Case Monoclonal antibodies

by

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Introduction

***Monoclonal antibodies** (**mAb**) are monospecific antibodies that are made by identical immune cells, which are all clones of a unique parent cell – in contrast to polyclonal antibodies, which are made from several different immune cells. Monoclonal antibodies (red in the figure below) have monovalent affinity, in that they all bind to the same epitope (the part of an antigen (blue) that is recognized by the antibody).*

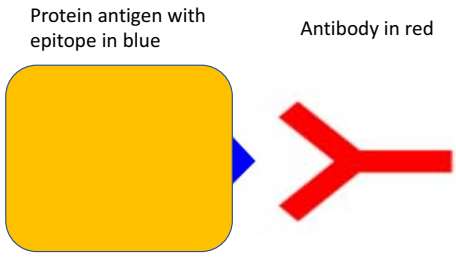

Figure. Monoclonal antibody binding to an epitope.

Monoclonal antibodies are widely used, not only for basic research and diagnostic purposes but also for treatment of several human conditions, such as transplant rejection, rheumatoid arthritis and breast cancer.

Monoclonal antibodies against the cytokine, Tumor Necrosis Factor (TNF), is a subgroup of monoclonal antibody products, that are used for treatment of different autoimmune diseases, such as rheumatoid arthritis. TNF is produced in

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harmful concentrations in many patients with this disease, and the monoclonal antibodies block the harmful activity of TNF.

Commercialisation of the monoclonal antibody technology for therapeutic use

It may take a long time for new technologies to mature to the point, where they can be applied for production of pharmaceutical drugs. For example, therapeutic monoclonal antibodies are currently a very popular technology for developing new pharmaceutical treatments of disease, but it took many years of development for this technology to be used for pharmaceutical treatments.

In 1975, Georges Köhler and César Milstein succeeded in making fusions of myeloma cell lines with B cells to create hybridoma cells, which were immortalized and could produce mouse antibodies specific to known antigens. They shared the Nobel Prize in Physiology or Medicine in 1984 for the discovery.

In 1988, Greg Winter and his team pioneered a technique to humanize the mouse monoclonal antibodies, eliminating the side reactions that many monoclonal antibodies of animal origin caused in some patients. Since then, fully human monoclonal antibodies were developed using different technologies, such as phage display and transgenic mice.

Timelines for commercialization of therapeutic monoclonal antibodies:
First publication in 1975 (no patent application filed).
First therapeutic murine monoclonal antibody: Orthoclone in 1986.
First therapeutic chimeric mouse-human monoclonal antibody: ReoPro in 1994.
First therapeutic humanized monoclonal antibodies: incl. Rituxan in 1997.
First therapeutic human monoclonal antibody: Humira in 2002.

Further refinements of the monoclonal antibody technology have been developed since the launch of Humira in 2002. Monoclonal antibody therapies came only in wide use with the maturation of technology development enabling large scale production of fully human monoclonal antibodies.

Innovation S curves and monoclonal antibodies

The technology of monoclonal antibodies is recognized as being highly disruptive compared to the practice of developing traditional, small-molecule therapeutics. Research suggests that technological evolution can be described by a logistic S-curve in which the monoclonal antibody technology advances rapidly before approaching limits that are based on the inherent properties of the technology (McNamee L.M. et.al. 2012).

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Patterns of the monoclonal antibody technology include periods of rapid growth and limits that can be approximated by a logistic S-curve, as well as the sequential emergence of new technologies.

Four distinct classes of monoclonal antibody technologies are historically distinguished on the basis of the fraction of the protein sequence that is derived from mouse and/or human sequences: mouse antibodies, chimeric hybrid antibodies, humanized hybrid antibodies, and fully human antibodies.

The publication record on monoclonal antibody technology developments has the features of S–curves. Publications on mouse monoclonal antibodies were the first to emerge, followed by those on chimeric, humanized and human monoclonal antibodies. Humanized and chimeric monoclonal antibodies entered an exponential phase of growth at the same time, but there are more publications on humanized than on chimeric monoclonal antibodies. More than 500 monoclonal antibodies have entered clinical trials. For mouse, chimeric and humanized antibodies, the number of publications is highly correlated with the number of patents and products entering trials each year (McNamee L.M. et.al. 2012).

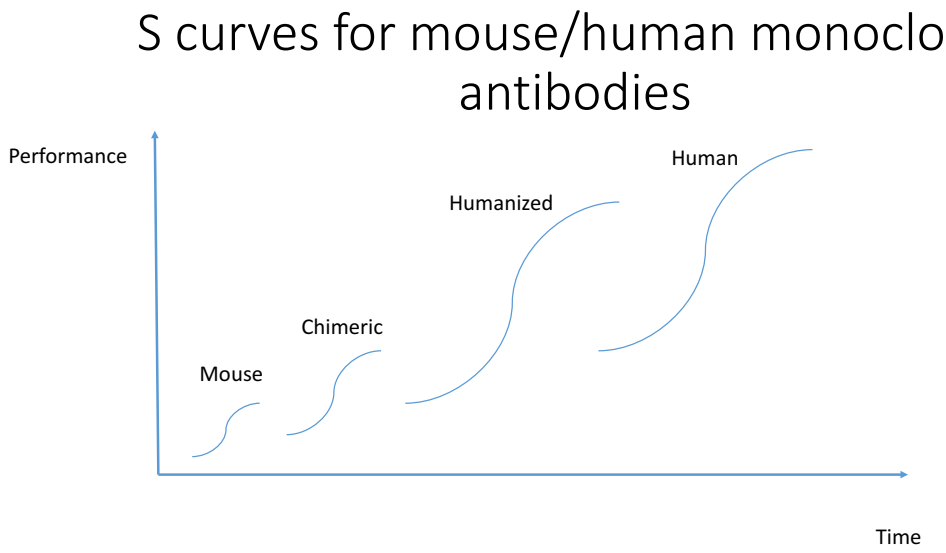

Figure. S curves for monoclonal antibodies.

Each of the technology improvements for monoclonal antibodies was invented explicitly to circumvent limitations of the previous technologies and to expand their therapeutic potential. For instance, mouse monoclonal antibodies elicit a strong, anti-mouse antibody response in humans, limiting their applications requiring repeated administration. In response, efforts were made to develop

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human monoclonal antibodies. Initial attempts failed because human hybridoma cell lines did not produce sufficient amounts of monoclonal antibodies. To circumvent this problem, chimeric and humanized mAbs were developed, which used mouse hybridoma technology in combination with recombinant DNA technology. Only with the advent of transgenic mouse and phage display technologies, which enabled methods for large-scale production of human antibodies, did the rate of publication on human monoclonal antibodies accelerate.

Rapid growth of publications in monoclonal antibody technologies corresponded with advances in complementary production technologies, including hybridomas and transgenic mice. In this respect, the patterns of early technology evolution parallel to the experience of many biotech companies. Biotech companies often have intellectual property and expertise related to the therapeutic modality, but sometimes lack component technologies – such as gene sequences, targets, delivery technologies, chemistries or manufacturing capabilities – that constitute essential resources or processes for successful product development.

Monoclonal antibodies for treatment of rheumatoid arthritis

The cytokine TNF alpha is found abundantly in the inflamed synovial tissue. TNF alpha is thought to play a role in several processes that mediate rheumatoid arthritis, including regulating the production of prostaglandins (enzymes which damage the joints), stimulating the proliferation of synovial fibroblasts, increasing the expression of adhesion molecules, and stimulating the production of other cytokines, including several types of interleukins. Thus, neutralising the activities of TNF alpha was found to be a novel way of treating rheumatoid arthritis. These findings identifying TNF as a target for treatment were made by researchers at academic institutions. The subsequent development of pharmaceutical products was made by companies based on in-licensing agreements and in-house developments in a closed innovation environment.

The first treatment of autoimmune disease by neutralising TNF alpha was the Remicade product from the company Centocor. Remicade (infliximab) is a humanized monoclonal antibody fragment, that directly binds to and inhibits TNF alpha. In September 1998, Remicade was approved for the treatment of Crohn's disease, an inflammatory disease that affects the gastrointestinal tract. Remicade was subsequently approved for treatment of rheumatoid arthritis in 2004. Treatment is conducted by intravenous infusion every two months. The average annual cost of the treatment was $5-8,000.

Almost at the same time Enbrel became the second pharmaceutical drug with a mechanism of action of neutralising TNF. Enbrel is a soluble TNF receptor

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which acts as a decoy to endogenous TNF. Enbrel was approved for marketing on November 2, 1998 and as second-line therapy for moderate to severe rheumatoid arthritis in patients, who did not respond adequately to one or more disease-modifying drugs, or in combination with methotrexate in patients not responding adequately to methotrexate alone. Treatment was twice a week in the patient's home. The average annual cost was $11,400.

These treatments were much more efficacious treatments of responding patients compared to other existing treatments. A major downside from a society cost point of view was the product pricing as illustrated by the pricing structure in the UK. One year treatment for an adult with rheumatoid arthritis was:

Enbrel: 8,450£
Remicade: 10,829£
Methotrexate (the existing standard treatment): 18-57£

For pharmaceutical companies these new monoclonal antibody treatments became important revenue drivers. The business field of monoclonal antibodies for treatment of cancer and autoimmune diseases such as rheumatoid arthritis attracted many companies.

The companies secured further growth by expanding the number of disease indications which could be treated by using the monoclonal antibodies. This created new commercial markets for the products without the need to repeat preclinical toxicity and safety activities or phase I clinical trials. Thus, Remicade, was approved first for Crohn´s disease in 1998, then rheumatoid arthritis in 1999, then ankylosing spondylitis in 2003, then psoriatic arthritis in 2004, then ulcerative colitis in 2005, then paediatric inflammatory bowel disease in 2005 and then psoriasis in 2006.
Remicade was developed at NYU School of Medicine and Centocor. Johnson & Johnson acquired Centocor in 1999. Remicade was licensed in the EU by Schering-Plough, which was acquired by Merck & Co in 2009.

Remicade has two drawbacks, intravenous injection is needed, and the antibody is a chimeric mouse-human antibody, which means that the immune system of treated patients responds to the foreign mouse part of the antibody and neutralises the effect of the treatment over time.

Thus, many companies, developed new anti-TNF alpha treatments based on fully human monoclonal antibodies.

The monoclonal antibody, Humira, became the first fully human monoclonal antibody against TNF alpha. Humira or Adalimumab was created using phage display technology and produced in a mammalian CHO cell line.
Humira was developed by Cambridge Antibody Technology (CAT) in collaboration with BASF Knoll. Abbott acquired BASF Knoll in 2000 and took

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over development, manufacturing and marketing of Humira. The Abbott spin-out company Abbvie got hold of the rights in 2013.
The antibody was commercialised using a similar commercialisation strategy of disease indication expansion as used for Remicade. Thus, Humira were approved for the following disease indications: rheumatoid arthritis (2002), psoriatic arthritis (2005), ankylosing spondylitis (2006), Crohn´s disease (2007), polyarticular juvenile idiopatic arthritis (2008), Psoriasis (2008), Ulcerative Colitis (2012) and paediatric Crohn´s disease (2012, EU).
Humira is administered to patient by subcutaneous injection using a Humira Pen or a prefilled syringe. Thus, patients were offered a more convenient self-injection every other week.

Competition developed in commercialising more anti TNF products with new products offering increased convenience to patients and/or more easy and less costly manufacturing processes.
One such product was Cimzia, Certolizumab pegol, a humanized antibody fragment conjugated to 40kDa polyethylene glycol, providing a longer half-life of the protein (and thus less frequently injections needed for patients). This smaller antibody fragment is manufactured in a less costly *E. coli* based manufacturing process.
Cimzia was developed by Celltech, which was acquired by UCB in 2004. The product was approved in several indications: Crohn´s disease (2008, US only), rheumatoid arthritis (2009) and psoriatric arthritis (2013, US).
The product is administered to patients by subcutaneous injections using a prefilled syringe by up to once monthly self-injections by a recognised ease of use device.

Competition was further expanded by companies pursuing strategies of developing monoclonal antibodies against other biological targets than TNF alpha such as Rituxan against the CD20 target and several monoclonal antibodies against the IL-12 target. With this strategy companies hope to develop treatments which also work for patients, who do not respond to the anti TNF alpha treatment.

Some companies develop small molecule pharmaceuticals acting against intracellular targets, which mediate the biological activities of immune factors such as TNF alpha.

Finally, some companies develop a biosimilar monoclonal antibody strategy as the patents of Remicade and Humira expired in 2015/2018 and 2016/2018 respectively.

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