

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**
Sylvie Rusakiewicz, Michaela Semeraro, Matthieu Sarabi, Mélanie Desbois, Clara Locher, Rosa Mendez, Nadège Vimond, Angel Concha, Federico Garrido, Nicolas Isambert, Loic Chaigneau, Valérie Le Brun-Ly, Patrice Dubreuil, Isabelle Cremer, Anne Caignard, Vichnou Poirier-Colame, Kariman Chaba, Caroline Flament, Niels Halama, Dirk Jäger, Alexander Eggermont, 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
- Précis:* 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 Schmitz, Xin Lai, David Engelmann, Faiz M. Khan, Olaf Wolkenhauer, and Brigitte M. Pützner
- Précis:* 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 Piryatinska, Trinidad Solis, and E. Alejandro Sweet-Cordero



Précis: 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

Précis: 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 Gioni, Arianna Calcinotto, Rodrigo Hess Michelini, Renato Longhi, Anna Mondino, and Matteo Bellone
- Précis:* 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

Matthew J. Riese, Liang-Chuan S. Wang, Edmund K. Moon, Rohan P. Joshi, Anjana Ranganathan, Carl H. June, Gary A. Koretzky, and Steven M. Albelda

Précis: Targeting of diacylglycerol kinases offers a general approach to enhance the function of chimeric antigen receptor T cells (CAR T cells), a promising new strategy for cancer immunotherapy.

3578

SOCS3 Transactivation by PPAR γ Prevents IL-17-Driven Cancer Growth

Hélène Berger, Frédérique Végran, Madijd Chikh, Federica Gilardi, Sylvain Ladoire, Hélène Bugaut, Grégoire Mignot, Fanny Chalmin, Mélanie Bruchard, Valentin Derangère, Angélique Chevriaux, Cédric Rébé, Bernhard Ryffel, Caroline Pot, Aziz Hichami, Béatrice Desvergne, François Ghiringhelli, 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, Geun 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.

MOLECULAR AND CELLULAR PATHOBIOLOGY

3615

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.

3625

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, Jianhua Chen, Qiaohong Meng, Aaron T. Irving, Die Wang, Elizabeth D. Williams, Jun-Ping Liu, Anthony J. Sadler, Bryan R.G. Williams, Lisong 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.

3638

Nkx2-8 Downregulation Promotes Angiogenesis and Activates NF- κ B in Esophageal Cancer

Chuyong Lin, Libing Song, Hui Gong, Aibin Liu, Xi Lin, Jueheng Wu, Mengfeng Li, and Jun Li

Précis: These findings define a new tumor suppressor in esophageal cancer, the downregulation of which contributes to NF- κ B activation and tumor angiogenesis.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

3649

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.

3661 **DOG1 Regulates Growth and IGFBP5 in Gastrointestinal Stromal Tumors**
Susanne Simon, Florian Grabellus, Loretta Ferrera, Luis Galiotta, Benjamin Schwindenhammer, 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.

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

Précis: 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. 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.

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

Précis: 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**
Calli A. Davison, Sienna M. Durbin, Matthew R. Thau, Victoria R. Zellmer, Sarah E. Chapman, Justin Diener, Connor Wathen, W. Matthew Leevy, and Zachary T. Schafer

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.

3716 **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.

3725 **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.

3737 **NF- κ B Regulates Radioresistance Mediated By β 1 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.

3749 **ING5 Is a Tip60 Cofactor That Acetylates p53 in Response to DNA Damage**
Nansong Liu, Jiadong Wang, Jifeng Wang, Rukai Wang, Zhongle Liu, Yao Yu, and Hong Lu

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

3761 **MTA1 Promotes STAT3 Transcription and Pulmonary Metastasis in Breast Cancer**
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

Précis: Endogenous levels of a prometastatic transcriptional coregulator are sufficient to support its function in metastasis, whether or not it is overexpressed in cancer.

3771

DDB2 Suppresses Epithelial-to-Mesenchymal Transition in Colon Cancer

Nilotpall Roy, Prashant V. Bommi, Upoor 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.

3783

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.

3796

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.

