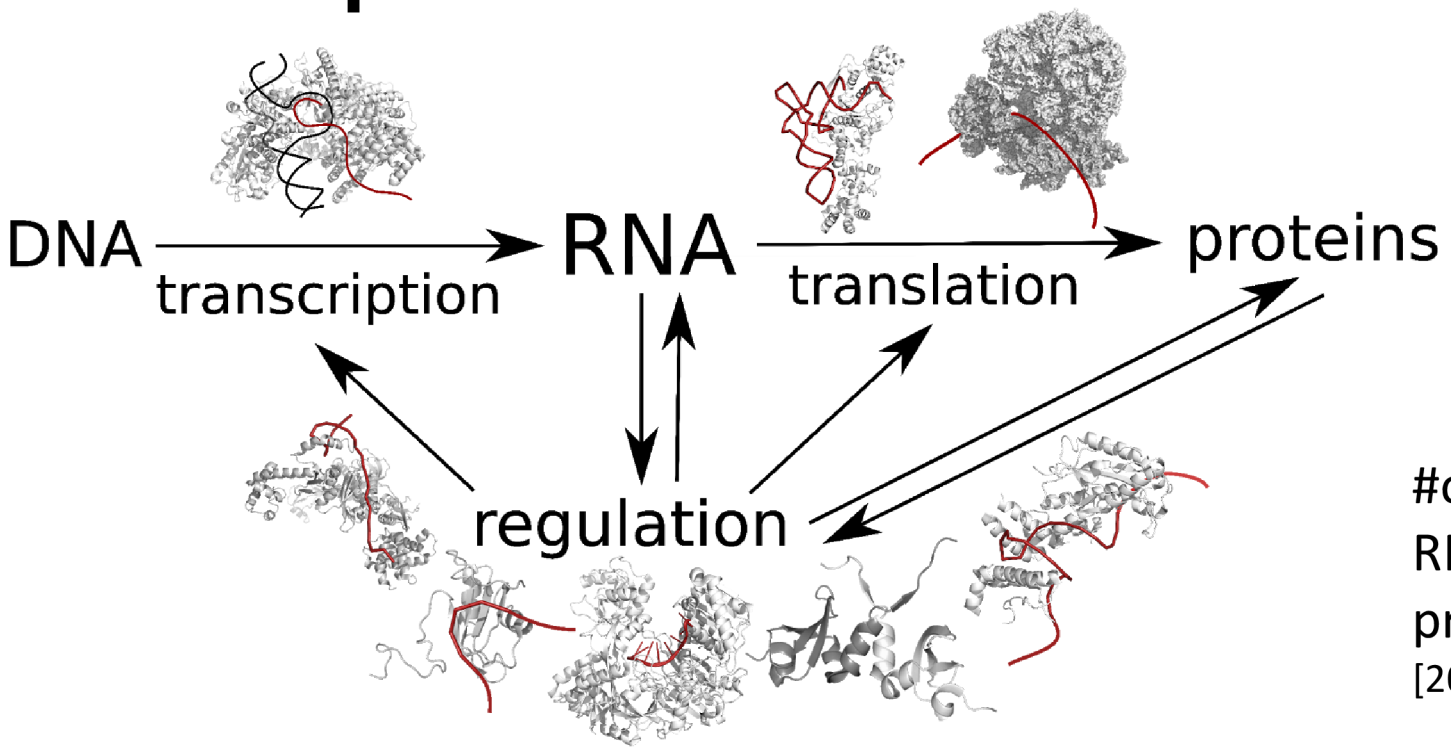
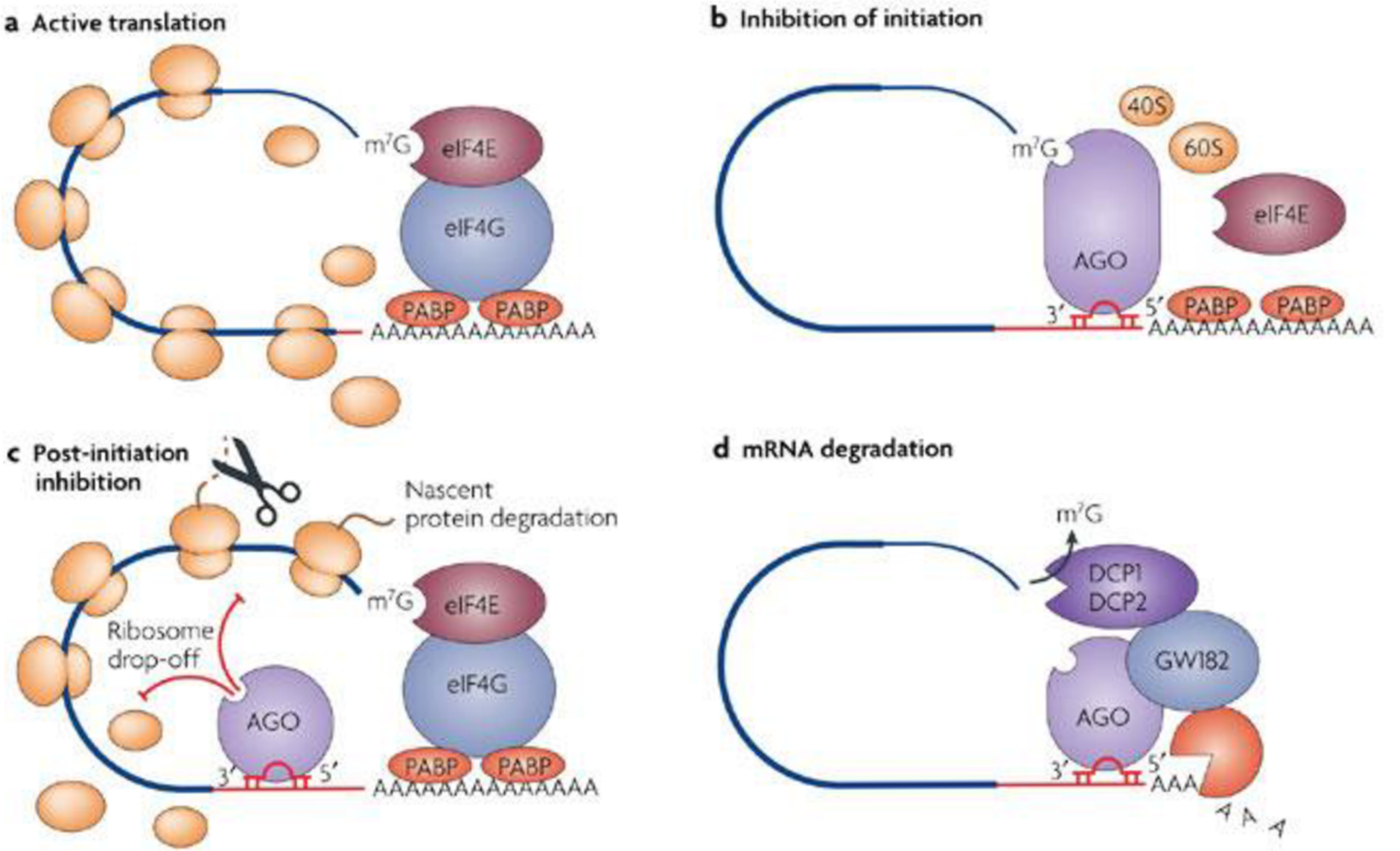
RNA-protein interactions



#of known human RNA binding proteins: 1900+ [2018]

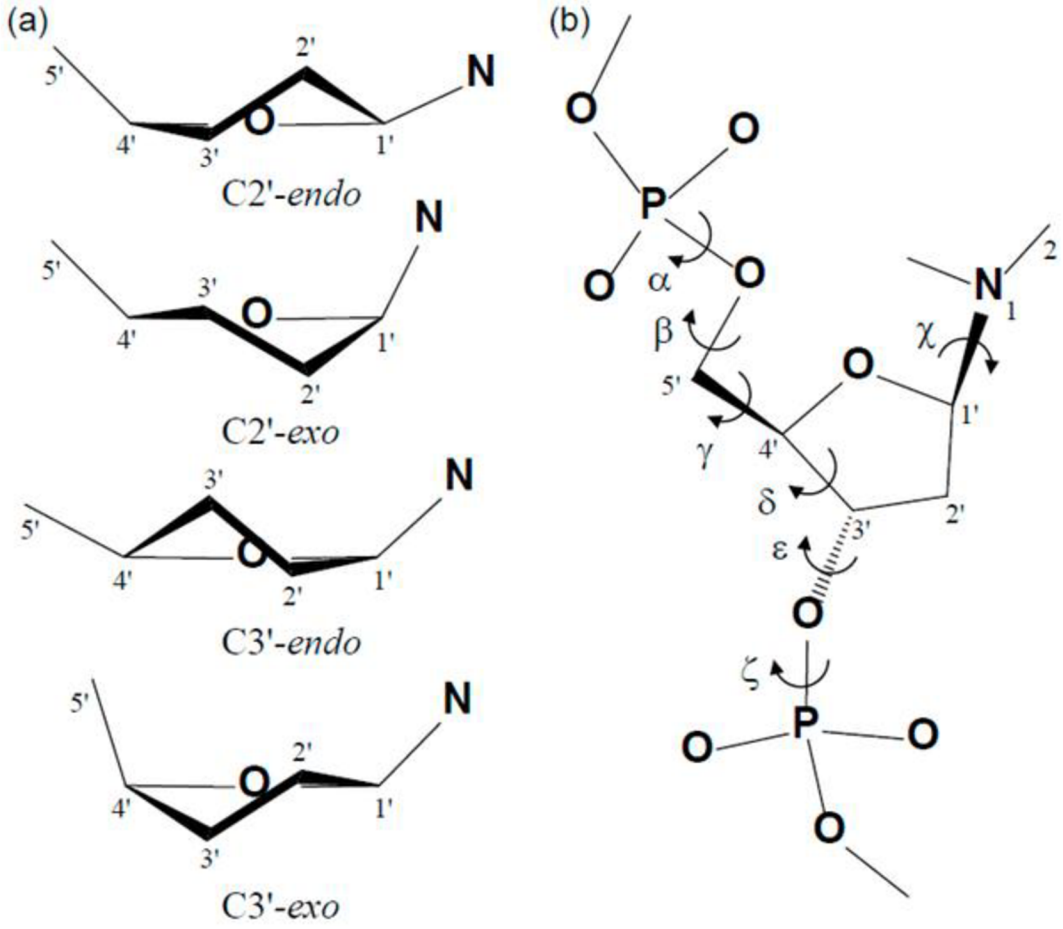
Effect of protein binding on RNA: stability, folding, mediating interactions with other molecules → RNA synthesis, maturation, transport, storage, degradation

→ gene expression, metabolism


a Active translation
m7G
eIF4E
eIF4G
PABP
PABP
AAAAAAAAAAAAAA
b Inhibition of initiation
40S
60S
m7G
eIF4E
AGO
3′
5′
PABP
PABP
AAAAAAAAAAAAAA
c Post-initiation inhibition
Nascent protein degradation
m7G
eIF4E
eIF4G
Ribosome drop-off
AGO
3′
5′
PABP
PABP
AAAAAAAAAAAAAA
d mRNA degradation
m7G
DCP1
DCP2
GW182
AGO
3′
5′
AAA
A A A

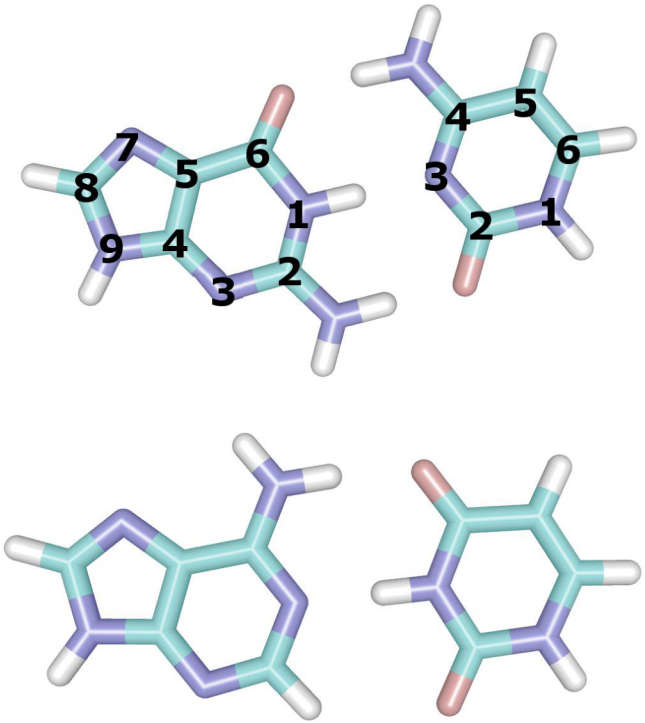
How do they interact?

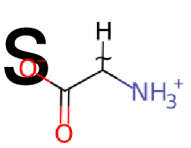
NA vs. proteins

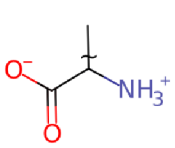


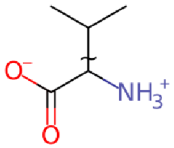
NA: flexible backbone
proteins: 2 backbone torsions

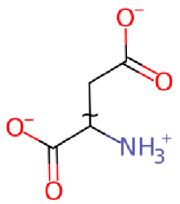
NA vs. proteins

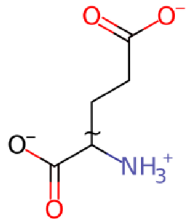


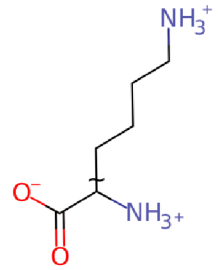

Glycine (G)

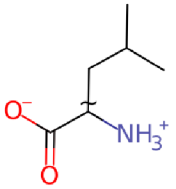

Alanine (A)

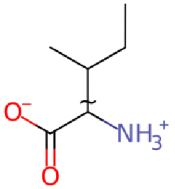

Valine (V)

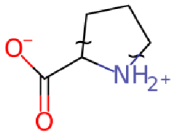

Aspartic Acid (D)

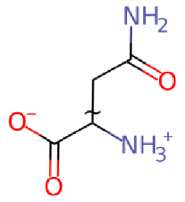

Glutamic Acid (E)

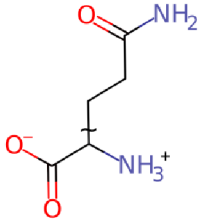

Lysine (K)

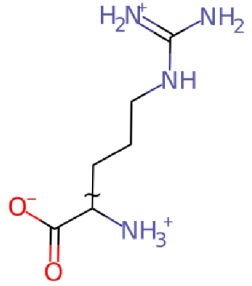

Leucine (L)

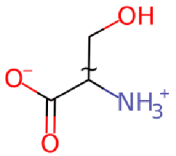

Isoleucine (I)

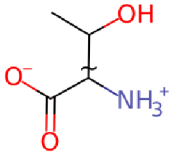

Proline (P)

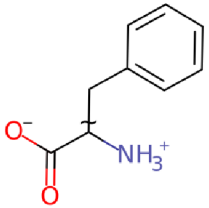

Asapragine (N)

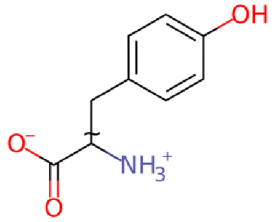

Glutamine (Q)

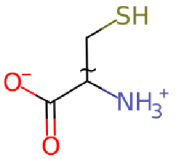

Arginine (R)

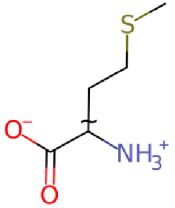

Serine (S)

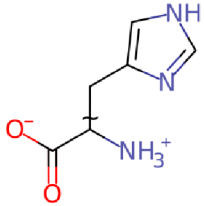

Threonine (T)

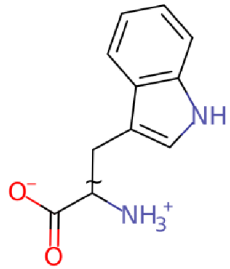

Phenylalanine (F)

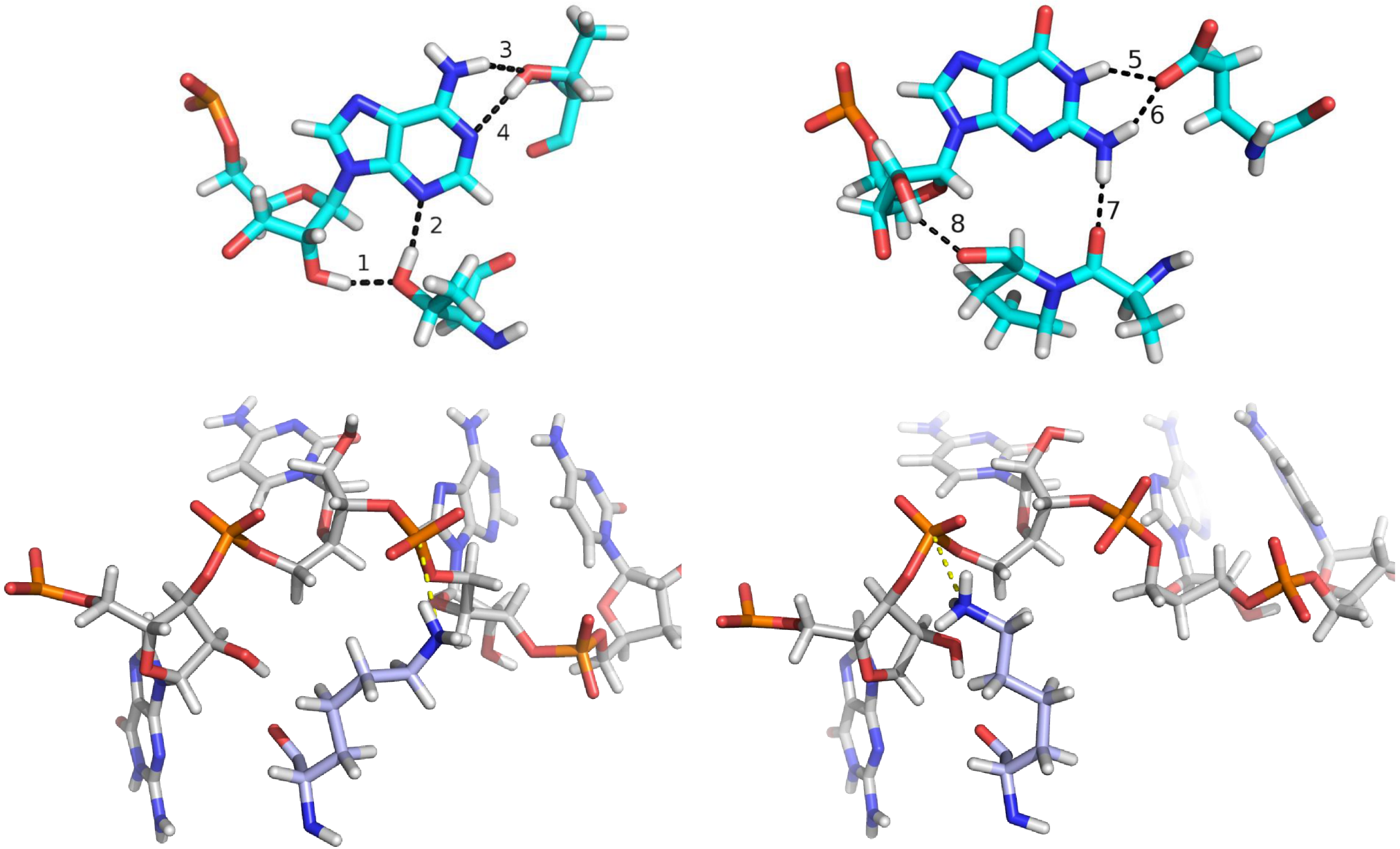

Tyrosine (Y)


Cysteine (C)


Methionine (M)


Histidine (H)


Tryptophan (W)


1
2
3
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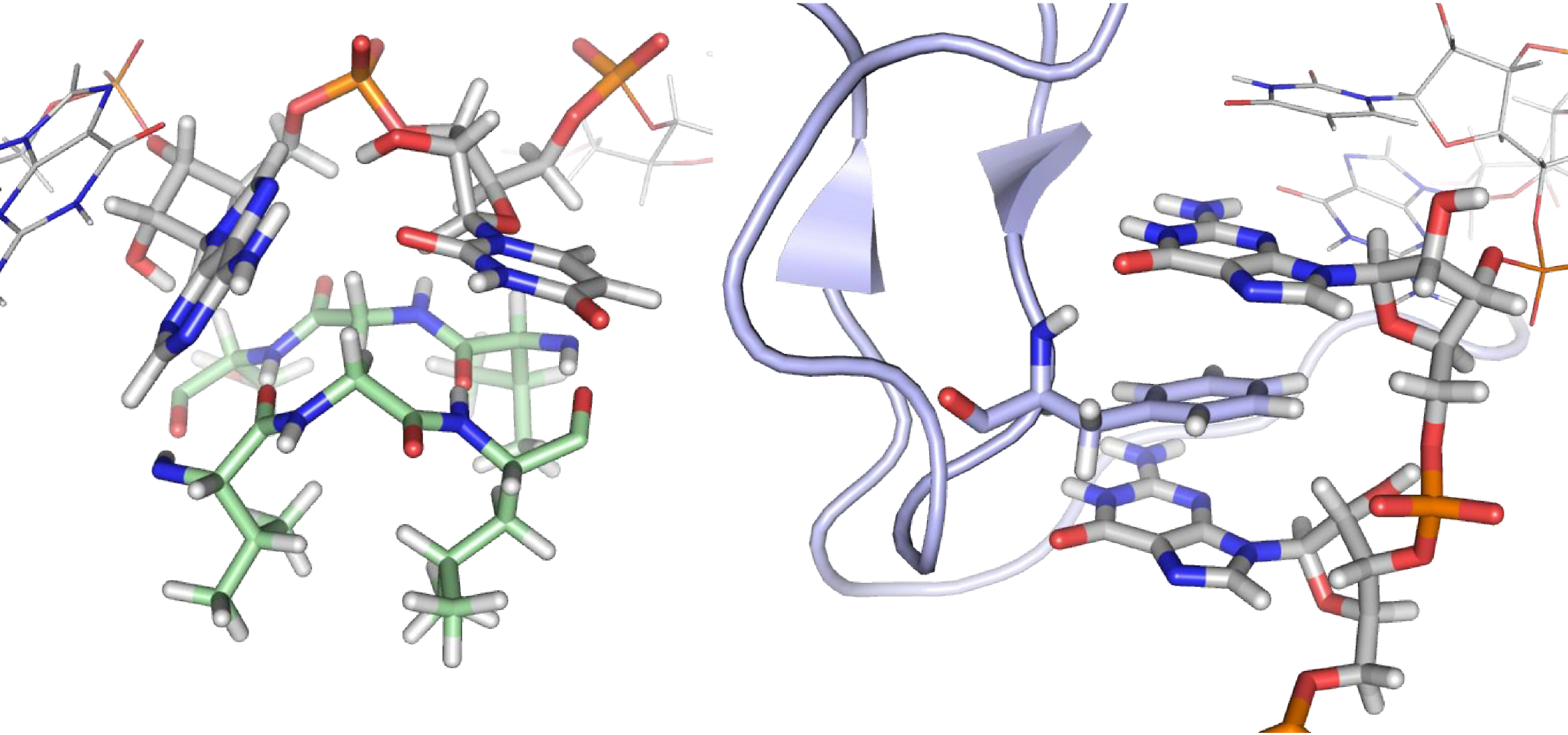
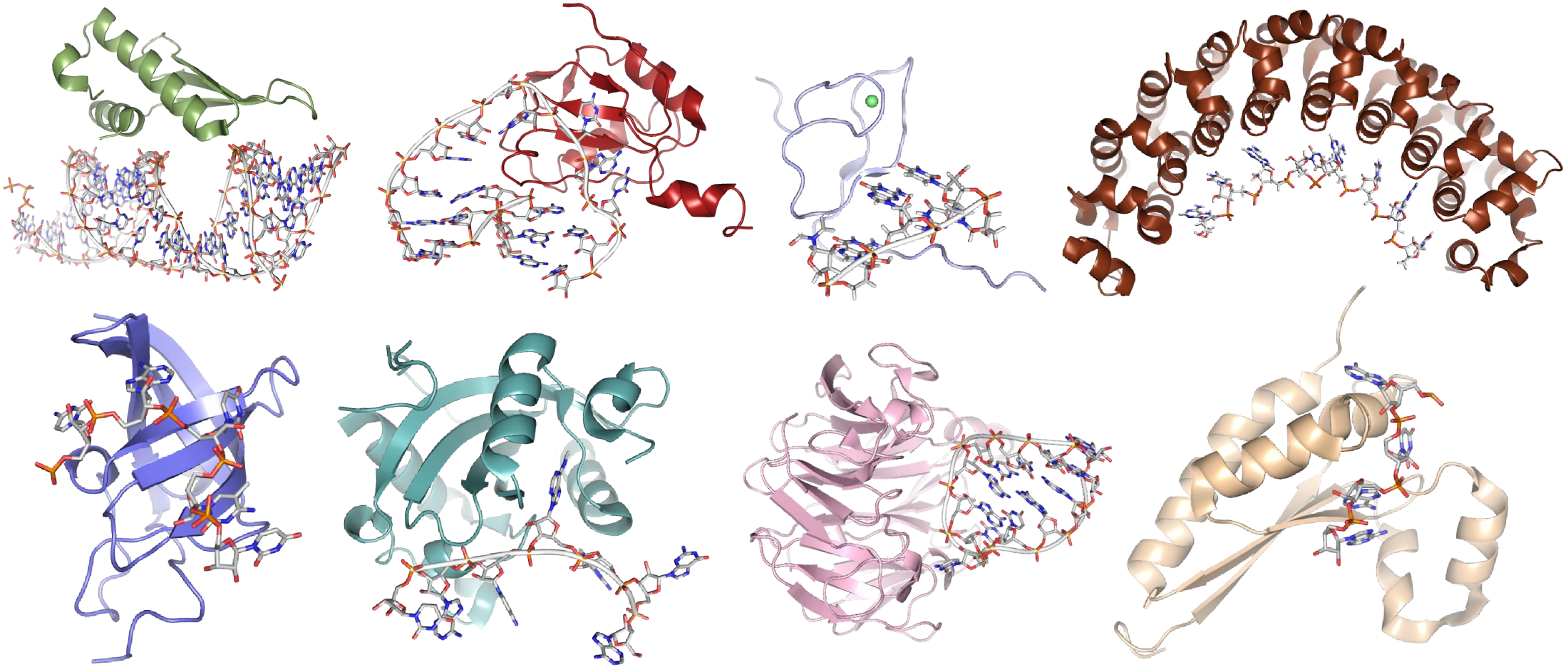


Driving forces for the interaction

Diversity of protein-RNA binding strategies: RNA-binding domains



Diversity of protein-RNA binding strategies: RNA-binding domains

for exaple: RRM

- ~650 of human proteins have at least one RRM (data from Pfam, Oct 2019)
- involved in: RNA editing, pre-mRNA processing, alternative splicing, mRNA stability and export, pre-rRNA complex formation, translation regulation, degradation

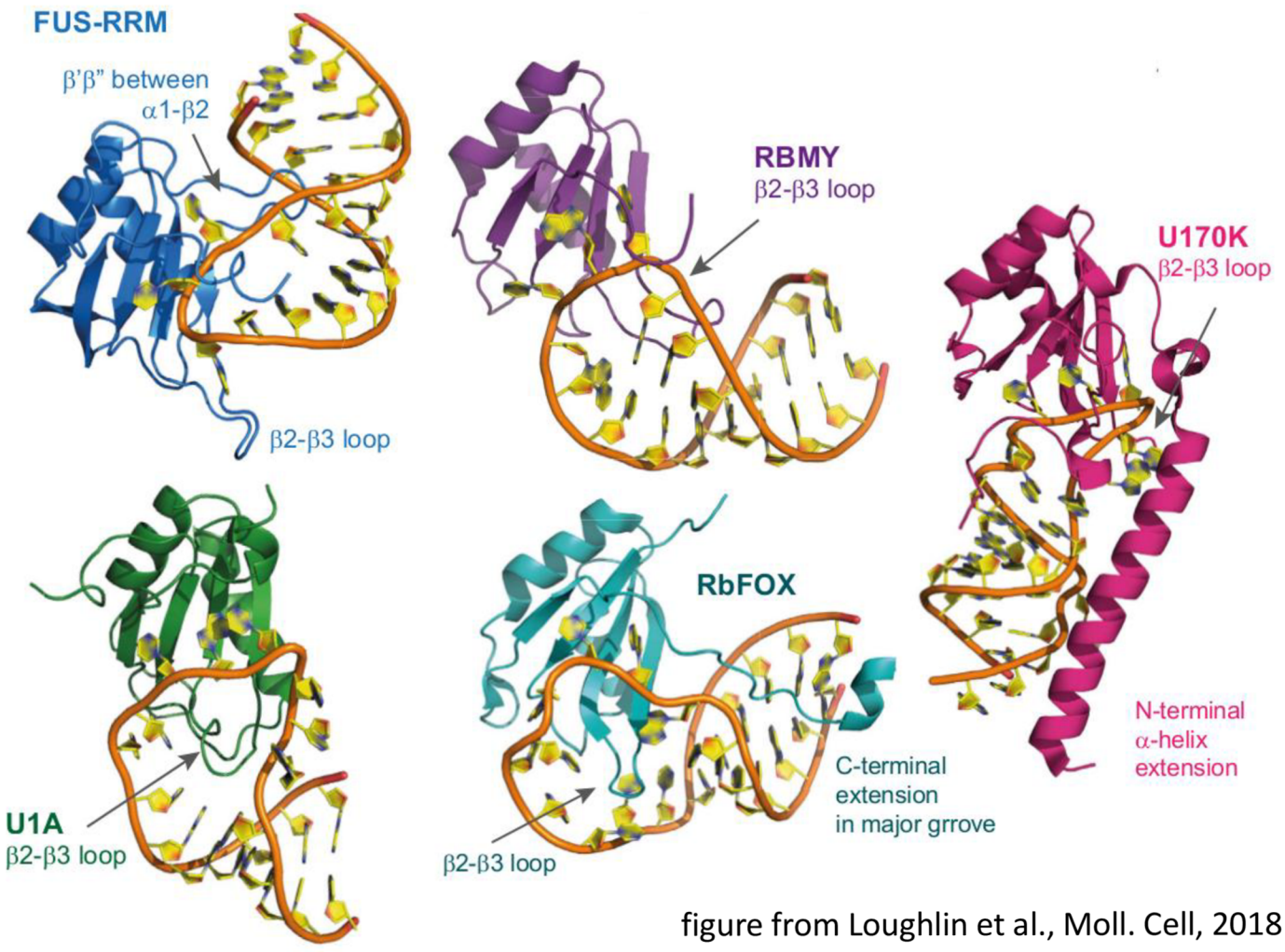


figure from Loughlin et al., Moll. Cell, 2018

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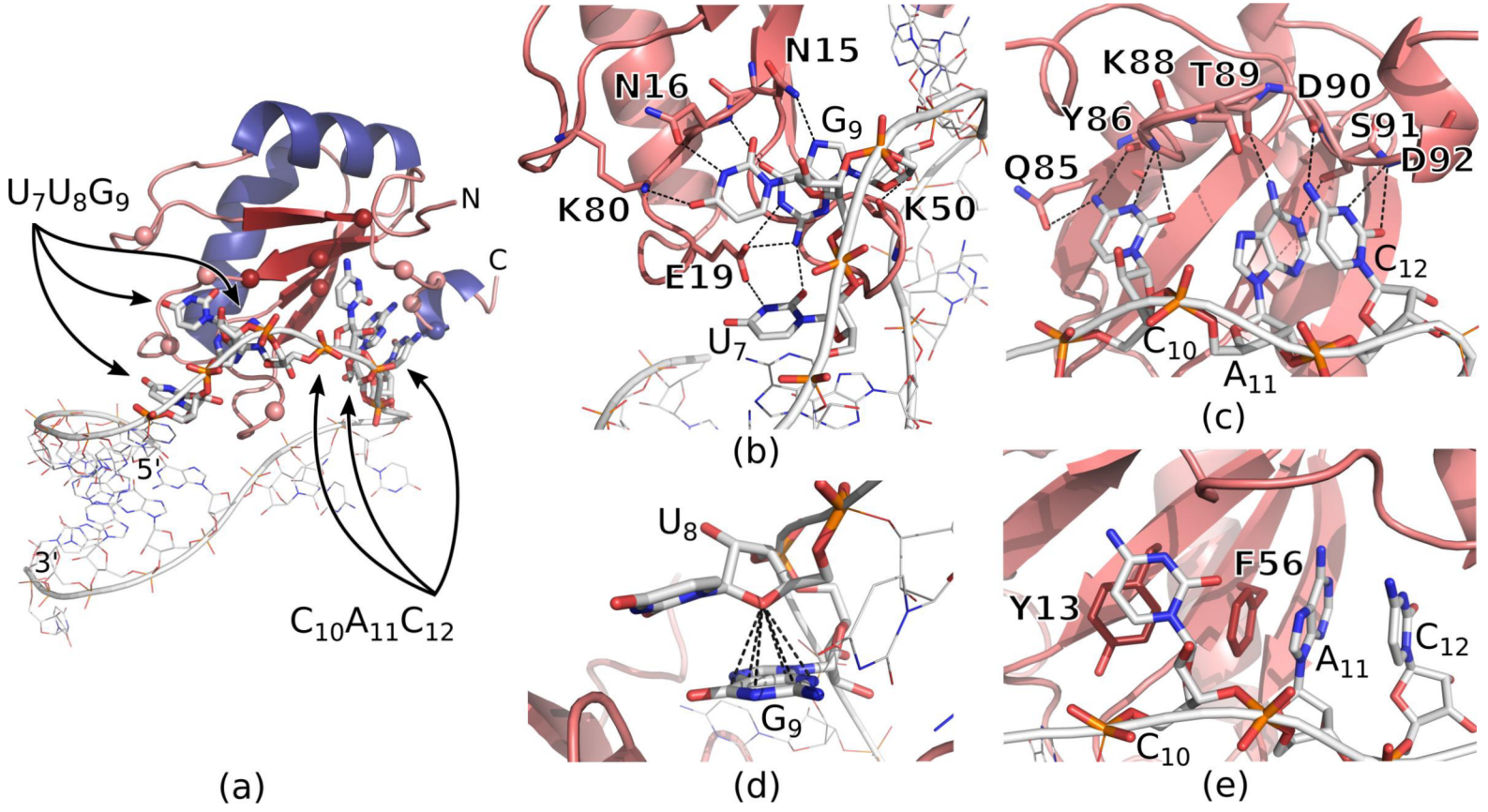
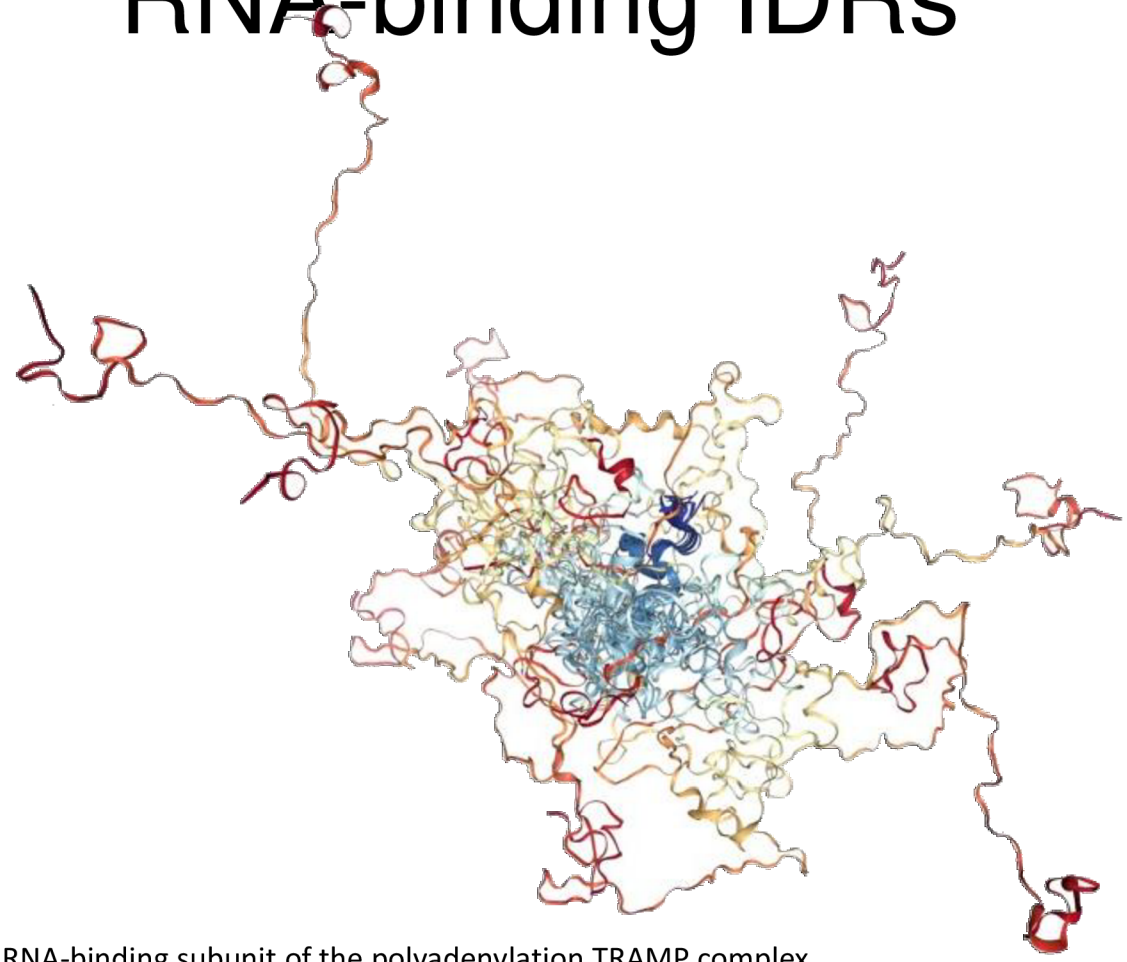


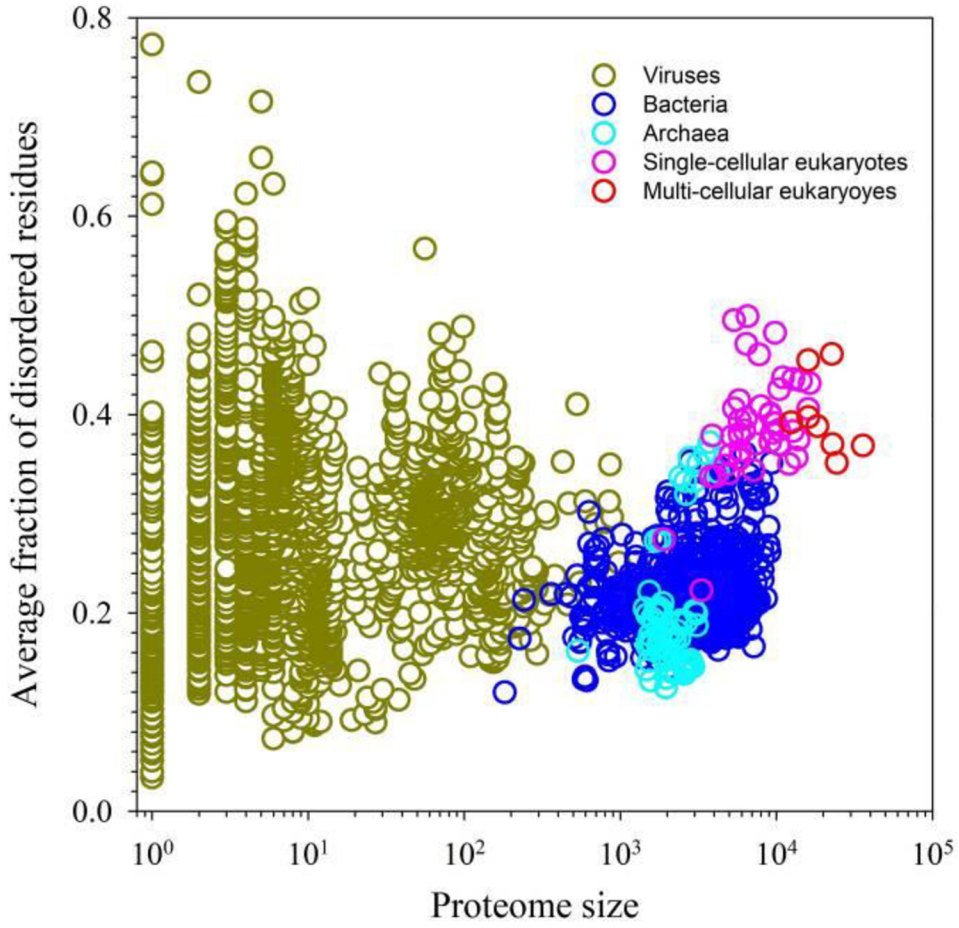
U1A + U1 snRNA hairpin, figure from Pokorna et al., J. Chem. Theory Comput., 2018

Diversity of protein-RNA binding strategies: RNA-binding IDRs

IDR = intrinsically disordered region



RNA-binding subunit of the polyadenylation TRAMP complex

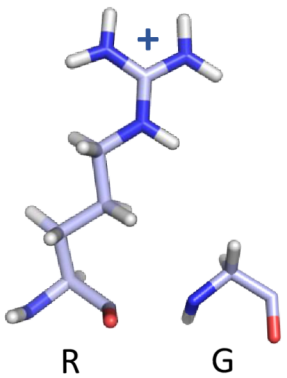


figures from Darling and Uversky, Front. Genet., 2018

Diversity of protein-RNA binding strategies: RNA-binding IDRs

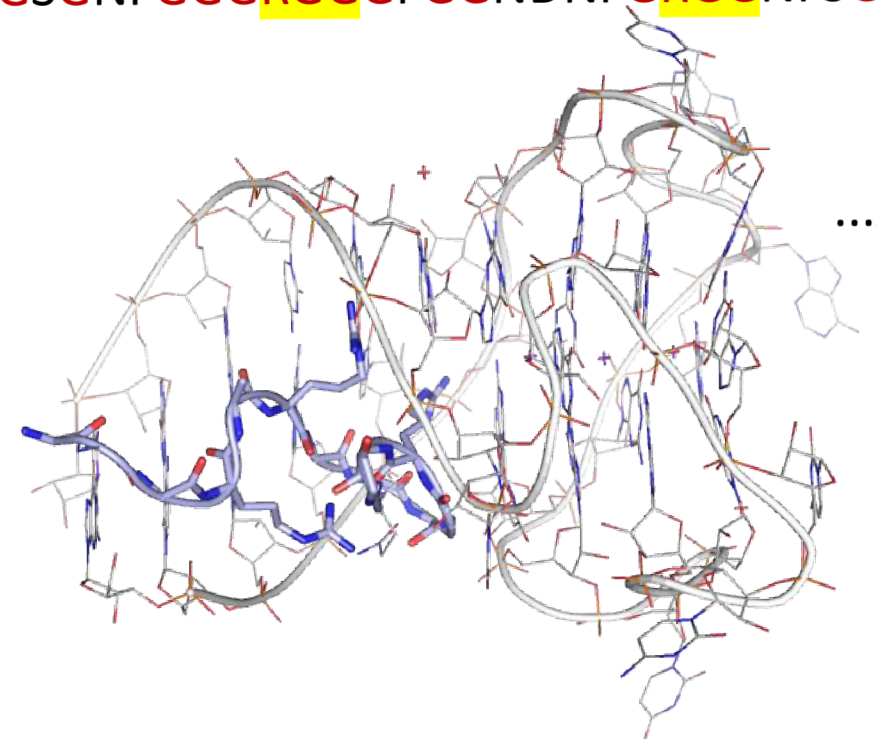
IDR = intrinsically disordered region

RGG/RG motif



...RGRSGSGNFGGGRGGGFGGNDNFGRGGNFSGRGGFGGSRGGGGYGG...

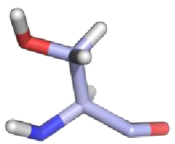
Fused in sarcoma RGG2 sequence



...ARGDGRRRGGGGRGQGGR...

segment of fragile X mental retardation protein + RNA G-quadruplex, PDB: 5de5

RS-rich regions

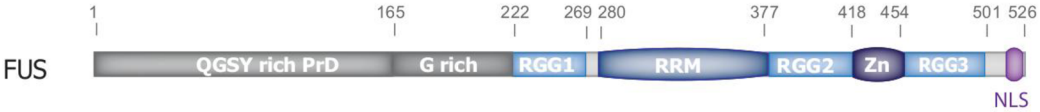


...GPRSPSYGRSRSRSRSRSRSRSRSNSRSRSYSPRRSRGSPRYSPRHSRSRSRT...

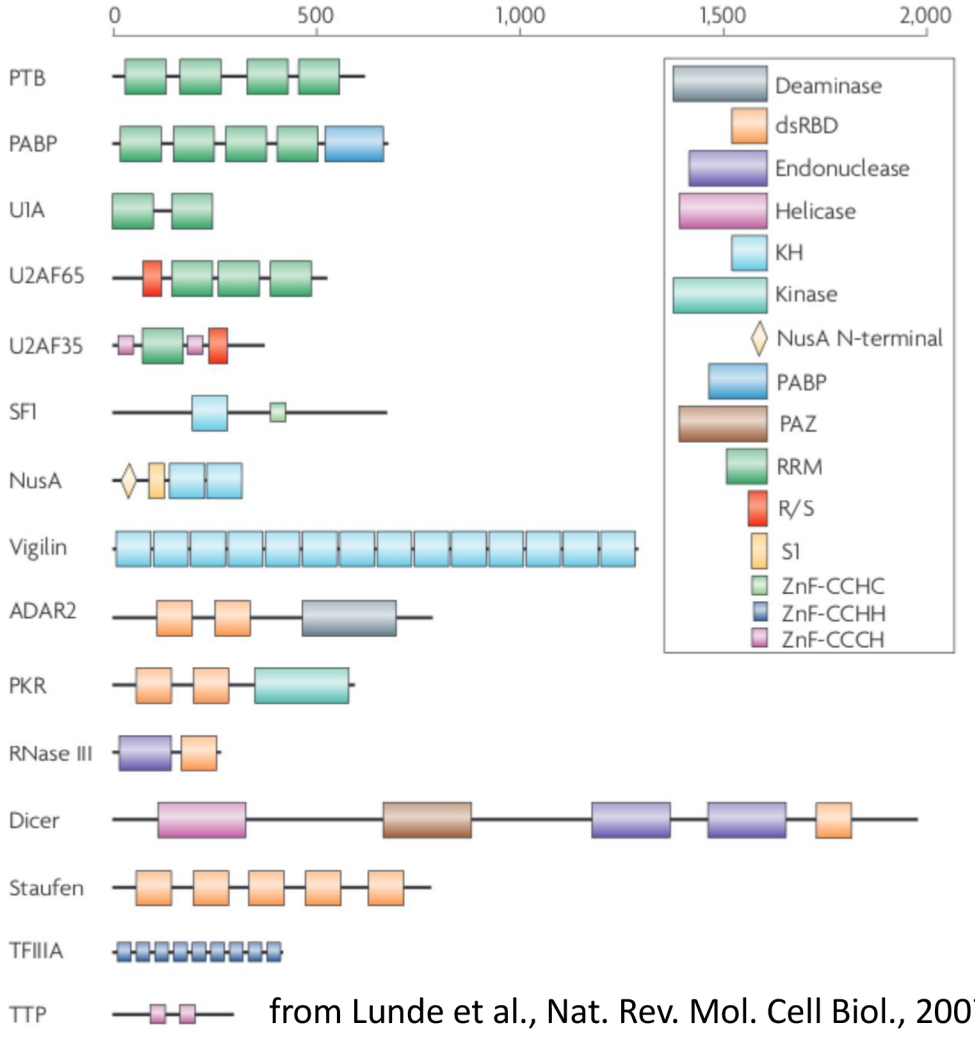
Serine/arginine-rich splicing factor 1, RS domain sequence

Modularity of RNA-binding proteins

domains, IDRs

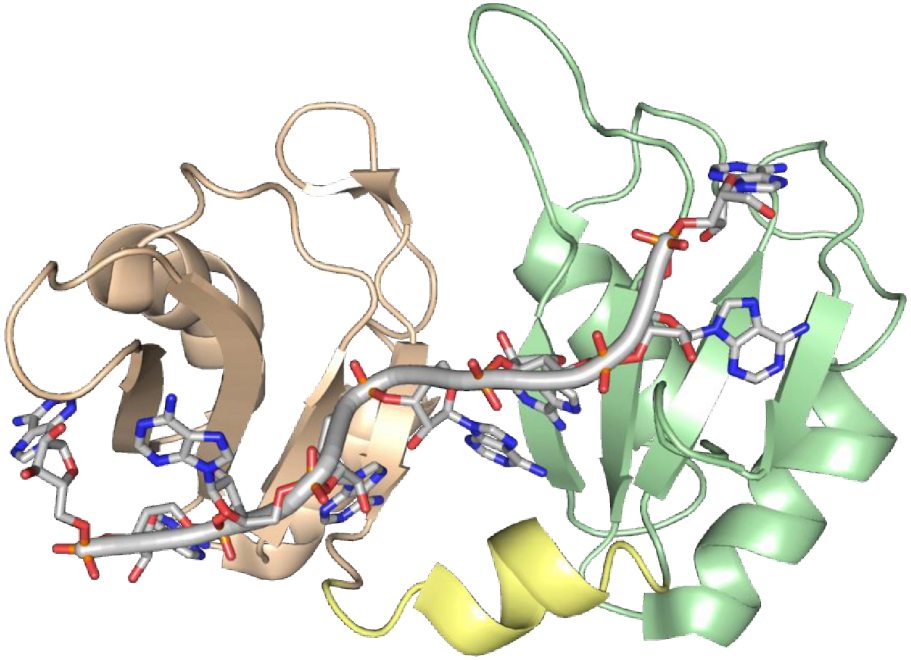


→ affinity, specificity

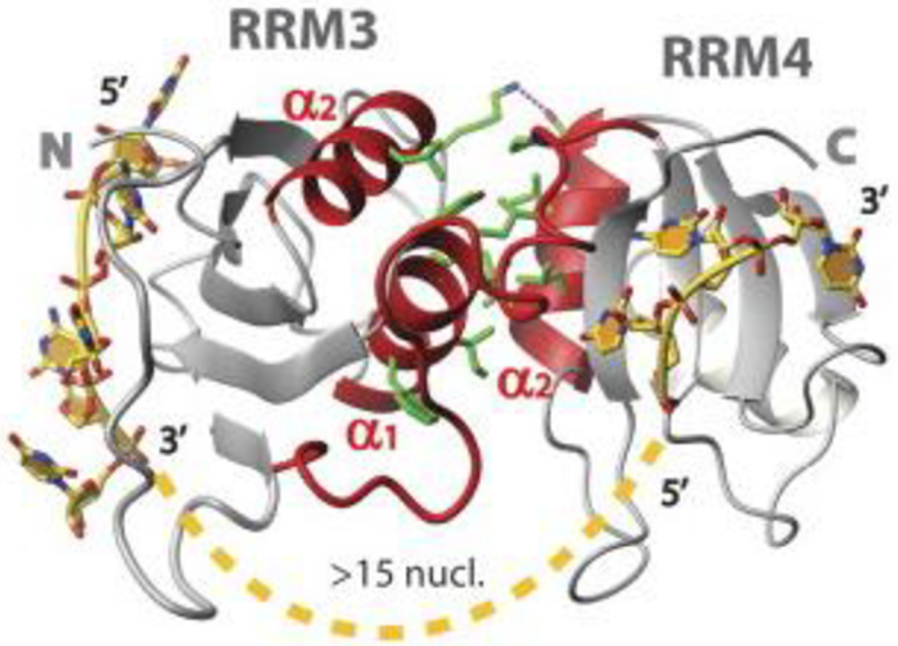


from Lunde et al., Nat. Rev. Mol. Cell Biol., 2007

Linkers

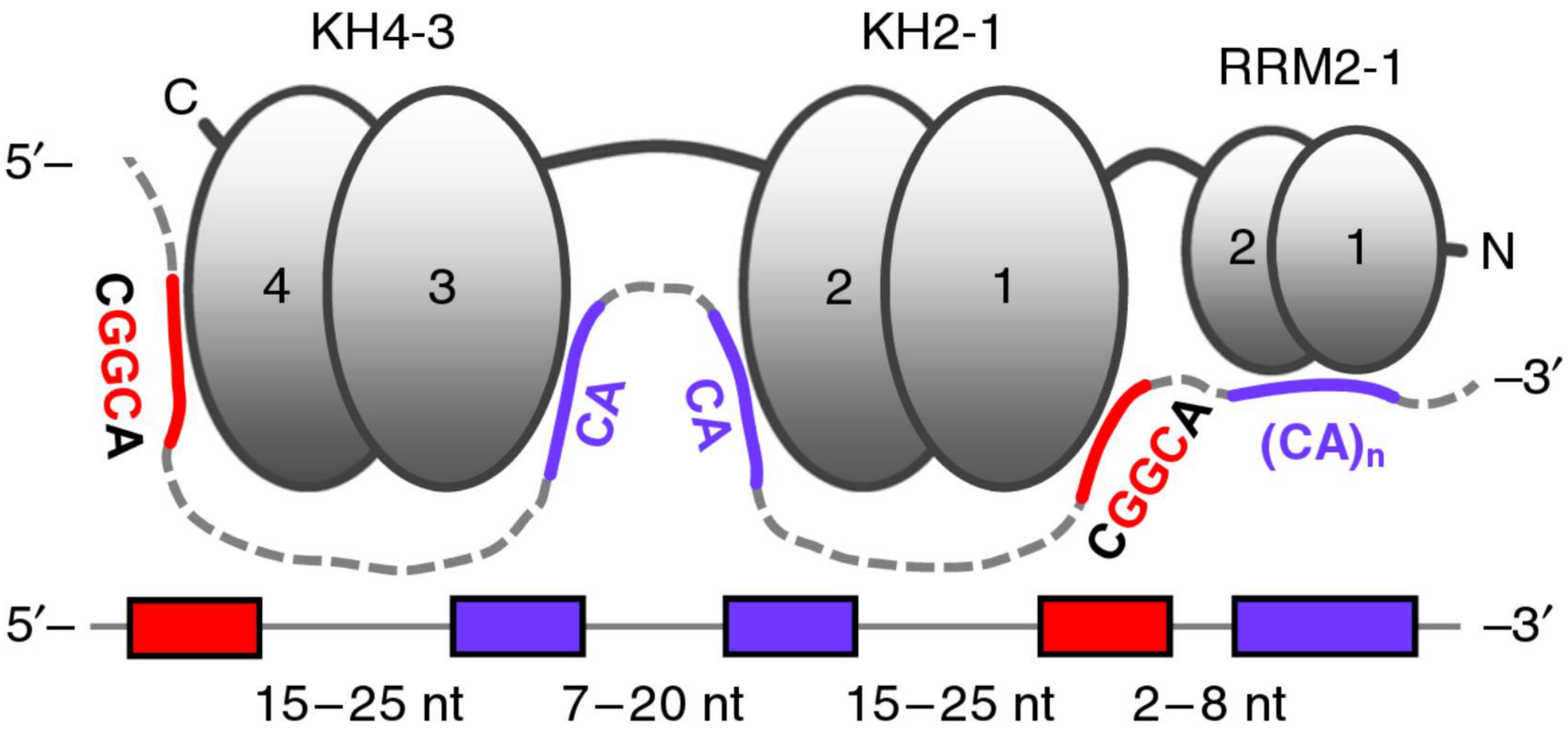


poly(A)-binding protein, PDB: 1cvj



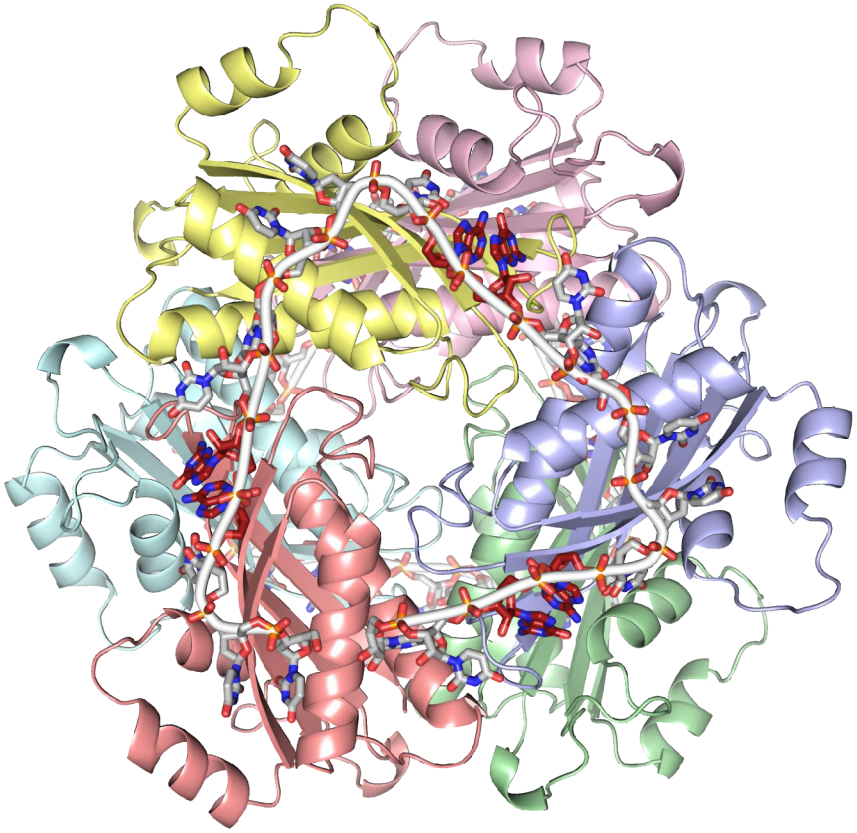
polypyrimidine tract binding protein, figure from Clery et al., Curr. Opin. Struct. Biol., 2008

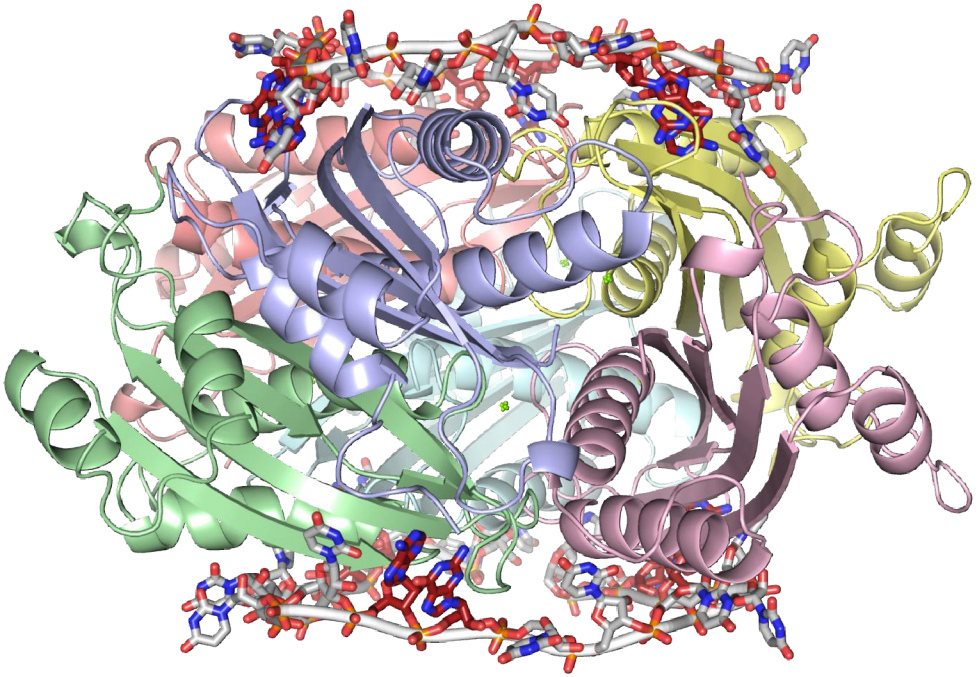
Modularity



insulin-like growth factor 2 mRNA-binding protein 3,figure from Schneider et al., Nat. Commun., 2019

Homomultimers – reading of repetitive motifs

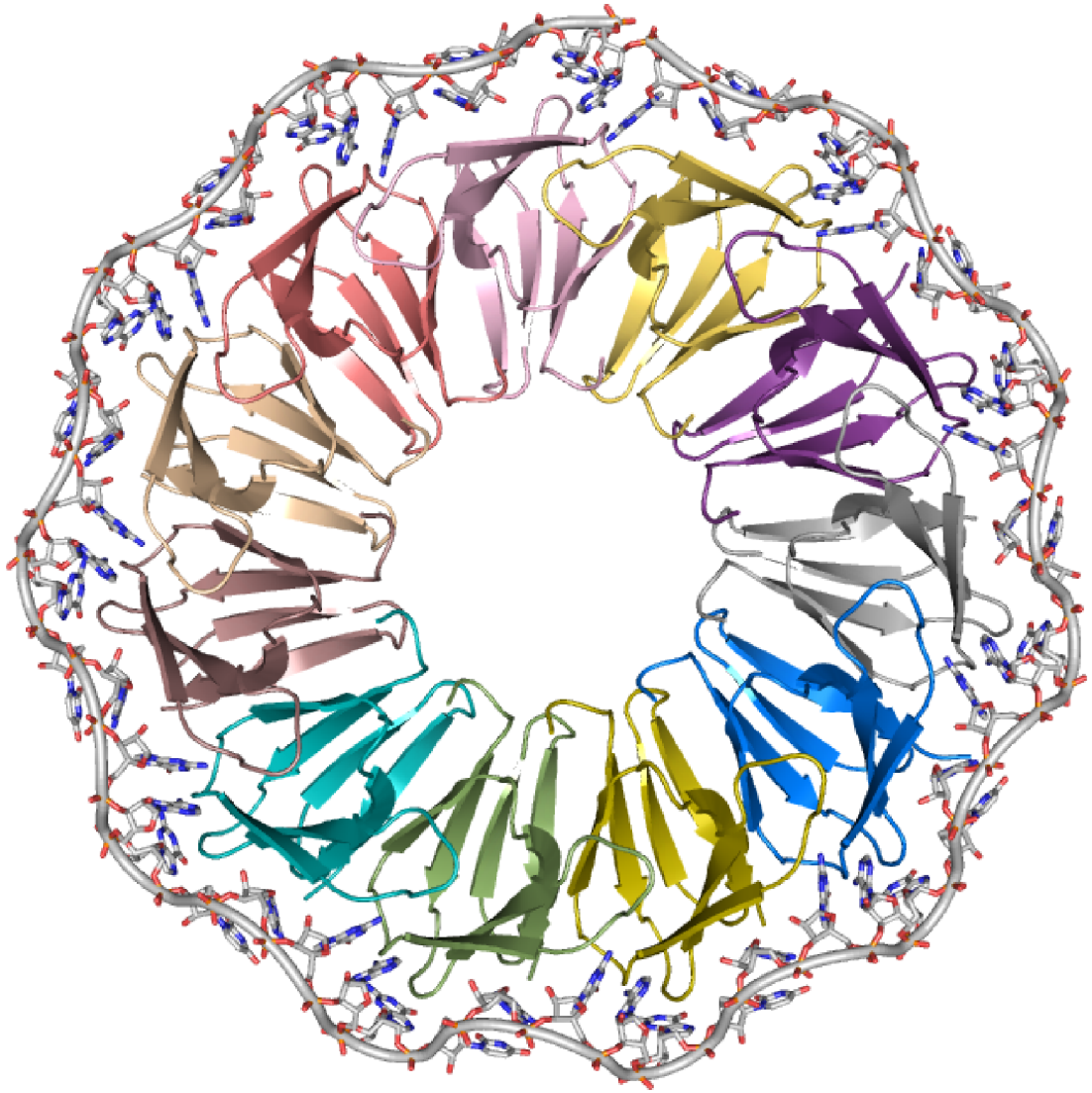




RNA:

NN**AG**NNNNN**AG**NNNNN**AG**NN

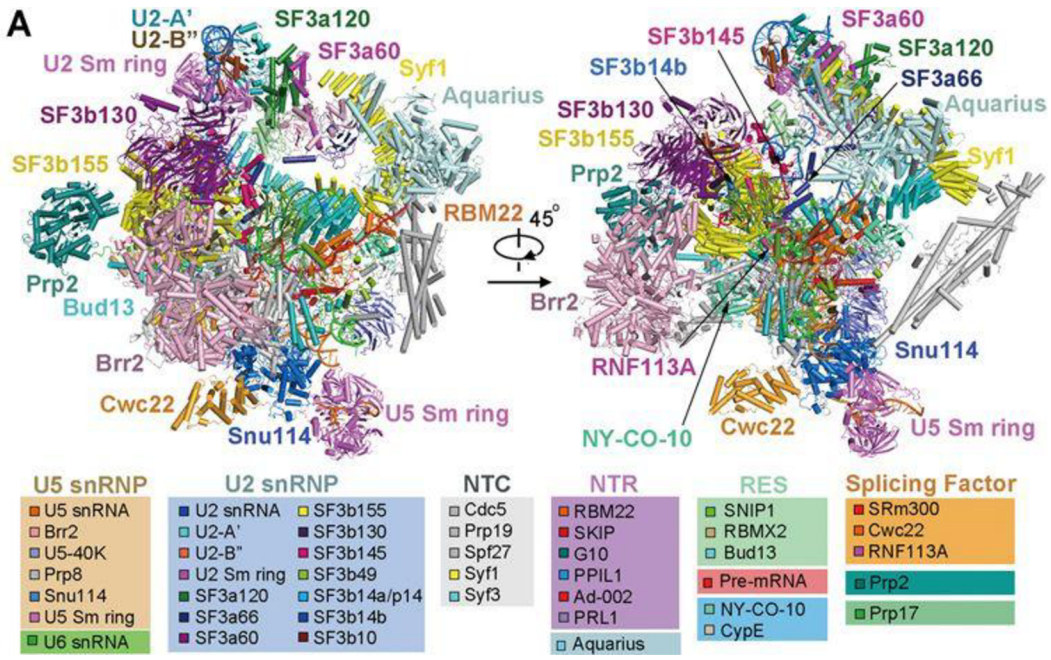
histidine utilization positive regulatory protein, PDB: 3boy



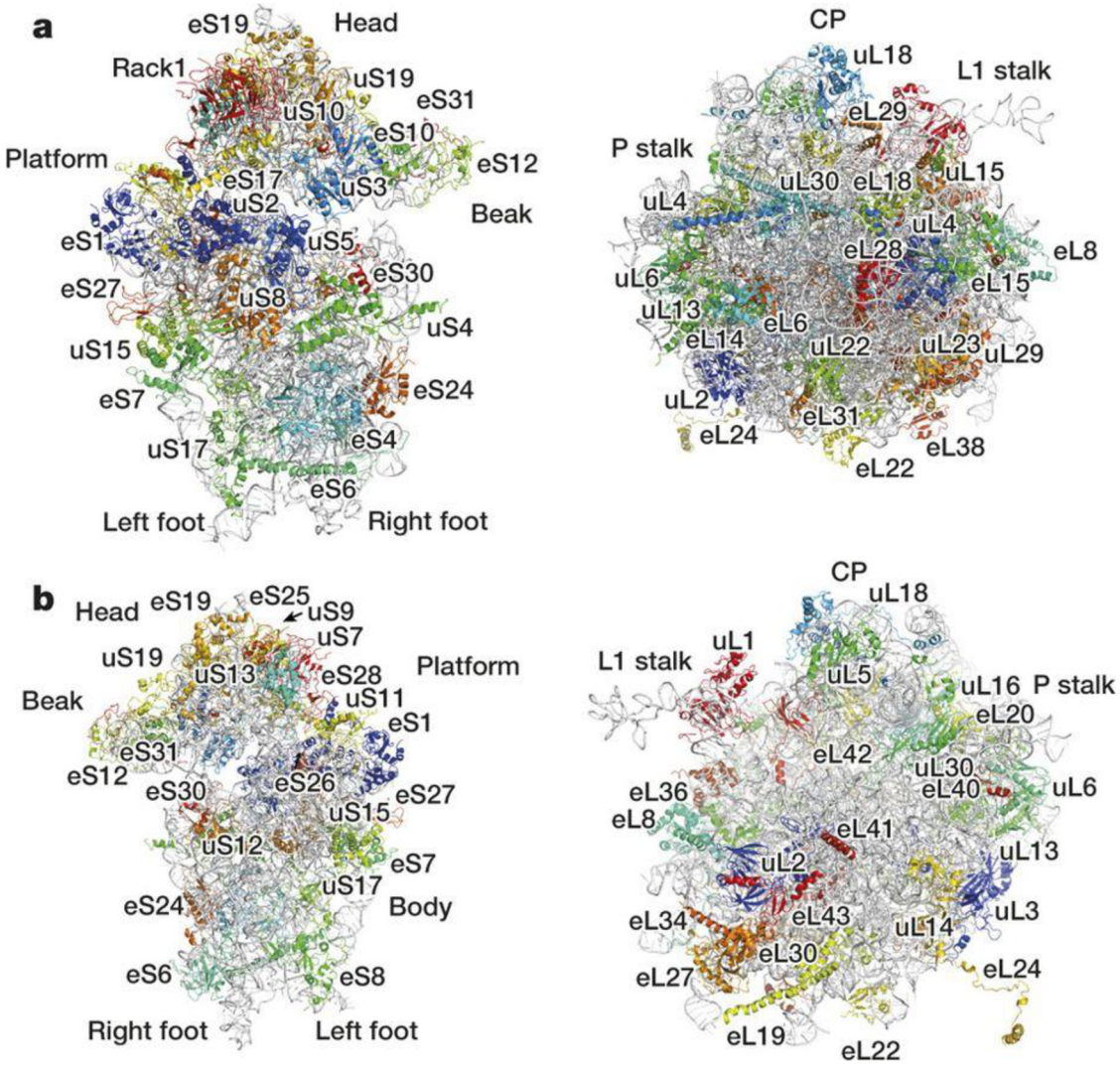
tryptophan RNA-binding attenuation protein, PDB: 1c9s

Large RNPs

RNP = ribonucleoprotein



human 80S ribosome, figure from Khatter et al., Nature, 2015



activated spliceosome (B^{act} state), figure from Zhang et al., Nature, 2018

Dynamics of RNA-protein binding