### Breaking Advances

**Highlights from Recent Cancer Literature**

**From the Editor's Chair**

**Perspectives on Emerging Trends in Cancer Research**

George C. Prendergast

**Reviews**

**Calcineurin Signaling as a Negative Determinant of Keratinocyte Cancer Stem Cell Potential and Carcinogenesis**

G. Paolo Dotto

**MYC and Metastasis**

Anita Wolfer and Sridhar Ramaswamy

### Priority Report

**Spontaneous Cytotoxic T-Cell Reactivity against Indoleamine 2,3-Dioxygenase-2**

Rikke Bæk Sørensen, Tania Køllgaard, Rikke Sick Andersen, Per thor Straten, and Mads Hald Andersen

**Précis:** IDO2-specific T cells are present among peripheral blood lymphocytes in cancer patients and are able to recognize and kill cancer cells.

### Integrated Systems and Technologies

**Genome-Wide Analysis of Alternative Splicing in Medulloblastoma Identifies Splicing Patterns Characteristic of Normal Cerebellar Development**

Francesca Menghi, Thomas S. Jacques, Martino Barenco, Ed C. Schwalbe, Steven C. Cliftord, Mike Hubank, and Jonathan Ham

**Précis:** Increasing evidence points to a critical role for dysregulated patterns of alternate splicing in driving tumorigenesis, here illustrated by implications of a failure of differentiation pathways in a little understood but deadly childhood tumor.

### Microenvironment and Immunology

**CCL11–CCR3 Interactions Promote Survival of Anaplastic Large Cell Lymphoma Cells via ERK1/2 Activation**

Tomomitsu Miyagaki, Makoto Sugaya, Takashi Murakami, Yoshihide Asano, Yayoi Tada, Takafumi Kadono, Hitoshi Okochi, Kunihiko Tamaki, and Shinichi Sato

**Précis:** Findings prompt a novel therapeutic approach to treat relapses of an aggressive form of lymphoma based on the discovery that a cell surface marker of disease functions as a critical autocrine growth receptor.

**Cancer Immunotherapy Using a Bispecific NK Receptor Fusion Protein that Engages both T Cells and Tumor Cells**

Tong Zhang and Charles L. Sentman

**Précis:** This study offers preclinical proof-of-concept for an interesting new biologic agent that stimulates effective host antitumor immunity, in support of clinical evaluation.

**Anti-IL-23 Monoclonal Antibody Synergizes in Combination with Targeted Therapies or IL-2 to Suppress Tumor Growth and Metastases**

Michele W.L. Teng, Bianca von Scheidt, Helene Duret, Jennifer E. Towne, and Mark J. Smyth

**Précis:** This study offers the first description of therapeutic activity for anti-IL-23 antibody in preclinical mouse models of cancer.

### Molecular and Cellular Pathobiology

**Protein Kinase C ô Is a Downstream Effector of Oncogenic K-ras in Lung Tumors**

Jennifer M. Symonds, Angela M. Ohm, Cristian J. Carter, Lynn E. Heasley, Theresa A. Boyle, Wilbur A. Franklin, and Mary E. Reiland

**Précis:** A protein kinase C isofrom implicated in apoptosis has a differential effect on cancer cell growth depending on the involvement of oncogenic KRAS in proliferation and survival, with potential implications on how to improve therapeutic targeting of mutant KRAS-driven tumors.
Shmt1 Heterozygosity Impairs Folate-Dependent Thymidylate Synthesis Capacity and Modifies Risk of Apcmin-Mediated Intestinal Cancer Risk
Amanda J. MacFarlane, Cheryl A. Perry, Michael F. McEntee, David M. Lin, and Patrick J. Stover

Précis: Folate-dependent thymidylate synthesis capacity modifies susceptibility to intestinal cancer, independent of cellular methylation potential.

Intragenic Rearrangement and Altered RNA Splicing of the Androgen Receptor in a Cell-Based Model of Prostate Cancer Progression
Yingming Li, Majid Alsagabi, Danhua Fan, G. Steven Bova, Ahmed H. Tewfik, and Scott M. Dehm

Précis: This study describes a novel genomic aberration in prostate cancer cells that is associated with aberrant RNA splicing of the androgen receptor, leading to synthesis of truncated receptors that drive resistance to androgen depletion therapy.

CARM1 Is an Important Determinant of ERα-Dependent Breast Cancer Cell Differentiation and Proliferation in Breast Cancer Cells
Mariam Al-Dhaheri, Jiacai Wu, Georgios P. Skiliris, Jun Li, Ken Higashimato, Yidan Wang, Kevin P. White, Paul Lambert, Yuerong Zhu, Leigh Murphy, and Wei Xu

Précis: Results define a histone arginine methyltransferase as a candidate theranostic target in ER-positive breast cancers, with implications to improve the diagnosis of well-differentiated tumors and potentially to improve the chance for cures.

Cep63 Recruits Cdk1 to the Centrosome: Implications for Regulation of Mitotic Entry, Centrosome Amplification, and Genome Maintenance
Harald Löfler, Anne Fechter, Marc Matuszewska, Rainer Saffrich, Martin Mistrik, Joachim Marhold, Christin Hornung, Frank Westermann, Jiri Bartek, and Alwin Krämer

Précis: The discovery how Cdk1 kinase is recruited to centrosomes advances understanding of how mitosis is controlled and why centrosome amplification and chromosomal breakage occur so commonly in cancer cells.

Oncogenic Synergism between ErbB1, Nucleolin, and Mutant Ras
Keren Farin, Sari Schokoroy, Roni Haklai, Ifat Cohen-Or, Galit Elad-Safdie, Merit E. Reyes-Reyes, Paula J. Bates, Adrienne D. Cox, Yoel Kloo, and Ronit Pinkas-Kramarski

Précis: This study describes a fascinating protein complex that might be targeted as a general approach to attack the many human cancers driven by EGF family receptors and Ras small GTPases.

HSulf-1 Modulates FGF2- and Hypoxia-Mediated Migration and Invasion of Breast Cancer Cells
Ashwani Khurana, Peng Liu, Pasquale Mellone, Laura Lorenzon, Bruno Vincenzi, Kaustubh Datta, Bo Yang, Robert J. Linhardt, Wilma Lingle, Jeremy Chien, Alfonso Baldi, and Viji Shridhar

Précis: This study describes regulation of heparan sulfatase-1 by hypoxia leading to increased cell migration and invasion in breast cancer cells.

Identification of a Tumor Suppressor Relay between the FOXP3 and the Hippo Pathways in Breast and Prostate Cancers
Weiquan Li, Lizhong Wang, Hiroto Katoh, Runhua Liu, Pan Zheng, and Yang Liu

Précis: Findings define a functional connection between two important tumor suppressor pathways in cancer, with potential theranostic implications.

IMP-1 Displays Cross-Talk with K-Ras and Modulates Colon Cancer Cell Survival through the Novel Proapoptotic Protein CYFIP2
Perry S. Mongroo, Felicite K. Noubissi, Miriam Cuatrecasas, Jiri Kalabis, Catrina E. King, Cameron N. Johnstone, Mark J. Bowser, Antoni Castells, Vladimir S. Spiegelman, and Anil K. Rustgi

Précis: Findings indicate that the Myc-interacting protein IMP-1 acts upstream of K-Ras to promote survival through a novel mechanism that may be important in colon cancer pathogenesis.

CARMA3 is Crucial for EGFR-Induced Activation of NF-κB and Tumor Progression
Tang Jiang, Brian Graberner, Yifan Zhu, Changying Jiang, Hongxiu Li, Yun You, Jingyu Lang, Mien-Chie Hung, and Xin Lin

Précis: Results elucidate how EGFR signaling leads to NF-κB activation and its role in tumor progression.
**Therapeutics, Targets, and Chemical Biology**

**Targeted Signal-Amplifying Enzymes Enhance MRI of EGFR Expression in an Orthotopic Model of Human Glioma**
Mohammed S. Shazeeb, Christopher H. Sotak, Michael DeLeo III, and Alexei Bogdanov Jr.

**Précis:** Findings define a signal amplification and contrast agent retention strategy for in vivo imaging of gliomas expressing EGFRvIII variants that are best suited to treatment with therapeutic EGFR antibodies.

**Heavy Chain Ferritin siRNA Delivered by Cationic Liposomes Increases Sensitivity of Cancer Cells to Chemotherapeutic Agents**
Xiaoli Liu, A.B. Madhankumar, Becky Slagle-Webb, Jonas M. Sheehan, Nadar Surguladze, and James R. Connor

**Précis:** Findings provide preclinical demonstration of a siRNA-based targeting and delivery approach that can be used to sensitize brain tumor cells to chemotherapy.

**Influence of Affinity and Antigen Internalization on the Uptake and Penetration of Anti-HER2 Antibodies in Solid Tumors**

**Précis:** Determining the factors that influence how effectively a therapeutic antibody can penetrate tumors is important for optimizing efficacious effects in cancer treatment.

**NRF2 Blockade Suppresses Colon Tumor Angiogenesis by Inhibiting Hypoxia-Induced Activation of HIF-1α**
Tae-Hyoung Kim, Eu-gene Hur, Su-Jin Kang, Jung-Ae Kim, Dinesh Thapa, You Mie Lee, Sae Kwang Ku, Yunjin Jung, and Mi-Kyoung Kwak

**Précis:** Findings show how blocking the NRF2 system, an important modifier of oxidative stress signaling in cells, could be an effective way to control tumor growth and angiogenesis.

**Prevention and Epidemiology**

**Contribution of Inherited Mutations in the BRCA2-Interacting Protein PALB2 to Familial Breast Cancer**
Silvia Casadei, Barbara M. Norquist, Tom Walsh, Sunday Stray, Jessica B. Mandell, Ming K. Lee, John A. Stamatoyannopoulos, and Mary-Claire King

**Précis:** This study characterizes the mutational spectrum of the tumor suppressor gene PALB2, which is mutated in a fraction of familial breast cancer patients and is particularly strongly associated with male breast cancer and pancreatic cancer.
MYC Phosphorylation, Activation, and Tumorigenic Potential in Hepatocellular Carcinoma Are Regulated by HMG-CoA Reductase
Zhongwei Cao, Hua Fan-Minogue, David I. Bellovin, Aleksey Yevtodiyenko, Julia Arzeno, Qiwei Yang, Sanjiv Sam Gambhir, and Dean W. Felsher

Precis: The ability of statins to suppress MYC oncogenic activity suggests their evaluation as novel adjuvant modalities in cancer therapy.

Human CD59 Inhibitor Sensitizes Rituximab-Resistant Lymphoma Cells to Complement-Mediated Cytolysis
Weiguo Hu, Xiaowen Ge, Tao You, Ting Xu, Jinyan Zhang, Gongxiong Wu, Zhihai Peng, Michael Chorev, Bertal H. Aktas, Jose A. Halperin, Jennifer R. Brown, and Xuebin Qin

Precis: Findings rationalize a tractable method to reduce or abolish resistance to rituximab, a monoclonal antibody therapy used widely to treat certain common blood malignancies.

Overcoming Temozolomide Resistance in Glioblastoma via Dual Inhibition of NAD+ Biosynthesis and Base Excision Repair
Eva M. Goellner, Bradford Grimme, Ashley R. Brown, Ying-Chih Lin, Xiao-Hong Wang, Kelsey F. Sugrue, Leah Mitchell, Ram N. Trivedi, Jiang-bo Tang, and Robert W. Sobol

Precis: Temozolomide resistance in glioblastoma can be overcome by dual inhibition of NAD+ biosynthesis and base excision repair.

Genetic Ablation of PKC Epsilon Inhibits Prostate Cancer Development and Metastasis in Transgenic Mouse Model of Prostate Adenocarcinoma

Precis: Findings provide first genetic evidence of the role of PKC epsilon in prostate cancer development and metastasis, suggesting novel preventive and therapeutic strategies.

DCAMKL-1 Regulates Epithelial–Mesenchymal Transition in Human Pancreatic Cells through a miR-200a–Dependent Mechanism

Precis: Findings indicate that a microtubule associated kinase previously identified as a pancreatic stem cell marker can serve as an effective therapeutic target in pancreatic cancer treatment.

Outgrowth of Drug-Resistant Carcinomas Expressing Markers of Tumor Aggression after Long-term TβRI/II Kinase Inhibition with LY2109761
Erin C. Connolly, Elise F. Saunier, David Quigley, Minh Thu Lau, Angela De Sapio, Byron Hann, Jonathan M. Yingling, and Rosemary J. Akhurst

Precis: Long-term pharmacological TGF-β receptor inhibition potentiates chemically-induced skin cancer progression and promotes outgrowth of a tumor type with molecular features which contrasts with short-term effects of TGF-β inhibition.

Zyxin Is a Critical Regulator of the Apoptotic HIPK2-p53 Signaling Axis
Johanna Crone, Carolina Glas, Kathrin Schultheiss, Jutta Moehlenbrink, Eva Krieghoff-Henning, and Thomas G. Hofmann

Precis: Findings identify Zyxin as novel regulator of DNA damage-induced cell death through controlling the HIPK2-p53 signaling axis.

Histone Methyltransferase EZH2 Induces Akt-Dependent Genomic Instability and BRCA1 Inhibition in Breast Cancer
Maria E. Gonzalez, Matthew L. DuPrie, Heather Krueger, Sofia D. Merajver, Alejandra C. Ventura, Kathy A. Toy, and Celina G. Kleer

Precis: Findings offer mechanistic insight into how elevated activity of an important chromatin modifier drives breast cancer progression.
Activation of the Aryl Hydrocarbon Receptor AhR Promotes Retinoic Acid–Induced Differentiation of Myeloblastic Leukemia Cells by Restricting Expression of the Stem Cell Transcription Factor Oct4
Rodica P. Bunaciu and Andrew Yen

Précis: Findings suggest a mechanism-based rationale to enhance the therapeutic effects of retinoic acid, which is used to treat certain cancers, through co-treatment with activators of AhR signaling.

miR-218 Suppresses Nasopharyngeal Cancer Progression through Downregulation of Survivin and the SLIT2-ROBO1 Pathway
Nehad M. Alajez, Michelle Lenarduzzi, Emma Ito, Angela B.Y. Hui, Wei Shi, Jeff Bruce, Shijun Yue, Shao H. Huang, Wei Xu, John Waldron, Brian O'Sullivan, and Fei-Fei Liu

Précis: Findings suggest a tumor suppressor function for the microRNA mi-218 that integrates control of two important cell survival and migratory mechanisms.

MAP Kinase-Interacting Kinase 1 Regulates SMAD2-Dependent TGF-β Signaling Pathway in Human Glioblastoma
Michal Grzmil, Pier Jr Morin, Maria Maddalena Lino, Adrian Merlo, Stephan Frank, Yuhua Wang, Gerald Moncayo, and Brian A. Hemmings

Précis: Findings identify a pathway that controls translation of key cancer-related RNAs including SMAD2, a key component of the TGF-β-signaling pathway, with implications for targeting deadly brain tumors more effectively.

LETTER TO THE EDITOR

Essential Requirement for PP2A Inhibition by the Oncogenic Receptor c-KIT Suggests PP2A Reactivation as a Strategy to Treat c-KIT+ Cancers — Letter
Amaury G. Dumont, David G. Reynoso, and Jonathan C. Trent

Précis: Findings suggest a mechanism-based rationale to enhance the therapeutic effects of retinoic acid, which is used to treat certain cancers, through co-treatment with activators of AhR signaling.

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CORRECTIONS

Correction: Glioblastoma Recurrence after Cediranib Therapy in Patients: Lack of "Rebound" Revascularization as Mode of Escape

Correction: Phospholipase D Meets Wnt Signaling: A New Target for Cancer Therapy

Correction: Breast Cancer Stem Cells Are Regulated by Mesenchymal Stem Cells through Cytokine Networks

Correction: Online Publication Dates for Cancer Research January 15, 2011 Articles
ABOUT THE COVER

Diminished angiogenesis in NRF2 knockdown colon cancer cells. Matrigel-loaded colon cancer cells (HCT116 and HT29) with stable expression of interfering RNA of NRF2 (NRF2i) were inoculated on the CAM of 10-day-old chicken embryos and the branch points of formed blood vessels were counted as a marker of angiogenesis. NRF2 knockdown cancer cells developed fewer blood vessels; the numbers of vessel branch points in HCT-NRF2i and HT-NRF2i cells reduced to 73% and 58% of those in the control cells (SCi). The data represent means ± SD of at least 8 embryos. For details, see the article by Kim and colleagues on page 2260 of this issue.