The future of monoclonal antibody technology

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With the rapid growth of monoclonal antibody-based products, new technologies have emerged for creating modified forms of antibodies, including fragments, conjugates and multi-specific antibodies. We created a database of 450 therapeutic antibodies in development to determine which technologies and indications will constitute the “next generation” of antibody products. We conclude that the antibodies of the future will closely resemble the antibodies that have already been approved for commercial sale.

Introduction

Now that monoclonal antibodies (mAbs) have become such an important part of the biopharmaceutical arena—with over 15 new therapeutic antibody products achieving US Food and Drug Administration (FDA) approval during the last ten years, the question is: What will the next generation of antibody products look like? We have seen an evolution from murine to humanized and human antibodies in what has been a largely successful effort to duplicate more precisely the characteristics of naturally occurring antibodies.1 In parallel, significant efforts have been made to improve on nature’s design with many variations on the antibody theme, e.g., fragments, antibody-drug conjugates and multi-specific molecules.2

Based on data collected during our extensive search for antibody-based product candidates in various stages of research and development within both industry and academia, our answer is that the future of mAb therapeutics will primarily, but not exclusively, be focused on humanized or fully human antibodies that most closely resemble naturally occurring antibodies. This observation does not diminish the fact that variations on antibody technology have already led to a number of new therapeutic products, and they are likely to continue to do so in the future, but it emphasizes that the vast majority of new products derived from any and all forms of antibody technology over the next decade will continue to be what we now consider “conventional” fully intact antibodies.

This conclusion, that antibodies reaching the market in the next then years will largely be the same as the current products, is based on a search for antibodies in various stages of research and development in biotech and pharmaceutical companies, as well as those being pursued in academic institutions. A survey of the publicly available literature identified over 450 antibodies that fit our selection criteria. We assumed that the various kinds of antibodies that ultimately reach the commercial market will do so in approximately the same proportions in which they exist in our data set of 450 antibodies. This represents, at best, an approximation, but more precise methods of prediction are not possible with the limited data currently available to date on success rates for any forms of antibodies other than conventional IgG antibodies.3 In general, since (1) fragments, conjugates and multi-specific antibodies tend to be in early development, (2) an insufficient number of them have progressed through clinical trials to establish a statistically meaningful predictive model for success and failure rates and (3) there is no evidence to date that these forms of antibodies will succeed at a higher rate than conventional antibodies, the proportions of successful products resulting from the various
Table 1. Monoclonal antibodies and fusion proteins approved in the US as of May 2008

| Trade and non-proprietary names | Type       | Indication   |
|---------------------------------|------------|--------------|
| Amevive (alefacept)             | Fusion     | Immunology   |
| Avastin (bevacizumab)           | Naked      | Oncology     |
| Bexxar (tosotumomab)            | Conjugate  | Oncology     |
| Campath (alemtuzumab)           | Naked      | Oncology     |
| Cimzia (certolizumab pegol)     | Fragment   | Immunology   |
| Enbrel (etanercept)             | Fusion     | Immunology   |
| Erbitux (cetuximab)             | Naked      | Oncology     |
| Herceptin (trastuzumab)         | Naked      | Oncology     |
| Humira (adalimumab)             | Naked      | Immunology   |
| Lucentis (ranibizumab)          | Fragment   | Ophthalmology|
| Mylotarg (gemtuzumab-ozogamicin)| Conjugate  | Oncology     |
| Ocrevus (abatacept)             | Fusion     | Immunology   |
| Orthoclone OKT-3                | Naked      | Immunology   |
| Raptiva (efalizumab)            | Naked      | Immunology   |
| Remicade (infliximab)           | Naked      | Immunology   |
| Retuxan (rituximab)             | Naked      | Oncology     |
| Simulect (basiliximab)          | Naked      | Immunology   |
| Soliris (eculizumab)            | Naked      | Immunology   |
| Synagis (palivizumab)           | Naked      | Infectious Disease |
| Tysabri (natalizumab)           | Naked      | Immunology   |
| Vectibix (panitumumab)          | Naked      | Oncology     |
| Xolair (omalizumab)             | Naked      | Immunology   |
| Zenapax (dabcizumab)            | Naked      | Immunology   |
| Zevalin (ibritumomab tiuxetan)  | Conjugate  | Oncology     |

Sources of Antibody Data

We collected publicly available information on therapeutic antibody candidates from the companies known to be involved in antibody development; relevant data was disclosed on company websites or in documents filed with the Securities and Exchange Commission and its equivalent in countries outside of the United States. A total of 161 antibodies identified in the DataMonitor 2007 “Monoclonal Antibodies Report,” which cites IMS Health R&D Focus as its data source, were reviewed, and the antibodies that were still in active development were included in the data set. Antibodies whose development had been terminated or for which no publicly available announcements or publications had issued for a period of five or more years, were excluded.

We included antibody candidates listed on websites of the licensing or technology transfer offices of 113 academic institutions and research institutes. These institutions included (1) the top 50 US institutions for research and development expense in science and engineering; (2) the top 25 U.S. medical schools for research, as ranked by US News and World Report in 2007; and (3) 31 of the “Top 50” universities for “Life Sciences and Biomedicine,” as ranked by the Times Higher Education Supplement. Only sources available in English were included. A total of 55 antibodies from academic sources were included; those that had been available for licensing for over six years were excluded.

The final data set included 450 antibodies for which sufficient information was available to classify each antibody within one of the following five categories: (1) naked, i.e., fully intact IgG molecules of any class or isotype; (2) fusion protein, i.e., an Ig constant domain genetically linked to one or more recombinant proteins; (3) antibody fragment, i.e., all or part of the variable region of a single Ig molecule (non-antibody-based molecules that mimic the binding patterns of antibody fragments were excluded); (4) conjugate, i.e., any form of antibody linked to another biologically active molecule, typically a chemical or biological toxin (but not including polyethelene glycol or other molecules employed primarily to affect antibody half-life); or (5) multi-specific, i.e., any genetically or chemically linked combination of two or more antibodies of different variable region binding specificities, most of which are bi-specific. Only antibodies intended for therapeutic use were included; diagnostic antibodies, polyclonal antibodies and antibodies isolated from patients were excluded.

It was possible to identify the lead indication, i.e., the most advanced indication in clinical trials or the indication generating the most sales in the case of commercial stage products, for 447 of the antibodies in the database. All antibodies were then classified into one of twelve categories: (1) cardiovascular, (2) diabetes, (3) hematology (other than hematological malignancies, which were included under oncology), (4) immunology, (5) infectious diseases, (6) musculoskeletal, (7) nephrology, (8) neurological, (9) oncology, (10) ophthalmology, (11) pain and (12) undisclosed.

Description of Data Set

As of May 2008, when this data was compiled, 25 antibodies had been approved by the FDA for sale as therapeutic products (Table 1). Antibodies receiving approval but subsequently withdrawn from the market, e.g., efalizumab, are included in the category of approved products; 64% of marketed products are naked, types of antibody technologies other than conventional IgG molecules may actually turn out to be lower than the percentages suggested below.
while fusion proteins, conjugates and fragments account for 12% each (Fig. 1). Immunology antibodies account for about half (52%), oncology for 36%, infectious disease 4% and several other areas, including organ transplant rejection, account for 8% when combined (Fig. 2).

The 425 antibodies in development, of which 217 (51%) were in clinical testing and 208 (49%) were preclinical, show a similar pattern. Naked antibodies represent an even larger percentage (74%), while conjugates increase to 16% of the total. Meanwhile, fragments and fusions decrease to 4% each and, although there are no FDA-approved multi-specifics, they represent 2% of the antibodies in development (Fig. 1). The vast majority were for oncology (59%), immunology (20%) and infectious disease (12%) (Fig. 2). Naked antibodies were distributed throughout the disease areas, but were heavily weighted in oncology (54%) and immunology (26%). Conjugates are primarily focused on oncology (91%); fragments were nearly evenly divided across the disease areas; fusion proteins were primarily found in immunology (50%) and oncology (25%); and most multi-specifics were for oncology (70%), with the rest in infectious disease.

**Discussion**

The field of mAbs was launched with Kohler and Milstein's initial report in 1975 of a method to produce fully intact murine IgG antibodies. Chimerization, humanization and fully human antibody technology followed seriatim over the next two decades and nearly all currently marketed antibodies are of these types. Because of the dominance of conventional, full-sized antibodies to date, it is tempting to see conjugates, fragments, fusion proteins and multi-specific antibodies as new, “next-generation” formats for future products and this impression is strengthened by some of the more recently developed technologies for directly creating fragments and multispecifics via phage or other libraries rather than by modifying conventional antibodies. It should be noted, however, that these types of antibodies have been available for at least 20 years. The first fragment (abciximab) and fusion protein (etanercept) were approved by FDA in 1994 and 1998, respectively, and multi-specific antibodies and conjugates were in clinical trials in the 1990s.

Historical usage patterns for the various antibody-related technologies may provide a reasonable basis for predicting future trends. For example, regardless of whether fragments are made directly through the application of library-based technologies or by separating the variable regions from the constant domain of a conventional antibody, it is still necessary to identify an appropriate therapeutic application for a product with the in vivo characteristics of an antibody fragment, i.e., a molecule that is much smaller than conventional antibodies, but with a considerably shorter half-life (unless the fragment is modified, which may increase its size) and no Fc region to mediate effector functions. Technologies for creating fragments have multiplied, but it is not necessarily the case that the potential applications for such fragments have followed suit. Over time, technologies will continue to develop that will enable fragments, conjugates, fusion proteins and multi-specific antibodies to be employed for a greater number of applications than has been the case to date, but, since the time from commencing the process of antibody creation to receiving regulatory approval for commercial sale of the resulting products is unlikely to be less than ten years, the antibodies described in this article should provide a reasonably...
clear picture of how the field is likely to develop between now and at least 2020.

Similarly, antibodies are currently being developed in essentially the same therapeutic areas as they exist on the market today, i.e., most are for oncology and immunology, followed by infectious diseases and a number of other indications. Oncology will clearly remain a robust arena for antibody development. While the percentage of candidates in development for immunology is lower than is found among currently marketed antibodies, and the percentages addressing oncology and infectious diseases are higher, it is unclear whether these changes are due to evolution of antibody technologies, the changing number of relevant disease targets in these areas or other factors.

Overall, in looking at both the nature of the antibody technologies employed for new therapeutic products and the potential indications that are likely to be addressed by those products, it appears that the next generation of antibody products will bear a close resemblance to the current generation.

Conflicts of Interest

The second author has financial interests in several companies developing monoclonal antibody technology or products. The authors are aware of no other conflicts of interest.

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