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

Amino acid attachment site

Anticodon

Accepter stem

D arm

Anticodon arm

T\_Ψ\_C arm

Variable arm

Anticodon
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-tRNA<sub>arg</sub> 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

- 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

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

Third bases have the least influence on codon meanings
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.
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**

- 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.

<table>
<thead>
<tr>
<th>5′-Anticodon Base</th>
<th>3′-Codon Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>G</td>
</tr>
<tr>
<td>A</td>
<td>U</td>
</tr>
<tr>
<td>U</td>
<td>A or G</td>
</tr>
<tr>
<td>G</td>
<td>U or C</td>
</tr>
<tr>
<td>I</td>
<td>U, C, or A</td>
</tr>
</tbody>
</table>
Wobble and Protein Synthesis
### Pairing Combinations with Wobble Concept

<table>
<thead>
<tr>
<th>Third Position Codon Base</th>
<th>First Position Anticodon Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>U, I</td>
</tr>
<tr>
<td>G</td>
<td>C, U</td>
</tr>
<tr>
<td>U</td>
<td>G, I</td>
</tr>
<tr>
<td>C</td>
<td>G, I</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>First Position Anticodon Base</th>
<th>Third Position Codon Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>U/C</td>
</tr>
<tr>
<td>C</td>
<td>G</td>
</tr>
<tr>
<td>A</td>
<td>U</td>
</tr>
<tr>
<td>U</td>
<td>A/G</td>
</tr>
<tr>
<td>I</td>
<td>A/U/C</td>
</tr>
</tbody>
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Rules of Wobble Hypothesis

JD Watson  FHC Crick

Five Rules Explain Arrangements of Synonyms
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

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 $A \rightarrow I$