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# Antibodies

M1 – Immunology Sequence

Winter 2009

University of Michigan
Medical School

1. **The polypeptides that make up an immunoglobulin.**

2. **Constant and variable regions of an immunoglobulin.**

3. **The immunoglobulin domain.**

4. **Framework and complementarity determining (hypervariable) regions within the variable region.**

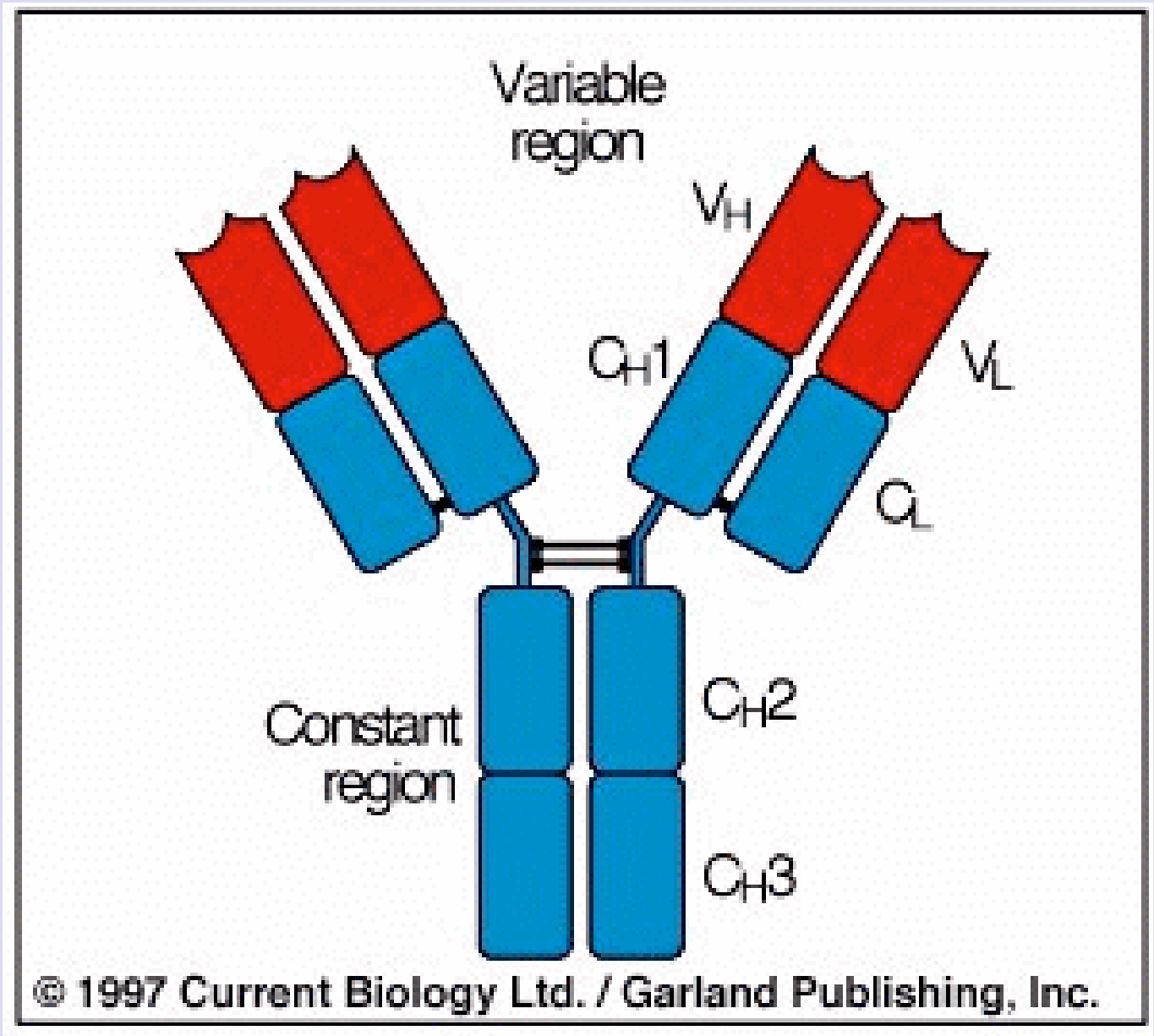
5. **Different functions of the different antibody classes and subclasses.**

**The structure of antibodies has been derived from monoclonal antibodies secreted by monoclonal plasmacytomas (or myelomas)--tumors of plasma cells.**

**All antibodies are made up of two polypeptides:**

**Two identical heavy chains of molecular weight 44-55 kD**

**Two identical light chains of molecular weight 24 kD**




PD-INEL

Janeway. Immunobiology: The Immune System in Health and Disease. Current Biology Ltd./Garland Publishing, Inc. 1997

**Constant region--the amino acid sequence is exactly the same, for one kind of immunoglobulin polypeptide. Always located in carboxy part of chain.**

**For light chains, residue numbers 108-214. Called κ, λ**

**Heavy chain: α, γ, δ, ε, μ**

**Subclasses of immunoglobulins, with different heavy chains**

**For example, γ1, γ2, γ3, and γ4**
**α1 and α2**

**All constant regions within a subclass have exactly the same sequence.**

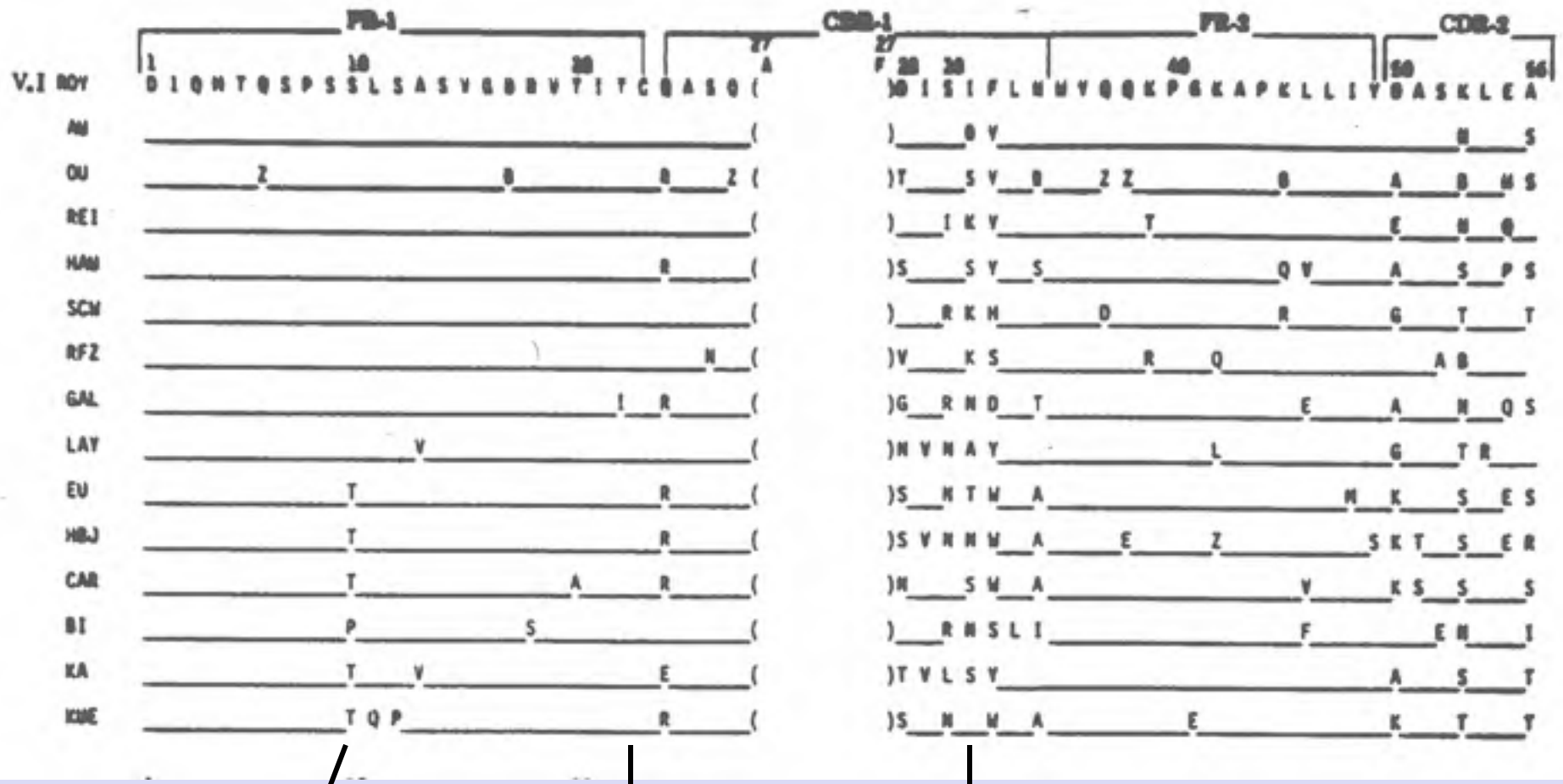
**For example, γ1 and γ2 are more closely related to each other than either is to α1.**

**Variable region--the amino acid sequence in the amino terminal part is never the same for two immunoglobulins.**

**For light chains, residues 1-107.**

**Wu and Kabat defined variability by an equation:**

$$\text{Variability} = \frac{\text{Number of different amino acids at a residue}}{\text{Frequency of the most frequent amino acid}}$$

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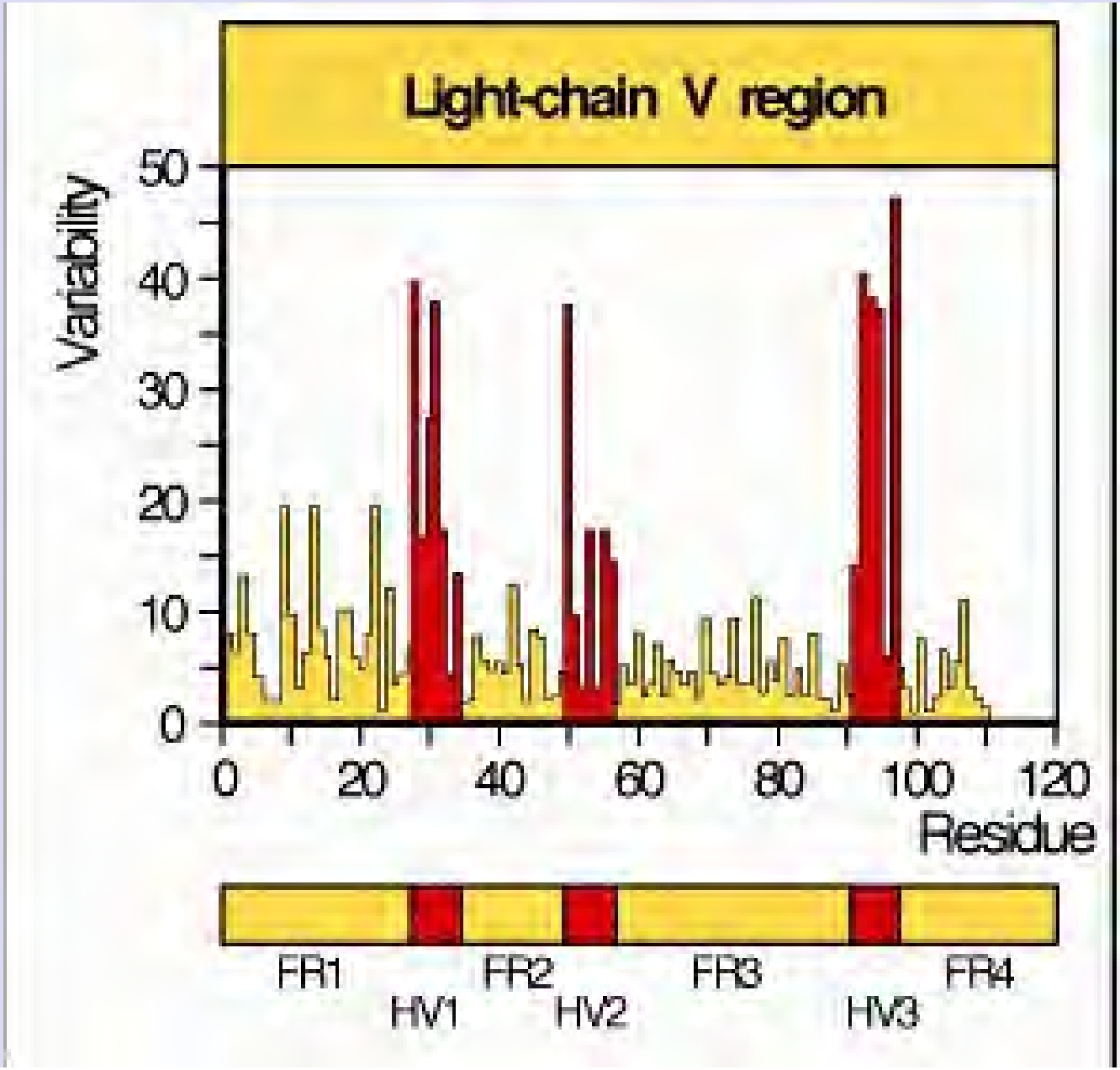


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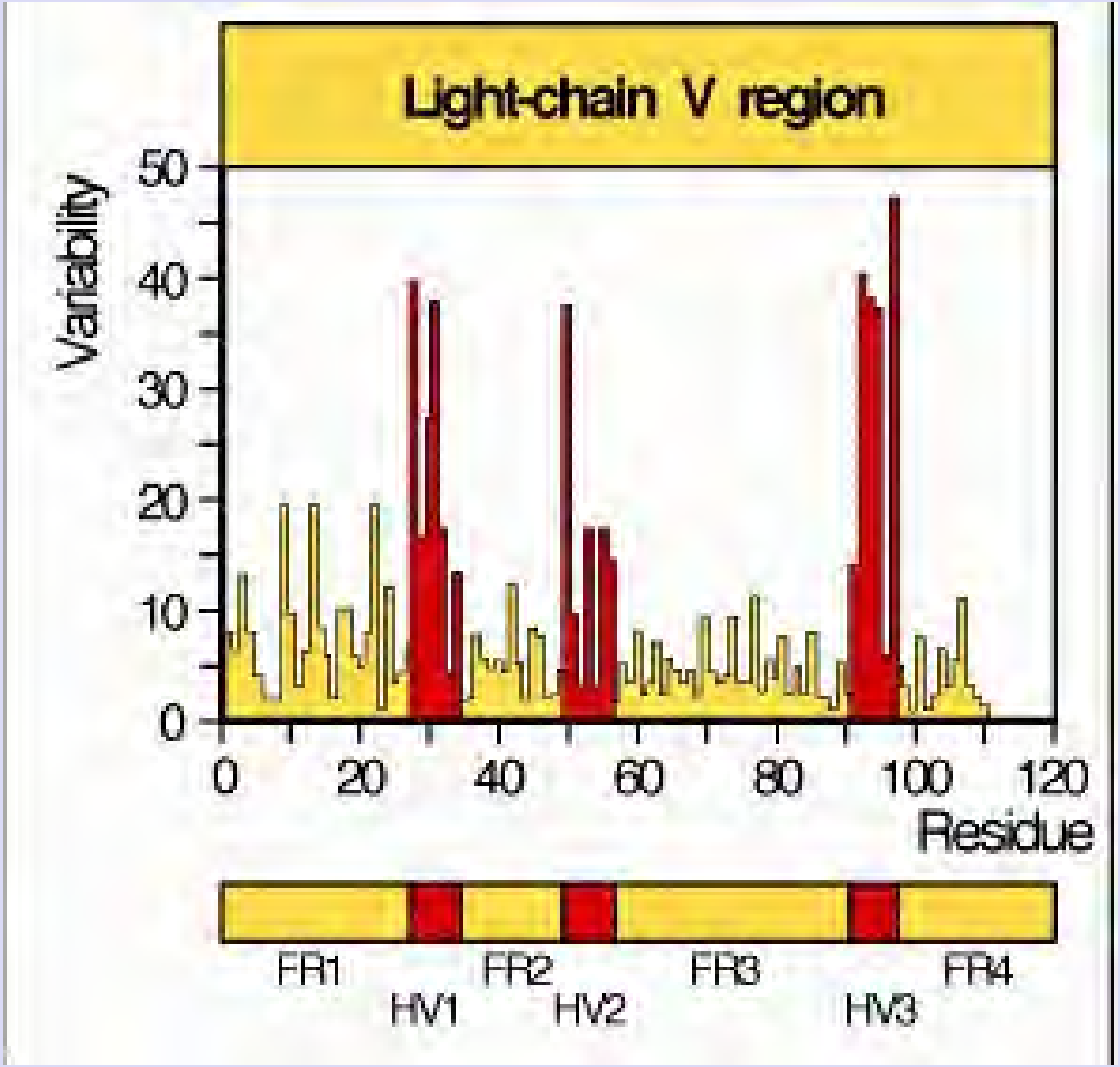
Janeway. Immunobiology: The Immune System in Health and Disease. Current Biology Ltd./Garland Publishing, Inc. 1997

**Variable regions are subdivided into hypervariable regions, which are clusters of residues with variability about 15-100.**

**The large number of different amino acids allow the hypervariable regions to form many different structures with different charge, hydrogen bond, and polarity distributions. The hypervariable regions come together to form the antigen binding site. Hence, another term for the hypervariable region is the complementarity determining region (CDR).**

**Framework regions are the clusters of amino acid residues between the hypervariable regions with variability of 1-20.**

**Framework regions are less variable because they form the scaffold upon which the variable region is built. Some residues within the framework regions are, in fact, invariant. For example, cys at residues 23 and 88.**

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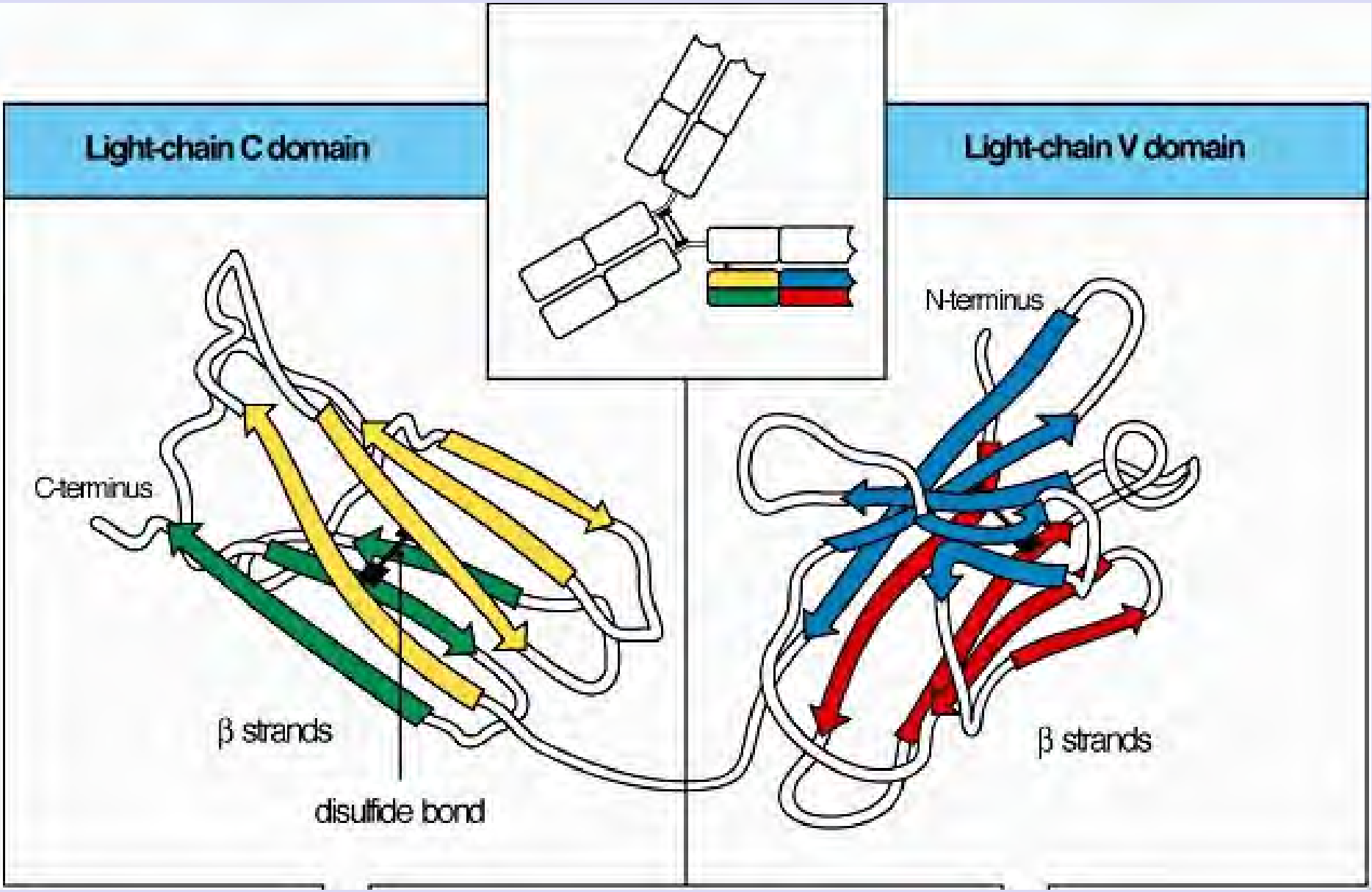
**Domains: ca. 110 amino acid units with disulfide bridge between two cysteines**

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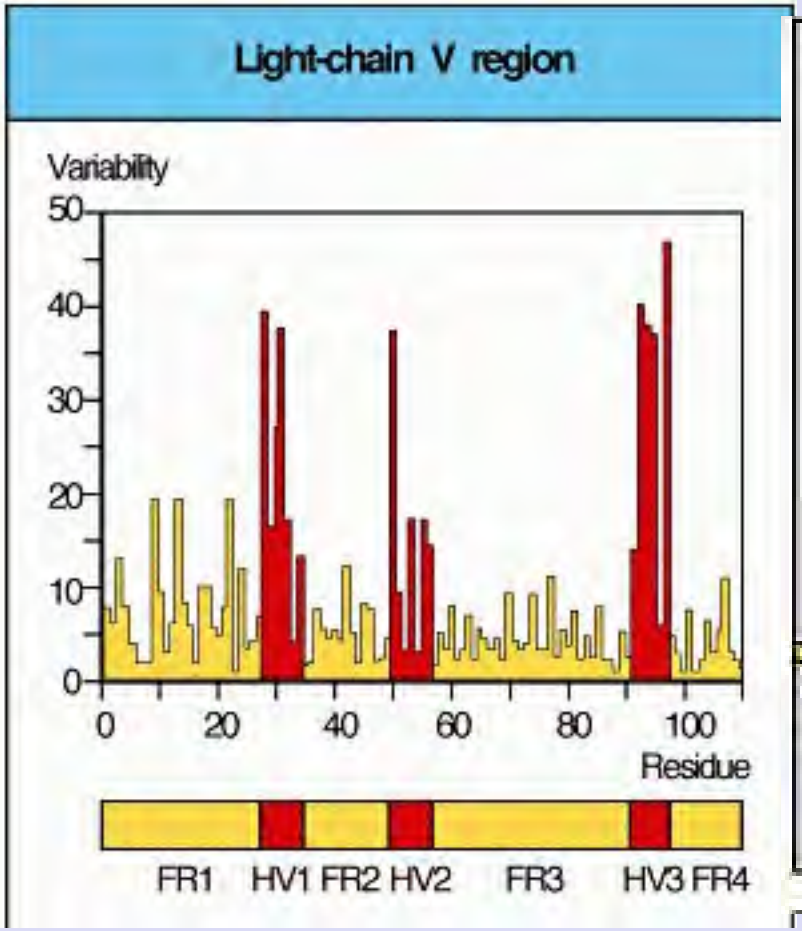


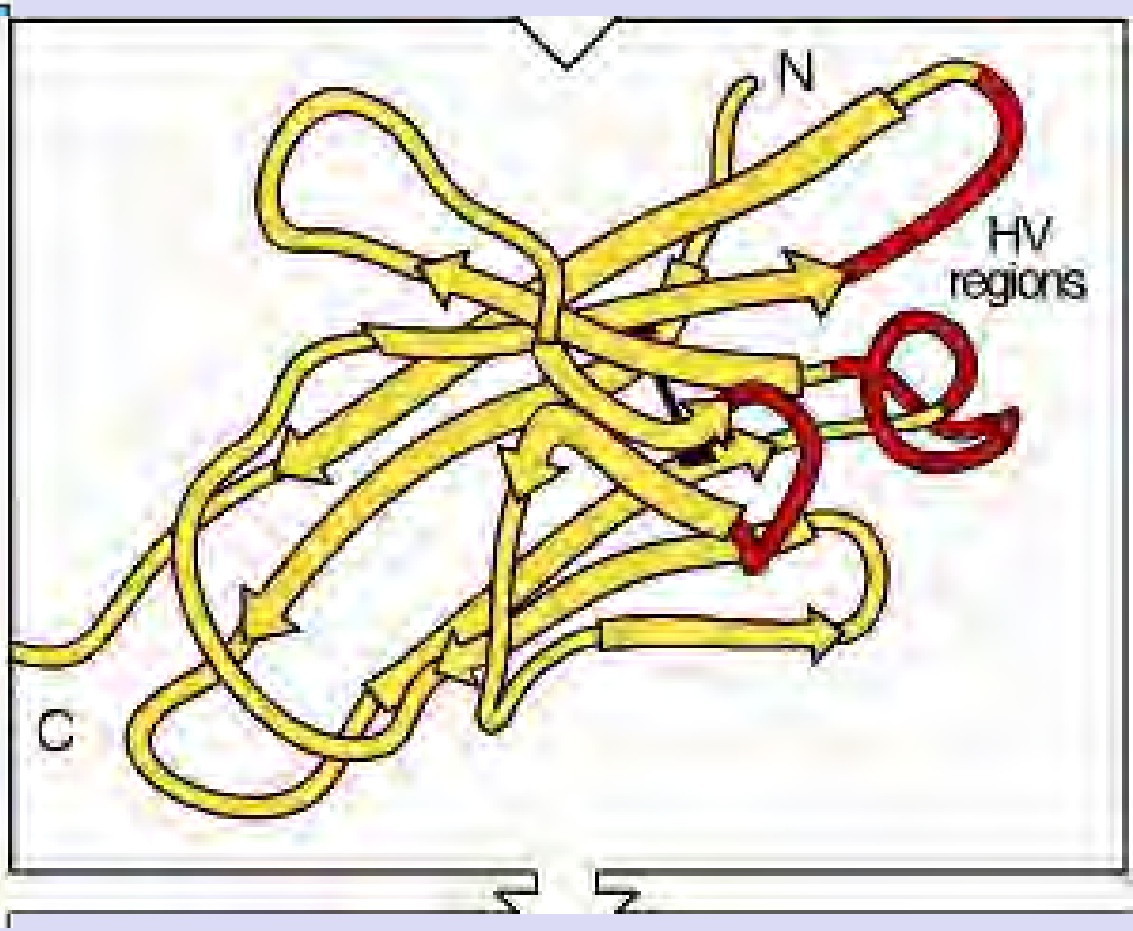


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**1. Variable and constant regions fold the same and are independent of each other. Two sets of parallel beta-pleated sheets perpendicular to the cys--cys bond.**

**2. Hypervariable residues are clustered near each other and form the antigen binding pocket. Hence, they are also called "complementarity determining region (CDR)". For example, in one antibody, tyr and arg interact with an antigenic phosphate via hydrogen bonding and charge neutralization.**

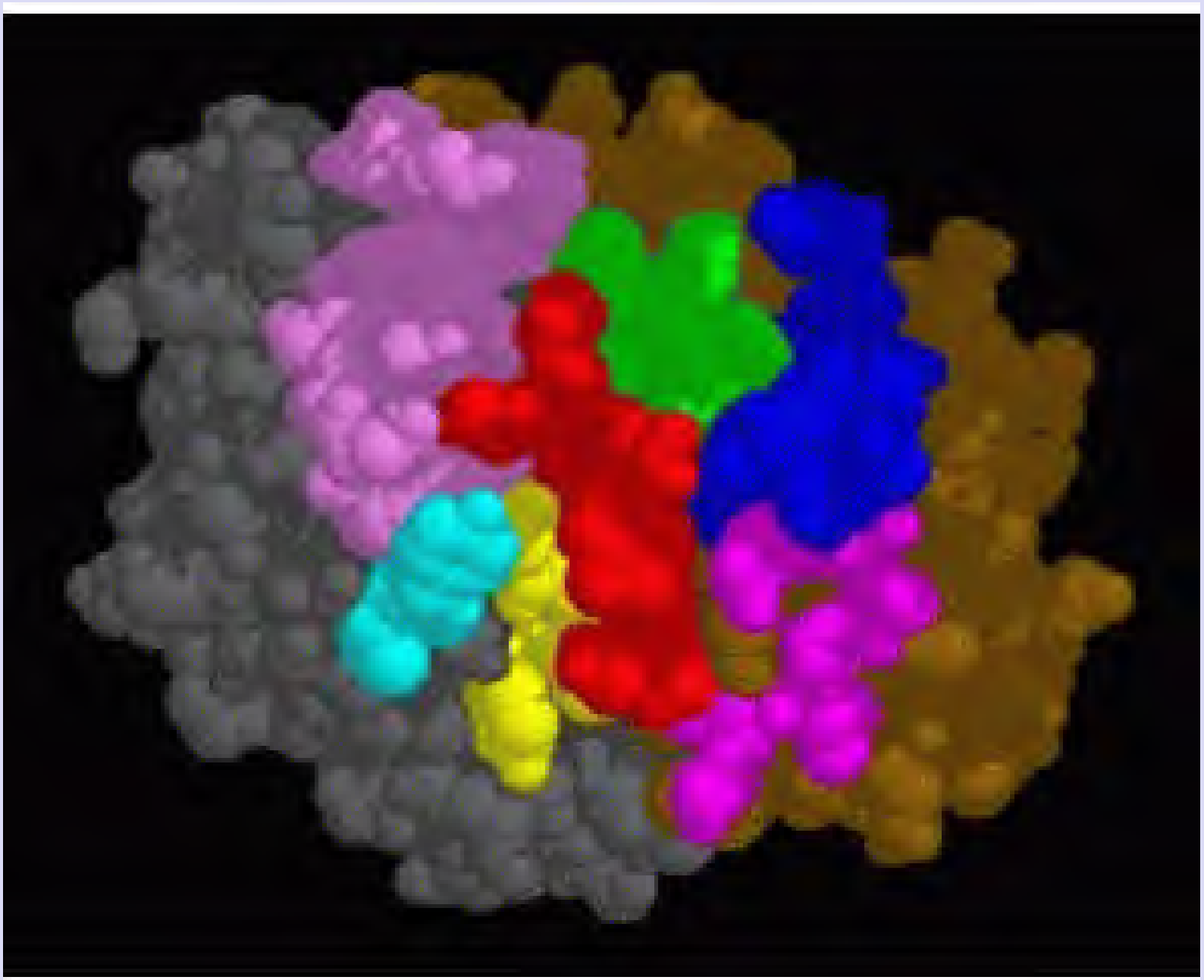
**3. The framework regions form the backbone of the immunoglobulin domain fold. The structure of the complementarity determining region is added upon this domain fold.**

**4. The immunoglobulin fold is used in many other proteins.**

**Space-filling model of an antibody binding its antigen, lysozyme**

**Lysozyme is in red.**

**Hypervariable regions in bright colors.**



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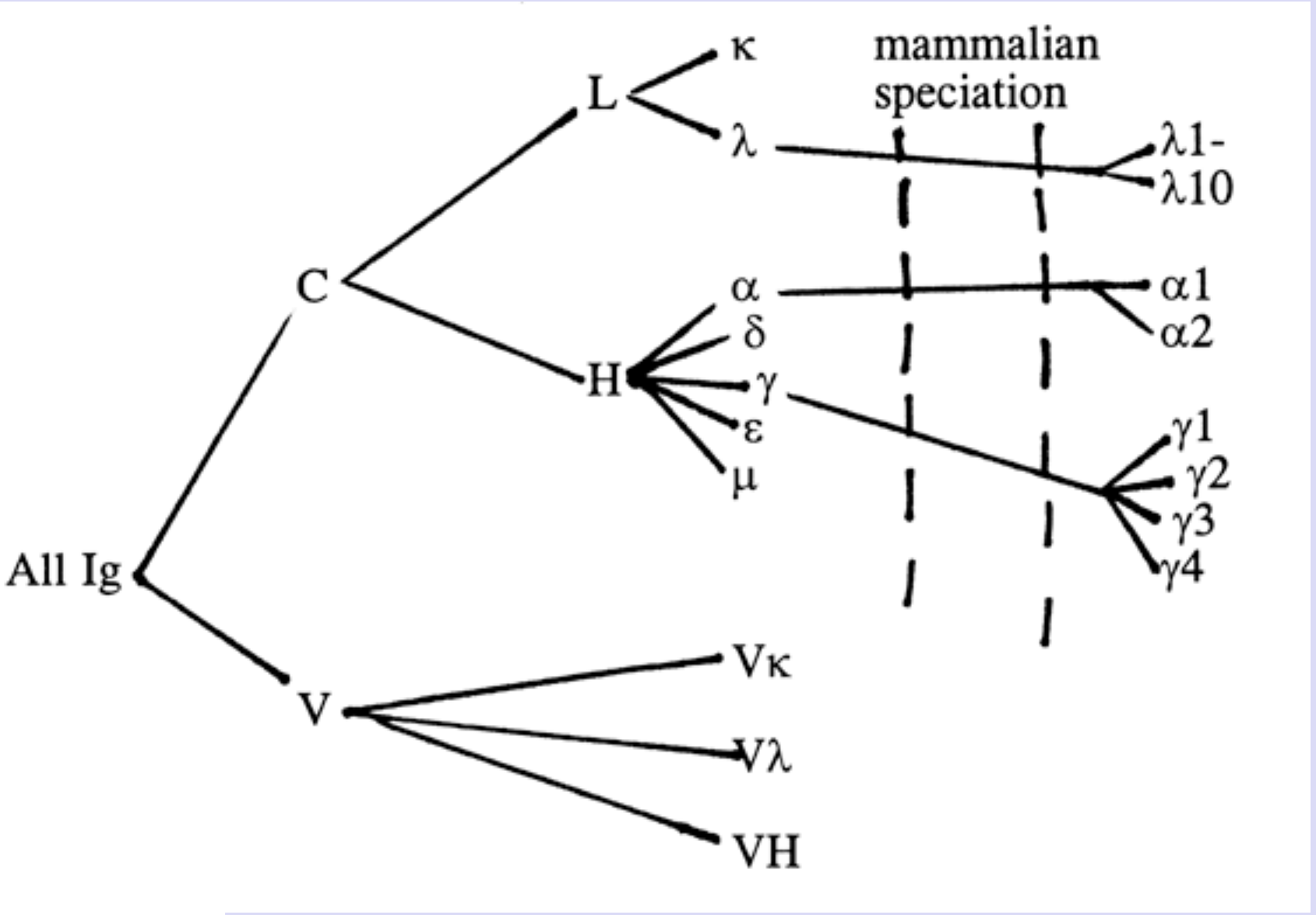


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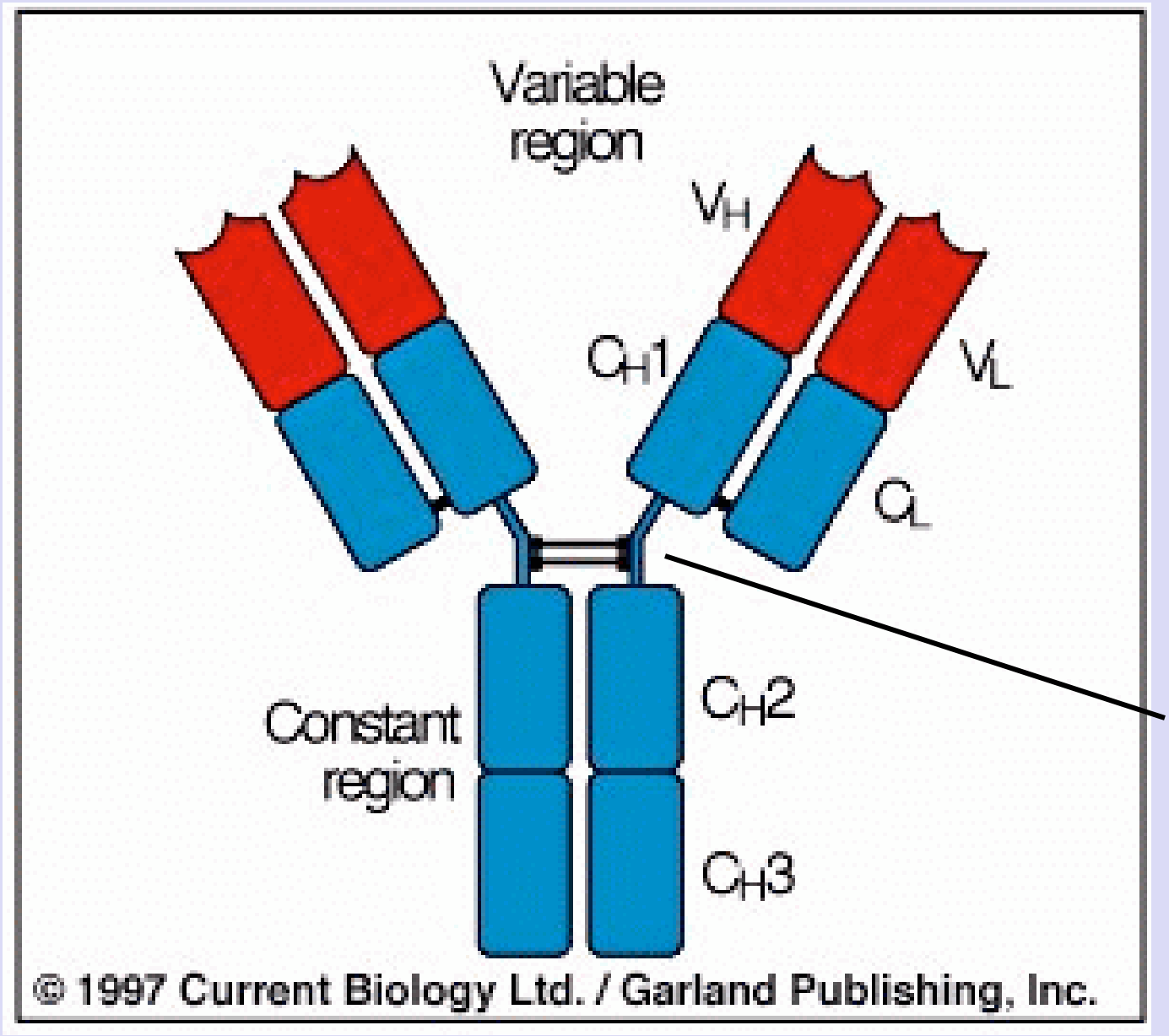
## Structure and function of antibody classes

| Class | H chain | C region domains | pro-rich hinge | serum |
|---|---|---|---|---|
| IgM | μ | 4 | no | 1.5 mg/ml |
| IgG | γ | 3 | yes | 13.5 |
| IgA | α | 3 | yes | 3.5 |
| IgE | ε | 4 | no | 0.003 |
| IgD | δ | 3 | yes | 0.03 |

IgM fixes complement, opsinin
IgG opsinin, some subclasses fix complement, cross placenta
IgA secreted at mucosal surfaces
IgE binds mast cells, allergies
IgD cell surface only




**Hinge**

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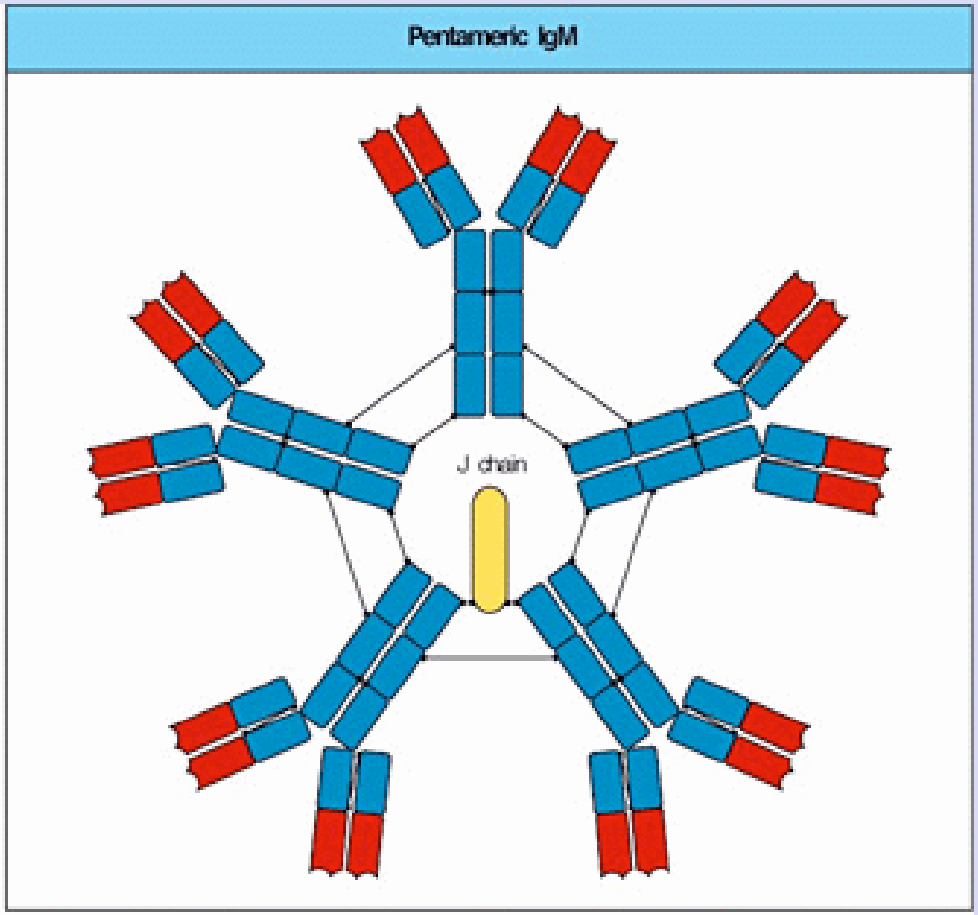
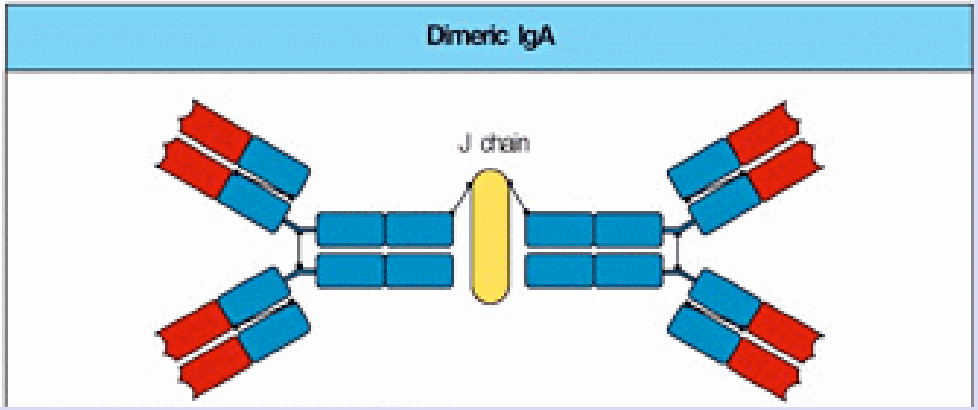
1. An individual immunoglobulin has either a κ or a λ light chain (but not both). Each type of immunoglobulin (e. g., IgG3) has within it immunoglobulins with κ light chains and immunoglobulins with λ light chains.

2. An opsinin is an antibody that enhances phagocytosis.

3. The hinge is a 20-30 amino acid region that is proline rich.

4. IgA includes attached secretory piece (70 kD glycoprotein), which protects IgA against proteolysis.




The secreted forms of IgM and IgA.

Formation of IgA dimers and IgM pentamers require covalent linkage to J chain.

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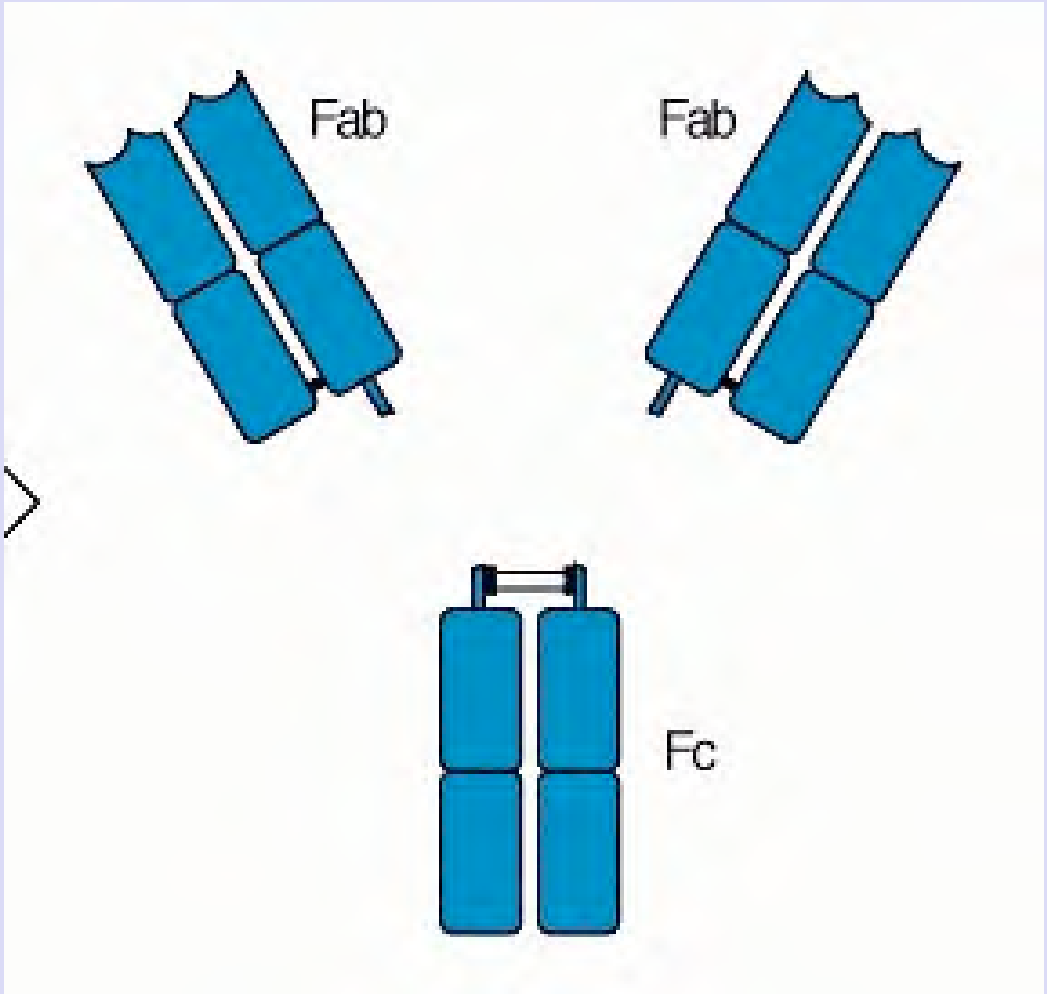
Janeway. Immunobiology: The Immune System in Health and Disease. Current Biology Ltd./Garland Publishing, Inc. 1997

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Fragments created by limited digestion of antibodies with proteolytic enzymes. Each class or subclass of heavy chain has a different amino acid sequence and hence a different Fc region.

**Different effecter functions of different classes and subclasses of antibodies are mediated by binding to specific Fc receptors.**

**Fcε RI on mast cells, eosinophils**

**poly Ig receptor on mucosal epithelia**

**Fcγ receptor on macrophages, neutrophils, eosinophils, etc.**

**Hence, because each subclass has a different constant region, different Fc receptors bind different classes and subclasses of immunoglobulins. Therefore, each subclass of immunoglobulin has a specific set of effecter functions. Even though all antibodies can use the same set of variable regions (bind the same epitopes), when those variable regions are found on different constant regions, the way a pathogen is handled <u>after binding</u> is different for each subclass.**

**It is important that an individual directs the expression of the appropriate subclass for a given pathogen.**

**Summary:**

1. **Five types of heavy chains (α, γ, δ, ε, and μ) and two types of light chains (κ and λ).**

2. **Both heavy and light chains have variable regions and constant regions.**

**3. The 110- (approximately) amino acid domain is the basic building block of an immunoglobulin.**

4. **Hypervariable regions fold together to form the complementarity determining region.**

   **Framework regions form the immunoglobulin domain fold.**

5. **Different antibody subclasses and classes have different structures and different functions.**

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