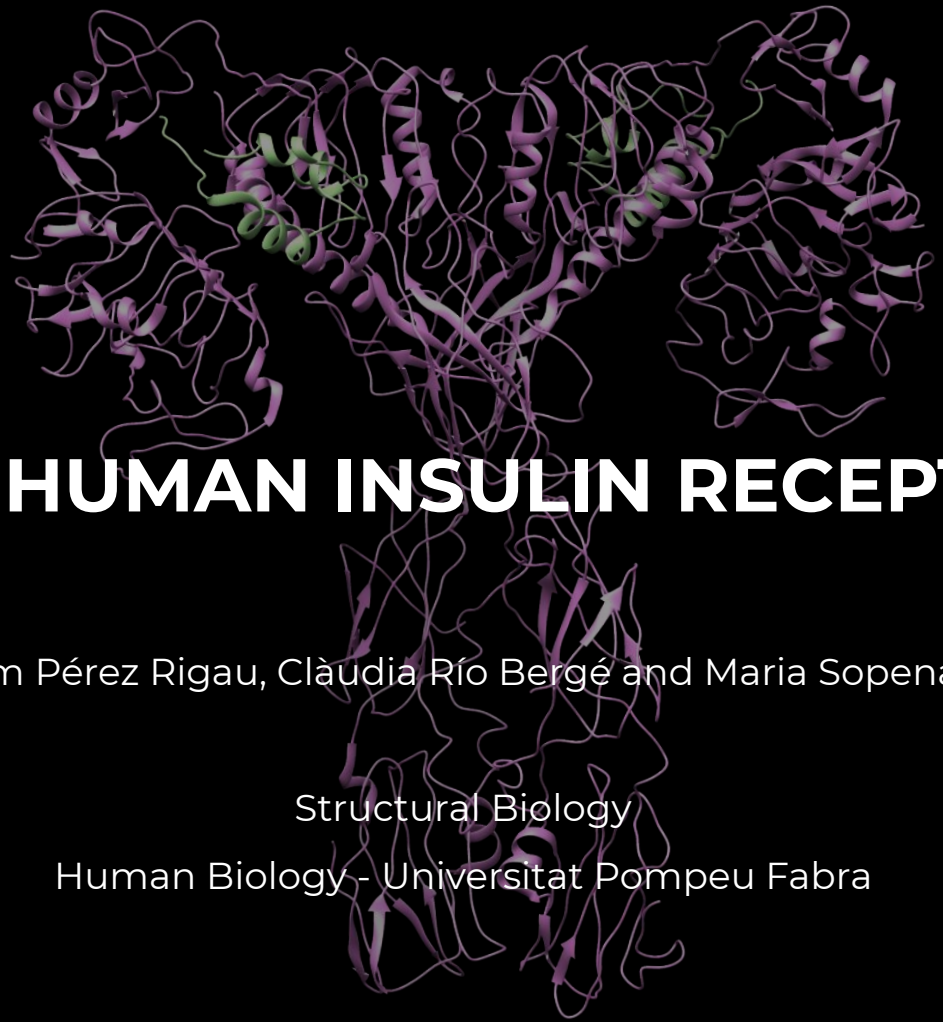


THE HUMAN INSULIN RECEPTOR

Guillem Pérez Rigau, Clàudia Río Bergé and Maria Sopena Rios

Structural Biology

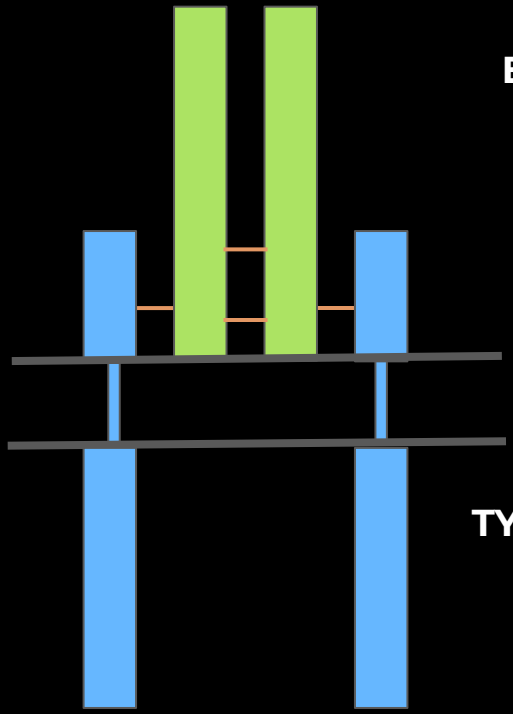
Human Biology - Universitat Pompeu Fabra

THE HUMAN INSULIN RECEPTOR

- Introduction
- IR structure
- Interaction IR-insulin
- Conformational changes upon insulin binding
- Comparison IR-IGF1R
- Evolution of IR
- Take home message
- Bibliography
- PEM questions

Introduction

INSULIN RECEPTOR

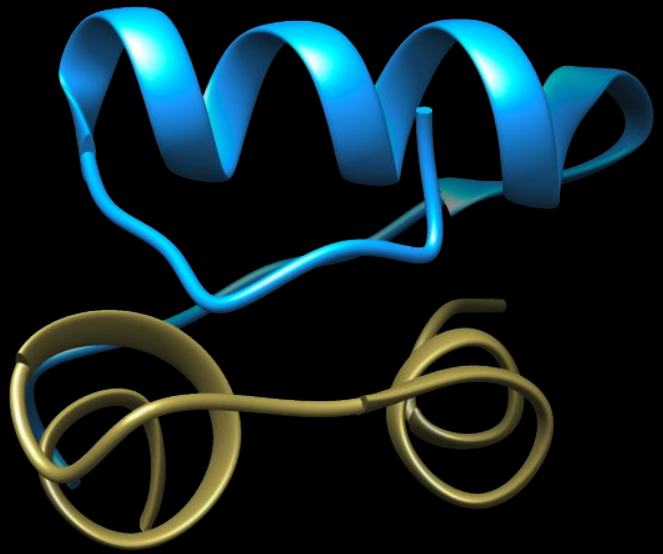


ECTODOMAIN
Interacts with insulin

TYROSINE-KINASE DOMAIN
Starts signalling pathways

- Receptor of tyrosine-kinase family
- Involved in glucose homeostasis and metabolism
- Homodimer composed by **alfa** and **beta** subunits linked by **disulfide bonds**

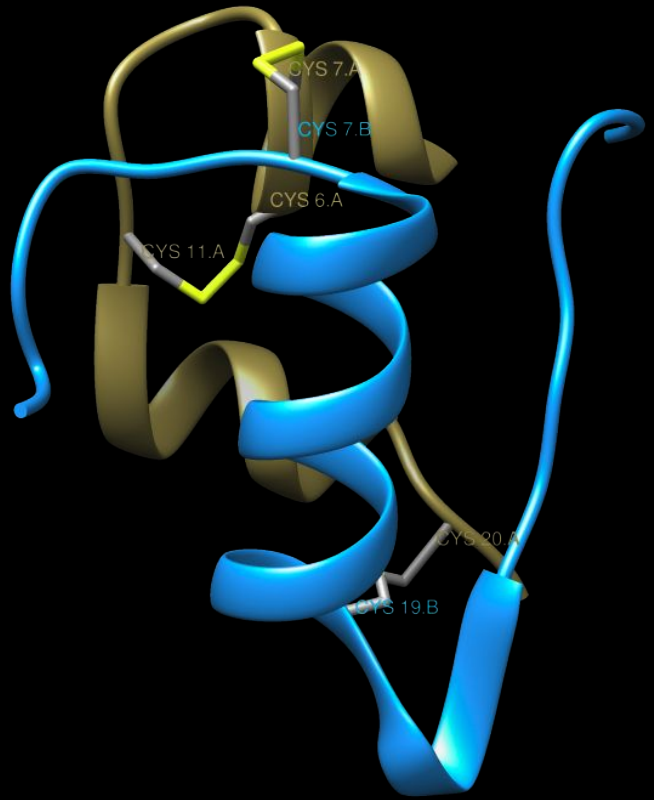
INSULIN



Monomer consisting in two chains:

- **Chain A**: N terminal and C terminal helices
- **Chain B**: Central helix

INSULIN



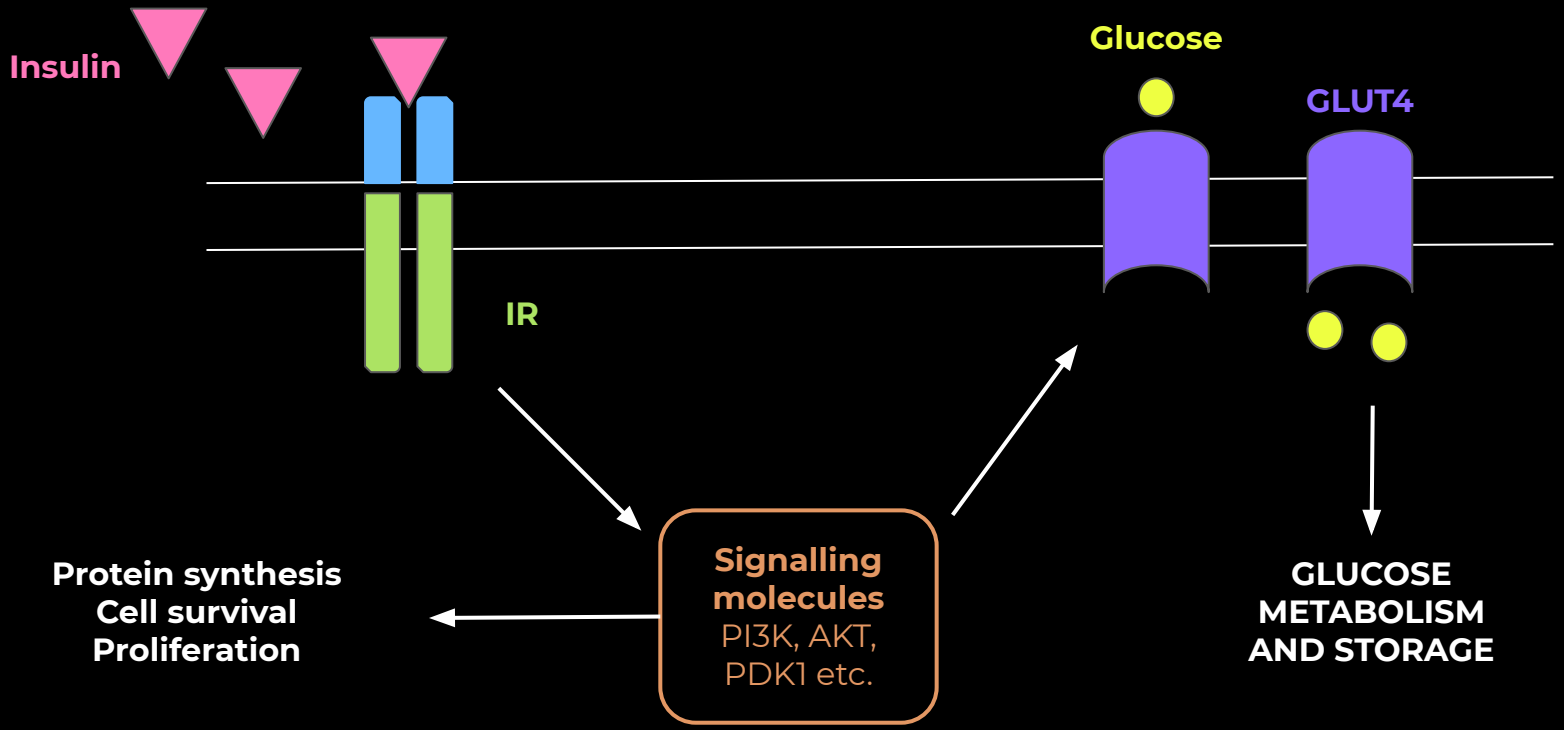
Disulfide bridges

A7	B7
A20	B19
A6	A11

INSULIN RECEPTOR FAMILY

	Insulin receptor	**IGF-1R**	**IGF-2R**	**IRR**
LIGAND	Insulin	IGF-1	IGF-2/M6P	unknown
FUNCTION	glucose homeostasis and metabolism	growth and anabolic processes	transport lysosomal acid hydrolase precursors	pH sensing receptor

SIGNALLING PATHWAY

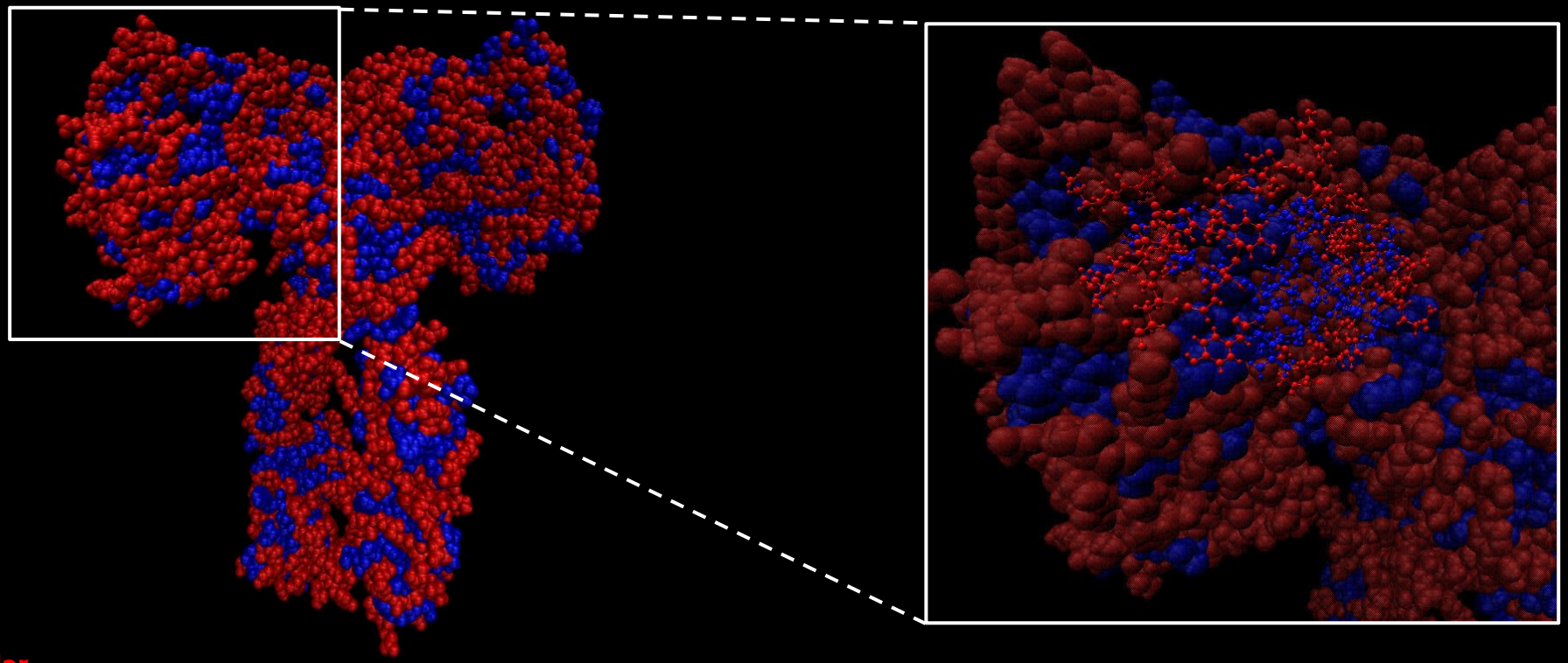


Adapted from Godsell, 2015

SCOP CLASSIFICATION

Class	Fold	Superfamily	Family	Protein
Small proteins	**Knottins** (small inhibitors, toxins, lectins) Disulfide-bound fold; contains beta-hairpin with two adjacent disulfides	Growth factor receptor domain	Growth factor receptor domain	Insulin receptor

POLARITY



Polar
Hydrophobic

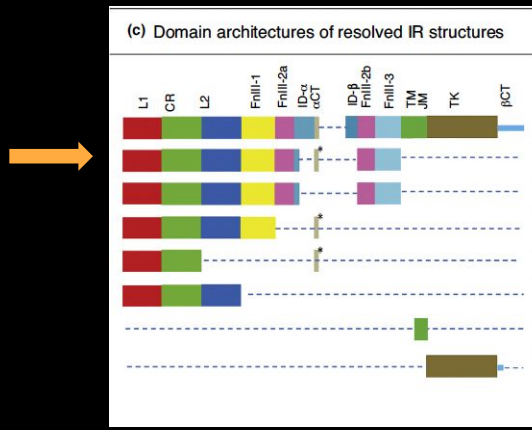
Insulin receptor structure

CRYSTALLOGRAPHY

No full-length structures of the Insulin Receptor.

- Large flexibility.
- Membrane-bound nature.

Structures deposited in the PDB database:

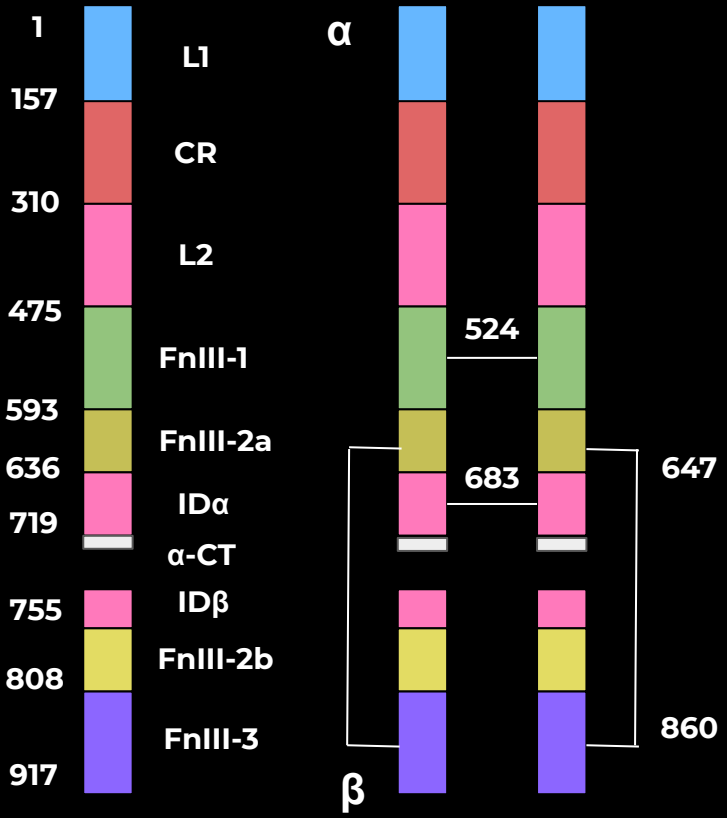


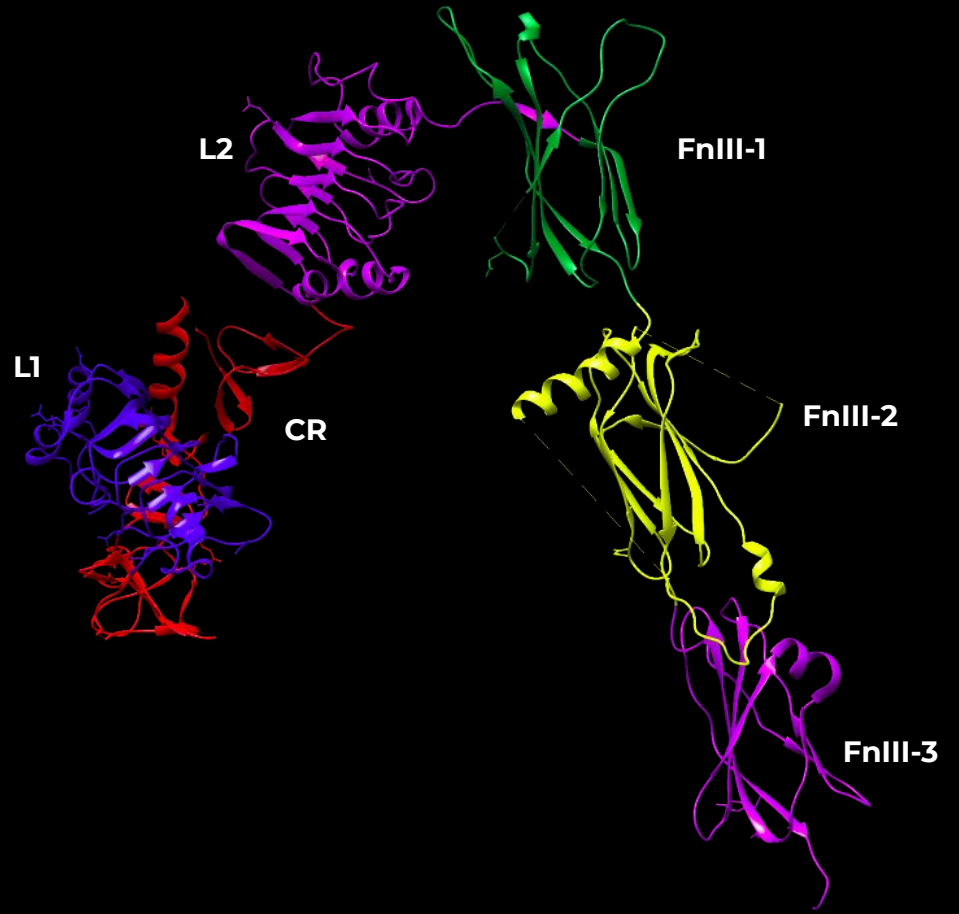
(c) Domain architectures of resolved IR structures	PDB IDs
	Composition of full-length IR (no structure)
	4ZXB [11], 3LOH [14]
	2DTG [13,78]
	3W14 [10]
	3W11, 3W12, 3W13 [10], 4OGA [29]
	2HR7 [23]
	2MFR [16]
	1IRK [9], 1IR3 [32], 1GAG [79], 1I44 [80], 1P14 [81], 2AUH [82], 2B4S [83], 3BU3, 3BU5, 3BU6 [84], 2Z8C [85], 4XLV [18]

Most complete ectodomain

Obtained from Ye L *et al*, 2017

IR OVERVIEW





Adapted from Croll T *et al*, 2017

L1 and L2

L1

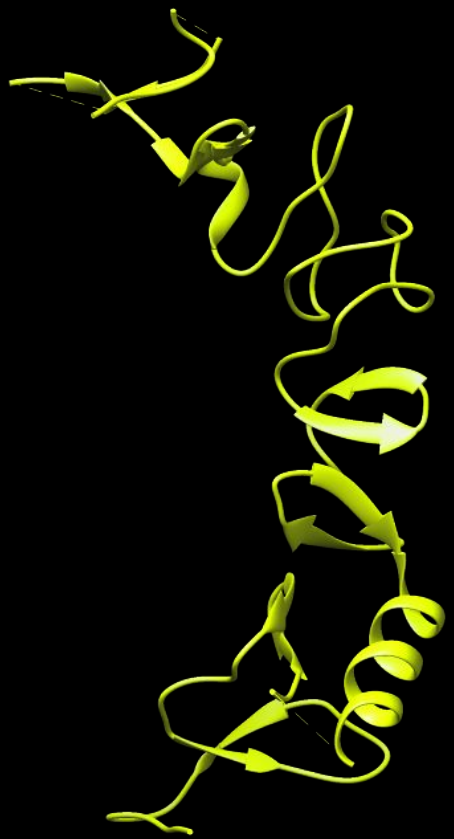
L2

LEUCINE-RICH DOMAIN

Curved horseshoe structures

Parallel beta sheets
Some helices

CR

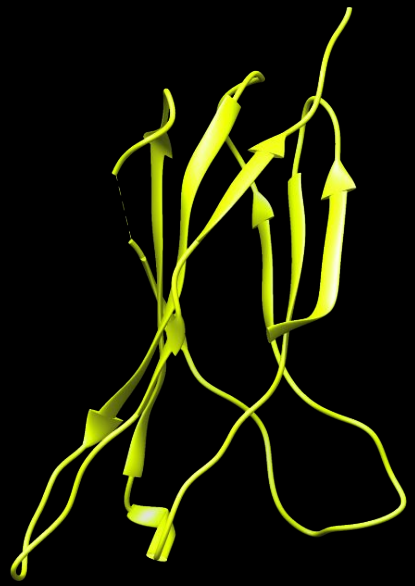


CYSTEINE-RICH DOMAIN

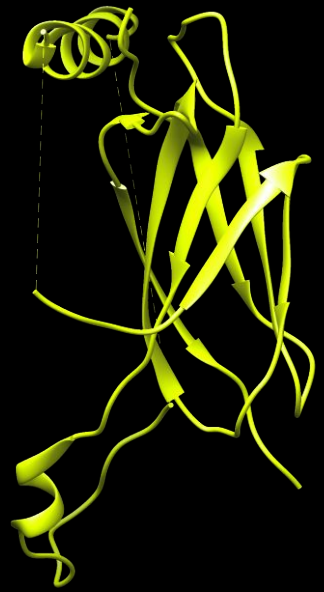
Furin-like cysteine region

Single helix on one side
Small antiparallel sheets

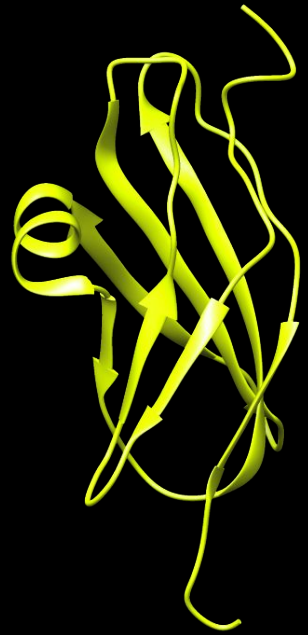
FnIII



FnIII-1



FnIII-2



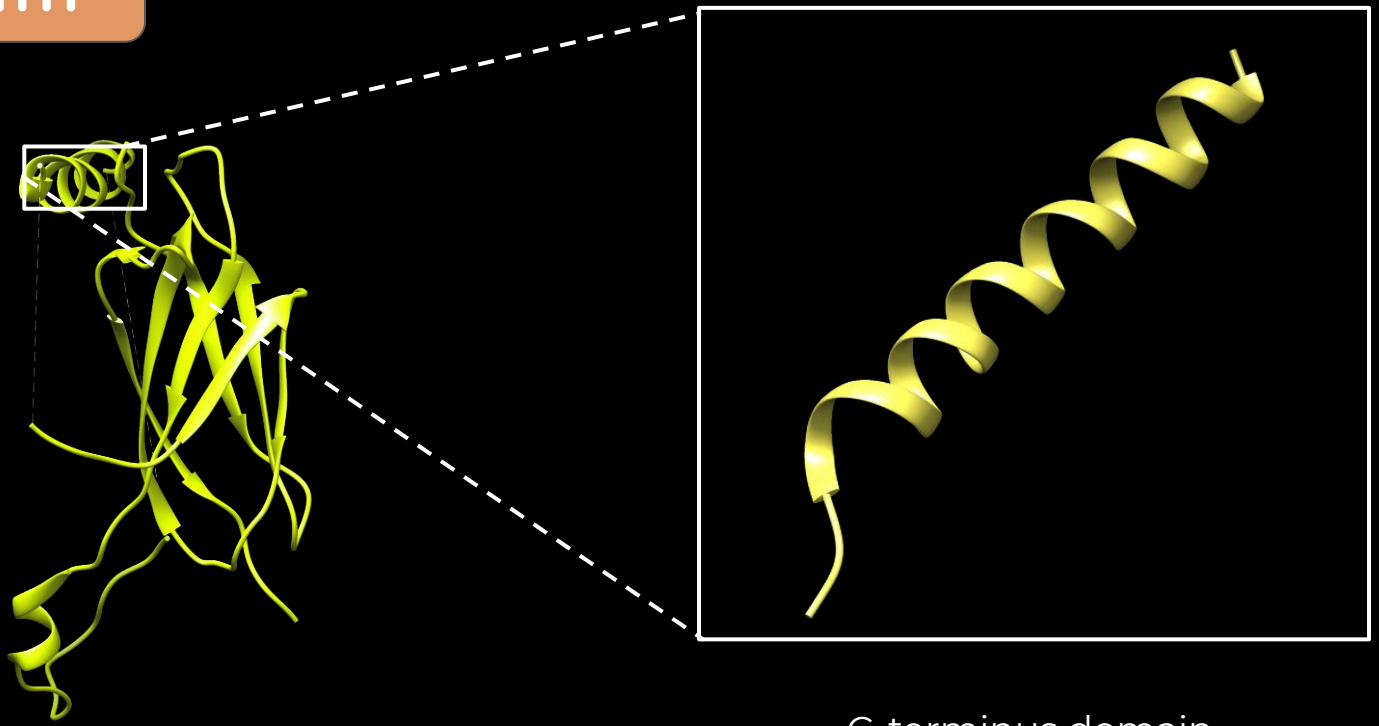
FnIII-3

FIBRONECTIN-TYPE III DOMAIN

Sandwich domain

Two antiparallel beta-sheets

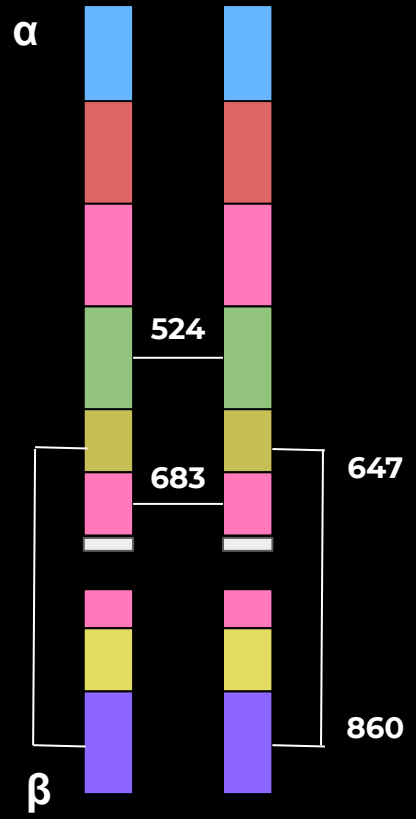
FnIII



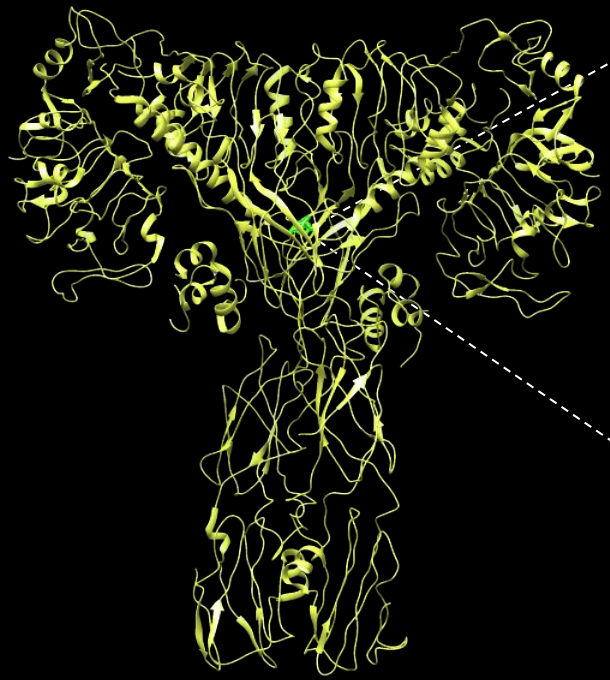
FnIII-2

C-terminus domain.
Key role in insulin binding

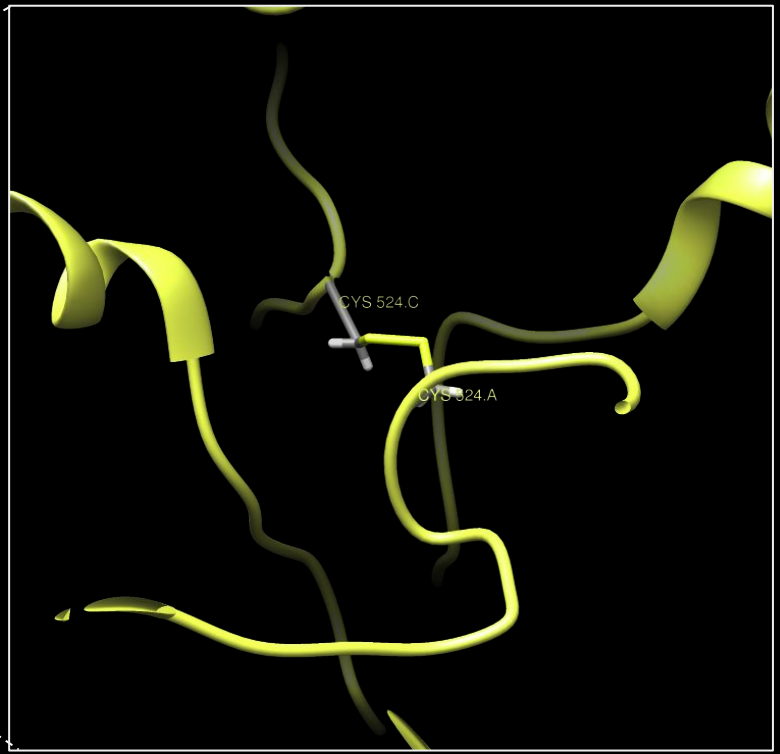
DISULFIDE BONDS



DISULFIDE BOND



Cys524 - Cys524



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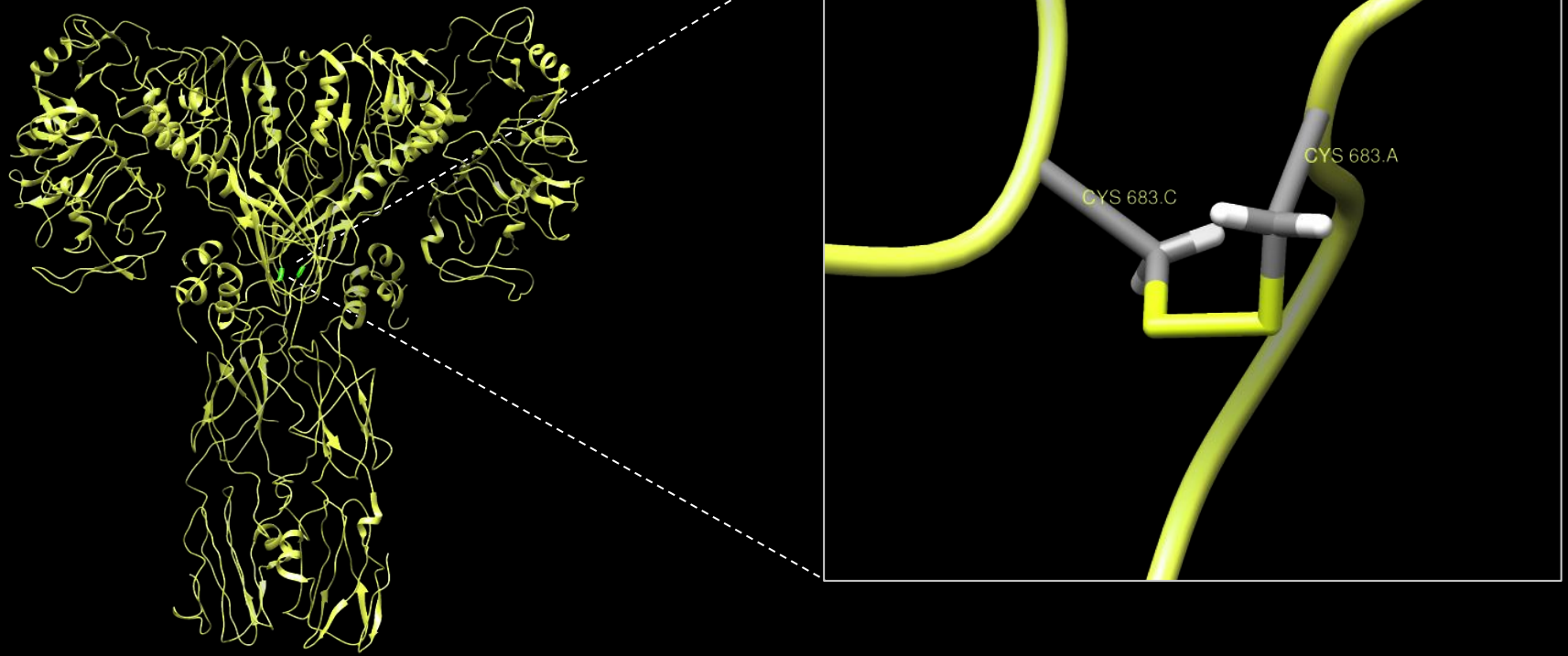
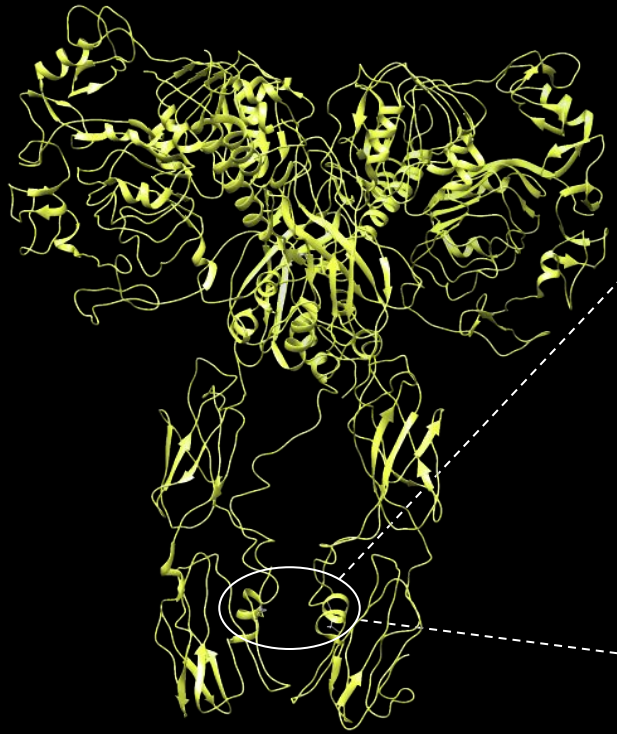


DISULFIDE BOND



Cys647 - Cys860

Interaction IR-insulin

METHODOLOGY

Interaction analysis:

1. Data from PDB structures-related articles ✘
2. Data from original PDB structures and other articles ✘
3. PISA prediction ✓

METHODOLOGY

Hydrogen bonds

XML

No disulfide bonds found
No covalent bonds found
No salt bridges found

##	Structure 1	Dist. [Å]	Structure 2
1	C:ARG 498[HH21]	2.48	E:CYS 7[SG]
2	C:ASN 711[OD1]	1.87	E:ILE 2[H]

Interfacing residues (not a contact table)

XML Display level: Residues

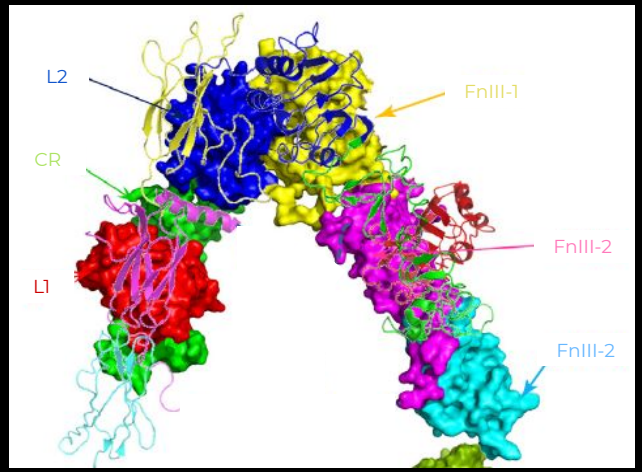
Inaccessible residues
Solvent-accessible residues
HSDC Residues making **H**ydrogen/**D**isulphide bond, **S**alt bridge or **C**ovalent link
Interfacing residues

ASA Accessible Surface Area, Å² **BSA** Buried Surface Area, Å² **$\Delta^i G$** Solvation energy effect, kcal/mol |||| Buried area percentage, one bar per 10%

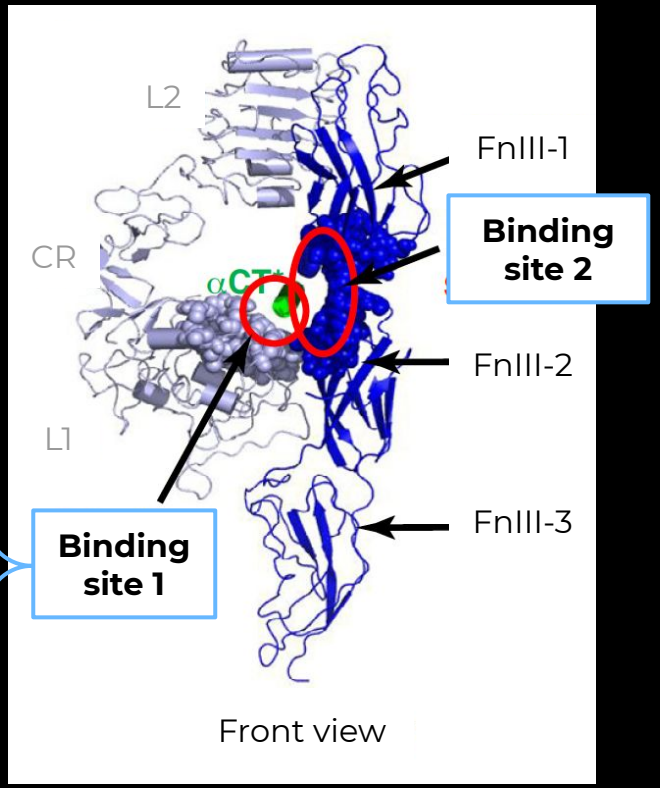
##	Structure 1	HSDC	ASA	BSA	$\Delta^i G$
1	C:HIS 1		168.50	0.00	0.00
2	C:LEU 2		35.11	0.00	0.00
3	C:TYR 3		37.41	0.00	0.00
4	C:PRO 4		105.23	0.00	0.00
5	C:GLY 5		23.79	0.00	0.00
6	C:GLU 6		123.28	0.00	0.00
7	C:VAL 7		103.25	0.00	0.00
8	C:CYS 8		18.77	0.00	0.00
9	C:PRO 9		78.90	0.00	0.00
10	C:GLY 10		36.97	0.00	0.00
11	C:MET 11		57.47	0.00	0.00
12	C:ASP 12		36.80	0.00	0.00
13	C:ILE 13		17.19	0.00	0.00
14	C:ARG 14		116.71	0.00	0.00
15	C:ASN 15		90.74	0.00	0.00
16	C:ASN 16		91.16	0.00	0.00
17	C:LEU 17		34.93	0.00	0.00

##	Structure 2	HSDC	ASA	BSA	$\Delta^i G$
1	E:GLY 1		60.88	21.34 ||||	0.30
2	E:ILE 2	H	120.78	80.79 |||||||	1.11
3	E:VAL 3		86.27	58.90 |||||||	0.94
4	E:GLU 4		123.21	6.51 |	0.00
5	E:GLN 5		79.57	17.90 |||	-0.21
6	E:CYS 6		44.06	0.00	0.00
7	E:CYS 7	H	109.69	50.90 |||||	1.03
8	E:THR 8		111.53	0.00	0.00
9	E:SER 9		65.60	0.00	0.00
10	E:ILE 10		146.88	0.00	0.00
11	E:CYS 11		26.38	0.00	0.00
12	E:SER 12		50.12	0.00	0.00
13	E:LEU 13		123.44	0.00	0.00
14	E:TYR 14		173.49	0.00	0.00
15	E:GLN 15		75.33	0.73 |	-0.01
16	E:LEU 16		43.26	4.51 ||	0.07
17	E:GLU 17		97.07	0.00	0.00

INTERACTION IR-INSULIN



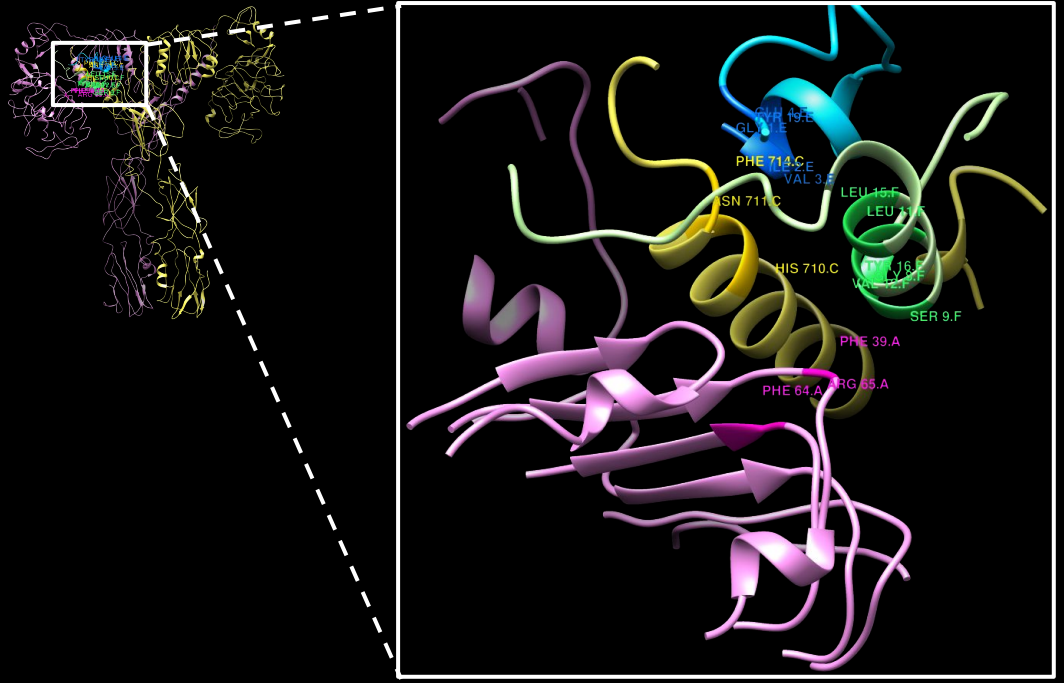
I
II
III
IV



Adapted from Ye L *et al*, 2017

BINDING SITE 1

The L1-αCT harbor



I

IR	Insulin
His710	ValA3
	GlyB8
	SerB9
	ValB12

III

IR	Insulin
Asn711	GlyA1
	ValA3
	GluA4

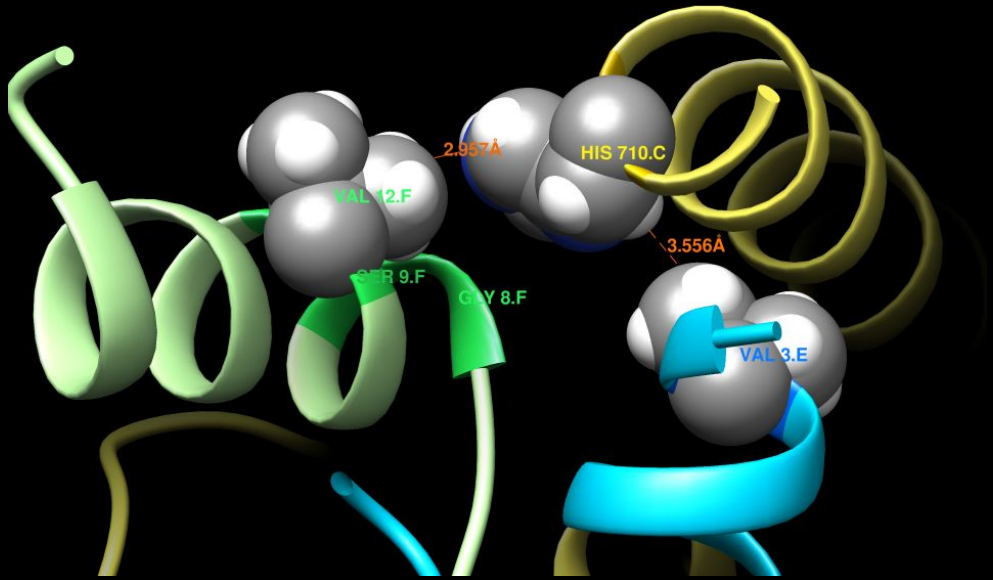
II

IR	Insulin
Phe714	GlyA1
	IleA2
	TyrA19
	LeuB11
	ValB12
	LeuB15

IV

IR	Insulin
Phe39	ValB12
Phe64	
Arg65	
Phe39	TyrB16

BINDING SITE 1: I

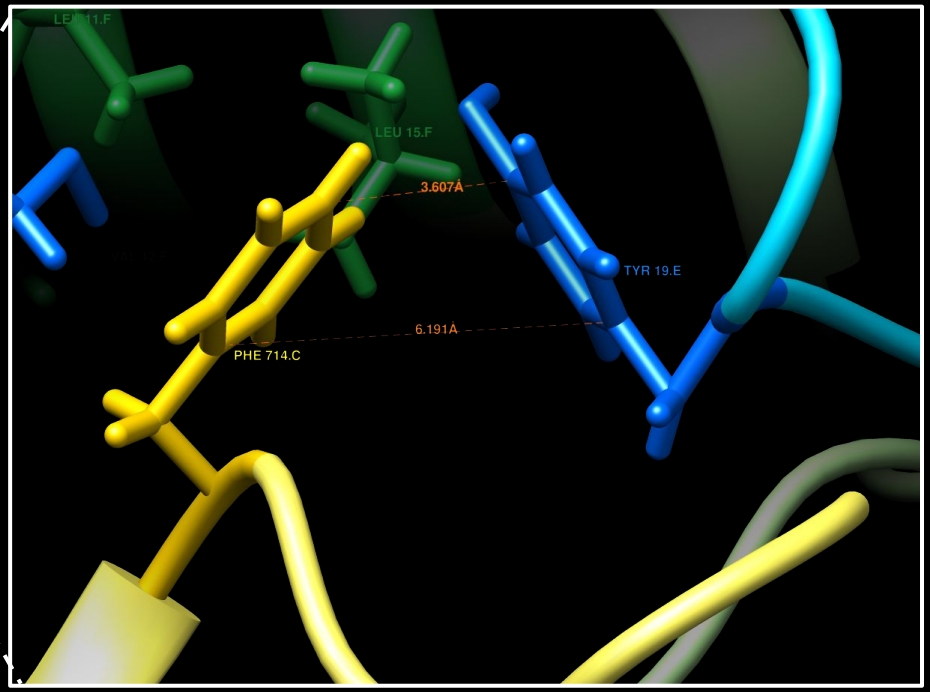


α-CT (IR)	Insulin	Type	Distance (Å)
His710	ValB12	VdW	2,975
	ValA3	VdW	3,556

BINDING SITE 1: II

α-CT (IR)	Insulin	Type	Distance (Å)
Phe714	TyrA19	π-int.	3,607-6,191 (-125,329 °)
	IleA2	VdW	≃ 2,8
	LeuB15	VdW	2,860

Hydrophobic pocket



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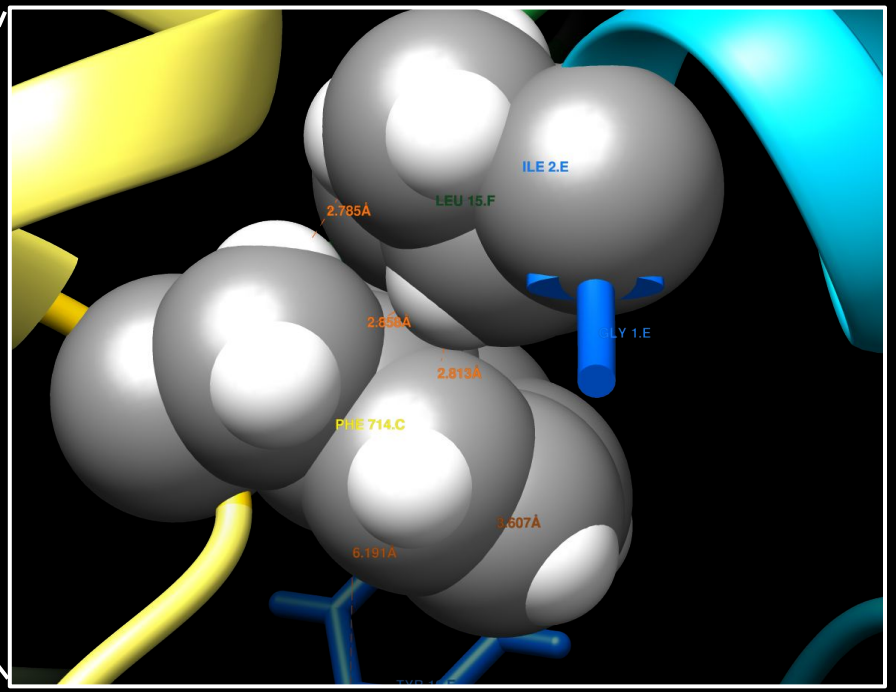

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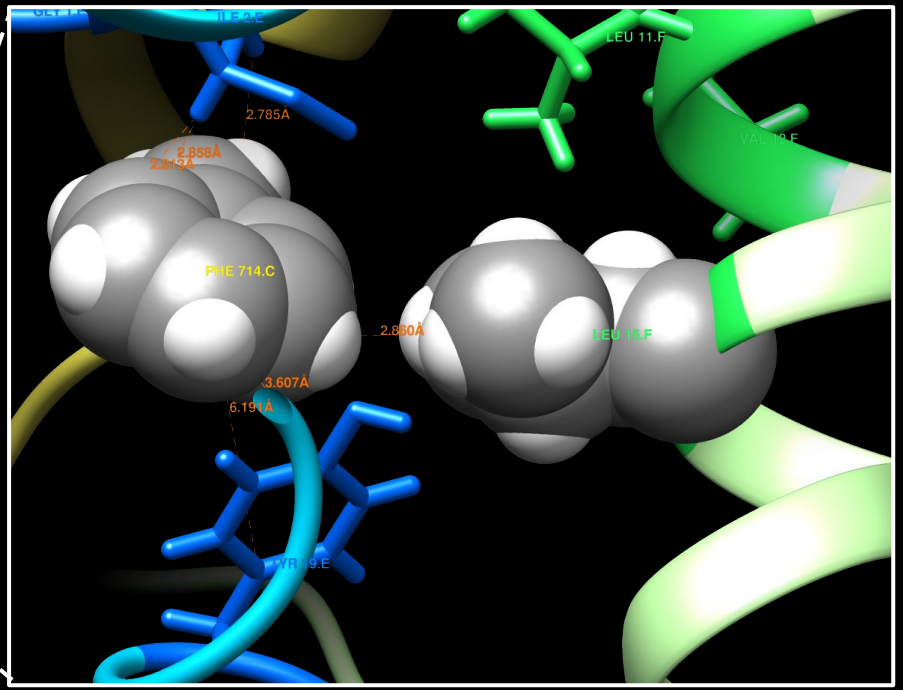
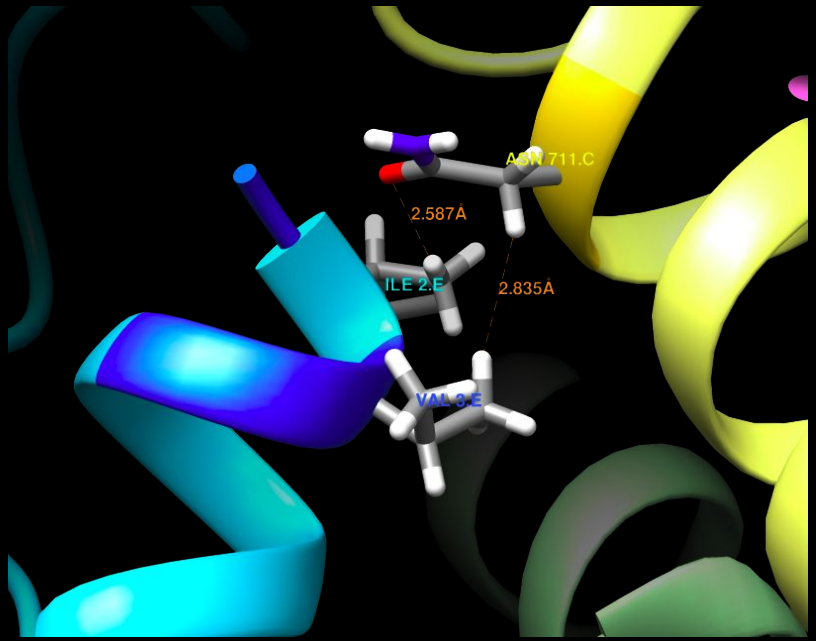
Hydrophobic pocket



BINDING SITE 1: III



α-CT (IR)	Insulin	Type	Distance (Å)
Asn711	GlyA1	VdW	-
	IleA2	VdW	2,587
	ValA3	VdW	2,835

BINDING SITE 1: III

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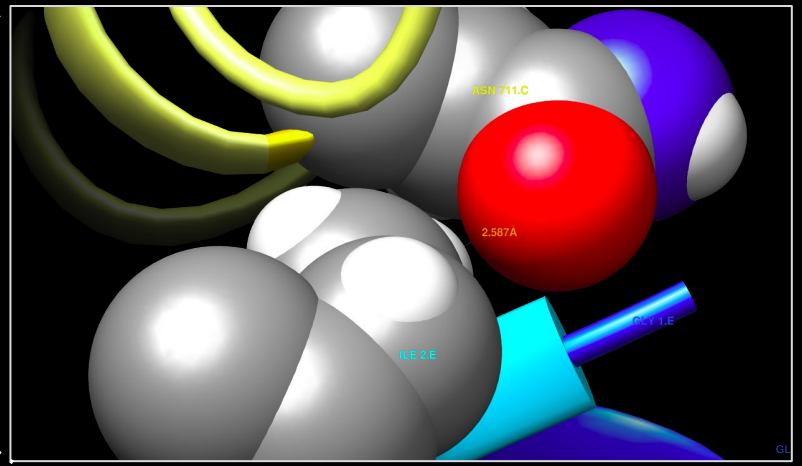
Asn711	GlyA1	VdW	-
	IleA2	VdW	2,587
	ValA3	VdW	2,835



BINDING SITE 1: III

α-CT (IR)	Insulin	Type	Distance (Å)
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	IleA2	VdW	2,587
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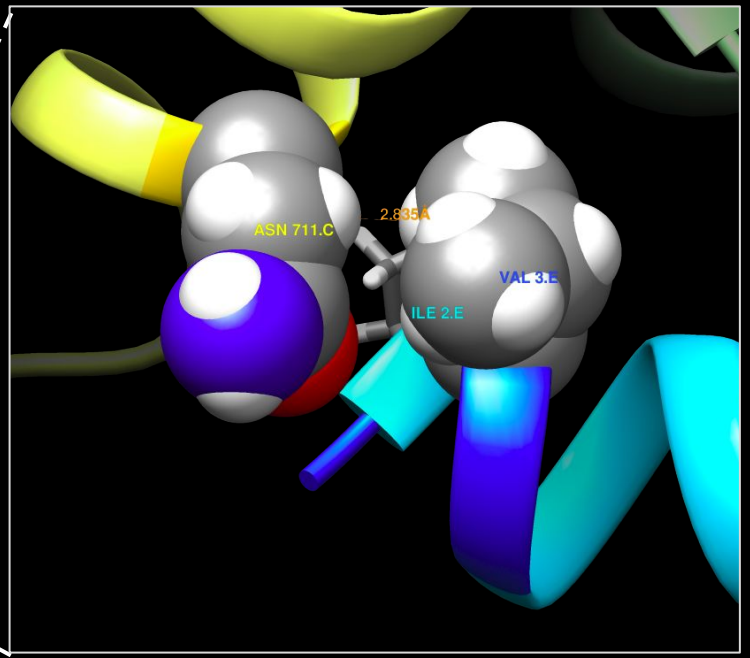

BINDING SITE 1: IV

L1 (IR)	Insulin	Type	Distance (Å)
Phe39	TyrB16	π-int.	3,459-4,018 (53,789 °)
Arg65	ValB12	VdW	2,394
Phe64	ValB12	VdW	4,471

Hydrophobic interaction

BINDING SITE 1: IV

L1 (IR)	Insulin	Type	Distance (Å)
Phe39	TyrB16	π-int.	3,459-4,018 (53,789 °)
Arg65	ValB12	VdW	2,394
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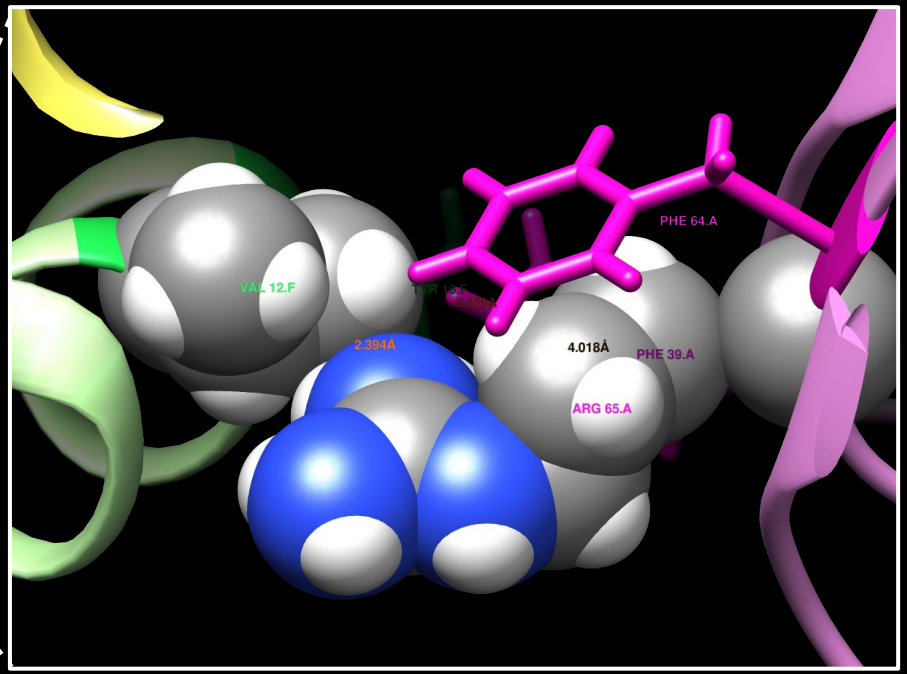

BINDING SITE 1: IV

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Phe39	TyrB16	π-int.	3,459-4,018 (53,789 °)
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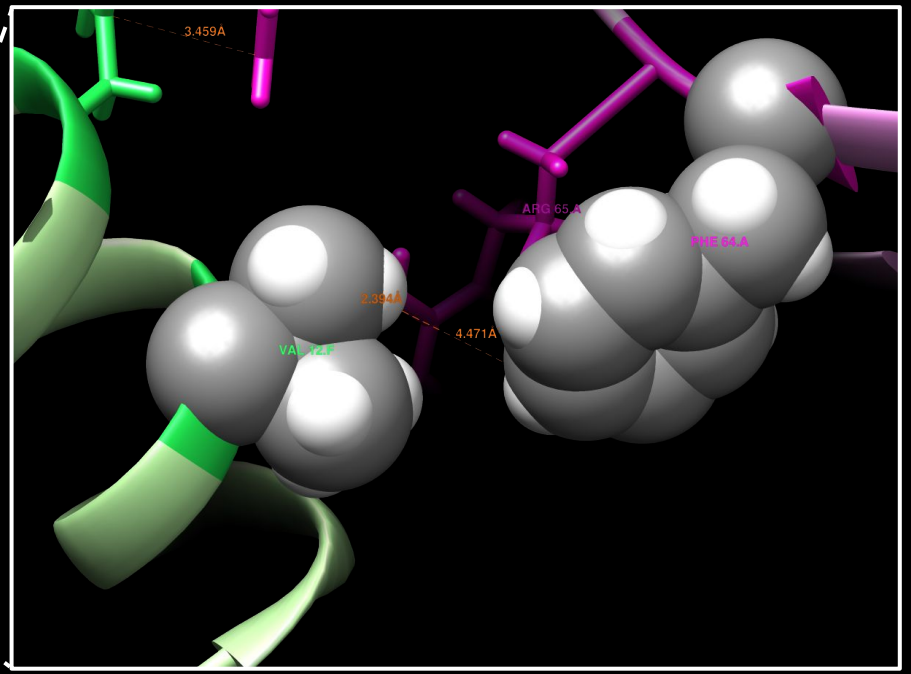
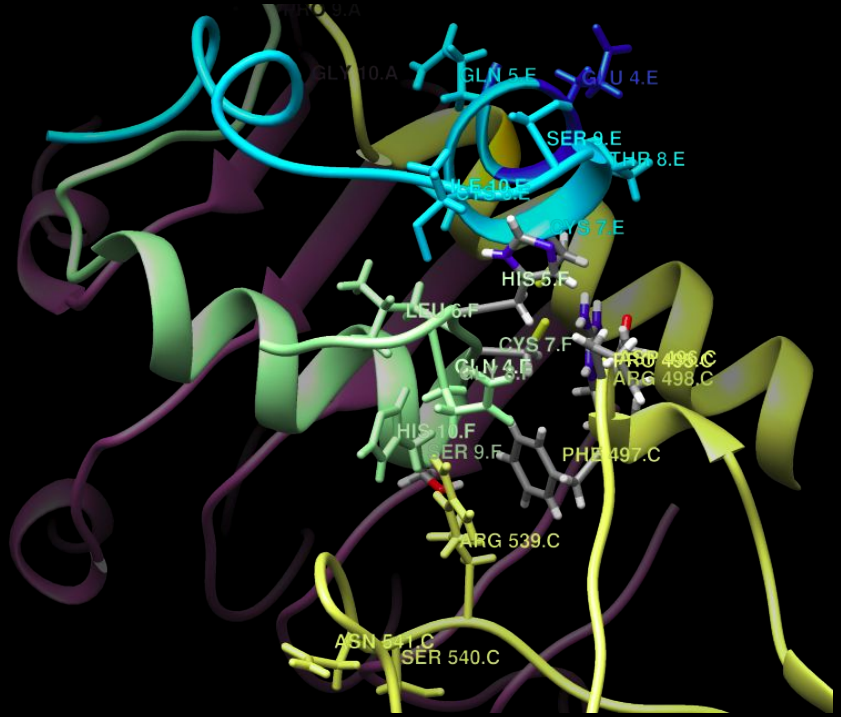
Hydrophobic interaction



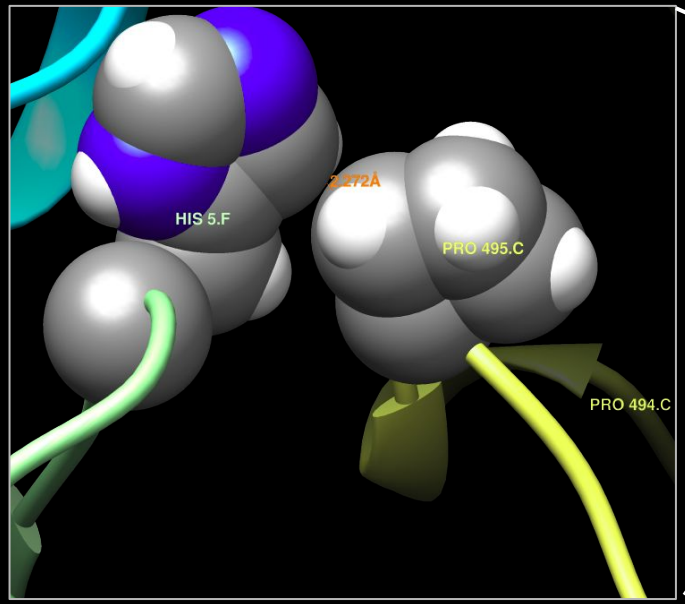
BINDING SITE 2

Junction of FnIII-1 and FnIII-2



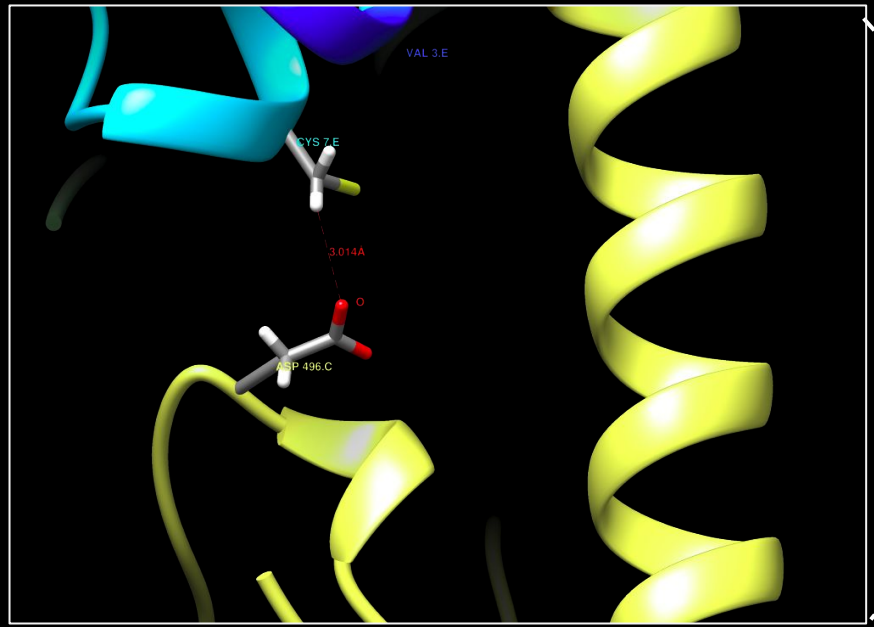
IR	Insulin
Pro495-Arg498	Chain B (Gln4-Gly10)
Arg539-Asn541	

BINDING SITE 2



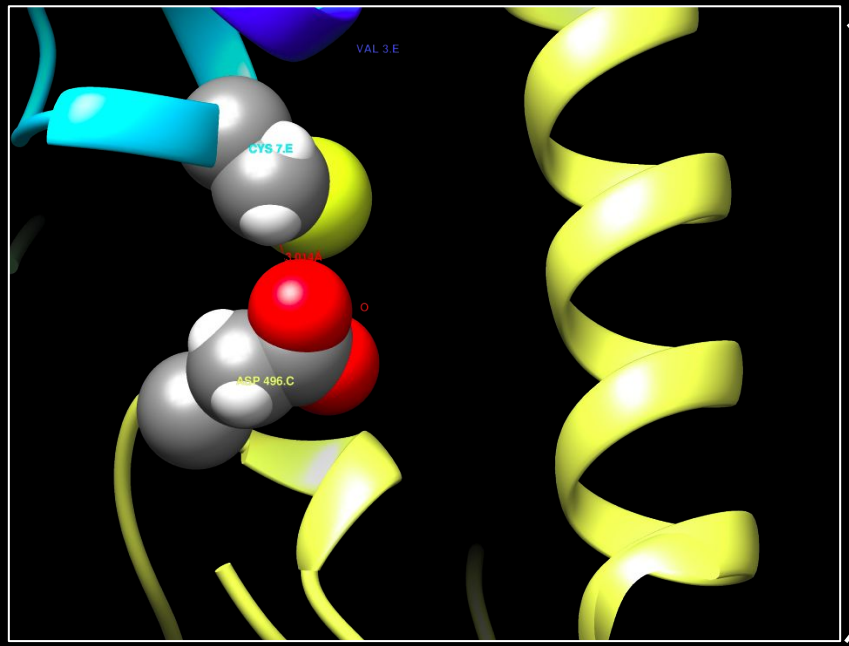
IR	Insulin	Type	Distance (Å)
Pro495	HisB5	VdW	2,272
Asp496	CysB7	VdW	3,014
Phe497	SerB9	VdW	3,466

BINDING SITE 2



IR	Insulin	Type	Distance (Å)
Pro495	HisB5	VdW	2,272
Asp496	CysB7	VdW	3,014
Phe497	SerB9	VdW	3,466

BINDING SITE 2



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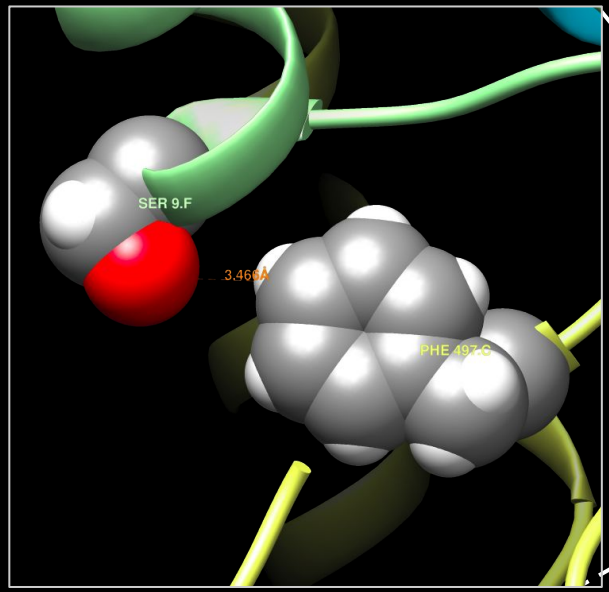
BINDING SITE 2



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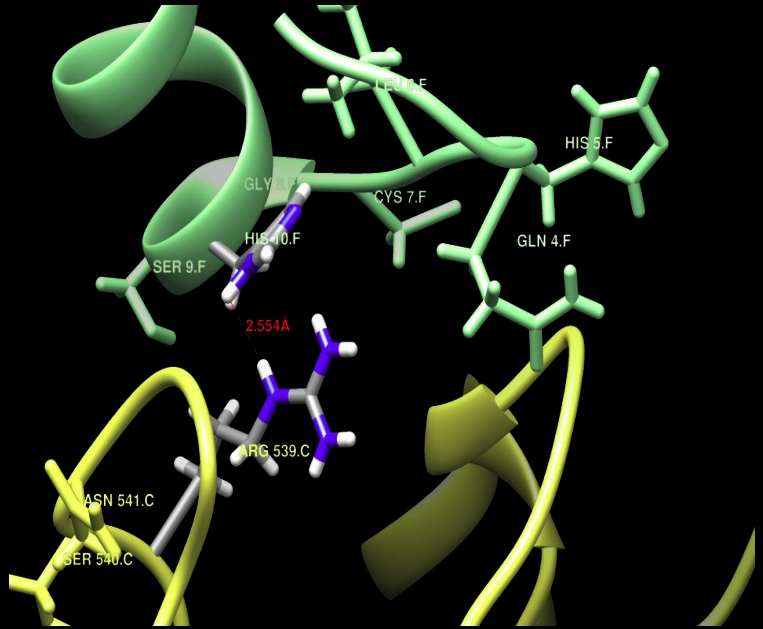
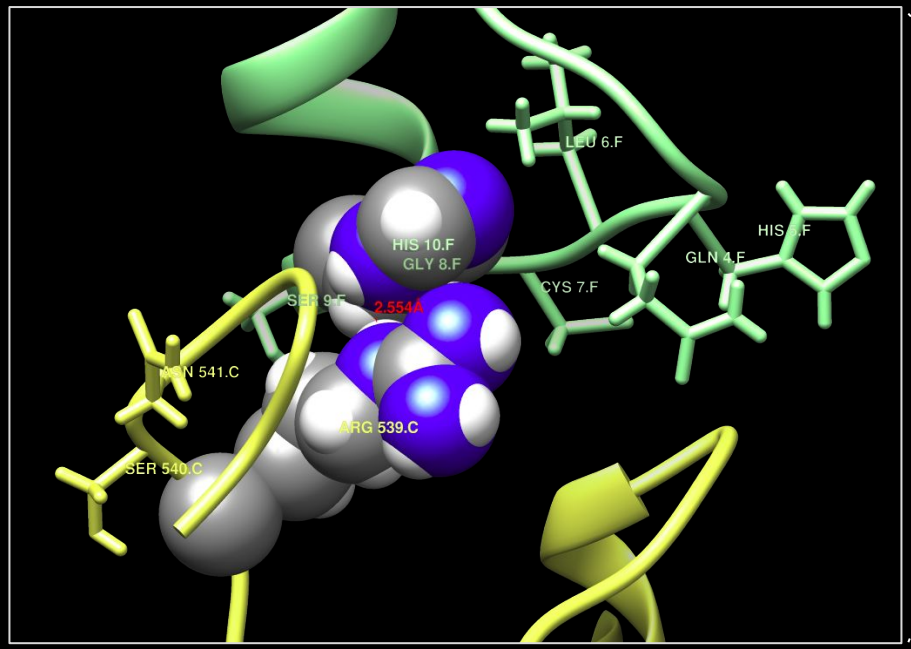
Phe497	SerB9	VdW	3,466

BINDING SITE 2



IR	Insulin	Type	Distance (Å)
Arg539	HisB10	VdW	2,554
Ser540	-	-	-
Asn 541	-	-	-

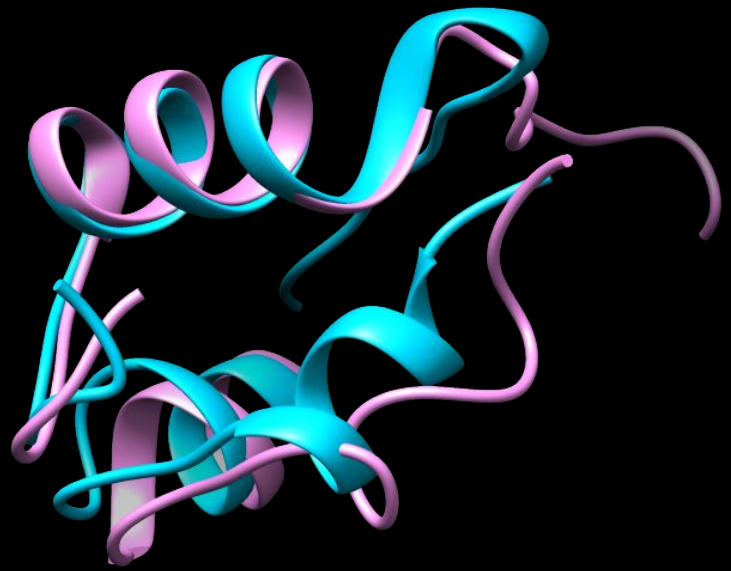
BINDING SITE 2



IR	Insulin	Type	Distance (Å)
Arg539	HisB10	VdW	2,554
Ser540	-	-	-
Asn 541	-	-	-

Conformational changes upon insulin binding

CONFORMATIONAL CHANGES INSULIN



RMSD = 5.604 Å

Insulin
Insulin bound to IR

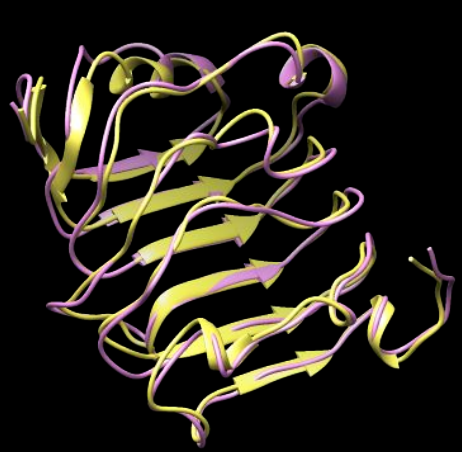
Conformational changes due to...

- IR interaction
- Crystallography

?

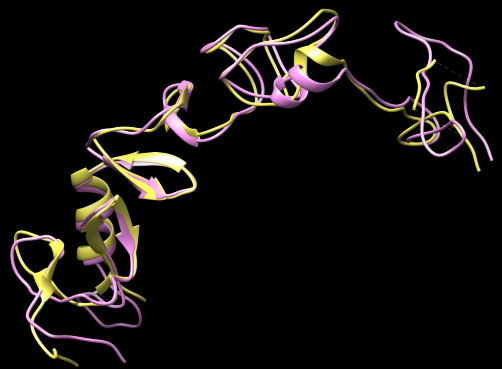
ROTATIONS

1. **Rotation of 35° of L2-CR-L1 domains**
2. **55° swing of CR-L1 domain**



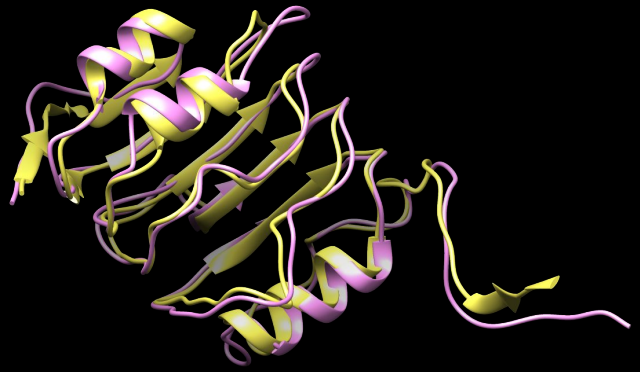
L1

RMSD = 1.194 Å



CR

RMSD = 2.242 Å



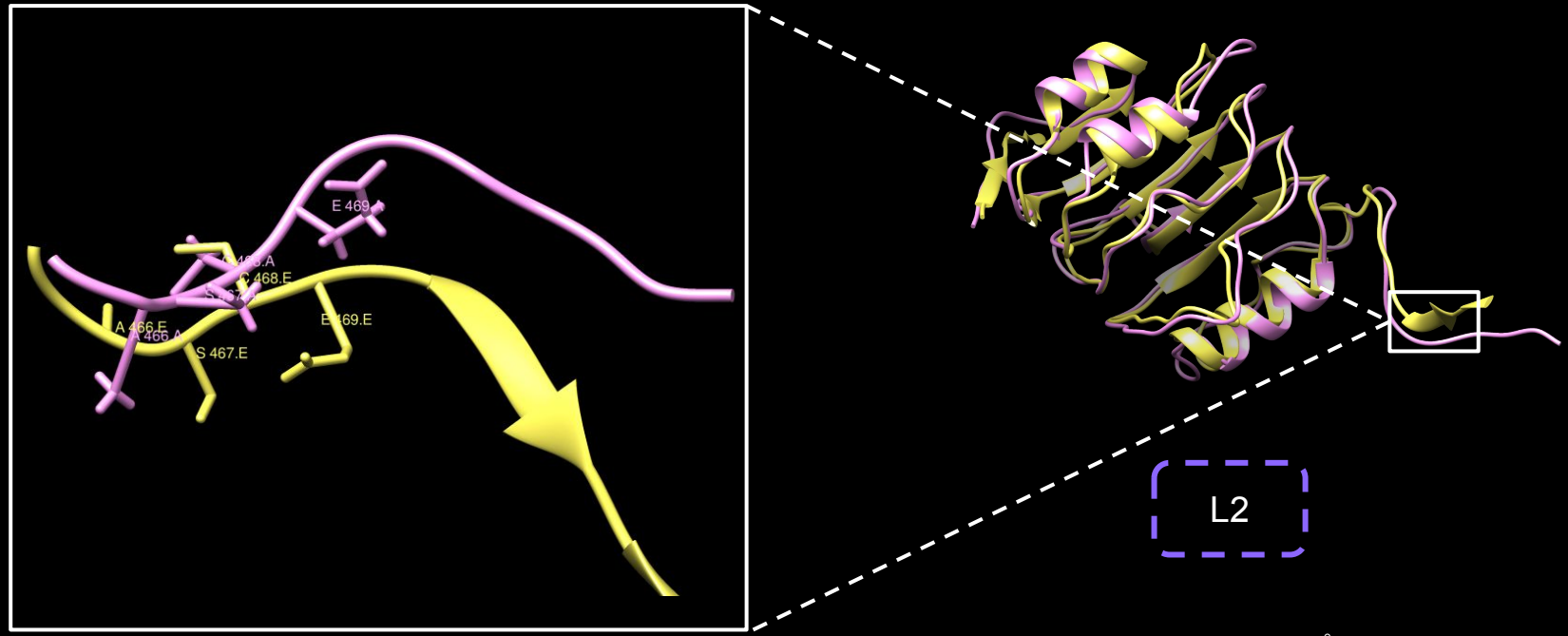
L2

RMSD = 2.374 Å

IR
IR+insulin

ROTATIONS

1 **Rotation of 35° of L2-CR-L1 domains**

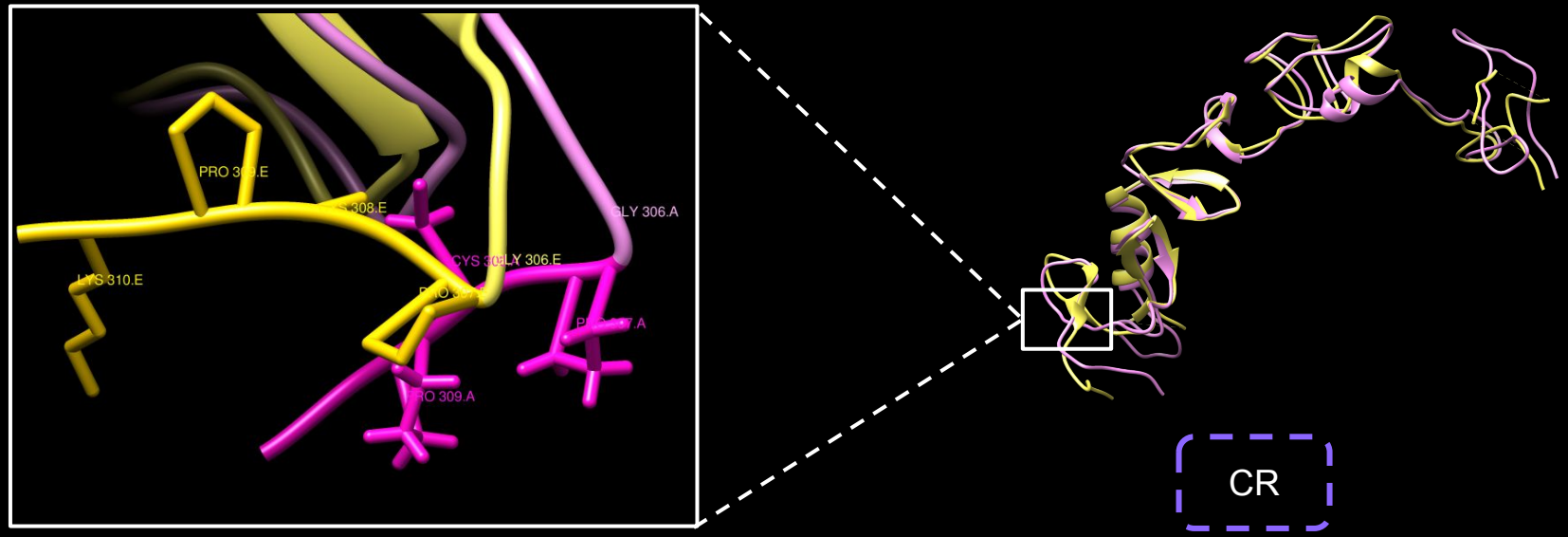


RMSD = 2.374 Å

IR
IR+insulin

ROTATIONS

2 **55° swing of the CR-L1 domain**

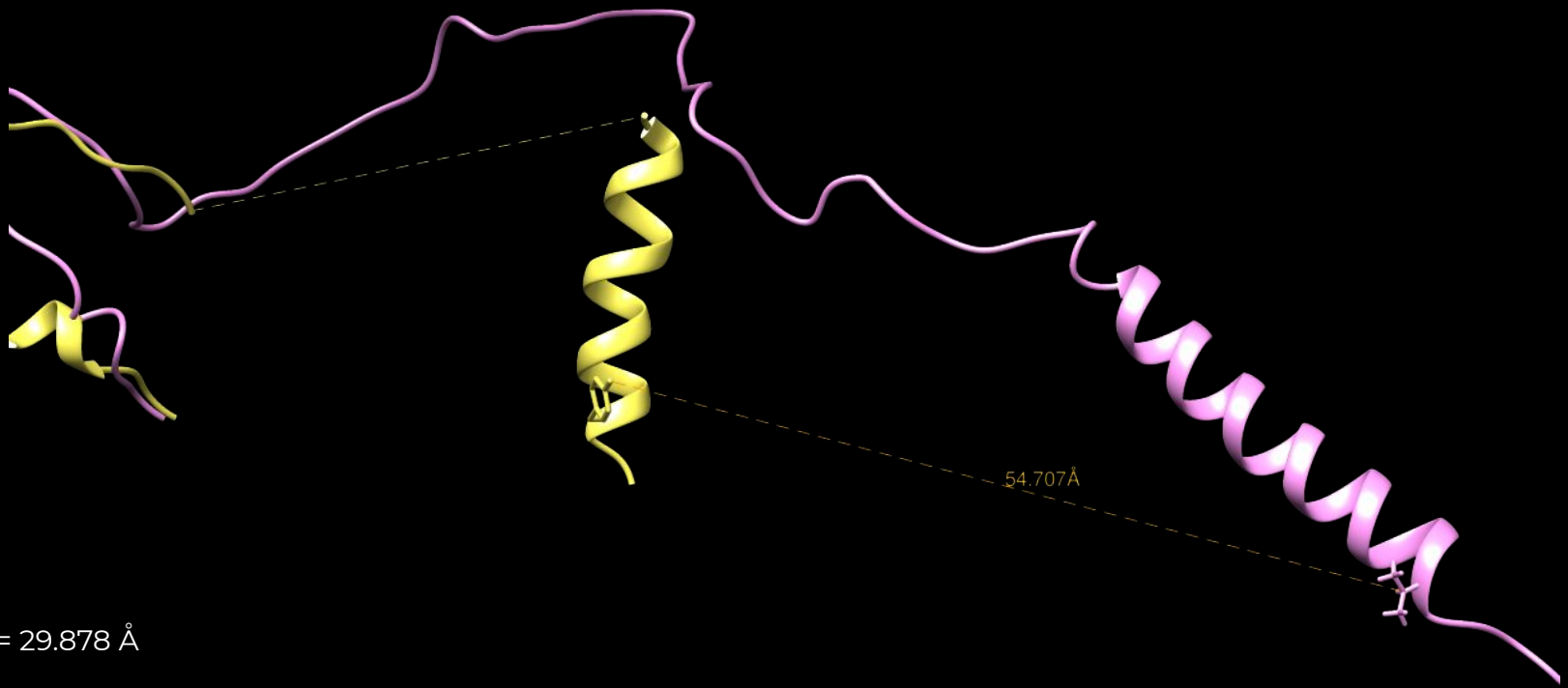


RMSD = 2.242 Å

IR
IR+insulin

alfa-CT

3 **Displacement of 55 Å of αCT domain**



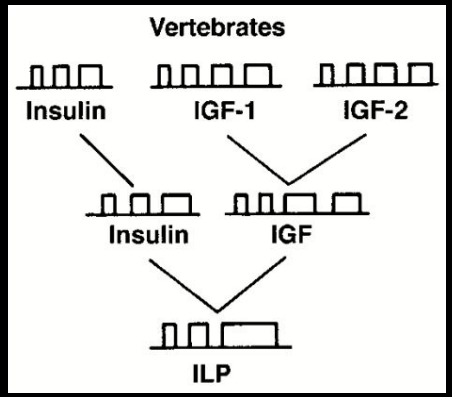
RMSD = 29.878 Å

IR
IR+insulin

Comparison IR-IGF1R

IGF1R-IR: comparison

- Hormone family: essential cellular physiological processes.
- The process of functional specialization is yet unknown.
- Origin: two rounds of gene duplication.



Adapted from Chan SJ *et al*, 2000

GENOMIC

SIMILARITIES

↑ degree of identity

12 exons with identical length

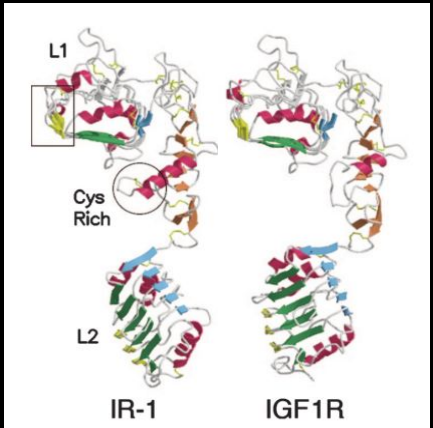
Strong selection pressure

DIFFERENCES

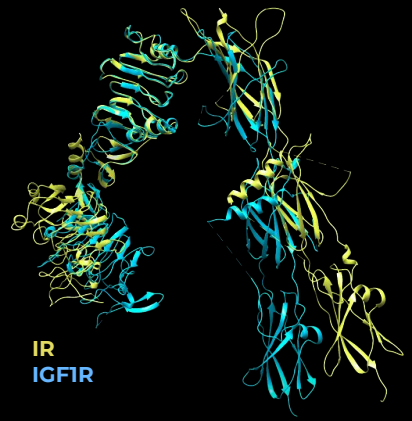
IGF-1R: 21 exons

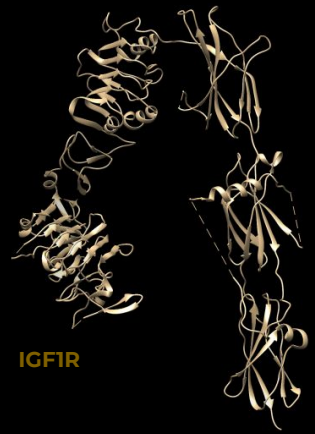
IR: 22 exons → 2 isoforms

IGF1R-IR: comparison



Adapted from Meizhen Lou *et al*, 2006





SIMILARITY

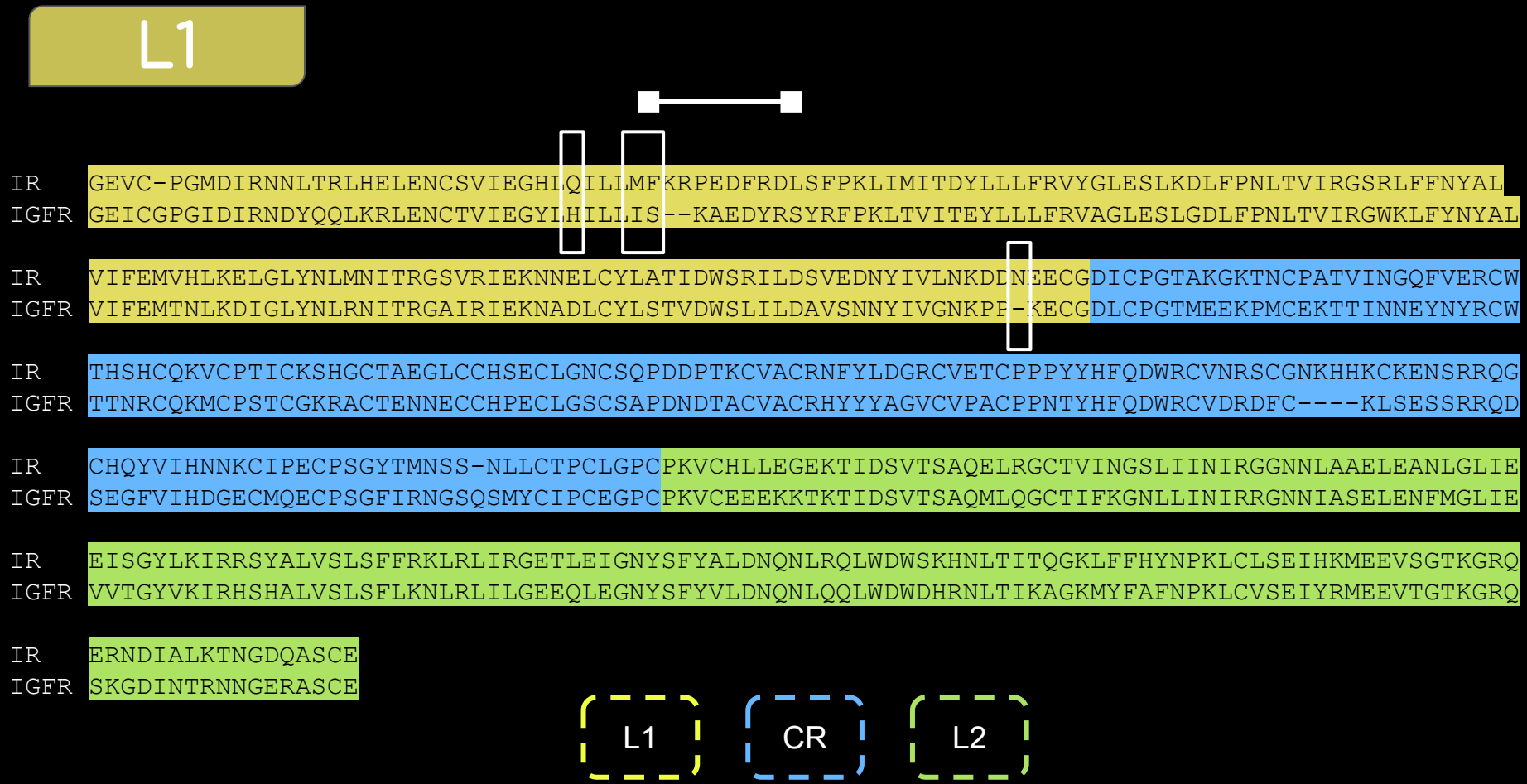
Same fold and domains

DIFFERENCES

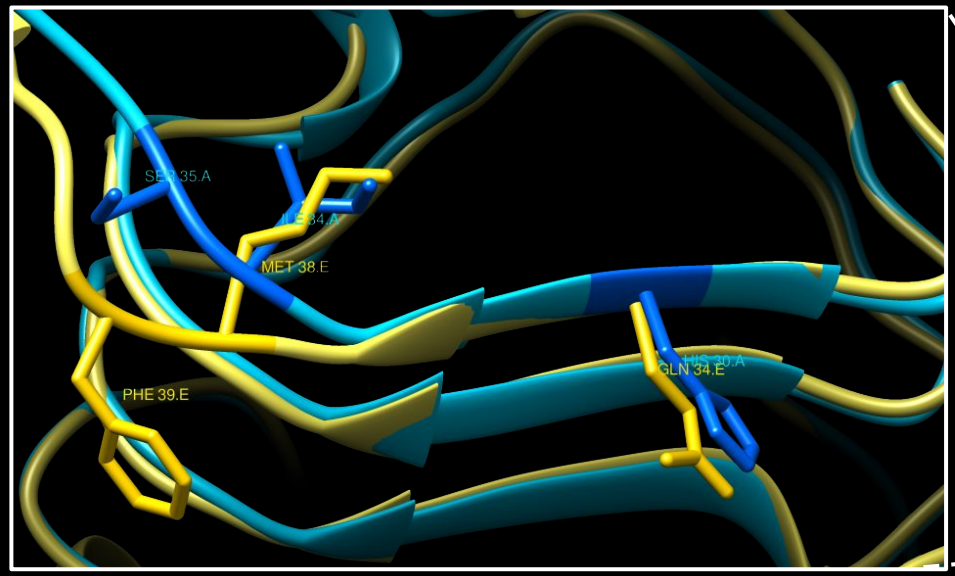
Sites of membrane entry → IGF-1R is more “compact”

Specific residues

**Further explained*


L1
IR GEVC-PGMDIRNNLTRLHELENCSVIEGHLQILLMFKRPEDFRDLSFPKLIMITDYLLLFRVYGLESLKDLFPNLTVIRGSRLFFNYAL
IGFR GEICGPGIDIRNDYQQLKRLENCTVIEGYLHILLIS--KAEDYRSYRFPKLTVITEYLLLFRVAGLESLGDLFPNLTVIRGWKLFYNYAL
IR VIFEMVHLKELGLYNLMNITRGSVRIEKNNELCYLATIDWSRILDSVEDNYIVLNKDDNEECGDICPGTAKGKTNCPATVINGQFVERCW
IGFR VIFEMTNLKDIGLYNLRNITRGAIRIEKNADLCYLSTVDWSLILDAVSNNYIVGNKPPKECGDLCPGTMEEKPMCEKTTINNEYNYRCW
IR THSHCQKVCPTICKSHGCTAEGLCCHSECLGNCSQPDDPTKCVACRNFYLDGRCVETCPPPYYHFQDWRCVNRSCGNKHHKCKENSRRQG
IGFR TTNRCQKMCPSTCGKRACTENNECCHPECLGSCSAPDNDTACVACRHYYYAGVCVPACPPNTYHFQDWRCVDRDFC----KLSESSRRQD
IR CHQYVIHNNKCIPECPSGYTMNSS-NLLCTPCLGPCPKVCHLLEGEKTIDSVTSAQELRGCTVINGSLIINIRGGNNLAAELEANLGLIE
IGFR SEGFVIHDGECMQECPSGFIRNGSQSMYCIPCEGPCPKVCEEEKKTKTIDSVTSAQMLQGCTIFKGNLLINIRRGNNIASELENFMGLIE
IR EISGYLKIRRSYALVSLSFFRKLRLIRGETLEIGNYSFYALDNQNLRQLWDWSKHNLTITQGKLFFHYNPKLCLSEIHKMEEVSGTKGRQ
IGFR VVTGYVKIRHSHALVSLSFLKNLRLILGEEQLEGNYSFYVLDNQNLQQLWDWDHRNLTIKAGKMYFAFNPKLCVSEIYRMEEVTGTKGRQ
IR ERNDIALKTNGDQASCE
IGFR SKGDINTRNNGERASCE
L1
CR
L2

L1: I

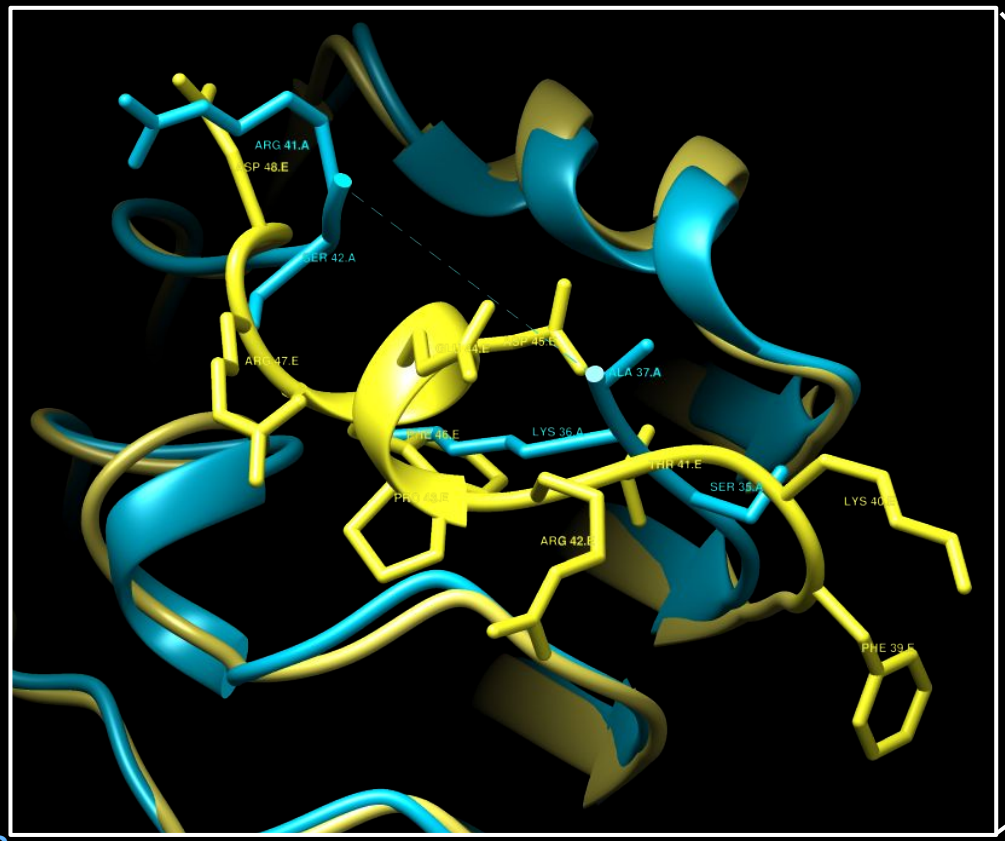


IR	IGF-1R
Gln34	Hys30
Met38	Ile34
Phe39	Ser35

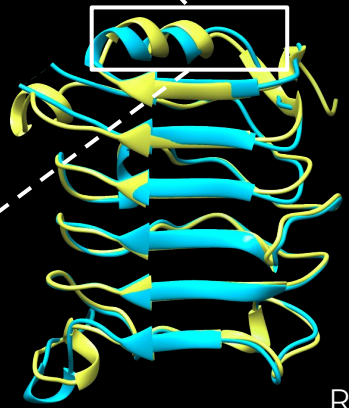
RMSD = 2.339 Å

IR
IGF1R

L1: II



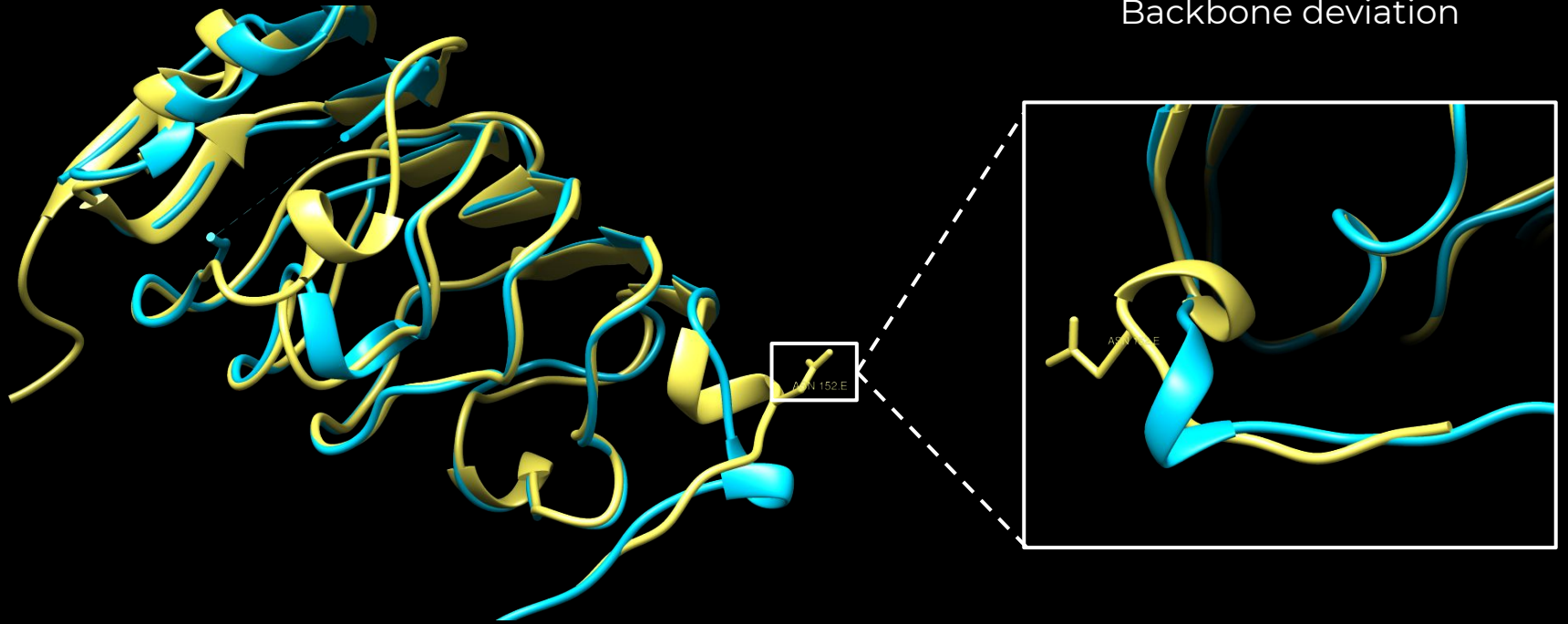
Most variable region
Addition of Lys and Pro in IR



IR
IGF1R

RMSD = 2.339 Å

L1: III



RMSD = 2.339 Å

IR
IGF1R

CR

```
IR    GEVC-PGMDIRNNLTRLHELENCSVIEGHLQILLMFKPRPEDFRDLSFPKLIMITDYLLLFRVYGLESLKDLFPNLTVIRGSRLFFNYAL
IGFR  GEICGPGIDIRNDYQQLKRLENCTVIEGYLHILLIS--KAEDYRSYRFPKLTVITEYLLLFRVAGLESLGDLFPNLTVIRGWKLFYNYAL

IR    VIFEMVHLKELGLYNLMNITRGSVRIEKNNELCYLATIDWSRILDSVEDNYIVLNKDDNEECGDICPGTAKGKTNCPATVINGQFVERCW
IGFR  VIFEMTNLKDIGLYNLRNITRGAIRIEKNADLCYLSTVDWSLILDAVSNNYIVGNKPP-KECGDLCPGTMEEKPMCEKTTINNEYNYRCW

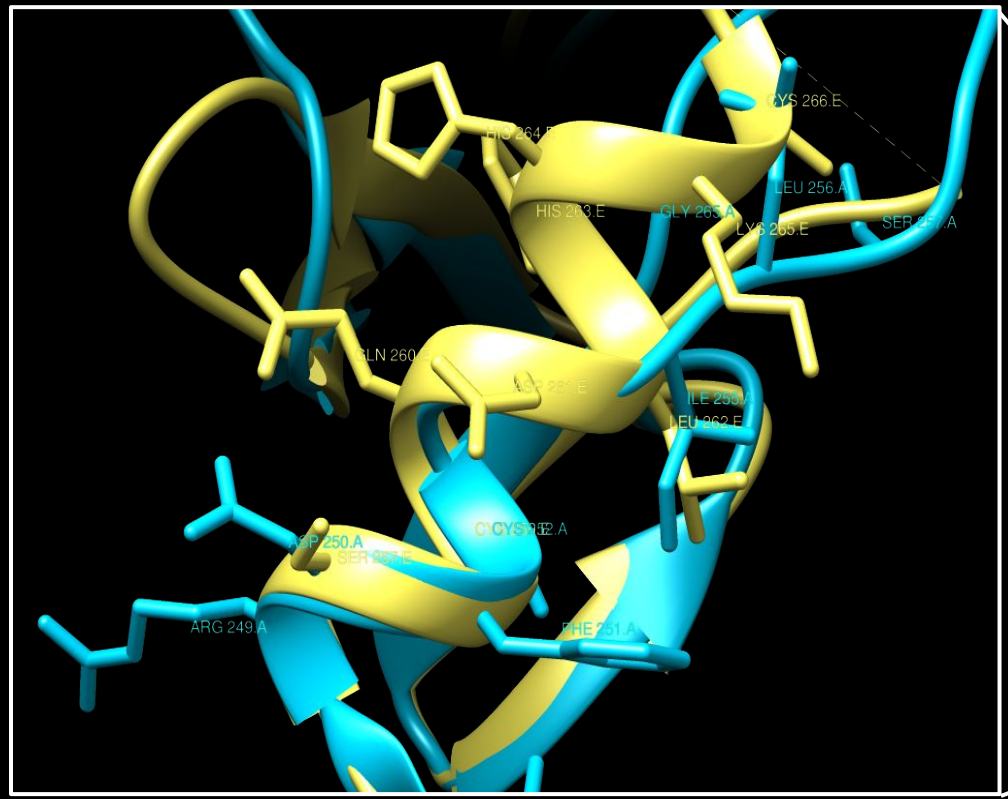
IR    THSHCQKVCPTICKSHGCTAEGLCCHSECLGNCSQPDDPTKCVACRNFYLDGRCVETCPPPYYHFQDWRCVNRSCGNKHHKCKENSRRQG
IGFR  TTNRCQKMCPSTCGKRACTENNECCHPECLGSCSAPDNDTACVACRHYYYAGVCVPACPPNTYHFQDWRCVDRDFC----KLSESSRRQD

IR    CHQYVIHNNKCIPECPSGYTMNSS-NLLCTPCLGPCPKVCHLLEGEKTIDSVTSAQELRGCTVINGSLIINIRGGNNLAAELEANLGLIE
IGFR  SEGFVIHDGECMQECPSGFIRNGSQSMYCIPCEGPCPKVCEEEKKTKTIDSVTSAQMLQGCTIFKGNLLINIRRGNNIASELENFMGLIE

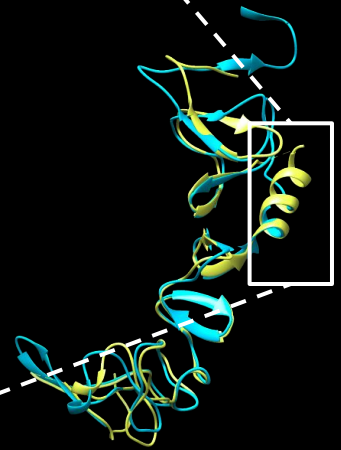
IR    EISGYLKIRRSYALVSLSFFRKLRLIRGETLEIGNYSFYALDNQNLRQLWDWSKHNLTITQGKLFFHYNPKLCLSEIHKMEEVSGTKGRQ
IGFR  VVTGYVKIRHSHALVSLSFLKNLRLILGEEQLEGNYSFYVLDNQNLQQLWDWDHRNLTIKAGKMYFAFNPKLCVSEIYRMEEVTGTKGRQ

IR    ERNDIALKTNGDQASCE
IGFR  SKGDINTRNNGERASCE
```

CR: I



4 residue insertion
(Gln, Lys, His, His)
Further extension of
α-helix of IR.
Stabilize with an
extra disulfide bond



RMSD = 2.735 Å

IR
IGF1R

L2

```
IR    GEVC-PGMDIRNNLTRLHELENCSVIEGHLQILLMFKPRPEDFRDLSFPKLIMITDYLLLFRVYGLESLKDLFPNLTVIRGSRLFFNYAL
IGFR  GEICGPGIDIRNDYQQLKRLENCTVIEGYLHILLIS--KAEDYRSYRFPKLTVITEYLLLFRVAGLESLGDLFPNLTVIRGWKLFYNYAL

IR    VIFEMVHLKELGLYNLMNITRGSVRIEKNNELCYLATIDWSRILDSVEDNYIVLNKDDNEECGDICPGTAKGKTNCPATVINGQFVERCW
IGFR  VIFEMTNLKDIGLYNLRNITRGAIRIEKNADLCYLSTVDWSLILDAVSNNYIVGNKPP-KECGDLCPGTMEEKPMCEKTTINNEYNYRCW

IR    THSHCQKVCPTICKSHGCTAEGLCCHSECLGNCSQPDDPTKCVACRNFYLDGRCVETCPPPYYHFQDWRCVNRSCGNKHHKCKENSRRQG
IGFR  TTNRCQKMCPSTCGKRACTENNECCHPECLGSCSAPDNDTACVACRHYYYAGVCVPACPPNTYHFQDWRCVDRDFC----KLSESSRRQD

IR    CHQYVIHNNKCIPECPSGYTMNSS-NLLCTPCLGPCPKVCHLLEGEKTIDSVTSAQELRGCTVINGSLIINIRGGNNLAAELEANLGLIE
IGFR  SEGFVIHDGECMQECPSGFIRNGSQSMYCIPCEGPCPKVCEEEKKTKTIDSVTSAQMLQGCTIFKGNLLINIRRGNNIASELENFMGLIE

IR    EISGYLKIRRSYALVSLSFFRKLRLIRGETLEIGNYSFYALDNQNLRQLWDWSKHNLTITQGKLFFHYNPKLCLSEIHKMEEVSGTKGRQ
IGFR  VVTGYVKIRHSHALVSLSFLKNLRLILGEEQLEGNYSFYVLDNQNLQQLWDWDHRNLTIKAGKMYFAFNPKLCVSEIYRMEEVTGTKGRQ

IR    ERNDIALKTNGDQASCE
IGFR  SKGDINTRNNGERASCE
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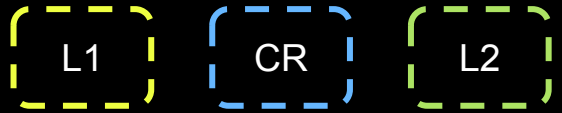
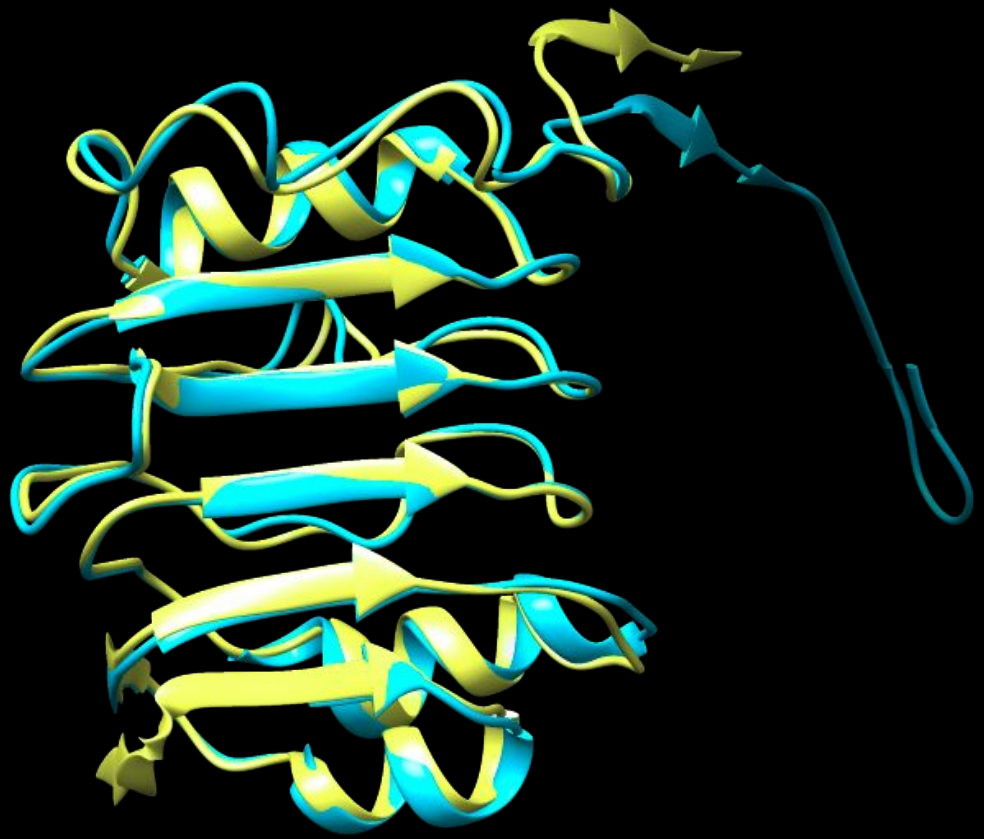
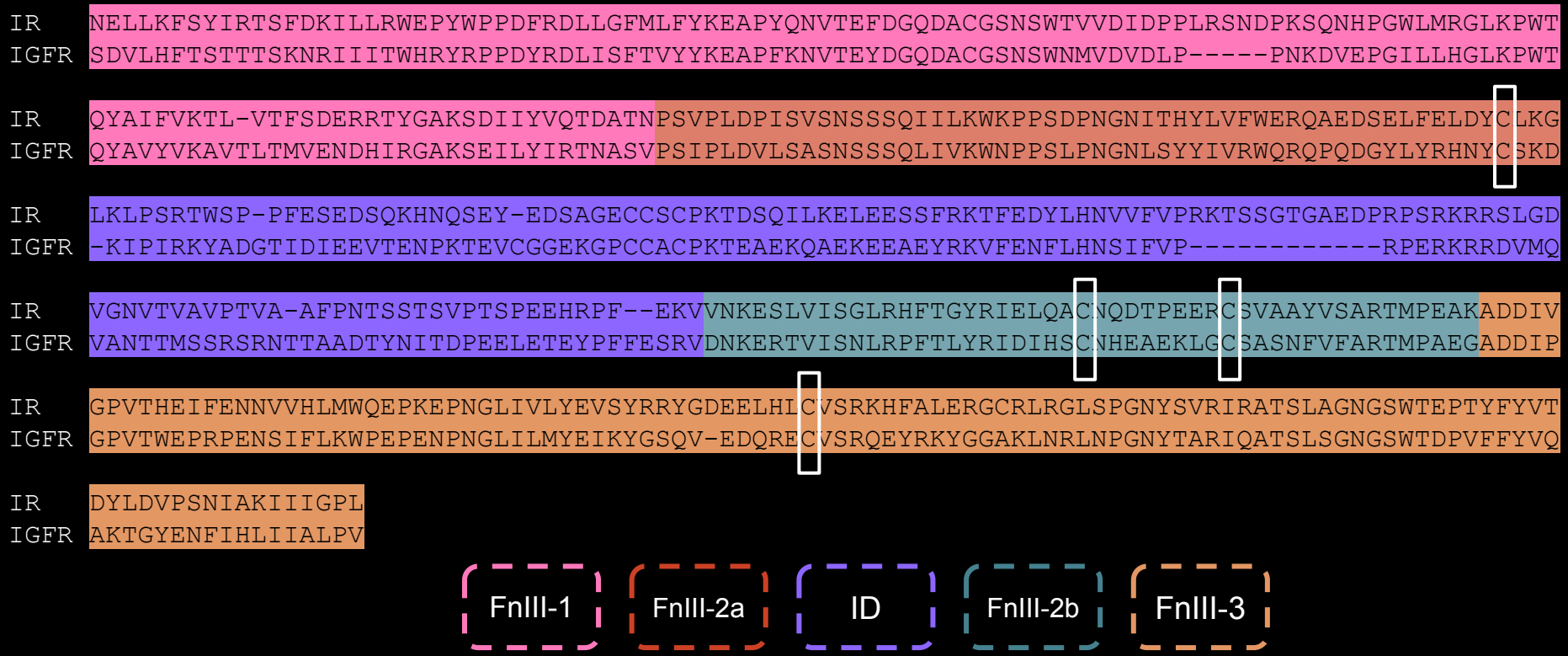


L2



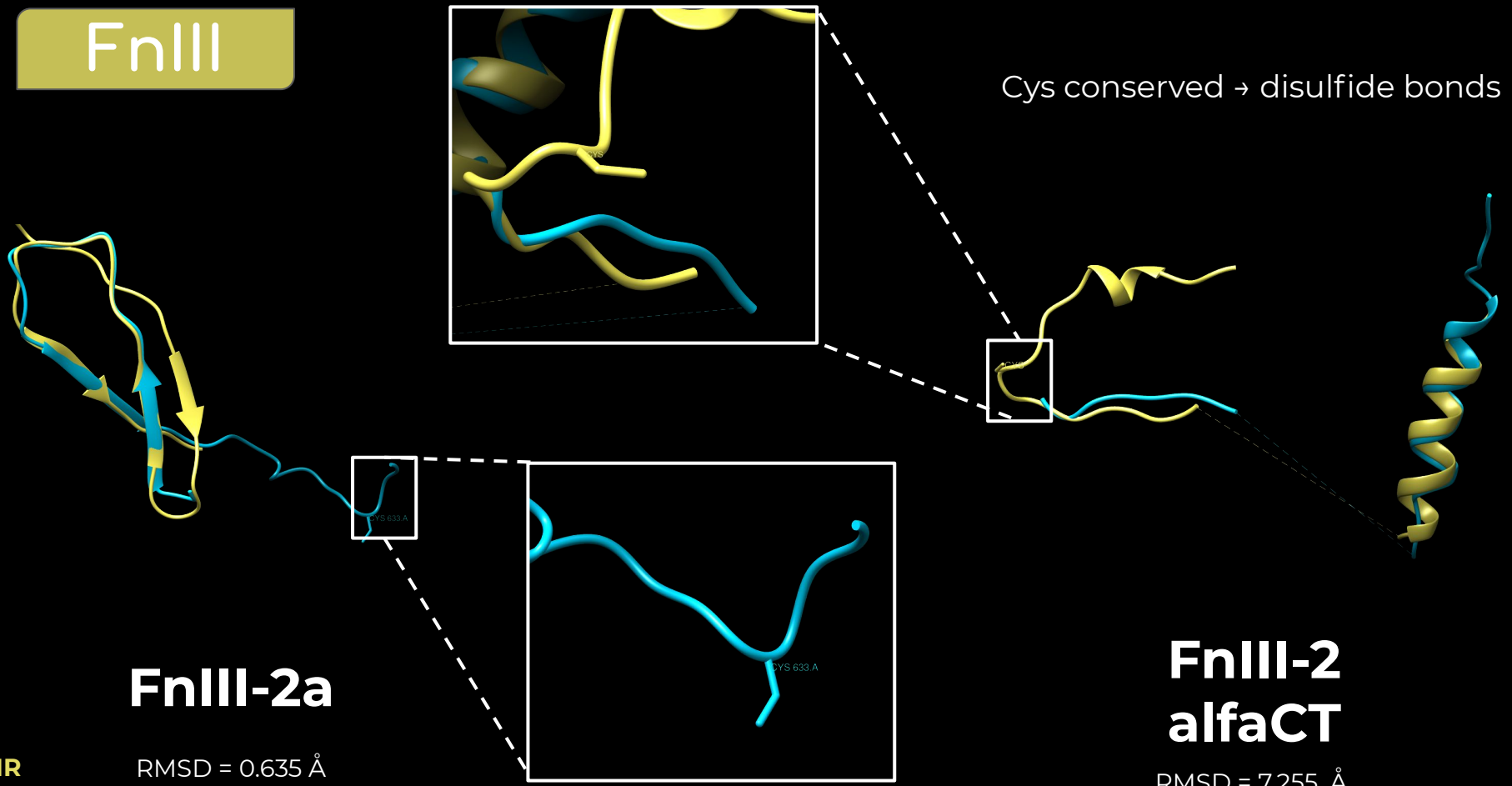
RMSD = 1.531 Å

IR
IGF1R


IR NELLKFSYIRTSFDKILLRWEPYWPPDFRDLLGFMLFYKEAPYQNVTEFDGQDACGSNSWTVVDIDPPLRSNDPKSQNHPGWLMRGLKPWT
IGFR SDVLHFTSTTTSKNRIIITWHRYRPPDYRDLISFTVYYKEAPFKNVTEYDGQDACGSNSWNMVDVDLP-----PNKDVEPGILLHGLKPWT
IR QYAIFVKTL-VTFSDERRTYGAKSDIIYVQTDATNPSVPLDPISVSNSSSQIILKWKPPSDPNGNITHYLVFWERQAEDSELFELDYCLKG
IGFR QYAVYVKAVTLTMVENDHIRGAKSEILYIRTNASVPSIPLDVLSASNSSSQLIVKWNPPSLPNGNLSYYIVRWQRQPQDGYLYRHNYCSKD
IR LKLPSRTWSP-PFESEDSQKHNQSEY-EDSAGECCSCPKTDSQILKELEESSFRKTFEDYLHNVVFVPRKTSSGTGAEDPRPSRKRRSLGD
IGFR -KIPIRKYADGTIDIEEVTENPKTEVCGGEKGPCCACPKTEAEKQAEKEEAEYRKVFENFLHNSIFVP-----------RPERKRRDVMQ
IR VGNVTVAVPTVA-AFPNTSSTSVPTSPEEHRPF--EKVVNKESLVISGLRHFTGYRIELQACNQDTPEERCSVAAYVSARTMPEAKADDIV
IGFR VANTTMSSRSRNTTAADTYNITDPEELETEYPFFESRVDNKERTVISNLRPFTLYRIDIHSCNHEAEKLGCSASNFVFARTMPAEGADDIP
IR GPVTHEIFENNVVHLMWQEPKEPNGLIVLYEVSYRRYGDEELHLCVSRKHFALERGCRLRGLSPGNYSVRIRATSLAGNGSWTEPTYFYVT
IGFR GPVTWEPRPENSIFLKWPEPENPNGLILMYEIKYGSQV-EDQRECVSRQEYRKYGGAKLNRLNPGNYTARIQATSLSGNGSWTDPVFFYVQ
IR DYLDVPSNIAKIIIGPL
IGFR AKTGYENFIHLIIALPV
FnIII-1
FnIII-2a
ID
FnIII-2b
FnIII-3

FnIII

Cys conserved → disulfide bonds



FnIII-2a

RMSD = 0.635 Å

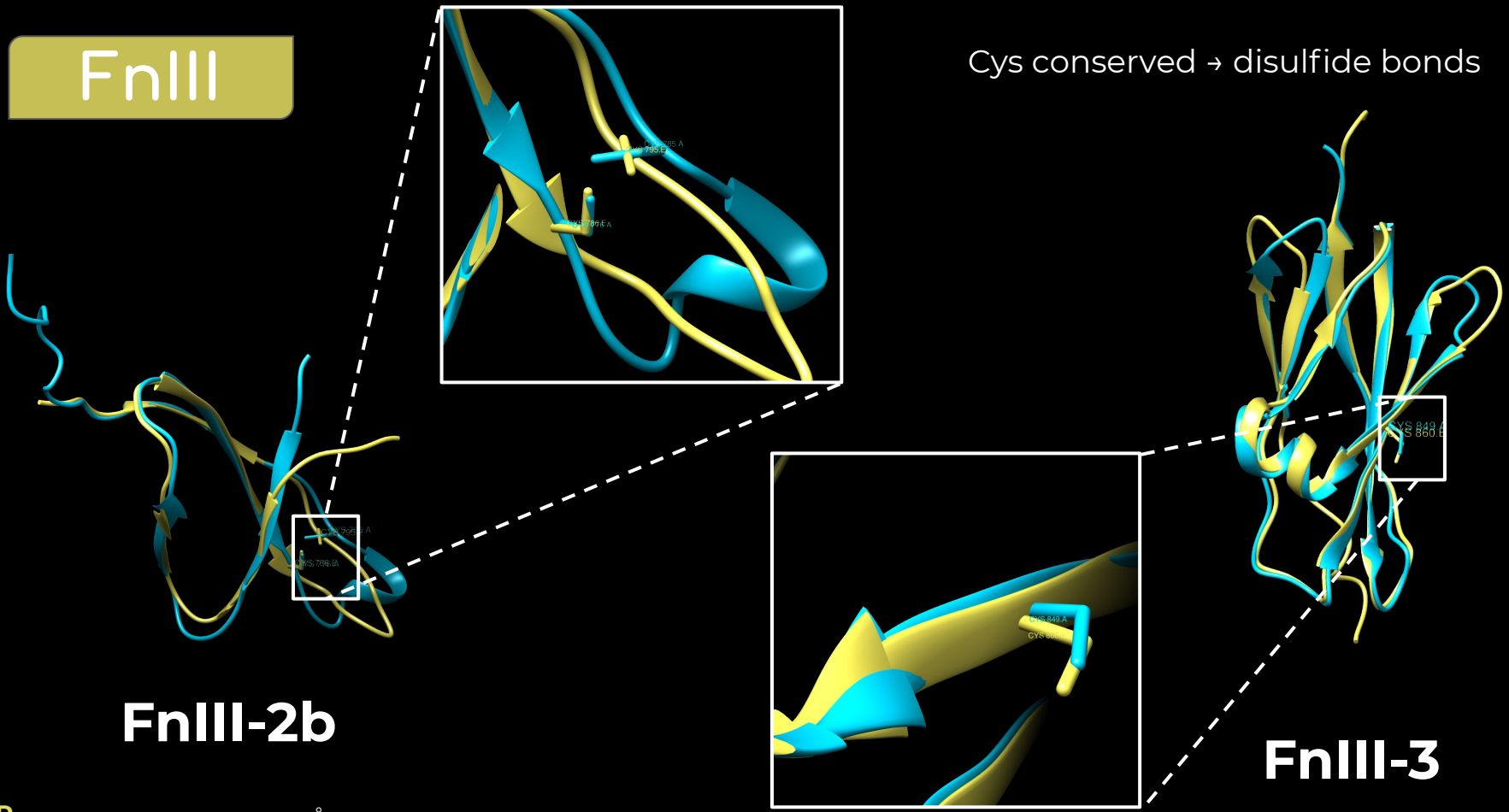
FnIII-2 alfaCT

RMSD = 7.255. Å

IR
IGF1R

FnIII

Cys conserved → disulfide bonds



FnIII-2b

RMSD = 3.084 Å

FnIII-3

RMSD = 1.303 Å

IR
IGF1R

Evolution of IR

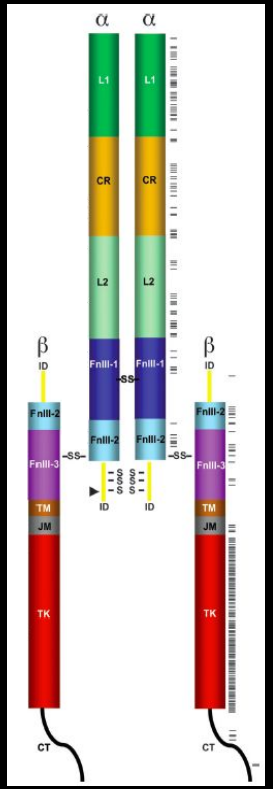
EVOLUTION

- The process of functional specialization is yet unknown.
- Duplication and divergence events occurred early.
  - Zebrafish: two insulin genes.
  - Protochordate amphioxus: single gene → ancestral vertebrate genes?

Vertebrates: primary structure conservation shows strong selection pressure.

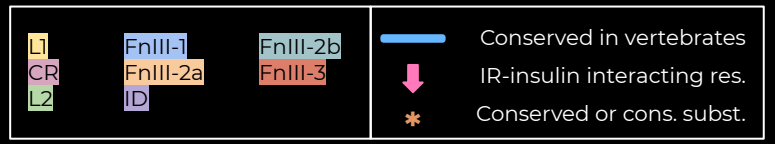
Invertebrates: insulin-like family members in *Drosophila melanogaster*, insects, molluscs... → Genetic evidence suggests high functional conservation.

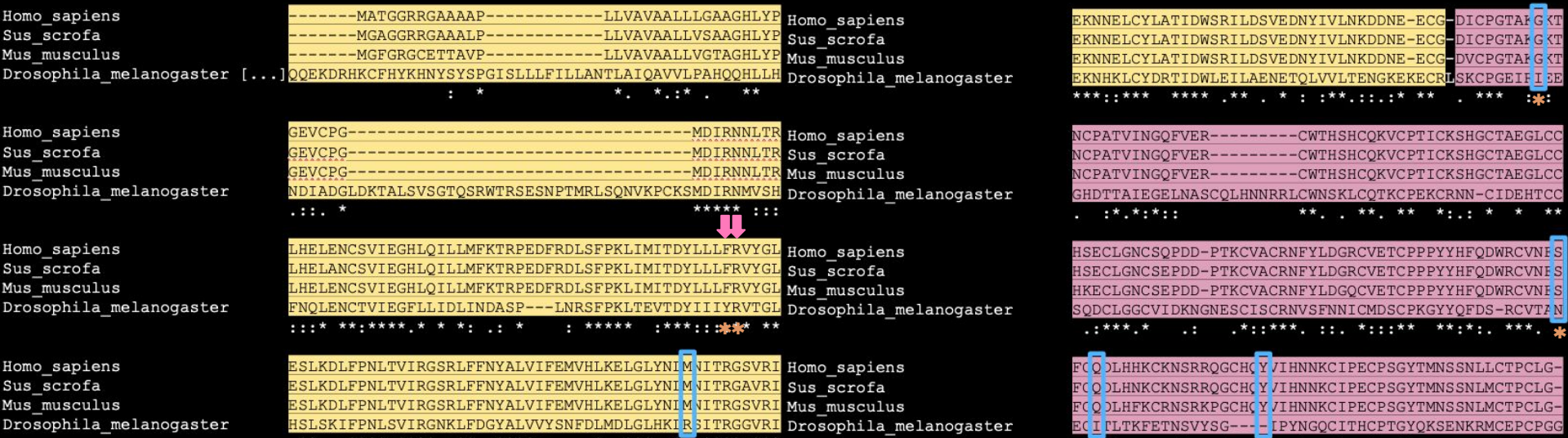
D. melanogaster:
- High degree of sequence conservation with human receptor.
- C-terminal extension. Related with signaling transduction.
- *In our MSA*: N-terminal extension.



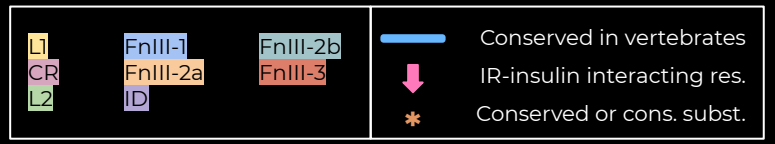
Adapted from Hernández-Sánchez C *et al*, 2008

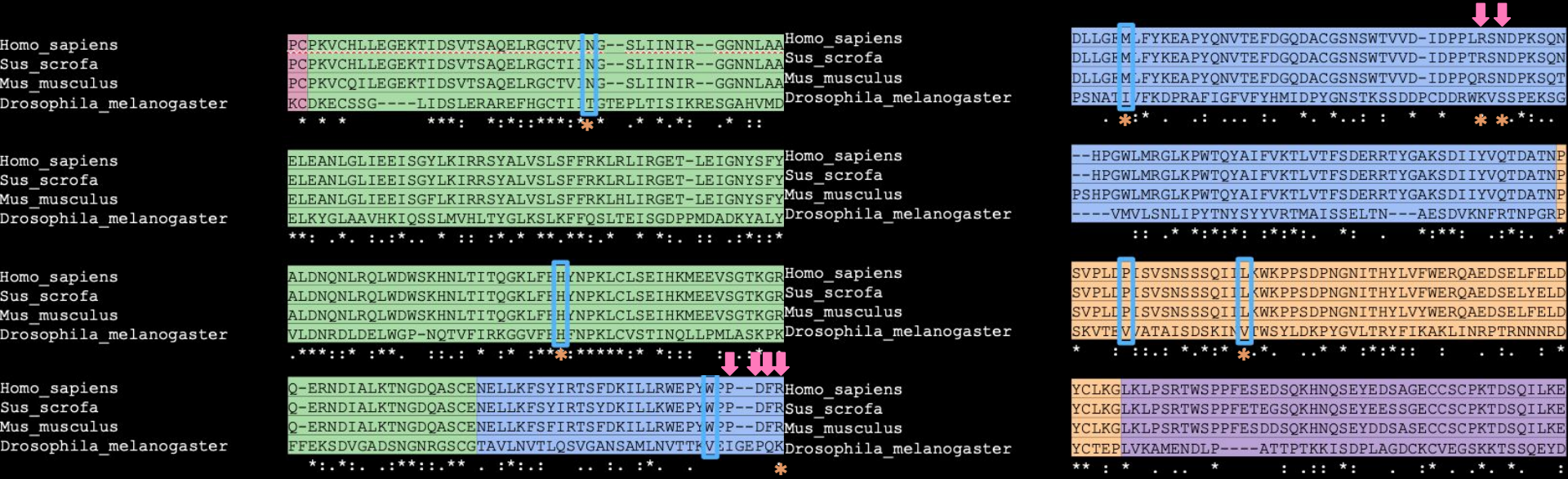
MSA


L1
CR
L2
FnIII-1
FnIII-2a
ID
FnIII-2b
FnIII-3
Conserved in vertebrates
IR-insulin interacting res.
Conserved or cons. subst.

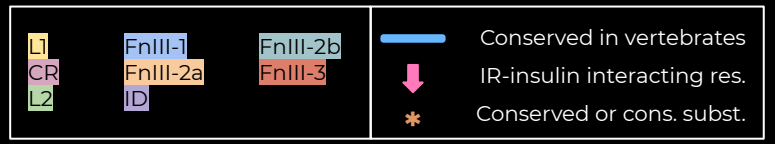

Homo_sapiens
Sus_scrofa
Mus_musculus
Drosophila_melanogaster [...]
Homo_sapiens
Sus_scrofa
Mus_musculus
Drosophila_melanogaster

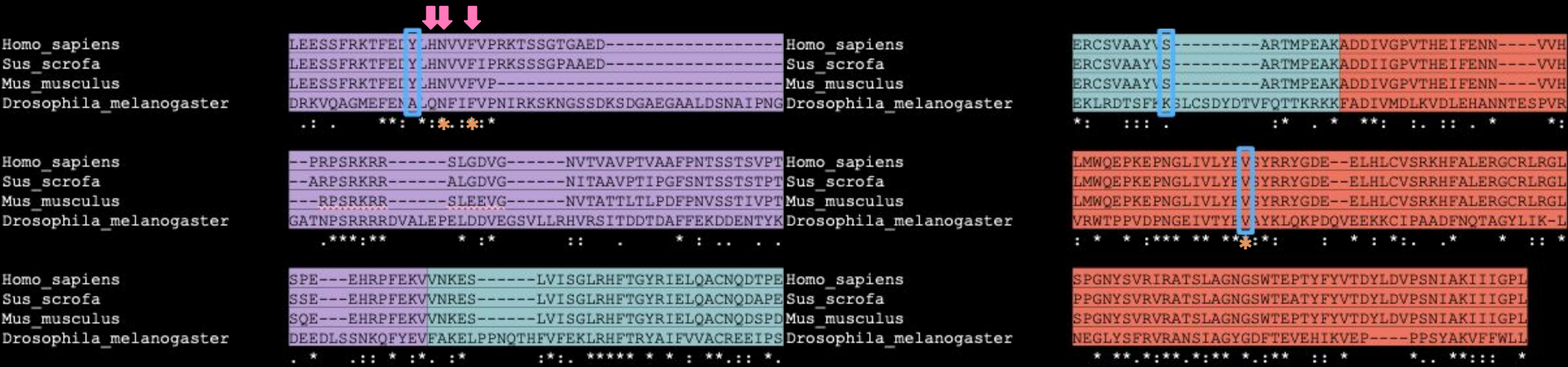
MSA


L1
CR
L2
FnIII-1
FnIII-2a
ID
FnIII-2b
FnIII-3
Conserved in vertebrates
IR-insulin interacting res.
Conserved or cons. subst.


Homo_sapiens
Sus_scrofa
Mus_musculus
Drosophila_melanogaster

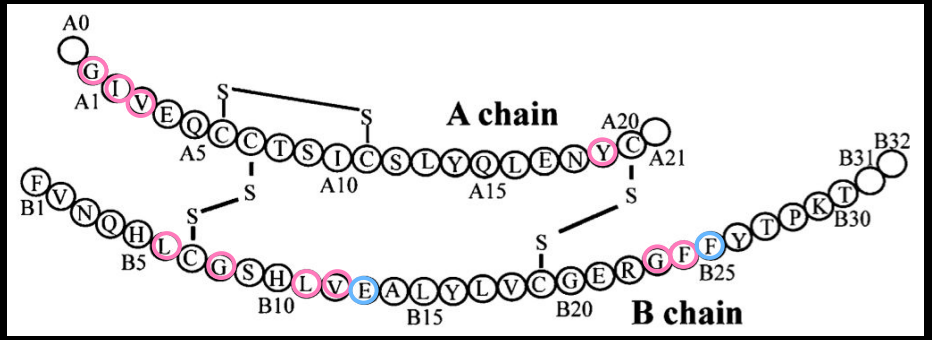
MSA


L1
CR
L2
FnIII-1
FnIII-2a
ID
FnIII-2b
FnIII-3
Conserved in vertebrates
IR-insulin interacting res.
Conserved or cons. subst.


Homo_sapiens
Sus_scrofa
Mus_musculus
Drosophila_melanogaster

INSULIN

In vertebrates



Adapted from Kwak SY *et al*, 2010

Fully conserved	
GlyA1	**GlyB8**
IleA2	**LeuB11**
ValA3	**ValB12**
TyrA19	GlyB23
LeuB6	PheB24

Conservative substitutions	
B13	B25
Glu → Asp	Phe → Tyr

Take home message

Take home message

- Insulin Receptor is produced as a **single polypeptide chain**.
- There is **no full PDB structure** of the IR due to the difficulty of crystallizing it.
- The **exact interaction** between IR and insulin is not yet well established.
- **IR** is very **conserved** among **evolution.** There is also a high conservation between IR and IGF-1R:
  - High identity even between vertebrates and invertebrates
  - This indicates that there is a strong selective pressure

- There are still several features to fully understand:
  - Site 2 of the IR-insulin interaction.
  - Functional specialization along evolution.

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THANKS FOR YOUR ATTENTION

PEM questions

PEM QUESTIONS

1. What kind of signalling does the insulin receptor have?

a. G-protein coupled.
b. Tyrosine kinase.
c. The two previous are true.
d. MAP kinase.
e. All of them are true.

2. Which domains form binding site 1?

1. L1
2. L2
3. alpha-CT
4. CR

a. 1, 2, 3
b. 1, 3
c. 2, 4
d. 4
e. 1, 2, 3, 4

3. Which of the following sentences is <u>FALSE</u>?

a. Receptors from insulin receptor family are IR, IGFR-1R, IGF-2R, IRR.
b. IR is stabilized by 4 disulfide bonds.
c. When IR is bound to the insulin it dimerizes and forms an homodimer.
d. IR and IGF-1R have the same quaternary structure.
e. All of them are true..

4. Leucine rich domains are formed by:

a. Four antiparallel beta strands.
b. Three parallel beta sheets on one side and some helices on the other.
c. Eight beta strands arranged in two four-stranded sheets
d. Single helix on one side connected by some beta-sheets
e. Eight alpha helixes

5. Leucine rich domains interacts with insulin with:

a. Disulfide bonds.
b. Hydrogen bonds.
c. VdW and hydrophobic interactions.
d. Salt bridge.
e. Ionic bond.

PEM QUESTIONS

6. Which of the following sentences is false?

a. Insulin receptor conformation changes upon Insulin binding.
b. As the disulfide bonds are not crucial for the insulin binding, they are not conserved between species.
c. Although the disulfide bonds are not crucial for the insulin binding, they perform an important function in Insulin receptor, so they are conserved between species.
d. Insulin can bind to IGF1R.
e. All of them are false.

7. Choose the correct answer:

a. Insulin receptor needs downstream proteins to activate GLUT4 transporter.
b. Insulin receptor is also related to cell survival and proliferation.
c. A and B are correct.
d. The receptor can directly open GLUT4 transporter.
e. All of them are correct.

8. Choose the incorrect answer:

a. There are several covalent interactions between IR and insulin.
b. The IR plays a role in metabolism.
c. The IR has two different isoforms.
d. Insulin can bind to IGF1R.
e. All of them are incorrect.

9. The IGF1R:

a. Has no relationship with IR.
b. Can not be aligned with the IR sequence.
c. Is a pH sensing receptor.
d. Shares a high degree of identity with IR.
e. None of the previous ones.

10. Choose the right answer:

a. The IR sequences along species show strong selection pressure.
b. There is a high conservation of the IR along vertebrates.
c. A and B are true.
d. There are no IR family members in invertebrates.
e. All of them are true.