

MILESTONES IN CANCER IMMUNOLOGY

- 1291 The 2015 William B. Coley Awards


CANCER IMMUNOLOGY AT THE CROSSROADS: BIostatISTICS

- 1292 Statistical Challenges in the Design of Late-Stage Cancer Immunotherapy Studies
Rosemarie Mick and Tai-Tsang Chen

CANCER IMMUNOLOGY MINIATURES

- 1299 Subacute CNS Demyelination after Treatment with Nivolumab for Melanoma
Catherine Maurice, Raphael Schneider, Tim-Rasmus Kiehl, Prashant Bavi, Michael H.A. Roehrl, Warren P. Mason, and David Hogg
Checkpoint blockade carries risks of immune-related adverse effects, but frequency and severity are unknown. A patient is described who received anti-CTLA-4 (ipilimumab), and then anti-PD-1 (nivolumab). The patient developed lethal subacute and progressive CNS demyelination.

PRIORITY BRIEFS

- 1303 PD-1 and PD-L1 Expression in Renal Cell Carcinoma with Sarcomatoid Differentiation
Richard W. Joseph, Sherri Z. Millis, Estrella M. Carballido, David Bryant, Zoran Gatalica, Sandeep Reddy, Alan H. Bryce, Nicholas J. Vogelzang, Melissa L. Stanton, Erik P. Castle, and Thai H. Ho
Sarcomatoid renal cell cancer (RCC) is an aggressive form of RCC that responds poorly to IL2 immunotherapy. Both PD-1 and PD-L1 were found expressed in sarcomatoid RCC samples, suggesting that blockade of the PD-L1/PD-1 pathway may have immunotherapeutic potential.
- 1308 PD-L1 Antibodies to Its Cytoplasmic Domain Most Clearly Delineate Cell Membranes in Immunohistochemical Staining of Tumor Cells
 Kathleen M. Mahoney, Heather Sun, Xiaoyun Liao, Ping Hua, Marcella Callea, Edward A. Greenfield, F. Stephen Hodi, Arlene H. Sharpe, Sabina Signoretti, Scott J. Rodig, and Gordon J. Freeman
Unambiguous assessment of the presence of PD-L1 in the membrane of tumor cells could increase its utility as a prognostic marker for PD-1 blockade treatment. Three monoclonal antibodies to PD-L1's cytoplasmic domain clearly demarcated membrane from cytoplasmic staining.

RESEARCH ARTICLES


- 1316 Simultaneous Targeting of FcγRs and FcαRI Enhances Tumor Cell Killing
Arianne M. Brandsma, Toine ten Broeke, Maaikje Nederend, Laura A.P.M. Meulenbroek, Geert van Tetering, Saskia Meyer, J.H. Marco Jansen, M. Alejandra Beltrán Buitrago, Sietse Q. Nagelkerke, István Németh, Ruud Ubink, Gerard Rouwendal, Stefan Lohse, Thomas Valerius, Jeanette H.W. Leusen, and Peter Boross
The efficacy of anticancer monoclonal antibodies (mAbs) is limited by the exhaustion of cellular effector mechanisms. The combination of IgG and IgA to two different tumor targets leads to enhanced cytotoxicity, providing a basis for therapeutic mAb improvements.
- 1325 Complement Factor H Antibodies from Lung Cancer Patients Induce Complement-Dependent Lysis of Tumor Cells, Suggesting a Novel Immunotherapeutic Strategy
Michael J. Campa, Elizabeth B. Gottlin, Ryan T. Bushey, and Edward F. Patz Jr
Select early-stage lung cancer patients never develop metastasis. Some of these patients have antibodies that inactivate a protein that protects tumor cells from complement lysis, thus making tumor cells more susceptible to being killed.
- 1333 Efficacy of a Cancer Vaccine against ALK-Rearranged Lung Tumors
Claudia Voena, Matteo Menotti, Cristina Mastini, Filomena Di Giacomo, Dario Livio Longo, Barbara Castella, Maria Elena Boggio Merlo, Chiara Ambrogio, Qi Wang, Valerio Giacomo Minero, Teresa Poggio, Cinzia Martinengo, Lucia D'Amico, Elena Panizza, Luca Mologni, Federica Cavallo, Fiorella Altruda, Mohit Butaney, Marzia Capelletti, Giorgio Inghirami, Pasi A. Jänne, and Roberto Chiarle
Lung cancers harboring ALK translocations are treated with protein kinase inhibitors, which can extend survival. A cancer vaccine against ALK induced strong immune responses and enhanced survival when used alone, or in combination with kinase inhibitors or checkpoint inhibitors.
- 1344 Progression of Lung Cancer Is Associated with Increased Dysfunction of T Cells Defined by Coexpression of Multiple Inhibitory Receptors
 Daniela S. Thommen, Jens Schreiner, Philipp Müller, Petra Herzig, Andreas Roller, Anton Belousov, Pablo Umana, Pavel Pisa, Christian Klein, Marina Bacac, Ozana S. Fischer, Wolfgang Moersig, Spasenija Savic Prince, Victor Levitsky, Vaios Karanikas, Didier Lardinois, and Alfred Zippelius
T cells within non-small cell lung cancer tumors acquire greater numbers, and more diversity, of inhibitory receptors as tumors progress, correlating with a loss in function as well as in their ability to be reactivated after anti-checkpoint treatment.

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- 1356** Prognostic Significance of CD169⁺ Lymph Node Sinus Macrophages in Patients with Malignant Melanoma
Yoichi Saito, Koji Ohnishi, Azusa Miyashita, Satoshi Nakahara, Yukio Fujiwara, Hasita Horlad, Takanobu Motoshima, Satoshi Fukushima, Masatoshi Jinnin, Hironobu Ihn, Motohiro Takeya, and Yoshihiro Komohara
Prognostic indicators are needed for malignant melanoma. The presence of high densities of CD169⁺ macrophages in the draining lymph nodes of patients significantly correlates with CTL infiltration and longer overall survival, providing a potentially useful biomarker.

- 1364** Effector CD8⁺ T-cell Engraftment and Antitumor Immunity in Lymphodepleted Hosts Is IL7R α Dependent
C. Bryce Johnson, Brian P. Riesenber, Bennett R. May, Stuart C. Gilreath, Guangfu Li, Kevin F. Staveley-O'Carroll, Elizabeth Garrett-Mayer, Shikhar Mehrotra, David J. Cole, and Mark P. Rubinstein
Adoptive cellular immunotherapy requires donor cells to survive and accumulate, which this study shows requires an IL12/IL7 axis in activated CD8⁺ T cells. IL12 leads to enhanced IL7R α expression and IL7 responsiveness, which maximizes antitumor efficacy.

- 1375** HDAC Inhibition Upregulates PD-1 Ligands in Melanoma and Augments Immunotherapy with PD-1 Blockade
David M. Woods, Andressa L. Sodr , Alejandro Villagra, Amod Sarnaik, Eduardo M. Sotomayor, and Jeffrey Weber
Combining other agents with immune-based approaches can enhance treatment for melanoma. PDL-1 gene expression was increased after inhibition of histone deacetylases. Combining PD-1-blockade immunotherapy with histone deacetylase inhibition increased responses in a mouse model of melanoma.

- 1386** Acknowledgment to Reviewers

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ABOUT THE COVER

Some patients with early stage non–small cell lung cancer never develop metastatic disease. Autoantibodies isolated from these individuals bind to a cryptic epitope of a complement-blocking protein called complement factor H (CFH). In the presence of CFH, cells are protected from complement killing. Given that the CFH epitope to which the autoantibodies bind is not normally exposed, these autoantibodies may be interfering with CFH only within tumors, relieving the block to complement, and making it possible to kill cancer cells that would otherwise be protected. The cover art (left) was inspired by the micrograph (right) of autoantibodies to CFH binding to the lung cancer cell line A549, and detected with AlexaFluor 647–conjugated anti-human IgG. Fluorescence micrograph image taken by Rebekah Dumm (Duke University Medical Center); artwork by Lewis Long. Read more about these autoantibodies in Campa et al., page 1325 in this issue of *Cancer Immunology Research*.

