

CANCER IMMUNOLOGY RESEARCH

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Kyoung Eun Lee and Marina Pasca di Magliano

See related article, p. 1170

PERSPECTIVE

1132 **Regulatory Considerations for Genome-Edited T-cell Therapies**

Julie K. Jadowsky, Ju-fang Chang, David H. Spencer, John M. Warrington, Bruce L. Levine, Carl H. June, Joseph A. Fraietta, and Nathan Singh

PRIORITY BRIEF

1136 **Identification of Core Techniques That Enhance Genome Editing of Human T Cells Expressing Synthetic Antigen Receptors**

Ju-Fang Chang, Nils Wellhausen, Nils W. Engel, Jack H. Landmann, Caitlin R. Hopkins, January Salas-McKee, Adham S. Bear, Mehmet E. Selli, Sangya Agarwal, Julie K. Jadowsky, Gerald P. Linette, Saar Gill, Carl H. June, Joseph A. Fraietta, and Nathan Singh

The most effective methods for integrating gene therapy and genome editing to develop advanced cell therapy products remain unclear. The authors identify key technical processes in human T-cell manipulation and present an optimized toolkit for multiplex engineering.

RESEARCH ARTICLES

1147 **Intracellular Osteopontin Promotes the Release of TNF α by Mast Cells to Restrain Neuroendocrine Prostate Cancer**

Roberta Sulsenti, Giuseppina B. Scialpi, Barbara Frossi, Laura Botti, Renata Ferri, Irene Tripodi, Annamaria Piva, Sabina Sangaletti, Davide Pernici, Valeria Cancila, Francesco Romeo, Claudia Chiodoni, Daniele Lecis, Francesca Bianchi, Irene Fischetti, Claudia Enriquez, Filippo Crivelli, Marco Bregni, Giuseppe Renne, Salvatore Pece, Claudio Tripodo, Carlo E. Pucillo, Mario P. Colombo, and Elena Jachetti

The authors show that SDC1-mediated TLR2/TLR4 stimulation triggers intracellular osteopontin in mast cells to promote TNF α release, which hampers lethal neuroendocrine prostate cancer. The results open new opportunities for mast cell-based immunotherapy in prostate cancer.

1170 **Pancreatic Epithelial IL17/IL17RA Signaling Drives B7-H4 Expression to Promote Tumorigenesis**

Susana Castro-Pando, Rian M. Howell, Le Li, Marilina Mascaro, Erika Y. Faraoni, Olivereen Le Roux, David Romanin, Virginia Tahan, Erick Riquelme, Yu Zhang, Jay K. Kolls, James P. Allison, Guillermina Lozano, Seyed J. Moghaddam, and Florencia McAllister

A comprehensive understanding of the role of IL17 in pancreatic cancer is lacking. The authors show pancreatic epithelial IL17RA-mediated reprogramming of the immune pancreatic landscape, partially through regulation of B7-H4 expression, promotes the early stages of pancreatic tumorigenesis.

See related Spotlight, p. 1130

1184 **Endoplasmic Reticulum Stress Potentiates the Immunosuppressive Microenvironment in Hepatocellular Carcinoma by Promoting the Release of SNHG6-Enriched Small Extracellular Vesicles**

Chengdong Liu, Xiaohan Zhou, Hanyi Zeng, Jiaping Yu, Wenwen Li, Wanli Zhang, Yanxia Liao, Haijian Wang, and Li Liu

How ER stress promotes HCC progression is unclear. The authors show that it induces HCC release of SNHG6-carrying sEVs, which potentiate the immunosuppressive TME. SNHG6 knockdown improves anti-PD1 efficacy, suggesting a way to reverse the immunosuppressive TME.

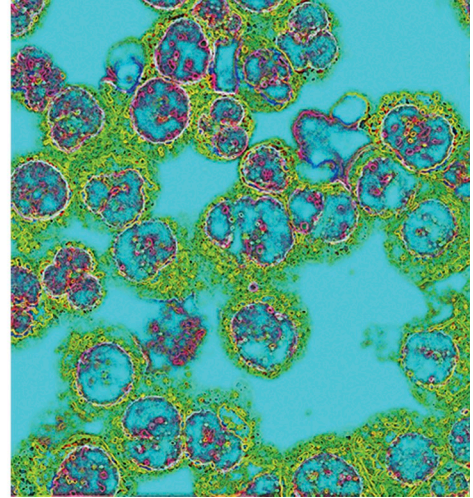
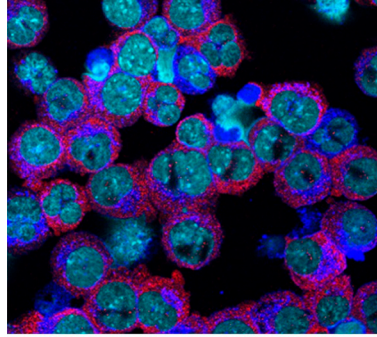
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- 1202 Nivolumab Reaches Brain Lesions in Patients with Recurrent Glioblastoma and Induces T-cell Activity and Upregulation of Checkpoint Pathways**
Signe K. Skadborg, Simone Maarup, Arianna Draghi, Annie Borch, Sille Hendriksen, Filip Mundt, Vilde Pedersen, Matthias Mann, Ib J. Christensen, Jane Skjøth-Ramussen, Christina W. Yde, Bjarne W. Kristensen, Hans S. Poulsen, Benedikte Hasselbalch, Inge M. Svane, Ulrik Lassen, and Sine R. Hadrup
The authors demonstrate that the anti-PD-1 nivolumab can reach and modify the GBM tumor microenvironment within 7 days of administration. Upregulation of compensatory immune checkpoint inhibition molecules may counter the benefits of nivolumab-induced intratumoral immune activation.
- 1221 Blockade of IL1 β and PD1 with Combination Chemotherapy Reduces Systemic Myeloid Suppression in Metastatic Pancreatic Cancer with Heterogeneous Effects in the Tumor**
Paul E. Oberstein, Andressa Dias Costa, Emily A. Kawaler, Victoire Cardot-Ruffino, Osama E. Rahma, Nina Beri, Harshabad Singh, Thomas A. Abrams, Leah H. Biller, James M. Cleary, Peter Enzinger, Brandon M. Huffman, Nadine J. McCleary, Kimberly J. Perez, Douglas A. Rubinson, Benjamin L. Schlechter, Rishi Surana, Matthew B. Yurgelun, S. Jennifer Wang, Joshua Remland, Lauren K. Brais, Naima Bollenrucher, Eugena Chang, Lestat R. Ali, Patrick J. Lenehan, Igor Dolgalev, Gregor Werba, Cibelle Lima, C. Elizabeth Keheler, Keri M. Sullivan, Michael Dougan, Cristina Hajdu, Maya Dajee, Marc R. Pelletier, Saloney Nazeer, Matthew Squires, Dafna Bar-Sagi, Brian M. Wolpin, Jonathan A. Nowak, Diane M. Simeone, and Stephanie K. Dougan
Analysis of paired baseline and on-treatment samples from patients with advanced pancreatic cancer enrolled in a clinical trial of anti-IL1 β , anti-PD1, and chemotherapy shows systemic changes in monocytes that are not translated to intratumoral changes in myeloid populations.
- 1236 Knocking Out CD70 Rescues CD70-Specific NanoCAR T Cells from Antigen-Induced Exhaustion**
Stijn De Munter, Juliane L. Buhl, Laurenz De Cock, Alexander Van Parys, Willem Daneels, Eva Pascal, Lucas Deseins, Joline Ingels, Glenn Goetgeluk, Hanne Jansen, Lore Billiet, Melissa Pille, Julie Van Duyse, Sarah Bonte, Niels Vandamme, Jo Van Dorpe, Fritz Offner, Georges Leclercq, Tom Taghon, Erik Depla, Jan Tavernier, Tessa Kerre, Jarno Drost, and Bart Vandekerckhove
CD70-specific CAR T cells are being developed for solid and liquid malignancies. The authors show that carcinoma *in situ* interactions between the CAR and endogenous CD70 push these cells toward exhaustion; knocking out CD70 prevents exhaustion and increases CAR T-cell functionality.
- 1252 Iron Boosts Antitumor Type 1 T-cell Responses and Anti-PD1 Immunotherapy**
Sarah Porte, Alexandra Audemard-Verger, Christian Wu, Aurélie Durand, Théo Level, Léa Giraud, Amélie Lombès, Mathieu Germain, Rémi Pierre, Benjamin Saintpierre, Mireille Lambert, Cédric Auffray, Carole Peyssonnaud, François Goldwasser, Sophie Vaultont, Marie-Clotilde Alves-Guerra, Renaud Dentin, Bruno Lucas, and Bruno Martin
The authors show that iron supplementation reactivates antitumor T-cell responses and improves anti-PD1 efficacy in mice. Preliminary analysis of plasma ferritin levels in patients with cancer treated with anti-PD1, suggests iron may also modulate anti-PD1 responses in humans.
- 1268 MerTK Induces Dysfunctional Dendritic Cells by Metabolic Reprogramming**
Eden Y. Zewdie, George M. Edwards, Debra M. Hunter, Henry Shelton Earp, and Alisha Holtzhausen
Resistance to anti-PD-1 remains a challenge clinically. The authors show a relationship between MerTK and DC metabolic reprogramming, contributing to an immunosuppressive tumor microenvironment and that reversing MerTK-dependent DC tolerizing dysfunction could help overcome anti-PD-1 resistance.
- 1286 PlexinB1 Inactivation Reprograms Immune Cells in the Tumor Microenvironment, Inhibiting Breast Cancer Growth and Metastatic Dissemination**
Giulia Franzolin, Serena Brundu, Carina F. Cojocar, Aurora Curatolo, Matteo Ponzio, Roberta Mastrantonio, Emiko Mihara, Atsushi Kumanogoh, Hiroaki Suga, Junichi Takagi, Luca Tamagnone, and Enrico Giraud
The authors show that PLXNB1 inhibition in the TME reprograms immune cells and vessels in TNBC models hampering tumor growth and metastasis, and enhancing the response to immunotherapy. Thus, PLXNB1 represents a promising therapeutic target for metastatic TNBC.

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ABOUT THE COVER

There is limited understanding of the biology of neuroendocrine prostate cancer (NEPC), which is a highly aggressive form of prostate cancer that can arise *de novo* or as tumors become resistant to hormone therapies. Through *in vitro* and *in vivo* preclinical analyses, Sulenti and colleagues show that syndecan-1 is an NEPC-specific ligand for TLR2/4 on mast cells in the tumor and that activation of a TLR2/4-MyD88-intracellular osteopontin pathway leads to mast-cell production of TNF α , which limits NEPC growth. In human samples, the mast cell number decreases as NEPC progresses, highlighting the clinical relevance of the data and identifying new potential targets for mast cell-based immunotherapies for prostate cancer. Read more in this issue on page 1155. Original image from Fig. 2E. Artwork by Lewis Long.



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