Potent Treatment of Renal Fibrosis: A Novel Inhibitor of HIPK2-Smad3 Interaction

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Renal fibrosis, featured by excessive accumulation of extracellular matrix (ECM), is a detrimental path of chronic kidney disease while lacking an effective treatment for 0.5 billion adults afflicted worldwide. TGF-β1/Smad3 pathway is a pivotal mediator of fibrosis, which is regulated by Homeodomain Interacting Protein Kinase 2 (HIPK2), a necessary factor of ECM production yet is poorly regulated using current non-specific inhibitors. This study elucidated the efficacy of a novel compound, BT173, to 1) specify its inhibition on Smad3 activity, 2) measure BT173's effect on HIPK2 activity, and 3) determine BT173's molecular interaction with HIPK2. Luciferase reporter assay confirmed BT173 significantly suppressed Smad3 activity in a dose response manner ($p < 0.05$), but the radiometric kinase assay found that BT173 had no inhibition in HIPK2 kinase activity, unlike current non-specific inhibitors. Molecular interaction study by DARTS test revealed BT173 directly bound to HIPK2, and co-immunoprecipitation found BT173 reduced HIPK2-Smad3 binding. The therapeutic potential of BT173 showed <10μM induced minimal toxicity to 293T cells. To conclude, this study provided a baseline modality for reducing HIKP2-Smad3 binding and showed BT173 suppressed HIPK2 regulated Smad3 without reducing HIKP2 activity. This unique property of BT173 suggested its ability to reduce ECM accumulation without causing severe side effects. Thus BT173 should be investigated further as a medical treatment that could reduce dialysis or kidney transplant rate associated with renal fibrosis, as well as fibrosis in other organs. BT173 was also recognized as a useful tool to manipulate Smad3 pathway in other Smad3-related disease studies.