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Plant Expression Systems Growing Rapidly

Use of the Technology for Vaccine Manufacture Leads the Way Toward Commercialization

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Most biotech professionals are aware that plant-based expression systems hold promise for cost-effective commercial-scale manufacture of recombinant proteins. But relatively few realize how near commercialization many of these are. With truly global, one-billion-doses-per-year-scale manufacturing facilities now under construction for influenza virus and other vaccine manufacture, these products have the potential to rapidly change the expression system landscape.

Plant expression systems are becoming practical alternatives to the standard expression systems that have been used for several decades for biopharmaceutical manufacture. As plant-based recombinant protein, particularly vaccine, manufacture comes online, this will change many of the current industry paradigms. Despite the advances, few in the biotech industry are familiar with plant expression systems and their advantages.

This is partly evidenced by the relatively few companies exploring these technologies for commercial production. BioPlan's recent survey of biopharmaceutical manufacturers reported that only 14% of respondents expected to increase manufacturing in the next five years using plant expression systems and only 10% projected expanding manufacturing capacity by >100% in the next five years using plant expression systems.

According to the study, most companies planning future capacity expansions report that their focus will continue to be on familiar mammalian cell, bacterial, and yeast expression technologies. Many will not look beyond these for regulatory reasons or simply due to inertia borne from unfamiliarity.

There are a large number of plant expression systems in various stages of development and commercialization available for licensing. This includes plants and technology platforms such as bioreactor culture of plant cells, algae, and moss; plants grown hydroponically or otherwise within greenhouses or other closed facilities; and common food crops and other plants grown in open fields.

New technologies are increasingly allowing customization of transformed plant cells for growth in culture or as whole plants, including knocking-out of plant genes related to plant-specific glycosylation of proteins capable of causing immune responses in humans and splicing-in of human and other glycosylation genes, allowing humanization or expression of human-like, nonimmunogenic recombinant proteins.

The first wave of plant-expressed proteins are expected to be vaccines either expressed in plants grown hydroponically or otherwise within greenhouses or controlled fields and plant cell culture. This is due to concerns about genetically modified (GM) plants cross-pollenating and/or being mixed with non-GM food crops, particularly in Europe. Cell culture and growth indoors or on secured outdoor fields are expected to present fewer environmental and public concerns than pharmaceuticals manufactured in traditional methods in food crops.

There are potentially significant cost savings through these plant-based technologies for manufacture of recombinant proteins. The costs of goods and the manufacture of recombinant proteins in most plant systems tend to be lower than that for conventional recombinant protein manufacture.

Much as with high-yield conventional recombinant protein manufacturing technologies, as upstream yield increases and costs decrease, downstream purification costs generally increase. Methods for pharmaceutical-grade purification of proteins from plants has lagged behind those associated with conventional recombinant methods, but improved large-scale plant protein purification technologies are maturing and will likely be available when needed.

The first commercial uses of recombinant protein technologies sometimes show up initially in veterinary vaccines. In January 2006, the USDA approved the first plant-made vaccine, Concert, from Dow AgroSciences. This is a recombinant Newcastle disease (poultry) vaccine manufactured from viral antigen expressed from culture of transformed tobacco plant cells.

Today, vaccines are the leading class of products involved in the commercialization of plant expression technologies. Many vaccines are currently in development. These are being led by influenza vaccines, with multiple world-scale manufacturing facilities now under construction.

As these technologies progress, plant-expressed vaccines are likely to have a substantial impact on the industry, and may ultimately change many of the current biopharmaceutical industry preferences for recombinant (glyco)protein manufacture.

Much of the funding for commercialization of plant expression technologies is originating from governments that realize that current vaccine technologies are inadequate. The U.S. government is the primary funder of new plant-based recombinant protein manufacturing technologies, particularly for influenza vaccine manufacture.

With conventional influenza vaccine manufacture primarily involving relatively slow and costly culture in vast quantities of chicken eggs, a method not capable of supplying the needs of major developed countries to immunize their populations, alternatives are being funded.

New manufacturing technologies for influenza and biodefense vaccines are needed to meet the rapid manufacture of vaccines. These technologies must be scalable to unprecedented levels, possibly as much as hundreds of millions of doses per week, to cover developed and developing countries' needs in case of a serious pandemic threat. It is the need for rapid production that is driving the development of many plant expression systems.

Companies developing commercial-scale plant expression systems have certain advantages over conventional technologies. They have been able to design manufacturing systems from the ground up, allowing incorporation of the latest and most cost-effective technologies, avoiding many of the limitations and legacy aspects of fermentation-based technologies.

Plant-expressed versions of many other vaccines can be expected to be developed in the future. This will include vaccines for diseases currently lacking any vaccine or for which the costs restrict access to a relatively affluent few. For example, some plant expression systems, similar to insect cell-based systems, do a very good job of expressing viral subunits that self-assemble into virus-like particles.

Once plant-based influenza and other vaccines come online, this is likely to cause a shift in vaccine manufacture, as the current virtual monopolies of a few companies making most of the world's vaccines are challenged. It is possible that new manufacturers may begin selling vaccines that may cost pennies to manufacture. Thus, more vaccines may become cheap commodity products.

Complementing this, new vaccine funding that comes through government and nongovernment organizations will require that vaccines be made available at unprecedented low costs. Plant expression technology is readily transferrable and is already on track for worldwide dissemination (licensing), unlike most recombinant technology that has largely been restricted to major developed countries.

Vaccines are currently a $20 billion/year industry, with many analysts projecting growth to $35 billion in five years. However, a few major pharma firms currently manufacture the great majority of the world's vaccine supply, and this is one of the reasons governments and philanthropies are sponsoring alternative manufacturing systems.

Eventually, due to the need for low-cost vaccines, much of the world's vaccine manufacturing capacity may be plant-based. New vaccines for diseases, for which none are currently available, will increasingly be manufactured in plant-based systems, with low manufacturing costs being irresistible compared to alternative manufacturing methods. Further, plant-based vaccines eliminate concerns about the risks associated with the use of animal-derived components in manufacture.

Eventually, greater proportions of vaccine manufacture may migrate to plant-based manufacture. This includes not just the current 12 commercial recombinant vaccines in either the U.S. or European markets, but more importantly recombinant versions of the ~85 nonrecombinant vaccines currently in these markets will likely be developed.

So far, the major international pharmaceutical and established biotechnology business model companies have largely avoided involvement in plant expression systems. This is expected to change, however, as these technologies mature and plant-expressed products enter the markets.

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