Abstract

Title of the thesis: "Drug repurposing and remodeling: A study of the potential antitumorigenic activity of chemotherapeutic drugs against experimental murine lymphoma".

Index No.: 151/21/Life Sc./27

Recent drug discovery based on drug repurposing,accelerated fastertherapeutic developmentas an alternative route than the conventional approach through identification of clinically relevant drug totally in a new indication. The known combinatorial drug regimen of lymphoma is associated with only five-years increment of survival along with increment of adverse side effect arises due to increasing drug resistance. After phase I clinical trial in oncology only 5% drug approved by FDA.The emergent need of small molecules which can prevail over the poor prognosis rate occurred in lymphoma. For enhancing the drug efficacy, circulation time and sustained release in lymphoma, the oncologic drug is further conjugated with polymer.

The thesis covered repurposing based drug development in two different approaches one is by anti-glioma drug delivery upon conjugating with a polymeric scaffold against lymphoma. In another approach of repurposing, non-oncologic drug remodeled by conjugating with a DNA intercalated moiety against lymphoma.

Herein to explore the objective of the anti-lymphoma drug development program, the molecule was synthesized, characterized of drug delivery device, upon conjugation with polymer for enhancing bio-availability and sustained release. Also, synthesis of DNA intercalated modified non-oncologic drug and their implication against lymphoma. Different bio-physical techniques the synthesized drug interaction with DNA was studied. The synthesized drug molecules were evaluated against *in vitro* and *in vivo* anti lymphoma activity.

Repurposing of anti-glioma drug temozolomide conjugated with the PAMAM dendrimer via a hydrazide bond to stabilize the active metabolite of temozolomide (MTIC) and can sustain for prolong time period in tumor microenvironment to enable tumoricidal activity against solid tumor like lymphoma. Our result indicates that the novel nano-construct devicerestricted the uncontrolled growth of lymphoma and have potential as an alternative drug against lymphoma and doxorubicin resistant lymphoma cells.

In another approach the modified non-oncologic drug artesunate was conjugated with DNA intercalating nitro and azide substituted naphthalimide moieties against lymphoma. Naphthalimide moiety was intercalated with DNA and its counter-part artesunate was able to bind with the minor groove of DNA, evidenced from the bio-physical interaction between synthesized drug and DNA. The synthesized 4-azide decorated naphthalimide conjugated artesunate showed diminished cytotoxicity, metastasis and growth arrest in human and murine lymphoma cells. The cellular uptake in both human and murine lymphoma was increased after conjugation of FITC with naphthalimide linked artesunate moiety. our research work delineated the azide decorated naphthalimide conjugated artesunate could be used as a potential drug against solid lymphoma.

The successful repurposing of temozolomide- polymer scaffold have the potential against lymphoma and doxorubicin resistant lymphoma cells, by inhibiting the tumor growth. Also, the repurposing non-oncologic drug artesunate after conjugated with DNA intercalated moiety, showed better therapeutic activity against lymphoma.The objective of drug discovery based on drug repurposing modulated drug delivery method and modified non-oncologic drug towards oncologic drug is established herewith.

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