The big thaw: waters freed from cryo-cooling yield dynamic protein-ligand interactions

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Water molecules are essential for protein structure and function. Depending on differences in their position and energy, waters are either retained and reshuffled or displaced upon ligand binding. This information can be used productively in ligand discovery. High-resolution crystal structures can detect the importance of water networks in protein-ligand interactions. However, as these are typically determined at cryogenic temperatures, resulting insights into water organization may be structurally precise but not biologically accurate. By collecting matched room-temperature and cryogenic datasets of the biomedical target Hsp90a bound to fragments and drugs, we identified changes in water networks that impact protein conformational distributions at the ligand binding interface. Overall, this work reveals implications for the discovery of Hsp90 selective drugs specifically, and, more generally, for the utility of leveraging cryogenically hidden protein and water conformations in drug discovery.