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FATTY LIVER DISEASE (NAFLD/NASH)

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Targeting Insulin Resistance for the Treatment of NASH

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The obesity epidemic has resulted in a dramatic escalation in the number of individuals with hepatic fat accumulation or steatosis. When not combined with excessive alcohol consumption, the broad term for this spectrum of disease is referred to as non-alcoholic fatty liver disease (NAFLD). A significant proportion of individuals with simple steatosis will progress to the severe form of the disease known as non-alcoholic steatohepatitis (NASH), involving hepatocyte damage, inflammation, and fibrosis. If left untreated, NASH can lead to more severe forms of liver disease such as cirrhosis, hepatocellular carcinoma, liver failure, and eventually necessitate liver transplantation. Due to this large clinical burden, research efforts have greatly expanded to better understand NAFLD pathogenesis and the mechanisms underlying the transition to NASH. Likewise, there are currently no approved agents for treating NAFLD/NASH, thus efforts to identify therapeutic targets and progress drug development have intensified in recent years.

Metabolic syndrome and insulin resistance are the most significant risk factors for the development of NAFLD and NASH. Indeed, 60-75% of type 2 diabetic subjects have NAFLD.[1,2] Many aspects of the pathophysiology of insulin resistance are directly causal to NAFLD development (**Figure 1**). Insulin-resistant adipose tissue is unable to appropriately inhibit lipolysis, and therefore, plasma free fatty acid delivery to the liver is increased. In exquisite labeling experiments, plasma free fatty acids were shown to comprise the source of ~60% of liver triglyceride (TAG) in NAFLD subjects.[3] Inadequate insulin signaling also results in increased insulin secretion from pancreatic β-cells and hyperinsulinemia, which can stimulate hepatic *de novo* lipogenesis.[4] Whether derived from free fatty acids or *de novo* lipogenesis, these lipids are largely converted to acyl-CoAs by acyl-CoA synthetases, complexed to glycerol-3-phosphate to create diacylglyceride, and lastly, a third acyl-CoA is added by diacylglycerol acyltransferase (DGAT) to form TAG. This TAG, as well as other lipids and sterols, are then stored inside lipid droplets. These lipid-bound organelles are thought to safely store and control the hydrolysis of these lipids. While somewhat controversial, accumulation of other lipid intermediate species such as diacylglycerols, ceramides, and acyl-CoAs in the liver has been linked to worsening insulin resistance. Other potential mechanisms for fat accumulation in hepatocytes include decreased fat oxidation and decreased fat secretion in the form of very low-density lipoprotein (VLDL) particles. Defects in fat secretion do not appear to be a driver of hepatic steatosis, as NAFLD subjects display greater VLDL secretion both basally and after "suppression" by insulin.[5] Fatty acid β-oxidation is decreased in animal models and humans with NAFLD/NASH.[6-8]

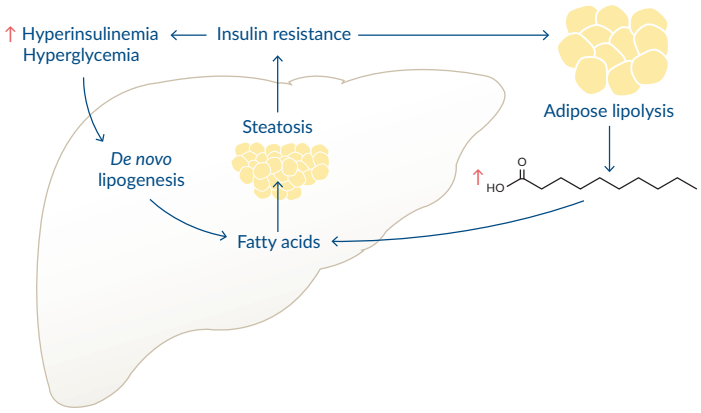

Figure 1. Insulin resistance drives hepatic steatosis.

PPARs as Drug Targets

Because insulin resistance is a direct driver of hepatic lipid accumulation and NASH pathology, the insulin sensitizing thiazolidinedione compounds (TZDs) were one of the earliest classes of drugs to be tested in NASH. Rosiglitazone and pioglitazone have both been used in animal models and human trials of NASH and improve almost all aspects of NASH pathology.[9-15] These TZD compounds are agonists of the nuclear transcription factor peroxisome proliferator-activated receptor γ (PPARγ).[16] PPARγ regulates a gene expression program for adipocyte differentiation and fatty acid storage. While lipid "sequestration" into adipose tissue could be protective against hyperlipidemia, this PPARγ activation with TZDs is associated with a number of side effects such as weight gain, edema, and bone mineral density loss and fracture risk,[17] which have greatly diminished the clinical use of TZDs. Interestingly, pioglitazone is a much weaker agonist of PPARγ compared to rosiglitazone,[16] but provides superior improvements in NASH histology, particularly with regards to fibrosis improvement.[18] These results have opened the door to the possibility that TZDs could have additional target(s) responsible for their pharmacology. Indeed, it was recently observed that TZDs can bind and inhibit the mitochondrial pyruvate carrier (MPC), which regulates pyruvate transport across the inner mitochondrial membrane into the mitochondrial matrix.[19-21] PPARγ-sparing TZD compounds

that retain full ability to bind the MPC (MSDC-0602K and MSDC-0160) have been developed.[19,22] MSDC-0602K was recently shown to improve NASH pathology in a mouse model[23] and is currently in a Phase 2B clinical trial for NASH. Inhibiting the MPC may improve NASH pathology by improving insulin sensitivity, enhancing fatty acid oxidation, attenuating the upregulated flux of carbon into the tricarboxylic acid (TCA) cycle,[6,24-26] and reducing hepatic stellate cell activation.[23]

Non-TZD compounds have also been developed, which agonize other PPAR isoforms such as PPARα and PPARδ, with or without PPARγ activation. In theory, these compounds may combine the insulin-sensitizing effects of targeting PPARγ with the increased fat oxidation effects of PPARα and the anti-inflammatory and fatty acid oxidation effects of PPARδ. Saroglitazar (PPARα/δ agonist) and IVA337/lanifibranor (pan-PPAR agonist) are currently in Phase 2, while elafibranor (PPARα/δ agonist) is in Phase 3 trials for NASH.

Non-PPAR Drug Targets

A number of compounds for other targets that improve insulin sensitivity are currently being developed for NASH. Agonists of the farnesoid X receptor (FXR) have been observed to improve insulin sensitivity and provide anti-inflammatory and antifibrotic effects in diabetic patients with NASH.[27] Obeticholic acid is a synthetic bile acid analog, which is the predominant compound for FXR agonism. However, a trial for obeticholic acid in NASH was terminated before completion due to low treatment efficacy and side effects such as pruritis and modest LDL cholesterol elevations.[28] FXR agonism for NASH will likely depend on whether newer synthetic agonists lacking the bile acid structure display benefits without similar side effects. Synthetic derivatives of fibroblast growth factors FGF19 and FGF21 can also regulate hepatic FXR and PPARγ coactivator 1 (PGC-1) activity and lead to improved insulin sensitivity and improvements in NAFLD/NASH[29] but require larger, longer term trials. These pharmacologic agents that likely have hepatocyte-specific actions in addition to their overall improved insulin sensitivity are depicted in **Figure 2**. The glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide predominantly promotes insulin secretion from pancreatic β-cells but can also improve insulin sensitivity.[30] GLP-1 receptor agonists provide additional metabolic effects, such as weight loss, that could be beneficial in NASH. However, these require further clinical testing. Inhibitors of DGAT-1 or DGAT-2 could potentially improve NASH by preventing TAG formation and forcing enhanced fatty acid oxidation. Indeed, pharmacologic or genetic inhibition of DGAT-1 or -2 in animal models has been shown to improve hepatic steatosis and fibrosis, as well as hepatic and global insulin sensitivity.[31-35] Intriguingly, DGAT-2 inhibition was reported to improve steatosis but exacerbate hepatic injury in the methionine-choline deficient mouse model of NASH.[36] Nevertheless, reducing DGAT expression or activity is still actively being explored to treat NASH, with both small molecule inhibitors and antisense oligonucleotides in clinical development. Lastly, analogs of the small secreted peptide encoded in the mitochondrial genome known as MOTS-c have been developed, which produce effects similar to insulin action, namely inhibition of adipose tissue lipolysis. These MOTS-c analogs (CB4209 and CB4211) improved NASH histology in a mouse model[37] and will likely progress to clinical trials in the near future.

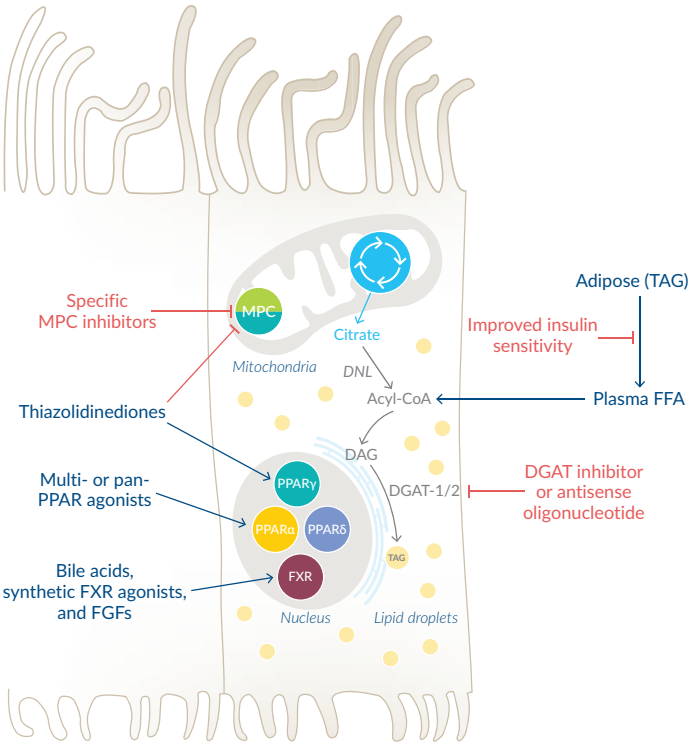

Figure 2. Hepatic targets of insulin sensitizing therapies in development for NASH.

Conclusions and Future Outlook

As insulin resistance and derangements in lipid metabolism are so intricately linked to the development of NAFLD, it is likely that targeting insulin sensitivity will provide the broadest spectrum of pharmacology for treating this disease. While research efforts and compound development are active for downstream pathology such as cell stress/death, inflammation, or antifibrotic compounds, it is hard to envision successful therapeutics that do not also address the core mechanisms of hepatic lipid accumulation.

› Continued on Page 3

However, the presence and degree of hepatic fibrosis is the number one predictor of adverse outcomes in NASH,[38] and therefore treatment strategies will need to prevent or reverse fibrosis. Deciphering how altered metabolism results in hepatocellular stress and death, inflammation, and increased fibrogenesis requires greater research effort. Better understanding this transition from steatosis to NASH, as well as how therapeutics reverse this pathology, remain the ultimate goals for this area of research.

Article References

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About the Author

Kyle S. McCommis, Ph.D.

Dr. McCommis is a research scientist who integrates molecular biology and physiology to study metabolic disease. In addition to better understanding disease pathophysiology, his lab investigates the mechanisms and efficacy of novel therapeutics. His research training began in cardiovascular physiology, and his projects in the lab still involve mitochondrial metabolism in heart failure. Since joining Washington University in 2013, Kyle has also focused on hepatic mitochondrial metabolism in relation to both the pathology and treatment of diabetes and fatty liver disease. He is currently an Assistant Professor of Medicine and will be opening a lab in the Saint Louis University Department of Biochemistry and Molecular Biology in May 2019.

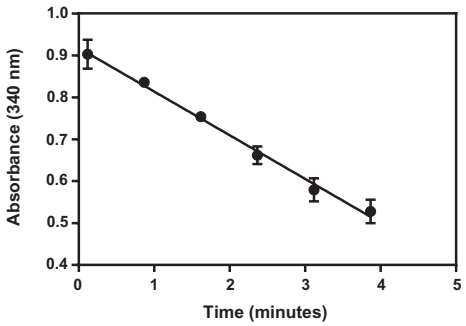
Tools to Study NAFLD/NASH

FEATURED NAFLD ASSAY KIT

Alanine Transaminase Colorimetric Activity Assay Kit

Item No. 700260

- Measure ALT activity in serum, plasma, tissue samples, and cell lysates
- Assay 47 samples in duplicate
- Measure ALT activity down to 0.006 U/ml
- Plate-based colorimetric measurement (340 nm)



Metabolism Assays

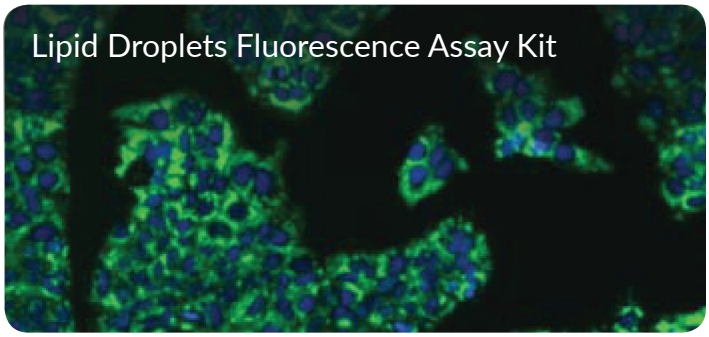
Item No.	Product Name	Measure	Sample Type(s)
10009381	Adipolysis Assay Kit	Adipolysis of triglycerides	Preadipocytes (*e.g.*, differentiated 3T3-L1 cells)
10007640	Cholesterol Fluorometric Assay Kit	Total cholesterol	Plasma, serum
700310	Free Fatty Acid Fluorometric Assay Kit	Free fatty acids	Plasma, serum, urine
10011725	Glycerol Cell-Based Assay Kit	Extracellular glycerol (triglyceride/fatty acid cycling rate)	Cultured cells
26619	Insulin (human) ELISA Kit - *Manufactured by Bertin Bioreagent*	Insulin	Cell culture supernatant, plasma, serum

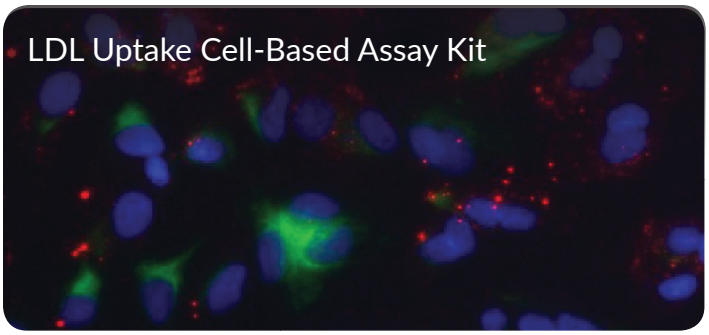
Metabolism Assays *(continued)*

Item No.	Product Name	Measure	Sample Type(s)
701350	α-Ketoglutarate Fluorometric Detection Assay Kit	Intracellular and extracellular α-ketoglutarate concentrations	Cultured cells
10010303	Triglyceride Colorimetric Assay Kit	Triglyceride levels	Cell lysates, tissue homogenates, plasma, serum
700320	Uric Acid Assay Kit	Uric acid (end product of human purine metabolism)	Plasma, serum, urine

Cell-Based Imaging Assays

Item No.	Product Name	Measure	Sample Type(s)
10006908	Adipogenesis Assay Kit	Lipid droplets	Preadipocytes (*e.g.*, differentiated 3T3-L1 cells)
10009779	Cholesterol Cell-Based Detection Assay Kit	Cholesterol uptake and localization	Cultured cells
500001	Lipid Droplets Fluorescence Assay Kit	Lipid droplets	Cultured cells
10011125	LDL Uptake Cell-Based Assay Kit	LDL uptake	Cultured cells
10012643	Steatosis Colorimetric Assay Kit	Excessive lipid accumulation	Cultured cells





Fluorescent Probes

Item No.	Product Name	Localization	Live Cell/Tissue Compatible	Fixed Cell Compatible
25892	BODIPY 493/503	Lipid droplets	✓	✓
25893	BODIPY 505/515	Lipid droplets	✓	✓
70440	Filipin III	Free cholesterol	✗	✓
25073	Filipin Complex	Various sterols	✗	✓
25911	IraZolve-L1™	Lipid droplets and endoplasmic reticulum	✓	✓
25907	ReZolve-L1™	Polar lipids and lipid-rich compartments	✓	✓

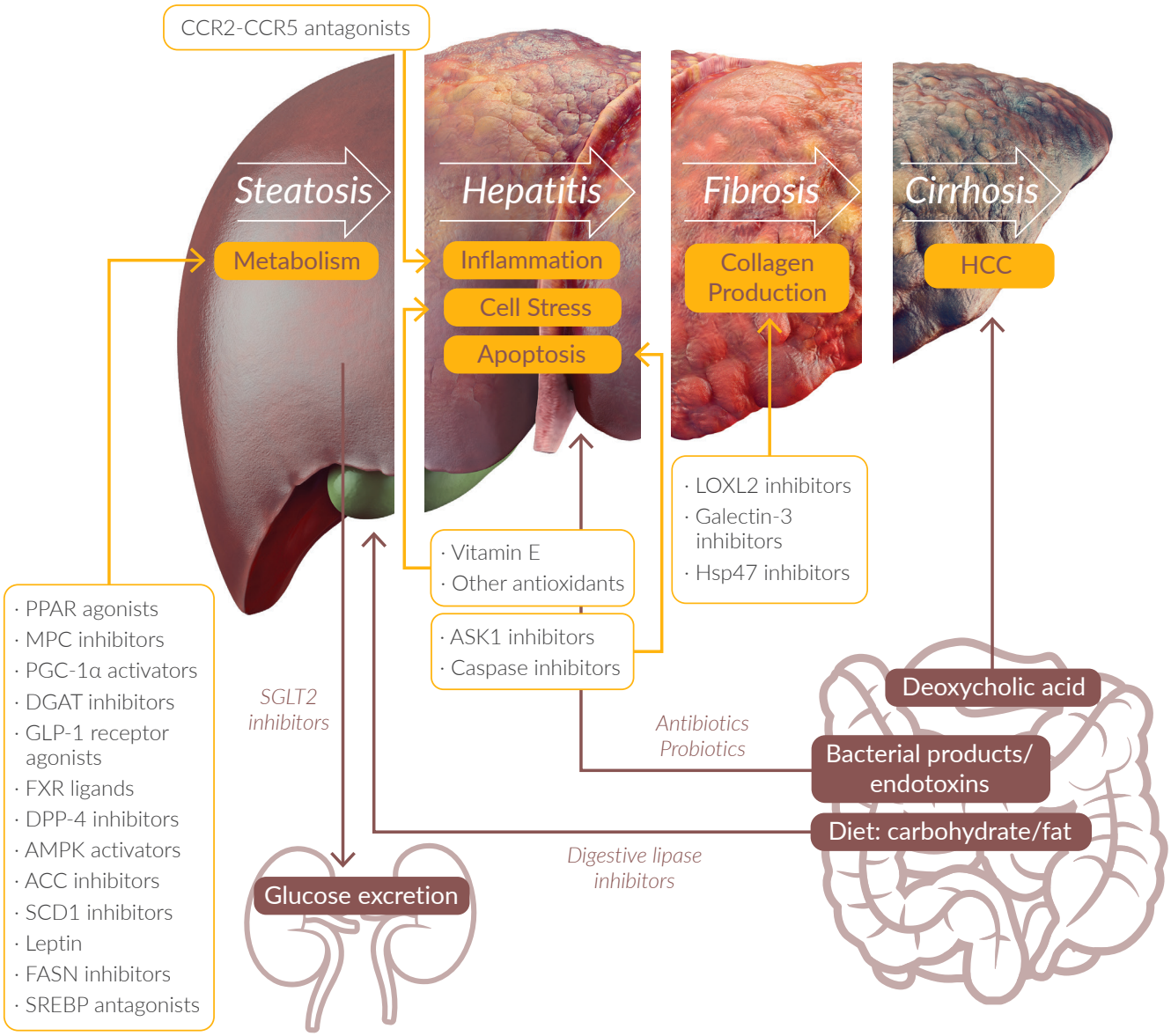
Standards

Item No.	Product Name	Purity
24919	Arachidonic Acid-d_{11} MaxSpec® Standard	≥95%
22787	C16 Ceramide-d_7 (d18:1-d_7/16:0)	≥99% (d_1-d_7)
22788	C18 Ceramide-d_7 (d18:1-d_7/18:0)	≥99% (d_1-d_7)
24379	C18 dihydro Ceramide (d18:0/18:0)	≥98%
24428	C18 dihydro Ceramide-d_3 (d18:0/18:0-d_3)	≥99% (d_1-d_3)
22789	C24 Ceramide-d_7 (d18:1-d_7/24:0)	≥99% (d_1-d_7)
22790	C24:1 Ceramide-d_7 (d18:1-d_7/24:1(15Z))	≥99% (d_1-d_7)

Item No.	Product Name	Purity
25546	Cholesterol-d_6	≥99% (d_1-d_6)
25265	Cholesterol-d_7	≥99% (d_1-d_7)
10005057	Docosahexaenoic Acid-d_5	≥99% (d_1-d_5)
10005056	Eicosapentaenoic Acid-d_5	≥99% (d_1-d_5)
9002193	Linoleic Acid-d_{11}	≥99% (d_1-d_{11})
10008650	1-Stearoyl-2-Arachidonoyl-*sn*-Glycerol	≥95%
10009872	1-Stearoyl-2-Arachidonoyl-*sn*-Glycerol-d_8	≥99% (d_1-d_8)

Therapeutically Targeting the Pathophysiology of NAFLD

An ideal drug candidate for NAFLD/NASH should 1) positively regulate abnormal lipid metabolism to reduce steatosis, hepatic inflammation, and injury; 2) improve underlying insulin resistance; and 3) induce antifibrotic responses. To aid in the pre-clinical discovery and optimization of novel compounds for the treatment of these diseases, Cayman has curated a large set of tools targeting the nuclear transcription factors, nuclear receptors, G protein-coupled receptors, and proteins of interest to this field.



EXPLORE PRODUCTS TARGETING NAFLD PATHOPHYSIOLOGY

Find biochemicals, assay kits, proteins, and antibodies on the following pages:

6
PPAR
PGC-1α
MPC

7
DGAT-1/2
GLP-1
DPP-4
AMPK

8
ACC
SCD1
FASN
Leptin
SREBP
SGLT2

9
HNF4α
TRβ
LXR
TGR5 & FXR

10
FFAR1 (GPR40)
FFAR4 (GPR120)

11
Antioxidants
Apoptosis Inhibitors
Chemokine Receptor Antagonists

Metabolic Homeostasis Targets

PPAR

Peroxisome proliferator-activated receptors (PPARs) have a critical role as master regulators of lipid and glucose metabolism and demonstrate anti-inflammatory properties in the liver. PPAR agonist-targeted therapies may be beneficial for NASH, but their effectiveness is still emerging.

Agonists

Item No.	Product Name	Target
21106	Amorfrutin A	PPARγ
19618	Amorfrutin B	PPARγ
71730	Ciglitazone	PPARγ
23508	Elafibranor	PPARα/δ
11908	GQ-16	PPARγ
13689	GW 1929	PPARγ
25572	Lanifibranor	pan-PPAR
18293	MHY908	PPARα/γ
10007853	Muraglitazar	PPARα/γ
71745	Pioglitazone	PPARγ
71740	Rosiglitazone	PPARγ
11086	SR 1664	PPARγ
71750	Troglitazone	PPARγ

Single-Step Screening Assays

PPARγ Ligand Screening Assay Kit
Item No. 10007685

PPARγ-LBD Ligand Screening Assay Kit
Item No. 600616

Discover our Guide to PPAR Function & Structure at the end of this issue!

PGC-1α

Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is a metabolic sensor involved in the expression of genes important to gluconeogenesis, fatty acid oxidation, lipid transport, and mitochondrial biogenesis. Activators of PGC-1α may help to regulate energy homeostasis during the development of NAFLD/NASH.

Inhibitor and Activator

Item No.	Product Name	Action
22084	SR 18292	Inhibitor
14121	ZLN005	Agonist

PGC-1α Gene Expression Target

Item No.	Product Name
11451	Irisin (human recombinant)
14625	Irisin Polyclonal Antibody

MPC

The mitochondrial pyruvate carrier (MPC) plays a role *via* the mTOR pathway in sensing and directing the effects of overnutrition on liver pathology that drive NAFLD. TZDs can directly interact with MPC and attenuate its activity. Mitochondrial targets of TZD insulin sensitizers (mTOTs) are being developed as inhibitors of the MPC.

mTOT Insulin Sensitizer

Item No.	Product Name
71748	MSDC-0160

MPC Inhibitors

Item No.	Product Name
23445	7ACC2
16980	UK 5099

Targeting Mitochondrial Substrate Oxidation Pathways

UK 5099
Item No. 16980

- Mitochondrial pyruvate carrier (MPC) inhibitor
- Prevents pyruvate transport into the mitochondria
- Shifts energy substrate utilization from glucose to amino acid and fatty acid oxidation

(+)-Etomoxir (sodium salt)
Item No. 11969

- Carnitine palmitoyltransferase 1 (CPT1) inhibitor
- Prevents fatty acyl-CoA transport into the mitochondria
- Shifts energy substrate utilization from fatty acid oxidation to glucose and amino acids

BPTES
Item No. 19284

- Glutaminase 1 (GLS1) inhibitor
- Prevents conversion of glutamine into glutamate
- Shifts energy substrate utilization from glutamine oxidation to fatty acids and pyruvate

DGAT-1/2

Diacylglycerol acyltransferase-1 and -2 (DGAT-1/2), which catalyze the final step in hepatocyte triglyceride biosynthesis, enable triglyceride accumulation in lipid droplets during early stages of NAFLD. Inhibitors of these enzymes may help to improve hepatic steatosis.

Inhibitors

Item No.	Product Name	Target
10012708	A-922500	DAGT-1
17774	Amidepsine A	DAGT
17775	Amidepsine D	DAGT
19440	Cochlioquinone A	DAGT
16425	PF-04620110	DAGT-1
17680	PF-06424439	DAGT-2
25807	T-863	DAGT-1

GLP-1

Glucagon-like peptide 1 (GLP-1)—an intestinal peptide that exerts its effects through the GLP-1 receptor—can increase glucose-dependent insulin secretion, stimulate β-cell proliferation, inhibit glucagon secretion, and increase satiety. GLP-1 receptor agonists may decrease hepatic lipogenesis in incidences of NAFLD.

Agonists

Item No.	Product Name
11096	Exendin-4 (acetate)
24727	Liraglutide

GLP Peptides

Item No.	Product Name
24755	GLP-1 (1-36) amide (human, rat) (trifluoroacetate salt)
24460	GLP-1 (1-37) (human, rat, mouse, bovine) (trifluoroacetate salt)
15069	GLP-1 (7-36) amide (trifluoroacetate salt)
24414	GLP-2 (human) (trifluoroacetate salt)
24756	GLP-2 (1-34) (human) (trifluoroacetate salt)
24757	GLP-2 (rat) (trifluoroacetate salt)

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DPP-4

Dipeptidyl peptidase 4 (DPP-4) degrades incretins such as GLP-1. DPP-4 inhibitors can reduce glucagon and glucose levels and increase insulin secretion. They also improve hepatic steatosis by downregulating SREBP-1c, SCD1, and FASN and upregulating PPARα and AMPK in the liver.

Inhibitors

Item No.	Product Name
23768	Alogliptin (benzoate salt)
21454	MK-3102
23697	Saxagliptin (hydrochloride)
13252	(–)-Sitagliptin (phosphate)
18504	Trelagliptin
14705	Vildagliptin

Convenient Screening Assay

DPP (IV) Inhibitor Screening Assay Kit
Item No. 700210

- Screen for DPP (IV) inhibitors
- Includes sitagliptin as a positive control inhibitor
- Plate-based fluorometric measurement (ex 530-540 nm, em 585-595 nm)

AMPK

AMP-activated protein kinase (AMPK) maintains energy homeostasis by decreasing ATP-consuming pathways and increasing ATP-producing pathways. AMPK activators inhibit *de novo* lipogenesis in the liver, increase fatty acid oxidation in the liver, and promote mitochondrial function in adipose tissue.

Activators

Item No.	Product Name
11900	A-769662
10010241	AICAR
14741	AMPK activator
10631	Ampkinone
19155	GSK621
13118	Metformin (hydrochloride)
17118	Niclosamide (ethanolamine salt)
10006726	PD 98059
21335	PT1
70970	U-0126
19475	YLF-466D
21644	ZLN024

ACC

Acetyl-CoA carboxylase (ACC) converts acetyl-CoA to malonyl-CoA, which contributes to *de novo* lipogenesis and helps to regulate fatty acid oxidation. AMPK phosphorylation of ACC or pharmacological inhibitors of ACC prevents *de novo* lipogenesis and increases mitochondrial fatty acid oxidation.

Inhibitors

Item No.	Product Name	Targets
17691	CP 640,186	ACC1 and ACC2
23961	ND-630	ACC1 and ACC2
21778	PF-05175157	ACC1 and ACC2
10005263	TOFA	ACC and fatty acid synthesis

SCD1

Stearoyl-CoA desaturase 1 (SCD1) is the rate-limiting enzyme in the biosynthesis of oleic acid and palmitoleic acid. Inhibitors of SCD1 may increase fatty acid oxidation by activating AMPK in the liver, preventing triglyceride accumulation in the liver during NASH.

Inhibitors

Item No.	Product Name
19123	A-939572
22478	Aramchol
10012562	CAY10566
16161	PluriSln 1
19379	SW203668
10007417	10-Thiastearic Acid

FASN

Fatty acid synthase (FASN) catalyzes the last step in fatty acid biosynthesis and is thought to be a major determinant of the maximal hepatic capacity to generate fatty acids by *de novo* lipogenesis. Inhibiting FASN may improve hepatic steatosis and inflammation.

Inhibitors

Item No.	Product Name
10005270	(±)-C75
10005647	Cerulenin
19957	Fasnall (benzenesulfonate)
19098	GSK837149A
20236	Icaritin
20940	ML-356
10005263	TOFA
19090	UCM05

Leptin

Leptin—a cytokine-type hormone mainly produced by adipocytes—plays a role in modulating lipid deposition in the liver. Because some patients with NASH demonstrate leptin deficiency, recombinant leptin therapy has been explored in clinical trials.

Assay Kits

Manufactured by Bertin Bioreagent

Item No.	Product Name
500010	Leptin (human) EIA Kit
10007609	Leptin (mouse/rat) EIA Kit
10007608	Leptin Receptor (human) EIA Kit

SREBP

Sterol regulatory element-binding protein (SREBP) regulates intracellular cholesterol and lipid levels by promoting the transcription of genes required for their synthesis. Inhibitors of SREBP may control the potentially lipotoxic role of hepatic cholesterol in NASH.

Inhibitors and Agonist

Item No.	Product Name	Action
11041	Betulin	Inhibitor
13562	Fatostatin (hydrobromide)	Inhibitor
22206	MBX-2982	Agonist

Assay Kits and Antibodies

Item No.	Product Name
10010854	SREBP-1 Transcription Factor Assay Kit
10007663	SREBP-2 Polyclonal Antibody
22728	SREBP-2 Polyclonal Antibody - Biotinylated
10007819	SREBP-2 Transcription Factor Assay Kit

SGLT2

Sodium-glucose cotransporter 2 (SGLT2) inhibitors decrease glucose reabsorption in renal proximal tubules, which has dual effects of insulin-independent glycemic control and caloric loss that may help to delay the onset of NASH.

Inhibitors

Item No.	Product Name
11574	Dapagliflozin
17375	Empagliflozin
23509	Tofogliflozin (hydrate)

HNF4α

Hepatocyte nuclear factor 4α (HNF4α), a nuclear hormone receptor expressed in liver, controls the basal expression of genes involved in bile acid, lipid, glucose, and drug metabolism. HNF4α antagonists can be used modulate the expression of known HNF4α target genes.

Antagonists

Item No.	Product Name
12032	BI-6015
12031	BIM5078

TRβ

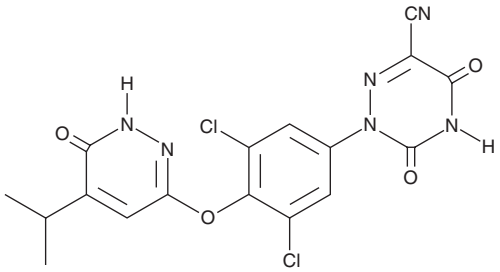
The thyroid hormone receptor β (TRβ) is expressed predominantly in the liver and the brain and functions to modulate cholesterol and liver triglycerides levels. TRβ agonists have shown sustained reduction in liver fat and other markers of NASH in clinical trials.

FEATURED PRODUCT

MGL-3196

Item No. 23845

TRβ agonist that lowers non-HDL cholesterol and liver triglycerides without affecting thyroid stimulating hormone levels in rat and rabbit models of hypercholesterolemia



LXR

Liver X receptors (LXRs) are closely related to intrahepatic inflammation and fibrosis. Liver-specific inverse agonists and antagonists are being studied for antifibrosis effects in NASH.

Antagonist and Inverse Agonist

Item No.	Product Name	Action
25443	GSK2033	LXRα and LXRβ antagonist
18771	SR9238	LXRα and LXRβ inverse agonist

TGR5 & FXR

G protein-coupled bile acid receptor (TGR5 or GP-BAR1) and farnesoid X receptor (FXR) have roles as master regulators of carbohydrate and lipid metabolism, glucose homeostasis, bile acid homeostasis, inflammation, and fibrosis. Activators of these receptors may remediate steatosis pathogenesis.

Agonists

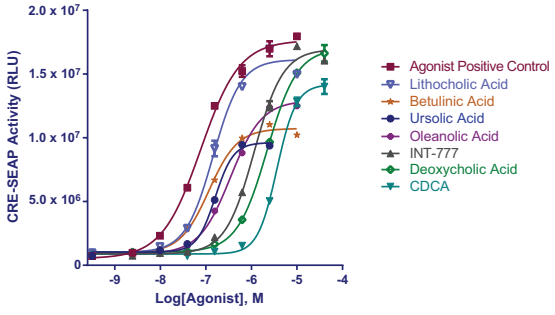
Item No.	Product Name	Target
11686	Betulinic Acid	TGR5
20756	Deoxycholic Acid	TGR5
9003230	Glycine-β-muricholic Acid	TGR5
20274	Glycodeoxycholic Acid	TGR5
21723	Glycolithocholic Acid	TGR5
10006611	GW 4064	FXR
20294	Hyodeoxycholic Acid	TGR5
17678	INT-777	TGR5
20253	Lithocholic Acid	TGR5
20275	Taurochenodeoxycholic Acid (sodium salt)	TGR5
15935	Taurodeoxycholic Acid (sodium salt)	TGR5
22669	Taurohyocholate	TGR5
21956	Taurohyodeoxycholic Acid	TGR5
20277	Tauroursodeoxycholic Acid	TGR5
20289	Tauro-β-muricholic Acid (sodium salt)	TGR5
16291	TGR5 Receptor Agonist	TGR5
15121	Ursodeoxycholic Acid (sodium salt)	TGR5
17369	Fexaramine	FXR
25748	Tropifexor	FXR
23350	XL335	FXR

Scalable Screening Assay

TGR5 (GP-BAR1) Reporter Assay Kit

Item No. 601440

- No stable cell line required, simply add regular HEK293 or HEK293T cells to the plate the day before assaying
- Positive control agonist included
- Obtain results within 24-30 hours after adding cells
- Amenable to high-throughput screening



FFAR1 (GPR40)

Free fatty acid receptor 1 (GPR40) is activated by long-chain fatty acids and several unsaturated fatty acids such as palmitoleic and docosahexaenoic acid. It induces the release of incretins and demonstrates direct insulinotropic and anti-inflammatory effects.

Agonists and Antagonists

Item No.	Product Name	Action
21815	AMG 837	Partial agonist
13143	CAY10587	Agonist
19388	DC260126	Antagonist
10008908	GW 1100	Antagonist
10008907	GW 9508	Agonist
24586	2-hydroxy Lauric Acid	Partial agonist
17335	TAK-875	Agonist
17035	TUG-891	Agonist

Assay Kit and Antibody

Item No.	Product Name
10007205	FFAR1 (GPR40) Polyclonal Antibody
601190	FFAR1 (GPR40) Reporter Assay Kit

FFAR4 (GPR120)

Free fatty acid receptor 4 (GPR120) is activated by both medium-chain and long-chain fatty acids. It is important for the differentiation of adipocytes and plays roles in metabolic balance and the suppression of inflammation.

Agonists and Antagonists

Item No.	Product Name	Action
17713	AH 7614	Antagonist
20602	Docosadienoic Acid methyl ester	Agonist
20749	13Z,16Z-Docosadienoic Acid	Agonist
16624	GPR120 Compound A	Agonist
17398	Grifolic Acid	Partial agonist
17712	GSK137647A	Agonist

Assay Kit and Antibodies

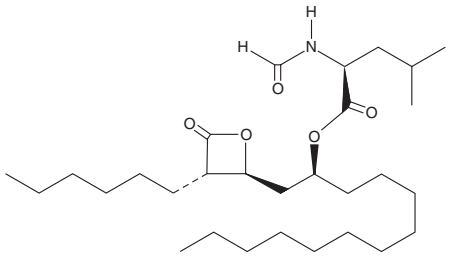
Item No.	Product Name
14265	FFAR4 (GPR120) (C-Term) Polyclonal Antibody
14904	FFAR4 (GPR120) (Internal) Polyclonal Antibody
15130	FFAR4 (GPR120) (N-Term) Polyclonal Antibody
601200	FFAR4 (GPR120) Reporter Assay Kit

FEATURED PRODUCT

Long-lasting gastrointestinal lipase inhibitor — blocks intestinal absorption of dietary fat

Orlistat

Item No. 10005426



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Oxidative Stress, Inflammation, and Apoptosis Targets

Antioxidants

Item No.	Product Name	Summary
25091	Calycosin	An isoflavone that scavenges 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals
24960	Chicoric Acid	A dicaffeoyl ester that reduces blood glucose levels and upregulates antioxidant enzymes
25197	Didymin	A flavonoid that reduces hydrogen peroxide-induced production of reactive oxygen species and increases superoxide dismutase, glutathione peroxidase, and catalase activity
70935	(−)-Epigallocatechin Gallate	A phenol that decreases oxidation of deoxyguanosine and tyrosine nitration
14127	Febuxostat	An antihyperuricemic nonpurine inhibitor of both the oxidized and reduced forms of xanthine oxidase
10005167	Genistein	An isoflavinoid shown to attenuate hepatic steatosis and inflammation
10739	Isoliquiritigenin	A flavonoid that induces nitric oxide synthase and reduces hepatic fat and triglyceride accumulation
19131	NK 252	An Nrf2 activator that activates the NQO1-antioxidant response element
23720	Tiopronin	A hepatoprotective antioxidant that reduces free radical production and reverses hepatocyte degeneration
25985	(±)-α-Tocopherol	A biologically active form of vitamin E that protects cellular membranes from oxidative damage
10072	Ursolic Acid	A pentacyclic triterpenoid with antioxidant properties that reverses increases in hepatic steatosis and levels of hepatic triglycerides and free fatty acids

Anti-Inflammatories

Item No.	Product Name	Summary
14181	Amlexanox	An inhibitor of TANK-binding kinase 1
11948	MN-001	An orally bioavailable anti-inflammatory agent that inhibits 5-lipoxygenase and phosphodiesterases 3 and 4
11726	Oleanolic Acid	A triterpenoid with anti-inflammatory, anti-hyperlipidemic, and hepatoprotective *in vivo* effects
18720	Pentoxifylline	A methylxanthine derivative shown to have anti-inflammatory activity
70675	*trans*-Resveratrol	A polyphenolic phytoalexin with anti-inflammatory effects
25217	Ruscogenin	A steroid sapogenin that reduces proteinuria and renal macrophage infiltration and decreases gene expression of inflammatory cytokines

Apoptosis Inhibitors

Item No.	Product Name	Summary
22204	Emricasan	A pan-caspase inhibitor
16226	NQDI-1	A specific inhibitor of apoptosis signal-regulating kinase 1
16209	*p*-nitro-Pifithrin-α	An inactivator of p53
20972	Selonsertib	An orally bioavailable inhibitor of apoptosis signal-regulating kinase 1
22083	XMU-MP-1	Inhibits pro-apoptotic, sterile 20-like kinases MST1 and MST2

Chemokine Receptor Antagonists

Item No.	Product Name	Summary
23927	Cenicriviroc	An orally bioavailable antagonist of C-C chemokine receptor type 5
17330	RS 504393	A selective antagonist of the MCP-1 receptor CCR2

Additional Inhibitors and Compounds of Interest

Item No.	Product Name	Summary
25990	APC 366 (trifluoroacetate salt)	Reduces collagen content and expression of PAR-2 and α-SMA
25214	Decursin	A phytochemical that reduces hepatic collagen expression, serum levels of ALT, AST, and ALP, and production of ROS
23230	Diethyl 1,4-dihydro-2,4,6-trimethyl-3, 5-pyridinedicarboxylate	An inhibitor of ferrochelatase that induces Mallory-Denk body formation in animal models of alcoholic hepatitis and NASH
14173	Naringenin	A flavonoid that directly down-regulates TGF-β1
13986	Pirfenidone	An orally bioavailable pyridone derivative that inhibits fibrosis and increases in hepatocyte apoptosis, lobular inflammation, and hepatic expression of fibrosis-related genes
21681	Solithromycin	A macrolide antibiotic that may improve histological parameters of NASH
22965	TM5441	An orally bioavailable inhibitor of plasminogen activator inhibitor 1 that protects against high-fat diet-induced NAFLD

Convenient Monitoring Assays

Item No.	Product Name	Summary
501030	Interleukin-6 (human) ELISA Kit	Measure IL-6 from human plasma, serum, synovial fluid, and other sample matrices
705002	Lipid Hydroperoxide (LPO) Assay Kit	Measure hydroperoxides directly utilizing the redox reactions with ferrous ions
701600	Mitochondrial ROS Detection Assay Kit	Fluorometrically assess mitochondrial ROS directly in living cells
601290	ROS Detection Cell-Based Assay Kit (DHE)	Fluorometrically measure ROS directly in living cells
10009055	TBARS Assay Kit	Measure MDA, a byproduct of lipid peroxidation, in plasma, serum, urine, tissue homogenates, and cell lysates
589201	TNF-α (human) ELISA Kit	Measure TNF-α from human plasma, serum, and other sample matrices
500850	TNF-α (mouse) ELISA Kit	Measure TNF-α from mouse plasma, serum, and other sample matrices

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Targeting PPARs:

A guide to function and structure

While PPARs display a high degree of homology at the protein level, each subtype exhibits distinct, noninterchangeable roles in energy metabolism that range from energy burning to energy storage. Learn more about their functions as fatty acid sensors and regulators of energy homeostasis at **www.caymanchem.com/PPARs**.

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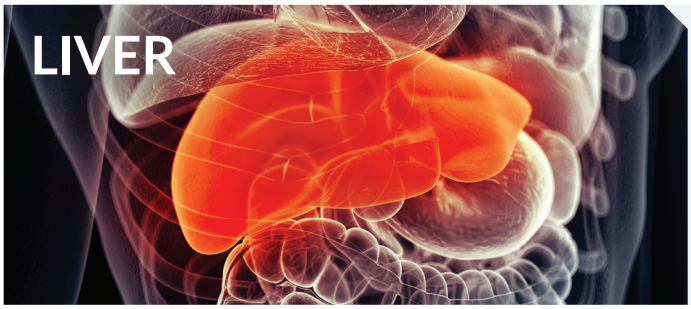
PPARδ
- ↑ Fatty acid oxidation
- ↑ Oxidative muscle fibers
- ↑ Obesity resistance
- ↑ Insulin sensitivity
- ↑ Energy uncoupling

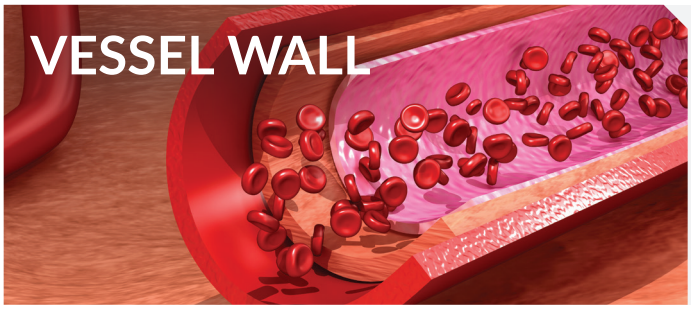
PPARα
- ↑ Fatty acid oxidation

PPARγ
- ↑ Insulin-mediated glucose uptake



PPARα
- ↑ Fatty acid oxidation
- ↑ Ketogenesis
- ↓ Plasma triglycerides
- ↑ Plasma HDL

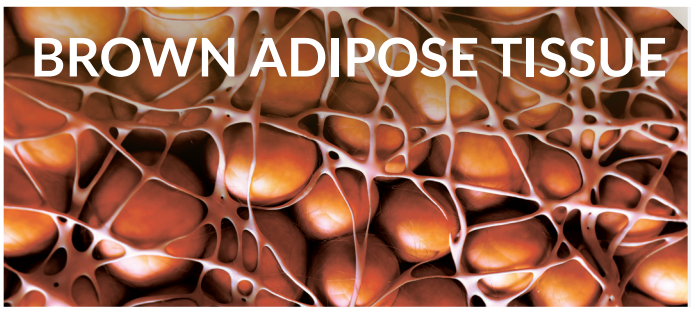
PPARγ
- ↑ Fatty acid storage
- ↑ Lipogenesis



PPARα & PPARγ
- ↓ Inflammation
- ↑ Reverse cholesterol transport

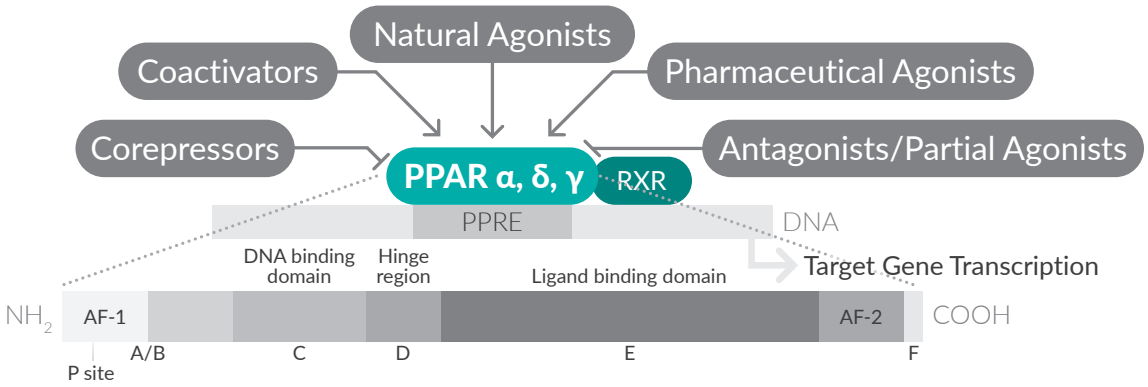
PPARδ
- ↓ Inflammation

PPARγ
- ↑ Adipogenesis
- Regulates adipokine production
- ↑ Lipid repartitioning to fat
- ↑ Insulin sensitivity
- ↑ Lipogenesis



PPARδ
- ↑ Fatty acid oxidation
- ↑ Energy uncoupling

PPARγ
- ↑ Adipogenesis



	PPARα*	PPARδ	PPARγ*
	1 99 173 239 466 468 A/B C D E F *Represents isoform 1, the canonical sequence in UniProt	1 71 145 211 439 441 A/B C D E F	1 136 210 238 503 505 A/B C D E F *Represents isoform 2, the canonical sequence in UniProt
Synonyms	NR1C1	FAAR NR1C2 NUC1 PPARβ	NR1C3
Coactivators	CITED2 CREBBP EP300 MED1 (PBP/DRIP205/TRAP220) NCOA1 (RIP160/SRC-1) NCOA2 (SRC-2) NCOA3 (SRC-3) PGC-1α PGC-1β PRIC295	EP300 NCOA1 (RIP160/SRC-1) NCOA2 (SRC-2) NCOA3 (SRC-3) PGC-1α	CREBBP EP300 FAM120B MED1 (PBP/DRIP205/TRAP220) NCOA1 (RIP160/SRC-1) NCOA2 (SRC-2) NCOA3 (SRC-3) NCOA4 NCOA6 NCOA7 PGC-1α PGC-1β PGC-2
Corepressors	NCOR1 RIP140 (NRIP1) SMRT (NCOR2)	NCOR1 NR0B2 RIP140 (NRIP1) SMRT (NCOR2) SPEN	GPS2 NCOR1 NR0B1 NR0B2 PER2 RIP140 (NRIP1) SMRT (NCOR2)
Selective Agonists	AM3102 Clofibrate (+)-Etomoxir (sodium salt) Fenofibrate GW 590735 GW 7647 GW 9578 8(S)-HETE Leukotriene B_4 N-Octadecyl-N'-propyl-sulfamide Oleoyl Ethanolamide	CAY10592 GW 0742 GW 501516	Amorfrutin A Amorfrutin B Azelaoyl PAF CAY10599 CDDO Ciglitazone GW 1929 Pioglitazone 15-deoxy-$\Delta^{12,14}$-Prostaglandin J_2 Rosiglitazone Troglitazone
Non-Selective and Dual Agonists	Bavachinin Bezafibrate CAY10514 CAY10573 Elafibranor (±)9-HODE (±)13-HODE Lanifibranor MHY908 Muraglitazar Tesaglitazar Wy 14643	Bavachinin Bezafibrate CAY10573 Elafibranor Lanifibranor	Bavachinin Bezafibrate CAY10514 CAY10573 (±)9-HODE (±)13-HODE Lanifibranor MHY908 Muraglitazar Tesaglitazar Wy 14643
Partial Agonists and Antagonists	GW 6471	GSK3787 Sulindac	BADGE Diclofenac FMOC-L-Leucine G3335 GW 9662 MCC-555 SR 202 T0070907

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