Strategies & Tools to Develop a Better GPCR Targeted Therapeutic

By Lisa Minor

GPCRs are one of the most pharmacologically successful drug targets with 26% of all drugs against this class[1]. GPCR-targeted therapeutics continues to be successful and in fact, 19% of newly approved drugs target GPCRs. The early generation of small molecule drugs targeted either orthosteric agonist or antagonist activity of these receptors' G-protein signaling pathway.

In recent years, we have discovered more about GPCRs including crystal structures, improvements in ligand design, differences in the signaling pathways and as well as how these receptors dimerize. The increase in understanding of GPCR signaling pharmacology comes about in part from better and more sensitive screening assays. From these tools we have learned that GPCRs are much more complicated than had been believed and hence much more interesting and potentially more valuable as drug discovery targets. Evidence shows that GPCRs signal through β-Arrestin in addition to G-proteins and that ligands can trigger biased signaling in one direction or the other[2]. This can have a therapeutic advantage such as the case of TRV-120023 in a heart failure indication, as this selective molecule against the Angiotensin-1 receptor (AT1R) can not only reduce blood pressure but also positively affect heart failure. Other ARBs (angiotensin receptor blockers) did not show this effect. The reason appears that TRV-120023 can block the effect of endogenous Angiotensin II while promoting cardiac contractility. Unlike its competitor ARB, Losartin, TRV-120023 activates MAPK and AKT signaling through the β-Arrestin pathway[3]. This type of signaling bias has obvious therapeutic ramifications and as a result, it appears that an important strategy would be to identify molecules that have selective patterns of signaling to see how they affect the desired pharmacology. This has the advantage of providing a molecule that may be efficacious toward the disease with reduced side effects due to the alternate signaling pathways.

An additional strategy is to identify allosteric modulators of GPCR's[2,4]. Positive allosteric molecules have an advantage that they only work in the presence of the native ligand thus amplifying the ligand's effect while having no activity on its own. Demonstration of potential therapeutic benefits of allosteric molecules and liabilities of screening strategies is seen with mGLUR5[5]. In this case, allosteric modulators of mGLUR5 were identified using a cell line transfected with an abundant amount of mGLUR5 receptors. These compounds were shown to have a liability of causing seizures in animals. However, when retested in a lower expressing cell line and native cells, it was possible to differentiate compounds that were allosteric agonists from those that were positive allosteric modulators. The allosteric modulators no longer demonstrated seizure liability while demonstrating effectiveness against the targeted therapeutic indication, schizophrenia. Negative allosteric modulators are also relevant against receptors that have native constitutive activity.

A critical necessity for taking advantage of the multiple signaling paradigms of GPCR's is to have the ability to measure them in robust functional assays in cells with the correct receptor expression and across appropriate orthologs to detect selectivity. A robust functional platform for the majority of GPCRs exists at Multispan. We have the capacity to measure and evaluate signaling bias as well as to test for positive and negative allosteric modulators. We have also retained the ability to measure traditional GPCR features such as ligand-receptor binding. We leverage our expertise by providing off-the-shelf products such as cell lines with validated assays, custom cell line generation with specific receptor expression profiles and assay development with the target of your choosing. In addition our screening services can help you jump start your program by using us as your assay development and screening team. With our help, we can move your programs rapidly from hit identification to hit-to-lead. In addition, we can continue working with you to optimize your compounds through lead development by testing in the primary screen, orthologs/paralogs GPCRs and GPCR safety liability panels specifically designed for your program. We have achieved a 100% return customer rate over our 10 years of business and pride ourselves on excellence. Let us be your GPCR drug discovery arm.

References:

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