Introduction to Antibodies

Samuel Schmitz Rosetta Workshop April 25th, 2017

What is an antibody?



Antibody terminology: Fv



Antibody terminology: Fab

"Fragment antigen-binding"

Antibody terminology: Ig

"Immunoglobulin" or *"full length antibody"*

- Binding to Fc receptors
- Placental transfer
- Complement binding site

The immunoglobulin domain fold





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

X-ray structure of the immunoglobulin fold.

Anthony S. Serianni

Complementarity determining regions



Recognition of antigen

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



Structure

Function

Sequence



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 <u>highly selective</u> to prevent auto-reactivity.
- Theoretically, there may exist up to 10¹¹ 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			
	/ [DC	J			

Antibody diversification is achieved primarily through three mechanisms



Junctional diversity



V(D)J gene sequences mapped to CDRs



Sequence/structure relationship



(66-74)	(75-84)	(85-96)	(97-104)	(105-117)	(118-128)
<u> </u>	<u> </u>	>	>		<u> </u>
66 74	75 84	85 89 96	97 104		
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YYKPSLE.S	RLGISVDTSK	NQFSLKLSFVSA	ADTAVYY <mark>C</mark>	ARHVRSGYPDTAYYFDK	WGQGTLVTVSS
				I D GENE I J C	GENE

IMGT DomainGapAlign

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







Early B cell development in detail

	Stem cell	Early pro- B cell	Late pro- B cell	Large pre-B cell pre-B receptor	Small pre-B cell	Immature B cell IgM	Mature B cell IgD IgM
	\bigcirc				8		8
H-chain genes	Germline	D-J rearrangement	V-DJ rearrangement	VDJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged
L-chain genes	Germline	Germline	Germline	Germline	V-J rearranging	VJ rearranged	VJ rearranged
lg status	None	None	None	μ heavy chain. Surrogate light chain. Pre-B-cell receptor on cell surface	μ chain in endoplasmic reticulum	μ heavy chain. λ or κ light chain. IgM on surface.	IgD and IgM on surface

Bone Marrow

Periphery

Affinity maturation is a fourth mechanism of antibody diversification



Humanized antibodies



Bispecific antibodies



Lewis, SM et al., Nat. Biotech., 2014

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