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.

KPT-350 (and other XPO1 inhibitors)

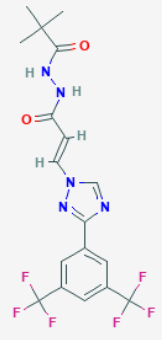
Evidence Summary

CNS penetrant XPO1 inhibitor with pleiotropic effects. May protect against neuroinflammation and proteotoxic stress, but similar drugs show a poor benefit to side effect profile in cancer.

Neuroprotective Benefit: KPT-350 may reduce neuroinflammation and partially alleviate nucleocytoplasmic transport defects, but effects are pleiotropic and dependent on cellular and environmental conditions.

Aging and related health concerns: XPO1 inhibition may promote autophagy, but has pleiotropic effects and is only marginally beneficial in cancer.

Safety: KPT-350 has not been clinically tested. Tested XPO1 inhibitors are associated with myelosuppression, gastrointestinal events, anorexia, low blood sodium, and neurological events. Poor benefit to side effect ratio in cancer.

Availability: In clinical trials and research use	**Dose**: Oral administration Dose not established for KPT-350	KPT-350 **Chemical formula:** $C_{18}H_{17}F_6N_5O_2$ **MW**: 449.3 g/mol  Source (PubChem)
Half-life: Unknown for KPT-350 6-7 hours for selinexor SINEs terminal half-life ~24 hours	**BBB**: KPT-350 is penetrant	
Clinical trials: None completed for KPT-350. Phase 1 in ALS is ongoing. >60 Clinical trials completed or ongoing for related drugs: selinexor, eltanexor, and verdinexor, primarily in cancer.	**Observational studies**: Evidence for nucleocytoplasmic transport defects in neurodegenerative disease, and XPO1 upregulation in cancer.	

What is it?

KPT-350 is a member of the class of selective inhibitor of nuclear export (SINE) compounds developed by Karyopharm Therapeutics, which acts as an inhibitor of the nuclear export protein exportin-1 (XPO1/CRM1). It was acquired by Biogen in 2018 (Press release), and was subsequently renamed BIIB100. SINEs act as **slowly reversible XPO1 inhibitors** through the covalent modification of the cysteine residue 528 on XPO1 [1]. Several SINE compounds are in clinical development for cancer by Karyopharm Therapeutics, including selinexor (KPT-330), which is approved for relapsed refractory multiple myeloma, eltanexor (KPT-8602), and verdinexor (KPT-335). XPO1 transports RNAs and proteins out of the nucleus which contain a nuclear export signal. Together with Ras related nuclear protein (RAN), importins and exportins control trafficking between the nucleus and cytoplasm [2]. XPO1 is a cancer target, so XPO1 inhibitors have primarily been tested for this indication. Due to evidence of nucleocytoplasmic transport defects in neurodegenerative diseases, the highly CNS penetrant KPT-350 is being developed for CNS indications, with clinical testing initiating in Amyotrophic Lateral Sclerosis (ALS).

Neuroprotective Benefit: KPT-350 may reduce neuroinflammation and partially alleviate nucleocytoplasmic transport defects, but effects are pleiotropic and dependent on cellular and environmental conditions.

Types of evidence:

- 3 observational studies (Evidence for nucleocytoplasmic defects in postmortem brain tissue in AD, MS, HD)
- Several laboratory studies (6 using KPT-350)

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

There is evidence indicating that nucleocytoplasmic transport is disrupted in various neurodegenerative diseases, but no research to date indicating whether XPO1 inhibitors have protective effects on cognitive function. XPO1 is upregulated in neurons in response to various types of damage, but is not clearly playing a causal role in driving pathology.

Alzheimer's disease: Amyloid, and other aggregation prone proteins, may promote defects in nucleocytoplasmic transport by altering expression and/or interfering with the transportation machinery [3]. While XPO1 was identified as a potential Aβ suppressor in a yeast model of Aβ toxicity [4], a case-control genetic study found no significant association of XPO1 as a modifier gene for late onset Alzheimer's disease (LOAD) [5].

Instead, **nucleocytoplasmic transport deficits appear to be driven by altered expression of XPO1's essential binding partner RAN**. Unlike XPO1 which only mediates transport of a subset of proteins and RNAs out of the nucleus, RAN interacts with both importins and exportins, and thus is critical for overall transport in both directions. In a microarray analysis of postmortem tissue, the expression of RAN was found to be 4.6-fold lower in the hippocampus and 5-fold lower in the superior frontal gyrus in AD patients (n=10) relative to controls (n=10) [3]. RAN levels were only decreased in disease affected brain regions and associated with decreased nuclear levels of nuclear proteins involved in transcription (RNA pol II) and epigenetic regulation (DMNT1). This suggests that while inhibiting importins such as XPO1 may help retain these proteins in the nucleus so they can perform their essential functions, it does not fix the underlying cause, and will not address the issue of reduced import of these proteins into the nucleus.

XPO1 could potentially play a role in promoting dementia in relation to the viral hypothesis of AD. Many viruses utilize host nuclear import and export proteins in the course of their lifecycle. XPO1 has been found to be involved in the spread of several viruses, including alphaviruses, HIV, dengue, and Herpes Simplex Virus [6; 7]. **Inhibiting XPO1 can sequester the viral capsid protein to the nucleus thereby reducing viral replication and titers**. Consequently, XPO1 inhibitors are in development as antiviral agents [8]. If, as has been hypothesized, the reactivation of the Herpes virus in the brain can trigger AD pathology [9], then XPO1 inhibitors could potentially prevent this process.

Human research to suggest benefits to patients with dementia: None

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

Nucleocytoplasmic transport: The cellular localization of proteins has been found to be disrupted in neurons in a variety of neurodegenerative diseases, which is indicative of defects in nucleocytoplasmic transport. Components of the nucleocytoplasmic transport machinery have been shown to be reduced in the context of aging, which may increase the susceptibility to proteotoxic stress [10]. In many cases, this is associated with the accumulation of cytoplasmic aggregates, which can further disrupt nuclear transport. The aberrant localization of nuclear proteins in the cytoplasm in neurons can interfere with axon cytoskeleton and promote axonal damage, and their retention in the nuclear compartment is neuroprotective [11].

As an exportin, XPO1 regulates cellular function through the controlled export of transcription factors, cell cycle regulators, or translation machinery from the nucleus [12]. However, since it is involved in the transport of over 200 proteins, **targeting XPO1 can have broad pleiotropic effects** depending on the cell type and cellular conditions.

Amyotrophic Lateral Sclerosis/Frontotemporal Dementia (ALS/FTD): TDP-43 mislocalizes to the cytoplasm where it aggregates and can contribute to pathology in ALS and FTD. It contains a nuclear export signal for XPO1, and thus its nuclear transport was thought to be regulated by XPO1. However, recent studies have indicated that the nuclear export signal on TDP-43 is non-functional, and it may instead accumulate in the cytoplasm through redundant pathways and/or passive diffusion [10; 13; 14]. Therefore, the therapeutic effects of KPT-350 in models of ALS/FTD may stem from a different mechanism, such as by inhibiting stress granule assembly [15]. It is possible that the benefit may be independent of nuclear transport altogether, since one study found that doses leading to nuclear export inhibition were neurotoxic, while levels that were therapeutically beneficial in preclinical models did not

affect nuclear transport [10]. However, nuclear transport was assessed by a reporter in this study, and thus may not be representative of all XPO1 transported factors.

Huntington's disease (HD): The nuclear-cytoplasmic distribution of nuclear pore complex-associated proteins has been found to be altered in the striatum of postmortem brains from patients with HD [16]. The disruption of RAN proteins is thought to produce a primary disruption in nuclear import. The inhibition of nuclear export with KPT-350 has been tested for its ability to compensate for the loss of nuclear import and exert neuroprotective effects in neurons expressing mutant huntingtin (mHtt). One study found that treatment with KPT-350 improved neuron viability and rescued nucleocytoplasmic defects [16]. However, another study found that this improvement was an artifact, and that KPT-350 was not neuroprotective, as any potential benefit may have been offset by the toxicity of accumulated nuclear mHtt [10].

Neuroinflammation: XPO1 is involved in the regulation of the inflammatory response primarily because it controls the nuclear localization of the NF-kB inhibitor, IkB [11]. The presence of nuclear IkB can prevent nuclear NF-kB from acting as a transcription factor and inducing its inflammatory response by disrupting the binding between NF-kB with the DNA and promoting its nuclear export [17]. The **inhibition of XPO1 can also lead to the sequestering of other inflammation-associated proteins**, such as Akt, Foxp1, and Stat1 [18; 19]. Therefore, XPO1 inhibitors mitigate neuroinflammation by regulating transcription factors, which in turn can reduce the production of pro-inflammatory cytokines. XPO1 inhibition may also promote the endogenous antioxidant response by enhancing the nuclear retention of Nrf2 [11].

Multiple Sclerosis (MS): XPO1 has been found to be elevated in the white matter lesions in the brain of MS patients (n=8) within neurons and $CD45^+$ monocytes, and XPO1 levels were increased by 80% in cortical gray matter relative to controls (n=5) [11]. KPT-350 was found to reduce the cumulative disease score by 75% in a rodent EAE model [11]. The protection against myelin damage was associated with less immune cell infiltration, cytokine expression, and peripheral immune cell proliferation.

Traumatic Brain Injury (TBI): In a rat model of TBI (controlled cortical impact), treatment with KPT-350 starting 2 hours after the injury reduced cell death and pro-inflammatory cytokine levels [18]. These were associated with improvements on behavioral measures of motor coordination and balance.

Duchenne Muscular Dystrophy (DMD): Chronic inflammation contributes to disease progression in DMD. KPT-350 was protective in slowing disease progression and reducing motor deficits in zebrafish and mouse models of DMD [19]. In DMD mice, there was a protective shift in the balance toward more

anti-inflammatory and less pro-inflammatory cytokines. Notably, this cytokine shift did not occur in wild-type mice, suggesting that the effects of XPO1 inhibition are dependent on the cellular environment.

APOE4 interactions: Not known

Aging and related health concerns: XPO1 inhibition may promote autophagy, but has pleiotropic effects and is only marginally beneficial in cancer.

Types of evidence:

- >20 clinical trials for selinexor or eltanexor in cancer
- No clinical or preclinical studies for KPT-350
- Numerous laboratory studies (primarily for cancer)

Lifespan: Potential benefit in promoting autophagy (preclinical in worms)

Since the nuclear pore complex plays critical roles in genome organization and cellular function, dysfunction of the nuclear pore complex could promote cellular aging [20]. Damage to nuclear pore complex components could increase nuclear permeability, resulting in a dysregulation of nuclear transport.

XPO1 controls the nuclear export of over 200 proteins, and XPO1 levels may be involved in regulating the balance between cell growth and survival by controlling the localization of various transcription factors [21]. A study examining the identity of its cargo found that **XPO1 is involved in the export of autophagy regulating proteins, and may act to inhibit the initiation of autophagy** [12]. Its effects on autophagy appear to be both mTOR dependent and independent. XPO1 controls the nuclear export of mTORC1 complex components and complex regulators, including TSC1-TSC2, as well as autophagy components including ATG3. XPO1 also controls the nuclear localization of the transcription factor, TFEB, which is an important regulator of autophagy and lysosomal function [22].

In *C. elegans*, inhibition of XPO1 with the SINE compound selinexor (KPT-330) extended lifespan by enhancing autophagy [22]. Since XPO1 inhibition can have pleiotropic systemic effects, it is not clear whether the benefits to proteostasis and lifespan would be translatable to higher order species, or whether they would be offset by other side effects.

Cancer: Potential minor benefit for XPO1 inhibition

Exportins, including XPO1, have primarily been studied for their role in cancer due to the role of nucleocytoplasmic transport in the control of proliferation and apoptotic pathways. XPO1 is considered an attractive target because its transport cargo includes a large number of tumor suppressors and oncoproteins [1]. The export of growth factors to the cytoplasm enhances tumor proliferation and survival, while the export of tumor suppressor transcription factors inactivates them, further driving tumor growth. XPO1 overexpression in both solid tumors and hematological malignancies is associated with poor prognosis and drug resistance [23].

However, the clinical experience with XPO1 inhibitors suggests that XPO1 may be a suboptimal drug target due to its pleiotropic effects which result in **a poor therapeutic benefit to side effect profile**. The SINE XPO1 inhibitor selinexor (KPT-330) has been tested in over 20 clinical trials for various cancers (Clinicaltrials.gov), however, the benefits were marginal or absent in most patients (FDA ODAC briefing). In June 2019 it was approved as a last line treatment in patients with multiple myeloma, after the FDA's Oncology Drug Advisory Committee initially recommended against accelerated approval for selinexor due to the difficulty of determining if the benefits outweighed the risks (Press Release). Selinexor continues to be tested in clinical trials for cancer, with 40 trials currently ongoing (Clinicaltrials.gov). The next generation SINE XPO1 inhibitor eltanexor (KPT-8602) was shown to have a slightly more favorable therapeutic profile in a Phase 1/2 trial in multiple myeloma patients (Karyopharm Press Release).

Safety: KPT-350 has not been clinically tested. Tested XPO1 inhibitors are associated with myelosuppression, gastrointestinal events, anorexia, low blood sodium, and neurological events. Poor benefit to side effect ratio in cancer.

Types of evidence:

- >20 clinical trials (For selinexor, eltanexor, or verdinexor)
- Only preclinical studies for KPT-350
- Numerous laboratory studies

In preclinical cell cultures studies, KPT-350 was found to exert minimal cytotoxicity in post-mitotic cells, including CNS cells, and only showed evidence of toxicity toward oligodendrocyte precursor cells (OPCs) at doses above the projected therapeutic range [11]. A cell culture study found that the efficacy/response to SINE XPO1 inhibitors is not correlated with the degree of XPO1 inhibition, but

rather may depend on the cellular distribution of XPO1 cargo within a given cell under a given set of conditions [24]. As a result, *ex vivo* responses by patient derived cells are variable [25], which may extend to variable clinical efficacy amongst different patients.

Due to the high number (>200) of proteins that are transported by XPO1, its inhibition would be expected to have pleiotropic effects and thus exert significant side effects. Clinical testing of the first XPO1 inhibitor, leptomycin B was discontinued due to high levels of cytotoxicity [1]. SINE compounds have a better toxicity profile because, unlike leptomycin B which is an irreversible inhibitor, SINE compounds are slowly reversible XPO1 inhibitors. While KPT-350 has not yet gone through clinical testing, other XPO1 inhibiting SINE compounds have been clinically tested, and shown to exhibit a consistent side effect profile. Appetite loss/weight loss is one of the prominent side effects of the clinically tested SINE compounds, and KPT-350 treatment led to dose-dependent weight loss in a preclinical rat model [10], suggesting that its side effect profile is likely to be similar to previously tested SINE compounds.

Selinexor (KPT-330) has been tested in over 2600 cancer patients, and the side effect profile primarily consists of **cytopenias, gastrointestinal events, constitutional symptoms, and hyponatremia** (low sodium blood levels) (FDA ODAC briefing). Constitutional symptoms are non-specific symptoms that affect several body systems, such as appetite loss and fatigue. In a Phase 1 study in patients with hematological malignancies, the most frequent adverse events were nausea, anorexia, fatigue, thrombocytopenia, and anemia. In the Phase 2 STORM trial (n=123), where selinexor was administered in combination with dexamethasone, 89.4% of patients experienced a treatment related adverse event, and 30.1% had a treatment related serious adverse event. There were 2 fatal adverse events of drug-related pneumonia and sepsis. The most common adverse events were thrombocytopenia (73.25%), anemia (65.9%), and neutropenia (38.2%), which were primarily grade 3 cytopenias. Gastrointestinal and constitutional events included nausea (69.9%), fatigue (62.6%), decreased appetite (53.7%), and hyponatremia, which were primarily grade 1/2, reversible, and manageable with supportive care.

While the severity of the hematological effects may be attributable to the patient population, the gastrointestinal and constitutional effects would be expected to occur across various patient populations, and could pose a risk for elderly or frail populations.

Selinexor use is also associated with neurological adverse events, such as dizziness, delirium, partial loss of consciousness, and confusion (Rxlist). These events were found in approximately 30% of relapsed refractory multiple myeloma patients in clinical trials (n=202). It is possible that the neurological side effects could be exacerbated with KPT-350 due to its higher degree of CNS penetrance.

Eltanexor (KPT-8602) is a next generation SINE XPO1 inhibitor that is expected to have similar potency but improved tolerability due to lower CNS penetration, based on preclinical studies [26]. The side effects were similar to selinexor, but lower in severity, in a Phase 1/2 study in multiple myeloma patients (n=39). The most common grade 1/2 adverse events were nausea (54%), fatigue (46%), anemia (38%), diarrhea (38%), dysgeusia (33%), weight loss (33%) and neutropenia (31%). The most common grade 3/4 events were thrombocytopenia (56%), neutropenia (26%), anemia (15%), leukopenia (15%) and hyponatremia (10%) (Karyopharm Press Release).

Verdinexor (KPT-335) has been tested in a Phase 1 sequential dose escalating study in healthy volunteers (n=32) from 5 to 100 mg (NCT02431364). No study results have been published, but it was reported that the number and grade of adverse events was comparable to placebo [27]. Verdinexor is also approved in veterinary use for canine lymphoma, where anorexia is the most common adverse event [28].

Sources and dosing:

KPT-350 is being developed for clinical use as the orally administered drug BIIB100 by Biogen, but a therapeutic dose has not yet been established. Selinexor (KPT-330) is marketed by Karyopharm Therapeutics under the tradename Xpovio® and is FDA approved as a last line treatment for relapsed refractory multiple myeloma. For this indication it is taken orally at 80 mg (20 mg tablets) 2x per week in conjunction with dexamethasone.

Research underway:

KPT-350 (BIIB100) is currently being tested in a Phase 1 Single Ascending Dose trial for ALS (NCT03945279). The study has an expected completion date of December 2020.

Search terms:

Pubmed, Google: KPT-350, BIIB100, Selinexor, Verdinexor, Eltanexor

- Alzheimer's disease, ALS, neurodegeneration, inflammation, aging, cancer, safety, clinical trials

Websites visited for KPT-350:

- Clinicaltrials.gov (KPT-350/BIIB100)
- Drugs.com (Selinexor)
- PubChem (KPT-350), (Selinexor/KPT-330), (Verdinexor/KPT-335), (Eltanexor/KPT-8602)

- DrugBank.ca (Selinexor), (Verdinexor)
- Cafepharma (Karyopharm/Selinexor)

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