0Cognitive 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.

TRPML1 Agonists

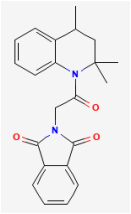
Evidence Summary

TRPML1 is an important regulator of autophagy and lysosomal function. Modulating it has the potential to help age-related diseases, but it is unclear whether that can be done safely or reliably.

Neuroprotective Benefit: TRPML1 activation may help restore lysosomal function and autophagy in neurons, but due to its numerous context-dependent effects, the impact of modulating it may vary by condition and individual.

Aging and related health concerns: TRPML1 regulates longevity-related pathways. Its modulation may benefit some cancers, but its sensitivity to specific environmental conditions may limit its therapeutic utility in other indications.

Safety: There is a dearth of evidence regarding the safety of TRPML1 agonists currently in preclinical development. Its ubiquitous expression and context-dependent activity raise the concern about the potential for side effects.

Availability: For research use	**Dose**: Not established	**ML-SA1** **Chemical formula:** $C_{22}H_{22}N_2O_3$
Half-life: Not established	**BBB**: Not established	**MW**: 362.4 g/mol
Clinical trials: None	**Observational studies**: None	 Source: PubChem

What is it?

Transient receptor potential channel mucolipin 1 (TRPML1) is an endolysosomal cation channel [1]. It is one of three TRPML channels expressed in humans. TRPML1 has ubiquitous expression, while TRPML2 and TRPML3 show more restrictive expression, primarily to immunological tissue. TRPML1 fluxes both monovalent (Na+≅ K+>Cs+) and divalent cations (Ba2+>Mn2+>Fe2+>Ca2+> Mg2+> Ni2+>Co2+> Cd2+>Zn2+>>Cu2+) (IUPHAR/BPS). It is involved in the maintenance of lysosomal and cellular Ca2+ homeostasis, as it interacts with other Ca2+ storage organelles, including the endoplasmic reticulum (ER) and mitochondria [2]. The biological consequences of its other ionic fluxes are less well understood, and similar to Ca2+, are likely context dependent [3]. TRPML1 plays numerous essential roles in the maintenance of lysosomal homeostasis. Most prominently, it is involved in the regulation of autophagy. Endogenously it is regulated by phosphoinositide, such that its activity is affected by lipid membrane composition. Its localization to the endolysosomal compartment is tied to its activation by the endolysosomal-specific phosphoinositide, PI(3,5)P2.

Due to increasing evidence regarding the role of lysosomal dysfunction in aging and age-related diseases, TRPML1 has emerged as a potential therapeutic target and several companies are working on developing TRPML1 modulators [2]. TRPML1 agonists have not yet been clinically tested, and most of the compounds used in research studies lack specificity for TRPML1 and/or have poor pharmacokinetic properties. There are several companies that appear to be developing TRPML1 agonists, primarily for neurodegenerative diseases, though they are in early stages. Due to the buzz around this target, there may be additional companies working on it which have not yet disclosed their target.

Caraway Therapeutics is developing a TRPML1 agonist, initially for a genetic form of Parkinson's disease, GBA-Parkinson's disease. They are still in early preclinical development.

Merck acquired *Calporta* in 2019, which was developing a TRPML1 agonist for lysosomal storage disorders and neurodegenerative diseases (Press release). The current status of development on this preclinical program is unclear.

Casma Therapeutics had been developing a TRPML1 agonist for muscular dystrophy and raised $50M in Series B financing towards this program in 2020 (Press release). As of 2022, TRPML1-TFEB is noted as a therapeutic target area, but there isn't any indication that they are still working on TRPML1 agonists, per se.

Neuroprotective Benefit: TRPML1 activation may help restore lysosomal function and autophagy in neurons, but due to its numerous context-dependent effects, the impact of modulating it may vary by condition and individual.

Types of evidence:

- Several laboratory studies

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

Genome-wide association studies (GWAS) studies implicate lysosomal genes in risk for dementia, and endolysosomal dysfunction has been identified as the earliest pathology in the context of Alzheimer's disease (AD) [4]. The accumulation of amyloid appears to stem from its inability to be properly degraded in deacidified lysosomes [5]. Deficits in lysosome exocytosis have also been implicated in the failure to clear tau and alpha-synuclein [6]. Together, these suggest that the maintenance or restoration of lysosomal function is critical for cognitive health.
Mutations in the endosomal/lysosomal ion channel, TRPML1, lead to the neurodevelopmental neurodegenerative disorder, Mucolipidosis type IV (MLIV) [7]. This lysosomal storage disorder results in mental retardation, motor deficits, and vision loss. The prominent neurological effects implicate TRPML1 as critical for the maintenance of lysosomal function in the brain. Most of the mechanistic studies regarding TRPML1 have been conducted in rodents, and there are limited studies looking at its activity in

human brain tissue. A proteomics study analyzing postmortem brain tissue from a patient with MLIV was conducted. In addition to changes in lysosome, autophagy, and inflammation-related proteins, there were prominent changes in apolipoproteins, such as an increase in ApoD, which is also elevated in other neurodegenerative conditions, such as AD [7]. In human iPSC-derived cortical neurons from ApoE4 carriers, TRPML1 activity was found to be reduced, resulting in elevated Ca2+ levels in the endolysosomal compartment [8]. Ultimately, more studies are needed assessing the contribution of TRPML1 to neurodegenerative disease in human tissue.

Human research to suggest benefits to patients with dementia:

TRPML1 agonists have not yet been tested in dementia patients.

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

Alzheimer's disease: UNCLEAR, HUMAN STUDIES NEEDED
TRPML1 plays numerous roles in the maintenance of lysosomal homeostasis [6]. Due to the evidence for prominent endolysosomal dysfunction in AD, TRPML1 has emerged as a potential therapeutic target. The preclinical data regarding the effect of boosting TRPML1 function has been mixed, which is likely a reflection of the context-dependent and multifaceted nature of this ion channel.
Lysosome deacidification is seen in the context of AD [5]. Mutations in presenilin (PS1) can lead to lysosomal deacidification through deficits in the function of vATPase, the proton pump which acidifies the lysosome [9]. In presenilin knockout cells, lysosomal Ca2+ efflux is elevated due to TRPML1 hyperactivity. The increased efflux of lysosomal Ca2+ leads to numerous downstream effects, leading to increases in cytosolic Ca2+ and the initiation of Ca2+-sensitive signaling cascades, such as autophagy induction, and altering levels of Ca2+ within coupled organelles, including mitochondria and the ER. In contrast to studies using other models where the enhancement of TRPML1 activity is therapeutic, the amelioration of deficits in this model system involves the reduction in TRPML1 activity. Notably, targeting TRPML1 alone was not sufficient to restore lysosomal function, as this is a secondary effect. Restoration required targeting the primary deficit, the acidification of the lysosome. This study attributed the hyperactivity of TRPML1 to elevated pH within the lysosome, though it is unclear whether this is a byproduct of this model system, as the vast majority of studies indicate that the maximum activity for TRPML1 is at pH 4.6, the average pH of the lysosomal lumen, and that its activity decreases at elevated pH [3]. In presenilin mutant cells, TRPML1 hyperactivity led to the stalling of late endosomes/lysosomes, resulting in a decrease in retrograde transport [10].

In other AD models, such as the APP/PS1 mouse, TRPML1 has been shown to be downregulated [11]. In this context, the activation of TRPML1 is protective, stemming from its role in the regulation of autophagy. TRPML1 interacts with autophagy pathways via multiple routes. TRPML1 is part of a positive feedback loop with TFEB and a negative feedback loop with mTORC1 [6; 12]. Calcium release from TRPML1 promotes the activation and nuclear translocation of TFEB, a transcription factor that serves as a master regulator of autophagy, which influences the expression of lysosome and autophagy-related genes. TRPML1 is one of its targets, thereby leading to a positive feedback loop. This process also increases lysosomal exocytosis, which facilitates the clearance of cellular debris and the recycling of essential cellular building blocks. TRPML1 can also promote autophagosome biogenesis in a TFEB-independent manner [13]. Additionally, TRPML1 contributes to the negative regulation of autophagy, which is necessary to prevent cell death [1]. TRPML1 can activate mTORC1, a negative regulator of autophagy, which in turn inhibits TRPML1 [14]. The cumulative effect of these feedback loops is to ensure that autophagy is finely tuned to the needs of the cell.

When functional, this system is neuroprotective. TRPML1-TFEB mediated lysosomal exocytosis prevents tau accumulation by promoting its exocytosis from the cell [6]. TRPML1 can also promote the clearance of amyloid, though this seems to be dependent on TRPML1-mediated acidification of the lysosome. In cell culture, low-density lipoprotein (LDL) led to lysosome de-acidification and increased levels of Aβ42 [15]. Treatment of the cells with the TRPML1 agonist, ML-SA1, led to lysosome acidification and reduced Aβ accumulation. A similar effect has been shown with this TRPML1 agonist in the context of HIV antiretroviral-mediated Aβ accumulation in de-acidified endolysosomes [16]. Promotion of lysosome acidification is expected to be a beneficial therapeutic strategy in AD. TRPML1 does not directly control lysosome acidification, but as a cation channel, it can influence the level of charge buildup across the membrane, and thus impact the activity of the proton pump [17]. However, the studies in different cell systems indicate that the overall impact of TRPML1 on pH and the other parameters it regulates, depends on the cellular environment. TRPML1 has extensive crosstalk with other Ca2+ storing organelles, and has the capacity to flux numerous cations, including several metals, such as iron, nickel, zinc, and copper [3]. This suggests that in a pathophysiological setting, where there is dysregulation in several of these interacting pathways, the net effect of activating TRPML1 may be difficult to predict. Empirical evidence is needed regarding the function of TRPML1 in the AD brain in humans, including whether it is uniformly affected across cell types, and the interindividual variability.

Parkinson's disease: POTENTIAL BENEFIT FOR SPECIFIC SUBTYPES (Preclinical)
In the MPTP model, treatment of male mice with the traditional Chinese herb, *Artemisia argyi Lev. et Vant*, also known as Chinese mugwort, (100 mg/kg) for two weeks, reduced the loss of dopaminergic neurons and associated motor deficits [18]. This was related to a reduction in the accumulation of reactive oxygen species (ROS), and enhanced autophagic clearance of alpha synuclein, due to the upregulation of TRPML1 activity. In iPSC-derived dopaminergic neurons from patients with PARK9 mutations, lysosomal calcium homeostasis is disrupted [19]. Loss of PARK9 leads to a reduction in lysosomal calcium levels. This, in turn, impairs lysosomal exocytosis, leading to the accumulation of alpha-synuclein. The activation of TRPML was able to restore lysosomal exocytosis in this model system. The generalizability of TRPML1 dysfunction to other genetic and sporadic forms of PD is unclear.

HIV-related cognitive impairment: POTENTIAL BENEFIT (Preclinical)
AD-like neuropathology, such as the accumulation of Aβ, is common in the context of HIV/AIDs. In a mouse model of HIV-related neuropathology (gp120/APP/PS1), there is an overproduction of sphingomyelins, which accumulated in the lysosome [20]. The sphingomyelin inhibits TRP channels, leading to the accumulation of calcium and Aβ within lysosomes. Treatment of the cells with a TRPML1 agonist reacidified the lysosomes and restored lysosomal calcium efflux, leading to a reduction in Aβ neuropathology. The antiretroviral drugs used to treat HIV themselves can also promote the accumulation of Aβ and lead to cognitive impairment. Several of these antiretrovirals, including, efavirenz, nevirapine, ritonavir, nelfinavir, darunavir, and dolutegravir, were found to de-acidify lysosomes, which promoted the secretion and accumulation of Aβ [16]. Additional treatment of the cells with the TRPML1 agonist, ML-SA1, reacidified the lysosomes and blocked the accumulation of Aβ. Not all antiretrovirals had this effect. Indeed, zidovudine and abacavir, acidified lysosomes, and cells treated with these drugs had lower levels of Aβ. Though more work is needed to verify the relevance *in vivo*, TRPML1 agonists may potentially be useful in reducing neuropathology in HIV-positive individuals treated with certain antiretrovirals.

Muscular dystrophy: POTENTIAL BENEFIT (Preclinical)
In a mouse model of muscular dystrophy (mdx), muscle specific overexpression of TRPML1 reduced pathology and improved muscle function [21]. Similarly, treatment with the TRPML1 agonist, ML-SA5 (2 to 5 mg/kg i.p.) staring at P14, reduced muscle cell death and improved treadmill exercise function in one month old mice. Treatment was associated with the activation of TFEB and the promotion of muscle repair mechanisms. It is unclear whether there is a critical window of intervention, and whether chronic use would be safe and lead to the maintenance of benefits.

APOE4 interactions: One study found that TRPML1 activity was reduced in ApoE4 expressing neurons, but it has not been established whether ApoE4 carriers are more likely to have reduced TRPML1 activity, or whether it is a relevant target *in vivo* [8].

Aging and related health concerns: TRPML1 regulates longevity-related pathways. Its modulation may benefit some cancers, but its sensitivity to specific environmental conditions may limit its therapeutic utility in other indications.

Types of evidence:

- Several laboratory studies

Longevity: TRPML1 REGULATES LONGEVITY-ASSOCIATED MECHANISM
Rapamycin has been shown to increase lifespan in animal models. It has pleiotropic effects, but one of the major presumed mechanisms by which it promotes longevity is through the modulation of autophagy via the inhibition of the mTOR complex. It was shown that TRPML1 can be activated by rapamycin, in an mTOR-independent manner [12]. It has been hypothesized that the induction of autophagy via TRPML-TFEB may be a major contributor to the anti-aging effects of rapamycin, though this requires further testing.

Cancer: POTENTIAL MIXED (Preclinical)
Both TRPML1 activators and inhibitors have shown utility in preclinical cancer models [1]. TRPML1 interacts with nutrient sensing pathways and plays an important role in the adaptive lysosomal response to nutrient starvation. This is particularly relevant for the growth and survival of cancer cells. TRPML1 has been shown to be overexpressed in some cancers, where its high levels are associated with better cancer cell growth and survival. But in other cases, the activation of TRPML1 can impair autophagy and lead to cell cycle arrest. Due to the nutrient starved conditions of the tumor microenvironment, cancer cells may be especially sensitive to changes in the activity level of TRPML1, such that levels that are either too high or too low can impede their growth and survival, by impacting autophagy and mitochondrial function [22]. It may also depend on the stage, as the induction of autophagy can slow growth early on, and then accelerate it at later stages [1]. Different cancers may preferentially benefit from different types of TRPML1 modulators. Cancer appears to be the condition best suited to a TRPML1-targeted therapy, due to the high sensitivity of these cells to TRPML1-mTORC1 signaling.

Ischemia: MIXED/UNCLEAR (Preclinical)
In contrast to other conditions where TRPML1 is associated with the induction of autophagy, it is associated with the inhibition of autophagic flux in some settings, such as ischemic/reperfusion (I/R) injury. In murine cardiomyocytes, TRPML1 activation in response to elevated reactive oxygen species (ROS) led to the release of lysosomal zinc and a disruption to autophagosome-lysosome fusion, resulting in an impairment of autophagic flux [23]. The expression of TRPML1 decreases during the ischemic period, and then increases during the reperfusion period. A similar pattern was seen in rat neurons, where the ROS-mediated hyperactivity of TRPML1 was detrimental [24]. Preconditioning induced a protective adaptation involving an interplay between TRPML1 and an ER Ca2+ channel, STIM1, such that the expression of TRPML1 stayed low during the reperfusion period [24]. Direct infusion of the TRPML1 agonist, ML-SA1 into the ventricles of mouse prior to a transient global cerebral ischemic injury was protective in reducing infarct volume, neurological deficits, and mortality [25]. It is unclear whether this agonist would also be protective if treatment had been started after the ischemic event, during the reperfusion period. In a model of myocardial ischemia/reperfusion, shRNA-mediated inhibition of TRPML1 administered one day after the injury was protective in reducing infarct size [23]. The different effects may stem from different tissue/cell types, I/R paradigms, timing of administration, or additional factors. While TRPML1 has been shown to be activated by ROS, studies indicate that it is differentially responsive to different sources of ROS, which in some cases were shown to have no effect or even inhibit TRPML1 [3; 26]. As such, the tissue conditions likely determine the activity level of TRPML1, suggesting it may be too variable to reliably target for this indication.

Safety: There is a dearth of evidence regarding the safety of TRPML1 agonists currently in preclinical development. Its ubiquitous expression and context-dependent activity raise the concern about the potential for side effects.

Types of evidence:

- Few laboratory studies

TRPML1 agonists are still in preclinical development and have not yet been tested for any clinical condition. The preclinical studies conducted thus far do not provide good insight into the potential safety of these compounds, as the vast majority of them are *in vitro*, due to the poor pharmacokinetic properties of the TRPML1 agonists commonly used in research [6]. Studies that have looked *in vivo*, have tended to be very short, lacking safety evaluations. Chronic dosing studies are needed.

There are several reasons why targeting TRPML1 could pose a potential safety concern. TRPML1 is ubiquitously expressed, so with a systemically administered drug, attempts to correct a deficit in TRPML1 in one cell type could lead to unintended consequences in other cell types. Due to its role in coordinating Ca2+ homeostasis across organelles [27], altering TRPML1 function could result in non-lysosomal effects, such as by affecting mitochondrial function and integrity [28]. More studies are needed regarding the effects of TRPML1 agonists in healthy cells of different tissue types. The other members of the TRPML family, TRPML2 and TRPML3 have more restricted expression, but they have important roles in immune cell function and pathogen defense [29]. There is evidence to suggest that these receptors can form heteromers, and that changes in TRPML1 can influence the activity of the other TRPMLs [30]. TRPML1 has multiple context-dependent functions, thus it will be critical to understand how TRPML1 contributes to a particular disease state, and whether it is a primary or secondary contributor to pathology. With the exception of MLIV, a definitive role for TRPML1 as a driver of disease pathology, has not been established, and more studies in human tissue are needed.

Drug interactions: Not established

Sources and dosing:

TRPML1 agonists, such as ML-SA1, are available from commercial suppliers for research use. They have not yet been clinically tested for any indication.

Research underway:

There are currently no clinical trials underway for TRPML1 agonists.

Search terms:
Pubmed, Google: TRPML1

- Agonists, Alzheimer's disease, Parkinson's disease, neurodegeneration, aging, cancer, cardiovascular

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