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.

GDF-11

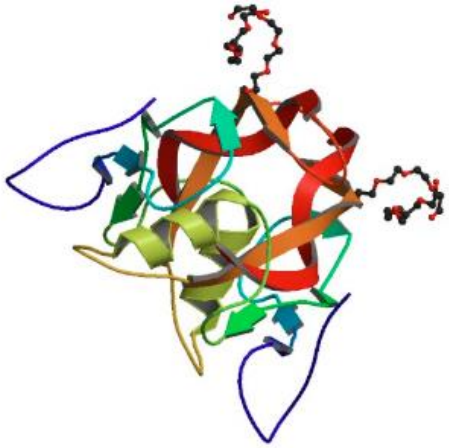
Evidence Summary

There is some interesting evidence that GDF11 may be an anti-aging factor, though several controversies still need to be resolved.

Neuroprotective Benefit: Several preclinical studies suggest that GDF11 may be beneficial in aged animals.

Aging and related health concerns: Although it is still controversial whether GDF11 levels decline with age, treatment with GDF11 has been beneficial in several disease models.

Safety: It is still unclear whether GDF11 treatment would be safe.

Availability: Not available, currently in development	**Dose**: Not established;	**Molecular Formula:** 407 amino acids **Molecular weight:** 12.5kDa (active ligand) **Source:** PDB 
Half life: Not known (will depend on the preparation of a final candidate).	**BBB**: Not penetrant (in rodents)	
Clinical trials: 0	**Observational studies**: 0	

What is it?

GDF11 was identified as a putative factor responsible for some of the beneficial effects of parabiosis. It is a member of the activin/myostatin subclass of the TGFβ superfamily. Initial reports (from the Lee/Wagers lab) that GDF11 declines with age were refuted by other groups claiming that the drop was actually due to cross-reactivity with GDF8, a protein that shares 90% homology with GDF11. Although Lee/Wagers acknowledged that the GDF11 antibody does cross-react with GDF8, they conducted further studies supporting the notion that GDF11 declines with age. Overall, the evidence is still unclear whether GDF11 declines with age or whether GDF11 would be a beneficial intervention.

Neuroprotective Benefit for: Several preclinical studies suggest that GDF11 may be beneficial in aged animals.

Types of evidence:

- One study of GDF11 levels in dementia patients
- Several preclinical studies in aged rodents and stroke models

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

None

Human research to suggest benefits to patients with dementia

Yang et al (2017) reported that GDF11 levels did not change with age or in dementia patients.

Mechanisms of action for neuroprotection identified from laboratory and clinical research

Four-week treatment

Zhang et al (2018) reported that twice daily treatment (totaling 0.1mg/kg) with rGDF11 in Alzheimer's mice improved cognition, had little effect on amyloid, increased VEGF expression around brain blood vessels, increased blood vessel density and cerebral blood flow, reduced expression of inflammatory proteins (GFAP and Iba-1) in the brain, and increased the expression of vascular-related proteins in the brain. Furthermore, treatment with rGDF (0.1mg/kg) in aged mice increased blood vessel density and increased neurogenesis in the subventricular zone (Katsimpardi et al, 2014).

Daily rGDF11 (1mg/kg) also increased hippocampal neurogenesis, blood vessel density, and synaptic density in aged animals. Three lines of evidence suggested that rGDF11 does not cross the blood brain barrier: the lack of downstream signaling in the brain after rGDF11 administration, the suggestion that rGDF11 inhibits the proliferation of neural stem cells *in vitro*, and no evidence of biotin-labeled rGDF11 in the brain after administration. Rather, rGDF11 was reported to act on brain endothelial cells which may mediate its downstream brain effects (Ozek et al, 2018).

Single dose

A single rGDF11 treatment also improved performance on a novel object recognition task in middle-aged, but not young, mice (Zhang et al, 2018).

Stroke

In an aged rodent model of intracerebral hemorrhage, daily rGDF11 treatment (0.1mg/kg started 28 days prior to hemorrhage) improved neurological outcomes, and reduced brain edema, microglial activation, apoptosis, oxidative stress, and mitochondrial damage (Anqi et al, 2019). In a rodent model of cerebral ischemia/reperfusion, daily rGDF11 (0.1mg/kg) improved behavioral outcomes, increased the proliferation of endothelial cells, and increased the number of cerebral blood vessels (Ma et al, 2018). In a rodent model of ischemic stroke, rGDF11 (0.1mg/kg) treatment 7 days after stroke increased the proliferation of stem cells, the proliferation of endothelial cells, the number of cerebral blood

vessels, the expression of BDNF and VEGF, the number of new neurons, and improved behavioral outcomes. These beneficial effects were blunted by coadministration of a TGF-β inhibitor (Lu et al, 2018).

APOE4 Effects
None Reported

Aging and related health concerns: Although it is still controversial whether GDF11 levels decline with age, treatment with GDF11 has been beneficial in several disease models.

Types of evidence:

- 7 studies on GDF11 levels in humans
- 5 human studies on the association of GDF11 levels with diabetes or cardiovascular disease, 2 human studies on the association of GDF11 levels and osteoporosis
- 6 studies on GDF11 levels in rodents
- 2 preclinical studies on lifespan with GDF11 treatment
- 4 preclinical studies on GDF11 as a treatment for cardiac hypertrophy
- 1 preclinical study of GDF11's effects on metabolism
- 2 preclinical studies on GDF11 treatment and cardiovascular disease
- Several preclinical studies on GDF11 treatment and other age-related diseases

Does GDF11 decline with age? – There is still no consensus whether GDF11 declines with age.

- ***Yes (rodent – immunoassay, binds to GDF11/GDF8)*:** The interest in GDF11 began in 2013 when a paper reported that four weeks of heterochronic parabiosis improved age-related cardiac hypertrophy in old mice. Using an aptamer-based proteomic screen, 13 analytes distinguished young mice from old mice. In aged mice, GDF11 protein was decreased in the plasma and the spleen, and GDF11 mRNA was decreased in the spleen (Loffredo et al, 2013, Lee/Wagers group). In anotherstudy, Sinha et al, 2014 reported that GDF11, but not GDF8 (myostatin), decline in the plasma and muscle with age.
- ***No (rodent, human – immunoassay that does not bind to GDF8)*:** These results were later disputed by several groups. A group at Novartis (Egerman et al, 2015) reported that the antibody used in Loffredo et al (2013) bound to both GDF11 and the related protein GDF8. They found that although GDF11/GDF8 monomers decreased with age, dimeric GDF11/GDF8 increased with age (dimeric GDF11/GDF8 was not presented in Loffredo et al, 2013). Egerman et

al, 2015 developed an assay that detected GDF11 but not GDF8. Although the assay was not sensitive enough to detect GDF11 in young or aged mice, there were trends for increased GDF11 in serum from aged rats and humans (n = 19). GDF11 mRNA in muscle tissue similarly increased with age in mice.

  - In a point/counterpoint (Harper et al, 2016), the two groups discussed possibilities for the divergent results. The Houser group (Smith et al) suggests that the Lee/Wagers group (Loffredo et al and Sinha et al) incorrectly measured GDF11 levels with an antibody that binds to both GDF11/GDF8 and did not show data for the dimeric form of GDF11/GDF8, which was greater in their study than the monomeric form. Lee/Wagers counter this response saying that they saw similar result with an antibody that was specific for GDF11 (data unpublished).

- ***Yes (mammals – immunoassay that bind to GDF11/GDF8 – controlled for IgG)*:** The Lee/Wagers group acknowledged that the GDF11 antibody binds to both GDF11/GDF8. They later reported (Poggioli et al, 2016) a reduction of GDF11/GDF8 in multiple mammalian species with age (mice, rats, horses, and sheep). Again, there were decreases in *Gdf11* gene expression in the spleen and kidney, but not in skeletal muscles. They reported there are other studies showing no reduction in *Gdf11* mRNA in skeletal muscle. They also suggested that the GDF11/GDF8 antibody also binds to purified IgG, and this is the dimeric band identified in Egerman et al (2015). Lee/Wagers reported that IgG is well-known to increase with age, and when they examined GDF11/GDF8 binding on serum from a mouse model that is incapable of producing IgG (Rag1 KO), the dimeric band is absent. IgG depletion from mouse serum also eliminated the dimeric band, suggesting that the increase in GDF11/GDF8 might be an artifact from an increase in IgG with age (Poggioli et al, 2016).
- ***No (humans – LC-MS/MS)*:** Using a quantitative LC-MS/MS method to detect GDF11 and GDF8, Schafer et al (2016) reported that GDF11 did not decline with age, while GDF8 (MSTN) declined with age in men but not women (n = 140).
- ***No (humans – immunoassay that does not bind to GDF8)*:** Liang et al (2019) reported that GDF11 increased in individuals in their 20s, remained relatively stable in individuals in their 30s-50s, and increased in elderly individuals (n = 152). They confirmed that the ELISA did no cross react with GDF8. There was also large variability in the study.
- ***No (human – LC-MS)*:** Using a multiplexed selected reaction monitoring assay and LC-MS, Semba et al (2018) reported a positive correlation with age for the GDF11 prodomain (r=0.3, p=0.001) and GDF11 (r=0.23, p=0.004). In this study, there was also a great deal of variability, questioning whether it is a good biomarker for individual levels or whether the changes really alter the aging process.

- ***No (humans – same immunoassay as Egerman et al, 2015)*:** GDF11 levels were positively correlated with age (r=0.22, p=0.001) in 238 elderly Chinese women (Jin et al, 2016).
- ***Yes (rodent)*:** Katsimpardi et al (2019) reported that GDF11 was detectable in young but not aged mice using a GDF11 antibody. However, injection of rGDF11 increased levels while injection of recombinant myostatin (rMST) had no effect (suggesting that levels of GDF11 declined below measurable levels in old animals). Long-term CR also increased serum GDF11 to levels found in young mice.
- ***No (human – immunoassay, no information on specificity)*:** Bueno et al (2016) reported that GDF11 was concentrated in platelets with low concentrations in the serum and plasma (n=23). Serum, but not plasma, GDF11 levels increased with age. They suggest that some of the discrepancies in previous studies could be due to the preparation of the blood before measurement.
- ***Yes (rodent – immunoassay, no information on specificity)*:** Zhou et al (2016) compared GDF11 levels across lifespan in two strains of mice and found that GDF11 declined with age in both strains. Then, examining the levels of GDF11 in 22 genetically diverse strains of mice, they estimated that 74.52% of the phenotypic variation of GDF11 levels in middle age were attributable to strain background. Higher levels of GDF11 at middle age were associated with increased lifespan (r^2=0.5234, p=0.0015). They identified 7 candidate genes that may be associated with GDF11 levels (Ano7, Kpna4, Adamts2, Dsp;Snrnp48, Dsp, Rnf144b, Nrxn1).

Lifespan

- ***No effect (rodent)*:** In a mouse model of accelerated aging, GDF11/GDF8 levels declined with age. Daily treatment with GDF11 (0.1mg/kg) did not increase lifespan (Freitas-Rodriguez et al, 2016).
- ***Benefit (fish)*:** In the fish *Nothobranchius guentheri*, GDF11 expression declined with age. Administration of rGDF11 reduced oxidative stress and senescent cells and increased lifespan (Zhou et al, 2019).

Cardiac hypertrophy

- ***Benefit (rodents)*:** Daily treatment with recombinant GDF11 (rGDF11) (0.1mg/kg, I.P.) over 30 days reduced the heart weight-to-tibia length ratio (their reported measure of cardiac hypertrophy) and reduced markers associated with cardiac hypertrophy. The investigators suggested this was specific for age-related cardiac hypertrophy as GDF11 treatment in young mice exposed to pressure overload had no effect on cardiac hypertrophy (Loffredo et al, 2013).

Four-week treatment with rGDF11 increased the frequency and DNA quality of satellite cells in the muscle. Four-week treatment before and seven-day treatment after cryoinjury increased the regenerative capacity of muscles. In uninjured muscle, rGDF11 improved mitochondrial morphology, increased the expression of PGC-1α (a regulator of mitochondrial biogenesis), and increased basal levels of autophagy. rGDF11 also increased endurance capacity (Sinha et al, 2014).

- ***Harm (rodents)*:** Similar to the Sinha et al (2014) experiment, Egerman et al, 2015 treated aged mice with rGDF11 (0.1mg/kg, I.P.) for 28 days before and seven days after cardiotoxin injury to skeletal muscle and saw no improvement in regenerative capacity after treatment and an impairment of muscle regeneration in young mice given high-dose GDF11 with a cardiotoxin injury to skeletal muscle . Another group at Boehringer Ingelheim (Smith et al 2015) reported that 28-day treatment with rGDF11 (0.1mg/kg) had no structural or functional effect on cardiac hypertrophy in 24-month-old mice, and, in fact, reported that aged hearts are not pathologically large as the heart/body weight ratio (which they claim is the correct measure) in aged mice is similar to younger mice.
    - In the point/counterpoint article (Harper et al, 2016), the Houser group suggested that the Lee/Wagers group did not properly prepare and characterize their rGDF11 and point to a subsequent study where Lee/Wagers had to use higher doses of rGDF11 to have an effect. Lee/Wagers acknowledges there were lot differences but suggested that they had properly characterized the recombinant protein. The Houser group also suggested that Lee/Wagers' measure of cardiac hypertrophy was incorrect. rGDF11 and parabiosis reduce body weight, and that heart weight reduces in line with body weight reduction. Measuring the heart weight-to-tibia length (which Lee/Wagers did) as a measure of cardiac hypertrophy likely produced an artifact whereas measuring heart weight-to-body weight is a more correct measure.

Metabolism

- ***Benefit (rodents):*** rGDF11 injection (1mg/kg, serum levels ~399pg/ml) into aged mice reduced body weight (no difference in food intake or activity) and visceral white adipose tissue (WAT) while muscle mass remained the same. Weight loss stabilized when mice were injected with rGDF11 for two weeks and then not injected for three weeks. rGDF11 treatment in aged mice was associated with a reduction in fasting insulin (but not non-fasting insulin), a reduction in IGF-1, and an increase in adiponectin levels (Katsimpardi et al, 2019).
- ***Null (humans – immunoassay, reported to be specific for GDF11)*:** Using an immunoassay reported by the manufacturer to be specific for GDF11, Anon-Hidalgo et al (2019) reported that

GDF11 levels increase into the 40s-50s and decline in the elderly (n=319). There was no association between GDF11 levels and gender, obesity, or glycemic status.

- **Harm (humans):** In a cross-sectional study, GDF11 levels were higher in patients with type 2 diabetes (T2DM) than in controls. This difference was driven by patients with T2DM and comorbid cardiovascular disease. GDF11 declined with age in control subjects (r=-0.50, p=0.0013) but did not decline with age in patients with T2DM (r=0.03, p=0.865) (Fadini et al, 2015).

Cardiovascular

- ***Harm (humans – LC-MS/MS)*:** GDF11 was increased in patients with diabetes, a history of previous cardiac conditions, and previous coronary artery bypass. GDF8 levels were not associated with any comorbid conditions. GDF11, but not GDF8, was also higher in frail individuals and predicted adverse outcomes after surgery (Schafer et al, 2016).
- ***Benefit (humans – immunoassay that binds to GDF11/GDF8)*:** In the Heart and Soul cohort (n = 928), higher GDF11/GDF8 were associated with lower age. Each SD increase in GDF11/GDF8 were associated with a reduced risk of heart failure hospitalization (HR = 0.79; 95%CI 0.64-0.97), stroke (HR = 0.69; 95%CI 0.45-1.02), myocardial infarction (HR = 0.75; 95%CI 0.59-0.95), and death (HR = 0.74; 95%CI 0.64-0.85) after a median follow-up of 8.9 years (Olson et al, 2015).
- ***Harm (rodents):*** Intramuscular injection of GDF11-expressing cells into the hindlimb of young mice reduced body weight and organ size, reduced heart mass, impaired heart function, reduced muscle mass, and impaired muscle function. Injection of GDF11-expressing cells increased circulating GDF11 by 37%, though the exact amount was not reported (Zimmers et al, 2017).
- ***Benefit (rodents; humans – immunoassay that binds to GDF11/GDF8)*:** Mei et al (2016) reported that rGDF11 administration or AAV-GDF11 treatment improved several metabolic and inflammatory measures (IL-6, TNFα, CRP, ox-LDL, triglycerides, free fatty acids, and glucose tolerance) in a mouse model of atherosclerosis (ApoE null with high fat diet) over 12 weeks. rGDF11 or AAV-GDF11 improved endothelial-dependent (but not independent) relaxation, reduced endothelial cell death, reduced plaque size, reduced the levels of inflammatory cytokines, reduced the number of infiltrating inflammatory cells, and improved phenotypic plaque stability.
    - In a study of 185 Chinese individuals, circulating GDF11/GDF8 levels were lower in overweight subjects (p=0.002), correlated with flow-mediated endothelium-dependent dilation (r=0.452), and declined with age.

Osteoporosis

- ***Harm (humans – same immunoassay as Egerman et al, 2015)*:** GDF11 levels were inversely correlated with bone mineral density (-0.19, $p<0.05$) in 238 elderly Chinese women, and those with GDF11 in the highest quartile had a greater prevalence of osteoporosis (lumbar spine OR = 2.7; 95%CI 1.3-5.7; femoral neck OR = 3.2; 95%CI 1.3-8.0) (Jin et al, 2016).
- ***Harm (humans – same immunoassay as Egerman et al, 2015)*:** In 169 postmenopausal Chinese women, serum GDF11 levels increased with age ($r=0.601$, $p<0.01$). There was also an inverse correlation between serum GDF11 and bone mineral density ($r=-0.15$, $p<0.05$) (Chen et al, 2016).

Rheumatoid arthritis

- ***Benefit (rodents)*:** In a rheumatoid arthritis model, rGDF11 suppressed inflammation, improved symptoms, and reduced arthritis pathology (Li et al, 2018).

Oxidative stress

- ***Benefit (rodents)*:** Using recombinant proteins from the fish *Nothobranchius guentheri*, Zhou et al (2019) reported that rGDF11, but not rGDF8, reduced the levels of advanced glycation end products, markers of senescent cells and lipofuscin in the liver, and protein and lipid oxidation.

Liver fibrosis

- ***Benefit (rodents)*:** GDF11 expression was upregulated in patients and rodents with liver fibrosis. Hepatic overexpression of GDF11 (AAV-GDF11) in a rodent model of liver fibrosis attenuated the disease (Dai et al, 2019).

Safety: It is still unclear whether GDF11 treatment would be safe.

Types of evidence:

- *Several studies on GDF11 levels in humans*
- *Several preclinical studies on treatment*

There are no reports of GDF11 administration in humans. Based on the preclinical and biomarker studies above, GDF11 treatment may have some harmful effects on cardiovascular disease and skeletal muscle (Zimmers et al, 2017). GDF11 is elevated in certain conditions such as diabetes, liver fibrosis, and osteoporosis (Dai et al, 2019, Jin et al, 2016, Schafer et al, 2016). Whether it is causative or an effect of these conditions is not known.

Drug interactions:
No known drug interactions.

Sources and dosing:
GDF11 is not currently available, and the optimal dose is unknown.

Research underway:
Elevian is developing GDF11 as a therapeutic for Alzheimer's disease. They are currently in preclinical studies.

Search terms:
GDF11

Websites:
Clinicaltrials.gov
Pubmed