

## BREAKING ADVANCES

- 2023 | **Highlights from Recent Cancer Literature**

## REVIEWS

- 2025 | **Genetic Susceptibility to Triple-Negative Breast Cancer**  
Kristen N. Stevens, Celine M. Vachon, and Fergus J. Couch
- 2031 | **The Multifaceted Role of the Microenvironment in Liver Metastasis: Biology and Clinical Implications**  
Gert G. Van den Eynden, Ali W. Majeed, Martin Illemann, Peter B. Vermeulen, Nigel C. Bird, Gunilla Høyer-Hansen, Rikke Løvendahl Eefsen, Andrew R. Reynolds, and Pnina Brodt

## PRIORITY REPORTS

- 2044 | **CUL3 and NRF2 Mutations Confer an NRF2 Activation Phenotype in a Sporadic Form of Papillary Renal Cell Carcinoma**  
Aikseng Ooi, Karl Dykema, Asif Ansari, David Petillo, John Snider, Richard Kahnoski, John Anema, David Craig, John Carpten, Bin-Tean Teh, and Kyle A. Furge  
*Précis: Hereditary and sporadic forms of a renal cell carcinoma subtype converge on activation of a nodal stress transcription factor that may be involved in all forms of this disease.*
- 2052 | **Differential Contributions of STAT5A and STAT5B to Stress Protection and Tyrosine Kinase Inhibitor Resistance of Chronic Myeloid Leukemia Stem/Progenitor Cells**  
Luana Casetti, Séverine Martin-Lannerée, Imen Najjar, Isabelle Plo, Sylvie Augé, Lydia Roy, Jean-Claude Chomel, Evelyne Lauret, Ali G. Turhan, and Isabelle Dusanter-Fourt  
*Précis: STAT5 activation plays a well-established role in a variety of malignancies in stem cell populations, but this is the first study to reveal different functional contributions of the related genes STAT5A and STAT5B to drug-induced stress responses and drug resistance, with implications for improving therapy.*

## CLINICAL STUDIES

- 2059 | **Plastin3 Is a Novel Marker for Circulating Tumor Cells Undergoing the Epithelial–Mesenchymal Transition and Is Associated with Colorectal Cancer Prognosis**  
Takehiko Yokobori, Hisae Inuma, Teppei Shimamura, Seiya Imoto, Keishi Sugimachi, Hideshi Ishii, Masaaki Iwatsuki, Daisuke Ota, Masahisa Ohkuma, Takeshi Iwaya, Naohiro Nishida, Ryunosuke Kogo, Tomoya Sudo, Fumiaki Tanaka, Kohei Shibata, Hiroyuki Toh, Tetsuya Sato, Graham F. Barnard, Takeo Fukagawa, Seiichi Yamamoto, Hayao Nakanishi, Shin Sasaki, Satoru Miyano, Toshiaki Watanabe, Hiroyuki Kuwano, Koshi Mimori, Klaus Pantel, and Masaki Mori  
*Précis: This study establishes a superior blood-based prognostic marker to gauge the risk of relapse in metastatic colorectal cancer, surpassing existing clinicopathologic factors.*

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2070 | **Targeting uPAR with Antagonistic Recombinant Human Antibodies in Aggressive Breast Cancer**  
Aaron M. LeBeau, Sai Duriseti, Stephanie T. Murphy, Francois Pepin, Byron Hann, Joe W. Gray, Henry F. VanBrocklin, and Charles S. Craik  
*Précis: Findings provide preclinical proof-of-concept that antagonistic human uPAR antibodies can provide useful diagnostic and therapeutic properties to improve treatment of aggressive triple-negative breast cancers.*
- 2082 | **Enhanced Sonographic Imaging to Diagnose Lymph Node Metastasis: Importance of Blood Vessel Volume and Density**  
Li Li, Shiro Mori, Mizuho Kodama, Maya Sakamoto, Shoki Takahashi, and Tetsuya Kodama  
*Précis: Ultrasonography methods to detect early changes in blood vessel volume and density in lymph nodes containing metastatic cells may offer earlier and more accurate criteria for diagnosis of lymph node metastasis, a critical staging and prognostic marker in many cancers.*

**MICROENVIRONMENT AND IMMUNOLOGY**

- 2093 **A Multifunctional Chimeric Chaperone Serves as a Novel Immune Modulator Inducing Therapeutic Antitumor Immunity**  
 Xiaofei Yu, Chunqing Guo, Huanfa Yi, Jie Qian, Paul B. Fisher, John R. Subjeck, and Xiang-Yang Wang  
*Précis:* A novel strategy targets the immunosuppressive tumor environment using a chimeric immune chaperone, leading to systemic T cell-mediated tumor inhibition.
- 2104 **Aire Deficiency Promotes TRP-1-Specific Immune Rejection of Melanoma**  
 Meng-Lei Zhu, Anil Nagavalli, and Maureen A. Su  
*Précis:* Findings define a pathway of autoimmune control in thymic epithelial cells that can modulate immune responses against melanoma in otherwise healthy individuals, with implications for enhancing immune responses to this deadly skin cancer.
- 2117 **Autoimmune Gastritis Mediated by CD4+ T Cells Promotes the Development of Gastric Cancer**  
 Thanh-Long M. Nguyen, Shradha S. Khurana, Clifford J. Bellone, Benjamin J. Capoccia, John E. Sagartz, Russell A. Kesman Jr, Jason C. Mills, and Richard J. DiPaolo  
*Précis:* Findings provide the first direct evidence that autoimmune gastritis supports the development of stomach cancer and also offer a useful new model to deepen knowledge of how inflammation drives malignancy in this setting.
- 2127 **Anti-CD20 Antibody Promotes Cancer Escape via Enrichment of Tumor-Evoked Regulatory B Cells Expressing Low Levels of CD20 and CD137L**  
 Monica Bodogai, Catalina Lee Chang, Katarzyna Wejksza, Jinping Lai, Maria Merino, Robert P. Wersto, Ronald E. Gress, Andrew C. Chan, Charles Hesdorffer, and Arya Biragyn  
*Précis:* Findings speak to the importance of tumor-evoked B-regulatory cells in driving immune escape and cancer progression, also suggesting a basis for understanding the procancerous risks of B cell-depleting therapies like rituximab.

**MOLECULAR AND CELLULAR PATHOBIOLOGY**

- 2139 **Distinct Effects of Ligand-Induced PDGFR $\alpha$  and PDGFR $\beta$  Signaling in the Human Rhabdomyosarcoma Tumor Cell and Stroma Cell Compartments**  
 Monika Ehnman, Edoardo Missiaglia, Erika Folestad, Joanna Selfe, Carina Strell, Khin Thway, Bertha Brodin, Kristian Pietras, Janet Shipley, Arne Östman, and Ulf Eriksson  
*Précis:* Distinct patterns of ligand-dependent activity for the two major forms of PDGF signaling were found in either the stromal or tumor cell compartments of aggressive muscle cell tumors, both of clinical relevance.
- 2150 **Cooperative Activation of Tissue-Specific Genes by pRB and E2F1**  
 Stephen Flowers, Fuhua Xu, and Elizabeth Moran  
*Précis:* This study offers novel mechanistic insights into why Rb deficiency is so closely associated with the development of osteosarcoma.
- 2159 **Loss of TGF- $\beta$  Adaptor  $\beta$ 2SP Activates Notch Signaling and SOX9 Expression in Esophageal Adenocarcinoma**  
 Shumei Song, Dipen M. Maru, Jaffer A. Ajani, Chia-Hsin Chan, Soichiro Honjo, Hui-Kuan Lin, Arlene Correa, Wayne L. Hofstetter, Marta Davila, John Stroehlein, and Lopa Mishra  
*Précis:* Intriguing findings suggest one mechanism through which TGF- $\beta$  signaling switches from tumor suppressing to tumor promoting during malignant progression.
- 2170 **FOXP3 Regulates Sensitivity of Cancer Cells to Irradiation by Transcriptional Repression of BRCA1**  
 Wei-quan Li, Hiroto Katoh, Lizhong Wang, Xiaochun Yu, Zhanwen Du, Xiaoli Yan, Pan Zheng, and Yang Liu  
*Précis:* A transcription factor implicated in immune tolerance and mutated in prostate and breast cancer cells is reported here to regulate DNA repair through the BRCA1 pathway, possibly directly linking DNA repair processes to immune escape in cancer.
- 2181 **Sunlight UV-Induced Skin Cancer Relies upon Activation of the p38 $\alpha$  Signaling Pathway**  
 Kangdong Liu, Donghoon Yu, Yong-Yeon Cho, Ann M. Bode, Weiya Ma, Ke Yao, Shengqing Li, Jixia Li, G. Tim Bowden, Ziming Dong, and Zigang Dong  
*Précis:* Solar UV, which includes UVA and UVB wavelengths contributing to skin cancers, must activate a MAPK-related stress pathway, with implications for prevention and treatment of these common malignancies.

2189 **FOXO3a Is a Major Target of Inactivation by PI3K/AKT Signaling in Aggressive Neuroblastoma**

Evan E. Santo, Peter Stroeken, Peter V. Sluis, Jan Koster, Rogier Versteeg, and Ellen M. Westerhout

*Précis:* This study highlights a pivotal role for FOXO3a in understanding the pathobiology of neuroblastoma and suggests its utility as a biomarker for prognosis and therapeutic responses to PI3K/AKT inhibitors being developed clinically.

2199 **Proteomic Analysis of Ubiquitin Ligase KEAP1 Reveals Associated Proteins That Inhibit NRF2 Ubiquitination**

Bridgid E. Hast, Dennis Goldfarb, Kathleen M. Mulvaney, Michael A. Hast, Priscila F. Siesser, Feng Yan, D. Neil Hayes, and Michael B. Major

*Précis:* Findings offer mechanistic insight into the broad cytoprotection afforded cancer cells that activate the NRF2 transcription factor, as a route to escape killing by cytotoxic therapeutic treatments.

## PREVENTION AND EPIDEMIOLOGY

2211 **Common Genetic Polymorphisms Modify the Effect of Smoking on Absolute Risk of Bladder Cancer**

Montserrat Garcia-Closas, Nathaniel Rothman, Jonine D. Figueroa, Ludmila Prokunina-Olsson, Summer S. Han, Dalsu Baris, Eric J. Jacobs, Nuria Malats, Immaculata De Vivo, Demetrius Albanes, Mark P. Purdue, Sapna Sharma, Yi-Ping Fu, Manolis Kogevinas, Zhaoming Wang, Wei Tang, Adonina Tardón, Consol Serra, Alfredo Carrato, Reina García-Closas, Josep Lloreta, Alison Johnson, Molly Schwenn, Margaret R. Karagas, Alan Schned, Gerald Andriole, Jr Robert Grubb, III, Amanda Black, Susan M. Gapstur, Michael Thun, William Ryan Diver, Stephanie J. Weinstein, Jarmo Virtamo, David J. Hunter, Neil Caporaso, Maria Teresa Landi, Amy Hutchinson, Laurie Burdett, Kevin B. Jacobs, Meredith Yeager, Joseph F. Fraumeni, Jr, Stephen J. Chanock, Debra T. Silverman, and Nilanjan Chatterjee

*Précis:* Smoking prevention strategies may have more public health impact on subsets of the population that are at elevated genetic risk.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

2221 **Erlotinib Prolongs Survival in Pancreatic Cancer by Blocking Gemcitabine-Induced MAPK Signals**

Koji Miyabayashi, Hideaki Ijichi, Dai Mohri, Motohisa Tada, Keisuke Yamamoto, Yoshinari Asaoka, Tsuneo Ikenoue, Keisuke Tateishi, Yousuke Nakai, Hiroyuki Isayama, Yasuyuki Morishita, Masao Omata, Harold L. Moses, and Kazuhiko Koike

*Précis:* Findings address clinical questions concerning why the EGFR inhibitor erlotinib benefits KRAS-mutant pancreatic cancer patients when combined with gemcitabine.

2235 **mTOR Inhibitors Block Kaposi Sarcoma Growth by Inhibiting Essential Autocrine Growth Factors and Tumor Angiogenesis**

Debasmita Roy, Sang-Hoon Sin, Amy Lucas, Raman Venkataramanan, Ling Wang, Anthony Eason, Veenadhari Chavakula, Isaac B. Hilton, Kristen M. Tamburro Blossom Damania, and Dirk P. Dittmer

*Précis:* Findings offer a new disease model and preclinical proof-of-concept for the use of mTOR inhibitors to treat a major HIV-associated cancer as well as related tumors that are also derived from endothelial cells.

2247 **Targeting the Deregulated Spliceosome Core Machinery in Cancer Cells Triggers mTOR Blockade and Autophagy**

Virginie Quidville, Samar Alsafadi, Aïcha Goubar, Frédéric Commo, Véronique Scott, Catherine Pioche-Durieu, Isabelle Girault, Sonia Baconnais, Eric Le Cam, Vladimir Lazar, Suzette Delalogue, Mahasti Saghatchian, Patricia Pautier, Philippe Morice, Philippe Dessen, Stéphan Vagner, and Fabrice André

*Précis:* Certain Sm components of snRNPs involved in RNA splicing may constitute appealing therapeutic targets for a generalized strategy to treat cancer.

2259 **HDAC6 Inhibition Restores Ciliary Expression and Decreases Tumor Growth**

Sergio A. Gradilone, Brynn N. Radtke, Pamela S. Bogert, Bing Q. Huang, Gabriella B. Gajdos, and Nicholas F. LaRusso

*Précis:* HDAC6 is essential in epithelial cells for formation of the primary cilia, organelles that are essential and sufficient to organize normal cell structure, growth, and function but that are disrupted during neoplastic transformation.

2271 **Cisplatin Resistance Associated with PARP Hyperactivation**

Judith Michels, Ilio Vitale, Lorenzo Galluzzi, Julien Adam, Ken André Olausson, Oliver Kepp, Laura Senovilla, Ibtissam Talhaoui, Justine Guegan, David Pierre Enot, Monique Talbot, Angélique Robin, Philippe Girard, Cédric Oréar, Delphine Lissa, Abdul Qader Sukkurwala, Pauline Garcia, Parviz Behnam-Motlagh, Kimitoshi Kohno, Gen Sheng Wu, Catherine Brenner, Philippe Dessen, Murat Saparbaev, Jean-Charles Soria, Maria Castedo, and Guido Kroemer

*Précis:* Results affect the use of PARP inhibitors in lung adenocarcinoma patients who relapse after cisplatin-based chemotherapy by suggesting a mechanism-based biomarker that can predict responses to PARP inhibitor monotherapy.

2281 **The Insulin Receptor Negatively Regulates the Action of Pseudomonas Toxin-Based Immunotoxins and Native Pseudomonas Toxin**

Xiu Fen Liu, David J. FitzGerald, and Ira Pastan

*Précis:* Attenuating the expression of the insulin receptor can specifically enhance the cytotoxic action of certain immunotoxins and has potential utility for immunoconjugates used in cancer treatment.

2289 **Inhibition of Protein Kinase CK2 Reduces Cyp24a1 Expression and Enhances 1,25-Dihydroxyvitamin D<sub>3</sub> Antitumor Activity in Human Prostate Cancer Cells**

Wei Luo, Wei-Dong Yu, Yingyu Ma, Mikhail Chernov, Donald L. Trump, and Candace S. Johnson

*Précis:* Results suggest an approach to enhance the potency of the anticancer effects of vitamin D<sub>3</sub> used to treat certain cancers by retarding the core mechanism in its degradation and clearance.

2310 **Cholesterol Loading and Ultrastable Protein Interactions Determine the Level of Tumor Marker Required for Optimal Isolation of Cancer Cells**

Jayati Jain, Gianluca Veggiani, and Mark Howarth

*Précis:* This important study systematically determined the factors affecting the isolation of cancer cells, with the potential to generally improve cancer diagnosis, prognosis, and therapeutic monitoring in patients.

2322 **A CD90<sup>+</sup> Tumor-Initiating Cell Population with an Aggressive Signature and Metastatic Capacity in Esophageal Cancer**

Kwan Ho Tang, Yong dong Dai, Man Tong, Yuen Piu Chan, Pak Shing Kwan, Li Fu, Yan Ru Qin, Sai Wah Tsao, Hong Lok Lung, Maria L. Lung, Daniel K. Tong, Simon Law, Kwok Wah Chan, Stephanie Ma, and Xin Yuan Guan

*Précis:* This is the first study to reliably identify a cancer stem cell population in esophageal cancer, an often aggressive disease with a rising incidence in developed countries that has no effective treatment.

2333 **TGF- $\beta$  Mediates Homing of Bone Marrow-Derived Human Mesenchymal Stem Cells to Glioma Stem Cells**

Naoki Shinojima, Anwar Hossain, Tatsuya Takezaki, Juan Fueyo, Joy Gumin, Feng Gao, Felix Nwajei, Frank C. Marini, Michael Andreeff, Jun-Ichi Kuratsu, and Frederick F. Lang

*Précis:* Findings affect the possible use of bone marrow-derived mesenchymal stem cells as delivery vehicles to treat deadly brain cancers by targeting the cancer stem-like cells that sustain these cancers.

2345 **Pirfenidone Inhibits Pancreatic Cancer Desmoplasia by Regulating Stellate Cells**

Shingo Kozono, Kenoki Ohuchida, Daiki Eguchi, Naoki Ikenaga, Kenji Fujiwara, Lin Cui, Kazuhiro Mizumoto, and Masao Tanaka

*Précis:* A promising antitumor agent may act by targeting the desmoplastic reaction in cancer, which generates a supportive fibroblast microenvironment particularly prevalent in pancreatic cancer.

## TUMOR AND STEM CELL BIOLOGY

2298 **Downregulation of the Novel Tumor Suppressor DIRAS1 Predicts Poor Prognosis in Esophageal Squamous Cell Carcinoma**

Ying-Hui Zhu, Li Fu, Leilei Chen, Yan-Ru Qin, Haibo Liu, Fajun Xie, Tingting Zeng, Sui-Sui Dong, Jiangchao Li, Yan Li, Yongdong Dai, Dan Xie, and Xin-Yuan Guan

*Précis:* A novel Ras-like protein is discovered to be pivotal to the pathogenesis of esophageal cancers that tend to be aggressive and rising in incidence in developed countries.

2357

### Sirtuin-1 Regulates Acinar-to-Ductal Metaplasia and Supports Cancer Cell Viability in Pancreatic Cancer

Elke Wauters, Victor J. Sanchez-Arévalo Lobo, Andreia V. Pinho, Amanda Mawson, Daniel Herranz, Jianmin Wu, Mark J. Cowley, Emily K. Colvin, Erna Ngwayi Njicop, Rob L. Sutherland, Tao Liu, Manuel Serrano, Luc Bouwens, Francisco X. Real, Andrew V. Biankin, and Ilse Rooman

**Précis:** This study addresses a key factor in the disruption of acinar cell differentiation in the pancreas, a situation that predisposes to the development of pancreatic cancer.

2368

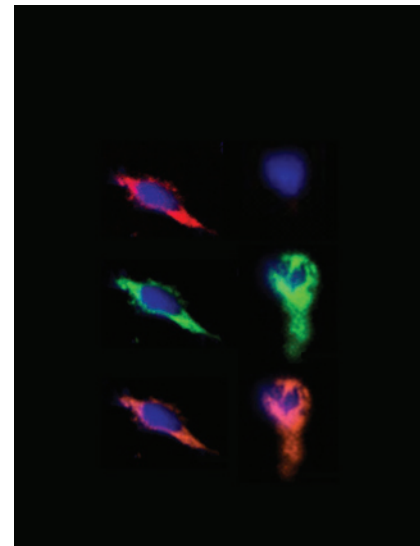
### ST6Gal-I Protein Expression Is Upregulated in Human Epithelial Tumors and Correlates with Stem Cell Markers in Normal Tissues and Colon Cancer Cell Lines

Amanda F. Swindall, Angelina I. Londoño-Joshi, Matthew J. Schultz, Naomi Fineberg, Donald J. Buchsbaum, and Susan L. Bellis

**Précis:** Results identify a sialyltransferase that may serve as a regulator of the stem-like phenotype in both normal and cancer cell populations.

## ABOUT THE COVER

Antibodies against epithelial cell adhesion molecule (EpCAM) and cytokeratins are commonly used to capture and detect circulating tumor cells (CTC). However, these approaches are potentially hampered by the fact that migratory cancer cells may undergo a process called the epithelial-mesenchymal transition that is characterized by downregulation of epithelial markers, including cytokeratins and EpCAM. Images are of EpCAM(-)/CD45(-) circulating tumor cells immunostained with antibodies against cytokeratin (red, top), PLS3 (green, middle), and vimentin (orange, bottom). All sections were counterstained with DAPI (blue). PLS3 was expressed on EpCAM(-) CTCs that displayed reduced cytokeratin staining, accompanied by strong staining for vimentin. For details, see article by Yokobori and colleagues on page 2059.



# Cancer Research

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