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.

DAPK1 Inhibitors

Evidence Summary

DAPK1 is a mediator of cell death but has other context-dependent effects stemming from complex regulation. Inhibitors may benefit neurodegenerative disease, but have been challenging to develop.

Neuroprotective Benefit: Inhibition of DAPK1 may protect against neuronal loss stemming from a variety of stressors. It may also protect against the accumulation of pathological tau.

Aging and related health concerns: DAPK1 inhibition may protect against ischemic heart damage. But, DAPK1 has mixed roles in cancer and immune responses, which could be protective or deleterious depending on the context.

Safety: DAPK1 inhibitors have not reached clinical testing and limited safety information is available from preclinical animal studies. They could potentially impact susceptibility/immune responses to cancer and infection.

Availability: In preclinical development/research use	**Dose**: Not established	**Chemical formula:** N/A **MW**: N/A
Half-life: N/A	**BBB**: N/A	
Clinical trials: None	**Observational studies**: Genetic variants in DAPK1 have been associated with AD risk in some ethnic groups. DAPK1 expression is associated with prognosis in various cancers.	

What is it?

Death-associated protein kinase 1 (DAPK1) is a Ca2+/calmodulin-regulated serine/threonine kinase involved in a variety of biological processes [1]. It was first identified as a regulator of cell death, but has subsequently been found to be involved in cell survival, cell motility, synaptic plasticity, and immune cell activation. As a result, DAPK1 has become a target of interest for a variety of conditions, especially cancer and neurodegenerative disease. The regulation of DAPK1 is highly complex, including various post-translational modifications which impact its stability and kinase activity. One of the key modifications is its autophosphorylation at Ser308, in the Ca2+-calmodulin-binding autoinhibitory domain, which serves to inhibit its kinase activity [1]. DAPK1 intersects with numerous signaling pathways through this complex network of regulatory modifications, such that the overall functional profile of DAPK1 is highly dependent upon the overall milieu of environmental signals, and thus displays highly context dependent activity. As a result, DAPK1 can promote opposite outcomes (e.g. cell death vs cell survival) based on the presence or absence of particular signaling partners in a given environment. This dichotomy is best understood in the context of cancer, particularly with respect to its relationship with the tumor suppressor p53.

Both DAPK1 activators and inhibitors have been considered to be therapeutic candidates, primarily for cancer, and neurodegenerative disease, respectively [1]. However, to date, DAPK1 has been very challenging to target from a medicinal chemistry perspective, in terms of creating selective small molecules with reasonable drug-like properties. As a result, the development of DAPK1 inhibitors remains at the early preclinical stage.

Neuroprotective Benefit: Inhibition of DAPK1 may protect against neuronal loss stemming from a variety of stressors. It may also protect against the accumulation of pathological tau.

Types of evidence:

- 4 gene association studies for DAPK1 variants and AD risk
- 4 studies assessing DAPK1 levels in human tissue
- Numerous laboratory studies

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

DAPK1 inhibitors have not yet advanced to the stage of clinical testing, so there is no human data to support their utility in cognition and dementia prevention. However, there is evidence from gene association studies that genetic variation in DAPK1 may differentially impact dementia risk.

The single nucleotide polymorphisms (SNPs) rs4878104 and rs4877365 were originally identified as candidate DAPK1 variants associated with late-onset Alzheimer's disease (AD) risk [2]. The association was further supported by a meta-analysis of six cohorts including 2,012 cases and 2,336 controls [2]. Homozygosity for the minor allele (TT) of rs4878104, located in intron 2 of the DAPK1 gene, was associated with lower AD risk (Odds Ratio: 0.7, 95% Confidence Interval 0.58 to 0.85). The cohorts in this study were comprised of participants from European descent, and the effect of these variants was relatively weak. While homozygosity for the minor allele conferred protection, risk was not meaningfully impacted in heterozygotes, carrying a single copy of this variant. The rs4877365 SNP was found to be in linkage disequilibrium with rs487804, and also associated with AD risk in a subset of the cohorts [2]. There is an allelic imbalance in DAPK1 expression, such that one allele has lower expression than the other. Both variants were also found to be associated with allele-specific expression, which could impact DAPK1 protein expression and activity levels, and may be the mechanism by which these variants modify AD risk [2]. This suggests that the overall impact of these variants may depend on the broader regulatory landscape, including the presence or absence of other modulating factors. Consistent with this idea, the relationship of these variants with AD risk has been shown to vary in cohorts from different ethnic groups [3; 4; 5]. In some cohorts, these variants do not show a significant relationship with AD risk, while in others, an association is observed with the opposite allele. A large gene association study including 20,161 AD cases and 40,590 controls found that the associations between the rs4878104 variant and AD were impacted by ethnicity [5]. The authors speculate that these differences may stem

from different linkage disequilibrium patterns. In European populations, the minor (T) allele was found to regulate DAPK1 expression [5]. Meanwhile, the minor and major (T vs C) alleles were reversed in Han Chinese participants [4]. Under this genetic background, the homozygosity for the minor allele (CC) of the rs4878104 variant was associated with lower risk for AD.
Overall, these studies suggest that variation in DAPK1 may impact AD risk, but due to complex regulation, it is difficult to predict the risk associated with a given DAPK1 genotype at the individual level.

Human research to suggest benefits to patients with dementia:

DAPK1 inhibitors have not yet been clinically tested, so their potential therapeutic utility for dementia is currently unclear. However, there is human data from blood and postmortem brain tissue to suggest that the elevation of DAPK1 may play a role in neurodegenerative processes and cognitive decline in the context of AD.

DAPK1 expression has been shown to be elevated in the hippocampus in postmortem brain tissue from patients with AD [6; 7]. However, a separate study found that DAPK1 protein levels were not significantly altered in brain tissue from the frontal cortex [8]. This may reflect a role for DAPK1 downstream of pathology, in which the induction of DAPK1 follows the course of disease progression, as the hippocampus is typically affected earlier in the disease course than the frontal cortex [8]. DAPK1 levels were also shown to be elevated in the plasma from AD patients, with higher DAPK1 levels modestly associated with worse cognition on the Montreal cognitive assessment (MoCA) [9].

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

DAPK1 contributes to neurodegeneration through various, often overlapping, mechanisms [1]. DAPK1 plays an important role in the induction of cell death both directly and indirectly. DAPK1 can induce cell death in response to a variety of different cell stress-related signals. Additionally, DAPK1 can also promote the accumulation of pathological forms of proteins by influencing their processing and modification. The accumulation of these pathological proteins can, in turn, induce a cellular stress response leading to the further upregulation of DAPK1, resulting in a feed-forward loop. While the downstream effect of neuronal loss is similar across a variety of neurodegenerative conditions, the initial stressors and upstream signaling pathways can vary. As a result, targeting DAPK1 as a downstream effector has been proposed as a therapeutic strategy.

DAPK1 knockout mice are viable with mild changes in synaptic function that normalize with maturation [10]. These animals do not have overt behavioral phenotypes or increased incidences of tumors, suggesting that compensatory processes may be induced during development, and that during adulthood, DAPK1 activity may be primarily triggered by cell stress, and thus most relevant in pathological contexts [11].

Alzheimer's disease (AD): POTENTIAL BENEFIT (preclinical)

Cell death: DAPK1 was first discovered for its role in IFN-γ-associated cell death, and has subsequently been found to act as a downstream mediator for numerous cell death signaling pathways [1]. DAPK1 becomes activated in response to a variety of cell stressors, including inflammatory mediators, oxidative stress, DNA damage, and excitotoxicity. Post-translational modifications of DAPK1 influence its ability to interact with and influence the activity of various interacting partners. The pro-apoptotic capacity of DAPK1 is influenced by its kinase activity, such that phosphorylation of DAPK1 at Ser375 by ERK increases its activity, while autophosphorylation at Ser308 decreases its pro-apoptotic capacity [1]. DAPK1 can trigger apoptotic cell death stemming from inflammatory mediators, such as IFN-γ, TNF-α, Fas, and TGF-β [1]. Through the phosphorylation of p53 at the Ser23 residue, DAPK1 can trigger p53-mediated apoptosis [1]. DAPK1 also influences cell death-related morphological changes by altering cytoskeletal structure, in part through the phosphorylation of myosin-II light chain [12]. In addition to activation of apoptotic pathways, DAPK1 can also suppress the expression of anti-apoptotic signaling. DAPK1 promotes oxidative stress-associated cell death via regulation of the JNK signaling pathway [12]. Activation of NDRG2 via DAPK1 phosphorylation appears to play a role in Aβ-associated neuronal cell death. DAPK1 can enhance Ca2+ flux through the NMDA receptor through the phosphorylation of the GluN2B subunit, triggering calcium overload-induced neuronal cell death [12]. DAPK1 can also facilitate autophagic cell death by regulating activation of the Vps34 complex [1].
DAPK1 inhibitors have been shown to protect against numerous cell death triggers in preclinical studies [1]. The ability to serve as an effector for such a wide variety of cell stressors makes DAPK1 an attractive target for neurodegenerative conditions with heterogenous etiologies, such as AD.

Tau: DAPK1 has been shown to promote tauopathy in response to various neuronal stressors by regulating proteins involved in the post-translational modification of tau. In cell culture, DAPK1 promoted the phosphorylation of tau at Thr231, Ser262, and Ser396 [12]. The most well-studied impact of DAPK1 on tau biology involves its role in regulating the prolyl isomerase Pin1, which catalyzes the conversion of p-tau231 between its cis and trans isomers [13]. The trans p-tau231 conformation is the

one associated with physiological activities, such as the stabilization of microtubules. The cis p-tau231 conformation takes on pathological functions, and its accumulation has been observed in a variety of tauopathies. Pin1 promotes the conversion from cis (pathological) to trans (physiological) tau, but its isomerase activity is dampened in response to neuronal stress due to the phosphorylation of Pin1 (at Ser71) by DAPK1, thereby allowing for the accumulation of cis p-tau [13]. Consequently, inhibition of DAPK1 can relieve the neuronal stress-related repression of Pin1 activity, thereby preventing the accumulation of pathological cis p-tau231 [14].
DAPK1 also appears to regulate other post-translational modifications of tau, including SUMOylation [15]. The SUMOlyation of tau promotes its phosphorylation and aggregation. DAPK1 was shown to facilitate the degradation of the de-SUMOlylating enzyme, SENP1, thereby resulting in the accumulation of SUMOylated and phosphorylated tau [15]. Inhibition of DAPK1 restored levels of SENP1 and mitigated the accumulation of pathological tau in preclinical models [15].

Amyloid: DAPK1 has been shown to promote both the pathological processing of amyloid and the toxicity of amyloid. DAPK1 has been shown to phosphorylate (Thr668) amyloid precursor protein (APP), facilitating amyloidogenic processing of APP, and accumulation of pathological Aβ [16]. Elevated levels of DAPK1 have been observed in conjunction with increased APP phosphorylation in postmortem brain tissue from AD patients [16]. Aβ aggregates can promote the stabilization of DAPK1, thereby enhancing its function, leading to a feed-forward cycle. DAPK1 deficiency was associated with a shift toward non-amyloidogenic APP processing in an AD mouse model (Tg2576) [16].
In addition to reducing the production of Aβ, inhibiting DAPK1 may also dampen the neurotoxic effects of aggregated Aβ. In primary neuronal cell culture, genetic or pharmacological inhibition of DAPK1 protected against Aβ-induced neuronal cell death [17]. Blocking the elevation of DAPK1 may protect against Aβ-associated excitotoxicity and Aβ-induced neuroinflammation [9; 18]. DAPK1 may also serve as an effector of Aβ-induced tauopathy [17]. The upregulation of DAPK1 kinase activity by Aβ enhances its capacity to modify the activity of tau regulating enzymes, such as Pin1, thereby driving the accumulation of pathological tau.
These studies suggest that targeting DAPK1 may protect against neurotoxic amyloidosis through both upstream and downstream mechanisms.

Synaptic Function: DAPK1 is most highly expressed in the brain during neural development [1]. In the adult brain, at least in rodents, expression is more refined to particular regions in the cerebral cortex, hippocampus, and cerebellum, where it appears to be involved in synaptic plasticity [1].

Comparative transcriptional profiling of the brains of mice with and without DAPK1 indicated that DAPK1 differentially impacts gene expression in different brain regions [19]. This was driven by effects on the regulation of transcription factor binding and activity. A quantitative phosphoproteomic analysis of differentially expressed and modified proteins in mouse hippocampal tissue, found that synapse-related proteins were overrepresented, suggesting a primary role for DAPK1 in presynaptic function [20].

DAPK1 has been shown to influence synaptic plasticity by regulating the synaptic movement of CaMKII, one of the master regulators of calcium-related synaptic plasticity [21]. Movement of CaMKII towards the synapse promotes a form of plasticity called long-term potentiation (LTP), while suppressing this movement can instead drive a form of plasticity called long-term depression (LTD) [21]. This process involves differential binding of CaMKII to the NMDA receptor subunit, GluN2B [21]. DAPK1 influences this process by competing for binding to GluN2B. Genetic deletion of DAPK1 alters presynaptic activity in young mice, resulting in an enhancement of LTD [10]. Notably, this effect weakened and normalized as the mice matured. DAPK1 appears to be dispensable for basal synaptic transmission during adulthood in physiological contexts, but excessive accumulation of DAPK1 at the synapse, as observed in pathological contexts, may disrupt synaptic function [12].

The upregulation of DAPK1 in the entorhinal cortex, which serves as an important interface between the hippocampus and neocortex, was associated with synaptic dysfunction and loss in an AD model [22]. Inhibition of DAPK1 protected against synaptic loss in the entorhinal cortex in AD mice, without impacting basal synaptic transmission in wildtype mice [22].

Excitotoxicity: DAPK1 is primed to serve as a mediator of excitotoxicity-induced neuronal loss. Excitotoxicity stems from excessive release of the glutamate neurotransmitter, resulting in overactivation of the glutamate NMDA receptor [23]. NMDA receptors can be located at the synapse as well as at extra-synaptic sites. The extra-synaptic receptors are activated in response to intense synaptic activity, and have been associated with excitotoxicity. The interaction of DAPK1 with the NMDA receptor subunit GluN2B can enhance conductance through the NMDA receptor. Excessive conductance through the extra-synaptic NMDA receptors results in calcium overload, and the induction of cell death processes. Preclinical studies have found that blocking brain insult-related elevations of DAPK1 can protect against excitotoxic cell death [24]. DAPK1 may mediate Aβ-induced excitotoxic cell death by enhancing the activity of GluN2B-containing NMDA receptors [9]. Knockdown of DAPK1 was shown to protect against Aβ oligomer-induced calcium overload and neuronal cell death [25].

Neuroinflammation: DAPK1 plays complex and context-dependent roles in the regulation of immune/inflammatory responses. Preclinical studies have shown that DAPK1 regulates inflammasome activation in microglial cells. DAPK1 inhibition prevented Aβ-induced IL-1β production and caspase-1 activation in cultured microglia, and blunted the IL-1β inflammatory response to LPS in mice [18]. This suggests that DAPK1 serves as a mediator of Aβ-induced inflammasome activation and downstream pathological neuroinflammatory responses.

Parkinson's disease: POTENTIAL BENEFIT (preclinical)
The upregulation of DAPK1 may contribute to neurodegeneration in PD via many of the same mechanisms observed in AD models. Preclinical studies suggest that DAPK1 may exacerbate synucleinopathy.
Proteomic profiling identified alpha synuclein as a synaptic protein differentially regulated by DAPK1 activity [20]. DAPK1 has been shown to directly phosphorylate alpha synuclein at Ser129 in cell culture, which promotes the formation of insoluble synuclein aggregates [26]. In mice, the overexpression of DAPK1 can induce PD-like phenotypes, such as synucleinopathy, dopaminergic cell death, and motor impairments [27]. DAPK1 was found to be elevated and associated with synucleinopathy in the MPTP mouse model of PD [27]. Genetic deletion of DAPK1 in dopaminergic neurons protected against MPTP-induced neuronal loss. Administration of a peptide blocking alpha synuclein phosphorylation at Ser129 also protected against PD-like phenotypes in the MPTP model [27].
DAPK1 is a member of the ROCO family of kinases; a protein family which also includes LRRK2, a protein associated with genetic forms of PD [28]. Both DAPK1 and LRRK2 play roles in calcium-dependent signaling and autophagy [28]. DAPK1 was found to be upregulated in a mouse model of the PD-associated LRRK2-P1446L mutation [29]. The upregulation of DAPK1 led to the induction of NF-κB activation, neuroinflammation, and dopaminergic cell death in this model. Protein-protein interaction analysis from human PD neurons places DAPK1 and LRRK2 within an interconnected node [29]. Additionally, transcriptional profiling of dopaminergic neurons from PD patients revealed a similar upregulation of DAPK1, suggesting that DAPK1 may be a relevant effector of dopaminergic neuronal loss in PD more broadly [29].

Huntington's disease (HD): POTENTIAL BENEFIT (preclinical)
DAPK1 may be an important driver of excitotoxic cell death in HD. Excitotoxicity is one of the major mechanisms of neuronal cell death in HD [30]. The loss of inhibitory GABAergic neurons in the striatum stemming from accumulation of mutant huntingtin results in excessive excitatory (glutamatergic) signaling, leading to overactivation of the NMDA receptor, and the associated induction of cell death

pathways [30]. In the YAC128 mouse model of HD, DAPK1 is activated in the striatum early in the disease course, where it is preferentially associated with extrasynaptic NMDA receptors through its interaction with the GluN2B subunit [31]. The phosphorylation of GluN2B at Ser1303 by DAPK1 enhances receptor conductance, resulting in the induction of calcium overload and associated cell death. Inhibition of DAPK1 normalizes extrasynaptic GluN2B/NMDA receptor activity, preventing neuronal loss in striatal neuron cultures [31].

Amyotrophic lateral sclerosis (ALS): POTENTIAL BENEFIT (preclinical)
Evidence from preclinical models suggests that DAPK1 may play a role in driving motor neuron death in ALS by inhibiting anti-apoptotic signals. Xiap is a potent inhibitor of apoptosis [32], and overexpression of Xiap has been shown to extend survival in mouse models of ALS [33]. DAPK1 was found to be upregulated in the context of ALS [34]. In the hSOD1^{G93A} model, DAPK1 inhibited Xiap, leading to the induction of apoptotic processes. Xiap activity was maintained when DAPK1 was silenced, resulting in the preservation of motor neuron survival [34].

Traumatic brain injury (TBI): POTENTIAL BENEFIT (preclinical)
Levels of DAPK1 have been shown to increase in the context of TBI and are associated with poor prognosis. The induction of DAPK1 drives injury-related tauopathy and excitotoxic neuronal cell death. Plasma levels of DAPK1 were found to be higher in TBI patients with poor outcomes relative to those with good outcomes (731.58 ± 273.15 pg/ml vs 483.99 ± 250.60 pg/ml) [35]. A similar pattern has also been observed in rodent TBI models. The expression of DAPK1 in affected brain regions was shown to increase early, within the first week after TBI in animal models [35]. Brain trauma-related hypoxia may be an important inducer of DAPK1. Genetic knockdown of DAPK1 protected against NMDAR-related excitotoxic neuronal loss and mitigated TBI-associated cognitive impairment [35].
Levels of cis p-tau are elevated in TBI and associated with severity [36]. DAPK1 deficiency protected against TBI-induced tauopathy and behavioral alterations in a mouse model [14].

Vascular Cognitive Impairment and Dementia (VCID): POTENTIAL BENEFIT (preclinical)
While tau tangle pathology is not a pathological feature of VCID, the dysregulation of tau, particularly with respect to the balance between cis and trans tau, may play a role in vascular cognitive impairment [37]. Impaired cerebral blood flow leading to insufficient tissue oxygen conditions may underlie the upregulation of DAPK1 in the context of cerebrovascular pathology. Levels of DAPK1-mediated Ser71 phosphorylated Pin1, which has reduced isomerase activity, were found to be increased in postmortem brain tissue from patients with VCID [37]. Consistent with the reduction in cis-to-trans isomerization,

levels of cis p-tau were also found to be increased in cortical brain tissue from patients with vascular dementia. Increases in DAPK1 and cis p-tau were also increased in the bilateral common carotid artery stenosis mouse model of VCID [37]. In this model, DAPKI deficiency prevented cis tau accumulation, and protected against cognitive (executive function) deficits, suggesting that cis tau accumulation may be a driver of cognitive impairment in VCID.

Stroke: POTENTIAL BENEFIT (preclinical)
DAPK1 has been implicated as a mediator of stroke-related neurodegeneration and neurological impairment in a variety of preclinical studies. The role of hypoxia/ischemia in the induction of DAPK1 was initially characterized through these stroke models [1]. A meta-analysis of 13 preclinical studies found that DAPK1 inhibition attenuated brain infarct volume, neurological functional impairments, and neurodegeneration in the context of cerebral ischemia [38]. A separate study found that the upregulation of DAPK1 may play a role in brain endothelial dysfunction in the context of ischemic stroke, such that deletion of DAPK1 in endothelial cells protected the integrity of the BBB in a mouse model [39]. Similar to other types of brain trauma, levels of cis p-tau have also been found to increase in the brain following ischemic injury, suggesting that tau dysregulation may play a role in post-stroke neurodegeneration and functional impairments [40].

Development of DAPK1 Inhibitors
Developing small molecule DAPK1 inhibitors with drug-like properties, suitable for *in vivo* use has been extremely challenging. There are several groups that are continuing to work to optimize the chemistry to develop clinically viable small molecule DAPK1 inhibitors [41; 42; 43].

Other groups have opted to take different approaches toward inhibiting DAPK1, such as targeting DAPK1 with degraders.
One group developed a hydrophobic tagging (HyT)-based degrader targeting the degradation of DAPK1 via the ubiquitin-proteosome system, called CJ1 [44]. This degrader had suitable properties for *in vivo* testing in rodent models, and was found to be BBB penetrant. The CJ1 degrader showed dose-dependent effects on tau pathology and synaptic degeneration in the AAV-hTau-P301L and hTau mouse models of tauopathy. CJ1 reduced levels of hyperphosphorylated tau, with preferential effects at certain phosphorylation sites (T231 and S396) that are more strongly associated with DAPK1.
This team has also developed a first-in-class PROTAC degrader targeting DAPK1, with a DC_{50} of 0.1196 µM [25].

Regulation via miRNAs: DAPK1 is regulated by numerous mechanisms, including a host of miRNAs. These may allow for more fine-tuned, cell-type specific, and context-specific regulation. Consequently, numerous miRNAs have been identified in different conditions and model systems. miR-124 was found to be a negative regulator of DAPK1 in TBI patients [35], and a rodent model of ischemic stroke [45]. miR-151-3p and miR-130a-3p were identified as regulators of Aβ-induced DAPK1 expression [46; 47]. miR-26a-5p was identified as a regulator of DAPK1 in models and found to be reduced in Parkinson's patients [27]. Due to the complexity and potential redundancy of miRNAs in DAPK1 regulation, targeting a specific miRNA is unlikely to be a useful therapeutic strategy for modulating DAPK1 in a disease setting.

AOE4 interactions: Not established

Aging and related health concerns: DAPK1 inhibition may protect against ischemic heart damage. But, DAPK1 has mixed roles in cancer and immune responses, which could be protective or deleterious depending on the context.

Types of evidence:

- 1 pan review of the prognostic role of DAPK1 across cancers
- Numerous laboratory studies

Cardiovascular disease: POTENTIAL BENEFIT (preclinical)
DAPK1 has been implicated in pathologies associated with cardiovascular disease, including ischemic cardiac cell death, hypertension, and atherosclerosis. The evidence primarily comes from preclinical studies and is somewhat limited relative to the understanding of the contribution of DAPK1 in other conditions [1].

Myocardial infarction: DAPK1 is expressed in cardiac tissue, and similar to the brain, is highly induced in response to hypoxic/ischemic injury. Several preclinical studies have found that inhibiting the ischemia-related induction of DAPK1 is cardioprotective [1]. DAPK1 may act as a driver of ferroptosis, a form of cell death associated with iron overload in response to oxidative stress [48]. SOX4 was shown to induce DAPK1 [48], while RNF146 promotes the degradation of DAPK1 [49], leading to the promotion and attenuation of ischemia-related ferroptosis, respectively. IGF2BP2 has shown to interact with a non-coding RNA, circ-DAPK1, to regulate hypoxia-related ferroptosis in vascular endothelial cells [50]. Thus,

differential activity of factors regulating DAPK1 can influence cardiac outcomes following ischemic injury.

Hypertension: DAPK1 was shown to promote vascular contractability by regulating myosin light chain phosphorylation [51]. In a rat model of spontaneous hypertension and a mouse model of angiotensin-II-induced hypertension, inhibition of DAPK1 attenuated hypertension-induced organ damage [51].

Atherosclerosis: DAPK1 has been implicated in the pathology of atherosclerosis via the regulation of inflammatory responses in macrophages. A study assessing genes that may underlie polycystic ovary syndrome (PCOS)-related atherosclerosis identified DAPK1 as a potential candidate [52]. DAPK1 was associated with responses in a variety of immune cell types, including macrophages and T cells. DAPK1 expression was also upregulated in macrophages following stimulation with oxidized-LDL [52]. The long non-coding RNA DAPK1-IT was also shown to be upregulated in macrophage-derived foam cells, and is implicated in the regulation of atherogenic inflammatory responses in macrophages [53].

Cancer: MIXED/ DAPK1 EXPRESSION ASSOCIATED WITH PROGNOSIS
Aberrant expression of DAPK1 is a common feature of many cancers [54]. It has also been associated with clinical outcomes with respect to survival and response to immunotherapy [54]. DAPK1 can influence cancer initiation and progression via multiple mechanisms, including cell death, cell survival, cell cycle regulation, immune cell activation, cell motility and tumor metastasis [54]. DAPK1 is largely considered to act as a tumor suppressor, however, in certain contexts, it acts as an oncogene. The directionality of the effect is cancer type dependent, influenced by the overall signaling milieu.
High expression of DAPK1 has been associated with better survival and outcomes in bladder urothelial carcinoma (BLCA), pheochromocytoma and paraganglioma (PCPG), kidney renal clear cell carcinoma (KIRC), thymoma (THYM), brain lower grade glioma (LGG), and lung adenocarcinoma (LUAD) [54]. In contrast, high expression of DAPK1 has been associated with worse survival and outcomes in colon adenocarcinoma (COAD), skin cutaneous melanoma (SKCM), prostate adenocarcinoma (PRAD), lung squamous cell carcinoma (LUSC), and stomach adenocarcinoma (STAD) [54].

One of the key determinants of whether DAPK1 exerts pro-death or pro-survival effects is the presence or absence of the tumor suppressor p53. DAPK1 and p53 are part of a reciprocal feedback loop that promotes the tumor suppressive activity of p53 [55]. DAPK1 is upregulated by p53, which then serves to stabilize p53 by inhibiting a negative regulator of p53 (MDM2). However, when p53 is mutated, DAPK1 activity triggers cell growth and survival pathways rather than cell death pathways due to its interaction

with the mTOR/SK6 pathway [56]. The TSC1/TSC2 complex is a negative regulator of mTOR. DAPK1 phosphorylation of TCS2 disrupts the TCS1/TCS2 complex, releasing the inhibition of mTOR, leading to the activation of cell growth signaling [56]. As such, in p53-mutant cancers, DAPK1 activation is oncogenic, rather than tumor suppressing.

Another important determinant of the outcome of DAPK1 activation in cancer relates to its context dependent role in immune system activation. Depending on the overall milieu of inflammatory mediators, DAPK1 can induce immune cell activation or suppression. As such, DAPK1 expression level has been associated with responsiveness to immunotherapy, such as anti-PD-1 and anti-CTLA-4, in several types of cancer [54]. One mechanism by which DAPK1 mediates anticancer effects is by regulating the activation and infiltration of antitumor cytotoxic CD8+ T cells [57]. mTOR signaling serves as an important mediator of T cell activation and functionality in response to environmental cues. The interaction between DAPK1 and mTOR is one of the regulators of this process [57]. Both the kinase and death domains of DAPK1 were shown to be important for T cell activation and regulating the expression of the homing receptors CD62L and CCR7, such that DAPK1 deficiency reduced the activation and migration capacity of cytotoxic T cells [57]. Therefore, DAPK1 acts in concert with other environmental signals to shape the immunological landscape of tumors.

Both DAPK1 activators and inhibitors have been proposed as anti-cancer therapeutics, as they may each have utility in different types of cancers depending on the signaling milieu. To date, neither have advanced to clinical development.

Immune system: MIXED (preclinical)
The impact of DAPK1 on immune responses is context dependent, depending on the cell type and the milieu of other immune modulating signals in the environment. DAPK1 plays important roles in pathogen defense, in terms of initial immune cell activation and then restraining immune responses to prevent prolonged pathological inflammation.

DAPK1 is a regulator and effector of interferon and inflammasome-mediated anti-pathogen responses [58; 59]. Typically expressed at low levels under physiological conditions, DAPK1 is induced in response to viral infection [60]. The overexpression of DAPK1 was shown to enhance virus-induced activation of the interferon-stimulated response element (ISRE) and the IFN-β promoter [60]. In turn, the type 1 interferon, IFN-β, promotes the activation of DAPK1 by influencing its phosphorylation at Ser308. However, DAPK1-mediated NLRP3 inflammasome activation is stimulus dependent, influenced by the

particular sensors triggered by different pathogens [58]. Toll-like receptors (TLRs) are important membrane-bound sensors involved in the detection of viral pathogens. The requirement for DAPK1 in NLRP3 activation varies depending on the TLRs triggered by a given pathogen [58]. A similar disparity appears to also apply to the other (sterile) inflammatory triggers that also activate these sensors in different cell types. For example, some groups have found that DAPK1 deficiency exacerbated inflammation in the intestine and lung [61; 62].

One group has found that DAPK1 signaling downstream of the type II interferon, IFN-γ, promotes a non-canonical form of autophagy called LC3-associated phagocytosis (LAP), which is a mechanism used in the clearance of fungal pathogens [58]. In addition to facilitating pathogen clearance, DAPK1 also suppressed NLRP3 activation in the lung to protect against a runaway inflammatory response in mice. This appears to be a translationally important mechanism, since DAPK1 genetic variation was found to influence susceptibility to fungal (Aspergillosis) infections in hematopoietic transplanted patients [58]. The DAPK1 rs1964911 SNP C/C genotype, in particular, was found to be associated with an increased incidence of fungal infection. Functional studies indicate that this genotype results in reduced DAPK1 induction coupled with enhanced inflammasome activation in peripheral blood cells [58].

DAPK1 also influences antiviral T cell responses through interactions with the mTOR pathway. DAPK1 has been shown to promote CD8+ T cell activation downstream of TCR and IL-2 via mTORC1 through its interaction with TSC2 [63]. In a mouse model, DAPK1 deficiency was associated with elevated viral titers coupled with a reduction in activated antiviral CD44+CD8+ T cells following viral infection (with the Armstrong strain of LCMV) [63].

In other contexts, DAPK1 can also restrain inflammatory responses by inhibiting T cell activation. DAPK1 has been reported to block T cell activation by preventing the activation of NF-κB signaling [64]. DAPK1 has also been shown to play a role in driving the immunosuppressive effects of mesenchymal stem cells (MSCs) [65]. DAPK1 can promote IL-10 mediated suppression of CD4+T cells by MSCs [65].

Overall, these studies indicate that DAPK1 influences stimulus-induced immune responses. Therefore, chronic inhibition could potentially influence susceptibility to pathogens and autoimmune conditions.

Safety: DAPK1 inhibitors have not reached clinical testing and limited safety information is available from preclinical animal studies. They could potentially impact susceptibility/immune responses to cancer and infection.

Types of evidence:

- Numerous laboratory studies

Due to the challenges in creating DAPK1 inhibitors with drug-like properties, the safety profile of DAPK1 inhibition is limited [51]. While some inhibitors have been tested acutely *in vivo* in animal models, the properties of these compounds have not allowed for comprehensive safety testing.

Most animal studies examining the impact of DAPK1 deficiency utilize genetic knockout of DAPK1. DAPK1 knockout mice are viable and generally do not exhibit overt phenotypes under basal conditions [51]. However, phenotypes do emerge under challenge conditions, such as an injury or infection. The downregulation of DAPK1 is associated with worse prognosis in many cancers, such that tumors that do occur may be more likely to progress [54]. While the DAPK1 deficient mice do not spontaneously develop tumors [11], some studies suggest that they have greater susceptibility to tumor growth [57]. Due to altered immune activation, DAPK1 knockout mice have been shown to have less productive immune responses to certain types of pathogens [58; 63]. In some cases, inflammatory responses were not properly contained in the absence of DAPK1, resulting in inflammatory tissue damage [58].
Due to potential compensatory responses stemming from lifelong DAPK1 deficiency, the genetic loss of DAPK1 may not be comparable to acute inhibition in specific disease contexts. DAPK1 inhibitors with properties suitable for chronic dosing in animal models will be needed to determine their potential safety profile.

The BBB penetrant hydrophobic tagging (HyT)-based degrader targeting DAPK1, CJ1, has undergone some preliminary safety testing [44]. It did not show evidence of cytotoxicity in primary neuronal cell culture. Hemolytic effects were not observed at doses up to 800 µg/mL. CJ1 was not associated with histological changes to major organs, or changes in serum markers of kidney and liver function in mice treated with the degrader at a dose of 20 mg/kg (i.p.) every other day for five weeks.

Drug interactions: Not established. DAPK1 interacts with numerous signaling pathways, thus inhibitors may have interactions with drugs which inhibit or activate signaling pathways that regulate or are regulated by DAPK1.

Sources and dosing:

Some DAPK1 inhibitors are available for research use, but these are primarily used in cell culture studies, as they have poor drug-like properties. DAPK1 inhibitors that would be suitable for clinical testing have not yet been developed.

Research underway:

DAPK1 inhibitors are currently in early preclinical development by various groups.

Search terms:

Pubmed, Google: DAPK1

- Alzheimer's disease, neurodegeneration, cognition, cancer, cardiovascular disease, safety

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