Supplemental Methods:

Baseline study participant characteristics:

All SCOT participants fulfilled the 1980 American College of Rheumatology (formerly the American Rheumatism Association) preliminary classification criteria for SSc. (1) They also fulfilled the following inclusion criteria: Diffuse cutaneous involvement (2); age 18-69 years; disease onset within the previous 5 years (defined as the first non-Raynaud's phenomenon symptom); early internal organ involvement with either pulmonary disease (DLco or FVC <70%) or prior scleroderma renal crisis. A detailed description of the inclusion and exclusion criteria is provided in the main clinical outcome manuscript. (3)

For the confirmation of the neutrophil and cytotoxic/NK signatures in an independent sample, individuals with SSc and unaffected controls enrolled in the UT Houston Divisional Repository were examined. All individuals with SSc fulfilled the 1980 American College of Rheumatology (formerly the American Rheumatism Association) preliminary classification criteria for SSc (1) and disease duration was less than 7 years (from the first non-Raynaud's phenomenon symptom). The unaffected controls did not have a systemic autoimmune disease and were not 1st degree relatives of an individual with SSc.

Gene expression profiling and analysis:

The laboratory personnel conducted all the molecular assays without knowledge of disease or treatment group assignment. Initial quality control analysis did not reveal any batch effect according to hybridization dates. The raw data were exported into and analyzed with BRB-ArrayTools (National Cancer Institute, USA). The data were normalized according to Quantile method. Transcripts whose log intensity variance was below the 75th percentile were filtered out. A total of 11830 transcript passed the filtering criteria. Transcripts were considered as differentially expressed if false discovery rate was less than 5% (4) in the multivariate permutation in order to control for spurious findings due to multiple testing. For comparison of SSc samples to unaffected controls an unpaired analysis was used while the analysis of longitudinal samples was performed using a paired analysis.

Modular analysis statistics:

Modular analysis using 62 curated whole blood modules was conducted using the original repertoire analysis described in (5). Briefly, the approach allows for both a "population" and "sample" level aggregation of the transcripts within each module for ease of biological interpretation. For a given comparison of interest, population level analysis summarizes each module by recording the percentage of statistically up and down regulated genes within the corresponding module in comparison to the reference group. A similar approach can be done at the sample level. The resulting proportions are typically plotted using circles and color coded red for up and blue for down regulation.

In addition to the traditional repertoire analysis, a gene set analysis was conducted using the QuSAGE algorithm (6) for the modular analysis of differentially expressed genes. QuSAGE tests whether the average log2 fold change of a gene set is different from zero. The method correctly adjusts for gene-to-gene correlations within a gene set and provides an easy interpretable metric for the magnitude of differential regulation. A threshold value of FDR<0.05 and Log2 fold

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change >0.25 was used to identify differentially expressed modules for the baseline vs. control analysis. Considering the smaller sample size in the longitudinal analysis (e.g. n=17 for 26-month), a threshold of value of FDR<0.1 and Log2 fold change >0.25 was used for these analyses.

Serum protein composite scores:

Concomitantly collected serum samples were stored at -80° C and not thawed until tested. Samples were send to the CLIA certified Myriad Rule Based Medicine Laboratory (Austin, TX) for proteomic studies. Levels of 100 proteins included in the proprietary InflammationMAP v. 1.0 and ImmunoMAP v. 1.0 were determined using a Luminex instrument. In addition the two low-abundance cytokines, IL-6 and IL-10 were determined using the ultra-sensitive Simoa assays (Quanterix, Massachusetts, USA) (7). All experiments were performed in one batch. For the analysis, proteins with levels below the lower limit of quantification (LLOQ) in more than 50% of baseline SSc samples were excluded from the analysis. A total of 80 proteins (75.5%) had detectable level in more than 50% of baseline SSc samples. For these proteins, levels below the LLOQ were replaced by the LLOQ while proteins above the upper limit of quantitation (ULOQ) were replaced with ULOQ. Protein data were available in 60 SCOT participants (33 CYC, 27 HSCT) and 59 unaffected controls. All protein data were log-transformed. Pearson correlation was calculated to examine the correlation between the upregulated IFN and neutrophil transcript modules (M1.2, M3.4, M5.15) and these 80 serum cytokines in the baseline SSc and control samples. P-values were corrected for multiple testing using Benjamini-Hochberg FDR method (4). Serum proteins with the correlation coefficient of 0.3 or above (≥ 0.3 or ≤ -0.3) and $p_{FDR} < 0.05$ were considered as showing moderate correlation with the transcript modules. In the present study, none of proteins showed a significant negative correlation according to the above criteria. Of note, although the proteins included in the composite scores were identified based on a statistical approach, the majority of proteins correlating with the two IFN modules (M1.2 and M3.4) are known IFN inducible chemokines. (8) Subsequently, a 95 percentile value in the data set was determined for each correlating serum protein. A weighted score was calculated for each serum protein according to a previously published method (8-11) by dividing its level by the 95 percentile value. Those with a value above 95 percentile were assigned a weighted score of 1. Subsequently, serum protein composite scores for each transcript profile was calculated by sum of the weighted values of all correlating serum proteins for each sample. As expected, the baseline neutrophil protein composite score showed a moderate correlation with the concomitantly collected neutrophil counts (rs=0.51, p<0.001) while the IFN protein composite scores did show a significant correlation with the neutrophil count (p=0.349 and p=0.44 for M1.2 and M3.4 protein composite scores, respectively). A paired t-test was utilized to examine the longitudinal change in the protein composite scores.

Correlation with clinical parameters:

Lung involvement is the primary disease related cause of death in SSc (12, 13). In the present study, 58 SCOT participants (93.5%) had signs of interstitial lung disease (ILD) on high resolution chest Computer tomography. FVC% was selected as the surrogate marker for lung involvement. FVC% is a validated clinical measure for SSc-ILD (14, 15). FVC% was calculated according to individual's age, sex, race, height, and weight. Furthermore, skin fibrosis is a

prominent source of morbidity in SSc. mRSS, a validated clinical measure for skin fibrosis (14, 16), was also examined in the present study. Spearman's correlation was used to correlate the percent change in the aforementioned clinical measures and transcript module composite scores.

Similarity Network Fusion analysis:

A Similarity Network Fusion analysis of multilevel longitudinal molecular data was performed in all SCOT participants with an available 26-month sample (n=35; 18 in CYC arm and 17 in the HSCT arm). Also 35 age-, and gender-matched unaffected controls were included.
Global gene expression profile of all transcripts whose log intensity variance was in the top 25% (n=11830) were included. Furthermore, all 80 longitudinally examined serum proteins were analyzed.
The processed gene and protein expression data were used to calculate the Spearman correlation among investigated samples at each level, separately. The two resulting similarity matrices were used to create a neighborhood networks to highlight the relationship among the closest neighbors.
The previously described Similarity Network Fusion approach was used (17) to merge the two networks created based on the gene expression and serum protein data. The Similarity Network Fusion iteratively passes the weight information of the edges between the networks to be fused so that the updated networks get more similar and eventually converge to an equal network. Weak connections are removed during the process. This is an effective process to integrate and analyze heterogeneous data by creating a coherent yet robust network. Subsequently, spectral clustering method (18) was applied to identify clusters at each molecular level and on the merged network.

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Supplemental results:

Itemization of available SCOT RNA samples in the per protocol population:

Among 62 participants included in the baseline study, 56 belonged to the per protocol population (HSCT= 26 and CYC=30). From whom, 46 eight-month samples (23 in each arm) as well as 35 twenty-six month samples (17 in HSCT and 18 in CYC) were investigated. In the HSCT per protocol group, 9 participants with baseline RNA sample did not have a follow-up sample at 26 months because 3 had died, 2 samples were not available in the SCOT biorepository, and 4 RNA samples were not of sufficient quality. In the CYC per protocol group, 12 participants with a baseline RNA sample did not have a follow-up sample at 26 months because 2 had died, 2 met the pre-defined organ failure endpoint, 1 withdrew, 2 samples were not available in the SCOT biorepository, and 5 RNA samples were not of sufficient quality.

Relationships among the neutrophil, IFN, and inverse Cytotoxic/NK cell modules in the baseline SCOT samples

The relationships among the four confirmed differentially-expressed SSc modules were investigated in the SCOT study. Supplemental Figure 2 shows an unsupervised clustering of these four modules in the baseline samples of SCOT participants compared to the average of controls. As shown in this Figure, the two IFN modules, M1.2 and M3.4 usually co-occur. This finding is also supported by the high correlation coefficient of rs=0.97 ($p<0.001$) between these two modules. An upregulation of the Neutrophil M5.15 and a down regulation of Cytotoxic/NK module M3.6 can exist independent of the IFN signature, as demonstrated by the insignificant correlation between these two modules with the IFN modules ($p=0.438$ and $p=0.179$ for correlation with M1.2, $p=0.475$ and $p=0.119$ for M3.4, respectively). The Neutrophil and NK/Cytotoxic modules showed a weak, but statistically significant inverse correlation in the baseline SSc samples (rs=-0.25, $p=0.047$).

Comparison of changes in the SSc transcript modules across the two treatment arms:

The changes in the SSc signatures were also compared between the two treatment arms. For this purpose two different analytic approaches were pursued. In the first analysis, the gene expression changes during the active treatment period (8-month to baseline) in the CYC arm was compared to transcript changes after immune recovery (26-month to baseline) in the HSCT arm. This analysis (Supplementary Table 9) showed that participants in the HSCT arm had significantly more decline in the IFN (M1.2 and M3.4) and Neutrophil (M5.15) modules ($p=0.019$, $p=0.044$, and $p<0.001$, respectively) and a significantly greater increase in the Cytotoxic/NK cell module ($p<0.001$). In the second analysis (Supplementary Table 10), the transcript changes at 26-month to baseline between the two treatment arms were compared. In the HSCT arm, a decline in gene expression over time for the IFN-M1.2 module and an increase in gene expression for the Cytotoxic/NK cell-M3.6 module differed significantly from changes observed in the CYC arm ($p=0.025$ and <0.0001, respectively). In modules IFN-M3.4 and Neutrophil-M5.15, declines in gene expression over time tended to be greater for the HSCT arm compared to CYC ($p=0.063$ and $p=0.079$, respectively).

Comparison of changes in the SSc protein composite scores across the two treatment arms:

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The changes in the serum protein composite scores were also compared between the two treatment arms in the subset of subjects with month 26 data. Similar to the transcript module analysis, two different analytic approaches were pursued. In the first analysis, the serum protein changes during active treatment period (8-month to baseline) in the CYC arm was compared to transcript changes after immune recovery (26-month to baseline) in the HSCT arm. This analysis showed that participants in the HSCT arm had significantly more decline in the IFN (M1.2 and M3.4) and Neutrophil (M5.15) protein composite score (mean difference [b]=-1.37, p=0.006; b=-1.36, p=0.012; and b=-0.35, p=0.02, respectively). In the second analysis, we compared the serum protein composite score changes at 26-month to baseline between the two treatment arms. In this analysis, the decline in IFN M1.2 and Neutrophil M5.15 protein composite scores over time was significantly greater in the HSCT arm compared to CYC arm (b=-1.25, p=0.047; b=-0.4, p=0.039), while the changes in the IFN M3.4, the protein composite score showed a similar trend (b=-1.24, p=0.069).

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Supplemental Table 1: Baseline demographic and clinical characteristics of SCOT participants and controls

Characteristic	HSCT Arm (n=27)	CYC Arm (n=35)	Controls (n=62)
Age, mean (SD), yr	45.8 (10.2)	46.4 (10.6)	47.0 (9.1)
Female, n (%)	14 (51.9)	25 (71.4)	39 (62.9)
Disease duration, yr	2 (1.1)	2.4 (1.3)	N/A
MRSS, mean (SD)	27.3 (7.2)	30.6 (10.6)	N/A
FVC%, mean (SD)	75.4 (14.6)	72.8 (16.6)	N/A
DLco%, mean (SD)	53.8 (7.2)	51.8 (8.2)	N/A
Whole Lung CAD > 0, n (%)	25 (92.6)	33 (94.3)	N/A

Abbreviations: CAD: Computer aided diagnosis system, CYC= Cyclophosphamide, FVC%= Forced vital capacity % predicted, HSCT= Hematopoietic stem cell transplantation, MRSS= Modified Rodnan Skin Score, SD= Standard deviation, yr= year

Supplementary Table 2: QuSAGE analysis results for the differentially expressed modules in comparison of baseline SCOT participant samples to unaffected controls

Module	Annotation	Log Fold Change*	P_{FDR}
M1.2	Interferon	0.7338	<0.001
M5.15	Neutrophils	0.4528	0.0015
M3.4	Interferon	0.3710	<0.0001
M4.4		-0.3409	<0.0001
M3.6	Cytotoxic/NK Cell	-0.3835	<0.0001
M2.3	Erythrocytes	-0.5095	<0.0001
M3.1	Erythrocytes	-0.5423	<0.0001

* Log fold change of a module is defined as the average log fold change of all transcripts contained in the module.

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Supplemental Table 3: Individuals with SSc and unaffected control characteristics enrolled in the UT Houston Divisional Repository (independent confirmation sample)

Characteristic	SSc (n=58)	Controls (n=40)
Age, mean (SD), yr	49.8 (15.1)	48.8 (14.7)
Female, n (%)	47 (81)	32 (80)
Diffuse cutaneous involvement	33 (56.9)	
Disease duration, yr	3.3 (1.8)	
MRSS, mean (SD)*	21.2 (10.1)	
FVC%, mean (SD)#	80.6 (24)	
On immunosuppressive agents, n (%)	17 (29.3)	

Abbreviations: DMARDs= Disease Modifying Anti-Rheumatic Drugs, FVC%= Forced vital capacity % predicted, MRSS= Modified Rodnan Skin Score, SD= Standard deviation, yr= year

* Available in 34 individuals with SSc

Available in 55 individuals with SSc

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Supplementary Table 4: QuSAGE analysis results for the differentially expressed modules in comparison of individuals with SSc to unaffected controls in the UT Houston Divisional Repository (independent confirmation sample)

Module	Annotation	Log Fold Change	P_{FDR}
M1.2	**Interferon *#**	**0.7135**	**<0.0001**
M3.4	**Interferon *#**	**0.3658**	**<0.0001**
M5.15	**Neutrophils *#**	**0.3493**	**0.0009**
M4.2	Inflammation	0.2552	0.0008
M5.12	Interferon	0.2290	<0.0001
M3.2	Inflammation	0.1908	0.0155
M5.1	Inflammation	0.0922	0.0061
M3.5	Cell Cycle	-0.0878	0.0269
M4.1	T-cells	-0.2410	0.0001
M3.6	**Cytotoxic/NK *#**	**-0.4022**	**<0.0001**

* These modules were also differentially expressed in the baseline SCOT samples in comparison to unaffected controls.

This independent sample included individuals with diffuse as well as limited cutaneous SSc. Confining the analysis to the 33 patients with diffuse cutaneous involvement in this sample also confirmed that modules M1.2, M3.4, M5.15, and M3.6 were differentially expressed compared to unaffected controls.

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Supplementary Table S5: Complete list of genes contained in the differentially expressed modules

M1.2 Module Interferon	M3.4 Module Interferon	M5.15 Module Neutrophil	M3.6 Module Cytotoxic/NK cell
BATF2	AIM2	ARG1	ABCB1
CMPK2	APOL6	AZU1	AUTS2
CXCL10	CARD17	BPI	CD160
DDX60	CCL8	CAMP	CD8A
EPSTI1	CEACAM1	CEACAM6	CLIC3
HERC5	DDX58	CEACAM8	CTSW
HES4	DHX58	COL17A1	EOMES
IFI44	EIF2AK2	CTSG	FASLG
IFI44L	FBXO6	DEFA1B	FCRL6
IFIT1	GALM	DEFA4	FGFBP2
IFIT3	GBP1	EIF1AY	FLJ14213
IFITM3	GBP3	ELANE	GNLY
ISG15	GBP4	HLA-DRB1	GPR114
LAMP3	GBP5	HLA-DRB5	GPR56
LY6E	GBP6	HP	GPR68
MX1	HERC6	LOC653600	GZMA
OAS1	IFI35	LTF	GZMH
OAS2	IFIH1	MMP8	GZMM
OAS3	IFIT2	MPO	HOPX
OASL	IFIT5	MS4A3	IFNG
OTOF	IFITM1	OLR1	IL2RB
RSAD2	INDO	RETN	KIAA1671
RTP4	IRF7	TCN1	KIR3DL2
SERPING1	LAP3		KLRC3
SPATS2L	LGALS3BP		KLRD1
TRIM6	LOC400759		KLRF1
XAF1	MOV10		KLRG1
	MT1A		KLRK1
	MT2A		LDOC1L
	OAS2		LOC642083
	PARP10		MCOLN2
	PARP12		NCALD
	PARP14		NCR3
	PARP9		NKG7
	PLSCR1		PLEKHF1
	PML		PPP2R2B
	PRIC285		PRF1
	SAMD9L		PRSS23
	SCO2		PYHIN1
	SEPT4		SAMD3
	SOCS1		SBK1
	STAT1		SH2D2A
	STAT2		SYTL2
	TIMM10		TARP
	TNFAIP6		TGFBR3
	TNFSF10		TSEN54
	TRIM22		ZNF683
	TRIM78P		
	UBE2L6		
	WARS		
	ZBP1		
	ZNF684		

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Supplementary Table S6: QuSAGE analysis results for differentially expressed modules in pairwise comparison of SCOT 26-month to baseline samples in the HSCT arm

Module	Annotation	Log Fold Change	P_{FDR}
M4.11	Plasma Cells	0.6695	0.0005
M4.10	B cell	0.6606	<0.0001
M3.6	**Cytotoxic/NK Cell***	**0.5464**	**<0.0001**
M4.15	T cells	0.3201	0.0129
M6.9		0.2516	0.0257
M4.6	Inflammation	-0.2645	0.0032
M1.2	**Interferon***	**-0.3272**	**0.0847**
M1.1	Platelet / Coagulation Cascade	-0.3364	0.0175
M5.15	**Neutrophils***	**-0.3384**	**0.0091**
M4.2	Inflammation	-0.3857	0.0084
M5.14		-0.396	0.0035
M6.13	Cell Death	-0.4063	0.0014
M2.1		-0.4347	0.0001
M3.2	Inflammation	-0.4574	0.0068
M4.13	Inflammation	-0.4669	0.0076

* These modules were also differentially expressed in the baseline SCOT samples in comparison to unaffected controls.

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Supplementary Table S7: QuSAGE analysis results for differentially expressed modules in comparison of SCOT 26-month samples in the HSCT arm to unaffected controls*

Module	Annotation	log.fold.change	P_{FDR}
M4.11	Plasma Cells	0.7990	<0.0001
M4.10	B cell	0.7412	<0.0001
M3.3	Cell Cycle	0.4065	<0.0001
M6.16	Cell Cycle / DNA Repair	0.3490	<0.0001
M3.5	Cell Cycle	0.3137	<0.0001
M6.9		0.3058	0.0003
M4.12		0.2891	0.0001
M6.7		0.2720	<0.0001
M6.12	Mitochondrial Stress	0.2643	<0.0001
M4.15	T cells	0.2639	0.0029
M4.7	Cell Cycle	0.2622	<0.0001
M5.10	Mitochondrial Respiration / Proteosome	0.2605	<0.0001
M5.6	Mitochondrial Stress / Proteasome	0.2506	<0.0001
M6.1		-0.2516	<0.0001
M5.7	Inflammation	-0.2605	<0.0001
M6.20		-0.2609	<0.0001
M4.6	Inflammation	-0.2619	<0.0001
M6.14		-0.3517	<0.0001
M6.13	Cell Death	-0.3644	<0.0001
M2.1		-0.3740	<0.0001
M5.14		-0.4139	<0.0001
M4.4		-0.4462	<0.0001
M4.2	Inflammation	-0.4825	<0.0001
M1.1	Platelet / Coagulation Cascade	-0.5255	<0.0001
M3.2	Inflammation	-0.5346	<0.0001
M4.13	Inflammation	-0.5687	<0.0001
M2.3	Erythrocytes	-0.6763	<0.0001
M3.1	Erythrocytes	-0.6886	<0.0001

* The four replicated SSc signature modules (M1.2, M3.4, M.5.15, and M3.6) are not listed in this table because they were not differentially expressed in this analysis

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Supplementary Table S8: QuSAGE analysis results for differentially expressed modules in pairwise comparison of SCOT 8-month to baseline samples in the CYC arm

Module	Annotation	Log Fold Change	P_{FDR}
M5.15	Neutrophils	0.4138	0.0076
M4.10	B cell	-0.4418	<0.0001

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Supplemental Table S9: Changes in SSc signature modules in comparison of HSCT arm after completion of immune recovery (26 month versus baseline, n= 17 pairs) to active treatment in the CYC arm (8 month versus baseline, n=23 pairs) based on QuSAGE analysis.

Module	Annotation	log.fold.change	p
M1.2	Interferon	-0.4517	0.019
M3.4	Interferon	-0.2151	0.044
M5.15	Neutrophil	-0.8207	<0.001
M3.6	Cytotoxic/NK Cell	0.5463	<0.001

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Supplemental Table S10: Comparison of changes in SSc signature modules in the HSCT to CYC arm at 26 month (n=17 pairs in HSCT and n= 18 pairs in CYC) based on QuSAGE analysis

Module	Annotation	log.fold.change	p
M1.2	Interferon	-0.4392	0.025
M3.4	Interferon	-0.2164	0.063
M5.15	Neutrophil	-0.3010	0.079
M3.6	Cytotoxic/NK Cell	0.5153	<0.001

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Supplemental Table S11: Serum proteins correlates of the two IFN transcript modules

Serum protein	Protein Abbreviation	M1.2 (IFN)		M3.4 (IFN)	
		r	P_{FDR}	r	P_{FDR}
Macrophage inflammatory protein-3 beta	MIP-3-beta	0.55	<0.001	0.60	<0.001
Beta-2 Microglobulin	B2M	0.43	<0.001	0.48	<0.001
B cell activating factor	BAFF	0.41	<0.001	0.38	<0.001
X6Ckine	X6Ckine	0.40	<0.001	0.43	<0.001
Interferon gamma Induced Protein-10	IP-10	0.39	<0.001	0.45	<0.001
Monocyte Chemotactic Protein-2	MCP-2	0.38	<0.001	0.40	<0.001
Tumor necrosis factor receptor -2	TNFR2	0.37	<0.001	0.43	<0.001
Interleukin – 6 (by Simoa assay)	IL-6-Simoa	0.35	0.001	0.38	<0.001
Tumor necrosis factor ligand superfamily member 13	APRIL	0.34	0.001	0.39	<0.001
Angiopoietin - 2	ANG-2	0.33	0.002	0.35	<0.001
B Lymphocyte Chemoattractant	BLC	0.33	0.002	0.34	0.001
Interleukin – 10 (by Simoa assay)	IL-10-Simoa	0.33	0.002	0.45	<0.001
C Reactive Protein	CRP	0.30	0.005	0.32	0.002
Monokine Induced.by Gamma Interferon	MIG	0.27*	0.01*	0.34	<0.001

* MIG was not included in the composite protein score of M1.2 because the inclusion criteria (r>0.3 and P_{FDR} <0.05) were not met.

Supplemental Table S12: Serum protein correlates of the neutrophil transcript module (5.15)

Serum protein	Protein Abbreviation	M 5.15 (neutrophil)	
		r	P_{FDR}
Matrix Metalloproteinase-3	MMP-3	0.37	0.001
Haptoglobin	Hp	0.35	0.003
Interluekin-1 Receptor Antagonist	IL-1ra	0.33	0.005
Angiopoietin-2	ANG-2	0.33	0.005

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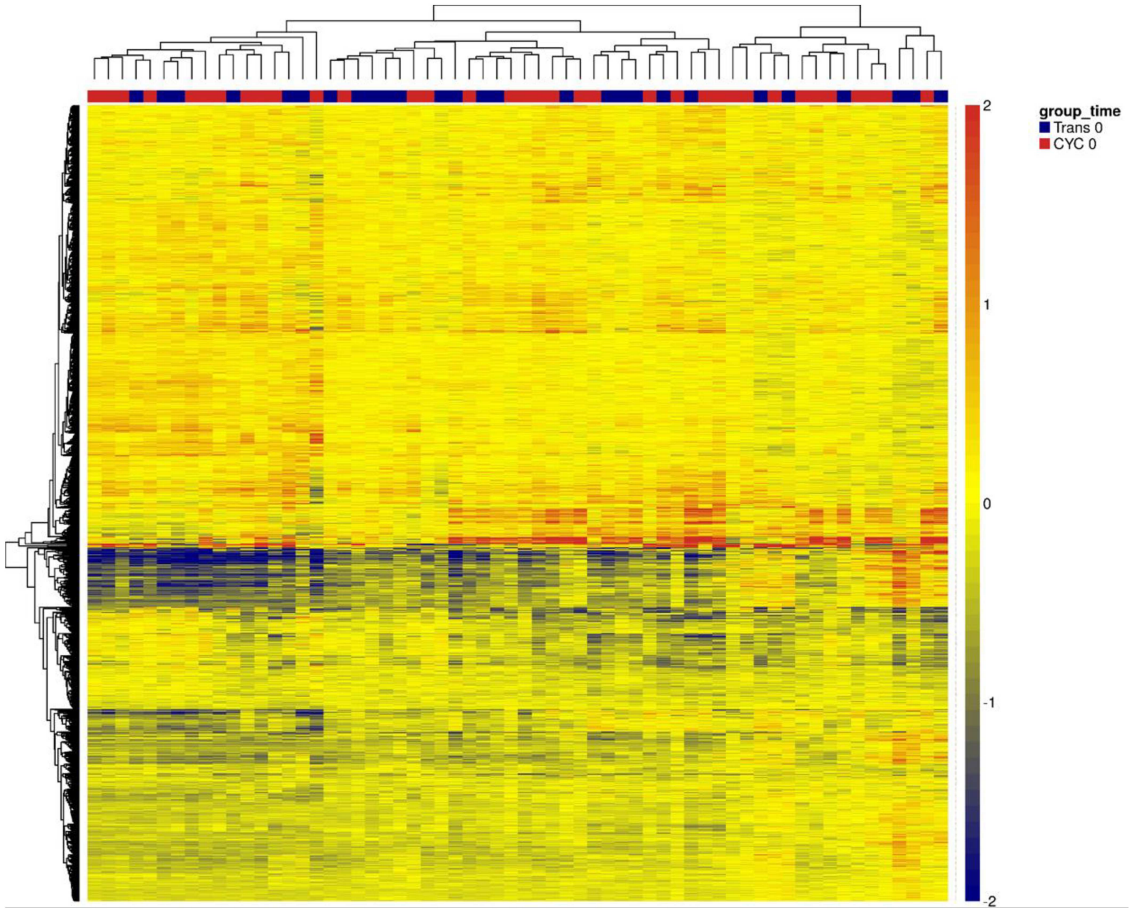
Supplemental Table S13: Pairwise T-test analysis of IFN and neutrophil serum protein scores after initiation of treatment compared to baseline samples

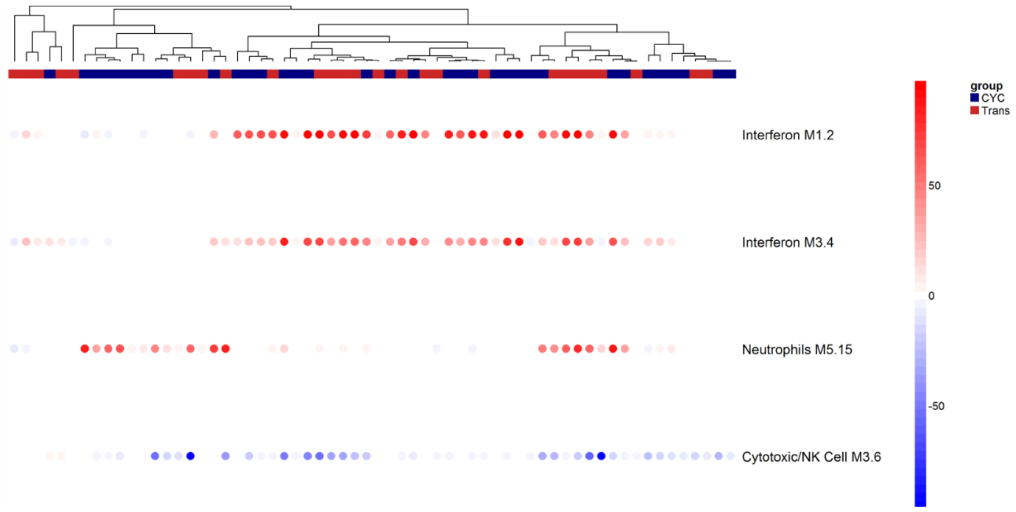
Serum protein Score	Time point	CYC Arm*			HSCT Arm #		
		b	95% CI	p-value	b	95% CI	p-value
1.2 Score (IFN)	8-month	-0.07	-0.69, 0.54	0.807	-0.1	-0.65, 0.45	0.697
3.4 Score (IFN)	8-month	-0.1	-0.76, 0.57	0.767	-0.09	-0.72, 0.54	0.774
5.15 Score (neutrophil)	8-month	-0.1	-0.3, 0.1	0.295	-0.17	-0.38, 0.03	0.097
1.2 Score (IFN)	26-month	-0.19	-1.19, 0.81	0.691	-1.44	-2.23, -0.65	**0.002**
3.4 Score (IFN)	26-month	-0.21	-1.28, 0.86	0.684	-1.45	-2.34, -0.56	**0.003**
5.15 Score (neutrophil)	26-month	-0.05	-0.37, 0.27	0.735	-0.46	-0.689, -0.221	**<0.001**

* In the CYC arm, month-8 visit represents samples taken during the active treatment period
# In the HSCT arm, month-26 visit represents samples taken after completion of immune recovery.

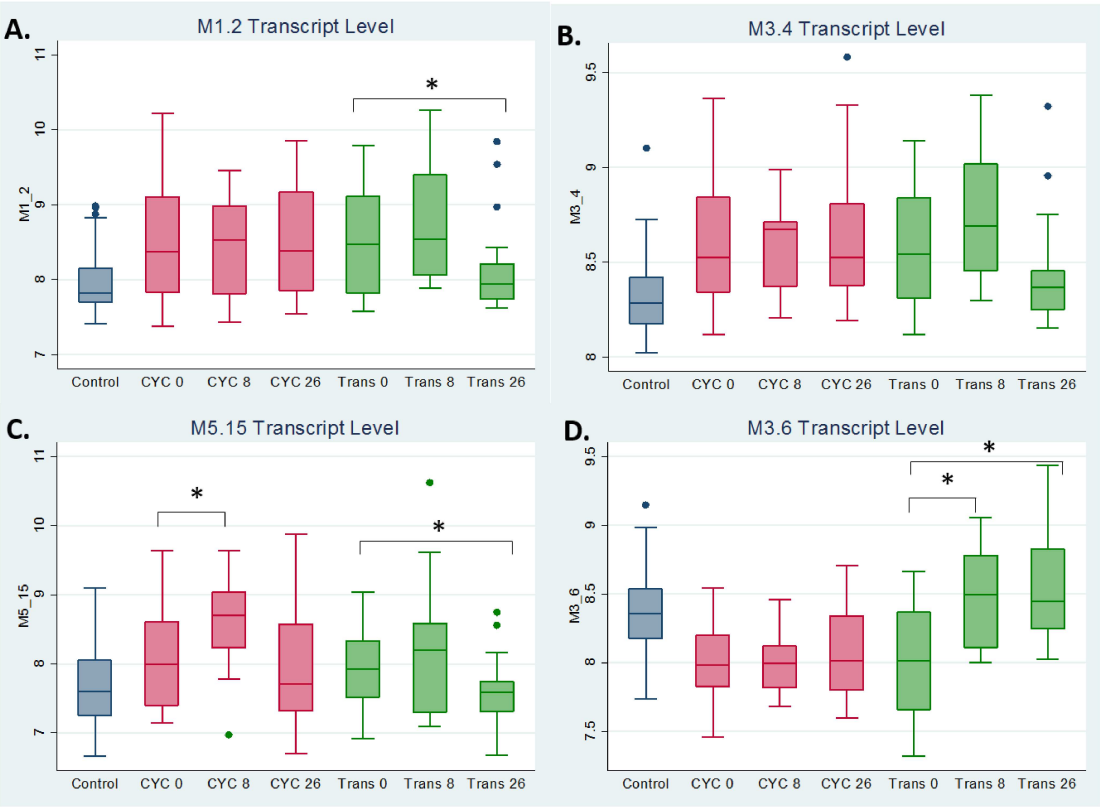


Supplementary Figure S1: Unsupervised hierarchical clustering based on 3168 transcripts detected in baseline SSc vs. control comparison. Rows and columns correspond to genes and 62 baseline SSc samples, respectively. Expression values are normalized to average expression in controls.
Top bar shows the treatment group assignment. Blue: HSCT; Red: Cyclophosphamide

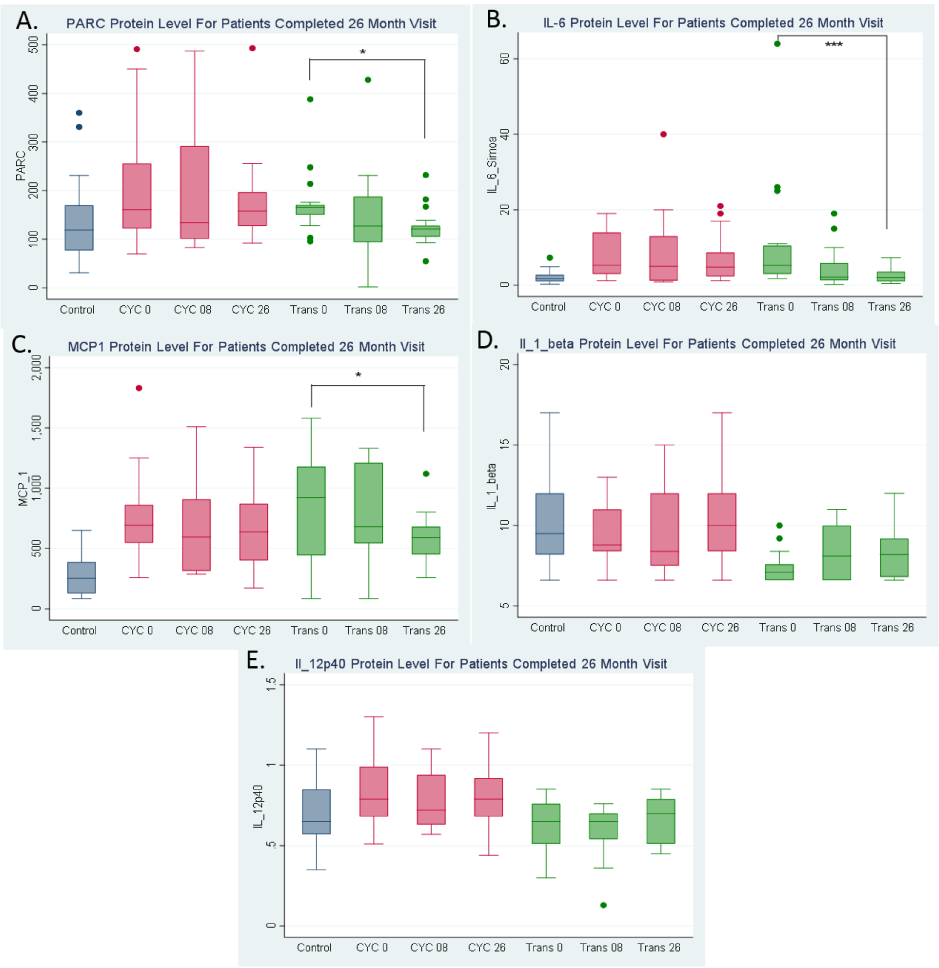
Assassi S, *et al. Ann Rheum Dis* 2019; 0:1371–1378. doi: 10.1136/annrheumdis-2019-215770



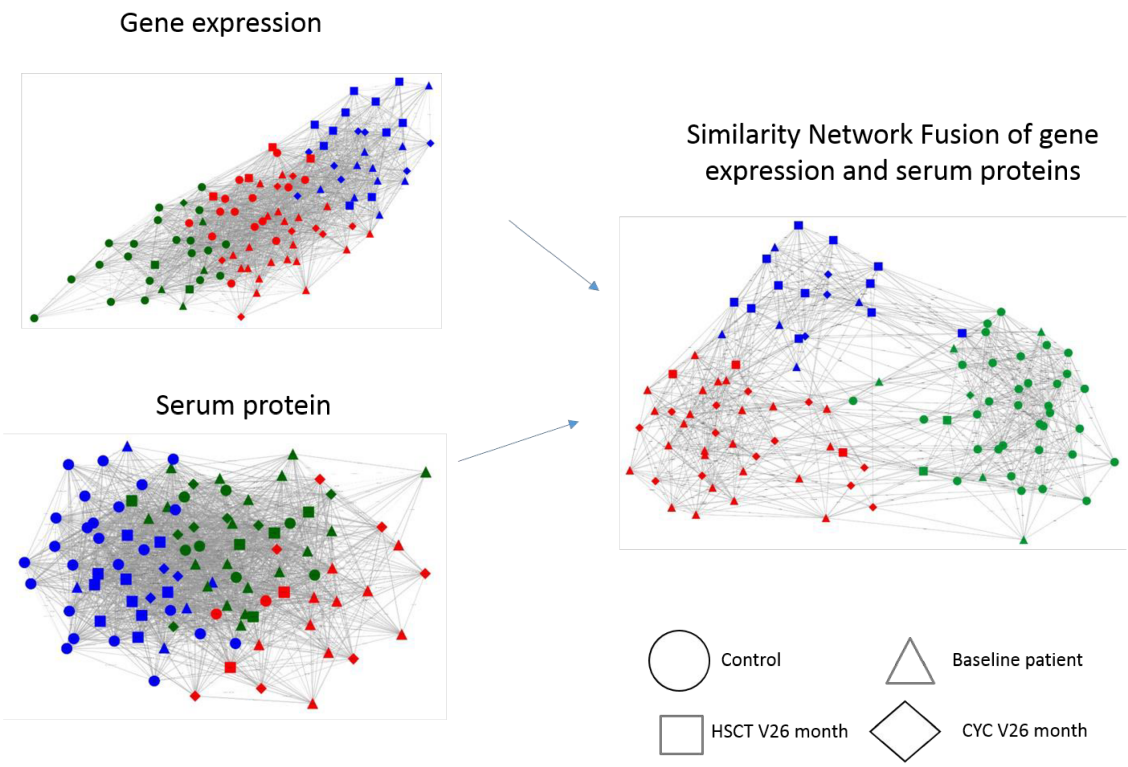
Supplementary Figure S2: Unsupervised hierarchical clustering of the four replicated differentially expressed modules in baseline samples of SCOT participants compared to the controls. While the two Interferon modules M1.2 and M3.4 highly correlate, the upregulated neutrophil module M5.15 and the down-regulated Cytotoxic/NK Cell module M3.6 can be present independent of the other modules.



Supplementary Figure S3: Longitudinal measurements of M1.2 (IFN-panel A), M3.4 (IFN-panel B), M5.15 (Neutrophil- panel C), M3.6 (Cytotoxic/NK-cell-panel D) transcript modules in 26-month completers. After immune recovery at the 26 month visit in the transplant arm, the IFN (M1.2), neutrophil (M5.15), Cytotoxic/NK cell (M3.6) showed significant changes toward values observed in unaffected controls, while similar changes were not observed in the cyclophosphamide arm. * Log 2 fold change >0.25 and FDR<0.1 in the paired comparison to baseline in the QuSAGE analysis. The displayed data at all time points are restricted to those participants that completed the 26-month visit.



Supplementary Figure S4: A-C: PARC (CCL-18), IL-6, and MCP-1 levels decreased significantly 26-month after HSCT while similar changes were not observed in the CYC arm. D, E: There were not any significant changes in IL-1b, and IL-12 levels in neither treatment arm. * $p<0.05$, ***$p<0.001$ in Wilcoxon Signed-Rank test



Supplementary Figure S5: Global gene expression and all available serum protein data were analyzed from controls (circle), baseline SCOT participants (triangle), HSCT- 26 month visit (square), and CYC - 26 month visit (diamond) time points for the multi-level analysis. First, three separate networks (blue, red, green) were built using global gene expression and serum protein data where each shape represents a unique sample. Then, these multi-level data were aggregated using the Similarity Network Fusion analysis according to Wang et al. Nat. Methods 11:333-337.

1. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum.* 1980;23:581-90.
2. Leroy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr., et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol.* 1988;15(2):202-5.
3. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, Pinckney A, Welch B, et al. Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma. *N Engl J Med.* 2018;378(1):35-47.
4. Y B, and Y H. *J Roy Statist Soc Ser B (Methodological).* 1995:289-300.
5. Chaussabel D, and Baldwin N. Democratizing systems immunology with modular transcriptional repertoire analyses. *Nat Rev Immunol.* 2014;14(4):271-80.
6. Yaari G, Bolen CR, Thakar J, and Kleinstein SH. Quantitative set analysis for gene expression: a method to quantify gene set differential expression including gene-gene correlations. *Nucleic Acids Res.* 2013;41(18):e170.
7. Rivnak AJ, Rissin DM, Kan CW, Song L, Fishburn MW, Piech T, et al. A fully-automated, six-plex single molecule immunoassay for measuring cytokines in blood. *J Immunol Methods.* 2015;424:20-7.
8. Bauer JW, Baechler EC, Petri M, Batliwalla FM, Crawford D, Ortmann WA, et al. Elevated serum levels of interferon-regulated chemokines are biomarkers for active human systemic lupus erythematosus. *PLoS Med.* 2006;3(12):e491.
9. Assassi S, Mayes MD, Arnett FC, Gourh P, Agarwal SK, McNearney TA, et al. Systemic sclerosis and lupus: points in an interferon-mediated continuum. *Arthritis Rheum.* 2010;62(2):589-98.
10. Baechler EC, Batliwalla FM, Karypis G, Gaffney PM, Ortmann WA, Espe KJ, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc Natl Acad Sci U S A.* 2003;100(5):2610-5.
11. Bauer JW, Petri M, Batliwalla FM, Koeuth T, Wilson J, Slattery C, et al. Interferon-regulated chemokines as biomarkers of systemic lupus erythematosus disease activity: a validation study. *Arthritis Rheum.* 2009;60(10):3098-107.
12. Steen VD, and Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis.* 2007;66(7):940-4.
13. Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis.* 2010;69(10):1809-15.
14. Furst D, Khanna D, Matucci-Cerinic M, Clements P, Steen V, Pope J, et al. Systemic sclerosis - continuing progress in developing clinical measures of response. *J Rheumatol.* 2007;34(5):1194-200.

15. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med.* 2006;354(25):2655-66.
16. Furst DE, Clements PJ, Steen VD, Medsger TA, Jr., Masi AT, D'Angelo WA, et al. The modified Rodnan skin score is an accurate reflection of skin biopsy thickness in systemic sclerosis. *J Rheumatol.* 1998;25(1):84-8.
17. Wang B, Mezlini AM, Demir F, Fiume M, Tu Z, Brudno M, et al. Similarity network fusion for aggregating data types on a genomic scale. *Nat Methods.* 2014;11(3):333-7.
18. J. SJM. *IEEE TRANSACTIONS ON PATTERN ANALYSIS AND MACHINE INTELLIGENCE*. 2000:888-905.