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IN THE SPOTLIGHT

128 Mystery Checkpoint Revealed: KIR3DL3 Finally Found a Ligand in HHLA2
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130 Health and Fitness at the Single-Cell Level
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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, Riyah P. Patel, Alison Slater, Carleen Cullinan, 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
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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 TIMG2. 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.
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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 Melaure, Cecilia Battistelli, Valeria Lucarini, Mirco Compagnone, Carmine Nicoletti, Aurora Castellano, Stefania Petrini, Marzia Ognibene, Annalisa Pezzolo, Lucia Di Marcello, 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 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, Houssine Abdul Sater, Jeffrey Schlom, and James W. Hodge

Treatment of established tumors with a combination “pentathrapy” 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.