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The gRASs Is Greener: Potential New Therapies in Lung Cancer with Acquired Resistance to KRASG12C Inhibitors ....................... 1874
M. Pinnelli and L. Trusolino
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Cheomerin Tips the Scales in ccRCC to Evade Ferrophosis ........ 1879
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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** 1952


**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 CD8+ T cells and opening therapeutic opportunities.

**Intrinsic Immunogenicity of Small Cell Lung Carcinoma Revealed by Its Cellular Plasticity** 1970


**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** 2019

W. Sheng, Y. Liu, D. Chakraborthy, 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. 1797

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 p53 to Drive Pancreatic Cancer Metastasis .................2094
Précis: Inhibition of CREB1 decoupled cooperation between oncogenic KRAS effectors and mutant p53, dampening mutant p53 gain of function, the activation of downstream prometastatic transcriptional networks, and PDAC metastasis.

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 KRASV96D 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 tricompact KRASG12C active-state inhibitor retained the ability to bind and inhibit KRASG12C/V96D and could overcome resistance. For more information, see the article by Tanaka, Lin, Li, and colleagues on page 1913.