



IUPHAR NOMENCLATURE

International Union of Basic and Clinical Pharmacology. CXXII. Applying an objective evaluation to the status of class A orphan G protein-coupled receptors



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ABSTRACT

In this review, we, on behalf of the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology, describe criteria for assessing the evidence for pairing receptors with endogenous/physiological ligands for formal receptor deorphanization. This process is illustrated through consideration of the class A G protein-coupled receptors (GPCRs) not yet formally paired with an endogenous/physiological ligand by the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology. Of the 67 orphan class A GPCRs considered, 25 class A GPCRs have no identified endogenous agonists, although 5 (*GPR21*, *GPR27*, *GPR52*, *GPR85*, and *GPR88*) have synthetic ligands that have the potential to be used as tools for uncovering physiological roles and further pharmacological properties of these receptors. Surprisingly, 6 orphan GPCRs (*GPR135*, *GPR152*, *GPR153*, *MRGPRF*, *MRGPRG*, and *MRGPRX3*) have no clear pharmacology or phenotype reported following genetic disruption. Thirty-two orphan GPCRs have been paired with at least 1 endogenous agonist (mainly lipids and their derivatives, peptides, and other metabolites), but further characterization is required from the scientific community to validate these results. We identify 10 orphan class A GPCRs for which there are plausible grounds for considering deorphanization: *GPR4* (protons), *GPR15* (*GPR15L*), *GPR31* (12S-hydroxyeicosatetraenoic acid), *GPR39* (zinc divalent ions, Zn^{2+}), *GPR65* (protons), *GPR68* (protons), *GPR132* (9-hydroxyoctadecadienoic acid), *GPR183* (7 α ,25-dihydroxycholesterol), *MRGPRD* (β -alanine), and *MRGPRX1* (bovine adrenal medulla peptide 8-22). The issue of nomenclature for these 10 GPCRs will be considered by further subcommittees of the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology. We hope this review will prompt further investigations into these members of the currently most widely clinically exploited protein superfamily.

Significance Statement: The use of systematic, rational nomenclature for drug targets provides a framework to ensure consistent identification and rapid recognition. Given that G protein-coupled receptors have fundamental physiological roles and are widespread targets of drugs in current clinical use, we hope the target summary and deorphanization criteria provided here will prompt renewed efforts to investigate these orphan receptors as regulators of physiology and as opportunities for future therapeutic exploitation.

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I. Introduction and scope

NC-IUPHAR is the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (<https://www.guidetopharmacology.org/nciuphar.jsp>). One of the central objectives of NC-IUPHAR is to provide guidelines for the nomenclature and classification of biological targets of drugs, which we present through an online, freely accessible data base at www.guidetopharmacology.org. The intention of the NC-IUPHAR-recommended nomenclature is to provide guidance on the naming of drug targets that is clear, logical, and consistent so that the broader scientific community avoids confusion and saves time and energy.

NC-IUPHAR has previously published a G protein-coupled receptor (GPCR) list,¹ which was updated to reflect preliminary pairings between orphan GPCRs and endogenous ligands, providing initial criteria for deorphanization.² In this reflection on the current state of this field of research, we update the criteria that NC-IUPHAR applies to progress the formal deorphanization of a receptor and use the class A GPCRs to illustrate the process.

Over the last 30 years, many publications from NC-IUPHAR have appeared in *Pharmacological Reviews* and have identified the preferred nomenclature for a number of families of class A GPCRs (Table 1). In the absence of a formal publication, NC-IUPHAR has established a nomenclature for several families communicated via the website www.guidetopharmacology.org. These include the bile acid receptor, dopamine receptors, galanin receptors, glycoprotein hormone receptors, gonadotropin-releasing hormone receptors, melanin-concentrating hormone receptors, melanocortin receptors, motilin receptor, neuromedin U receptors, neuropeptide FF/neuropeptide AF receptors,

neuropeptide S receptor, neuropeptide W/neuropeptide B receptors, neurotensin receptors, opioid receptors, platelet-activating factor receptor, prokineticin receptors, prolactin-releasing peptide receptor, QRFP receptor, tachykinin receptors, thyrotropin-releasing hormone receptors, and vasopressin and oxytocin receptors (Table 1).

A further 17 class A orphan GPCRs are associated with NC-IUPHAR subcommittees and may be regarded as "foster children" (Table 2). During the course of these discussions, the chemokine receptor subcommittee of NC-IUPHAR has suggested renaming *GPR182* as the newest member of the atypical chemokine receptor subfamily, ACKR5.³ We highlight this group of GPCR "foster children" to identify that, in the near future, NC-IUPHAR subcommittee panels will apply the systematic criteria we identify here to assess the status of these GPCRs in more detail.

Here, we evaluate the remaining group of 67 Class A GPCRs for their orphan status in a systematic, pragmatic manner.

II. Class A G protein-coupled receptor lacking a proposed endogenous/physiological ligand

Although there are data regarding the molecular nature and tissue expression levels of 26 class A GPCRs (Table 3), currently, there are no published data suggesting endogenous/physiological ligands that may activate them. Synthetic ligands have been reported for 5 orphan GPCRs (*GPR21*, *GPR27*, *GPR52*, *GPR85*, and *GPR88*), although these still require independent validation (Table 3). By contrast, 6 of these orphan GPCRs (*GPR135*, *GPR152*, *GPR153*, *MRGPRF*, *MRGPRG*, and *MRGPRX3*) have no reported pharmacology and no phenotype for genetic disruption in the public domain. *GPR135*, *GPR152*, *MRGPRE*, and *MRGPRG* were

Table 1
Human class A G protein-coupled receptor families, which the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology considers have an established endogenous/physiological ligand

Family	Family
5-Hydroxytryptamine receptors ^{88,89}	Melanin-concentrating hormone receptors
Acetylcholine receptors (muscarinic) ⁹⁰	Melanocortin receptors
Adenosine receptors ^{91,92}	Melatonin receptors ⁹³
Adrenoceptors ^{94,95}	Motilin receptor
Angiotensin receptors ^{96,97}	Neuromedin U receptors
Apelin receptor ^{98,99}	Neuropeptide FF/neuropeptide AF receptors
Bile acid receptor	Neuropeptide S receptor
Bombesin receptors ¹⁰⁰	Neuropeptide W/neuropeptide B receptors
Bradykinin receptors ¹⁰¹	Neuropeptide Y receptors ¹⁰²
Cannabinoid receptors ^{83,103}	Neurotensin receptors
Chemerin receptors ¹⁰⁴	Opioid receptors
Chemokine receptors ^{3,105–107}	Orexin receptors ^{108,109}
Cholecystokinin receptors ¹¹⁰	Oxoglutarate receptor ²
Complement peptide receptors ¹¹¹	P2Y receptors ¹¹²
Dopamine receptors	Platelet-activating factor receptor
Endothelin receptors ^{113,114}	Prokineticin receptors
Formylpeptide receptors ⁸⁵	Prolactin-releasing peptide receptor
Free fatty acid receptors ¹¹⁵	Prostanoid receptors ^{116–118}
G protein-coupled estrogen receptor ¹¹⁹	Proteinase-activated receptors ⁸²
Galanin receptors	QRFP receptor
Ghrelin receptor ¹²⁰	Relaxin family peptide receptors ^{121,122}
Glycoprotein hormone receptors	Somatostatin receptors ¹²³
Gonadotropin-releasing hormone receptors	Succinate receptor ²
Histamine receptors ^{124,125}	Tachykinin receptors
Hydroxycarboxylic acid receptors ¹²⁶	Thyrotropin-releasing hormone receptors
Kisspeptin receptor ¹²⁷	Trace amine receptor ¹²⁸
Leukotriene, lipoxin and 5-oxoicoatrienoic acid receptors ^{129–131}	Urotensin receptor ¹³²
Lysophospholipid (LPA) receptors ^{8,9}	Vasopressin and oxytocin receptors
Lysophospholipid (S1P) receptors ^{8,9}	

The citations indicated are IUPHAR nomenclature publications in Pharmacological Reviews.

expressed and screened against over 5000 endogenous compounds without identifying any hits.⁴ The Human Protein Atlas has combined bulk RNA sequencing data from 3 databases, but mRNA encoding *GPR152* and *MRGPRG* was not detected in 50 human tissues or organs. However, low levels of *GPR152* mRNA were reported following single-cell sequencing in endothelial cells and mononuclear phagocytes for the human heart. *MRGPRG* expression was also reported in specialized epithelial and germ cells using this technique. Only mRNA encoding *GPR135* and *GPR153* was reported to be widely distributed, although at low levels, with some evidence of protein expression using immunocytochemistry. *GPR135* mRNA was reported to be present in human cancers using

polymerase chain reaction.⁵ *MRGPRE* is reported in the brain and female reproductive organs, whereas *MRGPRX3* is reported in the salivary glands. Other members of the Mas-related GPCR family were originally identified in sensory neurons, but more information is needed regarding the precise cellular expression of mRNA and protein that may indicate potential roles in humans.

One of the aspirations of this review is to highlight opportunities for further research. Given the wealth of drugs in clinical use that target GPCRs, in particular, from class A,⁶ we suggest that additional investigation of these 26 receptors could potentially lead to useful therapeutic opportunities.

III. Developing criteria for the deorphanization process

The remaining 41 GPCRs were considered to have sufficient published data to be subject to closer scrutiny. The expert reviewers (taken from the listed co-authors) were recruited based on their experience with the topic, while also reflecting diversity in geography and gender, as well as representing both academic and industrial roles. Each reviewer was allocated three GPCRs as a primary reviewer and 6 GPCRs as a second reviewer, with an aim to get an independent (unbiased) evaluation and triangulation of the status of those GPCRs. Reviewers were not allocated orphan GPCRs where they had published original articles on that receptor.

The aim for the primary reviewers was to research the 3 assigned GPCRs and to update and/or correct the records in www.guidetopharmacology.org. In addition, primary reviewers summarized the evidence according to the evaluation checklist shown in Table 4. Secondary reviewers were not expected to research their topics to the same depth as primary reviewers but to accumulate sufficient evidence to make a judgment as to a 3-option outcome (strong, intermediate, and weak deorphanization cases evaluated as α , β , or γ —Table 5). For each receptor, at least 3 reviews were received. GPCRs were then ranked, both in terms of the

Table 2
Seventeen human class A orphan GPCR associated with the indicated NC-IUPHAR subcommittees (“foster children”)

NC-IUPHAR subcommittee/s	Target/s
Angiotensin receptors	Mas1
Bombesin receptors	BB ₃ receptor
P2Y receptors	GPR17
Leukotriene receptors	GPR18
Cannabinoid receptors	GPR55
	GPR119
Chemokine receptors	GPR182
Free fatty acid receptors	GPR42
	GPR84
Leucine-rich repeat-containing receptors	LGR4
	LGR5
	LGR6
Trace amine receptors	TAAAR2
	TAAAR5
	TAAAR6
	TAAAR8
	TAAAR9

NC-IUPHAR, Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology.

Table 3

Twenty-five human class A orphan GPCR for which there are currently no identified endogenous/physiological ligands

Target	Reported Signaling	Surrogate Ligands	Phenotype of Gene Disruption ^a	Comments
<i>GPR20</i>	Reported to couple constitutively to G _i ^{80,133}	-	-	A cryo-EM structure of the recombinant <i>GPR20</i> was suggested to compare with galanin receptors; the authors interpreted their observations to suggest the N terminus was able to activate the receptor in the absence of other ligands ¹³⁴
<i>GPR21</i>	Reported to couple constitutively to G _q ¹³⁵	GRA2 is reported to act as an inverse agonist ¹³⁶	Positive benefit in models of diabetes/obesity ^{137,138} were not observed in another study ¹³⁹	A complex mix of plasmalogens evoked phosphorylation of ERK and protein kinase B in mouse cultured hippocampal neurones that could be inhibited with shRNA directed against <i>GPR21</i> ¹⁴⁰ A cryo-EM structure of unliganded <i>GPR21</i> bound to G proteins has been reported ¹⁴¹
<i>GPR22</i>	Reported to couple constitutively to G _i ^{142,143}	-	An increased susceptibility to cardiac decompensation following aortic banding ¹⁴²	-
<i>GPR26</i>	Reported to couple constitutively to G _s ¹⁴⁴	-	Increased symptoms of anxiety and depression ¹⁴⁵ , hyperphagia and adiposity ¹⁴⁶	-
<i>GPR27</i>	Reported to couple constitutively to G _i ⁸⁰	5128535 ^{147–149} and PT-91 ¹⁴⁹ functioned as surrogate agonists, whereas Compound 1a was reported as an inverse agonist, ¹⁵⁰ although a further study was unable to confirm this activity ¹⁴⁸	A modestly reduced insulin gene transcription without altering glucose tolerance ¹⁵¹ Zebrafish showed altered insulin signaling and metabolite levels ¹⁵²	A complex mix of plasmalogens evoked phosphorylation of ERK and protein kinase B in mouse cultured hippocampal neurones that could be inhibited with shRNA directed against <i>GPR27</i> ¹⁴⁰
<i>GPR33</i>	Heterologous expression of the mouse receptor resulted in elevated inositol phosphates levels ¹⁵³	-	-	<i>GPR33</i> has been reported to bind radiolabeled cortisol. ¹⁵⁴ Human <i>GPR33</i> contains a premature stop codon within the coding sequence of the second intracellular loop ¹⁵³ Pseudogenes of <i>GPR33</i> predominantly occur in rodents (rat) and primates but not other mammals. ¹⁵³ Receptor inactivation may have occurred due to a rodent–hominoid-specific pathogen ¹⁵⁵ Proposed to act as a viral anchoring site ¹⁵⁶
<i>GPR45</i>	Reported to couple constitutively to G _i ⁸⁰ and to G _s ¹⁵⁷	-	Increased adiposity at weaning and reduced hypothalamic expression of <i>POMC</i> . ¹⁵⁸ Global disruption of <i>Gpr45</i> ¹⁵⁹ or selectively in the paraventricular nucleus of the hypothalamus was associated with obesity ¹⁵⁷	-
<i>GPR52</i>	Reported to recruit β -arrestin constitutively in an inactive state ¹⁶⁰	A number of synthetic agonists have been described, including compound 7a and 7m, ¹⁶¹ FTBMT, ¹⁶² derivative 17, ¹⁶³ BD442618, BD502657, ¹⁶⁴ HTL0041178, ¹⁶⁵ and sucralose ¹⁶⁶ Additionally, multiple antagonists/inverse agonists have been reported, including cannabidiol, O1918, ¹⁶⁷ and comp-43 ¹⁶⁸	Elevated locomotor response to the A _{2A} adenosine receptor antagonist istradefylline ¹⁶⁹	A crystal structure of <i>GPR52</i> with derivative 17 bound has been reported, with an interpretation that the ligand might act allosterically ¹⁷⁰
<i>GPR62</i>	Reported to couple constitutively to G _s ¹⁷¹	-	No overt phenotype ¹⁷¹ or impact on CNS myelination ¹⁷²	Reported to inhibit MT ₂ receptor coupling to β -arrestin ¹⁷³
<i>GPR78</i>	Reported to couple constitutively to cAMP production ¹⁴⁴	-	Overexpression of <i>GPR78</i> in mice was associated with a salivary gland dysfunction ¹⁷⁴	Pubmed gets <i>GPR78</i> confused with a 78 kDa glucose-regulated protein known as the endoplasmic reticulum chaperone BiP
<i>GPR82</i>	Reported to lack constitutive activity in recombinant expression ⁸⁰	-	A reduced body fat and weight, with increased insulin sensitivity and glucose tolerance ¹⁷⁵	Although lacking constitutive activity in recombinant expression, ⁸⁰ LysoPE and LysoPC were reported to act as inverse agonists ¹⁷⁶
<i>GPR85</i>	Reported to lack constitutive activity in recombinant expression ⁸⁰	Compound 1a ¹⁵⁰ and compound 3i ¹⁷⁷ are reported as inverse agonists Harmine has been reported to act as an inverse agonist ¹⁷⁸	Mild overexpression was associated with reduced brain mass, whereas increased brain mass was found in knockout animals ¹⁷⁹	-

<i>GPR88</i>	Reported to couple to G _i ^{143,180,181}	A number of small molecule agonists have been reported including 2-PCCA, ^{b,182} RTI-122, ¹⁸³ RTI-13951-33, ^{184,185} compound 2 [PMID: 24793972], ¹⁸¹ compound 99, ¹⁸⁶ and BI-9508 ¹⁸⁷	Gene disruption resulted in altered striatal signaling, ¹⁸⁸ reduced adiposity and reduced spontaneous food intake, ¹⁸⁹ increased alcohol intake ¹⁹⁰	A cryo-EM structure of GPR88 combined with G _{i1} has been described, where 2-PCCA bound as an allosteric modulator. ¹⁹¹ Reported to inhibit signaling through μ and δ opioid receptors ^{192,193} Reported to inhibit MT ₂ receptor coupling to β -arrestin ¹⁷³
<i>GPR135</i>	Reported to recruit β -arrestin constitutively, but failed to influence G _i /G _s pathways ¹⁷³	-	-	-
<i>GPR141</i>	-	-	Elevated immune response in leukocytes and experimental autoimmune encephalomyelitis ¹⁹⁴	-
<i>GPR148</i>	-	-	-	No orthologue exists in rodents
<i>GPR149</i>	-	-	Increased fertility in male mice, ¹⁹⁵ reduced oligodendrocyte progenitor cell maturation, ¹⁹⁶ and reduced weight gain on high-fat diet ¹⁹⁷	-
<i>GPR150</i>	Reported to couple constitutively to G _i ⁸⁰	-	-	-
<i>GPR152</i>	-	-	-	-
<i>GPR153</i>	Inferred to couple to G _i in a manner insensitive to pertussis toxin ¹⁹⁸	-	Reduced inflammatory signaling in models of stroke and experimental autoimmune encephalitis ¹⁹⁸	-
<i>GPR161</i>	Appears to function as a negative regulator of Sonic hedgehog signaling ^{199–202}	-	Reduced embryonic ciliary function ²⁰³	Variants of <i>GPR161</i> are associated with developmental disorders in man ^{204,205} A cryo-EM structure suggests the second extracellular loop may auto-activate the receptor. ⁸¹ Reported to act as a mechanosensor in neuronal cilia ²⁰⁶
<i>GPR176</i>	Reported to couple constitutively to G _i , ⁸⁰ to G _z in the suprachiasmatic nucleus ²⁰⁷ and to G _s in colorectal cancer cells ²⁰⁸	-	Knockout mice appeared superficially normal, but exhibited a shorter circadian period ²⁰⁷	Shows circadian variation in the suprachiasmatic nucleus. ²⁰⁷ Activation of <i>GPR176</i> was observed after co-incubation with a microwaved supernatant fraction from mouse brain ²⁰⁹
<i>MRGPRF</i>	-	-	-	Ang-1-7 was reported to inhibit arachidonic acid release in the presence of <i>MRGPRF</i> , ²¹⁰ although there was a lack of clarity whether this was an agonist or inverse agonist function
<i>MRGPRG</i>	-	-	-	-
<i>MRGPRX3</i>	-	-	-	<i>Mrgprx3</i> is a pseudogene in mice

CNS, central nervous system.

^aUnless noted otherwise, the phenotype is derived from mouse models.^b(1R, 2R)-2-pyridin-2-yl-cyclopropane carboxylic acid ((2S, 3S)-2-amino-3-methyl-pentyl)-(4'-propylbiphenyl-4-yl)-amide.

Table 4
Evaluation checklist used by reviewers of orphan G protein-coupled receptor

1 The crux	What is/are the suggested putative endogenous agonist/s?
2 Reproducibility	a Has the activity of this putative agonist been reproduced in the same signaling paradigm by a fully independent laboratory? ^a b Has the receptor been included in a published major screening program and with what outcome? ^b
3 Physiology	c Is the potency of the putative agonist consistent with a physiological function? d Are there plausible mechanisms for the putative agonist to reach bioactive concentrations in tissues expressing the receptor? Is the ligand:receptor pairing physiologically feasible?
4 Binding	Has binding of the putative agonist to the receptor been demonstrated? ^c
5 Agonist effects	e What responses does the putative agonist evoke in cells expressing the recombinant receptor? ^d f What responses does the putative agonist evoke in native cells/tissues expressing the receptor? g Does the putative agonist evoke a response in the absence of the receptor (off-target effects)?
6 Pharmacology	h If synthetic agonists have been described, how closely do they mimic the effects of the putative agonist? ^e i Are there antagonists that block the effects of the putative agonist (and/or synthetic agonists)? j Does inhibition (pharmacological or genetic) of the enzymes capable of producing or terminating the putative agonist alter the receptor's downstream signaling?
7 Genetic approaches	k Do genetic alterations (natural mutations/single nucleotide polymorphisms or man-made), which alter receptor sequence or expression levels, disrupt cellular/tissue/behavioral responses to the putative agonist? l In the case of peptide ligands, do genetic alterations of the coding gene result in changes in receptor expression?

LysoPE, lysophosphatidylethanolamine.

^aWere cells/cDNA independently derived?^bFor example, Southern et al.⁴^cThis might be displacement of labeled ligands or biophysical evidence. Although this is desirable, it would not be considered obligatory as it is often very challenging.^dCalcium elevations, β -arrestin recruitment, cAMP inhibition, receptor internalisation, etc.^eConsider the possibility of biased agonism.

judged strength of evidence and the convergence of evaluation from the reviewers. Thereafter, online sessions were conducted with the reviewers divided into 2 geographical sections, which allowed free discussions on the grading of the candidate GPCR across the entire panel of experts.

Of the criteria against which the receptors were compared, some are fundamental elements, such as the identification of a putative endogenous agonist (point 1) and the independent confirmation process (point 2). Point 2b identifies that literature searching for individual GPCRs may overlook mass screening investigations, such as Southern et al.⁴ Others relate to the physiological confirmation of the endogenous agonist (point 5) and whether tool compounds exist to dissect the pharmacological profile of the receptor (point 6). Genetic modification of the receptor, either as naturally occurring variants/single nucleotide polymorphisms or by molecular disruption (point 7), also provides evidence for the functional impact of the receptor.

Of these criteria, it is worthwhile to reflect on 2 specific points. First, identifying binding of the putative endogenous ligand to the receptor (point 4) can be challenging for a number of reasons. The generation of a radiolabeled analog may be tricky in terms of synthetic chemistry. Fluorescent analogs may be equally challenging to synthesize. Additionally, many endogenous ligands bind at high nanomolar to low micromolar concentrations, which are difficult to quantify using conventional radioligand binding techniques. The likelihood of the ligand binding to other cellular components could also be a factor in limiting the levels of specific binding. We consider demonstration of binding of the putative endogenous agonist not to be an essential prerequisite, although it is a desirable confirmation.

A more impactful criterion is whether there is the capacity to manipulate tissue levels of the putative endogenous ligand through modifying the enzyme activities involved in the synthesis

or degradation/transformation of the ligand (point 6c). A requirement for this step is obviously that these enzyme activities are known and that inhibitors are available. Although this criterion is also a high bar to overcome, it allows distinction between ligands that can activate the receptor *in vitro* and those that really activate the receptor *in situ*.

IV. Orphan class A G protein-coupled receptors with a proposed endogenous/physiological ligand

On the basis of triangulated reviews from the expert panel using these criteria, 31 GPCRs were identified as having limited evidence for deorphanization (Table 6). The most common reasons for this conclusion included a lack of confirmation by independent laboratories and questions about the physiological levels of the putative endogenous ligand/s in close proximity to the receptor, but particularly the “high bar” of the impact of manipulating levels of the putative endogenous agonist on receptor responsiveness (point 6c).

Analysis of the putative ligands for this group of orphan GPCRs suggests 3 major chemical classes: lipids and their derivatives, peptides, and other metabolites.

Multiple orphan GPCRs have been suggested to respond to lipids, including the lysophospholipids sphingosine 1-phosphate (S1P) (GPR3, GPR6, GPR12, GPR63, and P2RY10) and lysophosphatidic acid (GPR35, GPR87, and P2RY10) (Table 6). These 2 endogenous lysophospholipids activate 2 families of receptors that have some overlapping sequence similarities, such that S1P₁, S1P₂, S1P₃, S1P₄, S1P₅, and LPA₁, LPA₂, and LPA₃ receptors were initially described as a protein family derived from 8 endothelial differentiation genes.^{7–9} However, later-identified members of the LPA receptor family, LPA₄ and LPA₆, were sufficiently different in sequence that they were initially proposed as members of the P2Y receptor family.^{10,11} This illustrates the observation that although sequence similarities are useful as preliminary guides for nomenclature, the overriding factor in determining nomenclature must be pharmacological evidence.¹²

Other lipid derivatives suggested to activate orphan GPCRs in this group include fatty acids (GPR3, GPR6, and GPR12), lysophosphatidylserine (GPR34, GPR174, and P2RY10), phospholipids and their derivatives (GPR61 and GPR63), and a variety of oxidized fatty acid metabolites, including 20-hydroxyeicosatetraenoic acid (GPR75),

Table 5
Evaluation options identified by reviewers of orphan G protein-coupled receptor

α .	Enough evidence from independent laboratories to establish a strong case for deorphanization
β .	Remains an orphan receptor with some evidence for endogenous ligands and/or function, but requires independent confirmation
γ .	Remains an orphan receptor with limited evidence for function

Table 6

Thirty-two human class A orphan G protein-coupled receptor with reported putative endogenous/physiological agonists identified as having weak potential (rated β or γ by the reviewers) for deorphanization at the current time

Target	Proposed Physiological Agonist/s	Surrogate Agonist/s	Antagonists/Inverse Agonists	Comment
<i>GPR3</i>	S1P ²¹¹ Oleic acid, ²¹² ODA, and OEA ^{212,213}	Diphenyleneiodonium ^{212,214,215} and analogs ²¹⁶	AF64394 ^{212,217} and cannabidiol ²¹⁸ are reported to act as inverse agonists	Activation by S1P was not repeated in β -arrestin assays ^{4,20} Fluorescent analogs of AF64394 have been reported to bind to the recombinant receptor ²¹⁹ AF64394 is reported to bind to the membrane interface of a GPR3 homodimer based on cryo-EM studies ²²⁰
<i>GPR6</i>	S1P ^{211,221} Palmitoleic acid ²¹²	-	Cannabidiol, ²¹⁸ CVN264 ^{222–225} , CVN-424 (Solengeprase) ²²⁶ and CVN527 ²²⁷ are reported to act as inverse agonists	Activation by S1P was not repeated in β -arrestin assays ^{4,20} Reported to form functional heterodimers with LPA and S1P receptors ²²⁸
<i>GPR12</i>	S1P ^{211,221} SPC ²²⁹ Oleic acid ²¹²	Tyrosol ²³⁰ Multiple fungal-derived steroid-like compounds ²³¹	Cannabidiol ²³² is reported to act as an inverse agonist	Activation by S1P was not repeated in β -arrestin assays ^{4,20}
<i>GPR19</i>	Adropin ^{233,234}	-	-	Adropin was not effective in β -arrestin assays ^{4,20} Knockdown of <i>Gpr19</i> in H9c2 rat cardiac cells ²³⁵ or RAW264.7 mouse monocyte/macrophage cells ²³⁶ resulted in a reduced responsiveness to adropin. Similarly, siRNA targeting of <i>GPR19</i> in human primary fibroblasts attenuated the effects of adropin ²³⁷
<i>GPR25</i>	CXCL17 ^{238,239}	-	-	Reported to couple constitutively to Gi. ⁸⁰ Nonmammalian orthologues are reported to be activated by apelin and apela ²⁴⁰
<i>GPR32</i>	RvD1 ^{241,242} Lipoxin A ₄ ²⁴² Resolvin D3 ²⁴³	Compound 43 ²⁴² Multiple chemotypes were identified in a high-throughput screening assay ²⁴¹	An antibody directed against <i>GPR32</i> blocked RvD1-evoked responses in isolated human polymorphonuclear leukocytes ²⁴⁴ and blocked RvD3-evoked responses in a recombinant <i>GPR32</i> -expressing cell line ²⁴³	Studies in macrophages that express <i>GPR32</i> but not FPR2/ALX suggest RvD1 induced a pro-resolution phenotype (increased phagocytosis, blocked chemotaxis, reduced secretion of proinflammatory cytokines IL-1 β , IL-8, and MCP-1). This effect was reduced with siRNA against <i>GPR32</i> and was consistent with RvD1 as a pro-resolution molecule. ²⁴⁵ RvD1 was not effective in β -arrestin assays, ^{4,20} or in dynamic mass redistribution or internalization assays. ³⁹ <i>Gpr32</i> is a pseudogene in mice and rats ²⁴⁶ Radioligand binding studies have been performed in a cell line that expresses the FPR1/ALX receptor, which is also a receptor for RvD1, and binding of RvD1 to <i>GPR32</i> was inferred due to a binding remaining in the presence of FPR2/ALX agonist ²⁴²
<i>GPR34</i>	LysoPS ^{247–250}	Compound 14 was reported as a high-potency synthetic agonist with selectivity relative to <i>P2RY10</i> ²⁵¹ Compound M1 exhibited high potency in an assay for TGF- α shedding ²⁵⁰ M1 effects in primary microglia were lost following <i>Gpr34</i> knockdown ²⁵²	YL-365 ²⁵³ An antagonist has been claimed to block the effects of LysoPS in cultured cells, but a structure or source was not reported ²⁵⁴ (S)-3-(4-(benzyloxy)phenyl)-2-(2-phenoxyacetamido)propanoic acid derivatives ²⁵⁵ Aminoethyl-carbamoyl ATP was identified as an antagonist at the carp orthologue ²⁴⁸	The stimulatory effects of LysoPS were not reproduced in alternative studies ^{4,20,257} Genetic disruption of iPLA2-G6 reduced LysoPS and mimicked the effects of <i>Gpr34</i> knockdown in male mouse hearts ²⁵⁸ Cryo-EM structures of LysoPS bound to <i>GPR34</i> have been described ^{250,253,259}
<i>GPR35</i>	Kynurenic acid ^{4,260–262} 2-oleoyl-LysoPA ²⁶³ 5,6-dihydroxyindole-2-carboxylic acid ²⁶⁴ CXCL17 ²⁶⁵ 5HIAA ²⁶⁶	Z ^{261,262,267–269} NPPB ^{261,270} pamoic acid ^{261,262,269} cromoglicic acid ^{264,268,269} nedocromil ^{264,268} entacapone ²⁶² tyrphostin-51 ²⁶² furosemide ²⁷¹	Compound D2 ²⁵⁶ CID2745687 ^{261,273} ML145 ^{272,277}	There are large interspecies pharmacology differences between rat, mouse, and human <i>GPR35</i> . Kynurenic acid and zaprinast are up to 100-fold less potent at human than rat <i>Gpr35</i> , whereas pamoate is more active at the human receptor ²⁶⁹ The antagonists described are also higher affinity at the human orthologue compared to rodent receptors Humans have 2 isoforms of <i>GPR35</i> , whereas rodents have only one ²⁷⁸

(continued on next page)

Table 6 (continued)

Target	Proposed Physiological Agonist/s	Surrogate Agonist/s	Antagonists/Inverse Agonists	Comment
		bumetanide ²⁷¹ benserazide ²⁷² pyrogallol ²⁷² compound 83 ²⁷³ lodoxamide ²⁷⁴ Isobavachin ²⁷⁵ Pelargonidin ²⁷⁶		Isoforms show slightly different transducer coupling profiles/ bias ²⁷⁹ The effects of the chemokine CXCL17 have been contradicted by 2 other studies ^{274,280}
GPR37	Prosaptide ²⁸¹ neuroprotectin D ²⁸²	Neuropeptide head activator ²⁸³ Prosaptide TX14 ^{282,284} chlorogenic acid ²⁸⁵	-	Prosaptide and TX14 have both been reported as agonists of GPR37L1 Although it was reported that mammalian tissues contain a peptide of identical amino acid sequence to Hydra head activator, ²⁸⁶ there is currently no evidence for the presence of a gene encoding this peptide in any sequenced genome. However, the C-terminal tripeptide sequences of head activator and prosaptide are similar, which may explain the activity of head activator on GPR37 Neuroprotectin D has been reported as an agonist at BLT ₁ receptors ²⁸⁷ Binding of TX14 and neuroprotectin D, but not RvE1, was reported to recombinant GPR37 ²⁸² Maresin 1 is also reported to activate LGR6 ²⁹⁰ Mice with disrupted GPR50 showed reduced body weight and lower gains on high-fat diet, increased levels of exercise, ²⁹² as well as an impaired social recognition ²⁹³ Reported to selectivity inhibit MT ₁ receptor, not MT ₂ receptor, function upon coexpression ⁷⁹ Mitophagy may involve recruitment to the mitochondria ²⁹³ A ligand-free cryo-EM structure of GPR50 has been described ²⁹⁴
GPR37L1	Prosaptide ^{281,284,288} maresin 1 ²⁸⁹	-	-	
GPR50	Little-LEN bound to recombinant GPR50 in a cross-linking assay and inhibited cAMP formation ²⁹¹	-	-	
GPR61	A complex mix of plasmalogens evoked phosphorylation of ERK and protein kinase B in mouse cultured hippocampal neurones that could be inhibited with shRNA directed against GPR61 ¹⁴⁰ 1-(1Z-octadecenyl)-2-oleoyl-sn-glycero-3- phosphoethanolamine ²⁹⁵	-	Compound 1 was reported to act as an inverse agonist ²⁹⁶ Compound 15 was visualized bound to an intracellular site and acted as an inverse agonist ²⁹⁷	-
GPR63	S1P ^{298,299} dioleoylphosphatidic acid ²⁹⁸	-	Fingolimod appeared to function as an antagonist ²⁹⁹	S1P activation was not replicated. ²⁰ Unlike the <i>Xenopus</i> orthologue, mammalian GPR63 was not responsive to LysoPA ³⁰⁰
GPR75	CCL5/RANTES ^{301,302} 20-HETE ^{303,304}	(2-[[[(5Z,14Z)-20-hydroxyicosa-5,14- dienoyl]amino]acetic acid ³⁰⁵	CCL5/RANTES ³⁰⁴ 19-HEDE ³⁰⁶ Limonoid walrobsin A ³⁰⁷ N-disodium succinate-20- hydroxyeicosa-6 (Z), 15 (Z)- diencarboxamide (AAA) ³⁰⁸	Surface plasmon resonance provided evidence for 20-HETE binding to GPR75 ³⁰⁴ 20-HETE or CCL5 failed to evoke signaling with recombinant GPR75 in one report ³⁰⁹ A ligand-free cryo-EM structure of GPR75 has been described ³¹⁰
GPR83	Zn ²⁺ ³¹¹ PEN ^{39,312–314} FAM237A ^{315–317} FAM237B ³¹⁷	CPD1, CPD27 ³¹⁸	CPD25 ³¹⁸	One study observed responses to FAM237A in the absence of responses to PEN with recombinant GPR83 ³¹⁶ A further report failed to provide evidence for PEN-evoked responses in GPR83-expressing cells or to exhibit specific binding of iodinated PEN
GPR87	LysoPA ^{319–321}	-	Ki16425 and dioctanoylglycerol pyrophosphate ³¹⁹	In comparison with LysoPA-evoked signaling via LPA ₁ receptors, LysoPA-evoked signaling through GPR87 was much reduced, and specific binding of ³ H-LPA was not apparent ³²²
GPR101	GnRH-1-5 ^{323,324} N-3 Docosapentaenoic acid-derived resolvin D ₅ ³²⁵	AA-14 ³²⁶	-	-

<i>GPR139</i>	L-Phe and L-Trp ^{327–329} ACTH, α -MSH, and β -MSH ^{39,328}	LP-360924 ³³⁰ compound 1a ³³¹ (S)-3-chloro-N-(2-oxo-2-((1-phenylethyl)amino)ethyl)benzamide Compound 7c ³³² JNJ63533054 ³²⁷ TC0931 ³³³ JNJ63533054 ³³⁴ AC4 ³³⁵ zeltiazin (TAK-041) ³³⁶ JNJ63533054 ³³⁷ Compound 6 ³³⁸ Compound 33 ³⁴² Compound 22 ³⁴³ Compound 22 ³⁴⁴ Compound 33 ³⁴⁵ Compound 40 ³⁴⁶ Compound 20e ³⁴⁷ LY3325656 ³⁴⁸	LP-471756 ³³⁰ NCRW0105-E06 ^{338,339} JNJ3792165 ^{333,338} NCRW0005-F05 ³³⁸	Activation by ACTH, α -MSH, and β -MSH was not replicated in a later study ³³³ Recombinant <i>GPR139</i> has been labeled with ³ H-JNJ63533054 ^{327,333} A cryo-EM structure of an agonist-bound <i>GPR139</i> has been described ³³⁷
<i>GPR142</i>	L-Phe ³⁴⁰ L-Trp ³⁴¹			
<i>GPR146</i>	Proinsulin C-peptide ³⁴⁹ Cholesin C7orf50 ³⁵⁰			A study using <i>GPR146</i> revealed no response to C-peptide at concentrations of up to 33 μ M ³⁵¹
<i>GPR151</i>	Galanin ³⁵² Reported to be activated at acidic pH ³⁵³	-	-	A later study was unable to observe responses to galanin ³⁹
<i>GPR160</i>	CARTp ³⁵⁴	-	-	The suggestion that CARTp activates or binds to <i>GPR160</i> has not been supported in two subsequent studies ^{355,356}
<i>GPR162</i>	CART(55–102) ³⁵⁷	-	-	-
<i>GPR171</i>	BigLEN ³⁵⁸	MS0015203 ³⁵⁹	MS0021570_1 ³⁶⁰	-
<i>GPR173</i>	GnRH-1-5 ^{361,362} Phoenixin-14 ^{363–365} Phoenixin-20 ^{364,366} CCK-4 and CCK-8 ³⁶⁷	-	Compound 1a is reported as an inverse agonist ¹⁵⁰ devazepide and loxiglumide ³⁶⁷	-
<i>GPR174</i>	LysoPS ^{368–370} CCL21 ³⁷¹	Compound 12 ³⁷⁰	Compound 7d ³⁷²	Cryo-EM structures of LysoPS bound to <i>GPR174</i> have been reported ^{259,373,374}
<i>MAS1L</i>	Angiotensin II, angiotensin IV, and Ang-(1–7) ²¹⁰	-	-	-
<i>MRCPRE</i>	A conjugate of tryptophan linked to cholic acid generated by the gut microbiome ³⁷⁵	-	-	-
<i>MRGPRX2</i>	Cortistatin ^{4,376,377} PAMP-20 ^{377–380} LL-37 ³⁸¹ β -Defensins ³⁸² ATRA ³⁸³ CXCL14 ³⁷⁹ CXCL17 ³⁸⁴ Competence-stimulating peptide 1 ³⁸⁰	PMX-53 ³⁸⁵ complanadine A ³⁸⁶ ZINC-3573 ³⁸⁷ compound 48/80 ^{380,388,389} Murepavadin ³⁹⁰	Compound 1 and compound 2 ³⁹¹ GE1111 ^{392,393} PSB172656 ^{379,394}	<i>MRGPRX2</i> appears to respond to a wide range of basic compounds
<i>MRGPRX4</i>	Deoxycholic acid and chenodeoxycholic acid ^{395,396} Lithocholic acid ³⁹⁷ Bilirubin ³⁹⁸	PSB22034, PSB22040 ³⁹⁹	HEP50768 ⁴⁰⁰	A cryo-EM structure of 3-sulfodeoxycholic acid bound to <i>MRGPRX4</i> has been reported ⁴⁰¹ Deoxycholic acid was ineffective in a β -arrestin screen of <i>MRGPRX4</i> ⁴ <i>MRGPRX4</i> orthologs are not found in rodents <i>P2RY8</i> orthologs are not found in rodents A later study was unable to observe responses to LysoPA ³⁹
<i>P2RY8</i>	S-Geranylgeranyl-L-glutathione ⁴⁰²	-	-	
<i>P2RY10</i>	LysoPA and S1P ⁴⁰³ LysoPS ^{39,368–370}	9-o-C11 ³⁷⁰ Compounds 22, 33, and 34 ⁴⁰⁴ Compound 3r ⁴⁰⁵	Diocanoylglycerol pyrophosphate ⁴⁰³ JTE-013 ⁴⁰³	

5HIAA, 5-hydroxyindoleacetic acid; 19-HEDE, 19-hydroxyeicosa-5(Z) 14(Z)-dienoic acid; 20-HETE, 20-hydroxyeicosatetraenoic acid; ACTH, adrenocorticotrophic hormone; ATRA, All-*trans*-retinoic acid; OEA, N-oleoylethanolamine; ODA, oleamide; LysoPA, lysophosphatidic acid; LysoPS, lysophosphatidylserine; ML145, CID2286812, 2-hydroxy-4-[4-[(5Z)-5-[(E)-2-methyl-3-phenylprop-2-enylidene]-4-oxo-2-sulfanylidene-1,3-thiazolidin-3-yl]butanoylamino]benzoic acid; MSH, melanocyte-stimulating hormone; RvD1, resolvin D1; SPC, sphingosylphosphorylcholine.

lipoxin A4 (*GPR32*), maresin 1 (*GPR37L1*), neuroprotectin D1 (*GPR37*), and resolvin analogs (*GPR32* and *GPR101*). Ring-based lipids, including isoprenoid derivatives (*MRGPRX2* and all-*trans*-retinoic acid; *P2RY8* and *S*-geranylgeranyl-*L*-glutathione) and steroid derivatives (*MRGPRE* and a cholic acid conjugate; *MRGPRX4* and cholic acid derivatives), are also reported to activate orphan GPCRs in this group.

Two GPCRs (*GPR139* and *GPR142*) have been proposed to respond to aromatic amino acids, whereas several other orphan GPCRs have been suggested to be activated by oligopeptides active at established GPCRs, ranging from CCK-4 (*GPR173*) and the pentapeptide metabolite of gonadotropin-releasing hormone (*GPR101* and *GPR173*), to various metabolites of angiotensin II (*MAS1L*) and galanin (*GPR151*). Three orphan GPCRs (*GPR25*, *GPR35*, and *MRGPRX2*) have been reported to respond to the endogenous chemokine-like mediator CXCL17, whereas other chemokines have been reported to activate *GPR75* and *GPR174* (Table 6).

Other, less well-characterized peptides have been reported to activate *GPR19*, *GPR37*, *GPR37L1*, *GPR83*, *GPR146*, *GPR160*, *GPR162*, *GPR171*, *GPR173*, and *MRGPRX2* (see Table 6).

The remaining candidate endogenous ligands could be loosely grouped as metabolites, ranging from the inorganic agents, protons (*GPR151*) and zinc ions (*GPR83*) to amino acid and monoamine metabolites (*GPR35*) and bilirubin (*MRGPRX4*).

Based on these data, it would be a recommendation from NC-IUPHAR for further independent investigation of these preliminary pairings; of particular focus would be an assessment of the colocalization of patho/physiologically relevant concentrations of the putative endogenous agonist with the target GPCR.

V. Orphan class A G protein-coupled receptors with substantive evidence supporting endogenous/physiological ligand identification

For this group of class A GPCRs, the expert reviewers completed initial, independent assessments, which led to discussions across the whole group to reach a consensus, which evaluated them as stronger candidates for deorphanization (Table 7). As with the previous group lacking convincing evidence for deorphanization (Table 6), the putative endogenous ligands could initially be subdivided based on chemical classes.

A. Potential lipid-sensing G protein-coupled receptors: *GPR31*, *GPR132*, and *GPR183*

For all 3 of these GPCRs, synthetic agonists and antagonists have been described, which should facilitate the broader characterization of pathophysiological signaling.

GPR31: 12S-Hydroxyeicosatetraenoic acid (12S-HETE, (5Z,8Z,10E,12S,14Z)-12-hydroxyeicosa-5,8,10,14-tetraenoic acid) is derived from arachidonic acid through 12S-lipoxygenase activity. 12S-HETE was initially described to activate *GPR31* in recombinant systems in 2011.¹³ The authors investigated the potential for binding of a radiolabeled version, which they observed to have high affinity (pK_d value of 8.3). Functional analysis of these cells identified 12S-HETE-enhanced binding of guanosine 5'-O-(3-[³⁵S]thio)triphosphate with a potency of 9.5 (pEC_{50} value) and activation of extracellular signal-regulated kinase. In an independent analysis, 300 nM 12S-HETE inhibited cAMP-mediated reporter gene expression in CHO cells expressing human recombinant *GPR31*.¹⁴

In a model of liver ischemia-reperfusion injury, symptoms were abated in an identical manner by interfering with either 12S-lipoxygenase or *GPR31*.¹⁵

It should be noted that lactate and pyruvate have also been suggested to activate *GPR31*,^{16–18} and knockdown of *GPR31* in human intestinal dendritic cells attenuated pyruvate-evoked responses.¹⁶

Although the evidence for activation by 12S-HETE appears consistent in mouse and human recombinant receptors, evidence for the protein expression of *GPR31* in human tissues is limited.

GPR132: Particular oxylipins, oxidized metabolites of fatty acids, increased guanosine 5'-O-(3-[³⁵S]thio)triphosphate or binding, inositol phosphates accumulation, and elevated intracellular calcium in cells expressing recombinant *GPR132*.¹⁹ Specifically, 9(S)-hydroxyoctadecadienoic acid (9S-HODE), derived from linoleic acid, and 11-hydroxy-5,8,12,14-eicosatetraenoic acid, derived from arachidonic acid, are possible agonists. The potency of 9S-HODE for calcium mobilization was ~5.6 (pEC_{50} value). 9S-HODE and 11-hydroxy-5,8,12,14-eicosatetraenoic acid were confirmed as agonists in independent studies using recombinant *GPR132*, measuring β -arrestin accumulation,²⁰ and a yeast pheromone gene assay replicated the potency of 9S-HODE with a pEC_{50} value of 5.9.²¹

One reservation noted was that the reported plasma concentration of 9-hydroxyoctadecadienoic acid was 58 nM in healthy rats,²² although inflammation increased tissue levels in the sciatic nerve from ~150 to over 400 pmol/mg tissue.²³

GPR132 has also been reported to be activated by amino acid conjugates of fatty acids, including *N*-(3-hydroxypalmitoyl)glycine,²⁴ *N*-palmitoylglycine,^{21,25} and *N*-linoleoylglycine,²¹ although cryo-EM studies suggested a different binding profile compared with oxidized fatty acids.²⁵

There is contradictory literature about the impact of lysophospholipids on *GPR132* function. Responses to lysophosphatidylcholine (LysoPC) in isolated human neutrophils were blocked by an antibody directed at *GPR132*,²⁶ whereas a report that LysoPC and sphingosylphosphorylcholine activated *GPR132* has been retracted,²⁷ as has a report suggesting activation of *GPR132* by LysoPC.²⁸ Multiple reports suggest that LysoPC^{26,28} and LysoPS²⁶ can activate *GPR132* in vitro. LysoPC was also reported to block the effects of protons on *GPR132* signaling.²⁹ Whether these actions of lipid metabolites are mediated through an orthosteric or allosteric mechanism (see discussion below for *GPR68*) awaits further investigation.

GPR183: Oxysterols are a family of sterol derivatives, among which 7 α ,25-dihydroxycholesterol (7 α ,25-diOHC) is formed by the sequential hydroxylation of cholesterol by cholesterol 25-hydroxylase and CYP7B1.³⁰ Subsequent turnover of 7 α ,25-diOHC is mediated by hydroxyl- Δ -5-steroid dehydrogenase, 3 β - and steroid Δ -isomerase 7, leading to the production of bile acids.³⁰ Two publications in 2011 identified that 7 α ,25-diOHC activated recombinant *GPR183*^{31,32} with potencies (pEC_{50} values) of 8.9 (guanosine 5'-O-(3-[³⁵S]thio)triphosphate binding) and 8.7 (calcium mobilization).

³H-7 α ,25-diOHC was observed to bind specifically to the recombinant receptor by different groups with a range of K_d values of 450 pM³² to 24 nM.³³

Modification of the expression of cholesterol 25-hydroxylase, a synthetic enzyme for oxysterols, altered signaling through *GPR183*.^{31,34–36}

B. Potential peptide-sensing G protein-coupled receptors: *GPR15* and *MRGPRX1*

For these GPCRs, there are limited examples of synthetic agonists and antagonists, which will hamper further characterization of these receptors.

Table 7

Ten human class A orphan G protein-coupled receptor evaluated for orphan status and identified as having high potential for deorphanization at the current time

Target	Proposed Endogenous/ Physiological Agonist/s	Surrogate Agonist/s	Antagonists/Inverse Agonists	Comment
<u>GPR4</u>	Protons ^{48,49,406–408}	-	Compound 1 ⁴⁰⁹ GPR4 antagonist 3b ⁴¹⁰ Compound 39c ⁴¹¹ NE 52-QQ57 ^{412–414}	Cryo-EM structures have been reported ^{54,415–418}
<u>GPR15</u>	GPR15L ^{37,38,40,419} GPR15L (71-81) ^{39,419}	-	Antibodies directed against <i>GPR15</i> were described to block GPR15L-mediated T-cell recruitment ⁴²⁰	Binding of modified GPR15L to <i>GPR15</i> has been reported ^{38,40,419,421} A cryo-EM structure of GPR15 with GPR15L bound has been described ⁴²² GPR15L has also been reported to activate CXCR4 in vitro ⁴²³
<u>GPR31</u>	12S-HETE ^{13,14,424,425}	SB583831 and SB583355 ²¹	SAH2 ⁴²⁴	Radiolabeled 12S-HETE binding to recombinant <i>GPR31</i> has been described ^{13,425} 12S-HETE was ineffective in a β -arrestin screen of <i>GPR31</i> ⁴
<u>GPR39</u>	Zn ²⁺ ^{66,67,70,426}	TC-G 1008 ⁴²⁷ compound 15 ⁴²⁸ Cpmd1324 ^{429,430}	VC43 ⁴³¹ Compound 61 ⁴³²	Knockdown of <i>GPR39</i> in human HaCaT keratinocytes attenuated zinc-evoked responses ⁶⁹ A PET ligand for GPR39 in vivo has been described ⁴³³
<u>GPR65</u>	Protons ^{48,50,408,434}	-	Psychosine appeared to act as an agonist at the recombinant receptor, ⁴³⁵ although a later report suggested antagonist action at acid-induced signaling ⁵⁰	BTB09089 was initially reported as a positive allosteric modulator of <i>GPR65</i> , ^{436,437} and then later suggested to target RhoA instead ⁴³⁸
<u>GPR68</u>	Protons ^{48,49,408,436,439,440}	-	Ogremorphin ⁴⁴¹ Compound 18l ⁴⁴²	MS48107, ⁴⁴³ ogerin, ⁴³⁶ and lorazepam ^{55,436} have been described as positive allosteric modulators A cryo-EM structure has been described ⁴¹⁸
<u>GPR132</u>	9-HODE ^{19,21,25,444}	ONC212 ⁴⁴⁵ CP55940, SKF95667, SB583831, and SB583355 ²¹ NOX-6-7 ²⁵ T10418 ⁴⁴⁴ NIBR51 ⁴⁴⁸ T10418 ⁴⁴⁴	GSK1820795A ²¹ NOX-6-18 ²⁵	9-HODE, <i>N</i> -palmitoylglycine, and <i>N</i> -linoleoylglycine were ineffective in a β -arrestin screen of <i>GPR132</i> ⁴ Crystal structures of <i>GPR132</i> have been described with bound <i>N</i> -palmitoylglycine or 9 (S)-hydroxy-10,12-octadecadienoic acid ²⁵
<u>GPR183</u>	7 α ,25-dihydroxycholesterol ³¹ –33,446–449 7 α ,27-OHC, 7 α -OHC, 7 β -OHC, 7 β , 27-OHC, 7 β , 25-OHC, 25-OHC, OHC ^{31,32,446}		GSK682753A ^{450,451} NIBR189 ⁴⁴⁸ SAE14 ⁴⁵² compound 32 ⁴⁵³ compound 33 ⁴⁴⁷	Radiolabeled 7 α ,25-diOHC binding to recombinant <i>GPR183</i> has been described ^{31,32,450} Cryo-EM structures of <i>GPR183</i> bound with GSK682753A and 7 α ,25-diOHC have been reported ⁴⁵⁴
<u>MRGPRD</u>	β -alanine ^{4,56–58,455} Alamandine ⁶⁰	Diethylstilbestrol ⁵⁸ EP2825 and EP3945 ⁴⁵⁵	MU6840 ⁵⁸ PD123319 ⁶⁰ D-Pro ⁷ -Ang-(1–7) ⁶² Berberamine ^{459,461}	Alamandine and β -alanine displaced binding of a fluorescently labeled alamandine peptide in recombinant <i>MRGPRD</i> expression ⁵⁹ Cryo-EM structures have been reported of <i>MRGPRD</i> bound with EP2825 and EP3945 ⁴⁵⁵ ML382 is reported as a positive allosteric modulator of the receptor. ⁴³
<u>MRGPRX1</u>	Bovine adrenal medulla peptide 8-22 ^{4,42–45}	Chloroquine ⁴⁵⁶ compound 16 ^{457,458} FSLRY ⁴⁵⁹ fungal micasin ⁴⁶⁰		Cryo-EM structures of <i>MRGPRX1</i> bound with BAM8-22 have been described, ^{458,462} as well as the synthetic agonist compound 16 ⁴⁶³

OHC, hydroxycholesterol.

GPR15: A highly cationic 81-aa polypeptide with chemokine-like properties, isolated from pig gut, activated recombinant GPR15 in calcium mobilization assays.³⁷ A truncated peptide identified as GPR15L-(25–81) exhibited a potency (pEC_{50} value) of ~7.5 in this assay. An independent investigation, building on a patent disclosure, described the potency of full-length “GPR15L” in a GPR15- β -arrestin assay of 7.7.³⁸ Other fragments of or modified peptides from “GPR15L” were reported to activate recombinant GPR15 in assays of cAMP inhibition with a potency of 6.7³⁹ or ERK activation with a potency of ~8.2.⁴⁰

A fusion protein of “GPR15L” with the fragment crystallizable portion of human IgG bound specifically to cells expressing recombinant GPR15, but not to untransfected cells. The potency (pIC_{50} value) for “GPR15L” displacement of fusion protein binding was ~7.0.³⁸

Fragments of cystatin C have been proposed to activate GPR15, although through a distinct mechanism of action.⁴¹

Previous guidance on receptor nomenclature from NC-IUPHAR recommended that a receptor be named after its endogenous agonist.^{1,12} The potential re-naming of GPR15 is complicated, however, by the sequence of discovery, where an endogenous peptide was identified after the receptor was identified and named after the GPCR.

MRGPRX1: Proenkephalin A is a protein precursor of the endogenous opioid pentapeptide enkephalins but also produces a 22-aa fragment called bovine adrenal medulla peptide 22, which was found to activate the δ -opioid peptide receptor in vitro, as well as MRGPRX1.⁴² A truncated version, bovine adrenal medulla peptide 8-22 (BAM-8-22), exhibited selective activation of MRGPRX1 for calcium mobilization, with a potency (pEC_{50} value) of 7.5, without activity at δ opioid peptide receptor up to micromolar concentrations.⁴² Activation of MRGPRX1 by BAM-8-22 has been reproduced in subsequent independent investigations.^{4,43–45}

Specific binding of ³H-BAM-8-22 was observed using recombinant MRGPRX1 with a pK_d value of ~8.0.⁴² Chemokine CXCL17 has been reported to activate MRGPRX1 in vitro.⁴⁶

Peptide fragments of hemoglobin (hemorphins LVV-H7 and VV-H7) were identified in human platelets and activated recombinant MRGPRX1, albeit with much lower potency than BAM-8-22.⁴⁷

Studies in rodents are confounded because they lack orthologues of this receptor, so it will be challenging to investigate the manipulation of proenkephalin A expression and its influence on MRGPRX1 activity.

C. A potential family of proton-sensing G protein-coupled receptors: GPR4, GPR65, and GPR68

In normal plasma and extracellular fluids, pH is tightly regulated, but in inflammatory states and with some cancers, extracellular pH can drop below 7.3, which may have implications for signal transduction. At the time of writing, these 3 GPCRs have a limited repertoire of synthetic pharmacological tools, so an aspiration of this review is that more widespread attention on these receptors should facilitate drug discovery in this area.

GPR4, GPR65, and GPR68 constitute a subfamily with higher homology to each other in comparison to the remaining class A GPCRs. One common feature is a series of 3–5 extracellular histidine residues combined with a triad of “buried” acidic glutamate and aspartate residues.⁴⁸ It is suggested that superficial histidines act as proton sensors, leading to intramolecular rearrangements allowing the deeper acidic residues to promote coupling to G proteins, although the 3 orphans appear to have slightly different thresholds for proton activation. As indicated in Table 7, multiple independent reports support the influence of pathophysiological changes in extracellular pH as the stimulus for coupling of these 3 receptors to elevation of intracellular cAMP in the case of GPR4⁴⁹ and GPR65⁵⁰ or to calcium and cAMP signaling by GPR68.^{49,51}

Membrane lysophospholipids have been suggested to influence the function of this family of GPCR, although there is a lack of clarity in terms of whether these effects are consistent and/or a mechanism of allosteric regulation. For example, a report of GPR4 activation by sphingosylphosphorylcholine and LysoPC has been retracted²⁷ as has a report that sphingosylphosphorylcholine activated GPR68.⁵² Lysophosphatidic acid activation of the LPA₁ receptor has been reported to facilitate GPR68 action in vitro.⁵³ A recent cryo-EM study suggested that LysoPC bound to GPR4 allosterically to enhance receptor function.⁵⁴

GPR68 was also reported to respond to a number of endogenous peptides: OSTN (115–133), CARTPT (76–96), and Pomc (141–162).³⁹ This report has not yet been reproduced. Sulazepam was described to act as a low-potency inverse agonist for GPR68.⁵⁵

D. MRGPRD

β -Alanine is a naturally occurring alternative amino acid in mammalian systems, resulting from pyrimidine degradation, which has also been of interest as a potential anabolic dietary supplement and precursor for the dipeptide carnosine. β -Alanine evoked calcium mobilization and inhibition of cAMP formation in MRGPRD-expressing cells with a potency (pEC_{50} value) of 4.8.⁵⁶ Responses of MRGPRD to similar concentrations of β -alanine were confirmed by several subsequent independent investigations.^{4,57,58}

Decarboxylation of the amino terminus of angiotensin-1-7 converts aspartate to alanine, producing a heptapeptide named alamandine. It is suggested to be formed in the heart from Ang-1-7 metabolism and to be present in the blood.⁵⁹ In cells expressing MRGPRD, alamandine evoked cAMP formation with a bell-shaped profile, in which the stimulatory phase had a potency (pEC_{50} value) of 12.4.⁶⁰ Although alamandine has biological effects in preparations in which MRGPRD is expressed and is sensitive to a reported MRGPRD antagonist^{61–64}, the pairing does not appear to have been reproduced with the recombinant receptor.

There remains, therefore, a need for triangulation of observations, as well as the demonstration of pathophysiological levels of the putative endogenous agonists for MRGPRD.

E. GPR39

Zinc is an essential trace element, with multiple transporters identified for translocation of zinc ions in mammalian cells, and an estimated 10% of the human proteome has been identified as zinc-binding proteins.⁶⁵ Extracellular concentrations of zinc ions in the micromolar range were found to enhance inositol phosphates and cAMP generation in GPR39-expressing cells with potencies (pEC_{50} values) of 4.7 and 5.1, respectively.⁶⁶ A contemporaneous report identified that fractions of FBS that activated GPR39-expressing cells could be eliminated in the presence of EDTA.⁶⁷ In these cells, micromolar zinc ion concentrations evoked rapid intracellular calcium ion elevations. GPR39 activation by zinc ions has been proposed as a result of synaptic activity⁶⁸ or damage.⁶⁹

The suggested locus for zinc ion binding to GPR39 is through 2 N-terminal histidine residues.⁷⁰ Although this location for a canonical orthosteric ligand would be unique for a class A GPCR, the possibility has been raised that it is consistent with an allosteric ligand.

It has been reported that a fragment from the ghrelin precursor called obestatin was an agonist for GPR39.⁷¹ However, several independent groups have been unable to replicate this finding.^{66,72–74} The original authors have since confirmed that they could not reproduce their findings on obestatin binding and activation of GPR39 in vitro.⁷⁵

Two alternative, potentially orthosteric oxylipin agonists have been proposed for GPR39: 15-HETE (15-hydroxyeicosatetraenoic acid) and 14,15-epoxyeicosatrienoic acid.⁷⁶ In a search for binding proteins for 14,15-epoxyeicosatrienoic acid, an irreversible probe labeled GPR39 in mouse vascular smooth muscle cells. Among the other oxylipins investigated, only 15-HETE was also able to evoke extracellular signal-regulated kinase activation in transfected cells.⁷⁶ The responses to these eicosanoids were enhanced in the presence of 1 μ M zinc ions, a concentration that was ineffective alone. Zinc ions and 15-HETE were also synergistic when intracellular calcium ions were measured in mouse vascular smooth muscle cells. Notably, 15-HETE and 14,15-epoxyeicosatrienoic acid were ineffective in a β -arrestin screen of GPR39.⁴

To conclude, therefore, the relationship between GPR39, zinc ions, and eicosanoid/oxylipin analogs needs clarifying before a change in nomenclature is warranted.

VI. Conclusions

In this review, we have provided an extended evaluation checklist for NC-IUPHAR subcommittees to conduct an unbiased evaluation of the orphan status of class A GPCRs, and indeed for all receptors.

Information about 10 of the orphan class A GPCRs (Table 7) is sufficiently advanced that we can refer these to further subcommittees of NC-IUPHAR. We would advocate for the wider community to continue investigating these suggested pairings—-independent confirmation is a fundamental in science. Cell-based assay kits are available commercially to assist in those investigations, which should facilitate the investigations of receptor pharmacology. However, there remain challenges associated with determining the levels of endogenous ligands in the close environment of the receptor. In addition, for some of the putative endogenous/physiological ligands described, the enzymatic pathways for production and transformation remain obscure.

In considering the substantial numbers of class A GPCRs lacking a putative endogenous agonist or any substantive pharmacology (Table 3), we are prompted to pose a number of questions:

Does every GPCR need to have an endogenous agonist or physiological ligand? As with the ACKR family of atypical chemokine receptors, the possibility exists for a singular modality (e.g., through β -arrestin)³ rather than multiple downstream signaling pathways, and so we may consider that, for some of these receptors, the “correct” combination of agonist and signaling pathway may not have been tested. A further possibility is that some receptors may only be functional as part of an oligomeric complex. For family C GPCRs, there are examples of obligate heterodimers such as the GABA_B receptor⁷⁷ and the sweet taste receptor, TAS1R2/TAS1R3.⁷⁸ Although the same profile has not been described for class A GPCRs, a heterodimer between GPR50 and the MT₁ receptor has been described, in which GPR50 exerted an inhibitory effect on MT₁ receptor function.⁷⁹

A number of class A orphan GPCRs have been described as having high constitutive activity in recombinant expression,⁸⁰ whether this results from the particular cellular environment or from intrinsic structural properties of these receptors will require further investigation. GPR161 provides an example where there is evidence for autoactivation of the receptor by an intrinsic peptide sequence⁸¹ in a manner distinct from the proteinase-activated receptors.⁸²

Does every GPCR need to respond to a single endogenous ligand (or ligand family)? For the cannabinoid receptors, there are 2 distinct families of endogenous ligands, based on esters, such as 2-arachidonoylglycerol, and amides, such as anandamide,⁸³

whereas opioid receptors have multiple endogenous peptide agonists.⁸⁴ The nomenclature for such examples will need to be resolved on a case-by-case basis.

Additionally, there are examples of GPCRs for which the physiological agonist is derived from exogenous sources. For example, fMet-Leu-Phe is a bacterial product that activates formylpeptide receptors and prompts chemotaxis in neutrophils.⁸⁵ Similar GPCRs in the mouth and nasal passages, the taste and odorant receptors, would be expected to respond to dietary and environmental stimuli, although they are also expressed in internal organs separated from the exterior.⁸⁶

Does every species orthologue need to respond to the same endogenous ligand? Certainly, there are “complications” of evolution, which imply that orthologues may not be highly conserved across species, leading to distinct pharmacology. This is most obviously evident in the bitter taste receptors⁸⁶ and the Mas-related GPCR family,⁸⁷ where different receptor repertoires and distinct pharmacology are evident in human and rodent species.

In summary, although advances are being made in our understanding of the pharmacology, physiology, and biochemistry of these incredibly useful drug targets, it is apparent that there are still major opportunities for the future exploitation of these class A GPCRs.

Abbreviations

7 α ,25-diOHC, 7 α ,25-dihydroxycholesterol; 9S-HODE, 9(S)-hydroxyoctadecadienoic acid; 12S-HETE, 12S-hydroxyeicosatetraenoic acid; 15-HETE, 15-hydroxyeicosatetraenoic acid; BAM-8-22, bovine adrenal medulla peptide 8-22; GPCR, G protein-coupled receptor; LysoPA, lysophosphatidic acid; LysoPC, lysophosphatidylcholine; NC-IUPHAR, Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology; S1P, sphingosine 1-phosphate.

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Conflict of interest

Authors Stephen P.H. Alexander, Kirstie A. Bennett, Elena Faccenda, Julien Hanson, Paul A. Insel, Simon D. Harding, Eamonn Kelly, Kirill A. Martemyanov, Rick R. Neubig, Stefan Offermanns, Gunnar Schulte, Nicola J. Smith declare no conflict of interest. Andrew J. Brown was an employee of GlaxoSmithKline at the time of writing the manuscript and provides consultancy services to Rewind Therapeutics, Schrodinger, Linchpin.Bio, and Mironid. Michelle Glass is a consultant for Aelis Farma Ltd. David E. Gloriam is a part-time employee and warrant holder of Kvantify. Christopher J. Langmead holds shares in GlaxoSmithKline Ltd, Pacalis Therapeutics Pty Ltd and Phrenix Therapeutics Inc. He is also a part-time employee of Phrenix Therapeutics Pty Ltd and is the recipient of research funding from Servier. Pacalis, Phrenix, and Servier are all engaged in GPCR drug discovery. Christopher J. Langmead has also received payment for consultancy from Neumora Therapeutics Inc and Curie.Bio. Mette M. Rosenkilde is co-founder and minor shareholder of Antag Therapeutics and

Synklino, and consultant at Aikium. Huixian Wu is an employee of Pfizer Inc. Anthony P. Davenport is a member of scientific advisory boards on endothelin for Johnson & Johnson, ENB Therapeutics and Pharmazz.

Data availability

The review summarizes the published papers and all supporting data contained within the article.

CRediT authorship contribution statement

Drafted the manuscript and analyzed template data: Stephen Alexander. Contributed to generating receptor templates, analyses of relevant literature, and writing of the manuscript (listed alphabetically): Kirstie Bennett, Andrew Brown, Anthony Davenport, Elena Faccenda, Michelle Glass, David Gloriam, Simon Harding, Julien Hanson, Paul Insel, Eamonn Kelly, Chris Langmead, Kirill Martemyanov, Rick Neubig, Stefan Offermans, Mette M. Rosenkilde, Gunnar Schulte, Nicola Smith, and Huixian Wu.

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