Adapting antibodies for clinical use

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This is the second of three articles examining the development and clinical applications of monoclonal antibodies.

Techniques for antibody engineering are now overcoming the problems that have prevented monoclonal antibodies being used routinely in clinical practice. With chemical and genetic manipulation antibodies can be linked to bacterial toxins, enzymes, radionuclides, or cytotoxic drugs, allowing targeting of treatment. Antigen binding sites from antibodies raised in mice can be joined with human IgG to reduce immunogenicity. *In vitro* gene amplification and genetic engineering of bacteriophage have produced large antibody gene libraries and facilitated large scale production of human monoclonal antibodies with high specificity. The trickle of monoclonal antibodies into clinical practice may soon become a flood.

In our first article we described the early history of passive serotherapy, leading up to the discovery of monoclonal antibodies.¹ Once the potential of monoclonal antibodies was appreciated numerous useful diagnostic tests followed. However, it soon became apparent that murine monoclonal antibodies in their native form were unsuitable or ineffective for most therapeutic applications. Their fine structure differs significantly from that of human antibodies and in many cases the Fc portion is virtually unseen by human Fc receptors and complement proteins, resulting in failure to initiate human defence mechanisms (effector functions). Mouse monoclonal antibodies can also elicit a strong antimouse protein immune response that greatly reduces their circulating half life. These problems should not arise with human monoclonal antibodies, but they are much more difficult to make.¹ Fortunately, through developments in basic sciences solutions to these problems are emerging and the promise of human monoclonal antibody therapy is at last becoming a reality. The immunogenicity of rodent monoclonal can now be reduced, to improve their ability to recruit natural effector functions and increase their affinity. Many different antibody fragments can be produced and linked to various effector functions. More recently methods have begun to emerge for generating and screening large libraries of human antibodies entirely *in vitro*.

In this article we review some of the technical achievements of antibody engineering. Regardless of how a monoclonal antibody is produced, it may be desirable to tailor it to suit its intended application better. This can be achieved through chemical or genetic approaches. Figure 1 shows some of the possible modifications.

Chemical modification of monoclonal antibodies

PROTEOLYTIC CLEAVAGE

Controlled proteolytic cleavage of a purified monoclonal antibody gives several smaller fragments that can be separated chromatographically. Cleavage was important in the early elucidation of antibody structure and structure-function relations but also has therapeutic implications. Antibody fragments are sometimes preferable to intact antibodies as they have a shorter circulating half life and may penetrate tissues more rapidly.

FIG 1—Antibody fragments. Limited proteolytic cleavage of IgG removes the Fc portion yielding bivalent $F(ab')_2$ (100kDa) or monovalent Fab antigen binding fragments. Cloned T genes for Fab can be expressed in mammalian cells, yeast, or bacteria to produce functional recombinant Fab molecules. Toxins and enzymes can be fused to the recombinant Fab by genetic engineering. Smaller antibody fragments (Fv) can be produced in bacteria by coexpression of cloned V_H and V_L genes and stability is increased when V_H and V_L are linked (genetically) by a short peptide (single chain Fv or scFv). This can also be linked to toxins genetically

CHEMICAL COUPLING

Monoclonal antibodies and antibody fragments can be conjugated chemically to a variety of substances, including plant and bacterial toxins, enzymes, radionuclides, and cytotoxic drugs. In this way, an ineffective rodent antibody or antibody fragment may be armed with a potent effector mechanism. Fragments coupled to radioactive elements can also be used for *in vitro* imaging or cancer therapy. However, the chemical coupling processes can be inefficient or give rise to unstable products, and repeated cycles of antibody purification, modification, and repurification are time consuming and costly.

Genetic modification of monoclonal antibodies

In contrast to a hybridoma or the protein it secretes an antibody gene is highly versatile. It can be cut, joined to other genes, mutated randomly or non-randomly, and expressed in various cell types. The

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genes can be introduced into appropriate plasmid vectors and transfected into mammalian cells, bacteria, insect cells, or even plant cells for protein expression.

ANTIBODY FRAGMENTS

Antibody fragments similar to those generated by proteolytic cleavage can be generated from shortened versions of the heavy and light chain genes. The modified genes can then be transfected into bacteria² or mammalian cells where they produce functional Fv (variable fragment) or Fab (antigen binding fragment) which is then easily purified. Bacteria are unsuitable hosts for producing complete monoclonal antibodies because the Fc domain of antibodies produced in this way is non-functional.

ANTIBODY FUSION PROTEINS

Genetic engineering has been used to create chimeric molecules in which the variable domain of an antibody is genetically linked to an unrelated protein. In this way enzymes, toxins, and cytokines, for example, can be given novel binding specificities and can be produced in bacteria.³ The approach is made easier when the antibody moiety is expressed as a single chain Fv (scFv) molecule in which the heavy and light chain V domains are linked by a short peptide that does not seriously affect antigen binding. The antibody can then be expressed as a single protein from a single gene rather than as two chains that must subsequently associate somewhat inside the cell. Several bacterial toxin-scFv fusion proteins have been produced, and because they are smaller than intact antibodies, it is hoped they will prove able to penetrate tumours more efficiently.

Antibodies can also be expressed on the surface of cytotoxic effector cells, redirecting them to kill novel targets. This approach has been used to redirect T cells⁴ and has many potential applications to improve cellular immunotherapy.⁵

HUMANISATION

Chimeric antibodies—Genetic manipulation can also be used to make chimeric antibodies—that is, antibodies with rodent variable domains for antigen binding and human constant regions for recruiting effector functions.⁶ The initial stimulus to this research was the difficulty in producing human monoclonal antibodies of the desired specificity and affinity. The resultant molecule (fig 2) is largely human but binds with the

specificity of the parent monoclonal. Chimerisation enhances effector functions⁷ but a significant part of the molecule is still of rodent origin and recent human trials have shown that over half of humans mount an antitumour response after receiving a chimeric antibody.⁸

CDR grafted antibodies—Structural analysis of antibody-antigen complexes shows that the antigen binding surface of the antibody is formed by six hypervariable loops of amino acids called complementarity determining regions (CDRs).¹ These loops are mounted on relatively constant framework regions and by genetic manipulation can be transplanted (fig 2) from a rodent antibody on to a human framework. This produces a CDR grafted or humanised antibody with the same specificity as the rodent monoclonal antibody from which the loops were grafted.⁹ The process usually reduces the affinity of the antibody, but mutations can be made to restore full binding. Several antibodies have now been humanised¹⁰ and one has already been used with clear therapeutic benefit.¹¹

BISPECIFIC ANTIBODIES

Bispecific antibodies have two antigen binding sites, each with a different binding specificity. Conventionally, they have been produced by fusing two hybridoma lines to make a hybrid hybridoma¹² or by chemical cross linking of antibody fragments. Because of random pairing of heavy and light chains and of heavy chain-light chain heterodimers, on average less than 10% of the IgG secreted by a cell expressing two antibody genes displays both of the required specificities. Genetic techniques allow the production of constructs which facilitate the association of non-identical species. For example, one heavy chain has been tailed with a fos peptide and the other with a jun peptide (fos and jun are nuclear proteins which bind strongly to each other).¹³ Bispecific monoclonal antibodies have been used to cross link cytotoxic effector cells to targets that they would not otherwise recognise—for example, tumour cells—and the approach has been used with apparent benefit in the treatment of malignant gliomas.¹⁴ They can also be used to redirect toxins and enzymes to specific cellular targets.

Bispecific antibodies may also show greater target cell specificity than two monospecific antibodies. Target cells often express a constellation of antigens, each of which is found on certain normal host tissues. A bispecific antibody derived from monoclonal antibodies against two different antigens, expressed singly on separate host tissues but together on the target, should have more specific targeting properties than either monoclonal antibody alone.

Rapid cloning of antibody genes

No two antibody genes are identical so it might be expected that cloning each gene would be a tedious process. However, with the development of rapid methods based on the polymerase chain reaction cloning functional, rearranged V genes has become routine.

The polymerase chain reaction is a simple and elegant three step laboratory procedure for producing large numbers of faithful copies of a DNA sequence. In the first step double stranded template DNA is "melted" into single strands by heating to 95°C. This template DNA may be derived from any source, including the chromosomal DNA or messenger RNA of a mammalian cell. In the second step the reaction is cooled to allow annealing of oligonucleotide primers to the single stranded template. The synthetic oligonucleotide primers are composed of 15-30 deoxynucleotides (dA, dT, dC, and dG) which bind specifically to their complementary sequences on the single

FIG 2—Genetic manipulation to produce chimeric (left) or humanised (right) antibodies. The parts of mouse origin are shown in orange and those of human origin in white. In the humanised version only the antigen binding loops are of mouse origin

stranded DNA template. The precise sequence (and length) of each oligonucleotide can be predetermined to ensure highly specific binding to chosen target sequences at an appropriate annealing temperature. The minimal requirement is for two oligonucleotides, each complementary to a different strand of the target DNA, which flank the template sequence to be amplified. In the third (elongation) step, the template bound oligonucleotides prime synthesis (catalysed by a heat stable polymerase) of new DNA. Both strands of the template are duplicated between the primers, doubling the amount of DNA of interest. The whole cycle (lasting as little as three minutes) is repeated many times on an automated heating block and exponentially amplifies the DNA sequence.

Although they differ in the middle, all antibody V genes are similar at either end, which allows construction of oligonucleotide sets whose sequences recognise and bind to the terminals of most V genes and prime the polymerase chain reaction.¹⁵ Oligonucleotide sets are available for amplification of murine or human V genes.

It is now possible to amplify and rescue most of the antibody V genes from a diverse population of human or murine B cells, thereby generating an antibody gene library. This method works equally well with any type of B cell—resting B cells,¹⁶ antibody secreting plasma cells, or memory B cells¹⁷—and the starting material may be either RNA or DNA.

Whatever the source of the antibody gene library, its usefulness depends on the availability of a convenient system for expressing the genes and selecting those which encode the best antibodies. Until recently, the best system available was suitable for screening no more than a million transfected colonies of *Escherichia coli*,¹⁸ which is at least two orders of magnitude lower than the number of antibodies screened by an intact immune system. However, with the arrival of phage antibodies (see below),¹⁹ libraries containing at least 10⁸ different antibodies can now be screened.

Phage antibodies

Filamentous bacteriophage (hereafter referred to as phage) are pencil shaped viruses that infect bacteria. They attach to the surface of bacterial cells and inject their single stranded DNA genome through the cell wall. The infected bacterium does not die but continues to divide, distributing copies of the viral genome on to its progeny, which assemble and extrude perfect replicas of the invading phage. After overnight incubation, one millilitre of the bacterial culture supernatant contains over 10¹¹ progeny phage particles.

At one tip of the phage are a few (probably three) copies of a protein (gene III protein). This protein mediates the initial attachment of the phage to a bacterial cell. To make a phage antibody the gene for an antibody fragment is fused precisely to one end of gene III on the phage genome. When this modified phage DNA is transfected into a bacterial cell, the cell produces and extrudes progeny phage particles that not only display the appropriate antibody at their tip (in fusion with the gene III protein) but also contain a single copy of the antibody gene and are still able to infect bacteria almost as efficiently as unmodified phage. Antibodies displayed on the surface of phage are fully functional and will still bind their antigen specifically. Phage antibodies with the desired specificity can be purified from a mixed population because of their ability to bind antigen.¹⁹

Thus a phage antibody is the functional in vitro equivalent of a resting B cell. It contains an antibody gene and displays the corresponding functional antibody on its surface. It can be selected for its ability to recognise a particular antigen, whereupon it can be amplified by growth in bacterial culture. It is then simple to rescue the antibody gene, which can be used to produce large amounts of soluble antibody (like the plasma cell) or simply stored in the freezer (acting similarly to the memory cell).

Phage antibody libraries

The intact humoral immune system is essentially a large library of antibodies. After challenge with antigen the most suitable antibodies are selected, amplified, and affinity matured. If the whole process could be reproduced entirely in vitro, production of high affinity human monoclonal antibodies might be greatly simplified.²⁰ With phage antibody libraries (see below) this goal is fast becoming a reality and these should increase the pace at which antibody therapy develops.

If a phage antibody can be likened to a B cell, then a phage antibody library is the in vitro equivalent of the humoral immune system (fig 3). A phage antibody library is constructed by ligating an antibody gene library (amplified by the polymerase chain reaction) into the appropriate site on purified phage DNA. The ligated DNA is transfected into bacteria, which then manufacture large numbers of phage antibodies, and those with the desired binding specificities are selected by using soluble tagged antigen or an antigen coated surface. Although still in its infancy, phage technology looks set to make a major impact on antibody development.

Potential of phage antibody technology

HUMAN MONOCLONAL ANTIBODIES

Recently, the V genes from the lymphocytes of two healthy blood donors were cloned and expressed on the surface of bacteriophage. From this single phage library, consisting of 20 million clones, antibodies specific for a variety of test antigens were selected.¹⁶ This "natural" library approach greatly simplifies the generation of human antibodies.

Currently, B cell derived heavy chain and light chain (κ and λ) V genes are amplified separately and must subsequently be recombined for expression on phage. By this stage the original pairings between the heavy and light chains have been lost, leaving no option but to recombine the chains randomly before they are transfected into *E coli* for expression and screening.¹⁸ The in vitro antibody library is therefore dominated by heavy and light chain pairings that were not present in the original B cells. Alternative methods are being developed which retain the original pairings and thus

FIG 3—In vitro antibodies compared with the natural humoral immune system. The phage system allows all aspects of the humoral immune system to be mimicked in vitro

prepare the library as a faithful copy of the antibodies expressed on B cells.²¹ However, the random combinatorial approach may be an advantage for in vitro production of antiself antibodies (see below).

PHAGE "POLYCLONALS"

The natural immune response is polyclonal and thus a cocktail of monoclonal antibodies raised against a single antigen may be more effective than a single antibody. It has been so difficult to make human monoclonal antibodies that this approach has not been generally feasible. With phage antibody libraries, this may soon change. Already, starting from the bone marrow of a person infected with HIV, large numbers of human antibodies against HIV have been generated.²² Natural libraries will certainly improve in terms of both size and their starting genetic material, and thus it should be possible to isolate multiple human antibodies to any antigen from a single library of sufficient size in a few weeks. Eventually, the whole process may be automated.

Considerable effort is currently being devoted to constructing large phage antibody libraries, orders of magnitude larger than the entire antibody repertoire of the human immune system. In time, such libraries may supply all the antibodies and allow reproducible "polyclonal" human antisera against any antigen to be generated. By comparison, more conventional methods of tapping the immune system of an immunised mouse or human may seem inefficient, expensive, time consuming, and relatively cumbersome.

ANTISELF ANTIBODIES

Humans can legitimately be immunised with a variety of viral and bacterial proteins and their circulating B cells subsequently harvested for production of monoclonal antibodies. However, when the goal is to raise human monoclonal antibodies against self proteins (tumour antigens and lymphocyte markers, for example) immunisation is inappropriate. Firstly, it is unlikely to be successful since the educated human immune system has complex in built control mechanisms that prevent the production of potentially damaging high affinity antiself antibodies. Although a proportion of the normal B cell repertoire is intrinsically antiself, these antibodies tend to have relatively low affinity, are polyreactive and do not significantly damage host tissues. Secondly, if the state of self tolerance is broken by immunisation with self proteins, autoimmune disease may result. Phage antibody libraries may prove a rich and convenient source of high affinity human antiself antibodies. Because the original pairings of heavy and light chains are scrambled, most of the antibodies in a library differ from those in the B cells from which they were derived and may therefore be more likely to have a high affinity for self proteins. Several antibodies against human self proteins have already been extracted from one large human phage antibody library.¹⁶

AFFINITY MATURATION

Antibodies from natural phage libraries can have low affinities,¹⁶ but once again phage technology is providing the solution. Larger libraries are expected to provide higher affinity antibodies, but the phage system can also be used for affinity maturation. After isolating a low affinity antibody from a primary phage library, the genes can be diversified in several ways and used as the basis for a secondary phage library. Higher affinity variants of the original antibody can be selected from the secondary library (fig 3). In the immune system affinity maturation occurs by random mutation in antibody V genes during B cell division: occasionally such mutations result in improved affinity. This process can now be reproduced in the laboratory by using the

polymerase chain reaction under imperfect conditions to mutate the antibody gene and create a phage library of random mutants. Higher affinity variants can then be selected from this library.²³

Additional methods of diversifying the initial repertoire have been developed. For example, the heavy chain of a low affinity antibody can be retained in its original form and recombined with a large library of complementary light chains (or vice versa) to create a secondary "chain shuffled" library.²⁴ Also, any part of either chain can be held constant while other parts are diversified by polymerase chain reaction driven recombination with gene libraries or synthetic oligonucleotides.

In vitro affinity maturation on phage can be applied to any antibody regardless of its original source. This may prove useful for improving antibodies that have shown promise in clinical trials, particularly in view of the recent finding that increased affinity of an anti-tumour antibody was associated with improved therapeutic efficacy.²⁵

Future of antibody engineering

The technological trickery of antibody engineering is advancing more rapidly than it can be tested in therapeutic models. This presents a problem for pharmaceutical companies because in the time it takes them to scale up production methods for their most promising therapeutic monoclonal antibody, both the production method and the antibody may have been superseded. Notwithstanding, several companies have taken the plunge, and monoclonal antibodies are beginning to trickle into clinical practice. This trickle will probably soon become a flood and, faced with a plethora of cleverly conceived and constructed, but completing reagents, clinicians will benefit from an understanding of some of the principles of antibody therapy. The third article in this series tackles this issue and outlines those areas of medicine in which antibody therapy is likely to be valuable.

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Medical Education

Student selection

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This is the second in a series of articles examining the problems in medical education and their possible solutions

Medicine is often seen as a difficult university subject to enter, with medical schools choosing only the cream of students from many eager applicants. Certainly many schools spend considerable time, effort, and money on their selection process, but are they really getting a good return on this investment? Do we get the sort of medical students and doctors that we want? Are we even clear about what we want? Does it matter, anyway?

What do we want?

If medicine was simply a degree course like any other there would be little need for elaborate selection processes. Minimum scholastic achievement could be defined before entry to ensure that students had a fair chance of keeping up with the course, but places could then be awarded by lottery.

Most people, however, see the medical course as a vocational training. Applicants are expected to make medicine their career. Candidates are asked "Why do you want to be a doctor?" not "Why do you want to study medicine?" This is in sharp contrast with other degree courses. We do not, for example, expect all graduates in English to write or teach for a living. Nor do we insist that graduates from other facilities should "repay" society by obtaining any employment, much less in a specified field. A spattering of students who

study medicine for its own sake might even enhance the educational climate in many of our medical schools.

If we assume, however, that medical education will continue, for now, to be about training doctors the selection process becomes one of choosing people who will make good doctors. This immediately raises the problem of defining a good doctor. Is there really an essential common core of knowledge, skills, and attitudes that all doctors should have? In a profession like medicine there may well be niches for all—regardless of their particular interests, skills, and weaknesses. Specific aptitudes are doubtless important in selecting people for specialist training, but their relevance at the undergraduate stage is much less obvious.

Is there an end product?

If we could clearly identify the aims of undergraduate medical education we could begin to decide how best to select medical students. The General Medical Council defines the principal objective of basic medical education as providing "the knowledge, skills and attitudes which will provide a firm basis for future vocational training."¹

The only immediate requirement is to produce a graduate who can function as a preregistration house officer. This should enable an essential core of factual knowledge and clinical skills to be defined that all doctors should have mastered by the end of the course. They will then have to embark on a protracted postgraduate education in their chosen specialty. All medical graduates should therefore have the skills to enable them to continue learning beyond university.

In recent years the trend has been for medical schools to select only the most academically gifted applicants, with standard offers of places often depending on acquiring three "A" grades at A level. This attitude is now changing, more schools acknowledging that people with only moderate academic achievement can cope well with the course and often have more to offer in terms of personal skills, attitudes, and experience. Dr John Foreman, subdean of University College and Middlesex School of Medicine, University College, London, recently explained the school's reasons for setting low minimum requirements for entry: "Our standard offer of C, C, C is the lowest in the country.... We strongly believe C, C, C reflects the level of academic ability needed to follow the course. It gives us the scope to admit people below the academic average for medicine,

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How many young people like these will apply to and be accepted by medical schools?