

The three-dimensional structure of this antibody drug can be found at [www.drugbank.ca/drugs/DB00072](http://www.drugbank.ca/drugs/DB00072)

Let us dwell on the structure of the light chain and heavy chain for a moment. In testing and marketing any polypeptide drug, pharmaceutical companies are concerned with the following drug stability issues. First, it is the case that long-term storage of polypeptides results in the spontaneous deamination of residues of glutamine (Q) and asparagine (N). Deamination can occur at various steps in the manufacturing process, during shipment, and during storage. Also, oxidation of cysteine (C) residues can occur during manufacturing, shipping, and storage. These types of damage may lower the potency of polypeptide drugs. The reader will be able to find the locations of Q, N, and C in the polypeptide chains of trastuzumab.

### III. THE 20 CLASSICAL AMINO ACIDS

The following reviews the 20 classical amino acids. Twenty *classical* amino acids exist, and these are listed, along with their abbreviations, in Table 1.1. The *non-classical* amino acids include homocysteine, selenocysteine (47) methionine sulfoxide, ornithine, gamma-carboxyglutamate (GLA) (48) phosphotyrosine, hydroxyproline (49) sarcosine, and betaine. A *protein* is a long polypeptide that is a linear polymer of amino acids, typically about 100 to 500 amino acids in length. The term *oligopeptide* refers to shorter polymers of amino acids in the range of about ten to 50 amino acids. Some non-classical amino acids, such as homocysteine, exist only in the free state, and do not become incorporated into any polypeptide. But other non-classical amino acids, such as gamma-carboxyglutamate and phosphotyrosine, occur in naturally occurring proteins because of a process called *post-translational modification*.

Knowledge of the amino acids is needed to understand the following pharmacological issues:

- Stability during manufacturing and storage
- Point of attachment of polyethylene glycol (PEG)
- Unwanted immunogenicity
- Immunogenicity that is desired and essential for drug efficacy.

The following concerns *in vitro* stability. For drugs that are oligopeptides or proteins, stability during manufacturing and storage is an issue because of spontaneous deamidation. Aswad and co-workers have detailed the deamidation of biologicals

<sup>47</sup> Brody T. *Nutritional Biochemistry*, 2nd ed. San Diego, CA: Academic Press. 1999;21, 825–827.

<sup>48</sup> Brody T, Suttie JW. Evidence for the glycoprotein nature of vitamin K-dependent carboxylase from rat liver. *Biochim Biophys Acta*. 1987;923:1–7.

<sup>49</sup> Brody, T. *Nutritional Biochemistry*, 2nd ed. San Diego, CA: Academic Press. 1999;21, 619–623.