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

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.

RESEARCH ARTICLES

766 Adaptive NK Cells Resist Regulatory T-cell Suppression Driven by IL37
Dhiaf Safi, Keli L. Hippen, Amanda Lemire, Skyler Hying, Xianghua Luo, Todd Lenvik, Julie Curtisinger, 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.

767 A CS1-NKG2D Bispecific Antibody Collectively Activates Cytolytic Immune Cells against Multiple Myeloma

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

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 Tejeira, Sara Labiano, Saray Garasa, Iñaki Etxeberria, Eva Santamaria, Ana Rouzaut, Michel Enamorado, Arantza Azañilekuta, Susana Inoges, Elekabat Bolaños, Maria Angela Aznar, Alfonso R. Sanchez-Paulete, David Sancho, and Ignacio Melero

Agonistic antibodies to CD137 enhance the size and function of mitochondria in tumor-reactive cytotoxic CD8+ 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
Natnrater 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

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 modulated 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⁺ T-cell Help for the CTL Response upon Therapeutic DNA Vaccination into the Skin
Nikolina Babala, Astrid Bovens, Evert de Vries, Victoria Iglesias-Guimarais, 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⁺ T cells reveals that secreted vaccine protein best solicits CD4⁺ 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, Jae Bom Lee, Yoon Ho Kim, Samina Park, Hyun Joo Lee, In-Kyu Park, Chang-Hyun Kang, Ji-Young Yun, Ji-Young 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 Masueli, 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 Mesnygier, 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⁺ T-cell responses in an HPV model of cancer, resulting in tumor regression.

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.

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