BREAKING ADVANCES

4595 Highlights from Recent Cancer Literature

OBITUARY

4597 Emil Frei III, MD: In Memoriam (1924–2013)

REVIEWS

4599 A Road Map to Comprehensive Androgen Receptor Axis Targeting for Castration-Resistant Prostate Cancer
Nicholas Mitsiades

4606 Myeloid-Derived Suppressor Cells as Osteoclast Progenitors: A Novel Target for Controlling Osteolytic Bone Metastasis
Anandi Sawant and Selvarangan Ponnazhagan

PERSPECTIVE

4611 Cancer Research Advocacy: Past, Present, and Future
Jane Perlmuter, Shannon K. Bell, and Gwen Darien

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 Pouyssegur, and Patrick J. Cozzone

MICROENVIRONMENT AND IMMUNOLOGY

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

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 Mondo

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 Goëry, Caroline Flamant, Sylvie Busakiewicz, Vichnou Pouirier-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.
**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 Hsiiao, Meng-Yu Chiu, 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.

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**4722** Proteomic and Lipidomic Signatures of Lipid Metabolism in NASH-Associated Hepatocellular Carcinoma

Kyle Muir, Antoniaz 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.

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**4732** Posttranscriptional Regulation of PER1 Underlies the Oncogenic Function of IRE1α


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.

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**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.

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**4758** TR3 Modulates Platinum Resistance in Ovarian Cancer

Andrew J. Wilson, Annie Y. Liu, Joseph Roland, Oluwafumilayo B. Adebayo, Sarah A. Fletcher, James C. Slaughter, Jeannette Saskowski, Marta A. Crispens, Howard W. Jones III, Samuel James, Olufolakemi Fadayoi, and Dione 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.
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, Aizhi Zhao, Shree Joshi, Yi Cheng, Raphael Sandaltzopoulos, Hyun-Jeong Ra, Gwern Danet-Denoyers, Daniel J. Powell, Jr, and Nathalie Scholler

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

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

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

Pivotal Role of the Lipid Raft SK3–Orai1 Complex in Human Cancer Cell Migration and Bone Metastases

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

Docetaxel Conjugate Nanoparticles That Target α-Smooth Muscle Actin–Expressing Stromal Cells Suppress Breast Cancer Metastasis
Mami Murakami, Mark J. Ernsting, Eliusz Undzys, Nathan Holwell, Warren D. Foltz, and Shyh-Dar Li

Precise: A novel cytotoxic nanoparticle that specifically degrades stromal elements in the tumor microenvironment exhibits potent antitumor activity.
LIN28 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 Wiechmann, Rachel Schiff, Mario Giuliano, Helen Wong, Suzanne W. Fuqua, Alejandro Contreras, Carolina Gutierrez, Jian Huang, Sufeng Mao, Anne C. Pavlick, Anna Tsimelzon, Susan G. Hilsenbeck, Edward S. Chen, Pavel Zuloaga, Charles M. Perou, Chad A. Shaw, Mothaffar F. Rimawi, Jenny C. Chang, and Michael T. Lewis

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.

elf4B 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

Precis: Results identify the translation initiation factor elf4B 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. Miller, 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.

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

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

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.

TRAF6 Upregulates Expression of HIF-1α and Promotes Tumor Angiogenesis
Heng Sun, Xue-Bing Li, Yu 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

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