

CANCER IMMUNOLOGY RESEARCH

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Robert D. Schreiber and Philip D. Greenberg

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Sandra Demaria
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Ryan M. Shih and Yvonne Y. Chen
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RESEARCH ARTICLES

- 12 **Imaging α -GalCer-Activated iNKT Cells in a Hepatic Metastatic Environment**
Liane Babes, Raymond Shim, and Paul Kubes
Activating hepatic iNKT cells with α -GalCer has no effect on established colorectal tumors. However, prophylactic repeated dosing reduces liver metastases via enhancement of iNKT-cell responses, highlighting a potential therapeutic strategy for colorectal cancer patients with high metastatic risk.

- 26 **Neoadjuvant STING Activation, Extended Half-life IL2, and Checkpoint Blockade Promote Metastasis Clearance via Sustained NK-cell Activation**

Lauren E. Milling, Daniel Garafola, Yash Agarwal, Shengwei Wu, Ayush Thomas, Nathan Donahue, Josetta Adams, Nikki Thai, Heikyung Suh, and Darrell J. Irvine

Combining STING agonists, extended half-life IL2, and anti-PD-1 checkpoint blockade administered prior to surgical resection drives innate and adaptive antitumor immunity that controls the growth of intratumorally injected lesions and lung metastases in an NK cell-dependent manner.

See related Spotlight, p. 3

- 40 **Macrophage-Targeted Therapy Unlocks Antitumoral Cross-talk between IFN γ -Secreting Lymphocytes and IL12-Producing Dendritic Cells**

Christina Pfirschke, Rapolas Zilionis, Camilla Engblom, Marius Messemaker, Angela E. Zou, Steffen Rickelt, Nicolas A. Gort-Freitas, Yunkang Lin, Ruben Bill, Marie Siwicki, Jeremy Gungabeeson, Melissa M. Sprachman, Angela N. Marquard, Christopher B. Rodell, Michael F. Cuccarese, Jeremy Quintana, Maaz S. Ahmed, Rainer H. Kohler, Virginia Savova, Ralph Weissleder, Allon M. Klein, and Mikael J. Pittet

The CSF1R-targeting agent BLZ945 controls mouse lung adenocarcinoma and acts through a mechanism that converges on a core licensing loop between CSF1R-negative cells, which also mediate T cell-targeted immunotherapies.

See related Spotlight, p. 4

- 56 **B7-H3 Suppresses Antitumor Immunity via the CCL2-CCR2-M2 Macrophage Axis and Contributes to Ovarian Cancer Progression**

Taito Miyamoto, Ryusuke Murakami, Junzo Hamanishi, Kenji Tanigaki, Yuko Hosoe, Nathan Mise, Shiro Takamatsu, Yuka Mise, Masayo Ukita, Mana Taki, Koji Yamanoi, Naoki Horikawa, Kaoru Abiko, Ken Yamaguchi, Tsukasa Baba, Noriomi Matsumura, and Masaki Mandai

A role of B7-H3 in M2 macrophage-mediated immunosuppression in ovarian cancer is demonstrated. The data reveal B7-H3's potential as a therapeutic target to enhance antitumor responses in ovarian cancer, highlighting a differential role from other B7 family members.

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70 APOBEC Mutagenesis Inhibits Breast Cancer Growth through Induction of T cell-Mediated Antitumor Immune Responses

Ashley V. DiMarco, Xiaodi Qin, Brock J. McKinney, Nina Marie G. Garcia, Sarah C. Van Alsten, Elizabeth A. Mendes, Jeremy Force, Brent A. Hanks, Melissa A. Troester, Kouros Owzar, Jichun Xie, and James V. Alvarez

APOBEC mutagenic activity is shown to sensitize HER2-driven mammary tumors to immune checkpoint inhibition, an effect dependent on T-helper cells. Data highlight potential biomarkers that could be used to predict immunotherapy responses in patients with HER2⁺ breast cancer.

87 BET Inhibition Enhances TNF-Mediated Antitumor Immunity

Lisa C. Wellinger, Simon J. Hogg, Dane M. Newman, Thomas Friess, Daniela Geiss, Jessica Michie, Kelly M. Ramsbottom, Marina Bacac, Tanja Fauti, Daniel Marbach, Laura Jarassier, Phillip Thienger, Axel Paehler, Leonie A. Cluse, Conor J. Kearney, Stephin J. Vervoort, Joseph A. Trapani, Jane Oliaro, Jake Shortt, Astrid Ruefli-Brasse, Daniel Rohle, and Ricky W. Johnstone

Small molecules that target epigenetic regulators, such as BET inhibitors, can alter tumor cell responses to pro-inflammatory cytokines via modulation of prosurvival signaling pathways. Use of small-molecule agents in combination with immunotherapy increases tumor susceptibility to CTL killing.

108 Identification of Immunogenic MHC Class II Human HER3 Peptides that Mediate Anti-HER3 CD4⁺ Th1 Responses and Potential Use as a Cancer Vaccine

Amrita Basu, Gabriella K. Albert, Sabrina Awshah, Jashodeep Datta, Krithika N. Kodumudi, Corey Gallen, Amber Beyer, Keiran S.M. Smalley, Paulo C. Rodriguez, Derek R. Duckett, Peter A. Forsyth, Aixa Soyano, Gary K. Koski, Ricardo Lima Barros Costa, Heather Han, Hatem Soliman, Marie Catherine Lee, Pawel Kalinski, and Brian J. Czerniecki

Multiple immunogenic, promiscuous MHC class II HER3 peptides are identified and shown to induce potent human and mouse CD4⁺ Th1 responses. The data highlight HER3 as a potential target in both preventative and therapeutic settings.

126 Plexin-A4 Mediates Cytotoxic T-cell Trafficking and Exclusion in Cancer

Ward Celus, Ana I. Oliveira, Silvia Ravis, Heleen H. Van Acker, Ewout Landeloos, Jens Serneels, Sarah Trusso Cafarello, Yannick Van Herck, Roberta Mastrantonio, Arnaud Köhler, Abhishek D. Garg, Véronique Flamand, Luca Tamagnone, Jean-Christophe Marine, Mario Di Matteo, Bruno M. Costa, Oliver Bechter, and Massimiliano Mazzone

Knocking out Plexin-A4 promotes CTL proliferation and infiltration into the lymph nodes and tumor bed, boosting antitumor immunity of endogenous or adoptively transferred T cells. PLXNA4 downregulation in melanoma patient circulating CTLs is associated with response to ICIs.

142 Acknowledgment to Reviewers

ABOUT THE COVER

Metastasis after surgical resection of primary tumors is a frequent occurrence, and methods to prevent this are needed. Babes et al. demonstrate the utility of invariant (i) NKT cells in preventing liver metastasis. State-of-the-art *in vivo* imaging techniques show that repeated activation of iNKT cells with α -galactosylceramide (α -GalCer) increases their number and granularity in the liver, leading to inhibition of tumor growth and improved tumor immunity of metastatic tumors. The imaging approach serves to optimize how iNKT cells could be activated to induce antitumor cells for future therapeutics. The data also highlight a potential early intervention strategy to prevent, and/or treat patients who develop, liver metastasis. Read more in this issue on page 12. Original image from Fig. 7D. Artwork by Lewis Long.

