

ZINC

FINGERS

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2. Structural features of C2H2 Zinc Finger family
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INTRODUCTION

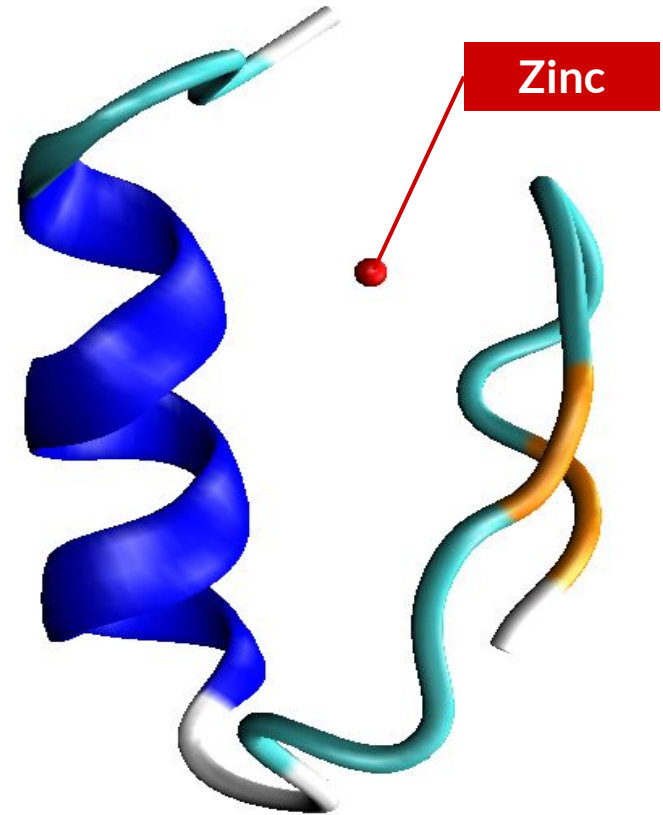
ZINC FINGERS

Zinc fingers are small protein structural motifs in which **zinc** plays a structural role contributing to the stability of the domain

IMPORTANT RESIDUES

- Cysteines
- Histidines
- Hydrophobic core
- The ones that bind nucleic acids

One of the most abundant and versatile DNA-binding motifs found in eukaryotes



ZINC FINGERS

STRUCTURAL DIVERSITY

FUNCTIONS

- Replication
- Transcription
- Translation
- Proliferation
- Mediate protein-protein interaction

in many cases it
involves **nucleic
acid binding**

STRUCTURAL CLASSIFICATION OF ZF

8 fold-groups

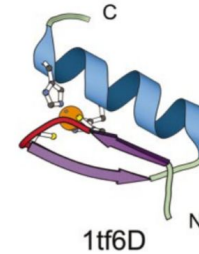
C2H2 like	1	5	Zn ₂ /Cys ₆
Gag knuckle	2	6	TAZ2 domain
Treble clef	3	7	Zinc binding loops
Zinc ribbon	4	8	Metallothionein

STRUCTURAL CLASSIFICATION OF ZF

C2H2 like

α -helix + 2 β -strands

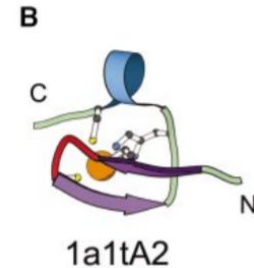
Zinc ligands: 2 zinc knuckle + 2 C-ter end of α -helix



Gag knuckle

Short helix + 2 short β -strands

Zinc ligands: 2 zinc knuckle + 2 at both ends of the short helix



zinc: orange
helices: cyan
zinc knuckle connecting the two β -strands: red

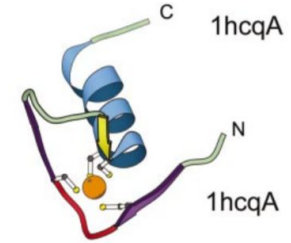
primary β -strands that neighbor the knuckle: purple
other β -strands: yellow
loops: light green

STRUCTURAL CLASSIFICATION OF ZF

Treble clef

α -helix + 2 β -strands

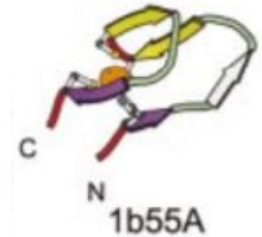
Zinc ligands: 2 zinc knuckle + 2 N-ter end of α -helix



Zinc ribbon

2 β -hairpins (4 β -strands)

Zinc ligands: 2 in each β -hairpin



zinc: orange
helices: cyan
zinc knuckle connecting the two β -strands: red

primary β -strands that neighbor the knuckle: purple
other β -strands: yellow
loops: light green

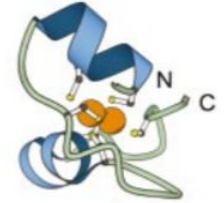
STRUCTURAL CLASSIFICATION OF ZF

Zn₂/Cys₆

1 or 2 α -helix

Zinc ligands: 2 from a helix and 2 from a loop

They can bind 2 Zn atoms

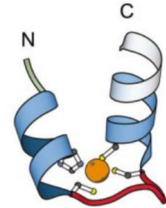


2hapC

TAZ2 domain

2 α -helix

Zinc ligands: 2 in each α -helix termini



1f81A2

zinc: orange
helices: cyan
zinc knuckle connecting the two β -strands: red

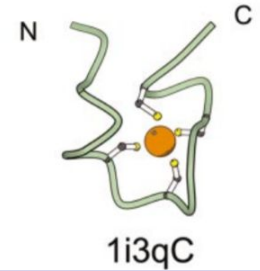
primary β -strands that neighbor the knuckle: purple
other β -strands: yellow
loops: light green

STRUCTURAL CLASSIFICATION OF ZF

Zinc binding loops

Not incorporated in secondary structure elements

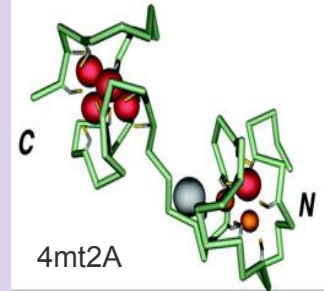
Zinc ligands: at least 3, very close to each other



Metallothionein

Cysteine-rich loops (60-70 residues)

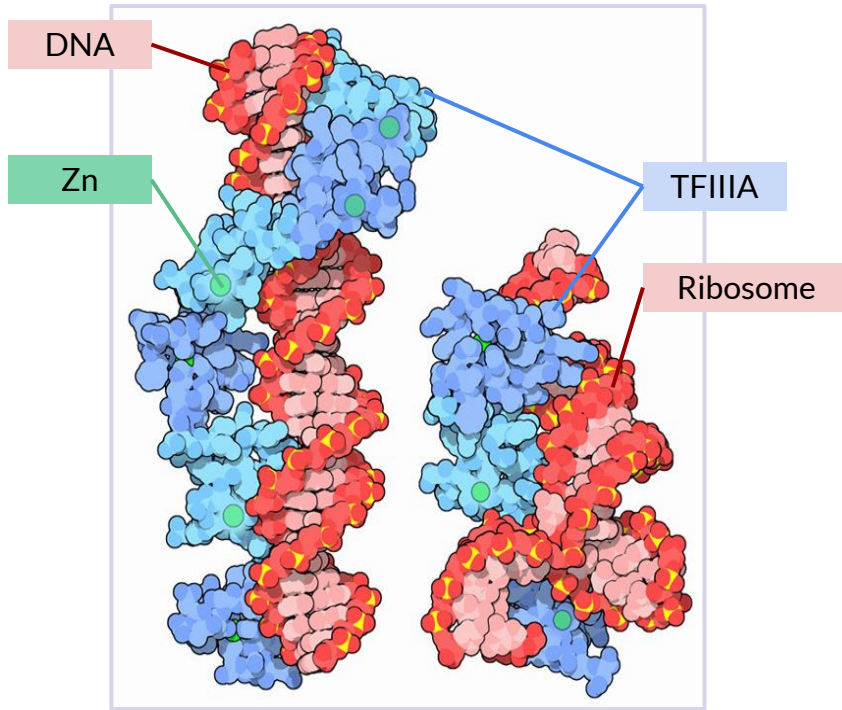
They can bind a variety of metals (e.g. cadmium, zinc, cobalt)



zinc: orange
helices: cyan
zinc knuckle connecting the two β -strands: red

primary β -strands that neighbor the knuckle: purple
other β -strands: yellow
loops: light green

C2H2 FINGER FAMILY



PDB101: Molecule of the Month: Zinc Fingers [Internet]. RCSB: PDB-101. 2021. Available from: <https://pdb101.rcsb.org/motm/87>

First discovered in the transcription factor IIIA (*Xenopus laevis*)

Basic features

- Repeated **28 - 30 aa** sequence
- Important residues:
 - 2 conserved **cysteines**
 - 2 conserved **histidines**
 - **Hydrophobic** residues
- Side chains from the α -helices interact with DNA/RNA

STRUCTURAL FEATURES OF C₂H₂ ZINC FINGER FAMILY

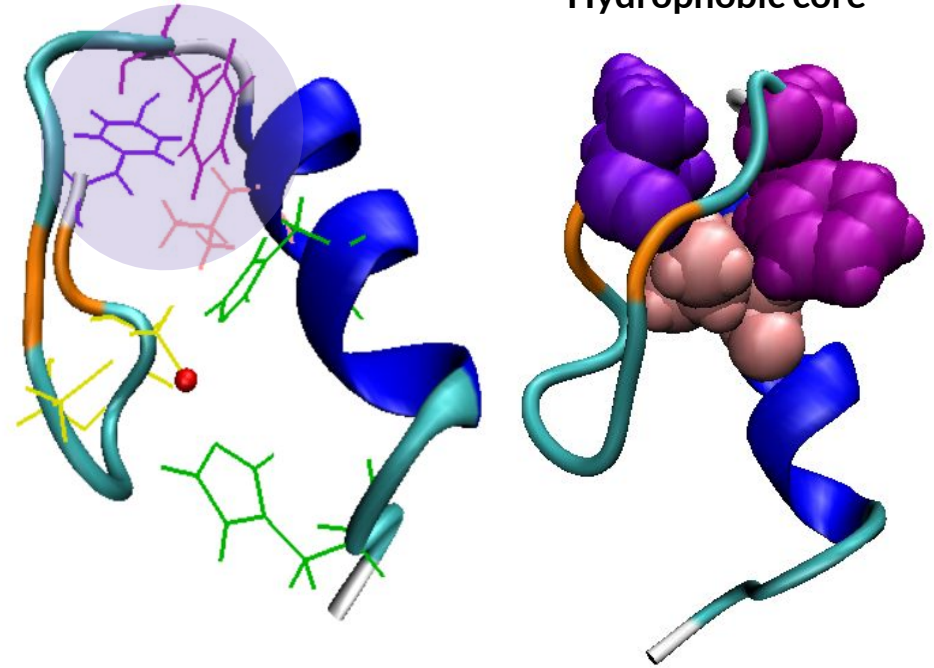
RESIDUES

CONSENSUS SEQUENCE

-Z-X₁₋₂-Cys-X₂₋₄-Cys-X₃-Z-X₅-Z-X₂-His-X₃₋₅-His

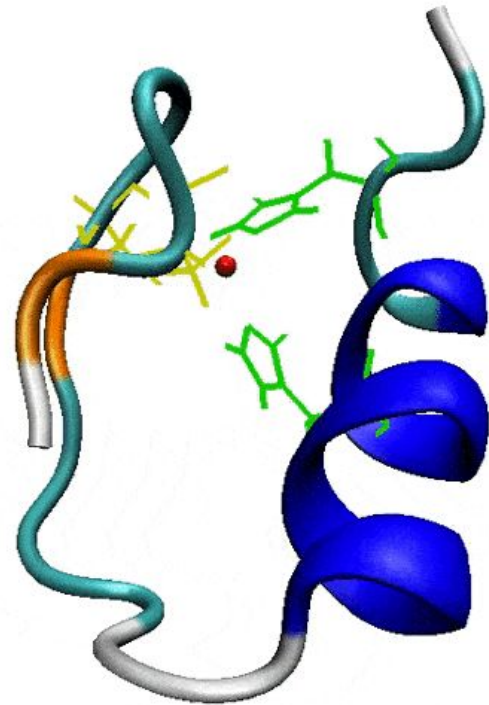
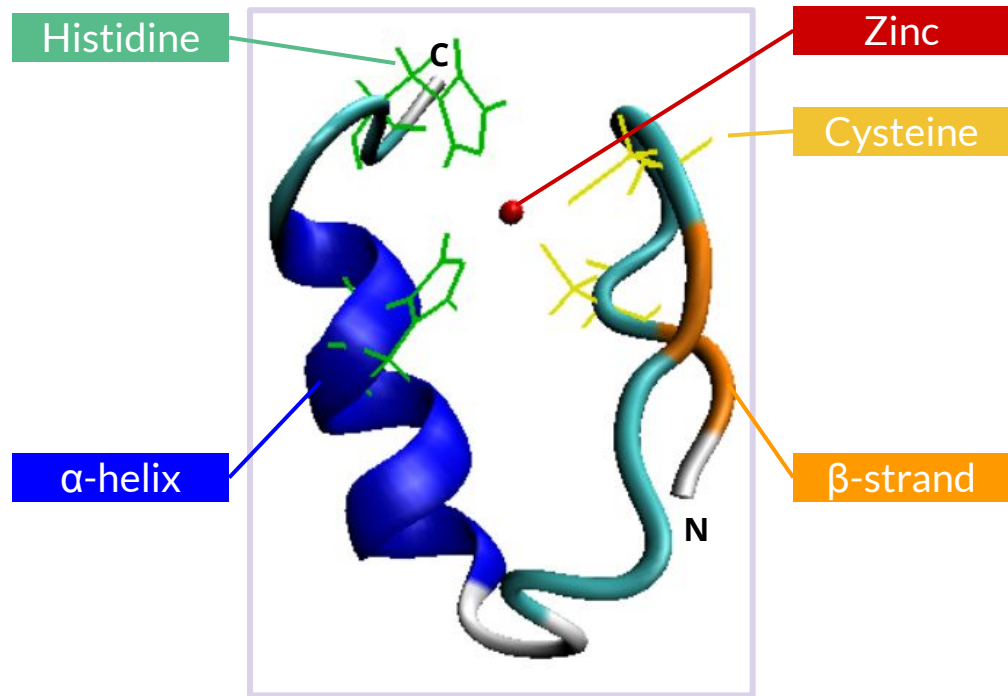
In the case of Xfn

-Leu-X₁₋₂-Cys-X₂₋₄-Cys-X₃-Phe-X₅-Leu-X₂-His-X₃₋₅-His



31 st Zinc finger from Zinc finger protein Xfn (*Xenopus laevis*)

FOLD



FOLD

α -helix

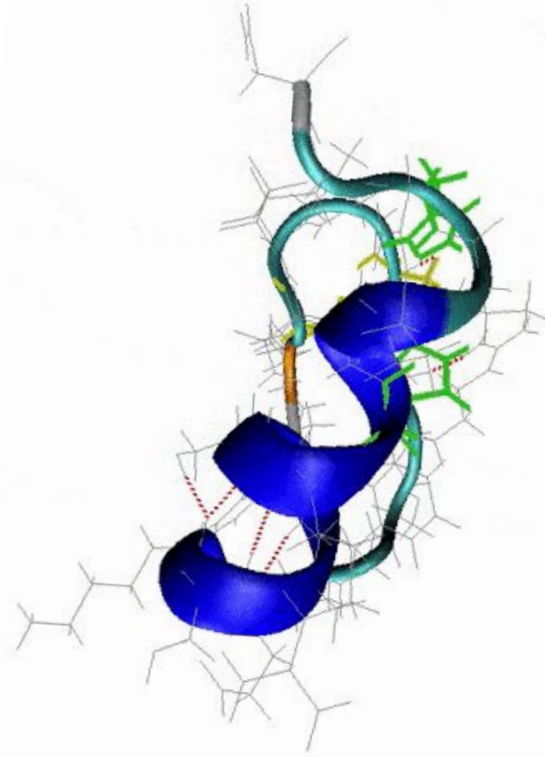
β -strand

Histidine

Cysteine

Zinc

Hydrogen
bonds



FOLDING PATHWAY OF ZINC FINGERS DURING ZINC BINDING

1

Coordination of conserved Cys residues

2

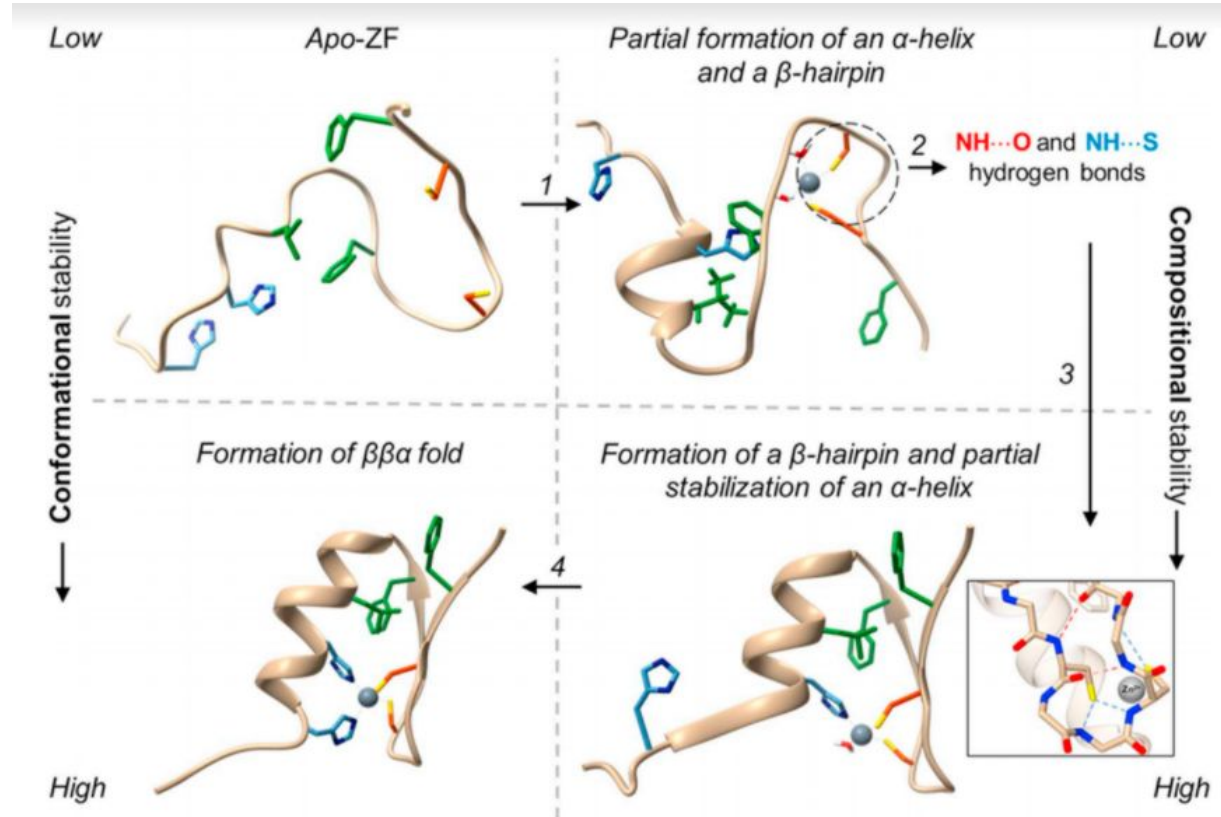
Hydrophobic collapse and formation of β -hairpin stabilized by H bonds

3

Coordination of Zn(II) to the N-terminal His residue

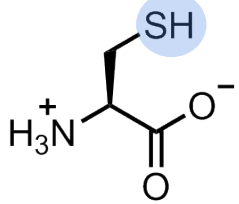
4

Binding of Zn(II) to C-terminal His residue



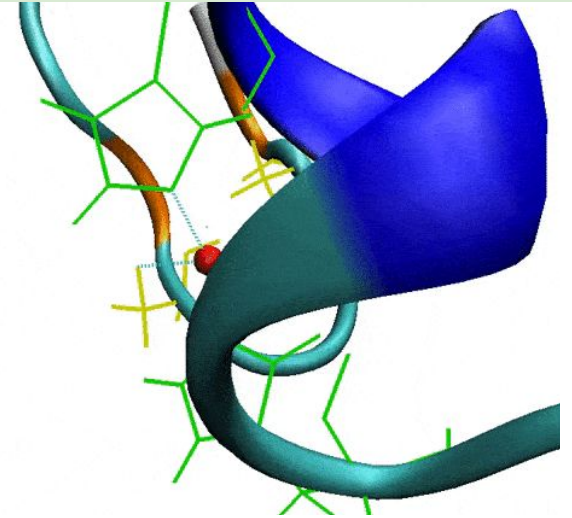
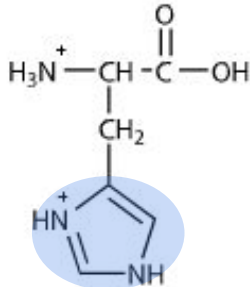
ZINC BINDING

Importance of the chemical properties of the amino acids binding to the Zn



Cysteine residue requires ionization of the R-SH group

Histidine residue requires ionization of the imidazole ring



Histidine

Cysteine

Zinc

ZINC BINDING

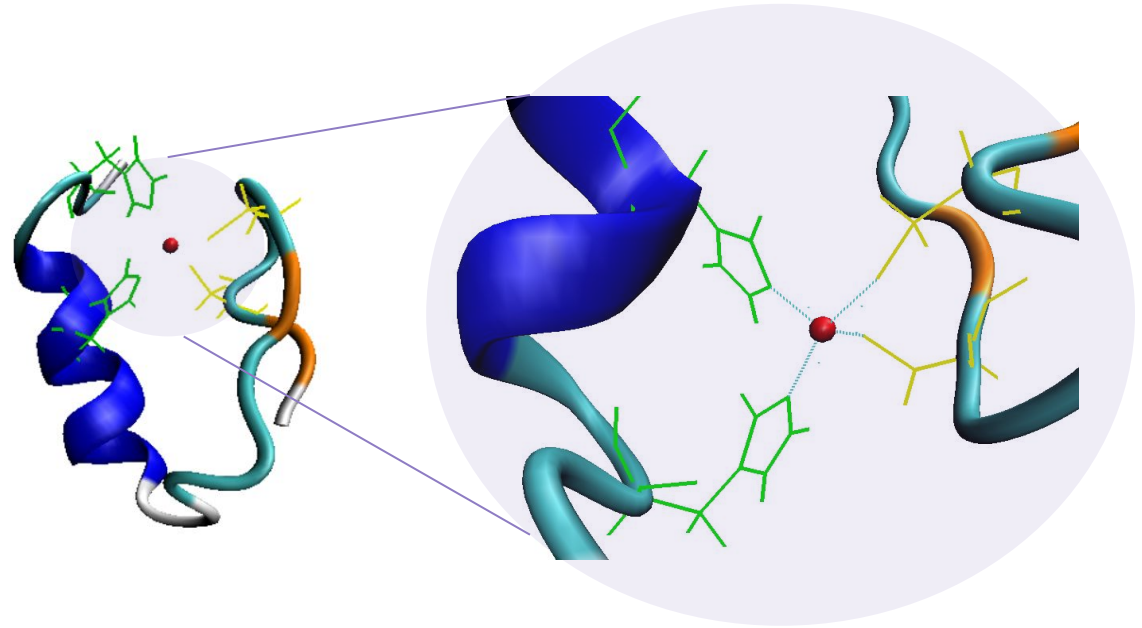
α -helix

β -strand

Histidine

Cysteine

Zinc



RESIDUE CONSERVATION

METHODOLOGY

Transcription factor IIIA (*Xenopus laevis*)



Orthologs

- *Homo sapiens*
- *Mus musculus*
- *Rattus norvegicus*
- *Ictalurus punctatus*
- *Saccharomyces cerevisiae*
- *Candida albicans*
- *Arabidopsis thaliana*

MSA

Residue conservation

-Z-X₁₋₂-Cys-X₂₋₄-Cys-X₃-Z-X₅-Z-X₂-His-X₃₋₅-His

TRANSCRIPTION FACTOR IIIA (*Xenopus laevis*)

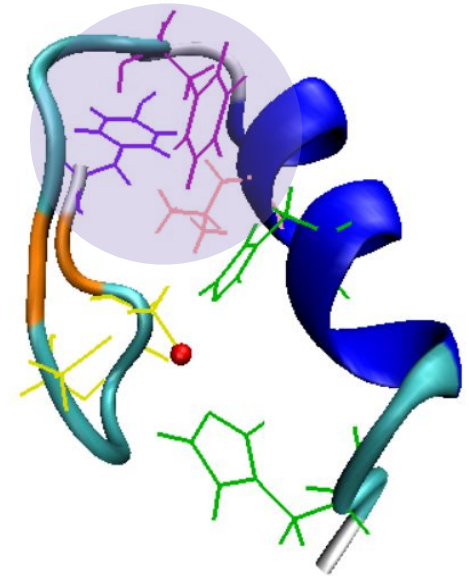
Zinc fingers

MAAKVASTSSEEAEGLVTEGEMGEKALPVVYKRYICSFADCGAAYNKNWKLQAHLCCKHT
GEKPFPCKEEGCEKGFSLHHLTRHSLTHTGEKNFTCDSDGCDLRFTTKANMKKHFNRFH
NIKICVYVCHFENCGKAFKKHNQLKVHQFSHTQQLPYECPHEGCDKRFSLPSRLKRHEKV
HAGYPCKKDDSCSFVGKTWTLYLKHVAECHQDLAVCDVCNRKFRHKDYLRDHQKTHEKER
TVYLCPRDGCDRSYTTAFNLRSHIQSFHEEQRPFVCEHAGCGKCFAMKKSLEKHSVVHDP
EKRKLKEKCPRPKRSLASRLTGYIPPKSKEKNASVSGTEKTDLSLVKNKPSGTETNGSLVL
DKLTIQ

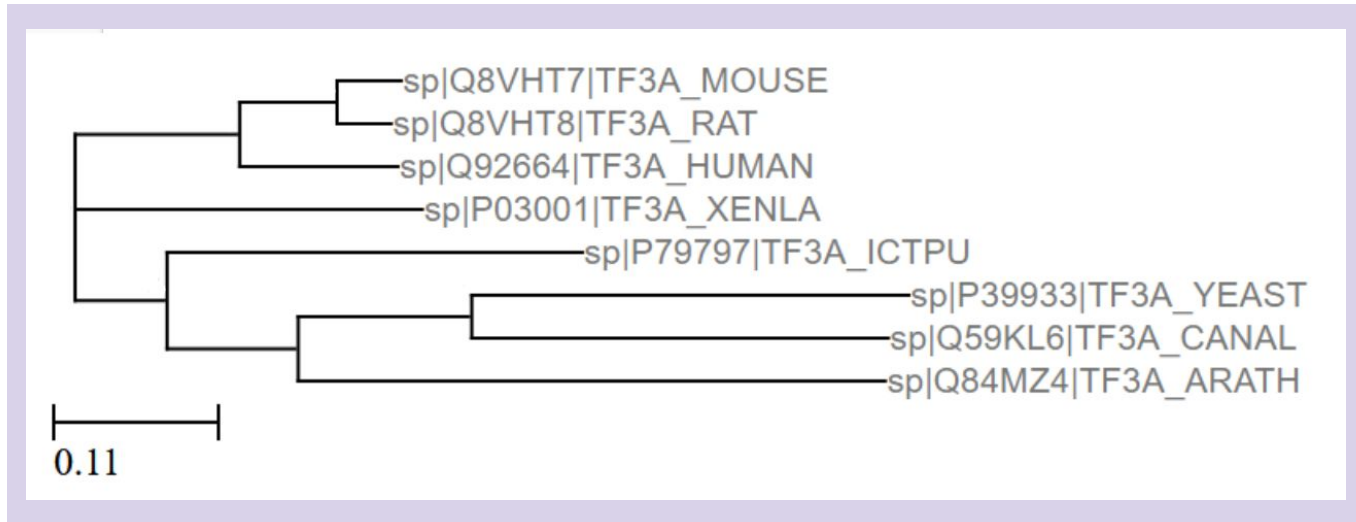
SEQUENCE ALIGNMENT OF ONE ZINC FINGER DOMAIN

sp Q8VHT7 TF3A_MOUSE	FVCDYEGCGKAFIRDYHLSRHVLIH
sp Q8VHT8 TF3A_RAT	FVCDYEGCGKAFIRDYHLSRHILIH
sp Q92664 TF3A_HUMAN	FVCDYEGCGKAFIRDYHLSRHILTH
sp P03001 TF3A_XENLA	FPCKEEGCEKGF TSLHHLTRHSLTH
sp P79797 TF3A ICTPU	FACDR--CDKTFCTRCQLTRHNLSH
sp P39933 TF3A_YEAST	FQC--DKCAKSFVKKSHLERHLYTH
sp Q59KL6 TF3A_CANAL	YKCTVEDCDKAFFRKSHLETHIVSH
sp Q84MZ4 TF3A_ARATH	FTCYVDDCAASYRRKDHLNRHLLTH

-Z-X₁₋₂-Cys-X₂₋₄-Cys-X₃-Z-X₅-Z-X₂-His-X₃₋₅-His



PHYLOGENETIC TREE



STRUCTURE

METHODOLOGY

31 st zinc finger domain from XFIN



Homologues

STAMP

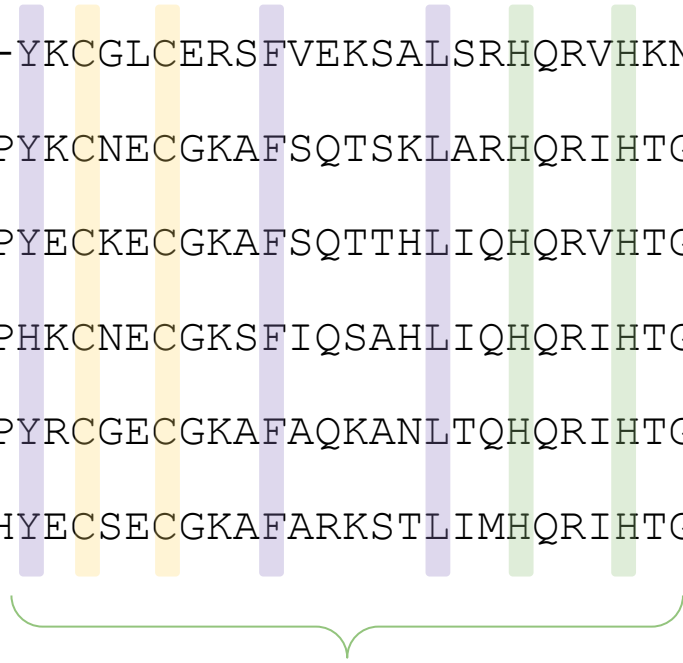
Structural alignment and superimposition

METHODOLOGY

PDB ID	Protein	Length	Zinc finger position
1znfA	31 st zinc finger from XFIN (<i>Xenopus</i>)	27	2-24
2ytrA	C2H2 type zinc finger of human ZNF347 (human)	46	13-35
2emkA	C2H2 type zinc finger of human ZNF 28 homolog (human)	46	13-35
2emmA	C2H2 type zinc finger of human ZNF 95 homolog (human)	46	13-35
2yrjA	C2H2-type zinc finger domain from ZNF473 (human)	46	13-35
2ytpA	C2H2 type zinc finger of human ZNF484 (human)	46	13-35

SEQUENCE ALIGNMENT

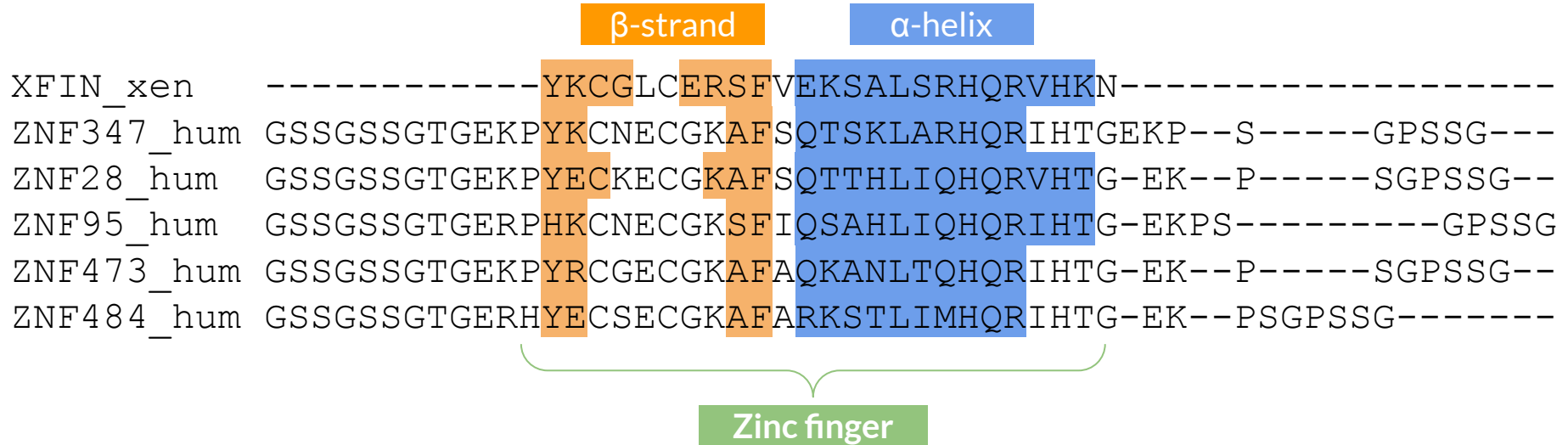
XFIN_xenopus	-----YKCGLCERSFVEKSALSRHQRVHKN-----
ZNF347_human	GSSGSSGTGEKPYKCNECGKAFSQTSKLARHQRIHTGEKPSGPSSG
ZNF28_human	GSSGSSGTGEKPYECKEKGAFSQTTHLIQHQRVHTGEKPSGPSSG
ZNF95_human	GSSGSSGTGERPHKCNECGKSFIQSAHLIQHQRIHTGEKPSGPSSG
ZNF473_human	GSSGSSGTGEKPYRCGECGKAFAQKANLTQHQRRIHTGEKPSGPSSG
ZNF484_human	GSSGSSGTGERHYECSEC GKAFARKSTLIMHQRIHTGEKPSGPSSG



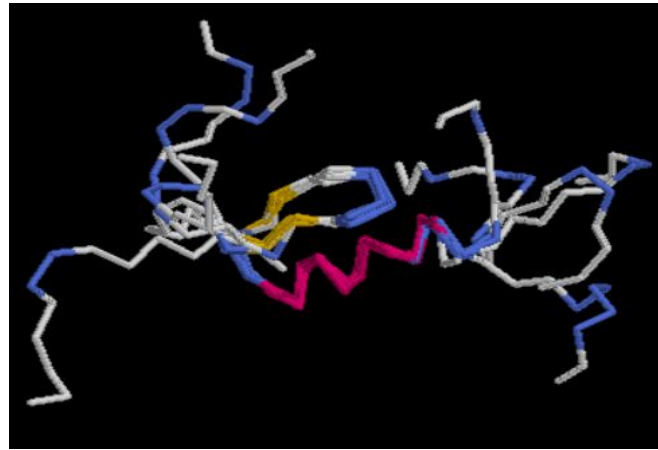
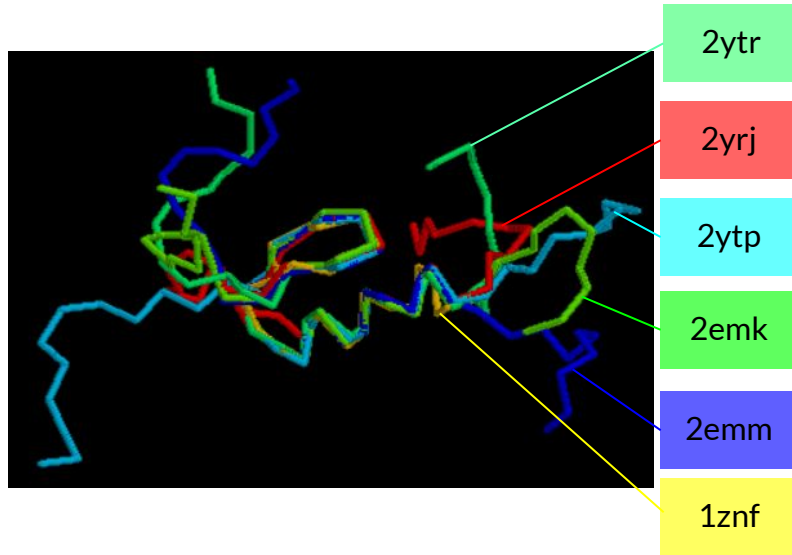
Hydrophobic His Cys

Zinc finger

STRUCTURAL ALIGNMENT



SUPERIMPOSITION



METHODOLOGY

PDB ID	Protein	Length	Number of ZF
1aayA	ZIF268 zinc fingers (mouse)	90	3
2prtA	Wilms Tumor Suppressor Protein Zinc Finger Domain (human)	119	4
1ubdC	Human YY1 zinc finger domain (human)	124	4
2gliA	Five-finger GLI (human)	155	5

SEQUENCE ALIGNMENT

Zinc fingers

```
ZIF268_mouse -----  
WT_human -----RP FMCAYPGCN---KRYFKLSHLQMHSR KH  
YY1_human -----T IACPHKGCT---KMFRDNSAMRKHLH TH  
GLI_human E TDCRWDGCSQEFDSQEQLVHHINSEH IHGERKE FVCHWGGCSREL RPFKAQYMLVVHMR RH
```

```
ZIF268_mouse ---RP YACPVE SCDRRFSRSD ELTRHIRI H TGQKP FQC--RICMRNFS-RSDHLTTHI RTHT  
WT_human TGEKP YQCDFKDCERRFSRSDQLKRHQRRH TGVKP FQC--KTCQRKFS-RSDHLKTHT RTHT  
YY1_human -GPRV HVC--AECGKAFV ESKLKRHQ LVH TGEKP FQCTFEGCGKRFS-LDFNLRTHV RIHT  
GLI_human TGEKP HKCTFEGCRKSYSRLENL KTHLRSH TGEKP YMCEHEGCSKAFSNASDRAKHQN RTHS
```

```
ZIF268_mouse GEKP FAC--DICGRKFARS DERKRHTKIH LR  
WT_human GEKP FSCRW PSCQKKFARSDELVRHHNMH --  
YY1_human GDRP YVCPFDGCNKKFAQSTNLKSHILTHA -  
GLI_human NEKP YVCKLP GCTKRYTDPSSLRKHVKT VH G
```


SEQUENCE ALIGNMENT

```

ZIF268_mouse  -----
WT_human      -----RPFMCAYPGCN---KRY  FKLSHLQMHSRKH
YY1_human     -----TIACPHKGCT---KMFRDNSAMRKHLH  TH
GLI_human     ETDCRWDGCSQEFDSQEQLVHHINSEHIHGERKEFVCHWGGCSREL RPFKAQYMLVVHMR  RH
  
```

```

ZIF268_mouse  ---RPYACPVESCDRRFSRSDELTRHIRIHTGQKPFQC--RICMRNFS-RSDHLTTHI  RTHT
WT_human      TGEKPYQCDFKDCERRFSRS DQLKRHQRRHTGVKPFQC--KTCQRKFS-RSDHLKTHT  RTHT
YY1_human     -GPRVHVC--AECGKAFVSSKLRHQLVHTGKPFQCTFEGCGKRFS-LDFNLRTHV  RIHT
GLI_human     TGEKPHKCTFEGCRKSYSRLENLKTHLRSHTGKPYMCEHEGCSKAFSNASDRAKHQN  RTHS
  
```

```

ZIF268_mouse  GEKPFAC--DICGRKFARS DERKRHTKIHLR
WT_human      GEKPFSCRWPSCQKKFARSDELVRHHNMH--
YY1_human     GDRPYVCPFDGCNKKFAQSTNLKSHILTHA-
GLI_human     NEKPYVCKLPGCTKRYTDPSSLRKHVKTVHG
  
```

Hydrophobic His Cys

STRUCTURAL ALIGNMENT

```

ZIF268_mouse -----
WT_human    ---RPFM-----CAYPGCNKRY--FKLSHL----Q
YY1_human   -----T-----IACPHKGCTK--MFRDNS----A
GLI_human    ETDCRWDGCSQEFDSQEQLVHHINSEHIHGERKEFVCHWG-----GCSRELRP-FKAQYM
  
```

```

ZIF268_mouse -----RP YACPVESCDRRFSR SDELTRHIRIHT GQKPFQC-RI--CMRNF SRS
WT_human     MHSRKHT--G-EKP YQCDFKDCERRFSR SDQLKRHQRRHTG VKPFQC-KT--CQRKF SRS
YY1_human    MRKHLHT--HGPRV HVCA-E-CGKA FVESSKLKRHQLVHTGEEKPFQC-TFEGCGKR RFSLD
GLI_human     LVVHMRRHTG-EKP HKCTFEGCRK SYSRLENLKT HLRSH TGEKPYMCEHEG-CSKAF SNA
  
```

```

ZIF268_mouse DHLTTHI-RTHTGEEKP FACDI-C-GRKFARS DERKRHTKI-HLR
WT_human     DHLKTHT-RTHTGEEKP FSCRWPSCQK KFARSDELVRHHNM-H--
YY1_human    FNLRTHV-RIHTGDRP YVCPFDGCNK KFAQSTNLKSHILT-HA-
GLI_human     SDRAKHQNRTHSNEKP YVCKLPGCTK RYTD PSSLRKHVKTVHG-
  
```

α-helix

β-strand

SUPERIMPOSITION



beta strand

alpha helix

SUPERIMPOSITION

2j7jA Transcription factor IIIA (*Xenopus*)



alpha helix

beta strand



2prt

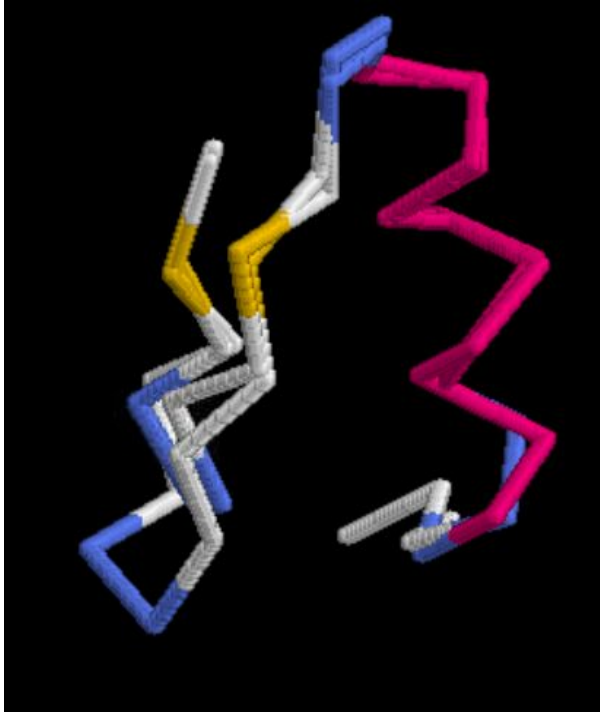
2gli

1ubd

2j7j

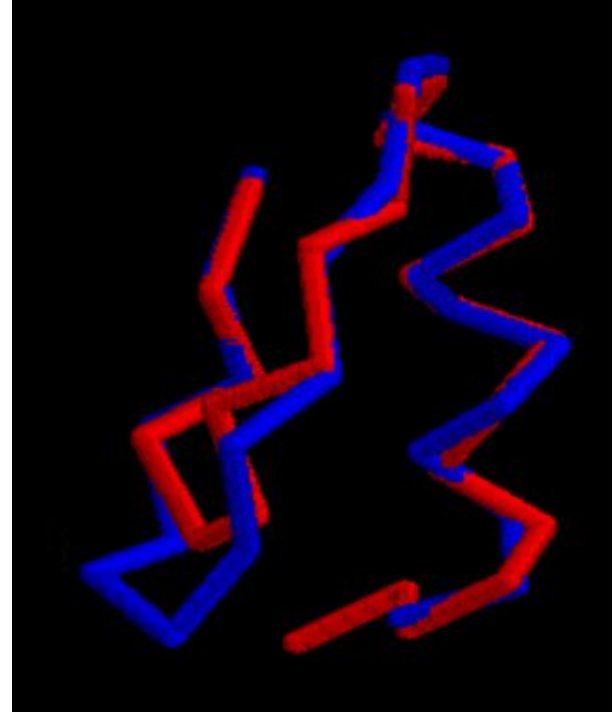
1aay

FREE ZF DOMAIN vs ZF IN A NUCLEIC ACID COMPLEX



alpha helix

beta strand



1aay → ZF bound to DNA

1znf → free ZF

FUNCTION

INTRODUCTION

Usually found in TF

RNA and protein binding

in fewer cases

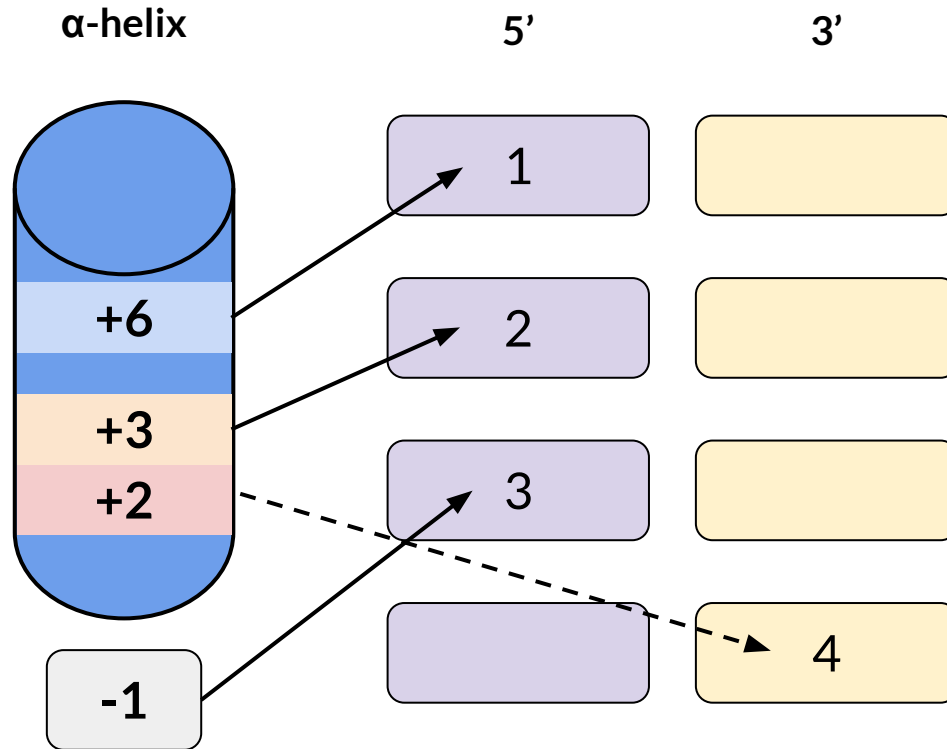
DNA binding

Amino acids of the α helix interact with bases in the **major groove**

1 zinc finger \rightarrow recognizes 3 nucleotides
TF have ~10 zinc fingers \rightarrow around 30 nt binding sites

CG rich regions

CANONICAL DOCKING ARRANGEMENT



ZF DNA BINDING: EGR-1

EGR-1: Early Growth Response Protein 1 (TF)

PDB: 1AAY

Protein ZIF268

Mus musculus

3 zinc fingers

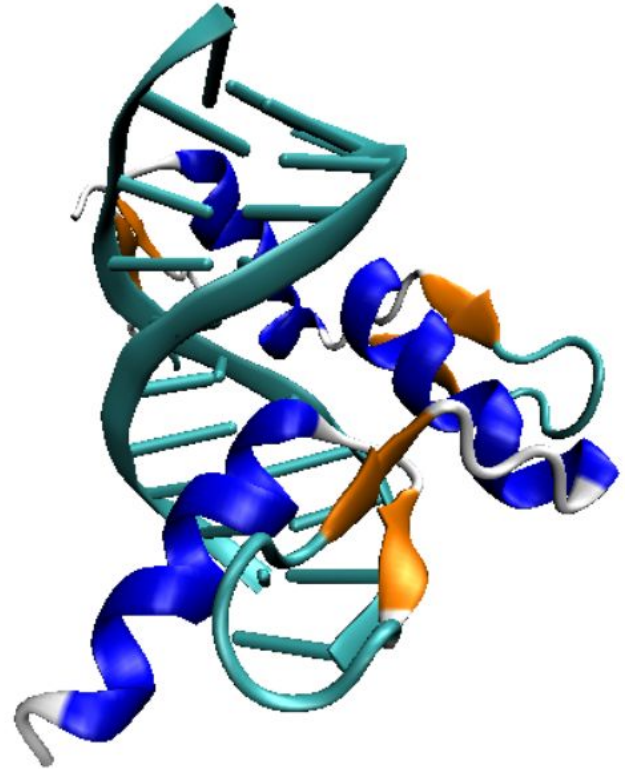
Consensus binding site

5' GCG TGG GCG 3'

zinc finger 1

zinc finger 2

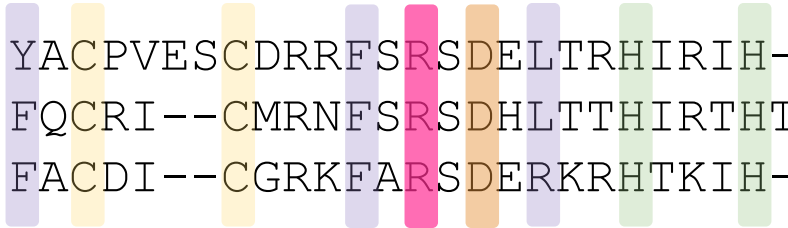
zinc finger 3



ALIGNMENTS

SEQUENCE ALIGNMENT

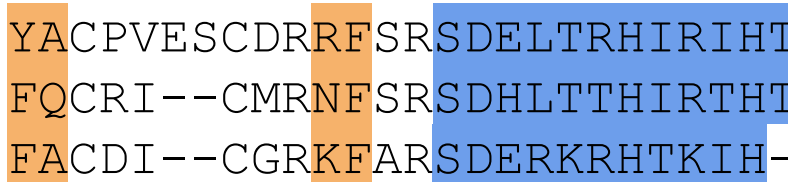
```
finger1 YACPVESCDRRFSRSDELTRHIRIH-
finger2 FQCRI--CMRNFSRSDHLTTHIRTHT
finger3 FACDI--CGRKFARSDERKRHTKIH-
```

The diagram shows a sequence alignment of three protein sequences. Vertical bars of various colors (purple, yellow, orange, pink, brown, light green) are placed behind the sequences to highlight conserved residues. Finger1 has residues Y, A, C, P, V, E, S, C, D, R, R, F, S, R, S, D, E, L, T, R, H, I, R, I, H. Finger2 has F, Q, C, R, I, two dashes, C, M, R, N, F, S, R, S, D, H, L, T, T, H, I, R, T, H, T. Finger3 has F, A, C, D, I, two dashes, C, G, R, K, F, A, R, S, D, E, R, K, R, H, T, K, I, H.

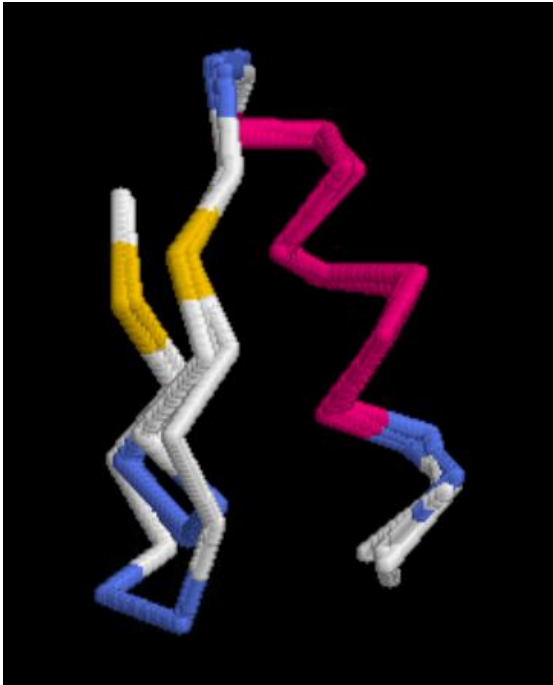
STRUCTURAL ALIGNMENT

```
finger1 YACPVESCDRRFSRSDELTRHIRIHT
finger2 FQCRI--CMRNFSRSDHLTTHIRTHT
finger3 FACDI--CGRKFARSDERKRHTKIH-
```

-1 2 3 6

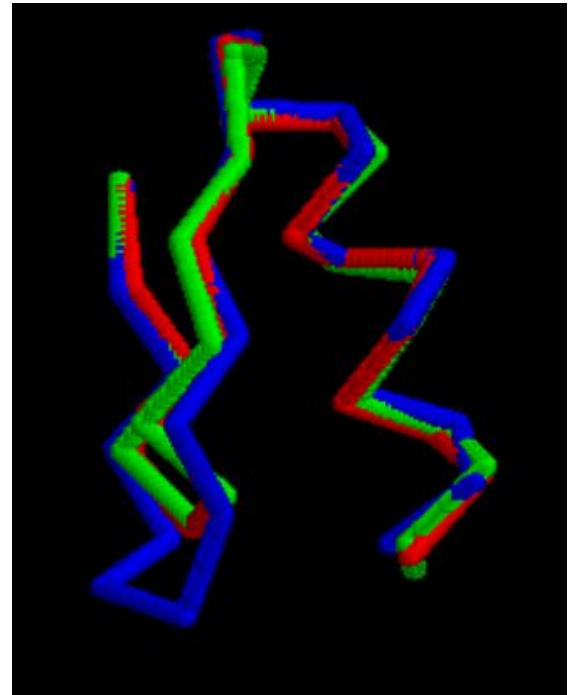
The diagram shows a structural alignment of the same three protein sequences. Colored boxes highlight structural elements: orange boxes highlight the first two residues (Y, A) of each sequence; a blue box highlights the last six residues (S, R, S, D, E, L) of each sequence. The labels -1, 2 3, and 6 are positioned above the sequences to indicate the positions of these elements.

SUPERIMPOSITION



alpha helix

beta strand



ZF1

ZF2

ZF3

INTERACTIONS OF EGR-1 WITH DNA

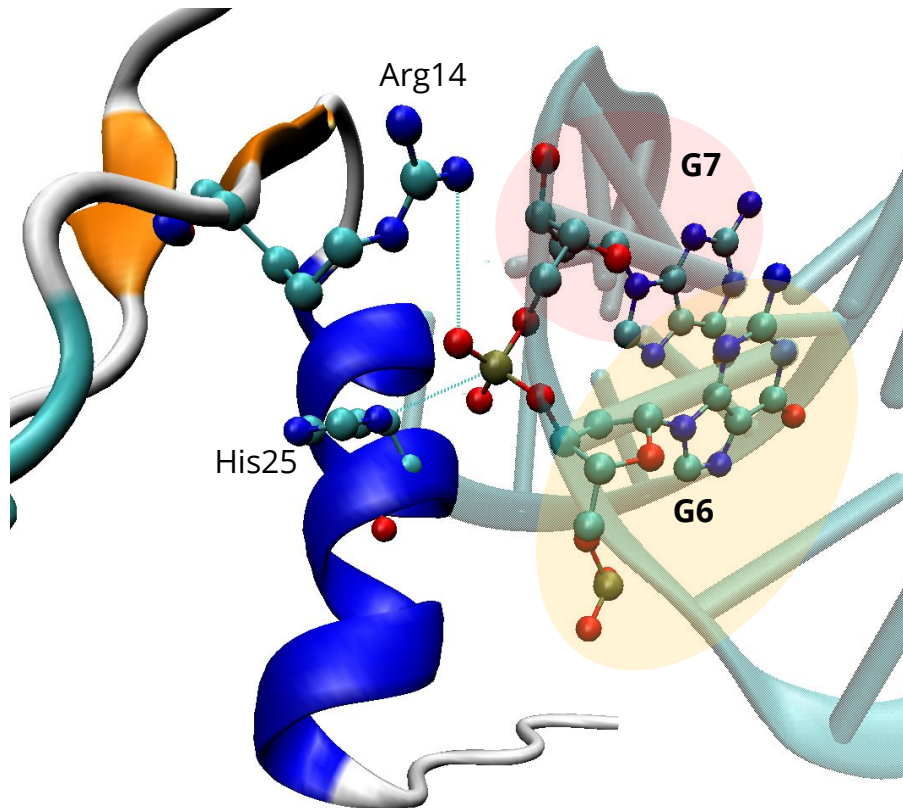
Non-specific interactions

Made with the **backbone** of the DNA

Specific interactions

Made with the **bases** of the DNA
(following the canonical docking arrangement)

NONSPECIFIC INTERACTIONS: Arg14, His25 - phosphate group



Second histidine residue that coordinates Zn ion

Arginine residues from the second beta strand

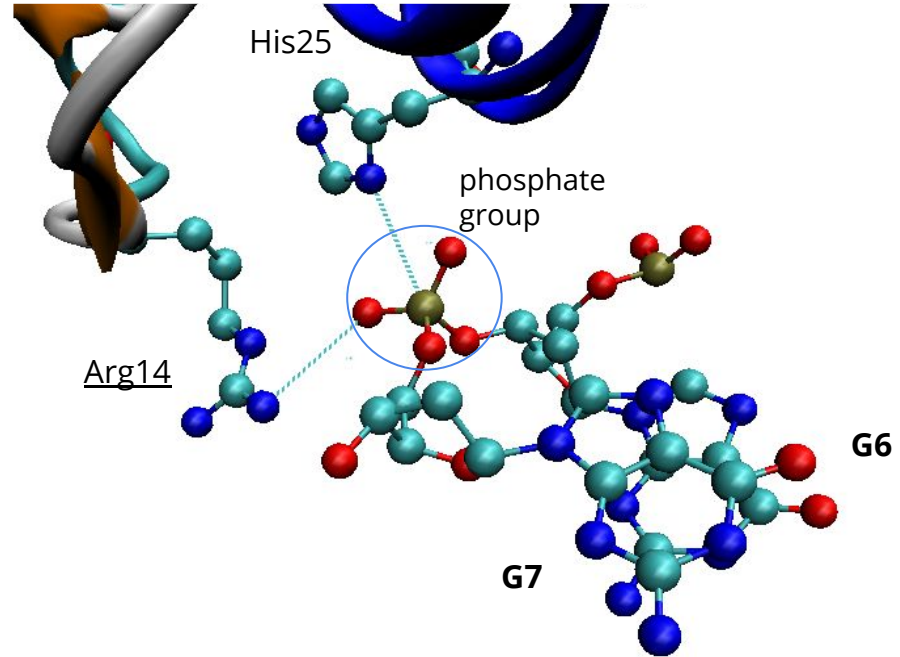
NONSPECIFIC INTERACTIONS: Arg14, His25 - phosphate group

2nd beta strand

ZF1 DRRFSR
ZF2 MRNFSR
ZF3 GRKFAR



is the function maintained?



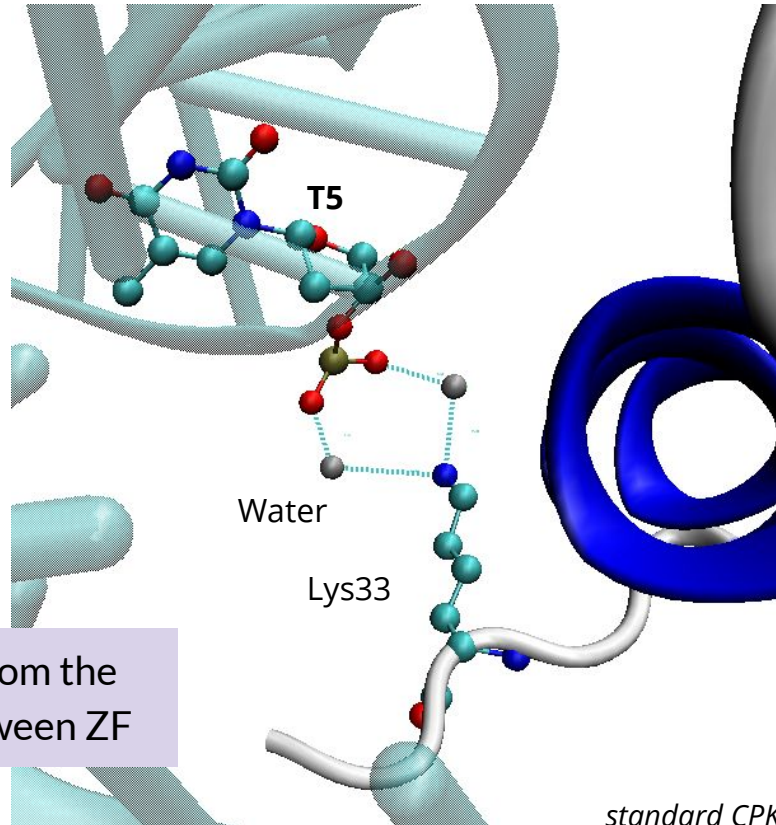
standard CPK color scheme, C in light blue

NONSPECIFIC INTERACTIONS: Lys33 - T5 water contact

	ZF1	ZF2
ZIF268_mouse	RIHTGQKPFQC	
WT_human	RRHTGVKPFQC	
YY1_human	LVHTGEKPFQC	
GLI_human	RSHTGEKPYMC	

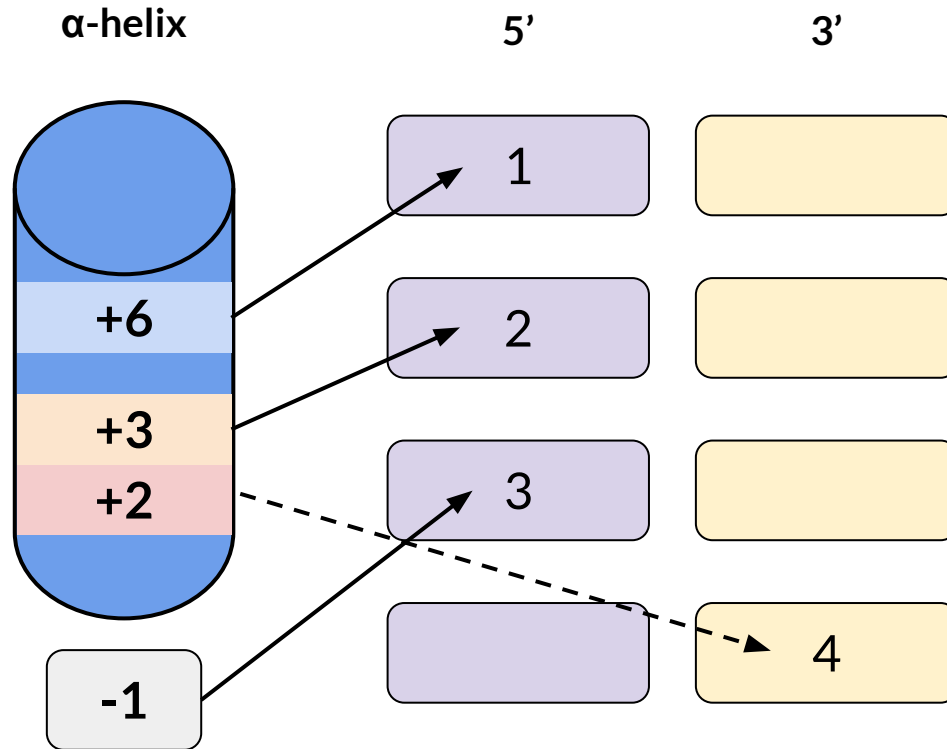
conserved

Lysine residues from the linker regions between ZF



standard CPK color scheme, C in light blue

CANONICAL DOCKING ARRANGEMENT



SPECIFIC INTERACTIONS: position -1

Contacts the third base on the primary strand of the subsite (5' -- G)

zinc finger 1 Arg18

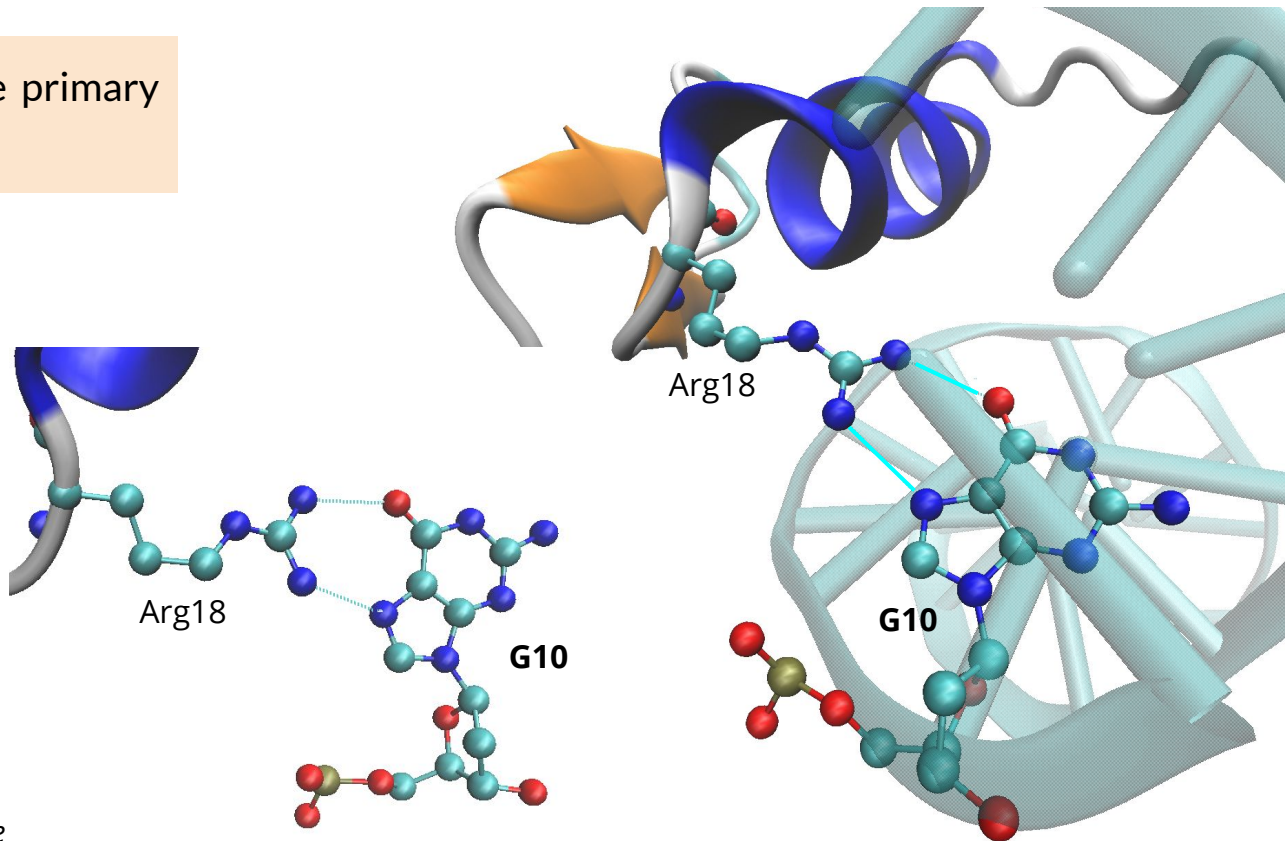
zinc finger 2 Arg46

zinc finger 3 Arg74



Interacts with guanine 10

standard CPK color scheme, C in light blue



SPECIFIC INTERACTIONS: position 2

zinc finger 1

Asp20

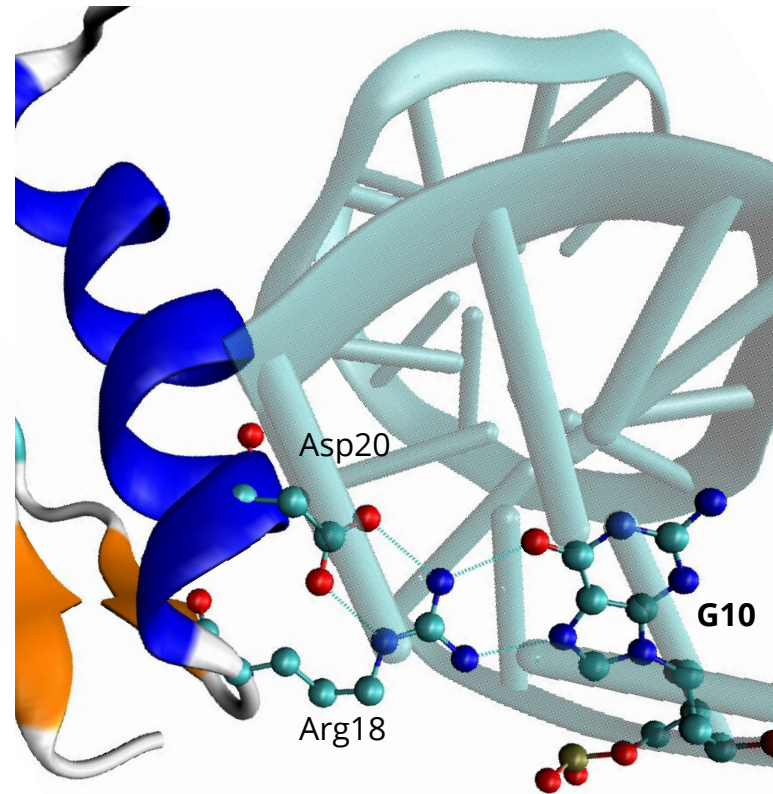
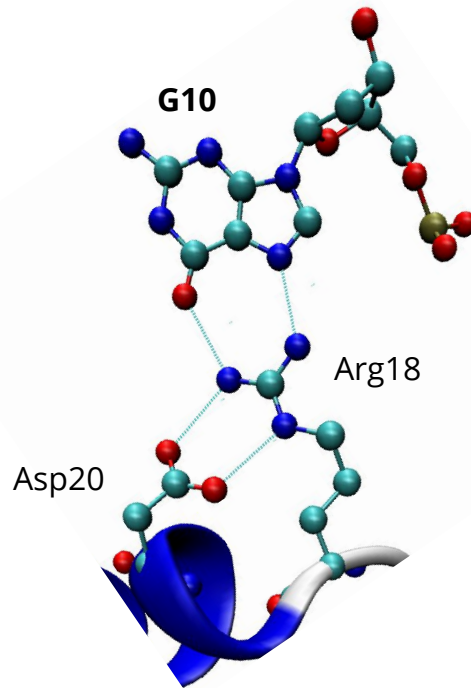
zinc finger 2

Asp48

zinc finger 3

Asp76

↓
Stabilizes Arg18



standard CPK color scheme, C in light blue

SPECIFIC INTERACTIONS: position 3

Contacts the second base on the primary strand of the subsite (5' - G-)

zinc finger 1

Glu21

zinc finger 2

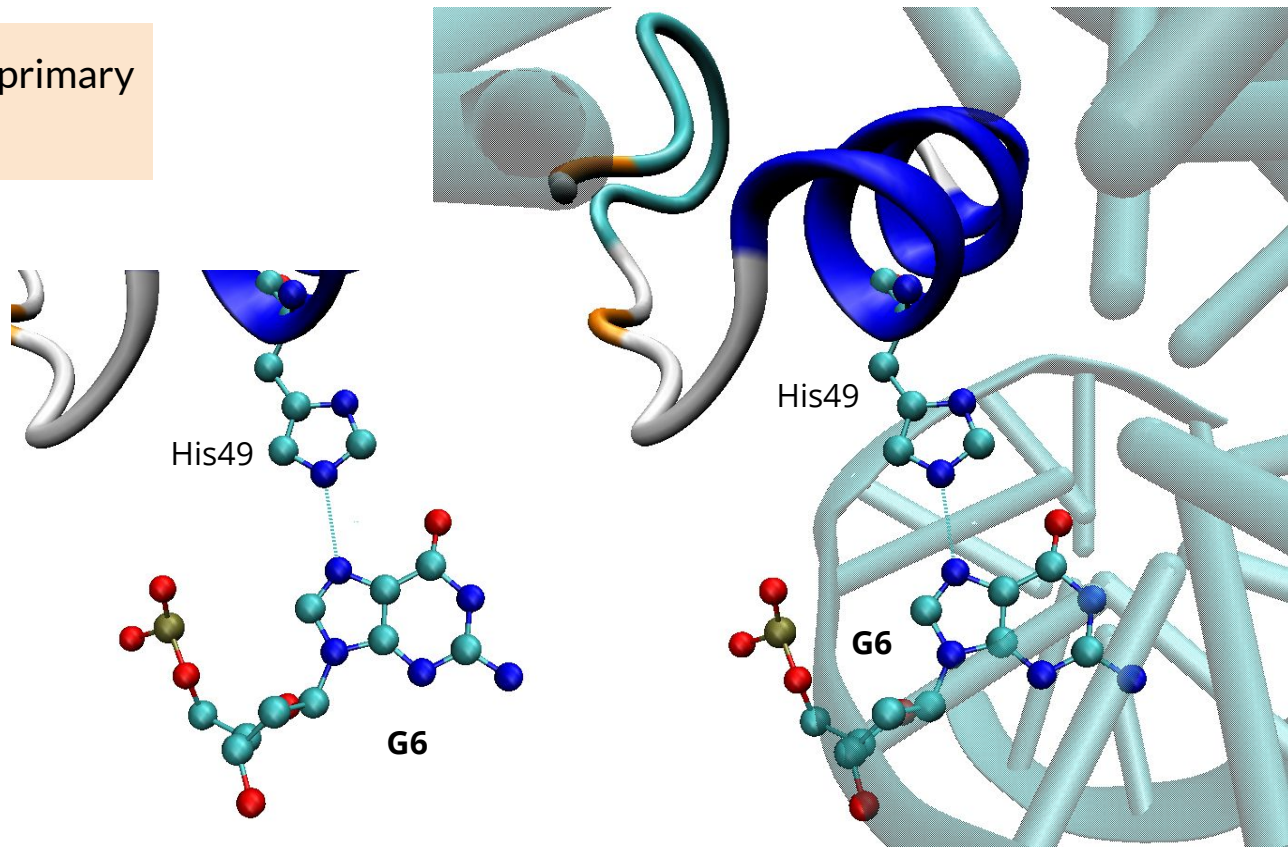
His49

zinc finger 3

Glu77



His49 interacts with guanine 6



standard CPK color scheme, C in light blue

SPECIFIC INTERACTIONS: position 6

Contacts the first base on the primary strand of the subsite (5' G--)

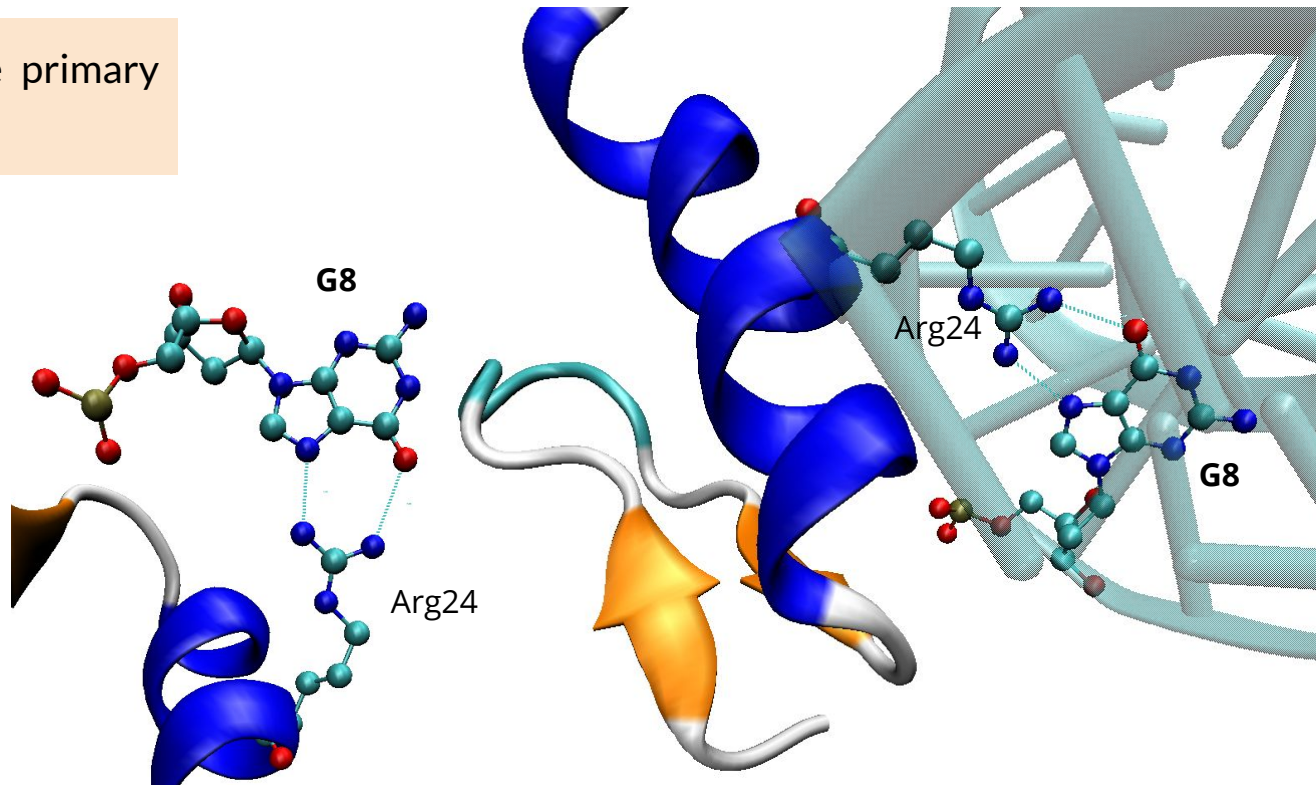
zinc finger 1 Arg24

zinc finger 2 Thr52

zinc finger 3 Arg80

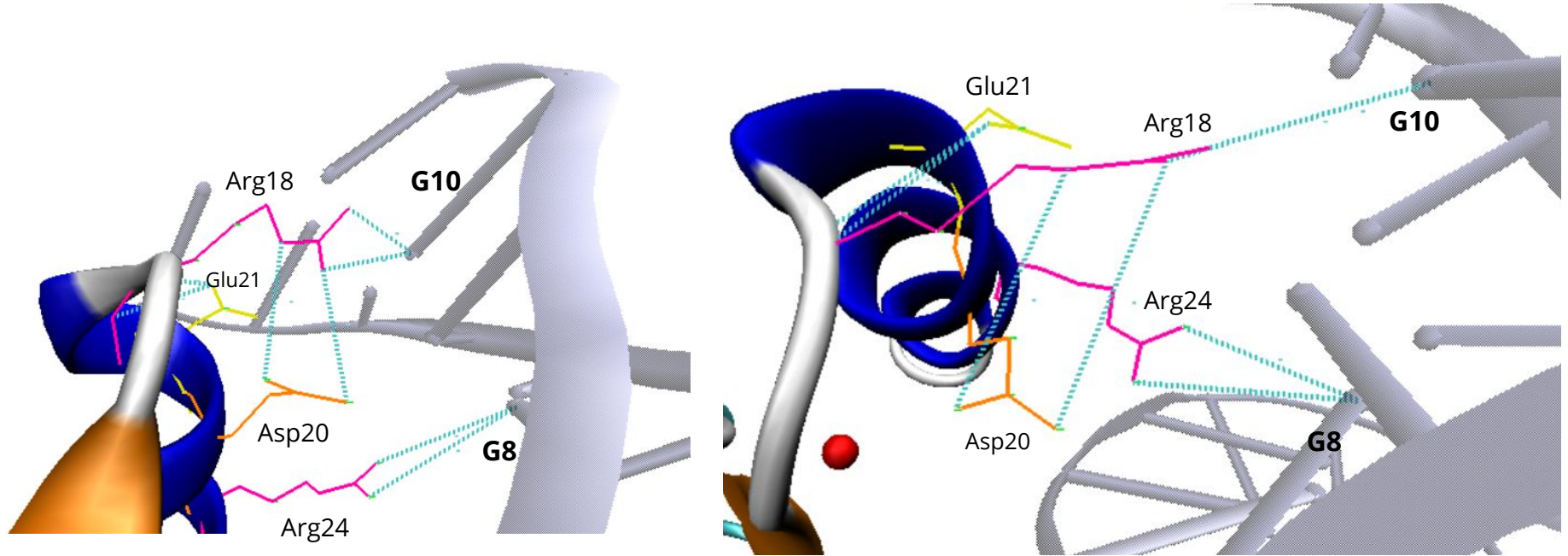


Arg24/80 interact with guanine 8



standard CPK color scheme, C in light blue

SPECIFIC INTERACTIONS OF ZF 1 OF THE EGR-1



TAKE HOME MESSAGES

The C2H2 ZF family constitutes one of the most **abundant and versatile DNA-binding motifs** found in eukaryotes

Residues interacting with DNA are not as conserved to allow different zinc fingers proteins to recognize a **number of DNA sequences**

Cysteines and Histidines are very **conserved** due to its interaction with zinc

Hydrophobic residues are also **conserved** to maintain the fold

Proteins from the C2H2 family share the **same structure**

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THANK



YOU!



QUESTIONS

1. How many Zn ions do zinc fingers from the C2H2 family bind?
 - a. 1
 - b. 2
 - c. 3
 - d. 4
 - e. None
2. What residues are important for binding zinc in the classical zinc fingers?
 - a. Cysteines
 - b. Histidines
 - c. **a and b are correct**
 - d. Cytosines
 - e. All of the above
3. The fold of classical zinc fingers is:
 - a. Two alpha helices
 - b. Three alpha helices
 - c. Two alpha helices and one beta strand
 - d. **An alpha helix and two beta strands**
 - e. None of the above

QUESTIONS

1. Choose the correct sentence:
 - a. Glutamic acid is considered an hydrophobic amino acid.
 - b. Transcription Factor IIIA was discovered and isolated from *Mus musculus*.
 - c. The C2H2 zinc finger structure varies among homolog proteins.
 - d. The number of zinc fingers is restricted to only 3 or 4.
 - e. **Residues that participate in the binding of zinc are highly conserved.**
2. Choose the correct sentence:
 - a. Conserved histidines are located in the beta strand.
 - b. The zinc finger undergoes a conformational change when it binds DNA.
 - c. **XFIN protein has more than 30 zinc fingers**
 - d. Residues that bind DNA are highly conserved.
 - e. Arginine 18 of EGR-1 interacts with an adenine.
3. How many nucleotides does a single classical zinc finger recognize?
 - a. 9
 - b. **3**
 - c. 1
 - d. 2
 - e. 4

QUESTIONS

1. Which of these positions are the most important for DNA binding according to the canonical docking arrangement?
 - a. Positions 3,4 and 6 of the alpha helix.
 - b. Positions 2,3,4 of the alpha helix.
 - c. Positions -1, 2, 3, 6 of the beta strand.
 - d. Positions -1, 2, 3, 6 of the alpha helix.**
 - e. Only position 6 of the alpha helix is important.
2. About the Early Growth Response protein 1, chose the wrong option:
 - a. It has 3 zinc fingers
 - b. It has a highly conserved Tyrosine**
 - c. It binds to DNA
 - d. It binds to a consensus site
 - e. It undergoes nonspecific and specific interactions with nucleic acids
3. Choose the false sentence about the interactions of ZIF268 with the nucleic acid:
 - a. Lysine 33 is important for nonspecific interactions.
 - b. Lysine 33 interacts with a thymine through a water contact.
 - c. Lysine 33 is only present in mice.**
 - d. Lysine 33 is highly conserved.
 - e. Lysine 33 is located in the linker region between zinc fingers.

QUESTIONS

1. The specific interactions in ZIF268 happen with the nitrogenated base:
 - a. A
 - b. C
 - c. **G**
 - d. T
 - e. Specific interactions are not with nitrogenated bases.