

Antibody Therapeutics

1. What is an Antibody?

Monoclonal antibodies are produced by the B-cells of the immune system and are a key component of the body's armoury for fighting disease. Each antibody is able to recognise and bind to a specific target, known as an antigen. Antibodies contribute to immunity in three ways: they prevent pathogens from entering or damaging cells by binding to them; they stimulate the removal of pathogens by macrophages and other cells by coating the pathogen, bringing it to the attention of these cells; and they trigger the destruction of pathogens by stimulating other immune responses such as the complement pathway.

Antibodies are composed of two identical heavy chain molecules and two light chains. The ability to bind to different antigens comes from the variable regions of the light and heavy chains (VL and VH), as the antigen binding site is formed at the interface of these two domains. Each variable region contains three Complementarity Determining Regions (CDRs), which are the most variable sections. These are the regions of the antibody that bind directly to the antigen. The diversity of the variable regions comes initially from the recombination of numerous genetic segments. Antibodies with higher specificity and affinity for particular targets are created in the body following antibody-antigen binding, as this triggers somatic mutation and mutants that are better at binding the antigen can be selected.

2. Drug development process

The process of developing an antibody drug involves several steps and can take many years. Before any drug candidates are selected researchers carry out numerous studies to confirm the validity of a particular target. Antibodies can then be found that interact with the target, for example by screening antibody libraries such as n-CoDeR[®]. As binding an antigen is only one feature of a successful therapeutic antibody, the drug candidates are tested both in vitro and in vivo to see which of them meets the requirements for efficacy and safety. The most successful candidate is taken forward to the next phase of development.

A larger amount of antibody is required for preclinical and clinical development, so production of the molecule needs to be ramped up. This involves creating stable mammalian cell lines that express and secrete the antibody, as these can be grown on a large scale in fermenters. Before studies can begin in humans, in vivo studies must be conducted to check the safety of the drug candidate and to answer questions about its behaviour, for example how long does the drug remain in the body and how is it broken down? These help to set an appropriate dose level for clinical studies which can be carried out following approvals from the relevant authorities. Three phases of clinical studies are required before a drug can be approved for sale. Phase I studies examine the safety and behaviour of the drug in healthy people; Phase II studies analyse the effects of the treatment in a small group of patients; and Phase III studies look at the drug's effect in a wider range of patients, comparing its effects to currently available treatments. If these are all successful then a drug may be approved for commercialisation.

3. BioInvent's approach

BioInvent is developing a number of antibody drugs, both on its own and in conjunction with partners. Three of these antibodies are currently in clinical development, TB-402, TB-403 and BI-204, and BI-505 is undergoing preclinical development.

To support the discovery of new antibody candidates, BioInvent has created a library of antibodies, called n-CoDeR[®], that contains 20 billion human antibody genes. These fully human antibodies all contain the same naturally occurring antibody framework structure but each has a different antibody binding segment. The way that the library has been designed means that it contains antibodies that can bind to a wider range of antigens than would be possible using naturally occurring antibodies alone. High affinity antibodies can be fished out of the library using cells, proteins or peptides as bait, leading to a wider variety of antibodies than found in nature. Because n-CoDeR[®] antibodies are fully human they are less likely to cause patients to launch an immune reaction against the antibody themselves. In addition, the framework has been designed to minimise the antibodies' immunogenicity and maximise its stability, making the antibodies ideal for developing into drugs.

4. Antibody market

Monoclonal antibodies (mAbs) are the fastest growing class of drugs with an annual growth rate of about 30 percent. In total, over 20 antibody drugs have been launched, generating sales of US \$25 billion in 2007 (US \$18 billion in 2006). The main advantages of using monoclonal antibodies are the high levels of specificity and affinity that the molecules have for their targets. This means that there is a reduced risk of associated side effects and an increased probability of creating a successful treatment. In addition, preclinical development tends to be faster and less costly than it is for small molecule drugs.

The first therapeutic mAbs were mouse antibodies specific for human protein targets. However, in the clinic these drugs frequently encountered problems caused by patients' immune responses against the mouse proteins. Technological advances have enabled the production of molecules with more human characteristics: chimeric; humanised; or fully human antibodies, reducing the problems of immunogenicity and enabling the success enjoyed by this treatment class.