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Cancer Research

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4611 **Cancer Research Advocacy: Past, Present, and Future**
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INTEGRATED SYSTEMS AND TECHNOLOGIES

4616 **Quantitative *In Vivo* Characterization of Intracellular and Extracellular pH Profiles in Heterogeneous Tumors: A Novel Method Enabling Multiparametric pH Analysis**
Norbert W. Lutz, Yann Le Fur, Johanna Chiche, Jacques Pouysségur, and Patrick J. Cozzone

Précis: *By providing important details on cancer acidity, pH calculations could help support the development of new cancer therapeutics targeting tumor metabolism.*

MICROENVIRONMENT AND IMMUNOLOGY

4629 **Tumor Promotion by Intratumoral Plasmacytoid Dendritic Cells Is Reversed by TLR7 Ligand Treatment**
Isabelle Le Mercier, Dominique Poujol, Amélien 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.*

4641 **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.*

4653 **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 Pawel 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.*

4663 **Potent Immunomodulatory Effects of the Trifunctional Antibody Catumaxomab**
Diane Goéré, Caroline Flament, Sylvie Rusakiewicz, 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.*

4674 **Intravital FLIM-FRET Imaging Reveals Dasatinib-Induced Spatial Control of Src in Pancreatic Cancer**
Max Nobis, Ewan J. McGhee, Jennifer P. Morton, Juliane P. Schwarz, Saadia A. Karim, Jean Quinn, Mike Edward, Andrew D. Campbell, Lynn C. McGarry, T.R. Jeffry Evans, Valerie G. Brunton, Margaret C. Frame, Neil O. Carragher, Yingxiao Wang, Owen J. Sansom, Paul Timpson, and Kurt I. Anderson

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

4687 **PLZF Confers Effector Functions to Donor T Cells That Preserve Graft-versus-Tumor Effects while Attenuating GVHD**
Arnab Ghosh, Amanda M. 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. Jenq, Olaf Penack, Alan M. Hanash, Cecilia Lezcano, George F. Murphy, Chen Liu, Michel Sadelain, Martin G. Sauer, Derek Sant'Angelo, and Marcel R.M. van den Brink

Précis: *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.*

4697 **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

Précis: *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

4711 **Histone Demethylase RBP2 Promotes Lung Tumorigenesis and Cancer Metastasis**
Yu-Ching Teng, Cheng-Feng Lee, Ying-Shiuan Li, Yi-Ren Chen, Pei-Wen Hsiao, Meng-Yu Chan, Feng-Mao Lin, Hsien-Da Huang, Yen-Ting Chen, Yung-Ming Jeng, Chih-Hung Hsu, Qin Yan, Ming-Daw Tsai, and Li-Jung Juan

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

4722 **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

Précis: *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.*

4732 **Posttranscriptional Regulation of *PER1* Underlies the Oncogenic Function of IREα**
Olivier Pluquet, Nicolas Dejeans, Marion Bouchecareilh, Stephanie Lhomond, Raphael Pineau, Arisa Higa, Maylis Delugin, Chantal Combe, Sandrine Loriot, Gaelle Cubel, Nathalie Dugot-Senant, Anne Vital, Hugues Loiseau, Sara J.C. Gosline, Said Taouji, Michael Hallett, Jann N. Sarkaria, Keith Anderson, Wenting Wu, Fausto J. Rodriguez, Jean Rosenbaum, Frédéric Saltel, Martin E. Fernandez-Zapico, and Eric Chevet

Précis: *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.*

4744 **Peroxiredoxin-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

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

4758 **TR3 Modulates Platinum Resistance in Ovarian Cancer**
Andrew J. Wilson, Annie Y. Liu, Joseph Roland, Oluwafunmilayo B. Adebayo, Sarah A. Fletcher, James C. Slaughter, Jeanette Saskowski, Marta A. Crispens, Howard W. Jones III, Samuel James, Oluwole Fadare, and Dineo Khabele

Précis: *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.*

4770 **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. Tochtrop, and Noa Noy

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

4781 **PanIN-Specific Regulation of Wnt Signaling by HIF2α during Early Pancreatic Tumorigenesis**
Angela Criscimanna, Li-Juan Duan, Julie A. Rhodes, Volker Fendrich, Emily Wickline, Douglas J. Hartman, Satdarshan P.S. Monga, Michael T. Lotze, George K. Gittes, Guo-Hua Fong, and Farzad Esni

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

4791 **Enhanced Radiation Sensitivity in HPV-Positive Head and Neck Cancer**
Randall J. Kimple, Molly A. Smith, Grace C. Blitzer, Alexandra D. Torres, Joshua A. Martin, Robert Z. Yang, Chimera R. Peet, Laurel D. Lorenz, Kwangok P. Nickel, Aloysius J. Klingelhutz, Paul F Lambert, and Paul M. Harari

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.*

PREVENTION AND EPIDEMIOLOGY

4801 **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

Précis: *Accumulating evidence argues that microRNA signatures derived from blood serum may offer simple quantitative tools for clinical prognosis and therapeutic development in many settings.*

4810 **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. Sluss, Bernard A. Rosner, and Susan E. Hankinson

Précis: *Elevated levels of plasma prolactin are associated with an increased risk of breast cancer, but only for 10 years after assessment of this risk marker, supporting a role for prolactin at later stages in breast carcinogenesis.*

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

4820 **Novel Recombinant Human B7-H4 Antibodies Overcome Tumoral Immune Escape to Potentiate T-Cell Antitumor Responses**
Denarda Dangaj, Evripidis Lanitis, Aizhi Zhao, Shree Joshi, Yi Cheng, Raphael Sandaltzopoulos, Hyun-Jeong Ra, Gwenn Danet-Desnoyers, Daniel J. Powell, Jr, and Nathalie Scholler

Précis: *Blockade of inhibitory T-cell receptor signals in the same general family as the CTLA-4 molecule targeted by ipilumumab (Yervoy) may offer a paradigm for simultaneous targeting of not only tumor cells, but also tumor-associated macrophages that drive immune escape.*

4830 **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

Précis: *Camptothecins used in cancer therapy may act to a major extent by targeting a p53-dependent microRNA.*

4840 **C-RAF Mutations Confer Resistance to RAF Inhibitors**
Rajee Antony, Caroline M. Emery, Allison M. Sawyer, and Levi A. Garraway

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

4852 **Pivotal Role of the Lipid Raft SK3–Orai1 Complex in Human Cancer Cell Migration and Bone Metastases**
Aurélie Chantôme, Marie Potier-Cartereau, Lucie Clarysse, Gaëlle Fromont, Séverine Marionneau-Lambot, Maxime Guéguinou, Jean-Christophe Pagès, Christine Collin, Thibauld Oullier, Alban Girault, Flavie Arbion, Jean-Pierre Haelters, Paul-Alain Jaffrès, Michelle Pinault, Pierre Besson, Virginie Joulin, Philippe Bougnoux, and Christophe Vandier

Précis: *This study links a therapeutically targetable potassium channel to bone metastasis, a common feature of advanced breast and prostate cancers that is generally untreatable.*

4862 **Docetaxel Conjugate Nanoparticles That Target α-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 novel cytotoxic nanoparticle that specifically degrades stromal elements in the tumor microenvironment exhibits potent antitumor activity.*

TUMOR AND STEM CELL BIOLOGY

4872 **_LIN28_ Expression in Malignant Germ Cell Tumors Downregulates _let-7_ and Increases Oncogene Levels**
Matthew J. Murray, Harpreet K. Saini, Charlotte A. Siegler, Jennifer E. Hanning, Emily M. Barker, Stijn van Dongen, Dawn M. Ward, Katie L. Raby, Ian J. Groves, Cinzia G. Scarpini, Mark R. Pett, Claire M. Thornton, Anton J. Enright, James C. Nicholson, Nicholas Coleman, and on behalf of the CCLG

Précis: *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.*

4885 **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 Wiechmann, Rachel Schiff, Mario Giuliano, Helen Wong, Suzanne W. Fuqua, Alejandro Contreras, Carolina Gutierrez, Jian Huang, Sufeng Mao, Anne C. Pavlick, Amber M. Froehlich, Meng-Fen Wu, Anna Tsimelzon, Susan G. Hilsenbeck, Edward S. Chen, Pavel Zuloaga, Chad A. Shaw, Mothaffar F. Rimawi, Charles M. Perou, Gordon B. Mills, Jenny C. Chang, and Michael T. Lewis

Précis: *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.*

4898 **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, Douglas Whitten, Lianfeng Zhang, Shile Huang, and Ji-Long Chen

Précis: *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.*

4909 **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

Précis: *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.*

4923 **Aptamer Identification of Brain Tumor–Initiating Cells**
Youngmi Kim, Qiulian Wu, Petra Hamerlik, Masahiro Hitomi, Andrew E. Sloan, Gene H. Barnett, Robert J. Weil, Patrick Leahy, Anita B. Hjelmeland, and Jeremy N. Rich

Précis: *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.*

4937 **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, Elsken van der Wall, Paul J. van Diest, Jos Jonkers, and Patrick W.B. Derksen

Précis: *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.*

4950 **TRAF6 Upregulates Expression of HIF-1α and Promotes Tumor Angiogenesis**
Heng Sun, Xue-Bing Li, Ya Meng, Li Fan, Min Li, and Jing Fang

Précis: *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

4960 **Retraction: Sp100 as a Potent Tumor Suppressor: Accelerated Senescence and Rapid Malignant Transformation of Human Fibroblasts through Modulation of an Embryonic Stem Cell Program**

CORRECTION

4962 **Correction: IKK4a/ARF Inactivation with Activation of the NF-κB/IL-6 Pathway Is Sufficient to Drive the Development and Growth of Angiosarcoma**

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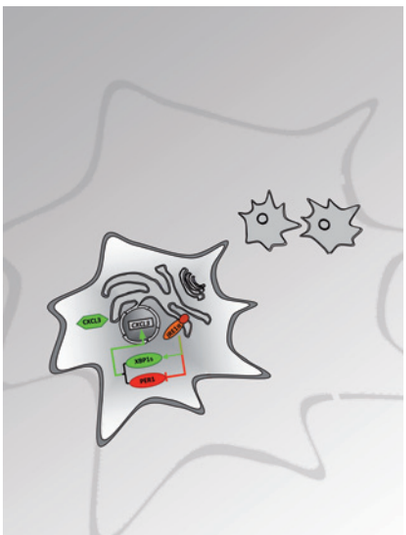
ABOUT THE COVER

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.