

Credit: Reimar Gaertner/UIG

substantial erythema with 24 h. Moreover, ticks on vaccinated animals fed poorly and started to detach by 48 h — with 80% of ticks detached from vaccinated animals by 96 h, as compared with 20% on unvaccinated animals.

To investigate whether the altered feeding behaviour affects the transmission of pathogens, B. burgdorferi-infected I. scapularis nymphs were placed on guinea pigs that were vaccinated either with 19ISP or with an mRNA vaccine encoding firefly luciferase. Each animal received three infected ticks. Assuming that humans are likely to remove a tick that causes erythema-related itching, the ticks were removed (in a double-blind manner) as soon as redness appeared. Three weeks after the challenge, 46% of control animals were infected with B. burgdorferi, whereas none of the vaccinated animals had been

from tumour cells compared with cultures of normal control tissue, and breast cancer cells from patients showed upregulation of the histamine synthesizing enzyme HDC. This suggested that increased synthesis of histamine may limit antitumour immune responses through effects on macrophages in the TME.

Indeed, in mouse tumour models, deficiency or blockade of macrophage HRH1 was associated with enhanced antitumour T cell activity and with improved antitumour responses. Detailed analyses indicated that HRH1 signalling in macrophages promotes a more immunosuppressive M2-like phenotype and promotes membrane localization of the immune inhibitory molecule VISTA. Notably, treatment with the H1-antihistamine fexofenedine reduced tumour expression of VISTA and improved ICB outcomes in several mouse tumour models.

As allergies are associated with high levels of histamine release, the authors examined how allergy impacts tumour immunity and ICB. In a mouse model of allergic airway disease, allergic mice showed accelerated growth infected. Gene expression analysis demonstrated the activation of several immune pathways by the vaccine, including T cell and B cell receptor signalling, chemokine, FccRI and IL-17 signalling, as well as natural-killer cell-mediated toxicity. Analyses of the bite site also indicated that the vaccine induced T cell responses.

This study shows that acquired tick resistance can be induced in guinea pigs by a multivalent mRNA vaccine and that it can prevent tick-borne *B.burgdorferi* infection, likely by limiting the duration of tick feeding. The authors hypothesize that the mRNA–LNP formulation may mimic natural tick bites by allowing for slow, continuous antigen delivery. If this approach can be translated to humans, it would be the first vaccine that does not directly target a pathogen or microbial target, but instead, its vector.

Alexandra Flemming

ORIGINAL ARTICLE Sajid, A. et al. mRNA vaccination induces tick resistance and prevents transmission of the Lyme disease agent. *Sci. Transl Med.* https://doi.org/10.1126/scitranslmed. abj9827 (2021)

of transplanted EMT6 mammary or CT26 colon tumours compared with non-allergic animals, but tumour growth could be blocked by fexofenedine treatment. EMT6 and CT26 tumours are normally susceptible to ICB, but allergic mice with these tumours became resistant to ICB. Strikingly, fexofenedine treatment restored the sensitivity of the tumours in these animals to ICB. Finally, the authors found that patients receiving ICB for various cancers, who had allergies or high plasma histamine levels before ICB therapy, also experienced poorer clinical outcomes.

Together, these data suggest that H1 antihistamines could represent useful adjuvant therapies for patients receiving ICB for cancer. As H1 antihistamines are relatively inexpensive, this could represent an important breakthrough in the clinic.

Yvonne Bordon

ORIGINAL ARTICLE Li, H. et al. The allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1. *Cancer Cell* https://doi.org/10.1016/j.ccell. 2021.11.002 (2021)

IN BRIEF

COVID-19

Cross-reactive memory T cells abort SARS-CoV-2 infection

A study in health-care workers showed that some people, despite likely exposure to SARS-CoV-2, never develop PCR or antibody positivity. Swadling et al. hypothesized that pre-existing cross-reactive memory T cells, as described in pre-pandemic samples, may lead to abortive seronegative infections in these individuals. Indeed, they found T cell and innate transcript evidence for abortive infections. They also showed that these individuals frequently had memory T cells directed at the early transcribed replication transcription complex, which has high sequence conservation between human seasonal coronaviruses and SARS-CoV-2. Boosting such T cells with vaccines may allow for pan-reactivity against endemic and emerging coronaviruses.

ORIGINAL ARTICLE Swadling, L. et al. Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2. Nature https://doi.org/10.1038/s41586-021-04186-8 (2021)

COVID-19

Defective viral genomes can protect against SARS-CoV-2 variants and other respiratory viruses

Based on the unexpected observation that the Sabin Poliovirus vaccine not only protects against polio but also against other viruses, Andino and colleagues explored whether virus-like entities can be used as broad-spectrum antivirals to stimulate innate immune defences. They generated a liposome-encapsulated poliovirus-derived defective viral genome (eTIP1) that was administered intranasally to mice infected with different respiratory viruses, including influenza, SARS-CoV-2 and its Alpha. Delta and Epsilon variants. eTIP1 reduced viral loads, facilitated adaptive immune responses and prevented lethal infections when given up to 48 hours before to 24 hours after viral exposure. Protection was dependent on eTIP1 being replication competent. The authors hypothesize that, by mimicking natural infection, eTIP1 recruits different arms of immunity, providing a potentially powerful broad-spectrum prophylactic and therapeutic weapon.

ORIGINAL ARTICLE Xiao, Y. et al. A defective viral genome strategy elicits broad protective immunity against respiratory viruses. *Cell* https://doi.org/10.1016/j.cell.2021.11.023 (2021)

COVID-19

Dexamethasone restrains neutrophils in severe COVID-19

Dexamethasone reduces mortality in patients with severe COVID-19, but the mechanism has been elusive. Using single-cell RNA sequencing and plasma proteomics. Rosin, Yipp, Biernaskie and colleagues investigated immune cell dynamics in patients with severe COVID-19 and acute respiratory distress syndrome (ARDS) who either did or did not receive dexamethasone, and compared these to patients with bacterial ARDS and healthy volunteers. COVID-19 seemed to promote the enrichment of specific neutrophil states characterized by enhanced type I interferon (IFN) activation (IFN^{active}) or by prostaglandin signalling. Dexamethasone treatment was associated with global alterations in neutrophil sub-states, a suppression of IFN networks, a depletion of IFN^{active} neutrophils and an expansion of immature and immunosuppressive neutrophils, indicating that dexamethasone limits neutrophil pathogenicity.

ORIGINAL ARTICLE Sinha, S. et al. Dexamethasone modulates immature neutrophils and interferon programming in severe COVID-19. *Nat. Med.* https://doi.org/10.1038/ s41591-021-01576-3 (2021)