

BREAKING ADVANCES

- 5647 | **Highlights from Recent Cancer Literature**

AACR CENTENNIAL SERIES

- 5649 | **AACR Centennial Series: The Biology of Cancer Metastasis: Historical Perspective**
James E. Talmadge and Isaiah J. Fidler

REVIEW

- 5670 | **Premetastatic Lung “Niche”: Is Vascular Endothelial Growth Factor Receptor 1 Activation Required?**
Dan G. Duda and Rakesh K. Jain

PRIORITY REPORTS

- 5674 | **PIK3CA Mutations in *In situ* and Invasive Breast Carcinomas**
Alexander Miron, Maria Varadi, Daniel Carrasco, Hailun Li, Lauren Luongo, Hee Jung Kim, So Yeon Park, Eun Yoon Cho, Gretchen Lewis, Sarah Kehoe, J. Dirk Iglehart, Deborah Dillon, D. Craig Allred, Laura Macconaill, Rebecca Gelman, and Kornelia Polyak

Précis: Intra-tumor heterogeneity and divergence in PI3K mutations between *in situ* and invasive areas of the same tumor occur in a subset of breast carcinomas.

- 5679 | **Recruitment of Myeloid but not Endothelial Precursor Cells Facilitates Tumor Regrowth after Local Irradiation**
Sergey V. Kozin, Walid S. Kamoun, Yuhui Huang, Michelle R. Dawson, Rakesh K. Jain, and Dan G. Duda

Précis: Findings suggest that an early rebound in bone marrow-derived monocytes recruited to tumor beds can promote tumor re-growth after radiotherapy.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 5686 | **Integrated Profiling Reveals a Global Correlation between Epigenetic and Genetic Alterations in Mesothelioma**
Brock C. Christensen, E. Andres Houseman, Graham M. Poage, John J. Godleski, Raphael Bueno, David J. Sugarbaker, John K. Wiencke, Heather H. Nelson, Carmen J. Marsit, and Karl T. Kelsey

Précis: Two-hit gene inactivation by gene deletion and methylation silencing is rare in mesothelioma, and requires investigation in other tumor types.

- 5695 | **Characterization of a Novel Mechanism of Genomic Instability Involving the SEI1/SET/NM23H1 Pathway in Esophageal Cancers**
Yan Li, Chang-Jun Nie, Liang Hu, Yanru Qin, Hai-bo Liu, Ting-Ting Zeng, Leilei Chen, Li Fu, Wen Deng, Shu-Peng Chen, Wei-Hua Jia, Chunyu Zhang, Dan Xie, and Xin-Yuan Guan

Précis: These findings define a novel mechanism of genomic instability and malignant progression in esophageal cancers, a deadly disease of increasing incidence in developed countries.

MICROENVIRONMENT AND IMMUNOLOGY

- 5706 | **Metastatic Growth from Dormant Cells Induced by a Col-I–Enriched Fibrotic Environment**
Dalit Barkan, Lara H. El Touny, Aleksandra M. Michalowski, Jane Ann Smith, Isabel Chu, Anne Sally Davis, Joshua D. Webster, Shelley Hoover, R. Mark Simpson, Jack Gauldie, and Jeffrey E. Green

Précis: Fibrosis involving certain ECM proteins at a metastatic site may induce otherwise dormant tumor cells to switch to a proliferative state, leading to recurrent aggressive disease.

- 5717 **Cyclic AMP Suppression Is Sufficient to Induce Gliomagenesis in a Mouse Model of Neurofibromatosis-1**
Nicole M. Warrington, Scott M. Gianino, Erin Jackson, Patricia Goldhoff, Joel R. Garbow, David Piwnica-Worms, David H. Gutmann, and Joshua B. Rubin

Précis: Findings offer in vivo evidence that brain region-specific differences in cAMP levels in tumor stroma may contribute to patterns of tumor formation.

- 5728 **Different Tumor Microenvironments Contain Functionally Distinct Subsets of Macrophages Derived from Ly6C(high) Monocytes**
Kiavash Movahedi, Damya Laoui, Conny Gysemans, Martijn Baeten, Geert Stangé, Jan Van den Bossche, Matthias Mack, Daniel Pipeleers, Peter In't Veld, Patrick De Baetselier, and Jo A. Van Ginderachter

Précis: Findings deepen biological understanding of tumor-associated macrophages (TAMs), offering insights into the origins, molecular phenotype, intratumoral localization and functions of distinct TAM subpopulations in lung and breast tumors.

- 5740 **Translocation of *Helicobacter pylori* CagA into Human B Lymphocytes, the Origin of Mucosa-Associated Lymphoid Tissue Lymphoma**
Wei-Cheng Lin, Hwei-Fang Tsai, Sung-Hsin Kuo, Ming-Shiang Wu, Chung-Wu Lin, Ping-I Hsu, Ann-Lii Cheng, and Ping-Ning Hsu

Précis: Results identify an *H. pylori*-derived protein as an oncoprotein that may be delivered into B cells where it associates with development of MALT lymphoma.

- 5749 **Low Ascorbate Levels Are Associated with Increased Hypoxia-Inducible Factor-1 Activity and an Aggressive Tumor Phenotype in Endometrial Cancer**
Caroline Kuiper, Ilona G.M. Molenaar, Gabi U. Dachs, Margaret J. Currie, Peter H. Sykes, and Margreet C.M. Vissers

Précis: Ascorbate insufficiency impairs hydroxylation reactions that switch off the hypoxia-inducible transcription factor HIF-1, promoting tumor aggressiveness.

- 5759 **Increased Expression of $\alpha 6$ Integrin in Endothelial Cells Unveils a Proangiogenic Role for Basement Membrane**
Luca Primo, Giorgio Seano, Cristina Roca, Federica Maione, Paolo Armando Gagliardi, Roberto Sessa, Marianna Martinelli, Enrico Giraudo, Laura di Blasio, and Federico Bussolino

Précis: Results demonstrate that $\alpha 6$ integrin plays an important role in vascular sprouting and tumoral angiogenesis.

- 5770 **Breast Carcinoma-Associated Fibroblasts Rarely Contain p53 Mutations or Chromosomal Aberrations**
Abdel Nasser Hosein, Min Wu, Suzanna L. Arcand, Sylvie Lavallée, Josée Hébert, Patricia N. Tonin, and Mark Basik

Précis: A study of cancer-associated fibroblasts derived from freshly resected breast cancers argues that genomic abnormalities in these cells occur rarely at best.

- 5778 **DC-HIL/Glycoprotein Nmb Promotes Growth of Melanoma in Mice by Inhibiting the Activation of Tumor-Reactive T Cells**
Mizuki Tomihari, Jin-Sung Chung, Hideo Akiyoshi, Ponciano D. Cruz, Jr., and Kiyoshi Ariizumi

Précis: Findings describe a pathway of immune escape in melanoma, the inhibition of which might improve immunotherapeutic responses in this deadly disease.

- 5788 **Tumor Antigen Epitopes Interpreted by the Immune System as Self or Abnormal-Self Differentially Affect Cancer Vaccine Responses**
Sean O. Ryan, Michael S. Turner, Jean Gariépy, and Olivera J. Finn

Précis: Study findings argue that immune responses to distinct epitopes on a tumor antigen influence tolerance versus immunity decisions that must be understood to design an effective cancer vaccine.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 5797 **The Mitogen-Activated Protein Kinase Kinase 4 Has a Pro-Oncogenic Role in Skin Cancer**
Katherine G. Finegan and Cathy Tournier

Précis: Results offer a preclinical genetic proof that the kinase MKK4 is essential to mediate Ras oncogenicity, supporting a rationale to target this kinase for cancer therapy.

- 5807 **Dysregulation of p53/Sp1 Control Leads to DNA Methyltransferase-1 Overexpression in Lung Cancer**
Ruo-Kai Lin, Chiu-Yi Wu, Jer-Wei Chang, Li-Jung Juan, Han-Shui Hsu, Chih-Yi Chen, Yun-Yueh Lu, Yen-An Tang, Yi-Chieh Yang, Pan-Chyr Yang, and Yi-Ching Wang
- Précis:* Findings identify a core mechanism of transcriptional dysregulation on DNA methyltransferase that promotes lung tumorigenesis and progression.
- 5818 **STAMP1 Is Both a Proliferative and an Antiapoptotic Factor in Prostate Cancer**
Ling Wang, Yang Jin, Yke Jildouw Arnoldussen, Ida Jonson, Su Qu, Gunhild M. Mælandsmo, Alexandr Kristian, Bjørn Risberg, Håkon Wæhre, Håvard E. Danielsen, and Fahri Saatcioglu
- Précis:* The six-pass transmembrane protein STAMP1 strongly promotes prostate growth and survival, possibly representing a novel biomarker or a therapeutic target for prostate cancer.
- 5829 **Cell-Permeable Peptide DEPDC1-ZNF224 Interferes with Transcriptional Repression and Oncogenicity in Bladder Cancer Cells**
Yosuke Harada, Mitsugu Kanehira, Yoshiko Fujisawa, Ryo Takata, Taro Shuin, Tsuneharu Miki, Tomoaki Fujioka, Yusuke Nakamura, and Toyomasa Katagiri
- Précis:* Findings define an oncogenic driver in bladder cancer along with a therapeutic strategy based on its attack.
- 5840 **DNMT3B7, a Truncated DNMT3B Isoform Expressed in Human Tumors, Disrupts Embryonic Development and Accelerates Lymphomagenesis**
Mrinal Y. Shah, Aparna Vasanthakumar, Natalie Y. Barnes, Maria E. Figueroa, Anna Kamp, Christopher Hendrick, Kelly R. Ostler, Elizabeth M. Davis, Shang Lin, John Anastasi, Michelle M. Le Beau, Ivan P. Moskowitz, Ari Melnick, Peter Pytel, and Lucy A. Godley
- Précis:* First in vivo modeling of cancer-associated DNA methylation changes suggests that truncated DNMT3B isoforms may contribute to the re-distribution of DNA methylation characterizing most if not all human tumors.
- 5851 **Mouse Models for the p53 R72P Polymorphism Mimic Human Phenotypes**
Feng Zhu, Martijn E.T. Dollé, Thomas R. Berton, Raoul V. Kuiper, Carrie Capps, Alexandra Espejo, Mark J. McArthur, Mark T. Bedford, Harry van Steeg, Annemieke de Vries, and David G. Johnson
- Précis:* Humanized mouse models expressing common polymorphic variants of p53 display differences in the apoptotic response to both ultraviolet and ionizing radiation.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 5860 **Runx Regulation of Sphingolipid Metabolism and Survival Signaling**
Anna Kilbey, Anne Terry, Alma Jenkins, Gillian Borland, Qifeng Zhang, Michael J.O. Wakelam, Ewan R. Cameron, and James C. Neil
- Précis:* Study identifies several enzymes in sphingolipid metabolism as direct targets of Runx transcription factors, providing a new link between the fields of lipid signalling and oncogenesis.
- 5870 **Microtubule-Disrupting Chemotherapeutics Result in Enhanced Proteasome-Mediated Degradation and Disappearance of Tubulin in Neural Cells**
Lyn M. Huff, Dan L. Sackett, Marianne S. Poruchynsky, and Tito Fojo
- Précis:* Important findings concern the basis for neurotoxic side-effects of a widely used class of chemotherapeutics, a common and severe problem in patient survivors.
- 5880 **Identification of a Metalloprotease-Chemokine Signaling System in the Ovarian Cancer Microenvironment: Implications for Antiangiogenic Therapy**
Anika Agarwal, Sarah L. Tressel, Rajani Kaimal, Marianthi Balla, Francis H. Lam, Lidija Covic, and Athan Kuliopulos
- Précis:* This study identifies a critical paracrine pathway that might be therapeutically targeted for ovarian cancer treatment.
- 5891 **HuR Regulates β -Tubulin Isoform Expression in Ovarian Cancer**
Giuseppina Raspaglio, Ilaria De Maria, Flavia Filippetti, Enrica Martinelli, Gian Franco Zannoni, Silvia Prislei, Gabriella Ferrandina, Shohreh Shahabi, Giovanni Scambia, and Cristiano Ferlini
- Précis:* Findings identify a mechanism contributing to the development of drug resistance in low oxygen, low nutrient tumor microenvironments.

5901	Genomic and Biological Characterization of Exon 4 KRAS Mutations in Human Cancer Manickam Janakiraman, Efsevia Vakiani, Zhaoshi Zeng, Christine A. Pratilas, Barry S. Taylor, Dhananjay Chitale, Ensar Halilovic, Manda Wilson, Kety Huberman, Julio Cezar Ricarte Filho, Yogindra Persaud, Douglas A. Levine, James A. Fagin, Suresh C. Jhanwar, John M. Mariadason, Alex Lash, Marc Ladanyi, Leonard B. Saltz, Adriana Heguy, Philip B. Paty, and David B. Solit <i>Précis:</i> Findings suggest there is a greater diversity in the type and effects of RAS mutant alleles in human cancers than presently appreciated, prompting the need to further define and evaluate the prognostic implications of Ras mutational status for individualized patient care.	5942	The Epidermal Growth Factor Receptor Antibody Cetuximab Induces Autophagy in Cancer Cells by Downregulating HIF-1α and Bcl-2 and Activating the Beclin 1/hVps34 Complex Xinqun Li and Zhen Fan <i>Précis:</i> Findings suggest that autophagy protects cancer cells from apoptosis induced by EGFR antagonists, suggesting strategies to block autophagy could enhance their therapeutic properties.
5912	Inhibition of ADP Ribosylation Prevents and Cures <i>Helicobacter-Induced</i> Gastric Preneoplasia Isabella M. Toller, Matthias Altmeyer, Esther Kohler, Michael O. Hottiger, and Anne Müller <i>Précis:</i> PARP inhibitors in clinical development may offer an immunotherapeutic strategy to prevent and reverse stomach cancers driven by <i>H. pylori</i> infections, an important problem worldwide.	5953	Epigenetic Regulation of Vitamin D 24-Hydroxylase/<i>CYP24A1</i> in Human Prostate Cancer Wei Luo, Adam R. Karpf, Kristin K. Deeb, Josephia R. Muindi, Carl D. Morrison, Candace S. Johnson, and Donald L. Trump <i>Précis:</i> Findings offer insight into mechanisms that control levels of vitamin D, which may prevent prostate cancer.
5923	Development of a Lung Cancer Therapeutic Based on the Tumor Suppressor MicroRNA-34 Jason F. Wiggins, Lynnsie Ruffino, Kevin Kelnar, Michael Omotola, Lubna Patrawala, David Brown, and Andreas G. Bader <i>Précis:</i> Study offers a proof of concept for systemic delivery of a tumor suppressor microRNA, obviating obstacles associated with viral-based delivery such as undesired immune responses, and addressing the need for pharmacological strategies to develop microRNAs as new drug principles.	5963	A Useful Approach to Identify Novel Small-Molecule Inhibitors of Wnt-Dependent Transcription Kenneth Ewan, Bożena Pająk, Mark Stubbs, Helen Todd, Olivier Barbeau, Camilo Quevedo, Hannah Botfield, Rodrigo Young, Ruth Ruddle, Lee Samuel, Alysia Battersby, Florence Raynaud, Nicholas Allen, Stephen W. Wilson, Branko Latinkic, Paul Workman, Edward MacDonald, Julian Blagg, Wynne Aherne, and Trevor Dale <i>Précis:</i> This report describes a useful system to identify Wnt pathway inhibitors, which represent an exciting area of therapeutic discovery in cancer.
5931	Src Family Kinase Inhibitor Saracatinib (AZD0530) Impairs Oxaliplatin Uptake in Colorectal Cancer Cells and Blocks Organic Cation Transporters Christopher J. Morrow, Mohammad Ghattas, Christopher Smith, Heinz Bönisch, Richard A. Bryce, D. Mark Hickinson, Tim P. Green, and Caroline Dive <i>Précis:</i> An experimental targeted therapeutic is found to inhibit uptake of a common cancer drug with which it might have been combined in clinic.	TUMOR AND STEM CELL BIOLOGY	
		5974	pp60^{c-Src} Phosphorylates and Activates Vacuolar Protein Sorting 34 to Mediate Cellular Transformation Dianne S. Hirsch, Yi Shen, Milos Dokmanovic, and Wen Jin Wu <i>Précis:</i> A novel linkage is elucidated in the means by which Src activates VPS34 and neoplastic cell transformation.
		5984	Hypoxic Conversion of SMAD7 Function from an Inhibitor into a Promoter of Cell Invasion Pekka T. Heikkinen, Marika Nummela, Terhi Jokilehto, Reidar Grenman, Veli-Matti Kähäri, and Panu M. Jaakkola <i>Précis:</i> Results offer mechanistic insights into why the growth inhibitory TGF-β effector protein Smad7 is overexpressed in hypoxic tumors.

5994	Nrdp1-Mediated Regulation of ErbB3 Expression by the Androgen Receptor in Androgen-Dependent but not Castrate-Resistant Prostate Cancer Cells Liqun Chen, Salma Siddiqui, Swagata Bose, Benjamin Mooso, Alfredo Asuncion, Roble G. Bedolla, Ruth Vinall, Clifford G. Tepper, Regina Gandour-Edwards, XuBao Shi, Xiao-Hua Lu, Javed Siddiqui, Arul M. Chinnaiyan, Rohit Mehra, Ralph W. deVere White, Kermit L. Carraway III, and Paramita M. Ghosh <i>Précis:</i> Findings describe a mechanism by which expression of ErbB3 in prostate cancer is androgen regulated in castration sensitive but not in castration resistant cells, contributing to malignant progression.	6036	Nuclear Alternate Estrogen Receptor GPR30 Mediates 17β-Estradiol-Induced Gene Expression and Migration in Breast Cancer-Associated Fibroblasts Antonio Madeo and Marcello Maggiolini <i>Précis:</i> Findings establish an alternate estrogen signaling pathway in cancer-associated fibroblasts that nurture tumor cells in the breast tumor microenvironment.
6004	Mitogen-Activated Protein/Extracellular Signal-Regulated Kinase Kinase 1^{act}/Tubulin Interaction Is an Important Determinant of Mitotic Stability in Cultured HT1080 Human Fibrosarcoma Cells Jia-ning Cao, Norazizah Shafee, Larry Vickery, Stefan Kaluz, Ning Ru, and Eric J. Stanbridge <i>Précis:</i> The mechanistic basis for a novel function for activated MEK in driving chromosome instability in cancer cells is described.	6047	Epigenetic Inactivation of the Potential Tumor Suppressor Gene <i>FOXF1</i> in Breast Cancer Pang-Kuo Lo, Ji Shin Lee, Xiaohui Liang, Liangfeng Han, Tsuyoshi Mori, Mary Jo Fackler, Helen Sadik, Pedram Argani, Tej K. Pandita, and Saraswati Sukumar <i>Précis:</i> Study identifies an epigenetically silenced tumor suppressor in breast cancer that is essential for cell cycle control and the maintenance of genomic stability.
6015	miRNA-96 Suppresses KRAS and Functions as a Tumor Suppressor Gene in Pancreatic Cancer Shuangni Yu, Zhaohui Lu, Changzheng Liu, Yunxiao Meng, Yihui Ma, Wugan Zhao, Jianping Liu, Jia Yu, and Jie Chen <i>Précis:</i> Findings validate an appealing new strategy to target K-Ras, a therapeutic target that has been challenging in practice, but attractive in principle, due to its frequent activation and causal role in common deadly cancers of the pancreas, lung, and colon.	6059	Tetraspanin CD151 Regulates Transforming Growth Factor β Signaling: Implication in Tumor Metastasis Rafał Sadej, Hanna Romanska, Dean Kavanagh, Gouri Baldwin, Takashi Takahashi, Neena Kalia, and Fedor Berditshevski <i>Précis:</i> A cell surface molecule that regulates function of laminin-binding integrins is found to be a positive modifier of TGF-β-mediated metastasis.
6026	Loss of Function of the Tumor Suppressor DKC1 Perturbs p27 Translation Control and Contributes to Pituitary Tumorigenesis Cristian Bellodi, Olya Krasnykh, Nikesha Haynes, Marily Theodoropoulou, Guang Peng, Lorenzo Montanaro, and Davide Ruggero <i>Précis:</i> Findings argue that mutations in an enzyme that modifies ribosomal RNA lead to deregulation of p27KIP1 translation, contributing to increased risk of somatic cancers, including pituitary tumors.	6071	Transiently Entrapped Circulating Tumor Cells Interact with Neutrophils to Facilitate Lung Metastasis Development Sung Jin Huh, Shile Liang, Arati Sharma, Cheng Dong, and Gavin P. Robertson <i>Précis:</i> A novel model has been developed in this study showing that neutrophils regulate lung metastasis development through physical interaction and anchoring of circulating tumor cells to endothelium.
		6083	MicroRNA Biogenesis Is Required for Myc-Induced B-Cell Lymphoma Development and Survival Maria Pia Arrate, Tiffaney Vincent, Jessica Odvody, Rekha Kar, Stephen N. Jones, and Christine M. Eischen <i>Précis:</i> Results deepen understanding of the requirements for microRNA biogenesis in oncogene-initiated lymphoma development and survival.

6093

Membrane Type 1-Matrix Metalloproteinase Cleaves Off the NH₂-Terminal Portion of Heparin-Binding Epidermal Growth Factor and Converts It into a Heparin-Independent Growth Factor

Naohiko Koshikawa, Hiroto Mizushima, Tomoko Minegishi, Ryo Iwamoto, Eisuke Mekada, and Motoharu Seiki

***Précis:** Findings reveal a regulatory mechanism for a heparin binding EGF family member that may impact therapeutic strategies based on EGFR targeting.*

CORRECTION

6106

Correction: The Human Ortholog of Granulocyte Macrophage Colony-Stimulating Factor and Interleukin-2 Fusion Protein Induces Potent *Ex vivo* Natural Killer Cell Activation and Maturation**LETTERS TO THE EDITOR**

6104

Tumor Regression Model of Cervical Cancer – Letter

Paoletta Mirk

6104

Tumor Regression Model of Cervical Cancer – Response

Jian Z. Wang, Zhibin Huang, Simon S. Lo, John C. Greco, Nina A. Mayr, William T.C. Yuh

ABOUT THE COVER

Representative images of the rapid infiltration by CD11b⁺ myeloid cells into 54A lung carcinoma tissue at 2 days after local irradiation of 21 Gray. Images are maximum intensity projections of tissue sections analyzed by confocal microscopy. Myeloid cells are shown in green (identified by CD11b immunostaining), and blood vessels are shown in red (identified by CD31 immunostaining); in blue, DAPI nuclear staining. Scale bar, 100 μ m. For details, see the article by Kozin and colleagues on page 5679 of this issue.

