In the last decade, therapeutic antibodies have become one of the most commercially successful classes of biopharmaceutical drugs. Major drug manufacturers who have successfully managed to occupy this new market, as well as biotechnology firms, some of which have experienced a quick growth and are now on par with the former, owe part of their success to suitable intellectual property (IP) strategies. This article provides an overview of the current thinking on antibody-related patents, and discusses strategies for protecting the antibody products of the future.

Introduction

Patent protection plays a crucial role in the pharmaceutical industry because of its reliance on rapidly changing technology. Because of high upfront disbursements for research and lengthy clinical development and approval procedures (with the respective outcomes by no means predictable), the industry depends on efficient patent protection to assure a sufficient return of investment. This phenomenon can be summed up in the phrase “no patent equals no product”. To ensure that the scientific development of new antibody drugs will continue in the future, it is thus important to co-develop suitable patent strategies.

Inventive Step/Non-Obviousness

Probably due to the rapid technological progress in the antibody industry, arguments that were accepted in support of sufficient inventiveness in the past may be rejected by the patent authorities.
as falling under the routine of a skilled artisan. In view of the fact that technologies for the production of a human antibody against every conceivable target are now state of the art (consider, e.g., native antibody libraries and phage display), the mere provision of a human antibody against a target the clinical implications of which are known would have difficulties to meet the inventive step/non-obviousness requirement. In other words, the antibody industry is, in some way, a victim of its own success.

In order to anticipate obvious objections during patent prosecution, applicants should add to their applications fall-back positions, like sequences describing the specific antibody in great detail and/or experimental data with respect to particular binding properties, aggregation behavior, blood clearance, cross-reactivity and the like. Such data can often be used as a last resort to obtain patent protection for the actual antibody. Further, most of these data may also be used to meet the written description and enablement requirement (see below). A look into pertinent databases, like the board of appeal decisions database of the EPO, shows that patent applications related to therapeutic antibodies have rarely been rejected for lack of inventive step/obviousness alone. One reason for this might be that applicants seem to provide sufficient data that can be used as fall-back positions.

**Written Description and Enablement Requirement**

The enablement requirement, which is common to both European and US patent law, strives to ensure that a skilled person can reproduce the subject matter of the invention without undue burden. One example is usually sufficient to provide enablement, as long as no evidence exists that embodiments falling under the scope of the patent are not enabled. In case such evidence exists, the patent examiner may decide to narrow the scope of the claims to the very embodiment for which enabling data have been presented.

One example for the increasing scrutiny with respect to sufficient enablement is given in EPO decision T0601/05, which is related to a first generation patent claiming human monoclonal antibodies (mAbs) that bind to human tumor necrosis factor (TNFα). The only method for the production of the claimed antibodies disclosed in the patent was the hybridoma technique developed by Köhler and Milstein in the 1970s. However, the board held that the hybridoma technique would not be suitable to prepare high affinity antibodies against TNFα because human peripheral blood cells cannot provide a route to high affinity, neutralizing antibodies against self-antigens, but only to low affinity antibodies.

An example for the ambiguous positions patent authorities have taken with respect to the enablement requirement is EP939804 assigned to Human Genome Sciences (HGS). Said patent comprises claims related to an antibody that binds specifically to Neutrokine-α, which is a member of the TNFα superfamily and was discovered by HGS on the basis of bioinformatic investigations alone. Regarding therapeutic implications, the patent comprised no experimental data, only tissue distribution data of Neutrokine-α mRNA. It was thus alleged that HGS had postulated a potential therapeutic use only on the basis of the known relationship to TNF. In decision T0018/09, the EPO judged, however, that the tissue distribution data suffice to provide a valid basis for an industrial application and may be used to develop appropriate means and methods for diagnosis and treatment and, therefore, maintained the patent in slightly amended form. A year before the UK High Court found the patent invalid for lack of industrial applicability, insufficiency and obviousness, said decision having effect for the UK only. This decision was confirmed by the UK Court of Appeal recently in decision Eli Lilly and Company vs. Human Genome Sciences.

In addition to the enablement requirement, US law also provides a written description requirement in order to ensure that the inventor had, at the filing date, full possession of the entire claimed subject matter. In Centocor Ortho Biotech, Inc. vs. Abbott Laboratories, Centocor sued Abbott for patent infringement by selling adalimumab (Humira®). Basis for the legal action was Centocor’s US7070775, which relates to human antibodies to human TNFα. The ‘775 patent is a continuation in part (CIP) of an earlier application by Centocor, which was related to chimeric antibodies. However, said earlier patent predated a patent by Abbott related to similar subject matter. The case has generated broad public interest due to a record verdict in the first instance under which Abbott was sentenced to pay $1.67 billion in damages. On appeal, the decision was fully reversed by the US Court of Appeals for the Federal Circuit (CAFC) only for lack of written description. The CAFC considered that most claims of the ‘775 patent lacked written description, because the specification did not describe the claimed human antibody, nor an antibody with a human variable region, and concluded that “the scope of Centocor’s right to exclude cannot overreach the scope of its contribution to the field of art as described in the patent specification.”

The written description requirement was recently confirmed in the CAFC decision Ariad vs. Eli Lilly, related to Ariad’s US6410516. The patent, which dealt with transcription factor NFκB and methods of reducing or altering its activity without indicating how this could actually be done, was found invalid for failure to meet the written description requirement. The decision fuels fears that the written description requirement discriminates against universities and start up ventures that have their emphasis in basic research. These entities are under constant pressure to secure their results at the earliest possible date, and to the broadest possible extent, in order to publish them or present them to potential licensees. A requirement for additional data in the future will increase the financial burden for these small or non-commercial entities.

**Novelty**

Contrary to increasing requirements as to inventive step/non-obviousness and to written description and enablement, the relevant authorities have lowered hurdles with respect to the novelty requirement.
Recent case law with respect to small molecules has strengthened the concept of selection inventions, which is established granting practice at the EPO already and which stipulates that the disclosure of a chemical class does not necessarily anticipate the novelty of an individual compound falling within this class (so called “genus-species anticipation,” according to which a species anticipates the genus, whereas the genus does not anticipate a species).

This means, for example, that, despite the fact that the racemate of a given structure is prior art, a patent related to only one enantiomer of said racemate may be considered novel, and thus patentable in case the inventive step requirement is met as well (e.g., due to difficult resolution of the racemate). This view has been consented by courts in the UK, Germany and the US with respect to the (+)-enantiomer of Citalopram (decisions Generics UK vs. Daichi, BGH Escitalopram and Forest Labs., Inc. vs. Ivax Pharm., Inc.).

In another example, courts in all three countries agreed that a given compound, which falls within the scope of a general formula disclosed in the prior art, can be considered novel if it is not mentioned explicitly in the latter, but only by means of a Markush group in which some substituents are designated as R1-RX. Courts in UK, Germany and the US came to similar results in cases related to the antipsychotic olanzapine (decisions Reddy’s vs. Eli Lilly, BGH Olanzapin and Eli Lilly & Co. vs. Zenith Goldline Pharm., Inc.).

Translated to biomolecules, this means that, e.g., a sequence claim related to a second generation antibody will be considered novel even if said claimed sequence is comprised in the similarity interval of a prior sequence disclosure (e.g., “SEQ ID No 1 or sequences having a similarity of >95% with the former”).

**Approaches to Protect Therapeutic Antibody Products**

The approaches to protect therapeutic antibody products have been previously discussed. In short, the respective antibody can be specified by (1) binding a specific target, (2) having specific binding characteristics against a given target, (3) reference to a specific deposited cell line or a specific production process or (4) by having, or being encoded by, a specific amino acid/DNA sequence with respect to the whole antibody or to sections thereof. Crucial issues for selecting the right strategy are the scope of protection that can be obtained with a given claim language, and the prospects of patent allowance by the patent authorities. Generally, for first generation antibody patents, a broad claim language could be used (e.g., by specifying the target only), thus providing a broad scope of protection, while in second or higher generation patents the claim language must be more restrictive (e.g., by specifying the amino acid/DNA sequence), thus providing only a narrow scope of protection. Said trend is illustrated, for example, by the history of patents protecting anti-TNFα antibodies (Table 2).

Higher generation antibody patents claim, in most cases, a sequence, at least with respect to one or more complementarity determining regions. In such case, the inventive step/obviousness requirement is met more easily, because according to well-established lines of argumentation, the skilled person would very unlikely find any incentive in the prior art to arrive at a specific sequence, at least if such sequence has not merely been isolated from nature, but is the subject of, e.g., an affinity maturation process. Further, the enablement/
European Medicines Agency (EMA), 16 draft guidelines recently published by the patent infringement. Under the respective amino acid residues to avoid a potential ket cannot simply substitute one or more cal (also called “biosimilar”) on the mar-

parties wanting to put a follow-on biologi-
an approved antibody therapeutic, third scope of equivalence and, if so, to what
whether or not such claim types enjoy a row, although to date it is still unclear of such claim language is quite nar-
the claims or the specification.

and enabled by merely mentioning it in
because a given sequence is fully disclosed disclosure hurdle is passed more easily
non to obtain antibody biosimilar status.17

Admittedly, the scope of protection of such claim language is quite nar-
row, although to date it is still unclear whether or not such claim types enjoy a scope of equivalence and, if so, to what extent. Further, if such patent protects an approved antibody therapeutic, third parties wanting to put a follow-on biologi-

(also called “biosimilar”) on the mar-
ket cannot simply substitute one or more amino acid residues to avoid a potential patent infringement. Under the respective draft guidelines recently published by the European Medicines Agency (EMA), 16 and subject to public consultation until May 31, 2011, the resulting antibody would most probably no longer qualify as a biosimilar, as amino acid sequence identity is considered to be a conditio sine qua non to obtain antibody biosimilar status.17

### Antibody Evolution

In view of expiring patent protection for first generation antibody therapeutics, major drug makers and biotechnology firms are currently in a process of developing second generation variants of their or their competitors’ antibodies. Generally, the improvements that eventually give rise to a patent allowance have been achieved by use of methods that are now consid-
ered to belong to the standard toolbox of antibody engineering, i.e., humanization, affinity maturation and glycoengineering techniques (Table 3).

### New Targets

While cellular signalling processes are well-understood, new potential targets for antibody therapy are still being discovered. Today, about 100 such targets are addressed by approved biopharma-
aceuticals, 18 but the spectrum of soluble proteins or membrane receptors that rep-
resent potential therapeutic targets should be much higher. Although the evaluation of a new target and the subsequent develop-
ment of a respective antibody are costly endeavors, recent advancements in anti-
body technology may accelerate the validation of new targets, in particular those relevent to cancer, autoimmune diseases, infectious diseases and neurodegenerative diseases.

Filing a patent application for an antibody against a new target is, usually, a safe bet. In case a patent application describes, and claims, a new protein that may play a physiological role in the human body, it is common to also draft a claim related to a theoretical antibody against said protein, i.e., an antibody which has not actually been manufactured. Such type of claim is routinely granted in the case when the target protein is novel and substantially defined, even if the applicant has not produced such an antibody or provides no data or enablement related to such antibody (see, for example, US decision Noelle vs. Lederman19 or EPO technical board decision T0542/95).20

In both cases, the rationale behind this position was that the provision and correct specification, of a novel protein X enables a skilled person to produce an antibody against said protein. Therefore, it is con-
sidered a fair reward for the applicant of protein X to be granted a claim related to a theoretical antibody against said protein.

However, publication of limited data for a protein that is part of a cellular signalling process does not automatically compromise the inventive step/non-obviousness of a patent claim related to an antibody against such protein. This is because it may remain unclear whether or not said moiety is involved in a pathogenic process and, if so, whether underexpression or overexpression, or expression of a dysfunctional or misfunctional product, is responsible for the pathologic condition, or if the moiety is causative for, or a conse-
quence of, said pathologic condition.

Ganymed (Mainz, Germany) devel-
pelled a series of antibodies against newly found antigens that are specific for dif-
derent types of cancer. The physiological role of these antigens is not fully clear. However, it seems that the respective anti-
bodies are not meant to interfere in cellular signalling processes, as is the case, for

| Table 3. 2nd generation antibodies and their key patents |
|---------------------------------|--------|----------------------------|-----------------|-----------------|
| **Second generation mAb INN** *(Trade name, Company)* | **Target** | **First generation mAb INN** *(Trade name, Company)* | **Alleged improvement** | **Key patent** |
| Ofatumumab (Arzerra, GlaxoSmithKline) | CD20 | Rituximab (Rituxan, Genentech) | Humanized | US7850962 |
| GA101 (Roche) | CD20 | Rituximab (Rituxan, Genentech) | Glycoengineered for better ADCC | EP1692182 |
| Golimumab (Simponi, Centocor) | Tumor necrosis factor α | Adalimumab (Humira, Abbvott) | Unclear (Centocor advertises better dosing frequency, but patent claims specific affinity to tumor necrosis factor α) | US7070775 |
| Motavizumab (Medimmun) | Respiratory syncytial virus | Palivizumab (Synagis, Medimmun) | Higher target affinity (50–70 fold) | US740851 |

ADCC, antibody-dependent cell-mediated cytotoxicity; CD, cluster of differentiation; INN, international non-proprietary name

| Table 4. Selected therapeutic antibodies against new targets |
|---------------------------------|--------|--------|-----------------|
| **Company** | **Drug name** | **Target** | **Key patent** |
| Ganymed | GT468 | Placental protein PLAC1 | EP2166021 |
| Merrimack | MM-111 | Human epidermal growth factor receptor (HER2 + HER3) | US7332580 |
| LPath | Sphingomab | Sphingosine-1-phosphate | US7829674 |

www.landesbioscience.com mAbs 313
example, in anti-VEGF therapy. The idea is rather to evoke antibody-dependent cell-mediated cytotoxicity responses against the respective cells.

LPath (San Diego, CA) has pursued a different concept. The company developed a mAb against a non-protein target, i.e., the sphingolipid sphingosine-1-phosphate, which is a tumor growth factor. LPath claims that this drug has a direct effect on angiogenesis in addition to a direct effect on tumor cells themselves, i.e., inhibition of metastasis, tumor cell growth and apoptosis, and thus combines effects of some marketed antibodies.

Merrimack (Cambridge, MA) is developing MM-111, which is an IgG-like bispecific antibody whereby, unlike natural antibodies, one arm binds the human epidermal growth factor receptor 2 (HER2) and a second arm binds the HER3 receptor. It is claimed that the antibody uses the HER2 target to block the HER3 pathway, as it appears that HER3 signalling is an important therapeutic target in HER2-positive cancers.21 Table 4 summarizes the above examples.

New Antibody Formats

Strictly speaking, when first introduced, formats such as chimerized antibodies, humanized antibodies, antigen binding fragments (Fab) and single chain variable fragments were considered new antibody formats, and were (or still are) subject to patent protection. The basic concept of rearranging and recombining different components of IgGs was further pursued in the last decade. Potential advantages of new antibody formats compared to 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 efficiency and ease of selection/screening. These advantages can be referred to to meet the inventive step/non-obviousness requirement in first generation patents claiming the respective antibody formats or their technology. Relevant patents on major advancements in this field are listed in Table 5.

In most cases, companies have first established, and protected, the basic enabling technologies related to the new format as such. In a subsequent step, specific drug candidates are developed, thereby forming the subject of respective patent applications.

One example resulting from a new antibody format is Symphogen’s (Lyngby, Denmark) Sym004, which is a recombinant IgG1 antibody product consisting of two antibodies targeting distinct non-overlapping epitopes in epidermal growth factor receptor (EGFR) extracellular domain III and which may, one day, compete with JmClone’s Cetuximab. In comparison to the latter, Sym004 is said to induce removal of the receptor from the cancer cell surface, leading to more pronounced cancer growth inhibition. The product is undergoing evaluation in a clinical Phase 1 study [NCT01117428] of patients with advanced solid tumors, and is pursued, among others, under the European Patent application EP2132292A1 and related patent family members. The basis for upcoming inventive step/non-obviousness considerations will probably be advantageous binding properties compared to prior art products (e.g., Cetuximab) due to the polyclonality of the product.

Another example is Philogen’s (Sovicille, Italy) L19-TNFα, which consists of the human antibody L19, which targets the extradomain B of fibronectin, fused to human TNF. In this construct, the L19 domain provides vascular targeting of the TNF domain to the site of disease, where the latter exerts its antitumor activity. The product is said to have superior anti-carcinogenic effect. Respective experimental data put the corresponding patent application ready for grant by the EPO, and the product candidate is now protected under EP1257297B1.

Yet another example is ATN-103, which is an anti-TNF Nanobody® developed by Ablynx (Ghent, Belgium) that is currently undergoing evaluation in clinical studies as a treatment for rheumatoid arthritis. ATN-103 targets the same antigen as the marketed antibody drugs Adalimumab (Humira®), Infliximab (Remicade®), Golimumab (Simponi®) and Certolizumab pegol (Cimzia®), as well as the fusion protein Etanercept (Enbrel®) and is said to have a variety of advantages related to administration and pharmacokinetics, which are currently used as a basis for inventive step/non-obviousness argumentation in the patent prosecution of European Patent Application EP1558647A1.

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.22 One reason for the increasing interest in these so-called “alternative scaffolds,” or “antibody mimetics,” is the barrier to entry into the field created by existing antibody IP. As with new antibody formats, potential advantages of new antibody mimetics 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 towards novelty and inventive step/non-obviousness. An overview of some selected approaches is shown in Table 6. Some product candidates derived from these approaches have already entered the clinical phase, while others are still in the preclinical phase.

Companies have in most cases first established and protected the basic scaffold technologies, and have then started to develop specific drug candidates, i.e., scaffold-based products that bind a given target. The approach has the risk that the respective patent applications meant to protect these products may not be considered as inventive/non-obvious by the respective authorities. The rationale behind such considerations is that both (1) the respective scaffold and its implicit advantages and (2) the respective target and its clinical implications were already known to the skilled person at the priority date of said second-generation patent application. The mere combination of a known scaffold and a known target, although novel, may thus be considered obvious to the skilled person.
| Company         | Technology | Technology name/candidate drug | Key technology patent |
|-----------------|------------|--------------------------------|-----------------------|
| Enzon          | Polyalkylene oxide-modified scFv | | US7150872 |
| Macrogenics    | Diabodies  |                                | US2007004909          |
| CAT            | Diabodies (scFv, potentially bispecific) | “BITE” | US7235641 |
| Micromet       | Bispecific scFv, directed against target antigen and CD3 on T cells | “TandAbs” | US2005089519 |
| Affimed        | Diabody-Diabody dimers | “Flexibodies” | US2005079170 |
| Unilever       | Camelid Antibodies (CH2-CH3-VHH) | “Nanobodies” ATN-103 (anti-TNF) | US2003088074 |
| Ablynx         | Camelid VHH |                                |                       |
| Domantis/GSK   | Variable regions of heavy (HV) or light (VL) chain (“Domain Antibodies”) | “dAb” | US2006280734 |
| Scancell       | Tumor epitopes on a IgG structure with unchanged FC domain | “Immunobody” | US2004146505 |
| Hybritech/Lilly| Trifunctional antibodies (Fab-Fab-Fab, maleimide linkers) | | US5273743 |
| Trion Pharma   | Trifunctional IgG, Fc binds accessory cells, Fab 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 |
| Vacciody 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 | “SlgA plAntibodies” | US6303341 |
| Trubion        | Variable regions of heavy (HV) and light (VL) chain + Fc (small modular immunopharmaceuticals) | “SMIP” | US2008227958 |
| Hapto/Pfizer   | Homodimeric heavy chain complex found in immunized nurse or dogfish sharks, lacking light chains | Novel Antigen Receptor (“NAR”) | US2005043519 |
| AdAlta         | Recombinant shark antibody domain library | “IgNAR” | US2009148438 |
| Xencor         | Altered Fc region to enhance affinity for Fcgamma receptors, thus enhancing ADCC | “XmAB” | US20080181890 |
| 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 | “Fcab” (antigen binding Fc) | US2009298195 |
|                 | IgG with two additional binding sites engineered into the CH3 domains | “mAb²” | US2009298195 |
| Symphogen      | Polyclonal antibody mixtures obtained by simultaneous expression; antibodies bind to different regions of the same antigen or multiple antigens | “Sympress” Sym004 (anti-EGFR) | EP2152872 |
| Genmab         | IgG4 antibodies with hinge region removed (no interaction with immune system) | “UniBody” | WO2010063785 |

ADCC, antibody-dependent cell-mediated cytotoxicity; CDR, complementarity-determining region; EGFR, epidermal growth factor receptor; mAbs, monoclonal antibodies; PlGF, placental growth factor; scFv, single chain variable fragment; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
Table 5 (continued). Selected new antibody formats and their key patents

| Company       | Technology                                                                 | Technology name/candidate drug                          | Key technology patent |
|---------------|---------------------------------------------------------------------------|----------------------------------------------------------|-----------------------|
| Regeneron     | Fusion peptides consisting of the extracellular domain of protein receptor and an Fc domain | VEGF trap extracellular segments of VEGFR1 and 2 and an Fc; binds VEGF-A and PlGF | US7087411             |
| Philogen      | Fusion proteins for targeted delivery of bioactive molecules to vascular sites of disease | “Vascular Targeting” L19-TNFα | US2010316602           |

ADCC, antibody-dependent cell-mediated cytotoxicity; CDR, complementarity-determining region; EGFR, epidermal growth factor receptor; mAbs, monoclonal antibodies; PlGF, placental growth factor; scFv, single chain variable fragment; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Table 6. Selected antibody mimetics and their key patents

| Company                          | Scaffold protein | Technology name | Size  | Example drug                  | Key technology patent |
|----------------------------------|------------------|-----------------|-------|------------------------------|-----------------------|
| Molecular Partners               | Ankyrin repeat proteins | "DARPins" | 10–19 kDa | MP0112 (Anti-VEGF) | US7417130             |
| Borean Pharma                    | C-Type Lectins   | "Tetranectins" |       |                              | US2004132094          |
| Affibody                         | A-domain proteins of S. aureus | "Affibodies" | 6 kDa | ABY-025 (Anti-HER2) | US5831012             |
| BioRexis/Pfizer                  | Transferrin      | "Transbodies"  |       |                              | US2004023334          |
| Pieris Proteolab                 | Lipocalins       | "Anticalin"    | 20 kDa| PRS-050                      | US7250297             |
| Adnexus/Bristol Myers Squibb    | 10th type III domain of fibronectin | "AdNectins" (Monobodies) | 10 kDa | Angiocept (CT-322; anti-VEGFR2) | US66818418           |
| Dyax                             | Kunitz domain protease inhibitors | ""           | 6 kDa | Ecallantide (anti-Kallikrein) | US2004209243          |
| Sci/Proteins GmbH                | Ubiquitin derived binders | "Afflin" | 10 kDa | SPVF2801-30 (anti-EDB) | US7838629             |
| Seleccore/Nascacell              | Cysteine knots or knottins | "Microbodies" |       |                              | US7186524             |
| General Hospital/Genetics Institute | Thioredoxin A scaffold | "Peptide aptamers" |       |                              | US6004746             |
| Archemix                         | Nucleic acid aptamers | "Alterases" |       | Pegaptanib (anti-VEGF); ARC1779 (anti-vWillebrandt) | US5475096             |
| Catalyst Biosciences             | Target specific proteases obtained by directed evolution | "Alterases" |       |                              | US2004146938          |
| Mosbach/Lund University          | 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 kDa |                              | US7803907             |
| Evogeneix/Cephalon               | CTLA4-based compounds | "Evibody" |       |                              | US7166697             |
| Covagen                          | Fyn SH3          | "Fynomers"     | 7 kDa |                              | US2010119446          |

CTLA, Cytotoxic T-Lymphocyte Antigen; EDB, extracellular domain B; HER, human epidermal growth factor receptor; kDa, kilo Dalton; VEGF, vascular endothelial growth factor.
Therefore, to obtain patent protection for such products, advantageous properties of the product, or, ideally, an unexpected synergism between the scaffold and the target, should be disclosed in the patent, in order to be at hand as fallback and, thus, would compete, if the market is pursued under PCT application No PCT/EP2010/069665.

**Conclusion**

The quick advancements of antibody technologies require a steady adaptation of patent strategies, to ensure that future products will still be protected by IP rights. While requirements as to inventive step/non-obviousness and written description and enablement seem to be on the rise, the hurdles with respect to the novelty requirement have been lowered. Companies and research institutions which are involved in the development of new therapeutic antibody products should develop an adequate IP expertise or seek expert advice, to account for these developments, in order to be able to protect their investments for research and development.

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