Regulation of protein-ligand binding affinity by hydrogen bond pairing

MOLECULAR BIOLOGY OFTEN deals with the mechanisms by which disease persists and harms the human body through interactions between pathogens and cells. One group of molecular biologists at Baylor College of Medicine in the US has long been examining these interactions, particularly in the context of Clostridium difficile, a bacterium that can cause severe diarrhoea and pseudomembranous colitis (inflammation of the large intestine). Associate Professor Tor Savidge has led research in this area for many years. More recently, the work he has undertaken in collaboration with Professor Deliang Chen has taken a surprising turn. In the past, the Tor Savidge Lab’s investigations have focused on the role of allosteric binding in disease processes. Allosteric binding is where a ligand binds to a site on a protein that is not its active site, but still prevents or facilitates the protein from functioning as it would otherwise. In one study, for example, the researchers looked at how chemicals in the body bound themselves allosterically with toxins produced by C. difficile to prevent their negative effects.

Investigations like this have big implications for the development of pharmaceuticals and medicine at the bedside. In a paper published in Science Advances, the researchers show that hydrogen (H), or H-bonds, regulate molecular interactions using a previously unknown mechanism.

H-bonds are behind a diversity of cellular functions because they are well-adapted to facilitate molecular interactions – but how exactly they regulate these interactions, and to what degree, has been a subject of scientific contention, because the H-bonding process competes with the abundant water found in biological systems. The donor-acceptor mechanism discovered by Chen and Savidge, however, provides guidance for the design of potent compounds by minimising competition with water. It also explains many observations previously made by experimenters by defining a novel parameter that now allows scientists to calculate the impact that water interactions have on biological processes.

By combining this discovery with their previous work, the investigators have been able to propose and optimise lead compounds targeting dietary melamine and C. difficile toxins through innovative drug design approaches that factor in interaction with water. These patented therapeutic solutions may be the first in a new wave of precision drug design that more deeply considers the environment in which drug-target interactions take place, and therefore achieve new pinnacles of efficacy, safety and cost effectiveness.

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**H-BOND PAIRING PRINCIPLE**

Strong binding and weak-weak H-bonding atoms form favourable interactions.

**ALLOSTERIC THERAPEUTICS**

Redesigned IP6(S) shows clinical efficacy by promoting structural changes that prematurely release the toxin warhead.