




REVIEW

# Re-highlighting the action of PPAR $\gamma$ in treating metabolic diseases [version 1; referees: 2 approved]

Sung Hee Choi<sup>1,2</sup>, Sung Soo Chung<sup>1,3</sup>, Kyong Soo Park  <sup>1,4</sup>

<sup>1</sup>Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea

<sup>2</sup>Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea

<sup>3</sup>Biomedical Research Institute, Seoul National University Hospital, Seoul, South Korea

<sup>4</sup>Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, South Korea

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### Abstract

Peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) is a member of the nuclear receptor family and plays an important role in adipocyte differentiation, glucose homeostasis, and insulin sensitivity. Thiazolidinediones (TZDs), synthetic ligands of PPAR $\gamma$ , have been used for the treatment of diabetes mellitus for two decades. TZDs were expected to be amazing drugs not only for type 2 diabetes but also for metabolic syndrome and atherosclerotic vascular disease because they can reduce both insulin resistance and inflammation in experimental studies. However, serious unwanted effects pushed TZDs back to an optional second-tier drug for type 2 diabetes. Nevertheless, PPAR $\gamma$  is still one of the most important targets for the treatment of insulin resistance and diabetes mellitus, and novel strategies to modulate PPAR $\gamma$  activity to enhance its beneficial effects and reduce unwanted adverse effects are anticipated. Recent studies showed that post-translational modification (PTM) of PPAR $\gamma$  regulates PPAR $\gamma$  activity or stability and may be a novel way to optimize PPAR $\gamma$  activity with reduced adverse effects. In this review, we will focus on recent advances in PTM of PPAR $\gamma$  and the mechanisms regulating PPAR $\gamma$  function as well as in the development of PPAR $\gamma$  modulators or agonists.

### Keywords

PPAR $\gamma$ , post-translational modification, metabolic disease

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**Corresponding author:** Kyong Soo Park ([kspark@snu.ac.kr](mailto:kspark@snu.ac.kr))

**Author roles:** **Choi SH:** Conceptualization, Data Curation, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Chung SS:** Conceptualization, Data Curation, Resources, Supervision, Writing – Original Draft Preparation; **Park KS:** Conceptualization, Data Curation, Resources, Supervision, Writing – Review & Editing

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## Introduction

Insulin resistance is the key pathophysiologic abnormality of many metabolic diseases such as type 2 diabetes mellitus, obesity, dyslipidemia, and cardiovascular diseases<sup>1</sup>. Therefore, reducing insulin resistance is the most important strategy for improving metabolic deterioration. Thiazolidinediones (TZDs), peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) agonists, have shown many beneficial effects not only by enhancing insulin sensitivity but also by demonstrating anti-inflammatory and antioxidant properties, whose actions are related to anti-atherosclerosis<sup>2,3</sup>. Thus, TZDs were considered a magic bullet for the treatment of type 2 diabetes and atherosclerosis. Indeed, TZDs demonstrated a preventive role for recurrent ischemic stroke in several clinical trials<sup>4</sup> and for restenosis after percutaneous coronary intervention (PCI)<sup>5-7</sup>. However, TZDs increased the risk of peripheral edema, bone loss, and congestive heart failure<sup>8-10</sup>. A meta-analysis of clinical trials showed that rosiglitazone significantly increased the risk of myocardial infarction<sup>11</sup>. Although later studies revealed that rosiglitazone did not increase the risk of heart attack and the US Food and Drug Administration (FDA) removed the warning labels from rosiglitazone-containing drugs regarding the issue of increasing heart attack in 2013, rosiglitazone's cardiovascular safety issue alongside the above-mentioned adverse effects still lead to many physicians hesitating to prescribe TZDs in their clinical practice. Nevertheless, PPAR $\gamma$  is still one of the most important targets for the treatment of insulin resistance and type 2 diabetes, and novel strategies to modulate PPAR $\gamma$  activity to enhance its beneficial effects and reduce unwanted adverse effects are strongly anticipated. Recent studies showed that post-translational modification (PTM) of PPAR $\gamma$  regulates PPAR $\gamma$  activity or stability and may be a novel way to optimize PPAR $\gamma$  activity with reduced adverse effects. In addition, selective PPAR $\gamma$  modulators (sPPAR $\gamma$ Ms), dual or pan PPAR agonists, have been developed and tested for their metabolic effects in animal studies and in some clinical trials.

## PPAR $\gamma$ , a therapeutic target for insulin resistance (Figure 1)

PPAR $\gamma$  is a master regulator of adipocyte differentiation. It is also involved in glucose homeostasis and insulin sensitivity. The expression of PPAR $\gamma$  is most abundant in adipose tissue<sup>12</sup>. Evidence has shown that the primary target of TZDs is adipose tissue, where it increases the expression of Glut4 and CAP<sup>13</sup>, and an animal model lacking PPAR $\gamma$  in adipose tissue had a significantly lower response to TZDs<sup>14,15</sup>. TZDs inhibit the expression of TNF- $\alpha$ , IL-6, and resistin in adipose tissue, which promote insulin resistance and chronic inflammation<sup>16,17</sup>, while TZDs increased the production of adiponectin and fibroblast growth factor 21 (FGF21), which enhance fatty acid oxidation and insulin sensitivity<sup>18,19</sup>. TZDs increase lipogenesis by aP2, LPL, CD36, fatty acid transport protein, PEPCK, and the glycerol transporter aquaporin 7<sup>2</sup> and make adipose tissue store more lipid, while TZDs remove lipid accumulation in other tissues such as muscle and liver<sup>20</sup>.

From these studies, it seems that improvement of insulin sensitivity in liver and muscle might be secondary to the effects of TZDs in adipose tissue. However, there is also evidence

showing that TZDs have an insulin-sensitizing effect on other peripheral organs. It has been demonstrated that ablation of liver PPAR $\gamma$  in mice reduced hepatic steatosis but worsened hyperlipidemia, triglyceride clearance, and muscle insulin resistance<sup>21</sup>. The expression of PPAR $\gamma$  in skeletal muscle is relatively low compared to adipose tissue, and the physiological significance of PPAR $\gamma$  in skeletal muscle has been shown to work indirectly in previous studies<sup>22</sup>. However, selective activation of PPAR $\gamma$  in skeletal muscle showed significant protection from high-fat diet-induced insulin resistance and associated changes in muscle phenotype, such as decreasing the quantity of lipid in myocytes and increasing the number of oxidative muscle fiber types<sup>23</sup>. It suggests that the activation of PPAR $\gamma$  can act directly on muscle tissue to improve insulin sensitivity. Macrophage PPAR $\gamma$  is also implicated in anti-inflammation and lipid metabolism<sup>24</sup>, and mice lacking macrophage PPAR $\gamma$  are more prone to whole-body insulin resistance<sup>25,26</sup>.

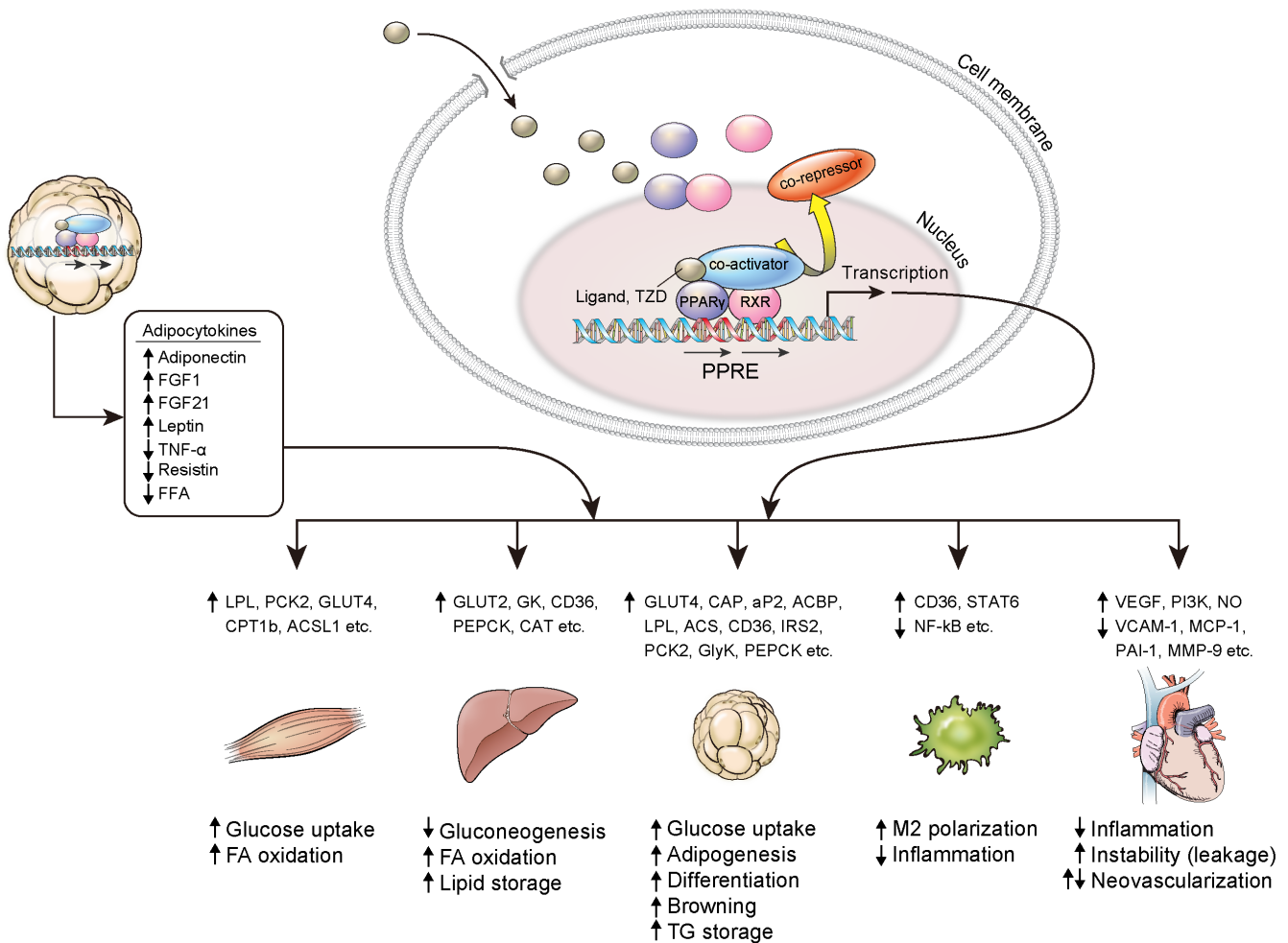
## PPAR $\gamma$ agonists and their effects on the vascular system: friend or foe?

PPAR $\gamma$  is expressed in the endothelium and vascular smooth muscle in the blood vessel wall<sup>27,28</sup>. Despite controversial cardiovascular effects of TZDs in humans, most experimental studies showed beneficial effects on vascular systems. TZDs inhibit the proliferation and migration of vascular smooth muscle cells (VSMCs), with potential favorable effects on atherosclerosis<sup>29,30</sup>. Smooth muscle-specific dominant-negative PPAR $\gamma$  transgenic mice showed a loss of nitric oxide responsiveness and high contractility<sup>31</sup>, which resulted in systolic hypertension. In humans, dominant-negative mutations of PPAR $\gamma$  are associated with early hypertension and insulin resistance<sup>32</sup>. Activation of PPAR $\gamma$  inhibits CCAAT/enhancer-binding protein- $\delta$  (C/EBP $\delta$ ), which is a well-known mediator of the proinflammatory response in vascular cells<sup>33</sup>.

TZDs also reduce activation and inflammation in endothelial cells by suppressing the expression of inflammation-associated genes<sup>34-37</sup>. On the other hand, TZDs induce vascular endothelial growth factor (VEGF) in endothelial cells and increase endothelial cell proliferation and migration by the Akt-dependent pathway<sup>38-40</sup>. In recent data, rosiglitazone significantly increased endothelial cell migration and vascular leakage in an animal study with increased VEGF expression and suppressed tight junction proteins, which caused instability of the endothelial membrane<sup>41</sup>. This result could be related to vascular permeability, peripheral edema, and congestive heart failure associated with the use of TZDs, contrary to their beneficial effect on vascular cells. We still need more concrete evidence to understand the role of TZDs in the whole vascular system under various conditions.

## Regulation of PPAR $\gamma$ by PTMs to reduce the side effects of TZDs

The PTM of PPAR $\gamma$  involves several pathways, including phosphorylation, SUMOylation, ubiquitination,  $\beta$ -O-linked N-acetylglucosamine modification (O-GlcNAcylation), and acetylation. These PTMs are known to regulate both PPAR $\gamma$  expression and its transcriptional activity<sup>42</sup> and have been recently suggested as a good modality for reducing the side effects of PPAR $\gamma$  activation by TZDs<sup>43</sup> (Figure 2).



**Figure 1. Effect of PPAR $\gamma$  activation on various tissues.** ACSL1, acyl-CoA synthetase long chain family member 1; CD36, cluster of differentiation 36; CPT1b, carnitine palmitoyltransferase 1B; FA, fatty acid; FFA, free fatty acid; FGF, fibroblast growth factor; GK, glucokinase; GLUT, glucose transporter; GlyK, glycerol kinase; IRS2, insulin receptor substrate 1; LPL, lipoprotein lipase; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; MCP-1, monocyte chemoattractant protein 1; MMP-9, matrix metalloproteinase 9; NO, nitric oxide; PAI-1, plasminogen activator inhibitor type 1; PCK2, peroxisome proliferator-activated receptor gamma 2 binding site; PEPCK, phosphoenolpyruvate carboxykinase; PI3K, phosphoinositide 3-kinase; PPAR $\gamma$ , peroxisome proliferator-activated receptor  $\gamma$ ; PPRE, peroxisome proliferator-activated receptor response element; RXR, retinoid X receptor; STAT6, signal transducer and activator of transcription 6; TG, triglyceride; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; TZD, thiazolidinedione; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

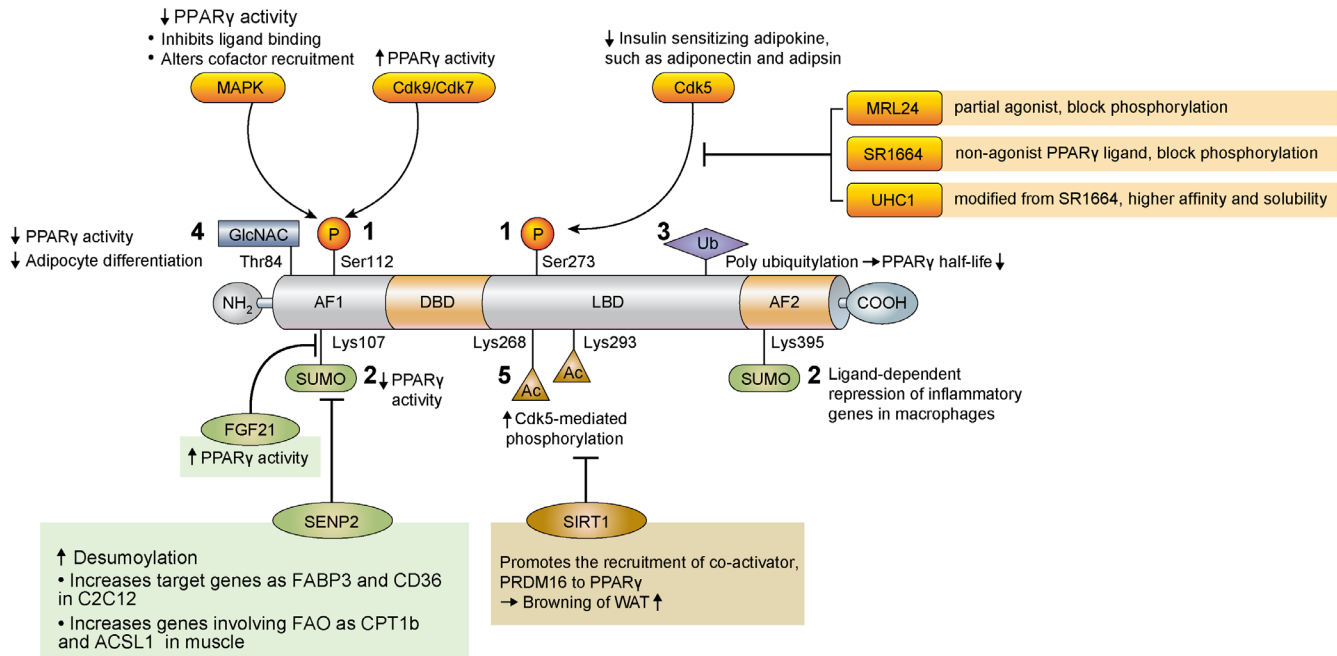
### Phosphorylation

Phosphorylation at serine 112 (S112) in the N-terminal AF-1 domain was first identified, and various studies revealed that net results of PPAR $\gamma$  phosphorylation may inhibit or stimulate its transcriptional activity depending on the cellular contexts and kinases involved<sup>44–48</sup>. Phosphorylation at S273 in the ligand-binding domain is mediated by cyclin-dependent kinase 5 (Cdk5), which is activated by pro-inflammatory stimuli and free fatty acids<sup>49</sup>. S273 phosphorylation affects the expression of insulin-sensitizing adipokines such as adiponectin and adipsin but not those affecting adipogenesis. PPAR $\gamma$  partial agonist MRL24 specifically blocks the phosphorylation of PPAR $\gamma$  at S273 and has higher anti-diabetic activity and fewer side effects than does rosiglitazone<sup>49</sup>. SR1664 and similar non-agonist PPAR $\gamma$

ligands were also developed for blocking cdk5-mediated phosphorylation and showed improved insulin sensitivity in high-fat diet-fed mice without causing side effects such as fluid retention and weight gain<sup>43,50</sup>. More recently, it has been reported that phosphorylation at S273 is also facilitated by MEK/ERK, and inhibition of MEK and ERK improves insulin resistance, suggesting that MEK and ERK inhibitors can be therapeutic targets for diabetes through the modulation of PPAR $\gamma$  function<sup>51</sup>.

### SUMOylation

Small ubiquitin-like modifier (SUMO) modification is a reversible process and may affect protein stability, transcriptional activity, and protein-protein interaction. PPAR $\gamma$  is known



**Figure 2. Regulation of PPAR $\gamma$  by post-translational modification.** Ac, acetyl; ACSL1, acyl-CoA synthetase long chain family member 1; AF1, activation function 1; AF2, activation function 2; CD36, cluster of differentiation 36; Cdk, cyclin-dependent kinase; CPT1b, carnitine palmitoyltransferase 1B; DBD, DNA-binding domain; FABP3, fatty-acid-binding protein 3, muscle and heart; FAO, fatty acid oxidation; FGF, fibroblast growth factor; GlcNAc, N-acetylglucosamine; LBD, ligand-binding domain; Lys, lysine; MAPK, mitogen-activated protein kinase; P, phosphate; PPAR $\gamma$ , peroxisome proliferator-activated receptor  $\gamma$ ; PRDM16, PR domain containing 16; SENP2, small ubiquitin-like modifier-specific protease 2; Ser, serine; SIRT1, sirtuin 1; SUMO, small ubiquitin-like modifier; Thr, threonine; Ub, ubiquitin; WAT, white adipose tissue.

as a target of SUMOylation. Lysine 107 (K107) of PPAR $\gamma$ 2 is the major SUMOylation site, and deSUMOylation of this site increases the transcriptional activity of PPAR $\gamma$ <sup>52</sup>. The K107R mutant form of PPAR $\gamma$  stimulates adipogenesis and suppresses neointimal formation after balloon injury more effectively than does the PPAR $\gamma$  wild-type form<sup>53,54</sup>. SUMOylation at K107 of PPAR $\gamma$  may be linked to S112 phosphorylation<sup>53</sup>. PPAR $\gamma$  SUMOylation at K107 is markedly increased in FGF21-knockout mice, suggesting that FGF21 regulates PPAR $\gamma$  SUMOylation by an unknown mechanism<sup>19</sup>. SUMOylation of PPAR $\gamma$  at K395 (K365 of PPAR $\gamma$ 1) is stimulated by PPAR $\gamma$  agonists, and this modification inhibits the transcription of inflammatory response genes, such as *iNOS*, through recruiting transcriptional repressors to the NF $\kappa$ B complex in macrophages<sup>55</sup>.

SUMO-specific protease 2 (SENP2) is the major deSUMOylation enzyme of PPAR $\gamma$ <sup>56</sup>. Overexpression of SENP2 in C2C12 cells effectively induces PPAR $\gamma$  target genes such as *Fabp3* and *Cd36* but not *Adrp*; thus, SENP2 can induce the expression of PPAR $\gamma$  target genes in a selective manner<sup>56</sup>. SENP2 deSUMOylates PPAR $\gamma$  and PPAR $\delta$  and activates genes involved in fatty acid oxidation such as *Cpt1b* and *Acs11*, which results in an increase of fatty acid oxidation in muscle. Interestingly, palmitate increases SENP2 expression via the TLR4-MyD88-NF $\kappa$ B

pathway. These results suggest that SENP2 is an important regulator of fatty acid metabolism in skeletal muscle<sup>57</sup>.

### Ubiquitination

Ubiquitination is the covalent attachment of ubiquitin, a 76-amino-acid peptide, to lysine residues in the substrate protein. PPAR $\gamma$  has a short half-life and is degraded by the polyubiquitin-proteasome pathway<sup>58</sup>. Inhibition of proteasome activity by proteasome inhibitors increases PPAR $\gamma$  stability, suggesting ubiquitin modification of PPAR $\gamma$  is an important determinant of PPAR $\gamma$  activity<sup>58</sup>. Several ubiquitin ligases, such as FBOX9 and Cul4B, and an ubiquitin-specific protease (HAUSP) targeting PPAR $\gamma$  have been identified, and an increase in PPAR $\gamma$  stability generally promotes PPAR $\gamma$  activity and adipogenesis<sup>59–61</sup>. Interestingly, PPAR $\gamma$  agonists, TZDs, stimulate the ubiquitination of PPAR $\gamma$ , which can be mediated by an ubiquitin ligase, Siah1<sup>58,62</sup>. Therefore, PPAR $\gamma$  ubiquitination may be differently regulated by several ubiquitin E3 ligases or proteases upon various conditions.

### O-GlcNAcylation

O-GlcNAcylation is the post-translational cycling of a single  $\beta$ -O-linked N-acetylglucosamine (O-GlcNAc) on the hydroxyl groups of serine or threonine residues of target proteins. A major



O-GlcNAc site in PPAR $\gamma$  is T84 in the AF-1 domain in PPAR $\gamma$ 2, and increased O-GlcNAcylation reduces its transcriptional activity and adipocyte differentiation<sup>63</sup>.

### Acetylation

Deacetylation at K268 and K293 by the NAD-dependent deacetylase sirtuin 1 (SIRT1) is necessary for the interaction of PPAR $\gamma$  with PRDM16, a transcriptional co-activator for the browning of WAT<sup>64</sup>. Therefore, SIRT1-dependent PPAR $\gamma$  deacetylation selectively regulates PPAR $\gamma$  activity.

### Other PPAR $\gamma$ modulators and agonists

Considering that patients with insulin resistance show many conjugated metabolic problems such as atherosclerosis, obesity, fatty liver, etc., there have been many efforts to develop sPPAR $\gamma$ Ms, dual or pan PPAR agonists, with potent efficacy but less-deleterious side effects.

sPPAR $\gamma$ Ms bind to the ligand-binding domain of PPAR $\gamma$  in many ways, which leads to different receptor conformations and cofactor functions<sup>65</sup>. INT131, a potent non-TZD sPPAR $\gamma$ M now in clinical trials, showed excellent glucose lowering with significantly less weight gain, edema with fluid retention, and cardiomegaly than do current TZDs<sup>66</sup>. Balaglitazone also showed positive effects in the treatment of patients with type 2 diabetes compared to placebo and pioglitazone (phase III clinical study, n = 409), better glycemic control, and less edema compared to pioglitazone 45 mg<sup>67</sup>. CMHX008 was also tested for its effects in *in vitro* and *in vivo* models, showing excellent results by far<sup>68</sup>.

PPAR $\alpha/\gamma$  dual activation has been the focus of new targets from many pharmaceutical companies, and several clinical trials have been performed in potential treatments such as muraglitazar, tesaglitazar, and aleglitazar. However, owing to unpredictable side effects, the studies were all stopped for further development. Unfortunately, muraglitazar increased cardiovascular events, tesaglitazar increased renal toxicity, and aleglitazar showed bone fractures, heart failure, and gastrointestinal side effects<sup>69–71</sup>. Recently, (E)-N-(4-(3-(5-bromo-4-hydroxy-2-methoxyphenyl)acryloyl)phenyl)-4-*tert*-butylbenzamide (SN158) showed anti-diabetic effects through PPAR $\alpha/\gamma$  dual activation. SN158 increased adipogenic differentiation of 3T3-L1 preadipocytes, enhanced fatty acid oxidation in hepatocytes, and increased glucose uptake in myotubes. It lowered plasma glucose and lipid levels in ob/ob mice without severe weight gain. Thus, it represents another candidate PPAR $\alpha/\gamma$  agonist to enhance many metabolic profiles in obesity-related diseases<sup>72</sup>.

There are some natural products which activate PPAR $\gamma$  and PPAR $\alpha$  simultaneously or activate the PPAR $\gamma$  dimer partner retinoid X receptor. Compared to full TZDs, these natural products usually show fewer side effects and comparable anti-diabetic effects<sup>73</sup>. Honokiol, amorfrutin 1, amorfrutin B, amorphastilbol, genistein, biochanin A, sargaquinoic acid, sargahydroquinoic acid, resveratrol, etc. were tested for their efficacy in *in vitro* and *in vivo* studies<sup>73</sup>.

The development of PPAR $\alpha/\gamma/\delta$  pan agonists as anti-diabetic, anti-obesity, or hypolipidemic drugs is still actively ongoing<sup>74,75</sup>. For example, IVA 337 is a potent and well-balanced pan PPAR agonist which showed promising results *in vitro* and *in vivo* and is expected to be used to treat patients with metabolic syndrome and non-alcoholic steatohepatitis<sup>76</sup>.

### Conclusion

PPAR $\gamma$  is still one of the most important targets for the treatment of insulin resistance and diabetes mellitus, even though current use of TZDs in clinical practice is limited because of undesirable adverse effects. Thus, novel strategies to modulate PPAR $\gamma$  activity to enhance its beneficial effects and reduce unwanted side effects have been strongly anticipated. Recent advances in understanding how PTM of PPAR $\gamma$  modulates PPAR $\gamma$  activity provide novel ways to optimize PPAR $\gamma$  activity with reduced adverse effects. In addition, selective PPAR $\gamma$  modulators, dual or pan PPAR agonists, have been developed and tested for their metabolic effects in animal studies and in some clinical trials.

We hope safer PPAR $\gamma$  agonists or modulators with excellent efficacy and fewer adverse effects will be available for treating metabolic diseases and insulin resistance in the near future.

### Competing interests

The authors declare that they have no competing interests.

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### References

- Laakso M, Kuusisto J: **Insulin resistance and hyperglycaemia in cardiovascular disease development.** *Nat Rev Endocrinol.* 2014; **10**(5): 293–302. [PubMed Abstract](#) | [Publisher Full Text](#)
- Tontonoz P, Spiegelman BM: **Fat and beyond: the diverse biology of PPAR $\gamma$ .** *Annu Rev Biochem.* 2008; **77**: 289–312. [PubMed Abstract](#) | [Publisher Full Text](#)
- Ceriello A: **Thiazolidinediones as anti-inflammatory and anti-atherogenic agents.** *Diabetes Metab Res Rev.* 2008; **24**(1): 14–26. [PubMed Abstract](#) | [Publisher Full Text](#)
- Lee M, Saver JL, Liao HW, et al.: **Pioglitazone for Secondary Stroke Prevention: A Systematic Review and Meta-Analysis.** *Stroke.* 2017; **48**(2): 388–93. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Patel D, Walitt B, Lindsay J, et al.: **Role of pioglitazone in the prevention of**



- restenosis and need for revascularization after bare-metal stent implantation: a meta-analysis. *JACC Cardiovasc Interv.* 2011; 4(3): 353–60.  
[PubMed Abstract](#) | [Publisher Full Text](#)
6. **F** Wang Z, Zhang T, Sun L, *et al.*: **Pioglitazone Attenuates Drug-Eluting Stent-Induced Proinflammatory State in Patients by Blocking Ubiquitination of PPAR.** *PPAR Res.* 2016; 2016: 7407153.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  7. Choi D, Kim SK, Choi SH, *et al.*: **Preventative effects of rosiglitazone on restenosis after coronary stent implantation in patients with type 2 diabetes.** *Diabetes Care.* 2004; 27(11): 2654–60.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  8. Bertie HD, Kalus JS, Jaber LA: **Thiazolidinediones and the risk of edema: a meta-analysis.** *Diabetes Res Clin Pract.* 2007; 76(2): 279–89.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  9. **F** Lago RM, Singh PP, Nesto RW: **Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials.** *Lancet.* 2007; 370(9593): 1129–36.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  10. **F** Billington EO, Grey A, Bolland MJ: **The effect of thiazolidinediones on bone mineral density and bone turnover: systematic review and meta-analysis.** *Diabetologia.* 2015; 58(10): 2238–46.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  11. **F** Nissen SE, Wolski K: **Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes.** *N Engl J Med.* 2007; 356(24): 2457–71.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
  12. Fajas L, Auboeuf D, Raspé E, *et al.*: **The organization, promoter analysis, and expression of the human PPARgamma gene.** *J Biol Chem.* 1997; 272(30): 18779–89.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  13. Ribon V, Johnson JH, Camp HS, *et al.*: **Thiazolidinediones and insulin resistance: peroxisome proliferator-activated receptor gamma activation stimulates expression of the CAP gene.** *Proc Natl Acad Sci U S A.* 1998; 95(25): 14751–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  14. He W, Barak Y, Hevener A, *et al.*: **Adipose-specific peroxisome proliferator-activated receptor gamma knock-out causes insulin resistance in fat and liver but not in muscle.** *Proc Natl Acad Sci U S A.* 2003; 100(26): 15712–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  15. Chao L, Marcus-Samuels B, Mason MM, *et al.*: **Adipose tissue is required for the antidiabetic, but not for the hypolipidemic, effect of thiazolidinediones.** *J Clin Invest.* 2000; 106(10): 1221–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  16. Peraldi P, Xu M, Spiegelman BM: **Thiazolidinediones block tumor necrosis factor-alpha-induced inhibition of insulin signaling.** *J Clin Invest.* 1997; 100(7): 1863–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  17. Stepan CM, Bailey ST, Bhat S, *et al.*: **The hormone resistin links obesity to diabetes.** *Nature.* 2001; 409(6818): 307–12.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  18. Berg AH, Combs TP, Du X, *et al.*: **The adipocyte-secreted protein Acrp30 enhances hepatic insulin action.** *Nat Med.* 2001; 7(8): 947–53.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  19. **F** Dutchak PA, Katafuchi T, Bookout AL, *et al.*: **Fibroblast growth factor-21 regulates PPARγ activity and the antidiabetic actions of thiazolidinediones.** *Cell.* 2012; 148(3): 556–67.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  20. Ye JM, Dzamko N, Cleasby ME, *et al.*: **Direct demonstration of lipid sequestration as a mechanism by which rosiglitazone prevents fatty-acid-induced insulin resistance in the rat: comparison with metformin.** *Diabetologia.* 2004; 47(7): 1306–13.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  21. Gavrilova O, Haluzik M, Matsusue K, *et al.*: **Liver peroxisome proliferator-activated receptor gamma contributes to hepatic steatosis, triglyceride clearance, and regulation of body fat mass.** *J Biol Chem.* 2003; 278(36): 34268–76.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  22. Norris AW, Chen L, Fisher SJ, *et al.*: **Muscle-specific PPARgamma-deficient mice develop increased adiposity and insulin resistance but respond to thiazolidinediones.** *J Clin Invest.* 2003; 112(4): 608–18.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  23. Amin RH, Mathews ST, Camp HS, *et al.*: **Selective activation of PPARgamma in skeletal muscle induces endogenous production of adiponectin and protects mice from diet-induced insulin resistance.** *Am J Physiol Endocrinol Metab.* 2010; 298(1): E28–37.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  24. Wahli W, Michalik L: **PPARs at the crossroads of lipid signaling and inflammation.** *Trends Endocrinol Metab.* 2012; 23(7): 351–63.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  25. **F** Hevener AL, Olefsky JM, Reichart D, *et al.*: **Macrophage PPAR gamma is required for normal skeletal muscle and hepatic insulin sensitivity and full antidiabetic effects of thiazolidinediones.** *J Clin Invest.* 2007; 117(6): 1658–69.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  26. **F** Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, *et al.*: **Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance.** *Nature.* 2007; 447(7148): 1116–20.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
  27. Marx N, Schönbeck U, Lazar MA, *et al.*: **Peroxisome proliferator-activated receptor gamma activators inhibit gene expression and migration in human vascular smooth muscle cells.** *Circ Res.* 1998; 83(11): 1097–103.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  28. Xin X, Yang S, Kowalski J, *et al.*: **Peroxisome proliferator-activated receptor gamma ligands are potent inhibitors of angiogenesis in vitro and in vivo.** *J Biol Chem.* 1999; 274(13): 9116–21.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  29. Li AC, Brown KK, Silvestre MJ, *et al.*: **Peroxisome proliferator-activated receptor gamma ligands inhibit development of atherosclerosis in LDL receptor-deficient mice.** *J Clin Invest.* 2000; 106(4): 523–31.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  30. Lim S, Lee KS, Lee JE, *et al.*: **Effect of a new PPAR-gamma agonist, lobeglitazone, on neointimal formation after balloon injury in rats and the development of atherosclerosis.** *Atherosclerosis.* 2015; 243(1): 107–19.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  31. Halabi CM, Beyer AM, de Lange WJ, *et al.*: **Interference with PPAR gamma function in smooth muscle causes vascular dysfunction and hypertension.** *Cell Metab.* 2008; 7(3): 215–26.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  32. Barroso I, Gurnell M, Crowley VE, *et al.*: **Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension.** *Nature.* 1999; 402(6764): 880–3.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  33. Takata Y, Kitami Y, Yang ZH, *et al.*: **Vascular inflammation is negatively autoregulated by interaction between CCAAT/enhancer-binding protein-delta and peroxisome proliferator-activated receptor-gamma.** *Circ Res.* 2002; 91(5): 427–33.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  34. Marx N, Mach F, Sauty A, *et al.*: **Peroxisome proliferator-activated receptor-gamma activators inhibit IFN-gamma-induced expression of the T cell-active CXC chemokines IP-10, Mig, and I-TAC in human endothelial cells.** *J Immunol.* 2000; 164(12): 6503–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  35. Jackson SM, Parhami F, Xi XP, *et al.*: **Peroxisome proliferator-activated receptor gamma activators target human endothelial cells to inhibit leukocyte-endothelial cell interaction.** *Arterioscler Thromb Vasc Biol.* 1999; 19(9): 2094–104.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  36. Pasceri V, Wu HD, Willerson JT, *et al.*: **Modulation of vascular inflammation in vitro and in vivo by peroxisome proliferator-activated receptor-gamma activators.** *Circulation.* 2000; 101(3): 235–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  37. Hong HK, Cho YM, Park KH, *et al.*: **Peroxisome proliferator-activated receptor gamma mediated inhibition of plasminogen activator inhibitor type 1 production and proliferation of human umbilical vein endothelial cells.** *Diabetes Res Clin Pract.* 2003; 62(1): 1–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  38. Dimmeler S, Dernbach E, Zeiher AM: **Phosphorylation of the endothelial nitric oxide synthase at ser-1177 is required for VEGF-induced endothelial cell migration.** *FEBS Lett.* 2000; 477(3): 258–62.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  39. Rikitake Y, Kawashima S, Yamashita T, *et al.*: **Lysophosphatidylcholine inhibits endothelial cell migration and proliferation via inhibition of the extracellular signal-regulated kinase pathway.** *Arterioscler Thromb Vasc Biol.* 2000; 20(4): 1006–12.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  40. Dimmeler S, Zeiher AM: **Akt takes center stage in angiogenesis signaling.** *Circ Res.* 2000; 86(1): 4–5.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  41. Ku YH, Cho BJ, Kim MJ, *et al.*: **Rosiglitazone increases endothelial cell migration and vascular permeability through Akt phosphorylation.** *BMC Pharmacol Toxicol.* 2017; 18(1): 62.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  42. van Beekum O, Fleskens V, Kalkhoven E: **Posttranslational modifications of PPAR-gamma: fine-tuning the metabolic master regulator.** *Obesity (Silver Spring).* 2009; 17(2): 213–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  43. Choi SS, Kim ES, Koh M, *et al.*: **A novel non-agonist peroxisome proliferator-activated receptor γ (PPARγ) ligand UHC1 blocks PPARγ phosphorylation by cyclin-dependent kinase 5 (CDK5) and improves insulin sensitivity.** *J Biol Chem.* 2014; 289(38): 26618–29.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  44. Hu E, Kim JB, Sarraf P, *et al.*: **Inhibition of adipogenesis through MAP kinase-mediated phosphorylation of PPARgamma.** *Science.* 1996; 274(5295): 2100–3.  
[PubMed Abstract](#)
  45. Adams M, Reginato MJ, Shao D, *et al.*: **Transcriptional activation by peroxisome proliferator-activated receptor gamma is inhibited by phosphorylation at a**

- consensus mitogen-activated protein kinase site. *J Biol Chem.* 1997; **272**(8): 5128–32.  
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Shao D, Rangwala SM, Bailey ST, *et al.*: Interdomain communication regulating ligand binding by PPAR-gamma. *Nature.* 1998; **396**(6709): 377–80.  
[PubMed Abstract](#) | [Publisher Full Text](#)
47. Rangwala SM, Rhoades B, Shapiro JS, *et al.*: Genetic modulation of PPARgamma phosphorylation regulates insulin sensitivity. *Dev Cell.* 2003; **5**(4): 657–63.  
[PubMed Abstract](#) | [Publisher Full Text](#)
48. Compe E, Drané P, Laurent C, *et al.*: Dysregulation of the peroxisome proliferator-activated receptor target genes by XPD mutations. *Mol Cell Biol.* 2005; **25**(14): 6065–76.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
49. **F** Choi JH, Banks AS, Estall JL, *et al.*: Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARgamma by Cdk5. *Nature.* 2010; **466**(7305): 451–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
50. **F** Choi JH, Banks AS, Kamenecka TM, *et al.*: Antidiabetic actions of a non-agonist PPAR $\gamma$  ligand blocking Cdk5-mediated phosphorylation. *Nature.* 2011; **477**(7365): 477–81.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
51. **F** Banks AS, McAllister FE, Camporez JP, *et al.*: An ERK/Cdk5 axis controls the diabetogenic actions of PPAR $\gamma$ . *Nature.* 2015; **517**(7534): 391–5.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
52. Ohshima T, Koga H, Shimotohno K: Transcriptional activity of peroxisome proliferator-activated receptor gamma is modulated by SUMO-1 modification. *J Biol Chem.* 2004; **279**(28): 29551–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Yamashita D, Yamaguchi T, Shimizu M, *et al.*: The transactivating function of peroxisome proliferator-activated receptor gamma is negatively regulated by SUMO conjugation in the amino-terminal domain. *Genes Cells.* 2004; **9**(11): 1017–29.  
[PubMed Abstract](#) | [Publisher Full Text](#)
54. Lim S, Ahn BY, Chung SS, *et al.*: Effect of a peroxisome proliferator-activated receptor gamma sumoylation mutant on neointimal formation after balloon injury in rats. *Atherosclerosis.* 2009; **206**(2): 411–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
55. **F** Pascual G, Fong AL, Ogawa S, *et al.*: A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. *Nature.* 2005; **437**(7059): 759–63.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. Chung SS, Ahn BY, Kim M, *et al.*: SUMO modification selectively regulates transcriptional activity of peroxisome-proliferator-activated receptor  $\gamma$  in C2C12 myotubes. *Biochem J.* 2011; **433**(1): 155–61.  
[PubMed Abstract](#) | [Publisher Full Text](#)
57. Koo YD, Choi JW, Kim M, *et al.*: SUMO-Specific Protease 2 (SEN2) is an Important Regulator of Fatty Acid Metabolism in Skeletal Muscle. *Diabetes.* 2015; **64**(7): 2420–31.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
58. Hauser S, Adelmant G, Sarraf P, *et al.*: Degradation of the peroxisome proliferator-activated receptor gamma is linked to ligand-dependent activation. *J Biol Chem.* 2000; **275**(24): 18527–33.  
[PubMed Abstract](#) | [Publisher Full Text](#)
59. Lee KW, Kwak SH, Koo YD, *et al.*: F-box only protein 9 is an E3 ubiquitin ligase of PPAR $\gamma$ . *Exp Mol Med.* 2016; **48**: e234.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. **F** Li P, Song Y, Zan W, *et al.*: Lack of CUL4B in Adipocytes Promotes PPAR $\gamma$ -Mediated Adipose Tissue Expansion and Insulin Sensitivity. *Diabetes.* 2017; **66**: 300–13.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
61. Lee KW, Cho JG, Kim CM, *et al.*: Herpesvirus-associated ubiquitin-specific protease (HAUSP) modulates peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) stability through its deubiquitinating activity. *J Biol Chem.* 2013; **288**(46): 32886–96.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
62. Kilroy G, Kirk-Ballard H, Carter LE, *et al.*: The ubiquitin ligase Siah2 regulates PPAR $\gamma$  activity in adipocytes. *Endocrinology.* 2012; **153**(3): 1206–18.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
63. Ji S, Park SY, Roth J, *et al.*: O-GlcNAc modification of PPAR $\gamma$  reduces its transcriptional activity. *Biochem Biophys Res Commun.* 2012; **417**(4): 1158–63.  
[PubMed Abstract](#) | [Publisher Full Text](#)
64. **F** Qiang L, Wang L, Kon N, *et al.*: Brown remodeling of white adipose tissue by SirT1-dependent deacetylation of Ppar $\gamma$ . *Cell.* 2012; **150**(3): 620–32.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
65. Higgins LS, Depaoli AM: Selective peroxisome proliferator-activated receptor gamma (PPARgamma) modulation as a strategy for safer therapeutic PPARgamma activation. *Am J Clin Nutr.* 2010; **91**(1): 267S–72.  
[PubMed Abstract](#) | [Publisher Full Text](#)
66. **F** Depaoli AM, Higgins LS, Henry RR, *et al.*: Can a selective PPAR $\gamma$  modulator improve glycemic control in patients with type 2 diabetes with fewer side effects compared with pioglitazone? *Diabetes Care.* 2014; **37**(7): 1918–23.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
67. Henriksen K, Byrjalsen I, Qvist P, *et al.*: Efficacy and safety of the PPAR $\gamma$  partial agonist balaglitazone compared with pioglitazone and placebo: a phase III, randomized, parallel-group study in patients with type 2 diabetes on stable insulin therapy. *Diabetes Metab Res Rev.* 2011; **27**(4): 392–401.  
[PubMed Abstract](#) | [Publisher Full Text](#)
68. Ming Y, Hu X, Song Y, *et al.*: CMHX008, a novel peroxisome proliferator-activated receptor  $\gamma$  partial agonist, enhances insulin sensitivity *in vitro* and *in vivo*. *PLoS One.* 2014; **9**(7): e102102.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
69. Nissen SE, Wolski K, Topol EJ: Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA.* 2005; **294**(20): 2581–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
70. Goldstein BJ, Rosenstock J, Anzalone D, *et al.*: Effect of tesaglitazar, a dual PPAR alpha/gamma agonist, on glucose and lipid abnormalities in patients with type 2 diabetes: a 12-week dose-ranging trial. *Curr Med Res Opin.* 2006; **22**(12): 2575–90.  
[PubMed Abstract](#) | [Publisher Full Text](#)
71. Lincoff AM, Tardif JC, Schwartz GG, *et al.*: Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial. *JAMA.* 2014; **311**(5): 1515–25.  
[PubMed Abstract](#) | [Publisher Full Text](#)
72. **F** Jung Y, Cao Y, Paudel S, *et al.*: Antidiabetic effect of SN158 through PPAR $\alpha/\gamma$  dual activation in *ob/ob* mice. *Chem Biol Interact.* 2017; **268**: 24–30.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
73. Wang L, Waltenberger B, Pferschy-Wenzig EM, *et al.*: Natural product agonists of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ): a review. *Biochem Pharmacol.* 2014; **92**(1): 73–89.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
74. **F** An HJ, Lee B, Kim SM, *et al.*: A PPAR Pan Agonist, MHY2013 Alleviates Age-Related Hepatic Lipid Accumulation by Promoting Fatty Acid Oxidation and Suppressing Inflammation. *Biol Pharm Bull.* 2018; **41**(1): 29–35.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
75. **F** Huang Y, Powers C, Moore V, *et al.*: The PPAR pan-agonist bezafibrate ameliorates cardiomyopathy in a mouse model of Barth syndrome. *Orphanet J Rare Dis.* 2017; **12**(1): 49.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
76. **F** Boubia B, Poupardin O, Barth M, *et al.*: Design, Synthesis, and Evaluation of a Novel Series of Indole Sulfonamide Peroxisome Proliferator Activated Receptor (PPAR)  $\alpha/\gamma/\delta$  Triple Activators: Discovery of Lanifibranor, a New Antifibrotic Clinical Candidate. *J Med Chem.* 2018; **61**(6): 2246–65.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)



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- Alexander Orekhov** Institute for Atherosclerosis Research, Skolkovo Innovative Center, Moscow, Russian Federation  
**Competing Interests:** No competing interests were disclosed.
- Laszlo Nagy**<sup>1,2</sup>, **Attila Pap**<sup>2</sup>  
<sup>1</sup> SBP Medical Discovery Institute, Florida, USA  
<sup>2</sup> Department of Biochemistry and Molecular Biology, University of Debrecen, Debrecen, Hungary  
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