Identification of Novel LEAD Compounds for Solute Transporter Protein Member 5 in Sensorineural Hearing Loss

Khan, Saaim (School: Cranbrook Kingswood School)

2 statistically likely, novel drug candidates for solute transporter protein member 5, SLC5, were identified in this study. Dysfunction of a roundworm orthologue of SLC5, sulp-5, was linked to sensorineural hearing loss (SNHL) in 2015. The goal of this project was to examine how this phenomenon in roundworms translates to humans and identify molecular drug candidates for SLC5 in an effort to advance SNHL treatability. Homology modeling with loop refinement and energy minimization was used to generate a competent 3D model of SLC5. The model was then subjected to rigorous topological shape analysis to identify its primary functional binding pocket. Upon detection of this binding pocket, 2 genetic variants were found directly on it, emphasizing the need for drug candidates specific to this functional surface on SLC5. With this knowledge in hand, a virtual protein-ligand docking screen of 8.1M drug candidates was conducted on SLC5 using a self-assembled 16 node HPC cluster. Through careful evaluation of docking results, ethyl 3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(L4) and 1-(4-(azanyl)butyl)-3-((methyl-azanyl)methyl)-1-azetidine(L1) were culled as the likely drug candidates for mitigation of SLC5 dysfunction. These predictions were further substantiated by a self-assembled probabilistic bootstrap computation model that yielded p-values of 4.02E-5 and 1.19E-18 respectively. Not only were these candidates identified with reputable statistical confidence, but the main functional binding pocket of SLC5 was discovered with precise residual accuracy. Furthermore, the accessibility of the binding pocket to genetic variance was pinpointed. With these discoveries, the future of molecular therapeutics for SNHL is brought appreciably closer to reality.

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