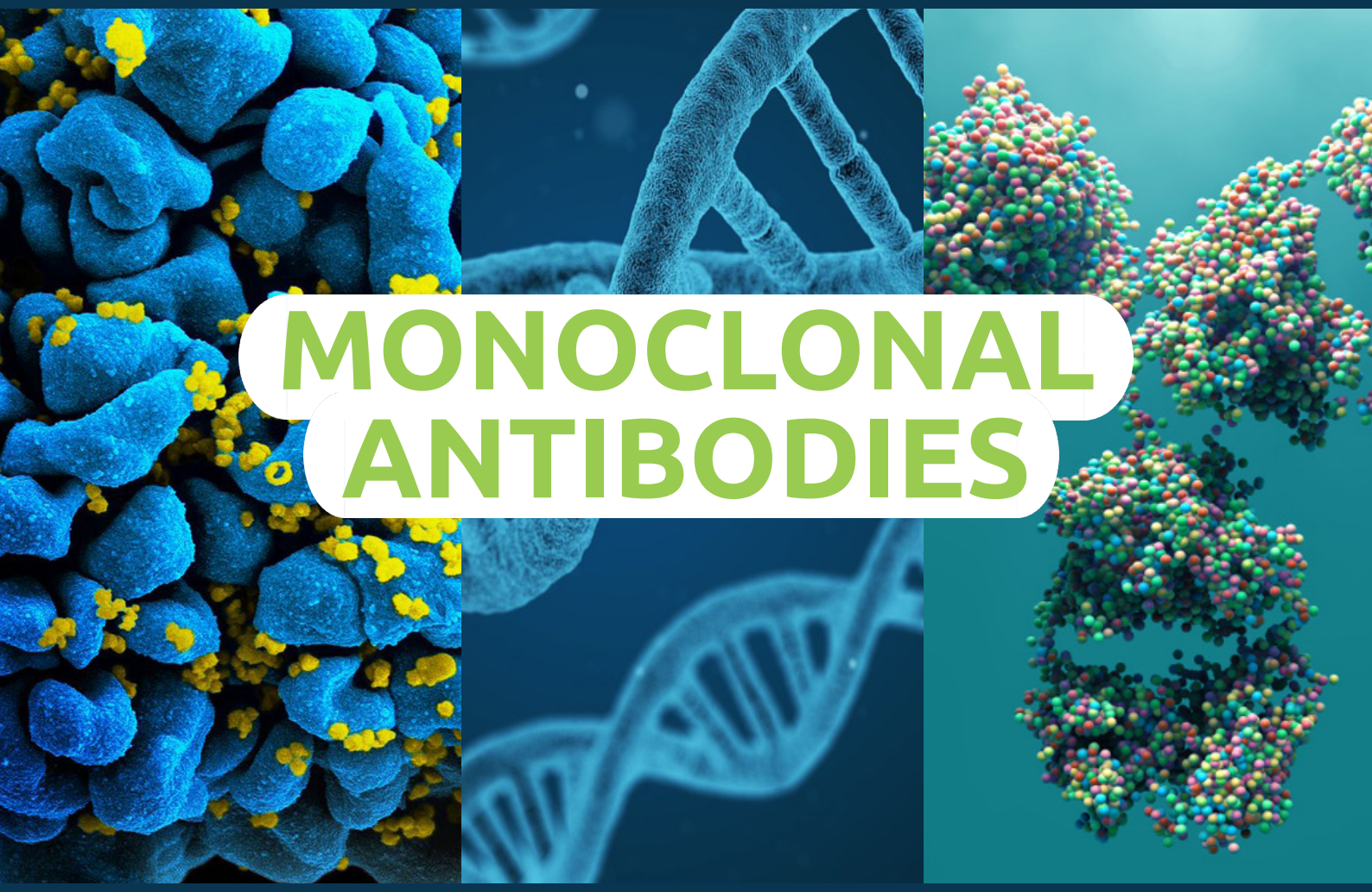
IMMUNOWATCH

Edition n°1 - February 2020



MONOCLONAL ANTIBODIES

MABDESIGN
THE IMMUNOTHERAPY NETWORK

INTRODUCTION

MabDesign's Immunowatch is a one-of-a-kind information monitoring newsletter in the field of immunotherapy. Its aim is to provide members of our association with the most recent and pertinent data gathered or generated through the key expertise of MabDesign and its collaborators in scientific research, business intelligence, market analysis and intellectual property.

Each edition will focus on one trending type of immunotherapy. It's general format will include a market study research, a selection of scientific publications, financial and economic information, a special opinion article and a section dedicated to intellectual property. The content of each edition will be decided by an editorial composed of two field experts, one from academia and one from the industry. Immunowatch is done in collaboration with the MAbMapping Unit of the Ambition Recherche & Développement (ARD) Biomédicaments 2020 Phase II programme, funded by the Centre Val de Loire region.

BIOPHARMACEUTICALS
Innovation Dynamics in Health
IN REGION CENTRE-VAL DE LOIRE

MABDESIGN
THE IMMUNOTHERAPY NETWORK

Région Centre-Val de Loire

Table of content

Editorial

Alain Beck

Alain Beck is the Senior Director of Biologics CMC & developability at Pierre Fabre and associate editor of the mAbs scientific journal.

As illustrated in this first issue of Immunowatch, 2019 was again a very successful year for antibody-based therapeutics. Taken just the case of Antibody-Drug Conjugates (ADCs), 3 new drugs have been approved (Polivy®, Padcev™ and Enhertu™). It is also important to note that frequently new antibody drugs are first registred in the US and then in Europe. This should encourage us to pursue our efforts with MabDesign to develop the immunotherapy network in France and abroad. In the field of biosimilars, near 30 antibodies or Fc-fusion proteins are approved in Europe (vs around 10 in the US!) which will contribute to offer less expensive drug to patient with the same quality. This also show that biotechnology paradigm «the process is the product" is no longer true. In addition, I would also highlight the December special issue of Medicine/ Sciences on Antibodies as a significant achievement for 2019 for the French-speaking antibody community. Finally, as chairman of MabDesign Scientific Advisory board (COSSF), I would acknowledge the progresses that have been made these last 12 months by MabDesign.

Hervé Watier

Hervé Watier is professor of immunology at the University of Tours, coordinator of the LabEx MAbImprove and of the ARD 2020 Biomédicaments.

It is a great honour and a considerable pleasure to introduce this very first issue of the ImmunoWatch newsletter, which will undoubtedly meet the needs of the Immunotherapy community. Indeed, it extends the MAbWatch weekly newsletter - greatly appreciated within the MAbImprove LabEx - by providing new dimensions and carrying a new ambition. This ImmunoWatch is also one of the outcomes of the MAbMapping collaborative project between MabDesign and MAbImprove, thanks to the ARD2020 Biopharmaceuticals programme. It stands as the latest result of the fruitful collaboration between the LabEx and the French industrial sector dedicated to monoclonals and immunotherapy.
Hope this ImmunoWatch will be the first of a very long series!

Francis Carré

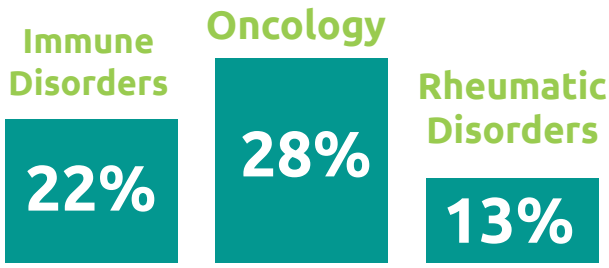
President of MabDesign

Dear colleagues and members,
I have the pleasure to introduce the first edition of IMMUNOWATCH, the information monitoring newsletter of MabDesign in the field of immunotherapy. I hope that you will enjoy this new semi-annual publication which furthers the commitment of MabDesign to support the French biopharmaceutical field. Thanking you in advance for your feedbacks and comments, let us wish Immunowatch a long-lasting existence.
With my warmest greetings.

Therapeutic monoclonal antibody market in 2019*

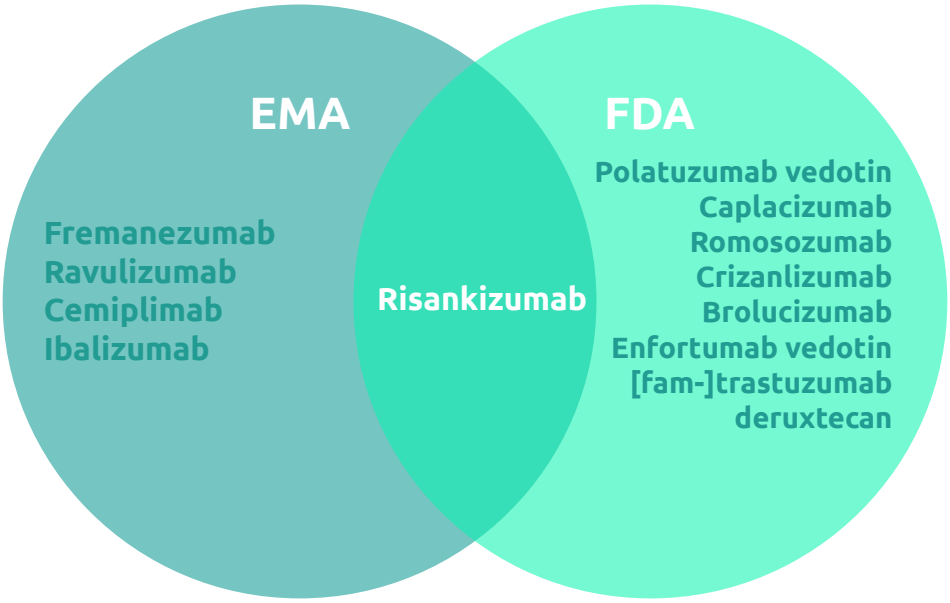
97

Antibodies currently available
excluding biosimilars



Top 3 therapeutic areas

List of therapeutic monoclonal antibodies approved in 2019[1]



90

Market value in 2019
in billion euros

mAbs in France

** All data has been generated by MabDesign unless stated otherwise*
1. Current as of 06/01/2020 Biosimilars are not included Source: antibodysociety.org

Top deals involving mAb in 2019

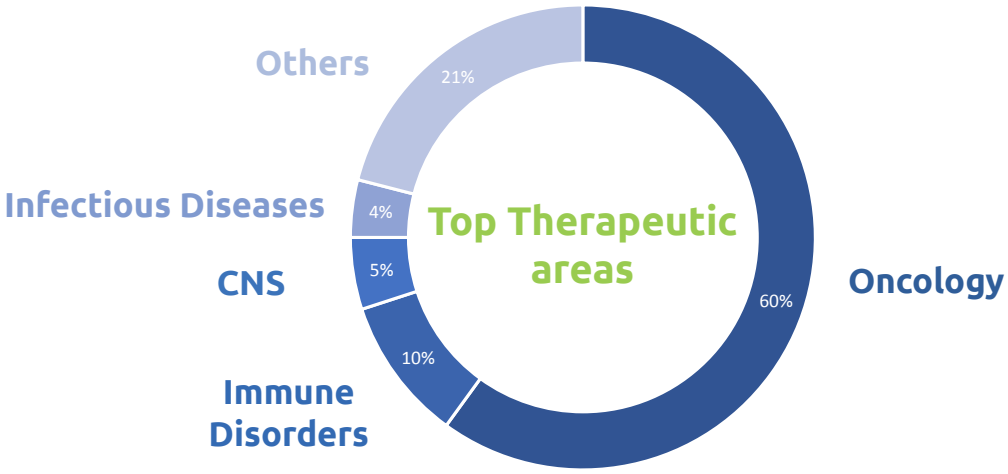
Companies involved	Monoclonal antibody involved	Deal value (US$m)
Acquisition of Alder Biopharmaceuticals Inc by H. Lundbeck AS	ALD-1613; ALD-1910; ALD-306; AD-319; ALD-806; ALD-901; eptinezumab	2 018
Acquisition of Kyowa Hakko Bio Co Ltd (95%) by Kirin Holdings Co Ltd	KM-2760	1 165
Acquisition of Tilos Therapeutics Inc by Merck & Co Inc	TL-01; TL-02; TL-03; TL-04; TL-05	773
Strategic alliance between Argenx SE and Halozyme Therapeutics Inc	efgartigimod alfa	540
Strategic alliance between Celgene Corp and Jounce Therapeutics Inc	JTX-8064	530
Acquisition of assets from NovImmune SA by Swedish Orphan Biovitrum AB	emapalumab; NI-1801; TG-1801	519
Strategic alliance between Genmab A/S and Janssen Biotech Inc	Monoclonal Antibody to Target CD38 for Oncology	275
Strategic alliance between Imbrium Therapeutics LP and TetraGenetics	IMB-2011010; IMB-2011200	273
Strategic alliance between BeiGene (Beijng) Co Ltd and BioAtla LLC	BA-3071	269

Deals where the exact value has not been disclosed are not included in the list.
Source : Global Data

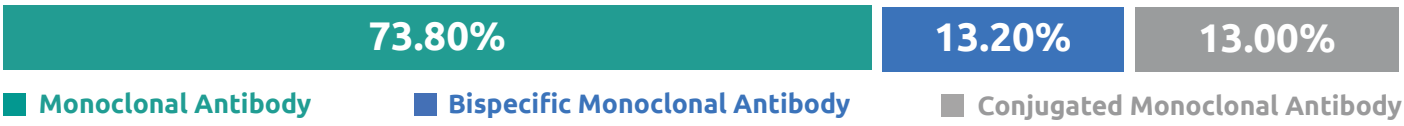
MAB PIPELINE IN 2019*

3257

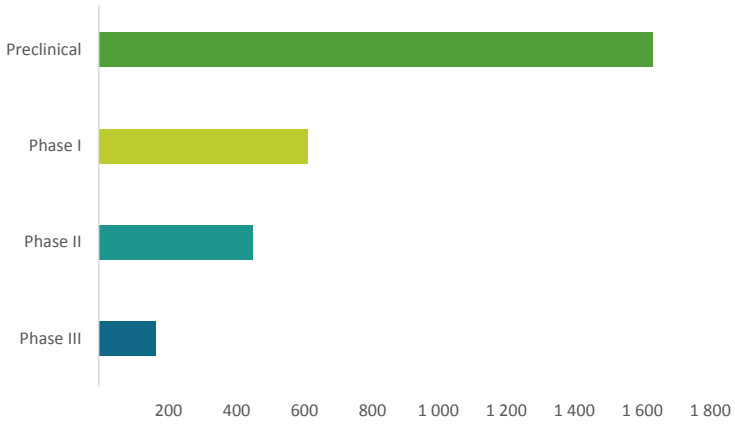
mAb-based therapies under development



Type of antibody being developed



Stage of development



List of therapeutic monoclonal antibodies currently under regulatory review[1]

Oblitoxaximab, emapalumab, polatuzumab vedotin, brolucizumab, crizanlizumab, isatuximab, satralizumab

Isatuximab, teprotumumab, inebilizumab, eptinezumab, leronlimab, sacituzumab govitecan, satralizumab, narsuplimab, tafasitamab, rEGNEB3

Regulatory Milestones

Orphan Drug Designation (Global)	38
Priority review (Global)	13
Breakthrough therapy (US)	11
Fast track (US)	10
Prime designation (EU)	2

French companies currently with mAbs in clinical phase

** All data has been generated by MabDesign unless stated otherwise*
1. Source: antibodysociety.org

Promega

Quantitative Cell based Biossays to advance Immunotherapy Programs

FcyR Effector Activity
. ADCC (FcyRIIIa, FcyRIIb)
. ADCP (FcyRIIIa, FcyRIIa,FcyRI)
. mADCC(FcyRIV, FcyRIII)

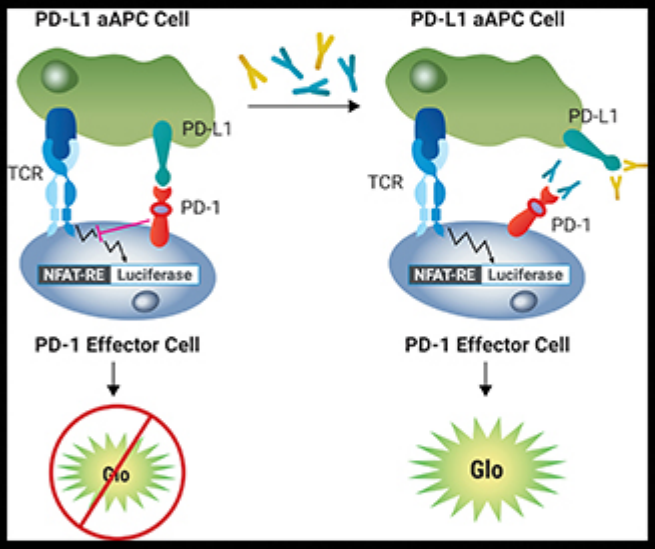
Immune Checkpoint
. PD-1, CTLA-4,TIGIT,LAG-3,TIM-3, ICOS, CD28, BTLA/HVEM

. GITR, 4-1BB, CD40, OX40, CD27, HVEM/LIGHT, DR3

. Combination Biossays

T-Cell Activation
. Bispecific Ab Development

Growth Factor & Cytokine Biosimilar targets
. IL-2, IL6, IL12, IL15, IL17, IL23
. VEGF, RANKL, TGF-ß



Representation of the PD-1/PD-L1 Blockade Biossay. The Bioassay consists of two genetically engineered cell lines, PD-1 Effector Cells and PD-L1 aAPC/CHO-K1 Cells. When co-cultured inhibits TCR mediated luminescence. WHen the ,PD-1/PD-L1 interaction is disrupted, TCR activation induces luminescence (via activation of the NFAT pathway) that can be detected by addition of Bio-Glo TM. Reagent and suantification with a luminometer.

Discover our portfolio functional biossays :
https://france.promega.com/products/reporter-bioassays/

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CHEMICAL COMPOUNDS VERSUS ANTIBODIES, THE CHOICE IS YOURS

Gavin Vuddamalay [‡] and Hervé Watier [†]

[‡] *Business intelligence and Intellectual Property Department, MabDesign*
[†] *LabEx MAbImprove, Université de Tours*

The use of natural chemical compounds to treat ailments dates back to ancient times with the Sumerians having, more than 5000 years ago, identified and used over 250 plants, including poppy, willow bark, henbane and mandrake, whose extracts are endowed with medicinal properties (1). Modern medicine would however attribute the first important historic milestone of synthetic chemical compounds to be used as drugs either to Felix Hoffmann's acetylsalicylic acid (first synthesized in 1887 and marketed under the name Aspirin by Bayer Laboratories) (2) or to Paul Ehrlich's magic bullet arsphenamine (first synthesized in 1907 and marketed under the name of Salvarsan Hoechst AG) (3).

Interestingly, the earliest reports of passive immunisation and hypothetical existence of antibodies also appeared at that same period of History. In 1890, Emil von Behring and Shibasabura Kitasato published their landmark article in which they showed that the transfer of serum from an animal actively immunised against diphtheria toxin to a non-immunised (naive) animal could protect the latter against an even fatal dose of the same toxin (4). A few years later, Paul Ehrlich proposed the side-chain model of immunity to account for this acquired resistance. According to this model, toxins would mediate their effect by binding to specific protein side chains on cells and inhibiting their physiological function. As a compensation mechanism, the cell would produce more of these side-chains and release them in the bloodstream where they would accumulate and serve as anti-toxin during subsequent exposures to the same toxin (5). While this side-chain model was incorrect, it did serve as the premise to our actual understanding of how antibodies are produced and exert their function.

Synthetic chemical compounds quickly gained momentum and thrived across the 20th century in the pharmaceutical field, fuelled by our mastering of chemistry and our growing understanding of the mechanism of action of these chemicals at the molecular level. The success of chemical compounds was maintained even after the epidemiological shift from infectious diseases to chronic/non-infectious diseases. Indeed, our ability to synthesize and screen chemical entities in both in vitro and in vivo models, independently of whether or not the exact endogenous targets were known, greatly contributed to the rise of immunosuppressive drugs, anti-cancer chemotherapies and neuroleptic drugs, among others. Passive immunisation proved more difficult to establish as a common form of treatment due to the difficulty of obtaining antibody preparations specifically directed against human antigens, contrarily to microbes. The immunogenicity of antibody preparations, raised in animals, led to anaphylactic reactions and serum sickness in humans. Aside from that, there was a lack of knowledge about endogenous antigens and scientific know-how to raise antibodies against them. The success of chemical compounds over antibodies is mirrored in the global drug market with 84,854 small molecules currently available (including generics) compared to 97 of monoclonal antibodies (excluding biosimilars)[1] .

1. Source: Global Data

The rebirth of antibody-based therapeutics was made possible with the advent of game-changing innovations as from the 1970's starting with the hybridoma technology and later on the recombinant DNA technologies responsible for chimeric and/or humanised antibody production, phage display and transgenic animals. In parallel to that, endogenous molecules including the different clusters of differentiation and their function were gradually being described, paving the way to target identification for monoclonal antibodies. With this newly acquired prominence, therapeutic antibodies seem to have limitless potential and their use as an alternative to chemical compounds is being advocated by numerous experts. We here provide key insights into the pros and cons for each category.

SIZE OF CHEMICAL SPACE AND ANTIBODY REPERTOIRE: FROM (IM)POSSIBLE TO PROBABLE

The first question that comes to mind is the scope of possibilities for each category. For chemical compounds, this can be estimated by the chemical space which corresponds to the number of potentially synthesizable and pharmacologically active molecules. According to the latest calculations, the theorical chemical space would be around 10^{60} in size, though this approximation may fluctuate depending on the method of calculation used (6, 7). However, to date, the greatest chemical library currently available contains only $9.6x10^{7}$ compounds[2] according to the National Institutes of Health's PubChem database. Concerning antibodies, the size of the human repertoire is estimated to be at 10^{26} antibodies (8), that of the mouse at 10^{13} (9) and the size of a phage display library at 10^{11} (10). Practically, the accessible antibody repertoires/libraries are therefore greater than the chemical libraries, although they are theoretically smaller.

GENERAL APPROACH WITH DRUG CANDIDATES

Identifying drug candidates from each category will intuitively require contrasting approaches. For antibodies, this will involve either animal immunisation with the target antigen followed by the screening of antibody-producing B lymphocytes or supernatants, or direct fishing out of the right antibody in available libraries by panning on the antigen. For chemical compounds, each candidate will have to be screened one by one to identify those interacting specifically with the target molecule. Importantly, both approaches can greatly benefit from computer aided drug design technologies. Finally, given the usual host-specificity of (monoclonal) antibodies hardly cross-reacting with animal antigen, preclinical evaluations of chemical molecules in animals still remain less limited.

2. https://pubchemdocs.ncbi.nlm.nih.gov/statistics accessed on the 12/12/2019

PHARMACOLOGY OF AN ANTIBODY AND OF A SMALL CHEMICAL MOLECULE AT THE LEVEL OF A GIVEN TARGET

To illustrate the pharmacological differences between the two types of molecules, we use the example of plasma kallikrein, which is a target enzyme for preventing hereditary angioedema. Among the different inhibitory drugs already or nearly to be approved, there is a human monoclonal IgG1 antibody, lanadelumab (11) and several chemical compounds including avoralstat (12). As depicted in Figure 1, a compound[3] of the same class as avoralstat will insert itself in the catalytic-active site while lanadelumab will quite literally cover the active site preventing any interaction with the substrate (high molecular weight kininogen) and hence the generation of bradykinin (13). Since proteases have highly conserved catalytic sites, small chemical molecules could possibly affect other proteases of the serine protease family, leading to an off-target effect in case of excessive dosage of the drug. By contrast, antibodies interact with a higher number of residues mostly outside the catalytic site and are less prone to be conserved within the same protease family members. For the same reasons, antibodies are also less prone to interact with orthologs in preclinical models. Table 1 compares the other major differences between an antibody and a small chemical molecule.

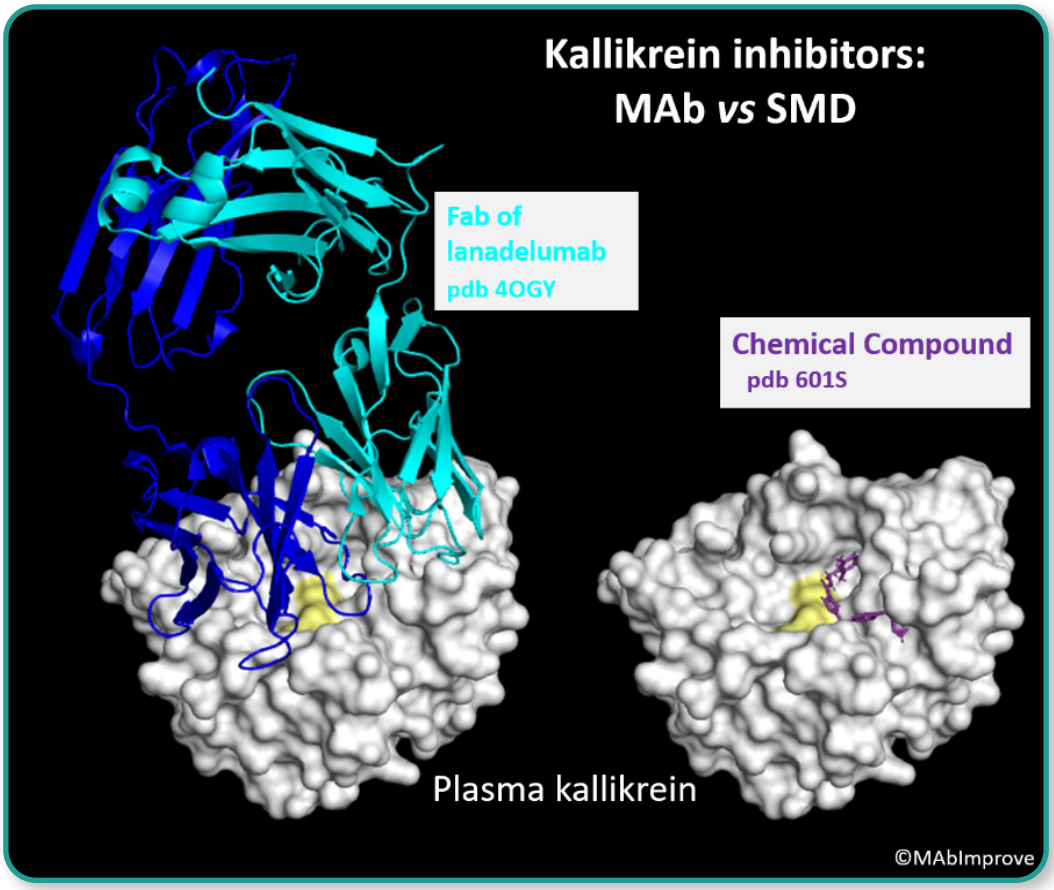

Figure 1 : The chemical compound (purple) inserts itself into the catalytic site (yellow) of plasma kallikrein whereas the Fab of lanadelumab (dark blue and light blue) covers it.

3. Formula : N-[(6-amino-2,4-dimethylpyridin-3-yl) methyl]-1-({4-[(1H-pyrazol-1-yl) methyl] phenyl} methyl)-1H-pyrazole-4-carboxamide

Pharmacology	Small molecule	Monoclonal antibody
neutralising effect through inhibition of protein-protein interaction	good	better
pharmacodynamics	single function (target interaction)	multiple functions through the Fab and the Fc
cell membrane barrier/intracellular targets	possible	impossible
Pharmacokinetics/half-life	usually short, often with daily dose (single or multiple)	half-life of recently marketed MAbs of the IgG class ranges between 8 to several weeks, allowing spacing the doses and improving patient's comfort (half-life of MAbs can be further modulated through their interaction with the protective receptor FcRn)
physiological barriers, notably blood-brain barrier	possible	limited
off-target toxicity	common	rare
metabolism	diverse metabolites whose effects and toxicity are difficult to predict	peptidic cleavage, without toxicity
relevance of animal models	variable; usually good	poor; non-human primate models required for toxicity studies
oral administration	possible	impossible (infusion only)
residues in the environment	frequent	entirely biodegradable

Table 1

CONCLUSION

With 10,757 candidates currently being developed (active status in the pipeline) as innovator drug worldwide[4] , small chemical molecules are still taking the lion's share in drug development and a turnaround of this trend is highly doubtful notably since targeting intracellular molecules (nucleus, signalling cascades, etc) remains the private turf of this category of compounds. However, since the first generation of monoclonal antibodies in 1975, followed by the licensing of Orthoclone OKT3 (muromonab-CD3) in 1986 (14), there has been a growing interest for field of therapeutic monoclonal antibodies as evidenced by the not-so-shy drug pipeline of monoclonal antibodies currently under development[5] . Both fields are expected to thrive with scientific advances regularly providing solutions to bypass technological barriers.

4. Source: Global Data
5. Refer to the pipeline infographics of this edition

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SCIENTIFIC HIGHLIGHTS OF 2019

As of going to press, more than 6000 scientific articles have been published in 2019 worldwide[1].The aim of this section is obviously not to cite all of them but rather to provide an overview of the scientific excellence of the mAb R&D field and of its translational nature. Our top picks below have been compiled with the help of our Editor-In-Chief, Alain Beck.

Structure, heterogeneity and developability assessment of therapeutic antibodies.

Xu Y, Wang D, Mason B, Rossomando T, Li N, Liu D, Cheung JK, Xu W, Raghava S, Katiyar A, et al. MAbs 2019, 11:239-264

This review outlines the different antibody quality attributes that are critical in mAb R&D together with the associated analytical methods to monitor those characteristics. A practical workflow is proposed as a best practice for developability assessment including in silico evaluation, extended characterization and forced degradation using appropriate analytical methods that allow characterization with limited material consumption and fast turnaround time.

Antibody-Cytokine Fusions : Versatile Products for the Modulation of Anticancer Immunity.

Neri D. Cancer Immunol Res 2019, 7:348-354

This review focuses on antibody-cytokine fusion proteins (also called «immunocytokines») as one class of biopharmaceuticals that can substantially improve the therapeutic index and, thus, the applicability of cytokine products. The various factors contributing to the in vivo performance of these cytokine-based therapeutics, including the target antigen, the antibody properties, the nature of the payload, the format of the fusion protein, the dose, and schedule, as well as their use in combination with other therapeutic modalities are discussed here.

Cutting-edge multi-level analytical and structural characterization of antibody-drug conjugates: present and future.

Beck A, D'Atri V, Ehkirch A, Fekete S, Hernandez-Alba O, Gahoual R, Leize-Wagner E, Francois Y, Guillarme D, Cianferani S. Expert Rev Proteomics 2019, 16:337-362

In this review, the authors have summarized the latest analytical and structural toolbox for the characterization of 1st, 2d and 3d generation ADCs since 2016. These emerging techniques allow a deep insight into important critical quality attributes (CQAs) that are related to ADC Chemistry Manufacturing and Control (CMC) as well as an improved understanding of in vitro and in vivo ADC biotransformations. State-of-the-art techniques, such as liquid chromatography, high resolution native and ion mobility mass spectrometry, multidimensional liquid chromatography and capillary electrophoresis hyphenated to mass spectrometry are discussed.

Interleukin-7 receptor blockade by an anti-CD127 monoclonal antibody in nonhuman primate kidney transplantation.

Mai HL, Nguyen TVH, Branchereau J, Poirier N, Renaudin K, Mary C, Belarif L, Minault D, Hervouet J, Le Bas-Berdardet S, et al. Am J Transplant 2019

In this study, Mai et al. assessed for the first time the effects of a blocking anti-human cluster of differentiation 127 (CD127) mAb administered in combination with low-dose tacrolimus or thymoglobulin in a life-sustaining kidney allograft model in baboons. Surprisingly the addition of an anti-CD127 mAb to the treatment protocols did not prolong graft survival compared to low-dose tacrolimus alone or thymoglobulin alone. unlike in rodents, in nonhuman primates, anti-CD127 mAb treatment does not decrease the absolute numbers of lymphocyte and lymphocyte subsets and does not effectively inhibit postdepletional T cell proliferation and homeostasis, suggesting that IL-7 is not a limiting factor for T cell homeostasis in primates.

1. Keyword search for «monoclonal + antibody» on pubmed-gov on 27/11/19

Bispecific antibodies: a mechanistic review of the pipeline.

Labrijn AF, Janmaat ML, Reichert JM, Parren P. Rev Drug Discov 2019, 18:585-608

Labrijn et al. review the current Bispecific antibodies (bsAb, term used to describe a large family of molecules designed to recognize two different epitopes or antigens) landscape from a mechanistic perspective. This paper provides key insights into bsAb formats, a timeline of conceptual and technical innovations contributing to the development of the therapeutic bsAb landscape and a comprehensive overview of the pipeline.

Harnessing innate immunity in cancer therapy.

Demaria O, Cornen S, Daeron M, Morel Y, Medzhitov R, Vivier E.Nature 2019, 574:45-56

In this review, the authors discuss the roles of innate immunity in antitumor responses, by highlighting the mechanisms by which innate immune cells can detect tumours, induce and amplify adaptive immune responses, and exert direct effector responses, and the mechanisms by which these responses are suppressed at the tumour bed. This article focuses on the molecules that have led to strong preclinical data or promising signals in early clinical trials.

Efficacy of the Antibody-Drug Conjugate W0101 in Preclinical Models of IGF-1 Receptor Overexpressing Solid Tumors.

Akla B, Broussas M, Loukili N, Robert A, Beau-Larvor C, Malissard M, Boute N, Champion T, Haeuw JF, Beck A, et al. Mol Cancer Ther 2019

In this original article, Akla et al. report a unique IGF-1R-targeted antibody-drug conjugate (ADC) W0101, designed to deliver a highly potent cytotoxic auristatin derivative selectively to IGF-1R overexpressing tumor cells. The ADC, which corresponds to the conjugation of a novel auristatin derivative drug linker to the monoclonal antibody hz208F2-4, induced potent tumor regression in certain mouse models with this potency correlating with the expression level of IGF-1R. In an MCF-7 breast cancer model with high-level IGF-1R expression, a single injection of W0101 3 mg/kg led to strong inhibition of tumor growth.

Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension.

Cork MJ, Thaci D, Eichenfield LF, Arkwright PD, Hultsch T, Davis JD, Zhang Y, Zhu X, Chen Z, Li M, et al. Br J Dermatol 2019

This paper studied the pharmacokinetics of dupilumab, and long-term safety and efficacy in adolescents with moderate-to-severe atopic dermatitis (AD). Results have been drawn from a global, multicentre, phase IIa, open-label, ascending-dose, sequential cohort study with a phase III open-label extension. They demonstrate the long-term safety and efficacy of dupilumab in adolescents with moderate-to-severe AD for up to 52 weeks of treatment, thus extending and reinforcing the findings from the 16-week dupilumab phase III trial. The data from these studies also support the use of dupilumab in combination with current standard of care (topical corticosteroids).

The rise of oncology biosimilars: from process to promise.

Verrill M, Declerck P, Loibl S, Lee J, Cortes J. Future Oncol 2019, 15:3255-3265

In this review, the authors describe the development and approval process of biosimilar medicines with the scope being restricted to biosimilars in therapeutic cancer care and using trastuzumab as an example. The paper includes a comprehensive overview of the development pathway for biosimilars together with their approval requirements. Aspects of product manufacturing and clinical development are also discussed.

Monalizumab: inhibiting the novel immune checkpoint NKG2A

van Hall T, Andre P, Horowitz A, Ruan DF, Borst L, Zerbib R, Narni-Mancinelli E, van der Burg SH, Vivier E. J Immunother Cancer 2019, 7:263

Here the authors review the latest data concerning NKG2A, an inhibiting receptor expressed on subsets of cytotoxic lymphocytes which engages the non-classical molecule HLA-E. Use of monalizumab, a blocking anti-human NKG2A mAb, in combination with other oncoimmunology compounds to treat cancer patients is extensively discussed.

VHH characterization. Comparison of recombinant with chemically synthesized anti-HER2 VHH.

Hartmann L, Botzanowski T, Galibert M, Jullian M, Chabrol E, Zeder-Lutz G, Kugler V, Stojko J, Strub JM, Ferry G, et al.. Protein Sci 2019, 28:1865-1879

In this original article, the authors provide key insights into VHH chemistry, biochemistry and therapeutic future. They investigated two different production strategies of this small antibody-like protein, using an anti-HER2 VHH as a model. The latter was either produced through total chemical synthesis or through expression in bacteria or yeast. Interestingly, there were no major differences between the recombinant and the synthetic protein in terms of structure or affinity.

Distinctive Low-Resolution Structural Features of Dimers of Antibody-Drug Conjugates and Parent Antibody Determined by Small-Angle X-ray Scattering.

Law-Hine D, Rudiuk S, Bonestebe A, Ienco R, Huille S, Tribet C. Mol Pharm 2019

The structural features of lysine-conjugated antibody-drug conjugate (ADC) from humanized IgG1 were studied by small-angle X-ray scattering (SAXS). Results from the SAXS structural study show in the present case that conjugation has favored innermost inter-ADC contacts in the dimer, which differ from the inter-mAb ones. In general, it is likely that many parameters affect inter-ADC association, including the chemical nature of linkers and drugs, degree of conjugation, conjugation sites, etc.

VISTA is an acidic pH-selective ligand for PSGL-1.

Johnston RJ, Su LJ, Pinckney J, Critton D, Boyer E, Krishnakumar A, Corbett M, Rankin AL, Dibella R, Campbell L, et al.Nature 2019, 574:565-570

Johnston et al. report that V-domain immunoglobulin suppressor of T cell activation (VISTA) engages and suppresses T cells selectively at acidic pH such as that found in tumour microenvironments. Multiple histidine residues along the rim of the VISTA extracellular domain mediate binding to the adhesion and co-inhibitory receptor P-selectin glycoprotein ligand-1 (PSGL-1). Antibodies engineered to selectively bind and block this interaction in acidic environments were sufficient to reverse VISTA-mediated immune suppression in vivo. These findings identify a mechanism by which VISTA may engender resistance to anti-tumour immune responses, as well as an unexpectedly determinative role for pH in immune co-receptor engagement.

Glycosylation of biosimilars: Recent advances in analytical characterization and clinical implications.

Duivelshof BL, Jiskoot W, Beck A, Veuthey JL, Guillarme D, D'Atri V. Anal Chim Acta 2019, 1089:1-18

In this review, the authors discuss the importance of glycan characterization on therapeutic proteins, with a particular focus on the analytical techniques applied for glycan profiling of biosimilar mAb products. In addition, they provide an overview of the biosimilar market in the EU and US and present a case study on infliximab biosimilars to illustrate the potential clinical implications of differences in glycan profile between originator and biosimilar mAb products.

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PROTECTING THERAPEUTIC ANTIBODIES

Raphaëlle GILLET [ǂ] and Nicolas BOUQUIN [ǂ]

[ǂ] Regimbeau, Paris

INTRODUCTION

Monoclonal antibodies account today for about half of the world's best-selling drugs, i.e. 8 out of 15 in 2018. However, a significant number of these drugs are now under the «attack» of biosimilars. Therefore, it is becoming increasingly important for developers of therapeutic antibodies to design strategies which ensure a broad protection for the commercialised drugs and successful enforcement in court. Moreover, protection has to be homogenised across the world, in as much as it is possible in view of the practices of the different patent offices. This article reviews the different approaches to protecting antibodies with a focus on the European perspective. While not looking for exhaustivity, it will illustrate various solutions that exist for claiming antibodies in Europe. To be patentable, biotech inventions such as antibodies have to meet the same criteria as those in other technological fields. In other words, they must be new (not already known/disclosed), involve an inventive step (not obvious) and be capable of industrial application. In addition, the description must give sufficient information for enabling the reproduction of the antibody and must support the claims. However, because of differences both structural and functional between antibodies and small molecules, the case law has often derived a specific approach to the patentability of antibodies, notably in respect of inventive step and sufficiency of disclosure. The challenge when seeking protection for a therapeutic antibody is to obtain claims that are solid enough to withstand any validity attack, but still broad enough to prevent competitors from commercialising their biobetters or biosimilars. Moreover, this must be integrated within a global strategy aiming at maximising the protection for the marketed drug.

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A BROAD PROTECTION

Antibodies are peculiar molecules. First and foremost, they are defined by the antigen they recognise. Consequently, the identification of a novel antigen will allow the inventor to claim successfully any antibody recognising this antigen. This confers the broadest possible protection. Such a claim will usually recite:

Antibody against <target X>.

The patentability of such claims was affirmed as early as the 90s by the Board of Appeals of the European Patent Office (EPO)[1] and has been maintained ever since. It also applies to the case where routine methods for generating an antibody against a known antigen have repeatedly failed. The inventor who is the first to develop a method allowing to raise antibodies against this specific antigen can expect receiving broad protection. In this case, the EPO considers the target to have been made available for the first time by the newly provided method[2] .

However, evidence will need to be provided to the EPO that the claimed method allows raising antibodies against the target protein. It also helps to be able to demonstrate that routine methods repeatedly failed. Such a broad protection is not available in the US anymore, where the Federal Circuit considered that an antibody defined only by the antigen it binds does not satisfy the written description requirement, a condition which is specific of U.S. patent law[3] .

THE NEED FOR AN UNEXPECTED PROPERTY

With the advent of whole-genome sequencing, the number of therapeutic targets not yet sequenced has become extremely reduced. It is thus more and more difficult to obtain broad protection for any antibody recognising a specific target antigen. A narrower protection may still be sought by defining the antibody by reference to functional and/or structural features. However, the critical issue of the inventiveness of thus-defined antibodies must then be addressed. By contrast to the EPO's approach for small molecules therapeutics, a unique structure will -generally- not be considered sufficient to confer inventive step to a new antibody directed to a previously known target. The EPO considers that identification of new antibodies against a specific, known target does not require undue experimentation.

This approach is similar to those of most other major patent offices, notably in China and Japan, but differs sensibly from the U.S. practice. A new antibody against a previously described target can only be inventive if it displays an unexpected property, i.e. a feature which distinguishes this antibody from the prior art and could not have been predicted from said art. This property may be e.g. a change in potency, a change in affinity, a reduced immunogenicity, the specific binding of a new epitope, the ability to compete with a known antibody, the ability to inhibit/stimulate ligand binding, the ability to inhibit/activate downstream functions; and it must be at least plausible that the claimed antibody does indeed possess this property[4] .

1. Board of Appeal decision T 512/94
2. Board of Appeal descision T 187/04
3. Amgen Inc. v. Sanofi (Fed. Cir. 2017)
4. Board of Appeal decision T 1329/04

All the antibodies encompassed by the claim must possess the unexpected property relied on for inventive step, either because this property is explicitly recited in the claims or because it is clear that all the antibodies having the claimed particular structure possess this property. Otherwise, the EPO will consider the claim not to be inventive over its entire scope and will request a limitation of the claim to those antibodies actually displaying the property. Further data may be provided to the EPO if needed at a later time point in the proceedings (but other patent offices, e.g., in China or Japan, may not accept such later-furnished data). This must be seen as an expedient, which is not recommended in common practice. First, there must be a connection to the feature(s) in the application as filed, i.e., it is not possible to rely on a feature identified after the application is filed. Moreover, assessment of inventive step will also rely on the data included in the application.

Nonetheless, the rule of thumb is that the greater the number of results in the application as filed, the easier it will be to obtain a claim covering several antibodies. It must be emphasised that the burden of proof for an alleged distinguishing property lies with the applicant. The applicant therefore generally has to demonstrate that the claimed antibody possesses this property and that this property could not have been predicted from the prior art. In this regard, at least some experimental data demonstrating the presence of this property in a representative number of antibodies must be provided in the application as filed. Of course, the greater number of results, the easier it will be to convince a patent Examiner. Providing no or only a few data in the application is likely to lead to inextricable difficulties during examination. For example, it is often difficult to obtain a claim directed to all the antibodies having a specific property when all the results in the application were obtained with a single antibody.

AN ANTIBODY DEFINED BY ITS FUNCTION

As mentioned above, when the antigen is already known, it is possible to define the antibody by a specific functional feature, in which case the resulting claim would for example recite:

Antibody against <target X> having < functional feature(s)>.

Such claims are broad in scope, since they encompass all the antibodies binding said target and displaying said functional feature. Any new or improved property such as the ones exemplified above may thus be used to better define the claimed antibody. The antibody claims may even be defined by negative features[5] . Combinations of functional features may be used as well to define the claimed antibody. Indeed, combining such features may improve the chances of getting a patent issued. Claims defining antibodies by their functional features may suffer from a lack of clarity and/or of sufficiency of description.

More importantly, they often raise questions of novelty, as it cannot be excluded that antibodies of the prior art already have this function, only undocumented. The EPO will be expecting that such functional features may be determined without ambiguity, e.g. by referring to a specific assay in the claim[6] . It will also be necessary to disclose in the application a way of repeatedly producing further antibodies having the claimed feature(s). This entails demonstrating - or at least making plausible - that the antibody possesses the function by providing experimental data in support. It is of course easier to make this point by relying on results present in the application as filed.

5. Board of Appeal decision T 2332/10
6. Board of Appeal descision T 1300/05

AN ANTIBODY DEFINED BY ITS STRUCTURE

More preferably, the antibody is defined by reference to a feature of the structure of the claimed immunoglobulin. The structure of antibodies is depicted in figure 1.

Most commonly, antibodies are claimed by reference to their CDRs, since they are generally considered as ensuring binding specificity. Dependent, i.e. narrower, claims may then be added, which define the antibody by reference to the sequences of its VH and VL or its complete chains.

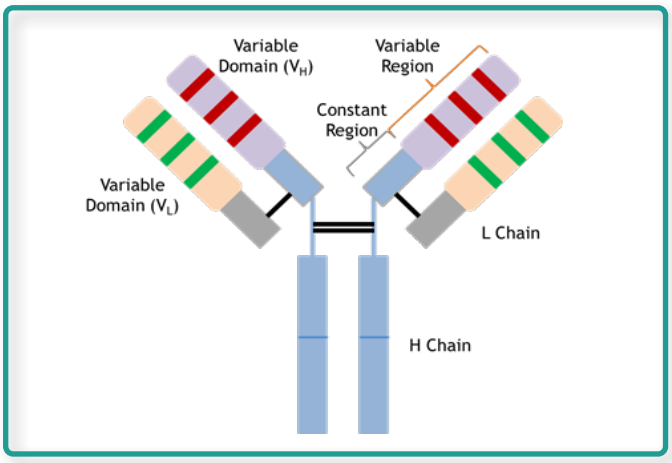

Figure 1: Structure of an immunoglobulin, comprising the light and the heavy chains, the constant and variable domains, and notably the CDRs of each chain (shown by red and green strips), which are responsible for the binding specificity of the immunoglobulin.

The usual practice of most patent offices is to require claimed antibodies to be defined by at least their six CDRs, such as for example:

Antibody against <target X>, wherein said antibody comprises a heavy chain variable region comprising CDR-H1 of SEQ ID NO. a1, CDR-H2 of SEQ ID NO. a2, and CDR-H3 of SEQ ID NO. a3; and a light chain variable region comprising CDR-L1 of SEQ ID NO. b1, CDR-L2 of SEQ ID NO. b2, and CDR-L3 of SEQ ID NO. b3.

Such claims are usually considered clear and enabled. In addition, except in extremely rare cases, such claims are new as well. In fact, most objections usually raised against this type of claim deal with inventive step. The EPO considers that all six CDRs are required for obtaining the unexpected property that is the basis for the inventiveness of the claimed antibodies. Sometimes, the Examiner will even insist that the antibody be defined by its VH and VL, depending upon the facts of the case.

In some cases, it will even be necessary to mention the specific isotype in the claim if it is required to obtain the unexpected property of the claimed antibody (e.g., a higher or lower ADCC). This said, it must be noted that under very specific circumstances the EPO appears ready to grant claims reciting fewer than 6 CDRs[7] .

7. Board of Appeal decision T 617/07

THERAPEUTIC USES

It is not uncommon to discover new indications for a therapeutic antibody, e.g. during clinical trial. New medical uses of previously-known antibodies can be protected as such, thus complementing the protection afforded by claims directed to the antibody drug itself. In fact, in Europe, new medical uses are not limited to the treatment of new indications stricto sensu but also encompass new modes of administration or new dosage regimens, or novel groups of patients to be treated. Such claims in Europe usually read:

Antibody against <target X> for use in treating <disease Y>.[8]

Such claims are extremely useful for conferring some protection beyond the term of the product patent, although their scope is strictly limited to the treatment of the new indication. Seeking protection for new medical uses is thus part of the general strategy set up designed to cover the antibody during its commercialisation. The most important issue relates to enablement. There must be enough information in the application as filed so that it is plausible to the skilled person that the antibody actually shows the claimed therapeutic efficacy[9] . This information does not have to be provided as clinical data.

Rather, any result obtained with a model which is known to be representative of the disease – animal, cellular, in vitro, etc. – can be used to demonstrate that the antibody is useful against the disease of the claim. Further results can be provided during examination; however, their only role is to complement the information already present in the application as filed. Such later-filed data cannot be the sole basis for demonstrating the existence of the therapeutic effect. Once again, it is absolutely crucial that the application is filed with as many data as possible.

CONCLUSION

While not pretending to be exhaustive, the present article gives a comprehensive overview of the various strategies used to protect therapeutic antibodies and medical uses thereof. It is indeed possible to define the claimed antibody in many different ways, but it should be kept in mind that, as illustrated on Figure 2, the scope of protection sought is inversely proportional to the probability of a patent to issue. Building a strong patent portfolio in the immunotherapy field should not be limited to the protection of the antibody per se, but rather explore the various claim types and scopes available throughout the lifespan of the project. Nonetheless, it is clear that, whatever the option considered, providing enough data in the application as filed is definitely the challenge for improving the global strategy of protection of immunotherapeutic inventions.

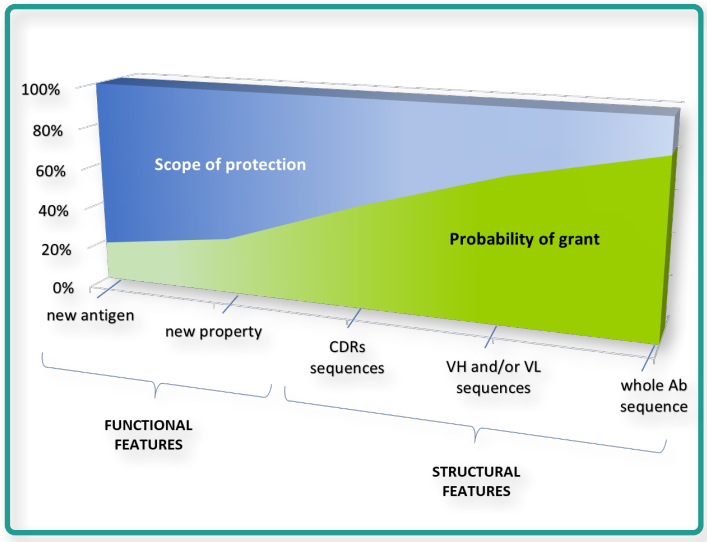

Figure 2: scope of protection vs. chances to have a patent granted

8. Note that claims to medical uses will be drafted differently in other countries according to the local practice
9. Board of Appeal decision T 609/02

About the authors

Raphaëlle Gillet

Raphaëlle GILLET is a French and European Patent Attorney. She has a Ph.D. in Molecular and Cellular Biology (Institut Cochin de Génétique Moléculaire, Paris), a MS in Cellular and Molecular Biology Development (Hôpital Necker, Paris) and she has a CEIPI Graduate (Distinction in Patents and Trademarks). She started her career in Industrial Property in 2001. After an initial experience in a biopharmaceuticals start-up, followed by twelve years' experience in an IP Law firm, Raphaëlle joined **REGIMBEAU** in 2014. She assists her clients and supports them in the development, management and defense of their portfolio. Raphaëlle also provides seminars and courses on Intellectual property, in order to make IP accessible to all.

Raphaëlle GILLET (gillet@regimbeau.eu)

Nicolas Bouquin

Nicolas BOUQUIN is a French and European Patent Attorney. He has a Ph.D. in Genetics and Physiology of Microorganisms (University of Paris XI) and is a Graduate from both the CEIPI Patents General Course and the CEIPI Industrial Property Law LLM. He has also completed the course on Patent Litigation in Europe organized by the CEIPI. Nicolas has worked for several years as a scientist, both in France and abroad, in the academics and for a pharmaceutical company, before moving to IP law. After a few years as an in-house patent attorney in a big pharma, Nicolas joined **REGIMBEAU** in 2009. He assists his clients in protecting and defending their innovations in all aspects of biotechnologies, with a special focus on pharmaceuticals and antibodies.

Nicolas BOUQUIN (bouquin@regimbeau.eu)

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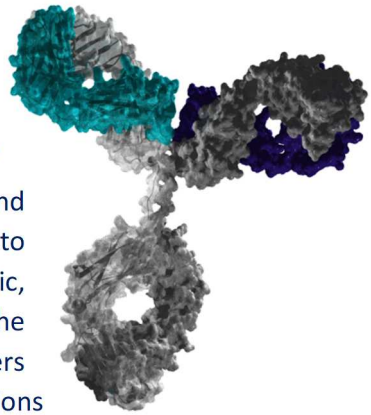

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Today, therapeutic monoclonal antibodies and biologics have become essential and extremely efficient tools for treating many dread affections from cancers to autoimmune / inflammatory diseases; It is especially with the arrival of chimeric, humanized and human forms that antibody immunotherapy has convinced (up to the Nobel Prize in 2018) and flourished. Indeed, more than a hundred biologic binders (including trifunctional antibodies, BiTE, scFv) have received marketing authorizations and opened real complementary routes to surgical and/or chemical treatments which otherwise can lead to failure.

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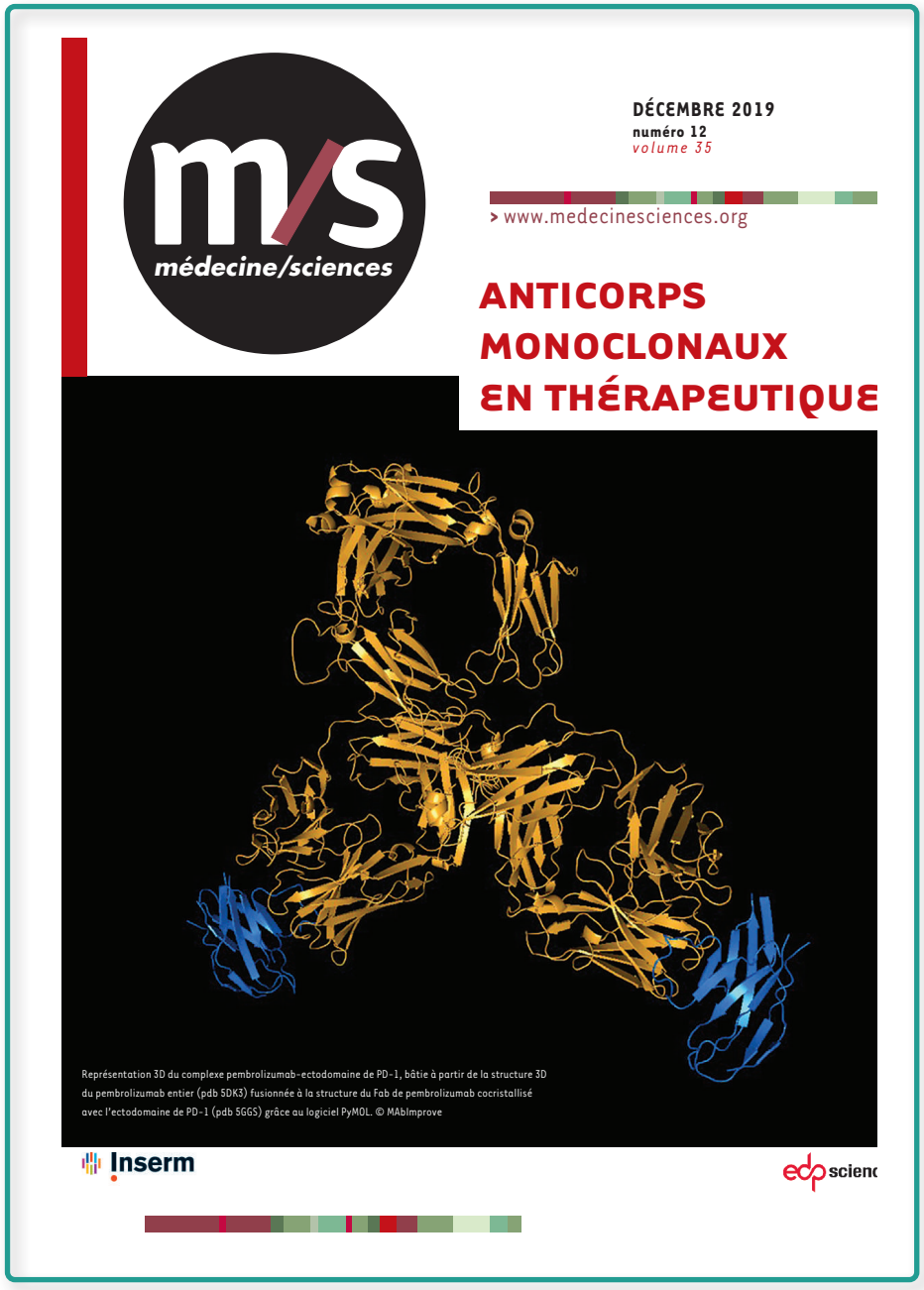
2019 marked the 10th anniversary of Médecine Sciences special edition on therapeutic monoclonal antibodies which was celebrated through the December edition of the international review being dedicated to the same field. MabDesign was honoured to have contributed to several articles in this issue.



The introductory remarks from the coordinators and the different articles can be accessed respectively at:

https://www.medecinesciences.org/fr/articles/medsci/full_html/2019/12/msc190282/msc190282.html
https://www.medecinesciences.org/fr/articles/medsci/abs/2019/12/contents/contents.html

List of abbreviations and acronyms

ADC : antibody-drug conjugate

ARD : Ambition Recherche & Développement

CDR : complementarity-determining regions

CNS: central nervous system

DNA: deoxyribonucleic acid

EMA: European Medicines Agency

EPO: European Patent Office

Fab: antigen-binding fragment

Fc: Fragment crystallizable

FcRn: neonatal Fc receptor

FDA: Food and Drug Administration

IgG: Immunoglobulin G

IP: intellectual property

R&D: research and development

mAb: monoclonal antibody

SMD: Small molecule drug

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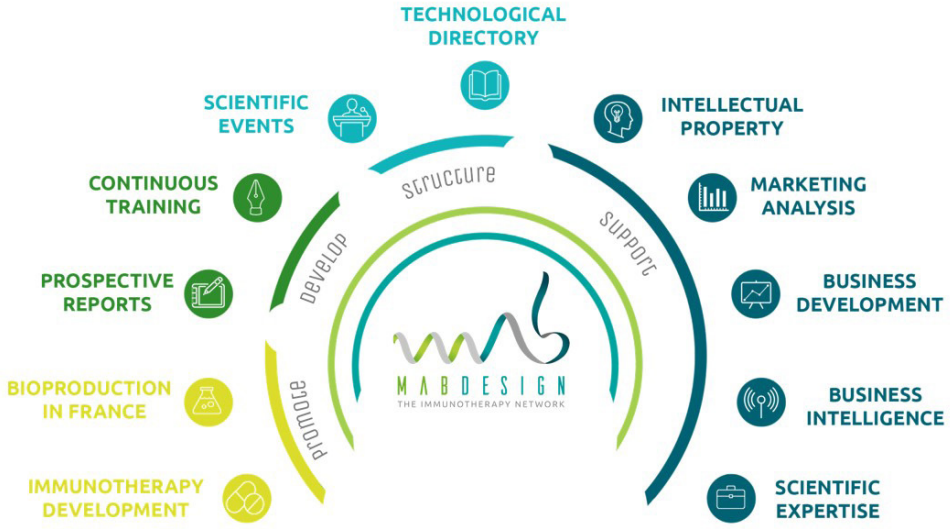
- **MABDESIGN** is a French membership organization in the field of immunotherapy. Created in 2014 MABDESIGN is managed by four competitivity clusters (Atlanpole Biotherapies, Eurobiomed, Lyonbiopole, Medicen) and three pharmaceutical companies (LFB, Pierre Fabre and Sanofi), and one biotech (DBV Technologies).



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