## **Supplemental Data**

## AMPK and PPAR $\delta$ Agonists

## **Are Exercise Mimetics**

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**Table S1. Gene targets unique to combined GW1516 treatment and exercise training.** The following genes were identified in microarray analysis as unique targets of combined GW1516 and exercise training. Down-regulated genes are in bold italics. (N=3, each pooled from 3 mice, p<0.05).

| DESCRIPTION   | LOCUS    | GW+Tr |
|---|----------|-------|
| ANGIOGENESIS  |          |       |
| CD55 antigen  | Cd55     | 0.56  |
| CARBOHYDRATE METABOLISM                             |          |       |
| phosphoenolpyruvate carboxykinase 1, cytosolic      | Pck1     | 3.518 |
| CYTOKINES   |          |       |
| interferon, alpha-inducible protein 27              | Ifi27    | 1.714 |
| FAT METABOLISM                                      |          |       |
| adipose differentiation related protein             | Adfp     | 2.009 |
| stearoyl-Coenzyme A desaturase 2                    | Scd2     | 1.849 |
| acetyl-Coenzyme A acetyltransferase 2               | Acat2    | 1.625 |
| ATP citrate lyase                                   | Acly     | 2.606 |
| adiponectin, C1Q and collagen domain containing     | Adipoq   | 3.082 |
| diacylglycerol O-acyltransferase 2                  | Dgat2    | 2.784 |
| gamma-glutamyl carboxylase                          | Ggcx     | 0.575 |
| lipase, hormone sensitive                           | Lipe     | 3.032 |
| monoglyceride lipase                                | Mgll     | 1.907 |
| resistin  | Retn     | 4.114 |
| CD36 antigen  | Cd36     | 1.584 |
| fatty acid binding protein 4, adipocyte             | Fabp4    | 2.189 |
| lipoprotein lipase                                  | Lpl      | 1.659 |
| HEAT SHOCK RESPONSE                                 |          |       |
| haptoglobin   | Нр       | 1.679 |
| MITOCHONDRIAL PROTEINS                              |          |       |
| 3-oxoacid CoA transferase 1                         | Oxct1    | 0.574 |
| microsomal glutathione S-transferase 1              | Mgst1    | 1.916 |
| OTHERS  |          |       |
| carbonic anhydrase 3                                | Car3     | 2.339 |
| cysteine dioxygenase 1, cytosolic                   | Cdo1     | 3.266 |
| DNA segment, Chr 4, Wayne State University 53,      | D4Wsu53e | 1.586 |
| expressed   |          |       |
| dynein cytoplasmic 1 intermediate chain 2           | Dync1i2  | 1.705 |
| fusion, derived from t(12;16) malignant liposarcoma | Fus      | 0.605 |
| (human)   |          |       |
| Kruppel-like factor 3 (basic)                       | Klf3     | 1.901 |
| lysosomal membrane glycoprotein 2                   | Lamp2    | 0.608 |
| neighbor of Punc E11                                | Nope     | 0.452 |
| thyroid hormone responsive SPOT14 homolog (Rattus)  | Thrsp    | 2.685 |

| cytochrome P450, family 2, subfamily e, polypeptide 1     | Cyp2e1        | 2.941 |
|---|---------------|-------|
| complement factor D (adipsin)                             | Cfd           | 2.828 |
| transketolase   | Tkt           | 2.256 |
| OXYGEN CARRIERS   |               |       |
| GPI-anchored membrane protein 1                           | Gpiap1        | 1.83  |
| solute carrier family 38, member 4                        | Slc38a4       | 0.579 |
| PROLIFERATION & APOPTOSIS                                 |               |       |
| RIKEN cDNA 1190002H23 gene                                | 1190002H23Rik | 0.543 |
| cell death-inducing DFFA-like effector c                  | Cidec         | 4.771 |
| SIGNAL TRANSDUCTION                                       |               |       |
| annexin A7  | Anxa7         | 0.544 |
| dual specificity phosphatase 7                            | Dusp7         | 1.661 |
| homeodomain interacting protein kinase 3                  | Hipk3         | 1.694 |
| insulin-like growth factor binding protein 5              | Igfbp5        | 1.772 |
| protein phosphatase 2 (formerly 2A), regulatory subunit   | Ppp2r1b       | 2.509 |
| A (PR 65), beta isoform                                   |               |       |
| protein tyrosine phosphatase-like (proline instead of     | Ptplb         | 2.38  |
| catalytic arginine), member b                             |               |       |
| STEROID BIOGENESIS  |               |       |
| retinol binding protein 4, plasma                         | Rbp4          | 2.065 |
| TRANSCRIPTION   |               |       |
| CCAAT/enhancer binding protein (C/EBP), alpha             | Cebpa         | 2.168 |
| nuclear receptor subfamily 1, group D, member             | Nr1d2         | 1.794 |
| 2(Reverb-b)   |               |       |
| TRANSPORT   |               |       |
| transferrin   | Trf           | 1.907 |
| archain 1   | Arcn1         | 1.617 |
| solute carrier family 1 (neutral amino acid transporter), | Slc1a5        | 1.939 |
| member 5  |               |       |
| RIKEN cDNA 1810073N04 gene                                | 1810073N04Rik | 2.326 |

Table S2. Genes regulated by combination of GW1516 treatment and exercise training in quadriceps. The following is a list of target genes identified by microarray analysis and categorized into functional classes. The down-regulated genes are in bold italics. Data is average of N=3 samples in each group (p<0.05). Combination of drug treatment and exercise created a gene signature in muscles that was unique from either treatment alone. Thirty-two percent of these genes encode enzymes of metabolic pathways such as fatty acid biosynthesis/storage (e.g. Fasn, Scd 1 & 2), uptake [e.g. Cd36, fatty acid binding proteins (Fabp) and Lpl] and oxidation [e.g. adiponectin, hormone sensitive lipase (*Lipe*), *Pdk4*, *Ucp3*]; and carbohydrate metabolism [e.g. fructose bisphosphate 2 (Fbp2), phosphoenolpyruvate carboxykinase 1 (Pck1), lactate dehydrogenase B], which along with oxygen transporters and mitochondrial proteins form the largest class of genes directly linked to muscle performance (Ikeda et al., 2002; Achten and Jeukendrup, 2004; Hittel et al., 2005; Civitarese et al., 2006; Nadeau et al., 2006; Kiens, 2006; Yamauchi et al., 2006). All but 4 of these genes were induced, suggestive of a general increase in oxidative capacity. Furthermore, additional pathways including angiogenesis (e.g. angiopoietin-like 4 protein/also a known regulator of lipid metabolism), signal transduction (e.g. adrenergic receptor  $\beta$ 3, insulin-like growth factor, insulin-like growth factor binding protein 5), transcription (e.g. Cebpa, Nr1d2, Nr4a2) and substrate transport (e.g. transferrin, chloride channel 5) were identified, implicating relevance to muscle remodeling and endurance (Nagase et al., 1996; Singleton and Feldman, 2001; Adams, 2002; Centrella et al., 2004; Lundby et al., 2005; Mahoney et al., 2005a and b; Ramakrishnan et al., 2005).

| DESCRIPTION   | LOCUS         | TR+GW |
|---|---------------|-------|
| ANGIOGENESIS  |               |       |
| angiopoietin-like 4   | Angptl4       | 5.495 |
| CD55 antigen  | Cd55          | 0.56  |
| CARBOHYDRATE METABOLISM   |               |       |
| fructose bisphosphatase 2   | Fbp2          | 2.808 |
| phosphoenolpyruvate carboxykinase 1, cytosolic                          | Pck1          | 3.518 |
| lactate dehydrogenase B   | Ldhb          | 2.541 |
| CYTOKINES   |               |       |
| interferon, alpha-inducible protein 27                                  | Ifi27         | 1.714 |
| interleukin 6 signal transducer   | Il6st         | 1.972 |
| FAT METABOLISM  |               |       |
| adipose differentiation related protein                                 | Adfp          | 2.009 |
| cDNA sequence BC054059  | BC054059      | 5.08  |
| RIKEN cDNA 2310076L09 gene  | 2310076L09Rik | 1.868 |
| hydroxysteroid (17-beta) dehydrogenase 12                               | Hsd17b12      | 2.376 |
| stearoyl-Coenzyme A desaturase 1  | Scd1          | 6.494 |
| stearoyl-Coenzyme A desaturase 2  | Scd2          | 1.849 |
| fatty acid synthase   | Fasn          | 6.323 |
| acetyl-Coenzyme A acyltransferase 2 (mitochondrial 3-oxoacyl-Coenzyme A | 1 222         | 1.026 |
| unorase)  | Acad          | 1.920 |
| adimensatin C10 and collegen domain containing                          | Adinag        | 2.349 |
| linese hormone constitue  | Adipoq        | 2.022 |
| mpase, normone sensitive  | Lipe          | 5.052 |
| maionyi-CoA decarboxyiase   | Milyca        | 1./81 |
| monogiyceride lipase  | MgII          | 1.907 |
| uncoupling protein 3 (mitochondrial, proton carrier)                    | Ucp3          | 2.943 |

| ATP citrate lyase   | Acly          | 2.606  |
|---|---------------|--------|
| carnitine palmitoyltransferase 1a, liver                      | Cpt1a         | 2.753  |
| diacylglycerol O-acyltransferase 2                            | Dgat2         | 2.784  |
| gamma-glutamyl carboxylase                                    | Ggcx          | 0.575  |
| glycerol-3-phosphate acyltransferase, mitochondrial           | Gpam          | 2.207  |
| pyruvate dehydrogenase kinase, isoenzyme 4                    | Pdk4          | 2.27   |
| resistin  | Retn          | 4.114  |
| acetyl-Coenzyme A acetyltransferase 2                         | Acat2         | 1.625  |
| ATP-binding cassette, sub-family B (MDR/TAP), member 1A       | Abcb1a        | 10.322 |
| CD36 antigen  | Cd36          | 1.584  |
| solute carrier family 27 (fatty acid transporter), member 1   | Slc27a1       | 3.58   |
| fatty acid binding protein 3, muscle and heart                | Fabp3         | 1.833  |
| fatty acid binding protein 4, adipocyte                       | Fabp4         | 2.189  |
| lipoprotein lipase  | Lpl           | 1.659  |
| diazepam binding inhibitor                                    | Dbi           | 1.936  |
| solute carrier family 27 (fatty acid transporter), 1          | Slc27a1       |        |
| HEAT SHOCK RESPONSE   |               |        |
| haptoglobin   | Нр            | 1.679  |
| heat shock protein 1B   | Hspa1b        | 8.845  |
| heat shock protein 90kDa alpha (cytosolic), class A member 1  | Hsp90aa1      | 1.513  |
| heat shock protein 9A   | Hspa9a        | 1.61   |
| DnaJ (Hsp40) homolog, subfamily B, member 1                   | Dnajb1        | 3.59   |
| OTHERS  |               |        |
| carbonic anhydrase 3  | Car3          | 2.339  |
| dynein cytoplasmic 1 intermediate chain 2                     | Dync1i2       | 1.705  |
| amyloid beta (A4) precursor-like protein 2                    | Aplp2         | 1.937  |
| catalase  | Cat           | 1.82   |
| crystallin, beta B1   | Crybb1        | 2.457  |
| cysteine dioxygenase 1, cytosolic                             | Cdo1          | 3.266  |
| lysosomal membrane glycoprotein 2                             | Lamp2         | 0.608  |
| neighbor of Punc E11  | Nope          | 0.452  |
| neuralized-like homolog (Drosophila)                          | Neurl         | 1.941  |
| retbindin   | Rtbdn         | 2.32   |
| serine (or cysteine) peptidase inhibitor, clade F, member 1   | Serpinf1      | 7.765  |
| serine (or cysteine) proteinase inhibitor, clade A, member 1a | Serpina1a     | 0.396  |
| surfeit gene 4  | Surf4         | 2.091  |
| thyroid hormone responsive SPOT14 homolog (Rattus)            | Thrsp         | 2.685  |
| acid phosphatase 5, tartrate resistant                        | Acp5          | 3.91   |
| DNA segment, Chr 4, Wayne State University 53, expressed      | D4Wsu53e      | 1.586  |
| erythroid differentiation regulator 1                         |               | 0.619  |
| fusion, derived from t(12;16) malignant liposarcoma (human)   | Fus           | 0.605  |
| huntingtin interacting protein 1 related                      | Hip1r         | 1.75   |
| kelch-like 7 (Drosophila)                                     | Klhl7         | 0.5    |
| Kruppel-like factor 3 (basic)                                 | Klf3          | 1.901  |
| Mpv17 transgene, kidney disease mutant-like                   | Mpv17l        | 1.988  |
| RIKEN cDNA C530043G21 gene                                    | C530043G21Rik | 1.5    |
| ligase III, DNA, ATP-dependent                                | Lig3          | 2.693  |
| cytochrome P450, family 2, subfamily e, polypeptide 1         | Cyp2e1        | 2.941  |
| complement factor D (adipsin)                                 | Cfd           | 2.828  |
| Transketolase   | Tkt           | 2.256  |
| amyloid beta (A4) precursor-like protein 2                    | Aplp2         | 1.937  |
| Myosin binding protein H                                      | Mybph         | 1.578  |
| MITOCHONDRIAL PROTEINS  |               |        |

| 3-oxoacid CoA transferase 1  | Oxct1          | 0.574   |
|--|----------------|---------|
| microsomal glutathione S-transferase 1   | Mgst1          | 1.916   |
| mitochondrial ribosomal protein L15  | Mrpl15         | 0.61    |
| solute carrier family 25 (mitochondrial carnitine/acylcarnitine translocase),  | 61.05.00       | 1.075   |
| memoer 20  | SIC25a20       | 1.865   |
| AIF-binaing casselle, sub-jamily E (OABF), member 1  | Abcel          | 0.550   |
| OXIGEN CARRIERS  | Calent         | 1.02    |
| GPI-anchored memorane protein 1  | Срарт          | 1.85    |
| niyogiooni   | NID<br>Slo28a4 | 1.378   |
| solule carrier jamily 56, member 4   | Sicsou4        | 1.622   |
| hemoglobin, beta adult minor chain   hemoglobin Y, beta-like embryonic   | пра-ат         | 1.032   |
| chain  | Hbb-b2   Hbb-y | 1.626   |
| PROLIFERATION & APOPTOSIS  |                |         |
| tripartite motif-containing 35   | Trim35         | 1.856   |
| RIKEN cDNA 1190002H23 gene   | 1190002H23Rik  | 0.543   |
| B-cell translocation gene 2, anti-proliferative  | Btg2           | 1.601   |
| cell death-inducing DFFA-like effector c   | Cidec          | 4.771   |
| cell death-inducing DNA fragmentation factor, alpha subunit-like effector A  | Cidea          | 49.625  |
| SIGNAL TRANSDUCTION  |                |         |
| annexin A7   | Anxa7          | 0.544   |
| adrenergic receptor, beta 3  | Adrb3          | 3.83    |
| dual specificity phosphatase 10  | Dusp10         | 0.579   |
| dual specificity phosphatase 7   | Dusp7          | 1.661   |
| homeodomain interacting protein kinase 3   | Hipk3          | 1.694   |
| insulin-like growth factor 2   | Igf2           | 1.635   |
| insulin-like growth factor binding protein 5   | Igfbp5         | 1.772   |
| protein phosphatase 2 (formerly 2A), regulatory subunit A (PR 65), beta  | Dr 2-11        | 2,500   |
| isolorm  | Ppp2r1b        | 2.509   |
| protein tyrosine phosphatase-like (proline instead of catalytic arginine).   | r ipn2         | 0.432   |
| member b   | Ptplb          | 2.38    |
| RAB5B, member RAS oncogene family  | Rab5b          | 1.603   |
| RAP2C, member of RAS oncogene family   | Rap2c          | 0.601   |
| transforming growth factor, beta receptor II   | Tgfbr2         | 2.13    |
| Ras-related GTP binding D  | Rragd          | 2.101   |
| 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma   | X7 1           | 1.07    |
|  | r wnag         | 1.8/    |
| STERVID BIOGENESIS   | A1.JL1 7       | 2.972   |
| aution and an antional and a second and as | Alunia/        | 3.862   |
| retinol binding protein 4, plasma  | кор4           | 2.065   |
| rransinyreun   | 107<br>Muhah   | 0.020   |
| myosin binding protein H   | Mybpn          | 1.578   |
| TRANSCRIPTION  | 76-261         | 1 0 4 7 |
| zinc inger protein 201   | ZIP201         | 1.847   |
| notchiess nonnolog 1 (Drosophila)  | Dhhn4          | 2.965   |
| retinoblastoma binding protein 4   | K00p4          | 2.805   |
| ankyrin repeat and SOCS box-containing protein 15  | Asb15          | 1.78    |
| activating transcription factor 3  | AU3            | 1.802   |
| CCAA I/ennancer binding protein (C/EBP), alpha   |                | 2.168   |
| early growth response 1  | Egrl           | 2.577   |
| Jorkneaa box U3a   | Foxo3a         | 0.634   |
| Jun-B oncogene   | Junb           | 1.792   |
| LIVI nomeobox transcription factor 1 alpha   | Lmx1a          | 4.106   |
| nuclear receptor subfamily 1, group D, member 2(Reverb-b)  | INTIG2         | 1.794   |
| nuclear receptor subfamily 4, group A, member 2 (NURR1)  | Nr4a2          | 1.776   |

| RNA polymerase 1-4   | Rpo1-4        | 2.498 |
|--|---------------|-------|
| sin3 associated polypeptide  | Sap30         | 0.551 |
| wingless-related MMTV integration site 7B                          | Wnt7b         | 4.449 |
| FBJ osteosarcoma oncogene  | Fos           | 3.9   |
| TRANSPORT  |               |       |
| seminal vesicle protein 2  | Svp2          | 0.014 |
| seminal vesicle secretion 5  | Svs5          | 0.095 |
| transferrin  | Trf           | 1.907 |
| archain 1  | Arcn1         | 1.617 |
| two pore channel 1   | Tpcn1         | 2.842 |
| solute carrier family 1 (neutral amino acid transporter), member 5 | Slc1a5        | 1.939 |
| chloride channel 5   | Clcn5         | 2.333 |
| claudin 5  | Cldn5         | 1.545 |
| albumin 1  | Alb1          | 0.245 |
| RIKEN cDNA 1810073N04 gene   | 1810073N04Rik | 2.326 |

**Table S3.** Selective GW1516 and/or exercise induced genes including heat shock proteins, metallothioneins and other stress biomarkers are not changed by the combination possibly reflecting a potential lessening of exercise-based damage (Liu and Steinacker, 2001; Jagoe et al., 2002; Koh, 2002; McArdle et al., 2002; Lecker et al., 2004). Data is average of N=3 samples in each group (p<0.05).

| DESCRIPTION                                 | LOCUS     | GW    | Tr    | Tr+GW |
|---|-----------|-------|-------|-------|
| heat shock protein 1                        | Hspb1     | 1.815 | 1.965 | -     |
| heat shock protein family, 7                |           |       |       |       |
| (cardiovascular)                            | Hspb7     | 3.414 | 1.753 | -     |
| DnaJ (Hsp40) homolog, subfamily A, 1        | Dnaja1    | -     | 1.545 | -     |
| heat shock protein 110                      | Hsp110    | -     | 1.587 | -     |
| serine (or cysteine) peptidase inhibitor H1 | Serpinh1  | -     | 2.198 | -     |
| DnaJ (Hsp40) homolog, subfamily A, 4        | Dnaja4    | 1.756 | 1.545 | -     |
|   |           |       |       |       |
| metallothionein 1                           | Mt1       | 2.364 | -     | -     |
| metallothionein 2                           | Mt2       | 2.151 | -     | -     |
|   |           |       |       |       |
| crystallin, alpha B                         | Cryab     | 1.561 | 1.52  | -     |
| crystallin, gamma F                         | Crygf     | 1.801 | 3.56  | -     |
|   |           |       |       |       |
| MAD homolog 3 (Drosophila)                  | Smad3     | 1.841 | 1.886 | -     |
| ankyrin repeat domain 1 (cardiac muscle)    | Ankrd1    | 4.235 | -     | -     |
|   |           |       |       |       |
| TNF receptor superfamily, 12a               | Tnfrsf12a | 1.759 | 1.782 | -     |
|   |           |       |       |       |
| Jun oncogene                                | Jun       | -     | 1.521 | -     |

**Table S4.** Targets common to exercise-PPAR $\delta$  and AMPK-PPAR $\delta$  gene signatures. Comparison of gene signature generated by either combined PPAR $\delta$  activation and exercise with that of PPAR $\delta$  and AMPK co-activation revealed 52 common target genes listed below. Data is average of N=3 samples in each group (p<0.05).

| DESCRIPTION   | LOCUS         | TR+GW  | AI+GW |
|---|---------------|--------|-------|
| ANGIOGENESIS  |               |        |       |
| angiopoietin-like 4   | Angptl4       | 5.495  | 2.917 |
|   |               |        |       |
| APOPTOSIS   |               |        |       |
| cell death-inducing DFFA-like effector c                    | Cidec         | 4.771  | 1.838 |
| cell death-inducing DNA fragmentation factor, alpha         |               |        |       |
| subunit-like effector A                                     | Cidea         | 49.625 | 1.842 |
| CARBOHYDRATE METABOI ISM                                    |               |        |       |
| lactate dehydrogenase B                                     | I dhb         | 2 541  | 1 917 |
| fructose hisphosphatase 2                                   | Edito<br>Fbn2 | 2.541  | 2 478 |
|   | 10p2          | 2.000  | 2.470 |
| FAT METABOLISM  |               |        |       |
| stearoyl-Coenzyme A desaturase 1                            | Scd1          | 6.494  | 1.78  |
| fatty acid binding protein 3, muscle and heart              | Fabp3         | 1.833  | 1.5   |
| pyruvate dehydrogenase kinase, isoenzyme 4                  | Pdk4          | 2.27   | 2.486 |
| uncoupling protein 3 (mitochondrial, proton carrier)        | Ucp3          | 2.943  | 2.792 |
| adiponectin, C1Q and collagen domain containing             | Adipoq        | 3.082  | 1.56  |
| diacylglycerol O-acyltransferase 2                          | Dgat2         | 2.784  | 2.14  |
| solute carrier family 27 (fatty acid transporter), member 1 | Slc27a1       | 3.58   | 2.195 |
| lipase, hormone sensitive                                   | Lipe          | 3.032  | 1.746 |
| solute carrier family 25 (mitochondrial                     |               |        |       |
| carnitine/acylcarnitine translocase), member 20             | Slc25a20      | 1.704  | 1.697 |
| CD36 antigen  | Cd36          | 1.584  | 1.513 |
| phosphoenolpyruvate carboxykinase 1, cytosolic              | Pck1          | 3.518  | 1.781 |
| fatty acid synthase   | Fasn          | 6.323  | 2.24  |
| fatty acid binding protein 4, adipocyte                     | Fabp4         | 2.189  | 1.81  |
| monoglyceride lipase  | Mgll          | 1.907  | 1.51  |
| acetyl-Coenzyme A acetyltransferase 2                       | Acat2         | 1.625  | 1.563 |
| acetyl-Coenzyme A dehydrogenase, long-chain                 | Acadl         | 2.549  | 1.992 |
| resistin  | Retn          | 4.114  | 1.756 |
| malonyl-CoA decarboxylase                                   | Mlycd         | 1.781  | 1.962 |
| transketolase   | Tkt           | 2.256  | 1.983 |
| ATP citrate lyase   | Acly          | 2.458  | 1.91  |
| HEAT SHOCK  |               |        |       |
| heat shock protein 90kDa alpha (cytosolic), class A member  |               |        |       |
| 1   | Hsp90aa1      | 1.455  | 0.616 |
| DnaJ (Hsp40) homolog, subfamily B, member 1                 | Dnajb1        | 3.59   | 0.604 |
|   |               |        |       |
| CYTOKINES   |               |        |       |
| interferon, alpha-inducible protein 27                      | Ifi27         | 1.714  | 1.537 |

| OTHERS  |            |       |       |
|---|------------|-------|-------|
| sarcolipin  | Sln        | 0.363 | 4.576 |
| thyroid hormone responsive SPOT14 homolog (Rattus)            | Thrsp      | 2.685 | 1.766 |
|   | 2310076L09 |       |       |
| RIKEN cDNA 2310076L09 gene                                    | Rik        | 1.868 | 2.117 |
| myosin, heavy polypeptide 2, skeletal muscle, adult           | Myh2       | 2.194 | 1.797 |
| surfeit gene 4  | Surf4      | 2.091 | 0.654 |
| acid phosphatase 5, tartrate resistant                        | Acp5       | 3.91  | 1.477 |
| serine (or cysteine) proteinase inhibitor, clade A, member 1a | Serpina1a  | 0.396 | 3.891 |
| cysteine dioxygenase 1, cytosolic                             | Cdo1       | 3.266 | 1.678 |
| erythroid differentiation regulator 1                         |            | 0.619 | 1.805 |
|   | 1810073N04 |       |       |
| RIKEN cDNA 1810073N04 gene                                    | Rik        | 2.326 | 1.628 |
| superoxide dismutase 3, extracellular                         | Sod3       | 1.606 | 1.617 |
| complement factor D (adipsin)                                 | Cfd        | 2.828 | 1.5   |
| cytochrome P450, family 2, subfamily e, polypeptide 1         | Cyp2e1     | 2.941 | 1.743 |
| catalase  | Cat        | 1.728 | 1.902 |
| early growth response 1                                       | Egr1       | 2.577 | 0.65  |
|   | _          |       |       |
| OXYGEN CARRIER  |            |       |       |
| hemoglobin, beta adult minor chain   hemoglobin Y, beta-      | Hbb-b2     |       |       |
| like embryonic chain  | Hbb-y      | 1.626 | 1.503 |
|   |            |       |       |
| STEROID BIOGENESIS  |            |       |       |
| retinol binding protein 4, plasma                             | Rbp4       | 2.065 | 2.225 |
|   |            |       |       |
| SIGNAL TRANSDUCTION   |            |       |       |
| adrenergic receptor, beta 3                                   | Adrb3      | 3.83  | 1.56  |
| protein tyrosine phosphatase-like (proline instead of         |            |       |       |
| catalytic arginine), member b                                 | Ptplb      | 2.38  | 1.569 |
| dual specificity phosphatase 7                                | Dusp7      | 1.661 | 1.672 |
|   |            |       |       |
| TRANSCRIPTION   |            |       |       |
| nuclear receptor subfamily 4, group A, member 2               | Nr4a2      | 1.776 | 0.437 |
|   |            |       |       |
| TRANSPORT   |            |       |       |
| solute carrier family 1 (neutral amino acid transporter),     |            |       |       |
| member 5  | Slc1a5     | 1.939 | 1.511 |
| two pore channel 1  | Tpcn1      | 2.842 | 1.487 |
| seminal vesicle secretion 5                                   | Svs5       | 0.095 | 2.243 |
|   |            |       |       |

| Table S5.  | Oxidative genes induced by AMPK agonist AICAR as w            | well as by transgenic |
|------------|---|-----------------------|
| over-expre | ession of VP16-PPAR $\delta$ in quadriceps of untrained mice. | Data is average of    |
| N=3 mice   | in each group (p<0.5).  |                       |

| Locus   | Description   | AICAR | VP-PPARd |
|---------|---|-------|----------|
| Aacs    | acetoacetyl-CoA synthetase  | 1.875 | 2.771    |
| Acly    | ATP citrate lyase   | 1.687 | 2.429    |
| Adipoq  | adiponectin   | 2.043 | 2.122    |
| Ak2     | adenylate kinase 2  | 1.486 | 1.173    |
| Apoe    | apolipoprotein E  | 1.403 | 1.959    |
| Cd36    | CD36 antigen  | 1.386 | 3.66     |
| Ces3    | carboxylesterase 3  | 1.516 | 1.869    |
| Cidea   | cell death-inducing DNA fragmentation factor, alpha subunit-like effector A | 5.021 | 2.356    |
| Dgat2   | diacylglycerol O-acyltransferase 2  | 2.034 | 2.147    |
| Elov16  | ELOVL family member 6   | 2.134 | 4.43     |
| Fabp4   | fatty acid binding protein 4, adipocyte                                     | 1.709 | 1.23     |
| Fasn    | fatty acid synthase   | 2.098 | 2.749    |
| Lep     | leptin  | 2.047 | 3.579    |
| Lipe    | lipase, hormone sensitive   | 1.64  | 2.203    |
| Lpl     | lipoprotein lipase  | 1.386 | 1.285    |
| Mgll    | monoglyceride lipase  | 1.503 | 2.816    |
| Mgst1   | microsomal glutathione S-transferase 1                                      | 1.602 | 1.905    |
| Nrip1   | nuclear receptor interacting protein 1                                      | 1.474 | 1.887    |
| Pck1    | phosphoenolpyruvate carboxykinase 1   | 2.68  | 2.169    |
| Pcx     | pyruvate carboxylase  | 1.393 | -        |
| Pdk4    | pyruvate dehydrogenase kinase, isoenzyme 4                                  | 1.321 | 5.06     |
| _       | peroxisome proliferator activated receptor                                  |       |          |
| Pparg   | gamma   | 3.027 | 2.334    |
| Retn    | resistin  | 1.891 | 1.641    |
| Scd1    | stearoyl-Coenzyme A desaturase 1  | 1.931 | 7.353    |
| Sdhd    | succinate dehydrogenase complex, subunit D                                  | 1.529 | 1.349    |
| Sfxn1   | sideroflexin 1  | 1.713 | 1.494    |
| Slc25a5 |   | 1.372 | 1.348    |
| Sult1a1 | sulfotransferase family 1A  | 2.021 | 1.996    |
| Tspo    | translocator protein  | 1.441 | 2.133    |
| Ucp1    | uncoupling protein 1  | 3.623 | 0.695    |
| Ucp3    | uncoupling protein 3  | 1.258 | 4.107    |



| (G) | Description                                    | Locus | GW+AI | VP-PPARð |
|-----|--|-------|-------|----------|
|     | ATP citrate lyase                              | Acly  | 1.648 | 3.095    |
|     | carnitine palmitoyltransferase 1b, muscle      | Cpt1b | 1.371 | 1.678    |
|     | fatty acid binding protein 3, muscle and heart | Fabp3 | 1.447 | 5.904    |
|     | fatty acid synthase                            | Fasn  | 2.24  | 2.749    |
|     | lipoprotein lipase                             | Lpl   | 1.113 | 1.72     |
|     | lipase, hormone sensitive                      | Lipe  | 1.746 | 2.203    |
|     | pyruvate dehydrogenase kinase, isoenzyme 4     | Pdk4  | 2.486 | 5.06     |
|     | stearoyl-Coenzyme A desaturase 1               | Scd1  | 1.78  | 7.353    |
|     | uncoupling protein 3                           | Ucp3  | 2.792 | 4.107    |

**Figure S1. PPARδ activation in muscle. (A-C)** Regulation of oxidative genes by GW1516 in wild type and PPARδ null primary muscle cells. (**D**) Muscle triglycerdise levels. (**E-F**) Epididymal fat to body weight ratio (**E**) and cross-sectional area (**F**) in indicated groups of mice. (**G**) List of selective oxidative genes induced in muscle by combined PPARδ and AMPK activation as well as VP16-PPARδ over-expression determined by microarray analysis. \* represents statistical significance between V and indicated groups (p<0.05, One Way ANOVA; post hoc: Dunnett's Multiple Comparison Test).



Figure S2. Synergistic regulation of muscle gene expression by PPAR $\delta$  and AMPK. (A) Venn diagram comparing GW, Tr and AI+GW target genes identified in microarray analysis of quadriceps. Data is an average of N=3 samples in each group. The selection criteria used a p<0.05 on Bonferroni's multiple comparison test. (B) Classification of AI+GW target genes.

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