# PROTEIN SYNTHESIS

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**Reading:** Molecular Biology of the Cell, 6th Edition. Chap. 6 pp. 333-351

## KEY CONCEPTS AND LEARNNG OBJECTIVES

1. The nucleotide sequence of DNA in the coding region of a protein-encoding gene is co-linear with the amino acid sequence of its protein product. These genes produce mRNA transcripts that dictate the ordered addition of specific amino acids into a growing polypeptide chain.
   a. What are the key features of the genetic code?
   b. Identify features of an mRNA that can affect its translation.
   c. Recognize translation start and translation stop codons.
   d. Given the genetic code, predict the sequence of a protein encoded by a DNA sequence.
   e. Given the genetic code, predict the effect common mutations will have on protein synthesis (mutation of a codon to a stop codon, mutation of a splice donor or acceptor site, frameshift, etc.)

2. Fidelity in protein synthesis is provided by the tRNAs that decode mRNA codons into an amino acid sequence, and by aminoacyl-tRNA synthetases that covalently attach the correct amino acids to their cognate tRNAs.
   a. Explain the difference between prokaryotic and eukaryotic cells with respect to aminoacyl-tRNA synthetases.
   b. Identify important structural features in tRNA molecules including features that contribute to fidelity in protein synthesis.
   c. Diagram the reactions required to produce an aminoacyl tRNA.
   d. Explain the role of editing by aminoacyl-tRNA synthetases in the fidelity of protein synthesis.

3. The ribosome coordinates protein synthesis in all cells. The ribosome is a molecular motor that walks down the length of an mRNA one codon at a time. At each codon, it recruits an aminoacyl-tRNA and catalyzes the formation of a peptide bond.
   a. List the major steps in protein synthesis.
   b. Draw the key steps in translation initiation, elongation, and termination for eukaryotic and prokaryotic cells, and identify the involved factors (focus on the factors discussed in lecture).
   c. Draw the interaction between a messenger RNA codon and its cognate tRNA, labeling the orientations (5’ and 3’ ends) of both RNA strands.
   d. Describe the Wobble phenomenon and explain it relationship to the existence of degeneracy in the genetic code.
   e. Describe the functions of the large and small ribosomal subunits in protein synthesis.
   f. Explain how translation is terminated.

4. Several protein factors that participate in protein synthesis possess a GTPase activity.
   a. List important protein factors with GTPase activity that participate in protein synthesis and describe their functions.
   b. Identify the specific steps in protein synthesis where GTP hydrolysis is thought to occur.
   c. Describe the function of guanine nucleotide exchange factors (GEFs) and their role in regulating protein synthesis.
d. Describe the cellular mechanisms that safeguard against the incorporation of incorrect amino acids into polypeptides and initiation at the wrong codon.
e. Explain the features of GTPases that facilitate their function as irreversible molecular switches in the regulation of cellular processes.

5. Prokaryotes and eukaryotes differ in certain genetic mechanisms. Some of the differences in transcription and translation are important as targets for antibiotics that act only on prokaryotic cells without harming host cells.
   a. Compare and contrast eukaryotic mRNA and prokaryotic mRNAs.
   b. Describe the characteristics of a Shine-Dalgarno sequence and explain its function in translation of prokaryotic messages.
   c. Describe the function of the 7-methylguanosine cap and poly-A tail in eukaryotic transcripts.
   d. Compare the antibiotic sensitivities of protein synthesis for both prokaryotes and eukaryotes.
   e. List the major steps involved in protein synthesis for both prokaryotes and eukaryotes. Compare and contrast major differences.

Resources:
Alberts Molecular Biology of the Cell, 6th edition is an excellent place to go if you need clarification. While I try to explain things clearly, each individual is unique with respect to how they learn. The text is outstanding, and it may explain things in a better way for you.
Figure designations refer to Molecular Biology of the Cell 6th edition. Full figure legends are available there.

I. The Genetic Code
The information in mRNA is read in groups of three nucleotides. The number of unique triplets that can be formed from 4 nucleotides is $4^3$ or 64 possible codons. As there are only 20 amino acids, but 64 possible codons, it was determined that there was more than one codon for most amino acids. When looking at the genetic code, you may notice that codons for the same amino acid tend to contain the same nucleotides in the first and second positions, and vary at the third position. There are also three amino acids that have 6 possible codons – four have the same nucleotides in the first and second positions, but the other two codons have different nucleotides in the first and second positions.

This is a list of a few key points you should know about the genetic code.
A. Three potential reading frames
When translating a nucleotide sequence into an amino acid sequence, the mRNA is read in the 5’ to 3’ direction in consecutive sets of three nucleotides. In principle, the same mRNA can specify three different amino acid sequences depending on which nucleotide is chosen as the first one. In reality, only one reading frame contains the actual message. The other two reading frames tend to have frequent stop codons (~ one in 20 codons).

Figure 6-49. The three possible reading frames of an mRNA.

II. Translation
A. Steps of Translation

B. Charging the tRNA
1. Characteristics of a tRNA
tRNA is transcribed by RNA pol III as a large precursor RNA that is extensively modified – there are over 50 possible modifications and one in every ten bases is modified. The pre-tRNA can also be spliced through a cut and paste mechanism. It is thought that the extensive modifications are essential to forming the precise final structure so that the codon and anticodon can base pair efficiently and with high affinity.

In eukaryotes, the CCA at the 3’ end of the tRNA is not part of the gene sequence. The 3’ end of the pre-tRNA is enzymatically removed and the non-templated CCA added. This CCA is important to the loading of the amino acid on the mature tRNA.

Figure 6-50. A tRNA molecule. (A) cloverleaf formation, (B) and (C) L-shaped forms that shows the tertiary structure. (E ) linear form and is color-coded to match A, B, and C.
2. **The anticodon and the Wobble base.**
The anticodon is a set of three consecutive nucleotides that pairs with the complementary codon in the mRNA. The third position of the codon is called the Wobble base. Some tRNAs are structured so that accurate base pairing is only required at the first two positions of the codon, and some mismatch is tolerable at the third position. This explains why many alternative codons for an amino acid differ only in the third nucleotide.

![Wobble base pairing. If the nucleotide listed in the first column is present in the third, or wobble, The cartoon to the right illustrates how guanine can base pair with either cytosine or uracil in the wobble position.](image-url)

3. **The 3’ acceptor stem and loading of the adenylated amino acid**
The aminoacyl tRNA synthetase is the enzyme the “charges” or loads the appropriate amino acid onto the correct tRNA. Charging a tRNA is a two step process. First, the amino acid is activated through linkage of its carboxyl group directly to AMP, forming an adenylated amino acid. This reaction is driven by the ATP that donates the AMP. The AMP-linked carboxyl group is then transferred to a hydroxyl group on the 3’ end of the tRNA. This joins the amino acid by an activated ester linkage to the tRNA and forms the final aminoacyl-tRNA.

In prokaryotes, a synthetase may couple the wrong amino acid to a tRNA, but the amino acid is then modified to match the tRNA. In eukaryotic cells, there is a different synthetase for each amino acid. Thus, in eukaryotes, it is essential that the synthetase select the correct tRNA and the correct amino acid for linkage.

![Amino acid tRNA.](image-url)
4. **Aminoacyl tRNA synthetase selection of its cognate tRNA**

The selection of the correct tRNA partner is a critically important step for high fidelity protein synthesis, and it is often referred to as the “second genetic code”. To accomplish this task, the synthetase physically interacts with the tRNA structure to determine it is the appropriate partner. Most synthetases rely primarily on the anticodon region and the 3’ acceptor arm to recognize their tRNA partner.

However, recognition of the tRNA based on the anticodon is not always possible. For example, six different codons specify serine; thus, seryl-tRNA synthetase must recognize six different anticodons including AGA and GCU, which are completely different. In these difficult cases, the synthetase must rely on other regions of the tRNA. This figure illustrates known positions that can be utilized by some synthetases to identify their cognate tRNA.

As much as each synthetase must recognize its cognate tRNA, it must not bind to any other tRNA. Each tRNA has a set of positive interactions that match the proper tRNA with the proper enzyme and a set of negative interactions that block binding of improper pairs. An example is aspartyl-tRNA synthetase where guanine-37 (immediately adjacent to the anticodon) is not involved in binding, but must be methylated to ensure the tRNA does not accidently bind to the arginyl-tRNA synthetase.
5. Aminoacyl tRNA synthetase selection of the correct amino acid
A two-step process is used to ensure that the appropriate amino acid is attached to the correct tRNA. First, the synthesis site in the synthetase has the highest affinity for the correct amino acid. Second, the synthetase has a proofreading or editing site to insure the correct amino acid is attached. The synthetase will attempt to push the amino acid into the editing site, and if it enters the site, it is recognized as an incorrect pairing and the amino acid will be removed.

Editing can occur prior to or after transfer of the adenylated amino acid to the tRNA. In pre-transfer editing, the incorrect amino acid is hydrolyzed by the synthetase in an ATP-dependent manner from the AMP. In post-transfer editing, the mischarged tRNA is deacetylated in an ATP-dependent manner. It is expected that selection of the correct amino acid is more error-prone than the selection of the tRNA because the amino acid is a much smaller molecule with fewer distinguishing characteristics.

6. Example: Prokaryote charging of tRNA^\text{Met}
The AUG codon represents methionine, and two types of tRNAs can carry this amino acid. One is used for initiation and the other for recognizing AUG codons during elongation. In prokaryotes, the initiator tRNA carries a modified methionine, formylmethionine. The initiator tRNA is known as tRNA^\text{Met} and when it has the modified methionine attached, it is known as fMet-tRNA^\text{Met}. The elongation tRNA is referred to as tRNA^\text{Met}_{\text{el}} and when loaded with methionine, it is known as Met-tRNA^\text{Met}_{\text{el}}. Interestingly, tRNA^\text{Met} is initially charged with standard methionine to create Met-tRNA^\text{Met}, then a Met-tRNA formyltransferase modifies the methionine to formylmethionine to give fMet-tRNA^\text{Met}.
Both tRNAs have the same anti-codon and the same synthetases is responsible for charging both tRNAs, so how does the synthetase tell the difference between the tRNAs so that only the correct tRNA undergoes the modification? The answer is by interacting with different regions of the tRNA other than the anticodon region. This figure highlights differences between the tRNAs with those used by the synthetases to distinguish between the tRNAs highlighted.

\[ s^4U, \text{ 4thiouridine} \]
\[ D, \text{ dihydrouridine} \]
\[ Cm, 2'-\text{O-methylcytidine} \]
\[ m^7G, 7\text{-methylguanosine}; \]
\[ T, 5\text{-methyluridine} \]
\[ \Psi, \text{ pseudouridine} \]
\[ t^6A, N^\gamma\text{threonylcarbamoyl-}
\text{adenosine} \]
\[ Gm, 2':\text{O-methylguanosine} \]
\[ ac^2C, N^\gamma\text{-acylcytidine} \]
\[ acp^3U, 3'-(3\text{-amino-3-}
\text{carboxypropyl})\text{juridine}. \]

C. Introduction to the ribosome

The eukaryotic ribosome is termed the 80S ribosome. "S" stands for Svedberg unit, and it refers to the sedimentation rate of the complex on ultracentrifugation. It is not a measure of size or weight so the numbers make no logical sense. The 80S ribosome is composed of the small ribosomal subunit (40S) and the large ribosomal subunit (60S). Each subunit is composed of rRNA and proteins. The same is true for the prokaryotic ribosome, except that the numbers are different. Here the 30S and 50S subunits complex to form the 70S ribosome.

Figure 6-61. A comparison of prokaryotic and eukaryotic ribosomes.
D. Translation Initiation

1. Prokaryote Translation Initiation

Differences between prokaryotic and eukaryotic translation are important as they are great places to target for development of new antibiotics. Prokaryote translation initiation is quite different from eukaryotes. It begins at AUG sequences, but only those that are proceeded by a Shine Dalgarno site. This is a purine-rich sequence of 3-9 bases that are positioned about 10 nucleotides upstream of the start codon (AUG or in some cases, GUG).

The Shine-Dalgarno sequence is complementary to the 3' end of the 16S rRNA in the prokaryotic 30S rRNA small ribosomal subunit. It will base pair with the 16S rRNA so the small ribosome correctly assembles on the translation initiation site. Thus, the AUG (or GUG) start codon is in the P-site of the 30S rRNA, which sets the reading frame for translation.
Prokaryote translation requires mRNA, the initiation tRNA with a bound fMet, the ribosomal subunits, and three initiation factors, IF1, IF2, and IF3.

A summary of the most important points regarding prokaryotic translation initiation is highlighted in the box. Below is a “step by step guide” with additional details to enhance your understanding.

* IF3 binds to the small ribosomal subunit (30S). It is the first factor to bind. It prevents the binding of the 50S large ribosomal subunit to the 30S subunit prior to binding of the Shine Dalgarno sequence and the initiation tRNA.

* IF1 binds to the small ribosomal subunit. It helps stabilize the 30S subunit. Some sources indicate IF1 binds to the A site and blocks incoming tRNAs from engaging prior to the start of elongation, but this is controversial.

* The 16S rRNA interacts with the Shine Dalgarno sequence through base pairing. This positions the 30S subunit so that the AUG (or GUG) start codon is in the P-site of the ribosome and sets the reading frame.

* IF2 (with a bound GTP) binds to fMet-tRNA\textsubscript{f} (the initiation tRNA with a bound formylmethionine) and together they bind the small ribosomal subunit. IF2 is the major factor promoting binding of the tRNA to the initiation complex. The GTP is required for binding but is not hydrolyzed at this time.

* IF3 is released

  * The 50S subunit joins with the 30S subunit to form the functional ribosome.

  * The IF2 bound GTP is hydrolyzed after the 50S subunit binds the 30S complex. The purpose of the hydrolysis is to release IF2 and IF1 from the complex so elongation can begin.
2. **Eukaryotic Translation Initiation**

Translation initiation is quite different in eukaryotic cells. The most important features of eukaryotic translation initiation are highlighted in the box with a more detailed explanation below.

*eIF2-GTP binds to the initiation tRNA. Availability of eIF2-GTP is an important regulatory step for translation.*

*eIF3, eIF1, and eIF1A bind to the small ribosomal subunit. They enhance the interaction of eIF2-GTP-Met-tRNAi with the small subunit. eIF3 inhibits association of the 60S subunit.*

*eIF2-GTP-Met-tRNAi binds to the 40S small ribosomal subunit, and the complex is recruited to the 5’ cap of the mRNA.*

*The 5’ cap region of the mRNA is bound by a complex of initiation factors. eIF4E is the cap binding protein that protects the mRNA from degradation and aids in determining the transcript is complete. eIF4G is required for binding of the small subunit, which is another important regulatory step (described later). eIF4A (with help from eIF4B and eIF4H) is a helicase that unwinds secondary structure at the 5’ end of the mRNA so the 40S subunit can scan for the first AUG. This complex of eIF4E, 4G, 4H, 4A and 4B is collectively called eIF4F.*

*The small ribosomal complex begins to scan for the first favorable AUG. This favorable context refers to a Kozak consensus sequence that surrounds the initiation codon and enhances the efficiency of translation initiation. The Kozak sequence does not bind to the ribosome, but simply puts the AUG into a context that encourages its recognition for initiation. The pre-initiation complex will skip the first AUG 5-10% of the time to find a more favorable one.*

*When the initiation AUG is identified, eIF5 stimulates hydrolysis of the eIF2-GTP. eIF2-GDP is released (along with other initiation factors) and Met-tRNAi is left in the P site of the ribosome. This promotes association of the 60S and 40S subunits. Elongation can begin.*

**Most of the control for translation occurs at the level of initiation.**

**Figure 6-70.** The initiation of protein synthesis in eukaryotes.
3. Reactivation of eIF2-GTP: a major regulatory step in translation
Reactivation of eIF2 is the rate limiting step of protein synthesis and is a major step in translation regulation. During protein synthesis, the GTP bound to eIF2 is hydrolysed to GDP. The GDP must be removed and replaced with GTP for eIF2 to participate in additional rounds of translation initiation. This reactivation or exchange is performed by a GEF (guanine nucleotide exchange factor) called eIF2B. Under normal conditions, eIF2-GDP binds to eIF2B, which induces a conformational change that makes the GTP binding site more accessible. The GDP is released and a GTP is bound in its place.

Figure 7-67. The eIF2 cycle.

Under conditions where a cell wants to inhibit protein synthesis (viral infection, apoptosis, nutrient or heme-deprivation, other stresses), eIF2-GDP is phosphorylated on serine-51. Several kinases can perform this task [heme-regulated kinase, protein kinases RNA-activated (PKR), protein endoplasmic reticulum kinases (PERK), general control nonderepressible 2 (Gcn2)] When phosphorylated, eIF2-GDP binds irreversibly to eIF2B. The GEF is then sequestered and inaccessible. Because there is a limiting amount of eIF2B in the cell, protein synthesis will quickly come to a halt.
E. Translation Elongation

1. The basics of polypeptide formation

The functional ribosome contains four binding sites- the A-, P-, E-sites and a binding site for the mRNA. The sites are very close together so that the reading frame is always maintained.

At the end of initiation, there is a Met-tRNA\textsubscript{A} in the P-site of the ribosome where the anticodon is base paired with the initiation codon (AUG). A tRNA with an anticodon complementary to the mRNA codon in the A-site will enter the ribosome. The interaction is only strong if there is a correct anticodon-codon pairing. The large ribosomal subunit will catalyze peptide bond formation between the amino acid in the P-site and the amino acid in the A-site. The carboxyl end of the peptide is released from the tRNA in the P-site and is joined to the free amino group of the amino acid linked to the tRNA in the A-site. The reaction is shown on the following page.

The reaction is accompanied by two conformational changes that shift the two tRNAs into the E-site and the P-site and move the mRNA forward exactly 3 nucleotides. Does the ribosome move or does the mRNA move? In the rough ER, the ribosomes are fixed so the mRNA must move, but for polyribosomes and free ribosomes in the cytosol, it is unknown which moves or if both move. Protein synthesis continues with the addition of the next amino acid in the polypeptide chain.

The mRNA is translated in the 5’ to 3’ direction and the peptide is prepared staring at the N-terminus. Synthesis is quite fast with eukaryotes adding about 2 amino acids per second.
This cartoon is a different view of how the ribosome functions with the A-, P-, and E-sites between the two ribosomal subunits.

Peptide bond formation is a nucleophilic addition-elimination reaction. The nitrogen on the amino acid being added attacks the carbonyl carbon of the amino acid attached to the tRNA in the P-site. A peptide bond is formed between the amino acids and water is released. The energy for the reaction comes from the high energy ester linkage formed during charging of the tRNA.
2. **Elongation requires elongation factors and GTP hydrolysis**

Two elongation factors are critical to eukaryotic translation: EF1α and EF2 (some references use the terms eEF1α and eEF2). Each is a GTP-binding protein; thus, two molecules of GTP are hydrolyzed each time an amino acid is added to a growing polypeptide chain.

EF1α-GTP binds to the aminoacyl-tRNA. It guides the tRNA to the A site of the ribosome and provides an opportunity for proofreading of the codon:anticodon match. EF1α introduces two lags during protein synthesis. The first lag is during GTP hydrolysis, and the second lag is when EF1α-GDP leaves the ribosome. This provides time for the tRNA to leave the ribosome if the codon:anticodon pairing is incorrect and prevent incorporation of the wrong amino acid into the protein. These two lags are largely responsible for the 99.9% accuracy of the ribosome in translating RNA into protein.

EF2-GTP uses the energy of GTP hydrolysis to reset the ribosome. The GTP hydrolysis induces a conformational change that moves the tRNAs in the P- and A-sites to the E- and P-sites, respectively and moves the mRNA forward by 3 nucleotides. EF2 is the target of diphtheria toxin (from *Corynebacterium diphtheriae*) and exotoxin A (from *Pseudomonas aeruginosa*).

In prokaryotes, elongation is quite similar to eukaryotes. The elongation factors have different names (EF1α = EF-Tu, EF2 = EF-G), and the GEF responsible for reactivating EF-Tu is termed EF-Ts. Their functions are the same in prokaryotic cells.

*Modified Figure 6-65.* There is an error in the textbook figure. The figure shows eukaryotic translation elongation, but the elongation factors are labeled as the prokaryotic factors, EF-Tu and EF-G. The figure in materials for this class have been modified to use the correct eukaryotic names: EF1α and EF2.
3. Reactivation of EF1α and EF2
As with other small GTPases, EF1α and EF2 are active when bound to GTP, but inactive when bound to GDP. EF1α-GDP binds to its GEF, EF1β, promoting the dissociation of GDP and binding of GTP. EF2 acts as its own GEF.

F. Translation Termination
In eukaryotes, the release factor, eRF, is a dimer composed of eRF1 and eRF3. eRF1 binds to all three stop codons, and eRF3 is a GTPase. eRF binds to the stop codon in the A-site of the ribosome. The bound GTP is hydrolyzed, and the ribosome catalyzes the addition of a water resulting in the release of the polypeptide. The protein synthesis machinery is disassembled and can be recycled for additional rounds of translation.

In prokaryotes, RF1 and RF2 recognize different stop codons. RF3 is the GTP binding protein similar to eRF3.

Figure 6-72 Termination of protein synthesis.
This is a summary of the different factors involved in translation in both prokaryotes and eukaryotes. Focus on the factors that were mentioned several times – eIF2, eIF4 (particularly 4A, 4E, 4G), EF1α, EF2, eRF.

G. Quality Control Mechanisms in Translation
Errors can arise at all steps of gene expression from transcription to protein folding. Errors in transcription, splicing, folding, or post-translational modification can all lead to non-functional or partially functional proteins; yet, translation itself appears to be the most error prone step in the path to creation of a functional protein. In a 2009 review article, Drummond and Wilke (Nat Rev Genet. 2009; 10: 715–724) argued that our knowledge regarding the error rate of translation is limited because “many mechanisms seem to have evolved to minimize the costs of erroneous protein synthesis.”

If we consider only translation, we can identify 5 “check points” or steps that we have discussed that are important factors in making protein synthesis as accurate as possible.
III. Comparison of Transcription and Translation in Prokaryotic and Eukaryotic Cells.
A. Important differences in transcription and translation between prokaryotic and eukaryotic cells.

(1) Site of Translation: In prokaryotic cells, transcription and translation are coupled. Protein synthesis can begin before mRNA synthesis is completed. In eukaryotic cells, transcription and translation are in separate compartments. mRNA is synthesized and processed in the nucleus and then transported to the cytoplasm for protein synthesis.

(2) RNA polymerase: There is one RNA polymerase in prokaryotic cells to transcribe all types of RNA while eukaryotic cells have a different polymerase for each of the three major RNA types.

(3) mRNA processing: Prokaryotic mRNAs are not capped, do not have a poly-A tail and are not spliced. The cap and the poly-A tail function in part to protect the eukaryotic mRNA as it transits from nucleus to the cytoplasm for translation. Because prokaryotic messages are transcribed and translated in the same compartment, the protection of the cap and poly-A tail are not required.

(4) mRNA structure: Both prokaryotic and eukaryotic mRNAs have a triphosphate group at the 5’ end, but only the eukaryotic mRNA acquires the 5’ cap, which is part of the structure recognized by the small ribosomal subunit. Therefore, protein synthesis usually begins at the start codon closest to the 5’ end of the mRNA. In prokaryotes, the 5’ end has no special significance, and there can be multiple ribosome binding sites (the Shine-Dalgamo sequence) in a single mRNA, each resulting in the synthesis of a different protein.

Internal ribosome entry sites (IRES) is an exception to this rule for eukaryotic mRNAs. IRES allow cap-independent translation to occur. This will be discussed in one of the lectures on gene expression.
(5) Ribosome structure: The rRNA and protein components of the ribosome differ between prokaryotes and eukaryotes, but in general, the function is relatively similar.

![Figure 6-61. Comparison of prokaryotic and eukaryotic ribosomes.](image)

B. Sensitivities to antibiotics.
Many antibiotics act on the transcription or translation machinery. Some act only on bacteria and take advantage of the differences between prokaryotic and eukaryotic transcription or translation. These are often used to treat patients. Other antibiotics target both prokaryotes and eukaryotes. These drugs can be used on patients, but only under conditions where the benefit to the patient outweighs the risk of damaging normal host cells. Actinomycin D may act on both prokaryotic and eukaryotic cells, but it is used as a cancer chemotherapy in children where it is often beneficial. Antibiotics that act only on eukaryotic cells are useful research tools.

Do not memorize this table. You will do that in Pharmacology next year! ☺

You need to understand the consequences of using antibiotics that work on bacteria only, on both bacteria and eukaryotes, or on eukaryotes alone.
IV. Creating a functional protein

Translation of an mRNA sequence into an amino acid sequence is not the end of the process of forming a protein. To function, the completed polypeptide chain must fold correctly into its three-dimensional conformation, bind any required co-factors, and/or assemble with any partner proteins required for its functional activity. Covalent modifications to select amino acids may also be required, such as glycosylation or phosphorylation. There are over 200 different types of covalent modifications that can occur.

Many of the features mentioned here – such as how do cells help newly synthesized proteins fold correctly and what happens when they don’t fold correctly – will be discussed in subsequent lectures.

Figure 6-77. Steps in the creation of a functional protein.