Receptor.AI is working towards selective inhibitors of CLC-K chloride channels to fight hypertension

LEWES, DELAWARE, USA, February 17, 2022 /EINPresswire.com/ -- The CLC channels belong to a large family of ionic channels which translocate chloride ions across the cell membranes. In humans, the CLC channels are associated with several hereditary diseases such as myopathy, osteopetrosis, Dent's disease and Bartter syndrome. The latter is characterized by low blood pressure caused by inherited malfunction of CLC channels, which suggests that blocking these channels could be an effective treatment of hypertension.

However, any treatment involving ionic channels requires extreme caution, precision, and selectivity because these proteins are present in almost any cell and take part in a multitude of biological processes. In humans, two very similar CLC channels CLC-Ka and CLC-Kb, are expressed not only in the kidney but also in the inner ear, performing the same function of maintaining the ionic balance in sensoric cells. Inhibiting either of them individually does not affect hearing, but blocking both results in deafness. Treating hypertension in expense of losing hearing is not an appealing idea, thus successful drugs should target either CLC-Ka or CLC-Kb, but not both of them.

Two types of the CLC-K channels are homologous by 95% and differ by just one amino acid in the ion conducting pore, which makes the development of selective drugs for them an extremely challenging task. To put the complexity of this challenge into context, most of the targets which are now in the pipelines of drug discovery companies, share less than 70% of their sequence with the closest homologs. It is not surprising that only few existing selective compounds inhibit CLC-K channels at millimolar concentrations, which is too high for any practical applications. Thus development of novel drugs with high affinity and selectivity against CLC-K channels is now of great demand.

The drug discovery startup Receptor.AI announced a new approach to finding selective CLC-K inhibitors using its advanced Artificial Intelligence AI platform. It is based on complementary usage of several AI-based techniques and in silico modeling. In the first stage, a 4D drug-target interaction model based on the graph neural networks is used to perform high-performance virtual screening of the large library of drug-like compounds. The model is trained on 3D structures and the large-scale dynamics of all known proteins with well-characterized ligands, including the channels from the CLC family. Very high performance of the AI model and proprietary techniques of clustering of the ultra-large chemical spaces allowed screening of a

whopping 10 billions compounds in just a few days. In the second stage, thousands of promising compounds are subject to the docking on the ensemble of representative channel conformations, which are extracted from extensive molecular dynamics trajectories. The docking parameters themselves were fine-tuned with the help of AI. Finally, the most successful candidate molecules are filtered by an AI-based ADME-Tox model to exclude those that are likely to be toxic or have poor pharmacological profile.

The usage of not only structural but also dynamic information greatly increases the chances of spotting subtle differences between CLC-Ka and CLC-Kb channels. Indeed, the company managed to identify several dozens of promising hit compounds, which exhibit selectivity against either CLC-Ka and CLC-Kb in silico. These compounds are going to be tested experimentally for activity and selectivity in collaboration with University of Texas Health Science Center at Houston, USA.

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