Resurgent Interest in Plant-Based Vaccines, Monoclonal Antibodies

Jeffrey L. Fox

After technical strategies for using plants to produce vaccines, monoclonal antibodies (mAbs), or other therapeutic or protective proteins and glycoproteins improved during the past decade, enthusiasm for these newer approaches grew because the products are proving effective, according to several proponents of this technology who spoke during the 2014 ASM Biodefense and Emerging Diseases Meeting, held last January in Washington, D.C.

An earlier dream of engineering genes encoding antigens into banana plants, from which to harvest edible vaccines to protect children against various diseases, is pretty much discarded, according to Charles Arntzen of Arizona State University in Tempe, who formerly embraced that dream. Instead of bananas, tobacco is now the preferred plant for production purposes, and greenhouse-grown tobacco plants are being genetically engineered to make plentiful, easy-to-harvest antigenic proteins, glycoproteins, and mAbs, he says.

These efforts were boosted several years ago through a “pioneering” investment from the Defense Advanced Research Projects Agency (DARPA), with resources going to universities such as Texas A&M and companies such as Medicago R&D in Quebec City, Quebec, Canada, and Kentucky Bio-Processing (KBP) in Owensboro, Ky., Arntzen says. Engineered tobacco plants go “into a death spiral” when the foreign proteins they are making peak. Plants then are harvested, and those antigenic proteins are purified—in ways that are “more cost effective” than for comparable material recovered from animal sources, he says. For example, the KBP production cycle takes about five weeks at a cost of $1 million, yielding enough good manufacturing practices (GMP)-quality material for a phase 1 clinical trial.

Several facilities are making a variety of GMP vaccine material, according to Vidadi Yusibov of Fraunhofer UAA Center for Molecular Biology in Newark, Del. He and his collaborators are developing a hemagglutinin protein as part of an influenza vaccine that is “no different from the standard egg-produced” vaccine, he says. In a phase 1 clinical study, this plant-produced material “raised no safety issues,” and the immunogenic responses were “quite adequate and comparable to the [conventional flu vaccine].”

Another alternative approach to making flu vaccines entails producing virus-like particles (VLP) in plants from the tobacco family, according to Mark-André D’Aoust of Medicago R&D, which was acquired last year by Mitsubishi Tanabe Pharma. The company is developing candidate flu vaccines geared to protecting against several circulating strains, including H5N1 and H7N9, he says. These experimental vaccines are well tolerated by mice, in which they induce both antibodies and cellular immune responses. The vaccines are advancing into phase 1 and 2 clinical trials.

In yet another approach, plants are being used to produce protective or therapeutic mAbs, including as agents for treating infections caused by Ebola virus, according to Gene Olinger Jr. of the National Institute of Allergy and Infectious Diseases facility in Fort De-
Surprise: Thioredoxins from Plants Found in Anaerobic Methanogen

Barry E. DiGregorio

Archaeal methanogens began producing thioredoxin (Trx) regulatory proteins, several of which are active in regulating physiology in green plants, long before photosynthesis arose, according to Biswarup Mukhopadhyay from Virginia Polytechnic Institute and State University in Blacksburg and his collaborators there and at the University of California, Berkeley. “Our work raises the possibility that Trx functioned in a complex redox regulatory network in anaerobic prokaryotes at least 2.5 billion years ago,” they note. Details appeared February 6, 2014 in the Proceedings of the National Academy of Sciences (doi:10.1073/pnas.1324240111).

In plants, Trx helps to regulate several fundamental processes, including the turning on and off of photosynthesis, growth and flowering, and development and germination of seeds. For the far more ancient archaeal methanogen *Methanocaldococcus jannaschii*, Trx helps to synchronize cellular processes, including methane production, Mukhopadhyay and his collaborators report. “Our work suggests that methanogens use a thioredoxin-based system for synchronizing metabolism with the availability of low-potential electrons such as those available from hydrogen, which they use for energy production,” he says. In that sense, this regulatory activity resembles what occurs in green plants during photosynthesis—when “light is used to generate low-potential electrons,” he adds. “Because methanogenesis developed before the oxygenation of Earth, it seems possible that Trx functioned…independently of oxygen, thus raising the question of whether a complex biological system of this type evolved at least 2.5 billion years ago.”

The concept that extant methanogens may contain biochemical strategies and motifs that provide a window into metabolism prior to the rise of oxygen is really attractive, but has been tricky to test independently using the geologic record,” says geobiologist Woodward Fischer of the California Institute of Technology in Pasadena, Calif. “Based on their work, one can imagine thioredoxin chemistry could have played diverse roles in anaerobic organisms prior to the rise of oxygen, including [providing] protection against tiny amounts of oxygen produced abiotically on the early Earth. We commonly think of redox stress as oxidative stress, but before the rise of oxygen, a bigger problem was how quickly cells could get rid of electrons.”

*M. jannaschii* and other methanogens are “extremely vulnerable” to oxygen, Fischer continues. “Protection from even intermittent oxygen is a much bigger problem for methanogens.”

Recent developments involving tuberculosis (TB) include:

- In March, Aeras of Rockville, Md., announced a clinical trial, enrolling nearly 1,000 adolescents in South Africa, to evaluate whether its experimental vaccine, H4, a fusion protein consisting of two antigens from *Mycobacterium tuberculosis* and the adjuvant called IC31, can prevent infections caused by this bacterial pathogen.
- Several synthetic antimicrobial peptides were effective at killing *M. tuberculosis* in vitro, albeit not as potently as kanamycin, according to George Belfort of Rensselaer Polytechnic Institute in Troy, N.Y., and his collaborators. He spoke during the March 2014 meeting of the American Chemical Society in Dallas, Tex.
- Between 2000 and 2010, TB prevalence fell by 57% in China—in large part due to a “massive scale-up” of the directly observed, short-course therapy strategy, according to Yu Wang from the Chinese Center for Disease Control and Prevention in Beijing, China, and his collaborators. Details appeared 18 March 2014 in The Lancet (doi:10.1016/S0140-6736(13)62639-2).
- About 1 million children in the United States develop TB annually (with about 32,000 of those cases being multidrug-resistant)—twice the number previously thought, according to Ted Cohen of Brigham and Women’s Hospital and Harvard Medical School in Boston, Mass., and his collaborators. Details appeared 23 March 2014 in The Lancet (doi:10.1016/S0140-6736(14)60195-1).