Vaccines

https://doi.org/10.1038/s41551-023-01008-2

A hydrogel-entrapped live virus immunization

Ningqiang Gong, Alex G. Hamilton & Michael J. Mitchell

Confining the Zika virus within a self-adjuvanting hydrogel that forms a subcutaneous inflammatory niche stimulates strong immune responses in mice without inducing infection.

Current vaccine candidates for the Zika virus (ZIKV) — a virus in the family *Flaviviridae*, first isolated in 1947 in the Zika forest in Uganda[1], that can induce microcephaly, congenital abnormalities and Guillain–Barré syndrome in pregnant women[2] — include inactivated vaccines, vector vaccines, virus-like-particle vaccines and other subunit vaccines, DNA vaccines and messenger RNA (mRNA) vaccines[3]. The viral particles or virus-derived peptides in inactivated vaccines, vector vaccines and subunit vaccines (which typically induce viral-specific immune responses) can be affected by pre-existing or de novo antiviral immunity, which restricts the level of immune responses induced[4]. For vaccines that do not require a vector for their delivery (such as mRNA vaccines), the expression of viral antigens in the body is rather transient. Therefore, to induce a strong antiviral immune response and maintain effective protection, they require repeat dosing. Moreover, mRNA is readily degraded and thus mRNA vaccines require cold-chain storage, which is a logistical constraint, particularly in less-wealthy parts of the world[5]. Also, nanoparticle-based vaccines can be designed to control, to some degree, the encapsulation, delivery and release of antigens and to enhance the potency and duration of the immune responses. Still, achieving spatiotemporal control of antigen delivery and activation remains difficult.

A living virus typically induces stronger immune responses than a vaccine[6] for it, yet the downstream risks of infection and rapid clearance of the virus by the immune system makes the use of live viruses as vaccines challenging. Now reporting in *Nature Biomedical Engineering*, Ruikang Tang and colleagues[7] describe a new strategy: a self-adjuvanting hydrogel trapping live ZIKV.

Tang and co-authors prepared the vaccine by simply mixing particles of live ZIKV (which are negatively charged) with chitosan oligosaccharide (which is positively charged and acts as an immune

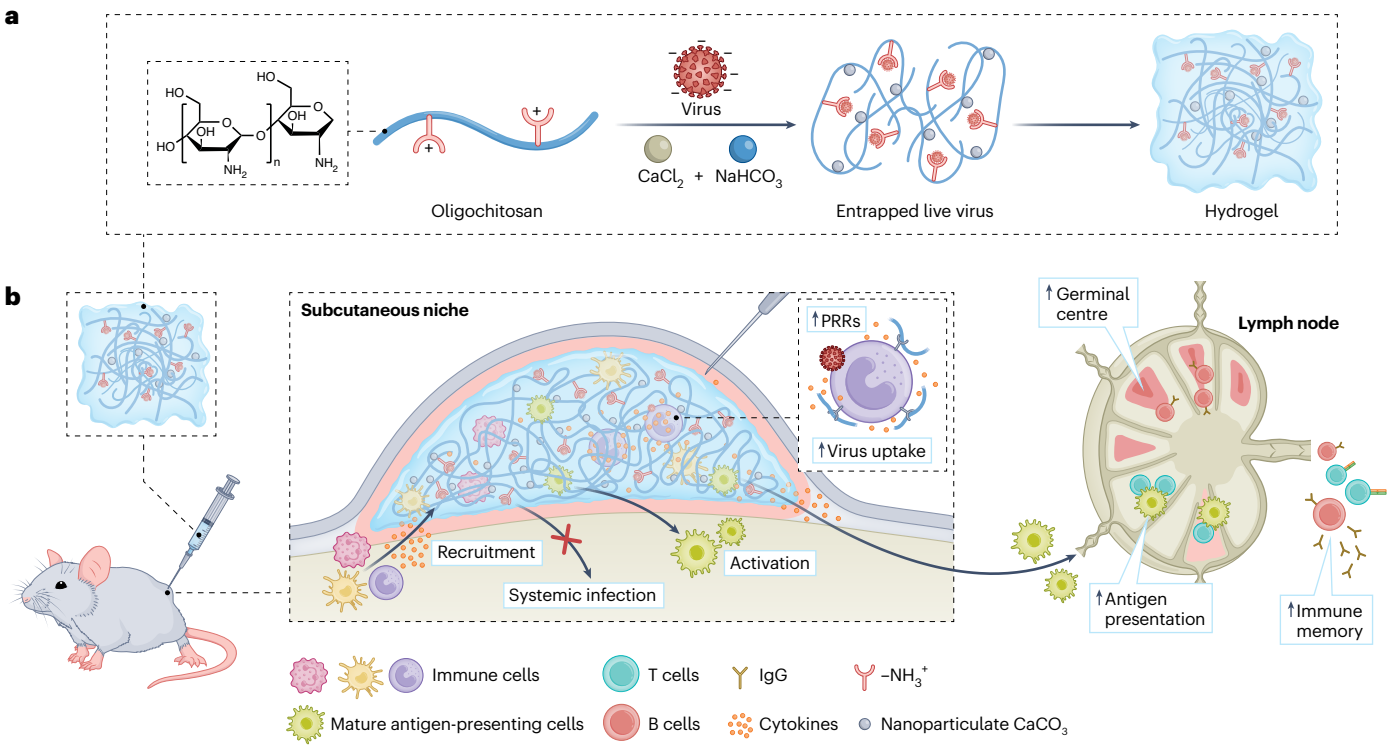

Fig. 1 | An entrapped live Zika virus as a vaccine. a, The hydrogel-based live-virus vaccine is prepared by mixing viral particles with chitosan oligosaccharide, calcium chloride, sodium bicarbonate and polyaspartic acid. **b**, On subcutaneous injection, the mixture undergoes a rapid sol–gel transition (from 4 °C to body temperature), which results in the formation of a hydrogel at the injection site. The hydrogel transforms into an inflammatory niche, where pattern-recognition receptors (PRRs) are activated to facilitate the recruitment of immune cells and the activation of innate immune responses. This leads to antigen presentation, to the elevation of germinal centre B cells, and to antigen cross-presentation in lymph nodes, inducing robust antigen-specific responses and immune memory. Figure adapted with permission from ref. [7], Springer Nature Ltd.

adjuvant), calcium chloride, sodium bicarbonate and polyaspartic acid. The mixture remained in solution state when kept at 4 °C, which facilitated its injectability and storage. Following subcutaneous injection in healthy mice, the mixture underwent a rapid sol–gel transition at body temperature, forming a hydrogel that remained at the injection site. The authors show that the structure of the hydrogel confined the ZIKV particles to the injection site and prevented the leakage of the virus from the material. Indeed, the hydrogel vaccine did not induce ZIKV infection in the mice. Instead, it established an engineered inflammatory niche that triggered the infiltration of immune cells into the scaffold, the engulfment of viral particles by the infiltrated immune cells, and the migration of infiltrated antigen-presenting cells to draining lymph nodes (Fig. 1). The formulation elicited robust and long-term humoral and cellular antiviral immunity.

In a mouse model of ZIKV infection, a single dose of a hydrogel with live ZIKV generated ZIKV-specific neutralizing antibody titres faster and at higher levels than inactivated ZIKV mixed with an adjuvant (PolyI:C or Alum). Tang and colleagues also evaluated the efficacy of a hydrogel harbouring inactivated ZIKV particles, with or without an adjuvant. The authors found that the immune responses elicited by the hydrogel formulation with entrapped inactive virus were inferior to those raised by the formulation with living ZIKV.

Tang and co-authors' findings suggest that trapping live viruses into such a subcutaneous biomaterial 'depot' can be safe and effective. The self-adjuvanted hydrogel vaccine could thus be harnessed to deliver a range of viruses as immunizations against infectious diseases. Moreover, the simplicity of the formulation would allow for rapid vaccine manufacturing, which would be an advantage for the production of strain-specific vaccines that lead to long-lasting protection with a single dose. Chitosan may trigger allergic reactions[8], yet other polysaccharides may provide similar entrapment and adjuvanting functionalities and retain the physicochemical properties of a particle-entrapping hydrogel that transforms a live virus into a vaccine.

Ningqiang Gong, Alex G. Hamilton & Michael J. Mitchell ✉
Department of Bioengineering, University of Pennsylvania, Philadelphia, PA, USA.
✉e-mail: mjmitch@seas.upenn.edu

Published online: 23 March 2023

References

1. Baud, D., Gubler, D. J., Schaub, B., Lanteri, M. C. & Musso, D. *Lancet* **390**, 2099–2109 (2017).
2. Pierson, T. C. & Diamond, M. S. *Nature* **560**, 573–581 (2018).
3. Zhou, K. et al. *Vaccines* **9**, 1004 (2021).
4. Bettini, E. & Locci, M. *Vaccines* **9**, 147 (2021).
5. Uddin, M. N. & Roni, M. A. *Vaccines* **9**, 1033 (2021).
6. Thompson, M. R., Kaminski, J. J., Kurt-Jones, E. A. & Fitzgerald, K. A. *Viruses* **3**, 920–940 (2011).
7. Hao, H. et al. *Nat. Biomed. Eng.* https://doi.org/10.1038/s41551-023-01014-4 (2023).
8. Wieckiewicz, M., Boening, K. W., Grychowska, N. & Paradowska-Stolarz, A. *Mini Rev. Med. Chem.* **17**, 401–409 (2017).

Competing interests

The authors declare no competing interests.