Supplementary Figure S1: Cross-sectional microarray analysis approach. Two separate analyses were performed: one comparing the gene expression profiles of untreated and IFN treated patients only (A), and another one comparing the gene expression profiles of untreated patients and healthy controls only (B). Differentially expressed genes were identified in the discovery data set and then validated in the replication data set. In the discovery data set, a variance filter (difference between the 10% and 90% quantiles > 0.7, yielding 6595 genes (A) or > 0.6, yielding 8678 genes (B)) was applied to normalized gene expression values in order to decrease the number of tested genes. Then, group 1 (untreated patients) was compared to group 2 (IFN treated patients or averaged controls) at any of the three measured time points. The union of genes at all three time points passing the FDR cutoff of 0.0001 (A) or 0.01 (B) were considered to be differentially expressed and assessed for differential expression in the replication data set. Here, the procedure was repeated: group 1 (untreated patients) was compared to group 2 (IFN treated patients or averaged controls) at all three measured time points, and the union of genes reaching a nominal p-value of 0.05 or smaller at any of these time points was considered to be replicated. vs.: versus, FDR: false discovery rate, Ctrls: Controls.
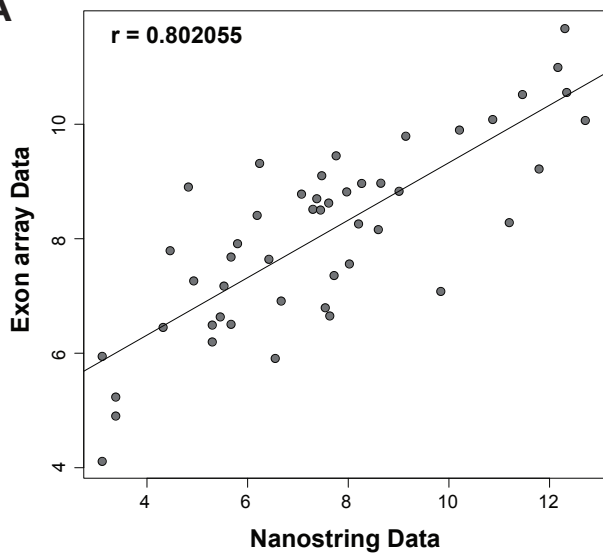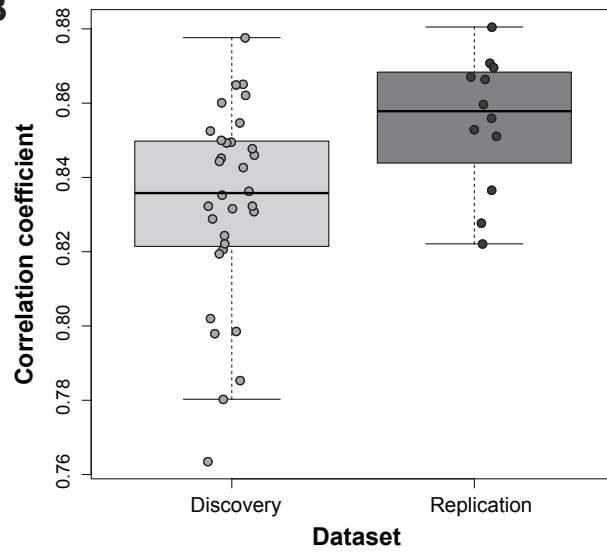
Supplementary Figure S2: Correlation of microarray data with an independent data set. RNA from 20 patients whose gene expression was profiled with the exon arrays were re-extracted and the expression of 48 selected genes and three housekeeping genes was assessed using Nanostring nCounter® assays. A: Correlation between the microarray and Nanostring data for one exemplary sample (log2 transformed relative expression values are shown). B: Correlation coefficients for all re-assessed samples, split by discovery and replication data set.
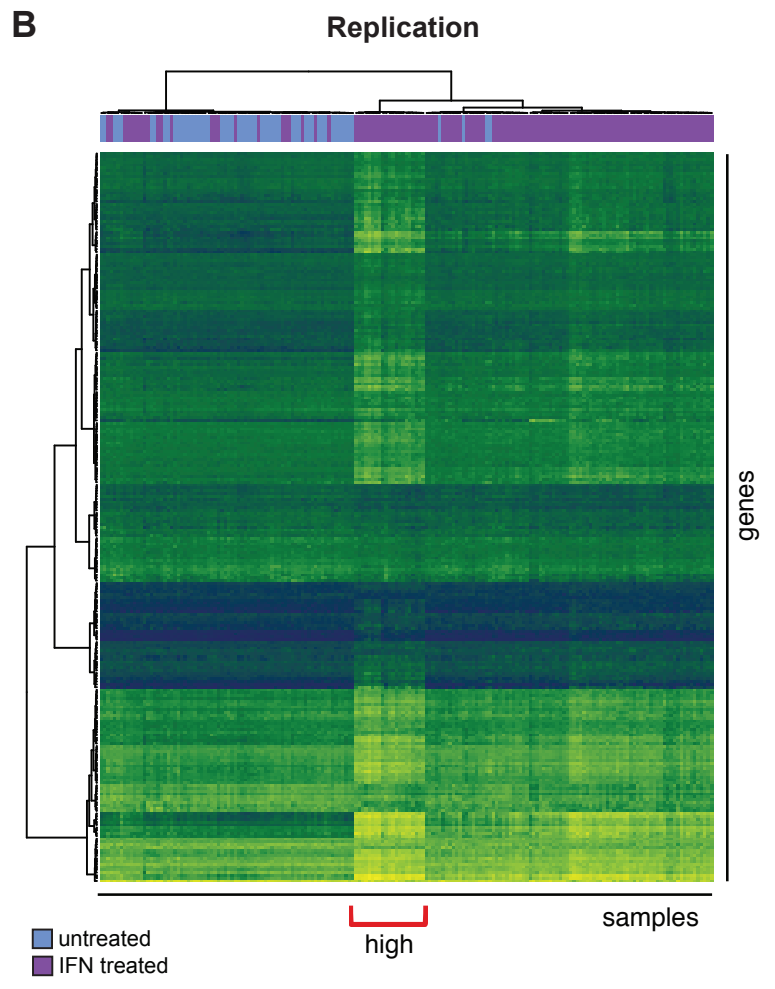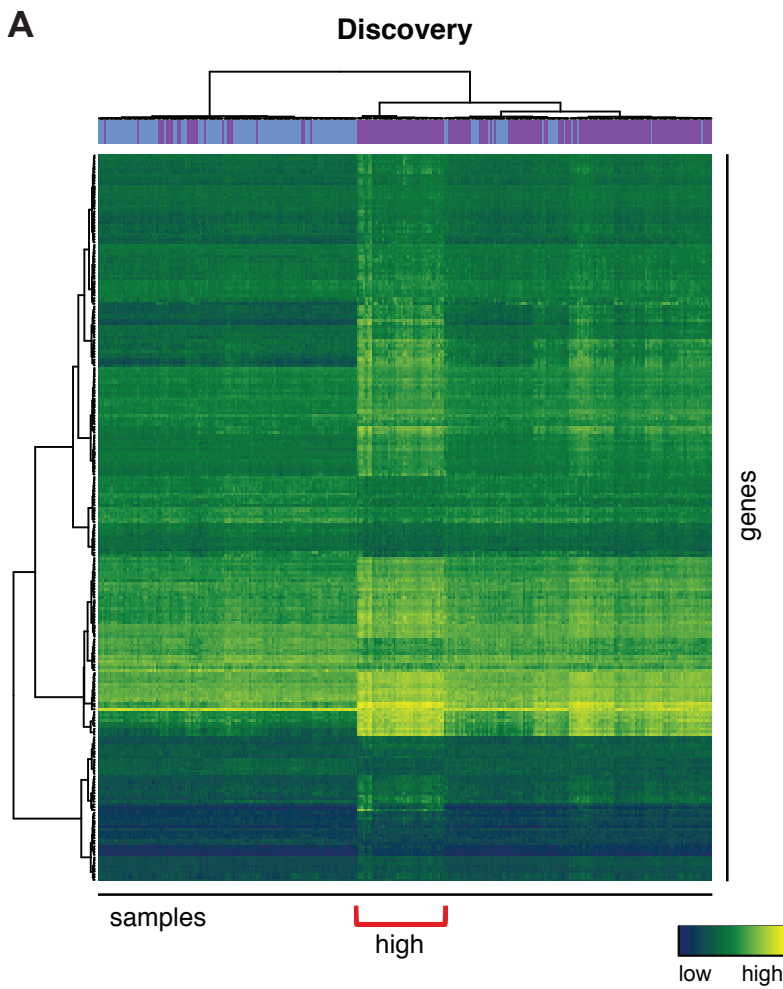
Supplementary Figure S3: Unsupervised hierarchical clustering of untreated and IFN treated patients according to expression of IFN signature genes in the discovery (A) and the replication (B) data sets. The rows are different genes, the columns reflect different experiments. The colored bar above the heatmap visualizes whether the patient was untreated (light blue) or IFN treated (violet). A subset of patients in both data sets shows an especially strong IFN response (high IFN gene expression; marked by red brackets). Dark blue depicts low, yellow high expression. Hierarchical clustering was performed using maximum distance and ward clustering.
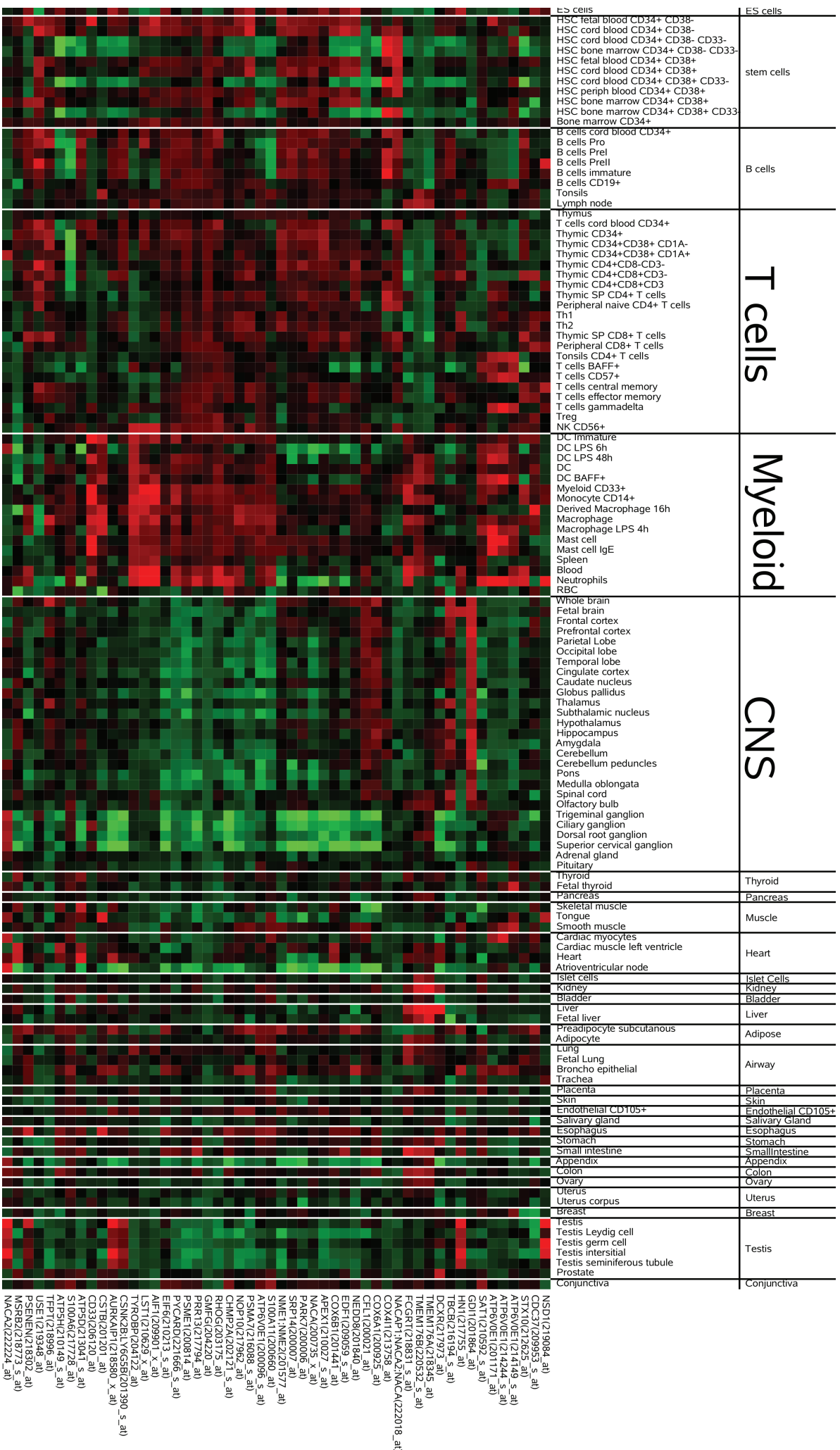
Supplementary Figure S4: Expression of a subset of the MS genes in different tissues. All genes of the MS signature, which were assessed in the Gene Expression Profiler, are displayed as rows in the heatmap (gene symbols and Affymetrix U133A array identifiers are given). Columns reflect different experiments, corresponding to different tissues. Green depicts low, red high expression.
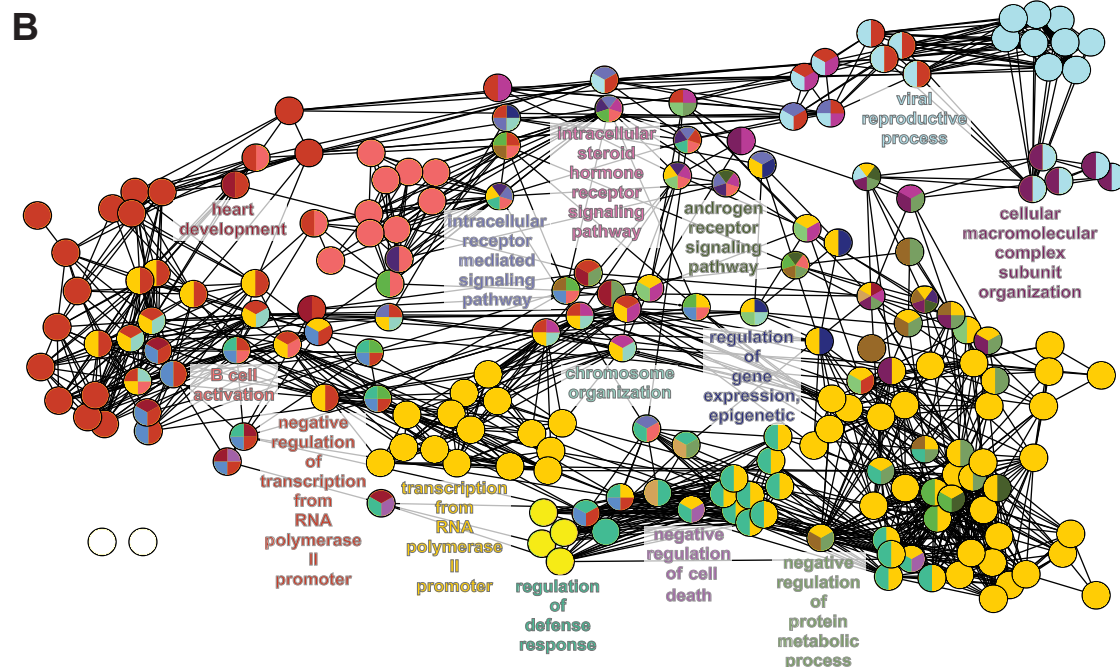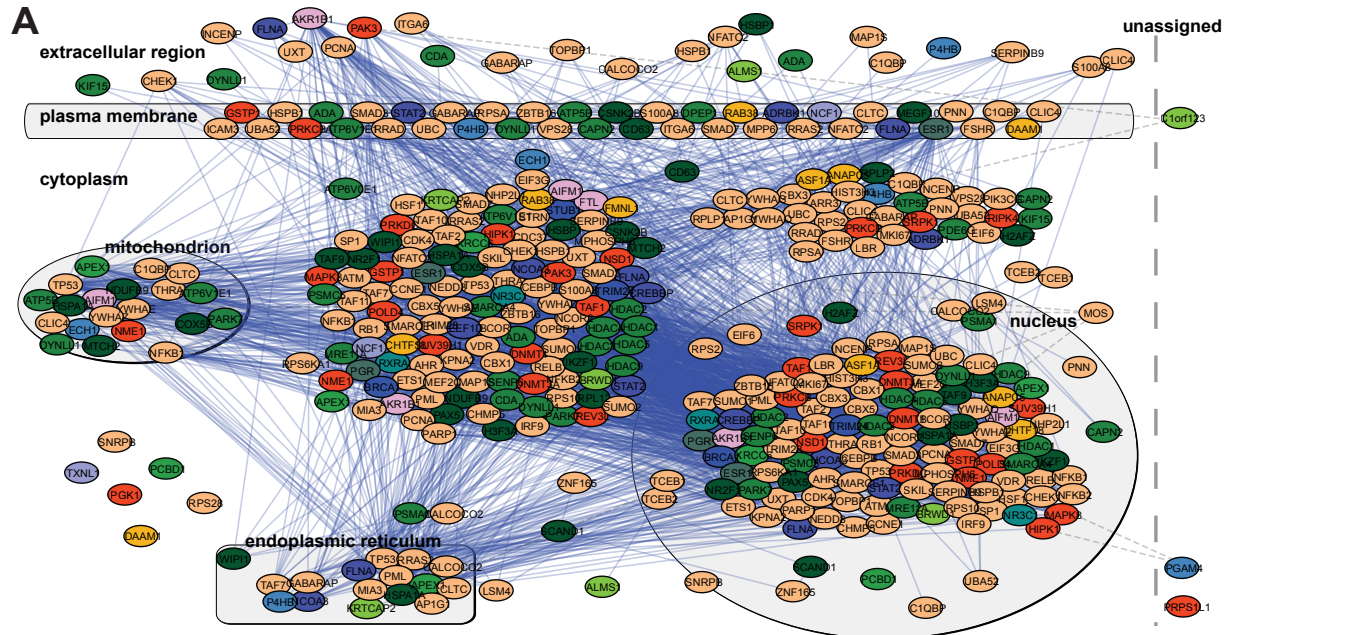
Supplementary Figure S5: Two network presentations of one representative module of the "MS network". The list of transcripts differentially expressed between MS and healthy controls was used to create protein-protein interaction networks based on the p-values reflecting confidence of differential expression. One network module, network 8, is depicted as representative network. All visualizations were created within Cytoscape. **A:** Mosaic-based visualization of all components of network 8. Proteins are displayed according to GOSlim cellular component. Colors are based on their molecular function: skin represents protein binding (GO:0005515), orange binding (GO:0005488), grass-green molecular function (GO:0003674), green hydrolase activity (GO:0016787), olive lyase activity (GO:0016829), red transferase activity (GO:0016740), pink oxidoreductase activity (GO:0016491), bright pink ligase activity (GO:0016874), light purple electron carrier activity (GO:0009055), purple molecular transducer activity (GO:0060089), teal lipid binding (GO:0008289), slate hormone binding (GO:0042562), blue isomerase activity (GO:0016853); dark green: unassigned. B: Visualization of GO categories enriched in network 8, as assessed by the Cytoscape plugin ClueGO.