IN THIS ISSUE

Highlighted research articles ......................... 621

NEWS IN BRIEF

Important news stories affecting the community ................. 624

NEWS IN DEPTH

Q&A: Brian Kennedy on Aging and Cancer ......................... 627
New Nanomedicines May Better Target Tumors ................. 628

RESEARCH WATCH

Selected highlights of recent articles of exceptional significance from the cancer literature ........ 629

ONLINE

For more News and Research Watch, visit Cancer Discovery online at http://CDnews.aacrjournals.org.

IN THE SPOTLIGHT

Second-Generation ALK Inhibitors: Filling the Non”MET” Gap ......................... 634
S.S. Ramalingam and F.R. Khuri
See article, p. 662

Soil Amendments That Slow Cancer Growth ......................... 637
C.M. Isacke and M.H. Barcellos-Hoff
See article, p. 716

VEGFA Genomic Amplification Tailors Treatment of HCCs with Sorafenib ......................... 640
X. Luo and G.-S. Feng
See article, p. 730

EML4–ALK Fusions: Propelling Cancer but Creating Exploitable Chaperone Dependence ........ 642
P. Workman and R. van Montfort

VIEWS

In Focus

Surviving Metabolic Stress: Of Mice (Squirrels) and Men ........ 646
W.N. Hait, M. Versele, and J.-M. Yang

REVIEW

Blood-Based Analyses of Cancer: Circulating Tumor Cells and Circulating Tumor DNA .......... 650
D.A. Haber and V.E. Velculescu

RESEARCH ARTICLES

The ALK Inhibitor Ceritinib Overcomes Crizotinib Resistance in Non–Small Cell Lung Cancer .... 662
Précis: Ceritinib, a next-generation ALK inhibitor, has potent activity in preclinical models of crizotinib-naïve and crizotinib-resistant ALK-rearranged non–small cell lung cancer.

See commentary, p. 634

Immune Cell–Poor Melanomas Benefit from PD-1 Blockade after Targeted Type I IFN Activation ........ 674
Précis: Type I IFN–associated inflammatory pathway activation combined with antibody blockade of the T-cell immunoinhibitory receptor PD-1 improves immune surveillance of melanomas.

Inflammation-Induced NFATc1–STAT3 Transcription Complex Promotes Pancreatic Cancer Initiation by Kras$^{G12D}$ ........ 688
Précis: Type I IFN–associated inflammatory pathway activation combined with antibody blockade of the T-cell immunoinhibitory receptor PD-1 improves immune surveillance of melanomas.

VEGFA Genomic Amplification Tailors Treatment of HCCs with Sorafenib ......................... 640
X. Luo and G.-S. Feng
See article, p. 730

EML4–ALK Fusions: Propelling Cancer but Creating Exploitable Chaperone Dependence ........ 642
P. Workman and R. van Montfort

Preclinical and Clinical Models of ALK-Inhibitor Resistance in ALK-Rearranged NSCLC

See article, p. 850

In Focus

Surviving Metabolic Stress: Of Mice (Squirrels) and Men ........ 646
W.N. Hait, M. Versele, and J.-M. Yang

Précis: NFATC1 expression is induced by inflammation and cooperates with KRAS$^{G12D}$ in pancreatic carcinogenesis by forming complexes with STAT3 at enhancer regions that regulate oncogenic gene networks.
Friboulet and colleagues report that ceritinib, a next-generation ALK inhibitor that is more selective and potent than crizotinib, is active in preclinical models of both crizotinib-naïve and crizotinib-resistant non-small cell lung cancer (NSCLC). Ceritinib retained activity against the most common crizotinib-resistant ALK mutants, although some secondary ALK mutations did confer resistance to both crizotinib and ceritinib. Structural analyses provided a mechanistic basis for these findings, as the most common secondary ALK mutations that inhibit binding of crizotinib are not predicted to impair ceritinib binding, but other mutations, which the authors have identified in patients with acquired resistance to ceritinib, are predicted to reduce ceritinib binding through steric hindrance or conformational changes of the ALK catalytic domain. For details, please see the article by Friboulet and colleagues on page 662.
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