Docking the B^0AT: Identification of novel amino acid transport inhibitors

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Mice lacking B^0AT1, an intestinal neutral amino acid uptake transporter, were found to be resilient to obesity and type II diabetes (T2D), while retaining high insulin sensitivity and a normal glucose metabolism. Accordingly, pharmacological inhibition of B^0AT1 is expected to reproduce this metabolic phenotype, and may ultimately provide a route to treating T2D. Here, we used computational docking studies in the screening of approximately 14,000 compounds to identify potential inhibitors of B^0AT1. Of these, 78 compounds were validated on a cell-line over-expressing human B^0AT1 using fluorescence and radiolabelled uptake assays. Amongst the tested compounds, we identified 27 novel inhibitors of B^0AT1, the most potent of which had an IC_{50} of 60μM.

In addition, we used molecular dynamics (MD) simulations to evaluate docking as a virtual screening tool. Our MD simulations suggest that due to the inability of docking programs to treat the receptor protein as a realistic flexible macromolecule, and due to their inability to account for access routes to a binding site, false positive binders can be identified.

Regardless, docking performs significantly better than random or manual compound selection based on substrate similarity, making it valuable in the discovery of novel targeted inhibitors. We anticipate inhibitors discovered here to be a novel foundation for the treatment of T2D.