IN BRIEF

COVID-19

Cross reactive T cells hold up against Omicron

After a flurry of articles describing antibody evasion by Omicron, several reports now detail cellular immune responses against the highly mutated SARS-CoV-2 variant. Investigating $CD4^+$ and $CD8^+$ T cells in vaccinated and convalescent individuals, these studies show a high degree of preservation of T cell epitopes between the ancestral strain and Omicron. However, the degree of cross-reactivity varied among individuals, likely as a consequence of genetic aspects of antigen presentation. Gao et al. report a significantly lower magnitude of responses to the Omicron spike protein in T cells from convalescent compared to BNT162b2 vaccinated individuals, indicating that 'boosting' may benefit those with 'natural immunity'. Keeton et al. also investigated patients hospitalized with Omicron and found a similar magnitude of T cell responses as previously observed in patients infected with other variants. A comprehensive analysis of T cell responses against variants from Alpha to Omicron, at different time points after vaccination (with BNT162b2, mRNA-1273, Ad26.CoV2.S or NVX-CoV2373), was presented by Tarke et al. It shows that 84% of $CD4^+$ and 85% of $CD8^+$ memory T cell responses to the Omicron spike protein are preserved, compared to an average of 90% and 87% respectively for the other variants. This contrasts sharply with a marked reduction of memory B cell recognition of Omicron spike. Overall, these observations could explain why vaccines or previous infection still provide robust protection against severe disease with Omicron, even when levels of neutralizing antibodies are insufficient to prevent infection, and indicate that viral evolution is not driven by T cell escape.

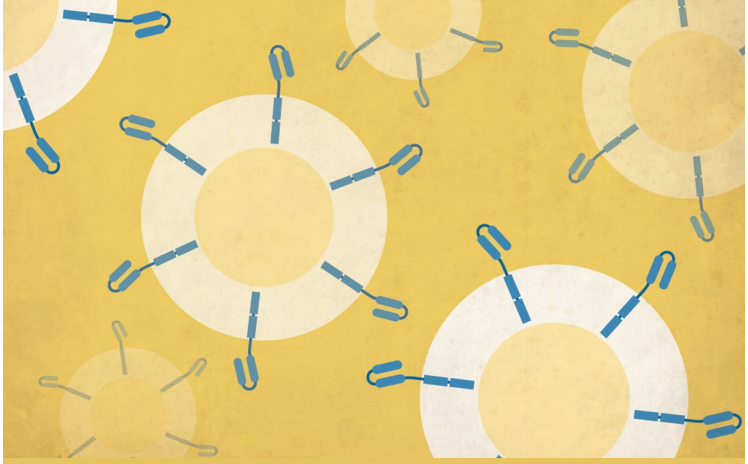
ORIGINAL ARTICLES Keeton, R. et al. T cell responses to SARS-CoV-2 spike cross-recognize Omicron. *Nature* https://doi.org/10.1038/s41586-022-04460-3 (2022) | Liu, J. et al. Vaccines elicit highly conserved cellular immunity to SARS-CoV-2 Omicron. *Nature* https://doi.org/10.1038/s41586-022-04465-y (2022) | Tarke, A. et al. SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron. *Cell* https://doi.org/10.1016/j.cell.2022.01.015 (2022) | Gao, Y. et. al. Ancestral SARS-CoV-2-specific T cells cross-recognize the Omicron variant. *Nat. Med.* https://www.nature.com/articles/s41591-022-01700-x (2022) | GeurtsvanKessel, C. H. et al. Divergent SARS CoV-2 Omicron-reactive T- and B cell responses in COVID-19 vaccine recipients. *Sci. Immunol.* https://doi.org/10.1126/sciimmunol.abo2202 (2022)

COVID-19

First glimpses into the mechanisms of Long COVID

Post-acute sequelae of COVID-19 (PASC), sometimes referred to as 'Long COVID', are observed in 30–70% of individuals post-SARS-CoV-2 infection. These can include loss of sense of smell, memory loss, fatigue, shortness of breath, gastrointestinal (GI) distress and other symptoms. Autoimmune processes and unresolved viral fragments have been proposed as causative, but experimental validation for these hypotheses is lacking. Now, a longitudinal multi-omic study of >300 patients by Su et al. reveals that some factors present at disease onset, such as pre-existing type 2 diabetes, latent EBV reactivation, circulating SARS-CoV-2 RNA fragments as well as specific autoantibodies, associate with specific PASC. The authors identified four different immune endotypes at 2–3 months post disease onset that differentially associate with PASC. Interestingly, they find that bystander activation of CMV-specific T cells during acute disease is associated with GI PASC. A second study by Vijayakumar et al. shows persistent immunological and proteomic abnormalities in the lungs of patients with ongoing respiratory symptoms after COVID-19, with continuing activation of $CD8^+$ T cells and elevated levels of proteins associated with apoptosis, tissue repair and epithelial injury.

ORIGINAL ARTICLES Su, Y. et al. Multiple early factors anticipate post-acute COVID-19 Sequelae. *Cell* https://doi.org/10.1016/j.cell.2022.01.014 (2022) | Vijayakumar, B. et al. Immuno-proteomic profiling reveals aberrant immune cell regulation in the airways of individuals with ongoing post-COVD-19 respiratory disease. *Immunity* https://doi.org/10.1016/j.immuni.2022.01.017 (2022)



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CANCER IMMUNOTHERAPY

Cytotoxic $CD4^+$ CAR T cells implicated in long-term leukaemia remission

Durable clinical responses after treatment with chimeric antigen receptor (CAR) T cells require the functional persistence of these cells. However, little is known about the fate of these cells once transferred to the patient. Now, a report by Melenhorst et al. in *Nature* presents a functional and molecular characterization of CAR T cells from two patients who have remained in remission for more than a decade after treatment for chronic lymphocytic leukaemia (CLL).

The patients had received CD19-targeted CAR T cells (CTL019) as part of a phase I clinical trial in 2010. The leukemic clone had been undetectable in both patients since 6 months after the infusion, whereas the CTL019 cells remained readily detectable for more than 10 years of follow-up. This provided a unique opportunity to study CAR T cell characteristics that are associated with long-term remission.

A longitudinal study using bulk and single-cell multi-omic approaches mapped the clonal evolution of the CAR T cells, with clones identified on the basis of their T cell receptor (TCR) β-chain rearrangement or the integration site of the CAR construct. The authors detected two phases of CAR T cell therapy response. The initial phase was dominated by cytotoxic $CD8^+$ CAR T cells, and in one patient also by $CD4^-CD8^-$γδCAR T cells that had upregulated the transcription factor Helios, which distinguished these cells from otherwise similar cytotoxic $CD8^+$ T cells. Unexpectedly, the long-term remission phase in both patients was dominated by a small number of highly activated $CD4^+$ CAR T cell clones, which constituted over 97% of CAR T cells at later timepoints.

These cells expressed the proliferation marker Ki67, the activation markers CD38, HLA-DR and CD95, the transcription factors EOMES and TOX, the checkpoint markers CTLA4, LAG3 and TIGIT, as well as the memory markers CD27 and CCR7.

Transcriptomic analysis further showed an enrichment in T cell activation, TCR signalling, oxidative phosphorylation, vesicle component and mitochondrial protein complex pathways, as well as an upregulation of *GZMK* and *GZMA*, which encode cytotoxic enzymes. When stimulated with CD19-expressing cells ex vivo, they upregulated the expression of CD107a, a marker of degranulation, as well as CCL4, perforin and granzyme A, indicative of direct cytotoxic function. These features suggest that long-persisting CAR T cells are cytotoxic, proliferating, and remain functionally active rather than exhausted.

Overall, these results reveal the surprising finding that long-term cytotoxicity against leukemic cells after CAR T cell treatment appears to be mediated by a limited number of metabolically active but checkpoint inhibitor-restrained cytotoxic $CD4^+$ CAR T cell clones.

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ORIGINAL ARTICLE Melenhorst, J. J. et al. Decade-long leukaemia remissions with persistence of $CD4^+$ CAR T cells. *Nature* https://doi.org/10.1038/s41586-021-04390-6 (2022)