WHAT WE'RE READING

1113
A Sampling of Highlights from the Literature

PRIORITY BRIEF

1114
Activation of CD8+ T Cells Contributes to Antitumor Effects of CDK4/6 Inhibitors plus MEK Inhibitors
Jessica L.F. Teh, Dan A. Erkes, Phil F. Chen, Manoela Tiago, Nicole A. Wilski, Conroy O. Field, Inna Chervoneva, Mitch P. Levesque, Xiaowei Xu, Reinhard Dummer, and Andrew E. Aplin
Although melanoma is treated with immune checkpoint inhibitors, many patients respond poorly. The success of MEK inhibitors and CDK4/6 inhibitors depends on an intact immune system. Combination therapy may improve response to checkpoint inhibitors.

RESEARCH ARTICLES

1122
Tenascin-C Orchestrates an Immune-Suppressive Tumor Microenvironment in Oral Squamous Cell Carcinoma
Tenascin-C, an extracellular matrix protein, contributes to immune suppression in head and neck tumors. Tenascin-C orchestrates immune-suppressive niches by directing spatial distribution of Tregs and myeloid cells, leading to invasive disease.

1139
Potent Cytolytic Activity and Specific IL15 Delivery in a Second-Generation Trispecific Killer Engager
Martin Felices, Todd R. Lenvik, Behiye Kodal, Alexander J. Lenvik, Peter Hinderlie, Laura E. Bendzick, Dawn K. Schirm, Michael F. Kaminski, Ron T. McElmurry, Melissa A. Geller, Craig E. Eckfeldt, Daniel A. Vallerà, and Jeffrey S. Miller
A next-generation NK-cell engager is developed, incorporating a specific anti-CD16 sequence that promotes IL15 delivery and acute myeloid leukemia killing. This trispecific engager could provide an off-the-shelf treatment capable of engaging endogenous NK cells for targeted cancer therapy.

1150
SRC-3 Functions as a Coactivator of T-bet by Regulating the Maturation and Antitumor Activity of Natural Killer Cells
Mengjia Hu, Yukai Lu, Yan Qi, Zihao Zhang, Song Wang, Yang Xu, Fang Chen, Yong Tang, Shilei Chen, Mo Chen, Changhong Du, Mingxiang Shen, Fengchao Wang, Yongping Su, Youcai Deng, and Junping Wang
The steroid receptor coactivator 3 (SRC-3) is involved in NK-cell maturation, with SRC-3 deficiency leading to decreased antitumor NK-cell responses. Specifically, T-bet recruits SRC-3 in NK cells, in turn regulating the transcription of T-bet target genes.

1163
CAMK1D Triggers Immune Resistance of Human Tumor Cells Refractory to Anti–PD-L1 Treatment
Valentina Volpin, Tillmann Michels, Antonio Sorrentino, Ayse N. Menevs, Gertrud Knoll, Madlen Ditz, Vladimir M. Milenkovic, Chih-Yeh Chen, Anchana Rathinasamy, Klaus Griewank, Michael Boutros, Sebastian Haferkamp, Mark Berneburg, Christian H. Wetzal, Anja Deckinger, Dirk Hose, Hartmut Goldschmidt, Martin Ehrenschwender, Mathias Witzens-Harig, Arpad Szoor, Gyorgy Vereb, Nisit Khandelwal, and Philipp Beckhove
CD40 Agonist Restores the Antitumor Efficacy of Anti-PD1 Therapy in Muscle-Invasive Bladder Cancer in an IFN I/II-Mediated Manner
Marine M. Leblond, Laure Tille, Sina Nassiri, Connie B. Gilfillan, Claire Imbratta, Martina Schmittnaegel, Carola H. Ries, Daniel E. Speiser, and Grégory Verdeil
Bladder cancer is resistant to anti-PD1 therapy. The combination of anti-PD1 plus a CD40 agonist overcomes anti-PD1 resistance, inducing T-cell-, macrophage-, and IFN I/II-dependent antitumor immunity.

Chemotherapeutic Tumor Microparticles Elicit a Neutrophil Response Targeting Malignant Pleural Effusions
Pingwei Xu, Ke Tang, Jingwei Ma, Huafeng Zhang, Dianheng Wang, Liyan Zhu, Jie Chen, Keke Wei, Jincheng Liu, Haiqing Fang, Liang Tang, Yi Zhang, Jing Xie, Yuying Liu, Rui Meng, Li Liu, Xiaorong Dong, Kunyu Yang, Gang Wu, Fei Ma, and Bo Huang
Tumor cell-derived microparticles packaging a chemotherapeutic agent can induce neutrophil responses, which contribute to tumor killing and malignant pleural effusion (MPE) reduction. The data suggest that the microparticles could be a potential MPE therapy in patients.

A Genetic Screen to Identify Gain- and Loss-of-Function Modifications that Enhance T-cell Infiltration into Tumors
Laura M. Rogers, Zhaoming Wang, Sarah L. Mott, Adam J. Dupuy, and George J. Weiner
An in vivo screen with the ability to induce gain-of-function mutations identifies genes that may enhance T-cell trafficking into tumors. These represent candidate targets that could be altered to enhance intratumoral trafficking of adoptively transferred T cells.

Enzalutamide, an Androgen Receptor Antagonist, Enhances Myeloid Cell-Mediated Immune Suppression and Tumor Progression
Camila R. Consiglio, Olga Udartseva, Kimberly D. Ramsey, Chioma Bush, and Sandra O. Gollnick
Androgen receptor (AR) antagonism is an effective treatment for prostate cancer patients, yet many experience tumor progression. AR blockade increases tumor growth by shifting myeloid cells to a protumoral phenotype via AMPK signaling.

Extracellular matrices contribute to the inherent immune-suppressive tumor microenvironment (TME) of head and neck squamous cell carcinoma (HNSCC). Tenasin-C, an extracellular matrix protein, is linked to the progression of HNSCC, yet its role in establishing an immune-suppressive TME is unclear. Using a 4NQO-induced model of HNSCC, the authors find that tenasin-C induces an immune-suppressive lymphoid stroma in a CCL21- and CCR7-mediated manner. Tenasin-C expression in the TME allows for the immobilization of CD11c+ cells in said tumor stroma, leading to Treg recruitment and establishment of a protumoral TME. Knockout of tenasin-C or CCR7 blockade reduces tumor growth and metastasis. Thus, inhibition of tenasin-C or CCR7 may represent potential treatments for HNSCC patients. To read more, Spenle and Louatau et al. begins on page 1122.