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Using transgenic plants and modified plant viruses for the development of treatments for human diseases

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Production of proteins in plants for human health applications has become an attractive strategy attributed by their potentials for low-cost production, increased safety due to the lack of human or animal pathogens, scalability and ability to produce complex proteins. A major milestone for plant-based protein production for use in human health was achieved when Protalix BioTherapeutics produced taliglucerase alfa (Elelyso®) in suspension cultures of a transgenic carrot cell line for the treatment of patients with Gaucher's disease, was approved by the USA Food and Drug Administration in 2012. In this review, we are highlighting various approaches for plant-based production of proteins and recent progress in the development of plant-made therapeutics and biologics for the prevention and treatment of human diseases.

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Introduction

Infectious diseases remain as one of the leading causes of mortality and morbidity in developing countries and are exacerbated by the lack of resources and infrastructure to prevent, treat and control diseases. Therefore, emerging and re-emerging pathogens have frequently resulted in epidemics in these countries. Over the past several decades, production of proteins in plants has been shown to be a promising approach for the manufacture of targets for human health applications. Plants, when compared to other production systems, offer some advantages, including ease of scaling and lack of human and animal pathogens [1–3] (Table 1).

This review focuses on several approaches that have been used to produce proteins in plants for prophylactic and therapeutic applications to combat human disease conditions. The various approaches for plant-based production of proteins are illustrated in Figure 1.

Transgenic plants

Stable nuclear and chloroplast transformations are the two approaches utilized to express heterologous recombinant proteins in plants. *Agrobacterium*-mediated stable transformation has a long history in plant genetic manipulation, and is achieved by stable integration of T-DNA into plant nuclear genome [4]. However, the approach is time consuming, with a lead time ranging from 12 to 18 months and typically has low levels of the target protein expressed [5]. Stable introduction of target genes into chloroplast genome, that is, chloroplast transformation or transplastomics, however, allows for higher levels of target expression as compared to nuclear transformation, largely due to the lack of gene silencing and high gene copy number [6], but it is technically difficult, lacks most post-translational modifications and has only been successful in a limited number of plant species.

Transient expression in plants

Transient expression of target proteins in plants using modified plant viruses or viral vectors integrated into binary vectors delivered via *Agrobacterium* [7,8••] is often considered a more robust approach when compared to stable transformation, due to its rapid production capabilities and relatively high protein expression [8••]. The majority of plant viral vectors used to date are based on single-stranded RNA viruses, such as tobacco mosaic virus, potato virus X and cowpea mosaic virus (CPMV), which encode for at least three proteins with functions in viral replication (replicase), encapsidation (coat protein) and movement from cell-to-cell (movement protein) [9]. The initial strategy involved production of recombinant proteins using plant viruses by exploiting their natural ability to infect (full virus) plants. However, this approach generally failed due to instability of viral genome modified by the introduction of large target genes [7]. This issue was largely resolved by using *Agrobacterium*-mediated gene delivery or agroinfiltration. The target gene can either be directly cloned into an *Agrobacterium* vector or through a modified plant viral vector which has been integrated into an *Agrobacterium* binary plasmid, and delivered into the plant tissues by infiltration with the transformed *Agrobacterium* [7,8••]. Agroinfiltration allows for high levels of target protein expression with the

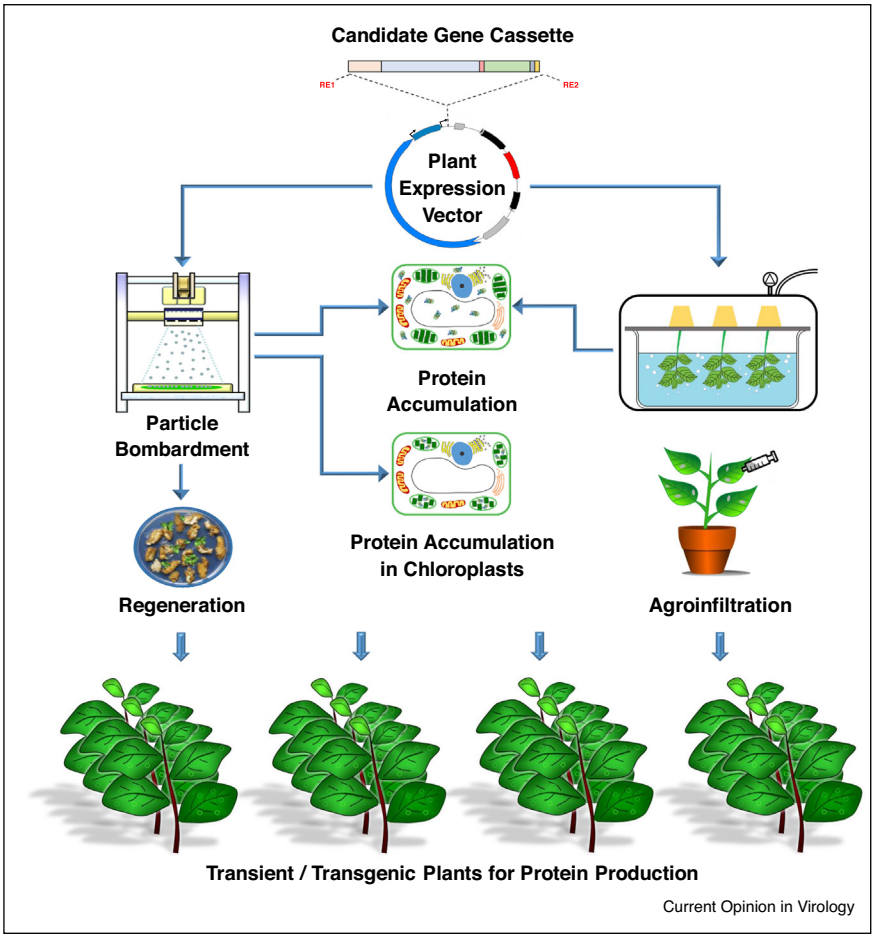
Table 1

General comparison of expression hosts for the production of heterologous proteins for medical and pharmaceutical applications

Expression host	Expression level	Production lead time	Production cost	Storage and distribution cost	Scale-up capacity	Glycosylation pattern	Risk of contamination
Bacterium	Medium — high	Short	Low	Moderate	High	None	High: endotoxins
Yeast	Low — high	Medium	Medium	Moderate	High	Incorrect: higher manosylation	Low
Insect cell culture	Low — high	Medium	High	Expensive	Medium	Incorrect: higher manosylation	High: baculovirus, mammalian viruses
Mammalian cell culture	Low — medium	Long	High	Expensive	Very low	Correct	High: mammalian viruses, prions, oncogenic DNA
Animal	Medium — high	Very long	High	Expensive	Low	Correct	High: mammalian viruses, prions, oncogenic DNA
Plant cell culture	Medium — high	Short	Low	Moderate	High	Minor difference	Low
Plant	Medium — high	Medium (transient[a]) Long (stable[b])	Very low	Inexpensive	Very high	Minor difference	Low

Note: Content is sourced partially from Ma *et al.* [1] and Yau *et al.* [13•]. Glycosylation pattern is compared to that of human counterpart.
[a] Refers to agroinfiltration on whole plants.
[b] Refers to stable nuclear and chloroplast transformations involving plant regeneration procedures.

Figure 1



Schematic illustration of the production of proteins in plants using transient expression (agroinfiltration) and transgenic (stable nuclear and chloroplast transformation) strategies.

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