

Medical Applications of Biotechnology • part 3

MABs and issues in biotechnology

LEARNING OBJECTIVES

- **Describe** MABs and explain how they are produced.
- **Describe** clinical applications of MABs.
- **Describe** the types of regulations governing biotechnology.
- **Explain** the financial implications of biotechnological products.
- **Explain** the issues relating to formulary selection and management of biotechnology drugs.

This third article in a three-part series discusses the uses, creation and clinical applications of monoclonal antibodies. The article also discusses major issues in biotechnology, including regulation, financial implications, and formulary selection and management.

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Monoclonal antibodies (MABs) are a successful biotechnology, with applications in the diagnosis and treatment of disease. MABs are exquisitely selective proteins (antibodies) that bind to only a single target. MABs have the ability to target unwanted cells and fuse

with substances such as toxins or radioisotopes to target very specific tissues in the body. Depending on the clinical setting, these targets may include antigens such as bacteria, hormones, tumor cell antigens, growth factors and a variety of other substances. MAB-derived medicines are on the market for the treatment of cancer, cardiovascular disease, Crohn's disease and rheumatoid arthritis, and for the prevention of organ rejection following transplantation. They are also used in imaging tumors for radiotherapy.

The process used to produce monoclonal antibodies is called hybridoma technology (see illustration on page 39). It begins when a mouse is immunized with an antigen that specifically stimulates production of a desired antibody targeted at that antigen. White blood cells that produce antibodies, called B-lymphocytes, are then isolated from the mouse's spleen. The resulting B-lymphocytes are fused with multiple myeloma cells, which are tumor cells that replicate continuously and rapidly.

Using cell fusion technology, these two cell types are merged into a single cell, called a hybridoma, containing the DNA and desirable qualities of both original cells. Each hybridoma is capable of producing large numbers of identical antibody molecules, and these are called monoclonal antibodies because they are produced by the identical offspring of a single, cloned, antibody-producing cell.

To date, four different types of MABs have been synthesized, including:

- **Murine (mouse) MABs:** These are easy to mass-produce, but are quickly cleared from the body and produce human anti-mouse antibodies, or HAMA reactions, a type of allergic reaction.
- **Human MABs:** These do not produce a HAMA response, but are difficult to produce.
- **Chimeric MABs:** These combine both mouse and human antibodies, are simpler to produce than human MABs, and are less likely to produce a HAMA response.
- **Humanized MABs:** These incorporate only the genes for specific binding sites from the mouse antibody into a human framework.

Clinical applications of MABs

Monoclonal antibodies act as specific probes that can be directed at the protein that induced their formation; therefore, they can be used as a precise tool in diagnostics, disease monitoring and therapy.

Monoclonal antibodies have the ability to directly attract immune cells to a targeted area for cell-mediated toxicity (an immune system process). They can also trigger an immune process called complement-mediated cytotoxicity, another way to destroy cells. MABs can act in other ways; for example:

- They can be directed at target molecules needed for cellular growth or differentiation.
- They can be conjugated with radioisotopes, toxins or drugs for targeted delivery to specific cells.
- The development of bispecific MABs,

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engineered to be directed to both tumor and immune system cells, enables the MAB to bind to two different cells at the same time to improve cell-mediated toxicity.

- MAB fragments can be directed toward site-specific antigens; the fragments' small size allows for greater access to tumors and other cells, and allows for rapid clearance from the body.

- MABs, particularly when conjugated with a radioisotope, can be used to diagnose and monitor disease (for example, when used with a CT scan).

Several MABs have recently been developed for the treatment of a variety of diseases. Agents such as radioconjugated MABs targeted toward B-lymphocytes are being used to treat non-Hodgkin's lymphoma, and MABs conjugated with chemotherapeutic agents are available for the treatment of colorectal, breast and ovarian cancers.

Regulation of biotechnology

While new advances in medicine related to biotechnology are announced almost daily, the public remains skeptical about its safety. As with any new advance, in order for biotechnologically derived products to be accepted by physicians and patients, it is necessary to provide assurance that these products are safe, have no long-term disadvantages and represent an improvement over previous therapies.

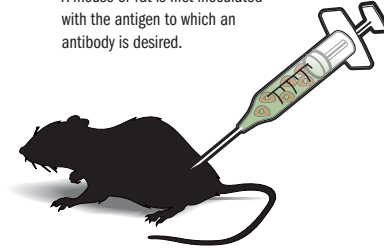
In 1975, the Asilomar Conference, a gathering of recognized molecular biologists, drew up guidelines to ensure the safety of recombinant DNA (rDNA) research. These guidelines were used by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) to develop government regulatory guidelines used to govern the use of rDNA technology in developing pharmaceutical agents for human use. While NIH guidelines have been modified many times since these initial guidelines went into effect, the RAC continues to regulate the use of biotechnology in the development of drugs.

Following drug development, the Food and Drug Administration regulates the use of drugs and "biologics" produced using biotechnology. The FDA uses guidelines

Production of murine monoclonal antibodies

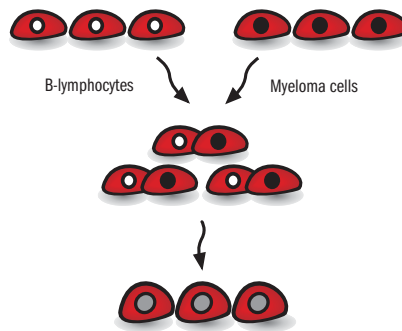
1 Injection of purified antigen

A mouse or rat is first inoculated with the antigen to which an antibody is desired.



2 Cell fusion

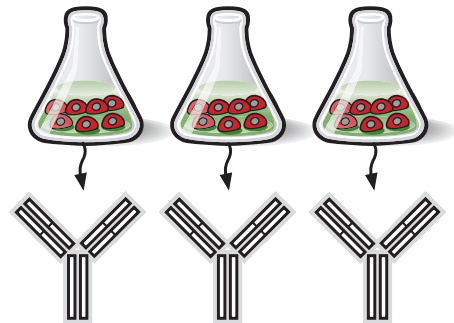
After the animal produces an immune response, its spleen (containing the lymphocyte cells) is removed. These cells are then fused to myeloma cells. The resulting fused cells retain properties of both parents and are known as hybridomas.



3 Hybridoma cells are selected out and seeded into wells.



4 Like the myeloma cells, hybridomas grow continuously and rapidly in culture. Like the lymphocytes from the immunized animal, they produce antibodies targeted at the injected antigen.



to make its review standards consistent for all agents derived through biotechnology, regardless of whether the product is considered a drug under the Food, Drug and Cosmetic Act or a biologic under the U.S. Public Health Service Act.

In September 2002, the FDA consolidated its responsibility for reviewing all new pharmaceutical products into its Center for Drug Evaluation and Research.

To ensure uniform safety and quality of drugs derived using biotechnology, the International Conference on Harmonization, which included scientists from industry and regulatory agencies, developed specifications that a product must meet in order to be marketed commercially. These specifications include:

- Testing to ensure the correct genetic sequence is incorporated into cells in genetic engineering processes.
- Testing cell banks to ensure no con-

taminants, such as viruses or bacteria, are present.

- Ensuring that viral strains used in biotechnological processes are inactivated.
- Using processes to ensure the removal of product-related impurities.
- Testing of the final product for identity, purity and potency.

Financial implications

Biotechnological products are expensive to produce, and consequently, they are costly medicines. However, they also represent the future of the pharmaceutical industry. Approximately 350 biotechnology drugs are in late clinical testing for diseases ranging from cancer to HIV to heart disease to Alzheimer's disease. Investment in biotechnology companies is growing, and investors are expected to be rewarded with substantial returns in the coming decades.

The next few years are also likely to see

enormous competition in sales of biologics. With the likelihood of \$15 billion in sales arising in the next four years as a wide range of biotech drugs lose their patents' exclusivity, the possibility of the legalization of generic biologics could have far-reaching implications across the industry. However, the Washington-based Biotechnology Industry Organization disputes whether the science to prove bioequivalence between generic and branded biologics exists yet.

More and more small biotechnology companies are joining forces with large, established pharmaceutical companies to develop these new drugs. These small companies have found that through licensing arrangements, buyouts or other arrangements, they can access large pharmaceutical companies' expertise and financial backing to conduct phase III testing, submit applications for approval to government regulatory agencies, and market and sell their products. It will become increasingly common for healthcare representatives at large pharmaceutical companies to represent products derived using biotechnology.

As representatives promote these new biotechnology drugs, they will likely encounter resistance to the drugs' high costs. However, these drugs are typically new and innovative approaches to therapy that overcome disadvantages found with other available therapies, or they may be the only treatment available. Healthcare representatives should be prepared to offer pharmacoeconomic information to support the cost-effective use of these innovative products.

Formulary selection and management

Some of the important considerations in formulary selection and management of biotechnology drugs include:

Pricing. In general, pricing can be expected to reflect the overall impact the new product will have on the market, including, in particular, the availability of alternative, therapeutically equivalent medical therapies.

Possible use for nonapproved indications. Many biotechnological agents tend to be associated with a wide range of non-approved indications, since many of these drugs have been extensively investigated

for numerous indications (and widely reported on in the literature).

Reimbursement. Restrictions on third-party reimbursement for nonapproved uses of biotechnological drugs may be a problem with many insurers and managed care organizations that exclude coverage for unlabeled uses of drugs. Preauthorization is usually required.

Impact on other therapies. The increasing use of biotechnological agents may have implications for the use of other pharmaceutical products as well. Biotechnological agents may play a role in combination therapy with traditional pharmaceutical agents.

Given all of these important considerations, it will be the responsibility of the healthcare representative to fully grasp the advantages of the more expensive biotechnological products over competing alternatives and to present this information effectively.

Moving products onto formulary or justifying their off-formulary use will also require an understanding of the principles and techniques of pharmacoeconomics and outcomes research, and the ability to apply this information where required. To a great extent, this may involve presenting product data in the context of the overall health outcome for the patient. It may also involve expanding the scope of discussion to include not just acquisition costs of a given product, but also overall costs affecting the institution or provider system as a whole.

Increasingly, large healthcare providers can be expected to develop policies and protocols regarding the use of biotechnological drugs. In some settings, this may simply translate into informal formulary and routine drug use monitoring. In others, it may involve specific prescribing protocols and clinical practice guidelines that tightly regulate the use of these products.

In developing such protocols, institutions and provider networks may collect and monitor their own outcomes data and utilize the data to analyze the economic impact of competing therapeutic alternatives. For the pharmaceutical industry, one advantage of this evolving orientation is that it provides strong incentives for using the most cost-effective treatments. In many clinical settings, this may translate into a tendency

toward the use of pharmaceutical therapies over more invasive – and costly – treatment alternatives. PR

The next series of articles will focus on managing business communication.



ARTICLE SUMMARY

- MAbs are exquisitely selective proteins (antibodies) that bind to only a single target.
- The process used to produce monoclonal antibodies is called hybridoma technology.
- To date, four different types of MAbs have been synthesized, including: murine (mouse) MAbs, human MAbs, chimeric MAbs and humanized MAbs.
- MAbs act as specific probes that can be used as precise tools in diagnostics, disease monitoring and therapy.
- The biotechnology industry is regulated in several ways.
 - The Recombinant DNA Advisory Committee of the NIH developed regulatory guidelines used to govern the use of rDNA technology in developing pharmaceuticals.
 - The FDA regulates the use of drugs and "biologics" through its Center for Drug Evaluation and Research.
 - The International Conference on Harmonization developed product specifications related to commercial marketing.
- Investment in biotechnology companies is growing, with substantial returns expected in the coming decades.
 - More and more small biotechnology companies will join forces with large, established pharmaceutical companies to develop new drugs.
 - It will become increasingly common for healthcare representatives at large pharmaceutical companies to represent products derived using biotechnology.
- Healthcare representatives may encounter resistance to the high costs of biotechnology drugs.
 - Representatives should be prepared to offer pharmacoeconomic information to support the cost-effectiveness of these drugs.
- Important considerations in formulary selection and management of biotechnology drugs include: pricing, possible use for nonapproved indications, reimbursement and impact on other therapies.
- Healthcare representatives must fully grasp the advantages of the more expensive biotechnological products over competing alternatives and present this information effectively.