## What We’re Reading

127  A Sampling of Highlights from the Literature

## In the Spotlight

128  Mystery Checkpoint Revealed: KIR3DL3 Finally Found a Ligand in HHLA2  
Kerry S. Campbell  
See related article, p. 156

## Masters of Immunology

129  About the Master  
See related article, p. 130

130  Health and Fitness at the Single-Cell Level  
Douglas R. Green  
See related article, p. 129

## 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. 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

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.I.H. Verkuijlen, Anton T.J. Tool, Michel van Houdt, Nezihe Köker, Mustafa Yavuz Köker, Özlem Keskin, Sinan Akbayram, Robin van Bruggen, Taco W. Kuipers, Hanke L. Matlung, and Timo K. van den Berg

## 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 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 Melaia, Cecilia Battistelli, Valeria Lucarini, Mirco Compagnone, Carmine Nicoletti, Aurora Castellano, Stefania Petrini, Marzia Ognibene, AnnaValeria Pezzolo, Lucia Di Marcotullio, Roberto Bej, 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 Muilwijk, Thao H. Nguyen, Emily F. Gaudiano, Isaac S. Harris, Martin W. Lefleur, Alison E. Ringel, Cong-Hui Yao, Kiran Kurmi, Vikram R. Junjaa, 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.

See related article, p. 227

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.

See related article, p. 214

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.

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.