Identifying important interactions at protein hotspots.

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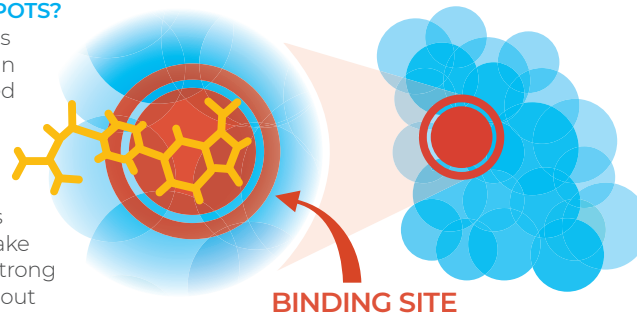
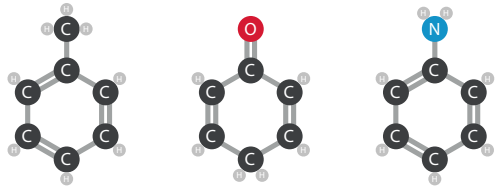
WHAT ARE PROTEIN HOTSPOTS?

Many drugs exert their effects by binding to proteins. Protein structures have pockets called binding sites where parts of molecular structures can bind to the protein.

Protein hotspots are regions within these pockets that make a large contribution to how strong binding is. Knowing more about them can aid drug design.

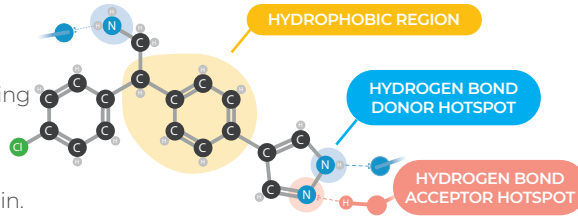




* Unstable in reality, but equivalent to the other probes for the purpose of this computational method

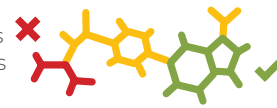
This study used three different molecular probes, shown to the left, to look for different favourable interactions on protein surfaces using computational methods. Protein regions were assigned a score based on how well the probes bound to them. The approach used was validated by comparison to previous data on 21 fragments, and effectively identified binding sites.

Several different interactions contribute to binding. This study maps interaction hotspot regions onto the protein. The highest scoring regions predict where fragments will bind. Molecules designed to better match the maps are likely to bind more strongly to the protein.



Why does this research matter?

Identifying important interactions for binding in protein hotspots can be useful for drug design, and could help medicinal chemists know how to structurally alter potential drug molecules.



Identifying interactions that determine fragment binding at protein hotspots.
C J Radoux, T S G Olsson, W R Pitt, C R Groom, T L Blundell,
J. Med. Chem. (2016), DOI: 10.1021/acs.jmedchem.5b01980

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