BREAKING ADVANCES

3481 Highlights from Recent Cancer Literature

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3483 From Integrative Genomics to Therapeutic Targets
Rachael Natrajan and Paul Wilkerson

3489 HER2 and Breast Cancer Stem Cells: More than Meets the Eye
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3494 APOBEC3 Cytidine Deaminases in Double-Strand DNA Break Repair and Cancer Promotion
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CLINICAL STUDIES

3499 Immune Infiltrates Are Prognostic Factors in Localized Gastrointestinal Stromal Tumors
Sylvie Rusakiewicz, Michaela Semeraro, Matthieu Sarabi, Mélanie Desbois, Clara Locher, Rosa Mendez, Nadège Vimond, Angel Concha, Federico Garrido, Nicolas Isambert, Loïc Chaigneau, Valérie Le Brun-Ly, Patrice Duhreuil, Isabelle Cremer, Anne Caignard, Vichnou Poirier-Colame, Kariman Chaba, Caroline Flament, Niels Halama, Dirk Jäger, Alexander Eggermont, Sylvie Bonvalot, Frédéric Commo, Philippe Terrier, Paule Opolon, Jean-François Emile, Jean-Michel Coindre, Guido Kroemer, Nathalie Chaput, Axel Le Cesne, Jean-Yves Blay, and Laurence Zitvogel

PÉRÈS: These findings encourage the prospective validation of immune biomarkers for optimal risk stratification of GIST, and they prompt clinical use of immunomodulators in conjunction with imatinib used to treat this disease.

INTEGRATED SYSTEMS AND TECHNOLOGIES

3511 Kinetic Modeling-Based Detection of Genetic Signatures That Provide Chemoresistance via the E2F1-p73/DNp73-miR-205 Network
Julio Vera, Ulf Schmitz, Xin Lai, David Engelmann, Faiz M. Khan, Olaf Wolkenhauer, and Brigitte M. Pützer

PÉRÈS: Experimental and in silico data were used with kinetic modeling to develop a model that can detect a genetic signature that confers aggressive phenotypes in cancer cells.

3525 Mathematical Modeling of Tumor Cell Proliferation Kinetics and Label Retention in a Mouse Model of Lung Cancer
Yanyan Zheng, Helen Moore, Alexandra Piryatinska, Trinidad Solis, and E. Alejandro Sweet-Cordero

PÉRÈS: Mathematical methods to quantitate the proportion and doubling time of cycling tumor cell subpopulations in tumors, which tend to respond relatively poorly to cytotoxic therapies, may provide a tool to assess preclinical models, in which direct observation of cell-cycle kinetics may not be readily experimentally accessible.

3534 Tumor–Immune Dynamics Regulated in the Microenvironment Inform the Transient Nature of Immune-Induced Tumor Dormancy
Kathleen P. Wilkie and Philip Hahnfeldt

PÉRÈS: Better understanding of immune-induced tumor dormancy may lead to insights into prognosis and improved therapy, for example by tilting host innate or adaptive responses toward those that favor tumor elimination over immune escape.

MICROENVIRONMENT AND IMMUNOLOGY

3545 Booster Vaccinations against Cancer Are Critical in Prophylactic but Detrimental in Therapeutic Settings
Alessia Ricupito, Matteo Grioni, Arianna Caciniotto, Rodrigo Hess Michelini, Renato Longhi, Anna Mondino, and Matteo Bellone

PÉRÈS: This study challenges the notion that repeatedly boosting tumor-bearing subjects with a vaccine can sustain protective, long-lasting antitumor immunity, instead showing that certain prime-boost strategies actually drive T-cell exhaustion rather than expansion and memory.
A Novel Model for Evaluating Therapies Targeting Human Tumor Vasculature and Human Cancer Stem–like Cells
Daniela Burgos-Ojeda, Karen McLean, Shoumei Bai, Heather Pulsaki, Yusong Gong, Ines Silva, Karl Skorecki, Maty Tzukerman, and Ronald J. Buckanovich

Précis: There remains a great need for preclinical models that can more accurately predict clinical responses to novel experimental therapeutic agents in development.

Enhanced Effector Responses in Activated CD8+ T Cells Deficient in Diacylglycerol Kinases

Précis: Targeting of diacylglycerol kinases offers a general approach to enhance the function of chimeric antigen receptor T cells (CART cells), a promising new strategy for cancer immunotherapy.

SOS3 Transactivation by PPARγ Prevents IL-17–Driven Cancer Growth
Hélène Berger, Frédérique Végran, Madjid Chikh, Federica Gilardi, Sylvain Ladoire, Hélène Bugault, Grégoire Mignot, Fanny Chalnmin, Mélanie Bruchard, Valentin Derangère, Angélique Chevriaux, Cédric Rébé, Bernhard Ryffel, Caroline Pot, Aziz Hichami, Béatrice Desvergne, François Ghiroghelli, and Lionel Apetoh

Précis: This study reveals new mechanistic insights into how inflammation supports cancer, and how blocking certain inflammatory pathways can restrict cancer.

Dual Blockade of PD-1 and CTLA-4 Combined with Tumor Vaccine Effectively Restores T-Cell Rejection Function in Tumors
Jaikumar Duraisawamy, Karen M. Kaluza, Gordon J. Freeman, and George Coukos

Précis: Combined checkpoint blockade is synergistic and strongly augments the efficacy of vaccination to restore T-cell exhaustion and promote tumor rejection.

BMP-6 in Renal Cell Carcinoma Promotes Tumor Proliferation through IL-10–Dependent M2 Polarization of Tumor-Associated Macrophages
Jae-Ho Lee, Geum Taek Lee, Seung Hyo Woo, Yun-Sok Ha, Seok Joo Kwon, Won-Jae Kim, and Isaac Yi Kim

Précis: Elevated IL-10 levels have been broadly associated with tumor tolerance and immune escape, but the basis for IL-10 upregulation and its critical cellular targets in tumors have not been fully clear.
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DDB2 Suppresses Epithelial-to-Mesenchymal Transition in Colon Cancer
Nilotpal Roy, Prashant V. Bommi, Uppoor G. Bhat, Shaumick Bhattacharjee, Indira Elangovan, Jing Li, Krushna C. Patra, Dragana Kopanja, Adam Blunier, Richard Benya, Srilata Bagchi, and Pradip Raychaudhuri

Precis: A nucleotide excision repair protein is found to function as an inhibitor of EMT, a phenotypic change in transformed epithelial cells that facilitates invasion and metastasis, suggesting a direct link between these processes during tumorigenesis.

GDNF–RET Signaling in ER-Positive Breast Cancers Is a Key Determinant of Response and Resistance to Aromatase Inhibitors
Andrea Morandi, Lesley-Ann Martin, Qiong Gao, Sunil Pancholi, Alan Mackay, David Robertson, Marketa Zvelebil, Mitch Dowsett, Ivan Plaza-Menacho, and Clare M. Isacke

Precis: This study addresses the clinical challenge of therapeutic resistance in oncology, in this case by defining an important tractable pathway of resistance to aromatase inhibitors used to fight ER-positive breast cancer.

ABOUT THE COVER
Inhibition of VEGF signaling reduces angiogenesis and slows tumor growth, but can also promote lymph node metastasis in some preclinical models. Studies of RIP-Tag2 transgenic mice revealed that inhibition of VEGF signaling by a function blocking anti-VEGF antibody or the receptor tyrosine kinase inhibitor sunitinib increased the number of intratumoral lymphatics, the proportion of lymphatics with tumor cells inside, and the incidence of lymph node metastasis. After the treatment, c-Met was upregulated in lymphatics in and around the tumors. Importantly, inhibition of c-Met by PF-04217903 administered with the angiogenesis inhibitor significantly reduced the abundance of intratumoral lymphatics, tumor cells inside lymphatics, and lymph node metastases. For details, see article by Sennino and colleagues on page 3692.
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