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In this Issue...

An Update on Ligands for Prostanoid Receptors

Robert Jones

The natural prostanoids arise from the activity of intracellular cyclo-oxygenase (COX) on polyunsaturated fatty acids released from membrane phospholipids. In the case of the most important substrate, arachidonic acid (20:4ω6), the first product is prostaglandin G_2 (PGG_2), which is then reduced to PGH_2 by an associated 15-hydroperoxidase [1]. Depending on the tissue, PGH_2 may be further metabolized by isomerases to PGD_2, PGE_2, PGI_2 (prostacyclin and TXA_2 and by a reductase to $PGF_{2\alpha}$.

The natural prostanoids perform a variety of physiological and pathological roles. The discovery of several E and F prostaglandins at particularly high concentrations in human semen stimulated interest in their actions on both male and female reproductive tracts [2]. PGE_2 and $PGF_{2\alpha}$ were shown to be potent stimulants of uterine smooth muscle and this triggered further research into their roles in normal parturition. In addition, analogs were synthesized for the safe induction of parturition. $PGF_{2\alpha}$ was also found to induce luteolysis in many laboratory and farm animals, and in some species has been shown to function as a uterine luteolytic hormone [3]. Thus, following release from the uterus, $PGF_{2\alpha}$ induces regression of the corpus luteum, a fall in progesterone level and termination of the estrus cycle. The therapeutic potential of this mechanism for post-coital contraception and the induction of abortion was soon recognized. However, the role of research interest waned with the realization that luteal regression in the human female is somewhat different to that in lower

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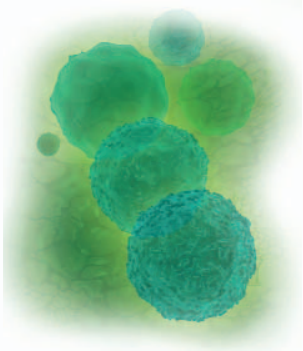
Application Note:

Improved *Ex Vivo* Expansion of Functional $CD34^+$ Cells Using Stemline™ II Hematopoietic Stem Cell Expansion Medium

Daniel W. Allison, Stacy L. Leugers, Barry J. Pronold, Gary Van Zant, and Laurel M. Donahue

Introduction

Hematopoietic stem cells (HSC) have the ability to repopulate the hematopoietic system by differentiating into all of the necessary erythroid, lymphoid, and myeloid lineages. Due to this rare ability, HSCs are used as therapeutic agents in the treatment of malignant and benign diseases of the blood forming and immune systems. There have been many advances in the area of clinical HSC research, but the availability of suitable cells for transplantation still remains a major limiting factor [1,2].



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An Update on Ligands for Prostanoid Receptors

Robert Jones

(continued from cover)

order animals. PGD_2 has had a chequered career, being implicated in the control of sleep [4] and as a mediator in allergen-induced disease [5]. The latter profile has been the subject of major new developments (see later).

The demonstration that TXA_2, a highly labile product of arachidonate metabolism in human platelets [6], could also activate this tissue and adjacent vascular smooth muscle cells stimulated enormous interest in its role in cardiovascular disease. Further impetus was added by the discovery of prostacyclin, which could be formed from PGH_2 in blood vessels and was also unstable in physiological milieu [7,8]. Prostacyclin had opposing actions to TXA_2 and the concept emerged of an imbalance between these agents contributing to various pathological states. Around the same time, the unique therapeutic profile of **aspirin** (acetyl salicyclic acid, Prod. No. **A 5376**) became apparent: at low doses it irreversibly inhibits TXA_2 biosynthesis in platelets without compromising the protective value of PGI_2 on the blood vessel, while at higher doses it suppresses the pro-inflammatory effects of PGE_2 similar to other COX inhibitors [9].

Classification of Prostanoid Receptors

It thus became clear that the five primary prostanoids exhibit distinctive pharmacological profiles. In the 1970s this was the starting point for defining five types of prostanoid receptor, referred to as DP, EP, FP, IP and TP [10], based on three experimental approaches:

- The ranking of agonist potencies on isolated tissue preparations (e.g. $PGD_2 > PGF_{2\alpha} > PGE_2 = PGI_2 = TXA_2$ signifies a DP receptor)
- The use of radiolabeled prostanoids (e.g. $[^3H]$-PGE_2) to identify saturable binding sites on cell membranes with appropriate affinity rankings for competing ligands
- The use of competitive receptor antagonists, although in some cases the specificity of the antagonist was relatively low.

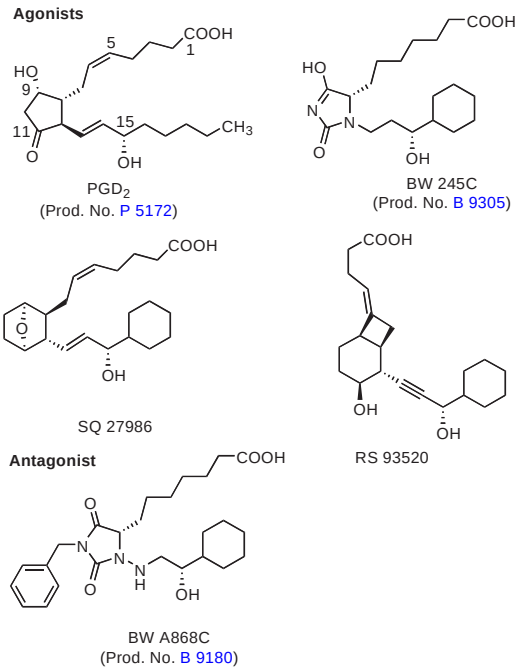
Further studies divided the EP receptor into four subtypes, each denoted by a subscript numeral (i.e. EP_1, EP_2, EP_3 and EP_4).

In the late 1990s, verification of this classification system came through the isolation and structural determination of the eight prostanoid receptors, and their expression in convenient cell lines [11]. In addition, the development of antagonists with higher affinity and specificity continued, although it is surprising that useful antagonists for the FP receptor and some EP receptors are only now emerging some 40 years after the discovery of PGE_2 and $PGF_{2\alpha}$.

Prostanoid receptors belong to the rhodopsin super family of G protein-coupled receptors, and their evolution from a common PGE ancestor has been postulated [12,13]. In general, DP, EP_2, EP_4 and IP receptors couple to adenylyl cyclase via G_s to produce inhibitory events, while EP_1, FP and TP receptors couple to phospholipase C via G_q to produce excitatory events. EP_3 receptors have the most complex molecular biology. They exist in several isoforms through RNA splicing and usually couple to G_i, but individual isoforms may also couple to G_q, G_s and $G_{12,13}$ [14].

Synthetic agonists for each prostanoid receptor have often been designed initially to resist metabolism, and in the case of PGI_2 and TXA_2 to be chemically stable as well. They often bear a close structural resemblance to the natural agonist, although non-prostanoid agonists exist for EP_3 and IP receptors. Antagonists have emerged from the chemical modification of a partial agonist, and more recently from high throughput screening assays using cloned prostanoid receptors. Useful ligands for each of the prostanoid receptors will be briefly discussed. The reader is also referred to the 'Prostanoid Receptors' chart in The Sigma-RBI Handbook - see http://www.sigma-aldrich.com/sigma/rbi-handbook/sg_ls_cs_rbibook_prostanoid.pdf

Figure 1. DP Receptor Ligands



The DP receptor mediates inhibition of platelet aggregation [15], relaxation of vascular smooth muscle [16] and plasma exudation [17]. Similar to other prostanoid receptors, an S-configuration for the C15-secondary alcohol in the natural prostanoid (PGD_2) is critically important to agonist activity. The hydantoin **BW 245C** (Prod. No. **B 9305**) has been widely used as a selective DP agonist [18-20]; it may exist as 9-oxo,11-oxo and 9,11-dioxo tautomers. Inversion of all chiral centers in the ring systems of prostacyclin analogs (e.g. RS-93520) [21,22] and PGH analogs (e.g. SQ 27986) [23] also leads to selective DP agonists.

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Ligands for Prostanoid Receptors...*(continued)*

The DP antagonist BW A868C, a relative of BW 245C, has proved useful in identifying DP receptors [20,24,25]. It behaves competitively (pA_2 7.8 - 9.5) and shows good specificity. However, its affinity for the EP_4 receptor (pA_2 5.1) may result in a right-shift of the concentration-response curve for PGE_2 in blood vessel preparations with highly sensitive EP_4 systems [26].

It has been known for some time that PGD_2 induces effects that cannot be attributed to either the classical DP receptor or FP and TP receptors; two examples are arterial constriction [27,28] and suppression of short-circuit current in colonic mucosa [29]. A major discriminating factor is the potent agonist activities of 15-oxo PGD_2 and the chemically more stable 13,14-dihydro-15-oxo PGD_2 on the non-classical receptor. Recently, a novel receptor identified as chemoattractant receptor-homologous molecule expressed on TH2 cells (CRTH2) with a similar agonist profile has been isolated from a mouse genomic library [30,31]. It is related to chemoattractant receptors such as the fMLP receptor, and is preferentially expressed in T helper type 2 cells, eosinophils and basophils, and when activated by PGD_2 leads to eosinophil activation. The COX inhibitor **indomethacin** (Prod. No. **I 7378**) is an agonist for the CRTH2 receptor [32]; its routine use to suppress prostanoid biosynthesis in isolated tissue systems may therefore require reconsideration. There is much interest in developing antagonists for this receptor as therapeutic agents for immunological diseases.

EP_1 receptors have a limited tissue distribution, and their activation causes contraction of smooth muscle in gut and trachea. 16,16-Dimethyl PGE_2 is a highly potent but non-selective EP_1 agonist [33], while 17-phenyl-ω-trinor PGE_2 is more selective, and in combination with **sulprostone** (Prod. No. **S 8692**) ($EP_3 > EP_1$) and SC-46275 ($EP_3 >> EP_1$) can be used to discriminate EP_1 and EP_3 receptors [34]. Some prostacyclin analogs are also potent EP_1 agonists, including iloprost, isocarbacyclin ($\Delta^{6,6a}$-6a-carba PGI_1) [33] and **carbacyclin** (6a-carba PGI_2; Prod. No. **C 3305**)) [34]. Recently, a 6-oxo PGE_1 analog, ONO-DI-004, has been described as an EP_1-selective agonist [35,36].

The first EP_1 antagonist was the dibenzoxazepine-hydrazide **SC 19220** (Prod. No. **S 3065**) [37]. More potent and selective congeners have followed (e.g. SC 51322) [38,39], and these show potential as analgesics. Certain PGH derivatives are also potent EP_1 antagonists (e.g. ONO 8711) [40], as are some biphenylene dibenzazocinones [41].

Figure 2. EP_1 Receptor Ligands

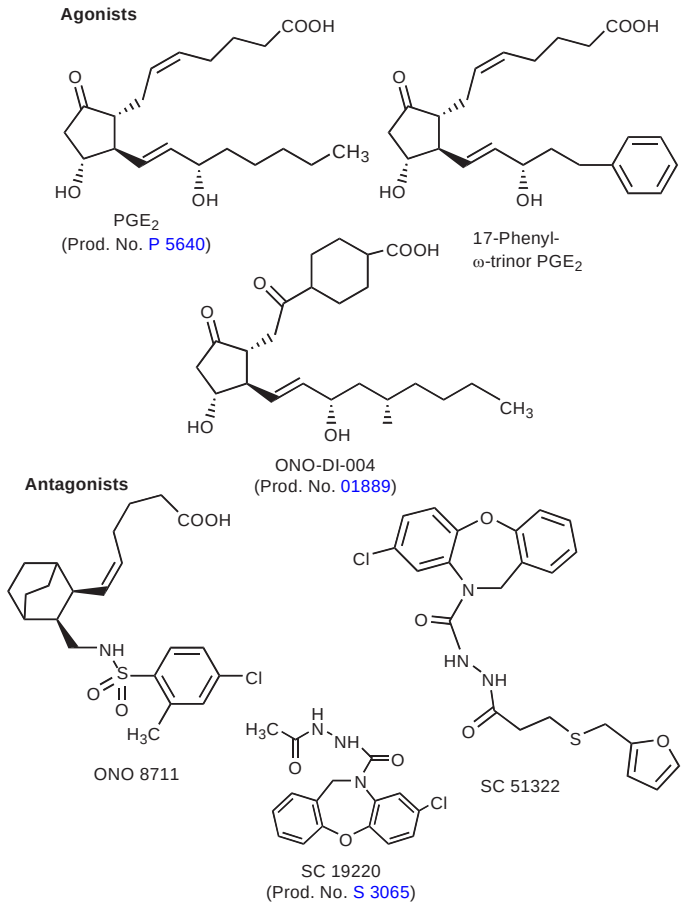
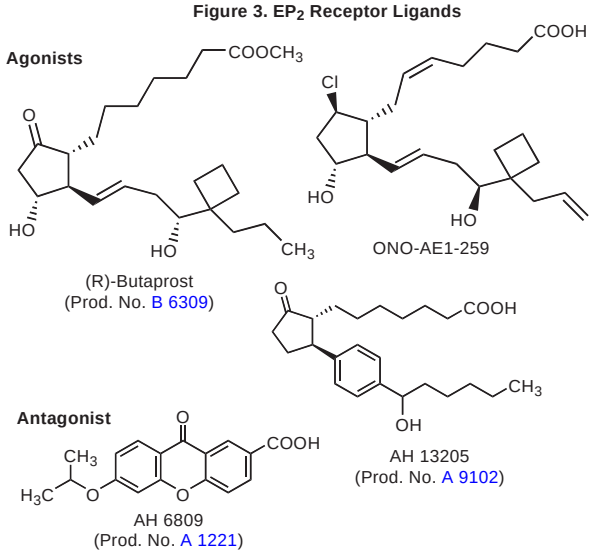


Figure 3. EP_2 Receptor Ligands



Activation of EP_2 receptors leads to relaxation of vascular, bronchial and reproductive smooth muscles. **Butaprost** (Prod. No. **B 6309**) [42] has been used as a selective EP_2 agonist for many years, but slow de-esterification of its C1-methyl ester to produce the biologically more active free acid may confound the discrimination of EP_2 and EP_4 receptors in some tissues. AH 13205 is a selective, but low-potency, EP_2 agonist [43]. ONO-AE1-259 is increasingly being used in preference to butaprost as it is more potent, although it does possess measurable affinity for the DP receptor [44]. A non-prostanoid EP_2 agonist, CP-533,536, has recently been reported [45].

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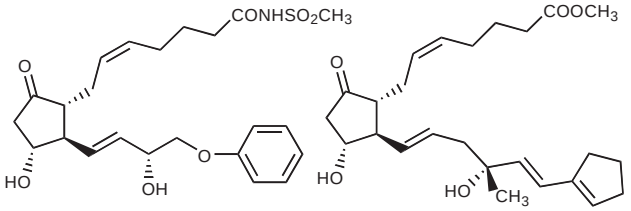
Ligands for Prostanoid Receptors...*(continued)*

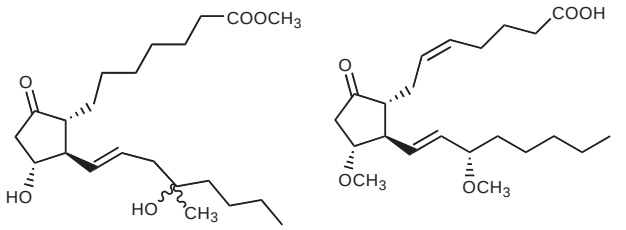
Figure 4. EP_3 Receptor Ligands

Agonists



Sulprostone
(Prod. No. S 8692)

SC 46275

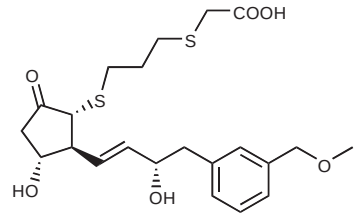


Misoprostol
(Prod. No. M 6932)

ONO-AE-248

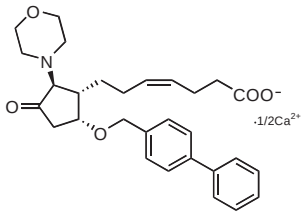
Figure 5. EP_4 Receptor Ligands

Agonist

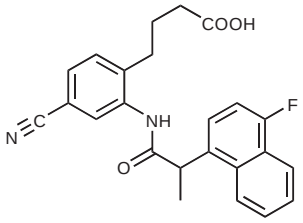


Antagonists

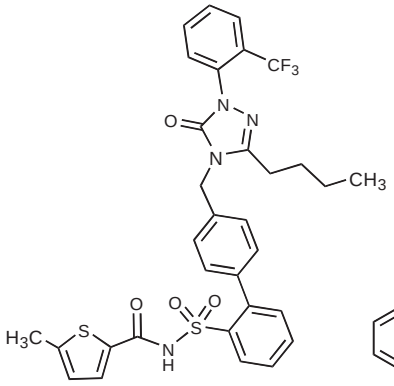
ONO-AE1-329



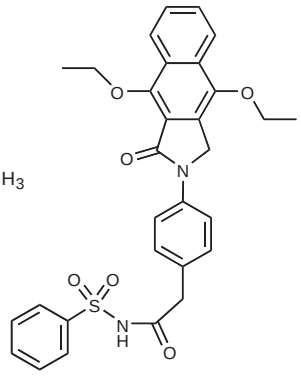
AH 23848
(Prod. No. A 8227)



ONO-AE3-208



L-161,982



GW 627368

Selective antagonists for the EP_2 receptor are not yet available. The xanthone carboxylic acid AH 6809 does block human EP_2 receptors [46], but it has similar affinities for DP and EP_1 receptors [47,48].

The EP_3 receptor has a wide tissue distribution and its multiple coupling capacity means that its pharmacology is varied. In brief, it mediates contraction of smooth muscle, including vascular and uterine smooth muscle, inhibition of lipolysis and gastric acid secretion, cytoprotection in the gut, enhancement of platelet aggregation, and induction of fever when injected into the ventricular system of the brain. Sulprostone is the most commonly used EP_3 agonist [48]; it has been used to control post-partum hemorrhage. SC-46275 is more potent and more selective [49,50]; again hydrolysis of its C1 methyl ester may occur within tissues, perhaps accounting for its slow onset of action in some instances. ONO-AE-248, the 11,15-bis-methyl ether of PGE_2, is also a selective EP_3 agonist, but appears to be less potent than SC-46275 [51]. **Misoprostol** (Prod. No. **M 6932**) is a potent EP_3 agonist, but also displays agonist activity at EP_2 and EP_4 receptors [52]. It is used as an adjunct to COX inhibitor therapy to reduce gastric irritation and bleeding in susceptible individuals. In combination with the progesterone antagonist **mifepristone** (Prod. No. **M 8046**), it can be used to induce abortion [53]. The non-prostanoid ONO-AP-324 (cf non-prostanoid prostacyclin mimetics in figure 7) is an EP_3 agonist that exhibits partial agonism on some preparations [54]. In contrast to the availability of a number of EP_3 agonists, EP_3 antagonists are just beginning to appear in the literature [55].

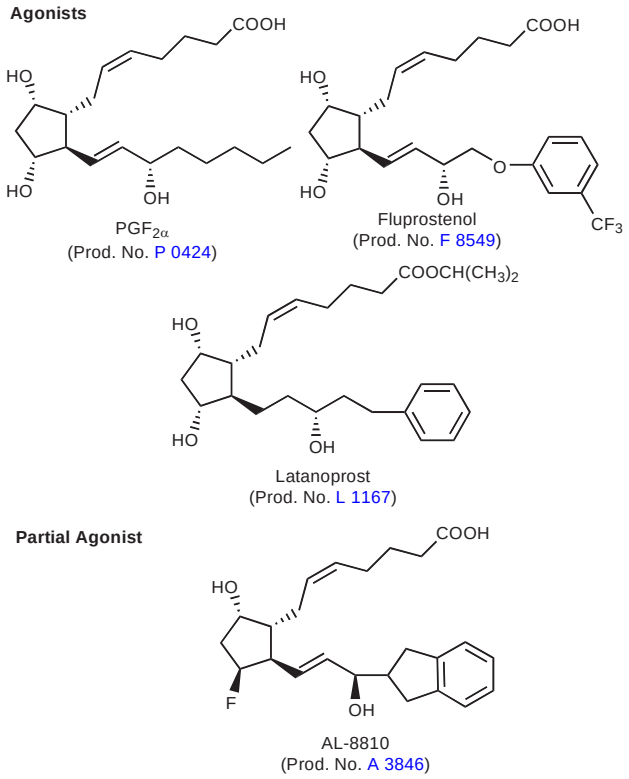
EP_4 systems in blood vessels are often highly sensitive, with threshold relaxation seen at concentrations of PGE_2 as low as 10^{-11} M [56]. Selective EP_4 agonists have not been available until recently; ONO-AE1-329 has a K_i of 10 nM for the recombinant mouse EP_4 receptor and greater than 10,000 nM for the other mouse prostanoid receptors [35]. Some prostacyclin analogs are moderately potent EP_4 agonists, for example, AFP-07 and cicaprost [39,57].

The TP receptor antagonist **AH 23848** (Prod. No. **A 8227**) [58] has found considerable utility as an EP_4 antagonist, although its affinity is low (pA_2 5.4) [56]. Recently, several potent and selective EP_4 antagonists have been described; L-161,982 [59], ONO-AE3-208 [60] and GW 627368 [61].

Modification of the terminal five-carbon unit in $PGF_{2\alpha}$ dramatically alters agonist selectivity [62-64]. A 16-*m*-trifluoromethylphenoxy moiety (as in **fluprostenol**, Prod. No. **F 8549**) confers high FP selectivity; 16-*m*-chlorophenoxy substitution (cloprostenol) is somewhat less favorable, while the 16-p-fluorophenoxy analog (ICI 799390) is a potent, non-selective EP_1, FP and TP agonist. Fluprostenol and cloprostenol are used to synchronize estrus and induce parturition in farm animals. The isopropyl ester of the (+)-enantiomer of fluprostenol (Travoprost) has recently been

Ligands for Prostanoid Receptors...*(continued)*

Figure 6. FP Receptor Ligands



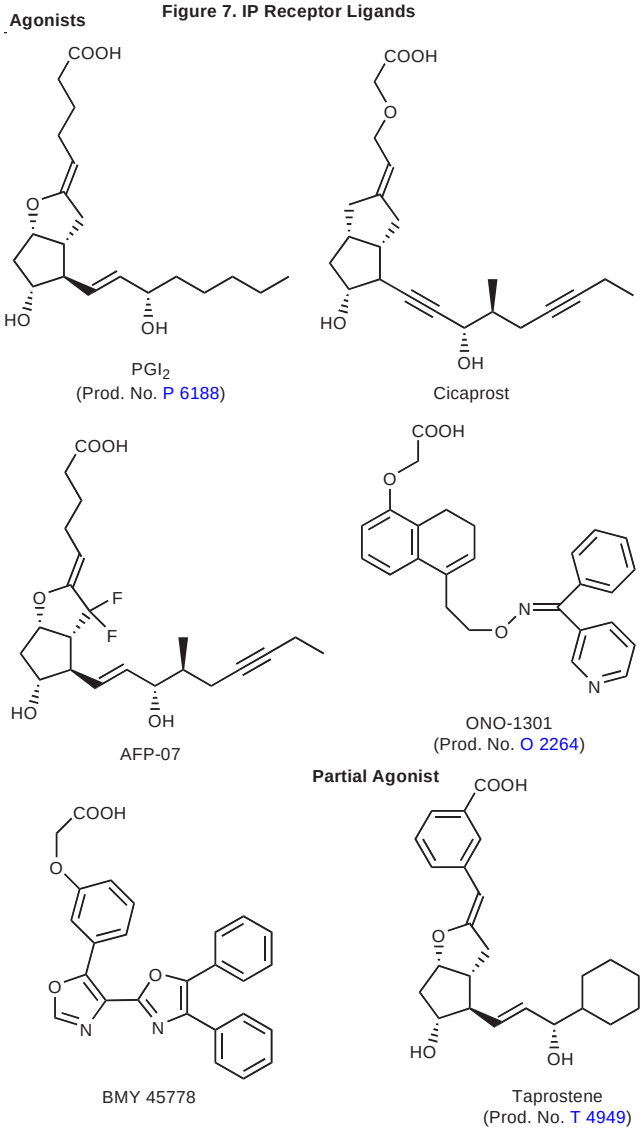
marketed for the treatment of glaucoma [65]. Other PGF analogs with a similar clinical usage include **latanoprost** (Prod. No. **L 1167**) and bimatoprost. It is generally assumed that these agents are lipophilic pro-drugs, and that after topical administration hydrolysis occurs within the eye to give the corresponding free acid as the more potent FP agonist [66]. However, in the case of bimatoprost, it has been proposed that the C1-ethyl amide remains intact within the eye and that a discrete receptor may be involved [67].

The PGF analog **AL-8810** (Prod. No. **A 3846**) is a partial agonist at FP receptors [68], and may represent a promising lead for the development of an FP antagonist.

The vinyl ether in prostacyclin is readily hydrated under physiological conditions, resulting in loss of its characteristic platelet-inhibition and vasodilator activities. The proton initially added to C5 may derive from the C1-carboxyl group or from the medium. Reducing negativity at C5 by appropriate substitution of fluorine confers high acid stability; one such agent AFP-07 is the most potent IP agonist reported to date [57,69]. Replacement of the 6a-oxygen with methylene is another stabilization strategy; these carbacyclins include carbacyclin itself [70], iloprost [71] and cicaprost [72]. Cicapost is a reasonably selective IP agonist [33] and has been used in many characterization studies. Steric hindrance to internal protonation is found in **taprostene** (Prod. No. **T 4949**), which has a meta-benzene ring inserted between C1 and C5 [73]; it behaves as a partial agonist at the IP receptor [57].

Early work on the EP series of TP antagonists showed that a diphenylmethoxime moiety in the ω-chain conferred IP agonist activity (e.g. EP 157) [74]. Other studies on analogs of octimibate, an ACAT (acyl-CoA: cholesterol acyltransferase) inhibitor [75], and 3,7-m-interphenylene-3-oxa PGE_1 [76] further established the importance of a 1,1- or 1,2-diarylheterocyclic group situated at a critical distance from the C1-carboxylate for IP agonist activity. These non-prostanoid prostacyclin mimetics were initially thought to be more effective inhibitors of platelet activation than vasodilators. However, this appears not to be the case, and they probably do not represent a therapeutic advance over prostacyclin and its close analogs in producing less systemic blood pressure depression at doses that suppress platelet activation and relieve pulmonary hypertension. BMY 45778 is the most potent of the non-prostanoids (77). Care is needed in using these agents to characterize IP receptors, since some of them inhibit PLC-dependent events via a mechanism independent of IP receptors [78]. Several IP receptor antagonists that are structurally unrelated to prostacyclin have recently been described in the patent literature [79].

Figure 7. IP Receptor Ligands



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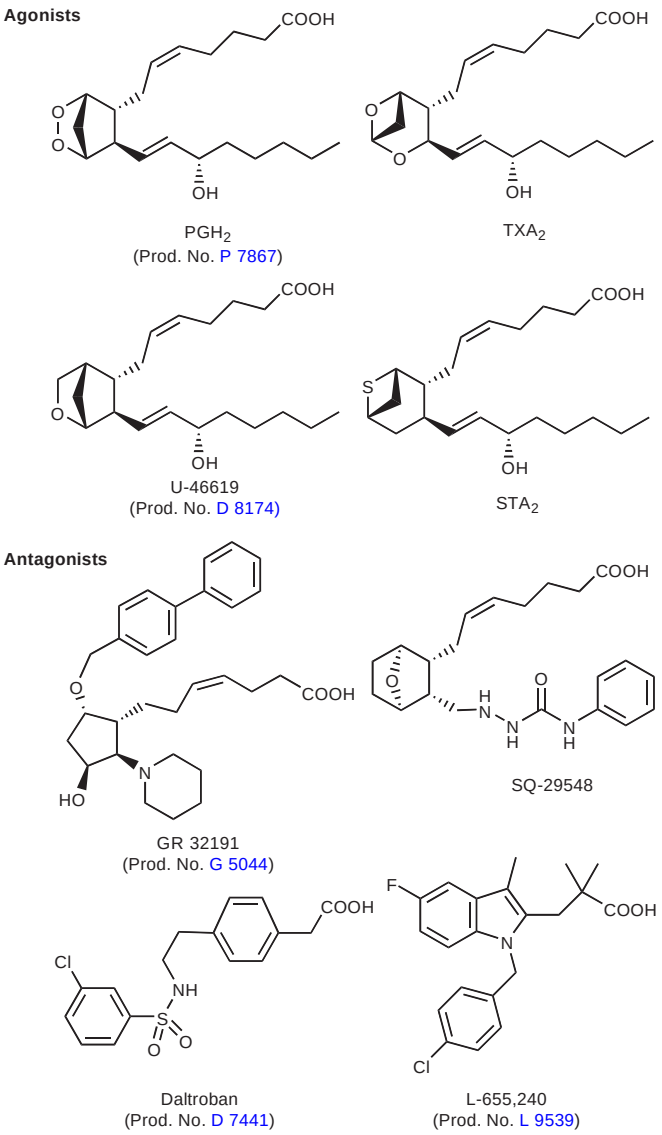
Ligands for Prostanoid Receptors...*(continued)*

Figure 8. TP Receptor Ligands



TP receptors mediate platelet aggregation, vasoconstriction and bronchoconstriction. In human platelets, two isoforms (α and β) of the TP receptor that are divergent in the carboxyl-terminal sequence have been identified [80], and both are activated by TXA_2 and its precursor PGH_2 [81]. The high instability and rapid metabolism of the natural agonists permits local hemostasis, while lessening their more dangerous accumulation in the systemic circulation. Many stable ring analogs have been synthesized, including 11,9-epoxymethano PGH_2 (U-46619), the most commonly used TP agonist in characterization studies [82]. Partial agonists are common, for example, 9,11-epoxymethano PGH_2, CTA_2 and PTA_2 [83,84]); STA_2 [85] is a full agonist. As with ICI 79939 in the PGF series, 16-*p*-halophenoxy substitution on PGH_2/TXA_2 analogs enhances TP agonism (e.g. EP 171, I-BOP) [86,87], and also renders the molecule resistant to deactivation by 15-hydroxyprostaglandin dehydrogenase. This type of molecule should be handled with great care in the laboratory, especially when dissolved in an organic solvent.

The obvious therapeutic potential of TP antagonists in the treatment of thrombotic disorders triggered intense chemical development in the 1980s. Many antagonists are prostanoid in structure, e.g. EP 092, S-145, **GR 32191** (Vapiprost; Prod. No. **G 5044**) and SQ 29538) [88-91], while others are not, e.g. **Daltroban** (Prod. No. **D 7441**) and L-655,240) [92]. GR 32191 and SQ 29538 are the most commonly used antagonists due to their high potency and specificity. A surmountable reversible blockade is usually obtained, although some of the more potent agents, e.g. BMS 180291 and GR 32191, deviate from simple competition in some preparations [93,94]. The therapeutic application of TP antagonists has been less than anticipated due to the emergence of low-dose aspirin therapy for various cardiovascular diseases [9]. Compounds that show both TP receptor antagonism and TX synthase inhibition are known [92]; they usually contain an appropriately positioned imidazolyl or *m*-pyridyl group (e.g. ONO-1301). Of these, Ridogrel has shown benefit in post-myocardial infarction patients [95].

Conclusions

The early expectations for prostanoids in the treatment of disease were unrealistically high. Nevertheless, there have been significant advances: PGI_2 in the treatment of pulmonary hypertension and $PGF_{2\alpha}$ analogs in the treatment of glaucoma are two examples. Further advances are promised based on the prevalence of prostanoid receptor protein/mRNA levels in disease states, the use of prostanoid receptor gene-knockout mice [96], and the development of truly selective receptor ligands. The following examples illustrate the continuing and intense activity in these areas: EP_4 mRNA markedly increased with the development of dextran sodium sulphate-induced colitis in the rat, while EP_2 mRNA showed little change [97]; local application of a selective EP_4 agonist increased femoral bone formation in wild-type and EP_1, EP_2 and EP_3 receptor knockout mice, but not in the EP_4 receptor knockout mouse [98]; EP_3 receptor deletion decreased susceptibility to thromboembolism [99] pointing to a pathological role for PGE_2 and a possible therapeutic use for an EP_3 antagonist; finally, EP_2 receptor knockout was associated with a reduced inflammatory response to ovalbumen challenge [100]. Inflammatory and immunological diseases are immensely complex however, and investigating the local interplay of the natural prostanoids can only be achieved with a battery of highly selective prostanoid antagonists.

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About the Author

Robert Jones received his Ph.D. from the School of Pharmacy, London University in 1970. He then joined the Department of Pharmacology at the University of Edinburgh as a Lecturer. As part of Eric Horton's prostaglandin team, he investigated the activities of the prostaglandins C and D, before collaborating with Norman Wilson to synthesize and test some of the first TP receptor antagonists. He was promoted to Reader in 1979. In 1991 he took up the Chair of Pharmacology at the Chinese University of Hong Kong, where he continued his studies on the characterization of prostanoid receptors. Having just retired from the Chinese University, he will soon take up a Visiting Professorship in the Department of Physiology and Pharmacology at the University of Strathclyde in Scotland.

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P 5172	**Prostaglandin D_2**
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P 5640	**Prostaglandin E_2**
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P 9807	**Prostaglandin J_2**
S 3065	**SC 19220**
S 8692	**Sulprostone**
T 4949	**Taprostene sodium**
T 0516	**Thromboxane B_2**