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.

Prosaposin

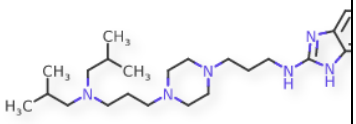
Evidence Summary

Targeting prosaposin may be a good neuroprotective therapeutic strategy to augment progranulin and lysosomal function, but more clinical data is needed, as early peptidomimetics had low clinical efficacy.

Neuroprotective Benefit: The stabilization or augmentation of prosaposin may help preserve lysosomal function, promote neurotrophic signaling, and enhance progranulin activity. Modulators may be most effective at very early stages.

Aging and related health concerns: Prosaposin may help maintain redox balance and cellular homeostasis during aging, but it is unclear how modulating it would influence the trajectory of aging. Peptidomimetics may marginally benefit neuropathy.

Safety: Limited clinical data suggests that short-term use of prosaposin stabilizers or peptidomimetics is safe. Longer term studies are needed.

Availability: In clinical trials and research use	**Dose**: Not established Prosaptide s.c. AZP2006 oral	**AZP2006** **Chemical formula:** $C_{25}H_{44}N_6$ **MW**: free base 428.67 g/mol  Source: Inxight Drugs
Half-life: AZP2006: >15 days Prosaptide: rapidly cleared	**BBB**: Prosaptide and AZP2006 are penetrant	
Clinical trials: Prosaptide was tested in Phase 2 trials for diabetic neuropathy (n=150) and HIV-related neuropathy (n=237). AZP2006 was tested in a Phase 1 trial (n=88) and is being tested in a Phase 2a trial for PSP (n=36).	**Observational studies**: Loss of prosaposin leads to lysosomal storage disorders. Levels of prosaposin can be prognostic markers for certain cancers.	

What is it?

Prosaposin is a regulator of lysosomal function and a neurotrophic factor. It is a glycoprotein which serves as a precursor to saposins (sphingolipid activator proteins) [1]. Prosaposin is trafficked to the lysosome, where it is cleaved by lysosomal enzymes, including cathepsin-D, to produce four saposins, A, B, C, and D. The saposins serve as activators for specific lysosomal hydrolases by making their lipid substrates bioavailable. More specifically, the saposins extract sphingolipids from the lysosomal membrane so that they can be used as substrates by the hydrolases. The different saposins act in a non-redundant fashion. Because each saposin acts on a different sphingolipid, the loss of one cannot be compensated by the others. The loss of saposin activity leads to lysosomal storage disorders. Prosaposin, and some of the saposins, are involved in the trafficking of other proteins within cellular compartments, and possibly between cells. Prosaposin can also be secreted from the cell, which may facilitate its role in shuttling components between cells. Secreted prosaposin can also interact with G-protein receptors on the cell surface to initiate intracellular signaling cascades, such as those involved in cell survival. Prosaposin has garnered attention as a therapeutic target due to its roles as a neurotrophic factor and as an interacting partner for progranulin, an immunomodulator and neurotrophic factor.

Prosaptides, which are prosaposin derivatives harboring only the neurotrophic region were clinically tested in neuropathy. Prosaptide™ is a 14-mer peptide based on the neuroactive region of prosaposin (saposin C1-5) that was being developed by Savient Pharmaceuticals, which acquired it from Myelos

Corporation, however, clinical development was terminated after lackluster efficacy in Phase 2 trials (Press release).

AZP2006 (INN: Ezeprogind) is an orally available small molecule which targets prosaposin to improve the stability of its interaction with progranulin [2]. It has a higher affinity for the prosaposin-progranulin complex (Kd = 201 nM) than toward prosaposin alone (Kd = 624 nM), thus it is expected to act more as a progranulin-modulating therapeutic than a prosaposin-modulating one. It is being developed by Alzprotect, and is currently being tested in a clinical trial for Progressive supranuclear palsy.

Neuroprotective Benefit: The stabilization or augmentation of prosaposin may help preserve lysosomal function, promote neurotrophic signaling, and enhance progranulin activity. Modulators may be most effective at very early stages.

Types of evidence:

- 3 studies of prosaposin in postmortem AD brain tissue
- Numerous laboratory studies

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

Mutations in prosaposin have been reported in cases of lysosomal storage disorders with neurological impairments [1]. Prosaposin is cleaved into four saposin proteins, A, B, C, and D. The saposins are involved in the abstraction of substrate lipids from the lysosomal membrane for hydrolysis by specific hydrolase enzymes. Due to hydrolase specificity, the different saposins cannot compensate for one another, thus the loss of each of the saposins leads to a different lysosomal storage disorder. In general, the target membrane lipids are sphingolipids, thus saposin deficiencies lead to the accumulation of lysosomal sphingolipids. Mutations in saposin C lead to atypical Gaucher's disease because saposin C is an essential activator of glucocerebrosidase [3]. Mutations in saposin A lead to a clinical presentation of Krabbe's disease, due to the accumulation of galactosylceramide [4]. Saposin B deficiencies lead to a Metachromatic leukodystrophy-like disorder characterized by elevated sulfatide [5]. Thus, prosaposin deficiency can result in the pathological accumulation of sphingolipids. Alterations in sphingolipid metabolism/the balance of sphingolipids are a common feature of many neurodegenerative diseases, including Alzheimer's disease (AD) [6]. There is evidence to suggest that the localization and function of

prosaposin is altered in AD and other dementias [7], though to date there is a lack of causal evidence linking changes in sphingolipids with changes in prosaposin in late life neurogenerative diseases.

Human research to suggest benefits to patients with dementia:

AZP2006, a small molecule targeting prosaposin, is currently being tested in a Phase 2a study in patients with Progressive supranuclear palsy (PSP) (NCT04008355). However, the study is primarily designed to test safety and pharmacokinetics, but exploratory biomarker outcomes may provide some preliminary evidence regarding its effects on disease progression.

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

Progranulin modulator: Progranulin is a secreted growth factor with neurotrophic properties. It is trafficked to the lysosome where it is cleaved into granulin peptides [8]. Mutations that reduce progranulin levels or function are a genetic cause of frontotemporal dementia (FTD). Reductions in progranulin levels/function have also been implicated in AD [9]. Augmentation of progranulin has been proposed as a therapeutic strategy for neurodegenerative disease [10]. One potential mechanism is via modulation of prosaposin, which plays a role in the trafficking and regulation of progranulin. In a genome-wide association study (GWAS)-biomarker study (n=920), the prosaposin locus was associated with plasma levels of progranulin [11]. In one cohort, the presence of each copy of the minor T allele in the rs1867977 single nucleotide polymorphism (SNP) was associated with a 0.28 standard deviation decrease in plasma progranulin levels. Similar results were seen in two validation cohorts, in which each copy was associated with a 0.21 and a 0.10 standard deviation decrease, respectively. Both loss and overexpression of prosaposin can lead to an increase in extracellular levels of progranulin. This is likely due to the physical interaction between progranulin and prosaposin, which influences their localization [12; 13]. The trafficking of progranulin to the lysosome occurs via two independent pathways in neurons. One involves an interaction with sortilin, while the other involves an interaction with prosaposin. There may be additional, yet to be identified, pathways that control progranulin trafficking in microglia [14]. In prosaposin deficient fibroblasts, progranulin accumulated in the endoplasmic reticulum (ER), resulting in increased sorting to secretary pathways, and leading to the elevated serum progranulin levels in prosaposin deficient mice [13]. Together these studies suggest that prosaposin is important for the lysosomal functions of progranulin.

AZP2006 is an orally available small molecule in clinical development for neurodegenerative diseases which augments the functional half-life of progranulin in the brain via stabilizing its interaction with prosaposin [2].

Lysosomal function: Prosaposin is important for proper lysosomal function. It acts as part of an intra-lysosomal network in conjunction with progranulin and pro-cathepsin D [15]. Prosaposin facilitates the trafficking of progranulin to the lysosome. Under conditions of cell stress, there is increased interaction between progranulin and prosaposin, in order to facilitate their transport to the lysosome. Thus, the augmentation or stabilization of this interaction may be therapeutically beneficial in the context of neurodegenerative diseases where there are increased levels of misfolded proteins and other cellular debris. Progranulin is important for the conversion of pro-cathepsin to active cathepsin D, which then cleaves prosaposin into its saposins, which facilitate the activity of specific sphingolipid lysosomal hydrolases. Loss of saposin activity leads to the pathological accumulation of lysosomal sphingolipids. Disruption to this network can impact the degradation of alpha-synuclein and may increase the risk for Parkinson's disease, and other neurodegenerative diseases.

Neuronal survival: Like progranulin, prosaposin can also be secreted in response to injury and exert neurotrophic properties. Blocking the interaction of these proteins with sortilin, results in secretion, rather than lysosomal targeting [16]. The neurotrophic effects of prosaposin are primarily mediated by G-protein signaling via the G-protein coupled receptors (GPCRs), GPR37 and GPR37L [17]. In response to cell stressors, such as oxidative stress, activation of these GPCRs with prosaposin promotes pro-survival signaling in neurons and glia, in cell culture. The neurotrophic region of prosaposin has been identified, and these peptides were demonstrated to have neuroprotective properties in preclinical models. An 18-mer peptide (LSELIINNATEELLIKGL) derived from the saposin C region of prosaposin protected against Aβ42-mediated neurotoxicity when injected subcutaneously 24 hours after an intracerebroventricular injection of Aβ42 in male mice [18]. The 18-mer peptide also reduced kainic acid-induced neurotoxicity in the hippocampus and cortex of male rats [19], and enhanced the survival of dopaminergic neurons in the MPTP model of Parkinson's disease in male mice [20]. Additionally, intracerebroventricular infusion of the peptide mitigated hippocampal neuronal loss in response to a transient global cerebral ischemic injury in male gerbils [21].
The unmodified peptides have low stability, so retro-inversion peptides were developed in which the primary sequence is reversed and the l-amino acids are replaced with d-amino acids, which have increased bioactivity relative to the native peptides [22]. For example, prosaptide D4 was found to be stable in the serum and brain with no degradation within 60 minutes of i.v. administration, while only

30% and 0% of prosaptide TX14(A) were detectable within 60 minutes of i.v. administration in the serum and brain, respectively. However, prosaptide D4's therapeutic utility may be low due to its 10-fold lower diffusion rate across the BBB. Prosaptide D5 (all D-isomer, LLEETANN DLL), which has sub nanomolar potency and is BBB penetrant, reduced infarct size when administered intramuscularly 3 or 6 hours after middle cerebral artery occlusion in male rats [23]. Similarly, prosaptide D5, administered subcutaneously, dose dependently reduced MPTP-induced dopaminergic neuron loss in male mice [24]. Its pro-survival effects likely involves both its lysosomal and neurotrophic properties. The loss of prosaposin in cultured human neurons, sensitizes the cells to oxidative stress and ferroptosis, suggesting it plays a role in redox homeostasis [25]. Notably, the loss of prosaposin did not affect cell survival under normal conditions, but led to rapid cell death when the cells were cultured in media lacking antioxidants. Additionally, prosaposin may protect cells through the maintenance of membrane lipid homeostasis. The loss of prosaposin was shown to impact the expression of cholesterol biosynthesis genes in human neurons [25], and altered cholesterol homeostasis in neurons has been implicated in AD [26].

Alzheimer's disease: POTENTIAL BENEFIT AT EARLY STAGES (Preclinical)
The abundance and localization of prosaposin has been shown to be altered in postmortem brain tissue from individuals with AD. The levels of neuronal prosaposin and progranulin decreases with the progression of neurofibrillary tangle pathology [7]. Additionally, the interaction between prosaposin and progranulin within neurons decreases. This may be related to a shift toward increased secretion, as evidenced by a shift in the localization of these proteins to extracellular Aβ plaques [27]. It may also involve an increase in lysosomal membrane leakage. In early stages of disease, lysosomes were found to be enriched in saposins, but deficient in hydrolases [28]. The enrichment of saposin C may activate lysosomal membrane permeabilization, resulting in the loss of lysosomal hydrolases, such as cathepsins. These dysfunctional lysosomes may then promote the accumulation of amyloid. This suggests that there is a disruption to the progranulin, prosaposin, pro-cathepsin network in lysosomes. Evidence from post-mortem brain tissue suggests that it may be precipitated by the loss of neuronal progranulin [7].

AZP2006 has been shown to be neuroprotective in *in vitro* and *in vivo* preclinical AD models [1]. It improved neuronal survival and synaptic integrity in cultured neurons exposed to Aβ42 and promoted the release of progranulin. Orally administered AZP2006 mitigated Aβ42 (intracerebroventricular)-induced short-term memory deficits in mice when administered at the start of the Aβ42 challenge. In the SAMP8 model, chronic administration of AZP2006 in the drinking water (3 mg/kg) prevented cognitive decline and mitigated AD pathology at 10 months of age when administered prior to the onset

of cognitive deficits (2 or 4 months of age) but had a more modest impact when administered later (starting at 6 months of age). This suggests that AZP2006, and other prosaposin-interacting therapeutics may be most beneficial at early/preclinical stages when the neuroprotective pathways impacted by progranulin and prosaposin are still intact and responsive to augmentation.

APOE4 interactions: Not established

Aging and related health concerns: Prosaposin may help maintain redox balance and cellular homeostasis during aging, but it is unclear how modulating it would influence the trajectory of aging. Peptidomimetics may marginally benefit neuropathy.

Types of evidence:

- 2 clinical trials for Prosaptide
- 5 observational studies on prosaposin levels in cancer
- Numerous laboratory studies

Lifespan: UNCLEAR

The impact of prosaposin on lifespan is not clear, but there is evidence to suggest that it may play a role in the maintenance of redox balance during aging. Prosaposin has been identified as a regulator of cellular coenzyme Q10 levels and may be important for the delivery of coenzyme Q10 to mitochondrial membranes [29]. The serum of centenarians is indicative of increased levels of oxidative stress. While serum coenzyme Q10 levels began to decline after age 76, prosaposin levels continued to progress with age, in this study. The elevation of serum prosaposin in centenarians may be a compensatory measure towards the reduction in coenzyme Q10. The impact of prosaposin on the mitigation of oxidative stress during aging is still unclear.

In *C. elegans*, an ortholog of prosaposin was identified as a regulator of mitochondrial function and longevity [30]. The nuclear transcription factor NFYB-1 was found to be important for the maintenance of mitochondrial cardiolipin levels, and its loss reduced lifespan. NFYB-1 acts as a repressor of the prosaposin ortholog, which suggests that elevated prosaposin may not be beneficial for longevity. However, it is unclear whether this specific interaction is relevant in mammals. Additionally, prosaposin shows a tendency to act as part of cellular homeostasis maintenance networks. Thus, it is likely that dysregulation of these networks, rather than specific changes to prosaposin per se, promotes aging.

Neuropathy: NO CLINICAL BENEFIT FOR TESTED PROSAPTIDE

Prosaptides were clinically tested for neuropathy, though clinical development has been discontinued. Prosaptide™ was tested in a placebo-controlled Phase 2 RCT in patients with diabetic neuropathy (n=150). It was self-administered subcutaneously at a dose of 1, 4, or 16 mg per day for 28 days. Although the results were not formally published, a separate study indicated that a significant reduction of pain was noted in the 4 mg arm, but that the efficacy may have been attenuated in severe neuropathies [31]. Prosaptide™ was subsequently tested in a double-blind placebo-controlled Phase 2 RCT (NCT00286377) in HIV-related sensory neuropathy (n=237) at a dose of 2, 4, 8, or 16 mg/day subcutaneously, in conjunction with their usual antiretroviral medication for six weeks [31]. Patients recorded pain using an electronic diary. A reduction in pain was seen in all arms, with no significant differences across arms, and the study was terminated early following a futility analysis.

In contrast, prosaptides showed benefit in a variety of preclinical pain models [16]. The discrepancy is likely related to the timing of administration relative to the nerve injury, as prosaptide appears to be most beneficial in reducing damage and enhancing repair shortly after the onset of nerve damage.

Prosaposin has been shown to promote cell survival and enhance myelination. The transport of membrane lipids needed for cell repair may also be a mechanism by which it promotes recovery. In female rats, prosaptide TX14(A) attenuated the loss of muscle mass following sciatic nerve injury by promoting myoblast fusion when given one day following the injury [32]. The administration of prosaptide counteracted the loss of endogenous prosaposin expression in the muscle following the injury. Similarly, in diabetic (streptozotocin-induced) female rats, treatment with prosaptide TX14(A) attenuated muscle denervation atrophy when administered immediately following sciatic nerve injury, but did not enhance functional (toe-spread) recovery [33].

Cancer: PROSAPOSIN LEVELS MAY SERVE AS A PROGNOSTIC MARKER

Prosaposin has been shown to promote mechanisms of cell survival [34], and is upregulated following the induction of cellular senescence [35]. While in most cases, high levels of prosaposin are associated with more aggressive tumors, prosaposin has multiple functions and can interact with several receptors, thus its effects can be dependent on the composition of the tumor environment.

Prostate cancer: Prosaposin is highly expressed in the reproductive system. Prosaposin has been shown to be overexpressed in a variety of metastatic prostate cancer cell lines, and high tissue expression is inversely associated with clinical stage [36]. Serum prosaposin levels were found to be significantly decreased in primary organ-confined prostate cancer, but increased in those with metastatic castrate-resistant prostate cancer.

Pancreatic cancer: Prosaposin has been shown to be highly expressed in various pancreatic cancer cell lines [37]. Rather than affect the proliferation capacity of the tumor cells, it appears to play a role in the modulation of the tumor microenvironment. High levels of prosaposin were associated with poor prognosis, as indicated by worse survival and higher rates of metastasis in pancreatic cancer. This appears to be driven by an effect on CD8+ T cells, such that higher prosaposin levels leads to lower levels of tumor-infiltrating CD8+ T cells.
Glioblastoma: Prosaposin acts as a neurotrophic and gliotrophic factor [17]. High expression in glioma promotes tumor growth [38]. Prosaposin shows a strong association with the mesenchymal subtype of glioma, as it is most highly expressed in this subtype.
Breast cancer: Prosaposin was found to promote the proliferation and survival of mammary tumors, and high levels were associated with poor prognosis in stage 1 breast cancer patients [39]. Prosaposin was also identified as a mediator of tamoxifen resistance in a functional screen [40]. High levels of prosaposin were associated with shorter progression-free survival.
Ovarian cancer: In a patient-derived tumor xenograft (PDX) model of metastatic ovarian cancer mouse model, treatment with the d1,3 prosaposin peptide (40 mg/kg) reduced tumor size by about half and had an anti-angiogenic effect [41]. The tumor regression may have been driven by the stimulation of the anti-tumor proteins p53 and thrombospondin-1. In the context of ovarian cancer, metastatic tumors had less prosaposin expression than primary tumors.

Atherosclerosis: ENDOGENOUS PROSAPOSIN MAY PLAY A ROLE (Preclinical)
Prosaposin may play a role in the priming of inflammatory macrophage activity in the context of atherosclerosis. In mouse models and human tissue, prosaposin expression was elevated in pro-atherosclerotic macrophages primed with oxidized low-density lipoprotein (oxLDL) [42]. The effect is driven by the role of prosaposin in immune cells. Saposins play an important role in immune cell priming by mobilizing membrane lipids for antigen presentation and activating CD1 on T cells. Since the prosaposin-targeted therapeutics developed thus far are focused on its interaction with progranulin and/or neurotrophic properties, it is unclear whether they would have any impact on this process.

Safety: Limited clinical data suggests that short-term use of prosaposin stabilizers or peptidomimetics is safe. Longer term studies are needed.

Types of evidence:

- 5 clinical trials (4 for prosaptide and 1 for AZP2006)

There is limited published data regarding the safety of prosaposin-targeting/mimicking therapeutics, but the available data is suggestive of a good safety profile.
Prosaptide™: In two Phase 1 clinical trials, subcutaneous injections up to 300 ug/kg were found to be safe in healthy controls, with no accumulation after repeated dosing [31]. In a Phase 2 trial in diabetic neuropathy, it was reported that similar treatment emergent adverse events were seen across placebo and prosaptide treatment arms, at all tested doses (up to 16 mg/day, subcutaneous). Additionally, no participants developed anti-prosaptide antibodies. In the Phase 2 RCT in HIV-related sensory neuropathy (n=237), there were no differences in the frequency of adverse events or laboratory toxicities between treatment and placebo groups with doses up to 16 mg/day (subcutaneous). The strong safety profile is consistent with prosaptide's short half-life and rapid clearance.

AZP2006: The company has reported that in Phase 1 testing in 88 healthy volunteers, orally administered AZP2006 at single doses from 3 to 500 mg, or multiple doses of 30, 60, or 120 mg daily for 10 days showed a good safety profile (alzforum).

Drug interactions: Not established

Sources and dosing:

AZP2006 is being developed by Alzprotect, and it is in clinical development for PSP. A therapeutic dose has not yet been established. Prosaptide [TX14(A)] is no longer in clinical development, but is available for research use from commercial suppliers.

Research underway:

AZP2006 is currently being tested in a Phase 2a RCT in Progressive supranuclear palsy (NCT04008355). The trial is expected to be completed in 2022.

Search terms:

Pubmed, Google: Prosaposin

- Alzheimer's disease, Parkinson's disease, neurodengeration, aging, lifespan, cancer, cardiovascular, neuropathic pain, clinical trial, safety

Websites visited for Prosaposin:

- Clinicaltrials.gov
- NIH Inxight Drugs

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