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T Cells Redirected to a Minor Histocompatibility Antigen Instruct Intratumoral TNFα Expression and Empower Adoptive Cell Therapy for Solid Tumors

Teresa Manzo, Tabea Sturmheit, Veronica Basso, Elisabetta Petrozziozza, Rodrigo Hess Michelini, Michela Riba, Massimo Freschi, Angela R. Elia, Matteo Grioni, Flavio Curnis, Maria Pia Protti, Ton N. Schumacher, Reno Debets, Melody A. Swartz, Angelo Corti, Matteo Bellone, and Anna Mondino

Précis: These results validate the importance of targeting both the tumor and its associated stroma in establishing the potency of a new combination therapy that can trigger efficacious alloimmune graft versus tumor effects.

Human Pancreatic Cancer Cells Induce a MyD88-Dependent Stromal Response to Promote a Tumor-Tolerant Immune Microenvironment

Daniel Delitto, Andrea E. Delitto, Bayli B. DiVita, Kien Pham, Song Han, Emily R. Hartlage, Brittney N. Newby, Michael H. Gerber, Kevin E. Behrns, Lyle L. Moldawer, Ryan M. Thomas, Thomas J. George Jr, Todd M. Brusko, Clayton E. Mathews, Chen Liu, Jose G. Trevino, Steven J. Hughes, and Shannon M. Wallet

Précis: Stromal cells respond to danger-associated factors secreted by pancreatic cancer cells, ultimately leading to profound stromal-mediated suppression of antitumor immunity.

Mesothelial Cells Create a Novel Tissue Niche That Facilitates Gastric Cancer Invasion

Masamitsu Tanaka, Sei Kuriyama, Go Itoh, Daichi Maeda, Akiteru Goto, Yutaro Tamiya, Kazuyoshi Yanagihara, Masakazu Yashiro, and Namiko Aiba

Précis: Peritoneal mesothelial cells generate a tissue microenvironment favorable to cancer cell infiltration, with possible therapeutic implications for blocking progression.

A Metastatic Mouse Model Identifies Genes That Regulate Neuroblastoma Metastasis

Bo Kyung A. Seong, Kelly E. Fathers, Robin Hallett, Christina K. Yung, Lincoln D. Stein, Samar Mouazaz, Lynn Kee, Cynthia E. Hawkins, Meredith S. Irwin, and David R. Kaplan

Précis: A new mouse model of human metastatic neuroblastoma was exploited to identify novel genes, signaling pathways, candidate therapeutics, and a prognostic gene expression that could improve the treatment of this deadly pediatric disease.

H-Ras and K-Ras Oncoproteins Induce Different Tumor Spectra When Driven by the Same Regulatory Sequences

Matthias Drosten, Lucia Simón-Carrasco, Isabel Hernández-Porras, Carmen G. Lechuga, María T. Blasco, Harrys K.C. Jacob, Salvatore Fabbiano, Nicoletta Potenza, José R. Bustelo, Carmen Guerra, and Mariano Barbacid

Précis: This study addresses the long-standing question about why H-Ras and K-Ras oncogenes are associated with induction of different tumor types, which results here suggest that subtle differences in MAP kinase signaling in tumor cells may offer one explanation for functional nonequivalence.
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**TUMOR AND STEM CELL BIOLOGY**

753  Castration Resistance in Prostate Cancer Is Mediated by the Kinase NEK6  
Atish D. Choudhury, Anna C. Schinzel, Maura B. Cotter,  
Rosina T. Lis, Katherine Labella, Ying Hee Lock,  
Francesca Izzo, Isil Guney, Michaela Bowden,  
Yvonne Y. Li, Jinal Patel, Emily Hartman, Steven A. Carr,  
Monica Schenone, Jacob D. Jaffe, Philip W. Kantoff,  
Peter S. Hammerman, and William C. Hahn  
Précis: These findings define a new kinase signaling pathway in mediating castration-resistant prostate cancer, the most aggressive form of the disease, with implications for the development of therapeutic agents needed for more effective control.

766  Transcriptional Regulator CNOT3 Defines an Aggressive Colorectal Cancer Subtype  
Paloma Cejas, Alessia Cavazza, C.N. Yandava,  
Víctor Moreno, David Horst, Juan Moreno-Rubio,  
Emilio Burgos, Marta Mendiola, Len Taing, Ajay Goel,  
Jaime Feliu, and Ramesh A. Shivdasani  
Précis: Expression of a little studied chromatin modifier appears to mark a subset of colon cancer cells with self-renewal properties, suggesting its use as a biomarker of early-stage colorectal cancers likely to have a poor prognosis.

780  S100A4 Elevation Empowers Expression of Metastasis Effector Molecules in Human Breast Cancer  
Thamir M. Ismail, Daimark Bennett,  
Angela M. Platt-Higgins, Morteta Al-Medhity,  
Roger Baraclough, and Philip S. Rudland  
Précis: These results suggest the existence of evolutionarily conserved pathways used by S100A4 to promote metastatic dissemination in the nervous system, which is not well understood but preferentially exploited by certain glandular tumors.

790  Aspirin Suppresses Growth in PI3K-Mutant Breast Cancer by Activating AMPK and Inhibiting mTORC1 Signaling  
Whitney S. Henry, Tyler Laszewski, Tiffany Tsang,  
Francisco Beca, Andrew H. Beck, Sandra S. McAllister, and Alex Toker  
Précis: These findings reposition aspirin as a tool to treat breast cancer cell growth, supporting a rationale for its combination with PI3K inhibitors in therapy.

802  Mouse Models of Pediatric Supratentorial High-grade Glioma Reveal How Cell-of-Origin Influences Tumor Development and Phenotype  
Smitha Sreedharan, Naga Prathyusha Maturi, Yuan Xie,  
Anders Sundström, Malin Jarvius, Sylwia Libard,  
Irina Alafuzoff, Holger Weishaupt, Marten Fryknäs,  
Rolf Larsson, Fredrik J. Swartling, and Lene Uhrbom  
Précis: These findings propose that the cell of origin may have an important role for clinicopathological features of HGG such as malignancy and drug sensitivity.

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ABOUT THE COVER

When the metastasis-inducing protein S100A4 is overexpressed in human cancers, it is often associated with poor prognosis. In a Drosophila model where protein expression is directed exclusively to the optic lobes, oncogenic RasVal12 produces GFP-labeled tumors within these structures (green fluorescence), but when coexpressed with S100A4, these tumors disseminate to the ventral nerve chord and elsewhere in the fly. Genetic and chemical blockades establish a metastatic pathway leading from S100A4 to a matrix metalloproteinase, MMP (red fluorescence). In human breast cancer, certain MMPs are coexpressed with S100A4 and are also associated with premature demise of patients from metastatic cancer. For details, see article by Ismail and colleagues on page 780.