Summary of the Research work

Title: Targeting telomerase using structure-based drug repurposing approach: A therapeutic strategy to investigate anti-cancer potential of FDA approved drugs.

Scientists have used the weakness of most of the cancers to rely on telomerase for their survival as a stratagem to devise some of the most effective anti-telomerase inhibitors. Many small-molecule telomerase inhibitors have also been identified but most of them are in preclinical or clinical trials. BIBR1532 is one of the most potent and selective telomerase inhibitors known till date but its exact molecular binding site in human telomerase is still not known. Many studies indicate that it binds in a hydrophobic FVYL pocket in the thumb domain of the enzyme and inhibits interaction of TERT and TERC components to prevent the telomere elongation and thus causing apoptosis of cancerous cells.

With the cues from rigorous literature and structural study, we have tried to establish the exact binding site of BIBR1532 in hTERT thumb domain using a molecular dynamics (MD) approach. Our study indicated that BIBR1532 binds in a new pocket 8.413Å away from its putative pocket while showing the conserved FVYL interactions here as well. Subsequently, we confirmed the same using a unique two-way approach wherein we designed two structure-based pharmacophore models for the putative and newly elucidated binding pocket. These pharmacophore models were screened through DrugBank Approved and investigational databases to obtain lead compounds from each of them. Fit value based funneling followed by filtering for druglikliness parameters like ADMET, Lipinski's rule of five and toxicity prediction studies were performed. The top hits from both the databases were docked in the two pockets to assess their binding affinities. The results established that the structural architecture of FVYL pocket in hTERT differed considerably from that of tcTERT. Several protruding residues inside the putative FVYL pocket in hTERT reduced the pocket volume and thus hindered the binding of any small molecule inhibitor there. In contrast the newly discovered pocket showed stable binding of BIBR1532 as well as the hit compounds. Ultimately, the validation of the stability of selected lead compounds in the thumb domain of hTERT was done by performing MD simulation studies with BIBR1532 as a positive control. Binding free energy was also calculated as a post MD study for all the lead drugs using MM-PBSA and MM-GBSA analysis. The compounds which showed stable dynamics results and negative binding free energy were shortlisted as top leads of the study.

We report the identification of five lead drugs from DrugBank database that can be repurposed as telomerase inhibitors after further in-vitro validation using TRAP assay. These FDA Approved drugs sanctioned for use, not only surmount the conventional hindrances of standard drug discovery pipeline which requires a lot of time and money but also signify a significant paradigm shift. This transformation enables the exploitation of established drugs, acknowledged for their safety and efficacy, to revolutionize the realm of cancer therapy. A successful clinical validation of these lead drugs as potent telomerase inhibitors will herald a remarkable and expedited emergence of anti-cancer pharmaceuticals which can be used standalone or in combination to already existing therapies. Furthermore, the identified

compounds themselves can be subject to modification or can serve as a foundation for designing novel inhibitors with comparable structures, thus ushering in a new era of anti-cancer agents.

29/8/23

Sr. Prof. Daman Saluja
(Supervisor and Nominator)
Chairperson, Research Council, University of Delhi
Joint Director, Delhi School of Public Health (DSPH), IoE
Medical Biotechnology Laboratory
Dr B.R Ambedkar Center for Biomedical Research (ACBR)
University of Delhi,
New Delhi, India-110007

प्रो० दमन सलूजा
Prof. Daman Saluja
डा. बी. आर. अम्बेडकर जैव चिकित्सा अनुसंधान केन्द्र
Dr. B. R. Ambedkar Center For Biomedical Research
दिल्ली विश्वविद्यालय, दिल्ली-११०००७/University of Delhi-110007