Molecular Cancer Therapeutics

Highlights

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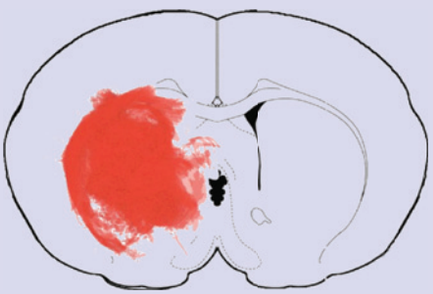
Selected Articles from This Issue



Nanoparticles for GBM Radiosensitization

King and Corso *et al.* Page 1456

Despite aggressive treatment including resection, chemotherapy and radiation, survival for individuals with glioblastoma is poor. In this article, the authors combine two techniques that allow them to achieve therapeutic radiosensitizer concentrations in the parenchyma, and have these levels retained for long time periods to allow a synergistic effect with fractionated radiotherapy. By using convection enhanced delivery, the blood brain barrier is bypassed, and a polymer nanoparticle formulation provides slow release of drug throughout the course of the radiotherapy regimen. These results have shown promising improvements in survival in an aggressive pre-clinical tumor model in rats, and suggest new approaches for treating brain tumors in humans.

U1 Adaptors Suppress KRAS and MYC in Pancreatic Cancer

Tsang and Dudgeon *et al.* Page 1445

The scientific premise that silencing mutant KRAS or MYC in mutant KRAS driven cancers using mouse models of cancer is well established. Despite this, therapeutics for these targets are unavailable in the clinic. Here, Tsang and colleagues have translated a novel oligonucleotide gene silencing technology (U1 Adaptor) to effectively target both KRAS and MYC in pancreatic cancer xenograft tumors. A new formulation of U1 Adaptor conjugated to tumor targeting peptides showed highly potent anti-tumor activity *in vitro* and *in vivo*. This will obviate the need for a nanoparticle delivery system.

MEDI0641: A Novel PBD-Based Anti-5T4 ADC

Harper *et al.* Page 1576

5T4 is an oncofetal antigen expressed on tumor cells, including cancer stem cells (CSCs), in many carcinomas. Here, Harper and colleagues evaluated anti-5T4 antibody-drug conjugates (ADCs) containing warheads exhibiting different mechanisms of action: a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer or a microtubule-destabilizing tubulysin. Although both ADCs demonstrated potent activity in preclinical tumor modes, only the PBD-conjugated ADC, MEDI0641, significantly inhibited CSCs *in vivo*, producing more durable responses. As more choices become available in developing ADCs, it is important to match the right technology against the right target for specific cancer patient populations.

Contribution of the Serine Synthesis Pathway to BRAF Inhibitor Resistance in Late-Stage Cancers

Ross *et al.* Page 1596

Vemurafenib is used to treat patients with unresectable metastatic melanoma harboring the *BRAF*-V600E mutation. Patients initially respond to the drug, but efficacy is reduced over time due to acquired-drug resistance and patients relapse. Ross and colleagues have identified serine biosynthesis as a critical component of the acquired- and intrinsic-resistance of vemurafenib in malignant tumor cells. The authors have demonstrated gemcitabine sensitized acquired-resistant metastatic melanoma cells, as well as the intrinsically resistant BRAF-WT pancreatic and non-small cell lung cancer cells, to vemurafenib and dabrafenib (a separate *BRAF*-V600E inhibitor). These results highlight the translational potential of gemcitabine in overcoming the resistance to BRAF inhibitors.

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