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    Kerry S. Campbell
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129  About the Master
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    Douglas R. Green
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#### PRIORITY BRIEFS

136  Combined BRAF, MEK, and CDK4/6 Inhibition Depletes Intratumoral Immune-Potentiating Myeloid Populations in Melanoma
    Emily J. Lelliott, Stefano Mangiola, Kelly M. Rambottom, 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
    Combined BRAF, MEK, and CDK4/6 inhibition is being tested in clinical trials for treating melanoma. The authors show this combination depletes tumor-associated myeloid cells in the tumor immune microenvironment, which renders tumors unresponsive to immune checkpoint blockade.

147  Kindlin3-Dependent CD11b/CD18-Integrin Activation Is Required for Potentiation of Neutrophil Cytotoxicity by CD47–SIRPα Checkpoint Disruption
    Panagiota Bouti, Xi Wen Zhao, Paul J.J.H. Verkuijlen, Anton T.J. Tool, Michel van Houdt, Nezihe Köker, Mustafa Yavuz Köker, Örzen Keskin, Sinan Akbayram, Robin van Bruggen, Taco W. Kuijpers, Hanke L. Matlung, and Timo K. van den Berg
    Neutrophil-mediated ADCC is dependent on CD11b/CD18-integrin-mediated conjugate formation and is controlled by CD47–SIRPα signaling. By using LAD3-derived neutrophils, it is demonstrated that CD47–SIRPα signaling controls CD11b/CD18-integrin inside-out activation during conjugate formation in a kindlin3-dependent manner.

#### RESEARCH ARTICLES

156  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 PD1; targeting this interaction could be immunotherapeutic.
    See related Spotlight, p. 128

170  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 Petri, Marzia Ognibene, Annalisa Pezzolo, Lucia Di Marchi, Roberto Be, Lorenzo Moretta, Vito Pistoia, Doriane 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.

184  Pharmacologic Screening Identifies Metabolic Vulnerabilities of CD8⁺ T Cells
    Jefte M. Drijvers, Jacob E. Gillis, Tara Muilwijk, Thao H. Nguyen, Emily F. Gaudiano, Isaac S. Harris, Martin W. LaFleur, Alison E. Ringel, Cong-Hui Yao, Kiran Kurmi, Vikram R. Juneja, 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, Houssen 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.