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Obesity-Induced Inflammation and Desmoplasia Promote Pancreatic Cancer Progression and Resistance to Chemotherapy .................. 852
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Macrophage PI3Kγ Drives Pancreatic Ductal Adenocarcinoma Progression ... 870
Précis: Inhibition of PI3Kγ expressed by tumor-associated macrophages restores antitumor CD8+ T-cell responses and suppresses pancreatic cancer growth and metastasis in mice.

GM-CSF Mediates Mesenchymal–Epithelial Cross-talk in Pancreatic Cancer ........... 886
Précis: Expression of GM-CSF by cancer-associated mesenchymal stem cells promotes pancreatic ductal adenocarcinoma growth and metastasis.

CRISPR Screens Provide a Comprehensive Assessment of Cancer Vulnerabilities but Generate False-Positive Hits for Highly Amplified Genomic Regions ............ 900
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Genomic Copy Number Dictates a Gene-Independent Cell Response to CRISPR/Cas9 Targeting ................. 914
Précis: CRISPR/Cas9 targeting reduces cancer cell proliferation and survival in a gene-independent manner based on target loci copy number.
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Pearson and colleagues performed a translational clinical trial in which patients with FGFR alterations were treated with the pan-FGFR inhibitor AZD4547. Responses occurred in 12.5% of patients with FGFR1-amplified breast cancer, and 33% patients with FGFR2-amplified gastroesophageal cancer. High-level, but not low-level, copy-number amplification of FGFR2 was associated with response to AZD4547, and was detectable in the plasma DNA of responding patients. FGFR1- and FGFR2-amplified cells both exhibited oncogene addiction with dependence on MAPK signaling, and high-level FGFR2-amplified cells also exhibited a unique dependence on FGFR-mediated PI3K–AKT signaling. These findings indicate that FGFR inhibitors may be more effective in tumors with high-level FGFR amplification and may guide clinical development of inhibitors targeting FGFR or other amplified receptor tyrosine kinases. For details, please see the article by Pearson and colleagues on page 838.