[L1] From target validation to proof-of-principle studies in man: novel approaches to the treatment of Pulmonary Arterial Hypertension

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Drug discovery is a multi-parameter optimisation process. Finding relevant drugable targets, discovering starting points for lead optimisation and creating novel chemical structures with appropriate biological properties within these constraints is challenging.

I will discuss two complimentary studies, both involving drugable G-protein coupled receptors (GPCRs): 5-HT1B and Apelin, which we believe are valid therapeutic targets for PAH (Pulmonary Arterial Hypertension), a severe condition that often results in heart failure and early death.

As an example of a small molecule drug optimisation strategy, recent work on 5-HT1B antagonists is put in the context of the drugability of the target, the desired physicochemical properties of the designed molecules and approaches to compound optimisation to create high affinity, selective molecules that are aimed at having low central nervous system (CNS) penetration. In tandem, we have also pursued a complimentary approach to treat PAH, developing biased Apelin receptor agonists (potent vasodilators with inotropic properties), which are small peptides. Peptides have very different criteria as potential drugs or as probes of therapeutic potential (compared to small molecules) but as a proof of principle, these have been progressed to studies in man, supporting our subsequent design of small molecule biased Apelin agonists for the treatment of PAH.

Significant input from computational studies including simulation, structure activity studies, pharmacophore elucidation and ADMEt prediction have accelerated the design process and enabling discovery of suitable molecules while gaining a deeper understanding of their biological mechanisms.