Bio-business in brief: Many a monoclonal

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Several monoclonal antibodies are used as drugs. After facing various technical challenges, most of these drugs came to the market only after 1995. The list of approved drugs in the US (provided) and in Europe is largely similar. Two monoclonals have been brought out by Indian companies, and a few more are under development in India. The importance of patenting as a pre-requisite for drug discovery is highlighted. The problems being faced by Indian academic scientists in patenting their inventions and innovations, and the solutions proposed by DBT, New Delhi are pointed out. Patents important to the development of monoclonals as drugs are listed. The nature of patent claims is discussed with examples from prominent monoclonal patents. The manner in which the life of a patent may be extended is also discussed with a case study. The factors that go into a business decision on whether or not to develop monoclonal therapeutics are briefly outlined. Finally, the importance of branding – for a product or for a company – is also touched upon.

Keywords: Branding, intellectual property, patent claims, therapeutic monoclonal antibodies.

MONOCLONAL antibodies that are available as drugs in the market have fiendishly difficult names: abciximab, bevacizumab, tositumumab, trastuzumab and so on. Fortunately there is a 'mab' in each one, and so you know a monoclonal when you see one. The companies were aware of this problem: the names above are the generic names and the corresponding proprietary or brand names are respectively, ReoPro, Avastin, Bexxar and Herceptin, all much easier than the 'mab' names.

Evolution of monoclonals as drugs

Although one monoclonal antibody was approved as a drug in the mid-1980s, the frequency increased only from mid-1990 onwards. Thus, the history of monoclonal antibodies as drugs is fairly recent. A few issues, mentioned below, dominated early efforts to convert monoclonals (hereafter, mAbs) to drugs.

The first issue relating converting a mAb to a drug relates to its degree of 'humanization'. In the original version of the technique to produce mAbs, a mouse-derived lymphocyte was fused with a myeloma to produce a hybridoma. It turns out that mouse-derived murine sequences are immunogenic to humans. There has, therefore, been an attempt to increase their degree of humanness, as illustrated in Figure 1. In chimeric mAbs, the Fc part is human. In humanized sequences, all except the complementarity determining regions (CDR) are human. In human mAbs, the entire molecule is a human sequence. Among the approved mAbs, only Bexxar and Orthoclone are murine. All others are human to some extent[1].

The different categories of mAbs are reflected in their generic names: a murine mAb ends with -omab (e.g. muromomab) and a chimeric one with -ximab (e.g. infliximab), a humanized mAb ends with -zumab (e.g. trastuzumab) and a fully human one with -umab (e.g. adalimumab).

The second issue confronting those who seek to turn mAbs into drugs has been that mAbs are, at several 100 kDa, bulky molecules, compared to small chemical compounds of molecular weight around 500 Da. This makes their commercial production a tricky and expensive process. This has led to various strategies to reduce the size of the antibody while retaining the critical parts. Among the mAbs approved so far, most are full-fledged molecules. However, ReoPro is a Fab fragment. Several mAbs in development are also much smaller than the full molecule. Thus, smaller molecules, including specific domains, domain combinations, fragments modified with polyethylene glycol (PEG), etc. are currently under clinical investigation as drug candidates[2].

And the third issue relates to the efficacy of the antibody. Although mAbs are effective because of their specificity, their time on the target often – but not always – needs to be higher. This functional affinity, or avidity, can be achieved by increasing the number of binding sites of the antibody. This is done by means of further protein engineering by increasing the number of variable domains per molecule, as illustrated in Figure 2 (adapted from Fernandez[3]).

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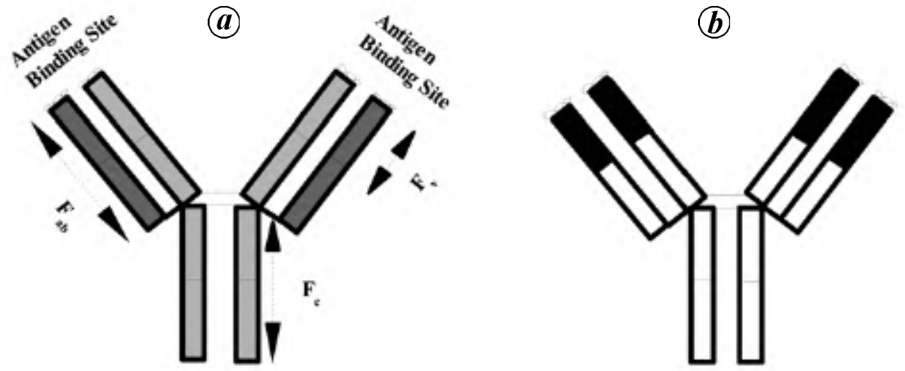

Figure 1. Diagrammatic representation of (*a*) murine and (*b*) chimeric antibodies. Shaded areas indicate murine sequences and white ones human. A humanized antibody would have even less area shaded than the chimeric, and a fully human sequence would be completely white.

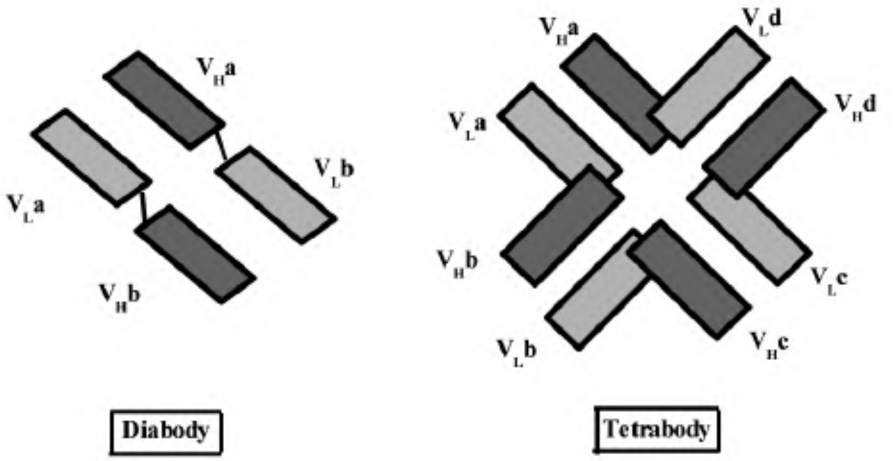

Figure 2. A diabody has two pairs of variable domains, each pair comprising the variable domains of a heavy (H) and a light (L) chain. A tetrabody has four such pairs of variable domains. (Adapted from Fernandez[3].)

mAbs as drugs: The status today

Currently, 19 mAbs are approved by the FDA as drugs for sale in the United States. The list (Table 1) can be found on the regularly updated list of approved biotech drugs on the site of the Biotechnology Industries Organization (http://www.bio.org/speeches/pubs/er/approveddrugs.asp) . There is also a consolidated, almost comprehensive list on the site of the antibody company, Medarex (http://www.medarex.com/Development/Therapeutics.htm). The corresponding list for Europe can be found at the EMEA site (http://www.emea.europa.eu/htms/human/epar/eparintro.htm). The lists for the US and Europe are largely similar, with 14 common molecules. There are just five unique molecules on the FDA list (Bexxar, Lucentis, Mylotarg, Orthoclone and ReoPro), and one on the list of the EMEA (Leukoscan).

The 19 FDA-approved mAb drugs fall into three categories: those for cancer (8), those targetting the immune system (8), and those targetting infectious agents (1) and others (2). These should soon be joined by more numbers, since many are in clinical trials. Reports in 2002[4] and 2004[5] claimed that 400 were in clinical trials, and a report in 2005[1] puts the number at over 150. Drug candidates continually enter and fail testing, e.g. the recent case[6] of TeGenero's mAb TGN1412. Whatever the exact figure, therefore, clearly there are many in the pipeline, including several in phase III trials.

Before we take a look at the drug candidates in phase III, let us consider the 'targets'. When it has been shown that the therapeutic effect is brought about by the drug binding to a given protein, this protein is called a 'validated target'. It is a safer scientific (and business!) decision to work with such a target, and as a result there are several cases of two or more drugs – mAbs or others – that have been developed that bind the same protein.

Janice Reichert (Tufts University Centre for the Study of Drug Development, Boston) who analyses trends in drug development published a report on the status of mAb drugs a couple of years ago[1]. Among those in phase

Table 1. List of monoclonal antibody therapeutics approved by the FDA. Based on data available with the Biotechnology Industry Organization (http://www.bio.org/speeches/pubs/er/approveddrugs.asp) and Medarex (http://www.medarex.com/Development/Therapeutics.htm)

Field	Brand name	Generic name	Indication, in brief	Molecular target*
Cancer	Avastin	Bevacizumab	Colorectal cancer	Anti-VEGF
	Erbitux	Cetuximab	Colorectal cancer	Anti-EGFR
	Bexxar	Tositumomab	Non-Hodgkin's lymphoma	Anti-CD20
	Rituxan	Rituximab	Non-Hodgkin's lymphoma	Anti-CD20
	Zevalin	Gemtuzumab	Non-Hodgkin's lymphoma	Anti-CD20
	Mylotarg	Ozogamicin	Leukaemia	Anti-CD33
	Campath	Alemtuzumab	Leukaemia	Anti-CD52
	Herceptin	Trastuzumab	Breast cancer	Anti-HER2
Immune system	Humira	Adalimumab	Rheumatoid and psoriatic arthritis, ankylosing spondilytis	Anti-TNFα
	Remicade	Infliximab	Rheumatoid arthritis, Crohn's disease	Anti-TNFα
	Orthoclone	Muromomab	Kidney transplant rejection	Anti-CD3
	Simulect	Basiliximab	Kidney transplant rejection	Anti-CD25
	Zenapax	Daclizumab	Kidney transplant rejection	Anti-CD25
	Raptiva	Efalizumab	Plaque psoriasis	Anti-CD11a
	Tysabri	Natalizumab	Multiple sclerosis	Anti-α4-integrin
	Xolair	Omalizumab	Asthma	Anti-IgE
Others	ReoPro	Abciximab	Reduction of blood clots	Anti-GPIIb/IIIa
	Synagis	Palivizumab	Respiratory syncitial virus	Anti-RSV
	Lucentis	Ranibizumab	Wet macular degeneration	Anti-VEGF

*Some abbreviations used: EGFR, Epidermal growth factor receptor; GP, Glycoprotein; Ig, Immunoglobulin; RSV, Respiratory syncitial virus; TNF, Tumour necrosis factor; VEGF, Vascular endothelial growth factor.

III testing, oncological candidates exceed by far any other category. Also, the fraction for infectious diseases and 'others' was far higher than in the group so far approved. There are about 15 antibodies in phase III clinical trials, where there is an approximately 50% chance of being approved. Five of the 15 hit the same targets (TNFα, EGFR, VEGF, CD3 and RSV) as current drugs. In addition, this list of Phase III drug candidates covers eight new targets: RANKL, CD4 receptor, CTLA 4, MRSA, C5, IL5, CD22 and carbonic anhydrase IX.

The 19 approved mAbs hit 14 targets. One of these targets is TNF (tumour necrosis factor). It was a dramatic discovery – by Ravinder Maini and Marc Feldmann of Imperial College, London – that blocking just one cytokine, TNF, proves so effective for patients of rheumatoid arthritis and other inflammatory diseases. Thus, there is an Indian connection, albeit a fourth-generation one!

Monoclonals from Indian companies

Annual sales[7] of mAb therapeutics were of the order of $10 billion in 2004, with six having global sales of over $500 million each[1] (see Box 1).

To the best of our knowledge, none of the mAbs counted above has undergone significant development in India. However, there is an urgent medical need for local companies to come out with affordable innovative mAbs in some shape or form. We know of a breast cancer patient in India who was told that each injection of herceptin would cost about Rs 70,000. She would need a shot every three

Box 1. Commercialization of mAbs

One of the drawbacks in pursuing these proteins in drug discovery is that due to their bulk, they cannot readily enter the cell. Thus, they are better suited to bind proteins on the cell surface. For an intracellular target, a small chemical entity might be the best drug. This is the kind of scientific reason why a particular path is chosen in drug discovery.

There may also be commercial reasons for choosing a particular strategy. It turns out that manufacturing of biologics is hundreds of times more expensive than manufacturing more typical pharmaceuticals. In addition, storage of the drug and its administration to a patient is more complicated for a biologic than for a chemical pharmaceutical.

It is true that the efficacy of each dose and therefore the number of doses is what determines the ultimate cost to the patient, and the variability in production yield results in a range of prices for any class of therapeutics. Nevertheless, an NGO in the United States has estimated the average market price of $1000 per dose for a biologic, compared to $3 for a chemical pharmaceutical leading to significantly higher prices for biological than pharmaceutical therapy (http://www.armscontrolcenter.org/archives/002252.php).

Anything that adds to the cost of a drug will decrease the company's competitiveness unless it is anticipated that large revenues will offset this expenditure. This is the reason some companies often choose not to pursue mAbs in their drug discovery programmes. Those that do so charge highly for their drugs, leading to the question of whether the price is worth the incremental benefit to the patient.

weeks, thereby costing over Rs 12 lakhs per year. This puts the drug out of the reach of most individuals in India.

Fortunately, two are in the market and a few others are in the pipeline. First, Bharat Serums and Vaccines manufactures Rhoclone, a mAb for an Rh-negative woman carrying an Rh-positive baby (http://www.bharatserums.com/mono.htm). This replaced the earlier horse serum, a dangerous product. Second, Biocon tied up with CIMAB, Cuba to develop an anti-EGFR antibody, BIOMAb EGFR, which reached the market in October 2006. EGFR, we note, is a validated target. Biocon has global manufacturing rights and marketing rights in India and the rest of South Asia, and hopes to become a supplier to the North American market (http://www.oralcancerfoundation.org/news/story.asp?newsId=1242). Shantha Biotechnics, through its subsidiary Shantha West in San Diego, has four fully human mAbs (RM1, RM2, RM3 and RM4) under development. These are against lung cancer, melanoma, pancreatic and breast cancer respectively. The mAb against lung cancer is in clinical trials (http://www.shanthabiotech.com/focus_areas_prodsegment.htm).

Other mAbs are in the pipeline. Dr Reddy's Laboratories is branching out from chemical therapeutics to biologics, including mAbs (http://www.drreddys.com/newsroom/popups/apr30_2007.htm). Zenotech, a company in Hyderabad, is also pursuing mAbs (http://www.zenotechlabs.com/htmlfiles/news_mcfeb05.htm). Finally, Prosetta Corporation in Mysore is working to produce mAbs against the different conformations adopted by a given protein.

The price of a drug developed by an Indian company is significantly cheaper than an imported equivalent. As has happened for hepatitis B vaccines in India (where the price dropped from over Rs 800 to Rs 30 per dose), any one Indian company developing and manufacturing a drug locally reduces the price somewhat, and several companies doing so reduces it manifold. Biocon's BIOMAB EGFR is 30–40% cheaper than the closest imported equivalent[8]. In the same vein, Zenotech hopes to launch a generic version of Rituxan for one-third the price of the original molecule from Genentech.

Protection of intellectual property

An important issue in launching a product, or even setting up a company, is building up the 'brand value' of the product, or company respectively. We briefly discuss the issue of branding in Box 2. However, perhaps even more important than branding is the intellectual property (IP) owned by a company and the IP on which a drug is built. Before discussing the IP of mAbs, let us consider patents, one of the several forms of IP protection that include copyrights, trademarks, geographical indications, etc.

A patent is a contract between an inventor and the State. It allows the inventor rights over his/her invention for a limited period of time in exchange for full disclosure of the invention. Do patents promote innovation or hinder it? This is debated and may vary with the case. Whatever the answer, patents are here to stay for the foreseeable future. And since most – but not all – drug development happens in for-profit companies, where there is no investment without IP protection, we need to take this protection seriously.

Our academics need to be aware of the patentability of their inventions. Our impression is that there are specific reasons why scientists in India do not, in general, patent their inventions. These are (i) lack of awareness about IP or lack of interest in it due to preoccupation with their scientific work; (ii) philosophical objections to fencing in inventions that would otherwise remain in the public domain from day one; (iii) lack of funds (and manpower) to file for patents, maintain them, and scan for and prosecute infringers; (iv) no tradition of, and therefore expertise in, identifying and protecting IP, at least partly due to lack of industrial interest; (v) delay caused by filing a patent application that endangers priority in academic publishing and (vi) a lack of adequate professional credit for patents awarded. Most of the concerns are, in principle, addressable and the number of patents would no doubt increase if appropriate steps are taken to do so.

The Department of Biotechnology's (DBT) Biotech Strategy Document (Draft), 2005 (http://www.dbtindia.nic.in/biotechstrategy/BiotechStrategy.pdf) has proposed several measures to improve the awareness of and competence in IP, and create or strengthen aspects of the national IPR infrastructure, as under.

1. According to the Budapest Treaty, it is only by depositing biological material in an internationally approved Depository that one can apply for a patent on the modified microorganism. DBT proposes to strengthen the Microbial Type Culture Collection at IMTECH, Chandigarh, and to establish other International Depository Authorities in the country.
2. The Department also plans to set up a Translational Research Centre with personnel dedicated to handling IP.
3. It plans to strengthen existing patent offices, set up new ones and also improve IP dispute resolution mechanisms.
4. DBT intends to provide tax relief based on expenditure incurred to file for IP rights abroad.
5. In the area of education, the Department plans to:

   (a) Incorporate IP into the education of life sciences students at the undergraduate and postgraduate level. This would sometimes be in the form of dual degrees in science and IPR.
   (b) Improve law students' knowledge of science and also of IP. This would include training patent attorneys in science.

Box 2. Branding

An important issue in business is the issue of branding. It can make all the difference in whether we remember the name of a drug or not, and therefore whether we purchase the drug or not. This is not merely due to the simplicity of the name, but also due to the positive feelings that the customer has for the name and the associated product due to high quality of the product or association of the product with something positive.

And a brand name can do more than ensure steady sales. Thus, Cambridge Antibody Technologies (CAT) 'leverages' the brand name of Cambridge, the town or the University. It implies that the company is utilizing technologies developed in Cambridge, or is connected in some other way to this illustrious town. It turns out that the company has connections with Sir Greg Winter. Prof. Winter, from the MRC's Laboratory of Molecular Biology, developed important techniques for humanizing mAbs, and today apparently 80% of MRC royalties are from the 'Winter patents' (http://www.domantis.com>Management). He is connected both to CAT and to Domantis, another company in the business of therapeutic mAbs.

Several other scientists from Cambridge University are also on the Scientific Advisory Boards of both companies.

Unfortunately, our universities and research institutes tend to have long names. It would not do to label a company Jawaharlal Nehru Antibody Technologies, nor Indian Institute of Science Nanotechnologies, let alone Centre for Cellular and Molecular Conotoxin Technologies.

So what can a brand new company do about its branding? One option is to think about it in general or technical terms, and many companies take this route. Immunomedics, Medimmune and Raven Biotechnologies – all companies dealing with antibody therapeutics – are perfectly valid names. In fact, trivial names (illustrated by Google and Yahoo) can become great brand names. Another way would be to 'leverage' the brand of something around you. Bangalore Genei leveraged the name of the city, perhaps reflecting its academic reputation. Today, certainly, Bangalore has a strong brand name even internationally and could be leveraged effectively. Come to think of it, the 'India' brand is gaining in strength abroad.

Although a foreign audience would not immediately recognize the Bharath in Bharath Biotech or the Shantha in Shantha Biotechnics, the names would resonate with Indian audiences and consumers, as would Gangagen. It is possible, also, that the Ganga has good enough international visibility and appeal to transcend national boundaries. So it was for the word 'dharma'. The company Dharmacon, dealing with synthetic RNA, has no known Indian connection. It started out as an independent company based in Colorado, and is now a subsidiary of Fisher Scientific.

This 'Indian' versus 'foreign' branding dilemma was captured by marketing guru Jagdeep Kapur in an address to the students of IIT-Bombay late in 2005, wherein he distinguished two types of brand names that could come out of India. One he called 'desi khara' and the other 'English marie' (that is, an 'Indian' name as exemplified by Gangagen on the one hand, and a 'Westernized' name such as Affibody on the other). He advised future entrepreneurs to choose carefully.

And on the website of his company Samsika (www.samsika.com), Kapur lists a publication entitled 'To build a big brand, have a small brand name'. Although Cambridge Antibody Technologies has not done this, they have captured the brand value of Cambridge while generally being known as CAT and thus having a small brand name as well!

So those planning to start a company need to give it a thought. If you are a scientist joining a CSIR laboratory, even if it is a new one, you would be joining a laboratory that has the CSIR brand name, built up over decades. However, if you are starting a new company, you have no ready-made brand name. In case you wish to derive value from a pre-existing brand name, you may have to get creative about it. You may wish to involve individuals whose very names have brand value. Or, you may wish to locate yourself in the incubator of IIT Bombay. Alternatively, you may wish to show the world that you have start-up funding from a prominent individual or institutional funder, thereby 'leveraging' his/her brand name.

Although business success boils down to performance, resilience and more than a little luck, capturing existing 'brand value' could give your company a head-start. There are further tips on branding, sometimes counter-intuitive ones, at the WIPO site (http://www.wipo.int/sme/en/documents/brand_choosing.htm). And there are, of course, the experts in person.

A positive brand image brings a company employees in the first place, keeps morale high, attracts funding and contracts, and perhaps softer treatment in case of trouble! Every institution has to build up and maintain a strong brand image to survive and flourish in an increasingly competitive environment.

Subsequently, the DBT has also spoken of setting up technology management offices in publicly funded research institutions (http://www.biospectrumindia.com/content/policy/10611091.asp). Most of the issues hampering our academic scientists will be attended to when all of these steps have been taken.

IP of mAbs

Kohler and Milstein, working at the Medical Research Council in the UK, developed the pivotal hybridoma technology to produce mAbs in 1975. However, they failed in their attempts to protect it[9]. The first patent in this area was awarded four years later, in 1979 (US 4,172,124). It covered the method of producing tumour antibodies, and was assigned to The Wistar Institute in Philadelphia (http://www.cambia.org/patentlens/simple.cgi).

The technology has travelled a long way since then. Murine, chimeric, humanized and human antibodies: each form of mAb is now patented. Other critical aspects – sequence of the antibody, the antigen to which the antibody binds, the process of production, the method of fragmentation, its chimerization or remodeling – have also been protected. And therefore to use any of these methods means that one has to take a license, failing which a significant part of the revenue goes to the patent holder as compensation for infringement.

Since existing patents cover all possible aspects of mAb production – also referred to as the 'patent stacking' around monoclonals – scientists have come up with second-generation antibodies. There have been a variety of developments and we list these below with reference to illustrative patents: modifications of glycosylation sites (US 5,714,350), altered antibody isotypes (US 5,500,362), mutations in antibody genes to improve functions (US 5,624,821), domain-deleted mAbs (US 6,818,748), mAb fragments (US 4,940,670), improved affinity or half life (US 5,990,296 and 5,225,540 respectively), humanized or fully human mAbs (US 6,056,957 and US 6,235,883 respectively) and so on.

The only relevant patent from India that we are aware of is from Shantha Biotech (US 5,744,585) that covers a mAb against lung carcinoma. Another application has been filed and is under review (http://www.shanthabiotech.com/rd_ip_patents.htm).

Important claims in some important mAb patents

It is the claims that legally define what protection is offered by a patent. We list below some important claims of one fundamental patent related to monoclonals (and four other examples are listed at http://www.ibab.ac.in/prog_IP.html). 'Old Cabilly' is the name by which this patent is commonly known, and refers to the first inventor, Schmuel Cabilly. The claims are numbered according to their original numbering in the granted patent. Emphasis, if any, has been added.

Note the following features of patent claims:

- No claim is more than one sentence. This has the advantage that a claim usually has a limited amount of information. Nevertheless, clauses in the form of (a), (b), (c), etc. are permitted, and we have encountered a claim from United States Patent 6,867,021 (unrelated to mAbs) with 457 words. Consequently, even a conceptually straightforward claim may end up as dense and repetitive prose, leaving the reader cross-eyed and irritable.
- In due course one begins to see that the wording of claims is highly repetitive in order to avoid any ambiguity. Two claims may say exactly the same thing, except for a couple of words. Those couple of words can change the meaning in a manner that is important from the point of view of patent coverage and therefore protection.
- The first claim in a patent is the broadest. Subsequent claims are narrower. Thus, the first claim may refer to sequences from 'a mammal'. The next claim may say '… wherein said mammal is a rodent'. The third claim will then declare '… wherein said rodent is a mouse'. Although it is amusing to read these claims, it is obvious that if one were to protect sequences only from a mouse, researchers could invent around one's patent by using sequences from some other mammal. Also, if one were to protect sequences from any mammal, that would be a broad claim, which carries the risk of being thrown out by the patent office. In either case, all the time, effort and money invested in obtaining protection would come to nought.
- There are different types of claims. Thus a *composition of matter* claim can explicitly state 'A composition comprising…'. Alternately it can simply state 'An altered antibody…' or 'A library for…'. A *process* can be claimed using the words 'A method of...' or 'A process for…'.
- One patent application can have both types of claims, those relating to *composition of matter* and to a *process*.

USPTO no. 4,816,567, the old Cabilly patent: There are a total of seven claims in this patent, of which we reproduce below claims 1, 2 and 3.

1. A *method* comprising

(a) preparing a DNA sequence encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first mammalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second, different mammalian species; (b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell; (c) transforming the host cell with the vector of (b); (d) culturing the host cell; and (e) recovering the chimeric heavy or light chain from the host cell culture.

2. The method of claim 1 wherein the first mammalian species is human.

3. A *composition* comprising a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen having a constant region homologous to a corresponding constant region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species.

Note that Claim 3 is almost identically worded to Claim 1(a). And yet, one is a *process*, or method, and the other a *composition of matter*.

Extending the life of a patent

Before starting a commercial research programme, it is best to evaluate one's freedom to operate. In order to obtain freedom to operate, one has to do due-diligence – a background check – to see if one's proposed product is inadvertently infringing someone else's patent.

For companies which already have a patent, which is on the verge of expiring, extending the life of the patent is one strategy to retain freedom to operate. Here we

Table 2. The history of a patent-related dispute

	Events	Comments
1.	1983: Genentech files for a US patent through the *USPTO* on 08.04.83.	The company claimed a method of preparing chimeric mAbs, where the constant domains are human sequences and variable domains come from any other mammal.
2.	1984: The company Celltech files for a US patent via a PCT application that entered *national phase* and became a US application on 23.03.84. Before filing a PCT application, it had filed an application in the UK on 18.03.83.	The company claimed a process to produce monoclonal fragments limited to variable domains, and cell lines and vectors carrying DNA sequences that code for these monoclonal fragments.
3.	1988: Genentech files for another patent on 10.06.88 in the US, a continuation-in-part application of the previous patent application.	In this application Genentech added all the claims of the above mentioned Celltech patent application to its own claims.
4.	1989: USPTO issues patents to both Celltech (4,816,397) and Genentech (4,816,567) on 28.03.89.	The Celltech patent is commonly known as the Boss patent and Genentech patent as the (old) Cabilly patent because of the names of the first inventors, Michael Boss and Schmuel Cabilly respectively.
5.	1990: Genentech appeals to the USPTO for interference between its (not yet granted) second application and Celltech's just granted patent (4,816,397).	Interference is the legal proceeding in which the PTO determines which inventor has priority. Whereas most countries award patents to the *first to file*, the US grants a patent to the *first to invent*.
6.	Since Celltech had filed a patent application (in the UK) before Genentech, so it was up to Genentech to prove that it was the first to invent. It submitted drafts of patent applications from the files of the inventor, Schmuel Cabilly.	The case continued for around 8 years.
7.	13.08.98: Genentech lost but appealed the decision and on 09.10.98 sought judicial review from the District Court.	
8.	2001: Celltech did not challenge this and the dispute was settled when the Boss patent was revoked and Genentech got another patent (6,331,415) in December 2001. The latter, also known as the new Cabilly patent, includes all the claims of the Boss patent and also all those of the old Cabilly patent.	It is rumoured that Genentech had an out-of-court settlement with Celltech, wherein it compensated Celltech with large royalties and licensing till 2018. In return, Genentech gained patent protection for 29 years (1989–2018) for a very fundamental patent in the history of monoclonals.
9.	2007: New Cabilly (6,331,415) has been revoked by the USPTO	MedImmune was one of the companies that had licensed '567 (for their product Synagis). Since '567 was to expire in 2006, MedImmune would not have had to pay any royalities from then on. However, since the same technology was also protected under New Cabilly, Genentech wanted royalties till 2018. MedImmune sued Genentech and won the case.

Notes: *National phase:* All patent applications have geographical limitations, generally limited to a single country. An applicant can file in any country. However, the applicant can also file with WIPO or the EPO, each of which represents many countries. Thus, in these cases, there is first an 'international phase', followed by a 'national phase'. When the patent application enters an individual country it is said to have entered the national phase. *First to file:* The first person to file a patent application in the patent office. *First to invent:* The first person to have made the invention or innovation (as recorded in diaries, lab notebooks, personal notes, etc.), irrespective of whether or not they have filed a patent application. EPO, European Patent Office; USPTO, United States Patent and Trademark Office; WIPO, World Intellectual Property Organization.

illustrate to what extent a company can go to extend the term of one of its most important patents. The case relates to Genentech, the big biotech company. We itemize in Table 2, the history of filing and granting of patents to two companies, Celltech and Genentech, both of whose work is in the area of mAbs and which relates to the issue at hand. Technical terms in italics are explained in Table 2. Others have been detailed elsewhere[10].

IP protection and reaching beneficiaries through commercialization are closely linked. IP may be produced in a company, in academia or some other non-profit. Let us take a quick look at what happens to this IP.

(a) IP produced in a company may not be developed further. It could simply be a source of revenue in case the IP is licensed to one or more companies. The IP needs to be protected for another company to express interest in licensing it.
(b) The company may, however, choose to develop a marketable product based on its innovations. If not suitably protected, a competitor could make the same innovation with better protection, invest in brand building and grab market share. In the latter scenario, the first company's investment into developing and marketing the product is strongly undermined.
(c) When the IP is produced in academia, it can be the basis for starting a company. As a start-up, the company needs a periodic infusion of cash. Investors will invest only if the innovation, or invention, is protected adequately leading to freedom to operate.
(d) The academic institution may choose instead to license the IP to a pre-existing company. As above, there will be no takers in the absence of strong IP protection.

An important point is that non-profits may choose to protect their IP and license it at modest rates to other (for-profit or non-profit) institutions that wish to take it to the market. The mere act of protecting IP neither implies nor guarantees that enormous profits will be made from the invention. Nevertheless, if there is any interest in IP reaching consumers, inventors must identify and protect their IP with vigilance.

Conclusion

A company does not enter the area of mAb therapeutics lightly. On the positive side, the technology is a powerful one, making for high specificity and fairly precise targetting, applicable to a wide variety of targets. mAbs are likely to be less toxic than chemical therapeutics and are potentially lucrative. On the flip side, their production is expensive, the products more delicate than 'chemical' pharmaceuticals and the patent stacking formidable. Each company needs to weigh the pros and cons carefully before deciding on whether or not to make mAb therapeutics.

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Note. Supplementary information is available at: http://www.ibab.ac.in/prog_IP.html

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