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1, 3-bis (3, 5-dichlorophenyl) urea compound 'COH-SR4' inhibits proliferation and activates apoptosis in melanoma

Kathryn Leake
Oncology Solutions, USA

The current clinical interventions in malignant melanomas are met with poor response to therapy due to dynamic regulation of multiple melanoma signaling pathways following administration of single target agents. In this context of limited response to single target agents, novel candidate molecules capable of effectively inducing tumor inhibition along with targeting multiple critical nodes of melanoma signaling assume translational significance. In this regard, we investigated the anti-cancer effects of a novel dichlorophenyl urea compound called COH-SR4 in melanoma. The SR4 treatment decreased the survival and inhibited the clonogenic potential of melanomas along with inducing apoptosis in the *in vitro* cultures. SR4 treatments lead to inhibition of GST activity along with causing G2/M phase cell cycle arrest. Oral administration of 4 mg/kg SR4 leads to effective inhibition of tumor burdens in both syngeneic and nude mouse models of melanoma. The SR4 treatment was well tolerated and no overt toxicity was observed. The histopathological examination of resected tumor sections revealed decreased blood vessels, decrease in the levels of angiogenesis marker, CD31, and proliferation marker Ki67, along with an increase in pAMPK levels. Western blot analyses of resected tumor lysates revealed increased PARP cleavage, Bim, pAMPK along with decreased pAkt, vimentin, fibronectin, CDK4 and cyclin B1. Thus, SR4 represents a novel candidate for the further development of mono and combinatorial therapies to effectively target aggressive and therapeutically refractory melanomas.

kleake@live.unthsc.edu