Clinical Cancer Research **Highlights**

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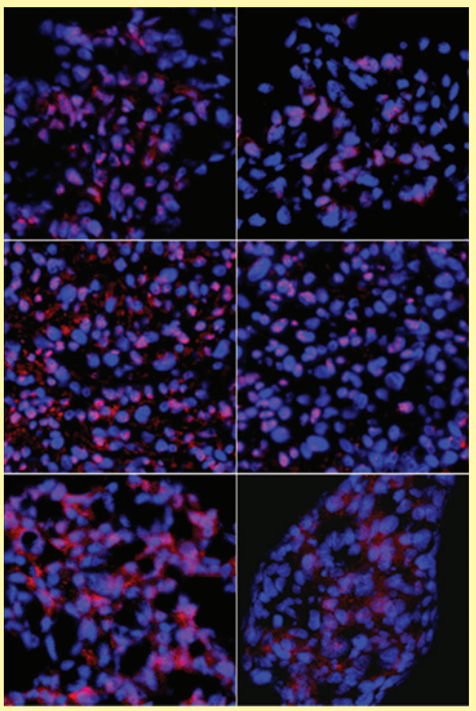
Selected Articles from This Issue



Phase I Study of SAR245408 in Patients with Solid Tumors

Shapiro *et al.* **Page 233**

Aberrant activation of the phosphatidylinositol-3-kinase (PI3K) pathway contributes to tumor cell growth, proliferation and survival, and may confer resistance to chemotherapy and targeted agents. Shapiro and colleagues have conducted a Phase 1 trial of SAR245408 (XL147), an orally bioavailable pan-class I PI3K inhibitor. Pathway inhibition in tumor and surrogate tissues and preliminary clinical activity were observed at tolerable doses, irrespective of tumor PI3K pathway molecular alterations. The results provide the groundwork for future monotherapy and combination studies.

CD137 Expression Identifies Tumor-Reactive TILs

Ye *et al.* **Page 44**

The association between of increased intratumoral T-cell accumulation and survival suggests the existence of naturally occurring tumor-reactive T-cells in human cancer. However, the immunobiology of spontaneous tumor-reactive T-cells in cancer is not well defined because identifying and validating these responses is difficult. Ye and colleagues elucidated CD137 as a biomarker for naturally occurring tumor-reactive T-cells in cancer and developed a rapid, accurate system to comprehensively isolate TILs with tumor-rejecting capability directly from resected human tumors. Thus, CD137 plays an important role in the immunobiology of human cancer, rationalizing its agonistic engagement *in vivo* and its use in TIL selection for adoptive immunotherapy trials.

IL7 Overcomes Treg Inhbition of CAR-Modified CTLs

Perna *et al.* **Page 131**

Adoptive transfer of virus-specific CTLs expressing a chimeric antigen receptor (CAR) represents a promising immunotherapy approach. However, regulatory T cells (Tregs) that are abundant within the tumor environment impair proliferation and function of CAR-redirected CTLs. Perna and colleagues exploited a modification of the IL-7/IL-7Rα axis in CAR-redirected CTLs to counter Treg inhibition. The authors found that IL-7, unlike IL-2, supports the antitumor activity of EBV-CTLs genetically manipulated to coexpress IL-7Rα and a GD2-specific CAR both *in vitro* and *in vivo* in the presence of Tregs. Thus, the proposed genetic modification may further improve the clinical outcome of CAR-modified CTLs.

Transient Hh Activation Rescued IR-Induced Hyposalivation

Hai *et al.* **Page 140**

Irreversible hyposalivation is common in head and neck cancer survivors treated with radiotherapy, for which no curative treatment is available currently. Hai and colleagues found that the Hedgehog signaling pathway in salivary glands was activated during functional regeneration after duct ligation but not activated after irradiation, and the transient activation of this pathway after irradiation rescued salivary gland hypofunction by preserving salivary stem/progenitor cells and the parasympathetic innervation in mice. Similar effects on expression of genes essential for these two aspects were observed in cultured human salivary epithelial cells, suggesting the potential of this strategy in treating radiotherapy-induced hyposalivation.