

Multiple Spectroscopies Reveal Dynamic Oligomerization of Functionally Active GPCRs

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G protein-coupled receptors (GPCRs) play a pivotal role in cellular signalling, highlighted by the fact that they form the target for ~40% of marketed pharmaceuticals. While evidence has been accumulating for the existence and functional significance of GPCR oligomers, the matter is still under debate, in part due to lack of consensus on morphological aspects, such as the receptor interfaces involved in oligomerisation, and their possible dynamic nature [1].

Neurotensin receptor 1 (NTS1) is one of few GPCRs that can be produced in *E. coli* in an active state, and has been implicated in a variety of conditions including schizophrenia and various cancers. NTS1 has been demonstrated by us to show lipid dependent functionality [2-5] and dimerise in lipid bilayers [6], however, there is still no structural or dynamics information on the receptor dimer.

Here, we combine single-molecule [5], and ensemble FRET, DEER, and *in silico* approaches to probe NTS1 dimerisation. The results support the presence of a concentration-dependent dynamic equilibrium between monomers and dimers, which could provide a means of regulation of receptor signalling and biased coupling *in vivo*.

[1] Ferré et al. (2014) *Pharmacol Rev* 66;

[2] Oates et al., (2012) *BBA – Biomembranes*, 1818:2228-2233.

[3] Adamson & Watts (2014) *FEBS Letts*, 588(24):4701–4707

[4] Dijkman & Watts A. (2015) *BBA – Biomembranes*, 1848(11):2889-2897

[5] Bolivar et al. (2016), *BBA – Biomembranes*, 1858(6):1278–1287

[6] Harding et al. (2009) *Biophys J* 96:964-973