

### **1.3.2.1 Antibody-Based Targeted Delivery**

Much research has been focused on antibody-based targeting as this was seen to be the “magic bullet” described by Ehrlich. Recently, antibody-directed targeting has progressed to the market: gemtuzumab ozogamicin (Mylotarg<sup>®</sup>) is an antibody against CD33 conjugated to calicheamicin for the treatment of leukaemia (Wyeth, 2003). This is the first antibody-drug conjugate to enter routine clinical use. Each antibody has 2-3 molecules of calicheamicin covalently bound to it. Once the conjugate is internalised calicheamicin is released in the endosome/lysosome via the degradation of a pH-sensitive linker and binds DNA in the minor groove causing double strand breaks which kills the cell. Trastuzumab (Herceptin<sup>®</sup>) is an antibody against the epidermal growth factor receptor 2 protein (HER2) (Genetech, 2000) for treating breast cancers that is available clinically. In this case the antibody itself is the therapy. This toxicity is described as antibody-dependent cellular cytotoxicity.

Although antibody-based targeting has been the most successful strategy so far and offers very selective targeting, with tumour specific antigens such as prostate-specific membrane antigen (PSMA) (Bander et al., 2003). However, the use of antibodies has several disadvantages:

- Identification of an appropriate antigen
- Difficulties in large scale production
- Cost
- Possible immune reactions – inducing the human anti-mouse antibody response
- Large size – limits number of antibodies which can be attached to a carrier
- Size limits tumour penetration (Bagshawe, 1995, Shadidi & Sioud, 2003)
- Blood clearance can be quick
- Internalisation of antigen/antibody complex does not always occur
- Cross-reactivity with normal tissue (Ross et al., 2004)

Methods to help overcome some of these disadvantages have been developed. For example: immune reactions are reduced by the production of humanised monoclonal antibodies, clearance can be decreased by pegylation (Leong et al., 2001), antibody fragments are being used to reduce their size. Internalisation is not required in all cases, e.g. radionuclide imaging (Ke et al., 2004).

Antibody-based targeting employed in non-viral gene delivery is discussed in Section 1.5.3.