A novel combinatorial platform for rapid selection and characterisation of different cyclic peptide stuctures against a wide range of protein targets

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Ligands based on cyclic peptides can combine favourable properties of proteins (good binding affinity and target specificity) and small molecule ligands (high stability, access to chemical synthesis, good diffusion properties), and are therefore suitable molecular structures for the development of therapeutics. Toward this goal we have recently developed a novel combinatorial platform to rapidly isolate and select different cyclic peptide binders against a wide range of protein targets. The platform allows screening of $>10^8$ molecules/hr and enables both engineering and characterisation of multiple biochemical properties concomitantly, including binding affinity, specificity, and stability. Moreover, the designed system is complementary to other existing in vitro high-throughput platforms and appears to be compatible with protein targets provided either in a soluble or in a cell membrane embedded form. Notably, isolated cyclic peptide binders showed binding affinities ranging from picomolar to low micromolar and they are specific for the targets of interest as they only weakly bind other similar proteins. Finally, X-ray structure determination of a cyclic peptide in complex with its respective target revealed the presence of large interaction surfaces, multiple hydrogen bonds and complementary charge interactions, thus explaining its high affinity and specificity.