

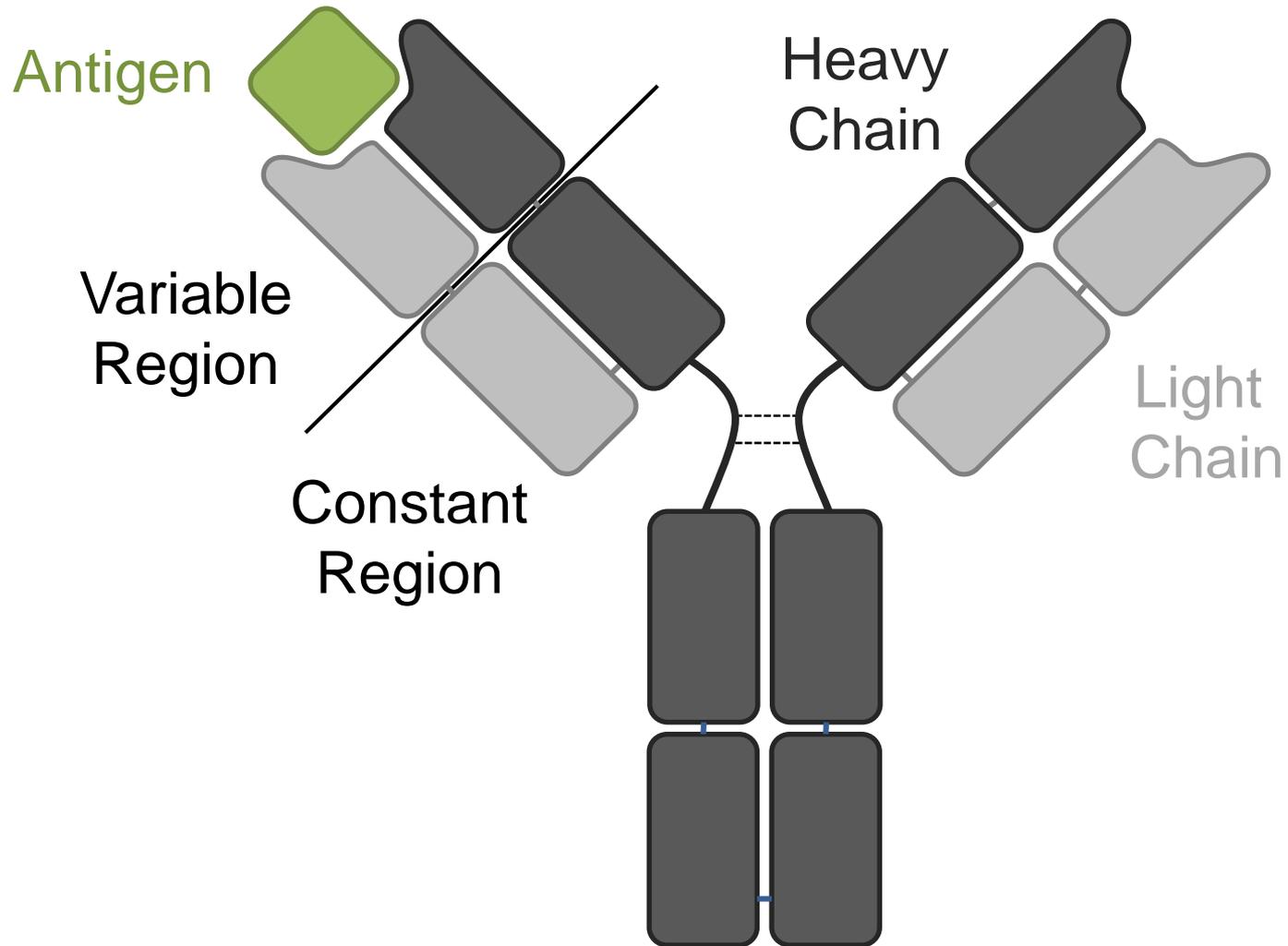
Introduction to Antibodies

Samuel Schmitz

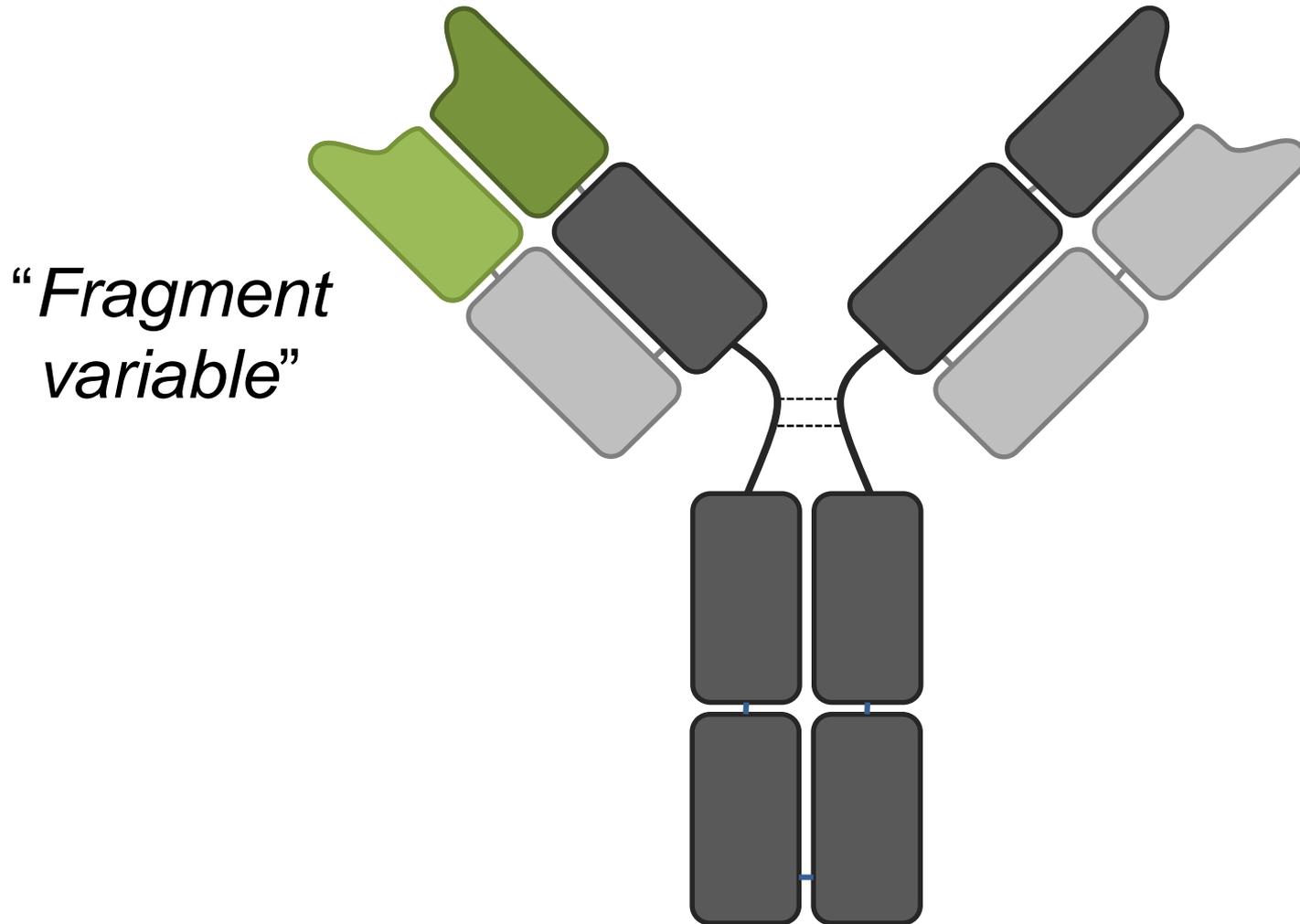
Rosetta Workshop

April 25th, 2017

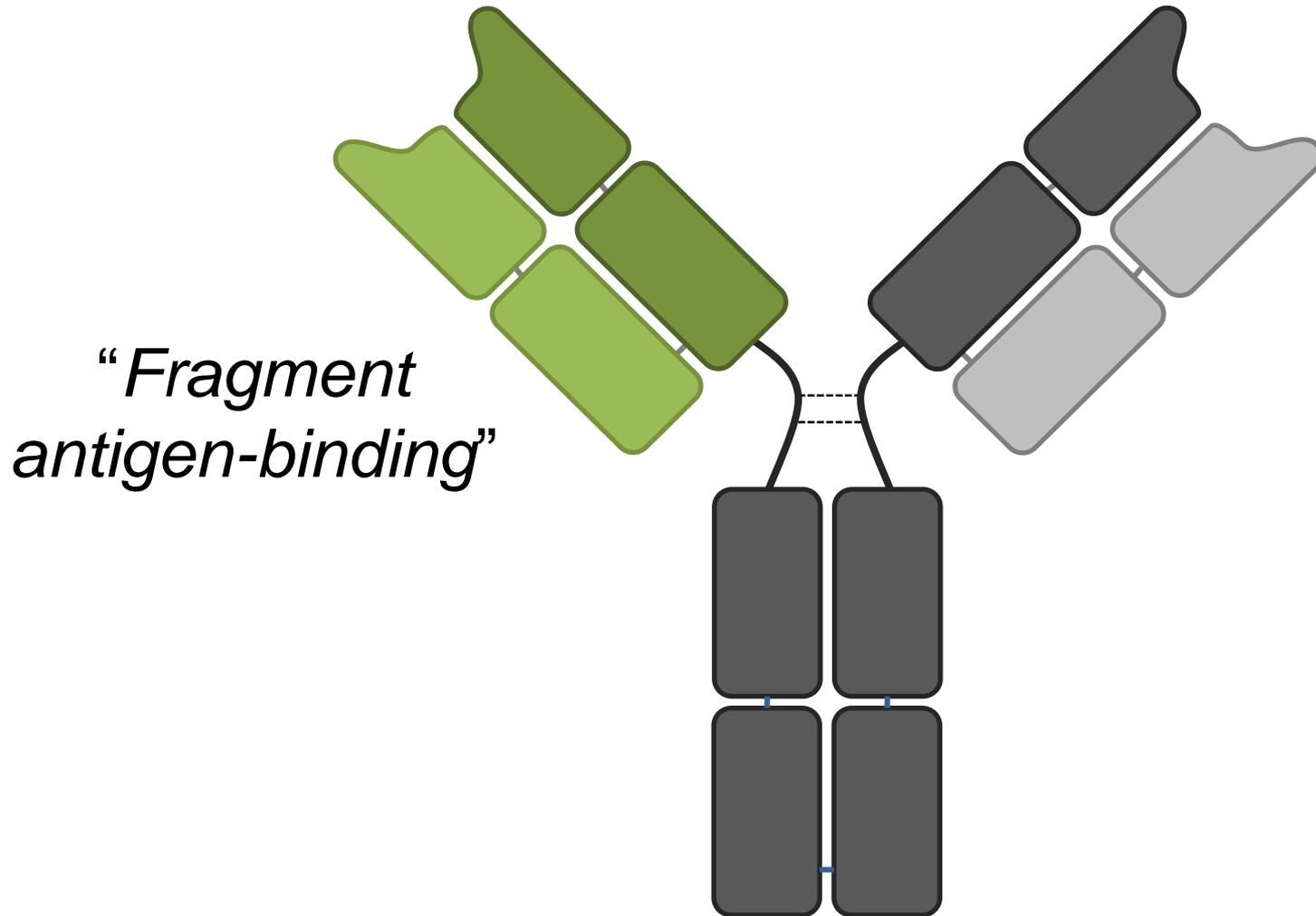
What is an antibody?



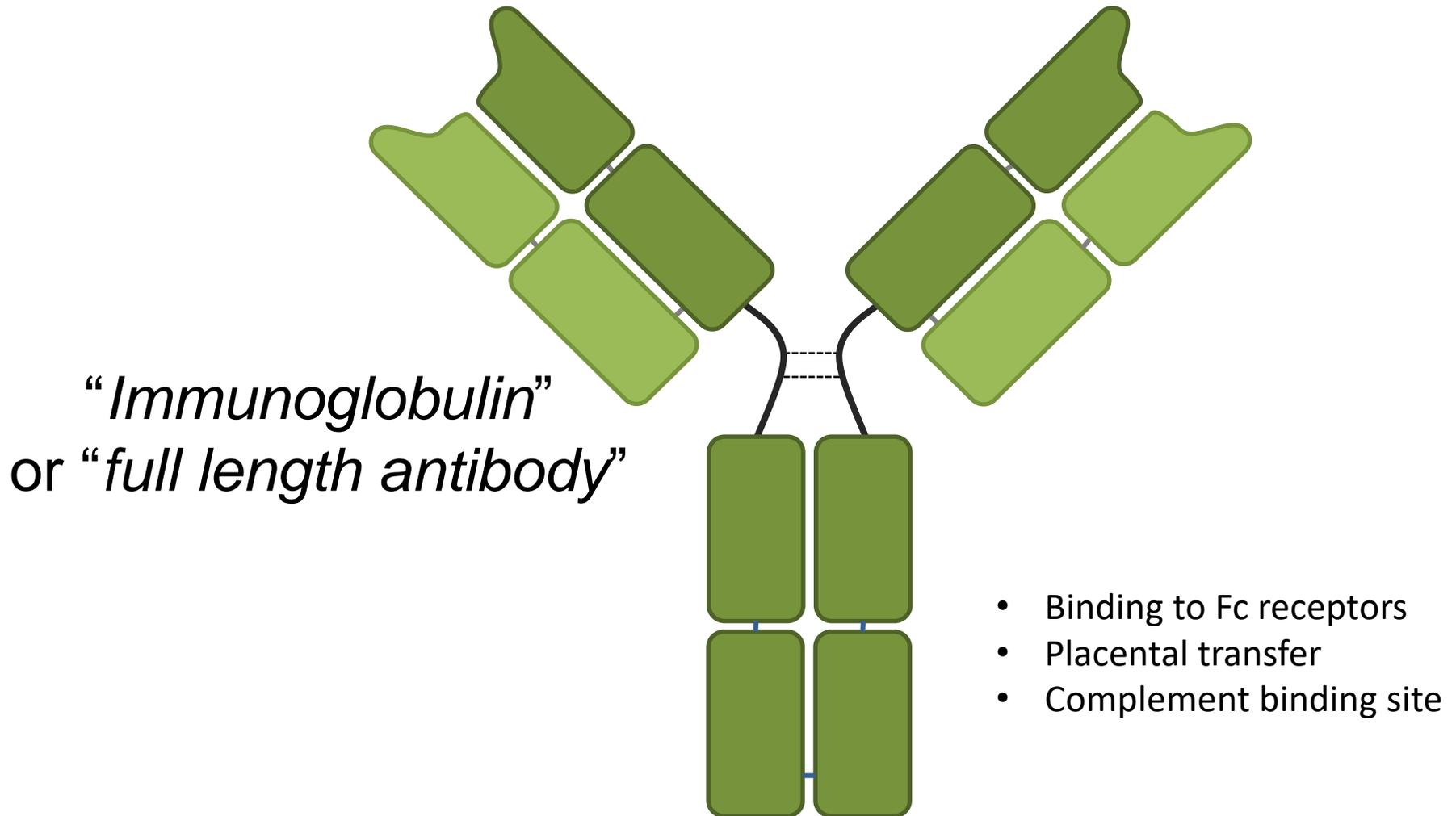
Antibody terminology: Fv



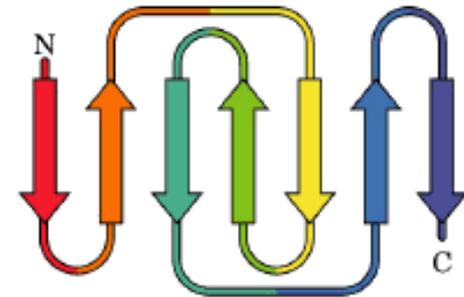
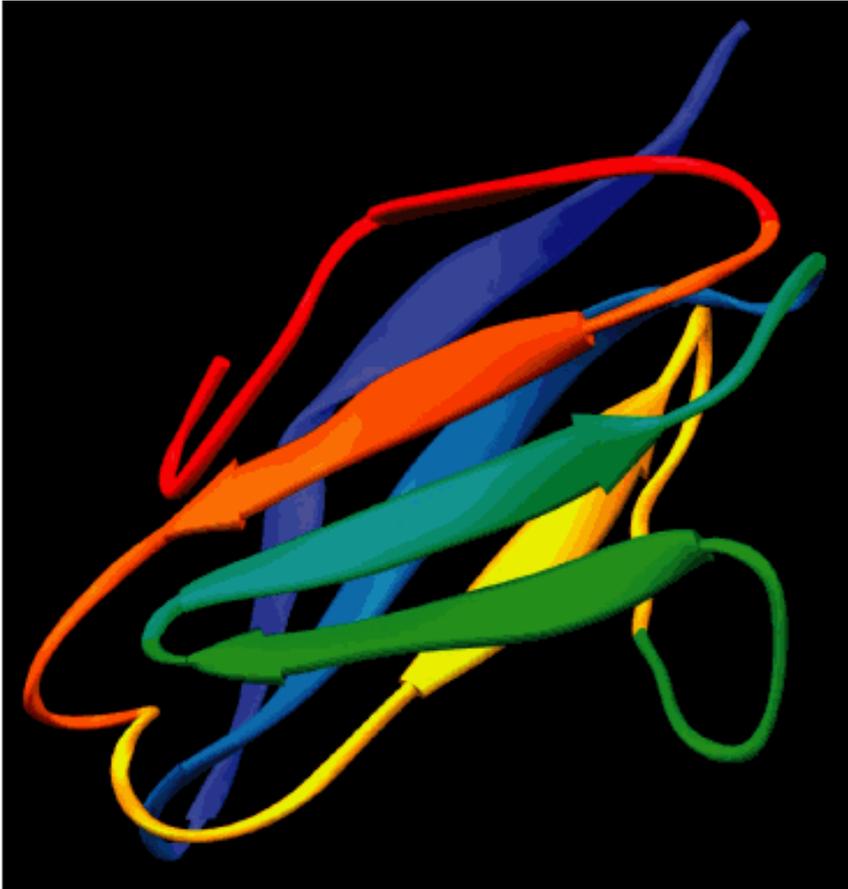
Antibody terminology: Fab



Antibody terminology: Ig



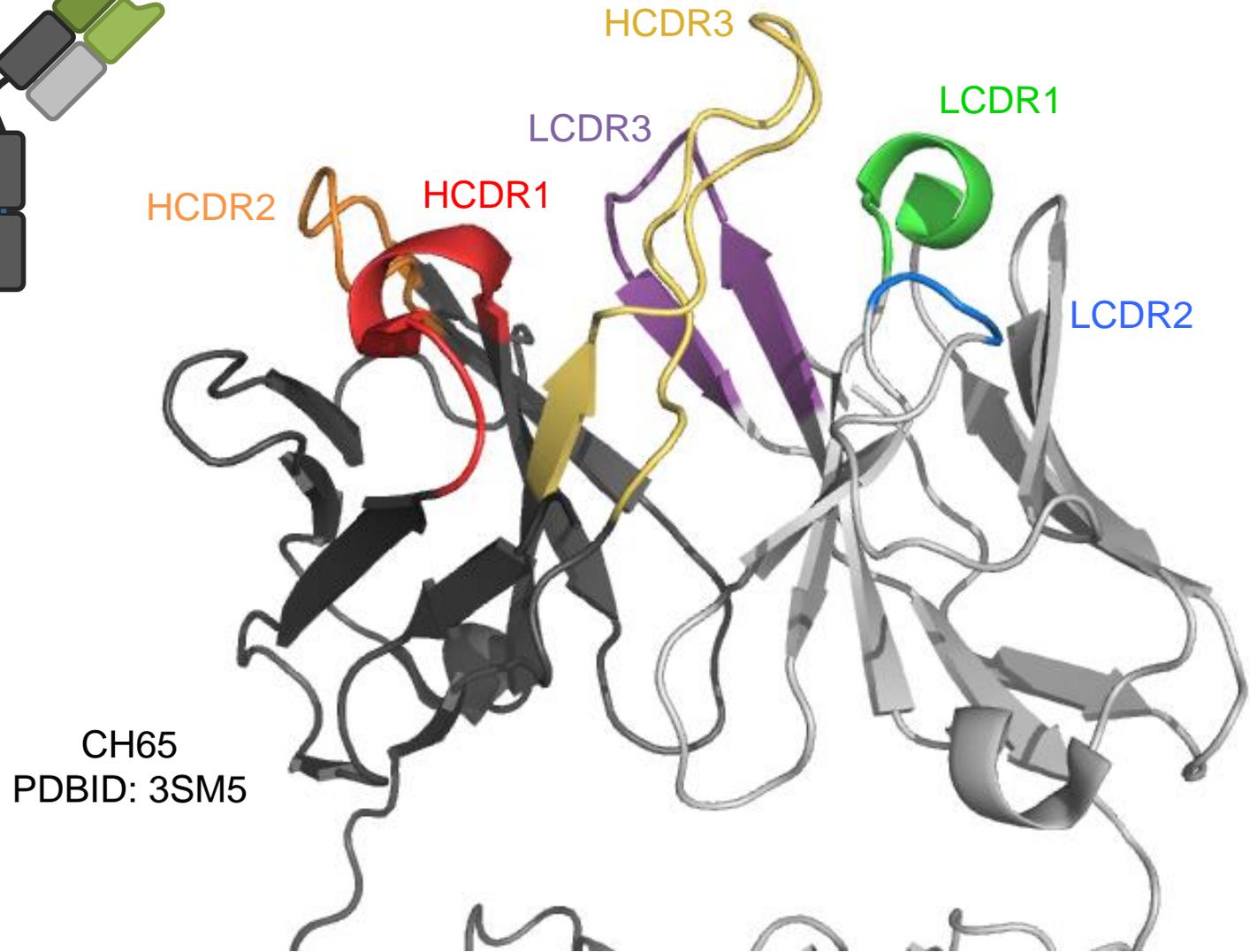
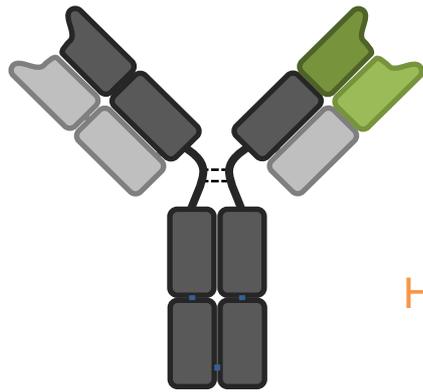
The immunoglobulin domain fold



stacked 4-stranded and
3-stranded antiparallel
 β -sheets

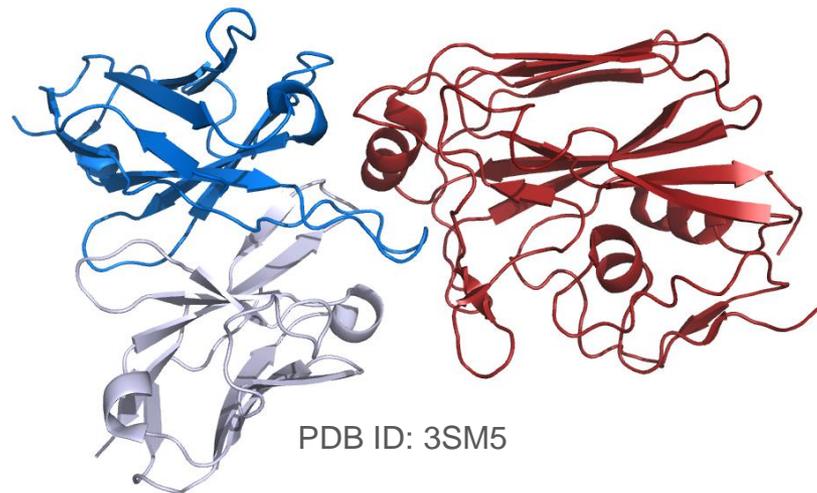
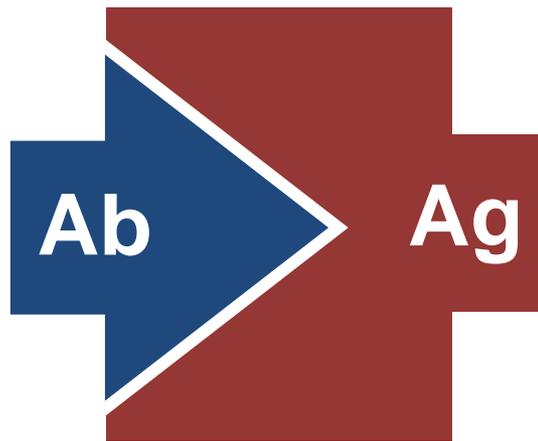
X-ray structure of the immunoglobulin fold.

Complementarity determining regions



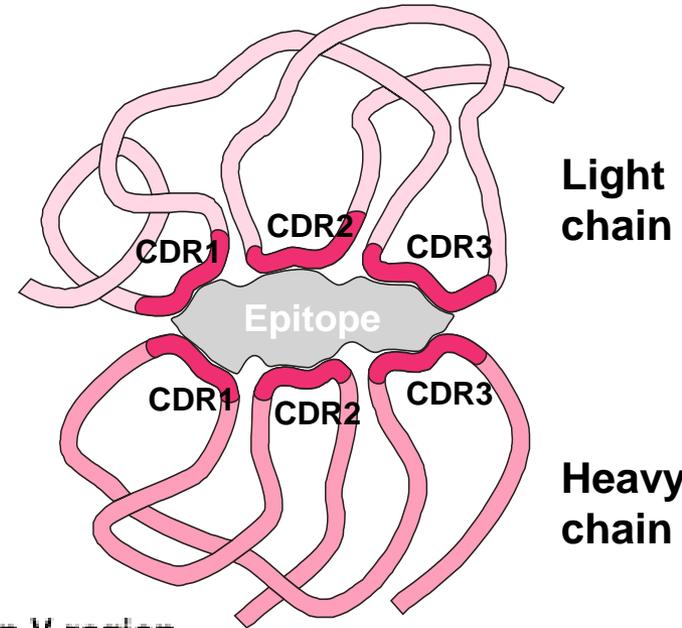
Recognition of antigen

Protein-protein interactions are determined by shape and physicochemical properties of solvent exposed loops, such as CDR loops.

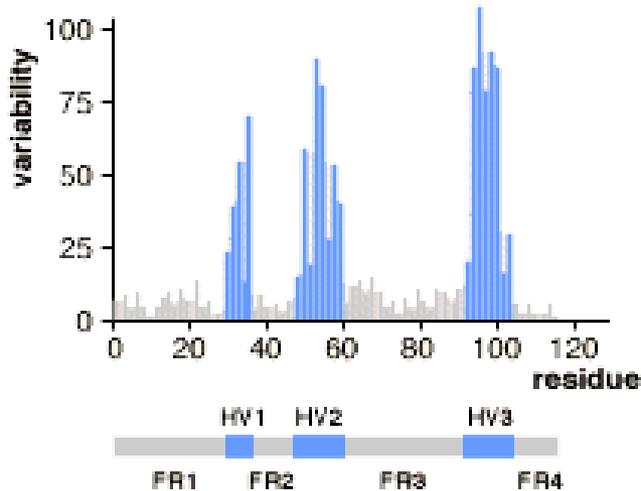


Sequence → Structure → Function

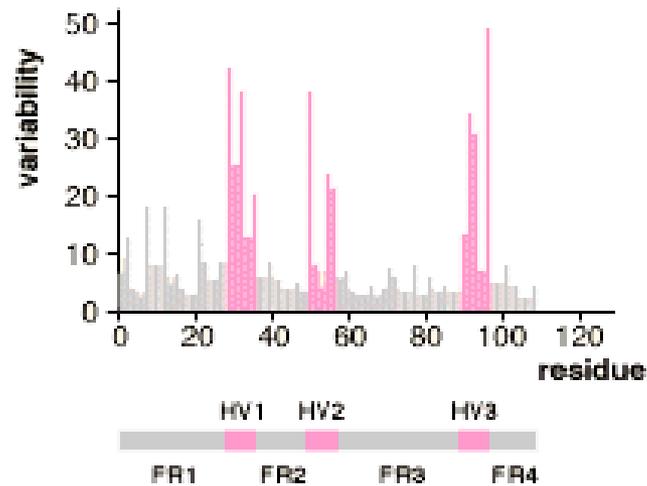
CDR are hypervariable



Heavy-chain V region



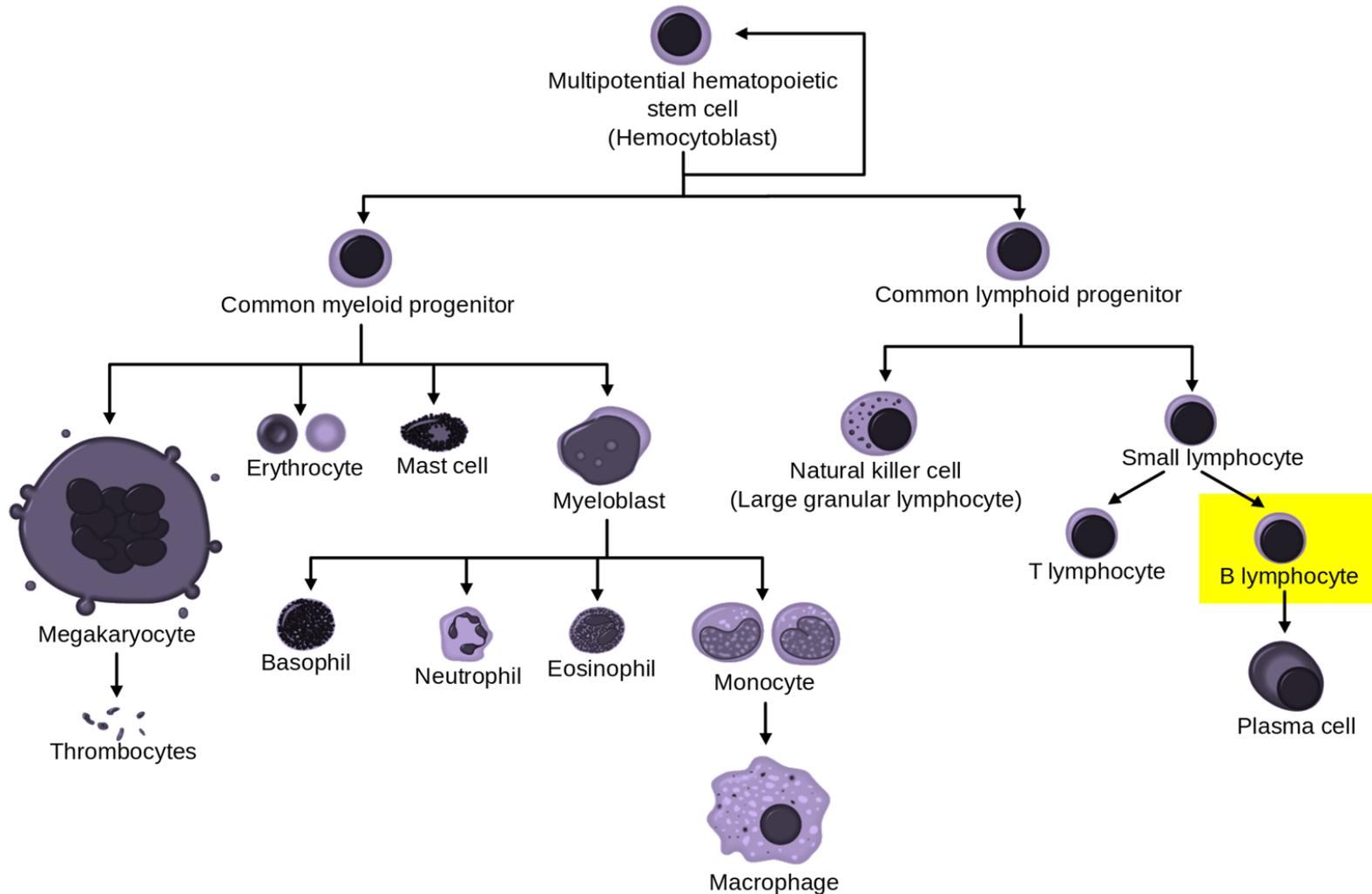
Light-chain V region



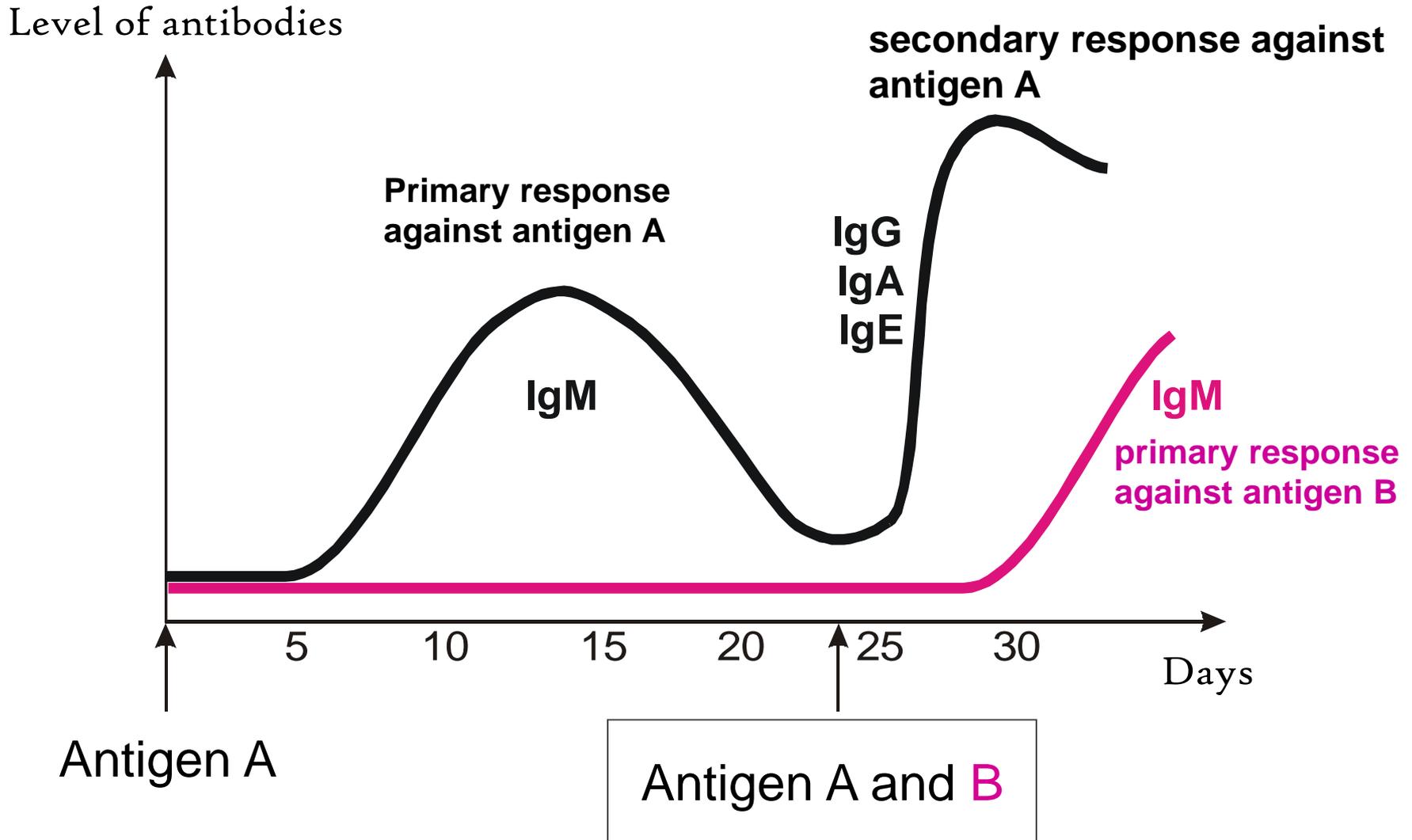
Diversification leads to specificity

- Antigenic space is nearly infinite.
- This can be resolved in two ways:
 - Few antibodies that each bind to many targets
 - Many antibodies that each bind to few targets
- Antibodies must be highly selective to prevent auto-reactivity.
- Theoretically, there may exist up to 10^{11} different antibody proteins in a single individual.

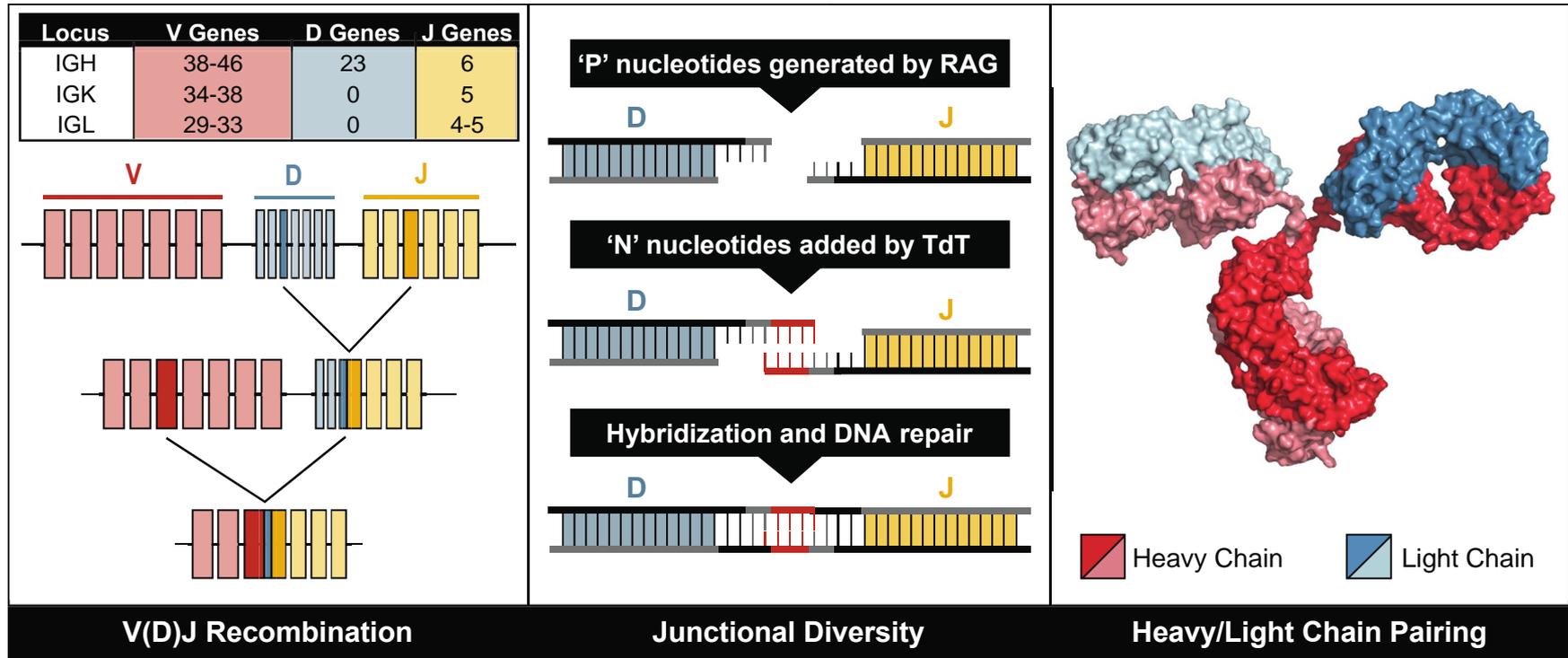
Antibodies are produced by B cells



Antibodies production during primary and secondary response

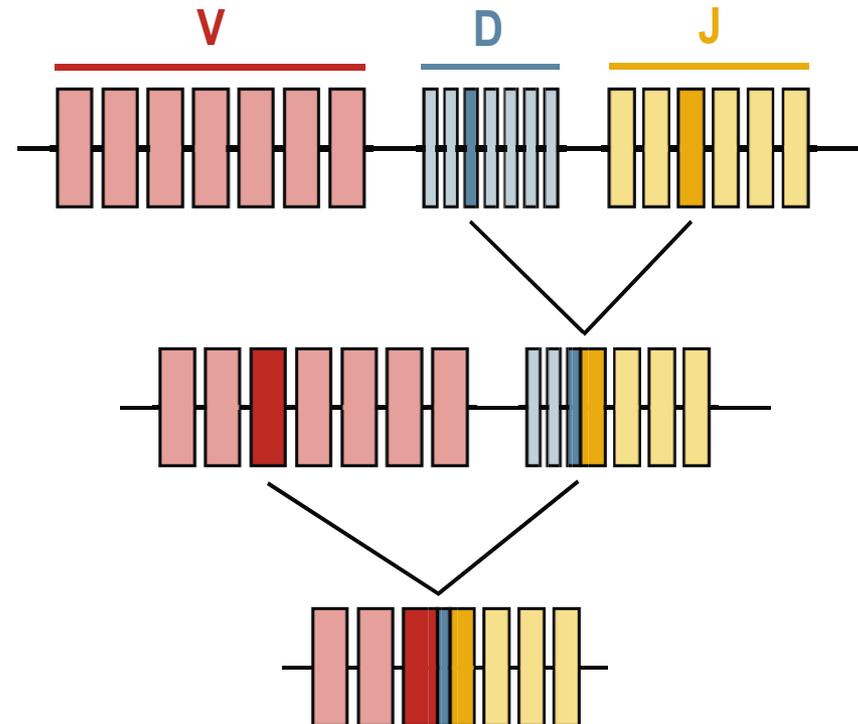


Antibody diversification is achieved primarily through three mechanisms

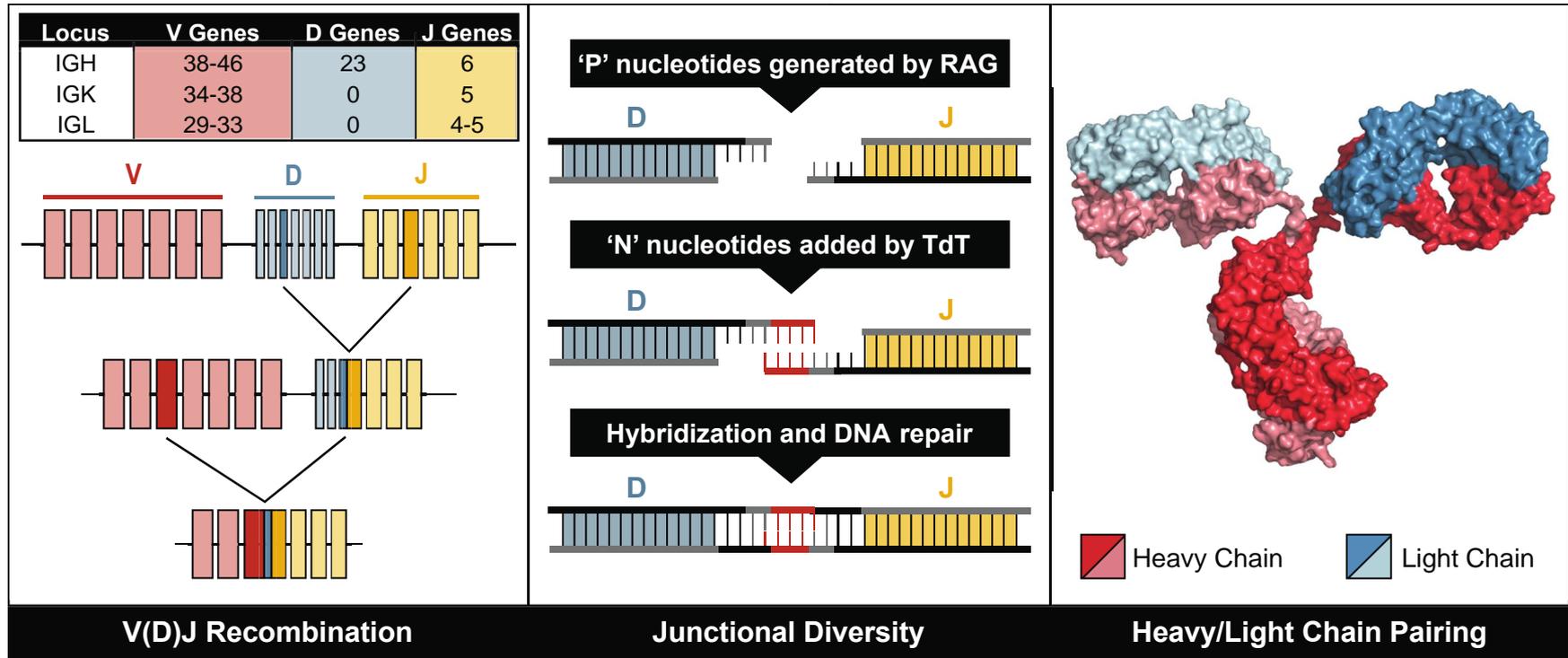


V(D)J recombination

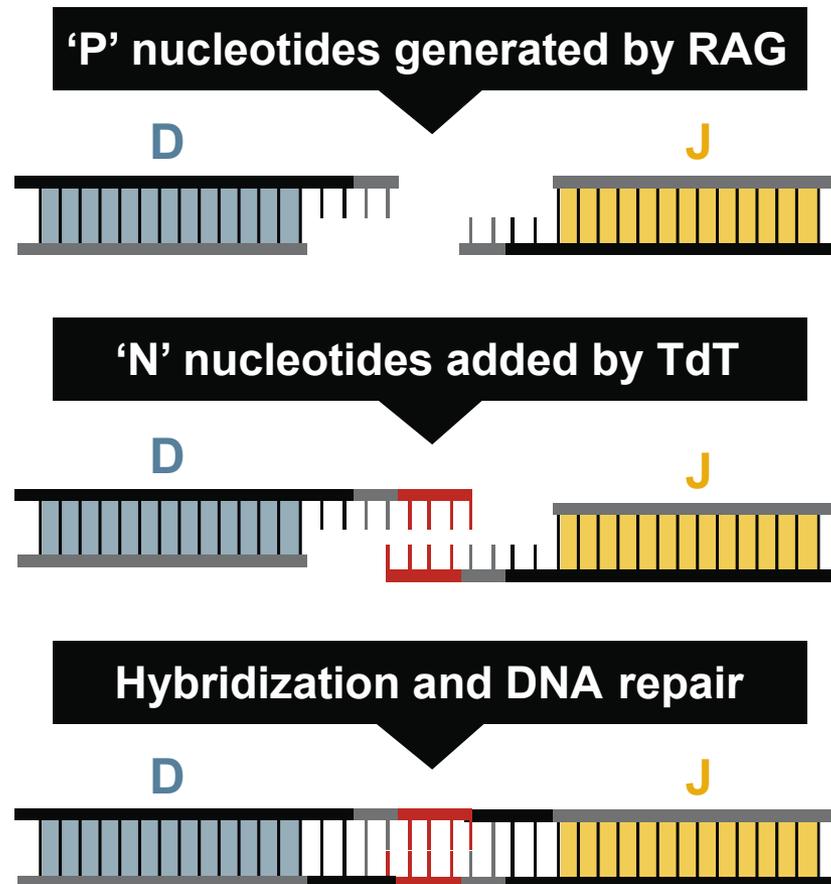
| Locus | V Genes | D Genes | J Genes |
|-------|---------|---------|---------|
| IGH | 38-46 | 23 | 6 |
| IGK | 34-38 | 0 | 5 |
| IGL | 29-33 | 0 | 4-5 |



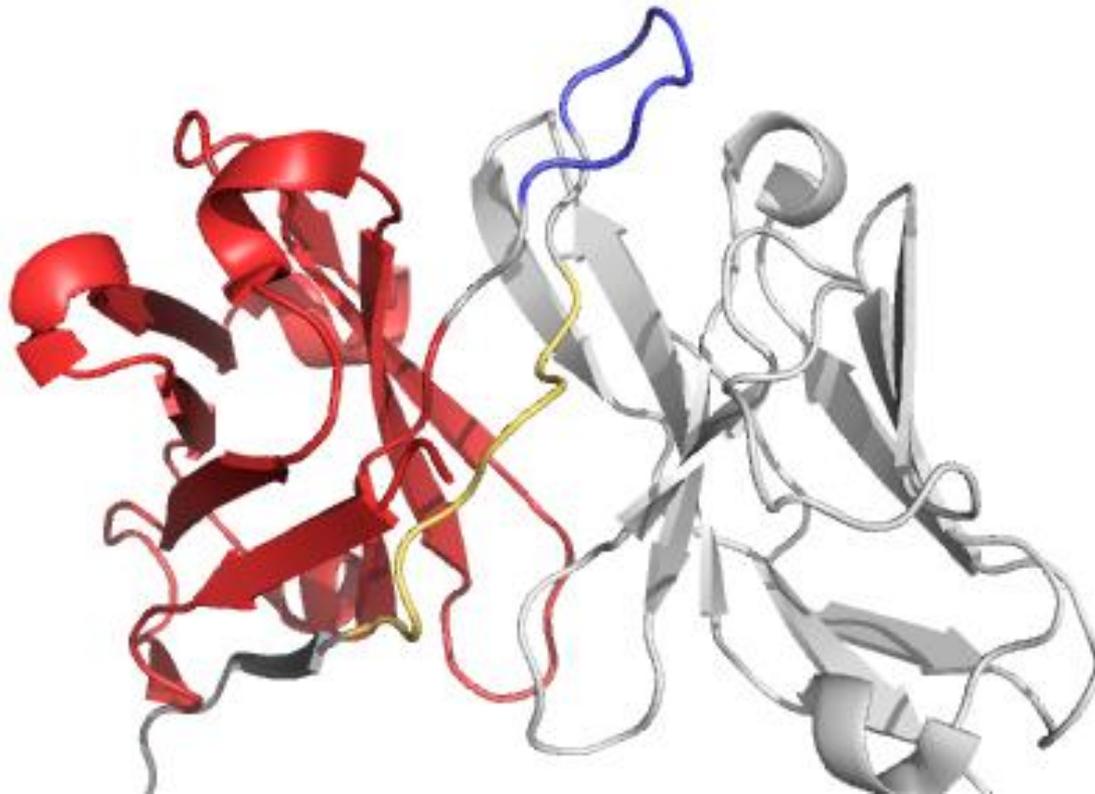
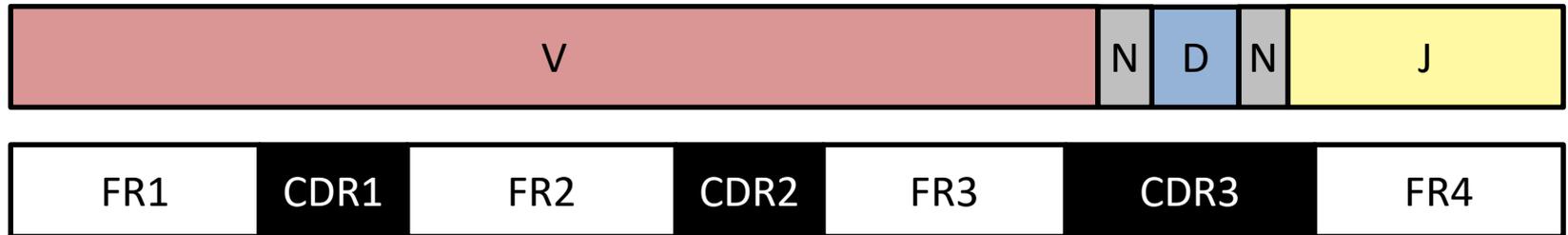
Antibody diversification is achieved primarily through three mechanisms



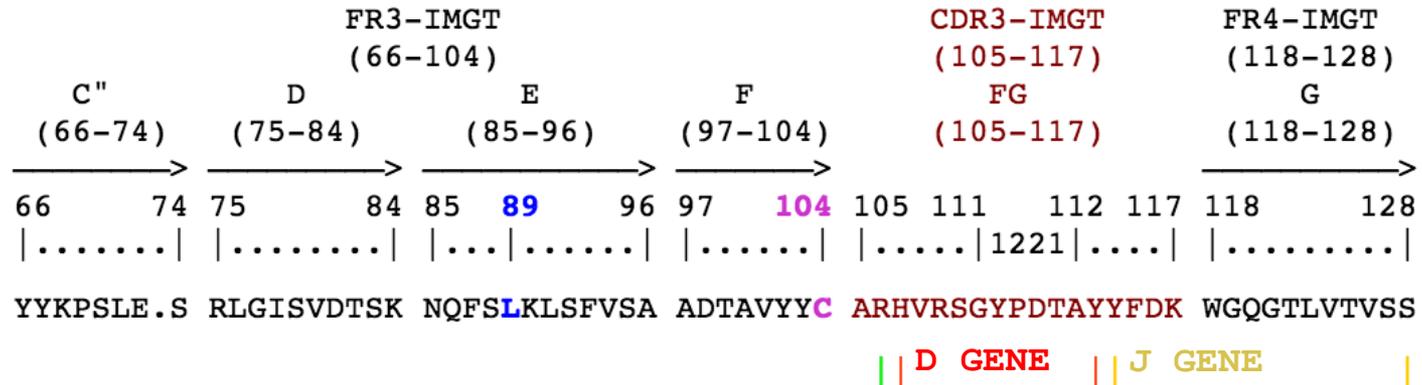
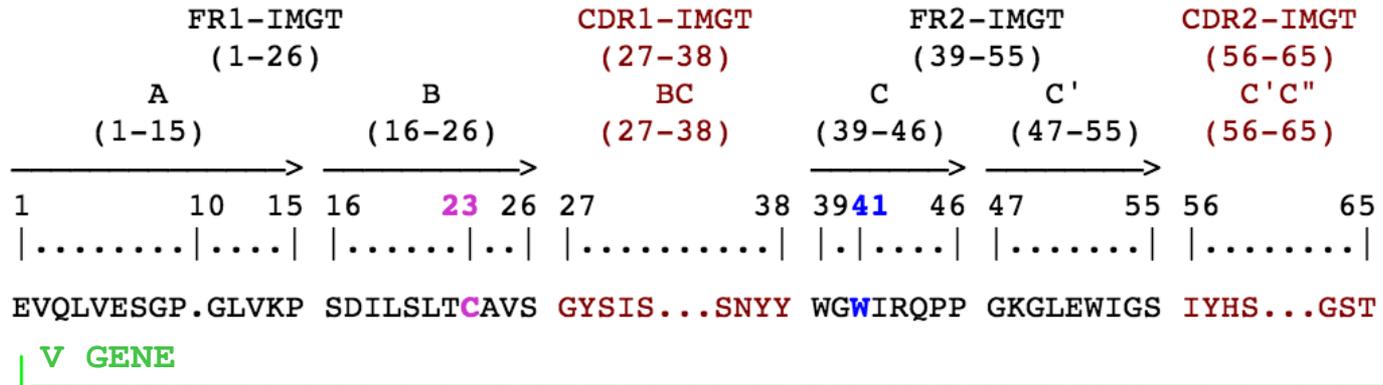
Junctional diversity



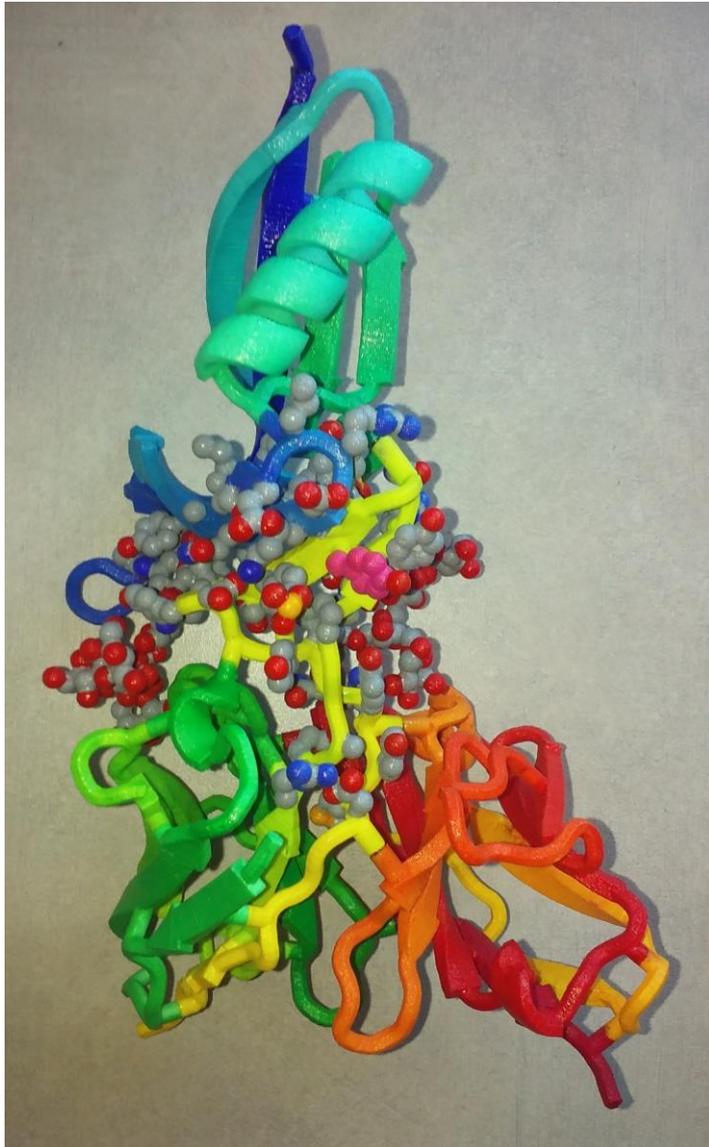
V(D)J gene sequences mapped to CDRs



Sequence/structure relationship



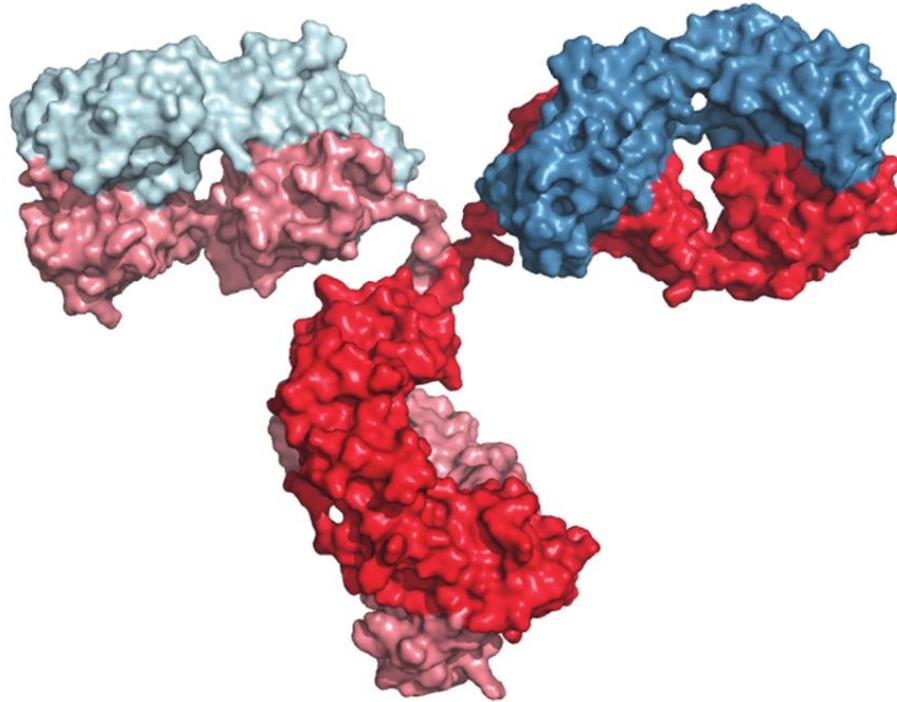
CDR3 Loop design



3D printed model of computationally redesigned HIV antibody with **enhanced neutralizing potency and breadth** in complex with HIV protein GP120 by former Meiler laboratory graduate student Jordan Willis

J. of clinical Investigation; 2015;
Vol. 125 (6): p 2523-31

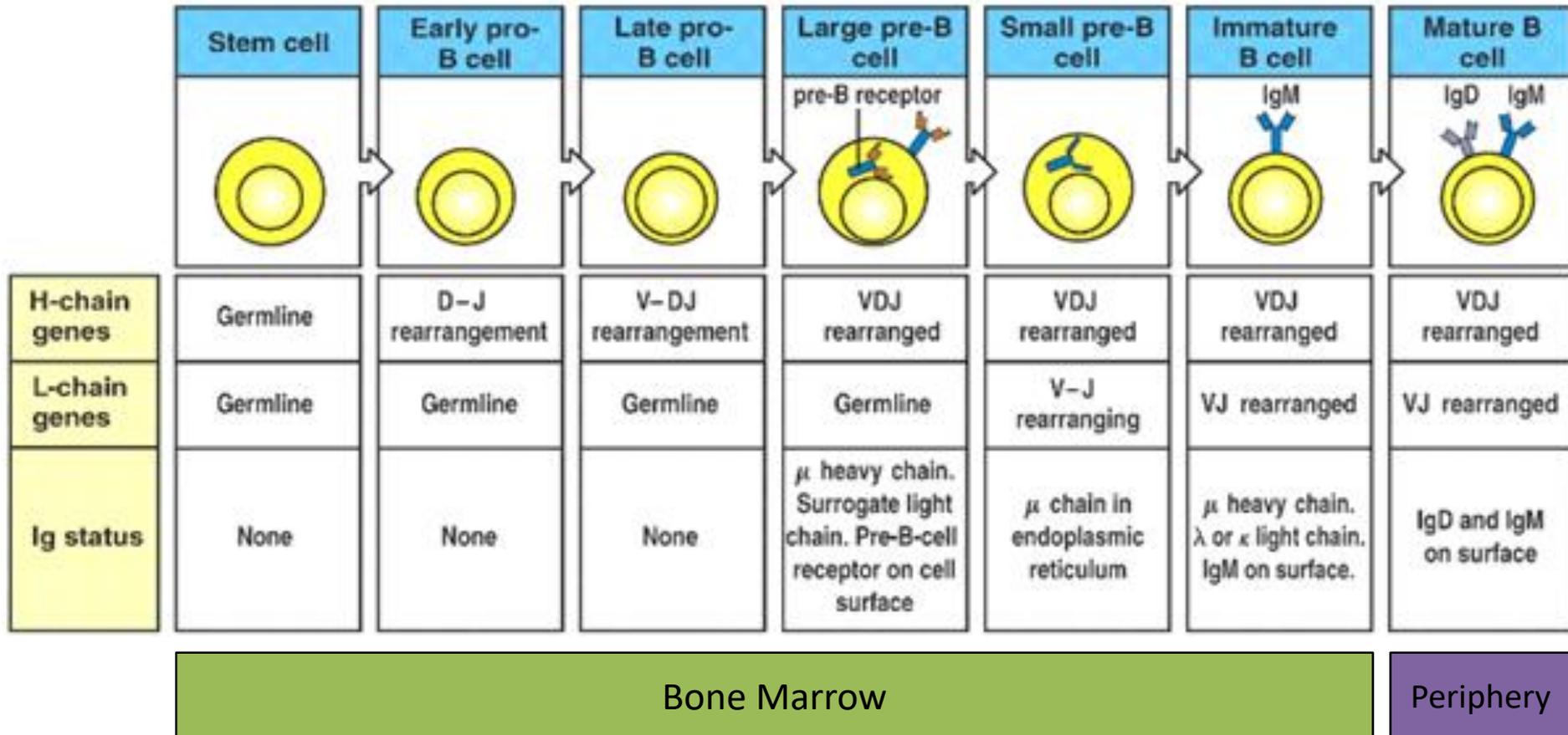
Heavy/light chain pairing



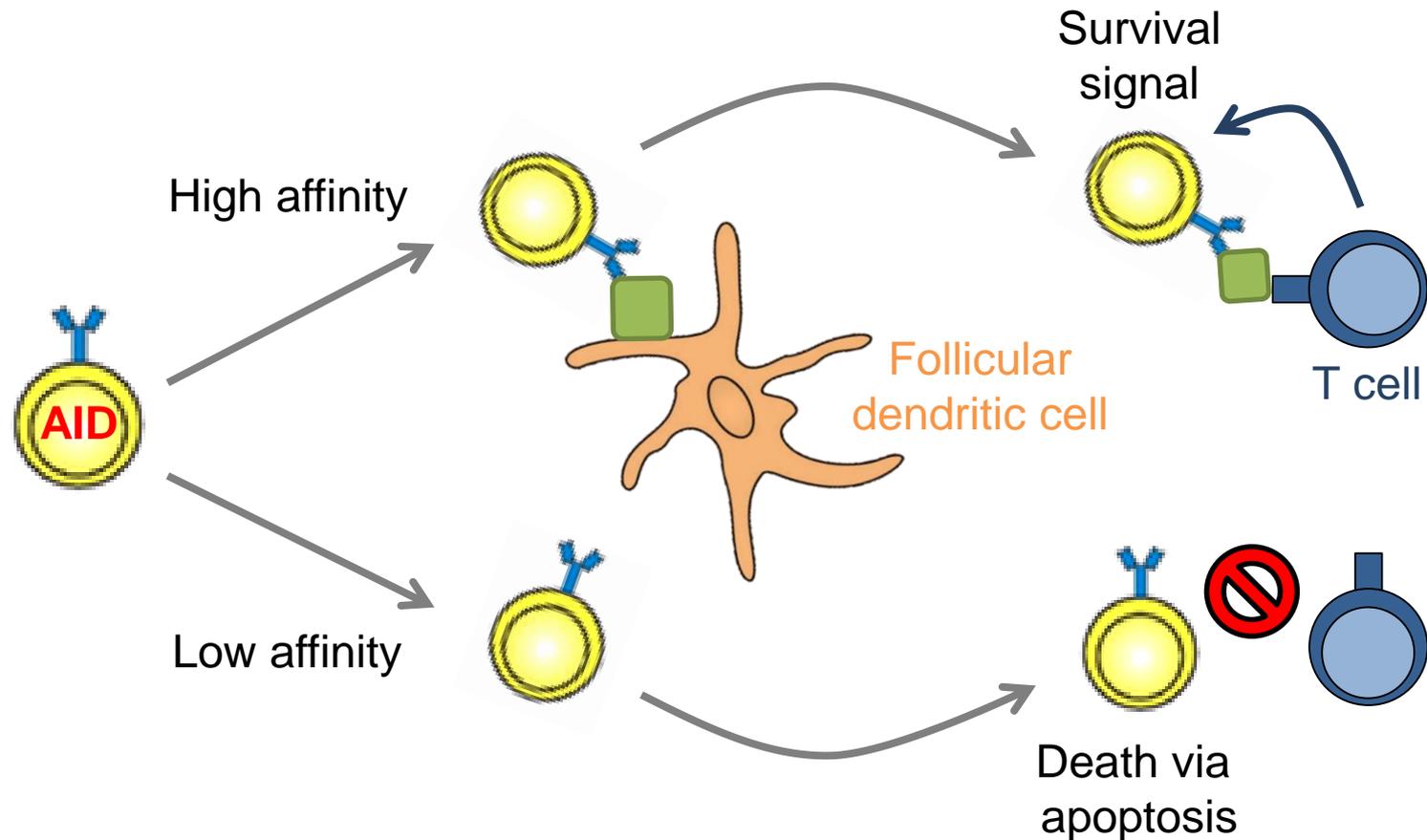
 Heavy Chain

 Light Chain

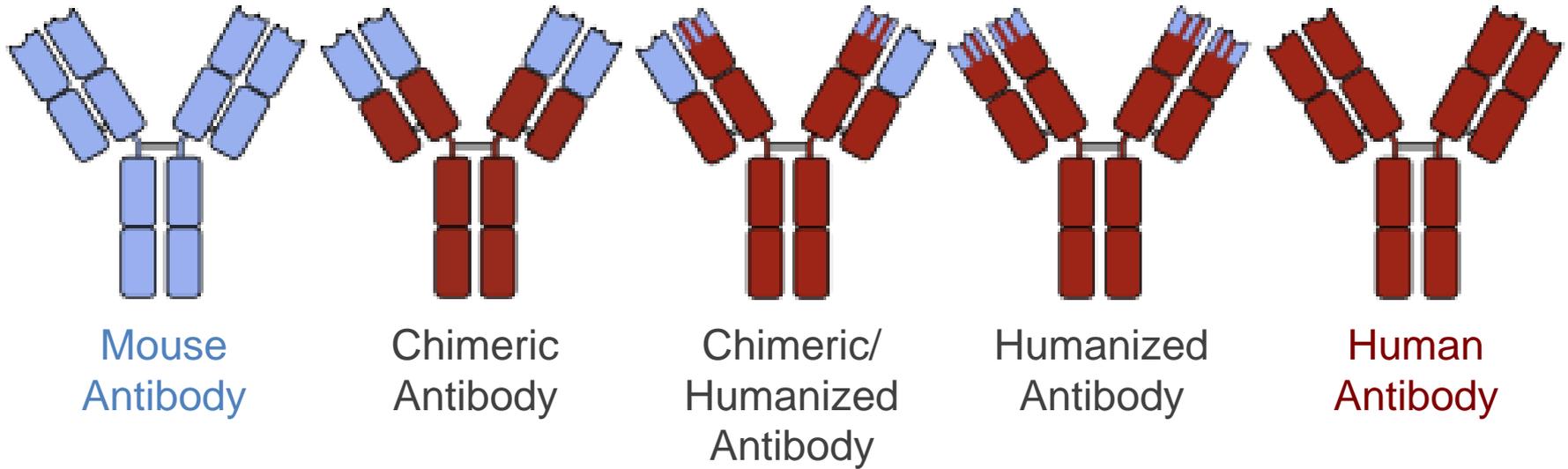
Early B cell development in detail



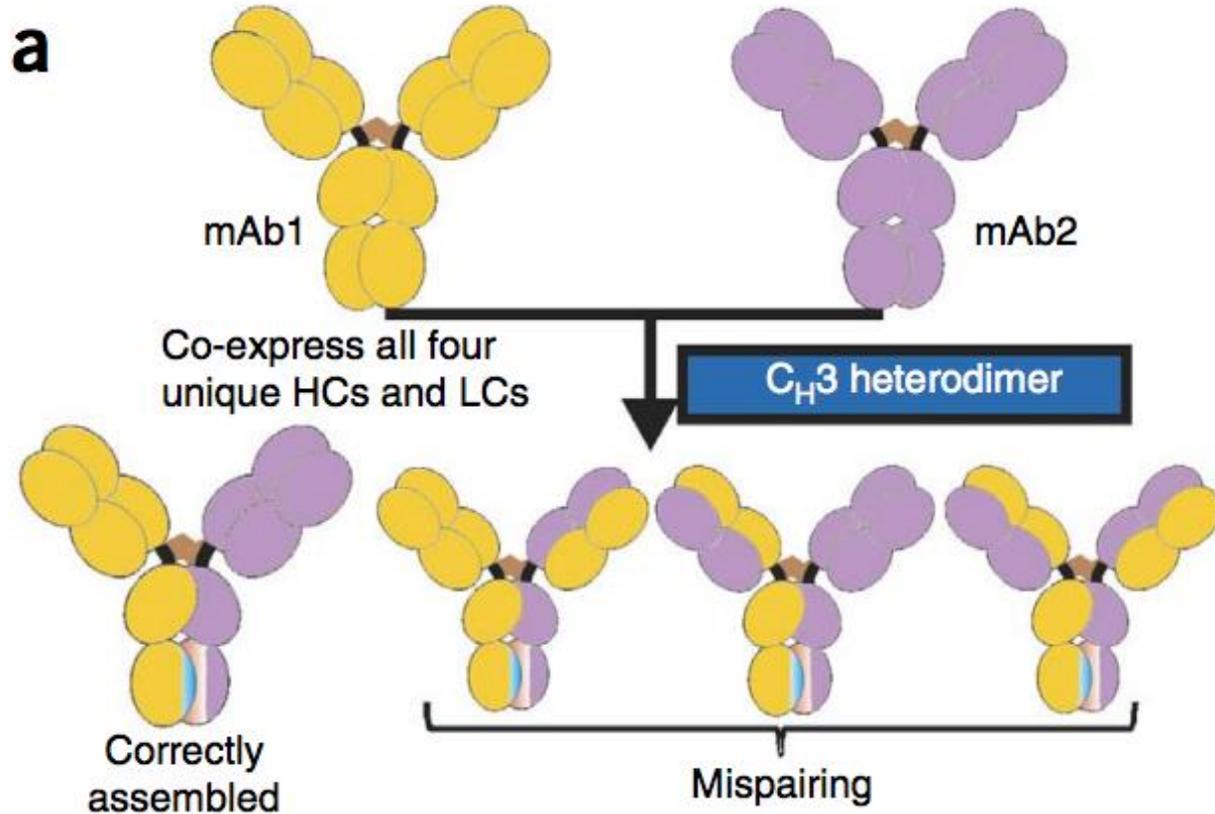
Affinity maturation is a fourth mechanism of antibody diversification



Humanized antibodies



Bispecific antibodies



Resources

- Antibody structure:
 - North, Lehmann and Dunbrack, J Mol Bio 2011
 - Morea, Tramontano, Rustici, Chothia and Lesk, J Mol Bio 1998
- Sequence analysis web tools:
 - IMGT V-Quest
 - IMGT DomainGapAlign
- Antibody numbering guide:
 - AHo's Amazing Atlas of Antibody Anatomy