

COX and VEGFR-2 inhibitors as potentiating agents of new HDAC inhibitors as epigenetic modulators in cancer

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Recently, among anticancer agents, of growing interest are the kinases inhibitors. Many of them are under clinical trials while some have been already approved by FDA as angiogenesis blockers (Vascular endothelial growth factor receptor 2 (VEGFR-2) inhibitors), such as Sunitinib and Vandetanib. HDACI (histone deacetylase inhibitors) are another newest drug group recently approved for the treatment of Cutaneous T-cell lymphoma (CTCL) (Wagner et al., 2010) and several others HDACIs are in pre-clinical and clinical stages. Interestingly, many scientific reports indicate the synergistic effects of the HDACI and VEGFR-2 inhibitors combination. Lately, has been proposed and showed that cycle oxygenases (COXs) inhibitors could reduce the adverse side effects upon HDACI administration. Furthermore, the anticancer effectiveness of COX-2 inhibitors in the treatment of gastric cancer animal models has been demonstrated (Thiel et al., 2011). Taking consideration of these observations we aim to study a new antiproliferative therapy with the combined use of three potentially synergic drug classes: HDACI, inhibitors of VEGFR-2 and COX-2. The antiproliferative evaluation of the more promising molecules will be evaluated both in vitro, in colangiocarcinoma and hepatocarcinoma cell lines trough MTT proliferation assay and Caspase3 Elisa kit, and in vivo models. Along with individual compound assays, synergistic effects will be also determined. The main findings derived from individual compound assay studies will be integrated and used to set-up the best combination of compounds for a multi-target approach that we expect to be highly effective against cancer.

References

- [1] Wagner et al. (2010) Histone deacetylase (HDAC) inhibitors in recent clinical trials for cancer therapy. *Clin Epigenetics*, 2010. 1(3-4): p. 117-136.
- [2] Thiel et al. (2011) Cyclooxygenase-2 and gastric cancer. *Cancer Metastasis Rev*, 2011. 30(3-4): p. 387-95.

Keywords

HDACI, VEGFR-2 and COX-2 inhibitors, antiproliferative effects.