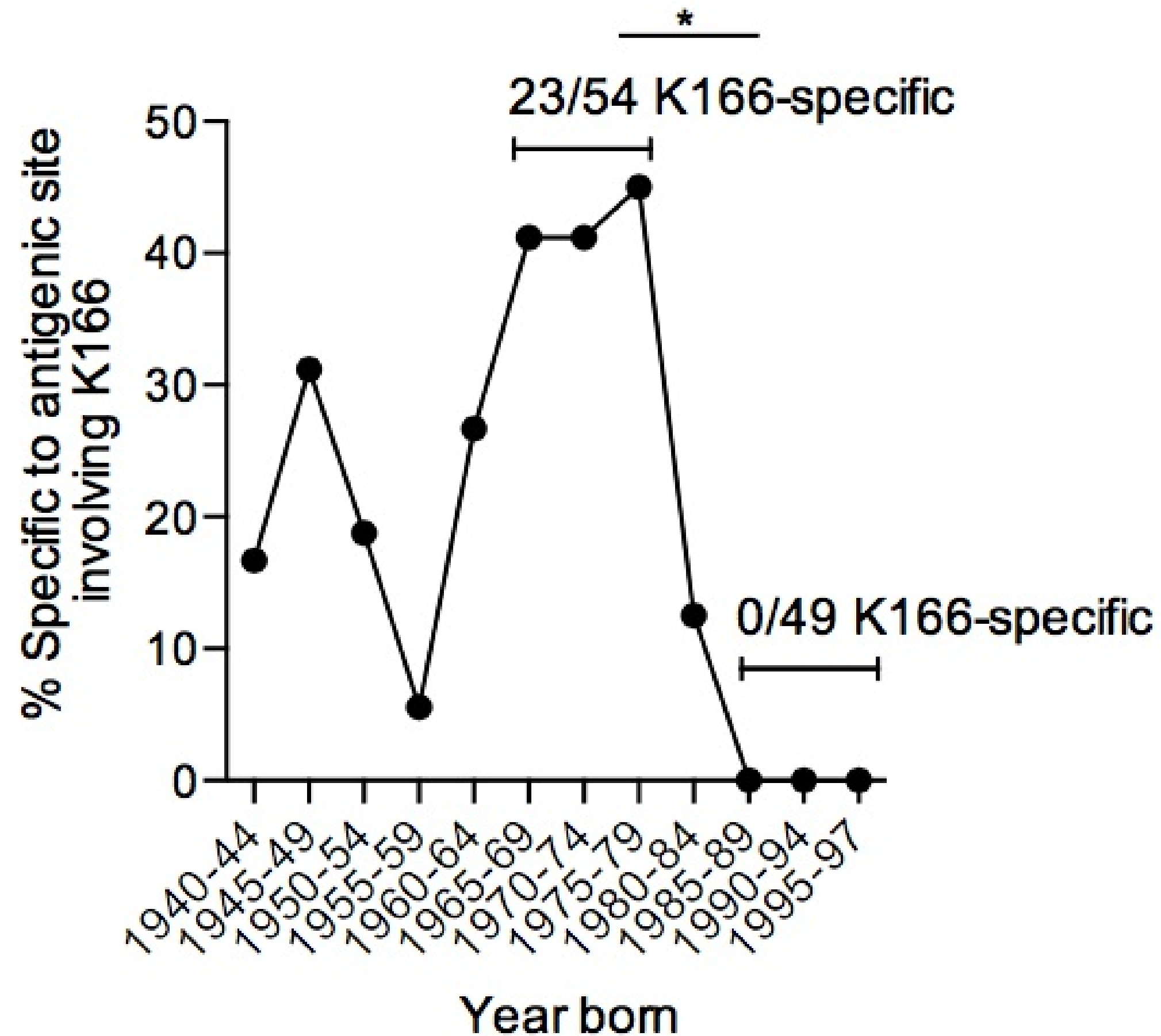


A story about a sample of people born between 1965 and 1979...

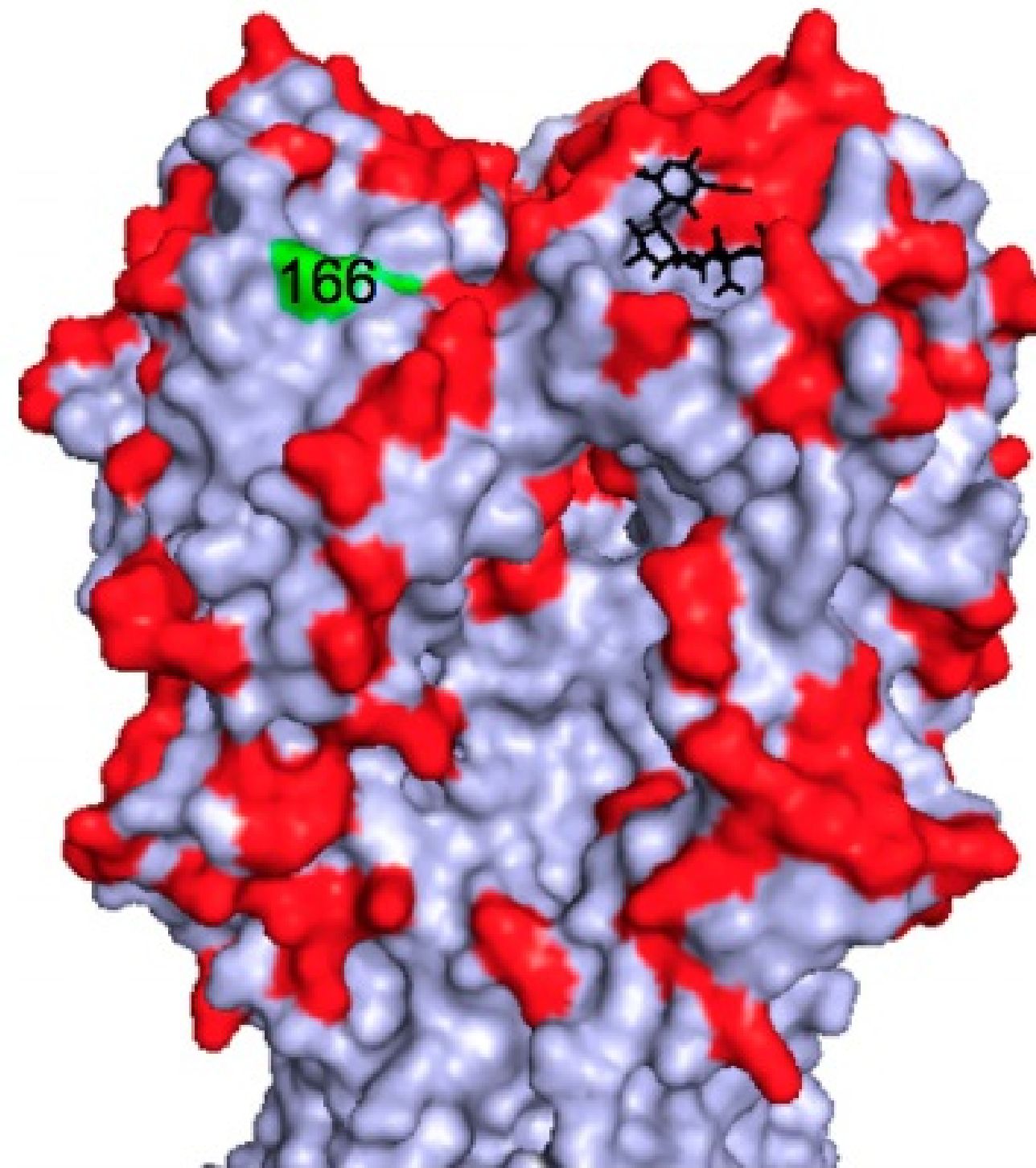
In 2013, H1N1 acquired K166Q



Uneven recognition

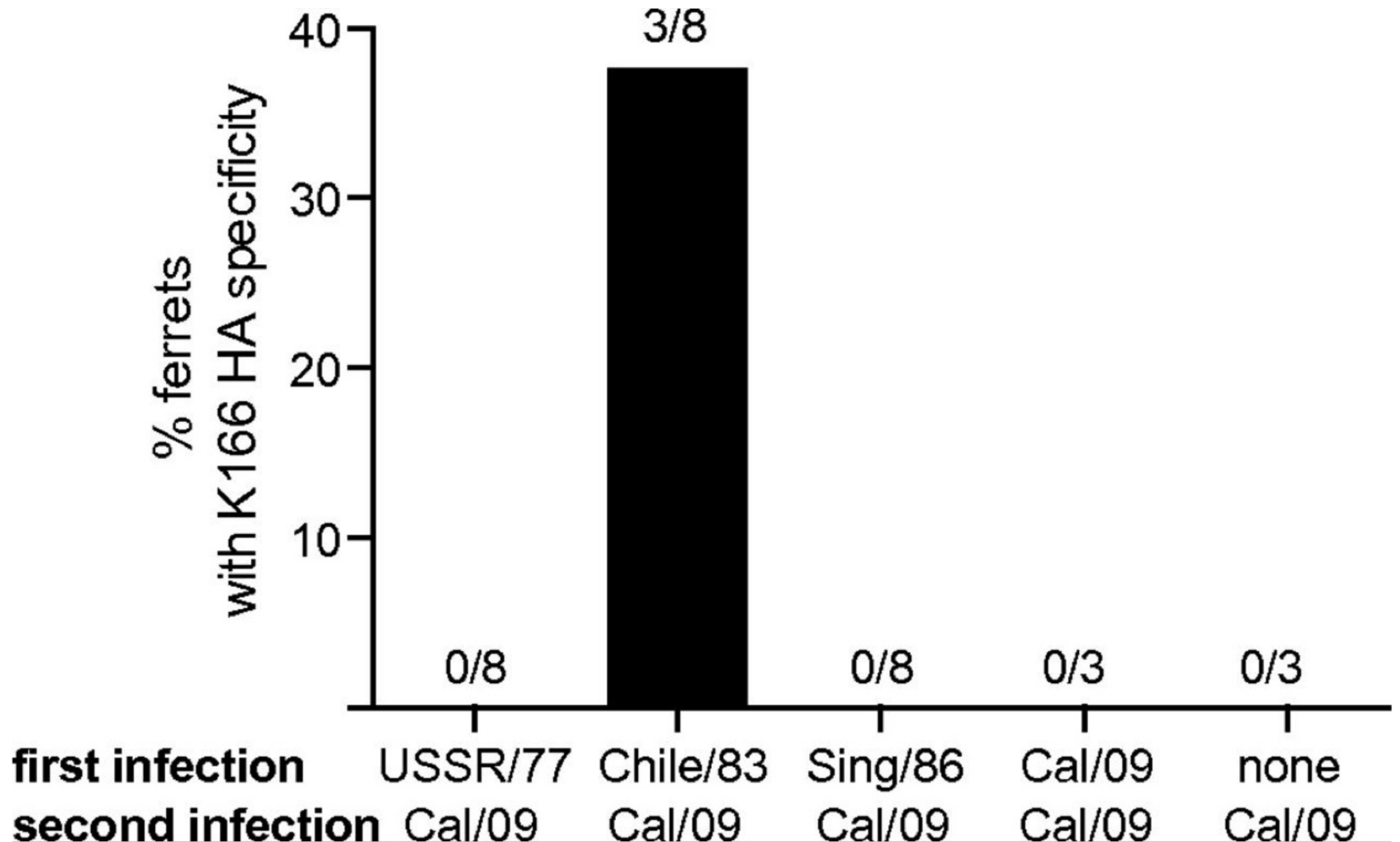


Homology with childhood strain

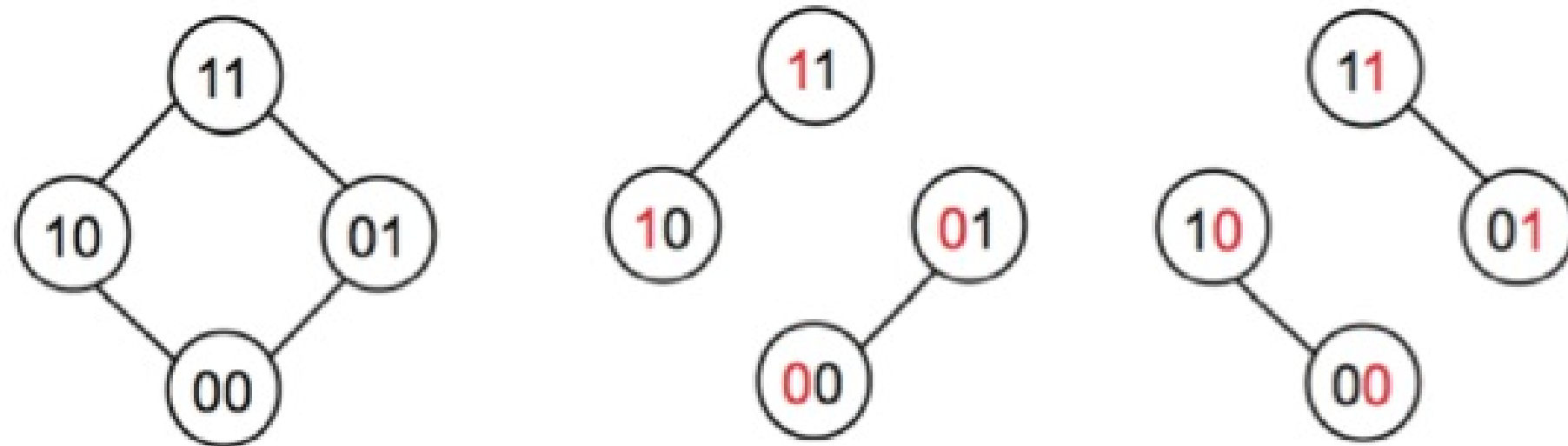


Homology between
A/Chile/01/1983 and
A/California/07/2009

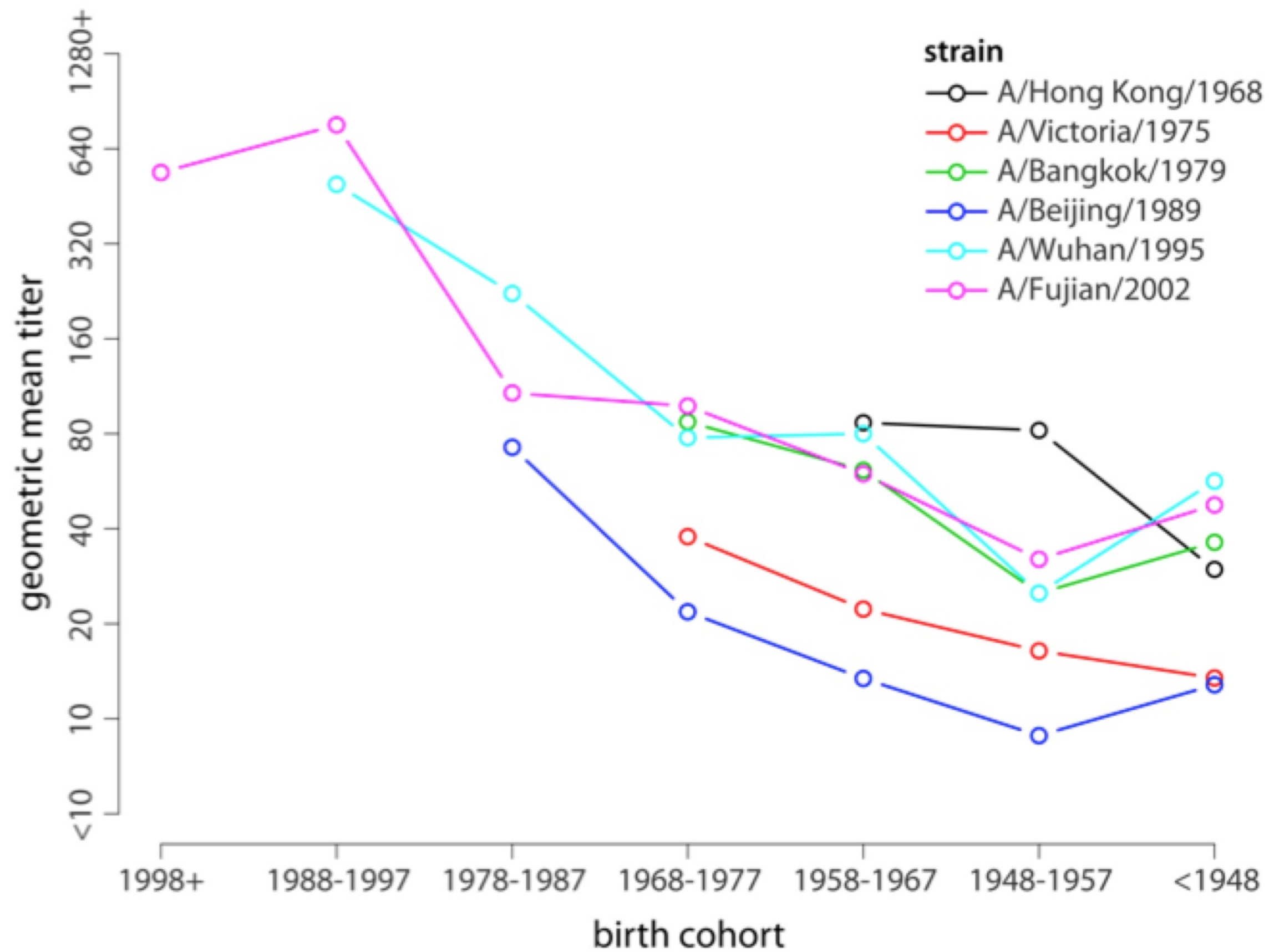
Recapitulation in ferrets



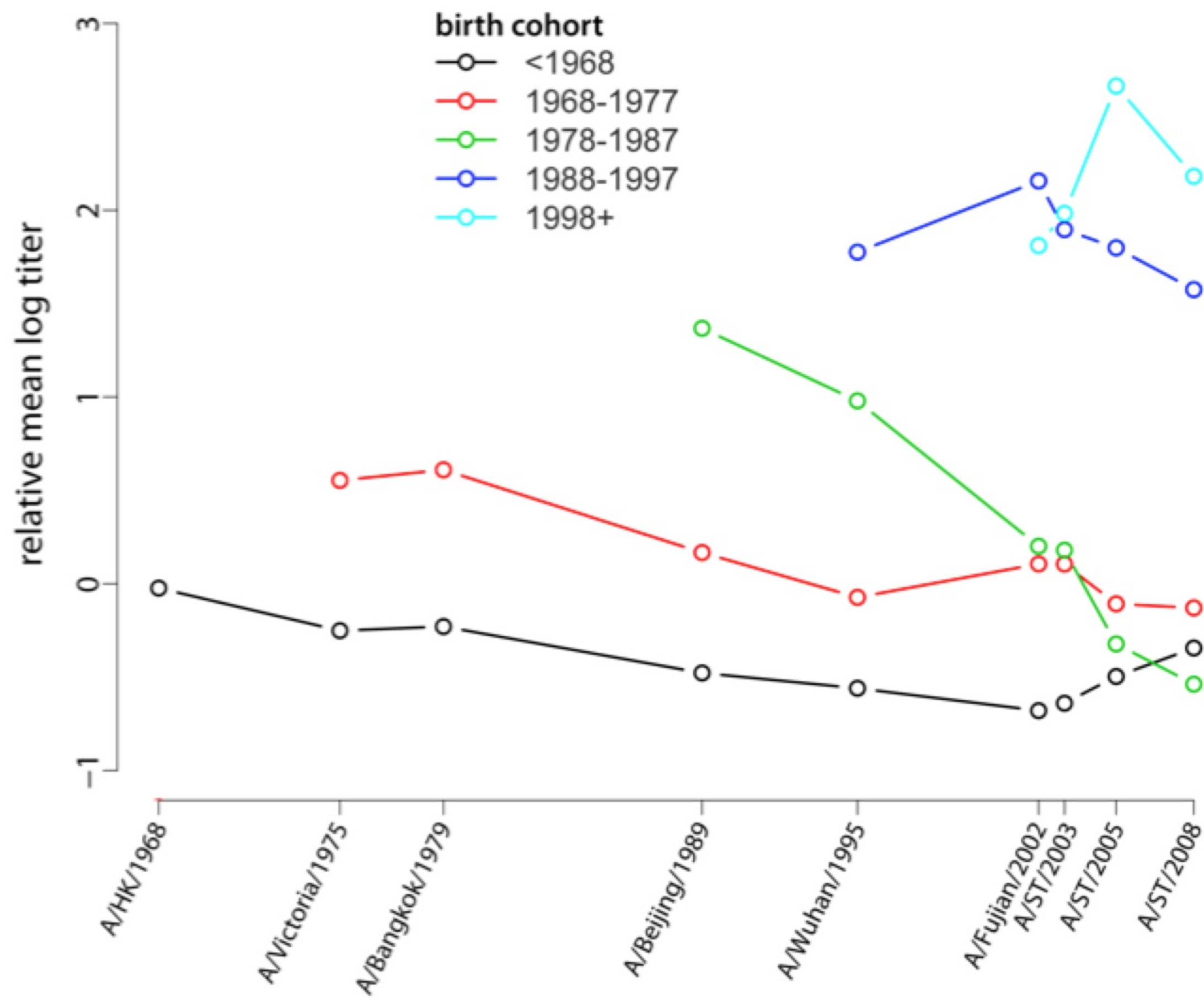
Strain phenotypes depend on host



Broad cohort-specific effects



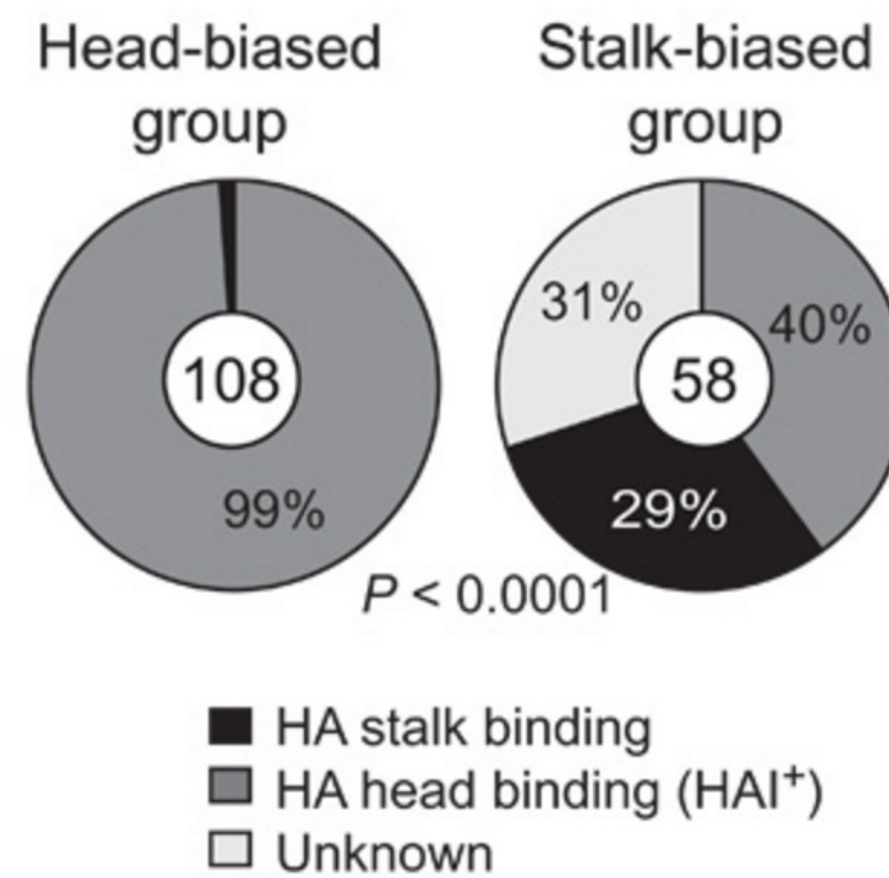
"Antigenic seniority"





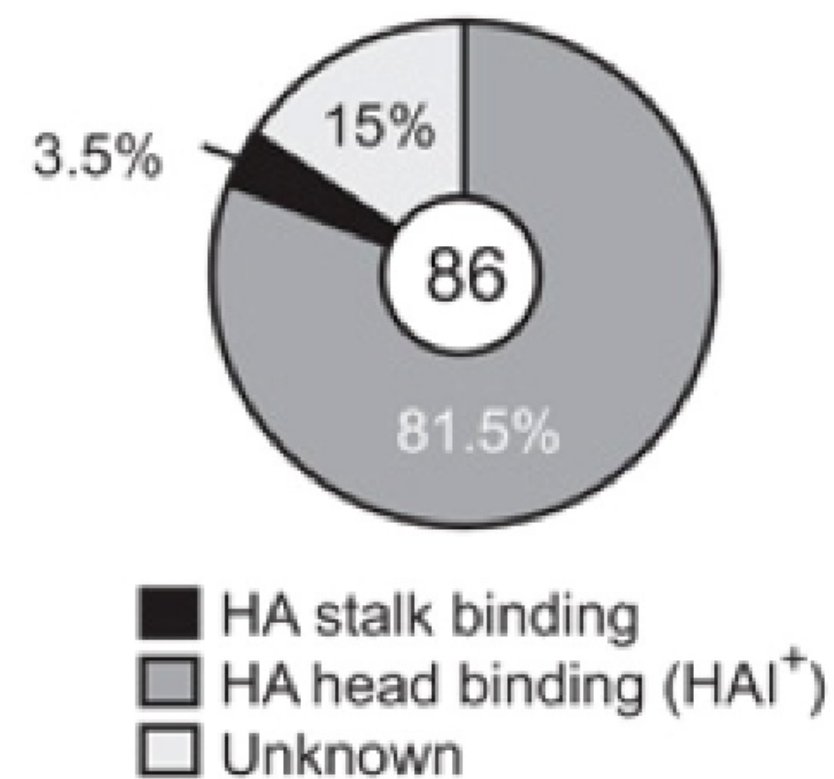
What's so special about early infections?

Response to 2009 H1N1 vaccine



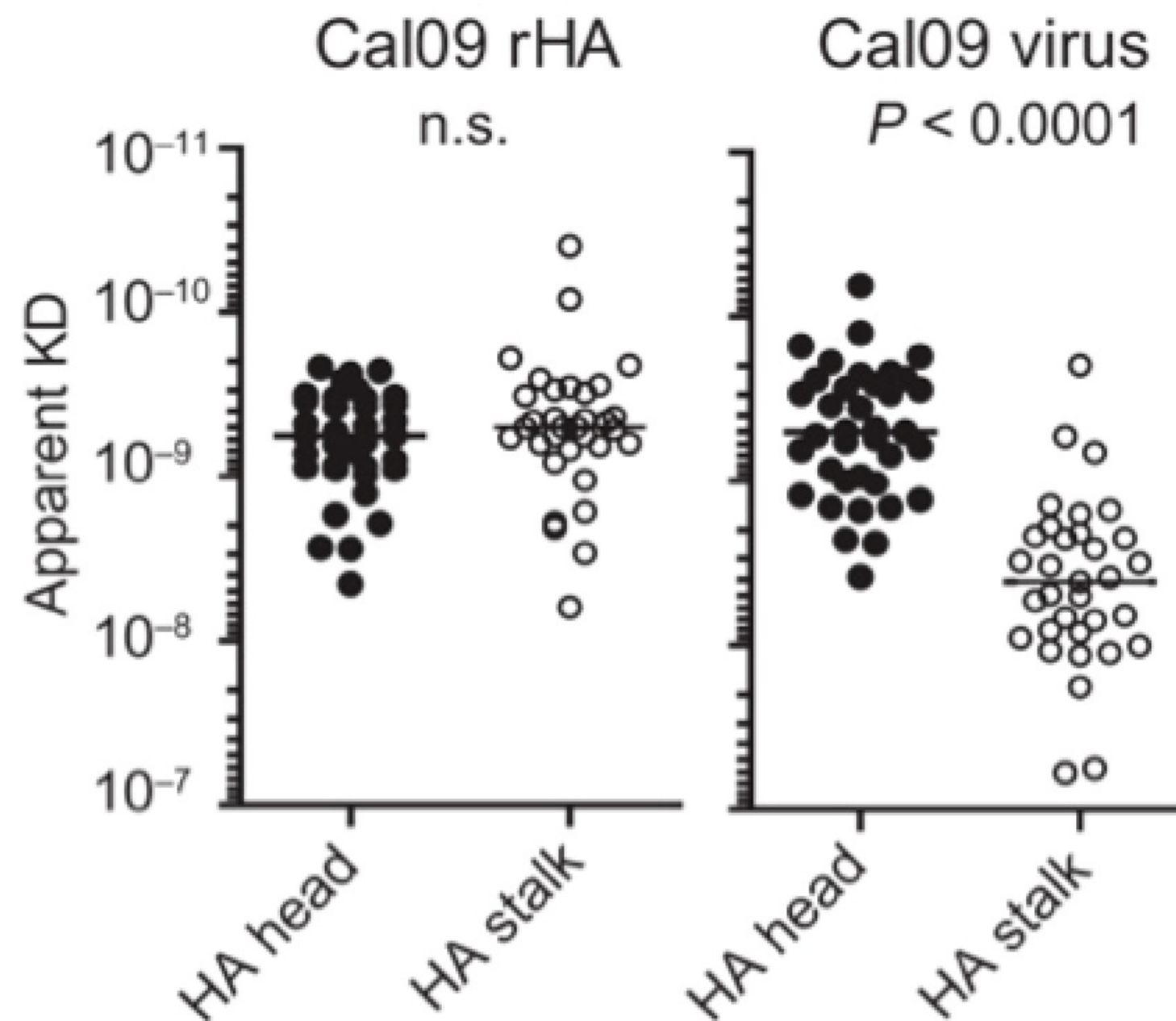
Andrews et al. 2015

Stalk responses can fade

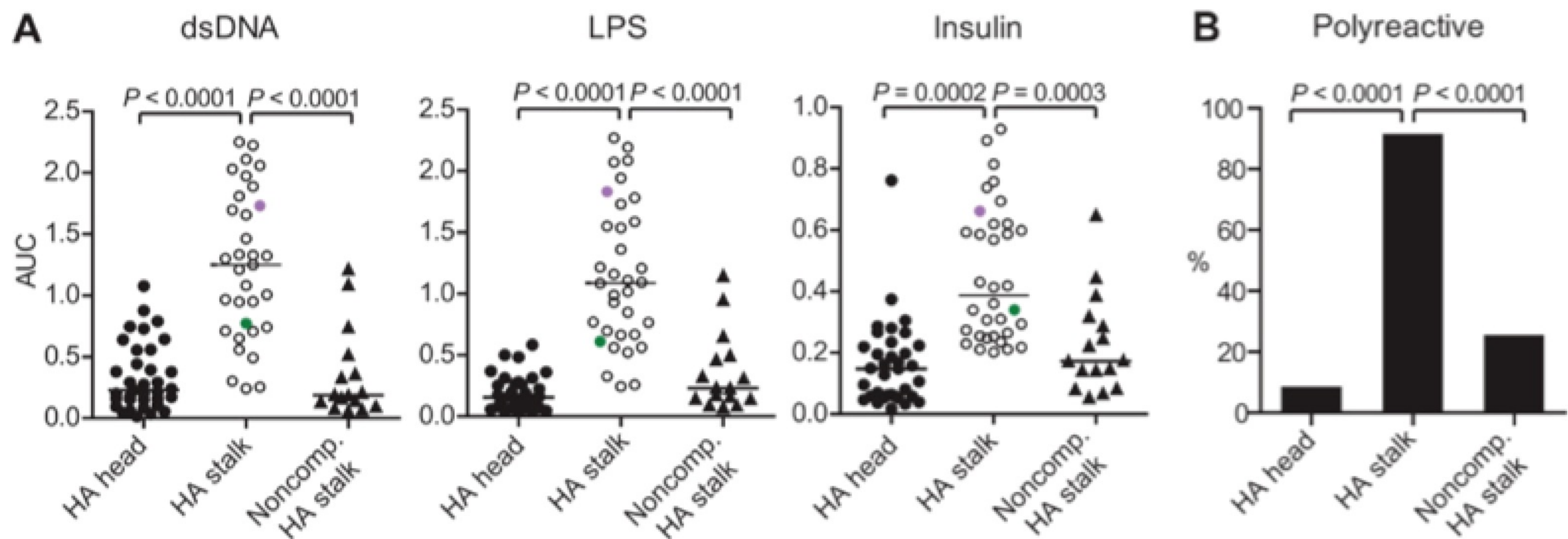


Andrews et al. 2015

Stalk antibodies bind with lower affinity



Stalk antibodies are more polyreactive



Andrews et al. 2015



Potential factors influencing specific antibody responses

Host genotype

Order (Age?) of infection

Immunogenicity

Autoreactivity