Structural Science Awakens – with a splash of water to the (inter)face

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Water molecules play crucial roles in biology. However, as water energetics are difficult to characterize experimentally, they are often ignored in ligand discovery or computational approaches are used in lieu to approximate their contributions to ligand binding. Here we describe an experimentally-driven approach in which we utilize variable-temperature, high-resolution crystallography and calorimetry to characterize the contributions of individual water molecules to ligand binding. By probing water organization via a protein mutation, we show that water networks can make dominant contributions to ligand binding. Further perturbation of water networks with ligand modifications provides pragmatic insights into relative changes in the free energy of binding. Overall, the work highlights the importance of water molecules in understanding and designing protein-ligand interactions.