Breaking Advances

3481 Highlights from Recent Cancer Literature

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3483 From Integrative Genomics to Therapeutic Targets
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3489 HER2 and Breast Cancer Stem Cells: More than Meets the Eye
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Perspective

3494 APOBEC3 Cytidine Deaminases in Double-Strand DNA Break Repair and Cancer Promotion
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Clinical Studies

3499 Immune Infiltrates Are Prognostic Factors in Localized Gastrointestinal Stromal Tumors
Sylvie Rusakiewicz, Michaela Semeraro, Matthieu Sarabi, Melanie Desbois, Clara Locher, Rosa Mendez, Nadège Vimon, Angel Concha, Federico Garrido, Nicolas Isambert, Loïc Chaingneau, Valérie Le Brun-Ly, Patrice Duhreuil, Isabelle Cremer, Anne Caignard, Vichnou Poirier-Colame, Kariman Chaba, Caroline Flamant, Niels Halama, Dirk Jäger, Alexander Egggermont, Sylvie Bonvalot, Frédéric Commo, Philippe Terrier, Paule Opolon, Jean-François Emile, Jean-Michel Coindre, Guido Kroemer, Nathalie Chaput, Axel Le Cesne, Jean-Yves Blay, and Laurence Zitvogel

Precis: These findings encourage the prospective validation of immune biomarkers for optimal risk stratification of GIST, and they prompt clinical use of immunomodulators in conjunction with imatinib used to treat this disease.

3503 Tumor–Immune Dynamics Regulated in the Microenvironment Inform the Transient Nature of Immune-Induced Tumor Dormancy
Kathleen P. Wilkie and Philip Hahnfeldt

Precis: Better understanding of immune-induced tumor dormancy may lead to insights into prognosis and improved therapy for example by tilting host innate or adaptive responses toward those that favor tumor elimination over immune escape.

Integrated Systems and Technologies

3511 Kinetic Modeling-Based Detection of Genetic Signatures That Provide Chemoresistance via the E2F1-p73/DNp73-miR-205 Network
Julio Vera, Ulf Schnitz, Xin Lai, David Engelmann, Faiz M. Khan, Olaf Wolkenhauer, and Brigitte M. Pützer

Precis: Experimental and in silico data were used with kinetic modeling to develop a model that can detect a genetic signature that confers aggressive phenotypes in cancer cells.

3525 Mathematical Modeling of Tumor Cell Proliferation Kinetics and Label Retention in a Mouse Model of Lung Cancer
Yanyan Zheng, Helen Moore, Alexandra Piriatinska, Trinidad Solis, and E. Alejandro Sweet-Cordero

Precis: Mathematical methods to quantitate the proportion and doubling time of cycling tumor cell subpopulations in tumors, which tend to respond relatively poorly to cytotoxic therapies, may provide a tool to assess preclinical models, in which direct observation of cell-cycle kinetics may not be readily experimentally accessible.

3534 Booster Vaccinations against Cancer Are Critical in Prophylactic but Detrimental in Therapeutic Settings
Alessia Ricupito, Matteo Grioni, Arianna Calcinotto, Rodrigo Hess Michelini, Renato Longhi, Anna Mondino, and Matteo Bellone

Precis: This study challenges the notion that repeatedly boosting tumor-bearing subjects with a vaccine can sustain protective, long-lasting antitumor immunity, instead showing that certain prime-boost strategies actually drive T-cell exhaustion rather than expansion and memory.
A Novel Model for Evaluating Therapies Targeting Human Tumor Vasculature and Human Cancer Stem–like Cells
Daniela Burgos-Ojeda, Karen McLean, Shoumei Bai, Heather Pulaski, Yusong Gong, Ines Silva, Karl Skorecki, Maty Tzukerman, and Ronald J. Buckanovich
Précis: There remains a great need for preclinical models that can more accurately predict clinical responses to novel experimental therapeutic agents in development.

Enhanced Effector Responses in Activated CD8+ T Cells Deficient in Diacylglycerol Kinases
Précis: Targeting of diacylglycerol kinases offers a general approach to enhance the function of chimeric antigen receptor T cells (CART cells), a promising new strategy for cancer immunotherapy.

SOCS3 Transactivation by PPARγ Prevents IL-17–Driven Cancer Growth
Hélène Berger, Frédérique Végran, Madijl Chikh, Federica Gilardi, Sylvain Ladoire, Hélène Bugaut, Grégoire Mignot, Fanny Chalmin, Mélanie Bruuchard, Valentin Derangère, Angélique Chevriaux, Cédric Rébé, Bernhard Ryffel, Caroline Pot, Aziz Ichcham, Béatrice Desvergne, François Gähringhelli, and Lionel Apetoh
Précis: This study reveals new mechanistic insights into how inflammation supports cancer, and how blocking certain inflammatory pathways can restrict cancer.

Dual Blockade of PD-1 and CTLA-4 Combined with Tumor Vaccine Effectively Restores T-Cell Rejection Function in Tumors
Jaikumar Duraiswamy, Karen M. Kaluza, Gordon J. Freeman, and George Coukos
Précis: Combined checkpoint blockade is synergistic and strongly augments the efficacy of vaccination to restore T-cell exhaustion and promote tumor rejection.

BMP-6 in Renal Cell Carcinoma Promotes Tumor Proliferation through IL-10–Dependent M2 Polarization of Tumor-Associated Macrophages
Jae-Ho Lee, Geum Taek Lee, Seung Hyo Woo, Yun-Sok Ha, Seok Joo Kwon, Wun-Jae Kim, and Isaac Yi Kim
Précis: Elevated IL-10 levels have been broadly associated with tumor tolerance and immune escape, but the basis for IL-10 upregulation and its critical cellular targets in tumors have not been fully clear.

YAP/TEAD–Mediated Transcription Controls Cellular Senescence
Qi Xie, Jing Chen, Han Feng, Shengyi Peng, Ursula Adams, Yujie Bai, Li Huang, Ji Li, Junjian Huang, Songshu Meng, and Zengqiang Yuan
Précis: These findings offer general significance in cancers in which cellular senescence acts as a tumor suppressor, with implications for novel therapeutic approaches to stanch tumor growth.

ATF3 Suppresses Metastasis of Bladder Cancer by Regulating Gelsolin-Mediated Remodeling of the Actin Cytoskeleton
Xiangliang Yuan, Liang Yu, Junhua Li, Guohua Xie, Tingting Rong, Liang Zhang, Jiuhua Chen, Qiaoqiang Meng, Aaron T. Irving, Die Wang, Elizabeth D. Williams, Jun-Ping Liu, Anthony J. Sadler, Bryan R.G. Williams, Lishong Shen, and Dakang Xu
Précis: Mechanistic findings identify a transcription factor that suppresses metastasis of bladder cancer cells, suggesting new markers and strategies to define and address aggressive bladder tumors.

Nkx2-8 Downregulation Promotes Angiogenesis and Activates NF-κB in Esophageal Cancer
Chuyong Lin, Libing Song, Hui Gong, Aibin Liu, Xi Lin, Juewang Wu, Mengfeng Li, and Jun Li
Précis: These findings define a new tumor suppressor in esophageal cancer, the downregulation of which contributes to NF-κB activation and tumor angiogenesis.

Targeting ROR1 Inhibits Epithelial–Mesenchymal Transition and Metastasis
Bing Cui, Suping Zhang, Liguang Chen, Jianqiang Yu, George F. Widhopf II, Jessie-F. Fecteau, Laura Z. Rassenti, and Thomas J. Kipps
Précis: As a pivotal step in what converts curable benign tumors to untreatable malignant cancers, the cellular process of EMT and the key factors regulating it remain an important focus of attention in identifying cancer-specific therapies.
**DOG1 Regulates Growth and IGFBP5 in Gastrointestinal Stromal Tumors**
Susanne Simon, Florian Grabellus, Loretta Ferrera, Luis Galietta, Benjamin Schwendenhammer, Thomas Mühlenberg, Georg Taeger, Grant Eilers, Juergen Treckmann, Frank Breitenbuecher, Martin Schuler, Takahiro Taguchi, Jonathan A. Fletcher, and Sebastian Bauer

*Précis:* These findings reveal a novel oncogenic mechanism in GIST that highlights the importance of the tumor microenvironment as a therapeutic target in this disease.

**Pak1 Kinase Links ErbB2 to β-Catenin in Transformation of Breast Epithelial Cells**
Luis E. Arias-Romero, Olga Villamar-Cruz, Min Huang, Klaus P. Hoflich, and Jonathan Chernoff

*Précis:* Important mechanistic insights suggest new therapeutic strategies to treat breast cancers that involve HER2 overexpression.

**ATR Inhibition Broadly Sensitizes Ovarian Cancer Cells to Chemotherapy Independent of BRCA Status**
Catherine J. Huntoon, Karen S. Flatten, Andrea E. Wahner Hendrickson, Amelia M. Huehls, Shari L. Sutor, Scott H. Kaufmann, and Larry M. Karnitz

*Précis:* Findings that directly affect clinical treatment of BRCA1/2-deficient cancer cells are provided in this study, which addresses long-standing questions of how to leverage these conditions to improve effective therapeutic targeting.

**Inhibition of c-Met Reduces Lymphatic Metastasis in RIP-Tag2 Transgenic Mice**
Barbara Sennino, Toshina Ishiguro-Oonuma, Brian J. Schriver, James G. Christensen, and Donald M. McDonald

*Précis:* VEGF inhibition increases expression of c-Met, which can promote lymph node metastases, with consequences for understanding how resistance arises to antiangiogenic therapies.

**Antioxidant Enzymes Mediate Survival of Breast Cancer Cells Deprived of Extracellular Matrix**

*Précis:* This study offers evidence that blocking antioxidant enzymes may help kill cancer cells that are poised to metastasize, a finding that is counterintuitive in light of a large body of literature encouraging antioxidant treatments to prevent cancer.

**FGFR1 Is Essential for Prostate Cancer Progression and Metastasis**
Feng Yang, Yongyou Zhang, Steven J. Ressler, Michael M. Ittmann, Gustavo E. Ayala, Truong D. Dang, Fen Wang, and David R. Rowley

*Précis:* Fibroblast growth factor signaling in prostate cancer is emerging as an important area of therapeutic potential, as shown in this study of FGFR1, which suggests a rationale to attack metastatic tumors.

**Androgen Receptor-Independent Function of FoxA1 in Prostate Cancer Metastasis**
Hong-Jian Jin, Jonathan C. Zhao, Irene Ogden, Raymond C. Bergan, and Jindan Yu

*Précis:* This study may explain why recurrent FoxA1 mutations that have been found to occur in prostate cancer contribute to malignant progression in this disease.

**NF-κB Regulates Radioresistance Mediated By β1 Integrin in Three-Dimensional Culture of Breast Cancer Cells**
Kazi Mokim Ahmed, Hui Zhang, and Catherine C. Park

*Précis:* The results of this study suggest a novel approach to radiosensitize malignant breast cancers by targeting a forward feedback cell adhesion pathway.

**ING5 Is a Tip60 Cofactor That Acetylates p53 in Response to DNA Damage**
Nansong Liu, Jiadong Wang, and Catherine C. Park

*Précis:* This study illuminates one of the mechanisms through which cells determine whether to undergo cell-cycle arrest or apoptosis after p53 activation.

**MTA1 Promotes STAT3 Transcription and Pulmonary Metastasis in Breast Cancer**

*Précis:* Endogenous levels of a prometastatic transcriptional coregulator are sufficient to support its function in metastasis, whether or not it is overexpressed in cancer.
DDB2 Suppresses Epithelial-to-Mesenchymal Transition in Colon Cancer
Nilotpal Roy, Prashant V. Bommi, Uppoor G. Bhat, Shaumick Bhattacharjee, Indira Elangovan, Jing Li, Krushna C. Patra, Dragana Kopanja, Adam Blunier, Richard Benya, Srilata Bagchi, and Pradip Raychaudhuri

Precis: A nucleotide excision repair protein is found to function as an inhibitor of EMT, a phenotypic change in transformed epithelial cells that facilitates invasion and metastasis, suggesting a direct link between these processes during tumorigenesis.

GDNF–RET Signaling in ER-Positive Breast Cancers Is a Key Determinant of Response and Resistance to Aromatase Inhibitors
Andrea Morandi, Lesley-Ann Martin, Qiong Gao, Sunil Pancholi, Alan Mackay, David Robertson, Marketa Zvelebil, Mitch Dowsett, Ivan Plaza-Menacho, and Clare M. Isacke

Precis: This study addresses the clinical challenge of therapeutic resistance in oncology, in this case by defining an important tractable pathway of resistance to aromatase inhibitors used to fight ER-positive breast cancer.

ABOUT THE COVER
Inhibition of VEGF signaling reduces angiogenesis and slows tumor growth, but can also promote lymph node metastasis in some preclinical models. Studies of RIP-Tag2 transgenic mice revealed that inhibition of VEGF signaling by a function blocking anti-VEGF antibody or the receptor tyrosine kinase inhibitor sunitinib increased the number of intratumoral lymphatics, the proportion of lymphatics with tumor cells inside, and the incidence of lymph node metastasis. After the treatment, c-Met was upregulated in lymphatics in and around the tumors. Importantly, inhibition of c-Met by PF-04217903 administered with the angiogenesis inhibitor significantly reduced the abundance of intratumoral lymphatics, tumor cells inside lymphatics, and lymph node metastases. For details, see article by Sennino and colleagues on page 3692.