In Focus

Tissue-Agnostic Drug Development: A New Path to Drug Approval ............... 2139
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REVIEW

Targeting EGFR Exon 20 Insertions in Non–Small Cell Lung Cancer: Recent Advances and Clinical Updates ............... 2145
C.B. Meador, L.V. Sequist, and Z. Piotrowska

RESEARCH BRIEF

Reducing Skin Toxicities from EGFR Inhibitors with Topical BRAF Inhibitor Therapy ............... 2158

Précis: In a phase I trial, topical application of a gel formulation of a BRAF inhibitor was safe and provided early evidence of improvement of acneiform rash induced by EGFR inhibitor therapy.

RESEARCH ARTICLES

Determinants of Response and Intrinsic Resistance to PD-1 Blockade in Microsatellite Instability–High Gastric Cancer ............... 2168

Précis: Prospective genomic and immunologic analysis of on-treatment tissue and peripheral blood provides insight into the heterogeneity of response to pembrolizumab monotherapy among patients with MSI-high gastric cancer.

See commentary, p. 2126

Integrative Bulk and Single-Cell Profiling of Premanufacture T-cell Populations Reveals Factors Mediating Long-Term Persistence of CAR T-cell Therapy ............... 2186

See commentary, p. 2126

Science in Society

From the Community to the Bench and Back Again: The Value of Patient and Community Engagement in Cancer Research ............... 2135
A.E. Leader and A.E. Aplin

See commentary, p. 2126
Précis: A bulk and single-cell atlas of premanufacture T-cells was generated from 71 patients on trial treated with anti-CD19 CAR T-cell therapy, and integrative analysis identified key molecular factors associated with clinical CAR T-cell persistence.

ZFTA-RELA Dictates Oncogenic Transcriptional Programs to Drive Aggressive Supratentorial Ependymoma ................. 2200

Précis: The ZFTA-RELA fusion protein engages DNA and regulates chromatin structure to direct transcriptional programs that lead to ependymoma brain tumor development.

ZFTA Translocations Constitute Ependymoma Chromatin Remodeling and Transcription Factors ............... 2216

Précis: Cross-species multi-omic and mouse modelling studies revealed ependymoma ZFTA (also known as C11orf95) fusion oncoproteins to be aberrant transcription factors with promiscuous chromatin binding and remodelling properties.

Cross-Species Genomics Reveals Oncogenic Dependencies in ZFTA/C11orf95 Fusion-Positive Supratentorial Ependymomas ...... 2230

Précis: Molecular refinement and cross-species genomics of supratentorial ependymoma revealed a central role for the fusion partner ZFTA associated with potential therapeutic vulnerabilities.

IFNα Is Critical for CAR T Cell–Mediated Myeloid Activation and Induction of Endogenous Immunity .......... 2248

Précis: In addition to direct antigen-dependent tumor targeting, CAR T-cell production of IFNα can activate host myeloid and T cells to induce antitumor immunity and promote effective CAR T-cell therapy for solid tumors.

Discovery of Candidate DNA Methylation Cancer Driver Genes .......... 2266

Précis: MethSig, a novel statistical framework for the analysis of DNA methylation changes in cancer, identifies candidate DNA methylation cancer driver events with high accuracy across cancer types and after relapse, as well as drivers predictive of clinical outcome.

Selective Modulation of a Pan-Essential Protein as a Therapeutic Strategy in Cancer .......... 2282

Précis: Functional genomic screens uncover nuclear export factor NXT1 as a selectively lethal dependency in neuroblastoma due to context-specific loss of its binding partner, the essential protein NXF1.

See commentary, p. 2129
Transcriptional Silencing of ALDH2 Confers a Dependency on Fanconi Anemia Proteins in Acute Myeloid Leukemia ..........2300


Précis: Blockade of the ubiquitination reaction catalyzed by Fanconi anemia proteins selectively suppresses leukemia cells by exploiting an epigenetics-based synthetic lethal interaction with the aldehyde detoxifying enzyme ALDH2.

NKX3.1 Localization to Mitochondria Suppresses Prostate Cancer Initiation ..........2316


Précis: Oxidative stress promotes NKX3.1 import to mitochondria where it restores oxidative phosphorylation and prevents cancer initiation, thus uncovering a nonnuclear function for a homeoprotein in suppression of cancer. See commentary, p. 2132

RB/E2F1 as a Master Regulator of Cancer Cell Metabolism in Advanced Disease ...............2334


Précis: Analysis of RB-deficient cancer revealed an E2F1-dependent reprogramming of cancer metabolism and increased reliance on glutathione synthesis, nominating a new avenue to target late-stage, RB-deficient cancers.

ON THE COVER

Focal increases in cytosine methylation at gene promoters are widespread in human cancers and thought to contribute to silencing of tumor suppressor genes, but tools are lacking to distinguish methylation events that are oncogenic drivers from those that are merely passengers. Pan and colleagues developed MethSig, a statistical inference framework that accounts for variations in the stochastic hypermethylation rate across the genome and between patients, analogous to approaches used to identify driver mutations. Application of MethSig to bisulfite sequencing data or DNA methylation array data identified specific promoter hypermethylation events as potential drivers among a large number of candidate methylation changes, several of which were confirmed to enhance cancer cell fitness, and identified methylation events associated with poor clinical outcome and relapse. Cover artwork by SciStories. For more information, see the article by Pan and colleagues on page 2266.

doi: 10.1158/2159-8290.CD-11-9-CVR