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# mPGES-1 as a Target for Cancer Suppression:

## A comprehensive invited review "Phospholipase $A_2$ and lipid mediators"

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## Abstract

Prostaglandin $E_2$ ($PGE_2$) is a bioactive lipid that can elicit a wide range of biological effects associated with inflammation and cancer. The physiological roles of $PGE_2$ are diverse, mediated in part through activation of key downstream signaling cascades *via* transmembrane EP receptors located on the cell surface. Elevated levels of COX-2 and concomitant overproduction of $PGE_2$ are often found in human cancers. These observations have led to the use of non-steroidal anti-inflammatory drugs (NSAIDs) as chemopreventive agents, particularly for colorectal cancer (CRC). Their long-term use, however, may be associated with gastrointestinal toxicity and increased risk of adverse cardiovascular events, prompting the development of other enzymatic targets in this pathway. This review will focus on recent efforts to target the terminal synthase, mPGES-1, for cancer chemoprevention. The role of mPGES-1 in the pathogenesis of various cancers is discussed. In addition, an overview of recent efforts to develop small molecule inhibitors that target the protein with high selectivity is also be reviewed.

### Keywords

mPGES-1; inflammation; $PGE_2$; cancer; mPGES-1 inhibitor

## I. Introduction

Prostaglandin $E_2$ ($PGE_2$) is a bioactive lipid that can elicit a wide range of biological effects associated with inflammation and cancer. $PGE_2$ and other prostaglandins (PGs) are derived from the enzymatic release of arachidonic acid (AA), which is rapidly metabolized by cyclo-oxygenase (COX) enzymes and subsequently converted into a panel of PGs by specific terminal PG synthases [1–3]. The physiological roles of $PGE_2$ are diverse, mediated in part through activation of key downstream signaling cascades *via* transmembrane EP receptors located on the cell surface [4]. Receptor-specific binding can activate diverse pathways that regulate cell proliferation, apoptosis, angiogenesis, inflammation and immune surveillance [3,5,6]. Elevated levels of COX-2 and concomitant overproduction of $PGE_2$ are often found in human

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colon adenomas and in adenocarcinomas [7]. These and other observations have led to the use of non-steroidal anti-inflammatory drugs (NSAIDs) as chemopreventive agents for treatment of cancers, including most recently the selective COX-2 inhibitors (e.g. celecoxib). For example, the regular use of NSAIDs has been shown in clinical trials to markedly reduce the relative risk of developing CRC by up to 40–50% [8–11]. However, long-term clinical use of these agents is not without risk, as they have been associated with gastrointestinal toxicity and an increased risk of adverse cardiovascular events [12–14].

## II. The prostaglandin $E_2$ synthase (*PTGES*) family

In recent years, a significant effort has thus been directed towards the development of other enzymatic targets within the arachidonic acid pathway, including the $PGE_2$ terminal synthases (PGES) [15]. The PGES family of proteins are the terminal synthases for the cloned to production of $PGE_2$, and three different gene products with PGES activity have been date, namely PTGES1, PTGES2 and PTGES3, encoding microsomal PGES-1 (mPGES-1), mPGES-2 and cytosolic PGES (cPGES), respectively [6]. mPGES-1 is a member of the MAPEG (membrane-associated proteins involved in eicosanoid and glutathione metabolism) superfamily [15], showing significant homology with other MAPEG superfamily proteins, including microsomal glutathione-S-transferase (GST)-1-like 1 (MGST-1), 5-lipoxygenase (LOX)-activating protein (FLAP) and leukotriene $C_4$ synthase (LTC4). mPGES-1 requires glutathione (GSH) as an essential cofactor for its enzymatic activity [15]. mPGES-1 expression is typically maintained at minimal levels in most normal tissues, although abundant and constitutive expression is detected in a limited number of organs, such as the lung, kidney, and reproductive organs. The closely related mPGES-2 has broader substrate specificity and exhibits some similarity in function to glutaredoxin and thioredoxin [6]. mPGES-2 is expressed constitutively in a variety of human tissues, and unlike mPGES-1, it is not induced by pro-inflammatory signals. cPGES is also expressed in a ubiquitous manner, and is thought to mediate constitutive $PGE_2$ biosynthesis based on its preferential coupling with COX-1 [16].

While several comprehensive reviews have recently been published describing the enzymatic properties of mPGES-1 and its potential involvement with a range of pathological conditions [6,17], this review will focus on recent reports that implicate mPGES-1 activity in the pathogenesis of cancer. In addition, we will provide an overview of recent efforts to develop small molecule inhibitors that target the protein with high selectivity.

## II. mPGES-1 plays a critical role in cancer cell growth

$PGE_2$ is widely recognized as a bioactive lipid metabolite with potent tumor promotion properties. $PGE_2$ activates a wide range of proliferative signals *via* its binding to a family of EP receptors [5,18,19]. Directly associated with increased $PGE_2$ production, clinical studies have shown increased levels of mPGES-1 present within a number of human cancers, including colon [20,21], lung [22], stomach [23], pancreas [24], cervix [25], prostate [26], papillary thyroid carcinoma [27], head and neck squamaous carcinoma [28] and brain tumors [29,30]. These studies are summarized in Table 1. Recently, Seo *et al.* [31] have reported that elevated levels of mPGES-1 and mPGES-2 are significantly correlated with a worse prognosis in late stages of colorectal cancer, suggesting that the $PGE_2$ synthases may play a key role during cancer progression.

The functional role of mPGES-1 has also been studied in cell culture systems. In one such study, co-transfection of COX-2 and mPGES-1 was found to induce a rapid proliferation in HEK-293 cells [16]. Moreover, HEK-293 cells co-transfected with COX-2 and mPGES-1 were found to form large, well-vascularized tumors when injected into the flanks of nude mice [20]. Two very recent papers have now been published examining the roles of mPGES-1 in lung and prostate cancer cell lines. In the study by Hanaka *et al.* (2009), mPGES-1 was knocked

down using shRNA in a prostate cancer cell line, DU145, and also in the non-small cell lung cancer cell line, A549. Following mPGES-1 knockdown, both cell lines showed a decrease in clonogenic capacity and also exhibited slower growth of xenograft tumors in nude mice [26]. Similarly, Kamei *et al*. [32] using siRNA silencing of mPGES-1 in Lewis lung carcinoma cells, also showed reduced cell proliferation, attenuated Matrigel invasiveness and increased extracellular matrix adhesion [32]. These studies clearly demonstrate the critical role that is played by mPGES-1 in a variety of cancer cells, and also provide the underlying rationale for strategies that have focused on chemopreventive targeting of this enzyme for cancer suppression.

Elevated levels of mPGES-1 are often observed concomitantly with COX-2 over-expression. In fact, *in vitro* studies have demonstrated that mPGES-1 is localized at the perinuclear membrane and endoplasmic reticulum and is in general functionally coupled with COX-2 [16,33,34], thereby enabling efficient generation of $PGE_2$ during inflammation [16,35]. Moreover, recent studies have shown that mPGES-1 expression can be specifically induced by lipopolysaccharide (LPS) in rat peritoneal macrophages [36], interleukin-1β (IL-1β) and tumor necrosis factor (TNF)-α in a human lung carcinoma cell line, A549 with or without induction of COX-2 [15,37]. However, studies with these diverse stimuli have clearly shown that mPGES-1 can also be functionally activated in the absence of induced COX-2 levels [37–39], providing evidence that these two enzymes can be independently regulated. This latter observation is important from the standpoint of drug targeting. It suggests the possibility that the enzymatic activity of mPGES-1 can be pharmacologically targeted with resultant suppression of $PGE_2$ production by mechanisms that circumvent the toxicity associated with inhibition of COX-2 activity.

## III. The role of mPGES-1 in gastrointestinal carcinogenesis

Experimental observations developed from cell culture studies, together with the well-recognized role of $PGE_2$ during tumor promotion, have provided the rationale for several recent *in vivo* studies focused on the impact of mPGES-1 on tumorigenesis. In a recent study from our laboratory, mPGES-1 deficient mice were found to exhibit a significant reduction in the number and size of intestinal tumors generated on an *Apc* mutant background [40]. Introduction of the *Ptges* gene deletion onto $Apc^{\Delta 14/+}$ mice reduced the number and size of intestinal tumors by up to 75% compared to mice with the wild-type gene [40]. A notable reduction (~50%) in the number of colon tumors was also observed. Interestingly, *mPGES-1* deficiency was associated with a disorganized vascular pattern within primary adenomas, confirming a key role for $PGE_2$ in tumor angiogenesis [40]. Consistent with these *in vivo* observations, recent findings by Kamei *et al.* [32] showed decreased growth of the Lewis lung carcinoma cell xenograft with concomitant decreases in the density of microvascular networks, the expression of pro-angiogenic vascular endothelial growth factor, and the activity of matrix metalloproteinase-2. However, the mechanism that underlies this defect in neovessel growth has not yet been clarified. In the mPGES-1 knockout study, *mPGES-1* deletion resulted in both reduced size and numbers of pre-neoplastic aberrant crypt foci (ACF) following treatment with the colon carcinogen, azoxymethane (AOM) [40]. Importantly, protection of the colonic mucosa was associated with a marked suppression of nuclear β-catenin translocation, a finding that confirms an earlier study from the Gutkind laboratory in which $PGE_2$ was shown to stimulate colon cancer cell growth through the EP2-Akt-GSK3β axis, leading to β-catenin nuclear translocation and accumulation [41]. In direct contrast to these findings, however, Elander *et al*. [42] reported that genetic deletion of mPGES-1 resulted in accelerated intestinal tumorigenesis in $Apc^{Min/+}$ mice. Tumor multiplicity in the intestine was increased by approximately 50% (80 vs. 38 tumors/intestine), while tumor burden was also significantly increased (1.64 vs. 1.12 mm) by genetic deletion of *Ptges* in comparison to the wild-type littermates [42]. Although these findings are inconsistent with the earlier study by Nakanishi

*et al*. [40], it is possible that environmental factors (e.g. bacterial colonization) may play a role in these disparate responses. This possibility is highlighted by the study of Maggio-Price *et al.* [43] in which SMAD3-deficient mice were sensitized to intestinal tumorigenesis by co-infection with *Helicobacter pylori.* In fact, *Helicoactor pylori* infection has been shown to enhance COX-2 and mPGES-1 expression [44]. Moreover, Nardone *et al.* [45] demonstrated that elevated levels of COX-2 and mPGES-1 were detected with patients with *Helicobacter pylori.* In any case, clarifying the role of mPGES-1 in intestinal carcinogenesis in pre-clinical studies is a key priority for the further development of small molecule inhibitors as potential chemopreventive agents.

## IV. Novel mPGES-1 inhibitors: Drug discovery with mPGES-1 as a molecular target

Despite providing an attractive target for cancer suppression, drug targeting of COX-2 activity has been associated with some clinical concern. For example, the cardiovascular events associated with rofecoxib treatment in the adenoma prevention trial (APPROVe) have been well documented [12,46]. In patients taking selective COX-2 inhibitors, increased risk of myocardial infarction (MI) and stroke [47,48], as well as increased mortality after MI [49], may be due to imbalanced production of pro-thrombotic eicosanoids (e.g. increased $TxA_2$) and anti-thrombotic eicosanoids (e.g. decreased $PGI_2$) [50]. However, a detailed analysis of the mPGES-1 knockout mouse model provides new evidence that much of this toxicity associated with COX-2 inhibition can potentially be circumvented. For example, mice deficient in mPGES-1 did not show alterations in the levels of $TxA_2$ $PGI_2$ or in heart tissue after experimentally induced MI [51]. Furthermore, deletion of mPGES-1 did not affect blood pressure when mice were crossed with low-density lipoprotein receptor (LDLR) knockout mice [52]. Moreover, Wu *et al.* [53] demonstrated absent or reduced levels of myocardial damage after coronary occlusion in mice lacking mPGES-1 compared to mice given the COX-2 inhibitor, celecoxib. Finally, Cheng *et al.* [54] report that genetic deletion of mPGES-1 in contrast to deletion, disruption, or inhibition of COX-2, does not result in hypertension or a predisposition to thrombosis in normo-lipidemic mice. Taken together, these findings suggest that selective mPGES-1 inhibitors may exhibit only minimal cardio-toxic side effects that are typically associated with COX-2 inhibitors.

To date, a limited number of compounds have been described that inhibit mPGES-1 activity *in vitro*. None as yet have been developed as anti-cancer agents. There are several examples of compounds that were developed to target COX-2 but also found to inhibit mPGES-1 activity as well. For example, NS-398 [2-cyclohexyloxy-4-nitrophenyl)-methanesulfonamide], is a COX-2 inhibitor that also inhibits mPGES-1 with an $IC_{50}$ of ~20mM *in vitro* [55]. NS-398 was developed in Japan as an aryl-sulfonamide derivative of the anti-inflammatory agent, nimesulide [56]. NS-398 demonstrates approximately 2,000-fold selectivity for COX-2 over COX-1; this is approximately 2-fold higher COX-2 selectivity than that demonstrated for Rofecoxib, and approximately 5-fold higher than that of Celecoxib [57–59]. In animal models, NS-398 was a potent anti-inflammatory agent [60]; however, it has poor bioavailability and has been found to generate hepatotoxic metabolites. Thus, NS-398 has not been further developed as a therapeutic agent. Similarly, 15-deoxy-$D^{12,14}$-prostaglandin $J_2$ inhibits mPGES-1 with an $IC_{50}$ of 0.3 mM [61]. Recently, a series of molecules based on the indole FLAP inhibitor, MK-866, have been developed. Several of these compounds show mPGES-1 selectivity compared to their ability to inhibit mPGES-2 or thomboxane synthase, with the lowest $IC_{50}$ value found being ~3 nM [57]. A group from Germany recently published a short report on pirinixic acid derivatives as novel dual inhibitors of mPGES-1 and 5-LOX [58]. Although exhibiting low micromolar activity in a cell-free assay, these compounds showed only weak inhibition of $PGE_2$ formation (63% at 33mM). Another group of compounds developed by Merck was recently reported to relieve pain in pre-clinical models of

inflammation [59]. MF-63 potently inhibited the human mPGES-1 enzyme ($IC_{50}$ of 1.3 nM), with a high degree (> 1,000-fold) of selectivity over other prostanoid synthases [59]. However, this compound has not yet been tested in animal cancer models. Finally, a well-known compound found in many oral preparations used for its anti-inflammatory effect on the oral mucosa, Triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol), has been reported to inhibit mPGES-1. Triclosan (Irgasan®) is widely used in soaps, deodorants, toothpastes, mouthwashes, and cleaning supplies and its anti-inflammatory effects have been attributed, at least in part, to its inhibition of $PGE_2$ biosynthesis. Thus considering the wide range of molecular structures that are available (Figure 1), there is the strong likelihood that novel structural analogs can ultimately be developed that may show high selectivity against mPGES-1 and effective suppression of $PGE_2$ generation as described under Figure 2.

## V. Summary and conclusions

As illustrated throughout this review, $PGE_2$ is an important bioactive lipid that plays a fundamental role in a variety of signaling pathways. Acting primarily through its interactions with the EP receptor family, $PGE_2$ elicits control over a range of cellular responses, ranging from angiogenesis to migration and proliferation [6]. While $PGE_2$ is also important in maintaining GI barrier function and integrity, its elevated production within the GI mucosa likely contributes to cancer pathogenesis [62]. Abundant data that has been generated both in cell culture systems as well as in pre-clinical mouse tumor models have provided considerable impetus for the continued development and refinement of mPGES-1 inhibitors. The strongest case for targeting mPGES-1 is based on promising chemoprevention trials that have targeted COX-2 for the suppression of colon adenomas. A major limitation of these trials, however, has been the unfortunate adverse events associated with long-term suppression of COX-2 activity, due in part to the reduced levels of other key prostanoids. Thus, the ability to specifically target mPGES-1, the terminal synthase in the production of $PGE_2$, without affecting the tissue levels of other important prostanoid molecules, offers the potential for therapeutic benefit without the potential toxicity associated with COX-2 inhibition.

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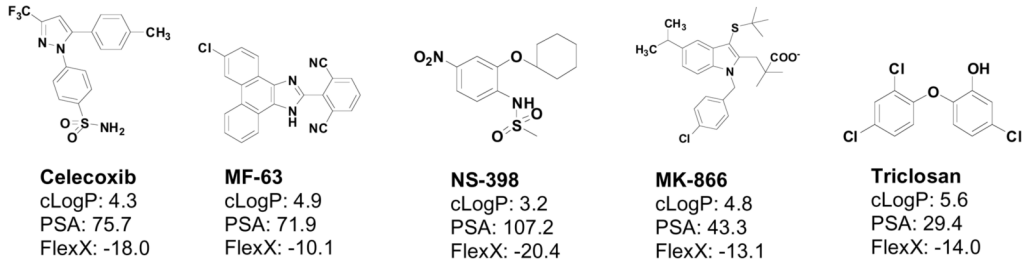


**Figure 1. Structures of known compounds that have mPGES-1 inhibitory action**

Several compounds have been examined for their inhibitory effects against mPGES-1 enzymatic activity *in vitro*. Solubility parameters (cLogP, Polarity Surface Area: PSA, FlexX) were determined by Sybyl 8.0/FlexX modeling program.

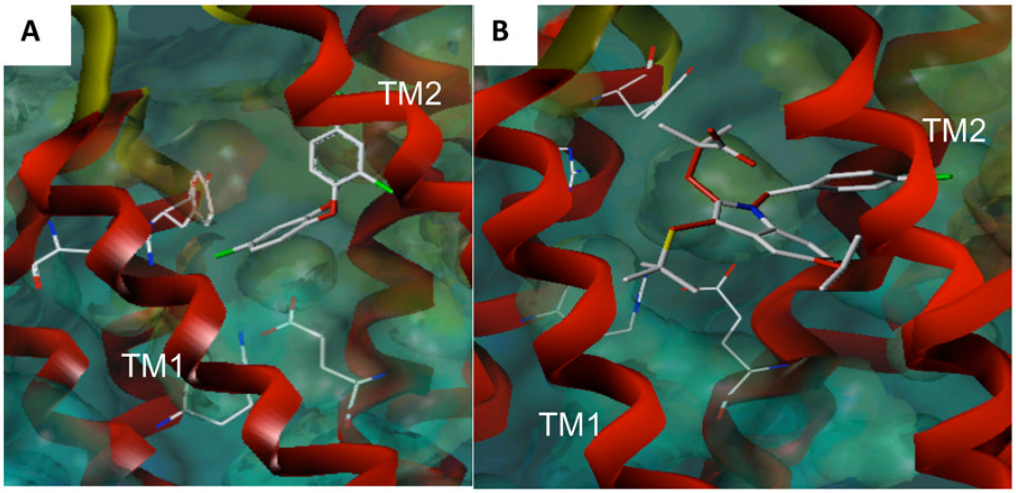


**Figure 2. Docking models of inhibitors within the mPGES-1 active site**

Docking studies were performed using Sybyl 8.0/FlexX modeling program for triclosan (A) and MK-886 (B). mPGES-1 crystal structure coordinates (3dww) were used. The active site residues interacting with both inhibitors include: Arg110, Arg126, Glu77 and Tyr117.

## Table 1

Increased levels of mPGES-1 are common in many human cancers.

| Cancer type | Detection method | Reference |
|---|---|---|
| NSCLC | Western blot, IHC | [22] |
| Colorectal adenomas, carcinomas | Western blot, IHC | [21] |
| Colorectal carcinomas | Western blot, qPCR, IHC | [31] |
| Gastric cancer | Western blot, IHC | [23] |
| Pancreatic cancer | q-PCR, Western blot, IHC | [24] |
| Cervical EpM, SIL, SCC | IHC | [25] |
| Prostate cancer | Western blot | [26] |
| Papillary thyroid carcinoma | IHC | [27] |
| HNSCCC | q-PCR | [28] |
| Low- and High-grade Gliomas | IHC | [30] |

EpM, cervical epithelial metaplasia; SIL, squamous intraepithelial lesions; SCC, squamous cell carcinoma

NSCLC, Non-small cell lung cancer

HNSCCC, Head and neck squamous cell carcinoma