

**P018** Determining the ligand binding selectivity for the parathyroid hormone receptors

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Parathyroid hormone receptor 1 (PTH1R) and PTH2R are members of the family B G protein-coupled receptor superfamily. The PTH1R is important in regulating mineral metabolism and bone turnover. Although PTH1R and PTH2R have over 50% identical sequences, they differ in terms of ligand binding and activation. PTH will bind to and activate both receptors, however PTHrP is very poor at both binding and activation at the PTH2R whilst being a full agonist at the PTH1R. Phe23 in PTHrP has been shown to be responsible for its binding selectivity between the two receptors, while His5 is responsible for the selectivity in activating the receptors.

The aim of this work is to determine the receptor residues responsible for determining PTHrP binding selectivity. Phe23 in PTHrP has been cross-linked to the PTH1R between residues 23-40, so it is assumed that the residue(s) responsible for determining binding selectivity are within this region. We have constructed a chimeric receptor consisting of the body of the PTH1R with residues 23-43 from the PTH2R. This receptor was shown to have increased selectivity for binding PTH over PTHrP, and [<sup>23</sup>Trp]PTHrP over PTHrP compared to the wild-type PTH1R. Further mutagenesis has narrowed down the motif responsible for this selectivity, suggesting a contact with the ligand at residue 23.