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1059 Human Th17 Immune Cells Specific for the Tumor Antigen MAGE-A3 Convert to IFN-γ–Secreting Cells as They Differentiate into Effector T Cells
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Précis: Naturally arising Th17 helper T cells that are specific for a common tumor antigen in cancer patients tend to convert into IFN-γ-secreting cells as they differentiate into effector T cells, a finding that encourages the development of methods to amplify them through immunotherapy.

1064 Ovarian Cancer Risk Associated with Inherited Inflammation-Related Variants

Précis: A large case–control study reveals that an inherited variant of the proinflammatory interleukin gene IL1A is associated with the risk of most types of ovarian cancer, offering powerful genetic support for a common role of inflammation in this disease.

1070 Immunotype and Immunohistologic Characteristics of Tumor-Infiltrating Immune Cells Are Associated with Clinical Outcome in Metastatic Melanoma
Gulsun Erdag, Jochen T. Scharfer, Mark E. Smolkin, Donna H. Deacon, Sofia M. Shea, Lynn T. Dengel, James W. Patterson, and Craig L. Slingluff Jr

Précis: The characteristics of immune infiltrates in metastases—an immunotype—may not only offer useful prognostic information but also the potential for personalized immunotherapy by tailoring strategies to manipulate the immunotype appropriately.

1081 Exploiting the Mutanome for Tumor Vaccination
John C. Castle, Sebastian Kreiter, Jan Diekmann, Mark E. Smolkin, Donna H. Deacon, Sofia M. Shea, Lynn T. Dengel, James W. Patterson, and Craig L. Slingluff Jr

Précis: This important study heralds strategies for personalized vaccinations of cancer patients, through the use of deep sequencing analysis, which shows that many nonsynonymous somatic mutations in a tumor are sufficient to confer antitumor activity to a peptide vaccine.
Tumor-Derived Chemokine CCL5 Enhances TGF-β–Mediated Killing of CD8+ T Cells in Colon Cancer by T-Regulatory Cells

Precis: This intriguing study tightens the emerging connections in cancer between inflammation, immune escape, and metastasis by showing how a chemokine implicated in inflammation and metastasis also drives immune escape by recruiting Treg cells that promote progression into tumors.

VEGF Receptor Inhibitors Block the Ability of Metronomically Dosed Cyclophosphamide to Activate Innate Immunity–Induced Tumor Regression
Joshua C. Doloff and David J. Waxman

Precis: Anti-VEGFR drugs can block beneficial antitumor immune responses that are triggered by periodic administration of cytotoxic chemotherapy, with implications for clinical trials that combine these drug classes.

Effective Treatment of Metastatic Forms of Epstein-Barr Virus–Associated Nasopharyngeal Carcinoma with a Novel Adenovirus-Based Adoptive Immunotherapy
Corey Smith, Janice Tsang, Leone Beagley, Daniel Chua, Victor Lee, Vivian Li, Denis J. Moss, William Coman, Kwok H. Chan, John Nicholls, Dora Kwong, and Rajiv Khanna

Precis: Early clinical findings reported in this study support the ongoing development of an immunotherapy for progressed forms of the most common throat cancer in the Far East, an endemic disease associated with EBV infections in a manner analogous to the association of HPV infections in cervical cancer.
**Kaposi Sarcoma Herpesvirus Promotes Endothelial-to-Mesenchymal Transition through Notch-Dependent Signaling**

Paola Gasperini, Georgrina Espigol-Frigole, Peter J. McCormick, Ombretta Salvucci, Dragan Maric, Thomas S. Ulrick, Mark N. Polizzotto, Robert Yarchtlan, and Giovanna Tosato

**Précis:** This study identifies a basis to understand the aggressiveness of a mesenchymal cancer that occurs commonly in AIDS patients, with implications for its better treatment with Notch pathway inhibitors currently being explored in clinical trials.

**DNA Methylation Does Not Stably Lock Gene Expression but Instead Serves as a Molecular Mark for Gene Silencing Memory**


**Précis:** Chromatin is a target for epigenetic cancer therapies that reactivate gene expression, but removal of DNA methylation signals is required first to achieve durable long-term effects.

**PREVENTION AND EPIDEMIOLOGY**

**Novel Genetic Markers of Breast Cancer Survival Identified by a Genome-Wide Association Study**


**Précis:** Genetic variants in the RAD51L1 gene implicated in DNA repair along with a second locus on chromosome 16 appear to predict the survival of breast cancer patients.

**Impact of Circulating Vitamin D Binding Protein Levels on the Association between 25-Hydroxyvitamin D and Pancreatic Cancer Risk: A Nested Case-Control Study**

Stephanie J. Weinstein, Rachael Z. Stolzenberg-Solomon, William Kopp, Helen Rager, Jarmo Virtamo, and Demetrius Albanes

**Précis:** Findings suggest an explanation for the adverse influence of vitamin D on risk of pancreatic cancer, which contrasts with some other solid tumors, with implications for how future risk association studies of vitamin D may be designed.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

**Cathepsin B Inhibition Limits Bone Metastasis in Breast Cancer**

Nimali P. Withana, Gahal Blum, Mansourh Sameni, Clare Slaney, Arulselvi Anbalagan, Mary B. Olive, Bradley N. Bidwell, Laura Edgington, Ling Wang, Kamiar Moin, Bonnie F. Sloane, Robin L. Anderson, Matthew S. Bogyo, and Belinda S. Parker

**Précis:** Important findings suggest a new strategy to block metastasis of breast cancer cells to bone, a common feature of malignant progression in breast cancer patients with few effective treatment options at present.

**B Effector Cells Activated by a Chimeric Protein Consisting of IL-2 and the Ectodomain of TGF-β Receptor II Induce Potent Antitumor Immunity**

Claudia Penafuerte, Spencer Ng, Norma Bautista-Lopez, Elena Birman, Kathy Former, and Jacques Galipeau

**Précis:** A chimeric protein composed of IL-2 and the extracellular part of the TGF-β type II receptor can stimulate B cells to induce complete protection against tumor challenge, with implications for cellular immunotherapy of cancer.

**RNAi-Mediated Targeting of Noncoding and Coding Sequences in DNA Repair Gene Messages Efficiently Radiosensitizes Human Tumor Cells**

Zhiming Zheng, Wooi Loon Ng, Xiangming Zhang, Jeffrey J. Olson, Chunhui Hao, Walter J. Curran, and Ya Wang

**Précis:** This study defines a generalized approach for highly efficient RNAi-based gene silencing, using a combinatorial targeting strategy to illustrate how knockdown of DNA repair genes can effectively radiosensitize tumor cells.

**LRIG1 Modulates Cancer Cell Sensitivity to Smac Mimetics by Regulating TNFα Expression and Receptor Tyrosine Kinase Signaling**

Longchuan Bai, Donna McEachern, Chao-Yie Yang, Jianfeng Lu, Haiying Sun, and Shaomeng Wang

**Précis:** This study provides key insights into the basis for resistance to IAP inhibitors, possibly critical to the successful clinical development of this new class of cancer drugs.
### TUMOR AND STEM CELL BIOLOGY

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**Précis:**
- This important study provides knowledge that can immediately be translated into the clinical setting to optimize cell-based cancer immunotherapies based on adoptive transfer of CD4+ T lymphocytes.
- Findings reveal that the turmeric spice component curcumin can act in a combinatorial manner to disrupt histone modification and androgen receptor signaling to control prostate cancer growth.
- An Akt substrate is identified as a critical oncogenic mediator in an aggressive type of pediatric cancer that has had an elusive molecular pathobiology.
- In addition to its well studied effects on tumor cell growth, senescence, and survival, p53 also acts in many ways to modify the cellular microenvironment, including through regulation of antiangiogenic factors.

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**Précis:**
- Genetic inactivation of the tumor suppressor protein Rb, and its relative p107, is sufficient to phenocopy the oncogenic activity of the human papillomavirus E7 oncoprotein in stimulating formation of head and neck cancer in mice, thereby establishing the importance of Rb/p107 functions in virally associated forms of this cancer which are rising rapidly in incidence.
- Results offer key mechanistic insights into how a major proinflammatory driver in the tumor microenvironment promotes epithelial-to-mesenchymal transition and stemness properties in breast cancer cells, with implications into how to therapeutically reverse these features of aggressive progression.
- Sox9, a gene active during embryogenesis and in adult stem cells, is found to be widely upregulated in various cancers where its expression is associated with unstrained cell proliferation, immortalization, and tumorigenesis.

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ABOUT THE COVER

A number of cathepsin proteases have been documented to promote tumor invasion and metastasis. However, the role of specific proteases in breast cancer metastasis and the therapeutic potential of their selective inhibition in clinically relevant models are not clear. Using 3D and \textit{in vivo} models, Withana and colleagues have shown that the cysteine protease cathepsin B has important roles in breast cancer metastasis and that therapeutic inhibition of this protease using small-molecule inhibitors dramatically decreases metastasis to lung and bone. The cover image was produced with fluorescent whole-body imaging using a cysteine cathepsin activity–based fluorescent probe (GB123) and the fluorescent diphosphonate probe Osteosense 750, which detects bone remodeling. The image shows cysteine cathepsin activity along the spine of mice bearing bone metastatic tumors. This activity is reduced in mice treated with the cathepsin B selective small-molecule inhibitor CA-074. For details, see the article by Withana and colleagues on page 1199 of this issue.
Cancer Research

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