ATB-346 a novel hydrogen sulfide-releasing anti-inflammatory drug induces apoptosis of human melanoma cells and inhibits melanoma development *in vivo*

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Increased cyclooxygenase-2 (COX-2) expression and enhanced prostaglandin E_2 (PGE_2) production are frequently attributed to the inflammation-associated cancers such as lung, colon, bladder, prostate and other cancer types. Hydrogen sulfide releasing non-steroidal anti-inflammatory drug (H_2S-NSAIDs) are an emerging novel class of compounds with significant anti-inflammatory properties (Wallace et al., 2010). They consist of a traditional NSAID to which an H_2S-releasing moiety is covalently attached.
We have recently demonstrated that H_2S donors inhibit melanoma cell proliferation (Panza et al., 2014). In the current study, we evaluated the potential beneficial effects of ATB-346 [2-(6-methoxynapthalen-2-yl)-propionic acid 4-thiocarbamoyl-phenyl ester], a H_2S-releasing derivative of Naproxen, in a murine model of melanoma.

Aims & Methods: We utilized cell culture and a mouse melanoma model to evaluate: the effect of ATB-346 on: i) *in vitro* growth of human melanoma cells; ii) *in vivo* melanoma development in mice.

Results: Cell culture studies demonstrated that ATB-346 reduced the *in vitro* proliferation of human melanoma cells and this effect was associated to induction of apoptosis and inhibition of NF-κB activation. Moreover ATB-346 had novel Akt signaling inhibitory properties. Daily oral dosing of ATB-346 (43 μmol/kg) significantly reduced melanoma development *in vivo* in mice.

Conclusion: ATB-346, a novel H_2S-NSAID, inhibits human melanoma cells proliferation by inhibiting pro-survival pathways associated to NF-κB activation. Oral treatment with ATB-346 inhibits melanoma growth *in vivo* in mice. Our results suggest that the combination of inhibition of cyclooxygenase and delivery of H_2S operated by ATB-346 may offer a promising alternative to existing therapies for melanoma.

References

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