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In the Spotlight

The gRASs Is Greener: Potential New Therapies in Lung Cancer with Acquired Resistance to KRASG12C Inhibitors .......................... 1874

M. Pinnelli and L. Trusolino

See article, p. 1913

Impaired CD4 T-cell Response to SARS-CoV-2: Rationale for PD-1 Blockade in Patients with Cancer and COVID-19? .............. 1877

B. Salomé and A. Horowitz

See article, p. 1982

Chemerin Tips the Scales in ccRCC to Evade Ferroptosis 1879

E. Reznik, H. Jiang, and A.A. Hakimi

See article, p. 2072

**Science in Society**

Rethinking Cancer Clinical Trial Conduct Induced by COVID-19: An Academic Center, Industry, Government, and Regulatory Agency Perspective .............. 1881


**Perspective**

Adaptive Evolution: How Bacteria and Cancer Cells Survive Stressful Conditions and Drug Treatment .......... 1886

M. Russo, A. Sogari, and A. Bardelli

**Review**

Tumor Immunity and Immunotherapy for HPV-Related Cancers ............... 1896

A.A. Shamseddine, B. Burman, N.Y. Lee, D. Zamarin, and N. Riaz

**Research Briefs**

Clinical Acquired Resistance to KRASG12C Inhibition through a Novel KRAS Switch-II Pocket Mutation and Polyclonal Alterations Converging on RAS–MAPK Reactivation ............... 1913


Précis: Serial cfDNA analysis identifies multiple clinical acquired resistance mechanisms to KRASG12C inhibitors that converge on RAS–MAPK reactivation, including a novel switch-II binding pocket mutation that disrupts inhibitor binding.

See commentary, p. 1874

Werner Helicase Is a Synthetic-Lethal Vulnerability in Mismatch Repair–Deficient Colorectal Cancer Refractory to Targeted Therapies, Chemotherapy, and Immunotherapy ............... 1923


Précis: Werner syndrome helicase (WRN) is a synthetic-lethal dependency in colorectal cancer models of resistance to current therapies, including...
immunotherapy, supporting WRN as a therapeutic candidate in patients with tumors refractory to existing treatments.

**Splicing Patterns in SF3B1-Mutated Uveal Melanoma Generate Shared Immunogenic Tumor-Specific Neoepitopes** 1938


**Précis:** Mutations of the SF3B1 splicing factor in uveal melanoma led to altered splicing of more than 1,000 junctions, generating tumor-specific shared neoantigens that were recognized by patient CDB⁺T cells and opening therapeutic opportunities.

**Intrinsic Immunogenicity of Small Cell Lung Carcinoma Revealed by Its Cellular Plasticity** 1952


**Précis:** Cellular profiling of small cell lung carcinoma revealed an immunogenic subtype marked by restored MHC I antigen presentation, regulated by EZH2, and associated with the potential to generate durable immunotherapy responses.

**Simultaneous Inhibition of LSD1 and TGFβ Enables Eradication of Poorly Immunogenic Tumors with Anti–PD-1 Treatment** 1970

W. Sheng, Y. Liu, D. Chakraborty, B. Debo, and Y. Shi

**Précis:** Depletion of histone demethylase LSD1 plus inhibition of downstream TGFβ cytokines eliminated refractory tumor models upon PD-1 blockade therapy and established immunologic memory against tumor rechallenge.

**RESEARCH ARTICLES**

**Preexisting and Post–COVID-19 Immune Responses to SARS-CoV-2 in Patients with Cancer** 1982


**Précis:** Immune responses to SARS-CoV-2 in patients with cancer reveal impaired T-cell response in hematologic malignancies with implications for COVID-19 outcome and the development of prophylactic and therapeutic measures.

See commentary, p. 1877

**Tilsotolimod with Ipilimumab Drives Tumor Responses in Anti–PD-1 Refractory Melanoma** 1996


**Précis:** Response to the combination of tilsotolimod and ipilimumab was associated with dendritic cell presence in the tumor pre-therapy and immune activation and expansion of tumor-associated T-cell clones early on-treatment.

**Leukocyte Heterogeneity in Pancreatic Ductal Adenocarcinoma: Phenotypic and Spatial Features Associated with Clinical Outcome** 2014


**Précis:** An immune atlas of 135 therapy-naive and neoadjuvant-treated human pancreatic ductal adenocarcinomas details inter- and intrapatient leukocyte heterogeneity, and features of immune contexture affecting clinical response to immune therapy.
Surface Proteomics Reveals CD72 as a Target for In Vitro–Evolved Nanobody-Based CAR-T Cells in KMT2A/MLL1-Rearranged B-ALL ..........2050
Précis: A small molecule inhibitor of CARM1, an epigenetic enzyme, sensitizes resistant tumors to immune attack.

Obesity-Dependent Adipokine Chemerin Suppresses Fatty Acid Oxidation to Confer Ferroptosis Resistance ..........2072
Précis: The obesity-driven adipokine chemerin promotes cancer-cell survival through inhibition of lipid metabolism, serving as a link between obesity and cancer development. See commentary, p. 1879

Oncogenic KRAS Recruits an Expansive Transcriptional Network through Mutant pS3 to Drive Pancreatic Cancer Metastasis ..........2094
Précis: Inhibition of CREB1 decoupled cooperation between oncogenic KRAS effectors and mutant pS3, dampening mutant pS3 gain of function, the activation of downstream prometastatic transcriptional networks, and PDAC metastasis.

ON THE COVER
Allele-specific inhibitors of KRASG12C such as MRTX849 (adagrasib) and AMG 510 (sotorasib) have moved into clinical testing and elicit responses in a subset of patients, particularly those with non-small cell lung cancer (NSCLC). However, responses are not durable, necessitating the characterization of acquired resistance mechanisms to guide future combination treatment strategies and development of next-generation KRAS inhibitors. Tanaka, Lin, Li, and colleagues analyzed serial cell-free DNA from a patient with KRASG12C-mutant NSCLC who initially had a partial response but then developed resistance to adagrasib. Polyclonal resistance alterations converging upon reactivation of RAS/MAPK signaling were identified, including a secondary KRASY96D mutation in the switch-II pocket where adagrasib and other inactive-state inhibitors bind that disrupts protein–drug interactions and confers resistance to these compounds in KRASG12C-mutant models. A functionally distinct tricomplex KRASG12C-active-state inhibitor retained the ability to bind and inhibit KRASG12C/Y96D and could overcome resistance. For more information, see the article by Tanaka, Lin, Li, and colleagues on page 1913.