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IMMUNOENGINEERING

Plant viruses join forces

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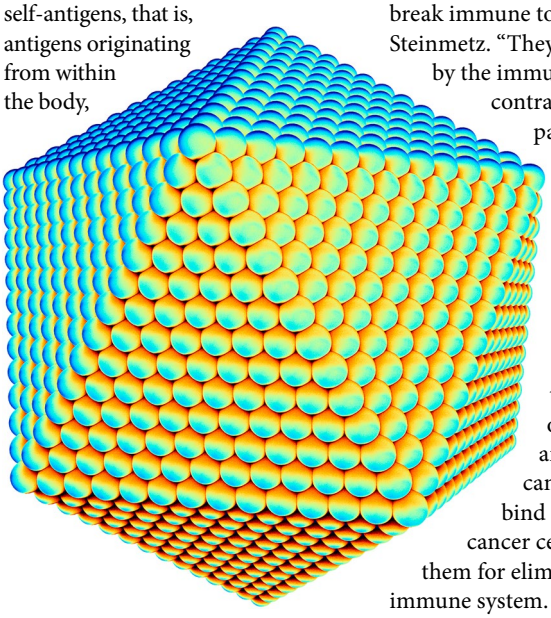
Cancer cells developed many ways to evade the surveillance of the immune system. Administration of antigens to trigger the production of antitumour antibodies and thus an immune response against tumour cells is a promising immunotherapeutic treatment strategy. Now, writing in the *Journal of the American Chemical Society*, Nicole Steinmetz and colleagues report a combinatorial treatment approach, in which an antigen is sequentially delivered by three different plant virus nanoparticles. This heterologous immunogenic vaccine is more efficient in reducing tumour burden than traditional homologous prime-boost strategies.

Many cancer cells display self-antigens, that is, antigens originating from within the body, which are not recognized by the immune system; for example, the human epidermal growth factor receptor 2 (HER2) is often overexpressed on highly aggressive breast cancer cells. To elicit an immune response against HER2$^+$ cancer cells and circumvent self-tolerance, HER2-derived B cell epitope peptides, such as CH401, can be administered, which leads to the production of HER2-specific antibodies.



Credit: Alfred Pasieka/Science Photo Library/Getty images

Steinmetz and colleagues developed a combinatorial vaccination approach using three different plant virus nanoparticles made of viral RNA and capsids, which can be chemically modified with the peptide. "We used plant viruses to break immune tolerance," explains Steinmetz. "They are recognized by the immune system, but in contrast to mammalian pathogens, are non-infectious and thus regarded as safe." The presentation of the CH401 peptide on the surface of the viral particles causes the production of HER2-specific antibodies, which can consequently bind to HER2$^+$ breast cancer cells to label them for elimination by the immune system.

Mice with HER2$^+$ breast cancer who received the heterologous vaccine survived longer and showed reduced tumour growth than mice who received a traditional homologous prime-boost, in which the same carrier and antigen are repeatedly administered. "The key innovation is that we use a combination of plant virus carriers," comments Steinmetz. "This helps to focus the immune system on the target tumour antigen and not on the carrier." Interestingly, although the different plant viruses elicit the response of different T helper (T_H) cell phenotypes, the sequential injection of the three viral carriers causes a T_H1 cell-dominant immune response. T_H1 cells efficiently activate CD8$^+$ T cells and natural killer cells, which can in turn attack cancer cells.

Steinmetz and colleagues now aim to dissect the design rules for the most effective combination. "There is a lot of room for future research to analyse which combination and administration order of plant viral carriers work best." The researchers further plan to investigate epitopes for other cancer types and for cardiovascular disease, and they want to test whether their combinatorial strategy could also be applied for autoimmune diseases, given the effect on T_H cell phenotypes.

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ORIGINAL ARTICLE Cai, H. et al. Heterologous prime-boost enhances the antitumor immune response elicited by plant-virus-based cancer vaccine. *J. Am. Chem. Soc.* **141**, 6509–6518 (2019)