

Developing C-reactive protein modulators as new treatments for inflammation

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C-reactive protein (CRP) is present in blood plasma as a homopentamer (pCRP), with its production regulated by cytokines such as interleukin-6. Upon tissue injury, bacterial stress or inflammation, the level of pCRP in blood increases a thousand fold. pCRP can bind to a wide variety of ligands, including bioactive lipids with phosphocholine, phosphoserine and phosphoethanolamine headgroups. These lipid headgroups are exposed on bacterial cell walls, fungi and yeast upon infection and on apoptotic cell membranes. Binding of pCRP to the lipid headgroups triggers the dissociation of the pentamer into an unfolded monomeric version (mCRP)¹ and leads to inflammation involved in many pathologies such as atherosclerosis. We have designed a set of compounds mimicking the binding of phosphocholine to pCRP, thereby blocking lipid binding and preventing the dissociation that onsets inflammation. The direct interaction of the compounds with pCRP was verified using differential scanning fluorimetry, microscale thermophoresis and surface plasmon resonance. The binding mode of the compounds was determined using X-ray crystallography and electron microscopy. The best phosphocholine mimetic had an affinity (K_D) of 105 μ M for pCRP and it was subsequently tested in ELISA assays, along with a variety of *in vitro* and *in vivo* models of inflammation. The iterative discovery pipeline (Figure 1) includes a range of biophysical assays to identify pCRP ligands that may ultimately serve as the basis for future drug development.

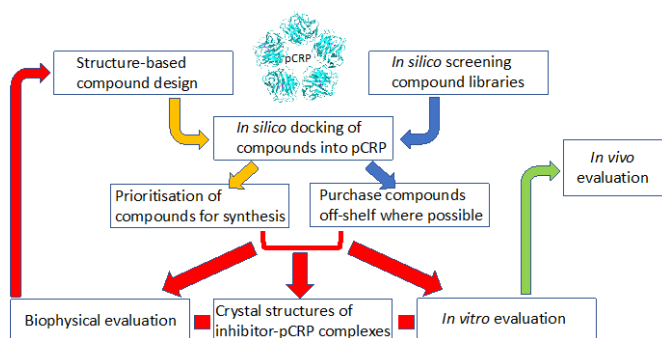


Figure 1: Schematic of the pipeline used for identifying and developing small molecule modulators of pCRP

1 Braig, D. *et al.* Transitional changes in the CRP structure lead to the exposure of proinflammatory binding sites. *Nat Commun* **8**, 14188, doi:10.1038/ncomms14188 (2017).