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Received: February 04, 2013**Published:** April 30, 2013**Citation:** Hefferon KL. (2013). Can plant-derived vaccines improve global human health?, Int J Virol Stud Res, 1(1e), 1-2.**doi:** <http://dx.doi.org/10.19070/2330-0027-130001e>

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Plants offer great advantages as production platforms for vaccines, antibodies and other biopharmaceutical proteins. Plant-derived vaccines provide an alternative to conventionally-made vaccines by enabling delivery to be safe and effective through the oral consumption of edible plant tissue. Since a large number of infectious diseases enter the body through mucosal surfaces including the gut, vaccines which can be expressed within edible plant tissue present a select advantage. Not only do the plant tissues act as the delivery vehicle, they protect the antigen as it passes through the harsh environment of the gastrointestinal tract. Another advantage lies in the fact that, in contrast to bacterial expression systems, plants are capable of producing recombinant antigens that undergo post-translational modifications which resemble their mammalian-derived counterparts. Moreover, the cost of producing proteins from plants is only a fraction of the cost of proteins produced from comparable mammalian cell culture systems.

Proteins derived from plant expression platforms may subtly differ from analogous mammalian cell cultures in terms of their respective glycosylation profiles. It is important to note that many mammalian therapeutic proteins are in fact glycoproteins and possess glycosylation motifs which are absent from plants. In addition to this, differences in glycosylation profiles between plant and mammalian expression systems may lead to adverse effects such as increases in allergenicity. Plants can be glyco-engineered to more closely resemble their mammalian counterparts; this can be accomplished by altering glycosylation pathways which are found exclusively in plants and by incorporating in their place the necessary glycosylation pathways which prevail in humans. Therapeutic proteins targeted to accumulate in the endoplasmic reticulum of plant cells have also been produced; these proteins lack undesirable post-translational modifications that normally exist in a plant cellular environment.

While plant transformation represents an original tactic to generate biopharmaceutical proteins, transient expression systems have also increased in popularity. Besides avoiding political controversy and lengthy time constraints involved in generating a transgenic plant, transient systems such as plant virus expression vectors are capable of producing high quantities of vaccine and other therapeutic proteins within a short time period (often within a week, depending on the virus/host plant system involved). Plant viruses have been engineered which express either a full-length vaccine protein or a subunit vaccine epitope which is displayed on the viral surface in the form of a fusion product with the virus coat protein. The selection of which plant expression platform to use for biopharmaceutical protein production can be determined by deciding which plant species is optimal, whether the system should involve cell culture or whole plants, and whether stable transformation or transient expression best fits the characteristics and predicted application of the therapeutic protein under investigation.

A principal driving force behind the application of plants as production platforms for vaccine and therapeutic proteins is to quickly generate inexpensive and safe vaccines which lack refrigeration requirements, in an attempt to combat preventable infectious diseases in developing countries, particularly those that continue to be the major cause of infant mortality.

The first proof-of-concept for a plant-derived vaccine was developed against Hepatitis B virus; this involved transgenic potatoes which were consumed by human volunteers and were shown to generate an immune response. Other plant-made vaccines have followed with encouraging results. For example, enterotoxigenic *E. coli* (ETEC) and Norwalk virus or Norovirus (NV) are considered to be two of the most devastating diarrheal diseases for children residing in developing countries today. Initial clinical trials involved the randomized, double-blind consumption of transgenic potato or corn expressing either LT-B or NV by healthy adults. Preliminary results indicated that substantial antibody responses were induced and protected the volunteers against challenge with these pathogens. Plant-derived vaccines and monoclonal antibodies directed toward other diseases considered to be significant challenges for developing countries, such as Human papillomavirus, and even Human immunodeficiency virus, have also been under development. Plant-derived vaccines could also be generated against largely neglected infectious diseases which tend to be poorly funded, such as Dengue fever virus and rabies virus.

While the scientific basis for the use of plant production platforms to generate biopharmaceutical proteins is now more clear and convincing than ever, will plant-made vaccines ever become a reality for developing countries and will they ever make a significant impact on the health needs of the world's poorest? Can this technology be marshaled to produce medicines which are not only low in cost and easy to increase in terms of scalability, but

can realistically address humanitarian needs?

Supporting data based upon initial basic research has elicited a general evolution toward human clinical trials for plant-derived vaccines. As encouraging results continue to accumulate, the answers to the above questions are under consideration more than ever. One piece of information that has provided a source of optimism is the fact that the vast majority of patent applications for plant-made pharmaceuticals have been generated at academic and publically funded research institutes. While it is certainly beneficial that the current intellectual property landscape may in fact provide a pathway that ensures freedom-to-operate (FTO) with fewer barriers than may be found in the corporate arena, strategies by which this knowledge can be shared and made accessible for developing countries remain unclear. Furthermore, a more detailed examination as to whether and how these vaccines could be produced in local, rural settings needs to be established and the appropriate policies governing such production should also be set in place. The impact that these details will have on the existing pharmaceutical industry and new challenges which develop

with respect to the changing relationship between multinational pharmaceutical companies and current healthcare suppliers for developing countries ought to be addressed as well.

As advances in this field remain murky at best at the moment, a concerted effort will be required to enable plant-derived vaccines to truly make their presence felt in the Third World.

While the battle is not yet over, there are plenty of reasons to feel optimistic. The research momentum that is building toward plant-derived vaccine development is strong, and success stories continue to accumulate. The fact that the general public has provided a wider acceptance of the technology than, for example, genetically modified foods, is also a good sign. There are already a number of organizations who specialize in supplying conventional vaccines for the rural poor in developing countries, and this provides a general road-map for success. The time is at hand for plant-derived vaccines to step up and take their final test, to make a real difference by improving global human health.