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.

LXR Agonists

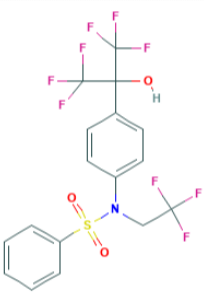
Evidence Summary

Some evidence suggests that LXR agonists may be beneficial for Alzheimer's disease or atherosclerosis; however, they increase plasma triglyceride levels which may increase the risk of metabolic disease and limit their use.

Neuroprotective Benefit: Preclinical evidence suggests that LXR agonists may be beneficial in Alzheimer's disease, but peripheral metabolic side effects may limit their use.

Aging and related health concerns: Some evidence suggests that LXR activators may reduce the risk of atherosclerosis; however, they may come with unwanted metabolic side effects such as an increase in serum triglyceride levels.

Safety: There is evidence that LXR agonists may increase levels of plasma triglycerides; however, the long-term impact of this increase has yet to be assessed.

Availability: Not currently available, in development	**Dose**: There is no approved LXR activator. Most studies for AD using the tool compound T0901317 have used about ~30mg/kg/day in rodents, though the long-term effects of LXR activation are still uncertain.	**Molecular Formula:** $C_{17}H_{12}F_9NO_3S$ **Molecular weight:** 481.3g/mol  Source: Pubchem (T0901317)
Half-life: Depends on the compound	**BBB**: Tool compounds possibly penetrant in animal models	
Clinical trials: At least five phase 1 clinical trials have been conducted, but none of the drugs have moved to phase 2	**Observational studies**: None	

What is it?

Liver X receptors (LXRs) are nuclear receptors that are ligand-activated transcription factors. There are two LXRs, LXRα (expressed in the liver, kidney, small intestine, spleen, and adrenal gland) and LXRβ (expressed ubiquitously). The LXRs can function as heterodimers with the retinoid X receptor (RXR) and are activated by either LXR agonists (such as oxysterol) or RXR agonists. Activation of LXRs increase expression of several genes involved with cholesterol metabolism including ABCA1, ABCG1, ABCG5, ABCG8, APOE, CETP, FAS, CYP7A1, and SREBP.

In the CNS LXRβ is expressed ubiquitously while LXRα is thought to be expressed in just microglia and in subcortical neurons. LXR receptors are also differentially expressed in different animal models. This makes the investigation of LXR agonists difficult with preclincial models as discussed further below (Honzumi et al, 2011).

Development of LXR agonists began in the early 2000s with the discovery of two tool compounds, T0901317 and GW3965, which are agonists for both LXRα and LXRβ. Unfortunately, although they are beneficial for atherosclerosis, LXRα agonism also induced hepatic lipogenesis and increases triglyceride

levels. It is thought that this occurs because LXR agonism upregulates SREBP1C in the liver which regulates hepatic lipogenesis (Hong and Tontonoz, 2014).

It has been difficult to develop LXRβ-specific ligands due to the similar ligand binding pockets. Another difficulty in developing LXR agonists is the differences in lipidology between mice and humans. For instance, mice lack CETP and carry most of their cholesterol in HDL rather than LDL, and LXR agonists in species that express CETP may increase LDL-c levels (Quinet et al, 2009).

Several LXR agonists have entered the clinic and are reported below.

LXR-623

LXR-623 is a partial agonist for both LXRα and LXRβ. It reduced atherosclerotic lesion size in LDLR-/- mice over 8 weeks by 66% and serum cholesterol in Golden Syrian hamsters and cynomolgus monkeys without increasing serum triglycerides (Quinet et al, 2009). In a phase 1 single ascending-dose study in healthy humans, it increased ABCA1 and ABCG1 in the blood but was associated with neurological and/or psychiatric side effects in a dose dependent manner, and the program was terminated (though it is not clear if these side effects were related to LXR agonism or an off-target effect) (Katz et al, 2009).

BMS-779788

BMS-779788 is an LXR agonist with partial selectivity for LXRβ. In cynomolgus monkeys it increased expression of plasma ABCG1 but also increased LDL-c and triglycerides (though not as much as the tool compound T0901317). A safety study has been completed, though the results have not been published and it is unclear whether the program is still in development (Kirchgessner et al, 2014; Hong and Tontonoz, 2014). Another LXRβ agonist, BMS-852927 also increase LDL-c levels and triglycerides in humans and primate models (Kirchgessner et al, 2016).

Hyodeoxycholic acid

Hyodeoxycholic acid was in development by AtheroNova and showed beneficial effects in LDL-/- mice over 15 weeks including a 37% reduction in fasting plasma glucose, a 44%-94% reduction in atherosclerotic lesion size (depending on the region studied), a reduction of plasma triglycerides, an increase in HDL-c, and an increase in cholesterol efflux (Shih et al, 2013). A phase 1 study was started, but the results are not known. AtheroNova filed for bankruptcy in 2015 due to financial issues.

Other compounds, such as CS-8080 and BMS-852927 have entered the clinic but have been terminated because of undisclosed reasons (Hong and Tontonoz, 2014).

Neuroprotective benefit: Preclinical evidence suggests that LXR agonists may be beneficial in Alzheimer's disease, but a peripheral metabolic side effects may limit their use.

Types of evidence:

- Nine preclinical studies

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

LXR receptors have been implicated in the development of AD pathology. In an Alzheimer's animal model (APP/PS1), LXRα and LXRβ knockout increased the development of amyloid plaques (Zelcer et al, 2007).

In an Alzheimer's animal model (Tg2576), treatment with an LXR activator, T091317, over 25 days (50mg/kg) at six months (a stage with insoluble amyloid but few plaques) increased gene expression of lipid metabolism (e.g., APOE, ABCA1, SREBP1c) and downregulated expression of genes involved with inflammation and cell death. It also reduced levels of insoluble beta-amyloid (Lefterov et al, 2007). In a male Alzheimer's animal model (APP/PS1), treatment with T0901317 increased the expression of ABCA1 in the hippocampus and reduced membrane cholesterol levels. It also reduced β-secretase activity and amyloid plaques. This was dependent on ABCA1 expression as inhibition of ABCA1 reduced the effects of T0901317 on β-secretase activity and membrane cholesterol levels (Cui et al, 2011). In another study, treatment with T091317 (30mg/kg) over 30 days reduced plaque load and astrogliosis in the prefrontal cortex and hippocampus in AD mice (APP/PS1) and reduced the expression of the inflammatory marker COX-2. It also increased the number of cholinergic neurons in the medial septal regions and the basal nucleus of Meynert and improved cognition (Cui et al, 2012).

In 9-month-old APP23 mice fed a high-fat/high-cholesterol diet over four months, treatment with T0901317 (~25mg/kg) improved cognition. It also reduced amyloid plaque load, soluble amyloid, and the numbers of beta-amyloid oligomers. The reduction in beta-amyloid oligomers was correlated with improvement in cognition (Fitz et al, 2010).

In very old AD mice (24-month-old 3xTg mice) short-term (six-day) treatment with GW3965 (50mg/kg) reduced astrogliosis (but increased microgliosis). It also increased the length of brain blood vessels (Sandoval-Hernandez et al, 2016).

However, in rats, 3- or 7-day treatment of T0901317 (30mg/kg) had no effect on cerebral spinal fluid (CSF) or brain levels of Aβ-40 though it did increase levels of ApoE (Wang et al, 2016). In addition, another study in aged APP/PS1 (21-month-old) AD mice reported that 40–60-day treatment with T0901317 (~30mg/kg) improved cognition but had no effect on amyloid plaques (Vanmierlo et al, 2008).

Intraocular injection of beta-amyloid activated NLRP3 and NF-κB and induced the expression of inflammatory cytokines (TNFα and IL-6) and activated microglia while reducing the expression of LXRα and LXRβ. Treatment with T0901317 reduced the expression of inflammatory markers and increased the expression of ABCA1 and LXRα but not LXRβ (Lei et al, 2017).

In vitro experiments using primary hippocampal neurons exposed to beta-amyloid oligomers suggest that treatment with an LXR activator GW3965 reduced markers of apoptosis and increased synaptic density (Baez-Becerra et al, 2017).

APOE4 Interactions: None reported

Aging and related health concerns: Some evidence suggests that LXR activators may reduce the risk of atherosclerosis; however, they may come with unwanted metabolic side effects such as an increase in serum triglyceride levels.

Types of evidence:

- Ten preclinical studies for cardiovascular disease
- Six preclinical studies on increases in lipid levels
- One preclinical study in peripheral neuropathy

In a rabbit model of atherosclerosis, treatment with T0901317 (1 or 3mg/kg/day over 1-8 weeks) increased lipid levels (triglycerides and LDL-c) but it reduced atherosclerotic lesion size (Honzumi et al, 2011). In a mouse model of atherosclerosis (ApoE-/- mice fed a high cholesterol diet), six-week treatment with T0901317 increased levels of triglycerides and HDL-c, but reduced levels of LDL-c. It also reduced atherosclerotic plaque size and improved vasomotor function (Chen et al, 2012). In another

study in the same mouse model of atherosclerosis, Chen et al (2015) reported that the combination of T0901317 with a mitogen-activated protein kinase kinase 1/2 (MEK 1/2) inhibitor over 16 weeks reduced atherosclerotic lesion size and prevented the increase in serum and liver triglycerides.

In an atherosclerotic mouse model (ApoE-/- with or without LXRα-/-), treatment with GW2965 reduced lesion size, and reduced levels of cholesterol. Levels of triglycerides were only increased in LXR+ animals (Bradley et al, 2007). In a hypertensive rat model, treatment with the LXR agonist GW3965 (10mg/kg/day) over seven days reduced blood pressure. It had no effect on endothelium-dependent relaxation, but it did reduce levels of inflammation in blood vessels (NF-κB and TNFα) (Han et al, 2018).

In a mouse model of carotid vascular injury, treatment with T090137 (30mg/kg/day) improved vascular regeneration in the heart after 14 days and increased endothelial progenitor cell proliferation and migration *in vitro* through the PI3K/Akt/eNos pathway (Yu et al, 2014).

In a rat model of pulmonary artery hypertension (PAH – monocrotaline-induced PAH), treatment with T0901317 improved hemodynamic outcomes and heart morphology. Treatment also reduced cell death in the heart and reduced level of inflammatory cytokines (e.g., IL-6 and TNFα) (Gong et al, 2017).

After four- and seven-week treatment with T0901317 in a model of cardiac hypertrophy (abdominal aortic constriction) there was reduced left ventricular weight. However, improvements were not seen in LXR-α-/- mice, suggesting that the T0901317 partially worked through the LXRα pathway (Kuipers et al, 2010).

AZ876 is a dual partial agonist of LXRα and LXRβ which has fewer side effects than T0901317 (it does not elevate plasma triglycerides as much). In another model of cardiac hypertrophy (transverse aortic constriction) 14-day treatment (20μmol/kg/day) reduced the increase in heart weight, reduced myocardial fibrosis, and improved cardiac function. It had no effect on blood pressure. It also reduced the increase in LXRα and LXRβ expression (Cannon et al, 2015).

In a study of myocardial ischemia reperfusion, a single injection of GW3965 (20mg/kg) improved cardiac function, but *in vitro*, it increased the concentration of triglycerides and lipid droplets in cardiomyocytes (Lei et al, 2012). *In vitro*, exposure of macrophages to LPS increased the expression of inflammatory cytokines such as TNFα, IL-6, and IL-1β. However, treatment with T0901317 reduced the increase in inflammatory cytokines and reduced the expression of pERK1/2 and p-p38MAPK (Xiao et al, 2016).

Metabolic disease

One concern with LXR activators is that they increase levels of lipids (especially triglycerides) in the plasma. One preclinical study reported that one-week treatment with T0901317 (10mg/kg/day) increased plasma levels of lipids and increased the levels of triglycerides in the heart in animals fed a low-fat diet. However, it only increased the levels of phospholipids in the heart in animals on a high fat diet but did not increase levels of other lipids in the heart (e.g., nonesterified fatty acids, diacylglycerol, free cholesterol, cholesterol esters, or ceramide) (Harasiuk et al, 2015). On the other hand, another study in an animal model of diabetes suggested that treatment with T0901317 did not increase levels of triglycerides or lipids in the heart compared to control animals (Harasiuk et al, 2016). An *in vitro* study suggested that treatment with T0901317 increased the expression of *FAS* (which is involved with lipogenesis and an increase in triglycerides in the plasma). *In vivo*, T0901317 increased levels of plasma triglycerides transiently (Joseph et al, 2002). In a hamster model of atherosclerosis, T0901317 reduced lesion size by 35% but increased triglyceride levels 3-fold (Srivastava, 2011).

These efffects may occur due to the activation of SREBP1c seen with tool compounds. One LXR activator, N,N-dimethyl,3β-hydroxy-cholenamide (DMHCA), was reported to reduce atherosclerotic lesion size in ApoE-/- mice as well as prevent the increase in triglyceride levels (Kratzer et al, 2008). In addition, another LXR agonist, WAY-252623, reduced atherosclerotic lesion size in mice while only transietly increasing triglyceride levels in humans, suggesting the nature of the drug (e.g., preference for a specific LXR and the binding profile) may be most important in determining the safety level (Quinet et al, 2009).

Peripheral Neuropathy

Eid et al (2020) reported that in patients with diabetic peripheral neuropathy there was reduced expression of LXRβ. In animal models of T1DM, treatment with an LXR activator (T0901317) reduced the production of reactive oxygen species.

Safety: There is evidence that LXR agonists may increase levels of plasma triglycerides; however, the long-term impact of this increase has yet to be assessed.

Types of evidence:

- Three clinical trials
- Multiple preclinical studies

Results from preclinical and clinical studies suggest that LXR agonists may increase lipid levels such as LDL-c and triglycerides, but long-term clinical trials have not confirmed this (see multiple studies above).

One of the difficulties in assessing safety profiles is that rodents transport lipids differently from primates and humans. All of the clinical studies with LXR agonists have been terminated, some due to safety issues (e.g., increase in triglycerides and one due to neurological disorders that may be off-target) and others due to unreported issues (Katz et al, 2009; Hong and Tontonoz, 2014; Kirchgessner et al, 2016). Future studies will be needed to see whether drugs can specifically inhibit LXRβ, and whether these will reduce the side effects of increased triglycerides in the plasma. To date, all clinical programs with LXR activators have been abandoned due to safety concerns such as an increase in triglycerides.

Drug interactions: The drug interactions are not clear; however, LXR agonists may increase LDL-c and triglyceride levels, so any drug that affects lipid levels could interact.

Dosing: There is no approved LXR activator. Most studies using the tool compound T0901317 have used about 30mg/kg/day in rodents, though the long-term effects of LXR activation are still uncertain.

Research underway: There is currently a study looking at LXR levels in bone marrow from diabetic retinopathy patients (NCT03403686).

Search terms:

lxr agonist + alzheimer, longevity, aging, cardiovascular, metabolism, neuropathy, apoe4

Websites visited:

Pubmed
Clinicaltrials.gov