Journal of Advances in Biology & Biotechnology

14(2): 1-11, 2017; Article no.JABB.34759
ISSN: 2394-1081

Technological and Patent Evolution of Murine Monoclonal Antibodies

Kátia dos Reis[1*], José Procópio Moreno Senna[1], Nei Pereira Júnior[2] and Maria Antonieta Peixoto Gimenes Couto[2]

[1]Institute of Technology in Immunobiology Biomanguinhos (Bio-Manguinhos), Oswaldo Cruz Foundation (Fiocruz), Av. Brasil, 4365 –Manguinhos, 21040-900, Rio de Janeiro, RJ, Brasil.
[2]Department of Engineering Biochemistry, Federal University of Rio de Janeiro (UFRJ), Av. Horácio Macedo, 2030, Centro de Tecnologia, Bloco E, sala E-203, Cidade Universitária 21941-909, Rio de Janeiro, RJ, Brasil.

Authors' contributions

This work was carried out as collaboration among all authors. All authors managed the literature searches and organized and wrote the primary manuscript. All authors also proofread the manuscript and approved the final manuscript.

Article Information

DOI: 10.9734/JABB/2017/34759
Editor(s):
(1) Laura Pastorino, Laboratory of Nanobioscience and Medical Informatic, Department Informatics, Bioengineering, Robotics and Systems Engineering (DIBRIS), University of Genoa, Italy.
Reviewers:
(1) Denong Wang, USA.
(2) Toshi Nagata, Hamamatsu University School of Medicine, Japan.
(3) Mahana, University Paris-Saclay, France.
Complete Peer review History: http://www.sciencedomain.org/review-history/20290

Review Article

Received 10th June 2017
Accepted 26th July 2017
Published 31st July 2017

ABSTRACT

Among the pharmaceutical products targeted for patent protection, monoclonal antibodies stand out. Technological advances involving monoclonal antibodies aim to minimize detrimental human immune responses to antibodies (e.g., human anti-murine antibodies [HAMA]) and increase the binding affinity of antibodies to their antigen, making them more specific for their therapeutic target. This work evaluates the main technological advances pertaining to monoclonal antibodies, from the creation of technology for the immortalization of cells to generate hybridomas through the generation of chimeric and humanized antibodies by genetic engineering techniques, phage display technology, and transgenic mice. It also aims to provide an overview of commercially available and patented murine monoclonal antibodies and to correlate the main players, markets, and therapeutic uses for which the antibodies were developed. The study of mMAB (murine monoclonal antibodies) proved to be of great importance to understand how the development of these antibodies and their

**Corresponding author: E-mail: katia.reis@bio.fiocruz.br;*

protection by patents affects their therapeutic use in cancer patients, in diagnostics, to treat inflammation, etc. The United States (US), Japan (JP), France (FR), and China (CN) constitute potential markets for these protected technological advances. Among current usage trends of three murine monoclonal antibodies whose patents have expired, the use of generic and/or biosimilar is evidenced, as well as the use of these assets to guarantee the protection of new products, new associated processes (e.g., new combinations, associations, or dosage forms), or new processes. The newest market trends related to patent protection in this technological area incorporate the use of monoclonal antibody fragments.

Keywords: Murine monoclonal antibodies; patents; Biopharmaceuticals; Intellectual property.

1. INTRODUCTION

Since the first description of hybridoma technology by Kohler and Milstein in the journal Nature in 1975 [1], the development and therapeutic applications of monoclonal antibodies have abounded. The first monoclonal antibody with a clinical application, OKT3®), was approved eleven years after Kohler and Milstein's article.

However, the fact that the administration of murine antibodies can induce an immune response against the injected animal protein in humans (e.g., human anti-murine antibodies [HAMA]), combined with low plasma half-life, means that few murine antibodies have been used effectively to treat humans [2]. The exception is the murine monoclonal antibody OKT3®, which is employed to treat tissue rejection; This antibody is tolerated well. Other commercial murine antibodies used to treat human patients include Zevalin® (also called Ibritumomab or Tiutexan), an antibody conjugated to Y-90, and Bexxar® (also called Tositumomab), which is conjugated to I-131; Both are indicated for the treatment of non-Hodgkin's lymphoma [3].

The need to overcome these limitations led to the development of the so-called chimera antibody. In chimeric antibodies, the sequence responsible for target recognition (i.e., the complementarity determining regions and frameworks of the heavy and light chains of the murine monoclonal antibody) are linked to a human constant region (Fc) by molecular engineering. This strategy assures three important properties of the new molecule: (i) reduction of adverse effects because approximately 70% of the new molecule is human rather than mouse [4]: (ii) plasmatic half-life and circulation time increase because the new antibody has a constant region capable of binding FcRn receptors, and (iii) better antibody activity due a human glycosylation pattern which promotes an interaction with the host immune system. Sherrie Morison developed this new approach in 1984 [4].

Data from 2009 indicates that six chimeric antibodies have been commercialized. Some of them are considered "blockbusters". These antibodies are ReoPro®-Abciximab®, Rituxan®-Rituximab®, Synagis®-Palivimumab®, Remicade®-Infliximab®, Simulect®-Basiliximab®, and Erbitux®-Cetuximab® [5]. These data confirm the efficacy of chimerizing murine monoclonal antibodies.

Despite the success presented by these six chimeric antibodies, molecular engineering techniques have advanced humanization strategies of therapeutic antibodies. For example, complementary determinant region (CDR) grafting was developed by Jones and collaborators in 1986 [6] and this technique conserves the murine CDR, while the remainder of the molecule is completely human. These "humanized" antibodies are approximately 85-90% of human sequence and are less immunogenic than murine and chimeric antibodies [4]. Currently, approximately 40% of commercialized monoclonal antibodies are humanized [2,6,7,8].

Over the next decade, a new approach was developed to create completely human antibodies. Humanized transgenic mice were created by replacing the full repertoire of murine IgG with a human repertoire [9]. Despite some problems, such as reduced levels of human IgG expression [10], these humanized mice produce human monoclonal antibodies employing the traditional hybridoma technology. These human antibodies represent an important part of licensed monoclonal-based therapies and tend to have an important role in the development of new therapeutic monoclonal antibodies. Besides obtaining monoclonal antibodies by hybridoma technology, *in vitro* selection methods can also

be employed. Panitumumab (also called Vectibix) was the first therapeutic humanized MAB approved. Humanized transgenic mice were used as a tool to develop this MAB; however, a CHO cell-based platform is employed for its large-scale production [11].

Antibody phage display (APD) is based on genetic engineering of bacteriophages (viruses that infect bacteria) and repeated rounds of antigen-guided selection and phage propagation [12]. This technique allows *in vitro* selection of MABs of virtually any specificity, greatly facilitating recombinant production of reagents for use in research and clinical diagnostics, as well as for pharmaceuticals for therapeutic use in humans (e.g., adalimumab®, the first fully human APD-derived MAB) [13]. By 2008, there were at least thirteen monoclonal antibodies derived from phage display platforms in clinical trials [14]. Most therapeutic monoclonal antibodies originate from platforms based on hybridoma technology and its derivatives (i.e., chimeras, humanized antibodies, and human antibodies obtained from transgenic animals). In contrast, phage display-derived antibodies originate from the pipelines of a few companies. Information on their development is more difficult to obtain; sometimes this information can only be found on the company's website [15].

Thus, the advent of *in vitro* phage display technology and the generation of transgenic mice expressing human variable domains have allowed the generation of fully human antibodies. In addition to the development of the strategies described above to obtain therapeutic monoclonal antibodies, a better understanding of factors that influence MAB immunogenicity has led to the development of *in silico* and *in vitro* tools to reduce clinical immunogenicity through deselection or deimmunization [16-18]. These tools allow for the identification of potential epitopes on the molecule and for the prediction of amino acid substitutions such that the new molecule is less immunogenic to the host without losing its activity.

Glycosylation of proteins is a complex and versatile post-translational modification that influences protein biological activity, conformation, stability, solubility, secretion, pharmacokinetics, and antigenicity [19]. Oligosaccharides at Asn297 on the immunoglobulins (IG), Fc region bind with Fcγ receptors (FcγRs) on leukocytes and C1 component of complement. This activates effector functions including antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) which are some mechanisms by which therapeutic antibodies function [20]. Improvement of immunoglobulin G Fc glycosylation is a rational strategy to improve efficacy of therapeutic MAB.

Chemoenzymatic glycoengineering is a recent approach which inserts a specific glycosylation to optimize effector functions of therapeutic MABs. This process consists of a deglycosylation step performed by an endo-β-N-acetylglucosaminidase (ENGase) followed by reglycosylation step performed by an ENGase-based glycosynthase to transfer a predefined N-glycan substrate to the innermost N-acetylglucosamine (GlcNAC) of the antibody [21].

Immunoglobulin Fc glycoengineering provides a strategy for the development of next-generation therapeutic MAB. This technique may enhance or silence Fc effector functions, thus, optimizing the safety, functionality, and efficacy of MABs.

These advancements have allowed for the development of safer therapeutic monoclonal antibodies with a lower risk of side effects due to the generation of HAMA by patients. Despite these advances, murine monoclonal antibodies obtained by hybridoma technology represent an important basis for the development of therapeutic antibodies. A major advantage of using these antibodies is the possibility of using the animal itself (mouse) for proving the efficacy (proof of principle). This is especially true for infectious bacterial diseases, where the probability of using a murine model is very high [22], and some cancers [23]. Prior investigation regarding the efficacy of a new monoclonal antibody prototype allows researchers to save time and resources, because non-consistent data promotes looking for alternatives before carrying out pre-clinical and clinical trials.

Within this context, the present work examines the evolution of technological strategies and patents pertaining to murine monoclonal antibodies between 1979 and 2014. To achieve this goal, the analysis was carried out by identifying holder countries, by checking the markets where this technology has been protected, and by examining the developmental phase of potential products. We also assess trends in production and patent protection pertaining to murine monoclonal antibodies.

2. METHODOLOGY

The used in this study was the Thomson Reuters Integrity Database, which is an analytical tool designed to provide information about drugs and pathologies. The platform helps researchers in various stages of research and development by providing integrated information in thirteen areas of knowledge: Disease Briefings, Targets and Pathways, Genomics, Biomarkers, Drugs and Biological, Pharmacology Experimental, Experimental Models, Pharmacokinetics/ Metabolism, Clinical Trials, Organic Synthesis, Companies and Research Institutes, Literature and Patents.

The database covers seven of the most representative patent offices in the world, The European Patent Office (EPO), The Japanese Patent Office (JPO), The United States Patent and Trademark Office (USPTO), Patent Cooperation Treaty System (PCT), China Patent & Trademark Office (CPO), Intellectual Property India (IPI), and Korean Industrial Property Office (KIPO).

For this study, the search strategy was performed using either "murine monoclonal antibodies" or “murine monoclonal antibody” in different search categories: quick search or advanced search. The records were retrieved and then categorized using the classifications of base integrity and analyzed. This set of records was used to assess the patenting of MABs.

3. RESULTS AND DISCUSSION

3.1 Macro Analysis

Between 1979 and 2014, searching for the term "murine monoclonal antibody”, we found 881 patent documents, whose temporal evolution is shown in Fig. 1. The low number of patents applied for in 2014 could be because many patent applications have not yet been published, due to the confidentiality term which corresponds to 18 months from the priority date. In the first ten years (1979-1989), the greatest number of priority occurred in 1984, with 20 patent documents deposited. After that, another peak occurred in 2002, and 25 patent applications were deposited. The year 2005 stands out with 41 applications deposited. The last peaks occurred in 2009 and 2011 with 95 and 109 documents, respectively, deposited. In 2011, 109 applications were deposited.

In the first ten years (1979-1989), the greatest number of priority occurred in 1984, with 20 patent documents deposited. After that, another peak occurred in 2002 and 25 patent applications were deposited. The year 2005 stands out because 41 applications deposited. The last peaks occurred in 2009 and 2011 with 95 and 109 documents, respectively, deposited. In 2011, 109 applications were deposited.

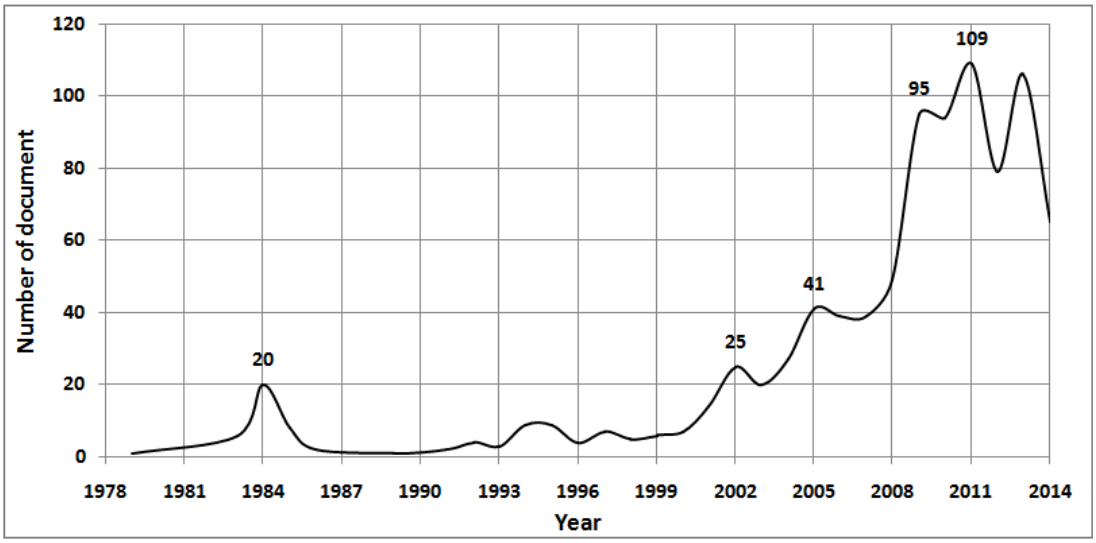

Fig. 1. Priority date versus number of documents between 1979-2014

A subset of priority applications for murine monoclonal antibody technology that corresponds to the period of 20 years was selected (1995-2014). Due the large number of documents, this cut has generated a subset of data containing 841 patent documents. Using this subset, the following analyzes were made as detailed below:

3.1.1 Analysis of Top 10 (countries, assignees, and targets)

Table 1 summarizes a general analysis relating to the applicant countries, applicant assignee, and target, which was the ten first positions, involved in murine monoclonal technology during the last 20 years and therefore called Top 10.

The first analysis refers to the types of assignee, categorized as academic and company (Fig. 2). Among applications filed by institutions categorized as academic, INSERM and University of California are the most expressive among the top ten in the rank. These two institutions together present approximately 35% of the patents documents deposited. The other assignees represent companies and correspond to 65% of the total. Among the companies, Roche stands out with the largest number of deposits (17). Corporations provide almost twofold more contributions than academic institutions.

Concerning the analysis of countries, Table 1 shows that the market potential for murine monoclonal antibody technology is geographically distributed in the United States (US), Japan (JP), France (FR), China (CN), Switzerland (CH), Germany (DE), the United Kington (GB), Korea (KR), Australia (AU), and Canada (CA).

The United States is the isolated leader in this area and has 377 documents filed, which is approximately four times more applications than those filed in Japan. Japan is in the second position with 91 documents. Even though China filed their first application in this area in 2011, this country is in the fourth position regarding the number of applications filed. Perceptual patents filed by the United States correspond to 46.3% of the total. Japan, France, China, Switzerland, the United Kingdom, and Germany appear with 11%, 7.5%, 6.0%, 4.7%, 3.7%, and 3.7%, respectively.

With regards to the Top 10 patent protection targets, shown in Fig. 3, it can be observed that cancer (41%), diagnostics (22%), infections (9%), and autoimmune disease (8%) are the most expressive targets. On the other hand, treatments of infections, transplant rejection, inflammation, rheumatoid arthritis, and asthma each appear in 2-3% of documents.

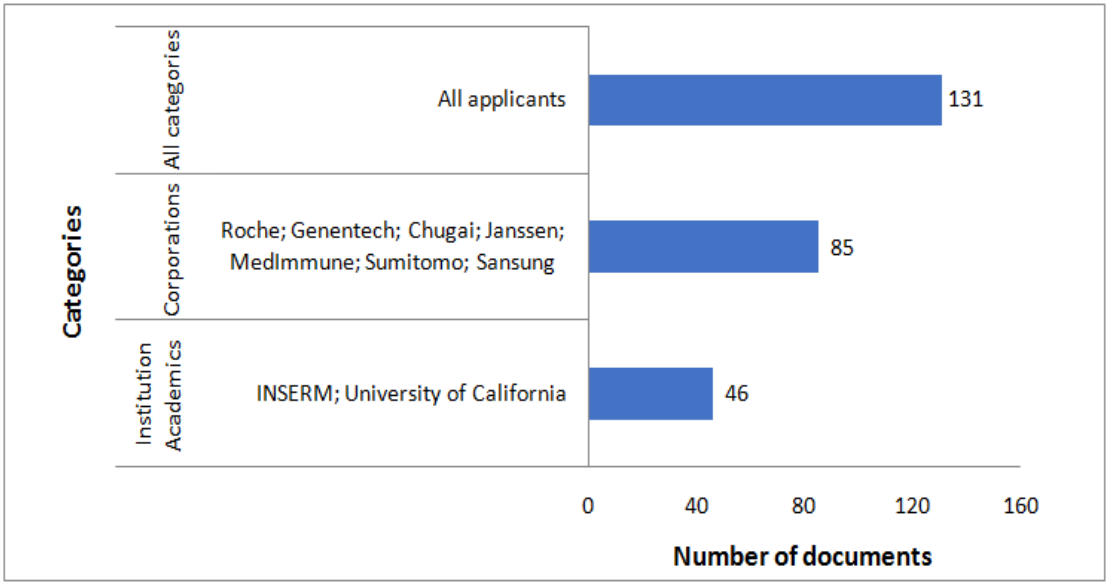

Fig. 2. Top 10 applicants categorized as either academic or corporate

Table 1. Ten first positions in murine monoclonal technology during the last 20 years (1995 to 2014)

	Priority date 1995-2014					
Top	**Top 10 Applications/assignee**		**Top 10 aplicant country**		**Top 10 target**	
	Applications/ assignee	**Number documents**	**Aplicant country**	**Number documents**	**Target**	**Number documents**
1	INSERM	31	United States	377	Cancer	362
2	Roche	16	Japan	91	Diagnostics	189
3	University of California	15	France	64	Inflammation	78
4	Genentech	13	China	61	Autoimmune disease	68
5	Chugai Pharmaceutical	12	Switzerland	44	Dementia, Alzheimer's type	39
6	Janssen Biotech	10	Germany	33	Rheumatoid arthritis	29
7	MedImmune	9	United Kingdom	29	Cardiovascular Disorders	24
8	Lpath	9	Korea, Republic of	23	Infections	24
9	Sumitomo Dainippon Pharma	8	Australia	19	Asthma	21
10	Samsung Electronics	8	Canada	16	Psoriasis	21
					Transplant rejection	21

3.2 Analysis of the Claims

For the analysis of the subset of data, the 841 patent documents related to murine monoclonal antibodies were subdivided in two groups: Group I included the claims that have over 50 patent documents and Group II included those that have fewer than 50 patent documents.

3.2.1 Group I

Fig. 4 shows Group I, classified by categories of applicants. It is observed that antibodies, drugs substances, methods of use, and combination products are the most protected type of claims. It should be noted that product claims (i.e., combination products, drugs substances, antibodies, etc.) appear in greater numbers compared to process claims (i.e., methods of use).

A partnership aimed at the development of murine monoclonal antibodies was evaluated. It was observed that the level of contributions between universities and corporations was the same as those partnerships between research institutions and universities. No contribution was observed by People (isolated inventor) in this area.

3.2.2 Group II

For Group II, which had less than 50 patent documents, it was noted that most important claims are related to process (48), compositions and dosage form (9), biomarkers (9), and fusion proteins (9). Other prominent groups refer to RNA interference and immune conjugates; both contained seven documents. Other initiative claims target cells and contained six documents (Fig. 5).

In Group II, process claims stand out in relation to product claims. In this group, there were more product claims than process claims, although the number of processes claimed were more expressive than the isolated types of products claimed. It was verified that, in the product category, there was more diversification and 13 different types of products (dosage form, biomarkers, fusion proteins, etc.) were found. Additionally, in Group II, academics are the most significant assignee of companies contrasted with the profile shown for Group I.

3.3 Murine Monoclonal Antibodies: Evaluation of Commercial Technologies

Table 2 shows information about the only three murine monoclonal antibodies approved by Food and Drug Administration (FDA), commercialized, and protected by patents in several countries during the last twenty years.

The oldest patent application in this area of technology is entitled “Monoclonal-antibody-producing hybrid cell line *E. coli*”. This claim describes a murine monoclonal antibody and its preparation as well as its diagnostic and therapeutic uses. This patent was deposited in 1979 by the North American company Ortho-McNeil-Janssen Pharmaceuticals Inc. [24]. Muromonab-CD3 or OKT-3®, an oral anti-CD3 (α-CD3) monoclonal antibody immunotherapy, was first launched in 1986 on the U.S. market for the treatment of kidney transplant rejection [25,30].

Subsequently, the product's scope was extended to include the treatment of liver transplant rejection and heart transplant rejection. In 2010, Ortho-McNeil-Janssen Pharmaceuticals Inc. developed a phase II trial that was initiated by NasVax LTD in Israel for the oral treatment of nonalcoholic steatohepatitis (NASH) in patients with metabolic syndrome; and in 2011, another phase II was initiated [26].

The second FDA-approved monoclonal antibody was Ibritumomab, which is an anti-CD20 monoclonal antibody derived from ATCC HB 111388 (hybridoma 2B8), and it was commercialized as Zevalin®. Radiolabeling of ibritumomab (2B8) with yttrium-90 produces Y2B8. The anti-CD20 monoclonal antibody labeled with yttrium-90, Ibritumomab Tiuxetan (SHL-749), was initially launched in 2002 for the treatment of relapsed or refractory low-grade, follicular, B-cell non-Hodgkin's lymphoma (NHL).

In October 2006, the companies Biogen Idec, Inc. and Schering AG (now Bayer) announced the start of a phase III clinical trial in the U.S. for the treatment of diffuse large B-cell lymphoma (DLBCL). However, no recent developments have been reported for this trial. In 2012, Spectrum Pharmaceuticals Inc. commenced a phase III clinical study for this indication. In Denmark, early clinical studies are under way for the treatment of mantle-cell lymphoma at Rigs Hospitalet. In the U.S., Bayer Health Care Pharmaceuticals (Bayer's subsidiary) filed a marketing authorization application (MAA) seeking approval for the first line treatment of follicular lymphoma. The MAA was approved in 2008.

RIT Oncology originally filed for approval in the U.S. to use ibritumomab tiuxetan for the treatment of patients with previously untreated follicular non-Hodgkin's lymphoma, who had achieved a partial or complete response to first-line chemotherapy. This indication was approved in 2009. RIT was a joint venture formed between CTI BioPharma (formerly known as Cell Therapeutics) and Spectrum Pharmaceuticals in 2008. This collaboration lasted until 2009, when the former sold its share to Spectrum. Originally developed by Biogen, the antibody was licensed to Schering on a worldwide basis for marketing and distribution, except for the U.S., where Spectrum Pharmaceuticals Inc. holds rights pursuant to a license agreement signed in 2007.

In Japan, ibritumomab tiuxetan is licensed to Nihon Schering KK. In 2005, the compound received orphan drug designation in Japan for the treatment of B-cell lymphoma. In 2008, a license agreement between Bayer and FUJIFILM RI Pharma was established for the marketing rights in Japan. In 2012, Spectrum Pharmaceuticals Inc. acquired the licensing rights to sell the product from Bayer outside of the U.S. In 2015, Spectrum Pharmaceuticals Inc. licensed the marketing rights in select territories such as Japan, Asia (except for India and China), Africa, the Middle East, and Latin America. In 2016, Servier Canada Inc. obtained exclusive rights to develop and commercialize the product in Canada [31].

Zevalin® is the only one of the three FDA-approved murine monoclonal antibodies that was deposited in Brazil in the form of a pipeline. Patent PPBR1100622 B1 was extinguished on 11/13/2012 [32].

The ending patent family for Bexxar® covers the use of a monoclonal antibody, labelled with iodine131, to target CD20 and Fab, Fab', or F(ab')2 portions thereof, for the imaging and immunotherapy of B-cell lymphoma and other neoplasms of a B-cell lineage [33].

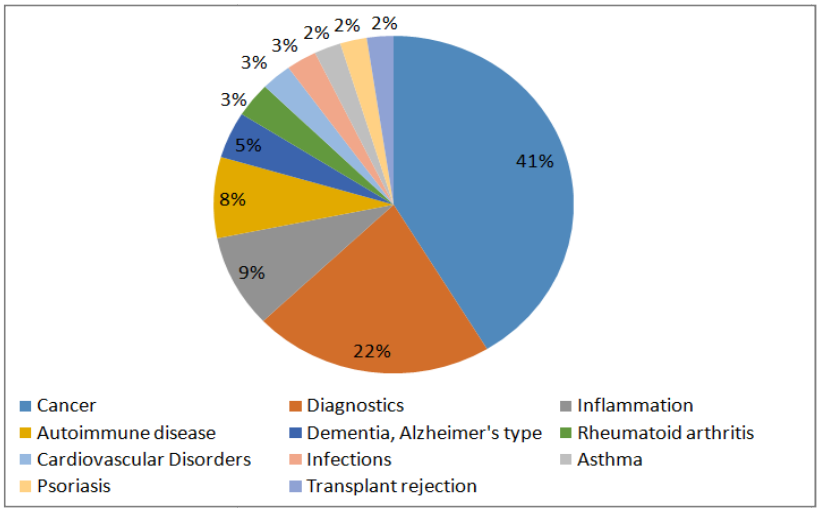

Fig. 3. Top 10 protected therapeutic targets

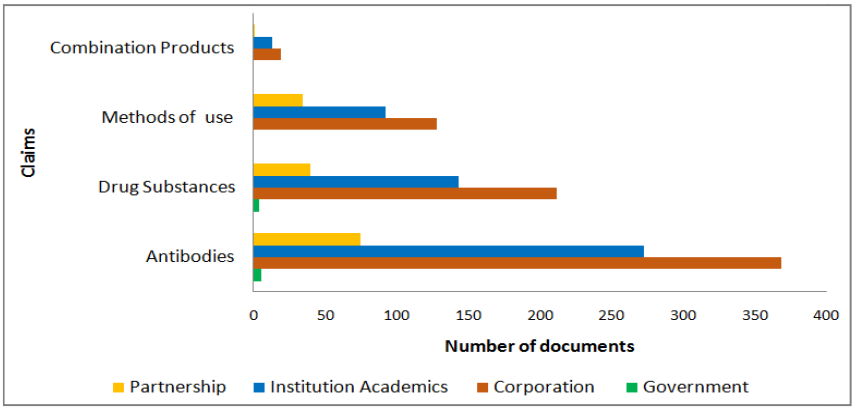

Fig. 4. Depicts the main claims of Group I classified by applicant category

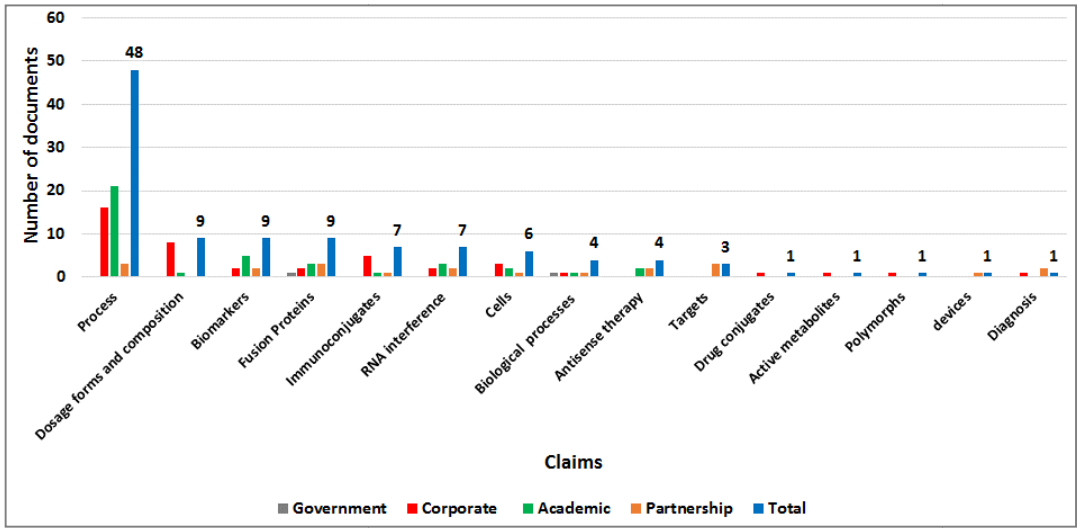

Fig. 5. Depicts the main claims of group II classified by applicant category

Table 2. Murine monoclonal antibodies approved by the FDA, commercialized, and patented during the last 20 years

Murine Monoclonal Antibodies			
	Brand name		
	Ortochone OKT3®	**Zevalin®**	**Bexxar®**
Chemical Name/Description	Murine monoclonal IgG2a antibody against the (CD3) antigen of human T - cells	Imnunoglobulin G1, anti-(human CD20 (antigen) (mouse monoclonal IDEC-Y2B8gamma. 1-chain) [30]	Combination regimen consisting of tositumomab followed by iodine (I131) tositumomab
Protein format	Murine IgG2a	Murine IgGκ conjugate, Y-90 or In-111	Murine IgG2a /ʎ-131
Molecular Target	CD3 on T-cells	CD20 on B-cells	CD20 on B-Cells
Generic Name	Muromomab-CD3®	MAb, B-cell radiation therapy, Mab, pan-B-ythrium, ibritumomab tiuxetan (pINN)	Mab, CD20-iodine 131; Tositumomab iodune-131
Product Category	Murine monoclonal antibody	Radiolabelled Monoclonal Antibodies	Combination; Radiolabelled Monoclonal Antibodies
Production Cell line	*E. coli*	CHO	Mammalian
Route & form	IV, Liquid	IV, Liquid	NHL
Filing date	04/25/1980	05/13/1997	09/16/1993
Est. Expiry Date	2000	11/13/2012	01/21/2014, 09/16/2013, 09/16/2015
Patent Number	JP 1989098478 US 4658019 US 4654210 EP 0018795 US 4361549 [23, 24 25,26]	WO 9411026 US5763137 EP1005870B1 PPBR1100622 B1 [31,32]	US5595721 US5843398 US6015542 [27,28,29]
Company	Ortho-McNeil-Janssen	Biogen Idec	Glaxo Smith Kline
Approval Data	06/19/1986	09/21/2002	06/27/2003
Major Indication	OTR	NHL	NHL

Abbreviations: E. coli-Escherichia coli; CHO-Chinese Hamster Ovary; OTR-Organ Transplantation Rejection, NHL-Non-Hodgkin's Lymphoma

4. CONCLUSION

The study of MAB proved to be of great importance to understand how the development and protection by patents of monoclonal antibodies influences their therapeutic, safe, and effective uses in diagnostics and the treatment of various diseases.

Despite academic and governmental agencies showing interest in the development of inventions in this area, companies are largely responsible for marketing these products and therefore can generate more inventions. Thus, companies require a greater quantity of patent documents. The Institute National de la Santé et de la Recherché Medical (INSERM) and the University of California are both categorized as academic institutions and were considered high assignees.

The United States, Japan, France, and China constitute potential markets for protection of this technological area. Although China has started protecting these technologies only recently (the first priority was filed in 2011), China appears 4th on the list of the Top 10 countries with the highest number of applications filed.

Of the three murine monoclonal antibodies approved by the FDA and marketed worldwide, Zevalin® was the only murine MAB protected as a patent pipeline.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975;256(5517):495-7.
2. Almagro C, Fransson J. Humanization of antibodies. Front. Biosci. 2008;13:1619–1633.
3. Tomblyn M. Radioimmunotherapy for B-cell non-Hodgkin lymphomas. Cancer Control. 2012;19(3):196-203.
4. Chames P, Van Regenmortel M, Weiss E, Baty D. Therapeutic antibodies: Successes, limitations, and hopes for the future. Br J Pharmacol. 2009;57(2):220-33.
5. Morison SL, MJ Johnson, LA Herzenber, VT Oi. Chimeric human antibody molecules: Mouse antigen-binding domains with human constant region domains. Proc. Natl. Acad. Sci. 1984; 81:6851-6855.
6. Zhiqiang A. Therapeutic Monoclonal Antibodies: From Bench to Clinic. A. John Wiley, Inc; 2009.
7. Jones PT, Dear PH, Foote J, Neuberger MS, Winter G. Replacing the complementarity-determining regions in a human antibody with those from a mouse. Nature. 1986;321(6069):522-5.
8. Buss NA, Henderson SJ, McFarlane M, Shenton JM, de Haan L. Monoclonal antibody therapeutics: history and future. Curr Opin Pharmacol. 2012;12(5):615-22.
9. Lonberg N. Human antibodies from transgenic animals. Nature Biotechnol. 2005;23:1117-1125.
10. Brüggemann M, Osborn MJ, Ma B, Hayre J, Avis S, Ludstron B, Buelow R. Human Antibody Production in Transgenic Animal. Arch. Immunol. Ther. Exp. 2015;63:101-108.
11. Mendez MJ, Green LL, Corvalan JR, et al. Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice. Nat. Genet. 1997;15:146-156.
12. Barbas CF, AS Kang; RA Lerner, SJ Benkovic. Assembly of combinatorial antibody libraries on phage surfaces: The gene III site. Proc. Natl. Acad. Sci. 1991; 88:7978-7982.
13. Rau R. Adalimumab (a fully human anti-tumors necrosis factor alpha monoclonal antibody) in the treatment of active rheumatoid arthritis: The initial results of five trials. Ann. Rheum. Dis. 2002;61(Suppl 2):ii70-3.
14. Thie H, Meyer T, Schirrmann T, Hust M, Dübel S. Phage display-derived therapeutic antibodies. Curr. Pharm. Biotechnol. 2008;9(6):439-46.
15. King C, Garza EN, Mazor R, Linehan JL, Pastan I, Pepper M, Baker D. Removing T-cell epitopes with computational protein design. Proc. Natl. Acad. Sci. 2014; 111(23):8577-82.
16. De Groot AS, Terry F, Cousens L, Martin W. Beyond humanization and deimmunization: Tolerization as a method for reducing the immunogenicity of biologics. Expert Rev. Clin. Pharmacol. 2013;6(6):651–662.
17. Parker AS, Griswold KE, Bailey-Kellogg C. Optimization of therapeutic proteins to

delete T-cell epitopes while maintaining beneficial residue interactions. J. Bio. Inform. Comput. Biol. 2011;9(2):207–229.
18. Dwek RA. Biological importance of glycosylation. Dev. Bio. Stand. 1998; 96:43-47.
19. Mimura Y, Katoh T, Saldova R, O'Flaherty R, Izumi T, Mimura-Kimura Y, Utsunomiya T, Mizukami Y, Yamamoto K, Matsumoto T, Rudd PM. Glycosylation engineering of therapeutic IgG antibodies: Challenges for the safety, functionality and efficacy. Protein Cell. 2017;1-16.
20. Giddens JP, Wang X. Chemoenzymatic glyco-engineering of monoclonal antibodies. Methl Mol, Biol. 2015; 1321:375-87.
21. Hall AE, Domanski PJ, Patel PR, Vernachio JH, Syribeys PJ, Gorovits EL, Johnson MA, Ross JM, Hutchins JT, Patti JM. Characterization of a protective monoclonal antibody recognizing *Staphylococcus aureus* MSCRAMM protein clumping factor A. Infect. Immun. 2003;71(12):6864-70.
22. Mandl SJ, Rountree RB, Dalpozzo K, Do L, Lombardo JR, Schoonmaker PL, Dirmeier U, Steigerwald R, Giffon T, Laus R, Delcayre A. Immunotherapy with MVA-BN®-HER2 induces HER-2-specific Th1 immunity and Alters the Intra tumoral Balance of Effector and Regulatory T cells. Cancer Immunol. Immunotherapy. 2012; 61(1):19-29
23. OrthoPharmaceutical Corp. Complement-fixing monoclonal antibody to human T cells. US; 1979. US06709232.
24. OrthoPharmaceutical Corp. Methods and compositions using complement fixing monoclonal antibody to human T cells; 1979. US06709232.
25. Ortho Pharmaceutical Corp. Monoclonal-antibody-producing hybrid cell line, antibody and method of preparing it, therapeutic composition containing it and its diagnostic and therapeutic uses; 1979. EP0018795.
26. Ortho Pharmaceutical Corp. Complement-fixing monoclonal antibody to human T cells and methods of preparing same; 1979. US 4361549.
27. Coulter Pharmaceutical. Radioimmunotherapy of lymphoma using anti-CD2; 1979. US5595721.
28. Coulter Pharmaceutical Inc. Radioimmunotherapy of lymphoma using anti-CD20 antibodies; 1993. US5843398.
29. Coulter Pharmaceutical Inc. Radioimmunotherapy of lymphoma using anti-CD20 antibodies; 1993. US6015542.
30. Murine monoclonal IgG2a antibody against the T3 (CD3) antigen of human T cells. Product report. Thomson Reuters Integrity; 2014.
Available:http://integrity-thomson-pharma.ez68.periodicos.capes.gov.br
(Last accessed 13 January 2014)
31. Anticorpo Anti-CD20 quimérico imunologicamente ativo e composição farmacêutica.
Available:http://gru.inpi.gov.br/pePI/servlet/patentServletController?action=detailEcodpedido=258952&Searcparamenter=PI1100622thomson-pharma.com.
(Last accessed 09 August 2016)
32. Combination of two radio-labeled Immunoconjugates Comprising Indium-111 (111In) or Yttrium-90 (90Y) Labeled Murine IgG1 kappa Monoclonal antibodies targeting CD20 antigen. Conjugated.
Available:http://integrity-thomson-pharma.ez68.periodicos.capes.gov.br.
(Last accessed 22 July 2016)
33. Combination regimen consisting of tositumomab followed by Iodine (I131) Tositumomab. Product report. Thomson Reuters Integrity; 2014.
Available:http://integrty.thomson-pharma.com
(Last acessed2 2 March 2014)

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/20290