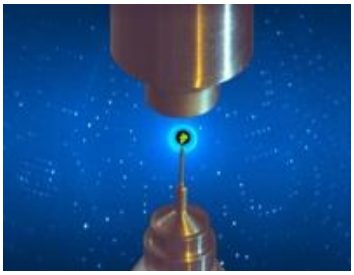

Contribution ID: **4** Type: **invited talk**

Neutron crystallography in the fight against COVID-19: Drug Design Targeting SARS-CoV-2 Main Protease

Thursday, 10 June 2021 15:30 (30 minutes)

COVID-19, caused by SARS-CoV-2, is a global health and economic catastrophe. The viral main protease (Mpro) is indispensable for SARS-CoV-2 replication and thus is an important target for small-molecule antivirals. Neutrons are an ideal probe to observe protonation states of ionizable amino acids at near-physiological temperature, directly determining their electric charges –crucial information for computer-assisted and structure-guided drug design. Our structures of Mpro collected at near-physiological temperatures revealed the reactivity of the catalytic cysteine, malleability of the active site, and binding modes of clinical protease inhibitors. Neutron crystal structures of ligand-free and covalent inhibitor-bound Mpro allowed direct observation of protonation states of all residues in a coronavirus protein. The catalytic Cys-His dyad exists in the reactive zwitterionic state, with both Cys145 and His41 charged, instead of the anticipated neutral state. Covalent inhibitor binding results in modulation of the protonation states, retaining the overall electric charge of the Mpro active site cavity. High-throughput virtual screening in conjunction with *in vitro* assays identified a non-covalent compound with micromolar affinity, used as a lead to design novel Mpro inhibitors. Our research is providing real-time data for atomistic design and discovery of Mpro inhibitors to combat the COVID-19 pandemic and prepare for future threats from pathogenic coronaviruses.

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