

Lipid alterations in chronic liver disease and liver cancer

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Table S1. Therapeutic targets of interest in pre-malignant liver diseases (cancer prevention) and primary liver cancer (cancer treatment).

Pathway	Target	CANCER PREVENTION					CANCER TREATMENT				
		Drug	Setting	Phase	Result	Ref	Drug	Setting	Disease	Result	Ref
De novo lipogenesis	ACC	PF-05221304	305 NAFLD 350 NASH with Liver Fibrosis	2	44% reduction in hepatic steatosis	NCT03248882 NCT04321031	AICAR	<i>In vitro</i> human hepatoma	HCC	Strong and cancer specific anti-growth effect	1,2
		GS-0976 Firsocostat	Patients with NASH and fibrosis)	2	Significant reduction in liver fat by 29%	NTC03449446 ³	ND-654	Male mice received oral dose of the drug	HCC	Improved survival when either used alone or in combination with sorafenib	4
			127 NAFLD	2	22% reduction of hepatic DNL decreased by 22%	NCT02856555 ⁵					
			Overweight males	1	Dose-dependent reduction of DNL was observed	NCT02876796 ⁶					
		MK-4074	11 healthy volunteers and murine model		Reduces hepatic steatosis but increases plasma triglycerides in mice	2					
	FASN	TVB-2640	142 NASH	2	Reduced steatosis, improved biochemical, inflammatory, and fibrotic markers	NCT03938246 ⁷	Orlistat	Cell models and murine models	HCC	antiproliferative efficacy HCC - most beneficial in AKT/mTOR related NAFLD-HCC cases	8
			330 NASH	2	Recruiting	NCT04906421		HCC cell line model	HCC	Displays antitumor activity	9
			12 Obese Men	1/2	Reduced hepatic DNL and decreased IHTG	NCT02948569 ¹⁰	C75	<i>In vitro</i> human HCC models	HCC	Growth arrest was seen which was partially modulated by p38 MAPK	11

		Cerulenin	Ob/Ob mice – injected intraperitoneally		Hepatic function in ob/ob mice was significantly improved	12	Triclosan	<i>In vitro</i> hepatoma	HCC	The inhibitor successfully downregulated FASN expression	13	
								HSC models	HCC	Reverted activated HSCs to a quiescent phenotype	14	
								<i>In vitro</i> human hepatoma models	HCC	The inhibitor has chemopreventative and anti-lipogenesis potential	15	
	SCD1	Aramchol	60 participants with NAFLD	2	Reduced steatosis NAFLD, improved metabolic fitness	NCT01094158 16	CAY10566	Human HCC cells	HCC	Reduced viability, induced autophagy and apoptosis of human HCC cells	17	
		CAY10566	HFD C57BL/6 mice		decreased hepatic steatosis	18	CAY10566	Human hepatoma (HepG2) cells	HCC	decreased proliferation and survival in cells; decreased concentration of MUFAs	19	
	TG synthesis	DGAT2	PF-06865571	350 NASH patients with Liver Fibrosis	2	Recruiting	NCT04321031					
PF-05221304			99 NAFLD	2	35% reduction in hepatic steatosis	NCT03776175 ²⁰						
Fatty Acid	CPT1	DGAT1					Tussiligaone	<i>In vitro</i> human hepatoma cell line	HCC	Reduced triglyceride synthesis in the cell line	21	
								Sulfo-N-succinimidyl	Human liver cancer cell lines	HCC	Migration rate was reduced in these cells	22
								Etomoxir	HFD and DEN-induced HCC	HCC	Ras-driven HCC was significantly ameliorated	23
Human hepatoma (HepG2) cells	HCC	Oxidative stress was caused in the cells	24									
FFA Uptake	CD36											

								Xenograft nude mice injected with human hepatoma (HepG2) cells	HCC	Etomoxir in combination with SOAT1 inhibitor significantly reduced tumour growth over 14 days	25
								Mice with β -catenin-activated HCC orally administered Etomoxir	HCC	3 weeks administration with etomoxir dropped the tumour bearing rate to 3% compared to 12% in controls	26
Transcriptional regulation	PPAR	Lobeglitazone	38 participants Type 2 Diabetes NAFLD	4	Reduced steatosis, and improved glycemic, liver, and lipid profiles	NCT02285205 ²⁷	Simvastatin	<i>In vitro</i> HCC cell lines	HCC	Inhibited the HIF-1 α /PPAR- γ /PKM2 axis and reduced proliferation in HCC cells	28
		Pioglitazone	184 NAFLD patients with impaired glucose regulation (IGR) or T2DM with pioglitazone or BBR	2	A decrease in aminotransferase (ALT) values to within the normal range was observed in 7 (58.3%) of the patients	NCT00633282 ²⁹					
		Saroglitazar	15 participants Liver Transplant; Complications NAFLD	2	Recruiting	NCT03639623					
		IWA337 (lanifibranor)	247 NASH	2	Liver enzyme levels decreased, levels of majority of lipid, inflammatory, fibrosis biomarkers improved	NCT03008070 ³⁰					
		IVA337	2000 NASH	3	Recruiting	NCT04849728					
		GFT505 (Elaftibrano r)	270 NASH	2	Resolved NASH, improved patients' cardiometabolic risk profile.	NCT01694849 ³¹					

SREBP	Fatostatin	Zebrafish model	NA	Highlights the importance of LXR α and SREBP1 in Cu-induced hepatic lipid deposition	32	Betulin	<i>In vitro</i> HCC cell lines	HCC	Helped to enhance the antitumor activity of Sorafenib by restricting glycolytic activity	33
	LXR	Oltipraz	60 participants	2	Twenty-four-week treatment significantly reduced the liver fat content in patients with NAFLD	NCT01373554 ³⁴				
283 participants			3	No results published	NCT02068339					
FXR	Obeticholic acid	283 NAFLD	2	Improved the histological features of NASH	NCT01265498 ³⁵	INT-767	Mice with oral administration of inhibitor in the diet	HCC	Tumour number and size were significantly reduced	36
		70 NAFLD	NA	Recruiting	NCT03836937		Obeticholic acid	Primary mixed iCCA cell cultures	CCA	Decreased proliferation, induced apoptosis, decreased spheroid formation
	Px-104	12 NAFLD	2	Improved insulin sensitivity and liver enzymes	NCT01999101 ³⁸					
	LMB7-63	350 NASH	2	Reduction of ALT, hepatic steatosis, weight and BMI	NCT02855164					
	EYP0-01a	16 NASH	1	No results published	NCT03976687					
	MET409	120 NAFLD	2	Reduced steatosis delivered	NCT04702490 ³⁹					
	TERN-101	101 NASH	2	The overall safety, pharmacokinetics, and pharmacodynamics profiles of the inhibitor was assessed	NCT04328077 ⁴⁰					

Sterol synthesis	HMCCR	Tropifexor	380 NASH	2	Recruiting	NCT04065841					
		Obeticholic acid	76 PSC	2	Reduced serum alkaline phosphatase	NCT02177136 ⁴¹					
		EYP001a	11 chronic HBV infection	1	No results published	NCT03320616					
		Cilofexor	419 non-cirrhotic adults with PSC	3	Ongoing	NCT03890120					
	HMCCR	Atorvastatin	84 NASH	2	LDLc in patients with NASH were mitigated with atorvastatin	NCT02633956 ⁴²	Atorvastatin	34 HCC patients on sorafenib	HCC	Terminated (slow enrolment)	NCT03275376
			150 NAFLD	NA	Withdrawn	NCT01987310		240 BCLC 0 HCC receiving complete ablation or tumour resection	HCC	Recruiting	NCT03024684
			70 participants	2	Recruiting	NCT04679376	160 HCC	HCC	Neither sorafenib nor pravastatin seemed to provide benefit	NCT01357486 ⁴³	
		Simvastatin	700 PSC	3	Recruiting	NCT04133792	Pravastatin	474 patients with HCC	HCC	No results published	NCT01903694
		Pitavastatin	50 overweight, insulin-resistant men	NA	Compared with placebo, pitavastatin did not affect hepatic or whole-body insulin sensitivity, and it did not reduce liver fat.	NCT02290106 ⁴⁴		216 patients, advanced HCC	HCC	No results published	NCT01418729
		Rosuvastatin	64 NAFLD	4	No results published	NCT03434613		1 HCC patient	HCC	No results published	NCT03219372

Sphingolipid metabolism	ASBT/IBAT	Volixibat / SHP626	200 participants having itching associated with PSC	2	Recruiting	NCT04663308	Statin	350 participants, patients who received liver transplant as treatment for HCC	HCC	No results published	NCT03490461	
			197 participants with more than 5 % steatosis and NASH without cirrhosis	2	Terminated as the inhibitor did not meet the interim endpoint, and due to diarrhea being the most common side effects in patients	NCT02787304 ⁴⁶	Statin	3 participants	HCC	No results published	NCT02819869	
			84 overweight and obese adults	1	Initial success in improvement of the patients' conditions	NCT02287779 ⁴⁷	Bamnet-UD2	Subcutaneous injection into nude mice	CCA	Tumour growth inhibition in cells expressing ASBT more efficiently than cisplatin	45	
	SK2	K145	Intraperitoneal injection to ob/ob mice		Reduced steatosis and liver function recovery	48	ABC294640	21 solid tumour patients (1 CCA)	CCA	Partial response at 250 mg qd	NCT01488513 ⁴⁹	
								105 participants with CCA	CCA	Ongoing	NCT03377179	
								Human CCA cells	CCA	Inhibited proliferation and caspase-dependent apoptosis in CCA cells	50	
								Human CCA cells	CCA	Inhibits CCA cell growth	51	

							Mouse xenograft models	HCC	Decrease in S1P levels in mice after treatment for 5 weeks	52
S1P1R	FTY720/ fingolimod	Oral administration to diet-induced mouse model of NAFLD		Reduced steatosis, liver TGs, ceramides	53	FTY720/ fingolimod	HCC-bearing rats subjected to orthotopic liver transplantation	HCC	Tumour recurrence was suppressed, and survival increased significantly	54
SK1						Icaritin	<i>In vitro</i> HCC cell lines, xenograft SCID mice	HCC	Potent antitumor activity <i>in vitro</i> , inhibition of tumour growth in mice	NCT2820 6952 ⁵⁵

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