

CANCER IMMUNOLOGY RESEARCH

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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. Cheng, 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**

Caroline Spenlé, Thomas Loustau, Devadarssen Murdamoothoo, William Erne, Stephanie Beghelli-de la Forest Divonne, Romain Veber, Luciana Petti, Pierre Bourdely, Matthias Mörgelin, Eva-Maria Brauchle, Gérard Cremel, Vony Randrianarisoa, Abdouramane Camara, Samah Rekima, Sebastian Schaub, Kelly Nouhen, Thomas Imhof, Uwe Hansen, Nicodème Paul, Raphael Carapito, Nicolas Pythoud, Aurélie Hirschler, Christine Carapito, Hélène Dumortier, Christopher G. Mueller, Manuel Koch, Katja Schenke-Layland, Shigeyuki Kon, Anne Sudaka, Fabienne Anjuère, Ellen Van Obberghen-Schilling, and Gertraud Orend

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. Vallera, 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, Mingqiang 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. Menevse, Gertrud Knoll, Madlen Ditz, Vladimir M. Milenkovic, Chih-Yeh Chen, Anchana Rathinasamy, Klaus Griewank, Michael Boutros, Sebastian Haferkamp, Mark Berneburg, Christian H. Wetzel, Anja Seckinger, Dirk Hose, Hartmut Goldschmidt, Martin Ehrenschrwender, Mathias Witzens-Harig, Arpad Szoor, Gyorgy Vereb, Nisit Khandelwal, and Philipp Beckhove

Genetic screens identify the kinase CAMK1D as a regulator of antitumor immune resistance in anti-PD-L1-refractory cancer. CAMK1D activation in tumor cells, through CTL stimulation of the Fas receptor, inhibits caspase-mediated cell death of anti-PD-L1-refractory tumors.

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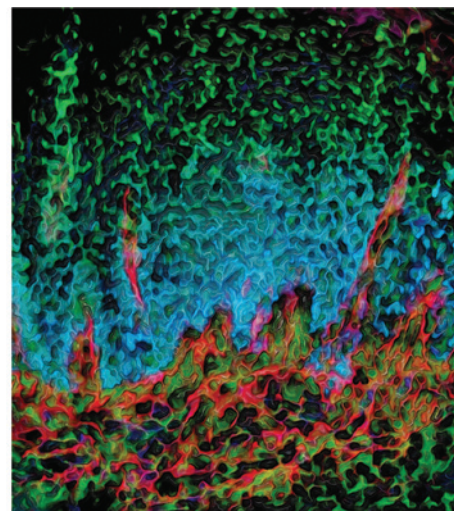
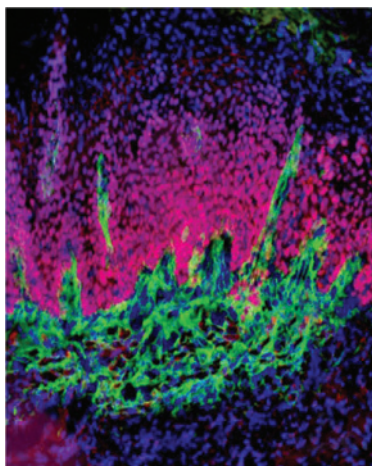
- 1180** **CD40 Agonist Restores the Antitumor Efficacy of Anti-PD1 Therapy in Muscle-Invasive Bladder Cancer in an IFN I/II-Mediated Manner**
Marine M. Leblond, Laure Tillé, Sina Nassiri, Connie B. Gilfillan, Claire Imbratta, Martina Schmittnaegel, Carola H. Ries, Daniel E. Speiser, and Grégory Verdeil
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.
- 1193** **Chemotherapeutic Tumor Microparticles Elicit a Neutrophil Response Targeting Malignant Pleural Effusions**
AC 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.
- 1206** **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.
- 1215** **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.

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ABOUT THE COVER

Extracellular matrices contribute to the inherent immune-suppressive tumor microenvironment (TME) of head and neck squamous cell carcinoma (HNSCC). Tenascin-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 tenascin-C induces an immune-suppressive lymphoid stroma in a CCL21- and CCR7-mediated manner. Tenascin-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 tenascin-C or CCR7 blockade reduces tumor growth and metastasis. Thus, inhibition of tenascin-C or CCR7 may represent potential treatments for HNSCC patients. To read more, Spenlé and Loustau et al. begins on page 1122. Immunofluorescence staining from the Orend laboratory. Artwork by Lewis Long.



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