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Watermap Originates in Dehydron-Based Drug Design

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Drug-based targeted therapy demands skillful and subtle molecular design. The ease with which water may be locally removed from around the target protein provides a striking blueprint that steers the design process. To that effect, local de-wetting propensities have been mapped on the aqueous interface of the target proteins. These maps have served as precursors to WaterMap, now the gold standard in the field.

Molecular targeted therapy involves the design of small molecules that bind dysfunctional proteins that need to be functionally impaired for therapeutic purposes [1-3]. Drug optimization represents a major bottleneck in the discovery pipeline because the physical principles underlying drug-target affinity and selectivity are not fully understood; despite delusional remarks to the contrary [1-3].

Lead optimization has been increasingly influenced by the identification of labile water molecules at the interface with the target protein [4-7]. These molecules are expected to be displaced upon drug binding. The emerging design principle resulting from this simple observation was originally introduced in 2007 [4] in what constitutes a precursor to the WaterMap® software (Schrödinger, Inc.) [5,7]. Thus, the maps of "local de-wetting propensities" scanning the protein interface are regarded as epistructural blueprints for drug discovery [4,6], and in fact provide the guidance and inspiration to Water Map computations. The latter estimate the free energy cost associated with the transferring of water molecules from the protein interface to bulk solvent [7]. Thus, interfacial water molecules removed at a minimal thermodynamic expense [8] represent hot spots in the new drug-design blueprints.

The drug discovery process relies heavily on the engineering of drug-target interfaces representing associations with controlled affinity and specificity [1,7]. As noted in 2007 [4], labile hydration patterns in the target protein provide suitable "epistructural" (around the structure) blueprints. Thus, it has been shown that water becomes easily removable when found in the vicinity of certain packing defects in proteins known as dehydrons [1]. Dehydrons represent water-exposed backbone hydrogen bonds, and drugs may be optimized to expel dehydron-neighboring water upon association with the target protein [1,8]. Since dehydron patterns are not conserved across homologous proteins, dehydrons have become targetable features to control specificity, as recent forays in target deconvolution show [1].

After our solvent-centric approaches to drug design [4,8], the free energy cost associated with transferring water molecules from the protein interface to the bulk solvent became computationally accessible through the WaterMap® software [5,7]. Thus, the identification of labile water molecules at the interface, also known as "de-wetting patterns" [1,4], ultimately gave rise to an alternative computational strategy whereby "hot" water molecules were identified as those with a higher free energy content. Be as it may, the WaterMap concept of free energy content of a single water molecule is ill defined, since no thermodynamic ensemble may be associated with a single water molecule within the protein solvation shell.

Due to nanoscale confinement, water vicinal to dehydrons becomes frustrated in its hydrogen bonding coordination as it binds to the backbone carbonyl [1]. This is consistent with the "high free energy content" caused by the low entropy of confined water around backbone amides, as computed by WaterMap [5]. However, removing water from the vicinity of the dehydron stabilizes and strengthens the underlying hydrogen bond [8]. This is a favorably three-body effect (Figure 1), certainly not included in the WaterMap computation. More specifically, the three bodies are the amide, carbonyl, and the nonpolar group incorporated as the ligand is optimized to selectively remove interfacial water. In fact, the three-body effect contributes to lowering the free energy cost associated with displacement of the water molecule. The water-displacing moiety in the ligand can interact favorably with the two polar entities hydrogen bonded to each other [4]. Such three-body contributions are overlooked in WaterMap computations, notwithstanding the fact that they are of the same magnitude as the entropic gain associated with water transfer to bulk solvent [1,8].

The de-wetting propensity maps of 2007 [4] as well as the subsequent WaterMap software seek to introduce novel physical

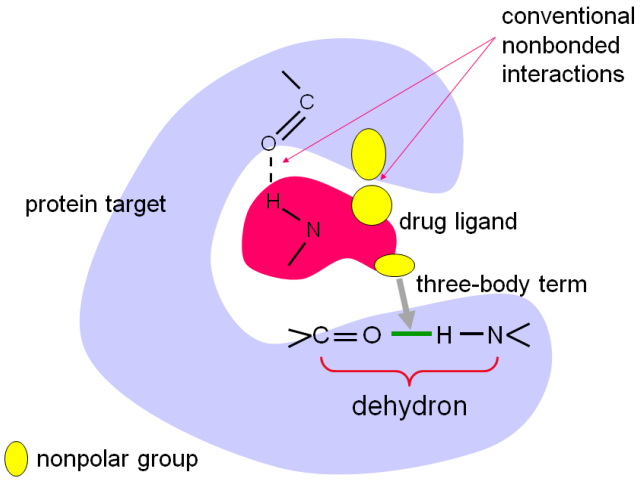

Figure 1. Three-body contribution in dehydron-based drug design.

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insights to rationalize design steps and improve the efficiency of the drug discovery process. As first noted in Fernández et al. [4] and developed subsequently [7], the exclusion of labile water molecules located at the interface with the target protein provides important cues for drug design. Water removal around target polar pairs is as important for drug design as engineering pairwise matches across the drug-target interface. These observations argue for the need to include advanced modeling, as originally provided by the maps of local de-wetting propensity, to improve drug design.

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