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CANCER IMMUNOLOGY RESEARCH

# WHAT WE'RE READING

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

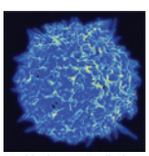
## Using bispecific antibodies to target tumor cells driven by RAS or p53

*Bispecific antibodies can activate T cells that target tumor cells expressing mutant RAS and p53 neoantigens (Bridging the Gap by Mike via Flickr)*

Developing therapeutics that target the mutant RAS and p53 proteins that drive many tumors has proven challenging. Hsiue et al. and Douglass et al. report the development of bispecific antibodies that target mutant p53 and RAS, respectively. After using mass spectrometry to identify a p53 neoantigen, Hsiue et al. screened a phage library to select an scFV specific for the neoantigen–HLA complex. This scFV was used to generate a bispecific antibody that induces T cells to kill tumor cells in a neoantigen-specific manner. Using the same approach, Douglass et al. were able to generate a bispecific antibody that induces T-cell killing of tumor cells expressing mutant RAS. Future studies will investigate whether such bispecific antibodies have therapeutic potential.

*Hsiue EH-C, . . ., Zhou S.* ***Science*** *2021 Mar 5;371:eabc8697.*
*Douglass J, . . ., Zhou S.* ***Sci Immunol*** *2021 Mar 1;6:eabd5515.*

## Immunogenic chemotherapy enhances recruitment of CAR-T cells to lung tumors and improves antitumor efficacy when combined with checkpoint blockade

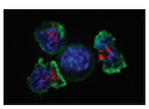


*Healthy human T cell (from National Institute of Allergy and Infectious Diseases via Flickr)*

Consistent with previous studies testing CAR-T cells as a treatment for solid tumors, Srivastava et al. find that in patients with breast or lung cancer expressing receptor tyrosine kinase-like orphan receptor 1 (ROR1) who receive cyclophosphamide/fludarabine pretreatment for lymphodepletion, ROR1 CAR-T cells infiltrate tumors poorly and become dysfunctional rapidly. In mice, adding oxaliplatin to cyclophosphamide for lymphodepletion induces tumor macrophage production of T cell–recruiting chemokines, enhancing tumor infiltration by ROR1 CAR-T cells. These data are clinically relevant, as lymphodepletion with oxaliplatin/cyclophosphamide is shown to improve tumor infiltration by ROR CAR-T cells in a patient with ROR$^+$ breast cancer.

*Srivastava S, . . ., Riddell S.* ***Cancer Cell*** *2021 Feb 8;39:193–208. e10.*

## Identification of circulating antitumor CD8$^+$ T cells



*Killer T cells surround a cancer cell (by Alex Ritter, Jennifer Lippincott Schwartz, and Gillian Griffiths via NCI Visuals Online)*

Characterizing tumor-specific T cells in the blood has great therapeutic value. Pauken et al. perform single-cell RNA and TCR sequencing of CD8$^+$ T cells in paired blood and tumor samples and identify NKG2D, CD39, and CXCR1 as candidate markers for tumor-specific CD8$^+$ T cells. Lucca et al. perform similar experiments in melanoma patients and show that circulating T cells exhibit similar effector gene signatures as TCR-matched tumor-infiltrating T cells but do not have exhaustion gene signatures. These results help identify selective markers for tumor-specific CD8$^+$ T cells in the blood.

*Pauken KE, . . ., Singer M.* ***J Exp Med*** *2021 Mar 2;218:e20200920.*
*Lucca LE, . . ., Hafler DA.* ***J Exp Med*** *2021 Mar 2;218:e20200921.*

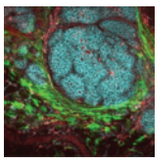
## Metabolic regulation of regulatory T cells


*Lactic acid metabolism promotes Tregs (from Fig. 1 of de la Cruz-Lopez, Front Immunol 2019)*

Immune cell metabolism can impact the efficacy of cancer immunotherapy. Watson et al. show that regulatory T cells (Treg) are metabolically flexible. Treg function and stability are impaired by high-glucose conditions, but Tregs can upregulate pathways involved in lactic acid metabolism, and this maintains their suppressive phenotype in the tumor microenvironment (TME). Zappasodi et al. find that anti–CTLA-4 promotes destabilization of Tregs in the TME. This is dependent on glycolysis and CD28 signaling and results in Tregs gaining a more effector phenotype in tumors lacking LDHA (lactic acid dehydrogenase A). These two articles shed light on the complexity of metabolic regulation occurring in the TME.

*Watson MJ, . . ., Delgoffe GM.* ***Nature*** *2021 Feb 15. DOI: 10.1038/s41586-020-03045-2.*
*Zappasodi R, . . ., Merghoub T.* ***Nature*** *2021 Feb 15. DOI: 10.1038/s41586-021-03326-4.*

## A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells



*Breast tumor microenvironment (by Joseph Szulczewski, David Inman, Kevin Eliceiri, and Patricia Keely via NCI Visuals Online)*

The landscape of tumor-infiltrating myeloid cells (TIM) among different tumor types remains poorly understood. Cheng et al. perform pan-cancer single-cell transcriptional analysis of TIMs from 210 patients across 15 cancer types. Highlights of the data include: The ratio of *TNF*$^+$ to *VEGFA*$^+$ mast cells is associated with prognosis in nasopharyngeal cancer; cDC1-derived *LAMP3*$^+$ cDCs express higher IL12B and BTLA, whereas cDC2-derived *LAMP3*$^+$ cDCs show higher expression of CD1E and CCL17; and proangiogenic tumor-associated macrophages have distinct markers in different cancer types. Together, these results point to the heterogeneity of TIMs and new approaches to therapeutic targeting of TIMs.

*Cheng S, . . ., Zhang Z.* ***Cell*** *2021 Feb 4;184:792–809. e23.*

## Overcoming resistance to anti–PD-1 therapy in melanoma patients

*The gut microbiota can impact immunotherapy (by DataBase Center for Life Science via Wikimedia Commons)*

The gut microbiome composition correlates with efficacy of immune checkpoint blockade, but whether this can be leveraged to overcome therapy resistance is not clear. Two clinical studies by Davar et al. and Baruch et al. address this and show that fecal microbiota transplantation in combination with anti–PD-1 is safe and efficacious in patients with anti–PD-1 refractory melanoma. Some patients had complete or partial responses, and responders had distinct expression, proteomic, and metabolic signatures, as well as alteration of the microbiota composition. The data from these two clinical studies highlight a novel treatment option to overcome anti–PD-1 resistance in melanoma.

*Davar D, . . ., Zarour HM.* ***Science*** *2021 Feb 5;371:595–602.*
*Baruch EN, . . ., Boursi B.* ***Science*** *2021 Feb 5;371:602–9.*