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editorial

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Can plant expression solve the biologics production dilemma?

The biologics sector is booming with over 1000 products in clinical development but bringing these to market is by no means straightforward. Along with regulatory challenges, production of biologics has traditionally been risk averse due to the high cost and impact of failure. However, significant pressure to reduce time to market and cost of production is now resulting in the emergence of new disruptive expression platforms.

The concept of using plants to produce recombinant proteins, sometimes referred to as plant molecular farming (PMF) or pharming (PMP), has been around as a nascent field for many years. Human growth hormone, initially produced in tobacco and sunflower in 1986, was the first-plant-derived recombinant therapeutic protein. By 2011, more than twenty PMF pharmaceuticals were in preclinical or clinical trials. Several are already on the market, including Elelyso, a plant-produced enzyme replacement therapy for Gaucher's disease.

Although plant expression represents a promising system for the production of human pharmaceutical proteins which is fast, low cost and easily scalable, the technology has historically been held back by the significant underfunding for research and development, as the industry instead focused on improving the safety profiles and yields of mammalian and bacterial systems. This is unsurprising, as all of the first biologic drugs were produced in these systems, and because pharma and biotech have invested heavily in developing them to meet the understandably strict regulatory requirements.

Recent advances in plant biotechnology have led to the emergence of PMF as a commercially viable next-generation platform that can offer substantial benefits to the industry. In the past, taking the leap of switching to plant-based systems posed too much of an economic and financial risk. Now that the technology has matured, the advantages of its low capital costs, rapid expression, and high scalability are increasingly hard to ignore.

One of the key milestones in the technology's maturation has been the development of transient expression systems capable of producing high levels of RNA transcription and protein translation. This has enabled high yield, scalable production of pharmaceuticals and non-pharmaceutical products, turning plant-based production systems into a practical, cost effective, and competitive choice for the development of vaccines, antibodies, and enzymes.

Leaf Expression Systems is one such innovator. The sole UK manufacturer currently producing biopharmaceuticals in plants, Leaf is a spin out company from the John Innes Centre on the Norwich Research Park. It was set up in 2017 to commercialise Hypertrans®, a technology developed in 2007 by Professor George Lomonossoff, who was awarded the BBSRC Innovator of the Year award in 2012 for his work.

While traditional plant-based technologies are based around the generation of stable transgenic plants, a process that can take anywhere from several months to years to establish plant lines, Hypertrans® is a transient expression system, making it much faster and more agile as a production platform.

Transient expression enables the production of significant quantities of proteins, vaccines or biomolecules within 12 weeks

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of elucidating the gene sequence of the desired protein. The gene is cloned into the expression plasmid, which is then transferred to *Agrobacterium*, which can naturally transfer DNA to plants. The *Agrobacterium* is vacuum infiltrated into the plant leaves where it transfers the gene to the plant. The gene is then expressed by the plant to produce the protein in its leaf tissue. The plant leaves are harvested and blended, and the proteins are extracted and purified based on their biochemical properties using traditional chromatographic techniques.

The plants grow rapidly, infiltration is a simple process, and within a week or two of the plants being infiltrated the product can be harvested and purified. Plant-based systems also have the advantage of not using any animal-based products in the manufacturing process – either upstream or downstream, removing a considerable regulatory concern over product purity and potential adventitious infection of patients.

Any protein-based drugs could potentially be produced in plants. For example, Leaf has recently produced several therapeutic antibodies, including an HIV antibody and a bevacizumab (Avastin) biosimilar to further exemplify the technology. Another example is Medicago's plant-expressed flu vaccine, currently in Phase 3 clinical trials. Leaf is about to launch a new online product catalogue allowing customers to buy a range of plant-produced research proteins directly from the website for the first time.

Due to the inherent scalability of plant-based protein production, combined with the transient nature of the system, it is the ideal platform for antibody and vaccine generation where speed is essential. The adoption of this technology would enable industry to respond much more rapidly to disease outbreaks where a transient solution contains the outbreak while big pharma develops more permanent solutions, as was recently exemplified during the 2014 Ebola outbreak where the plant-produced antibody combination, Zmapp (Mapp Biopharmaceutical), was deployed.

Compared with mammalian or microbial systems, where scale-up can often be problematic, the benefits in terms of speed, simplicity, regulatory compliance and sheer predictability are substantial. The plants can be grown in controlled growing rooms, greenhouses, or in the field, making scale-up simple as production can easily move from lab (μg - mg) to pilot (mg-g) to industrial scale (g-kg) when required. The plants themselves (Leaf Expression Systems uses *Nicotiana benthamiana*, a close relative of the tobacco plant) are cheap, easy to cultivate, and have efficient biomass production.

The technology also supports the 'fail fast' principle for potential drug candidates. Plant systems can quickly provide adequate quantities to conduct initial studies, enabling organisations to make critical decisions regarding which actives to terminate and which ones to proceed with. Plant molecular farming is significantly more cost-effective than established mammalian or microbial systems, facilitating R&D throughput and accelerating novel drugs both into the clinic and, eventually, the market. Such acceleration to market has a significant impact by generating additional revenues from an extended patent life.

Plant molecular farming has finally come of age, and the major hurdle it now faces is the conservatism of the sector. As more and more plant-produced biopharmaceuticals make their way through the developmental and regulatory pipeline, we should expect to see renewed interest and acceptance of plant expression as a revolutionary new tool for biologics production.