ABSTRACT

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Title of diploma thesis:

ISOCITRATE DEHYDROGENASE 2 INHIBITOR ENASIDENIB SYNERGIZES DAUNORUBICIN CYTOTOXICITY BY TARGETING ALDO-KETO REDUCTASE 1C3

Treatment with anthracyclines is crucial in treating several oncologic disorders. However, several molecular mechanisms hinder the effectivity of anthracyclines, which is a significant obstacle in cancer therapy. Carbonyl reducing enzymes (CREs), a type of NAD(P)H-dependent oxidoreductase, contribute to anthracycline resistance by reducing these drugs to fewer active alcohols. These enzymes also play a role in the proliferation and differentiation of cancer cells, leading to increased tumour aggressiveness. Therefore, targeting these enzymes is essential for effective anticancer therapy.

This study aimed to uncover the potential off-targets of the isocitrate dehydrogenase (IDH) inhibitor enasidenib (ENA) that could counteract the resistance to anthracycline, specifically in relation to the detoxification role of CREs. For this, we screened the ability of ENA to inhibit different recombinant CREs that can reduce daunorubicin (Daun) to daunorubicinol (Daun-ol). Furthermore, we evaluated how ENA counteracts the metabolism of Daun in different human cell lines that express the Aldo-keto reductase 1C3 (AKR1C3) either endogenously (A549) or exogenously (HCT116). Moreover, the potential synergistic effect of ENA on Daun cytotoxicity was quantified in the same cell models. ENA was found to selectively inhibit AKR1C3-mediated inactivation of Daun both over the recombinant enzyme and in cell lines expressing AKR1C3, which contributed to synergizing Daun cytotoxicity to overcome resistance. This study provides in vitro evidence of ENA targeting the anthracycline resistance actor AKR1C3 at clinically achievable concentrations, thus, suggesting that ENA could be combined with anthracyclines to improve their therapeutic efficacy.