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.

TRPM2 Inhibitors

Evidence Summary

TRPM2 inhibitors may protect against oxidative stress damage by preventing toxic Ca^{2+} overload, but effects are likely cell type and context dependent, and full safety risks are not clear.

Neuroprotective Benefit: TRPM2 inhibition may protect against oxidative stress-related neuronal death, but neuroprotection may be sex-dependent. May be best suited to acute indications because prolonged inhibition may disrupt cellular bioenergetics.

Aging and related health concerns: TRPM2 inhibitors may be best suited for sensitizing cancer cells to chemotherapy and protecting against cell loss in ischemic-reperfusion injuries. But they may exacerbate diabetic hyperglycemia.

Safety: Safety data is confounded by a lack of specific inhibitors, but studies in TRPM2 knockout animals suggest that chronic inhibition may increase infection risk. Organ type selective inhibitors would be expected to have the best safety profile.

Availability: Non-specific inhibitors for research use	**Dose**: N/A	**Chemical formula:** N/A **MW**: N/A
Half-life: N/A	**BBB**: Varied	
Clinical trials: None	**Observational studies**: None for inhibitors. TRPM2 is overexpressed and associated with worse outcomes in a variety of cancers.	

What is it?

Transient receptor potential melastatin 2 (TRPM2) is a non-selective cation channel localized to the plasma membrane with Ca^{2+} permeability [1]. It is a thermosensitive channel that can be activated upon exposure to temperatures above 35°C (95°F) in combination with an agonist. The preferred endogenous agonist for the TRPM2 channel is ADP ribose (ADPR), which is generated by poly (ADP-ribose) polymerase (PARP) through an NAD+ dependent mechanism. TRPM2 is also activated in response to Ca^{2+}, and the combination of Ca^{2+} with ADPR is synergistic with respect to channel activation. The production of ADPR increases under conditions with elevated production of reactive oxygen species (ROS), thus TRPM2 activity is highest in the context of oxidative stress. Ca^{2+} entry through TRPM2 regulates a variety of Ca^{2+} dependent processes, including cellular bioenergetics, in a cell type specific manner [2]. However, sustained elevated Ca^{2+} entry through TRPM2 can lead to cytotoxic Ca^{2+} overload. TRPM2 inhibitors have been in preclinical development to prevent pathological Ca^{2+} overload, but thus far it has been challenging to develop a specific inhibitor with good pharmacokinetic properties.

Neuroprotective Benefit: TRPM2 inhibition may protect against oxidative stress-related neuronal death, but neuroprotection may be sex-dependent. May be best suited to acute indications because prolonged inhibition may disrupt cellular bioenergetics.

Types of evidence:

- 1 gene association study for a TRPM2 variant in ALS and PD
- 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*:**

Alzheimer's disease: POTENTIAL BENEFIT (Preclinical)
TRPM2 is widely expressed in the CNS, in neurons and glial cells [3; 4]. It has not yet been established whether TRPM2 levels or activity is dysregulated in the brain of human patients with Alzheimer's disease (AD), but cell culture and animal models suggest that TRPM2 mediates Aβ-related neurotoxicity, particularly with respect to neuroinflammatory responses and oxidative stress damage [5]. TRPM2 is activated in response to oxidative stress, and markers of oxidative stress have been shown to be elevated in the AD brain [6], suggesting that the environment of the AD brain could facilitate the overactivation of TRPM2. There is evidence that TRPM2 is increased in AD-affected brain regions, such as the hippocampus, in other neurological conditions characterized by elevated oxidative stress. For example, individuals with depression show elevated markers of oxidative stress [7], and hippocampal expression of TRPM2 was shown to be upregulated in people with major depressive disorder [8].

Spatial memory deficits in the Barnes maze and Morris water maze, were reduced in aged (15 months old) male APP/PS1 AD mouse model mice deficient in TRPM2 [9]. While plaque burden was unchanged, these mice had reduced levels of ER stress and synaptic damage relative to APP/PS1 mice with TRPM2. Non-specific TRPM2 inhibitors, such as ACA (N-(p-amylcinnamoyl)anthranilic acid), have been shown to ameliorate okadaic acid and scopolamine-induced memory impairment in rats by preserving mitochondrial integrity and neuronal survival [10; 11]. The protective efforts were associated with a reduction of oxidative toxicity, including a preservation of the levels of glutathione and associated antioxidant enzymes (SOD, GSH-PX), and a reduction in the levels of oxidized lipids.

In cell culture, the addition of Aβ, augments the activity of the TRPM2 channel [12]. TRPM2 activation is part of a feedback loop that propagates oxidative stress damage and neuroinflammation [5; 13]. Aβ stimulates the production of ROS and activates PARP-1, which leads to the production of ADPR, the endogenous agonist of the TRPM2 channel. The activation of the TRPM2 channel leads to a rise in intracellular Ca^{2+} levels, which influences the activity of Ca^{2+} sensitive proteins and downstream signaling. PARP-1 can be activated by Ca^{2+} sensitive signaling pathways, such as the MEK/ERK signaling pathway, leading to further activation of TRPM2. Excessive activation of TRPM2 can lead to ionic dyshomeostasis, particularly with respect to calcium and zinc, and subsequent neurotoxicity. Treatment

of mouse primary hippocampal neurons with non-specific TRPM2 inhibitors, including ACA, and 2-APB, was found to protect against Aβ-mediated cell death and restore levels of endogenous antioxidants, such as glutathione [14].

Excessive activation of TRPM2 leads to lysosomal and mitochondrial dysfunction. Homeostatic maintenance of the free intracellular Zn^{2+} is crucial for the preservation of the antioxidant response [15]. Zn^{2+} is a component of some antioxidant enzymes which reduce the generation of ROS, but at high intracellular concentrations it enters mitochondria where it induces mitochondrial fragmentation and dysfunction and promotes the production of ROS, leading to the activation of apoptotic processes [12]. The ROS-mediated activation of TRPM2 can induce the release of Ca^{2+} and Zn^{2+} from lysosomes, which further increases intracellular levels, and leads to lysosomal dysfunction [16]. In lung cells, TRPM2 mediated Ca^{2+} and Zn^{2+} dyshomeostasis results in a reduction in the degradative capacity of lysosomes and impairment of autophagic flux [17]. It is not yet clear whether a similar impairment occurs in neurons, but if it does, it could contribute to the buildup of toxic misfolded proteins in neurodegenerative diseases.

TRPM2 is also involved in Aβ-related microglial activation in cell culture. The addition of Aβ to cultured microglia can promote the secretion of proinflammatory cytokines, such as TNFα, in a TRPM2 dependent manner [12]. The influx of Ca^{2+} following TRPM2 channel activation promotes NLRP3 inflammasome activation, the cleavage of caspase-1, and secretion of IL-1β [18]. These Ca^{2+} mediated changes transform microglia into a proinflammatory state. Ca^{2+} overload can also disrupt astrocyte signaling and function, which utilize Ca^{2+} waves for cellular communication.

TRPM2 overactivation can also induce neurovascular dysfunction and damage. Aβ can induce oxidative and nitrosative stress on cerebrovascular endothelial cells, leading to DNA damage, PARP-1 activation, APDR generation, TRPM2 activation, and Ca^{2+} overload [19]. The nitration of TRPM2 (at tyrosine residue Y1485 in mice), can promote pathogenic autophagy, leading to brain pericyte injury, and disruption of the microvasculature [20].

Age-related cognitive impairment: POTENTIAL BENEFIT (Preclinical)
TRPM2 knockout male mice were found to be resistant to age-related cognitive impairment, based on performance on the Y-maze and novel object recognition tasks [21]. These aged mice also had less neuroinflammation and white matter damage. TRPM2 activation is projected to be increased with age due to age-related changes in the expression of endogenous antioxidants. The antioxidant glutathione

(GSH) has been found to act as an endogenous inhibitor of the TRPM2 channel, thus as GSH levels decline, TRPM2 activity increases [22]. The combination of low GSH and high TRPM2 then increases the susceptibility of aged neurons to oxidative damage [23].

Parkinson's disease: POTENTIAL BENEFIT (Preclinical)
TRPM2 overactivation is implicated in oxidative stress mediated neurotoxicity in the substantia nigra. TRPM2 expression was found to be increased in the substantia nigra of patients with Parkinson's disease (PD), based on postmortem brain tissue analysis (n=8 PD, n=6 controls) [24]. TRPM2 channel activation may participate in ROS modulated spontaneous firing rate and burst firing in the substantia nigra and thus may contribute to altered firing patterns in PD patients [25; 26]. Mitochondrial toxins, such as paraquat and MPTP, used to induce a PD-like state in cellular and animal models, increase ROS levels and activate TRPM2, leading to a cycle of Ca^{2+} overload, neuroinflammation, and cell death [24; 27; 28; 29]. Aged male rats were found to be more susceptible to paraquat-mediated neurotoxicity than their younger counterparts, due to increased TRPM2 activation and Zn^{2+} dysregulation [27]. The non-selective TRPM2 inhibitors, 2-APB and AG490, partially preserved motor function and attenuated the loss of dopaminergic neurons in the MPTP and 6-OHDA toxin-induced rodent models of PD, respectively [30; 31]. The mechanisms of TRPM2-associated oxidative stress damage appear to be similar for dopaminergic neurons as those described for hippocampal neurons following Aβ-related oxidative stress damage.

Although TRPM2 overactivation is associated with Ca^{2+} overload and neurotoxicity, physiological **activation of TRPM2 appears to influence mitochondrial function and metabolism**. In a gene association study involving individuals of Western Pacific descent, a missense variant in TRPM2 was found to confer susceptibility to Guamanian amyotrophic lateral sclerosis (ALS) and parkinsonian-dementia [32]. The variant, TRPM2P1018L, produces a missense change in the channel protein whereby proline 1018 is replaced by a leucine, and this change produces channels that inactivate, especially under conditions of high Ca^{2+}. This suggests that disruption to the tonic influx mediated by TRPM2 under physiological conditions may impair neuronal metabolism and increase their vulnerability to oxidative damage. Consequently, chronic inhibition of TRPM2 may negatively impact mitochondrial function. Additionally, in some species, TRPM2 has the features of being a chanzyme, or an ion channel with an enzymatic motif. It contains the enzymatic domain NudT9-H in its C-terminus, and may play a role in ADPR catabolism [33]. ADPR is hydrolyzed by NudT9 pyrophosphatase in most organs, but this enzyme is defective in the brain. In mice, the loss of TRPM2 was found to disrupt ADPR catabolism, leading to an excess accumulation of ADPR and a reduction in AMP levels. This shift, particularly the decline in AMP

can lead to an impairment in autophagy, as well as an imbalance in synaptic transmission. However, the evidence to date suggests that human TRPM2 does not possess this enzymatic activity [34]. Even if it did, the enzymatic activity is not associated with its channel activity, therefore, it should be possible to specifically target the channel activity of TRPM2 in the development of therapeutic inhibitors.

Cerebral ischemic injury: POTENTIAL BENEFIT MAY BE SEX DEPENDENT (Preclinical)
Preclinical animal models indicate that TRPM2 plays a role in ischemic/hypoxic cerebral injury. Deletion or inhibition of TRPM2 protects against neuronal loss, neuroinflammation, and cognitive dysfunction in models where damage is driven by the generation of ROS and oxidative stress [35]. Neuroprotection was not demonstrated in the context of permanent middle cerebral artery occlusion (pMCAO), which is a model that lacks reperfusion [36]. Under these conditions, pathological mechanisms other than ROS generation may predominate, and/or the damage may be too severe for TRPM2 inhibition to compensate. Based on the protective effect in transient models, TRPM2 appears to play a role specifically in reperfusion-related injury [37]. Notably, the neuroprotective effect of TRPM2 inhibition during ischemic insult has a sex effect, and was only observed in males. In a focal transient MCAO model, inhibition of TRPM2 before the ischemic injury, or (3 hours) after reperfusion reduced infarct volume in both young and aged male mice, but had no effect in female mice [38]. A similar sex effect was seen in neuroprotection against oxygen-glucose in primary neurons derived from male and female mice [39]. It is hypothesized that the use of alternative metabolic pathways in the metabolism of NAD+ and production of ADPR may contribute to the male-specific effects of TRPM2 activation and inhibition in the context of ischemic injury [39]. The neuroprotective sex effect also appears to be age-dependent, as it was not observed in the context of cerebral ischemic-reperfusion injury in juvenile (P0-P25) mice [40]. Treatment with the BBB penetrant TRPM2 inhibitor, tatM2NX (20 mg/kg, i.v.), administered 30 minutes following reperfusion did not protect against hippocampal cell death in either males or females. It did, however, reduce impairments to synaptic plasticity (LTP) with immediate and delayed (two weeks post injury) treatment, in both sexes. The different effects in juveniles and adults may be related to differences in the contribution of different CNS cell types and/or in functional coupling. TRPM2 was found to physically interact with the NMDA receptor, GluN2A and GluN2B subunits, and this interaction potentiated NMDAR surface expression and activity [41]. NMDARs can bidirectionally influence neuronal cell death and survival. This interaction occurred with extrasynaptic NMDARs, which is notable because downstream signaling is different following activation of synaptic and extrasynaptic NMDARs, such that the enhancement of extrasynaptic NMDAR Ca^{2+} and signaling inhibits neuron survival. The use of a membrane permeable peptide that specifically interferes with the interaction between TRPM2 and NMDAR, TAT-EE3, reduced infarct size and neurological deficits in the rodent MCAO model. Since only

male mice were used in this study, it is unclear whether the treatment effect is influenced by sex. The interaction between TRPM2 and NMDAR may be facilitated by the activation of Protein kinase C (PKC) under conditions of oxidative stress. TRPM2 may also influence the bias toward NMDAR-mediated cell death signaling by influencing the relative balance of GluN2A and GluN2B subunits. The enhancement of cell survival signaling in TRPM2 deficient neurons was found to be associated with a shift in the balance toward more GluN2A relative to GluN2B [36]. These studies suggest that the differential effects of TRPM2 on cell survival may be related to the expression, composition, and activity of NMDARs.
The protective effect of TRPM2 inhibition in ischemic-reperfusion injury may also stem from the activation of autophagic flux [42]. TRPM2 deficient neurons show an increase in autophagosomes following oxidative injury, which is related to the regulation of the AMPK-mTOR pathway. A similar impact to autophagy was seen in the context of hepatic ischemic-reperfusion injury, where TRPM2 deficiency led to a reduction in mTOR activation, leading to increased autolysosome formation and enhanced autophagic flux [43]. TRPM2-mediated inhibition of autophagy also led to the activation of the NLRP3 inflammasome, and associated inflammatory cell damage. It should be noted that these studies were carried out in male mice. Meanwhile, the alteration of TRPM2 activity was shown to exacerbate nitrosative stress-induced human vascular pericyte injury [44]. The tyrosine nitration of TRPM2 at Y1485 led to a change in channel properties consistent with a functional downregulation of channel activity. This channel alteration was associated with the induction of ER stress and autophagic flux, which worsened pericyte injury.
The novel TRPM2 inhibitor, A23 (3 mg/kg i.v. given 3 hours after reperfusion onset), which was derived from ACA and shows selectivity over TRPM8, TRPV1, and PLA2, reduced infarct volume (38.9 ± 4.7%) and improved neurological scores in male mice in a transient MCAO model, with comparable efficacy to edaravone [45].

Depression: POTENTIAL BENEFIT (Preclinical)
Gene variants in TRPM2 have been associated with bipolar disorder. The single nucleotide polymorphism (SNP) rs1556314 (G allele) was found to be associated with bipolar disorder in a case-control dataset including 300 Caucasian families [46]. A separate case-control (178 cases; 268 controls) study found that there was a borderline interaction between the rs749909 SNP in TRPM2 and the rs4375 SNP in iPLA2β [47]. These genes play convergent roles regarding intracellular calcium regulation and cellular oxidative stress, suggesting that these pathways may be relevant in the pathophysiology of this psychiatric condition. Elevated oxidative stress is also implicated in major depressive disorder, and TRPM2 was found to be elevated in postmortem brain tissue from patients with depression [8]. In a mouse model, chronic unpredictable stress leads to increased production of ROS, TRPM2 activity, and

hyperactivation of cyclin-dependent kinase 5 (Cdk5) [35]. TRPM2 deficient male mice show protection against the stress-induced elevation of ROS, Cdk5 activity, and depressive-like phenotypic behaviors. A study testing the ability of commonly used anti-depressants to activate TRPM2 *in vitro* found that only duloxetine demonstrated a clear effect, however, the low potency suggests that it may not occur at clinically relevant doses [48].

APOE4 interactions: Not known.

Aging and related health concerns: TRPM2 inhibitors may be best suited for sensitizing cancer cells to chemotherapy and protecting against cell loss in ischemic-reperfusion injuries. But they may exacerbate diabetic hyperglycemia.

Types of evidence:

- 7 observational studies for associations between TRPM2 expression and cancer outcomes
- Numerous laboratory studies

Diabetes: POTENTIAL MIXED (Preclinical)
Based on the roles for TRPM2 in different cell types, inhibition of TRPM2 would be expected to exacerbate pancreatic dysfunction in the context of diabetes, but to alleviate some of the associated conditions, such as vascular dysfunction, neuropathy, and cognitive dysfunction.
TRPM2 is involved in the stimulation of glucose-stimulated insulin secretion in pancreatic β-cells [49]. It potentiates Ca^{2+}-dependent insulin granule exocytosis from β-cells. Glucagon like peptide-1 (GLP-1) promotes this process, while ghrelin attenuates it by affecting levels of cAMP to activate or inhibit TRPM2, respectively [50; 51]. TRPM2 deficient mice have reduced levels of insulin secretion and impaired glucose tolerance [49]. The importance of this pathway in humans has not yet been established, but a gene association study suggests that it may play a role. In a case-control study of type 2 diabetics (n=922), three TRPM2 variants, rs2838553, rs2838554, and rs4818917 were inversely associated with homeostasis model assessment of β-cell function (HOMA-%B), but were not significantly associated with HOMA-insulin resistance (HOMA-IR), fasting glucose levels, hemoglobin A1c levels [52].

Although the inhibition of TRPM2 may exacerbate glucose intolerance, it may also protect against high glucose induced oxidative stress damage in the vasculature and nervous system. In human vascular endothelial cells, stress-induced TRPM2 channel activation led to the redistribution of Zn^{2+} from

lysosomes to mitochondria, leading to mitochondrial fragmentation [53]. In a rat model of streptozotocin-induced diabetes, treatment with a TRPM2 inhibitor (2-aminoethoxydiphenyl borate, 2-APB) ameliorated cognitive impairment based on behavioral tasks, and restored expression of memory-associated proteins, including CaMKII, PSD95, and BDNF [54]. Treatment with the antioxidant N-acetylcysteine (NAC) was protective against oxidative stress damage and Ca^{2+} overload in diabetic neurons in this model through inhibition of TRPM2 [55]. TRPM2 deficiency was also found to be protective against streptozotocin -induced diabetic neuropathy resulting from hyperglycemia-related oxidative stress in peripheral sensory neurons [56].

Cardiovascular: POTENTIAL MIXED (Preclinical)
There is conflicting evidence based on preclinical models as to whether TRPM2 promotes or protects against cardiac ischemic damage, suggesting that it has context dependent activity in cardiac tissue [2]. In the heart, low levels of ROS are produced in respiring mitochondria, and may lead to the tonic entry of TRPM2 mediated Ca^{2+} entry, which is important for bioenergetic maintenance under physiological conditions [57]. However, in response to ischemic/reperfusion injury, sustained elevated Ca^{2+} entry through TRPM2 channels can lead to pathogenic Ca^{2+} overload and disrupt bioenergetic maintenance [2]. Consequently, whether TRPM2 activity is beneficial or deleterious depends on the degree of activation and the injury conditions. This suggests that TRPM2 inhibition may be beneficial during acute ischemic-reperfusion cardiac injury to dampen oxidative stress damage, but prolonged inhibition may impair basal respiratory function in cardiac tissue.
TRPM2 plays a role in regulating endothelial Ca^{2+} homeostasis and endothelial function [19]. Endothelial Ca^{2+} signaling is involved in angiogenesis, and endothelial TRP channels play a role in VEGF mediated vascular remodeling [58]. This could promote aberrant vascularization of tumor tissue, but also promote the restoration of blood flow following injury. ROS increase vascular endothelial permeability, and TRPM2 inhibition may help reduce vascular oxidative damage, mitigate inflammation, and maintain barrier integrity [59]. Due to this interplay, combining VEGF inhibitors (e.g. axitinib) with PARP inhibitors (e.g. olaparib) may reduce the risk for vascular complications in cancer patients [45]. Patients treated with the anti-VEGF bevacizumab in combination with the PARP inhibitor olaparib show lower rates of hypertension relative to those treated with anti-VEGF therapy alone. In cultured human vascular smooth muscle cells and mouse mesenteric artery preparations, treatment with axitinib led to an increase in ROS, PARP activity, pro-inflammatory markers, and endothelial dysfunction, and hypercontractile responses [45]. These effects could be attenuated through the use of PARP or TRPM2 inhibitors.
The loss of inhibitory factors regulating TRPM2 activity may contribute to vascular endothelial cell dysfunction in response to oxidative stress. Oxidative stress-induced activation of TRPM2 has been

shown to involve PKC activity [60]. In endothelial cells, oxidative stress-activated PKC phosphorylated a truncated (short) isoform of TRPM2 (TRPM2-S) at Ser 39 [61]. TRPM2-S inhibits the activity of full length TRPM2, and this modification disrupts the interaction between TRPM2-S and TRPM2, resulting in the disinhibition of TRPM2. A separate study found that TRPM2-S is an unstable protein, such that the dimerization between the two isoforms results in the polyubiquitination and degradation of TRPM2, leading to a reduction in surface expression levels [62]. Approaches that boost the expression of TRPM2-S could represent another therapeutic strategy to dampen the activation of TRPM2, and thus prevent calcium dysregulation and the induction of cell death in response to oxidative stress [60].
Aside from cancer, the biological rationale for TRPM2 inhibitors is strongest for ischemic-reperfusion injuries, suggesting it they may have greater therapeutic utility for these indications. Protective effects from TRPM2 genetic deficiency or non-selective inhibitors have been seen in a variety of ischemic-reperfusion injury models including several different organ systems. Inhibiting the overactivation of TRPM2 following a massive oxidative insult protects against cell loss, which helps preserve organ function.

Atherosclerosis: POTENTIAL BENEFIT (Preclinical)
The expression of TRPM2 was found to be elevated in carotid arteries containing atherosclerotic plaques relative to regions without signs of atherosclerosis, in patient tissue (n=32) [63]. In a mouse model of hypercholesterolemia (AAV-PCSK9), TRPM2 knockout mice had less macrophage infiltration and smooth muscle cell migration, along with reduced expression of cell adhesion markers, inflammatory cytokines, and ROS within aortic plaques [63]. The overall atherosclerotic plaque load was also reduced. The effect appears to be mediated by the impact to immune and vascular cells, as TRPM2 had no effect on circulating cholesterol levels. Treatment with the non-selective TRPM2 inhibitor ACA (25 mg/kg) also reduced aortic plaque load in the ApoE-/- mouse model of atherosclerosis. Use of the non-selective TRPM2 inhibitors ACA and 2-APB also reduced aortic reactivity towards 5-HT [64]. These studies suggest that TRPM2 activation may contribute to pathological vascular remodeling and inflammation in response to lipid overload-mediated oxidative stress.

Cancer: POTENTIAL BENEFIT (Preclinical)
The opposing roles for TRPM2 in healthy cells and cancer cells with respect to cell survival and mitochondrial function highlights the context-dependent function of TRPM2. Many tumor cells reside in an environment characterized by high levels of oxidative stress, which leads to the activation of TRPM2. In contrast to healthy cells, where excessive TRPM2 activity leads to the induction of cell death pathways, elevated TRPM2 can instead promote cell survival pathways in cancer cells, due to differential

expression and activity of downstream signaling players. TRPM2 is highly expressed in a variety of cancers including, breast cancer, prostate cancer, pancreatic cancer, gastric cancer, lung cancer, melanoma, leukemia, and neuroblastoma [2; 65]. In cell culture and xenograft models, TRPM2 promotes cancer cell survival. Ca^{2+} influx through TRPM2 channels is important for the maintenance of the cellular bioenergetics that facilitate tumor cell growth, and when this influx is inhibited tumor cells show evidence of mitochondrial dysfunction and increased ROS production [65]. TRPM2 is normally localized to the plasma membrane, but in tumor cells a large percentage of TRPM2 is localized to the nucleus, which may account for its unique roles in DNA damage repair and the promotion of cell survival in these cells [65]. However, the role of TRPM2 is cancer type dependent, as TRPM2 activation has been found to promote tumor cell apoptosis in some cancer cells, including bladder cancer and glioblastoma [65].

Gastric cancer: TRPM2 expression was found to be inversely associated with survival in patients with gastric cancer (n=876) (Hazard Ratio [HR]: 1.261, p=0.0071) [66]. In cell culture, inhibition of TRPM2 reduces cell survival, impairs mitochondrial function, dysregulates autophagy, and sensitizes gastric cancer cells to chemotherapeutic agents [66; 67].

Pancreatic cancer: In patients with pancreatic ductal adenocarcinoma (n=159), the mutation status of TRPM2 was significantly inversely correlated with patient survival ($P=1.0416\times10^{-2}$), and high expression of TRPM2 was also associated with worse survival ($P=4.2253\times10^{-2}$) [68]. The expression level of TRPM2 was shown to increase with disease progression and was inversely associated with overall survival (Pearson's coefficient −0.88) and progression-free survival (Pearson's coefficient −0.85) in patients with pancreatic cancer (n=64) [69]. The expression of TRPM2 was correlated with the expression of PKC/MAPK pathways. In cell culture, TRPM2 overexpression was associated with increased proliferation and migratory capacity [68]. Overexpression of TRPM2 increased tumor weight in a nude mice tumor-bearing model (BXPC-3 cells), and promoted tumor cell migration and invasion in transwell assays [69].

Lung cancer: In cancerous tissue from non-small cell lung cancer patients (n=60) the long noncoding RNA (lncRNA), TRPM2-AS, was found to be upregulated (5.78 ± 1.35 fold) and positively correlated with tumor stage and size [70]. Elevated TRPM2-AS expression was also associated with worse survival (HR: 1.239, p=0.003). In cell culture, knockdown of TRPM2-AS inhibited proliferation and promoted apoptosis of the lung cancer cells. TRPM2-AS is a lncRNA that is an antisense to TRPM2, but its *in vivo* function, including its potential ability to modulate TRPM2 activity or expression is not well understood.

Prostate cancer: The antisense lncRNA, TRPM2-AS, was found to be overexpressed in prostate cancer based on both tumor tissues and prostate tumor cell lines [71]. In an analysis of clinical parameters, high TRPM2-AS expression was associated with poor prognosis, as these tumors had an enhanced proliferation rate.

Neuroblastoma: High TRPM2 expression was associated with worse event free survival in patients with stage 4 non-MYCN amplified neuroblastoma patients in the Cangelosi (n =198) and Seeger (n=102) databases [72]. Cancer cells with high TRPM2 show greater migration and invasion capability stemming from increased expression of α1, αv, β1, and β5 integrins and increased activity of the FOXM1 and E2F1 transcription factors. Deletion of TRPM2 sensitized neuroblastoma cells (SH-SY5Y) to the chemotherapeutic doxorubicin [73]. TRPM2 deficient cancer cells showed lower levels of FOXM1 and E2F1-related gene expression, higher levels of ROS, and reduced cell viability. The expression of the short isoform, TRPM2-S, which acts as a dominant-negative, led to a reduction in the expression and signaling of hypoxia-inducible factor (HIF)-1/2α, which prevented the induction of protective mitochondrial adaptations, and thus increased the sensitivity of the neuroblastoma cells to oxidant stress [74].

Melanoma: Knockdown of TRPM2 with siRNA promoted cell death in human melanoma cell lines (SK-Mel-23, UKRV-Mel-4 and UKRV-Mel-5), without affecting the survival of non-cancerous keratinocytes [75]. TRPM2 was found to be localized to the nucleus, rather than the cell membrane, in the melanoma cell lines.

Retroperitoneal liposarcoma: In a study of clinically relevant biomarkers for disease-free survival (n=57 patient samples), TRPM2 was identified as a protective prognostic factor [76]. The protective effect was driven by expression of the short isoform, TRPM2-S, which is an alternatively spliced isoform with a truncated C-terminus that acts as a dominant-negative towards full-length TRPM2 in reducing the flow of Ca^{2+}. Expression of TRPM2-S increased the susceptibility of cancer cells to oxidative stress-related apoptotic cell death, but could potentiate cell growth and survival under conditions of normoxia.

Neuropathic pain: POTENTIAL BENEFIT DURING INDUCTION PHASE (Preclinical)

The role of TRPM2 in neuropathic pain is derived from its ability to modulate peripheral and central neuroinflammation, rather than influencing physiological nociceptive pain mechanisms [56]. TRPM2 activation contributes to the secretion of chemokines and cytokines from immune cells that results in the induction of neuropathic pain, including increased mechanical allodynia and heat pain sensitivity [77]. In rodent models, TRPM2 expression is increased in the spinal cord and dorsal root ganglia acutely after peripheral nerve injury, and TRPM2 inhibition during this acute phase can block the induction of neuropathic pain [77]. The protective effects are associated with the reduction of oxidative stress induced neuroinflammation and circuit modification. TRPM2 deficiency was found to be protective against the induction of neuropathic pain in a variety of models that involve oxidative stress, including the monosodium iodoacetate-induced osteoarthritis pain model, the inflammatory demyelinating (multiple sclerosis-like) experimental autoimmune encephalomyelitis model, paclitaxel-induced

peripheral neuropathy model, and streptozotocin-induced diabetic neuropathy model [56]. However, it was not protective in models where pain was not associated with neuroinflammation and oxidative stress injury. Additionally, TRPM2 activity appears to play a role in the acute induction of neuropathic pain, but not in its maintenance, as inhibition of TRPM2 during the chronic phase offered no benefit [77].

Safety: Safety data is confounded by a lack of specific inhibitors, but studies in TRPM2 knockout animals suggests chronic inhibition may increase infection risk. Organ type selective inhibitors would be expected to have the best safety profile.

Types of evidence:

- Numerous laboratory studies

Due to the difficulty in developing specific TRPM2 inhibitors with good *in vivo* pharmacokinetic properties, animal studies have primarily used non-specific inhibitors, thus it can be difficult to tease apart the exact contribution for TRPM2 in terms of potential side effects [78]. Similarly, interpretation of potential safety signals from TRPM2 knockout animals can be confounded by developmental or compensatory effects.

Based on preclinical studies, the primary potential safety concerns for TRPM2 inhibitors are the impairment of glucose tolerance and increased risks for complications from infection due to immune system dysregulation. TRPM2 plays an important role in immune and inflammatory responses. The loss of TRPM2 is associated with impairment of monocyte activation and neutrophil migration [59]. This impairment of innate immune responses may increase vulnerability to infection. Neutrophils act as the first line of defense against pathogens, and TRPM2 was shown to be involved in the FcγRIIIb-mediated rise in calcium in neutrophils, which is involved in the formation of neutrophils extracellular traps (NET) [79]. TRPM2 does not appear to be involved in the differentiation or activation of T lymphocytes [80]. The loss of TRPM2 is not expected to interfere with normal thermosensation, however, it may compromise the ability of the body to regulate temperature in the context of high fevers [81]. It has been hypothesized that TRPM2 may serve as a brake to prevent excessive fever responses, as TRPM2 deficiency was found to reduce survival in rodents exposed to endotoxins and some types of pathogens [81].

Since TRPM2 expression is widespread, and it plays various cell-type dependent roles, it may be necessary to develop inhibitors that preferentially target TRPM2 in different organ systems. TRPM2 channels form tetramers, so the association of different splice variants may modulate the channel structure and function [2]. If certain combinations are organ type specific, it may be possible to specifically target them, and minimize side effects in other organ systems. TRPM2 activity could also potentially be modulated via the regulation of its endogenous inhibitors and activators, such as the alternative splice isoformTRPM2-S, and the activating kinase PKC.

Sources and dosing:

There are currently no specific TRPM2 inhibitors available for clinical use. Non-specific inhibitors including - 2-aminoethoxydiphenyl borate (2-APB), N-(p-amylcinnamoyl)anthranilic acid (ACA), clotrimazole and flufenamic acid, are available for research use.

Research underway:

Research into the function and disease contribution of TRPM2 has been hampered by the lack of specific inhibitors with good PK properties. A variety of research groups have been involved in development of these inhibitors. A group at Janssen recently reported on the development of JNJ-28583113, which is a potent, brain penetrant inhibitor for TRPM2, but has poor metabolic stability [78]. ADPR analogs show good specificity and selectivity, however, they are limited by a lack of cell permeability [82]. The peptide tat-M2NX is specific, cell-permeable, and BBB penetrant, which makes it a good tool compound for *in vivo* studies. However, its development is limited because it is poorly immunogenic and cannot be used orally [37]. Several groups are working on developing novel inhibitors, including a group in China that developed several selective compounds that protect cells *in vitro* [83], as well as A23, which was orally bioavailable and showed neuroprotection *in vivo* [45]. Further optimization is necessary to develop an inhibitor that would be suitable for clinical use.

Search terms:

Pubmed, Google: TRPM2 Inhibitors

- Alzheimer's disease, Parkinson's disease, ischemia, oxidative stress, inflammation, aging, cardiovascular, diabetes, cancer, pain, thermosensation

References:

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