OUTLOOK

Development trends for human monoclonal antibody therapeutics

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Abstract | Fully human monoclonal antibodies (mAbs) are a promising and rapidly growing category of targeted therapeutic agents. The first such agents were developed during the 1980s, but none achieved clinical or commercial success. Advances in technology to generate the molecules for study — in particular, transgenic mice and yeast or phage display — renewed interest in the development of human mAbs during the 1990s. In 2002, adalimumab became the first human mAb to be approved by the US Food and Drug Administration (FDA). Since then, an additional six human mAbs have received FDA approval: panitumumab, golimumab, canakinumab, ustekinumab, ofatumumab and denosumab. In addition, 3 candidates (raxibacumab, belimumab and ipilimumab) are currently under review by the FDA, 7 are in Phase III studies and 81 are in either Phase I or II studies. Here, we analyse data on 147 human mAbs that have entered clinical study to highlight trends in their development and approval, which may help inform future studies of this class of therapeutic agents.

Human monoclonal antibodies (mAbs) are the fastest-growing category of mAb therapeutics entering clinical study[1–3]. Although the technologies developed in the 1970s and early 1980s to produce murine (rodent-derived) mAbs could be applied to produce human candidates[4], few human mAbs entered clinical development owing to manufacturing challenges. Murine antibodies are easier to produce, but are limited by safety issues and diminished efficacy owing to the immunogenicity of the mouse-derived protein sequences.

In the mid-1980s, several avenues were explored to improve the characteristics of therapeutic mAbs, based in part on the hypothesis that reducing the extent of, or eliminating, mouse-derived sequences would reduce mAb immunogenicity (BOX 1). One path focused on the development of mAbs that contained a combination of rodent-derived and human-derived sequences, resulting in chimeric and humanized mAbs. These versions constituted the majority of candidates in clinical study during the 1990s (FIG. 1), and two-thirds of the 24 mAbs currently on the market in the United States are either chimeric or humanized products.

An alternative path focused on the generation of human mAbs from transgenic-mouse technologies and phage-display technologies. However, patent disputes impeded broad use of these methods and contributed to the dearth of candidates in the clinic during the 1990s. During the 2000s, human mAbs constituted 45% of the mAb candidates in the clinic (FIG. 1), and 88 are now in clinical development. So far, seven human mAbs have been approved for marketing in the United States: adalimumab (Humira; Abbott), panitumumab (Vectibix; Amgen), golimumab (Simponi; Centocor), canakinumab (Ilaris; Novartis), ustekinumab (Stelara; Johnson & Johnson), ofatumumab (Arzerra; Genmab) and denosumab (Prolia; Amgen). Moreover, three candidates are undergoing review by the US Food and Drug Administration (FDA): raxibacumab and belimumab, both under development by Human Genome Sciences, and ipilimumab, under development by Bristol-Myers Squibb.

To determine trends in the clinical study of human mAbs, we analysed data for a total of 147 candidates that entered clinical study between 1985 and 2008, focusing primarily on the 131 candidates that entered studies after 1996 (see BOX 2 for an explanation of data sources and methods). Owing to the large body of literature on these mAbs, only limited references to the primary literature are given. We analysed data for human mAbs as a single cohort and stratified the data by clinical indication and source technology to determine developmental trends and rates of approval success in the United States. Our results should inform the future research and development of these therapeutics.

Clinical development, 1985–1996

Human mAb therapeutics first entered the clinic in the mid-1980s, but only 16 human mAbs that fit the selection criteria (BOX 2) entered clinical development during the 12-year period of 1985–1996. By contrast, 131 human mAbs were first studied in the clinic during the following 12-year period (1997–2008) (FIG. 2). As recombinant DNA technology was at an early stage of development in the 1980s, human mAbs could be produced through only a few methods — for example, through the generation of human hybridomas derived from human lymphocytes and from myeloma cell lines[5–7] or from immortalization of primary human lymphocytes using the Epstein–Barr virus[8,9]. Although these approaches were innovative at the time, they proved to be unreliable, produced insufficient quantities of antibodies and were vulnerable to contamination[4,10]. An additional limitation was that the source cells were lymphocytes from patients, who produced the cells through natural processes; for ethical reasons, it was not possible to 'immunize' patients with an experimental antigen in a controlled manner and then collect the resulting lymphocytes. Early human mAbs evaluated in the clinic were therefore limited to targets relevant to infectious diseases (62.5%) and cancer (37.5%).

Box 1 | **Immunogenicity of human monoclonal antibodies**

The immunogenicity of therapeutic proteins, including monoclonal antibodies (mAbs), affects the safety and efficacy of these products[40]. Immune responses to therapeutic mAbs are undesirable as they can neutralize the action of therapeutic mAbs[41], and hypersensitivity can result in morbidity and mortality[42]. For example, development of antibodies against adalimumab (Humira; Abbott) has been associated with lower serum drug levels and poor clinical response[43,44].

Development of human mAbs was based on the hypothesis that they would prove to be less immunogenic than chimeric or humanized mAbs, both of which contain some murine-derived protein sequences. In general, eliminating rodent sequences reduces the frequency of mAb-targeted immune responses and hypersensitivity reactions[45]. For example, only 1% of patients treated with panitumumab (Vectibix; Amgen) tested positive for neutralizing antibodies[46,47]. By contrast, the presence of pretreatment serum autoantibodies (approximately 22% of patients) against the chimeric mAb cetuximab (Erbitux; Bristol-Myers Squibb/Merck/ImClone Systems) was significantly associated with patient hypersensitivity[48]. However, the immunogenicity of specific mAb candidates cannot be predicted based only on the amount of non-human sequence in the molecule. This is because various other factors can affect immunogenicity rates — for example, the type of disease being treated[43,49] or the concomitant administration of immunosuppresive agents[50]. In addition, immunogenicity rates can vary between studies. Different methods in different studies, such as enzyme-linked immunosorbent assay or surface plasmon resonance, may be used to quantify drug-specific antibodies[51], and the results reported will depend on the sensitivity of the assay[52].

Several lines of thought suggest that it is unreasonable to expect human mAb therapeutics to have immunogenicity rates of zero. For example, humans are diverse in genotype and phenotype, and immunoglobulin G allotypes differ within and between populations[53]. In addition, the ability of the human immune system to generate natural anti-idiotypic antibodies is well documented[54]; the presence of such antibodies in polyclonal intravenous immunoglobulin preparations may contribute to the efficacy of the products[55]. Various methods to reduce the immunogenicity of human mAbs have been suggested, such as production of allotypical variants of mAb products to match the specific immunoglobulin gene segment alleles found in the genomes of distinct patient populations, or the use of protein engineering on the complementarity-determining region of the mAb[53,56]. Although the causes of, and potential solutions to, immunogenicity of human mAbs are still being investigated, it is clear that immunogenicity must be included as part of the overall evaluation of the risk to benefit ratio for patients[57].

Fifteen out of the 16 early human mAb candidates were terminated during clinical development. One candidate — nebacumab (Centoxin; Centocor) — was approved for marketing, but the product was subsequently withdrawn. Nebacumab was a human hybridoma-derived endotoxin-specific immunoglobulin M (IgM) mAb. It was approved for the treatment of sepsis or Gram-negative bacteraemia[11] and was the first human therapeutic mAb to be reviewed by a regulatory agency. Statistically significant benefits that were observed post-hoc in sub-populations in a multi-centre, randomized, double-blind, placebo-controlled clinical trial[12] supported marketing approval in several European countries and in New Zealand. A marketing application was submitted in the United States, but a second study required by the FDA[13,14], the CHESS trial, was terminated early when an interim analysis found a non-statistically significant increase in mortality in patients without Gram-negative bacteraemia treated with the antibody[15]. Centocor voluntarily withdrew the product and suspended further development.

Clinical development, 1997–2008

In the late 1990s, human mAb therapeutics derived from transgenic-mouse or phage-display technologies first entered clinical development. Between 1997 and 2008, a total of 131 human mAbs entered clinical study, at a rate of least 11 per year between 2001 and 2008 (FIG. 2). Of the 131 candidates, 88 were in active clinical development, with 7 in Phase III studies, 51 in Phase II and 30 in Phase I. A total of 7 were approved for marketing by the FDA, 3 are undergoing review by the FDA and the clinical study of 33 was discontinued.

Approved human mAbs

Seven human mAbs have been approved in the United States and in the European Union (TABLE 1). The first product (adalimumab) was approved by the FDA in 2002, with the second following in 2006. Notably, a total of four human mAbs were approved by the FDA in 2009.

Adalimumab is specific for tumour necrosis factor (TNF) and was the first human mAb approved by the FDA. The product, which was developed using phage-display technology from Cambridge Antibody Technology, was approved in December 2002 as a treatment for adult patients with moderately to severely active rheumatoid arthritis. Adalimumab was subsequently approved by the FDA for the following indications: psoriatic arthritis (in 2005), ankylosing spondylitis (in 2006) and Crohn's disease (in 2007), as well as for juvenile idiopathic arthritis and chronic plaque psoriasis (both in 2008). Adalimumab is also approved for the treatment of these diseases in the European Union. According to the manufacturer, adalimumab generated US$4.5 billion in global sales in 2008 (REF. 16).

Panitumumab is a human mAb that is specific for epidermal growth factor receptor (EGFR) and was discovered using Abgenix's XenoMouse technology. The product was approved by the FDA in September 2006 for EGFR-expressing refractory metastatic colorectal carcinoma. The clinical development programme comprised a total of 15 studies initiated before approval, including 10 Phase I studies[17]. The product was given accelerated approval based on results from one randomized, controlled trial involving 463 patients who showed prolongation of the time to disease progression from 60 days to 97 days, but no impact on overall survival[18]. In December 2007, the European Commission granted conditional marketing approval for panitumumab as a treatment for EGFR-expressing metastatic colon cancer. Panitumumab generated global sales of $153 million in 2008.

Golimumab is a TNF-specific IgG1 mAb that was approved in April 2009 by the FDA for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. The mAb was generated using Medarex's UltiMab transgenic mouse platform. Although both adalimumab and golimumab are human TNF-specific mAbs, golimumab has a once per month subcutaneous dosing regimen, whereas adalimumab is administered every other week[19]. In October 2009, golimumab was approved in the European Union as a once per month, subcutaneous therapy for the treatment of moderate to severe, active rheumatoid arthritis, of active and progressive psoriatic arthritis, and of severe, active ankylosing spondylitis.

Canakinumab, an interleukin-1β (IL-1β)-specific IgG1 mAb derived from the UltiMab platform technology was approved by the FDA in June 2009 as a treatment for cryopyrin-associated periodic syndromes (CAPS), which include rare genetic fever disorders such as Muckle–Wells syndrome.

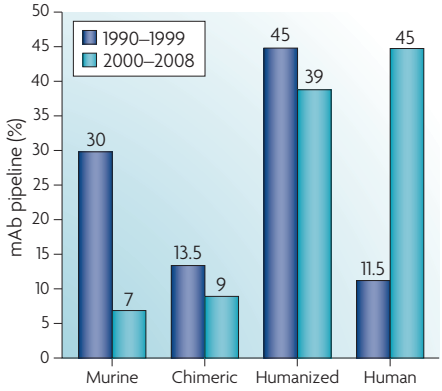

Figure 1 | **Percentage of four types of mAbs in clinical development during the periods 1990–1999 and 2000–2008.** Monoclonal antibodies (mAbs) that entered clinical study sponsored by commercial firms between 1990 and 1999 and between 2000 and 2008 were classified according to their sequence source: murine only, chimeric (murine variable regions and human constant regions), humanized (human with murine complementarity-determining regions), and human only. These data demonstrate the substantial increase in the clinical study of human mAbs in the 2000s, a trend towards reduced use of humanization and chimeric candidates, and a dramatic reduction in the number of murine mAbs in clinical development in the 2000s.

Approval was based on a single Phase III trial[20], as well as on smaller proof-of-concept studies[21]. CAPS are rare, with the number of patients with CAPS living in the United States estimated to be in the hundreds or low thousands. In October 2009, canakinumab was approved in the European Union for patients with CAPS as young as 4 years old. Canakinumab is currently in early-stage studies for the treatment of other disorders, including rheumatoid arthritis, gout and diabetes mellitus.

Ustekinumab, another UltiMab-derived product, targets the p40 subunit shared by IL-12 and IL-23. The mAb was approved by the FDA in September 2009 as a treatment for plaque psoriasis. Two Phase III studies in patients with moderate to severe plaque psoriasis have been completed, as well as a third Phase III study comparing ustekinumab with etanercept (Enbrel; Amgen/Pfizer), a fusion protein that targets TNF, in the same patient population[22]. In January 2009, the European Commission approved ustekinumab for treating moderate to severe plaque psoriasis in adults. Ustekinumab is also currently in Phase II studies as a treatment for sarcoidosis, and in Phase III studies as a treatment for palmoplantar pustular psoriasis, palmoplantar pustulosis or psoriatic arthritis.

Ofatumumab is a CD20-specific mAb generated from the UltiMab platform. It targets a CD20 epitope that is distinct from the epitope targeted by rituximab (Rituxan/MabThera; Genentech/Biogen Idec/Roche), the pioneering CD20-specific chimeric mAb. Rituximab was approved for the treatment of non-Hodgkin's lymphoma in 1997, and subsequently has also received regulatory approval for the treatment of rheumatoid arthritis and chronic lymphocytic leukaemia[23,24]. Ofatumumab was approved by the FDA in October 2009, and given a conditional approval by the European Commission in April 2010, for the treatment of chronic lymphocytic leukaemia that is refractory to the humanized mAb alemtuzumab (Campath; Genzyme) and the nucleoside analogue fludarabine. Ofatumumab is under Phase III evaluation in patients with non-Hodgkin's lymphoma and in patients with rheumatoid arthritis[25].

Denosumab, a mAb specific for receptor activator of nuclear factor-κB ligand (RANKL), was approved by the FDA in June 2010 for the treatment of postmenopausal osteoporosis (PMO) in women. Trials have also been conducted to support a prevention indication for PMO, as well as for the treatment and prevention of bone loss in patients undergoing hormone ablation therapy for prostate or breast cancer[26]. Denosumab was approved in Europe for the treatment of PMO and of bone loss in patients with prostate cancer undergoing hormone ablation therapy. It is also undergoing regulatory review in Switzerland, Australia and Canada for one or more of these indications.

Although not yet approved, three human mAbs — raxibacumab, belimumab and ipilimumab — are currently undergoing review by the FDA. Human Genome Sciences is the sponsor of both raxibacumab and belimumab, and Bristol-Myers Squibb is sponsoring ipilimumab. Raxibacumab binds *Bacillus anthracis* protective antigen and has been developed as a treatment for inhalation anthrax[27]. Human Genome Sciences initiated the delivery of 20,000 doses of raxibacumab to the US Strategic National Stockpile for emergency use under a contract with the US Biomedical Advanced Research and Development Authority, and an additional 45,000 doses were ordered in July 2009.

Belimumab is a human mAb specific for B lymphocyte stimulator, and was identified through use of phage-display-based technologies in collaboration with Cambridge Antibody Technology. GlaxoSmithKline and Human Genome Sciences submitted marketing applications to both the FDA and the European Medicines Agency in June 2010 for the use of belimumab in systemic lupus erythematosus. This submission is based primarily on clinical and biomarker improvements in two pivotal Phase III trials in systemic lupus erythematosus — BLISS-52 and BLISS-76, which collectively involved 1,684 patients with this disease globally[28] — as well as favourable post-hoc analyses of Phase II studies[29]. If the application is successful, belimumab will be the first new therapeutic approved for systemic lupus erythematosus in 50 years. GlaxoSmithKline and Human Genome Sciences are further

Box 2 | **Analysis criteria**

Since it was founded in 1976, the Tufts Center for the Study of Drug Development has collected data on the clinical study and approval of therapeutics and vaccines. Data for monoclonal antibodies (mAbs) were collected by surveying pharmaceutical and biotechnology firms, from public documents and from commercially available databases (IDdb3, IMS R&D Focus and PharmaProjects). Data were updated with all changes that were noted until June 2010.

The data set comprises a total of 147 human mAbs that entered clinical study sponsored by commercial firms between January 1985 and December 2008, 131 of which entered study between 1997 and 2008. The status of the candidates was as follows: 88 were in clinical studies and not yet approved in any country (30 in Phase I, 51 in Phase II and 7 in Phase III); 3 were under regulatory review by the US Food and Drug Administration; 7 were approved in the United States; and 49 were discontinued. Candidates in Phase I or II were assigned to Phase II, and products in Phase II or III were assigned to Phase III. The human mAb data were compared with data for humanized mAbs that entered clinical study between 1988 and 2008 ($n = 167$) and between 1997 and 2008 ($n = 133$).

Approval success calculations were based on data for candidates with known fates (market approval in the United States or discontinuation of all clinical studies). Percentage completion was defined as the percentage of candidates with a known fate in a given cohort. Clinical-phase transition probabilities were calculated as follows: the number of candidates that successfully completed a given phase was divided by the difference between the number of candidates that entered the phase and those that were still in the phase at the time of the calculation. Transitions occurring between phases of clinical studies conducted worldwide were included.

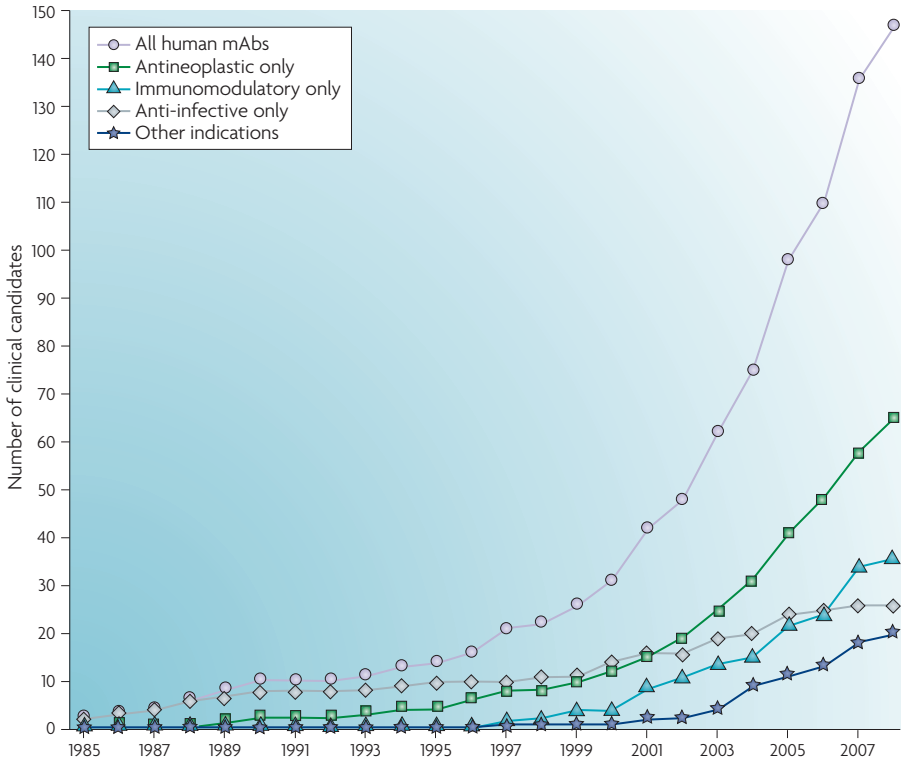

Figure 2 | **Cumulative number of human mAbs entering clinical study between 1985 and 2008.** The primary therapeutic category for the development of human monoclonal antibodies (mAbs) that entered clinical study sponsored by commercial firms between 1985 and 2008 was determined. The cumulative numbers of human mAbs that entered development for antineoplastic, immunomodulatory, anti-infective and all other indications were tabulated. These data demonstrate the rapid growth in human mAbs in clinical research generally, and the particularly high rates of development of antineoplastic and immunomodulatory human mAbs.

sponsoring a series of Phase II studies of belimumab in rheumatoid arthritis, Sjögren's syndrome, Waldenstrom's disease and pre-transplantation desensitization.

Ipilimumab is an immunostimulatory mAb that targets cytotoxic T lymphocyte antigen 4 (CTLA4). The candidate was derived from Medarex's UltiMab transgenic mouse technology and is under clinical development by Bristol-Myers Squibb. A marketing application was submitted to the FDA and the European Medicines Agency in June 2010 for the use of ipilimumab as a second-line treatment for metastatic melanoma. Recent Phase III study results indicate that ipilimumab alone or in combination with a gp100 peptide vaccine improved the overall survival of patients with metastatic melanoma who had received previous treatment[30]. Ipilimumab has been evaluated in Phase II studies of non-small cell lung cancer, breast cancer and prostate cancer, as well as brain metastases. Bristol-Myers Squibb is planning Phase III studies of ipilimumab in non-small cell lung cancer and in prostate cancer.

Approval success rates

Probabilities of success (POS) values, such as cumulative approval in the United States and transition rates between clinical phases, have inherent limitations when the calculations involve cohorts with high percentages of candidates in clinical study, as is the case for human mAbs. Calculated values will vary until fates for all candidates are known. POS values for human mAbs that entered clinical study after 1996 are preliminary estimates because fates of only 31% of the 131 candidates are known (7 approved, 33 terminated), and only 20 reached Phase III trials. In addition, the values are likely to be underestimates because clinical development of therapeutic mAbs takes an average of approximately 6 years, and so the human mAb candidates that entered clinical study during the past 6 years have not had sufficient time for approval.

Nevertheless, POS values are crucial for the decision-making process used by investors, as well as for strategic planning by the biopharmaceutical industry, and even preliminary estimates can be useful. Based on the current data, the cumulative approval rate for human mAbs is 17.5%, which will increase to 23% if raxibacumab, belimumab and ipilimumab are approved. Transition rates between clinical phases (which include data for candidates currently in studies) for the human mAbs were 89% for transitions between Phase I to II; 51% for transitions between Phase II to III; and 73% for transitions between Phase III to approval by the FDA (FIG. 3).

The cumulative approval success rate for human mAbs is slightly higher than the 15% value that we have calculated for humanized mAbs, which first entered commercial clinical development in 1988 (BOX 2). As economic conditions, regulatory climate and competitive landscape can change over time, we also compared POS values for human and humanized mAbs that entered clinical development in the same period (1997–2008). The cumulative approval success rate was 17.5% for the human mAb cohort (7 approvals per 40 candidates with known fates) and 9% for the humanized mAb cohort (5 approvals per 53 candidates with known fates). Transition rates for Phase I to II and Phase II to III were higher for the human mAbs, but the Phase III to approval rate was lower (FIG. 3). Final fates were known for 31% and 40% of the human and humanized mAbs developed in this period, respectively, and the rates may change as the final fates for more candidates are determined.

Clinical indications

Primary therapeutic indications were identified for the 131 human mAbs that entered clinical study after 1996. Overall, most mAb therapeutics, regardless of sequence source, are developed as treatments for cancer or immunological disorders[1–3]. This is also the case for human mAbs, with 59 (45%) studied for cancer and 36 (28%) for immunological disorders. These proportions have remained fairly constant since 1997 (FIG. 2).

Of the 59 antineoplastic mAbs, fates are known for only 13 (22%): 2 are approved products (panitumumab and ofatumumab) and 11 candidates were terminated. The cumulative approval success rate is 15% based on currently available data. Most of the 46 human antineoplastic mAbs that are in clinical studies are at the early stages of the process, with 5 in Phase III trials and 1 (ipilimumab) in regulatory review in the United States and in the European Union. Immunomodulatory human mAbs have a higher cumulative approval success rate (33%) than either the antineoplastic or the

Table 1 | **Human mAbs approved or under FDA review***

Human mAb (trade name; company name)	Description	Indication of first US approval	FDA designations	Date of first US (EU) approval
Adalimumab (Humira; Abbott)	TNF-specific, IgG1κ	Rheumatoid arthritis	S	31 Dec 2002 (8 Sep 2003)
Panitumumab (Vectibix; Amgen)	EGFR-specific, IgG2κ	Colorectal cancer	P, FT, AA	27 Sep 2006 (3 Dec 2007)
Golimumab (Simponi; Centocor)	TNF-specific, IgG1	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	S	24 Apr 2009 (1 Oct 2009)
Canakinumab (Ilaris; Novartis)	IL-1β-specific, IgG1κ	Cryopyrin-associated periodic syndromes	P, O	18 Jun 2009 (23 Oct 2009)
Ustekinumab (Stelara; Johnson & Johnson)	IL-12/IL-23 p40-specific, IgG1	Plaque psoriasis	S	25 Sep 2009 (16 Jan 2009)
Ofatumumab (Arzerra; Genmab)	CD20-specific, IgG1	Chronic lymphocytic leukaemia	P, FT	26 Oct 2009 (19 Apr 2010)
Denosumab (Prolia; Amgen)	RANKL-specific, IgG2	Treatment of postmenopausal osteoporosis‡	S	1 Jun 2010 (26 May 2010)
Raxibacumab	PA-specific, IgG1	Inhalation anthrax	P, FT, O	Under review by the FDA
Belimumab	B lymphocyte stimulator-specific, IgG1	Systemic lupus erythematosus	P, FT	Under review by the FDA and the EMA
Ipilimumab	CTLA4-specific, IgG1	Metastatic melanoma	P, FT, O	Under review by the FDA and the EMA

AA, accelerated approval; CTLA, cytotoxic T lymphocyte-associated antigen; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drug Administration; FT, FDA fast track drug; Ig, immunoglobulin; IL, interleukin; mAb, monoclonal antibody; O, FDA orphan drug; P, priority review; PA, *Bacillus anthracis* protective antigen; RANKL, receptor for activation of nuclear factor-κB ligand; S, standard review; TNF, tumour necrosis factor. *As of June 2010. ‡Also approved in Europe for the treatment of bone loss in patients with prostate cancer undergoing hormone ablation therapy.

overall human mAb cohort. This calculation was based on data for only 12 molecules for which definite fates are known, including adalimumab, golimumab, canakinumab, ustekinumab and 8 terminated candidates. Of the 24 human immunomodulatory mAb candidates currently in clinical development, 8 are in Phase I, 13 are in Phase II, 2 are in Phase III and belimumab is undergoing regulatory review in the United States and in the European Union.

An additional 36 human mAbs that entered clinical study after 1996 were studied for non-traditional indications — that is, disorders that are not cancer or immunological in nature. Half of these were treatments for infectious diseases, with a focus on nosocomial, anthrax and chronic viral infections[31]. The remaining 18 candidates were studied for conditions such as osteoporosis, respiratory disorders, muscular dystrophy, Alzheimer's disease and pain. Of the 36 candidates, 1 (denosumab) has been approved, 1 (raxibacumab) is undergoing review by the FDA (TABLE 1) and 14 were terminated. The current cumulative success rate for mAbs studied as treatments for these non-traditional indications is 6.6%, which will rise to 12.5% if raxibacumab is approved for inhalation anthrax. The 20 candidates in clinical development were all in either Phase I or II studies.

Molecular targets

The target of a therapeutic antibody is a major determinant of its efficacy and safety profile. Antigenic targets were identified for 125 of the 131 human mAbs (TABLE 2). These mAbs targeted a total of 89 unique antigens, and only 22 antigens were targeted by two or more human mAbs. Seven antigens — CTLA4, EGFR, fibronectin, insulin-like growth factor 1 receptor (IGF1R), transforming growth factor-β (TGFβ), TNF and TNF-related apoptosis-inducing ligand receptor 2 (TRAILR2) — were targeted by more than two human mAbs. Of the 125 mAbs, 55 (44%) targeted antigens that are relevant to antineoplastic diseases, 36 (29%) targeted antigens relevant to immunological diseases and 17 (14%) targeted antigens relevant to infectious diseases.

Of the 55 anticancer candidates with known targets, 19 mAbs (33%) were specific for only 5 targets: IGF1R (6 mAbs), TRAILR2 (4 mAbs), EGFR (3 mAbs), CTLA4 (3 mAbs) and fibronectin (3 mAbs). Of these, only EGFR was among the ten most frequently targeted antigens for all anticancer mAbs studied in the clinic from 1980 to 2005 (REF. 32), suggesting that developers of human mAbs may be focusing on novel therapeutic strategies. Nevertheless, at least some human mAbs share oncology targets with therapeutic mAbs approved by the FDA, including EGFR (target of panitumumab and cetuximab) and CD20 (target of rituximab, ibritumomab tiuxetan (Zevalin; Spectrum Pharmaceuticals), iodine-131 tositumomab (Bexxar; GlaxoSmithKline) and ofatumumab). Most of the anti-neoplastic human mAbs target cell-surface molecules; only two were known to target soluble factors (hepatocyte growth factor and platelet-derived growth factor).

By contrast, 24 out of the 36 immunomodulatory mAbs with known targets were raised against cytokines and serum factors. Interleukins constitute the largest target group; targeted antigens include IL-1β, IL-6, IL-8, IL-12, IL-13, IL-15, IL-18, IL-17A and IL-20. Ten out of the 36 mAbs target markers of leukocyte activity and differentiation, and are in early-phase clinical trials. Two immunomodulatory human mAbs with targets that are unique compared with those of marketed mAbs are currently in Phase II studies: briakinumab (developed by Abbott), which targets the p40 subunit common to IL-12 and IL-23, and AIN457 (developed by Novartis), which is an IL-17A-specific mAb.

The 18 human mAbs intended for the treatment of infectious diseases are a highly heterogeneous group. Ten are directed against targets implicated in viral infections, including HIV (six mAbs), viral hepatitis (three mAbs) and rabies (one mAb); several of these candidates are cocktails of more than one human mAb. Six human mAbs target bacterial antigens, of which four are bacterial cytotoxins, such as *Clostridium difficile* enterotoxins (MK-3415A; developed by Merck and Co.) and anthrax protective antigen (raxibacumab), and three target cellular features of *Pseudomonas aeruginosa*

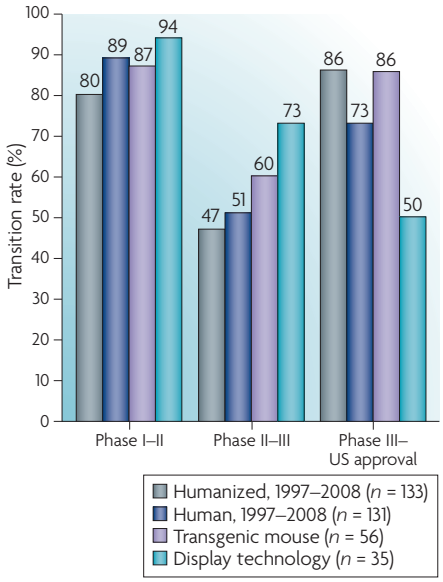

Figure 3 | **Transition rates between clinical phases for human mAbs.** The historical rates of transition from Phase I to II, Phase II to III and Phase III to review by the US Food and Drug Administration are depicted. The review to approval rate was 100% for all human monoclonal antibodies (mAbs) in the categories presented. Data for human mAbs derived from transgenic mouse and display technologies are shown separately and data for humanized mAbs are included for comparison.

(KB001; developed by Kalobios/Sanofi Pasteur, and panobacumab; developed by Kenta Biotech) and methicillin-resistant *Staphylococcus aureus* (Aurograb; developed by Novartis). Finally, one human mAb (efungumab; developed by Novartis) targets candidal heat shock protein 90, an intracellular antigen released during infection.

Platform technologies

We were able to identify the platform technologies that were used to develop 103 (79%) of the 131 mAbs analysed. Despite the availability of innovative approaches to sample natural human immune responses for the creation of mAbs[10], most therapeutic human mAbs in clinical study were derived from either immunization of transgenic mice expressing human antibody genes or phage-display recombinants. The first candidate molecules from both technologies entered clinical development in the late 1990s, so performance differences cannot be attributed to time-dependent variables.

Use of transgenic mice expressing human immunoglobulins avoids human anti-mouse antibody responses and maintains the technical advantages of mouse hybridomas. Of the 103 candidates from identified platforms, 56 were produced in transgenic mice; 6 were approved for marketing (panitumumab, golimumab, canakinumab, ustekinumab, ofatumumab and denosumab), and 15 were terminated. The current cumulative approval success rate is therefore 29%, a higher rate than that currently calculated for human mAbs as a whole (17.5%). In particular, candidates derived from transgenic mouse platforms have considerably higher Phase II to III and Phase III to approval transition rates than those of the entire cohort of human mAbs (FIG. 3). Again, it is important to note that these rates will change to some extent over time as fates for more human mAb candidates are determined in the future. The two primary technologies for generating human mAbs from transgenic mice were first described in 1994 (REFS 33,34) and use two different engineering approaches to inactivate endogenous mouse genes and to insert exogenous human immunoglobulin genes[35,36].

A total of 34 human mAbs were identified as being derived from Medarex's HuMAb, UltiMab, TC Mouse or KM Mouse platforms. Four of these candidates have been approved (golimumab, canakinumab, ustekinumab and ofatumumab), 1 (ipilimumab) is under regulatory review, 7 were terminated and 22 are now in clinical studies (7 at Phase I, 14 at Phase II and 1 at Phase III). Although immunoglobulin isotype was not known for all the candidates, the majority of Medarex platform-derived molecules were IgG1 (at least 21 mAbs). Of the total 34 mAbs, 16 (47%) were intended for the treatment of cancer, 13 (38%) for immunological conditions and 3 (9%) were anti-infective agents.

The XenoMouse platform developed by Abgenix, which was acquired by Amgen in 2005, was used for the development of at least 18 human mAbs. Two (panitumumab and denosumab) are approved, nine are in clinical study (two at Phase II, five at Phase II and two at Phase III) and seven are discontinued. Most of the XenoMouse-derived candidates were IgG2 (11 mAbs), four were IgG1, one was IgG4 and two were of unknown isotype. Two-thirds of the mAbs were cancer treatments; only two (11%) were for immunological conditions and one (6%) was an anti-infective agent.

Other transgenic mouse-based platforms, such as Regeneron's VelocImmune and XTL Biopharmaceuticals' Trimera, have each yielded at least one early-stage candidate.

A second popular approach for producing human mAbs is the recombinant expression of human antigen-binding fragments in a bacteriophage and subsequent selection is based on desirable antigen-binding properties[37–39]. This technology was used to create at least 35 human mAbs that entered clinical development. Unlike transgenic mouse technologies, phage-display is used by numerous companies, including MedImmune Cambridge (formerly Cambridge Antibody Technology), Dyax, MorphoSys, BioInvent and NeuTec.

One phage-display-derived mAb (adalimumab) has been approved, and two (raxibacumab and belimumab) are under review by the FDA. In addition, 3 phage-display-derived mAb candidates are in Phase I, 19 are in Phase II and 3 are in Phase III. So far, development of seven mAbs has been discontinued. The current cumulative approval success rate for all phage-display-based technologies is 12.5%, although this is

Glossary

Allotype
Antibody allotypes are defined by their polymorphism within the immunoglobulin heavy and light chains. Natural allelic genetic variation in the constant region of genes in humans may predispose a given patient to anti-drug antibody responses if the drug is a foreign allotype.

Ankylosing spondylitis
A chronic condition of unknown aetiology that is characterized by inflammation of the joints of the spine and pelvis. Disease progression may result in fusion of the joints.

Anti-idiotypic antibody
An antibody that targets the hypervariable antigen-binding domain of an exogenous immunoglobulin, including therapeutic monoclonal antibodies. As the constant regions are fairly conserved, with the exception of allotypic differences, many anti-immunoglobulin responses will be directed against the highly variable, antigen-binding domain.

Cryopyrin-associated periodic syndromes
(CAPS). A group of rare, inherited autoimmune disorders associated with over-secretion of interleukin-1 that may cause inflammation of the skin, eyes, bones, joints and meninges.

Phage-display technologies
A method involving the use of bacteriophages to select desirable antibody variable domains based on their binding properties.

Pre-transplant desensitization
In the recipient patient, reduction of antibody-producing cells or the amount of circulating antibodies that might target foreign tissue prior to transplantation of an organ.

Systemic lupus erythematosus
A chronic, inflammatory autoimmune disease affecting connective tissue throughout the body.

based on results for a small number of candidates. This rate is lower than that observed for all human mAbs (17.5%) and for the transgenic-mouse-derived human mAbs (29%); however, if raxibacumab and belimumab are approved, the cumulative approval success rate will increase to 30%. Human mAbs derived from phage-display technology have high Phase I to II and Phase II to III transition rates, but the Phase III to approval rate is currently 50% (FIG. 3).

None of the 35 mAbs known to be derived from phage display was identified as IgG2, which is an interesting observation given the diversity of phage-display platforms. Of those with known isotypes, 20 were IgG1 and 9 were IgG4. Cambridge Antibody Technology was responsible for 15 phage-display-derived human mAbs, including adalimumab and four terminated candidates; these therefore have a cumulative success rate of 20% so far, which is comparable to that of Medarex platform-derived mAbs. Cambridge Antibody Technology has also produced a substantial number of IgG4 molecules (7 out of 9 IgG4 mAbs are known to be derived from phage-display technology).

Table 2 | **Antigenic targets of human mAbs in development***

Antigen	Therapeutic category	No. of human mAbs
Bacillus anthracis PA	Infectious disease	2
CD30	Cancer	2
CD40	Cancer	2
Clostridium difficile enterotoxin	Infectious disease	2
CTLA4	Cancer	3
EGFR	Cancer	3
EPCAM	Cancer	2
Fibronectin	Cancer	3
GM-CSF	Immunological disease	2
HER3	Cancer	2
HIV gp41	Infectious disease	2
IGF1R	Cancer	6
IL-6	Immunological disease	2
IL-8	Immunological disease	2
IL-12	Immunological disease	2
Integrins	Immunological disease	2
PDGF	Cancer, immunological disease	2
PSMA	Cancer	2
Tenascin	Cancer	2
TGFβ	Immunological, ophthalmic and fibrotic diseases	3
TNF	Immunological disease	3
TRAILR2	Cancer	4
Unknown	Cancer, immunological disease	6

CTLA4, cytotoxic T lymphocyte-associated antigen 4; EGFR, epidermal growth factor receptor; EPCAM, epithelial cell adhesion molecule; GM-CSF, granulocyte–macrophage colony-stimulating factor; gp, glycoprotein; HER3, human epidermal growth factor receptor 3 (also known as ERBB3); IGF1R, insulin-like growth factor 1 receptor; IL, interleukin; mAb, monoclonal antibody; PA, protective antigen; PDGF, platelet-derived growth factor; PSMA, prostate-specific membrane antigen (also known as FOLH1); TGF, transforming growth factor; TNF, tumour necrosis factor; TRAILR2, tumour necrosis factor-related apoptosis-inducing ligand receptor 2 (also known as TNFRSF10B). *This table lists molecules that were targets for a minimum of two human mAbs that entered clinical study between 1997 and 2008.

Conclusions

The acquisition of mAb technology companies, including Abgenix, Cambridge Antibody Technology and Medarex, by major drug companies is an indication of the pharmaceutical industry's increasing interest in human mAb therapeutics. Our analyses indicate that human mAbs are a rich source of new therapeutics, with 7 approved in the United States, 3 under review by the FDA, 7 in late-stage development and 81 in early-stage development. Although limited data are available, the current POS rates for human mAbs are similar or superior to those for current humanized mAb candidates. The cumulative approval success rate for human mAbs is currently 17.5%, although this could change substantially in the coming years depending on the fate of the high percentage of candidates that are still in clinical study.

We found that human mAbs are primarily in development for the treatment of cancer and immunological disorders. The cumulative approval rate for immunomodulatory human mAbs (33%) is higher than that for the antineoplastic (15%) candidates. This difference is also observed when chimeric and humanized therapeutic mAbs are considered[1]. The majority of human mAbs were derived from transgenic mouse technologies and from phage-display technologies, although human hybridoma and transformed cells have also been used to produce human mAbs.

The two transgenic mouse technologies have so far generated six mAbs that gained approval (29% POS) and one candidate that is under review by the FDA. The heterogeneous mix of phage-display technologies collectively have generated one marketed product (12.5% POS) and two candidates that are under review by the FDA. The earliest transgenic-mouse-derived and phage-display-derived human mAbs entered clinical development in the same year, so timing cannot account for the differences. However, if raxibacumab, belimumab and ipilimumab are approved, phage-display-derived human mAbs will have demonstrated preliminary POS rates comparable to mouse-derived human mAbs (30% versus 32%, respectively). A potential disincentive to the use of the transgenic mouse platform is that the intellectual property is controlled by only a few companies, and so access may be costly. Phage-display technologies are particularly advantageous when target antigens are shared by humans and mice.

With the current trend towards developing targeted therapeutics, the focus on human mAbs is likely to intensify owing to a perceived low level of immunogenicity of these agents (BOX 1). The pharmaceutical and biotechnology industry, regulatory agencies, physicians and patients have now gained sufficient experience with mAbs to view them as little different from any other therapeutic. The data so far indicate that mAbs derived from human sequences by various technologies are effective in addressing novel therapeutic targets, and

are likely to be less immunogenic than those with rodent-derived sequences. There is considerable unmet medical need in the three main areas of study for investigational human mAbs — cancer, immunological and infectious diseases — and these emerging agents could therefore provide valuable new treatment options.

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doi:10.1038/nrd3229
Published online 3 September 2010

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Competing interests statement
The authors declare no competing financial interests.

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