### 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 Perlmutter, 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 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, 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 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 Goëté, Caroline Flamant, Sylvie Busakiewicz, Vichnou Poirier-Colame, Oliver Kepp, Isabelle Martinis, Julienes 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


Précis: 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

Arnab Ghosh, Amanda M. Holland, Yildirim Dogan, Nury L. Yin, Uttam K. Rao, Lauren E. Young, Mallory L. West, Natalie V. Singer, Hae Lee, Il-Kang Na, Jennifer J. Tsai, Robert R. Jenq, Olaf Penack, Alan M. Hanash, Cecilia Leczcano, George F. Murphy, Chen Liu, Michel Sadelain, Martin G. Sauer, Derek San'tAngelo, 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 immunotherapy 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

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

Histone Demethylase RBP2 Promotes Lung Tumorigenesis and Cancer Metastasis

Yu-Ching Teng, Cheng-Feng Lee, Ying-Shina Li, Yi-Ren Chen, Pei-Wen Hisiao, Meng-Yu Chian, 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.

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.

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.

Peroxisiderox-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.

TR3 Modulates Platinum Resistance in Ovarian Cancer

Andrew J. Wilson, Annie Y. Liu, Joseph Roland, Oluwafumilayo B. Adebayo, Sarah A. Fletcher, James C. Slaughter, Jeanette Saskowski, Marta A. Crispens, Howard W. Jones III, Samuel James, Oluwafe 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.
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

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

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

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


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. Sassi, 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.

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-Desnoyers, 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.

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

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

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 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, Elijus 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

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.

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 Schaff, Mario Giuliano, Helen Wong, Suzanne W. Fuqua, Alejandro Contreras, Carolina Gutierrez, Jian Huang, Sufeng Mao, Anne C. Pavlick, Jennifer E. Hanning, Emily M. Barker, Stijn van Dongen, Dawn M. Ward, Katie L. Raby, Ian J. Groves, Ton Peeters, Edward van der Wall, Paul J. van Diest, Jos Jonkers, and Patrick W.B. Derksen

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.

elf4B Phosphorylation by Pim Kinases Plays a Critical Role in Cellular Transformation by Abi Oncogenes
Jianling Yang, Jun Wang, Ke Chen, Guijie Gao, Ruijiao Xi, Paul B. Rothman, Douglas Whitten, Lianfeng Zhang, Shile Huang, and Ji-Long Chen

Précis: Results identify the translation initiation factor elf4B as a critical substrate of Pim kinases, which mediate the activity of Abi oncogenes, suggesting this factor as a candidate therapeutic target in Abi-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

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.

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.

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. Braumiller, Jeroen F. Vermeulen, Petra van der Groep, Ton Peeters, Elskens 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.

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