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## BREAKING ADVANCES

4953  
Highlights from Recent Cancer Literature

## REVIEWS

4955  
**Emerging Potential of Therapeutic Targeting of Ubiquitin-Specific Proteases in the Treatment of Cancer**  
Anupama Pal, Matthew A. Young, and Nicholas J. Donato

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**Sonic Hedgehog Signaling in Basal Cell Nevus Syndrome**  
Mohammad Athar, Changzhao Li, Arianna L. Kim, Vladimir S. Spiegelman, and David R. Bickers

## PERSPECTIVE

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**Obesity, Cholesterol Metabolism, and Breast Cancer Pathogenesis**  

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4983  
**High-Throughput Time-Resolved FRET Reveals Akt/PKB Activation as a Poor Prognostic Marker in Breast Cancer**  
Selvaraju Veeriah, Pierre Leboucher, Julien de Naurois, Nirmal Jethwa, Emma Nye, Tamara Bunting, Richard Stone, Gordon Stamp, Véronique Calleja, Stefanie S. Jeffrey, Peter J. Parker, and Banaéfshé Larijani

**Précis:** Using a novel quantitative imaging platform to determine the status of an activated biomarker in cancer patients may better identify high-risk patients who could benefit from a suitable targeted drug therapy.

## MICROENVIRONMENT AND IMMUNOLOGY

4996  
**Neutralizing Murine TGFβR2 Promotes a Differentiated Tumor Cell Phenotype and Inhibits Pancreatic Cancer Metastasis**  
Katherine T. Ostapoff, Bercin Kutluç Cenik, Miao Wang, Risheng Ye, Xiaoqiong Xu, Desiree Nugent, Moriah M. Hagopian, Mary Topalovski, Lee B. Rivera, Kyla D. Carroll, and Rolf A. Brekken

**Précis:** This study demonstrates that TGFβ signaling in stromal cells directly affects tumor cell plasticity and the metastatic capacity of pancreatic tumors.

5008  
**TLR7 Promotes Tumor Progression, Chemotherapy Resistance, and Poor Clinical Outcomes in Non–Small Cell Lung Cancer**  
Saradiya Chatterjee, Lucile Crozet, Diane Damotte, Kristina Iribarren, Catherine Schramm, Marco Alifano, Audrey Lupo, Julien Cherfils-Vicini, Jeremy Goc, Sandrine Katsahian, Mohammad Younes, Marie Caroline Dieu-Nosjean, Wolf Herman Fridman, Catherine Sautès-Fridman, and Isabelle Cremer

**Précis:** Activation of an immune stimulatory molecule, TLR7, studied mainly in immune cells but also highly expressed in human lung carcinoma cells, confers powerful tumor growth advantage that may be mediated in part by NF-κB, perhaps helping explain its contributions to cancer.

5019  
**Optimal Effector Functions in Human Natural Killer Cells Rely upon Autocrine Bone Morphogenetic Protein Signaling**  
Neil C. Robson, Laura Hidalgo, Tristan McAlpine, Heng Wei, Víctor G. Martínez, Ana Entrena, Gustavo J. Melen, Andrew S. MacDonald, Alexander Phythin-Adams, Rosa Sacedón, Eugene Maraskovsky, Jonathan Cebon, Manuel Ramírez, Angeles Vicente, and Alberto Varas

**Précis:** The TGFβ superfamily members BMP-2 and BMP-6 are produced by and are required to support the optimal functions of natural killer immune cells, suggesting new ways to enhance the powerful capability of these cells to eradicate tumors.

5032  
**Stress Signaling from Human Mammary Epithelial Cells Contributes to Phenotypes of Mammographic Density**  
Rosa Anna DeFilippis, Colleen Fordyce, Kelley Patten, Hang Chang, Jianxin Zhao, Gerald V. Fontenay, Karla Kerlikowske, Bahram Parvin, and Thea D. Tlsty

**Précis:** These findings provide new insights into how high mammographic density arises in the breast and why this condition is associated with breast cancer risk, with implications for the definition of novel invention targets to prevent breast cancer.

5045  
**Molecular Homology and Difference between Spontaneous Canine Mammary Cancer and Human Breast Cancer**  
Deli Liu, Huan Xiong, Angela E. Ellis, Nicole C. Northrup, Carlos O. Rodriguez Jr, Ruth M. O’Regan, Stephen Dalton, and Shaying Zhao

**Précis:** This study of spontaneous mammary cancers that arise in dogs offers a novel perspective on critical questions in breast cancer research.
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**Molecular and Cellular Pathobiology**

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**Therapeutics, Targets, and Chemical Biology**

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**Précis:** These preclinical findings offer a rationale to empower therapeutic effects of T-cell checkpoint-based immunotherapeutics that block PD-1 and CTLA-4 by reprogramming of immunosuppressive myeloid cells that are abundant in the tumor microenvironment.

**Précis:** This study suggests mechanistic insights into a long recognized but little understood phenomenon in radiotherapy, the abscopal effect, which refers to antitumor benefits outside the irradiated field.

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**Précis:** Blocking an important mechanism of immune escape in glioma mediated by galectin-1 overexpression may be sufficient to restore the ability of natural killer cells to eradicate this type of brain cancer, without the need of adaptive immune functions.

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**Précis:** This study demonstrates that BMP4 can inhibit metastasis by reducing NF-κB activity in tumor cells, leading to a suppression of G-CSF secretion and a consequential reduction in the number of metastases promoting myeloid-derived suppressor cells.

**Précis:** This study identifies a potential molecular foothold in epigenetic therapy aimed at altering transcriptional programs in cancer cells to selectively trigger their demise.
5195 Armed Oncolytic Virus Enhances immune Functions of Chimeric Antigen Receptor–Modified T Cells in Solid Tumors
Nobuhiro Nishio, Jula Diaoconu, Hao Liu, Vincenzo Cerullo, Ignazio Caruana, Valentina Hoyos, Lisa Bouchier-Hayes, Barbara Savoldo, and Gianpietro Dotti

 précis: This cytokine/chemokine–armed virus described in this report may improve the effectiveness of CAR T-cell therapy in solid tumors, where this therapy has not been nearly as effective as in liquid tumors.

5206 FLT3 Kinase Inhibitor TTT-3002 Overcomes Both Activating and Drug Resistance Mutations in FLT3 in Acute Myeloid Leukemia
Hayley S. Ma, Bao Nguyen, Amy S. Duffield, Li Li, Allison Galanis, Allen B. Williams, Patrick A. Brown, Mark J. Levis, Daniel J. Leahy, and Donald Small

 précis: A new small molecule inhibitor of FLT3, which can overcome all mutations documented to date, in this driver of acute myeloid leukemia, also exhibits superior pharmacologic properties that lend appeal for this agent as an effective next-generation therapeutic in this setting.

5218 TLR9 Is Critical for Glioma Stem Cell Maintenance and Targeting
Andreas Herrmann, Gregory Cherryholmes, Anne Schroeder, Jillian Phallen, Darya Alizadeh, Hong Xin, Tianyi Wang, Heeyoung Lee, Christoph Lahtz, Piotr Swiderski, Brian Armstrong, Claudia Kowolik, Gary L. Gallia, Michael Lim, Christine Brown, Behnam Badie, Stephen Forman, Marcin Kortylewski, Richard Jove, and Hua Yu

 précis: The discovery that the toll-like receptor TLR9 is expressed in stem-like cells in an aggressive brain cancer may offer a useful tool for treatment strategies in this setting.

TUMOR AND STEM CELL BIOLOGY

5229 ADAM9 Promotes Lung Cancer Metastases to Brain by a Plasminogen Activator-Based Pathway
Chen-Yuan Lin, Hung-Jen Chen, Cheng-Chung Huang, Liang-Chuan Lai, Tzu-Pin Lu, Guan-Chin Tseng, Ting-Ting Kuo, Qian-Yu Kuok, Jennifer L. Hsu, Shian-Ying Sung, Mien-Chie Hung, and Yuh-Pyng Sher

 précis: These findings highlight the integrated view for ADAM9 in lung cancer brain metastases and indicate that targeting of ADAM9-regulated pathways may be a rational approach to inhibit cancer metastases.

5244 5-Lipoxygenase Is a Candidate Target for Therapeutic Management of Stem Cell–like Cells in Acute Myeloid Leukemia
Jessica Roos, Claudia Oancea, Maria Heinssmann, Dilawar Khan, Hannelore Held, Astrid S. Kahnt, Christoph Lahtz, Piotr Swiderski, Brian Armstrong, Claudia Kowolik, Gary L. Gallia, Michael Lim, Christine Brown, Behnam Badie, Stephen Forman, Marcin Kortylewski, Richard Jove, and Hua Yu

 précis: These findings suggest that targeting the 5-lipoxygenases may help eradicate cancer stem cell–like cells in acute myeloid leukaemias, with immediate implications for clinical evaluation in patients.
miR149 Functions as a Tumor Suppressor by Controlling Breast Epithelial Cell Migration and Invasion
Annabell Bischoff, Bettina Huck, Bettina Keller, Michaela Strotbek, Simone Schmid, Melanie Boerries, Hauke Busch, Dafne Müller, and Monilola A. Olayioye

Précis: These findings define the molecular function of miR-149, which is downregulated in aggressive and often untreatable basal-like breast cancers, with potential implications for the design of future miRNA-based therapeutics in this disease setting.

RB Family Tumor Suppressor Activity May Not Relate to Active Silencing of E2F Target Genes
Tinke L. Vormer, Kamila Wojciechowicz, Marleen Dekker, Sandra de Vries, Anja van der Wal, Elly Delzenne-Goette, Sjalin H. Naik, Ji-Ying Song, Jan-Hermen Dannenberg, Jacob B. Hansen, and Hein te Riele

Précis: These provocative findings suggest that RB tumor suppressor activity does not require interaction with LxCxE-containing proteins, implying it may not involve silencing of E2F target genes as previously thought.

Runx2 Is a Novel Regulator of Mammary Epithelial Cell Fate in Development and Breast Cancer

Précis: These results establish a novel function for Runx2 of mammary cell fate and breast cancer that may offer a novel generalized route for therapeutic interventions in this malignancy.

Ubiquitin-like Protein FAT10 Promotes the Invasion and Metastasis of Hepatocellular Carcinoma by Modifying β-Catenin Degradation
Rongfa Yuan, Kai Wang, Junwen Hu, Chen Yan, Ming Li, Xin Yu, Xiaxia Liu, Jun Lei, Wuhua Guo, Linquan Wu, Kui Hong, and Jianghua Shao

Précis: These findings link two drivers of invasion and metastasis in liver cancer and identify a novel pathway for β-catenin control that may have relevance in other cancers.

CORRECTION

Correction: Enhancing Reproducibility in Cancer Drug Screening: How Do We Move Forward?
ABOUT THE COVER

Non-invasive in vivo imaging of gene-modified human hematopoietic stem cells and their progeny can be achieved using positron image tomography (PET), shown here as coronal and sagittal plane overlays on X-ray computed tomography scans. Imaging after systemically administered $^{18}$F-FHBG reveals accumulation of probe localized to areas of hematopoietic engraftment such as the humerus, tibia, femur, vertebrae, sternum, and thymus. Background probe uptakes in the gastrointestinal tract and gall bladder, present in non-humanized NSG and mock-transduced humanized mice, have been artificially masked for clarity. For details, see article by Gschweng on page 5173.