The histone deacetylase inhibitor ITF2357 targets oncogenic BRAF in human melanoma cells

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ITF2357 (Givinostat) is a potent antineoplastic histone deacetylase inhibitor which is currently used in clinical trials for leukemias and myelomas and in the therapy for systemic juvenile idiopathic arthritis.

Here evidence is provided that ITF2357 reduces the viability of human melanoma SK-Mel28 cells thereby inducing cell death. This compound was more efficacious than SAHA, another well known HDAC inhibitor belonging to the same class of hydroxamic acids. Moreover, we demonstrated for the first time that ITF2357 determines in SK-Mel28 cells a remarkable reduction in the level of oncogenic B-Raf, the product of the BRAF V600E mutated gene in melanoma. Western blot analysis showed that the decrease of oncogenic B-Raf induced by ITF2357 is dose and time dependent. This effect was accompanied with a decrease in the level of phosho-ERK confirming the blockage of the B-Raf mitogenic pathway.

To potentiate the inhibition of this pathway, the MEK inhibitor UO126 was used in combination with ITF2357. The results indicated that this compound increases the effect of ITF2357 on cell death. Intriguingly, UO126 not only reduced ERK phosphorylation, as a confirmation of MEK inhibition, but also consistently reduced the level of B-Raf when combined with ITF2357.

These preliminary results suggest that ITF2357, either alone or in combination with UO126, can be considered a good candidate in melanoma targeted therapy and ongoing studies will further clarify the mechanism of oncogenic B-Raf inhibition.