INDUSTRIAL PILOT PROJECT

Targeting UrdA for potential treatment of type 2 diabetes with structure-based drug design using X-ray crystallography

THE INDUSTRIAL CHALLENGE

The aim was to explore a novel target of Implexion Pharma AB for potential treatment of type 2 diabetes. The target selection was based on the recent finding that the amino acid-derived metabolite imidazole propionate (ImP), produced by the bacterial enzyme urocanate reductase (UrdA) in patients with type 2 diabetes, can contribute to impaired glucose tolerance and reduced insulin signaling. Thus, blocking ImP production would potentially reduce diabetic symptoms in patients. Challenges lies in validation and improvement of inhibitors targeting UrdA, which can be tackled by structure-based drug design utilizing X-ray crystallography.

WHY USING A LARGE SCALE FACILITY

Structure-based drug design is a successful technique to develop and improve biopharmaceutical drugs, but it requires access to synchrotrons with brilliant beam lines, as home-source X-ray data collection gives much lower resolution. The BioMAX beamline of the MAX IV synchrotron in Lund is an ideal experimental station to collect high-resolution data on small crystals, facilitating the success of the proposed project.

HOW THE WORK WAS DONE

Several candidate compounds that block UrdA activity had been identified, and the structure-function relationship was investigated for three relevant candidate drugs by resolving X-ray data using the BioMAX beamline of MAX IV. X-ray data was collected for the UrdA-inhibitor complexes at the beamline, and software available at MAXIV were used to determine the structures. High-resolution structures were retrieved which enabled us to have thorough discussions of the structure-function relationship, leading to new molecules currently being synthesized.

THE RESULTS AND EXPECTED IMPACT

Several candidate compounds blocking UrdA activity were identified, and 3D-structures in complex with UrdA were determined for all three candidate drugs (see figures). Thus, this program has finished the hit identification process successfully with identification of hit series with good chances for developing into drug-like compounds. The next step will be to transfer into hit-to-lead phase and lead optimization, which will require more structural data complemented with clinical data. Before the project started, Implexion Pharma had not realized the advantages of having access to experimental structural data during drug development, compared to only utilizing computational data. Thus, the project has scientifically been very successful and strengthened the consortium of Lund University and Implexion Pharma.

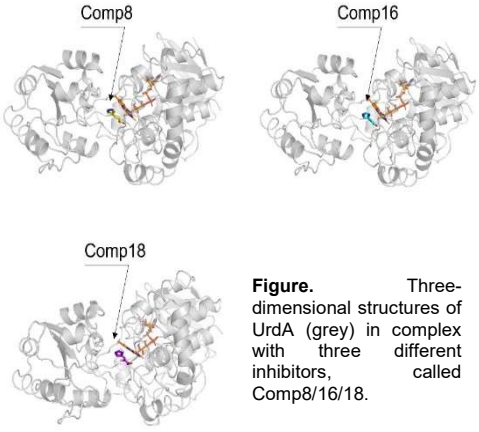

Figure. Three-dimensional structures of UrdA (grey) in complex with three different inhibitors, called Comp8/16/18.

"Collaborating with experts in X-ray crystallography and having access to state of the art structure determination has fueled our hit development program leading to potential new drugs" /Fredrik Bäckhed, Implexion Pharma

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