In Focus
Colorectal Cancer: Looking for Answers in the Microbiota
C. Jobin

REVIEW
The Basic Principles of Chimeric Antigen Receptor Design
M. Sadelain, R. Brentjens, and I. Rivière

RESEARCH BRIEF
Biallelic Deleterious BRCA1 Mutations in a Woman with Early-Onset Ovarian Cancer

Précis: The presence of a dysfunctional BRCA1 BRCT domain variant in trans with a known deleterious BRCA1 mutation was documented in a woman with early-onset ovarian carcinoma.

See commentary, p. 376

RESEARCH ARTICLES
First-in-Humans Trial of an RNA Interference Therapeutic Targeting VEGF and KSP in Cancer Patients with Liver Involvement

Précis: A lipid nanoparticle multitarget siRNA formulation is deliverable to tumors and shows evidence of on-target activity in patients with advanced cancers enrolled in a phase I trial.
Multifunctional T-cell Analyses to Study Response and Progression in Adoptive Cell Transfer Immunotherapy .......... 418
Précis: Single-cell immune monitoring of patients receiving adoptive cell transfer therapy reveals time-dependent changes in adoptively transferred and endogenous T-cell functionality.
See commentary, p. 379

Targeted Inhibition of the Molecular Chaperone Hsp90 Overcomes ALK Inhibitor Resistance in Non-Small Cell Lung Cancer .......... 430
Précis: Inhibition of HSP90 with ganetespib may represent an alternative or complementary therapeutic strategy for treatment of ALK-positive non-small cell lung cancer.

RHOA-FAK Is a Required Signaling Axis for the Maintenance of KRAS-Driven Lung Adenocarcinomas .......... 444
Précis: RHOA-FAK signaling is a genotype-specific therapeutic target in aggressive KRAS-mutant, INK4A/ARF-deficient non-small cell lung cancers.

Primary Melanoma of the CNS in Children Is Driven by Congenital Expression of Oncogenic NRAS in Melanocytes ....... 458
Précis: Early embryonic NRAS mutation promotes melanocyte proliferation and induces early-onset primary melanoma of the central nervous system but not cutaneous melanoma.
See commentary, p. 382

Tabernero and colleagues report the results of a phase I dose-escalation and expansion study assessing the safety, activity, and pharmacodynamics of ALN-VSP, a lipid nanoparticle containing siRNAs against vascular endothelial growth factor A (VEGFA) and kinesin spindle protein (KSP), in patients with advanced solid tumors with liver involvement. One patient with metastatic endometrial cancer had a complete response and 3 patients (2 with metastatic renal cell carcinoma and 1 with metastatic pancreatic neuroendocrine tumor) experienced disease stabilization. Post-treatment tumor biopsies showed evidence of intratumoral delivery, increased VEGFA mRNA cleavage, and decreased VEGFA and KSP mRNA levels compared with pre-treatment biopsy samples, consistent with an on-target response and an RNAi mechanism of action. For details, please see the article by Tabernero and colleagues on page 406.

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- Reprioritizing Cancer Clinical Studies
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- Analyses Suggest Risks with mTOR Inhibitors
- Ramucirumab Aids Gastric Cancer Survival

ON THE COVER
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