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.

P2Y1R Inhibitors

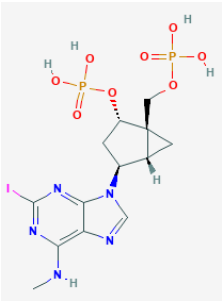
Evidence Summary

P2Y1R inhibition has anti-platelet effects and may protect against excitotoxicity, but due to its context dependent properties, there is conflicting evidence, and the translatability of the models is unclear.

Neuroprotective Benefit: P2Y1R inhibition may help preserve synaptic function and reduce excitotoxicity by normalizing astrocytic activity, but additional normalization of global purinergic dysfunction may be required for therapeutic benefit.

Aging and related health concerns: P2Y1R inhibitors may have anti-platelet properties and reduce thrombosis risk when paired with P2Y1R inhibitors.

Safety: P2Y1R inhibitors have not been tested in humans. Preclinical studies suggest that they increase bleeding risk, and due to its widespread expression, there is potential for additional side effects throughout the body.

Availability: Research use	**Dose**: Not established	MRS2500 **Chemical formula:** $C_{13}H_{18}IN_5O_8P_2$ **MW**: 561.16 g/mol  Source: PubChem
Half-life: N/A	**BBB**: N/A	
Clinical trials: None	**Observational studies**: None	

What is it?

P2Y1 is a purinergic receptor that is activated in response to extracellular purines [1]. It is a G-protein coupled receptor (GPCR) that is **preferentially activated by ADP**, and has a lower affinity toward ATP. It is coupled to Gq proteins and activates phospholipase C (PLC), leading to the hydrolysis of phosphatatidylinositol-4,5-bisphosphatase (PIP2) to generate IP3 and diacylglycerol. This leads to the activation of IP3 mediated Ca^{2+} channels and an increase in intracellular Ca^{2+} levels. Consequently, P2Y1R primarily mediates its effects by influencing Ca^{2+} levels and signaling. P2Y1R is widely expressed throughout the body, but is enriched in the brain. P2Y1R plays a critical role in platelet activation, so the development of P2Y1R inhibitors has been of interest as a potential anti-platelet therapy. Preclinical studies suggest that P2Y1R inhibitors may also have therapeutic value for neurological diseases associated with excitotoxicity, such as epilepsy and Alzheimer's disease. However, the downstream effects of P2Y1R signaling are highly context dependent, which could limit the therapeutic utility of P2Y1R targeted drugs.

Neuroprotective Benefit: P2Y1R inhibition may help preserve synaptic function and reduce excitotoxicity by normalizing astrocytic activity, but additional normalization of global purinergic dysfunction may be required for therapeutic benefit.

Types of evidence:

- 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: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Purinergic signaling influences neuronal network excitability and dynamics, thus it can lead to network dysfunction when it gets disrupted [2]. Extracellular purines, including adenosine, ADP, and ATP, can act as neuromodulators to influence neurotransmitter release through engagement with P1 and P2 receptors. Each receptor is preferentially activated by a particular purine, but many respond to multiple purines with varying affinities. Consequently, **responses are complex and context dependent involving both synergistic and antagonistic cross-talk amongst the different receptors** [3]. Changes to the expression of purinergic receptors during aging may play a role in age-related cognitive decline and neurodegenerative disease impairing synaptic network maintenance [4; 5]. These changes promote a network imbalance toward more excitation and less inhibition, which increases susceptibility to excitotoxicity. In the hippocampus, ATP tends to promote inhibition, while aging reduces the physiological secretion of ATP as well as the density of ATP responsive receptors [5].

While **purinergic signaling is important for the maintenance of synaptic function under physiological conditions**, purinergic signaling can also promote neurotoxicity under pathological conditions [3]. Purines can serve as danger signals, released by damaged cells in response to cellular trauma. In this context, the concentrations of extracellular purines vastly exceed the levels involved in normal physiological responses, which can result in a different pattern of purinergic receptor activation. **Chronically elevated purines can alter the purinergic signaling profile in a manner that promotes neuroinflammation, synaptic dysfunction, and excitotoxicity**. Under these conditions, inhibition of purinergic receptors whose upregulation contributes to the pathological phenotype may be neuroprotective. However, due to the fact that purinergic signaling involves the complex interplay of

multiple receptor types, it is not clear whether targeting a single dysregulated receptor will be sufficient for therapeutic efficacy, or if it is necessary to modulate multiple receptors to correct the network dysfunction.

P2Y1R is widely expressed in the CNS and helps orchestrate the purinergic signaling response involving a complex interplay amongst neurons, astrocytes, microglia, and endothelial cells [3]. The literature regarding the contribution of P2Y1R to various neurological disorders has been contradictory due to the context dependent nature of P2Y1R signaling [6]. Under different pathological conditions, there can be preferential dysregulation of P2Y1R on a particular cell type, which due to the interconnectedness of purinergic signaling, can lead to complex changes across the cellular network in the CNS [3]. As a result, the contribution of P2Y1R can vary across disease models, leading to discrepancies where P2Y1R inhibition is beneficial in one model, while P2Y1R activation is beneficial in a different model for the same disease. In general, *in vitro* models are more likely to show protective effects for P2Y1R activation, whereas in the more complex *in vivo* environment, P2Y1R inhibition is more likely to offer benefit, suggesting that the protective effects stemming from P2Y1R activation in one cell type, as shown *in vitro*, are negated by a broader network dysfunction *in vivo* [2]. However, due to its context dependent nature, animal models may not accurately convey the changes in purinergic and P2Y1R signaling that take place in the context of various human diseases, and it will only be possible to get a sense of transability/efficacy of P2Y1R inhibitors through clinical testing in humans.

Alzheimer's disease: POTENTIAL BENEFIT (Preclinical)
Postmortem brain tissue from Alzheimer's disease (AD) patients provides **evidence for altered expression of P2Y1R in AD.** In the hippocampus, there is an upregulation of P2Y1R on astrocytes. The astrocytes upregulating P2Y1R are those in a reactive-like state, which includes the Aβ plaque-associated astrocytes [7]. The cellular localization of P2Y1R on neurons is also altered in the context of AD. In the control brain, P2Y1R is primarily localized to the cell surface in the cell body and proximal dendrites of pyramidal neurons of the entorhinal cortex, whereas in the AD brain, P2Y1R was localized intracellularly and associated with neurofibrillary tangles [8]. The overall levels of P2Y1R are also reduced, which is thought to be due to the loss of neurons, rather than the loss of neuronal expression per se. This expression pattern suggests that in AD there is an enhancement of purinergic signaling through P2Y1R on astrocytes, along with a decrease in neurons. Since purinergic signaling through the astroglial-neuronal network is important for the maintenance of synaptic function, this shift in the balance of P2Y1R signaling within the network can lead to cognitive impairment.

Although there are differences across models, collectively the evidence from AD models suggests that there is a **dysregulation of P2Y1R signaling which is primarily driven by a pathological upregulation on astrocytes**. Astrocytes form a functional syncytium, whereby they are connected via gap junctions, and signals can propagate across the syncytium [9]. This most commonly occurs in the form of Ca^{2+} waves, and purinergic signaling is a major driver of these waves. Since the primary response to P2Y1R activation is IP3 mediated increases in intracellular Ca^{2+}, changes to the expression of P2Y1R on astrocytes can have a profound impact on Ca^{2+} responses and waves through the astrocyte network. Due to neuro-glial coupling, these astrocytic Ca^{2+} transients modulate neurotransmitter release, neuronal excitability, and synaptic plasticity. One of the best studied effects of the astrocytic Ca^{2+} elevations is the triggering of glutamate release and subsequent activation of metabotropic glutamate receptors (mGluRs) on neurons.

In AD models, the upregulation of P2Y1R drives astrocyte hyperreactivity and widespread network dysfunction. These pathological effects may be driven by microglia and a pro-inflammatory environment. Within a pro-inflammatory environment, microglia release purines, which activate P2Y1R on astrocytes. The purinergic signal then gets amplified through the astrocyte network. Microglia can also regulate the expression of P2Y1R on astrocytes via inflammatory cytokine signaling. The downregulation of astrocytic P2Y1R by microglia-derived signals promotes a neuroprotective phenotype, while its upregulation promotes a neurotoxic phenotype [10].

In the APP/PS1 AD mouse model, treatment with broad P2 receptor or P2Y1R specific inhibitors normalizes astrocyte hyperreactivity, and restores the balance between homeostatic and reactive astrocytes [11]. The effect appears to be mediated through the normalization of astrocytic calcium levels. Notably, P2Y1R is an important mediator of Ca^{2+} waves in reactive astrocytes under pathological conditions, but under physiological conditions, inhibition of P2Y1R does not significantly affect astrocyte activity. Intracerebroventricular infusion of P2Y1R antagonists normalized neuronal-astroglial network activity, restored synaptic integrity and plasticity, and attenuated cognitive decline based on performance in the Barnes maze in late stage AD mice [7]. These effects were also related to the normalization of astrocytic Ca^{2+} and associated signaling. In $APP^{NL\text{-}F/NL\text{-}F}$ mice, P2Y1R inhibition was able to restore network excitability by blocking P2Y1R on astrocytes and calretinin interneurons [12]. The calretinin interneurons show resistance to Aβ toxicity in this model, whereas other interneurons are more vulnerable. Since calretinin interneurons disinhibit the network, the combination of increased P2Y1R on astrocytes and calretinin interneurons enhances overall network excitation.

P2Y1R may also influence cerebral vascular dysfunction in the context of AD. As part of the neuro-vascular unit, astrocytes play a role in regulating cerebral blood flow, particularly in response to neuronal activity. Astrocyte Ca^{2+} signaling can trigger either vasoconstriction or dilation depending on the metabolic state of the brain tissue [13]. APP mice are prone to spontaneous blood vessel changes, particularly arterial constrictions, which may be related to the P2Y1R mediated astrocytic Ca^{2+} transients [11]. The effects may be exacerbated by age-related changes in P2Y1R expression on vascular cells, which shift the balance in favor of vasoconstriction, resulting in reduced cerebral blood flow [14]. P2Y1R on activated platelets may also contribute to the development of cerebral amyloid angiopathy [15]. This suggests that P2Y1R inhibition may potentially improve cerebrovascular function in AD.

Under physiological conditions, P2Y1R plays important roles in neuronal function, and it is not clear whether in pathological conditions, such as AD, P2Y1R inhibition negatively impacts these neuronal functions, or whether these functions are already compromised due to purinergic network dysfunction, in which case the inhibition does not have a significant additional impact. One function that is of particular interest for AD and other neurodegenerative diseases, is the role of P2Y1R in regulating neurogenesis [16].

Parkinson's disease: UNCLEAR
P2Y1R is very highly upregulated on neurons in the substantia nigra in rats. In the Parkinson's disease (PD) model, in which the rat brain is lesioned by the neurotoxin 6-OHDA, there is a rearrangement of purinergic receptors in the striatum and substantia nigra [17]. Most P2X and P2Y receptors decrease on GABAergic and dopaminergic neurons, while some P2YRs increase on astrocytes. It has not been established whether modulation of P2Y1R would be beneficial in the context of PD.

Epilepsy: POTENTIAL BENEFIT (Preclinical)
There is conflicting evidence on whether inhibition or activation of P2Y1R is beneficial for epilepsy based on animal model studies. However, one study determined that the discrepancies can be attributed to the context dependent nature of P2Y1R signaling [6]. Pretreatment with P2Y1R inhibitors prior to the induction of status epilepticus exacerbates epiliform activity, whereas P2Y1R inhibitors administered after the onset act as anticonvulsants. This suggests that from a therapeutic standpoint, P2Y1R inhibitors may be beneficial for reducing seizures in patients with epilepsy.

P2Y1R has been found to be upregulated in the brain in response to status epilepticus in mice [18]. P2Y1R contributes to excitotoxicity, particularly glutamate (NMDAR)- mediated neurotoxicity in rodents

[19]. Additionally, excessive entry of Ca^{2+} into neurons through NMDAR channels induces axonal damage [19]. Although there are differences across models, the neurotoxic effects appear to involve dysregulation of P2Y1R and Ca^{2+} within microglia, astrocytes, and neurons. The upregulation of P2Y1R on microglia is associated with pro-inflammatory effects, while the activation of P2Y1R in astrocytes alters Ca^{2+} transients in a manner that promotes the release of glutamate, and the elevated glutamatergic transmission in neurons promotes seizure activity and excitotoxicity [18; 19; 20]. Treatment with P2Y1R inhibitors in epileptic rodent models reduces seizure-associated brain damage, and in some models can suppress seizures [6; 18; 19; 20].

Stroke/Brain injury: POTENTIAL BENEFIT (Preclinical)
The context dependent nature of purinergic signaling has also led to discrepancies in the efficacy of P2Y1R inhibitors with respect to ischemic or traumatic brain injury. Several *in vitro* studies have found that the activation of P2Y1R activates an antioxidant response, and is protective against ischemic damage. However, trauma induces very high levels of extracellular purines, which has a broad range of effects, and it is the dynamic interplay of these responses *in vivo* that determines whether the activation of P2Y1R mitigates or exacerbates injury. In patients with acute minor ischemic stroke (n=426), poor outcomes (myocardial infarction and death) were not associated with any one gene, but with gene-gene interactions between multiple platelet-associated genes, including P2YRs [21]. A separate study in patients with ischemic stroke (n=614) found that gene-gene interactions among TXA2R rs1131882, P2Y1 rs1371097 and GPIIIa rs2317676 had a synergistic influence on the risk for carotid stenosis (Odds ratio (OR): 2.72, 95% Confidence Interval (CI) 1.28 to 7.82, P = 0.001) [22].

The general consensus is that P2Y1R activation usually contributes to network dysfunction in stroke/brain injury, but the degree to which it participates likely depends on the type, location, duration, and severity of the brain trauma [23]. Based on the available evidence, P2Y1R inhibitors are expected to reduce neurological damage, by reducing inflammation and excitotoxicity.

APOE4 interactions: Not known

Aging and related health concerns: P2Y1R inhibitors may have anti-platelet properties and reduce thrombosis risk when paired with P2Y1R inhibitors.

Types of evidence:

- Numerous laboratory studies

Thrombosis: POTENTIAL BENEFIT IN COMBINATION WITH P2Y12 INHIBITOR (Preclinical)
P2Y1R is one of the major purinergic receptors on platelets. Both P2Y1R and P2Y12R are preferentially responsive to ADP, and co-activation of the two receptors is necessary for full platelet activation and aggregation [24]. Currently, only P2Y12R inhibitors have been approved for use as anti-platelet agents, but the synergistic inhibition of P2Y1R and P2Y12R is expected to be more effective, and may be particularly useful for patients with an inadequate anti-platelet response to aspirin. Chronic aspirin use is associated with a compensatory increase in ADP-associated platelet activation and an upregulation of P2Y1R on platelets [25]. The combination of P2Y1R and P2Y12 inhibitors was shown to be more effective than aspirin in inhibiting platelet activation in cell culture [26]. However, anti-platelet efficacy is dependent on the manner in which the platelets are stimulated, as the P2Y1R inhibitors are only effective towards ADP-dependent activation [27].

An antibody targeting the ligand binding domain (EL2) of P2Y1R called EL2Ab (administered intravenously- IV) prolonged occlusion time in the $FeCl_3$ thrombosis model in mice [27]. Treatment with the specific P2Y1R antagonist, MRS2500, reduced thrombosis weight by 57 ± 1% at a dose of 0.09 mg/kg + 0.14 mg/kg/h IV and by 88 ± 1% at a dose of 0.45 mg/kg + 0.68 mg/kg/h IV in cynomolgus monkeys in the ECAT model of thrombosis [28]. GLS-409, a dual antagonist for P2Y1R and P2Y12R, inhibited recurrent coronary thrombosis in a canine model, and also showed reversible anti-platelet activity toward ADP-mediated activation of human platelets *in vitro* [24; 29]. These studies suggest that P2Y1R inhibitors may be beneficial for patients with acute coronary syndromes at risk for thrombosis [29]. Though P2Y1R inhibitors are associated with lower bleeding risk, they will likely need to be combined with other anti-platelet agents (aspirin and P2Y12 inhibitors), which increases the bleeding risk.

Atherosclerosis: POTENTIAL BENEFIT (Preclinical)
Purinergic signaling plays a role in the regulation of the vasculature. P2Y1R is one of the dominant purinergic receptors on endothelial cells, though there are vessel and species-specific differences in expression [30]. Activation of endothelial purinergic receptors by ATP typically triggers vasodilation,

however, in the context of endothelial damage, the activation of P2 receptors on smooth muscle cells induces vasoconstriction. Vascular damage can transform previously productive purinergic responses into pathological ones.

In rodents, **endothelial P2Y1R is involved in vascular inflammation**. In ApoE-/- mice, treatment with the P2Y1R inhibitor MRS2500 led to a decrease in the expression of vascular adhesion molecules, leading to decreased infiltration of leukocytes into arteries in response to inflammatory stimuli [31]. The anti-inflammatory effect of P2Y1R inhibition was associated with reduced p38 MAPK signaling. In cell culture, stimulation with ApoB100 danger-associated signal 1 (ApoBDS-1), a native peptide derived from Apolipoprotein B-100 (ApoB100) of LDL, induces pro-inflammatory responses, and the transmigration of leukocytes through activated vascular endothelial cells [32]. This effect involved several signaling pathways including p38 MAPK, and was partially dependent on ADP-mediated activation of P2Y1R. ApoE-/- mice deficient in P2Y1 have reduced vascular inflammation and expression of vascular adhesion molecules, which was accompanied by a reduction in the size of atherosclerotic lesions [33]. The ability of ADP to promote endothelial cell migration and proliferation via P2Y1R, may also contribute to the progression of atherosclerosis [30].

Diabetes: POTENTIAL MIXED (Preclinical)
The release of ATP from pancreatic β-cells acts as a positive autocrine signal to promote insulin secretion. Activation of pancreatic P2Y receptors, especially P2Y1R, activates PLC and increases production of diacylglycerol, which in turn activates PDK1 signaling [34]. The activation of this pathway is thought to maintain insulin secretion in the context of metabolic stress, and may be involved in regulating insulin in nondiabetics who are overweight or obese. A study in human islets found that this pathway was elevated in the islets from nondiabetic donors who were overweight or obese. The disruption of this pathway may impair glucose-stimulated insulin secretion and promote β-cell dysfunction in patients with type 2 diabetes.

Stimulation of this pathway is hypothesized to be beneficial for diabetes, by improving β-cell secretory function. A P2Y1R agonist called 3A, which is an analogue of 2-MeS-ADP, was found to have good stability and pharmacokinetic properties [35]. In the streptozotocin-induced and db/db mouse models of diabetes, 3A treatment normalized glucose levels. However, a pure P2Y1R agonist might be expected to exacerbate the vascular complications associated with diabetes. 3A also displays anti-platelet activity, which appears to be due to the inhibition of P2Y12. It is likely that some type of mixed P2Y modulator

would be needed to account for the pleiotropic effects of P2YRs and purinergic signaling on diabetes-associated pathology.

Cancer: POTENTIAL MIXED (Preclinical)
P2Y1R likely has multifaceted roles in cancer. Some studies suggest that P2Y1R activation has a pro-apoptotic effect in cancer cells via ERK1/2 activation, and it may also regulate cancer cell growth [36]. The effects are likely to be cancer type dependent, as P2Y1R has been shown to be able to activate or inhibit the P13K/AKT pathway in different cancer cells. Additionally, P2Y1R may affect tumor growth by promoting angiogenesis. Although P2Y1R modulation may have benefit for particular tumor types when used in combination with other therapies, it appears that P2Y1R modulators alone are unlikely to have clinical anti-cancer efficacy.

Neuropathic pain: POTENTIAL BENEFIT (Preclinical)
Expression of P2Y1R is increased in the spinal cord in response to nerve injury in rats, and this upregulation appears to play a role in the induction of neuropathic pain. Treatment with the P2Y1R inhibitor MRS2500 (intrathecal) within 1 to 3 days of injury prevented the upregulation of P2Y1R and reduced tactile allodynia, however, when administered 14 days after injury, the anti-allodynia effects were mitigated [37]. This suggests that P2Y1R plays a greater role in the induction than in the maintenance of neuropathic pain. The P2Y1R inhibitor MRS2179 (intrathecal) also attenuated tactile allodynia and spontaneous pain in a cancer-induced bone pain model in rats by inhibiting the ERK1/2 pathway [38].

Safety: P2Y1R inhibitors have not been tested in humans. Preclinical studies suggest that they increase bleeding risk, and due to its widespread expression, there is potential for additional side effects throughout the body.

Types of evidence:

- Several laboratory studies

P2Y1R inhibitors have not yet been clinically tested. Significant safety concerns have not emerged from the short-term preclinical animal studies conducted thus far, but the majority of the studies were not designed to assess safety. The primary safety concern addressed for P2Y1R inhibitors is **bleeding risk**,

due to the role of P2Y1R in platelet activation and aggregation. The P2Y1R inhibitors MRS2500 and EL2Ab increased bleeding time in rodents [27; 39], and MRS2500 also increased bleeding time in cynomolgus monkeys [28]. The P2Y1/P2Y12 inhibitor GLS-409 increased bleeding time by 30% at a dose of 0.054 mg/kg IV bolus followed by a continuous intravenous infusion of 0.0018 mg/kg/min [24], but at lower doses (Dose 1: 0.054 mg/kg bolus + 0.00018 mg/kg/min infusion maintained for 2 hours; Dose 2: 0.0054 mg/kg bolus + 0.00018 mg/kg/min infusion for 2 hours), GLS-409 was effective in canine models of thrombosis without significantly increasing bleeding time [29].
This suggests that P2Y1R inhibitors, particularly at high doses are likely to increase bleeding risk, and have drug interactions with other agents that increase the risk for bleeding.

Due to the widespread expression of P2Y1R and its context dependent nature, there is a high potential for side effects with the modulation of P2Y1R, but the effects may vary depending on the clinical population.

Sources and dosing:

There are no P2Y1R inhibitors available for clinical use. Several P2Y1R inhibitors are available for research use including MRS2179 and MRS2500, however, they do not have suitable drug properties for clinical use. The P2Y1R/P2Y12R dual antagonist GLS-409 was developed by GLSynthesis, but the development prospects of this inhibitor are unclear.

Research underway:

P2Y1R inhibitors are still in preclinical development, and there are no clinical studies yet underway.

Search terms:
Pubmed, Google: P2Y1 +

- Alzheimer's disease, Parkinson's disease, stroke, epilepsy, excitotoxicity, inflammation, cardiovascular, diabetes, aging, cancer, neuropathy, safety

Websites visited for P2Y1R inhibitors:

- PubChem (MRS2500, MRS2179)

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