

IP Issues of Therapeutic Antibodies

Ulrich Storz

Abstract The high investments necessary to bring an antibody therapeutic to the market require a sound patent strategy. Although compound protection provides the broadest scope of protection, other ways of follow-up protection should be considered by innovators to achieve as long protection as possible. Further, in case a theoretical antibody against a given target is already prior art, innovators should be aware of methods to create compound protection for second or higher generation antibodies.

Keywords Patent • IP • Antibodies • Compound • Protection • Biosimilars

1 Introduction

Therapeutic antibodies are the fastest growing group of protein therapeutics. With a limited set of underlying technologies, drugs for a wide area of indications, including cancer, autoimmunity, neurodegeneration, and infections, can be generated.

Table 1 shows the therapeutical antibodies which have, in 2010, achieved global sales of one billion USD or more (data taken from company information).¹

¹ *Note* The phrase “key patent” refers to only one member of a patent family that exists for the product. INN, international non-proprietary name.

U. Storz (✉)
Michalski Huettermann & Partner Patent Attorneys, Neuer Zollhof 2,
40221 Duesseldorf, Germany
e-mail: st@mhpatent.de

Table 1 Therapeutic mAbs which have, in 2010, achieved global sales ≥ 1 billion USD

Antibody	Brand name	Company	Key indication	Target	Key IP right US	Key IP right EP	Global sales in 2010 (billion USD)
Infliximab	Remicade	J&J	Rheumatoid Arthritis	TNF α			8.0
Bevacizumab	Avastin	Roche	Colon cancer	VEGF-A	US7060269	EP0666868 EP1167384 EP1325932	6.8
Rituximab	Rituxan	Roche	Non Hodgkin Lymphoma	CD20	US5736137	EP06669836	6.7
Adalimumab	Humira	Abbott	Rheumatoid Arthritis	TNF α	US6090382 US6509015	EP0929578	6.5
Trastuzumab	Herceptin	Roche	Breast Cancer	HER2/neu	US6719971	EP0590058	5.5
Cetuximab	Erbix	BMS	Colon, head, and neck cancer	EGFR	US6217866	EP0359282	3.2
Ranibizumab	Lucentis	Novartis	Wet Macular degeneration	VEGF-A	US6407213	EP0940468	3.1
Natalizumab	Tysabri	Roche	Multiple sclerosis	α^4 -integrin	US5840299	EP0804237	1.75
Omalizumab	Xolair	Roche	Allergic Asthma	IgE Fc	US6267958	EP0841946	1.1
Palivizumab	Synagis	Novartis	RSV infection	RSV protein F	US5824307	EP0783525	1.0

As discussed earlier in this book series,² the development of a new drug is a costly and time-consuming matter. According to a study performed by the Tufts Center for the Study of Drug Development, the estimated average costs of developing a new Biologic are 1.2 billion USD,³ while development times are slightly longer than those reported for small molecule drugs.⁴

In order to recover the expenses invested into research and development of new biopharmaceutics, particularly into a new antibody, patents are an indispensable tool, as they provide an exclusive right with respect to the protected subject matter. Only the patentee, or his licensee, is thus allowed to exploit the invention commercially, e.g., by marketing the protected antibody.

Antibodies are proteins and, as such, chemical compounds. For this reason, antibody patents are subject to similar principles as patents related to small molecular drugs, although some differences apply, particularly with respect to inventive step.⁵ The basic principles for protecting antibody compounds will be discussed in the following. Further, additional ways to create follow-up protection for antibody therapeutics are discussed.

2 Compound Protection

Compound protection is probably the most important protection antibody companies can rely on, as it provides an exclusive right to offer and sell the respective antibody on different markets. Furthermore, while patents protecting a particular technology expire after, roughly, two decades, it remains still possible to achieve compound protection for a new antibody even after expiry of the respective method patents used to generate, or produce, the said new antibody.

Different possibilities exist to specify an antibody in a patent. As a general rule, the specification of an antibody by its target provides the broadest scope of protection, but can only be achieved at a very early stage, e.g., when the target has been discovered and “deorphaned”, i.e., attributed with a physiological role. A patent protecting second or higher generation antibodies against the said target has, usually, a narrower scope, because more technical details (e.g., structural or functional) are required in the patent claim to make it novel over the prior art. In even later stages, combinations comprising an antibody against the said target plus one or more other compounds, or dosage regimen or new medical uses of the said antibody, can be claimed, yet patents of this type have an even narrower scope of

² Storz (2010).

³ Average Cost to Develop a New Biotechnology Product Is \$1.2 Billion. Tufts Center for the Study of Drug Development, November 9, 2006. Available at <http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69>. Accessed on October 27, 2009.

⁴ Grabowski et al. (2006).

⁵ Stewart et al. (2011).

protection, allowing, e.g., off-label use by personal prescription. In the following, the different types of protection will be discussed briefly. In Table 2, examples are given for each type.

2.1 *Specification by Target*

In case a new protein has been discovered and a therapeutic use thereof has been disclosed, both the European Patent Office (EPO) and the United States Patent and Trademark Office (USPTO) grant claims related to a theoretical antibody against the said protein,^{6,7} even if the applicant has not produced a real antibody, or provides no data or enablement related to such antibody. Claims of such type have, obviously, the broadest scope, as they encompass all future antibodies against the said target put into practice later on (i.e., during the 20 years after filing of the target patent). The offices' rationale is that the provision of a novel protein X enables a skilled artisan to produce an antibody against said protein. Therefore, it is considered a fair reward for the applicant of protein X to be granted a claim related to an antibody against the protein. Once granted, the scope of protection of such claim extends to next generation antibodies against protein X as well. This means that somebody who provides a well-defined antibody against protein X will be, in his right to practice, dependent on the assignee of the first-generation patent, despite the fact that the said assignee has never provided a "real" antibody, and although he himself might as well be awarded a Patent on his antibody.

While cellular signaling processes are today well understood, new potential targets for antibody therapy are still being discovered. Today, about 100 such targets are addressed by approved biopharmaceuticals,⁸ but the spectrum of soluble proteins or membrane receptors yet undiscovered that represent potential therapeutic targets should be much higher. Although the evaluation of a new target and the subsequent development of a respective antibody are costly endeavors, recent advancements in antibody technology may accelerate the validation of new targets, in particular those relevant to cancer, autoimmune diseases, infectious diseases, and neurodegenerative diseases. Patents which merely claim any conceivable antibody against a new target will thus be a frequent sight even in the future.

However, with respect to the currently established targets (see Table 1), the respective patents are about to expire, or have already expired. In case a company develops a second antibody against a target addressed by these antibodies, other strategies are necessary to protect such second generation antibodies.

⁶ EPO decision T542/95.

⁷ *Noelle v. Lederman*, 355 F.3d 1343, 2004 U.S. App. LEXIS 774.

⁸ Overington et al. (2006).

Table 2 Examples for wording of antibody compound claims

Specification by	Example	Claim wording
Target	US5654407 (Bayer)	1. A composition comprising human monoclonal antibodies that bind specifically to human tumor necrosis factor alpha.
Target-independent function	US7214775 B2 (Biowa)	1. An antibody composition comprising antibody molecules, wherein 100% of the antibody molecules comprising a Fc region comprising complex N-glycoside-linked sugar chains bound to the Fc region through N-acetylglucosamine of the reducing terminal of the sugar chains do not contain sugar chains with a fucose bound to the N-acetylglucosamines.
Epitope	US8080247 (Janssen)	1. An isolated human anti-IL-12 antibody, wherein said antibody binds to a conformational epitope of the IL-12 protein comprising residues 15, 17–21, 23, 40–43, 45–47, 54–56, and 58–62 of the amino acid sequence of SEQ ID NO:9.
Sequence CDR	EP1309691 (J&J)	1. An antibody comprising the heavy chain complementarity determining regions (CDRs) and variable framework regions (FRs) of mAb TNV148 as described in Fig. 4; and the light chain CDRs and variable FRs of mAb TNV 148 as described in Fig. 5; optionally further comprising the specified substitution from proline to serine in FR3 of mAb TNV148B as described in Fig. 4.
Sequence VL and VH	EP0590058 (Genentech)	3. A humanized Antibody which comprises a VL domain comprising the polypeptide sequence DIQMTQSPSSLSASVGDRTITCRASQ DVNTAWAWYQQKPGKAPKLLIYSASF LESGVPSRFSGRSGTDFTLTISSLQPE DFATYYCQQHYTTPPTFG QGTKVEIKRT and a VH domain comprising the polypeptide sequence EVQLVESGGGLVQPGGSLRLSCAASGFNIK DTYIHWVRQAPGKGLEWVARIYPTNGY TRYADSVKGRFTISADTSKNTAY LQMNSLRAEDTAVYYCSRWGGDG FYAMDVWGQGLVTVSS.
Target affinity	US6090382 (Abbot)	1. An isolated human antibody, or an antigen binding portion thereof that dissociates from human TNF α with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard in vitro L_{929} assay with an IC_{50} of 1×10^{-7} or less
Competitive binding	US7595378 (Genmab)	4. An isolated human monoclonal antibody which binds to human EGFR, competes with antibody 225, but does not compete with antibody 528.
Deposited cell	US6582959 (Genentech)	A monoclonal antibody produced by the hybridoma cell deposited under American Type Culture Collection Accession Number ATCC HB10709.
Product-by-process	RE32011 (Scripps)	8. An antibody which catalyzes hydrolysis of beta -amyloid at Val39–Val40, Phe19–Phe20 or Phe20–Ala21 of SEQ ID NO: 1, the antibody being produced by a method comprising immunizing an animal with a transition state analog which mimics the transition state that beta-amyloid adopts during hydrolysis, the transition state analog being selected from a group consisting of statine and phenylalanine-statine.

2.2 Specification by Target-Independent Functional Properties

Antibodies can have functional properties which are target-independent. The development of such a new functional property can thus give rise to a patent the scope of which extends to all antibodies, irrespective of the target they bind, which have such property. This can, for example, apply to increased effector function by sequence engineering (e.g., US7863419 by Biogen) or post-translational glycoengineering of the Fc region (e.g., US7214775 by Biowa, or EP1071700 by Glycart), to increased serum half-life by Fc glycoengineering (e.g., US7361740 by Protein Design Labs), or to increased antibody-dependent cell cytotoxicity (ADCC) by using a novel expression system which, as such, creates an N-glycan structure which is essentially fucose-free (e.g., WO2011107520 by Cilian AG).

2.3 Specification by Epitope

Another way to create patent protection for a second generation antibody is to claim a specificity against a given epitope, or subdomain, of a target, in case the said epitope has not yet been described as clinically relevant. This approach makes sense in case the target as such has already been described, particularly when blocking only a specific epitope instead of the whole target may yield at least a theoretical benefit. However, the scope of a patent claiming an antibody against a specific epitope of a given target will not encompass antibodies against other epitopes of the same target.

This has been, for example, decided by a US District Court⁹ recently in a case where Genentech and Biogen sued GlaxoSmithKline (GSK) and Genmab for infringement of a patent protecting Rituxan, namely by GSK's Arzerra. Both Arzerra and Rituxan target CD20; however, Arzerra binds an epitope of the latter different from Rituxan, and with a different affinity. US Patent 7682612 claims the treatment of Chronic Lymphatic Leukemia by administration of an anti-CD20 antibody, and is thus not per se restricted to a particular epitope thereof. However, in order to overcome an office objection related to lack of enablement, Biogen has, during the patent prosecution, stated that the term "anti-CD20 antibody" shall mean antibodies having similar affinity and specificity as Rituxan. The respective court construed the patent claims as being restricted to anti-CD20 antibodies having similar affinity and specificity as Rituxan and thus concluded that Arzerra would not fall under the scope of the said patent. Although the claim language as such was not restricted to Rituxan, the court construed the claim in such way because of the applicant's statements made in the prosecution history.

⁹ U.S. District Court for the Southern District of California; case 10-CV-00608 BEN (GS) of Oct 17, 2011.

2.4 *Specification by Target-Dependent Functional Properties*

Another way to create patent protection for a second generation antibody is to specify the latter through target-dependent functional properties, e.g., binding affinity against a given target, or competitive binding. The former is often done by claiming a minimum affinity to a target. In such case, all later antibodies having even better affinity will fall under the scope of protection of such patents, even if they have no material relationship to the antibody which has been provided by the patentee. Existing patents with these claims are a real threat to competitors, particularly to those specializing in antibody optimization (“Biobetters”).

2.5 *Specification by Sequence*

Yet another way to create patent protection for a second or higher generation antibody is to specify a sequence thereof. Claimed sequences are commonly specified in such a way that, besides the mere sequence, a certain similarity interval (e.g., 85%) is comprised as well. In antibody claims, this makes little sense as the specificity of a given antibody is highly dependent on its sequence. Therefore, second or higher generation antibody claims are commonly drafted in such form that a DNA or AA sequence is claimed (e.g., SEQ ID No 1), sometimes together with possible variations (e.g., R112T). The scope of protection is thus clearly defined, yet quite narrow. Competitors which replace one of the claimed residues by a residue which is not claimed thus no longer fall under the literal scope of the patent, although the antibody may retain its function despite such modification.

Most legal systems provide doctrines of equivalents to anticipate situations as discussed above. As a rule of thumb, German judges¹⁰ tend to provide a broader scope of equivalence than UK judges,¹¹ although attempts have been made under the European Patent Convention to establish a uniformal definition of the term “equivalent”.¹² There is, however, no court decision in the US or in Europe which has yet defined the scope of equivalence for biosequence claims. This means that it is uncertain how far a competitor must amend the claimed sequence to make sure not to be sued for equivalent infringement.

It is yet noteworthy that, after the “Festo” decision issued by the U.S. Supreme Court,¹³ legal action related to equivalent infringements can no longer be enforced

¹⁰ Three-step approach, as applied in the BGH decisions “Kunststoffrohrteil”, “Schneidmesser I”, “Schneidmesser II”, “Custodiol I”, “Custodiol II”, GRUR 2002, 511–531.

¹¹ “Catnic test” as applied in *Kirin-Amgen, Inc. v. Hoechst Marion Roussel Ltd.* (2004) UKHL 46 (2004-10-21).

¹² Article 2 of the Protocol on the Interpretation of Article 69 EPC.

¹³ *Festo Corp. versus Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002).

in the US if, during patent prosecution, the scope of the patent has been narrowed in such a way that the alleged infringement is no longer covered by the literal scope of protection (so-called “prosecution history estoppel”).

The effect of this ruling on antibody sequence claims which are narrowed down during prosecution (e.g., from a sequence claim reciting “amino acid Seq. ID No. 1 and any sequence which has 85% identity to the former” to a claim which is restricted to the mere Seq. ID No. 1) has not made its way into case law yet, but it is to be expected that, in such case, competitors can easily circumvent the scope of protection by amending a single amino acid residue only. This requires that applicants draft their patent claims with caution, while competitors should always have a look at the patent prosecution history.

Because of the legal uncertainties with respect to the equivalence problem, applicants should restrict the length of the claimed sequence to the bare minimum needed to meet the novelty/inventive step requirement. From that perspective, it is preferable to only specify e.g. one or more CDRs in the claims, instead of a full variable domain, let alone a full heavy or light chain, because for a competitor it is much more difficult to replace one or more amino acids in the CDRs than, say, in the Fc region, at least in case he does not want to compromise the binding behavior of his antibody.

However, even in case an antibody claim has been narrowed down, during prosecution, to the exact sequence of either a CDR, or even of heavy and/or light chain, and given that the mere substitution of one amino acid residue in the claimed sequence would isolate a competitor from patent infringement because of an unexpectedly restrictive claim interpretation by the courts with virtually no scope of equivalence, fallback positions still exist for innovators.

In that case, a patentee could still take benefit from the strict rules the European Medicines Agency (EMA) applies for follow-on biologics (also called biosimilars)¹⁴ for which an accelerated approval under the biosimilar pathway¹⁵ is requested. In order to qualify as a biosimilar, the EMA requires that the follow-on biologic has exactly the same amino acid sequence as the innovator biologic.¹⁶ In case a competitor modifies the amino acid sequence of a given innovator biologic in order to avoid patent infringement, it is quite unlikely that his follow-on version would qualify for accelerated approval, at least in Europe. This means that the said competitor would have to go through full scale approval to obtain market authorization—quite an unattractive option for most biosimilar manufacturers.

¹⁴ Biosimilars will be discussed in a later volume of this book series.

¹⁵ See, among others, guideline EMEA/CHMP/42832/2005.

¹⁶ The EMA defines Biosimilars as follows: “The active substance of a similar biological medicinal product must be similar, in molecular and biological terms, to the active substance of the reference medicinal product. For example, a medicinal product containing interferon alfa-2a (...) should refer to a reference medicinal product containing as its active substance interferon alfa-2a. Therefore, a medicinal product containing interferon alfa-2b could not be considered as the reference medicinal product”.

2.6 Specification by Deposited Cell Line or Product-by-Process

The deposition of a cell line, e.g., a hybridoma cell line or a transfected host cell line, may be an adequate way of specifying an antibody in order to avoid sequencing errors and typographical errors, or to provide enabling information for features which relate to post-translational modifications (e.g., unusual glycosylation patterns). The deposition process is subject to laws and bylaws provided by the respective Patent legislations, while the respective claim language simply refers to the deposition nomenclature of the deposited cell line. Product-by-process claims define a compound by the way it has been produced, but still remain veritable compound claims. The claim language is, for example, “Antibody obtained by process X”. While before the EPO, such claim type is only allowable if the antibody cannot be defined in a sufficient manner on its own (e.g., by binding properties or sequence), there seems to be no such restrictions in the US.

It is important that both Deposited Cell Line claims and Product-by-Process claims provide full compound protection irrespective of the actual method used (which means that the above claim is actually read as “Antibody obtainable by process X”), at least in Europe,¹⁷ whereas in the US the case law is inconsistent for Product-by-Process claims. In a case related to a method of preparing Factor VIII,¹⁸ the Court of Appeals for the Federal Circuit held that product-by-process claims were to be construed as product claims, independent of how the product was made, while in the younger case another panel of the same court held that such claims are limited to a product that is prepared by the specific process steps recited therein.¹⁹ Therefore, it appears that in the US, product-by-process claims are merely disguised process claims, in that they only protect a claimed compound in case it has actually been produced with the specified method.

3 Other Types of Follow-Up Protection

Once compound protection of a given antibody has expired, other types of protection are still available which can be used to extend the term of protection for the said antibody. In most cases, however, the scope of protection which can be achieved is smaller than with compound protection. In the following, the most important options for follow-up protection will be discussed. A summary is given in Table 3.

¹⁷ *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ 2nd 1001 (Fed. Cir. 1991).

¹⁸ *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ 2nd 1001 (Fed. Cir. 1991).

¹⁹ *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1300 (Fed. Cir. 2009).

3.1 *Second Medical Use*

In some cases, a novel indication (second medical use) for a known antibody is discovered at a later stage (as it was the case with Avastin, which turned out to be effective also for the treatment of age-related macular degeneration). Such novel indication can give rise to a second or higher generation patent, too. The respective patent claim for such use will be as follows: “Antibody XY for the treatment of disease Z”. It is to be noted that in Europe such wording does not qualify as a method of treatment (which is not patentable under EPC), after the EPC has been revised in 2007,²⁰ thus making the Swiss-type claim wording obsolete.²¹

In the US, such claim wording is not accepted, as “use” is not a claim category provided by the U.S. Patent Act.²² Therefore, the claim wording should be as follows: “A process comprising administering a composition comprising Antibody XY to a human in an amount effective for treating a disease Z”.

Applicants must however be aware that, in case the compound protection for a given antibody has expired, they cannot avoid offlabel use of a biosimilar of the said antibody for the protected second medical indication upon individual prescription. However, patentees can block a competitor from advertising and even labeling his follow-on biological with respect to the said indication. Further, particular constellations exist in which the said competitor can be sued for indirect infringement.

3.2 *Combination Therapy*

In some cases, the use of an antibody together with another agent (e.g., another antibody, a chemotherapeutic drug, or the like) turns out to have beneficial or even synergistic effects (see for example the combination of Methotrexate and anti-TNF α Antibody for the treatment of rheumatoid arthritis, as claimed in Abbott’s US7223394). The respective claim wording for such a combination could for example read as follows: “Use of Antibody XY in combination with agent Z”, or “Composition comprising Antibody XY and agent Z for the treatment of disease Z”. Other patents related to combination therapies are ImClone’s US6811779 (combination of VEGF antibody and radiation), Yeda’s US6217866 (combination

²⁰ Article 54(5) EPC.

²¹ The Swiss-type claim wording (“Use of a substance or composition X for the manufacture of a medicament for treatment of disease or condition Y”) had been found acceptable by the enlarged board of appeal in decision G 5/83 avoid a violation of the exclusion of therapeutic methods under old EPC (Article 52 (4) EPC 1973).

²² 35 U.S.C. 101: “Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a Patent therefore”.

Table 3 Other possibilities for second or higher generation of antibody patents

Type	Example	Claim language
Second medical use	EP1616572 (Genentech)	1. Use of rituximab in the manufacture of a medicament for treatment of chronic lymphocytic leukemia (CLL) in a human patient, wherein the medicament is for administration to the human patient at a first dose of 375 mg/m ² and subsequent dosage of 500–1500 mg/m ²
Combination therapy	EP1169059 (Aventis)	1. A pharmaceutical combination, comprising Docetaxel and rhuMAb HER2
Dosage regimen	EP1616572 (Genentech)	1. Use of rituximab in the manufacture of a medicament for treatment of chronic lymphocytic leukemia (CLL) in a human patient, wherein the medicament is for administration to the human patient at a first dose of 375 mg/m ² and subsequent dosage of 500–1500 mg/m ²
Formulation	EP1687031 (Merck)	1. Aqueous composition consisting of a solvent which consists at least partly of water, an anti-EGFR (epidermal growth factor receptor) antibody, a buffer, an amino acid, a surfactant, and sodium chloride as isotonic agent

of EGFR antibody and chemotherapy, and Aventis' EP1169059 (pharmaceutical combination, comprising Docetaxel, and rhuMAb HER2).

Patents claiming combination therapies will become particularly important with the introduction of personalized medicine, where particular drug combinations may be selected to treat a patient with a given genetic predisposition. Further, similar issues apply with respect to offlabel use and indirect infringement as discussed above with second medical use.

3.3 Dosage Regimen

In 2010, the Enlarged Board of Appeal of the EPO made clear that even a new dosage regimen of a known drug or drug combination can be subject of a patent if the said regimen has surprising, or beneficial, properties.²³ The respective claim wording for such combination could, for example, read as follows: "Use of compound A for the treatment of disease X by administration once per day prior to sleep", or "Use of compound A for treatment of disease X, wherein the medicament is administered to the patient at a first dosage Y and subsequent dosage Y."

Because such claim type is relatively new, it is difficult, to date, to predict what kind of evidence an applicant has to provide to meet the inventive step requirement for such claim.

Further, similar issues apply with respect to offlabel use and indirect infringement as discussed above with second medical use.

²³ Decision G2/08.

3.4 Formulation and Galenics

In the small molecule pharma market, the filing of second or higher generation patents protecting a new formulation or galenic of a drug is well-established practice to extend the protection for a given drug, and has been accepted by the courts, too.²⁴ Formulations play an even more important role in antibody drugs, because the latter are extraordinarily large molecules (IgG have about 150 kD) which can be the subject of aggregation and artifacts occurring during storage. Further, a new formulation can give rise to a new way of administration of a given antibody. Because formulation claims and many galenic claims can be drafted as compound claims (“Formulation comprising antibody X, buffer Y and agent Z”) they cannot be bypassed by off-label use, although third parties can formulate the said antibody in a different way in case the compound protection for the said antibody has expired.

4 New Antibody Formats

Protein therapeutics which are derived from the general IgG concept are commonly called “new antibody formats”. Established formats such as chimerized antibodies, (e.g., US5585089 assigned to Protein Design Labs), humanized antibodies (e.g., US5859205 assigned to Celltech), antigen binding fragments (Fab), single chain variable fragments (scFv, e.g., US5260203 assigned to Enzon), and Receptor-Fc fusion peptides (e.g., US5610279 assigned to Roche for Enbrel) were, strictly speaking, considered “new antibody formats” when first introduced. The basic concept of rearranging and recombining different components of IgGs was further pursued in the last decade.

The potential advantages of new antibody formats compared with full-size molecules depend on the respective nature of the format, and encompass, for example, lack of glycosylation, lack of disulfide bridges, reduced molecular weight, better stability and serum half-life, better tissue penetration, lower immunogenicity, straightforward transfer from animal trials to humans, suitability for oral administration, expression advantages (e.g., expression in *E. coli* or yeast instead of Chinese hamster ovary cells), higher expression efficiency, and ease of selection/screening. These advantages can be referred to meet the inventive step/non-obviousness requirement in patents claiming the respective antibody formats or their technology. Some patents protecting major advancements in this field are listed in Table 4.

²⁴ Unigene Labs., Inc. v. Apotex, Inc. 06-CV-5571 (Fed. Cir. 2011).

Table 4 Examples for patents protecting new antibody formats

Company	Technology	Technology name/ candidate drug	Key IP right
Enzon	Polyalkylene oxide-modified scFv		US7150872
Macrogenics	Diabodies		US2007004909
CAT	Diabodies (scFv ₂ , potentially bispecific)		US5837242
Micromet	Bispecific scFv ₂ directed against target antigen and CD3 on T cells	“BITE”	US7235641
Affimed	Diabody–Diabody dimers	“TandAbs”	US2005089519
Affimed	scFv -Diabody-scFv	“Flexibodies”	US2005079170
Unilever	Camelid antibodies (CH2-CH3-VHH) ₂		US6838254
Ablynx	(camelid VHH)	“Nanobodies” <i>ATN-103 (anti-TNF)</i>	US2003088074
Domantis/ GSK	Variable regions of heavy (VH) or light (VL) chain (“Domain Antibodies”)	“dAb”	US2006280734
Scancell	Tumor epitopes on a IgG structure with unchanged FC domain	“Immunobody”	US2004146505
Hybritech/ Liliy	Trifunctional antibodies (Fab-Fab-Fab, maleimide linkers)		US5273743
Trion Pharma	Trifunctional IgG, Fc binds accessory cells, Fabs bind CD3, and tumor antigen	“Triomab”	US6551592
Affitech	Antibodies with T cell epitopes between β-strands of constant domains, and new V-regions specific for antigen presenting cells	“Troybodies”	US6294654
Affitech	Antibody fragments that cross-link antigen and antibody effector molecules	“Pepbodies”	US2004101905
Vaccibody AS	Bivalent homodimers, each chain consisting of scFv targeting unit specific for antigen presenting cells	“Vaccibody”	US2004253238
Planet Biotechnology	IgA (two IgG structures joined by a J chain and a secretory component), expressed in a plant host, secretory component replaced by a protection protein	“SIgA plAntibodies”	US6303341
Trubion	Variable regions of heavy (VH) and light (VL) chain + Fc (small modular immunopharmaceuticals)	“SMIP”	US2008227958
Haptogen/ Pfizer	Homodimeric heavy chain complex found in immunized nurse sharks, lacking light chains	“NAR” (Novel Antigen Receptor)	US2005043519
AdAlta	Recombinant shark Antibody domain library	“IgNar”	US2009148438
Xencor	Altered Fc region to enhance affinity for Fc gamma receptors, thus enhancing ADCC	“XmAB”	US20080181890

(continued)

Table 4 (continued)

Company	Technology	Technology name/ candidate drug	Key IP right
Arana	New world primate framework + non-new world primate CDR	“syn-humanisation”	US2008095767
City of Hope	Dimerized construct comprising CH3 + VL + VH	“minibody”	US5837821
Seattle Genetics	Antibody–drug conjugate technology with enzyme-cleavable linkers		WO2009117531
Epitomics	Humanized rabbit antibodies with increased target affinity	“RabMAbs”	US2005033031
F-Star	CH2 and CH3 domains with two identical antigen binding sites engineered into the CH3 domains IgG with two additional binding sites engineered into the CH3 domains	“Fcab”(antigen binding Fc)	US2009298195
		“mAb ² ”	US2009298195
Symphogen	Polyclonal antibody mixtures obtained by simultaneous expression; antibodies bind to different regions of the same antigen or multiple antigens	“Sympress” <i>Sym004 (anti EGFR)</i>	EP2152872
Genmab	IgG4 antibodies with hinge region removed (no interaction with immune system)	“UniBody”	WO2010063785
Regeneron	Human bispecific mAbs Fusion peptides consisting of the extracellular domain of protein receptor + Fc domain	“UniBody”	US2010105874
		<i>VEGF trap</i> extracellular segments of VEGFR1 and 2 + Fc, binds VEGF-A + PLGF	US7087411
Roche		<i>Enbrel</i>	US5610279
Philogen	Fusion proteins for targeted delivery of bioactive molecules to vascular sites of disease	“Vascular Targeting” <i>L19-TNF-α</i>	US2010316602

5 Antibody Mimetics

Proteins not belonging to the immunoglobulin family, and even non-proteins such as aptamers or synthetic polymers, have also been suggested as alternatives to antibodies.²⁵ One reason for the increasing interest in these so-called “alternative scaffolds”, or “antibody mimetics”, is the blocking effect created by existing antibody patents. As with new antibody formats, potential advantages of new

²⁵ Gebauer and Skerra (2009).

Table 5 Examples for patents protecting new antibody mimetics

Company	Scaffold protein	Technology name	Size kDa	Example drug	Key IP right
Molecular Partners	Ankyrin Repeat Proteins	“DARPin’s”	10–19	MP0112 (Anti VEGF)	US7417130
Borealis Pharma	C-Type Lectins	“Tetranections”			US2004132094
Affibody	A-domain proteins of <i>S.aureus</i>	“Affibodies”	6	ABY-025 (anti Her2)	US5831012
BioRexis/Pfizer	Transferrin	“Transbodies”			US2004023334
Pieris Proteolab	Lipocalins	“Anticalin”	20	PRS-050	US7250297
Adnexus/Bristol	10th type III domain of fibronectin	“AdNectins”	10	Angiocept (anti VEGFR2)	US6818418
Myers Squibb		(Monobodies)			
Dyax	Kunitz domain protease inhibitors		6	Ecaltantide (anti Kallikrein)	US2004209243
Scil Proteins GmbH	Ubiquitin derived binders	“Affilin”	10	SPV2801–30 (anti-EDB)	US7838629
	Gamma Crystallin derived binders		20		
Selecore/Nascacell	Cysteine knots or knottins	“Microbodies”			US7186524
General Hospital/	Thioredoxin A scaffold	“peptide aptamers”			US6004746
Genetics Institute					
Archemix	Nucleic acid aptamers			Macugen (anti VEGF); ARC1779 (anti vWillebrandt)	US5475096
Catalyst Biosciences	Target specific proteases obtained by directed evolution	“Alterases”			US2004146938
Mosbach/Lund	Artificial antibodies produced by molecular imprinting of polymers	“plastic Antibodies”			US2004157209
Phylogica	Peptide libraries from bacterial genomes	“Phylomers”			US6994982
NextBiomed	SH-3 domains				US6794144
Gliknik	Antibody mimetics	“Stradobody”			US2010239633
Avidia/Amgen	“A domains” of membrane receptors stabilized by disulfide bonds and Ca ²⁺	“Avimers” “Maxibodies”	9–18		US7803907
Evogenix/Cephalon	CTLA4-based compounds	“Evibody”			US7166697
Covagen	Fyn SH3	“Fynomers”	7		US2010119446

antibody mimetics, which may give rise to sufficient inventive steps, depend on their respective structural characteristics. These specific advantages may be used as a basis for patentability, i.e., in order to meet the requirements toward novelty and inventive step/non-obviousness. Some selected approaches are shown in Table 5. Some product candidates derived from these approaches have already entered the clinical phase, while others are still in the preclinical phase.

6 Conclusion

The high investments necessary to bring an antibody therapeutic to the market require a sound patent strategy. Although compound protection provides the broadest scope of protection, other ways of follow-up protection should be considered by innovators to achieve as long protection as possible. Further, in case a theoretical antibody against a given target is already prior art, innovators should be aware of methods to create compound protection for second or higher generation antibodies.

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