

**P024** Expression of mammalian GPCRs in *C. elegans* generates novel behavioural responses to human ligands  
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GPCRs play a crucial role in many biological processes and represent a major class of drug targets. However, purification of GPCRs for biochemical study is notoriously difficult. *Caenorhabditis elegans* is a soil-dwelling, nematode that uses GPCRs expressed in chemosensory neurons to detect bacteria and environmental compounds, making this an ideal system for studying *in vivo* GPCR-ligand interactions. We sought to test this by functionally expressing two medically important mammalian GPCRs, somatostatin receptor 2 (Sstr2) and chemokine receptor 5 (CCR5) in the gustatory neurons of *C. elegans*. Expression of Sstr2 and CCR5 in gustatory neurons allow *C. elegans* to specifically detect and respond to somatostatin and MIP-1 $\alpha$  respectively in a robust avoidance assay. We demonstrate that mammalian heterologous GPCRs can signal via different endogenous G<sub>a</sub> subunits in *C. elegans*, depending on which cells it is expressed in. Pre-exposure of GPCR transgenic animals to its ligand leads to receptor desensitisation and behavioural adaptation to subsequent ligand exposure, providing further evidence of integration of the mammalian GPCRs into the *C. elegans* sensory signalling machinery. In structure–function studies using a panel of somatostatin-14 analogues, we identified key residues involved in the interaction of somatostatin-14 with Sstr2. Our results illustrate a remarkable evolutionary plasticity in interactions between mammalian GPCRs and *C. elegans* signalling machinery, spanning 800 million years of evolution.