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**Abstract**—In 2005, the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) published a catalog of all of the human gene sequences known or predicted to encode G protein-coupled receptors (GPCRs), excluding sensory receptors. This review updates the list of orphan GPCRs and describes the criteria used by NC-IUPHAR to recommend the pairing of an orphan receptor with its cognate ligand(s). The following recommendations are made for new receptor names based on 11 pairings for class A GPCRs: hydroxycarboxylic acid receptors [ $\text{HCA}_1$  (*GPR81*) with lactate,  $\text{HCA}_2$  (*GPR109A*) with 3-hydroxybutyric

acid,  $\text{HCA}_3$  (*GPR109B*) with 3-hydroxyoctanoic acid]; lysophosphatidic acid receptors [ $\text{LPA}_4$  (*GPR23*),  $\text{LPA}_5$  (*GPR92*),  $\text{LPA}_6$  (*P2Y5*)]; free fatty acid receptors [ $\text{FFA}_4$  (*GPR120*) with omega-3 fatty acids]; chemerin receptor (*CMKLR1*; ChemR23) with chemerin; *CXCR7* (*CMKOR1*) with chemokines CXCL12 (SDF-1) and CXCL11 (ITAC); succinate receptor (*SUCNR1*) with succinate; and oxoglutarate receptor [*OXGR1* with 2-oxoglutarate]. Pairings are highlighted for an additional 30 receptors in class A where further input is needed from the scientific community to validate these findings. Fifty-seven human class A receptors (excluding pseudogenes) are still considered orphans; information has been

**ABBREVIATIONS:** Ang-(1-7), angiotensin-(1-7); BAM22, bovine adrenal medulla peptide 22; CMKLR1, chemokine-like receptor 1; CysLT, cysteinyl leukotriene; ERK, extracellular signal-regulated kinase; FFA, free fatty acid; GLP-1, glucagon-like peptide-1; GPCR, G protein-coupled receptor; HCA, hydroxycarboxylic acid; 12-(S)-HETE, 12-(S)-hydroxyeicosatetraenoic acid; ID no., identification number; ITAC, interferon-inducible T-cell  $\alpha$  chemoattractant; LPA, lysophosphatidic acid; LPI, lysophosphatidylinositol; LysoPS, lysophosphatidylserine; MRG, Mas-related GPCR; NAGly, *N*-arachidonoylglycine; NC-IUPHAR, International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification;  $7\alpha,25$ -OHC,  $7\alpha,25$ -dihydroxycholesterol; PAMP-20, proadrenomedullin N-terminal 20 peptide; RvD1, resolvin D1; S1P, sphingosine 1-phosphate; SDF-1, stromal cell-derived factor-1.

provided where there is a significant phenotype in genetically modified animals. In class B, six pairings have been reported by a single publication, with 28 (excluding pseudogenes) still classified as orphans. Seven orphan receptors remain in class C, with one pairing described by a single paper. The objective is

to stimulate research into confirming pairings of orphan receptors where there is currently limited information and to identify cognate ligands for the remaining GPCRs. Further information can be found on the IUPHAR Database website (<http://www.iuphar-db.org>).

## I. Introduction

The sequencing of the human genome has allowed the IUPHAR (International Union of Basic and Clinical Pharmacology) Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) to catalog all of the human gene sequences potentially encoding G protein-coupled receptors (GPCRs), excluding sensory receptors. In addition to established transmitter systems, the classification in *Pharmacological Reviews* (see Foord et al., 2005) and in the IUPHAR Database (IUPHAR-DB) (see Sharman et al., 2011) included “orphan” GPCRs for which the endogenous ligand(s) was not known. Since this publication, considerable progress has been made in screening artificially expressed receptors to identify the cognate endogenous ligand (for example, see Zhang et al., 2011; Civelli, 2012; Yoshida et al., 2012). Where understanding of the physiology, pharmacology, and pathology has begun to emerge, the receptor has been officially classified and named (usually after the endogenous ligand following IUPHAR nomenclature conventions) and published in *Pharmacological Reviews* (<http://www.iuphar-db.org/nciupharPublications.jsp>). Physiologic functions have now been assigned to a number of receptors previously designated as orphans. These include the family of free fatty acid receptors (FFA1–FFA3) (Stoddart et al., 2008); neuropeptide B and W as ligands NPBW1 (*GPR7*) and NPBW2 (*GPR8*) (Singh and Davenport, 2006); the protein encoded by the APJ gene (Ishida et al., 2004), now classified as the apelin receptor (Pitkin et al., 2010); *GPR30* as the estrogen GPCR (GPER) (Revankar et al., 2005; Thomas et al., 2005; Wang et al., 2008; Martensson et al., 2009; Prossnitz and Barton, 2011); *GPR54* as the kisspeptin receptor (Kirby et al., 2010); *GHS-R1a* as the ghrelin receptor (Davenport et al., 2005); the TA<sub>1</sub> receptor activated by endogenous trace amine ligands, including tyramine (IUPHAR-DB no. 2150) and  $\beta$ -phenylethylamine (IUPHAR-DB no. 2144) (Maguire et al., 2009); and *GPR131* as the bile acid receptor (GPBA) (Maruyama et al., 2002). This review extends the number of receptors where these criteria have been met, particularly where replicated by independent groups, which are shown for class A GPCRs in Table 1.

To reflect the dynamic nature of the field, where a single paper exists describing a new pairing, a list is maintained on IUPHAR-DB (<http://www.iuphar-db.org/latestPairings.jsp>) (Table 2). This review also reports on a third group still considered orphans (Table 3). In a small number of instances, the pairing is retracted because it cannot be repeated. In some cases, “surrogate” ligands for

orphan GPCRs (drugs or small molecules that can be used as tool compounds that act on targets for which the endogenous ligand is not yet known) have been identified, and these can be used as pharmacological tools to explore the function and therapeutic potential of these proteins. The alternative approach is to focus on significant phenotypes in genetically modified animals, and this information has been included. Orphan GPCRs have been identified that have activity in the absence of an endogenous ligand or work in concert with other receptors and may not have a cognate endogenous ligand. Finally, a small number of genes are listed, initially identified as orphan GPCRs, which are pseudogenes, at least in some individuals.

Thirty human receptors in class A are currently supported by a single publication; or where there is more than one independent publication, the results are not concordant or relevant committees are waiting for the accumulation of unequivocal pharmacological evidence for a formal adoption of nomenclature. Fifty-seven receptors (excluding pseudogenes) are still considered orphans. In class B, six pairings have been reported by a single publication, with an additional 28 (excluding pseudogenes) still classified as orphans. Seven orphan receptors remain in class C, with one pairing described by a single paper.

A number of orphan GPCRs were able to be deorphanized because of their close similarity to other receptors or paralogs. These are thought to have arisen by gene duplication and might therefore be expected to have similar ligands. Some of the receptors described in this review are groups of paralogs such as *GPR3*, *GPR6*, and *GPR12*. Conversely, however, GPCRs with disparate evolutionary origins can bind and respond to the same ligands. For example, the relaxins are able to activate RXFP1 and -2, which are 757 and 737 amino acids in length and share ~60% amino acid sequence similarity, with 10 leucine-rich repeats in their large N-terminal extracellular domains. In contrast, RXFP3 and -4, which are also activated by relaxins, have short N-terminal extracellular domains and contain only 469 and 374 amino acid residues. Receptors have been listed alphabetically in the tables, and reviews (including Lagerström and Schiöth, 2008; Strotmann et al., 2011) should be consulted for detailed analysis of the phylogenetic relationships.

We have endeavored to identify all key papers reporting pairings by carrying out systematic searches, using current as well as previous gene names for the orphan receptors in classes A, B, and C as they appear

TABLE 1

Recommendations for formal receptor nomenclature based on new pairings of class A orphan receptors with cognate ligands

Gene symbols are those approved by the HUGO Gene Nomenclature Committee (<http://www.genenames.org/>) (Seal et al., 2011). Where the phenotype of the knockout mouse has been published, this is indicated: Further information can be obtained from the IUPHAR Database (<http://www.iuphar-db.org/>) (Sharman et al., 2011) and the Mouse Genome Database at Mouse Genome Informatics (Eppig et al., 2012).

Endogenous Ligand	Official IUPHAR Nomenclature	Previous Nomenclature	Approved Human Gene Symbol	Knockout Mouse	Phenotype Reported
Chemerin (RARRES2, resolvin E1, TIG2)	Chemerin	CMKLR1	<i>CMKLR1</i>	Yes	Yes
CXCL12 (SDF-1), CXCL11 (ITAC)	CXCR7	CMKOR1	<i>CXCR7</i>	Yes	Yes
Omega-3 fatty acids	FFA4	GPR120/GPR129	<i>O3FAR1</i>	Yes	Yes
Lactate	HCA <sub>1</sub>	GPR81/GPR104	<i>HCAR1</i>	Yes	Yes
D-β-Hydroxybutyrate	HCA <sub>2</sub>	GPR109A	<i>HCAR2</i>	Yes	Yes
3-Hydroxyoctanoate	HCA <sub>3</sub>	GPR109B	<i>HCAR3<sup>a</sup></i>	No	
LPA	LPA <sub>4</sub>	GPR23	<i>LPAR4</i>	Yes	Yes
LPA	LPA <sub>5</sub>	GPR92/GPR93	<i>LPAR5</i>	Yes	Yes
LPA	LPA <sub>6</sub>	P2RY5	<i>LPAR6</i>	No	
2-Oxoglutarate	Oxoglutarate	GPR91	<i>OXGR1</i>	No	
Succinate	Succinate	GPR99	<i>SUCNR1</i>	Yes	Yes

<sup>a</sup> Gene absent in mice.

in the IUPHAR-DB. It is not possible to include all papers that refer to some aspect of a particular orphan receptor, but where appropriate and where they exist, we have added selected references to more detailed reviews, which should be consulted for further information. To provide readers with access to a wide range of chemical information and the biologic activity data for the ligands listed in this review, IUPHAR-DB Ligand identification numbers (ID no.) are provided (within parentheses). Readers may either enter the Ligand ID no. into the “Quick text search” box on the IUPHAR-DB website (<http://www.iuphar-db.org>) or navigate to the ligand search tools page (<http://www.iuphar-db.org/DATABASE/chemSearch.jsp>) and select “IUPHAR/GRAC Ligand ID” in the “Chemical identifier” search box. The review excludes sensory receptors, which are curated by the Olfactory Receptor DataBase (ORDB) (<http://senselab.med.yale.edu/ordb/>).

## II. Criteria for Deorphanization

Several criteria are used by NC-IUPHAR in considering the assignment of an endogenous ligand to a receptor. Firstly, two or more refereed papers from independent research groups should demonstrate activity of the ligand at the receptor, with a potency that is consistent with a physiologic function. Reproducibility of the pairing is the minimum criterion, particularly to avoid false positives that might arise in high-throughput screens or for other reasons. In some cases, although two independent groups have reported a pairing, others have failed to reproduce this. We have indicated where pairings remain controversial to identify areas where more research is required for NC-IUPHAR to make a definitive statement and that are under active consideration by the relevant subcommittees. Occasionally, reported pairings are retracted, and these are recorded on the IUPHAR-DB (<http://www.iuphar-db.org/latestPairings.jsp>).

As a particular field evolves, the following additional criteria may support and strengthen the initial pairing,

although it is recognized that these are exacting and are unlikely to be met in all instances. Preferably, both radioligand binding (although it is recognized that some endogenous ligands may not be suitable for labeling or the density of receptors may be too low to detect) and functional assays should be employed, both in vitro and in native tissues. Selective agonists should mimic and selective antagonists should block the action of the endogenous ligand. Secondly, the putative endogenous ligand should be present in tissues in appropriate concentrations. Further evidence for the pairing of orphan GPCRs with cognate endogenous ligands may be obtained at the anatomic level; there should be plausible mechanisms for the proposed ligand to reach physiologically significant concentrations in tissues expressing its cognate receptor, either through local synthesis or by transport to the tissue, e.g., as a hormone. For neuropeptides, indirect techniques such as immunocytochemistry and in situ hybridization of the precursor mRNA can provide useful evidence. Small molecules that are candidate ligands for receptors may be detected using a variety of techniques including radioimmunoassay and mass spectrometry associated with gas chromatography or high-performance liquid chromatography. Deleting the gene encoding the receptor in mice, exploiting a naturally occurring deletion in human tissues, or RNA silencing should abolish receptor characteristics, such as radioligand binding or physiologic/pharmacological actions of the endogenous ligand in functional assays. Conversely, receptor overexpression may be expected to potentiate these actions.

Many of the recently proposed ligands are lipids, which pose distinct difficulties for assignment as endogenous orthosteric ligands. Firstly, concentration-response relationships are almost always difficult to assess due to detergent and surfactant effects, binding to proteins such as albumin, and formation of micelles. Secondly, by modification of membrane properties or insertion into membranes, lipids can block or reveal the effects of allosteric modulators; membrane interactions can also

TABLE 2

Reported pairings of orphan receptors with cognate ligands reported by a single paper

Gene symbols are those approved by the HUGO Gene Nomenclature Committee (<http://www.genenames.org/>) (Seal et al., 2011). Where the phenotype of the knockout mouse has been published, this is indicated; Further information can be obtained from the IUPHAR Database (<http://www.iuphar-db.org/>) (Sharman et al., 2011) and the Mouse Genome Database at Mouse Genome Informatics (Eppig et al., 2012).

Putative Endogenous Ligand	Approved Human Gene Symbol	Knockout Mouse	Phenotype Reported
Class A			
Chemerin	<i>GPR1</i>	Yes	No
S1P	<i>GPR3</i>	Yes	Yes
Protons	<i>GPR4</i>	Yes	Yes
S1P	<i>GPR6</i>	Yes	Yes
S1P	<i>GPR12</i>	Yes	Yes
Nucleotides and CysLTs (leukotriene C <sub>4</sub> , leukotriene D <sub>4</sub> , UDP, UDP-galactose)	<i>GPR17</i>	Yes	Yes
NAGly	<i>GPR18</i>	No	
12-(S)-HETE	<i>GPR31<sup>a</sup></i>	No	
RvD1	<i>GPR32<sup>a</sup></i>	No	
LPS	<i>GPR34</i>	Yes	Yes
Kynurenic acid, 2-acyl LPA	<i>GPR35</i>	No	
Neuropeptide head activator <sup>b</sup>	<i>GPR37</i>	Yes	Yes
Zn <sup>2+</sup>	<i>GPR39</i>	Yes	Yes
L-α-LPI	<i>GPR55</i>	Yes	Yes
Protons	<i>GPR65</i>	Yes	Yes
Protons	<i>GPR68</i>	Yes	Yes
CCL5 (RANTES)	<i>GPR75</i>	No	
Medium-chain fatty acids	<i>GPR84</i>	Yes	Yes
LPA	<i>GPR87</i>	Yes	Yes
Oleoylethanolamide	<i>GPR119</i>	Yes	Yes
Protons	<i>GPR132</i>	Yes	Yes
Oxysterols	<i>GPR183</i>	Yes	Yes
R-spondins	<i>LGR4</i>	Yes	Yes
R-spondins	<i>LGR5</i>	Yes	Yes
R-spondins	<i>LGR6</i>	No	
Ang-(1-7)	<i>MAS1</i>	Yes	Yes
β-Alanine	<i>MRGPRD</i>	Yes	Yes
BAM22	<i>MRGPRX1<sup>c</sup></i>	No	
Cortistatin, PAMP	<i>MRGPRX2<sup>c</sup></i>	No	
LPA, S1P	<i>P2RY10</i>	No	
Class B			
Phosphatidylserine	<i>BAI1</i>	No	
C1q-like proteins	<i>BAI3</i>	No	
Decay accelerating factor	<i>CD97</i>	Yes	No
Collagen type III	<i>GPR56</i>	Yes	Yes
Neurexins, teneurin-2	<i>LPHN1</i>	Yes	Yes
FLRT3	<i>LPHN3</i>	Yes	No
Class C			
Calcium, amino acids, and osteocalcin	<i>GPRC6A</i>	Yes	Yes

<sup>a</sup> Pseudogene in mice.

<sup>b</sup> See discussion in text as to whether neuropeptide head activator is an endogenous ligand.

<sup>c</sup> Gene absent in mice.

drive allosteric changes in receptor conformation and also change the surface charge around channels and receptors. Studies of the crystal structure of the S1P<sub>1</sub> receptor fused to T4 lysozyme in complex with an antagonist sphingolipid mimic have been particularly instructive (Hanson et al., 2012). Lipid ligands are thought to gain access to the binding pocket from within the membrane bilayer rather than from the extracellular compartment.

In parallel, there has been a major revolution in lipid metabolomics, with up to 3000 lipids being detectable in small biologic membrane samples, and precise changes of these lipids may be followed in, for example, pathologic situations. However, this expensive methodology has not been applied to any of the studies claiming lipids as the endogenous agonists of receptors, so the question of whether closely related lipids may be more preponderant (and active) than the studied

species is a clear concern for nomenclature. NC-IUPHAR will continue to apply the criteria for evaluating pairing of lipids with GPCRs that are used for non-lipid ligands but encourages authors to take these reservations into account for future studies.

In the absence of a cognate endogenous ligand, genetically modified mice and overexpression of genes encoding target receptors can provide evidence for a physiologic or pathophysiological role. For example, the *GPR3* gene has been mapped to the candidate Alzheimer's disease linkage region and is predominantly expressed in the central nervous system. It is thought to be a constitutively active orphan GPCR and has been identified as a modulator of amyloid-β production. Overexpression of *GPR3* stimulated amyloid-β production in an Alzheimer's disease mouse model, whereas knocking out the *GPR3* gene prevented accumulation of the amyloid-β peptide (Thathiah et al., 2009).

TABLE 3  
Orphan receptors

Gene symbols are those approved by the HUGO Gene Nomenclature Committee (<http://www.genenames.org/>) (Seal et al., 2011). Where the phenotype of the knockout mouse has been published, this is indicated. Further information can be obtained from the IUPHAR Database (<http://www.iuphar-db.org/>) (Sharman et al., 2011) and the Mouse Genome Database at Mouse Genome Informatics (Eppig et al., 2012).

Approved Human Gene Symbol	Knockout Mouse	Phenotype Reported
Class A		
BB <sub>3</sub>	Yes	Yes
GPR15	No	
GPR19	Yes	Yes
GPR20	Yes	No
GPR21	Yes	No
GPR22	Yes	Yes
GPR25	No	
GPR26	Yes	Yes
GPR27	No	
GPR33 <sup>a</sup>	No	
GPR37L1	Yes	Yes
GPR42 <sup>b, c</sup>	No	
GPR45	No	
GPR50	Yes	Yes
GPR52	No	
GPR61	Yes	No
GPR62	No	
GPR63	No	
GPR78	No <sup>b</sup>	<sup>b</sup>
GPR79 <sup>c</sup>	No <sup>d</sup>	<sup>d</sup>
GPR82	Yes	Yes
GPR83	Yes	No
GPR85	Yes	Yes
GPR88	Yes	Yes
GPR101	No	
GPR135	No	
GPR139	No	
GPR141	No	
GPR142	No	
GPR146	No	
GPR148 <sup>b</sup>	No	
GPR149	Yes	Yes
GPR150	No	
GPR151	Yes	No
GPR152	No	
GPR153	No	
GPR160	No	
GPR161	Yes	No
GPR162	No	
GPR171	No	
GPR173	No	
GPR174	No	
GPR176	No	
GPR182	No	
MASIL <sup>b</sup>	No	
MRGPRE	Yes	Yes
MRGPRF	No	
MRGPRG	No	
MRGPRX3	No <sup>d</sup>	
MRGPRX4 <sup>b</sup>	No	
OPN3	No	
OPN5	No	
P2RY8 <sup>b</sup>	No	
TAAR2	No	
TAAR3 <sup>c</sup>	No	
TAAR4P <sup>c</sup>	No	
TAAR5	No	
TAAR6	No	
TAAR8	No	
TAAR9	No	
Class B		
BAI2	Yes	Yes
CELSR1	Yes	Yes
CELSR2	Yes	Yes
CELSR3	Yes	Yes
ELTD1	Yes	No
EMR1	Yes	Yes
EMR2 <sup>b</sup>	No	

(continued)

TABLE 3—Continued

Approved Human Gene Symbol	Knockout Mouse	Phenotype Reported
EMR3 <sup>b</sup>	No	
EMR4P <sup>c</sup>	No	
GPR64	Yes	Yes
GPR97	Yes	No
GPR98	Yes	Yes
GPR110	No	
GPR111	No	
GPR112	No	
GPR113	No	
GPR114	No	
GPR115	No	
GPR116	No	
GPR123	No	
GPR124	Yes	Yes
GPR125	Yes	No
GPR126	Yes	Yes
GPR128	No	
GPR133	No	
GPR144	No	
GPR157	No	
LPHN2	No	
Class C		
GPR156	No	
GPR158	No	
GPR179	Yes	Yes
GPRC5A	Yes	Yes
GPRC5B	Yes	Yes
GPRC5C	Yes	No
GPRC5D	No	

<sup>a</sup> Pseudogene in most individuals.<sup>b</sup> Gene absent in rats and mice.<sup>c</sup> Pseudogene in man.

The results suggest that the *GPR3* protein may be a potential therapeutic target for the treatment of Alzheimer's disease, leading to the development of surrogate ligands in the absence of knowledge of the endogenous transmitter (Thathiah et al., 2009).

### III. Recommendations for Formal Receptor Nomenclature Based on New Pairings of Orphan Receptors with Cognate Ligands

#### A. Class A

1. *Hydroxycarboxylic Acid Receptors: HCA<sub>1</sub>* (GPR81)/*Lactate, HCA<sub>2</sub>* (GPR109A)/*3-Hydroxybutyric Acid, and HCA<sub>3</sub>* (GPR109B)/*3-Hydroxyoctanoic Acid*. A family of three structurally related receptors has been named the hydroxycarboxylic acid (HCA) receptors (Offermanns et al., 2011). HCA<sub>1</sub> (*GPR81*) is activated by lactic acid (IUPHAR-DB ID nos. 2932, 2934) (Cai et al., 2008; Ahmed et al., 2010), HCA<sub>2</sub> (*GPR109A*; also known as *PUMA-G*) by β-D-hydroxybutyric acid (IUPHAR-DB ID no. 1593) (Taggart et al., 2005), and HCA<sub>3</sub> (*GPR109B*; also known as *HM74*) is activated by the β-oxidation intermediate 3-hydroxyoctanoic acid (IUPHAR-DB ID no. 2933) (Ahmed et al., 2009). The endogenous ligands of these receptors are unusual as they are of relatively low potency (in the millimolar range) compared with other endogenous GPCR ligands, although the endogenous ligand of HCA<sub>3</sub> (3-hydroxyoctanoic acid) activates its receptor at micromolar concentrations. HCA<sub>2</sub> and HCA<sub>3</sub> are also activated by nicotinic

acid (Tunaru et al., 2003). This receptor family was first named the nicotinic acid receptor family. However, this nomenclature is inappropriate because nicotinic acid is not an endogenous ligand. HCA<sub>1</sub> and HCA<sub>2</sub> are present in humans and rodents, whereas HCA<sub>3</sub> is probably the result of a recent gene duplication of the HCA<sub>2</sub> receptor and is only present in primates. All three receptors are particularly highly expressed in adipocytes, where they are thought to couple to G<sub>i</sub> proteins to cause antilipolytic effects. This has led to the development of a number of synthetic agonists, albeit of comparatively low affinity, that induce antidyslipidemic effects similar to those of nicotinic acid, the original surrogate ligand for HCA<sub>2</sub>. However, recently Luring et al. (2012) found that synthetic agonists of HCA<sub>2</sub> receptor do not fully mimic the lipid effects of nicotinic acid. Other pharmacological tools are limited. There are currently no selective antagonists or allosteric modulators for any of these receptors.

2. *Lysophosphatidic Acid Receptors: LPA<sub>4</sub> (GPR23), LPA<sub>5</sub> (GPR92), and LPA<sub>6</sub> (P2Y5).* Lysophosphatidic acid (LPA; IUPHAR-DB ID no. 2906) is a membrane-derived lipid, which mediates its actions via a cluster of three structurally related GPCRs, LPA<sub>1–3</sub>. These receptors mediate a wide range of physiologic actions. Recently, two structurally dissimilar receptors, previously designated as orphans, have been added to the LPA receptor family. They bind LPA with high affinity (Chun et al., 2010), despite having closer sequence similarity to P2Y receptors. This suggests evolution of LPA responsiveness via two lineages. *GPR23* (also known as *P2Y9* and *P2Y5*-like) is activated by LPA (IUPHAR-DB ID no. 2906) (Noguchi et al., 2003) and has been classified as LPA<sub>4</sub>. The receptor is present in humans, rats, and mice and, interestingly, is located on the X chromosome in each species. The receptor is reported to couple to multiple G proteins (G<sub>12/13</sub>, G<sub>q/11</sub>, G<sub>i</sub>, and G<sub>s</sub>). Agonists and antagonists selective for LPA<sub>4</sub> over other LPA receptors have not been developed. One group reported that LPA<sub>4</sub> receptor-deficient mice displayed no overt abnormalities but that LPA<sub>4</sub>-deficient mouse embryonic fibroblasts were hypersensitive to LPA-induced cell migration, suggesting that the receptor is a suppressor of LPA-dependent cell migration and invasion (Lee et al., 2008b). A second group (Sumida et al., 2010) showed that a subset of LPA<sub>4</sub>-deficient embryos did not survive gestation and displayed hemorrhages and/or edema in many organs, concluding that LPA<sub>4</sub> regulates establishment of the structure and function of blood and lymphatic vessels during mouse embryogenesis.

The orphan receptor *GPR92* has been classified as LPA<sub>5</sub>, which is activated by LPA (IUPHAR-DB ID no. 2906) (Kotarsky et al., 2006; Lee et al., 2006). Agonists and antagonists selective for LPA<sub>5</sub> over other LPA receptors have not been developed, although there appears a preference for ether LPA analogs over ester LPA analogs (Williams et al., 2009) and targeted

disruption of the LPA<sub>5</sub> gene causes a pain phenotype (Lin et al., 2012).

The gene initially termed *6H1* (Kaplan et al., 1993) was subsequently renamed *P2RY5* due to sequence homology with P2Y receptors (Webb et al., 1996). LPA (IUPHAR-DB ID no. 2906) was proposed as a ligand for P2Y5 (Pasternack et al., 2008; Yanagida et al., 2009). Pasternack et al. (2008) identified homozygous truncating mutations in the *P2RY5* (now *LPAR6*) gene and found the receptor to be essential for the maintenance of human hair growth. We recommend *P2Y5* be classified as LPA<sub>6</sub>.

3. *FFA4 (GPR120) and Omega-3 Fatty Acids.* FFAs are essential nutritional components and, in addition, activate a family of three GPCRs (FFA1–FFA3), which play critical roles in physiology and pathophysiology, particularly in metabolic disorders. *GPR120* is abundantly expressed in intestine and functions as a receptor for saturated and unsaturated long-chain FFAs including palmitoleic acid,  $\alpha$ -linolenic acid (IUPHAR-DB ID no. 1049), and docosahexaenoic acid (IUPHAR-DB ID no. 1051) linked to the G<sub>q/11</sub> pathway (Hirasawa et al., 2005). The authors showed that the main physiologic action of *GPR120* by FFAs was the secretion of glucagon-like peptide-1 (GLP-1) in vitro and in vivo and an increase in circulating insulin. This has important therapeutic implications, as GLP-1 is the most potent insulinotropic incretin.

*GPR120*-deficient mice fed high-fat diets developed obesity, glucose intolerance, and fatty liver with decreased adipocyte differentiation and lipogenesis and enhanced hepatic lipogenesis. Conversely, in humans, *GPR120* expression in adipose tissue is significantly higher in obese individuals than in lean controls, owing to a deleterious nonsynonymous mutation that inhibits *GPR120* signaling activity. Furthermore, this variant increased the risk of obesity in European populations. The authors of this study (Ichimura et al., 2012) concluded that these studies show that dysfunction of *GPR120* leads to obesity in both mouse and man. However, further studies are required to understand these apparently contradictory results.

*GPR120* knockout mice (as well as FFA1 receptor knockout mice) showed a diminished taste preference for linoleic acid and oleic acid and diminished neurophysiological responses to several fatty acids, showing that FFA1 and *GPR120* mediate the taste of fatty acids (Cartoni et al., 2010). We recommend *GPR120* be classified as FFA4.

4. *The Chemerin Receptor (Chemokine-like Receptor; CMKLR1; ChemR23) and Chemerin.* Wittamer et al. (2003) first identified chemerin (IUPHAR-DB ID no. 2945), a potent 14-kDa chemoattractant protein of a novel class, in biological fluids as the product of the human tazarotene-induced gene-2 (*Tig-2*; current gene symbol, *RARRS2*). It is secreted in the plasma as a

precursor of low biologic activity, which upon proteolytic cleavage of its COOH-terminal domain is converted to an agonist of *CMKLR1* (Luangsay et al., 2009), the chemerin receptor. The pairing was confirmed by Meder et al. (2003) and Zabel et al. (2005). Chemerin, acting via this receptor, induces the migration of macrophages and dendritic cells in vitro, suggesting a proinflammatory role, whereas in vivo studies using chemerin receptor-deficient mice suggest an anti-inflammatory action (Luangsay et al., 2009). Responses to chemerin that are abolished in receptor knockout mice include migration of dendritic cells and macrophages (Luangsay et al., 2009; Bondue et al., 2011a), adhesion of peritoneal exudate cells to fibronectin (Hart and Greaves, 2010), and enhancement of microbial particle clearance and apoptotic neutrophil ingestion by macrophages (Cash et al., 2010). Chemerin/*CMKLR1* interaction also promotes adipogenesis and angiogenesis (for review, see Yoshimura and Oppenheim, 2011). We recommend *CMKLR1* be classified as the chemerin receptor.

Resolvins are a family of potent lipid mediators derived from both eicosapentaenoic acid (IUPHAR-DB ID no. 3362) and docosahexaenoic acid (IUPHAR-DB ID no. 1051) (see Uddin and Levy, 2011). Resolvin E1 (IUPHAR-DB ID no. 3333), a potent anti-inflammatory and proresolving mediator derived from eicosapentaenoic acid generated during the resolution phase of inflammation, has also been reported as a ligand for the chemerin receptor (Arita et al., 2007). To date, this pairing has not been confirmed, and another group has failed to reproduce the activity of resolvin E1 on the chemerin receptor in binding and a range of functional assays (Bondue et al., 2011b).

5. *CXCR7 (CMKOR1) with CXCL12 (SDF-1) and CXCL11 (ITAC)*. The chemokines stromal cell-derived factor-1 (SDF-1), also known as chemokine (C-X-C motif) ligand 12 (CXCL12), and interferon-inducible T-cell  $\alpha$  chemoattractant (ITAC), also known as CXCL11, bind with high affinity to *CXCR7* and promote cell migration (Balabanian et al., 2005; Burns et al., 2006). *CXCR7* does not signal through classic G protein-coupled mechanisms and has been proposed to function as a nonsignaling receptor that either mediates CXCL12 internalization and degradation or forms heterodimers with *CXCR4* to modify *CXCR4* downstream signaling (Zhu and Murakami, 2012). However, there is now convincing evidence that *CXCR7* is a functional receptor, signaling through  $\beta$ -arrestin to activate mitogen-activated protein kinases (Rajagopal et al., 2010; Zhu and Murakami, 2012). Intriguingly, in zebrafish, *CXCR7* has been shown to shape gradients of CXCL12 for optimal signaling at *CXCR4* to mediate gonadal germ cell migration (Boldajipour et al., 2008). The phenotype of *CXCR7*-deficient mice included postnatal lethality and cardiovascular defects (Sierro et al., 2007; Gerrits et al., 2008).

6. *Succinate Receptor (SUCNR1 GPR91) with Succinate; Oxoglutarate Receptor (OXGR1 GPR99) with*

*2-Oxoglutarate ( $\alpha$ -Ketoglutarate)*. Succinate (IUPHAR-DB ID no. 3637) and 2-oxoglutarate ( $\alpha$ -ketoglutaric acid; IUPHAR-DB ID no. 3636) are intermediates of the citric acid cycle present at micromolar concentrations in blood and are regulated by respiration, metabolism, and renal mechanisms. He et al. (2004) proposed that SUCNR1 (*GPR91*) functions as a receptor for succinate, with an EC<sub>50</sub> of 56  $\mu$ M in an aequorin assay, coupling to a pertussis toxin-sensitive G<sub>i</sub>/G<sub>o</sub> and pertussis toxin-insensitive G<sub>q</sub> pathways. They also proposed another closely related GPCR, OXGR1 (*GPR99*), to be activated by 2-oxoglutarate, with an EC<sub>50</sub> of 70  $\mu$ M via a G<sub>q</sub>-mediated pathway. Both pairings have been replicated in a  $\beta$ -arrestin assay (Southern et al., 2013), also at high EC<sub>50</sub> values of 800  $\mu$ M for succinate binding to SUCNR1 and 130  $\mu$ M for 2-oxoglutarate binding to OXGR1. In *Gpr91* knockout mice, there was an impairment in renin release from the kidney in response to high glucose levels, thought to be mediated by a paracrine signaling pathway involving accumulation of succinate and activation of *GPR91* (Toma et al., 2008). Consistent with this, succinate increased blood pressure in rats and mice—an effect abolished in *Gpr91*-deficient mice (He et al., 2004). We recommend *SUCNR1* be classified as the succinate receptor, and *OXGR1* be classified as the oxoglutarate receptor.

#### B. Class B

No recommendations.

#### C. Class C

No recommendations.

### IV. Pairings of Orphan Receptors with Cognate Ligands Reported by a Single Paper or Where a Formal Pairing Is Yet To Be Agreed

The following is a list of 32 receptors for which single publications have claimed to identify the endogenous ligand; alternatively, input from the scientific community is needed to reproduce and validate these findings. The minimum criterion for NC-IUPHAR to recommend that an orphan receptor receives official recognition is that the pairing of the ligand with the receptor should be repeated by at least one independent laboratory, with no overlap between the researchers, ideally by a different assay. The majority of papers discussed below have used artificially expressed receptors linked to a reporter system; the density of receptors per cell can be substantially higher than in native tissues with the potential for false positives.

#### A. Class A

1. *GPR1 and Chemerin*. On the basis of its homology to *CMKLR1*, Barnea et al. (2008) identified chemerin (IUPHAR-DB ID no. 2945) as a GPR1 ligand using a  $\beta$ -arrestin assay. An iodinated C-terminal peptide

fragment of chemerin (149–157 amino acids of full-length chemerin; chemerin C-terminal peptide; IUPHAR-DB ID no. 3422) bound to *GPR1*-transfected cells with a single binding site ( $K_d$  of 5.3 nM), similar to the  $K_d$  of 4.9 nM for *CMKLR1*-transfected cells. However, in a  $\beta$ -arrestin recruitment assay, chemerin had an  $EC_{50}$  of 240 pM at *GPR1* compared with 3 nM for *CMKLR1*. A C-terminal peptide fragment, chemerin 145–157, also bound to *GPR1* in a  $\beta$ -arrestin assay (Southern et al., 2013). Chemerin also binds to *CCRL2* (see below; Leick et al., 2010), which is thought to be a nonsignaling receptor that functions to reduce the local concentration of the molecule (Zabel et al., 2008).

2. *GPR3/GPR6/GPR12 and Sphingosine 1-Phosphate*. Currently, there are five lysophospholipid receptors, which have been classified as  $S1P_1$ – $S1P_5$  receptors because their endogenous ligand is accepted to be the lysophospholipid sphingosine 1-phosphate (S1P; IUPHAR-DB ID no. 911). *GPR3*, *GPR6*, and *GPR12* are phylogenetically related to the  $S1P$ , LPA, and melanocortin receptors (Gloriam et al., 2007). They were proposed to be three additional  $S1P$  receptors following screening of 200 bioactive lipids (Uhlenbrock et al., 2002), but this result was not replicated in a  $\beta$ -arrestin-based assays by two different groups (Yin et al., 2009, Southern et al., 2013). S1P was also suggested to be a high-affinity ligand for *GPR6* in a study by Ignatov et al. (2006). All three receptors display significant constitutive activation of adenylate cyclase (through  $G_s$ ) and calcium mobilization (through  $G_i$ ), which can be modulated by S1P and dihydro sphingosine 1-phosphate (IUPHAR-DB ID no. 2921) with nanomolar  $EC_{50}$  values.

3. *GPR4/GPR65/GPR68/GPR132 (G2A) and Protons*. In biological systems, carbon dioxide exists in equilibrium with bicarbonate and protons ( $H^+$ ), which must be sensed to be able to maintain cellular pH. The cluster of structurally related GPCR genes encoding *GPR4* (Ludwig et al., 2003; Tobo et al., 2007), *GPR65* (Wang et al., 2004), *GPR68* (Ludwig et al., 2003), and *GPR132* (Murakami et al., 2004) have been proposed to function as proton-sensing receptors detecting acidic pH (Seuwen et al., 2006). This family was originally reported to respond to lipids such as sphingosylphosphorylcholine, lysophosphatidylcholine, and psychosine, but these reports have been retracted (Zhu et al., 2001; Witte et al., 2005) and others have found negative regulation of these receptors by high micromolar concentrations of lipids not to be specific (Seuwen et al., 2006). The current balance of opinion is in favor of proton sensing. The physiologic role of this family in sensing pH is beginning to emerge (Kostenis, 2004; Meyer zu Heringdorf and Jakobs, 2007). Yang et al. (2007) reported that deletion of the *GPR4* gene in mice leads to partially penetrant vascular abnormalities during development and speculated that the receptor functions in blood vessel pH sensing. Gene disruption of *GPR4* is also associated with

reduced sensitivity to vascular endothelial growth factor-evoked angiogenesis (Wyder et al., 2011).

4. *GPR17: Dual Receptor for Cysteinyl Leukotrienes/ Nucleotides*. *GPR17* is phylogenetically related to the nucleotide (P2Y) and cysteinyl leukotriene (CysLT) receptors (Gloriam et al., 2007) and may provide an ancestral link to the two families. Both CysLTs (with  $EC_{50}$  values in the nanomolar range) and uracil nucleotides ( $EC_{50}$  in the micromolar range) have been reported to activate *GPR17*, leading to both adenylate cyclase inhibition and intracellular calcium increases (Ciana et al., 2006). Benned-Jensen and Rosenkilde (2010) confirmed the activation of *GPR17* by uracil nucleotides but were unable to demonstrate activation or binding by CysLTs. A third group (Maekawa et al., 2009) was not able to demonstrate activation of *GPR17* by either UDP-glucose or CysLTs and instead proposed that *GPR17* functions as a negative regulator of the CysLT<sub>1</sub> receptor response to leukotriene D<sub>4</sub>. In vivo inhibition of *GPR17* or in vivo knockdown by antisense molecules reduced ischemic damage in a rat focal ischemia model, suggesting that *GPR17* may be a target mediating brain damage by nucleotides and CysLTs (Ciana et al., 2006).

5. *GPR18 and N-Arachidonoylglycine, Cannabinoid Ligands*. Kohno et al. (2006) screened a lipid library and identified an endogenous ligand, *N*-arachidonoylglycine (NAGly; IUPHAR-DB ID no. 3635) by measuring an increase in intracellular  $Ca^{2+}$  concentration in *GPR18*-transfected cells. NAGly also inhibited forskolin-induced cAMP production in a pertussis toxin-sensitive manner in the *GPR18*-transfected CHO cells, with an  $EC_{50}$  value of 20 nM. *GPR18* is mainly expressed in lymphoid cell lines, such as spleen and thymus, with moderate expression in brain, testis, ovary, and lung, and the authors suggested that *GPR18* might be involved in regulation of the immune system. NAGly has been suggested to be an endogenous metabolite of the endocannabinoid anandamide (*N*-arachidonoyl ethanolamine; IUPHAR-DB ID no. 2364), differing only in a change in the oxidation state of the carbon  $\beta$  to the amido nitrogen that greatly reduces agonist activity at cannabinoid receptors CB<sub>1</sub> and CB<sub>2</sub>. NAGly is present in a range of tissues including skin, small intestine, kidney, and testis and displays distinct antinociceptive and anti-inflammatory activities. McHugh et al. (2010) have suggested that NAGly mediates these actions via a putative “abnormal cannabidiol” receptor, which is *GPR18*. More recently, *GPR18* has been confirmed to respond to NAGly (McHugh et al., 2012) but also to the prototypic CB<sub>1</sub> and CB<sub>2</sub> cannabinoid receptor ligand,  $\Delta^9$ -tetrahydrocannabinol (IUPHAR-DB ID no. 2424). In contrast, the pairing of NAGly and  $\Delta^9$ -tetrahydrocannabinol could not be repeated in a  $\beta$ -arrestin assay (Southern et al., 2013). The nomenclature of *GPR18* is currently being considered by the cannabinoid receptor subcommittee of NC-IUPHAR.

6. *GPR31 and 12-(S)-Hydroxyeicosatetraenoic Acid*. 12-(S)-Hydroxyeicosatetraenoic acid [12-(S)-HETE; IUPHAR-DB ID no. 3404] is a 12-lipoxygenase metabolite of arachidonic acid (IUPHAR-DB ID no. 2391), which produces a number of cellular responses including cytoskeletal remodeling to facilitate cell chemotaxis and secretion of proteinases and vascular endothelial growth factor leading to an angiogenic response. 12-(S)-HETE treatment of cancer cells also enhanced the expression of integrins and fibronectin, which prolong cell survival. *GPR31* displayed high-affinity binding for tritiated 12-(S)-HETE ( $K_d = 5$  nM), and unlabeled 12-(S)-HETE stimulated guanosine 5'-3-*O*-(thio)triphosphate coupling in the membranes of *GPR31*-transfected cells, with an  $EC_{50}$  of 0.28 nM (Guo et al., 2011). In concordance, *GPR31* is phylogenetically closest to the OXE receptor (for which the ligand is 5-oxo-6,8,11,14-eicosatetraenoic acid; IUPHAR-DB ID no. 3391) (Gloriam et al., 2007).

7. *GPR32 and Resolvin D1*. By use of a  $\beta$ -arrestin assay, Krishnamoorthy et al. (2010) demonstrated that resolvin D1 (RvD1; IUPHAR-DB ID no. 3934), which is produced physiologically from the oxidation of docosahexaenoic acid (IUPHAR-DB ID no. 1051), had a remarkably high  $EC_{50}$  value of 4 pM. The aspirin-triggered epimer of RvD1 (AT-RvD1) and stable synthetic analogs 17(*R/S*)-methyl RvD1 and RvD1-ME were equally potent. These compounds also stimulated  $\beta$ -arrestin binding in cells expressing recombinant human formyl peptide receptors *ALX/FPR2* (*ALX/FPR2* is also considered a lipoxin  $A_4$  receptor and thought to bind peptides and two classes of lipids, the lipoxins and resolvins). Krishnamoorthy et al. (2012) suggest that RvD1 mediates the resolution of acute inflammation by interaction with these two receptors. Resolvin D5 has been reported to activate *GPR32* by Chiang et al. (2012). In contrast, the pairing of RvD1 with *GPR32* could not be repeated in a recent  $\beta$ -arrestin assay (Southern et al., 2013).

8. *GPR34 and Lysophosphatidylserine*. *GPR34* is phylogenetically related to the P2Y receptor family (Gloriam et al., 2007). Lysophosphatidylserine (LysoPS; IUPHAR-DB ID no. 4064) is thought to function as an immunologic regulator as it augments the degranulation of peritoneal mast cells where *GPR34* is abundantly expressed. LysoPS caused a pertussis toxin-sensitive decrease in the cAMP level of CHO cells expressing *GPR34*, with an  $EC_{50}$  value of 270 nM. These cells did not respond to structurally related phospholipids examined, including lysophosphatidylethanolamine, lysophosphatidylcholine, LPA, S1P, and phosphatidylserine (Sugo et al., 2006). LysoPS has also been reported as the activating ligand by others (Iwashita et al., 2009; Kitamura et al., 2012), with the suggestion that the receptor prefers fatty acid substitution in the *sn*-2 position (Kitamura et al., 2012). In contrast, in a detailed phylogenetic study, Ritscher et al. (2012)

concluded that LysoPS had no or very weak agonistic activity at most vertebrate *GPR34* orthologs investigated and that the search for the endogenous agonist should consider additional chemical entities.

9. *GPR35 and Kynurenic Acid/2-Acyl Lysophosphatidic Acid*. Wang et al. (2006a) first reported that kynurenic acid (IUPHAR-DB ID no. 2918) was an agonist of *GPR35*; this observation has since been replicated in functional assays releasing interleukin 4 (Fallarini et al., 2010) and in a  $\beta$ -arrestin assay (Southern et al., 2013), but controversy remains whether the endogenous ligand reaches sufficient tissue concentrations to activate the receptor (Kuc et al., 2008). 2-Acyl lysophosphatidic acid (2-oleoyl-LPA; IUPHAR-DB ID no. 2936) has also been proposed as an endogenous ligand (Oka et al., 2010b). Zaprinast (IUPHAR-DB ID no. 2919), a cyclic GMP-selective phosphodiesterase (PDE5A/PDE6) inhibitor, is reported to be an agonist for *GPR35* (Taniguchi et al., 2006). *GPR35* is also activated by the loop diuretic drugs bumetanide (IUPHAR-DB ID no. 4837) and furosemide (frusemide; IUPHAR-DB ID no. 4839) (Yang et al., 2012), the pharmaceutical adjunct pamoic acid (IUPHAR-DB ID no. 2920) (Neubig, 2010; Zhao et al., 2010), gallic acid, wedelolactone (Deng et al., 2012), D-luciferin (Hu et al., 2012), and multiple metabolites of tyrosine (IUPHAR-DB ID no. 4791) (Deng et al., 2012), but it is unclear whether these compounds are selective for this receptor.

10. *GPR37 and Neuropeptide Head Activator*. The neuropeptide head activator (IUPHAR-DB ID no. 2496), originally isolated from the freshwater coelenterate hydra (*Hydra attenuata*), is a mitogen for all types of cells in *Hydra* as well as mammalian cell lines of neuronal or neuroendocrine origin. Electrophysiological recordings in frog oocytes and in mammalian cell lines as well as  $Ca^{2+}$  mobilization assays revealed nanomolar affinities ( $EC_{50}$  value of 3 nM) for activation of *GPR37*. An inhibitory G protein-mediated signal transduction and treatment with head activator resulted in internalization of *GPR37*. Overexpression of *GPR37* led to aggregate formation, retention of the receptor in the cytoplasm, and low survival rates of transfected cells, leading to the suggestion that misfolded *GPR37* contributes to the cell death that can be detected in conditions such as Parkinson's disease (Rezgaoui et al., 2006).

*GPR37* has been reported to associate with and regulate the dopamine transporter, while gene disruption results in altered striatal signaling (Marazziti et al., 2007, 2011). Although the isolation of a peptide of identical amino acid sequence to *Hydra* head activator from human hypothalamus, bovine hypothalamus, and rat intestine has been reported (Bodenmuller and Schaller, 1981), its existence in mammals is unclear because there is currently no evidence for the presence of a precursor gene for this peptide in any sequenced genome. However, it is possible that the precursor protein may lie within an unsequenced part of the genome. Interestingly, *GPR37* overexpression in

HEK cells can induce cellular autophagy, which may prevent the selective degeneration of *GPR37*-expressing neurons, as reported for Parkinson's and related neurodegenerative diseases (Marazziti et al., 2009). The pairing of *GPR37* with neuropeptide head activator could not be replicated in a recent  $\beta$ -arrestin assay (Southern et al., 2013).

**11. *GPR39 and Zn<sup>2+</sup> but Retraction of Obestatin as Cognate Ligand.*** The initial reported pairing of *GPR39* with the novel peptide obestatin (IUPHAR-DB ID no. 5336), derived from the precursor of the appetite-stimulating hormone ghrelin (Zhang et al., 2005), could not be repeated; [<sup>125</sup>I]Obestatin did not bind *GPR39*, and obestatin was without action on *GPR39*-transfected cells in various functional assays (cAMP production, calcium mobilization, and *GPR39* internalization) (Lauwers et al., 2006; Chartrel et al., 2007; Holst et al., 2007; Tremblay et al., 2007). Zhang et al. (2007) have since confirmed that they could not reproduce their findings on obestatin binding and activation of *GPR39* receptors in vitro. The results they originally obtained may have been caused by contamination of the sample of obestatin by impurities and loss of binding by the labeled analog as a result of labeling with iodine. The authors are to be commended for publishing the reasons for being unable to repeat their original study. Zn<sup>2+</sup> ions have since been proposed as the cognate ligand (Holst et al., 2007; Yasuda et al., 2007; Sharir et al., 2010; Popovics and Stewart, 2011). There are conflicting reports concerning the effects of disruption of *GPR39* on body weight (Moechars et al., 2006; Tremblay et al., 2007). The receptor is expressed in pancreatic  $\beta$  cells, and there is evidence for a role of *GPR39* in the regulation of glucose homeostasis (Petersen et al., 2011).

As described above, a significant number of pairings of GPCRs with putative endogenous ligands are currently supported by a single paper and await independent confirmation by other groups. A number of pairings have been formally retracted. For example, the reported pairing of *GPR39* by obestatin (IUPHAR-DB ID no. 5336) (Zhang et al., 2005) could not be repeated in various in vitro assays (Chartrel et al., 2007). Nevertheless, more than 50 papers have subsequently described the physiologic and pharmacological actions of the peptide, including acting as an anorectic hormone, decreasing food intake, reducing body weight gain, regulating sleep, and affecting cell proliferation. To date, no alternative receptor or transducing mechanism has been identified.

**12. *GPR55 and Lysophosphatidylinositol.*** *GPR55* was identified as an orphan GPCR abundantly expressed in human caudate nucleus and putamen but not in hippocampus, cerebellum, frontal cortex, or liver (Sawzdargo et al., 1999). A number of reviews have highlighted the confusion arising from studies investigating the pharmacology of *GPR55* (Godlewski et al., 2009; Ross, 2009, 2011; Pertwee et al., 2010; Sharir and Abood, 2010). It is unclear why there are discrepancies between different

laboratories, although it may be that the use of distinct host cells with distinct repertoires of potential signaling partners and the analysis of distinct signaling pathways may contribute to the variation in agonist profiles. From these studies, however, a certain level of consensus has been attained identifying lysophosphatidylinositol (LPI; IUPHAR-DB ID no. 4028) as an endogenous agonist (Oka et al., 2007). The activation of *GPR55* by LPI has been described by numerous groups (Lauckner et al., 2008; Waldeck-Weiermair et al., 2008; Henstridge et al., 2009, 2010; Kapur et al., 2009; Whyte et al., 2009; Yin et al., 2009; Bondarenko et al., 2010; Ford et al., 2010; Oka et al., 2010a; Ishiguro et al., 2011; Pineiro et al., 2011; Southern et al., 2013). Commercially available LPI is primarily plant-derived, containing mixtures of fatty acid substituents with a majority of medium-chain saturated and monounsaturated fatty acids at the 1-position of LPI (Oka et al., 2009). It has been suggested that a 2-isomer of LPI, 2-arachidonoyl-*sn*-glycero-3-phosphoinositol (arachidonoyl LPI; IUPHAR-DB ID no. 4029), present at levels similar to the endogenous cannabinoid 2-arachidonoylglycerol (IUPHAR-DB ID no. 729) (Sugiura et al., 1995; Artmann et al., 2008; Oka et al., 2009), is a more realistic candidate for an endogenous *GPR55* ligand (Oka et al., 2009). The biologic activity of 2-arachidonoyl LPI was markedly higher than those of other molecular species of LPI tested as activators of extracellular signal-regulated kinase (ERK) or elevation of intracellular calcium ions in heterologous expression studies of *GPR55* (Oka et al., 2009). It should be noted, however, that LPI has actions independent of *GPR55*, in inhibiting the plasma membrane Na<sup>+</sup>/K<sup>+</sup>-ATPase (Bondarenko et al., 2010) and regulating endothelial cell BK<sub>Ca</sub> channels, allowing an enhancement of activity at times when the channel activity was low and reducing channel activity at higher levels of channel stimulation (Bondarenko et al., 2010). The nomenclature of *GPR55* is currently under consideration by the cannabinoid receptor subcommittee of NC-IUPHAR.

**13. *GPR75 and CCL5 (RANTES).*** A single paper reports that the chemokine CCL5 (RANTES; IUPHAR-DB ID no. 758) stimulates Ca<sup>2+</sup> mobilization and inositol trisphosphate formation in cells transfected with *GPR75* (Ignatov et al., 2006). However, the pairing of CCL5 and *GPR75* could not be repeated in a recent  $\beta$ -arrestin assay (Southern et al., 2013).

**14. *GPR84 and Medium-Chain FFAs.*** A single paper has reported the pairing of medium-chain FFAs with carbon chain lengths of 9–14 with *GPR84* (Wang et al., 2006b). Medium-chain FFAs mediated calcium mobilization, inhibited cAMP production, and stimulated [<sup>35</sup>S]GTP binding via a pertussis toxin-sensitive G<sub>i/o</sub> pathway. *GPR84* is expressed in leukocytes and induced in monocytes/macrophages upon activation by lipopolysaccharide, stimulating proinflammatory cytokines, suggesting that *GPR84* may link fatty acid metabolism to

immunologic regulation (Wang et al., 2006b). *GPR84* is highly expressed in the bone marrow, and T cells from *GPR84* knockout mice displayed augmented interleukin-4 production in response to stimulation with anti-CD3, suggesting a role for *GPR84* in regulating early interleukin-4 gene expression in activated T cells (Venkataraman and Kuo, 2005). Currently there is insufficient evidence to recommend that *GPR84* be classified as FFA5.

15. *GPR87 and LPA*. A single paper reports that in CHO cells stably expressing *GPR87* fused with  $G\alpha_{16}$  protein, LPA (IUPHAR-DB ID no. 2906) induced transient increases in intracellular  $Ca^{2+}$ , with a low  $EC_{50}$  value of 40 nM. Calcium increases were blocked by LPA receptor antagonists and by RNA silencing of *GPR87*. *GPR87* was shown to be more closely related to the P2Y and P2Y-related receptors than to LPA receptors (Nonaka et al., 2005), but none of the nucleotides or their derivatives activated *GPR87* (Tabata et al., 2007).

16. *GPR119 and Derivatives of Oleate*. *GPR119* is expressed in pancreatic  $\beta$  cells and the gastrointestinal tract and appears to be activated by multiple derivatives of the medium-chain monounsaturated fatty acid oleate (IUPHAR-DB ID no. 1054), including lysophosphatidylcholine (IUPHAR-DB ID no. 2508) (Soga et al., 2005), *N*-oleoylethanolamine (IUPHAR-DB ID no. 2661) (Overton et al., 2006, Ning et al., 2008; Southern et al., 2013), *N*-oleoyldopamine (Chu et al., 2010), and 2-oleoylglycerol (IUPHAR-DB ID no. 5112) (Hansen et al., 2011).

When fed a low-fat diet, *GPR119* knockout mice had normal plasma glucose and lipids but lower body weights and lower postprandial levels of GLP-1. Nutrient-stimulated GLP-1 release was attenuated (Lan et al., 2009). *GPR119* has evolved into a potential target for the next generation of compounds to treat type 2 diabetes mellitus, with numerous publications describing synthetic ligands, some of which are commercially available. Both the preclinical and clinical data suggest that *GPR119* agonists will be promising antidiabetic drugs (Shah and Kowalski, 2010). The nomenclature of *GPR119* is currently being considered by the cannabinoid receptor subcommittee of NC-IUPHAR.

17. *GPR182 and Adrenomedullin*. Kapas et al. (1995) reported that *GPR182* was a receptor for adrenomedullin (IUPHAR-DB IDs nos. 683, 697, 3589), but Kennedy et al. (1998) failed to replicate this finding, and therefore, the endogenous ligand of this receptor remains unknown.

18. *GPR183 (EBI2) and Oxysterols*. Two independent reports (Hannedouche et al., 2011; Liu et al., 2011) have proposed oxysterols as ligands for *GPR183*. Liu et al. (2011) isolated oxysterols from porcine spleen extracts and demonstrated that  $7\alpha,25$ -dihydroxycholesterol ( $7\alpha,25$ -OHC; IUPHAR-DB ID no. 4350) was the most potent endogenous ligand of this receptor, with a  $K_d$  of 450 pM.  $7\alpha,25$ -OHC is synthesized from cholesterol by the sequential action of cholesterol 25-hydroxylase

and CYP7B1 (25-hydroxycholesterol 7- $\alpha$ -hydroxylase). Consistent with  $7\alpha,25$ -OHC as an endogenous ligand, inhibition of CYP7B1 with clotrimazole reduced the content of  $7\alpha,25$ -OHC in the mouse spleen and mimicked the phenotype of preactivated B cells from *gpr183*-deficient mice (Liu et al., 2011), and mice deficient in cholesterol 25-hydroxylase had a similar phenotype to *GPR183* knockout mice (Hannedouche et al., 2011). Oxysterols can affect immune and inflammatory responses as well as cholesterol metabolism, and these effects are normally thought to be by via nuclear hormone receptors rather than a GPCR.

19. *P2Y10 and S1P/LPA*. The gene encoding *P2Y10 (P2RY10)* was originally named on the basis of sequence similarity to other P2Y receptors, but subsequent phylogenetic analyses have shown that *P2Y10* is most closely related in sequence to receptors for platelet-activating factor (IUPHAR-DB ID no. 1831) and LPA (IUPHAR-DB ID no. 2906) (Gloriam et al., 2007). S1P (IUPHAR-DB ID no. 911) and LPA stimulated increases in intracellular  $Ca^{2+}$  in CHO cells stably expressing *P2Y10* fused with a  $G\alpha_{16}$  protein, with  $EC_{50}$  values of 53 and 130 nM, respectively (Murakami et al., 2008). These responses were blocked by S1P and LPA receptor antagonists and by RNA silencing of *P2Y10* in these cells. In mice, *P2Y10* was widely expressed, including in reproductive organs, brain, lung, and skeletal muscle. The authors concluded that *P2Y10* is a dual lysophospholipid receptor, but it has not yet been accepted as an LPA receptor by NC-IUPHAR.

20. *MAS1 and Angiotensin-(1-7)*. Angiotensin-converting enzyme 2 metabolizes angiotensin II (IUPHAR-DB ID no. 2504) to angiotensin-(1-7) [Ang-(1-7), IUPHAR-DB ID no. 582], which functions as a vasodilator and antiproliferative agent. Santos et al. (2003) first provided evidence that some of the actions of Ang-(1-7) are mediated via the *MAS1* receptor. Ang-(1-7) bound to *MAS1*-transfected cells and elicited arachidonic acid (IUPHAR-DB ID no. 2391) release. Deletion of the *Mas1* gene in mice abolished the binding of Ang-(1-7) in mouse kidney and abolished the antidiuretic action of the peptide after an acute water load (Santos et al., 2003). *Mas1*-deficient mouse aortas lost Ang-(1-7)-induced relaxation responses. For further information on the effect of deleting the *MAS1* receptor, see Alenina et al. (2008).

21. *LGR4, LGR5, and LGR6 and R-Spondins*. *LGR4*, *LGR5*, and *LGR6* were first identified as a family of structurally distinct seven-transmembrane receptors with homology to glycoprotein hormone receptors (Hsu et al., 1998, 2000). R-spondins (IUPHAR-DB ID nos. 3697, 3698, 3699, 3700, 4383) are a group of secreted proteins that enhance Wnt/ $\beta$ -catenin signaling, which plays essential roles in embryonic development and in the self-renewal and maintenance of adult stem cells. Carmon et al. (2011) demonstrated that *LGR4* and *LGR5* bind the R-spondins with high affinity and mediate the potentiation of Wnt/ $\beta$ -catenin signaling by enhancing the

phosphorylation of the Wnt coreceptor *LRP6*. Gong et al. (2012) showed that *LGR6* also binds and responds to R-spondins, and de Lau et al. (2011) reported that each of the four R-spondins can bind to *LGR4*, *LGR5*, and *LGR6*. However, these receptors do not couple to G proteins or to  $\beta$ -arrestin, suggesting that they do not function as conventional GPCRs (Gong et al., 2012). *LGR5* is a marker of stem cells in the base of intestinal crypts and in hair follicles; significant data support *LGR5*<sup>+</sup> stem cells as cells of origin for colorectal carcinoma and also implicate *LGR5* as a mediator of tumor aggression (Kleist et al., 2011).

**22. Mas-Related GPCRs:** MRGPRD with  $\beta$ -Alanine; MRGPRX1 with Bovine Adrenal Medulla Peptide 22 (BAM22); MRGPRX2 with Cortistatin-14. Of the eight human Mas-related GPCRs (MRGs), four (*MRGPRD*, *MRGPRE*, *MRGPRF*, and *MRGPRG*) have clear orthologs in rodents, whereas the cluster of genes including human *MRGPRX1*, *MRGPRX2*, *MRGPRX3*, and *MRGPRX4* is found only in primates and is replaced in rodents with a family of genes (>25 in mice; ~10 in rats) that have no obvious human counterparts (Dong et al., 2001). Certain rodent MRGs have been reported to respond to adenine (Bender et al., 2002) and to RF-amide peptides including neuropeptide FF (Han et al., 2002; Lee et al., 2008a), but the relevance of these findings to man is unclear. MRGs are expressed predominantly in small-diameter sensory neurons of the dorsal root ganglia, where there is emerging evidence that they may be mediators of histamine-independent itch (Liu et al., 2009; Wilson et al., 2011).

$\beta$ -Alanine (IUPHAR-DB ID no. 2365) induced the rapid mobilization of intracellular  $\text{Ca}^{2+}$  in CHO cells expressing human, rat, or mouse *MRGPRD* (*TGR7*) in a concentration-dependent manner, with  $\text{EC}_{50}$  values of 15, 14, and 44  $\mu\text{M}$ , respectively (Shinohara et al., 2004). Responses to  $\beta$ -alanine were pertussis toxin-sensitive (Shinohara et al., 2004; Crozier et al., 2007).  $\beta$ -Alanine activated *MRGPRD* in a  $\beta$ -arrestin assay with a similar  $\text{EC}_{50}$  value of 15  $\mu\text{M}$  (Southern et al., 2013). [<sup>3</sup>H] $\beta$ -Alanine bound to *MRGPRD*-expressing CHO cells, but compounds structurally related to  $\beta$ -alanine, including L-glycine (IUPHAR-DB ID no. 727), L-alanine (IUPHAR-DB ID no. 720), taurine (IUPHAR-DB ID no. 2379), and L-anserine, did not stimulate intracellular calcium. Milasta et al. (2006) also demonstrated that cells expressing *MRGPRD* responded to  $\beta$ -alanine. There was evidence that responses to  $\beta$ -alanine (elevations of intracellular  $\text{Ca}^{2+}$ , phosphorylation of mitogen-activated protein kinases ERK1 and ERK2, and receptor internalization) could be modulated by the formation of heterodimers with *MRGPRE* (Milasta et al., 2006).

Bovine adrenal medulla peptide 22 (BAM22) is a C-terminally extended form of Met-enkephalin produced by proteolytic cleavage of the opioid peptide precursor proenkephalin A. Lembo et al. (2002) found that BAM22 was the most potent compound evoking a

concentration-dependent release of intracellular calcium in cells stably expressing the human *MRGPRX1* (which they called sensory neuron-specific receptor 3 or *SNSR3*), with an  $\text{EC}_{50}$  value of 13 nM. Many of the classic opioid peptides were inactive at *MRGPRX1*, and classic opioid antagonists such as naloxone were inactive as antagonists. Chen and Ikeda (2004) and Solinski et al. (2010) confirmed that BAM22 is an agonist of *MRGPRX1*, and this has been replicated in a  $\beta$ -arrestin assay (Southern et al., 2013). Chloroquine, an antimalarial drug that frequently produces itch as a side effect, activates *MRGPRX1*, consistent with a possible role for this receptor in mediating histamine-independent itch (Liu et al., 2009).

Robas et al. (2003) reported that cortistatin-14 (IUPHAR-DB ID no. 2007), a neuropeptide related to somatostatin but encoded by a different gene (de Lecea et al., 1996), stimulated intracellular calcium in cells expressing human *MRGPRX2*, with an  $\text{EC}_{50}$  of 25 nM. A number of other cyclic peptides showed high nanomolar potency. Kamohara et al. (2005) confirmed this pairing but also found that the endogenous peptides proadrenomedullin N-terminal 20 peptide (PAMP-20; IUPHAR-DB ID no. 4057) and its N-terminally truncated analog, PAMP-12 (IUPHAR-DB ID no. 4056), also activated the receptor with a similar potency in calcium mobilization. Cortistatin-14 was also shown to bind to *MRGPRX2* in a  $\beta$ -arrestin assay (Southern et al., 2013).

*MRGPRX2* coupled with  $\text{G}_q$  and  $\text{G}_i$ . Nothacker et al. (2005) showed in structure-activity studies that both cortistatin and PAMP bind to and activate *MRGPRX2* at the same binding site owing to a common internal structural motif that is centered around an octapeptide that alternates aromatic and basic amino acids, and both peptides were proposed as surrogate ligands for this receptor. Nonpeptide *MRGPRX2* receptor agonists have been identified (Malik et al., 2009).

### B. Class B

All of the orphans in this subfamily are called adhesion receptors in some classifications (see, for example, Lagerström and Schiöth, 2008); a defining feature of this subfamily is the presence of a GPCR proteolytic site-containing stalk region. None of the following putative ligands has been demonstrated to signal through conventional G protein-coupled mechanisms (although see GPR56 below).

**1. BAI1 and Phosphatidylserine.** A single paper reports phosphatidylserine (IUPHAR-DB ID no. 3638) as a ligand for *BAI1*, which has a role in the engulfment and subsequent degradation of apoptotic cells (Park et al., 2007; reviewed in Bratton and Henson, 2008).

**2. BAI3 and C1q-like Proteins.** C1q-like proteins are small, secreted proteins of unknown function that are synthesized from four genes in mammals, expressed almost exclusively in brain, and produced in differential patterns by specific types of neurons. According to one

report, C1q-like proteins bind to the extracellular thrombospondin-repeat domain of *BAI3* with high affinity and act, at least in part, to regulate synapse formation and/or maintenance (Bolliger et al., 2011).

3. *CD97 and Decay Accelerating Factor*. Several groups have reported that decay accelerating factor (CD55), a regulatory protein of the complement cascade, is a ligand of CD97 (Hamann et al., 1996; Qian et al., 1999; Lin et al., 2001). Thy-1 (CD90) has been reported to bind to CD97, and this interaction has been proposed to play a role in the regulation of leukocyte trafficking by facilitating adhesion of polymorphonuclear cells to activated endothelial cells (Wandel et al., 2012). Chondroitin sulfate has been reported to be a ligand of both CD97 and *EMR2* (Stacey et al., 2003).

4. *GPR56 and Collagen Type III*. Collagen, type III,  $\alpha$ -1 (gene symbol, *COL3A1*) has been proposed as the ligand of *GPR56* (Luo et al., 2011), signaling by activating RhoA through coupling to  $G_{12/13}$ . Transglutaminase 2, a major crosslinking enzyme in the extracellular matrix, has also been proposed as a ligand of *GPR56* (Xu and Hynes, 2007).

5. *LPHN1 and LPHN3*. The massive synaptic exocytosis caused by the black widow spider venom  $\alpha$ -latrotoxin is thought to be due to toxin binding to two distinct receptor families: the latrophilin group of class B GPCRs (*LPHN1*, -2, and -3) and the neurexins (neurexin-1, -2, and -3), which are presynaptic membrane proteins. *LPHN1* has been proposed to be a ligand of neurexins, producing a stable intercellular adhesion complex (Boucard et al., 2012). Lasso, a splice variant of teneurin-2, a brain-specific orphan cell surface receptor with a function in neuronal pathfinding and synaptogenesis (Silva et al., 2011) and FLRT3, a member of the FLRT family of leucine-rich repeat transmembrane proteins (O'Sullivan et al., 2012), have been reported to be endogenous postsynaptic ligands for *LPHN1* and *LPHN3*, respectively.

### C. Class C

1. *GPRC6A and Calcium, Amino Acids, and Osteocalcin*. *GPRC6A* has been reported to sense both nutrient-derived factors, such as calcium and amino acids (Christiansen et al., 2007; Pi et al., 2012); testosterone (Pi et al., 2010); and the bone-derived hormone osteocalcin (Oury et al., 2011; Pi et al., 2011).

## V. Orphan Receptors with Activity in Absence of an Endogenous Ligand, Activation by Surrogate Ligands, or Significant Phenotype in Genetically Modified Animals

Although ligands for orphan GPCRs continue to be identified, there is also evidence that some may have functions in the absence of an endogenous transmitter through constitutive activity or by modulating the activity of other GPCRs via dimerization. These

receptors may still represent a druggable target by the discovery of synthetic ("surrogate") ligands. Other seven-transmembrane receptors may not signal via conventional pathways such as G proteins but still function to modulate the actions of transmitters.

A. *Constitutively Active GPCRs*. Constitutive activity is defined by receptor signaling in the absence of a ligand and has mainly been detected using in vitro studies measuring downstream signaling, which may be reduced by the action of inverse agonists. Constitutive activity has been reported for a number of established receptors and in many cases characterized further by the use of inverse agonists. Constitutive activity has been reported in a number of orphan receptors, but it does not necessarily mean that an endogenous ligand does exist: Ligands acting at a constitutively active receptor can act as agonists, antagonists, and/or inverse agonists. Secondly, there is no formal definition of what magnitude of basal signaling in the absence of a ligand constitutes intrinsic activity. However, the existence of constitutive activity, particularly when caused by amino acid mutations or other variants, combined with the development of inverse agonists at these receptors has the potential for new strategies for drug development, and with the above caveats, we have highlighted this information where it exists in the literature. Constitutive activity has been reported for *EBI2* (Rosenkilde et al., 2006), *GPR3* (Eggerickx et al., 1995), *GPR6* (Uhlenbrock et al., 2002), *GPR12* (Uhlenbrock et al., 2002), *GPR17* (Bened-Jensen and Rosenkilde, 2010), *GPR18* (Qin et al., 2011), *GPR20* (Hase et al., 2008), *GPR22* (Adams et al., 2008), *GPR26* (Jones et al., 2007), *GPR39* (Holst et al., 2004), *GPR61* (Toyooka et al., 2009), *GPR78* (Jones et al., 2007), and *MAS1* (Canals et al., 2006).

B. *C5AR2 (GPR77, C5L2)*. *C5AR2* (Klos et al., 2013) is the first example of a naturally occurring seven-transmembrane segment receptor that is both obligately uncoupled from G proteins and a negative modulator of signal transduction through the  $\beta$ -arrestin pathway (Bamberg et al., 2010).

C. *CCRL1 (CCX-CKR), CCRL2 (CRAM), CCBP2 (D6), and DARC*. These proteins do not appear to couple to G proteins or, in some cases, do not signal through defined pathways. They could all be considered as chemokine binding proteins or "scavengers" that remove chemokines from the local environment, but there is no consensus and no systematic classification can be currently justified. *CCRL2* is thought to be a nonsignaling receptor that binds chemerin (IUPHAR-DB ID no. 2945) and increases the local concentration of the peptide (Zabel et al., 2008).

The nomenclature of this family of receptors, which also includes *CXCR7 (CMKOR1*; see section III.A.5 for further information), is currently being considered by the chemokine receptor subcommittee of NC-IUPHAR.

D. *GPR50 Is a Negative Regulator of  $MT_1$  and  $MT_2$* . *GPR50* (melatonin-related receptor) is structurally related to the melatonin receptors,  $MT_1$  and  $MT_2$ , but

does not bind melatonin, and its endogenous ligand has not been identified. *GPR50* heterodimerizes constitutively and specifically with  $MT_1$  to abolish high-affinity agonist binding and G protein coupling. Although *GPR50* also heterodimerizes with  $MT_2$ , this had no effect on function and  $MT_2$  in intact cells (Levoye et al., 2006).

GPR50 knockout mice showed resistance to diet-induced obesity but lost less weight than wild-type mice when fasted (Ivanova et al., 2008). The mice entered torpor much more readily than wild-type mice in response to fasting or 2-deoxyglucose administration and displayed attenuated responses to leptin and a suppression of thyrotropin-releasing hormone (Bechtold et al., 2012).

## VI. Pseudogenes

Pseudogenes are genomic DNA sequences that display homology to known functional genes but that during the course of evolution acquired mutations that render them nonfunctional. This is often thought to occur when a gene is duplicated and the new copy has an evolutionary window within which it can acquire new functions leading to its preservation, or deleterious mutations may accumulate so that function is irreversibly lost. Thus, a given gene can be functional in some species but not in others. Inactivating mutations can be anywhere in the gene and lead to loss of function at the levels of gene transcription, pre-mRNA processing, translation, or protein folding. The most readily identified disablements are stop codons and frameshifts.

It is fairly obvious that a gene is a pseudogene when it has acquired numerous premature termination codons or shifts in reading frame. NC-IUPHAR has not been concerned about such obvious pseudogenes. However, there are a number of borderline cases that should be considered since our perception of whether they are functional is subject to change. These cases typically have a single mutation leading to a truncated receptor protein. Indeed, there are several cases in which the mutation is now known to be polymorphic, so that the gene appears to be functional in some portion of the human population.

**A. GPR33.** *GPR33* is phylogenetically related to the chemerin receptor (*CMKLR1*) and *GPR1* and has been proposed to function as a chemoattractant receptor (Rompler et al., 2005). It was listed as a functional gene in Foord et al. (2005) but is inactivated by a premature termination codon in a number of species (Rompler et al., 2005). *GPR33* appears to be a pseudogene in most individuals, with a premature stop codon at amino acid 140 in the second cytoplasmic loop (Rompler et al., 2005; Bohnekamp et al., 2010; Zhang et al., 2010). According to the National Center for Biotechnology Information dbSNP database (Sherry et al., 2001), this polymorphism, rs17097921, gives the truncated allele in 100% of Europeans but an active Arg140 allele in 2–8% of Asians and Africans.

**B. TAAR2 and TAAR9.** Two of the trace amine receptors are inactivated in a portion of the human population. There is a polymorphism in *TAAR2* (rs8192646) producing a premature stop codon at amino acid 168 in 10–15% of Asians. *TAAR9* (formerly *TRAR3*) appears to be functional in most individuals but has a polymorphic premature stop codon at amino acid 61 (rs2842899) with an allele frequency of 10–30% in different populations (Vanti et al., 2003). *TAAR3* (formerly *GPR57*) and *TAAR4* (current gene symbol, *TAAR4P*) are thought to be pseudogenes in man though functional in rodents (Lindemann et al., 2005).

**C. GPR42.** Human *GPR42* is closely related to *GPR41* (free fatty acid receptor FFA3) and is thought to have arisen from a tandem duplication of *GPR41* in the human lineage. Mutagenesis studies have shown that conversion of arginine 174 in the *GPR41* protein to tryptophan (found in *GPR42*) abolishes the response to short-chain fatty acids, raising the possibility that *GPR42* might be a translated but inactive pseudogene (Brown et al., 2003). It has been proposed that *GPR42* could potentially be a functional gene in a significant fraction of the human population (Liaw and Connolly, 2009), but the very close sequence similarity of *GPR41* and *GPR42* (six nucleotide differences in the coding sequence) make this very difficult to assess.

**D. GPR79.** *GPR79* is a full-length gene in both dog and rodents but is a pseudogene in human (Haitina et al., 2009). The human *EMR4* gene (class B: current gene symbol, *EMR4P*) has a single base deletion in the eighth coding exon compared with other primates and mouse, leading to the expression of a truncated amino-terminal domain of 232 amino acids (Hamann et al., 2003; Caminschi et al., 2006). This protein lacks any of the transmembrane domains of the *EMR4* GPCR from other species. There is a second open reading frame capable of encoding a seven-transmembrane GPCR with a 93-amino-acid amino-terminal domain but there is no evidence for its translation. Thus, human *EMR4* should be considered as a probable pseudogene, although the 232-amino-acid secreted protein may have biologic function.

**E. GnRH2.** In addition to the classic gonadotrophin-releasing hormone receptor (the GnRH receptor), some species possess a second GnRH2 receptor. This gene is absent from the genomes of rats and mice, but a functional gene is present in some primates; the human gene was listed as functional in Foord et al. (2005), but it was subsequently shown that the human gene contains a frameshift mutation and a premature stop codon that would result in translation of a nonfunctional receptor (Morgan et al., 2003). The neuropeptide Y receptor y6 is a pseudogene in human and pig and is absent in rat but generates a functional receptor in rabbit and mouse (Matsumoto et al., 1996; Rose et al., 1997; Starback et al., 2000).

## VII. Conclusion

Since the original NC-IUPHAR classification of GPCRs in the human genome (Foord et al., 2005), significant progress has been made in assigning endogenous ligands, particularly in class A, and pharmacological tools continue to be developed to delineate these new transmitter systems. There is preliminary evidence for pairings of endogenous ligands of 32 GPCRs in class A, 6 in class B, and 1 in class C, but further research is needed to replicate (or refute) these proposals, particularly as a number of initial claims have been retracted. Most, if not all, human orphan receptors have now been expressed in cell lines, but despite intense effort particularly by the pharmaceutical industry, there is no public information about the cognate ligand for a significant number of them. It is possible that the remaining receptors may function without ligands by being constitutively active or by modulating the activity of other GPCRs, for example, by dimerization (Levoye et al., 2006; Geng et al., 2012). It is clear from knockout studies in mice and genetic deletions in man that these receptors may have a physiological or pathophysiological role and can still be exploited as drug targets in the absence of an identifiable ligand. Further information on all the orphan receptors described in this review can be found on the IUPHAR Database website at <http://www.iuphar-db.org>.

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### Authorship Contributions

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*Wrote or contributed to the manuscript:* Davenport, Alexander, Sharman, Pawson, Benson, Mpamhanga, Bonner, Neubig, Pin, Spedding, Harmar.

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