

CANCER IMMUNOLOGY RESEARCH

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1262 **Spatial UMAP and Image Cytometry for Topographic Immuno-oncology Biomarker Discovery**
Nicolas A. Giraldo, Sneha Berry, Etienne Becht, Deniz Ates, Kara M. Schenk, Elizabeth L. Engle, Benjamin Green, Peter Nguyen, Abha Soni, Julie E. Stein, Farah Succaria, Aleksandra Ogurtsova, Haiying Xu, Raphael Gottardo, Robert A. Anders, Evan J. Lipson, Ludmila Danilova, Alexander S. Baras, and Janis M. Taube
The authors developed and validated a multiplex immunofluorescence data-analysis pipeline and spatial UMAP algorithm. These user-friendly tools enable the quantification and visualization of spatial arrangements of immune populations in the tumor microenvironment and associated immuno-oncology topographic biomarker development.

RESEARCH ARTICLES

1270 **Simultaneous Engagement of Tumor and Stroma Targeting Antibodies by Engineered NK-92 Cells Expressing CD64 Controls Prostate Cancer Growth**
Hallie M. Hintz, Kristin M. Snyder, Jianming Wu, Robert Hullsiek, James D. Dahlvang, Geoffrey T. Hart, Bruce Walcheck, and Aaron M. LeBeau
The data in this study suggest targeting the tumor stroma and malignant cells with engineered natural killer cells and therapeutic antibodies could overcome immunotherapy resistance in prostate cancer and result in a next-generation targeted therapy approach.

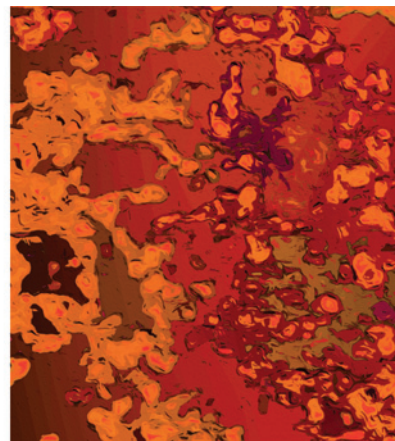
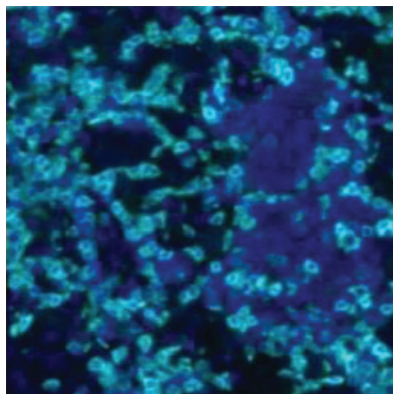
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- 1283 The Fibronectin–ILT3 Interaction Functions as a Stromal Checkpoint that Suppresses Myeloid Cells**
Kevin J. Paavola, Julie M. Roda, Vicky Y. Lin, Peirong Chen, Kyle P. O’Hollaren, Richard Ventura, Suzanne C. Crawley, Betty Li, Hung-I H. Chen, Seth Malmersjö, Nikolai A. Sharkov, Geoffrey Horner, Wei Guo, Alan K. Kutach, Kalyani Mondal, Zhen Zhang, Joshua S. Lichtman, Christina Song, Lee B. Rivera, Wenhui Liu, Jian Luo, Yan Wang, Mark J. Solloway, Bernard B. Allan, Avantika Kekatpure, Shelley R. Starck, Raj Haldankar, Bin Fan, Chun Chu, Jie Tang, Martina Molgora, Marco Colonna, Daniel D. Kaplan, and Jer-Yuan Hsu
In this study, the fibronectin–ILT3 interaction is shown to represent a “stromal checkpoint” through which the extracellular matrix actively suppresses tumor-associated myeloid cells. Therapeutics targeting this interaction can potentially reprogram suppressive myeloid cells, increasing antitumor immune responses.
- 1298 Targeting the Atf7ip–Setdb1 Complex Augments Antitumor Immunity by Boosting Tumor Immunogenicity**
Hai Hu, Alireza Khodadadi-Jamayran, Igor Dolgalev, Hyunwoo Cho, Sana Badri, Luis A. Chiriboga, Briana Zeck, Miguel Lopez De Rodas Gregorio, Catriona M. Dowling, Kristen Labbe, Jiehui Deng, Ting Chen, Hua Zhang, Paul Zappile, Ze Chen, Beatrix Ueberheide, Angeliki Karatza, Han Han, Michela Ranieri, Sittinon Tang, George Jour, Iman Osman, Antje Sucker, Dirk Schadendorf, Aristotelis Tsigos, Kurt A. Schalper, Vamsidhar Velcheti, Hsin-yi Huang, Yujuan Jin, Hongbin Ji, John T. Poirier, Fei Li, and Kwok-Kin Wong
Using a CRISPR-based suppressor screen, the authors identify Atf7ip and Setdb1 as epigenetic regulators of tumor antigen expression and presentation. Genetic deficiency in these regulators enhances antitumor immunity, suggesting a new immunotherapeutic strategy for overcoming tumor immune evasion.
- 1316 Arginase 1–Based Immune Modulatory Vaccines Induce Anticancer Immunity and Synergize with Anti-PD-1 Checkpoint Blockade**
Mia Aaboe Jørgensen, Stefano Ugel, Mie Linder Hübbe, Marco Carretta, Maria Perez-Penco, Stine Emilie Weis-Banke, Evelina Martinenaite, Katharina Kopp, Marion Chapellier, Annalisa Adamo, Francesco De Sanctis, Cristina Frusteri, Manuela Iezzi, Mai-Britt Zocca, Daniel Hargbøll Madsen, Ayako Wakatsuki Pedersen, Vincenzo Bronte, and Mads Hald Andersen
ARG1-targeting vaccines are shown to activate antitumor immunity and modulate the tumor microenvironment in multiple tumor models without causing toxicity. The anti-tumor effect of ARG1 vaccines was boosted by anti-PD-1 checkpoint blockade, highlighting potential use as an immunotherapy.
- 1327 Characteristics of Immune Memory and Effector Activity to Cancer-Expressed MHC Class I Phosphopeptides Differ in Healthy Donors and Ovarian Cancer Patients**
Amanda M. Lulu, Kara L. Cummings, Erin D. Jeffery, Paisley T. Myers, Dennis Underwood, Rachel M. Lacy, Kimberly A. Chianese-Bullock, Craig L. Slingluff Jr, Susan C. Modesitt, and Victor H. Engelhard
In this study, healthy donors are shown to have preexisting memory and active responses to a broad array of cancer-expressed MHC class I-restricted phosphopeptides, whereas cancer patient responses are limited, suggesting a way to enhance cancer immunotherapy.
- 1342 CD8⁺ T-cell Immune Surveillance against a Tumor Antigen Encoded by the Oncogenic Long Noncoding RNA *PVT1***
Yasuhiro Kikuchi, Serina Tokita, Tomomi Hirama, Vitaly Kochin, Munehide Nakatsugawa, Tomoyo Shinkawa, Yoshihiko Hirohashi, Tomohide Tsukahara, Fumitake Hata, Ichiro Takemasa, Noriyuki Sato, Takayuki Kanaseki, and Toshihiko Torigoe
The oncogenic lncRNA *PVT1* gives rise to an immunogenic HLA I-restricted peptide in patients with colorectal cancer. The data demonstrate that T cells from patients can recognize peptides resulting from alterations in noncoding regions of the genome.
- 1354 β 2-Integrin Adhesion Regulates Dendritic Cell Epigenetic and Transcriptional Landscapes to Restrict Dendritic Cell Maturation and Tumor Rejection**
Carla Guenther, Imrul Faisal, Manlio Fusciello, Maria Sokolova, Heidi Harjunpää, Mette Ilander, Robert Tallberg, Maria Kristina Vartiainen, Ronen Alon, Jose-Maria Gonzalez-Granado, Vincenzo Cerullo, and Susanna Carola Fagerholm
This study reveals that β 2-integrin-mediated adhesive interactions contribute to shaping DC programming. Disrupting β 2-integrin adhesion switches DCs to a mature, migratory phenotype that enhances antitumor responses, opening new avenues for optimization of DC-based cancer immunotherapy.

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ABOUT THE COVER

Multiplex immunofluorescence (mIF) is a powerful technology that enables visualization of the spatial relationships between cells in the tumor microenvironment (TME). Using tumor tissue from 93 patients with metastatic melanoma, Giraldo et al. developed and validated a mIF data-analysis pipeline and spatial uniform manifold approximation and projection (UMAP) algorithm to cluster and visualize the data. This approach revealed that PD-L1 and PD-1 expression intensity was spatially encoded in the TME. For example, PD-L1 expression intensity was highest on CD163⁺ cells in neighborhoods with a high density of CD8⁺ cells. The differences in spatial clustering correlated with distinct clinical outcomes, highlighting the potential for using this approach to identify prognostic and predictive immuno-oncology biomarkers. Read more in this issue on page 1262. Original image from Fig. 1B. Artwork by Lewis Long.



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