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MODES OF REGULATED CELL DEATH IN CANCER
Fueling the Fire: Inflammatory Forms of Cell Death and Implications for Cancer Immunotherapy ...................... 245
E. Koren and Y. Fuchs

SOMATIC HLA CLASS I LOSS IS A WIDESPREAD MECHANISM OF IMMUNE EVASION WHICH REFINES THE USE OF TUMOR MUTATIONAL BURDEN AS A BIOMARKER OF CHECKPOINT INHIBITOR RESPONSE .......... 282
Précis: Across cancer types, loss of heterozygosity at the locus encoding HLA-I was an independent prognostic factor for response to immune checkpoint blockade, and its predictive power improved when combined with measures of tumor mutation burden.

Lower Airway Dysbiosis Affects Lung Cancer Progression .......... 293
Précis: Lower airway dysbiosis characterized by excessive colonization with oral commensal microbes, particularly *Veillonella parvula*, was a predictor of poor prognosis in lung cancer, and in vivo experiments supported a role for *V. parvula* colonization in decreasing survival.

See commentary, p. 224

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**RESEARCH ARTICLES**

Personalized Antibodies for Gastroesophageal Adenocarcinoma (PANGEA): A Phase II Study Evaluating an Individualized Treatment Strategy for Metastatic Disease ............. 308


**Précis:** In a phase II clinical trial, personalized antibodies plus molecularly targeted chemotherapy improved median overall survival and the one-year survival rate in patients with gastroesophageal adenocarcinoma relative to historical survival data.

Clinicogenomic Analysis of FGFR2-Rearranged Cholangiocarcinoma Identifies Correlates of Response and Mechanisms of Resistance to Pemigatinib .................... 326


**Précis:** In patients with cholangiocarcinoma harboring FGFR fusions or rearrangements, response to the FGFR1–3 inhibitor was equally likely regardless of the type of genomic alteration, and resistance mutations affected the FGFR2 kinase domain.

Selection of Oncogenic Mutant Clones in Normal Human Skin Varies with Body Site ................ 340


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**Précis:** Genetic analyses of healthy aged human epidermal cells revealed skin site–specific mutational signatures, with common skin cancer sites exhibiting more potentially oncogenic mutations and with high variability in mutations under positive selection among sites.

See commentary, p. 227

Genetically Defined, Syngeneic Organoid Platform for Developing Combination Therapies for Ovarian Cancer ............ 362


**Précis:** Organoids representing high-grade serous ovarian cancer were developed; these organoids exhibited varying sensitivities to chemotherapy drugs and elicited different immune responses, suggesting they may serve as a novel platform for discovery.

Genetically Defined Syngeneic Mouse Models of Ovarian Cancer as Tools for the Discovery of Combination Immunotherapy .................. 384


**Précis:** To address the inability of current high-grade serous tubo-ovarian carcinoma models to accurately recapitulate immunotherapy responses, a new mouse model was developed; proof-of-concept experiments uncovered follistatin as a mediator of response.

A TLR3 Ligand Reestablishes Chemotherapeutic Responses in the Context of FPR1 Deficiency .......... 408


**Précis:** The TLR3 ligand polyinosinic-polycytidylic acid improved the efficacy of chemotherapy observed in the context of FPR1 loss-of-function mutation, which occurs in 30% of individuals and diminishes the antitumor immune response following chemotherapy.
Timed Ang2-Targeted Therapy Identifies the Angiopoietin-Tie Pathway as Key Regulator of Fatal Lymphogenous Metastasis ................................. 424
Précis: A hindrance to the study of metastasis via lymphatic vessels with lymph nodes as intermediate sites was overcome using a genetically engineered mouse model-derived allograft model, the use of which uncovered the Ang2-Tie2 pathway as a critical dependency.

Netrin G1 Promotes Pancreatic Tumorigenesis through Cancer-Associated Fibroblast-Driven Nutritional Support and Immunosuppression ...................... 446
Précis: The glutamatergic presynaptic protein Netrin-G1 was found to be a major contributor to the metabolic and immunosuppressive tumor microenvironment in pancreatic ductal adenocarcinoma, and blocking Netrin-G1 in vivo suppressed tumorigenesis.
See commentary, p. 230

The RNA m6A Reader YTHDF2 Maintains Oncogene Expression and Is a Targetable Dependency in Glioblastoma Stem Cells ...480
Précis: In glioblastoma stem cells, YTHDF2 (which reads mRNA for the modified nucleotide N6-methyladenosine) stabilized MYC and VEGFA transcripts via an IGFBP3-mediated mechanism, and blocking IGF–IGF1R signaling in vivo hindered glioblastoma growth.

The Hepatic Microenvironment Uniquely Protects Leukemia Cells through Induction of Growth and Survival Pathways Mediated by LIPG .............. 500
Précis: Liver-infiltrating leukemia stem cells in mice acquired a proliferative, chemotherapy-resistant phenotype characterized by overexpression of the gene encoding the lipase LIPG, which was sufficient to induce the same phenotype in non–liver-infiltrating leukemia cells.

Correction

Correction: Impact of PD-1 Blockade on Severity of COVID-19 in Patients with Lung Cancers .......................... 520

The risk of skin cancers such as basal cell carcinoma and squamous cell carcinoma varies greatly across the body, and it is known that healthy aged skin cells often harbor cancer driver mutations, but whether these observations are connected has not been determined. Fowler and colleagues discovered that the mutation density in healthy human skin differed from location to location across the body. Common sites for skin cancer, such as the forearm, bore more mutations than uncommon sites, and the mutation profile suggested UV radiation as a cause. Interestingly, not only was there selection for cancer-associated mutations in healthy skin, but the DNA repair mechanisms used varied based on site. For more information, see the article by Fowler and colleagues on page 340.