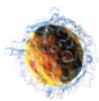
CANCER IMMUNOLOGY RESEARCH

WHAT WE'RE READING

A Sampling of Highlights from the Literature
Article Recommendations from Our Deputy and Senior Editors

Engineering T cells with $WT1_{37–45}$ peptide–specific TCRs shows preclinical efficacy



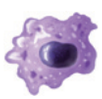
T cells expressing $WT1_{37–45}$-specific TCRs kill AML cells (by BruceBlaus via Wikimedia Commons)

T cells engineered to express T-cell receptors (TCR) targeting intracellular tumor antigens have potential for treating cancer. Two studies identify HLA-A*02:01–restricted TCRs specific for Wilms' tumor antigen 1 (WT1) peptide $WT1_{37–45}$ as candidates for clinical translation. Ruggiero et al. show that T cells engineered to express such TCRs significantly reduce tumor growth in xenograft models of acute myeloid leukemia (AML), acute lymphoblastic leukemia, and glioblastoma. Lahman et al. show that generation of $WT1_{37–45}$ is immunoproteasome independent, which is important because AML recurrence in one patient they treated with T cells expressing an HLA-A*02:01–restricted, $WT_{126–134}$-specific TCR occurred because of loss of immunoproteasome processing of WT1.

Ruggiero E, . . ., Bonini C. ***Sci Trans Med*** *2022 February 9;14. DOI:10.1126/scitranslmed.abg8027.*

Lahman MC, . . ., Greenberg PD. ***Sci Trans Med*** *2022 February 9;14. DOI:10.1126/scitranslmed.abg8070.*

PERK is a critical metabolic hub for immunosuppressive function in macrophages



PERK signaling promotes M2 macrophage immunosuppressive function (by Nodhtsmith via Wikimedia Commons)

Intratumoral macrophage phenotype is determined by the signals the cells receive from the tumor microenvironment. Raines et al. identify new molecular pathways that promote the activation and immunosuppressive function of M2 macrophages. They find that tumor-associated macrophages from patients with lung carcinoma are characterized by increased activity of protein kinase RNA-like ER kinase (PERK) signaling. This promotes an immunosuppressive phenotype in macrophages through metabolic reprograming and histone demethylation. Inhibition of PERK signaling reduces growth of B16-F10 tumors. This is associated with reduced numbers and immunosuppressive activity of intratumoral macrophages, suggesting PERK signaling inhibition as a potential therapeutic approach to target macrophages.

Raines LN, . . ., Huang SCC. ***Nature Immunol*** *2022;23:431–445.*

CRISPR activation and interference screens decode stimulation responses in primary human T cells

CRISPR technology allows for characterization of T-cell functional regulators (by Clipart Panda via Clipart Panda)

Identifying regulators of cytokine production upon cellular activation has had its limitations. Using novel CRISPR screens, Schmidt et al. identify regulators of IL2 and IFNγ production by T cells. Distinct cytokine profiles are identified and characterize T cells during various states of activation. The data highlight screening that can be performed to determine how T cells can be reprogramed and could be used to better design immunotherapy for the treatment of cancer.

Schmidt R, . . ., Marson A. ***Science*** *2022 February 4;375. DOI:10.1126/science.abj4008.*

Prediction modeling in cancer

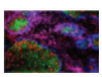
Prediction modeling could be used to identify patients who will respond to immune checkpoint blockade (by Eva K. via Wikimedia Commons)

Identifying markers of therapy response and patient outcome is an unmet clinical need. Patil et al. find that plasma cells in tumoral tertiary lymphoid structures are a biomarker of overall survival in patients treated with immune checkpoint blockade (ICB), an effect independent of tumor $CD8^+$ T cells and PD-L1 expression. Asrir et al. identify tumor-associated high endothelial venules as key players for lymphocyte entry into tumors and associated with survival and response to combination ICB. These two studies highlight key immune mechanisms and biomarkers that could be potentially used to improve treatment strategies for patients with cancer.

Asrir A, . . ., Girard JP. ***Cancer Cell*** *2022 March 14;40:318–334.e9.*

Patil NS, . . ., Shames DS. ***Cancer Cell*** *2022 March 14;40:289–300.e4.*

Looking back at CAR T-cell therapy outcomes



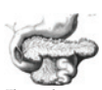
CAR T cells are being developed for many types of cancer (from Fig. 7B of Kantari-Mimoun et al., Cancer Immunol Res 2021)

Patient data following chimeric-antigen receptor (CAR) T-cell therapy are critical to ongoing clinical development. Through longitudinal analysis of two patients with chronic lymphocytic leukemia who achieved lasting complete remission after CD19-specific CAR T-cell therapy in 2010, Melenhorst et al. find that CAR T cells persist for more than a decade, with a population of highly activated $CD4^+$ CAR T cells dominating in both patients. Majzner et al. report that three of four patients with H3K27M-mutant diffuse midline glioma who received GD2-specific CAR T cells intravenously and then intracerebroventricularly had clinical and radiographic improvement. These studies provide new insights that will inform continued CAR T-cell development for hematological malignancies and solid tumors.

Melenhorst JJ, . . ., June CH. ***Nature*** *2022;602:503–509.*

Majzner RG, . . ., Monje M. ***Nature*** *2022 February 7;14. DOI:10.1038/s41586-022-04489-4.*

Fungal mycobiome drives IL-33 secretion and type 2 immunity in pancreatic cancer



The mycobiome facilitates pancreatic tumor progression (Pancreas, in Opera Omnia via Wellcome Collection)

T helper 2 cells (T_H2) and innate lymphoid cells 2 (ILC2) infiltrate pancreatic ductal adenocarcinomas (PDAC) and secrete cytokines that promote tumorigenesis. Alam et al. identify KrasG12D-regulated IL33 as a mediator of T_H2 and ILC2 recruitment in mouse models of PDAC. Fungal species found in the gut and tumor microenvironment induce tumor cell IL33 secretion by activating the dectin-1 receptor and downstream Src–Syk–CARD9 pathway. Anti-fungal treatment reduces T_H2 and ILC2 infiltration and reduces tumor growth, highlighting a novel mechanism by which the PDAC tumor mycobiome can regulate the pro-tumorigenic inflammatory response and suggesting a potential therapeutic strategy.

Alam A, . . ., Dey P. ***Cancer Cell*** *2022 February 14;40:153–167.E11.*

doi: 10.1158/2326-6066.CIR-10-4-WWR