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4960 Noncanonical IL6 Signaling-Mediated Activation of YAP Regulates Cell Migration and Invasion in Ovarian Clear Cell Cancer
Walid J. Azar, Elizabeth L. Christie, Chris Mitchell, David S. Liu, George Au-Yeung, and David D.L. Bowtell
This study defines the requirements for and mechanisms of noncanonical signaling by IL6 in human ovarian clear cell adenocarcinoma cell lines and identifies combinatorial therapeutic approaches to be explored clinically.

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TUMOR BIOLOGY AND IMMUNOLOGY

4986 Futibatinib Is a Novel Irreversible FGFR 1–4 Inhibitor That Shows Selective Antitumor Activity against FGFR-Deregulated Tumors
Hiroshi Sootome, Hidenori Fujita, Kenjiro Ito, Hiroaki Ochiiwa, Sachie Otsuki, Kaoru Funabashi, Akihiro Miura, Takeshi Sagara, Satoru Ito, Hiroaki Ochiiwa, Yayoi Fujioka, Kimihiro Ito, Manner
Preclinical characterization of futibatinib, an irreversible FGFR–4 inhibitor, demonstrates selective and potent antitumor activity against FGFR-deregulated cancer cell lines and xenograft models, supporting clinical evaluation in patients with FGFR-driven tumors.

4998 Hypoxia Alters the Response to Anti-EGFR Therapy by Regulating EGFR Expression and Downstream Signaling in a DNA Methylation-Specific and HIF-Dependent Manner
Mahelet Mamo, I. Chae Ye, Josh W. DiGiacomo, Je Yeon Park, Bradley Downs, and Daniele M. Gilkes
Hypoxia sensitizes breast cancer cells to EGFR inhibitors in an HIF1α- and a methylation-specific manner, suggesting patients with hypoxic tumors may benefit from EGFR inhibitors already available to the clinic.

β-Galactosylceramidase Promotes Melanoma Growth via Modulation of Ceramide Metabolism
Mirella Belleri, Giuseppe Paganini, Daniela Coltrini, Roberto Ronca, Daniela Zìzìöli, Michela Corsini, Andrea Barbieri, Elisabetta Grillo, Stefano Calza, Roberto Bresciani, Eugenio Maiorano, Mauro G. Mastropasqua, Tiziana Annese, Arianna Giacomini, Domenico Ribatti, Josefin Casas, Thierry Levade, Gemma Fabrias, and Marco Presta
Data from zebrafish embryos, murine and human cell melanoma lines, and patient-derived tumor specimens indicate that β-galactosylceramidase plays an oncogenic role in melanoma and may serve as a therapeutic target.

Local Targeting of NAD⁺ Salvage Pathway Alters the Immune Tumor Microenvironment and Enhances Checkpoint Immunotherapy in Glioblastoma
Ming Li, Ameya R. Kirtane, Juri Kiyokawa, Hiroaki Nagashima, Aaron Lopes, Zain A. Tirmizi, Christine K. Lee, Giovanni Traverso, Daniel P. Cahill, and Hiroaki Wakimoto
Microparticle-mediated local inhibition of NAMPT modulates the tumor immune microenvironment and acts cooperatively with anti-PD-1 checkpoint blockade, offering a combination immunotherapy strategy for the treatment of GBM.

EpCAM Signaling Promotes Tumor Progression and Protein Stability of PD-L1 through the EGFR Pathway
This study shows that treatment with an EpCAM neutralizing antibody promotes apoptosis while decreasing PD-L1 protein to enhance cytotoxic activity of CD8⁺ T cells.

FGFR1 Is Critical for RBL2 Loss-Driven Tumor Development and Requires PLCG1 Activation for Continued Growth of Small Cell Lung Cancer
Kee-Beom Kim, Youngchul Kim, Christopher J. Rivard, Dong-Wook Kim, and Kwon-Sik Park
This study identifies RBL2 and PLCG1 as critical components of amplified FGFR1 signaling in SCLC, thus representing potential targets for biomarker analysis and therapeutic development in this disease.

CD122-Selective IL2 Complexes Reduce Immunosuppression, Promote Treg Fragility, and Sensitize Tumor Response to PD-L1 Blockade
Justin M. Drerup, Yilun Deng, Sri Lakshmi Pandeswara, Álvaro S. Padrón, Ryan M. Reyes, Xinyue Zhang, Jenny Mendez, Aijie Liu, Curtis A. Clark, Wanjiao Chen, Yi-Ting Chuang, Kai-Chi Chen, William Wei-Fu Tsuei, Chun-Hsin Lan, Mei-Ying Liao, Shao-Hsi Hung, Yi-Ting Chuang, Kai-Chi Chen, William Wei-Fu Tsuei, and Han-Chung Wu
These findings present CD122-targeted IL2 complexes as an advancement in cancer immunotherapy, as they reduce Treg immunosuppression, improve antitumor immunity, and boost PD-L1 immune checkpoint blockade efficacy in distinct tumors and anatomic locations.
A Functional Genomic Screen Identifies the Deubiquitinase USP11 as a Novel Transcriptional Regulator of ERα in Breast Cancer

A newly identified role for USP11 in ERα transcriptional activity represents a novel mechanism of ERα regulation and a pathway to be exploited for the management of ER-positive breast cancer.

Generalized Additive Mixed Modeling of Longitudinal Tumor Growth Reduces Bias and Improves Decision Making in Translational Oncology

This work generalizes the statistical linear mixed modeling paradigm for summarizing longitudinally measured preclinical tumor volume studies to encompass studies with nonlinear and nonmonotonic group response patterns in a statistically rigorous manner.

Glutamate Is a Noninvasive Metabolic Biomarker of IDH1-Mutant Glioma Response to Temozolomide Treatment
Elavarasan Subramani, Marina Radoul, Chloe Najac, Georgios Batsios, Abigail R. Molloy, Donghyun Hong, Anne Marie Gillespie, Romelyn Delos Santos, Pavithra Viswanath, Joseph F. Costello, Russell O. Pieper, and Sabrina M. Ronen

These findings show that glutamate can be used as a noninvasive, imageable metabolic marker for early assessment of tumor response to temozolomide, with the potential to improve treatment strategies for mutant IDH1 patients.

Integrating Mathematical Modeling with High-Throughput Imaging Explains How Polyploid Populations Behave in Nutrient-Sparse Environments
Gregory J. Kimmel, Mark Dane, Laura M. Heiser, Philipp M. Altrock, and Noemi Andor

This study identifies the double-edged sword of high ploidy as a prerequisite to personalize combination therapies with cytotoxic drugs and inhibitors of signal transduction pathways such as MTOR-is.

Modeling Resistance and Recurrence Patterns of Combined Targeted–Chemoradiotherapy Predicts Benefit of Shorter Induction Period
David M. McClatchy, Henning Willers, Aaron N. Hata, Zofia Piotrowska, Lecia V. Sequist, Harald Paganetti, and Clemens Grassberger

A biomathematical framework based on fundamental principles of evolution and radiobiology for in silico clinical trial design allows clinicians to optimize administration of TKIs before chemoradiotherapy in oncogene-driven NSCLC.

Postdiagnostic Fruit and Vegetable Consumption and Breast Cancer Survival: Prospective Analyses in the Nurses’ Health Studies
Maryam S. Farvid, Michelle D. Holmes, Wendy Y. Chen, Bernard A. Rosner, Rulla M. Tamimi, Walter C. Willett, and A. Heather Eliassen

A large-scale study shows that high fruit and vegetable consumption may be associated with better overall survival among breast cancer patients, while high fruit juice consumption may be associated with poorer prognosis.
ABOUT THE COVER

Stored lipid droplets promote pancreatic tumor cell migration. The image shows BxPC-3 pancreatic tumor cells migrating in a wound healing assay following loading with oleic acid. Lipid droplets (yellow, BODIPY-FL-C12), actin (red, phalloidin), and nuclei (blue). For details, see article by Rozeveld and colleagues on page 4932.