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.

ANGPTL4-Targeted Therapies

Evidence Summary

Genetic lowering of ANGPTL4 is associated with a beneficial cardiometabolic profile. ANGPTL4 therapies in early clinical development may show utility for reducing residual cardiovascular risk.

Neuroprotective Benefit: ANGPTL4 impacts brain vascular remodeling. It may play an acute neuroprotective role but induce pathological changes with chronic elevation. The clinical neurological impact of modulating peripheral ANGPTL4 is unclear.

Aging and related health concerns: Genetic ANGPTL4 inhibition is associated with better cardiovascular health and glucose homeostasis. Early clinical studies suggest similar benefits from therapeutic inhibition in those with hypertriglyceridemia.

Safety: ANGPTL4 lowering therapies show reasonable short-term safety, with injection reactions as the primary concern to date. Animal models indicate a possible risk for mesenteric lymph node lipid accumulation in the context of a high-fat diet.

Availability: In clinical trials	**Dose**: Not established, but both clinically tested therapies (MAR001 and Lipisense) are administered via subcutaneous injection.	**Chemical formula:** N/A **MW**: N/A
Half-life: Not yet reported.	**BBB**: Therapies currently in clinical testing are not penetrant.	
Clinical trials: MAR001 has been tested in a Phase 1 trial in healthy volunteers (n=56) and Phase 1b/2a for hypertriglyceridemia (n=55). A Phase 2b for hypertriglyceridemia is planned. Lipisense has been tested in Phase 1 trials in healthy volunteers (n=54; n=24), and a Phase 2a trial for hypertriglyceridemia is ongoing (n=23).	**Observational studies**: Gene association and Mendelian randomization studies indicate that ANGPTL4 inactivating gene variants are linked with decreased risk for coronary artery disease and type 2 diabetes.	

What is it?

Angiopoietin-like 4 (ANGPTL4) is one of the members of the angiopoietin-like protein family involved in the regulation of plasma lipids, along with ANGPTL3 (see ANGPTL3 Therapies Report) and ANGPTL8 [1]. It is expressed in a wide variety of tissues, but is most highly expressed in tissues involved in metabolic regulation, namely the liver and adipose tissue. ANGPTL4 exerts a variety of tissue-specific and context-dependent functions, which are facilitated by tissue-specific post-translational processing. One of the key functions of ANGPTL4 is the regulation of the enzyme lipoprotein lipase (LPL). ANGPTL4 inhibits LPL activity under fasting conditions, which allows for the mobilization of fatty acids (in the form of triglycerides) between metabolically active tissue compartments to meet the energy needs of the organism. Under conditions of hyperlipidemia, heightened levels of ANGPTL4 appear to contribute to cardiovascular disease. This is supported by genetic evidence from individuals with variants in ANGPTL4 [2]. Despite the improved cardiometabolic health observed in individuals with ANGPTL4 inactivating variants, ANGPTL4 had been considered a risky target due to adverse phenotypes observed in ANGPTL4 deficient mice. However, subsequent phenome analyses suggest that those safety concerns may not be relevant in humans [3]. Dysregulation of ANGPTL4 has also been observed in other age-related

conditions, such as cancer, stroke, and dementia [4], but, currently, clinical development is limited to cardiometabolic indications, particularly hypertriglyceridemia and type 2 diabetes.

There are currently two ANGPTL4 targeted therapies in clinical development.

MAR001 is a first-in-class humanized and affinity-matured monoclonal antibody targeting ANGPTL4 in clinical development by Marea Therapeutics. It was shown to bind to recombinant human ANGPTL4 with a K_D of 10 pM and prevent the inhibition of human LPL *in vitro* with an EC_{50} value of 1.5 nM [5]. It has been tested in a Phase 1 trial in healthy volunteers, and a Phase 1b/2a trial in patients with hypertriglyceridemia and metabolic dysfunction. A Phase 2b trial of MAR001 in patients with elevated triglycerides and remnant cholesterol is scheduled to initiate in the second half of 2025 (NCT07028749).

Lipisense® (also called A24110He) is an antisense oligonucleotide (ASO) targeting ANGPTL4 in clinical development by Lipigon Pharmaceuticals. It is conjugated to N-acetylgalactosamine (GalNAc), which allows for liver-directed targeting, thus Lipisense is designed to silence ANGPTL4 expression specifically in the liver. Lipisense was developed in collaboration with Secarna's LNAplus™ technology platform, but Lipigon holds the patents. Lipigon is collaborating with Leaderna Therapeutics, a spin-off of HitGen, to develop Lipisense in the Greater China region (China, Hong Kong, Taiwan and Macau) (Press release). To date it has been tested in healthy volunteers in Phase 1 trials in Sweden and China, and is currently being tested in a Phase 2a trial in patients with hypertriglyceridemia and type 2 diabetes.

Neuroprotective Benefit: ANGPTL4 impacts brain vascular remodeling. It may play an acute neuroprotective role but induce pathological changes with chronic elevation. The clinical neurological impact of modulating peripheral ANGPTL4 is unclear.

Types of evidence:

- 2 observational biomarker studies in AD
- 2 biomarker studies in ischemic stroke
- 3 biomarker studies in cerebrovascular disease
- Several laboratory studies

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

ANGPTL4-targeted therapies have not been examined for cognitive health. Gene association studies indicate that ANGPTL4-inactivating variants are associated with reduced risk for type 2 diabetes [3; 6], while preclinical studies with ANGPTL4 lowering interventions find evidence for protection from diet-induced obesity, both of which are established risk factors for dementia [7]. To date, studies assessing the impact of ANGPTL4-inactivating variants on health conditions have not reported an effect on dementia incidence [3; 6], but the role of ANGPTL4 in the brain is also a relatively understudied area.

Human research to suggest benefits to patients with dementia:

ANGPTL4-targeted therapies have not yet been tested in dementia patients.

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

Alzheimer's disease: SERUM ANGPTL4 IS INCREASED IN AD
The dysregulation of lipid metabolism is widely observed in the AD brain. Alterations in ANGPTL4 may play a role in microglial lipid accumulation and inflammation [8]. Based on observational data from 51,662 UK Biobank participants, serum levels of ANGPTL4 were found to be elevated in AD patients relative to controls, particularly in the subset of AD patients with obesity [8]. A similar pattern of increased ANGPTL4 was observed in mouse models of both AD and obesity [8]. In cultured microglia, ANGPTL4 is highly induced under conditions of lipid overload. Preclinical studies suggest that elevated ANGPTL4 may promote microglial aging, based on the expression of markers related to senescence, oxidative stress, and inflammation [8]. Together, this suggests that obesity may prime microglia for pathological changes associated with AD by triggering lipid accumulation and the expression of ANGPTL4.

A study assessing plasma proteins associated with cognitive resiliency identified ANGPTL4 as one of the top candidate proteins [9]. Notably, this association was only observed in ApoE4 carriers. As both ApoE and ANGPTL4 play roles in lipid mobilization and processing, the mechanism likely involves the dysregulation of lipids, such as heightened lipid accumulation in glia. In contrast to the association of elevated systemic levels, postmortem AD brain tissue analysis suggests that cellular levels of ANGPTL4 may be decreased in astrocytes, neurons, and neurovascular cells [9]. This likely reflects the cell type specific and context dependent effect of ANGPTL4, in which increases in peripheral circulating levels may promote or result from adverse changes in the brain, while ANGPTL4 may play protective roles in

key brain cell populations (as has been observed in the context of ischemic stroke models), such that its downregulation in those cells is detrimental.

Cerebrovascular disease: CONTEXT-DEPENDENT ROLE IN VASCULAR REMODELING
ANGPTL4 has been shown to be upregulated under conditions of hypoxia and plays a role in vascular remodeling [4]. Whether this vascular remodeling is beneficial or pathological depends on the context, such as the time after cerebrovascular injury and the impacted cell types. Preclinical studies suggest that ANGPTL4 may play a protective role during acute ischemic stroke, while studies in patient tissue indicate that its expression is altered in the context of vascular dementia and its chronic upregulation may lead to pathological changes to the brain vasculature.

Acute ischemic stroke: ANGPTL4 MAY HAVE ACUTE NEUROPROTECTIVE EFFECTS
Serum levels of ANGPTL4 were observed to increase in the context of acute ischemic stroke in a case-control study including 389 patients with ischemic stroke (1,113.30 pg/mL; interquartile range [IQR]: 673.42 to 1967.50) and 133 controls (876.18 pg/mL; IQR: 571.68 to 1523.05) (Odds Ratio [OR]: 1.03, 95% Confidence Interval [CI] 1.02 to 1.06) [10]. Serum levels of ANGPTL4 increased in conjunction with clinical severity, as has been observed in other observational studies [10; 11]. Notably, the increase occurs in response to the injury, such that levels peak during the acute phase, and then decrease within 1 to 2 weeks. Preclinical studies suggest that the post-injury rise in ANGPTL4 may have neuroprotective effects, including the maintenance of vascular integrity, modulation of postischemic inflammation, and mitigating neuronal loss [10]. For example, recombinant ANGPTL4 attenuated infarct size and behavioral deficits in a transient ischemic stroke mouse model when administered intravenously immediately prior to the ischemic event or during the reperfusion period [12]. The preservation of the vascular endothelial barrier involved the maintenance of VEGFR2-VE-cadherin complexes.

Cerebral small vessel disease: ANGPTL4 IS ELEVATED IN VASCULAR DEMENTIA
ANGPTL4 was found to be upregulated in the postmortem brain tissue of patients with capillary cerebral amyloid angiopathy (CAA), and may play a role in the increased microvascular density [13]. Plasma levels of ANGPTL4 were also increased in patients with vascular dementia relative to those with subjective memory complaints. Cell culture studies indicate that ANGPTL4 is upregulated in reactive astrocytes, particularly under hypoxic conditions, and its secretion from the glial cells stimulates the migration and sprouting of brain endothelial cells, suggesting it promotes angiogenesis [13].
An observational study including 171 patients with cerebral small vessel disease found that median serum ANGPTL4 was higher in patients with cognitive impairment (6.14 ng/mL, 25th percentile: 3.9; 75th

percentile: 9.27) relative to those with normal cognition (3.05 ng/mL, 25th percentile: 2.18; 75th percentile: 3.87) (OR: 2.062, 95% CI 1.591 to 2.674) [14]. ANGPTL4 levels were inversely associated with global cognition, as well as several subdomains, including visuospatial space, executive function, naming, attention, language, and memory. ANGPTL4 levels were also associated with the severity of white matter hyperintensities (WMH), such that those with moderate WMH had higher levels than those with mild WMH [14].
Alternations in vascular ANGPTL4 may also contribute to vascular dysfunction in AD. Altered communication between endothelial cells and pericytes was shown to augment pro-angiogenic VEGFA-VEGFR2 signaling in the AD brain [15]. Elevated expression of ANGPTL4 in pericytes appears to be one of the drivers of this vascular remodeling program.

APOE4 interactions: A proteomics study found that ANGPTL4 was inversely associated with cognitive resiliency in ApoE4 carriers [9], suggesting that, with respect to cognitive health, ApoE4 carriers may particularly benefit from ANGPTL4 lowering therapies. However, to date, ANGPTL4 therapies have not been tested for impacts to cognition, so this remains a theoretical benefit.

Aging and related health concerns: Genetic ANGPTL4 inhibition is associated with better cardiovascular health and glucose homeostasis. Early clinical studies suggest similar benefits from therapeutic inhibition in those with hypertriglyceridemia.

Types of evidence:

- 1 meta-analysis of studies assessing prognostic role of ANGPTL4 in cancer
- 2 clinical Phase 1 trials in healthy volunteers for Lipisense
- 2 clinical trials (Phase 1 and Phase 1b/2a) in hypertriglyceridemia for MAR001
- 6 gene association studies for ANGPTL4 and cardiometabolic outcomes
- Numerous laboratory studies

Cardiovascular disease: POTENTIAL BENEFIT
Gene variant-based lowering of ANGPTL4 activity is associated with protective cardiometabolic phenotypes [16]. Studies utilizing ANGPTL4-lowering therapies suggest that the impact varies depending on baseline cardiometabolic health, such that improvements, in terms of lipid and glucose parameters, are only apparent in those with hyperlipidemia and metabolic dysfunction. The differential impact likely relates to differences in the level of circulating ANGPTL4. When levels of ANGPTL4 are already low,

further reduction may not offer a meaningful benefit. It is currently unclear the degree to which therapeutic targeting of ANGPTL4 can prevent the future development of cardiometabolic dysfunction, in those with good health at baseline, by preventing age-related increases in ANGPTL4.

Mendelian randomization and gene association studies: *ANGPTL4 LOWERING IS ASSOCIATED WITH CARDIOPROTECTION*

Variants in ANGPTL4 were found to be associated with variation in triglyceride levels in a gene analysis study in a multi-ethnic cohort (n= 3,551) [17]. The E40K variant, in particular, had a significant association with lower triglyceride levels, such that median triglyceride levels were 29 mg/dL lower in carriers of the variant, relative to non-carriers. The E40K variant reduces the ability of ANGPTL4 to inhibit LPL and is thus considered an inactivating variant [2]. Similar associations were observed in two other cohorts (n =15,792 and n=10,135), such that median triglyceride levels were lower by 16 mg/dL and 17 mg/dL, respectively, while HDL-C levels were 3 to 5 mg/dL higher in E40K heterozygote carriers [17]. In the multi-ethnic cohort, the E40K variant was found to be more common in European American participants, with a minor allele frequency of 1.3%, relative to African American or Hispanic participants.

Since this initial finding, the association between ANGPTL4 variants and triglyceride levels has been replicated in a variety of other cohorts. Subsequent studies have also found an association between ANGPTL4 inactivating variants, such as E40K, and a lower incidence of coronary artery disease (CAD). A study using the DiscovEHR cohort (n=42,930) found that compared to non-carriers, median triglyceride levels were 13% lower, while HDL-C levels were 7% higher in carriers of the E40K allele [2]. Triglyceride levels were similarly reduced by 13% and HDL-C levels increased by 9% in carriers of other ANGPTL4-inactivating mutations, relative to non-carriers. Lower rates of CAD were observed in carriers of the E40K variant (per allele OR: 0.81, 95% 0.70 to 0.92) and novel ANGPTL4-inactivating variants (OR: 0.56, 95% CI 0.32 to 1.00), relative to non-carriers. This association has been replicated in additional cohorts, such that the E40K variant was associated with 16% lower odds of CAD (OR: 0.84, 95 % CI 0.81 to 0.87) in a meta-analysis of GWAS studies of cardiometabolic diseases and traits [6].

Mendelian randomization studies suggest a causal relationship between ANGPTL4 and CAD. An analysis including 488,139 participants in the UK Biobank study found that genetically predicted triglyceride lowering stemming from ANGPTL4 variants reduced the odds of CAD (OR: 0.44, 95% CI 0.37 to 0.53) [16]. Notably, this reduction in CAD risk was greater than what was observed for genetically proxied LPL activation (OR: 0.64), suggesting that ANGPTL4 impacts CAD risk via both LPL dependent and LPL independent mechanisms. A separate Mendelian randomization analysis similarly found that genetically

lowered levels of circulating ANGPTL4 reduced the odds of CAD (OR: 0.57 per standard deviation protein; 95% CI 0.47 to 0.70) [3].

Residual risk: *POTENTIAL BENEFIT THROUGH REDUCTION OF TRL REMNANTS*
The mechanism of cardioprotection afforded by the E40K variant and phenotypically similar ANGPTL4 inactivating variants is thought to stem primarily from its role in reducing levels of circulating triglycerides by allowing for a higher level of LPL activity [3; 16]. LPL is the rate-limiting enzyme in the hydrolysis (breakdown) of triglycerides from triglyceride-rich lipoproteins (TRLs), such as VLDL and chylomicrons [18]. The triglycerides themselves are not necessarily harmful, however, the remnants of the TRLs have been shown to be highly atherogenic. When triglyceride levels are below 100 mg/dL, TRL remnants typically do not accumulate, however, when triglyceride levels are elevated and the breakdown of TRLs is impaired, TRL remnants start to build up and cause vascular damage [18]. Thus, high levels of circulating triglycerides are considered a type of surrogate indicator of high TRL remnants. These TRL remnants are highly enriched in cholesterol, and are thought to be one of the key components of residual cardiovascular risk, or the maintained elevated risk for adverse cardiovascular events despite intensive lowering of LDL-C. By enhancing the lipolysis of TRLs, ANGPTL4 inhibiting therapies are expected to reduce levels of TRL remnants, and thus lower cardiovascular risk [1].

This mechanism of reducing TRL remnant-related residual risk by augmenting the activity of LPL is similar to that of ANGPTL3-lowering therapies (see ANGPTL3 Therapies report), however, the overall impacts of targeting ANGPTL4 and ANGPTL3 are not the same [1]. While both ANGPTL4 and ANGPTL3-lowering therapies and gene variants effectively lower triglyceride levels, they have differential impacts on other lipoproteins and metabolic parameters [3]. ANGPTL3-lowering therapies tend to reduce both LDL-C and HDL-C levels, while ANGPTL4-lowering tends to slightly increase HDL-C levels without meaningfully impacting LDL-C. ANGPTL4 lowering is also associated with improved glucose control and anti-obesogenic effects.
These differences stem from differential localization, processing, and interacting partners of these proteins. ANGPTL3 and ANGPTL4 are induced during opposite metabolic states, as ANGPTL3 is induced in response to feeding, while ANGPTL4 is induced in response to a prolonged fast [19]. Post-prandial insulin triggers ANGPTL3 to inhibit LPL in heart and skeletal muscle, meanwhile, insulin inhibits ANGPTL4 in adipose tissue, with a net result that triglycerides are directed to adipose tissue for storage [1]. In a fasted state, the ANGPTL4 inhibits adipose LPL resulting in the release of triglycerides from adipose tissue into circulation, which can then be utilized for energy by heart and skeletal muscle. This cycle is facilitated by interactions with ANGPTL8, which is also induced by feeding. The ANGPTL3-ANGPTL8

complex enhances the capacity of ANGPTL3 to inhibit LPL. In contrast, the ANGPTL4-ANGPTL8 complex reduces the capacity of ANGPTL4 to inhibit LPL. Due to this interplay, the loss of any of these ANGPTLs can result in a net increase in LPL activity, and concomitant reduction in triglyceride levels, though the effect will be most readily observed at different metabolic (fed vs fasted) states.
In addition to inhibiting LPL, ANGPTL3 also inhibits endothelial lipase, which is thought to influence the modulation of HDL-C and LDL-C [1]. ANGPTL4 inhibits hepatic lipase activity in the liver, leading to an opposite effect on HDL-C levels. One study suggests that ANGPTL4 may also inhibit endothelial lipase, but not when it is complexed with ANGPTL8, and may be another way that ANGPTL4 impacts HDL levels [20].

ANGPTL4 has a variety of tissue-specific and context-dependent effects. While the production and secretion of ANGPTL3 is restricted to the liver, ANGPTL4 is produced by a variety of different tissues, and predominantly secreted by highly metabolic tissues, such as the liver and adipose tissue [19].
ANGPTL4 can be cleaved to produce a 15kDa N-terminal fragment and a 37 kDa C-terminal fragment, which have different, and sometimes opposing downstream activities [4]. The LPL inhibiting activity of ANGPTL4 is housed in the N-terminal region, thus only the full-length and N-terminal fragments can influence LPL activity. The C-terminal fragment has been implicated in a variety of other non-lipid metabolic processes. Both fragments may influence cardiovascular health [19].
Some of the tissue specificity comes from differential cleavage and secretion. Adipose tissue secretes primarily full-length ANGPTL4, while the liver secretes a high proportion of cleaved ANGPTL4 [19]. The majority of circulating ANGPTL4 is in the form of the C-terminal fragment, suggesting that it is predominantly derived from the liver [19]. The circulating full length and N-terminal forms tend to be complexed with ANGPTL8.
The presence of different forms with different context-dependent effects may explain why there is a higher degree of discrepancy across studies using recombinant protein overexpression of ANGPTL4, compared to those testing the effects of genetic deficiency.

Consequently, the manner in which ANGPTL4 is targeted in therapeutic interventions could have different downstream effects, depending on which organs and forms of the protein are targeted. Genetic strategies can target both tissue and circulating forms, while antibodies are typically restricted to acting on circulating forms. The optimal type of intervention may vary depending on the indication. Additionally, which populations will obtain greater benefit from ANGPTL4 therapies relative to ANGPTL3 therapies requires further study. To date, ANGPTL3 therapies appear to have better utility for refractory hypercholesterolemia and mixed dyslipidemia, while ANGPTL4 therapies may be best suited to those

with hypertriglyceridemia and metabolic syndrome. The ongoing clinical studies using different types of ANGPTL4-lowering therapies should start to provide some clarity.

A caveat of preclinical studies assessing the impact of ANGPTL4-lowering interventions is the differential expression patterns of ANGPTL4 across species, particularly when comparing mice with humans. In mice, ANGPTL4 is predominantly expressed in adipose tissue, whereas in humans ANGPTL4 appears to be expressed to a similar degree in liver and adipose tissue [19]. As such, ANGPTL4 deficiency in mice is associated with phenotypes not observed in humans with ANGPTL4-inactivating variants, such as lymphadenopathy and LDL-C lowering [3; 6]. Therefore, caution is warranted in the interpretation and potential translation of rodent studies targeting ANGPTL4.

Due to these complexities, the clinical development of ANGPTL4-targeted therapies has lagged behind those targeting ANGPTL3. To date, only two ANGPTL4-targeting therapies have undergone clinical testing. They take different approaches to targeting ANGPTL4. One approach involves the systematic reduction in circulating ANGPTL4 using a monoclonal antibody (mAb), while another involves the genetic silencing of specifically liver-expressed ANGPTL4 with an antisense oligonucleotide (ASO). Currently, both therapies are being developed for hypertriglyceridemia.

ANGPTL4-targeted therapies in clinical development:

mAb

MAR001 is humanized mAb targeting circulating ANGPTL4 in clinical development by Marea Therapeutics.

Treatment with MAR001, at a dose of 450 mg, administered via subcutaneous injection reduced mean levels of fasting triglycerides by -47.2% (90% CI -61.0% to -33.4%) relative to baseline, and a placebo-adjusted change of -68.6% (90% CI -97.4% to -39.8%) in participants with elevated triglycerides (n=12) (mean baseline level 289.5 mg/dL ±113.7) [21]. A comparable degree of triglyceride lowering was not observed in participants without elevated triglycerides at baseline at an equivalent dose, as mean placebo-adjusted fasting triglycerides were reduced by -16.7% (90% CI -60.7% to 27.4%) and -35.9% (90% CI -59.4% to -12.4%) at day 15, in cohorts with baseline triglyceride levels of 69.0 mg/dL ± 28.2 (n=32) and 145.9 mg/dL ±70.2 (n=12), respectively. This is consistent with what has been observed with ANGPTL4 lowering in animal models.

In the cohort with elevated triglycerides, treatment with MAR001 also resulted in significant placebo-adjusted reductions in levels of remnant cholesterol by -65.6% (-94.2% to -36.9%) and postprandial

triglyceride excursion by -72.5% (-112.1% to -32.9%). Increases in HDL-C levels by 13.5% (2.6% to 24.5%) were also observed, with no significant effects on LDL-C.

MAR001 has also been tested at a dose of 150, 300 or 450 mg administered via subcutaneous injection every two weeks (q2w) for 12 weeks in a randomized, double-blind, placebo-controlled Phase 1b/2a trial in 55 participants with metabolic dysfunction, as defined by hypertriglyceridemia (≥151 mg/dL and ≤496 mg/dL) and a history of type 2 diabetes, or a screening homeostatic model assessment for insulin resistance (HOMA-IR) value >2.2 and abdominal obesity [21]. All tested doses led to significant reductions in fasting triglycerides, and remnant cholesterol at week 12 (see table below), while only the highest dose significantly impacted levels of HDL-C (by +19.0%, 90% CI 10.2% to 27.8%) and non-HDL-C (by -7.1%, 90% CI -14.7% to -0.6%). None of the doses significantly altered levels of LDL-C.

Placebo-adjusted mean change (90% CI)	150 mg	300 mg	450 mg
Triglycerides	-40.6% (-70.1% to -11.2%)	-50.3% (-88.0% to -12.7%)	-52.7% (-77.0% to -28.3%)
Remnant cholesterol	-37.4% (-66.1% to -8.8%)	-49.3% (-85.8% to -12.8%)	-52.5% (-76.1% to -28.9%)

Based on the results of these studies, MAR001 will be tested in a randomized, double-blind, parallel-group, placebo-controlled Phase 2b trial in patients with elevated triglycerides and remnant cholesterol (TYDAL-TIMI 78) (NCT07028749).

In a non-human primate model of hypertriglyceridemia, single subcutaneous doses (3 mg/kg) of MAR001 resulted in reduced plasma triglycerides by up to 58%, non-HDL-C by 38%, apoB by 30%, and remnant cholesterol by 59% [5].

ASO

Lipisense® (A24110He) is an ASO directed towards ANGPTL4 currently in clinical development by Lipigon Pharmaceuticals for hypertriglyceridemia. It is conjugated to N-acetylgalactosamine (GalNAc) to facilitate liver-specific silencing of ANGPTL4 [22]. GalNAc binds to the asialoglycoprotein receptor, which is specifically expressed on hepatocytes, thus, GalNAc conjugation should allow for selective uptake into

the liver. This targeting system has been used by a variety of other clinically tested gene silencing therapies, primarily for cardiovascular-related indications.
The liver is thought to be the primary source for circulating ANGPTL4 [19]. Therefore, specifically targeting ANGPTL4 produced in the liver is expected to be a mechanism of reducing systematic ANGPTL4, while preserving local production in other tissues, which may play important or potentially beneficial physiological functions. Lipisense has been tested in two Phase 1 clinical trials, and is currently undergoing testing in a Phase 2 trial.

In a Phase 1 SAD/MAD trial in 54 healthy volunteers, Lipisense demonstrated target engagement through the dose-dependent lowering of plasma ANGPTL4 levels (Press release). The effect was long-lasting, such that placebo-adjusted levels of ANGPTL4 were reduced by up to -29% (95% CI -55% to -3%) at 90 days after the last dose (Press release). Consistent effects on apoB or cholesterol were not observed (Ph2a study protocol). It should be noted that due to low levels of circulating ANGPTL4 in a healthy population, it is difficult to observe treatment effects, in terms of lipid and metabolic changes, in this type of study. Lipisense was reported to exert a similar profile in a separate Phase 1 study conducted in 24 healthy volunteers in China (Press release).

A randomized, double-blind, placebo-controlled Phase 2 trial is currently testing Lipisense in 23 patients with type 2 diabetes and hypertriglyceridemia (fasting triglyceride levels ≥ 1.7 mmol/L) (EUCT number: 2023-509091-42-00). According to the trial protocol, Lipisense is being tested at a dose of 36 mg per week for four weeks, administered subcutaneously. The primary outcome is safety and tolerability. Exploratory outcomes include impacts to the lipid profile and glucose parameters. Topline results are expected at the end of 2025.

Lipigon has also tested liver-directed ASOs targeting ANGPTL4 in preclinical studies in mice and monkeys [22]. In mice, subcutaneous injection with GalNac-conjugated ASOs reduced hepatic expression of ANGPTL4 by around 70%, and reduced fasting triglyceride levels [22]. The ASOs also altered ANGPTL4 activity in adipose tissue, resulting in a shift of triglycerides from white to brown fat. Additionally, the ASOs reduced non-HDL-cholesterol levels. Notably, the effects on lipids, fat accumulation, and glucose tolerance were observed in models of atherosclerosis and obesity, and not necessarily apparent in healthy, normal weight animals.

Type 2 Diabetes: POTENTIAL BENEFIT
Several observational and Mendelian randomization studies have indicated that in addition to reducing the risk for cardiovascular disease, ANGPTL4-lowering variants are associated with lower risk for type 2 diabetes. This association is not observed with ANGPTL3-lowering variants, and likely stems from the LPL-independent metabolic related functions of ANGPTL4, such as those induced by the C-terminal fragment [3; 16].

Carriers of the E40K ANGPTL4 inactivating variant were observed to have a lower incidence of type 2 diabetes relative to non-carriers (OR: 0.89, 95% CI 0.85 to 0.92), based on a meta-analysis of 58,124 participants in the DiscovEHR cohort plus 82,766 diabetes cases and 498,761 controls from 13 additional studies [23]. This was coupled with lower levels of fasting glucose and better insulin sensitivity. A similar association with reduced odds of type 2 diabetes was observed in the context of other prospective ANGPTL4-lowering variants (OR: 0.71, 95% CI 0.49 to 0.99) [23].
A Mendelian randomization analysis examining causal relationships between 4,907 circulating protein levels with disease states identified ANGPTL4 as one of the plasma proteins positively associated with type 2 diabetes (OR: 1.35, 95% CI 1.13 to 1.61) using a sample size of 490,089 participants [24].
Genetically lowered ANGPTL4 also reduced the odds of type 2 diabetes (OR: 0.73 per standard deviation protein 95% CI 0.57 to 0.94) in a separate Mendelian randomization study assessing the impact of gene variants on cardiometabolic endpoints [3].
Serum levels of the ANGPTL4-ANGPTL8 complex were found to be twice as high in diabetic patients (n=93) relative to non-diabetics (n=99) in an observational study [20]. This likely stems from elevated insulin levels due to insulin resistance resulting in the equivalent to a chronic 'fed' state.

Preclinical studies
Improved glucose tolerance and fat loss: In a mouse model of diet-induced obesity, hepatic deficiency of ANGPTL4, via genetic deletion or ASO-mediated silencing, protected against weight (fat mass) gain, glucose intolerance, liver steatosis, and atherosclerosis [25]. These mice exhibited higher oxygen consumption and energy expenditure. These metabolic effects appear to stem from the induction of fatty acid oxidation due to the activation of hepatic AMPK. This process leads to an increase in the production of reactive oxygen species (ROS), which, in turn, sustains the activation of AMPK.
However, the relationship between ANGPTL4 is complex and tissue dependent. In skeletal muscle, ANGPTL4 can activate AMPK and enhance exercise performance. As a result, ANGPTL4 deficient mice have been shown to exhibit reduced exercise endurance [19].

Levels of ANGPTL4 were found to decrease in both liver and adipose tissue in mice treated with liver-targeted ANGPTL4 ASOs, in a study by a different group [26]. These mice also exhibited decreased food intake, weight gain, and better glucose tolerance when subject to a high-fat diet.

Increased brown fat activation: A separate study using hepatic silencing of ANGPTL4 via ASOs observed similar phenotypes in a mouse model of hyperlipidemia [22]. The silencing of ANGPTL4 promoted the transfer of triglycerides from white adipose tissue, which is primarily involved in lipid storage, to the thermogenic brown adipose tissue, resulting in increased lipolysis and energy utilization.
Cold exposure, the primary physiological trigger for brown fat activation, facilitates the transfer of lipids from white to brown adipose tissue through the differential regulation of ANGPTL4 [19]. Cold exposure triggers the upregulation of ANGPTL4 in white adipose tissue, thus promoting the release of triglycerides, meanwhile cold also triggers the downregulation of ANGPTL4 in brown adipose tissue, leading to increased triglyceride uptake and utilization for energy.

ANGPTL4 levels are increased in both the brain (hypothalamus) and skeletal muscle in diabetic mouse models, which appears to stem from the dysregulation of insulin [27]. In addition to the role of peripheral ANGPTL4 in altering energy expenditure through the partitioning of lipids to more metabolically active tissues for utilization, central ANGPTL4 may impact feeding behavior by influencing metabolic crosstalk between glia and neurons.

It is important to note that ANGPTL4 is sensitive to metabolic states and thus its impacts are also metabolic state dependent. The effects on lipid and glucose profiles in models of obesity do not necessarily shift to comparable degrees in the absence of metabolic disease. For example, ANGPTL4 deficient mice fed normal chow did not show the significant changes in glucose levels and tolerance observed in mice fed a high-fat diet [23].

Diabetic cardiomyopathy: Preclinical studies also suggest that elevated ANGPTL4 may play a role in diabetic cardiomyopathy through the regulation of oxidative stress signaling [28]. In cultured cardiomyocytes, recombinant ANGPTL4 exacerbated cell death under conditions of high glucose, while siRNA-mediated silencing of ANGPTL4 had a protective effect [28].

Cancer: ANGPTL4 IS A PROGNOSTIC FACTOR FOR VARIOUS TYPES OF CANCER
ANGPTL4 has been identified as a prognostic factor in several types of cancer. Various mechanisms have been identified by which ANGPTL4 contributes to cancer progression, such as the regulation of

angiogenesis, cell proliferation, as well as cell invasion and metastasis [29]. The effects of ANGPTL4 are highly dependent on the tumor microenvironment, thus ANGPTL4 has been implicated in pro-tumorigenic and anti-tumorigenic activities in different tumor types. These different effects likely stem from differential post-translational processing of ANGPTL4, such as cleavage, glycosylation, and oligomerization, as well as differential expression of its interacting partners [30]. Full length and cANGPTL4 generally promote malignancy and metastasis, stimulating cell growth and survival pathways such as PI3K and ERK [29]. In contrast, nANGPTL4, the fragment traditionally involved in lipid metabolism, may have anti-metastatic and anti-angiogenic properties, such as through the inhibition of WNT signaling.

A meta-analysis including 3,268 cancer patients found that, while there was variability across cancer types, increased expression of ANGPTL4 was more likely to be associated with worse overall survival, (HR: 1.40, 95% CI 1.29 to 1.50), more advanced stage (OR: 2.26, 95% CI 1.23 to 4.14), lymph node metastasis (OR: 2.07, 95% CI 1.25 to 3.44,), vascular invasion (OR: 2.13, 95% CI 0.93 to 4.89), and lymphatic invasion (OR: 2.19, 95% CI 1.52 to 3.16) [31]. A multi-omics analysis indicated that ANGPTL4 upregulated epithelial-to-mesenchymal transition in a majority of the examined tumor types [31]. In addition, ANGPTL4 was associated with gene networks involved in hypoxia, VEGF-A complex, TGF-β pathways, and extracellular matrix organization. Its role in metastasis appears to depend largely on TGF-β signaling.

ANGPTL4 has been found to be associated with poor prognosis in numerous cancers, including colorectal cancer, breast cancer, gallbladder cancer, cervical cancer, and pancreatic cancer [29; 31]. A clinical trial is currently ongoing (NCT05214885) testing the utility of several proteins, including ANGPTL4, as potential biomarker of hypoxia in patients with renal clear cell carcinoma.
In a study including 205 patients with ductal carcinoma breast cancer, high ANGPTL4 expression was associated with worse overall survival (RR: 2.034, 95% CI 0.534 to 3.567) and worse disease-free survival (RR: 2.353, 95% CI 0.733 to 3.403) [32]. The lower rates of survival likely stem from the relationship between ANGPTL4 expression and tumor metastasis.
Mendelian randomization analysis (using the EPIC and UK Biobank databases) suggests a causal relationship between circulating ANGPTL4 and colorectal cancer risk, such that genetically lower levels of ANGPTL4 were associated with decreased risk (Odds ratio per standard deviation [ORSD] decrease: 0.76, 95%CI: 0.66 to 0.89) [33]. Lower colon tumor expression of ANGPTL4 was also associated with reduced risk of all-cause mortality and colon-cancer specific mortality (HR: 0.66, 95% CI 0.50 to 0.87). Notably, this relationship was not related to the effect of ANGPTL4 on triglycerides, but rather likely

stems from the downregulation of genes involved in cell proliferation and the epithelial-mesenchymal transition.
The inhibition of ANGPTL4 has been shown to have anti-tumorigenic properties in preclinical studies, particularly with respect to inhibiting cell migration and metastasis, suggesting that it may be a viable therapeutic strategy for cancers in which high ANGPTL4 is associated with poor prognosis [29].
ANGPTL4 inhibiting therapies have not yet been clinically tested for cancer. Therapies for cardiovascular indications target the full-length version and focus on the modulation of lipid metabolism mediated by nANGPTL4, and thus may not be well-suited for use in cancer. Due to the outsized role of cANGPTL4 in tumor biology, a different type of therapeutic may be needed, such as a mAb or inhibitor that specifically targets the cANGPTL4 fragment.

Psoriasis: POTENTIAL BENEFIT (Preclinical)
ANGPTL4 was identified as a hub gene upregulated in psoriasis lesions [34]. In preclinical rodent models, treatment with recombinant ANGPTL4 exacerbated skin inflammation and clinical phenotypes, while siRNA-mediated silencing of ANGPTL4 mitigated inflammation in keratinocytes [34].

Safety: ANGPTL4 lowering therapies show reasonable short-term safety, with injection reactions as the primary concern to date. Animal models indicate a possible risk for mesenteric lymph node lipid accumulation in the context of a high-fat diet.

Types of evidence:

- 4 clinical trials for ANGPTL4 targeted therapies
- 4 gene-phenome association studies of ANGPTL4 variants and health outcomes
- Numerous laboratory studies

Phenotypes observed in ANGPTL4 deficient mice led to safety concerns regarding the feasibility of therapeutically targeting ANGPTL4 [2]. These mice accumulate lipids in their mesenteric lymph nodes, resulting in lymphadenopathy, a massive acute phase response, intestinal fibrosis, chylous ascites, and peritonitis [6; 26]. Notably, these phenotypes are only induced in the context of a diet high in saturated fats. The accumulation of lipid-filled Touton cells and lesions in the mesenteric lymph nodes was also observed in ANGPTL4 humanized male mice predisposed to hypertriglyceridemia (ApoE-/-) treated with the ANGPTL4 mAb REGN1001 [2]. Mice with liver specific deletion of ANGPTL4 do not exhibit mesenteric lymph node inflammation under high fat feeding, which suggested that liver-directed therapies may

offer a superior safety profile [25]. However, mice treated with liver-directed ANGPTL4 ASOs can show evidence of mild lipid accumulation, inflammation, and transaminase elevations in the liver, while on a high-fat diet [22; 26].
Phenome studies including individuals with homozygous inactivating mutations in ANGPTL4 suggest that the phenotypes observed in ANGPTL4-deficient mice are likely not applicable to humans. Rates of lymphadenopathy, and intestinal or abdominal disorders are not elevated in these individuals [2; 3; 6]. One study found that the presence of the E40K inactivating variant did not meaningfully increase risk for any of the 1,589 tested diseases [6].

mAbs
MAR001 has been generally well-tolerated in clinical trials to date [21]. In a Phase 1 single ascending dose (SAD) trial including healthy participants (n=44) and those with elevated triglycerides (n=12) adverse events were generally mild, and only two were considered treatment related, including an injection-site extravasation in a participant receiving MAR001 at a dose of 150 mg and a hematoma in one participant who received MAR001 at a dose of 450 mg [21]. Anti-drug antibodies were not observed with single dose administration in this study. MAR001 demonstrated a similar safety profile in a Phase 1b/2a trial in 55 participants with metabolic dysfunction [21]. There were no dose-dependent trends in adverse events. Gastrointestinal events were the most common adverse event of special interest, particularly at the highest dose (29.4%), though at the lower doses, rates were similar to placebo (15-20%). There were no treatment-related changes in inflammatory biomarkers, or worsening of metabolic parameters in either study. Additionally, there were no treatment-related changes in the hepatic fat fraction or changes to mesenteric lymph node size or number, based on MRI. There were also no new cases of mesenteric inflammation.

In a toxicology study in non-human primates (cynomolgus monkeys), treatment with MAR001 up to 30 mg/kg every two weeks for 15 weeks did not induce any histological findings in animals on a standard diet, though there was evidence for slight mesentery foamy macrophage formation in animals fed a high fat diet [5]. However, there was no enlargement of the lymph nodes with macrophage infiltrates, nor evidence of fibrosis, inflammation, or degeneration. A similar trend was observed in animals treated for 36 weeks. There was no evidence for clinical pathology or systemic inflammation in the MAR001 treated animals. The tested dose of 30 mg/kg is ten times the efficacious dose in this species, indicating a reasonable margin of safety.

A prior preclinical study testing a different mAb (REGN1001) targeted to ANGPTL4 observed the accumulation of lipids in the mesenteric lymph nodes in female, but not male, non-human primates fed a high-fat diet [2].

ASO

Lipisense was shown to have a reasonable safety profile in Phase 1 trials in healthy volunteers to date (Press release). In a SAD study testing single subcutaneous doses of 2, 6, 18, 36, 72 and 144 mg, systemic exposure was largely dose proportional at doses above 18 mg (Ph2a study protocol). The MAD study tested 6, 12 and 36 mg doses administered subcutaneously once per week for four weeks. Levels of the drug increased sub-proportionally with increasing dose, and there was no evidence of accumulation. Adverse events were common, occurring in 18 out of 30 participants in the SAD study and 21 out of 24 participants in the MAD study. There were no serious adverse events, and most treatment-emergent adverse events were mild, with the exception of one case of moderate severity rash. The primary adverse events were injection site reactions, including erythema, swelling, suspected granulomatous skin reactions, pruritus, and pain, some of which lasted for several weeks and healed with skin discoloration. The injection reactions were more common in those treated with Lipisense relative to placebo (89% vs 0%) (Press release). There were no clinically significant changes for pulse, blood pressure, body weight, electrocardiogram (ECG) measures, or physical examination.
A press release reported that the safety profile was similar in a separate Phase 1 trial conducted in healthy volunteers in China, though details were not provided. The Phase 2 trial in patients with type 2 diabetes and hypertriglyceridemia is currently ongoing, and safety results are not yet available.
Weekly injections of GalNAc-conjugated ASOs targeting ANGPTL4 were well-tolerated in non-human primates (cynomolgus monkeys) when administered at subcutaneous doses up to 30 mg/kg for four weeks [22].

Together these studies suggest that the effects observed in ANGPTL4 deficient rodents are not relevant for humans. But, until long-term clinical studies are completed, adherence to a lower fat diet may still be advisable in participants receiving treatment with ANGPTL4-lowering therapies, as a precautionary measure.

Drug interactions: Drug interactions have not yet been established, however, there will likely be interactions with other therapeutic agents which modulate ANGPTL4. PPARs regulate ANGPTL4, so there may be interactions with PPAR modulators, such as fibrates [19]. The PPAR agonist fenofibrate is known to increase plasma levels of ANGPTL4. ANGPTL4 can be induced by glucocorticoids, while some anti-

diabetic drugs, including SGLT2 inhibitors, decrease levels of ANGPTL4 [35]. As an LPL inhibitor, therapies targeting ANGPTL4 may also interact with LPL inhibitors, such as orlistat.

Sources and dosing:

ANGPTL4-lowering therapies are currently in clinical development for hyperlipidemia, and not yet approved for any indication. The optimal dosing may depend on the indication.
MAR001 is a mAb targeting ANGPTL4 in clinical development by Marea Therapeutics. It was tested at a dose of 450 mg every 2 weeks in patients with hypertriglyceridemia in a Phase 1b/2a trial. It is administered via subcutaneous injection.
Lipisense® is a liver-directed ASO targeting ANGPTL4 in clinical development by Lipigon Pharmaceuticals. In an ongoing Phase 2a trial in patients with hypertriglyceridemia, it is being tested at a dose of 36 mg per week, administered via subcutaneous injection.

Research underway:

Lipisense is being tested in a Phase 2a randomized, double-blind, placebo-controlled trial in patients with elevated plasma triglyceride levels (EUCT number:2023-509091-42-00). The study has an expected completion date in late 2025.

MAR001 will be tested in the Phase 2b randomized, double-blind, parallel-group, placebo-controlled trial in patients with elevated triglycerides and remnant cholesterol (TYDAL-TIMI 78) (NCT07028749). The study has an estimated start date in the second half of 2025 and an estimated completion date in 2026.

Search terms:
Pubmed, Google: ANGPTL4

- Alzheimer's, stroke, neuroprotection, cardiovascular, diabetes, metabolism, cancer, fibrosis, clinical trial, safety

Websites visited for ANGPTL4 Therapies:

- Clinicaltrials.gov (MAR001)
- euclinicaltrials.eu (Lipisense)

References:

1. Sylvers-Davie KL, Davies BSJ (2021) Regulation of lipoprotein metabolism by ANGPTL3, ANGPTL4, and ANGPTL8. *American journal of physiology Endocrinology and metabolism* **321**, E493-e508https://pmc.ncbi.nlm.nih.gov/articles/PMC8560382/.

2. Dewey FE, Gusarova V, O'Dushlaine C *et al.* (2016) Inactivating Variants in ANGPTL4 and Risk of Coronary Artery Disease. *The New England journal of medicine* **374**, 1123-1133https://pmc.ncbi.nlm.nih.gov/articles/PMC4900689/.

3. Landfors F, Henneman P, Chorell E *et al.* (2024) Drug-target Mendelian randomization analysis supports lowering plasma ANGPTL3, ANGPTL4, and APOC3 levels as strategies for reducing cardiovascular disease risk. *European heart journal open* **4**, oeae035https://pmc.ncbi.nlm.nih.gov/articles/PMC11182694/.

4. Wang X, Chang HC, Gu X *et al.* (2025) Adipose Factor ANGPTL4: Its Role in Aging Mechanisms and Associated Diseases. *Clinical interventions in aging* **20**, 911-929https://pmc.ncbi.nlm.nih.gov/articles/PMC12219161/.

5. Cummings BB, Bouchard PR, Milton MN *et al.* (2025) An ANGPTL4 inhibitory antibody safely improves lipid profiles in non-human primates. *EBioMedicine* **117**, 105748https://pmc.ncbi.nlm.nih.gov/articles/PMC12173019/.

6. Gagnon E, Bourgault J, Gobeil É *et al.* (2024) Impact of loss-of-function in angiopoietin-like 4 on the human phenome. *Atherosclerosis* **393**, 117558https://pubmed.ncbi.nlm.nih.gov/38703417/.

7. Livingston G, Huntley J, Liu KY *et al.* (2024) Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *The Lancet* **404**, 572-628https://doi.org/10.1016/S0140-6736(24)01296-0.

8. Li N, Wang X, Lin R *et al.* (2024) ANGPTL4-mediated microglial lipid droplet accumulation: Bridging Alzheimer's disease and obesity. *Neurobiology of disease* **203**, 106741https://pubmed.ncbi.nlm.nih.gov/39577812/.

9. Walker KA, An Y, Moghekar A *et al.* (2024) Proteomic analysis of APOEε4 carriers implicates lipid metabolism, complement and lymphocyte signaling in cognitive resilience. *Molecular neurodegeneration* **19**, 81https://pmc.ncbi.nlm.nih.gov/articles/PMC11526661/.

10. Guo F, Zheng C, Yang T *et al.* (2025) Serum Angiopoietin-Like Protein 4 as a Biomarker for Acute Ischemic Stroke Severity and Dynamic Changes. *Brain and behavior* **15**, e70337https://pmc.ncbi.nlm.nih.gov/articles/PMC11839744/.

11. He XW, Shen YG, Zhu M *et al.* (2016) Angiopoietin-like protein 4 serum levels and gene polymorphisms are associated with large artery atherosclerotic stroke. *Journal of the neurological sciences* **362**, 333-338https://pubmed.ncbi.nlm.nih.gov/26944173/.

12. Bouleti C, Mathivet T, Coqueran B *et al.* (2013) Protective effects of angiopoietin-like 4 on cerebrovascular and functional damages in ischaemic stroke. *Eur Heart J* **34**, 3657-3668https://pubmed.ncbi.nlm.nih.gov/23674618/.

13. Chakraborty A, Kamermans A, van Het Hof B *et al.* (2018) Angiopoietin like-4 as a novel vascular mediator in capillary cerebral amyloid angiopathy. *Brain : a journal of neurology* **141**, 3377-3388https://pubmed.ncbi.nlm.nih.gov/30462206/.

14. Zhao J, Zhang S, Wang X *et al.* (2024) Correlation between serum ANGPTL4 levels and white matter hyperintensity and cognitive impairment in patients with cerebral small vessel disease. *Brain and behavior* **14**, e3401https://pmc.ncbi.nlm.nih.gov/articles/PMC10839130/.

15. Wang M, He A, Kang Y *et al.* (2025) Novel genes involved in vascular dysfunction of the middle temporal gyrus in Alzheimer's disease: transcriptomics combined with machine learning analysis. *Neural regeneration research* **20**, 3620-3634https://pmc.ncbi.nlm.nih.gov/articles/PMC11974667/.

16. Gagnon E, Gill D, Chabot D *et al.* (2025) Evaluating the Cardiometabolic Efficacy and Safety of Lipoprotein Lipase Pathway Targets in Combination With Approved Lipid-Lowering Targets: A Drug Target Mendelian Randomization Study. *Circulation Genomic and precision medicine* **18**, e004933https://pmc.ncbi.nlm.nih.gov/articles/PMC7617573/.

17. Romeo S, Pennacchio LA, Fu Y *et al.* (2007) Population-based resequencing of ANGPTL4 uncovers variations that reduce triglycerides and increase HDL. *Nature genetics* **39**, 513-516https://pmc.ncbi.nlm.nih.gov/articles/PMC2762948/.

18. Ginsberg HN, Packard CJ, Chapman MJ *et al.* (2021) Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society. *European Heart Journal* **42**, 4791-4806https://doi.org/10.1093/eurheartj/ehab551.

19. Kersten S (2021) Role and mechanism of the action of angiopoietin-like protein ANGPTL4 in plasma lipid metabolism. *Journal of lipid research* **62**, 100150https://pmc.ncbi.nlm.nih.gov/articles/PMC8666355/.

20. Chen YQ, Pottanat TG, Siegel RW *et al.* (2021) Angiopoietin-like protein 4 (ANGPTL4) is an inhibitor of endothelial lipase (EL) while the ANGPTL4/8 complex has reduced EL-inhibitory activity. *Heliyon* **7**, e07898https://pmc.ncbi.nlm.nih.gov/articles/PMC8417300/.

21. Cummings BB, Joing MP, Bouchard PR *et al.* (2025) Safety and efficacy of a novel ANGPTL4 inhibitory antibody for lipid lowering: results from phase 1 and phase 1b/2a clinical studies. *Lancet (London, England)* **405**, 1923-1934https://pubmed.ncbi.nlm.nih.gov/40383129/.

22. Modder M, Het Panhuis WI, Li M *et al.* (2024) Liver-targeted Angptl4 silencing by antisense oligonucleotide treatment attenuates hyperlipidaemia and atherosclerosis development in APOE*3-Leiden.CETP mice. *Cardiovascular research* **120**, 2179-2190https://pmc.ncbi.nlm.nih.gov/articles/PMC11687395/.

23. Gusarova V, O'Dushlaine C, Teslovich TM *et al.* (2018) Genetic inactivation of ANGPTL4 improves glucose homeostasis and is associated with reduced risk of diabetes. *Nature communications* **9**, 2252https://pmc.ncbi.nlm.nih.gov/articles/PMC5997992/.

24. Fan M, Li N, Huang L *et al.* (2025) Exploring Potential Drug Targets in Multiple Cardiovascular Diseases: A Study Based on Proteome-Wide Mendelian Randomization and Colocalization Analysis. *Cardiovascular therapeutics* **2025**, 5711316https://pmc.ncbi.nlm.nih.gov/articles/PMC11870767/.

25. Singh AK, Chaube B, Zhang X *et al.* (2021) Hepatocyte-specific suppression of ANGPTL4 improves obesity-associated diabetes and mitigates atherosclerosis in mice. *The Journal of clinical investigation* **131**https://pmc.ncbi.nlm.nih.gov/articles/PMC8409581/.

26. Deng M, Kutrolli E, Sadewasser A *et al.* (2022) ANGPTL4 silencing via antisense oligonucleotides reduces plasma triglycerides and glucose in mice without causing lymphadenopathy. *Journal of lipid research* **63**, 100237https://pmc.ncbi.nlm.nih.gov/articles/PMC9270256/.

27. Vienberg SG, Kleinridders A, Suzuki R *et al.* (2015) Differential effects of angiopoietin-like 4 in brain and muscle on regulation of lipoprotein lipase activity. *Molecular metabolism* **4**, 144-150https://pmc.ncbi.nlm.nih.gov/articles/PMC4314546/.

28. Dai L, Xie Y, Zhang W *et al.* (2021) Weighted Gene Co-Expression Network Analysis Identifies ANGPTL4 as a Key Regulator in Diabetic Cardiomyopathy via FAK/SIRT3/ROS Pathway in Cardiomyocyte. *Frontiers in endocrinology* **12**, 705154https://pmc.ncbi.nlm.nih.gov/articles/PMC8488438/.

29. Park MS, Kim SE, Lee P *et al.* (2024) Potential role of ANGPTL4 in cancer progression, metastasis, and metabolism: a brief review. *BMB reports* **57**, 343-351https://pmc.ncbi.nlm.nih.gov/articles/PMC11362140/.

30. La Paglia L, Listì A, Caruso S *et al.* (2017) Potential Role of ANGPTL4 in the Cross Talk between Metabolism and Cancer through PPAR Signaling Pathway. *PPAR research* **2017**, 8187235https://pmc.ncbi.nlm.nih.gov/articles/PMC5274667/.

31. Younis OM, Dhaydel AS, Alghwyeen WF *et al.* (2025) The role of ANGPTL4 in cancer: A meta-analysis of observational studies and multi-omics investigation. *PloS one* **20**, e0320343https://pmc.ncbi.nlm.nih.gov/articles/PMC11999138/.

32. Zhao J, Liu J, Wu N *et al.* (2020) ANGPTL4 overexpression is associated with progression and poor prognosis in breast cancer. *Oncology letters* **20**, 2499-2505https://pmc.ncbi.nlm.nih.gov/articles/PMC7399784/.

33. Yarmolinsky J, Lee MA, Lau E *et al.* (2025) Proteogenomic and observational evidence implicate ANGPTL4 as a potential therapeutic target for colorectal cancer prevention. *Journal of the National Cancer Institute*https://pubmed.ncbi.nlm.nih.gov/40511612/.

34. Zuo Y, Dai L, Li L *et al.* (2022) ANGPTL4 Regulates Psoriasis via Modulating Hyperproliferation and Inflammation of Keratinocytes. *Frontiers in pharmacology* **13**, 850967https://pmc.ncbi.nlm.nih.gov/articles/PMC9289168/.

35. Wen Y, Zhang X, Liu H *et al.* (2024) SGLT2 inhibitor downregulates ANGPTL4 to mitigate pathological aging of cardiomyocytes induced by type 2 diabetes. *Cardiovascular diabetology* **23**, 430https://pmc.ncbi.nlm.nih.gov/articles/PMC11619200/.