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.

NPTX2 Modulator

Evidence Summary
NPTX2 levels serve as a biomarker associated with cognitive decline and prognosis in several cancers, but it has yet to be established whether modulation is therapeutically beneficial.

**Neuroprotective Benefit:** Decreased NPTX2 levels are associated with cognitive decline, likely indicative of synapse loss. NPTX2 plays an important role in maintaining synaptic plasticity and inhibitory-excitatory balance in the CNS.

**Aging and related health concerns:** NPTX2 becomes increasingly repressed with age, and its dysregulation is associated with worse prognosis in a variety of cancers.

**Safety:** No safety data is currently available for NPTX2 modulation, but it is known to have context dependent effects, and may influence cancer progression.
What is it?

Neuronal pentraxin 2 (NPTX2), also known as Narp, is an immediate early gene, which is rapidly transcribed in response to neuronal activity [1]. It plays a critical role in synaptic plasticity, particularly in preventing hyperexcitability by restoring inhibitory-excitatory circuit balance. It is widely expressed in the brain, but it is also expressed in other organ systems throughout the body. All of its functions have not yet been fully characterized, and NPTX2 has primarily been utilized as a biomarker for neurodegenerative diseases and cancer. It is not yet clear whether the changes in NPTX2 levels drive disease processes or are a byproduct of them.

Neuroprotective Benefit: Decreased NPTX2 levels are associated with cognitive decline, likely indicative of synapse loss. NPTX2 plays an important role in maintaining synaptic plasticity and inhibitory-excitatory balance in the CNS.

Types of evidence:
- 2 meta-analyses (of biomarker studies assessing NPTX2 expression in schizophrenia)
- 13 biomarker observational studies (NPTX2 expression in AD, PD, chronic headache)
- Several laboratory studies (for basic biology of NPTX2, none for modulators)

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
There is currently no research indicating whether the modulation of NPTX2 can prevent or slow cognitive decline, but there is evidence from biomarker studies that downregulation of NPTX2 is
associated with cognitive decline in several neurodegenerative diseases. It is not yet known whether the changes in NPTX2 are causal or correlative in the context of cognitive decline.

**Alzheimer’s disease: NPTX2 LEVELS REDUCED**

Studies examining both postmortem brain tissue and cerebrospinal fluid (CSF) from Alzheimer’s disease (AD) patients have found a **dramatic decrease in NPTX2 levels**, which is associated with cognitive decline.

**Postmortem tissue:** In a cohort study (Baltimore Longitudinal Study of Aging cohort) assessing differentially expressed proteins in the postmortem frontal cortex (medial frontal gyrus) between AD and controls 45 significantly differentially expressed synaptic proteins were identified, including NPTX2, which was downregulated 3.3-fold in the AD brain [2]. Another study found that NPTX2 was downregulated in all cortical regions. There may be some regional variability since a separate study using samples from frontal cortex did not find an overall significant difference in NPTX2 levels, but did find an inverse correlation between NPTX2 and plaque load (r = −0.46, p = 0.01) [3]. The change in NPTX2 appears to be more closely associated with changes in cognition compared to the presence of AD-related pathology. While reduced in patients with clinical AD, NPTX2 was not reduced in people with asymptomatic or pre-AD, who had evidence of AD pathology in the brain, but were cognitively normal [4].

**CSF:** Relative to controls (mean level 1067 pg/ml), CSF levels of NPTX2 have been found to be reduced in both AD (mean level 296 pg/ml) and mild cognitive impairment (MCI) patients [4]. In this cohort, NPTX2 levels were associated with hippocampal atrophy (r=0.438, p=0.015), and measures of cognitive performance including the Dementia Rating Scale (r=0.467, p=0.009), the Digit Symbol Substitution test (r=0.446, p=0.029), the Wisconsin Card Sorting test (r=0.445, p=0.038), the Semantic Verbal Fluency test (r=0.385, p=0.043), the Visual Reproduction task (r=0.432, p=0.035), and the California Verbal Learning test (r=0.520, p=0.019).

In the BICARD study cohort, a 0.5-fold change in CSF levels of NPTX2 was measured in AD patients, and the change in NPTX2 in combination with changes in levels of PKM (pyruvate kinase) or with YWHAG (14-3-3 protein gamma) offered the best discrimination between AD and controls with area under the curve (AUCs) of 0.935 and 0.933, respectively [5]. In a separate study involving the BIOCARD cohort, higher CSF levels of NPTX2 were associated with greater functional connectivity in the salience/ventral attention network, which is related to better performance on a composite measure of executive
function [6]. Low levels of NPTX2 were associated with higher likelihood of MCI amongst individuals with low cognitive reserve scores (Odds ratio (OR): 3.11, 95% Confidence Interval (CI) 1.07 to 9.01, P= 0.037). NPTX2 was identified as the top candidate in a study seeking to identify biomarkers connected to inflammation that were predictive of AD [7]. Higher CSF levels of NPTX2 were associated with higher MMSE (β =1.24±0.22, P<.001), lower CDR-sum of boxes (β=−0.81±0.15, P<.001) and lower ADAScog-11 (β±SE=−3.34±0.54, P<.001), such that high NPTX2 was indicative of less memory decline (R²=0.560, P<.001). Higher NPTX2 was also associated with less brain (medial temporal lobe) atrophy (R²= 0.287, P<.001), likely because the loss of neurons will result in a loss of neuron-associated NPTX2.

A study comparing controls, MCI, and AD found that the decline in NPTX2 (low NPTX2 hazard ratio HR: 2.01, 95% CI 1.22 to 3.33) was a better predictor of the transition from MCI to AD than neurofilament light (Nfl) (low Nfl HR: 0.92, 95% CI 0.58 to 1.54) [8]. The combination of decreased CSF NPTX2 plus increased tau offered the best discrimination between AD and controls (AUC: 0.937, 95% CI 0.888 to 0.986). Consistent with the other studies, the biomarker of NPTX2/tau correlated with measures of cognition (CVLT immediate, CVLT delay, MDRS, CDR-sum of boxes) in AD and MCI patients.

**Exosomes:** NPTX2 has been identified and quantified in plasma neuron-derived exosomes. Compared to age-matched controls, the levels of NPTX2 were decreased in AD exosomes (Control 2656 ± 343 vs AD 1250 ± 123 pg/ml) [9]. The levels of associated synaptic proteins NRXN2α, AMPA4, and NLGN1, were also decreased, and the decline in these four synaptic proteins correlated with cognitive loss.

**Frontotemporal dementia:** CSF NPTX2 LEVELS DECREASED

CSF levels of NPTX2 were characterized in the GENFI cohort of frontotemporal dementia (FTD) patients consisting of 106 pre-symptomatic and 54 symptomatic carriers GRN, C9orf72 or MAPT mutations, along with 70 healthy non-carriers [10]. The study found that symptomatic carriers (median 643 pg/mL, Interquartile range IQR 301 to 872) had lower CSF levels of NPTX2 than pre-symptomatic carriers (1003 pg/mL IQR 624 to 1358), or non-carriers (990 pg/mL IQR 597 to 1373). NPTX2 levels could distinguish symptomatic from pre-symptomatic mutation carriers with an AUC of 0.71 (95% CI 0.63 to 0.80), using an optimal cut-off of 895 pg/mL (sensitivity 82%, specificity 56%). NPTX2 levels correlated with several clinical disease severity measures, and grey matter volume, and inversely correlated with Nfl. NPTX2 decreased around symptom onset, and levels were predictive of decline in phonemic verbal fluency and the Clinical Dementia Rating scale plus FTD module in a longitudinal sub-cohort.
**Dementia with Lewy bodies:** CSF NPTX2 LEVELS DECREASED

NPTX2 was identified as a candidate biomarker for Dementia with Lewy bodies (DLB). CSF levels of NPTX2 were reduced in DLB in comparison with controls, as well as in relation to other neurodegenerative diseases, including AD and Parkinson’s disease, and the decrease was associated with cognitive decline, based on the MMSE [11]. Although an effective biomarker, this study found that the combination of VGF, SCG2 and PDYN was optimal for differentiating DLB with other clinical groups.

*Human research to suggest benefits to patients with dementia:* None

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

**Synaptic maintenance:** NPTX2 is an activity dependent synaptogenic immediate early gene [12]. It is best understood for its role in excitatory synapse formation, particularly through the clustering and activation of glutamatergic AMPA receptors, and is an important mediator of both developmental and adult synaptic plasticity [13]. It typically binds to its receptor NPTXR to function as a trans-synaptic organizer of synapses [14]. NPTX2 is a Ca²⁺ dependent lectin released from presynaptic terminals and then binds the glycoprotein network surrounding synapses [4]. The synaptic accumulation of NPTX2 is dependent on the integrity of the perisynaptic extracellular network [15]. On parvalbumin interneurons, it binds GluA4 subunit containing AMPA receptors [13], and GluA4 subunit levels tend to be associated with NPTX2 levels to an increasing degree during aging [4]. NPTX2 binding also enhances GluA1 function. Neuronal pentraxins, such as NPTX2, mediate cell adhesion, which trap AMPA receptors on the neuronal cell surface at synaptic sites, and can activate signaling cascades that organize postsynaptic specializations [14]. Therefore, the loss of NPTX2/NPTXR activity can negatively impact synaptogenesis and synaptic maintenance. NPTX2 is also bidirectionally regulated by brain derived neurotrophic factor (BDNF), and NPTX2 mediates BDNF-induced synaptic plasticity [16]. The Val66Met single nucleotide polymorphism (SNP), which leads to reduced BDNF levels, also reduces NPTX2 expression [16]. NPTX2 expression in the brain declines with age, and may contribute to age-related cognitive dysfunction.

**Inhibitory-excitatory circuit balance:** Neuronal pentraxins play essential roles in controlling hippocampal network properties [13]. Mice lacking NPTX2/NPTXR have reduced feedforward inhibition, leading to altered rhythms and a propensity towards epilepsy [13]. NPTX2 is required for the homeostatic scaling of excitatory synapses on some subtypes (parvalbumin) of inhibitory interneurons [17]. Homeostatic scaling is the capacity of neurons to maintain synaptic activity within a dynamic range, such as by using negative feedback when activity is chronically elevated. In essence, NPTX2 strengthens
inhibitory circuits in order to control cortical excitability. Consequently, NPTX2 is implicated in a variety of neurological disorders involving an inhibitory-excitatory imbalance, including AD. A meta-analysis of NPTX2 expression in brain tissue found that it was significantly decreased in individuals with schizophrenia [18]. This finding could not be replicated in blood samples, but this may represent a lack of correlation between the blood and brain samples in these individuals [19]. Altered epigenetic modification (methylation) of NPTX2 was also found in women with chronic headache [20]. In mice, loss of NPTX2 altered hippocampal neuronal activity in response to stress, and led to increased anxiety-like behaviors [21]. These findings suggest that the decline of NPTX2 levels in AD may also contribute to some of the non-cognitive symptoms, such as agitation.

Inflammation: Pentraxins play a role in innate immunity and acute inflammatory responses. Neuronal pentraxins can act as concentration dependent pro- or anti-inflammatory cytokines, such that the specific inflammatory effects are context dependent [22]. Therefore, elevated or reduced NPTX2 could have negative impacts in different contexts. The long form pentraxins, which includes NPTX2, are hypothesized to act in a similar manner to acute phase proteins by activating the complement system and binding and clearing extracellular debris. This is projected to contribute to pentraxin’s modulation of synaptic plasticity by refining synaptic sites [7]. For example, NPTX2 can facilitate synapse formation by clearing extracellular debris to anchor AMPA receptors.

Parkinson's disease: NPTX2 LEVELS ELEVATED
Whole genome expression analysis of postmortem brain tissue revealed that NPTX2 is the most highly upregulated gene (>800%) in the substantia nigra in Parkinson's disease (PD) [23], and has been confirmed in a separate study [24]. It is associated with alpha synuclein aggregates in the substantia nigra and cortex [23]. The upregulation of NPTX2 is thought to exacerbate disease in the context of PD, based on preclinical models where the increase in NPTX2 reduces diminished dopaminergic neuron viability, and enhanced autophagy of dopaminergic neurons. In the MPTP model, increased NPTX2 resulted in increased dopaminergic neuron autophagy [25]. The increase in NPTX2 in this model was attributed to the inhibition of the miRNA miR-221-3p, which normally represses NPTX2. In the 6-OHD mouse model of PD, NPTX2 was found to be the gene most significantly associated with L-DOPA induced dyskinesia [26]. The massive increase in NPTX2 may lead to excessive synaptic remodeling, the induction of inflammatory pathways, and ultimately cell death.

APOE4 interactions: Unclear
One study examining the ability of CSF NPTX2 to serve as a biomarker for AD and cognitive decline found that higher levels of NPTX2 were related to less amyloid pathology for non-APOE4 carriers, but not for APOE4 carriers [7]. In a separate study, the association between NPTX2 and functional connectivity was not modified by ApoE4 status [6].

**Aging and related health concerns:** NPTX2 becomes increasingly repressed with age, and its dysregulation is associated with worse prognosis in a variety of cancers.

**Types of evidence:**
- 18 Biomarker observational studies (NPTX2 methylation or expression in aging or cancer)
- Several laboratory studies (for basic biology of NPTX2, one in cancer for an inhibitor)

**Aging: METHYLATION OF NPTX2 INCREASES WITH AGE**

NPTX2 has been identified as a gene where the methylation status of its promoter changes in an age-dependent manner. The promoter becomes increasingly hypermethylated with age, which is indicative of a decrease in gene expression. The DNA methylation pattern of NPTX2 has been used in combination with other genes to establish epigenetic age estimators, primarily for use in forensic science. In the blood (n=23) and saliva (n=44) of participants ranging in age from 5 to 72, a regression model for NPTX2 methylation changes found a modest correlation between predicted and chronological age ($R^2 = 0.654$), with an average difference of 9.2 years [27].

An epigenetic signature of aging was identified from differential methylation of (27,578) CpG islands using datasets from tissues throughout the body [28]. Nineteen CpG sites were found to be consistently hypermethylated with aging. The combination of hypermethylated sites in NPTX2, TRIM58, GRIA2 and KCNQ1DN along with a hypomethylated CpG site in BIRC4BP were incorporated into a model which had a difference between predicted and actual age of about 11 years. In the blood of females (n=80, age range 18 to 91), the changes in methylation (of CpG islands) of the genes NPTX2, KCNQ1DN, GRIA2, and TRIM58 resulted in an approximately 11-year difference between predicted and real age, with 7.2 years error absolute mean differences [29]. The NPTX2 CpG island used in this study was located on chromosome 7: 98245805–98247759.

The methylation of CpG sites in the promoters of the EDARADD ($r = 0.96$), TOM1L1 ($r = 0.90$), and NPTX2 ($r = 0.92$), were found to be linear with age over a range of five decades based on saliva samples in a study of 34 male identical twin pairs (aged 21 to 55) that was validated in a cohort of 31 males and 29 females (aged 18 to 70) [30]. A regression model using these genes explained 73% of the variance in age, and predicted the age with an average accuracy of 5.2 years.
In blood samples from an ethnically Chinese Han population, CpG islands in ASPA, (chr17: 3326318) ITGA2B (chr17: 39823253; chr17: 39823255) and NPTX2 (chr7: 98083772; chr7: 98083770) were identified as age-related biomarkers [31]. A regression model using ASPA, both sites in ITGA2B and one site in NPTX2 (chr7: 98083770) explained 82% of variation in age (adjusted $R^2 = 0.819$), and the mean absolute difference from chronological age was 7.870 years.

**Cancer: Cancer Type Dependent Effects**

The role of NPTX2 in cancer is cancer type dependent. In some cancers, NPTX2 acts as a tumor suppressor, and hypermethylation of the NPTX2 promoter is associated with worse prognosis, while in other cancers NPTX2 is oncogenic, and overexpression results in worse outcome. Part of the discrepancy may depend on whether NPTX2 and its receptor NPTXR are normally expressed in a given tissue type. Ectopic expression of NPTX2 may result in interactions with alternative receptors.

**Pancreatic Cancer: Methylated NPTX2 Associated with Worse Outcome**

NPTX2 acts as a tumor suppressor in pancreatic cancer by reducing migration while promoting cell cycle arrest and cell death [32]. While the promoter of NPTX2 is largely unmethylated in normal pancreatic tissue, it is hypermethylated in pancreatic carcinomas, resulting in significantly reduced expression of NPTX2 in pancreatic cancer cells relative to adjacent healthy tissue [33]. The methylation status of NPTX2 in pancreatic juice could also be used to discriminate between malignant pancreatic cancer and benign neoplasms or chronic pancreatitis [34]. Using a cutoff of 1.39 in a quantitative methylation specific PCR assay, aberrant NPTX2 methylation was detected in 61.3% (19 of 31) in patients with pancreatic cancer, 50.0% (5 of 10) of patients with malignant intraductal papillary mucinous neoplasm, 0% in patients with benign intraductal papillary mucinous neoplasm and 8.7% (2 of 23) of patients with chronic pancreatitis.

The methylation status of NPTX2 has also been identified as a prospective plasma biomarker for pancreatic cancer. NPTX2 hypermethylation was found to be significantly higher in patients with pancreatic cancer (n=104) compared with those with chronic pancreatitis (n=60), with a sensitivity and specificity of 80% and 76%, respectively [35]. The methylation of NPTX2 in plasma has been replicated in a separate study (pancreatic cancer 74.5%, chronic pancreatitis 50%, healthy control 14.2%). Higher methylation levels were detected in those with late stage metastasized disease, and high NPTX2 methylation was associated with worse survival (HR: 3.2, 95% CI 1.6 to 6.6) [36]. Elevated NPTX2 methylation may also serve as a prognostic marker for those with chronic pancreatitis who are likely to develop pancreatic cancer.
Colorectal cancer: ELEVATED NPTX2 ASSOCIATED WITH WORSE PROGNOSIS

NPTX2 acts as an oncogene in colorectal cancer. NPTX2 overexpression promotes cancer cell proliferation and migration in colorectal cancer cell lines through the activation of the Wnt/β-catenin signaling pathway [37]. Both mRNA and protein expression of NPTX2 were found to be increased in tumor tissue, and the increased expression level was associated with disease progression and poor prognosis [37]. In patients with rectal cancer treated with neoadjunct chemoradiation, baseline NPTX2 levels were predictive of therapeutic response, while post-treatment levels served as a read-out of response [38]. Patients with tumors expressing low levels of NPTX2 at baseline (n = 13) had better responses, with 38.5% and 46.1% of patients achieving complete or moderate response, respectively. These patients also had better disease-free survival. In patients with high NPTX2 at baseline (n = 27), only 11.1% and 18.5% achieved complete or moderate response, respectively. Following treatment, NPTX2 mRNA levels were significantly decreased (fold change 30.4) in those with complete response to treatment relative to partial or non-responders.

Renal cancer: ELEVATED NPTX2 ASSOCIATED WITH WORSE SURVIVAL

NPTX2 is oncogenic in renal cancer. A patient gene array (n=72 tumor and matched samples) found that NPTX2 expression was significantly increased at all stages of clear cell renal cell carcinoma [39]. Based on a study using The Cancer Genome Atlas Program datasets found that NPTX2 was upregulated more than 15-fold in renal cell carcinoma, and high expression was associated with worse overall survival and disease-free survival [40]. The overexpression of NPTX2 in these patients was attributed to the downregulation of miR-96, which normally inhibits NPTX2. Cell culture studies indicate that overexpression of NPTX2 promotes renal cancer cell viability and metastasis through its interactions with the AMPA receptor GluA4 subunit, which is upregulated in metastatic kidney tissue compared with healthy kidney tissue [39].

Glioblastoma: METHYLATION OF NPTX2 ASSOCIATED WITH WORSE PROGNOSIS

The contribution of NPTX2 in glioblastoma is unclear, though the majority of the data supports it having a tumor suppressor role. Based on tumor samples from The Cancer Genome Atlas Program (n=44), hypermethylation of the NPTX2 was associated with high risk in glioblastoma [41]. In cell culture studies, NPTX2 overexpression induced cancer cell apoptosis, inhibited growth, and reduced NF-κB activation via AKT inhibition [41]. A separate study (n=100) found that NPTX2 methylation alone was not significantly associated with patient survival, but it was highly codependent with the methylation of other genes, and this concomitant gene methylation was associated with patient survival [42]. For example, NPTX2 was co-methylated with AREG (37.1%), and median survival time was higher for
patients where both were unmethylated (14.1 months, 95% CI 1.8 to 26.4) compared to patients where they were methylated (4.9 months, 95% CI 1.4 to 8.4). NPTX2 levels were also found to be significantly downregulated in glioblastoma tissues, which is consistent with the hypermethylation [43]. However, in this study, NPTX2 levels were inversely associated with survival, suggesting that high levels of NPTX2 may not be beneficial for glioblastoma patients.

Part of the complexity may stem from the endogenous role of NPTX2 in regulating neuronal circuitry. Gliomas have been shown to form synapses with healthy neurons and integrate into neuronal circuits, and this process typically involves AMPA receptor mediated glutamatergic transmission and hyperexcitability [44]. In this context, elevated NPTX2 would be expected to be beneficial by reducing network excitability, and thus reducing the integration of gliomas, but it is possible that the activity of NPTX2 is altered in the glioma tumor microenvironment.

**Neuroblastoma**: ELEVATED NPTX2 ASSOCIATED WITH WORSE SURVIVAL
NPTX2 and NPTXR were found to be elevated in neuroblastoma (Schwannian stroma-poor, stage IV), and elevated NPTX2 was associated with poor survival [29]. Both proteins were found to be concentrated near tumor blood vessels, and in cell culture, blocking these pentraxins reduced adhesion between neuroblastoma cells and vascular cells. In female mouse models (orthotopic and pseudometastatic), treatment with anti-NPTX2 or anti-NPTXR antibodies reduced tumor volume.

**Ewing sarcoma**: METHYLATION OF NPTX2 ASSOCIATED WITH WORSE SURVIVAL
Within primary tumor samples (n=41) and Ewing sarcoma cancer cell lines, NPTX2 was consistently methylated (frequency 61%) [45]. The hypermethylation of NPTX2, leading to transcriptional silencing, was associated with poor survival.

**Diabetes**: UNCLEAR ROLE
The role of NPTX2 in the pancreas, and its potential contribution to diabetes has not been well studied at this point. NPTX2 is expressed in the islets of Langerhans, the cells that regulate glucose levels in the pancreas [46]. Glutamate is known to regulate insulin secretion [47]. NPTX2 expression was reported to be reduced in islets from patients with type 1 diabetes in a small study [48]. One study found that LKB1 and AMPK regulate NPTX2 expression and glutamatergic signaling in pancreatic beta cells [49]. GLP-1 has beta cell protective effects, and streptozotocin damaged islets treated with GLP-1 gene therapy were found to upregulate NPTX2 [50]. It is unclear whether, NPTX2 contributes to beta cell protection.
Safety: No safety data is currently available for NPTX2 modulation, but it is known to have context dependent effects, and may influence cancer progression.

Types of evidence:

- 31 Biomarker observational studies (NPTX2 methylation or expression)
- Several laboratory studies (for basic biology of NPTX2, none for modulators)

There are currently no drugs developed to specifically modulate NPTX2 levels and/or activity. It is clear from biomarker studies, that both very high and very low levels of NPTX2 can be associated with disease processes, depending on the context. This suggests, that the safest and most effective NPTX2 targeted therapeutics will be those that are directed toward normalizing NPTX2 levels. Due to its context dependent roles, modulating NPTX2 may have different side effects in different organ systems.

Based on its dual role as a tumor suppressor and oncogene in different types of tumors, the modulation of NPTX2 may potentially increase the risk for some types of cancer.

Sources and dosing:

There are currently no NPTX2 modulatory drugs available.

Research underway:

There are preclinical efforts underway to develop NPTX2 modulators.

Search terms:

Pubmed, Google: NPTX2 +

- Alzheimer’s disease, Parkinson’s disease, neurodegeneration, biomarker, aging, cancer, diabetes, inflammation

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