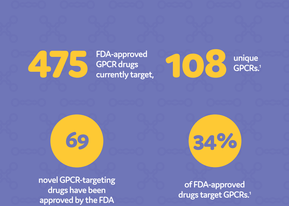
G PROTEIN-COUPLED RECEPTORS IN DRUG DISCOVERY

Analyzing Current Trends, Novel Drugs, Targets, and Indications

G protein-coupled receptors (GPCRs) are the largest human membrane protein family. These receptors play a diverse role in numerous physiological processes and possess 'druggable' sites making them an attractive pharmacological target. It is estimated that up to half of all marketed drugs act by binding to GPCRs.[1,2] This infographic aims to summarize approved and novel drugs, GPCR targets, and indications.

GPCR STRUCTURE AND ACTIVATION[3]



GPCRs have seven hydrophobic transmembrane domains (yellow). In the presence of an agonist the inactive form (A) is 'stimulated' and the receptor conformation changes (B), altering its association with the alpha subunit (Gα) of the neighboring G protein. GDP is exchanged for GTP and the activated G protein alpha subunit dissociates from the beta and gamma subunits (dark purple). The dissociated alpha subunit and beta-gamma dimer are now able to diffuse laterally within the membrane, interacting with other proteins, stimulating cell signaling pathways.

475 FDA-approved GPCR drugs currently target, **108** unique GPCRs.[1]

69 novel GPCR-targeting drugs have been approved by the FDA in the past 5 years.[1]

34% of FDA-approved drugs target GPCRs.[1]

CURRENT STATE OF PLAY: NON-OLFACTORY GPCR FAMILY DRUG TARGETS[3]

DISEASE INDICATIONS: PAST, PRESENT, AND FUTURE

GPCR targeted-therapeutics are effective for a number of disease areas.

1 PSYCHIATRIC AND NEUROLOGICAL DISORDERS

Multiple Sclerosis · Alzheimer's Disease
Huntington Disease · Fragile X Syndrome
are all associated with GPCR neurotransmission

26% of all FDA-approved GPCR drugs target central nervous system (CNS) diseases.[1]

Did you know?
>70 potential GPCR agents are currently in clinical development for CNS diseases.[1]

>50% of all non-olfactory GPCRs are in the brain's cerebral cortex.

A multitude of psychiatric and neurological disorders are caused by incorrect GPCR mediated neurotransmission, making GPCRs a promising target for these conditions.[1,4]

2 METABOLIC DISORDERS

Diabetes Mellitus · Diabetic Neuropathy · Obesity

In 2005, the GLP1 receptor agonist, exenatide, was the first GPCR-targeted drug approved for Type 2 diabetes (T2D). Numerous other injectable drugs are now available including liraglutide, lixisenatide, and albiglutide.

Current therapeutics for T2D, and associated diseases, work by targeting 11 distinct GPCRs, another 25 potential GPCR targets are currently being explored in clinical trials.[1]

Several GPCRs located in the CNS, known to control feeding, may provide novel targets for the treatment of obesity.[5]

3 ONCOLOGY

21 FDA-approved anti-neoplastic GPCR drugs mediate their effects via 14 different GPCRs.[1]

Novel GPCR targets currently under investigation for the treatment of cancer include **Wnt signaling pathway proteins** and **chemokine receptors**.[1]

Did you know?
>20 GPCR agents are currently in clinical development as potential cancer treatments.[1]

Examples of approved anti-neoplastic GPCR drugs include:

Degarelix (Gonadotropin-releasing hormone (GnRH) receptor antagonist), approved for patients with advanced prostate cancer.

Vismodegib (Smoothened (SMO) receptor inhibitor) , approved as a treatment for basal cell carcinoma.

Sonidegib (SMO receptor inhibitor), also approved for the treatment of basal cell carcinoma.

Repurposing existing GPCR drugs is a smart way to reduce the time and cost of bringing a medicine to market, so it is not surprising that 33% of approved GPCR drugs are used for more than 1 indication.[1] A great number of non-olfactory GPCRs remain unexploited (>50%),[1] demonstrating that there may still be many potential targets for future therapeutics.

Recent advances in GPCR crystallography[6] have identified 44 novel GPCR structures and >200 ligand-receptor complexes are now presented across all classes of human GPCRs. The clear druggability of GPCRs and their intricate role in multiple disorders highlights the importance of driving drug discovery forward in this area.

References

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