

The long and winding road to antibody therapeutics

John McCafferty

University of Cambridge; Department of Biochemistry; Cambridge, UK

Most of the 400,000 patients who have received the drug adalimumab (Humira) will be aware that they have been given an antibody drug. Many will know that it is used to treat auto-immune diseases such as rheumatoid arthritis, ankylosing spondylitis, chronic plaque psoriasis and Crohn disease. Some may even realise that adalimumab acts by neutralising tumour necrosis factor (TNF), an important pro-inflammatory mediator. Very few of those patients however (or even the medics who prescribe it) will know or care about phage display, the underlying technology which led to the creation of the drug which they receive.

Scientists involved in the development and first use of phage display 20 years ago, can forgive this careless neglect of the facts! The process of drug development is a long one. In the case of adalimumab, the process started in 1993, when BASF Pharma commissioned Cambridge Antibody Technology (CAT) to make a TNF neutralizing human antibody, using the newly described phage display technology. Within 2 years, the lead compound that became adalimumab had been identified and the drug candidate passed onto a new journey. The expertise of many hundreds of professionals steered the candidate drug through pre-clinical and clinical testing, manufacturing, regulatory affairs, approval and marketing. The smaller companies involved at the outset were swallowed up into larger organizations. Many thousands of patients participated in clinical trials leading to the approval of this drug in 2002. Unsurprisingly, the focus on the initial drug discovery technology blurs as the product passes from one group of professionals to the next. What matters to patients and clinicians in

the end is that the drug works and is available for their benefit.

Those who have contributed to the development of drug discovery technologies and indeed manufacturing technologies need not be depressed! To be in a position to discuss your technology in relation to patient awareness (or lack of it!) is itself a privilege. Few people get to see the fruits of their efforts turn into life-changing patient benefit. As with most scientific endeavors, there are many contributors to this success story ranging from those working directly on the drug through to the community of researchers who publish in their field and who inspire and invigorate their peers at meetings and presentations.

Beyond adalimumab, there is even greater satisfaction for the technology pioneers in the knowledge that this will not be a "one-off". Phage display, together with more recent display technologies such as ribosome and yeast display are likely to provide many more binding molecules of exquisite specificity over the coming years for the benefit of patients. Other technologies have been developed, adding to the armory of tools available for drug discovery. For example, immunization of transgenic mice, where murine antibody genes have been replaced by human antibody genes, have provided an additional route to generation of antibody-based drug leads. Transgenic mouse technology has been particularly successful in delivering 4 approved drugs, including 3 in the last 18 months targeting IL12 (ustekinumab; Stelara™), CD20 (ofatumumab; Arzerra) and TNF (golimumab; Simponi™). While the emergence of antibody drugs from display technologies has lagged behind transgenic mice,

(in part due to a complex intellectual property landscape and freedom to operate issues), more antibody drugs from display technologies are on the way. For example, belimumab (BENLYSTA®), which controls B-cell activity and reduces auto-antibody production in systemic lupus erythematosus (SLE), will hopefully be approved later in 2010. Belimumab, which was generated by CAT in association with Human Genome Sciences, will be the first new treatment for SLE in 50 years. In addition, raxibacumab is undergoing regulatory review in the United States and a variety of other antibodies from display technologies and transgenic mice are in advanced clinical trials.

The field of therapeutic antibodies has come a long way in the last 20 years. In 1990 there was a single murine antibody approved for therapy. Now there are nearly 30 approved products, many of which have come from "humanization" of murine monoclonal antibodies. It has become clear that antibodies make effective therapeutics (although intracellular targets are still "off-limits"). More importantly an armory of mature technologies is available for the creation of binding molecules to provide drugs of the future.

The creation of human antibodies has become reliable and the bottlenecks for antibody drug development now lie elsewhere. As more pharmaceutical companies circle around fewer viable targets, the identification of new validated targets will become a limitation for drug developers in the coming years. Furthermore, the cost and timescales involved impose additional and significant limitations to drug development. Any progress in reducing the escalating costs and increasing regulatory burden would not only reduce

Correspondence to: John McCafferty; Email: jm635@cam.ac.uk

Submitted: 07/19/10; Accepted: 07/19/10

Previously published online: www.landesbioscience.com/journals/mabs/article/13088

DOI: 10.4161/mabs.2.5.13088

healthcare costs, but should increase the availability of antibody drugs to wider groups of patients and permit the development of more refined combination therapies.

2010 marks the 20th anniversary of the development of phage display and researchers and drug developers will come together in Cambridge this autumn to celebrate. Like others before them they have learned that the journey from drug discovery technologies to an approved therapeutic is a long one, but ultimately a very satisfying one.

©2010 Landes Bioscience.
Do not distribute.