Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

EP2 Antagonists

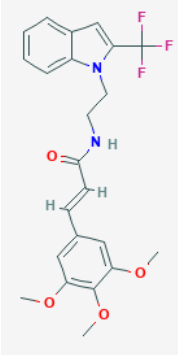
Evidence Summary

EP2 mediates much of the proinflammatory signaling of prostaglandin E2, and its inhibition is likely safer than upstream COX-2 inhibition, but long-term safety has not been established.

Neuroprotective Benefit: Selective EP2 inhibition may mitigate the damaging pro-inflammatory responses of prostaglandins, while preserving the neuroprotective effects, but efficacy may require treatment during a discrete therapeutic window.

Aging and related health concerns: EP2 is an important regulator of blood flow in the retina and kidney, such that EP2 inhibition may exacerbate hypertension, kidney dysfunction, and glaucoma, but may benefit some types of cancers.

Safety: EP2 inhibition is expected to avoid the toxicities of COX-2 inhibition, but it could impact blood pressure and natriuresis, especially in men. The effects of chronic EP2 inhibition are unknown, and safety studies in humans are needed.

Availability: Research use	**Dose**: Not established	**TG6-10-1** **Chemical formula:** $C_{23}H_{23}F_3N_2O_4$ **MW**: 448.4 g/mol  Source: PubChem
Half-life: Varies	**BBB**: Penetrant and non-penetrant inhibitors exist	
Clinical trials: One Phase 1 safety trial (n=56) for PF-04418948, then development terminated.	**Observational studies**: None for EP2 antagonists, specifically. NSAID use/COX-2 inhibition is associated with dementia prevention in some epidemiological studies, but associated with disease worsening at symptomatic stages.	

What is it?

Prostaglandin E2 (PGE2) receptor 2 (EP2) is one of the four EP receptors that mediates cellular responses to PGE2 [1]. EP2 is a G-protein coupled receptor which leads to the activation of adenyl cyclase and increases levels of cyclic AMP, which can drive protein kinase A (PKA) or exchange factor directly activated by cAMP (EPAC)-dependent signaling, depending on the cell type [2]. Cyclooxygenase-2 (COX-2) is an enzyme that catalyzes the synthesis of prostaglandins [3]. The various prostaglandins mediate their effects through the activation of receptors, and can have both protective and deleterious effects depending on the receptor activated and the cellular context. One of the most common targets of the prostaglandins is the regulation of the immune system, and EP2 is associated with the induction of pro-inflammatory responses following cellular damage. Non-selective COX inhibitors, such as non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to mitigate this inflammation and inflammation-associated pain. Selective COX-2 inhibitors have been taken off the market or contain black box warnings due to increased risk for cardiovascular toxicity. Due to toxicity issues with COX-2 inhibitors, new classes of drugs which act more selectively on areas further downstream are being developed to try to maximize the anti-inflammatory effects while mitigating toxicity. EP2 has been implicated as a primarily pro-inflammatory receptor, such that EP2 antagonists are projected to have a better therapeutic profile [1]. To date four distinct classes of EP2 antagonists have been developed, which

include both brain-penetrant and brain impermeable compounds. None are currently available for clinical use, but some have been used extensively in preclinical studies.

PF-04418948 was developed by Pfizer and is peripherally restricted [4]. It was tested in a Phase 1 clinical trial, but subsequent development was discontinued.

Compound 52 was developed by Amgen and is BBB penetrant [5]. It has been used in preclinical rodent studies, but it does not appear that it will continue to be developed for clinical use.

TG6-10-1 and next generation analogs have been developed by Emory University [6; 7] . TG6-10-1 is BBB penetrant, while some of the other tested analogs have low BBB penetrance. Its development has been hindered by low aqueous solubility, but some of the newer analogs have more favorable pharmacokinetic properties.

Neuroprotective Benefit: Selective EP2 inhibition may mitigate the damaging pro-inflammatory responses of prostaglandins, while preserving the neuroprotective effects, but efficacy may require treatment during a discrete therapeutic window.

Types of evidence:

- 2 meta-analyses observational studies of NSAID use for AD prevention
- 1 meta-analysis on RCTs for NSAIDs in AD
- 3 biomarker studies for PGE2 in AD
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

The data regarding the effects of NSAIDs in Alzheimer's disease (AD) prevention are mixed. Epidemiological studies have shown that the use of non-selective COX-2 inhibitors, such as NSAIDs, may delay or reduce the risk of dementia. A meta-analysis of 16 cohort studies (n= 236,022 participants) indicated that NSAID use was associated with reduced risk for AD (Relative risk [RR], 0.81, 95% Confidence Interval [CI] 0.70 to 0.94) [8; 9]. However, the protective effect is only apparent with COX-2 inhibition in cognitively normal individuals, which may be characterized as treatment during asymptomatic or pre-clinical stages [10]. The timing of the intervention appears to be critical to the effect, as modeling suggests the transition from potential benefit to no effect or harm for COX-2 inhibition occurs within the pre-clinical stages [11]. This is consistent with a change in the inflammatory profile and its effects on disease throughout the course of AD.

Dysregulation in the prostaglandin pathway has been found to be an early feature in AD pathogenesis. A metabolic profiling study (n=45) found that the PGE2 biosynthesis pathway was one of the most affected pathways in the cerebrospinal fluid (CSF) during early stages when comparing cognitively normal, mild cognitive impairment (MCI), and AD [12]. The pattern was consistent with studies showing that CSF PGE2 was increased five-fold in patients with probable AD (n=14) [13], and that CSF PGE2 is highest during MCI and decreases with increasing disease severity (n=68) [14].

While COX-2 inhibitors inhibit downstream processes of the prostaglandin pathway, including EP receptor activation, the particular expression of EP2 within AD patients or its contribution to the potential protective effects of NSAIDs has not been determined. Studies in preclinical models of acute neurological injury suggest that EP2 inhibitors may be most effective during a particular therapeutic window that coincides with the period of COX-2 induction and prostaglandin synthesis [15]. The epidemiological and biomarker data in AD support a similar conclusion such that treatment during the pre-clinical phase that precedes and can thus thwart the massive increase of PGE2 in the brain during the MCI stage would be the most effective for preventing or slowing cognitive decline, however, without better biomarkers it will be difficult to accurately target this optimal window.

Human research to suggest benefits to patients with dementia:

In contrast to some epidemiological studies showing a protective effect for NSAIDs in cognitively normal individuals, clinical trials have either failed to find a benefit or showed a worsening of cognitive decline for COX-2 inhibition in patients with pre-existing dementia [16]. This is likely related to the changing inflammatory trajectory over the course of the disease. COX-2 is an upstream player in the prostaglandin pathway; thus, it blocks a large suite of downstream activities, some of which are associated with anti-inflammatory or neuroprotective effects [10]. Preclinical studies suggest that EP2 mediates the damaging inflammatory events downstream of PGE2, thus selectively inhibiting EP2 may mitigate the deleterious inflammatory effects while preserving the neuroprotective ones mediated by other receptors, such as EP4, but further studies are necessary to determine the impact of selective EP2 inhibition in the context of dementia.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Age-related cognitive decline: POTENTIAL BENEFIT (Preclinical)

EP2 activation is associated with maladaptive inflammatory responses during aging in preclinical models. EP2 activation in response to PGE2 influences the metabolic state of myeloid cells in a manner which reduces mitochondrial respiration and leaves the cells in an energy-deficient state [17]. Plasma levels of

PGE2 are elevated in the context of aging, which promotes the metabolic dysfunction of myeloid cells. In mice, deletion of EP2 within myeloid cells (Cd11bCre;EP2$^{lox/lox}$) prevented the age-related change in bioenergetics. The maintenance of myeloid cells' metabolism during aging also prevented age-related increases in pro-inflammatory cytokines, the pro-inflammatory polarization of myeloid cells, as well as the loss of their phagocytic capacity. The preservation of myeloid cell function also prevented age-related declines in spatial memory on the Barnes maze and object location memory tasks in these animals. A similar age-related decline in myeloid cell bioenergetics is seen in human monocyte-derived macrophages, which can be reversed in cell culture through the use of EP2 antagonists. Mouse models suggest that EP2 inhibitors can also reverse the age-related declines in myeloid cell bioenergetics and function *in vivo*. Use of both the brain-penetrant EP2 inhibitor compound 52 (10 mg/kg for one month) and the non-brain-penetrant PF-04418948 (2.5 mg/kg for six weeks) were able to reverse neuroinflammatory phenotypes and spatial memory deficits in aged (22–24-month-old) mice. This suggests that in the context of age-related neuroinflammation, at least in mice, that the EP2-mediated pro-inflammatory effects are driven by blood-borne immune cells which migrate into the CNS. This is consistent with higher expression of EP2 on peripheral myeloid cells relative to CNS resident microglia, and the low basal levels in the adult brain [18]. It is unclear, however, whether EP2 inhibitors could be safely used in the chronic manner needed to maintain myeloid cell bioenergetics throughout the life course.

Alzheimer's disease: POTENTIAL BENEFIT DURNG PRODROMAL PHASE (Preclinical)

Preclinical studies predominantly indicate that EP2 activation is deleterious in the context of AD models, however, the effects may depend on the stage of disease. In line with the association of PGE2 with disease course in humans, EP2 modulation appears to be most influential during the prodromal phases, which are modeled by transgenic animals carrying familial AD mutations during the pre-symptomatic phase [10]. In the APPSwe-PS1ΔE9 model, loss of EP2 reduces oxidative stress damage [19]. This was accompanied by a reduction in the pro-inflammatory microglial response which occurs prior to significant Aβ accumulation, as well as a decline in Aβ levels at later stages. This suggests that EP2 signaling contributes to the propagation of Aβ-related inflammation and oxidative stress. Conditional deletion of EP2 from microglia prevented neuroinflammation and an associated decline in cognitive performance on the novel object recognition task in response to intracerebroventricular injection of Aβ42 [20]. Similarly, the deletion of EP2 from microglia mitigated spatial memory deficits in nine-month-old male APPSwe-PS1ΔE9 mice. The loss of EP2 modulated the insulin-like growth factor 1 (IGF1) signaling cascade, which may have mediated some of the neuroprotective effects. Cell culture studies indicate that EP2 activation inhibits microglial phagocytosis, such that blocking EP2 promotes the

phagocytosis and clearance of Aβ [21; 22]. Some studies have produced contradictory results, in which EP2 activation is neuroprotective in AD models [23]. However, these studies generally use congenital global EP2 knockouts and are confounded by cognitive impairments in these animals that stem from the absence of EP2 during neural development [24; 25].

In cognitive aging, the detrimental effects appear to be primarily mediated by EP2 activation in migrating peripheral immune cells [17], whereas in AD and other neurological disorders, EP2 activation on resident CNS cells appears to play a greater role. It is unclear whether EP2 inhibition starting at symptomatic stages when pathology was already present would be effective in the context of AD. For acute neurological injury, the optimal treatment period tends to coincide with the period of COX-2 induction [15], thus it is likely to be most effective during the prodromal period before PGE2 levels have been shown to be elevated in the brain.

Epilepsy: POTENTIAL BENEFIT FOR ACUTE EPILEPTIC EVENT OVER DISCRETE THERAPEUTIC WINDOW (Preclinical)

Several EP2 inhibitors, including brain-penetrant and non-brain-penetrant compounds have been tested in preclinical rodent models of status epilepticus. Beneficial effects were seen in the context of the pilocarpine-induced, kainic acid-induced, and diisopropylfluorophosphate-induced models of status epilepticus, however the specific effects were dependent on the model and the therapeutic dosing scheme [6; 15; 18; 26; 27; 28; 29]. EP2 inhibitors do not prevent the induction of seizures or modify their course. Instead, they influence the inflammatory response to the seizures mediated by COX-2 induction. The studies in these rodent models indicate inhibiting EP2 can blunt the infiltration of peripheral immune cells, particularly monocytes, into the brain, leading to less inflammation in seizure-affected brain regions. However, peripheral restricted EP2 inhibitors, such as TG8-260, are not effective in mitigating seizure-related neurodegeneration [29]. The ability of brain penetrant EP2 inhibitors, such as TG6-10-1, to protect against hippocampal cell loss, BBB breakdown, and cognitive impairments suggests that EP2 must also be inhibited on CNS resident cells themselves, namely neurons and microglia, to achieve meaningful neuroprotection. One of the protective mechanisms may involve preventing the abnormal activation of brain derived neurotrophic factor (BDNF) secretion and TrkB signaling in response to seizure-evoked PGE2 [28]. The effects of immune cell activation following an injury vary over time such that some responses exacerbate injury while others can promote healing. Consequently, therapies that influence immune responses often have an optimal therapeutic window. The optimal therapeutic window for starting TG6-10-1 was found to be between two to four hours after the induction of status epilepticus in mice, which coincided with the timing of COX-2 induction and prostaglandin synthesis [15]. The optimal window may vary for different EP2 inhibitors depending on

their pharmacokinetic properties. This suggests that EP2 inhibitor treatment should be aligned with the typical period of COX-2 induction in the context of an acute neurological injury, but their utility in neurological diseases with chronic inflammatory processes is less clear. Additionally, due to the models used, the experiments were primarily carried out in male rodents, thus it is unclear whether similar therapeutic effects would be seen in females.

Stroke: POTENTIAL BENEFIT (Preclinical)

Preclinical studies have been mixed as to whether EP2 activation plays a beneficial or detrimental role in the context of cerebral ischemic injury. The mixed results likely stem from the context-dependent nature of EP2 expression and signaling. The expression and downstream effects of EP2 vary between the period of development and adulthood, thus the effects seen in congenital EP2 knockouts may stem from altered development and compensatory events [24; 25]. Similarly, primary neural cell cultures are typically derived from embryonic or early postnatal animals, thus the EP expression pattern is more reminiscent of the developmental state. Thus, these models may not accurately recapitulate the effect of EP2 inhibition following a cerebral injury state in the adult. Indeed, EP2 activation has primarily shown protective effects for cerebral ischemic injury in the congenital knockout and primary cell culture-based studies [30], while EP2 activation was found to worsen injury in adult mice [31]. Using conditional transgenic mouse models, one study found that loss of EP2 during adulthood was cerebroprotective in mice in the middle cerebral artery occlusion (MCAO) model of cerebral ischemia, while overexpression of EP2 in neurons exacerbated injury in adult mice [31]. The use of EP2 inhibitors supports a protective role for EP2 inhibition in the context of cerebral ischemic injury in adult animals. Compound 52 (10 mg/kg at 4.5 and 24 hours) reduced neurological deficits and infarct volume in the MCAO model in three-month-old male mice [31]. Similarly, treatment with TG6-10-1 (5 or 10 mg/kg at 4.5, 12, and 24 hours) also reduced neurological deficits, infarct volume, and pro-inflammatory cytokine expression in three-month-old male mice in the MCAO model [32]. Since these experiments were conducted in males, it is unclear whether females would also benefit. Due to the differential inflammatory responses seen between males and females in other studies, there is reason to expect a sex difference in therapeutic responses.

APOE4 interactions: Some studies suggest that the presence of ApoE4 may promote PGE2 secretion and associated pro-inflammatory responses [33; 34]. If PGE2-related inflammation plays a larger role in the context of ApoE4, then ApoE4 carriers may preferentially benefit for EP2 antagonists, though this has not yet been established.

Aging and related health concerns: EP2 is an important regulator of blood flow in the retina and kidney, such that EP2 inhibition may exacerbate hypertension, kidney dysfunction, and glaucoma, but may benefit some types of cancers.

Types of evidence:

- 1 Phase 3 clinical trial for EP2 agonist OMDI in glaucoma
- 1 gene association study for PTGER2 with hypertension
- Numerous laboratory studies

Hypertension: POTENTIAL TO INCREASE BLOOD PRESSURE (Preclinical)

Prostaglandins play a role in the regulation of blood flow. Both EP2 and EP4 induce vasodilatory responses through the elevation of cAMP [35]. Studies suggest that EP4 may be the major mediator of the systemic vasorelaxation response to PGE2 in humans, while EP2 plays an important role in modulating renal blood flow.

***Essential hypertension*:** In a case-control gene association study (n= 266 cases and 253 controls), the rs17197 single nucleotide polymorphism (SNP) in the EP2 receptor gene (PTGER2) was associated with essential hypertension in men, with the A/A genotype associated with increased risk (Odds ratio [OR] 1.59, 95% CI 1.02 to 2.48) [36]. The effect was not seen in women, which is consistent with a sex-effect in EP receptor expression and sensitivity to EP-related effects on systolic blood pressure seen in rodent models [37]. The study was conducted in individuals of Japanese descent, and it is not known whether a similar association is present in other ethnic groups.

***Salt-sensitive hypertension*:** High salt intake increases the expression of COX-2, leading to increased synthesis of PGE2 in the kidney. Infusion of PGE2 to the kidney leads to increased urine volume and urine sodium excretion in mice [38]. EP2 mediates the effects of PGE2 on renal medullary blood flow and its natriuretic response. In contrast to the hypotensive response to systemic PGE2 seen in wildtype mice, PGE2 induces hypertension in $EP2^{-/-}$ mice, due to its effects on sodium and water balance [37]. These EP2 knockout mice are extremely salt sensitive and develop systolic hypertension in response to a high salt diet [37]. This effect is likely related to the relationship between PGE2 and the renin-angiotensin system, which affects water and sodium reabsorption, and thus blood pressure, by influencing the release of aldosterone [39]. EP2 has been shown to be involved in mediating this relationship.

Pulmonary arterial hypertension: EP2 receptor expression was found to be elevated in human pulmonary arterial smooth muscle cells in patients with pulmonary arterial hypertension [40]. In human lung sections, the anti-proliferative actions of Treprostinil, a prostacyclin used for the treatment of pulmonary arterial hypertension, were found to stem from the activation of the EP2 receptor [40]. This suggests that EP2 may be a primary mediator of vasodilation in small pulmonary vessels, such that EP2 agonists may be beneficial, while EP2 antagonists may aggravate pulmonary hypertension.

Kidney disease: POTENTIAL HARM BY PROMOTING FIBROSIS/MIXED (Preclinical)

The data are mixed regarding the potential effect of EP2 in kidney disease, which stems from its context-dependent nature, such that its effects may vary depending on the model used. EP2 activation has been shown to have anti-fibrotic effects through the inhibition of TGF-β signaling [35]. The EP2 agonist, butaprost, has an anti-fibrotic effect in the mouse model of unilateral ureteral obstruction-induced renal fibrosis, and in TGF-β-induced fibrosis in human precision-cut kidney slices [41]. In models of autosomal dominant polycystic kidney disease, the effects of EP2 activation were contradictory between *in vitro* and *in vivo* models. In 3D cultures of kidney cells, PGE2 promoted cytogenesis via activation of the EP2 and EP4 receptors, while in transgenic mouse models, EP2 (PF-04418948) and EP4 antagonists worsened kidney disease fibrosis. The *in vivo* effect is consistent with other models showing that EP2 activation has an anti-fibrotic effect. A separate study indicates that EP2 activation may drive secondary hyperparathyroidism in patients with end-stage renal disease [42]. Overall, the preclinical studies suggest that EP2 inhibition has greater potential to exacerbate kidney disease, though it may offer benefits in the context of certain kidney-related disorders.

Neuropathic pain: POTENTIAL BENEFIT (Preclinical)

Microglial activation is hypothesized to be involved in the pathogenesis of neuropathic pain. Preclinical studies suggest that PGE2 plays a role in the maintenance of neuropathic pain by promoting microglial chemotaxis and activation [43]. Elevated levels of BDNF in the dorsal root ganglia and spinal cord also contribute to neuropathic pain [44]. PGE2 also stimulates the synthesis of BDNF. These effects of PGE2 are mediated by the EP receptors. EP2 was shown to be involved in PGE2-associated microglial chemotaxis and BDNF synthesis in rodent and cell culture models, however, multiple EP receptors appear to be involved, and it is unclear which EP receptor plays the most influential role in the induction and maintenance of injury-related neuropathic pain in humans [43; 44].

Glaucoma: POTENTIAL HARM DUE TO ROLE OF EP2 IN OCULAR HYPERTENSION

EP2 activation regulates ocular hemodynamics to promote vasodilation, and EP2 activators have shown clinical benefit in the context of primary open-angle glaucoma (POAG) or ocular hypertension. In a Phase 3 noninferiority clinical trial (NCT02623738) comparing the EP2 agonist omidenepag isopropyl (OMDI) 0.002% with the standard of care, latanoprost 0.005%, once daily for four weeks, OMDI was found to be noninferior to latanoprost for reducing intraocular pressure (OMDI −5.93 ± 0.23 mmHg vs −6.56 ± 0.22 mmHg; 95% CI between groups: 0.01 to 1.26) [45]. Latanoprost is a prostanoid FP receptor agonist, which increases aqueous outflow via the uveoscleral pathway, while OMDI increases aqueous humor outflow via both the conventional and uveoscleral pathways. Based on Phase 3 trial results, OMDI (Eybelis, Santen Pharmaceuticals) was approved for glaucoma or ocular hypertension in Japan in 2018. Benefits have been confirmed in a real-world post-marketing survey involving 981 patients in Japan, where there was an average reduction in intraocular pressure from 16.6 mmHg to 13.8 mmHg by seven months (aao.org/2020). Due to the benefits seen with EP2 agonists in reducing intraocular pressure, EP2 antagonists are likely to exacerbate ocular hypertension.

Cancer: POTENTIAL BENEFIT/CANCER-TYPE DEPENDENT (Preclinical)

PGE2 is implicated in a variety of cancer cell-related signaling, however, different EP receptors will differentially modulate these effects in different tumor types [46]. Therefore, the overall effect of modulating the COX-2/PGE2 pathway will depend on the composition of EP receptors and their downstream effectors, within a given tumor environment. EP4 antagonists have been clinically tested in cancer. EP2 has been implicated in inflammatory responses, immune cell-mediated growth factor induction, angiogenesis, and metastasis [47]. While EP2 antagonists show promise in preclinical cancer models, none have been clinically tested for this indication, thus far, likely due to their suboptimal drug properties.

EP2 expression has been shown to be dysregulated in a variety of cancers, and in some cases is associated with prognosis. For example, high EP2 signaling is associated with tumor aggressiveness in neuroblastoma [48], while high EP2 was associated with higher survival in EP3-negative, galectin-3-high cervical cancer [49]. EP2 antagonists have been shown to inhibit tumor cell growth and invasion in various cell culture assays [50], as well as in *in vivo* rodent models. In a xenograft model of SK-N-AS neuroblastoma cells in athymic nude mice, systemic treatment with the brain impermeant EP2 inhibitor TG6-129 (10 or 20 mg/kg) decreased tumor weight by 35% and 40%, respectively [48]. There were also dose-dependent reductions in the tumor proliferative index and angiogenesis. Tumor formation was suppressed in the mouse model of AOM/DSS-induced colon tumorigenesis using the EP2 inhibitor PF-04418948 (10 mg/kg) [51].

Endometriosis: POTENTIAL BENFIT BUT POSSIBLE IMPACT ON FERTILITY (Preclinical)

Endometriosis involves the aberrant growth of endometrial tissue outside of the uterus, which can lead to pelvic pain and infertility. Current therapeutic options are limited to hormonal treatments, but preclinical studies suggest that EP2 and EP4 receptor antagonists could be effective by limiting the growth of the excess endometrial tissue. PGE2 promotes the growth of the lesions in endometriosis via activation of the EP2 and EP4 receptors [52]. In mice, the inhibition of EP2 reduces endometrial tissue growth and survival and reduces hyperalgesia responses [53]. In patient-derived endometrial stromal cells EP2 and EP4 levels were elevated, and an EP2 antagonist (PF-04418948) inhibited the production of pro-inflammatory mediators, including IL-1β-induced IL-6 and IL-8 [52]. However, additional studies in human reproductive tissue are needed to determine potential effects of EP2/EP4 inhibition on fertility. A global knockout of EP2 in mice is associated with reduced fertility in females due to impaired fertilization and a pre-implantation defect [37]. It is unclear if this is species specific, or related to abnormal reproductive system development in the congenital knockout.

Safety: Selective EP2 inhibition is expected to avoid the toxicities of COX-2 inhibition, but it could impact blood pressure and natriuresis, especially in men. The effects of chronic EP2 inhibition are unknown, and safety studies in humans are needed.

Types of evidence:

- 1 Phase 1 clinical trial for EP2 antagonist PF-04418948
- Numerous laboratory studies

Only one EP2 antagonist, the brain-impermanent PF-04418948, has been clinically tested in humans. This compound was tested in a Phase 1 safety study in healthy volunteers (n= 56) (NCT01002963), however, Pfizer discontinued clinical development of the compound following this study.

Clinical development of EP2 antagonists has been hampered by a lack of compounds with optimal drug-like properties, though a variety of medicinal chemistry efforts are underway to improve on existing compounds [1]. Other challenges to clinical development include the lack of clear target engagement measures specific to EP2 activity. While the pharmacokinetic properties, including bioavailability and brain permeability, have been extensively tested and described in preclinical rodent models for several of the EP2 inhibitors used in preclinical research studies, extensive safety testing has not been reported for any of these compounds [4; 5; 7; 26; 29]. Crucially, the studies conducted thus far have used acute dosing paradigms ranging from days to weeks, with no chronic long-term study involving treatment for several months. Long-term use of NSAIDs and COX-2 inhibitors is associated with cardiovascular and

gastrointestinal toxicities (FDA). Selectively targeting EP2 is expected avoid many of the side effects associated with broad COX-2 inhibition, however, it is unclear how many, if any, of the side effects associated with chronic COX-2 inhibition can be attributed to EP2.

Preclinical studies attest to the dynamic expression and signaling of EP2 which can lead to different effects for EP2 inhibition across models and species. Genetic deletion of EP2 in mice is associated with a variety of negative phenotypes, some of which are attributed to developmental defects [25; 37], but for others it is unclear whether they would be phenocopied by chronic inhibition in an adult. Due to the role of PGE2-EP2 signaling in vasodilatory and anti-fibrotic effects in the kidney, EP2 antagonism could potentially exacerbate kidney dysfunction in some populations. The effects on the cardiovascular system in humans, particularly with respect to blood pressure regulation, will require further study.

Sex-effect: Genetic knockouts of EP2 in mice highlight sex differences in susceptibility to conditions influenced by EP2 such as fertility problems in females and a greater propensity toward salt-sensitive hypertension in males [37]. A gene association study supports the notion that EP2 may play a greater role in blood pressure regulation in males in humans as well [36]. Due to sex differences in outcomes for the models used, many preclinical studies, particularly those involving acute neurological injury have predominantly used male animals, thus it is unclear whether EP2 antagonists will offer similar benefit (or harm) for males and females, and needs to be addressed.

Drug interactions: Potential drug interactions are not known, and will likely depend on the particular EP2 antagonist being used, however, there may be some overlap with interactions seen for NSAIDs or COX-2 inhibitors. Due to the role of EP2 in ocular hemodynamics, the use of EP2 antagonists may be contraindicated in patients with ocular hypertension or glaucoma.

Sources and dosing:

There are currently no EP2 antagonists available for human use. Some, such as PF-04418948 and TG6-10-1, are available for research use from commercial suppliers.

Research underway:

There are no clinical trials underway for EP2 antagonists. There are ongoing research studies and medical chemistry efforts to develop better EP2 antagonists and test them in preclinical models.

Search terms:

Pubmed, Google: EP2 antagonists/inhibitors +

- Alzheimer's disease, neurodegeneration, brain, aging, cardiovascular, cancer, kidney, clinical trial

Websites visited for EP2 Antagonists:

- Clinicaltrials.gov
- PubChem (PF-04418948, TG6-10-1)
- DrugBank.ca (PF-04418948)

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