Monoclonal antibody therapeutics: Leading companies to maximise sales and market share

Karl Ziegelbauer and David R. Light

Date Received (in revised form): 26th October, 2007

Karl Ziegelbauer
is a Vice President for Protein Therapeutics at Bayer HealthCare AG. He received his PhD from the University of Tübingen. For the past 14 years, he has been involved in drug discovery in various positions with increasing responsibilities in Germany, Japan, and the United States. His experience covers all aspects of drug discovery in various indications up to proof of concept in humans as well as lifecycle management and research alliance management.

David R. Light
received his PhD from the University of Wisconsin and completed a fellowship at the Massachusetts Institute of Technology before joining the newly formed Biocatalysis Department (later Genencor) in Genentech. He joined Berlex, a wholly owned subsidiary of Schering AG, as a protein chemist to develop biologic therapeutics including soluble thrombomodulin in Cardiovascular Research and later was project team leader of the factor Xa inhibitor project. Most recently, he headed the Antibody Technology Group focussing on antibody targets in cancer before joining the Protein Therapeutics group in Bayer.

Abstract

A close look at the biology and pharmacology of monoclonal antibodies reveals both their continuing promise as therapeutic agents to address unmet medical needs, as well as a number of challenges to the future discovery and development of this unique class of biologics. A remarkably consistent experience of reliable clinical efficacy and safety ensures that Biotech and Pharma have strong incentives to accelerate the antibody drug discovery process. Their attractive commercial potential invites consideration of potential challenges to the future expansion of the monoclonal antibody drug market. Four challenges arise from scientific and technical aspects of the antibody drug format: drug target limitations, biodistribution limitations, species specificity issues, and limitations to the route of administration and four challenges are based in the commercial and clinical use of antibody drugs: cost of goods, product differentiation within the antibody market, competition from small molecule drugs, and price sensitivity of clinical acceptance. Despite these challenges and recent setbacks, such as the withdrawal and subsequent relaunch of Tysabri and the TGN1412 Phase I disaster, the prevailing opinion is that monoclonal antibodies will continue to be safe and effective medicines that are worthy of commercialisation.

Journal of Commercial Biotechnology (2008) **14,** 65–72. doi:10.1057/palgrave.jcb.3050081;
Published online 27 November 2007;

Keywords: *monoclonal antibody drugs, biologic therapeutics, antibody market*

Correspondence: Karl Ziegelbauer, Protein Therapeutics, Bayer HealthCare AG, Wuppertal 42096, Germany
Tel: +49 202 36 5293
Fax: +49 202 36 4585
E-mail: karl.ziegelbauer@bayerhealthcare.com

INTRODUCTION

The usage of immune horse antiserum to treat severe infectious diseases such as tetanus and diphtheria at the end of the 19th century was

the first application of therapeutic antibody drugs. Over a century of experience with biological drug products derived from human or animal serum followed, including polyclonal immunoglobulin antibodies to treat severe infections and snake bites, as well as the development of serum protein drug products to treat genetic or acquired deficiency diseases such as diabetes and haemophilia. This valuable knowledge base in the production, formulation, delivery, and clinical usage of serum-derived protein drugs set the stage for the rapid expansion of biotechnology-derived protein therapeutics beginning in the 1980s driven by advances in both recombinant DNA and monoclonal antibody technologies. These early years also previewed challenges that continue to impact the development of protein-based therapeutics including the formation of antibodies by patients that may neutralise the activity of a biological drug or trigger adverse reactions ranging from mild fever to life-threatening anaphylactic shock during repeated treatments.

Over two decades of the current biotechnology era has been characterised by intense research to develop antibody-based drugs beginning with the first clinical testing of mouse monoclonal antibodies. Now the industry standard has shifted away from non-human and chimaeric antibodies to focus on fully human or humanised antibody drug candidates. Significant advances in the discovery of human monoclonal antibody drug candidates have resulted in novel approaches utilising both *in vivo* and *in vitro* methods. *In vivo* approaches focus the power of the vertebrate adaptive immune system to directly create potent human antibodies in transgenic animals or non-human antibodies that are subsequently humanised. *In vitro* approaches are driven by advances in antibody library design[1] and these antibody libraries are subsequently used for selecting and increasing the affinity of human antibodies displayed on ribosomes, phage, bacteria, yeast, and mammalian cells derived from human B-cells. The potential of this accumulated technology is truly impressive, allowing the formation of polyclonal mixtures of fully human monoclonal antibodies with a thousand-fold improved potency and the potential to treat severe infectious diseases such as botulism.[2]

THE CURRENT ANTIBODY DRUG MARKET

The natural role of antibodies is to block infectious disease by binding foreign agents or infected cells leading to activation of the host immune system. Only one of the 21 current marketed drugs (Synagis, respiratory syncytial virus, MedImmune) and none of 38 advanced clinical antibody drug candidates, however, are designed for this type of application.[3] Some antibody drugs or drug candidates that target leukaemia, lymphoma, or severe autoimmune disease do bind to B-cell or T-cell-associated surface antigens (CD-20 or CD-52) in order to trigger depletion of their target cells by complement or Fcγ-receptor-mediated mechanisms; however, cell depletion by the immune system is not the goal of the majority of antibody therapeutics. Instead, the field has advanced by discoveries that create new functionalities for monoclonal antibodies, including receptor binding to modify activation, prevent dimerisation, trigger internalisation, block proliferation, or induce apoptosis, binding, and neutralisation of cytokines or growth factors, and targeting chemical, protein, or radioactive toxins to target cells. Largely as a result of the discovery of these and other novel functionalities, antibody drugs are now breakthrough therapies for a variety of diseases, especially in the area of oncology and severe immunological disease indications.

The current market size for monoclonal antibodies is estimated to be over $20bn (US). This market is dominated by five antibody drugs Avastin (bevacizumab), Herceptin (trastuzumab), Humira (adalimumab), Remicade (infliximab), and Rituxan (rituximab), which together account for ~80 per cent of market. In some estimates, the

antibody market is projected to grow to $30bn or even more over the next 3–6 years, driven mainly by oncology applications.[4,5] This growth will include a mixture of new therapeutic applications for marketed antibody drugs, improved antibodies aimed at clinically validated targets, and the introduction of novel antibody drugs to novel targets.

Recent trends indicate that large Biotech increasingly relies on an ageing portfolio of approved protein therapeutics;[6] therefore, these projected market increases may need to be adjusted if the rate of successful launches leading to novel antibody drugs begins to slow. Biotech and Pharma, however, have a compelling incentive to accelerate the antibody drug discovery process because the commercial aspects of this drug modality remain very impressive. Therapeutic antibodies have a high drug approval success rate once they reach clinical testing (29 per cent for chimaeric antibodies, 25 per cent for humanised antibodies compared to a success rate of approximately 11 per cent for small molecules).[7] In addition, much of the development and clinical experience that is gained from the generation and optimisation of one antibody product can be readily applied to subsequent therapeutic antibodies, diminishing some of the development, manufacturing, and clinical risks that are intrinsic to drug development.

Owing to their exquisite specificity and ability to affect unique biological functions, monoclonal antibodies have the potential to provide a continued source of effective, safe, and reliable therapies. The introduction of such new therapies will benefit patients having a variety of debilitating diseases that otherwise respond poorly to alternate approaches. Based on the impact of the successful discovery of novel antibody functions on the current portfolio of antibody drugs, it is likely that the ability to continue to engineer novel functionalities by using new antibody formats will drive the expansion of the antibody drug market in the future.

POTENTIAL CHALLENGES TO THE FUTURE OF ANTIBODY DRUGS

The discovery of a continued stream of monoclonal antibody-based therapies offers tremendous opportunities for Pharma and Biotech companies, but also harbours a variety of scientific and commercial challenges. Currently, 21 monoclonal antibodies are approved for therapeutic use, 11 of which are humanised, five chimaeric, three of murine origin, while only two are fully human antibodies. In contrast, of 38 antibodies in advanced clinical testing, 31 are either humanised (14) or fully human (17). These numbers confirm that human antibodies are now the standard of the industry, whether obtained by *in vivo* (immunisation) or *in vitro* (antibody display) methods. Given the large number of antibodies in clinical trials or preclinical development, it is clear that technologies for the discovery of human antibodies are not rate limiting. Rather, the key to success will either be to identify the most effective, novel, and proprietary target in a complex pathological setting, or to identify a more effective approach to a known target, and both will be guided by emerging target validation approaches.

It is instructive to consider eight challenges to the future expansion of the monoclonal antibody drug market. Four of these challenges arise from scientific and technical aspects of the antibody drug format: drug target limitations, biodistribution limitations, species specificity issues, and limitations to the route of administration. The remaining four challenges arise from a consideration of the commercial and clinical usage of antibody drugs: cost of goods, product differentiation within the antibody market, competition from small molecule drugs, and price sensitivity of clinical acceptance.

Drug target limitations

Following intravenous injection, antibody drugs access targets in the extracellular and vascular

space. The Fc domain of the IgG format interacts with the endothelial FcRn receptor, facilitating access to the perivascular space after transient movement through the endothelium; however, the interior of these endothelial cells is not targeted. Antibody immunotoxin conjugates utilise antibody internalisation following receptor binding, but the goal of this application is delivery of the toxin payload to the intracellular space, not delivery of the antibody itself, which is rapidly hydrolysed. Disulphides that are needed to maintain the dimeric structure of the IgG format break down in the reducing environment of the intracellular cytosol and deactivate the potent binding of the antibody. Thus, antibody drugs are limited to extracellular targets.

The consequence of this limitation can be appreciated by considering the rich list of intracellular drug targets, several of which are targeted by small molecule drugs that are market leaders. These intracellular targets include HMG-CoA reductase (statins), nuclear hormone receptor agonists or antagonists (glucocorticoid, oestrogen, progesterone, etc), phosphodiesterase (PDE5), immunophilins (cyclosporine, FK506), and kinases (receptor tyrosine kinase, thymidine kinase). Even when limited to the extracellular arena, there appears to be a preference for prominent antigens on extracellular domains or soluble ligand targets. Thus, a notable omission from the list of extracellular targets that have been addressed by advanced antibody candidates include the seven-transmembrane receptors. In this large and ubiquitous family of membrane receptors are the G-protein coupled receptors (GPCR) that are often therapeutic targets for small molecule drugs. Technical advances may expand the range of extracellular targets for antibody drugs to include the GPCRs; however, it is not likely that the natural limitations of antibodies will be overcome to allow access to valuable intracellular targets.

Biodistribution limitations

Significant biodistribution and tissue penetration challenges limit the application of antibody drugs. Solid tumours make up the majority of human cancers (~85 per cent). To date, nine antibodies have been approved for the treatment of human cancers, but only three target solid tumours and one of these, bevacizumab, is actually directed towards a soluble ligand target, not to its cell surface receptor expressed on cells inside the solid tumour tissue. This suggests that additional barriers are associated with the treatment of solid tumours that are not present for haematological malignancies. These limitations need to be addressed before the successful treatment of human solid tumours by antibody drugs can expand. Even greater challenges may exist for other disease indications in privileged tissue like the central nervous system. When faced with these challenging biodistribution applications, the high-molecular-weight IgG format may ultimately fail to achieve the required tissue penetration. In the future, this natural antibody format may be replaced by protein drugs derived from alternate antibody formats or antibody mimetic scaffolds. It remains to be determined whether these molecules are able to more effectively access poorly vascularised tumours or tissues protected by the blood–brain barrier.

Species specificity issues

One of the valuable properties of antibody drugs is their exquisite specificity, allowing them to bind one particular epitope in the presence of many other similar binding targets. This may, however, lead to extended preclinical development times for antibody drugs because antibodies to a human target may not bind the similar target molecule in species commonly used for efficacy or safety testing (mouse, rat, rabbit, dog, etc). In addition, well-known recent clinical results indicate that the species specificity of Fc receptor binding must be given greater consideration during development of future antibody drugs.

There is not one universally accepted solution to the issue of species specificity of

antibody epitope recognition; however, there are a number of potential solutions, all of which add time or require significantly more resources for antibody drug discovery. One potential solution is to develop two separate antibodies in parallel in order to include one antibody that recognises the antigen in a species used for animal testing. Another solution is to establish transgenic mice expressing both the human target protein and the necessary human auxiliary proteins in order to allow testing of human-specific antibodies in transgenic mouse models. A third potential solution is to screen antibodies that recognise both the human and the mouse antigen and advance only those candidate antibodies with dual species specificity. This option harbours the potential risk of discarding unique antibodies to a functional human epitope not found on the mouse homologue. A final potential option would be to complete the entire concept validation studies *in vitro* utilising human cell or tissue-based models. Then, the first *in vivo* proof of concept would be in human clinical studies; however, the acceptance of this approach is problematic in the post-TGN1412 era.

The major lesson arising from the disastrous clinical testing of TGN1412 (anti-CD28 IgG T cell superagonist) is that special caution is needed in the design and execution of 'first in man' clinical trials.[8] In addition, however, based on this tragic event, an increased emphasis on preclinical consideration of Fc receptor interactions is likely to be required by regulatory agencies.[9] The 'cytokine storm' was not found during preclinical testing of TGN1412 in cynomolgus monkeys, indicating that species differences in Fc receptor binding may be important for IgG tests even in non-human primates. Functional aspects of the traditional IgG format can be finely tuned by post-translational glycosylation in a proprietary production cell line or by Fc engineering to selectively trigger effector functions such as antibody-dependent cellular cytotoxicity. It is clear that the Fc portion of the monoclonal antibody plays a significant role in the extended serum half-life that is now expected for this class of biological drugs. Thus, Fc modifications must achieve the right balance of clearance, Fc receptor functionality, and clinical safety. Modification or elimination of Fc receptor binding altogether may be included as a motivation to pursue alternatives to the traditional IgG format. Various new antibody formats as well as mimetics are being pursued, but there is limited or no clinical experience with most of these antibody formats and mimetics. The jury is still out on whether one of the many emerging novel scaffolds that eliminate Fc receptor binding can effectively substitute for monoclonal antibodies in the mid-term. It is likely, however, that preclinical development issues based on species-specific target recognition will continue to challenge both antibody and antibody mimetic-based drug candidates.

Limitations to the route of administration

Four of the top five selling antibody drugs and 16 of the 21 approved antibody drugs are administered by intravenous infusion. Several antibody drugs are approved for subcutaneous injection. Selected antibodies either are approved or have been successfully tested in the clinic using other routes of administration often designed for a specific indication including intramuscular (palivizumab), intravitreal (ranibizumab), intracoronary (abciximab), and intraperitoneal, intraventricular, or intralesional (rituximab). Subcutaneous injection offers the possibility of self-injection by the patient; however, a comparison of the TNFα antagonists infliximab (intravenous infusion) and adalimumab (subcutaneous injection) showed equivalent short-term efficacy despite this difference in the route of administration.[10] Over the course of long-term treatment, self-administration and ease of use may be anticipated to impact patient compliance and acceptance of antibody drugs. Insulin represents a protein therapeutic that is readily

delivered by subcutaneous injection, but over the years more acceptable delivery methods have been actively sought due to market demand. In the case of insulin, both the popular insulin pen technologies utilising extremely small, short needles as well as inhaled insulin powder (Exubera) have subsequently been developed. When the relatively low molecular weight of insulin (~5,800 Da) is compared to the high molecular weight of the IgG format (~150,000 Da) found in the majority of approved antibody drugs, it is clear that further technical advances will be needed to achieve the ease of use of pen injection or inhalation technologies. An additional potential benefit of the lower molecular weight of either alternate antibody formats (~25,000–75,000 Da) or antibody mimetics (~9,000–15,000 Da) may be to allow expanded routes of administration. If any of these improved routes of administration are realised they will represent an important milestone for the development of these alternatives to traditional antibody drugs.

Cost of goods (COGS)

Significant costs are associated with the identification, optimisation, and production of monoclonal antibodies due to the cost of manufacturing and intellectual property considerations. Because of their complex structure, monoclonal antibodies in the IgG format are generally limited to production in mammalian cells. These large protein drugs (~150,000 Da) require post-translational modifications and critical disulphide bonds for full activity. The usual route of production in either Chinese hamster ovary (CHO) or mouse myeloma (NS0) cell lines is often expensive and time consuming. The technologies to discover and produce monoclonal antibodies have been heavily patented and companies that are active in this field often need to acquire one or more licenses, either research or commercial. These intellectual property costs are not associated with a single patent and not limited to the antibody molecule itself, but may include a collection of technologies needed for antibody drug generation, optimisation, and production. These technologies may include, among others, affinity maturation, humanisation methods, the expression systems (promoter and poly A sequence), and cell lines used to produce the antibody with the appropriate post-translational modifications needed to ensure the desired functionality. The cumulative costs associated with licensing these technologies are often referred to as 'stacking royalty' payments.

Product differentiation within the antibody market

Within the TNFα antagonist arena, different routes of administration have not yet distinguished similar antibody products with respect to short-term efficacy. This indication is not unique in having several approved antibody drugs or antibody drug candidates in advanced development. Marketed antibody drugs and advanced candidates are often directed to the same target and there are apparently four TNFα antagonists (infliximab, adalimumab, golimumab, certolizumab) in addition to the Fc fusion protein etanercept, five antibodies targeting the B cell receptor CD20 (rituximab, ibritumomab, tositumomab, ofatumumab, ocrelizumab), five to the EGF receptor EGFR (cetuximab, panitumumab, matuzumab, nimotuzumab, zalatumumab), and three to VEGF/VEGFR signalling (bevacizumab, ranibizumab, CDP-791) in addition to the Fc fusion VEGF-Trap. A simple list is not a fair comparison and in some cases the antibody formats are different (immunotoxin versus naked antibody, or IgG versus Fab), the indications are different (solid tumour versus macular degeneration, lymphoma versus arthritis), or the approach to the target is different (soluble ligand versus receptor extracellular domain); however, it is clear that the potential to differentiate between similar antibody products will represent a challenge to the industry.

Competition from small molecule drugs

In addition to the need to differentiate antibody drugs from each other, there is emerging pressure from small molecule drugs directed toward similar targets as the antibodies. No good solution has been found to the daunting technical challenge of finding small molecules that can bind and block tight protein–protein interactions. Antibodies are excellent agents for binding one protein and preventing binding of its biological partner. Small molecule drugs are not likely to compete directly with antibodies using this mechanism, but the therapeutic targets of antibody drugs may be addressed by alternate mechanisms taking advantage of the ability of small molecule drugs to antagonise intracellular targets. Growth factor receptors often are comprised of an extracellular domain suitable for antibody binding and an intracellular kinase domain that may be antagonised by small molecule inhibitors. Lapatinib (Glaxo Smith Kline) is an example of one such oral receptor tyrosine kinase inhibitor that targets both EGFR (ErbB-1) and HER2 (ErbB-2) receptors and that may compare favourably with antibody drugs to these targets. Similarly, by inhibiting the tyrosine kinase domains of VEGFR-1, VEGFR-2, and VEGFR-3 and other receptors (Raf, PDGFR-B, KIT, FLT-3, and RET), the oral drug Nexavar (Bayer) may compare favourably to antibodies targeting VEGF/VEGFR signalling. In the future, combined treatment that includes both antibody and small molecule drugs may prove most effective for life-threatening diseases. It is likely, however, that further challenges to the ability of antibodies to address drug targets will arise from advances in the ability to identify small molecule leads to the same targets.

Price sensitivity of clinical acceptance

The cost issues for antibody therapies do not end when the antibody drug has been successfully produced and packaged. Antibody drugs targeting cancer rarely cure this disease, especially in the advanced stages of cancer. For maximum benefit, antibody cancer drugs are usually administered in combination with chemotherapy or radiotherapy. These combined treatments significantly increase the total cost to the patient. For example, the FOLFOX regimen (Fluorouracil, leucovorin, and oxaliplatin) costs nearly $12,000 dollars for an 8-week course compared to approximately $21,000 for FOLFOX combined with the antibody drug bevacizumab, but the combination with antibody drug results in a significant increased benefit in the median survival time.[11] Improved benefits in the clinic will drive Biotech and Pharma to work with clinicians to find ways to continue to improve the costs of antibody therapies. National healthcare providers, however, may be reluctant to pay for the high cost of antibody drugs. Recently, the National Institute for Health and Clinical Excellence in the United Kingdom was widely criticised when it failed to recommend cetuximab and bevacizumab for advanced bowel cancer based on their estimate that these drugs were not cost-effective in the treatment of metastatic colorectal cancer.[12] Thus, a final challenge will be to identify antibody drugs that are efficacious therapeutics and that are recognised as cost-effective by healthcare providers.

In summary, monoclonal antibodies, along with their derivatives and conjugates, provide tremendous opportunity in the mid-term for the discovery of new treatments for diseases with high unmet medical need. Despite recent setbacks such as the withdrawal and subsequent relaunch of Tysabri and the TGN1412 Phase I disaster, the prevailing opinion is that monoclonal antibodies will continue to be safe and effective medicines. Emerging technologies in novel antibody formats and mimetics will further provide opportunities to improve this unique class of biological drugs and will help to ensure their continued commercial success.

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