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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**
A C 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 Cullinane, 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, Ozlem 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**
Rupal S. Bhatt, Abdulla Berjis, Julie C. Konge, Kathleen M. Mahoney, Alyssa N. Klee, Samuel S. Freeman, Chun-Hau Chen, Opeyemi A. Jegede, Paul J. Catalano, Jean-Christophe Pignon, Maura Sticco-Ivins, Baogong Zhu, Ping Hua, Jo Soden, Jie Zhu, David F. McDermott, Antonio R. Arulanandam, Sabina Signoretti, and Gordon J. Freeman

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

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 Melaiu, Cecilia Battistelli, Valeria Lucarini, Mirco Compagnone, Carmine Nicoletti, Aurora Castellano, Stefania Petrini, Marzia Ognibene, Annalisa Pezzolo, Lucia Di Marcotullio, Roberto Bei, Lorenzo Moretta, Vito Pistoia, Doriana 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 Muijlwijk, 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.

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200 **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.

214 **Oxidized Lipoproteins Promote Resistance to Cancer Immunotherapy Independent of Patient Obesity**
Niloufar Khojandi, Lindsey M. Kuehm, Alexander Piening, Maureen J. Donlin, Eddy C. Hsueh, Theresa L. Schwartz, Kaitlin Farrell, John M. Richart, Elizabeth Geerling, Amelia K. Pinto, Sarah L. George, Carolyn J. Albert, David A. Ford, Xiufen Chen, Justin Kline, and Ryan M. Teague

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.

See related article, p. 227

227 **Fructose Promotes Cytoprotection in Melanoma Tumors and Resistance to Immunotherapy**
Lindsey M. Kuehm, Niloufar Khojandi, Alexander Piening, Lauryn E. Klevorn, Simone C. Geraud, Nicole R. McLaughlin, Kristine Griffett, Thomas P. Burris, Kelly D. Pyles, Afton M. Nelson, Mary L. Preuss, Kevin A. Bockerstett, Maureen J. Donlin, Kyle S. McCommis, Richard J. DiPaolo, and Ryan M. Teague

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.

See related article, p. 214

239 **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 Fujii, Houssein 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.

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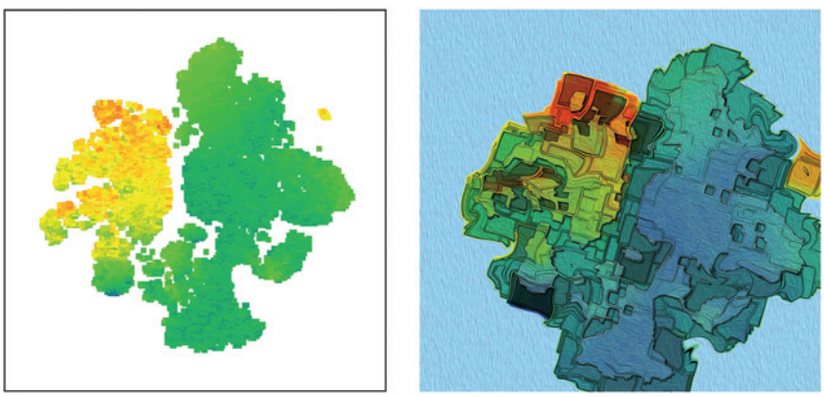
ABOUT THE COVER

Combined BRAF, MEK, and CDK4/6 inhibition is an emerging therapy for the treatment of $BRAF^{V600E}$ 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 $BRAF^{V600E}$ 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, this 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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