Nature Reviews Drug Discovery | Published online 2 Feb 2017; doi:10.1038/nrd.2017.6

RECEPTOR PHARMACOLOGY

Picking the pocketome for orphan receptor ligands

G protein-coupled receptors (GPCRs) are a well-established class of drug target, but several members of this family, so-called orphan GPCRs, remain pharmacologically intractable owing to lack of knowledge about their cognate ligands or their structures. Now, Ngo *et al.* report a new approach to classify GPCRs according to receptor binding site characteristics and use this method to identify surrogate ligands for the orphan receptor GPR37L1.

Loop Images Ltd/Alamy Stock Photo

Attempts to rationally identify orphan GPCR ligands involve looking for similar and well-characterized GPCRs that have established ligands, but defining receptor similarity is challenging. Previous attempts have relied on receptor sequence homology (such information is available for orphan GPCRs), but this property is not always predictive of pharmacological similarity.

In the current study, the researchers used detailed crystallographic information that is available for 27 well-characterized GPCR–ligand complexes (which collectively represent the GPCR 'pocketome'), focusing in particular on the persistence and strength of interactions between amino acid residues in the receptor binding pocket and the ligand. They calculated a 'fingerprint' of ligand contact strength for each receptor.

Next, the authors used this information to calculate the similarity of pairs of GPCRs based on important binding site residues. They termed this method contact-informed neighbouring pocket, or 'CoINPocket'. When applied retrospectively, the method successfully identified numerous GPCR pairs with known pharmacological similarities.

Having validated the CoINPocket approach in well-studied GPCR pairs, Ngo *et al.* turned to the more challenging area of orphan GPCRs. They found that the CoINPocket score correctly predicted pharmacological similarity between CXCR4 and the now deorphanized ACKR3, which are two phylogenetically distinct chemokine receptors that share the endogenous ligand CXCL12.

Importantly, the team were able to use this method to identify pharmacological neighbours of the orphan receptor GPR37L1. This receptor was initially classified as an endothelin receptor-like protein owing to sequence similarity with the endothelin receptor, but was subsequently found not to bind endothelin.

CoINPocket scores showed that GPR37L1 clusters closely to the receptors for bombesin, orexin and neuropeptide S (NPS). Using a luciferase reporter assay in HEK293 cells transfected with GPR37L1, the researchers tested eight orexin receptor antagonists, one bombesin receptor antagonist and one NPS receptor antagonist for activity at the orphan receptor. Two orexin receptor antagonists and the NPS receptor antagonist were confirmed to be specific surrogate ligands for GPR37L1, representing a 30% success rate in using CoINPocket to identify orphan receptor hits.

The authors suggest that this approach could be transferred to other receptor classes and should help to improve understanding of orphan receptor biology as well as guiding the selection of ligands for drug development.

Katie Kingwell

ORIGINAL ARTICLE Ngo, T. *et al.* Orphan receptor ligand discovery by pickpocketing pharmacological neighbors. *Nat. Chem. Biol.* **13**, 235–242 (2017)