BREAKING ADVANCES

3481  Highlights from Recent Cancer Literature

REVIEWS

3483  From Integrative Genomics to Therapeutic Targets
Rachael Natrajan and Paul Wilkerson

3489  HER2 and Breast Cancer Stem Cells: More than Meets the Eye
Hasan Korkaya and Max S. Wicha

PERSPECTIVE

3494  APOBEC3 Cytidine Deaminases in Double-Strand DNA Break Repair and Cancer Promotion
Roni Nowarski and Moshe Kotler

CLINICAL STUDIES

3499  Immune Infiltrates Are Prognostic Factors in Localized Gastrointestinal Stromal Tumors

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.

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, Faiy M. Khan, Olaf Wolkenhauer, and Brigitte M. Pfitzer

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, Helene 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  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.

MICROENVIRONMENT AND IMMUNOLOGY

3545  Booster Vaccinations against Cancer Are Critical in Prophylactic but Detrimental in Therapeutic Settings
Alessia Ricupito, Matteo Grioni, Arianna Calciniotto, 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.
3555

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.

3566

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.

3578

SOCS3 Transactivation by PPARγ Prevents IL-17–Driven Cancer Growth

Hélène Berger, Frédérique Végran, Madjid Chikh, Federica Gilardi, Sylvain Ladoire, Hélène Bugaut, Grégoire Mignot, Fanny Chalmin, Mélanie Bruchard, Valentin Derangere, Angélique Chevriaux, Cédric Rébé, Bernhard Ryll, Caroline Pot, Aziz Hichami, Béatrice Desvergne, François Giringhelli, and Lionel Apetoh

Précis: This study reveals new mechanistic insights into how inflammation supports cancer, and how blocking certain inflammatory pathways can restrict cancer.

3591

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.

3604

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 Hye 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.
**TUMOR AND STEM CELL BIOLOGY**

3692 **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

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

3704 **Antioxidant Enzymes Mediate Survival of Breast Cancer Cells Deprived of Extracellular Matrix**

**Precis:** 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.

3661 **DOG1 Regulates Growth and IGFBP5 in Gastrointestinal Stromal Tumors**
Susanne Simon, Florian Grabellus, Loretta Ferrera, Luis Galietta, Benjamin Schwindenhammer, Thomas Mühlenberg, Georg Taeger, Grant Eilers, Juergen Treckmann, Frank Breitenbuecher, Martin Schuler, Takahiro Taguchi, Jonathan A. Fletcher, and Sebastian Bauer

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

3671 **Pak1 Kinase Links ErbB2 to β-Catenin in Transformation of Breast Epithelial Cells**
Luis E. Arias-Romero, Olga Villamar-Cruz, Min Huang, Klaus P. Hoeflich, and Jonathan Chernoff

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

3683 **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. Huerbs, Shari L. Sutor, Scott H. Kaufmann, and Larry M. Karnitz

**Precis:** 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.

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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

**Précis:** 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

**Précis:** 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.

Sox2 Requirement in Sonic Hedgehog-Associated Medulloblastoma
Julia Ahlfeld, Rebecca Favaro, Pierfrancesco Pagella, Hans A. Kretzschmar, Silvia Nicolis, and Ulrich Schüller

**Précis:** This study links a core pathogenic driver of an aggressive pediatric tumor to a central regulator of cancer stem-like function, with potential therapeutic implications.

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.