nature portfolio

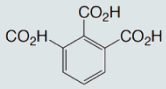
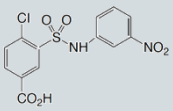
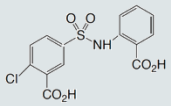
https://doi.org/10.1038/s41573-021-00367-2

Supplementary information

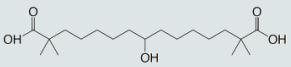
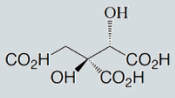
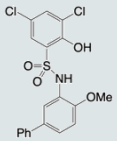
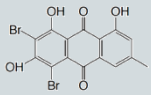
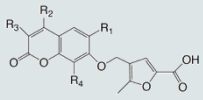
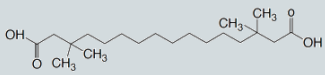
Lipogenesis inhibitors: therapeutic opportunities and challenges

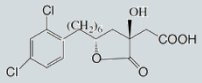
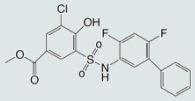
In the format provided by the authors and unedited

Supplementary Table 1 | CIC Inhibitors

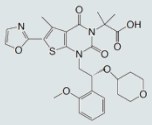
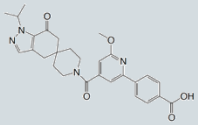
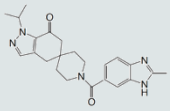
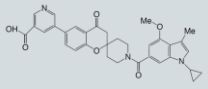
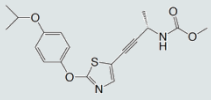
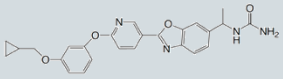
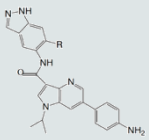
Compound (Developer)	Chemical structure	Binding domain /Potency in biochemical assays	Observed effects	Development stage
Benzenetricarboxylate Benzene-1,3,5-tricarboxylic acid		Citrate-binding sites[1] *Ki*=0.07-0.16mM[1,2]	↓triglycerides in primary hepatocytes[3] ↓GSIS[4] ↓cancer cell growth[5]	Preclinical
CPTI-1 4-Chloro-3-[[(3-nitrophenyl)amino]sulfonyl]-benzoic acid *(Rosalind Franklin University of Medicine and Science, USA)*		Citrate-binding sites[1] *Ki*=0.048-0.07mM[1]	↓ cancer cell growth[5] ↓inflammation[6]	Preclinical
CPTI-2 2-(4-Chloro-3-nitro-benzenesulfonylamino)-benzoic acid *(Lombardi Comprehensive Cancer Center, USA)*		Citrate-binding sites[7] K_D=3.5μM[7]	↓hepatic steatosis[8] ↓hyperlipidemia[8] ↓body weight[8] ↓fasting glucose[8] ↑glucose tolerance[8] ↑insulin sensitivity[8] ↓cancer cell growth[7]	Preclinical

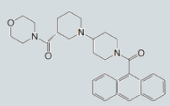
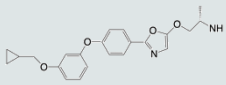
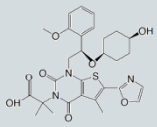
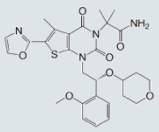
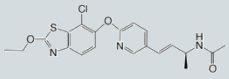
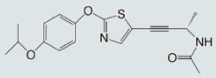
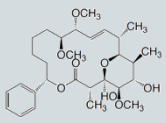
Supplementary Table 2 | ACLY Inhibitors (with selected references)

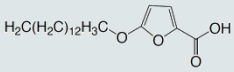
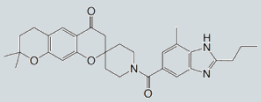
Compound (Developer)	Chemical structure	Binding domain /Potency in biochemical assays	Observed effects	Development stage
Bempedoic Acid (ETC1002) 8-hydroxy-2,2,14,14-tetramethyl pentadecanedioic acid *(Esporion Therapeutics, USA)*		CoA-binding site[9] *Ki*=2μM[9]	↓weight gain[9-13] ↓hepatic steatosis[9] ↓atherosclerotic lesions[9,13] ↓hyperlipidemia[14-16] ↓hyperinsulinema[11] ↓hyperglycmeia[11] ↓diabetes onset & worsening[16] ↓HCC[17]	Approved for primary hypercholesterolemia and established atherosclerotic CVD.
Hydroxycitrate *(1,2-Dihydroxypropane-1,2,3-tricarboxylic acid)*		Citrate-binding site[18] *Ki*=0.15μM[19]	↓weight gain[20,21] ↓food intake[20,21] ↓dyslipidemia[20] ↓fatty acid synthesis[20,22] ↓cholesterol synthesis[22] ↑fatty acid oxidation[23] ↓renal calcium oxalate [24] ↓inflammation[21] ↓oxidative stress[25] ↓platelet aggregation[26] ↓tumor growth[27] ↓ GSIS[28]	Clinical trials on obesity and T2D have been terminated (NCT01238887 NCT00699413) Currently a clinical trial on urine chemistries is underway (NCT03348228)
BMS-303141 (2-hydroxy-N-phenyl benzenesulfonamide derivate) *(Bristol-Myers Squibb Pharmaceutical Research Institute, USA)*		No binding site reported IC_{50}=0.13μM[29]	↓weight gain[29] ↓hyperlipdemia[29] ↓hyperglycemia[29] ↓cancer cell growth[30]	Preclinical
Emodin derivates *(Harvard Medical School, USA)*		Allosteric site in the citrate-binding domain[31] IC_{50}=3-30μM[31]	↓cancer cell growth[31]	Preclinical
Furan carboxylate derivatives (4-substituted-2-furoic acid) *(Harvard Medical School, USA)*		Allosteric site in the citrate-binding domain[32] IC_{50}=4.1-11.9μM[32]	↓cancer stem cells[32]	Preclinical
MEDICA-16 ββ'-Methyl-substituted, Cl6, α,ϖ-dicarboxylic acids *(Hadassah Medical School, Israel)*		Citrate-binding site[33] *Ki*=16μM[33]	↓weight gain[34] ↓hepatic steatosis[35] ↓hyperlipidemia[36] ↓atherosclerotic lesion[36] ↑insulin sensitivity[37] ↑beta cell apoptosis[38] ↓virus replication: WNV[39]	Preclinical

SB-204990 (3R,5S)-rel-5-[6-(2,4-dichlorophenyl)hexyl]tetrahydro-3-hydroxy-2-oxo-3-furanecetic acid *(SmithKline Beecham Pharmaceuticals Ltd, UK)*		Citrate-binding site[40] *Ki*=1μM[40]	↓hyperlipidemia[41,42] ↓oxidative stress[43] ↓inflammation[43] ↑beta cell apoptosis[38] ↓platelet aggregation[26] ↓xenograft tumor[44,45] ↓osteoblast differentiation[46]	Preclinical
NDI-091143 (Methyl 3-chloro-5-(N-(4,6-difluoro-[1,1'-biphenyl]-3-yl) sulfamoyl)-4-hydroxybenzoate) *(Nimbus Therapeutics, USA)*		Allosteric site in the citrate-binding domain[47] *Ki*=0.07μM[47]	no functional studies reported	Discovery

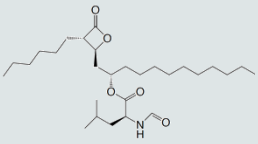
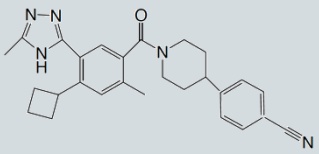
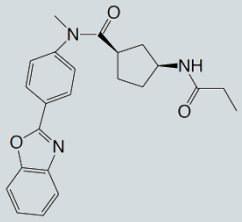
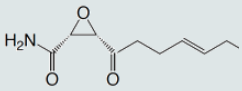
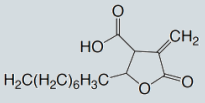
Supplementary Table 3 | ACC inhibitors (with selected references)

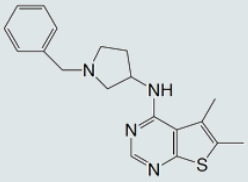
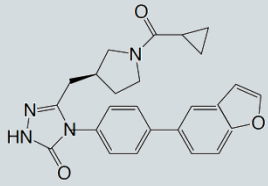
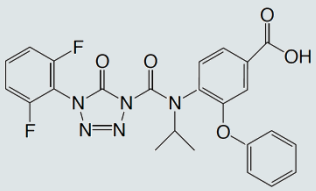
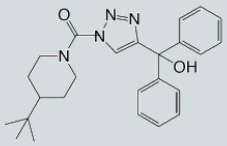
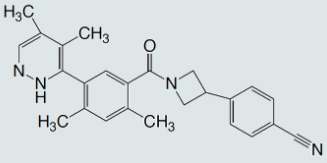
Compound (Developer)	Chemical structure	Binding domain /Potency in biochemical assays	Observed effects	Development stage
Firsocostat (ND-630) 1,4-dihydro-1-[(2R)-2-(2-methoxyphenyl)-2-[(tetrahydro-2H-pyran-4-yl)oxy]ethyl]-α,α,5-trimethyl-6-(2-oxazolyl)-2,4-dioxo-thieno[2,3-d]pyrimidine-3(2H)-acetic acid *(Nimbus Therapeutics, USA)*		AMPK phosphorylation site in BC domain [48] IC_{50}= 2.1nM (hACC1)[48] 6.1nM (hACC2)[48]	↓weight gain[48] ↓hepatic steatosis[48-51] ↓liver fibrosis marker[49-51] ↓hepatic DNL[49,52] ↓plasma triglycerides in rodents[48] ↑plasma triglycerides in humans[50] ↑insulin sensitivity[48]	A phase 2 clinical trial in NASH has recently been completed (NCT02856555)
PF-05221304 *(Pfizer Inc, USA)*		Potentially CT domain IC_{50}= 13nM(hACC1)[53] 9nM(hACC2)[53]	↓hepatic steatosis[54,55] ↓liver fibrosis markers[54] ↓hepatic DNL[54,56,57] ↑fatty acid oxidation[54] ↓inflammation markers[54]	A phase 2 clinical trial have been completed on NAFLD (NCT03248882 NCT03776175)
PF-05175157 1,4-Dihydro-1'-[(2-methyl-1H-benzimidazol-6-yl)carbonyl]-1-(1-methylethyl)-spiro[5H-indazole-5,4'-piperidin]-7(6H)-one *(Pfizer Inc, USA)*		CT domain[57] IC_{50}= 27nM (hACC1)[57] 33nM (hACC2)[57]	↓hepatic DNL[57] ↑fatty acid utilization[57] ↓platelet count[58] ↓facial sebum[59] ↓viral infection[60]	Phase 2 clinical trials on T2D and acne vulgaris have been terminated (NCT01792635 NCT02100527)
MK-4074 (5-(1'-(1-cyclopropyl-4-methoxy-3-methyl-1H-indole-6-carbonyl)-4-oxospiro[chromane-2,4'-piperidin]-6-yl)nicotinic acid) *(Merck &Co, USA)*		No binding site reported IC_{50}= ~3nM(hACC1)[61] ~3nM(hACC2)[61]	↓hepatic steatosis[61] ↓liver fibrosis[62] ↑plasma triglycerides[61]	A phase 1 clinical trial has been completed on NAFLD (NCT01431521)
A-908292 Methyl (S)-(4-(2-(4-isopropoxyphenoxy)thiazol-5-yl)but-3-yn-2-yl)carbamate *(Abbott Laboratories, USA)*		No binding site reported IC_{50}= >30μM (hACC1) [63] 0.023μM (hACC2)[63]	↓muscle malonyl-Co[63] ↓hepatic malonyl-C[63] ↓plasma triglycerides[64] ↓hyperglycemia[64]	Preclinical
Benzoxazole derivative-1b *(Takeda, Japan)*		No binding site reported IC_{50}= 1.5nM (hACC1)[65] 140nM (hACC2)[65]	↓malonyl-CoA in xenograft tumor[65] ↓tumor growth[65]	Preclinical
Carboxamide derivative-1k *(Takeda, Japan)*		No binding site reported IC_{50}= 170nM (hACC1)[66] 2μM (hACC2)[66]	↓malonyl-CoA in xenograft tumor[66]	Preclinical

CP-640186 (3R)-1'-(9-Anthrylcarbonyl)-3-(morpholin-4-ylcarbonyl)-1,4'-bipiperidine *(Pfizer Inc, USA)*		Biotin binding site in the CT domain[67] IC_{50}= 53nM (rACC1)[68] 61nM (rACC2)[68]	↑fatty acid oxidation[68] ↓fatty acid synthesis[68] ↓body weight[69] ↓hepatic steatosis[69] ↓hyperlipidemia[69] ↓hyperglycemia[69] ↓cancer cell growth[70]	Preclinical
Monocyclic derivative-1q *(Takeda, Japan)*		No binding site reported IC_{50}= 0.58nM(hACC1)[71] >10μM (hACC2)[71]	↓malonyl-CoA in xenograft tumor[71]	Preclinical
ND-654 2-(1-((R)-2-(((1s,4S)-4-hydroxycyclohexyl)oxy)-2-(2-methoxyphenyl)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,4-dihydrothieno[2,3-d]pyrimidin-3(2H)-yl)-2-methylpropanoic acid *(Nimbus Therapeutics, USA)*		AMPK phosphorylation site in BC domain[72] IC_{50}= 3nM(hACC1)[72] 8nM(hACC2)[72]	↓HCC growth[72] ↑HCC survival[72] ↓hepatic steatosis[72] ↓hepatic DNL[72] ↓plasma triglycerides[72] ↓inflammation[72]	Preclinical
ND-646 (R)-2-(1-(2-(2-methoxyphenyl)-2-((tetrahydro-2H-pyran-4-yl)oxy)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,4-dihydrothieno[2,3-d]pyrimidin-3(2H)-yl)-2-methylpropanamide *(Nimbus Therapeutics, USA)*		AMPK phosphorylation site in BC domain[73] IC_{50}= 3.5nM(hACC1)[73] 4.1nM(hACC2)[73]	↓fatty acid synthesis[73] ↓lung tumor growth[73] ↓xenograft tumor[73]	Preclinical
Olefin derivate-2e *(Shionogi & Co., Ltd, Japan)*		No binding site reported IC_{50}= 1950nM (hACC1)[74] 1.9nM (hACC2)[74]	↓muscle malonyl-CoA[74]	Preclinical
***(S)*-9c** *(Boehringer Ingelheim Pharma GmbH&Co, USA)*		No binding site reported IC_{50}= >30μM (hACC1)[75] 0.07μM (hACC2)[75]	↓ muscle malonyl-CoA[75] ↓intramyocellular lipids[75] ↓skeletal muscle glucose uptake[75] ↓hyperglycemia[75] ↓plasma triacylglycerol[75]	Preclinical
Soraphen A *(1R,2S,5S,10S,11R,12E,14S,15S,16S,17S,18R)-1,17-dihydroxy-10,11,18-trimethoxy-2,14,16-trimethyl-5-phenyl-4,19-dioxabicyclo[13.3.1]nonadec-12-en-3-one* *S1A)*		BC domain[76] Ki=2.1nM yACC[76]	↓weight gain[77] ↓fatty acid synthesis[77] ↑fatty acid oxidation[78] ↑insulin sensitivity[77] ↓cancer cell growth[79] ↓autoimmune disease[80] ↓virus replication: HCV[81], HIV[82] ↓pathogenic T cells in graft-host disease[83] ↓autophagy[84]	Preclinical

			↓cerebral ischemic injury[85] ↓endothelial cell migration[86]	
TOFA 5-(Tetradecyloxy)-2-furoic acid		No binding site reported IC_{50}=2.5μM[87] (rACC)	↓fatty acid synthesis[88] ↓cholesterol synthesis[88] ↑fatty acid oxidation[88] ↓cancer cell growth[89] ↑microtubule reformation in cystic fibrosis[90] ↓corneal barrier homoestasis[91] ↓virus replication: rotavirus, WNV[39]	Preclinical
WZ66 *(China Pharmaceutical University, China)*		CT domain[92] IC_{50}= 435.9nM (ACC1) [92] 141.3 nM (ACC2)[92]	↓hepatic steatosis[92] ↓hepatic stellate cell activation[92] ↓inflammation[92]	Preclinical

Supplementary Table 4 | **FAS Inhibitors** (with selected references)

Compound (Developer)	**Chemical structure**	**Binding domain /Potency in biochemical assays**	**Observed effects**	**Development stage**
Orlistat N-formyl-L-leucine (1S)-1-[[2S,3S]-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester		TE domain[93] IC_{50}=100nM[93]	↓cancer cell growth[93,94] ↓viral infection[95]	Approved for weight management
TVB-2640 4-(1-(4-Cyclobutyl-2-methyl-5-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl)piperidin-4-yl)benzonitrile *(Sagimet Biosciences, USA)*		KR domain[96] IC_{50} <0.05μM	↓hepatic DNL[97] ↓viral replication: SARS-CoV-2[98]	Phase 1 and 2 clinical trials on NASH and cancer are underway (NCT04906421 NCT03808558 NCT03179904 NCT03032484 NCT02980029)
FT-4101 *(Forma Therapeutics, USA)*	not disclosed	KR domain[99] IC_{50} =40nM[99]	↓hepatic DNL[99] ↓hepatic steatosis[99]	A phase 1/2 clinical trial has been terminated .
BI-99179 (1*R*,3*S*)-*N*-[4-(1,3-Benzoxazol-2-yl)phenyl]-*N*-methyl-3-(propanoylamino)cyclopentane-1-carboxamide *(Boehringer Ingelheim Pharma GmbH & Co, Germany)*		KR domain[100] IC_{50}=79nM[100]	↓cancer cell growth[100]	Preclinical
Cerulenin 2R,3S)-3-[(4E,&E)-nona-4,7-dienoyl]oxirane-2-carboxamide		KS domain[101] IC_{50}=4.5μM[101]	↓food intake[102] ↓cancer cell growth[101] ↓virus replication: EVP[103], WNV[104] ↓bacterial growth[105]	Preclinical
C75 4-Methylene-2-octyl-5-oxotetrahydrofuran-3-carboxylic acid *(Johns Hopkins Medical Institutions, USA)*		KR domain[106] IC_{50}=15.5μM[107]	↓body weight[108,109] ↓food intake[108,109] ↓hepatic steatosis[110] ↑fatty acid oxidation[108] ↓fatty acid synthesis[108] ↓hyperinsulinemia[109] ↓hyperglycemia[109] ↓cancer cell growth[108] ↓viral infection: EVP[103]	Preclinical

			HCV[110],rotavirus[111], WNV[102] ↓neurogenesis[112]	
Fasnall 5,6-Dimethyl-N-[1-(phenylmethyl)-3-pyrrolidinyl]thieno[2,3-d]pyrimidin-4-amine *(Duke University School of Medicine, USA)*		KR, MAT, ER domains[96] IC_{50} = 3.71μM[114]	↓cancer cell growth [114] ↓virus replication:HIV[115]	Preclinical
GSK2194069 (S)-4-(4-(Benzofuran-5-yl)phenyl)-3-((1-(cyclopropanecarbonyl)pyrrolidin-3-yl)methyl)-1H-1,2,4-triazol-5(4H)-one *(GlaxoSmithKline, USA)*		KR domain[116] IC_{50}=7.7nM[116]	↓fatty acid synthesis[116] ↓cancer cell growth[94]	Preclinical
IPI-9119 4-(4-(2,6-difluorophenyl)-N-isopropyl-5-oxo-4,5-dihydro-1H-tetrazole-1-carboxamido)-3-phenoxybenzoic acid *(Dana-Farber Cancer Institute, USA)*		TE domain[117] IC_{50}=0.3nM[117]	↓DNL in cancer cells[117] ↓metastatic castration-resistant prostate cancer cells and xenografts growth[117]	Preclinical
MP-ML-24-N1 *(University Hospital Tuebingen, Germany)*		TE domain[94] IC_{50}=1.6μM[94]	↓cancer cell growth[94]	Preclinical
TVB-3166 4-(1-(5-(3,4-Dimethyl-1H-pyrazol-5-yl)-2,4-dimethylbenzoyl)azetidine-3-yl)benzonitrile *(Sagimet Biosciences, USA)*		KR domain[96] IC_{50} = 42nM[118]	↓cancer cell growth[118]	Preclinical

References:

1. Aluvila, S., Sun, J., Harrison, D.H, Walters, D.E. & Kaplan, R.S. Inhibitors of the mitochondrial citrate transport protein: validation of the role of substrate binding residues and discovery of the first purely competitive inhibitor. *Mol Pharmacol*. **77**:26-34 (2010).
2. Klingenberg, M. Kinetic study of the tricarboxylate carrier in rat liver mitochondria. *Eur J Biochem*. **26**:587-94 (1972).
3. Sun, Q. et al. Regulation on Citrate Influx and Metabolism through Inhibiting SLC13A5 and ACLY: A Novel Mechanism Mediating the Therapeutic Effects of Curcumin on NAFLD. *J Agric Food Chem*. doi: 10.1021/acs.jafc.1c03105 (2021).
4. Joseph, J.W. et al. The mitochondrial citrate/isocitrate carrier plays a regulatory role in glucose-stimulated insulin secretion. *J Biol Chem*. **281**:35624-32 (2006).
5. Catalina-Rodriguez, O. et al. The mitochondrial citrate transporter, CIC, is essential for mitochondrial homeostasis. *Oncotarget*. **3**:1220-35 (2012).
6. Infantino, V., Iacobazzi, V., Menga, A., Avantaggiati, M.L. & Palmieri, F. A key role of the mitochondrial citrate carrier (SLC25A1) in TNFα- and IFNγ-triggered inflammation. *Biochim Biophys Acta*. **1839**:1217-1225 (2014).
7. Fernandez, H.R. et al. The mitochondrial citrate carrier, SLC25A1, drives stemness and therapy resistance in non-small cell lung cancer. *Cell Death Differ*. **25**:1239-1258 (2018).
8. Tan, M. et al. Inhibition of the mitochondrial citrate carrier, Slc25a1, reverts steatosis, glucose intolerance, and inflammation in preclinical models of NAFLD/NASH. *Cell Death Differ*. **27**:2143-2157 (2020).
9. Pinkosky, S.L. et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun*. **7**:13457 (2016).
10. Cramer, C.T. et al. Effects of a novel dual lipid synthesis inhibitor and its potential utility in treating dyslipidemia and metabolic syndrome. *J Lipid Res*. **45**:1289-1301 (2004).
11. Pinkosky, S.L. et al. AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC-1002, a novel small molecule regulator of lipid and carbohydrate metabolism. *J Lipid Res*. **54**:134-151 (2013).
12. Banach, M. et al. Association of Bempedoic Acid Administration With Atherogenic Lipid Levels in Phase 3 Randomized Clinical Trials of Patients With Hypercholesterolemia. *JAMA Cardiol*. **5**:1–12 (2020).
13. Burke, A.C. et al. Bempedoic Acid Lowers Low-Density Lipoprotein Cholesterol and Attenuates Atherosclerosis in Low-Density Lipoprotein Receptor-Deficient (*LDLR*$^{+/-}$ and *LDLR*$^{-/-}$) Yucatan Miniature Pigs. *Arterioscler Thromb Vasc Biol*. **38**:1178-1190 (2018).
14. Pinkosky, S.L., Groot, P.H.E., Lalwani, N.D. & Steinberg, G.R. Targeting ATP-Citrate Lyase in Hyperlipidemia and Metabolic Disorders. *Trends Mol Med*. **23**:1047-1063 (2017).

15. Laufs, U. et al. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. *J Am Heart Assoc*. **8**:e011662 (2019).

16. Ray, K.K. et al. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. *N Engl J Med*. **380**:1022-1032 (2019).

17. Gu, L. et al. The IKKβ-USP30-ACLY Axis Controls Lipogenesis and Tumorigenesis. *Hepatology*. **10**.1002/hep.31249 (2020).

18. Wei, Q., Mei, L., Yang, Y., Ma, H., Chen, H., Zhang, H. & Zhou, J. Design, synthesis and biological evaluation of novel spiro-pentacylamides as acetyl-CoA carboxylase inhibitors. *Bioorg Med Chem*. **26**:3866-3874 (2018).

19. Watson, J.A., Fang, M. & Lowenstein, J.M. Tricarballylate and hydroxycitrate: substrate and inhibitor of ATP: citrate oxaloacetate lyase. *Arch Biochem Biophys*.**35**:209-217 (1969).

20. Sullivan, C. & Triscari, J. Metabolic regulation as a control for lipid disorders. I. Influence of (--)-hydroxycitrate on experimentally induced obesity in the rodent. *Am J Clin Nutr*.**30**:767-776 (1977).

21. Asghar, M., Monjok, E., Kouamou, G., Ohia, S.E., Bagchi, D. & Lokhandwala, M.F. Super CitriMax (HCA-SX) attenuates increases in oxidative stress, inflammation, insulin resistance, and body weight in developing obese Zucker rats. *Mol Cell Biochem*. **304**:93-99 (2007).

22. Triscari, J. & Sullivan, A.C. Comparative effects of (--)-hydroxycitrate and (+)-allo-hydroxycitrate on acetyl CoA carboxylase and fatty acid and cholesterol synthesis in vivo. *Lipids*. **12**:357-363 (1977).

23. Tomita, K., Okuhara, Y., Shigematsu, N., Suh, H. & Lim, K. (-)-hydroxycitrate ingestion increases fat oxidation during moderate intensity exercise in untrained men. *Biosci Biotechnol Biochem*. **67**:1999-2001 (2003).

24. Chung, J., Granja, I. & Taylor, MG., Mpourmpakis, G., Asplin, J.R. & Rimer, J.D. Molecular modifiers reveal a mechanism of pathological crystal growth inhibition. *Nature*. **536**:446-50 (2016).

25. Goudarzvand, M. et al. Hydroxycitric acid ameliorates inflammation and oxidative stress in mouse models of multiple sclerosis. *Neural Regen Res*. **11**:1610-1616 (2016).

26. Michno, A., Skibowska, A., Raszeja-Specht, A., Cwikowska, J. & Szutowicz, A. The role of adenosine triphosphate citrate lyase in the metabolism of acetyl coenzyme a and function of blood platelets in diabetes mellitus. *Metabolism*. **53**:66-72 (2004).

27. Abolhassani, M. et al. Screening of well-established drugs targeting cancer metabolism: reproducibility of the efficacy of a highly effective drug combination in mice. *Invest New Drugs*. **30**:1331-1342 (2012).

28. Flamez, D., Berger, V., Kruhøffer, M., Orntoft, T., Pipeleers, D. & Schuit, F.C. Critical role for cataplerosis via citrate in glucose-regulated insulin release. *Diabetes*. 51:2018-24 (2002).

29. Li, J.J. et al. 2-hydroxy-N-arylbenzenesulfonamides as ATP-citrate lyase inhibitors. *Bioorg Med Chem Lett*. **17**:3208-3211 (2007).

30. Shah S, Carriveau WJ, Li J, Campbell SL, Kopinski PK, Lim HW, Daurio N, Trefely S, Won KJ, Wallace DC, Koumenis C, Mancuso A, Wellen KE. Targeting ACLY sensitizes castration-resistant prostate cancer cells to AR antagonism by impinging on an ACLY-AMPK-AR feedback mechanism. *Oncotarget*. **7**:43713-43730 (2016).

31. Koerner, S.K.Design and synthesis of emodin derivatives as novel inhibitors of ATP-citrate lyase. *Eur J Med Chem*. **126**:920-928 (2017).

32. Jernigan, F.E., Hanai, J.I., Sukhatme, V.P. & Sun, L. Discovery of furan carboxylate derivatives as novel inhibitors of ATP-citrate lyase via virtual high-throughput screening. *Bioorg Med Chem Lett*. **27**:929-935 (2017).

33. Rose-Kahn, G. & Bar-Tana, J. Inhibition of lipid synthesis by beta beta'-tetramethyl-substituted, C14-C22, alpha, omega-dicarboxylic acids in cultured rat hepatocytes. *J Biol Chem*. **260**:8411-8415 (1985).

34. Russell, J.C. et al. Hypolipidemic effect of beta, beta'-tetramethyl hexadecanedioic acid (MEDICA 16) in hyperlipidemic JCR:LA-corpulent rats. *Arterioscler Thromb*. **11**:602-609 (1991).

35. Bar-Tana, J., Rose-Kahn, G. & Srebnik, M. Inhibition of lipid synthesis by beta beta'-tetramethyl-substituted, C14-C22, alpha, omega-dicarboxylic acids in the rat in vivo. *J Biol Chem*. **260**:8404-8410 (1985).

36. Russell, J.C., Amy, R.M., Graham, S.E., Dolphin, P.J., Wood, G.O. & Bar-Tana, J. Inhibition of atherosclerosis and myocardial lesions in the JCR:LA-cp rat by beta, beta'-tetramethylhexadecanedioic acid (MEDICA 16). *Arterioscler Thromb Vasc Biol*. **15**:918-923 (1995).

37. Mayorek, N., Kalderon, B., Itach, E. & Bar-Tana, J. Sensitization to insulin induced by beta,beta'-methyl-substituted hexadecanedioic acid (MEDICA 16) in obese Zucker rats in vivo. *Diabetes*. **46**:1958-64 (1997).

38. Chu, K.Y, Lin, Y., Hendel, A., Kulpa, J.E., Brownsey, R.W. & Johnson, J.D. ATP-citrate lyase reduction mediates palmitate-induced apoptosis in pancreatic beta cells. *J Biol Chem*. **285**:32606-32615 (2010).

39. Merino-Ramos, T., Vázquez-Calvo, Á., Casas, J., Sobrino, F., Saiz, J.C. & Martín-Acebes, M.A. Modification of the Host Cell Lipid Metabolism Induced by Hypolipidemic Drugs Targeting the Acetyl Coenzyme A Carboxylase Impairs West Nile Virus Replication. *Antimicrob Agents Chemother*. **60**:307-315 (2015).

40. Pearce, N.J. et al.The role of ATP citrate-lyase in the metabolic regulation of plasma lipids. Hypolipidaemic effects of SB-204990, a lactone prodrug of the potent ATP citrate-lyase inhibitor SB-201076. *Biochem J*. **334**:113-9 (1998).

41. Gribble, A.D. et al. ATP-Citrate lyase as a target for hypolipidemic intervention. 2. Synthesis and evaluation of (3R,5S)-omega-substituted-3-carboxy-3, 5-dihydroxyalkanoic acids and their gamma-lactone prodrugs as inhibitors of the enzyme in vitro and in vivo. *J Med Chem*. **41**:3582-95 (1998).s

42. van Vlijmen, B.J. et al. Apolipoprotein E*3-Leiden transgenic mice as a test model for hypolipidaemic drugs. *Arzneimittelforschung*. **48**:396-402 (1998).

43. Infantino, V., Iacobazzi, V., Palmieri, F. & Menga, A. ATP-citrate lyase is essential for macrophage inflammatory response. *Biochem Biophys Res Commun*. **440**:105-11 (2013).

44. Zhang, C. et al. Cullin3-KLHL25 ubiquitin ligase targets ACLY for degradation to inhibit lipid synthesis and tumor progression. *Genes Dev*. **30**:1956-70 (2016).

45. Hatzivassiliou, G. et al. ATP citrate lyase inhibition can suppress tumor cell growth. *Cancer Cell*. **8**:311-321 (2005).

46. Shares, B.H., Busch, M., White, N., Shum, L. & Eliseev, R.A. Active mitochondria support osteogenic differentiation by stimulating β-catenin acetylation. *J Biol Chem*. **293**:16019-16027 (2018).

47. Wei, J. et al. An allosteric mechanism for potent inhibition of human ATP-citrate lyase. *Nature*. **568**:566-570 (2019).

48. Harriman, G. et al. Acetyl-CoA carboxylase inhibition by ND-630 reduces hepatic steatosis, improves insulin sensitivity, and modulates dyslipidemia in rats. *Proc Natl Acad Sci U S A*. **113**:E1796-E1805 (2016).

49. Lawitz, E.J. et al. Acetyl-CoA carboxylase inhibitor GS-0976 for 12 weeks reduces hepatic de novo lipogenesis and steatosis in patients with nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol*. **16**:1983–1991.e3 (2018).

50. Loomba, R. et al. GS-0976 Reduces Hepatic Steatosis and Fibrosis Markers in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology*. **155**:1463-1473.e6 (2018).

51. Matsumoto, M. et al. Acetyl-CoA carboxylase 1 and 2 inhibition ameliorates steatosis and hepatic fibrosis in a MC4R knockout murine model of nonalcoholic steatohepatitis. *PLoS One*. **15**:e0228212 (2020).

52. Stiede, K. et al. Acetyl-coenzyme A carboxylase inhibition reduces de novo lipogenesis in overweight male subjects: A randomized, double-blind, crossover study. *Hepatology*. **66**:324-334 (2017).

53. Huard, K. et al. Optimizing the Benefit/Risk of Acetyl-CoA Carboxylase Inhibitors through Liver Targeting. *J Med Chem*. **63**:10879-10896 (2020).

54. Ross, T.T. et al. Acetyl-CoA Carboxylase Inhibition Improves Multiple Dimensions of NASH Pathogenesis in Model Systems. *Cell Mol Gastroenterol Hepatol*. S2352-345X(20)30090-4 (2020).

55. Calle, R.A. et al. ACC inhibitor alone or co-administered with a DGAT2 inhibitor in patients with non-aclhoholic fatty liver disease: two parallel, placebo-controlled, randomized phase 2a trial. *Nat Med.* Doi:10.1038/s41591-021-01489-1.(2021).

56. Bergman, A., Carvajal-Gonzalez, S., Tarabar, S., Saxena, A.R., Esler, W.P. & Amin, N.B. Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Liver-Targeting Acetyl-CoA Carboxylase Inhibitor (PF-05221304): A Three-Part Randomized Phase 1 Study. *Clin Pharmacol Drug Dev*. **9**:514-526 (2020).

57. Griffith, D.A. et al. Decreasing the rate of metabolic ketone reduction in the discovery of a clinical acetyl-CoA carboxylase inhibitor for the treatment of diabetes. *J Med Chem*. **57**:10512-10526 (2014).

58. Kelly, K.L. et al. De novo lipogenesis is essential for platelet production in humans. *Nat Metab.* **2**:1163-1178 (2020).

59. Carvajal-Gonzalez, S. et al. Human sebum requires de novo lipogenesis, which is increased in acne vulgaris and suppressed by acetyl-CoA carboxylase inhibition. *Sci Transl Med*. **11**:eaau8465 (2019).

60. Jiménez de Oya, N. et al. Targeting host metabolism by inhibition of acetyl-Coenzyme A carboxylase reduces flavivirus infection in mouse models. *Emerg Microbes Infect.* **8**:624-636 (2019).

61. Kim, C.W. et al. Acetyl CoA Carboxylase Inhibition Reduces Hepatic Steatosis but Elevates Plasma Triglycerides in Mice and Humans: A Bedside to Bench Investigation. *Cell Metab*. **26**:394-406.e6 (2017).

62. Zhang, J. et al. Molecular Profiling Reveals a Common Metabolic Signature of Tissue Fibrosis. *Cell Rep Med*. **1**:100056 (2020).

63. Gu, Y.G. et al. Synthesis and structure-activity relationships of N-{3-[2-(4-alkoxyphenoxy)thiazol-5-yl]-1- methylprop-2-ynyl}carboxy derivatives as selective acetyl-CoA carboxylase 2 inhibitors. *J Med Chem*. **49**:3770-3773 (2006).

64. Waring, J.F. et al. Gene expression analysis in rats treated with experimental acetyl-coenzyme A carboxylase inhibitors suggests interactions with the peroxisome proliferator-activated receptor alpha pathway. *J Pharmacol Exp Ther*. **324**:507-16 (2008).

65. Mizojiri, R. et al. The identification and pharmacological evaluation of potent, selective and orally available ACC1 inhibitor. *Bioorg Med Chem Lett*. **29**:126749 (2019).

66. Mizojiri, R. et al. Design and synthesis of a novel 1H-pyrrolo[3,2-b]pyridine-3-carboxamide derivative as an orally available ACC1 inhibitor. *Bioorg Med Chem*. **27**:2521-2530 (2019).

67. Zhang, H., Tweel, B., Li, J. & Tong, L. Crystal structure of the carboxyltransferase domain of acetyl-coenzyme A carboxylase in complex with CP-640186. *Structure*. **12**:1683-1691 (2004).

68. Harwood, H.J. Jr. et al. Isozyme-nonselective N-substituted bipiperidylcarboxamide acetyl-CoA carboxylase inhibitors reduce tissue malonyl-CoA concentrations, inhibit fatty acid synthesis, and increase fatty acid oxidation in cultured cells and in experimental animals. *J Biol Chem*. **278**:37099-37111 (2003).

69. Liu, T., Gou, L., Yan, S. & Huang, T. Inhibition of acetyl-CoA carboxylase by PP-7a exerts beneficial effects on metabolic dysregulation in a mouse model of diet-induced obesity. *Exp Ther Med*. **20**:521-529 (2020).

70. Hess, D., Chisholm, J.W. & Igal, R.A. Inhibition of stearoylCoA desaturase activity blocks cell cycle progression and induces programmed cell death in lung cancer cells. *PLoS One*. **5**:e11394 (2010).

71. Mizojiri, R. et al. Discovery of Novel Selective Acetyl-CoA Carboxylase (ACC) 1 Inhibitors. *J Med Chem*. **61**:1098-1117 (2018).

72. Lally, J.S.V. et al. Inhibition of Acetyl-CoA Carboxylase by Phosphorylation or the Inhibitor ND-654 Suppresses Lipogenesis and Hepatocellular Carcinoma. *Cell Metab.* **29**:174-182.e5 (2019).

73. Svensson, R.U. et al. Inhibition of acetyl-CoA carboxylase suppresses fatty acid synthesis and tumor growth of non-small-cell lung cancer in preclinical models. *Nat Med*. **22**:1108-1119 (2016).

74. Nishiura, Y. et al. Discovery of a novel olefin derivative as a highly potent and selective acetyl-CoA carboxylase 2 inhibitor with in vivo efficacy. *Bioorg Med Chem Lett*. **28**:2498-2503 (2018).

75. Glund S, Schoelch C, Thomas L, Niessen HG, Stiller D, Roth GJ, Neubauer H. Inhibition of acetyl-CoA carboxylase 2 enhances skeletal muscle fatty acid oxidation and improves whole-body glucose homeostasis in db/db mice. *Diabetologia*. **55**:2044-53 (2012).

76. Weatherly, S.C., Volrath, S.L. & Elich, T.D. Expression and characterization of recombinant fungal acetyl-CoA carboxylase and isolation of a soraphen-binding domain. *Biochem J*. **380**:105-110 (2004).

77. Schreurs, M., van Dijk, T.H., Gerding, A., Havinga, R., Reijngoud, D.J. & Kuipers, F. Soraphen, an inhibitor of the acetyl-CoA carboxylase system, improves peripheral insulin sensitivity in mice fed a high-fat diet. *Diabetes Obes Metab*. **11**:987-991 (2009).

78. Cordonier, E.L., Jarecke, S.K., Hollinger, F.E. & Zempleni, J. Inhibition of acetyl-CoA carboxylases by soraphen A prevents lipid accumulation and adipocyte differentiation in 3T3-L1 cells. *Eur J Pharmacol*. **780**:202-208 (2016).

79. Corominas-Faja, B. et al. Chemical inhibition of acetyl-CoA carboxylase suppresses self-renewal growth of cancer stem cells. *Oncotarget*. **5**:8306-8316 (2014).

80. Berod, L. et al. De novo fatty acid synthesis controls the fate between regulatory T and T helper 17 cells. *Nat Med*. **20**:1327-1333 (2014).

81. Koutsoudakis, G. et al. Soraphen A: A broad-spectrum antiviral natural product with potent anti-hepatitis C virus activity. *J Hepatol*.**63**:813-821 (2015).

82. Fleta-Soriano, E. et al. The Myxobacterial Metabolite Soraphen A Inhibits HIV-1 by Reducing Virus Production and Altering Virion Composition. *Antimicrob Agents Chemother*. **61**:e00739-17 (2017).

83. Raha, S. et al. Disruption of de novo fatty acid synthesis via acetyl-CoA carboxylase 1 inhibition prevents acute graft-versus-host disease. *Eur J Immunol*. **46**:2233-2238 (2016).

84. Gross, A.S. et al. Acetyl-CoA carboxylase 1-dependent lipogenesis promotes autophagy downstream of AMPK. *J Biol Chem*. **294**:12020-12039 (2019).

85. Wang, X. et al. ACC1 (Acetyl Coenzyme A Carboxylase 1) Is a Potential Immune Modulatory Target of Cerebral Ischemic Stroke. *Stroke*. **50**:1869-1878 (2019).

86. Glatzel, D.K. et al. Acetyl-CoA carboxylase 1 regulates endothelial cell migration by shifting the phospholipid composition. *J Lipid Res*. **59**:298-311 (2018).

87. Bianchi, A., Evans, J.L., Nordlund, A.C., Watts, T.D. & Witters, L.A. Acetyl-CoA carboxylase in Reuber hepatoma cells: variation in enzyme activity, insulin regulation, and cellular lipid content. *J Cell Biochem*. **48**:86-97 (1992).

88. Fukuda, N. & Ontko, J.A. Interactions between fatty acid synthesis, oxidation, and esterification in the production of triglyceride-rich lipoproteins by the liver. *J Lipid Res*. **25**:831-842 (1984).

89. Wang, C., Xu, C., Sun, M., Luo, D., Liao, D.F. & Cao, D. Acetyl-CoA carboxylase-alpha inhibitor TOFA induces human cancer cell apoptosis. *Biochem Biophys Res Commun.* **385**:302-6 (2009).

90. Rymut, S.M. et al. Acetyl-CoA carboxylase inhibition regulates microtubule dynamics and intracellular transport in cystic fibrosis epithelial cells. *Am J Physiol Lung Cell Mol Physiol.* **316**:L1081-L1093 (2019).

91. Mao-Qiang, M., Elias, P.M. & Feingold, K.R. Fatty acids are required for epidermal permeability barrier function. *J Clin Invest*. **92**:791-8 (1993).

92. Gao, Y.S. et al. WZ66, a novel acetyl-CoA carboxylase inhibitor, alleviates nonalcoholic steatohepatitis (NASH) in mice. *Acta Pharmacol Sin*. **41**:336-347 (2020).

93. Kridel, S.J., Axelrod, F., Rozenkrantz, N. & Smith, J.W. Orlistat is a novel inhibitor of fatty acid synthase with antitumor activity. *Cancer Res*. **64**:2070-2075 (2004).

94. Singha, P.K. et al. Evaluation of FASN inhibitors by a versatile toolkit reveals differences in pharmacology between human and rodent FASN preparations and in antiproliferative efficacy in vitro vs. in situ in human cancer cells. *Eur J Pharm Sci*. **149**:105321 (2020).

95. Hitakarun, A. et al. Evaluation of the Antiviral Activity of Orlistat (Tetrahydrolipstatin) Against Dengue Virus, Japanese Encephalitis Virus, Zika Virus and Chikungunya Virus. *Sci Rep.* 10:1499 (2020).

96. Menendez, J.A. & Lupu, R. Fatty acid synthase (FASN) as a therapeutic target in breast cancer. *Expert Opin Ther Targets*. **21**:1001-1016 (2017).

97. Syed-Abdul, M.M. et al. Fatty Acid Synthase Inhibitor TVB-2640 Reduces Hepatic de Novo Lipogenesis in Males With Metabolic Abnormalities. *Hepatology*. **72**:103-118 (2020).

98. Chu, J.et al. Pharmacological inhibition of fatty acid synthesis blocks SARS-CoV-2 replication. *Nat Metab*. Doi:10.1038/s42255-021-00479-4 (2021).

99. Beysen, C. et al. Inhibition of fatty acid synthase with FT-4101 safely reduces hepatic de novo lipogenesis and steatosis in obese subjects with non-alcoholic fatty liver disease: Results from two early-phase randomized trials. *Diabetes Obes Metab*. **23**:700-710 (2021).

100. Kley, J.T., Mack, J., Hamilton, B., Scheuerer, S. & Redemann, N. Discovery of BI 99179, a potent and selective inhibitor of type I fatty acid synthase with central exposure. *Bioorg Med Chem Lett*. **21**:5924-5927 (2011).

101. Morisaki ,N. et a. Effect of side-chain structure on inhibition of yeast fatty-acid synthase by cerulenin analogues. *Eur J Biochem*. **211**:111-5 (2020).

102. Dridi, S. et al. FAS inhibitor cerulenin reduces food intake and melanocortin receptor gene expression without modulating the other (an)orexigenic neuropeptides in chickens. *Am J Physiol Regul Integr Comp Physiol*. **291**:R138-47 (2006).

103. Li, Y., Webster-Cyriaque, J., Tomlinson, C.C., Yohe, M. & Kenney, S. Fatty acid synthase expression is induced by the Epstein-Barr virus immediate-early protein BRLF1 and is required for lytic viral gene expression. *J Virol*. **78**:4197-206 (2004).

104. Martín-Acebes, M.A., Blázquez, A.B., Jiménez de Oya, N., Escribano-Romero, E. & Saiz, J.C. West Nile virus replication requires fatty acid synthesis but is independent on phosphatidylinositol-4-phosphate lipids. *PLoS One*. **6**:e24970 (2011).

105. Heath, R.J., White, S.W. & Rock, C.O. Lipid biosynthesis as a target for antibacterial agents. *Prog Lipid Res*. **40**:467-97 (2001).

106. Pandey, P.R., Liu, W., Xing, F., Fukuda, K., & Watabe, K. Anti-cancer drugs targeting fatty acid synthase (FAS). *Recent Pat Anticancer Drug Discov*. **7**:185-197 (2012).

107. Wang, X. et al. Novel fatty acid synthase (FAS) inhibitors: design, synthesis, biological evaluation, and molecular docking studies. *Bioorg Med Chem*. **17**:1898-904 (2009).

108. Thupari, J.N., Landree, L.E., Ronnett, G.V. & Kuhajda, F.P. C75 increases peripheral energy utilization and fatty acid oxidation in diet-induced obesity. *Proc Natl Acad Sci U S A*. **99**:9498-9502 (2002).

109. Shimokawa, T., Kumar, M.V. & Lane, M.D. Effect of a fatty acid synthase inhibitor on food intake and expression of hypothalamic neuropeptides. *Proc Natl Acad Sci U S A*. **99**:66-71 (2002).

110. Thupari, J.N., Kim, E.K., Moran, T.H., Ronnett, G.V. & Kuhajda, F.P. Chronic C75 treatment of diet-induced obese mice increases fat oxidation and reduces food intake to reduce adipose mass. *Am J Physiol Endocrinol Metab*. **287**:E97-E104 (2004).

111. Yang. W. et al. Fatty acid synthase is up-regulated during hepatitis C virus infection and regulates hepatitis C virus entry and production. *Hepatology*. **48**:1396-1403 (2008).

112. Gaunt, E.R., Cheung, W., Richards, J.E., Lever, A. & Desselberger, U. Inhibition of rotavirus replication by downregulation of fatty acid synthesis. *J Gen Virol*. **94**:1310-1317 (2013).

113. Chorna, N.E. et al. Fatty acid synthase as a factor required for exercise-induced cognitive enhancement and dentate gyrus cellular proliferation. *PLoS One*. **8**:e77845 (2013).

114. Alwarawrah, Y. et al. Fasnall, a Selective FASN Inhibitor, Shows Potent Anti-tumor Activity in the MMTV-Neu Model of HER2(+) Breast Cancer. *Cell Chem Biol*. **23**:678-688 (2016).

115. Kulkarni, M.M. et al. Cellular fatty acid synthase is required for late stages of HIV-1 replication. *Retrovirology*. **14**:45 (2017).

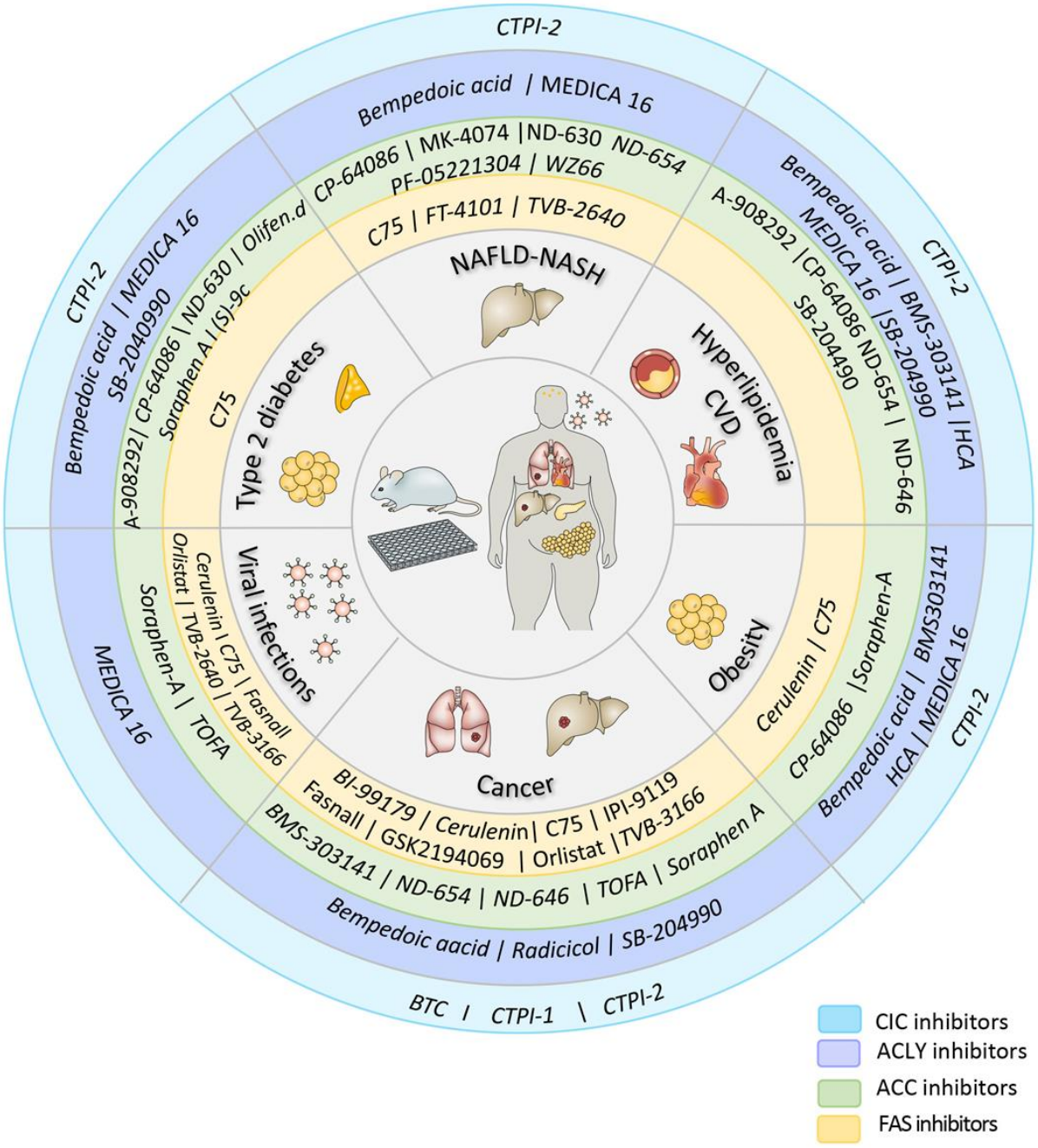
116. Hardwicke, M.A. et al. A human fatty acid synthase inhibitor binds β-ketoacyl reductase in the keto-substrate site. *Nat Chem Biol*. **10**:774-779 (2014).

117. Zadra, G. et al. Inhibition of de novo lipogenesis targets androgen receptor signaling in castration-resistant prostate cancer. *Proc Natl Acad Sci U S A*. **116**:631-640 (2019).

118. Ventura, R. et al. Inhibition of de novo Palmitate Synthesis by Fatty Acid Synthase Induces Apoptosis in Tumor Cells by Remodeling Cell Membranes, Inhibiting Signaling Pathways, and Reprogramming Gene Expression. *EBioMedicine*. **2**:808-824 (2015).

Supplementary Figure 1 | Diseases impacted by DNL inhibitors

Pharmacological inhibition of DNL enzymes impacts various pathological conditions associated with aberrant lipid metabolism. ACLY inhibitors are shown in blue, ACC inhibitors in green and FAS inhibitors in yellow. Compounds that affect obesity, NAFLD-NASH, hyperlipidemia-CVD, T2D, cancer and viral infection have been presented in each enzyme inhibition.
CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver diseases; NASH, non-alcoholic steatohepatitis. CVD, cardiovascular diseases; NAFLD, non-alcoholic fatty liver diseases; NASH, non-alcoholic steatohepatitis.


CTPI-2
Bempedoic acid | MEDICA 16
CP-64086 | MK-4074 | ND-630 ND-654
PF-05221304 | WZ66
C75 | FT-4101 | TVB-2640
NAFLD-NASH
Hyperlipidemia
CVD
Obesity
Cerulenin | C75
CP-64086 | Soraphen-A
Bempedoic acid | BMS303141
HCA | MEDICA 16
CTPI-2
Bempedoic acid | BMS-303141 | HCA
MEDICA 16 | SB-204990
A-908292 | CP-64086 ND-654 | ND-646
SB-204490
Cancer
BI-99179 | Cerulenin | C75 | IPI-9119
Fasnall | GSK2194069 | Orlistat | TVB-3166
BMS-303141 | ND-654 | ND-646 | TOFA | Soraphen A
Bempedoic aacid | Radicicol | SB-204990
BTC | CTPI-1 | CTPI-2
Viral infections
Cerulenin | C75 | Fasnall
Orlistat | TVB-2640 | TVB-3166
Soraphen-A | TOFA
MEDICA 16
Type 2 diabetes
C75
A-908292 | CP-64086 | ND-630 | Olifen.d
Soraphen A I (S)-9c
Bempedoic acid | MEDICA 16
SB-2040990
CTPI-2
CIC inhibitors
ACLY inhibitors
ACC inhibitors
FAS inhibitors