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RESEARCH ARTICLES
Adenosine 2A Receptor Blockade as an Immunotherapy for Treatment-Refractory Renal Cell Cancer ................. 40
Précis: The adenosine 2A receptor antagonist ciforadenant was well tolerated and exhibited clinical activity in patients with refractory renal cell carcinoma in a first-in-human, phase I clinical trial.
See commentary, p. 16

The KRASG12C Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients .............. 54
Précis: The KRASG12C inhibitor MRTX849 exhibited antitumor efficacy alone and in combination in multiple KRASG12C-mutant mouse models as well as in two representative patients in a phase Ib clinical trial with KRASG12C-mutant tumors.
See commentary, p. 20

PTEN Loss Mediates Clinical Cross-Resistance to CDK4/6 and PI3Kα Inhibitors in Breast Cancer .......... 72
Précis: Loss of PTEN causes resistance to CDK4/6 inhibitors in ER+ breast cancer via reducing localization of p27 to the nucleus, increasing CDK4/6 and CDK2 activity in PTEN-deficient cells.

Circulating Tumor Cells Exhibit Metastatic Tropism and Reveal Brain Metastasis Drivers ................. 86

Précis: The axon-guiding protein SEMA4D enabled human circulating breast cancer cells to cross the blood–brain barrier in mice, where MYC promoted their survival by upregulating the antioxidant enzyme GPX1, providing a molecular basis for brain metastasis.

Atypical KRAS\textsuperscript{G12R} Mutant Is Impaired in PI3K Signaling and Macropinocytosis in Pancreatic Cancer ................. 104

Précis: KRAS\textsuperscript{G12R}, a mutation common in pancreatic ductal adenocarcinoma (PDAC) but not in other cancers driven by KRAS\textsuperscript{G12} mutations, causes defects in PI3K signaling and KRAS-independent macropinocytosis, a metabolic process required for PDAC growth. See commentary, p. 23

MAIT Cells Promote Tumor Initiation, Growth, and Metastases via Tumor MR1 ........... 124

Précis: In vivo experiments showed that mucosal-associated invariant T cells promoted lung metastasis in mice in a mechanism dependent on tumor-expressed MHC class I-related protein and suppression of lymphocyte function.

ID1 Mediates Escape from TGF\(\beta\) Tumor Suppression in Pancreatic Cancer .... 142

Précis: Dysregulated expression of inhibitor of differentiation 1, an inhibitor of progenitor-cell differentiation, may explain how pancreatic ductal adenocarcinoma cells that maintain normal TGF\(\beta\)-pathway function escape apoptosis.

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ON THE COVER Genetic inactivation of the TGF\(\beta\) pathway is observed in only about half of pancreatic ductal adenocarcinomas (PDAC), yet preventing TGF\(\beta\)-mediated apoptosis of premalignant cells is thought to be important for PDAC development. Huang and colleagues found that dysregulated expression of inhibitor of differentiation 1 (ID1) may explain this phenomenon. Many PDAC cells exhibited high ID1 expression despite retaining TGF\(\beta\)-pathway activity, and ID1 downregulation in PDAC cells led to apoptosis. The pathologically sustained expression of ID1 appears to uncouple the TGF\(\beta\)-mediated epithelial–mesenchymal transition from apoptosis, enabling PDAC cells to survive without genetic inactivation of the TGF\(\beta\) pathway. For details, please see the article by Huang and colleagues on page 142.
**CANCER DISCOVERY**

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