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.

P2Y6R Agonist

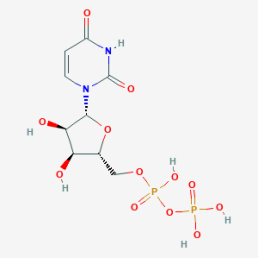
Evidence Summary

P2Y6R activation promotes microglial phagocytosis, but also drives vascular inflammation, so agonists may exacerbate cardiovascular disease. Short term safety is good, but long-term safety is unknown.

Neuroprotective Benefit: P2Y6R stimulation promotes microglial activation and phagocytosis which may facilitate amyloid clearance, but may also promote neuroinflammation and neuronal loss.

Aging and related health concerns: P2Y6R activity is associated with the exacerbation of hypertension, atherosclerosis, neuropathic pain, and cancer metastasis in preclinical models, but may benefit glaucoma.

Safety: The agonist GC021109 was safe in short Phase 1 trials, but long-term safety has not been established. Effects may vary in different patient populations.

Availability: Research use	**Dose**: Not established	Endogenous agonist: **UDP** **Chemical formula:** $C_9H_{14}N_2O_{12}P_2$ **MW**: 404.16 g/mol  Source: PubChem
Half-life: Not reported	**BBB**: Not reported	
Clinical trials: Two Phase 1 studies for GC021109 in healthy controls (n=44) and mild/moderate AD (n=36).	**Observational studies**: None	

What is it?

The P2Y6 receptor (P2Y6R) is a G-protein coupled receptor (GPCR) which belongs to the class of purinergic receptors. In response to extracellular nucleotides, P2Y purinergic receptors initiate intracellular signaling cascades. P2Y6R is preferentially activated by the pyrimidine uridine diphosphate (UDP). In response to UDP, the coupled G protein activates the phosphatidylinositol-calcium second messenger system, leading to an increase in intracellular calcium, and the activation of downstream calcium regulated signaling pathways. Therefore, the effects of P2Y6R activation can vary across cell types depending on which signaling pathways are preferentially affected. The actions of P2Y6R are best understood in microglia and macrophages, where they induce phagocytosis and activation. Since different diseases have been tied to both increased and decreased P2Y6R signaling, there are efforts underway for the development of antagonists and agonists as therapeutic agents. Most have only been used in preclinical research thus far, but the P2Y6R agonist, GC021109, has been tested in Phase 1 RCTs and is in development for Alzheimer's disease.

Neuroprotective Benefit: P2Y6R stimulation promotes microglial activation and phagocytosis which may facilitate amyloid clearance, but may also promote neuroinflammation and neuronal loss.

Types of evidence:

- 1 clinical trial (Phase 1b mild to moderate AD n=36)
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

Human research to suggest benefits to patients with dementia:

The orally bioavailable P2Y6R agonist GC021109 was tested in a Phase 1b trial in patients with mild to moderate Alzheimer's disease (n=36) (NCT02386306). GC021109 is a prodrug nucleoside which is phosphorylated *in vivo* to the nucleotide GC011002 that selectively activates P2Y6R (EC50 20 nM) [1]. The company conducting the trial, GliaCure, reported that the pooled results from the multiple ascending dose study showed a statistically significant change in cerebrospinal fluid (CSF) levels of amyloid, relative to placebo (Press release). However, aside from movement on this biomarker, it is not clear if this drug benefits patients in a clinically meaningful manner.

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

Alzheimer's disease: POTENTIAL MIXED BENEFIT/HARM (Preclinical)

P2Y receptors are widely expressed and contribute to a variety of processes in the CNS [2]. Since many of the receptors have overlapping functions, it may be necessary to modulate multiple receptors in order to achieve a biological effect. However, since the functional consequence of P2Y receptor activation can also vary in a cell-type and context dependent manner, beneficial effects in one cell type or context may be counteracted by negative effects in other cells. Moreover, studies in postmortem brain tissue and preclinical models suggest that P2Y6 may not be the major purinergic receptor that is dysregulated in Alzheimer's disease (AD) [2], and that the potential efficacy of P2Y6R modulators may wane with disease progression [3].

P2Y6R promotes microglial phagocytosis in response to UDP [4], thus decreased expression and/or activity of P2Y6R could lead to impaired clearance of Aβ and promote the expansion of Aβ plaques. P2Y4R, which is activated by ATP, has also been found to play a role in clearing soluble Aβ by stimulating pinocytosis [5]. However, a small study examining **post-mortem brain tissue from AD patients (n=29) and age-matched controls (n=12) found that the expression of both P2Y6R and P2Y4R was largely unchanged** in the parietal cortex [2]. Meanwhile, P2Y2R expression was selectively decreased in affected brain regions and this decline correlated with neuropathological Aβ plaques (Spearman $\rho = -0.69$, $p < 0.01$) and tau tangles (Spearman $\rho = -0.67$, $p < 0.01$). P2Y2R is activated in response to both adenosine and uridine nucleotides. It is involved in the non-amyloidogenic proteolytic processing of amyloid precursor protein (APP) and growth factor mediated neuronal differentiation.

In the 5XFAD and APP/PS1 mouse models of AD, there is both an impairment of microglial phagocytosis and decrease in the expression of P2Y6R with disease progression [3]. The **decrease in P2Y6R was most prominent in plaque-associated microglia, and led to a decline in normal physiological responses to UDP in these cells**, including the modulation of K+ currents. The microglia also showed altered responses to ATP, suggesting that there is an overall dysregulation of purinergic signaling in these cells. Notably, P2Y6R agonists, such as UDP, were only effective at promoting microglial phagocytosis in young 5XFAD mice, prior to the accumulation of neuropathology [3], suggesting that P2Y6R agonists may not have therapeutic efficacy in the context of established disease. Additionally, P2Y6R plays a role in the loss of stressed but viable neurons through the process of phagoptosis [6], thus under conditions of inflammation or other cellular stress, P2Y6R agonists may potentially reduce neuronal survival.

Inflammation-associated neuronal loss: POTENTIAL HARM (Preclinical)

P2Y6R is upregulated on microglia in response to neuronal damage, where it may act as a sensor for the release of UDP by the damaged cells [4]. The activation of **P2Y6R then triggers microglial phagocytic pathways, and can facilitate the engulfment of stressed, but viable, neurons**. The activation of toll-like receptors (TLRs) on microglia in response to various cell stresses including, inflammation, oxidative stressors, and Aβ, results in the release of oxidants from microglia which induce neurons to reversibly expose the 'eat me' signal phosphatidylserine [6; 7]. These stressed neurons are then primed to be engulfed by phagocytic microglia. Experiments in rodents have shown that treatment with the P2Y6R antagonist MRS2578 can prevent the phagoptosis mediated delayed loss of neurons following exposure to inflammatory and oxidative stressors [6]. While the activation of microglial phagocytosis through P2Y6R may be beneficial in the context of acute damage by clearing apoptotic cells and cellular debris which can interfere with regeneration [8; 9], the prolonged activation of P2Y6R may exacerbate damage [6]. This suggests that P2Y6R agonists could potentially mitigate neurological damage if administered acutely following CNS trauma, however, they may be less suitable for chronic disease.

Parkinson's disease: POTENTIAL HARM (Preclinical)

Clinical biomarker and preclinical studies indicate that the expression of P2Y6R is elevated in the context of Parkinson's disease (PD), which may stem from elevated levels of inflammation and/or oxidative stress. **mRNA expression of P2Y6R was found to be increased in the peripheral blood mononuclear cells (PBMCs) from patients with PD** (n=145) relative to age-matched healthy controls (n=170) with an area under the curve (AUC) of 0.785 (95% Confidence Interval (CI) 0.734 to 0.838) [10]. The expression of P2Y6R was also impacted by age, such that the difference was 3.9-fold for those under age 60 and between 2.5 to 3.5-fold for those aged 60 to 79, but the differences were not significant between PD

and healthy controls in those over age 80. Peripheral P2Y6R expression was not associated with disease duration or severity. The increase in P2Y6R was partially attributed to elevated ERK1/2 signaling.

In preclinical models, treatment with the P2Y6R inhibitor MRS2578 mitigated oxidative stress damage and microglial activation in response to the oxidative neurotoxins 6-OHDA and MPP+ [11; 12]. Since the protective effects were seen when P2Y6R was inhibited during the time of toxin exposure, they are primarily associated with reducing the initial extent of neurological damage in these acute models. It is unclear whether P2Y6R plays a meaningful role in propagating deleterious inflammatory processes in the context of chronic disease.

APOE4 interactions: Unknown

Aging and related health concerns: P2Y6R activity is associated with the exacerbation of hypertension, atherosclerosis, neuropathic pain, and cancer metastasis in preclinical models, but may benefit glaucoma.

Types of evidence:

- 3 observational studies (P2Y6R expression and cancer prognosis)
- Numerous laboratory studies

Cardiovascular disease

P2Y6R is expressed in the heart and vasculature and participates in a variety of processes critical to cardiovascular function. **P2Y6R plays different roles in development and disease based on changes in the expression pattern and microenvironment context**. In development, the expression of P2Y6R in cardiac tissue protects against cardiac hypertrophy [13], while in adulthood elevated P2Y6R may promote deleterious cardiac remodeling associated with hypertension and atherosclerosis [14].

Hypertension: POTENTIAL HARM (Preclinical)

Extracellular nucleotides play a key role in the regulation of vascular tone [15; 16]. The nucleotides are primarily released by endothelial cells and erythrocytes in response to cellular stressors, including hypoxia, sheer stress, mechanical strain, and low pH [15]. The extracellular nucleotides act on P2Y receptor coupled Gq proteins to increase intracellular levels of Ca2+, which triggers changes in vascular tone depending on the cell type. **Activation of P2Y6R on smooth muscle cells leads to vasoconstriction,**

while activation on endothelial cells promotes vascular relaxation. Studies in rodent and human vessels have shown that the vascular response to the nucleotides varies depending on the expression pattern of the various P2Y receptors. For example, in mice P2Y6R is the primary contractile receptor in large diameter segments of the coronary artery, but in small diameter vessels it promotes relaxation [15]. In human vessels, P2Y6R induces the contraction of cerebral arteries, but does not significantly contribute to vasoregulation of the major gastrointestinal artery, where other P2Y receptors play a more prominent role [17]. Consequently, P2Y6R agonists, such as UDP, can exert different functional responses throughout the body.

P2Y6R has been shown to promote angiotensin-II induced hypertension and adverse cardiac remodeling in preclinical models [18]. Angiotensin-II promotes vasoconstriction, vascular smooth muscle proliferation, and the hardening of vessel walls. In rodents and human vascular smooth muscle cells, the loss or inhibition of P2Y6R attenuates angiotensin-II induced vascular dysfunction [18; 19]. P2Y6R was shown to form a stable heterodimer with the angiotensin receptor AT1R, which reduces the turnover of AT1R and biases the downstream signaling cascades to drive G-protein dependent vascular hypertrophy [18]. The increased expression of P2Y6R on vascular smooth muscle cells during aging is hypothesized to contribute to age-related vascular remodeling and dysfunction. In mice, P2Y6R expression was found to be elevated in the heart in the context of myocardial infarction and pressure overload [16; 20]. Blockade of P2Y6R protected against heart failure, and fibrotic cardiac remodeling by inhibiting the induction of pro-fibrotic genes (ANP, β-MHC, procollagen type I, periostin, and TGF-β2) and Rho-GTPase activity in vascular cells [16; 20]. This suggests that P2Y6R agonists could exacerbate age-related cardiovascular pathology.

***Atherosclerosis*:** POTENTIAL HARM (Preclinical)

The activation of P2Y6R by UDP can propagate vascular inflammation by inducing the release of chemokines/cytokines and expression of adhesion molecules which facilitate leukocyte recruitment to the vessel wall [21]. **Expression of P2Y6R is increased in atherosclerotic vessels** in multiple animal models, which is consistent with its upregulation in the context of chronic inflammation [21; 22; 23]. Activation of P2Y6R by its endogenous agonist, UDP, **promotes the secretion of pro-inflammatory mediators** (IL-6, IL-8, MCP-1) in macrophages, and induces the migration and adhesion of leukocytes to the vessel wall [21; 22].

Due to the cell type and context dependent effects of P2Y6R, there have been discrepancies in how the loss of P2Y6R impacts atherosclerosis across studies. Studies using cell type specific P2Y6R knockouts suggest that P2Y6R on vascular cells promotes the recruitment of leukocytes, and the elevated

expression and pro-atherogenic properties of P2Y6R in atherosclerotic plaques are primarily due to the presence of the bone-marrow derived immune cells themselves in the vessels [22]. In some models, the loss of P2Y6R was associated with a decrease in atherosclerotic plaques, macrophage load, and pro-inflammatory mediators in the vessels [21; 23]. However, in other models due to counteracting effects of P2Y6R on other cell types, such as a role in decreasing the formation of aneurysms, global knockouts of P2Y6R were not protected against atherosclerosis [22]. These studies suggest that a targeted approach, such as one that only affects bone-marrow derived cells, would be needed in order to safely and effectively modulate P2Y6R as a therapeutic intervention for atherosclerosis.

Neuropathic pain: POTENTIAL HARM (Preclinical)

Purinergic receptors are involved in the development and maintenance of neuropathic pain. Therefore, **P2Y6R agonists would be expected to exacerbate neuropathic pain**. In rodent models, P2Y6R has been shown to play a role in modulating the inflammatory response in part through the regulation of JAK/STAT3 signaling and microglial activation [24]. However, discrepancies across models suggest that the specific contribution of P2Y6R to neuropathic pain may depend on the duration and location of the injury. Species specific differences in P2Y6R expression may also play a role. The P2Y6R inhibitor MRS2578 was able to inhibit the development of neuropathic pain following spinal cord injury in rats when administered near the time of injury [24; 25], however, it was not effective in reducing mechanical hypersensitivity in mice when treatment was initiated two weeks after injury [26].

P2Y6R may also contribute to pain by **promoting prostaglandin mediated inflammation**. The enzyme COX2, which is the target of anti-inflammatory NSAIDs, catalyzes the formation of prostaglandins from arachidonic acid as well as the formation of prostaglandin glycerol esters (PGE-Gs) from the endocannabinoid 2-arachidonoylglycerol [27]. Prostaglandins and PGE-Gs are lipid signaling molecules involved in inflammation and hyperalgesia. P2Y6R was identified as the signal transduction receptor for PGE2-G. PGE2-G was found to be a more potent agonist of P2Y6 with an EC50 of 1pM, compared to its best characterized endogenous agonist UDP, which has an EC50 of 50 nM [27]. Injection of PGE2-G into the hind paw of mice elicits hyperalgesia, which can be blocked by co-administration of the P2Y6R antagonist MRS2578 [28]. PGE2-G/P2Y6R mediated signaling is also implicated in the pain associated with sickle cell disease, in a mouse model [28]. Overall, these studies suggest that P2Y6R agonists may potentiate pain.

Glaucoma: POTENTIAL BENEFIT (Preclinical)

Elevated intraocular pressure (IOP) is one of the primary risk factors for developing glaucoma. P2Y6R has been identified as a potential target for the treatment of glaucoma due to its role in regulating IOP in mice. P2Y6R activity in non-pigmented epithelial cells of the ciliary body was shown to influence the dynamics of the aqueous humor, the fluid between the cornea and lens of the eye, by inhibiting its production [29]. Mice lacking P2Y6R show evidence of hypertensive glaucoma-like optic neuropathy, including elevated IOP and retinal ganglion cell loss [29]. Topical application of the endogenous P2Y6R agonist, UDP, reduced IOP in wildtype mice. A modified form of UDP, 5-OMe-UDP(α-B) called 1A, was also shown to be effective at reducing IOP when administered topically to the eye in two rabbit models of glaucoma [30].

Cancer: POTENTIAL HARM/MIXED (Preclinical)

P2Y6R is implicated in tumor metastasis and chemoresistance in several types of cancer, including colorectal and breast cancers. Nucleotide signaling modulates the inflammatory profile of the tumor microenvironment [31]. P2Y6R expression was found to be elevated in breast cancer tissue, and the expression was positively correlated with malignancy and poor prognosis [32]. Similarly, P2Y6R was elevated in colorectal cancer tumors relative to the surrounding tissue, and increased expression of P2Y6R was associated with decreased probability of survival in renal cancer [33].

Loss or inhibition of P2Y6R reduced colorectal tumor burden, tumor vascularization, and tumor metastasis, while the **P2Y6R agonist UDP promoted metastasis** in mouse models [31; 32; 33]. P2Y6R signaling may influence the pre-metastatic niche to promote metastasis, and the chemotherapy induced release of nucleotides, including UDP, may help drive this process [31]. **P2Y6R may prime the pre-metastatic niche** by facilitating the infiltration of neutrophils [31]. P2Y6R also activates MAPK signaling, which in turn activates MMP-9, a key driver in tumor metastasis [32]. However, the role of P2Y6R is likely to be tumor type dependent, depending on both the expression of P2Y6R and the tumor environment.

Diabetes: POTENTIAL MIXED (Preclinical)

Due to differences in the effects of P2Y6R activation across tissues, it is unclear whether the net effect would be positive or negative for individuals with diabetes. P2Y6R agonists have been shown to protect pancreatic islet cells and promote glucose dependent insulin release in mice [34]. However, the expression and activation of P2Y6R on Agouti-related protein (AgRP)-expressing neurons in the hypothalamus which control feeding was found to promote overeating and insulin resistance [35]. This

suggests that elevated activity of P2Y6R in the hypothalamus could contribute to obesity and metabolic dysfunction.

Safety: The agonist GC021109 was safe in short Phase 1 trials, but long-term safety has not been established. Effects may vary in different patient populations.

Types of evidence:

- 2 clinical trials (Phase 1 studies in healthy volunteers (n=44) and mild AD (n=36) for GC021109)
- Numerous laboratory studies

The P2Y6R agonist GC021109 was found to be safe and well tolerated in a Phase 1a single ascending dose (oral 0.0014, 0.014, 0.14, 1.4, or 4.2 mg/kg) study in healthy volunteers (n=44) (NCT02254369) and a Phase 1b multiple ascending dose (oral 1, 10, or 30 mg) study in patients with mild to moderate AD (n=36) (NCT02386306), as reported by the sponsor (Press release). All adverse events were mild and did not require drug discontinuation. Other P2Y6R agonists have not been clinically tested.

Preclinical studies suggest that P2Y6R exerts a variety of effects throughout the body, so the therapeutic profile and risk for side effects will likely vary across patients based on differences in P2Y6R expression as well as the expression of other signaling pathways that interact with P2Y6R. Potential complications of systemically administered agonists include increased pain, vascular inflammation, and hypertension [27; 36]. Since P2Y6R influences immune cell function, its modulation could potentially alter the body's immune response to pathogens. One study found that in the CNS, the circadian expression of P2Y6R influenced the microglial response to the bacteria *Porphyromonas gingivalis* [37], and suggests that P2Y6R agonists may elicit a heightened neuroimmune response to pathogens in the CNS.

Sources and dosing:

There are currently no approved P2Y6R agonists available as therapeutic agents. GC021109 is in clinical development for AD by GliaCure and has been tested in an oral formulation in single doses up to 4.2 mg/kg in healthy volunteers (NCT02254369) and multiple doses up to 30 mg for 28 days in patients with mild to moderate AD (NCT02386306). The P2Y6R agonist MRS2693 is available for research use from commercial suppliers. The potent P2Y6R agonist 1A [5-OMe-UDP(α-B)] has been in preclinical development for glaucoma [30] by GlaucoPharm Ltd, which is a startup from the Israeli incubator Youdim Pharmaceuticals, but it is unclear if this drug is still being developed for eventual clinical use.

Research underway:

There are currently no clinical trials underway testing P2Y6R agonists.

Search terms:

Pubmed, Google: P2Y6

- Alzheimer's, Parkinson's, neurodegeneration, inflammation, agonist, neuropathic pain, cardiovascular, cancer, diabetes, clinical trial, safety

Websites visited for P2Y6 Agonist:

- Clinicaltrials.gov (GC021109)
- PubChem (UDP)
- DrugBank.ca (Purinergic Agents)

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