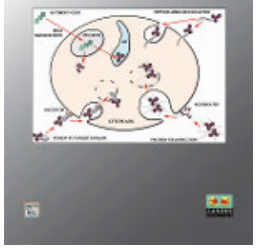

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Antibody-based therapeutics to watch in 2011

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This overview of 25 monoclonal antibody (mAb) and five Fc fusion protein therapeutics provides brief descriptions of the candidates, recently published clinical study results and on-going Phase 3 studies. In alphanumeric order, the 2011 therapeutic antibodies to watch list comprises AIN-457, bapineuzumab, brentuximab vedotin, briakinumab, dalotuzumab, epratuzumab, farletuzumab, girentuximab (WX-G250), naptumomab estafenatox, necitumumab, obinutuzumab, otelixizumab, pagibaximab, pertuzumab, ramucirumab, REGN88, reslizumab, solanezumab, T1h, teplizumab, trastuzumab emtansine, tremelimumab, vedolizumab, zalutumumab and zanolimumab. In alphanumeric order, the 2011 Fc fusion protein therapeutics to watch list comprises aflibercept, AMG-386, atacicept, Factor VIII-Fc and Factor IX-Fc. Commercially-sponsored mAb and Fc fusion therapeutics that have progressed only as far as Phase 2/3 or 3 were included. Candidates undergoing regulatory review or products that have been approved may also be in Phase 3 studies, but these were excluded. Due to the large body of primary literature about the candidates, only selected references are given and results from recent publications and articles that were relevant to Phase 3 studies are emphasized. Current as of September 2010, the information presented here will serve as a baseline against which future progress in the development of antibody-based therapeutics can be measured.

Introduction

The pharmaceutical and biotechnology industry is currently investing substantial resources in the development of antibody-based therapeutic products. Novel monoclonal antibodies (mAbs) have been entering clinical study at a rate of over 40 per year since 2007 and new products are being approved at a steady pace.[1] Hundreds of mAbs, as well as novel Fc fusion proteins that are composed of binding peptides or proteins fused to the Fc domain of immunoglobulin G, are undergoing clinical study as potential treatments for disease. By the end of 2010, a total of 30 of these candidates (25 mAb and five Fc fusion protein) were in Phase 2/3 or Phase 3 clinical studies sponsored by commercial firms, and these are included on the 2011 antibody-based therapeutics to watch list.

A total of 26 mAbs in commercially-sponsored Phase 2/3 or Phase 3 clinical studies were included on the 2010 antibodies to watch list.[2] In alphanumeric order by mAb name, these candidates were: 131-I mAb 81C6, bapineuzumab, belimumab, briakinumab, dalotuzumab, epratuzumab, farletuzumab, figitumumab, galiximab, girentuximab (WX-G250), inotuzumab ozogamicin, ipilimumab, mepolizumab, naptumomab estafenatox, ocrelizumab, otelixizumab, pagibaximab, pertuzumab, ramucirumab, reslizumab, solanezumab, tanezumab, teplizumab, trastuzumab emtansine, vedolizumab and zalutumumab.

Nine of the 26 mAbs on the 2010 list were not included in the 2011 version for various reasons. Two mAbs (belimumab and ipilimumab) advanced to regulatory review, all studies of two mAbs (galiximab and 131-I mAb 81C6) were suspended or terminated and development of five (figitumumab, inotuzumab ozogamicin, mepolizumab, ocrelizumab and tanezumab) reverted to Phase 2 studies. New to the 2011 list are eight mAbs that entered a first Phase 3 clinical study or re-entered a Phase 3 study since September 2009. In alphanumeric order by mAb name, these are: AIN-457, brentuximab vedotin, necitumumab, obinutuzumab, REGN88, T1h, tremelimumab and zanolimumab. Two (trelimumab and zanolimumab) were previously in Phase 3 studies that were terminated prior to 2009, and so were not on the "antibodies to watch in 2010" list. As a consequence of these changes to the 2010 list, there are 25 "antibodies to watch" in 2011. The complete list of the 25 mAbs in alphanumeric order by target appears in **Tables 1, 3 and 5**.

Information about mAbs that are in regulatory review or approved for marketing by the United States Food and Drug Administration (US FDA) are listed in **Tables 2, 4 and 6** for comparison. Two mAbs, catumaxomab and nimotuzumab, that are approved for marketing outside of the US should also be noted. **Catumaxomab** (Removab®; Fresenius Biotech GmbH, Trion Pharma) is a mouse/rat-derived, bispecific mAb that targets the epithelial cell adhesion molecule (EpCAM) on tumor cells and CD3 on T cells.[3] The product was approved for marketing in the European Union in April 2009 for treatment of patients with malignant ascites. Catumaxomab is in an on-going Phase 3 study [NCT00822809] as a treatment of malignant ascites due to epithelial cancer.

Nimotuzumab (BIOMAb-EGFR, Thera-CIM; Biocon, YM Biosciences, Oncosciences) is a humanized IgG1 mAb that targets the epithelial growth factor receptor (EGFR).[4] The product is approved for marketing in a number of

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Table 1. Monoclonal antibodies in Phase 3 studies as treatments for cancer indications

Sponsoring company	International non-proprietary name	Target and type	Indication of Phase 3 study	FDA designations for Phase 3 study indication
Active Biotech Research	Naptumomab estafenatox	5T4; Fab conj. to staph. enterotoxin A	Advanced renal cell carcinoma	
Wilex AG	Girentuximab	Carbonic anhydrase ix; IgG1	Non-metastatic renal cell carcinoma	O
TenX Biopharma/Genmab	Zanolimumab	CD4; IgG1	Cutaneous T-cell lymphoma	FT, O
Glycart/Genentech/Biogen Idec	Obinutuzumab	CD20; IgG1	Chronic lymphocytic leukemia	
Seattle Genetics	Brentuximab vedotin	CD30; IgG1; conjugated to monomethyl auristatin E	Hodgkin lymphoma	FT, O
Pfizer	Tremelimumab	CTLA-4; IgG2	Metastatic melanoma	
Genmab	Zalutumumab	EGFR; IgG1	Head and neck cancer	FT
ImClone	Necitumumab	EGFR; IgG1	Non-small cell lung cancer	
Morphotek	Farletuzumab	Folate receptor α; IgG1	Ovarian cancer	O
Genentech	Trastuzumab emtansine	HER2; IgG1 conj. to DM1	Locally advanced or metastatic breast cancer	
Genentech	Pertuzumab	HER2; IgG1	Metastatic breast cancer	
Merck, Pierre Fabre	Dalotuzumab	IGF-1R; IgG1	Metastatic colorectal cancer	
Imclone Systems/Eli Lilly	Ramucirumab	VEGFR2; IgG1	Metastatic gastric or gastroesophageal junction adenocarcinoma; breast cancer; hepatocellular carcinoma	

Information current as of September 1, 2010. CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte-associated antigen; EGFR, epidermal growth factor receptor; Fab, antigen-binding fragment; FDA, US Food and Drug Administration; FT, fast track designation; HER2, human epidermal growth factor receptor; IGF-1R, insulin-like growth factor-1 receptor; O, orphan drug designation; VEGFR2, vascular endothelial cell growth factor receptor 2. International non-proprietary naming convention: -umab, human; -zumab, humanized; -ximab, chimeric; -momab, murine.

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Table 2. Monoclonal antibodies in FDA review or approved as treatments for cancer indications

International non-proprietary name	Trade name	Target and type	Indication under review or first approved	FDA approval year
Ofatumumab	Arzerra	CD20; human IgG1	Chronic lymphocytic leukemia	2009
Tositumomab-I131	Bexxar	CD20; murine IgG2a	Non-Hodgkin lymphoma	2003
Ibritumomab tiuxetan	Zevalin	CD20; murine IgG1	Non-Hodgkin lymphoma	2002
Rituximab	Rituxan	CD20; chimeric IgG1	Non-Hodgkin's lymphoma	1997
Gemtuzumab ozogamicin	Mylotarg	CD33; humanized IgG4	Acute myeloid leukemia	2000*
Alemtuzumab	Campath-1H	CD52; humanized IgG1	Chronic myeloid leukemia	2001
Ipilimumab	Pending	CTLA-4; human IgG1	Advanced melanoma	Pending (PDUFA action date Dec. 25, 2010)
Panitumumab	Vectibix	EGFR; human IgG2	Colorectal cancer	2006
Cetuximab	Erbitux	EGFR; chimeric IgG1	Colorectal cancer	2004
Trastuzumab	Herceptin	HER2; humanized IgG1	Breast cancer	1998
Bevacizumab	Avastin	VEGF; humanized IgG1	Colorectal cancer	2004

Information current as of September 1, 2010. *Voluntarily withdrawn from US market. CD, cluster of differentiation; EGFR, epidermal growth factor receptor; CTLA, cytotoxic T-lymphocyte-associated antigen; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor; PDUFA, Prescription Drug User Fee Act; VEGF, vascular endothelial growth factor. International non-proprietary naming convention: -umab, human; -zumab, humanized; -ximab, chimeric; -momab, murine.

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Table 3. Monoclonal antibodies in Phase 3 studies as treatments for immunological indications

Sponsoring company	International non-proprietary name	Target and type	Indication of Phase 3 study	FDA designations for Phase 3 study indication
Millennium/Takeda	Vedolizumab	α4 β7 integrin; IgG1	Moderate-to-severe Crohn disease; ulcerative colitis	
Tolerx	Otelixizumab	CD3; IgG1	Type 1 diabetes mellitus	O
Macrogenics/Eli Lilly	Teplizumab*	CD3; IgG1	Type 1 diabetes mellitus	O
Biocon/CIMAB SA	T1h	CD6; humanized IgG1	Psoriasis	
Immunomedics/UCB	Epratuzumab	CD22; IgG1	Systemic lupus erythematosus	FT
Cephalon	Reslizumab	IL-5; IgG4	Eosinophilic esophagitis	O
Regeneron	REGN88	IL-6R; human IgG1	Ankylosing spondylitis, rheumatoid arthritis	
Abbott	Briakinumab**	IL-12/23; IgG1	Plaque psoriasis	
Novartis	AIN-457	IL-17A; human IgG1	Uveitis	

Information current as of September 1, 2010. CD, cluster of differentiation; FDA, US Food and Drug Administration; FT, fast track designation; IL, interleukin; O, orphan drug designation. International non-proprietary naming convention: -umab, human; -zumab, humanized. *Note added in proof: In a press release issued in October 2010, Lilly announced that the primary endpoint in the PROTÉGÉ study (NCT00385697) had not been met and enrollment and dosing in the PROTÉGÉ and PROTÉGÉ Encore (NCT00920582) studies were suspended. **Note added in proof: In a press release issued in October 2010, Abbott announced that marketing applications for briakinumab were filed in the US and Europe during the third quarter of 2010.

Table 4. Monoclonal antibodies in FDA review or approved as treatments for immunological indications

International non-proprietary name	Trade name	Target and type	Indication under consideration or first approved	FDA approval year
Belimumab	Pending	B-lymphocyte stimulator; human IgG1	Systemic lupus erythematosus	Pending (PDUFA action date Dec. 9, 2010)
Eculizumab	Soliris	C5; humanized IgG2/4	Paroxysmal nocturnal hemoglobinuria	2007
Muromonab-CD3	Orthoclone Okt3	CD3; murine IgG2a	Reversal of kidney transplant rejection	1986#
Basiliximab	Simulect	IL2R; chimeric IgG1	Prevention of kidney transplant rejection	1998
Daclizumab	Zenapax	IL2R; humanized IgG1	Prevention of kidney transplant rejection	1997#
Efalizumab	Raptiva	CD11a; humanized IgG1	Psoriasis	2003#
Tocilizumab	Actemra	IL6R; humanized IgG1	Rheumatoid arthritis	2010
Ustekinumab	Stelara	IL12/23; human IgG1	Plaque psoriasis	2009
Canakinumab	Ilaris	IL1β; human IgG1	Muckle-Wells syndrome	2009
Omalizumab	Xolair	IgE; humanized IgG1	Asthma	2003
Natalizumab	Tysabri	α4 integrin; humanized IgG4	Multiple sclerosis	2004
Golimumab	Simponi	TNF; human IgG1	Rheumatoid and psoriatic arthritis, ankylosing spondylitis	2009
Certolizumab pegol	Cimzia	TNF; humanized Fab, pegylated	Crohn disease	2008
Adalimumab	Humira	TNF; human IgG1	Rheumatoid arthritis	2002
Infliximab	Remicade	TNF; chimeric IgG1	Crohn disease	1998

Information current as of September 1, 2010. #Voluntarily withdrawn from US market. C5, complement 5; CD, cluster of differentiation; FDA, US Food and Drug Administration; IL, interleukin; PDUFA, Prescription Drug User Fee Act; TNF, tumor necrosis factor. International non-proprietary naming convention: -umab, human; -zumab, humanized; -ximab, chimeric; -momab, murine.

countries, e.g., India, Cuba, Argentina, Columbia, Ivory Coast, Gabon, Ukraine, Peru and Sri Lanka as a treatment for patients with squamous cell carcinoma of the head and neck; Cuba, Argentina, Philippines and Ukraine as a treatment for glioma in pediatric and adult patients and China for patients with nasopharyngeal cancer. Nimotu-zumab is in commercially-sponsored, ongoing Phase 3 studies in patients with glioblastoma multiforma (NCT00753246) and patients with advanced nasopharyngeal cancer (NCT01074021).

With six products in FDA review or approved and five candidates in Phase 3 studies, Fc fusion protein therapeutics are a growing class of antibody-based molecules that have been included on the 2011 watch list. In alphanumeric order, the 2011 Fc fusion protein therapeutics to watch list comprises aflibercept, AMG-386, atacicept, Factor VIII-Fc and Factor IX-Fc (**Table 7**). For comparison,

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Table 5. Monoclonal antibodies in Phase 3 studies as treatments for non-traditional indications

Sponsoring company	International non-proprietary name	Target and type	Indication of Phase 3 study	FDA designations for Phase 3 study indication
Biosynexus	Pagibaximab	Lipoteichoic acid; IgG1	Prevention of staphylococcal sepsis in very low birth weight neonates	O
Lilly	Solanezumab	Amyloid beta; IgG1	Alzheimer disease	
Pfizer, Janssen	Bapineuzumab	Amyloid beta; IgG1	Alzheimer disease	FT

Information current as of September 1, 2010. FDA, US Food and Drug Administration; FT, fast track designation; O, orphan drug designation. International non-proprietary naming convention: -zumab, humanized; -ximab, chimeric.

Table 6. Monoclonal antibodies in FDA review or approved as treatments for non-traditional indications

International non-proprietary name	Trade name	Target and type	Indication under consideration or first approved	FDA approval year
Raxibacumab	Pending	*B. anthrasis* PA; human IgG1	Anthrax infection	Pending
Abciximab	Reopro	GPIIb/IIIa; chimeric IgG1 Fab	Prevention of blood clots in angioplasty	1994
Denosumab	Prolia	RANK-L; human IgG2	Bone loss	2010
Motavizumab	Pending	RSV; humanized IgG1	Prevention of respiratory syncytial virus infection	Pending
Palivizumab	Synagis	RSV; humanized IgG1	Prevention of respiratory syncytial virus infection	1998
Ranibizumab	Lucentis	VEGF; humanized IgG1 Fab	Macular degeneration	2006

Information current as of September 1, 2010. FDA, US Food and Drug Administration; GP; glycoprotein; PA, protective antigen; RANK-L, receptor activator of NFκb ligand; RSV, respiratory syncytial virus; TNF, tumor necrosis factor; VEGF, vascular endothelial cell growth factor.

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Table 7. Fc fusion protein therapeutics in Phase 3 studies for any indication

Sponsoring company	International non-proprietary or code name	Description	Indications of Phase 3 study	FDA designations for Phase 3 study indication
Regeneron/Sanofi-aventis/Bayer	Aflibercept	Extracellular domains of VEGFR1 and VEGFR2 fused to Fc of human IgG1	Ovarian cancer with symptomatic malignant ascites, prostate, small cell lung, colorectal and pancreatic cancers*; wet age-related macular degeneration; central retinal vein occlusion	FT (for symptomatic malignant ascites)
Amgen	AMG 386	Angiopoietin-1 and -2 binding peptide fused to Fc of human IgG1	Epithelial ovarian, primary peritoneal or fallopian tube cancers*	
ZymoGenetics/ Merck Serono	Atacicept	Extracellular domain of transmembrane activator and calcium-modulating ligand interactor fused with Fc of human Ig	Systemic lupus erythematosus	
Biogen Idec/Swedish Orphan Biovitrum	Factor VIII-Fc	Factor VIII fused to Fc of human IgG1	Severe hemophilia A	
Biogen Idec/Swedish Orphan Biovitrum	Factor IX-Fc	Factor IX fused to Fc of human IgG1	Hemophilia B-associated hemorrhagic events	O

Data current as of September 2010. *Five separate Phase 3 studies, with one in each indication. **Single Phase 3 study [NCT01204749] in which patients may have any of these indications; listed on clinicaltrials.gov as not yet open for participation as of September 2010. FDA, United States Food and Drug Administration; FT, fast track; O, orphan drug; VEGFR, vascular endothelial growth factor receptor.

information about Fc fusion proteins that are in regulatory review or approved for marketing by the FDA are listed in Table 8.

Commercially-sponsored mAb and Fc fusion protein therapeutics that have progressed only to Phase 2/3 or Phase 3 were included. Candidates undergoing regulatory review or products already on the market may also be in Phase 3 studies, but these were excluded. MAbs in development sponsored solely by academic, government and non-profit organizations were also excluded. Due to the large body of primary literature about the 30 candidates on the 2011 watch list, only selected references are given, and results from recent publications and articles that were relevant to Phase 3 studies are emphasized. Current as of September 2010, the information presented here will serve as a baseline against which future progress in the development of antibody-based therapeutics can be measured.

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