Monoclonal Antibodies: Pipeline Analysis and Competitive Assessment

Mark C. Via
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by Mark C. Via

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Executive Summary

Monoclonal antibodies, or mAbs, are highly specific antibodies produced in the laboratory by a variety of methods. In the nearly 35 years since the first process for creating mAbs was introduced, they have remained a centerpiece of the growing biotechnology industry. Thirty therapeutic mAbs have been approved around the world, including 24 in the United States, several of which have attained blockbuster status, with sales reaching the coveted billion-dollar mark and well beyond. Five drugs—Rituxan (rituximab), Remicade (infliximab), Avastin (bevacizumab), Herceptin (trastuzumab), and Humira (adalimumab)—generated sales of over $4 billion each in 2008, and global sales for this entire sector surpassed $30 billion in that year.

This report reviews the broad drug development effort that is focused on bringing improved mAb-based products to the market, concentrating on those used for therapeutic applications. It surveys the latest technologies being applied to the development of these compounds and profiles the major companies, drugs, and projects. It then draws conclusions about the future market potential for mAbs and discusses some of the major challenges faced by the industry.

The first-generation mAbs were murine (derived from mice), but these were soon discovered to have weaknesses. They were targeted for neutralization by the human immune system and also induced the formation of damaging immune complexes. The biotech industry devoted years to reducing the immunogenicity of mAbs, developing the technologies—detailed in this report—to progress from chimeric, to humanized, to fully human antibodies. These succeeding generations of mAbs have demonstrated incremental improvements in safety and activity, and the industry is currently in the middle of a major shift from murine toward humanized and human products. Much work has also been done on altering antibodies’ outward form to boost their efficacy, enable them to more readily penetrate tumors, enhance their
ability to stimulate beneficial immune responses, or otherwise improve their characteristics. Into this realm fall such constructions as antibody fragments, diabodies, synthetic antibodies, bispecific antibodies, and antibody conjugates. This report looks at some of the engineered forms of antibodies and the companies that are leading the way in this research. Other complementary technologies, such as PEGylation and glycosylation, are also discussed.

The report goes on to evaluate the current state of mAb drug development. It identifies more than 250 therapeutic products now in clinical trials, which are largely concentrated in the areas of cancer, immunological and inflammatory diseases, and infectious diseases. Beyond these, hundreds more candidates are at the preclinical stage of development. Reviewed here are the products that are already available, those in clinical development, and those still at the preclinical stage that are likely to play an important role in the advancement of the field.
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Anti-idiotype Monoclonal Antibodies for Cancer

Anti-idiotype monoclonal antibodies target other antibodies. They work by binding to the variable domain of the antibody, which ordinarily binds antigens. Thus, anti-idiotype antibodies essentially function as surrogate antigens, stimulating an immune response against the antigen that was targeted by the original antibody. Although no anti-idiotype antibodies have reached the market yet, several are in development. However, several companies that brought these products into late-stage development stumbled in the past few years, slowing the prospects for commercialization of this class of mAb. ImClone Systems, together with partner Merck KGaA (now Merck Serono), developed IMC-BEC2 (mitumomab), a murine anti-idiotype antibody that mimics the GD3 antigen, a ganglioside expressed on the surface of most small-cell lung tumors. In June 2004, the companies announced that an international Phase III trial of the mAb did not meet its primary end point, improved survival, and in 2005 they terminated the project. Titan Pharmaceuticals (South San Francisco, CA) had been conducting clinical development of three anti-idiotype mAbs: CeaVac (antibody 3H1), which mimics CEA, for colorectal and lung cancers; TriAb (antibody 11D10), which mimics HMFG (human milk fat globule), for non-small-cell lung and breast cancers; and TriGem (antibody 1A7), which induces an immune response to GD2 ganglioside, for melanoma. In 2003, Titan discontinued internal activities in the development of these three mAbs because a Phase III study of CeaVac for colorectal cancer did not meet its primary end point.

Menarini Group

Menarini (Florence, Italy) is conducting Phase III development of abagovomab (formerly ACA125), a murine anti-idiotype mAb originally developed by CellControl Biomedical Laboratories, a German firm, for ovarian cancer. The drug functionally mimics the CA125 antigen, inducing humoral and cellular anti-CA125 immunity. It is different from United Therapeutics’ (Silver Spring, MD) OvaRex (oregovomab), which binds circulating CA125, at which point the antibody-antigen complex reprograms the immune system to recognize the antigen as foreign and triggers an immune response against both antigen and tumor. (OvaRex was dropped from development in late 2007 after failed to provide a significant benefit in Phase III trials.) In a Phase II trial in patients with advanced ovarian cancer in whom standard
therapies had proved ineffective, treatment with abagovomab elicited a specific anti-idiotype antibody response in 68.1% of patients; in that subgroup, median survival time was 23.4 months, compared with 4.9 months for nonresponders. In December 2006, Menarini initiated an international Phase III trial called MIMOSA (Monoclonal Antibody Immunotherapy for Malignancies of the Ovary by Subcutaneous Abagovomab) to evaluate the mAb as maintenance therapy in 870 patients with ovarian cancer who achieved complete responses with first-line chemotherapy. Results are expected in 2010.

Onyxax

Onyxax's (London, UK) Onyxax-105 (105AD7) is a human anti-idiotype mAb that mimics CD55, an antigen overexpressed on many cancer types that is believed to protect tumor cells from immune attack. Phase I trials in colorectal cancer and pediatric osteosarcoma have been completed, and Onyxax is using the results to further develop a second-generation antibody to enter preclinical studies.

Conjugated Monoclonal Antibodies for Cancer

One popular approach to increasing the potency of antibodies is to use their target specificity to deliver therapeutic payloads to target cells, typically cancer cells. Here, mAbs are tagged with a toxic substance such as a radioisotope, a toxin, or a small-molecule therapeutic, which assumes the usual duties of the effector system by killing the target cell. More information on the different types of conjugates can be found in Section 2.5. Three mAbs on the market fall into this category: Mylotarg, a humanized anti-CD33 antibody conjugated to calicheamicin for acute myeloid leukemia, and Zevalin and Bexxar, radiolabeled murine anti-CD20 antibodies for NHL. Table 3.3 lists 34 conjugated mAbs in clinical trials.
### Table 3.3. Conjugated Monoclonal Antibodies in Clinical Trials for Cancer

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<tr>
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<td>Bexxar (tositumomab)</td>
<td>Murine anti-CD20 mAb conjugated to iodine 131</td>
<td>CLL, multiple myeloma, Hodgkin’s disease</td>
<td>Phase II</td>
</tr>
<tr>
<td>ImmunoGen</td>
<td>IMGN242</td>
<td>Humanized anti-CaAg mAb (C242) conjugated to DM4</td>
<td>Gastric cancer</td>
<td>Phase II</td>
</tr>
<tr>
<td>ImmunoGen</td>
<td>IMGN388</td>
<td>Human anti-αv integrin mAb conjugated to DM4</td>
<td>Cancer</td>
<td>Phase I</td>
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### Table 3.3. Conjugated Monoclonal Antibodies in Clinical Trials for Cancer (cont.)

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<th>Product</th>
<th>Type</th>
<th>Indication</th>
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<tr>
<td>ImmunoGen</td>
<td>IMGN901</td>
<td>Humanized anti-CD56 mAb (N901) conjugated to DM1</td>
<td>Multiple myeloma, other cancers</td>
<td>Phase I</td>
</tr>
<tr>
<td>Immunomedics</td>
<td>131I-labetuzumab</td>
<td>Humanized anti-CEA mAb (labetuzumab) conjugated to iodine 131</td>
<td>Liver metastases of colorectal cancer</td>
<td>Phase II</td>
</tr>
<tr>
<td>Immunomedics</td>
<td>IMMU-102 (90Y-epratuzumab)</td>
<td>Humanized anti-CD22 mAb (epratuzumab) conjugated to yttrium 90</td>
<td>NHL</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Immunomedics</td>
<td>IMMU-107 (90Y-clivatuzumab tetraxetan)</td>
<td>Humanized anti-MUC1 mAb (clivatuzumab) conjugated to yttrium 90</td>
<td>Pancreatic cancer</td>
<td>Phase Ib</td>
</tr>
<tr>
<td>Medarex</td>
<td>MDX-1203</td>
<td>Human anti-CD70 mAb conjugated to minor-groove-binding alkylating agent</td>
<td>Renal cell carcinoma, NHL</td>
<td>Phase I</td>
</tr>
<tr>
<td>MedImmune</td>
<td>CAT-8015</td>
<td>Murine anti-CD22 Fv antibody fragment conjugated to Pseudomonas exotoxin PE38</td>
<td>Hairy cell leukemia, CLL, NHL</td>
<td>Phase I</td>
</tr>
<tr>
<td>Merck Serono</td>
<td>EMD 273063 (hu14.18-IL2)</td>
<td>Humanized anti-GD2 mAb (hu14.18) conjugated to IL-2</td>
<td>Melanoma, pediatric neuroblastoma</td>
<td>Phase II</td>
</tr>
<tr>
<td>Merck Serono</td>
<td>Tucotuzumab celmoleukin (EMD 273066; huKS-IL2)</td>
<td>Humanized anti-EpCAM mAb (KS) conjugated to IL-2</td>
<td>Small-cell lung cancer</td>
<td>Phase II</td>
</tr>
<tr>
<td>Pain Therapeutics (San Mateo, CA)</td>
<td>188Re-PTI-6D2</td>
<td>Murine anti-melanin mAb (6D2) conjugated to rhenium 188</td>
<td>Melanoma</td>
<td>Phase I</td>
</tr>
<tr>
<td>Peregrine Pharmaceuticals</td>
<td>Cotara</td>
<td>Chimeric Tumor Necrosis Therapy antibody (chTNT-1B) (targeting histone H1/DNA complexes) conjugated to iodine 131</td>
<td>Glioblastoma</td>
<td>Phase II</td>
</tr>
<tr>
<td>Philogen (Siena, Italy)</td>
<td>L19-IL2</td>
<td>Human anti-ED-B fibronectin antibody (L19) conjugated to IL-2</td>
<td>Renal cell carcinoma, melanoma, pancreatic cancer</td>
<td>Phase II</td>
</tr>
<tr>
<td>Philogen</td>
<td>Teleukin (F16-IL2)</td>
<td>Human anti-A1 tenascin-C antibody (F16) conjugated to IL-2</td>
<td>Breast cancer, ovarian cancer, lung cancer</td>
<td>Phase I</td>
</tr>
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*Continued*
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Additional detail about some of the candidates in development is provided below.

**Active Biotech**

Active Biotech’s (Lund, Sweden) Anyara (naptumomab estafenatox; ABR-217620) is a recombinant fusion protein consisting of an anti-5T4 Fab moiety conjugated to the superantigen variant SEA/E-20. The oncofetal antigen 5T4 is expressed on more than 95% of tumors from patients with renal cell carcinoma, NSCLC, and pancreatic cancer. Anyara is a second-generation tumor-targeted superantigen (TTS) based on an earlier conjugate, ABR-214936 (anatumomab mafenatox),

**Table 3.3. Conjugated Monoclonal Antibodies in Clinical Trials for Cancer (cont.)**

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<tr>
<td>Philogen</td>
<td>Tenarad (F16-131I)</td>
<td>Human anti-A1 tenascin-C antibody (F16) conjugated to iodine 131</td>
<td>Cancer, hematologic malignancies</td>
<td>Phase I</td>
</tr>
<tr>
<td>Philogen; Bayer Schering Pharma</td>
<td>L19-131I</td>
<td>Human anti-ED-B fibronectin antibody (L19) conjugated to iodine 131</td>
<td>Cancer, hematologic malignancies</td>
<td>Phase II</td>
</tr>
<tr>
<td>Philogen; Bayer Schering Pharma</td>
<td>L19-TNF</td>
<td>Human anti-ED-B fibronectin antibody (L19) conjugated to TNF</td>
<td>Melanoma, colorectal cancer</td>
<td>Phase II</td>
</tr>
<tr>
<td>Progenics Pharmaceuticals; Seattle Genetics</td>
<td>PSMA-ADC</td>
<td>Human anti-PSMA mAb conjugated to monomethyl auristatin E</td>
<td>Prostate cancer</td>
<td>Phase I</td>
</tr>
<tr>
<td>Provenance Biopharmaceuticals</td>
<td>DI-Leu16-IL2</td>
<td>Anti-CD20 mAb conjugated to IL-2</td>
<td>NHL</td>
<td>Phase I</td>
</tr>
<tr>
<td>Sanofi-Aventis; ImmunoGen</td>
<td>SAR3419</td>
<td>Humanized anti-CD19 mAb conjugated to DM4</td>
<td>NHL</td>
<td>Phase I</td>
</tr>
<tr>
<td>Seattle Genetics</td>
<td>SGN-35</td>
<td>Chimeric anti-CD30 mAb conjugated to monomethyl auristatin E</td>
<td>Hodgkin’s disease, anaplastic large-cell lymphoma, other hematologic cancers</td>
<td>Phase III</td>
</tr>
<tr>
<td>UCB; Wyeth</td>
<td>CMC544</td>
<td>Humanized anti-CD22 antibody conjugated to calicheamicin</td>
<td>NHL</td>
<td>Phase II</td>
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Abbreviations: AML, acute myeloid leukemia; CEA, carcinoembryonic antigen; CLL, chronic lymphocytic leukemia; EpCAM, epithelial cell adhesion molecule; Fab, antibody fragment; hCG, human chorionic gonadotropin; IL, interleukin; ITP, immune thrombocytopenic purpura; NHL, non-Hodgkin’s lymphoma; NSCLC, non-small-cell lung cancer; PSMA, prostate-specific membrane antigen; TNF, tumor necrosis factor.

*Source: Insight Pharma Reports*
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About
Cambridge Healthtech Institute

Founded in 1992, Cambridge Healthtech Institute (CHI) strives to develop quality information resources that provide valuable new insights and competing points of view while offering balanced coverage of the latest developments in the life sciences industry. Basic research related to commercial implications is covered, with heavy emphasis placed on end-user insights into new products and technology as well as coverage of the strategy behind the business.

Cambridge Healthtech Institute (CHI) is the preeminent life science network for leading researchers and business experts from top pharmaceutical, biotech, and academic organizations. CHI’s integrated portfolio of products and services includes Cambridge Healthtech Institute Conferences, the Pharmaceutical Strategy Series, Barnett International, Insight Pharma Reports, Cambridge Marketing Consultants, Cambridge Meeting Planners, Cambridge Healthtech Associates, and Cambridge Healthtech’s Media Group, which includes several eNewsletters, Bio-IT World magazine, as well as Lead Generation Programs and Custom Solution Packages.

For a comprehensive listing and detailed information about our products and services, please continue reading below or visit our web site at www.chicorporate.com.

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(www.healthtech.com)

For the past 15 years, Cambridge Healthtech Institute (CHI) has developed more than 700 conferences, which have attracted over 60,000 attendees from around the world. CHI is the industry leader in offering quality programs that provide valuable new insights and competing points of view while offering balanced coverage of the latest developments in the life science industry. Leading researchers and business experts from top pharmaceutical, biotech, and academic organizations present their most current findings in a forum that features panel discussions and audience participation.
Each year, CHI organizes over 100 annual events geared to the biotech and pharmaceutical industries with specific focuses on Biomarkers, Genomics, Proteins and Proteomics, Drug Discovery & Development, IT and Informatics, Chemistry, Diagnostics & Safety, and Business. CHI’s flagship conference events include:

- Beyond Genome
- PepTalk: The Protein Information Week
- World Pharmaceutical Congress
- PEGS: The Essential Protein Engineering Summit
- Bio-IT World Conference & Expo
- Molecular Medicine Tri-Conference

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The Pharmaceutical Strategy Series (PSS) programs have been designed to help the R&D leaders and corporate executives assess business opportunities, enhance corporate value, and forecast the economic and regulatory landscape within the rapidly changing pharmaceutical and biotechnology industries. PSS chooses the most topical issues to cover, based largely on advice given by the PSS Advisory Board. The Advisory Board is comprised of decision-makers at most of the world’s leading pharmaceutical companies. Presentations in each Executive Forum will give you the ideas, information, and resources you need to make faster and smarter decisions.

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Barnett, formerly a division of PAREXEL International, is a recognized leader in clinical education and training for all levels of staff involved in the drug development process. In addition, Barnett is the well-known publisher of the Bio/Pharmaceutical R&D Statistical Sourcebook and other reference manuals that help research facilities ensure compliance by providing updates about the latest federal regulations, while offering executives valuable information garnered from real-world studies, analyses, and widely respected industry opinion leaders. For more information on Barnett’s publications and educational programs, visit www.barnettinternational.com.

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Insight Pharma Reports is the premier life sciences information provider offering unparalleled coverage of key issues in drug discovery and development. The reports are used by leading pharmaceutical, biotech, diagnostic, and other life science companies to keep abreast of the latest developments in pharmaceutical R&D and their potential applications and business impacts. The reports are written by experts in consulting and industry, and are supported by hundreds of hours of primary and secondary research. Insight Pharma Reports provide comprehensive coverage of salient issues in a concise, well-organized format.

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The Marketing Services group is an ideal solution for companies seeking assistance in all aspects of life sciences direct marketing. CHI’s Marketing Services continues to be chosen #1 over our competitors for one reason – We deliver results that impact the bottom-line with many services to choose from! Services include list rentals, direct marketing, product and service alerts, and mail piece designs.
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Cambridge Meeting Planners (CMP), a division of Cambridge Healthtech Institute, has a highly professional, experienced team dedicated to providing you with the finest services to match any budget. With five meeting planners who combined have over 50 years of experience in the field, CMP has extensive working relationships with hotels and vendors guaranteeing you superior service with all of your contract negotiation needs.

CMP is available to manage all of your preplanning and onsite meeting needs, including site selection, contracting, audio visual/food and beverage selection, hiring/managing security and temps, etc. CMP is there for you whether you need help planning a reception for 1000 or a working dinner meeting for 20 professionals. CMP can manage your entire event from soup to nuts and make your vision a reality. Types of events include:

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- Tradeshows
- Usergroup meetings
- Product launches
- Focus groups
- Client appreciation events
- Team building excursions
- Recreational and hospitality programs
- And many more. Please visit our web site for a more detailed list.

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Cambridge Healthtech Associates (CHA) is the leading organizer and facilitator of biopharmaceutical collaboration. CHA reduces the costs of R&D by bringing together different companies to work cooperatively to evaluate novel technologies, assess vendors in emerging global markets and address other areas of shared concern. This is accomplished through short, six-month collaborative projects, market research surveys, roundtable summits, virtual meetings (via tele/web conference) and the Drug Safety Executive Council (an exclusive online community of industry leaders). For more information, visit [www.chacorporate.com](http://www.chacorporate.com).

**Cambridge Healthtech Media Group** (www.chmediagroup.com)

Cambridge Healthtech Media Group, a division of Cambridge Healthtech Institute, delivers content to decisionmakers through its print, online, and electronic products designed to serve the life sciences community. The Media Group’s editors are at the pulse of the market and disseminate ground-breaking news, analysis, trends, and insights that shape the life science industry through a suite of published resources—Bio-IT World magazine—CHI’s flagship publication, three topic-specific eNewsletters, and web sites.

**Bio-IT World** (www.bio-itworld.com)

*Bio-IT World* magazine—CHI’s flagship publication—publishes critical insights, analysis, and opinion on the enabling technologies propelling the spread of information and the passage of drug candidates through the drug discovery process. *Bio-IT World’s* focus is increasingly one that explores the tools and results of predictive biology, drug discovery, informatics, and personalized medicine. The magazine also focuses on the strategic decisions made by companies in this area and the impact on the company’s performance.
A few key areas covered in-depth include: recent advances in whole genome analysis and next-generation sequencing, data handling technologies, the vast potential of adaptive clinical trials, in silico modeling, cheminformatics, electronic data capture, and much more. Please visit www.bio-itworld.com to view more feature articles on the life sciences industry and to subscribe.

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- **Bio-IT World Weekly Update** (www.bio-itworld.com)
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