Biotechnology and Bioprocess Engineering 15: 709-715 (2010)
DOI 10.1007/s12257-009-3113-1

Review

Current Perspectives on Therapeutic Antibodies

Soomin Yoon, Yong-Sung Kim, Hyunbo Shim, and Junho Chung

Received: 8 November 2009 / Revised: 26 February 2010 / Accepted: 12 April 2010

Abstract Since the first monoclonal antibody, muromonab-CD3, was approved for therapeutic use in 1986, numerous molecules have been targeted using therapeutic antibody technology, resulting in 26 therapeutic antibodies being approved by the US FDA as of November, 2009. Initial concerns regarding antibody drugs focused on immunogenicity, short serum half-life, and weak efficacy. As the types of antibodies progressed from murine to chimeric, humanized, and fully human antibodies, great progress has been made in immunogenicity and *in vivo* instability issues. For example, humanized antibodies, such as bevacizumab, exhibit less than 0.2% immunogenicity and a 20 day serum half-life, which is comparable to native immunoglobulin. Some recently developed antibodies are exceedingly efficacious and have become first-line therapy for their target diseases. Here, we address and analyze all clinically approved therapeutic antibodies to date by discussing immunogenicity, half-life, and efficacy.

Keywords: efficacy, immunogenicity, serum half-life, therapeutic monoclonal antibody

Soomin Yoon, Junho Chung*
Department of Biochemistry and Molecular Biology, Seoul National University College of Medicine and Cancer Research Institute, Seoul National University, Seoul 110-799, Korea
Tel: +82-2-740-8242; Fax: +82-2-763-6317
E-mail: jjhchung@snu.ac.kr; junhochung@me.com

Yong-Sung Kim
Department of Molecular Science and Technology, Division of Applied Chemistry and Biological Engineering, Ajou University, Suwon 443-749, Korea

Hyunbo Shim
Department of Life Science and Division of Life and Pharmaceutical Sciences, Ewha Womans University, Seoul 120-750, Korea

1. Introduction

The first clinically available monoclonal antibody was muromonab-CD3 (Orthoclone OKT-3), a murine antibody that was approved by the United States Food and Drug Administration (FDA) in 1986. Eight years later in 1994, abciximab (ReoPro), the first chimeric antibody composed of variable regions from a mouse antibody and constant regions from a human antibody, was approved. Just 3 years later, daclizumab (Zenapax) was approved. Daclizumab is an improved version of an engineered antibody called humanized antibody, where only complementarity-determining regions (CDRs) of mouse antibodies were grafted onto the corresponding regions of a human antibody. Subsequently, adalimumab (Humira), the first fully human antibody, was approved in 2002. Currently, 26 monoclonal antibodies excluding efalizumab (Raptiva), which was withdrawn from the market, are available for human use (Table 1). Hundreds more are undergoing clinical trials for treating diseases such as cancers, immune disorders, and infections. The therapeutic antibody market was worth $32 billion in 2008, commanding over 30% of the biological drug market and is expected to account for 9% of the total pharmaceutical market by 2012. This rapid growth was made possible by overcoming numerous initial concerns. Here, we review the current status of therapeutic antibodies, focusing on their immunogenicity, serum half-life, and therapeutic efficacy.

1.1. Immunogenicity

One of the primary difficulties of developing antibody therapeutics is the potential immunogenic response when the drugs are administered to humans, because an antibody is a macromolecule that can behave as an immunogen. An undesired immune response against an antibody leads to its rapid clearance or even induce life-threatening side effects including anaphylactic shock. Numerous factors influence

Table 1. Immunogenicities and half-lives of therapeutic antibodies approved in the United States

No	Generic name	Trade name	mAb type	Antigen	US approval date	Immunogenicity (%)	Isotype	Route	Half-life (days)
1	Muromonab-CD3	Orthoclone OKT3	murine	CD3	19.06.1986	50	IgG2aκ	IV	0.3 ~ 0.75
2	Ibritumomab tiuxetan	Zevalin	murine	CD20	19.02.2002	< 2	IgG1κ	IV	1.25
3	Tositumomab-I131	Bexxar	murine	CD20	27.06.2003	< 8	IgG2aλ	IV	2.7
4	Abciximab	Reopro	chimeric	GPIIb/IIIa, vitronectin	22.12.1994	0.5 ~ 14	Fab	IV	< 0.006
5	Rituximab	Rituxan	chimeric	CD20	26.11.1997	1.1 ~ 11	IgG1κ	IV	22
6	Basiliximab	Simulect	chimeric	CD25	12.05.1998	6 ~ 44	IgG1κ	IV	4 ~ 10.4
7	Infliximab	Remicade	chimeric	TNFα	24.08.1998	8 ~ 37	IgG1κ	IV	7.7 ~ 9.5
8	Cetuximab	Erbitux	chimeric	EGFR	12.02.2004	5	IgG1κ	IV	0.38 ~ 9.6
9	Daclizumab	Zenapax	humanized	CD25	10.12.1997	14 ~ 34	IgG1κ	IV	20
10	Palivizumab	Synagis	humanized	RSVgpF	19.06.1998	1.4 ~ 11	IgG1κ	IM	20
11	Trastuzumab	Herceptin	humanized	HER-2	25.09.1998	< 0.2	IgG1κ	IV	11 ~ 23
12	Gemtuzumab ozogamicin	Mylotarg	humanized	CD33	17.05.2000	< 0.2	IgG4κ	IV	1.8 ~ 6
13	Alemtuzumab	Campath	humanized	CD52	07.05,2001	1.9 ~ 8.3	IgG1κ	IV	0.5 ~ 6
14	Omalizumab	Xolair	humanized	IgE	20.06.2003	< 0.1	IgG1κ	SC	26
15	Efalizumab	Raptiva	humanized	CD11a (LFA-1)	16.10.2003 (8.06.2009 withdrawal)	6.3	IgG1κ	SC	5
16	Bevacizumab	Avastin	humanized	VEGF	26.02.2004	< 0.2	IgG1κ	IV	20
17	Natalizumab	Tysabri	humanized	a1 subunit of α4β1 and α4β7 integrins	11.23.2004	6 ~ 9	IgG4κ	IV	7 ~ 15
18	Ranibizumab	Lucentis	humanized	VEGF-A	30.06.2006	1 ~ 8	Fab	IVT*	ND**
19	Eculizumab	Soliris	humanized	Complement C5	16.03.2007	2	IgG2/4κ	IV	7.9 ~ 14.8
20	Certolizumab pegol	Cimzia	humanized	TNFα	22.04.2008	8	Fab'-PEG	SC	13
21	Tocilizumab	Actemra	humanized	IL-6	11.01.2010	2	IgG1κ	IV	6.3
22	Adalimumab	Humira	human	TNFα	31.12.2002	5 ~ 12	IgG1κ	SC	7.5
23	Panitumumab	Vectibix	human	EGFR	28.09.2006	1 ~ 4.6	IgG2κ	IV	7.5
24	Golimumab	Simponi	human	TNFα	24.04.2009	4	IgG1κ	IV	14
25	Canakinumab	Ilaris	human	IL-1β	18.06.2009	< 1.6	IgG1κ	SC	26
26	Ofatumumab	Arzerra	human	CD20	26.10.2009	< 0.7	IgG1κ	IV	14

*IVT: intravitreal injection.
**ND: not determined.

the immunogenicity of antibody therapeutics such as the physicochemical properties of the antibody (purity, stability, and solubility), clinical factors (dose, route of administration, heterogeneity of the disease, and patient features), and concomitant treatments with other agents [1].

1.2. Murine antibodies

Muromonab-CD3, the first monoclonal antibody approved by the FDA, originated from a mouse and was recognized as foreign when injected into patients, eliciting blocking antibodies in 50% of patients. This is referred to as a human anti-mouse antibody (HAMA) response. These antibodies interfere with the binding of muromonab-CD3 to T cells and decrease its therapeutic effect [2]. HAMA responses can also interfere with tumor imaging [3,4] and radioimmunotherapy [5]. Edrecolomab (Panorex), a murine antibody approved for clinical use in Germany in 1995, shows immunogenicity in 100% of patients [6]. The high immunogenicity of murine antibodies provoked the development of recombinantly engineered antibodies in an attempt to reduce immunogenicity [7]. Two murine therapeutic antibodies, ibritumomab tiuxetan (Zevalin) and tositumomab-I131 (Bexxar), were approved in 2002 and 2003 and showed an anti-antibody response in less than 2 and 8% of patients, respectively [8,9]. Although these antibodies show relatively low immunogenicity, that of all other murine therapeutic antibodies is very high, ranging from 50 to 100% in non-immunocompromised patients [10].

1.3. Chimeric antibodies

A chimeric antibody is a recombinant antibody molecule composed of variable regions from mouse antibodies and

constant regions from human antibodies. Abciximab is a Fab molecule and the first chimeric therapeutic antibody developed. Human anti-chimeric antibody occurs in 6% of patients prior to re-administration, 27% after re-administration, and 44% after four or more exposures. Immunogenicity against abciximab leads to thrombocytopenia in 0.5 ~ 1% of patients after the first exposure and in 10 ~ 14% of patients after the second exposure [11]. Severe thrombocytopenia (< 20,000/mL) was observed in approximately 0.7% of patients with the first treatment, and in 4% of patients upon re-treatment [9]. Rituximab (Rituxan) was the first chimeric antibody to exhibit a full IgG form. It is immunogenic in 1.1% of patients with low grade or follicular non-Hodgkin's lymphoma and in 11% of patients with rheumatoid arthritis [12]. Another chimeric antibody, basiliximab (Simulect), was immunogenic in two of 138 renal transplantation patients previously not exposed to muromonab-CD3 and in four of 34 patients who subsequently received muromonab-CD3 [13]. Infliximab (Remicade) shows immunogenicity in 37% of patients with rheumatoid arthritis without immunosuppressant therapy, in 24% with some immunosuppressant therapy, and in 8% of patients who received the recommended repeated treatment dose regimens with methotrexate [14]. Cetuximab (Erbitux) induced non-neutralizing antibodies in 5% of evaluable patients without an apparent effect on its safety or antitumor activity [15]. Given these observations, it can be concluded that chimeric antibodies induce immunogenic antibody responses in up to 44% of patients medicated with therapeutic antibodies.

1.4. Humanized antibodies

Daclizumab was the first humanized antibody generated by grafting CDRs from a non-human antibody into a human antibody framework. Low titers of antibodies against daclizumab were detected in 14 and 34% of adult and pediatric patients treated, respectively, although none of the antibodies affected the efficacy, safety, serum levels or any other clinically relevant parameters [16]. The incidence of anti-palivizumab (Synagis) antibody following the fourth injection was 1.1% in a placebo group and 0.7% in a palivizumab injected group. In pediatric patients receiving palivizumab for the second season, one of 56 patients (1.8%) exhibited transient, low titer reactivity [17]. Among 903 women with metastatic breast cancer, anti-trastuzumab (Herceptin) antibody was detected in only one patient by enzyme immunoassay, although this patient did not experience an allergic reaction [18]. In a phase 2 clinical study, antibodies against gemtuzumab ozogamicin (Mylotarg), which treats CD33+ acute myeloid leukemia, were not detected in any of the 277 patients, including the 20 patients who received more than one course of the study drug. Two patients in a phase 1 study developed antibody titers against the calicheamicin/calicheamicin-linker portion of gemtuzumab ozogamicin after three doses, but they showed no clinical symptoms [19]. Alemtuzumab (Campath) is a humanized antibody developed using CDRs from a rat monoclonal antibody. Anti-alemtuzumab antibodies were detected in 11 of 133 (8.3%) previously untreated patients by enzyme immunoassay. Among these 11 patients, two patients were weakly positive for neutralizing activity. Four of 211 (1.9%) previously treated patients had antibodies to alemtuzumab following treatment [20]. Low titers of antibodies against omalizumab (Xolair) were detected by enzyme immunoassay in only one of 1,723 patients, or less than 0.1% of all patients treated [21]. In patients evaluated for antibodies to efalizumab (Raptiva), which was approved by the FDA on October 16, 2003 and then voluntarily withdrawn on June 8, 2009 due to the risk of progressive multifocal leukoencephalopathy, predominantly low-titer antibodies were detected in 6.3% (67/1,063) of patients [22]. None of the 500 patients treated with bevacizumab (Avastin), primarily in combination with chemotherapy, showed any titer of anti-bevacizumab antibody when enzyme immunoassays were performed on sera [23]. Approximately 9% of patients receiving natalizumab (Tysabri) developed detectable antibodies at least once during treatment, and approximately 6% of patients were positive for anti-natalizumab antibody on more than one occasion. Up to 82% of patients who became antibody-positive persistently developed detectable antibodies by 12 weeks. Anti-natalizumab antibodies were neutralizing *in vitro*, and their presence was correlated with a reduction in serum natalizumab levels. Persistent antibody-positivity resulted in a substantial decrease in the effectiveness of natalizumab. The risk of increased disability and the annualized relapse rate were similar in persistently antibody-positive natalizumab-treated patients and placebo patients [24]. Ranibizumab (Lucentis) is a humanized Fab against vascular endothelial growth factor, developed as an intravitreal injection drug for treating neovascular age-related macular degeneration. The pre-treatment incidence of immunoreactivity to ranibizumab was 0 ~ 3% across treatment groups. After a monthly dosing with ranibizumab for 12 to 24 months, low titers of antibodies to ranibizumab were detected in 1 ~ 8% of patients [25]. Low titers of antibodies to eculizumab (Soliris) were detected in three of 196 (2%) treated patients with paroxysmal nocturnal hemoglobinuria (PNH). No apparent correlation of anti-eculizumab antibody development with clinical response was observed [26]. Certolizumab pegol (Cimzia) is a PEGylated Fab fragment of a humanized tumor necrosis factor (TNF) inhibitor monoclonal antibody and was approved in 2008 [27]. It showed immunogenicity in

8% of patients treated [28,29]. In a controlled clinical study in which a total of 2,876 patients were tested for anti-tocilizumab (Actemra) antibodies for 6 months, 46 patients (2%) developed anti-tocilizumab antibodies, five patients developed a medically significant hypersensitivity reaction leading to withdrawal, and only 30 patients (1%) developed neutralizing antibodies [30].

Non-immunogenicity or near non-immunogenicity was achieved in four humanized antibodies, which can be regarded as a meaningful achievement compared to the much more immunogenic chimeric antibodies.

1.5. Fully human antibodies

Currently, five fully human antibodies are approved by the FDA. The first fully human antibody, adalimumab, was immunogenic in 5% (58 of 1,062) of adult patients with rheumatoid arthritis. These antibodies are neutralizing *in vitro*. Patients treated with concomitant methotrexate had a lower rate of antibody development than patients on adalimumab monotherapy (1% vs. 12%) [31]. The immunogenicity of panitumumab (Vectibix) was evaluated using an enzyme immunoassay and a real-time interaction assay. When tested by enzyme immunoassay, neutralizing anti-panitumumab antibody occurred in one of 613 patients (< 1%). However, the antibody level was significantly higher when detected by real-time interaction assay and was found in 28 of 613 patients (4.6%) [32]. Antibodies to golimumab (Simponi) were detected in 57 (4%) treated patients across the phase 3 trials through week 24. Of the patients with a positive antibody response to golimumab in the phase 2 and 3 trials, most were determined to have neutralizing antibodies to golimumab, as measured by a cell-based functional assay [33]. When a specific biosensor binding assay was used to detect antibodies directed against canakinumab (Ilaris) in patients who received it, none of the 60 patients with cryopyrin-associated periodic syndrome (CAPS) were positive for treatment-emergent binding antibodies at the time points tested. In that study, 31 of 60 patients with CAPS were exposed to canakinumab for more than 48 weeks [34]. The most recently developed fully human antibody is ofatumumab (Arzerra), directed against CD20 and used in treating patients with chronic lymphocytic leukemia. The overall immunogenicity rate was approximately 0.7%, with only two of 274 patients showing a positive signal for anti-ofatumumab antibodies [35]. This is encouraging, given that it is the first fully human antibody to achieve < 1% immunogenicity. The four previously developed fully human antibodies were not able to or not yet proven to reach immunogenicities of less than 1%, while four humanized antibodies did achieve this goal.

1.6. Serum half-life

Immunoglobulin G (IgG) has a relatively long serum half-life compared to other recombinant proteins due to neonatal Fc receptor (FcRn)-mediated recycling [36]. FcRn intercepts IgGs that are otherwise destined for lysosomal degradation, extending their serum half-lives much longer than those of other proteins.

The first murine monoclonal antibody, muromonab-CD3, has the shortest half-life of from 0.3 to 0.75 days [2]. This is thought to be due to rapid lysosomal degradation, as FcRn is unable to recognize murine Fc [37]. Another murine antibody, ibritumomab tiuxetan, also has a relatively short half-life of 1.25 days [8]. The half-life of tositumomab-I131 is 2.7 days [9]. Given that the serum half-life of native IgG (except for IgG3) is 23 days [38], the extremely short serum half-lives of the murine antibodies were rather disappointing.

The free plasma concentrations of the chimeric Fab, abciximab, decrease rapidly, with an initial half-life of less than 10 min and a second phase half-life of approximately 30 min [11]. The first chimeric IgG to have a relatively long half-life comparable to native immunoglobulin is rituximab, which has an average half-life of 22 days [12]. However, this optimal serum half-life has not been achieved in other chimeric antibodies developed. The serum half-lives of infliximab, cetuximab, and basiliximab are 8.6, 4.6, and 7.2 days, respectively [13,15].

The average half-life of the first humanized antibody, daclizumab, is 20 days [16]. Conversely, for gemtuzumab ozogamicin, alemtuzumab, and efalizumab, the mean half-life is less than 6 days, which is relatively short for a humanized antibody [19,20,22]. Natalizumab, eculizumab, and certolizumab pegol, in the form of a PEGylated Fab fragments, exhibit serum half-lives of 7 ~ 15 days [24,26, 27]. The average half-lives of palivizumab and bevacizumab are 20 days, according to a population pharmacokinetic analysis [17,23]. The half-life of trastuzumab alone averages 10 days, and in a study of women receiving adjuvant therapy for breast cancer, the mean half-life of trastuzumab was 16 days [18]. Tocilizumab, which was approved most recently, has a relatively short half-life of 6.3 days [30]. Omalizumab has the longest half-life of 26 days [21].

The fully human antibodies adalimumab and panitumumab exhibit serum half-lives of approximately 7.5 days [31,32], whereas golimumab has a serum half-life of 14 days [33]. Canakinumab shows a serum half-life of 26 days [34]. The most recently developed antibody against CD20, ofatumumab, has a serum half-life of 14 days [35].

Serum half-lives greater than 20 days, which is equivalent to a natural antibody, have been achieved by one chimeric, four humanized, and one fully human antibody.

1.7. Therapeutic efficacy

Antibody therapeutics was initially recognized as less toxic but less efficacious compared to small molecule drugs. For example, the first therapeutic antibody, muromonab-CD3, reversed 94% of renal transplantation rejections compared to a 75% reversal rate obtained with conventional high-dose steroid treatment ($p = 0.006$). However, the 1 and 2 year patient survivals were 85 and 75% for muromonab-CD3 and 90 and 85% for steroid-treated patients, respectively, which is not a significant difference between the two groups [2].

There are, however, antibodies with sufficient efficacies, such as palivizumab, eculizumab, and canakinumab. Currently, palivizumab treatment is the only strategy that has demonstrated consistent efficacy for reducing respiratory syncytial virus (RSV) infection hospitalization in high-risk children. In the IMpact Trial, palivizumab prophylaxis treatment resulted in a 55% overall decrease of RSV-related hospitalization compared to placebo-treated controls. Data obtained from the Palivizumab Outcomes Registry indicate total RSV hospitalization rates of 2.9% compared to 4.8% reported in the Impact-RSV trial [39]. Additionally, the TRIUMPH trial revealed that eculizumab is effective at stabilizing hemoglobin levels and reducing transfusion requirements in patients with classical PNH [40]. Hemoglobin stabilization was maintained in 48.8% of patients in the eculizumab-treated group and in 0% in the placebo-treated group ($p < 0.001$). Further, a median of 0 units of packed red cells were transfused in the eculizumab-treated group, compared with a median of 10 units in the placebo-treated group ($p = 0.001$). The eculizumab-treated group also showed significant improvements in patient quality of life. In a clinical trial in which 35 patients with CAPS were enrolled, canakinumab induced a rapid remission of symptoms in most patients [41].

Additionally, several scientific efforts have been made to produce more efficacious antibody therapeutics, resulting in the development of more than two therapeutic antibodies against the same targets, such as CD20, TNF-α, and epidermal growth factor receptor (EGFR). The different properties of each antibody, such as epitope, affinity, isotype, toxicity, serum half-life, and immunogenicity can result in improved therapeutic efficacy, justifying the rationale to develop follow-up antibodies even though an antibody against the same target is already in clinical use. Antibodies to CD20 are good examples of the chronological progression of antibodies. In a randomized multicenter clinical study of patients with relapsed, refractory low-grade, follicular or B-cell non-Hodgkin's lymphoma, the overall response rate in 73 patients randomized to receive ibritumomab tiuxetan was 80% (with 30% complete responses), which was statistically higher than the 56% overall response rate (with 16% complete responses) observed in the 70 patients who received rituximab ($p = 0.002$) [42]. The estimated median duration of response was 13.9 months (1.0–47.6+) for patients receiving ibritumomab tiuxetan and 11.8 months (1.2–49.7+) for patients receiving rituximab. Interestingly, ibritumomab tiuxetan produced an overall response rate of 74 with 15% complete responses among the patients refractory to rituximab [43]. The estimated median duration of the response was 6.4 months (0.5–49.9+), and the estimated median time to disease progression was 6.8 months.

Notably, more recently developed antibodies do not always perform better. At present, two anti-EGFR antibodies are approved for clinical use. The chimeric antibody cetuximab can be used alone or in combination with cytotoxic chemotherapy as treatment for patients with metastatic squamous cell carcinoma of the head and neck, colorectal cancer, and non small cell lung cancer [15, 44,47]. The observed median progression-free survival was between 7.2 and 10.2 months. A fully human antibody, panitumumab, was approved later for use as monotherapy for third-line treatment of colorectal cancer that is refractory to fluoropyrimidines, oxaliplatin, or irinotecan. In 2007, panitumumab was approved by the European Medicines Agency for use in patients with colorectal cancer carrying a normal wild type K-ras gene. The median progress-free survival was 1.9 months in the best supportive care (BSC) plus panitumumab group, whereas it was 1.7 in the BSC group and 2.9 months in the normal wild type K-ras gene group. Anti-EGFR monoclonal antibodies provided clinical benefit to only 15% of patients treated. Moreover, the use of these drugs has contributed to only a modest overall survival benefit in comparison to commonly practiced BSC [48].

A variety of new approaches to enhance the efficacies of therapeutic antibodies have been actively pursued. Catumaxomab (Removab) was approved by the European Commission for the treatment of malignant ascites by intraperitoneal injection on April 20, 2009. It is a bispecific antibody with binding specificities for human epithelial cell adhesion molecule (EpCAM) on cancer cells and for human CD3 antigen on all T lymphocytes. Given its intact Fc region, catumaxomab also has the potential to recruit accessory cells essential for a complex immune response. In clinical trials, the efficacy of the treatment with paracentesis and catumaxomab in patients with malignant ascites due to EpCAM-positive carcinomas was significantly superior to that with paracentesis alone in terms of puncture-free survival rate and the first time point of therapeutic ascites puncture [49]. Other common approaches include antibody-drug conjugates. Trastuzumab-DM1, a HER2 antibody-drug conjugate, showed robust single-agent activity in patients with HER2-positive metastatic

breast cancer who have progressed while receiving HER2-directed therapy [50].

It is now clear that antibody drugs are evolving from their native form into hybrid molecules such as bispecific antibodies, antibody-drugs, and isotope conjugates with new and enhanced therapeutic functionality.

2. Conclusion

We can now easily develop therapeutic antibodies with high affinities in safe, specific, and non-immunogenic forms using high-throughput methods. Based on these technological achievements, major efforts are now focused on improving antibody efficacy. One of the great advantages of antibody therapeutics is their exquisite specificity for drug targets. Therefore, very accurate information is provided about the *in vivo* functions of drug targets based on preclinical and clinical data. Nearly all of the beneficial or hazardous effects can be explained in a mechanistic way. This cumulative information will eventually lead to more effective combined antibody therapeutic treatments that increase efficacy and reduce side effects. Combined treatment can be actively initiated after antibody therapeutics become significantly more affordable, possibly by the introduction of biosimilar antibodies, which has already been achieved in one case [51] and is currently being explored [52].

References

1. Swann, P. G., M. Tolnay, S. Muthukkumar, M. A. Shapiro, B. L. Rellahan, and K. A. Clouse (2008) Considerations for the development of therapeutic monoclonal antibodies. *Curr. Opinion Immunol.* 20: 493-499.
2. Norman, D. J., L. Chatenoud, D. Cohen, M. Goldman, and C. F. Shield (1993) Consensus statement regarding OKT3-induced cytokine-release syndrome and human antimouse antibodies. *Transplant. Proc.* 25: 89-92.
3. Ledermann, J. A., R. H. J. Begent, K. D. Bagshawe, S. J. Riggs, F. Searle, M. G. Glaser, A. J. Green, and R. G. Dale (1988) Repeated antitumour antibody therapy in man with suppression of the host response by cyclosporine-A. *British Jl Cancer* 58: 654-657.
4. Leitha, T., R. Walter, W. Schlick, and R. Dudczak (1991) TC-99M-anti-CEA radioimmunoscintigraphy of lung adenocarcinoma. *Chest* 99: 14-19.
5. Riva, P., M. Marangolo, S. Lazzari, M. Agostini, G. Sarti, G. Moscatelli, G. Franceschi, A. Spinelli, and G. Vecchietti (1989) Locoregional immunotherapy of human ovarian-cancer-preliminary-results. *Nuclear Med. Biol.* 16: 659-666.
6. Mellstedt, H. (1992) The clinical significance of HAMA in patients treated with mouse monoclonal antibodies. *Cell biophys.* 21: 153-165.
7. Kuusreichel, K., L. S. Grauer, L. M. Karavodin, C. Knott, M. Krusemeier, and N. E. Kay (1994) Will immunogenicity limit the use, efficacy, and future-development of the therapeutic monoclonal antibodies? *Clin. Diagn. Lab. Immunol.* 1: 365-372.
8. Biogen IDEC (2002) Zevalin full prescribing information.
9. Kaminski, M. S., A. D. Zelenetz, O. W. Press, M. Saleh, J. Leonard, L. Fehrenbacher, T. A. Lister, R. J. Stagg, G. F. Tidmarsh, S. Kroll, R. L. Wahl, S. J. Knox, and J. M. Vose (2001) Pivotal study of iodine I 131 Tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J. Clin. Oncol.* 19: 3918-3928.
10. Hwang, W. Y. K. and J. Foote (2005) Immunogenicity of engineered antibodies. *Methods* 36: 3-10.
11. Tcheng, J. E., D. J. Kereiakes, A. M. Lincoff, B. S. George, N. S. Kleiman, D. C. Sane, D. B. Cines, R. E. Jordan, M. A. Mascelli, M. A. Langrall, L. Damaraju, A. Schantz, M. B. Effron, and G. A. Braden (2001) Abciximab readministration: Results of the ReoPro readministration registry. *Circulation* 104: 870-875.
12. Genentech (1997) Rituxan full prescribing information.
13. Novartis (1998) Simulect full prescribing information.
14. Centocor (1998) Remicade full prescribing information.
15. Imclone Systems (2004) Erbitux full prescribing information.
16. Protein Design Lab (1997) Zenapax full prescribing information.
17. Medimmune (1998) Synagis full prescribing information.
18. Genentech (1998) Herceptin full prescribing information.
19. Wyeth (2000) Mylotarg full prescribing information.
20. Millenium/LEX (2001) Campath full prescribing information.
21. Genentech (2003) Xolair full prescribing information.
22. Genentech (2003) Raptiva full prescribing information.
23. Imclone Systems (2004) Avastin full prescribing information.
24. Biogen IDEC (2004) Tysabri full prescribing information.
25. Genentech (2006) Lucentis full prescribing information.
26. Alexion Pharmaceuticals (2007) Soliris full prescribing information.
27. UCB (2008) Cimzia full prescribing information.
28. Lichtenstein, G. R., J. F. Colombel, R. Bloomfield, and W. J. Sandborn (2008) Long-term safety of an anti-TNF drug by duration of exposure compared to non-anti-TNF exposed patients with Crohn's disease: Novel data from the certolizumab pegol development program. *Gastroenterol.* 134: 68.
29. Rivkin, A. (2009) Certolizumab Pegol for the Management of Crohn's Disease in Adults. *Clin. Therapeutics.* 31: 1158-1176.
30. Genentech (Roche) (2010) Actemra prescribing information.
31. Abbott (2002) Humira full prescribing information.
32. Amgen (2006) Vectibix full prescribing information.
33. Centocor (2009) Simponi full prescribing information.
34. Novartis (2009) Ilaris full prescribing information.
35. GlaxoSmithKline (2009) Arzerra full prescribing information.
36. Roopenian, D. C. and S. Akilesh (2007) FcRn: the neonatal Fc receptor comes of age. *Nature Rev. Immunol.* 7: 715-725.
37. Kacskovics, I., Z. Kis, B. Mayer, A. P. West, N. E. Tiangco, M. Tilahun, L. Cervenak, P. J. Bjorkman, R. A. Goldsby, O. Szenci, and L. Hammarstrom (2006) FcRn mediates elongated serum half-life of human IgG in cattle. *Int. Immunol.* 18: 525-536.
38. Thurmann, P. and S. Harder (1996) Criteria for the appropriate drug utilisation of immunoglobulin. *Pharmacoeconomics* 9: 417-429.
39. Wang, D., C. Cummins, S. Bayliss, J. Sandercock, and A. Burls (2008) Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: A systematic review and economic evaluation. *Health Technol. Assessment* 12: 1-86.
40. Hillmen, P., N. S. Young, J. Schubert, R. A. Brodsky, G. Socie, P. Muus, A. Roth, J. Szer, M. O. Elebute, R. Nakamura, P. Browne, A. M. Risitano, A. Hill, H. Schrezenmeier, C. Fu, J. Maciejewski, S. A. Rollins, C. F. Mojcik, R. P. Rother, and L. Luzzatto (2006) The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N. Engl. J. Med.* 355: 1233-1243.
41. Lachmann, H. J., I. Kone-Paut, J. B. Kuemmerle-Deschner, K. S.

Leslie, E. Hachulla, P. Quartier, X. Gitton, A. Widmer, N. Patel, P. N. Hawkins, and C. S. G. Canakinumab (2009) Use of Canakinumab in the Cryopyrin-Associated Periodic Syndrome. *N. Eng. J.Med.* 360: 2416-2425.

42. Witzig, T. E., C. A. White, L. I. Gordon, G. A. Wiseman, C. Emmanouilides, J. L. Murray, J. Lister, and P. S. Multani (2003) Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-Hodgkin's lymphoma. *J. Clin. Oncol.* 21: 1263-1270.
43. Witzig, T. E., I. W. Flinn, L. I. Gordon, C. Emmanouilides, M. S. Czuczman, M. N. Saleh, L. Cripe, G. Wiseman, T. Olejnik, P. S. Multani, and C. A. White (2002) Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J. Clin. Oncol.* 20: 3262-3269.
44. Thienelt, C. D., P. A. Bunn, N. Hanna, A. Rosenberg, M. N. Needle, M. E. Long, D. L. Gustafson, and K. Kelly (2005) Multicenter phase I/II study of cetuximab with paclitaxel and carboplatin in untreated patients with stage IV non-small-cell lung cancer. *J. Clin. Oncol.* 23: 8786-8793.
45. Saltz, L. B., N. J. Meropol, P. J. Loehrer, M. N. Needle, J. Kopit, and R. J. Mayer (2004) Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J. Clin. Oncol.* 22: 1201-1208.
46. Humblet, Y., E. Vega-Villegas, R. Mesia, A. Awada, L. Geoffrois, C. Borel, R. Hitt, N. Amellal, E. H. Bessa, and J. Bourhis (2006) Phase I study of cetuximab in combination with cisplatin or carboplatin and 5-fluorouracil (5-FU) in patients (pts) with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). *J. Clin. Oncol.* 24(18): 2866-2872.
47. Martinelli, E., R. De Palma, M. Orditura, F. De Vita, and F. Ciardiello (2009) Anti-epidermal growth factor receptor monoclonal antibodies in cancer therapy. *Clin. Exp. Immunol.* 158: 1-9.
48. EMEA (2009) Summary of product characteristics.
49. American Society of Clinical Oncology (ASCO) 45th Annual Meeting (2009) poster No.1017.
50. http://www.abxis.com/eng/products/products_Frm.asp?cmd = 301.
51. http://www.celltrion.com/03_BIO/bio01-02.asp?menu_num = 1.