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Drug Discovery Gets an Academic Push

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In the Spotlight
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
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New Routes to Old Places: PIK3R1 and PIK3R2 Join PIK3CA and PTEN as Endometrial Cancer Genes
S. Herrero-Gonzalez and A. Di Cristofano
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Research Brief
C-Raf Is Required for the Initiation of Lung Cancer by K-Ras<sup>61D2</sup>
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<sup>61D2</sup>-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.

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

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

Kras, Pten, NF-κB, and Inflammation: Dangerous Liaisons
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Ovarian Cancer Spheroids Use Myosin-Generated Force to Clear the Mesothelium...144
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 .................158
Précis: PTEN is shown to be a tumor suppressor in human PDAC and controls NF-κB-dependent transcription via PI3K-AKT signaling.

High Frequency of PIK3R1 and PIK3R2 Mutations in Endometrial Cancer Elucidates a Novel Mechanism for Regulation of PTEN Protein Stability ..........170
Précis: High frequency of mutations in endometrial endometrial cancers leads to PI3K pathway activation.

ON THE COVER
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.