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Targeting PNPLA3 to Treat MASH and MASH Related Fibrosis and Cirrhosis

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is caused by metabolic triggers and genetic predisposition. Among the genetic MASLD risk variants identified today, the common *PNPLA3* 148M variant exerts the largest effect size of MASLD heritability. The PNPLA3 148M protein is causatively linked to the development of liver steatosis, inflammation and fibrosis in experimental studies and is therefore an appealing target for therapeutic approaches to treat this disease. Several PNPLA3 targeted approaches are currently being evaluated in clinical trials for the treatment of metabolic dysfunction-associated steatohepatitis (MASH), the most severe form of MASLD and promising proof of principle data with reduced liver fat content in homozygous *PNPLA3* 148M risk allele carriers has been reported from phase 1 trials following hepatic silencing of *PNPLA3*. Thus, targeting PNPLA3, the strongest genetic determinant of MASH may hold promise as the first precision medicine for the treatment of this disease. A histological endpoint-based phase 2b study has been initiated and several more are expected to be initiated to evaluate treatment effects on histological MASH and liver fibrosis in participants being homozygous for the *PNPLA3* 148M risk allele variant. The scope of this mini-review is to briefly describe the *PNPLA3* 148M genetics, function and preclinical experimental evidence with therapeutic approaches targeting PNPLA3 as well as to summarise the PNPLA3 based therapies currently in clinical development.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD, previously NAFLD) is now a leading aetiology of chronic liver disease worldwide [1–3]. It encompasses a spectrum of conditions from benign hepatic steatosis to the more aggressive variant metabolic dysfunction-associated steatohepatitis (MASH, previously NASH) characterised by inflammation and fibrosis which can progress to cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease, and is also a leading indication for liver transplantation [4, 5]. The prevalence of MASLD and MASH is highly dependent on individual risk factors such as obesity and type 2 diabetes but there are also ethnic differences with a higher risk occurring in the Hispanic population compared to people of European Caucasian background [5–8].

In 2008, Romeo and Hobbs discovered in a genome-wide association study (GWAS) that a single nucleotide polymorphism in

Summary

- *PNPLA3* rs738409, 148M, is the strongest genetic risk allele variant for MASLD, MASH and metALD related fibrosis and cirrhosis.
- *PNPLA3* 148M induces liver steatosis, inflammation and fibrosis in preclinical experimental studies.
- Silencing of PNPLA3 148M improves MASH and liver fibrosis in liver cellular systems and humanised transgenic mouse models.
- Several PNPLA3 targeted therapies are being investigated in clinical trials and proof of principle with reduction in liver fat content has been demonstrated.
- Further research and histology and non-invasive test-based phase IIb studies are needed to assess treatment effects on histological MASH and liver fibrosis to develop novel precision medicine approaches targeting PNPLA3.

the *patatin-like phospholipase domain-containing 3* (*PNPLA3*) gene (rs738409, encoding an isoleucine to a methionine amino acid switch in the PNPLA3 protein, 148M), was strongly associated with increased liver fat content and inflammation. Interestingly, the risk allele variant was most common in Hispanics, the group most susceptible to developing MASLD, MASLD-related advanced fibrosis and cirrhosis [9, 10]. Since then, several genetic allele variants have been associated with protection against or increased risk of MASLD and some of these including *PNPLA3* are pursued as potential therapeutic targets to treat the disease [11, 12]. In this mini-review we will summarise the recent progress in targeting PNPLA3 as a potential precision medicine to treat MASH in patients carrying the *PNPLA3* 148M risk allele.

2 | PNPLA3 Genetics in Liver Disease

Since the initial discovery of the genetic link between *PNPLA3* 148M with steatohepatitis [9], this variant has been found to be associated with a broad spectrum of liver diseases including MASH, liver fibrosis, cirrhosis, and HCC [13–16]. In a recent large MASLD longitudinal cohort study from Japan, all of the 80 individuals who developed HCC were carriers of the *PNPLA3* 148M risk allele variant [17]. The 148M variant is also associated with early disease diagnosis and increased liver-related mortality [18, 19]. In recent large GWAS on liver cirrhosis, the risk conferred by *PNPLA3* 148M was markedly amplified by obesity, diabetes, and alcoholic intake for liver-related outcomes, relationships that were among the strongest gene–environment interactions detected in man [14, 20]. In addition, homozygous 148M individuals with portal hypertension had double the risk of hepatic decompensation and liver-related mortality [21]. When it comes to chronic hepatitis C, almost all persons can today achieve a sustained virological response upon treatment with antivirals. However, the *PNPLA3* 148M genotype was independently associated with newly diagnosis of HCC in chronic hepatitis C individuals who achieved a sustained virological response [22]. Thus, a therapy targeting hepatic PNPLA3 might have a broader usage beyond the treatment of MASH.

There is also human genetics evidence supporting the concept of targeting PNPLA3 for the treatment of MASH in that another *PNPLA3* genetic variant, p.E434K (rs2294918), is associated with reduced liver *PNPLA3* mRNA levels and protection from MASLD [23].

The *PNPLA3* 148M variant has also been reported to be associated with marginal protection from coronary artery disease (CAD) using a recessive but not an additive genetic model [24], a finding that was not replicated in another study using the same Coronary Artery Disease Genome-wide Replication and Meta-analysis plus the CAD (CARDIoGRAMplusC4D, www.CARDIOGRAMPLUSC4D.org) database or in an extended database from Denmark [25]. The discrepancy between these studies likely relates to the very small effect size of the 148M variant. The *PNPLA3* 148M variant has also been associated with a slightly decreased risk for acne, gout and gallstones [26]. When it comes to potential side effects with a PNPLA3 targeted therapy it is important to keep in mind that current strategies are liver-specific and that silencing or modulation of the 148M protein will not restore endogenous PNPLA3 148I enzymatic function. However, it will be important to monitor potential side effects in the ongoing clinical trials.

3 | PNPLA3 148M Mechanisms in Liver Disease Pathophysiology

PNPLA3 is a membrane protein that is located on hepatic lipid droplets where it hydrolyses triglycerides and retinol esters in hepatocytes and stellate cells, respectively, and the PNPLA3 148M variant has reduced hydrolase activity [27, 28]. Furthermore, PNPLA3 also has a weak acyltransferase activity which is lost in the 148M variant [29]. In humans, the 148M variant is associated with increased hepatic retention of polyunsaturated fatty acids (PUFAs) due to impaired transacylation of PUFAs from diacylglycerol to phosphatidylcholine synthesis [30]. In line, PNPLA3 was recently shown under lipogenic conditions to exert its lipolytic function preferentially on triglycerides-enriched PUFAs, a fatty acid that is important for phospholipid desaturation in the process of secretion of triglyceride-rich lipoproteins and the 148M variant was claimed to be a loss of function with regards to this activity [31]. Silencing or modulation of PNPLA3 in homozygous 148M risk allele carriers would likely not affect this process since endogenous wildtype PNPLA3 enzymatic function will not be restored. However, if the 148M enzyme has a partial loss of function when it comes to lipolysis of PUFA-enriched triglycerides, either directly or indirectly through an inhibitory action of other lipases, one could expect a further increase in PUFAs in triglycerides following PNPLA3 silencing or modulation in homozygous 148M risk allele carriers. Carriers of the 148M variant have hepatic mitochondrial dysfunction leading to decreased *de novo* lipogenesis and channelling of carbons to ketogenesis which also characterise the progression of MASLD [32]. Furthermore, *PNPLA3* 148M was also recently suggested to induce morphological changes in the Golgi apparatus such as enhanced lipid droplet-Golgi contact sites [33].

Importantly, overexpression of human *PNPLA3* 148M (in contrast to overexpression of 148I) specifically in hepatocytes causes MASH and liver fibrosis in mice fed a Western diet supplemented with sugar water [34]. This finding demonstrates that the risk allele variant in hepatocytes can influence the full disease spectrum and thus be the target cell for PNPLA3 silencing or modulation as a potential therapy. Furthermore, normal 148M expression levels, achieved by introducing the 148M variant into the mouse *Pnpla3* gene led to hepatic steatosis in mice fed with a high sucrose-containing diet [35, 36]. Helen Hobbs's lab has elegantly demonstrated that the PNPLA3 148M protein can escape ubiquitination-assisted proteasomal degradation [37], a process recently reported to specifically involve a membrane-bound E3 ubiquitin ligase named bifunctional apoptosis regulator (BFAR) [38]. This will lead to the accumulation of PNPLA3 148M protein levels on hepatocyte lipid droplets in mice and humans [37–39]. However, the 148M protein can still bind to a joint co-activator with adipose triglyceride lipase (ATGL, or PNPLA2) named 1-acylglycerol-3-phosphate O-acyltransferase (ABHD5, or comparative gene identification-58, CGI-58), leading to reduced lipid remodelling on lipid droplets in hepatocytes [40]. Thus, the 148M variant behaves both as a loss of function in terms of enzymatic activity and as a gain of new function with negative transactivation activity due to accumulation of the inactive protein on lipid droplets overall causing a toxic hepatic environment.

In addition to promoting hepatic lipid accumulation, overexpression of PNPLA3 148M in hepatocytes of mice fed a Western diet supplemented with sugar water increases oxidative stress, ceramide levels and signal transducer and activator of transcription 3 (STAT3) activation promoting liver inflammation and fibrosis [34]. Interestingly, in human pluripotent stem cell-derived multicellular liver cultures of hepatocytes, stellate cells and macrophages cultured under lipotoxic MASLD-inducing conditions, the 148M variant elevated interleukin-6 (IL-6)/STAT3 and NF-κB activity thereby accelerating the MASLD phenotype [41]. These findings support that PNPLA3 148M is not just associated with MASLD, but is causatively linked to the disease, suggesting that targeting the PNPLA3 148M protein could be a viable therapeutic strategy as a precision medicine for MASH in individuals who are carriers of the risk allele variant.

4 | Preclinical Proof of Concept Targeting PNPLA3 148M

Several independent groups have presented preclinical proof of concept studies in MASH by silencing *PNPLA3*/*Pnpla3* using different modalities (Table 1). Silencing hepatic *Pnpla3* using an N-acetylgalactosamine (GalNAc)-conjugated antisense oligonucleotide (ASO) improved MASH and liver fibrosis in homozygous *Pnpla3* 148M knock-in mice fed with a MASH-inducing diet [35]. Ablation of hepatic *Pnpla3* in homozygous *Pnpla3* 148M knock-in mice using virally expressed short hairpin RNA improved hepatic steatosis [42]. Furthermore, silencing of human *PNPLA3* in mice with overexpression of human *PNPLA3* 148M in hepatocytes and fed a Western diet supplemented with sugar water, alleviated MASH (including ballooned hepatocytes) and liver fibrosis [34].

It has been challenging to develop small molecule degraders or modulators of PNPLA3 partly due to the intracellular location on lipid droplet membranes. However, proof of concept has been demonstrated with a proteolysis-targeting chimera (PROTAC) approach improving hepatic steatosis. In this study, a modified bacterial dehalogenase (Halo) tag was expressed as a fusion protein with PNPLA3 which was then recognised by the PROTAC machinery to promote ubiquitylation and degradation of the Halo-PNPLA3 protein [42]. To develop a PROTAC based therapy to reduce endogenous PNPLA3 protein levels, a specific binder to PNPLA3 needs first to be identified. When it comes to small molecule modulators of PNPLA3, momelotinib was identified in a screen of clinical stage compounds to reduce *PNPLA3* expression levels and intracellular lipid content in a human multilineage 3D spheroid model of MASH [43]. Momelotinib is a Janus kinase (JAK) inhibitor that was recently approved for the treatment

TABLE 1 | Preclinical proof of concept targeting PNPLA3 148M in vivo in mice for the treatment of MASH and liver fibrosis.

Mouse model	Treatment modality	Results	References
Pnpla3 I148M knock-in mice on high fructose diet	Virally expressed short hairpin RNA	Reduced liver steatosis	BasuRay et al. [42]
Pnpla3 I148M knock-in mice on high sucrose diet	GalNac-ASO	Reduced liver steatosis	Lindén et al. [35]
Mice with AAV overexpression of Halo-tagged human PNPLA3 148M on high sucrose diet	PROTAC targeting of Halo-tagged PNPLA3 protein	Reduced liver steatosis	BasuRay et al. [42]
Pnpla3 I148M knock-in mice on MASH-inducing diet	GalNac-ASO	Reduced liver steatosis, inflammation, NAS, and fibrosis	Lindén et al. [35]
Mice with AAV overexpression of human *PNPLA3* 148M on high fat Western diet and sugar in drinking water (WDSW)	siRNA in lipid nanoparticles	Reduced liver steatosis, ballooning, inflammation, NAS, and fibrosis	Banini et al. [34]

Abbreviations: AAV, adeno-associated virus; GalNAc, *N*-acetylgalactosamine; Halo, modified bacterial dehalogenase; MASH, metabolic dysfunction-associated steatohepatitis; NAS, NAFLD activity score; Pnpla3, patatin-like phospholipase domain-containing protein 3; PROTAC, proteolysis-targeting chimera.

of myelofibrosis [44]. Momelotinib however also inhibits non-JAK kinases and the reduction in *PNPLA3* gene expression was largely attributed to inhibition of bone morphogenic protein (BMP) signalling rather than via the JAK pathway [43]. Adverse events observed with momelotinib include thrombocytopenia, diarrhoea, nausea and vomiting, dizziness, peripheral neuropathy, and increases in liver function tests [44], which may preclude development as a therapy for MASH. However, it would be interesting to further explore the signalling pathways affected by momelotinib treatment in relation to modulation of PNPLA3 activity.

Importantly, the expression levels of *PNPLA3* are highly regulated by fasting and refeeding via the sterol regulatory element binding protein-1c (SREBP-1c) transcription factor which is induced by insulin and liver X receptor (LXR) agonists [45]. It is therefore critical to determine direct effects on *PNPLA3* expression levels versus indirect effects mediated by the nutritional status. Recently, small molecule inhibition of diacylglycerol acyltransferase 2 (DGAT2) was found to direct diacylglycerol into phospholipid synthesis leading to increased amounts of phosphatidylethanolamine (PE) in the endoplasmic reticulum (ER) resulting in reduced hepatic SREBP-1 cleavage, fatty acid synthesis as well as decreased accumulation and secretion of triglycerides from the liver. DGAT2 inhibition was also associated with reduced hepatic *PNPLA3* mRNA expression levels [46]. Thus, therapeutic approaches that lower SREBP-1c mediated lipogenesis could indirectly lower PNPLA3 activity at least to some extent, and combined inhibition of DGAT2 and acetyl-coenzyme A carboxylase (ACC) is currently being pursued as a potential treatment for MASH [47, 48].

5 | PNPLA3 Therapies in Clinical Development

There are today several ASO and siRNA-based *PNPLA3* targeting approaches being evaluated in clinical trials (Table 2 and Figure 1). AZD2693 is a GalNAc-conjugated ASO targeting hepatic *PNPLA3* mRNA and subsequently protein production. The results from randomised single-blind, placebo-controlled single ascending dose (SAD) and double-blind, placebo-controlled multiple ascending dose (MAD) trials were recently presented (https://www.journal-of-hepatology.eu/article/S0168-8278(24)00598-1/abstract). In the SAD trial, up to 110 mg was evaluated in obese but otherwise healthy volunteers while in the MAD trial, three monthly doses of 25, 50, and 80 mg were evaluated in participants with presumed MASH and homozygous for the *PNPLA3* 148M risk allele. These phase 1 studies evaluated the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects of AZD2693. The 80 mg MAD cohort was included to assess target engagement measured as *PNPLA3* mRNA knock-down in liver biopsies at baseline and 1 week after the third dose. AZD2693 was well tolerated and there were no serious adverse events that lead to discontinuations in any of the studies. The PK profile was in line with other ASOs with a rapid absorption and distribution and a half-life ranging from 14 to 22 days. In MAD, AZD2693 treatment led to a reduction in placebo-corrected liver fat content of up to 15% (50 mg). In the 80 mg target engagement MAD study cohort, a mean knockdown of liver *PNPLA3* mRNA by close to 90% from baseline was observed. Interestingly, there was a dose-dependent increase of PUFAs in serum triglycerides indicating that homozygosity for 148M does not result in a complete loss of lipolytic function on PUFAs in triglycerides [30, 31]. In addition, high-sensitivity C-reactive protein (hs-CRP) levels were reduced upon treatment, indicating a decreased inflammatory activity. AZD2693 has been progressed into the FORTUNA phase IIb trial in participants with histologically confirmed MASH and homozygote for the *PNPLA3* 148M risk allele (NCT05809934). The primary outcome will be to assess histological resolution of MASH with improvement in fibrosis as a secondary measure.

ARO-PNPLA3 (formerly JNJ-75220795) is a PNPLA3 GalNAc-siRNA that has been studied in randomised, double-blind, placebo-controlled phase 1 trials in homozygous and heterozygous carriers of the *PNPLA3* 148M risk allele with liver steatosis (https://ir.arrowheadpharma.com/news-releases/news-release-details/arrowhead-pharmaceuticals-gains-full-rights-nash-candidate-aro) and the results were recently published [49]. ARO-PNPLA3/JNJ-75220795 was administered as a single injection at escalating doses from 10 to 400 mg or at a single dose level of 75 mg and the participants were followed for 24 weeks. The PK profile increased approximately proportionally with increasing doses and was compatible with a rapid liver uptake. Treatment of participants being homozygous for the *PNPLA3* 148M risk allele with ARO-PNPLA3/JNJ-75220795 reduced liver fat content of up to 39% from baseline placebo-corrected (46% non-placebo corrected) at the highest dose level (400 mg) with no clinically meaningful changes in any safety parameters, no serious or severe AEs or discontinuations, and mostly mild AEs reported. Interestingly, there was no effect on liver fat content in heterozygous *PNPLA3* 148M risk allele carriers at any of the doses studied [49]. No target engagement with knockdown of liver *PNPLA3* mRNA or protein levels or effects on fatty acid composition in circulating lipids were reported from these clinical trials.

LY3849891 is a PNPLA3 GalNac-siRNAs in SAD/MAD trials in carriers of the *PNPLA3* 148M risk allele with liver steatosis. ALN-PNP, another GalNac siRNA, is in a SAD trial in healthy volunteers. AMG 609 is a *PNPLA3* 148M allele selective GalNac siRNA [50] that has been evaluated in a SAD trial in patients with MASLD. However, AMG 609 is no longer listed on the Amgen pipeline webpage so the project may not be active at this point.

PF-07853578, an orally available PNPLA3 modulator has been assessed in phase 1 trials evaluating safety, tolerability, and pharmacokinetics in healthy adult participants. We are expecting to see these results in the near future.

6 | Future Perspectives and Summary

Following the recent FDA approval of resmetirom (https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-liver-scarring-due-fatty-liver-disease), there is now a treatment option for MASH [51]. In addition, there are several late-stage clinical trials evaluating for

TABLE 2 | PNPLA3 therapies in clinical development.

Drug name (company)	Modality	Clinical stage	Clinical trial IDs	Main results presented from phase I trials in homozygous 148M carriers
AZD2693 (AstraZeneca)	GalNac-ASO	Phase IIb	NCT05107336[a], NCT04142424[a], NCT04483947[a], NCT05919069[c], NCT05809934[c]	• Well tolerated • PK profile increased proportionally with increasing doses compatible with a rapid liver uptake • Dose-dependent reduction in placebo-corrected liver fat content of up to 15% (50 mg) • Mean knockdown of liver *PNPLA3* mRNA by close to 90% from baseline (80 mg) • Dose-dependent increase in polyunsaturated fatty acids in circulating triglycerides • Decreased serum high-sensitivity C-reactive protein levels
ARO-PNPLA3 (previously JNJ-75220795) (Arrowhead)	GalNAc-siRNA	Phase I	NCT04844450[a], NCT05039710[d]	• Well tolerated • PK profile increased approximately proportionally with increasing doses compatible with a rapid liver uptake • Dose-dependent reduction in placebo-corrected liver fat content of up to 39% (400 mg)
LY3849891 (Eli Lilly/ Dicerna)	GalNAc-siRNA	Phase I	NCT05395481[b]	Data not available
ALN-PNP (Alnylam/Regeneron)	GalNAc-siRNA	Phase I	NCT05648214[b], NCT06024408[b]	Data not available
PF-07853578 (Pfizer)	SM modulator	Phase I	NCT05890105[a]	Data not available

Note: Data from www.clinicaltrials.gov.
Abbreviations: ASO, antisense oligonucleotide; GalNAc, N-acetylgalactosamine; PK, pharmacokinetic; PNPLA3, patatin-like phospholipase domain-containing protein 3; siRNA, small interfering RNA; SM, small molecule.
[a]Completed.
[b]Recruiting.
[c]Active, not recruiting.
[d]Terminated.

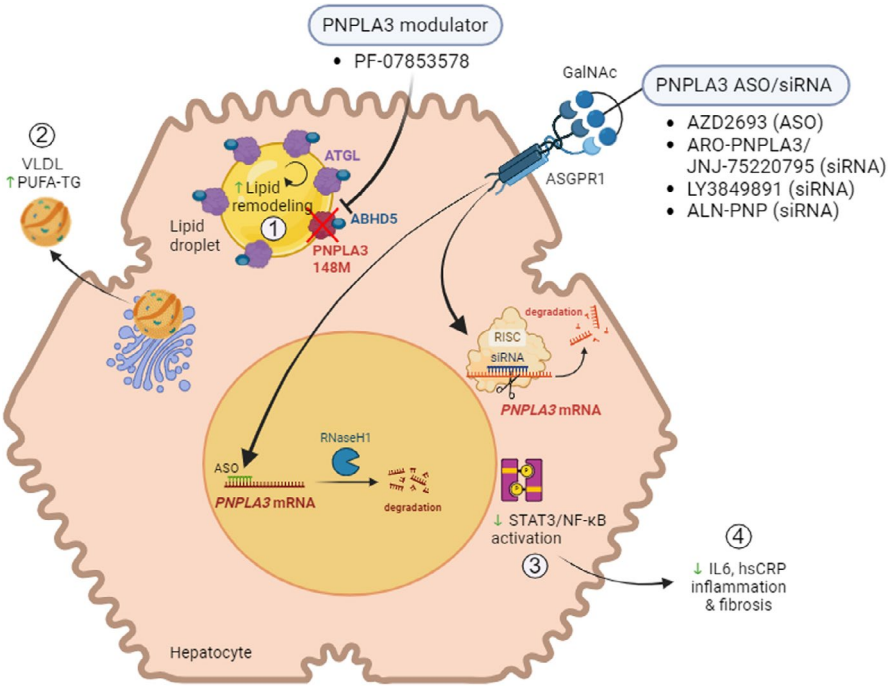

FIGURE 1 | PNPLA3 targeting strategies in clinical development and proposed hepatocyte mechanisms in MASH. Silencing or modulation of PNPLA3 in *PNPLA3* 148M risk allele carriers lead to: (1) increased availability of the joint co-activator ABHD5 for ATGL activation leading to an increased lipid remodelling in lipid droplets, (2) increased PUFAs in VLDL triglycerides, (3) decreased STAT3 and NF-κB activation leading to (4) decreased levels of IL6 and hsCRP, inflammation and fibrosis. ABHD5, 1-acylglycerol-3-phosphate O-acyltransferase; ASGPR1, asialoglycoprotein receptor 1; ASO, antisense oligonucleotide; GalNAc, N-acetylgalactosamine; hsCRP, high-sensitivity C-reactive protein; IL6, interleukin 6; MASH, metabolic dysfunction-associated steatohepatitis; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PNPLA3, patatin-like phospholipase domain-containing protein 3; PUFA-TG, polyunsaturated fatty acids in triglycerides; RNaseH1, Ribonuclease H1; RISC, RNA-induced silencing complex; siRNA, small interfering RNA; STAT3, signal transducer and activator of transcription 3; VLDL, very low-density lipoprotein. Created with BioRender.com.

instance various incretin-like therapies for the treatment of MASH targeting different metabolic drivers of the disease [5]. Since *PNPLA3* 148M is the strongest genetic driver for MASH, it will be important for future studies to explore the efficacy of emerging MASH therapies in the different *PNPLA3* genetic segments in order to identify opportunities for combination or add-on therapies. Furthermore, a liver-targeted PNPLA3-based therapy will likely not affect the body weight or systemic metabolic drivers of MASH. Therefore, targeting PNPLA3, the main genetic risk factor for MASH will hopefully have at least an additive effect when given on top of future standard of care. Recently, a functional interaction between the female sex through the oestrogen receptor-α and the *PNPLA3* 148M genetic variant was demonstrated that may contribute to the increased prevalence of MASLD in women post menopause [52]. It will therefore also be interesting to explore potential sex differences in response to a PNPLA3-targeted therapy. In addition, targeting PNLA3 might have a broader usage beyond MASH, including cirrhosis, preventing hepatic decompensation, MASLD with increased alcoholic intake (MetALD), alcoholic-associated liver disease (ALD) and following antiviral treatment of hepatitis C [14, 21, 22], that could be explored in dedicated clinical trials. In addition, there is an association between the *PNPLA3* 148M genetic variant and chronic kidney disease. PNPLA3 is expressed in renal podocytes, pericytes, and proximal tubule cells so the association could either be due to a direct role of PNPLA3 in the kidney and/ or indirectly via the progression of MASLD [53]. More research is needed to better understand the role of PNPLA3 in the kidney and if the current PNPLA3 silencing/modulatory strategies could add benefits also in kidney disease. To identify individuals carrying the *PNPLA3* 148M genetic risk factor it will be important to develop a companion diagnostics test, and this could also be important for other genetic variants in MASH for potential polygenic risk score stratification. For instance, the protective genetic variant in the gene *HSD17β13* (rs72613567, T to TA insertion) has been shown to partially mitigate the genetic risk of *PNPLA3* 148M in liver disease [54]. Thus, combined silencing or modulation of both PNPLA3 and HSD17β13 could in principle be explored in individuals with MASH carrying both the risk allele in *PNPLA3* and the non-protective allele in *HSD17β13*. However, when considering potential combination therapies, both entities need to contribute to the beneficial effects with an acceptable side effect profile.

In summary, since the discovery of the genetic link between *PNPLA3* and MASLD, great progress has been made in exploring PNPLA3 as a drug discovery target to treat the disease. There are now both promising preclinical data and emerging clinical data supporting the concept of targeting hepatic PNPLA3 as a future precision medicine opportunity for the treatment of MASH which holds great promise for individuals with MASH carrying the strongest genetic risk factor for this disease.

Author Contributions

D.L. wrote the manuscript. G.T. and R.L. revised the manuscript with intellectual input. All authors reviewed and approved the final manuscript.

Conflicts of Interest

D.L. is employed by AstraZeneca and may own company stock or possess stock options. G.T. is employed by Pfizer and may own company stock or possess stock options. R.L. serves as a consultant to Aardvark Therapeutics, Altimmune, Arrowhead Pharmaceuticals, AstraZeneca, Cascade Pharmaceuticals, Eli Lilly, Gilead, Glympse bio, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Lipidio, Madrigal, Neurobo, Novo Nordisk, Merck, Pfizer, Sagimet, 89 bio, Takeda, Terns Pharmaceuticals and Viking Therapeutics. R.L. has stock options in Sagimet biosciences. In addition, his institution received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, Novo Nordisk, Pfizer, Sonic Incytes and Terns Pharmaceuticals. Co-founder of LipoNexus Inc.

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