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Adedeji K. Adebayo and Harikrishna Nakshatri

## CANCER RESEARCH HIGHLIGHTS

**4322** A Time and Place for Inhibiting Autophagy

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See related article, p. 4429

## MOLECULAR CELL BIOLOGY

**4325** Targeting STAT5 Signaling Overcomes Resistance to IDH Inhibitors in Acute Myeloid Leukemia through Suppression of Stemness

Alex C.H. Liu, Severine Cathelin, Yitong Yang, David L. Dai, Dhanoop Manikoth Ayyathan, Mohsen Hosseini, Mark D. Minden, Anne Tierens, and Steven M. Chan

A CRISPR knockout screen identifies a mechanism of resistance to IDH inhibitors in AML involving activated STAT5 signaling, suggesting a potential strategy to improve the clinical efficacy of IDH inhibitors.

**4340** MNX1-AS1 Promotes Phase Separation of IGF2BP1 to Drive c-Myc-Mediated Cell-Cycle Progression and Proliferation in Lung Cancer

Qingqing Zhu, Chongguo Zhang, Tianyu Qu, Xiyi Lu, Xuezhi He, Wei Li, Dandan Yin, Liang Han, Renhua Guo, and Erbao Zhang

MNX1-AS1 drives phase separation of IGF2BP1 to increase c-Myc and E2F1 signaling and to activate cell-cycle progression to promote proliferation in NSCLC.

## TUMOR BIOLOGY AND IMMUNOLOGY

**4359** Quantitative Spatial Profiling of Immune Populations in Pancreatic Ductal Adenocarcinoma Reveals Tumor Microenvironment Heterogeneity and Prognostic Biomarkers

Haoyang Mi, Shamilene Sivagnanam, Courtney B. Betts, Shannon M. Liudahl, Elizabeth M. Jaffee, Lisa M. Coussens, and Aleksander S. Popel

Quantitative image analysis of PDAC specimens reveals intertumoral and intratumoral heterogeneity of immune populations and identifies spatial immune architectures that are significantly associated with disease prognosis.

**4373** Depletion of Conventional Type-1 Dendritic Cells in Established Tumors Suppresses Immunotherapy Efficacy

Alvaro Teijeira, Saray Garasa, Carlos Luri-Rey, Carlos de Andrea, Maria Gato, Carmen Molina, Tsuneyasu Kaisho, Assunta Cirella, Arantza Azpilikueta, Steffanie K. Wculek, Josune Egea, Irene Olivera, Inmaculada Rodriguez, Ana Rouzaut, Vladislav Verkusha, Karnele Valencia, David Sancho, Pedro Berraondo, and Ignacio Melero

These findings reveal the intratumoral behavior of cDC1 dendritic cells in transgenic mouse models and demonstrate that the efficacy of immunotherapy regimens is precluded by elimination of these cells.

**4386** Stress-Mediated Attenuation of Translation Undermines T-cell Activity in Cancer

Brian P. Riesenbergh, Elizabeth G. Hunt, Megan D. Tennant, Katie E. Hurst, Alex M. Andrews, Lee R. Leddy, David M. Neskey, Elizabeth G. Hill, Guillermo O. Rangel Rivera, Chrystal M. Paulos, Peng Gao, and Jessica E. Thaxton

Proteasome function is a necessary cellular component for endowing T cells with tumor killing capacity by mitigating translation attenuation resulting from the unfolded protein response induced by stress in the tumor microenvironment.

**4400** Loss of LOXL2 Promotes Uterine Hypertrophy and Tumor Progression by Enhancing H3K36ac-Dependent Gene Expression

Xufeng Lu, Dazhuan E. Xin, Juanjuan K. Du, Quanli C. Zou, Qian Wu, Yanan S. Zhang, Wenhai Deng, Jicheng Yue, Xing S. Fan, Yuanyuan Zeng, Xiaju Cheng, Xue Li, Zhaoyuan Hou, Man Mohan, Ting C. Zhao, Xiaomei Lu, Zhijie Chang, Liyan Xu, Yu Sun, Xiongbing Zu, Yu Zhang, and Y. Eugene Chinn

LOXL2 loss reprograms the epigenetic landscape to promote uterine cancer initiation and progression and repress the efficacy of anti-PD-1 immunotherapy, indicating that LOXL2 is a tumor suppressor.

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## 4414 Endothelial RBPJ Is Essential for the Education of Tumor-Associated Macrophages

Elisenda Alsina-Sanchis, Ronja Mülfarth, Iris Moll, Sarah Böhn, Lena Wiedmann, Lorea Jordana-Urriza, Tara Ziegelbauer, Eleni Zimmer, Jacqueline Taylor, Francesca De Angelis Rigotti, Adrian Stögbauer, Benedetto Daniele Giaimo, Adelheid Cerwenka, Tilman Borggrefe, Andreas Fischer, and Juan Rodriguez-Vita

Endothelial Notch signaling favors immunosuppression by increasing CXCL2 secretion to stimulate CD44 expression in macrophages, facilitating their education by tumor cells.

## 4457 Epithelial-to-Mesenchymal Transition Supports Ovarian Carcinosarcoma Tumorigenesis and Confers Sensitivity to Microtubule Targeting with Erlubulin

Gwo Yaw Ho, Elizabeth L. Kyran, Justin Bedo, Matthew J. Wakefield, Darren P. Ennis, Hasan B. Mirza, Cassandra J. Vandenberg, Elizabeth Lieschke, Andrew Farrell, Anthony Hadla, Ratana Lim, Genevieve Dall, James E. Vince, Ngee Kiat Chua, Olga Kondrashova, Rosanna Upstill-Goddard, Ulla-Maja Bailey, Suzanne Dowson, Patricia Roxburgh, Rosalind M. Glasspool, Gareth Bryson, Andrew V. Biankin; for the Scottish Genomes Partnership, Susanna L. Cooke, Gayanie Ratnayake, Orla McNally, Nadia Traficante; for the Australian Ovarian Cancer Study, Anna DeFazio, S. John Weroha, David D. Bowtell, Iain A. McNeish, Anthony T. Papenfuss, Clare L. Scott, and Holly E. Barker  
Genomic analyses and preclinical models of ovarian carcinosarcoma support the conversion theory for disease development and indicate that microtubule inhibitors could be used to suppress EMT and stimulate antitumour immunity.

## TRANSLATIONAL SCIENCE

### 4429 Transient Systemic Autophagy Inhibition Is Selectively and Irreversibly Deleterious to Lung Cancer

Khoosheh Khayati, Vrushank Bhatt, Taijin Lan, Fawzi Alogaili, Wenping Wang, Enrique Lopez, Zhixian Sherrie Hu, Samantha Gokhale, Liam Cassidy, Masashi Narita, Ping Xie, Eileen White, and Jessie Yanxiang Guo

Transient loss of systemic autophagy causes irreversible damage to tumors by suppressing cancer cell metabolism and promoting antitumor immunity, supporting autophagy inhibition as a rational strategy for treating lung cancer.

See related commentary, p. 4322

### 4444 Sustained Aurora Kinase B Expression Confers Resistance to PI3K Inhibition in Head and Neck Squamous Cell Carcinoma

Pooja A. Shah, Vaishnavi Sambandam, Anne M. Fernandez, Hongyun Zhao, Tuhina Mazumdar, Li Shen, Qi Wang, Kazi M. Ahmed, Soma Ghosh, Mitchell J. Frederick, Jing Wang, and Faye M. Johnson  
Aurora B signaling facilitates resistance to PI3K inhibition in head and neck squamous cell carcinoma, suggesting that combined inhibition of PI3K and Aurora kinase is a rational therapeutic strategy to overcome resistance.

## CONVERGENCE AND TECHNOLOGIES

### 4474 Doxorubicin-Loaded Polymeric Meshes Prevent Local Recurrence after Sarcoma Resection While Avoiding Cardiotoxicity

Eric M. Bressler, Ngoc-Quynh Chu, Robert C. Sabatelle, David A. Mahvi, Jenny T. Korunes-Miller, Fumiaki Nagashima, Fumito Ichinose, Rong Liu, Mark W. Grinstaff, Yolonda L. Colson, and Chandrajit P. Raut

A proof-of-principle study in animal models shows that a novel local drug delivery approach can prevent tumor recurrence as well as drug-related adverse events following surgical resection of soft tissue sarcomas.

## ABOUT THE COVER

Pancreatic ductal adenocarcinoma is a highly aggressive disease with poor prognosis. Elucidating the biology of the tumor immune microenvironment (TiME) can provide vital insights into mechanisms of tumor progression. A computational pathology framework was developed to delineate the subtle distinctions in TiME spatial architectures for prognostic biomarker discovery. Spatial networks within the TiME were constructed to model topological cell-cell interactions. For details, see article by Mi and colleagues on page 4359.

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