Uncovering new ligandable sites in STEP (STriatal-Enriched protein tyrosine Phosphatase)

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PTPs (protein tyrosine phosphatases) are a family of enzymes heavily involved in cell signalling pathways, the dysregulation of which has been implicated in numerous diseases [1]. STEP (STriatal-Enriched protein tyrosine Phosphatase) is a PTP expressed in the brain, involved in motor control and cognition. STEP is a validated drug target for neurological disorders including Alzheimer's and Parkinson's disease, with both genetic and pharmacological inhibition of STEP shown to improve cognitive function and hippocampal memory [2,3]. Seven crystal structures of human STEP plus one of mouse STEP are currently available from the Protein Data Bank [4,5], two of which have bound allosteric small-molecule activators [6]. However, much remains to be discovered about the ligandability and potential for allostery at various sites in STEP, which would have tremendous implications for drug design to combat neurological diseases. In this work, we soaked STEP crystals with a variety of ligands, including small-molecule inhibitors previously shown to covalently target the conserved active-site Cys residue and block catalytic activity in other PTP family members, but untested with STEP [7,8]. The resulting high-resolution X-ray diffraction datasets and crystal structures reveal that, surprisingly, these inhibitors target a novel site involving a covalent bond to a different surface Cys that is unique to KIM-type PTPs such as STEP. Moreover, in other soaked structures, we observe a serendipitously bound endogenous metabolite under the catalytic WPD loop in the active site, whose biological relevance is not yet clear. Overall, our findings may have implications for uncovering previously unknown allosteric pathways and regulatory mechanisms in STEP.

Figure 1. Unforeseen new metabolite bound to the catalytic Cys and PTP Inhibitor III covalently bound to a new binding site.