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## Using neutrons to elucidate the molecular details of enzyme isoform selectivity by small molecule inhibitors.

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Human carbonic anhydrase IX (CA IX) expression is activated by hypoxic condition in aggressive, metastatic tumors. Cancer patients positive for CA IX have generally a poor prognosis. CA IX has emerged as an important cancer target, but efforts to develop isoform selective inhibitors are complicated by the presence of 14 other CA isoforms that share high sequence and structural similarity. This leads to off-target inhibitor binding and side effects. Recent studies showed that saccharin (SAC) already shows some isoform discrimination, and that conjugating SAC to a glucose molecule (Saccharin-Glucose Conjugate, SGC) further improves the Ki against CA IX by 2-fold.

Ligand binding to proteins are mediated through numerous interactions, including: H-bonding directly and/or through intervening waters, electrostatic interactions with charged or polar amino acid side chains, metal coordination, energetic changes through water displacement, aromatic ring stacking, or other hydrophobic interactions. As neutrons scatter strongly from atomic nuclei of light atoms  $^1\text{H}$  (Hydrogen), and its isotope  $^2\text{H}$  (Deuterium), it is possible to use neutron protein crystallography (NPX) to “see” the light atoms and any interactions they are involved with. (e.g. H-bonds).

We used joint X-ray and neutron crystallography methods to determine the crystal structures of a CA IX mimic alone and in complex with SAC and SGC, respectively. Our analyses reveal the molecular details of solvent displacement upon ligand binding, the H-bonding between the ligands and the proteins, involvement of water-mediated H-bonds, and the remodeling of H-bonds to accommodate ligand binding. The structures and analysis also provide an explanation for the observed CA isoform selectivity of the ligand under study.

### Topic

Biology

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