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Long Noncoding RNA TINCR-Mediated Regulation of Acetyl-CoA Metabolism Promotes Nasopharyngeal Carcinoma Progression and Chemoresistance  
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TINCR-mediated regulation of a PADI4–MAPK–MMP2/9 signaling pathway plays a critical role in NPC progression and chemoresistance, marking TINCR as a viable therapeutic target in this disease.

5189  
Evolution of the Epigenetic Landscape in Childhood B Acute Lymphoblastic Leukemia and Its Role in Drug Resistance  

This study suggests a major role for epigenetic mechanisms in driving clonal evolution in B-ALL and identifies novel pathways associated with drug resistance.

5203  
Epigenetic Inactivation of α-Internexin Accelerates Microtubule Polymerization in Colorectal Cancer  
Yingjie Li, Liangliang Bai, Huichuan Yu, Du Cai, Xiaolin Wang, Baoyuan Huang, Shaoyong Peng, Meijin Huang, Guangwen Cao, Andrew M. Kaz, William M. Grady, Jianping Wang, and Yanxin Luo

This work provides insight into the epigenetic inactivation of INA, a novel identified tumor suppressor, which increases microtubule polymerization during colorectal cancer progression.

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### MOLECULAR CELL BIOLOGY

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Stromal SNAI2 expression enhances the tumorigenicity of luminal B HER2+ breast cancers and can identify a subset of patients with poor prognosis, making SNAI2 a potential therapeutic target for this disease.

See related commentary, p. 5164

| 5231 | Phosphorylation Control of p53 DNA-Binding Cooperativity Balances Tumorigenesis and Aging | Oleg Timofeev, Lukas Koch, Constantin Niederau, Alina Tscherner, Jean Schmelkert, Maria Klimovich, Sabrina Elmsmäuer, Marie Zeitlinger, Marco Memberger, Andrea Nist, Christian Osterburg, Volker Dötsch, German Mouse Clinic Consortium, Martin Hrabě de Angelis, and Thorsten Stiewe |

These findings demonstrate that p53 tumor suppressor activity is reduced by DNA-binding domain phosphorylation to prevent aging and identify this phosphorylation as a potential target for cancer therapy.

### TUMOR BIOLOGY AND IMMUNOLOGY

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<td>Hypoxia Induces Transcriptional and Translational Downregulation of the Type I IFN Pathway in Multiple Cancer Cell Types</td>
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These findings characterize a new mechanism of immunosuppression by hypoxia via downregulation of the type I IFN pathway and its autocrine/paracrine effects on tumor growth.

| 5257 | SIRT1-Mediated Expression of CD24 and Epigenetic Suppression of Novel Tumor Suppressor miR-1185-1 Increases Colorectal Cancer Stemness | Teh-Wei Wang, Edward Chern, Chao-Wei Hsu, Kuo-Chang Tseng, and Hsiao-Mei Chao |

A novel tumor suppressor miR-1185-1 is involved in molecular regulation of CD24- and SIRT1-related cancer stemness networks, marking it a potential therapeutic target in colorectal cancer.

| 5270 | A Novel Inhibitor of HSP70 Induces Mitochondrial Toxicity and Immune Cell Recruitment in Tumors | Thibaut Barnoud, Jessica C. Leung, Julia I-Ju Leu, Subhasree Basu, Adi Narayana Reddy Poli, Joshua L.D. Parris, Alexandra Indeglia, Tetyana Martynyuk, Madeline Good, Keerrthana Gnanapradeepan, Emilio Sansevierio, Rebecca Moeller, Hsin-Yao Tang, Joel Cassel, Andrew V. Kossenkov, Qin Liu, David W. Speicher, Dmitry I. Gabrilovich, Joseph M. Salvino, Donna L. George, and Maureen E. Murphy |

These findings describe a novel HSP70i that disrupts mitochondrial proteostasis, demonstrating single-agent efficacy that induces immunogenic cell death in treated tumors.

| 5282 | A Global and Integrated Analysis of CINSARC-Associated Genetic Defects | Tom Leslye and Frédéric Chibon |

These findings demonstrate that CINSARC is associated with a variety of genomic aberrations that contribute to higher risk for metastasis and may serve as a prognostic factor in sarcomas and beyond.

| 5305 | Hes1 Is Essential in Proliferating Ductal Cell-Mediated Development of Intrahepatic Cholangiocarcinoma | Tomoaki Matsumori, Yuzu Kodama, Atsushi Takai, Masahiro Shikawa, Yoshihiro Nishikawa, Tomonori Matsumoto, Haruhiko Takaeda, Saiko Marui, Hirokazu Okada, Tomonori Hirano, Takeshi Kuniwa, Yuko Sagabe, Nobuyuki Kakuchi, Teruko Tomono, Atsushi Mima, Toshihiro Morita, Tatsuki Ueda, Motoyuki Tsuda, Yuki Yamauchi, Katsuaki Kuriyama, Yojiro Sakuma, Yuji Ota, Takahisa Maruno, Norimitsu Utsa, Hiroyuki Marusawa, Ryoichiro Kageyama, Tsutomu Chiba, and Hiroshi Seno |

This study contributes to the identification of the cells of origin that initiate ICC and suggests that HES1 may represent a therapeutic target in ICC.

| 5317 | Fibrobast-Derived IL33 Facilitates Breast Cancer Metastasis by Modifying the Immune Microenvironment and Driving Type 2 Immunity | Ophir Shani, Tatiana Vorobyov, Lea Monteran, Dor Lavie, Noam Cohen, Yael Raz, Galia Tserfaty, Camila Avivi, Iris Barshack, and Neta Erez |

This study elucidates a novel role for fibrobast-derived IL33 in facilitating breast cancer lung metastasis by modifying the immune microenvironment at the metastatic niche towards type 2 inflammation.
5330 A Hyperactive RelA/p65-Hexokinase 2 Signaling Axis Drives Primary Central Nervous System Lymphoma


A set of clinically relevant CNSL xenografts identifies a hyperactive RelA/p65-hexokinase 2 signaling axis as a driver of progression and potential therapeutic target for treatment and provides a foundational preclinical platform.

5344 Melphalan and Exportin 1 Inhibitors Exert Synergistic Antitumor Effects in Preclinical Models of Human Multiple Myeloma

Joel G. Turner, Yan Cui, Alexis A. Bauer, Jana L. Dawson, Juan A. Gomez, Jongh Heal Kim, Christopher L. Cubitt, Taiga Nishihori, William S. Dalton, and Daniel M. Sullivan

Inhibition of exportin 1 with selinexor synergistically sensitizes human multiple myeloma to melphalan by inhibiting Fanconi anemia pathway-mediated DNA repair.

5355 Nanoengineered Disruption of Heat Shock Protein 90 Targets Drug-Induced Resistance and Relieves Natural Killer Cell Suppression in Breast Cancer


This study uncovers a molecular mechanism linking drug-induced resistance and tumor immunity and provides novel engineered solutions that target these mechanisms in the tumor and improve immunity, thus mitigating off-target effects.

5367 Combined Inhibition of SHP2 and MEK Is Effective in Models of NFI-Deficient Malignant Peripheral Nerve Sheath Tumors


Combined inhibition of MEK and SHP2 is effective in models of NFI-MPNST, both those naïve to and those resistant to MEKI, as well as in the MPNST precursor lesion pleomorphic neurofibroma.

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TRANSLATIONAL SCIENCE

5330 A Hyperactive RelA/p65-Hexokinase 2 Signaling Axis Drives Primary Central Nervous System Lymphoma


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CONVERGENCE AND TECHNOLOGIES

5408 Autofluorescence Imaging of 3D Tumor–Macrophage Microscale Cultures Resolves Spatial and Temporal Dynamics of Macrophage Metabolism


These findings show that high-throughput drug screening identifies therapies for medulloblastoma that cannot be predicted by genomic or transcriptomic analysis.

CORRECTION

5424 Correction: p62/SQSTM1 Cooperates with Hyperactive mTORC1 to Regulate Glutathione Production, Maintain Mitochondrial Integrity, and Promote Tumorigenesis


Label-free metabolic imaging and microscale culture technologies enable monitoring of single-cell macrophage metabolism, migration, and function in the 3D tumor microenvironment.

AC AC icon indicates Author Choice

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Malignant peripheral nerve sheath tumors (MPNST) are aggressive soft tissue sarcomas that have a propensity to occur in individuals with neurofibromatosis type 1. Biallelic NF1 alteration is nearly universally found in MPNST and its loss disrupts negative regulation of RAS activity in these cancer cells. By interrogation of kinome activity through an unbiased screen and targeted evaluation of the signaling response to MEK inhibition, Wang and colleagues have identified global activation of upstream receptor tyrosine kinases (RTK), converging on activation of RAS, as a mechanism limiting the sensitivity to MEK inhibition. An inhibitor of the protein tyrosine phosphatase SHP2, a critical mediator of RAS signal transduction downstream of multiple RTK, given in combination with MEK inhibitor, represents a potential therapeutic strategy to overcome the loss-of-feedback–associated upstream activation. The combination is effective in preclinical models of MPNST. For details, see article by Wang and colleagues on page 5367.