Performing a High-Throughput Virtual Screening (HVTS) to identify potential therapeutic targets of YB-1 protein

Karkoutly O[1,2,5], Dhasmana A[2,5], Ezell KL[1,2,5], Doxtater KD[2,5], Dhevan V[3,4], Chauhan SC[2,5], Tripathi MK[2,5]

[1]Department of Biology, College of Sciences, The University of Texas Rio Grande Valley, McAllen, TX 78539, USA.

[2]South Texas Center of Excellence in Cancer Research, School of Medicine, University of Texas Rio Grande Valley, McAllen TX 78504, USA.

[3]Valley Baptist Hospital, Harlingen, TX 78550, USA.

[4]Department of Surgery, School of Medicine, University of Texas Rio Grande Valley, Edinburg, TX 78501, USA.

[5]Department of Immunology and Microbiology, School of Medicine, University of Texas Rio Grande Valley, McAllen, TX 78504, USA.

Background: Hepatocellular carcinomas (HCCs) is a primary malignancy of the liver. Hispanic-Texans have several risk factors and disparities that compound the risk of HCC diagnosis and treatment. The most used chemotherapeutic drug against HCC is sorafenib, but many liver cancers have developed a resistance to this drug. The knockdown of Y-box binding protein-1 (YB-1) has been shown to greatly increase sensitivity to sorafenib. In this study, we will discuss identification of potential YB-1 inhibitors, which can lead to re-sensitization of liver cancer cells to sorafenib.

Methodology: The RCSB protein data bank (*pdb)* was used to retrieve the crystal structure of YB1, while the DrugBank database was used to obtain a list of experimental and approved drugs. A multiple sequence alignment (MSA) of YB-1 & Lin28 was done by Clustal Omega. Biovia Discovery Studio 2020 was used to visualize 3D models and perform a High-Throughput Virtual Screening (HTVS), which includes rigid docking via the LibDock extension, flexible docking via the CDocker extension, and a pharmacokinetic profiling via an ADMET analysis.

Results: The cold shock domain of YB-1 was found to be conserved with Lin28, as a known transcription factor. 22 drug candidates were identified through HTVS. The best six show a decent binding ability in both rigid and flexible dockings and have been previously tested in different cancer types to some extent.

Conclusion: We were able to identify six potential drug candidates for inhibiting our protein of interest, YB-1. Studies are in progress to test them on sorafenib-resistant HCC cell lines.