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# Cancer Research

January 1, 2013 • Volume 73 • Number 1

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## PRIORITY REPORT

- 12 | **mTOR Inhibitor RAD001 Promotes Metastasis in a Rat Model of Pancreatic Neuroendocrine Cancer**  
Stefan E. Pool, Sander Bison, Stuart J. Koelewijn, Linda M. van der Graaf, Marleen Melis, Eric P. Krenning, and Marion de Jong
- Précis:* This study reinforces emerging concerns that the administration of mTOR inhibitors in cancer patients may actually confer higher risk of progression in some settings, possibly because of mTOR inhibition in the immune microenvironment, as opposed to tumor cells that may not be therapeutically desirable.

## CLINICAL STUDIES

- 19 | **Targeting CD4<sup>+</sup> T-Helper Cells Improves the Induction of Antitumor Responses in Dendritic Cell–Based Vaccination**  
Erik H.J.G. Aarntzen, I. Jolanda M. De Vries, W. Joost Lesterhuis, Danita Schuurhuis, Joannes F.M. Jacobs, Kalijn Bol, Gerty Schreibelt, Roel Mus, Johannes H.W. De Wilt, John B.A.G. Haanen, Dirk Schadendorf, Alexandra Croockewit, Willeke A.M. Blokk, Michelle M. Van Rossum, William W. Kwok, Gosse J. Adema, Cornelis J.A. Punt, and Carl G. Figdor
- Précis:* This clinical study shows that to be effective, a cancer immunotherapy must coactivate CD4<sup>+</sup> T cells, suggesting that future immunotherapy trials should aim at activating CD4<sup>+</sup> T helper cells in an antigen-specific manner.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 30 | **Genomic Profiling of Isolated Circulating Tumor Cells from Metastatic Breast Cancer Patients**  
Mark Jesus M. Magbanua, Eduardo V. Sosa, Ritu Roy, Lauren E. Eisenbud, Janet H. Scott, Adam Olshen, Dan Pinkel, Hope S. Rugo, and John W. Park
- Précis:* Findings describe a sound method to explore genomic events in cancer progression as well as monitor the efficacy of targeted therapies in clinical trials in a relatively noninvasive and low-cost manner.
- 41 | **Single-Molecule Genomic Data Delineate Patient-Specific Tumor Profiles and Cancer Stem Cell Organization**  
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- Précis:* A novel quantitative approach that enables the measurement of patient-specific tumor characteristics extends insights into the great cellular complexity in cancer and offers a paradigm shift in molecular profiling, with implications for personalized treatment.

## MICROENVIRONMENT AND IMMUNOLOGY

- 50 | **RhoB Differentially Controls Akt Function in Tumor Cells and Stromal Endothelial Cells during Breast Tumorigenesis**  
Shiva Kazerounian, Damien Gerald, Minzhou Huang, Y. Rebecca Chin, Durga Udayakumar, Ningning Zheng, Rebekah K. O'Donnell, Carole Perruzzi, Lee Mangiante, Jacob Pourat, Thuy L. Phung, Arturo Bravo-Nuevo, Sharon Shechter, Stephanie McNamara, James B. DuHadaway, Olivier N. Kocher, Lawrence F. Brown, Alex Toker, George C. Prendergast, and Laura E. Benjamin
- Précis:* RhoB is generally considered a cancer suppressor gene, but in vivo studies reveal that it exerts positive effects on angiogenesis that supercede its negative impact on cancer cells themselves, thereby illustrating how differential functions of a signaling protein in stromal cells can complicate the challenge of developing therapeutics that can effectively target cancer pathophysiology rather than cancer cells in isolation.

- 62 **Vaccination with Antigen-Transfected, NKT Cell Ligand-Loaded, Human Cells Elicits Robust *In Situ* Immune Responses by Dendritic Cells**  
 Kanako Shimizu, Takuya Mizuno, Jun Shinga, Miki Asakura, Kazuhiro Kakimi, Yasuyuki Ishii, Kenichi Masuda, Tomoji Maeda, Hidetoshi Sugahara, Yusuke Sato, Hirokazu Matsushita, Keigo Nishida, Kenichi Hanada, Jan Dorrie, Niels Schaft, Kara Bickham, Hisashi Koike, Tsuyoshi Ando, Ryoza Nagai, and Shin-ichiro Fujii  
*Précis:* Preclinical proof-of-principle studies establish a new cell-based therapy to coordinate the activation of innate and adaptive immunity against tumors as an effective strategy for cancer immunotherapy.
- 74 **Augmenting Antitumor T-Cell Responses to Mimotope Vaccination by Boosting with Native Tumor Antigens**  
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*Précis:* Results show that the antitumor response to peptide-variant vaccines are markedly enhanced by subsequent immunization with the native antigen.
- 86 **A Unique Galectin Signature in Human Prostate Cancer Progression Suggests Galectin-1 as a Key Target for Treatment of Advanced Disease**  
 Diego J. Laderach, Lucas D. Gentilini, Laura Giribaldi, Victor Cardenas Delgado, Lorena Nugnes, Diego O. Croci, Nader Al Nakouzi, Paula Sacca, Gabriel Casas, Osvaldo Mazza, Margaret A. Shipp, Elba Vazquez, Anne Chauchereau, Jeffery L. Kutok, Scott J. Rodig, María T. Elola, Daniel Compagno, and Gabriel A. Rabinovich  
*Précis:* The dynamically regulated expression signature for an important class of cell surface glycan-binding molecules in prostate cancer suggest a tractable target for antiangiogenic therapy in advanced disease.
- 97 **Preventing Postoperative Metastatic Disease by Inhibiting Surgery-Induced Dysfunction in Natural Killer Cells**  
 Lee-Hwa Tai, Christiano Tanese de Souza, Simon Bélanger, Lundi Ly, Almohanad A. Alkayyal, Jiqing Zhang, Julia L. Rintoul, Abhirami A. Ananth, Tiffany Lam, Caroline J. Breitbart, Theresa J. Falls, David H. Kirn, John C. Bell, Andrew P. Makrigiannis, and Rebecca A. Auer  
*Précis:* Despite recent encouraging results, oncolytic viruses have yet to find their niche in current cancer treatment, but they might be applied as neoadjuvant therapies to inhibit metastasis after surgical resection of tumors, by boosting the innate immune system that is suppressed post-operatively.
- 108 **Angiopoietin-2 Functions as a Tie2 Agonist in Tumor Models, Where It Limits the Effects of VEGF Inhibition**  
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*Précis:* This study challenges prevailing views in revealing that Angiopoietin-2 functions as a Tie2 activator in tumors, playing a protective rather than a destabilizing role in tumor endothelial cells.
- 119 **Dose-Dense Chemotherapy Improves Mechanisms of Antitumor Immune Response**  
 Chih-Long Chang, Yun-Ting Hsu, Chao-Chih Wu, Yan-Zen Lai, Connie Wang, Yuh-Cheng Yang, T.-C. Wu, and Chien-Fu Hung  
*Précis:* Dose-dense chemotherapy appears to improve the prognosis of patients with drug-resistant disease, however, the mechanistic basis for this effect has been undefined.
- 128 **PD-1-Expressing Tumor-Infiltrating T Cells Are a Favorable Prognostic Biomarker in HPV-Associated Head and Neck Cancer**  
 Cécile Badoual, Stéphane Hans, Nathalie Merillon, Cordélia Van Ryswick, Patrice Ravel, Nadine Benhamouda, Emeline Levionnois, Mevyn Nizard, Ali Si-Mohamed, Nicolas Besnier, Alain Gey, Rinat Rotem-Yehudar, Hélène Pere, Thi Tran, Coralie L. Guerin, Anne Chauvat, Estelle Dransart, Cécile Alanio, Sebastien Albert, Beatrix Barry, Federico Sandoval, Françoise Quintin-Colonna, Patrick Bruneval, Wolf H. Fridman, Francois M. Lemoine, Stephane Oudard, Ludger Johannes, Daniel Olive, Daniel Brasnu, and Eric Tartour  
*Précis:* Findings prompt a need to revisit the significance of PD-1-positive T cells that infiltrate tumors, where PD-1 detection may reflect a previous immune response against tumors that may be reactivated by PD-1/PD-L1 blockade.
- 139 **Antitumor Immunotherapeutic and Toxic Properties of an HDL-Conjugated Chimeric IL-15 Fusion Protein**  
 Maria C. Ochoa, Jessica Fioravanti, Inmaculada Rodriguez, Sandra Hervas-Stubbs, Arantza Azpilikueta, Guillermo Mazzolini, Alfonso Gúrpide, Jesus Prieto, Julian Pardo, Pedro Berraondo, and Ignacio Melero  
*Précis:* A strategy of IL-15 conjugation to a cholesterol-carrying lipoprotein can eradicate aggressive metastatic cancer in mice due to enhanced NK activity and CTL memory.

150 **Spatiotemporal Assessments of Dermal Hyperemia Enable Accurate Prediction of Experimental Cutaneous Carcinogenesis as well as Chemopreventive Activity**

Raymond L. Konger, Zhengbin Xu, Ravi P. Sahu, Badri M. Rashid, Shama R. Mehta, Deena R. Mohamed, Sonia C. DaSilva-Arnold, Joshua R. Bradish, Simon J. Warren, and Young L. Kim

*Précis:* Spatial and temporal analysis of focal areas of inflammatory hyperemia can predict not only whether tumors will form, but also where they will form during experimental skin carcinogenesis.

195 **Characterization of Rearrangements Involving the ALK Gene Reveals a Novel Truncated Form Associated with Tumor Aggressiveness in Neuroblastoma**

Alex Cazes, Caroline Louis-Brennetot, Pierre Mazot, Florent Dingli, Bérangère Lombard, Valentina Boeva, Romain Daveau, Julie Cappo, Valérie Combaret, Gudrun Schleiermacher, Stéphanie Jouannet, Sandrine Ferrand, Gaëlle Pierron, Emmanuel Barillot, Damarys Loew, Marc Vigny, Olivier Delattre, and Isabelle Janoueix-Lerosey

*Précis:* The description of a novel truncated form of the ALK receptor shows that genomic rearrangements constitute an alternative mechanism to ALK point mutations, resulting in receptor activation in neuroblastoma, which is of importance in the context of ALK-targeted therapy in neuroblastoma patients.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

160 **Autophagy Control by the VEGF-C/NRP-2 Axis in Cancer and its Implication for Treatment Resistance**

Marissa J. Stanton, Samikshan Dutta, Heyu Zhang, Navatha S. Polavaram, Alexey A. Leontovich, Pia Hönscheid, Frank A. Sinicrope, Donald J. Tindall, Michael H. Muders, and Kaustubh Datta

*Précis:* Findings suggest that the effects of an angiogenic pathway on autophagy may mediate tumor cell survival in the face of chemotherapy, contributing to drug resistance.

205 **PNUTS Functions as a Proto-Oncogene by Sequestering PTEN**

Sridhar Kavela, Swapnil R. Shinde, Raman Ratheesh, Kotapalli Viswakalyan, Murali D. Bashyam, Swarnalata Gowrishankar, Mohana Vamsy, Sujit Pattnaik, Subramanyeshwar Rao, Regulagadda A. Sastry, Mukta Srinivasulu, Junjie Chen, and Subbareddy Maddika

*Précis:* A protein phosphatase subunit responsible for its nuclear targeting is found to bind PTEN and block its tumor suppressor activity.

172 **S100A9 Is a Novel Ligand of EMMPRIN That Promotes Melanoma Metastasis**

Toshihiko Hibino, Masakiyo Sakaguchi, Shoko Miyamoto, Mami Yamamoto, Akira Motoyama, Junichi Hosoi, Tadashi Shimokata, Tomonobu Ito, Ryoji Tsuboi, and Nam-ho Huh

*Précis:* Findings establish the role of a receptor for a tissue damage-associated molecule in melanoma metastasis, offering proof-of-concept for a novel strategy to limit this deadly process.

215 **p38 $\alpha$  Inhibits Liver Fibrogenesis and Consequent Hepatocarcinogenesis by Curtailing Accumulation of Reactive Oxygen Species**

Toshiharu Sakurai, Masatoshi Kudo, Atsushi Umemura, Guobin He, Ahmed M. Elsharkawy, Ekihiro Seki, and Michael Karin

*Précis:* An important stress kinase and its chaperone target appear to play an important role in protecting the liver against long-term ROS damage that promotes chronic inflammation driving formation of most liver cancers.

184 **Critical Role for the Receptor Tyrosine Kinase EPHB4 in Esophageal Cancers**

Rifat Hasina, Nathan Mollberg, Ichiro Kawada, Karun Mutreja, Geetanjali Kanade, Soheil Yala, Mosmi Surati, Ren Liu, Xiuqing Li, Yue Zhou, Benjamin D. Ferguson, Vidya Nallasura, Kenneth S. Cohen, Elizabeth Hyjek, Jeffery Mueller, Rajani Kanteti, Essam El Hashani, Dorothy Kane, Yutaka Shimada, Mark W. Lingen, Aliya N. Husain, Mitchell C. Posner, Irving Waxman, Victoria M. Villaflor, Mark K. Ferguson, Lyuba Varticovski, Everett E. Vokes, Parkash Gill, and Ravi Salgia

*Précis:* A targetable kinase overexpressed in all histological stages of esophageal cancer may provide an important therapeutic target to treat this disease, which while rising in incidence, remains mainly untreatable.

225 **Novel DNA Damage Checkpoints Mediating Cell Death Induced by the NEDD8-Activating Enzyme Inhibitor MLN4924**

Jonathan L. Blank, Xiaozhen J. Liu, Katherine Cosmopoulos, David C. Bouck, Khristofer Garcia, Hugues Bernard, Olga Tayber, Greg Hather, Ray Liu, Usha Narayanan, Michael A. Milhollen, and Eric S. Lightcap

*Précis:* Findings expand our understanding of how cancer cells respond to replication stress, which due to the genomic disorganization of most tumor cells is experienced more acutely in cancer.

235 **Inhibiting Interactions of Lysine Demethylase LSD1 with Snail/Slug Blocks Cancer Cell Invasion**  
Giovanna Ferrari-Amorotti, Valentina Fragiasso, Roza Esteki, Zelia Prudente, Angela Rachele Soliera, Sara Cattelani, Gloria Manzotti, Giulia Grisendi, Massimo Dominici, Marco Pieraccioli, Giuseppe Raschella, Claudia Chiodoni, Mario Paolo Colombo, and Bruno Calabretta

*Précis:* Results offer proof-of-concept for a tractable approach to inhibit the Snail-Slug signaling pathway of cancer cell invasion by reversing epithelial-mesenchymal transition.

246 **SpliceArray Profiling of Breast Cancer Reveals a Novel Variant of NCOR2/SMRT That Is Associated with Tamoxifen Resistance and Control of ER $\alpha$  Transcriptional Activity**  
Luduo Zhang, Chun Gong, Samantha L.Y. Lau, Nan Yang, Oscar G.W. Wong, Annie N.Y. Cheung, Janice W.H. Tsang, Kelvin Y.K. Chan, and Ui-Soon Khoo

*Précis:* Gene expression profiling studies to classify and prognose breast cancer have been disappointing, because they have yielded little if any concordance, but the microarrays used for these studies did not take into account RNA splice variants that may provide more useful gene expression signatures.

## PREVENTION AND EPIDEMIOLOGY

256 **Genome-Wide Association Study Reveals Novel Genetic Determinants of DNA Repair Capacity in Lung Cancer**  
Li-E Wang, Olga Y. Gorlova, Jun Ying, Yawei Qiao, Shih-Feng Weng, Annette T. Lee, Peter K. Gregersen, Margaret R. Spitz, Christopher I. Amos, and Qingyi Wei

*Précis:* A predictive DNA repair phenotype measured in peripheral lymphocytes was validated as an independent risk factor for lung cancer, with specific genetic determinants investigated in a two-stage analysis.

265 **A Classification Model for BRCA2 DNA Binding Domain Missense Variants Based on Homology-Directed Repair Activity**

Lucia Guidugli, Vernon S. Pankratz, Namit Singh, James Thompson, Catherine A. Erding, Christoph Engel, Rita Schmutzler, Susan Domchek, Katherine Nathanson, Paolo Radice, Christian Singer, Patricia N. Tonin, Noralane M. Lindor, David E. Goldgar, and Fergus J. Couch

*Précis:* An assay that can measure the homology-directed repair activity of BRCA2 can predict the cancer pathogenicity of missense mutations in this tumor suppressor gene, possibly impacting the ability to predict cancer susceptibilities in patients harboring those mutations.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

276 **PIK3CA Mutation H1047R Is Associated with Response to PI3K/AKT/mTOR Signaling Pathway Inhibitors in Early-Phase Clinical Trials**

Filip Janku, Jennifer J. Wheler, Aung Naing, Gerald S. Falchook, David S. Hong, Vanda M. Stepanek, Siqing Fu, Sarina A. Piha-Paul, J. Jack Lee, Rajyalakshmi Luthra, Apostolia M. Tsimberidou, and Razelle Kurzrock

*Précis:* This study defines pharmacodynamic markers to predict responsiveness or resistance to a plethora of experimental clinical agents being developed to therapeutically inhibit the PI3K/Akt/mTOR signaling pathway in cancer.

285 **Kinase Pathway Dependence in Primary Human Leukemias Determined by Rapid Inhibitor Screening**

Jeffrey W. Tyner, Wayne F. Yang, Armand Bankhead III, Guang Fan, Luke B. Fletcher, Jade Bryant, Jason M. Glover, Bill H. Chang, Stephen E. Spurgeon, William H. Fleming, Tibor Kovacsovic, Jason R. Gotlib, Stephen T. Oh, Michael W. Deininger, Christian Michel Zwaan, Monique L. Den Boer, Marry M. van den Heuvel-Eibrink, Thomas O'Hare, Brian J. Druker, and Marc M. Loriaux

*Précis:* Interrogation of leukemia cells with a kinase inhibitor library allows for computational prediction of kinase pathway dependence and identifies candidate therapies for patients.

297 **EGFR/JIP-4/JNK2 Signaling Attenuates Cetuximab-Mediated Radiosensitization of Squamous Cell Carcinoma Cells**

Iris Eke, Lydia Schneider, Claudia Förster, Daniel Zips, Leoni A. Kunz-Schughart, and Nils Cordes

*Précis:* Blockades to the mechanism by which EGFR targeting is naturally attenuated in vivo have the potential to increase the efficacy of anti-EGFR therapies in clinic.

307 **Targeting Truncated Retinoid X Receptor- $\alpha$  by CF31 Induces TNF- $\alpha$ -Dependent Apoptosis**

Guang-Hui Wang, Fu-Quan Jiang, Ying-Hui Duan, Zhi-Ping Zeng, Fan Chen, Yi Dai, Jie-Bo Chen, Jin-Xing Liu, Jie Liu, Hu Zhou, Hai-Feng Chen, Jin-Zhang Zeng, Ying Su, Xin-Sheng Yao, and Xiao-Kun Zhang

*Précis:* A natural product that targets an RXR-mediated cell survival pathway may offer a new strategy to kill cancer cells.



319 **Superior Penetration and Retention Behavior of 50 nm Gold Nanoparticles in Tumors**

Shuaidong Huo, Huili Ma, Keyang Huang, Juan Liu, Tuo Wei, Shubin Jin, Jinchao Zhang, Shengtai He, and Xing-Jie Liang

*Précis:* This work reveals that smaller nanoparticles are more effective than larger particles at delivering drugs to tumor cells, with implications for many kinds of cancer nanotherapy studies.

331 **ABL Regulation by AXL Promotes Cisplatin Resistance in Esophageal Cancer**

Jun Hong, DunFa Peng, Zheng Chen, Vikas Sehdev, and Abbes Belkhir

*Précis:* Esophageal cancers rising in incidence, possibly due to reductions in gastric *H. pylori* infections in developed countries, are commonly resistant to cytotoxic chemotherapies that remain a current standard of care.

373 **STAT5 Is Crucial to Maintain Leukemic Stem Cells in Acute Myelogenous Leukemias Induced by MOZ-TIF2**

Winnie F. Tam, Patricia S. Hähnel, Andrea Schüller, Benjamin H. Lee, Rachel Okabe, Nan Zhu, Saskia V. Pante, Glen Raffel, Thomas Mercher, Gerlinde Wernig, Ernesto Bockamp, Daniel Sasca, Andreas Kreft, Gertraud W. Robinson, Lothar Hennighausen, D. Gary Gilliland, and Thomas Kindler

*Précis:* Findings suggest that disruption of pathogenic signals from STAT5 may powerfully disable an aggressive and mainly untreatable leukemia.

385 **E3 Ubiquitin Ligase RNF126 Promotes Cancer Cell Proliferation by Targeting the Tumor Suppressor p21 for Ubiquitin-Mediated Degradation**

Xu Zhi, Dong Zhao, Zehua Wang, Zhongmei Zhou, Chunyan Wang, Wenlin Chen, Rong Liu, and Ceshi Chen

*Précis:* In defining an E3 ubiquitin ligase as a target for new cancer treatments, this study reveals mechanistic insights into the control of a pivotal cell cycle inhibitor.

## TUMOR AND STEM CELL BIOLOGY

341 **MicroRNAs Regulate Tumor Angiogenesis Modulated by Endothelial Progenitor Cells**

Prue N. Plummer, Ruth Freeman, Ryan J. Taft, Jelena Vider, Michael Sax, Brittany A. Umer, Dingcheng Gao, Christopher Johns, John S. Mattick, Stephen D. Wilton, Vito Ferro, Nigel A.J. McMillan, Alexander Swarbrick, Vivek Mittal, and Albert S. Mellick

*Précis:* Tumor vascularization mediated by bone marrow-derived vascular progenitor cells relies upon certain microRNAs that may offer novel targets for antiangiogenic therapy.

353 **A Preclinical Mouse Model of Invasive Lobular Breast Cancer Metastasis**

Chris W. Doornebal, Sjoerd Klarenbeek, Tanya M. Braumuller, Christiaan N. Klijn, Metamia Ciampriotti, Cheei-Sing Hau, Markus W. Hollmann, Jos Jonkers, and Karin E. de Visser

*Précis:* This study reports a model of metastatic cancer that may improve the ability to predict clinical responses to novel therapies against metastatic disease, where there remains the greatest need of accurate predictions for new clinical agents being tested.

364 **NF- $\kappa$ B Activity Regulates Mesenchymal Stem Cell Accumulation at Tumor Sites**

Ryosuke Uchibori, Tomonori Tsukahara, Hiroyuki Mizuguchi, Yasushi Saga, Masashi Urabe, Hiroaki Mizukami, Akihiro Kume, and Keiya Ozawa

*Précis:* This study offers a basis to understand the tumor-targeting abilities of mesenchymal stem cells, which have been studied as vectors for the more efficient delivery of cancer gene therapies, with implications for how to best direct their application in this setting.

395 **Immune-Dependent and Independent Antitumor Activity of GM-CSF Aberrantly Expressed by Mouse and Human Colorectal Tumors**

Rocio G. Urduinguo, Agustin F. Fernandez, Angela Moncada-Pazos, Covadonga Huidobro, Ramon M. Rodriguez, Cecilia Ferrero, Pablo Martinez-Camblor, Alvaro J. Obaya, Teresa Bernal, Adolfo Parra-Blanco, Luis Rodrigo, Maria Santacana, Xavier Matias-Guiu, Beatriz Soldevilla, Gemma Dominguez, Felix Bonilla, Santiago Cal, Carlos Lopez-Otin, and Mario F. Fraga

*Précis:* Granulocyte-macrophage colony-stimulating factor (GM-CSF) is overexpressed in a subset of colon tumors, which when coupled with expression of GM-CSF receptor leads to a strong antitumor activity.

406 **Cisplatin Selects for Multidrug-Resistant CD133<sup>+</sup> Cells in Lung Adenocarcinoma by Activating Notch Signaling**

Yu-Peng Liu, Chih-Jen Yang, Ming-Shyan Huang, Chi-Tai Yeh, Alexander T.H. Wu, Yu-Cheng Lee, Tsung-Ching Lai, Chien-Hsin Lee, Ya-Wen Hsiao, Jean Lu, Chia-Ning Shen, Pei-Jung Lu, and Michael Hsiao

*Précis:* This important study suggests that Notch pathway inhibitors may prevent the emergence of drug-resistant cancer stem cells selected by platinum-based chemotherapy, which is used to treat many types of human cancer.

417 **A Tumorigenic MLL-Homeobox Network in Human Glioblastoma Stem Cells**  
Marco Gallo, Jenny Ho, Fiona J. Coutinho, Robert Vanner, Lilian Lee, Renee Head, Erick K. M. Ling, Ian D. Clarke, and Peter B. Dirks  
*Précis:* This seminal study provides the first evidence for a functional MLL-homeobox transcription factor network that contributes to the stem cell functions supporting glioblastoma tumorigenicity.

428  **$\alpha$ -Catulin Drives Metastasis by Activating ILK and Driving an  $\alpha$ v $\beta$ 3 Integrin Signaling Axis**  
Chen-Hsien Liang, Szu-Ying Chiu, I-Ling Hsu, Yi-Ying Wu, Yao-Tsung Tsai, Jhen-Yu Ke, Szu-Hua Pan, Yi-Chiung Hsu, Ker-Chau Li, Pan-Chyr Yang, Yuh-Ling Chen, and Tse-Ming Hong  
*Précis:* Findings reveal a novel signaling axis of invasion and metastasis in lung adenocarcinoma that offers therapeutic targets to treat this aggressive disease.

439 **MIG-7 Controls COX-2/PGE2-Mediated Lung Cancer Metastasis**  
Ming-Yi Ho, Shu-Mei Liang, Shao-Wen Hung, and Chi-Ming Liang  
*Précis:* Findings identify a prognostic marker and therapeutic target expressed highly selectively in many types of human metastatic tumor cells where COX-2 and PGE-2 levels are elevated.

450 **Constitutive HER2 Signaling Promotes Breast Cancer Metastasis through Cellular Senescence**  
Pier Davide Angelini, Mariano F. Zacarias Fluck, Kim Pedersen, Josep Lluís Parra-Palau, Marc Guiu, Cristina Bernadó Morales, Rocio Vicario, Antonio Luque-García, Nerea Peiró Navalpotro, Jordi Giralt, Francesc Canals, Roger R. Gomis, Josep Taberner, José Baselga, Josep Villanueva, and Joaquín Arribas  
*Précis:* It is increasingly clear that cell senescence cannot be understood simply as a mechanism of tumor suppression in cancer, because it can also promote development of later stages in malignant progression as this study reveals mechanistically.

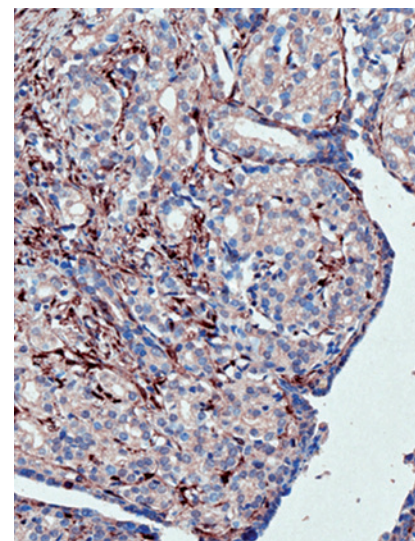
459 **Production of Gastrointestinal Tumors in Mice by Modulating Latent TGF- $\beta$ 1 Activation**  
Kotaro Shibahara, Mitsuhiko Ota, Masahito Horiguchi, Keiji Yoshinaga, Jonathan Melamed, and Daniel B. Rifkin  
*Précis:* Sophisticated genetic manipulations in the mouse that can finely tune TGF- $\beta$  expression in the lower gastrointestinal tract can strongly influence the incidence and frequency of tumors formed there.

## CORRECTION

469 **Correction: Cyclin D2–Cyclin-Dependent Kinase 4/6 Is Required for Efficient Proliferation and Tumorigenesis following Apc Loss**

## ABOUT THE COVER

Galectins, a family of endogenous glycan-binding proteins, play different roles in tumor-related processes including tumor transformation, metastasis, angiogenesis, and tumor-immune escape. In spite of considerable progress in elucidating the role of individual galectins in tumor biology, an integrated portrait of the galectin network in different tumor microenvironments is missing. Laderach and colleagues identified a unique galectin signature during human prostate cancer progression characterized by lower levels of galectins-3, -4, -9 and -12, no changes in galectin-8 expression, and dramatic upregulation of galectin-1. In human prostate cancer tissue, galectin-1 expression correlated with the presence of blood vessels in advanced disease. This endogenous lectin promoted prostate cancer angiogenesis through mechanisms that were independent of classical proangiogenic factors, suggesting a tractable independent target for prostate cancer therapy in advanced stages of the disease. For details, please see the article by Laderach and colleagues on page 86.



# Cancer Research

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