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### INTEGRATED SYSTEMS AND TECHNOLOGIES

**3511** Kinetic Modeling-Based Detection of Genetic Signatures That Provide Chemoresistance via the E2F1-p73/DNp73-miR-205 Network
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Yanyan Zheng, Helen Moore, Alexandra Piryatinska, Trinidad Solis, and E. Alejandro Sweet-Cordero

### MICROENVIRONMENT AND IMMUNOLOGY

**3545** Booster Vaccinations against Cancer Are Critical in Prophylactic but Detrimental in Therapeutic Settings
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**3550** Tumor–Immune Dynamics Regulated in the Microenvironment Inform the Transient Nature of Immune-Induced Tumor Dormancy
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**3570** Tumor–Immune Dynamics Regulated in the Microenvironment Inform the Transient Nature of Immune-Induced Tumor Dormancy
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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.
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

Precis: 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

Precis: 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.

SOC3 Transactivation by PPARγ Prevents IL-17–Driven Cancer Growth
Hélène Berger, Frédérique Végran, Madjid Chikh, Federica Gilardi, Sylvain Ladoire, Hélène Buguault, Grégoire Mignot, Fanny Chalmin, Mélanie Bruchard, Valentin Derangère, Angélique Cheviroux, Cédric Rébé, Bernhard Ryffel, Caroline Pot, Aziz Hichami, Béatrice Desvergne, François Ghiringhelli, and Lionel Apetoh

Precis: 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
Jaikumar Duraiswamy, Karen M. Kaluza, Gordon J. Freeman, and George Coukos

Precis: 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

Precis: 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.
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<td>3661</td>
<td><strong>DOG1 Regulates Growth and IGFBP5 in Gastrointestinal Stromal Tumors</strong></td>
<td>Susanne Simon, Florian Graheilus, Loretta Ferrera, Luis Galietta, Benjamin Schwindenhammer, Thomas Mülthenerg, Georg Taeger, Grant Eilers, Juergen Treckmann, Frank Breitenbuecher, Martin Schuler, Takahiro Taguchi, Jonathan A. Fletcher, and Sebastian Bauer</td>
<td><em>Précis</em>: These findings reveal a novel oncogenic mechanism in GIST that highlights the importance of the tumor microenvironment as a therapeutic target in this disease.</td>
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<td>3671</td>
<td><strong>Pak1 Kinase Links ErbB2 to β-Catenin in Transformation of Breast Epithelial Cells</strong></td>
<td>Luis E. Arias-Romero, Olga Villamar-Cruz, Min Huang, Klaus P. Hoeltl, and Jonathan Chernoff</td>
<td><em>Précis</em>: Important mechanistic insights suggest new therapeutic strategies to treat breast cancers that involve HER2 overexpression.</td>
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<td>3683</td>
<td><strong>ATR Inhibition Broadly Sensitizes Ovarian Cancer Cells to Chemotherapy Independent of BRCA Status</strong></td>
<td>Catherine J. Huntoon, Karen S. Flatten, Andrea E. Wahner Hendrickson, Amelia M. Huehls, Shari L. Sutor, Scott H. Kaufmann, and Larry M. Karnitz</td>
<td><em>Précis</em>: 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.</td>
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<td>3692</td>
<td><strong>Inhibition of c-Met Reduces Lymphatic Metastasis in RIP-Tag2 Transgenic Mice</strong></td>
<td>Barbara Sennino, Toshina Ishiguro-Oonuma, Brian J. Schriver, James G. Christensen, and Donald M. McDonald</td>
<td><em>Précis</em>: VEGF inhibition increases expression of c-Met, which can promote lymph node metastases, with consequences for understanding how resistance arises to antiangiogenic therapies.</td>
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<td>3704</td>
<td><strong>Antioxidant Enzymes Mediate Survival of Breast Cancer Cells Deprived of Extracellular Matrix</strong></td>
<td>Calli A. Davison, Sienna M. Durbin, Matthew R. Thau, Victoria R. Zellmer, Sarah E. Chapman, Justin Diener, Connor Watlien, Matthew Leavy, and Zachary T. Schaler</td>
<td><em>Précis</em>: 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.</td>
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<td>3761</td>
<td><strong>MTA1 Promotes STAT3 Transcription and Pulmonary Metastasis in Breast Cancer</strong></td>
<td>Suresh B. Pakala, Suresh K. Rayala, Rui-An Wang, Kazufumi Ohshiro, Prakriti Mudvari, Sirigiri Divijendra Natha Reddy, Yi Zheng, Ricardo Pires, Sandra Casimiro, M. Radhakrishna Pillai, Luis Costa, and Rakesh Kumar</td>
<td><em>Précis</em>: Endogenous levels of a prometastatic transcriptional coregulator are sufficient to support its function in metastasis, whether or not it is overexpressed in cancer.</td>
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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.

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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.