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.

MARK4 Inhibitors

Evidence Summary

Elevated activity of MARK4 drives tau pathology, cancer cell migration, and inflammation. Specificity and selectivity will be critical for good safety, but inhibitors with good *in vivo* properties do not yet exist.

Neuroprotective Benefit: Inhibition of elevated MARK4 to normal levels may mitigate tau pathology and neuroinflammation.

Aging and related health concerns: MARK4 inhibition may suppress cancer metastasis, and prevent inflammation-related adverse metabolic remodeling.

Safety: The *in vivo* safety of MARK4 inhibitors has not been established. The safety profile will likely depend on the specificity of the inhibitor toward MARK4 relative to other related kinases.

Availability: Compounds that inhibit MARK4 *in vitro* are available for research use.	**Dose**: N/A	**Chemical formula:** N/A **MW**: N/A
Half-life: N/A	**BBB**: N/A	
Clinical trials: None	**Observational studies**: MARK4 is elevated in Alzheimer's disease and associated with tau pathology. Elevated MARK4 is associated with poor survival in metastatic cancers.	

What is it?

MAP/microtubule affinity-regulating kinase 4 (MARK4) is part of the PAR family of serine/threonine kinases, which are involved in the regulation of cell polarity [1]. MARKs regulate the organization of microtubule arrays. MARK4 promotes the phosphorylation of microtubule-associated proteins, resulting in the destabilization and disintegration of microtubule networks. MARK4 expression is highest in the brain. Tau is one of the major microtubule-associated proteins that is phosphorylated directly and indirectly by MARK4, thus MARK4 inhibitors have been proposed as a potential therapeutic for neurodegenerative tauopathies, such as Alzheimer's disease. MARK4 is also dysregulated in some cancers, such as glioma, and MARK4 inhibitors are also being developed for this indication.

Neuroprotective Benefit: Inhibition of elevated MARK4 to normal levels may mitigate tau pathology and neuroinflammation.

Types of evidence:

- 3 gene association studies for MARK4 and AD
- 2 studies of MARK4 expression in the human brain
- 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: MARK4 ELEVATED IN THE AD BRAIN AND ASSOCIATED WITH TAU

MARK4 has been implicated as an Alzheimer's associated gene, however, the effect size of MARK4 variants on AD risk is generally small and heterogenous across ethnic populations. The variant rs597668, in which T is the wildtype allele and C is the minor risk-associated allele, located at the 19q13.3 locus near the genes EXOC3L2, BLOC1S3, and MARK4 was found to be non-significantly associated with late onset AD (LOAD) based on a dataset of 3,297 AD patients and 4,296 controls from 11 case-control series from the US and Europe [2]. The effect was significant (Odds ratio [OR] 1.16, 95% Confidence Interval [CI] 1.03 to 1.30), and similar to a prior study (OR 1.15, 95% CI 1.11 to 1.20) prior to adjustment. However, the association was tempered by adjustment for ApoE4 (OR 1.08, 95% CI 0.99 to 1.19). In a population of Han Chinese (598 AD, 607 controls), there was no significant association of rs597668 with AD [3]. A genetic analysis from 100 brain and 355 blood samples from sporadic AD cases found that although somatic variants in MARK4 could be detected in a few cases, these were unlikely to be a major driver of sporadic AD [4].

A double *de novo* mutation in the linker region of MARK4, ΔG316E317D, was identified in a case of early onset AD [5]. This mutation led to increased tau phosphorylation. In a fly model, overexpression of either wildtype MARK4 or this double-mutant version increased tau phosphorylation at Serine-262 and Serine-356 and tau-mediated neurodegeneration [6]. The effects of the mutant MARK4 were more potent, and involved additional mechanisms of tau dysregulation.

In postmortem brain tissue, MARK4 expression is below the limit of detection in healthy brain tissue, but MARK4 expression is elevated in the AD brain [7; 8]. In AD, phosphorylated MARK4 is found in granulovacuolar degeneration bodies. MARK4 colocalizes with and levels are correlated with Serine-262 phosphorylated tau. MARK4-tau interactions are correlated with Braak stages in the hippocampus.

Tau toxicity: MARK4 regulates microtubule dynamics through the phosphorylation of microtubule-associated proteins, including tau [9]. Elevated expression of MARK4 leads to the disintegration of microtubule networks via excessive phosphorylation. MARK4 phosphorylates tau at locations with microtubule binding repeats, such as Serine-262 and Serine-356, which generates a form of phospho-tau with high seeding capacity [6]. CDK5, another serine/threonine kinase that phosphorylates tau, phosphorylates MARK4, which leads to its activation [10]. MARK4 can also be activated via phosphorylation from the serine/threonine kinase liver kinase B1 (LKB1) [11]. Therefore, inhibitors of CDK5 or LKB1 may also serve as MARK inhibitors.

White matter injury may prime the nervous system for tau-mediated neurodegeneration by promoting the upregulation of MARK4 in neurons. In response to axonal injury, MARK4 is involved in dendrite remodeling [12]. Thus, the neuronal upregulation of MARK4 could be one of the mechanisms by which traumatic brain injuries and strokes increase the risk for AD.

Inflammation: MARK4 was shown to bind to the NLRP3 inflammasome, which is important for its spatial localization in the cell [13]. This interaction brings NLRP3 to the microtubule-organizing center, which allows for the formation of a single inflammasome speck complex per cell. MARK4 also promotes the recruitment of NLRP3 to mitochondria. Through these mechanisms, MARK4 plays a role in the regulation of NLRP3 activation. MARK4 null mice show a weakened response to an inflammatory stimulus, peritoneal injection of monosodium urate crystals, driven by a failure of NLRP3 inflammasome activation and downstream effectors, such as IL-1β production and neutrophil migration.

APOE4 interactions: Not established

Aging and related health concerns: MARK4 inhibition may suppress cancer metastasis, and prevent inflammation-related adverse metabolic remodeling.

Types of evidence:

- 2 studies of MARK4 expression in cancer
- 1 study of MARK4 expression in diabetes
- 1 study of MARK4 expression in atherosclerosis
- Numerous laboratory studies

Cancer: ELEVATED MARK4L ASSOCIATED WITH WORSE PROGNOSIS

Dysregulated MARK4 expression is associated with some cancers, such as glioma [14]. MARK4 has two alternatively spliced isoforms, MARK4L (long) and MARK4S (short), which differ in their C-terminal regions. MARK4S is highly expressed in normal brain tissue, while MARK4L is elevated in neurogenic regions and in gliomas. A high ratio of MARK4L/MARK4S is associated with tumor grade. MARK4L shows nuclear localization, where it appears to play a role in cell cycle progression. In glioma cell lines, MARK4 promotes cell migration and proliferation. Consequently, inhibition of cancer cell line migration and proliferation is used in phenotype screens and validation assays for the screening and development of MARK4 inhibitors. In general, screen identified MARK4 inhibitors reduce cancer cell line growth without

significantly impacting the viability of non-cancer human cell lines [15; 16]. The difference is likely due to differences in expression level and/or isoform of MARK4 in the different cell lines.

PCC0208017 was identified as a novel inhibitor of MARK3 and MARK4, and was found to have anti-tumor activity in a (male) mice xenograft GL261 cell-induced glioma model [17]. This inhibitor was also found to be blood-brain-barrier permeable and have a good oral pharmacokinetic profile.

In breast cancer cells (MDA-MB-231), MARK4 was found to be a regulator of the Hippo pathway, which is important cell growth [18]. The kinase activity of MARK4 promotes the nuclear localization and activation of YAP/TAZ, which promotes cell growth. Loss of MARK4 activity inhibits the proliferation and migration of MDA-MB-231 breast cancer cells. The microRNA miR-515-5p has been identified as a tumor suppressor in ER-positive breast cancer. Levels of miR-515-5p are correlated with survival in patients with metastatic breast or lung cancer [19]. The tumor suppressor activity of miR-515-5p was found to be related to its ability to silence MARK4. The overexpression of miR-515-5p prevents MARK4 mediated cancer cell migration and triggers cell cycle arrest.

These studies suggest that MARK4 inhibitors may be beneficial for gliomas and metastatic cancers with MARK4 dysregulation.

Metabolic disease: MARK4 PROMOTES INFLAMMATION AND OXIDATIVE STRESS IN THE CONTEXT OF HIGH-FAT/HIGH SUGAR DIETS (Preclinical)

As a member of the AMPK family, MARK4 plays a role in metabolic regulation. MARK4 promotes adipose tissue inflammation and oxidative stress. In wildtype male mice, MARK4 expression is induced in response to a high-fat diet, leading to an impairment of mitochondrial oxidative respiration, increased reactive oxygen species (ROS), elevated inflammatory cytokines, and decreased activity of endogenous antioxidant enzymes in adipose tissue [20]. These effects were counteracted by PPARγ, which acts as a negative regulator of MARK4. Accordingly, male MARK4 knockout mice show protection against some of the deleterious metabolic effects of a high-fat diet. These mice were protected against diet-induced obesity through increased energy expenditure, due to their hyperactivity and hypermetabolism. Glucose homeostasis was improved in these mice, due to increased expression and activity of AMPK kinase, and they showed higher insulin sensitivity. MARK4 inhibits the browning of white adipose tissue by inducing autophagy of brown adipose tissue [21]. MARK4 male knockout mice show elevated levels of thermogenic brown adipose tissue activity, which contributes to their decreased mass of white adipose tissue [20]. It is unclear whether a similar sex difference occurs in humans, and whether females may also show beneficial metabolic adaptations toward MARK4 inhibition.

There is evidence to suggest that MARK4 plays a similar role as a metabolic regulator in humans, and may contribute to metabolic dysregulation in diabetes. MARK4 expression was found to be elevated in peripheral blood mononuclear cells (PBMCs) from patients with type 2 diabetes (n=50) relative to healthy controls (n=30) [22]. The increase in MARK4 was accompanied by increased expression of the NLRP3 inflammasome, and its downstream mediators, IL-1β and IL-18. These may be related, since MARK4 has been shown to promote NLRP3 activation. High glucose conditions lead to the induction of MARK4, suggesting that high-fat and high-sugar diets may lead to a pathological upregulation of MARK4, which sets off a metabolism disrupting inflammatory cascade. The induction of MARK4 may be due to the high glucose-related inhibition of the histone methyltransferase SET8. The expression of SET8 is also decreased following hepatic ischemic/reperfusion injury, and similarly results in the induction of MARK4 and the NLRP3 inflammasome [23]. Downregulation of MARK4 could prevent the inflammatory damage following hepatic injury in mice.

Atherosclerosis: MARK4 PROMOTES VASCULAR INFLAMMATION (Preclinical)

MARK4 expression was found to be increased in atherosclerotic lesions in human carotid tissue in combination with NLRP3 in myeloid cells [24]. The joint expression of MARK4 and NLRP3 was associated with elevated levels of the inflammatory cytokines, IL-1β and IL-18, which are downstream of NLRP3 inflammasome activation. In mice, the loss of MARK4 in bone marrow-derived cells reduced the size of atherosclerotic lesions as well as levels of inflammasome-related pro-inflammatory cytokines. The upregulation of MARK4 may also play a role in vascular remodeling in the context of diabetes. High glucose conditions lead to the induction of the transcription factor, ELF3, which is a regulator of MARK4 in vascular endothelial cells, and promotes vascular inflammatory processes [22].

Myocardial infarction: MARK4 REGULATES CARDIAC CONTRACTILITY (Preclinical)

MARK4 is involved in the regulation of cardiomyocyte contractility through the modulation of microtubule dynamics and stability [25]. MARK4 promotes the phosphorylation of microtubule-associated protein-4 (MAP4), which initiates a cascade leading to microtubule detyrosination. Microtubule detyrosination is prevalent in the context of cardiomyopathy, and inhibiting this process improves cardiomyocyte contractility. Mice lacking MARK4 had preserved cardiac function, as measured by left ventricular ejection fraction, in the context of ischemic heart injury, which was associated with a reduction in microtubule detyrosination. This suggests that MARK4 inhibitors may preserve cardiac function in the context of myocardial infarction.

Safety: The *in vivo* safety of MARK4 inhibitors has not been established. The safety profile will likely depend on the specificity of the inhibitor toward MARK4 relative to other related kinases.

Types of evidence:

- Numerous laboratory studies

MARK4 inhibitors are still in early preclinical development [11]. Most of the inhibitors identified thus far have only shown inhibition of MARK4 *in vitro*, and showed some phenotypic activity of MARK4 inhibition, such as cancer cell growth inhibition, or the inhibition of tau phosphorylation in cell culture. Many of these are natural products, and are hampered by poor bioavailability or other pharmacokinetic issues that limit their *in vivo* utility. Some of the identified MARK4 inhibitors include the polyphenols naringenin, rosmarinic acid, rutin, vanillin, the xanthone α-mangostin, and the bile acid cholic acid [15; 16; 26; 27; 28]. Other novel small molecules showing MARK4 inhibitory capacity *in vitro* include arylaldoxime/5-nitroimidazole hybrids, and isatin-triazole hydrazones [29; 30]. The acetylcholinesterase inhibitors donepezil and rivastigmine show MARK4 inhibition *in vitro* [31], and methylene blue has also shown MARK4 inhibition in cell culture and in Drosophila [32].

OTSSP167 (hydrochloride), an inhibitor of MELK, a related AMPK-family serine/threonine kinase shows inhibition toward MARK4, *in vitro*, as well [33]. It also highlights the potential difficulty of developing a MARK4 specific inhibitor, without impacting related family members. MARK4 has 75% homology with other MARKs (1-3) [17]. PCC0208017 is a novel inhibitor of MARK3 and MARK4, which shows *in vivo* oral pharmacokinetic properties. It could be detected in the plasma and brain at a dose of 50 mg/kg in mice, and showed anti-tumor properties in a xenograft cancer model at a dose of 100 mg/kg.

The safety profile for a dual inhibitor may be reasonable for acute treatment in the context of cancer, however, there may be concerns for more chronic conditions. MARK4 knockout mice show normal growth and survival, while knockouts for MARK2 or MARK3 have stunted growth and hypofertility [20]. Although some of the effects may be of developmental origin, inhibition of MARKs in the absence of overexpression increases the risk for side effects. For example, MARK kinase activity has a variety of important cellular functions, including neurotransmission [1]. Inhibition of MARK4 activity negatively impacted the firing rate of wild type neurons, but restored neurotransmission in Aβ-treated neurons where MARK4 levels were elevated [34]. This suggests that it may be critical to reduce MARK4 levels toward normal, without completely inhibiting its activity past a particular threshold. It remains to be determined whether specific MARK4 inhibitors with appropriate pharmacokinetic and pharmacodynamic properties can be developed.

Drug interactions: Drug interactions for MARK4 inhibitors have not been established.

Sources and dosing:

MARK4 inhibitors are not available for human use, though some inhibitors identified through screens are available for research use from commercial suppliers.

Research underway:

There are drug discovery programs underway to develop MARK4 inhibitors.

Search terms:

Pubmed, Google: MARK4

- Alzheimer's disease, neurodegeneration, cancer, diabetes, cardiovascular, inhibitors

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