BREAKING ADVANCES

Highlights from Recent Cancer Literature

OBITUARY

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

REVIEWS

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

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

PERSPECTIVE

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

INTEGRATED SYSTEMS AND TECHNOLOGIES

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

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.

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 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.

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.
**Histone Demethylase RBP2 Promotes Lung Tumorigenesis and Cancer Metastasis**

Yu-Ching Teng, Cheng-Feng Lee, Ying-Shiuah Li, Yi-Ren Chen, Pei-Wen Hsiaoa, Meng-Yu Chan, Feng-Mao Lim, Hsien-Da Huang, Yen-Ting Chen, Yung-Ming Jeng, Chih-Hung Hsu, Qin Yan, Ming-Daw Tsai, and Li-Jung Juan

**Precisé:** 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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**Intravital FLIM-FRET Imaging Reveals Dasatinib-Induced Spatial Control of Src in Pancreatic Cancer**


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

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**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 E. Young, Mallory L. West, Natalie V. Singer, Hae Lee, Il-Kang Na, Jennifer J. Tsai, Robert R. Jeng, Olaf Penack, Alan M. Hanash, Cecilia Leczano, George F. Murphy, Chen Liu, Michel Sadelain, Martin G. Sauer, Derek San'tAngelo, and Marcel R.M. van den Brink

**Precisé:** This study describes a strategy to improve the qualities of adoptive cell therapies that are available for immunotherapy of cancer, focusing particularly on the reduction of undesirable graft-versus-host side effects.

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**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

**Precisé:** 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.

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**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

**Precisé:** 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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**Posttranscriptional Regulation of PER1 Underlies the Oncogenic Function of IRE1α**


**Precisé:** 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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**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

**Precisé:** 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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**TR3 Modulates Platinum Resistance in Ovarian Cancer**

Andrew J. Wilson, Annie Y. Liu, Joseph Rolando, Oluwafumilayo B. Adebayo, Sarah A. Fletcher, James C. Slaughter, Jeannette Saskowski, Marta A. Crispens, Howard W. Jones III, Samuel James, Oliviae Fadare, and Dineo Khabele

**Precisé:** 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 vonLintig, Darcie Seachrist, Gregory P. Tochtrup, and Noa Noy

Precise: 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.

PanIN-Specific Regulation of Wnt Signaling by HIP2ox 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

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

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, Chiera M. Peet, Laurel D. Lorenz, Kwangok P. Nickel, Aloysius J. Klingelhutz, Paul F. Lambert, and Paul M. Harari

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

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

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

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. Slass, Bernard A. Rosner, and Susan E. Hankinson

Precise: 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.
TUMOR AND STEM CELL BIOLOGY

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 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, Ana C. Pavlick, Amber M. Froehlich, Ji-Long Chen 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.

eIF4B Phosphorylation by Pim Kinases Plays a Critical Role in Cellular Transformation by Ab1 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 eIF-4B as a critical substrate of Pim kinases, which mediate the activity of Ab1 oncogenes, suggesting this factor as a candidate therapeutic target in Ab1-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.
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.

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