Apoptotic beta cell death is an underlying cause majorly for type I and to a lesser extent for type II diabetes. Recently, MST1 kinase was identified as a key apoptotic agent in diabetic condition. In this study, I have examined MST1 and closely related kinases namely, MST2, MST3 and MST4, aiming to tackle diabetes by exploring ways to selectively block MST1 kinase activity.

The first investigation was directed towards evaluating possibilities of selectively blocking the ATP binding site of MST1 kinase that is essential for the activity of the enzymes. Structure and sequence analyses of this site however revealed a near absolute conservation between the MSTs and very few changes with other kinases. The observed residue variations also displayed similar physicochemical properties making it hard for selective inhibition of the enzyme. Second, possibilities for allosteric inhibition of the enzyme were evaluated. Analysis of the recognized allosteric site also posed the same problem as the MSTs shared almost all of the same residues.

The third analysis was made on the SARAH domain, which is required for the dimerization and activation of MST1 and MST2 kinases. MST3 and MST4 lack this domain, hence selectivity against these two kinases can be achieved. Other proteins with SARAH domains such as the RASSF proteins were also examined. Their interaction with the MST1 SARAH domain were evaluated to mimic their binding pattern and design a peptide inhibitor that interferes with MST1 SARAH dimerization. In molecular simulations the RASSF5 SARAH domain was shown to strongly interact with the MST1 SARAH domain and possibly preventing MST1 SARAH dimerization. Based on this, the peptidic inhibitor was suggested to be based on the sequence of RASSF5 SARAH domain. Since the MST2 kinase also interacts with RASSF5 SARAH domain, absolute selectivity might not be achieved.

Keywords: Diabetes, beta-cell apoptosis, MST kinase, RASSF, SARAH domain, inhibitor design, structure, sequence, molecular dynamics simulations