CANCER IMMUNOLOGY AT THE CROSSROADS

502 Hallmarks of T-cell Exit from Quiescence
Nicole M. Chapman and Hongbo Chi

PRIORITY BRIEF

509 Human GUCY2C-Targeted Chimeric Antigen Receptor (CAR)-Expressing T Cells Eliminate Colorectal Cancer Metastases
CAR-T cells targeting GUCY2C were generated that eradicated GUCY2C-expressing human colorectal cancer xenografts in mice. This therapy has the potential to be translated to human studies investigating CAR-T targets for colorectal cancer immunotherapy.

RESEARCH ARTICLES

517 CD16A Activation of NK Cells Promotes NK Cell Proliferation and Memory-Like Cytotoxicity against Cancer Cells
Jens H.W. Pahl, Joachim Koch, Jana-Julia Gotz, Annette Arnold, Uwe Reusch, Thorsten Ganule, Erich Rajkovic, Martin Treder, and Adelheid Cerwenka
Pre-activation via CD16A, a potent cytotoxicity receptor engaged by therapeutic bispecific antibodies, promoted NK cell proliferation and expansion. These CD16A-experienced NK cells exerted memory-like enhanced cytotoxicity and IFNγ production upon restimulation with tumor cells.

528 Urinary Bladder Cancer Tregs Suppress MMP2 and Potentially Regulate Invasiveness
Tregs localized to the invasive front of human bladder tumors inhibited the expression of MMP2, an enzyme that cleaves extracellular matrix and promotes metastasis. Therefore, caution should be exercised in the clinical targeting of Tregs in inflammation-driven cancers.

539 AMD3100 Augments the Efficacy of Mesothelin-Targeted, Immune-Activating VIC-008 in Mesothelioma by Modulating Intratumoral Immunosuppression
Binghao Li, Yang Zeng, Patrick M. Reeves, Chongzhao Ran, Qianyu Liu, Xiying Qu, Yingying Liang, Zhao Liu, Jianping Yuan, Pierre R. Leblanc, Zhaoming Ye, Ann E. Sluder, Jeffrey A. Gelbard, Timothy A. Beauns, Huabiao Chen, and Mark C. Poznansky
CXCR4 antagonist AMD3100 promoted conversion of Tregs to helper-like cells and reduced PD-1 expression on CD8+ T cells in mesothelioma. The combination of AMD3100 with a mesothelin-targeting immune stimulator, VIC-008, controlled tumors and prolonged survival of tumor-bearing animals.

552 Cross-Talk between Myeloid-Derived Suppressor Cells and Mast Cells Mediates Tumor-Specific Immunosuppression in Prostate Cancer
Elena Jachetti, Valeria Cancila, Alice Rigoni, Lucia Bongiovanni, Barbara Cappetti, Beatrice Belmonte, Claudia Enriquez, Patrizia Casalini, Paola Ostano, Barbara Frossi, Sabina Sangaletti, Claudia Chiodoni, Giovanna Chiorino, Carlo E. Pacilio, Claudio Tripodo, and Mario P. Comombo
In a mouse model of prostate cancer, the incidence of adenocarcinoma was reduced when mast cells were lacking, correlating with a regained ability to mount a tumor-specific T-cell response. Mast cell inhibition required CD40L-CD40 interaction with myeloid suppressors.

566 Caspase-1 from Human Myeloid-Derived Suppressor Cells Can Promote T Cell–Independent Tumor Proliferation
Qi Zeng, Juan Fu, Michael Korner, Mikhail Gorbounov, Peter J. Murray, Drew Pardoll, David L. Masica, and Young J. Kim
MDSCs from HNSCC patients exhibited upregulated caspase-1, a member of the inflammasome complex, and directly promoted tumor cell proliferation. Silencing caspase-1 activity in a mouse model reduced tumor growth, suggesting that targeting caspase-1 could have therapeutic potential.

578 Protumor Steering of Cancer Inflammation by p50 NF-κB Enhances Colorectal Cancer Progression
Chiara Porta, Alessandro Ippolito, Francesca Maria Consonni, Lorenzo Carraro, Giuseppe Celesti, Carmen Correale, Fabio Grizzi, Fabio Pasqualini, Silvia Tartari, Maurizio Rinaldi, Paolo Bianchi, Fiorella Balzac, Stefania Vetrano, Emilia Turco, Emilio Hirsch, Luigi Laghi, and Antonio Sica
The p50 NF-κB subunit was identified as a key driver of the tumor-promoting reprogramming of TAMs, which could modulate the tumor microenvironment in colorectal cancer, demonstrating its potential as a candidate for prognostic and targeted therapeutic intervention.
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>594</td>
<td>Rapid Construction of Antitumor T-cell Receptor Vectors from Frozen Tumors for Engineered T-cell Therapy</td>
<td>Takemasa Tsuji, Akira Yoneda, Junko Matsuzaki, Anthony Miliotto, Courtney Ryan, Richard C. Koya, and Kunle Odunsi</td>
<td>Tumor-specific TCR α and β chain pairs were efficiently identified from a retroviral library of randomly paired TCRs recovered from frozen tumor biopsies and selected by tetramers. Therapeutic T cells expressing these TCRs had potent antitumor activity.</td>
</tr>
<tr>
<td>605</td>
<td>Improving CART-Cell Therapy of Solid Tumors with Oncolytic Virus–Driven Production of a Bispecific T-cell Engager</td>
<td>Anna Wing, Carlos Alberto Fajardo, Avery D. Posey Jr, Carolyn Shaw, Tong Da, Regina M. Young, Ramon Alemany, Carl H. June, and Sonia Guedan</td>
<td>The efficacy of chimeric antigen receptor T-cell therapy was improved by oncolytic-adenovirus delivery of a bispecific T-cell engager to the tumor microenvironment. T-cell activation was increased and tumor resistance overcome as a result of its dual antigen specificity.</td>
</tr>
<tr>
<td>617</td>
<td>Sustained Persistence of IL2 Signaling Enhances the Antitumor Effect of Peptide Vaccines through T-cell Expansion and Preventing PD-1 Inhibition</td>
<td>Hussein Sultan, Takumi Kumai, Valentyna I. Fesenkova, Aaron E. Fan, Juan Wu, Hyun-II Cho, Hiroya Kobayashi, Yasuaki Harabuchi, and Esteban Celis</td>
<td>IL2 signaling improves potency of peptide vaccines but at the cost of toxicity. Improving persistence of IL2 avoids toxicity and promotes antitumor T cells by enhancing their expansion and preventing PD-1 inhibition.</td>
</tr>
</tbody>
</table>

**ABOUT THE COVER**

Regulatory T cells contribute to the protumor environment in cancer. Large numbers in tumors, or a high regulatory T:CD8⁺ T cell ratio, is associated with a poor prognosis. However, that relationship is not always found in urinary bladder cancer. Winerdal et al. first established that the regulatory T cells in human bladder cancers are functionally suppressive like other regulatory T cells. They then observed that these regulatory T cells suppressed tumor and macrophage production of MMP2, a metalloproteinase that aids metastasis. Thus, higher numbers of regulatory T cells congregating at the invasive front of a tumor correlated with survival. Read more in this issue on page 528. Original micrograph from the Winquist laboratory shows a bladder tumor infiltrated and surrounded by brown T cells, some of which are regulatory. Artwork by Lewis Long.