Isostericity and Tautomerism in Nucleic Acid Base Pairs

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2014

Die Welt zerfällt in Tatsachen.

L. WITTGENSTEIN

Le monde se disloque en faits.

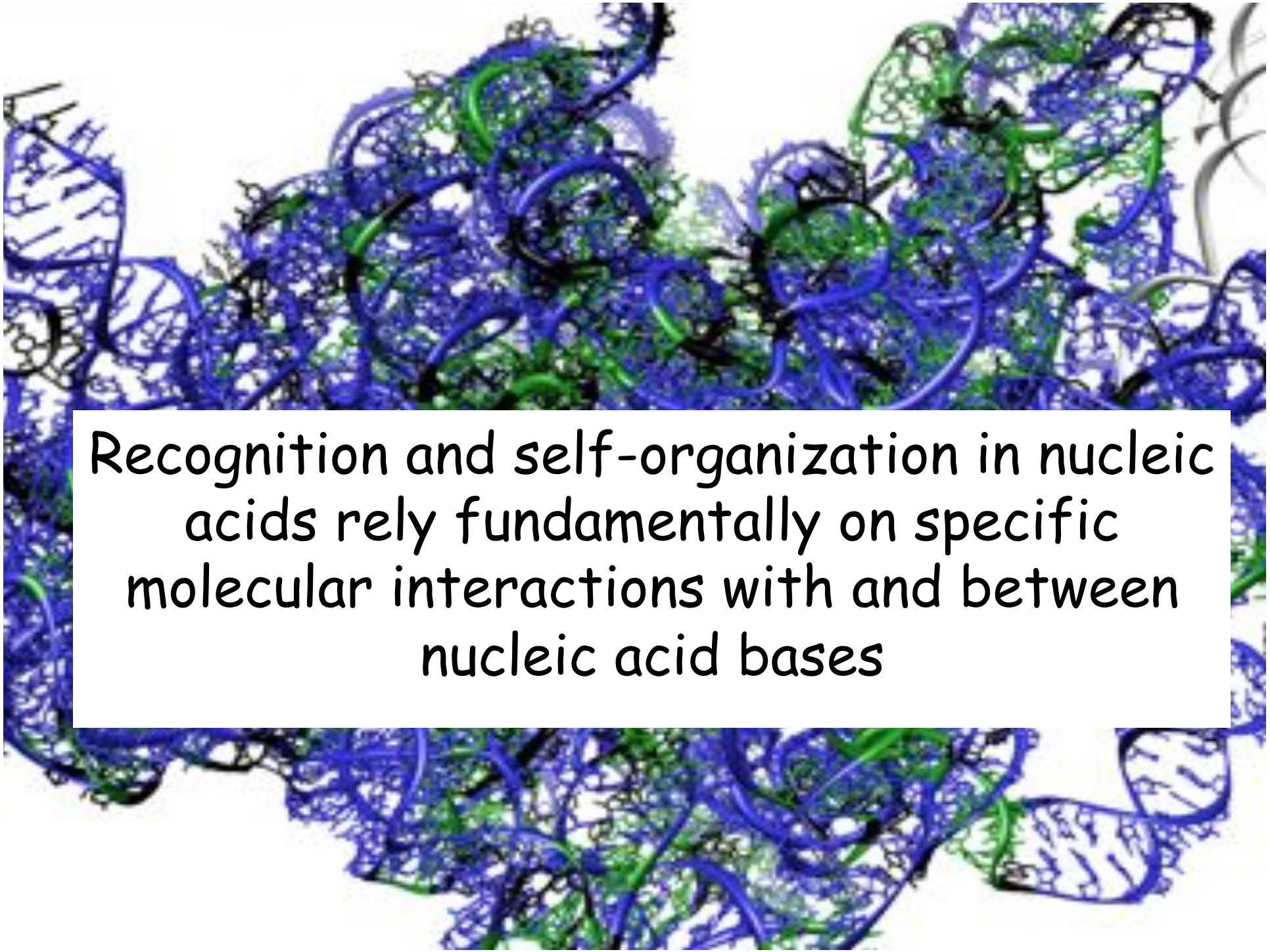
The world breaks up in facts.

RNA was selected because of its inherent potential for molecular evolution

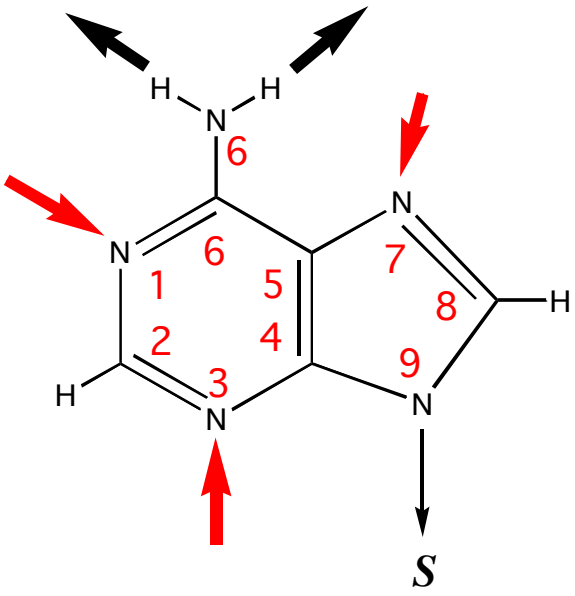
The amazing amount of
‘molecular neutrality’
compatible

with RNA evolution
and
RNA architecture,
networks and functions.

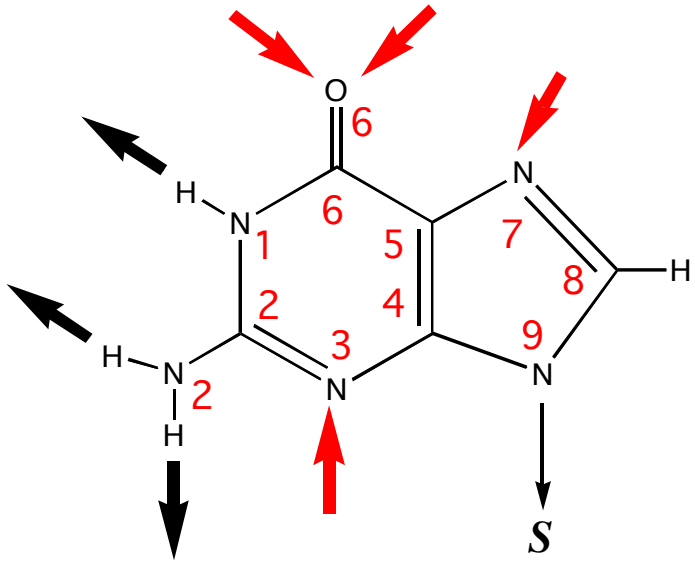
Molecular neutrality is anchored in the non-covalent molecular interactions occurring in RNA molecules in salted water



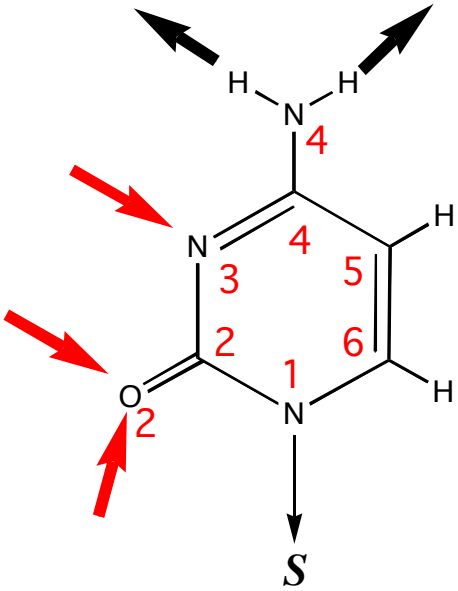
Recognition and self-organization in nucleic acids rely fundamentally on specific molecular interactions with and between nucleic acid bases


H
N
H
6
N
1
6
5
N
7
8
H
2
4
9
H
3
N
N
S

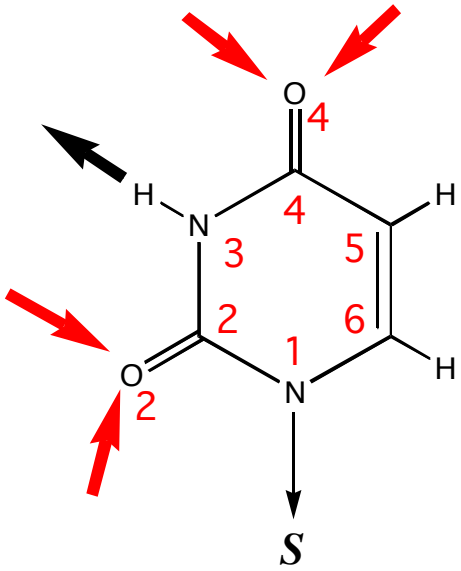
(A)


O
6
H
N
1
6
5
N
7
8
H
2
4
9
H
N
2
3
N
N
H
S

(G)

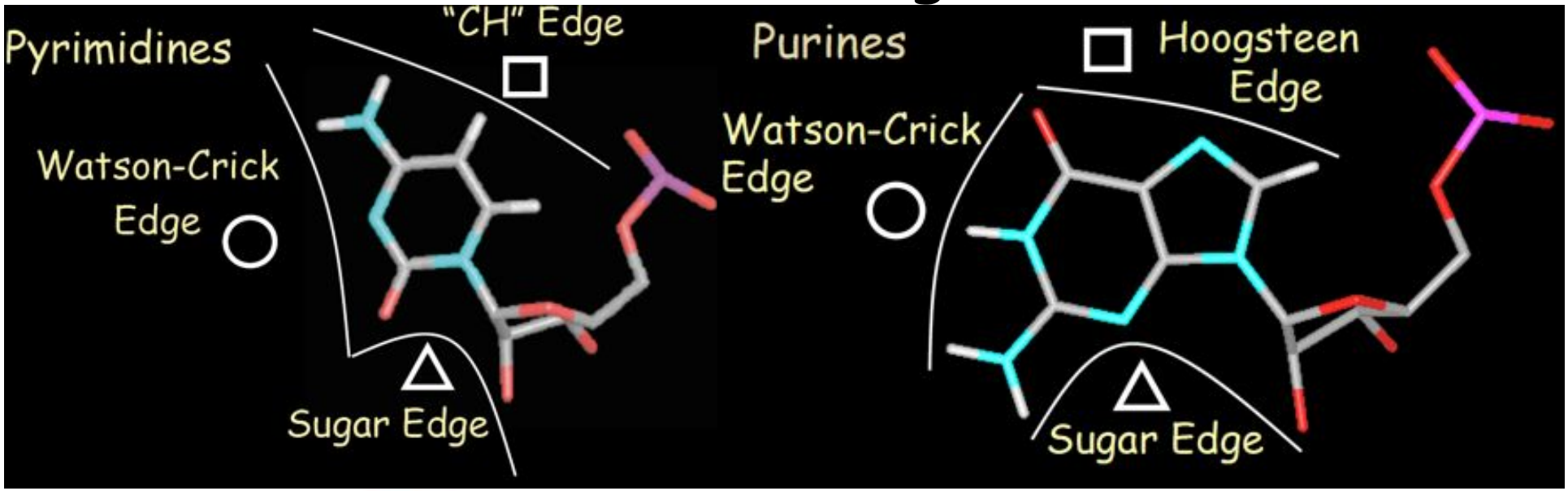

H
N
H
4
N
3
4
5
H
2
6
O
2
1
N
H
S

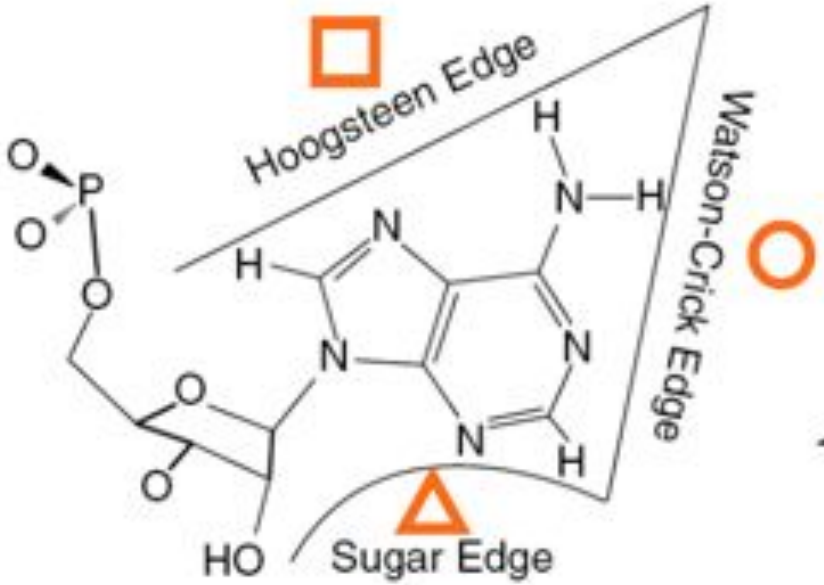
(C)

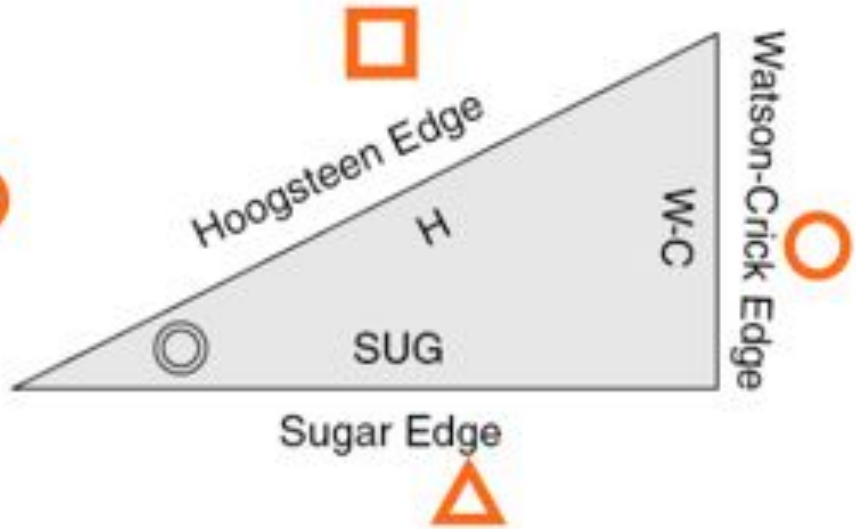

O
4
H
N
3
4
5
H
2
6
O
2
1
N
H
S

(U)

Each base has three edges available for H-bonding



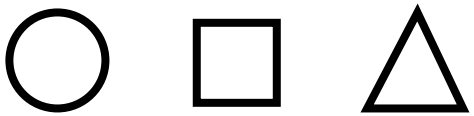


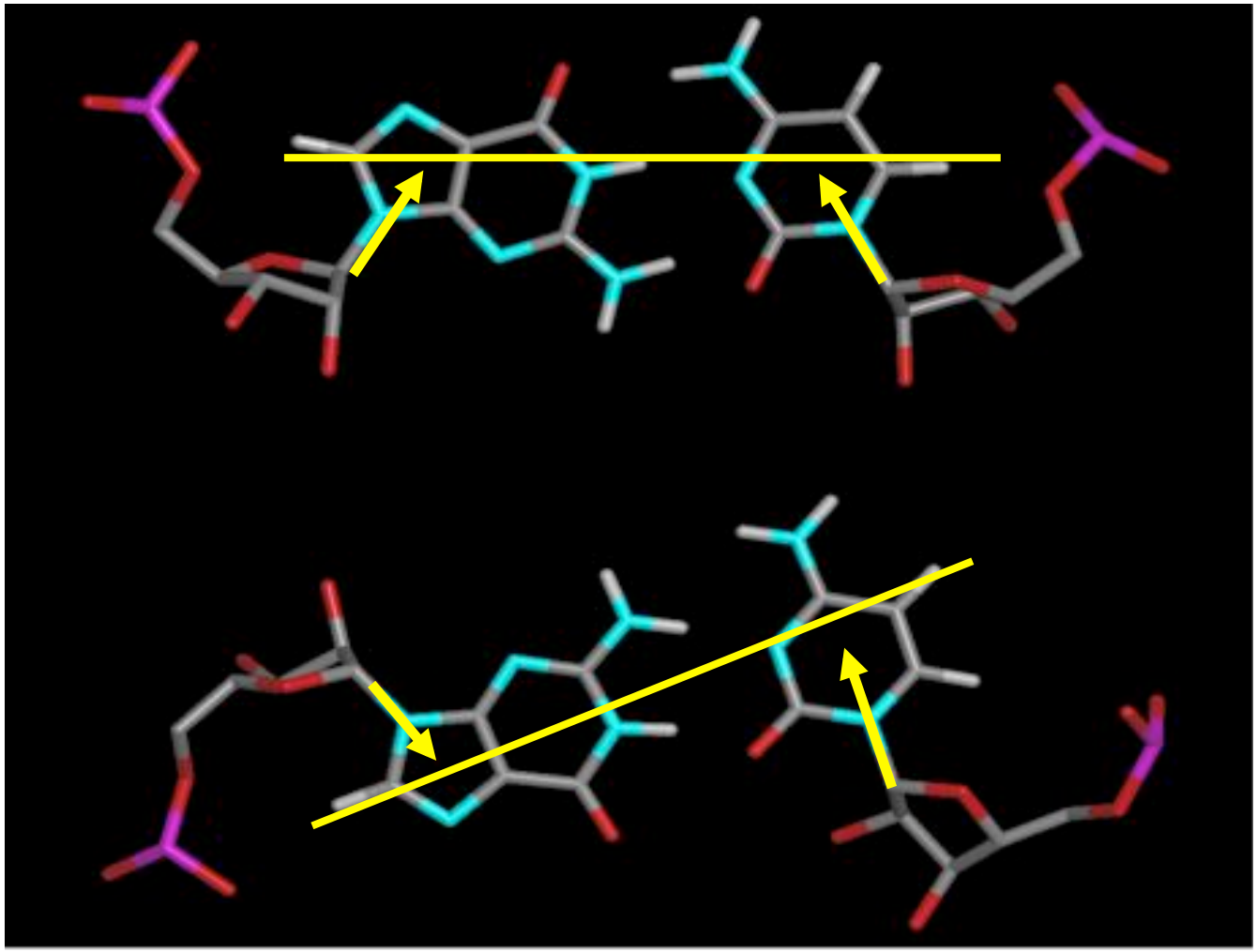


Two lines of approach

- *Cis* (*default*)

- *Trans*



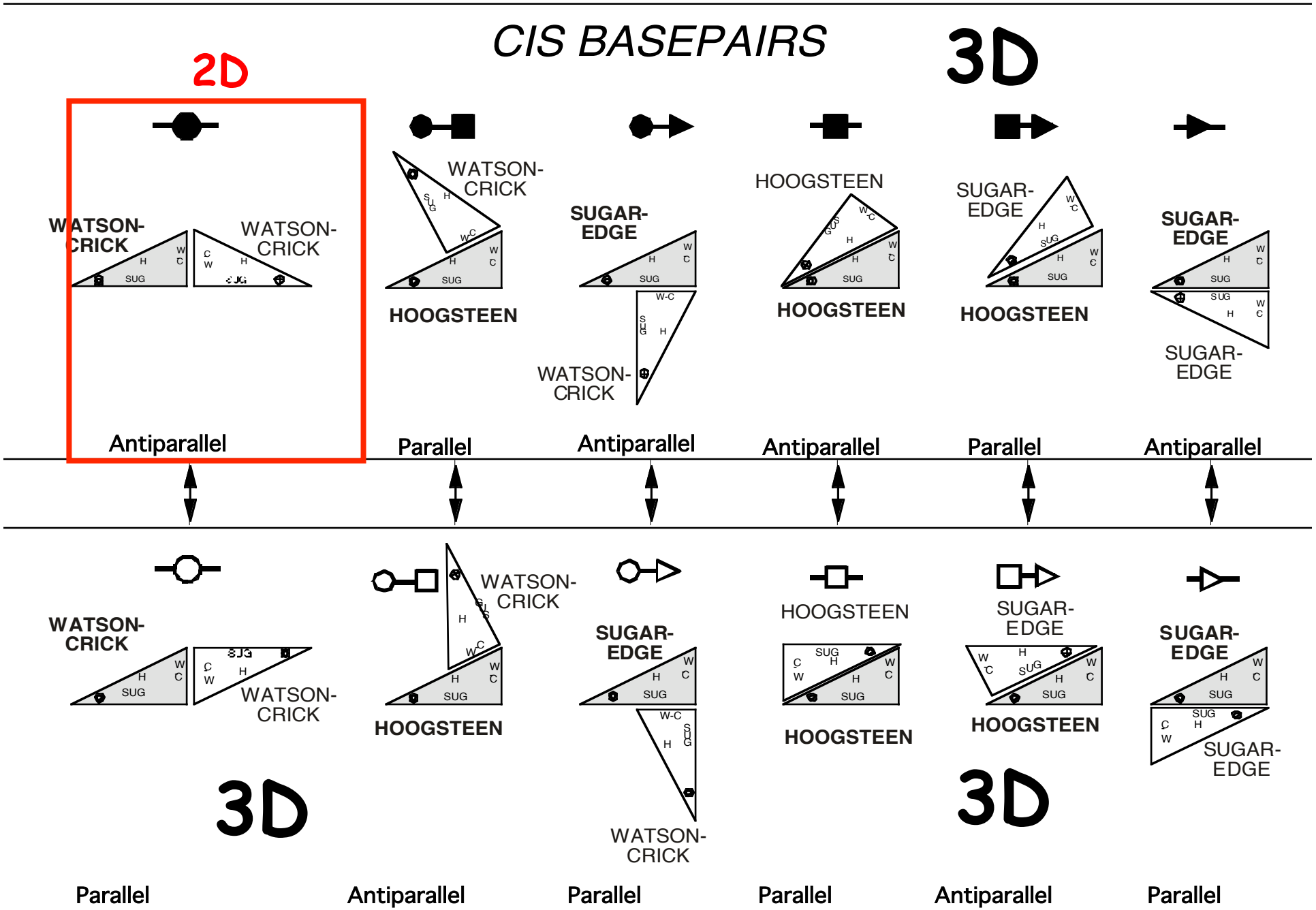


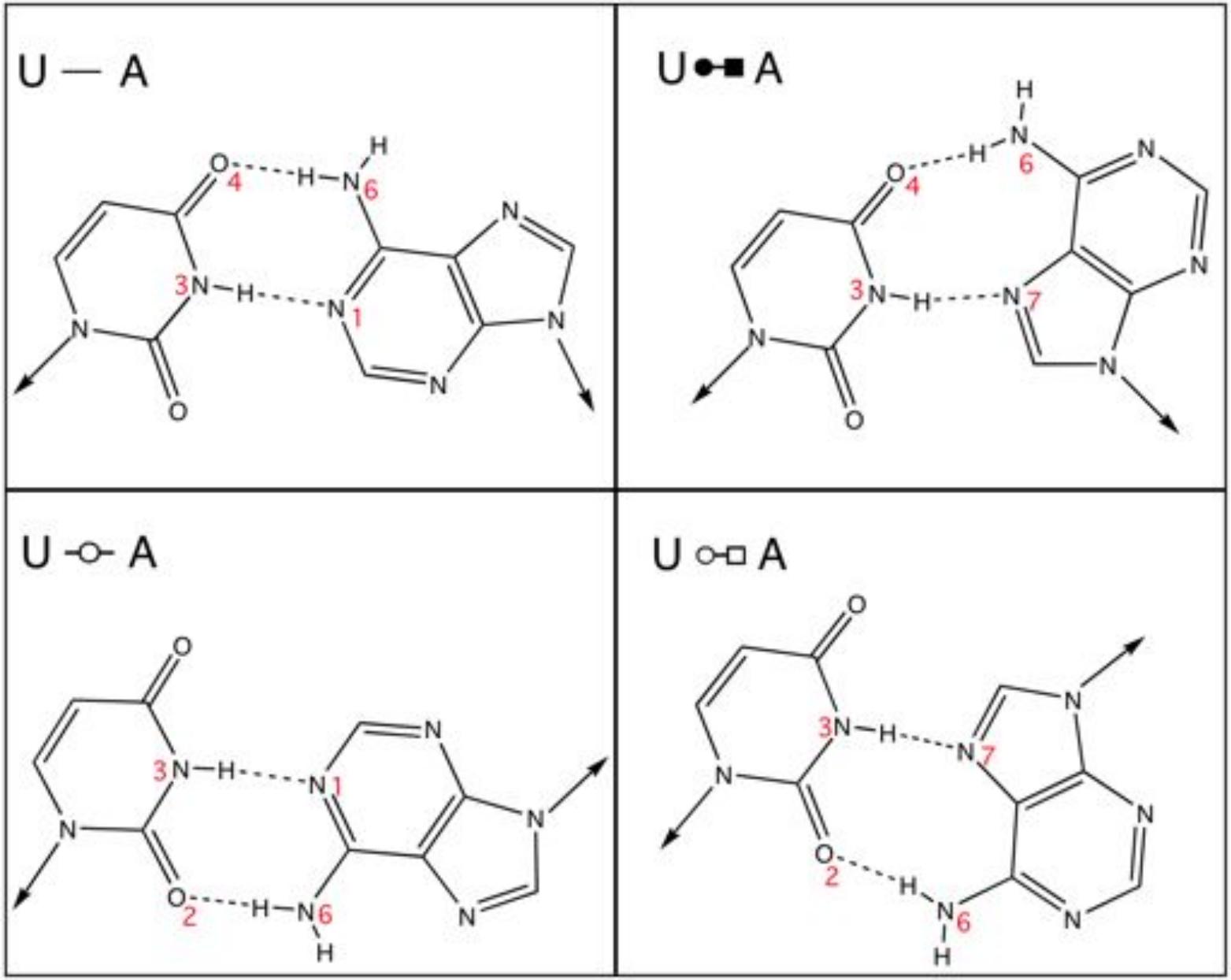
Edge-to-Edge Pairing Families

$$\left.\begin{array}{c}\text{Watson-Crick}\\ \text{Hoogsteen}\\ \text{Sugar-edge}\end{array}\right\}\left\{\begin{array}{c}\text{Watson-Crick}\\ \text{Hoogsteen}\\ \text{Sugar-edge}\end{array}\right\}\left\{\begin{array}{l}\text{Cis}\\ \text{Trans}\end{array}\right.$$

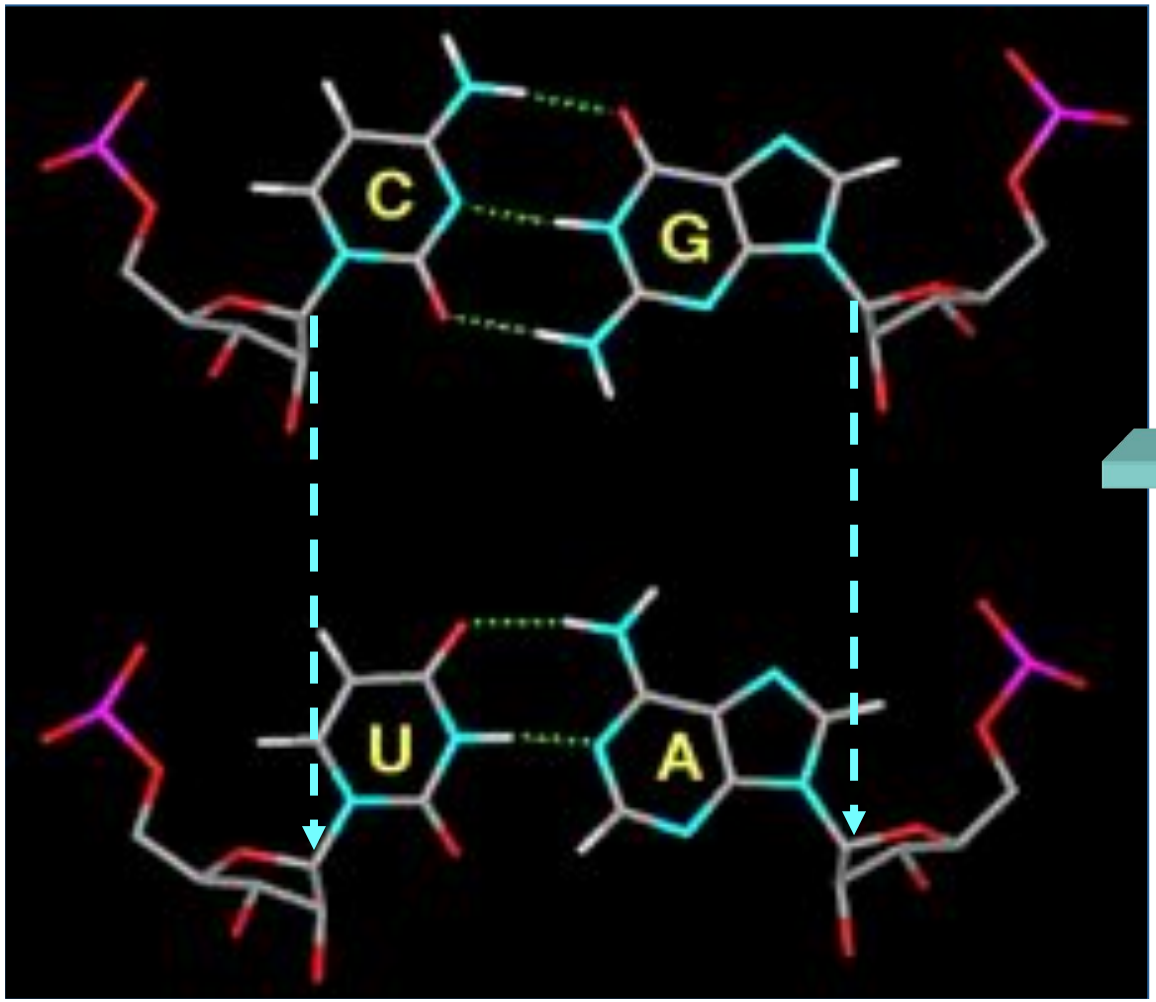
$$= \text{12 Basic Families}$$

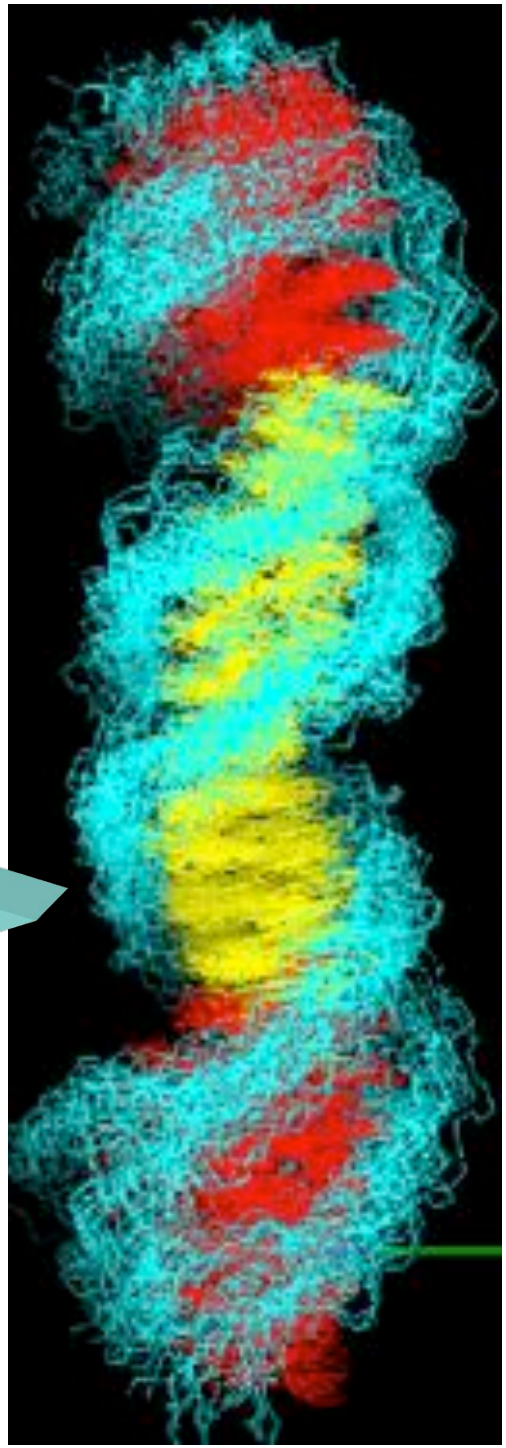
RNA **7**, 499 (2001)

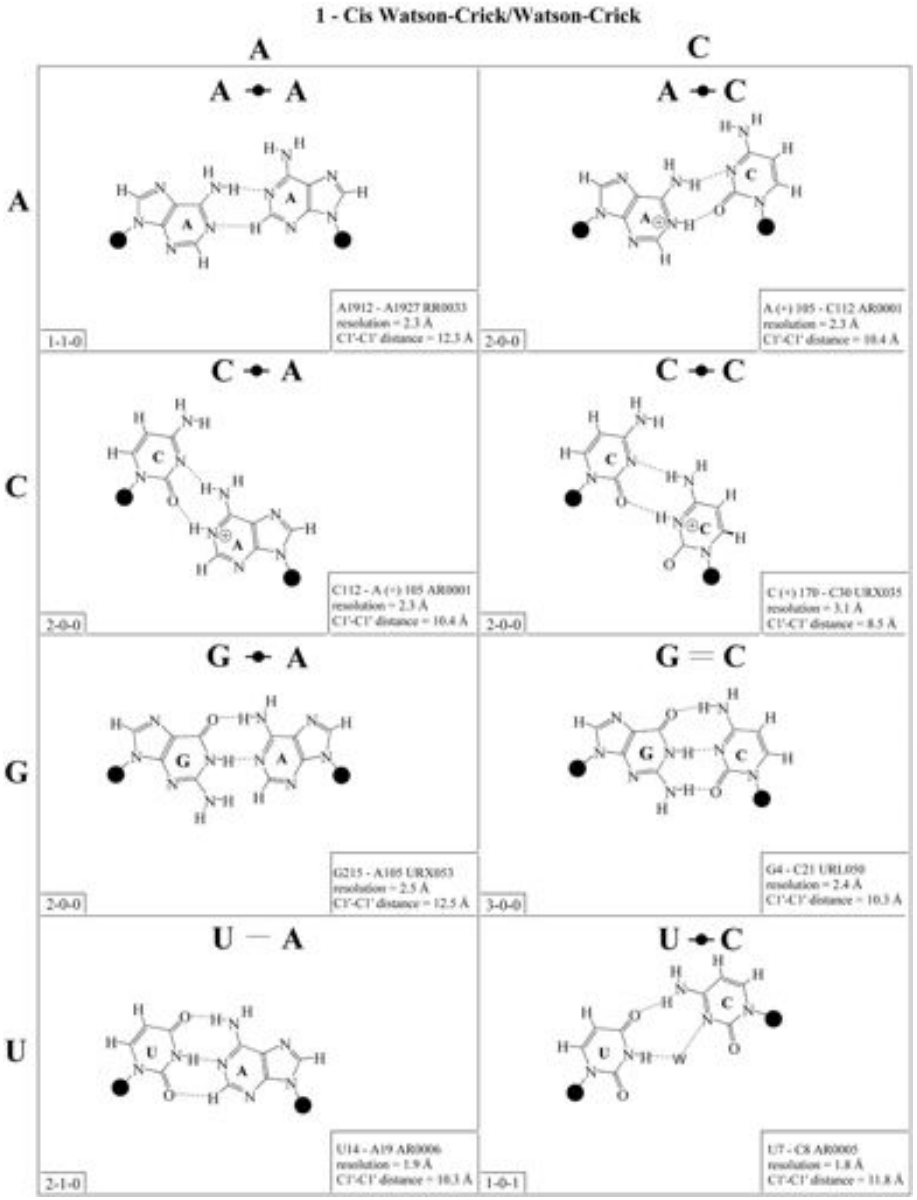

CIS BASEPAIRS
2D
3D
WATSON-CRICK
WATSON-CRICK
Antiparallel
WATSON-CRICK
HOOGSTEEN
Parallel
SUGAR-EDGE
WATSON-CRICK
Antiparallel
HOOGSTEEN
HOOGSTEEN
Antiparallel
SUGAR-EDGE
HOOGSTEEN
Parallel
SUGAR-EDGE
SUGAR-EDGE
Antiparallel
WATSON-CRICK
WATSON-CRICK
3D
Parallel
WATSON-CRICK
HOOGSTEEN
Antiparallel
SUGAR-EDGE
WATSON-CRICK
Parallel
HOOGSTEEN
HOOGSTEEN
Parallel
SUGAR-EDGE
HOOGSTEEN
3D
Antiparallel
SUGAR-EDGE
SUGAR-EDGE
Parallel
TRANS BASEPAIRS

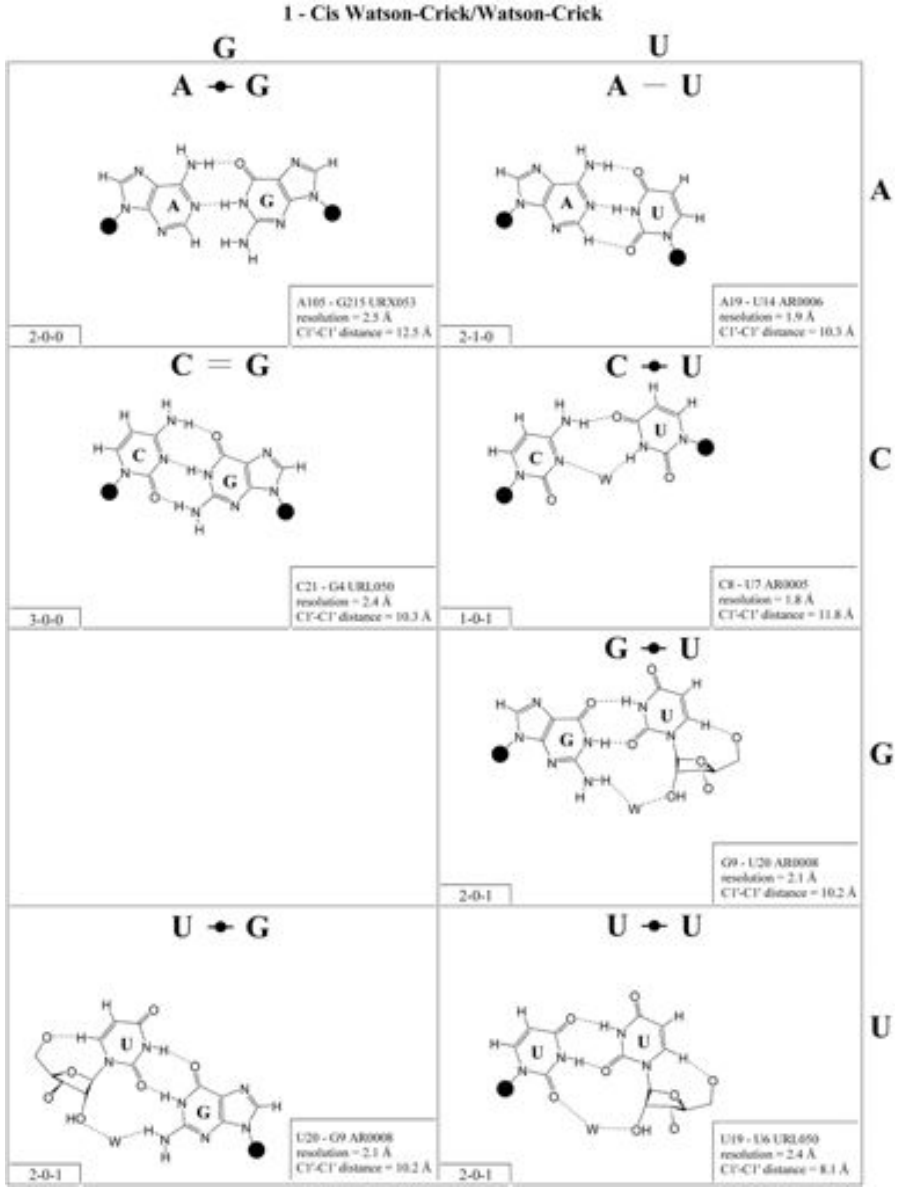

U — A
U ●-■ A
U -○- A
U ○-□ A

Watson-Crick pairs Are isosteric









Nucl. Acids Res. 2002 30:3497-3531

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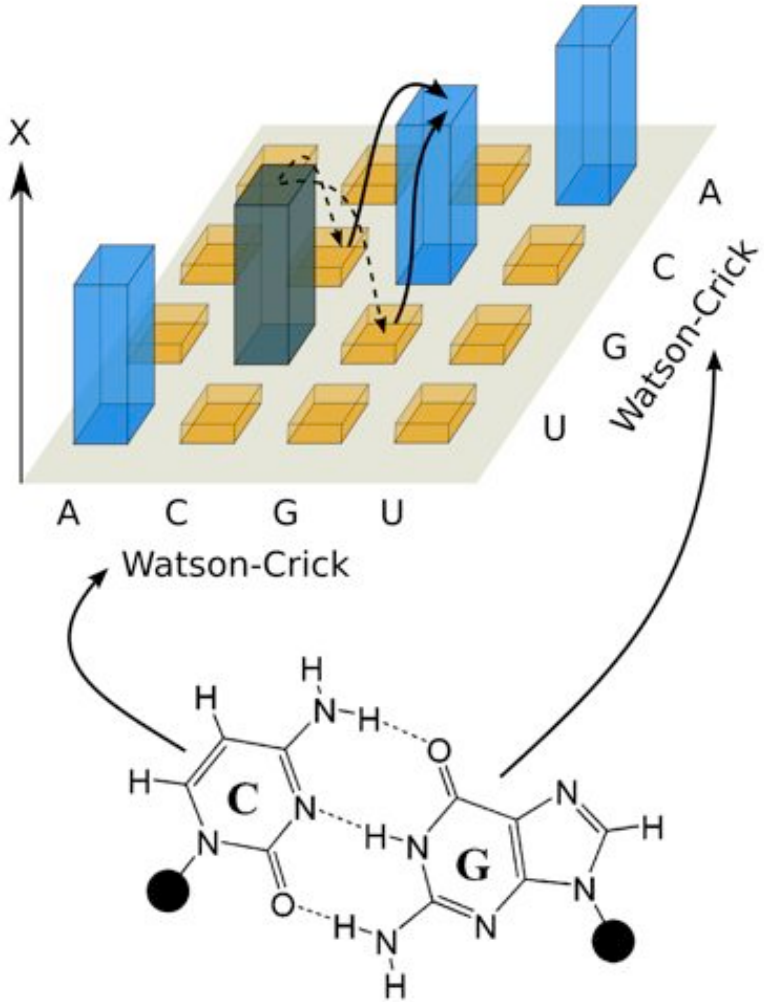
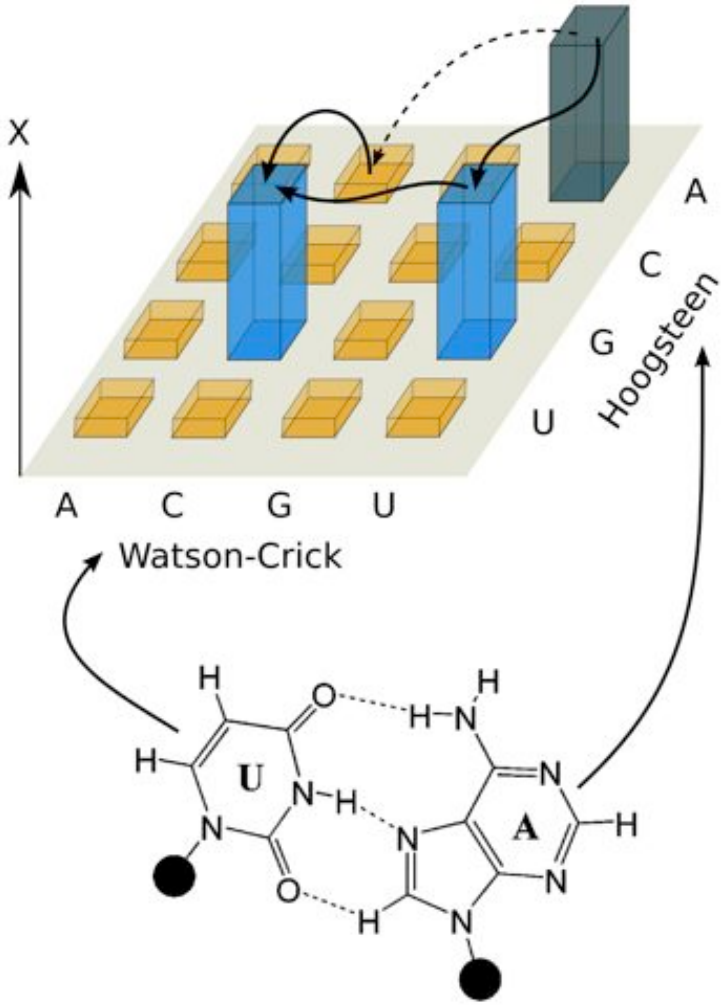
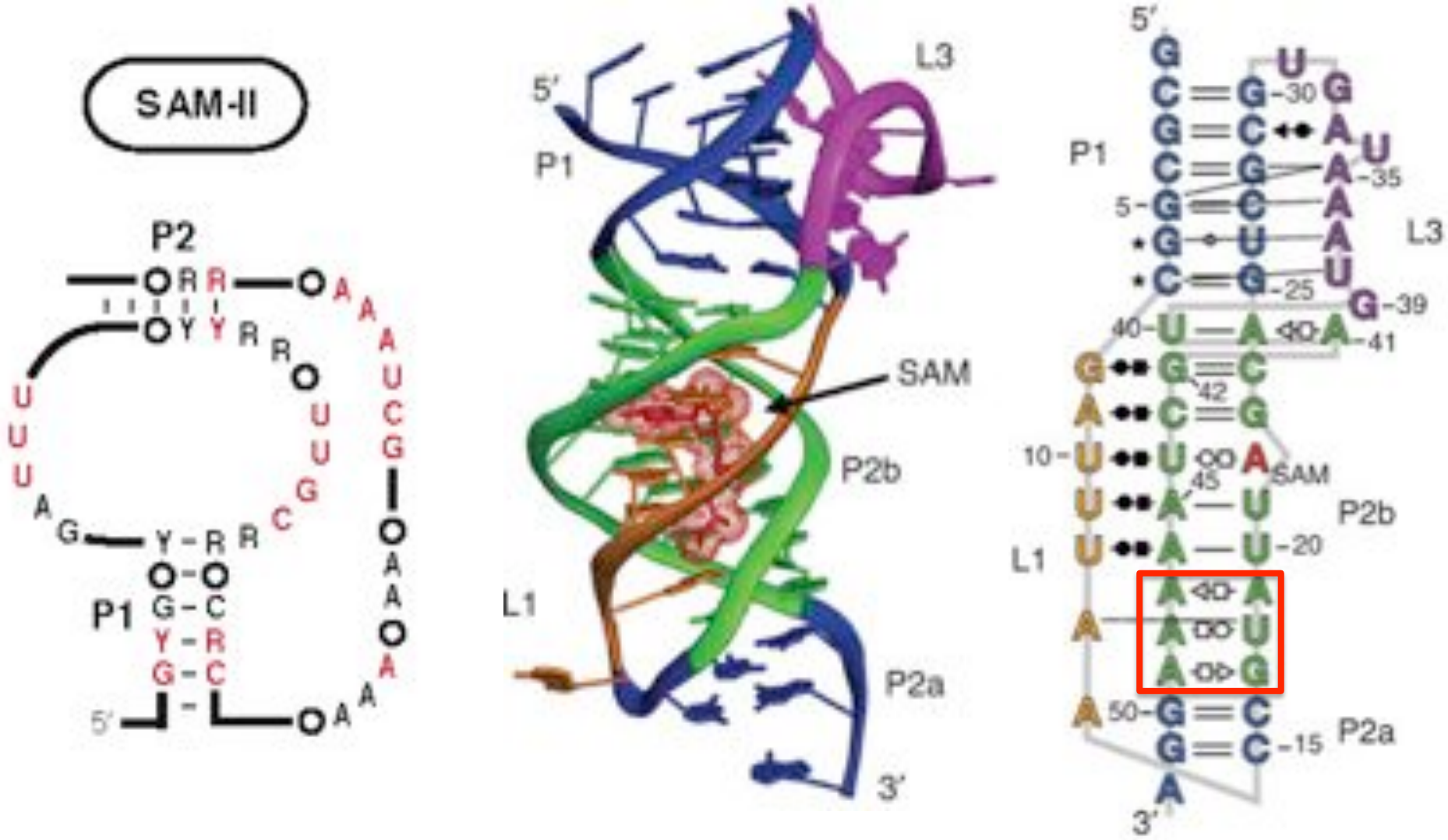
Nucleic Acids Research

In **coevolution**, a change from one state to the other implies a simultaneous substitution event at a different position.



Neutral networks connect different sequence states, distant by only one mutation, that possess the same fitness.

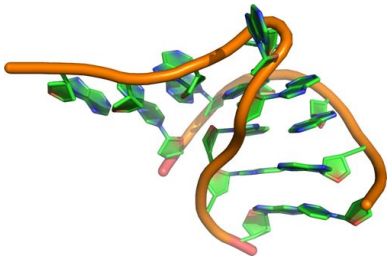




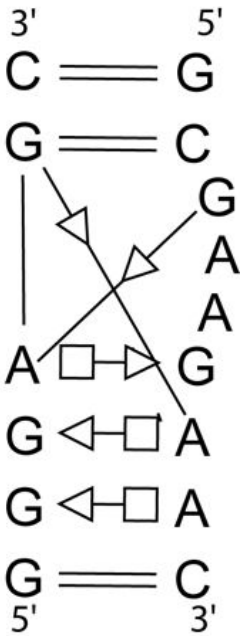
Structure of the SAM-II riboswitch bound to S-adenosylmethionine

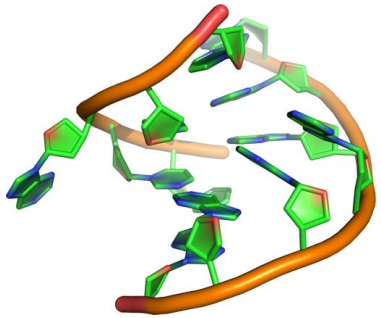
Gilbert, Rambo, Van Tyne, & Batey, Nature Struct & Mol Biol 15, 177 (2008)

A MODULE is an ensemble of ordered non-Watson-Crick basepairs.

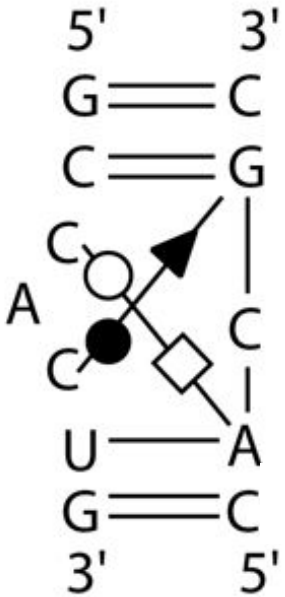


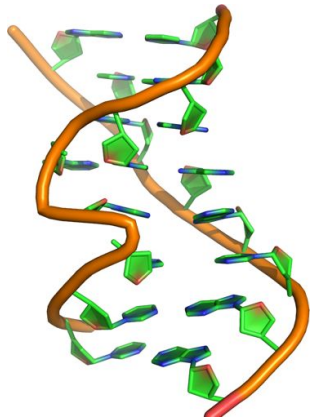
K-turn



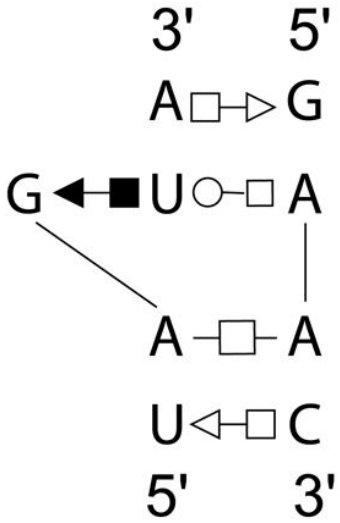


C-motif

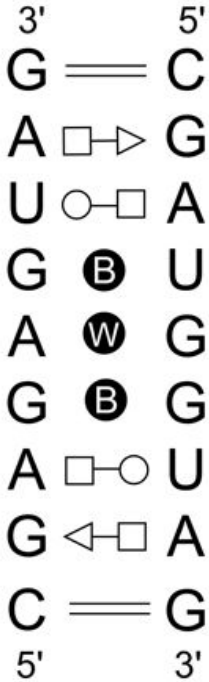


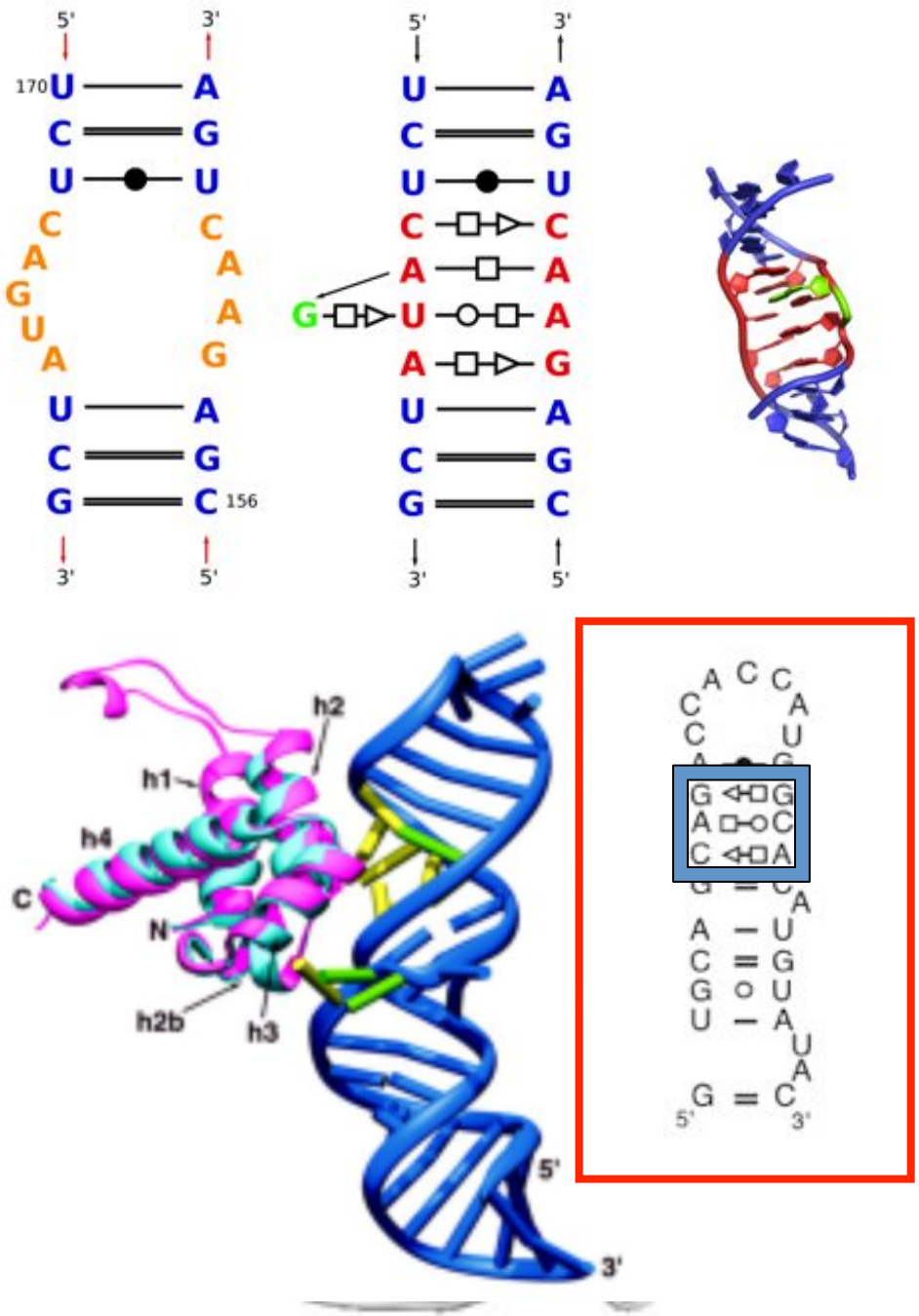


Sarcin motif



Loop-E motif





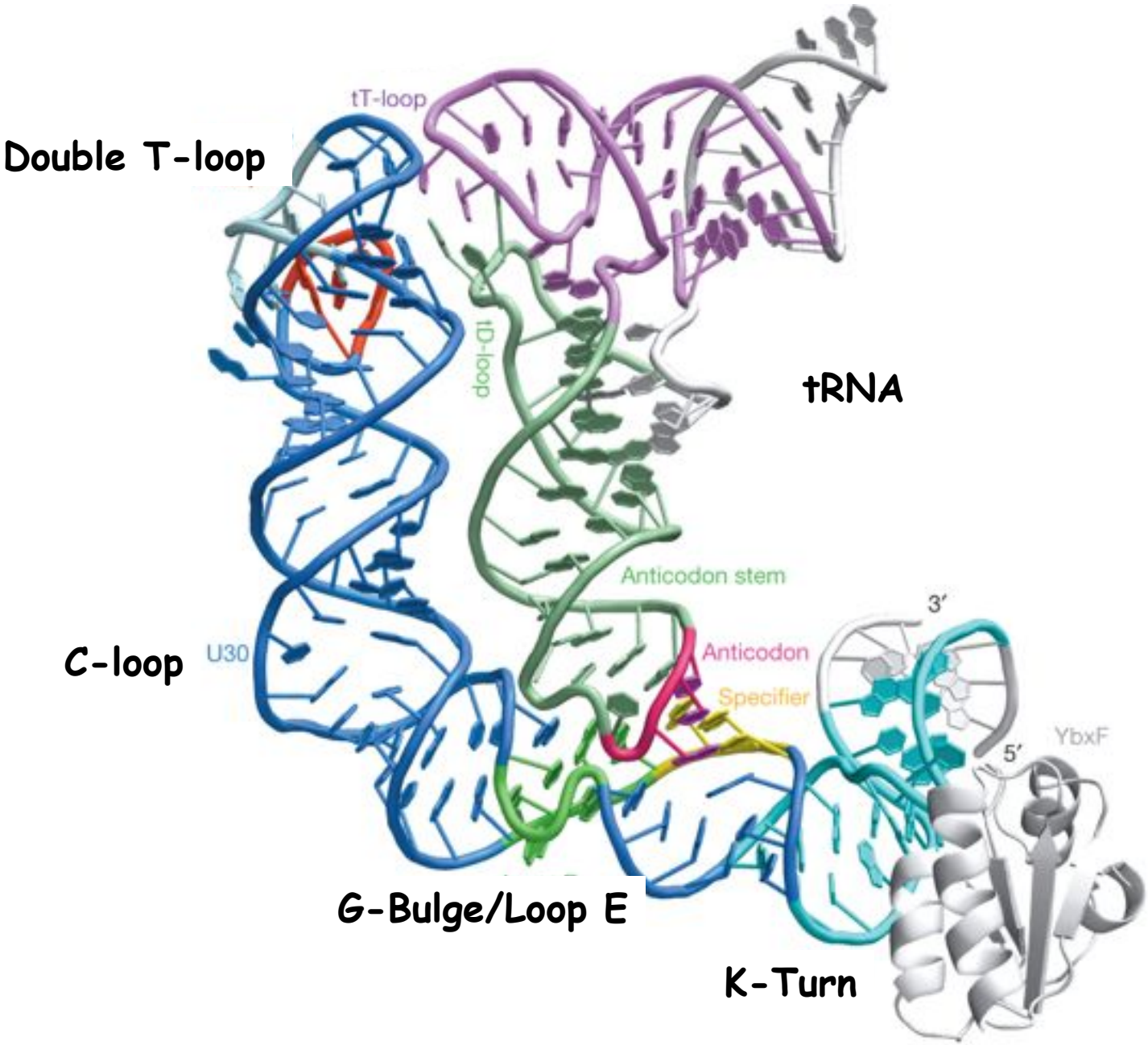
-Limited number of identical modules

- Occurrence in all types of RNAs across all kingdoms of life

- Modules organize internal loops, junctions, bind ligands and proteins

- Modules are key to RNA self-assembly

R T Batey et al. Science 2000;287:1232-1239

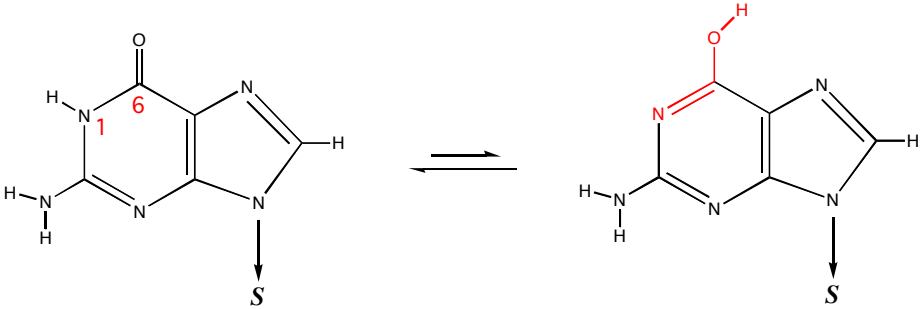


Overall structure of the T-box stem I in complex with tRNA.

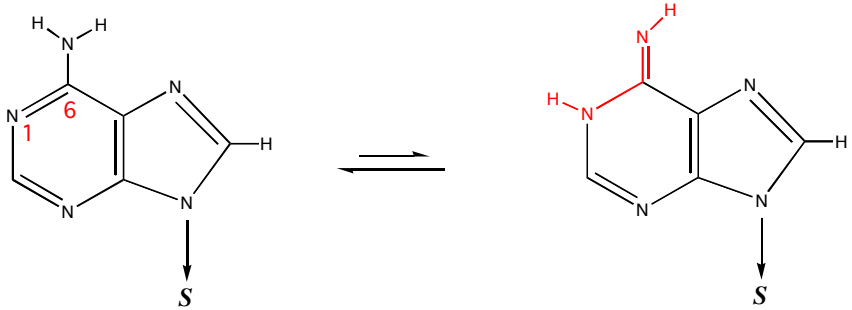
Zhang, J. & Ferré-D'Amaré, A.R. *Nature 500, 363-366 (2013)*

nature

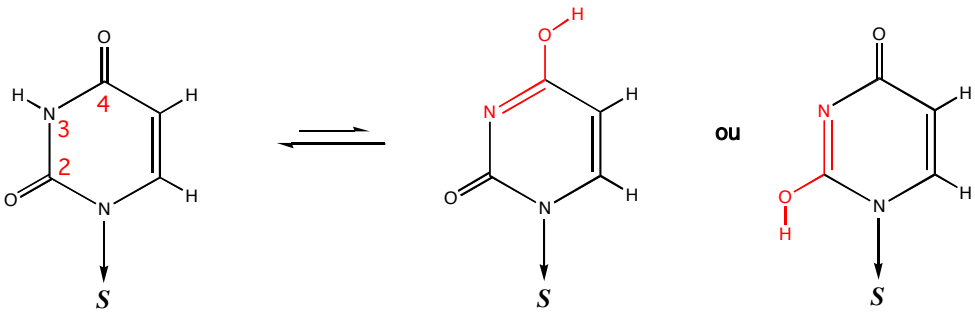
G



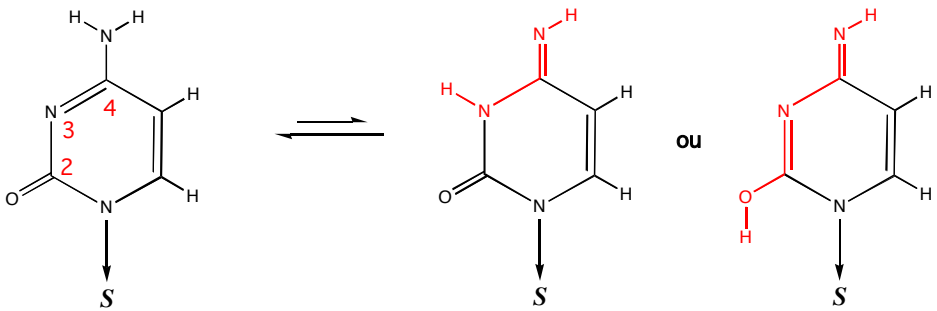
A



U



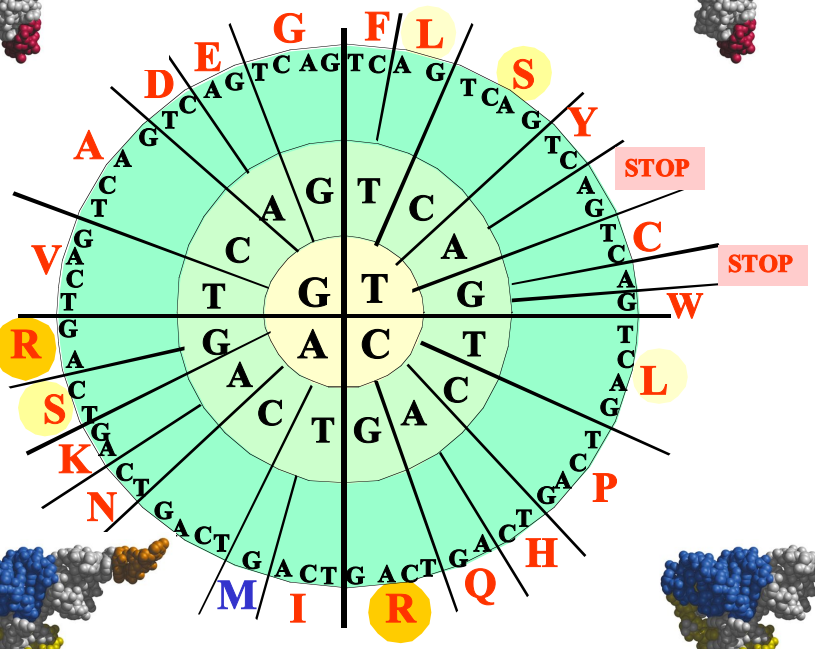
C



What About tautomeric forms in recognition?

Are they used?

Decoding of the genetic code


G
F
L
S
Y
STOP
C
STOP
W
L
P
H
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V
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D
E
G
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C
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G
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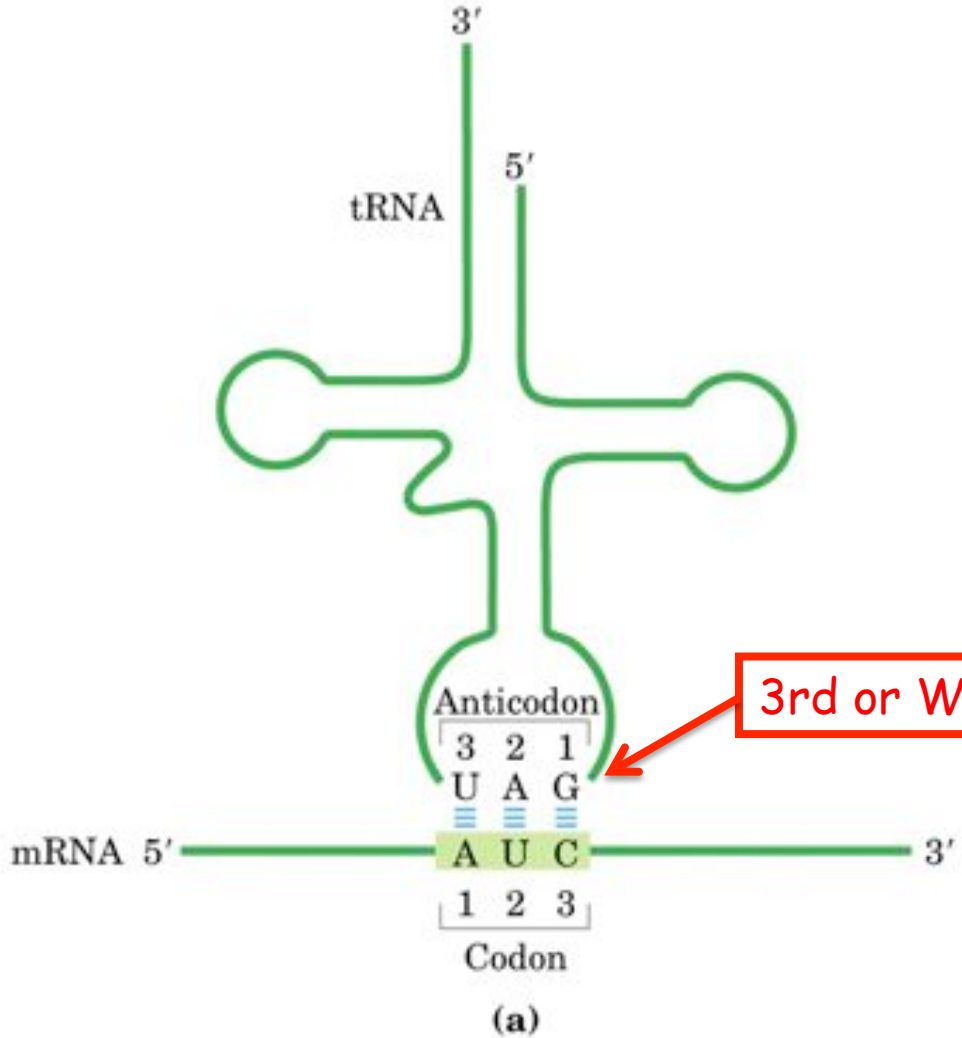
A

Decoding Fidelity

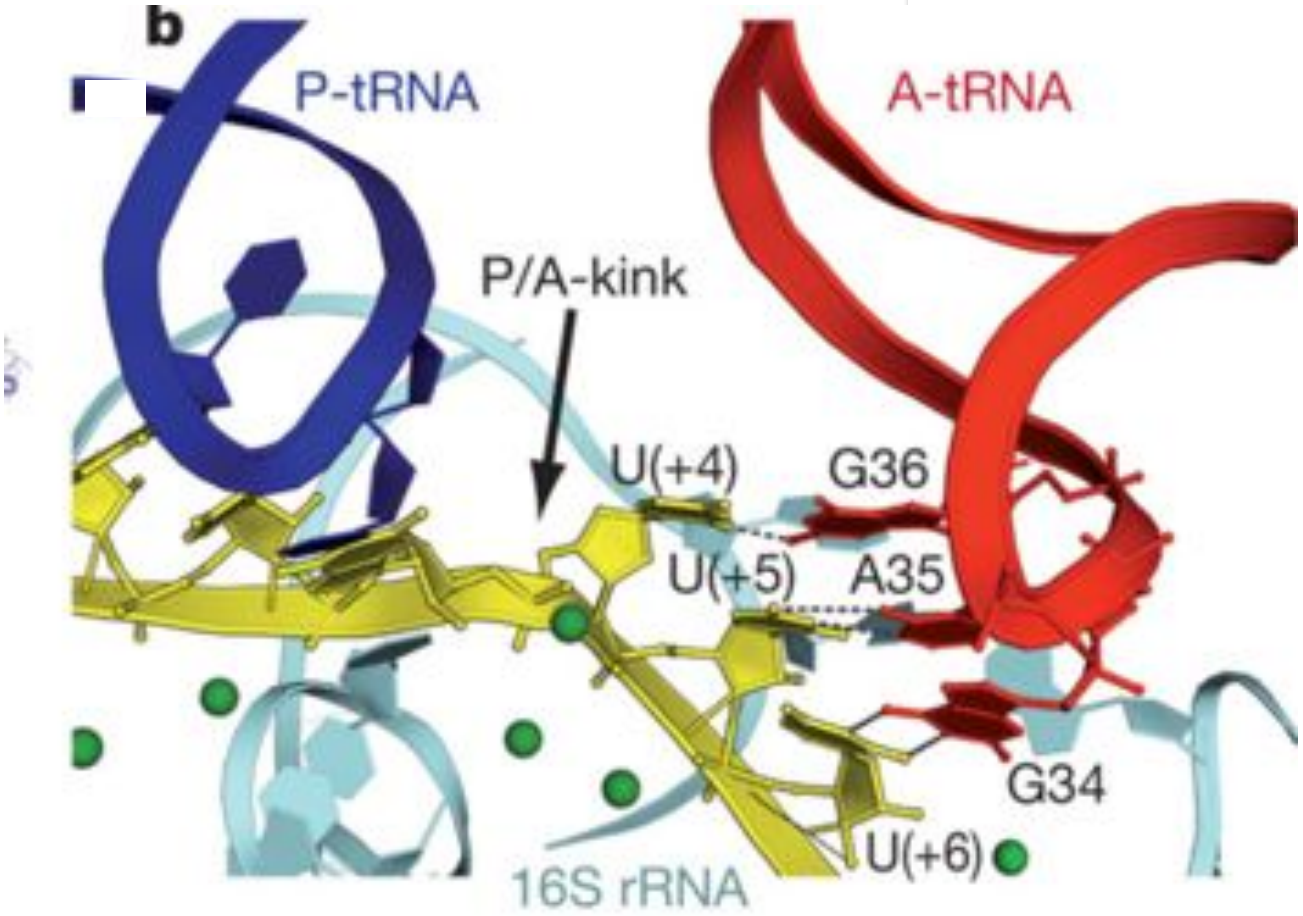
Decoding = Distinguish between cognate and near-cognate aminoacyl tRNAs

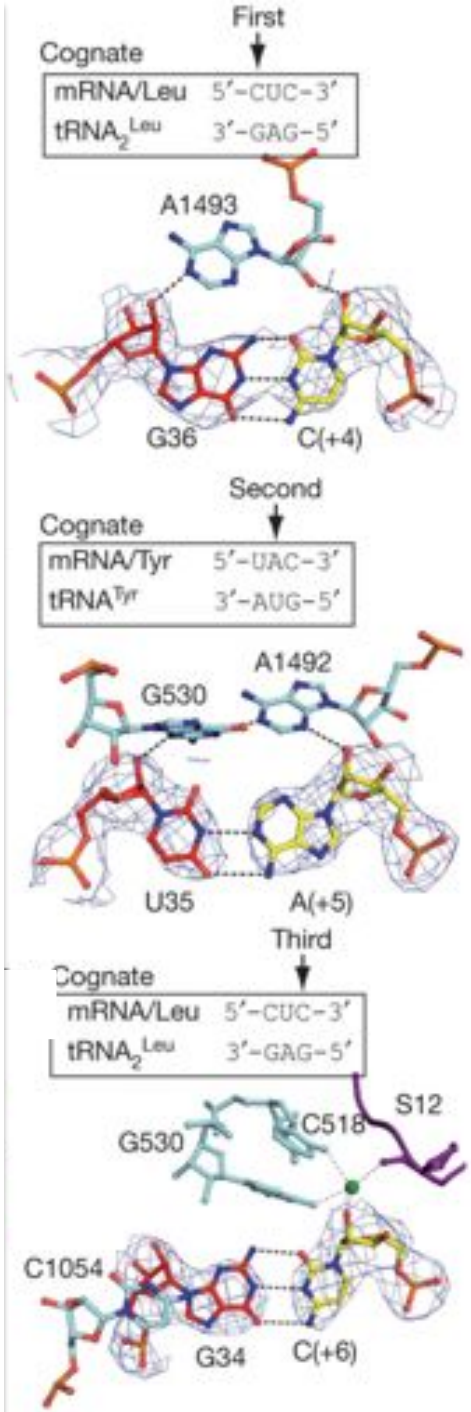


Error rate ≈ 10^{-4}

A tRNA leading to a GoU/UoG pair at the first or second position of the anticodon/codon helix is called a near-cognate tRNA

3rd or Wobble position : GoU pair is « allowed »





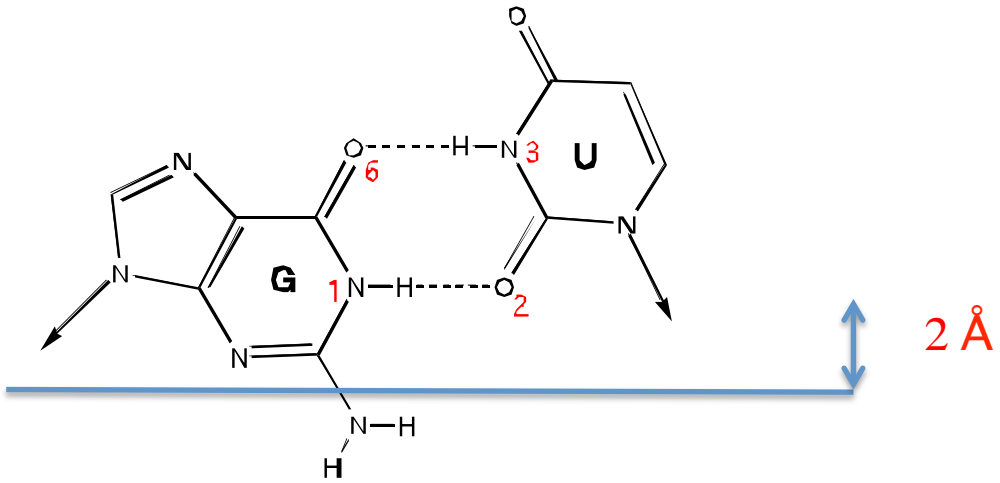
Codon–anticodon interactions in the decoding centre on the 70S ribosome.

nature N Demeshkina *et al*. *Nature* **484**, 257(2012)

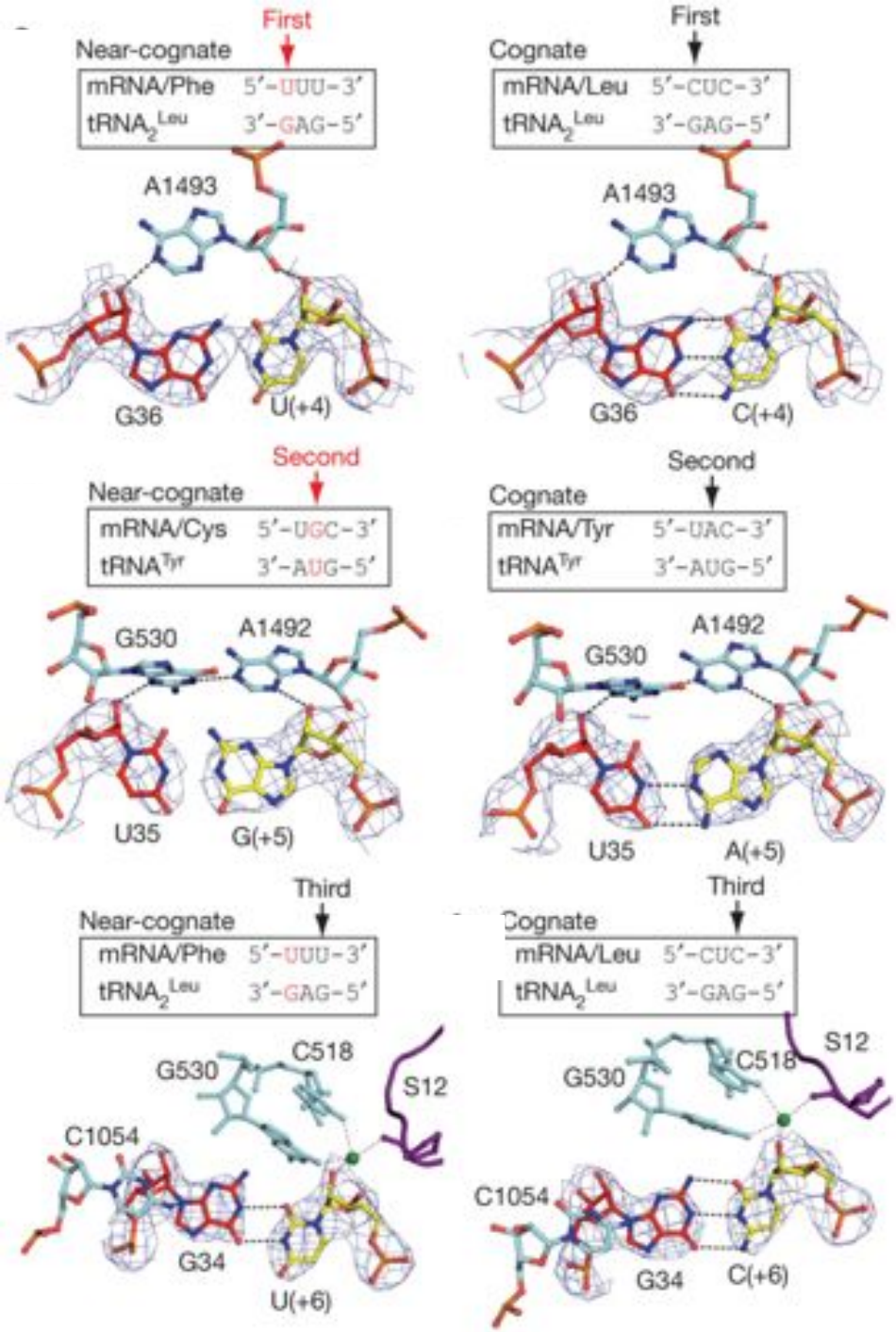
What happens with near-cognate tRNAs?

When a G=C pair is replaced by a GoU pair?

Usual GoU wobble



Except at the third position (the usual Wobble position), GoU pairs adopt a Watson-Crick like geometry

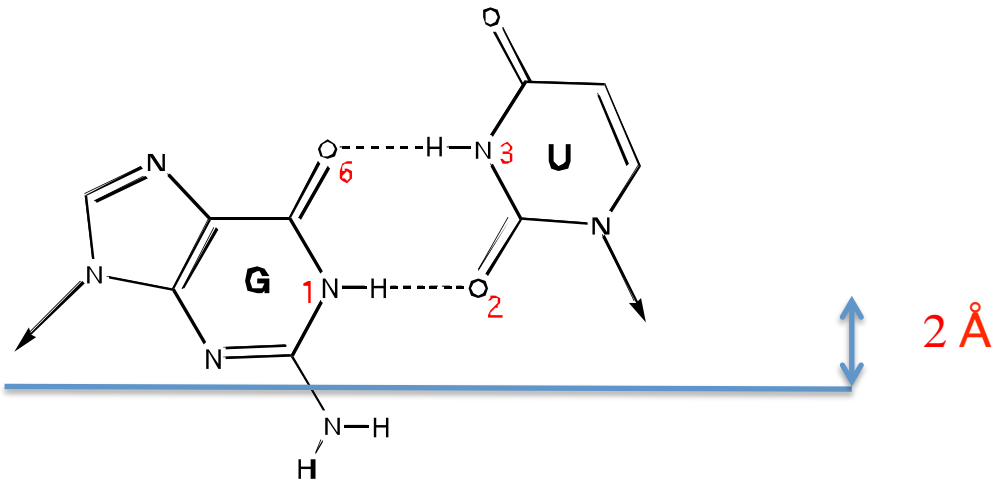


The decoding center imposes strict Watson-Crick geometrical constraints on the first and second base pairs in the codon-anticodon mini-helix.

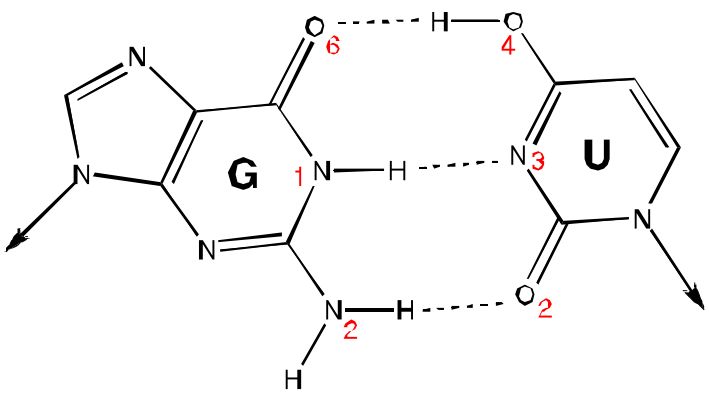
Codon–anticodon interactions in the decoding centre on the 70S ribosome.

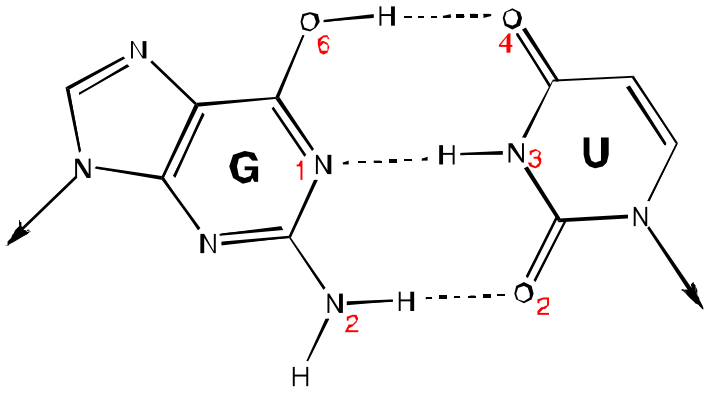
nature N Demeshkina *et al*. *Nature* **484**, 257(2012)

Usual GoU wobble



GoU pair in Watson-Crick like geometry with keto-enol tautomerism of U (left) or G (right)



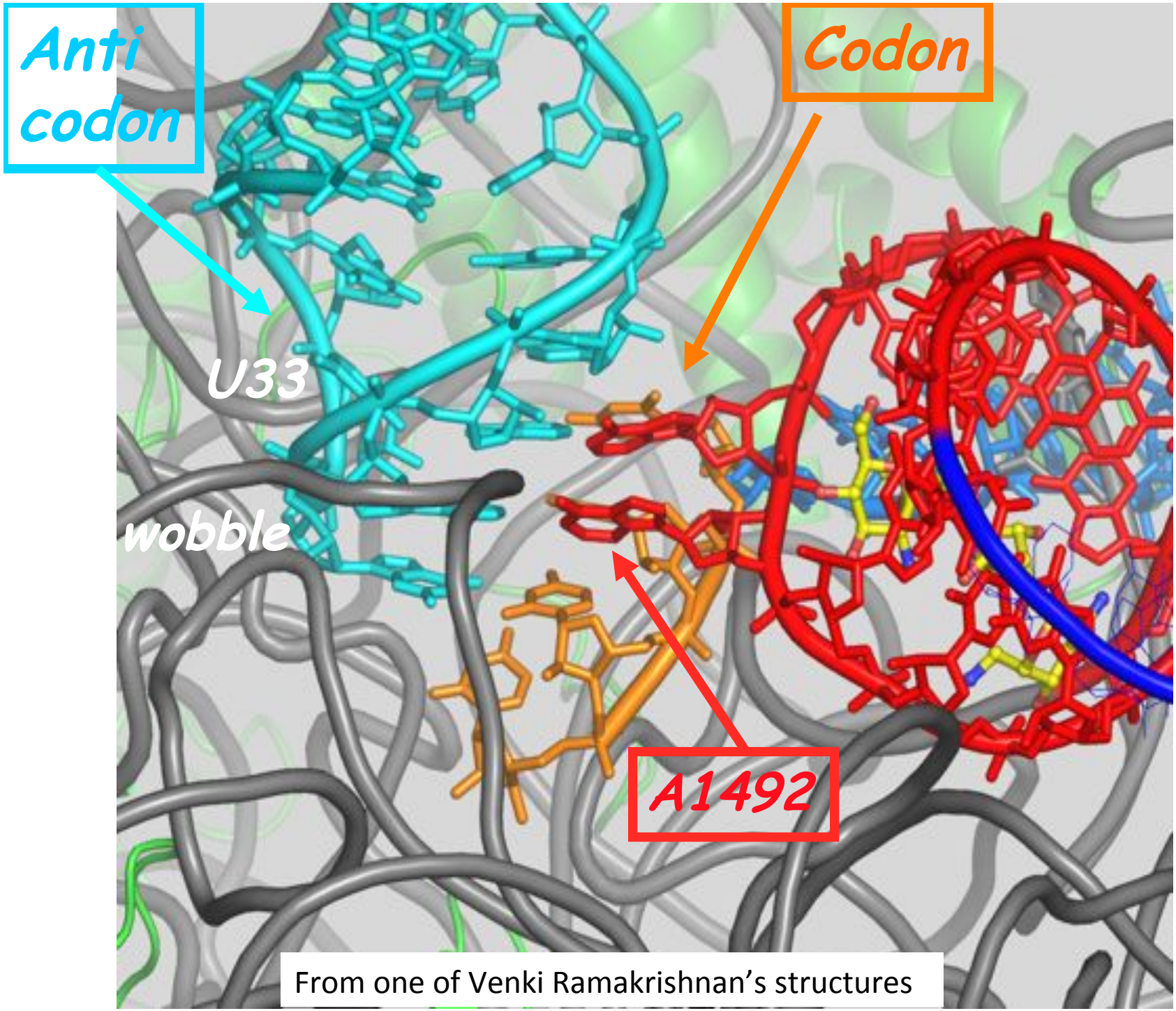


The ribosomal GRIP

The ribosomal active site is designed to bind tightly

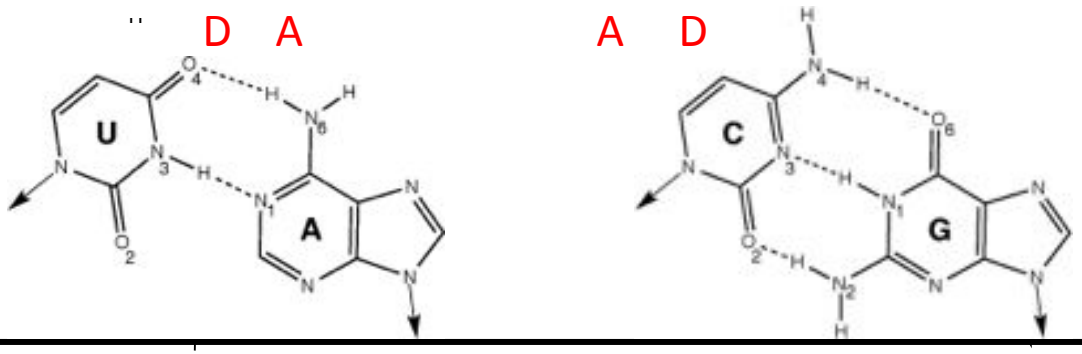
Watson-Crick GEOMETRY at all 3 positions

« The main factor in fidelity is active site tightness » E.T. Kool

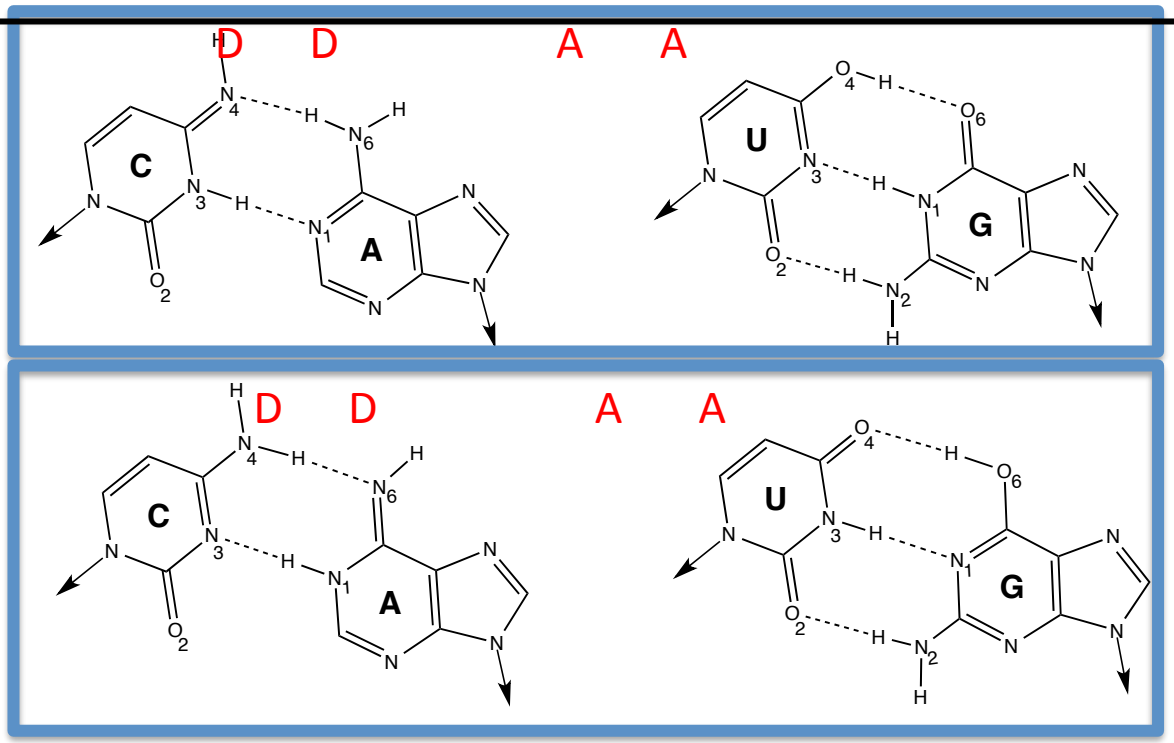


From one of Venki Ramakrishnan's structures

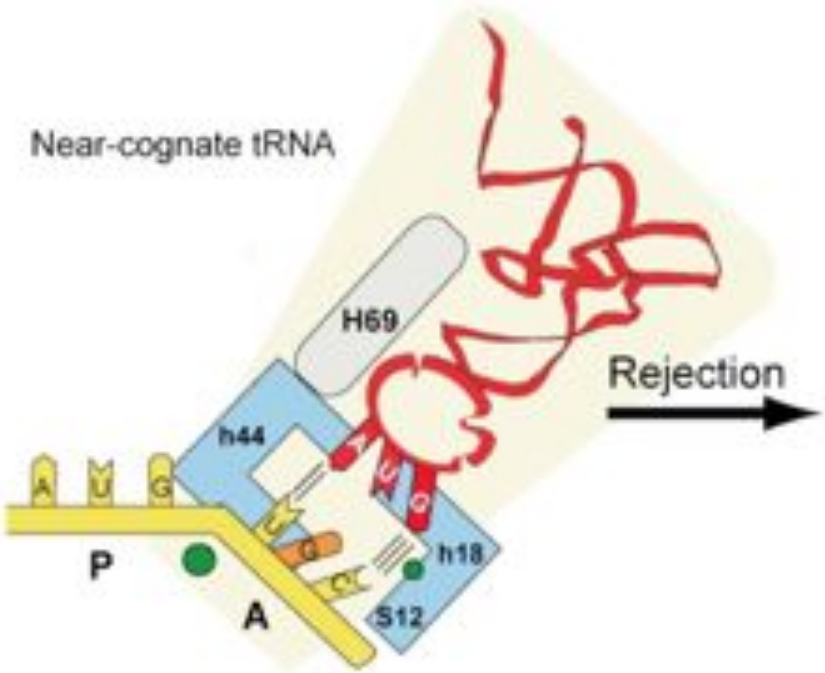
Major Groove



Recognition in the Minor Groove cannot discriminate against tautomeric base pairs



Minor Groove



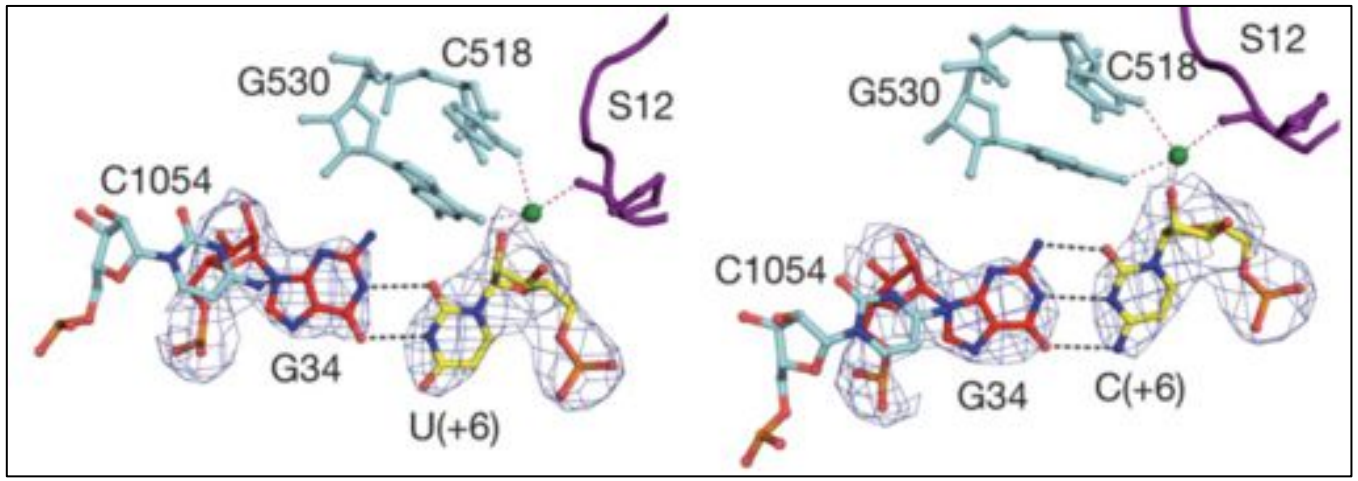
A near-cognate Watson-Crick G•U pair can be trapped if a tautomerization event has occurred (1 in 10,000) or is rejected because of the wobble geometry

Tautomerism ratio is similar to error rate

1 in 10^4 !

nature N Demeshkina *et al*. *Nature* **484**, 257(2012)

At the 3rd position

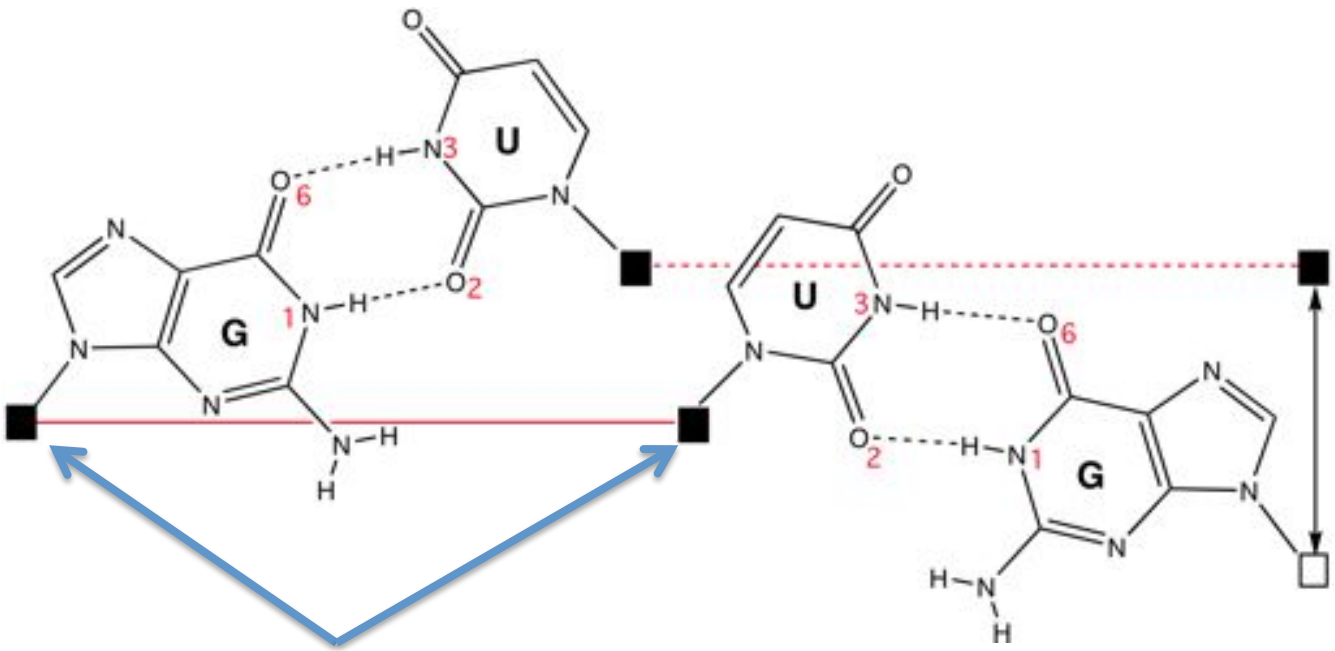


Uridine in the anticodon (U34)

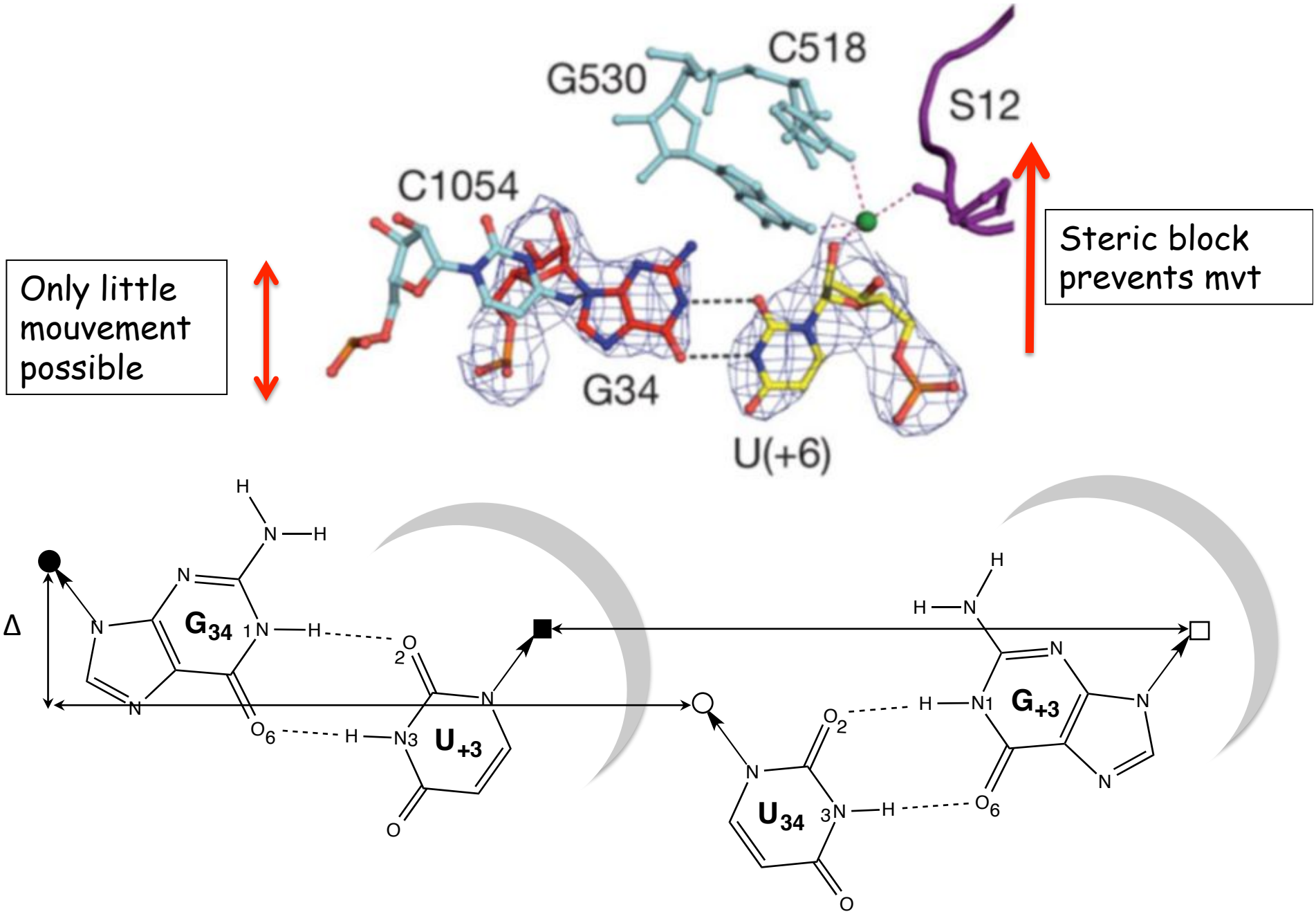
versus

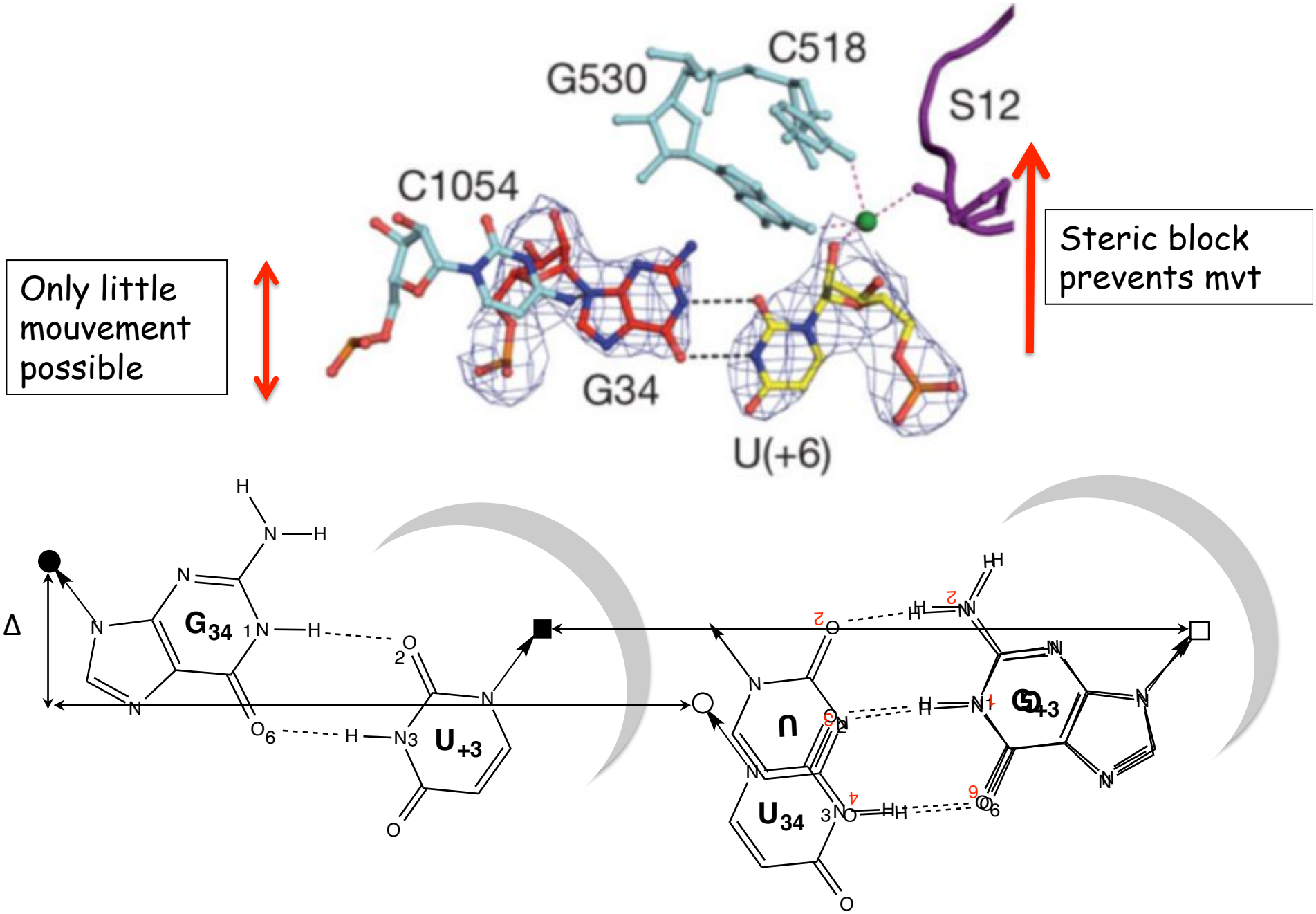
Guanine in the mRNA (G34)

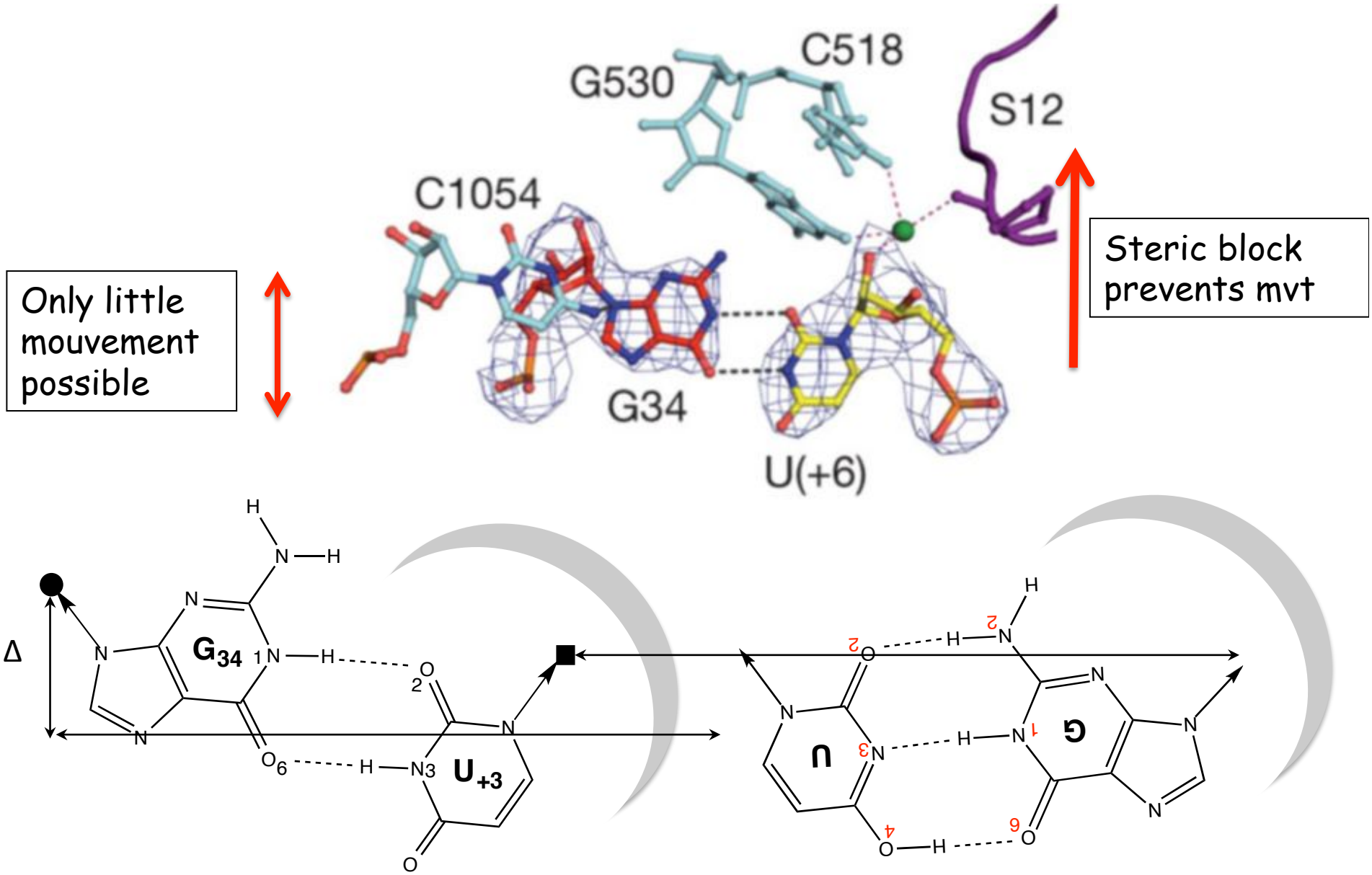
A UoG pair is not isosteric to a GoU pair

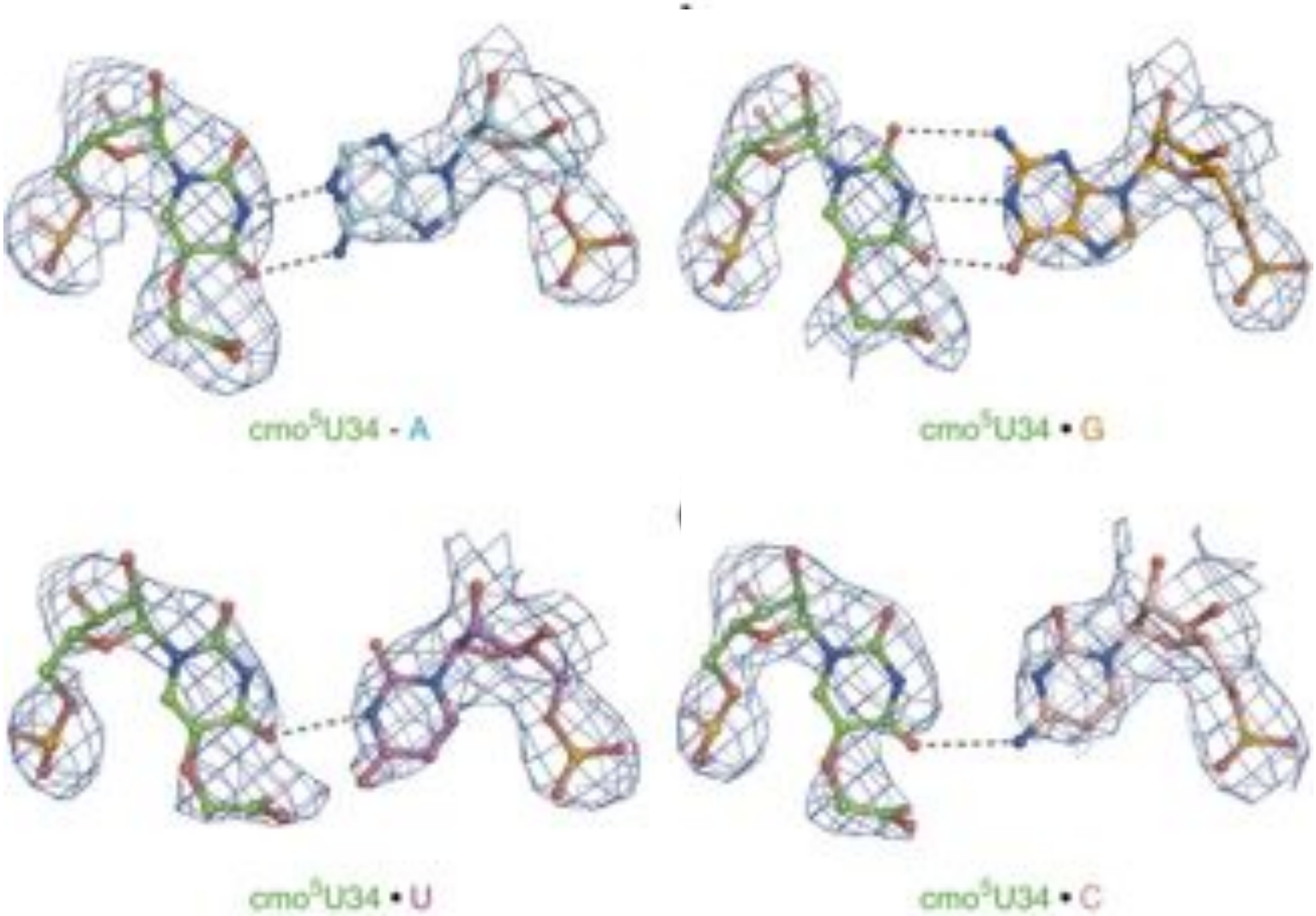


Position 34 (wobble) in the anticodon

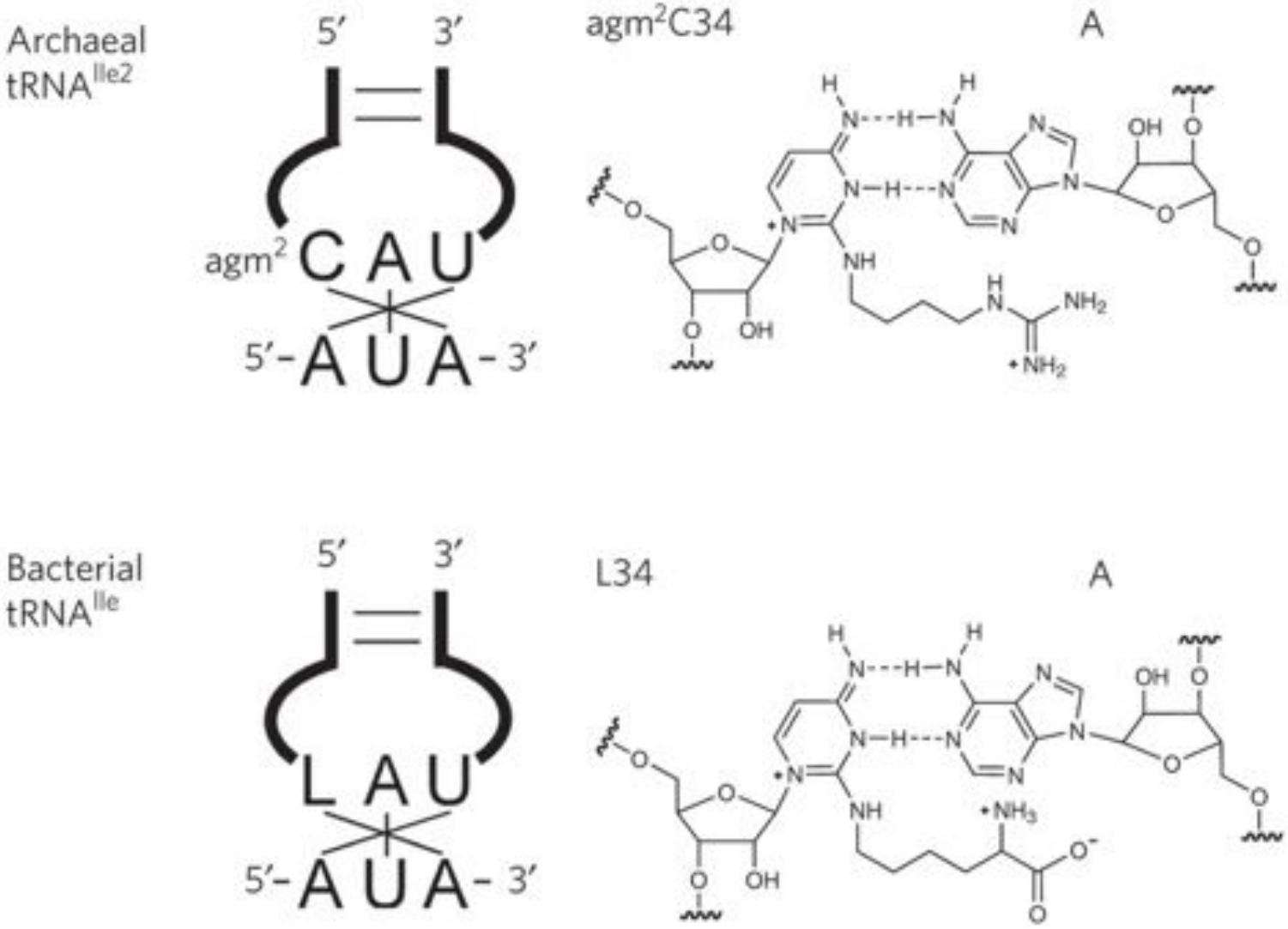

C518
G530
S12
C1054
Only little mouvement possible
Steric block prevents mvt
G34
U(+6)
Δ
G34
U+3
U34
G+3


C518
G530
S12
C1054
G34
U(+6)
Only little mouvement possible
Steric block prevents mvt
Δ
G34
U+3
U34
G+3


C518
G530
S12
C1054
G34
U(+6)
Only little mouvement possible
Steric block prevents mvt
Δ
G34
U+3
G
U



Nature Structural & Molecular Biology 14, 498 - 502 (2007)
Albert Weixlbaumer, Frank V Murphy, IV, Agnieszka Dziergowska, Andrzej Malkiewicz, Franck A P Vendeix, Paul F Agris & V Ramakrishnan.



Nature Chemical Biology 6, 277–282 (2010)

Many examples of pathologies linked to lack of tRNA modifications

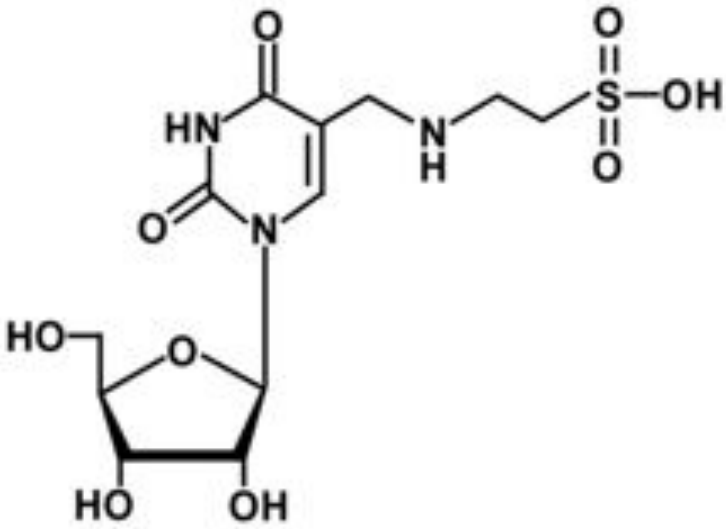
Human mitochondrial diseases associated with tRNA wobble modification deficiency

Two major syndromes of human mitochondrial diseases

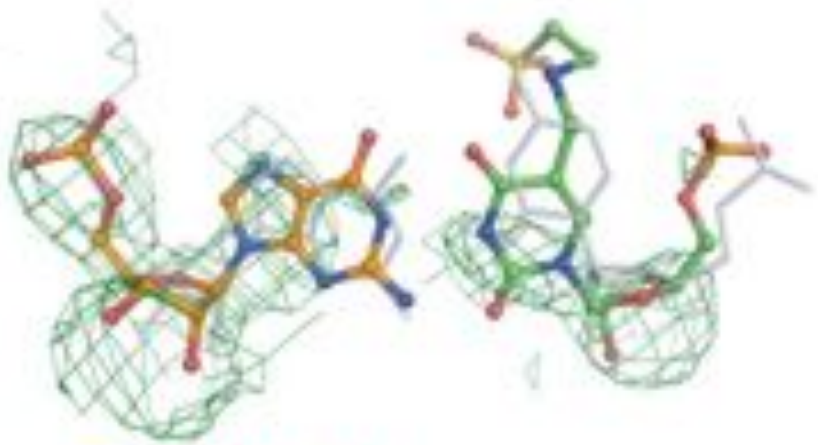
MELAS
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes

MERFF
Myoclonus epilepsy associated with ragged-red fibers

Taurine derivatives in mammalian mt tRNAs



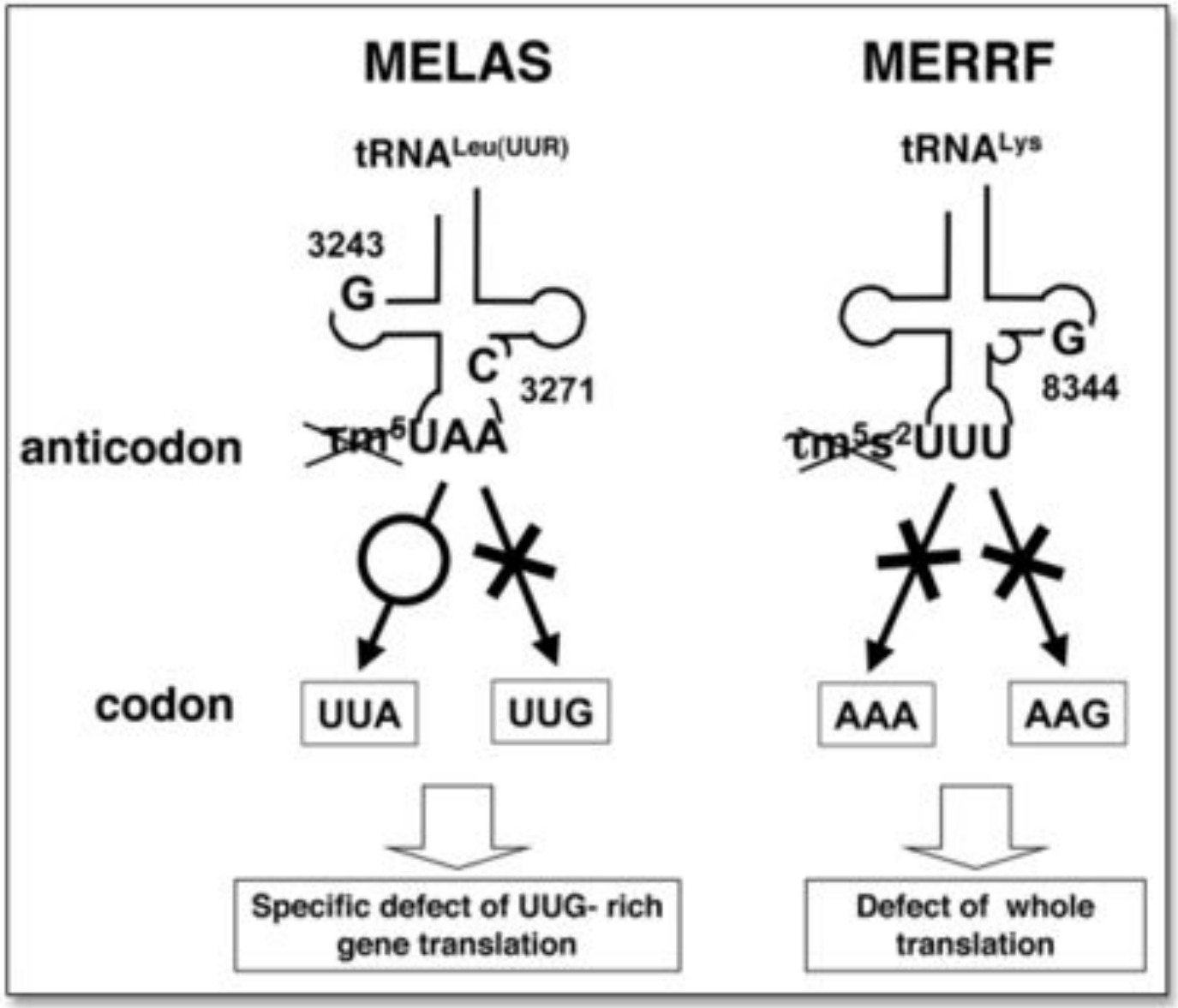
τm5U



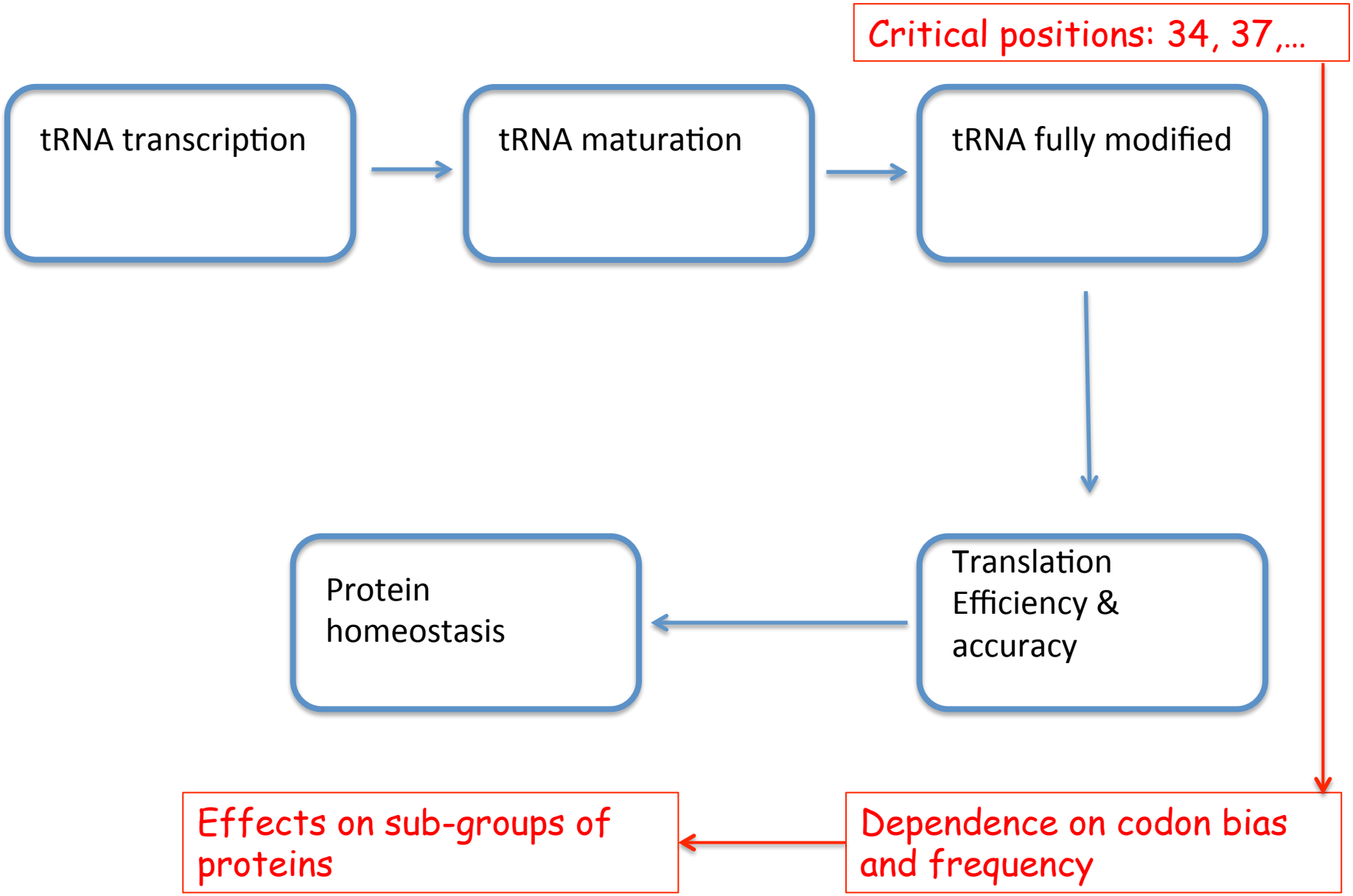
G • τm5U vs G • U

GoU with Watson-Crick like geometry

Kurata S et al.
J. Biol. Chem (2008) 283:18801-18811



Kirino, et al, Proc Natl. Acad. Sci. USA **101**, 15070–15075 (2004).
Suzuki, T, et al. EMBO J. 21, 6581-9 (2002).


Critical positions: 34, 37,...
tRNA transcription
tRNA maturation
tRNA fully modified
Translation Efficiency & accuracy
Protein homeostasis
Dependence on codon bias and frequency
Effects on sub-groups of proteins

Summary on fidelity

- Geometry is key in recognition and fidelity
- Tautomeric base pairs cannot be geometrically recognized by the ribosomes and polymerases
- Tautomerism constitutes a source of errors in translation and replication fidelity

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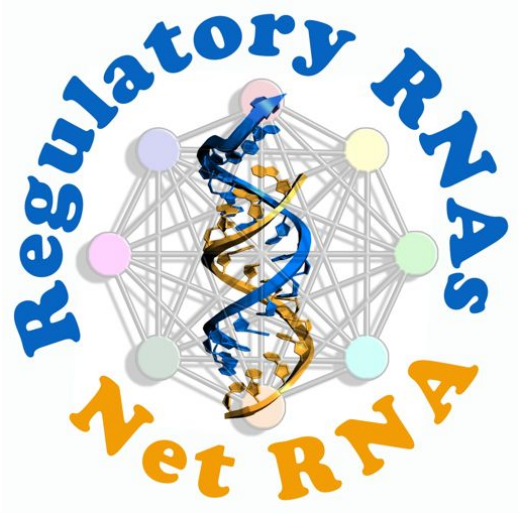
N. Leontis (BGSU-Ohio)