

## HIGHLIGHTS FROM THE LITERATURE

- 717 What We're Reading

## RESEARCH ARTICLES

- 718** Development of Aggressive Pancreatic Ductal Adenocarcinomas Depends on Granulocyte Colony Stimulating Factor Secretion in Carcinoma Cells  
Michael W. Pickup, Philip Owens, Agnieszka E. Gorska, Anna Chytil, Fei Ye, Chanjuan Shi, Valerie M. Weaver, Raghu Kalluri, Harold L. Moses, and Sergey V. Novitskiy  
*Aggressive PDAC correlates with increased G-CSF production and accumulation of immunosuppressive cells. Treatment of mouse models with gemcitabine and anti-G-CSF was efficacious. Analysis of clinical data indicates a subset of patients for whom this treatment might be effective.*

- 730** Using Antigen-Specific B Cells to Combine Antibody and T Cell–Based Cancer Immunotherapy  
Kerstin Wennhold, Martin Thelen, Hans Anton Schlößer, Natalie Hausteiner, Sabrina Reuter, Maria Garcia-Marquez, Axel Lechner, Sebastian Kobold, Felicitas Rataj, Olaf Utermöhlen, Geothy Chakupurakal, Sebastian Theurich, Michael Hallek, Hinrich Abken, Alexander Shimabukuro-Vornhagen, and Michael von Bergwelt-Baildon  
*B-cell effector functions could be exploited for cancer immunotherapy. A two-pronged approach in mice, combining antigen-specific CD40-activated B cells with antigen-specific plasma cells, induced a successful T-cell antitumor immune response, demonstrating potential for translation.*

- 744** Clonal Expansion and Interrelatedness of Distinct B-Lineage Compartments in Multiple Myeloma Bone Marrow  
Leo Hansmann, Arnold Han, Livius Penter, Michaela Liedtke, and Mark M. Davis  
*Only some multiple myeloma patients benefit from cellular immunotherapies. A single-cell, high-throughput methodology was developed that determines the phenotypic range of a given B- or plasma cell clone, which could aid identification of those most likely to respond.*

- 755** Concurrent PD-1 Blockade Negates the Effects of OX40 Agonist Antibody in Combination Immunotherapy through Inducing T-cell Apoptosis  
Rajeev K. Shrimali, Shamim Ahmad, Vivek Verma, Peng Zeng, Sudha Ananth, Pankaj Gaur, Rachel M. Gittelman, Erik Yusko, Catherine Sanders, Harlan Robins, Scott A. Hammond, John E. Janik, Mikayel Mkrtichyan, Seema Gupta, and Samir N. Khleif  
*Simultaneous treatment of mice with checkpoint inhibitor anti-PD-1 and agonist anti-OX40 negated the benefits of anti-OX40 alone, due to increased apoptosis of CD8<sup>+</sup> T cells. Thus, for clinical success, sequencing optimization for combination immunotherapy is crucial.*

- 767** The Tumor Microenvironment Regulates Sensitivity of Murine Lung Tumors to PD-1/PD-L1 Antibody Blockade  
Howard Y. Li, Maria McSharry, Bonnie Bullock, Teresa T. Nguyen, Jeff Kwak, Joanna M. Poczobutt, Trisha R. Sippel, Lynn E. Heasley, Mary C. Weiser-Evans, Eric T. Clambey, and Raphael A. Nemenoff  
*In several mouse lung cancer models, response to PD-1/PD-L1 inhibitors depended on the cancer cells as well as the tumor microenvironment. Blocking PD-L1 expression in either the cancer cells or the host limited tumor growth.*

- 778** MICA-Expressing Monocytes Enhance Natural Killer Cell Fc Receptor-Mediated Antitumor Functions  
Amanda R. Campbell, Megan C. Duggan, Lorena P. Suarez-Kelly, Neela Bhawe, Kallan S. Opheim, Elizabeth L. McMichael, Prashant Tripathi, Robin Parihar, Eric Luedke, Adrian Lewis, Bryant Yung, Robert Lee, David Raulet, Susheela Tridandapani, Veronika Groh, Lianbo Yu, Vedat Yildiz, John C. Byrd, Michael A. Caligiuri, and William E. Carson III  
*Natural killer (NK) cells secrete immunostimulatory factors like IFN $\gamma$  in response to tumors. Engagement of monocyte MICA and NK cell NKG2D promoted and enhanced the NK response to HER2<sup>+</sup> breast tumors treated with mAb to HER2 in a murine model.*

- 790** A Multikinase and DNA-PK Inhibitor Combination Immunomodulates Melanomas, Suppresses Tumor Progression, and Enhances Immunotherapies  
Alexander K. Tsai, Asra Y. Khan, Christina E. Worgo, Lucy L. Wang, Yuanyuan Liang, and Eduardo Davila  
*Regorafenib and NU7441 are targeted therapies that immunomodulated a heterogeneous panel of melanomas. The compounds favorably altered T-cell phenotype and function, and cooperated with existing immunotherapies to suppress melanoma progression in a murine tumor model.*

# Table of Contents

## 804 Role of NOX2-Derived Reactive Oxygen Species in NK Cell-Mediated Control of Murine Melanoma Metastasis



### Melanoma Metastasis

Ebru Aydin, Junko Johansson, Faisal Hayat Nazir, Kristoffer Hellstrand, and Anna Martner

*Inhibition of NOX2 in mice reduced melanoma metastasis through a natural killer cell and interferon- $\gamma$ -based mechanism. Pharmacological inhibition of NOX2, alone or combined with immunostimulatory strategies, could provide an approach to preventing hematogenous dissemination of melanoma cells.*

## 821 Role for High-Affinity IgE Receptor in Prognosis of Lung Adenocarcinoma Patients

Dalam Ly, Chang-Qi Zhu, Michael Cabanero, Ming-Sound Tsao, and Li Zhang

*Understanding the immune cells present during lung cancer development would help guide new immunotherapies. Using genomic information, immune-related genes are described that predict patient prognosis and show that mast cells are favorable for lung cancer patient survival.*

## 812 Primary Tumors Limit Metastasis Formation through Induction of IL15-Mediated Cross-Talk between Patrolling Monocytes and NK Cells



Hiroshi Kubo, Sofia Mensurado, Natacha Gonçalves-Sousa, Karine Serre, and Bruno Silva-Santos

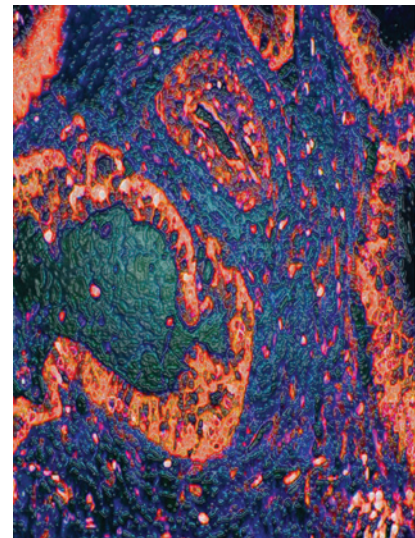
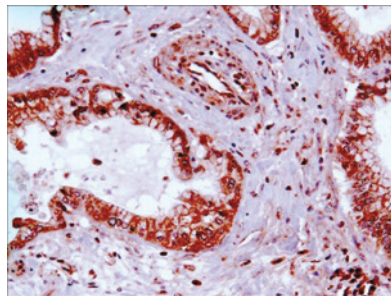
*This study identifies an IL15-dependent immune network against cancer metastasis, with the use of a model that delineated tumor establishment from metastasis formation. IL15 produced by patrolling monocytes was found to activate NK cells that then inhibited metastasis.*

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## ABOUT THE COVER

Tumor survival depends on a nurturing environment and a tumor's ability to "stay below the radar" of the immune surveillance network. In this month's issue, Pickup et al. have identified a key molecule produced by pancreatic ductal carcinomas, G-CSF (granulocyte colony-stimulating factor), which induced developing granulocytes to differentiate into myeloid suppressor cells and promoted a protumor microenvironment. Removing G-CSF while subjecting mice with aggressive pancreatic ductal tumors to treatment with gemcitabine (a DNA synthesis inhibitor) had therapeutic benefit. A subset of patients have mutations that abrogate TGF $\beta$  signaling (similar to the mouse models used), so targeting G-CSF in these patients could potentially enhance their responses to treatment. Read more starting on page 718. Micrograph from Fig. 4C. Artwork by Lewis Long.



# Cancer Immunology Research

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