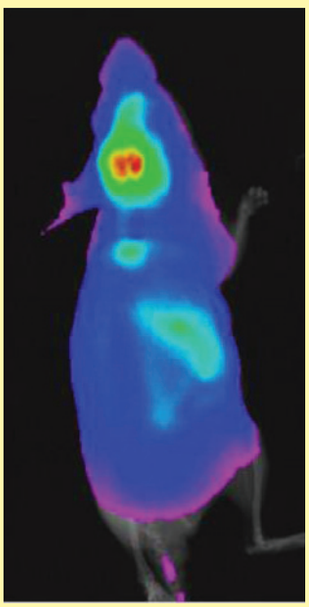
Molecular Cancer Therapeutics

Highlights

January 2015 • Volume 14 • Number 1

Selected Articles from This Issue



Peptide–mAb Conjugate Crosses the Blood–Brain Barrier

Regina *et al.* Page 129

Tumor-targeting monoclonal antibodies represent a major advance in oncology therapy; however, due to their limited brain permeability, mAbs are not generally effective against brain tumors. Conjugation of an anti-HER2 mAb with Angiopep-2, a peptide recognized by LRP1 (low-density lipoprotein receptor-related protein 1), results in ANG4043, which enters brain physiologically, targets $HER2^+$ tumors, and increases survival in mice bearing intracranial tumors. The Angiopep conjugation to mAbs, as well as to previously reported small molecules, is applicable in general to create brain-penetrant therapeutics for brain malignancies and other CNS disorders.

Repurposing the Antihelmintic Mebendazole as a Hedgehog Inhibitor

Larsen *et al.* Page 3

Activation of the Hedgehog pathway is a feature of many different types of cancer, including highly lethal brain tumors. Accordingly, small molecules that can antagonize Hedgehog signaling are being developed as new anticancer drugs. Larsen and colleagues demonstrate that mebendazole, a widely used antiparasitic, can inhibit Hedgehog pathway activation by preventing the formation of the primary cilium, a tubulin-based cellular organelle that functions as a signaling hub. The off-label use of mebendazole as a Hedgehog inhibitor provides a promising new option for the management of brain tumors and other tumor types in which Hedgehog activation is prevalent.

Characterization of TAS-116: A Novel HSP90 Inhibitor

Ohkubo *et al.* Page 14

HSP90 inhibitors simultaneously affect multiple cancer-related proteins; therefore, they have potential use in advanced cancer treatment. However, because HSP90 also functions in normal cells, it is essential to balance efficacy and toxicity to maximize the antitumor potential of HSP90 inhibitors. Ohkubo and colleagues report on the biological activity of TAS-116, a novel, orally active HSP90α and β selective inhibitor. TAS-116 showed antitumor activity without detectable ocular toxicities in a rat model, due to greater TAS-116 distribution in target tumor tissues than in non-target eye tissues. The favorable therapeutic index of TAS-116 thus highlights its therapeutic potential.

BAI1 and Nestin in Breast Cancer Brain Metastases

Meisen *et al.* Page 307

Treatment options for breast cancer brain metastases are limited and new therapies are needed. Here, Meisen and colleagues discovered the relationship of multifunctional brain angiogenesis inhibitor 1 (BAI1) and nestin expression with breast cancer brain metastases. Higher BAI1 expression is associated with better patient survival and higher nestin expression is significantly correlated with breast cancer lung and brain metastases. The application of 34.5ENVE, a Nestin-targeted oncolytic virus expressing a therapeutic extracellular fragment of BAI1 destroyed breast cancer brain metastases in two different immune-competent murine models of the disease. The results of these studies warrant the clinical investigation of 34.5ENVE for breast cancer brain metastases.

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Mol Cancer Ther 2015;14:1.