CANCER RESEARCH
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8259 Functional MicroRNA Is Transferred between Glioma Cells
Mark Katakowski, Benjamin Buller, Xinli Wang, Thomas Rogers, and Michael Chopp

Précis: miRNA that is transcribed in one cancer cell can be transported by innate mechanisms to a neighboring cell where it can regulate translation, providing direct evidence that RNA can act as a signaling molecule.

8268 DLC1 Negatively Regulates Angiogenesis in a Paracrine Fashion
Yi-Ping Shih, Yi-Chun Liao, Yuan Lin, and Su Hao Lo

Précis: Attenuation of a Rho GTPase regulatory protein in prostate cancers may drive cancer progression by promoting VEGF-mediated angiogenesis.

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8276 Transcriptome Analysis Reveals that p53 and β-Catenin Alterations Occur in a Group of Aggressive Adrenocortical Cancers
Bruno Ragazzon, Rossella Libé, Sébastien Gaujoux, Guillaume Assié, Amato Fratticci, Pierre Launay, Eric Clauser, Xavier Bertagna, Frédérique Tissier, Aurélien de Reyniès, and Jérôme Bertherat

Précis: Study reveals important respective roles of p53 and β-catenin in adrenocortical carcinoma development, delineating distinct tumor subgroups and outcomes.

8282 Transcriptional Activation by pRB and Its Coordination with SWI/SNF Recruitment
Stephen Flowers, George R. Beck, Jr., and Elizabeth Moran

Précis: Findings reveal the essential role for recruitment of a specific chromatin-remodeling complex by the retinoblastoma protein in transactivation.

8288 MicroRNA Expression and Clinical Outcomes in Patients Treated with Adjuvant Chemotherapy after Complete Resection of Non–Small Cell Lung Carcinoma

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Précis: Rapid and sensitive pharmacodynamic assays that can handle very small patient samples are needed to assist the clinical development of targeted therapeutics.

8309 | Early Detection of Recurrent Breast Cancer Using Metabolite Profiling
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Précis: Metabolic profiling of blood serum by NMR and mass spectroscopy can detect breast cancer relapse before it occurs, opening a window of opportunity for patients and oncologists to improve treatment.

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Katherine L. Cook, Linda J. Metheny-Barlow, E. Ann Tallant, and Patricia E. Gallagher

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8329 | Heparanase Enhances Local and Systemic Osteolysis in Multiple Myeloma by Upregulating the Expression and Secretion of RANKL
Yang Yang, Yongsheng Ren, Vishnu C. Ramani, Li Nan, Larry J. Suva, and Ralph D. Sanderson

Précis: Study provides important mechanistic insights into the action of a key driver of bone metastasis.

8339 | Peptide Vaccination after T-Cell Transfer Causes Massive Clonal Expansion, Tumor Eradication, and Manageable Cytokine Storm
Long V. Ly, Marjolein Sluijter, Mieke Versluis, Gre P.M. Luyten, Sjoerd H. van der Burg, Cornels J.M. Melief, Martine J. Jager, and Thorbald van Hall

Précis: Study describes refinements to active immunotherapy by adoptive T-cell transfer that can heighten effective antitumor T-cell responses in non-lymphodepleted hosts, prompting clinical investigations.

8347 | Cdc42-Interacting Protein 4 Promotes Breast Cancer Cell Invasion and Formation of Invadopodia through Activation of N-WASp
Christina S. Pichot, Constandina Arvanitis, Sean M. Hartig, Samuel A. Jensen, John Bechill, Saad Marzouk, Jindan Yu, Jeffrey A. Frost, and Seth J. Corey

Précis: Cell membrane remodeling proteins containing BAR domains are a functionally unique class of proteins being found to contribute to cell migration and invadopodia formation in invasive breast cancers.

8357 | Differential Effects of VEGFR-1 and VEGFR-2 Inhibition on Tumor Metastases Based on Host Organ Environment
Yoon-Jin Lee, Daniel L. Karl, Ugwuji N. Maduekwe, Courtney Rothrock, Sandra Ryeom, Patricia A. D’Amore, and Sam S. Yoon

Précis: VEGF promotes tumor angiogenesis primarily through activation of VEGFR-2, but vascularization of liver metastases is dependent on VEGFR-1 activation.

8368 | CD4+ T-Cell Help in the Tumor Milieu Is Required for Recruitment and Cytolytic Function of CD8+ T Lymphocytes
Rinke Bos and Linda A. Sherman

Précis: Antitumor efficacy of tumor-specific CD8 T cells relies upon two T-cell helper functions that must be delivered within the tumor microenvironment.
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<td>Précis: Findings argue that overexpression of Sp transcription factor Sp2 occurring in a variety of human cancers is likely to have significant functional impact.</td>
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<td>Précis: Study defines key mechanisms by which a central oncogenic driver in melanoma can trigger cell senescence, with implications for understanding the relationships between cancer and aging.</td>
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<td>Précis: Discovery of a new mechanism of ER regulation mediated by HER2 fragments suggests a new strategy to improve patient responses to endocrine therapy in breast cancer.</td>
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The miR-17-92 Cluster of MicroRNAs Confers Tumorigenicity by Inhibiting Oncogene-Induced Senescence
Lixin Hong, Maoyi Lai, Michelle Chen, Changchuan Xie, Rong Liao, Young Jun Kang, Changchun Xiao, Wen-Yuan Hu, Jiahuaui Han, and Peiqing Sun

Précis: Study defines a mechanistic basis to understand the pro-oncogenic role of an important microRNA gene cluster in cancer.

Danger Signaling Protein HMGB1 Induces a Distinct Form of Cell Death Accompanied by Formation of Giant Mitochondria
Georg Gdynia, Martina Keith, Jürgen Kopitz, Marion Bergmann, Anne Fassl, Alexander N.R. Weber, Julie George, Tim Kees, Hans-Walter Zentgraf, Otmar D. Wiestler, Peter Schirmacher, and Wilfried Roth

Précis: When released into the tissue environment by damaged cells, the DNA binding protein HMGB1 stimulates an inflammatory response from innate immune cells and a distinct necrosis-like form of cancer cell death with therapeutic potential.

Human Papillomavirus Infection and Reinfection in Adult Women: the Role of Sexual Activity and Natural Immunity
Helen Trottier, Silvaneide Ferreira, Patricia Thomann, Maria C. Costa, Joao S. Sobrinho, José Carlos M. Prado, Thomas E. Rohan, Luisa L. Villa, and Eduardo L. Franco

Précis: This study has important public health implications concerning vaccination of adult women to prevent cervical cancer.

Hierarchical Clustering of Human Papilloma Virus Genotype Patterns in the ASCUS-LSIL Triage Study
Nicolas Wentzensen, Lauren E. Wilson, Cosette M. Wheeler, Joseph D. Carreon, Patti E. Gravitt, Mark Schiffman, and Philip E. Castle

Précis: Findings suggest a novel approach to complex HPV genotype patterns in cervical disease that can address disease misclassification and HPV genotype distributions in different populations.

D. Michal Freedman, Anne C. Looker, Christian C. Abnet, Martha S. Linet, and Barry I. Graubard

Précis: In this prospective study in NHANES III, overall cancer mortality risks were unrelated to baseline vitamin D status.

Detection of Elevated Plasma Levels of Epidermal Growth Factor Receptor Before Breast Cancer Diagnosis among Hormone Therapy Users
Sharon J. Pitteri, Lynn M. Amon, Tina Busald Buson, Yuzheng Zhang, Melissa M. Johnson, Alice Chin, Jacob Kennedy, Chee-Hong Wong, Qing Zhang, Hong Wang, Paul D. Lampe, Ross L. Prentice, Martin W. McIntosh, Samir M. Hanash, and Christopher I. Li

Précis: Findings suggest a marker that may make it possible to predict the emergence of breast cancer, particularly among women treated with menopausal hormone therapy.

Zoledronic Acid Reduces Bone Loss and Tumor Growth in an Orthotopic Xenograft Model of Osteolytic Oral Squamous Cell Carcinoma

Précis: A combination of noninvasive imaging methods reveals inhibitory effects of the clinical drug zoledronic acid on bone resorption in oral squamous cell carcinoma.

A New Paradigm for Aptamer Therapeutic AS1411 Action: Uptake by Macropinocytosis and Its Stimulation by a Nucleolin-Dependent Mechanism
E. Merit Reyes-Reyes, Yun Teng, and Paula J. Bates

Précis: Results suggest a new model to understand the activity of a quadruplex-forming oligonucleotide therapeutic in phase II clinical trials, which may be generally relevant to drug delivery and gene therapy strategies.
DNA Damage Recognition via Activated ATM and p53 Pathway in Nonproliferating Human Prostate Tissue
Sari Jäämaa, Taija M. af Hällström, Anna Sankila, Ville Rantanen, Hannu Koistinen, Ulf-Håkan Stenman, Zhewei Zhang, Zhiming Yang, Angelo M. De Marzo, Kimmo Taari, Mirja Ruutu, Leif C. Andersson, and Marikki Laiho

Précis: Human prostate tissue shows unexpected activation of DNA damage response signaling pathway markers implicating susceptibility of the luminal cells to DNA damage.

Heat Shock Protein 90 Inhibition Depletes LATS1 and LATS2, Two Regulators of the Mammalian Hippo Tumor Suppressor Pathway
Catherine J. Huntoon, Monica D. Nye, Liyi Geng, Kevin L. Peterson, Karen S. Flatten, Paul Haluska, Scott H. Kaufmann, and Larry M. Karnitz

Précis: Findings identify an important mechanism by which HSP90 inhibitors currently being tested in clinical trials may disable a tumor suppressor pathway and promote tumorigenesis.

FTY720 (Fingolimod) Sensitizes Prostate Cancer Cells to Radiotherapy by Inhibition of Sphingosine Kinase-1
Dmitri Pchejetski, Torsten Bohler, Leyre Brizuela, Lysann Sauer, Nicolas Doumerc, Muriel Golzio, Vishal Salunkhe, Justin Teissié, Bernard Malavaud, Jonathan Waxman, and Olivier Cuviellier

Précis: Radiosensitizing properties of a sphingolipid analogue FTY720 (Fingolimod) in clinical testing for multiple sclerosis offer a rationale for its application in prostate cancer treatment.

Cediranib/AZD2171 Inhibits Bone and Brain Metastasis in a Preclinical Model of Advanced Prostate Cancer
Juan Juan Yin, Luhua Zhang, Jeeva Munasinghe, R. Ilona Linnoila, and Kathleen Kelly

Précis: Findings support the utility of applying antiangiogenic therapies to treat advanced cancer patients with metastasis.

F3-Targeted Cisplatin-Hydrogel Nanoparticles as an Effective Therapeutic That Targets Both Murine and Human Ovarian Tumor Endothelial Cells In vivo
Ira Winer, Shouyan Wang, Youg-Eun Koo Lee, Wenzhe Fan, Yusong Gong, Daniela Burgos-Ojeda, Greg Spahlhinger, R. Kopelman, and Ronald J. Buckanovich

Précis: Ovarian cancers may be highly responsive to strategies that target the tumor vasculature, increasing interest in focusing on such strategies to improve therapeutic outcomes.

Telomerase Inhibition Potentiates the Effects of Genotoxic Agents in Breast and Colorectal Cancer Cells in a Cell Cycle–Specific Manner
Raina A. Tamakawa, Helen B. Fleisig, and Judy M.Y. Wong

Précis: Results suggest that the protective role of telomerase in cell cycle–restricted DNA damage repair can be exploited for combined anticancer chemotherapy.

γ-Tocotrienol Inhibits Pancreatic Tumors and Sensitizes Them to Gemcitabine Treatment by Modulating the Inflammatory Microenvironment
Ajaikumar B. Kunnumakkara, Bokyung Sung, Jayaraj Ravindran, Parmeswaran Diagaradjane, Amit Deourukkar, Sanjit Dey, Cemile Koca, Vivek R. Yadav, Zhiming Tong, Juri G. Gelovani, Sushovan Guha, Sunil Krishnan, and Bharat B. Aggarwal

Précis: Preclinical findings strongly encourage clinical evaluation of a novel derivative of vitamin E as an adjuvant treatment with standard of care chemotherapy in pancreatic cancer patients.

Targeted Radiosensitization of Cells Expressing Truncated DNA Polymerase β
Sari Neijenhuis, Manon Verwijs-Janssen, Lenie J. van den Broek, Adrian C. Begg, and Conchita Vens

Précis: This study demonstrates the feasibility of tumor-targeted radiosensitization in tumor cells exhibiting BER/SSBR deficiencies.
Loss of PTEN Expression by Blocking Nuclear Translocation of EGR1 in Gefitinib-Resistant Lung Cancer Cells Harboring Epidermal Growth Factor Receptor–Activating Mutations
Chizuko Yamamoto, Yuji Basaki, Akihiko Kawahara, Kazutaka Nakashima, Masayoshi Kage, Hiroto Izumi, Kimitoshi Kohno, Hidetaka Uramoto, Kosue Yasumoto, Michihiko Kuwano, and Mayumi Ono

Précis: Results reinforce the therapeutic importance of PTEN expression in treatment of lung adenocarcinoma with EGFR targeting drugs.

Histone Methyltransferase MLL1 Regulates MDR1 Transcription and Chemoresistance
Hairong Huo, Pellegrino G. Magro, E. Christy Pietsch, Brijesh B. Patel, and Kathleen W. Scotto

Précis: Findings suggest an approach to attack drug resistance in acute lymphoblastic leukemias and other cancers where oncogenic activations of MLL1 occur.

Basal and Treatment-Induced Activation of AKT Mediates Resistance to Cell Death by AZD6244 (ARRY-142886) in Braf-Mutant Human Cutaneous Melanoma Cells
Y.N. Vashisht Gopal, Wanleng Deng, Scott E. Woodman, Kakajan Komurov, Prahlad Ram, Paul D. Smith, and Michael A. Davies

Précis: Findings offer a rationale for combining an MEK inhibitor with a PI3K-AKT pathway inhibitor to improve the treatment of malignant melanomas with a Braf mutation.

Tumor Cell Kill by c-MYC Depletion: Role of MYC-Regulated Genes that Control DNA Double-Strand Break Repair
Kaisa R. Luoto, Alice X. Meng, Amanda R. Wasylishen, Helen Zhao, Carla L. Coackley, Linda Z. Penn, and Robert G. Bristow

Précis: Findings suggest that anti-MYC agents may prevent genetic instability but may not be useful for radiosensitization or chemosensitization of cancer cells.

Phosphorylation of RalB Is Important for Bladder Cancer Cell Growth and Metastasis
Hong Wang, Charles Owens, Nidhi Chandra, Mark R. Conaway, David L. Brautigan, and Dan Theodorescu

Précis: Mechanistic findings suggest specific tactics to blunt RalGTPase signaling that could offer an effective approach to treat metastatic bladder cancer.

Synthetic Lethality Screens Reveal RPS6 and MST1R as Modifiers of Insulin-like Growth Factor–1 Receptor Inhibitor Activity in Childhood Sarcomas

Précis: Probing of the IGF-1 receptor axis in childhood sarcomas reveals resistance mechanisms through activation of alternative tyrosine kinases.

BRCA1-IRIS Overexpression Promotes Cisplatin Resistance in Ovarian Cancer Cells
Kerri L. Chock, Jamie M.S. Allison, Yoshiko Shimizu, and Wael M. ElShamy

Précis: Mechanistic study suggests novel strategies to defeat therapeutic resistance in ovarian cancer, which persists as a top priority to improve clinical treatment of this disease.
**8822**

**EGFR Promotes Lung Tumorigenesis by Activating miR-7 through a Ras/ERK/Myc Pathway That Targets the Ets2 Transcriptional Repressor ERF**

Yu-Ting Chou, Hua-Heng Lin, Ying-Chang Lien, Yuan-Hung Wang, Chun-Fu Hong, Yu-Rung Kao, Sheng-Chieh Lin, Ying-Che Chang, Shu-Yu Lin, Shu-Jen Chen, Hua-Chien Chen, Shauh-Der Yeh, and Cheng-Wen Wu

*Précis:* Findings identify the microRNA miR-7 as a modulator of EGFR-mediated oncogenesis with important potential applications as a theranostic target in lung cancer.

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**8832**

**Characterization of a Candidate Tumor Suppressor Gene Uroplakin 1A in Esophageal Squamous Cell Carcinoma**

Kar Lok Kong, Dora L. Kwong, Li Fu, Tim Hon Man Chan, Leilei Chen, Haibo Liu, Yan Li, Ying-Hui Zhu, Jong Bi, Yan-Ru Qin, Simon Ying Kit Law, and Xin-Yuan Guan

*Précis:* A tetraspanin cell surface receptor represents an important new theranostic marker in esophageal cancer, a deadly disease with a rising incidence in developed countries.

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**8842**

**In vivo Imaging of Inflammation- and Tumor-Induced Lymph Node Lymphangiogenesis by Immuno–Positron Emission Tomography**

Viviane Mumprecht, Michael Honer, Benjamin Vigl, Steven T. Proulx, Eveline Trachsel, Manuela Kaspar, Nadja E. Banziger-Tobler, Roger Schibli, Dario Nerli, and Michael Detmar

*Précis:* Proof-of-concept for a strategy of noninvasive imaging of lymph node lymphangiogenesis could permit early detection of metastasis in cancer patients.

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**8852**

**Prognostic and Therapeutic Implications of Distinct Kinase Expression Patterns in Different Subtypes of Breast Cancer**

Giampaolo Bianchini, Takayuki Iwamoto, Yuan Qi, Christopher Coutant, Christine Y. Shiang, Bailang Wang, Libero Santarpia, Vicente Valero, Gabriel N. Hortobagyi, W. Fraser Symmans, Luca Gianni, and Lajos Pusztai

*Précis:* Study findings indicate that kinases regulating mitosis and immune functions convey distinct prognostic information that varies by clinical subtype, suggesting strategies to combine kinase inhibitors for therapeutic benefit.

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**8863**

**Maternal Embryonic Leucine Zipper Kinase Is Upregulated and Required in Mammary Tumor-Initiating Cells In vivo**

Lionel W. Hebbard, Jochen Maurer, Amber Miller, Jacqueline Lesperance, John Hassell, Robert G. Oshima, and Alexey V. Terskikh

*Précis:* Results offer preclinical proof-of-concept for targeting a little-studied kinase as a therapeutic strategy to destroy breast cancer-initiating cells.

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**8874**

**Tumorigenic and Metastatic Activity of Human Thyroid Cancer Stem Cells**

Matilde Todaro, Florio Iovino, Vincenzo Eterno, Patrizia Cammareri, Guido Gambara, Virginia Espina, Gaspare Gulotta, Francesco Dieli, Silvia Giordano, Ruggero De Maria, and Giorgio Stassi

*Précis:* Aldehyde dehydrogenase overexpression identifies thyroid cancer stem cells that could promote the development of novel approaches for thyroid malignancy.

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**8886**

**Ionizing Radiation Activates the Nrf2 Antioxidant Response**


*Précis:* A delayed adaptive mechanism of radioprotection is described that might be manipulated to mitigate complications of radiotherapy in normal tissues which arise late after radiation exposure.

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**8896**

**Protein Tyrosine Phosphatase Receptor Type H9253 Is a Functional Tumor Suppressor Gene Specifically Downregulated in Chronic Myeloid Leukemia**

Marco Della Peruta, Giovanni Martinelli, Elisabetta Moratti, Davide Pintani, Marzia Vezzalini, Andrea Mafficini, Tiziana Grafone, Ilaria Iacobucci, Simona Soverini, Marco Murineddu, Fabrizio Vinante, Cristina Tecchio, Giovanna Piras, Attilio Gabas, Maria Monne, and Claudio Sorio

*Précis:* Findings identify a novel clinically relevant tumor suppressor gene in chronic myelogenous leukemia.
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| **Enhanced Genetic Instability and Dasatinib Sensitivity in Mammary Tumor Cells Lacking NEDD9**  
Mahendra K. Singh, Eugene Izumchenko, Andres J. Klein-Szanto, Brian L. Egleston, Marina Wolfson, and Erica A. Golemis  
**Précis:** Although Nedd9 overexpression may act as a driver and biomarker for tumor aggressiveness, genetic deficiency in Nedd9 in mice selects for development of hyperaggressive mammary tumors.  |
| 8917  |
| **Gprc5a Deletion Enhances the Transformed Phenotype in Normal and Malignant Lung Epithelial Cells by Eliciting Persistent Stat3 Signaling Induced by Autocrine Leukemia Inhibitory Factor**  
Yulong Chen, Jong Deng, Junya Fujimoto, Humam Kadara, Taoyan Men, Dafna Lotan, and Reuben Lotan  
**Précis:** Findings reveal a mechanistic basis for understanding the tumor suppressor function of a G protein–coupled receptor expressed in normal lung epithelial cells.  |
| 8927  |
| **Tissue-Specific Pathways for Estrogen Regulation of Ovarian Cancer Growth and Metastasis**  
Monique A. Spillman, Nicole G. Manning, Wendy W. Dye, Carol A. Sartorius, Miriam D. Post, Joshua Chuck Harrell, Britta M. Jacobsen, and Kathryn B. Horwitz  
**Précis:** Estrogen regulates unique genes in ovarian cancers that promote lymph node metastasis.  |
| 8937  |
| **Tuberous Sclerosis Complex 1: An Epithelial Tumor Suppressor Essential to Prevent Spontaneous Prostate Cancer in Aged Mice**  
Raleigh D. Kladney, Robert D. Cardiff, David J. Kwiatkowski, Gary G. Chiang, Jason D. Weber, Jeffrey M. Arbeit, and Zhi Hong Lu  
**Précis:** Findings suggest that maintaining control of the nodal growth regulatory mTOR complexes during aging is crucial to prevent prostate cancer, the most common cancer in men.  |

**CORRECTIONS**

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| **Cell Signaling by Urokinase-type Plasminogen Activator Receptor Induces Stem Cell–like Properties in Breast Cancer Cells**  
Minji Jo, Boryana M. Eastman, Drue L. Webb, Konstantin Stoletov, Richard Klemke, and Steven L. Gonia  
**Précis:** Plasminogen activators and their receptors are well known to be involved in cancer cell migration and invasion, but this is the first study to show that they also induce cancer stem cell–like properties.  |
| 8959  |
| **Overexpression of the Protein Tyrosine Phosphatase PRL-2 Correlates with Breast Tumor Formation and Progression**  
Serge Hardy, Nau Nau Wong, William J. Muller, Morag Park, and Michel L. Tremblay  
**Précis:** Evidence garnered from clinical specimens and mouse models defines an important new driver of breast cancer invasion and metastasis.  |
| 8968  |
| **Correction: Colorectal Tumors Are Effectively Eradicated by Combined Inhibition of β-Catenin, KRAS, and the Oncogenic Transcription Factor ITF2**  |
| 8969  |
| **Correction: Activation of Murine Double Minute 2 by Akt in Mammary Epithelium Delays Mammary Involution and Accelerates Mammary Tumorigenesis** |
ABOUT THE COVER

9L gliosarcoma cells expressing cel-miR-67 transfer cel-miR-67 to naïve 9L cells. Coculture of cel-miR-67–expressing 9L cells with those that expressed a luciferase reporter containing a complementary sequence to cel-miR-67 results in suppression of luciferase protein expression in the acceptor cells. This image reveals colocalization of cel-miR-67 (dark dots, in situ hybridization signal) with eGFP in 9L cells that do not express cel-miR-67. These findings indicate that glioma cells can transfer functional miRNA from one cell to another. Thus, miRNA serves as an intercellular signaling molecule in glioma. For details, see the article by Katakowski and colleagues on page 8259 of this issue.