

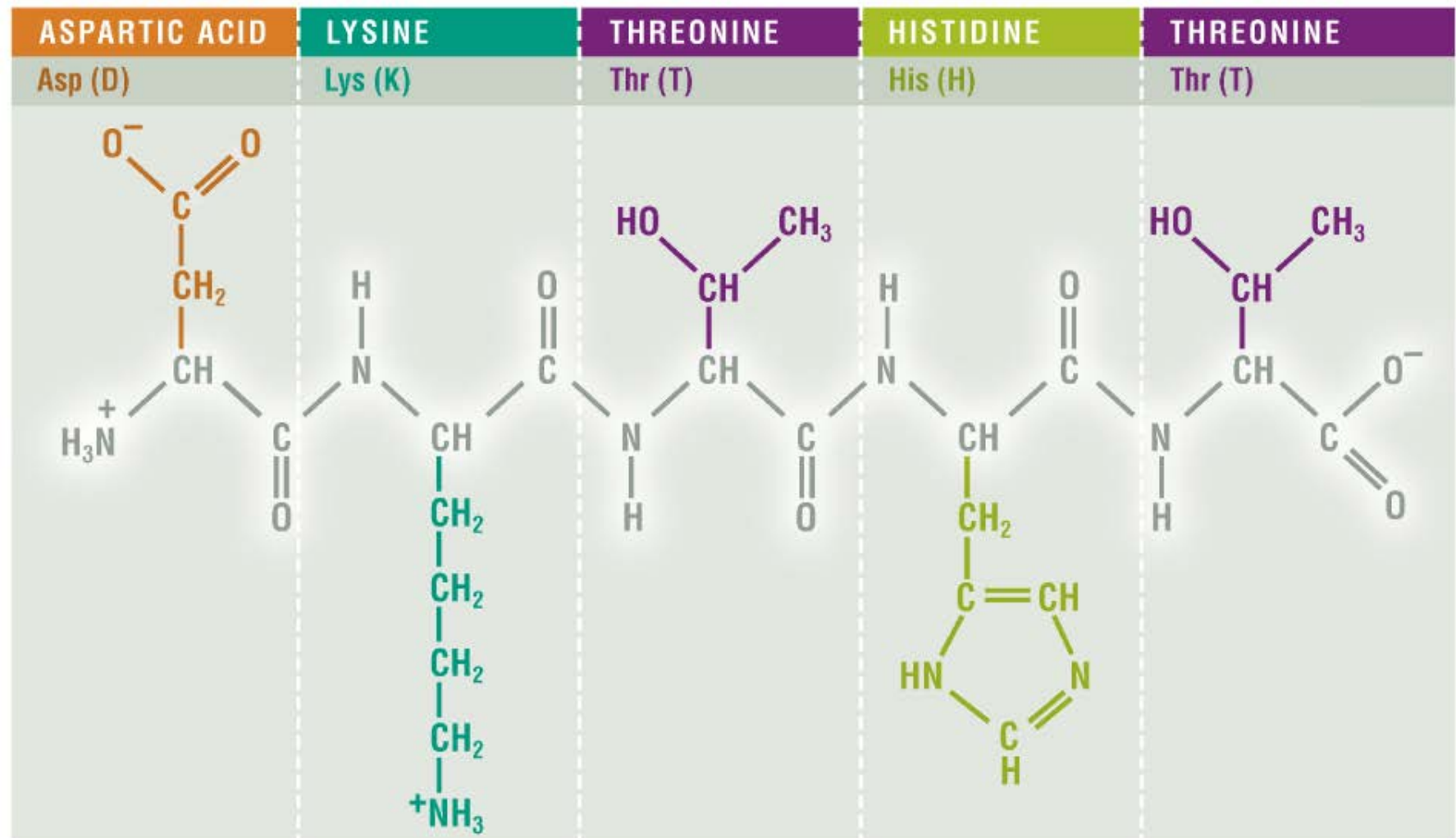
There Are 20 Naturally Occurring Amino Acids in Nature

AMINO ACID	ABBREVIATIONS	
	1-LETTER	3-LETTER
Alanine:	A	Ala
Arginine:	R	Arg
Asparagine:	N	Asn
Aspartic Acid:	D	Asp
Cysteine:	C	Cys
Glutamic Acid:	E	Glu
Glutamine:	Q	Gln
Glycine:	G	Gly
Histidine:	H	His
Isoleucine:	I	Ile

AMINO ACID	ABBREVIATIONS	
	1-LETTER	3-LETTER
Leucine:	L	Leu
Lysine:	K	Lys
Methionine:	M	Met
Phenylalanine:	F	Phe
Proline:	P	Pro
Serine:	S	Ser
Threonine:	T	Thr
Tryptophan:	W	Trp
Tyrosine:	Y	Tyr
Valine:	V	Val

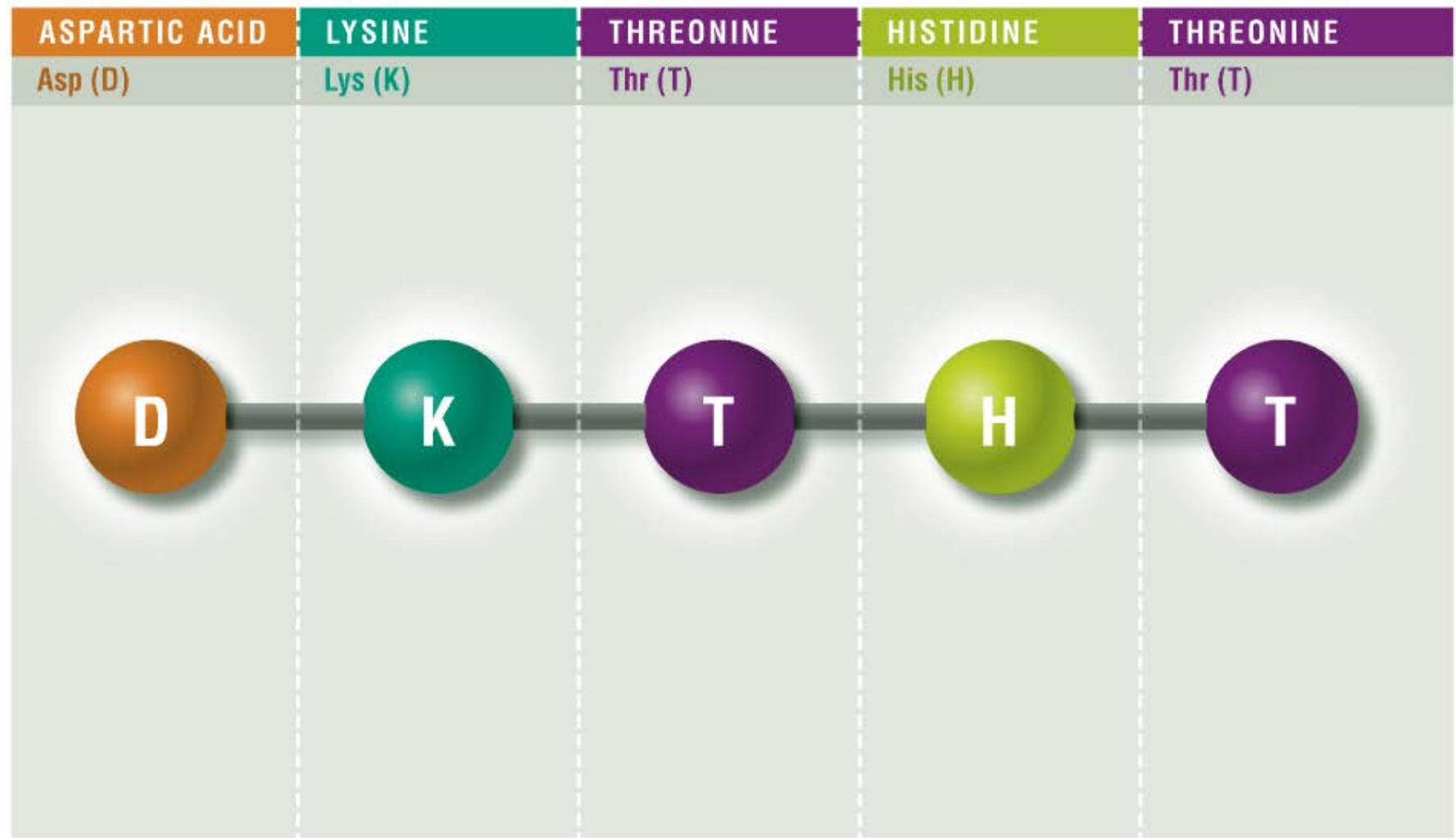
Amino Acid Residues Linked Together by Peptide Bonds Form a Polypeptide or Protein Chain

■ Peptide backbone

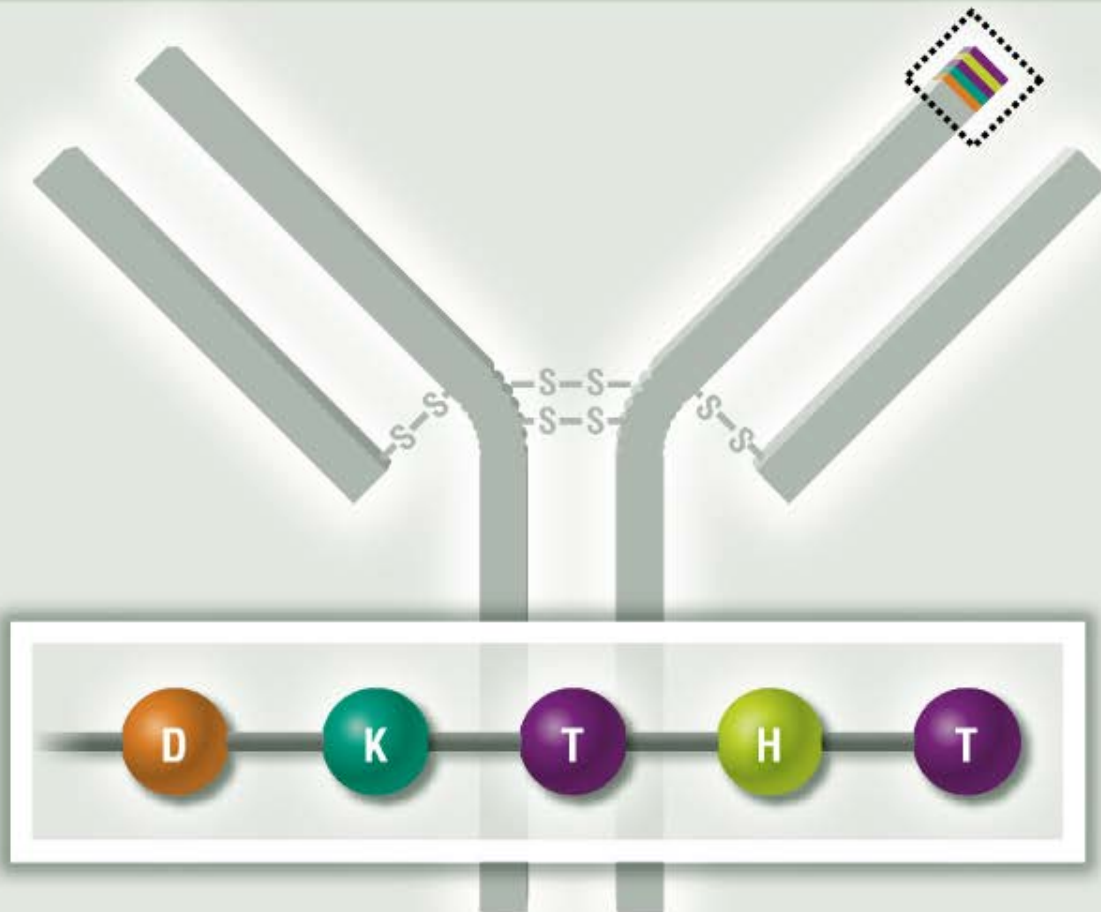


Amino Acid Residues Linked Together by Peptide Bonds Form a Polypeptide or Protein Chain

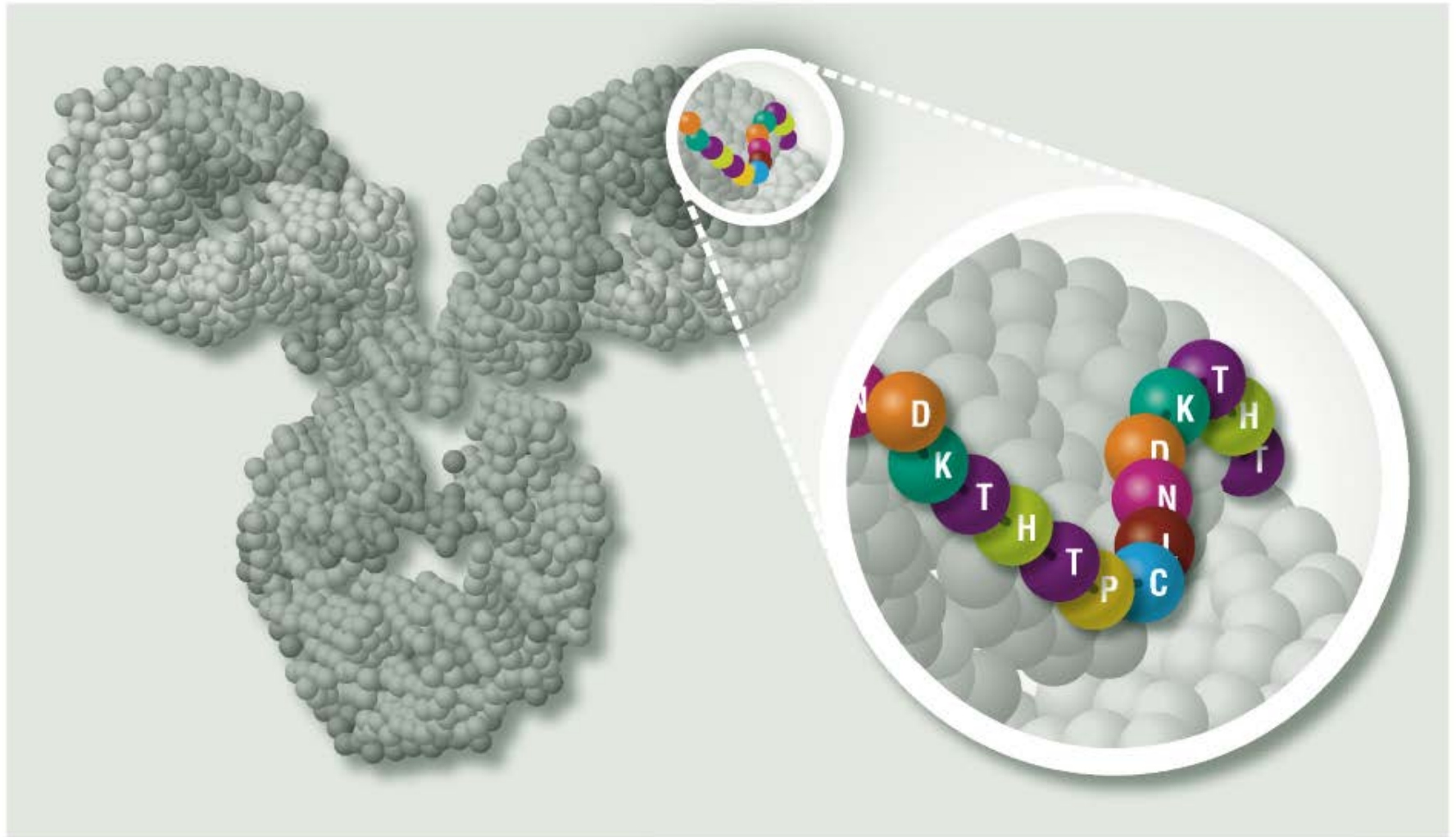
■ Peptide backbone



Amino Acid Residues Linked Together by Peptide Bonds Form a Polypeptide or Protein Chain

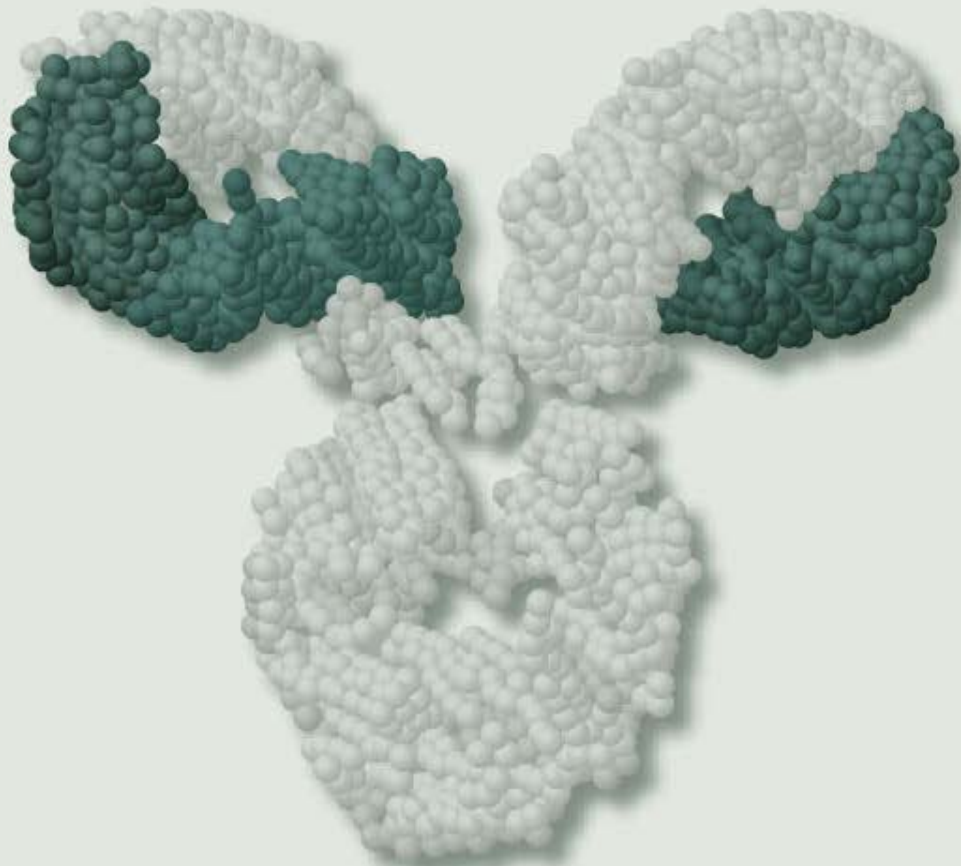


The Precise Order of the Amino Acid Residues in a Protein Chain Determines Its Shape, Which, in Turn, Determines Its Biological Activity



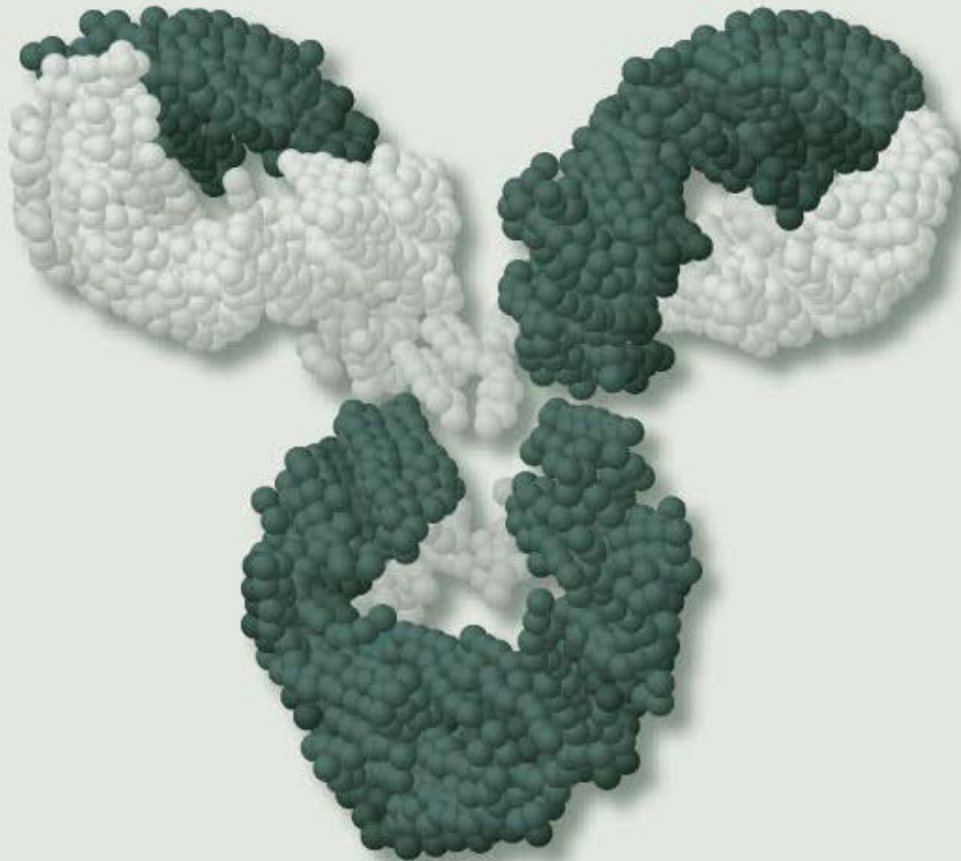
The Individual Heavy Chains and Light Chains in an Antibody Molecule Associate to Adopt a “Y Shape”

Light Chains



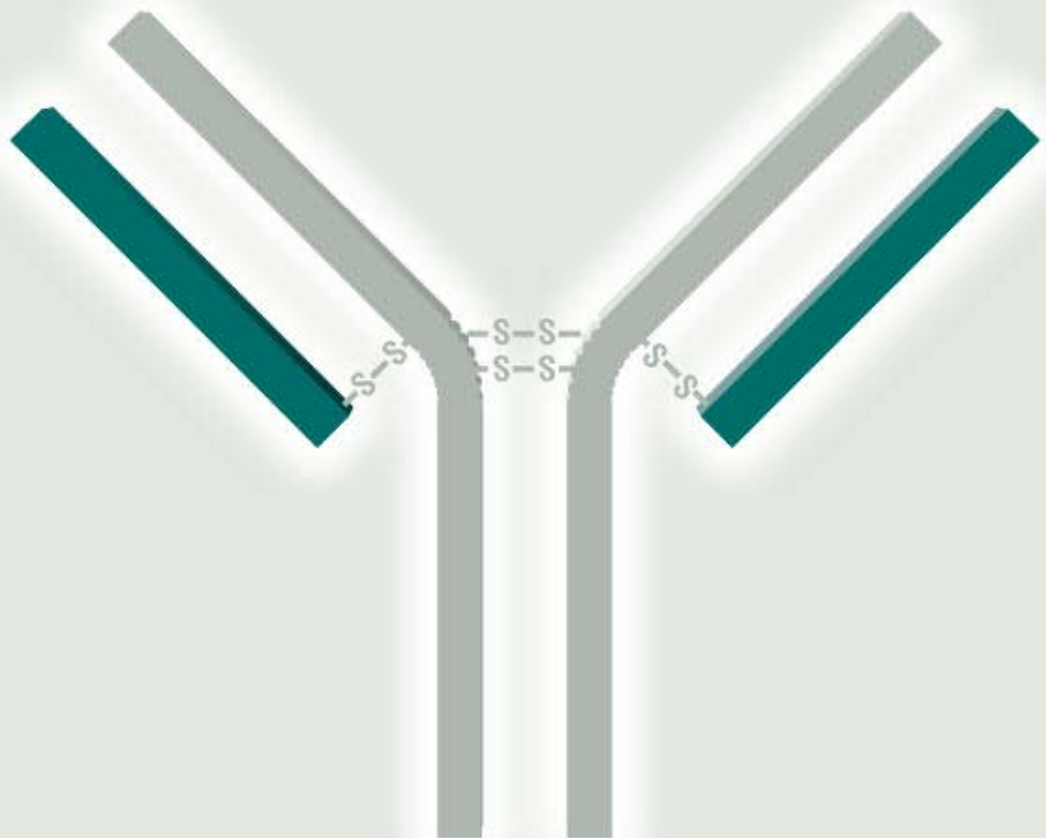
The Individual Heavy Chains and Light Chains in an Antibody Molecule Associate to Adopt a “Y Shape”

Heavy Chains



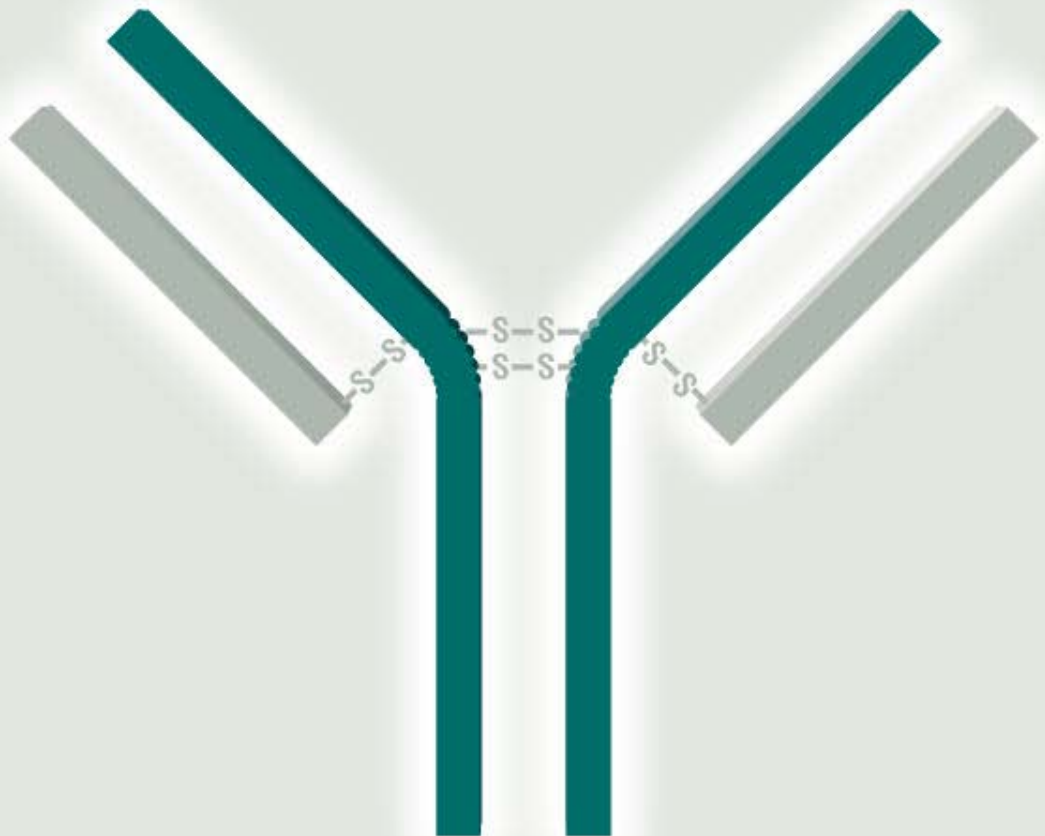
The Structure of an Antibody Molecule

Light Chains



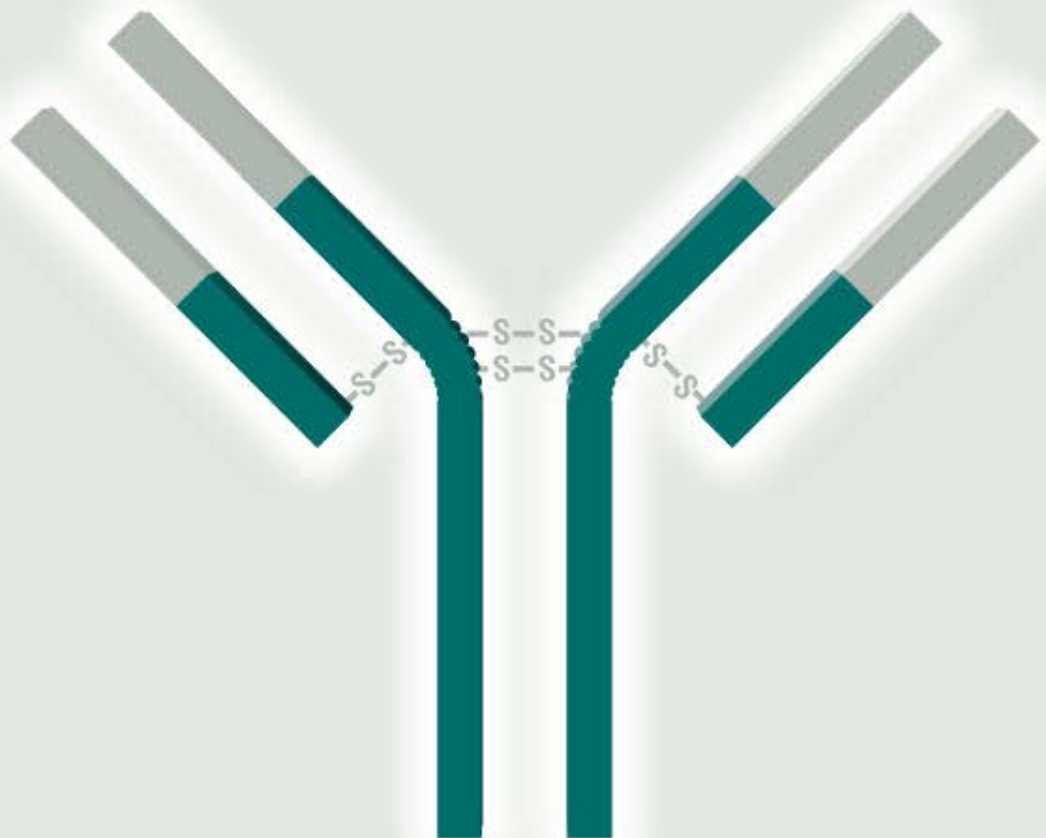
The Structure of an Antibody Molecule

Heavy Chains



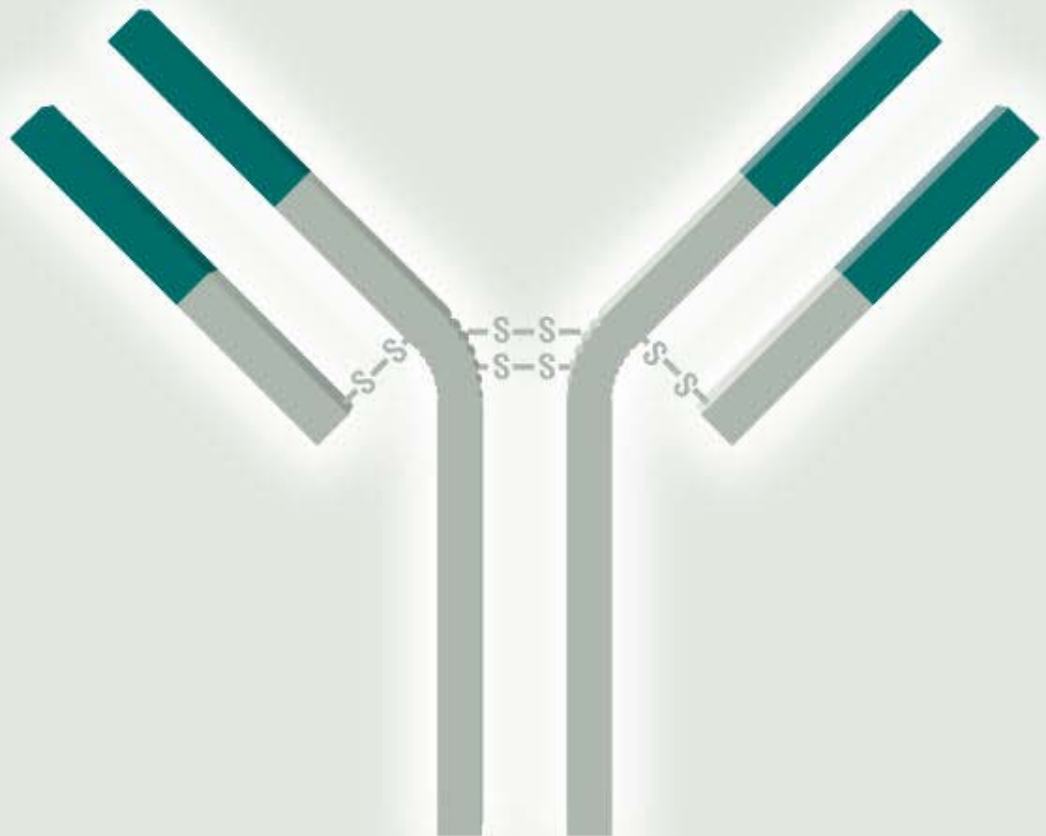
The Structure of an Antibody Molecule

Constant Domain



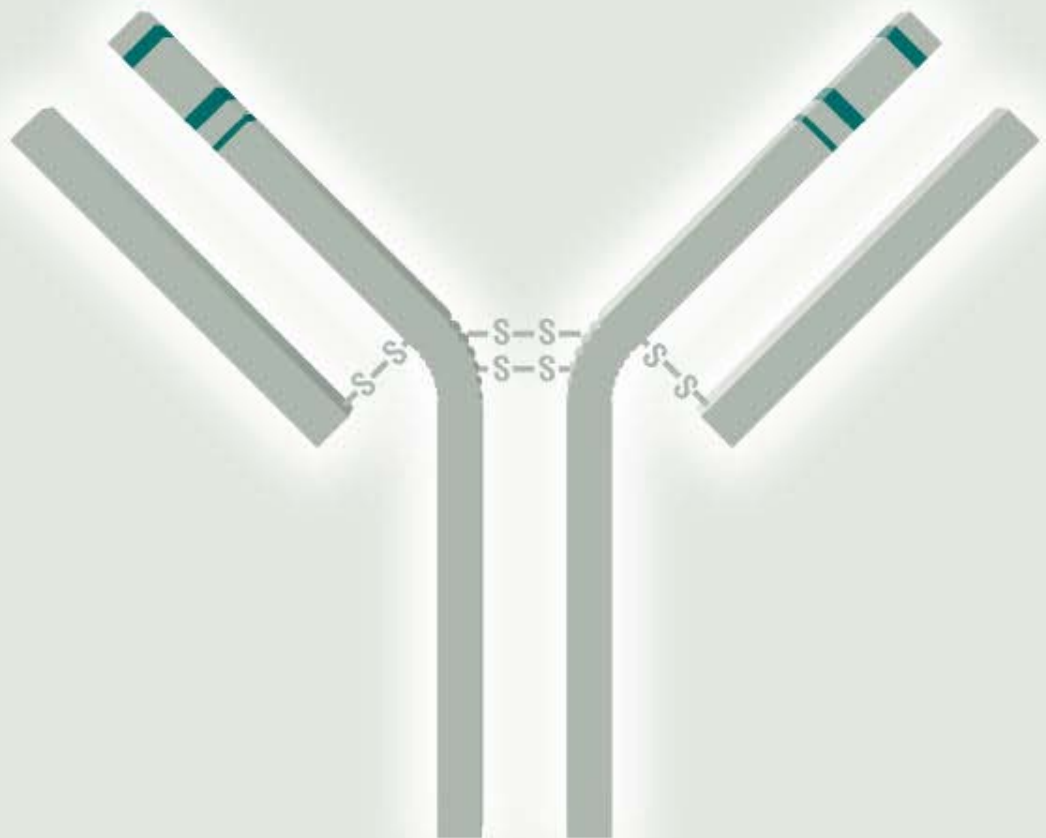
The Structure of an Antibody Molecule

Variable Domain



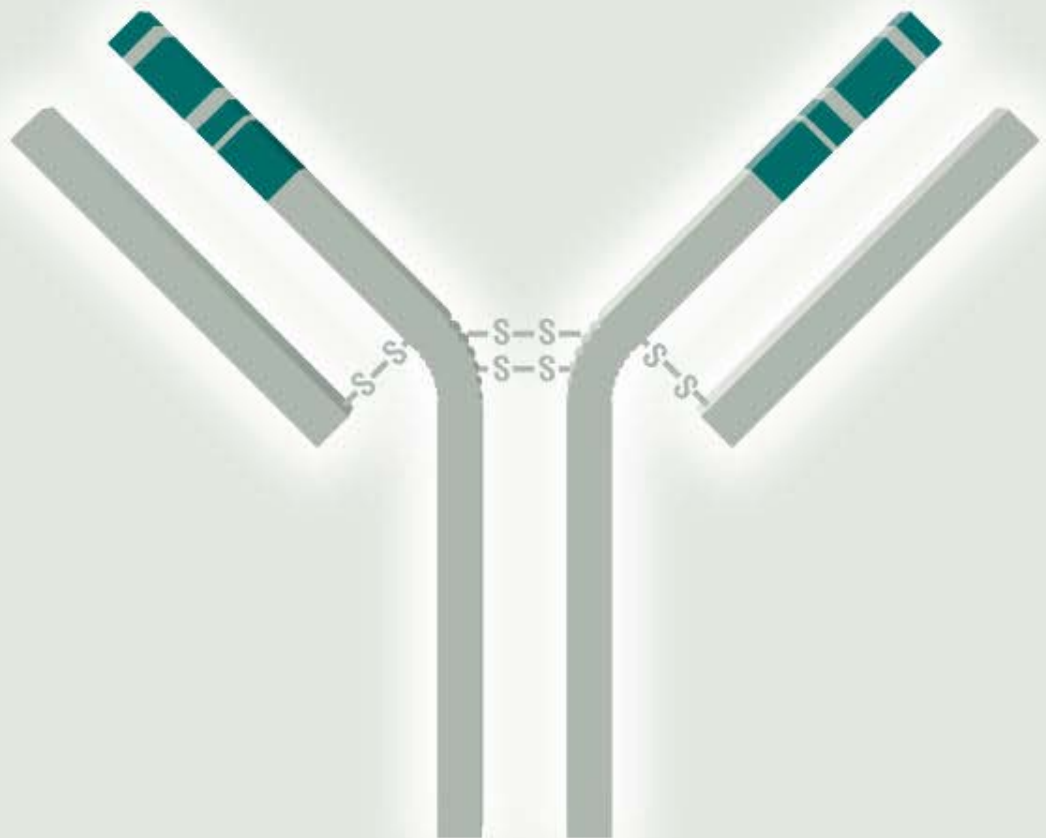
The Structure of an Antibody Molecule

*Heavy Chain
Complementarity
Determining
Regions (CDRs)*



The Structure of an Antibody Molecule

*Heavy Chain
Framework Regions*



Evolution of Genetically Engineered Therapeutic Monoclonal Antibodies

Murine Monoclonal Antibody

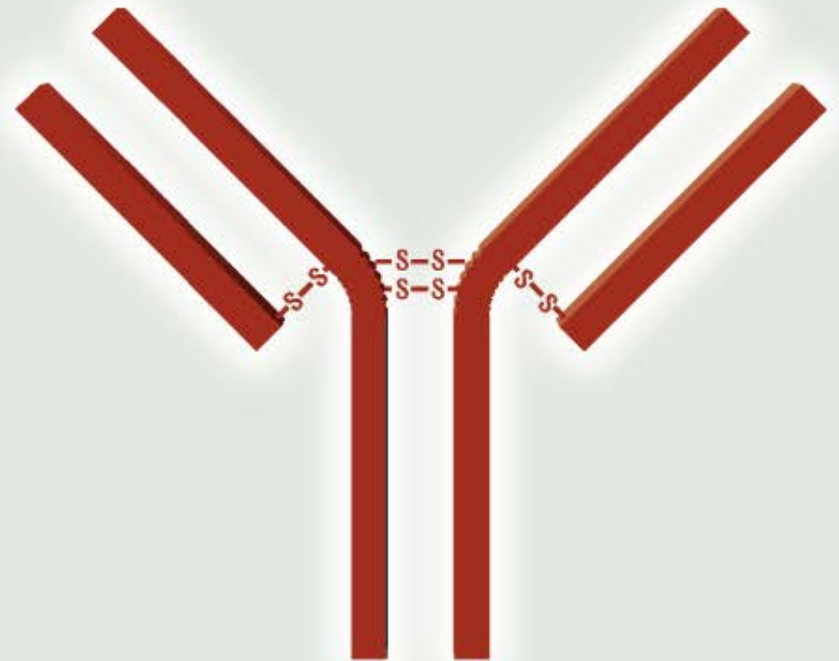
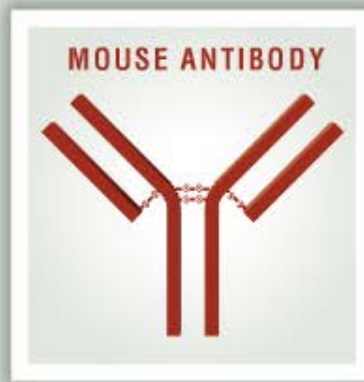
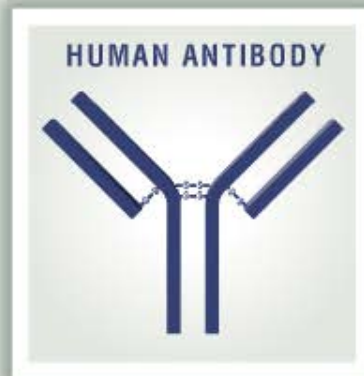
Chimeric Antibody

CDR-Grafted Antibody

CDR-Grafted Antibody with

Murine Monoclonal Antibody

***PROBLEM:
ATTACKED
IMMEDIATELY BY
NATIVE HUMAN
ANTIBODIES
(HAMA RESPONSE)***



Evolution of Genetically Engineered Therapeutic Monoclonal Antibodies

Murine Monoclonal Antibody

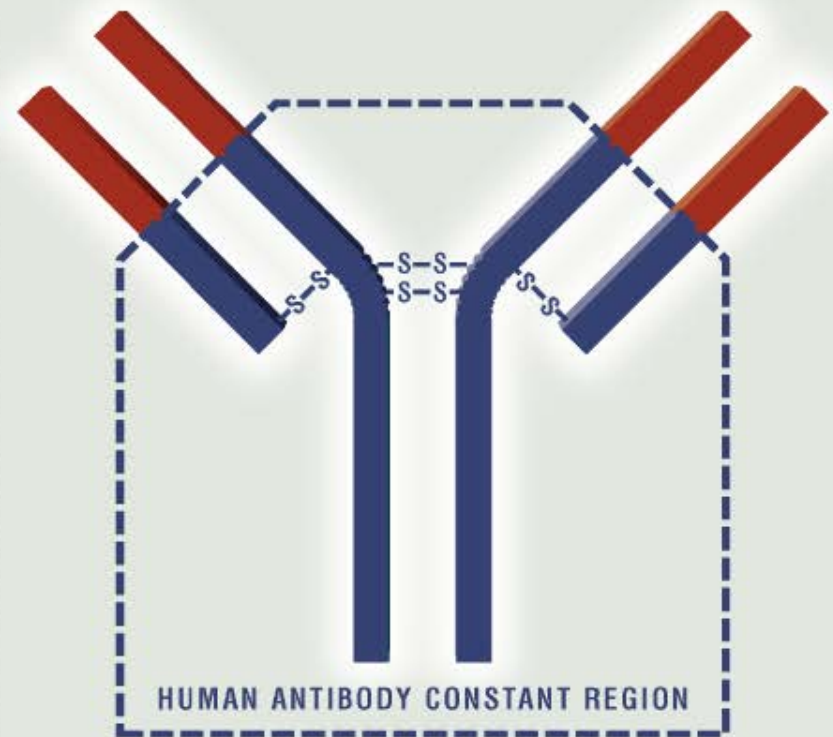
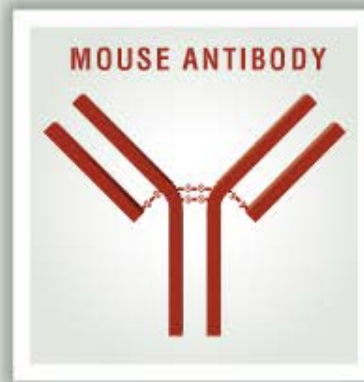
Chimeric Antibody

CDR-Grafted Antibody

CDR-Grafted Antibody with

Chimeric Antibody

Constant region of the mouse antibody is replaced with the constant region from a human antibody.



Evolution of Genetically Engineered Therapeutic Monoclonal Antibodies

Murine Monoclonal Antibody

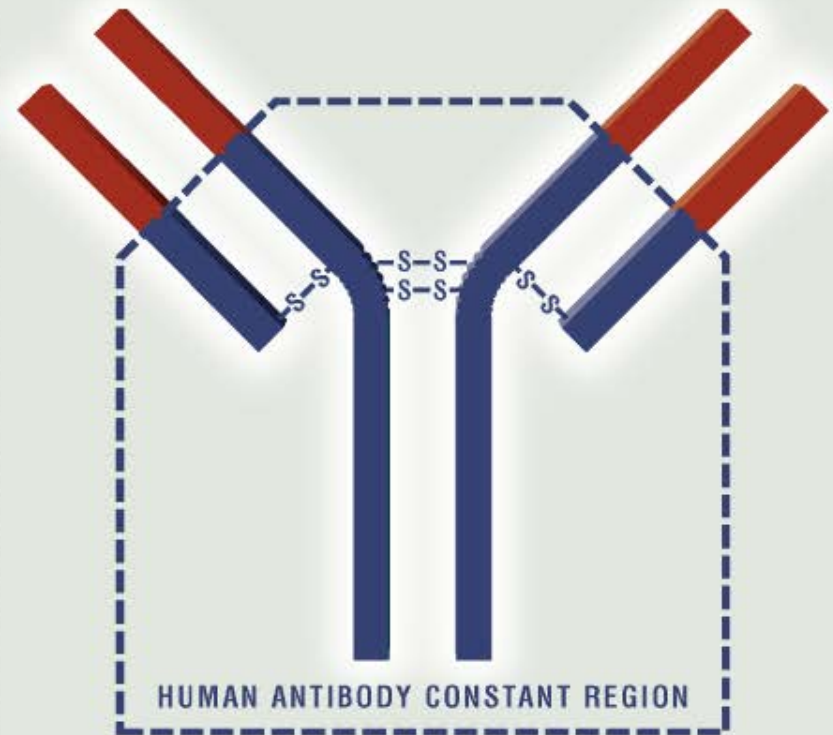
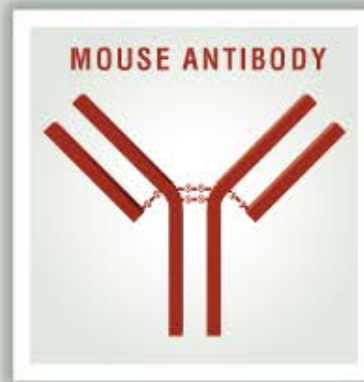
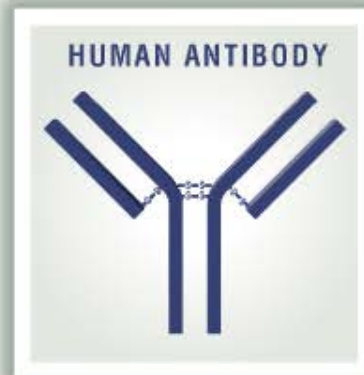
Chimeric Antibody

CDR-Grafted Antibody

CDR-Grafted Antibody with

Chimeric Antibody

- **REDUCTION, BUT NOT ELIMINATION, OF HAMA RESPONSE**



Evolution of Genetically Engineered Therapeutic Monoclonal Antibodies

Murine Monoclonal Antibody

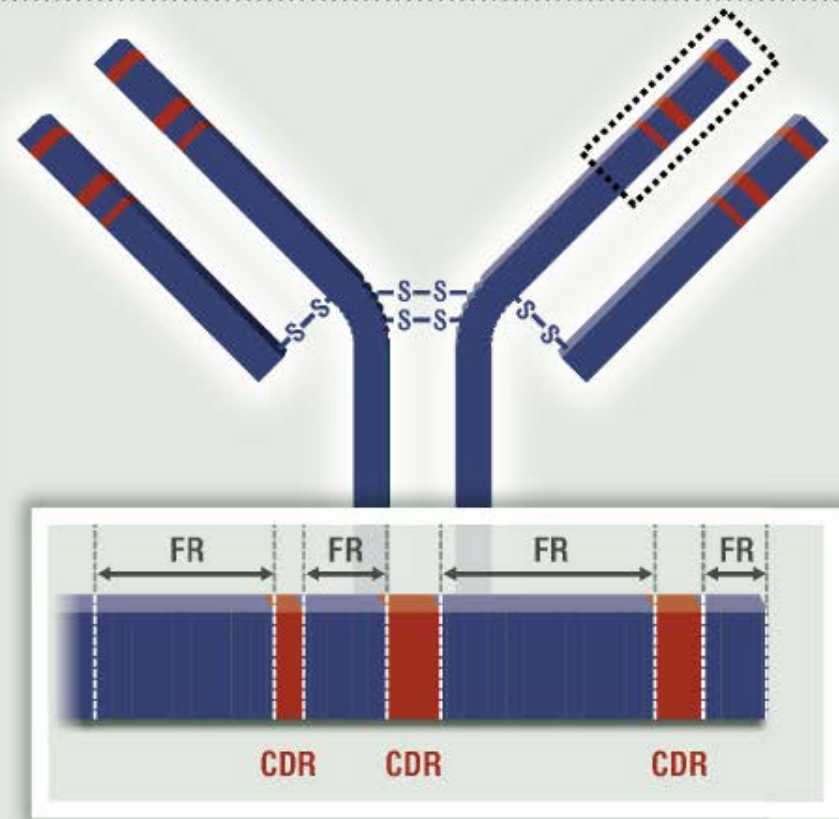
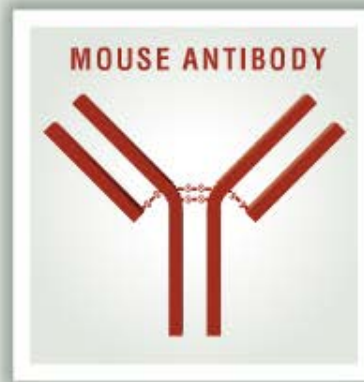
Chimeric Antibody

CDR-Grafted Antibody
(Winter)

CDR-Grafted Antibody with

CDR-Grafted Antibody (Winter)

CDRs (or at least a portion thereof) from the variable region of a mouse antibody are grafted onto the framework regions of a known human antibody.



Evolution of Genetically Engineered Therapeutic Monoclonal Antibodies

Murine Monoclonal Antibody

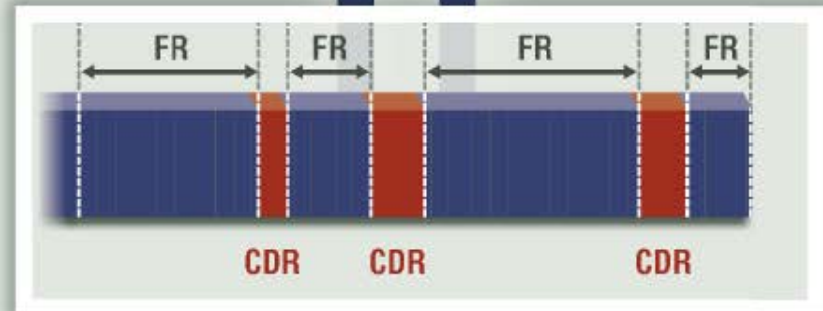
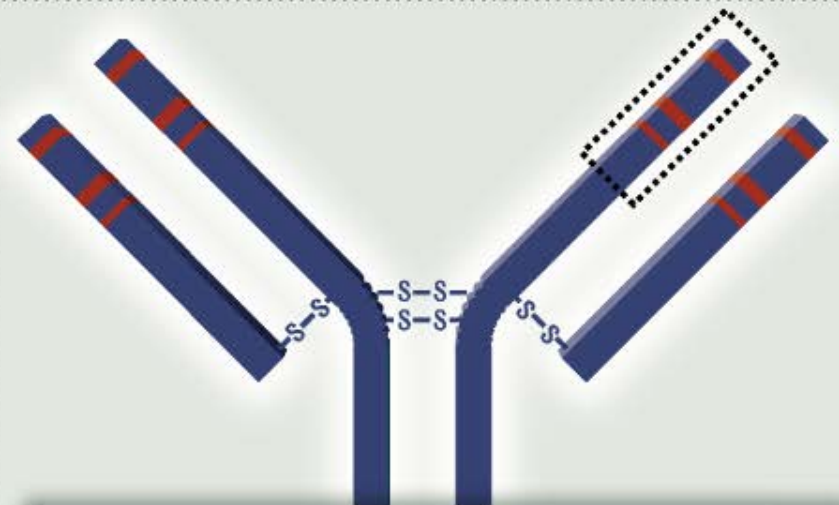
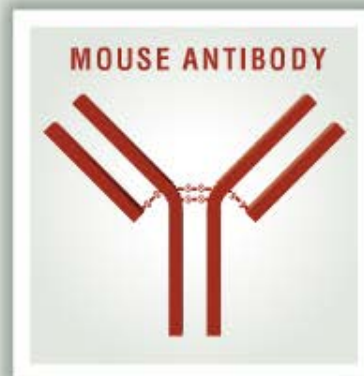
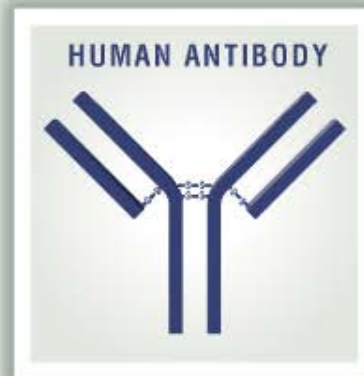
Chimeric Antibody

CDR-Grafted Antibody
(Winter)

CDR-Grafted Antibody with

CDR-Grafted Antibody (Winter)

- **FURTHER
REDUCTION OF
HAMA RESPONSE**
- **POTENTIAL
DECREASE IN
ANTIGEN BINDING**



Evolution of Genetically Engineered Therapeutic Monoclonal Antibodies

Murine Monoclonal Antibody

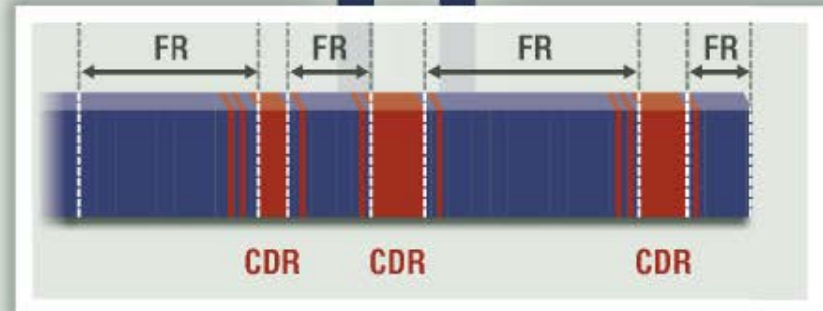
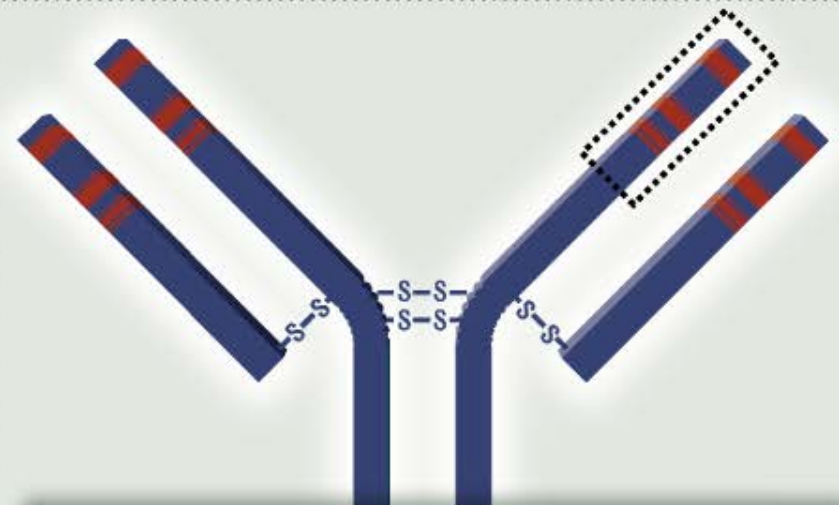
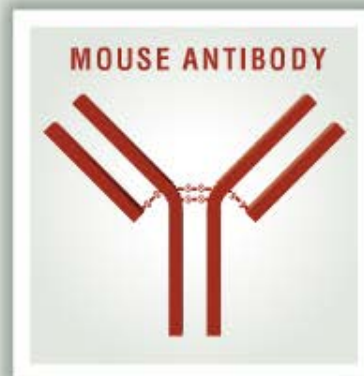
Chimeric Antibody

CDR-Grafted Antibody

CDR-Grafted Antibody with
Framework Changes (Queen)

CDR-Grafted Antibody with Framework Changes (Queen)

In addition to CDRs, certain amino acids in the framework of the variable region of a mouse antibody are grafted into a known human antibody.



Evolution of Genetically Engineered Therapeutic Monoclonal Antibodies

Murine Monoclonal Antibody

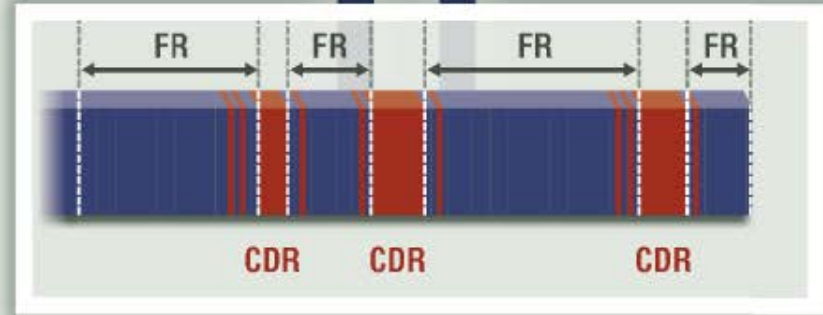
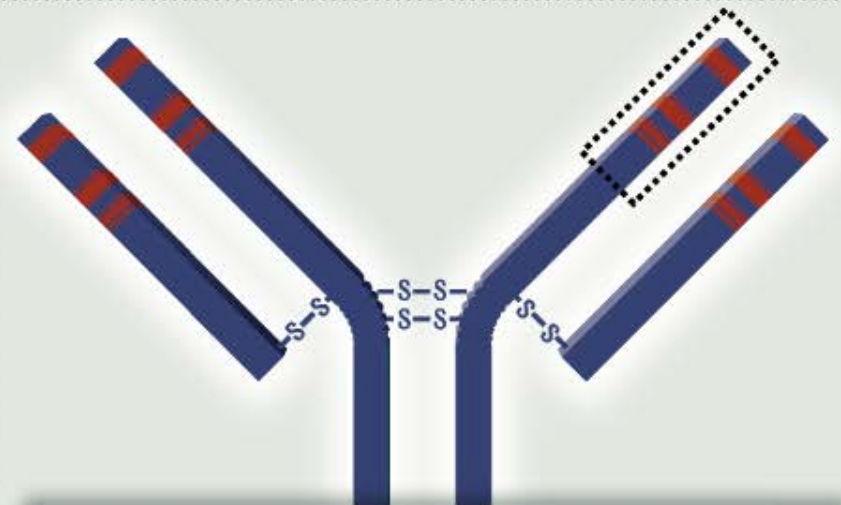
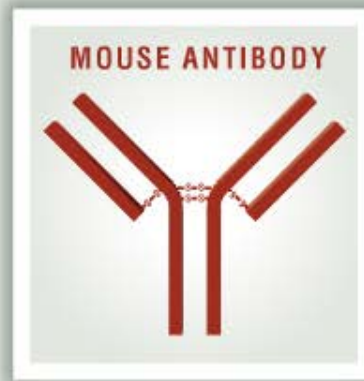
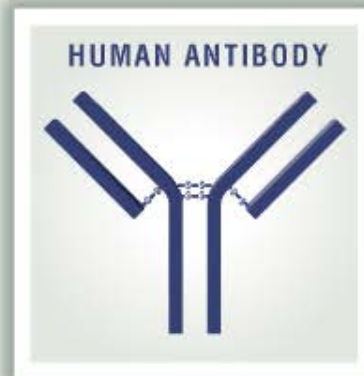
Chimeric Antibody

CDR-Grafted Antibody

CDR-Grafted Antibody with
Framework Changes (Queen)

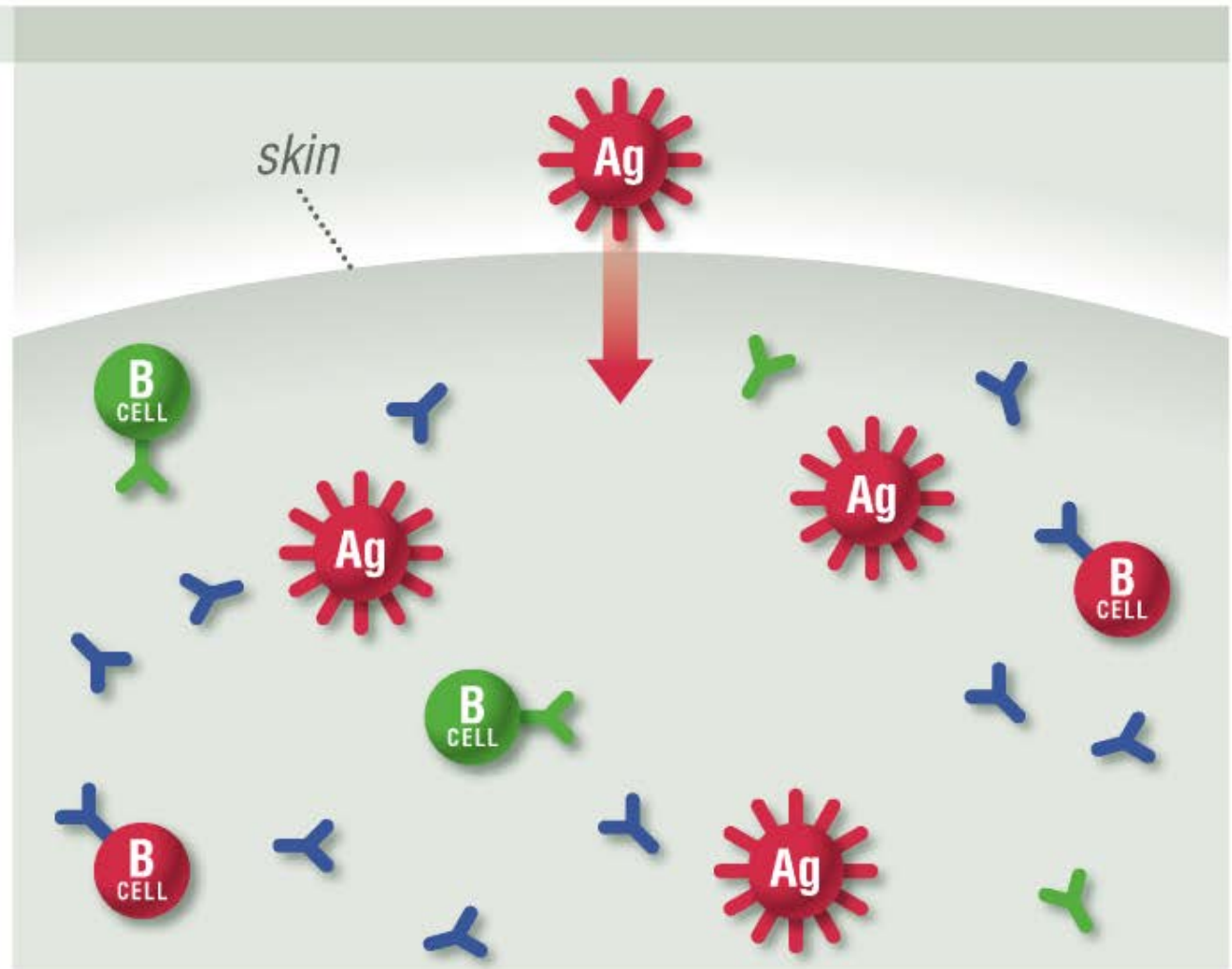
CDR-Grafted Antibody with Framework Changes (Queen)

- **RESTORES
ANTIGEN BINDING**



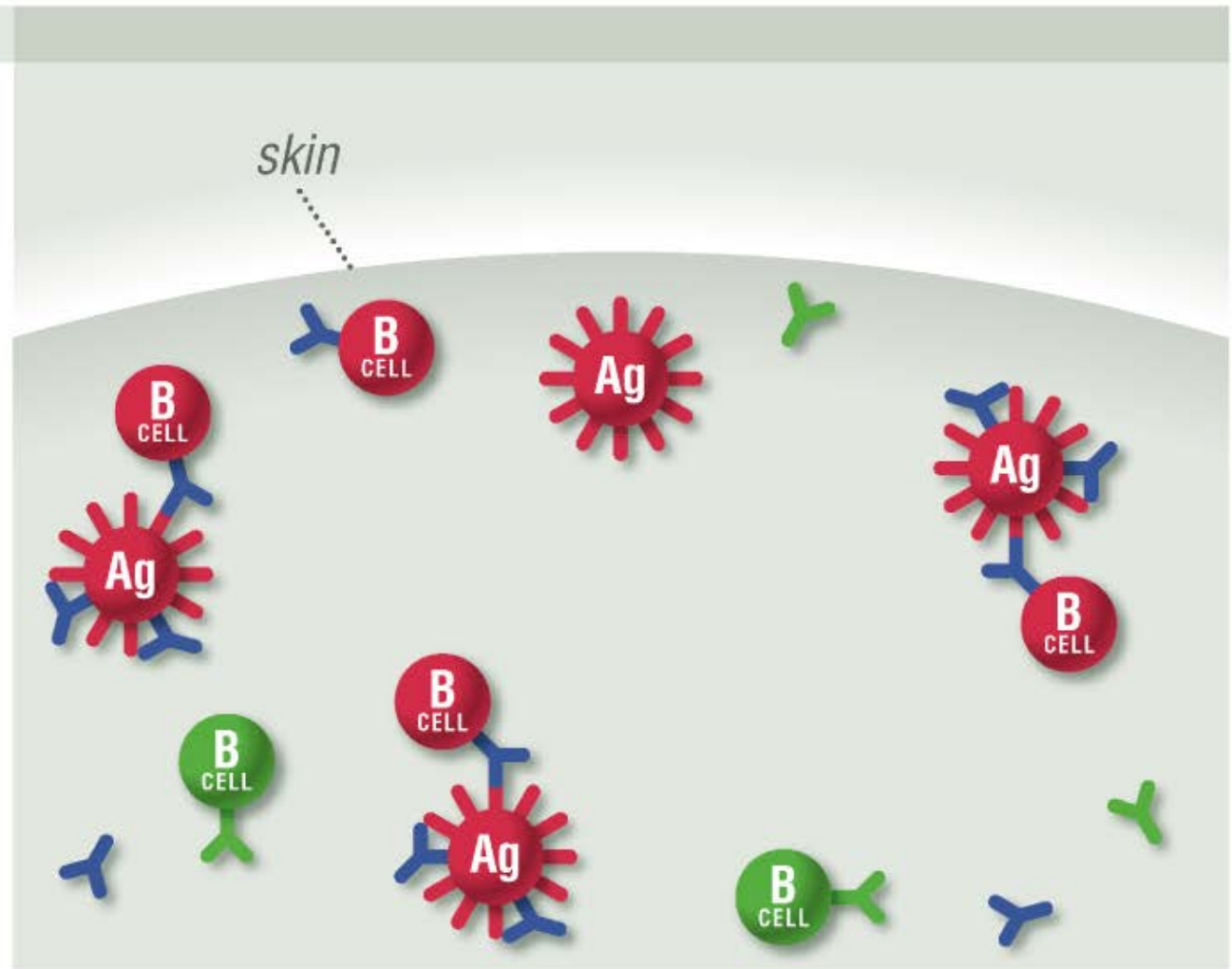
The Human Immune Response

The antigen, i.e. bacteria, enters the body and begins to multiply.



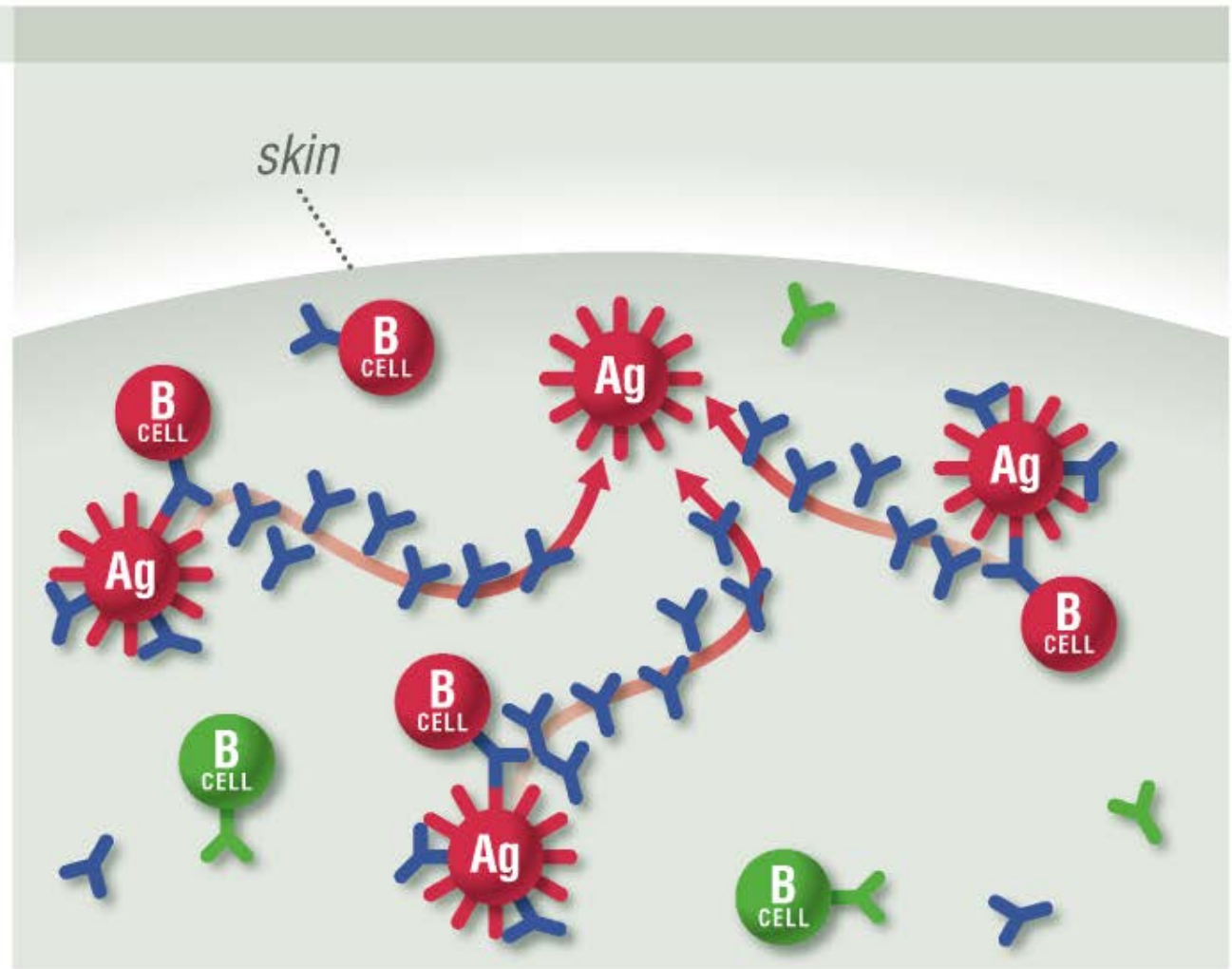
The Human Immune Response

Certain B cells (lymphocytes) recognize a specific foreign antigen.



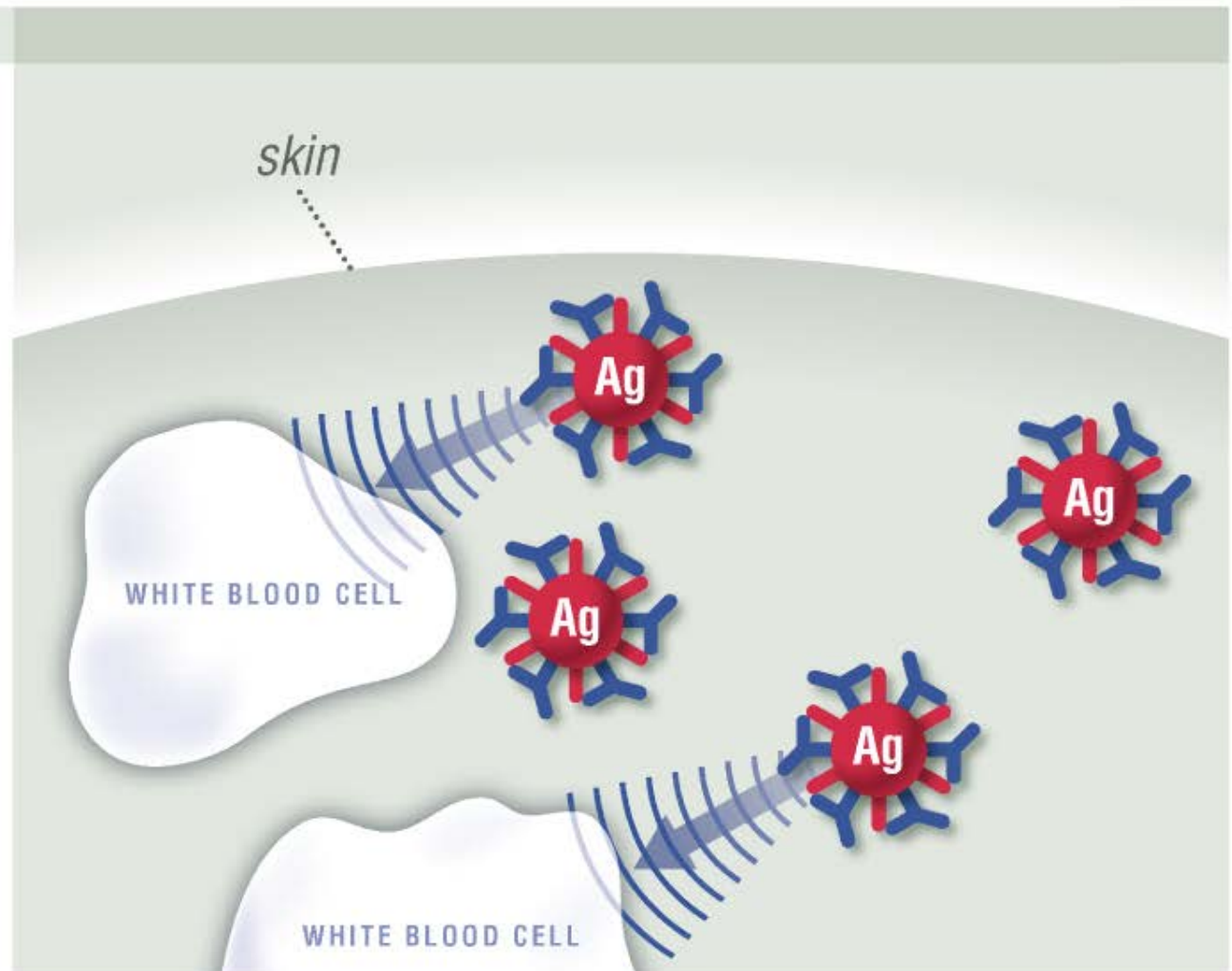
The Human Immune Response

Antigens trigger B cells to produce many antibodies specific to the target antigen.



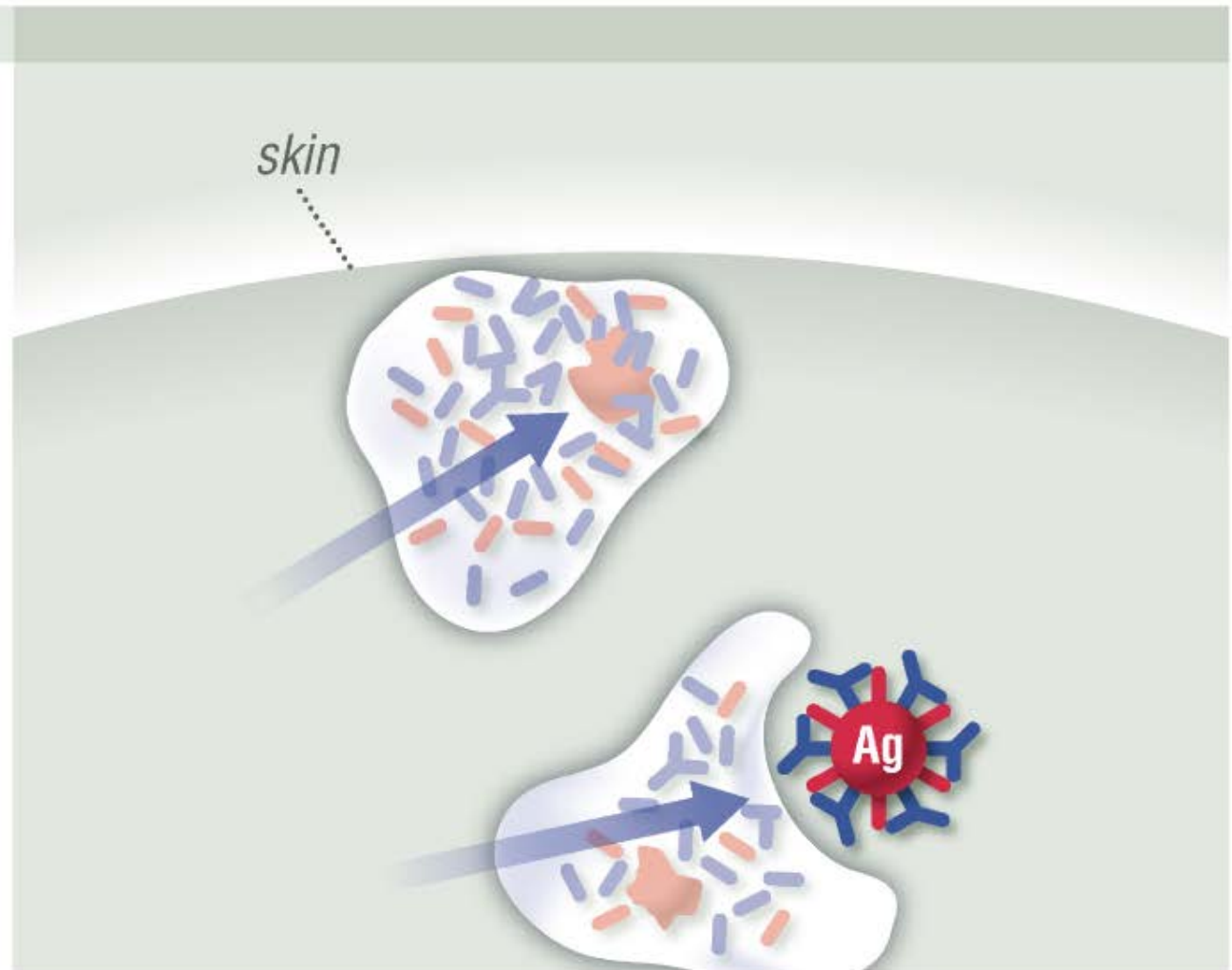
The Human Immune Response

The antibodies surround the antigen, flagging it for an immune system response.



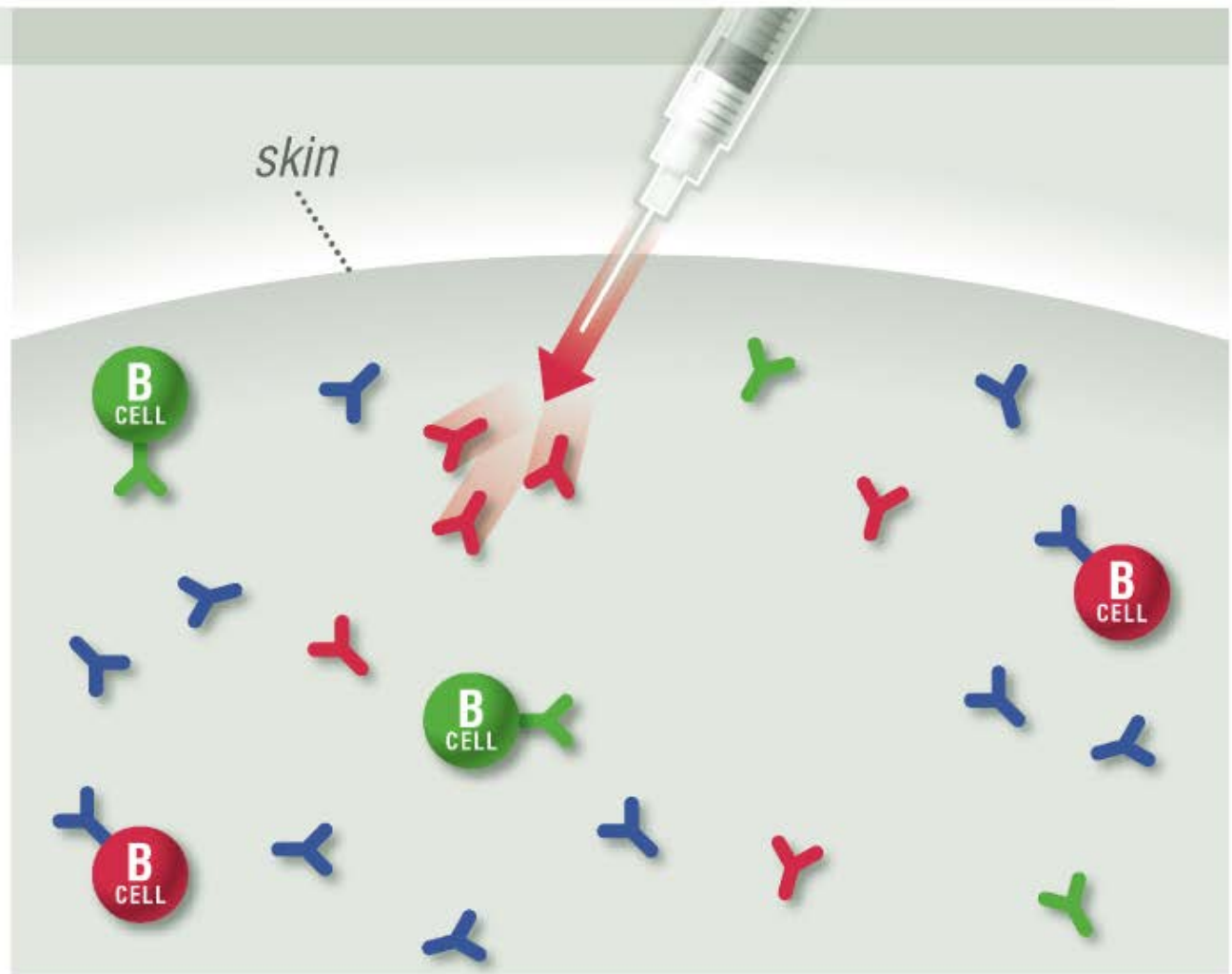
The Human Immune Response

White blood cells attracted by the antibodies surround and destroy the target antigen.



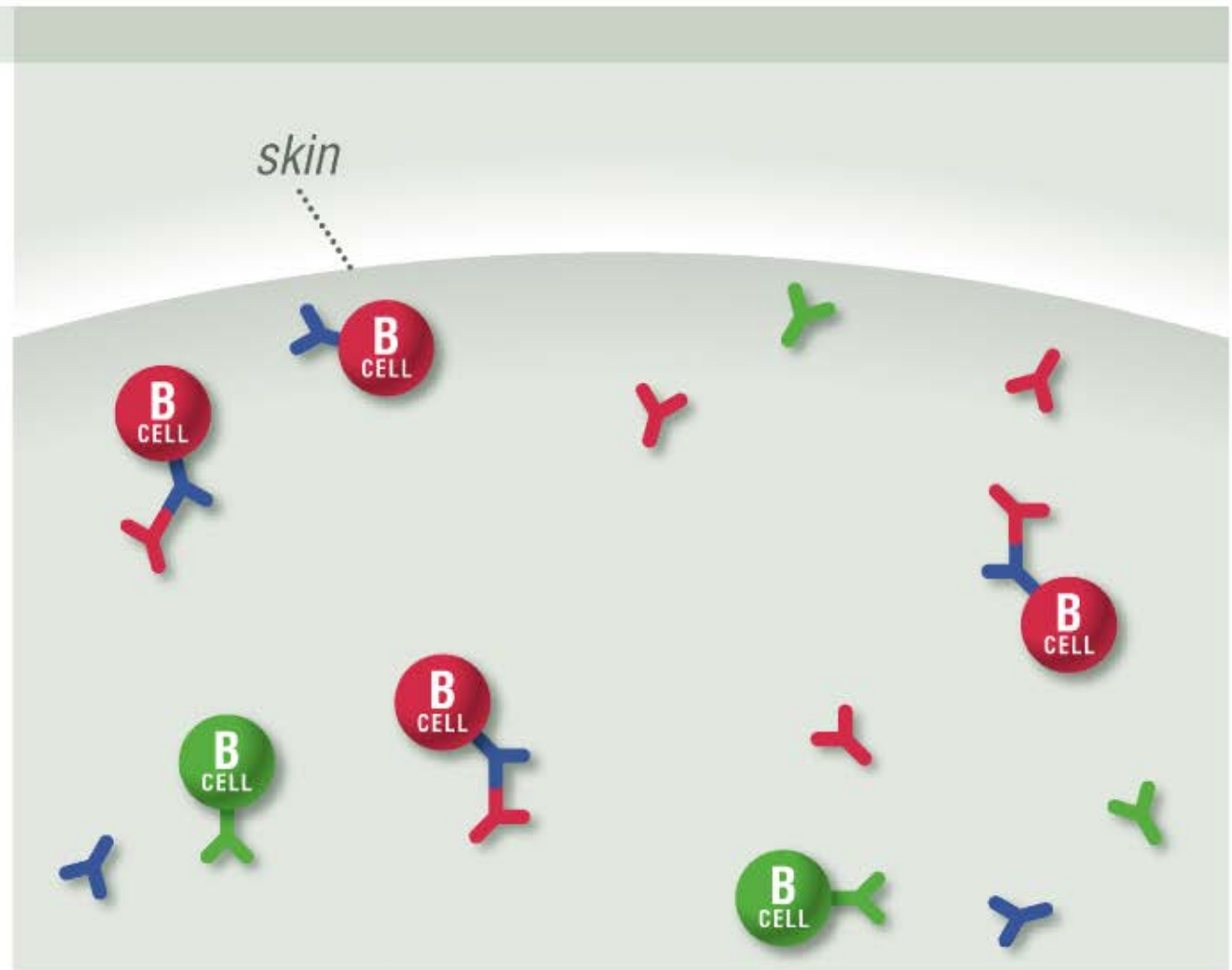
Human Anti-Mouse Antibody (HAMA) Response

Therapeutic monoclonal mouse antibodies are injected into a human.



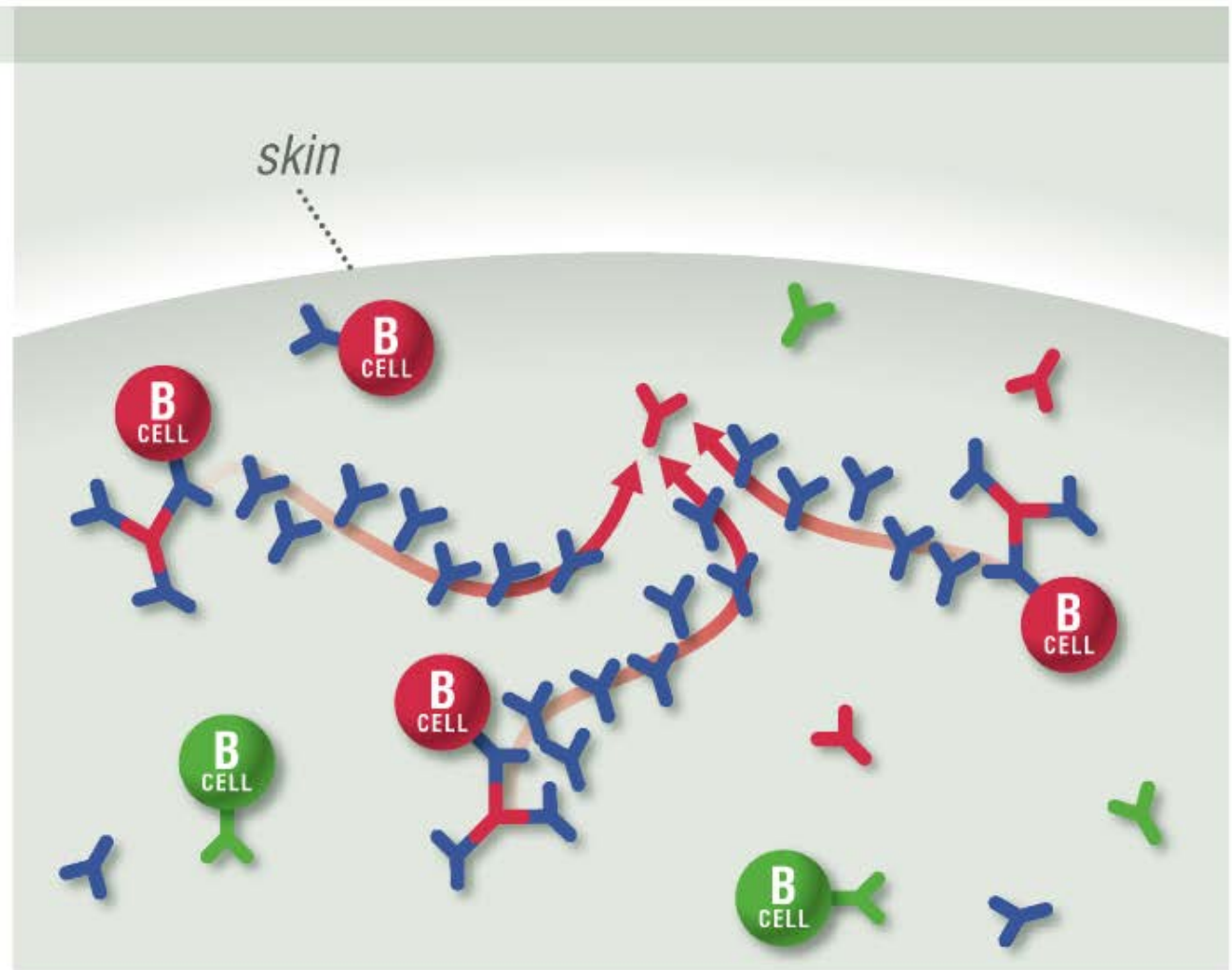
Human Anti-Mouse Antibody (HAMA) Response

The human recognizes the mouse antibody as foreign and raises an immune response to it.



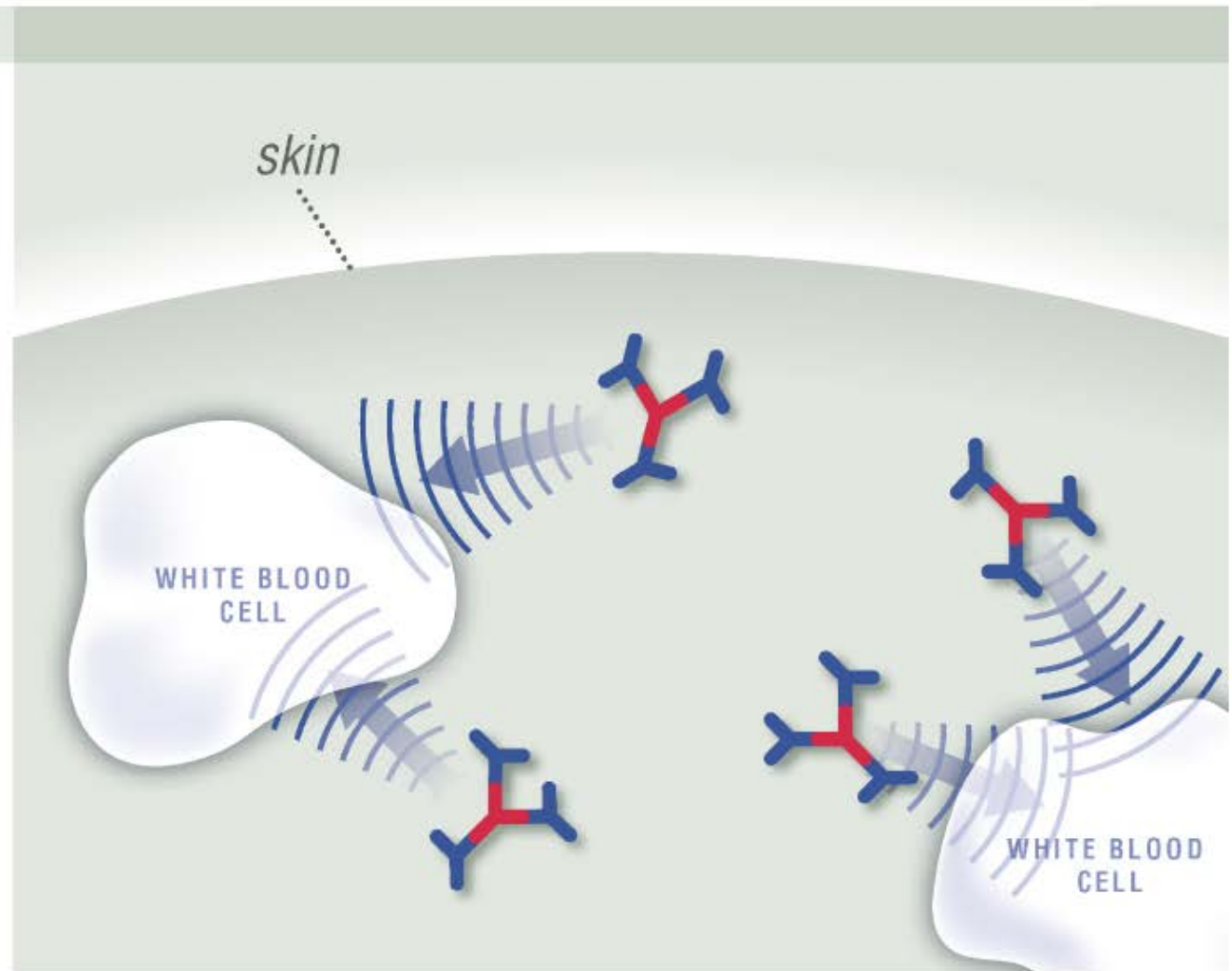
Human Anti-Mouse Antibody (HAMA) Response

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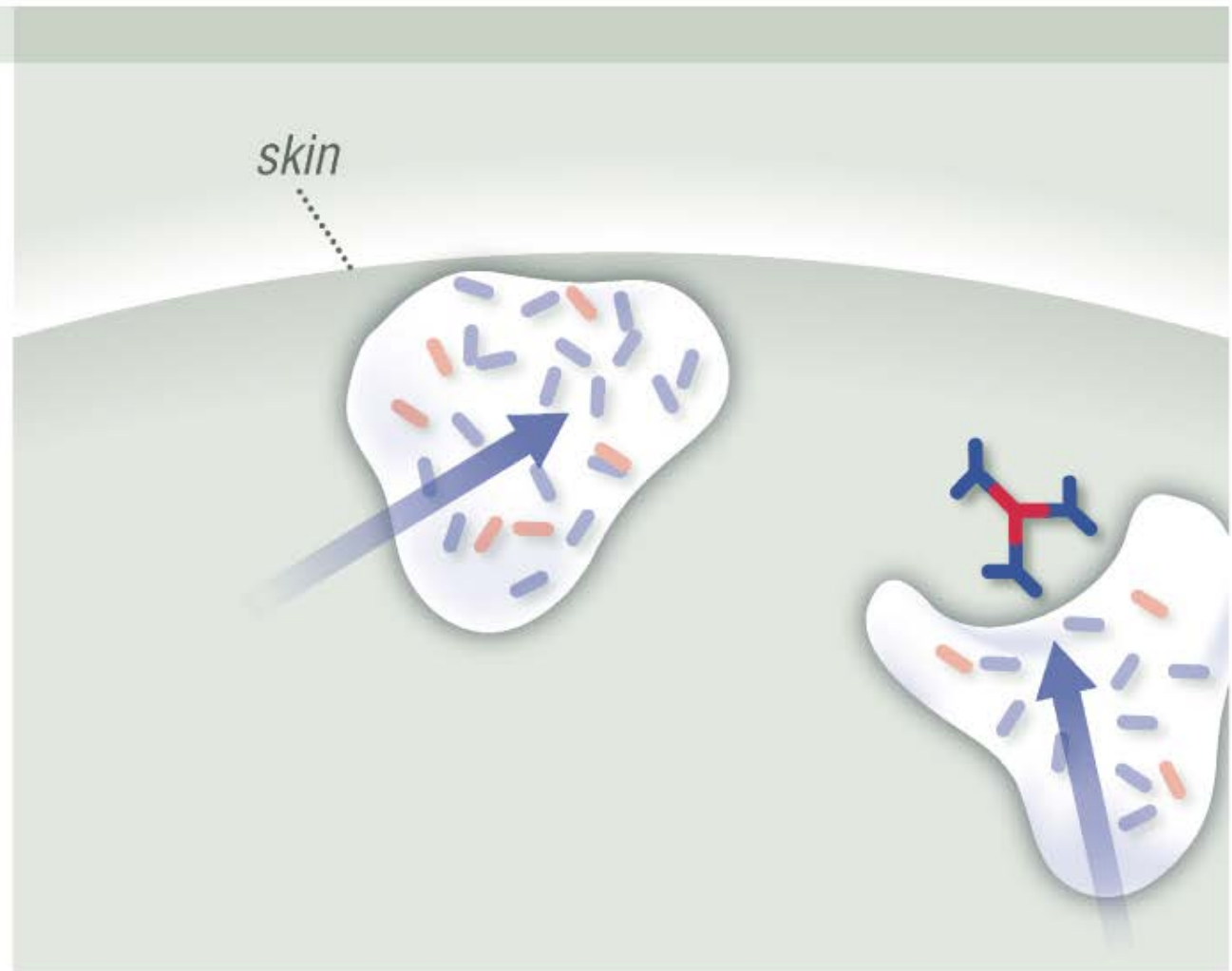
Human Anti-Mouse Antibody (HAMA) Response

The human recognizes the mouse antibody as foreign and raises an immune response to it.



Human Anti-Mouse Antibody (HAMA) Response

The human recognizes the mouse antibody as foreign and raises an immune response to it.



Claim 1 of the '927 Patent

ELEMENT

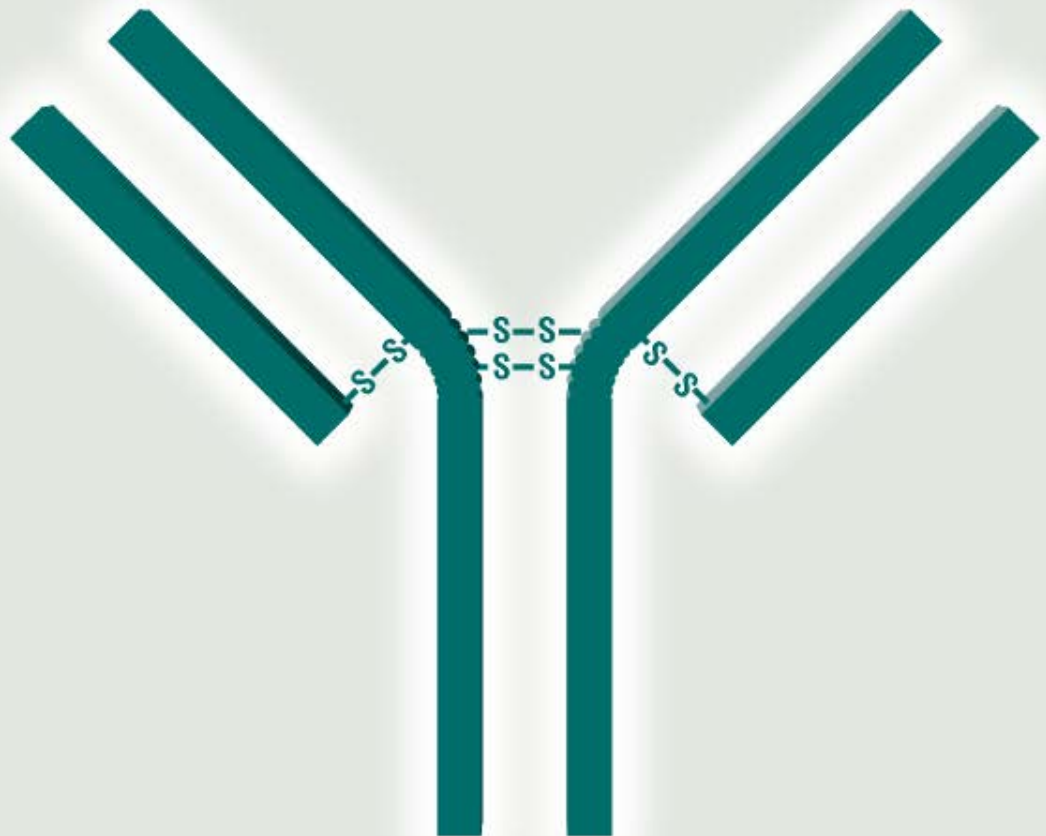
- 1 An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain,
- 2 said composite heavy chain having a variable domain including complementarity determining regions (CDRs) and framework regions,
- 3 wherein said framework regions of said variable domain comprise predominantly human acceptor antibody heavy chain framework region residues,
- 4 the remaining heavy chain framework region residues corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen,
- 5 wherein, according to the Kabat numbering system, in said **composite heavy chain:** said CDRs comprise donor residues at residues 31 to 35, 50 to 58, and 95 to 102;
- 6 and said framework regions comprise donor residues at amino acid residues 6, 24, 48, 49, 71, 73, and 78.

Claim 1 of the '927 Patent

Element 1

1

An **antibody molecule** having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain....

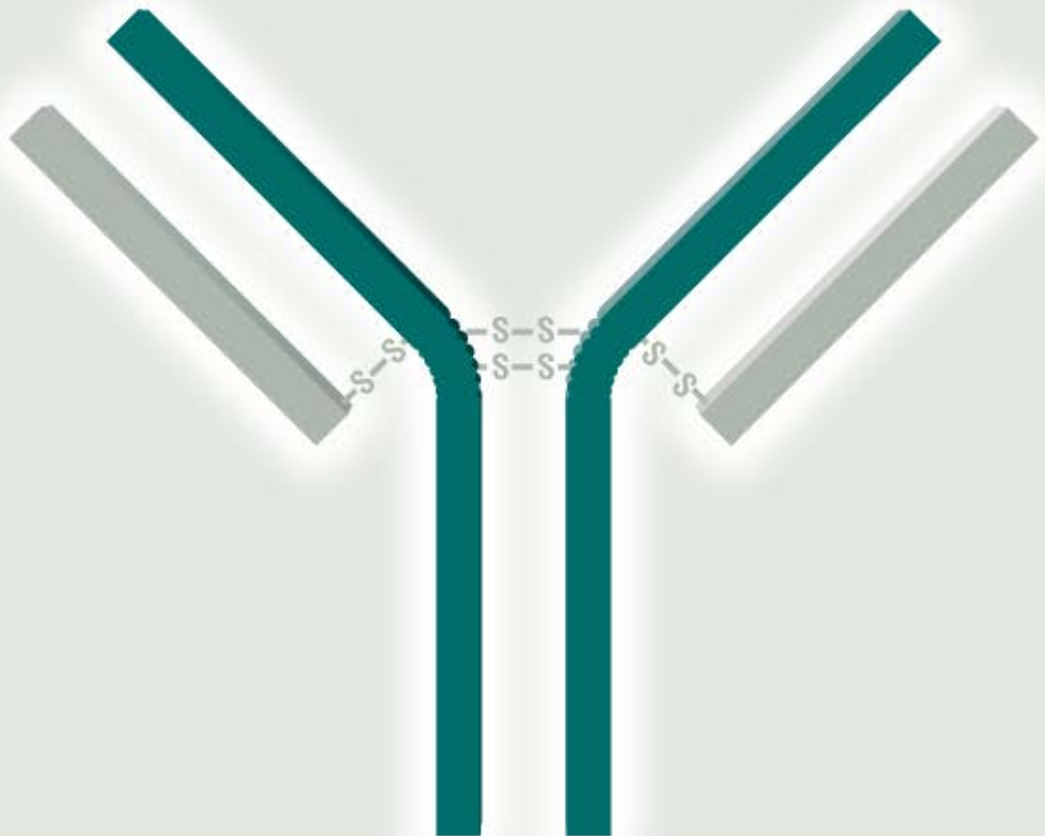


Claim 1 of the '927 Patent

Element 1

1

An antibody molecule having affinity for a predetermined antigen and comprising a composite **heavy chain** and a complementary light chain....

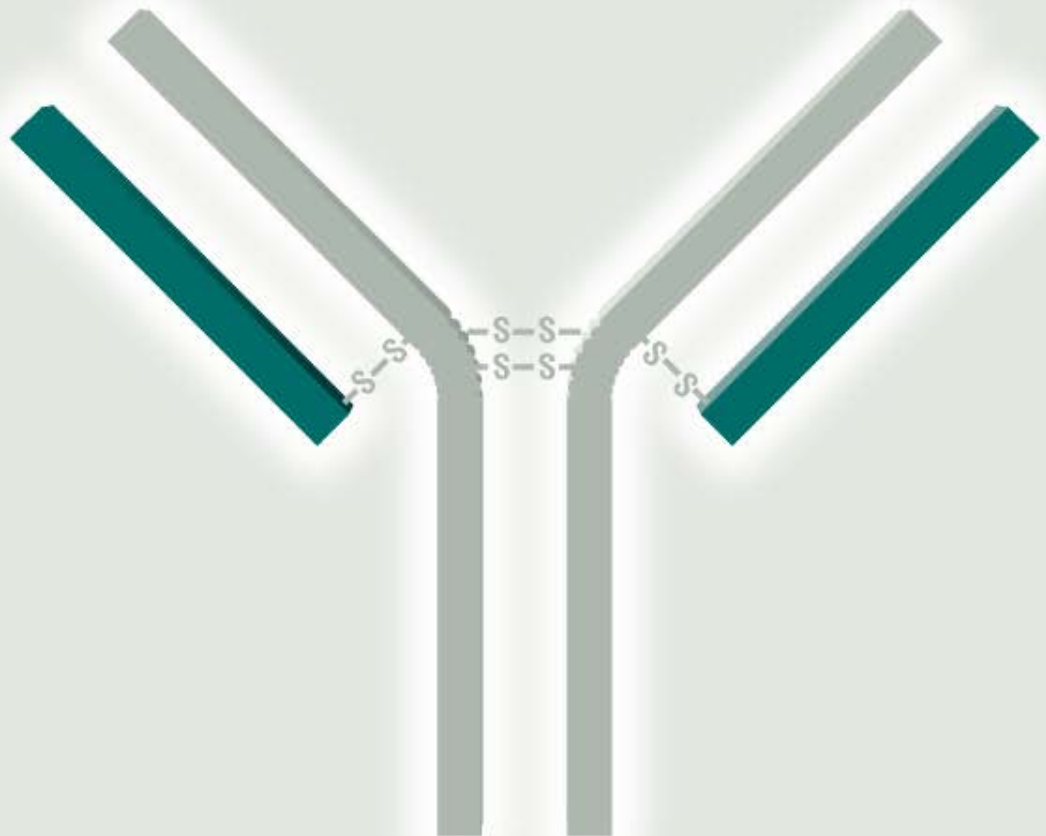


Claim 1 of the '927 Patent

Element 1

1

An antibody molecule
having affinity for a
predetermined antigen
and comprising a
composite heavy chain
and a complementary
light chain....

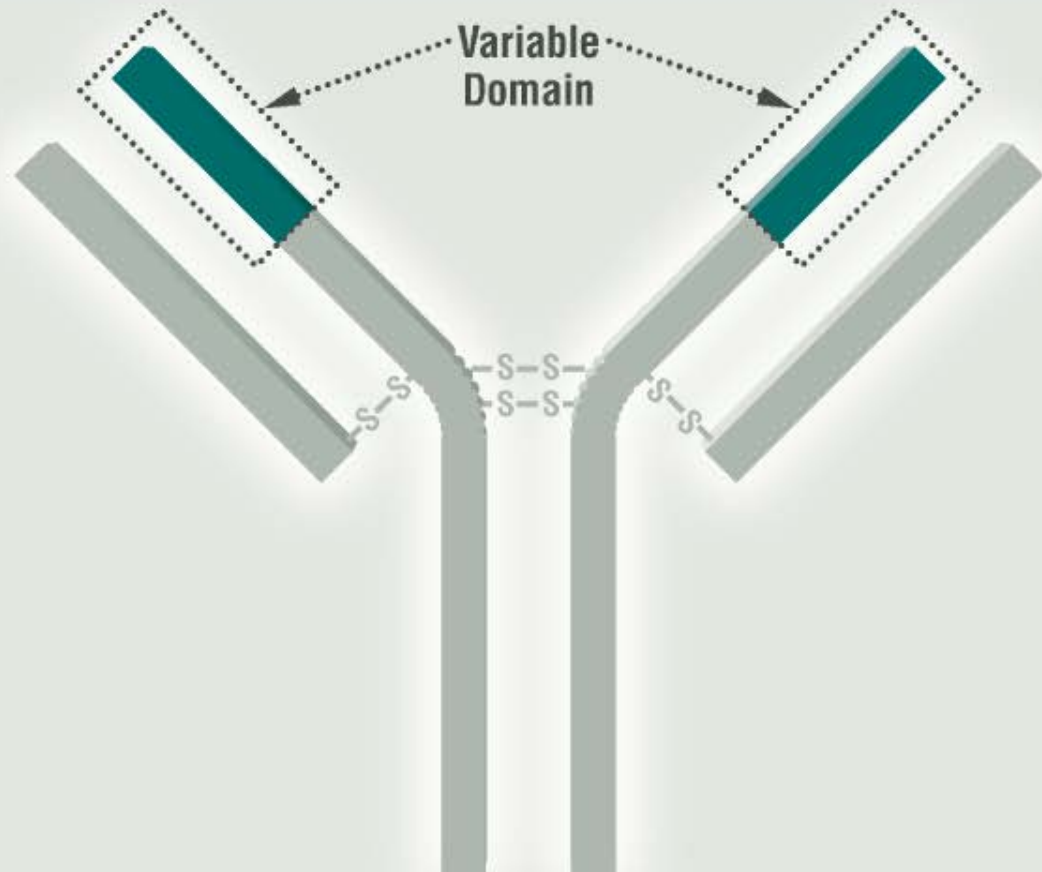


Claim 1 of the '927 Patent

Element 2

2

...said composite
heavy chain having a
variable domain
including
complementarity
determining regions
(CDRs) and
framework regions...

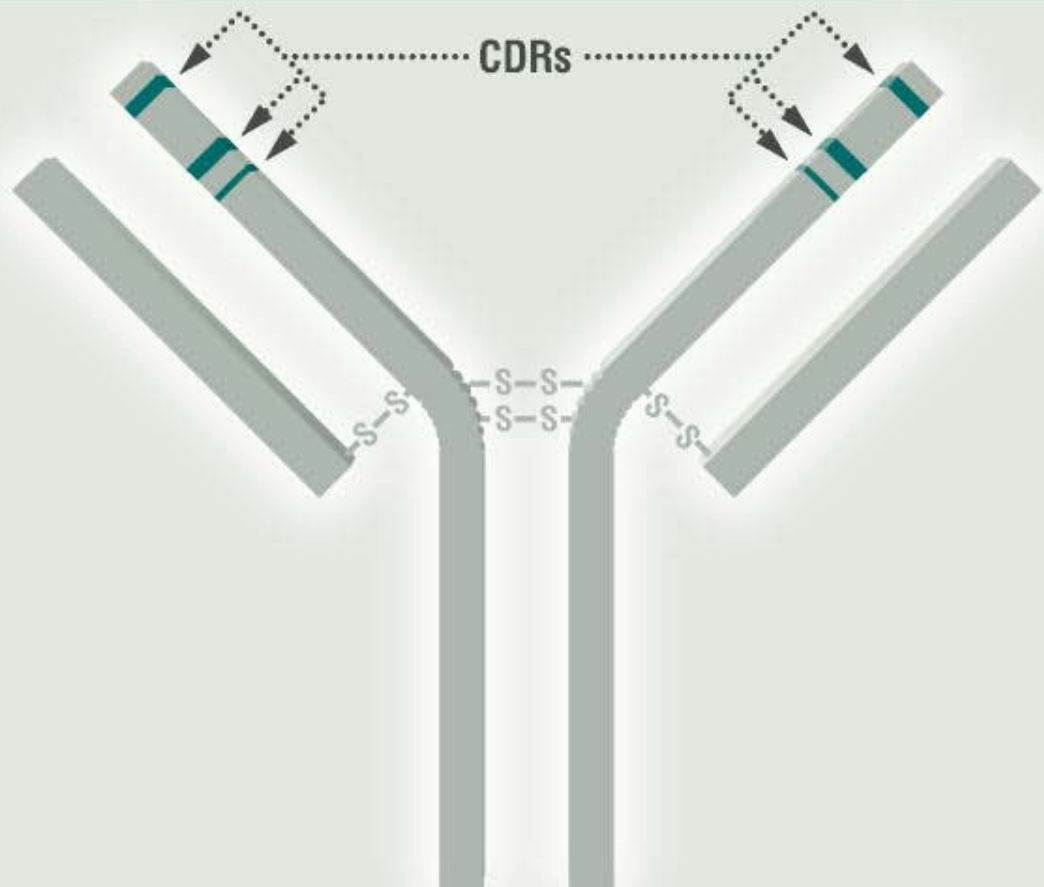


Claim 1 of the '927 Patent

Element 2

2

...said composite heavy chain having a variable domain including
complementarity determining regions (CDRs) and framework regions...

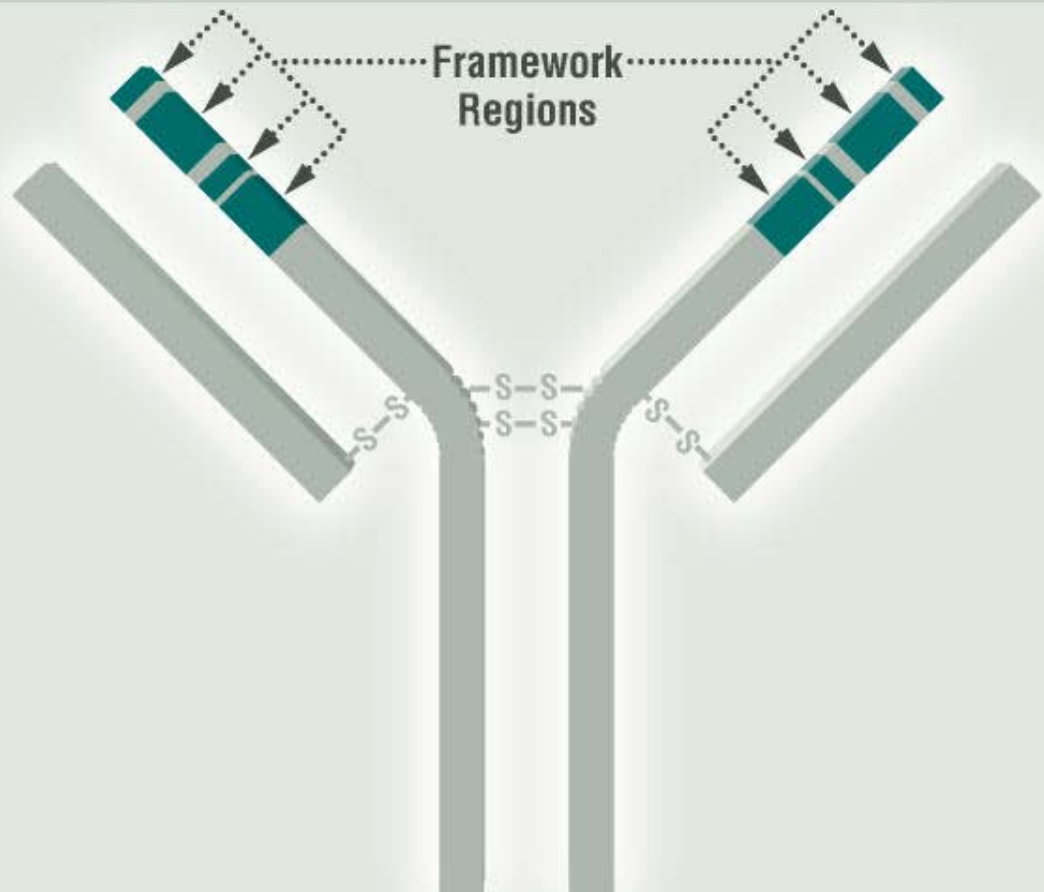


Claim 1 of the '927 Patent

Element 2

2

...said composite heavy chain having a variable domain including complementarity determining regions (CDRs) and **framework regions**...



Claim 1 of the '927 Patent

Elements 3 and 4

3

...wherein said framework regions of said variable domain comprise **predominantly human acceptor antibody heavy chain framework region residues,**

■ HUMAN "ACCEPTOR" RESIDUE



Composite Antibody



Human "Acceptor" Antibody

Claim 1 of the '927 Patent

Elements 3 and 4

3

...wherein said framework regions of said variable domain comprise **predominantly human acceptor antibody heavy chain framework region residues**,

4

the **remaining heavy chain framework region residues** corresponding to the equivalent residues in a **donor** antibody having affinity for said predetermined antigen...

■ HUMAN "ACCEPTOR" RESIDUE

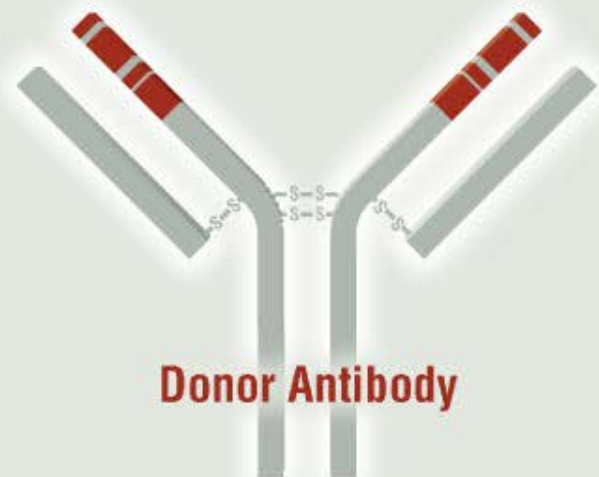
■ DONOR RESIDUE



Composite Antibody



Human "Acceptor" Antibody



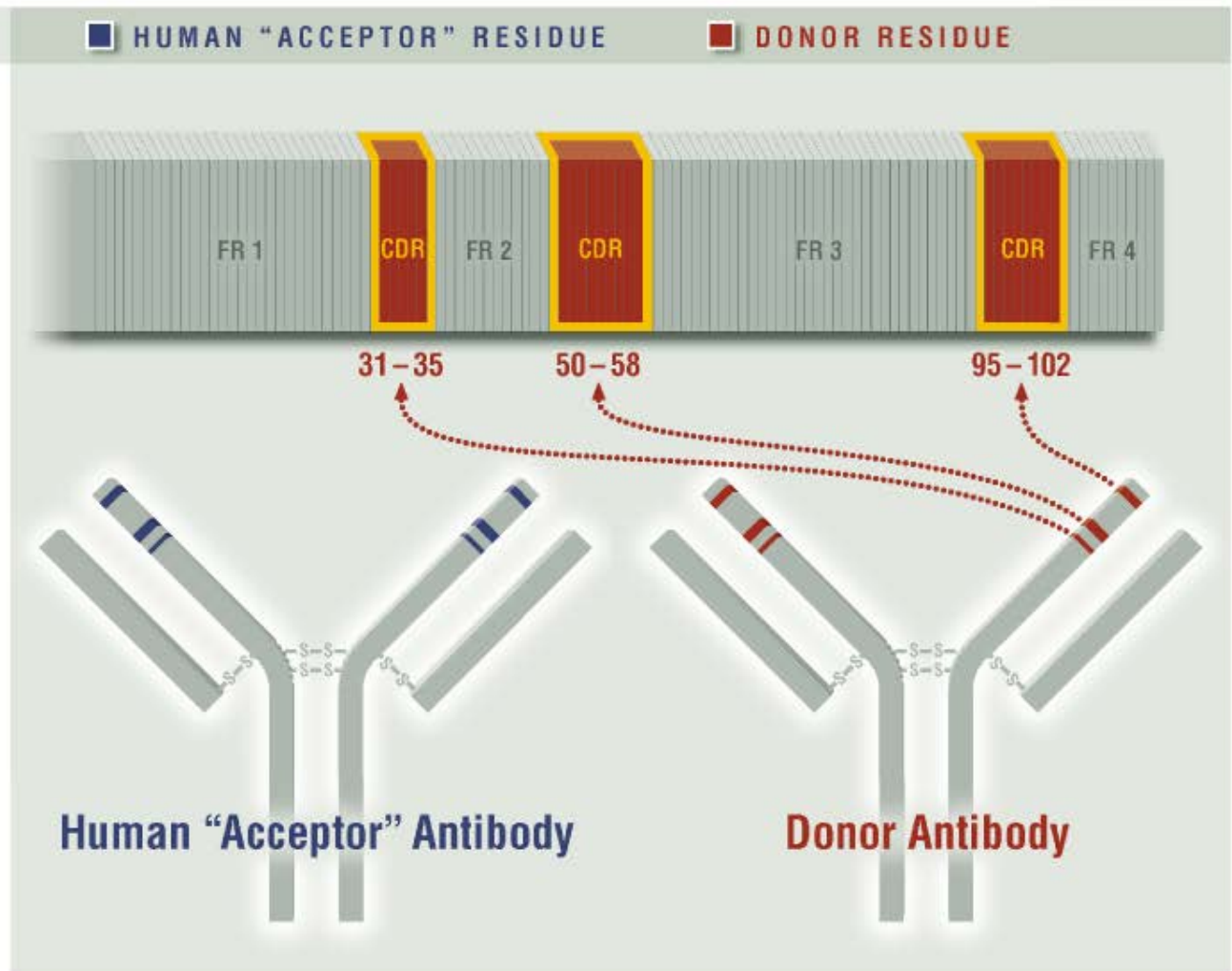
Donor Antibody

Claim 1 of the '927 Patent

Element 5

5

...wherein, according to the Kabat numbering system, in said composite heavy chain: said **CDRs** comprise donor residues at residues 31 to 35, 50 to 58, and 95 to 102...



Claim 1 of the '927 Patent

Element 6

6

...and said framework regions comprise **donor residues** at amino acid residues 6, 24, 48, 49, 71, 73, and 78.

