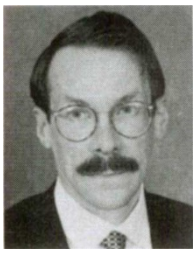
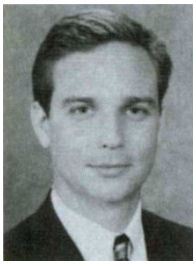
W. SCOTT HARKONEN
KEITH A. GREGG

Back to the future with polyclonal antibodies



W. Scott Harkonen is vice president of medical and regulatory affairs at Univax Biologics (Rockville, MD).



Keith A. Gregg is product manager at Univax Biologics (Rockville, MD).

Ten years ago, monoclonal antibodies (MAbs) were widely believed to have significant therapeutic advantages over conventional polyclonal antibodies. Yet over the past few years, it's the polyclonals that can boast the most success in clinical trials and subsequent approvals by the Food and Drug Administration (FDA, Bethesda, MD). In 1991, the FDA licensed MedImmune's (Gaithersburg, MD) CytoGam, a polyclonal for use in the prevention of cytomegalovirus infection. Two other polyclonals are currently under FDA review: MedImmune's Respivir for the prevention of respiratory syncytial virus infection and Univax Biologics' (Rockville, MD) WinRho SD for the treatment of idiopathic thrombocytopenic purpura. Numerous other polyclonals are either in or about to enter clinical trials. MAbs, however, have largely met with disappointment.

SPAs

MAbs are produced from transformed cell lines cultured in either mouse ascites or *in vitro* production systems. Polyclonals, on the other hand, are immunoglobulins purified from pooled human plasma and, consequently, are fully human proteins. Polyclonals derived from plasma obtained from nonimmunized donors are known as standard intravenous immunoglobulins (IVIGs). Polyclonals derived from plasma selected for high titers of antibodies specific for a particular antigen, or from persons specifically immunized with a vaccine containing that antigen, are known as specific IVIGs or specific polyclonal antibodies (SPAs).

SPAs hold a distinguished place in the history of medicine. The earliest of these products—most of which were derived from immunized animal sera—were the first antiinfectious agents capable of targeting specific diseases, the first so-called "magic bullets." Polyclonal antitoxins for diphtheria and tetanus infections were introduced in the 1890s by Emil von Behring, and a number of other preparations quickly followed. These early preparations established themselves as effective agents for neutralizing viruses and toxins, as well as for enhancing bacterial opsonophagocytosis. Years later, polyclonal antilymphocyte globulins were shown to be effective immunosuppressive agents for use in organ transplantation.

For his contributions to the field of passive immunotherapy using polyclonals, in 1901 von Behring received the first Nobel Prize ever awarded in Physiology or Medicine. For the next 50 years, until the introduction of antibiotic therapy, polyclonals remained the primary method of treatment for and protection from serious infectious disease.

It wasn't until the 1940s, when Edward Cohn, a Harvard University (Cambridge, MA) professor, developed a process to fractionate immunoglobulin from human plasma that human polyclonals became available. The Cohn process remains the most common production process today, although newer column-fractionation processes are being introduced. To date, over 19 different polyclonal products are licensed for use in the U.S., with annual sales of $350 million.

So if polyclonals are already well established, why the renewed interest now? There are several reasons. First, advances in antibody-purification methods now allow these products to be administered intravenously, making it possible to deliver higher doses than was possible with the older intramuscular formulations. Second, advances in immunization research have produced a number of new vaccines, some of which are being used as immunizing agents to generate high titers of antibodies in plasma donors, thereby opening up the possibility of a number of new SPAs.

Another feature of SPAs generating interest is the ability to use these agents prophylactically to prevent disease, as well as in treatment. This is possible because of the prolonged half life of SPAs in the circulation of fully three to four weeks. As a result, high-risk patients can be protected from infection for up to a month following a single administration of SPA. MAbs, in contrast, are often cleared from the circulation in a matter of hours or days, severely hampering their use in long-term prophylaxis. Furthermore, because SPAs are true human antibodies, they do not elicit undesirable immune responses after repeated doses.

Safety

Potential clinical applications of SPAs, for which there are products currently in development, include postexposure immunoprophylaxis of HIV infection following occupational exposure, protection against *Staphylococcal aureus* infection in severe trauma victims, prevention of sepsis and bacteremia in intensive-care patients, and blockade of allergic symptoms following exposure to allergen. Another SPA under development is targeted against the *Pseudomonas aeruginosa* infections that plague patients with cystic fibrosis.

In 1990, a Consensus Development Conference sponsored by the FDA and the National Institutes of Health (Bethesda, MD) was convened to review the safety and efficacy of human polyclonals. It concluded that these products are safe, based on over 40 years of clinical use. There has been no documented transmission of either hepatitis B or HIV from polyclonal products currently licensed in the U.S., unlike the experience with Factor VIII and Factor IX. Nonetheless, the collection and processing of polyclonal plasma are highly regulated by the FDA, and as an additional "fail safe" precaution against a new, unknown viral contaminant, many manufacturers voluntarily include a virus-inactivation step in their production process.

The future for SPAs looks promising. The growing, worldwide problem of bacterial resistance to antibiotics is leading to an increasing demand for alternative methods to prevent and protect against infectious diseases. In addition, the changing health-care environment will place a greater emphasis on approaches to disease prevention, such as vaccines and SPAs. ///