### Table of Contents

**November 1, 2014 • Volume 74 • Number 21**

#### BREAKING ADVANCES

5935  
Highlights from Recent Cancer Literature

#### REVIEWS

5937  
Phenotype Switching: Tumor Cell Plasticity as a Resistance Mechanism and Target for Therapy  
Kristel Kemper, Pauline L. de Goeje, Daniel S. Peeper, and Renée van Amerongen

5942  
αvβ6 Expression in Myoepithelial Cells: A Novel Marker for Predicting DCIS Progression with Therapeutic Potential  
Michael D. Allen, John F. Marshall, and J. Louise Jones

#### PRIORITY REPORT

5948  
Synergy between the NAMPT Inhibitor GMX1777(8) and Pemetrexed in Non–Small Cell Lung Cancer Cells Is Mediated by PARP Activation and Enhanced NAD Consumption  
Manuel Chan, Michel Gravel, Alexandre Bramoullié, Gaëlle Bridon, Dina Avizonis, Gordon C. Shore, and Anne Roublon  
**Précis:** This study shows how new NAD-depleting drugs offer a way to leverage the efficacy of clinical agents that target dihydrofolate reductase, used widely in the oncology clinic, in deadly lung adenocarcinomas

#### CLINICAL STUDIES

5955  
A Quantitative Sensory Analysis of Peripheral Neuropathy in Colorectal Cancer and Its Exacerbation by Oxaliplatin Chemotherapy  
Mariana de Carvalho Barbosa, Alyssa K. Kosturakis, Cathy Eng, Gwen Wendelschafer-Crabb, William R. Kennedy, Donald A. Simone, Xin S. Wang, Charles S. Cleeland, and Patrick M. Dougherty  
**Précis:** This clinical study illuminates a connection between the pattern of effects in peripheral neuropathy, a major scourge of successful cancer treatment, with the specific nerve fiber types most vulnerable to cytotoxic chemotherapy, with important implications for how to focus future work to ameliorate risks of this important survivor challenge.

#### INTEGRATED SYSTEMS AND TECHNOLOGIES

5963  
Network Modeling of TGFβ Signaling in Hepatocellular Carcinoma Epithelial-to-Mesenchymal Transition Reveals Joint Sonic Hedgehog and Wnt Pathway Activation  
Steven Nathaniel Steinway, Jorge G.T. Zañudo, Wei Ding, Carl Bart Rountree, David J. Feith, Thomas P. Loughran Jr, and Reka Albert  
**Précis:** In preclinical models of liver cancer, results define a network of signaling pathways that regulate epithelial-mesenchymal transition and might be targeted to blunt malignant progression.

5978  
Modeling Lung Cancer Evolution and Preclinical Response by Orthotopic Mouse Allografts  
Chiara Ambrogio, Francisco J. Carmona, August Vidal, Mattia Falcone, Patricia Nieto, Octavio A. Romero, Sara Puertas, Miguel Vizoso, Ernest Nadal, Teresa Poggio,Montserrat Sánchez-Cespedes, Manel Esteller, Francisca Mulero, Claudia Voena, Roberto Chiarle, Mariano Barbadic, David Santamaría, and Alberto Villanueva  
**Précis:** Orthoallografts grown from murine primary non–small cell lung cancers recapitulate both the histopathological features and therapeutic responses seen clinically in advanced human disease, potentially improving preclinical modeling needed for effective drug development in this setting.

#### MICROENVIRONMENT AND IMMUNOLOGY

5989  
The Alarmin HMGN1 Contributes to Antitumor Immunity and Is a Potent Immunoadjuvant  
Feng Wei, De Yang, Poonam Tewary, Yana Li, Sandra Li, Xin Chen, O.M. Zack Howard, Michael Bustin, and Joost J. Oppenheim  
**Précis:** An HMGB1-related protein that also functions as a danger signal/alarmin to promote T-cell immunity is found to contribute to T cell-dependent antitumor responses, with implications for its possible use as an adjuvant to heighten responses to cancer vaccines.
### Table of Contents

**5999** MYCN-Dependent Expression of Sulfatase-2 Regulates Neuroblastoma Cell Survival  
Valeria Solari, Lucia Borriello, Gianluca Turcatel, Hiroyuki Shimada, Richard Spoto,  
G. Esteban Fernandez, Shahab Asgharzadeh, Edwin A. Yates, Jeremy E. Turnbull, and  
Yves A. DeClerck  

Precis: An enzyme responsible for modifying extracellular proteoglycans appears to be an important mediator of the effects of the MYCN oncogene in a deadly pediatric tumor, offering new insights into how MYCN drives malignancy by altering the tumor microenvironment.

**6010** Vaccine-Elicited CD8\(^+\) T Cells Cure Mesothelioma by Overcoming Tumor-Induced Immunosuppressive Environment  
Zhiwu Tan, Jingying Zhou, Allen K.L. Cheung, Zhe Yu, Ka-Wai Cheung, Jianguo Liang,  
Haibo Wang, Boon Kiat Lee, Kwan Man, Li Liu, Kwok-Yung Yuen, and Zhivei Chen  

Precis: DNA vaccination can achieve complete cure of mesothelioma by eliciting enhanced CD8\(^+\) T cells that can overcome the tumor-induced immunosuppressive environment.

**6022** Adverse Immunoregulatory Effects of 5FU and CPT11 Chemotherapy on Myeloid-Derived Suppressor Cells and Colorectal Cancer Outcomes  
Julia Kanterman, Moshe Sade-Feldman, Moshe Biton, Elinar Ish-Shalom, Audrey Lasry,  
Aviya Goldshtein, Ayala Hubert, and Michal Baniyash  

Precis: 5FU/CPT11, a combination chemotherapy regimen used widely in patients with gastrointestinal cancers, may reinforce immunosuppression and thereby limits the benefits to be gained by recruiting the immune system to improve patient treatment.

**6048** Reducing CD73 Expression by IL1\(\beta\)-Programmed Th17 Cells Improves Immunotherapeutic Control of Tumors  
Shilpak Chatterjee, Krishnamurthy Thyagarajan, Pravin Kesarwani, Jin H. Song,  
Myroslawa Soloshchenko, Jianing Fu, Stefanie R. Bailey, Chenthamarkshan Vasu,  
Andrew S. Kraft, Chrystal M. Paulos, Xue-Zhong Yu, and Shikhar Mehrotra  

Precis: These findings show that including TGF\(\beta\) in ex vivo cultures used to program Th17 cells damages their immunotherapeutic potential, and they show how this potential can be more potently realized for adoptive T-cell immunotherapy in cancer patients.

**6048** Promoting Thiol Expression Increases the Durability of Antitumor T-cell Functions  
Pravin Kesarwani, Amir A. Al-Khami, Gina Scurti,  
Krishnamurthy Thyagarajan, Gina Scurti,  
Shahid Husain, Quan Fang, Osama S. Naga, Patricia Simms, Gyda Beeson,  
Christina Voelkel-Johnson, Elizabeth Garrett-Mayer, Craig C. Beeson,  
Michael I. Nishimura, and Shikhar Mehrotra  

Precis: Higher cell surface expression of thiol groups on T cells is associated with superior in vivo persistence and antitumor activity, with implications for improving T cell preparations used in adoptive immunotherapy for patients.

**6060** ipH4102, a Humanized KIR3DL2 Antibody with Potent Activity against Cutaneous T-cell Lymphoma  
Anne Marie-Cardine, Nicolas Viaud, Nicolas Thonnart, Rachel Joly, Stéphanie Chanteux,  
Laurent Gauthier, Cécile Bonnafous, Benjamin Rossi, Mathieu Bléry, Carine Paturel,  
Armand Bensussan, Martine Bagot, and Hélène Sicard  

Precis: This study offers a preclinical proof of concept for development of a novel therapy that targets one of the most relevant tumor antigens in cutaneous T-cell lymphoma, where there remains unmet medical need.

**6071** Whole-Genome Sequencing of Asian Lung Cancers: Second-Hand Smoke Unlikely to Be Responsible for Higher Incidence of Lung Cancer among Asian Never-Smokers  
Vidhya G. Krishnan, Philip J. Ebert, Jason C. Ting,  
Elaine Lim, Swee-Seong Wong, Audrey S.M. Teo,  
Yong G. Yue, Hui-Hoon Chua, Xiwen Ma,  
Gary S.L. Loh, Yuhao Lin, Joanna H.J. Tan, Kun Yu,  
Shenli Zhang, Christoph Reinhard, Daniel S.W. Tan,  
Brock A. Peters, Stephen E. Lincoln,  
Dennis G. Ballinger, Jason M. Laramie,  
Geoffrey B. Nilsen, Thomas D. Barber, Patrick Tan,  
Axel M. Hillmer, and Pauline C. Ng  

Precis: This whole genome study of Asian lung cancer patients, the largest performed to date, refutes the long-standing presumption that Asian never-smokers have a higher incidence of lung cancer due to secondhand smoke, which does not appear to be the case.
Table of Contents

6082 HTLV-1 bZIP Factor HBZ Promotes Cell Proliferation and Genetic Instability by Activating OncomiRs
Céline Vernin, Morgan Thenoz, Christiane Pinatel, Antoine Gessain, Olivier Gout, Marie-Hélène Delfau-Larue, Nicolas Nazaret, Catherine Legras-Lachuer, Eric Wattel, and Franck Mortreux

 précis: As one of the few viruses definitively linked to cancer, HTLV-1 retains interest as a tool to gain insights into the pathogenic origins of cancer, hereby challenging the long-standing idea that the viral gene product Tax is most critical in directing early leukemogenesis.

6094 ALK-Dependent Control of Hypoxia-Inducible Factors Mediates Tumor Growth and Metastasis
Cinzia Martinengo, Teresa Poggio, Matteo Menotti, Maria Stella Scalzo, Cristina Ambrogio, Elisa Pellegrino, Ludovica Riera, Roberto Viva, Domenico Ribatti, Fabio Pastorino, Patrizia Perri, Mirco Ponzoni, Qi Wang, Claudia Voena, and Roberto Chiarle

 précis: This study offers a rationale to explore ALK kinase inhibitors as effective treatments for certain lymphomas and small cell lung cancers, where ALK activity affects hypoxia responses and angiogenesis.

6107 Metastatic Heterogeneity of Breast Cancer Cells Is Associated with Expression of a Heterogeneous TGFβ-Activating miR424–503 Gene Cluster
Yun Li, Wei Li, Zhe Ying, Han Tian, Xun Zhu, Jun Li, and Mengfeng Li

 précis: These findings define a microRNA cluster that controls the intensity of TGFβ signaling and metastatic response in breast cancer cells, with possible implications in cancer-associated deregulation of TGFβ signaling generally.

6119 Stress Response Protein Cipr Links Inflammation and Tumorigenesis in Colitis-Associated Cancer
Toshiharu Sakurai, Hiroshi Kashida, Tomohiro Watanabe, Satoru Hagiwara, Tsuneziku Mizushima, Hideki Iijima, Naoshi Nishida, Hiroki Higashitsuji, Jun Fujita, and Masatoshi Kudo

 précis: A little-studied RNA binding protein is found to act as a positive modifier of inflammation-driven colon cancers, contributing to the development of inflammatory bowel disease as well as colitis-associated cancer in established preclinical models.

6129 Molecular Characterization of Chronic-type Adult T-cell Leukemia/Lymphoma
Noriaki Yoshida, Kennosuke Karube, Atae Utsunomiya, Kunihiro Tsukasaki, Yoshitaka Imai, Naoya Taira, Naokuni Uike, Akira Umino, Kotaro Arita, Miyuki Suguro, Shinobu Tsuzuki, Tomohiro Kinoshita, Koichi Ohshima, and Masao Seto

 précis: A comprehensive genomic analysis of a rare subtype of chronic type adult T-cell leukemia/lymphoma identifies markers that predict emergence of the more acute, deadly subtype.

6139 Definition of Smad3 Phosphorylation Events That Affect Malignant and Metastatic Behaviors in Breast Cancer Cells
Eunjin Bae, Misako Sato, Ran-Ju Kim, Mi-Kyung Kwak, Kazuhiro Naka, Jungsoo Gim, Mitsukata Kadota, Binwu Tang, Kathleen C. Flanders, Tae-Aug Kim, Sun-Hee Leem, Taesung Park, Fang Liu, Lalage M. Wakefield, Seong-Jin Kim, and Akira Ooshima

 précis: These findings reveal a key mechanism favoring metastatic progression of breast cancers to the lung, with implications for how to prevent or treat this process clinically.

6150 Pro-Oncogenic Role of Alternative p38 Mitogen-Activated Protein Kinases p38γ and p38δ, Linking Inflammation and Cancer in Colitis-Associated Colon Cancer
Paloma del Reino, Dayanira Alsina-Beauchamp, Alejandra Escós, M.ª Isabel Cerezo-Guisado, Ana Risco, Noelia Aparicio, Rafal Zur, Marian Fernandez-Estévez, Elena Collantes, Jose Montans, and Ana Cuenda

 précis: These findings offer a sound preclinical rationale to strongly consider the p38γ and p38δ stress-activated kinases as potential therapeutic targets for colon cancer treatment.

BRCA1 Suppresses Epithelial-to-Mesenchymal Transition and Stem Cell Dedifferentiation during Mammary and Tumor Development
Feng Bai, Ho Lam Chan, Alexandria Scott, Matthew D. Smith, Cheng Fan, Jason L. Herschkowitz, Charles M. Perou, Alan S. Livingstone, David J. Robbins, Anthony J. Capobianco, and Xin-Hai Pei

 précis: This study offers the first genetic evidence that the BRCA1 gene acts directly to suppress epithelial-mesenchymal transition during breast tumorigenesis, offering an explanation for why BRCA1 mutation carriers are prone to aggressive basal-like breast cancers.
A Recurrent Activating PLCG1 Mutation in Cardiac Angiosarcomas Increases Apoptosis Resistance and Invasiveness of Endothelial Cells
Kristin Kunze, Tilmann Spieker, Ulrike Gamerding, Kerstin Nau, Johannes Berger, Thomas Dreyer, Jürgen R. Sindermann, Andreas Hoffmeier, Stefan Gattenlöcher, and Andreas Brauninger

Précis: Mutation of PLCG1 identified in rare tumor may provide insights into apoptosis resistance and invasion.

Genetic Deletion of AEG-1 Prevents Hepatocarcinogenesis

Précis: This potentially seminal study unravels a novel role for the AEG-1 oncogene in shaping the tumor microenvironment in a manner that is essential for liver cancer development.

Vitamin D Suppresses Leptin Stimulation of Cancer Growth through microRNA
Ravi Kasiappan, Yuefeng Sun, Panida Lungchukiet, Waise Quarni, Xiaohong Zhang, and Wenlong Bai

Précis: This study suggests that vitamin D supplements may help obese women reduce their risk of cancer.

Therapeutic Targeting of BRCA1-Mutated Breast Cancers with Agents That Activate DNA Repair
Elizabeth Alli, David Solow-Cordero, Stephanie C. Casey, and James M. Ford

Précis: This work offers a preclinical proof of concept for a wholly new approach to chemoprevention in carriers of BRCA1 mutations as a strategy to reduce the prevalence of BRCA1-associated malignancy.

Pretargeted Dual-Modality Immuno-SPECT and Near-Infrared Fluorescence Imaging for Image-Guided Surgery of Prostate Cancer

Précis: This study describes a major advancement to methods used in surgical resections of primary prostate cancer, where image-guided techniques are increasingly important and can extend time to progression in patients.

Pancreatic Cancer–Specific Cell Death Induced In Vivo by Cytoplasmic-Delivered Polyinosine–Polycytidylic Acid
Praveen Bhoopathi, Bridget A. Quinn, Qin Gui, Xue-Ning Shen, Steven R. Grossman, Swadesh K. Das, Devanand Sarkar, Paul B. Fisher, and Luni Emdad

Précis: These findings offer a preclinical proof of concept for immediate evaluation of an immune adjuvant that also triggers apoptosis in pancreatic cancer cells, as a novel type of immunochemotherapy to treat pancreatic cancer.

A Small-Molecule Modulator of the Tumor-Suppressor miR34a Inhibits the Growth of Hepatocellular Carcinoma
Zhangang Xiao, Chi Han Li, Stephen L. Chan, Feiyue Xu, Lu Feng, Yan Wang, Jian-Dong Jiang, Joseph J.Y. Sung, Christopher H.K. Cheng, and Yangchao Chen

Précis: These findings offer preclinical proof of concept for a lead small molecule candidate as a new class of therapeutic for liver cancer, based on restoration of miR-34a tumor suppressor function.
Activated d16HER2 Homodimers and SRC Kinase Mediate Optimal Efficacy for Trastuzumab

Lorenzo Castagnoli, Manuela Iezzi, Gaia C. Ghedini, Valentina Ciravolo, Giulia Marzano, Alessia Lamoliniara, Roberta Zappasodi, Patrizia Gasparini, Manuela Campiglio, Augusto Amici, Claudia Chiodoni, Arianna Palladini, Pier Luigi Lollini, Tiziana Triulzi, Sylvie Menard, Patrizia Nanni, Elda Tagliafue, and Serenella M. Pupa

Précis: Mouse genetic and clinical results establish the variant HER2 signaling axis as a marker for optimal responses to trastuzumab treatment, with immediate clinical implications.

Effective Cancer Vaccine Platform Based on Attenuated Salmonella and a Type III Secretion System


Précis: This study describes an orally administered Salmonella-based vector system that can present tumor antigens to the immune system in a manner that yields potent antitumor responses, offering a novel platform for the engineering of more effective cancer vaccines.

Targeted Noninvasive Imaging of EGFR-Expressing Orthotopic Pancreatic Cancer Using Multispectral Optoacoustic Tomography

Shaniee V. Hudson, Justin S. Huang, Wenyuan Yin, Sabrin Albeituni, Jamie Rush, Anil Khanal, Jun Yan, Brian P. Ceresa, Hermann B. Frieboes, and Lacey R. McNally

Précis: The technology described in this report offers the potential to detect pancreatic tumors with higher specificity and sensitivity, in both the preclinical and clinical settings, than existing technology permits.

miR326 Maturation Is Crucial for VEGF-C-Driven Cortactin Expression and Esophageal Cancer Progression

Chih-Chen Hong, Pai-Sheng Chen, Jien Chiu, Ching-Feng Chiu, Ching-Yao Yang, Michael Hsiao, Yi-Wen Chang, Yang-Hao Yu, Mien-Chie Hung, Nai-Wen Hsu, Shue-Gwo Shiah, Nan-Yung Hsu, and Jen-Liang Su

Précis: These findings offer insights into how a key driver of esophageal cancer enhances its robust invasive and metastatic properties, with potential implications for the development of new biomarkers or therapies in this setting.

Distinct Subpopulations of Head and Neck Cancer Cells with Different Levels of Intracellular Reactive Oxygen Species Exhibit Diverse Stemness, Proliferation, and Chemosensitivity

Ching-Wen Chang, Yu-Syuan Chen, Shiu-Huey Chou, Chia-Li Han, Yu-Ju Chen, Cheng-Chieh Yang, Chih-Yang Huang, and Jeng-Fan Lo

Précis: These findings suggest that strategies to stimulate low intracellular ROS levels, found here to be associated with stemness and chemoresistance in head and neck squamous cancers, should be explored clinically in combination with conventional chemotherapy.

PAD2 Overexpression in Transgenic Mice Promotes Spontaneous Skin Neoplasia


Précis: These findings provide a mechanistic rationale to target a highly tractable enzyme to prevent or treat inflammation-associated skin carcinomas.

SCCA1/SerpinB3 Promotes Oncogenesis and Epithelial–Mesenchymal Transition via the Unfolded Protein Response and IL6 Signaling

Namratha Sheshadri, Joseph M. Catanzaro, Alex J. Bott, Yu Sun, Erica Ullman, Emily I. Chen, Ji-An Pan, Song Wu, Howard C. Crawford, Jianhua Zhang, and Wei-Xing Zong

Précis: A protease inhibitor that is overexpressed in many human cancers is found to promote tumorigenesis by upregulating IL6 signaling in the tumor microenvironment.
Table of Contents

6330 Transient SNAIL1 Expression Is Necessary for Metastatic Competence in Breast Cancer
Hung D. Tran, Krishna Luitel, Michael Kim, Kun Zhang, Gregory D. Longmore, and David D. Tran
Précis: These findings provide a compelling genetic rationale to target metastasis by impeding a major regulator of this process despite its transient requirement.

6341 Holo-Retinol–Binding Protein and Its Receptor STRA6 Drive Oncogenic Transformation
Daniel C. Berry, Liraz Levi, and Noa Noy
Précis: Results suggest that the blood carrier of vitamin A and its cell surface transporter and signaling receptor STRA6 may comprise novel targets for cancer therapy.

6352 Ceramide Kinase Promotes Tumor Cell Survival and Mammary Tumor Recurrence
Ania W. Payne, Dhruv K. Pant, Tien-Chi Pan, and Lewis A. Chodosh
Précis: Results identify an actionable pathway in breast cancer patients that might be blocked during chemotherapy to limit tumor recurrence and extend survival.

6364 Notch Signaling Drives Stemness and Tumorigenicity of Esophageal Adenocarcinoma
Zhiqiang Wang, Thiago G. Da Silva, Ke Jin, Xiaoxing Han, Prathibha Ranganathan, Xiaoxia Zhu, Avencia Sanchez-Mejias, Feng Bai, Bin Li, Dennis Liang Fei, Kelly Weaver, Rodrigo Vasquez-Del Carpio, Anna E. Moscovitz, Vadim P. Koshenkov, Lilly Sanchez, Lynne Sparling, Xin-Hai Pei, Dido Franceschi, Afonso Ribeiro, David J. Robbins, Alan S. Livingstone, and Anthony J. Capobianco
Précis: This study provides a preclinical proof of concept for the repositioning of gamma-secretase inhibitors, previously evaluated in clinical trials, as a new treatment for aggressive esophageal cancers.

ABOUT THE COVER
Astrocyte elevated gene-1 (AEG-1) is an oncogene that is overexpressed in all cancers. Although the oncogenic function of AEG-1 has been studied in tumor cells, as yet the role of AEG-1 in tumor microenvironment cells has not been analyzed. Using immunofluorescence it was documented that AEG-1 is expressed at a high level in macrophages, and functional studies documented that macrophage AEG-1 plays an important role in regulating NF-κB activation and thereby initiation of hepatocarcinogenesis. For details, see article by Robertson and colleagues on page 6184.