Prospective
The APL Paradigm and the “Co-Clinical Trial” Project
C. Nardella, A. Lunardi, A. Patnaik, L. C. Cantley, and P. P. Pandolfi

REVIEW
The Drug-Induced Degradation of Oncoproteins: An Unexpected Achilles’ Heel of Cancer Cells
J. Ablain, R. Nasr, A. Bazarbachi, and H. de Thé

C-Raf Is Required for the Initiation of Lung Cancer by K-Ras
F. A. Karreth, K. K. Frese, G. M. DeNicola, M. Baccarini, and D. A. Tuveson
Précis: C-Raf, but not B-Raf, is required for K-Ras-induced tumorigenesis and should be considered an important therapeutic target.

Temporal Dissection of Tumorigenesis in Primary Cancers
Précis: Next-generation sequencing is used to temporally order the occurrence of genetic aberrations in epithelial cancer.

New Insight Puts CRAF in Sight as a Therapeutic Target
A. P. Rebocho and R. Marais
Commentary on Karreth et al., p. 128

The First Line of Intra-abdominal Metastatic Attack: Breaching the Mesothelial Cell Layer
Commentary on Iwanicki et al., p. 144

Kras, Pten, NF-κB, and Inflammation: Dangerous Liaisons
P. J. Chiao and J. Ling
Commentary on Ying et al., p. 158

New Routes to Old Places: PIK3R1 and PIK3R2 Join PIK3CA and PTEN as Endometrial Cancer Genes
S. Herrera-Gonzalez and A. Di Cristofano
Commentary on Cheung et al., p. 170
Ovarian Cancer Spheroids Use Myosin-Generated Force to Clear the Mesothelium

M. P. Iwanicki, R. A. Davidowitz, M. R. Ng, A. Besser, T. Muranen, M. Merritt, G. Danuser, T. Ince, and J. S. Brugge

Précis: Time-lapse video microscopy shows that ovarian cancer spheroids clear the mesothelium via myosin-generated force.

PTEN Is a Major Tumor Suppressor in Pancreatic Ductal Adenocarcinoma and Regulates an NF-κB–Cytokine Network


Précis: PTEN is shown to be a tumor suppressor in human PDAC and controls NF-κB-dependent transcription via PI3K-AKT signaling.

Cheung and colleagues report aberrations in the PI3K pathway occur in a majority of endometrioid endometrial cancers, with coordinate mutations of multiple pathway members being more common than predicted by chance. Multiple gain-of-function PIK3R1 and PIK3R2 mutations result in the stabilization of PTEN protein with likely contribution from the ubiquitin-proteasome degradative pathway, as depicted by the cover. For details, please see the article by Cheung and colleagues on page 158.

High Frequency of PIK3R1 and PIK3R2 Mutations in Endometrial Cancer Elucidates a Novel Mechanism for Regulation of PTEN Protein Stability


Précis: High frequency of mutations in endometrioid endometrial cancers leads to PI3K pathway activation.
## CANCER DISCOVERY

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