INDUSTRIAL PILOT PROJECT

Binding of novel peptides to a new cell membrane target on pancreatic beta cells

THE INDUSTRIAL CHALLENGE

Follicum AB, an early stage company, develops drugs based on tissue repair peptides with potential use in a range of disease areas. Understanding the binding and structure/function relationship of peptides to their newly identified receptor is important for the drug development process and subsequent optimization of drug candidates.

WHY USING A LARGE SCALE FACILITY

X-ray crystallography is the best established method to investigate molecular interactions of drugs and receptors to high resolution atomic details (2-3 Å) is normally beyond Follicums reach. It directly provides a three-dimensional model mapping the interaction which is essential to develop and optimize peptides into successful drug candidates. Rational peptide design requires not only high-resolution structural information of the peptide drug candidate itself but also of the complex with its receptor. The use of synchrotron radiation is important to get accurate data at high resolution. This allows to precisely trace the amino acid interactions facilitating further modelling and understanding of the interface between the peptide and the receptor.

HOW THE WORK WAS DONE

The project was performed in a collaboration between Follicum, Lund University Diabetes Center (LUDC) and SARomics Biostructures (a leading Swedish expert in the field of structural biology). The binding parts of the receptor and target protein NRP1 were produced in laboratory scale using cell cultures. NRP1 in complex with different peptides were purified and subsequently set up for crystallization to produce well-diffracting crystals. Thereafter, structural data were collected on the I04 beamline at Diamond Light Source, UK, and analyzed. Previously published crystal structures of NRP1 were utilized to investigate any corresponding or overlapping binding of other molecules to the same part of NRP1.

The structural results obtained were further translated to biological function and establishement of mode of action using different *in vitro* models.

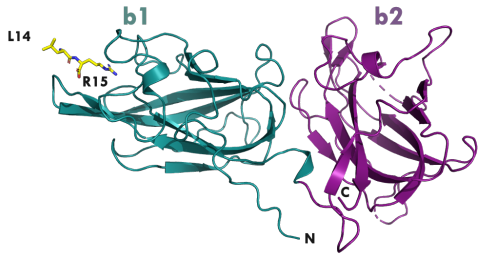

Figure. Overview of the structure of NRP1 b1 and b2 domains (in green and purple) with peptide (shown in yellow sticks).

THE RESULTS AND EXPECTED IMPACT

With the concerted efforts from the different fields of expertise involved, it was possible to determine the crystal structure of NRP1 in complex with a peptide at 1.55 Å in resolution. The binding has also been confirmed using traditional laboratory techniques at LUDC using both the purified NRP1 protein, commercially available NRP1 and binding on human cells, with focus on beta cells, islets and endothelial cells. The provided structural insight of the NRP1/peptide complex will enable further design of the peptide structure and sequence.

The biological effect of the peptides was evaluated in different cell types, highlighting their protective ability. All together, the obtained obesrvations improved the development process of one of the company's peptide platforms through rational peptide design.

"The collaboration using synchrotron has resulted in an even better understanding of how one of our therapeutic peptide families affects important receptors on cells involved in tissue repair. This facilitates continued preclinical work, and increases the opportunities to establish commercial cooperation with global pharmaceutical companies" /Jan Alenfall, Follicum AB

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