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.

Olamkicept

Evidence Summary

Specifically blocks trans IL-6 signaling associated with pathogenic inflammation and may benefit colitis. Safer than anti-IL-6 mAbs, but not ideal for CNS indications due to lack of BBB penetrance.

Neuroprotective Benefit: May help mitigate pathogenic neuroinflammation, but needs to be administered directly to the CNS and could potentially alter brain excitability.

Aging and related health concerns: May reduce pathogenic inflammatory processes associated with elevated IL-6 trans signaling in colitis and cardiovascular disease.

Safety: Good safety profile in short term clinical studies. The risks of long-term use have yet to be determined. May potentially interfere with liver regeneration.

Availability: In clinical trials	**Dose**: Not established Tested at 600 mg IV q2w in clinical trials	**Recombinant Protein** **MW for sgp130Fc** ~ 129 kDa (depending on level of glycosylation)
Half-life: 5 days	**BBB**: Not penetrant	
Clinical trials: Phase 2 for irritable bowel syndrome (n=20), and ulcerative colitis (n=90).	**Observational studies**: None for Olamkicept. Elevated levels of IL-6 trans signaling components associated with adverse cardiovascular events	

What is it?

Olamkicept (FE999301, TJ301, sgpFc), is a recombinant protein that acts as an **inhibitor of IL-6 trans signaling** [1]. IL-6 signaling involves the interaction of IL-6 in complex with the IL-6 receptor (IL-6R) with the membrane bound gp130 receptor. Classical IL-6 signaling involves a membrane bound form of IL-6R, while trans signaling involves the soluble form (sIL-6R). A soluble form of gp130 (sgp130) also exists in the body which acts as an endogenous inhibitor of trans signaling by binding to the IL-6/sIL-6R complex and preventing it from activating the membrane bound gp130 receptor. At least three different isoforms of spg130 have been identified based on molecular weight, and they have different tissue distribution and inhibitory capacity [2]. Olamkicept contains the extracellular domain of the signal transducing subunit of sgp130 fused to a human IgG1 Fc fragment (sgp130Fc).

In healthy adults, sgp130 is found in the serum at a concentration of 100-400 ng/mL, while sIL-6R is around 50 ng/mL, and IL-6 levels are very low, in the picogram range (1-5 pg/mL) [1]. Theoretically, the excess endogenous levels of sgp130 should be sufficient to inhibit IL-6 trans signaling, however, studies in healthy adults indicate that *in vivo*, these levels of sgp130 did not effectively block trans signaling [3]. sgp130 has approximately 100-fold higher affinity to the IL-6/sIL-6R complex compared to IL-6 or sIL-6R alone [4]. In the blood, the majority of IL-6 is free rather than complexed, such that levels of the complex are below the limit of detection in healthy individuals [3]. As levels of IL-6 rise, more complex is formed. Therefore, the inhibitory capacity of sgp130 depends on the levels of IL-6, sIL-6R, and sgp130. The addition of the Fc antibody to spg130 increases its sensitivity toward the IL-6/sIL-6R complex, thus making it **10 to 100 times more potent at inhibiting IL-6 trans signaling relative to endogenous sgp130**, but still leaves physiological levels of trans signaling intact [3].

As a specific inhibitor of IL-6 trans signaling, olamkicept is expected to have a better therapeutic profile than anti-IL-6/6R monoclonal antibodies (mAbs) which target both trans and classical signaling. Olamkicept is being developed for inflammatory bowel disorders by Ferring Pharmaceuticals and I-MAB Biopharma. It is being tested in clinical trials for irritable bowel syndrome and ulcerative colitis.

Neuroprotective Benefit: May help mitigate pathogenic neuroinflammation, but needs to be administered directly to the CNS and could potentially alter brain excitability.

Types of evidence:

- 1 observational study (spg130 levels in patients with subarachnoid hemorrhage)
- Several laboratory 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:

Studies where sgp130Fc was expressed selectively in the CNS in transgenic animals through the use of cell restricted promoters (CNS levels reach 250-350 ng/mL), or administered directly to the CNS via intracerebroventricular injection, suggest that IL-6 trans signaling may play a role in controlling the balance of excitatory and inhibitory signaling, particularly within the prefrontal cortex [5; 6; 7]. The consequences of altering IL-6 trans signaling on brain excitability and synaptic function appear to depend on age, underlying pathophysiology, and duration of therapeutic intervention, suggesting considerable variation in therapeutic efficacy across patient populations.

Peripherally expressed sgp130Fc (levels reach 20-30 ug/mL in peripheral tissues), which **does not cross the blood-brain barrier (BBB) at an appreciable level**, did not impact hippocampal dependent or independent memory in mice [8]. This indicates that peripheral sgp130Fc is unlikely to directly affect cognitive function when the BBB is intact. However, it could indirectly influence cognitive function via altering sleep architecture. Peripheral expression of sgp130Fc increased awake time in mice, and inhibited the slow-wave sleep rebound that usually follows sleep deprivation [9]. Since peripheral IL-6 trans signaling appears to play a role in promoting slow wave sleep, which is important for memory consolidation, its inhibition through sgp130Fc could potentially impair cognition in the long-term.

Neuroinflammation

Pathological neuroinflammation during aging may involve elevated IL-6 trans signaling. In mice, aged animals have higher cerebrospinal fluid (CSF) levels of sIL6-R than their younger counterparts, but levels of the endogenous inhibitor sgp130 remain unchanged, suggesting **older animals have higher levels of trans signaling in response to IL-6** [10]. This, in turn, makes the microglia more susceptible to activation, leading to higher numbers of pro-inflammation primed microglia in the aged brain. Addition of sgp130Fc at a level which compensates for the increase in sIL-6R could then potentially mitigate age-related neuroinflammation.

Cerebral vasospasm: Potential benefit (based on biomarkers)

The time course of IL-6, sIL-6R, and sgp130 was monitored in the CSF of nine patients following subarachnoid hemorrhage onset [11]. IL-6 increased immediately after onset, while the rise in sIL-6R and sgp130 was delayed by about 24 hours. The soluble receptors appear to have been acting in a buffering complex to mitigate IL-6 driven signaling. Notably, the decline in sgp130 levels after day 5 was associated with an increased risk for cerebral vasospasm, suggesting that continued dampening of IL-6 trans signaling could prevent this deleterious complication.

APOE4 interactions: Unknown

Aging and related health concerns: May reduce pathogenic inflammatory processes associated with elevated IL-6 trans signaling in colitis and cardiovascular disease.

Types of evidence:

- 2 Phase 2 RCTs for IBS and ulcerative colitis
- 18 observational studies on serum levels of sgp130, IL-6, and sIL-6R
- Numerous laboratory studies

Colitis: Potential benefit

Olamkicept is currently being tested in a double-blind, placebo-controlled Phase 2 RCT for patients with ulcerative colitis (n=90) (NCT03235752). An open-label Phase 2 study (n=20) for patients with irritable bowel syndrome testing 600 mg olamkicept intravenously (IV) in seven infusions over 12 weeks completed in 2018, but the results have not been posted (EUCTR2016-000205-36-DE). Olamkicept is

initially being tested in indications involving inflammation of the colon likely because a preclinical study in mice found that IL-6 mediated phosphorylation of STAT3 was driven by IL-6 trans signaling in the colon, while sgp130Fc had only partial or minimal effectiveness at blocking IL-6 mediated STAT3 phosphorylation in the lung or liver [12]. In mice, increased IL-6 signaling exacerbates colitis and promotes the induction of colitis-associated colorectal cancer, while blocking trans signaling with sgp130Fc (50 ug i.p.) prevented these inflammatory and proliferative effects in response to toxin exposure [13].

Cancer: Mixed potential benefit/harm depending on tumor type

IL-6 secreted by M2 macrophages promotes tumor formation in some types of cancer [14]. However, the effects of IL-6 may depend on whether it is engaging in classical signaling via the membrane IL-6R or trans signaling via the sIL-6R. Serum levels of sgp130 were found to be increased in cancer patients (n=74) relative to controls, and there was a correlation in levels of sgp130 and the cell adhesion molecule sICAM-1 in patients with disease progression [15]. This study does not address whether the progression is due to an elevation in IL-6 signaling that is not effectively being inhibited by sgp130, or due to the inhibition of trans signaling by sgp130. A study in patients with biliary tract cancer (n=367) found that higher expression of IL-6 mRNA in the tumor was associated with better survival, and in cell culture sgp130Fc treatment promoted tumor cell proliferation and migration [16].

Meanwhile, blocking trans signaling with sgp130Fc was found to reduce tumor growth or formation in preclinical models of colorectal, lung, and pancreatic cancers [17; 18; 19]. Notably, IL-6 and/or sIL-6R have been found to be upregulated in serum and tumor tissues in patients with these types of cancer, implicating IL-6 trans signaling in disease pathogenesis. These studies suggest that sgp130Fc may be beneficial for a subset of cancer patients with high levels of IL-6 trans signaling. However, the efficacy of anti-IL6/6R mAbs seen in preclinical models has largely failed to translate to patients, and only marginal benefits have been achieved when used in combination therapies, thus unless the simultaneous inhibition of classical signaling limits the efficacy of the mAbs, potential benefits from sgp130Fc therapy are also likely to be marginal in this population.

Liver disease: Potential harm in inhibiting IL-6 trans signaling (preclinical)

Based on preclinical studies, IL-6 mediated inflammation in the liver is driven by classical signaling, and **inhibition of trans signaling may exacerbate damage in some contexts**. In the methionine and choline deficiency induced model of non-alcoholic steatohepatitis (NASH), IL-6 is not elevated, and sgp130Fc had no effect on steatosis or liver inflammation [20]. While the choice of model may have played a role

in the outcome of this study, other studies suggest sgp130Fc is unlikely to be protective against IL-6 mediated liver inflammation. In C57Bl/6 mice, IL-6 mediated STAT3 phosphorylation in the liver was shown to be driven by classical signaling, and could not be inhibited by sgp130Fc [12]. Furthermore, IL-6 trans signaling was shown to play a protective role in acute acetaminophen-induced liver injury in mice by promoting the refiling of hepatocyte glycogen stores [21]. In this context, inhibition of trans signaling with sgp130Fc (250 ug i.p.) induced hepatocyte cell death.

Bone healing: Potential benefit (preclinical)

IL-6 plays a role tissue repair, including fracture callus remodeling. In mice, it was found the protective effects of IL-6 are mediated by classical signaling, while trans signaling impaired recovery [22]. Treatment with sgp130Fc (0.5 mg/kg i.p.) following femur injury improved bone healing based on accelerated cartilage to bone transformation, enhanced bony bridging of the fracture gap, and improved mechanical callus properties.

Spg130 as a biomarker for cardiovascular health

Components of IL-6 trans signaling, including IL-6, sIL-6R, and sgp130 have been assessed in a variety of observational studies as **potential biomarkers for disease risk and severity**. However, these studies can be difficult to interpret if the components are not reported in relation to one another. A rise in IL-6 could activate both classical and trans signaling. A rise in sIL-6R in conjunction with IL-6 could indicate increased trans signaling, however, it depends on how much of the IL-6/sIL-6R complex is bound by the inhibitory receptor, sgp130. The time course and longitudinal trajectory of these components is also critical for meaningful interpretation. A rise in sgp130 typically follows a rise in IL-6, thus high levels of spg130 could be a compensatory response to elevated IL-6 signaling, in which case high sgp130 (in absolute terms) would be associated with an inflammatory disease state. However, if the rise in sgp130 is blunted relative to the level of IL-6, particularly in the context of chronic inflammation, then low sgp130 (in relative terms) would be associated with an IL-6 mediated inflammatory disease state. Consequently, several studies have found that elevated levels of sgp130 up to around the 75th percentile are associated with worse outcome, likely indicative of elevated IL-6, while those with the highest levels >90th percentile had the best outcomes, likely indicative of a high endogenous IL-6 buffering capacity [23; 24]. While most studies do not capture the complete array of IL-6 components, the collection supports a **role for elevated IL-6 trans signaling in cardiovascular pathology**.

Cardiovascular disease: Potential benefit (based on sgp130 biomarker) Elevated

IL-6 trans signaling is associated with increased risk for adverse cardiovascular events. In patients (n=369) admitted to the hospital following ST elevation myocardial infarction (STEMI), IL-6 increased by three-fold within 24 hours and declined within 2 weeks in conjunction with the rise in components of the buffer complex, sIL-6R and sgp130 [25]. Higher levels of IL-6 were associated with larger infarct size and lower left ventricular ejection fraction, suggesting that trans signaling promoted cardiac damage.

In Swedish 60-year-old adults (n=4232), each 0.1 unit increase in the ratio of the active trans signaling complex (IL-6/sIL-6R) to the sgp130 containing buffered complex (IL-6/sIL-6R/sgp130) was associated with an increase in the risk for cardiovascular events (Hazard Ratio HR: 1.31, 95% Confidence Interval (CI) 1.13 to 1.51) [23]. Amongst those classified as low risk for cardiovascular events based on LDL-c ≤ 4 mmol/l, having an elevated active to buffered IL-6 complex ratio was associated increased cardiovascular event risk (HR: 1.59; 95% CI 1.24 to 2.05) [26]. Individuals with a **high IL-6 trans signaling complex ratio and high LDL-c (>4 mmol/l) were found to be at the highest risk for cardiovascular events** (HR: 2.17; 95% CI 1.68 to 2.80).

Atherosclerosis: Potential benefit (preclinical)

In patients with coronary artery disease, individuals with coronary lesions (n=128) had higher circulating levels of IL-6 and lower levels of spgp130 relative to those without lesions (n=48) [27]. There was an inverse correlation between level of sgp130 and atherosclerosis severity based on Gensini Score (r=-0.295, P<0.001). In a separate study of Chinese men with coronary artery disease (n=254), serum sgp130 levels were decreased relative to controls (n=122) and were positively correlated with estradiol levels [28]. A preclinical study in mice (Ldlr-/- on high fat diet), supports a mechanistic role for IL-6 trans signaling in atherosclerosis [29]. Blocking trans signaling in these mice using sgp130Fc (0.5 mg/kg i.p. 2x/week) inhibited STAT3 phosphorylation in the aorta, which reduced endothelial cell activation, cell adhesion molecule (ICAM-1 and VCAM-1) expression, and monocyte infiltration. Treatment also promoted the induction of anti-atherosclerotic regulatory T cells. These changes resulted in a regression of the atherosclerotic plaques. Notably, these changes occurred independently from changes to serum lipid levels, which are affected by classical IL-6 signaling.

Diabetes: Unclear

Several studies have found an association between sgp130 levels and metabolic dysfunction, including insulin resistance. In women with polycystic ovary syndrome (n=78), serum sgp130 was inversely correlated with insulin sensitivity (r=-0.36) [30]. In adults over age 65 (n=997), an association of sgp130

with metabolic syndrome lost significance after adjustment for insulin resistance [31]. This is expected to be related to the activation of IL-6 mediated inflammatory processes, however, the **direction of the relationship between IL-6 or sgp130 with insulin resistance is still unclear**. IL-6 and sIL-6R have been shown to increase glucose transport in an insulin independent manner, and may play an important role in energy utilization during exercise. IL-6 has also been shown to increase GLP-1 and Lp(a) synthesis [32]. An observational study (n=485), found that patients with type 2 diabetes had high levels of 1L-6 and comparatively lower levels of the sIL-6R/sgp130 buffer [32]. Meanwhile, atherosclerotic individuals without diabetes had lower than average levels of sIL-6R and sgp130, but because IL-6 was not elevated, the buffer system was still able to keep IL-6 trans signaling in check. These studies suggest that type 2 diabetic patients have unchecked IL-6 signaling, but more information is needed to determine whether blocking IL-6 trans signaling with sgp130Fc would have long-term benefits for glucose regulation.

Safety: Good safety profile in short term clinical studies. The risks of long-term use have yet to be determined. May potentially interfere with liver regeneration.

Types of evidence:

- 2 Phase 1 clinical trials (Healthy adults, Crohn's disease)
- Several laboratory studies

Olamkicept has been tested for safety and tolerability in single ascending dose (SAD) and multiple ascending dose (MAD) Phase 1 studies in healthy volunteers and in patients with Crohn's disease for up to 4 weeks of weekly IV infusions. According to the clinical trial protocol for NCT03235752, olamkicept demonstrated good safety in the Phase 1 studies showing dose-proportional exposure from 0.75 to 750 mg and no dose-dependent trends in adverse events (Protocol CTJ301UC201). However, the full study details have not been made available. Based on its mechanism of action, as a modified version of the endogenous IL-6 trans signaling inhibitor, sgp130, olamkicept would be expected to be well tolerated at low doses. Since sgp130Fc is 10 to 100 times more effective at inhibiting trans signaling relative to endogenous sgp130, olamkicept may produce side effects at high doses which completely inhibit trans signaling. Additionally, *in vitro* studies have found that at very high concentrations under conditions where molar levels of sIL-6R exceed those of IL-6, sgp130Fc can inhibit both trans and classical IL-6 signaling [12], and would have a side effect profile similar to anti-IL-6R mAbs. Therefore, the relevant therapeutic window likely depends on an individual's levels of IL-6 and sIL-6R.

Although IL-6 mediated effects on tissue repair are primarily driven by classical signaling, in some tissues, such as the liver, trans-signaling also plays a role in regenerative processes [4]. Similarly, some cancers driven by classical IL-6 signaling may be exacerbated by the inhibition of trans signaling.

The drug-drug interactions for olamkicept have not been established, but olamkicept would be expected to have interactions with other therapeutics that influence IL-6 levels or signaling.

Sources and dosing:

Olamkicept is being developed for inflammatory bowel conditions including irritable bowel syndrome and ulcerative colitis. The optimized form of spg130Fc, olamkicept, was originally developed by Conaris Research Institute, which holds the patent. It was licensed to Ferring Pharmaceuticals for clinical development. They tested olamkicept in a Phase 2 open label trial for irritable bowel syndrome in which 600 mg olamkicept was given IV in seven infusions over 12 weeks. In 2016, Ferring granted rights to I-MAB Biopharma (China) for the development of olamckicept for autoimmune conditions, with the option for worldwide rights (Press Release). I-MAB is currently testing olamkicept in a Phase 2 RCT for ulcerative colitis at 300 mg and 600 mg given IV over 12 weeks with infusions on days 0, 14, 28, 42, 56, 70 (i.e. every two weeks). A dosing schedule that is clinically safe and effective has not yet been established.

Research underway:

Olamkicept is currently being tested in a Phase 2 double blind, placebo controlled RCT for ulcerative colitis (n=90) sponsored by I-MAB Biopharma (NCT03235752). The trial has an estimated completion date in June 2020.

Search terms:

Pubmed, Google: Olamkicept, sgp130Fc, TJ301, FE999301 +

- Alzheimer's disease, cognition, inflammation, aging, colitis, cardiovascular, cancer, diabetes, clinical trial, safety

Websites visited for Olamkicept:

- Clinicaltrials.gov
- PubChem

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