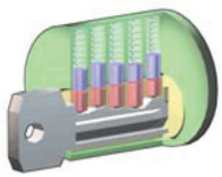
Cancer Immunology Research

Literature Highlights: Impactful Papers Published Elsewhere

Article Recommendations from Our Deputy and Senior Editors

Selective targeting of engineered T cells using orthogonal IL-2 cytokine-receptor complexes

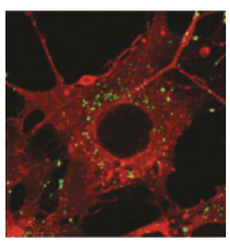


Engineering safer immunolocks and keys (by Wapcaplet via Wikimedia Commons)

IL2 therapy is used with caution due to adverse events at IL2 concentrations that are clinically useful. A modified IL2 receptor, which only binds to a modified form of IL2, was inserted into T cells destined for adoptive antitumor therapy. The modified IL2 was designed to only bind the modified receptor, and, as administration of this modified IL2 activates only the transferred T cells, the IL2 provides not only therapeutic benefit but also is not associated with identifiable toxicity.

Sockolosky JT, . . ., Garcia KC. **Science** 2018 Mar 2;359:1037–42.

Cancer-associated fibroblasts induce antigen-specific deletion of $CD8^+$ T cells to protect tumor cells



Fibroblast engulfing debris (From Lakins et al.)

Tumor fibroblasts were found to engulf and process tumor cell debris, then cross-present it to T cells. However, instead of activating T cells, this presentation is suppressive and reduces T-cell viability. The T-cell death results from increased expression of FasL and PD-L2 on the fibroblasts that, in turn, activates Fas and PD-1 pathways in the T cells. Blockade of these interactions restored antigen-specific T-cell killing of tumor cells.

Lakins MA, . . ., Shields JD. **Nat Commun** 2018 Mar 5. DOI: 10.1038/s41467-018-03347-0.

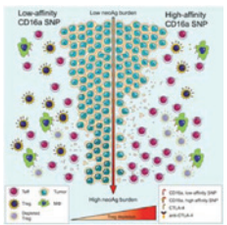
Macrophage manipulation to improve antitumor responses

Tumor-associated macrophage clusters (from Perry et al., Fig. 2)

Immunotherapeutics are hampered by suppressive elements in the tumor microenvironment, including M2 (suppressive) macrophages. Perry et al., using an authochthonous mouse model (mutant Braf/Pten) of melanoma, and Hoves et al., primarily with the MC38 model, show that activating CD40 while inhibiting CSF-1R signaling changes transcriptional modules, reduces M2s, increases inflammatory macrophages, and improves tumor control. The effects are strong, but not permanent, and both $CD8^+$ T cells and macrophages are necessary for tumor eradication.

Perry CJ, . . ., Kaech SM. **J Exp Med** 2018 Feb 7;215:877–93.
Hoves S, . . ., Ries CH. **J Exp Med** 2018 Feb 7;215:859–76.

Fc effector function contributes to the activity of human anti–CTLA-4 antibodies

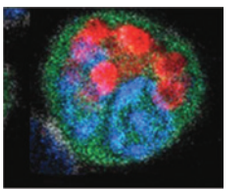


Fc affinity affects checkpoint blockade effectiveness (from Arce Vargas et al.)

Optimization of the interaction between human FcγRs and anti–CTLA-4 in humanized mice expressing human FcγRs efficiently depletes Tregs and controls tumor growth. However, removal of Tregs is only important in tumors that are highly inflamed and infiltrated by $CD8^+$ T cells. Patients carrying FcγR polymorphisms with higher binding affinities for IgGs, and that have higher neoantigen burdens, show greater responses to CTLA-4 blockade.

Arce Vargas F, . . ., Quezada SA. **Cancer Cell** 2018 Mar 22. DOI: 10.1016/j.ccell.2018.02.010.

4-1BB costimulation regulates antitumor T-cell metabolic function and enhances immunotherapies



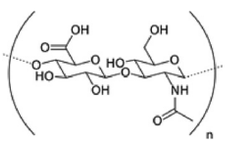
4-1BB–activated mitochondria (from Teijeira et al., Fig. 6)

Removing checks on T-cell activation is often insufficient for reactivating $CD8^+$ T cells. Inducing 4-1BB signaling while blocking PD-1 (Menk et al.) or during adoptive T-cell therapy (Teijeira et al.) induces robust antitumor immunity in mouse models of melanoma or colon cancer. 4-1BB appears to regulate mitochondrial mass and function, reprogramming the metabolic state of antitumor T cells to counter exhaustion.

Menk AV, …, Delgoffe GM. **J Exp Med** 2018 Mar 6. DOI: 10.1084/jem.20171068.

Teijeira A, …, Melero I. **Cancer Immunol Res** 2018 Apr. DOI: 10.1158/2326-6066.CIR-17-0767.

Extended release of perioperative immunotherapy prevents tumor recurrence and eliminates metastases



Core of hydrogel (by Edgar181 via Wikimedia Commons)

Surgery removes primary tumors, but the wound healing process produces an immunosuppressive environment that may be conducive to regrowth of residual tumor cells and distal metastasis. Placing a hydrogel laced with agonists for innate immune responses into post-surgical wounds from which tumors had been extracted resulted in activation of innate and specific antitumor responses and a decrease in metastasis.

Park CG, . . ., Goldberg MS. **Sci Transl Med** 2018 Mar 21;10: eaar1916.