

# Cancer Research

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## 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  **$\alpha$ v $\beta$ 6 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 Bramoullé, Gaëlle Bridon, Daina Avizonis, Gordon C. Shore, and Anne Roulston

**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 TGF $\beta$  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-Céspedes, Manel Esteller, Francisca Mulero, Claudia Voena, Roberto Chiarle, Mariano Barbacid, 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 HMGB1 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.

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- 5999 MYCN-Dependent Expression of Sulfatase-2 Regulates Neuroblastoma Cell Survival**  
Valeria Solari, Lucia Borriello, Gianluca Turcatel, Hiroyuki Shimada, Richard Sposto, G. Esteban Fernandez, Shahab Asgharzadeh, Edwin A. Yates, Jeremy E. Turnbull, and Yves A. DeClerck  
*Précis:* 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<sup>+</sup> 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 Zhiwei Chen  
*Précis:* DNA vaccination can achieve complete cure of mesothelioma by eliciting enhanced CD8<sup>+</sup> 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, Eliran Ish-Shalom, Audrey Lasry, Aviya Goldshtein, Ayala Hubert, and Michal Baniyash  
*Précis:* FOLFIRI, 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.
- 6036 Promoting Thiol Expression Increases the Durability of Antitumor T-cell Functions**  
Pravin Kesarwani, Amir A. Al-Khami, Gina Scurti, Krishnamurthy Thyagarajan, Navtej Kaur, 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  
*Précis:* 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.

- 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  
*Précis:* 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.
- 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  
*Précis:* 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.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 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  
*Précis:* 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 second-hand smoke, which does not appear to be the case.

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- 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 Mastini, Chiara Ambrogio, Elisa Pellegrino, Ludovica Riera, Roberto Piva, 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 non-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 TGF $\beta$ -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 TGF $\beta$  signaling and metastatic response in breast cancer cells, with possible implications in cancer-associated deregulation of TGF $\beta$  signaling generally.
- 6119 Stress Response Protein Cirp Links Inflammation and Tumorigenesis in Colitis-Associated Cancer**  
Toshiharu Sakurai, Hiroshi Kashida, Tomohiro Watanabe, Satoru Hagiwara, Tsunekazu Mizushima, Hideki Iijima, Naoshi Nishida, Hiroaki 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 Imaizumi, 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, Kazuhito Naka, Jungsoo Gim, Mitsutaka 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 p38 $\gamma$  and p38 $\delta$ , Linking Inflammation and Cancer in Colitis-Associated Colon Cancer**  
Paloma del Reino, Dayanira Alsina-Beauchamp, Alejandra Escós, M<sup>a</sup> 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 p38 $\gamma$  and p38 $\delta$  stress-activated kinases as potential therapeutic targets for colon cancer treatment.
- 6161 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 I. 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.

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**6173 A Recurrent Activating *PLCG1* Mutation in Cardiac Angiosarcomas Increases Apoptosis Resistance and Invasiveness of Endothelial Cells**

Kristin Kunze, Tilmann Spieker, Ulrike Gamerdinger, Kerstin Nau, Johannes Berger, Thomas Dreyer, Jürgen R. Sindermann, Andreas Hoffmeier, Stefan Gattenlöhner, and Andreas Bräuninger

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

**6184 Genetic Deletion of *AEG-1* Prevents Hepatocarcinogenesis**

Chadia L. Robertson, Jyoti Srivastava, Ayesha Siddiq, Rachel Gredler, Luni Emdad, Devaraja Rajasekaran, Maaged Akiel, Xue-Ning Shen, Chunqing Guo, Shah Giashuddin, Xiang-Yang Wang, Shobha Ghosh, Mark A. Subler, Jolene J. Windle, Paul B. Fisher, and Devanand Sarkar

**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.

**6194 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.

## PREVENTION AND EPIDEMIOLOGY

**6205 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.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**6216 Pretargeted Dual-Modality Immuno-SPECT and Near-Infrared Fluorescence Imaging for Image-Guided Surgery of Prostate Cancer**

Susanne Lütje, Mark Rijpkema, David M. Goldenberg, Catharina M. van Rij, Robert M. Sharkey, William J. McBride, Gerben M. Franssen, Cathelijne Frielink, Wijnand Helfrich, Wim J.G. Oyen, and Otto C. Boerman

**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.

**6224 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 immunotherapy to treat pancreatic cancer.


**6236 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.


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- 6248** **Activated d16HER2 Homodimers and SRC Kinase Mediate Optimal Efficacy for Trastuzumab**  
 Lorenzo Castagnoli, Manuela Iezzi, Gaia C. Ghedini, Valentina Ciravolo, Giulia Marzano, Alessia Lamolinara, Roberta Zappasodi, Patrizia Gasparini, Manuela Campiglio, Augusto Amici, Claudia Chiodoni, Arianna Palladini, Pier Luigi Lollini, Tiziana Triulzi, Sylvie Menard, Patrizia Nanni, Elda Tagliabue, 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.

- 6260** **Effective Cancer Vaccine Platform Based on Attenuated *Salmonella* and a Type III Secretion System**  
Xin Xu, Wael A.H. Hegazy, Linjie Guo, Xiuhua Gao, Amy N. Courtney, Suhrab Kurbanov, Daofeng Liu, Gengwen Tian, Edwin R. Manuel, Don J. Diamond, Michael Hensel, and Leonid S. Metelitsa  
*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.

- 6271** **Targeted Noninvasive Imaging of EGFR-Expressing Orthotopic Pancreatic Cancer Using Multispectral Optoacoustic Tomography**  
Shanice 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.

## TUMOR AND STEM CELL BIOLOGY

- 6280** **miR326 Maturation Is Crucial for VEGF-C-Driven Cortactin Expression and Esophageal Cancer Progression**  
 Chih-Chen Hong, Pai-Sheng Chen, Jean Chiou, Ching-Feng Chiu, Ching-Yao Yang, Michael Hsiao, Yi-Wen Chang, Yang-Hao Yu, Mien-Chie Hung, Nai-Wen Hsu, Shine-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.

- 6291** **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.

- 6306** **PAD2 Overexpression in Transgenic Mice Promotes Spontaneous Skin Neoplasia**  
John L. McElwee, Sunish Mohanan, Sachi Horibata, Kelly L. Sams, Lynne J. Anguish, Dalton McLean, Iva Cvitaš, Joseph J. Wakshlag, and Scott A. Coonrod  
*Précis:* These findings provide a mechanistic rationale to target a highly tractable enzyme to prevent or treat inflammation-associated skin carcinomas.

- 6318** **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.

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**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, Xiaoqing 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

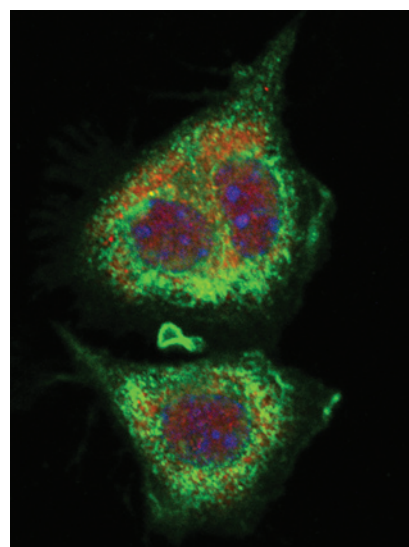
**Précis:** *This study provides a preclinical proof of concept for the repositioning of gamma-secretase inhibitors, previously evaluated in clinical trials, as a new treatment for aggressive esophageal cancers.*

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## 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- $\kappa$ B activation and thereby initiation of hepatocarcinogenesis. For details, see article by Robertson and colleagues on page 6184.



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