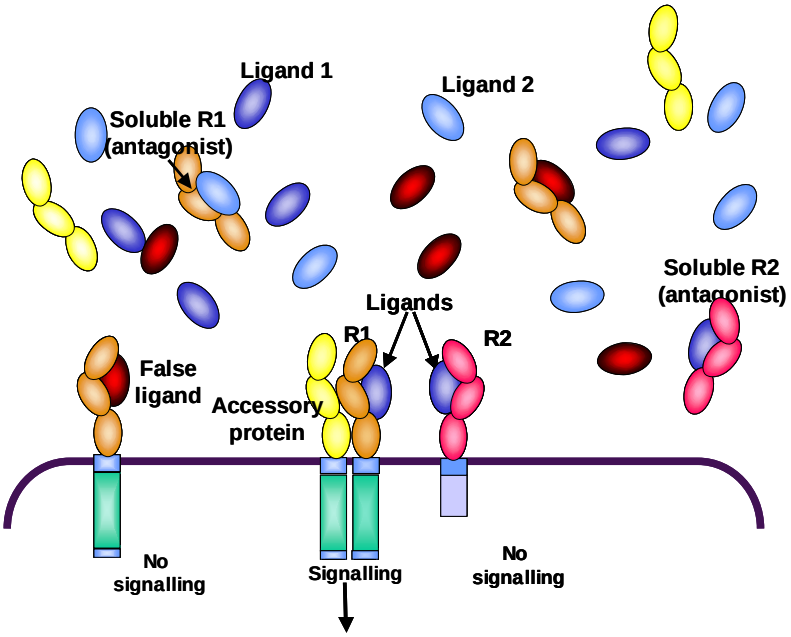
Anti-receptor antibodies: is it better to displace the dummy ligand?

Monoclonal antibodies have the potential to be excellent therapeutic proteins; it is possible to optimise the antibody to only bind the designated target, reducing the off-target side effects common to small molecule drugs. The ability to more precisely design the binding of the antibody allows work to be performed determining the optimal mechanism before the antibody is produced.

The schematic below shows a (simplified!) arrangement of one example target system: it has two ligands and two receptors, only one of which is capable of completing the signal (requiring a further accessory protein) if it is membrane-bound, with any soluble forms only "mopping up" spare ligand. Furthermore, there is an endogenous antagonist of the receptors – a dummy ligand if you will.



Suppose that we wish to target the membrane-bound receptor in such a system. The dummy ligand can often be a critical determinant of the behaviour of the entire system due to its abundance and variation in response to disease. This poses an interesting problem with respect to an anti-receptor antibody: is it better for the antibody to displace the dummy ligand when it binds the receptor, or to bind a distinct part of the receptor and still allow the dummy ligand to function? One might imagine that this can be ascertained *in vitro*: add either mechanism of antibody to a mixture of receptor and dummy ligand, and measure which leaves the least free receptor. Aside from requiring antibodies of both mechanisms, it has been a feature of antibody programs that the turnover of the target proteins is a key determinant of the effect of the antibody and so *in vitro* assay, as a steady-state system, can be misleading.

We would like the Study Group to build a model for a system of a ligand, dummy ligand and signalling and dummy receptor, with an anti-receptor antibody, and considering the turnover of the proteins. We would like the Group to determine whether either mechanism is advantageous and, if so, under what circumstances and how this relates to *in vitro* measurements of the system.