Contents

September 2013 • Volume 3 • Number 9

In This Issue
Highlighted research articles 953

News in Brief
Important news stories affecting the community 958

News in Depth
Q&A: Crystal Mackall, John Maris on Pediatrics 961
Stopping Breast Cancer Before It Starts 962

Research Watch
Selected highlights of recent articles of exceptional significance from the cancer literature 963

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

Views

In The Spotlight
Epigenetic Approaches for Chemosensitization of Refractory Diffuse Large B-Cell Lymphomas 968
J.J. Steinhardt and R.B. Gartenhaus
See article, p. 1002

Resistance Emerges to Second-Generation Antiandrogens in Prostate Cancer 971
W.G. Nelson and S. Yegnasubramanian
See article, p. 1020
See article, p. 1030

Say What? The Activity of the Polyamine Biosynthesis Inhibitor Difluoromethylornithine in Chemoprevention Is a Result of Reduced Thymidine Pools? 975
R.A. Casero Jr
See article, p. 1072

Research Articles

Mechanism-Based Epigenetic Chemosensitization Therapy of Diffuse Large B-Cell Lymphoma 1002
Précis: Treatment with DNA methyltransferase inhibitors overcomes chemoresistance in high-risk DLBCL via demethylation and reactivation of SMAD1.
See commentary, p. 968

A Clinically Relevant Androgen Receptor Mutation Confers Resistance to Second-Generation Antiandrogens Enzalutamide and ARN-509 1020
Précis: An ARF876L mutation confers ligand-specific resistance and is found in the circulating tumor DNA of ARN-509-treated patients with progressive castration-resistant prostate cancer.
See commentary, p. 971

Review
Cell-Autonomous and Non-Cell-Autonomous Mechanisms of HGF/MET–Driven Resistance to Targeted Therapies: From Basic Research to a Clinical Perspective 978
S. Corso and S. Giordano

Research Brief
Dominant Role of Oncogene Dosage and Absence of Tumor Suppressor Activity in Nras-Driven Hematopoietic Transformation 993
Précis: Increased expression of mutant Nras, not loss of wild-type Nras, drives transformation in the hematopoietic lineage.

In This Issue

Important news stories affecting the community 958

Q&A: Crystal Mackall, John Maris on Pediatrics 961
Stopping Breast Cancer Before It Starts 962

Selected highlights of recent articles of exceptional significance from the cancer literature 963

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

Epigenetic Approaches for Chemosensitization of Refractory Diffuse Large B-Cell Lymphomas 968
J.J. Steinhardt and R.B. Gartenhaus
See article, p. 1002

Resistance Emerges to Second-Generation Antiandrogens in Prostate Cancer 971
W.G. Nelson and S. Yegnasubramanian
See article, p. 1020
See article, p. 1030

Say What? The Activity of the Polyamine Biosynthesis Inhibitor Difluoromethylornithine in Chemoprevention Is a Result of Reduced Thymidine Pools? 975
R.A. Casero Jr
See article, p. 1072

Mechanism-Based Epigenetic Chemosensitization Therapy of Diffuse Large B-Cell Lymphoma 1002
Précis: Treatment with DNA methyltransferase inhibitors overcomes chemoresistance in high-risk DLBCL via demethylation and reactivation of SMAD1.
See commentary, p. 968

A Clinically Relevant Androgen Receptor Mutation Confers Resistance to Second-Generation Antiandrogens Enzalutamide and ARN-509 1020
Précis: An ARF876L mutation confers ligand-specific resistance and is found in the circulating tumor DNA of ARN-509-treated patients with progressive castration-resistant prostate cancer.
See commentary, p. 971

Cell-Autonomous and Non-Cell-Autonomous Mechanisms of HGF/MET–Driven Resistance to Targeted Therapies: From Basic Research to a Clinical Perspective 978
S. Corso and S. Giordano

Dominant Role of Oncogene Dosage and Absence of Tumor Suppressor Activity in Nras-Driven Hematopoietic Transformation 993
Précis: Increased expression of mutant Nras, not loss of wild-type Nras, drives transformation in the hematopoietic lineage.
An F876L Mutation in Androgen Receptor Confers Genetic and Phenotypic Resistance to MDV3100 (Enzalutamide) ........................................... 1030


Précis: A recurring androgen receptor (AR) mutation identified in enzalutamide-resistant prostate cancer cells converts enzalutamide from an AR antagonist to an AR agonist.

See commentary, p. 971

Systematic Interrogation of 3q26 Identifies TLOC1 and SKIL as Cancer Drivers .... 1044


Précis: The coamplified genes TLOC1 and SKIL cooperate to induce transformation via regulation of distinct tumor phenotypes.

Parallel RNA Interference Screens Identify EGFR Activation as an Escape Mechanism in FGFR3-Mutant Cancer ......................... 1058


Précis: Activation of EGFR signaling specifically limits the sensitivity of FGFR3-activated bladder cancer cells to FGFR inhibitors.

Unbiased Metabolite Profiling Indicates that a Diminished Thymidine Pool Is the Underlying Mechanism of Colon Cancer Chemoprevention by Alpha-Difluoromethylornithine .............. 1072


Précis: The cytostatic effects of α-difluoromethylornithine (DFMO) are attributable to reduced cellular thymidine levels caused by depletion of an essential cofactor of thymidine synthase.

See commentary, p. 975

Clozel and colleagues found that low-dose DNA methyltransferase (DNMT) inhibitor treatment induced DNA hypomethylation and a senescence-like phenotype in chemorefractory diffuse large B-cell lymphoma (DLBCL) cells and enhanced the sensitivity of these cells to doxorubicin. In addition, DNMT inhibition upregulated the expression of several hypermethylated genes including SMAD1 in refractory DLBCL cell lines and primary tumors, indicative of epigenetic reprogramming. SMAD1 reactivation sensitized resistant cells to growth inhibition by doxorubicin, whereas SMAD1 depletion augmented chemoresistance. Furthermore, in a phase I clinical trial of newly diagnosed, high-risk patients with DLBCL, DNMT inhibitor pretreatment prior to standard chemoimmunotherapy was well tolerated and resulted in a high rate of complete remission, supporting further investigation of this therapeutic combination in DLBCL. For details, please see the article by Clozel and colleagues on page 1002.

For more News and Research Watch, visit Cancer Discovery online at http://CDnews.aacrjournals.org. Online-only News stories include the following:

- Prostate Cancers Get Nerved Up
- Afatinib Approved for Advanced NSCLC
- UK Launches 100,000-Genome Initiative
- Myriad Genetics Sues BRCA Diagnostic Rivals
- MGN1703 Maintenance Therapy Extends PFS in Colorectal Cancer
- FDA Exercises Its Authority to Regulate Tobacco Products

AC icon indicates Author Choice
For more information please visit http://www.aacrjournals.org

ON THE COVER

Clozel and colleagues found that low-dose DNA methyltransferase (DNMT) inhibitor treatment induced DNA hypomethylation and a senescence-like phenotype in chemorefractory diffuse large B-cell lymphoma (DLBCL) cells and enhanced the sensitivity of these cells to doxorubicin. In addition, DNMT inhibition upregulated the expression of several hypermethylated genes including SMAD1 in refractory DLBCL cell lines and primary tumors, indicative of epigenetic reprogramming. SMAD1 reactivation sensitized resistant cells to growth inhibition by doxorubicin, whereas SMAD1 depletion augmented chemoresistance. Furthermore, in a phase I clinical trial of newly diagnosed, high-risk patients with DLBCL, DNMT inhibitor pretreatment prior to standard chemoimmunotherapy was well tolerated and resulted in a high rate of complete remission, supporting further investigation of this therapeutic combination in DLBCL. For details, please see the article by Clozel and colleagues on page 1002.