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Investment critical for lucrative plant-based vaccine market

University of Cape Town (UCT) scientists, who spent two decades researching plant-made vaccines before turning their attention to COVID-19 when the pandemic hit, have successfully reported the expression of the near-full length SARS-CoV-2 spike vaccine in plants.

This work leverages recent advances in the Biopharming Research Unit (BRU) to produce viral surface glycoproteins in plants, by providing elements of the human intracellular folding machinery. This strategy forms part of a new research initiative to develop novel approaches to producing vaccines against emerging viruses in plants.

Their recent work, shared as a preprint entitled *Calreticulin co-expression supports high level production of a recombinant SARS-CoV-2 spike mimetic in Nicotiana benthamiana*, is proof-of-concept that their technology platform can be applied to producing a vaccine for an emerging virus, like SARS-CoV-2.

Cheaper, faster, safer, scalable

However, without the critical investment necessary for further development and to move their research beyond the laboratory, its potential is unlikely to be realised.

"With sufficient investment and development we could actually have a vaccine platform to service the needs not only of South Africa, but also of the continent," says UCT postdoctoral scientist and lead author on the paper, Dr Emmanuel Margolin, stressing that plants offer a potentially cheaper, faster, safer and highly scalable means of producing pharmaceutically-relevant proteins.

Typically, modern virus vaccines are produced in mammalian cells, which is highly expensive and requires the kind of infrastructure that is mostly absent in developing countries. This makes plant-based vaccine manufacturing an increasingly attractive alternative, Margolin points out, as both the infrastructure and the costs to scale up production are potentially lower.

Margolin and his co-authors released the paper on the preprint server *bioRxiv* in June last year, due to the potential impact of their findings on what was by that time a global race to produce a COVID-19 vaccine.

For the study, Margolin and his co-authors studied the production of a SARS-CoV-2 spike mimetic in *Nicotiana benthamiana*, an Australian tobacco-related species widely used in the field of plant virology.

Explaining their motivation, Margolin says that plant-based subunit vaccine production has long been viewed as a cheaper alternative. However, when compared to mammalian cells,

low expression yields and differences along the secretory pathway have impeded the production of certain viral glycoproteins which have potential as vaccines.

Important proof-of-concept may develop platform for emerging viruses

While their recent work has dramatically improved the production of many viral surface proteins in plants, they are also developing approaches to modify glycosylation and support processing events which may not otherwise occur adequately in plants, he adds.

"Our ongoing research is examining why it is so difficult to produce surface proteins of virus in plants. In many cases, the level of viral glycoproteins accumulation is too low for it to be feasible, and in some cases protein folding may not be optimal. Our approach has been to identify bottlenecks in the plant system, and then to systematically fix them by introducing human folding machinery into the plant," Margolin explains.

Margolin's work has shown that some of the folding proteins in plants are different, and that calreticulin is often a significant bottleneck to high level expression of many viral surface proteins in the system.

"We observed that when we expressed the calreticulin at the same time as the viral glycoprotein, we elevated the levels of production by, in some cases, as much as 10- to 20-fold," he reveals.

In short, they demonstrated the potential of molecular engineering to boost the production of viral glycoproteins in plants, while supporting the feasibility of plant-based production of SARS-CoV-2 spike-based vaccines.

"This was an important proof-of-concept because our work was ultimately trying to develop a platform that we can use for emerging viruses," Margolin says.

Lucrative plant-based vaccine market

In October 2020, a Japanese company launched Phase 1 clinical trials for its plant-derived norovirus vaccine, while two months later, a United States (US) bioprocessing company announced its plant-based COVID-19 vaccine was entering Phase 1 clinical trials.

Margolin says UCT's approach is slightly different from the work being conducted in Canada and the US: "We're trying to support production in plants by engineering the folding machinery, which makes our work unique. It's a lucrative investment opportunity, considering that one estimate predicts that the plant-based vaccine market will rise from $40 million to $600 million over the next seven years."

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Issued by: UCT Communication and Marketing Department

Ridovhona Mbulaheni
Media Liaison Assistant
Communication and Marketing Department
University of Cape Town
Rondebosch
Tel: (021) 650 2333
Cell: (064) 905 3807
Email:ridovhona.mbulaheni@uct.ac.za
Website: www.uct.ac.za