

BREAKING ADVANCES

- 2585** Highlights from Recent Cancer Literature

REVIEWS

- 2587** Evaluating Robustness and Sensitivity of the NanoString Technologies nCounter Platform to Enable Multiplexed Gene Expression Analysis of Clinical Samples

Margaret H. Veldman-Jones, Roz Brant, Claire Rooney, Catherine Geh, Hollie Emery, Chris G. Harbron, Mark Wappett, Alan Sharpe, Michael Dymond, J. Carl Barrett, Elizabeth A. Harrington, and Gayle Marshall

- 2594** Network-Based Approaches to Understand the Roles of miR-200 and Other microRNAs in Cancer

Cameron P. Bracken, Yeesim Khew-Goodall, and Gregory J. Goodall

PRIORITY REPORT

- 2600** High-Frequency Targetable EGFR Mutations in Sinonasal Squamous Cell Carcinomas Arising from Inverted Sinonasal Papilloma

Aaron M. Udager, Delphine C.M. Rolland, Jonathan B. McHugh, Bryan L. Betz, Carlos Murga-Zamalloa, Thomas E. Carey, Lawrence J. Marentette, Mario A. Hermsen, Kathleen E. DuRoss, Megan S. Lim, Kojo S.J. Elenitoba-Johnson, and Noah A. Brown

Précis: These results identify a role for activating EGFR mutations in sinonasal squamous cell carcinomas arising from inverted papillomas, providing the first genetic evidence of a biologic link between these tumors and demonstrating the opportunity for targeted therapy with irreversible EGFR inhibitors.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2607** Quantifying the Landscape for Development and Cancer from a Core Cancer Stem Cell Circuit
Chunhe Li and Jin Wang

Précis: A pictorial "cancer landscape" theory described in this study offers quantitative insights into underlying mechanisms of cancer stem-like cell formation and the interplay with normal development, with possible applications to a variety of disease-related regulatory networks.

MICROENVIRONMENT AND IMMUNOLOGY

- 2619** Blocking Tumor Necrosis Factor α Enhances CD8 T-cell-Dependent Immunity in Experimental Melanoma

Florie Bertrand, Julia Rochotte, Céline Colacios, Anne Montfort, Anne-Françoise Tilkin-Mariamé, Christian Touriol, Philippe Rochemaux, Isabelle Lajoie-Mazenc, Nathalie Andrieu-Abadie, Thierry Levade, Hervé Benoist, and Bruno Ségui

Précis: This study challenges the view that TNF in the inflammatory microenvironment of melanoma is protumorigenic, with immediate implications for possible clinical evaluation of the effects of anti-TNF antibodies in melanoma treatment.

- 2629** Chemotherapy-Derived Inflammatory Responses Accelerate the Formation of Immunosuppressive Myeloid Cells in the Tissue Microenvironment of Human Pancreatic Cancer

Shintaro Takeuchi, Muhammad Baghdadi, Takahiro Tsuchikawa, Haruka Wada, Toru Nakamura, Hirotake Abe, Sayaka Nakanishi, Yuu Usui, Kohtaro Higuchi, Mizuna Takahashi, Kazuho Inoko, Syoki Sato, Hironobu Takano, Toshiaki Shichinohe, Ken-ichiro Seino, and Satoshi Hirano

Précis: These findings challenge the use of therapeutic regimens employing GM-CSF as part of a cancer vaccine by providing preclinical evidence that GM-CSF ablation may benefit patients with pancreatic cancer, who generally respond poorly to chemotherapy, through helping defeat a powerful immune escape mechanism.

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- 2641** Genetic Regulation of Fate Decisions in Therapeutic T Cells to Enhance Tumor Protection and Memory Formation
Pedro Veliça, Mathias Zech, Sian Henson, Angelika Holler, Teresa Manzo, Rebecca Pike, Pedro Santos e Sousa, Lei Zhang, Bernhard Schiedlmeier, Martin Pule, Hans Stauss, and Ronjon Chakraverty
Précis: These findings suggest translational strategies to generate heterogeneous T-cell immunity against cancer by manipulating functions of mTORC1 subunits that balance T-effector cell differentiation and self-renewal.

- 2653** Neutrophil Extracellular Traps Accumulate in Peripheral Blood Vessels and Compromise Organ Function in Tumor-Bearing Animals
Jessica Cedervall, Yanyu Zhang, Hua Huang, Lei Zhang, Julia Femel, Anna Dimberg, and Anna-Karin Olsson
Précis: These findings suggest seminal insights into why organ failure occurs in cancer patients, including those with limited tumor loads, due to the collateral damage that tumors inflict systemically on inflammation and vascular function in organs unaffected by metastasis.

- 2663** Macrophages Regulate the Systemic Response to DNA Damage by a Cell Nonautonomous Mechanism
Anat Geiger-Maor, Avital Guedj, Sharon Even-Ram, Yoav Smith, Eithan Galun, and Jacob Rachmilewitz
Précis: This study reveals how macrophages act non-cell autonomously to assist neighboring cells to repair damaged DNA, illuminating a novel physiologic mechanism that helps maintain genomic integrity.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 2674** miR-181a-5p Inhibits Cancer Cell Migration and Angiogenesis via Downregulation of Matrix Metalloproteinase-14
Yiyi Li, Cem Kescu, Anna Banach, Qian Zhang, Ashleigh Pulkoski-Gross, Deborah Kim, Jingxuan Liu, Eric Roth, Ellen Li, Kenneth R. Shroyer, Paula I. Denoya, Xiaoxia Zhu, Longhua Chen, and Jian Cao
Précis: This study provides important new information about the regulation of a critical cell surface protease in mediating invasion and metastasis by many types of human solid cancers.

- 2686** NKX3.1 Suppresses TMPRSS2-ERG Gene Rearrangement and Mediates Repair of Androgen Receptor-Induced DNA Damage
Cai Bowen, Tian Zheng, and Edward P. Gelmann
Précis: Loss of the suppressor gene NKX3.1 in premalignant prostate cells predisposes them to defective DNA repair, thereby increasing risks of TMPRSS2-ERG oncogene rearrangement that is critical early in malignant transformation.

- 2699** Repair versus Checkpoint Functions of BRCA1 Are Differentially Regulated by Site of Chromatin Binding
Michael Goldstein and Michael B. Kastan
Précis: These findings demonstrate that spatially distinct forms of the tumor suppressor BRCA1 are recruited to sites of DNA double-strand breaks with distinctive differential functions in DNA repair and checkpoint signaling.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 2708** NIAK2 Amplification Coupled with PTEN Deficiency Promotes Melanoma Development via CDK Activation
Takeshi Namiki, Tomonori Yaguchi, Kenta Nakamura, Julio C. Valencia, Sergio G. Coelho, Lanlan Yin, Masakazu Kawaguchi, Wilfred D. Vieira, Yasuhiko Kaneko, Atsushi Tanemura, Ichiro Katayama, Hiroo Yokozeki, Yutaka Kawakami, and Vincent J. Hearing
Précis: This study defines a novel gene activation event that is critical for progression of cutaneous melanomas, with implications that rationalize their treatment with CDK2 inhibitors.

- 2716** A Novel Cinnamon-Related Natural Product with Pim-1 Inhibitory Activity Inhibits Leukemia and Skin Cancer
Jong-Eun Kim, Joe Eun Son, Hyein Jeong, Dong Joon Kim, Sang Gwon Seo, Eunjung Lee, Tae Gyu Lim, Jong Rhan Kim, Yengo Raymond Kimbung, Hanyong Chen, Ann M. Bode, Ki Won Lee, and Zigang Dong
Précis: These results offer preclinical proof of concept for a cinnamon compound with potent anticancer activity based on direct targeting of a pro-oncogenic kinase.

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2729 Hepatocellular Shuttling and Recirculation of Sorafenib-Glucuronide Is Dependent on Abcc2, Abcc3, and Oatp1a/1b

Aksana Vasilyeva, Selvi Durmus, Lie Li, Els Wagenaar, Shuiying Hu, Alice A. Gibson, John C. Panetta, Sridhar Mani, Alex Sparreboom, Sharyn D. Baker, and Alfred H. Schinkel

Précis: These results suggest broad relevance of a hepatocyte shuttling process known as "hepatocyte hopping"—a novel concept in clinical pharmacology—for detoxification of targeted cancer drugs that undergo hepatic glucuronidation, such as sorafenib.

2737 Paracrine Effect of NRG1 and HGF Drives Resistance to MEK Inhibitors in Metastatic Uveal Melanoma

Hanyin Cheng, Mizue Terai, Ken Kageyama, Shinji Ozaki, Peter A. McCue, Takami Sato, and Andrew E. Aplin

Précis: These findings offer a preclinical proof of concept for the combination of MEK inhibitor plus a growth factor receptor targeting antibody in the treatment of highly aggressive uveal melanomas.

TUMOR AND STEM CELL BIOLOGY

2749 Tracking and Functional Characterization of Epithelial–Mesenchymal Transition and Mesenchymal Tumor Cells during Prostate Cancer Metastasis

Marcus Ruscetti, Bill Quach, Eman L. Dadashian, David J. Mulholland, and Hong Wu

Précis: EMT prostate tumor cells, which transition readily between epithelial and mesenchymal states, can recapitulate each stage of the metastatic cascade, supporting the use of therapeutic agents that target tumor cell plasticity for the treatment of lethal metastatic prostate cancer.

RETRACTION

2760 Retraction: Concurrent Suppression of Integrin α_5 , Radixin, and RhoA Phenocopies the Effects of miR-31 on Metastasis

CORRECTION

2761 Correction: miR145 Targets the SOX9/ADAM17 Axis to Inhibit Tumor-Initiating Cells and IL6-Mediated Paracrine Effects in Head and Neck Cancer



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ABOUT THE COVER

TNF α plays a central, but still enigmatic, role in melanoma. Using immunofluorescence, it was found that TNF deficiency or blockade enhanced intratumor content of high endothelial venules surrounded by high CD8⁺ T lymphocyte density. Consequently, the tumor growth of melanoma cell lines expressing MHC-I molecules at high levels was dramatically impaired. Counteracting TNF signaling may potentiate the immune response in melanoma. For details, see article by Bertrand and colleagues on page 2619.

