BREAKING ADVANCES

7735 Highlights from Recent Cancer Literature

REVIEW

7737 Microtentacles Tip the Balance of Cytoskeletal Forces in Circulating Tumor Cells
Michael A. Matrone, Rebecca A. Whipple, Eric M. Balzer, and Stuart S. Martin

7742 Mesenchymal Stromal Cells Expressing ErbB-2/neu Elicit Protective Antitumor Immunity In vivo, Which Is Paradoxically Suppressed by IFN-γ and Tumor Necrosis Factor-α Priming
Raphaëlle Romieu-Mourez, Moïra François, Amanda Abate, Marie-Noëlle Boivin, Elena Birman, Dana Bailey, Jonathan L. Bramson, Kathy Forner, Yoon-Kow Young, Jeffrey A. Medin, and Jacques Galipeau

Précis: Results reveal a novel cellular mechanism of immune surveillance in which mesenchymal stromal cells can serve as antigen-presenting cells to trigger antitumor immune responses.

PRIORITY REPORT

7747 Oncogene-Driven Intrinsic Inflammation Induces Leukocyte Production of Tumor Necrosis Factor That Critically Contributes to Mammary Carcinogenesis
Sabina Sangaletti, Claudio Tripodo, Chiara Ratti, Silvia Piconese, Rossana Porcasi, RosaLa Salcedo, Giorgio Trinchieri, Mario P. Colombo, and Claudia Chiiodoni

Précis: Pericytes that surround endothelial cells in mature blood vessels are shown to be critical cellular targets of the procancerous activities of TNF during mammary carcinogenesis.

INTEGRATED SYSTEMS AND TECHNOLOGIES

7748 Optical Detection of Buccal Epithelial Nanoarchitectural Alterations in Patients Harboring Lung Cancer: Implications for Screening

Précis: A novel noninvasive optical technology can be used to accurately distinguish smokers with or without neoplasia, with potential for lung cancer screening.
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<td>7788</td>
<td>Selective Depletion of Foxp3+ Regulatory T Cells Improves Effective</td>
<td>Katjana Klages, Christian T. Mayer, Katharina Lahl, Christoph Loddenkemper, Michele W.L. Teng, Shin Foong Ngio, Mark J. Smyth, Alf Hamann, Jochen Huehn, and Tim Sparwasser</td>
<td>First study to show that depleting FoxP3+ T regulatory cells along with vaccination can trigger regression of established melanomas.</td>
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<tr>
<td>7800</td>
<td>Conditional Regulatory T-Cell Depletion Releases Adaptive Immunity</td>
<td>Michele W.L. Teng, Shin Foong Ngio, Bianca von Scheidt, Nicole McLaughlin, Tim Sparwasser, and Mark J. Smyth</td>
<td>First demonstration that established spontaneous and experimental tumors can regress following specific, complete, and delayed regulatory T-cell depletion.</td>
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<td>7810</td>
<td>Protein Kinase D1 Suppresses Epithelial-to-Mesenchymal Transition</td>
<td>Cheng Du, Chuanyou Zhang, Sazzad Hassan, Md. Helal Uddin Biswas, and K.C. Balaji</td>
<td>Factors that regulate the epithelial-mesenchymal transition in cancer are of great importance given the common role of this program in driving invasion and metastasis.</td>
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<td>7820</td>
<td>eIF2α Kinase PKR Modulates the Hypoxic Response by Stat3-Dependent</td>
<td>Andreas I. Papadakis, Efrosyni Paraskeva, Philippos Peidis, Hala Muaddi, Suiyang Li, Leda Raptis, Kostas Pantopoulos, George Simos, and Antonis E. Koromilas</td>
<td>Findings reveal a novel tumor suppressor function of the eIF2α kinase PKR that acts through the control of Stat3 rather than eIF2a.</td>
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<td>7830</td>
<td>H3K9 Histone Methyltransferase G9a Promotes Lung Cancer Invasion and</td>
<td>Min-Wei Chen, Kuo-Tai Hua, Hsin-Jung Kao, Chia-Chun Chi, Lin-Hung Wei, Gunmar Johansson, Shine-Gwo Shiah, Pui-Sheng Chen, Yung-Ming Jeng, Tsu-Yao Cheng, Tsung-Ching Lai, Jeng-Shou Chang, Yi-Hua Jan, Ming-Hsien Chien, Chih-Jen Yang, Ming-Shyan Huang, Michael Hsiao, and Min-Liang Kuo</td>
<td>First study to show that depleting FoxP3+ T regulatory cells along with vaccination can trigger regression of established melanomas.</td>
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<td>7851</td>
<td>Fibroblast Growth Factor Receptor 4 Regulates Tumor Invasion by Coupling</td>
<td>Nami Sugiyama, Markku Varjosalo, Pipsa Meller, Jouko Lohi, Marko Hyytiäinen, Sami Kilpinen, Olli Kallioniemi, Signe Ingvarsen, Lars H. Engelholm, Jussi Taipale, Kari Alitalo, Jorma Keski-Oja, and Kaisa Lehti</td>
<td>Findings define a key new regulatory mechanism of epithelial-to-mesenchymal transition that involves an FGF receptor isoform previously linked to tumor progression.</td>
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<td>7862</td>
<td>HER-2 Signaling, Acquisition of Growth Factor Independence, and</td>
<td>Aliccia Bollig-Fischer, Michele Dziubinski, Alaina Boyer, Ramsi Haddad, Craig N. Giroux, and Stephen P. Ethier</td>
<td>Findings suggest that mutational-activated and ligand-activated forms of growth factor receptors regulate distinct transcription programs that differentially affect motility, stress response, and stem cell properties.</td>
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MicroRNA Mediates DNA Demethylation Events Triggered by Retinoic Acid during Neuroblastoma Cell Differentiation
Sudipto Das, Niamh Foley, Kenneth Bryan, Karen M. Watters, Isabella Bray, Derek M. Murphy, Patrick G. Buckley, and Raymond L. Stallings

Précis: Findings establish a significant role for microRNA function in the mechanism by which tumor growth is blocked by retinoic acid, widely used to treat certain pediatric and adult tumors.

The RB-E2F1 Pathway Regulates Autophagy
Hong Jiang, Vanesa Martin, Candelaria Gomez-Manzano, David G. Johnson, Marta Alonso, Erin White, Jing Xu, Timothy J. McDonnell, Naoki Shinojima, and Juan Fueyo

Précis: Findings provide a mechanistic explanation for the relevance of RB status in cancer development and its resistance to therapies.

Ratio of miR-196s to HOXC8 Messenger RNA Correlates with Breast Cancer Cell Migration and Metastasis
Yong Li, Maoxiang Zhang, Huijun Chen, Zheng Dong, Vadivel Ganapathy, Muthusamy Thangaraju, and Shuang Huang

Précis: Findings define an miRNA family in metastasis suppression and suggest its use in predicting breast cancer metastatic capability.

RasGRP3 Contributes to Formation and Maintenance of the Prostate Cancer Phenotype
Dazhi Yang, Noemi Kedei, Luowei Li, Juan Tao, Julia F. Velasquez, Aleksandra M. Michalowski, Balázs I. Tóth, Rita Marincsák, Attila Varga, Tamás Biro, Stuart H. Yuspa, and Peter M. Blumberg

Précis: Findings define an important signaling element upstream of Ras in metastatic prostate cancer, which may constitute a novel therapeutic target for treatment of androgen-independent disease.

Dietary Fish Oil Alters T Lymphocyte Cell Populations and Exacerbates Disease in a Mouse Model of Inflammatory Colitis

Précis: Findings that fish oil enriched with DHA can promote colitis and colon adenocarcinoma in mice indicate that supplements for clinical benefit should be approached with caution, particularly in individuals with chronic inflammatory conditions such as inflammatory bowel diseases.
Synergistic Chemosensitivity of Triple-Negative Breast Cancer Cell Lines to Poly(ADP-Ribose) Polymerase Inhibition, Gemcitabine, and Cisplatin

Kedar Hastak, Elizabeth Alii, and James M. Ford

Précis: Findings address the clinical challenge faced by women with "triple-negative" breast cancers which lack hormone receptors or HER2 amplification, an aggressive disease presently without effective treatment options.

Apatinib (YN968D1) Reverses Multidrug Resistance by Inhibiting the Efflux Function of Multiple ATP-Binding Cassette Transporters

Yan-jun Mi, Yong-ju Liang, Hong-bing Huang, Hong-yun Zhao, Chung-Pu Wu, Fang Wang, Li-yang Tao, Chuan-zhao Zhang, Chun-Ling Dai, Amit K. Tiwari, Xiao-xu Ma, Kenneth Kin Wah To, Suresh V. Ambudkar, Zhe-Sheng Chen, and Li-wu Fu

Précis: A tyrosine kinase inhibitor in clinical trials is found to also inhibit multidrug resistance, perhaps expanding its clinical applications in combination with conventional chemotherapeutic drugs.

Tubulin-Targeting Chemotherapy Impairs Androgen Receptor Activity in Prostate Cancer

Meng-Lei Zhu, Craig M. Horbinski, Mark Garzotto, David Z. Qian, Tomasz M. Beer, and Natasha Kyprianou

Précis: The therapeutic effects of taxanes in castration-resistant prostate cancers are linked to their effects on androgen signaling.

Role of LIM and SH3 Protein 1 (LASP1) in the Metastatic Dissemination of Medulloblastoma

Christopher Traenka, Marc Remke, Andrey Korshunov, Sebastian Bender, Thomas Hielshcer, Paul A. Northcott, Hendrik Witt, Marina Ryzhova, Jörg Felsberg, Axel Benner, Stephanie Riester, Wolfram Scheurlen, Thomas G.P. Grunewald, Andreas von Deimling, Andreas E. Kulozik, Guido Reifenberger, Michael D. Taylor, Peter Lichter, Elke Butt, and Stefan M. Pfister

Précis: Findings define and functionally characterize an independent prognostic biomarker involved in the most common malignant brain tumor of childhood.

Aberrant Silencing of Cancer-Related Genes by CpG Hypermethylation Occurs Independently of Their Spatial Organization in the Nucleus


Précis: Extensive chromatin changes at promoters in cancer cells appear to occur locally without preference for nuclear position or repositioning.

Cell Surface Tetraspanin CD9 Mediates Chemoresistance in Small Cell Lung Cancer

Satoshi Kohmo, Takashi Kijima, Yasushi Otani, Masahide Morii, Toshiyuki Minami, Ryo Takahashi, Izumi Nagatomo, Yoshiito Takeda, Hiroshi Kida, Shoo Goya, Mitsuhiro Yoshida, Toru Kumagai, Isao Tachibana, Soichiro Yokota, and Ichiro Kawase

Précis: Findings rationalize antibody attack of a cell surface tetraspanin to reverse drug resistance in highly aggressive small cell lung cancers, which tend to relapse rapidly in resistant forms after initial therapy.

A Novel, Selective, and Efficacious Nanomolar Pyridopyrazinone Inhibitor of V600EBRAF

Steven Whittaker, Delphine Ménard, Ruth Kirk, Lesley Ogilvie, Douglas Hedley, Alfonso Zambon, Filipa Lopes, Natasha Preece, Helen Manne, Sareena Rana, Maryou Lambros, Jorge S. Reis-Filho, Richard Marais, and Caroline J. Springer

Précis: A novel orally bioavailable drug selectively inhibits oncogenic mutants of the BRAF kinase thus eliciting major therapeutic responses in melanomas where BRAF mutations are common.

Contextual Synthetic Lethality of Cancer Cell Kill Based on the Tumor Microenvironment

Norman Chan, Isabel M. Pires, Zuzana Bencokova, Carla Coackley, Kaisa R. Luoto, Nirmal Bhogal, Minalini Lakshman, Ponnari Gottipati, F. Javier Oliver, Thomas Hellday, Ester M. Hammond, and Robert G. Bristow

Précis: Findings broaden the potential application of small molecule inhibitors of the DNA repair polymerase PARP-1, which are currently in clinical trials.
8055

*Genome-wide Analysis of Novel Splice Variants Induced by Topoisomerase I Poisoning Shows Preferential Occurrence in Genes Encoding Splicing Factors*

Stéphanie Solier, Jennifer Barb, Barry R. Zeeberg, Sudhir Varma, Mike C. Ryan, Kurt W. Kohm, John N. Weinstein, Peter J. Munson, and Yves Pommier

*Précis:* Findings explain the abnormal splicing of a large number of genes in response to the generation of topoisomerase I cleavage complexes trapped by certain DNA damaging drugs.

8066

*Aerobic Glycolysis Suppresses p53 Activity to Provide Selective Protection from Apoptosis upon Loss of Growth Signals or Inhibition of BCR-Abl*

Emily F. Mason, Yuxing Zhao, Pankuri Goraksha-Hicks, Jonathan L. Coloff, Hugh Gannon, Stephen N. Jones, and Jeffrey C. Rathmell

*Précis:* This study demonstrates the role of cell metabolism in sensitivity to targeted therapy and suggests that metabolic manipulations may enhance the efficacy of the tyrosine kinase inhibitor Gleevec.

8077

*hsa-miR-191 Is a Candidate Oncogene Target for Hepatocellular Carcinoma Therapy*

Eran Elyakim, Eiran Sitbon, Alexander Faerman, Sarit Tabak, Eve Montia, Liron Belanis, Avital Dov, Eric G. Marcussen, C. Frank Bennett, Ayelet Chajut, Dalia Cohen, and Noga Yerushalmi

*Précis:* Findings offer preclinical proof of concept for a rational strategy to improve treatment of liver cancer, a deadly disease that is particularly common in the Far East.

8088

*Prostate Cancer Radiosensitization through Poly(ADP-Ribose) Polymerase-1 Hyperactivation*

Ying Dong, Erik A. Bey, Long-Shan Li, Wareef Kabbani, Jingsheng Yan, Xian-Jin Xie, Jer-Tsong Hsieh, Jinming Gao, and David A. Boothman

*Précis:* Findings prompt clinical evaluation of β-lapachone (Arq501) as a radiosensitizer for prostate cancer, based on definition of a targeting strategy that exploits overexpression of oxi-doreductase NQO1 and hyperactivation of PARP-1.

8097

*Activity of the Novel Dual Phosphatidylinositol 3-Kinase/Mammalian Target of Rapamycin Inhibitor NVP-BEZ235 against T-Cell Acute Lymphoblastic Leukemia*

Francesca Chiarini, Cecilia Grimaldi, Francesca Ricci, Pier Luigi Tazzari, Camilla Evangelisti, Andrea Ognibene, Michela Battistelli, Elisabetta Falciari, Fraia Melchionda, Andrea Pession, Pasqualepaolo Pagliaro, James A. Mc Kubrey, and Alberto M. Martelli

*Précis:* Preclinical proof of concept study indicates that a novel orally available dual inhibitor of PI3K and mTOR may be a highly effective therapeutic to treat T-cell acute lymphoblastic leukemia.

8108

*IFN Induces miR-21 through a Signal Transducer and Activator of Transcription 3–Dependent Pathway as a Suppressive Negative Feedback on IFN-Induced Apoptosis*

Chuan He Yang, Junming Yue, Meiyun Fan, and Lawrence M. Pfeffer

*Précis:* An oncogenic microRNA overexpressed in many human cancers is shown for the first time in this study to regulate interferon-induced apoptosis.

8117

*De novo Lipogenesis Protects Cancer Cells from Free Radicals and Chemotherapeutics by Promoting Membrane Lipid Saturation*

Evelien Rysman, Koen Brusselmans, Katryn Scheys, Leen Timmermans, Rita Derua, Sebastian Munch, Paul P. Van Veldhoven, David Wallregny, Veerle W. Danieils, Jelle Machiels, Frank Vanderhoydonc, Karine Smans, Etienne Waelkens, Guido Verhoeven, and Johannes V. Swinnen

*Précis:* De novo fatty acid synthesis promotes membrane lipid saturation and helps cancer cells to survive both carcinogenic and therapeutic insults.

8127

*Epithelial-to-Mesenchymal Transition Promotes Tubulin Detyrosination and Microtubules that Enhance Endothelial Engagement*

Rebecca A. Whipple, Michael A. Matrone, Edward H. Cho, Eric M. Balzer, Michele I. Vitolo, Jennifer R. Yoon, Olga B. Ioffe, Kimberly C. Tuttle, Jing Yang, and Stuart S. Martin

*Précis:* Findings elucidate microtubule alterations that prime invasive tumor cells for metastatic reattachment after they have entered the bloodstream.
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<td>8138</td>
<td>Chemotrap-1: An Engineered Soluble Receptor That Blocks Chemokine-Induced Migration of Metastatic Cancer Cells In vivo</td>
<td>Silvia Lanati, Darryl R. Dunn, Myriam Roussigné, Maxine S. Emmett, Virginie Carriere, Denis Jullien, Jessica Budge, Justin Fryer, Monique Erard, Françoise Cailler, Jean-Philippe Girard, and David O. Bates</td>
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<td>8149</td>
<td>Cyclin D2–Cyclin-Dependent Kinase 4/6 Is Required for Efficient Proliferation and Tumorigenesis following Apc Loss</td>
<td>Alicia M. Cole, Kevin Myant, Karen R. Reed, Rachel A. Ridgway, Dimitris Athineos, Gijs R. Van den Brink, Manessa Vunacun, Hans Clevers, Alan R. Clarke, Peter Sicinski, and Owen J. Sansom</td>
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<td>8159</td>
<td>Carcinoembryonic Antigen Interacts with TGF-β Receptor and Inhibits TGF-β Signaling in Colorectal Cancers</td>
<td>Ying Li, Hong Cao, Zhongxian Jiao, Suresh B. Pakala, Divijendra Natha Reddy Sirigiri, Wenpin Li, Rakesh Kumar, and Lopa Mishra</td>
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<td>8169</td>
<td>Unique DNA Methylation Patterns Distinguish Noninvasive and Invasive Urothelial Cancers and Establish an Epigenetic Field Defect in Premalignant Tissue</td>
<td>Erika M. Wolff, Yoshitomo Chihara, Fei Pan, Daniel J. Weisenberger, Kimberly D. Siegmund, Kokichi Sugano, Kiwata Kawashima, Peter W. Laird, Peter A. Jones, and Gangning Liang</td>
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<td>8179</td>
<td>Impact of Stromal Sensitivity on Radiation Response of Tumors Implanted in SCID Hosts Revisited</td>
<td>Mónica García-Barros, Tin Hwe Thin, Jerry Maj, Carlos Cordon-Cardo, Adriana Haimovitz-Friedman, Zvi Fuks, and Richard Kolesnick</td>
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<td>8187</td>
<td>Vascular Endothelial Growth Factor Receptor-1 Signaling Promotes Mobilization of Macrophage Lineage Cells from Bone Marrow and Stimulates Solid Tumor Growth</td>
<td>Masashi Muramatsu, Seiji Yamamoto, Tsuyoshi Osawa, and Masabumi Shibuya</td>
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<td>8199</td>
<td>Silencing of Thrombospondin-1 Is Critical for Myc-Induced Metastatic Phenotypes in Medulloblastoma</td>
<td>Limei Zhou, Daniel Picard, Young-Shin Ra, Meihua Li, Paul A. Northcott, Yagi Hu, Duncan Stearns, Cynthia Hawkins, Michael D. Taylor, James Rutka, Sandy D. Der, and Annie Huang</td>
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<td>8211</td>
<td>Vascular Endothelial Growth Factor Receptor-1 Signaling Promotes Mobilization of Macrophage Lineage Cells from Bone Marrow and Stimulates Solid Tumor Growth</td>
<td>Masashi Muramatsu, Seiji Yamamoto, Tsuyoshi Osawa, and Masabumi Shibuya</td>
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<td>8222</td>
<td>Modulation of Gene Expression and Tumor Cell Growth by Redox Modification of STAT3</td>
<td>Li Li, Shing-hu Cheung, Emma L. Evans, and Peter E. Shaw</td>
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**Précis:**
- Study describes a tractable strategy to treat systemic cancers by sequestering a chemokine known to drive metastasis.
- Apc loss is the key initiating event in colorectal cancer and thus finding target genes that are required for the phenotypes of Apc loss is vital.
- A common clinical marker of cancer progression may also represent a potential therapeutic target, thereby serving as a theranostic molecule.
- Findings offer compelling evidence that noninvasive and invasive bladder tumors arise via distinct epigenetic pathways.
- DNA damage-mediated endothelial clonogenic lethality plays a mandatory role in the complex pathophysiologic mechanism of tumor cure by SDRT, and provides an explanation for the wild-type SDRT responses reported in tumors implanted in SCID mice.
- Study offers proof of concept for an effective therapeutic strategy to treat medulloblastoma, a common pediatric brain cancer where more effective treatments are greatly needed.
- Findings indicate that STAT3 is subject to redox control that influences its ability to promote breast cancer cell proliferation and resistance to oxidative stress.
The Myc–miR-17–92 Axis Blunts TGFβ Signaling and Production of Multiple TGFβ-Dependent Antiangiogenic Factors
Michael Dew, Jamie L. Fox, Stacy Hultine, Prema Sundaram, Wenge Wang, Yingqiu Y. Liu, Emma Furth, Gregory H. Enders, Wafik El-Deiry, Janell M. Schelter, Michele A. Cleary, and Andrei Thomas-Tikhonenko

Précis: Results elucidate a microRNA- and TGFβ-dependent mechanism through which c-Myc acts to control tumor angiogenesis.

LETTERS TO THE EDITOR

Intraprostatic Steroidogenic Enzymes – Letter
Elahe Mostaghel, Peter S. Nelson, Colleen Nelson, and R. Bruce Montgomery

Intraprostatic Steroidogenic Enzymes – Response
Johannes Hofland, Wytske M. van Weerden, Guido Jenster, Fritz H. Schröder, and Frank H. de Jong

ABOUT THE COVER
Tubulin-based microtentacles facilitate epithelial-endothelial attachment. Confocal imaging of human mammary epithelial cells (HMLE) transfected with GFP-Membrane (green) engaging a confluent monolayer of mCherry-labeled (red) human bone endothelial cells. Top, angle, and side views show that HMLE cells remain rounded without observable microtentacles (left vertical panel set). HMLE cells that have undergone an epithelial-to-mesenchymal transition via stable Twist expression display microtentacles, which increase endothelial cell attachment (right vertical panel set). For details, see the article by Whipple et al. on page 8127 of this issue.