https://doi.org/10.1038/s41587-023-01899-1

Plant cell-based drug delivery enhances affordability of biologics

A Correspondence published recently in *Nature Biotechnology* discussed the socioeconomic potential and commercial feasibility of plant molecular farming[1]. This Correspondence also mentioned the risks of new products and platforms while leaving out discussion of important new biologic products made using plant biotechnology. Here, we highlight recent advances in plant molecular farming, focusing on methods of drug delivery (oral, topical, patches and chewing gum) and the advantages of using plant molecular farming methods to reduce production costs, thereby enhancing affordability and global access.

Oral delivery of protein drugs is one of the most challenging methods to develop, but it is the most preferred by patients. The mucosa of the human small intestine offers a large absorption surface area (30 m^2). Protein drugs should be bioencapsulated for protection from degradation by stomach acids and enzymes, and the use of plant cells for delivery is ideally suited for this purpose. Human digestive enzymes cleave α-linkages, but plant cell wall polymers are linked by β-1,4–1,6 bonds, and therefore therapeutic proteins bioencapsulated within plant cell wall are protected from human digestion[2–6]. However, gut microbes produce enzymes that cleave the β-linkages of plant cell wall polymers to release the protein drugs[2–6]. The final challenge is delivery across the gut epithelium to the immune or circulatory system, which is accomplished by fusion to tags that are proteolytically cleaved or by direct delivery to circulation through the gut–liver axis. This approach has enabled alleviation of cardiovascular conditions by oral ACE2 (ref. 2), regulation of blood sugar levels by oral insulin in the same manner as natural insulin[3] and acceleration of diabetic bone fracture healing by oral IGF-1 (ref. 4).

Another intriguing oral delivery application is the induction of antigen-specific tolerance to prevent formation of anti-drug antibodies such as those formed in replacement therapy for genetic diseases or to treat autoimmunity or allergies. For example, suppression of anti-drug antibodies from injected drugs[5] or gene therapy[6] has been demonstrated with oral delivery of blood clotting factors bioencapsulated in plant cells. Successful translation of this approach led to regulatory approval of Palforzia, a defatted peanut flour containing precise quantities of the major peanut allergens, Ara h 1, 2, 3 and 6. Oral delivery of Palforzia is effective in desensitizing people who are allergic to peanuts. In a phase 3 trial, 67% of subjects taking the peanut flour were able to tolerate 600 mg of peanut protein, compared to only 4% of those on placebo[7].

Topical delivery has unique advantages, especially the delivery of higher doses to the target site. Topically delivered plant cell-based biologics are promising candidates for the prevention of anaphylaxis against food allergens as demonstrated in the recent completion of a phase 3 trial of peanut proteins administered to toddlers aged 1–3 years[8]. Use of the same peanut proteins used in oral delivery but loaded onto adhesive patches was safe and efficacious in inducing tolerance against peanut allergens. Delivery of allergens at an early stage of life is more efficacious in tolerance induction, and the topical delivery method is best suited for infants 6–12 months of age.

Chewing gums containing small molecules (for example, aspirin, nicotine, vitamins or xylitol) are attractive delivery options because they are offered with the desired taste and flavor. Until recently, biologics had not been delivered via chewing gum. A recent study reported CTB-ACE2 produced in lettuce as a chewing gum formulation to debulk SARS-CoV-2 in swab or saliva samples in patients with COVID-19 (ref. 9). The authors confirmed neutralization of SARS-CoV-2 Beta, Delta and Omicron strains upon treatment with CTB-ACE2 chewing gum of saliva or swab samples from patients with COVID-19 (ref. 10). The US Food and Drug Administration (FDA) has approved the evaluation of ACE2 chewing gum to decrease SARS-CoV-2 infection and transmission in phase 1/2 clinical trials (Investigational New Drug application number 154807, NCT05433181)[10]. The authors in this study also demonstrated the antiviral efficacy of a lectin (FRIL) from lablab bean at neutralizing different strains of SARS-CoV-2 and potent influenza virus strains H1N1 and H3N2 (ref. 10). Saliva contain diverse pathogenic viruses, and control of aerosol salivary droplets is key to preventing virus transmission.

Biologics are unavailable or unaffordable to the large majority of the global population because of the way they are produced

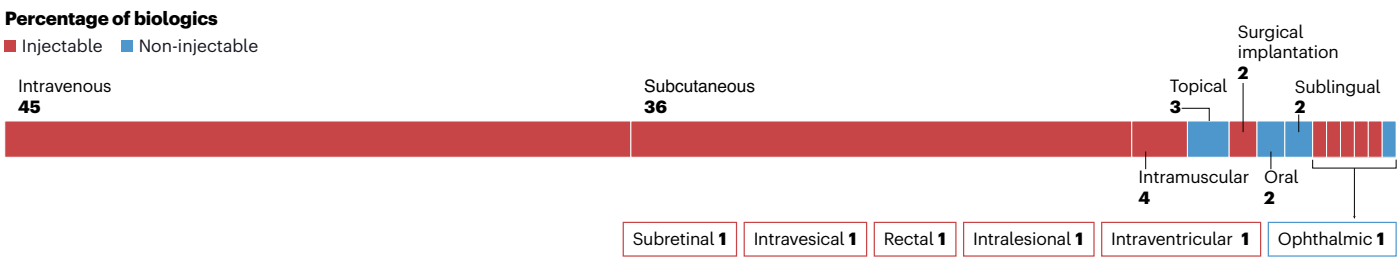

Fig. 1 | FDA-approved biologic drug delivery methods and percentage of each method since 2015. Data are from the Center for Biologics Evaluation and Research (Biological Approvals by Year) and Center for Drug Evaluation and Research (Purple Book) database through December 2022. The FDA has approved 89 protein drugs since 2015, excluding monoclonal antibodies and vaccines. Red indicates that an injection or other invasive method is required for delivery.

and delivered. The estimated average cost to develop a new biological product is ~$2.6 billion (ref. 11). Among FDA-approved biologics since 2015, >90% are injectable drugs (Fig. 1), and these are produced in prohibitively expensive fermentation systems, requiring purification and cold chain for storage and transportation. These challenges became quite evident when only 2.2% of COVID-19 vaccines were available for low-income countries and 19 million doses were discarded in Africa due to lack of cold chain[12]. While oral or topical drugs are preferred by patients because of their affordability and convenience, only two oral and four topical biologic drugs were approved by the FDA since 2015.

Per capita prescription drug spending in the United States is the highest in the world. The interquartile range of biological product prices ranged from $18,861 to $288,759 between 2008 and 2021 (ref. 13). To achieve affordability, new modes of protein drug production and delivery are urgently needed. In this context, it should be pointed out that the cost of Palforzia for 360 capsules with peanut cells (annual dose) is ~$2,500, <3% of the median annual price of biologics ($84,508)[13]. This median price excludes prohibitively expensive gene therapy drugs[14,15]. Hemophilia A drug Roctavian (valoctocogene roxaparvovec) costs $2.9 million per patient[15] and Hemgenix (etranacogene dezaparvovec) for hemophilia B costs $3.5 million per patient[15].

In summary, the FDA has approved biologics made in plant cells for oral and topical delivery. Biologics in freeze-dried plant cells are stable for months or years at ambient temperature and can be applied without purification. They substantially reduce the overall developmental costs from production to the conduct of clinical trials, facilitated by oral and topical delivery. Consequently, plant cell-based biologics will not only help fulfill the therapeutic potential of delivering functional proteins but also address limitations of current delivery systems of protein injections or gene therapy. The future of plant molecular farming is bright and will lead to many more FDA-approved protein therapeutics in the future.

Henry Daniell[1] ✉, Rachel J. Kulchar[1], Roland W. Herzog[2], Mike Kulis[3] & Kam W. Leong[4]

[1]Department of Basic and Translational Sciences, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA, USA. [2]Herman B Wells Center for Pediatric Research, Indiana University, Indianapolis, IN, USA. [3]Department of Pediatrics, University of North Carolina, Chapel Hill, NC, USA. [4]Department of Biomedical Engineering, Columbia University, New York, NY, USA.
✉e-mail: hdaniell@upenn.edu

Published online: 07 August 2023

References

1. Benvenuto, E. et al. *Nat. Biotechnol.* https://doi.org/10.1038/s41587-023-01812-w (2023).
2. Daniell, H. et al. *Biomaterials* **233**, 119750 (2020).
3. Daniell, H. et al. *Biomaterials* **298**, 122142 (2023).
4. Park, J. et al. *Biomaterials* **233**, 119591 (2020).
5. Srinivasan, A. et al. *Plant Biotechnol. J.* **19**, 1952–1966 (2021).
6. Butterfield, J. S. S. et al. *Cell. Immunol.* https://doi.org/10.1016/j.cellimm.2023.104742 (2023).
7. Vickery, B. P. et al. *N. Engl. J. Med.* **379**, 1991–2001 (2018).
8. Greenhawt, M. et al. *N. Engl. J. Med.* **388**, 1755–1766 (2023).
9. Daniell, H. et al. *Mol. Ther.* **30**, 1966–1978 (2022).
10. Daniell, H. et al. *Biomaterials* **288**, 121671 (2022).
11. DiMasi, J. A., Grabowski, H. G. & Hansen, R. W. *J. Health Econ.* **47**, 20–33 (2016).
12. Loembé, M. M. & Nkengasong, J. N. *Immunity* **54**, 1353–1362 (2021).
13. Rome, B. N., Egilman, A. C. & Kesselheim, A. S. *J. Am. Med. Assoc.* **327**, 2145–2147 (2022).
14. Hopkins, J. S. New $2.9 million gene therapy promises to remake hemophilia treatment. *The Wall Street Journal* (29 June 2023).
15. Naddaf, M. *Nature* **612**, 388–389 (2022).

Acknowledgements

Research from the Daniell lab on oral or topical delivery was supported US National Institutes of Health grant R01 HL 107904 and Commonwealth of Pennsylvania, Department of Community and Economic Development grants.

Author contributions

H.D. wrote the first and edited subsequent drafts. M.K. and H.D. wrote the peanut allergy sections. R.W.H. and H.D. wrote the hemophilia sections. R.J.K. collected data on FDA-approved biologics and created Fig. 1. K.W.L. edited several drafts.

Competing interests

H.D. and R.W.H. are patentees in plant-based oral tolerance induction and were previously funded by Novo Nordisk, Bayer, Shire and Takeda. H.D. is a patentee in chewing gum or oral drug delivery technologies using plant cells, and several industry partnerships for advancing clinical trials are in progress. A complete list of patents is available at http://scholar.google.com/citations?user=7sow4jwAAAAJ&hl=en. All other authors declare no competing interests.