Studies in mice lacking the acetylcholine receptor Chrna7 confirmed the effect of acetylcholine on haematopoiesis and indicated that it signals through stromal niche cells: wild-type bone marrow cells transplanted into irradiated Chrna7-/- mice showed the similar increase in myelopoiesis to Cd19-Cre;Chatfl/fl mice, as did mice with a specific deletion of Chrna7 in stromal bone marrow cells. Single-cell RNA sequencing of bone marrow cells identified nine cell types that express Chrna7 in the bone marrow niche and localize close to acetylcholine-expressing B cells. Cxcl12 was one bone marrow niche factor that was downregulated in Chrna7-/- stromal cells in Cd19-Cre;Chatfl/fl mice, and blockade of CXCL12-induced signalling suggested a functional role for this factor in constraining leukocyte production. Gene expression analysis also suggested that in the absence of B cell-derived acetylcholine, bone marrow niche cells adopt a more inflammatory phenotype.

Finally, the authors examined the implications of acetylcholine-mediated regulation of haematopoiesis in mouse models of cardiovascular disease. In an atherosclerosis model, Cd19-Cre;Chatfl/fl mice developed larger atherosclerotic plaques with a greater accumulation of myeloid cells than control mice. Similarly, following acute myocardial infarction (MI) induced by coronary ligation, Cd19-Cre;Chatfl/fl mice showed elevated myeloid cells in infarcted hearts and poorer survival than control mice. Moreover, wild-type mice treated with acetylcholine esterase inhibitor (raising acetylcholine levels) before induction of MI led to curtailed supply of inflammatory myeloid cells to the blood and infarcts, giving rise to less severe disease. Finally, the observation that acute MI occurring in patients taking donepezil was associated with a lower increase in blood leukocytes suggests that harnessing cholinergic signalling could be therapeutically opportune for inflammatory cardiovascular disease.

Lucy Bird

IN BRIEF

COVID-19

Are variant-specific vaccines warranted?

The efficacy of current COVID-19 vaccines wanes over time, and viral variants, particularly Omicron, have lost many of the binding sites for neutralizing antibodies — leading to large numbers of breakthrough infections in vaccinated individuals. Vaccine boosters can restore protection (at least for a few months), and variant-specific boosters are currently being trialled. In a mouse model of COVID-19, Ying et al. demonstrate that boosting with an Omicron-specific version of mRNA-1273, as compared to the ‘original’ mRNA-1273, leads to enhanced protection against Omicron. However, full vaccination with the Omicron-adapted vaccine provided poor cross-protection against the ancestral virus. Meanwhile, Gagne et al. compared mRNA-1273 and Omicron-matched booster shots in macaques that had been vaccinated with mRNA-1273 months earlier. Following challenge with Omicron, both boosters induced 70–80% cross-protective B cells and provided complete protection in the lungs as well as comparable, limited protection in the upper airways. Given the uncertainty around potential new variants, broad protection may be preferable to variant-specific protection.

ORIGINAL ARTICLES Gagne, M. et al. mRNA-1273 or mRNA-Omicron boost in vaccinated macaques elicits similar B-cell expansion, neutralizing antibodies and protection against Omicron. Cell https://doi.org/10.1016/j.cell.2022.03.038 (2022); Ying, B. et al. Boosting with variant-matched or historical mRNA vaccines protects against Omicron infection in mice. Cell https://doi.org/10.1016/j.cell.2022.01.031 (2022)

COVID-19

New tool to investigate spike-specific CD4+ T cells

Both CD8+ and CD4+ T cells against the SARS-CoV-2 spike protein have been associated with reduced severity of COVID-19, indicating a role for T cells in limiting viral pathogenesis. In addition, spike-specific CD4+ T follicular helper (Tfh) cells support B cell maturation and neutralizing antibody production. Using a novel peptide–MHC tetramer to track human spike-specific CD4+ T cells, Wragg et al. now demonstrate that SARS-CoV-2 infection or vaccination induces robust CXCR5+ T-memory and circulating Tfh cell responses, which are efficiently recalled upon antigen re-exposure and may contribute to long-term protection against SARS-CoV-2.

ORIGINAL ARTICLE Wragg, K. M. et al. Establishment and recall of SARS-CoV-2 spike-epitope-specific CD4+ T cell memory. Nat. Immunol. https://doi.org/10.1038/s41590-022-01175-z (2022)

COVID-19

Do individuals who have recovered from COVID-19 still benefit from being vaccinated?

To address this question, Cerqueira-Silva et al. analysed the national disease surveillance and vaccination databases from Brazil to estimate the effectiveness of CoronaVac, ChAdOx1 nCoV-19, BNT162b2 and Ad26.COV2.S in individuals with previous SARS-CoV-2 infection. All four vaccines conferred a high degree of protection against second symptomatic infections (ranging from 39.4% (CoronaVac) to 64.8% (BNT162b2)) and death (>80% for all two-dose vaccines) in previously infected individuals. Another study by Nordström et al. of Swedish nationwide registers also found that ‘hybrid immunity’ (from both infection and vaccination) provided additional protection compared to virus-induced immunity alone.

ORIGINAL ARTICLE Cerqueira-Silva, T. et al. Effectiveness of CoronaVac, ChAdOx1 nCoV-19, BNT162b2, and Ad26.COV2.S among individuals with previous SARS-CoV-2 infection in Brazil: a test-negative, case-control study. Lancet Infect. Dis. https://doi.org/10.1016/S1473-3099(22)00160-2 (2022); Nordström, P. et al. Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden. Lancet Infect. Dis. https://doi.org/10.1016/S1473-3099(22)00140-2 (2022)