Design and synthesis of novel antagonists at family B G-protein coupled receptors

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G-protein coupled receptors (GPCRs) represent the single largest target for current therapeutic drugs. GPCRs are divided into several families; the largest of these is the A-family and medicinal chemists have had great success in designing drugs to act on this family. However, the family B includes many attractive therapeutic targets but it has proved far harder to design agents that act on these receptors. A small number of family B GPCRs form a complex with a family of accessory proteins called RAMPs (*1*). These include receptors for CGRP, adrenomedullin and amylin; important in migraine, regulation of blood pressure/blood vessel growth and diabetes (*2*, *3*). It has proved possible to develop CGRP antagonists and these are in clinical trials for migraine. Importantly, the antagonists interact with both the extracellular domains of the GPCR (CLR) and the RAMP (RAMP1) (*4*). A crystal structure now shows exactly how one of the antagonists (olcegepant), binds to these two proteins (*5*).

The project will take this structure and 1) understand how other CGRP antagonists (*6*) interact with it and 2) construct homology models of the adrenomedullin (CLR and RAMP2 or RAMP3) and amylin receptors (the calcitonin receptor in combination with all three RAMPs). Using this information, we will design antagonists that ought to bind with high affinity to these receptors. A selection of these will be synthesised and examined for biological activity.

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