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Cancer Research

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BREAKING ADVANCES

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- 3901 **The Microculture-Kinetic (MiCK) Assay: The Role of a Drug-Induced Apoptosis Assay in Drug Development and Clinical Care**
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PRIORITY REPORTS

- 3906 **Primary Tumor Hypoxia Recruits CD11b⁺/Ly6C^{med}/Ly6G⁺ Immune Suppressor Cells and Compromises NK Cell Cytotoxicity in the Premetastatic Niche**
Jaclyn Sceneay, Melvyn T. Chow, Anna Chen, Heloise M. Halse, Christina S.F. Wong, Daniel M. Andrews, Erica K. Sloan, Belinda S. Parker, David D. Bowtell, Mark J. Smyth, and Andreas Möller
Précis: This striking study shows how hypoxia in primary tumors, which is known to be associated with poor prognosis, leads to changes that can promote immune escape in the premetastatic niche of distal organs, creating a prometastatic environment.
- 3912 **VEGF Exerts an Angiogenesis-Independent Function in Cancer Cells to Promote Their Malignant Progression**
Ying Cao, Guangqi E, Enfeng Wang, Krishnendu Pal, Shamit K. Dutta, Dafna Bar-Sagi, and Debabrata Mukhopadhyay
Précis: VEGF expressed by cancer cells not only attracts blood vasculature but also acts directly on cancer cells by binding neuropilin-1 receptors there to cause cancer cell de-differentiation, contributing to malignant progression in a totally new way that has not been appreciated previously.

MICROENVIRONMENT AND IMMUNOLOGY

- 3919 **Neutrophils Promote Liver Metastasis via Mac-1–Mediated Interactions with Circulating Tumor Cells**
Jonathan D. Spicer, Braedon McDonald, Jonathan J. Cools-Lartigue, Simon C. Chow, Betty Giannias, Paul Kubes, and Lorenzo E. Ferri
Précis: This study describes a novel immune-modulatory mechanism involving neutrophils, which interact with circulating tumor cells in the blood to facilitate metastasis.
- 3928 **BRAF Inhibitor Vemurafenib Improves the Antitumor Activity of Adoptive Cell Immunotherapy**
Richard C. Koya, Stephen Mok, Nicholas Otte, Kevin J. Blacketer, Begonya Comin-Anduix, Paul C. Tumeh, Aspram Minasyan, Nicholas A. Graham, Thomas G. Graeber, Thinle Chodon, and Antoni Ribas
Précis: Targeted therapeutics that produce robust clinical responses are likely benefiting from inherent adjuvant effects that degrade immune escape, a feature that could be leveraged most effectively by combinatorial uses in settings such as that described here.
- 3938 **Chronic Autophagy Is a Cellular Adaptation to Tumor Acidic pH Microenvironments**
Jonathan W. Wojtkowiak, Jennifer M. Rothberg, Virendra Kumar, Karla J. Schramm, Edward Haller, Joshua B. Proemsey, Mark C. Lloyd, Bonnie F. Sloane, and Robert J. Gillies
Précis: An acidic tumor microenvironment induces a prolonged autophagic response necessary for tumor cell survival under acidic conditions commonly observed in solid tumors.
- 3948 **The Human TLR Innate Immune Gene Family Is Differentially Influenced by DNA Stress and p53 Status in Cancer Cells**
Maria Shatz, Daniel Menendez, and Michael A. Resnick
Précis: Toll-like receptors, which detect both infection and sterile tissue damage, are targets for adjuvant immune therapies, including on cancer cells, where p53 and chromosome status may affect their signaling outputs.

3958

Trifunctional Bispecific Antibodies Induce Tumor-Specific T Cells and Elicit a Vaccination Effect

Nina Eissler, Peter Ruf, Josef Mysliwicz, Horst Lindhofer, and Ralph Mocikat

Précis: T-cell-activating signals that can be triggered by trifunctional bispecific antibodies make them superior for eliminating tumor cells due to their ability to induce polyvalent protective T-cell responses against tumor-derived peptides.

3967

Immunogenic Tumor Cell Death Induced by Chemoradiotherapy in Patients with Esophageal Squamous Cell Carcinoma

Yoshiyuki Suzuki, Kousaku Mimura, Yuya Yoshimoto, Mitsuaki Watanabe, Yu Ohkubo, Shinichirou Izawa, Kazutoshi Murata, Hideki Fujii, Takashi Nakano, and Koji Kono

Précis: Findings demonstrate that chemoradiation induces tumor-antigen specific T-cell responses in patients with esophageal squamous cell carcinoma, providing proof-of-principle for immunogenic cell death.

3977

The Proinflammatory Myeloid Cell Receptor TREM-1 Controls Kupffer Cell Activation and Development of Hepatocellular Carcinoma

Juan Wu, Jiaqi Li, Rosalba Salcedo, Nahid F. Mivechi, Giorgio Trinchieri, and Anatolij Horuzsko

Précis: Findings reveal a pivotal mediator of chronic inflammatory processes in a myeloid-like cell type of the liver that underpins the development and progression of liver cancer.

3987

Opposing Roles for IL-23 and IL-12 in Maintaining Occult Cancer in an Equilibrium State

Michele W. L. Teng, Matthew D. Vesely, Helene Duret, Nicole McLaughlin, Jennifer E. Towne, Robert D. Schreiber, and Mark J. Smyth

Précis: Findings illustrate opposing roles for the important cytokines IL-23 and IL-12 in determining the outgrowth versus dormancy of occult neoplasia, implying long-term cancer risks of using IL-12/23p40 antibodies for clinical treatment of autoimmune disorders.

3997

Neogenesis of Lymphoid Structures and Antibody Responses Occur in Human Melanoma Metastases

Arcadi Cipponi, Marjorie Mercier, Teofila Seremet, Jean-François Baurain, Ivan Théate, Joost van den Oord, Marguerite Stas, Thierry Boon, Pierre G. Coulie, and Nicolas van Baren

Précis: Striking findings show the ectopic development of functional lymphoid structures within melanoma metastases, suggesting that tumors not only direct tolerizing adaptive immune responses in draining lymph nodes but also do so directly within the tumor microenvironment itself.

MOLECULAR AND CELLULAR PATHOBIOLOGY

4008

Cervical Cancers Require the Continuous Expression of the Human Papillomavirus Type 16 E7 Oncoprotein Even in the Presence of the Viral E6 Oncoprotein

Sean F. Jabbar, Soyeong Park, Johannes Schweizer, Marthe Berard-Bergery, Henry C. Pitot, Denis Lee, and Paul F. Lambert

Précis: This study demonstrates that cervical cancer progression depends on continuous expression of human papillomavirus E7 oncoprotein, suggesting that it is a legitimate target for treatment and prevention of cervical cancer.

4017

A Zebrafish Model to Study and Therapeutically Manipulate Hypoxia Signaling in Tumorigenesis

Kirankumar Santhakumar, Emma C. Judson, Philip M. Elks, Sarah McKee, Stone Elworthy, Ellen van Rooijen, Sarah S. Walmsley, Stephen A. Renshaw, Simon S. Cross, and Fredericus J.M. van Eeden

Précis: This study describes a novel zebrafish model that might speed the identification and development of strategies to blunt the effects of hypoxia-induced HIF activation, which is widely implicated in malignant progression and therapeutic resistance in solid tumors.

4028

The Retinoblastoma Gene Undergoes Rearrangements in BRCA1-Deficient Basal-like Breast Cancer

Göran Jönsson, Johan Staaf, Johan Vallon-Christersson, Markus Ringnér, Sofia K. Gruvberger-Saal, Lao H. Saal, Karolina Holm, Cecilia Hegardt, Adalgeir Arason, Rainer Fagerholm, Camilla Persson, Dorte Grabau, Ellinor Johnsson, Kristina Lövgren, Linda Magnusson, Päivi Heikkilä, Bjarni A. Agnarsson, Oskar T. Johannsson, Per Malmström, Mårten Fernö, Håkan Olsson, Niklas Loman, Heli Nevanlinna, Rosa B. Barkardottir, and Åke Borg

Précis: Many aggressive breast cancers of the basal-like subtype that are deficient in BRCA1 also appear to be deficient in Rb tumor suppressor function, with potential therapeutic implications for the application of Cdk inhibitors in this tumor subset.

4037

MiR-96 Downregulates REV1 and RAD51 to Promote Cellular Sensitivity to Cisplatin and PARP Inhibition

Yemin Wang, Jen-Wei Huang, Philamer Calses, Christopher J. Kemp, and Toshiyasu Taniguchi

Précis: Findings define the function of a microRNA in cancer cells that downregulates both a homologous recombination factor and a translesion DNA synthesis polymerase, perhaps offering a generalized strategy to improve the efficacy of cytotoxic chemotherapy in advanced cancers.

4047	<p>Neuropilin-1 Stimulates Tumor Growth by Increasing Fibronectin Fibril Assembly in the Tumor Microenvironment</p> <p>Usman Yaqoob, Sheng Cao, Uday Shergill, Kumaravelu Jagavelu, Zhimin Geng, Meng Yin, Thiago M. de Assuncao, Ying Cao, Anna Szabolcs, Snorri Thorgeirsson, Martin Schwartz, Ju Dong Yang, Richard Ehman, Lewis Roberts, Debabrata Mukhopadhyay, and Vijay H. Shah</p> <p><i>Précis:</i> A protein that functions as a VEGF receptor may also alter extracellular matrix assembly, with implications for how to target myofibroblasts that express it as a strategy to therapeutically reprogram the tumor microenvironment.</p>	4085	<p>NAC1 Is an Actin-Binding Protein That Is Essential for Effective Cytokinesis in Cancer Cells</p> <p>Kai Lee Yap, Stephanie I. Fraley, Michelle M. Thiaville, Natini Jinawath, Kentaro Nakayama, Jianlong Wang, Tian-Li Wang, Denis Wirtz, and Ie-Ming Shih</p> <p><i>Précis:</i> This study reveals an actin-binding function for a protein previously implicated in transcriptional regulation, perhaps providing a novel foundation to develop unique actin-targeting agents as a generalized strategy for cancer therapy.</p>
4060	<p>LRP1B Deletion in High-Grade Serous Ovarian Cancers Is Associated with Acquired Chemotherapy Resistance to Liposomal Doxorubicin</p> <p>Prue A. Cowin, Joshy George, Sian Fereday, Elizabeth Loehrer, Peter Van Loo, Carleen Cullinane, Dariush Etamadmoghadam, Sarah Ftouni, Laura Galletta, Michael S. Anglesio, Joy Hendley, Leanne Bowes, Karen E. Sheppard, Elizabeth L. Christie, Australian Ovarian Cancer Study, Richard B. Pearson, Paul R. Harnett, Viola Heinzelmann-Schwarz, Michael Friedlander, Orla McNally, Michael Quinn, Peter Campbell, Anna deFazio, and David D.L. Bowtell</p> <p><i>Précis:</i> This extensive genomics study of patients with the most common form of ovarian cancer, which reveals the daunting extent of intratumoral heterogeneity present in different lesions from the same patient, identifies a lipid transport molecule that acts as a positive modifier of a form of acquired drug resistance that occurs commonly in patients with relapsed disease.</p>	4097	<p>Caveolin-1 Increases Aerobic Glycolysis in Colorectal Cancers by Stimulating HMGA1-Mediated GLUT3 Transcription</p> <p>Tae-Kyu Ha, Nam-Gu Her, Min-Goo Lee, Byung-Kyu Ryu, Jin-Hee Lee, Jikhyon Han, Seong-In Jeong, Min-Ju Kang, Nam-Hoon Kim, Hyo-Jong Kim, and Sung-Gil Chi</p> <p><i>Précis:</i> Findings suggest how a key regulator of lipid raft formation acts to promote aerobic glycolysis in colon cancer cells, providing a mechanistic basis to understanding its oncogenic function in certain human cancers.</p>
4074	<p>Alternate Splicing of the p53 Inhibitor HDMX Offers a Superior Prognostic Biomarker than p53 Mutation in Human Cancer</p> <p>Kristiaan Lenos, Anna M. Grawenda, Kirsten Lodder, Marieke L. Kuijjer, Amina F.A.S. Teunisse, Emmanouela Repapi, Lukasz F. Grochola, Frank Bartel, Pancras C.W. Hogendoorn, Peter Wuerl, Helge Taubert, Anne-Marie Cleton-Jansen, Gareth L. Bond, and Aart G. Jochemsen</p> <p><i>Précis:</i> Findings advance understanding of p53 control and suggest a broadly useful biomarker to personalize therapeutic interventions in treatment of many types of human cancer.</p>	4110	<p>Critical Function for Nuclear Envelope Protein TMEM209 in Human Pulmonary Carcinogenesis</p> <p>Takashi Fujitomo, Yataro Daigo, Koichi Matsuda, Koji Ueda, and Yusuke Nakamura</p> <p><i>Précis:</i> Findings identify a critical role for a tissue-selective nuclear envelope protein in lung cancer, which by promoting c-Myc expression may offer a novel disease-selective therapeutic target in this setting.</p>
		4119	<p>Resistance of Glioblastoma-Initiating Cells to Radiation Mediated by the Tumor Microenvironment Can Be Abolished by Inhibiting Transforming Growth Factor-β</p> <p>Matthew E. Hardee, Ariel E. Marciscano, Christina M. Medina-Ramirez, David Zagzag, Ashwatha Narayana, Scott M. Lanning, and Mary Helen Barcellos-Hoff</p> <p><i>Précis:</i> This study offers immediate translational impact by suggesting that TGF-β inhibitors under study might be applied combinatorially to heighten the responsiveness of glioblastoma to radiotherapy, which is used widely as a standard of care for treatment but with limited efficacy.</p>
		4130	<p>MLK3 Regulates Paxillin Phosphorylation in Chemokine-Mediated Breast Cancer Cell Migration and Invasion to Drive Metastasis</p> <p>Jian Chen and Kathleen A. Gallo</p> <p><i>Précis:</i> Important mechanistic findings suggest a potentially important new therapeutic target in metastatic breast cancer.</p>

4141 **Perturbation of Rb, p53, and Brca1 or Brca2 Cooperate in Inducing Metastatic Serous Epithelial Ovarian Cancer**

Ludmila Szabova, Chaoying Yin, Sujata Bupp, Theresa M. Guerin, Jerome J. Schlomer, Deborah B. Householder, Maureen L. Baran, Ming Yi, Yurong Song, Wenping Sun, Jonathan E. McDunn, Philip L. Martin, Terry Van Dyke, and Simone Difilippantonio

Précis: This study describes novel murine models of metastatic ovarian cancer that histologically resemble their human counterparts, offering useful tools for pathobiologic and preclinical therapeutic studies.

4178 **Mithramycin Represses Basal and Cigarette Smoke–Induced Expression of ABCG2 and Inhibits Stem Cell Signaling in Lung and Esophageal Cancer Cells**

Mary Zhang, Aarti Mathur, Yuwei Zhang, Sichuan Xi, Scott Atay, Julie A. Hong, Nicole Datrice, Trevor Upham, Clinton D. Kemp, R. Taylor Ripley, Gordon Wiegand, Itzak Avital, Patricia Fetsch, Haresh Mani, Daniel Zlott, Robert Robey, Susan E. Bates, Xinmin Li, Mahadev Rao, and David S. Schrupp

Précis: Targeting growth factor receptors in cancer may be ill advised in some patients, because alternative splice isoforms in the tumor can confer different functions depending on whether the receptor is expressed in tumor cells versus tumor stromal cells.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

4154 **Tankyrase and the Canonical Wnt Pathway Protect Lung Cancer Cells from EGFR Inhibition**

Matias Casás-Selves, Jihye Kim, Zhiyong Zhang, Barbara A. Helfrich, Dexiang Gao, Christopher C. Porter, Hannah A. Scarborough, Paul A. Bunn Jr., Daniel C. Chan, Aik Choon Tan, and James DeGregori

Précis: A genome-wide short hairpin RNA screen identifies a role for the canonical Wnt signaling pathway in the maintenance of NSCLC cells during EGFR inhibition and suggests that simultaneous targeting may improve clinical outcome in lung cancer patients.

4165 **Nanobody-Based Targeting of the Macrophage Mannose Receptor for Effective In Vivo Imaging of Tumor-Associated Macrophages**

Kiavash Movahedi, Steve Schoonooghe, Damya Laoui, Isabelle Houbracken, Wim Waelput, Karine Breckpot, Luc Bouwens, Tony Lahoutte, Patrick De Baetselier, Geert Raes, Nick Devoogdt, and Jo A. Van Ginderachter

Précis: This study offers a broadly applicable tool to visualize tumor-associated macrophages, which are of great importance in the tumor microenvironment to malignant progression and therapeutic response.

4193 **BCL2 Suppresses PARP1 Function and Nonapoptotic Cell Death**

Chaitali Dutta, Tovah Day, Nadja Kopp, Diederik van Bodegom, Matthew S. Davids, Jeremy Ryan, Liat Bird, Naveen Kommajosyula, Oliver Weigert, Akinori Yoda, Hua Fung, Jennifer R. Brown, Geoffrey I. Shapiro, Anthony Letai, and David M. Weinstock

Précis: BCL2-expressing cancer cells resistant to apoptosis can be killed by BH3 mimetics that target the interaction between BCL2 and a DNA repair protein.

4204 **HG-829 Is a Potent Noncompetitive Inhibitor of the ATP-Binding Cassette Multidrug Resistance Transporter ABCB1**

Gisela Caceres, Robert W. Robey, Lubomir Sokol, Kathy L. McGraw, Justine Clark, Nicholas J. Lawrence, Said M. Sebt, Michael Wiese, and Alan F. List

Précis: Results offer preclinical validation of a highly effective new inhibitor of the P-glycoprotein that is widely responsible for acquired clinical resistance to cytotoxic chemotherapy, with significant therapeutic promise for treating many types of multidrug-resistant malignancies.

4214 **Carbonyl Reductase 1 Offers a Novel Therapeutic Target to Enhance Leukemia Treatment by Arsenic Trioxide**

Miran Jang, Yeonghwan Kim, Hyeran Won, Sangbin Lim, Jyothi K.R. Amarjargal Dashdorj, Yoo Hong Min, Si-Young Kim, Kevan M. Shokat, Joohun Ha, and Sung Soo Kim

Précis: This study shows how to extend the applications of arsenic trioxide for improving treatment of many types of leukemia.

- 4225 **CDK Inhibitors Upregulate BH3-Only Proteins to Sensitize Human Myeloma Cells to BH3 Mimetic Therapies**
Shuang Chen, Yun Dai, Xin-Yan Pei, Jennifer Myers, Li Wang, Lora B. Kramer, Mandy Garnett, Daniella M. Schwartz, Florence Su, Gary L. Simmons, Justin D. Richey, Dustin G. Larsen, Paul Dent, Robert Z. Orlowski, and Steven Grant

***Précis:** This study offers preclinical proof-of-concept for a therapeutic combination of pan-CDK inhibitors with pan-BH3 mimetics in patients with refractory hematologic malignancies.*

- 4262 **Dysfunction of Nucleus Accumbens-1 Activates Cellular Senescence and Inhibits Tumor Cell Proliferation and Oncogenesis**
Yi Zhang, Yan Cheng, Xingcong Ren, Tsukasa Hori, Kathryn J. Huber-Keener, Li Zhang, Kai Lee Yap, David Liu, Lisa Shantz, Zheng-Hong Qin, Suping Zhang, Jianrong Wang, Hong-Gang Wang, Ie-Ming Shih, and Jin-Ming Yang

***Précis:** This study offers new insights into mechanisms of senescence and how its bypass is important for tumor development and progression.*

TUMOR AND STEM CELL BIOLOGY

- 4238 **Bone-Derived IGF Mediates Crosstalk between Bone and Breast Cancer Cells in Bony Metastases**
Toru Hiraga, Akira Myoui, Nobuyuki Hashimoto, Akira Sasaki, Kenji Hata, Yoshihiro Morita, Hideki Yoshikawa, Clifford J. Rosen, Gregory R. Mundy, and Toshiyuki Yoneda

***Précis:** This study offers new insights into the little understood process of bone metastasis by breast cancers, with implications for the application of IGF antagonists to arrest this debilitating and deadly pathway of cancer progression.*

- 4250 **TRPM7 Is Required for Breast Tumor Cell Metastasis**
Jeroen Middelbeek, Arthur J. Kuipers, Linda Henneman, Daan Visser, Ilse Eidhof, Remco van Horsen, Bé Wieringa, Sander V. Canisius, Wilbert Zwart, Lodewyk F. Wessels, Fred C.G.J. Sweep, Peter Bult, Paul N. Span, Frank N. van Leeuwen, and Kees Jalink

***Précis:** Findings implicate a calcium channel that is overexpressed in breast cancer cells as a critical mediator of metastasis, with implications for developing more effective antimetastatic drugs.*

- 4276 **BMP4 Administration Induces Differentiation of CD133⁺ Hepatic Cancer Stem Cells, Blocking Their Contributions to Hepatocellular Carcinoma**
Lixing Zhang, Hefen Sun, Fangyu Zhao, Ping Lu, Chao Ge, Hong Li, Helei Hou, Mingxia Yan, Taoyang Chen, Guoping Jiang, Haiyang Xie, Ying Cui, Xiaowu Huang, Jia Fan, Ming Yao, and Jinjun Li

***Précis:** High-dose treatment with a TGF- β -related growth factor can block the contribution of liver cancer stem cells to malignant development and chemoresistance, perhaps offering a broad-spectrum therapeutic strategy in this disease.*

CORRECTION

- 4286 **Correction: Scaling Laws for Plasma Concentrations and Tolerable Doses of Anticancer Drugs**

ABOUT THE COVER

Because of the torturous vasculature of solid tumors and the diffusion limitations of oxygen, cancer cells routinely encounter hypoxic conditions. Immunohistochemistry of pimonidazole hydrochloride, a nitroimidazole with hypoxic selectivity, identifies a ring of cells (brown) that define the hypoxic border between well-oxygenated and necrotic tissue. Cancer cells depend on glycolysis to meet energetic demands when deprived of oxygen; as a result, these hypoxic regions are expected to be acidic. In response to acidic environments, cells exhibit chronic elevated autophagic activity, a phenotype that is partially reversible *in vivo* following buffer therapy with sodium bicarbonate. For details, see article by Wojtkowiak and colleagues on page 3938.

