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G-PROTEIN COUPLED RECEPTORS (GPCR) AS DRUG TARGETS

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ABSTRACT

Protein Coupled Receptors (GPCRs) are proteins extensively expressed, and they wind the cell membrane seven times (Salon, Lodowski and Palczewski, 2011 p. 902). GPCRs also respond to a wide range of stimuli which include lipids, peptides, and cations (Ghanemi, 2015 p. 115). GPCRs are seen as the target for non-oncology drugs.Therefore, precisely, GPCRs control the majority of pathways for signal changes, which are pertinent in cancer cells (Lappano and Maggiolini, 2011 p. 47). GPCRs are frequently hijacked by malignant cells given the fact that they control and crosstalk with critical pathways (Zhang, Scoumanne and Chen, 2010 p. 112).

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INTRODUCTION

G-protein Coupled Receptors (GPCRs) are proteins widely xpressed, and they wind the cell membrane seven times (Salon, Lodowski and Palczewski, 2011 p. 902). GPCRs also respond to a wide range of stimuli which include lipids, peptides, and cations (Ghanemi, 2015 p. 115). Recent studies have been able to predict that humans have approximately eight hundred GPCRs. These GPCRs can be categorized into five major phylogenetic families that are Adhesion, Secretin, Glutamate, Rhodopsin, and Frizzled/Taste2 families (Miao and McCammon, 2017 p. 328). Regardless of the family, GPCR are targets that are highly appealing for pharmacological manipulation by allosteric ligands, molecule compounds that are small in size, recombinant proteins, or antibodies (Lundstrom, 2009 p. 58). There are approximately forty-six GPCRs that currently serve as targets of drug used for management of a large number of diseases (Dunworth and Caron, 2009). These health complications include pain, alcoholism, hypertension, obesity, HIV, and psychotic disorders.

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On the other hand, this property leaves a variety of GPCRs as possible drug targets (Lappano and Maggiolini, 2011 p. 48). The medical as well as biological importance of GPCRs is currently well established and extensively documented. GPCRs critical regulatory elements in the body in a wide variety of processes that is normal and pathological as it plays different roles in the tissues and cells in the body (Zhang, Scoumanne and Chen, 2010 p. 113). Similarly, the extent of the distribution of GPCR across almost all of the body tissues and organs also makes it able to accomplish most of its roles (Jiang and Bajpayee, 2009, p. 24). These qualities make GPCRs to continue being an essential element in focus in drug discovery and therapeutic opportunities. The super family of GPCR receptors functions in identification of an extensive array of chemicals which include hormones, nutrients, and odorants amongst others (New and Wong, 2007 p. 2). The receptors can respond only to a precise range of chemical arrangements given the fact that they have specialized domains which are ligand-binding in nature (Tuteja, 2009 p. 942). The distinctive property offers exceptional spots for high accord and precision to drug binding. The body widely uses the feature which restricts the GPCRs articulation to a narrow target tissues. The body uses this property to give room for highly precise inter-organ crosstalk (Reimann and Gribble, 2015 p. 231).

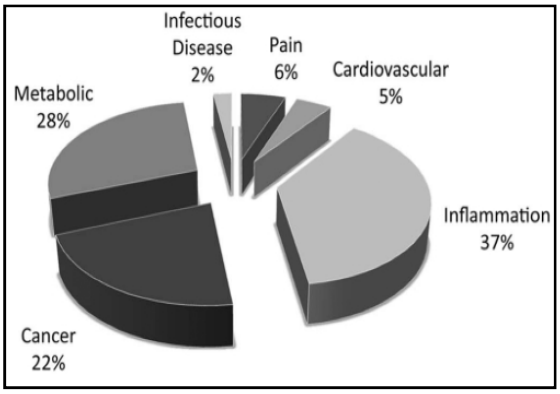

Figure 1. Opportunities for GPCR-targeted antibody therapeutics

Table 1. GPCR-targeted antibody candidates

Receptor target	Disease indication
C3aR	Asthma
FPRL	Alzheimer disease
(ALX-0651)	Cancer
(AT009)	Cancer
(HGS 004)	HIV
CCR2 (MLN1202)	Inflammation
GCG-R (AMG477)	Type 2 diabetes
VPAC-1	Thrombocytopenia
CXCR3 (AT0010)	Inflammation

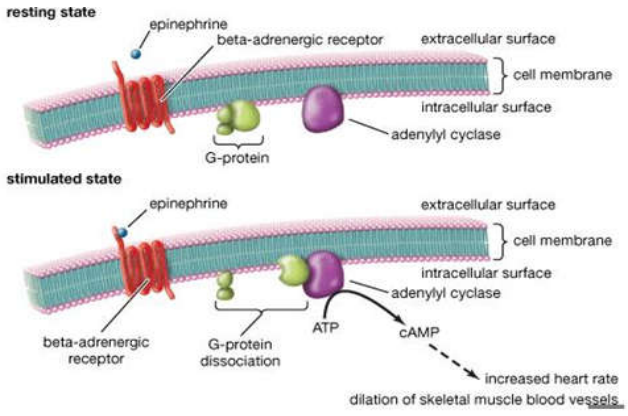

Figure 2. Epinephrine-stimulated cAMP synthesis

Table 2.Top selling drugs that target GPCRs (Schalop and Allen, 2017 p. 1)

Trade name	Generic name	Indication
Abilify	Aripiprazole	schizophrenia, bipolar disorders, depression
Seroquel	Quetiapine	bipolar disorders, neuro-degenerative disorders
Plavix	Clopidogrel	anti-clotting
Diovan	Valsartan	blood pressure
Zyprexa	Olanzapine	Schizophrenia
Singulair	Montelukast	Asthma

The new drug therapies that are GPCR-based utilize the cell explicitly of receptor expression to attain commencement of a chosen variety of target tissues (Research Features, 2017 p. 1). The drug therapies have an aim of fooling the body to believe that it has just eaten a meal. Consequently, it enhances secretion of glucose-dependent insulin hence reducing hunger (Lappano and Maggiolini, 2011 p. 50). Overtime, GPCRs search as targets for drug finding has been able to significantly benefit from the growth and acceptance of techniques that are high-throughput in the pharmacological evaluations and therapeutic chemistry (Venkatakrishnan et al., 2013 p. 186; Salon, Lodowski, and Palczewski, 2011).

The ease of access of these apparatus in combination with a GPCR objective palette has successfully given an opportunity to scientists to quickly monitor GPCRs of particular therapeutic concern (Du and Xie, 2012 p. 1110). Moreover, researchers have also been able to speedily give detailed analysis upon possible leads during the process of resulting drug development, thus starting revitalization in GPCR pharmacology (Research Features, 2017 p. 1).

Therapeutic Significance: The locality and function of GPCRs in the cell are some of the factors that determine the medical essence of GPCRs (Holliday, Watson and Brown, 2012 p. 5; Salon, Lodowski and Palczewski, 2011). The material position and nature of GPCRs offers an undeviating means for the conversion of extracellular communication into intracellular reply (Research Features, 2017 p. 1). Through this means while also because GPCRs live together with the effectors and the neurotransmitters, the GPCR system gets the ability to function in a way that it modulates a wide array of cellular phenomena (Salon, Lodowski, and Palczewski, 2011 p. 916). These events are controlled by the requirements of the served tissues and organs. The GPCRs are associated with joint biological actions which include the control of ion transportation crossways the plasma membrane, management of cell division or proliferation, modulation of neuronal firing, modulation of homeostasis, and cell morphology modification (Miao and McCammon, 2017 p. 330). In the instances that any of these essential processes go wrong, the results have the potential of leading into chronic or acute human diseases which can include asthma, cardiovascular disease and stroke amongst other conditions (Ghanemi, 2015 p. 118). Mutations in GPCRs are also linked to other diseases which include retinitis pigmentosa, infertility in females, and dominant and recessive obesity amongst other conditions.

Molecular Properties: The fundamental doctrine describing the first interaction of the receptor, GPC and the G protein, its proximal partner, is straightforward, regardless of the complexity of these elements (Schalop and Allen, 2017 p. 1). Nonetheless, the details net ailing the GPCR signaling in aggregate are complex. Immediately after the adoption of an "active," the intracellular domains within the GPCR interrelate with the G protein heterotrimeric complex, which is membrane-associated and GDP-charged (Salon, Lodowski, and Palczewski, 2011 p. 912). G protein then undergoes GDP or GTP exchange succeeding dissociation of G alpha and G beta subunits which then act together with precise downstream intracellular effectors systems (Zhang, Scoumanne, and Chen, 2010 p. 114). The activation of numerous heterocomplexes and cycling of the G alpha via active and inactive configurations through a hydrolysis cycle of the GTP gives room for immediate intensification and sequential regulation of the first signaling event of the receptor-ligand (McNeely, Naranjo, and Robinson, 2012 p. 1456). Through the desensitization process, there is blockage of the active conformation of the receptor while the agonist dissociation or deactivation leads to the attenuation of the signals (Kontoyianni, 2014 p. 39). The next activities of these effector systems are categorized into four primary segments. These segments include inhibition of the production of cAMP, stimulation of the creation of cAMP, activation of plasma membrane proton flux, and inhibition of the output of cAMP.

The Drug Discovery Process: The drug discovery process first begins with the ability to understand how GPCRs

function. The ability to understand GPCRs function processes is essential in the development of the appropriate drug (Smith, 2015 p. 6). It is necessary to realize that GPCRs survive in two dissimilar states which are the active and inactive states which bind the G protein (Lundstrom, 2009 p. 55). Given the fact that some drugs have the duty of stopping the receptors from working, they are often targeted to the inactive state (Hutchings et al., 2017 p. 793). On the other hand, some drugs have the obligation of activating the receptors and should hence be targeted to the active state (Congreve et al., 2012 p. 4283). However, the dynamic states of receptors are known to be less steady when compared to the inactive condition hence making it entirely complicated to decide their structures.

GPCRs, Desirable Therapeutic Targets in Oncology: GPCRs are seen as the target for non-oncology drugs. Drugs targeting GPCRs include both agonists and antagonists used in the treatment of diseases affecting nearly all the major organs systems in the body which has central nervous system (CNS), respiratory, cardiovascular, urogenital, and metabolic systems (Reimann and Gribble, 2015 p. 231).

GPCRs regulate an extensive range of cellular processes that are vital for cancer and are hence desirable targets for cancer drugs (Congreve et al., 2012 p. 4285). The cellular processes controlled by GPCRs include chemo-resistance, cellular proliferation, self-renewal, stress signaling, apoptosis, angiogenesis, immune evasion, invasion, and metastasis (Dunworth and Caron, 2009 p. 651). Therefore, precisely, GPCRs control the majority of pathways for signal changes, which are pertinent in cancer cells (Lappano and Maggiolini, 2011 p. 47). GPCRs are frequently hijacked by malignant cells given the fact that they control and crosstalk with critical pathways (Zhang, Scoumanne and Chen, 2010 p. 112). Analysis of the genomes of cancer indicates that there are mutations in GPCRs in about 20 percent of all cases of diseases. Also, G proteins are vulnerable to genetic alternation (Salon, Lodowski, and Palczewski, 2011 p. 905). Even though the case whereby GPCRs have been mutated are less when compared to other oncology pathways, there has been an increasing recognition that pharmacological engagement of GPCRs offers an opportunity to securely block different tumorigenic signals in spite of challenges in drug discovery (Insel et al., 2017 p. 183).

Molecular Mechanisms of GPCR Signaling: The canonical way for the modulation of molecular signaling occurs via orthosteric receptor effects using the direct interaction of ligand-binding or through restriction of accessibility to the region of ligand-binding of the receptor (Schirone et al., p 3; McNeely et al., 2012). The above is the means through which a large number of signal modulation is achieved (Seifert, 2005 p. 17). Nonetheless, currently, there has been an observation of some substitute mechanisms within a few membrane proteins that may contain broad applicability in drug targeting of the membrane protein (Reimann and Gribble, 2015 p. 231; McNeely et al., 2012). Allosteric ligands do not automatically have an effect on ligand binding at the orthosteric site through the binding site that is traditionally recognized (de Opakua et al., 2017 p. 163; McNeely et al., 2012).

Ligands have the power of modulating the pharmacological reaction to management by merging the impacts of ortho- and allosteric binding (Zhang, Scoumanne and Chen, 2010 p. 112). Hence, ligands fine-tune the impact associated with treatment by the use of signaling mechanism (Schirone et al., p 3). The nature of the approach also has the potential of taking alleviating side effects when they take advantage of the profiles of the membrane protein of the differential expression (Lundstrom, 2009 p. 53). Another factor that has been found to modulate the signaling in the receptors is the protein-protein interactions. Nonetheless, the proteins that are part of these interactions can be further modified by phosphorylation (Kontoyianni, 2014 p. 37).

Also, the lipid surroundings of the plasma membrane offer a line suggested to have the power of modifying receptor activity (Lappano and Maggiolini, 2011 p. 47). In conclusion, GPCRs are extensively expressed receptors in the cell surface and have been effectively subjugated for the management of a range of human illnesses (Dunworth and Caron, 2009). GPCRs represent proteins families which are targeted by the drug discovery process given the fact that they are crucial molecular sensors for various physiological processes (Salon, Lodowski and Palczewski, 2011). Currently, studies have been able to identify multiple GPCRs imperative for development and function in the lymphatic vascular. Therefore, GPCR provides therapeutic opportunities given the facts that they are known to be essential targets for drugs.

REFERENCES

Congreve, M., Langmead, C., Mason, J. and Marshall, F. 2011. Progress in Structure Based Drug Design for G Protein-Coupled Receptors. *Journal of Medicinal Chemistry*, 54(13), pp.4283-4311.

de Opakua, A., Parag-Sharma, K., DiGiacomo, V., Merino, N., Leyme, A., Marivin, A., Villate, M., Nguyen, L., de la Cruz-Morcillo, M., Blanco-Canosa, J., Ramachandran, S., Baillie, G., Cerione, R., Blanco, F. and Garcia-Marcos, M. 2017. Molecular mechanism of Gαi activation by non-GPCR proteins with a Gα-Binding and Activating motif. Nature Communications, 8, p.15163.

Du, C. and Xie, X. 2012. G protein-coupled receptors as therapeutic targets for multiple sclerosis. *Cell Research*, 22(7), pp.1108-1128.

Dunworth, W. and Caron, K. 2009. G Protein-Coupled Receptors as Potential Drug Targets for Lymphangiogenesis and Lymphatic Vascular Diseases. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 29(5), pp.650-656.

Dunworth, W.P. and Caron, K.M., 2009. G protein–coupled receptors as potential drug targets for lymphangiogenesis and lymphatic vascular diseases. *Arteriosclerosis, thrombosis, and vascular biology*, 29(5), pp.650-656.

Ghanemi, A. 2015. Targeting G protein coupled receptor-related pathways as emerging molecular therapies. *Saudi Pharmaceutical Journal*, 23(2), pp.115-129.

Holliday, N., Watson, S. and Brown, A. 2012. Drug Discovery Opportunities and Challenges at G Protein Coupled Receptors for Long Chain Free Fatty Acids. *Frontiers in Endocrinology*, 2.

Hutchings, C., Koglin, M., Olson, W. and Marshall, F. 2017. Opportunities for therapeutic antibodies directed at G-protein-coupled receptors. *Nature Reviews Drug Discovery*, 16(11), pp.787-810.

Insel, P., Wilderman, A., Zambon, A., Snead, A., Murray, F., Aroonsakool, N., McDonald, D., Zhou, S., McCann, T., Zhang, L., Sriram, K., Chinn, A., Michkov, A., Lynch, R., Overland, A. and Corriden, R. 2015. G Protein-Coupled

Receptor (GPCR) Expression in Native Cells: "Novel" endoGPCRs as Physiologic Regulators and Therapeutic Targets. *Molecular Pharmacology*, 88(1), pp.181-187.

Jiang, M. and Bajpayee, N. 2009. Molecular Mechanisms of Go Signaling. *Neurosignals*, 17(1), pp.23-41.

Kontoyianni, M. 2014. G Protein Coupled Receptors: Druggability and Structural Aspects. *Journal of Autacoids*, 05(01).

Lappano, R. and Maggiolini, M. 2011. G protein-coupled receptors: novel targets for drug discovery in cancer. *Nature Reviews Drug Discovery*, 10(1), pp.47-60.

Lundstrom, K. 2006. Latest development in drug discovery on G protein-coupled receptors. Curr Protein Pept. Sci., 7(5), pp. 465-70.

Lundstrom, K. 2009. An Overview on GPCRs and Drug Discovery: Structure-Based Drug Design and Structural Biology on GPCRs. *Methods in Molecular Biology*, pp.51-66.

Lundstrom, K. 2016. New winds in GPCR-based drug discovery. *Future Medicinal Chemistry*, 8(6), pp.605-608.

McNeely, P., Naranjo, A. and Robinson, A. 2012. Structure-function studies with G protein-coupled receptors as a paradigm for improving drug discovery and development of therapeutics. *Biotechnology Journal*, 7(12), pp.1451-1461.

McNeely, P.M., Naranjo, A.N. and Robinson, A.S., 2012. Structure□function studies with G protein□coupled receptors as a paradigm for improving drug discovery and development of therapeutics. Biotechnology journal, 7(12), pp.1451-1461.

Miao, Y. and McCammon, J. 2017. Enhanced Simulations and Drug Discovery of a Muscarinic G-Protein-Coupled Receptor. *Biophysical Journal*, 112(3), pp.328a-329a.

New, D. and Wong, Y. 2007. Molecular mechanisms mediating the G protein-coupled receptor regulation of cell cycle progression. Journal of Molecular Signaling, 2, p.2.

Reimann, F. and Gribble, F. 2015. G protein-coupled receptors as new therapeutic targets for type 2 diabetes. *Diabetologia*, 59(2), pp.229-233.

Reimann, F. and Gribble, F. 2015. G protein-coupled receptors as new therapeutic targets for type 2 diabetes. *Diabetologia*, 59(2), pp.229-233.

Research Features. 2017. Challenges and solutions: G protein-coupled receptors as novel drug targets. Retrieved from: http://researchfeatures.com/2017/06/19/challenges-and-solutions-g-protein-coupled-receptors-as-novel-drug-targets/

Salon, J., Lodowski, D. and Palczewski, K. 2011. The Significance of G Protein-Coupled Receptor Crystallography for Drug Discovery. *Pharmacological Reviews*, 63(4), pp.901-937.

Salon, J.A., Lodowski, D.T. and Palczewski, K., 2011. The significance of G protein-coupled receptor crystallography for drug discovery. *Pharmacological reviews*, 63(4), pp.901-937.

Schalop, L. and Allen, J. 2017. GPCRs, Desirable Therapeutic Targets in Oncology. Retrieved from: https://www.biosciencetechnology.com/article/2017/01/gpcrs-desirable-therapeutic-targets-oncology

Schirone, L., Forte, M., Palmerio, S., Yee, D., Nocella, C., Angelini, F., Pagano, F., Schiavon, S., Bordin, A., Carrizzo, A., Vecchione, C., Valenti, V., Chimenti, I., De Falco, E., Sciarretta, S. and Frati, G. 2017. A Review of the Molecular Mechanisms Underlying the Development and Progression of Cardiac Remodeling. Oxidative Medicine and Cellular Longevity, 2017, pp.1-16.

Seifert, R. (2005). *G Protein-Coupled Receptors as Drug Targets: Analysis of Activation and Constitutive Activity*.

Smith, N. (2015). Drug Discovery Opportunities at the Endothelin B Receptor-Related Orphan G Protein-Coupled Receptors, GPR37 and GPR37L1. *Frontiers in Pharmacology*, 6.

Tuteja, N. 2009. Signaling through G protein coupled receptors. Plant Signaling & Behavior, 4(10), pp. 942–947

Venkatakrishnan, A., Deupi, X., Lebon, G., Tate, C., Schertler, G. and Babu, M. 2013. Molecular signatures of G-protein-coupled receptors. Nature, 494(7436), pp.185-194.

Zhang, Y., Scoumanne, A. and Chen, X. 2010. G Protein-Coupled Receptor 87: a Promising Opportunity for Cancer Drug Discovery. *Mol Cell Pharmacol*, 2(3): 111–116.

Zhang, Y., Scoumanne, A. and Chen, X. 2010. G Protein-Coupled Receptor 87: a Promising Opportunity for Cancer Drug Discovery. *Molecular and Cellular Pharmacology*. 2(3), pp.111-116]

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