CANCER DISCOVERY

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MINI REVIEW Targeting Cancer-Derived Adenosine: New Therapeutic Approaches 879
A. Young, D. Mittal, J. Stagg, and M.J. Smyth

RESEARCH BRIEFS

Inflammatory Myofibroblastic Tumors Harbor Multiple Potentially Actionable Kinase Fusions 889
C.M. Lovly, A. Gupta, D. Lipson, G. Otto, T. Brennan, C.T. Chung, S.C. Borinstein, J.S. Ross, P.J. Stephens, V.A. Miller, and C.M. Coffin

Précis: Most inflammatory myofibroblastic tumors contain kinase gene fusions involving *ALK*, *ROS1*, or *PDGFRB* that may be targetable with clinically available tyrosine kinase inhibitors.

See commentary, p. 870

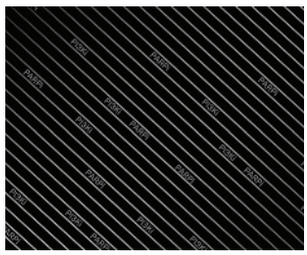
Vulnerabilities of *PTEN–TP53*-Deficient Prostate Cancers to Compound PARP–PI3K Inhibition 896
E. González-Billalabeitia, N. Seitzer, S.J. Song, M.S. Song, A. Patnaik, X.-S. Liu, M.T. Epping, A. Papa, R.M. Hobbs, M. Chen, A. Lunardi, C. Ng, K.A. Webster, S. Signoretti, M. Loda, J.M. Asara, C. Nardella, J.G. Clohessy, L.C. Cantley, and P.P. Pandolfi

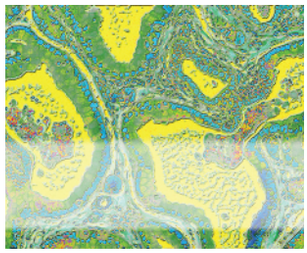
Précis: The PARP inhibitor olaparib has limited efficacy in advanced prostate cancer models with *PTEN/TP53* loss due to hyperactivation of AKT, which can be counteracted with combined PARP/PI3K blockade.

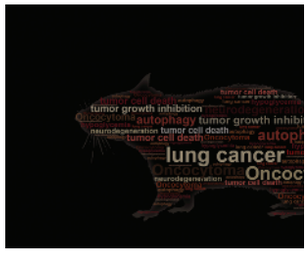
Autophagy Is Critical for Pancreatic Tumor Growth and Progression in Tumors with p53 Alterations 905
A. Yang, N.V. Rajeshkumar, X. Wang, S. Yabuuchi, B.M. Alexander, G.C. Chu, D.D. Von Hoff, A. Maitra, and A.C. Kimmelman

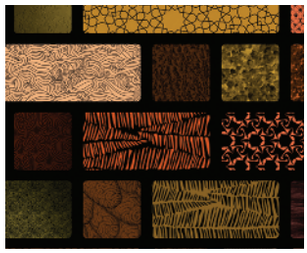
Précis: Loss of autophagy enhances pancreatic tumor initiation but impairs tumor progression and improves survival independent of p53 status.

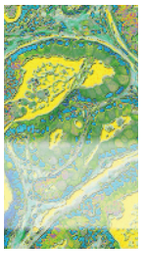
See commentary, p. 873

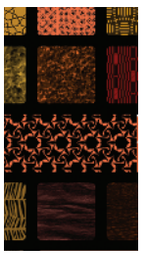












RESEARCH ARTICLES

Autophagy Is Required for Glucose Homeostasis and Lung Tumor Maintenance 914

G. Karsli-Uzunbas, J.Y. Guo, S. Price, X. Teng, S. V Laddha, S. Khor, N.Y. Kalaany, T. Jacks, C.S. Chan, J.D. Rabinowitz, and E. White

Précis: Acute inhibition of autophagy impairs the regulation of glucose metabolism and selectively suppresses the growth of established KRAS-driven lung tumors in mice.

See commentary, p. 873

NSD3–NUT Fusion Oncoprotein in NUT Midline Carcinoma: Implications for a Novel Oncogenic Mechanism 928

C.A. French, S. Rahman, E.M. Walsh, S. Kühnle, A.R. Grayson, M.E. Lemieux, N. Grunfeld, B.P. Rubin, C.R. Antonescu, S. Zhang, R. Venkatramani, P.D. Cin, and P.M. Howley

Précis: Impaired differentiation and increased proliferation in NMC requires formation of a NSD3–BRD4–NUT complex that can be targeted by bromodomain inhibitors.

PTEN-Deficient Tumors Depend on AKT2 for Maintenance and Survival 942

Y.R. Chin, X. Yuan, S.P. Balk, and A. Toker

Précis: Specific depletion of AKT2 but not AKT1 or AKT3 in *PTEN*-deficient cancer cells results in p21-mediated apoptosis and prostate tumor regression.

EGFR Variant Heterogeneity in Glioblastoma Resolved through Single-Nucleus Sequencing 956

J.M. Francis, C.-Z. Zhang, C.L. Maire, J. Jung, V.E. Manzo, V.A. Adalsteinsson, H. Homer, S. Haidar, B. Blumenstiel, C.S. Pedamallu, A.H. Ligon, J.C. Love, M. Meyerson, and K.L. Ligon

Précis: Glioblastoma is characterized by subpopulations of cells with heterogeneous *EGFR* variant expression, which likely cooperate in driving tumor progression and treatment resistance.

See commentary, p. 876

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ON THE COVER

Chin and colleagues found that knockdown or pharmacologic inhibition of AKT2 but not AKT1 induced apoptosis in established tumor spheroids derived from *PTEN*-deficient prostate, breast, and glioblastoma cell lines, indicating that this isoform is essential for *PTEN*-deficient tumor survival. AKT2 depletion resulted in upregulation of p21 and BAX and downregulation of insulin-like growth factor 1 receptor; knockdown of p21, but not BAX, rescued apoptosis induced by AKT2 depletion, suggesting that p21 is a downstream target of AKT2. Importantly, although AKT1 silencing exhibited a largely cytostatic effect in prostate cancer xenografts, AKT2 depletion increased p21 levels, stimulated apoptosis, and promoted tumor regression. These results indicate that AKT2 is required for the maintenance of *PTEN*-deficient tumors and highlight the need for preclinical development of AKT2-selective inhibitors. For details, please see the article by Chin and colleagues on page 942.