TMU-0324, A Novel Class I Histone Deacetylase Inhibitor, Inhibits Human Colorectal Cancer Growth in vitro and in vivo

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Cancer has been the top of ten leading causes of death in Taiwan since 1980s. In addition, there was about 15.3 % for new cancer patients happened in colon, rectum, sigmoid colon and anus of yearly all new cancer cases based on the research and statistics report published in 2016 from Health Promotion Administration, Ministry of Health and Welfare. Recently, there are more and more publications to support that cancer progression are correlated with epigenetic modification and it may be related to histone deacetylates (HDACs) proteins overexpression. Therefore, it has been a promising strategy to discover and develop newly HDAC inhibitors for cancer treatment. The purpose of this study is to evaluate the anticancer activity of a novel small molecule, TMU-0324, which demonstrated great HDAC inhibition potency especially targeting Class I HDAC isoforms. In addition, this new chemical entity also showed good anti-tumor effects among multiple human cancer cell lines. TMU-0324 was chosen for further researches on its pharmacological action in colorectal cancer (CRC) through in vitro and in vivo assays.

According to study results, we found that TMU-0324 predominantly reduced the human colorectal cancer cell viability by inducing apoptosis, which increased sub-G1 population. The caspasases activation and PARP (Poly ADP-ribose polymerase) inhibition were both observed after treating TMU-0324. Furthermore, TMU-0324 could induce hyperacetylation of some targets that HDACs work on such as histone 3, alpha-tubulin. TMU-0324 demonstrated superior antitumor effects than two reference drugs, (Belinostat a.k.a PXD-101), the pan-HDAC inhibitor approved by USFDA in 2014 for treating peripheral T-cell lymphoma, and Entinostat (MS-275), the ongoing phase II Class I selective HDAC inhibitor to treat both solid and hematological cancers. In addition, TMU-0324 repressed CRC cell migration and cell invasion capability concentration-proportionally. From the CRC xenograft animal study results for TMU-0324, it presented tumor suppressive effect without observing apparent toxicity. In summary, the in vitro and in vivo study results support that TMU-0324 has good anti-tumor capability especially CRC and this novel small molecule has the potential to treat colorectal cancer in the future.