4.3 CARBOHYDRATE VACCINES

Cell surfaces are covered by a complex array of glycoproteins, and these oligosaccharides have a crucial role in modulating cell–cell and cell–matrix interactions. Changes in this glycosylation pattern are a universal feature of tumor cells; therefore, these carbohydrate structures may serve as antigens for the elaboration of vaccines.[81] Several families of carbohydrates are expressed at higher levels in malignant cells; these tumor-associated carbohydrate antigens (TACAs) can be classified as follows:

1. Glycolipids, which contain a carbohydrate linked to a ceramide lipid that anchors the structure to the lipid bilayer of the cell membrane. They are further subdivided into several families, including the gangliosides (e.g., GM1), the globo- series (e.g., Globo-H), and the lacto- and neolacto- series (e.g., Lewis^y or Le^y).
2. Glycoproteins, including Tn, TF, and STn, in which the carbohydrate is covalently linked to the hydroxyl group of serine or threonine residues in the protein.

TACAs have several advantages for the preparation of vaccines. Because they are the most common antigens on the surface of cancer cells, their presence correlates very well with cancer progression, and they are shared by many cancer cell types. Furthermore, there is strong experimental evidence that anti-TACA immune responses increase the survival rate of cancer patients. The main obstacle to the development of anti-TACA vaccines has been problems with their isolation and purification from natural sources, which has required the development of methodology allowing their preparation by total synthesis.[82]

The first generation of synthetic anticancer vaccines to be evaluated on humans were monomeric because they were constructed from a single carbohydrate antigen conjugated to a carrier protein, most often the keyhole limpet hemocyanin (KLH) protein. The first antigen to be studied was Globo-H, a hexasaccharide that is overexpressed in the surfaces of several types of tumors, including colon, lung, ovary, and prostate, followed by Lewis^y (Le^y) and fucosyl GM1 (Figure 12.7). The most advanced of these compounds is the Globo-H–KLH construct shown in Figure 12.8, which is in phase II/III clinical trials for breast cancer.

The mucins are a group of glycoproteins that are overexpressed on tumor cell surfaces, and they show clusters of several carbohydrate domains. In an effort to achieve a resemblance to these structures, a second generation of monomeric anticancer vaccines was designed, which contained several units of mono- and disaccharides present in the mucins. These compounds are exemplified by the structures shown in Figure 12.9, and many of them are under clinical evaluation.

Monovalent vaccines have the disadvantage that they do not account for the presence of multiple carbohydrate antigens on the surface of tumor cells. One approach to solving this problem is the simultaneous administration of several antigens that have been previously shown to be associated to a particular type of cancer. Although this *polyvalent monomeric approach* has been shown to be successful in clinical trials, it does have some shortcomings, including the following:

1. The use of increased amounts of the carrier protein.
2. The need to carry out as many bioconjugation steps as antigens are present in the vaccine because each antigen is conjugated to a protein. These steps are low yielding and difficult to reproduce, and they constitute the bottleneck of the synthetic process.
3. The need for regulatory validation of each component of the mixture of antigens.