Rational development of bicyclic peptides targeting the Grb7 cancer target

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The design of potent and specific peptide inhibitors to therapeutic targets is of enormous utility for both proof-of-concept studies and for the development of potential new therapeutics. Here we describe the development of a specific inhibitor of the Grb7-SH2 domain involved in cancer progression. Grb7 is an adapter protein, aberrantly co-overexpressed with erbB-2 and identified as an independent prognostic marker in breast cancer. Grb7 signals the activation of erbB-2 which plays a key role in disregulated cell growth in cancer. Grb7 also mediates signalling from focal adhesion kinase (FAK) exacerbating cell migration and the metastatic potential of cells. It is thus a prime target for the development of novel anti-cancer therapies.

We have structurally characterised a cyclic peptide (G7-18NATE) that is a specific inhibitor of Grb7 and inhibits cellular growth and migration in cancer cell lines[1]. Based on this we have developed a series of second generation bicyclic peptides that show enhanced affinity and maintained specificity for the Grb7-SH2 domain as analysed using SPR[2]. Interestingly, X-ray crystallographic structural studies revealed an unexpected binding mode resulting in inhibitor redesign[3]. We have also developed cyclic peptides that incorporate carboxymethylphenylalanine and carboxyphenylalanine as phosphotyrosine mimetics, and shown using X-ray crystallography the way in which this also contributes to improved binding[4]. Finally, we have shown that by combining these two strategies we are able to achieve peptides with affinities in the nM range that still maintain target specificity.

References
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