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.

Lrp1 Modulators

Evidence Summary

Lrp1 has a variety of essential functions, mediated by a diverse array of ligands. Therapeutics will need to target specific interactions.

Neuroprotective Benefit: Lrp1-mediated interactions promote Aβ clearance, Aβ generation, tau propagation, brain glucose utilization, and brain lipid homeostasis. The therapeutic effect will depend on the interaction targeted.

Aging and related health concerns: Lrp1 plays mixed roles in cardiovascular diseases and cancer, dependent on context. Lrp1 is dysregulated in metabolic disease, which may contribute to insulin resistance.

Safety: Broad-spectrum Lrp1 modulators are untenable therapeutics due to the high potential for extensive side effects. Therapies that target a specific Lrp1-ligand interaction are expected to have a better therapeutic profile.

Availability: Research use S16 is in clinical trials	**Dose**: N/A	**Chemical formula:** N/A **MW**: N/A
Half life: N/A	**BBB**: Angiopep is a peptide that facilitates BBB penetrance by interacting with Lrp1	
Clinical trials: S16, an Lrp1 agonist was tested in healthy volunteers (n=10) in a Phase 1 study.	**Observational studies**: sLrp1 levels are altered in Alzheimer's disease, cardiovascular disease, and metabolic disease	

What is it?

Low-density lipoprotein receptor-related protein (Lrp1) is a multi-functional receptor involved in endocytosis, cell signaling, energy homeostasis, and lipid metabolism [1]. It is ubiquitously expressed, and **plays a role in a variety of essential cellular functions**, such that a global deletion is embryonic lethal. Due to its myriad functions, broad-spectrum activation or inhibition of Lrp1 is not considered a viable therapeutic strategy. Instead, therapies will likely need to target a specific Lrp1-ligand interaction. Lrp1 is comprised of two non-covalently bound subunits, the N-terminal α domain, and the C-terminal β domain [2]. The extracellular α domain contains four ligand binding clusters. Each ligand binding cluster contains different charge densities and hydrophobic patches, which allow for distinct ligand interactions per cluster [3]. As a result, it is possible to selectively target specific ligand-family interactions, at least for some ligands.

Only a few of these types of therapeutics have been clinically tested thus far. SP16 is a cardioprotective specific Lrp1 agonist being developed by Serpin Pharma for myocardial infarction [1]. GRN1005 (ANG1005) contains an Lrp1-interacting peptide called angiopep-2, which promotes BBB transport via Lrp1. It is being developed by Angiochem Inc, for cancer. The company has several other angiopep-containing drugs in their preclinical pipeline.

Neuroprotective Benefit: Lrp1-mediated interactions promote Aβ clearance, Aβ generation, tau propagation, brain glucose utilization, and brain lipid homeostasis. The therapeutic effect will depend on the interaction targeted.

Types of evidence:

- 1 meta-analysis of gene association studies
- 4 biomarker studies for sLrp1 levels
- Numerous laboratory studies

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

No Lrp1 specific modulators have been clinically tested in neurological diseases. Statins, which are widely used cholesterol-lowering agents, are known to increase vascular expression of Lrp1, which is expected to enhance the clearance of Aβ [2]. While not conclusive, the majority of evidence suggests that statin treatment may lower dementia risk, although it is not known whether the modulation of Lrp1plays any role [4].

Human research to suggest benefits to patients with dementia: None

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

Alzheimer's disease: LRP1 PLAYS A MIXTURE OF ROLES IN AD

Lrp1 plays an integral role in a variety of processes that are impacted in Alzheimer's disease (AD). While the majority of its activities appear to be beneficial with respect to AD, activities that negatively impact AD have also been reported. Overall, Lrp1 itself cannot be considered as good or bad, as **it is the sum of its interactions with its multitude of partners that control whether it exerts a net positive or negative effect in a given context.** Consequently, a meta-analysis of gene association studies concluded that Lrp1 variants were not significantly associated with AD (Odds ratio OR: 1.05, 95% Confidence Interval CI 0.91 to 1.21), although individual studies report associations [5]. Because the impact of an Lrp1 variant is context dependent with respect to one's overall genetic makeup and environmental factors, the functional effects can be difficult to detect when examining a heterogenous population. The associations appear to be driven by a combinatorial effect when individuals have an Lrp1 variant in addition to a variant in another gene known to be involved in AD which can interact with Lrp1. In this

way, the same Lrp1 variant could be associated with reduced AD risk when in combination with one AD-variant, but increased AD risk when combined with a different AD-variant.

Overall Lrp1 levels tend to decline in the context of aging and AD, however, there appear to be local differences and time dependent changes throughout the progression of the disease [2]. Several studies suggest that there may be compensatory upregulation of Lrp1, at least in particular cell types, early in the disease course, and then a decline in advanced disease, which may stem from extensive (Lrp1 expressing) neuronal loss [6]. Furthermore, the levels may not be as relevant as the functional status of Lrp1. Both the expression level and functional modifications of Lrp1 are dependent on the cellular milieu. There is evidence to suggest that in the context of AD, Lrp1 undergoes modifications that impair some of its AD-mitigating functions [2].

Due to its context-dependent nature, the effect of Lrp1 is variable across AD animal models, with some showing benefit for elevating Lrp1, while others show benefit for reducing it. One of the challenges for assessing Lrp1 inhibition is that most studies use Lrp1 knockout animals, and the complete loss of all of Lrp1's functions, many of which are integral to cellular homeostasis, may confound the interpretation, and not accurately convey the effects of a more targeted therapeutic reduction. Another common approach is the use of the endogenous Lrp1 inhibitor RAP, which has the capacity to inhibit all known Lrp1 interactions to date. From a therapeutic standpoint, Lrp1 modulators will need to specifically target particular Lrp1-ligand interactions in order to leave other essential functions intact. Both activators and inhibitors could be viable, depending on the particular Lrp1-ligand interaction being targeted.

Aβ clearance: LRP1 FACILITATES Aβ CLEARANCE

The clearance of Aβ from the CNS is Lrp1's best characterized role in the context of AD. Lrp1 is expressed on vascular endothelial cells and choroid cells where it facilitates the transcytosis of Aβ out of the brain via the blood-brain-barrier (BBB) or blood-CSF-barrier [2]. Membrane-bound Lrp1 is cleaved into a soluble form (sLrp1) that circulates in plasma and typically sequesters 70 to 90% of plasma Aβ [7]. sLrp1-Aβ creates a peripheral sink that favors the efflux of Aβ from the CNS into the periphery. In healthy controls, sLrp1 levels were correlated with plasma Aβ40 levels, however, this correlation is lost in AD patients, suggesting a loss of the peripheral sink effect due to decreased levels of sLrp1 (244.6 vs 315.3 ng/ml, $p = 0.004$) [8]. In AD, there was also a 30 to 35% decrease in the amount of sLrp1-bound Aβ [7]. This may have been driven by the increased (280%) oxidation of sLrp1, which has a lower affinity to Aβ [7].

However, under some conditions Lrp1-mediated Aβ transport may promote vascular accumulation of Aβ. In this case, Aβ gets taken up into vascular smooth muscle cells instead of entering the circulation [9]. The degree of vascular accumulation may depend on levels of ApoE-containing HDL, as these particles can promote the transport of Aβ across the vascular wall into the circulation.

Hepatic Lrp1 also plays an important role in the systemic clearance of Aβ [10]. Metabolic disease can dampen the capacity of the liver to clear Aβ by reducing the expression of hepatic Lrp1. This may be one of the mechanisms by which metabolic and liver diseases increase AD risk.

Aβ generation: LRP1 CONTRIBUTES TO Aβ GENERATION

While Lrp1 has a prominent role in Aβ clearance, it can also affect its generation by influencing amyloid precursor protein (APP) processing [2]. Lrp1 plays a role in mediating endocytosis, and Lrp1-APP interactions mediate the internalization of APP into endosomal compartments in a manner that promotes amyloidogenic cleavage. In some AD models, Lrp1's effects on Aβ generation overwhelm those on Aβ clearance, highlighting the heterogeneity in the dominant effect of Lrp1 in different contexts [11].

Synaptic integrity: LRP1'S REGULATION OF LIPIDS IS ESSENTIAL FOR SYNAPSES

The maintenance of lipid homeostasis is critical for synaptic function [12]. The lipid membrane composition can modulate the composition of membrane-associated proteins. Cholesterol and sphingolipids are particularly important for lipid rafts, which are the regions that receptors embed and congregate. These regions are essential for protein clusters at synapses, such as the post-synaptic density. The loss of these cholesterol-rich regions can lead to a depletion of synaptic receptors, and thus a loss of synaptic integrity. In mice, the loss of Lrp1 from the forebrain led to a defect in brain lipid homeostasis resulting in progressive synaptic loss and neurodegeneration [13]. The loss of neuronal cholesterol led to a loss of glutamate NMDA receptor subunits.

Lrp1 interacts with lipoproteins in its regulation of lipid metabolism. ApoE is one of the lipoproteins that interacts with Lrp1 to deliver lipids, especially cholesterol, to neuronal synaptic sites [14]. However, this process is disrupted in AD, and is most impacted by the presence of the ApoE4 variant. ApoE can form complexes with Aβ, and these complexes enter synapses via Lrp1. In the control brain, the Aβ undergoes lysosomal degradation, but in the AD brain, the internalized Aβ is not readily cleared and builds up within the synaptic terminals [15]. Additionally, in AD, these complexes tend to be poorly lipidated, resulting in altered lipid levels as well as synaptic accumulation of Aβ. It is unclear whether targeting these complexes would be a therapeutically viable option, since they may also play a role in the

clearance of Aβ out of the CNS via the BBB. While ApoE4 appears to have lower affinity for soluble Aβ, leading to reduced clearance, higher levels of insoluble Apo-Aβ synaptic aggregates were detected in ApoE4 carriers, suggesting that ApoE4 carriers may preferentially benefit from such an intervention.

Neurons with a familial AD mutation (PS1ΔE9) were found to have an impairment in endocytic delivery of lipoproteins from the soma to the axon, which impedes synaptic maintenance [16]. The decline in lipoprotein endocytosis was attributed to a decrease in surface expression of Lrp1.

These studies all suggest that maintenance of Lrp1 mediated lipoprotein transport is crucial for synaptic preservation.

Energy homeostasis: REDUCED LRP1 IN DIABETES ASSOCIATED WITH COGNITIVE IMPARIMENT

Individuals with type 2 diabetes and mild cognitive impairment (MCI) had significantly lower levels of plasma sLrp1 relative to type 2 diabetics with normal cognition [17]. sLrp1 levels were positively associated with Montreal Cognitive Assessment (MoCA), Digit Span Test, and Clock Drawing Test scores. In this study, high sLrp1 levels were found to protect against MCI in type 2 diabetics (OR: 0.971, p = 0.005). Higher sLrp1 levels were also found to protect cognition in those with type 1 diabetes [18]. Increased cerebrospinal fluid (CSF) sLrp1 levels were associated with better attention, speed of processing, and white matter integrity. The increase in sLrp1 may be a response to increased Aβ levels, such that higher sLrp1 levels are associated with better Aβ clearance.

Lrp1 plays a central role in the regulation of energy homeostasis via lipid metabolism and insulin signaling. Lrp1 interacts with insulin receptor β to regulate insulin signaling and glucose uptake in the brain [19]. The effects on glucose uptake are primarily mediated through the insulin-regulated glucose transporters, GLUT3 and GLUT4. Insulin promotes the expression of Lrp1, which can enhance Aβ clearance. Hyperglycemia, or insulin deficient conditions suppress Lrp1, which may promote glucose hypometabolism in the brain. These effects may be exacerbated by a high-fat diet [20]. In the APP overexpressing mouse model of AD, chronic high-fat diet induced fatty liver disease accelerated pathological progression of AD, which was correlated with a reduction in brain Lrp1 expression [6]. Metabolic disturbances may drive dysregulation of Lrp1, which then exacerbates the impairment to energy homeostasis, ultimately leading to neuronal stress and loss.

Tau propagation: LRP1 PROMOTES TAU SPREADING

Lrp1 was found to have a significant gene interaction with tau, with respect to AD risk. Although neither single nucleotide polymorphism (SNP) was significantly associated with AD on its own, the combination

of a SNP in tau (intron 9, rs2471738, T allele) with a SNP in Lrp1 (exon 3, rs1799986, T allele) was associated with a six times higher risk for AD (OR: 6.20, 95% CI 1.74 to 22.05, p=0.005), in a case-control study (n=246) [21]. Individuals with this Lrp1 variant had higher brain levels of Lrp1, suggesting that this combination increases a pathological interaction between Lrp1 and tau. A separate small study (n=33) found that levels of an endogenous Lrp1 inhibitor, RAP, were inversely associated with tau levels in the AD brain [22].

Preclinical studies support a role for Lrp1 in tau spreading. Tau spread was reduced in a tau mouse model (AAV-GFP-P2A-hTau) when Lrp1 was knocked down [23]. In neuronal cell culture, genetic silencing of Lrp1 or treatment with the Lrp1 inhibitor, RAP, blocked tau uptake. The effect is mediated by an interaction between tau and subdomain 4 of Lrp1. Blocking this specific interaction may help mitigate tau spread, and those containing both the Lrp1 and tau synergistic variants would be expected to benefit preferentially.

APOE4 interactions: Lrp1 acts as a receptor for ApoE to facilitate cellular transport of lipids/cholesterol. ApoE may also contribute to the Lrp1-mediated clearance of Aβ. The interaction between ApoE and Lrp1 appears to be protective against Aβ in the context of the E2 and E3 variants, but to exacerbate pathology in the context of E4 [24]. In postmortem brain tissue, levels of insoluble Aβ were inversely associated with Lrp1 levels in E3/E3, but were positively associated with Lrp1 levels in E4 carriers [24]. ApoE-Aβ complex aggregates were also found at a higher level in the synaptic terminals of E4 carriers [15]. ApoE4 tends to be poorly lipidated relative to other ApoE variants, and the altered lipid profile may account for many of the negative phenotypes associated with the E4 variant.

While interfering with the ApoE-Lrp1 interaction may reduce some of the deleterious effects associated with cellular transport of ApoE4, it could potentially further disrupt overall lipid homeostasis. In heterozygous E4 carriers (i.e. E3/E4 or E2/E4), selective disruption of the ApoE4-Lrp1 interaction may mitigate E4-related pathology, while preserving the important lipid carrying functions of ApoE in general. E4 status will likely need to be a consideration of any Lrp1-based therapy for AD.

Aging and related health concerns: Lrp1 plays mixed roles in cardiovascular diseases and cancer, dependent on context. Lrp1 is dysregulated in metabolic disease, which may contribute to insulin resistance.

Types of evidence:

- 1 meta-analysis of 18 gene association studies
- 3 clinical trials (AAT and GRN1005)
- 2 gene association studies for Lrp1 and SCAD
- Numerous laboratory studies

Coronary disease: LRP1 PLAYS MIXED CONTEXT DEPENDENT ROLES

Lrp1 gene variants have been associated with increased risk and adverse outcomes for non-atherosclerotic coronary diseases, particularly in women. Although the effects are context dependent, many preclinical and a couple of early phase clinical studies suggest that Lrp1-mediating signaling is cardioprotective [1]. The discrepancy likely lies in the particular Lrp1-interaction/signaling pathways activated under different conditions.

In a plasma biomarker study (n=5,404), individuals who exhibited a coronary artery disease event had higher levels of sLrp1 (2.45 µg/mL, 95% CI 0.43 to 8.31 vs. 2.07 µg/mL, 95% CI 0.40 to 6.65 µg/mL, $p < 0.001$), such that elevated sLrp1 was associated with increased risk for coronary artery disease events (Hazard ratio HR: 1.30, 95% CI 1.01 to 1.67, $p = 0.039$) [25]. In a gene association study (n=489), female carriers of the Lrp1 SNP (rs1466535) T allele had a 5.6-fold higher risk for cardiovascular mortality (HR: 5.61, 95% CI 1.98 to 15.85, p=0.001) [26]. The presence of the T allele resulted in increased Lrp1 plasma levels (C/C genotype 20,994 ± 7,131 pg/ml, C/T 21,534 ± 7,969 pg/ml, T/T 23,409± 5,651 pg/ml). Elevated coronary Lrp1 increases the risk for spontaneous coronary artery dissection (SCAD), which is a tear in the wall of a coronary artery that reduces blood flow to the heart and can lead to a heart attack or sudden cardiac death [27]. SCAD predominantly affects young to middle-aged women. A genome association study including 484 women with SCAD and 1477 controls found that the Lrp1 SNP at 12q13.3 (rs11172113) T allele was associated with SCAD (OR: 1.67, 95% CI 1.42 to 1.97; $p = 3.62 \times 10^{-10}$) [27]. A similar association was seen in a replication cohort of 523 women. A separate gene association study (n=5, 533) found that the loci 12q13.3, within Lrp1, was also associated with SCAD in females (OR: 1.52, 95% CI 1.26 to 1.83, $p < 5 \times 10^{-8}$) [28]. These adverse outcomes may be driven by Lrp1's role in the modulation of vascular extracellular matrix remodeling, through the regulation of matrix metalloproteases, such as MMP-9 [27].

Lrp1 interacts with a variety of plasma proteases, including serine protease inhibitors (SERPINs) [1]. Several SERPINS act as Lrp1 agonists and induce cardioprotective pro-survival signaling.

A clinical feasibility trial (NCT01936896)(n=10) was conducted for the SERPIN alpha-1-antitrypsin (AAT) (Prolastin C), which is a non-selective Lrp1 agonist, in ST segment elevation acute myocardial infarction (STEMI) [29]. The administration of AAT (60 mg/kg IV) within 12 hours reduced C-reactive protein (CRP) levels, indicative of a blunted inflammatory response, and reduced estimated infarct size. AAT patients also had better one-year outcomes relative to historical controls. SP16 (Ac-VKFNKPFVFLNleIEQNTK-NH2) is a synthetic peptide designed to be a more selective Lrp1 agonist [30]. It contains the motif in AAT (FVFLM) that allows for binding to Lrp1. SP16 shows anti-inflammatory and cardioprotective properties in preclinical models. SP16 is being developed by Serpin Pharma, and is undergoing testing in a small (n=10) clinical trial (NCT04225533) to assess its anti-inflammatory effects in STEMI, following successful completion of a phase 1 trial in healthy volunteers (NCT03651089).

Atherosclerosis: LRP1 INFLUENCES INTRACELLULAR LIPID ACCUMULATION

Lrp1 is generally considered to be atheroprotective, as it protects against vascular smooth muscle cell proliferation, apoptotic death within plaques, and lesional inflammation [31]. Lrp1 expression is induced in response to cholesterol-lowering statins, which contributes to cholesterol and lipoprotein clearance [2]. Circulating sLrp1 can be a biomarker for atherosclerotic-related conditions since LDL lipoproteins can induce the shedding of membrane Lrp1 to its sLrp1 form in vascular smooth muscle cells, and levels decrease in response to statin treatment [32]. Lrp1 plays a critical role in the regulation of cellular cholesterol homeostasis. Lrp1 interacts with TGFβ to induce Wnt5a, which limits intracellular cholesterol accumulation by inhibiting biosynthesis and enhancing export [33]. Cholesterol efflux in macrophages is enhanced by induction of the ABCA1 transporter via an Lrp1- mediated signaling pathway [34].

However, Lrp1 also interacts with aggregated LDL, which is a potent inducer of intracellular cholesterol ester accumulation and the formation of foam cells. This interaction involves the cluster II CR9 domain of Lrp1(Gly1127-Cys1140) [35]. A peptide specifically targeting this region (H-GDNDSEDNSDEENC-NH2) was developed, called P3, and was shown to protect against LDL aggregation, and the accumulation of lipids in macrophages and vascular smooth muscle cells in preclinical models, without appearing to interfere with the other essential functions of Lrp1 [35; 36]. This specific interaction- targeting approach is likely to be the most effective method for Lrp1-directed therapeutic development.

Metabolic disease: LRP1 REGULATES INSULIN SIGNALING

Lrp1 is an important regulator of energy homeostasis, and metabolic syndromes are associated with Lrp1 dysregulation [37]. Insulin induces the expression of Lrp1, which then interacts with insulin receptor β to promote insulin signaling. However, under hyperglycemic conditions, Lrp1 expression is suppressed. Lrp1 is highly expressed in the liver, where it **is involved in controlling lipid metabolism/clearance and insulin sensitivity**. Some anti-diabetic drugs have been found to increase hepatic Lrp1 expression, which may contribute to their insulin sensitizing effects [38]. Lrp1 also regulates leptin signaling, an adipose-derived hormone that acts in the hypothalamus to inhibit hunger and fat storage [39]. Lrp1 is required for leptin receptor complex-mediated activation of STAT3. Loss of Lrp1 within the hypothalamus results in an obesity phenotype in mice, due to the loss of leptin signaling.

A meta-analysis of 18 studies examined the relationship between Lrp1 variants and anthropometric traits and found that body mass index (BMI) was 0.726 kg/m^2 lower in African Americans carrying the A allele of Lrp1 rs1800141 [40]. In Caucasian Americans, there was a genotype-nutrient effect, such that the effect of saturated fatty acid intake on anthropomorphic traits was exacerbated in the presence of the Lrp1 rs2306692 T allele. BMI was 0.107 kg/m^2 greater and waist circumference was 0.267 cm greater in T allele carriers with high saturated fatty acid intake. The synergistic effect may be due to the effect of impaired Lrp1-leptin signaling in the context of fatty acid-induced hypothalamic dysregulation.

These studies suggest that a decline in Lrp1 expression and/or function due to overnutrition may further exacerbate metabolic dysfunction, and that restoration of Lrp1 may be one of the mechanisms by which some therapeutics exert their protective effects against metabolic syndromes.

Fatty liver disease: LRP1 PROMOTES HEPATIC LIPID CLEARANCE

Chylomicron remnants, which are comprised of dietary lipids, are taken up into the liver for clearance by Lrp1 [41]. The absence of Lrp1 in mice exacerbates high-fat diet induced hepatic steatosis and insulin resistance, along with cholesterol-induced inflammation and fibrosis [41; 42]. Overnutrition states involving hyperglycemia and excess fat intake converge to dampen expression of hepatic Lrp1, which in turn, promotes lipid accumulation and exacerbates metabolic dysfunction.

Cancer: LRP1 PLAYS MIXED CONTEXT DEPENDENT ROLES

Lrp1 appears to play mixed roles in cancer. Lrp1 can promote tumor cell migration through regulation of matrix metalloproteases, MMP-2 and MMP-9 [43]. It can also promote tumor cell survival via insulin receptor and kinase signaling, such as ERK and JNK. However, the **effects are highly dependent on the**

tumor microenvironment, including the presence of Lrp1 ligands and co-receptors [44]. In some cancers a decrease in Lrp1 is associated with poor prognosis, while it is the opposite for other cancers. The methylation of Lrp1 has also been implicated as a diagnostic factor for some cancers.

From a therapeutic perspective, Lrp1 is primarily being developed as part of a drug delivery system to enhance the transport of chemotherapeutics into the CNS. Angiopep-2 is a 19 amino acid sequence derived from the Kunitz domain of known Lrp1 ligands [45]. GRN1005 (also called ANG1005) is a peptide-drug conjugate of paclitaxel with angiopep-2. It is 86-fold more brain penetrant than paclitaxel alone. It was tested in a phase 1 clinical trial (NCT00539383) in patients with advanced solid tumors (n=56), including patients with brain metastases (n=41) [46]. Five of the 20 patients treated at the maximum dose (650 mg/m^2) showed partial responses, including shrinkage of brain lesions. GRN1005 also showed evidence of BBB penetrance and transport of cytotoxic levels of paclitaxel into the tumor in a trial for malignant glioma (NCT00539344) [47].

Safety: Broad-spectrum Lrp1 modulators are untenable therapeutics due to the high potential for extensive side effects. Therapies that target a specific Lrp1-ligand interaction are expected to have a better therapeutic profile.

Types of evidence:

- 1 clinical trial for SP16 in healthy volunteers
- Numerous laboratory studies

Due to its ubiquitous expression and essential roles in a variety of homeostatic functions, targeting Lrp1 in a global manner is not a viable therapeutic strategy. The genetic knockout mouse is embryonic lethal, and some conditional knockouts show evidence of obesity, insulin resistance, abnormal lipid accumulation, and/or neurodegeneration, depending on the targeted cell type [13; 19; 39]. Although there are some therapies, primarily peptides, in development that target interactions between Lrp1 and a specific ligand (or family of ligands), the work has been predominantly preclinical. Due to the multi-domain structure of Lrp1, where each domain mediates interactions with distinct ligands [3], it is plausible to develop inhibitors toward very specific interactions, without disrupting other ligand-family interactions. Each of these therapies would have a distinct safety profile.

SP16 is a specific Lrp1 agonist mediating the interaction with protease-inhibitor complexes (SERPINs) to inhibit inflammation and promote pro-survival pathways. It is derived from the sequence of the SERPIN AAT, but is expected to have an improved therapeutic profile over the plasma-based AAT products. SP16

was tested in a phase 1 trial (NCT03651089) in healthy volunteers (n=24), at a single dose of 0.0125, 0.050, or 0.200 mg/kg administered subcutaneously. Results have not yet been posted, but a recent review by the principal investigator of the trial indicated that SP16 was safe and well-tolerated in this trial [1].

While there are some commonly used drugs that are known to modulate Lrp1 expression, particularly statins, Lrp1 is not the primary target of these drugs, and thus side effects cannot be conclusively tied to Lrp1 modulation.

Drug interactions: Lrp1 inhibitors or activators may interact with other drugs with the capacity to modulate Lrp1 levels, such as statins. However, it likely depends on the specificity/selectivity of the Lrp1 modulator toward a particular ligand interaction. Lrp1 inhibitors that are less specific may interact with anti-diabetic drugs, and would likely need to be contraindicated in populations with diabetes/metabolic disease.

Sources and dosing:

Selective Lrp1 modulators are not available for therapeutic use. SP16 is in clinical development by Serpin Pharma, and is currently in a Phase 1/2 trial for myocardial infarction. It is a peptide-based therapeutic with subcutaneous administration.

Research underway:

SP16 is being tested in a Phase 1/2 trial in ST segment elevation myocardial infarction (STEMI) (NCT04225533), with an estimated completion date in 2022.

GRN1005 (ANG1005) is being tested in a Phase 3 trial HER2-negative breast cancer with brain (leptomeningeal) metastases (NCT03613181), with an estimated completion date in 2023.

Search terms:

Pubmed, Google: Lrp1

- Alzheimer's disease, cardiovascular disease, diabetes, cancer, clinical trial

Websites visited for Lrp1 Modulators:

- Clinicaltrials.gov (SP16, GRN1005)

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