MSc by research

Safer drugs: Modifying immunogenicity in plant produced products

Alastair McGinness*, David Gervais[1], David Evans[2], Verena Kriechbaumer[2]

Manufacturing "safer" drugs

Most bioproduction host systems lack the qualities for end product to be used in high-risk or high-throughput situations such as lifelong disorders, immune deficient individuals or the extremely young and old.

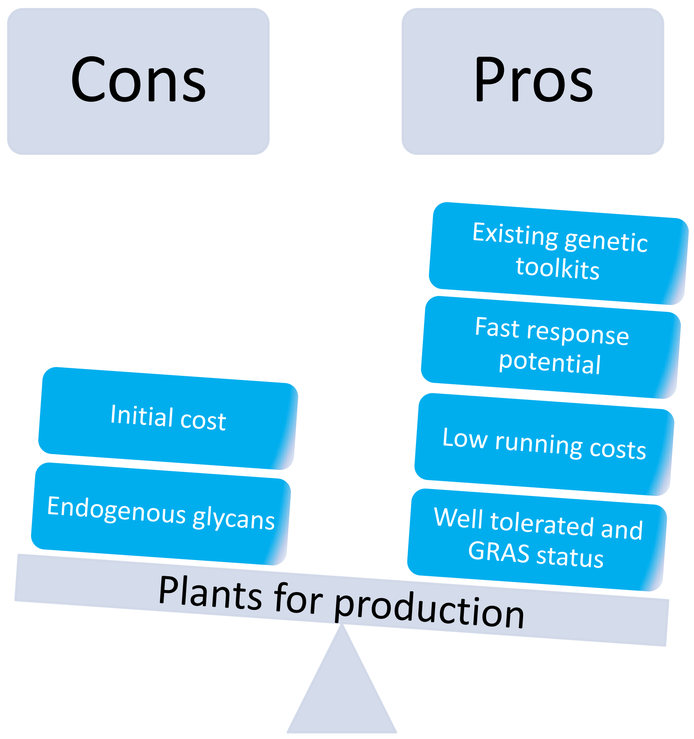
	Mammalian cells	Bacteria	Yeasts	Plants
Human glycosylation	✓	×	×	With modification
Immunogenic contaminants	×	✓	✓	✓
Low cost	×	✓	✓	✓
High yield	×	✓	✓	✓
Low growth complexity	×	×	×	✓

Plant based drug production

Plants offer the potential of scalable, affordable, correctly-folded protein in a host innately tolerated across human applications, without serious contamination threats

Efficacy has been evidenced in production of virus-like proteins (VLPs) for vaccine usage, and production of human enzyme replacement therapies.

As plants are ubiquitously tolerated in our diets, advancements in gene technology have led to the potential of edible vaccines and drugs: pharmaceuticals expressed inside edible plant tissue that can deliver pharmacological efficacy orally.



Challenges

- Specific human glycosylation is often **essential** for effective function and has serious effects on solubility, stability and elimination time
- Plants **do not have** the endogenous mammalian glycosylation enzymes to achieve fully "humanized" proteins
- Some endogenous plant glycans are considered unsafe for pharmaceutical applications, and may pose a barrier to use of plant products

Aims

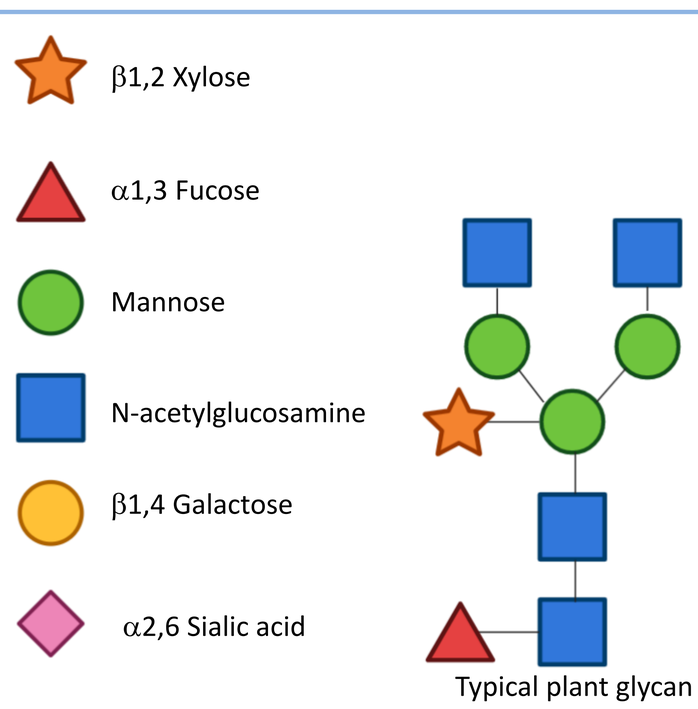
- To explore expression of mammalian glycosylation enzymes transiently in a plant system as a means of humanising high value plant products
- Reducing product immunogenicity to establish a plant system for safer drug manufacture

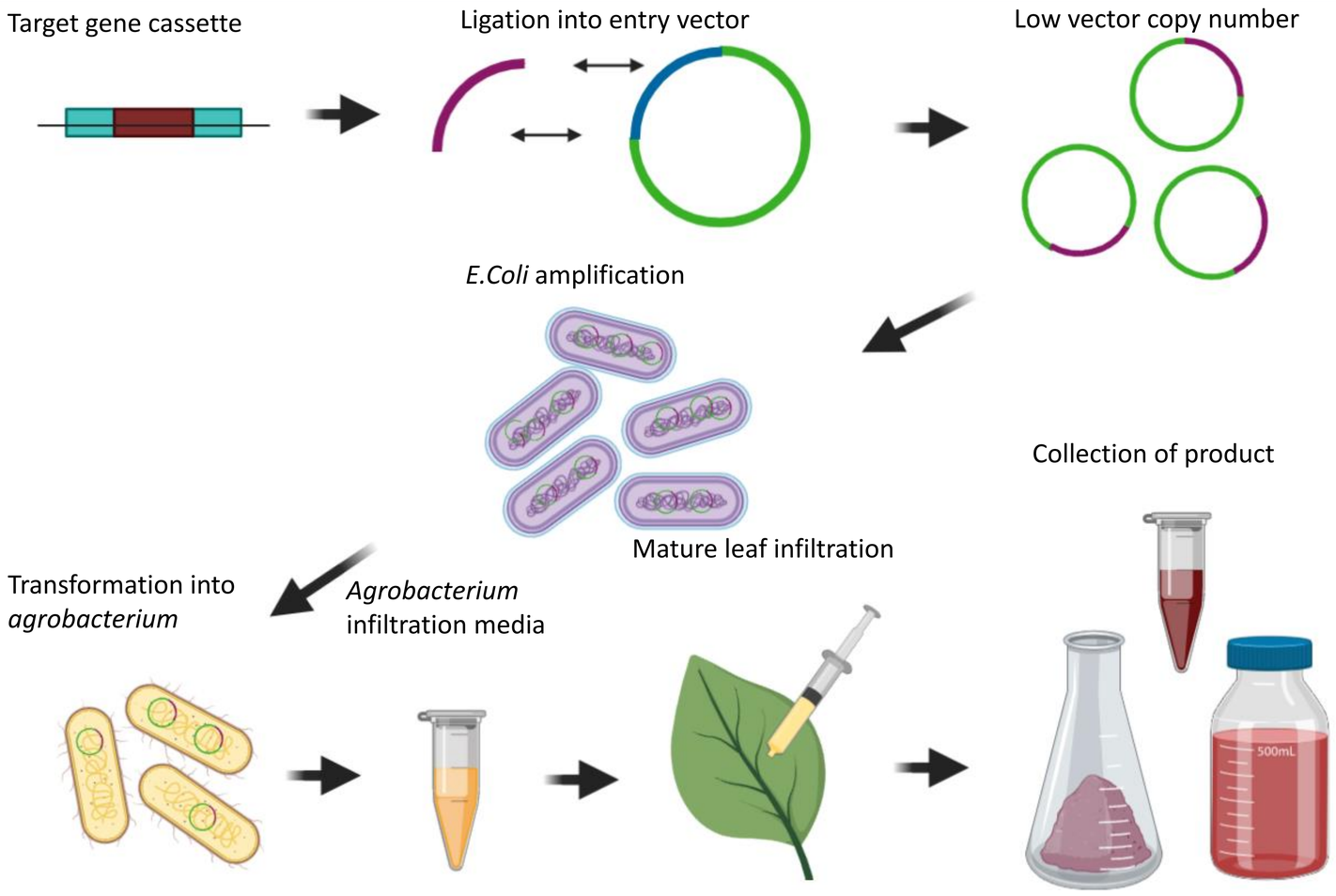
Modifying glycosylation

Glycosylation is post-translational modification of products by sugar addition performed by host systems. Glycans are integral to the function and efficacy of the associated protein. Glycomodification requires addition of the relevant enzyme within the correct compartment of the Golgi, or removal of the endogenous enzyme.

Core Fucose, Xylose and Lewis-a bodies are all epitopes of endogenous glycosylation conserved in most higher plants screened for use in therapeutics production. Each of these glycans are potentially immunogenic in humans.

To "humanise" any plant product, hosts would require gene insertions of mammalian glycosylation enzymes, and genetic knock-out of any endogenous enzymes producing sugars with immunogenic or off-target effects.





Biomolecule production

Agrobacterium-mediated infiltration is a common means by which a genetic payload can be delivered into mature plant tissues to produce transient alterations to gene expression.

Depending on the design and sequence of the genetic cassette delivered, this can be the knock-in of new genetic material e.g. a mammalian enzyme, or the knock-out of existing genes, such as endogenous glycosylation enzymes.

Transient infiltration of mature plants is an effective investigative tool, and a means to rapid production for a variety of responses. For example, the Zmapp Ebola vaccine was produced transiently in tobacco plants in response to the 2014 West Africa Ebola outbreak. The production cycle from genes, mature tobacco plant infiltration and harvesting of antibodies was complete in a few months, considerably shorter than existing production platforms.

1. Porton Biopharma, Manor Farm Rd, Salisbury SP4 0JG
2. Oxford Brookes University, Campus, Headington, Oxford OX3 0BP
In partnership with Porton Biopharma Ltd

References:
1. Burnett, M., Burnett, A., (2019) "Therapeutic recombinant protein production in plants: Challenges and opportunities". *Plants, People, Planet*. 00: 1– 12.
2. Ward, B., Landry, N., Trépanier, S., Mercier, G., Dargis, M., Couture, M., D'Aoust, M., Vézina, L., (2014) "Human antibody response to N-glycans present on plant-made influenza virus-like particle (VLP) vaccines", *Vaccine*, Volume 32, Issue 46, 2014, Pages 6098-6106, ISSN 0264-410X,
3. Bosch, D., Schots, A., (2010), "Plant glycans: Friend or foe in vaccine development?. Expert review of vaccines", 9. 835-42. 10.1586/erv.10.83.
4. Qiang, C., Davis, K., (2016), "The potential of plants as a system for the development and production of human biologics", *F1000Research*, 5. 912. 10.12688/f1000research.8010.1.