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.

Amyloid-beta oligomer receptor inhibitors (BMS-984923)

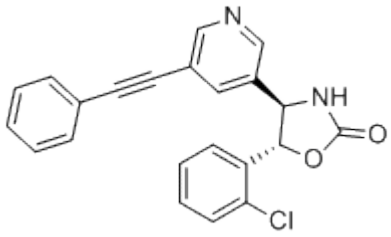
Evidence Summary

The Aβo receptor hypothesis is interesting as a potential method to reduce Aβo-mediated synaptic dysfunction, and preclinical data suggest that BMS-984923 may be effective in Alzheimer's disease.

Neuroprotective Benefit: Preclinical data suggests that BMS-984823 may prevent Aβo-mediated toxicity without having effects on other aspects of Alzheimer's (e.g. inflammation).

Aging and related health concerns: Not expected to impact other age-related diseases based on this mechanism of action.

Safety: Preliminary preclinical data suggests no safety issues with this drug, though clinical trials or preclinical toxicology studies have not been conducted.

Availability: Not Available	**Dose**: Currently in dose-finding studies	**Chemical formula:** $C_{22}H_{15}ClN_2O_2$ **MW:** 374.82  **Source:** ProbeChem
Half life: 3 hours (in animals)	**BBB**: Penetrant (in animals)	
Clinical trials: N/A	**Observational studies**: None	

What is it?

BMS-984923 is a silent allosteric modulator (SAM) of mGluR5 that blocks amyloid beta oligomer (Aβo)/prion protein (PrP^c) toxicity without affecting normal glutamate signaling. mGluR5 is a transmembrane, G-protein coupled receptor physically linked to the GluN2 (NR2) subunit of the NMDA receptors (NMDARs). It is localized peri-synaptically at the post-synaptic membrane of glutamatergic neurons. Activation of mGluR5 increases calcium levels inside the cell prompting protein kinase C (PKC) activation (Kumar et al, 2015).

Growing evidence suggests that Aβos, rather than amyloid plaques themselves, are neurotoxic in Alzheimer's disease. For instance, individuals with the Osaka mutation (a small group of individuals in Japan), develop dementia without the presence of amyloid plaques. Cerebral spinal fluid (CSF) in these patients show increased levels of high-molecular weight amyloid species, presumably Aβos. Preclinical studies have implicated Aβos in the development of tau pathology, impairment of axonal transport, synaptic degeneration, oxidative stress, insulin resistance, and neuroinflammation (Cline et al, 2018).

The Aβo/PrP^c hypothesis is that Aβos binds to the prior protein (PrP^c) on the cellular membrane. This can alter synaptic signaling and calcium influx and can activate Fyn kinase which then increases tau phosphorylation.

Summary of data (Benefit, no change)

Drug	Clinical	Preclinical in vivo	Preclinical in vitro	Post-mortem in situ	Post-mortem expression of protein	Pathway elucidated	Other modalities	Genetic evidence
BMS-984823	None	Cognition, amyloid, inflammation, synapses	Aβo binding, LTP		Aβo bound to PrP^C; pFyn ↑; Pyk2/PrP^C coupling ↓	mGluR5-PrP^C-Fyn kinase	PrP^C antibody, mGluR5 antagonist; genetic deletion	Pyk2 SNP

Neuroprotective Benefit: Preclinical data suggests that BMS-984823 may prevent Aβo-mediated toxicity without having effects on other aspects of Alzheimer's (e.g. inflammation).

Types of evidence:

- 1 preclinical study using BMS-984823
- Multiple preclinical and post-mortem tissue studies for the receptor

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
None

Human research to suggest benefits to patients with dementia
None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Lauren et al (2009) showed that Aβos bind to PrP^C and inhibit synaptic plasticity (measured by LTP) in hippocampal slices. Inhibition of LTP was prevented in PrP^C knock-out mice and with the application of a PrP^C antibody. PrP^C is coupled to mGluR5 through intracellular mediators Homer1b/c, CaMKII, and proline tyrosine kinase 2 beta (Pyk2 – also a reported Alzheimer's risk gene – Wang et al, 2015; Khondoker et al, 2015) (Haas et al, 2016).

Acute exposure of mouse brain slices to Aβos increases phosphorylation of both Pyk2 and CaMKII. In an Alzheimer's animal model, Pyk2 phosphorylation is increased while CaMKII phosphorylation is decreased

(CaMKII phosphorylation is also reduced in Alzheimer's brain tissue). Genetic reduction of both PrP^C and mGluR5 (in mGluR5 heterozygous knockout mice), but not individually, reduced phosphorylation of Pyk2 and CaMKII in the presence of Aβos. Similarly, genetic reduction of both PrP^C and mGluR5 prevented the reduction of LTP in the presence of Aβos. These results suggest that both PrP^C and mGluR5 are important for Aβo-mediated synaptic dysfunction. Finally, genetic reduction of PrP^C and mGluR5 in an Alzheimer's animal model had no effect on plaque levels, astro- or microgliosis, or levels of IL-1β; however, it did increase synaptic markers (SV2a and PSD95) and survival (Haas et al, 2016).

Aβos were reported to increase the clustering of mGluR5 at synapses in cell culture studies, resulting in a reduction of glutamate NMDA receptors (GluN1 subunit) at synapses and an increase intracellular calcium levels. These effects were reduced with the co-application of an mGluR5 antagonist (Renner et al, 2010).

The coupling of Homer1b/c and Pyk2 to PrP^C were also reported to be decreased in the Alzheimer's mouse hippocampus and Alzheimer's, but not Parkinson's, post-mortem brain tissue (Haas et al, 2016). Aβos (specifically dimers and trimers, not monomers or Aβ*56) from post-mortem Alzheimer's tissue were also reported to increase Fyn kinase phosphorylation, which required PrP^C, and increase hyperphosphorylated tau, linking Aβos and PrP^C to Alzheimer's pathology (Um et al, 2012; Larson et al, 2012).

In human post-mortem tissue, Aβos were bound to PrP^C in Alzheimer's brain tissue but not in tissue from non-demented subjects. This binding was preferential for high molecular weight Aβos (Dohler et al, 2014; Zou et al, 2011). An increase in phosphorylated Fyn was also reported in post-mortem tissue from patients with Alzheimer's and mild cognitive impairment (MCI) (Larson et al, 2012).

These studies are supported by studies showing that in PrP^C knock-out Alzheimer's mice there is no change in amyloid plaques or gliosis but improvements in memory, survival, and synaptic density (Gimbel et al, 2010, Haas et al, 2016). Injection of an anti-PrP^C antibody over two weeks in 8-month old Alzheimer's mice improved cognitive performance and increased synaptic markers without altering levels of amyloid plaques or Aβos (Chung et al, 2010). Another anti-PrP^C antibody (AZ59) which binds to the Aβo binding site on PrP^C reduced the interaction of PrP^C with mGluR5. Weekly injections (total of 5-7 injections) in aged Alzheimer's mice improved cognitive performance and increased synaptic density without altering levels of amyloid plaques, astro- or microgliosis. Other studies have also reported beneficial effects of anti-PrP^C antibodies in Alzheimer's animal models. (Cox et al, 2019).

However, the hypothesis that PrP^C mediates Aβo-induced toxicity is not without controversy. One study reported that Aβo intracerebral injections induced memory impairment in both wild type and PrP^C knock-out mice, despite showing that Aβos bind to PrP^C (Balducci et al, 2010). In another study, LTP was not rescued in hippocampal slices from 4-month-old APP/PS1/PrP^C knock-out mice (Calella et al, 2010). Finally, in 6-8-month-old J20 mice, PrP^C knock-out increased mortality and had no effect on cognition (Cisse et al, 2011).

Some explanations have been proposed for the discrepant findings. For example, the type of Aβos that bind to PrP^C may not be present in certain models at certain ages. In J20 mice, for instance, a large pool of soluble oligomers are not seen until 16 months of age (Purro et al, 2018), while Cisse et al (2011) examined mice at 6-8 months. Another study looked at an acute injection of Aβos, which may mediate toxicity through other mechanisms.

Importantly, PrP^C may not be the only receptor to bind to Aβo. Other putative Aβo-binding proteins, most localized at the synapse, include GluN1, GluA2, α7 nicotinic acetylcholine receptor, RAGE, insulin receptor, $p75^{NTR}$, β_2-adrenergic receptors, Fz Wnt receptor, NL1, reelin, GM_1 ganglioside, and LRP1. To address this, Smith et al (2019) conducted a standardized screen with putative Aβo-binding proteins expressed in non-neuronal cells and found that only three (PrP^C, NgR1, and LilrB2) bound to synthetic Aβos and Aβos from Alzheimer's post-mortem brain tissue (only PrP^C and NgR1 bound to postmortem Aβos). PrP^C accounted for 50% of the Aβo binding, while NgR1 and LilrB2 accounted for 20% of the binding, suggesting there is at least one other Aβo-binding protein.

However, the only receptors found to bind to Aβos, or alter Aβo signaling, in unbiased screens include PrP^C, FcγRIIB, and sigma-2/PGRMC1 (Purro et al, 2018).

BMS-984923

BMS-984923 was initially developed by Bristol Myers Squibb (Huang et al, 2016). Initial pharmacokinetic (PK) studies suggested that brain levels were nearly as high as plasma levels, it had good bioavailability, and its half-life in mice was 3 hours (Haas et al, 2017).

In vitro, BMS-984923 reduced the interaction of PrP^C with mGluR5 in the presence of Aβos. Although it does not interfere with basal glutamate signaling, in hippocampal slices BMS-984923 prevented the reduction in LTP in the presence of Aβos. In aged APP/PS1 mice, 4-week treatment with BMS-984923 (3.75mg/kg bid) improved cognitive performance on multiple tests. It had no effect on amyloid plaque load or astro- and microgliosis. However, BMS-984923 increased synaptic density (SV2A and PSD95

staining) and prevented the activation of Pyk2, CaMKII, and eEF2. In triple transgenic Alzheimer's mice, BMS-984923 (7.5mg/kg/day) over 4 weeks reduced the levels of soluble and insoluble phosphorylated tau (Haas et al, 2017).

The authors hypothesize that BMS-984923 stabilizes the mGluR5 conformation, preventing conformational change in the presence of Aβos and binding to PrP^C.

APOE4
None Reported

Aging and related health concerns: Not expected to impact other age-related diseases based on this mechanism of action.

Safety: Preliminary preclinical data suggests no safety issues with this drug, though clinical trials and preclinical toxicology studies have not been conducted.

Types of evidence:

- 1 preclinical study

One preclinical study did not report any safety issues with the use of BMS-984923 (Haas et al, 2017).

Drug interactions:
No drug interactions are currently known or anticipated from the mechanism of action.

Sources and dosing:
Not currently in clinical trials, so dose is unknown.

Research underway:
No clinical studies underway

Search terms:

- Prion + Alzheimer
- BMS-984823

Websites:
Clinicaltrials.gov
Pubmed

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.