**BREAKING ADVANCES**

1539 Highlights from Recent Cancer Literature

**REVIEWS**

1541 Accuracy of Molecular Data Generated with FFPE Biospecimens: Lessons from the Literature
Sarah R. Greytak, Kelly B. Engel, B. Paige Bass, and Helen M. Moore

1548 Mesoscopic and Macroscopic Optoacoustic Imaging of Cancer
Adrian Taruttis, Gooitzen M. van Dam, and Vasilis Ntziachristos

**PRIORITY REPORT**

1560 Evaluating Patient-Derived Colorectal Cancer Xenografts as Preclinical Models by Comparison with Patient Clinical Data
Manoel Nunes, Patricia Vrignaud, Sophie Vacher, Sophie Richon, Astrid Lièvre, Wulfran Cacheux, Louis-Bastien Weiswald, Gerald Massonnet, Sophie Chateau-Joubert, André Nicolas, Coletic Dib, Weidong Zhang, James Watters, Donald Bergstrom, Sergio Roman-Roman, Ivan Bieche, and Virginie Dangles-Marie

Précis: This study highlights the translational relevancy of patient-derived colorectal cancer xenografts in both therapeutic response and genomic profiles.

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

1567 Impact of Metabolic Heterogeneity on Tumor Growth, Invasion, and Treatment Outcomes
Mark Robertson-Tessi, Robert J. Gillies, Robert A. Gatenby, and Alexander R.A. Anderson

Précis: Models that incorporate tumor heterogeneity highlight the risks of cytotoxic and antiangiogenic treatment due to their potential to select for cell populations with more aggressive behaviors, reinforcing "watchful-waiting" clinical attitudes toward more indolent early-stage cancers such as breast and prostate cancer.

**MICROENVIRONMENT AND IMMUNOLOGY**

1580 Chaperone Hsp47 Drives Malignant Growth and Invasion by Modulating an ECM Gene Network
Jieqing Zhu, Gaofeng Xiong, Hanjiang Fu, B. Mark Evers, Binhua P. Zhou, and Ren Xu

Précis: These findings define a microRNA-controlled nodal hub that regulates expression and deposition of extracellular matrix proteins needed to drive malignant growth and invasion of breast cancer cells, with potential implications for therapy and prevention in this disease.

1592 Notch Suppresses Angiogenesis and Progression of Hepatic Metastases
Debarshi Banerjee, Sonia I. Hernandez, Alejandro Garcia, Thaned Kangsamaksin, Emily Sbiroli, John Andrews, Lynn Ann Forrester, Na Wei, Angela Kadenhe-Chiwehe, Carrie J. Shawber, Jan K. Kitajewski, Jessica J. Kandel, and Darrell J. Yamashiro

Précis: This important preclinical study suggests a new perspective on the clinical risks of Notch inhibitors in development for cancer treatment based on evidence that these agents may facilitate formation of metastatic lesions in the liver.

1603 Antitumor Immunity Triggered by Melphalan Is Potentiated by Melanoma Cell Surface–Associated Calreticulin
Aleksandra M. Dudek-Petić, Gabriela B. Ferreira, Angelika Muchowicz, Jasper Wouters, Nicole Prada, Shaun Martin, Santeri Kiviluoto, Magdalena Winiarska, Louis Boon, Chantal Mathieu, Joost van den Oord, Marguerite Stas, Marie-Lise Gougeon, Jakub Golab, Abhishek D. Carg, and Patrizia Agostinis

Précis: Immunogenic effects of a limb-perfused chemotherapeutic used for locoregional treatment of melanoma can be leveraged by coadministration of a sterile danger signal that can heighten antitumor immunity.

1615 MDSC and TGFβ Are Required for Facilitation of Tumor Growth in the Lungs of Mice Exposed to Carbon Nanotubes

Précis: Studies in a mouse model of nanomaterial-induced pulmonary inflammation show how myeloid-derived suppressor cells act to condition a local tissue niche to support growth of lung cancer.
Interleukin-5 Facilitates Lung Metastasis by Modulating the Immune Microenvironment

Précis: These results establish a network of allergic inflammatory circuitry that can be co-opted by metastatic cancer cells to facilitate lung colonization, suggesting new therapeutic interventions to target this pathway as an antimetastatic strategy.

IL10 and PD-1 Cooperate to Limit the Activity of Tumor-Specific CD8⁺ T Cells
Zhaojun Sun, Julien Fourcade, Ornella Pagliano, Joe-Marc Chauvin, Cindy Sander, John M. Kirkwood, and Hassane M. Zarour

Précis: This study shows that IL10 blockade cooperates with PD-1 antibodies to more effectively counteract T-cell immunosuppression in melanoma, with immediate implications for the use of IL10 neutralizing antibodies to improve immune checkpoint therapy in patients with advanced melanoma.

High-Mobility Group Box 1 Promotes Hepatocellular Carcinoma Progression through miR-21–Mediated Matrix Metalloproteinase Activity
Man Chen, Yao Liu, Patrick Varley, Ying Chang, Xing-xing He, Hai Huang, Daolin Tang, Michael T. Lotze, Jusheng Lin, and Allan Tsou

Précis: This study examines a pathway of chronic sterile inflammatory signaling in the liver that may be sufficient to drive malignant progression in the absence of viral infections such as HBV and HCV, which are widely but not universally involved in liver cancer development.

MyD88-Dependent Signaling Decreases the Antitumor Efficacy of Epidermal Growth Factor Receptor Inhibition in Head and Neck Cancer Cells
Adam T. Koch, Laurie Love-Homan, Madelyn Espinosa-Cotton, Aditya Stanam, and Andrean L. Simons

Précis: These findings suggest mechanism-based approaches to improve the efficacy of EGFR inhibitors used to treat head and neck cancer.

Genetic and Pharmacological Screens Converge in Identifying FLIP, BCL2, and IAP Proteins as Key Regulators of Sensitivity to the TRAIL-Inducing Anticancer Agent ONC201/TIC10
Joshua E. Allen, Vanun V. Prabhlu, Mala Talekar, A. Pieter I. van den Heuvel, Boza Lim, David T. Dicker, Jennifer L. Fritz, Adam Beck, and Waik S. El-Deiry

Précis: This preclinical study identifies and mechanistically rationalizes the use of a set of predictive biomarkers that may help advance phase I/II clinical evaluations of a novel TRAIL-inducing cancer drug.

Ibrutinib Exerts Potent Antifibrotic and Antitumor Activities in Mouse Models of Pancreatic Adenocarcinoma

Précis: The results of this important study provide a preclinical rationale for evaluation of the clinical efficacy of the recently approved Bruton tyrosine kinase inhibitor ibrutinib in patients with pancreatic cancer.

Induction of Vasculogenic Mimicry Overrides VEGF-A Silencing and Enriches Stem-like Cancer Cells in Melanoma
Caroline I. Schnegg, Moon Hee Yang, Subrata K. Ghosh, and Mei-Yu Hsu

Précis: This preclinical study highlights the potential risk of anti-VEGF treatments owing to a selective pressure for an adaptive resistance mechanism that empowers the development of stem-like cancer cells, with implications for the design of combination therapies that can improve outcomes in patients.

Wnt/β-Catenin Small-Molecule Inhibitor CWP232228 Preferentially Inhibits the Growth of Breast Cancer Stem-like Cells
Gyu-Beom Jang, In-Sun Hong, Ran-Ju Kim, Su-Youn Lee, Se-Jin Park, Eun-Sook Lee, Jung Hyuck Park, Chi-Ho Yun, Jae-Uk Chung, Kyoung-June Lee, Hwa-Yong Lee, and Jeong-Seok Nam

Précis: These findings highlight a candidate therapeutic agent that may target stem-like cells as well as bulk tumor cells and lead to more effective treatment of breast cancer.

MOLECULAR AND CELLULAR PATHOBIOLOGY

TUMOR AND STEM CELL BIOLOGY
FOXP3 Controls an miR-146/NF-κB Negative Feedback Loop That Inhibits Apoptosis in Breast Cancer Cells
Runhua Liu, Cong Liu, Dongguan Chen, Wei-Hsiung Yang, Xiuping Liu, Chang-Gong Liu, Courtney M. Dugas, Fei Tang, Pan Zheng, Yang Liu, and Lizhong Wang
Précis: FOXP3 is a master regulator of regulatory T cells that limit antitumor immunity, but it also functions as an X-linked tumor suppressor gene in breast cancer, where the pathways it controls may offer direct therapeutic targets.

FOXP3–miR-146–NF-κB Axis and Therapy for Precancerous Lesions in Prostate
Runhua Liu, Bin Yi, Shi Wei, Wei-Hsiung Yang, Karen M. Hart, Priyanka Chauhan, Wei Zhang, Xicheng Mao, Xiuping Liu, Chang-Gong Liu, and Lizhong Wang
Précis: FOXP3 is best known as an expression biomarker for regulatory T cells that promote immune escape in cancer, but it can be altered in prostate tumor cells themselves, where it directly participates in tumorigenesis.

IKKb Enforces a LIN28B/TCF7L2 Positive Feedback Loop That Promotes Cancer Cell Stemness and Metastasis
Chong Chen, Fengqi Cao, Lipeng Bai, Yan Liu, Junling Xie, Wei Wang, Qin St, Jian Yang, Antao Chang, Dong Liu, Dachuan Liu, Tsung-Hsien Chuang, Rong Xiang, and Yunping Luo
Précis: This important study defines a nodal positive feedback loop that reinforces cancer stemness driven by pro-inflammatory processes, with important implications for understanding progression and metastasis and for conceptualizing a novel generalized intervention in advanced cancers.

RIP1 Kinase Is an Oncogenic Driver in Melanoma
Précis: These findings reveal a well-established regulator of cell death to be an oncogenic driver, with potential implications for its candidacy as a therapeutic target in melanoma.

Modification of Helicobacter pylori Peptidoglycan Enhances NOD1 Activation and Promotes Cancer of the Stomach
Giovanni Suarez, Judith Romero-Gallo, M. Blanca Pianezelo, Ge Wang, Robert J. Maier, Lennart S. Forsberg, Parasitoo Azadi, Martin A. Gomez, Pelayo Correa, and Richard M. Peek, Jr.
Précis: This study provides mechanistic insights into how chronic infections of the stomach with the bacteria H. pylori increase risks of developing gastric cancer.

Hyperthermia Sensitizes Glioma Stem-like Cells to Radiation by Inhibiting AKT Signaling
Précis: These preclinical findings show how hyperthermia treatments can reduce the inherent radioresistance of glioma stem cells, with clinical implications for improving the treatment of glioblastoma.

CORRECTIONS

Correction: Fearful Symmetry: Subversion of Asymmetric Division in Cancer Development and Progression

Correction: Autophagic Survival in Resistance to Histone Deacetylase Inhibitors: Novel Strategies to Treat Malignant Peripheral Nerve Sheath Tumors

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ABOUT THE COVER

Bruton’s tyrosine kinase inhibitor ibrutinib triggers reduction of collagen content (red staining) in tumors from a transgenic mouse model of pancreatic ductal adenocarcinoma (PDAC). This dramatic reduction in fibrosis is accompanied by a decrease in Ki-67-positive proliferating cells, CD11b⁺ leukocytes, and F4/80⁺ macrophages. Overall, ibrutinib extends survival of PDAC-bearing mice as monotherapy or in combination with the standard of care chemotherapy gemcitabine. For details, see article by Massó-Vallés and colleagues on page 1675.