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The present status of finding drugs based on GPCRs to treat metabolic diseases

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ABSTRACT :

Finding substances that alter the activity of GPCRs to increase or decrease signal transduction cascades in different cell types and tissues is one method used in current drug discovery. As a result of this approach, new medications have been created to treat a wide range of illnesses, such as mental health issues, HIV/AIDS, cardiovascular disease, some types of cancer, and Type 2 diabetic mellitus (T2DM). These achievements support the further investigation of GPCRs as disease targets and offer important insights that should aid in the development of new therapeutic drugs. This paper examines the state of GPCR drug discovery today, focusing on initiatives to create novel compounds for the treatment of obesity and type 2 diabetes. We examine past attempts to develop GPCR-based medications to treat metabolic diseases in order to identify the contributing variables that led to their success and failure in this attempt.

Keyword:cardiovascular disease;diabetes; cancer; HIV/AIDS; GPCR

Introduction

A vast family of heptahelical proteins that traverse the plasma membrane, known as GPCRs, have developed to convert extracellular signals into intracellular reactions (Lefkowitz, 2007). Many times, it is stated that 20–50% of medicines that are approved work in some way through GPCRs (Santos et al., 2017). To transduce signals, GPCRs often couple to two primary groups of intracellular effector proteins: β-arrestins and heterotrimeric G-proteins (Lefkowitz, 2007). According to Lefkowitz (2007), heterotrimeric G-proteins control well-known biochemical processes as cAMP production, phospholipase C activation, ion channel function, and small GTPase signaling. On the other hand, β-arrestins stimulate alternate signal transduction pathways such kinase cascades and desensitize GPCRs (Lefkowitz, 2007). The literature provides a thorough explanation of the nuances of canonical GPCR biology and signal transduction, and as such is outside the purview of this analysis. Members of the GPCR family exhibit selective responses to a very broad range of ligands, such as protons, photons, tiny chemical compounds, lipids, carbohydrates, peptides, and big proteins (Alexander et al., 2017a). Furthermore, a wide variety of GPCRs show preferential distribution across tissues, organs, and cell types. Unsurprisingly, a large number of distinct GPCRs have been studied as possible treatment targets for obesity, cardiovascular disease, and Type 2 diabetes mellitus (T2DM). In the hopes of offering guidance for upcoming initiatives, we assess the results of focusing on single GPCRs for T2DM and metabolic disorders in this study. This review is not designed to be comprehensive; rather, it is meant to highlight some of the topics we believe should be discussed.

Summary

Most people agree that GPCRs are the ideal target class to find new therapeutic agents and are very susceptible to drug development (Roth and Kroeze, 2015; Santos et al., 2017). According to the GRAFS (or Class) nomenclature, the GPCR phylogenetic tree represents five families of transmembrane receptors: glutamate (Class C), adhesion (Class B2), frizzled (Class F), and secretin (Class B1) (Alexander et al., 2017a). More than 400 olfactory receptors and over 300 possible drug-target receptors make up the GPCR-ome (Roth and Kroeze, 2015). About 150 of these 300 drug-target GPCRs are orphan receptors, meaning that no endogenous ligand has been identified for them. Biological function, protein structure, natural ligand, and other factors vary among the GPCR drug-target set druggability of each GPCR separately.

There are numerous pharmaceutical approaches to target GPCRs. Despite being clearly explained, these ideas are nevertheless important to list (see Table 1). In summary, agents that target the biology of GPCRs can work indirectly. For example, injectable antibodies can sequester the natural agonist ligand (as seen in the case of migraines; Dick et al., 2014). Alternatively, small molecules enzyme inhibitors can prevent the endogenous agonist from being degraded. Dipeptidyl peptidase-4 (DPP4) inhibitors can prevent the degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), respectively, and enhance the effects of GLP-1 receptor and GIP receptor activation (Ahren, 2007). Traditional gene therapy techniques like antisense and siRNA, as well as more recent techniques like CRISPR, have showed some promise, but One of the approaches' limitations has been the delivery of drugs One can categorize molecules that function by directly binding GPCRs into

two groups: orthosteric molecules, which bind in the same pocket as the natural ligand, and allosteric molecules, which bind in a different pocket. It is well known how orthosteric GPCR ligands work pharmacologically. An antagonist (such as histamine H1 receptor antagonists for allergies) works by preventing the natural ligand from stimulating a GPCR (Sadek and Stark, 2016). Agonists, like the β2-adrenoceptor agonists for asthma, imitate the endogenous agonist's cellular pharmacology (adrenaline in the case of the β2-adrenoceptor) and usually have a longer half-life. The identification and characterization of GPCR allosteric modulators have received a lot of interest lately. These compounds work together with the naturally occurring orthosteric ligand to enhance receptor signaling (positive can reduce receptor signaling (negative allosteric modulator) or inhibit it (positive allosteric modulator). These compounds usually function by maintaining specific receptor conformations and adjusting the effectiveness or affinity of an orthosteric ligand. As per Jensen and Brauner-Osborne (2007), cinacalcet is a PAM of the calcium sensing receptor that is used for the treatment of hypoparathyroidism. In terms of selectivity, mechanism and kinetics of action, and the capacity to modify receptors for which the orthosteric site looks undruggable using conventional methods, allosteric modulators provide a number of potential advantages over orthosteric compounds. Regretfully, only patchy clinical success has been reported to far with GPCR allosteric modulators. There are also more classifications of pharmacological ligands, such as biased, inverted, bitopic, and kinetically selective ligands, as well as partial agonists. It is outside the purview of this to discuss these this page, but the literature has thoroughly reviewed them.

The need for GPCRs in medicine for metabolic diseases

The prevention and treatment of the epidemic of type 2 diabetes, obesity, and associated co-morbidities is one of the most important medical needs of the twenty-first century (Zimmet et al., 2014). More than half a billion people are expected to develop T2DM by 2035. It is very likely that throughout the past century, nutritional and socioeconomic changes have contributed significantly to this epidemic. Given the scope and gravity of the impending issue, it is likely that an expanded toolkit for the pharmacological treatment of various illnesses will be required in addition to prophylactic measures. The development of novel therapeutic strategies must consider the fact that highly coordinated signaling networks connecting the enteric nervous system control glucose homeostasis and energy consumption the central nervous system (CNS). On the other hand, when an excessive caloric intake results in significant lipid accumulation and the development of obesity, the normal interaction between the systems regulating glucose disposal and energy expenditure may become dysregulated. Increased visceral fat inside the abdomen and ectopic lipid accumulation in non-adipose organs like the liver and skeletal muscle are the hallmarks of this illness. Increases in intracellular lipid content and intermediate metabolites such acetyl-CoA, DAG, and different ceramides are linked to the development of insulin resistance in obese individuals (Samuel and Shulman, 2016). Since muscle makes up the majority of the body's glucose usage, reduced insulin sensitivity in this tissue is especially harmful to overall glucose regulation. Moreover, decreased adipocyte insulin action stimulates lipolysis, which raises the availability of fatty acids for absorption through the liver. Due to the increased flux of pre-formed fatty acids, hepatic triglyceride synthesis is increased by re-esterification, and acetyl-CoA from fatty acid oxidation is elevated, promoting gluconeogenesis

and ultimately leading to overall hyperglycemia (Samuel and Shulman, 2016). Impaired glucose tolerance and type 2 diabetes eventually result if an increase in insulin secretion by pancreatic beta cells is insufficient to make up for it (DeFronzo and Tripathy, 2009). It is still unclear whether underlying genetic basis influences the beginning of T2DM and/or predisposes susceptibility to it. However, the majority of genetic loci linked to T2DM risk are involved with insulin production and pathways controlling pancreatic islet formation, which is consistent with the important physiological deficits that characterize the disease's course (Shungin et al., 2015). Additionally, it's becoming evident that genetic variation indicates a the brain's involvement in the risk of obesity as obesity is linked to genes that regulate the hypothalamic pathways that regulate energy expenditure and food intake (Shungin et al., 2015). These genetic results are consistent with other mounting evidence of a "brain-centered glucoregulatory system" that integrates the intricate regulation of glucose homeostasis through cooperation with islets (Schwartz et al., 2013). It should be possible to identify new therapeutic targets by defining the neural circuitry that supports glucose homeostasis, many of which may be GPCRs.

GPCR-targeted medication discovery: historical perspectives on type 2 diabetes and obesity

Both academic institutions and the pharmaceutical sector have made significant investments in basic science, target validation, drug discovery, and drug development related to GPCR-targeted pharmaceuticals. The molecular cloning of the β-adrenoceptor in 1986 foreshadowed the genomic era of GPCR discovery (Lefkowitz, 2007). As a result, multiple genes encoding GPCRs for hormones, neurotransmitters, and regulatory peptides—many of which had been proposed decades earlier—were identified. Numerous articles, patents, and clinical trials demonstrate how the present molecular biology toolkit for GPCRs has fueled drug discovery research toward the development of several experimental compounds for treating metabolic illnesses. We have compiled a top 20 list of what in order to streamline our investigation We consider these to be the most thoroughly investigated and historically promising GPCRs for obesity and type 2 diabetes that have been tested in people. Out of these, we also highlight in brief vignettes some of the most extensively studied GPCRs on the melanocortin MC4 receptor, the orphan receptor GPR119, the free fatty acid FFA1 receptor/(GPR40), the glucagon receptor, the β3-adrenoceptor, the cannabinoid CB1 receptor, and the glucagon-like peptide-1 (GLP-1) receptor.

Why is it so difficult to translate from mice to humans?

The primary counter-regulatory hormone to insulin, glucagon, was first identified pharmacologically in the 1970s (Rodbell, 1973). However, heterologous expression of this receptor was not achievable until the glucagon receptor was cloned in 1993 (Jelinek et al., 1993). This made it possible to conduct structure-function investigations and started the process of identifying antibody and small chemical antagonists (Pearson et al., 2016). Antagonizing glucagon receptors has the ability to lower blood glucose levels; however, studies in diabetic rodent models using glucagon receptor antisense oligonucleotides and glucagon receptor-null mice also showed that strong interference in this pathway causes compensatory alpha-cell proliferation in the pancreas (Sloop et al., 2004). In the end, a number of antibodies and tiny glucagon molecules Receptor antagonists were discovered to be potential anti-diabetic medications; some of these drugs even demonstrated efficacy in human studies (Pearson et al., 2016). It is unknown, nevertheless, if glucagon receptor antagonists will eventually be submitted

to and approved by regulatory bodies based on the overall benefit-risk analysis. One potential limitation of GCGR antagonists is that their impact on body weight may be limited to hyperglycemia. In this context, the β3-adrenoceptor was one of the first GPCR targets studied to lower obesity. According to Lowell and Bachman (2003), these receptors are found in brown (thermogenic) adipocytes in both humans and animals. Activating these receptors has been shown to increase energy expenditure, encourage weight reduction, and enhance insulin action. β3-adrenoceptor antagonists, like CL-316243, decreased food consumption and induced weight loss and enhanced insulin sensitivity in animals by stimulating lipolysis and thermogenesis (Susulic et al., 1995). The development of novel orally accessible β3-adrenoceptor agonists has been greatly stimulated by genetic evidence from obese T2DM humans (Walston et al., 1995) and β3-adrenoceptor knockout mice (Susulic et al., 1995). These findings promote in vitro and preclinical pharmacological studies. Nonetheless, research conducted in people using several β3-adrenoceptor agonists showed minimal impact on body weight, energy expenditure, and lipolysis (Larsen et al., 2002). The fact that β3-adrenoceptors are expressed only in brown adipocytes, which are comparatively rare in humans, as opposed to both white and brown adipocytes in rodents, may account for this lack of effectiveness (Ito et al., 1998). Additionally, rodent stimulation of β3-adrenoceptors Humans lack the effect that white adipose tissue has on stimulating lipolysis, which is required to drive the β-oxidation of fatty acids in brown adipose tissue (Lowell and Bachman, 2003). α-melanocyte stimulating hormone (α-MSH) analogues, which are derived from the proopiomelanocortin (POMC) gene, demonstrated comparable potential in preclinical investigations. They were found to inhibit food intake and stimulate energy expenditure in both dietary (DIO) and genetic, leptin-deficient rodent models of obesity and diabetes (e.g., ob/ob, agouti, and db/db mouse models) (Fisher et al., 1999). In fact, a certain population of brainstem and hypothalamus arcuate nucleus-containing POMC neurons is stimulated by the adipokine leptin to initiate POMC signaling (Berglund et al., 2012). The central nervous system's MC4 receptors are activated by α-MSH analogues, which has anti-obesity actions. In line with the outcomes of α-MSH analogue delivery, genetic null mutations of Severe obesity is caused by either POMC or MC4 receptors in both humans and mice (Tao, 2009). The effects of α-MSH treatment on weight loss in patients with POMC deficiency in humans are particularly intriguing (Kuhnen et al., 2016). Nevertheless, it is unclear how α-MSH analogs affect body weight in the overall population of obese patients (Krishna et al., 2009). Perhaps in human research, the negative effects on the cardiovascular system have proven dose-limiting. Future research should investigate whether α-MSH analogues with different pharmacokinetic properties can cause cardiovascular side effects to exhibit tachyphylaxis after repeated doses, the pharmacology of partial agonists, and whether or not PAMs can be used safely and effectively to modulate MC4 receptors in obese and type 2 diabetic patients.

The control of food intake is mediated by the endocannabinoid system body mass and metabolism in the periphery. Blockade of CB1 receptors reduces food intake and body weight and increases insulin sensitivity, according to genetic and pharmacological findings in humans and animals (Kang, 2013). The first CB1 receptor antagonist to reach the clinic and be approved as a new medication in Europe for the treatment of obesity and metabolic disorders was SR141716, also known as rimonabant (Lafontan et al., 2007). The enthusiasm surrounding this novel treatment for obesity, however, was short-lived as rimonabant caused serious neuropsychiatric side effects in clinical settings, leading to the drug's removal from distribution. Thus, rimonabant's clinical failure occurred due to unresolved safety concerns, despite the fact

that the genetic and pharmacological validation of CB1 receptor antagonists in the central nervous system for the treatment of obesity was effective demonstrated by preclinical research. Lately, in obese diabetic preclinical models, peripherally-restricted, non-brain penetrant CB1 receptor antagonists have shown promise (Hsiao et al., 2015). Therefore, the clinical development of a CB1 receptor antagonist for metabolic disorders may still be possible in the future.

Since the lysophospholipid receptor GPR119 is present in both pancreatic beta cells and the intestinal L and K cells, it has drawn a lot of interest as a potential new target for diabetes treatment. Important results demonstrating GPR119 agonists enhance insulin and incretin secretion and reduce body weight in mice, hence supporting the therapeutic potential of this receptor (Ritter et al., 2016). These results are consistent with a decrease in post-prandial GLP-1 secretion shown in investigations using Gpr119 null mice (Lan et al., 2009) GPR119 agonists have advanced into clinical studies at several businesses. None, nevertheless, have advanced into Phase II development as of yet (Kang, 2013). Although it is widely acknowledged that these substances are well tolerated, research has been stopped mainly because of their ineffectiveness non controlling blood sugar (Katz et al., 2012). These findings provide yet another illustration of the challenges associated with extrapolating rodent model success signals to human glucose reduction. It has been demonstrated that small molecule agonists of a similar GPCR, the long-chain fatty acid FFA1 receptor (previously GPR40), increase insulin production and decrease blood glucose in T2DM patients and diabetic rodents (Yashiro et al., 2012; Mancini and Poitout, 2015). In line with these findings, fatty acids' stimulatory effects on insulin secretion are lost in animals lacking the FFA1 receptor (Lan et al., 2008). Remarkably, a recent study demonstrates that FFA1 receptor agonists or potentiators can raise GLP-1 in obese rats to levels high enough to decrease food intake and body weight (Gorski et al., 2017). Clinical trials for a number of FFA1 receptor agonists have begun, with varying degrees of success. In Phase I trials, the early compound AMG-837 did not reduce glucose (Luo et al., 2012). In Phase III trials, TAK-875, an additional agonist, did, however, show persistent glucose decrease when used as a monotherapy (Mancini and Poitout, 2015). Unfortunately, TAK-875 is no longer being developed in the clinic because of a potential hepatotoxicity risk. Similar to glucagon receptor antagonists, the precise mechanism of action remains unknown despite significant efforts by the academic and industrial scientific community FFA1 receptor agonists will be submitted for regulatory consideration at this time. In conclusion, a wide range of issues can impede the development of preclinical ideas into fully developed medications that could be given to patients. These can include things like inexplicable lack of efficacy in the clinic, safety signals, non-translatable animal models, and commercial problems. It is helpful to look at the GLP-1 receptor agonists as an illustration of successful GPCR drug discovery in contrast to this list of failures.

GLP-1 receptor agonist therapy has been a major success.

A foundational understanding of the glucose-regulatory functions of these peptides was provided by the discovery and characterization of the physiological actions of the incretin hormones, GIP and GLP-1, and their corresponding receptors (both secretin family members), in the late 1980s and mid-1990s (Drucker, 2006). The stage was set by this work for the clinical trials of many GLP-1 receptor agonists in the 2000s. Remarkably, preclinical and clinical studies describing GLP-1's capacity to improve glucose-dependent insulin secretion, control gastric transit, and

decrease food intake were the primary driving force behind the pursuit of these agents—rather than genetic research. Moreover, examinations of the documented Glp-1r null mouse lines have not shown significant physiological consequences from the receptor's absence (Hansotia et al al., 2004). GLP-1 receptor agonists were effectively created and are now ingrained in the current algorithm for treating type 2 diabetes (T2DM) since these drugs enhance glucose homeostasis and reduce body weight, despite the lack of "genetic validation" that is sometimes required as key proof. Given the etiology and progressive nature of type 2 diabetes, it is evidently desirable to be able to reduce energy intake and improve peripheral glucose elimination. The pleiotropic effects that GLP-1 receptor agonists produce by working on a variety of cell types and target tissues are a major factor in their effectiveness (Drucker, 2016). Likewise, a multitude of receptors and signal transduction pathways have the ability to modulate endogenous GLP-1 production, rendering it an essential site for pharmacological intervention Another effective class of medications is small molecule inhibitors of DPP4, the enzyme that renders incretins inactive. We won't go into depth about them here because they have been thoroughly reviewed in the literature. Exendin-4, a powerful GLP-1 receptor agonist extracted from the salivary gland of the Gila monster lizard (39 amino acids, 53% similarity with GLP-1) (Eng et al., 1992), is a powerful GLP-1 receptor agonist. The majority of the pharmaceutical development of agonists targeting the GLP-1 receptor has been focused on engineering strategies to prolong the pharmacokinetic properties of native GLP-1. Liraglutide, dulaglutide, and albiglutide are some of the analogues of GLP-1. All of these medications enhance glycaemic control and provide some degree of weight reduction, despite minor variations in the efficacy responses for these substances reported from different clinical trials. As a whole, this therapeutic class is well tolerated; nevertheless, rapid dose escalation is frequently limited because to the occurrence of nausea (Harris and McCarty, 2015). In large cardiovascular outcome trials for liraglutide, the benefit of GLP-1 receptor agonist therapy has been studied beyond reducing body weight and glycaemic management. These studies shown that liraglutide medication decreased the rate of myocardial infarction, stroke, and death from cardiovascular causes, which is consistent with improved overall cardiometabolic health (Marso et al., 2016). Moreover, liraglutide-treated high-risk individuals experienced decreased rates of cardiovascular events (Marso et al., 2016). Liraglutide 3.0 mg, a larger dose than the recommended 1.8 mg, was approved after studies shown its efficacy as an adjuvant therapy for weight management when used in conjunction with diet and exercise for this from the FDA. Undoubtedly, a significant advancement in the field of metabolic disease has been made with the proof that GLP-1 receptor agonism enhances cardiovascular results and has anti-obesity benefits in humans. The mechanism(s) by which this occurs is still a major subject of inquiry, even though it has been established that activation of GLP-1 receptors lowers body weight by decreasing energy intake as opposed to enhancing fat oxidation.

Investigating GPCR-based strategies to raise GLP-1 levels in circulation

The effectiveness of DPP4 inhibitors and direct acting GLP-1 receptor agonists in stabilizing endogenously produced GLP-1 has led to more recent efforts to enhance GLP-1 secretion from intestinal L cells and other incretins, like GIP from K cells. GLP-1 levels are markedly elevated after bariatric surgery, and the improvement in metabolic disorders that has been reported is believed to be partially attributable to these elevated levels (Jorgensen et al., 2013). Is it possible for medications that target the L cell directly to increase GLP-1 levels to levels reported during

bariatric surgery or to levels higher than those found with present therapeutics? Initially, attempts to target GPCRs expressed on the L cell produced potential GPR119 and bile acid TGR5 GPBA receptor. Positive results have not materialized for the GPBA receptor agonist SB-756050 or the dual FXR and GPBA receptor agonist INT-767, despite their advancement to the clinic (Hodge et al., 2013). The use of GPBA receptor agonists may be restricted because of on-target bad pharmacology, even though these drugs have demonstrated strong GLP-1 secretagogue activity and can enhance glucose management in animal models. They also appear to cause gallbladder filling. (Li et al., 2011). It has been proposed that intestinally limited GPBA receptor agonists can be used to mitigate undesired on-target pharmacology (Duan et al., 2015). Humans with T2DM have been studied for the effectiveness of the GPR119 agonist GSK1292263 (Nunez et al., 2014), although neither GLP-1 nor GIP levels were affected by this substance It helps patients' glycemic regulation. As previously indicated, certain agonists that target the FFA1 receptor cause the production of GLP-1, which offers a fresh approach to addressing the incretin system. Hauge et al. (2016) discovered that first-generation FFA1 receptor agonists, such as TAK-875, selectively act on islet beta cells and boost insulin production with no effect on GLP-1 secretion. This may be due to their selective coupling to Gαq signal transduction pathways. Newer classes of FFA1 receptor agonists, on the other hand, appear to couple to both the Gs and Gq pathways, increasing GLP-1 secretion (Hauge et al., 2016). This makes these compounds far more appealing as potential therapeutic agents. The attraction of this kind of medication may be increased by the possibility that FFA1 receptor agonists will promote enough GLP-1 secretion to help with weight loss of the molecule. Lengthy-chain and ω-3 fatty acids also activate a similar receptor, FFA4/GPR120. In addition to causing anti-lipolytic, insulin-sensitizing, and anti-inflammatory effects via acting on adipose tissue and macrophages, activation of FFA4 receptors causes GLP-1 release from the L-cell in rodents (Oh et al., 2014). Though a lot of work has gone into creating FFA4 receptor agonists, it doesn't seem like any have advanced to the point of clinical testing. Proof that simultaneous activation of FFA1 and FFA4 receptors has dual glucose-lowering and insulin-sensitizing effects in animal models has led to the advancement of an intriguing notion (Oh et al., 2014; Satapati et al., 2017). A dual FFA1/FFA4 receptor agonist has been suggested to be a very excellent anti-diabetic medication because it affects a number of important physiological systems and tissues, including macrophages, adipocytes, beta cells, and L cells, which are all considered essential for a successful antidiabetic agent. Inhibiting signaling pathways that adversely affect GLP-1 release is another possible strategy to raise endogenous GLP-1 concentrations. Due to its ability to block GLP-1 release, the hormone somatostatin is important in the gut. It has been demonstrated that blocking the somatostatin SST5 receptor increases GLP-1 secretion, lending credence to this theory (Farb et al., 2017). SST5 receptor antagonists have been reported by various groups; however, information from clinical trials assessing this mechanism in humans has not been made public. Additional initiatives to deep mine GPCRs expressed in the majority of entero-endocrine cell types have a number of possible novel targets to investigate separately or in combination have been revealed; the ultimate objective is to elicit a therapeutically significant increase in GLP-1 and other incretins that can resemble those observed in bariatric surgery.

A glimpse at GPCR drug discovery's future in metabolic disorders

Drug discovery is plagued by failure on every front. The estimate that more than 99% of initiatives started in preclinical industrial labs fail to produce new medications serves as an

example of this (Paul et al., 2010). This is typified by the success rate of developing medicines for T2DM for all target classes, not just GPCRs. Only four classes of novel target-engaged T2DM medications have been introduced in the last 30 years: oral PPARγ agonists (thiazolidinediones), injectable GLP-1 analogues and oral DPP4 inhibitors, injectable amylin receptor agonist pramlintide, and oral glucose reabsorption inhibitors (oral SGLT2 inhibitors). In our view, there isn't a clear-cut fix or miraculous remedy that can be used to transform the field of metabolic disease medication discovery using GPCRs.

As we wrap up this review article, we provide ten questions that summarize some of the most important aspects to take into account while starting and advancing a GPCR drug discovery campaign. These questions also serve to establish the current paradigm for drug development.

What validation target is it? Will activating the GPCR effectively address the intended pathophysiology? This can include a broad range of data, such as phenotypes of knockout mice, human genetic data, effective drugs in the clinic, and convincing results from preclinical models utilizing tool molecules. One notable example is the GLP-1 receptor, which is the most important GPCR therapeutic target for type 2 diabetes despite lacking significant validation features in human genetics or mouse deletion models.

Do preclinical models have predictive power? of medicinal effectiveness? If not, it will be challenging to find and create a medication. It is evident that certain GPCRs, like the GPR119 and the β3-adrenoceptor, exhibit strong effectiveness in rodents; however, this does not translate to curing human illness.

Will this be a safe approach? Because metabolic drugs are usually taken for an extended period of time, there is increased scrutiny about their safety. Target engagement is typically not as high in natural biological processes as it is in manufactured compounds. In certain situations, the supra-pharmacological activity of synthetic compounds may result in toxicity or unfavorable side effects. Strong clinical and preclinical efficaciousness were shown by ligands for the CB1 and GPBA receptors, respectively. Nevertheless, those efforts were abandoned due to safety concerns.

Is it possible in terms of technology? What is the likelihood that technical achievement? Exist any fundamental scientific issues that will never be resolved in a reasonable amount of time, such as those involving selectivity, potency, adsorption, metabolism, excretion, and toxicology?

Do target engagement and translational pharmacology have preclinical and clinical biomarkers? Have a way to demonstrate that the chemical is truly engaging the target if it moves forward into clinical development.

These initial five inquiries are primarily of a scientific nature and arise at the onset of undertakings. In order to get answers, organizations may frequently concentrate on these initial issues and carry out experiments.

How does the medication's effectiveness stack up against the current gold standard of care, which could be a biosimilar or generic drug?

What is the therapeutic landscape and how does the medication fit into the therapy paradigm? resemble in more than ten years?

Is it possible to create a strong position on intellectual property?

Is there a market for the novel medication? How likely is it all in terms of product cost, patent life, anticipated market, etc.?

Is it possible to produce efficacy evidence that would allow payers to reimburse the product? The previous standard for obtaining FDA approval for a medication is statistical significance. Nowadays, in order to receive reimbursement, pharmaceuticals must demonstrate a significant benefit to the healthcare system.

Although these unanswered concerns are more commercial and medical in nature and are frequently beyond the purview of a scientist specializing in GPCRs, it is nevertheless crucial to be aware of them in situations with limited resources.

Conflict of interest: none

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