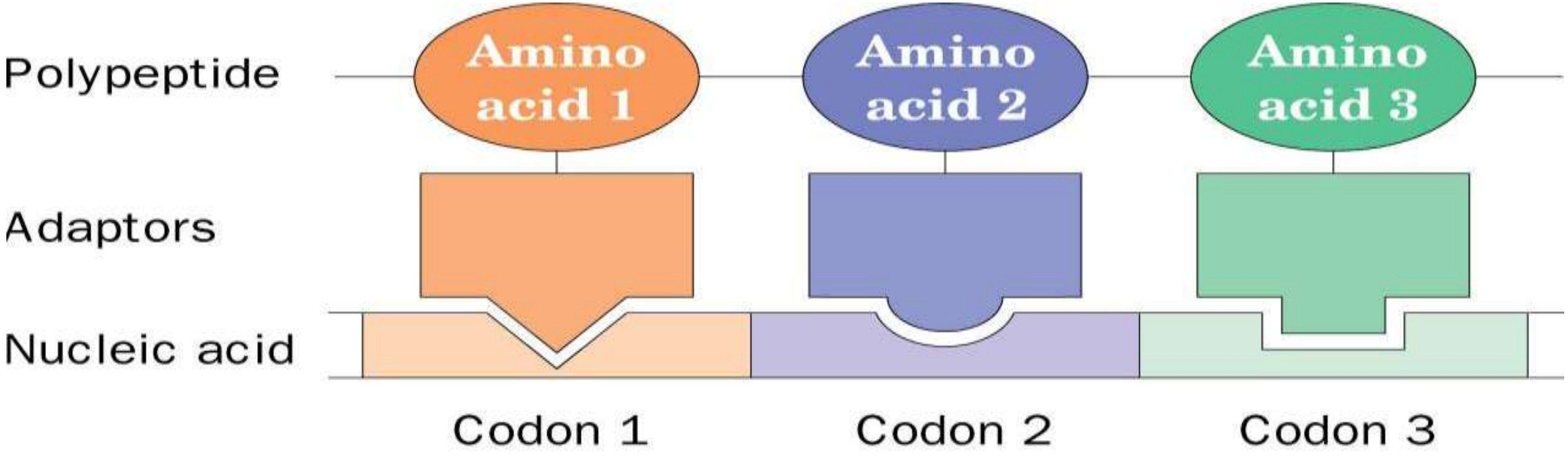
SOS in Biochemistry, Jiwaji University, Gwalior
M.Sc. II Semester (2019-20)
Paper BCH 201: Fundamentals of Molecular Biology (Unit IV)

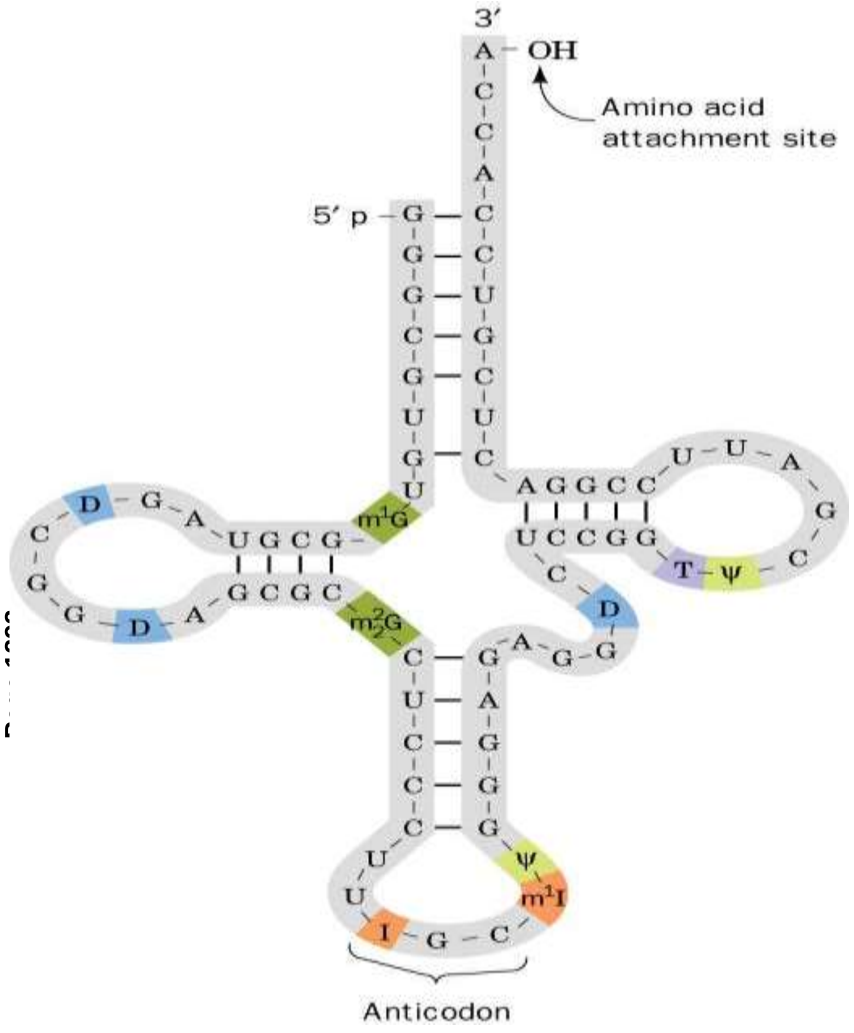
WOBBLE HYPOTHESIS

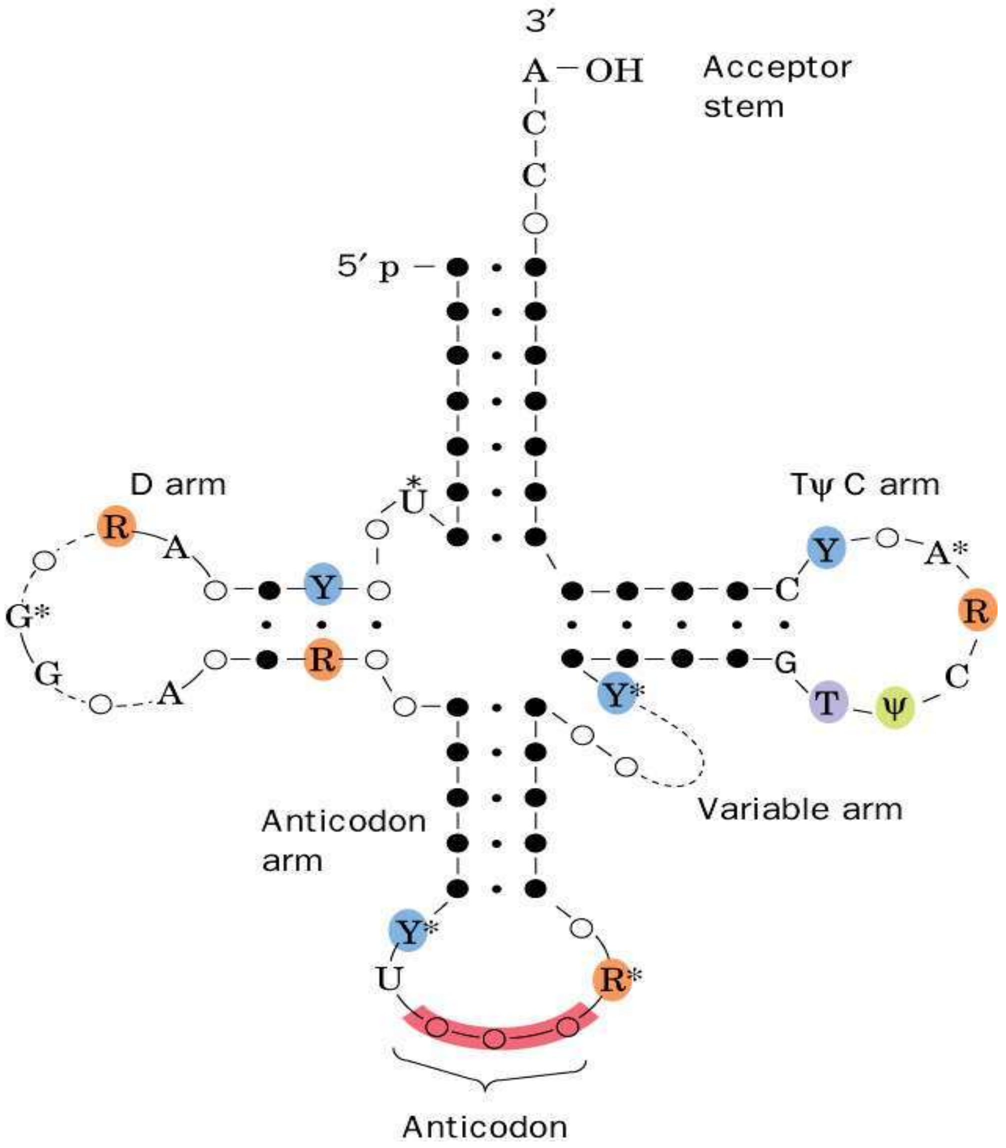
The Adaptor Hypothesis

It postulates that the genetic code is read by molecules that recognize a particular codon and carry the corresponding amino acid.



Cloverleaf Secondary Structure of tRNA





Codon Translation by Aminoacyl tRNAs

- **Each tRNA has an anticodon sequence that allows it to pair with the codon for its cognate amino acid in the mRNA.**
- **Because base pairing is involved, the orientation of this interaction will be complementary and antiparallel.**
- **The arg-tRNAarg has an anticodon sequence, *UCG*, allowing it to pair with the arginine codon CGA.**
- **The anticodon sequence in tRNA is antiparallel and complementary to the codon translated in mRNA.**

Wobble

- Many amino acids are specified by more than one codon (redundancy). Frequently, a tRNA can translate more than one of these codons, sparing the cell from making multiple tRNAs to carry the same amino acid.

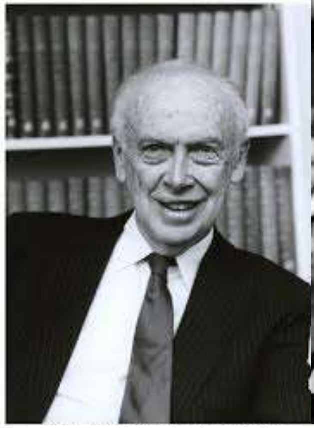
- For instance, the arg-tRNAarg can translate both the CGA and the CGG codons that specify arginine. This phenomenon is known as "Wobble" and can be summarized as follows:

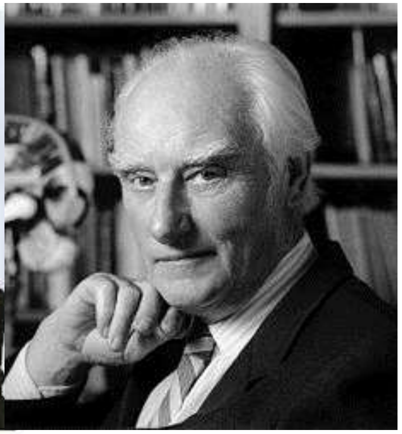
  - Correct base pairing is required at the first position of the codon (third of anticodon) and the second position of the codon (second of anticodon).

  - The third position of the codon does not always need to be paired with the anticodon (e.g., it is allowed to "wobble" in some cases).

Wobble Hypothesis

- This proposal was made by Crick in 1965


JD Watson


FHC Crick

- Explains the arrangements of synonyms in the genetic code.
- Or Explain both the response of same tRNA molecule to several codons and pattern of redundancy of the genetic code

As per Wobble Hypothesis

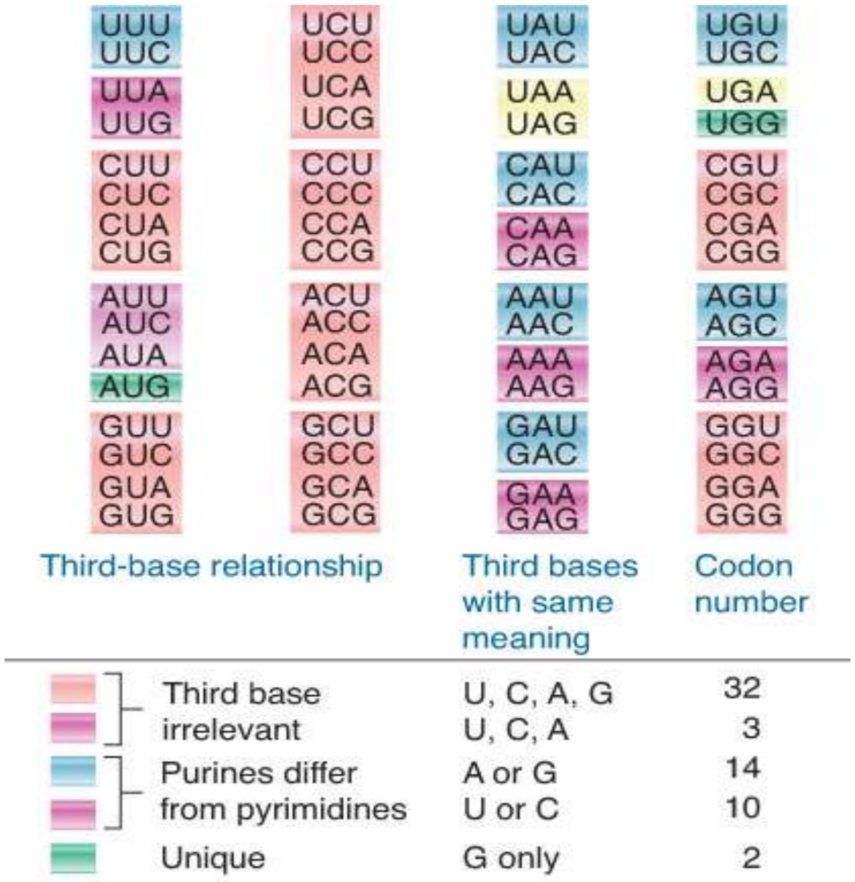
- **At least 32 tRNAs are required to translate all 61 triplet codons. 1 is used for the initiation codon.**
- **Most cells have > 32 codons.**
- **Mammals have ≥ 150 tRNAs.**

Third-Base Degeneracy

(and the Wobble Hypothesis)

- **Codon-anticodon pairing is the crucial feature of the "reading of the code"**
- **But what accounts for "degeneracy": are there 61 different anticodons, or can you get by with fewer than 61, due to lack of specificity at the third position?**
- **Crick's Wobble Hypothesis argues for the second possibility - the first base of the anticodon (which matches the 3rd base of the codon) is referred to as the "wobble position"**

Codon–Anticodon Recognition Involves Wobbling



UUU	UCU	UAU	UGU
UUC	UCC	UAC	UGC
UUA	UCA	UAA	UGA
UUG	UCG	UAG	UGG
CUU	CCU	CAU	CGU
CUC	CCC	CAC	CGC
CUA	CCA	CAA	CGA
CUG	CCG	CAG	CGG
AUU	ACU	AAU	AGU
AUC	ACC	AAC	AGC
AUA	ACA	AAA	AGA
AUG	ACG	AAG	AGG
GUU	GCU	GAU	GGU
GUC	GCC	GAC	GGC
GUA	GCA	GAA	GGA
GUG	GCG	GAG	GGG

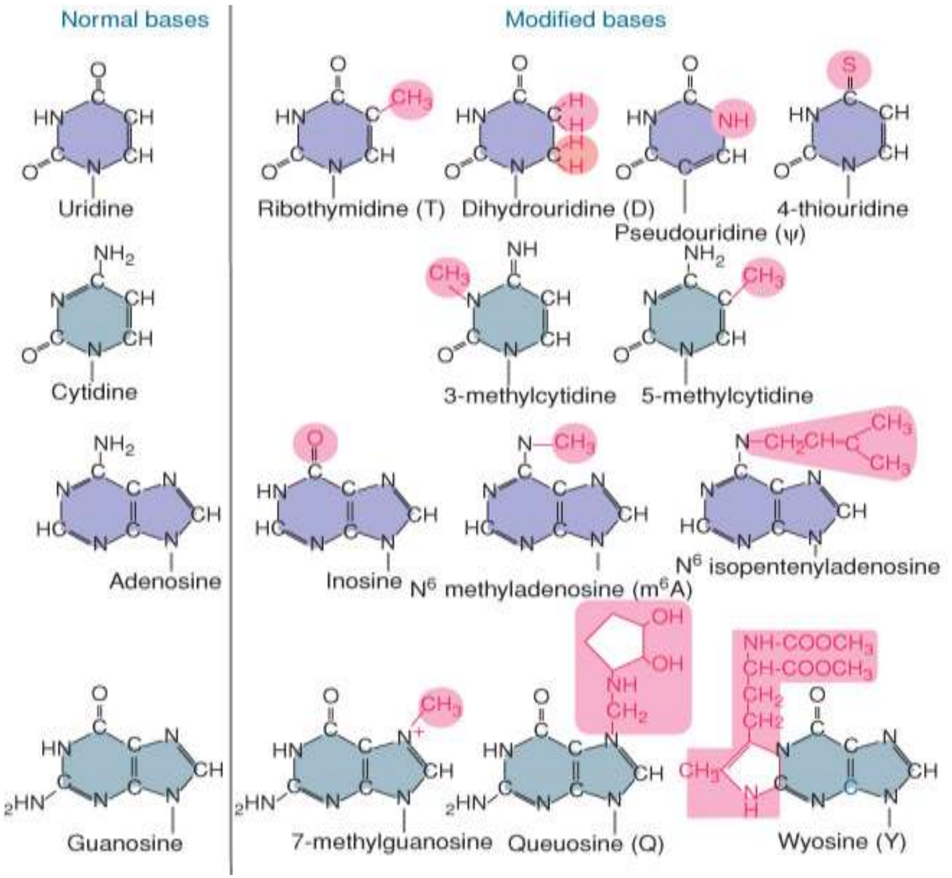
Third-base relationship		Third bases with same meaning	Codon number
🟥	Third base irrelevant	U, C, A, G	32
🟪		U, C, A	3
🟦	Purines differ from pyrimidines	A or G	14
🟪		U or C	10
🟩	Unique	G only	2

Third bases have the least influence on codon meanings

- **Multiple codons that represent the same amino acid most often differ at the third base position (the wobble hypothesis).**

tRNA Contains Modified Bases

- 90 examples of modified bases in tRNAs have been reported.
- Modification usually involves direct alteration of the primary bases in tRNA, but there are some exceptions in which a base is removed and replaced by another base.

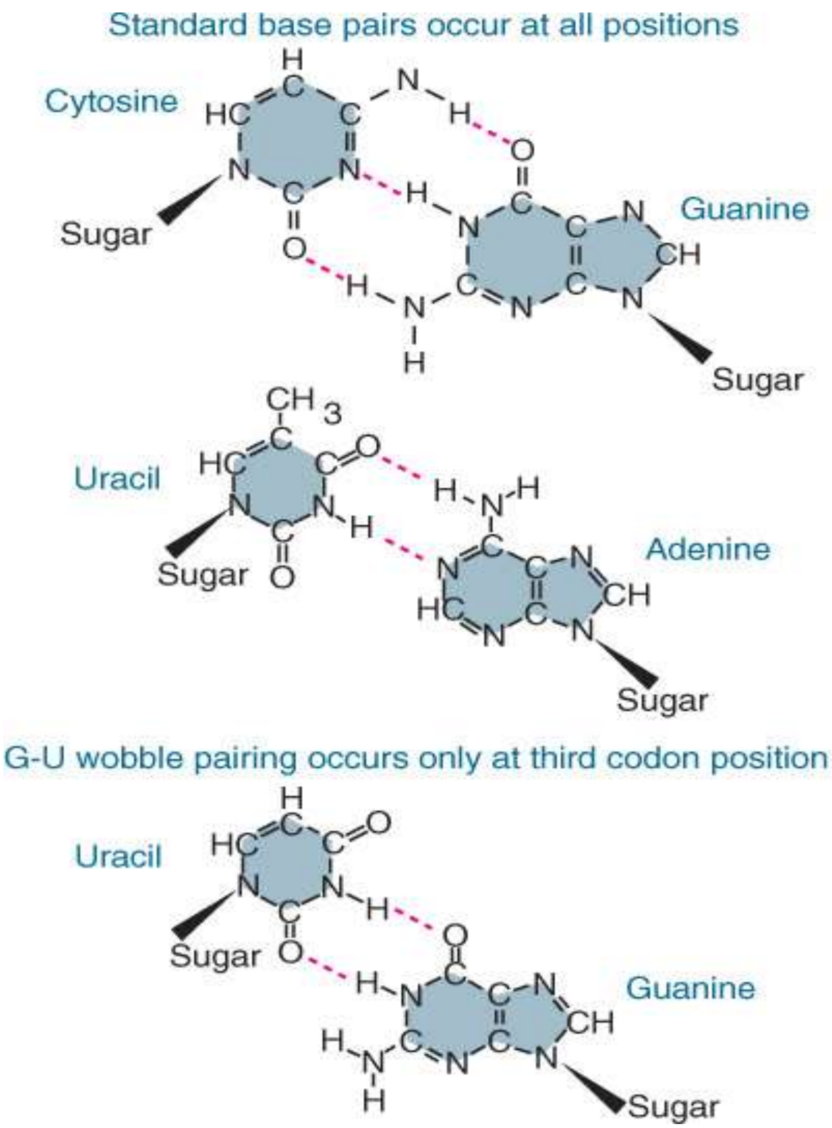


Each of the four bases in tRNA can be modified

Functions of tRNA Modified Bases

- Known functions of modified bases are to confer increased stability to tRNAs and to modulate their recognition by proteins and other RNAs in the translational apparatus.

Codon–Anticodon Recognition Involves Wobbling


Standard base pairs occur at all positions

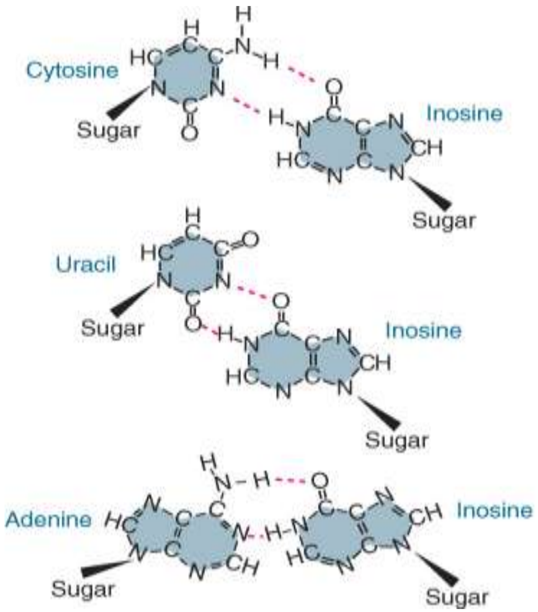
G-U wobble pairing occurs only at third codon position

- The pairing between the first base of the anticodon and the third base of the codon can vary from standard Watson-Crick base pairing according to specific wobble rules.

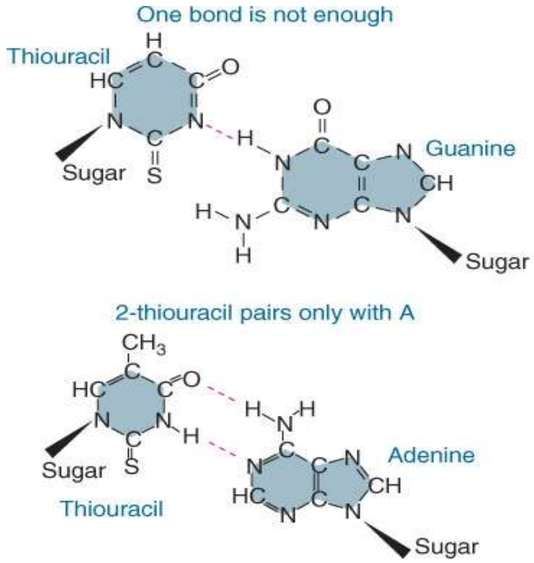
Wobble in base pairing allows G-U pairs to form between the third base of the codon and the first base of the anticodon.

Modified Bases Affect Anticodon–Codon Pairing

- **Modifications in the anticodon affect the pattern of wobble pairing and therefore are important in determining tRNA specificity.**



Inosine can pair with U, C, or A.



Modification to 2-thiouridine restricts pairing to A alone because only one H-bond can form with G.

The Wobble Hypothesis

- **The first two bases of the codon make normal (canonical) H-bond pairs with the 2nd and 3rd bases of the anticodon**
- **At the remaining position, less stringent rules apply and non-canonical pairing may occur**
- **The rules: first base U can recognize A or G, first base G can recognize U or C, and first base I can recognize U, C or A (I comes from deamination of A)**
- **Advantage of wobble: dissociation of tRNA from mRNA is faster and protein synthesis too**

Allowed Wobble Pairing Combinations in the Third Codon–Anticodon Position.

5′-Anticodon Base	3′-Codon Base
C	G
A	U
U	A or G
G	U or C
I	U, C, or A

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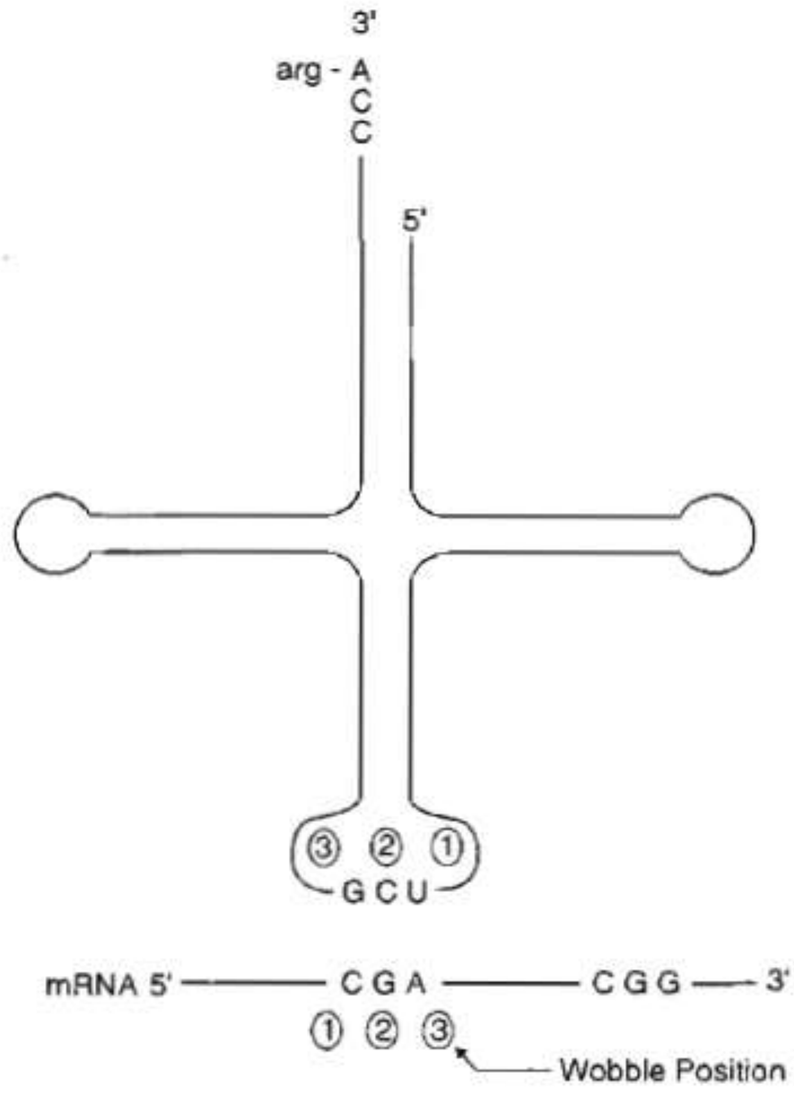
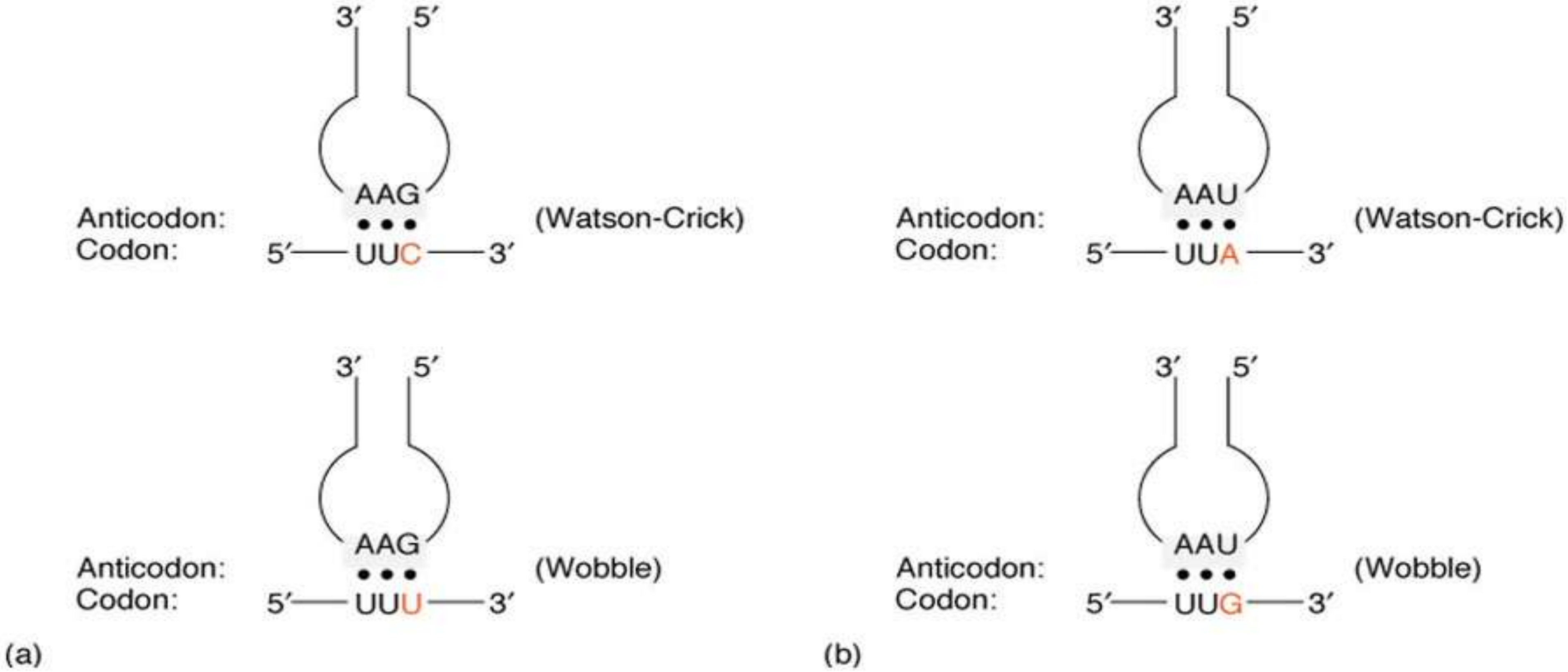


Wobble and Protein Synthesis


3′
5′
AAG
Anticodon:
Codon:
5′ UUC 3′
(Watson-Crick)
3′
5′
AAU
Anticodon:
Codon:
5′ UUA 3′
(Watson-Crick)
3′
5′
AAG
Anticodon:
Codon:
5′ UUU 3′
(Wobble)
3′
5′
AAU
Anticodon:
Codon:
5′ UUG 3′
(Wobble)
(a)
(b)

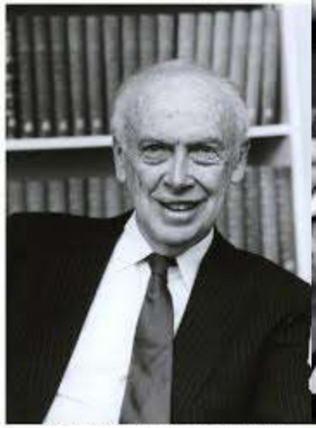
Pairing Combinations with Wobble Concept

Third Position Codon Base	First Position Anticodon Base
A	U, I
G	C, U
U	G, I
C	G, I

Alternatively

First Position Anticodon Base	Third Position Codon Base
G	U/C
C	G
A	U
U	A/G
I	A/U/C

Rules of Wobble Hypothesis



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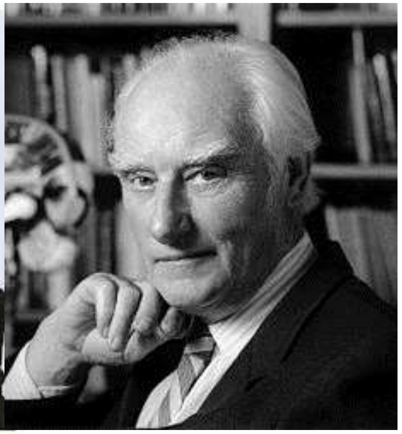

FHC Crick

Five Rules Explain Arrangements of Synonyms

Rule - 1

The codon XYC and XYU are always synonym.

a) **If anticodon to XYC codon is GY’X’ then this anticodon can also pair with XYU, because G can pair with U in the third position of a codon**

b) **If the anticodon to XYC codon is IY’X’ then it can pair with codons XYU, XYA and XYC**

Thus:

No anticodon can only pair with codon XYC and not with XYU codon

Or only with codon XYU and not with XYC codon

Rule - 1

………continued

c) If the anticodon to codon XYU is AY'X'

- Then this codon XYU can also pair with anticodons GY'X' and IY'X'

- **However, A is not found in the first position of an anticodon (except in the mt anticodon for glycine)**
- **Because the enzyme anticodon deaminase acts at this position to convert A → I**