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#### Cancer Research

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**Précis:** Findings establish mechanisms by which a growth inhibitory steroid can inhibit medulloblastoma, a common and aggressive pediatric tumor. Findings suggest the possibility of a mechanism-based, serum-based diagnostic assay for detecting pancreatic cancer. A strategy to target extracellular matrix deposited by cancer cells can selectively enhance the killing effects of radiation.
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**MOLECULAR AND CELLULAR PATHOBIOLOGY**
Phosphorylation and Activation of Cell Division Cycle Associated 5 by Mitogen-Activated Protein Kinase Play a Crucial Role in Human Lung Carcinogenesis

Minh-Hue Nguyen, Junkichi Koinuma, Koji Ueda, Tomoo Ito, Eiju Tsuchiya, Yusuke Nakamura, and Yataro Daigo

Précis: Findings offer a mechanistic rationale for a new approach for lung cancer treatment with small molecule inhibitors of the ERK kinase-substrate pathway that is aberrantly activated in lung cancer cells.

Altered Dynamics of Intestinal Cell Maturation in Apc1638N/+ Mice

Donghai Wang, Rossanna C. Pezo, Georgia Corner, Cristina Sison, Martin L. Lesser, Shuilesh M. Shenoy, John M. Mariadason, Robert H. Singer, and Leonard H. Augenlicht

Précis: In situ imaging of transcription sites in single intestinal cells along villi reveal that key pathways of transcriptional control are far more dynamic than previously appreciated in maintaining tissue homeostasis and organization that are disrupted during tumorigenesis.

Taspase1 Functions as a Non-Onco Gene Addiction Protease that Coordinates Cancer Cell Proliferation and Apoptosis

David Y. Chen, Han Liu, Shugaku Takeda, Ho-Chou Tu, Satoru Sasagawa, Brian A. Van Tine, Dongsu Lu, Emily H-Y. Cheng, and James J-D. Hsieh

Précis: Findings rationalize therapeutic interest in developing inhibitors of a druggable protease that may have a selective role in supporting cancer cell proliferation and survival.

ADAM17 Regulates Epidermal Growth Factor Receptor Expression through the Activation of Notch1 in Non–Small Cell Lung Cancer


High-Mobility Group A1 Proteins Regulate p53-Mediated Transcription of Bel-2 Gene

Francesco Esposito, Mara Tornincasa, Paolo Chieffi, Ivana De Martino, Giovanna Maria Pierantoni, and Alfredo Fusco

Précis: Findings identify a potentially important, broad acting new mechanism of anti-apoptosis in cancer.

Poly(ADP-Ribose) Polymerase Is Hyperactivated in Homologous Recombination–Defective Cells

Ponnari Gottipati, Barbara Vischioni, Niklas Schultz, Joyce Solomon, Helen E. Bryant, Tatjana Djureimovic, Natalia Issaeva, Kate Sleeth, Ricky A. Sharma, and Thomas Hellday

Précis: Mechanistic findings suggest insights into how PARP inhibitors kill BRCA1/2-defective cancer cells and how to identify tumors that are sensitive to this new class of experimental clinical therapeutics.

High Wnt Signaling Represses the Pro-apoptotic Proteoglycan Syndecan-2 in Osteosarcoma Cells

François-Xavier Dieudonné, Allison Marion, Eric Haÿ, Pierre Jacques Marie, and Dominique Modrowski

Précis: Novel mechanistic insights into an important oncogenic pathway of Wnt signaling in osteosarcoma are revealed.

Confirmation of Linkage to and Localization of Familial Colon Cancer Risk Haplotype on Chromosome 9q22

Courtney Gray-McGuire, Kishore Guda, Indra Adrianto, Chee Paul Lin, Leanna Natale, John D. Potter, Polly Newcomb, Elizabeth M. Poole, Cornelia M. Ulrich, Noralane Lindor, Ellen L. Goode, Brooke L. Fridley, Robert Jenkins, Loic Le Marchand, Graham Casey, Robert Haile, John Hopper, Mark Jenkins, Joanne Young, Daniel Buchanan, Steve Gallinger, Mark Adams, Susan Lewis, Joseph Willis, Robert Elston, Sanford D. Markowitz, and Georgia L. Wiesner

Précis: This linkage and association study confirms and markedly refines the position of a 9q susceptibility locus for familial colon neoplasia.

Colorectal Cancer Incidence Trends in the United States and United Kingdom: Evidence of Right- to Left-Sided Biological Gradients with Implications for Screening

Rafael Meza, Jihyoun Jeon, Andrew G. Renehan, and E. Georg Luebeck

Précis: Biomathematical models of incidence trends in colorectal cancer argue for age, sex and site-directed approaches to population screening.
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<td>Yiyu Dong, Aimin Li, Jianbo Wang, Jason D. Weber, and Loren S. Michel</td>
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Hong Yang, Brian Higgins, Kenneth Kolinsky, Kathryn Packman, Zenaida Go, Raman Iyer, Stanley Kolis, Sylvia Zhao, Richard Lee, Joseph F. Grippo, Kathleen Schostack, Mary Ellen Simcox, David Heimbrook, Gideon Bollag, and Fei Su

Précis: Striking first report of the preclinical efficacy of a mutant Raf kinase-specific inhibitor augurs promise for its ongoing clinical development.

TUMOR AND STEM CELL BIOLOGY

5528 The Polycomb Group Protein Bmi-1 Is Essential for the Growth of Multiple Myeloma Cells
Zainab Jagani, Dmitri Wiederschain, Alice Loo, Dan He, Rebecca Mosher, Paul Fordjour, John Monahan, Michael Morrissey, Yung-Mae Yao, Christoph Lengauer, Markus Warmuth, William R. Sellers, and Marion Dorsch

Précis: An oncogenic Polycomb group protein found to be a critical driver in multiple myelomas, one of the most deadly blood cancers.

5539 Effects of Ionizing Radiation on Self-Renewal and Pluripotency of Human Embryonic Stem Cells
Kitchener D. Wilson, Ning Sun, Mei Huang, Wendy Y. Zhang, Andrew S. Lee, Zongjin Li, Shan X. Wang, and Joseph C. Wu

Précis: Human embryonic stem cells maintain their tumorigenic potential even after significant ionizing radiation exposures.

5549 A Mouse Model of Melanoma Driven by Oncogenic KRAS
Carla Milagre, Nathalie Dhomen, Felipe C. Geyer, Robert Hayward, Maryou Lambros, Jorge S. Reis-Filho, and Richard Marais

Précis: Mouse model findings offer evidence that KRAS activation may be a founder event in melanoma.

5558 Shedding of RANKL by Tumor-Associated MT1-MMP Activates Src-Dependent Prostate Cancer Cell Migration
Aaron L. Sabbota, Hyeong-Reh Choi Kim, Xiaoning Zhe, Rafael Fridman, R. Daniel Bonfil, and Michael L. Cher

Précis: Findings establish a mechanism of prostate cancer cell invasion that is enhanced by a protease-directed autocrine loop amenable to therapeutic attack.

5567 Extracellular Protease ADAMTS9 Suppresses Esophageal and Nasopharyngeal Carcinoma Tumor Formation by Inhibiting Angiogenesis

Précis: Tumor suppressive effects of an extracellular protease implicated in aerodigestive cancers are mediated by anti-angiogenic effects.

5577 Frequent Attenuation of the WWOX Tumor Suppressor in Osteosarcoma Is Associated with Increased Tumorigenicity and Aberrant RUNX2 Expression
Kyle C. Kurek, Sara Del Mare, Zaidoun Salah, Suhail Abdeen, Hussain Sadiq, Suk-hee Lee, Eugenio Gaudio, Nicola Zanesi, Kevin B. Jones, Barry DeYoung, Gail Amir, Mark Gebhardt, Matthew Warman, Gary S. Stein, Janet L. Stein, Jane B. Lian, and Rami I. Aqeilan

Précis: Findings establish the pathobiological significance of a suspected tumor suppressor in human osteosarcoma, a very aggressive bone cancer, with potential prognostic and therapeutic implications.

5587 Compensatory Upregulation of Tyrosine Kinase Etk/BMX in Response to Androgen Deprivation Promotes Castration-Resistant Growth of Prostate Cancer Cells
Bojie Dai, Hege Chen, Shengjie Guo, Xi Yang, Douglas E. Linn, Feng Sun, Wei Li, Zhiyong Guo, Kexin Xu, Oekyung Kim, Xiantian Kong, Jonathan Melamed, Shaopeng Qiu, Hegang Chen, and Yun Qiu

Précis: Findings identify a compensatory mechanism activated in prostate after androgen ablation, apparently contributing to androgen resistance.

5597 Inhibition of the Sodium-Potassium-Chloride Cotransporter Isoform-1 Reduces Glioma Invasion
Brian R. Haas and Harald Sontheimer

Précis: Findings rationalize an immediate opportunity to reposition a drug presently used for non-cancer indications as a treatment for primary brain tumors.
Exchange Protein Directly Activated by Cyclic AMP Increases Melanoma Cell Migration by a Ca²⁺-Dependent Mechanism
Erdene Baljinnyam, Mariana S. De Lorenzo, Lai-Hua Xie, Mizuka Iwatsubo, Suzie Chen, James S. Goydos, Martha C. Nowycky, and Kousaku Iwatsubo

Précis: A novel mechanism is described for invasive migration of melanoma cells, suggesting new routes to attack metastatic disease.

Atoh1 Inhibits Neuronal Differentiation and Collaborates with Gli1 to Generate Medulloblastoma-Initiating Cells
Olivier Ayrault, Haotian Zhao, Frederique Zindy, Chunxu Qu, Charles J. Sherr, and Martine F. Roussel

Précis: Findings define two transcription factors that are sufficient to transform a neuronal progenitor into a tumor-initiating cell in the common childhood brain tumor medulloblastoma.

Alternatively Spliced RAGEv1 Inhibits Tumorigenesis through Suppression of JNK Signaling
Anastasia Z. Kalea, Fiona See, Evis Harja, Maria Arriero, Ann Marie Schmidt, and Barry I. Hudson

Précis: Findings define a mechanism through which a novel theranostic biomarker in cancer may be used to suppress malignant disease.

ABOUT THE COVER
RG7204 (PLX4032) is a small molecule inhibitor that selectively blocks the activity of oncogenic BRAFV600E kinase. The BRAFV600E mutation is common in several human cancers, with especially high prevalence in melanoma. In the present study, Yang and colleagues describe the effect of RG7204 on tumor cells. RG7204 suppresses ERK activation and cellular proliferation in tumor cells with BRAFV600E but not in cells expressing only wild-type BRAF. Significantly, RG7204 treatment caused partial or complete tumor regressions and improved survival of animals bearing BRAFV600E tumors, demonstrating potent antitumor activity. These preclinical efficacy data generated in several melanoma xenograft models have foreshadowed the clinical results observed in a multi-center Phase I trial that has been enriched with metastatic melanoma patients testing positive for the BRAFV600E mutation. For details, see the article by Yang and colleagues on page 5518 of this issue.
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