Tumor Promotion by Intratumoral Plasmacytoid Dendritic Cells Is Reversed by TLR7 Ligand Treatment
Isabelle Le Mercier, Dominique Poujoj, Amélie Sanlaville, Vanja Sisirak, Michael Gobert, Isabelle Durand, Bertrand Dubois, Isabelle Treilleux, Jacqueline Marvel, Jaromir Vlach, Jean-Yves Blay, Nathalie Bendriss-Vermare, Christophe Caux, Isabelle Puisieux, and Nadège Goutagny
Précis: This study suggests a new use in breast cancer treatment for synthetic ligands of TLR7 like imiquimod that are used widely as immunomodulators in clinic.

Vaccine-Instructed Intratumoral IFN-γ Enables Regression of Autochthonous Mouse Prostate Cancer in Allogeneic T-Cell Transplantation
Rodrigo Hess Michelini, Teresa Manzo, Tabea Sturmheit, Veronica Basso, Martina Rocchi, Massimo Freschi, Joanna Listopad, Thomas Blankenstein, Matteo Bellone, and Anna Mondino
Précis: Findings argue that cancer vaccines that improve antitumor T-cell responses can cooperate strongly with allogeneic bone marrow transplants to convert them into effective treatments for solid tumors.

IL-18–Primed Helper NK Cells Collaborate with Dendritic Cells to Promote Recruitment of Effector CD8+ T Cells to the Tumor Microenvironment
Jeffrey L. Wong, Erik Berk, Robert P. Edwards, and Paweł Kalinski
Précis: Results advance understanding of how NK cells can provide an initial stimulus to orchestrate the attraction of dendritic cells and additional effector cells into the cancer microenvironment.

Potent Immunomodulatory Effects of the Trifunctional Antibody Catumaxomab
Diane Goëry, Caroline Flamant, Sylvie Busakiewicz, Vichnou Poirier-Colame, Oliver Kepp, Isabelle Martins, Julien Pesquet, Alexander Eggermont, Dominique Elias, Nathalie Chaput, and Laurence Zitvogel
Précis: This study reports a comprehensive dissection of the immunomodulatory effects of a bispecific mAb specific for a widely expressed tumor cell adhesion molecule and the T-cell molecule CD3, which is one of the first bispecific mAbs to be explored in clinic.
Intravital FLIM-FRET Imaging Reveals Dasatinib-Induced Spatial Control of Src in Pancreatic Cancer

Precis: Defining the spatial and temporal factors that limit drug targeting in live tumors could help optimize the preclinical development of new therapeutic agents.

PLZF Confers Effector Functions to Donor T Cells That Preserve Graft-versus-Tumor Effects while Attenuating GVHD
Arman Ghosh, Amanda A. Holland, Yildirim Dogan, Nury L. Yim, Uttam K. Rao, Lauren F. Young, Mallory L. West, Natalie V. Singer, Hae Lee, Il-Kang Na, Jennifer J. Tsai, Robert R. Feng, Olaf Penack, Alan M. Hanash, Cecilia Lezcano, George F. Murphy, Chen Liu, Michel Sadelain, Martin G. Sauer, Derek Sant’Angelo, and George F. Murphy

Precis: This study describes a strategy to improve the qualities of adoptive cell therapies that use alloreactive T cells for immune treatment of cancer, focusing particularly on the reduction of undesirable graft-versus-host side effects.

Progesterone Receptor Signaling in the Microenvironment of Endometrial Cancer Influences Its Response to Hormonal Therapy
Deanna M. Janzen, Miguel A. Rosales, Daniel Y. Paik, Daniel S. Lee, Daniel A. Smith, Owen N. Witte, M. Luisa Iruela-Arispe, and Sanaz Memarzadeh

Precis: Striking findings show that the efficacy of hormonal therapy in endometrial cancer is not related to effects on cancer cells, but rather to effects on stromal cells where the progesterone receptor is necessary and sufficient to mediate antitumor effects in the microenvironment.

MOLECULAR AND CELLULAR PATHOBIOLOGY

Histone Demethylase RBP2 Promotes Lung Tumorigenesis and Cancer Metastasis
Yu-Ching Teng, Cheng-Feng Lee, Ying-Shiuann Li, Yi-Ren Chen, Pei-Wen Hsiao, Meng-Yu Chau, Feng-Mao Lin, Hsien-Da Huang, Yen-Ting Chen, Yang-Ming Jeng, Chih-Hung Hsu, Qin Yan, Ming-Daw Tsai, and Li-Jung Juan

Precis: Findings establish an oncogenic function in lungs for an Rb binding protein that modifies chromatin, with implications for malignant progression in this tissue.

Proteomic and Lipidomic Signatures of Lipid Metabolism in NASH-Associated Hepatocellular Carcinoma
Kyle Muir, Antonious Hazim, Ying He, Marion Peyressatre, Do-Young Kim, Xiaoling Song, and Laura Beretta

Precis: This study reveals a role for lipid-modifying enzymes in liver cancer, identifying in particular a specific type of long-chain polyunsaturated fatty acid participating in nonalcoholic steatohepatitis and liver cancer risk.

Posttranscriptional Regulation of PER1 Underlies the Oncogenic Function of IRE6

Precis: Circadian rhythms that may affect chemotherapeutic efficacy are linked here for the first time to the unfolded protein response, a signaling pathway widely activated in cancer that plays an important role in tumor aggressiveness.

Peroxiside-2 Represses Melanoma Metastasis by Increasing E-Cadherin/β-Catenin Complexes in Adherens Junctions
Doo Jae Lee, Dong Hoon Kang, Mina Choi, Yang Ji Choi, Joo Young Lee, Joo Hyun Park, Yoon Jung Park, Kyung Wha Lee, and Sang Won Kang

Precis: In discovering a specific antioxidant enzyme that can repress melanoma metastasis, this study also suggests a tractable new direction to treat this deadly disease.

TR3 Modulates Platinum Resistance in Ovarian Cancer
Andrew J. Wilson, Annie Y. Liu, Joseph Roland, Oluwafunmilayo B. Adebayo, Sarah A. Fletcher, James C. Slaughter, Jeannette Saskowski, Marta A. Crispens, Howard W. Jones III, Samuel James, Oluwofemi Fadare, and Dione Khabele

Precis: There remains great interest in determining general strategies to overcome resistance to platinum compounds that are used very widely to treat cancer, including ovarian cancer.
GENETIC ABLATION OF THE FATTY ACID-BINDING PROTEIN FABP5 SUPPRESSES HER2-INDUCED MAMMARY TUMORIGENESIS
Liraz Levi, Glenn Lobo, Mary Kathryn Doud, Johannes von Lintig, Darcie Seachrist, Gregory P. Tochtrup, and Noa Noy

PATHWAY-BASED SERUM microRNA ENHANCED RADIATION SENSITIVITY IN PanIN-SPECIFIC REGULATION OF Wnt GENETIC ABOLITION OF THE FATTY ACID-BINDING PROTEIN FABP5 SUPPRESSES HER2-INDUCED MAMMARY TUMORIGENESIS
Liraz Levi, Glenn Lobo, Mary Kathryn Doud, Johannes von Lintig, Darcie Seachrist, Gregory P. Tochtrup, and Noa Noy

PREVENTION AND EPIDEMIOLOGY
PATHWAY-BASED SERUM microRNA PROFILING AND SURVIVAL IN PATIENTS WITH ADVANCED STAGE NON–SMALL CELL LUNG CANCER
Yan Wang, Jian Gu, Jack A. Roth, Michelle A.T. Hildebrandt, Scott M. Lippman, Yuanqing Ye, John D. Minna, and Xifeng Wu

A 20-YEAR PROSPECTIVE STUDY OF PLASMA PROLACTIN AS A RISK MARKER OF BREAST CANCER DEVELOPMENT
Shelley S. Tworoger, A. Heather Eliassen, Xuehong Zhang, Jing Qian, Patrick M. Sasso, Bernard A. Rosner, and Susan E. Hankinson

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY
NOVEL RECOMBINANT HUMAN B7–H4 ANTIBODIES OVERCOME TUMORAL IMMUNE ESCAPE TO POTENTIATE T-CELL ANTITUMOR RESPONSES
Denarda Dangaj, Evripidis Lanitis, Aiizhi Zhao, Shreer Joshi, Yi Cheng, Raphael Sandaltzopoulos, Hyun-Jeong Ra, Gwenn Danet-Desnoyers, Daniel J. Powell, Jr, and Nathalie Scholler

TRANSCRIPTION POISONING BY TOPOISOMERASE I IS CONTROLLED BY GENE LENGTH, SPlice SITES, AND miR-142-3P
Stéphanie Solier, Michael C. Ryan, Scott E. Martin, Sudhir Varma, Kurt W. Kohn, Hongfang Liu, Barry R. Zeeberg, and Yves Pommier

C-RAF MUTATIONS CONFER RESISTANCE TO RAF INHIBITORS
Rajee Antony, Caroline M. Emery, Allison M. Sawyer, and Levi A. Garraway

PIVOTAL ROLE OF THE LIPID RAFT SK3–ORAI1 COMPLEX IN HUMAN CANCER CELL MIGRATION AND BONE METASTASES

DOXETAXEL CONJUGATE NANOPARTICLES THAT TARGET a-SMOOTH MUSCLE ACTIN–EXPRESSING STROMAL CELLS SUPPRESS BREAST CANCER METASTASIS
Mami Murakami, Mark J. Ernsting, Elijus Undzys, Nathan Holwell, Warren D. Foltz, and Shyh-Dar Li

Précis: A protein that delivers fatty acids to the transcription factor PPARY is critical for mammary tumor development, rationalizing the development of FABP5 inhibitors to prevent or treat breast cancer.

Précis: This study identifies root signaling connections between hypoxia control and the Wnt and Smad4 pathways in early development of pancreatic cancer.

Précis: Activation of residual p53 in HPV+ head and neck cancers may explain why this type of disease has a relatively better outcome in patients.

Précis: These findings may provide a rationale for the future development of allosteric or pan-RAF inhibitors that disrupt the RAF dimerization interface.

Précis: A novel cytotoxic nanoparticle that specifically degrades stromal elements in the tumor microenvironment exhibits potent antitumor activity.
LIPI28 Expression in Malignant Germ Cell Tumors Downregulates let-7 and Increases Oncogene Levels

Precis: This study defines a common oncogenic pathway in malignant germ cell tumors (GCT) and offers preclinical initial proof of concept for its targeting potential in this setting.

A Renewable Tissue Resource of Phenotypically Stable, Biologically and Ethnically Diverse, Patient-Derived Human Breast Cancer Xenograft Models
Xiaomei Zhang, Sofie Claerhout, Aleix Pratt, Lacey E. Dobrolecki, Ivana Petrovic, Qing Lai, Melissa D. Landis, Lisa Wierchmann, Rachel Schiffr, Mario Giuliano, Helen Wong, Suzanne W. Fuqua, Lianfeng Zhang, Shile Huang, and Ji-Long Chen

Precis: This well-characterized collection of human breast cancer xenografts will serve as a foundation for conduct of "animal clinical trials" to evaluate experimental therapeutics, as well as a resource for mechanistic studies of treatment resistance and metastasis.

eIF4B Phosphorylation by Pim Kinases Plays a Critical Role in Cellular Transformation by Abl Oncogenes
Jianling Yang, Jun Wang, Ke Chen, Guijie Guo, Ruijiao Xi, Paul B. Rothman, Douglass Whitten, Lianfeng Zhang, Shile Huang, and Ji-Long Chen

Precis: Results identify the translation initiation factor eIF-4B as a critical substrate of Pim kinases, which mediate the activity of Abl oncogenes, suggesting this factor as a candidate therapeutic target in Abl-induced cancers.

Canonical Wnt Signaling Is Required for Pancreatic Carcinogenesis
Yaqing Zhang, John P. Morris IV, Wei Yan, Heather K. Schofield, Austin Gurney, Diane M. Simeone, Sarah E. Millar, Timothy Hoey, Matthias Hebrok, and Marina Pasca di Magliano

Precis: This study establishes a causal role for WNT pathway signaling in the development and progression of K-ras-initiated pancreatic cancers, with therapeutic implications for the use of WNT pathway antagonists in this deadly disease.

TRAF6 Upregulates Expression of HIF-1α and Promotes Tumor Angiogenesis
Heng Sun, Xue-Bing Li, Ya Meng, Li Fan, Min Li, and Jing Fang

Precis: A factor well studied in the TNF response and implicated in innate and adaptive immune control is established in this study to control tumor angiogenesis.

Retraction: Sp100 as a Potent Tumor Suppressor: Accelerated Senescence and Rapid Malignant Transformation of Human Fibroblasts through Modulation of an Embryonic Stem Cell Program
Ron C.J. Schackmann, Sjoerd Klarenbeek, Eva J. Vlug, Suzan Stelloo, Miranda van Amersfoort, Milou Tenhagen, Tanya M. Braumuller, Jeroen F. Vermeulen, Petra van der Groep, Ton Peeters, Elksen van der Wall, Paul J. van Diest, Jos Jonkers, and Patrick W.B. Derksen

Precis: Based on conditional mouse models of metastatic breast cancer that are immunocompetent and clinically relevant, the current study provides an alternate rationale for therapeutic intervention of p120-catenin negative invasive breast cancer.

IKK4a/ARF Inactivation with Activation of the NF-κB/IL-6 Pathway Is Sufficient to Drive the Development and Growth of Angiosarcoma
Ron C.J. Schackmann, Sjoerd Klarenbeek, Eva J. Vlug, Suzan Stelloo, Miranda van Amersfoort, Milou Tenhagen, Tanya M. Braumuller, Jeroen F. Vermeulen, Petra van der Groep, Ton Peeters, Elksen van der Wall, Paul J. van Diest, Jos Jonkers, and Patrick W.B. Derksen

Precis: This work illustrates a general method to prospectively isolate tumor-initiating cells, the imaging and targeting of which may be important for improving therapeutic outcomes in individual patients.

Loss of p120-Catenin Induces Metastatic Progression of Breast Cancer by Inducing Anoikis Resistance and Augmenting Growth Factor Receptor Signaling
Ron C.J. Schackmann, Sjoerd Klarenbeek, Eva J. Vlug, Suzan Stelloo, Miranda van Amersfoort, Milou Tenhagen, Tanya M. Braumuller, Jeroen F. Vermeulen, Petra van der Groep, Ton Peeters, Elksen van der Wall, Paul J. van Diest, Jos Jonkers, and Patrick W.B. Derksen

Precis: This study establishes a causal role for WNT pathway signaling in the development and progression of K-ras-initiated pancreatic cancers, with therapeutic implications for the use of WNT pathway antagonists in this deadly disease.

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ABOUT THE COVER

Schematic representation of the IRE1α-dependent activation loop that controls tumor cell adaptation. Tumor cell is presented in light gray, stromal cells in dark gray. Proteins are represented by circles, with upregulation in green and downregulation in red. Connections following stress-mediated activation of IRE1α are presented in green for activation and red for inhibition. For details, see article by Pluquet and colleagues on page 4732.