TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER
Graduate School *of* Biomedical Sciences™

Dissertation Defense

Redox-based Repurposed Drugs as Potent and Rational Inhibitors of the Human DNA Repair Protein MGMT for Increased Efficacy of Anticancer Alkylating Agents

Presented by:

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ABSTRACT:

MGMT (O^6-Methylguanine-DNA methyltransferase) is an antimutagenic DNA repair protein that confers resistance to anticancer alkylating agents. Current clinical strategies to curtail MGMT using pseudosubstrate inhibitors have met with limited success. My research dealt with novel design and discovery of two repurposed drugs as inhibitors for human MGMT. I exploited the reactivity of the active site cysteine (Cys145) and its propensity to undergo conjugation with thiol compounds or S-nitrosylation by NO-donors. Two brain penetrating non-toxic drugs with established uses in other diseases, namely, the disulfiram (alcohol aversion) and nitroaspirin (cardiovascular /NSAID) were found to be highly effective and transient inhibitors of MGMT in cell culture and animal models. These drug treatments led to a rapid degradation of MGMT accompanied by enhanced alkylation damage and antitumor efficacy. Another study showed that the thiol-reactive drugs also inactivate various redox-sensitive proteins (p53, NF-κB, Ub-E1). A physical and functional interaction of estrogen receptor-α with MGMT protein was also uncovered and exploited for improved breast cancer therapy using alkylating agents.

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