

## WHAT WE'RE READING

- 755** Literature Round-Up: Impactful Published Papers

## MILESTONES IN CANCER IMMUNOLOGY

- 756** The Sixth Annual AACR–CRI Lloyd J. Old Award in Cancer Immunology

## CANCER IMMUNOLOGY MINIATURE

- 758** **The Clinical Activity of PD-1/PD-L1 Inhibitors in Metastatic Non–Clear Cell Renal Cell Carcinoma**  
Rana R. McKay, Dominick Bossé, Wanling Xie, Stephanie A.M. Wankowicz, Abdallah Flaifel, Raphael Brandao, Aly-Khan A. Lalani, Dylan J. Martini, Xiao X. Wei, David A. Braun, Eliezer Van Allen, Daniel Castellano, Guillermo De Velasco, J. Connor Wells, Daniel Y. Heng, Andre P. Fay, Fabio A. Schutz, JoAnn Hsu, Sumanta K. Pal, Jae Lyun Lee, James J. Hsieh, Lauren C. Harshman, Sabina Signoretti, Robert J. Motzer, Darren Feldman, and Toni K. Choueiri  
*A multicenter pooled analysis revealed modest antitumor activity of PD-1/PD-L1 inhibitors in patients with rare kidney cancer subtypes.*

## RESEARCH ARTICLES

- 766** **Adaptive NK Cells Resist Regulatory T-cell Suppression Driven by IL37**  
Dhifaf Sarhan, Keli L. Hippen, Amanda Lemire, Skyler Hying, Xianghua Luo, Todd Lenvik, Julie Curtsinger, Zachary Davis, Bin Zhang, Sarah Cooley, Frank Cichocki, Bruce R. Blazar, and Jeffrey S. Miller  
*Cross-talk between NK cells and Tregs, mediated by IL37 binding its receptor, altered expression of TIM3 and PD-1 on canonical, but not adaptive, NK cells. Increasing adaptive NK cells or blocking Treg suppression mechanisms could enhance immunotherapy.*
- 776** **A CS1-NKG2D Bispecific Antibody Collectively Activates Cytolytic Immune Cells against Multiple Myeloma**  
Wing Keung Chan, Siwen Kang, Youssef Youssef, Erin N. Glankler, Emma R. Barrett, Alex M. Carter, Elshafa H. Ahmed, Aman Prasad, Luxi Chen, Jianying Zhang, Don M. Benson Jr, Michael A. Caligiuri, and Jianhua Yu  
*A bispecific antibody (biAb) was engineered that targeted multiple myeloma cells while simultaneously activating human innate and adaptive cytolytic effector cells. In vivo, this biAb prolonged mouse survival and enhanced the immunological synapse between tumor cells and effectors.*


- 788** **IL22 Promotes *Kras*-Mutant Lung Cancer by Induction of a Protumor Immune Response and Protection of Stemness Properties**  
Nasim Khosravi, Mauricio S. Caetano, Amber M. Cumpian, Nese Unver, Cynthia De la Garza Ramos, Oscar Noble, Soudabeh Daliri, Belinda J. Hernandez, Berenice A. Gutierrez, Scott E. Evans, Samir Hanash, Andrei M. Alekseev, Yi Yang, Seon Hee Chang, Roza Nurieva, Humam Kadara, Jichao Chen, Edwin J. Ostrin, and Seyed Javad Moghaddam  
*IL22 promoted *Kras* mutant lung cancer by providing a tumor cell-supporting, inflammatory microenvironment. Its knockout in a murine lung cancer model restored antitumor responses, highlighting the potential to target this cytokine early in the treatment of this cancer.*

- 798** **Mitochondrial Morphological and Functional Reprogramming Following CD137 (4-1BB) Costimulation**  
Alvaro Teixeira, Sara Labiano, Saray Garasa, Iñaki Etxeberria, Eva Santamaría, Ana Rouzaut, Michel Enamorado, Arantza Azpilikueta, Susana Inoges, Elixabet Bolaños, Maria Angela Aznar, Alfonso R. Sánchez-Paulete, David Sancho, and Ignacio Melero  
*Agonistic antibodies to CD137 enhance the size and function of mitochondria in tumor-reactive cytotoxic CD8<sup>+</sup> T cells. These effects give rise to augmented respiratory capacities and are required for the immunotherapeutic activities of CD137 stimulation.*

- 812** **CAR-T Cells Surface-Engineered with Drug-Encapsulated Nanoparticles Can Ameliorate Intratumoral T-cell Hypofunction**  
Natnaree Siriwon, Yu Jeong Kim, Elizabeth Siegler, Xianhui Chen, Jennifer A. Rohrs, Yarong Liu, and Pin Wang  
*CAR-T cells were conjugated to A2aR antagonist-loaded nanoparticles to overcome an immunosuppressive, adenosine-rich TME. Treating tumor-bearing mice with drug-conjugated CAR-T cells enhanced tumor control and survival, as well as improved antitumor efficacy of the CAR T-cell treatment.*

- 825** **Tumor-Specific Inhibition of *In Situ* Vaccination by Distant Untreated Tumor Sites**  
Zachary S. Morris, Emily I. Guy, Lauryn R. Werner, Peter M. Carlson, Clinton M. Heinze, Jasdeep S. Kler, Sara M. Busche, Abigail A. Jaquish, Raghava N. Sriramaneni, Lakesha L. Carmichael, Hans Loibner, Stephen D. Gillies, Alan J. Korman, Amy K. Erbe, Jacquelyn A. Hank, Alexander L. Rakhmilevich, Paul M. Harari, and Paul M. Sondel  
*Untreated tumor sites antagonize the systemic and local antitumor immune response to an *in situ* vaccination regimen. This effect is radiation sensitive and may be mediated by tumor-specific regulatory T cells harbored in the untreated tumor sites.*

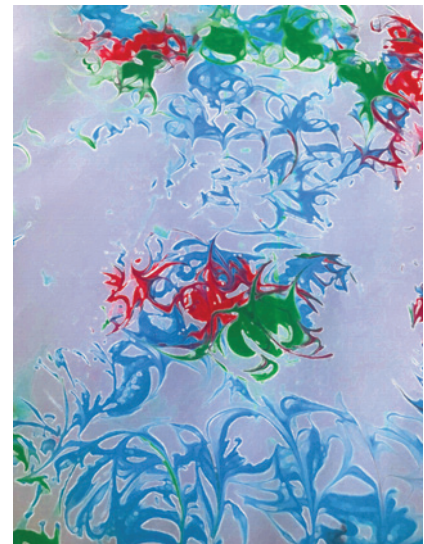
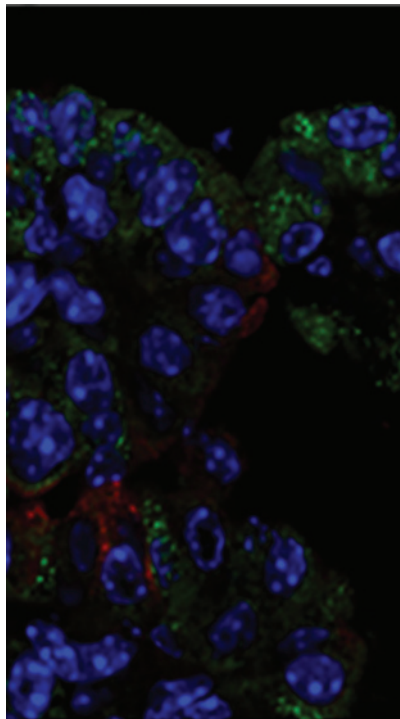
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- 835** **Subcellular Localization of Antigen in Keratinocytes Dictates Delivery of CD4<sup>+</sup> T-cell Help for the CTL Response upon Therapeutic DNA Vaccination into the Skin**  
Nikolina Bábala, Astrid Bovens, Evert de Vries, Victoria Iglesias-Guimaraes, Tomasz Ahrends, Matthew F. Krummel, Jannie Borst, and Adriaan D. Bins  
*Optimal vaccination relies on the confluence of multiple factors. An examination of how subcellular localization of antigen affects priming of CD8<sup>+</sup> T cells reveals that secreted vaccine protein best solicits CD4<sup>+</sup> T-cell help, leading to efficient CTL priming.*
- 848** **Whole Exome and Transcriptome Analyses Integrated with Microenvironmental Immune Signatures of Lung Squamous Cell Carcinoma**  
 Jeong-Sun Seo, Ji Won Lee, Ahreum Kim, Jong-Yeon Shin, Yoo Jin Jung, Sae Bom Lee, Yoon Ho Kim, Samina Park, Hyun Joo Lee, In-Kyu Park, Chang-Hyun Kang, Ji-Young Yun, Jihye Kim, and Young Tae Kim  
*Subtypes of lung cancer are revealed by patterns of genomic alteration and immune infiltration. These patterns of mutation and immune cell presence could be used to guide choices of immunotherapy in a subtype-specific manner.*
- 860** **Drug-Induced Senescent Multiple Myeloma Cells Elicit NK Cell Proliferation by Direct or Exosome-Mediated IL15 Trans-Presentation**  
Cristiana Borrelli, Biancamaria Ricci, Elisabetta Vulpis, Cinzia Fionda, Maria Rosaria Ricciardi, Maria Teresa Petrucci, Laura Masuelli, Agnese Peri, Marco Cippitelli, Alessandra Zingoni, Angela Santoni, and Alessandra Soriani  
*Low-dose chemotherapy induced a senescent phenotype in multiple myeloma cells, which enhanced expression of IL15 and membrane IL15/IL15RA complex. This promoted IL15 trans-presentation that enhanced NK cell activation and proliferation, providing insights for the use of senescence-based therapies.*
- 870** **Nanobody–Antigen Conjugates Elicit HPV-Specific Antitumor Immune Responses**  
Andrew W. Woodham, Ross W. Cheloha, Jingjing Ling, Mohammad Rashidian, Stephen C. Kolifrath, Maia Mesyngier, Joao N. Duarte, Justin M. Bader, Joseph G. Skeate, Diane M. Da Silva, W. Martin Kast, and Hidde L. Ploegh  
*A targeted purely protein-based therapeutic vaccine elicits CD8<sup>+</sup> T-cell responses in an HPV model of cancer, resulting in tumor regression.*

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## ABOUT THE COVER

Inflammation is a known driver of some cancers, and cytokines involved in this tumor-promoting process are being investigated. However, the role of IL22, a cytokine present in patients' primary lung tumors and sera, has yet to be rigorously investigated. Khosravi et al. establish IL22 as an essential promoter of KRAS mutant lung cancer and identify the mechanism of tumor promotion by IL22. Comparison of mice with and without this cytokine showed that IL22's absence significantly reduced infiltration of tumor-supportive inflammatory cells into lung tumors and was detrimental to tumor proliferation, angiogenesis, and stemness. Thus, a lack of IL22 enhances antitumor responses and reduces tumor burden. Read more in this issue on page 788. Original immunofluorescence image from Fig. 5A. Artwork by Lewis Long.



# Cancer Immunology Research

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