IN BRIEF

COVID-19

A new set of genes linked to critical COVID-19

This study compared whole genome sequences from over 7,000 patients critically ill with COVID-19 with the genomes of more than 48,000 matched controls (that is, similar individuals in the general population were matched to each patient). The authors identified 23 gene variants that predispose to critical COVID-19, including 16 variants that had not previously been reported. Notable among these variants were genes linked to interferon responses (*IFNA10, PLSCR1, IL10RB*), leukocyte differentiation (*BCL11A*) and myeloid cell recruitment and function (*SELE, ICAM5, CD209*). The study also provides the first genetic evidence to support a causal role for coagulation and platelet activation in critical COVID-19, with *F8* and *PDGFRL* identified as risk variants. Overall, the data strengthen the idea that a failure to control viral replication and dysregulation of the inflammatory and coagulation responses are key mechanisms that drive the development of severe COVID-19.

ORIGINAL ARTICLE Kousathanas, A. et al. Whole genome sequencing reveals host factors underlying critical Covid-19. *Nature* https://doi.org/10.1038/s41586-022-04576-6 (2022)

COVID-19

Social distancing plus rapid vaccination prevents emergence of SARS-CoV-2 variants

It is hoped that worldwide vaccination will help to end the COVID-19 pandemic, but vaccination combined with relaxed social distancing is likely to drive vaccine resistance. Can policymakers prevent the emergence of vaccine-resistant variants of SARS-CoV-2? To address this, Lobinska et al. used mathematical modelling to assess the evolution of vaccine-resistant strains of SARS-CoV-2 in the presence of dynamic social distancing. They used real-world infection and vaccination data from six countries to inform their model and conclude that if the rate of vaccination is slow, resistance is likely to emerge even if social distancing is maintained. However, under fast vaccination, the emergence of variants can be prevented if social distancing is maintained during vaccination. They caution that social distancing measures should be maintained until the daily number of infections is substantially decreased. Allowing a large number of daily infections can only be counterbalanced by very high vaccination rates — otherwise vaccine-resistant variants of SARS-CoV-2 are likely to emerge.

ORIGINAL ARTICLE Lobinska, G. et al. Evolution of resistance to COVID-19 vaccination with dynamic social distancing. *Nat. Hum. Behav.* **6**, 193–206 (2022)

COVID-19

Comparing paediatric COVID-19 with MIS-C

Paediatric COVID-19 (pCOVID-19) is rarely severe, but a small minority of children infected with SARS-CoV-2 develop a multisystem inflammatory syndrome (MIS-C). This study describes distinct immunological signatures in pCOVID-19 versus MIS-C. While pCOVID-19 was characterized by robust type I interferon (IFN) responses, MIS-C was associated with IFNγ-dependent and NF-κB-dependent signatures, activation of extracellular matrix and increased levels of circulating SARS-CoV-2 Spike protein. The study also confirmed an earlier report linking MIS-C with the combination of the HLA-A*02, HLA-B*35 and HLA-C*04 alleles. Understanding the unique immunopathology of pCOVID-19 compared with MIS-C may guide better therapies for children infected with SARS-CoV-2.

ORIGINAL ARTICLE Sacco, K. et al. Immunopathological signatures in multisystem inflammatory syndrome in children and pediatric COVID-19. *Nat. Med.* https://doi.org/10.1038/s41591-022-01724-3 (2022)

CANCER IMMUNOTHERAPY

Bispecific agonist boosts anti-tumour T cells via GITR

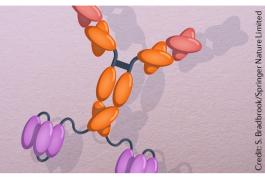Credit: S. Bradbrook/Springer Nature Limited

The costimulatory receptor GITR plays a key role in regulating effector functions in T cells, and antibody-based GITR agonists have entered clinical trials for cancer. However, the therapeutic efficacy of these agents has been limited, which is thought to be due to suboptimal receptor clustering. Now, Alvarez and colleagues demonstrate that a bispecific molecule that consists of a PD1-targeted antibody fused to a multimeric GITR ligand can inhibit tumour growth in animal models.

GITR is a costimulatory member of the TNF receptor superfamily. It is expressed by regulatory T (T$_{reg}$) cells and co-expressed with the checkpoint inhibitor PD1 on activated and memory T cells. In mouse models, GITR stimulation with agonistic antibodies or GITR ligands (GITR-L) has anti-cancer activity by promoting the accumulation of CD8$^+$ T cells and depleting T$_{reg}$ cells in tumours.

The authors of this study investigated whether a PD1/GITR-L bispecific antibody construct could overcome the immune escape frequently observed in patients with PD-1/PD-L1-targeted therapeutics, and improve upon the performance of current GITR agonist antibodies. To this end, they designed a mouse and a human version of an anti-PD1–GITR-L bispecific, where the anti-PD1 activity enhances the ability of the fused GITR-L multimer to induce GITR clustering in an FcγR-independent fashion.

In mouse models of solid tumours (including anti-PD1-resistant tumours), treatment with the mouse bispecific resulted in a dose-dependent increase in activated, memory and proliferating CD4$^+$ and CD8$^+$ T cells in the blood, tumour-draining lymph nodes (TDLNs) and the tumour, as well as a reduction in T$_{reg}$ cells and exhausted T cells in the tumour microenvironment. Similar results were obtained with the human bispecific in humanized mouse tumour models. The constructs were highly effective in inducing dose-dependent inhibition of tumour growth, prolonging survival and even inducing full tumour regression in some models. Target co-engagement on immune cells was shown to be crucial for anti-tumour efficacy.

Interestingly, the authors demonstrate that the bispecific has a different mechanisms of action compared to a combination of PD1 and GITR-targeted antibodies. It has a higher propensity for inducing immune activity in TDLNs and tumours and specifically activates CD8$^+$ T cells and promotes the formation of CD8$^+$ memory T cells.

Overall, the bispecific showed better anti-tumour efficacy compared to monotherapies targeting either PD1 or GITR, or a combination of such therapeutics. Moreover, the bispecific showed favourable pharmacokinetics/pharmacodynamics and excellent tolerability in cynomolgous monkeys.

These studies suggest that bispecific agonists targeting GITR may prevent immune escape of tumours in patients who do not respond to PD1/PDL1 targeted therapies and present a promising new therapeutic approach.

Alexandra Flemming

ORIGINAL ARTICLE Chan, S. et al. An anti-PD1-GITR-L bispecific agonist induces GITR clustering-mediated T cell activation for cancer immunotherapy. *Nat. Cancer* https://doi.org/10.1038/s43018-022-00334-9 (2022)