SUPPLEMENTAL METHODS

Expression data pre-processing

For each therapeutic trial, baseline and post-treatment samples for improvers and non-improvers were pre-processed separately. Non-centered gene expression data were imputed for missing values and collapsed to unique genes via corresponding GenePattern (Reich et al., 2006) modules with default settings and median-centered via Cluster 3.0 (de Hoon et al., 2004).

Functional enrichment analyses and differential pathway expression

All functional enrichment analyses throughout the work were performed using the gprofiler function in the gProfileR R package (Reimand et al., 2011) with default parameters. Differentially expressed pathways were identified using Gene Set Enrichment Analysis (GSEA) (Subramanian et al., 2005) and the Hallmark database (Liberzon et al., 2015). Hallmarks with False Discovery Rate $\leq$5% were treated as significant. GSEA runs were done via the GenePattern module with default settings except for permutation type, which was changed to 'gene set' due to the small sample sizes.

Hallmarks hit by multiple drugs were investigated in more detail. For each drug, core enrichment genes (genes that contribute most to the enrichment) for a given significant Hallmark were compared to core enrichment genes from this Hallmark hit by other drugs. This way, for each Hallmark we generated core enrichment gene signatures hit by multiple drugs.

Functional association between drug signatures

For performing functional associations between drug signatures, the top-ranking 250 genes from each signature were considered the "gene set" for that drug. Those gene symbols were converted to Entrez IDs using gconvert as implemented in the gProfileR R package (Reimand et al., 2011). Functional association scores (z-scores) were calculated as described in Huttenhower, et al. (Huttenhower et al., 2009) and Greene, et al. (Greene et al., 2015). Briefly, for drug pair *i* and *j*, the t-statistic between the two gene sets is calculated as follows:

$$t_{i,j} = \frac{X_w - X_b}{s_x} \ , \ s_x = \sqrt{\frac{{s_w}^2}{n_w} + \frac{{s_b}^2}{n_b}}$$

where X_w is the mean weight of all edges between the drug gene sets, X_b is the mean weight of all edges incident to either gene set in the GIANT skin network, and *s* and *n* are the standard deviation and size of the distributions. The z-score (functional association statistic) was calculated by generating a null distribution (1,000 random gene set pairs of the same sizes as drug gene sets *i* and *j*), where ti,j is the t-statistic between the drug pair (as calculated above) and μ and s are the mean and standard deviation of the null distribution, respectively.

$$z_{i,j} = \frac{t_{i,j} - \mu}{s}$$

Figure S2A, **S2B** and **S2C** were generated by calculating the functional association between different drugs' improver signatures, non-improver signatures, and the same drugs' improver and non-improver signatures ("within drug"), respectively.

Functional module analyses

Functional modules were detected using the top edges version of the GIANT skin network downloaded from the GIANT webserver (giant.princeton.edu). Fast-greedy modularity maximization (as implemented in the igraph R package (v0.7) (Csardi and Nepusz, 2006)) was applied iteratively until all communities were 150 genes or smaller. This was motivated by the fact that the average size of hallmark gene sets is ~150 genes and the average size of canonical pathways is ~50 genes. A histogram size of the functional modules detected is supplied as **Figure S4**.

For the improver lists, the SVM scores of genes in functional modules were compared to the overall SVM score distribution by two-sided Wilcoxon test. The raw p-values were Bonferroni adjusted; only functional modules with Bonferroni adj. $p < 0.001$ were further considered. We calculated the intersection between drugs' top or bottom 20 significant functional modules (as ranked by median SVM score [improver lists]) to generate **Table 2**. For the comparison of functional modules between the abatacept and MMF improver lists, SVM scores were standardized (we calculated z-scores).

Fresolimumab base and MMF post list comparisons

The extrapolated version of rank biased overlap (RBO) was calculated using the gespeR package (Schmich et al., 2015). The extrapolated RBO formula (Webber et al., 2010) is:

$$RBO_{EXT}(L,S,l,s) = \frac{1-p}{p}\left(\sum_{d=1}^{l}\frac{X_d}{d}p^d + \sum_{d=s+1}^{l}\frac{X_s(d-s)}{sd}p^d\right) + \left(\frac{X_l - X_s}{l} + \frac{X_s}{s}\right)p^l$$

where p is a weighting parameter (we selected $p = 1$ to place an emphasis on the top of the list), L and S are lists of depths l and s respectively, and d is the depth. X refers to the overlap (size of

the intersection) of lists S and T at the specified depth. The null distribution displayed in **Figure 4A** was generated by permuting the gene symbol labels of the MMF post ranked list. The KS-like test described as part of Connectivity Map (Lamb et al., 2006) was implemented in R. The permuted p-value was calculated by generating a null distribution of the KS statistic for gene sets of the same size (250 genes).

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SUPPLEMENTAL FIGURES

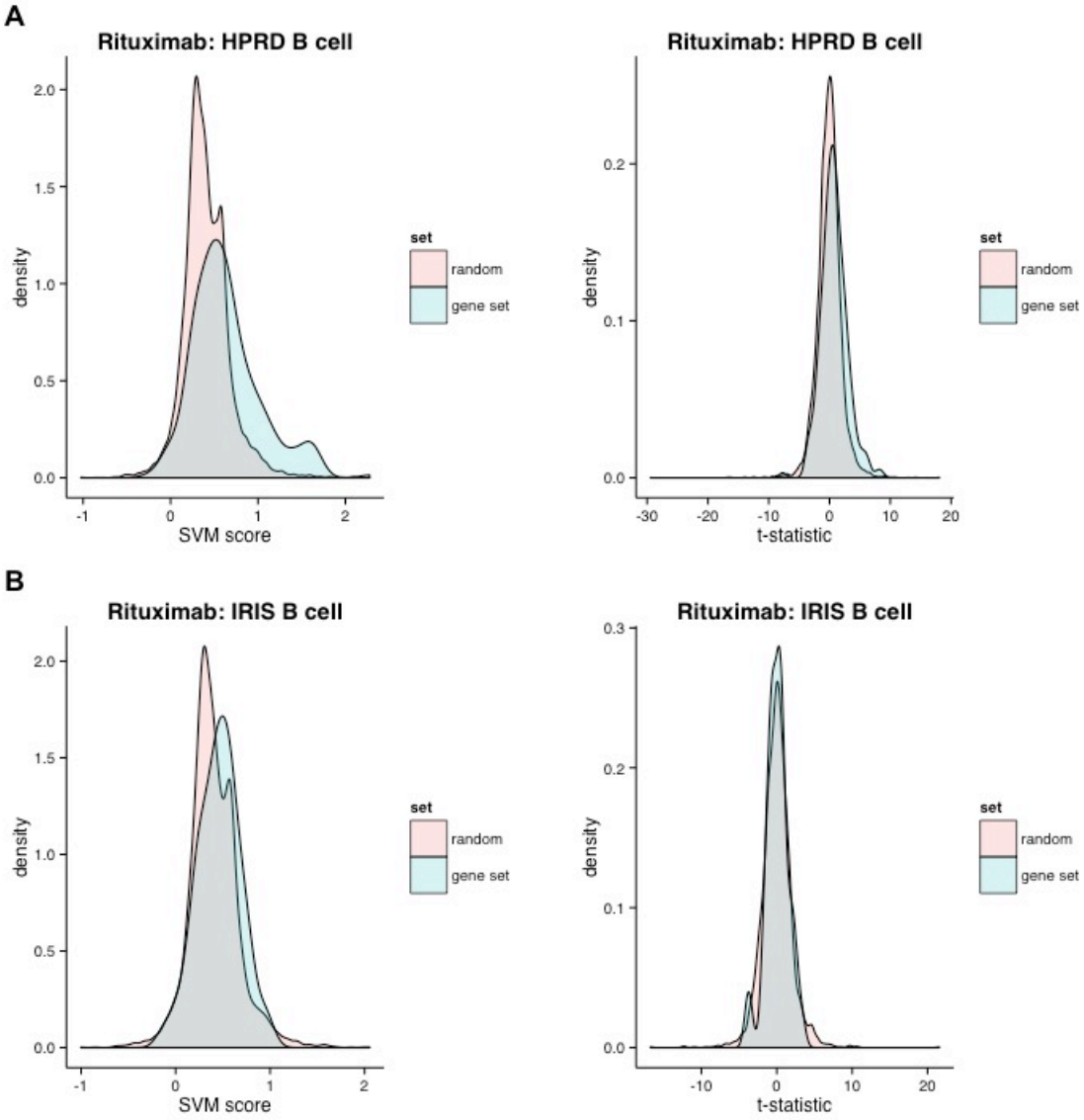

Figure S1. B cell genes, at either the gene expression (IRIS) or protein (HPRD) level, have significantly higher rituximab SVM scores than random gene sets of the same size. IRIS SVM score Mann-Whitney-Wilcoxon p = 0.029, IRIS t-statistic Mann-Whitney-Wilcoxon p = 0.38.

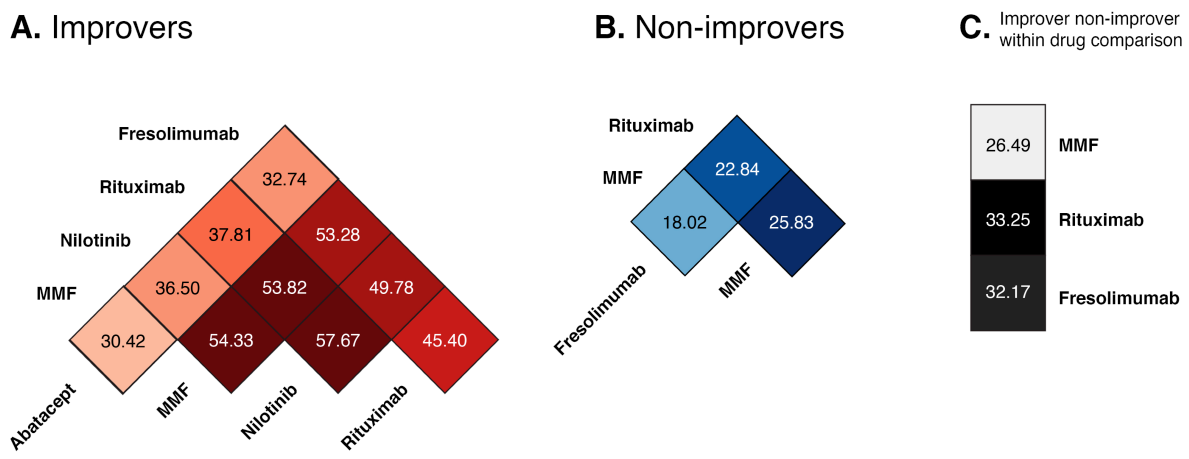

Figure S2. Z-scores were calculated to measure functional association between different drug signatures. Drug signatures were the 250 top-ranked genes (SVM scores) or all genes with positive scores (whichever list was smaller). High scores are indicative of significant association between signatures. (A) Improver signature associations. Genes that decrease post-treatment in improvers are highly significantly functionally related, suggesting common pathways are necessary for the resolution of skin disease regardless of drug mechanism of action. (B) Non-improver signature associations. Genes that decrease during treatment in patients with stable or slightly worse skin disease severity are functionally related, but less so than improver drug signatures. (C) Improver and non-improver signatures from the same drug — 'within drug' association — are significantly functionally related suggesting some common perturbation or 'treatment-effect' that can be detected using this approach. Network analysis techniques can be used to distinguish treatment network signature from improvement.

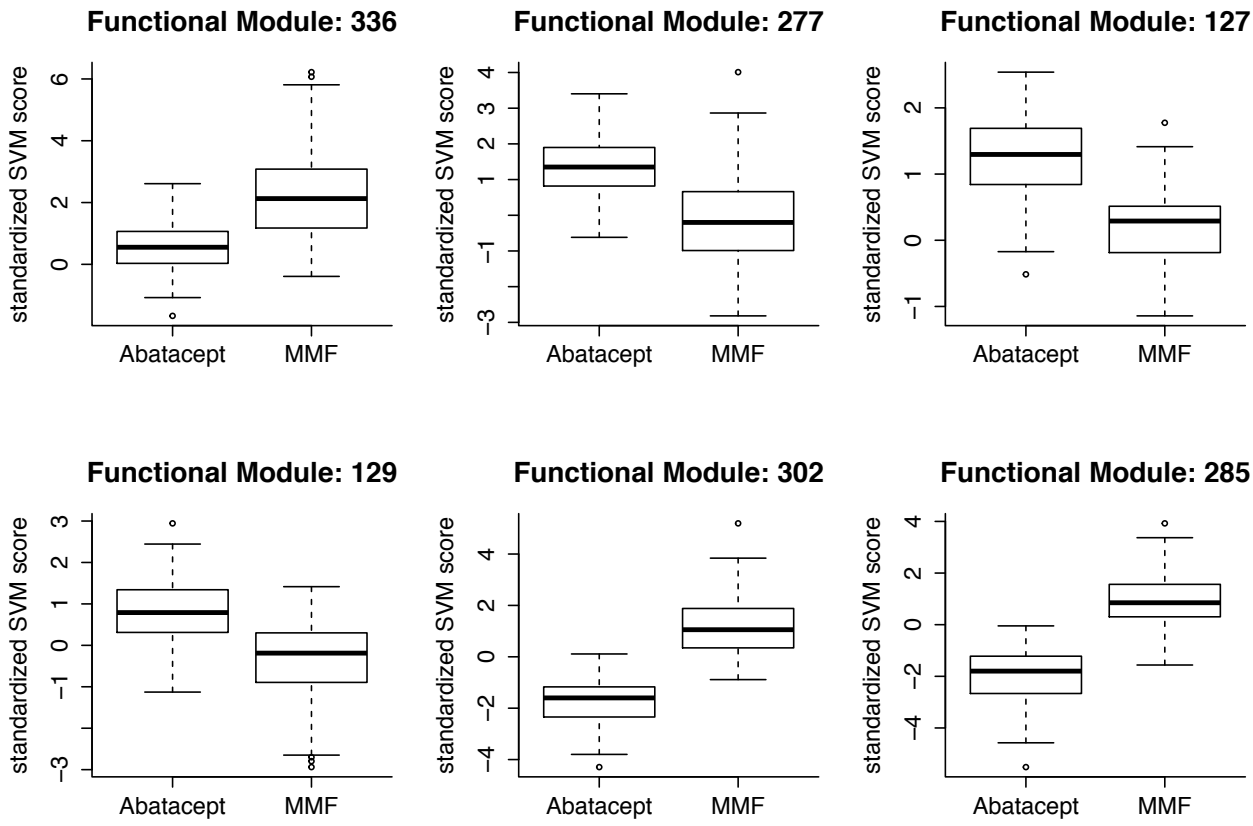

Figure S3. Boxplots of selected functional modules with significantly different standardized SVM scores between abatacept and MMF. Wilcoxon test, Bonferroni adj. $p < 0.0001$.

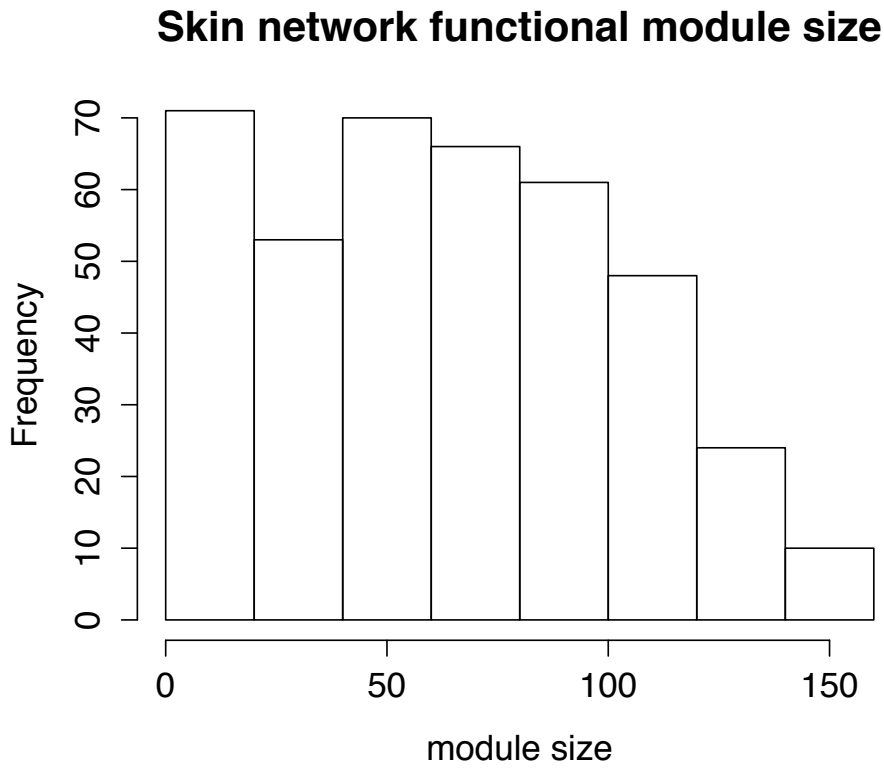

Figure S4. Distribution of genome-wide GIANT skin network functional module size (number of genes/vertices/nodes).

SUPPLEMENTAL TABLES

Treatment	N of patients in original study	N of patients included in this study[1]	Study type	GEO accession number	NCT number
Abatacept	7 (10)[2]	6	Phase 1, 2/RCT	GSE66321	NCT00442611
Fresolimumab	15	10	Phase 1	GSE55036	NCT01284322
MMF	34	18	Open-label	GSE76886	NCT00853788
Nilotinib	10	6	Phase 2/pilot	GSE65405	NCT01166139
Rituximab	13	11	Pilot	GSE32413	NA

Table S1. Detailed information about clinical trials analyzed in this study.

[1] – number of patients for which baseline and post-treatment gene expression data were available

[2] – abatacept study was the only one in which patients were randomized to placebo (3/10). In order to be consistent, we have excluded gene expression data available for placebo patients from this study (2/3).

GEO – Gene Expression Omnibus, NCT – National Clinical Trial, RCT – randomized controlled trial, NA – information not available.

Functional Module	Selected Enriched Biological Processes
Higher in Abatacept	
127	REACTOME Immunoregulatory interactions between a Lymphoid and Non-Lymphoid cell, GO BP positive regulation of gamma-delta T cell activation, GO BP interleukin-12 production, GO BP defense response to bacterium
129	GO BP vasculature development, GO BP angiogenesis, KEGG Wnt signaling, KEGG Vascular smooth muscle contraction
277	GO BP positive regulation of angiogenesis, GO BP elastic fiber assembly, GO CC complex of collagen trimers, REACTOME Collagen biosynthesis and modifying enzymes
Higher in MMF	
285	REACTOME DNA repair, KEGG Cell Cycle, GO BP cellular response to DNA damage stimulus, GO BP ATP-dependent chromatin remodeling
302	REACTOME G2/M Checkpoints, REACTOME Separation of Sister Chromatids, GO BP small GTPase mediated signal transduction, GO BP CENP-A containing chromatin organization
336	REACTOME RIG-I/MDA5 mediated induction of IFN-alpha/beta pathways, REACTOME Antigen processing-Cross presentation, GO BP response to type I interferon, GO BP negative regulation of viral life cycle

Table S2. Selected functional modules with significantly different standardized SVM scores between abatacept and MMF. Wilcoxon test, Bonferroni adj. $p < 0.0001$. Functional enrichment was performed using gProfileR (Reimand et al., 2011). GO BP and CC stand for Gene Ontology Biological Process and Cellular Component, respectively.

Drugs	Hallmarks	Common core enrichment genes
All	*EMT*	*IGFBP3, LOXL2, MMP3, PTX3, THBS1, TNC, VCAM1*
Abatacept MMF Nilotinib Rituximab	*Allograft rejection*	*BCL3, CCL2, CCR1, FAS, FYB, GZMA, GZMB, HLA-DMA, IFNGR1, LTB, SRGN, TNF, WARS*
	Apoptosis	*CASP1, FAS, GPX1, PPT1, TAP1, TNF, TNFRSF12A*
	Complement	*C3, CASP1, CDH13, GCA, GZMA, GZMB, LAP3, LTF, PLEK, PLSCR1, SERPINE1*
	IFNA response	*BATF2, CASP1, CD74, IFI35, IFIH1, IFIT3, IFITM1, IRF7, IRF9, LAMP3, LAP3, LPAR6, NMI, PARP9, PLSCR1, SAMD9, SAMD9L, SP110, WARS*
	IFNG response	*APOL6, BATF2, CASP1, CCL2, CD74, CXCL9, FAS, GZMA, HLA-DMA, HLA-G, IFIH1, IFIT3, IFITM3, IL18BP, IRF7, LAP3, LYSMD2, NFKB1, NMI, OASL, PLSCR1, SLAMF7, SP110, TAP1, VAMP5, VCAM1, WARS*
	IL6/JAK/STAT3 signaling	*A2M, CSF2RA, FAS, IFNGR1, IL1R1, LTB, SOCS3, STAT1, TNF, TNFRSF12A*
	Inflammatory response	*CCL2, CYBB, GPR183, IL15RA, IL1R1, LAMP3, NFKB1, NMI, SERPINE1*
	TNFA/NFKB signaling	*BCL3, BHLHE40, CCL2, CYR61, DRAM1, KLF10, NFKB1, NFKB2, NFKBIE, PANX1, PLAU, PLEK, PTX3, RELB, SERPINE1, TAP1, TNC, TNF*
Abatacept Fresolimumab Nilotinib Rituximab	*TGFB signaling*	*SERPINE1, THBS1*

Table S3. Hallmarks downregulated post-treatment in improvers.