A Novel MDM2 Inhibitor, SM13, Induces p53-Dependent Apoptosis In Vascular Smooth Muscle Cell.

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Background: p53 is a known tumor suppressor which leads to apoptotic events in after cellular damage, and it regulates cell cycle arrest and apoptosis. p53 is active in vascular hyperplastic lesions, where it regulates apoptosis of rat aorta Vascular Smooth Muscle Cell (VSMC). Targeting p53 may be, therefore, a novel therapeutic approach for the treatment of restenosis. We have recently characterized a new compound, SM13, which is able to increase p53 by disrupting p53-MDM2 interaction, and its ubiquitination and degradation.

Purpose of the study is to evaluate p53 ability to inhibit VSMC proliferation.

Results: First, we confirmed in VSMC that SM13 efficiently reduces p53/MDM2 interaction and increases p53 levels. SM13 inhibited VSMC proliferation and DNA synthesis in response to FBS 5% in a time dependent manner. Accordingly, the phosphorylation of RB, marker of cell cycle progression, was reduced in SM13 treated cells. In order to evaluate the effect of SM13 on apoptosis, we analyzed the activation of caspase 3. SM13 increased the levels of cleaved caspase 3 suggesting that it regulates proliferation in vitro by inducing p53-dependent apoptosis.

Conclusion: our results demonstrate the effectiveness of SM13 to reduce VSMC proliferation, through the activation of a p53-dependent apoptotic pathway and suggest to test it for treatment of vascular disease, in experimental animal model.