

BREAKING ADVANCES

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

REVIEWS

- 629 | **PTEN Level in Tumor Suppression: How Much Is Too Little?**
Arkaitz Carracedo, Andrea Alimonti, and Pier Paolo Pandolfi
- 634 | **Cancer Stem Cell Niche: The Place to Be**
Tijana Borovski, Felipe De Sousa E Melo, Louis Vermeulen, and Jan Paul Medema

PERSPECTIVE

- 640 | **Breast Cancer Racial Disparities: Unanswered Questions**
Foluso O. Ademuyiwa, Stephen B. Edge, Deborah O. Erwin, Heather Orom, Christine B. Ambrosone, and Willie Underwood III

PRIORITY REPORTS

- 645 | **MicroRNA-1258 Suppresses Breast Cancer Brain Metastasis by Targeting Heparanase**
Lixin Zhang, Peggy S. Sullivan, Jerry C. Goodman, Preethi H. Gunaratne, and Dario Marchetti
- Précis: Brain metastases in cancers of the breast and other tissues which are poorly clinically managed might be attacked by a microRNA-based strategy to downregulate an important glycolytic enzyme known to support metastasis.*

- 655 | **Demethylation of RB Regulator MYPT1 by Histone Demethylase LSD1 Promotes Cell Cycle Progression in Cancer Cells**
Hyun-Soo Cho, Takehiro Suzuki, Naoshi Dohmae, Shinya Hayami, Motoko Unoki, Masanori Yoshimatsu, Gouji Toyokawa, Masashi Takawa, Taiping Chen, Julia K. Kurash, Helen I. Field, Bruce A.J. Ponder, Yusuke Nakamura, and Ryuji Hamamoto

Précis: Findings comprise a novel cell cycle regulatory mechanism mediated by histone methylation and demethylation dynamics, revealing its significance to human carcinogenesis.

- 661 | **Cyclophosphamide Induces Differentiation of Th17 Cells in Cancer Patients**
Sophie Viaud, Caroline Flament, Mustapha Zoubir, Patricia Pautier, Axel LeCesne, Vincent Ribrag, Jean-Charles Soria, Virginie Marty, Philippe Vielh, Caroline Robert, Nathalie Chaput, and Laurence Zitvogel

Précis: Results may impact clinical management of cancers treated with the alkylating agent cyclophosphamide, based on its effects on the differentiation of proinflammatory Th17 cells.

CLINICAL STUDIES

- 666 | **High PTP4A3 Phosphatase Expression Correlates with Metastatic Risk in Uveal Melanoma Patients**
Cécile Laurent, Fabien Valet, Nathalie Planque, Licia Silveri, Selma Maacha, Océane Anezo, Philippe Hupe, Corine Plancher, Cécile Reyes, Benoit Albaud, Audrey Rapinat, David Gentien, Jérôme Couturier, Xavier Sastre-Garau, Laurence Desjardins, Jean-Paul Thiery, Sergio Roman-Roman, Bernard Asselain, Emmanuel Barillot, Sophie Piperno-Neumann, and Simon Saule

Précis: Findings offer a mechanism-based approach to treat an unusually aggressive form of cancer.

675 **Phase I Assessment of New Mechanism-Based Pharmacodynamic Biomarkers for MLN8054, a Small-Molecule Inhibitor of Aurora A Kinase**
Arijit Chakravarty, Vaishali Shinde, Josep Tabernero, Andres Cervantes, Roger B. Cohen, E. Claire Dees, Howard Burris, Jeffrey R. Infante, Teresa Macarulla, Elena Elez, Jordi Andreu, Edith Rodriguez-Braun, Susana Rosello, Margaret von Mehren, Neal J. Meropol, Corey J. Langer, Bert O'Neil, Douglas Bowman, Mengkun Zhang, Hadi Danaee, Laura Faron-Yowe, Gary Gray, Hua Liu, Jodi Pappas, Lee Silverman, Chris Simpson, Bradley Stringer, Stephen Tirrell, Ole Petter Veiby, Karthik Venkatakrishnan, Katherine Galvin, Mark Manfredi, and Jeffrey A. Ecsedy

Précis: Findings demonstrate effective targeting of the key mitotic kinase Aurora A in first-in-human clinical trials of an experimental small-molecule inhibitor tested as an anticancer therapy.

705 **The Molecular Basis of Synergism between Carboplatin and ABT-737 Therapy Targeting Ovarian Carcinomas**
Harsh Vardhan Jain and Michael Meyer-Hermann

Précis: A new approach to model cancer therapy reconciles existing observations for the combined action of carboplatin and ABT-737 against ovarian cancers, predicting optimal drug doses and scheduling.

716 **Three-Dimensional Culture of Mouse Renal Carcinoma Cells in Agarose Macrobeads Selects for a Subpopulation of Cells with Cancer Stem Cell or Cancer Progenitor Properties**

Barry H. Smith, Lawrence S. Gazda, Bryan L. Conn, Kanti Jain, Shirin Asina, Daniel M. Levine, Thomas S. Parker, Melissa A. Laramore, Prithy C. Martis, Horatiu V. Vinerean, Eric M. David, Suizhen Qiu, Carlos Cordon-Cardo, Richard D. Hall, Bruce R. Gordon, Carolyn H. Diehl, Kurt H. Stenzel, and Albert L. Rubin

Précis: Results reveal a simple method to select tumor cell subpopulations that have cancer stem cell or progenitor cell properties.

INTEGRATED SYSTEMS AND TECHNOLOGIES

686 **Pharmacokinetic Modeling of Tumor Bioluminescence Implicates Efflux, and Not Influx, as the Bigger Hurdle in Cancer Drug Therapy**
Hoon Sim, Kristin Bibee, Samuel Wickline, and David Sept

Précis: A novel combination of pharmacokinetic modeling and bioluminescence imaging reveals that drug transport in and out of tumors depends strongly on tumor volume.

693 **Dynamic Mathematical Modeling of IL13-Induced Signaling in Hodgkin and Primary Mediastinal B-Cell Lymphoma Allows Prediction of Therapeutic Targets**
Valentina Raia, Marcel Schilling, Martin Böhm, Bettina Hahn, Andreas Kowarsch, Andreas Raue, Carsten Sticht, Sebastian Bohl, Maria Saile, Peter Möller, Norbert Gretz, Jens Timmer, Fabian Theis, Wolf-Dieter Lehmann, Peter Lichter, and Ursula Klingmüller

Précis: Data-based mathematical modeling of the JAK/STAT pathway in lymphoma cells identifies novel therapeutic targets.

725 **Hydrophilic Agarose Macrobead Cultures Select for Outgrowth of Carcinoma Cell Populations That Can Restrict Tumor Growth**

Barry H. Smith, Lawrence S. Gazda, Bryan L. Conn, Kanti Jain, Shirin Asina, Daniel M. Levine, Thomas S. Parker, Melissa A. Laramore, Prithy C. Martis, Horatiu V. Vinerean, Eric M. David, Suizhen Qiu, Alison J. North, C. Guillermo Couto, Gerald S. Post, David J. Waters, Carlos Cordon-Cardo, Richard D. Hall, Bruce R. Gordon, Carolyn H. Diehl, Kurt H. Stenzel, and Albert L. Rubin

Précis: Encapsulated, growth-restricted tumor cells can secrete proteins that block the growth of freely-growing cancer cells, with implications for understanding tumor progression and treatment.

736

Analysis of the T-Cell Receptor Repertoires of Tumor-Infiltrating Conventional and Regulatory T Cells Reveals No Evidence for Conversion in Carcinogen-Induced Tumors

James P. Hindley, Cristina Ferreira, Emma Jones, Sarah N. Lauder, Kristin Ladell, Katherine K. Wynn, Gareth J. Betts, Yogesh Singh, David A. Price, Andrew J. Godkin, Julian Dyson, and Awen Gallimore

Précis: T regulatory cell accumulation in tumors might not occur as a result of a conversion of conventional tumor-infiltrating T cells, suggesting that there may be distinct effects of the tumor microenvironment on these two cell populations to manipulate for therapeutic benefit.

747

Spatial Regulation of RhoA Activity during Pancreatic Cancer Cell Invasion Driven by Mutant p53

Paul Timpson, Ewan J. McGhee, Jennifer P. Morton, Alex von Kriegsheim, Juliane P. Schwarz, Saadia A. Karim, Brendan Doyle, Jean A. Quinn, Neil O. Carragher, Mike Edward, Michael F. Olson, Margaret C. Frame, Valerie G. Brunton, Owen J. Sansom, and Kurt I. Anderson

Précis: In vivo findings show how dynamic and spatial regulation of RhoA in pancreatic cancer cells controls their invasive capability, highlighting deficiencies in cell culture models and revealing new opportunities for cancer selective drug targeting.

758

Ra1A Function in Dermal Fibroblasts Is Required for the Progression of Squamous Cell Carcinoma of the Skin

Adam G. Sowalsky, Addy Alt-Holland, Yulia Shamis, Jonathan A. Garlick, and Larry A. Feig

Précis: Definition of stroma fibroblast functions that support tumors are of increasing interest to target for cancer therapy.

768

Cyclophosphamide Synergizes with Type I Interferons through Systemic Dendritic Cell Reactivation and Induction of Immunogenic Tumor Apoptosis

Giovanna Schiavoni, Antonella Sistigu, Mara Valentini, Fabrizio Mattei, Paola Sestili, Francesca Spadaro, Massimo Sanchez, Silvia Lorenzi, Maria Teresa D'Urso, Filippo Belardelli, Lucia Gabriele, Enrico Proietti, and Laura Bracci

Précis: Findings offer mechanistic insight into how many clinically efficacious cytotoxic chemotherapies may work by combining tumor cell killing facilitating tumor antigen presentation to the immune cells and a systemic stimulation of the immune system to attack the tumor.

In Vivo Profiling of Hypoxic Gene Expression in Gliomas Using the Hypoxia Marker EF5 and Laser-capture Microdissection

Diane Marotta, Jayashree Karar, W. Timothy Jenkins, Monika Kumanova, Kevin W. Jenkins, John W. Tobias, Donald Baldwin, Artemis Hatzigeorgiou, Panagiotis Alexiou, Sydney M. Evans, Rodolfo Alarcon, Amit Maity, Cameron Koch, and Constantinos Koumenis

Précis: This is the first study to examine how low oxygen conditions impact in vivo gene regulation in the context of a solid tumor.

790

Tumor Cell Invasion Is Promoted by Interstitial Flow-Induced Matrix Priming by Stromal Fibroblasts

Adrian C. Shieh, Hallie A. Rozansky, Boris Hinz, and Melody A. Swartz

Précis: Interstitial flow directs fibroblast invasion and matrix remodeling in the tumor microenvironment, making it more permissive to tumor invasion.

801

Agonist Anti-CD137 mAb Act on Tumor Endothelial Cells to Enhance Recruitment of Activated T Lymphocytes

Asís Palazón, Alvaro Teijeira, Iván Martínez-Forero, Sandra Hervás-Stubbs, Carmen Roncall, Iván Peñuelas, Juan Dubrot, Aizea Morales-Kastresana, José Luis Pérez-Gracia, M. Carmen Ochoa, Laura Ochoa-Callejero, Alfredo Martínez, Alfonso Luque, Joseph Dinchuk, Ana Rouzaut, Maria Jure-Kunkel, and Ignacio Melero

Précis: Findings offer a novel mechanistic explanation for the anticancer effects of agonist monoclonal antibodies to the immune stimulatory molecule 4-1BB (CD137), which is currently in clinical trials for cancer treatment.

812

Induction of Monocyte Chemoattractant Protein-1 and Interleukin-10 by TGFβ1 in Melanoma Enhances Tumor Infiltration and Immunosuppression

Nancy Díaz-Valdés, María Basagoiti, Javier Dotor, Fernando Aranda, Iñaki Monreal, José Ignacio Riezu-Boj, Francisco Borrás-Cuesta, Pablo Sarobe, and Esperanza Feijó

Précis: Findings reveal how TGF-β induces two known factors implicated in melanoma progression and how inhibition of this cytokine may have therapeutic effects.

822 **TGF- β Promotion of Gli2-Induced Expression of Parathyroid Hormone-Related Protein, an Important Osteolytic Factor in Bone Metastasis, Is Independent of Canonical Hedgehog Signaling**

Rachelle W. Johnson, Mai P. Nguyen, Susan S. Padalecki, Barry G. Grubbs, Alyssa R. Merkel, Babatunde O. Oyajobi, Lynn M. Matrisian, Gregory R. Mundy, and Julie A. Sterling

Précis: Findings define a key pathway of bone destruction in breast cancers that have metastasized to bone, with implications for novel therapeutic strategies to reduce cancer-associated bone disease in patients.

862 **Invasive Prostate Carcinoma Driven by c-Src and Androgen Receptor Synergy**
Houjian Cai, Ivan Babic, Xiao Wei, Jiaoti Huang, and Owen N. Witte

Précis: Src mutations are not common in prostate cancer, but Src overexpression that occurs during progression increases expression of the androgen receptor that may contribute strongly to promoting development of aggressive disease.

873 **LATS2 Is a Tumor Suppressor Gene of Malignant Mesothelioma**

Hideki Murakami, Tetsuya Mizuno, Tetsuo Taniguchi, Makiko Fujii, Futoshi Ishiguro, Takayuki Fukui, Shinya Akatsuka, Yoshitsugu Horio, Toyoaki Hida, Yutaka Kondo, Shinya Toyokuni, Hirotaka Osada, and Yoshitaka Sekido

Précis: This is the first report to unambiguously define genetic inactivation in a human malignancy of the tumor suppressor LATS2, which functions in the Hippo signaling cascade of cell growth control.

MOLECULAR AND CELLULAR PATHOBIOLOGY

832 **Src and Caveolin-1 Reciprocally Regulate Metastasis via a Common Downstream Signaling Pathway in Bladder Cancer**

Shibu Thomas, Jonathan B. Overvest, Matthew D. Nitz, Paul D. Williams, Charles R. Owens, Marta Sanchez-Carbayo, Henry F. Frierson, Martin A. Schwartz, and Dan Theodorescu

Précis: Findings suggest that the Src oncogene actually functions as a suppressor in cancers of the bladder and perhaps other organs.

842 **BCR/ABL Stimulates WRN to Promote Survival and Genomic Instability**

Artur Slupianek, Tomasz Poplawski, Stanislaw K. Jozwiakowski, Kimberly Cramer, Dariusz Pytel, Ewelina Stoczynska, Michal O. Nowicki, Janusz Blasiak, and Tomasz Skorski

Précis: This study suggests insights into how the BCR/ABL oncogenic kinase pathway induces genomic instability.

852 **miRNA-7 Attenuation in Schwannoma Tumors Stimulates Growth by Upregulating Three Oncogenic Signaling Pathways**

Okay Saydam, Ozlem Senol, Thomas Würdinger, Arda Mizrak, Gokhan Baris Ozdener, Anat O. Stemmer-Rachamimov, Ming Yi, Robert M. Stephens, Anna M. Krichevsky, Nurten Saydam, Gary J. Brenner, and Xandra O. Breakefield

Précis: Findings offer the first microRNA profiling analysis of human schwannoma tumors, revealing critical roles for miR-7 and its targets EGFR, Pak1, and Ack1 in controlling tumor growth.

884 **14-3-3 σ Exerts Tumor-Suppressor Activity Mediated by Regulation of COP1 Stability**

Chun-Hui Su, Ruiying Zhao, Fanmao Zhang, Changju Qu, Bo Chen, Yin-Hsun Feng, Liem Phan, Jian Chen, Hua Wang, Huamin Wang, Sai-Ching J. Yeung, and Mong-Hong Lee

Précis: This mechanistic study reveals how DNA damage controls an important regulator of p53 turnover, with broad implications for carcinogenesis and therapeutic response to DNA damaging agents.

895 **Intracellular CD24 Inhibits Cell Invasion by Posttranscriptional Regulation of BART through Interaction with G3BP**

Keisuke Taniuchi, Isao Nishimori, and Michael A. Hollingsworth

Précis: Mechanistic study reveals how an intracellular molecule that associates with RNA-containing stress granules can inhibit cancer cell invasiveness and metastasis.

906 **MDC1 Cleavage by Caspase-3: A Novel Mechanism for Inactivating the DNA Damage Response during Apoptosis**
Stéphanie Solier and Yves Pommier

Précis: Findings suggest that cleavage of an important mediator of DNA damage checkpoint responses may be a key cellular decision point for engaging repair or cell death pathways.

914 **FUS/TLS Is a Novel Mediator of Androgen-Dependent Cell-Cycle Progression and Prostate Cancer Growth**
Greg N. Brooke, Rachel L. Culley, D. Alwyn Dart, David J. Mann, Luke Gaughan, Stuart R. McCracken, Craig N. Robson, Bradley Spencer-Dene, Simon C. Gamble, Sue M. Powell, Robin Wait, Jonathan Waxman, Marjorie M. Walker, and Charlotte L. Bevan

Précis: Findings address the question of how androgens regulate the cell cycle in prostate cancer, defining the RNA-binding protein FUS as a key link between androgen receptor signalling and cell cycle progression.

925 **Phosphorylation Regulates c-Myc's Oncogenic Activity in the Mammary Gland**
Xiaoyan Wang, Melissa Cunningham, Xiaoli Zhang, Sara Tokarz, Bryan Laraway, Megan Troxell, and Rosalie C. Sears

Précis: c-Myc activity in vivo is differentially regulated by Threonine 58 and Serine 62 phosphorylation.

937 **The Integrin $\alpha_v\beta_{3-5}$ Ligand MFG-E8 Is a p63/p73 Target Gene in Triple-Negative Breast Cancers but Exhibits Suppressive Functions in ER⁺ and erbB2⁺ Breast Cancers**
Chuanwei Yang, Tetsu Hayashida, Nicole Forster, Cuiqi Li, Dejun Shen, Shyamala Maheswaran, Li Chen, Karen S. Anderson, Leif W. Ellisen, Dennis Sgroi, and Emmett V. Schmidt

Précis: A molecule that likely contributes to pathogenesis of aggressive triple-negative breast cancers may have potential use as a blood serum biomarker in breast cancer patients.

946 **Hippo/Mst1 Stimulates Transcription of the Proapoptotic Mediator NOXA in a FoxO1-Dependent Manner**
Karel Valis, Lubomir Prochazka, Evzen Boura, Jaromira Chladova, Tomas Obsil, Jakub Rohlena, Jaroslav Truksa, Lan-Feng Dong, Stephen J. Ralph, and Jiri Neuzil

Précis: Findings document a novel Hippo pathway involved in the promotion of apoptosis in response to anticancer agents.

955 **Reduced SMAD7 Leads to Overactivation of TGF- β Signaling in MDS that Can Be Reversed by a Specific Inhibitor of TGF- β Receptor I Kinase**
Li Zhou, Christine McMahon, Tushar Bhagat, Cristina Alencar, Yiting Yu, Melissa Fazzari, Davendra Sohal, Christoph Heuck, Krishna Gundabolu, Chun Ng, Yongkai Mo, Wa Shen, Amittha Wickrema, Guanghui Kong, Ellen Freidman, Lubomir Sokol, Giannis Mantzaris, Andrea Pellagatti, Jacqueline Boulwood, Leonidas C. Plataniias, Ulrich Steidl, Lei Yan, Jonathan M. Yingling, Michael M. Lahn, Alan List, Markus Bitzer, and Amit Verma

Précis: Myelodysplastic syndrome resulting from activation of TGF- β signaling in hematopoietic cells might be targeted by small molecule inhibitors of the type I TGF- β receptor, currently being evaluated in clinical trials.

964 **Disruption of a Sirt1-Dependent Autophagy Checkpoint in the Prostate Results in Prostatic Intraepithelial Neoplasia Lesion Formation**
Michael J. Powell, Mathew C. Casimiro, Carlos Cordon-Cardo, Xiaohong He, Wen-Shuz Yeow, Chenguang Wang, Peter A. McCue, Michael W. McBurney, and Richard G. Pestell

Précis: A longevity regulator in lower eukaryotes functions as a tumor suppressor in mammalian prostate by inducing autophagy and inhibiting the formation of prostate intraepithelial neoplasia.

976 **Angiocrine Factors Modulate Tumor Proliferation and Motility through EphA2 Repression of Slit2 Tumor Suppressor Function in Endothelium**
Dana M. Brantley-Sieders, Charlene M. Dunaway, Meghana Rao, Sarah Short, Yoonha Hwang, Yandong Gao, Deyu Li, Aixiang Jiang, Yu Shyr, Jane Y. Wu, and Jin Chen

Précis: Findings elucidate a novel mechanism of tumor suppression in which a factor secreted by vascular endothelial cells in tumors can suppress the growth of nearby tumor cells.

PREVENTION AND EPIDEMIOLOGY

988 **Effect of Maternal and Postweaning Folic Acid Supplementation on Mammary Tumor Risk in the Offspring**
Anna Ly, Hanna Lee, Jianmin Chen, Karen K. Y. Sie, Richard Renlund, Alan Medline, Kyoung-Jin Sohn, Ruth Croxford, Lilian U. Thompson, and Young-In Kim

Précis: Findings in a rodent model raise concerns that folic acid supplementation widely employed in pregnant women may significantly increase the risk of mammary tumors in their offspring.

998 **Smad4 Inactivation Promotes Malignancy and Drug Resistance of Colon Cancer**

Panagiotis Papageorgis, Kuanghung Cheng, Sait Ozturk, Yi Gong, Arthur W. Lambert, Hamid M. Abdolmaleky, Jin-Rong Zhou, and Sam Thiagalingam

Précis: Results define a molecular mechanism that explains how loss of function of the tumor suppressor *Smad4* corresponding to LOH at chromosome 18q21 promotes colorectal cancer progression.

1009 **Alpha- versus Beta-Particle Radiolabeled Therapy in a Human Prostate Cancer Model (²¹³Bi-DOTA-PESIN and ²¹³Bi-AMBA versus ¹⁷⁷Lu-DOTA-PESIN)**

Damian Wild, Michael Frischknecht, Hanwen Zhang, Alfred Morgenstern, Frank Bruchertseifer, Julie Boisclair, Anne Provencher-Bolliger, Jean-Claude Reubi, and Helmut R. Maecke

Précis: A short-lived radioactive isoform of bismuth may offer an outstanding tool to improve alpha-emitter radiotherapy of recurrent androgen-independent prostate cancers.

1019 **Three-Dimensional Collagen I Promotes Gemcitabine Resistance in Pancreatic Cancer through MT1-MMP-Mediated Expression of HMG2**

Surabhi Dangi-Garimella, Seth B. Krantz, Morgan R. Barron, Mario A. Shields, Michael J. Heiferman, Paul J. Grippo, David J. Bentrem, and Hidayatullah G. Munshi

Précis: Results show how fibrosis deposition in pancreatic cancer contributes to resistance to standard-of-care chemotherapy, offering a novel mechanistic approach to improve sensitivity and outcomes.

1029 **Dual IGF-I/II-Neutralizing Antibody MEDI-573 Potently Inhibits IGF Signaling and Tumor Growth**

Jin Gao, Jon W. Chesebrough, Susan A. Cartledge, Sally-Ann Ricketts, Leonard Incognito, Margaret Veldman-Jones, David C. Blakey, Mohammad Tabrizi, Bahija Jallal, Pamela A. Trail, Steven Coats, Klaus Bosslet, and Yong S. Chang

Précis: Findings describe a first-in-class therapeutic antibody that effectively targets both IGF-I and IGF-II signaling pathways that contribute to driving many human cancers.

1041 **Targeting the p38 MAPK Pathway Inhibits Irinotecan Resistance in Colon Adenocarcinoma**

Salomé Paillas, Florence Boissière, Frédéric Bibeau, Amélie Denouel, Caroline Mollevi, Annick Causse, Vincent Denis, Nadia Vezzio-Vié, Laetitia Marzi, Cédric Cortijo, Imade Ait-Arsa, Nadav Askari, Philippe Pourquier, Pierre Martineau, Maguy Del Rio, and Céline Gongora

Précis: Mechanistic findings reveal a strategy to reduce resistance to a chemotherapy used widely in colorectal cancer.

1050 **A Mammaglobin-A Targeting Agent for Noninvasive Detection of Breast Cancer Metastasis in Lymph Nodes**

Narges K. Tafreshi, Steven A. Enkemann, Marilyn M. Bui, Mark C. Lloyd, Dominique Abrahams, Amanda S. Huynh, Jongphil Kim, Stephen R. Grobmyer, W. Bradford Carter, Josef Vagner, Robert J. Gillies, and David L. Morse

Précis: This work describes an imaging platform for the noninvasive assessment of breast cancer axillary lymph node status, eliminating the need for operation in patients without nodal involvement.

1060 **ETV6-NTRK3-Mediated Breast Epithelial Cell Transformation Is Blocked by Targeting the IGF1R Signaling Pathway**

Cristina E. Tognon, Aruna M. Somasiri, Valentina E. Evdokimova, Genny Trigo, Evett E. Uy, Nataliya Melnyk, Joan M. Carboni, Marco M. Gottardis, Calvin D. Roskelley, Michael Pollak, and Paul H.B. Sorensen

Précis: Findings in a chimeric oncogene-driven model that mimics the clinical phenotype of human secretory breast cancers encourage the evaluation of IGF1 receptor inhibitors for treatment of this disease, a form of invasive ductal carcinoma.

1071 **Oncogenic Kras Promotes Chemotherapy-Induced Growth Factor Shedding via ADAM17**

Sandra Van Schaeybroeck, Joan N. Kyula, Audrey Fenton, Catherine S. Fenning, Takehiko Sasazuki, Senji Shirasawa, Daniel B. Longley, and Patrick G. Johnston

Précis: Findings suggest that colorectal tumors driven by mutant KRAS may be susceptible to MEK inhibitors in clinical development due to disruption of an extracellular protease pathway that controls receptor shedding.

1081 **Multiple Mutations and Bypass Mechanisms Can Contribute to Development of Acquired Resistance to MET Inhibitors**

Jie Qi, Michele A. McTigue, Andrew Rogers, Eugene Lifshits, James G. Christensen, Pasi A. Jänne, and Jeffrey A. Engelman

Précis: Findings underscore the capability of cancer cells to simultaneously develop drug resistance by several mechanisms, highlighting the daunting challenges faced by targeted strategies for cancer therapy.

1092 **Hedgehog Signaling Drives Cellular Survival in Human Colon Carcinoma Cells**

Tapati Mazumdar, Jennifer DeVecchio, Ting Shi, Janay Jones, Akwasi Agyeman, and Janet A. Houghton

Précis: This study of the critical role of the Hedgehog pathway in cellular survival in colon cancer suggests an approach to target activator functions of downstream Gli transcription factors as an anticancer strategy in colon cancer.

1103 **EGFR Nuclear Translocation Modulates DNA Repair following Cisplatin and Ionizing Radiation Treatment**

Gianmaria Liccardi, John A. Hartley, and Daniel Hochhauser

Précis: Understanding the mechanism of EGFR modulation of DNA repair and EGFR subcellular localization will improve the design of successful molecular targeting therapies.

1135 **NKX2.2 Suppresses Self-Renewal of Glioma-Initiating Cells**

Teruyuki Muraguchi, Shingo Tanaka, Daisuke Yamada, Akira Tamase, Mitsutoshi Nakada, Hideo Nakamura, Takayuki Hoshii, Takako Ooshio, Yuko Tadokoro, Kazuhito Naka, Yasushi Ino, Tomoki Todo, Jun-ichi Kuratsu, Hideyuki Saya, Jun-ichiro Hamada, and Atsushi Hirao

Précis: This study defines a homeodomain transcription factor essential for oligodendroglial differentiation as a key conserved regulator of stem cell properties in the most aggressive form of brain cancer.

1146 **The Novel Metastasis Promoter Merm1/Wbscr22 Enhances Tumor Cell Survival in the Vasculature by Suppressing Zac1/p53-Dependent Apoptosis**

Youya Nakazawa, Hiroyuki Arai, and Naoya Fujita

Précis: A novel metastasis promoting gene with structural similarity to methyltransferases may act by limiting p53-mediated apoptosis in cancer cells after extravasion into the vasculature, suggesting a novel strategy to limit metastatic progression.

1156 **EphB3 Is Overexpressed in Non-Small-Cell Lung Cancer and Promotes Tumor Metastasis by Enhancing Cell Survival and Migration**

Xiao-Dan Ji, Guo Li, Yu-Xiong Feng, Jiang-Sha Zhao, Jing-Jing Li, Zhi-Jian Sun, Shuo Shi, Yue-Zhen Deng, Jun-Feng Xu, Yin-Qiu Zhu, H. Phillip Koeffler, Xiang-Jun Tong, and Dong Xie

Précis: Findings offer initial proof-of-concept for an important cell-cell interaction molecule as a potential theranostic target in lung cancer.

TUMOR AND STEM CELL BIOLOGY

1115 **Notch3 Activation Promotes Invasive Glioma Formation in a Tissue Site-Specific Manner**

Tarran J. Pierfelice, Karisa C. Schreck, Louis Dang, Laura Asnaghi, Nicholas Gaiano, and Charles G. Eberhart

Précis: Findings identify distinct capabilities of the Notch receptors in initiation of CNS tumors, where Notch antagonists may offer important new therapeutic options.

1126 **hPuf-A/KIAA0020 Modulates PARP-1 Cleavage upon Genotoxic Stress**

Hao-Yen Chang, Chi-Chen Fan, Po-Chen Chu, Bo-En Hong, Hyeon Jeong Lee, and Mau-Sun Chang

Précis: Mechanistic findings suggest that a little understood nucleolar protein may contribute significantly to genotoxic stress response and chemotherapy sensitivity in cancer cells.

1167 **Δ Np63 α Confers Tumor Cell Resistance to Cisplatin through the AKT1 Transcriptional Regulation**

Tanusree Sen, Nilkantha Sen, Mariana Brait, Shahnaz Begum, Aditi Chatterjee, Mohammad Obaidul Hoque, Edward Ratovitski, and David Sidransky

Précis: Findings reveal a mechanism of resistance to platin drugs in ovarian cancer with implications of a rationale to evaluate AKT inhibitors presently in clinical development as a tactic to reverse or prevent resistance and extend patient survival.

1177 **Nm23-H1 Indirectly Promotes the Survival of Acute Myeloid Leukemia Blast Cells by Binding to More Mature Components of the Leukemic Clone**

Andrew J. Lilly, Farhat L. Khanim, Rachel E. Hayden, Quang T. Luong, Mark T. Drayson, and Christopher M. Bunce

Précis: Discovery of a signaling process between immature and more mature leukemia cell subpopulations suggests new insights into how the emergence of heterogeneity in a tumor clone may affect how it expands.

1187 **Human Papillomavirus E7 Enhances Hypoxia-Inducible Factor 1-Mediated Transcription by Inhibiting Binding of Histone Deacetylases**

Jason M. Bodily, Kavi P.M. Mehta, and Laimonis A. Laimins

Précis: The ability of HPV E7 oncoprotein to displace histone deacetylases from HIF-1 transcription complexes may represent an important new aspect of its pathogenic functions.

CORRECTIONS

1197 **Correction: Anti-Vascular Endothelial Growth Factor Therapies as a Novel Therapeutic Approach to Treating Neurofibromatosis-Related Tumors**

1198 **Correction: Correlating Phosphatidylinositol 3-Kinase Inhibitor Efficacy with Signaling Pathway Status: *In silico* and Biological Evaluations**

1199 **Correction: Intrinsic Cooperation between p16^{INK4a} and p21^{Waf1/Cip1} in the Onset of Cellular Senescence and Tumor Suppression *In vivo***

1200 **Correction: Androgen-Induced *TMPRSS2:ERG* Fusion in Nonmalignant Prostate Epithelial Cells**

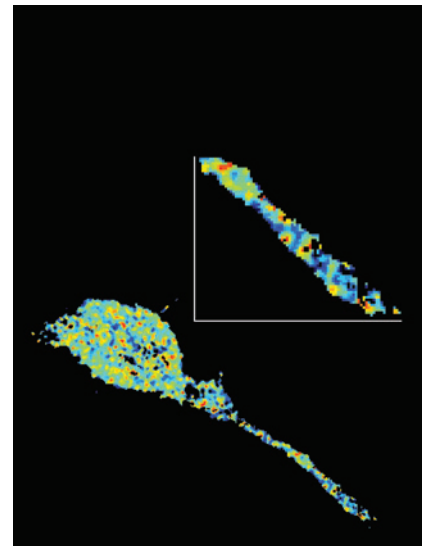
RETRACTION

1196 **Retraction: The Chemokine Receptor CXCR6 and Its Ligand CXCL16 Are Expressed in Carcinomas and Inhibit Proliferation**

Janneke Ogink, Bas Kreike, Dimitry Nuyten, Karin E. de Visser, and Ed Roos

ABOUT THE COVER

Spatial regulation of molecules within the cell plays a vital role in the biological outcome of key signaling events. Here, Timpson and colleagues have assessed at subcellular resolution the spatial regulation of RhoA activity in primary pancreatic ductal adenocarcinoma (PDAC) cells during invasion within a three-dimensional organotypic matrix and in live animals. Using multiphoton-based FLIM-FRET, they observe a discrete fraction of high RhoA activity at the poles of invading cells that is sensitive to drug treatment and correlates with invasion *in vivo*. The cover image represents a cell expressing a GFP-RFP Raichu-RhoA reporter and the corresponding life-time map of RhoA activity within mutant p53R172H PDAC cells during invasion. This work highlights that RhoA is not only necessary for invasion but that precise spatial regulation may govern invasion efficiency *in vivo*. For more details, see the article by Timpson and colleagues on page 747 of this issue.



Cancer Research

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