Polyclonal antibodies step out of the shadows

After decades in the shadow of monoclonal antibodies, therapeutic polyclonal antibodies are undergoing a renaissance. The first recombinant human polyclonal antibodies to enter the clinic could spearhead a new generation of antibody treatments. The new-generation antibodies that are taking advantage of the latest technologies may offer therapeutic advantages over monoclonals or existing polyclonal therapies. But companies will have to overcome production and regulatory hurdles before they get very far into clinical development.

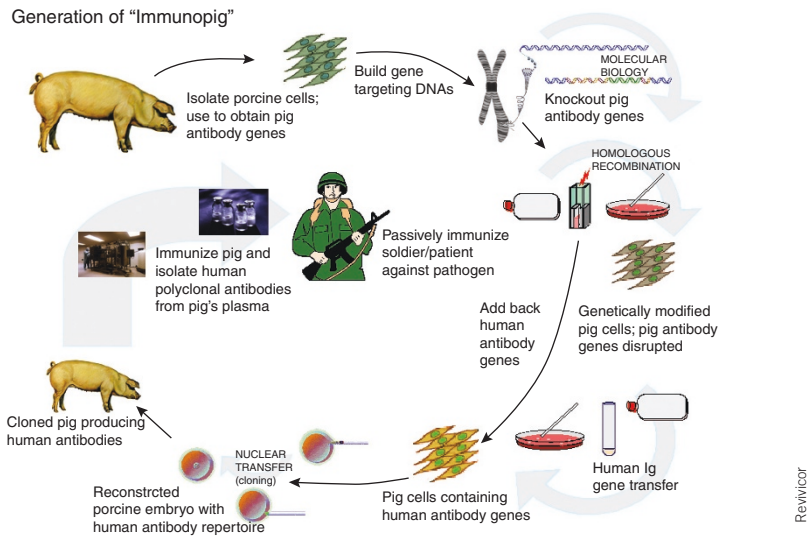
Ever since the discovery in the 1970s and 1980s of hybridomas and ways to recombine and amplify DNA, monoclonal antibody therapies have been in the ascendancy. But the inability of monoclonals to address targets that mutate or require binding at multiple sites has left market opportunities for polyclonals.

"The body's natural reaction to antigens is polyclonal, so it's not a question of will they work," says Jacqueline Sharon, a pathologist at Boston University School of Medicine. The key is "to produce them in a standardized and unlimited way. Once you get that, there's no question they will work."

Over the past century or so, the traditional way of obtaining polyclonal antibodies, so-called immunoglobulin therapies, involves the harvesting of immunized human or animal serum, which is of limited supply. Polyclonal antibodies derived in this manner also can be associated with serious toxicities (serum sickness) and the risk of transmitting infections.

Biotech companies are addressing these problems via two radically different approaches. The first and most advanced, which is the basis for Copenhagen-based Symphogen's business, involves isolating the variable light and heavy (VL-VH) region of gene pairs from antibody-producing plasma cells harvested from the sera of immune individuals, screening these phage-displayed Fab pairs against target antigens, and transferring the resultant selected pairs to a mammalian vector containing the requisite immunoglobulin constant (C) region genes to enable production of functional antibodies.

The key to Symphogen's technology is maintaining consistent composition with every batch of their product, says John Haurum, CFO. To do this , the company has developed a mammalian expression vector that transfers the antibody genes into the exact same genomic site in the Chinese hamster ovary cells used in manufacture. And since "not all antibodies are good," says Sharon, "the technique allows you to pick out the great antibodies and eliminate any deleterious antibodies." Symphogen has partnered with London-based AstraZeneca to develop what could be the first recombinant human polyclonal antibody thereapy.



Description of Revivicor's technology to produce polyclonal antibodies in pigs.

But for some experts it's not clear yet that Symphogen's technique will pass regulatory authorities' standards for consistency. "The authorities are going to ask them to characterize the antibodies individually," says Yann Echelard, vice president of R&D at GTC Biotherapeutics in Framingham, Massachusetts. If they can't put the same amount of each antibody into every dose, "that's a showstopper for getting approved," he says. Although Symphogen's product is at preclinical stage, scientists may begin clinical trials as early as November 2006, Haurum says.

The second innovative approach to producing polyclonal antibodies involves the application of gene targeting/nuclear transfer (cloning) technology in animals to replace partially or completely animal immunoglobulin genes with analogous genes from humans (see scheme above). At least four companies (**Table 1**) are following this line of research, which for large animal systems still faces some technical challenges: cows, pigs and rabbits still produce part animal, part human antibodies. Scientists say that by knocking out more genes, or knocking out key parts of the genes, the animals can produce a greater percentage of fully human antibodies.

A potential drawback of this second approach is that the animal serum containing the antibodies may transmit animal diseases or other contaminating materials, requiring expensive purification processes. "These technical issue need to be resolved," says Echelard. "Once they achieve that, the real work will start as they focus on finding an indication and a clinical strategy.

Emily Waltz, New York

Table 1 Selected companies producing polyclonals in animals

Company Name	Bioreactor	Gene targeting
Hematech, (Sioux Falls, South Dakota), a subsidiary of Kirin Brewery (Tokyo)	Cows	Artificial chromosomes carrying human antibody genes are transferred to bovine fibroblasts in which endogenous immunoglobulin genes have been inactivated.
Medarex	Mice	Mouse antibody genes inactivated and replaced with human antibody genes.
Revivicor, (Blacksburg, Virginia)	Pigs	Researchers knock out one allele of each antibody-encoding gene in a somatic cell and replace it with a human gene.
Therapeutic Human Polyclonals (Mountain View, California)	Rabbits	Insertion of only key segments of human antibody gene sequences.