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Plant-derived vaccines

Quebec-based Medicago is transforming the use of plant-based technologies to rapidly develop and produce novel vaccines and therapeutic proteins.

Plants are among the world's most prolific protein producers; in contrast to protein production via cell cultures or eggs, which is relatively complicated and time-consuming, plants express proteins of varying complexity and glycosylation patterns with high efficiency. So Medicago, a clinical-stage biopharmaceutical company located in Quebec, Canada, is harnessing a plant-based transient expression process to produce pharmaceutical-grade proteins in a matter of weeks.

"Compared to alternative production systems, our proprietary plant-based manufacturing platform has many advantages, including faster lead time, scalability and versatility," said Nathalie Charland, Medicago's senior director of scientific and medical affairs. "The rapid nature of our vaccine and therapeutic protein production unlocks many potential ways in which we can better respond to infectious diseases and public health challenges."

Medicago's production process starts with the synthesis of genetic sequence coding for a particular protein. This sequence is then introduced into *Agrobacterium tumefaciens*, a bacterial vector that can transfer genetic material to plants only. The plant in question, *Nicotiana benthamiana*, is a close relative of tobacco indigenous to Australia, has a fast growth rate, is a non-food crop, and is easy to work with. It is dipped into a bath of the modified *Agrobacterium*, which, with the assistance of a vacuum, is soaked up by the plant. The *Agrobacterium* transfers the genetic material into the leaf tissue, which then produces and accumulates the recombinant product for 6–8 days. At this point, the leaves are harvested (**Fig. 1**) and the proteins are extracted and purified under pharmagrade conditions.

"There is no risk of introducing mutations that can impact vaccine efficacy and it takes only 5–6 weeks for Medicago to produce a clinical-grade vaccine this way, compared to 4–6 months for egg- and cell-based production methods," said Charland. "While the speed and accuracy of the system are ideal for vaccines, our plant-based platform is extremely versatile and can be used for producing all sorts of therapeutic proteins, such as monoclonal antibodies."

Fig. 1 | Plants being harvested at the Medicago production facility in Durham, North Carolina.

Medicago's lead QIV

Medicago's lead product is a quadrivalent influenza vaccine (QIV) that is currently in phase 3 trials. The QIV is produced as virus-like particles (VLPs) consisting of a lipid bilayer studded with disease-specific protein antigens. Mimicking the native structure of viruses, VLPs are better recognized by the immune system—their size, structure, and repeated antigen patterns prompt an improved immune response compared with that initiated by split or recombinant subunit vaccines. But because they do not contain the core genetic material, they are noninfectious and unable to replicate. "VLPs are an exciting approach to vaccine development," said Charland. "Unlike current influenza vaccines that are manufactured using a live virus, VLP-based vaccines do not require an actual sample of the infectious agent, just the genetic sequence of its proteins. In addition, plants used for their manufacture are not susceptible to external threats such as avian flu, which can significantly impact the production of egg-based vaccines."

Clinical studies in more than 2,800 people have shown that Medicago's QIV safely triggers multiple aspects of the immune response, inducing broader/stronger immunogenicity than that achieved with a different licensed vaccine and potentially protecting against drifted strains. The QIV, which would be the first human plant-derived vaccine on the market, is expected to be available in time for the 2020–2021 Northern Hemisphere flu season, after completion of an ongoing phase 3 efficacy study in 10,000 healthy adults.

Significant platform potential

Rapid and accurate production of vaccines and therapeutic antibodies is critical for an effective response to health threats before they become global pandemics. Medicago is well positioned to help government agencies by rapidly delivering key vaccines and developing antibodies against infectious pathogens.

Once the genetic sequence from a pathogen has been isolated, protein production can usually be started within just a few weeks, rather than months. And unlike that of conventional bioreactors, the capacity of the plant-based system is eminently scalable—10,000 plants require the same growth conditions as just one, and greenhouse-based manufacturing facilities can be built quickly and economically to meet urgent or growing needs. Medicago currently has a pilot production facility at its headquarters in Quebec City, and a fully automated greenhouse and state-of-the-art extraction and purification unit in Research Triangle Park in North Carolina, USA. A new facility soon to be under construction in Quebec will increase production capacity substantially, to up to 50 million doses of QIV per year, thus demonstrating Medicago's capability to address emerging diseases.

Meanwhile, the company has an aggressive discovery and development program aided by its VLP*Express* high-throughput screening platform, which enables the rapid expression, purification, and testing of candidate proteins. In what is essentially a scaled-down version of the plant-production process, up to 200 target proteins a week can be expressed in a handful of plants, purified, and screened to identify the best candidates for further investigation. The platform has allowed Medicago to investigate VLP vaccines for more than 20 targets—among them rotavirus, norovirus, pandemic flu, West Nile virus, and hepatitis B—and is enabling the development of a range of other products, including monoclonal antibodies for immunotherapies.

Medicago is keen to expand its portfolio in infectious diseases, oncology, and neurodegenerative diseases, and is open to evaluating different partnership options in those fields. "Our versatile platform can be applied to many different areas," said Charland. "The opportunities are limitless."

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