

# MONOCLONALS

## the billion dollar molecules of the future

In 1975, two British scientists thought of creating a mouse antibody that could be replicated or 'cloned' to produce identical copies. Identical copies with identical modes of action had the potential to be a drug. They had launched what was to be one of biotechnology's best ideas. If the pair could mimic the immune system's 'seek and destroy' capability by pre-designing antibodies for all manner of disease targets, it should be possible to block or activate cellular activity to order. It was an elegant concept opening up a raft of therapeutic possibilities, particularly in the area of cancer. Here it might be possible to attach a chemotherapy drug to an antibody. The antibody's specificity for a particular disease target would guide the chemo drug only to the cancerous cells and not the healthy ones. The concept, therefore, was excellent, but the use of mice monoclonals had drawbacks. The human body did not like antibodies from mice anymore than it liked the flu virus, so the antibodies themselves triggered an immune response and were destroyed. This 'immunogenicity' issue was to occupy researchers for another 20 or so years before it became possible to craft a monoclonal antibody (mAb) that would be acceptable to the human immune system.

**A**fter rather a long period in the desert, monoclonal antibody drugs are once again generating a wave of excitement. Over the past five years, a stream of successful products in this new class has reached the market. Thanks to several innovations, sophisticated molecular biology and computer modelling, the technology has matured and the immunogenicity issue has largely been resolved. The new drugs are inspiring a degree of confidence among clinicians and patients, based on their efficacy and minimal side effects.

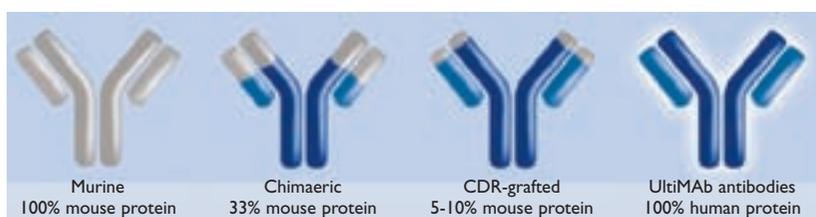
Today there are 17 monoclonal antibody drugs on the market bringing new hope in hitherto

untreatable diseases. A further six lead drugs are in the final stages of clinical trials and approximately 150 new products are in the pipeline with about 60 companies active in the field. Monoclonal antibody drugs are outpacing traditional pharmaceuticals both in regulatory approvals and sales.

By 2010, Datamonitor predicts annual sales worldwide will reach \$30 billion. Already we have seen brands in the first generation of monoclonals achieve sales of more than a billion dollars. The big new drivers in the market are Herceptin and Avastin. Both are from Genentech, one of the oldest biotech companies, and now fully owned by Roche. Herceptin, for treating advanced HER2

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## Therapeutics



**Figure 1**  
Evolution of monoclonal antibody technologies/  
Medarex/ABG Sundal Collier  
Research Report

breast cancer, had sales of \$1.6 billion in 2005; Avastin, for metastatic colorectal cancer had sales of \$1.2 billion.

Rituxan, another product from the Genentech/Roche label, developed for the treatment of leukaemia and non-Hodgkin's lymphoma sold \$3.1 billion of product in 2005 and Remicade, from Johnson & Johnson (J&J) and Schering-Plough for rheumatoid arthritis and Crohn's disease, achieved sales of £3.4 billion.

### Scientific struggle

Interestingly, these first super successful products are from the earlier phase of monoclonal antibody technology. As we have said, the attraction of antibodies as therapies is that they can be both targeted missiles – blocking or activating cellular activity – and drug transporters – eg delivering cytotoxic drugs directly to tumour cells.

The body naturally produces antibodies when a disease antigen appears in the form of a virus or bacteria or other alien threat, such as transplanted tissue. The antibody will recognise the alien, bind with a receptor on the alien's cell surface and eliminate the offending visitor from the body.

This ability to select and even discriminate between similar antigens is the 'specificity' that earns the accolade of 'smart bomb'. Because monoclonals can confine their biological activity to specific targets on specific cells, the possibility of side-effects is reduced. Reduced side-effects or low toxicity make for successful drugs.

The 25 years it took to perfect the technology for making antibodies work as medicines is attributable in part to positive scientific struggle but also to negative patent complexities. Meanwhile, as the technology for making drugs was evolving, monoclonals were useful tools as laboratory reagents and diagnostics (Figure 1).

There were effectively three stages in the maturing of antibody technology. Kohler and Milstein made the first antibody by fusing mouse myeloma cells with antibody-secreting cells from an immunised mouse. This resulting fusion or hybridoma had two magic ingredients: unlimited growth potential derived from the cancerous myeloma cells plus the programmed specificity of the antibody (Figure 2).

The second stage was for these test-bed drugs to become less mouse and more man. From the first murine stage, researchers developed a part murine-part human, chimaeric antibody. Remicade (rheumatoid arthritis and Crohn's disease) belongs to this chimaeric stage of monoclonals.

Then, third, came the 'humanised' versions, using only the murine amino acids that made the binding site in an otherwise, human antibody. This technology was developed by US company PDL BioPharma, formerly Protein Design Labs.

Humanised antibody drugs include Roche's Herceptin, Wyeth's Mylotarg, for acute myeloid leukaemia and bone marrow cancer, and Xolair for persistent allergic asthma (Genentech and Novartis).

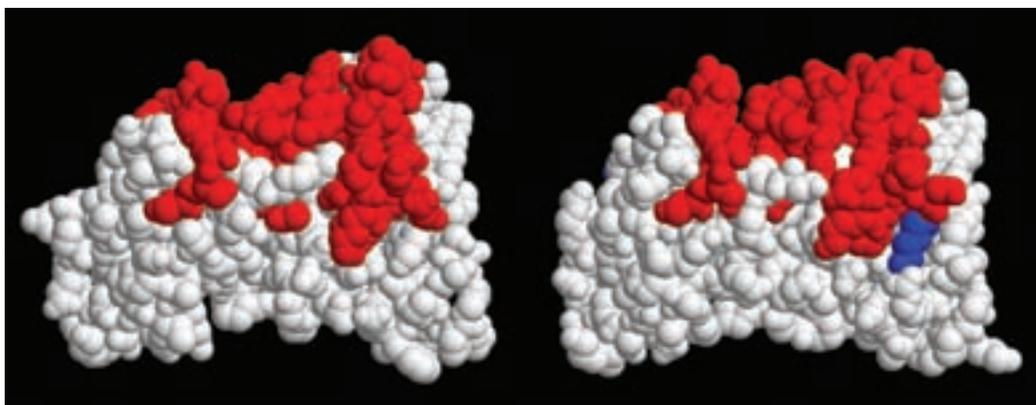
Although predominantly 'human' there remains the risk of these drugs triggering an immune reaction. Even with fully-human monoclonal antibodies immunogenicity is a much reduced but residual issue, as the body can still respond to any foreign matter with an immune response. These fully human monoclonals are achieved in two ways, either using transgenic mouse technology or library technology.

The transgenic mice used have a 'human' immune system which, when challenged by any antigen, will produce human antibodies which can then be harvested. Medarex and Abgenix (now Amgen) make use of this approach.

The other technology for generating these antibodies is the type used by BioInvent as well as Morphosys and Cambridge Antibody Technology (CAT) (now Astra Zeneca). Here a library of

**Table 1:** Top six mAbs on the market (2005 sales \$m)

Remicade	RA, Crohn's, psoriasis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis	J&J/Schering-Plough	3,477
Rituxan (US) MAbThera (Europe)	Non-Hodgkin's Lymphoma, RA	Genentech/Roche Biogen Idec	3,154
Herceptin	Breast cancer	Genentech/Roche	1,629
Humira	RA/psoriatic arthritis	CAT/Abbott	1,400
Avastin	Metastatic colorectal cancer	Genentech	1,264
Synagis	RSV lower respiratory tract infections	Abbott/ MedImmune	1,063



**Figure 2**

Monoclonal Antibody: variable domain. Three-dimensional model of the variable domains of a mouse antibody (left) and a humanised antibody (right). The framework regions are shown in white, and the CDRs are indicated in red. To generate the humanised antibody, the CDRs from the mouse antibody were transplanted, along with key framework amino acids (blue) that were identified by analysis of the model, into a human framework. (Molecular models courtesy of Shankar Kumar, PDL BioPharma)

antibody fragments is made from shuffling human genetic material to produce many different variations of antibodies. A target is ‘put on a hook’ and thrown into the library pool and antibodies that bind are ‘fished out’. The advantage is that there is no need, as in transgenic models, to obtain an immune response.

Humira from CAT, an anti-TNF (Tumour Necrosis Factor) treatment for rheumatoid arthritis (RA), leads the way as the first commercial, fully-human monoclonal antibody drug. Marketed by Abbott, it first appeared in 2003.

Using its patented library technology, n-CoDeR®, BioInvent is developing monoclonals from its library of more than 20 billion differentiated antibody fragments (Figure 3).

Fully-human monoclonal antibodies are seen as third generation mAbs, with chimaeric being first generation and humanised (PDL), second. Moving along the third generation pipeline is Vectibix (panitumumab) a fully human mAb for metastatic colorectal cancer. This is expected to be launched by Amgen by the end of 2006. Just into the clinic is MDX-1106 from Medarex which has potential in cancer and infectious disease.

Meanwhile, first generation mAbs are now moving into new indications adding considerable value to each brand. From this March, Erbitux was cleared for use in treating head and neck cancer, a first for this disease. Remicade (RA and Crohn’s) now has an expanded indication for psoriatic arthritis.

With human antibodies as drugs now a reality, the technological challenge for the industry is not making antibodies but selecting the best targets or disease pathways for them to attack.

### Patent puzzle

Taking out patents is core to protecting intellectual property in the biotechnology and pharmaceutical sectors, but particularly in the field of genetic

engineering, extant patents on multiple small molecular manipulations leave the researcher constantly looking for the next piece of the patent jigsaw before moving forward.

There are just eight companies that mainly control the rights to the antibody technology for developing human and humanised mAbs. Not all the holders of these patents in the early days of mAb technology were ready to share this expertise. This and some of the ensuing patent contests took up a lot of management time, doubtless slowing the whole process down and leaving big pharma a little uneasy about collaborating with companies embroiled in litigation.

“While patents obviously protect intellectual property they can also become barriers to discovery,” says Professor Carl Borrebaeck of Lund University, scientific adviser to BioInvent. He has been involved in monoclonal antibody research from the early 1980s.

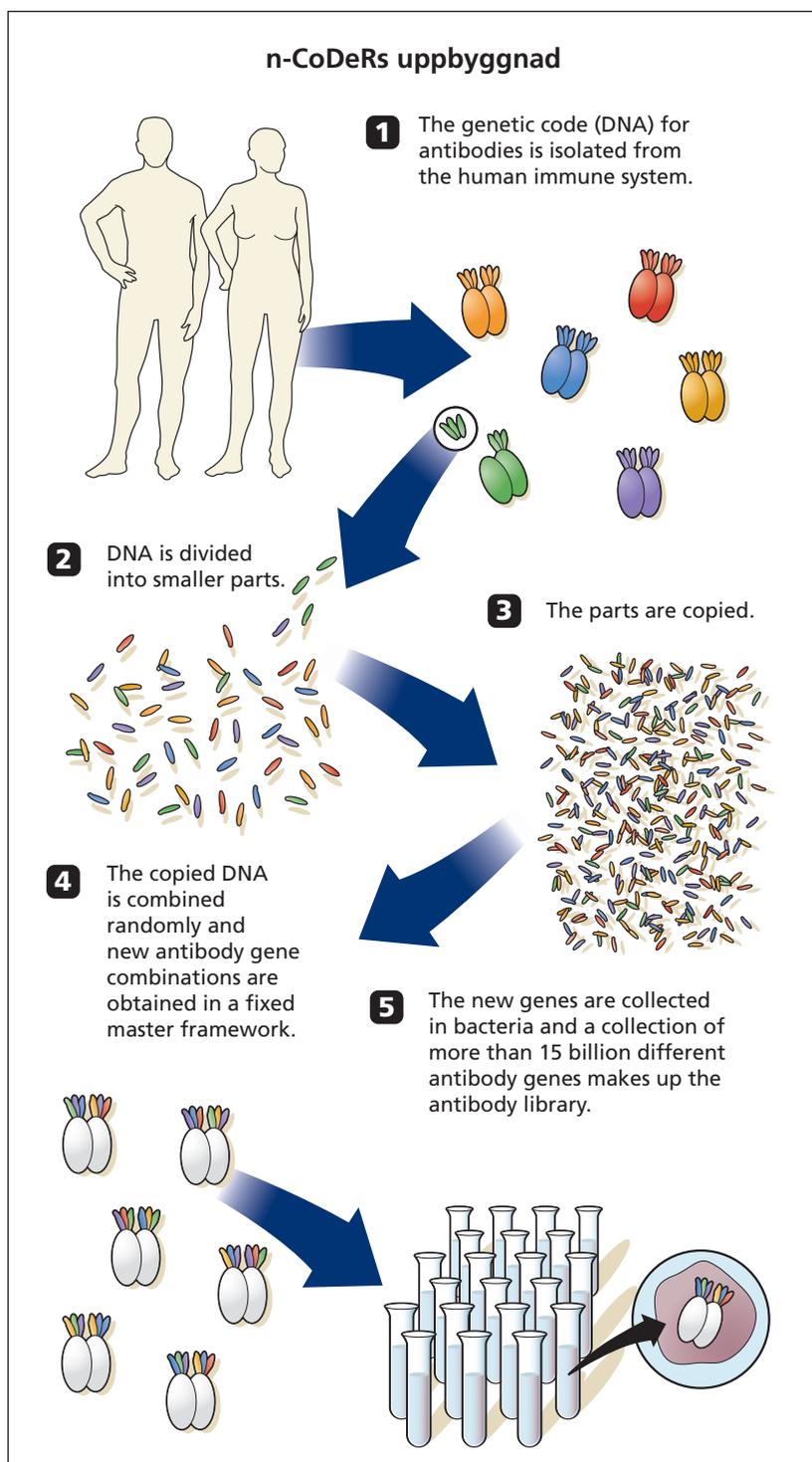
He says: “We are meeting the same problems now in the mapping of the human proteome, which at present is largely a non-profitable academic endeavour. Ideally we would use mAbs to help identify proteins that are involved in human disease. We either pay for licences or take longer by trying to find alternative methods that don’t infringe patents.

“Even the National Institutes of Health in the US concedes that the IP situation for mAb development is difficult.

“BioInvent’s monoclonal antibody library is used for in-house discovery programmes as well as industry collaborations. We have to sign up to several licences to be able to manipulate our own material. Fortunately we have the key licences in perpetuity.”

PDL BioPharma developed pivotal research that pioneered the method for the second stage of development, the humanised mouse antibodies. Licensing out its technology in the past made PDL

## Therapeutics



**Figure 3**  
BioInvent's n-CoDeR®  
Antibody Library Technology

BioPharma something of a gatekeeper on monoclonal development and provided the company with a lucrative revenue stream.

Seven marketed products have used PDL's technology including Herceptin, Avastin, Xolair, Raptiva, Synagis, Mylotarg, and Zenapax, with royalties providing more than 50% of PDL

BioPharma's annual \$280 million revenues. The relevant technology is, as we've said, now being overtaken and PDL BioPharma is moving into developing its own drugs and building up a sales force.

Whether the IP situation will prove too expensive or too difficult for the smaller entrepreneurs to break into the sector is uncertain. As Max Hermann, Head of Life Sciences at ING says: "Patents never stopped a drug getting to market."

Companies have to accept that biotechnology is strewn with patents. However, if the patent pool is in even fewer hands after more pharma acquisitions, it could hamper access and hinder progress in the shorter term.

In the longer term monoclonal technology will move on and some of the patents will cease to retain their grip.

### Waiting game

The pioneering of monoclonal antibodies has largely been achieved at the hands of the biotechnology industry. To a biologist the antibody-as-drug makes lots of sense. "It was clear that monoclonals were going to have a major impact," is Hermann's view.

But the rather more conservative pharmaceutical industry mostly waited on the sidelines. "They either disbelieved the concept or didn't like it," says Hermann. "They stuck to their view that small molecules (chemical drugs) always win out."

So rather late in the day the big pharma companies are buying into the business, through collaborations or straight acquisitions. Witness Astra Zeneca's takeover this year of the UK's longest serving antibody company, CAT. The deal valued CAT at £702 million (\$1,263 million).

Amgen, a company that has been around since the early days of biotech, developed the hugely successful recombinant protein products Epogen and Neupogen, and also Enbrel, a hybrid fusion protein made of an antibody and a receptor. The company is now buying up Abgenix, the innovator of the transgenic mice technology for producing human antibodies.

There was one earlier, rather costly, foray by big pharma into the sector. In 2001 Bristol Myers Squibb (BMS) paid \$1 billion for a 20% stake in ImClone after cetuximab for colorectal cancer was granted fast-track development status by the FDA. Within a year the drug was rejected by the FDA but Erbitux eventually made its first sales last year.

### TNF success story

Despite big pharma's faith in small molecule drugs, they never gained mastery over biologics in the battle with TNF. Finding monoclonals against the TNF target responsible for the inflammatory cascade in

RA has been the sector's biggest success so far, and this sub sector alone is worth about \$8 billion (2005 figures). Already established are J&J's Remicade, Amgen's Enbrel and CAT's Humira.

With only 13% of RA patients currently on one of these drugs, and no other drugs available that actually tackle, rather than mask, the symptoms, there is obviously huge market potential.

With monoclonal antibodies taking an increasing share of all product approvals, big pharma will be looking at those biotech companies with promising lead products. Drug development collaborations with biotech, in-licensing deals or straight acquisitions are likely to be a continuing pattern as more pharma companies realise that it is time to get a share of the action.

### Higher success rate

It is widely recognised that monoclonals have a higher success rate in their development phases than conventional drugs. This is another important factor in assessing this market. In 2002, 30% of all newly approved drugs were either monoclonal antibodies or recombinant proteins, up from 6% in 1999, according to Tufts Center for the Study of Drug Development.

Steve Projan, VP of biological technologies at Wyeth Research, commented recently in *The Scientist*: "Biologics are the drugs of the future because they are targeted, causing fewer side-effects than traditional drugs. Moreover most agents are injectable, making it harder for people to buy them at lower cost over the Internet. It's easier to manage the biopharmaceutical market."

At the moment mAbs, which are large molecules that do not readily convert to pill form, have to be injected or infused. Protein-based drugs, the other strand of successful biologics, require daily dosing. But the pharmacokinetics and formulation technology has improved sufficiently that subcutaneous administration for fully-human antibodies products can be made once or twice a month.

### Looking into the future

In looking at the future lifespan of a drug, you normally have to consider when the patent will run out and other companies can apply to manufacture a generic version of the drug. With monoclonals, the situation is a little different. As Mark J. Belsey put it in *Nature Reviews*, Vol. 5, July 2006: "Given that the innovator's cell line plays a key role in determining the mAb's characteristics, the proprietary nature of the cell line makes it difficult to recreate a genuine biosimilar (generic version of a biologic drug)."

As Bjorn Andersson, biotech analyst at RedEye, puts it: "You will not get exactly the same drug from another manufacturer. I don't think we will see generics for a long time, if at all. "It is more likely that new kinds of technology, such as antibody fragments, will be used to achieve the same effects as monoclonals."

Companies such as Ablynx and Domantis are pursuing this route, which may represent the next generation of antibody technology.

Another approach is polyclonal antibodies which can target more complex diseases such as bacterial or fungal infections as they are able to bind to multiple epitopes. Symphogen with its 'Symphobodies' is one of the leaders in the area.

Andersson also sees big pharma approaching mAbs from different perspectives, such as novel methods of delivery. "If they can't make them into a pill, maybe they will come up with a nasal spray."

"The two mature sectors of biologic drugs are recombinant protein therapeutics (such as Amgen's Neupogen), and monoclonal antibodies. Between them they are set to generate more than 90% of total biotech sales from 2004 to 2010." (*Nature Reviews*, Vol. 5, July 2006).

In the monoclonal antibody market we are looking at a class of drugs where quick generation of drug leads and faster early development has been demonstrated, and there is a low attrition or failure rate in development.

There is a strong safety profile for these drugs due to their selectivity and specificity, and the dosing regime of once or twice a month is more convenient than for, say, the recombinant protein drugs.

A last word from Alex Lindstrom, analyst at ABG Sundal Collier AB: "The positives for the sector are that monoclonals are fairly easy to develop, they work and are safe. They are one of the best performing areas in the biotech sector." **DDW**

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