



April 15, 2016 • Volume 76 • Number 8

BREAKING ADVANCES

- 2055** Highlights from Recent Cancer Literature

CANCER RESEARCH 75th ANNIVERSARY COMMENTARIES

- 2057** Human Cancers Express a Mutator Phenotype: Hypothesis, Origin, and Consequences
Lawrence A. Loeb
- 2060** Jacob, Monod, the Lac Operon, and the PajMa Experiment—Gene Expression Circuitry Changing the Face of Cancer Research
Stephen B. Baylin

REVIEWS

- 2063** The Role of Cholesterol in Cancer
Omer F. Kuzu, Mohammad A. Noory, and Gavin P. Robertson
- 2071** Implications of Extracellular Vesicle Transfer on Cellular Heterogeneity in Cancer: What Are the Potential Clinical Ramifications?
Anoek Zomer and Jacco van Rheenen

PRIORITY REPORTS

- 2076** STING Promotes the Growth of Tumors Characterized by Low Antigenicity via IDO Activation
Henrique Lemos, Eslam Mohamed, Lei Huang, Rong Ou, Gabriela Pacholczyk, Ali S. Arbab, David Munn, and Andrew L. Mellor
- Précis:* While the DNA sensor STING can activate powerful antitumor immune responses, this study shows that it can also tolerize the immune microenvironment of weakly antigenic tumors, with implications to broaden the numbers of tumors that may respond strongly to cancer immunotherapy.

- 2082** Frequency and Dynamics of Leukemia-Initiating Cells during Short-term *Ex Vivo* Culture Informs Outcomes in Acute Myeloid Leukemia Patients
Emmanuel Griessinger, Fernando Anjos-Afonso, Jacques Vargaftig, David C. Taussig, François Lassailly, Thomas Prebet, Véronique Imbert, Marielle Nebout, Norbert Vey, Christian Chabannon, Andrew Filby, Frederic Bollet-Quivogne, John G. Gribben, Jean-François Peyron, and Dominique Bonnet

Précis: This study describes an accessible approach to reliably capture the intrinsic biological features of leukemic stem cells, offering a clinically relevant tool for the prognostic assessment of patient outcome upon AML diagnosis.

- 2087** TALEN-Mediated Inactivation of PD-1 in Tumor-Reactive Lymphocytes Promotes Intratumoral T-cell Persistence and Rejection of Established Tumors

Laurie Menger, Anna Sledzinska, Katharina Bergerhoff, Frederick Arce Vargas, Julianne Smith, Laurent Poirot, Martin Pule, Javier Hererro, Karl S. Peggs, and Sergio A. Quezada

Précis: This proof-of-concept study demonstrates that advanced adoptive T-cell therapies for cancer can be enhanced by genomic editing strategies to bypass immune checkpoints.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2094** *In Vivo* Visualization and Characterization of Epithelial–Mesenchymal Transition in Breast Tumors

Zhen Zhao, Xiaoping Zhu, Kemi Cui, James Mancuso, Richard Federley, Kari Fischer, Gao-jun Teng, Vivek Mittal, Dingcheng Gao, Hong Zhao, and Stephen T.C. Wong

Précis: An *in vivo* method to visualize features of epithelial-mesenchyme transition reveals tumor cell-microenvironment interactions that foster metastatic behaviors and therapeutic strategies best suited to suppress them.

- 2105** Transcriptome Analysis of Triple-Negative Breast Cancer Reveals an Integrated mRNA-lncRNA Signature with Predictive and Prognostic Value

Yi-Zhou Jiang, Yi-Rong Liu, Xiao-En Xu, Xi Jin, Xin Hu, Ke-Da Yu, and Zhi-Ming Shao

Précis: This prospective observational study reports a simple biomarker signature of triple-negative breast cancer that can predict risks of disease relapse and the clinical benefit of commonly employed taxane chemotherapy, addressing needs in a disease that can be aggressive in some but not all patients.

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MICROENVIRONMENT AND IMMUNOLOGY

2115 Redundant Innate and Adaptive Sources of IL17 Production Drive Colon Tumorigenesis



Franck Housseau, Shaoguang Wu, Elizabeth C. Wick, Hongni Fan, Xinqun Wu, Nicolas J. Llosa, Kellie N. Smith, Ada Tam, Sudipto Ganguly, Jane W. Wanyiri, Thevambiga Iyadorai, Ausama A. Malik, April C. Roslani, Jamunarani S. Vadivelu, Sara Van Meerbeke, David L. Huso, Drew M. Pardoll, and Cynthia L. Sears

Précis: These findings suggest redundant sources for the cytokine IL17 in bacteria-induced colon carcinogenesis, stressing the importance of therapeutically targeting IL17 itself rather than its cellular sources.

2125 Myeloid-Derived Suppressor Cells Express Bruton's Tyrosine Kinase and Can Be Depleted in Tumor-Bearing Hosts by Ibrutinib Treatment



Andrew Stiff, Prashant Trikha, Robert Wesolowski, Kari Kendra, Vincent Hsu, Sarvani Uppati, Elizabeth McMichael, Megan Duggan, Amanda Campbell, Karen Keller, Ian Landi, Yiming Zhong, Jason Dubovsky, John Harrison Howard, Lianbo Yu, Bonnie Harrington, Matthew Old, Sean Reiff, Thomas Mace, Susheela Tridandapani, Natarajan Muthusamy, Michael A. Caligiuri, John C. Byrd, and William E. Carson III

Précis: The Bruton's tyrosine kinase inhibitor ibrutinib impairs the generation and function of myeloid-derived suppressor cells in multiple malignancies, supporting a preclinical rationale for its use as an immunotherapy.

2137 Agonist-Mediated Activation of STING Induces Apoptosis in Malignant B Cells



Chih-Hang Anthony Tang, Joseph A. Zundell, Sujeewa Ranatunga, Cindy Lin, Yulia Nefedova, Juan R. Del Valle, and Chih-Chi Andrew Hu

Précis: These findings show how STING agonists can be used directly to eradicate neoplastic B cells, suggesting their potential therapeutic value in treatment of B-cell malignancies.

2153 Inherent and Tumor-Driven Immune Tolerance in the Prostate Microenvironment Impairs Natural Killer Cell Antitumor Activity

Christine Pasero, Gwenaeille Gravis, Mathilde Guerin, Samuel Granjeaud, Jeanne Thomassin-Piana, Palma Rocchi, Maria Paciencia-Gros, Flora Poizat, Mélanie Bentobji, Francine Azario-Cheillan, Jochen Walz, Naji Salem, Serge Brunelle, Alessandro Moretta, and Daniel Olive

Précis: This study suggests that immune escape in prostate cancer entails a suppression of natural killer cell activity, suggesting strategies to restore their function as a pivotal therapeutic approach in patients.

2166 Activation of the MDA-5-IPS-1 Viral Sensing Pathway Induces Cancer Cell Death and Type I IFN-Dependent Antitumor Immunity

Xiaofei Yu, Hongxia Wang, Xia Li, Chunqing Guo, Fang Yuan, Paul B. Fisher, and Xiang-Yang Wang

Précis: These findings reveal a role for a viral sensing pathway in the induction of antitumor immunity, offering an opportunity for therapeutic targeting in novel cancer immunotherapy modalities.

2177 Detection of an Immunogenic HERV-E Envelope with Selective Expression in Clear Cell Kidney Cancer

Elena Cherkasova, Claire Scrivani, Susan Doh, Quinn Weisman, Yoshiyuki Takahashi, Nanae Harashima, Hisayuki Yokoyama, Ramaprasad Srinivasan, W. Marston Linehan, Michael I. Lerman, and Richard W. Childs

Précis: These findings define a promising disease-specific targeting strategy for the development of kidney cancer immunotherapy.

2186 ILK Induction in Lymphoid Organs by a TNF α -NF- κ B-Regulated Pathway Promotes the Development of Chronic Lymphocytic Leukemia



Peter W. Krenn, Sebastian W. Hofbauer, Susanne Pucher, Evelyn Hutterer, Elisabeth Hinterseer, Ursula Denk, Daniela Asslauer, Sylvia Ganghammer, Christina Sternberg, Daniel Neureiter, Fritz Aberger, Sara A. Wickström, Alexander Egle, Richard Greil, and Tanja N. Hartmann

Précis: These findings support the development of targeted therapies for cancer that aberrantly express the multifunctional kinase ILK.

MOLECULAR AND CELLULAR PATHOBIOLOGY

2197 Genomic Profiling of Pediatric Acute Myeloid Leukemia Reveals a Changing Mutational Landscape from Disease Diagnosis to Relapse



Jason E. Farrar, Heather L. Schuback, Rhonda E. Ries, Daniel Wai, Oliver A. Hampton, Lisa R. Trevino, Todd A. Alonzo, Jaime M. Guidry Auvil, Tanja M. Davidsen, Patee Gesuwan, Leandro Hermida, Donna M. Muzny, Ninad Dewal, Navin Rustagi, Lora R. Lewis, Alan S. Gamis, David A. Wheeler, Malcolm A. Smith, Daniela S. Gerhard, and Soheil Meshinchi

Précis: These findings reveal a complex evolution in the mutational landscape of a common pediatric leukemia, suggesting potentially actionable therapeutic targets.



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- 2206** Mutant p53 Promotes Epithelial Ovarian Cancer by Regulating Tumor Differentiation, Metastasis, and Responsiveness to Steroid Hormones
Yi A. Ren, Lisa K. Mullany, Zhilin Liu, Alan J. Herron, Kwong-Kwok Wong, and JoAnne S. Richards

Précis: A p53 mutation that occurs frequently in high-grade ovarian tumors is found to have powerful effects on metastasis, steroid hormone responses, and cell fate plasticity in serous and mucinous tumor subtypes.

- 2219** Prolyl Hydroxylase 3 Attenuates MCL-1–Mediated ATP Production to Suppress the Metastatic Potential of Colorectal Cancer Cells
Praveenkumar Radhakrishnan, Nadine Ruh, Jonathan M. Harnoss, Judit Kiss, Martin Mollenhauer, Anna-Lena Scherr, Lisa K. Platzer, Thomas Schmidt, Klaus Podar, Joseph T. Opferman, Juergen Weitz, Henning Schulze-Bergkamen, Bruno C. Koehler, Alexis Ullrich, and Martin Schneider

Précis: This study shows that the molecular oxygen sensor PHD3 functions as a metastasis suppressor in colorectal cancer, with cautions for use of PHD inhibitors as therapeutics in patients with advanced cancers.

- 2231** Immunoregulatory Protein B7-H3 Reprograms Glucose Metabolism in Cancer Cells by ROS-Mediated Stabilization of HIF1 α



Sangbin Lim, Hao Liu, Luciana Madeira da Silva, Ritu Arora, Zixing Liu, Joshua B. Phillips, David C. Schmitt, Tung Vu, Steven McClellan, Yifeng Lin, Wensheng Lin, Gary A. Piazza, Oystein Fodstad, and Ming Tan

Précis: This seminal work defines a broader and previously unrecognized role for the T-cell immunoregulatory protein B7-H3 in cancer cell metabolism, suggesting the therapeutic use of metabolic inhibitors in malignancies that overexpress B7-H3.

- 2243** PR55 α Subunit of Protein Phosphatase 2A Supports the Tumorigenic and Metastatic Potential of Pancreatic Cancer Cells by Sustaining Hyperactive Oncogenic Signaling

Ashley L. Hein, Parthasarathy Seshacharyulu, Satyanarayana Rachagani, Yuri M. Sheinin, Michel M. Ouellette, Moorthy P. Ponnusamy, Marc C. Mumby, Surinder K. Batra, and Ying Yan

Précis: These findings offer preclinical proof of principle for a regulatory subunit of the protein phosphatase 2 holoenzyme as a candidate therapeutic target in pancreatic cancer.

- 2254** Identification of RNA-Binding Protein LARP4B as a Tumor Suppressor in Glioma

Hideto Koso, Hungtsung Yi, Paul Sheridan, Satoru Miyano, Yasushi Ino, Tomoki Todo, and Sumiko Watanabe

Précis: An RNA-binding protein absent from most human gliomas is found to function as a tumor suppressor in this setting, revealing new insights into posttranscriptional mechanisms of cell growth and apoptotic control.

- 2265** Melanoma Cells Block PEDF Production in Fibroblasts to Induce the Tumor-Promoting Phenotype of Cancer-Associated Fibroblasts

Nkechiyere G. Nwani, Maria L. Deguiz, Benilde Jimenez, Elena Vinokour, Oleksii Dubrovskiy, Andrey Ugolkov, Andrew P. Mazar, and Olga V. Volpert

Précis: Melanoma cells override tumor suppression programs in neighboring stromal cells by a mechanism that facilitates the conversion of normal fibroblasts into cancer-associated fibroblasts, fostering a tumor promoting environment.

- 2277** Stomach-Specific Activation of Oncogenic KRAS and STAT3-Dependent Inflammation Cooperatively Promote Gastric Tumorigenesis in a Preclinical Model

Stefan Thiem, Moritz F. Eissmann, Joachim Elzer, Anna Jonas, Tracy L. Putoczki, Ashleigh Poh, Paul Nguyen, Adele Preaudet, Dustin Flanagan, Elizabeth Vincan, Paul Waring, Michael Buchert, Andrew Jarnicki, and Matthias Ernst

Précis: This study describes a new preclinical model of gastric cancer that underscores the importance of both oncogene activation and aberrant inflammation in gastric epithelial cells to the onset and progression of tumorigenesis.

PREVENTION AND EPIDEMIOLOGY

- 2288** A Meta-analysis of Individual Participant Data Reveals an Association between Circulating Levels of IGF-I and Prostate Cancer Risk



Ruth C. Travis, Paul N. Appleby, Richard M. Martin, Jeff M.P. Holly, Demetrius Albanes, Amanda Black, H. Bas Bueno-de-Mesquita, June M. Chan, Chu Chen, Maria-Dolores Chirlaque, Michael B. Cook, Mélanie Deschasaux, Jenny L. Donovan, Luigi Ferrucci, Pilar Galan, Graham G. Giles, Edward L. Giovannucci, Marc J. Gunter, Laurel A. Habel, Freddie C. Hamdy, Kathy J. Helzlsouer, Serge Hercberg, Robert N. Hoover, Joseph A.M.J.L. Janssen, Rudolf Kaaks, Tatsuhiko Kubo, Loïc Le Marchand, E. Jeffrey Metter, Kazuya Mikami, Joan K. Morris, David E. Neal, Marian L. Neuhouser, Kotaro Ozasa, Domenico Palli, Elizabeth A. Platz, Michael N. Pollak, Alison J. Price, Monique J. Roobol, Catherine Schaefer, Jeannette M. Schenk, Gianluca Severi, Meir J. Stampfer, Pär Stattin, Akiko Tamakoshi, Catherine M. Tangen, Mathilde Touvier, Nicholas J. Wald, Noel S. Weiss, Regina G. Ziegler, Timothy J. Key, and Naomi E. Allen, on behalf of the Endogenous Hormones, Nutritional Biomarkers and Prostate Cancer Collaborative Group

Précis: This study encompasses the largest collaborative analysis of individual data as yet in addressing the relationship between insulin-like growth factors and prostate cancer risk.

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THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 2301** **Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor-Positive Breast Cancer**
Maria Teresa Herrera-Abreu, Marta Palafox, Uzma Asghar, Martín A. Rivas, Rosalind J. Cutts, Isaac Garcia-Murillas, Alex Pearson, Marta Guzman, Olga Rodriguez, Judit Grueso, Meritxell Bellet, Javier Cortés, Richard Elliott, Sunil Pancholi, José Baselga, Mitch Dowsett, Lesley-Ann Martin, Nicholas C. Turner, and Violeta Serra
Précis: These results illustrate that breast cancer cells can adapt quickly to cell-cycle blockades imposed by CDK4/6 inhibitors being used in clinic, acquiring resistance mechanisms that enable alternate means of S phase entry, yet also highlighting strategies to prevent the acquisition of therapeutic resistance to these agents.
- 2314** **MCAM and LAMA4 Are Highly Enriched in Tumor Blood Vessels of Renal Cell Carcinoma and Predict Patient Outcome**
Joseph W. Wragg, Jonathan P. Finnity, Jane A. Anderson, Henry J.M. Ferguson, Emilio Porfiri, Rupesh I. Bhatt, Paul G. Murray, Victoria L. Heath, and Roy Bicknell
Précis: Newly identified markers of blood vessels in renal tumors may offer an opportunity to selectively target the tumor vasculature in this setting.
- 2327** **Resistance to Anti-VEGF Therapy Mediated by Autocrine IL6/STAT3 Signaling and Overcome by IL6 Blockade**
Alexandra Eichten, Jia Su, Alexander P. Adler, Li Zhang, Ella Ioffe, Asma A. Parveen, George D. Yancopoulos, John Rudge, Israel Lowy, Hsin Chieh Lin, Douglas MacDonald, Christopher Daly, Xunbao Duan, and Gavin Thurston
Précis: These findings suggest that cancer patients undergoing anti-VEGF therapy may benefit from analysis of circulating IL6 levels as a predictive response marker, as well as cotreatment with an IL6 receptor targeting antibody.
- 2340** **The Error-Prone DNA Polymerase κ Promotes Temozolomide Resistance in Glioblastoma through Rad17-Dependent Activation of ATR-Chk1 Signaling**
Chenghao Peng, Zhengxin Chen, Shuai Wang, Hong-Wei Wang, Wenjin Qiu, Lin Zhao, Ran Xu, Hui Luo, Yuanyuan Chen, Dan Chen, Yongping You, Ning Liu, and Huibo Wang
Précis: Increased activity of a DNA repair pathway that can reverse the damage created by temozolomide, a chemotherapeutic drug used to treat glioblastoma, may explain why drug resistance in this setting tends to be clinically problematic.
- 2354** **p28-Mediated Activation of p53 in G₂-M Phase of the Cell Cycle Enhances the Efficacy of DNA Damaging and Antimitotic Chemotherapy**
Tohru Yamada, Tapas K. Das Gupta, and Craig W. Beattie
Précis: Delivery of a small p53-activating peptide that can safely increase the cytotoxicity of DNA damaging or antimitotic cancer drugs may offer one more twist on p53-based strategies to widen the therapeutic window for cancer drug responses.
- 2366** **Hypoxic Signaling and the Cellular Redox Tumor Environment Determine Sensitivity to MTH1 Inhibition**
Lars Bräutigam, Linda Pudelko, Ann-Sofie Jemth, Helge Gad, Mohit Narwal, Robert Gustafsson, Stella Karsten, Jordi Carreras Puigvert, Evert Homan, Carsten Berndt, Ulrika Warpman Berglund, Pål Stenmark, and Thomas Helleday
Précis: This study illustrates how zebrafish can serve as a useful model to investigate the relationship between redox imbalance and hypoxic signaling in oncogenesis at the level of the tumor microenvironment.
- 2376** **Cancer Differentiating Agent Hexamethylene Bisacetamide Inhibits BET Bromodomain Proteins**
Lisa M. Nilsson, Lydia C. Green, Somsundar Veppil Muralidharan, Dağsu Demir, Martin Welin, Joydeep Bhadury, Derek T. Logan, Björn Walse, and Jonas A. Nilsson
Précis: These findings suggest a new perspective on patient recruitment to ongoing BET inhibitor clinical trials.
- 2384** **The Deubiquitinase USP9X Maintains DNA Replication Fork Stability and DNA Damage Checkpoint Responses by Regulating CLASPIN during S-Phase**
Edel McGarry, David Gaboriau, Michael D. Rainey, Umberto Restuccia, Angela Bachi, and Corrado Santocanale
Précis: These findings highlight a role for an important deubiquitinating enzyme in maintaining genomic stability during DNA replication, offering new mechanistic clues to its tumor suppressor functions in various cancers.



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TUMOR AND STEM CELL BIOLOGY

- 2394** **Inflammation-Dependent IL18 Signaling Restricts Hepatocellular Carcinoma Growth by Enhancing the Accumulation and Activity of Tumor-Infiltrating Lymphocytes**
Geoffrey J. Markowitz, Pengyuan Yang, Jing Fu, Gregory A. Michelotti, Rui Chen, Jianhua Sui, Bin Yang, Wen-Hao Qin, Zheng Zhang, Fu-Sheng Wang, Anna Mae Diehl, Qi-Jing Li, Hongyang Wang, and Xiao-Fan Wang
Précis: These findings resolve a long-standing contradiction regarding a tumor suppressive role for IL18 in established liver cancers.
- 2406** **Cyclin E Associates with the Lipogenic Enzyme ATP-Citrate Lyase to Enable Malignant Growth of Breast Cancer Cells**
Kimberly S. Lucenay, Iman Doostan, Cansu Karakas, Tuyen Bui, Zhiyong Ding, Gordon B. Mills, Kelly K. Hunt, and Khandan Keyomarsi
Précis: These findings establish a novel relationship between cyclin E and lipid metabolism pathways in breast cancer oncogenesis, with potential implications for therapeutic interventions.
- 2419** **KLF4-Mediated Suppression of CD44 Signaling Negatively Impacts Pancreatic Cancer Stemness and Metastasis**
Yongmin Yan, Zhiwei Li, Xiangyu Kong, Zhiliang Jia, Xiangsheng Zuo, Mihai Gagea, Suyun Huang, Daoyan Wei, and Keping Xie
Précis: These findings elucidate the tumor suppressive mechanism by which KLF4 regulates the stemness and metastatic potential of pancreatic cancer cells, strengthening the preclinical rationale for early phase clinical trials of targeted KLF4 activation in aggressive solid tumors.
- 2432** **Pharmacological Targeting of the Histone Chaperone Complex FACT Preferentially Eliminates Glioblastoma Stem Cells and Prolongs Survival in Preclinical Models**
Josephine Kam Tai Dermawan, Masahiro Hitomi, Daniel J. Silver, Qiulian Wu, Poorva Sandlesh, Andrew E. Sloan, Andrei A. Purmal, Katerina V. Gurova, Jeremy N. Rich, Justin D. Lathia, George R. Stark, and Monica Venere
Précis: These findings offer a preclinical proof of concept for development of an anticancer drug class termed curaxins, which appear to preferentially kill stem cells in glioblastoma that are thought to be responsible for the aggressiveness of this disease.
- 2443** ***Drosophila* Brat and Human Ortholog TRIM3 Maintain Stem Cell Equilibrium and Suppress Brain Tumorigenesis by Attenuating Notch Nuclear Transport**
Subhas Mukherjee, Carol Tucker-Burden, Changming Zhang, Kenneth Moberg, Renee Read, Costas Hadjipanayis, and Daniel J. Brat
Précis: Investigations in a *Drosophila* brain tumor model reveal an evolutionarily conserved mechanism, which controls the self-renewal of glioma stem-like cells, suggesting new potential strategies to attack Notch-driven tumorigenesis.
- 2453** **Cyclin A1 and P450 Aromatase Promote Metastatic Homing and Growth of Stem-like Prostate Cancer Cells in the Bone Marrow**
Regina Miftakhova, Andreas Hedblom, Julius Semenas, Brian Robinson, Athanasios Simoulis, Johan Malm, Albert Rizvanov, David M. Heery, Nigel P. Mongan, Norman J. Maitland, Cinzia Allegrucci, and Jenny L. Persson
Précis: These results suggest that local production of steroids and MMPs in the bone marrow may provide a suitable microenvironment for prostate cancer stem-like cells to establish metastatic growths, with implications for how to target bony metastases in patients with advanced prostate cancer.
- 2465** **A Three-Dimensional Organoid Culture System Derived from Human Glioblastomas Recapitulates the Hypoxic Gradients and Cancer Stem Cell Heterogeneity of Tumors Found *In Vivo***
Christopher G. Hubert, Maricruz Rivera, Lisa C. Spangler, Qiulian Wu, Stephen C. Mack, Briana C. Prager, Marta Couce, Roger E. McLendon, Andrew E. Sloan, and Jeremy N. Rich
Précis: This study presents an important new tool to probe the diversity of glioblastoma cell phenotypes and microenvironmental nuances, which contribute to progression, by enabling investigations in a highly disease-relevant and tractable *ex vivo* culture system.
- 2478** **Activated KRAS Cooperates with MLL-AF4 to Promote Extramedullary Engraftment and Migration of Cord Blood CD34⁺ HSPC But Is Insufficient to Initiate Leukemia**
Cristina Prieto, Ronald W. Stam, Antonio Agraz-Doblas, Paola Ballerini, Mireia Camos, Julio Castaño, Rolf Marschalek, Aldeheid Bursen, Ignacio Varela, Clara Bueno, and Pablo Menendez
Précis: These findings support genomic studies conducted in other leukemias that show KRAS mutations are subclonal and lost at relapse.

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RETRACTIONS

- 2490** Retraction: Immunity to Murine Prostatic Tumors: Continuous Provision of T-Cell Help Prevents CD8 T-Cell Tolerance and Activates Tumor-Infiltrating Dendritic Cells
- 2491** Retraction: High-Avidity T Cells Are Preferentially Tolerized in the Tumor Microenvironment

CORRECTION

- 2492** Correction: Lens Epithelium-Derived Growth Factor Is an Hsp70-2 Regulated Guardian of Lysosomal Stability in Human Cancer



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ABOUT THE COVER

In commemoration of the 75th anniversary of *Cancer Research*, the Journal Editors have identified some of the most impactful articles published throughout the Journal's history. This year, *Cancer Research* has published and will continue to publish commentaries from authors, Editors, and other leaders in the field, reflecting on these important articles and how the field has continued to advance. This issue's cover offers a look back at some classic and distinctive covers from the Journal's rich history, featuring some key players, locations, and findings, and highlighting the impact the Journal has had in advancing cancer research and the mission of the AACR. For a more in-depth look at *Cancer Research* through the years, an interactive Anniversary timeline, and an archive of all Commentaries, please visit http://cancerres.aacrjournals.org/site/misc/75th_anniversary/CR75_timeline.html#timeline.



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