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Which are the antibodies to watch in 2012?

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As we enter the new year of 2012, the realm of antibody therapeutics development seems full of possibilities for antibodies to watch. The commercial pipeline of antibody-based therapeutics continues to grow and now totals nearly 350 candidates. The molecular diversity of the candidates, especially those for cancer, is remarkable. Modified antibodies, such as antibody-drug conjugates (ADCs), bispecific antibodies, Fc or glyco-engineered antibodies and antibody fragments/domains, now comprise more than half of the anticancer antibodies at Phase 1 and ~40% of those at Phase 2 and Phase 3. These types of modified antibodies have not been developed as frequently for other disorders, by comparison, ~90% of antibodies developed for non-cancer indications are unmodified IgG, but development of the new formats for inflammatory and autoimmune disorders is expected to grow. In addition, antibody mixtures and antibodies with indirect mechanisms of action (e.g., agonism of immune activation receptors or antagonism of immune inhibitory receptors) are entering clinical study more frequently.

With all of these possibilities, which are the antibodies to watch this year? The approaches I've described are important to track because they are critical to the long-term success of antibody-based therapeutics, but the candidates currently at Phase 3 are always worth watching because they comprise the pool from which new-marketed products will soon emerge. The list of Phase 3 candidates changes frequently as studies are completed and decisions are made regarding the development path of the molecules. With each passing year, some candidates progress to regulatory review, some revert to Phase 2 studies and some are terminated.

As of early November 2011, a total of 25 candidates are on my list of Phase 3 antibody-based therapeutics to watch in 2012. The majority of these are undergoing evaluation as treatments for cancer or immunological diseases; only four (16%) are therapies for other indications. The 12 anticancer Phase 3 candidates include seven canonical IgG1s, as well as two ADCs (inotuzumab ozogamicin, trastuzumab emtansine), a Fab conjugated to staphylococcal enterotoxin A (naptumomab estafenatox), a glyco-engineered mAb (obinutuzumab) and a peptibody composed of a peptide fused with an Fc (AMG 386) (**Table 1**). Compared with the anticancer mAbs, the nine antibodies being evaluated in Phase 3 studies of patients with immunological disorders are limited in their molecular diversity (**Table 2**). All nine are full-length mAbs that are either IgG1 (78%) or IgG4 (22%). Only four antibody-based therapeutics are in Phase 3 studies for indications that are not classified as cancer or immunological diseases (**Table 3**). Two fusion proteins (Factor VIII-Fc, Factor IX-Fc) are in Phase 3 studies of hemophilia patients, and two full-length IgG1s are being evaluated in Phase 3 studies of patients with Alzheimer disease.

Last, but not least, of the antibody-based therapeutics to watch in 2012 are the biosimilars. The area of biosimilar antibody development is positioned for substantial growth as the European Medicines Agency re-evaluates their 2005 guideline on similar biological medicinal products and the US Food and Drug Administration issues their first guidance specifically addressing biosimilar product development. Companies are already evaluating biosimilar versions of rituximab (e.g., from Probiomed and Sandoz), infliximab (e.g., from Celltrion), trastuzumab (e.g., from Celltrion and Shanghai CP Guojian Pharmaceutical Co., Ltd.) and etanercept (e.g., from Hanwha Chemical and EMS) in Phase 3 studies. If the results are suitable, this new year may see the first approval of a biosimilar antibody in the European Union.

Although there are ample hot areas of antibody development to watch in 2012, the year will definitely hold challenges for both large and small companies. The current global economic turmoil has had a chilling effect on investments in drug development because it is a costly, time-consuming and risky business. A goal of new drug development is the production of products that fulfill unmet medical needs, but the development of the new antibody formats poses scientific and regulatory challenges that introduce an additional degree of uncertainty to the process. The biosimilar product development process also includes uncertainty because data requirements for approval are not yet clear. Regardless of whether they are positive or negative, 2012 is sure to include events in antibody-based therapeutics development that I look forward to reporting to you during the year.

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Table 1. Antibody-based therapeutics in Phase 3 studies as treatments for cancer indications

Sponsoring company	International non-proprietary name	Target; description	Indication of Phase 3 study
Active Biotech Research	Naptumomab estafenatox	5T4; Fab conjugated to staph. enterotoxin A	Advanced renal cell carcinoma*
Amgen	AMG 386	Angiopoietin-1 and -2; target-binding peptide fused to Fc of human IgG1	Epithelial ovarian, primary peritoneal or fallopian tube cancers
Wilex AG	Girentuximab	Carbonic anhydrase ix; IgG1	Non-metastatic renal cell carcinoma
Abbott/Bristol-Myers Squibb	Elotuzumab	CD2; IgG1	Multiple myeloma
TenX Biopharma/Genmab	Zanolimumab	CD4; IgG1	Mycosis fungoides or Sezary syndrome
Glycart/Genentech/ Biogen Idec	Obinutuzumab	CD20; glyco-engineered IgG1	Chronic lymphocytic leukemia; non-Hodgkin lymphoma; advanced diffuse large B-cell lymphoma
Pfizer	Inotuzumab ozogamicin	CD22; IgG1 conjugated to calicheamicin	Relapsed/refractory aggressive non-Hodgkin lymphoma
ImClone	Necitumumab	EGFR; IgG1	Non-small cell lung cancer
Morphotek	Farletuzumab	Folate receptor α; IgG1	Ovarian cancer; adenocarcinoma of the lung
Genentech	Trastuzumab emtansine	HER2; IgG1 conjugated to DM1	Locally advanced or metastatic breast cancer
Genentech	Pertuzumab	HER2; IgG1	Metastatic breast cancer
Imclone Systems/Eli Lilly	Ramucirumab	VEGFR2; IgG1	Metastatic gastric or gastroesophageal junction adenocarcinoma; breast cancer; non-small cell lung cancer; hepatocellular carcinoma; colorectal cancer

Note: Information current as of October 31, 2011. *Study NCT00420888 listed as Phase 2/3 on clinicaltrials.gov web site. Abbreviations: CD, cluster of differentiation; EGFR, epidermal growth factor receptor; Fab, antigen-binding fragment; HER2, human epidermal growth factor receptor; VEGFR2, vascular endothelial cell growth factor receptor 2. International non-proprietary naming convention: -umab, human; -zumab, humanized; -ximab, chimeric; -momab, murine.

Table 2. Antibody-based therapeutics in Phase 3 studies as treatments for immunological indications

Sponsoring company	International non-proprietary name	Target; description	Indication of Phase 3 study
Millennium/ Takeda	Vedolizumab	α4 β7 integrin; IgG1	Moderate-to-severe Crohn disease; ulcerative colitis
Lilly	Tabalumab; LY-2127399	B cell activating factor; IgG4	Systemic lupus erythematosus; rheumatoid arthritis
Biocon/CIMAB SA	Itolizumab	CD6; IgG1	Psoriasis
Genentech	Ocrelizumab	CD20; IgG1	Multiple sclerosis
Immunomedics/UCB	Epratuzumab	CD22; IgG1	Systemic lupus erythematosus
GlaxoSmithKline	Mepolizumab	IL-5; IgG1	Hypereosinophilic syndrome
Cephalon	Reslizumab	IL-5; IgG4	Eosinophilic asthma
Regeneron	Sarilumab; REGN88	IL-6R; IgG1	Ankylosing spondylitis, rheumatoid arthritis
Novartis	Secukinumab	IL-17A; IgG1	Moderate to severe plaque-type psoriasis; psoriatic arthritis; ankylosing spondylitis; rheumatoid arthritis

Note: Information current as of October 31, 2011. Abbreviations: CD, cluster of differentiation; IL, interleukin. International non-proprietary naming convention: -umab, human; -zumab, humanized.

Table 3. Antibody-based therapeutics in Phase 3 studies as treatments for other indications

Sponsoring company	International non-proprietary name	Target; description	Indication of Phase 3 study
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
Lilly	Solanezumab	Amyloid beta; IgG1	Alzheimer disease
Pfizer, Janssen	Bapineuzumab	Amyloid beta; IgG1	Alzheimer disease

Note: Information current as of October 31, 2011. International non-proprietary naming convention: -umab, human.