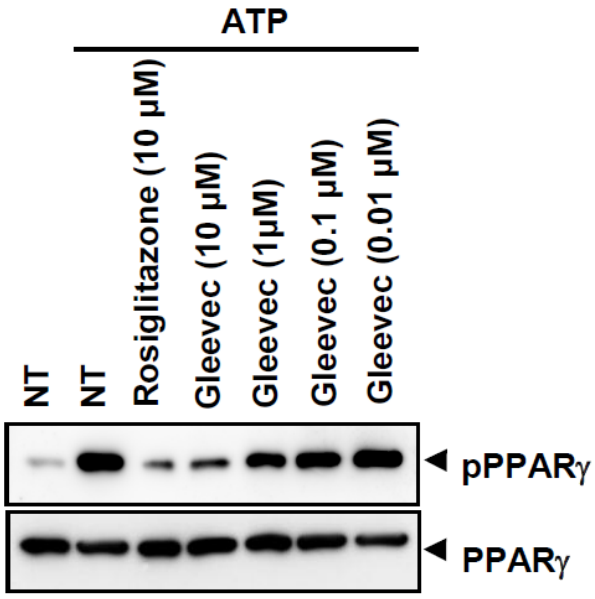
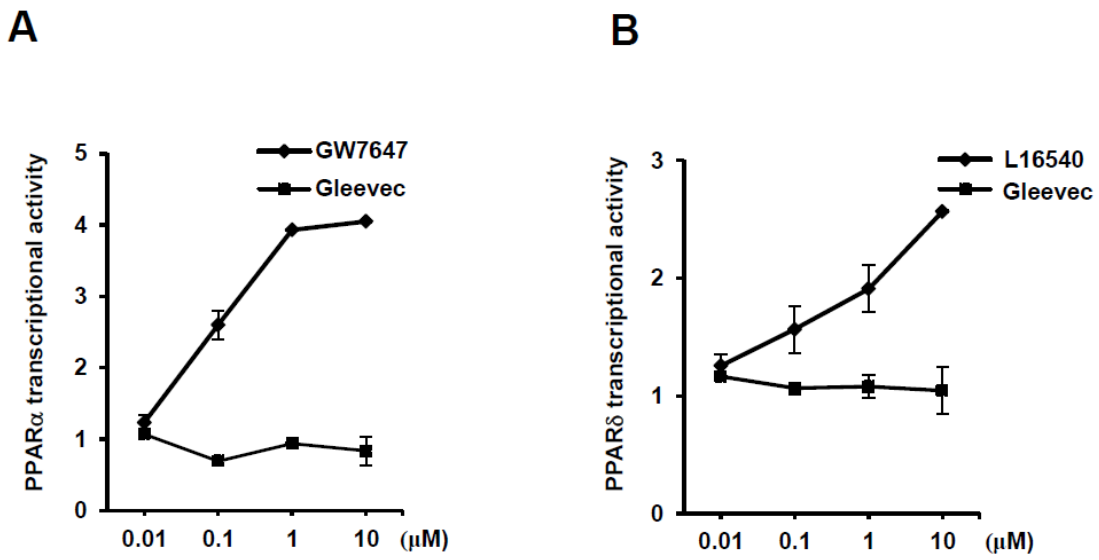
SUPPLEMENTARY DATA

Supplementary Figure 1. Gleevec blocks ERK-mediated PPARγ phosphorylation.*In vitro* ERK kinase assay on full-length PPARγ incubated with rosiglitazone or Gleevec.



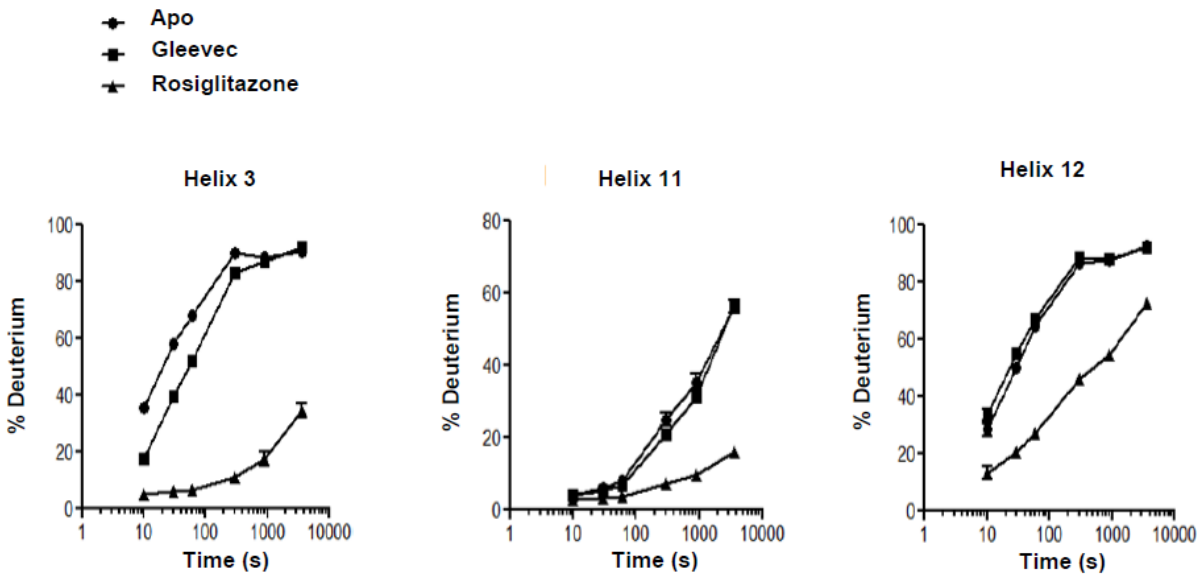
SUPPLEMENTARY DATA

Supplymentary Figure 2. Gleevec does not activate PPARα and PPARδ. Transcriptional activity of a PPAR-derived reporter gene in HEK-293 cells following treatment with GW7647, L165041 or Gleevec.



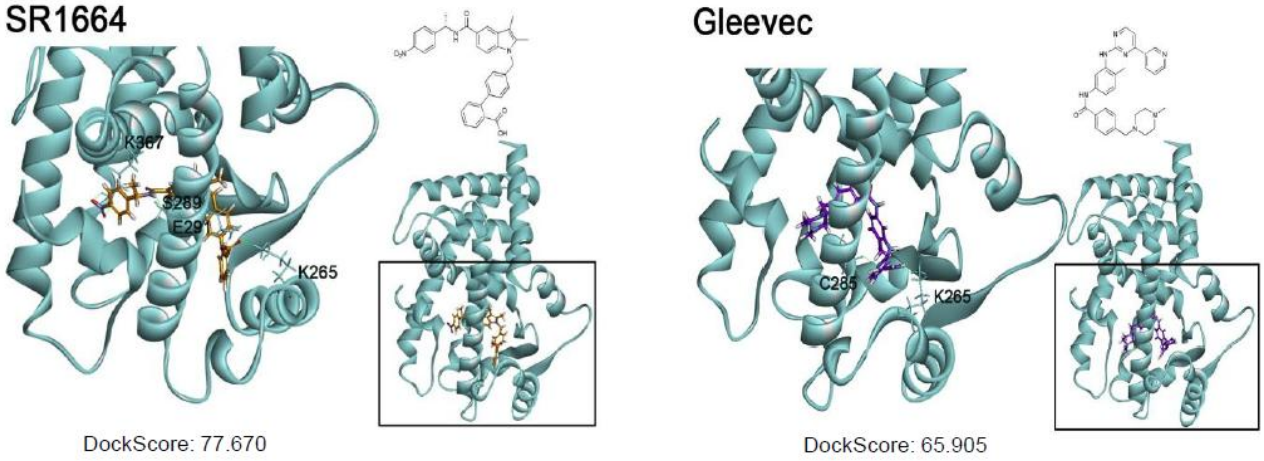
SUPPLEMENTARY DATA

Supplementary Figure 3. Gleevec Induced Perturbation in conformational dynamics of PPARg detected by HDX-MS. Differential HDX results are mapped onto the PPARg crystal structure (3PRG) comparing the apo ligand binding domain of PPARγ in the presence of either Gleevec or rosiglitazone. 10 μM of HIS-PPARγ LBD protein was preincubated with 1:2 molar excess of compounds. 5 μl of protein solution was mixed with 20 μl of D2O-containing HDX buffer (20 mM KPO4 pH 7.4, 50 mM KCl) and incubated at 4°C for 10s, 30s, 60s, 900s and 3,600s. On-exchange was quenched and the protein denatured with 25 μl of quench solution (0.1 % v/v TFA in 3 M urea). Samples were then passed through an immobilized pepsin column and the resulting peptides were trapped on a C8 trap column. The bound peptides were gradient-eluted (5-50 % CH3CN w/v and 0.3 % w/v formic acid) across a C18 HPLC column for 5 min at 4°C. The eluted peptides were subjected to electrospray ionization directly coupled to a high resolution Orbitrap mass spectrometer (Thermo Fisher, MA, USA). Each HDX experiment was carried out in triplicate and the intensity weighted average m/z value (centroid) of each peptide isotopic envelope was calculated with in-house HDX Workbench software.



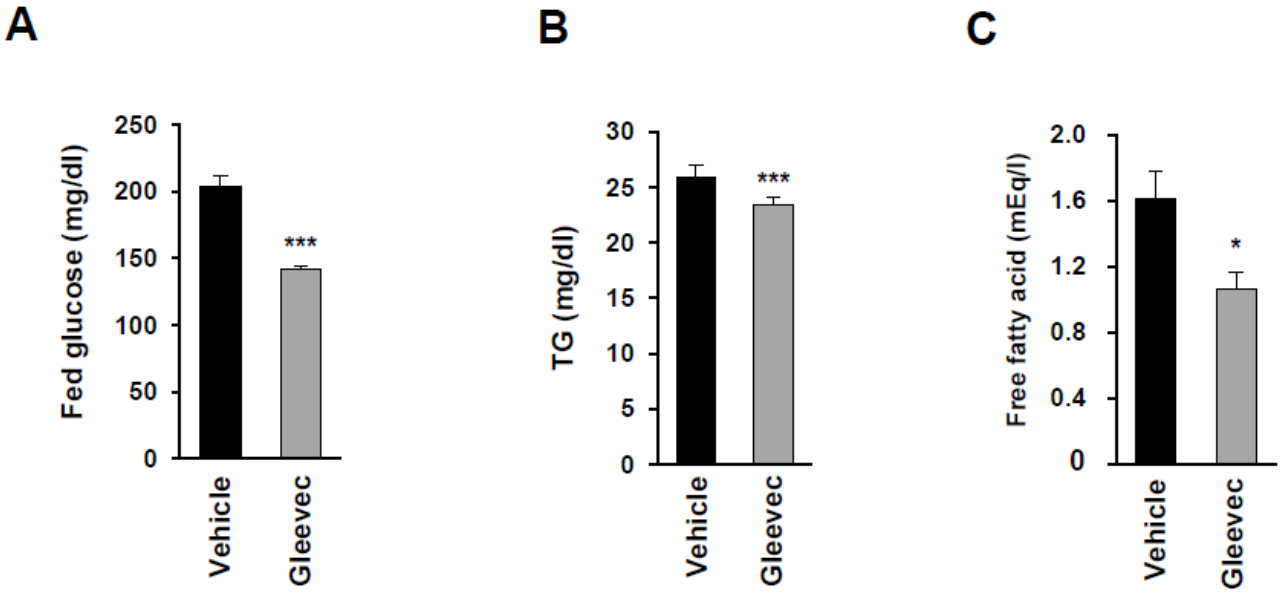
SUPPLEMENTARY DATA

Supplementary Figure 4. Binding mode of SR1664 or Gleevec to PPARγ LBD. Docking simulation was performed with crystal structure of PPARγ LBD (PDB ID: 2hfp) and Discovery Studio® 1.7 (Accelrys). The binding pose was predicted by docking simulation using the Discovery Studio 1.7® program. PPARγ ligand-binding pockets were defined from receptor cavities, and the LigandFit module implemented in the Receptor-Ligand Interaction protocol was used for detailed calculations. X-ray crystal structure of PPARγ ligand binding domain (2hfp) was used in the docking simulation and the subsequent structural analysis with the Discovery Studio Visualizer 3.0® program (Accelrys Software Inc., CA, USA).



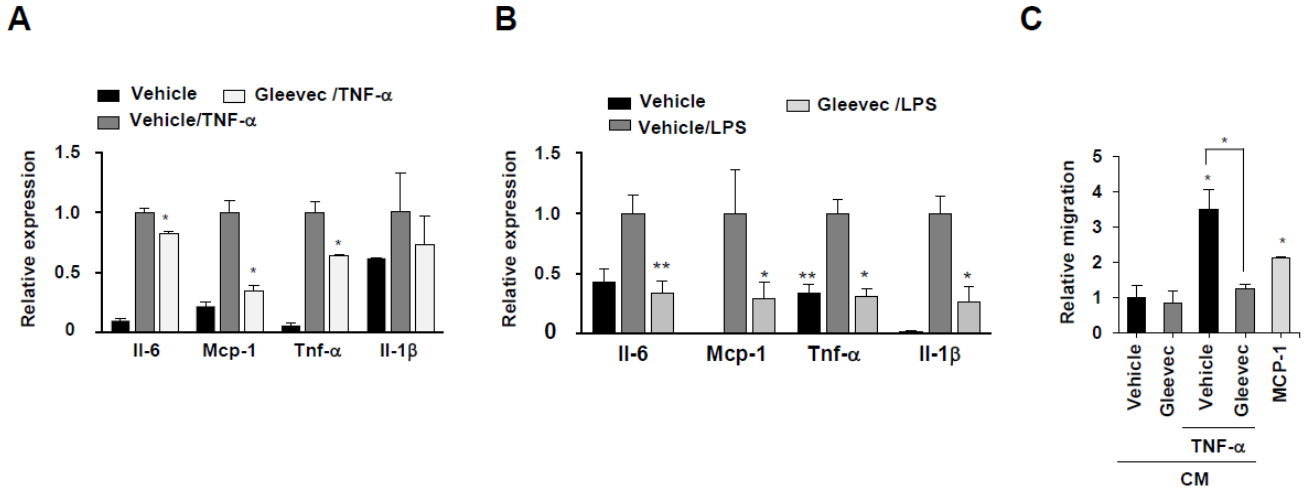
SUPPLEMENTARY DATA

Supplementary Figure 5. The effect of Gleevec on blood glucose level and plasma level of triglyceride and free fatty acid in HFD-fed mice. Fed blood glucose level (*A*) and serum level of triglyceride (*B*) and FFAs (*C*) in HFD mice treated with Gleevec for 7 days or 21 days (same as in Fig. 3*C*). Error bars are S.E.M. ***p<0.001 compared with vehicle



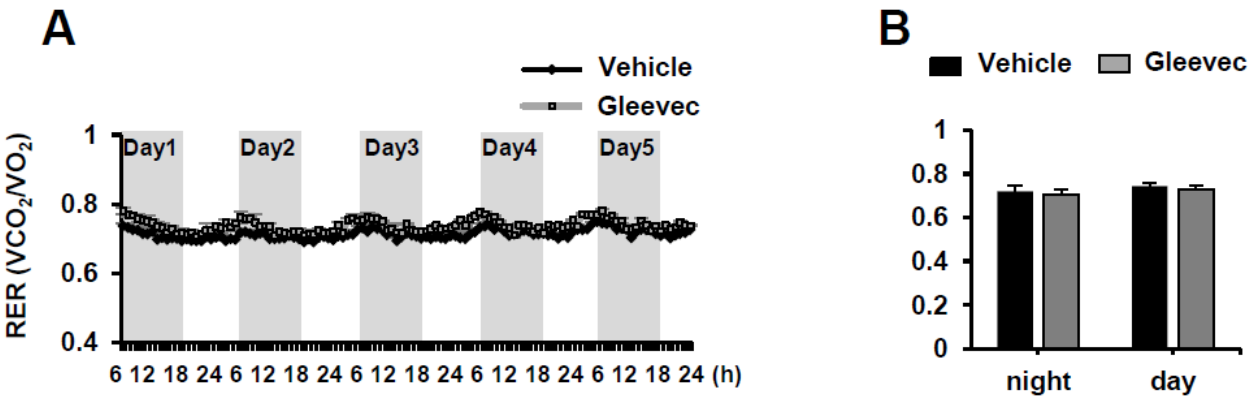
SUPPLEMENTARY DATA

Supplementary Figure 6. The effect of Gleevec on inflammation in adipocytes and macrophages. Fully differentiated 3T3-L1 adipocytes (*A*) and primary macrophages isolated from bone-marrow (*B*) were treated with Gleevec for 24 h and stimulated with TNF-a (50 ng/ml) for 3 h or LPS (10 ng/ml) for 6 h, respectively. Expression of pro-inflammatory cytokines was determined by qPCR (n=3). (*C*) Migratory capacity of Raw264.7 macrophages were measured using an *in vitro* transwell chemotaxis assay (n=5). Mature 3T3-L1 adipocytes were used for preparation of conditioned media (CM). 3T3-L1 adipocytes were stimulated by TNF-a (10 ng/ml) for 24 h after pre-treatment with the indicated concentration of Gleevec for 24 h in serum-free DMEM. For the migration, 100,000 Raw264.7 cells were placed in the upper chamber of a 5 μm polycarbonate filter (24-transwell format; Corning, Lowell, MA, USA), whereas adipocyte conditioned medium or MCP-1 (10 ng/ml) treatment was placed in the lower chamber. After 3 h of migration, cells were fixed in formalin and stained with 4', 6-diamidino-2-phenylindole and observed.All of represented error bars are S.E.M. **p*<0.05, ***p*<0.01, ****p*<0.001 compared with vehicle.



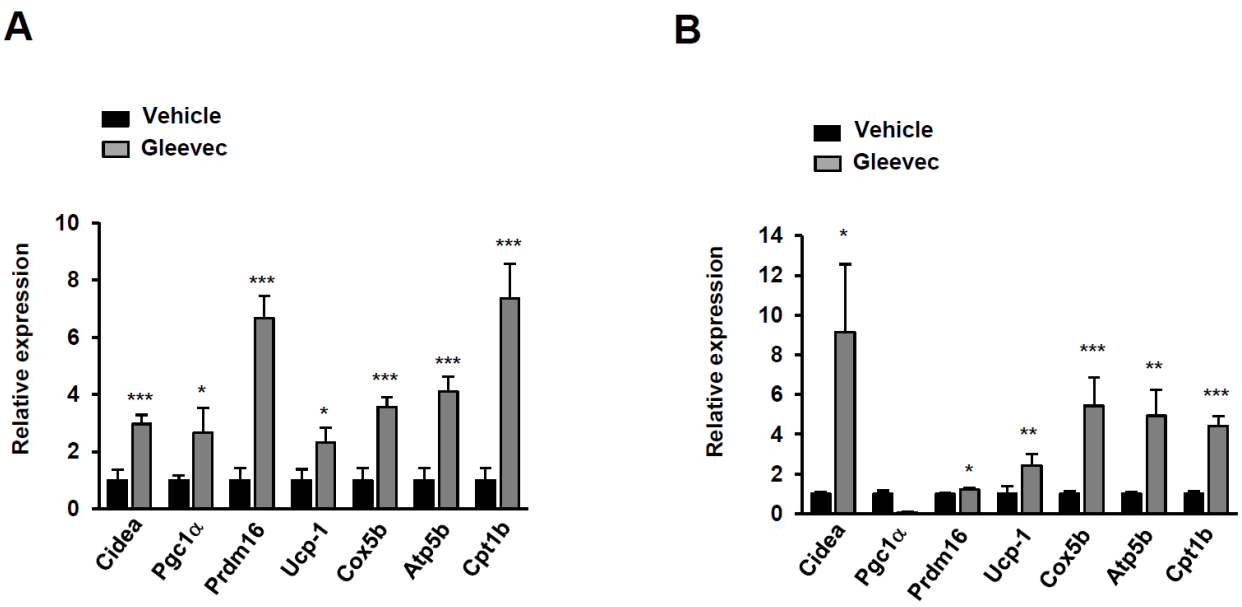
SUPPLEMENTARY DATA

Supplementary Figure 7. The effect of Gleevec on respiratory exchange ratio (RER) in HFD-fed mice. The RER for 5 days in HFD-fed mice treated with Gleevec for 21 days (*A*) and the average quantification for 12 h light and 12 h dark period in *A.*



SUPPLEMENTARY DATA

Supplementary Figure 8. The effect of gleevec on thermogenic program in brown adipose tissue (BAT) of HFD-fed mice. Expression of thermogenic and β-oxidation genes was determined by qPCR in interscapular brown adipose tissue (BAT) of gleevec-treated HFD-fed mice for 21 days without (*A*) or with 9 h cold challenge (*B*). Error bars are S.E.M. (n=7).*p<0.05, **p<0.01 and ***p<0.001 compared with vehicle.



SUPPLEMENTARY DATA

Supplementary Figure 9. The effect of Gleevec on *Ucp-1* and *Pgc-1a* in isolated stromal vascular fraction (SVF) of sWAT.Fully differentiated sWAT SVF cells were treated with Gleevec for 3 days. Expression of *Ucp-1* and *Pgc-1α* were determied by qPCR following treatment of forskolin (10 μM) for 4 h. Error bars are S.E.M. (n=3). ***p<0.001 compared with forskolin-untreated vehicle. n.s, not significant