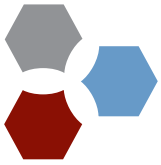

Feature

"Biologics and biologic products"

The U.S. Food and Drug Administration (FDA; www.fda.gov) describes biologic products as substances composed of sugars, proteins, nucleic acids, or complex combinations of these materials, as well as living entities such as cells and tissues. Biologic medicines are thus substances created through biological processes intended for medicinal purposes. The term "biologics" has evolved from a colloquialism in the lexicon of the pharmaceutical industry, reflecting a growing trend that many biologics are protein-based drugs being produced through recombinant DNA technologies. Professionals working in this area expect that advances in molecular biology, genomics, and medicine will lead to the development of new biologic drugs designed for targeted treatment of many health problems, including rare and orphan diseases.

All substances extracted from living organisms intended for medical purposes qualify as biologic medicines, such as blood products, organs and tissues, hormones, and stem cells.

The American Cancer Society (ACS) describes "biologic therapy" as a treatment that uses proteins normally found in the body to fight disease (www.cancer.org). The realm of biologic medicine mandated by the ACS primarily focuses on immunotherapy; however, biologic therapy is more than this. For example, enzyme replacement therapy (ERT) is an expanding area of medicine due to advances in genomics that qualifies as biologic therapy because it involves delivery of an enzyme to patients with a particular enzyme deficiency. The FDA has recently approved the production of glucocerebrosidase (GCD) enzyme for treatment of Type 1 Gaucher disease by Protalix Biotherapeutics through a carrot cell expression system.

All substances extracted from living organisms intended for medical purposes qualify as biologic medicines, such as blood products, organs and tissues, hormones, and stem cells. Vaccines qualify, as should gene therapy agents, for they typically involve recombinant viruses that deliver specific genetic materials to patients with critical gene defects. The first approval of a gene therapy treatment occurred in July 2012, when the European Medicines Agency (EMA) recommended Glybera® for lipoprotein lipase deficiency (the cause of severe pancreatitis). Although the first gene therapy experiment was approved in 1990, clinical successes over the past five years promise treatments for diseases of the immune system, blood disorders, and vision.

In contrast, modern antibiotics do not qualify as biologic medicines. Although initially described as substances produced by microorganisms that antagonize the growth of other microorganisms, antibiotics comprise hundreds of currently marketed drugs now categorized as small molecules. They were traditionally secondary metabolites, such as penicillin; synthetic compounds, such as sulfonamides, were excluded from this group. Many of the antibiotics available today, such as rifampicin, are semi-synthetic versions of natural compounds and are therefore not included among biologic medicines.

Other products originating from biological sources that do not qualify as biologic medicines include herbal medicines, naturopathic products, functional foods, and nutraceuticals. Although ingredient analyses and purity standards for these healthcare products are becoming increasingly sophisticated, they are not subjected to the same testing and regulations as pharmaceutical drugs. Certified biologics should be distinguished from these as they will have successfully passed through a gauntlet of pre-clinical, safety and clinical trials, earning recognition as bona fide pharmaceuticals.

What are biologics used for?

Traditional biochemical procedures were used to purify the first biologic drugs, such as gamma globulin from blood and insulin from animal sources. In 1977, the modern biopharmaceutical industry was founded when Genentech produced human somatostatin in bacteria. Since then, biologic drugs have been made through recombinant DNA technology for therapies in oncology, hematology, rheumatology, immunology, endocrinology, gastrology, and virology. For example, recombinant DNA technology has been used to develop current production systems for insulin (Humulin®), erythropoietin (Epogen®, Procrit®, Aranesp®, others), growth hormone (somatropin), and monoclonal antibodies (mAb).

MAbs and therapeutic proteins are the most important biologic medicines in a rapidly growing biopharmaceutical marketplace expected to reach between $140B to $220B by 2017[1, 2]. More than 200 therapeutic proteins and vaccines are available worldwide, with thousands more in development for treatments in all fields of medicine. To date, 31 mAbs have been approved by the FDA (www.accessdata.fda.gov/scripts/cder/drugsatfda/).

The next major expansion of the biopharmaceutical market will occur in the area of biosimilars (also known as follow-on biologics, and as subsequent-entry biologics in Canada), as patent protection is beginning to expire for many therapeutic proteins. Pharmaceutical companies entering this sector are expected to be able to offer generic versions of innovator biopharmaceuticals at prices discounted by 20% to 30%. In support of this, the Obama administration passed the U.S.

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"Patient Protection and Affordable Care Act" in 2010, creating an abbreviated licensure pathway for products demonstrated to be biosimilar or interchangeable with FDA-approved drugs.

Where are biologics headed in the future?

Subsequent entry biologics (SEB) have renewed competition in this area, causing "big pharma" companies to develop second generation biopharmaceuticals. Because of this, patients with disease indications that already have available drugs can anticipate seeing new entries with increased efficacy, safety, and reduced side-effects. These new drugs will, of course, come with renewed patent protection for big pharma and higher prices for patients due to development costs.

Antibody fragments offer a new platform for biologics development. As well as being cheaper to produce than full-size mAbs, these molecules may offer deeper tissue penetration and quick clearance after administration, making them ideal for the delivery of a toxic payload such as a radionuclide to the cells of a tumour. Because they can be developed with unique binding specificities against novel targets far more quickly than mAbs, they are also ideal components for personalized medicines. PlantForm Corporation (www.plantformcorp.com) has recently patented an innovative technology that rapidly creates fully functional antibodies using antibody fragments in a plug-and-play fashion (see the accompanying figure).

Fusion proteins have tremendous potential as biologic drugs. A classic example is etanercept (Enbrel®, approved in 1998), which combines an antibody constant region with a receptor for human tumour necrosis factor (TNF), making it capable of binding and subsequently clearing TNF from a patient, thereby reducing inflammation. As another example, the first bispecific antibody, catumaxomab (Removab®), was approved in the European Union in 2009; this biologic works by simultaneously binding a cancer epitope and a T-lymphocyte marker, bringing killer immunocytes together with target cancer cells. As the possibilities for such "designer" proteins are in theory limitless, new developments involving fusion proteins will be an exciting area to follow in the area of biologics.

Advances in immunology and related fields will lead to the development of biologics for the treatment of deadly diseases. For example, researchers at the National Microbiology Laboratory in Winnipeg and the University of Manitoba recently developed three mAbs that bind and attenuate the Ebola virus[3]. Antibodies and vaccines against other pathogens such as HIV, the cause of AIDS, are also under development in leading international laboratories, promising preventive and curative treatments for these devastating diseases.

Although the cost of modern biologics is generally quite high, with treatment regimens costing hundreds of thousands of dollars for some diseases, improvements in production methods will eventually lead to competitively priced drugs with wider availabilities. Plant-based production systems are less expensive to build and operate than mammalian cell bioreactors, the standard pharmaceutical system for biologics production, resulting in reduced production costs. Significant challenges remain to improve the manufacture, therapeutic efficacy, and global availability of biologics, yet in spite of these challenges, scientific discovery continues to drive the development of new and improved biologics through a pipeline that is providing new and exciting therapeutics for effective treatments of many medical diseases. ❖

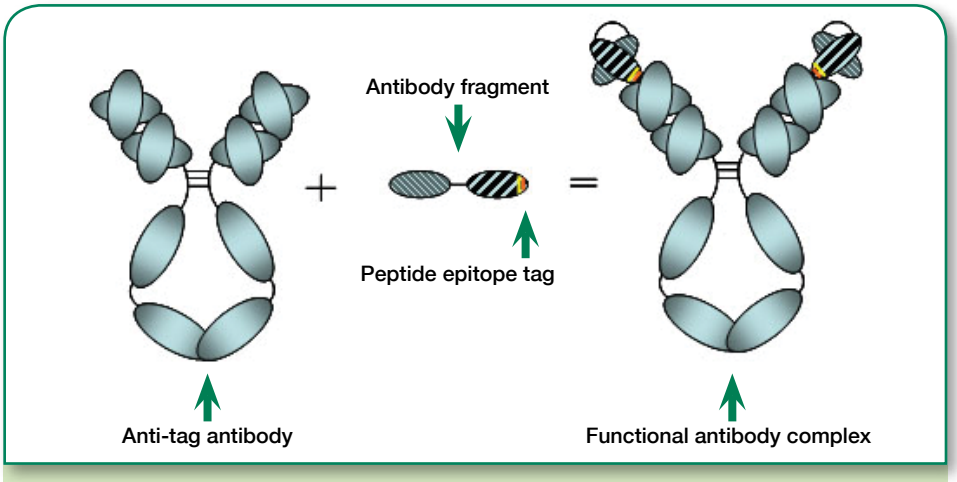

Figure: Plug-and-play customized antibody drugs are assembled by combining peptide epitope-tagged antibody fragments with an anti-tag IgG antibody. Antibody fragments (middle) are smaller, less expensive, and easier to develop and produce than full-size antibodies. PlantForm Corporation is working toward the development of customized or personal medicines by adding a specific peptide epitope tag (yellow and orange stripes) to antibody fragments and combining these with a dedicated anti-tag antibody (left) that binds the epitope. This combination re-creates fully functional antibodies (right) with unique affinities that are specified by the antibody fragments.

References:

1. PRNewswire, The Global Pharmaceutical Market is Expected to Mature to $220 Billion by 2016, in Spite of the Inclement Effects of the Healthcare Reform Bill. *Markets and Markets* (http://www.prnewswire.com/news-releases/the-global-pharmaceutical-market-is-expected-to-mature-to-220-billion-by-2016-in-spite-of-the-inclement-effects-of-the-healthcare-reform-bill-115001144.html) 2011.
2. GBI-Research, Therapeutic Proteins Market to 2017 – High Demand for Monoclonal Antibodies will Drive the Market. *ReportLinker* (http://www.reportlinker.com/p0610883-summary/Therapeutic-Proteins-Market-to-High-Demand-for-Monoclonal-Antibodies-will-Drive-the-Market.html) 2011.
3. Qiu, X.; Audet, J.; Wong, G.; Pillet, S.; Bello, A.; Cabral, T.; Strong, J. E.; Plummer, F.; Corbett, C. R.; Alimonti, J. B.; Kobinger, G. P., Successful Treatment of Ebola Virus-Infected Cynomolgus Macaques with Monoclonal Antibodies. *Science Translational Medicine* 2012, 4, (138), Published ahead of print 13 June 2012 138ra81.

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