Chemoprevention of Breast Cancer by Fish Oil in Preclinical Models: Trials and Tribulations
Carina Signori, Karam El-Bayoumy, Jose Russo, Henry J. Thompson, John P. Richie, Terryl J. Hartman, and Andrea Manni

Resuscitating Cancer Immunosurveillance: Selective Stimulation of DLL1-Notch Signaling in T cells Rescues T-cell Function and Inhibits Tumor Growth
Yuhui Huang, Luping Lin, Anil Shanker, Anshu Malhotra, Li Yang, Mikhail M. Dikov, and David P. Carbone

Downregulation of RBMS3 Is Associated with Poor Prognosis in Esophageal Squamous Cell Carcinoma
Yan Li, Leilei Chen, Chang-jun Nie, Ting-ting Zeng, Haibo Liu, Xueying Mao, Yanru Qin, Ying-Hui Zhu, Li Fu, and Xin-Yuan Guan

FLT3 Ligand Enhances the Cancer Therapeutic Potency of Naked RNA Vaccines
Sebastian Kreiter, Mustafa Diken, Abderraouf Selmi, Jan Dickmann, Sebastian Attig, Yves Husemann, Michael Koslowski, Christoph Huber, Özlem Türeci, and Ugur Sahin

Effects of Photoacoustic Imaging and Photothermal Ablation Therapy Mediated by Targeted Hollow Gold Nanospheres in an Orthotopic Mouse Xenograft Model of Glioma
Wei Lu, Marites P. Melancon, Chiyi Xiong, Qian Huang, Andrew Elliott, Shaoli Song, Rui Zhang, Leo G. Flores II, Juri G. Gelovani, Lihong V. Wang, Geng Ku, R. Jason Stafford, and Chun Li

Precis: Multifunctional targeted hollow gold nanospheres serve as a new cancer theranostic platform for both photoacoustic imaging and photothermal ablation therapy.


Precis: This study reports an adjuvant strategy to strengthen the antitumor effects achieved by lymph node injection with naked RNA encoding tumor antigens, optimizing a safe and simple vaccination strategy for cancer immunotherapy.
**Early Detection of Tumor Cells by Innate Immune Cells Leads to T<sub>reg</sub> Recruitment through CCL22 Production by Tumor Cells**

Julien Faget, Cathy Biota, Thomas Bachelot, Michael Gobert, Isabelle Treilleux, Nadège Goutagny, Isabelle Durand, Sophie Leon-Goddard, Jean Yves Blay, Christophe Caux, and Christine Ménétrier-Caux

**Précis:** This important study addresses the key question of how early tumor cells evolve the ability to escape roving innate immune cells by recruiting tumor-promoting T regulatory cells (Tregs), thought to be central drivers of cancer progression.

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**MOLECULAR AND CELLULAR PATHOBIOLOGY**

6153

**Proto-oncogene PBF/PTTG1IP Regulates Thyroid Cell Growth and Represses Radioiodide Treatment**

Martin L. Read, Greg D. Lewy, Jim C.W. Fong, Neil Sharma, Robert I. Seed, Vicki E. Smith, Erica Gentilin, Adrian Warfield, Margaret C. Eggo, Jeffrey A. Knauf, Wendy E. Leadbeater, John C. Watkinson, Jayne A. Franklyn, Kristien Boelaert, and Christopher J. McCabe

**Précis:** A little-characterized proto-oncogene in thyroid hyperplasia and neoplasia functions in blocking the chief route of radioiodine uptake, which is vital for clinical treatment of thyroid cancer.

6165

**miR-375 Is Activated by ASH1 and Inhibits YAP1 in a Lineage-Dependent Manner in Lung Cancer**

Eri Nishikawa, Hirotaka Osada, Yasumasa Okazaki, Chinatsu Arima, Shuta Tomida, Yoshio Tatematsu, Ayumu Taguchi, Yukako Shimada, Kiyoshi Yanagisawa, Yasushi Yatabe, Shinya Toyokuni, Yoshitaka Sekido, and Takashi Takahashi

**Précis:** Findings provide insight into the molecular determinants of small cell lung cancers with neuroendocrine features, which tend to be aggressive and difficult to treat.

6174

**Cyclin D1 and Cdk4 Mediate Development of Neurologically Destructive Oligodendroglioma**

Daniel Ciznadia, Yuhui Liu, Stephanie M. Pyonteck, Eric C. Holland, and Andrew Koff

**Précis:** This seminal in vivo study establishes that the Cyclin D1-Cdk4 complex—the central regulator of cell proliferation in human cancer cells—is not only important in tumor cells but also in stromal cells of the surrounding microenvironment that are critical for tumor outgrowth.

6184

**Wnt5a Suppresses Epithelial Ovarian Cancer by Promoting Cellular Senescence**

Benjamin G. Bitler, Jasmine P. Nicodemus, Hua Li, Qi Cai, Hong Wu, Xiang Hu, Tianyu Li, Michael J. Birrer, Andrew K. Godwin, Paul Cairns, and Rugang Zhang

**Précis:** Findings define a tumor suppressor function that when downregulated in ovarian cancer patients confers a poor prognosis for outcomes.

6195

**Genome-wide Methylation Analysis Identifies Genes Specific to Breast Cancer Hormone Receptor Status and Risk of Recurrence**

Mary Jo Fackler, Christopher B. Umbricht, Danielle Williams, Pedram Argani, Leigh-Ann Cruz, Vanessa F. Merino, Wei Wen Teo, Zhe Zhang, Peng Huang, Kala Visvananthan, Jeffrey Marks, Stephen Ethier, Joe W. Gray, Antonio C. Wolff, Leslie M. Cope, and Saraswati Sukumar

**Précis:** Methylome analysis of primary breast cancers led to the identification of 40 markers that segregated ER+ from ER- breast cancers and 32 markers that predicted risk of recurrence, and sets the stage for further discovery in samples from large clinical trials.

6208

**MicroRNA-708 Induces Apoptosis and Suppresses Tumorigenicity in Renal Cancer Cells**

Sharanjot Saini, Soichiro Yamamura, Shahana Majid, Varahram Shabryari, Hiroshi Hirata, Yuichiro Tanaka, and Rajvir Dahiya

**Précis:** This study reveals a major suppressor role for a little-studied microRNA in the pathogenesis of a highly aggressive kidney malignancy, mediated in large part by its ability to inhibit expression of the antiapoptotic protein survivin, which is widely overexpressed in human cancers.
A Mutation Threshold Distinguishes the Antitumorigenic Effects of the Mitochondrial Gene MTND1, an Oncogranus Function

Giuseppe Gasparre, Ivana Kurelac, Mariantonietta Capristo, Luisa Iommarini, Anna Ghelli, Claudio Cecarelli, Giordano Nicoletti, Patrizia Nanni, Carla De Giovanni, Valerio Carelli, Giovanni Romeo, Michela Rugolo, and Anna Maria Porcelli

Précis: This study reinterprets the role of mitochondrial DNA mutations in cancer progression and adds a novel functional definition for metabolic genes with a threshold-dependent lethality effect.

MicroRNA-32 Upregulation by 1,25-Dihydroxyvitamin D3 in Human Myeloid Leukemia Cells Leads to Bim Targeting and Inhibition of AraC-Induced Apoptosis

Elzbieta Gecek, Xuening Wang, Xiuping Liu, Chang-Gong Liu, and George P. Studzinski

Précis: Treatment of acute myeloid leukemias that remain poorly managed in the clinic may benefit from agents that can block the expression of a microRNA that limits expression of the pro-apoptotic protein Bim.

Common Breast Cancer Susceptibility Loci Are Associated with Triple-Negative Breast Cancer


Précis: This first report from a large consortium identifies variants in the ESRI, MERIT40, RAD51L1, and TOX3 genes that were found to be highly significantly associated with risk of triple negative breast cancer.

Androgen-Independent Molecular Imaging Vectors to Detect Castration-Resistant and Metastatic Prostate Cancer

Zuyue Karen Jiang, Makoto Sato, Liu H. Wei, Chinghai Kao, and Lily Wu

Précis: A prostate cancer-specific but androgen-independent imaging reporter system is shown to be useful for detecting advanced castration-resistant prostate cancer, including disseminated bony metastases.

EGF Receptor Inhibition Radiosensitizes NSCLC Cells by Inducing Senescence in Cells Sustaining DNA Double-Strand Breaks

Meng Wang, Fabian Morsbach, David Sander, Liliana Gheorghiu, Akash Nanda, Cyril Benes, Malte Kries, Mechuilar Krause, Ekkehard Dikomey, Michael Baumann, Jochen Dahm-Daphi, Jeffrey Sedlmaier, and Henning Willers

Précis: This study offers a mechanistic rationale to reposition EGF inhibitors used widely in the clinic as radiosensitizers in lung cancer.

Celecoxib Promotes c-FLIP Degradation through Akt-Independent Inhibition of GSK3

Shuzhen Chen, Wei Cao, Ping Yue, Chunhai Hao, Fadlo R. Khuri, and Shi-Yong Sun

Précis: Mechanistic findings reveal insights into how celecoxib may promote cancer cell death by promoting turnover of c-FLIP, a chief regulator of the death receptor pathway of apoptosis.
Transplantation of β-Endorphin Neurons into the Hypothalamus Promotes Immune Function and Restricts the Growth and Metastasis of Mammary Carcinoma
Dipak K. Sarkar, Changqing Zhang, Sengottuvelan Murugan, Madhavi Dokur, Nadka I. Boyadjieva, Maria Ortigüela, Kenneth R. Reuhl, and Sepide Mojtehedzadeh

Précis: Stress blunts the effects of a mood-altering molecule that appears to affect the innate immune response to tumors, suggesting a role in tumorigenesis for an inflammatory reflex that integrates neuronal and immune signaling in the body.

ABOUT THE COVER

β-endorphin (bEP) neuron activation prevents the growth and metastasis of mammary tumor cells by altering autonomic nervous system activities that enhance innate immune functions. Sarkar and colleagues identified the mechanism by which bEP cell transplantation into the brain prevents mammary carcinogenesis by showing that the transplants’ antimetastatic effect, along with stimulation of cytotoxic function of immune cells and production of anti-inflammatory cytokines, is reversed by the treatment with an opiate antagonist, naloxone (NAL), to block bEP, the β-receptor agonist metaproterenol (MET) to activate sympathetic neurotransmission, or the nicotine acetylcholine receptor antagonist methyllycaconitine (MLA) to prevent parasympathetic neurotransmission. For details, see the article by Sarkar and colleagues on page 6282 of this issue.
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