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Kerry S. Campbell

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**Combined BRAF, MEK, and CDK4/6 Inhibition Depletes Intratumoral Immune-Potentiating Myeloid Populations in Melanoma**
Emily J. Lelliott, Stefano Mangiola, Kelly M. Ramsbottom, Magnus Zethoven, Lydia Lim, Peter K.H. Lau, Amanda J. Oliver, Luciano G. Martelotto, Laura Kirby, Claire Martin, Riyaben P. Patel, Alison Slater, Carleen Cullinan, Anthony T. Papenfuss, Nicole M. Haynes, Grant A. McArthur, Jane Oliaro, and Karen E. Sheppard

## Research Articles

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**KIR3DL3 Is an Inhibitory Receptor for HHLA2 that Mediates an Alternative Immunoinhibitory Pathway to PD1**

The B7 family member HHLA2 delivers costimulatory signals via TMIGD2. The data show that KIR3DL3 is an inhibitory receptor for HHLA2 and that HHLA2 is expressed in kidney cancer separately from PDL1; targeting this interaction could be immunotherapeutic.

See related Spotlight, p. 128

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**Nutlin-3a Enhances Natural Killer Cell–Mediated Killing of Neuroblastoma by Restoring p53-Dependent Expression of Ligands for NKG2D and DNAM-1 Receptors**
Irene Veneziani, Paola Infante, Elisa Ferretti, Ombretta Melaui, Cecilia Battistelli, Valeria Lucarini, Mirco Compagnone, Carmine Nicoletti, Aurora Castellano, Stefania Petrini, Marzia Ognibene, Annalisia Pezzolo, Lucia Di Marcotullio, Roberto Bei, Lorenzo Moretta, Vito Pistoia, Dorian Fruci, Vincenzo Barnaba, Franco Locatelli, and Loredana Cifaldi

Nutlin-3a, a small molecule antagonizing the inhibitory MDM2–p53 interaction, has a p53-dependent immunomodulatory effect on neuroblastoma. Nutlin-3a increases neuroblastoma’s susceptibility to NK-cell killing, highlighting how this compound could be prospectively employed for an NK cell–based immunotherapy.

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**Pharmacologic Screening Identifies Metabolic Vulnerabilities of CD8⁺ T Cells**
Jefte M. Drijvers, Jacob E. Gillis, Tara Muilwijk, Thao H. Nguyen, Emily F. Gaudiano, Isaiah S. Harris, Martin W. LaFleur, Alison E. Ringel, Cong-Hui Yao, Kiran Kurmi, Vikram R. Juneca, Justin D. Trombley, Marcia C. Haigis, and Arlene H. Sharpe

It is challenging to develop metabolism-targeted therapeutics because T cells and cancer cells have similar metabolic properties. The authors develop an in vitro pharmacologic screening platform and highlight ferroptosis as a metabolic vulnerability of CD8⁺ T cells.
Targeted Deletion of CXCR2 in Myeloid Cells Alters the Tumor Immune Environment to Improve Antitumor Immunity
Jinming Yang, Chi Yan, Anna E. Vilgelm, Sheau-Chiann Chen, Gregory D. Ayers, Christopher A. Johnson, and Ann Richmond
Myeloid cell CXCR2 affects not only suppressive MDSCs but also B cells, especially the B1b subset. CXCL11-producing B cells are key and impact infiltration and activation of effector CD8+ T cells in the tumor microenvironment.

Oxidized Lipoproteins Promote Resistance to Cancer Immunotherapy Independent of Patient Obesity
The influence of obesity on cancer immunotherapy is not clear. This study shows oxidized LDL promotes resistance to immunotherapy by suppressing T-cell function and driving tumor cytoprotection mediated by heme oxygenase-1 (HO-1), suggesting HO-1 is a promising therapeutic target.

Fructose Promotes Cytoprotection in Melanoma Tumors and Resistance to Immunotherapy
Dietary fructose can be utilized by tumor cells and promotes cytoprotection by inducing HO-1 expression, thereby impacting TIL responses and immunotherapy outcomes. The data highlight a novel immune evasion mechanism and a potential therapeutic target.

Therapy of Established Tumors with Rationally Designed Multiple Agents Targeting Diverse Immune–Tumor Interactions: Engage, Expand, Enable
Kellsye P. Fabian, Anthony S. Malamas, Michelle R. Padget, Kristen Solocinski, Benjamin Wolfson, Rika Fuji, Houssine Abdul Sater, Jeffrey Schlom, and James W. Hodge
Treatment of established tumors with a combination “pentatherapy” regimen leads to T-cell activation while decreasing Treg suppression. The data highlight how the combination of multimodal immunotherapy agents can engage, enhance, and enable adaptive antitumor responses.

Combined BRAF, MEK, and CDK4/6 inhibition is an emerging therapy for the treatment of BRAFV600E melanoma, but the immunomodulatory effects of this combination remain unexplored. Using flow cytometry and single-cell RNA sequencing, Lelliott et al. show that the triple therapy markedly alters the tumor immune microenvironment in a mouse model of BRAFV600E melanoma. Specifically, this combination therapy promotes high levels of lymphocyte infiltration but simultaneously depletes immune-potentiating myeloid subsets, including proinflammatory macrophages and CD103+ dendritic cells (DC). This lowered frequency of CD103+ DCs correlates with resistance to immune checkpoint blockade (ICB) in mice and poor responses to ICB in patients. The study has implications for clinical trial design, as it highlights that, despite potent tumor-intrinsic effects, the triple therapy may adversely impact antitumor immunity. Read more in this issue on page 136. Original image from Fig. 1I. Artwork by Lewis Long.
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