



Compounds with Antimalarial Activity May Also Inhibit Metastasis

Çelik *et al.* _____ Page 2497

Ezrin is a cytoplasmic protein that regulates diverse cellular functions related to metastasis. Due to structural homology between ezrin inhibitors and some antimalarial compounds, Çelik and colleagues screened compounds from MMV Malaria Box for their ability to directly bind ezrin. Several compounds with antimalarial activity bound to ezrin protein and inhibited ezrin's function in cell motility in zebrafish embryos and cancer cells. These findings suggest a potential new application for some of the antimalarial compounds in cancer therapy. Furthermore, the new mechanism of action suggests that antimalarial compounds may have been targeting the human ezrin protein to prevent parasite growth.

AZD4547 Can Overcome Resistance to MET Inhibitor

Jo, Choi, and Shin *et al.* _____ Page 2613

In this study, Jo, Choi, Shin, and colleagues demonstrated that human hepatocellular carcinoma cells (HCC) exhibit different sensitivities to a MET inhibitor, depending on the phosphorylation status of FGFR. Results showed that human HCC displayed differing sensitivity to MET inhibition dependent on phospho-FGFR1 and 2. Moreover, treatment of primary cancer cells isolated from patients with HCC expressing both phospho-FGFR1 or 2 and phospho-MET with the MET inhibitor did not induce cell death, whereas treatment with the FGFR inhibitor AZD4547 did. Therefore, the findings may provide a rationale for the clinical development of FGFR inhibitors, such as AZD4547, for selected patients with hepatocellular carcinoma expressing phospho-MET and phospho-FGFR.

Seribantumab Delays Resistance and Restores Sensitivity to Letrozole

Curley and Sabnis *et al.* _____ Page 2642

Heregulin-driven ERBB3 signaling represents a common mechanism of resistance to drug therapy in cancer. To investigate its role in mediating resistance to the aromatase inhibitor letrozole, Curley, Sabnis, and colleagues used an *in vivo* model of postmenopausal ER⁺, HER2⁻ breast cancer. Prolonged exposure to letrozole resulted in activation of ERBB3 signaling, and cotreatment with seribantumab, a heregulin-blocking anti-ERBB3 antibody, delayed the onset of resistance to letrozole and restored sensitivity *in vivo*. These findings are consistent with a recent clinical trial in which cotreatment with seribantumab and exemestane resulted in prolonged progression-free survival relative to exemestane alone in a subgroup of patients expressing heregulin in their tumors.

Cutaneous Melanoma Invasion in Human 3D Skin Equivalents

Hill *et al.* _____ Page 2665

Currently available *in vitro* and *in vivo* models of early melanoma invasion are not fully representative of the human skin microenvironment. Hill and colleagues have developed and optimized a fully humanised 3D skin equivalent consisting of a stratified epidermis, a basement membrane containing type IV and VII collagens, and a dermal compartment of human fibroblast-generated extracellular matrix of sufficient thickness to allow investigation of early melanoma invasion. Comparison with human melanoma *in situ* and metastatic melanoma indicates this model accurately recreates the early stages of human melanoma progression.

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