



Contribution ID: 71

Type: **Invited talk**

The hunt for enzyme isoform specific ligand binding: using neutron crystallography to elucidate selective inhibition of carbonic anhydrase by saccharin-based ligands.

Tuesday 8 December 2020 13:00 (40 minutes)

Up-regulation of carbonic anhydrase IX (CA IX) expression is an indicator of cancer metastasis and is associated with poor cancer patient prognosis. As such, CA IX has emerged as an attractive cancer target for diagnosis, cancer staging, imaging, and also treatment. However, due to the high level of sequence conservation between human variants of the enzyme, development of isoform-specific inhibitors has been largely unsuccessful. In this study, a CA IXmimic construct that mimics the CA IX active site while maintaining CA II characteristics that make it amenable to crystallography. The mimic construct is based on CA II but with seven point mutations introduced to match the greater active site region with >96% identity to that of CA IX. The structures of CA IXmimic unbound and in complex with saccharin (SAC) and a saccharin-glucose conjugate (SGC) were determined using joint X-ray and neutron protein crystallography. Previously, SAC and SGC have been shown to display CA isoform inhibitor selectivity in assays but X-ray crystal structures failed to reveal the basis of this selectivity. Joint X-ray and neutron crystallographic studies have shown which active site residues play a role and how solvent displacement and H-bonding re-organization occurs prior to - or upon - SAC and SGC binding. Specifically, these observations highlighted the importance of residues 67 (Asn in CA II, Gln in CA IX) and 130 (Asp in CA II, Arg in CA IX) in selective CA inhibitor targeting.

Authors: KORUZA, Katarina; MAHON, Brian; BLAKELEY, Matthew; OSTERMANN, Andreas; SCHRADER, Tobias; MCKENNA, Robert; KNECHT, Wolfgang; FISHER, Zoe (European Spallation Source ERIC)

Presenter: FISHER, Zoe (European Spallation Source ERIC)

Session Classification: MLZ Users 2020 - Structure Research

Track Classification: UM: Structure Research