**BREAKING ADVANCES**

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**REVIEW**

3437 | **Systemic DNA Damage Related to Cancer**

**MEETING REPORT**

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**PRIORITY REPORTS**

3447 | **Paradoxical Relationship between Chromosomal Instability and Survival Outcome in Cancer**
Nicolai J. Birkbak, Aron C. Eklund, Qiuyan Li, Sarah E. McClelland, David Endesfelder, Patrick Tan, Iain B. Tan, Andrea L. Richardson, Zoltan Szallasi, and Charles Swanton

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

3459 | **Role for Stromal Heterogeneity in Prostate Tumorigenesis**
Maria A. Kiskowski, Roger S. Jackson, Jheelam Banerjee, Xiaohong Li, Minchul Kang, Juan M. Iturregui, Omar E. Franco, Simon W. Hayward, and Neil A. Bhowmick

**MICROENVIRONMENT AND IMMUNOLOGY**

3482 | **Endoglin Regulates Cancer–Stromal Cell Interactions in Prostate Tumors**
Diana Romero, Christine O’Neill, Aleksandra Terzic, Liangru Contois, Kira Young, Barbara A. Conley, Raymond C. Bergan, Peter C. Brooks, and Calvin P.H. Vary

3494 | **Expression of Id-1 Is Regulated by MCAM/MUC18: A Missing Link in Melanoma Progression**
Maya Zigler, Gabriel J. Villares, Andrey S. Dobroff, Hua Wang, Li Huang, Russell B. Braeuer, Takafumi Kamiya, Vladislava O. Melnikova, Renduo Song, Ran Friedman, Rhoda M. Alani, and Menashe Bar-Eli
Tumor-Evoked Regulatory B Cells Promote Breast Cancer Metastasis by Converting Resting CD4⁺ T Cells to T-Regulatory Cells
Purevdorj B. Olkhanud, Bazarragchaa Damdinsuren, Monica Bodogai, Ronald E. Gress, Ranjan Sen, Katarzyna Wojkowska, Enkhzol Malchinkhuu, Robert P. Wersto, and Arya Biragyn

**Précis:** Findings indicate that tumor-evoked regulatory B cells are crucial for lung metastasis, acting to convert resting T cells to regulatory T cells that promote immune escape in the target tissue.

Reprogramming CD19-Specific T Cells with IL-21 Signaling Can Improve Adoptive Immunotherapy of B-Lineage Malignancies
Harjeet Singh, Matthew J. Figliola, Margaret J. Dawson, Helen Huls, Simon Olivares, Kirsten Switzer, Tiejuan Mi, Sourindra Maiti, Partow Kebriaei, Dean A. Lee, Richard E. Champlin, and Laurence J.N. Cooper

**Précis:** Findings reveal that addition of IL-21 to culture provides an extrinsic reprogramming signal to generate effective T-cell immunotherapy.

Unraveling Cancer Chemoinmunotherapy Mechanisms by Gene and Protein Expression Profiling of Responses to Cyclophosphamide
Federica Moschella, Mara Valentini, Eleonora Arici, Iole Macchia, Paola Sestili, Maria Teresa D’Urso, Cristiano Alessandri, Filippo Belardelli, and Enrico Proietti

**Précis:** Rapidly growing interest in combined regimens of chemoinmunotherapy is based upon emerging evidence that the efficacy of certain chemotherapeutic agents relies upon coordinate immune stimulatory effects.

Anti-TIM3 Antibody Promotes T Cell IFN-γ-Mediated Antitumor Immunity and Suppresses Established Tumors
Shin Foong Ngio, Bianca von Scheidt, Hisaya Akiba, Hideo Yagita, Michele W. L. Teng, and Mark J. Smyth

**Précis:** The first antibody targeting investigations for a little studied T-cell co-inhibitory receptor establish single agent activity and mechanism of action in multiple preclinical mouse models of cancer and primary carcinogenesis.

miR-125b Is Methylated and Functions as a Tumor Suppressor by Regulating the ETS1 Proto-oncogene in Human Invasive Breast Cancer
Yan Zhang, Li-Xu Yan, Qi-Nian Wu, Zi-Ming Du, Jing Chen, Ding-Zhuo Liao, Ma-Yan Huang, Jing-Hui Hou, Qiu-Liang Wu, Mu-Sheng Zeng, Wen-Lin Huang, Yi-Xin Zeng, and Jian-Yong Shao

**Précis:** This study identifies an oncogenic transcription factor as a key target of a tumor suppressive microRNA that is downregulated in various types of invasive cancer, including breast cancer.

Human Glioma Growth Is Controlled by MicroRNA-10b
Galina Gabriely, Ming Yi, Ravi S. Narayan, Johann M. Niers, Thomas Wurdinger, Jaime Imitola, Keith L. Ligon, Santosh Kesari, Christine Esau, Robert M. Stephens, Bakhos A. Tannous, and Anna M. Krichevsky

**Précis:** Findings characterize the oncogenic functions of microRNA-10b in glioma biology by in silico, in vitro and in vivo approaches.
Bcl-2 Inhibits Nuclear Homologous Recombination by Localizing BRCA1 to the Endomembranes
Corentin Laulier, Aurélia Barascu, Josée Guirouilh-Barbat, Gaëlle Pennarun, Catherine Le Chalony, François Chevalier, Gaëlle Palierne, Pascale Bertrand, Jean Marc Verbavatz, and Bernard S. Lopez

Précis: Findings suggest a new tumor suppressor function and new mode of regulation for BRCA1, with general implications for understanding the role of homologous recombination in the maintenance of genome stability.

Deciphering the Molecular Events Necessary for Synergistic Tumor Cell Apoptosis Mediated by the Histone Deacetylase Inhibitor Vorinostat and the BH3 Mimetic ABT-737
Adrian P. Wiegmans, Amber E. Alsop, Michael Bots, Leonie A. Cluse, Steven P. Williams, Kellie-Marie Banks, Rachael Ralli, Clare L. Scott, Anna Frenzel, Andreas Villunger, and Ricky W. Johnstone

Précis: An extensive analysis of the basis for cancer cell death synergy between two important new classes of molecular targeted therapies stimulates interest in evaluation of their clinical combination.

Epigenetic Silencing of MicroRNA-203 Dysregulates ABL1 Expression and Drives Helicobacter-Associated Gastric Lymphomagenesis
Vanessa J. Craig, Sergio B. Cogliatti, Hubert Rehrauer, Thomas Wiindisch, and Anne Müller

Précis: Progression of H. pylori-associated gastritis to gastric MALT lymphoma is epigenetically regulated by promoter methylation of a microRNA that regulates the ABL oncogene.

Following Cytochrome c Release, Autophagy Is Inhibited during Chemotherapy-Induced Apoptosis by Caspase 8–Mediated Cleavage of Beclin 1
Hua Li, Peng Wang, Quanhong Sun, Wen-Xing Ding, Xiao-Ming Yin, Robert W. Sobol, Donna B. Stolz, Jian Yu, and Lin Zhang

Précis: This study provides direct evidence that cleavage of Beclin 1 by caspases functions as a critical switch for turning off autophagy for effective killing of cancer cells.

The Dual EGFR/HER2 Inhibitor Lapatinib Synergistically Enhances the Antitumor Activity of the Histone Deacetylase Inhibitor Panobinostat in Colorectal Cancer Models
Melissa J. LaBonte, Peter M. Wilson, Will Fazzone, Jared Russell, Stan G. Louie, Anthony El-Khoueiry, Heinz-Josef Lenz, and Robert D. Ladner

Précis: Findings provide a preclinical rationale to combine HDAC inhibitors with EGFR and HER2-targeted therapies in clinical trials seeking to improve colorectal cancer treatment.

Contribution of Abcc10 (Mrp7) to In Vivo Paclitaxel Resistance as Assessed in Abcc10−/− Mice

Précis: This is the first study to define an ATP-binding transporter other than P-glycoprotein that mediates cytotoxic sensitivity to taxanes.

STAT3 Mediates Resistance to MEK Inhibitor through MicroRNA miR-17
Bingbing Dai, Jieru Meng, Michael Peyton, Luc Girard, William G. Bornmann, Lin Ji, John D. Minna, Bingliang Fang, and Jack A. Roth

Précis: This study suggests strategies to overcome resistance to MEK kinase inhibitors which are presently being evaluated in clinical trials.

Differential Expression of S6K2 Dictates Tissue-Specific Requirement for S6K1 in Mediating Aberrant mTORC1 Signaling and Tumorigenesis
Caterina Nardella, Andrea Lunardi, Giusepppe Fedele, John G. Clohessy, Andrea Alimonti, Sara C. Kozma, George Thomas, Massimo Loda, and Pier Paolo Pandolfi

Précis: Findings suggest clinical evaluation of S6 kinase inhibitors in a subset of adrenal gland tumors lacking the tumor suppressor PTEN.
Effects of Carbon Ion Beam on Putative Colon Cancer Stem Cells and Its Comparison with X-rays
Xing Cui, Kazuhiko Oonishi, Hirohiko Tsujii, Takeshi Yasuda, Yoshitaka Matsumoto, Yoshiya Furusawa, Makoto Akashi, Tadashi Kamada, and Ryuichi Okayasu

Précis: This is the first study to show that carbon ion beam therapy may have advantages over photon beam therapy in targeting cancer stem-like cells for destruction.

ΔNp63 Versatilely Regulates a Broad NF-κB Gene Program and Promotes Squamous Epithelial Proliferation, Migration, and Inflammation
Xinpeng Yang, Hai Lu, Bin Yan, Rose-Anne Romano, Yansong Bian, Jay Friedman, Praveen Duggal, Clint Allen, Ryan Chuang, Reza Ehsanian, Han Si, Satrajit Sinha, Carter Van Waes, and Zhong Chen

Précis: Mechanistic findings reveal how the interaction of two key epidermal regulatory transcription factors orchestrate inflammatory changes characteristic of injury and malignant transformation.

Does the Hepatitis B Antigen HBx Promote the Appearance of Liver Cancer Stem Cells?
Alla Arzumanyan, Tiffany Friedman, Irene O.L. Ng, Marcia M. Clayton, Zhaozhi Li, and Mark A. Feitelson

Précis: This work establishes a link between chronic HBV infection and liver cancer by showing that the virus oncoprotein, HBx, promotes the appearance of "stemness" markers.

PHLDA1 Expression Marks the Putative Epithelial Stem Cells and Contributes to Intestinal Tumorigenesis

Précis: A novel marker of epithelial stem cells is suggested that functionally contributes to the migration and proliferation in colon cancer cells.

Interaction between FGFR-2, STAT5, and Progesterone Receptors in Breast Cancer
Juan P. Cerliani, Tomás Guillarroy, Sebastián Giulianelli, José P. Vaque, J. Silvio Gutkind, Silvia I. Vanzulli, Rubén Martins, Eduardo Zeitlin, Caroline A. Lamb, and Claudia Lanari

Précis: This study shows that activated nuclear FGFR-2 interact with hormone receptors and STAT5 to induce hormone related breast cancer growth.

Correction: Oncogenic Synergism between ErbB1, Nucleolin, and Mutant Ras

ABOUT THE COVER
Breast cancer induces the generation of regulatory B cells (tBregs) from resting B cells. As a result, tBregs convert T cells into Tregs which infiltrate CCL17/CCL22-expressing lungs to protect metastasizing cancer cells from NK cells. For details, see the article by Olkhunud and colleagues on page 3505 of this issue.
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