Supplementary Information

Drugs that reverse disease transcriptomic signatures are more effective in a mouse model of dyslipidemia

Allon Wagner\textsuperscript{1,2,*}, Noa Cohen\textsuperscript{1}, Thomas Kelder\textsuperscript{3,#}, Uri Amit\textsuperscript{4,5}, Elad Liebman\textsuperscript{6}, David M. Steinberg\textsuperscript{7}, Marijana Radonjic\textsuperscript{3,#} & Eytan Ruppin\textsuperscript{1,8,9,*}

\textsuperscript{1} The Blavatnik School of Computer Science, Tel Aviv University, Tel Aviv 69978, Israel; 
\textsuperscript{2} Department of Electrical Engineering and Computer Science, University of California, Berkeley, Berkeley, CA 94720-1770, USA; 
\textsuperscript{3} Microbiology and Systems Biology, TNO, 3700 AJ Zeist, the Netherlands; 
\textsuperscript{4} Neufeld Cardiac Research Institute, Tel Aviv University, Tel Aviv 69978, Israel; 
\textsuperscript{5} Regenerative Medicine Stem Cells and Tissue Engineering Center, Sheba Medical Center, Tel Hashomer 52621, Israel; 
\textsuperscript{6} Department of Computer Science, University of Texas at Austin, Austin, TX 78712, USA; 
\textsuperscript{7} Department of Statistics and Operations Research, Tel Aviv University, Tel Aviv 69978, Israel; 
\textsuperscript{8} The Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel; 
\textsuperscript{9} Department of Computer Science, Institute of Advanced Computer Sciences (UMIACS) & the Center for Bioinformatics and Computational Biology, University of Maryland, College Park, MD 20742, USA; 
\# Current affiliation: EdgeLeap B.V., Hooghiemstraiplein 15, 3514 AX Utrecht, the Netherlands; 
* To whom correspondence should be addressed.

E-mail: (AW) allonwag@post.tau.ac.il; (ER) ruppin@post.tau.ac.il
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Supplementary Results

1. **Reversal of disease phenotypes in the gene expression spaces**

   It is reasonable to assume that effective clinical interventions should reverse disease-induced pattern to the gene expression of affected organs. We therefore tested whether the treated animals tended to lie closer in the gene expression space to the healthy (LFD) group than did the untreated HFD group (see also Supplementary Figure 1). Formally, for each treatment group we computed the TDIs of animals in that group, and ran a two-sample t-test between them and the TDIs of the untreated HFD (16 weeks) group. The following table presents the one-sided p-values with which the null hypothesis of equal means for the TDIs of both groups can be rejected in favor of the alternative that the treatment led to a smaller mean TDI. P-values were adjusted to multiple hypotheses testing by the Benjamini-Hochberg (BH) method.

| Experimental group          | Liver BH-adjusted p-value | Adipose BH-adjusted p-value |
|-----------------------------|---------------------------|-----------------------------|
| Dietary intervention (DLI)  | 0.0001                    | 4e-7                        |
| Rosiglitazone               | 0.0287                    | 0.1560                      |
| Pioglitazone                | 0.0918                    | 0.0516                      |
| Metformin                   | 0.0189                    | N/A                         |
| Glibenclamide               | 0.0094                    | N/A                         |
| Sitagliptin                 | 0.1081                    | N/A                         |
| Atorvastatin                | 0.2065                    | N/A                         |
| Salicylate                  | 0.1081                    | 0.0378                      |
| T0901317                    | 0.9338                    | 2e-5                        |
| Fenofibrate                 | 0.9338                    | N/A                         |
| Rofecoxib                   | 0.0469                    | N/A                         |

2. **Intra-group variability**

   Figure 2a-b suggests that there exists considerable variability in the transcriptomic effects of some of the treatments. For example, animals treated with salicylate do not tend to cluster together in both adipose and the liver, whereas animals treated with rosiglitazone tend to cluster together in the gene expression space. In order to better study intra-group variability, hierarchical clustering of the animals in the gene expression space was conducted. Results are shown in Supplementary Figures 3-4. Dendrograms were created with the Euclidean metric, conforming to the rest of the study, and with average linkage. Unlike the PCA plots, which show only the first two principal components, and thus do not capture the entire variability in the data, the dendrograms were computed based on all the dimensions of the gene expression.
spaces. Nevertheless, the trends that they show are similar to those that can be observed in the PCA plots.

First, in both tissues, the LFD animals cluster together, and most of the dietary lifestyle intervention (DLI) animals cluster with them. The dietary intervention is so successful at reversing disease gene expression patterns that these animals become practically indistinguishable from the animals that were fed LFD throughout the experiment. In the case of adipose tissue, the T0901317 cluster with LFD and DLI animals, yet still forms a distinct subgroup, in contrast to LFD and DLI which are “mixed together”. Yet, this occurs only in adipose; in the liver the T0901317 group is distinct from the LFD+DLI cluster.

Second, there exists large intra-group variability due to which many of the animals do not cluster with other animals from the same treatment group. Two notable exceptions occur: in the adipose tissue, rosiglitazone and pioglitazone cluster together and distinctly from other drugs. The same happens with fenofibrate and T0901317 in the liver. This seems to occur because each of these four compounds activates a key regulator that is expressed in the tissue in which it exerts considerable transcriptomic changes, whereas the other drugs either work through other mechanisms that have a subtler effect or exert their primary effect in tissues that were not examined in the current study, such as pancreatic β-cells (see Supplementary Table 2).

3. **GSEA analysis**

Gene set enrichment analysis (GSEA, (Subramanian *et al*, 2005)) was conducted to detect pathways that are enriched in genes that are either upregulated or downregulated in each treatment group compared with the HFD-16weeks group. Comparisons of the LFD and HFD-9weeks groups with the HFD-16weeks groups were made as well for the sake of completeness. The analysis was limited to gene sets from the collection of canonical KEGG pathways in the Molecular Signatures Database (MSigDB) v4.0 (accession: CP:KEGG; 186 gene sets in total) so as to retain statistical power in the face of multiple comparison. On the other hand, we emphasize that input to GSEA consisted of all the genes whose expression was measured, and not only the subset of top differentially-expressed genes that was used to define the gene expression space for the purpose of TDI computations (Methods).

Gene sets were downloaded from MSigDB (www.broadinstitute.org/gsea/msigdb; accessed July 2014) and translated from human gene identifiers to mouse gene identifiers using homology data from the Jackson laboratory (www.informatics.jax.org; accessed July 2014). GSEA software available from the Broad Institute (v2.1.0; www.broadinstitute.org/gsea/index.jsp; accessed July 2014) was run with default parameters. We note that phenotype permutation was used to assess the statistical significance of the enrichment scores. Phenotype permutation is more stringent and biologically reasonable than gene set permutation (Subramanian *et al*, 2005), and was therefore preferred despite the limits
it poses on statistical power in experiments with small number of samples in each group (our dataset typically has 8 animals per group).

Overall, the results agreed with prior expectations. Major hepatic and adipotic pathways were indeed modulated in the study animals by the drugs that are known to target them. Fenofibrate upregulated peroxisome proliferator-activated receptors (PPAR) signaling in the liver; fenofibrate, atorvastatin and T0901317 modulated hepatic fatty acid metabolism. Pioglitazone and rosiglitazone activated PPAR signaling and genes associated with fatty acid metabolism in white adipose. An exception to that was metformin, which did not alter any hepatic pathway in a statistically-significant way. This does not seem to stem from under-dosage because the dosage used was comparable to the one given in previous studies (250 mg/kg, 0.25% w/w), alleviated some of the clinical phenotypes of the disease (Radonjic et al, 2013), and significantly decreased the hepatic TDI compared with untreated HFD group (Supplementary Results 1). The indiscernibility of metformin’s effects in GSEA analysis may thus stem from the lack of statistical power.

Interestingly, pro-inflammatory pathways were downregulated in adipose gene expression in the LFD and DLI groups compared with the HFD group, which accords with the importance of adipose-related inflammatory processes in HFD-induced pathologies (Wellen & Hotamisligil, 2003; Berg & Scherer, 2005). Nonetheless, inflammatory pathways were upregulated in the liver by T0901317, which is also apparent in direct inspection of the expression of known pro-inflammatory genes (Supplementary Results 5). The hepatic inflammatory response is probably associated with the deleterious physiological outcomes observed in T0901317 mice, most notably abnormal hepatomegaly (see main text in the results subsection “Non-restorative alterations to the gene expression are associated with unfavorable outcomes”).

GSEA results also accord with observations that were reached in this study through other means: first, the dietary regimen seems particularly effective in inducing the opposite transcriptomic patterns than HFD. In both tissues there are multiple pathways which are altered between the LFD and the untreated HFD group due to HFD-feeding, and are altered in the opposite direction by DLI; the same reversal occurs in none or only in a handful of the drugs in each case, and only those that were shown to exert the most positive effect in the study animals. Second, taking the number of significantly altered gene sets as a proxy for the magnitude of the drug effect, we find that the drugs that had the most significant effects are the same ones that exert the largest effects as seen in the gene expression space (Supplementary Figure 12).

One result that we did not anticipate was the frequent occurrence of the KEGG_RIBOSOME gene set among the significantly altered ones in the liver. This gene set is upregulated in the liver by pioglitazone, rosiglitazone, fenofibrate, and T0901317 compared with the HFD group. Moreover, it is downregulated in the LFD and DLI group compared with the HFD
group, suggesting that this pathway’s downregulation is a phenotype associated with HFD and rectified by DLI. The gene set is also upregulated in the animals fed HFD for 9 weeks compared with the ones fed HFD for 16 weeks, which may be interpreted as a sign that this pathway’s downregulation should be associated with a late phase in the disease progression and as a marker for a severe form of the disease state. Indeed, it has been recently shown that HFD-feeding repressed liver ribosomal RNA transcription in both wildtype (C57BL6) mice fed HFD and in an obese mouse model (ob/ob) fed normal diet compared with wildtype mice fed a normal diet (Oie et al, 2014).

Another noteworthy effect occurs in the liver, where T0901317 downregulated the gene set KEGG_COMPLEMENT_AND_COAGULATION_CASCADES compared with the HFD group. A similar result was previously reported in a zebrafish study of T0901317’s hepatic effects (Sukardi et al, 2012), suggesting that it is not accidental but rather concerns a conserved biological mechanism in the two species. In our data, rosiglitazone (yet not pioglitazone) had the opposite effect and significantly upregulated this gene set in the liver. The gene set was significantly downregulated in the adipose tissue of the LFD group, yet not in the livers of the LFD animals.

4. Alternative definitions of TDI

4.1. GSEA-based methods

We define the Transcriptome Deviation Index as the Euclidean distance in the gene expression space between an animal and the mean of the healthy (low-fat diet) animals. Note that the gene expression space is defined through genes that are differentially expressed between the HFD and LFD groups, and are thus associated with the disease phenotypes. A different approach was taken by several previous studies (Lamb et al, 2006; Iorio et al, 2010; Sirota et al, 2011; Pacini et al, 2013) that sought inverse correlations between drug and disease profiles derived from gene expression data, and applied Gene Set Enrichment Analysis (GSEA) (Subramanian et al, 2005) towards that purpose. Briefly, these studies computed a score that is based on the Kolmogorov-Smirnov statistic and quantifies the extent by which genes that are up-regulated in the disease profile tend to be up-regulated in the treatment profile and, similarly, genes that are down-regulated in the disease profile tend to be down-regulated in the treatment profile. Negative scores occur when genes that are up-regulated by the disease tend to be down-regulated by the treatment, and vice-versa, and suggest that the drug might be effective in treating the disease. Following (Sirota et al, 2011), these score are denoted DDS (which stands for drug-disease-score, although here they are applied in the case of the non-pharmacological dietary intervention, and in an individual manner, see below).

TDIs and DDSs are thus two ways to quantify the success of a treatment to reverse gene expression patterns induced by the disease. Treatments that successfully act towards this goal should have both small (close to 0) TDIs and small (“very negative”) DDSs compared with
unsuccessful treatments. Therefore, one expects TDIs and DDSs to be directly correlated; we verified that a strong correlation indeed exists.

DDSs were computed for each animal in the dataset studied here. There are minute differences between the ways the scores are computed in the various studies that used a GSEA-based approach; we followed (Sirota et al, 2011). As in the TDIs, a) DDSs were computed separately for the adipose and for the liver gene expression, and b) DDSs were computed for each individual animal, rather than for an entire treatment group. Thus, DDSs offer an alternative quantification for the tissue-specific reversal of the HFD gene expression patterns in a certain animal. As expected, TDIs and DDSs are highly correlated (Supplementary Figure 5; Pearson rho = 0.97, 0.96, p-values < 1.4e-38, 3.4e-62 for the adipose and liver tissues, respectively). On the other hand, the definition of TDIs allows a simple decomposition of the TDI into two orthogonal components: one that corresponds to disease reversal, and one which is associated with adverse outcomes (Supplementary Figure 13a). It is not as straightforward to do the same for GSEA-based scores, and therefore the definition of TDIs that is presented in the main text was chosen for the current study.

4.2. Genes mapped to multiple probes

A subtle choice in the definition of TDIs concerns the way probes that are mapped to multiple genes are handled. We opted for the most data-driven approach, and treated each probe as a separate feature, thus accommodating the possibility that a particular probe might be much more correlated with disease phenotypes than other probes mapped to the same gene. We verified, however, that our results do not depend on this choice. Similar results are obtained when all the probes that are associated with a particular gene are collapsed into a single feature.

5. Up-regulation of pro-inflammatory genes in the T0901317 treatment group

T0901317 and fenofibrate are associated with unfavorable physiological outcomes that are indicative of liver pathologies, and particularly with notable hepatomegaly (see main text and Supplementary Figure 14), as well as with large non-restorative alterations in the liver gene expression (Supplementary Figures 12a, 13b). We hypothesized that these unfavorable phenotypes are accompanied by hepatic inflammation (Reddy & Sambasiva Rao, 2006). Therefore, we tested whether 13 known inflammatory genes were up-regulated in the livers of mice treated with one of these drugs compared with untreated HFD mice (one-sided t-test; p-values were adjusted to multiple hypotheses by the Benjamini-Hochberg method; significance level was set at 5%). No significantly up-regulated genes were observed in the fenofibrate group. However, 6 out of the 13 tested genes were significantly up-regulated in the T0901317 (we stress that the comparison is with the untreated HFD group and not with the LFD group): MCP-1, CD86, EMR-1, ICAM-1, VCAM-1, and IL-1β. In addition, TNF-α was up-regulated, but not
in a statistically-significant manner (adjusted p-value = 0.11, unadjusted p-value = 0.036). The other 6 genes that were tested are: SELE, SELP, NOS-1, NOS-2, IL-6, IL-18.
Supplementary Figures

1. **Supplementary Figure 1: Transcriptome deviations indices**
   
   (a) Liver and (b) adipose TDI distribution of the different experimental groups
2. Supplementary Figure 2: Global physiological deviation indices

GPDI distribution of the different experimental groups
3. Supplementary Figure 3: Hierarchical clustering in the liver gene expression space

Dendrogram was built with Euclidean distances and average linkage. Each leaf in the dendrogram corresponds to one animal, and leaf labels denote the treatment group to which the animal belonged. Two clusters are highlighted. The first (blue, bottom part of the dendrogram) contains all the LFD animals, and 6 out of the 8 dietary intervention animals. The second (pink, upper part of the dendrogram) contains all the animals treated with the lipid-modulating drugs fenofibrate and T0901317. Both of which activate master transcription factor that are highly expressed in the liver. See Supplementary Results 2 and main text for details.
4. Supplementary Figure 4: Hierarchical clustering in the adipose gene expression space

Dendrogram was built with Euclidean distances and average linkage. Each leaf in the dendrogram corresponds to one animal, and leaf labels denote the treatment group to which the animal belonged. Two clusters are highlighted. The first (blue, upper part of the dendrogram) contains all the LFD animals, most of the dietary intervention animals, and all the animals treated with T0901317. The second (pink, bottom part of the dendrogram) contains almost all the animals treated with the thiazolidinediones (TZDs) rosiglitazone and pioglitazone. These two drugs activate a master transcription factor that is highly expressed in adipose. See Supplementary Results 2 and main text for details.
5. **Supplementary Figure 5: Correlation between GSEA-based scores and TDIs**

Scatter plots of DDSs, which are GSEA-based scores (see Supplementary Results 4.1) that measures a drug’s ability to reverse the transcriptomic patterns of the disease, and the Transcriptome Deviation Indices (TDIs), which quantify the same ability via other means. We find that the two are highly correlated both when computed for (a) liver and (b) white adipose gene expression. X and y axes are TDIs and DDSs, respectively. Each dot represents one animal, color-coded according to its treatment group as in the rest of the study. Pearson correlation coefficients and their corresponding p-values are given for each tissue.
6. **Supplementary Figure 6: Spearman correlations of TDI, GPDI, and MDI**

This figure parallels Figure 2 of the main text, except that it presents Spearman correlations and their respective p-values instead of Pearson correlations. Accordingly, the x and y axes of each panel present the ranked values rather than the actual values. For example, the x coordinates of panel (a) are the rank of each animal’s adipose TDI with respect to all the animals for which adipose TDI was available.

![Panel A: Spearman correlation between ranked adipose TDI and ranked GPDI.](image)

\[ \rho = 0.91 \quad p < 10^{-16} \]

![Panel B: Spearman correlation between ranked liver TDI and ranked GPDI.](image)

\[ \rho = 0.50 \quad p < 9.6 \times 10^{-7} \]

![Panel C: Spearman correlations between ranked liver TDI and ranked MDI.](image)

\[ \rho = 0.45 \quad p < 1.5 \times 10^{-5} \]

\[ \rho = 0.27 \quad p < 0.008 \]
7. **Supplementary Figure 7: Liver metabolome space**

First two principal components of the liver metabolome space. Each dot represents one animal; color codes denote the different experimental groups. The dashed arrow connects the HFD centroid (yellow square) to the LFD centroid (yellow triangle), and denotes the direction of a reversal of the gene expression or physiological state back to the norm.
8. **Supplementary Figure 8: White adipose TDI correlation with individual PDIs**

Each panel presents the ranked PDI values of a particular physiological marker (y-axis) as a function of the ranked adipose TDI (x-axis). Each dot represents one animal, color-codes denote the different experimental groups. The dashed lines are linear regression lines. Refer to Supplementary Table 1 for complete details concerning the physiological markers. The Spearman correlations values and their respective p-values are given in Supplementary Table 7.
9. **Supplementary Figure 9: Liver TDI correlation with individual PDIs**

Each panel presents the ranked PDI values of a particular physiological marker (y-axis) as a function of the ranked liver TDI (x-axis). Each dot represents one animal, color-codes denote the different experimental groups. The dashed lines are linear regression lines. Refer to Supplementary Table 1 for complete details concerning the physiological markers. The Spearman correlations values and their respective p-values are given in Supplementary Table 7.
10. Supplementary Figure 10: Liver MDI correlation with individual PDIs

Deviations from the baseline liver metabolome (MDI) are correlated with deviations from the normal physiology (PDIs) in markers that are known to be associated with liver functions. Bar lengths represent the Spearman correlations between the hepatic MDI and PDIs of the measured 26 physiological markers. The liver has a central role in lipid metabolism, reflected in the relatively high correlations of its MDI and the physiological markers at the bottom part of the figure. WAT stands for white adipose tissue, ratio visc/sub WAT for ratio of visceral to subcutaneous WAT. Asterisks mark statistically-significant correlations (using the Benjamini-Hochberg correction for multiple hypotheses testing with a 5% FDR level). One marker (plasma MCP-1) had a negative correlation of -0.11 with the liver MDI, which is not shown in this figure.
11. Supplementary Figure 11: Liver MDI correlation with individual PDIs (scatter plots)

Each panel presents the ranked PDI values of a particular physiological marker (y-axis) as a function of the ranked liver MDI (x-axis). Each dot represents one animal, color-codes denote the different experimental groups. The dashed lines are linear regression lines. Refer to Supplementary Table 1 for complete details concerning the physiological markers. The Spearman correlations values and their respective p-values are given in Supplementary Table 8.
12. **Supplementary Figure 12: Drugs that induce major non-restorative gene expression alterations**

This figure reproduces Figure 1a-b from the main text, highlighting the four “outlier” drugs, Fenofibrate (pink) and T0901317 (purple) in the liver, and the two thiazolidinediones rosiglitazone (dark cyan) and pioglitazone (light cyan). These drugs induce major gene expression changes that are not congruent with reversal of the disease transcriptomic patterns. The direction of reversal is denoted by the dashed arrow that connects the HFD centroid (yellow square, circled in red) to the LFD centroid (yellow triangle, circled in blue).
13. **Supplementary Figure 13: Non-restorative gene expression alterations are associated with unfavorable physiological outcomes**

(a) A schematic illustration demonstrating the definition of non-restorative gene expression alterations. The gene expression space of a particular tissue is shown. Blue, red, and green markers represent LFD, untreated HFD, and treated HFD subjects, respectively. The dashed axis goes from the HFD mean to the LFD mean (yellow square and triangle, respectively). The treatment effects on each subject can be decomposed into two components: (1) reversal of the disease-induced gene expression patterns, which operates along the direction of the axis that goes from the HFD mean to the LFD mean, and (2) additional alterations which are orthogonal to that axis and hence incongruent with the healthy (LFD) state (Methods). We term the latter "non-restorative alterations" and hypothesize that they are associated with unfavorable physiological outcomes. (b-c) The distributions of the magnitudes of non-restorative alterations to the (b) liver and (c) white adipose gene expression induced by the various drugs. In (b) experimental groups are ordered from left to right in the same order that they appear in the legend; in (c) the groups are ordered from left to right as follows: DLI, pioglitazone, rosiglitazone, salicylate, T0901317. Evidently, four drugs induce the largest non-restorative alterations: fenofibrate and T0901317 in the liver and rosiglitazone and pioglitazone in white adipose (compare Figure 1a-b and Supplementary Figure 12). (d) a schematic illustration of the method employed to detect unfavorable outcomes in the physiological data available in the studied animals. Intuitively, a marker was considered as manifesting an unfavorable outcome of a certain treatment if its values in the treated animals were even farther from the LFD baseline than its values in the untreated HFD animals. This is exemplified in the illustration: while the untreated HFD animals (red bar) have higher blood triglycerides levels than the LFD animals (blue bar), the animals treated with a certain bar (green bar) have even higher blood triglycerides than the untreated HFD animals. Hence, the marker represents an unfavorable outcome of the treatment in this case. See the main text for a complete definition that also quantifies the statistical significance of the observation.
14. **Supplementary Figure 14: Unfavorable drug outcomes in physiological marker data**

This figure highlights the statistically-significant unfavorable physiological outcomes that were ascribed to particular drugs. Each panel presents the distribution of one physiological marker, with each bar representing one experimental group, color-coded as in the rest of the paper. Refer to Supplementary Table 1 for details concerning the measured markers, their units etc. A marker was considered as an unfavorable outcome of a certain treatment if its values in the treated animals were even farther from the baseline than its values in the untreated HFD animals in a statistically-significant manner (see main text for details). The figure shows all the statistically-significant associations of an unfavorable physiological outcome and a drug found in the data (i.e., the panels correspond to all the markers, interpreted as unfavorable outcomes, for which a statistically-significant association with at least one drug is detected; boxes shown in the panel correspond to the all the drugs which were associated with this unfavorable outcome). Note that an exception was made in the case of fenofibrate, which was not associated with elevated plasma triglycerides and atherosclerotic lesion area as unfavorable outcomes in a statistically significant manner; it is shown in those panels only for completeness of the presentation. One LFD outlier in the right panel of the middle row had a value of 1.6, but was clipped to a value of 3 (dashed line) for the sake of visualization.
# Supplementary Tables

1. **Supplementary Table 1: List of physiological markers measured in the study animals**

WAT = White Adipose Tissue. 
The termination column indicates the time point at which these markers were measured: 9 weeks for the HFD-9wks group, and 15 or 16 weeks for the other groups.

|   | Physiological marker                              | Units               | Fasted / non-fasted | Termination |
|---|--------------------------------------------------|---------------------|---------------------|-------------|
| 1 | Body weight                                      | g                   | non-fasted          | t=16/t=9    |
| 2 | Liver weight                                     | mg                  | non-fasted          | t=16/t=9    |
| 3 | Heart weight                                     | mg                  | non-fasted          | t=16/t=9    |
| 4 | Visceral WAT                                     | mg                  | non-fasted          | t=16/t=9    |
| 5 | Gonadal WAT                                      | mg                  | non-fasted          | t=16/t=9    |
| 6 | Subcutaneous WAT                                 | mg                  | non-fasted          | t=16/t=9    |
| 7 | Total WAT (visceral + gonadal + subcutaneous)    | mg                  | non-fasted          | t=16/t=9    |
| 8 | Ratio visceral / subcutaneous WAT                 | mg/mg               | non-fasted          | t=16/t=9    |
| 9 | Kidneys weight (total both kidneys)              | mg                  | non-fasted          | t=16/t=9    |
|10 | Liver triglycerides                              | mmol/mg liver       | non-fasted          | t=16/t=9    |
|11 | Atherosclerotic lesion area (*)                  | log_{10}(um^2)      | non-fasted          | t=16/t=9    |
|12 | Urine glucose                                    | mM                  | non-fasted          | t=15/t=9    |
|13 | Plasma cholesterol                               | mM                  | fasted              | t=15/t=9    |
|14 | Plasma triglycerides                             | mM                  | fasted              | t=15/t=9    |
|15 | Plasma glucose                                   | mM                  | fasted              | t=15/t=9    |
|16 | Plasma insulin                                   | ng/ml               | fasted              | t=15/t=9    |
|17 | Plasma glucagon                                  | pg/ml               | non-fasted          | t=16/t=9    |
|18 | Plasma E-selectin                                | ng/ml               | fasted              | t=15/t=9    |
|19 | Plasma VCAM                                      | ug/ml               | fasted              | t=15/t=9    |
|20 | Plasma MCP-1                                     | pg/ml               | non-fasted          | t=16/t=9    |
|21 | Plasma adiponectin                               | ug/ml               | fasted              | t=15/t=9    |
|22 | Plasma leptin                                    | ng/ml               | non-fasted          | t=16/t=9    |
|23 | Plasma resistin                                  | ng/ml               | non-fasted          | t=16/t=9    |
|24 | HOMA insulin resistance                          | (**)                | fasted              | t=15/t=9    |
|25 | QUICKI insulin resistance                        | (***)               | fasted              | t=15/t=9    |
|26 | ACR (urine albumin /                             | ug/mg               | fasted              | t=15/t=9    |
(*) The marker was log-transformed because it was highly skewed, and followed an approximately normal distribution much more closely after taking the log. Note that (Radonjic et al, 2013) did not carry a similar transformation.

(**) computed as \((\text{fasting glucose} \times \text{fasting insulin})/22.5\), fasting glucose in mmol/l and fasting insulin in mU/l (Matthews et al, 1985).

(***) computed as \(1/ [\log(\text{fasting insulin}) + \log(\text{fasting glucose})]\), fasting insulin in uU/ml and fasting glucose in mg/dl (Katz et al, 2000).
2. **Supplementary Table 2: Drug mechanism of action**

The mechanism of action of drugs studied in this paper. Data is based on Drugbank (Law *et al*., 2013) (accessed July 2014) except where otherwise noted.

| Drug       | Mechanism of action                                                                                                                                                                                                                                                                                                                                 |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| metformin  | Metformin’s mechanism of action is two-fold, inhibiting liver glucose production, and additionally augmenting peripheral glucose uptake, mainly in muscles. These effects are believed to be partly mediated by activation of liver kinase B1 (LKB-1) (Shaw *et al*., 2005), which in turn regulates 5’ adenosine monophosphatase-activated protein kinase (AMPK), a key sensor of cellular metabolism and energetics. Nonetheless, metformin has been reported to improve glucose tolerance in liver AMPK-deficient mice (Foretz *et al*., 2010), which suggests that part of its effects occur through AMPK-independent pathways (Rena *et al*., 2013). |
| glibenclamide | Glibenclamide is a second generation sulfonylurea, which stimulate insulin secretion by pancreatic β cells. Sulfonylureas bind to a sulfonylurea receptor that is associated with inward rectifying adenosine triphosphate (ATP)-sensitive potassium channels in β cells. Binding of a sulfonylurea inhibits the efflux of potassium ions through the channels and results in depolarization that opens voltage-gated calcium channels. This leads to calcium influx and to the release of preformed insulin (Nolte Kennedy, 2012). |
| sitagliptin | Sitagliptin inhibits the enzyme dipeptidyl peptidase-4 (DPP-4), which degrades the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic peptide (GIP). Incretins act on pancreatic β-cells to enhance glucose-dependent insulin secretion. Therefore, suppressing their degradation by DPP-4 improves glycemic control (Waget *et al*., 2011; Mudaliar & Henry, 2012). |
| pioglitazone | Pioglitazone and rosiglitazone are thiazolidinediones (TZDs), which exert their antidiabetic effects through activation of the gamma isoform of the peroxisome proliferator-activated receptor (PPARγ), a transcription factor that is highly expressed in adipose tissue, and is known to be a key regulator of adipogenesis and insulin sensitivity (Escher *et al*., 2001; Larsen *et al*., 2003; Evans *et al*., 2004; Vasudevan & Balasubramanyam, 2004; Poulsen *et al*., 2012; Ahmadian *et al*., 2013). Activation of PPARγ receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization. Thus, TZDs improve glycemic control in type 2 diabetic patients through insulin sensitization, rather than increased insulin secretion by pancreatic β cells (Soccio *et al*., 2014). |
| fenofibrate | The chief mode of action of fenofibrate is binding to PPARα, a transcription factor that is highly expressed in the liver (as well is in brown, but not white, adipose cells) (Escher *et al*., 2001; Evans *et al*., 2004; Oosterveer *et al*., 2009; Poulsen *et al*., 2012). Upon its activation PPARα heterodimerizes with retinoid X receptor (RXR); the heterodimers
recognize specific PPARα response elements and modulate the expression of genes responsible for fatty acids and cholesterol metabolism (Staels et al, 1998). The decrease in plasma triglycerides induced by fibrates has been attributed to an inhibition of the synthesis and secretion of VLDL by the liver and increased degradation of triglyceride-rich lipoproteins through the expression of lipoprotein lipase and a decreased expression of apolipoprotein CIII (Forcheron et al, 2002).

| T0901317 | T0901317 is a synthetic Liver X Receptor (LXR) agonist. LXR has two isoforms, one of them (LXRβ) is ubiquitously expressed, whereas the other (LXRα) is restricted to particular tissues, including the liver. LXRs regulates lipid and cholesterol metabolism and also have anti-inflammatory properties (Schultz et al, 2000; Steffensen & Gustafsson, 2004; Ulven et al, 2005; Zhao & Dahlman-Wright, 2010). T0901317 has been found unsuitable for clinical use due to its pleotropic effects, but LXRs continue to be studied as an attractive drug targets (Jakobsson et al, 2012; Hong & Tontonoz, 2014). |
| atorvastatin | Atorvastatin lowers LDL cholesterol by inhibiting hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate in the cholesterol biosynthesis pathway. Ample evidence support that statins’ protective cardiovascular effects is not restricted to cholesterol metabolism but may also be related to their anti-inflammatory properties (Tousoulis et al, 2014). |
| salicylate | Salicylates are anti-inflammatory compounds that inhibit the activity of both types of cyclooxygenase (COX-1 and COX-2) and thus suppress platelet thromboxane synthesis. The artificial derivative acetylsalicylic acid, better known as aspirin, is broadly used to prevent atherosclerotic complications, most importantly myocardial infarction and ischemic stroke (Awtry & Loscalzo, 2000; Campbell et al, 2007; American Diabetes Association, 2013). Aspirin effectively inhibits platelet aggregation, yet this effect is partly mediated through its acetyl group (Furst et al, 2012; Steinberg et al, 2013). There may also be other mechanisms through which salicylates exert their favorable effects, such as inhibition of the pro-inflammatory κ-light-chain-enhancer of activated B cells (NF-κB) signaling pathway ((Kopp & Ghosh, 1994) but see also (Frantz et al, 1995; Steinberg et al, 2013) ), and activation of AMPK (Hawley et al, 2012; Steinberg et al, 2013) that is also a target of metformin (see above). Notably, it has long been observed that salicylates have positive outcomes in in diabetic patients (Williamson, 1901; Gilgore, 1960; Gilgore & Rupp, 1962; Baron, 1982; Hundal et al, 2002; Shoelson, 2002; Goldfine et al, 2013). |
| rofecoxib | Rofecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor, which has been withdrawn in 2004 worldwide by Merck & Co, due to an increased risk of cardiovascular events (Praticò & Dogné, 2005). |
3. **Supplementary Table 3: GSEA analysis of the liver transcriptome**

Gene set enrichment analysis (GSEA, (Subramanian et al, 2005)) of the effects of the pharmacological and dietary interventions was conducted on the hepatic transcriptome. The analysis sought KEGG gene sets that were enriched with either upregulated or downregulated genes when comparing the treated animals with the untreated HFD-16weeks group. Comparisons of the LFD and HFD-9weeks groups with the HFD-16weeks groups were made as well for the sake of completeness. The table lists all the KEGG gene sets that were enriched at FDR < 25%. See Supplementary Results 3 for full details of the analysis.

Table columns:

- **Direction:**
  - up = upregulated in the treatment group compared with the HFD-16weeks group.
  - down = downregulated in the treatment group compared with the HFD-16weeks group.
- **Gene set size:** number of genes in the gene set
- **ES, NES:** Enrichment Score and Normalized Enrichment Score, respectively. See (Subramanian et al, 2005).

| Gene set                          | Direction | Gene set size | ES     | NES     | Nominal p-value | FDR q-value |
|----------------------------------|-----------|---------------|--------|---------|----------------|-------------|
| Metformin                        | up        | 53            | -0.52  | -2.28   | 0              | 0.001       |
| Glibenclamide                    | No enriched gene sets |
| Sitagliptin                      | No enriched gene sets |
| Rosiglitazone                    | up        | 53            | -0.52  | -2.28   | 0              | 0.001       |
|                                  | up        | 67            | -0.46  | -1.86   | 0              | 0.036       |
| Pioglitazone                     | down      | 22            | 0.61   | 1.91    | 0.002          | 0.051       |
|                                  | up        | 53            | -0.46  | -1.97   | 0              | 0.015       |
|                                  | up        | 38            | -0.47  | -1.67   | 0.024          | 0.247       |
|                                  | up        | 24            | -0.52  | -1.64   | 0.006          | 0.234       |
|                                  | up        | 65            | -0.44  | -1.63   | 0.004          | 0.187       |
| Fenofibrate                      | up        | 53            | -0.58  | -2.23   | 0              | 0           |
|                                  | up        | 72            | -0.61  | -1.99   | 0              | 0.007       |
|                                  | up        | 38            | -0.77  | -1.88   | 0              | 0.022       |
| Pathway                                                                 | Direction | Z-Score | p-Value | Fold Change |
|------------------------------------------------------------------------|-----------|---------|---------|-------------|
| KEGG_PPAR_SIGNALING_PATHWAY                                            | up        | -0.75   | 0.018   | 65          |
| KEGG_ALZHEIMERS_DISEASE                                               | up        | -0.4    | 0.015   | 129         |
| KEGG_OXIDATIVE_PHOSPHORYLATION                                        | up        | -0.47   | 0.02    | 94          |
| KEGG_PARKINSONS_DISEASE                                               | up        | -0.45   | 0.05    | 92          |
| KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION                        | up        | -0.51   | 0.044   | 41          |
| KEGG_PROPANOATE_METABOLISM                                            | up        | -0.61   | 0.07    | 27          |
| KEGG_GLYCEROPHOSPHOLIPID_METABOLISM                                   | up        | -0.46   | 0.102   | 67          |
| KEGG_GLYCEROlipid_METABOLISM                                          | up        | -0.57   | 0.096   | 42          |
| KEGG_HUNTINGTONS_DISEASE                                              | up        | -0.34   | 0.099   | 136         |
| KEGG_BIOSYNTHESIS_OF_UNSATURATED_FAT ACIDS                            | up        | -0.76   | 0.092   | 19          |
| KEGG_LYSINE_DEGRADATION                                               | up        | -0.46   | 0.087   | 40          |
| KEGG_TRYPTOPHAN_METABOLISM                                            | up        | -0.51   | 0.088   | 35          |
| KEGG_BETA_ALANINE_METABOLISM                                          | up        | -0.59   | 0.145   | 21          |
| KEGG_FRUCTOSE_AND_MANNOSE_METABOLISM                                  | up        | -0.45   | 0.161   | 31          |
| KEGG_ALPHA_LINOLENIC_ACID_METABOLISM                                  | up        | -0.62   | 0.162   | 17          |
| KEGG_ARACHIDONIC_ACID_METABOLISM                                      | up        | -0.52   | 0.158   | 56          |
| KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY                                  | up        | -0.36   | 0.22    | 62          |
| T0901317                                                               | down      | 0.47    | 0.235   | 67          |
| KEGG_COMPLEMENT_AND_COAGULATIONCASCADE                                | down      | 0.56    | 0.182   | 30          |
| KEGG_GLYCINE_SERINE_AND_THREONINE_METABOLISM                           | down      | 0.48    | 0.149   | 27          |
| KEGG_ALANINE ASPARTATE_AND_GLUTAMATE_METABOLISM                        | down      | 0.5     | 0.127   | 30          |
| KEGG_BASAL_TRANSCRIPTION_FACTORS                                      | down      | 0.61    | 0.119   | 15          |
| KEGG_ONE_CARbon_POOL_BY_FOLATE                                        | down      | 0.67    | 0.004   | 53          |
| KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY                                | down      | 0.51    | 0.068   | 66          |
| KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS                                 | down      | 0.53    | 0.055   | 83          |
| KEGG_VIRAL_MYOCARDITIS                                                | up        | -0.56   | 0.084   | 58          |
| KEGG_RETINOL_METABOLISM                                               | up        | -0.6    | 0.081   | 54          |
| KEGG_METABOLISM_OF_XENOBiotics_BY_CYTOCHROME_P450                     | up        | -0.6    | 0.087   | 57          |
| KEGG_FATTY_ACID_METABOLISM                                            | up        | -0.61   | 0.08    | 38          |
| KEGG_ARACHIDONIC_ACID_METABOLISM                                      | up        | -0.65   | 0.073   | 56          |
| KEGG_ALZHEIMERS_DISEASE                                               | up        | -0.36   | 0.076   | 129         |
| KEGG_APOPTOSIS                                                        | up        | -0.41   | 0.073   | 73          |
| KEGG_DRUG_METABOLISM_CYTOCHROME_P450                                  | up        | -0.57   | 0.081   | 57          |
| KEGG_GLYCEROPHOSPHOLIPID_METABOLISM                                   | up        | -0.46   | 0.079   | 67          |
| KEGG_COLORECTAL_CANCER                                                | up        | -0.45   | 0.08    | 56          |
| KEGG_FC_EPSILON RI_SIGNALING_PATHWAY                                  | up        | -0.45   | 0.074   | 73          |
| KEGG_UNOLEIC_ACID_METABOLISM                                          | up        | -0.65   | 0.081   | 28          |
| KEGG_LEISHMANIA_INFECTION                                             | up        | -0.65   | 0.089   | 59          |
| KEGG_LYSOSOME                                                         | up        | -0.36   | 0.11    | 111         |
| KEGG_TYPE_1_DIABETES_MELLITUS                                        | up        | -0.59   | 0.106   | 36          |
| KEGG_PARKINSONS_DISEASE                                               | up        | -0.42   | 0.103   | 92          |
| KEGG_NODLIKE RECEPTOR_SIGNALING_PATHWAY                               | up        | -0.48   | 0.103   | 43          |
| Pathway                                      | Significance | p-value | Adjusted p-value |
|----------------------------------------------|--------------|---------|------------------|
| KEGG_OXIDATIVE_PHOSPHORYLATION              | up           | 94      | -0.36            |
| KEGG_PPAR_SIGNALING_PATHWAY                 | up           | 65      | -0.58            |
| KEGG_RENAL_CELL_CARCINOMA                   | up           | 63      | -0.37            |
| KEGG_LEUKOCYTE_TRANSENDOTHelial_MIGRATION    | up           | 98      | -0.4             |
| KEGG_ALLOGRAFT_REJECTION                    | up           | 31      | -0.61            |
| KEGG_GRAFT_VERSUS_HOST_DISEASE              | up           | 28      | -0.67            |
| KEGG_CELL_ADHESION_MODELS_CAMS             | up           | 112     | -0.45            |
| KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATWAY    | up           | 91      | -0.47            |
| KEGG_ASTHMA                                  | up           | 22      | -0.7             |
| KEGG_VEGF_SIGNALING_PATHWAY                 | up           | 67      | -0.35            |
| KEGG_BIOSYNTHESIS_OF_UNSATURATED_FATACIDS   | up           | 19      | -0.67            |
| KEGG_BLOOD_CANCER                           | up           | 36      | -0.4             |
| KEGG_FRUCTOSE_AND_MANNOSMETABLISM           | up           | 31      | -0.36            |
| KEGG_GLYCEROLIPID_METABOLISM                | up           | 42      | -0.49            |
| KEGG_HUNTINGTONS_DISEASE                    | up           | 136     | 0.3              |
| KEGG_PROPOANOATE_METABOLISM                 | up           | 27      | -0.5             |
| KEGG_Ether_LIPID_METABOLISM                 | up           | 29      | -0.48            |
| KEGG_SPHINGOIPID_METABOLISM                 | up           | 31      | -0.46            |
| KEGG_HEMATOPOIETIC_CELL_LINEAGE             | up           | 72      | -0.51            |
| KEGG_NON_SMALL_CELL_LUNG_CANCER            | up           | 48      | -0.35            |
| KEGG_PENTOSE_PHOSPHATE_PATHWAY              | up           | 25      | -0.49            |
| KEGG_MAPK_SIGNALING_PATHWAY                 | up           | 225     | -0.34            |
| KEGG_PS3_SIGNALING_PATHWAY                  | up           | 59      | -0.42            |
| KEGG_THYROID_CANCER                         | up           | 23      | -0.37            |
| KEGG_GLUTATHIONE_METABOLISM                 | up           | 45      | -0.47            |
| KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION    | up           | 63      | -0.45            |
| KEGG_ENDOCYTOSIS                            | up           | 144     | -0.3             |
| KEGG_PATHOGENIC_ESCHERICHIA_COLI_INFECTION  | up           | 42      | -0.42            |
| KEGG_PROSTATE_CANCER                        | up           | 95      | -0.33            |
| KEGG_CHRONIC_MYELOID_LEUKEMIA               | up           | 63      | -0.36            |
| KEGG_PANCREATIC_CANCER                      | up           | 65      | -0.33            |
| KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY | up       | 99      | -0.39            |
| KEGG_AUTOIMMUNE_THYROID_MEDIATED_CYTOTOXICITY| up       | 44      | -0.48            |
| KEGG_PATHWAYS_IN_CANCER                     | up           | 305     | -0.3             |
| KEGG_ECM_RECEPOTOR_INTERACTION              | up           | 72      | -0.4             |
| KEGG_CHEMOKINE_SIGNALING_PATHWAY            | up           | 149     | -0.35            |
| KEGG_REGULATION_OF_ACTIN_CYTOSKELETON       | up           | 181     | -0.31            |
| KEGG_GLYCOLYSIS_GLUCONEOGENESIS             | up           | 49      | -0.39            |
| KEGG_SYSTEMIC_LUPUSERYTHEMATOSUS            | up           | 98      | -0.4             |

**Atorvastatin**

| Pathway                                      | Significance | p-value | Adjusted p-value |
|----------------------------------------------|--------------|---------|------------------|
| KEGG_SNARE_INTERACTIONS_IN_VESICULAR_TRANSPORT | down        | 32      | 0.48             |
| KEGG_PROPOANOATE_METABOLISM                  | up           | 27      | -0.6             |
| KEGG_FATTY_ACID_METABOLISM                   | up           | 38      | -0.5             |
| Salicylate | No enriched gene sets |
|-----------|---------------------|
| Rofecoxib | No enriched gene sets |
| **KEGG_MISMATCH_REPAIR** | **down** | 22 | 0.58 | 1.76 | 0.002 | 0.227 |
| **LFD** | **KEGG_GLYCOLYSIS_GLUCONEOGENESIS** | **down** | 49 | 0.44 | 1.7 | 0.002 | 0.611 |
|  | **KEGG_RIBOSOME** | **up** | 53 | -0.48 | -1.99 | 0.004 | 0.016 |
|  | **KEGG_DRUG_METABOLISM_CYTOCHROME_P450** | **up** | 57 | -0.57 | -1.76 | 0.002 | 0.105 |
|  | **KEGG_RIBOSOME** | **up** | 53 | -0.55 | -1.71 | 0.002 | 0.113 |
|  | **KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450** | **up** | 57 | -0.55 | -1.7 | 0.002 | 0.092 |
|  | **KEGG_TYROSINE_METABOLISM** | **up** | 33 | -0.58 | -1.65 | 0.01 | 0.117 |
|  | **KEGG_SPLICEOSOME** | **up** | 81 | -0.32 | -1.64 | 0.006 | 0.114 |
|  | **KEGG_N_GLYCAN_BIOSYNTHESIS** | **up** | 42 | -0.39 | -1.63 | 0.03 | 0.105 |
|  | **KEGG_TRYPTOPHAN_METABOLISM** | **up** | 35 | -0.43 | -1.55 | 0.035 | 0.182 |
|  | **KEGG_LINOLEIC_ACID_METABOLISM** | **up** | 28 | -0.61 | -1.55 | 0.012 | 0.162 |
|  | **KEGG_PROTEIN_EXPORT** | **up** | 20 | -0.55 | -1.51 | 0.074 | 0.198 |
|  | **KEGG_CYSTEINE_AND_METHIONINE_METABOLISM** | **up** | 28 | -0.47 | -1.47 | 0.07 | 0.229 |
|  | **KEGG_ASCORBATE_AND_ALDARATE_METABOLISM** | **up** | 19 | -0.57 | -1.46 | 0.076 | 0.225 |
|  | **KEGG_ALANINE_ASPARTATE_AND_GLUTAMATE_METABOLISM** | **up** | 27 | -0.42 | -1.44 | 0.047 | 0.245 |
|  | **KEGG_SELENOAMINO_ACID_METABOLISM** | **up** | 23 | -0.45 | -1.44 | 0.101 | 0.23 |
|  | **KEGG_FATTY_ACID_METABOLISM** | **up** | 38 | -0.35 | -1.44 | 0.118 | 0.215 |
|  | **KEGG_PHENYLALANINE_METABOLISM** | **up** | 16 | -0.56 | -1.43 | 0.057 | 0.216 |
|  | **KEGG_NITROGEN_METABOLISM** | **up** | 17 | -0.59 | -1.41 | 0.087 | 0.233 |
| **HFD-9weeks** | **KEGG_RIBOSOME** | **up** | 53 | -0.51 | -2.05 | 0 | 0.001 |
| **DLI** | **KEGG_RIBOSOME** | **up** | 53 | -0.53 | -2.05 | 0 | 0.004 |
|  | **KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450** | **up** | 57 | -0.54 | -1.73 | 0 | 0.11 |
|  | **KEGG_DRUG_METABOLISM_CYTOCHROME_P450** | **up** | 57 | -0.55 | -1.72 | 0 | 0.082 |
|  | **KEGG_RETINOL_METABOLISM** | **up** | 54 | -0.48 | -1.6 | 0.006 | 0.191 |
|  | **KEGG_PHENYLALANINE_METABOLISM** | **up** | 16 | -0.62 | -1.58 | 0.041 | 0.191 |
|  | **KEGG_NITROGEN_METABOLISM** | **up** | 17 | -0.64 | -1.51 | 0.049 | 0.246 |
4. **Supplementary Table 4: GSEA analysis of the adipose transcriptome**

This table presents the results of an analysis parallel to the one presented in Supplementary Table 3, conducted on the white adipose, rather than the liver, transcriptome. Refer to the legend of Supplementary Table 3 for further details.

| Gene set                              | Direction | Gene set size | ES   | NES   | Nominal p-value | FDR q-value |
|---------------------------------------|-----------|---------------|------|-------|-----------------|-------------|
| **Rosiglitazone**                     |           |               |      |       |                 |             |
| KEGG_HUNTINGTONS_DISEASE              | up        | 136           | -0.55| -2.02 | 0               | 0.005       |
| KEGG_PARKINSONS_DISEASE               | up        | 92            | -0.65| -1.95 | 0               | 0.005       |
| KEGG_ALZHEIMERS_DISEASE               | up        | 129           | -0.44| -1.9  | 0.002           | 0.011       |
| KEGG_AMINOACYL_TRNA_BIOSYNTHESIS      | up        | 37            | -0.55| -1.86 | 0.012           | 0.014       |
| KEGG_PEROXISOME                       | up        | 72            | -0.58| -1.79 | 0.012           | 0.026       |
| KEGG_CITRATE_CYCLE_TCA_CYCLE         | up        | 28            | -0.83| -1.78 | 0.002           | 0.024       |
| KEGG_OXIDATIVE_PHOSPHORYLATION       | up        | 94            | -0.58| -1.77 | 0.002           | 0.023       |
| KEGG_PPAR_SIGNALING_PATHWAY           | up        | 65            | -0.62| -1.63 | 0.004           | 0.087       |
| KEGG_FATTY_ACID_METABOLISM            | up        | 38            | -0.69| -1.62 | 0.024           | 0.09        |
| KEGG_REGULATION_OF_AUTOPHagy         | up        | 30            | -0.48| -1.6  | 0.006           | 0.088       |
| KEGG_LYSINE_DEGRADATION               | up        | 40            | -0.51| -1.57 | 0.028           | 0.103       |
| KEGG_CARDIAC_MUSCLE_CONTRACTION       | up        | 54            | -0.43| -1.54 | 0.011           | 0.124       |
| KEGG_VALINE_LEUCINE_AND_ISOUCINE_D_EGRADATION | up     | 41            | -0.55| -1.5  | 0.085           | 0.151       |
| KEGG_GLYCEROPHOSPHOLIPID_METABOLISM   | up        | 67            | -0.39| -1.47 | 0.019           | 0.175       |
| KEGG_PYRUVATE_METABOLISM              | up        | 33            | -0.54| -1.47 | 0.09            | 0.17        |
| KEGG_TASTE_TRANSDUCTION               | up        | 41            | -0.46| -1.42 | 0.033           | 0.222       |
| **Pioglitazone**                      |           |               |      |       |                 |             |
| KEGG_TYPE_I_DIABETES_MELLITUS         | down      | 36            | 0.55 | 1.44  | 0.053           | 0.246       |
| KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION | down   | 63            | 0.44 | 1.44  | 0.028           | 0.245       |
| KEGG_PEROXISOME                       | up        | 72            | -0.59| -1.86 | 0.002           | 0.044       |
| KEGG_FATTY_ACID_METABOLISM            | up        | 38            | -0.69| -1.83 | 0               | 0.035       |
| KEGG_PPAR_SIGNALING_PATHWAY           | up        | 65            | -0.62| -1.7  | 0               | 0.119       |
| KEGG_AMINOACYL_TRNA_BIOSYNTHESIS      | up        | 37            | -0.47| -1.66 | 0.031           | 0.139       |
| KEGG_CITRATE_CYCLE_TCA_CYCLE         | up        | 28            | -0.74| -1.63 | 0.008           | 0.148       |
| KEGG_PARKINSONS_DISEASE               | up        | 92            | -0.44| -1.62 | 0.033           | 0.139       |
| KEGG_BETA_ALANINE_METABOLISM          | up        | 21            | -0.53| -1.6  | 0.013           | 0.146       |
| KEGG_REGULATION_OF_AUTOPHagy         | up        | 30            | -0.46| -1.56 | 0               | 0.184       |
| KEGG_PYRUVATE_METABOLISM              | up        | 33            | -0.53| -1.53 | 0.029           | 0.223       |
| KEGG_LYSINE_DEGRADATION               | up        | 40            | -0.44| -1.49 | 0.046           | 0.263       |
| KEGG_HUNTINGTONS_DISEASE              | up        | 136           | -0.35| -1.49 | 0.075           | 0.242       |
| **T0901317**                          |           |               |      |       |                 |             |
| No enriched gene sets                 |           |               |      |       |                 |             |
| **Salicylate**                        |           |               |      |       |                 |             |
| KEGG_PARKINSONS_DISEASE               | up        | 92            | -0.46| -1.81 | 0.006           | 0.127       |
| KEGG_AMINOACYL_TRNA_BIOSYNTHESIS      | up        | 37            | -0.49| -1.8  | 0.014           | 0.077       |
| **LFD**                               |           |               |      |       |                 |             |
| KEGG_PATHWAY                                      | State | Value   | p-value | Adjusted p-value | 
|--------------------------------------------------|-------|---------|---------|------------------| 
| KEGG_SYSTEMIC_LUPUSERYTHEMATOSUS                 | down  | 98      | 0.59    | 1.72             | 0       | 0.203    |
| KEGG_ALLOGRAFT_REJECTION                         | down  | 31      | 0.62    | 1.7              | 0.004   | 0.18     |
| KEGG_LEISHMANIA_INFECTION                        | down  | 59      | 0.65    | 1.69             | 0.016   | 0.141    |
| KEGG_GRAFT_VERSUS_HOST_DISEASE                   | down  | 28      | 0.63    | 1.68             | 0.006   | 0.131    |
| KEGG_TYPE_1_DIABETES_MELLITUS                    | down  | 36      | 0.56    | 1.67             | 0.006   | 0.121    |
| KEGG_LYSOSOME                                    | down  | 111     | 0.51    | 1.66             | 0.029   | 0.112    |
| KEGG_PATHOGENIC_ESCHERICHIA_COLI_INFECTION       | down  | 42      | 0.49    | 1.64             | 0.004   | 0.121    |
| KEGG_CELL_CYCLE                                  | down  | 108     | 0.48    | 1.64             | 0.008   | 0.109    |
| KEGG_SPHINGOLIDＵMETABOLISM                       | down  | 31      | 0.56    | 1.63             | 0.014   | 0.103    |
| KEGG_TOLL LIKE RECEPTOR_SIGNALING_PATHWAY         | down  | 91      | 0.5     | 1.62             | 0.006   | 0.101    |
| KEGG_PS3_SIGNALING_PATHWAY                       | down  | 59      | 0.48    | 1.56             | 0.018   | 0.125    |
| KEGG_EPITHELIAL_CELL_SIGNALING_IN_HELICOBACTER_PYLOРИN_INFECTION | down  | 59      | 0.4     | 1.56             | 0.015   | 0.154    |
| KEGG_NOD LIKE RECEPTOR_SIGNALING_PATHWAY         | down  | 43      | 0.47    | 1.56             | 0.036   | 0.155    |
| KEGG_HOMOLOGOUS_RECOMBINATION                    | down  | 23      | 0.47    | 1.54             | 0.052   | 0.161    |
| KEGG_ECM_RECEPTOR_INTERACTION                    | down  | 72      | 0.43    | 1.54             | 0.006   | 0.154    |
| KEGG_HEMATOPOIETIC_CELL_LINEAGE                 | down  | 72      | 0.5     | 1.54             | 0.028   | 0.147    |
| KEGG_OTHER_GLYCAN_DEGRADATION                    | down  | 15      | 0.57    | 1.53             | 0.05    | 0.15     |
| KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY           | down  | 66      | 0.5     | 1.52             | 0.04    | 0.157    |
| KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY           | down  | 97      | 0.47    | 1.48             | 0.056   | 0.194    |
| KEGG_GLIOMA                                      | down  | 54      | 0.41    | 1.48             | 0.044   | 0.185    |
| KEGG_PRIMARY_IMMUNODEFICIENCY                    | down  | 32      | 0.62    | 1.48             | 0.04    | 0.18     |
| KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY   | down  | 99      | 0.45    | 1.47             | 0.039   | 0.188    |
| KEGG_CELL_ADHESION_MOLECULES_CAMS               | down  | 112     | 0.43    | 1.47             | 0.014   | 0.19     |
| KEGG_VIBRIO_CHOLERA_E_INFECTION                 | down  | 46      | 0.41    | 1.45             | 0.053   | 0.205    |
| KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION | down  | 37      | 0.55    | 1.45             | 0.075   | 0.2      |
| KEGG_FC_EPSILON_RI_SIGNALING_PATHWAY             | down  | 73      | 0.43    | 1.44             | 0.049   | 0.206    |
| KEGG_COMPLEMENT_AND_COAGULATION_CASCADES         | down  | 67      | 0.39    | 1.44             | 0.008   | 0.199    |
| KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS            | down  | 83      | 0.44    | 1.42             | 0.085   | 0.212    |
| KEGG_JAK_STAT_SIGNALING_PATHWAY                  | down  | 140     | 0.33    | 1.41             | 0.006   | 0.225    |
| KEGG_APOPTOSIS                                   | down  | 73      | 0.33    | 1.41             | 0.087   | 0.219    |
| KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION        | down  | 63      | 0.43    | 1.41             | 0.079   | 0.216    |
| KEGG_VIRAL_MYOCARDITIS                           | down  | 58      | 0.42    | 1.4              | 0.097   | 0.215    |
| KEGG_CHEMOKINE_SIGNALING_PATHWAY                 | down  | 149     | 0.39    | 1.39             | 0.034   | 0.229    |
| KEGG_PROTEASOME                                  | down  | 41      | 0.38    | 1.38             | 0.181   | 0.24     |
| KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION      | down  | 219     | 0.36    | 1.37             | 0.016   | 0.243    |
| KEGG_CITRATE_CYCLE_TCA_CYCLE                    | up     | 28      | -0.63   | -1.7             | 0.01    | 0.149    |
| KEGG_VALINE_LEUCINE_AND_ISOULEUCINE_DEGRADATION  | up     | 41      | -0.57   | -1.69            | 0.004   | 0.105    |
| KEGG_PROPOANOATE_METABOLISM                      | up     | 27      | -0.56   | -1.67            | 0.012   | 0.107    |
| KEGG_AMINOCYCL_TRNA_BIOSYNTHESIS                 | up     | 37      | -0.46   | -1.66            | 0.025   | 0.096    |
| KEGG_BETA_ALANINE_METABOLISM                     | up     | 21      | -0.53   | -1.65            | 0.01    | 0.084    |
| KEGG_NICOTINATE_AND_NICOTINAMIDE_METABOLISM      | up     | 18      | -0.52   | -1.52            | 0.027   | 0.24     |
| Pathway                                      | Direction | FDR  | Z-score | q-value | Adj. p-value |
|----------------------------------------------|-----------|------|---------|---------|--------------|
| KEGG_FRUCTOSE_AND_MANNOSE_METABOLISM         | down      | 31   | 0.55    | 1.78    | 0.002        |
| KEGG_AMINOACYL_TRNA_BIOSYNTHESIS             | up        | 37   | -0.48   | -1.78   | 0.018        |
| KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION | up        | 41   | -0.55   | -1.68   | 0.006        |
| KEGG_SELENOAMINO_ACID_METABOLISM            | up        | 23   | -0.54   | -1.67   | 0.016        |
| KEGG_PROPAANOATE_METABOLISM                 | up        | 27   | -0.5    | -1.65   | 0.02         |
| KEGG_CITRATE_CYCLE_TCA_CYCLE                | up        | 28   | -0.65   | -1.61   | 0.028        |

| Pathway                                      | Direction | FDR  | Z-score | q-value | Adj. p-value |
|----------------------------------------------|-----------|------|---------|---------|--------------|
| KEGG_ASTHMA                                   | down      | 22   | 0.59    | 1.59    | 0.029        |
| KEGG_ECM_RECEPTOR_INTERACTION                | down      | 72   | 0.48    | 1.57    | 0.018        |
| KEGG_LEISHMANIA_INFECTION                     | down      | 59   | 0.51    | 1.52    | 0.061        |
| KEGG_PROPAANOATE_METABOLISM                  | up        | 27   | -0.58   | -1.89   | 0.002        |
| KEGG_CITRATE_CYCLE_TCA_CYCLE                 | up        | 28   | -0.62   | -1.73   | 0            |
| KEGG_BUTANOATE_METABOLISM                    | up        | 31   | -0.62   | -1.71   | 0.002        |
| KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION | up        | 41   | -0.53   | -1.69   | 0.025        |
| KEGG_LYSINE_DEGRADATION                      | up        | 40   | -0.45   | -1.61   | 0.014        |
| KEGG_PYRUVATE_METABOLISM                     | up        | 33   | -0.5    | -1.58   | 0.077        |
5. **Supplementary Table 5: Probes used to construct the liver gene expression space**

N/A = Not available

| nuID | Entrez gene ID | Gene symbol | Synonym | Illumina probe ID |
|------|----------------|-------------|---------|------------------|
| 1    | 72056          | 1810055G02Rik | 1810055G02Rik | ILMN_2650275    |
| 2    | 70113          | Odf3b       | 2010001J22Rik | ILMN_1251371    |
| 3    | 69134          | Fam25c      | 2200001115Rik | ILMN_2678637    |
| 4    | N/A            | N/A         | 2310047D13Rik | ILMN_2543108    |
| 5    | 71003          | Prss41      | 4931440B09Rik | ILMN_2650180    |
| 6    | 27413          | Abcb11      | Abcb11   | ILMN_2758509    |
| 7    | 26874          | Abcg5       | Abcg5    | ILMN_2725781    |
| 8    | 67470          | Abcg8       | Abcg8    | ILMN_2789904    |
| 9    | 216725         | Adamts2     | Adamts2  | ILMN_2729103    |
| 10   | 216725         | Adamts2     | Adamts2  | ILMN_1226259    |
| 11   | 268822         | Adck5       | Adck5    | ILMN_2918317    |
| 12   | 71562          | Afmid       | Afmid    | ILMN_2702894    |
| 13   | 71562          | Afmid       | Afmid    | ILMN_2702894    |
| 14   | 71562          | Afmid       | Afmid    | ILMN_2702894    |
| 15   | 71562          | Afmid       | Afmid    | ILMN_2702894    |
| 16   | 71562          | Afmid       | Afmid    | ILMN_2702894    |
| 17   | 71562          | Afmid       | Afmid    | ILMN_2702894    |
| 18   | 71562          | Afmid       | Afmid    | ILMN_2702894    |
| 19   | 71562          | Afmid       | Afmid    | ILMN_2702894    |
| 20   | 71760          | Agxt2l1     | Agxt2l1  | ILMN_2661820    |
| 21   | 71760          | Agxt2l1     | Agxt2l1  | ILMN_1229990    |
| 22   | 269378         | Ahcy         | Ahcy     | ILMN_2852533    |
| 23   | 432720         | Akr1c19     | Akr1c19  | ILMN_3160292    |
| 24   | 107747         | Aldh1l1     | Aldh1l1  | ILMN_3100276    |
| 25   | 107747         | Aldh1l1     | Aldh1l1  | ILMN_3027287    |
| 26   | 74018          | Als2        | Als2     | ILMN_2620053    |
| 27   | 12306          | Anxa2       | Anxa2    | ILMN_2657175    |
| 28   | 11808          | Apoa4       | Apoa4    | ILMN_2834123    |
| 29   | 66113          | Apoa5       | Apoa5    | ILMN_2641301    |
| 30   | 11813          | Apoc2       | Apoc2    | ILMN_2647820    |
| 31   | 11865          | Arntl       | Arntl    | ILMN_2707510    |
| 32   | 74008          | Arsg        | Arsg     | ILMN_2732601    |
| 33   | 27053          | Asns        | Asns     | ILMN_2643513    |
| 34   | 27053          | Asns        | Asns     | ILMN_3006123    |
|   |   |   |   |   |
|---|---|---|---|---|
| 35 | HRAuB61uPgBuu_e0N4 | 54140 | Avpr1a | Avpr1a | ILMN_1242999 |
| 36 | InQzHfuo.UrM870f8 | 230789 | Fam76a | BC008163 | ILMN_1242176 |
| 37 | iUo5eQoCq13KFVw0g | 227622 | BC029214 | BC029214 | ILMN_2768209 |
| 38 | H5u.9cAXTJHuJ_nhU | 208164 | Fam180a | BC064033 | ILMN_2833163 |
| 39 | 9UngQivg80jTVEJWe | 63857 | Bcmo1 | Bcmo1 | ILMN_2713638 |
| 40 | fmsnpXAXSpQzrn3Nw | 71911 | Bdh1 | Bdh1 | ILMN_1231553 |
| 41 | N6lXjusorjS_RukIlo | 12111 | Bgn | Bgn | ILMN_2964042 |
| 42 | Tcqlplve.M.6BfXgo | 20899 | Bhlhe40 | Bhlheb2 | ILMN_1249378 |
| 43 | QGSk6CkmF5Qpwqbk | 55950 | Bri3 | Bri3 | ILMN_2700334 |
| 44 | HERI41YuB1XREflSk | 110382 | C8b | C8b | ILMN_1227404 |
| 45 | TrfRi5fopUuYfl3g | 67426 | Adck3 | Cabc1 | ILMN_2800813 |
| 46 | 90TfnULVf1BDP0ufeQ | 12338 | Capn6 | Capn6 | ILMN_2695143 |
| 47 | rq3K7qDfp603_X3np4 | 23831 | Car14 | Car14 | ILMN_2973824 |
| 48 | Zb.t7_jc75937GgSsM | 231214 | Car14 | Car14 | ILMN_2973824 |
| 49 | HnENch10g0C99R2s | 20308 | Clpx | Clpx | ILMN_2613869 |
| 50 | We9.KTeMv1kt6TwKT4 | 270166 | Clpx | Clpx | ILMN_2613869 |
| 51 | xnLoik_v1SeqU8sEk | 270166 | Clpx | Clpx | ILMN_3154849 |
| 52 | cX26Ex0T0p.60_dw9P0 | 68396 | Nat8 | Cml4 | ILMN_1216539 |
| 53 | 0UCfEod46vuDv7nPXs | 107581 | Col16a1 | Col16a1 | ILMN_1248099 |
| 54 | EJWl20G7n3r_5dQl9o | 246277 | Csad | Csad | ILMN_2810624 |
| 55 | il5QPrtRabohNP_vsg | 107869 | Cth | Cth | ILMN_2733193 |
| 56 | x5Ioh9Lz.kV_wBkp9Q | 55985 | Cxcl13 | Cxcl13 | ILMN_2760019 |
| 57 | fuYqk6Cjk5vioFJyKU | 13074 | Cyp1a17a | Cyp1a17a | ILMN_2874352 |
| 58 | IVSeuZc911N95yxe | 13077 | Cyp1a2 | Cyp1a2 | ILMN_2739847 |
| 59 | ZuheVBzq_FOCVqF7g | 13077 | Cyp1a2 | Cyp1a2 | ILMN_2795106 |
| 60 | Qbi0qqDwmeelmd5F9s | 13082 | Cyp26a1 | Cyp26a1 | ILMN_2691295 |
| 61 | xsnnRFFX3HvvdQ11Ck | 13094 | Cyp2b9 | Cyp2b9 | ILMN_2617625 |
| 62 | HS.3j1_787s1PfiwAw | 13095 | Cyp2c29 | Cyp2c29 | ILMN_2769991 |
| 63 | 9e40V4p.DOef1EeeHc | 13096 | Cyp2c37 | Cyp2c37 | ILMN_2691060 |
| 64 | Z3unFwKfw9Hn9RHoRE | 13096 | Cyp2c37 | Cyp2c37 | ILMN_2691059 |
| 65 | 3dTNe0HPKhN3dHXdE | 72082 | Cyp2c55 | Cyp2c55 | ILMN_2736539 |
| 66 | QXtc7F5N6y1_ODpKj | 226105 | Cyp2c70 | Cyp2c70 | ILMN_1245514 |
| 67 | 6ko4jY4p3IQqpF1R4s | 13112 | Cyp3a11 | Cyp3a11 | ILMN_2753183 |
| 68 | ZdV9Ad1F.SfE.CflfM | 13118 | Cyp4a12b | Cyp4a12b | ILMN_1217072 |
| 69 | I7bUp7Yw1SgfG7N6i | 28042 | Ept1 | D5Swus178e | ILMN_1253323 |
| 70 | xUut6UnK5WClO0OSEA | 13170 | Dbp | Dbp | ILMN_2616226 |
| 71 | 9XVJXSiRs8MLlE6g | 13171 | Dbt | Dbt | ILMN_2820948 |
| 72 | Wgp9kCnOZw6iSt0kk | 13190 | Dct | Dct | ILMN_1251894 |
| 73 | BWhQei4VUJwpTn02w | 67880 | Dcrr | Dcrr | ILMN_2868280 |
| 74 | BTT1iEL_.5xN_e7mdk | 13195 | Ddc | Ddc | ILMN_2628647 |
|   | Description | Accession | Score | Description | Accession | Score | Description | Accession | Score |
|---|-------------|-----------|-------|-------------|-----------|-------|-------------|-----------|-------|
| 75 | KX0hOexHHq4eoeBSA5w | 54722 | Dfna5 | Dfna5h | ILMN_2652482 |
| 76 | NVQpex1EUfocTEXAek | 23856 | Dido1 | Dido1 | ILMN_1257214 |
| 77 | iv7XgrWekiHolSp4v4 | 13370 | Dio1 | Dio1 | ILMN_2772070 |
| 78 | 3deCOG0AnQ107UP_Uc | 13370 | Dio1 | Dio1 | ILMN_2647234 |
| 79 | Edk7qf_wfrK7qiieU | 13436 | Dnmt3b | Dnmt3b | ILMN_1252310 |
| 80 | r18pXoRCYf4VluVFSI | 207521 | Dtx4 | Dtx4 | ILMN_2651706 |
| 81 | xuYs4mVP66QQsviKCo | 67603 | Ear12 | Ear12 | ILMN_2925711 |
| 82 | rk0UtooggRfMVdjFBQ | 503845 | Ear4 | Ear4 | ILMN_2868480 |
| 83 | uWCefi1Yf7deee_ofs | 13370 | Dnmt3b | Dnmt3b | ILMN_1252310 |
| 84 | QqPtGFPOOghOAU6Xgk | 13909 | Ces3b | EG13909 | ILMN_2733745 |
| 85 | ohKcUISD0gDUKJXaX0 | 241041 | Gm4956 | EG241041 | ILMN_2911009 |
| 86 | xuYs4mVP66QQsviKCo | 13370 | Ear12 | Ear12 | ILMN_2925711 |
| 87 | 6pwHkgiNnm6CRq4Uhc | 12686 | Eps8l2 | Eps8l2 | ILMN_2652757 |
| 88 | BtfjSTYO.gVG5ehl9U | 14571 | Gpld1 | Gpld1 | ILMN_2892441 |
| 89 | ciiXb5RL_UsEuo9h6l | 229599 | Gm129 | Gm129 | ILMN_3102736 |
| 90 | fVKd59.VePVD_zA7O8 | 14251 | Flot1 | Flot1 | ILMN_1241618 |
| 91 | XuXu1lPoJXoor6HlM | 114142 | Foxp2 | Foxp2 | ILMN_3140000 |
| 92 | ceJOSiX85pYjV1j4m | 56473 | Fads2 | Fads2 | ILMN_2713071 |
| 93 | BUcx053u7DFvFE164 | 76267 | Fads1 | Fads1 | ILMN_2607786 |
| 94 | iVR64ld3mUJOk_FKI | 56636 | Fgf21 | Fgf21 | ILMN_2682207 |
| 95 | HUnxR5FU9bq9M3t0k | 98845 | Fpsg | Fpsg | ILMN_2747070 |
| 96 | ceJOSiX85pYjV1j4m | 13587 | Ear2 | Ear2 | ILMN_1232396 |
| 97 | QUuV5FCPjzfSVNUPw | 14068 | F7 | F7 | ILMN_2708871 |
| 98 | f0b5DgKp.VXdcbEc | 14026 | Evl | Evl | ILMN_2911009 |
| 99 | ceJOSiX85pYjV1j4m | 13909 | Ear12 | Ear12 | ILMN_2925711 |
| 100 | HUnxR5FU9bq9M3t0k | 13436 | Dnmt3b | Dnmt3b | ILMN_1252310 |
| 101 | ceJOSiX85pYjV1j4m | 14251 | Flot1 | Flot1 | ILMN_1241618 |
| 102 | ishlTUNDudqAu9.PQ | 114142 | Foxp2 | Foxp2 | ILMN_3140000 |
| 103 | ciiXb5RL_UsEuo9h6l | 14026 | Evl | Evl | ILMN_2708871 |
| 104 | HUnxR5FU9bq9M3t0k | 98845 | Fpsg | Fpsg | ILMN_2747070 |
| 105 | ceJOSiX85pYjV1j4m | 13909 | Ear2 | Ear2 | ILMN_1232396 |
| 106 | ceJOSiX85pYjV1j4m | 13909 | Ear2 | Ear2 | ILMN_1232396 |
| 107 | ceJOSiX85pYjV1j4m | 13909 | Ear2 | Ear2 | ILMN_1232396 |
| 108 | ceJOSiX85pYjV1j4m | 13909 | Ear2 | Ear2 | ILMN_1232396 |
| 109 | ceJOSiX85pYjV1j4m | 13909 | Ear2 | Ear2 | ILMN_1232396 |
| 110 | ceJOSiX85pYjV1j4m | 13909 | Ear2 | Ear2 | ILMN_1232396 |
| 111 | ceJOSiX85pYjV1j4m | 13909 | Ear2 | Ear2 | ILMN_1232396 |
| 112 | ceJOSiX85pYjV1j4m | 13909 | Ear2 | Ear2 | ILMN_1232396 |
| 113 | ceJOSiX85pYjV1j4m | 13909 | Ear2 | Ear2 | ILMN_1232396 |
| 114 | ceJOSiX85pYjV1j4m | 13909 | Ear2 | Ear2 | ILMN_1232396 |
|   |   |   |   |
|---|---|---|---|
| 115 | NJHru_Oil3SgeXsO4 | 15109 | Hal | Hal | ILMN_2984332 |
| 116 | ZbUXeGnTTVhflitQU | 15486 | Hsd17b2 | Hsd17b2 | ILMN_1213811 |
| 117 | cLqnxnXuuGuvImOeBA | 53415 | Htatip2 | Htatip2 | ILMN_2603834 |
| 118 | 9caWIY4gu1RESdpwA | 114663 | Impa2 | Impa2 | ILMN_2662160 |
| 119 | 00sAkrngdsL3yn1V2l | 16326 | Inhbe | Inhbe | ILMN_1229605 |
| 120 | WnVP3Unt99eX0_ghO | 54139 | Irf6 | Irf6 | ILMN_1216279 |
| 121 | Z6j0IP1p0iglonomI | 16768 | Lag3 | Lag3 | ILMN_2719811 |
| 122 | BvVHSxU0_fuzh_ggqU | 16792 | Laptm5 | Laptm5 | ILMN_1217849 |
| 123 | Zi6gH_T93dfNffsITU | 16854 | Lgals3 | Lgals3 | ILMN_1223317 |
| 124 | l3tR_9ECSX0Ru0ulvY | N/A | N/A | LOC100043671 | ILMN_1258600 |
| 125 | WzolT1HoVo263eF5Dos | N/A | N/A | LOC100045567 | ILMN_1256633 |
| 126 | 0LT9Hsu5Egm3t6u1_4 | N/A | N/A | LOC100046232 | ILMN_2595732 |
| 127 | 9QVQKdenG8zEiZDs48 | N/A | N/A | LOC100047046 | ILMN_2635387 |
| 128 | WXonq6AfxZtF5s4e4U | N/A | N/A | LOC100047937 | ILMN_2706906 |
| 129 | EDaQVXoSlxU6vkgU4 | N/A | N/A | LOC100047937 | ILMN_2703392 |
| 130 | fYmCiJ3SoSMcB3Sleo | N/A | N/A | LOC100048733 | ILMN_2759344 |
| 131 | TXXrfnp9PICE6TP43o | N/A | N/A | LOC676420 | ILMN_2749958 |
| 132 | 9j54e08a6R0Tg3qRck | 67580 | Lrrc18 | Lrrc18 | ILMN_2728504 |
| 133 | ZqeTe7.IdhTfo3wuiC | 67867 | Lrrc28 | Lrrc28 | ILMN_2700699 |
| 134 | 6bDKE3kBENOSVQOFk0 | 109245 | Lrrc39 | Lrrc39 | ILMN_2746123 |
| 135 | H6d6uvhK_nuoXeen5w | 17304 | Mfge8 | Mfge8 | ILMN_3133448 |
| 136 | QKnnHuDOUKHh6IydoE | 76574 | Mfsd2a | Mfsd2 | ILMN_1225764 |
| 137 | IVLRI1UbMduqBezafl | 23945 | MglI | MglI | ILMN_2700408 |
| 138 | ufUF1J6F6KORFXwe4O1 | 17347 | Mknn2 | Mknn2 | ILMN_2733887 |
| 139 | L6J5Foh46d5mK05I5 | 64144 | Mllt1 | Mllt1 | ILMN_2756121 |
| 140 | HhKuXzH_9y5PUK79Kk | 71054 | Mmd2 | Mmd2 | ILMN_1252636 |
| 141 | Bjei8NMDqXqNMUzns | 338467 | Morc3 | Morc3 | ILMN_2874739 |
| 142 | QOSkuuzuHrz56t9Gc | 381269 | Mreg | Mreg | ILMN_2976159 |
| 143 | 05ncVLXohClUSiu4A | 17925 | Myo9b | Myo9b | ILMN_2612484 |
| 144 | ESdC5ZVdFID3Qevluw | 83814 | Nedd4l | Nedd4l | ILMN_2878501 |
| 145 | BXSkiToPsMuEXGNZog | 56349 | Net1 | Net1 | ILMN_2610771 |
| 146 | lq_HS1e1DKMX5nkA | 106582 | Nrm | Nrm | ILMN_2733524 |
| 147 | HeEU03ekX1FD0CkKUy | 18391 | Sigmar1 | Oprs1 | ILMN_1238081 |
| 148 | 0ICkYov4fTdBK2Tqkg | 23972 | Papss2 | Papss2 | ILMN_2638349 |
| 149 | 9saUkCQQejFTr0ceo | 18551 | Pcsk4 | Pcsk4 | ILMN_1245529 |
| 150 | BVLOluj18sdP_issS6k | 18551 | Pcsk4 | Pcsk4 | ILMN_1252464 |
| 151 | WK01VH0eUSWOX0CkFk | 72599 | Pdia5 | Pdia5 | ILMN_1255177 |
| 152 | 0WOCH_FL_4KHXe120 | 72599 | Pdia5 | Pdia5 | ILMN_2607066 |
| 153 | okuH9Eko4dUT6_NEQ | 27273 | Pdk4 | Pdk4 | ILMN_1259322 |
| 154 | xll76CD_TsSoLZo6Iu | 55983 | Pdzn3 | Pdzn3 | ILMN_3156010 |
| ID | Gene Symbol | Description | Start Position | End Position | Reference Gene Expression Count |
|----|-------------|-------------|----------------|--------------|----------------------------------|
| 155 | Kkat9rwr54Qngut7U | Per1 | 18626 | Per1 | ILMN_2813484 |
| 156 | 9ndl7mOOPIbiX5aElo | Per2 | 18627 | Per2 | ILMN_2987862 |
| 157 | flCTUle.38g7ufEau0 | Per2 | 18627 | Per2 | ILMN_2987863 |
| 158 | of33UCE7qfQ60uk6g | Pik3cb | 74769 | Pik3cb | ILMN_2680549 |
| 159 | uJ5QgSar9ZpddOGZQ | Pnkd | 56695 | Pnkd | ILMN_1221275 |
| 160 | 97qi0pCSldX0Ra90Q | Cyth1 | 19157 | PsCd1 | ILMN_2868827 |
| 161 | BFnSNVPS54LALHi.1HxQ | Pxnmp4 | 59038 | Pxnmp4 | ILMN_2688639 |
| 162 | BtFOPzWQJSpYHXLJF4 | Raet1b | 19369 | Raet1b | ILMN_3158725 |
| 163 | Ti11cUh3F3kJfQ10uk6g | C27a6 | 74769 | C27a6 | ILMN_2680549 |
| 164 | NVamOKn.0.XXsesHS0 | Rps6ka1 | 20111 | Rps6ka1 | ILMN_2975718 |
| 165 | 6uKWXSPh7ItR7vn6U | Rtp3 | 235636 | Rtp3 | ILMN_2600744 |
| 166 | fn6VEsk0nPUzXQ.k9U | N/A | 104175 | N/A | ILMN_1224855 |
| 167 | rXFU7v7Ax3p9f6V4oo | Sbkb1 | 14664 | Sbkb1 | ILMN_2680549 |
| 168 | I3f0.rFexVL3m2XXO | Scnn1a | 20276 | Scnn1a | ILMN_2729607 |
| 169 | f5L3JN6N4kdeEcqVdQ | Selenbp2 | 20342 | Selenbp2 | ILMN_2939652 |
| 170 | 0e9h1NdAfzoeyurl5I | Serpin1b1a | 66222 | Serpin1b1a | ILMN_1231573 |
| 171 | 627v5cTXs7ud1rgigg | Scl13a2 | 20500 | Scl13a2 | ILMN_2646369 |
| 172 | Eu4U7Te4u_77OT6U | Scl17a8 | 216227 | Scl17a8 | ILMN_2806439 |
| 173 | EvXnQo_oVct1EkvQNU | Scl45a3 | 212980 | Scl45a3 | ILMN_1218226 |
| 174 | xrtPe03uQc8.X_ov10 | Scl5a6 | 330064 | Scl5a6 | ILMN_1225056 |
| 175 | WVLnI57uSByr.AtbK8 | Slc6a9 | 14664 | Slc6a9 | ILMN_2667384 |
| 176 | Wl9kIX_8eku9.eCUWo | Slc2a1 | 24059 | Slc2a1 | ILMN_2961216 |
| 177 | ZcLkvi6p5fft1KYNPE | Snhg11 | 319317 | Snhg11 | ILMN_2952098 |
| 178 | Kcs_FcINeITM7.U4k | Srpc25 | 66442 | Srpc25 | ILMN_1255960 |
| 179 | INNUBTI3_Kw7_4ngBl | Srpc25 | 66442 | Srpc25 | ILMN_2901180 |
| 180 | iop7gpDpDbxsJCI7c | Spinct2 | 20733 | Spinct2 | ILMN_2645845 |
| 181 | NJWFB17Dk33RmIeHo | Spre2d1 | 114715 | Spre2d1 | ILMN_2490252 |
| 182 | lXOaeKE5Xq64svsYKU | Srpx2 | 68792 | Srpx2 | ILMN_2698728 |
| 183 | BXbuURDtiBEcpu3U | St3gal1 | 20442 | St3gal1 | ILMN_2749178 |
| 184 | HJWBS6gXqmOkCuCO7c | Stx18 | 71116 | Stx18 | ILMN_2612350 |
| 185 | 9QNvaCAvUCd16CFLU.Vc | Sult1c2 | 69083 | Sult1c2 | ILMN_2612973 |
| 186 | W33pV4V7n6linnauld | Suox | 211389 | Suox | ILMN_2912532 |
| 187 | KJX559ff_v_7KL96I | Synv1 | 74126 | Synv1 | ILMN_2628258 |
| 188 | IoCX6Tr3sCd_xZ6IBo | Tgfbi | 21810 | Tgfbi | ILMN_2834379 |
| 189 | EzinRbomCFI7inu_X8 | Thbs2 | 21826 | Thbs2 | ILMN_2635229 |
| 190 | ZkQoBoHqG41755gR9R0 | Tcld2 | 380712 | Tcld2 | ILMN_2814385 |
| 191 | iXuHLOb1FICWdz.rd4 | Tmem184b | 223693 | Tmem184b | ILMN_2697433 |
| 192 | 69lUiowc.thCBkDeU | Tmem218 | 66279 | Tmem218 | ILMN_2639402 |
| 193 | WUKRQQ5.fUneouL3A4 | Tmem86a | 67893 | Tmem86a | ILMN_2645662 |
| 194 | KX9e6SCUoQjoohCh.4 | Tfnsf19 | 29820 | Tfnsf19 | ILMN_2793522 |
| ID  | Gene Symbol | Gene Name  | Transcript ID  |
|-----|-------------|------------|----------------|
| 195 | rVddRQh9795x.59IpY | Trem2 | ILMN_2992709 |
| 196 | 00e5PHiFe0QJ97VURI | Ube2e2 | Ube2e2 ILMN_2792485 |
| 197 | ou9N69yF6jF5bnsRP0 | Ugp2 | ILMN_1244631 |
| 198 | iUcxJceWC1rxKYOKR8 | Usp2 | Usp2 ILMN_1240264 |
| 199 | iX93et.k.fXrWOAk3U | Wfdc2 | Wfdc2 ILMN_1236758 |
| 200 | 9MHuVJwX7COD6ok1Xc | Zfx | Zfx ILMN_3024592 |
### Supplementary Table 6: Probes used to construct the adipose gene expression space

N/A = Not available

| nulID          | Entrez gene ID | Gene symbol | Synonym | Illumina probe ID |
|----------------|---------------|-------------|---------|-------------------|
| 1              | ZteIg.IKU0FNffMaBc | Fam198b     | 1110032E23Rik  | ILMN_1235811    | 68659          |
| 2              | l6Fws33vr8U_l9dXil | Hilpda      | 2310016C08Rik  | ILMN_2926198    | 69573          |
| 3              | E7SbiV6hXaPugD13lc | Snrnp25     | 3300001G02Rik  | ILMN_2990229    | 78372          |
| 4              | 6hVAOYKB_rNKU.TXSE | Txlng       | 4932441K18Rik  | ILMN_2895908    | 353170         |
| 5              | KjUJK_qBfrHsd39y.l | Unc79       | 9030205A07Rik  | ILMN_1222844    | 217843         |
| 6              | 6lW51dcMvXqd.c_4e0 | Aacs        | Aacs     | ILMN_1253601     | 78894          |
| 7              | ftkShJ80XeBLxUUCkC | Abi3bp      | Abi3bp   | ILMN_3132588     | 320712         |
| 8              | 319TZTj77S1vVTSI | Acsm3       | Acsm3    | ILMN_3111685     | 20216          |
| 9              | 6Uq7r41x1W5195QHc | Adap2       | Adap2    | ILMN_2589256     | 216991         |
| 10             | QOXISulC_CupHr20E | Adb3        | Adb3     | ILMN_2764057     | 11556          |
| 11             | 0YhXaS5RQRfQYBLeCc | Adssl1      | Adssl1   | ILMN_1245079     | 11565          |
| 12             | E5UV.6uaKQ44EE_uEU | Agt         | Agt      | ILMN_1227398     | 11606          |
| 13             | xeKOEg2Ufql155RQ0 | Angpt1      | Angpt1   | ILMN_1226520     | 11600          |
| 14             | Bp96ngxplq1x1_Kks | Angpt1      | Angpt1   | ILMN_2874422     | 72713          |
| 15             | QA57CW61NuAqR60 | Aox3        | Aox3     | ILMN_2640097     | 71724          |
| 16             | Wkcf55Lq_qgPxcetOx | Ar         | Ar       | ILMN_2684075     | 11835          |
| 17             | Zd556UHip5_iKeB76A | Arghap25   | Arghap25 | ILMN_3155245     | 232201         |
| 18             | Ku0qNaNl6170Q4LTO4 | Arl4a      | Arl4a    | ILMN_3144984     | 11861          |
| 19             | KjCLigMV8.une8Q64 | Asns        | Asns     | ILMN_2636755     | 27053          |
| 20             | f0r444Djit5JdUg1fQ | Asns        | Asns     | ILMN_3006123     | 27053          |
| 21             | EuOr7vudbng57dll3U | Atp1b1     | Atp1b1   | ILMN_2767615     | 11931          |
| 22             | 964X7_BV3tf_5WvG40 | Atp6v0a1   | Atp6v0a1 | ILMN_1247682     | 11975          |
| 23             | Wn eup8xSUQJauVfUcE | Ces1f      | AU018778 | ILMN_1238140     | 234564         |
| 24             | oRbp9UIf7ijwEfeLk | Fam83f     | AW544981 | ILMN_2759499     | 213956         |
| 25             | 9kS5dRoisuFKeVOKA | Fam20c     | BC004044 | ILMN_1240719     | 80752          |
| 26             | TiHKrXu3I3_TXJUkK | Bcat1      | Bcat1    | ILMN_3131478     | 12035          |
| 27             | NsXQgcWTZRFqelfXo | Birc5       | Birc5    | ILMN_2681241     | 11799          |
| 28             | xyNBQI59dAkkTt1Kg | Blnk       | Blnk     | ILMN_2726931     | 17060          |
| 29             | 3oj91x4d40Ikvw53sQQ | Bvra      | Bvra     | ILMN_1257284     | 109778         |
| 30             | QsudAtXBOet7h7n7I | Bmp3       | Bmp3     | ILMN_1235433     | 110075         |
| 31             | EUjpcTv4HIMLMu592I | Bnc2       | Bnc2     | ILMN_2721466     | 242509         |
| 32             | cUo_Sahd7F7Gktld3c | C2         | C2       | ILMN_2612895     | 12263          |
| 33             | ZSjteFN1U.Suz5Pag | C6         | C6       | ILMN_1216720     | 12274          |
| 34             | xoo0Kd6ljwJkC5efpK | C6         | C6       | ILMN_2798129     | 12274          |
| 35             | ZyG.Rv7o9x_1JF3pGk | Car13      | Car13    | ILMN_1249727     | 71934          |
|   | Gene Name  | Description | Accession | Log2 Fold Change |
|---|------------|-------------|-----------|-----------------|
| 36 | oUkI41Q4sp6lnElol0U | Ccl2 | ILMN_1245710 | 20296 |
| 37 | 3GtcKjKJ7eyg7gEtG6U | Ccl7 | ILMN_2835117 | 20306 |
| 38 | WIMh666trRoN5xE4Ck | Ccnd1 | ILMN_2601471 | 12443 |
| 39 | 0pTleuurUaDev7h0Ao | Ccnd1 | ILMN_1221503 | 12443 |
| 40 | 9VRK1X6vKBH_o7rw | Cd6 | ILMN_2769330 | 12511 |
| 41 | 6ud.ePdPWO_k.e9Y | Ccl7 | ILMN_2754698 | 12523 |
| 42 | TlIk.BB159orVWuJQ | Cited2 | ILMN_2905866 | 17684 |
| 43 | NQhFSDqcRMQaFRTSTs | Cldn10 | ILMN_1214954 | 58187 |
| 44 | 6vuQijB7XRDLX1Cndew | Cldn10 | ILMN_2723576 | 58187 |
| 45 | E1eId60nnuP3N8ddJE | Clec4b1 | ILMN_2603898 | 69810 |
| 46 | 6UTR3kXeyi0X7wnfuE | Clic6 | ILMN_2667635 | 209195 |
| 47 | 3Uumgk2HqfOF_k0DHQ | Cpa2 | ILMN_3083163 | 12870 |
| 48 | QXtc7F5N6y1.ODpKjk | Cytip | ILMN_2764112 | 72832 |
| 49 | cd3RON9XwV6i5Rs0sc | Cyp2f2 | ILMN_1245514 | 226105 |
| 50 | QXtc7F5N6y1.ODpKjk | Cyp2c70 | ILMN_2702903 | 13107 |
| 51 | TurRSxLdz6F.9Iqmnk | Dbf4 | ILMN_2952661 | 27214 |
| 52 | ohnL5seXnXDsR505SA | Dda1 | ILMN_1256676 | 69219 |
| 53 | KX0hOexHHq4eo8SA5w | Dfn5 | ILMN_2652482 | 54722 |
| 54 | HJ0ed5SeoBR1115K49g | Dido1 | ILMN_3016099 | 23856 |
| 55 | Epfl51zUdB1Rjci4l6o | Dnajb13 | ILMN_2667257 | 69387 |
| 56 | cSI9q.d17.PIKOxe5l | Dnmt3l | ILMN_3112268 | 54427 |
| 57 | 6or1pxp3kQvrm5F5Ts | Dnmt3l | ILMN_1250149 | 54427 |
| 58 | Tu3ExUudMii_elYp6A | Dpep2 | ILMN_2692315 | 319446 |
| 59 | ftr.NR15zdBrB5fuQ | Dusp15 | ILMN_2675090 | 252864 |
| 60 | BUEiVRLX13_rHY9KTo | Ebf2 | ILMN_1251248 | 13592 |
| 61 | r7azVIFkisiQV17VSUI | Esig8 | ILMN_2824741 | 240916 |
| 62 | Kul1UI6d8n_QheCwk | Cela1 | ILMN_2693403 | 109901 |
| 63 | 6or1pxp3kQvrm5F5Ts | Dnmt3l | ILMN_3112268 | 54427 |
| 64 | o6fySSV69FVTlHo14 | Ephx1 | ILMN_2664224 | 13849 |
| 65 | KIwO0.Cf188D_B.Btboro | Fabp5 | ILMN_1235908 | 16592 |
| 66 | BJC0O0s3u7lDnvFE164 | Fads1 | ILMN_2607786 | 76267 |
| 67 | Te1.kUCsDgcl.PRh1U | Fam13a | ILMN_1224427 | 58909 |
| 68 | rod6umOmNflufJT51w | Fgr4 | ILMN_2631161 | 246256 |
| 69 | 3U4IEGDQbJ54qQBip0 | Fgf13 | ILMN_1257196 | 14168 |
76  NdF7E7ELXXtPo.pG4E  Fgf13  Fgf13  ILMN_2745480  14168
77  ceJosi8X5pYJLJzm14  Fgf21  Fgf21  ILMN_2710698  56636
78  WNo1OQKdsr2EJ1557E  Fn3k  Fn3k  ILMN_1223313  63828
79  HKKxKSlohol4h.IJcJ4  Gadd45b  Gadd45b  ILMN_2900653  17873
80  uJkv6ERJHp13Z0teQQ  Gas6  Gas6  ILMN_2686327  14456
81  Ts3sEd_GLXsUbhQVe4r  Gata6  Gata6  ILMN_2868133  14465
82  KofgiYf8Qa6d6f7eg  Accsl  Gm1967  ILMN_2787817  381411
83  ucf7QByWqFReTQSSg  Got111  Got111  ILMN_1246289  76615
84  orHq1.d7R2u0ujDu70  Gpc1  Gpc1  ILMN_2635784  14733
85  lltVHgiXTS7pTc7puc  Gpc3  Gpc3  ILMN_2719973  14734
86  ofiNeOAHiBi_hZ1vU  Gpd2  Gpd2  ILMN_1247257  14571
87  uh7f2CMAwpMT1Dggrg  Gpnmb  Gpnmb  ILMN_2614655  93695
88  QXideEA8w6i6an_70uY  Gpnmb  Gpnmb  ILMN_2648669  93695
89  KuEKqJjx6gi4PNe4z4  Gpr64  Gpr64  ILMN_3113571  237175
90  cupqXVeJW3uuU1flk8  Gpx3  Gpx3  ILMN_2715546  14778
91  cWPcQpTv0ifUIJ1xY  Grhl1  Grhl1  ILMN_1246419  195733
92  um3u0PShOHhigaWjk  Gsta3  Gsta3  ILMN_1241437  14859
93  0ikP9Xqnk4OJoEaK  Gsta3  Gsta3  ILMN_3138685  14859
94  9wgyXkFaC0ijl11L6U  Gsta4  Gsta4  ILMN_2892441  14860
95  cV41eX9NKeARX3cgP8  Gtse1  Gtse1  ILMN_2908070  29870
96  cfShFuf37tMeXc9K1U  H2-DMb1  H2-DMb1  ILMN_1244977  14999
97  rCVML.d5dfvqG7pU  H2-M2  H2-M2  ILMN_2964185  14990
98  0eTXFa3vip3hTp.NBQ  Hn1l  Hn1l  ILMN_2851251  52009
99  052VBWp1ieVeCmftEo  Igfbp2  Igfbp2  ILMN_1236788  16008
100  NeC5B5t1dJx2in51Q  Inmt  Inmt  ILMN_2803249  21743
101  o.IEt2o._7_Hxt7UE  Is1l  Is1l  ILMN_2727472  16392
102  NAEqrqCbpZd_R5.tlo  Itpk1  Itpk1  ILMN_2723920  217837
103  KweVopFpXqXykXQof8  Kcnh2  Kcnh2  ILMN_1244402  16511
104  WoYOSJwYoGCoKCEKeK  Kcnj14  Kcnj14  ILMN_2898924  211480
105  WfpZSUkSa1d_EcX3.A  Kif22  Kif22  ILMN_2762326  110033
106  3lwkiWCo9a9oV1k8  Krt19  Krt19  ILMN_2614462  16669
107  u7ZSxV_g02UGTolIq  Lama1  Lama1  ILMN_2973288  16772
108  r15qfhufa4yODAHIV0  Lat2  Lat2  ILMN_3143483  56743
109  WJdnNUKfesLPEK100  Lctl  Lctl  ILMN_1235276  235435
110  Zi6gH_T93dfNffsITQ  Lgals3  Lgals3  ILMN_1223317  16854
111  0XTaMU6s6QAgpw597g  Lilrb4  Lilrb4  ILMN_1236702  14728
112  Eoj31cQOxfTepjo5k  Lipf  Lipf  ILMN_2863532  67717
113  l3tr_9ECX0Ru0uVY  N/A  LOC100043671  ILMN_1258600  N/A
114  xPKK7Os8nk0e7o7Q3w  N/A  LOC100048295  ILMN_2470646  N/A
115  9n1EZxdJ6n3PwKISDU  Lrig3  Lrig3  ILMN_1213273  320398
|   |   |   |
|---|---|---|
| 116 | KojfYEAZ6rlZVYNUv8 | Ltc4s | Ltc4s | ILMN_2658687 | 17001 |
| 117 | TV_c3RbcXiU7E5r.0A | Maob | Maob | ILMN_2719069 | 109731 |
| 118 | oIxFDyV4JICQijMjko | Matk | Matk | ILMN_2743902 | 17179 |
| 119 | IIooody5Ac3XRFy7o | Mcm10 | Mcm10 | ILMN_2970532 | 70024 |
| 120 | NSQPrTu7P.Uy1Rfok | Meis1 | Meis1 | ILMN_1218266 | 17268 |
| 121 | QgLU4MsDBJcqnXUo | Mest | Mest | ILMN_2642417 | 17294 |
| 122 | QAfQngywMElyqSddSo | Mest | Mest | ILMN_2642418 | 17294 |
| 123 | Wkg.XAHlKTwgeTe5SI | Mest | Mest | ILMN_2846904 | 17896 |
| 124 | u3XiGfhX5H0vl0vhA | Mfge8 | Mfge8 | ILMN_2771034 | 17304 |
| 125 | rk69IpQevzewvw99Qu | Mmp9 | Mmp9 | ILMN_1250421 | 17381 |
| 126 | TnLSisq7m869K0h7s | Myl4 | Myl4 | ILMN_2610744 | 56177 |
| 127 | lxs_h0T9t93hUQX1eg | Net1 | Net1 | ILMN_2813830 | 71904 |
| 128 | E5dCSZvdF1d3QeLuw | Ned4l | Ned4l | ILMN_2654186 | 83814 |
| 129 | WoiQ9Hu3pu6CCTeCQ | Ned9 | Ned9 | ILMN_2654186 | 18003 |
| 130 | BX5KToPsMuEXNzOg | Net1 | Net1 | ILMN_2610771 | 56349 |
| 131 | uVX_3Qeg4EBFbpLHk | Net1 | Net1 | ILMN_3151722 | 56349 |
| 132 | cSSjc6EqBO_v1y78Y | Nt5e | Nt5e | ILMN_2813830 | 23959 |
| 133 | cR0N1ViJ7w6LfV5P78 | Nup210 | Nup210 | ILMN_2662191 | 75475 |
| 134 | xfhbv3t3yPB71hVrl | Olfm1 | Olfm1 | ILMN_1240615 | 56177 |
| 135 | TrM1JfVImKS7s4sWWY | Oplah | Oplah | ILMN_2662191 | 75475 |
| 136 | 36JxLaeq_eOjF5s5p4 | Palld | Palld | ILMN_3092653 | 72333 |
| 137 | 30P_lzh18nR79eqdSk | Paqr7 | Paqr7 | ILMN_1220363 | 71904 |
| 138 | BkRuB6F8qQn4iL3Yc | Paqr9 | Paqr9 | ILMN_2752524 | 75552 |
| 139 | xqRAhEBWqFBWDhDK6A | Paqr9 | Paqr9 | ILMN_3094043 | 75552 |
| 140 | iwg0glTgZHggQku8I4 | Pcolce2 | Pcolce2 | ILMN_1238603 | 76477 |
| 141 | HppPfCoi3o.Plgr.U | Pcolce2 | Pcolce2 | ILMN_2678421 | 76477 |
| 142 | NroTT0kgQlulgvp5U | Pde1a | Pde1a | ILMN_3146952 | 18573 |
| 143 | Er0qyRKHXZP15.VYa | Pfkb4 | Pfkb4 | ILMN_2712668 | 207198 |
| 144 | WVTrrz15x7dQQ7lq9Y | Pfkp | Pfkp | ILMN_1237695 | 56421 |
| 145 | l6Vqz8nXp.N2.lehG | Phca | Phca | ILMN_2681057 | 66190 |
| 146 | u3qJzCX3p93HuR75P78 | Phkg1 | Phkg1 | ILMN_2769795 | 18682 |
| 147 | Bippi1PoCHdefTFiktig | Pik3r1 | Pik3r1 | ILMN_2473531 | 18708 |
| 148 | ITFifiLOyTE6VKOec | Pik3r1 | Pik3r1 | ILMN_3114641 | 18708 |
| 149 | clMewrlnRlJ5w4ocDK | Pon1 | Pon1 | ILMN_2676379 | 18979 |
| 150 | 055edLlh.3T4EqdxHI | Plp | Plp | ILMN_3155363 | 19041 |
| 151 | WbUQ4p3UB0cd9VAkc | Prc1 | Prc1 | ILMN_2757125 | 233406 |
| 152 | WECCiS2xjU1JJiAFFI | Prlr | Prlr | ILMN_286899 | 19116 |
| 153 | ToXo1xuTkd0eInl | Prlr | Prlr | ILMN_2617005 | 19116 |
| 154 | QOk99O6HX241mDmXU | Prtn3 | Prtn3 | ILMN_2758029 | 19152 |
| 155 | fSSK0gpx1Nc1Nbx0k | Ptprd | Ptprd | ILMN_2501929 | 19266 |
| 156 | HuV4x1JlrScnEjU1zU | Ptprd | Ptprd | ILMN_3103904 | 19266 |
| 157 | 6Bf.A4l4xe79IP6Ub4 | Ptpre | Ptpre | ILMN_2826916 | 19267 |
| 158 | NdVTx6VjhlPfegOc | Pvalb | Pvalb | ILMN_1218223 | 19293 |
| 159 | HXenoTnnL3vb69rUo | Rab7f1 | Rab7f1 | ILMN_2681186 | 226422 |
| 160 | fbZuXex_91Ju59ViDM | Rasgrf1 | Rasgrf1 | ILMN_1233146 | 19417 |
| 161 | 3tm5d7H73Um7n1WIMw | Rasgrf1 | Rasgrf1 | ILMN_2699663 | 19417 |
| 162 | Em577s8ygd_Q3X1fo | Rgs1 | Rgs1 | ILMN_2625377 | 50778 |
| 163 | fg7qSK6U_iPvsd4otI | Ripk4 | Ripk4 | ILMN_2840856 | 72388 |
| 164 | 0ClAZ.epZNunZBJZCM | Rrad | Rrad | ILMN_1219106 | 56437 |
| 165 | KI7mXoxHl0.9BCZAfY | Mtsu1 | scl33870.2_144 | ILMN_2459676 | 102103 |
| 166 | 9NWdNt3eUG.7gBwCDU | Sema5a | Sema5a | ILMN_2604422 | 20356 |
| 167 | ZVnTbd3lBv_4AcAg1w | Sema5a | Sema5a | ILMN_2604422 | 20356 |
| 168 | ENKH_CgN1JGehUqR1o | Sept9 | Sept9 | ILMN_2602185 | 53860 |
| 169 | lUoKas8mK7fljNItLu0 | Sfxn1 | Sfxn1 | ILMN_2675569 | 14057 |
| 170 | 3BKFvDfBTn3Xi5ehUQ | Sfxn1 | Sfxn1 | ILMN_2675569 | 14057 |
| 171 | 9Sc0s8mK7fljNItLu0 | Sfxn1 | Sfxn1 | ILMN_2675569 | 14057 |
| 172 | 3BKvfBFBTn3Xi5ehUQ | Sfxn1 | Sfxn1 | ILMN_2675569 | 14057 |
| 173 | NVt4_n_itd94n_.Snc | Slc44a1 | Slc44a1 | ILMN_1241827 | 100434 |
| 174 | NVT4_n.itd94n_.Snc | Slc5a7 | Slc5a7 | ILMN_1243388 | 63993 |
| 175 | WRJbxV3xej62c4ih2U | Scl15a3 | Scl15a3 | ILMN_2987709 | 65221 |
| 176 | ZVqd5c7uxUe6HqAfR8 | Scl1a3 | Scl1a3 | ILMN_2634317 | 20512 |
| 177 | HdwkxN3NS0ot357SK4 | Scl2a13 | Scl2a13 | ILMN_2925424 | 239606 |
| 178 | 6HSPnOqKp.nqAph13A | Scl2a3 | Scl2a3 | ILMN_2616565 | 20527 |
| 179 | HeV7LUoJHbV7BobA_p4 | Scl44a1 | Scl44a1 | ILMN_1241827 | 100434 |
| 180 | BCAEi4P_VBO3uV9TY | Slc5a7 | Slc5a7 | ILMN_1243388 | 63993 |
| 181 | 9pUj1_1Ls_wlf2f2Xo | Scl15a3 | Scl15a3 | ILMN_2987709 | 65221 |
| 182 | Kcs_FcIiNITM7.4U4 | Scl1a3 | Scl1a3 | ILMN_2634317 | 20512 |
| 183 | INNUTI3_KW7T_4ngBI | Spc25 | Spc25 | ILMN_2901180 | 66442 |
| 184 | cp0UGek5_K.cfsAllk | Stambpl1 | Stambpl1 | ILMN_1252400 | 76630 |
| 185 | 3urlUy_Xo8UyyRA11U | Steap2 | Steap2 | ILMN_2797726 | 74051 |
| 186 | HdBm3_.F.QVXjoCjpc | N/A | N/A | ILMN_2678838 | N/A |
| 187 | foV3nu3uG_sxTuXuNu74 | Syp | Syp | ILMN_2630182 | 20977 |
| 188 | ofKGRaeWбуr67yplSw | Tek1 | Tek1 | ILMN_1239718 | 21689 |
| 189 | fuUIrTSr.v8LCcoOl | Thbd | Thbd | ILMN_1249767 | 21824 |
| 190 | u3hn55b.r.n5eUaDuo | Timp1 | Timp1 | ILMN_3103896 | 21857 |
| 191 | rcUiw0Wfs_X1Lgg1KfuQ | Timp1 | Timp1 | ILMN_2769918 | 21857 |
| 192 | fKiX1Cu1D5XN3q3qkg | Tnfrsf12a | Tnfrsf12a | ILMN_2424299 | 27279 |
| 193 | 6sD1_MVEB833uX00uk | Tpcn2 | Tpcn2 | ILMN_1236133 | 233979 |
| 194 | 9Kj_fs8reOl7I0tMjQ | Tph2 | Tph2 | ILMN_2460179 | 216343 |
| 195 | H0_UblkKqOeXtG_V6c | Tst | Tst | ILMN_2493175 | 22117 |
|   |     |     |     |     |     |
|---|-----|-----|-----|-----|-----|
| 196 | ijqhRqjmuOIJCWP10 | Ubd | Ubd | ILMN_2426853 | 24108 |
| 197 | reORWLYxdHH.pXv9d8 | Ugt3a2 | Ugt3a2 | ILMN_2658355 | 223337 |
| 198 | Qv5OTwY14KC14QtFP4 | Upk1b | Upk1b | ILMN_2936646 | 22268 |
| 199 | rgXkn3K4f6SP_XmgpM | Wfdc1 | Wfdc1 | ILMN_2466164 | 67866 |
| 200 | HiliOOkuc8CXdM3_AF0 | Xpnpep2 | Xpnpep2 | ILMN_1248998 | 170745 |
7. Supplementary Table 7: Correlations of liver and adipose TDIs with individual PDIs

The table lists the Spearman correlations and their respective p-values between liver and adipose TDIs and the PDIs of individual physiological markers. P-values were adjusted to multiple hypotheses testing by the Benjamini-Hochberg (BH) method. Refer to Supplementary Table 1 for complete details concerning the physiological markers.

| Physiological marker | Adipose Spearman rho | BH-adjusted p-value | Liver Spearman rho | BH-adjusted p-value |
|-----------------------|----------------------|---------------------|--------------------|---------------------|
| 1 Body weight         | 0.84                 | 2.6e-17             | 0.34               | 2.9e-04             |
| 2 Liver weight        | 0.16                 | 1.2e-01             | 0.52               | 1.4e-08             |
| 3 Heart weight        | 0.37                 | 2.1e-03             | 0.04               | 3.9e-01             |
| 4 Visceral WAT        | 0.75                 | 7.2e-12             | 0.32               | 6.0e-04             |
| 5 Gonadal WAT         | 0.84                 | < 1e-17             | 0.27               | 2.8e-03             |
| 6 Subcutaneous WAT    | 0.84                 | 2.6e-17             | 0.31               | 8.0e-04             |
| 7 Total WAT (visceral + gonadal + subcutaneous) | 0.85 | < 1e-17 | 0.28 | 2.7e-03 |
| 8 Ratio visceral / subcutaneous WAT | 0.59 | 5.3e-07 | 0.22 | 1.4e-02 |
| 9 Kidneys weight (total both kidneys) | 0.01 | 4.7e-01 | 0.29 | 1.9e-03 |
| 10 Liver triglycerides | 0.54 | 4.8e-06 | 0.61 | 5.5e-12 |
| 11 Atherosclerotic lesion area | 0.19 | 1e-01 | 0.43 | 1.2e-05 |
| 12 Urine glucose      | 0.18                 | 1.1e-01             | 0.27               | 3.8e-03             |
| 13 Plasma cholesterol | 0.59                 | 5.3e-07             | 0.76               | 2.5e-21             |
| 14 Plasma triglycerides | 0.50 | 3.3e-05 | 0.64 | 1.8e-13 |
| 15 Plasma glucose     | 0.38                 | 1.6e-03             | 0.15               | 6.6e-02             |
| 16 Plasma insulin     | 0.70                 | 3.4e-10             | 0.42               | 1.2e-05             |
| 17 Plasma glucagon    | 0.06                 | 3.5e-01             | 0                  | 5.1e-01             |
| 18 Plasma E-selectin  | 0.39                 | 1.4e-03             | 0.16               | 6.6e-02             |
| 19 Plasma VCAM        | 0.50                 | 2.5e-05             | 0.38               | 6.5e-05             |
| 20 Plasma MCP-1       | 0.06                 | 3.5e-01             | 0.14               | 9.2e-02             |
| 21 Plasma adiponectin | 0.50                 | 2.8e-05             | 0.02               | 4.4e-01             |
| 22 Plasma leptin      | 0.86                 | 2.6e-17             | 0.36               | 2.3e-04             |
| 23 Plasma resistin    | 0.67                 | 1.1e-08             | 0.09               | 2.1e-01             |
| 24 HOMA insulin resistance | 0.68 | 1.9e-09 | 0.37 | 7.0e-05 |
| 25 QUICKI insulin resistance | 0.60 | 5.3e-07 | 0.40 | 3.4e-05 |
| 26 ACR (urine albumin / creatinine ratio) | 0.76 | 2.4e-10 | 0.27 | 5.5e-03 |
8. **Supplementary Table 8: Correlations of liver MDI with individual PDIs**

The table lists the Spearman correlations and their respective p-values between liver MDI and the PDIs of individual physiological markers. P-values were adjusted to multiple hypotheses testing by the Benjamini-Hochberg (BH) method. Refer to Supplementary Table 1 for complete details concerning the physiological markers.

| Physiological marker                                      | Spearman rho | BH-adjusted p-value |
|-----------------------------------------------------------|--------------|---------------------|
| 1. Body weight                                            | 0.12         | 2.5e-01             |
| 2. Liver weight                                           | 0.49         | 5.1e-07             |
| 3. Heart weight                                           | 0.11         | 2.5e-01             |
| 4. Visceral WAT                                           | 0.02         | 5.1e-01             |
| 5. Gonadal WAT                                            | 0            | 5.4e-01             |
| 6. Subcutaneous WAT                                       | 0.12         | 2.5e-01             |
| 7. Total WAT (visceral + gonadal + subcutaneous)          | 0.02         | 5.1e-01             |
| 8. Ratio visceral / subcutaneous WAT                      | 0.12         | 2.5e-01             |
| 9. Kidneys weight (total both kidneys)                    | 0.35         | 5.8e-04             |
| 10. Liver triglycerides                                   | 0.31         | 2.4e-03             |
| 11. Atherosclerotic lesion area                           | 0.16         | 1.7e-01             |
| 12. Urine glucose                                         | 0.09         | 3.2e-01             |
| 13. Plasma cholesterol                                    | 0.42         | 3.5e-05             |
| 14. Plasma triglycerides                                  | 0.36         | 3.4e-04             |
| 15. Plasma glucose                                        | 0            | 5.5e-01             |
| 16. Plasma insulin                                        | 0.12         | 2.5e-01             |
| 17. Plasma glucagon                                       | 0.05         | 4.3e-01             |
| 18. Plasma E-selectin                                     | 0.30         | 3.2e-03             |
| 19. Plasma VCAM                                           | 0.09         | 3.2e-01             |
| 20. Plasma MCP-1                                          | -0.11        | 8.7e-01             |
| 21. Plasma adiponectin                                    | 0.01         | 5.1e-01             |
| 22. Plasma leptin                                         | 0.07         | 3.42e-01            |
| 23. Plasma resistin                                       | 0.08         | 3.42e-01            |
| 24. HOMA insulin resistance                              | 0.07         | 3.42e-01            |
| 25. QUICKI insulin resistance                             | 0.07         | 3.42e-01            |
| 26. ACR (urine albumin / creatinine ratio)                | 0.24         | 3.5e-02             |
9. **Supplementary Table 9: Adverse side-effects of drugs in the current study**

The following is a comprehensive list of adverse side-effects of the drugs included in the current study as stated in the package inserts provided by the manufacturers. Highlighted in bold letters are side-effects which were investigated or could have been inferred from the physiological data collected in the animal model studied here. Superscript numbers refer to the physiological parameters relevant to the highlighted side effects as follows: 1. Body weight 2. Plasma glucose 3. Liver weight 4. Liver triglycerides 5. Heart weight 6. Atherosclerotic lesion area 7. Plasma cholesterol 8. Kidneys weight 9. ACR (urine albumin/creatinine ratio).

Side-effects data was downloaded from the SIDER database (http://sideeffects.embl.de/; accessed December 2014; (Kuhn et al., 2010)), which aggregates package-insert information from several public sources, among which are the US Food and Drug Administration (FDA) and Health Canada. SIDER lists side-effects using the Medical Dictionary for Regulatory Activities (MedDRA) – a standardized medical terminology that facilitates sharing of information concerning medical products (see http://www.meddra.org/; accessed December 2014).

Note, however, that the side-effects listed here are ones that pertain to human patients and may not apply to the mouse model studied here. In addition, the list is comprehensive and includes rare side-effects that may not be observed in a limited-scale study even if they occur in the animal model.

| Drug | PubChem Compound ID | Adverse side-effects |
|------|---------------------|----------------------|
| metformin | 4091 | Abdominal discomfort, Abdominal distension, Abdominal pain, Abdominal pain upper, Abnormal faeces, Abscess, **Acute prerenal failure**<sup>8,9</sup>, Anaemia, Anaemia megaloblastic, **Angina pectoris**<sup>6</sup>, **Angina unstable**<sup>6</sup>, **Angiopathy**<sup>6</sup>, Aortic dissection, Asthenia, **Azotaemia**<sup>8,9</sup>, Blood disorder, **Blood glucose decreased**<sup>2</sup>, Breast disorder, **Cardiac disorder**<sup>5,6</sup>, Chest discomfort, Chest pain, Chills, Connective tissue disorder, Constipation, Decreased appetite, Dehydration, Dermatitis, Diarrhoea, Discomfort, Dizziness, Dysgeusia, Dyspepsia, Dyspnœa, Ear pain, Emotional distress, Epigastric discomfort, Erythema, Eye disorder, Fatigue, Feeling abnormal, Flatulence, Flushing, Fungal infection, Gastric disorder, Gastroenteritis, Gastrointestinal disorder, Gastrointestinal pain, Gastrointestinal tract irritation, Headache, **Hepatitis**<sup>3,4</sup>, Hyperhidrosis, Hypertension, Hypoaesthesia, **Hypoglycaemia**<sup>2</sup>, Ill-defined disorder, Immune system disorder, Infection, Infestation, Influenza, Lactic acidosis, Lethargy, **Liver function test abnormal**<sup>3,4</sup>, Loss of consciousness, Malaise, Mediastinal disorder, Migraine, Muscle spasms, Musculoskeletal discomfort, Myalgia, Nail disorder, Nasal congestion, Nasopharyngitis, |
| Glibenclamide | 3488 |
|---------------|------|
| Abdominal distension, Abdominal pain, Agranulocytosis, Anaemia, Angioedema, Aplastic anaemia, Arthralgia, Asthenia, Cholestasis, Diarrhoea, Dyspepsia, Dyspnnoea, Erythema, Erythropenia, Gastrointestinal disorder, Gastrointestinal pain, Haemolytic anaemia, Hepatic failure\(^3,4\), Hepatic function abnormal\(^3,4\), Hepatitis\(^3,4\), Hypersensitivity, Hyponatraemia, Hypopituitarism, Hypotension, Inappropriate antidiuretic hormone secretion, Jaundice, Jaundice cholestatic, Leukocytoclastic vasculitis, Leukopenia, Liver disorder\(^3,4\), Malnutrition, Musculoskeletal discomfort, Myalgia, Nausea, Nephropathy\(^8,9\), Nervous system disorder, Pain, Pancytopenia, Photosensitivity reaction, Porphyria, Porphyria non-acute, Pruritus, Purpura, Rash, Shock, Thrombocytopenia, Urticaria, Vascular purpura, Vasculitis, Vision blurred, Visual impairment, Vomiting |

| Sitagliptin | 4369359 |
|-------------|--------|
| Abdominal discomfort, Abdominal pain, Abdominal pain upper, Anaphylactic shock, Angina pectoris\(^6\), Angioedema, Angiopathy\(^6\), Anxiety, Aortic dissection, Arthralgia, Asthenia, Back pain, Blood glucose decreased\(^2\), Blood glucose increased\(^2\), Breast disorder, Bronchitis, Bundle branch block, Cardiac disorder\(^6,6\), Cellulitis, Chest pain, Connective tissue disorder, Constipation, Cough, Decreased appetite, Dermatitis, Diarrhoea, Discomfort, Dizziness, Dysmenorrhoea, Dyspepsia, Eczema, Erectile dysfunction, Eye disorder, Face oedema, Fatigue, Feeling abnormal, Flatulence, Gastric ulcer, Gastritis, Gastroenteritis, Gastrointestinal disorder, Gastrointestinal pain, Gastrooesophageal reflux disease, Headache, Helicobacter gastritis, Hepatic steatosis\(^1,4\), Hepatobiliary disease, Herpes virus infection, Herpes zoster, Hyperglycaemia\(^2\), Hypersensitivity, Hypertension, Hypoesthesia, Hypoglycaemia\(^2\), Hypotension, Ill-defined disorder, Infection, Infestation, Influenza, Insomnia, Malaise, Mediastinal disorder, Mental disorder, Migraine, Muscle spasms, Muscle tightness, Musculoskeletal discomfort, Musculoskeletal pain, Myalgia, Nasopharyngitis, Nausea, |
| Drug       | Code | Common Adverse Effects |
|------------|------|------------------------|
| rosiglitazone | 7799 | Neck pain, Nephrolithiasis, Nervous system disorder, Neuropathy peripheral, Oedema, Oedema peripheral, Oesophagitis, Oropharyngeal pain, Orthostatic hypotension, Osteoarthritis, Pain, Pain in extremity, Parosmia, Pharyngitis, Pneumonia, Rash, Reflux oesophagitis, Respiratory tract infection, Retching, Sciatica, Sinus congestion, Sinus headache, Sinusitis, Skin disorder, Somnolence, Tooth infection, Toothache, Tracheobronchitis, Ulcer, Upper respiratory tract infection, Urethral disorder, Urinary tract disorder, Urinary tract infection, Urticaria, Vertigo, Viral diarrhoea, Vision blurred, Vomiting, Weight increased |
| pioglitazone | 4829 | Abdominal pain, Acute coronary syndrome, Alanine aminotransferase increased, Anaemia, Anaphylactic shock, Angioedema, Arthralgia, Astenia, Back pain, Cardiac disorder, Cardiac failure, Cardiac failure congestive, Constipation, Cough, Dermatitis, Diabetic retinal oedema, Diarrhoea, Dizziness, Dysmenorrhoea, Effusion, Fatigue, Gastrointestinal pain, Headache, Hepatic failure, Hyperbilirubinaemia, Hyperglycaemia, Hypertension, Hypoglycaemia, Increased appetite, Infarction, Influenza, Ischaemia, Ketonuria, Macular oedema, Musculoskeletal discomfort, Myocardial infarction, Myocardial ischaemia, Nasopharyngitis, Nausea, Oedema, Oropharyngeal pain, Pain, Pleural disorder, Pleural effusion, Pruritus, Pulmonary oedema, Rash, Respiratory tract infection, Sinusitis, Social avoidant behaviour, Upper respiratory tract infection, Urticaria, Visual acuity reduced, Volume blood increased, Vomiting, Weight increased |
| fenofibrate | 3339 | Abdominal pain, Acne, Acute coronary syndrome, Alanine aminotransferase increased, Alopecia, Alveolitis, Amblyopia, Anaemia, Angina pectoris, Anorectal disorder, Anxiety, Arrhythmia, Arthralgia, Arthritis, Arthropathy, Aspartate |
aminotransferase increased, Asthenia, Asthma, Atrial fibrillation, Back pain, Bladder pain, Blindness, Blood alkaline phosphatase increased, Blood bilirubin increased, Blood creatine phosphokinase increased, **Blood creatinine increased**\(^8,9\), Blood lactate dehydrogenase increased, Blood urea increased, Blood uric acid increased, Body temperature increased, Bronchitis, Bursitis, Calculus urinary, Candidiasis, Cardiac fibrillation, **Cardiovascular disorder**\(^5,6\), Cataract, Chest pain, Cholecystitis, Cholelithiasis, Colitis, Conjunctivitis, Constipation, Coronary artery disease, Cough, Cyst, Cystitis, Cystitis noninfecive, Decreased appetite, Deep vein thrombosis, Dermatitis, Dermatitis contact, Diarrhoea, Discomfort, Disturbance in sexual arousal, Dizziness, Dry mouth, Duodenal ulcer, Dyspepsia, Dyspnnea, Dysuria, Ear infection, Ear pain, Ecchymosis, Eczema, Electrocardiogram abnormal, Embolism, Eosinophilia, Erectile dysfunction, Eructation, Erythema, Extrasystoles, Eye disorder, Fatigue, Feeling abnormal, Flatulence, Fungal skin infection, Gamma-glutamyltransferase increased, Gastritis, Gastroenteritis, Gastrointestinal disorder, Gastrointestinal pain, Gout, Gynaecomastia, Haemoglobin, Haemorrhage, Haptoglobin decreased, Headache, **Hepatic cirrhosis**\(^3,4\), **Hepatic function abnormal**\(^3,4\), **Hepatic steatosis**\(^3,4\), **Hepatitis**\(^3,4\), Hernia, Herpes simplex, Herpes virus infection, Herpes zoster, Hyperhidrosis, Hypersensitivity, Hypertonia, Hyperuricaemia, **Hypoglycaemia**\(^2\), Hypotension, Ill-defined disorder, Increased appetite, **Infarction**\(^6\), Infection, Influenza, Insomnia, Jaundice, Laboratory test abnormal\(^2,7,5\), Laryngitis, Leukopenia, Libido decreased, **Liver function test abnormal**\(^3,4\), Lymphadenopathy, Malaise, Migraine, Multiple hereditary exostosis, Muscle spasms, Muscular weakness, Musculoskeletal discomfort, Myalgia, **Myocardial infarction**\(^6\), Myositis, Nail disorder, Nausea, Nervousness, Neuralgia, Oedema, Oedema peripheral, Oesophagitis, Osteoarthritis, Otitis media, Pain, Palpitations, Paraesthesia, Peptic ulcer, Pharyngitis, Phlebitis, Photosensitivity reaction, Pneumonia, Pollakiuria, Prostatic disorder, Pruritus, Pulmonary embolism, Rash, Rash maculo-papular, Rectal haemorrhage, Refraction disorder, **Renal failure**\(^8,9\), **Renal failure acute**\(^8,9\), **Renal impairment**\(^8,9\), Respiratory disorder, Rhabdomyolysis, Rhinitis, Sinusitis, Skin disorder, Skin ulcer, Somnolence, Tachycardia, Tenosynovitis, Tension, Thrombocytopenia, Thrombosis, Tooth disorder, Ulcer, Unintended pregnancy, Urticaria, Varicose vein, Vasodilation procedure, Venous thrombosis, Ventricular extrasystoles, Vertigo, Visual acuity reduced, Visual impairment, Vomiting, Vulvovaginal candidiasis, Vulvovaginal mycotic infection,
T0901317  447912

(*) This compound was never approved for use in humans, and therefore has no SIDER entry. There exist, however, multiple reports that implicate LXR agonists, including T0901317, in impaired lipid metabolism and hepatic dysfunction (Schultz et al, 2000; Chisholm et al, 2003; Lund et al, 2003; Millatt et al, 2003; Zanotti et al, 2008; Jung et al, 2011). Administration of LXR-623, a synthetic LXR agonist, to healthy human subjects led to neurological and psychiatric adverse events (Katz et al, 2009).

While the physiological data studied here allows detection of adverse treatment outcomes related to disruption of lipid metabolism and liver functions, it is not rich enough to study adverse events related to the central nervous system.

atorvastatin  60822 (atorvastatin calcium)

Abdominal discomfort, Abdominal pain, Abnormal dreams, Acne, Affect lability, Ageusia, Aggression, Agitation, Alanine aminotransferase increased, Alopecia, Amblyopia, Amnesia, Anaemia, Anaphylactic shock, Angioedema, Anorectal discomfort, Arrhythmia, Arthralgia, Arthritis, Asthenia, Asthma, Back pain, Biliary colic, Bladder pain, Blood creatine phosphokinase increased, Blood magnesium decreased, Body temperature increased, Breast enlargement, Bronchitis, Bursitis, Cells in urine, Cerebral haemorrhage, Cheilitis, Chest pain, Cholestasis, Colitis, Constipation, Coordination abnormal, Cystitis, Cystitis noninfective, Deafness, Death, Decreased appetite, Dermatitis, Dermatitis contact, Diarrhoea, Discomfort, Disturbance in sexual arousal, Dizziness, Dry eye, Dry mouth, Dry skin, Duodenal ulcer, Dysgeusia, Dyspepsia, Dysphagia, Dyspnoea, Dysuria, Ecchymosis, Eczema, Ejaculation disorder, Enteritis, Epididymitis, Epistaxis, Erectile dysfunction, Eruption, Erythema, Erythema multiforme, Eye haemorrhage, Face oedema, Fatigue, Feeling abnormal, Fibrocystic breast disease, Flatulence, Fluid retention, Gastric disorder, Gastric ulcer, Gastritis, Gastroenteritis, Gastrointestinal pain, Generalised oedema, Gingival bleeding, Glaucoma, Glossitis, Gout, Haematuria, Haemoglobin, Haemorrhage, Haemorrhagic stroke, Headache, Hepatic failure, Hepatitis, Hyperglycaemia, Hyperhidrosis, Hyperkinesia, Hypersensitivity, Hypertonia, Hypoaesthesia, Hypoglycaemia, Hypotension, Ill-defined disorder, Incontinence, Increased appetite, Infection, Influenza, Insomnia, Ischaemic stroke, Jaundice, Jaundice cholestatic, Joint swelling, Libido decreased, Liver function test abnormal, Loss of consciousness, Lymphadenopathy,
| Condition                                      | Salicylate | Rofecoxib |
|------------------------------------------------|------------|-----------|
| Malaise, Melaena, Memory impairment, Metrorrhagia, Micturition urgency, Migraine, Mood swings, Mouth ulceration, Muscle contracture, Muscle fatigue, Muscle rigidity, Muscle spams, Muscular weakness, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Myopathy, Myositis, Nasopharyngitis, Nausea, Neck pain, Nephritis, Nephrolithiasis, Neuropathy peripheral, Nightmare, Nocturia, Nuchal rigidity, Oedema, Oedema peripheral, Oesophagitis, Oropharyngeal pain, Orthostatic hypotension, Pain, Pain in extremity, Palpitations, Pancreatitis, Paralysis, Parosmia, Pharyngitis, Phlebitis, Photosensitivity reaction, Pneumonia, Pollakiuria, Proctalgia, Pruritus, Rash, Rectal haemorrhage, Rectal tenesmus, Refraction disorder, Rhabdomyolysis, Rhinitis, Seborrhoeic dermatitis, Shock, Sinusitis, Skin ulcer, Somnolence, Stomatitis, Swelling, Syncope, Tendinous contracture, Tenosynovitis, Thrombocytopenia, Tinnitus, Torticollis, Toxic epidermal necrolysis, Transient ischaemic attack, Ulcer, Urinary incontinence, Urinary retention, Urinary tract infection, Urticaria, Uterine haemorrhage, VIIth nerve paralysis, Vaginal haemorrhage, Vasodilation procedure, Vision blurred, Vomiting, Weight increased, White blood cells urine positive |
| Anaemia, Anaphylactic shock, Angioedema, Asthma, Confusional state, Deafness, Diarrhoea, Dyspepsia, Feeling abnormal, Haematemesis, Hearing impaired, Hyperhidrosis, Hypersensitivity, Leukopenia, Melaena, Nausea, Oedema, Pruritus, Purpura, Rash, Somnolence, Thirst, Thrombocytopenia, Tinnitus, Ulcer, Urticaria, Vascular purpura, Vertigo, Vomiting |
| Abdominal distension, Abdominal pain, Abdominal pain upper, Abdominal tenderness, Abscess, Acute coronary syndrome, Agranulocytosis, Alopecia, Alveolar osteitis, Alveolitis, Anaemia, Analgesic therapy, Anaphylactic shock, Anaphylactoid reaction, Angina pectoris, Angina unstable, Angioedema, Anxiety, Aphthous stomatitis, Aplastic anaemia, Arrhythmia, Arthralgia, Arthropathy, Asthenia, Asthma, Atopy, Atrial fibrillation, Back pain, Basal cell carcinoma, Bladder pain, Blister, Body temperature increased, Bradycardia, Breast cancer, Breast mass, Bronchitis, Bronchospasm, Bursitis, Calculus urinary, Cardiac |
| Salicylate is not listed in SIDER; we provide here the information for its artificial derivative acetylsalicylic acid (aspirin). |
| Rofecoxib is not listed in SIDER; we provide here the information for its artificial derivative rofecoxib. |
| Condition                                                                 |
|--------------------------------------------------------------------------|
| Heart failure                                                          |
| Cardiac failure congestive                                              |
| Cardiac fibrillation                                                    |
| Cellulitis                                                              |
| Cerebrovascular accident                                               |
| Cerumen impaction                                                      |
| Chest pain                                                              |
| Chills                                                                   |
| Cholecystitis                                                           |
| Colitis                                                                 |
| Confusional state                                                       |
| Congenital anomaly                                                      |
| Conjunctivitis                                                          |
| Constipation                                                            |
| Cough                                                                   |
| Cyst                                                                      |
| Cystitis                                                                |
| Cystitis noninfective                                                   |
| Death                                                                   |
| Deep vein thrombosis                                                    |
| Dental caries                                                           |
| Dermatitis                                                              |
| Dermatitis atopic                                                       |
| Dermatitis bullous                                                      |
| Dermatitis contact                                                      |
| Developmental delay                                                     |
| Diaphragmatic hernia                                                    |
| Diarrhoea                                                               |
| Disability                                                              |
| Discomfort                                                              |
| Dizziness                                                               |
| Dry mouth                                                               |
| Dry throat                                                              |
| Duodenal perforation                                                    |
| Duodenal ulcer                                                          |
| Dysgeusia                                                               |
| Dyspepsia                                                               |
| Dyspnoea                                                                |
| Dysuria                                                                 |
| Ear infection                                                           |
| Embolism                                                                |
| Epigastric discomfort                                                   |
| Epilepsy                                                                |
| Epistaxis                                                               |
| Erythema                                                                |
| Fatigue                                                                 |
| Feeling abnormal                                                        |
| Flatulence                                                              |
| Fluid retention                                                         |
| Flushing                                                                |
| Fungal infection                                                        |
| Gastric disorder                                                        |
| Gastric perforation                                                     |
| Gastric ulcer                                                           |
| Gastritis                                                               |
| Gastroenteritis                                                         |
| Gastrointestinal disorder                                               |
| Gastrointestinal haemorrhage                                            |
| Gastrointestinal pain                                                   |
| Gastrooesophageal reflux disease                                       |
| Haematochezia                                                           |
| Haematoma                                                               |
| Haemoglobin                                                             |
| Haemorrhage                                                             |
| Haemorrhoids                                                            |
| Hallucination                                                           |
| Heart rate irregular                                                    |
| Hepatic failure                                                         |
| Hepatitis                                                               |
| Hernia                                                                  |
| Herpes simplex                                                          |
| Herpes zoster                                                           |
| Hypercholesterolaemia                                                   |
| Hyperhidrosis                                                           |
| Hyperkalaemia                                                           |
| Hypersensitivity                                                        |
| Hypertension                                                            |
| Hypertensive crisis                                                     |
| Hypoesthesia                                                            |
| Hyponatraemia                                                           |
| Infarction                                                              |
| Infection                                                               |
| Influenza                                                               |
| Insomnia                                                                |
| Intestinal obstruction                                                 |
| Jaundice                                                                |
| Joint swelling                                                          |
| Laryngitis                                                              |
| Leukocytoclastic vasculitis                                            |
| Leukopenia                                                              |
| Loss of consciousness                                                  |
| Lymphoma                                                                |
| Meningitis                                                              |
| Meningitis aseptic                                                     |
| Menopausal symptoms                                                     |
| Menopause                                                               |
| Menstrual disorder                                                      |
| Mental disorder                                                         |
| Mouth ulceration                                                        |
| Muscle spasms                                                          |
| Muscular weakness                                                       |
| Musculoskeletal discomfort                                             |
| Musculoskeletal pain                                                    |
| Musculoskeletal stiffness                                              |
| Myalgia                                                                 |
| Myocardial infarction                                                  |
| Myopathy                                                                |
| Nasal congestion                                                        |
| Nausea                                                                  |
| Neoplasm                                                                |
| Neoplasm malignant                                                     |
| Nephritis                                                               |
| Neuropathy peripheral                                                   |
| Nocturia                                                                |
| Obstruction                                                             |
| Oedema                                                                  |
| Oedema peripheral                                                       |
| Oesophageal disorder                                                    |
| Oesophageal ulcer                                                       |
| Oesophagitis                                                            |
| Oral disorder                                                           |
| Oral infection                                                          |
| Osteoarthritis                                                          |
| Otitis media                                                            |
| Pain in extremity                                                       |
| Palpitations                                                           |
| Pancreatitis                                                            |
| Pancytopenia                                                            |
| Paraesthesia                                                            |
| Pelvic pain                                                             |
| Pharyngitis                                                             |
| Photosensitivity reaction                                               |
| Pneumonia                                                               |
| Procedural pain                                                         |
| Pruritus                                                                |
| Pulmonary congestion                                                    |
| Pulmonary embolism                                                      |
| Pulmonary oedema                                                        |
| Rash                                                                    |
| Renal failure                                                           |
| Renal failure acute                                                     |
| Renal failure chronic                                                   |
| Respiratory tract congestion                                           |
| Respiratory tract infection                                             |
| Rhinitis                                                                |
| Rhinitis allergic                                                       |
| Sciatica                                                                |
| Shock                                                                   |
| Sinusitis                                                               |
| Somnolence                                                              |
| Stomatitis                                                              |
| Swelling                                                                |
| Syncope                                                                 |
| Tachycardia                                                             |
| Tenderness                                                              |
| Tendonitis                                                              |
| Thrombocytopenia                                                        |
| Thrombosis                                                              |
| Tinnitus                                                                |
| Tonsillitis                                                             |
| Tooth impacted                                                          |
| Toothache                                                               |
| Toxic epidermal necrolysis                                              |
| Transient                                                               |
| ischaemic attack<sup>6</sup>, Tubulointerstitial nephritis<sup>8,9</sup>, Ulcer, Upper respiratory tract infection, **Urinary retention**<sup>8</sup>, Urinary tract infection, Urticaria, Vaginal infection, Vaginal inflammation, Vasculitis, Venous insufficiency, Venous thrombosis, Ventricular extrasystoles, Vertigo, Viral diarrhoea, Viral infection, Vision blurred, Vomiting, **Weight increased**<sup>6</sup>, Xerosis |
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