

CANCER IMMUNOLOGY RESEARCH

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Ziran Zhao and Jan Joseph Melenhorst

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RISING STARS IN CANCER IMMUNOLOGY

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Amanda W. Lund

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PRIORITY BRIEF

1047 **TGF β and CIS Inhibition Overcomes NK-cell Suppression to Restore Antitumor Immunity**

Fernando Souza-Fonseca-Guimaraes, Gustavo R. Rossi, Laura F. Dagley, Momeneh Foroutan, Timothy R. McCulloch, Jumana Yousef, Hae-Young Park, Jennifer H. Gunter, Paul A. Beavis, Cheng-Yu Lin, Soroor Hedyeh-Zadeh, Tania Camilleri, Melissa J. Davis, and Nicholas D. Huntington

Targeting multiple inhibitory checkpoints of NK-cell effector function, CIS and TGF β , unveils new combinatorial NK cell-based immunotherapy that might have broad therapeutic interventions, particularly in settings of NK cell-adoptive cell therapy.

RESEARCH ARTICLES

1055 **Regulatory Programs of B-cell Activation and Germinal Center Reaction Allow B-ALL Escape from CD19 CAR T-cell Therapy**

Nam Gyu Im, Amy Guillaumet-Adkins, Megha Wal, Anna J. Rogers, Julia Frede, Claire C. Havig, Jing Yang, Praveen Anand, Sarah K. Stegmann, Johannes M. Waldschmidt, Noori Sotudeh, Leili Niu, Jordan Voisine, Michal R. Schweiger, Clemens Grassberger, Jens G. Lohr, and Birgit Knoechel

The authors show CD19-expressing B-ALL cells can employ regulatory programs of normal B-cell activation and germinal center reaction to transcriptionally downregulate and maintain lower CD19 expression, allowing for enhanced survival in the early phases of CAR T-cell exposure.

See related Spotlight, p. 1040

1069 **Design and Validation of Inducible TurboCARs with Tunable Induction and Combinatorial Cytokine Signaling**

Regina J. Lin, Andrew R. Nager, Spencer Park, Janette Sutton, Cecilia Lay, Zea Melton, Yi Zhang, Bijan Boldajipour, Thomas J. Van Blarcom, Siler H. Panowski, Barbra J. Sasu, and Javier Chaparro-Riggers

Inducible Turbo (iTurbo) CAR T cells engineered to express homodimeric chimeric cytokine receptors are demonstrated to exhibit potent antitumor efficacy. Data highlight the flexibility and user-programmable nature of the iTurbo CAR T-cell platform to improve tumor control.

1084 **Using CD69 PET Imaging to Monitor Immunotherapy-Induced Immune Activation**

Kimberly J. Edwards, Bryan Chang, Hasan Babazada, Katheryn Lohith, Daniel H. Park, Michael D. Farwell, and Mark A. Sellmyer

A radiolabeled CD69-directed antibody, [89Zr]-DFO-H1.2F3, combined with PET imaging, shows promise as a noninvasive method to assess early response to immune checkpoint blockade *in vivo*, with increased uptake in the tumors and lymphoid tissue of blockade-responsive tumor-bearing mice.

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1095 **Long Noncoding RNA *MIR4435-2HG* Suppresses Colorectal Cancer Initiation and Progression By Reprogramming Neutrophils**
Hongfei Yu, Chaoyi Chen, Fengyan Han, Jinlong Tang, Mengli Deng, Yumiao Niu, Maode Lai, and Honghe Zhang
Long noncoding (lnc) RNA *MIR4435-2HG* can regulate neutrophils/PMN-MDSCs in colorectal cancer (CRC). Data identify this lncRNA as a tumor suppressor in the tumor stroma, rather than as an oncogene in tumor cells, highlighting a potential therapeutic target in CRC.

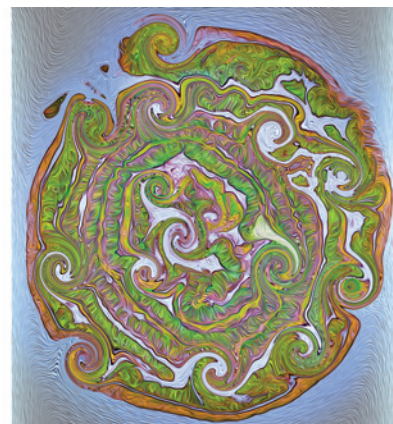
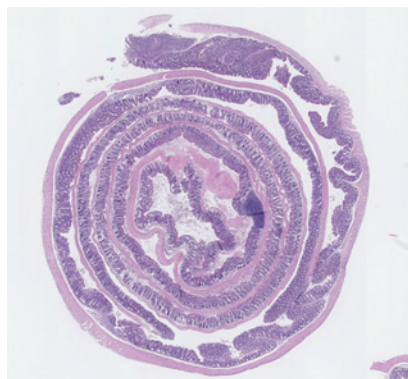
1111 **CD8⁺ T-cell Responses Are Boosted by Dual PD-1/VEGFR2 Blockade after EGFR Inhibition in *Egfr*-Mutant Lung Cancer**
Kazuya Nishii, Kadoaki Ohashi, Shuta Tomida, Takamasa Nakasuka, Atsuko Hirabae, Sachi Okawa, Jun Nishimura, Hisao Higo, Hiromi Watanabe, Hirohisa Kano, Chihiro Ando, Go Makimoto, Kiichiro Ninomiya, Yuka Kato, Toshio Kubo, Eiki Ichihara, Katsuyuki Hotta, Masahiro Tabata, Shinichi Toyooka, Heiichiro Udono, Yoshinobu Maeda, and Katsuyuki Kiura
Egfr-mutant lung cancer exhibits a noninflamed tumor microenvironment (TME). Here, data demonstrate that the scheduling of EGFR inhibition with dual PD-1/VEGFR2 blockade is vital for optimum efficacy and induction of CD8⁺ T cell-dominant responses in the TME.

1127 **Adenosine-Deaminase-Acting-on-RNA-1 Facilitates T-cell Migration toward Human Melanoma Cells**
Naama Margolis, Hanna Moalem, Tomer Meirson, Gilli Galore-Haskel, Ettai Markovits, Erez N. Baruch, Bella Vazel, Avner Yeffét, Julia Kanterman-Rifman, Assaf Debby, Michal J. Besser, Jacob Schachter, and Gal Markel
The factors that increase tumor-cell chemotactic potential to allow T-cell infiltration remain unclear. The authors find that ADAR1 induction as a result of T-cell/melanoma interactions facilitates tumor infiltration by T cells and may alter response to immunotherapy.

1141 **Sensory Nerves Impede the Formation of Tertiary Lymphoid Structures and Development of Protective Antimelanoma Immune Responses**
Kavita Vats, Oleg Kruglov, Bikram Sahoo, Vishal Soman, Jiying Zhang, Galina V. Shurin, Uma R. Chandran, Pavel Skums, Michael R. Shurin, Alex Zelikovsky, Walter J. Storkus, and Yuri L. Bunimovich
Sensory neurons are shown to play a critical role in the modulation of antitumor immune responses and the formation of tertiary lymphoid structures in melanoma. Data highlight afferent innervation as a potential novel target for cancer immunotherapy.

ABOUT THE COVER

A better understanding of long noncoding RNA (lncRNA) function in the tumor microenvironment (TME) is needed. LncRNA *MIR4435-2HG* is known to be an oncogenic driver in tumor cells. However, Yu, Chen, and Han et al. find that expression of *MIR4435-2HG* in tumor cells did not affect colorectal cancer (CRC) proliferation, migration, or invasion *in vitro*. Instead, *MIR4435-2HG* is found to be a tumor suppressor in the CRC stroma, where its expression in neutrophils contributes to suppressing CRC progression. Neutrophils deficient in *MIR4435-2HG* expression promote CRC progression via alteration of metabolism in the TME, which in turn, enhances immune suppression by polymorphonuclear myeloid-derived suppressor cells. The data highlight a potential lncRNA therapeutic target in CRC. Read more in this issue on page 1095. Original image from Fig. 1D. Artwork by Lewis Long.



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