Bicycles® (bi-cyclic peptides) as novel therapeutics to treat antimicrobial infection

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Bicycles are formed by constraining short linear peptides into a stabilized bi-cyclic structure using a central chemical scaffold. This constraint confers attractive drug-like properties, including the potential for high affinity to the designated target. It also allows the peptides in the two loops to adopt biologically relevant secondary and tertiary structures, such as alpha helices and loops – these are features often found in proteins and protein ligands, allowing Bicycles to effectively mimic protein-protein interactions.

A unique phage display-screening platform has been developed which allows rapid identification of Bicycles specific for potential high value therapeutic targets. The platform has been optimised over many years to be efficient, allowing tuning of the development of these Bicycles to precisely address each specific therapeutic application.

There are many examples of bicyclic peptides among marketed antibiotics and given the current urgent need for new antibiotics this suggested that Bicycles would be a modality well suited to deliver new agents.

The identification of Bicycles binding to Penicillin Binding Protein 3 (PBP3) of e.coli will be described as well as preliminary structure activity relationships. Strategies to deliver the Bicycles across the outer membrane of gram negative organisms, thus allowing potent antibacterial activity in wild type organisms will be outlined [1] and illustrated by the profile of a lead compound

[1] James M. Wagstaff, Matthew Balmforth, Nick Lewis et al , *ACS Infect. Dis,* **2020**, 6, 9, 2355–2361