SCALABLE APPROACHES TO FRAGMENT SCREENING OF FULL-FUNCTIONALLY GPCRS

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G-protein coupled receptors (GPCRs) are the primary class of drug targets with approximately 30% of all approved medicines targeting these receptors. In recent years there has been a renaissance in GPCR drug discovery, which has been driven the advance of structural biology and biophysical techniques to the analysis of this challenging class of membrane proteins. However, in order to develop proteins suitable for structural biology, receptors are often stabilized by point mutations to restrict conformational flexibility and thus 'lock' the receptor into one conformation, resulting in a loss of the pharmacological function. In contrast, 'wild type' receptors are capability of the full pharmacological function by virtue of their ability to explore the full range of conformational space. Therefore, biophysical screening methods against the wild-type receptor would be advantageous. Surface plasmon resonance (SPR) is a label-free, biophysical technology that enables measurement of direct binding of compounds to proteins in real-time. SPR analysis enables a full kinetic profile, including k_{on} and k_{off}, can be obtained for each compound and the technology has the sensitivity and throughput to enable screening of small fragment libraries. Expressing, purifying and capturing sufficient levels of active wild-type GPCRs to develop SPR assays routinely is challenging. In this presentation we will present our latest results demonstrating of a scalable method for the successful development of SPR assays to a wide range of wild-type GPCRs and exploit these assays for fragment screening and kinetic characterisation to discovery novel ligands.