WHAT WE'RE READING

1037  A Sampling of Highlights from the Literature

MILESTONES IN CANCER IMMUNOLOGY

1038  The Seventh Annual AACR-CRI Lloyd J. Old Award in Cancer Immunology

CANCER IMMUNOLOGY AT THE CROSSROADS

1040  Recharacterizing Tumor-Infiltrating Lymphocytes by Single-Cell RNA Sequencing
   Lei Zhang and Zemin Zhang

CANCER IMMUNOLOGY MINIATURES

1047  BCMA-Targeted CAR T-cell Therapy plus Radiotherapy for the Treatment of Refractory Myeloma Reveals Potential Synergy

RESEARCH ARTICLES

1054  RORγ Agonists Enhance the Sustained Antitumor Activity through Intrinsic Tc17 Cytotoxicity and Tc1 Recruitment
   Xikui Liu, Elizabeth M. Zawidzka, Hongxiu Li, Charles A. Irsch, Jenna Dunbar, Dick Bousley, Weiping Zou, Xiao Hu, and Laura L. Carter
   Tumor evasion can ensue from too few infiltrating cytotoxic T cells—type 1 (Tc1) or 17 (Tc17)—or infiltration of dysfunctional effectors. RORγ agonists augmented Tc17 survival and lytic activity and directed recruitment of other functional effector cells.

1064  Targeting Hypoxia-Induced Carbonic Anhydrase IX Enhances Immune-Checkpoint Blockade Locally and Systemically
   The prognosis for breast cancer and melanoma patients is worse if their tumors metabolically regulate pH, promoting an acidic microenvironment, through enzymes like CAIX. Inhibition of CAIX plus blockade of immune checkpoints boosts antitumor responses by buffering acids.

1079  Hypoxia-Induced VISTA Promotes theSuppressive Function of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment
   Jie Deng, Jiannan Li, Aurelien Sarde, J. Louise Lines, Yu-Chi Lee, David C. Qian, Do v A. Pechenick, Richard Manivanh, Isabelle Le Mercier, Christopher H. Lowrey, Frederick S. Varn, Chao Cheng, David A. Leib, Randolph J. Noelle, and Rodwell Mabaera
   VISTA, induced on MDSCs by hypoxia in the tumor microenvironment, enhances suppression of both CD4⁺ and CD8⁺ T cells. This mechanism of hypoxia-driven immune escape and checkpoint resistance suggests a translational approach to combination therapies.

1091  Tumor Cells Hijack Macrophage-Produced Complement C1q to Promote Tumor Growth
   Lubka T. Roumenina, Marie V. Daugan, Remi Noé, Florent Petitprez, Yann A. Vano, Rafael Sanchez-Salas, Eileen Becht, Julie Meillerous, Bénédicte Le Clec'h, Nicolas A. Giraldi, Nicolas S. Merle, Cheng-Ming Sun, Virginie Verkarre, Pierre Val d i re, Janick Selves, Laetitia Lacroix, Olivier Delour, Isabelle Vandenberge, Celine Thuilliez, Sonia Keddani, Imene B. Sahlhi, Eric Barret, Pierre Ferré, Nathalie Corvalia, Alexandre Passioukov, Eric Chetaille, Marina Botto, Aurélien de Reynies, Stephane Marie Oudard, Arnaud Mejean, Xavier Cathelineau, Catherine Sautès-Fridman, and Wolf H. Fridman
   The density of C1q-producing TAMs and C4d deposits, hallmarks of complement activation, are negative prognostic factors in human clear-cell renal cell carcinoma. Thus, the classical complement pathway is a potential therapeutic target for this cancer.

1065  Combination Therapy for Treating Advanced Drug-Resistant Acute Lymphoblastic Leukemia
   Yorleny Vicioso, Hermann Gram, Rose Beck, Abhishek Asthana, Keman Zhang, Derek P. Wong, John Letterio, and Renhui Parmarwan
   Blocking BAFF-R early in ALL promotes killing of leu kemic cells. However, if given at later disease stages, efficacy is limited due to TGFβ. Combining VAY736 and a TGFβR1 inhibitor improved treatment efficacy in advanced and drug-resistant ALL.
Inhibition of the NKp44-PCNA Immune Checkpoint Using a mAb to PCNA
Kiran Kandu, Sumita Gosh, Rithajit Sarkar, Avishay Edri, Michael Brusilovsky, Orly Gesher-Halalim, Rami Yossef, Avishai Shemesh, Jean-Charles Soria, Vladimir Lazar, Ben-Zion Joshua, Kerry S. Campbell, Moshe Elkabets, and Angel Porgador
An immune checkpoint blocking antibody was developed against cancer cell surface PCNA, a ligand for NK-cell protein NKp44. Tests of the antibody in mice bearing patient-derived xenografts showed promise for overcoming tumor resistance to immunotherapy.

Targeting the YB-1/PD-L1 Axis to Enhance Chemotherapy and Antitumor Immunity
Zhen Tao, Haitong Ruan, Lin Sun, Dong Kuang, Yongchun Song, Qi Wang, Tao Wang, Yi Hao, and Ke Chen
The YB-1 signaling axis promotes tumor immune evasion and multidrug resistance. When targeted, chemoresistance decreased and antitumor responses were enhanced, suggesting an avenue for treating tumor multidrug resistance and immunosuppressive tumor microenvironments.

Reduced Neoantigen Expression Revealed by Longitudinal Multionics as a Possible Immune Evasion Mechanism in Glioma
Whole exome and RNA sequencing of paired primary and recurrent glioma specimens revealed decreased neoantigen expression at recurrence. Evidence of persistent immune responses suggests immune selection pressure as a possible mechanism, despite treatment with standard, non-immune-based regimens.

A Gene Signature Predicting Natural Killer Cell Infiltration and Improved Survival in Melanoma Patients
Joseph Cursons, Fernando Souza-Fonseca-Guimaeraes, Momennat Foroutan, Ashley Anderson, Frederic Hollande, Soroor Hedyeh-Zadeh, Andreas Behren, Nicholas D. Huntingdon, and Melissa J. Davis
Innate immunity can provide new targets for immunotherapy. Singcore, a gene-set scoring method, revealed that NK cell infiltration correlated with improved patient survival rates. Stromal and tumor elements, as well as cytokines involved in NK function were investigated.

Correction: Performance Evaluation of MHC Class-I Binding Prediction Tools Based on an Experimentally Validated MHC–Peptide Binding Data Set
The tumor microenvironment is comprised of several factors that can limit antitumor responses. One such factor is low pH, which results in an acidic environment that can dampen immune responses. Carbonic anhydrase IX (CAIX) is a hypoxia-induced regulatory enzyme that can modulate extracellular pH. Chafe et al. show that this enzyme is associated with risk of metastasis and worse overall outcome in patients with melanoma. Targeting CAIX with a small-molecule inhibitor alleviates extracellular acidification by altering the glycolytic metabolism of melanoma cells, allowing antitumor responses to ensue. Combining the CAIX-targeting small-molecule inhibitor with immune checkpoint blockade in breast cancer and melanoma models sensitizes the tumors to the therapy, boosts antitumor responses, and reduces tumor growth and metastases. These data highlight how targeting CAIX in solid tumors is a potential strategy to improve therapeutic responses and survival of patients. Read more in this issue on page 1064. Original image from Fig. 1A. Artwork by Lewis Long.