



IMMUNOGLOBULIN G

Marina Cabasés, Laura Ciaran, Marta Díez, Laura Enriquez

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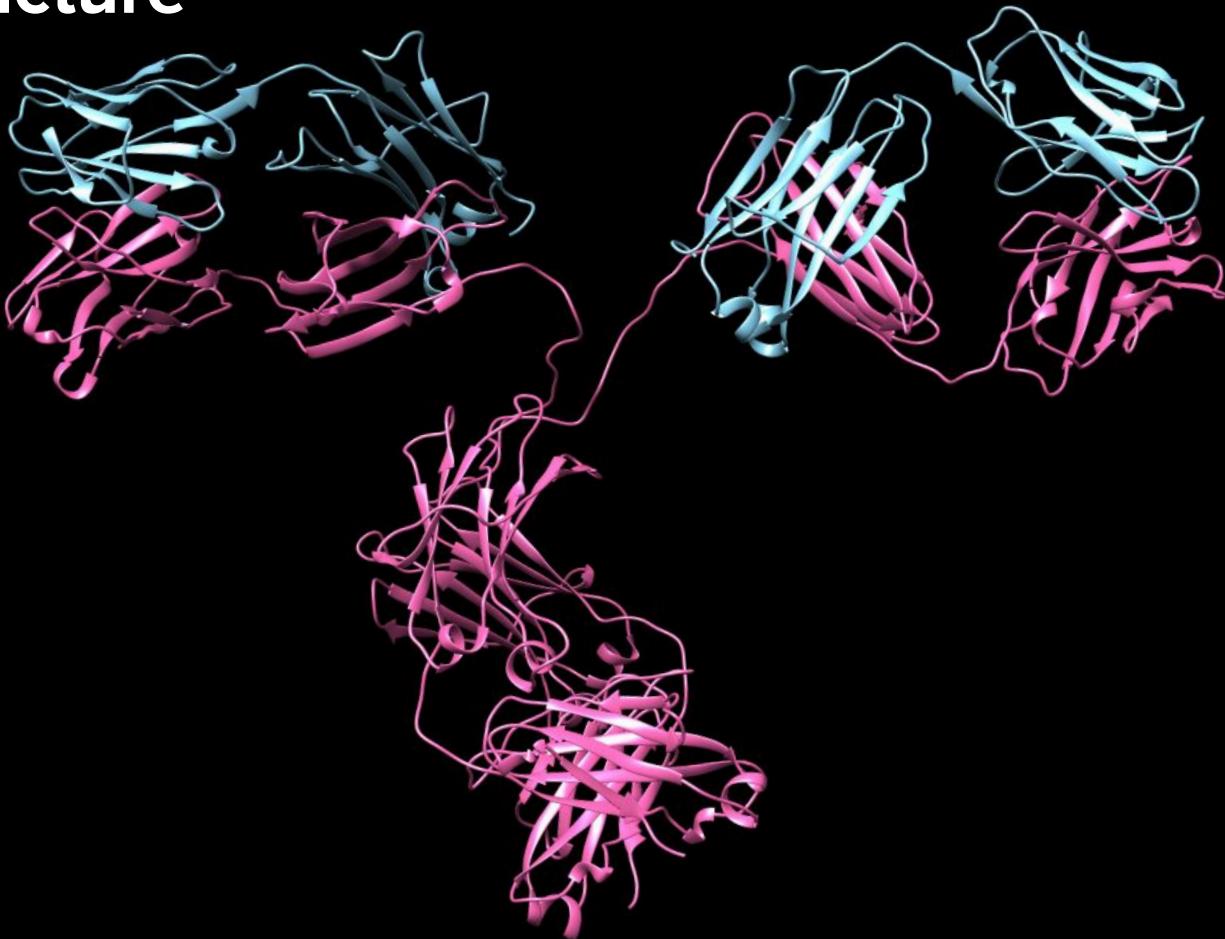
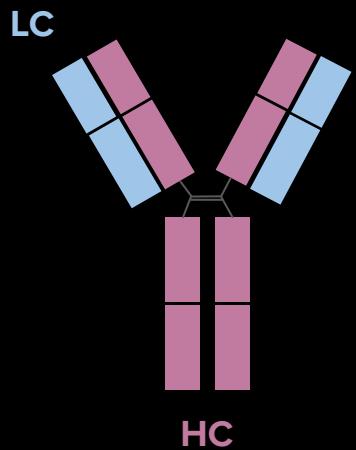
6. IgG - antigen interaction

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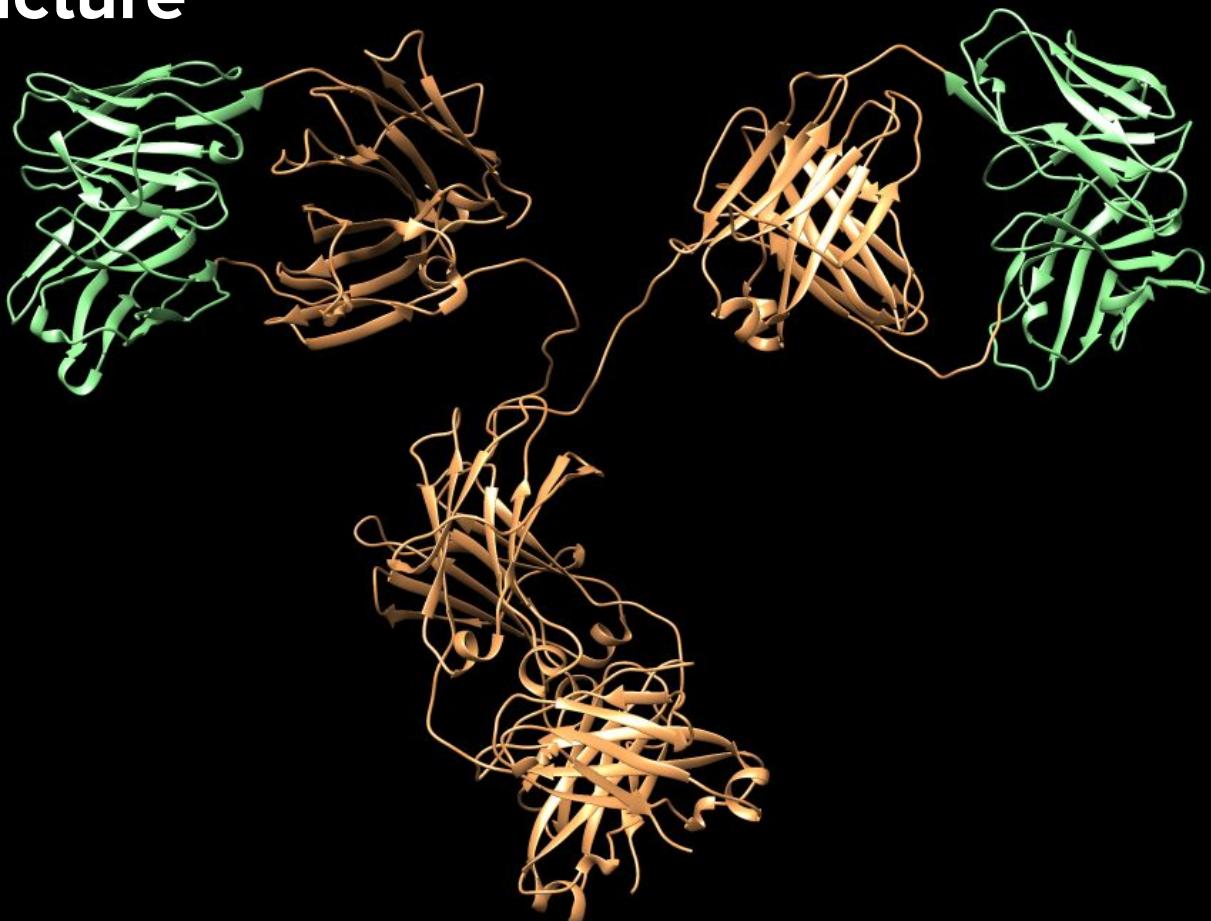
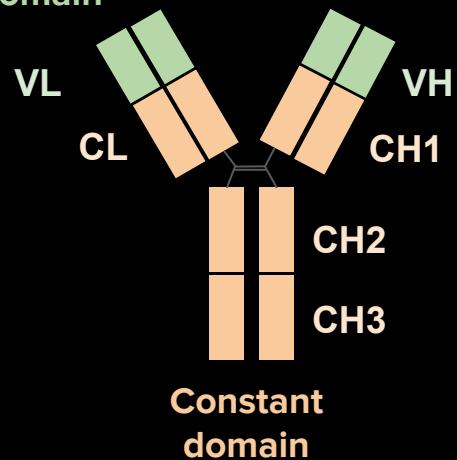
BASIC CONCEPTS

Introduction: Structure

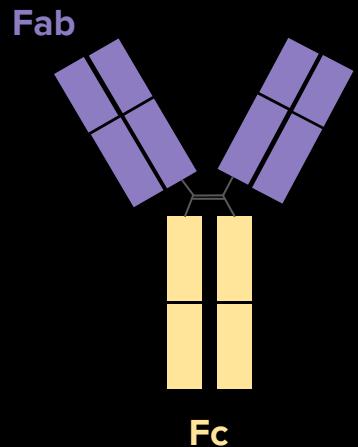


Introduction: Structure

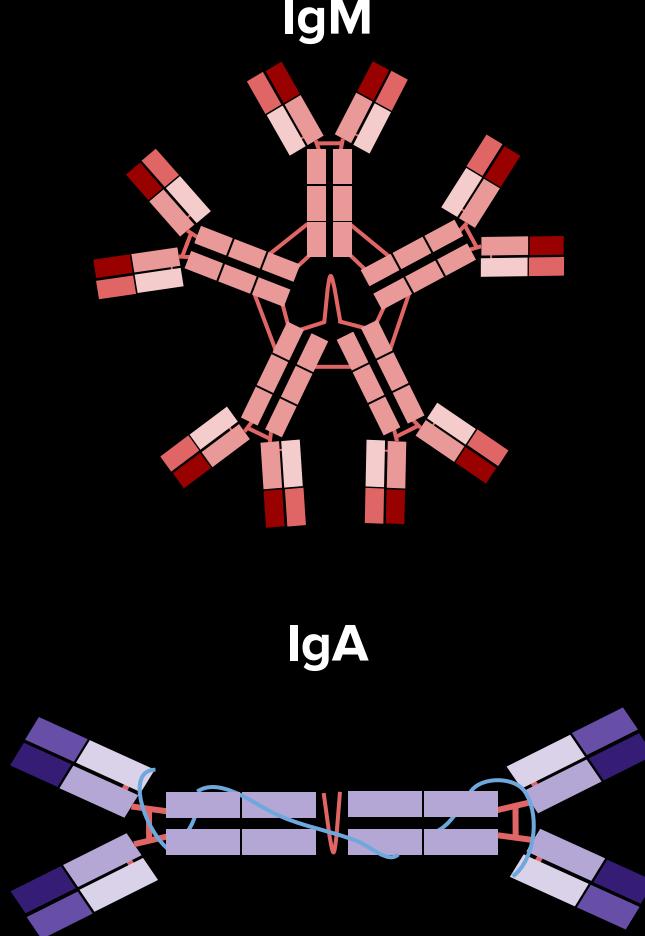
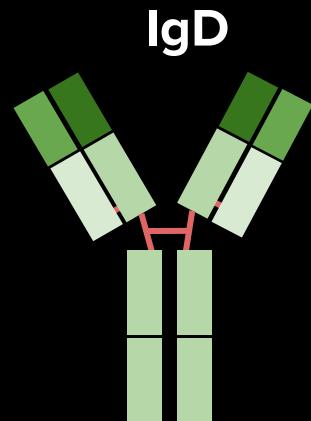
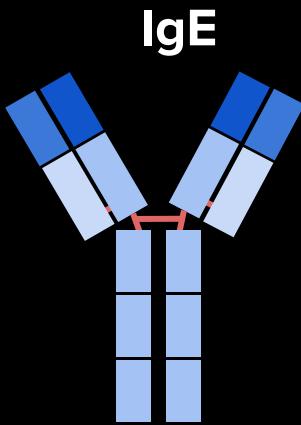
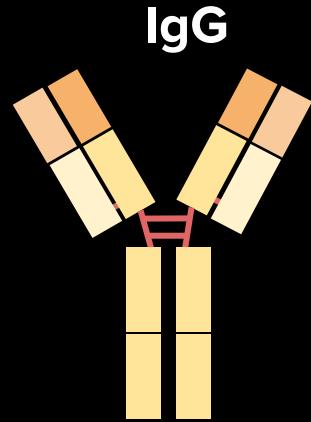
Variable
domain



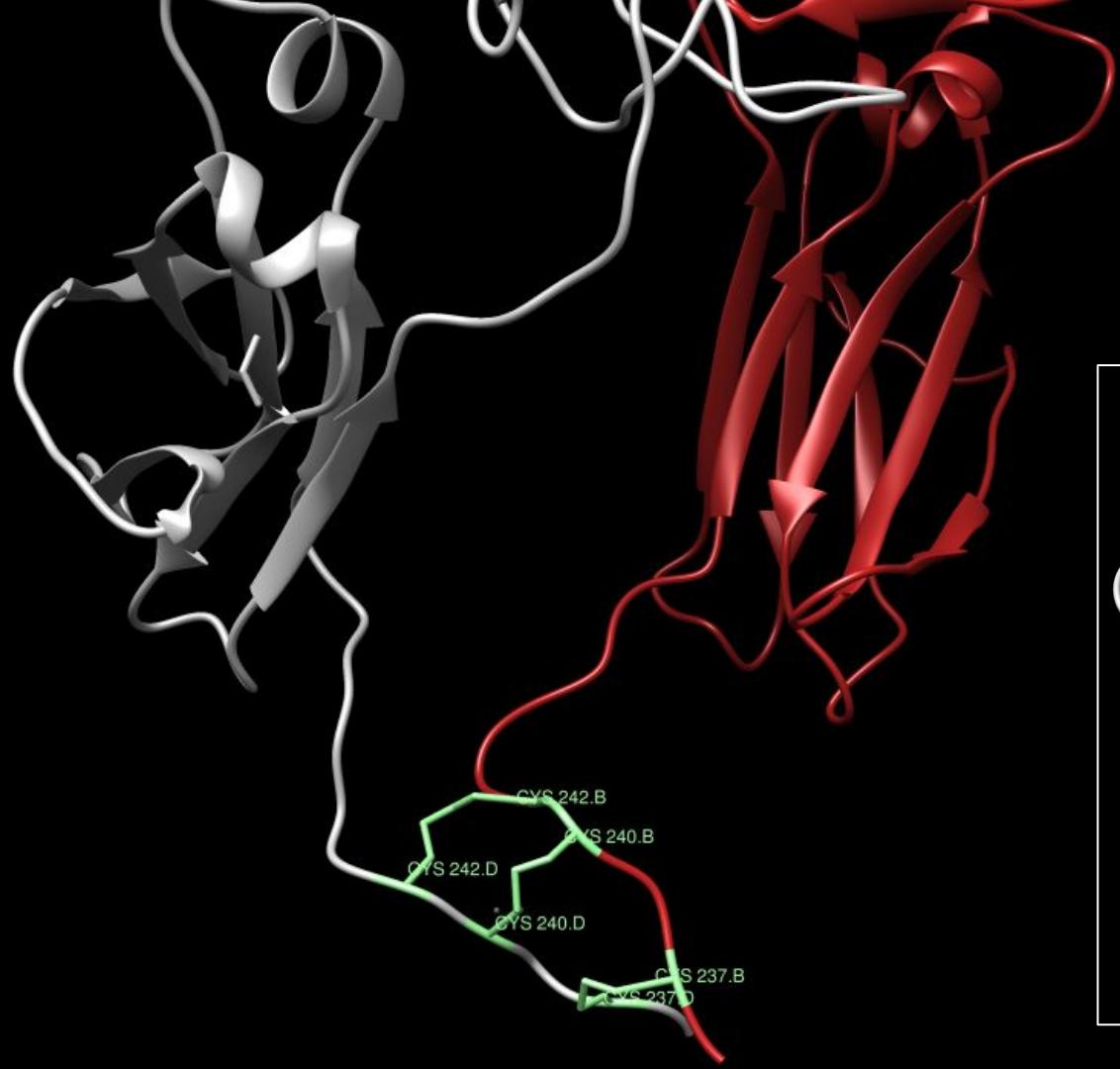
Introduction: Structure



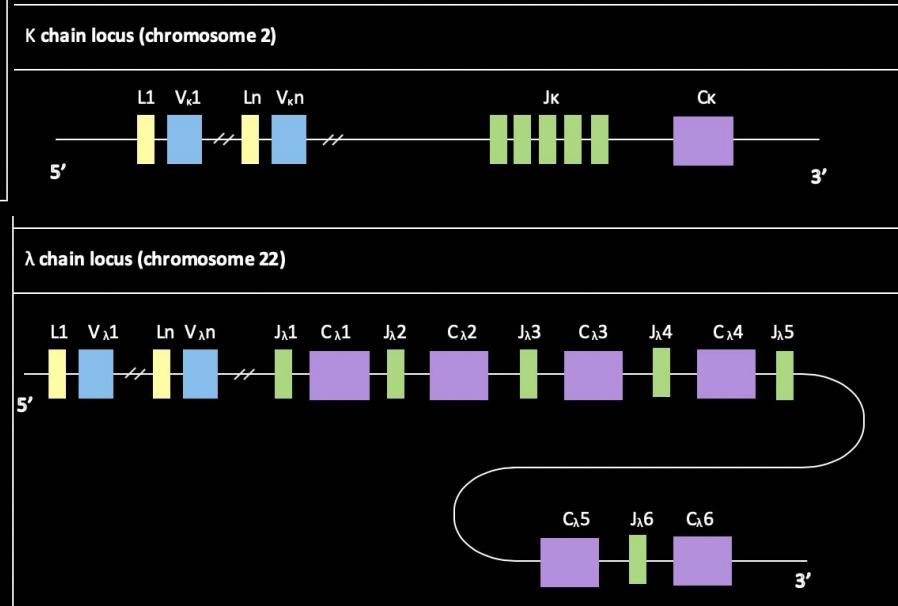
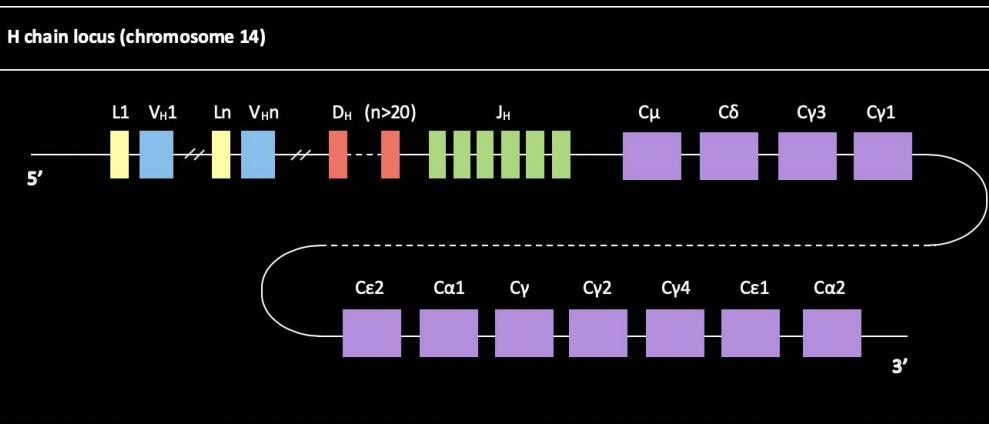
Introduction: Isotypes



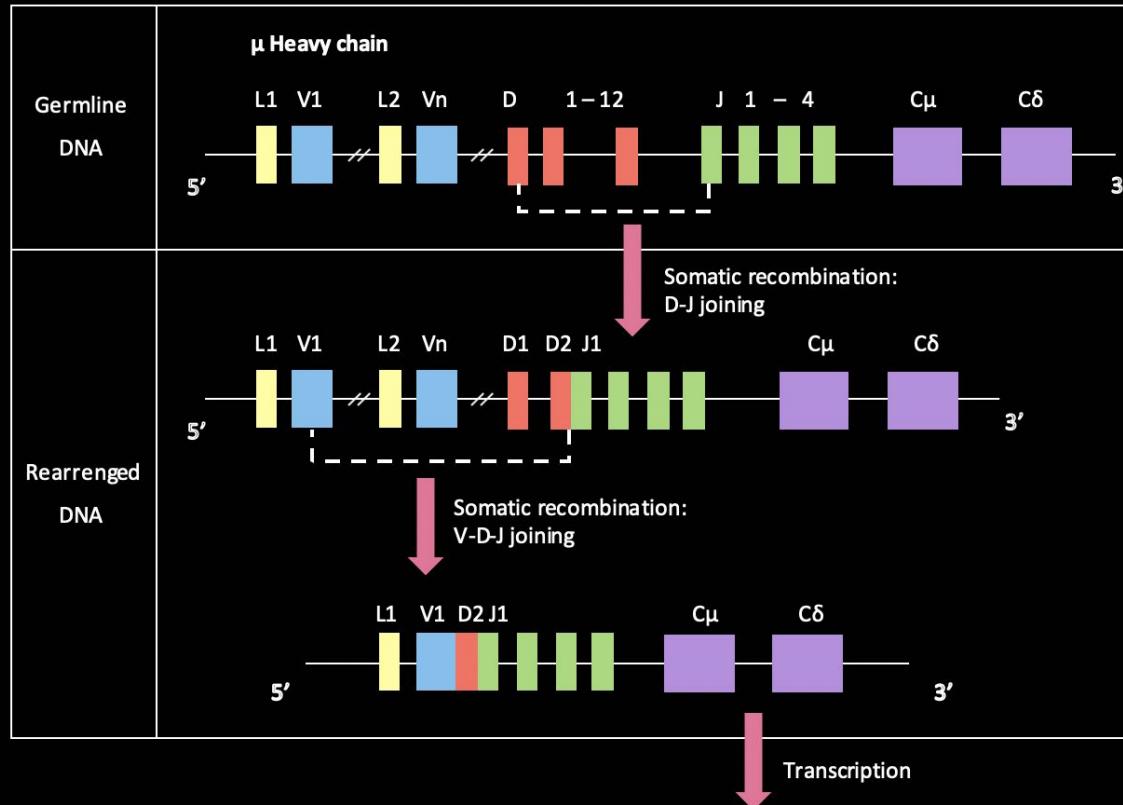
Introduction: Stabilization



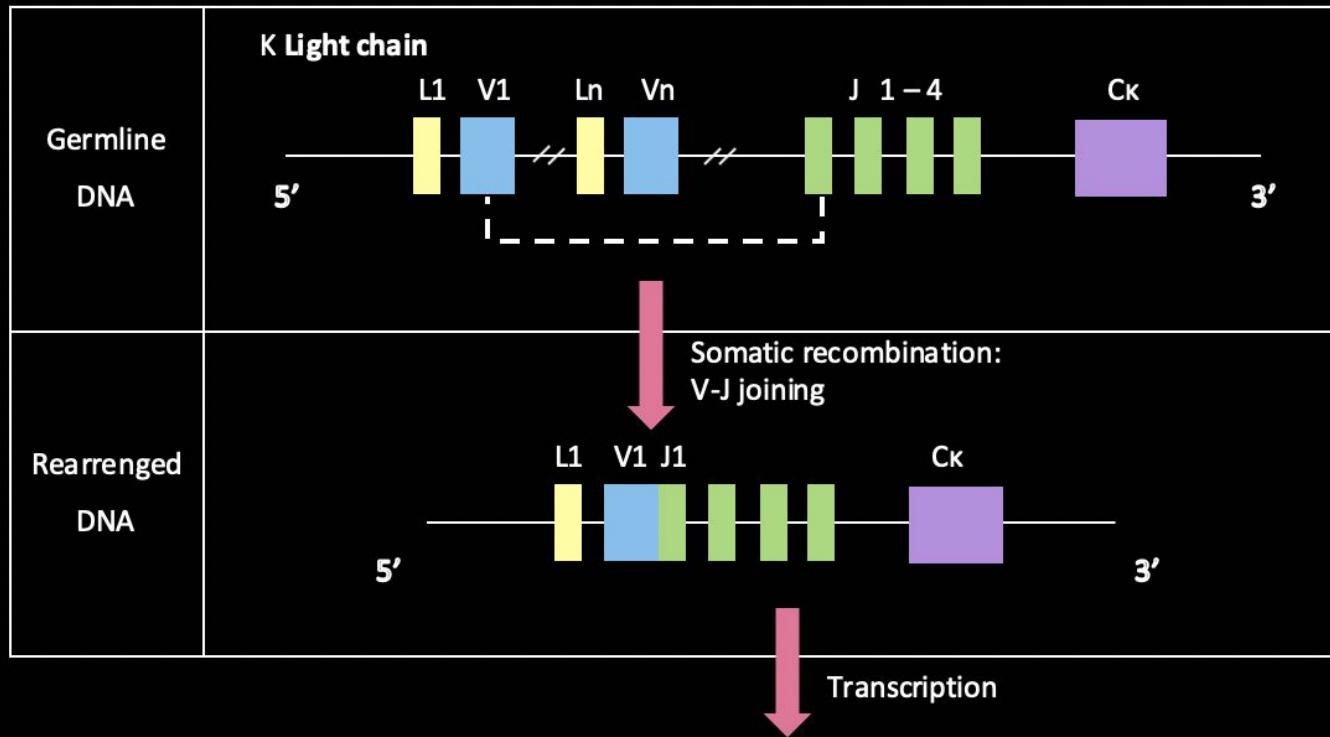
Introduction: Immunoglobulin rearrangement



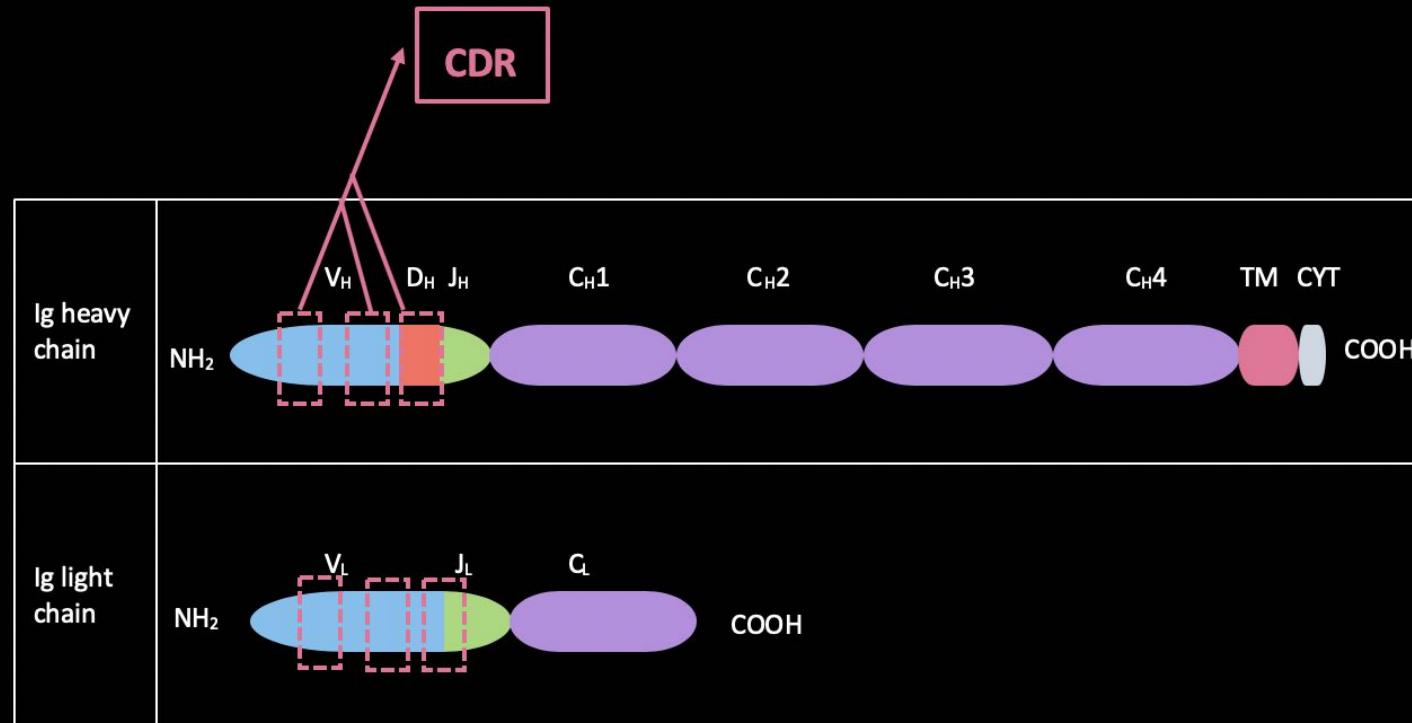
Introduction: Immunoglobulin rearrangement



Introduction: Immunoglobulin rearrangement



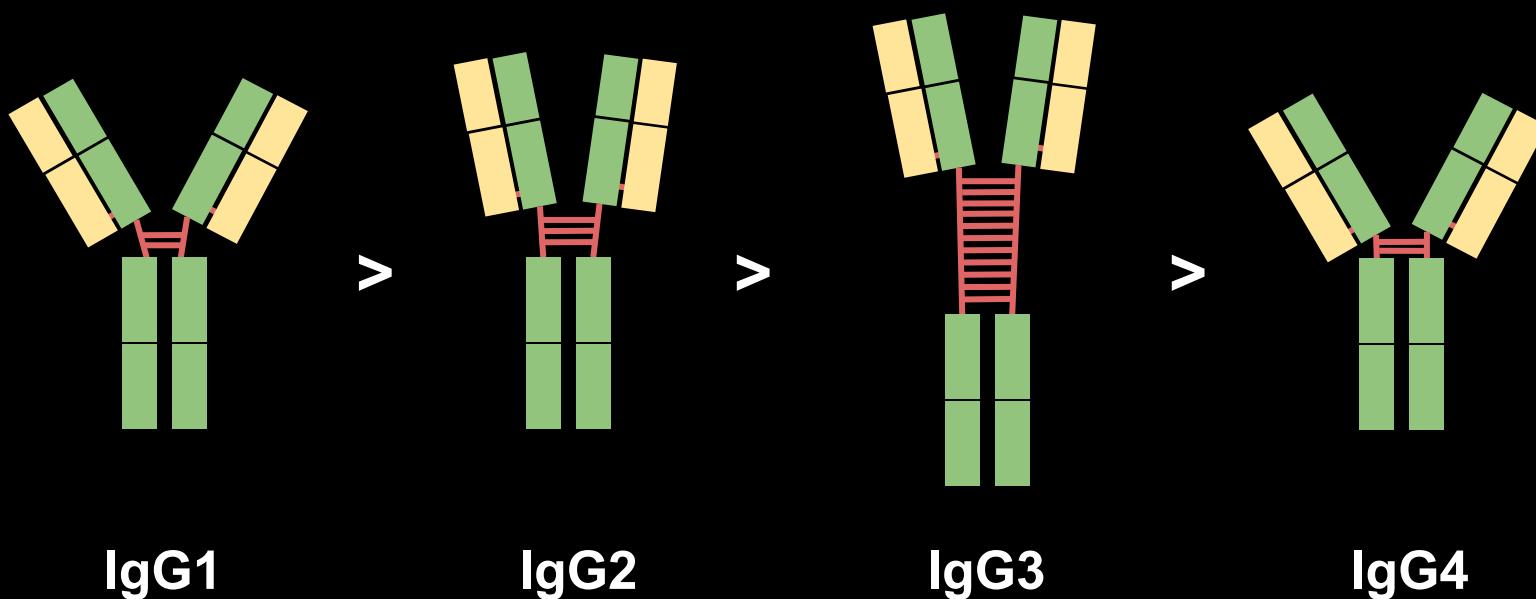
Introduction: Immunoglobulin rearrangement



IMMUNOGLOBULIN G

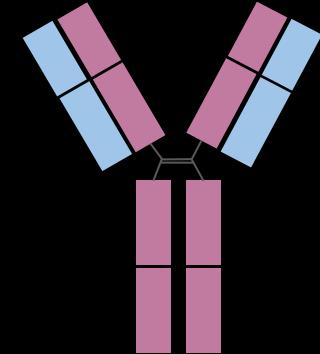
Immunoglobulin G: subclasses

The four subclasses of IgG differ in the structure of the hinge

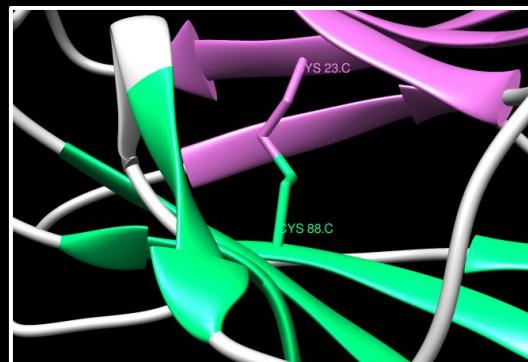
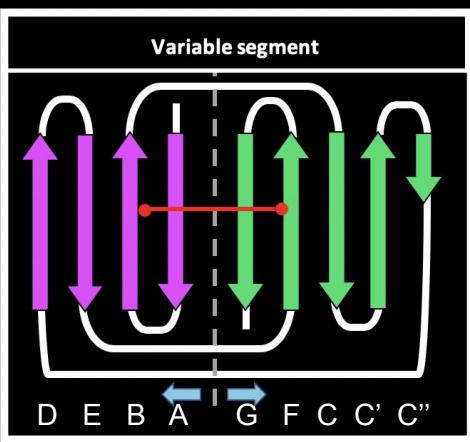
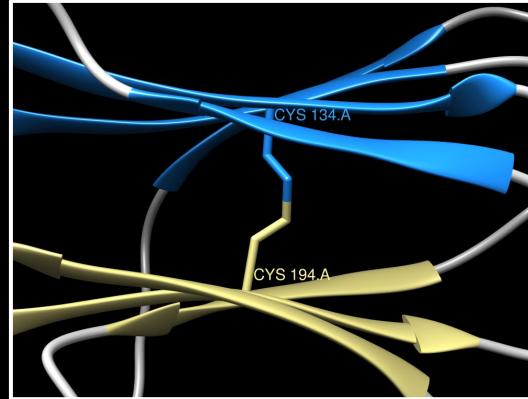
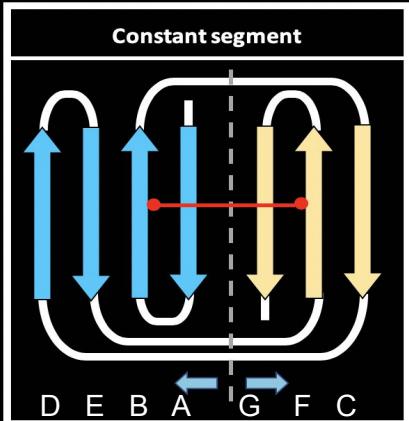
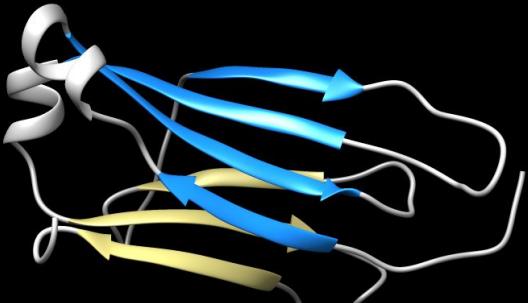
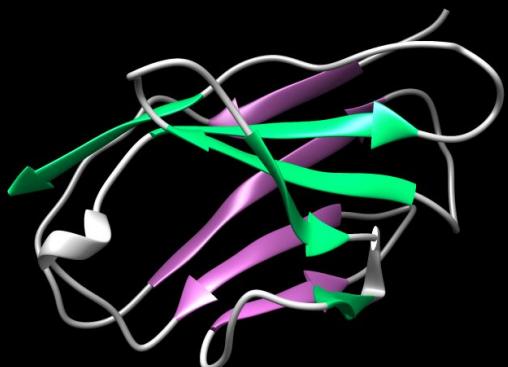
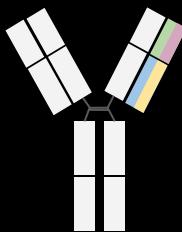


Immunoglobulin G: SCOP classification

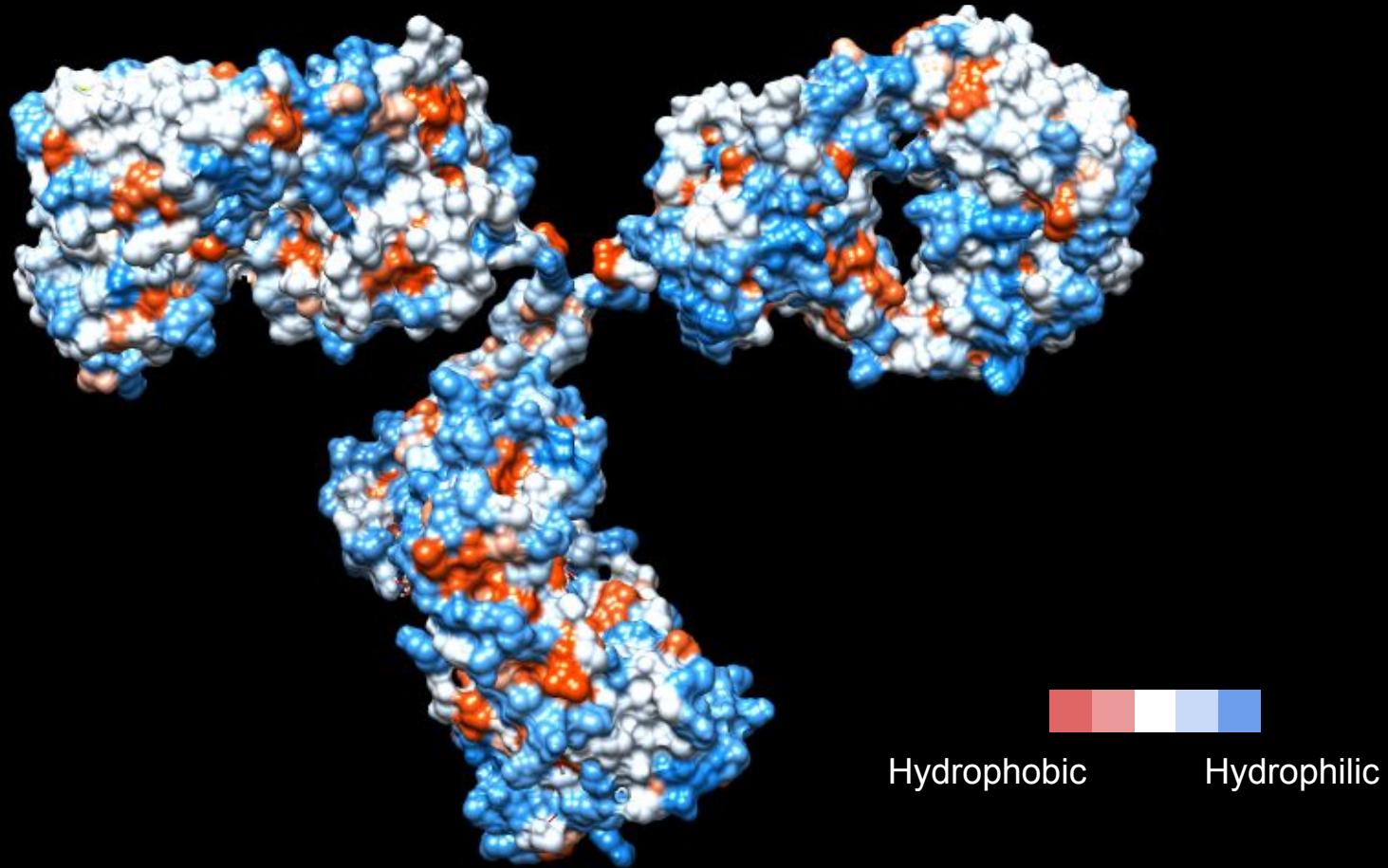
- Class → All-β proteins
- Fold → Immunoglobulin like
- Superfamily → Immunoglobulin
- Family:
 - **V set domains: antibody variable domain-like**
 - I set domains: are found in several cell adhesion molecules.
 - **C1 set domains: antibody constant domain-like**
 - C2 set domains: Ig-like domains resembling the antibody constant domain



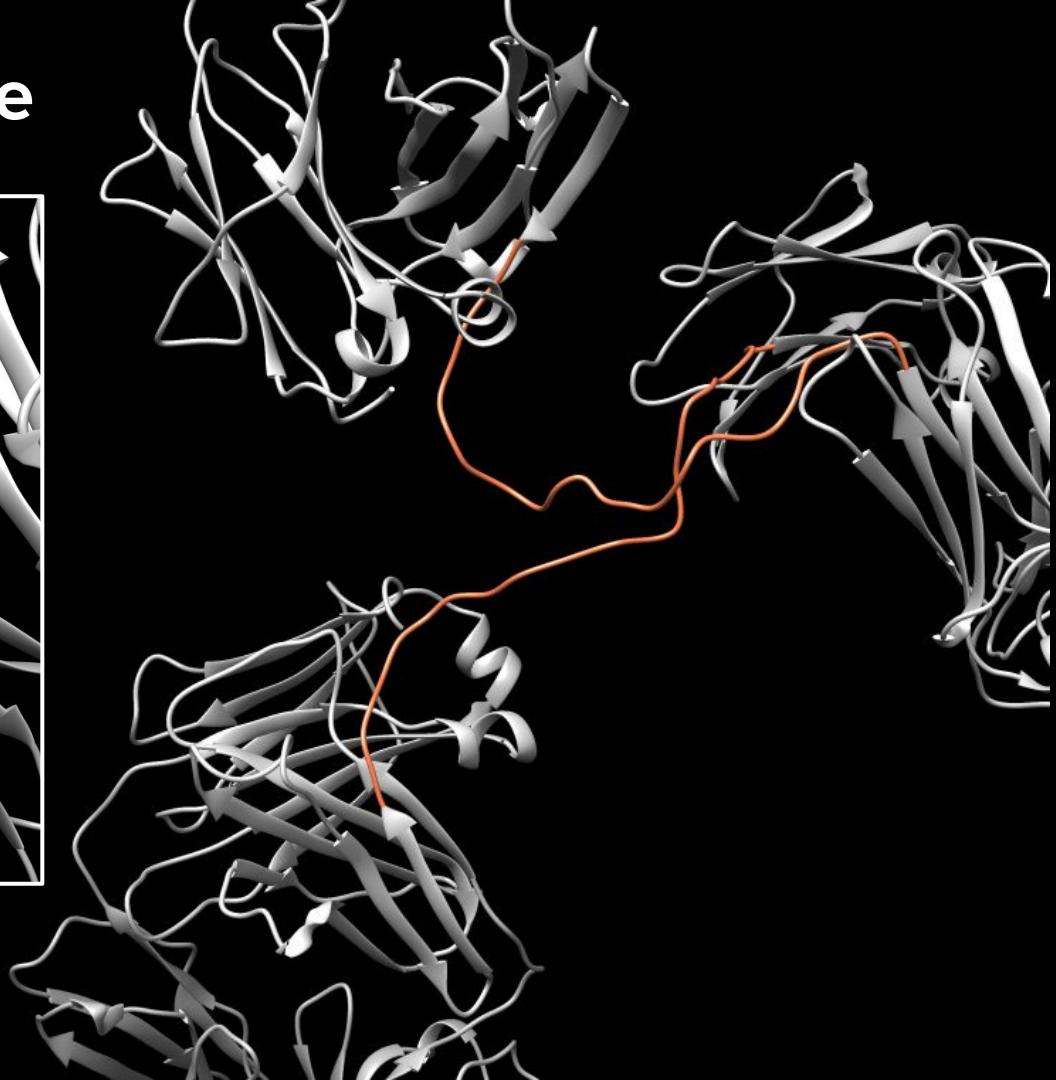
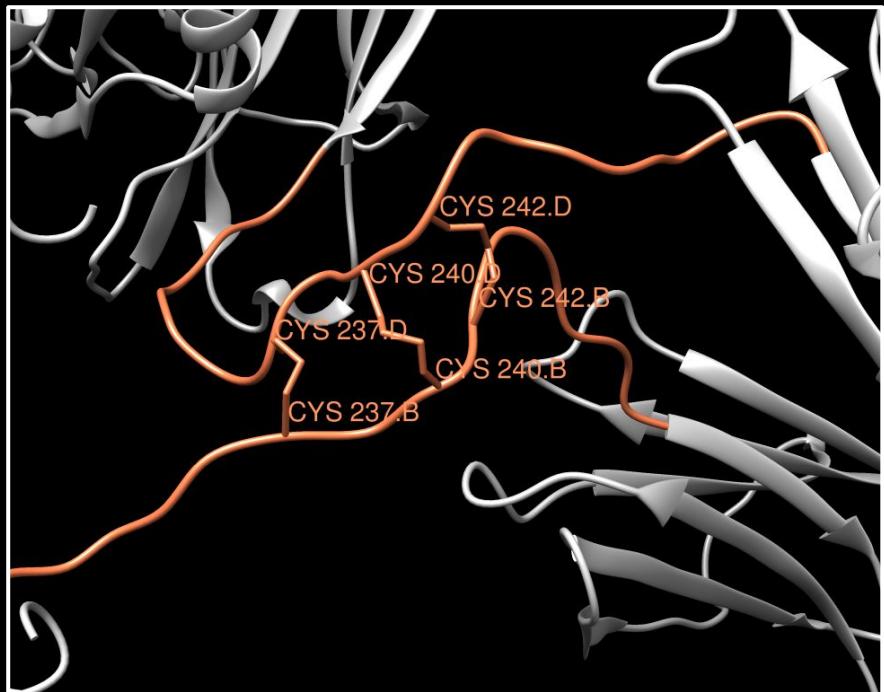
Immunoglobulin G: Fold



Immunoglobulin G: Architecture

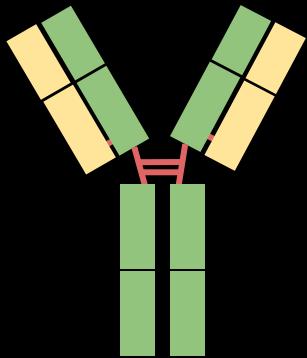


Immunoglobulin G: Hinge

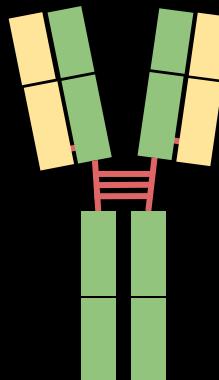


Immunoglobulin G: hinge

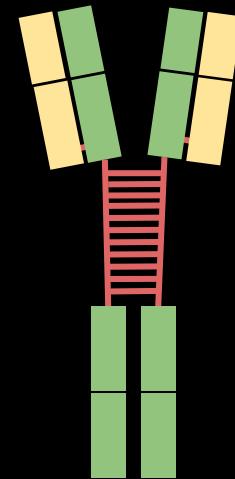
The four subclasses of IgG differ in the structure of the hinge



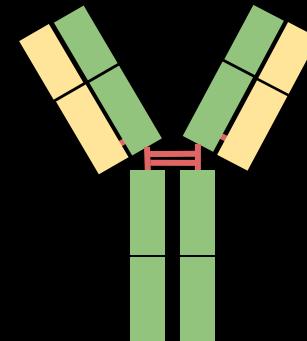
IgG1



IgG2



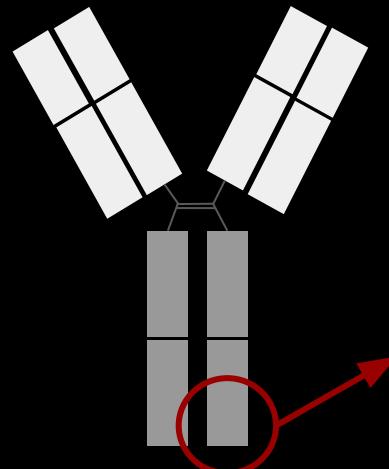
IgG3



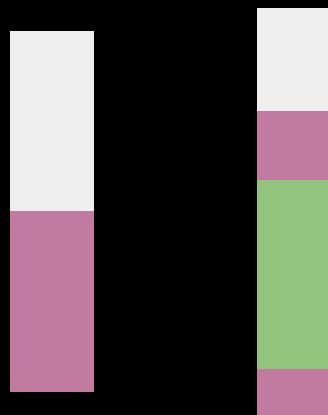
IgG4

IgG FRAGMENT CRYSTALLIZABLE REGION (Fc)

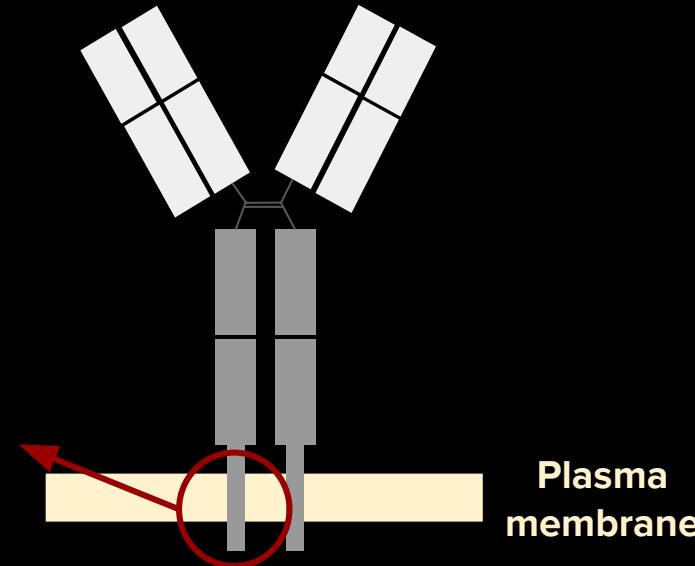
Fc: Soluble vs Surface



Soluble antibody



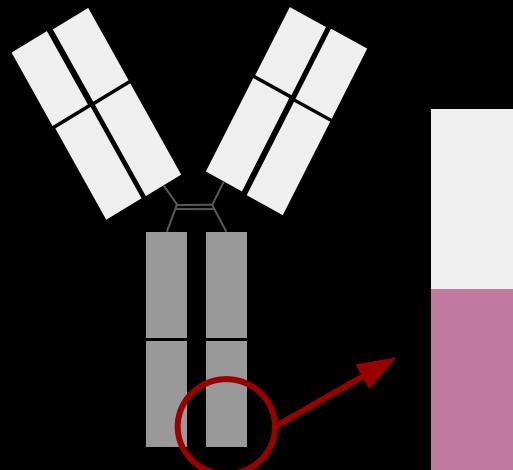
Hydrophilic
Hydrophobic



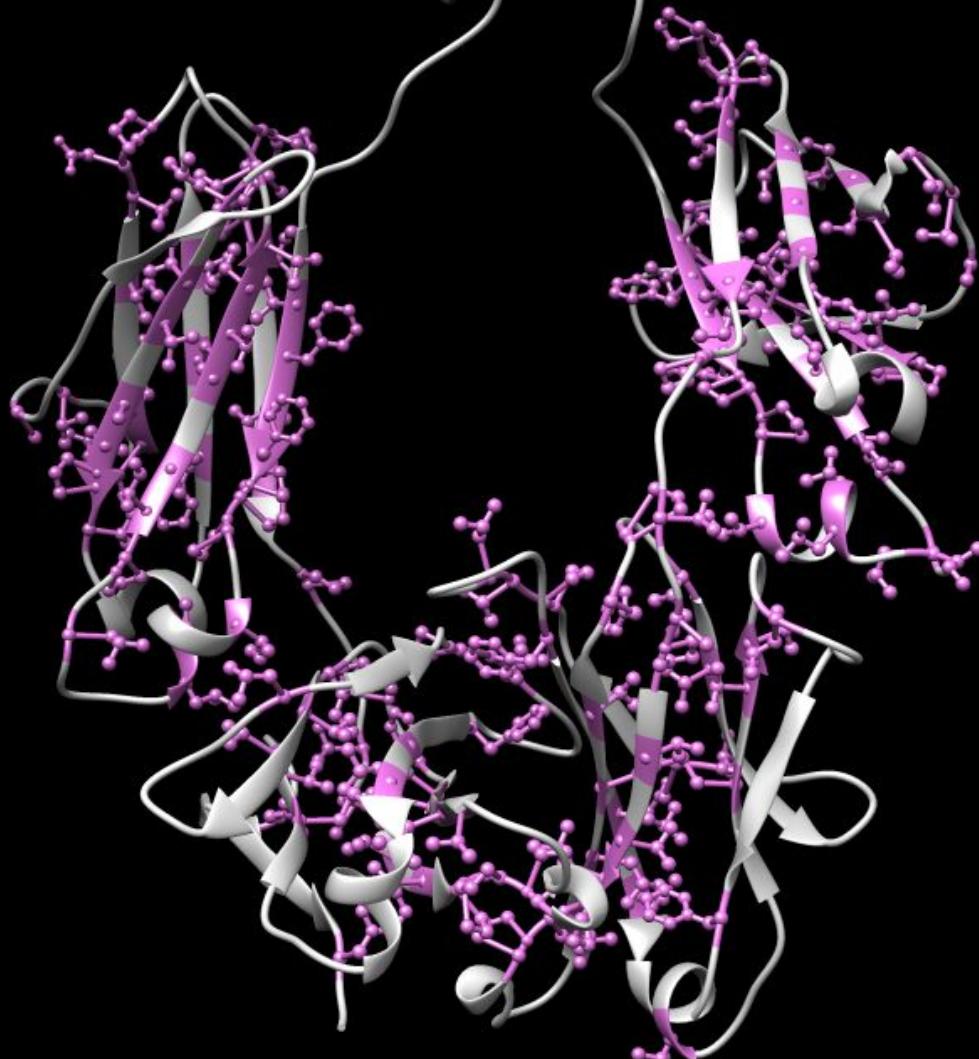
Surface antibody

Plasma
membrane

Fc: Soluble IgG

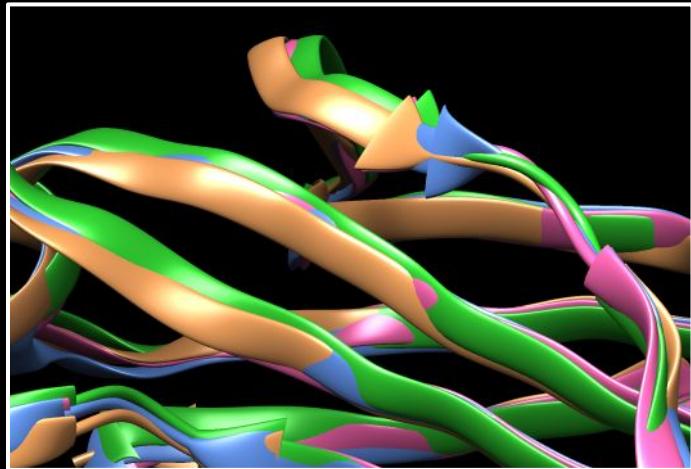
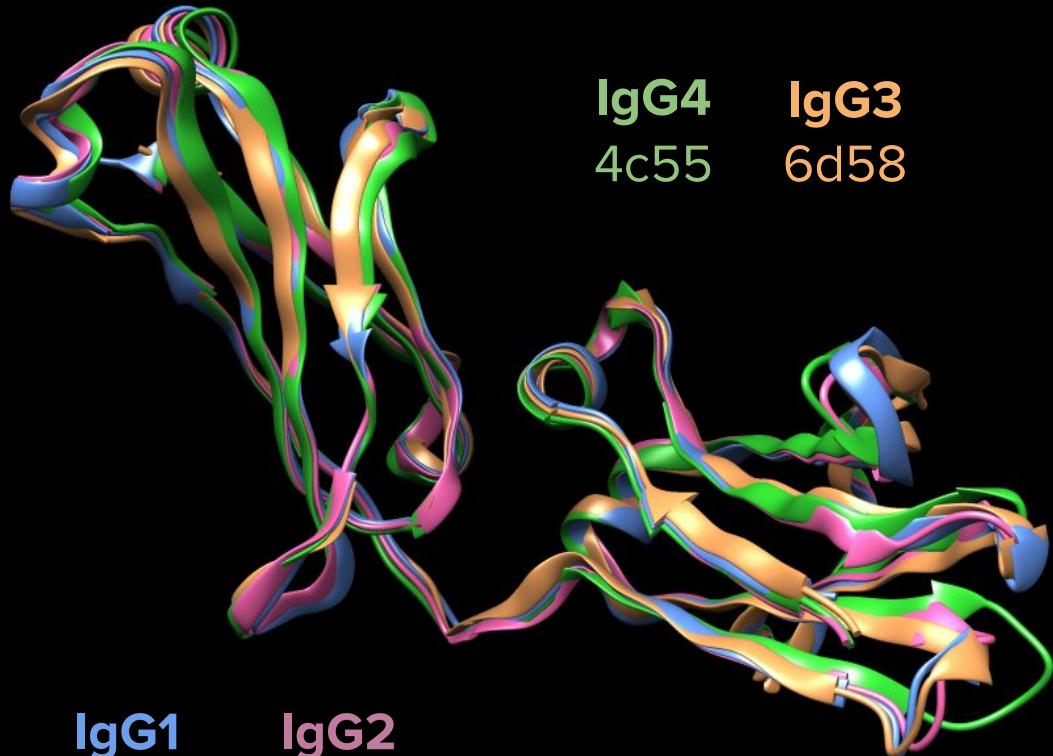


Soluble antibody



Fc: Subtypes comparison

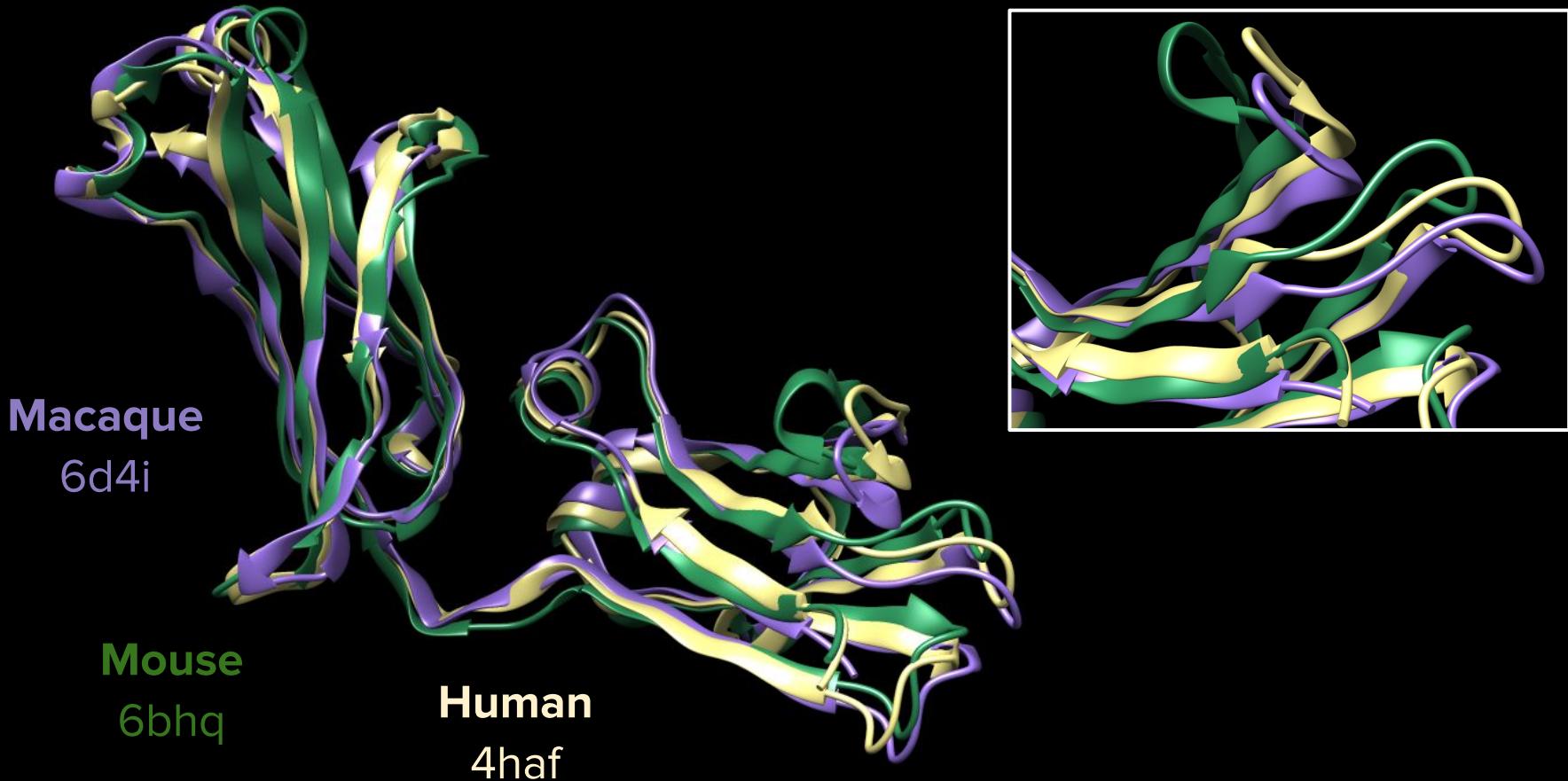
Fc: Subtypes comparison



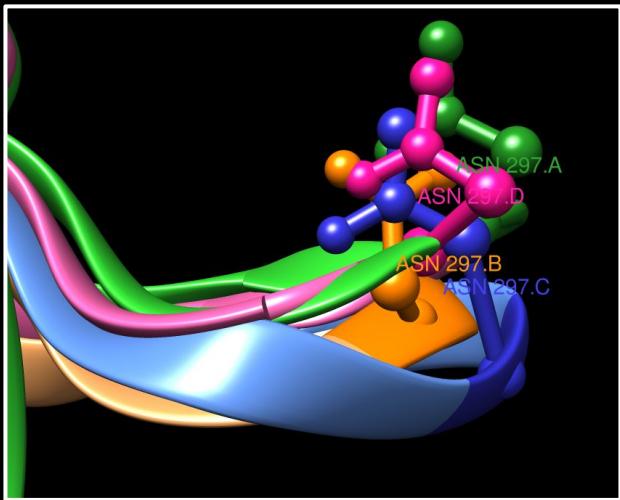
Fc: IgG2 among species

4HAF	VECPPCPAP-PVAGPSVFLFPPPKDTLMISRTPEVTCVVVDVSHEDPEV
6BHQ	KECPPCAAPDLLGGPSVFIGPPKIKDVLMISLSPMVTCVVVDVSEDDPDV
6D4I	STCPCPAE-LLGGPSVFLFPPPKDTLMISRTPEVTCVVVDVSQEEPDV *****.* :*****:**** *.* *** :* *****.*:***:*
4HAF	QFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKV
6BHQ	QISWFVNNVEVHTAQQTQTHREDYNSTLRVSVALPIQHQDWMSGKEFKCKV
6D4I	KFNWYVDGVEVHNAQTKPREEQFNSTYRVSVLTVTHQDWLNGKEYTCKV :***:***:***:***:***:***:*** .***:***:***:***
4HAF	SNKGLPAPIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
6BHQ	NNRALPSPIEKTI SKPRGPVRAPQVYVLPPPAEEMTKKEFSLTCMITGFL
6D4I	SNKALPAPRQKTVSKTKGQPREPQVYTLPPPREELTKNQVSLTCLVKGFY .***:***:***:***:***:***:***:***:***:***:***:***
4HAF	PSDI AVEWESNGQPENNYKTPPPMLDSDGSFFLYSKLTVDKSRWQQGVNF
6BHQ	PAEI AVDWTSNGRTEQNYKNTATVLDSDGSYFMYSKLRVQKSTWERGSLF
6D4I	PSDI VVEWESNGQPENTYKTPPVLDSDGSYFLYSKLTVDKSRWQQGNTF * :***:***:***:***:***:***:***:***:***:***:***:***
4HAF	SCSVMHEALHNHYTQKSLSLSPGK
6BHQ	ACSVVHEGLHNHLTTKTI SRSLGK
6D4I	SCSVMHEALHNHYTQKSLSLSPGK :***:***:***:***:***:***

Fc: IgG2 superimposition

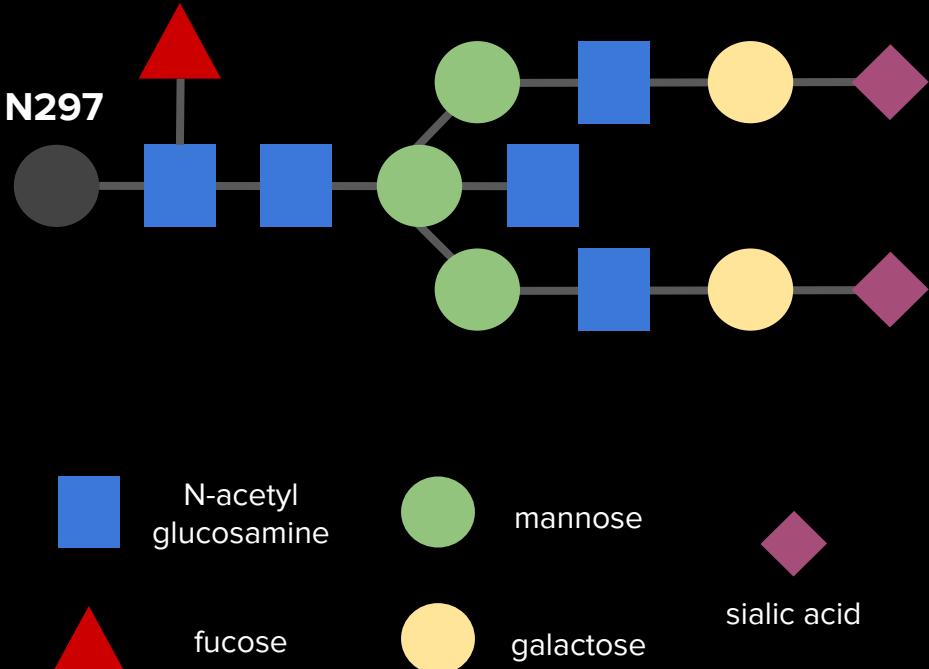
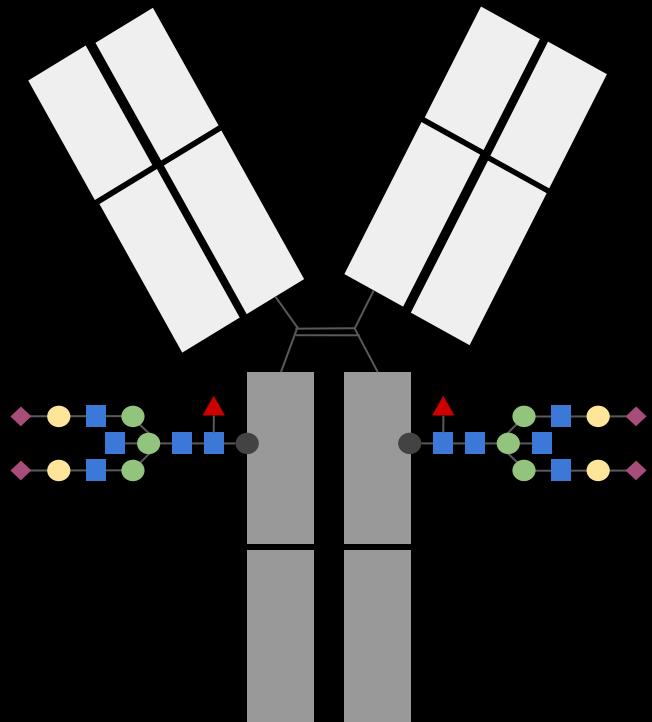


Fc: N-glycosylation



Asn 297

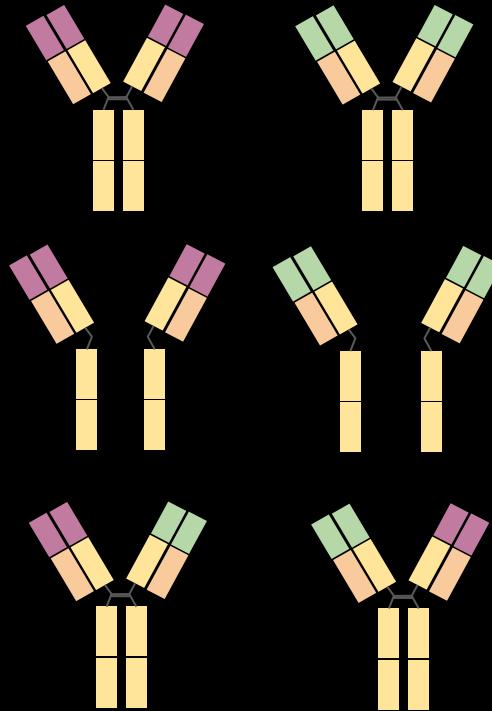
Fc: N-Glycosylation



IgG4 Fab-ARM EXCHANGE (FAE)

FAE

- Separation of the 2 IgG4 heavy chains to form 'half-molecules' comprising just 1 heavy and light chain.
They recombine to create bispecific antibodies.
- Two determinants enable IgG4 to undergo FAE, namely the core hinge and the Cy3–Cy3 domain interface
- Imply both covalent and non-covalent interactions

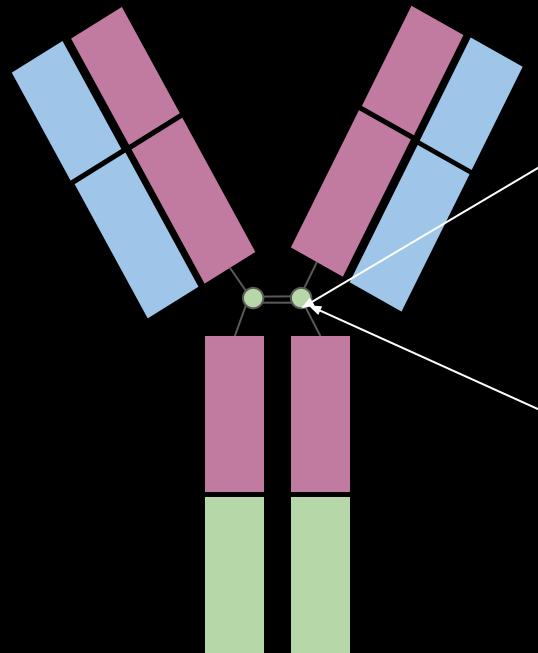


228

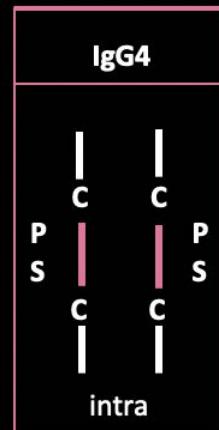
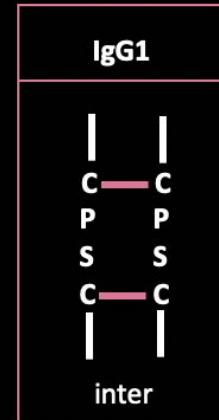
IgG1 EPKSCDKTHTCPPCPAPELLGGP

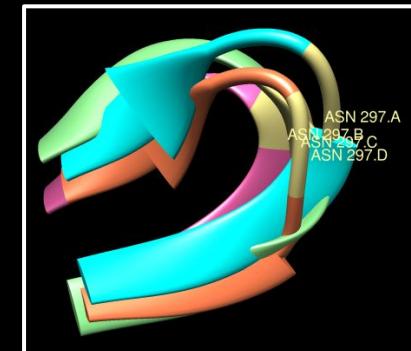
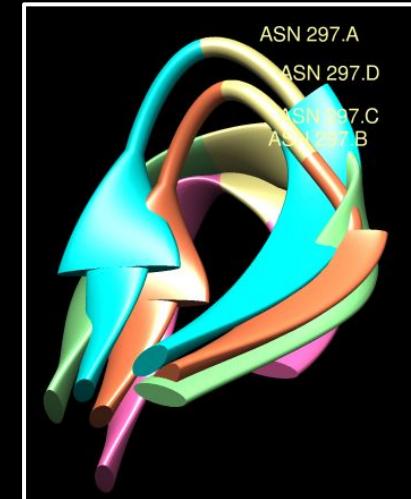
IgG4 ESKYGPPCPSPCPAPELLGGP

FAE



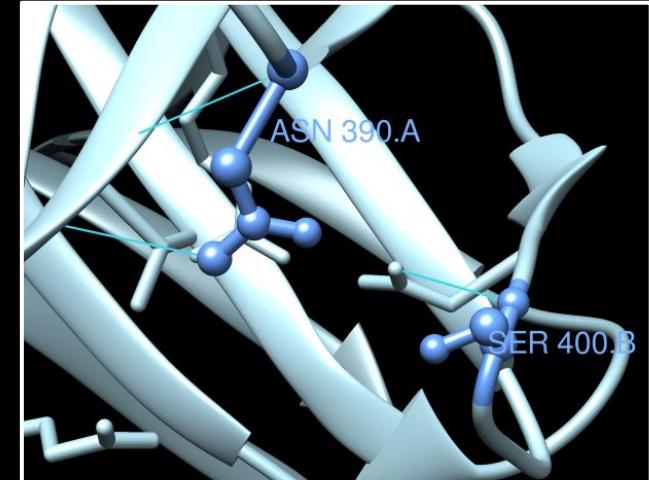
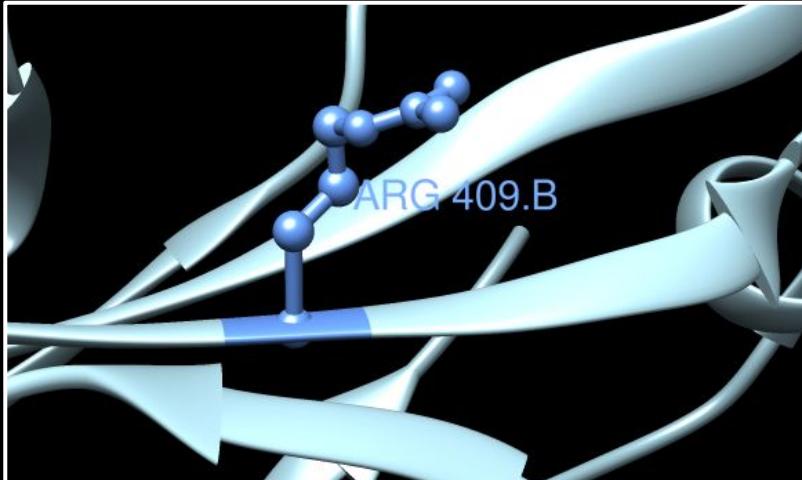
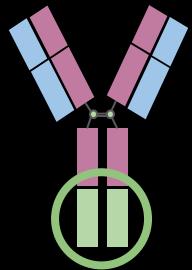
IgG1	IgG4
E	
P	
K	
S	E
C	S
D	K
K	Y
T	G
H	P
T	P
C	C
P	P
P S (228)	
C	C
P	P
A	A





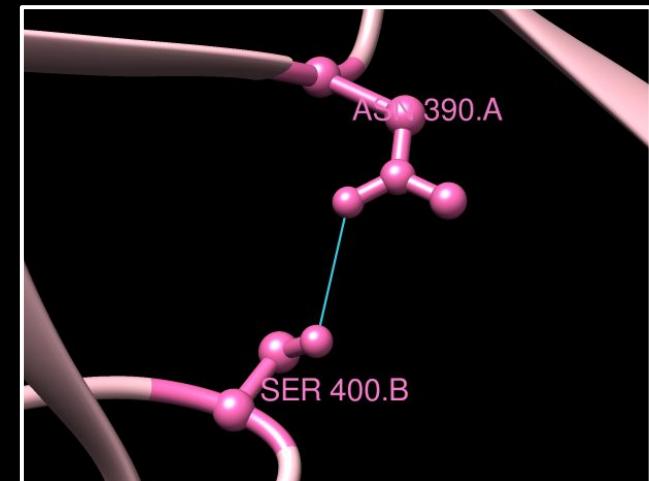
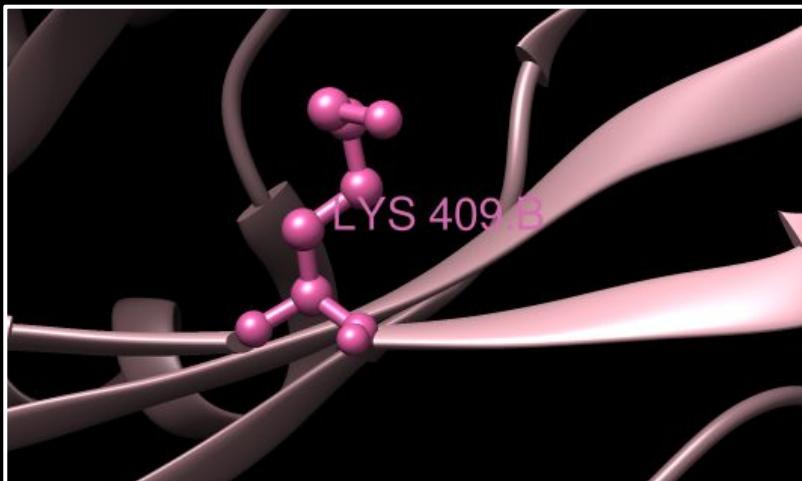
IgG4

4b53



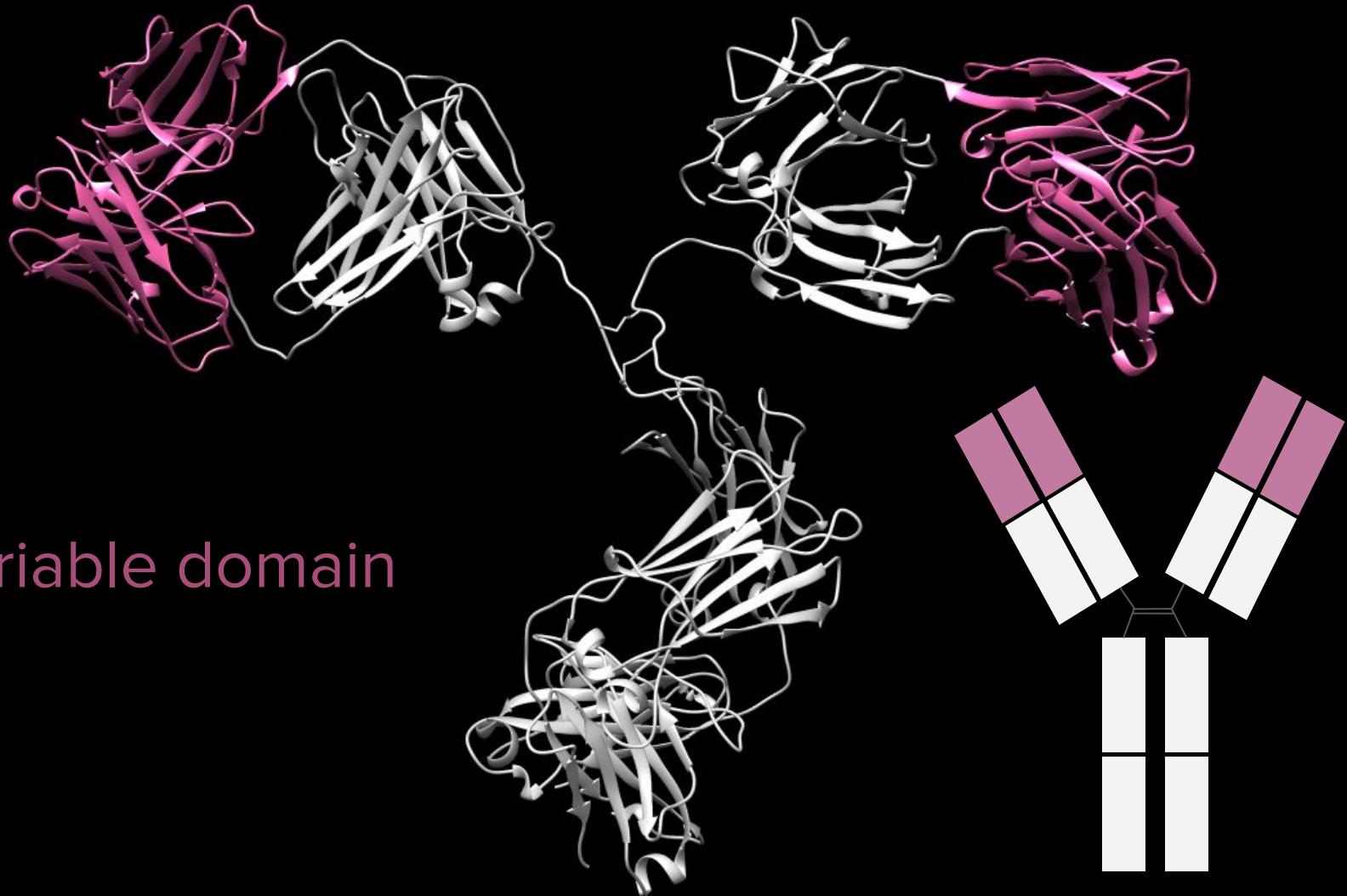
IgG1

3ave



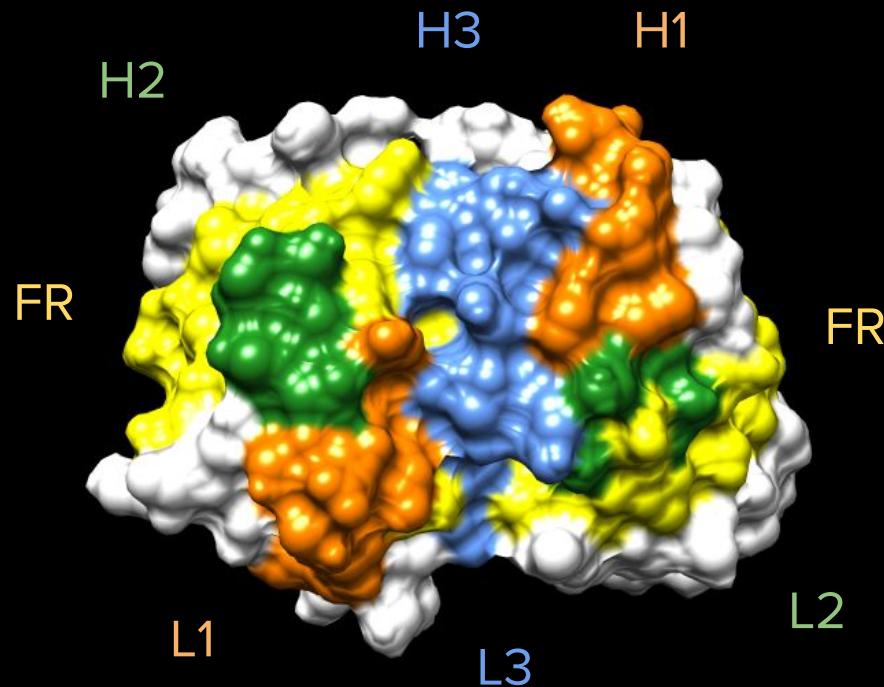
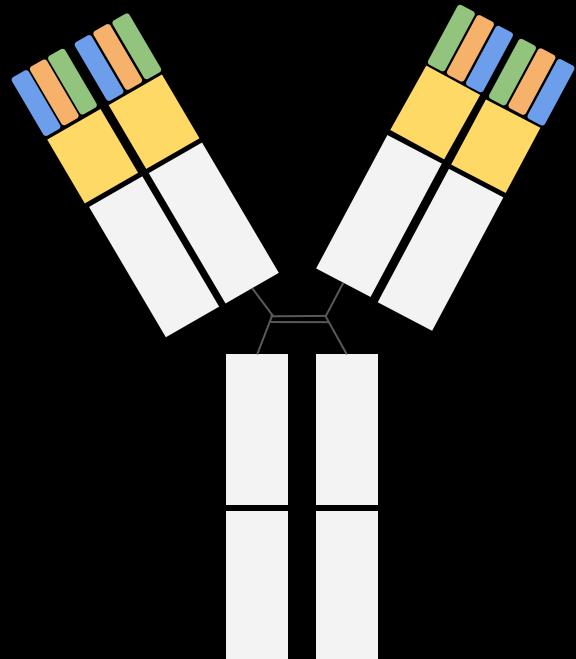
IgG VARIABLE DOMAIN

Variable domain



HYPERVARIABILITY

Complementarity-determining regions (CDRs)



HYPERVARIABILITY

Light chains (lambda type)

1gigl	QAVVTQESALTSPGETVTLTCRSSTGAVTTSNYANWVQEKPDHLFTGLI	GGTNN	RAPGW		
1mfal	QIVVTQESALTSPGETVTLTCRSSTGTVTSGNHANWVQEKPDHLFTGLI	GDTNN	RAPGW		
1indl	-AVVTQESALTSPGETVTLTCRSSTGAVTTSNYANWVQEKPDHLFTGLI	GGTNN	RAPGW		
2fb4l	QSVLTQPPSASGTPGQRVTISCGTSSNIGS-STVNWYQQLPGMAPKLLI	YRDA	RPSGW		
2rhea	ESVLTQPPSASGTPGQRVTISCTGSATDIGS-NSVIWYQQVPGKAPKLLI	YNDL	LPSGW		
8faba	--ELTQPPSVSVPQGTARITCS--ANALPN-QYAYWYQQKPGRAPVMVIYKDTQ	RPSGI			
	*** .: : ***: . :*** : : . . . * *: * . *: . . .				
1gigl	PARFSGSLIGDKAALTITGAQTEDEAIYFCALWYSNHW--V	FGGGT	KLTVLGQPKSSPSW		
1mfal	PARFSGSLIGDKAALTITGAQPEDEAIYFCALWSNNHW--I	FGGGT	KLTVLGQG-----		
1indl	PARFSGSLIGDKAALTITGAQTEDEARYFCALWYSNLW--V	FGGGT	KLTVLGQPKSSPSW		
2fb4l	PDRFSGSKSGASASLAIGGLQSEDETYYCA	AWDVS	LNAYVFGTGT	KVTVLGQPKANPTW	
2rhea	SDRFSASKSGTSASLAISGLESEDEADYYCA	AWNDS	LDEPGFGGGT	KLTVLGQPK-----	
8faba	PQRFSSSTSGTTVTLTISGVQAEDEADYYCQ	AWDNSAS	--I	FGGGT	KLTVLGQPKAAPSW
	.* * .: * .***: *: * . *: . *: ***:*****				

HYPERVARIABILITY

Light chains
(kappa type)

1fgvl
1fvca
1igml
1vfaa
1flrl
2cgrl
1tetl
2fbjl
1hila
2imma

DIQMTQSPSSLSASVGDRVITITCRASQDINN-----YLNWYQQKPGKAPKLLIYYTSTL
DIQMTQSPSSLSASVGDRVITITCRASQDVNT-----AVAWYQQKPGKAPKLLIYSASFL
DIQMTQSPSSLSASVGDRVITITCQASQDISN-----YLAWYQQKPGKAPELRIYDASNL
DIVLTQSPASLSASVGETVTITCRASGNIHN-----YLAWYQQKQGKSPQLLVYYTTTL
DVVMTQTPLSLPVSLGDQASISCRSSQSLVHS-NGNTYLRWYLQKPGQSPKVLIIYKVSNR
ELVMTQSPSLPVSLGDQASISCRPSQSLVHS-NGNTYLHWYLQKPGQSPKLLIYRVSNR
DVLMQTPLSLPVSLGDQASISCKSSQSVHS-SGNTYFEWYLQKPGQSPKLLIYKVSNR
EIVLTQSPAITAASLGQKVITCSASSSVSS-----LHWYQQKSGTSPKPWIYEISKL
DIVMTQSPSSLTVTAGEKVTMSCTSQQSLFNSGKQKNYLTWYQQKPGQPPKVLIIYWASTR
DIVMTQSPSSLSVSAGERVTMSCKSSQSLNSGNQKNFLAWYQQKPGQPPKLLIYGASTR
: : *:** . .: *: .::* .* .: . * * * * .*: :* : :

1fgvl
1fvca
1igml
1vfaa
1flrl
2cgrl
1tetl
2fbjl
1hila
2imma

ESGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQGNTLPPTFGAGTKVEIK-----
YSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRT-----
ETGVPSRFSGSGSGTDFTFTISSLQPEDPEDIATYYCQQYQNLPLTFGPGTKVDIKRTVAAPS
ADGVPSRFSGSGSGTQYSLKINSLQPEDFGSYYCQHFWSTPRTFGGGTKLEIKR-----
FSGVPDRFSGSGSGTDFTLKRVEAEDLGVYFCSQSTHVPWTFGGGTKLEIKRADAAPT
FSGVPDRFSGSGSGTAFTLKRVEAEDLGVYFCSQGTHVPYTFGGGTKLELKRADAAPT
FSGVPDRFSGSGSGTDFTLKRVEAEDLGVYYCFQGSHIPFTFGSGTKLEIKRADAAPT
ASGVPARFSGSGSGTSYSLTINTMEAEDAIIYYCQWWTYPLITFGAGTKLELKRADAAPT
ESGVPDFRTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSNPLTFGGGKLELKRADAAPT
ESGVPDFRTGSGSGTDFTLTISSVQAEDLAVYYCQNDHSYPLTFGAGTKLELKR-----
*** *:** * *** ::*. ::** . * : *** *:** :

Framework

L1

L2

L3

HYPERVARIABILITY

Heavy chains

Framework

H1

H2

H3

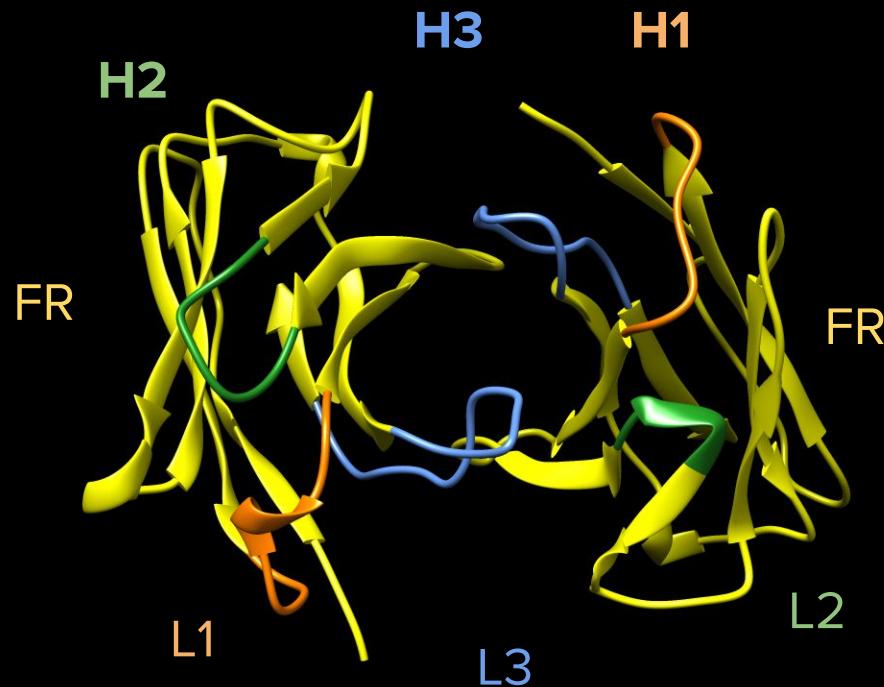
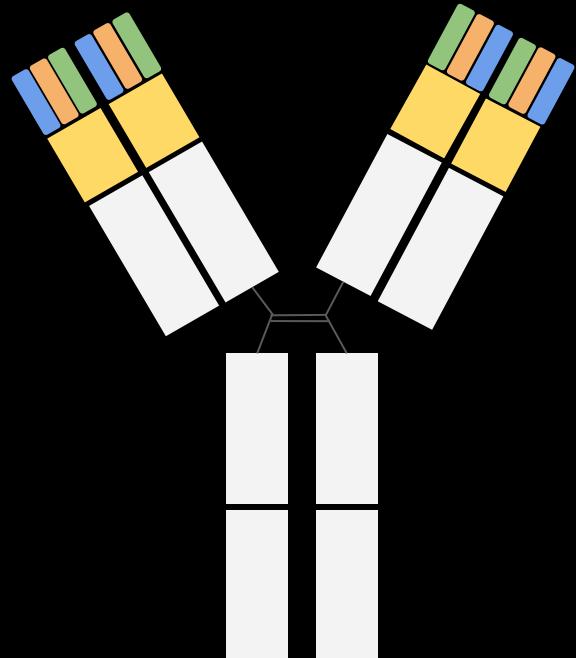
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2cgrh
1teth
1hilb
1indh
1flrh
1gigh
1vfab
1fgvh
1fvcb
1igmh
2fbjh
2fb4h
8fabb

EVQVQQSGTVVARPGASVKMSCKA**SGYTF**TNYWMHWIKQRPGQGLEWIGAIYPG--NSAT
RVQLLES~~GAEL~~MPKGASVQISCKA**TGYTF**SEYWIEWVKERPGHGLEWIGEILPG--SGRT
QIQLVQSGPELKT~~PGET~~VRISCKA**SGYTF**TTYGM~~SWV~~KQTPGKGF~~KWM~~G~~W~~INTY--SGVP
EVQLVESGGDLV~~KPGG~~SLK~~L~~SCA**SGFS**FSSYGM~~SWV~~RQTPD~~KR~~LEWVATISNG--GGY
EVTLVESGGDSV~~KPGG~~SLK~~L~~SCA**SGFTL**SGETMS~~WV~~RQTP~~EK~~RL~~EWV~~ATTLSG--GGF
EVKLD~~E~~TGGGLVQPG~~RP~~M~~KL~~SCA**SGFTF**SDYWM~~NWV~~RQ~~SPE~~KGLEWV~~QA~~QIRNKP~~Y~~NYET
QVQLKESGPGLVAPSQSL~~SIT~~CTV**SGFLL**ISNGVHWVRQ~~PPG~~KGLEWLGV~~I~~WAG--GNT
QVQLQESGPGLVAPSQSL~~SIT~~CTV**SGFSL**TG~~Y~~GVN~~WV~~RQ~~PPG~~KGLEWLGM~~I~~WGD--GNT
EVQLVESGGGLVQPGGSLRLSCA**SGYTF**TEYTMHW~~MR~~QAPGKGLEWV~~AGIN~~PK--NGT
EVQLVESGGGLVQPGGSLRLSCA**SGFNI**KDTYIH~~WV~~RQ~~APG~~KGLEWV~~VARI~~YPT--NGY
EVHLLES~~GGN~~LVQPGGSLRLSCA**SGFTN**I~~IF~~VMS~~WV~~RQ~~APG~~KGLEWVSGVFGS--GGNT
EVKLLES~~GGN~~LVQPGGSLRLSCA**SGFDF**SKY~~W~~MS~~WV~~RQ~~APG~~KGLEWIGEIH~~PD~~--SGTI
EVQLVQSGGGVVQPG~~RS~~LRLSCS**SGFIF**SSYAM~~Y~~WVRQ~~APG~~KGLEWV~~VAI~~IWDD--GSDQ
AVKLVQAGGGVVQPG~~RS~~LRLSC**IA****SGFTF**SN~~Y~~GMHWVRQ~~APG~~KGLEWV~~VAVI~~WYN--GSRT

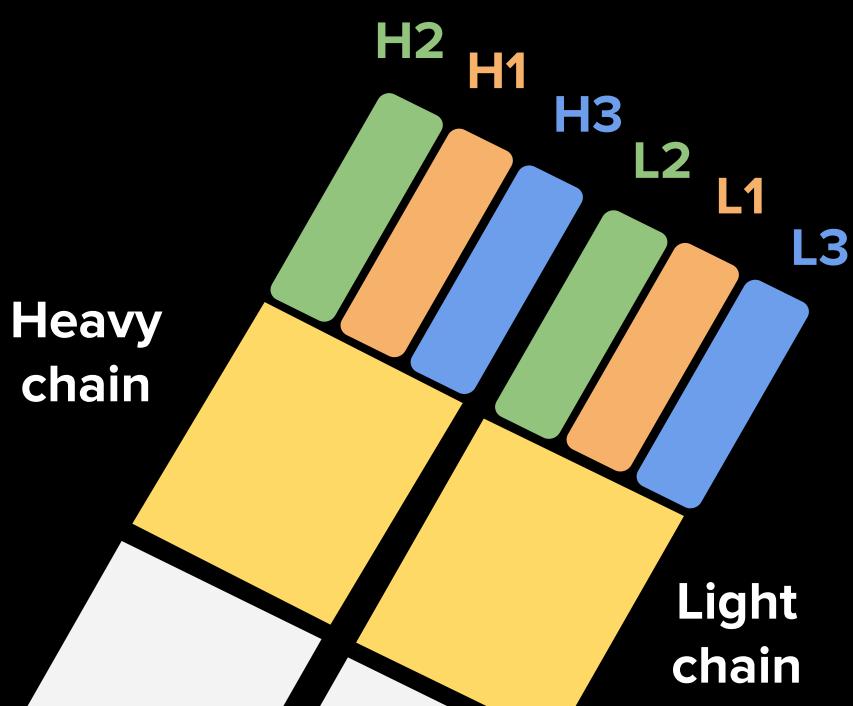
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FYSASVKGRFTISRDNAQNNLYLQLNSLRSEDTALYFCASHR-----FVHWGH
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HYPERVARIABILITY

Complementarity-determining regions (CDRs)



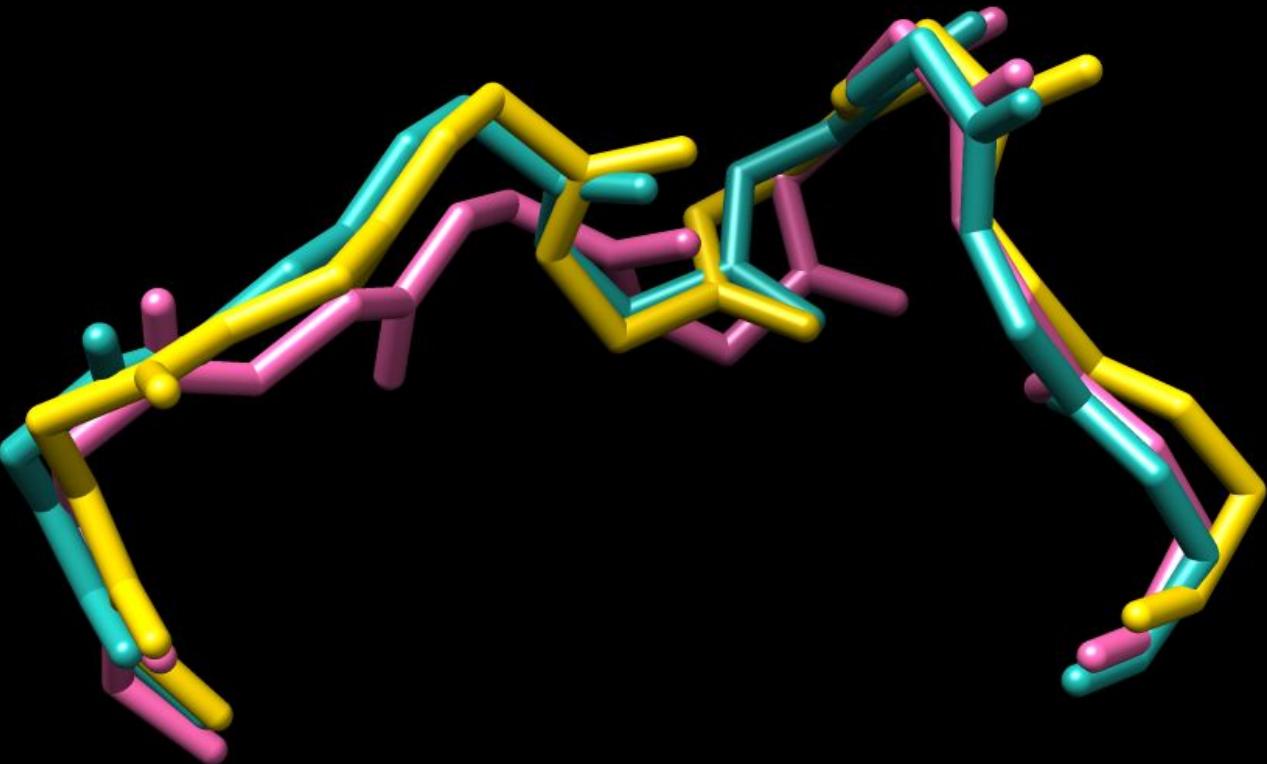
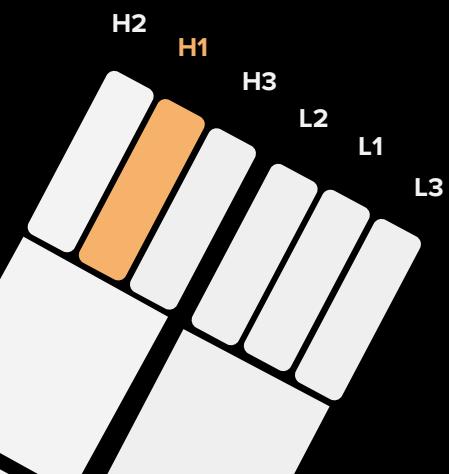
CANONICAL STRUCTURES



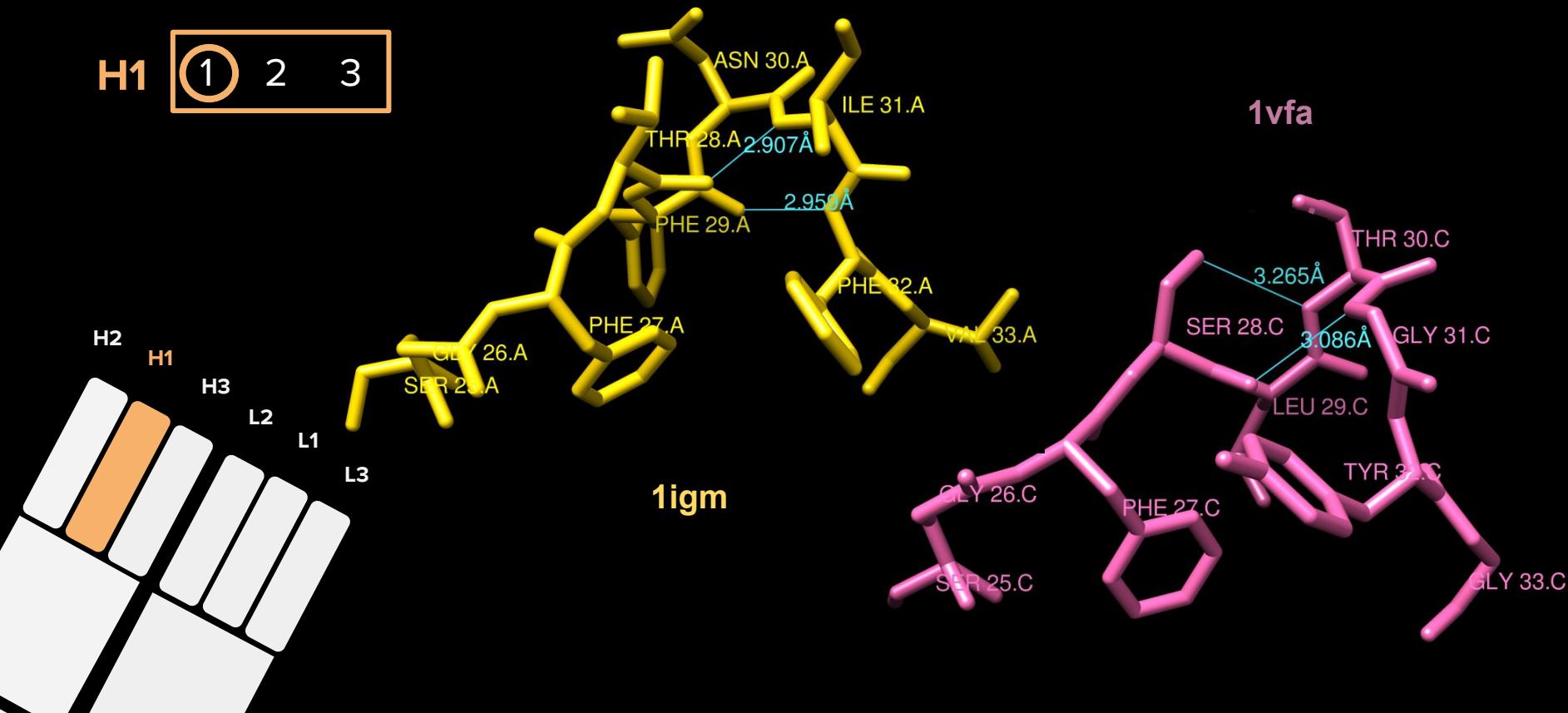
H1	H2	H3
1 2 3	1 2 3 4	No canonical structure
L1	L3	L2
Kappa 1 2a 2b 3 4 5 6 Lambda 1 2 3 4	Only 1	Kappa 1 2 3 4 5 6 Lambda 1 2

CANONICAL STRUCTURES

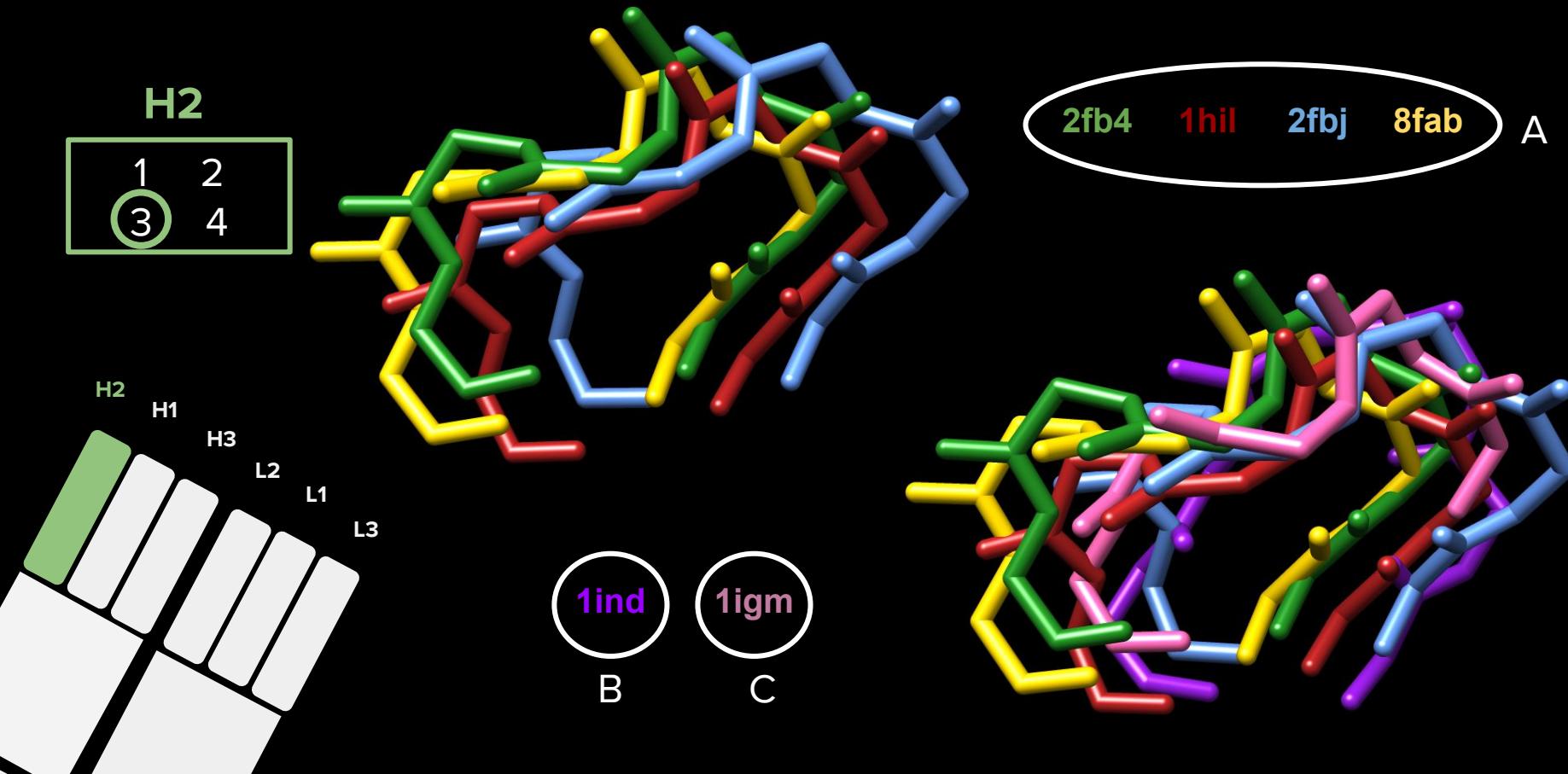
H1 1 2 3



CANONICAL STRUCTURES

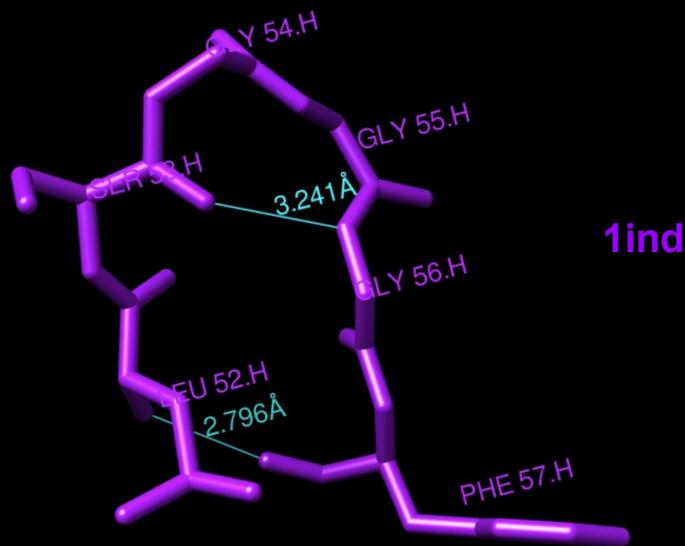
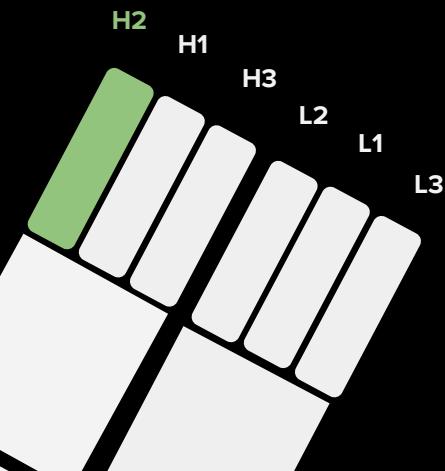
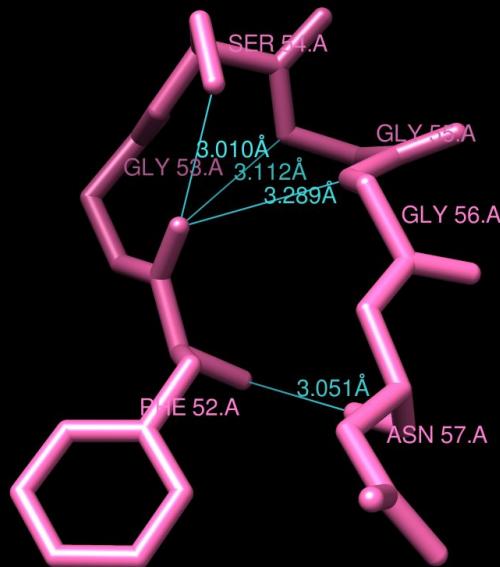
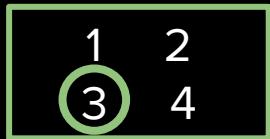


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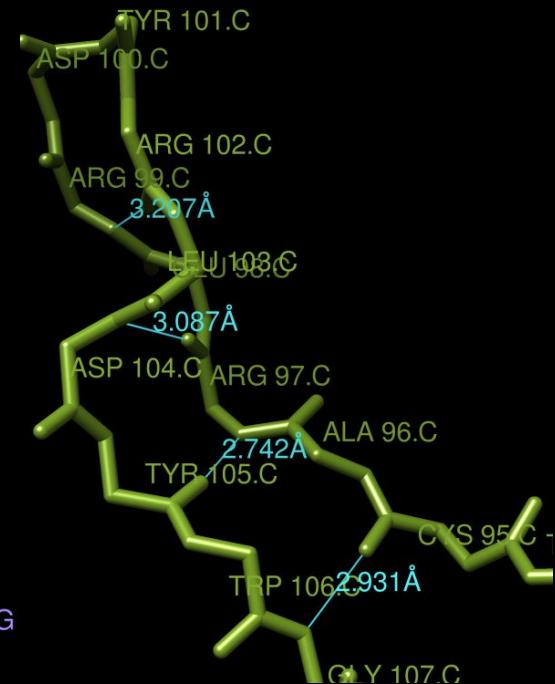
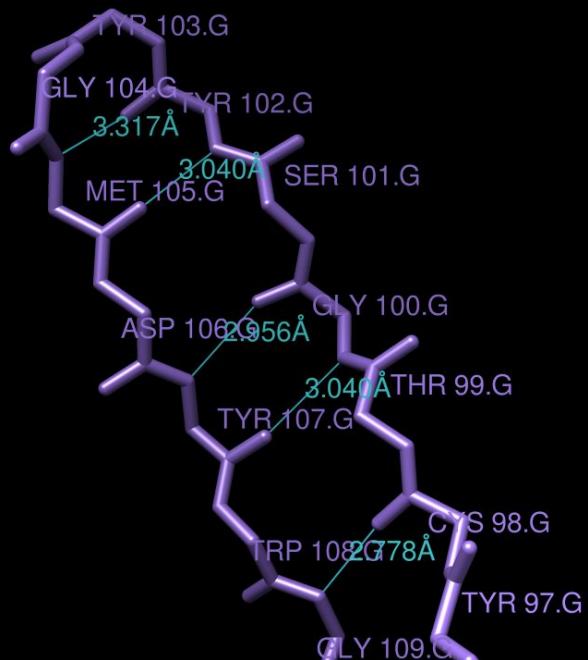
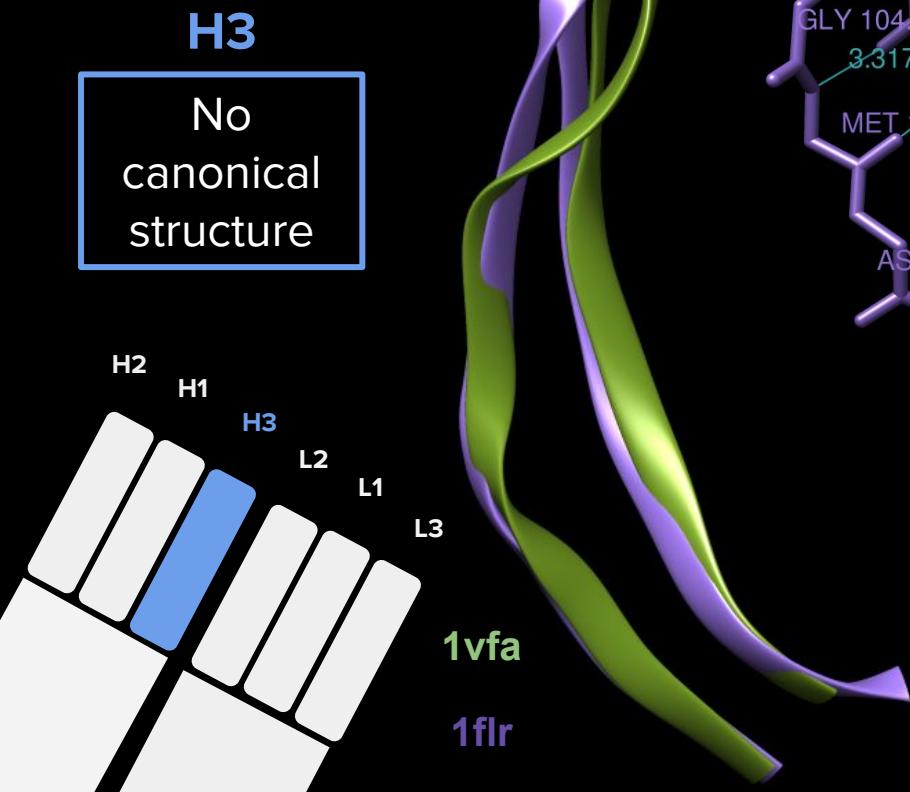


CANONICAL STRUCTURES

H2



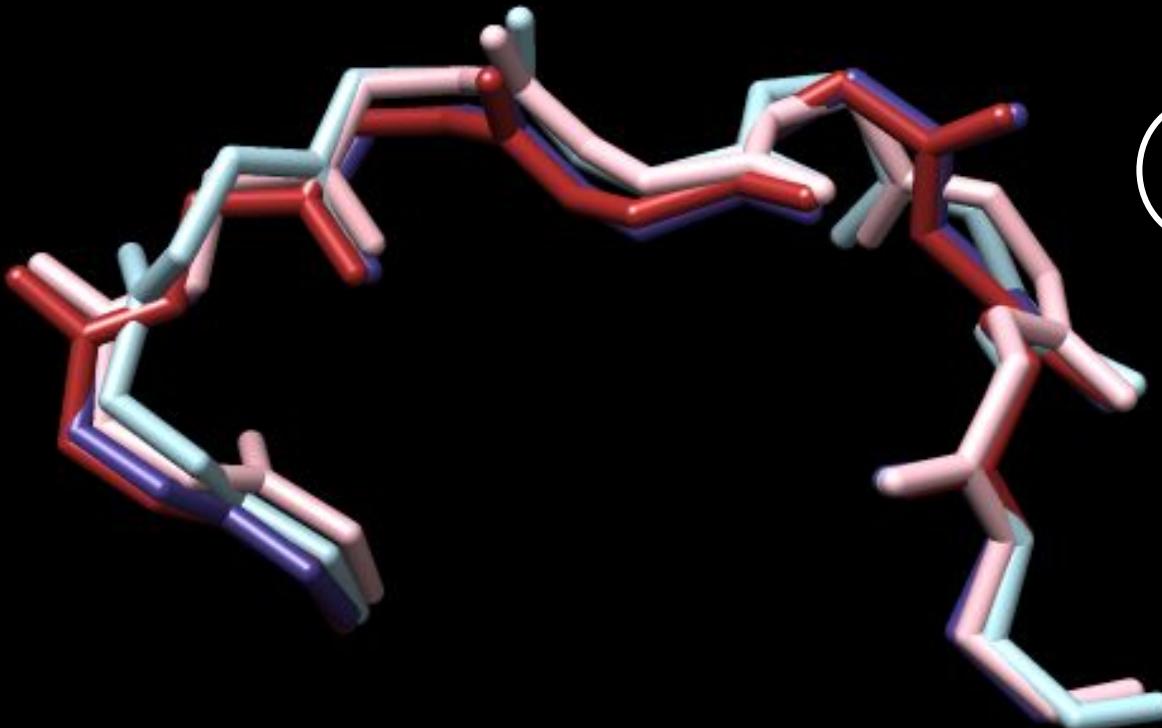
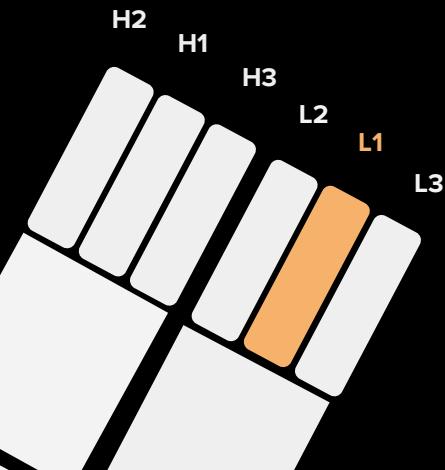
CANONICAL STRUCTURES



CANONICAL STRUCTURES

L1

Kappa			
1	2	3	
4	5	6	
Lambda			
1	2	3	4



1igm
1fvc

A
1fgv
1vfa

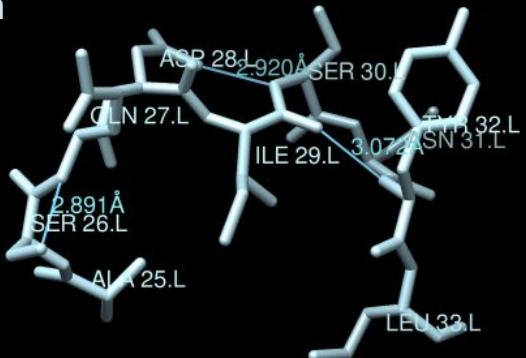
B

CANONICAL STRUCTURES

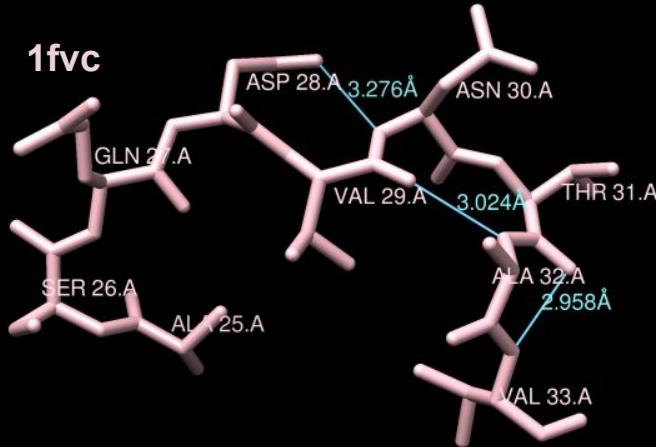
L1



1igm



1fvc



H2

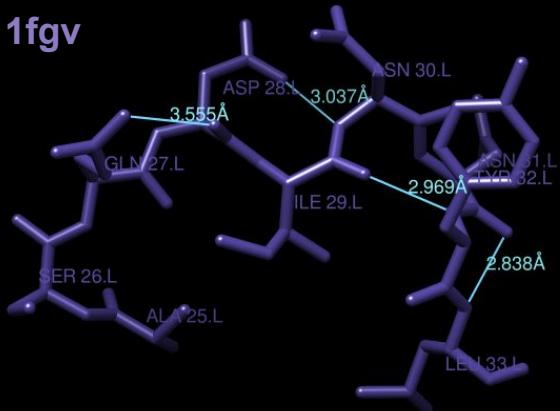
H1

H3

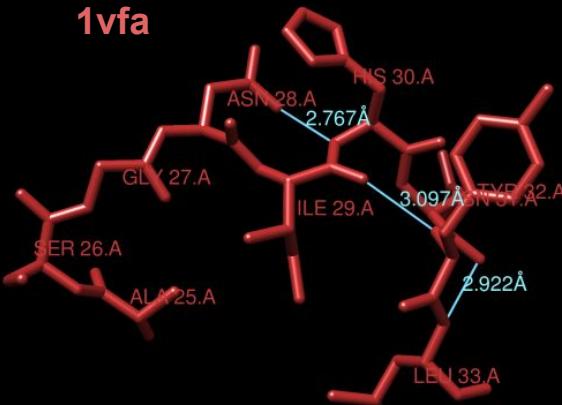
L2

L3

1fgv



1vfa



CANONICAL STRUCTURES

L1

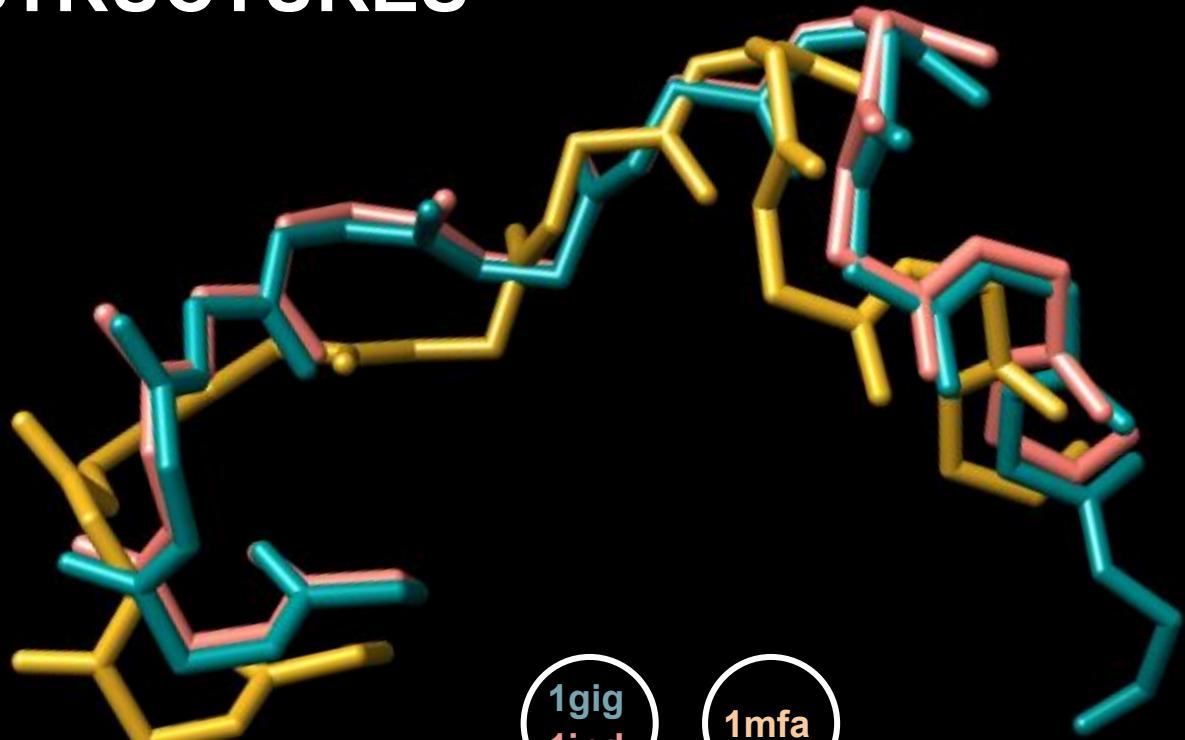
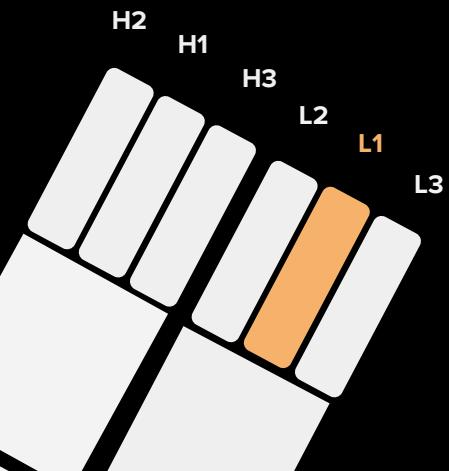
Kappa

1 2 3

4 5 6

Lambda

1 2 3 4



A

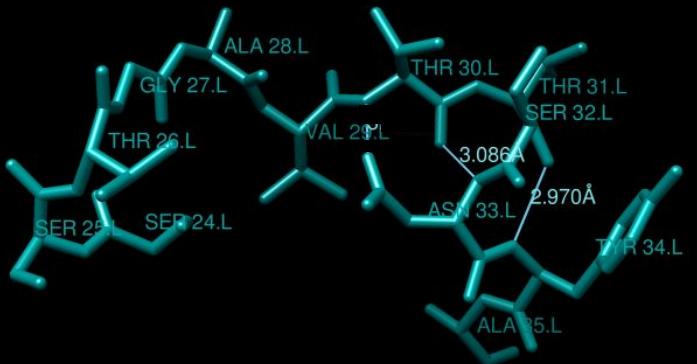
B

CANONICAL STRUCTURES

L1

Kappa		
1	2	3
4	5	6
Lambda		
1	2	3
4		

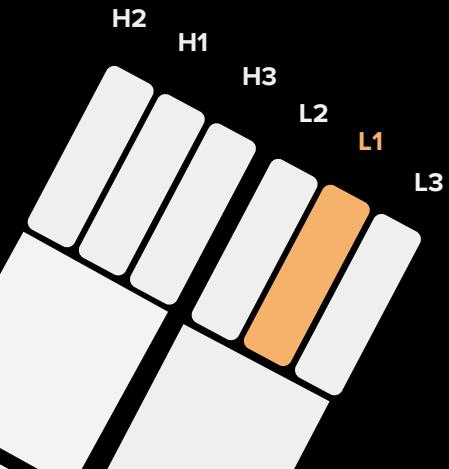
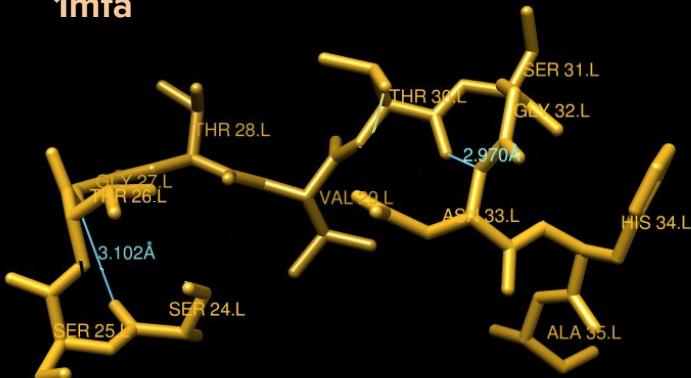
1gig



1ind



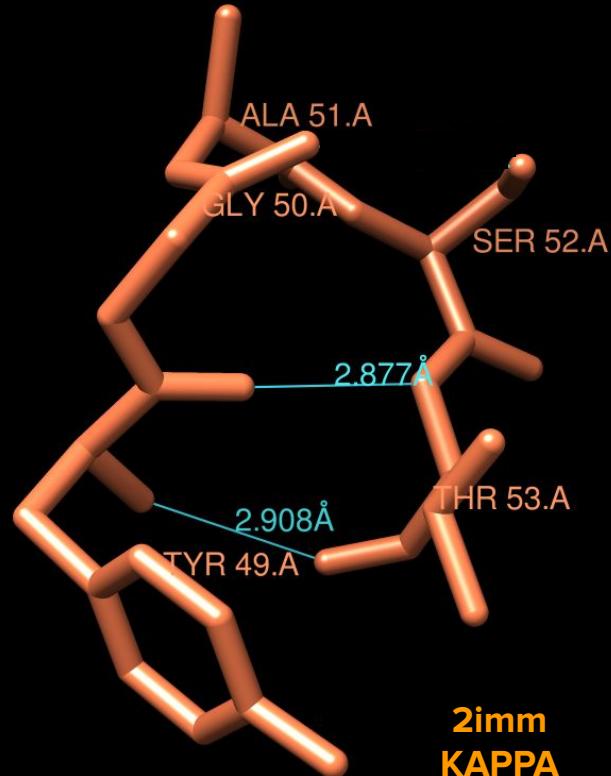
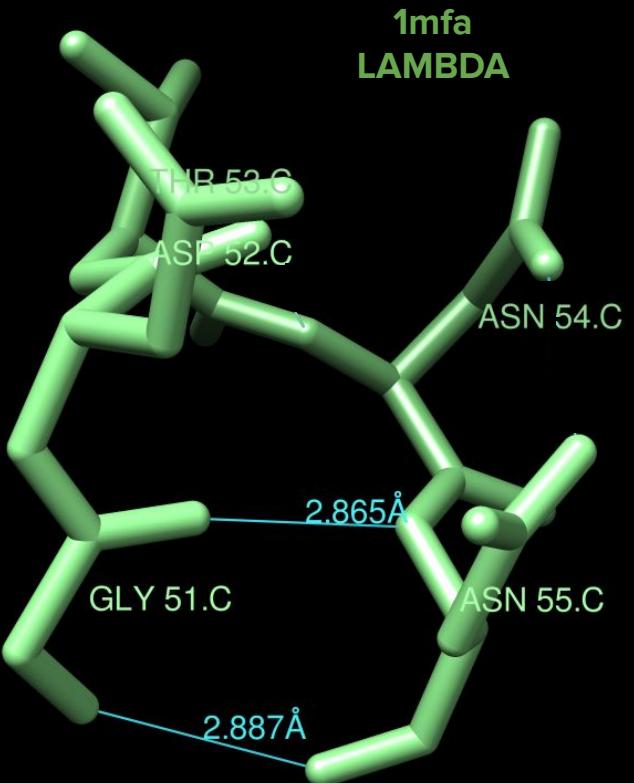
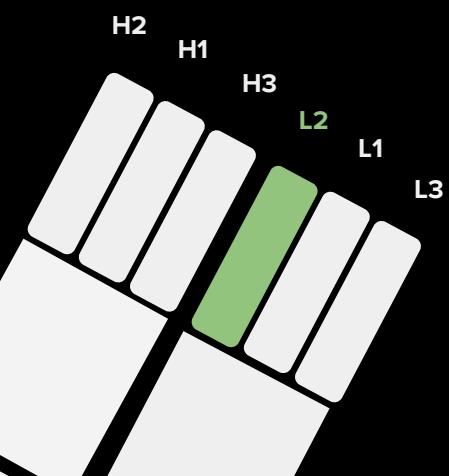
1mfa



CANONICAL STRUCTURES

L2

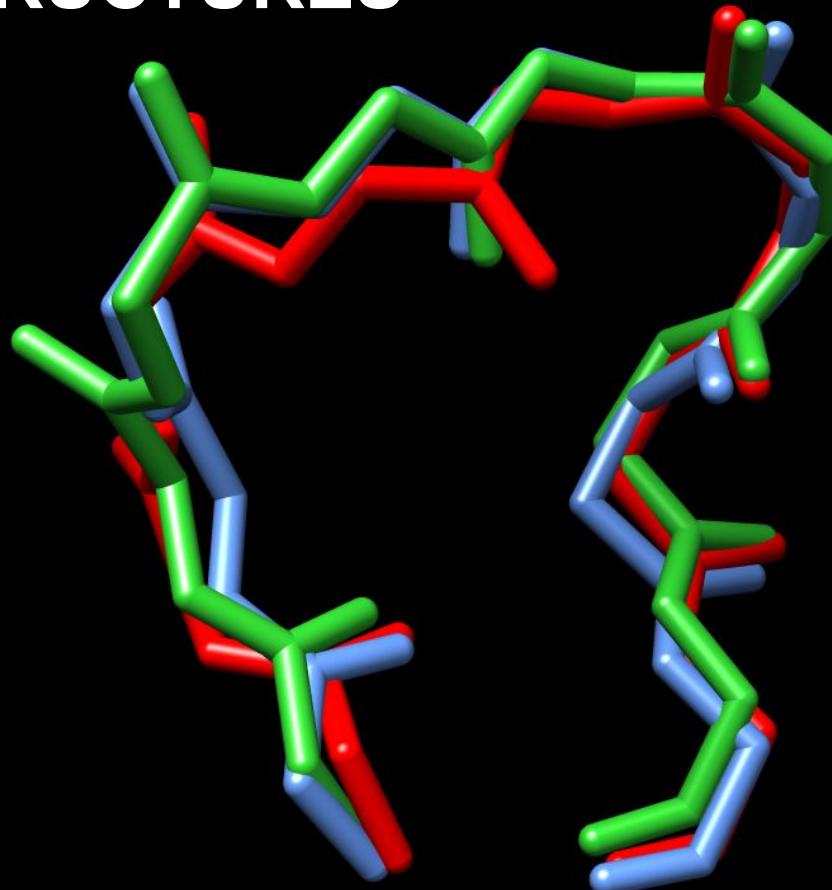
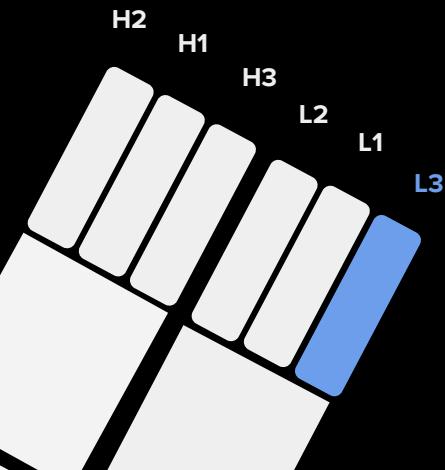
Only 1



CANONICAL STRUCTURES

L3

	Kappa					
1	2	3	4	5	6	
Lambda						
1	2					

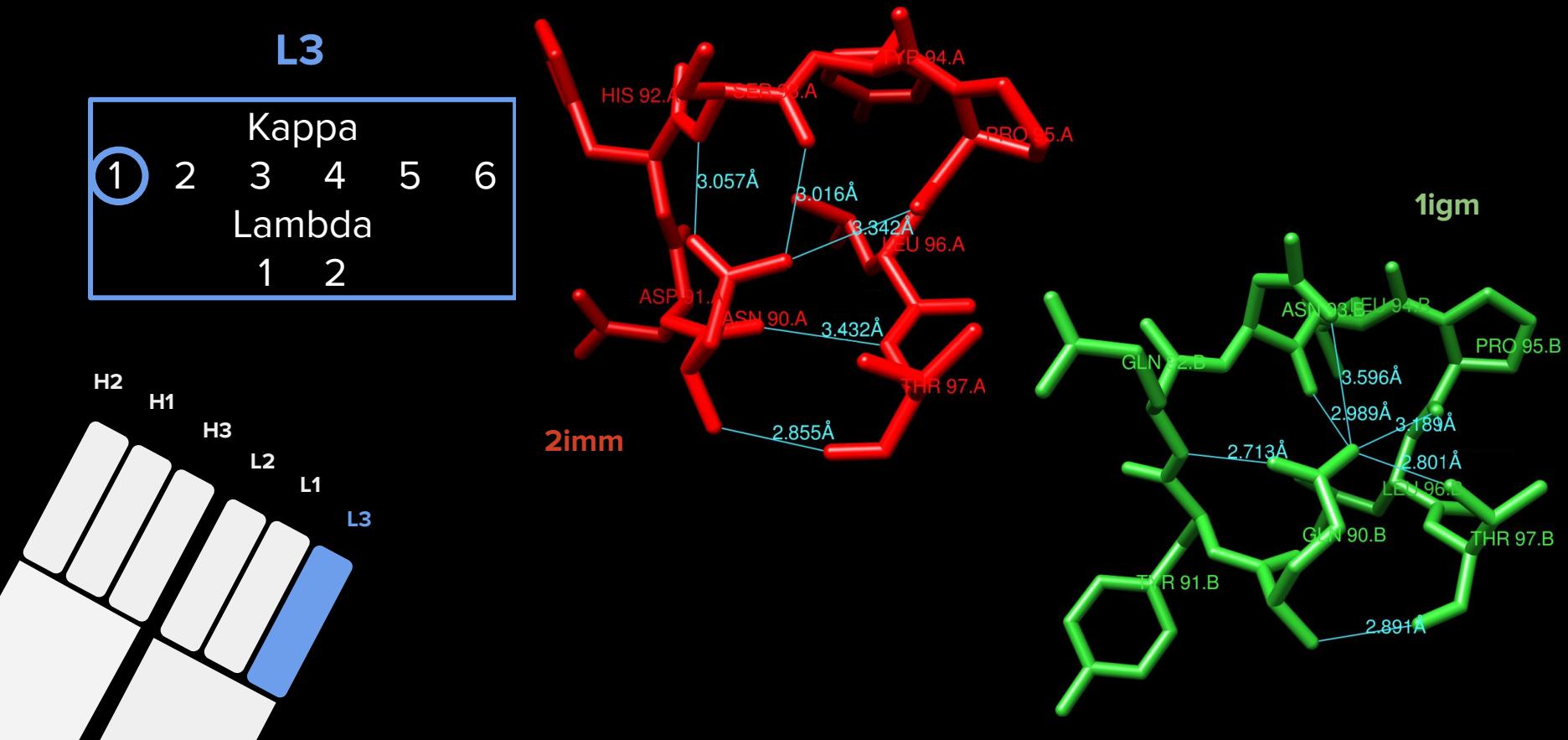


2imm

1igm

1fvc

CANONICAL STRUCTURES



CANONICAL STRUCTURES

L3

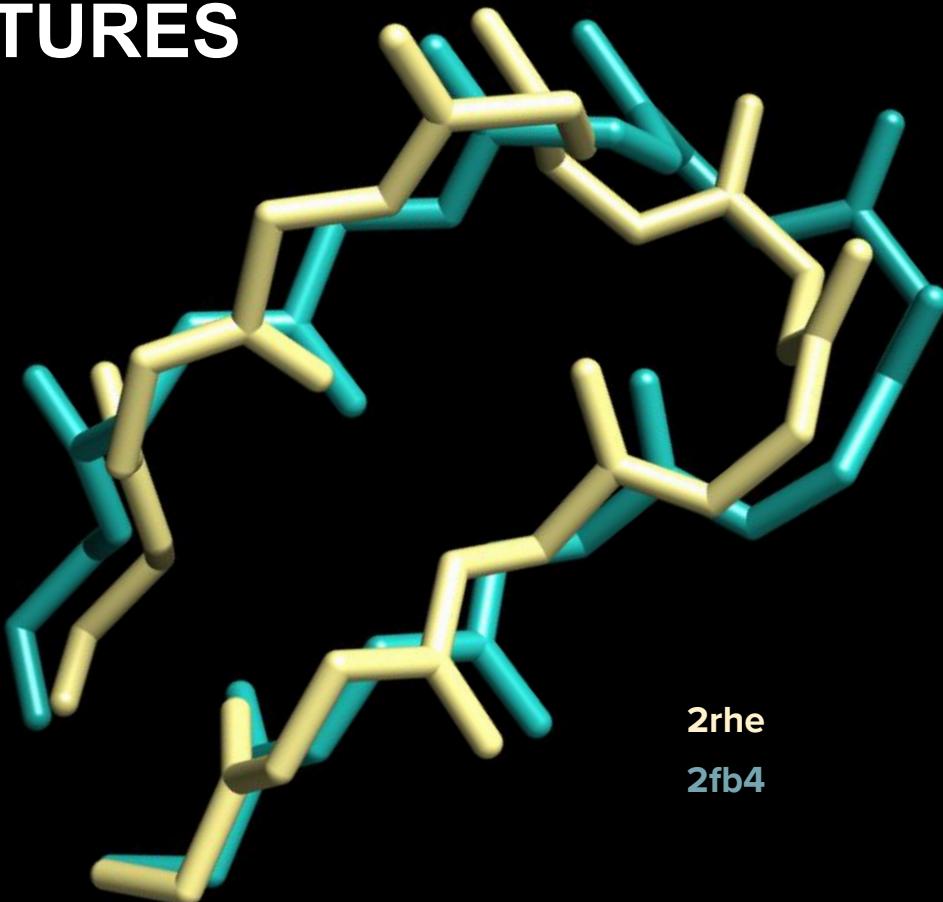
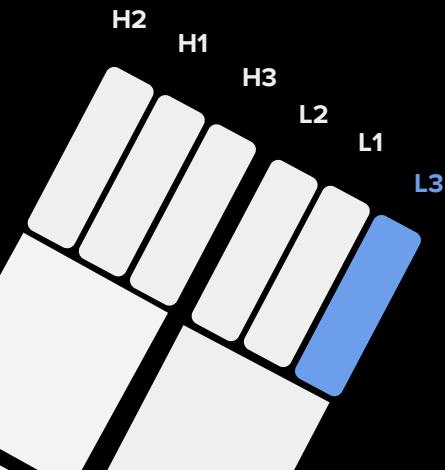
1	2	3	4	5	6

Kappa

1 2 3 4 5 6

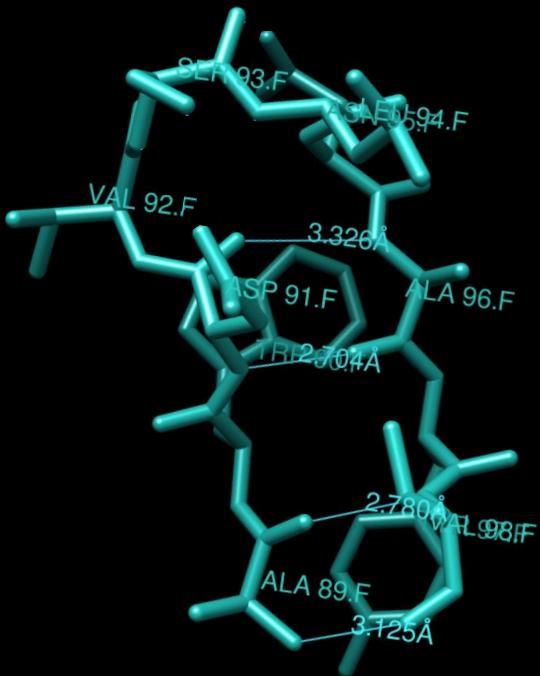
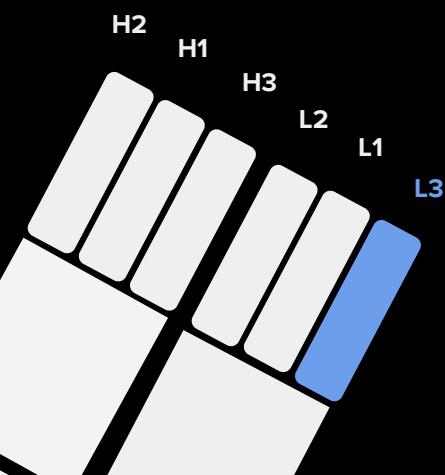
Lambda

1 2

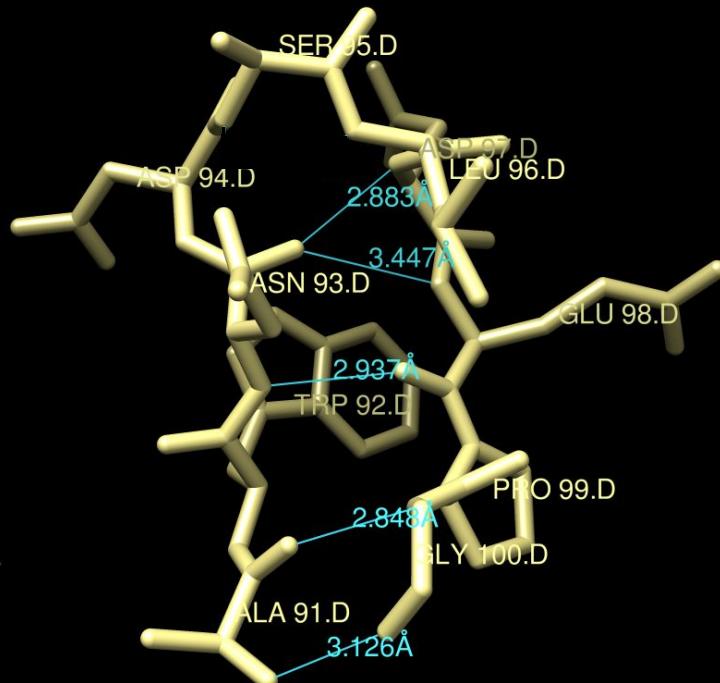


CANONICAL STRUCTURES

L3



2fb4



2rhe

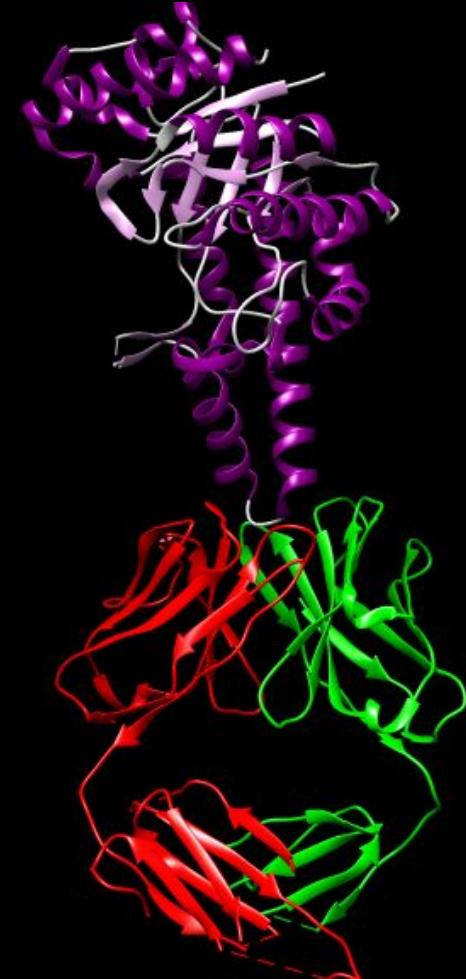
IgG - ANTIGEN INTERACTION

IgG-antigen

The forces involved in non covalent interactions are:

- Electrostatic forces
- Hydrogen bonds
- Van der Waals
- Hydrophobic forces
- Pi-cation interaction

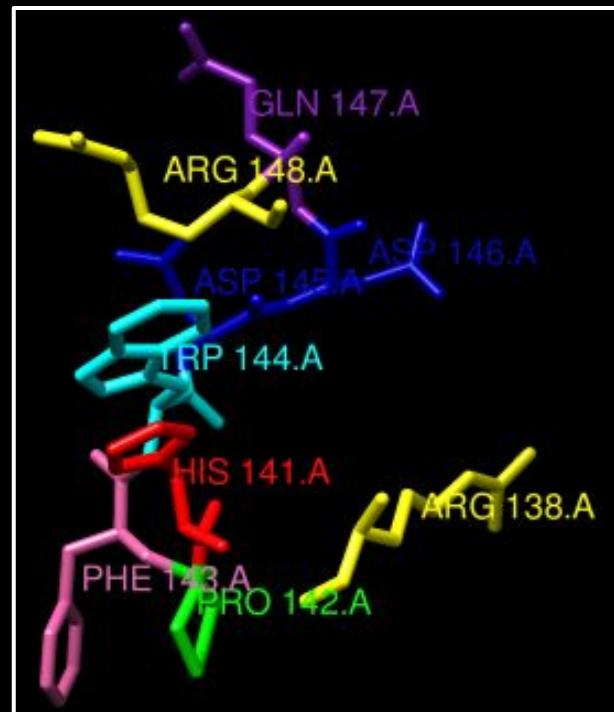
The immunoglobulins have many aromatic aminoacids in antigen binding site which participate mainly in Van der Waals and hydrophobic interactions.



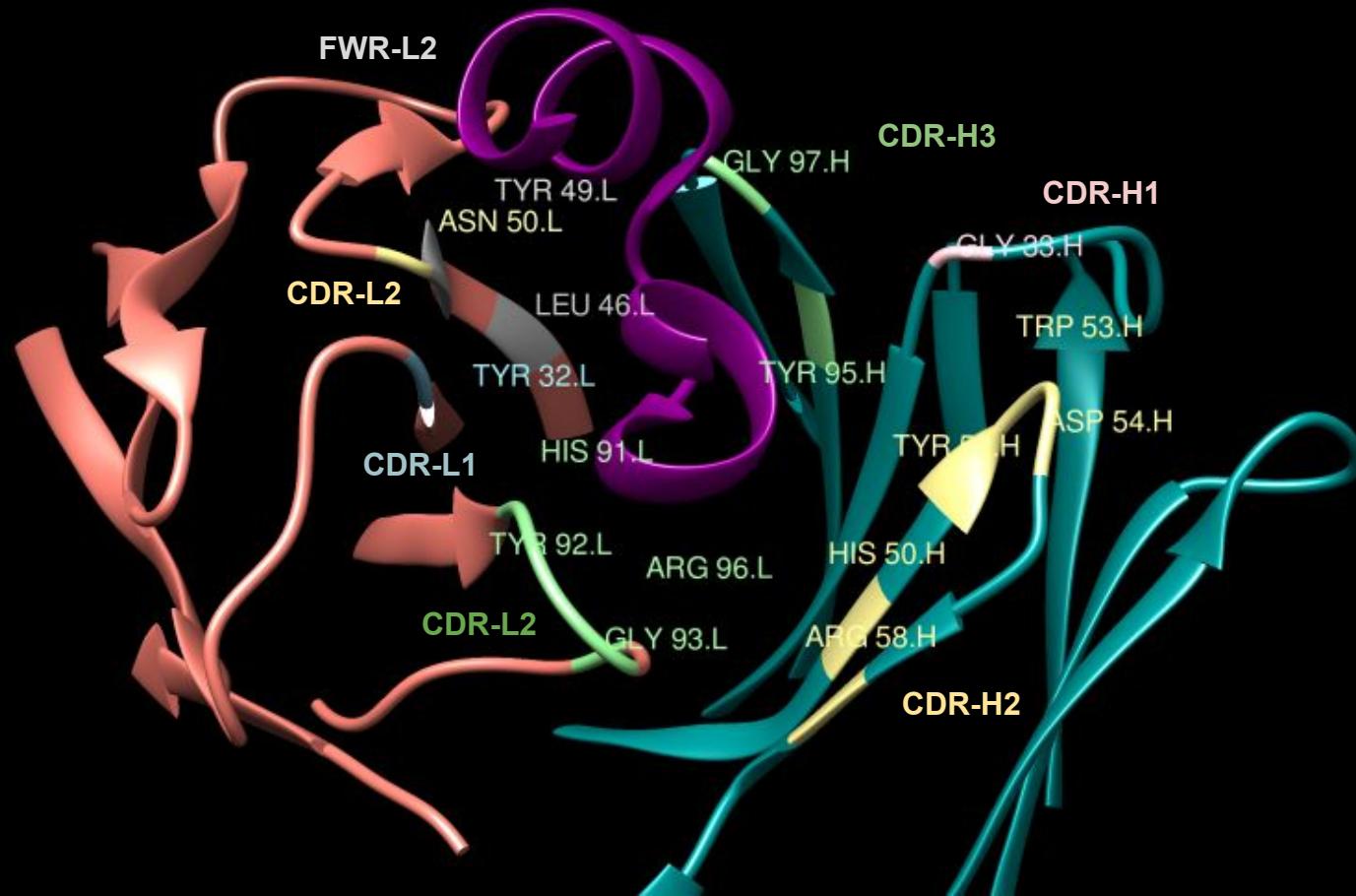
IgG-Hyaluronidase: Fold and Epitope



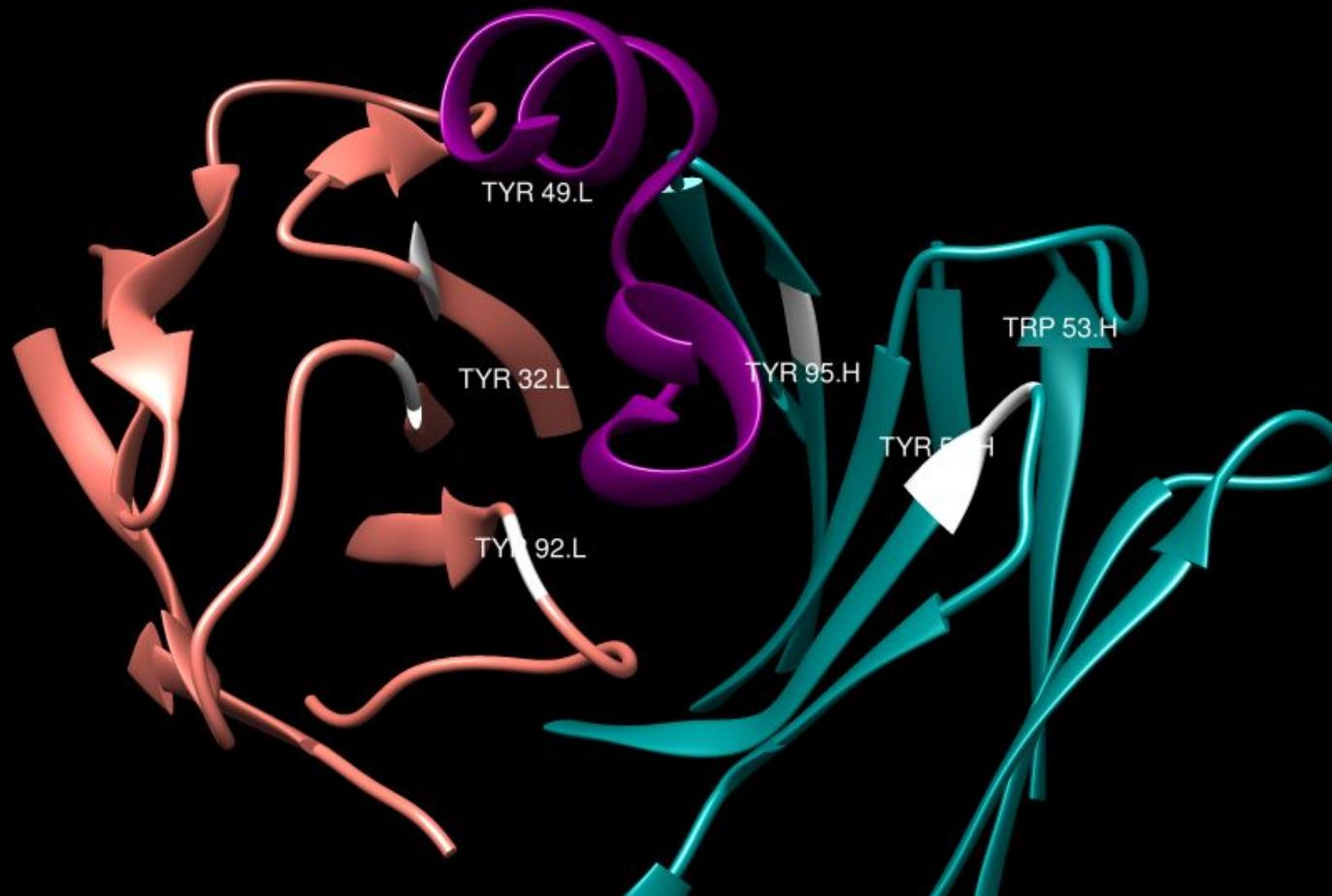
R+HPFWDDQR



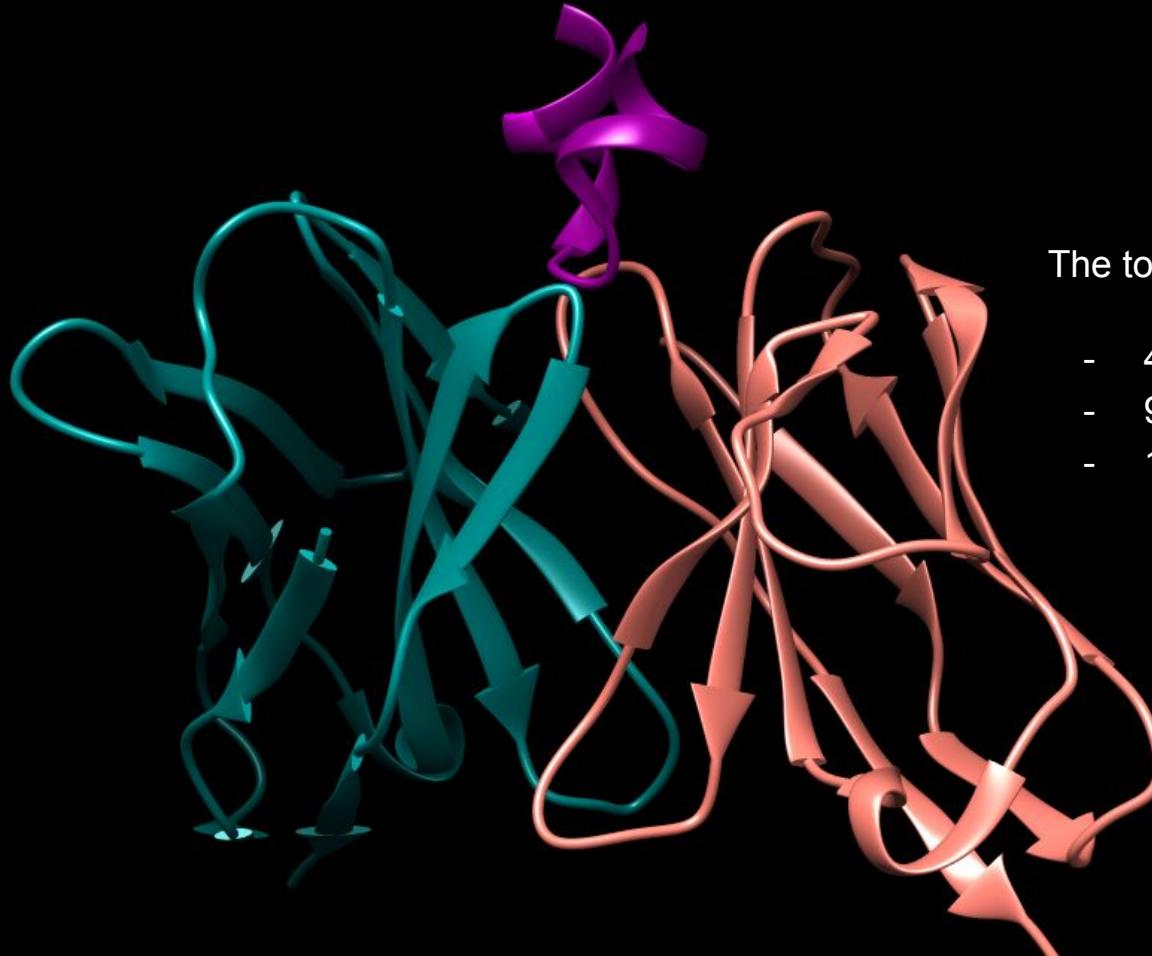
IgG-hyaluronidase: Fab-Hyal interaction



IgG-hyaluronidase: Aromatic aminoacids



IgG-hyaluronidase: Fab-Hyal interaction

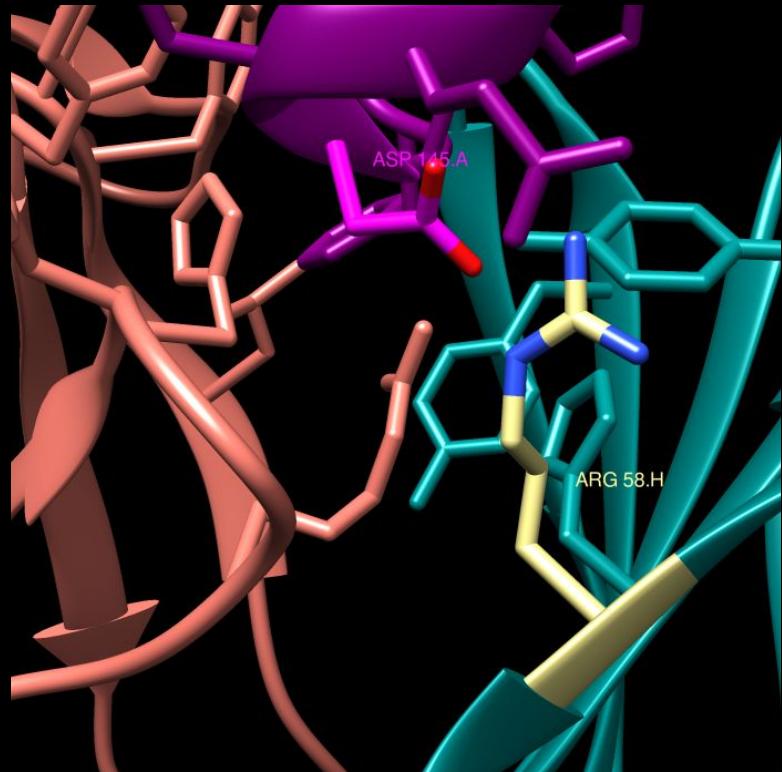


The total number of Hyal/Fab interactions:

- 4 salt bridges
- 9 hydrogen bonds
- 11 Van der Waals

IgG-hyaluronidase: Salt bridges

CDR-H2: ARG 58 - ASP 145, 3.2 Å

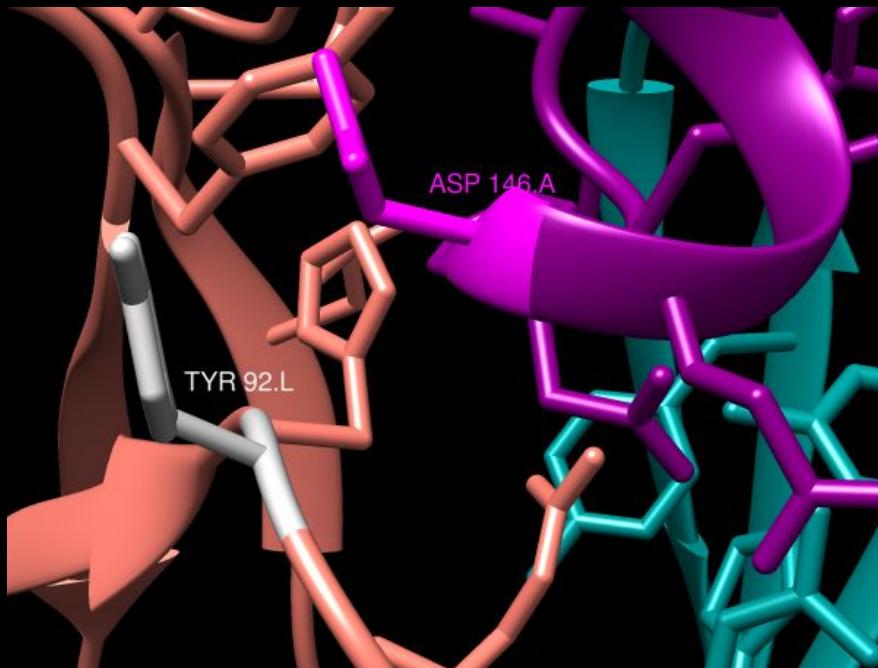


CDR-H2: ASP 54 - ARG 148, 3.2 Å

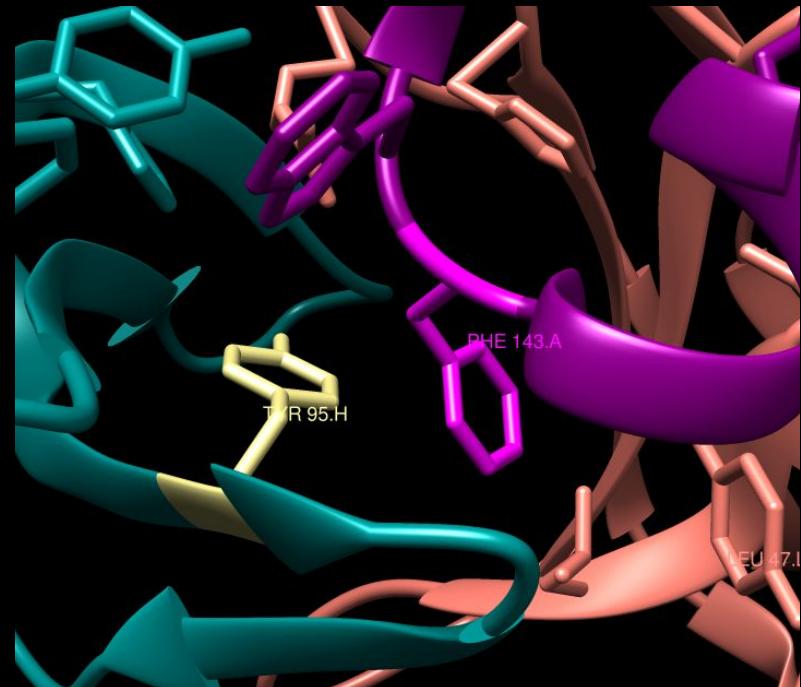


IgG-hyaluronidase: Van der Waals

CDR-L3: TYR 92 - ASP 146, 3.6 Å

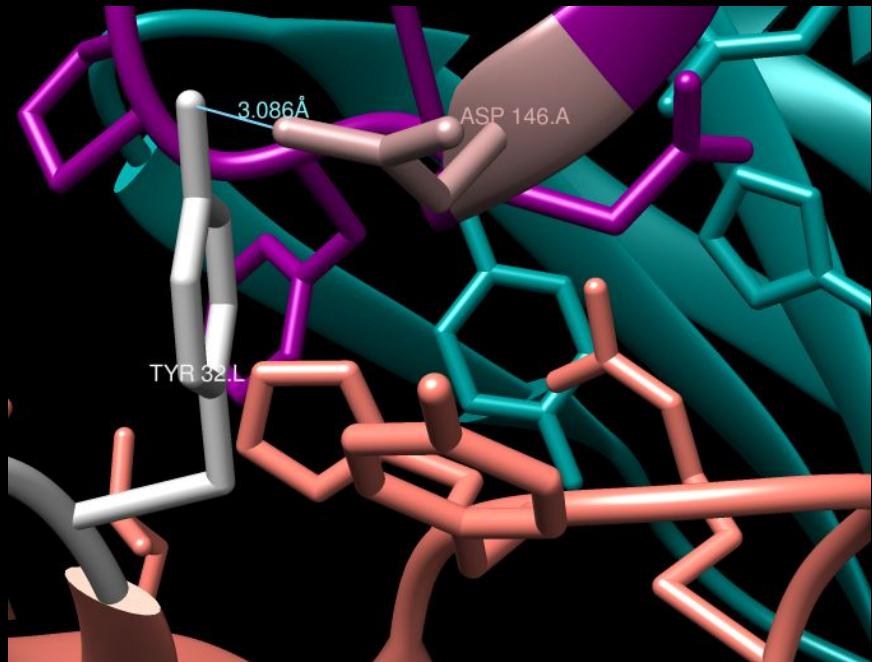


CDR-H3: TYR 95 - PHE 143, 3.5 Å

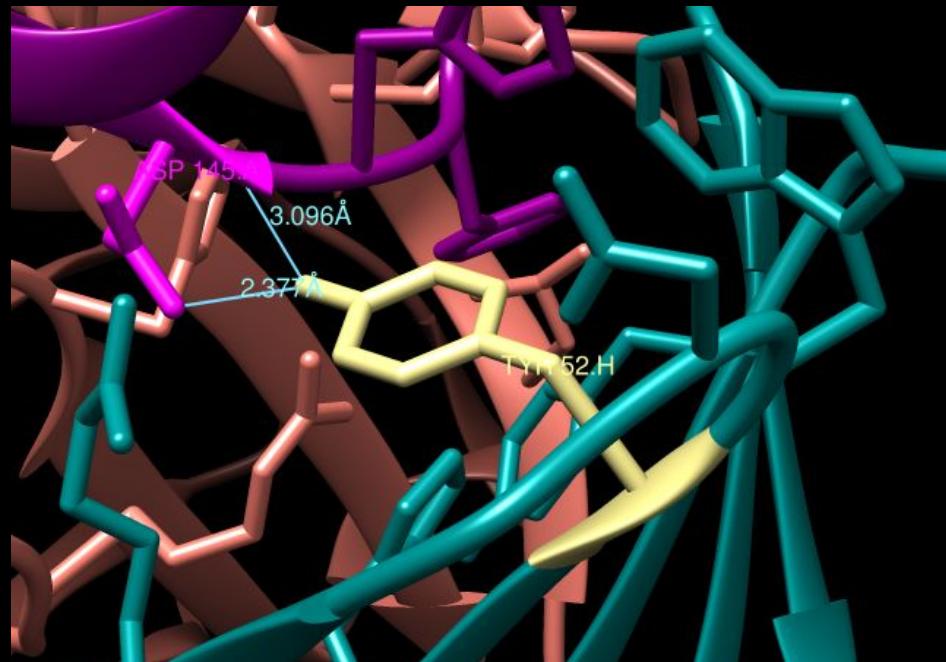


IgG-hyaluronidase: Hydrogen bonds

CDR-L1: TYR 32 - ASP 146, 3.1 Å



CDR-H2: TYR 52 - ASP 145, 3.1 Å



IgG - Fc γ RI INTERACTION

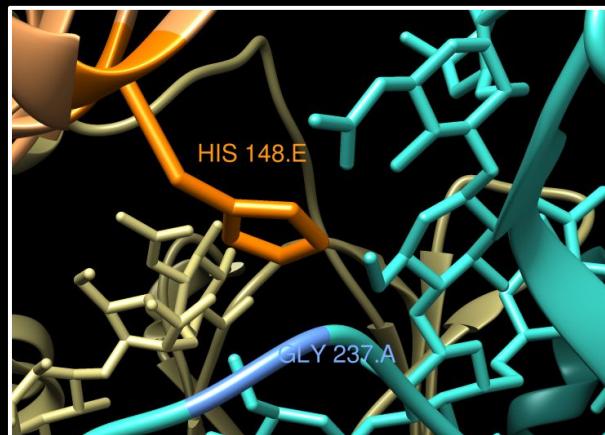
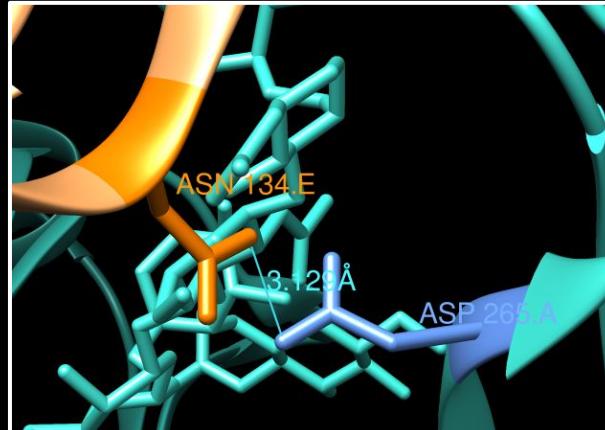
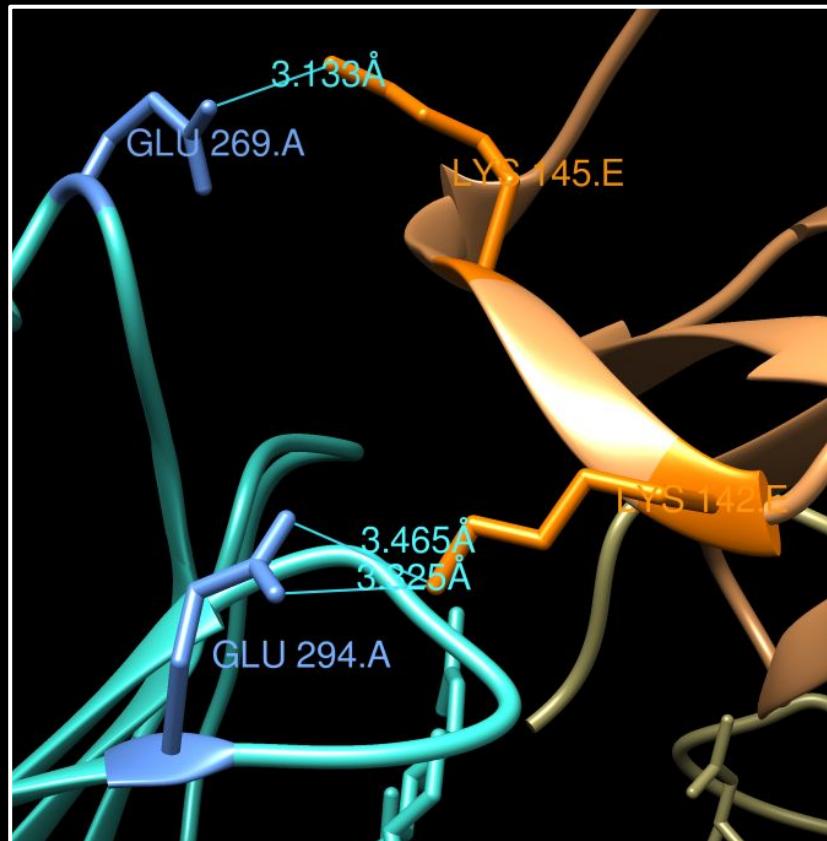
IgG-Fc γ RI

Fc γ RI

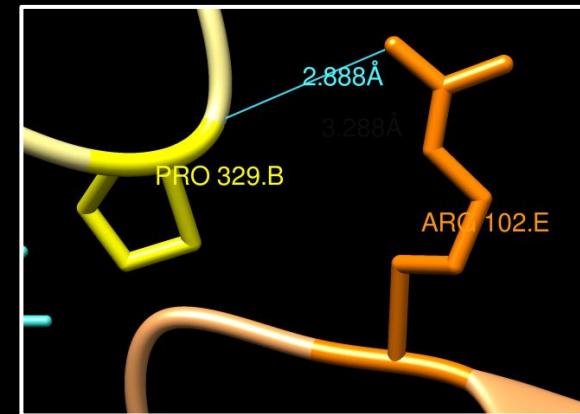
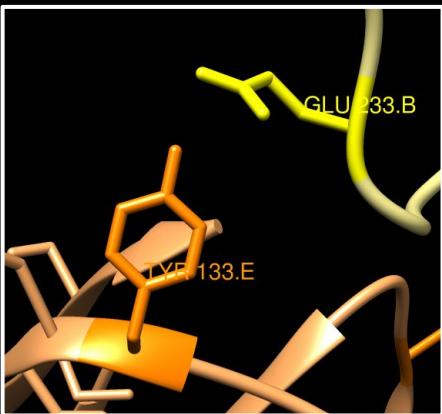
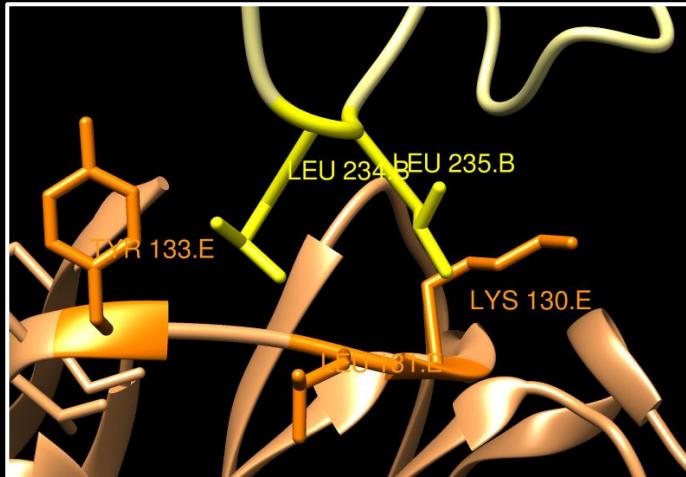
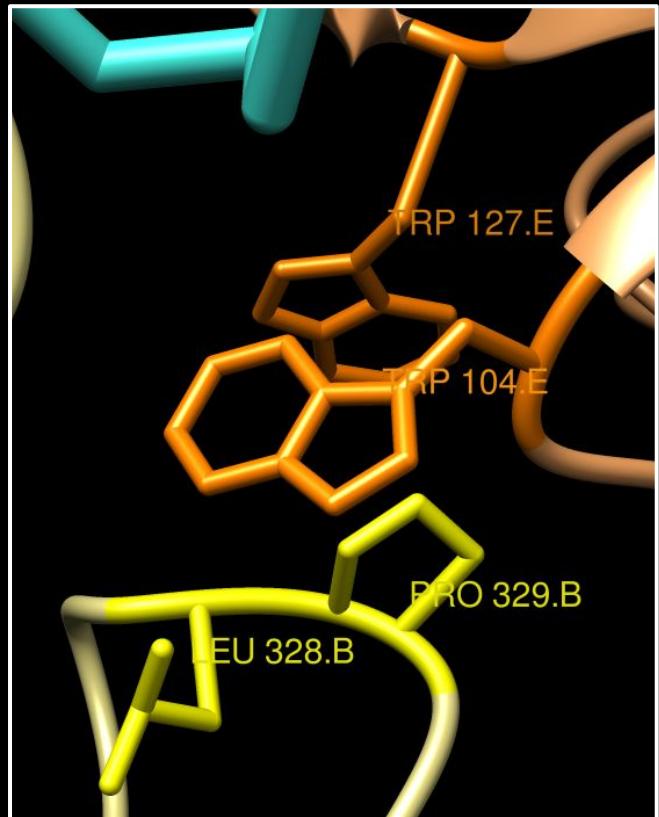
Fc IgG1



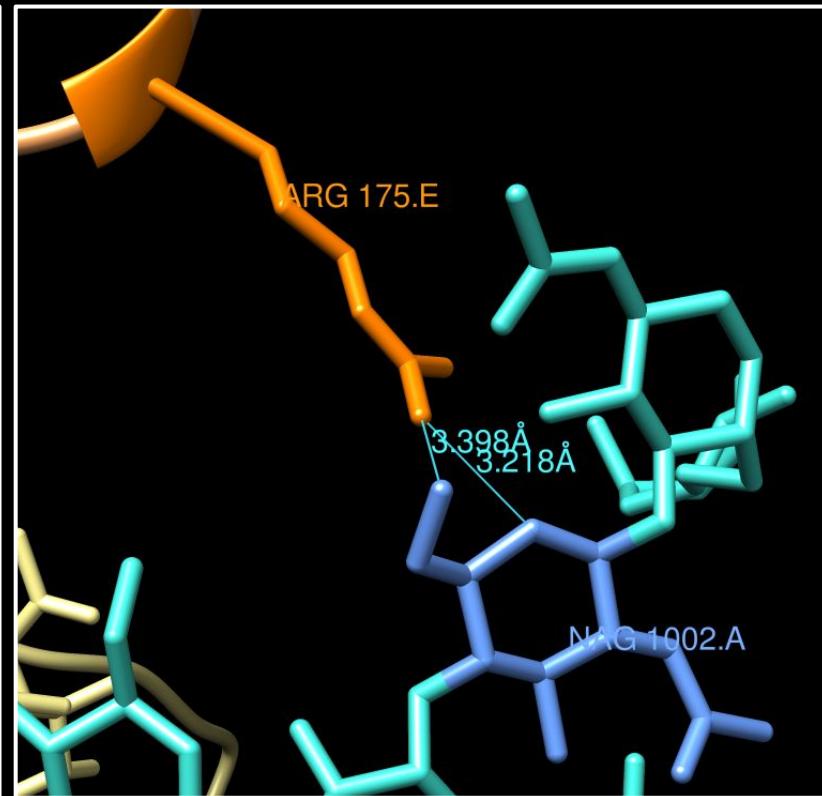
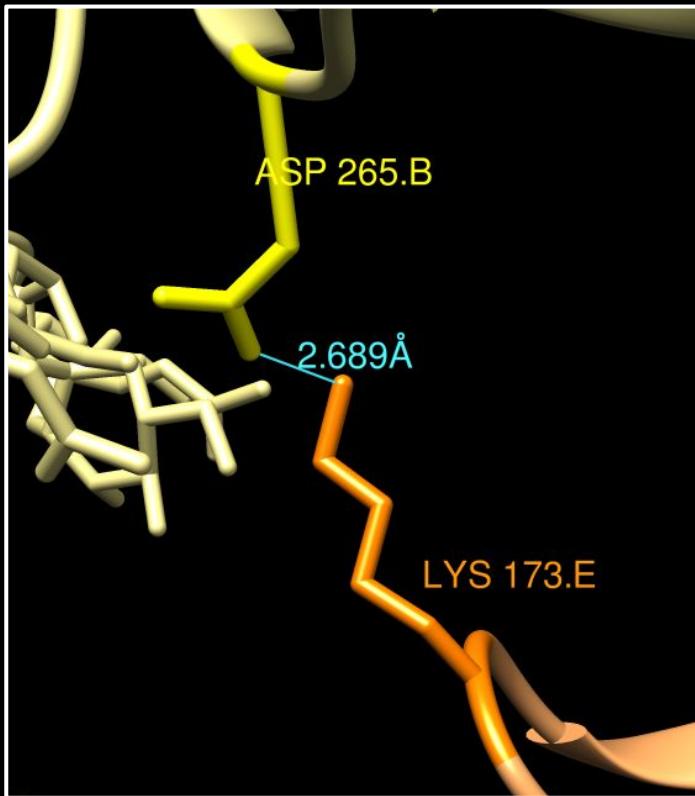
IgG-Fc γ RI: Region 1



IgG-Fc γ RI: Region 2



IgG-Fc γ RI: Region 3



CONCLUSIONS

- The immunoglobulins have an important function in the **immune system**.
- The **diversity** of immunoglobulins allows them to recognize specifically a great variety of **antigens**, as we have seen in hyaluronidase-IgG1 interaction.
- The Ig domain is formed by **two β -sheets** built up with several **antiparallel β -strands** with a **Greek key** topology. These β -sheets are covalently linked with a **disulfide bond**.
- The flexibility of the immunoglobulin is conferred, in large part, by the **hinge region**.

- The heavy chain can exist in two forms: a soluble one and a surface one.
- The Fc of immunoglobulins is majorly conserved in the IgG.
- N-glycosylation plays a key role in the interactions with the effector cells.
- The **CDRs** are the hypervariable regions of the immunoglobulin. They contribute to its specificity and form the **antigen binding site**. There are 3 in the light chain (**L1, L2** and **L3**) and 3 in the heavy chain (**H1, H2** and **H3**).
- Although the great variation of the CDRs, they have small main chain conformations that are called **canonical structures**.

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Questions

About the basic concepts of immunoglobulins:

- a) Structural differences in Fab fragment are the basis for five different isotypes classes of immunoglobulins.
- b) In immunoglobulin G the disulfide bonds are formed between cysteine residues of constant domain 2 close to the hinge.**
- c) The Fc fragment are formed by the association of variable and constant domains of light chain, and the variable and constant 1 domains of heavy chain.
- d) There are four different types of light chain.
- e) There are three loci that encode for heavy chain.

The difference between the fold of the variable domain and the constant domain is:

- a) The constant domain contains two extra β -strands called C' and C''
- b) The constant domains hasn't got a Greek Key topology
- c) a and b are true
- d) The variable domain contains two extra β -strands called C' and C''**
- e) There is no difference between them

About the Fab arm exchange, which of the following is false:

- a) It is characteristic from IgG3**
- b) Involves that the core hinge forms intra- rather than inter heavy chain disulfide bonds
- c) It affects both, covalent and non covalent interaction
- d) Half molecules can recombine to create bispecific immunoglobulines
- e) All of them are true

The flexibility of the immunoglobulin is conferred in large part by:

- a) The constant domain
- b) The variable domain
- c) The hinge**
- d) The light chain
- e) The heavy chain

About the Fc from immunoglobulin G:

- a) It is not mostly conserved between species
- b) The cysteines that form the disulphide bonds vary between IgGs
- c) There are two possible forms of the heavy chain that differ in the N-terminal end
- d) There are few possible glycosylation patterns
- e) When the glycosylation is removed the effector functions are impaired**

Which determinant enables IgG4 to undergo Fab arm exchange?:

- a) The hinge
- b) CH3-CH3 domain interface
- c) a and b are true**
- d) CDR L1
- e) All of them are true

About the interaction between hyaluronidase and IgG1:

- a) The hyaluronidase fold is a Beta-alfa-Beta motif.
- b) The epitope is mostly continuous and composed of twenty consecutive residues.
- c) The apolar residues form most of the contacts with Ag.
- d) The hydrophobic residues are located predominantly at the periphery of Hyal binding surface.
- e) The total number of polar Hyal/Fab interactions comprises 4 salt bridges and 9 hydrogen bonds.**

About the Complementary Determining Regions (CDRs):

- a) They are only found in the light chain and its function is to bind with the antigen
- b) They are only found in the heavy chain and its function is to bind with the antigen
- c) They are only found in the light chain and its function is to stabilize the immunoglobuline
- d) They are found in both heavy and light chains and its function is to bind with the antigen**
- e) They are found in both heavy and light chains and its function is to stabilize the immunoglobuline

About the canonical structures of the Complementary Determining Regions (CDRs), mark the false sentence:

- a) All of the CDRs have canonical structures**
- b) The canonical structures are small number of main chain conformations
- c) L2 only have one canonical structure
- d) The H3-CDR is the one with more variability
- e) There are different canonical structures for the same CDR in lambda light chain and in kappa light chain

About the IgG1-Fc γ RI mark the correct answer:

1. There are no van der Waals interactions in any region
2. We can find three hydrophobic clusters
3. The interactions are with domains D1 and D2 from the receptor
4. The receptor also interacts with the glycan bound to the Fc of the immunoglobulin

a) 1, 2, 3

b) 1 i 3

c) 2 i 4

d) 4

e) 1, 2, 3, 4

