**Annotation of co-expression modules to biological function**

To identify common biological functions of the genes within each module, overrepresentation analysis on the Gene Ontology (GO) was performed. For 10 out of 14 modules, a significant overrepresentation (adjusted p-value < 0.01) in at least one GO term was found (Table 1). The module for which the most significantly enriched GO terms were identified was module B, annotated to immune and inflammation related functions. Metabolic process related GO terms were enriched for module genes from module A, module C (lipid and acyl-CoA metabolism), and module M (electron transport chain). The term “regulation of primary metabolic processes” was enriched with genes from module H, implying a regulatory role for the proteins encoded by the genes in this module. The module G was enriched for circadian rhythm genes, in concordance with previous findings that hepatic circadian rhythm gene expression is strongly affected by HFD [1].

**Correlation of co-expression to disease parameters**

For the 14 modules with a valid eigengene, correlations were calculated with each of the 16 disease parameters measured in the ADT dataset. In total, 10 significant correlations between modules and disease parameters were found (|r| > 0.75, p < 1E-7, Table 1). These correlations include 4 co-expression modules (A, B, C, E) and 4 different parameters (liver weight, atherosclerosis, cholesterol, and triglycerides), with much overlap between these disease parameters (Supplementary figure 3-1, see below).

The disease parameters related to dyslipidemia, which were previously found to be deteriorated after both drug interventions (plasma and intrahepatic triglycerides, cholesterol, atherosclerotic lesion area, liver weight) correlated with multiple co-expression modules. In contrast, although glycemia / insulin sensitivity related disease parameters (glucose, insulin, QUICKI) and obesity (body weight, epididymal fat weight) are fully resolved by T0901317 and partly by fenofibrate [1], no co-expression module correlated with these parameters. This indicates that hepatic target activation determines changes in dyslipidemia rather than disglycemia.

**Selection of co-expression modules driven by interventions**

Since the co-expression network was generated based on data from all intervention groups (HFD, DLI, T0901317 and fenofibrate) there is a possibility that some interventions determine the correlations within the module more than others. To investigate which modules are driven by which treatments, we performed over-representation analysis of differentially expressed genes (DEGs) relative to the control (HFD) group (Supplementary table 3-1, see below). An enrichment with DEGs for a given intervention indicates that the gene expression in the module is affected by that intervention and thus that the module may be relevant for explaining the link between the intervention target and disease parameter.

Several modules showed a distinct enrichment for specific interventions, such as two modules that were enriched for DLI but not drug interventions (E, G), modules enriched for both drug interventions but not DLI (D, M), and modules enriched specifically for T0901317 (J, L), or fenofibrate (K). Interestingly, several modules were enriched specifically for DEGs of drug interventions and not for DEGs of HFD...
(D, J, L, M), which indicates the underlying mechanisms are not inherent to the disease induced by HFD but are nevertheless affected by drug intervention. For example, module M is enriched for genes for which the protein products participate in the electron transport chain, which are expected to increase especially after intervention with both fenofibrate and T0901317 [2], as result of increased hepatic fatty acid oxidation. Three modules (H, I, F) were not enriched for any of the diet or drug interventions. These modules also showed very poor correlations with any of the disease parameters, and their gene co-expression may be due to confounding factors not directly related to the disease process.

In addition to over-representation analysis, the DEGs for interventions were split into three groups indicating genes for which the expression is either reversed compared to HFD condition (changed in HFD vs chow and changed in opposite direction for intervention vs HFD), regulated in the same direction, i.e. deregulated compared to HFD condition (changed in HFD vs chow, and in same direction for intervention vs HFD), or specific for the intervention (not changed in HFD vs chow, but changed in intervention vs HFD). This provides insight in which intervention may revert, aggravate, or introduce additional deregulation of module genes.

The results for the three modules with significant GO annotation and correlation to a disease parameter (A, B, C) are shown in Table 2. All three modules are enriched for genes differentially expressed after HFD, which are largely reversed by DLI. This is in concordance with the observed improvement by DLI of the disease parameters correlating with these modules. In contrast, the drug interventions further deregulate nearly all genes in the module that were also regulated by HFD. These opposite effects match the observed deterioration of the corresponding disease parameters by both drug interventions. In addition, the modules show a large part of additional genes regulated by drugs that were not deregulated by disease, indicating that the drug interventions target or result in different metabolic and immune-related mechanisms than those related to disease progression.

Module B, annotated to immune response and inflammation related processes, was most strongly enriched with DEGs for the T0901317 intervention. Notably, the majority of DEGs (141 out of 146) in the module were upregulated by T0901317 compared to HFD and show the opposite response for DLI where these are downregulated compared to HFD. These genes include genes encoding for several macrophage markers (CD14, CD68, LYZ), and immune cell specific proteins (CD86, CD74, CD83, CD52, CD53, Rac2).

**Tables & Figures**
Supplementary Figure 3-1: Heatmap of the correlations between all modules with a valid eigengene (rows) and all disease parameters (columns). Each cell displays the correlation coefficient and corresponding p-value. Each cell is shaded by correlation coefficient, where red is positive correlation and green is negative correlation.

| Treatment | moduleSize | moduleDeg | pvalue | reversed | deregulated | additional | reversed % | deregulated % | additional % |
|-----------|------------|-----------|--------|----------|-------------|------------|-----------|--------------|-------------|
| D (green) |            |           |        |          |             |            |           |               |             |
| 16wkHighFat | 185        | 16        | 0.998804 | 0        | 0           | 0          | 0         | 7            | 0           |
| LifeStyle | 185        | 16        | 0.743861 | 12       | 0           | 7          | 0         | 63,15789     | 0           |
| Fenofibrate | 185       | 62        | 2.9506   | 9        | 2           | 51         | 0         | 14,51613     | 0           |
| T0901317 | 185        | 121       | 2.82E-29 | 13       | 3           | 105        | 7         | 10,7438      | 2,479339    |
| B (red)   |            |           |        |          |             |            |           |               |             |
| 16wkHighFat | 185        | 16        | 5,32E-23 | 0        | 18          | 76,62338   | 0         | 23,37662     | 86,77686    |
| LifeStyle | 161        | 79        | 9,62E-31 | 59       | 0           | 18         | 0         | 76,62338     | 23,37662    |
| Fenofibrate | 161       | 31        | 0.539475 | 1        | 9           | 21         | 0         | 3,225806     | 29,03226    |
| T0901317 | 185        | 146       | 7,58E-68 | 1        | 72          | 73         | 69        | 0.684932     | 49,31507    |
| J (cyan)  |            |           |        |          |             |            |           |               |             |
| 16wkHighFat | 83         | 4         | 0.999591 | 0        | 0           | 0          | 0         | 9            | 0           |
| LifeStyle | 83         | 9         | 6,33054  | 0        | 0           | 9          | 0         | 0            | 100         |
| Fenofibrate | 83        | 26        | 0.005977 | 1        | 0           | 25         | 0         | 3,846154     | 96,15385    |
| T0901317 | 83         | 71        | 9,32E-30 | 4        | 0           | 67         | 5         | 5,633803     | 94,3662     |
| N (orange)|            |           |        |          |             |            |           |               |             |
|               |        |      |            |      |   |   |  NaN |   NaN |   NaN |
|---------------|--------|------|-----------|------|---|---|------|-------|-------|
| **16wkHighFat**| 22     | 13   | 4.91E-06  |      |   |   |       |       |       |
| **Lifestyle**  | 22     | 0    | 1         | 0    | 0 | 0 |       |       |       |
| **Fenofibrate**| 22     | 8    | 0,046651  | 0    | 3 | 5 |       | 37.5  | 62.5  |
| **T0901317**  | 22     | 15   | 4.59E-05  | 0    | 8 | 7 |       | 53.3333| 46.6667|
| **A (yellow)** | 197    | 49   | 0,000726  |      |   |   |       |       |       |
| **Lifestyle**  | 197    | 46   | 1.98E-06  | 26   | 0 | 20|       | 56,52174| 0     | 43,47826|
| **Fenofibrate**| 197    | 157  | 2.36E-76  | 0    | 36| 121|       | 22,92994| 77,07006|
| **T0901317**  | 197    | 194  | 1.03E-109 | 0    | 48| 146|       | 24,74227| 75,25773|
| **E (royalblue)** | 51     | 43   | 5.49E-27  |      |   |   |       |       |       |
| **Lifestyle**  | 51     | 26   | 4.82E-12  | 26   | 0 | 0 | 100  | 0      | 0     |
| **Fenofibrate**| 51     | 17   | 0,012487  | 0    | 13| 4  |       | 76,47059| 23,52941|
| **T0901317**  | 51     | 11   | 0,821625  | 1    | 7 | 3  |       | 9,090909| 63,63636| 27,27273|
| **H (purple)** | 118    | 9    | 0,997686  |      |   |   |       |       |       |
| **Lifestyle**  | 118    | 10   | 0,888987  | 7    | 0 | 3 | 70   | 0      | 30    |
| **Fenofibrate**| 118    | 35   | 0,004349  | 2    | 1 | 32 |       | 5,714286| 2,857143| 91,42857|
| **T0901317**  | 118    | 27   | 0,827919  | 2    | 0 | 25 |       | 7,407407| 0     | 92,59259|
| **I (greenyellow)** | 112    | 3    | 0,999999  |      |   |   |       |       |       |
| **Lifestyle**  | 112    | 10   | 0,848432  | 1    | 0 | 9 | 10   | 0      | 90    |
| **Fenofibrate**| 112    | 4    | 1         | 0    | 0 | 4 | 0    | 0      | 100   |
| **T0901317**  | 112    | 2    | 1         | 0    | 0 | 2 | 0    | 0      | 100   |
| **K (lightyellow)** | 54     | 29   | 1,67E-10  |      |   |   |       |       |       |
| **Lifestyle**  | 54     | 5    | 0,763991  | 5    | 0 | 0 | 100  | 0      | 0     |
| **Fenofibrate**| 54     | 28   | 8,29E-08  | 21   | 0 | 7 | 75   | 0      | 25    |
| **T0901317**  | 54     | 16   | 0,335     | 12   | 0 | 4 | 75   | 0      | 25    |
| **G (magenta)** | 125    | 92   | 4,26E-47  |      |   |   |       |       |       |
| **Lifestyle**  | 125    | 56   | 6,13E-21  | 54   | 0 | 2 |       | 96,42857| 0     | 3,571429|
| **Fenofibrate**| 125    | 7    | 0,999998  | 5    | 2 | 0 |       | 71,42857| 28,57143| 0     |
| **T0901317**  | 125    | 10   | 1         | 2    | 4 | 4 | 20   | 40     | 40    |
| **C (black)**  | 142    | 59   | 2,04E-13  |      |   |   |       |       |       |
| **Lifestyle**  | 142    | 52   | 4,99E-15  | 40   | 0 | 12|       | 76,92308| 0     | 23,07692|
| **Fenofibrate**| 142    | 125  | 3,55E-71  | 0    | 51| 74 |       | 40,8   | 59,2  |
| **T0901317**  | 142    | 123  | 4,24E-52  | 1    | 50| 72 |       | 8,813008| 40,65041| 58,53659|
| **F (blue)**   | 369    | 21   | 1         |      |   |   |       |       |       |
| **Lifestyle**  | 369    | 40   | 0,695422  | 13   | 0 | 27|       | 32,5   | 0     | 67,5  |
| **Fenofibrate**| 369    | 9    | 1         | 0    | 0 | 9 | 0    | 0      | 100   |
| **T0901317**  | 369    | 21   | 1         | 5    | 1 | 15 |       | 23,80952| 4,761905| 71,42857|
| **L (darkgreen)** | 41     | 13   | 0,008985  |      |   |   |       |       |       |
**Supplementary table 3-1:** Results of the over-representation analysis of differentially expressed genes (DEGs) relative to the control (HFD) group in the modules. The same as table 2, but showing results for all modules with a valid eigengene.

**References:**

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