Supplementary Material

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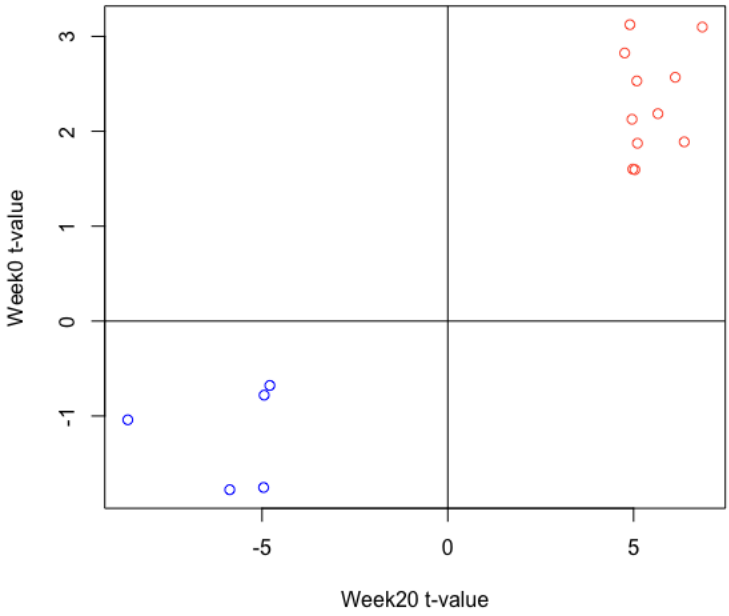
Supplementary Table 1. Preservation of gene expression differences between baseline and response time point (week 20).

Symbol	Accession	Definition	FCh wk0	P wk0	FCh wk20	P wk20
Significant genes at baseline						
PIK3CD	NM_005026.2	phosphoinositide-3-kinase, catalytic, delta polypeptide (PIK3CD)	-1.56	7.10E-18	-1.22	0.3
CX3CL1	NM_002996.3	chemokine (C-X3-C motif) ligand 1 (CX3CL1)	1.94	7.40E-12	1.96	**0.0019**
PLS3	NM_005032.3	plastin 3 (T isoform) (PLS3)	1.71	2.00E-10	1.65	0.059
DIXDC1	NM_033425.1	DIX domain containing 1 (DIXDC1)	1.90	9.30E-10	1.69	**0.01**
HCLS1	NM_005335.3	hematopoietic cell-specific Lyn substrate 1 (HCLS1)	-1.63	4.40E-09	-1.68	0.076
TMOD1	NM_003275.1	tropomodulin 1 (TMOD1)	2.10	1.60E-08	1.76	**0.029**
PCOLCE2	NM_013363.2	procollagen C-endopeptidase enhancer 2 (PCOLCE2)	2.45	3.30E-07	2.39	0.061
PPP1R3C	NM_005398.3	protein phosphatase 1, regulatory (inhibitor) subunit 3C (PPP1R3C)	2.13	3.60E-07	2.09	**0.011**
CRTAP	NM_006371.3	cartilage associated protein (CRTAP)	1.58	4.80E-07	1.33	0.11
PRELP	NM_002725.3	proline/arginine-rich end leucine-rich repeat protein (PRELP), transcript variant 1	2.02	6.40E-07	1.79	0.11
DKFZP686-A01247	NM_014988.1	hypothetical protein (DKFZP686A01247)	2.30	7.10E-07	1.78	**0.033**
ADA	NM_000022.2	adenosine deaminase (ADA)	-1.73	7.10E-07	-1.45	0.08
NT5DC2	NM_022908.1	5'-nucleotidase domain containing 2 (NT5DC2)	-1.86	7.70E-07	-1.23	0.44
UNQ689	NM_212557.1	RSTI689 (UNQ689)	5.09	9.50E-07	5.53	**0.0018**

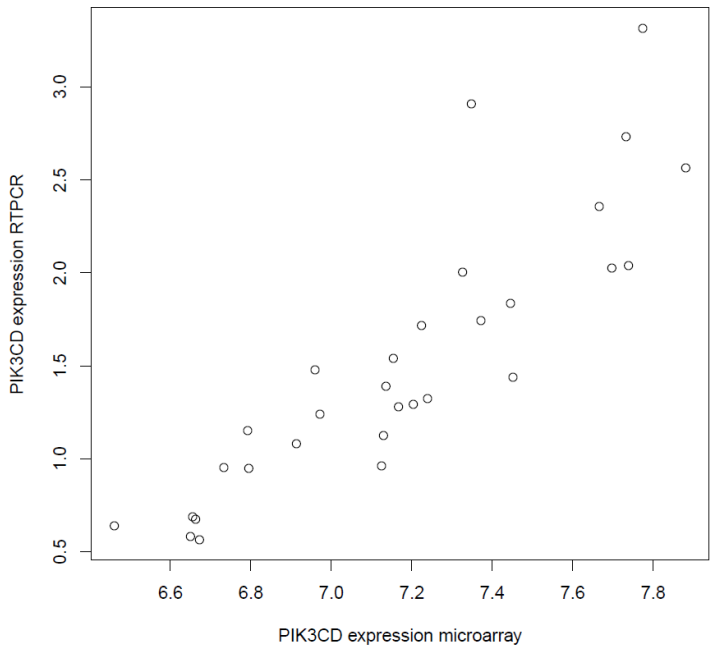
SERPINH1	NM_001235.2	serpin peptidase inhibitor, clade H (heat shock protein 47), member 1, (collagen binding protein 1) (SERPINH1)	-1.66	1.70E-06	-1.30	0.5
OR2A9P	NR_002157.1	olfactory receptor, family 2, subfamily A, member 9 pseudogene (OR2A9P) on chromosome 7.	2.01	1.90E-06	1.71	**0.0047**
Significant genes at week 20						
RPS6KA2	NM_001006932.1	ribosomal protein S6 kinase, 90kDa, polypeptide 2	-1.58	0.074	-1.53	3.10E-07
LIPA	NM_000235.2	lipase A, lysosomal acid, cholesterol esterase (Wolman disease)	-1.14	0.34	-1.50	1.50E-07
ALPL	NM_000478.2	alkaline phosphatase, liver/bone/kidney	-1.38	0.58	-2.77	7.90E-07
PDE4B	NM_002600.2	phosphodiesterase 4B, cAMP-specific	1.03	0.88	1.57	1.10E-07

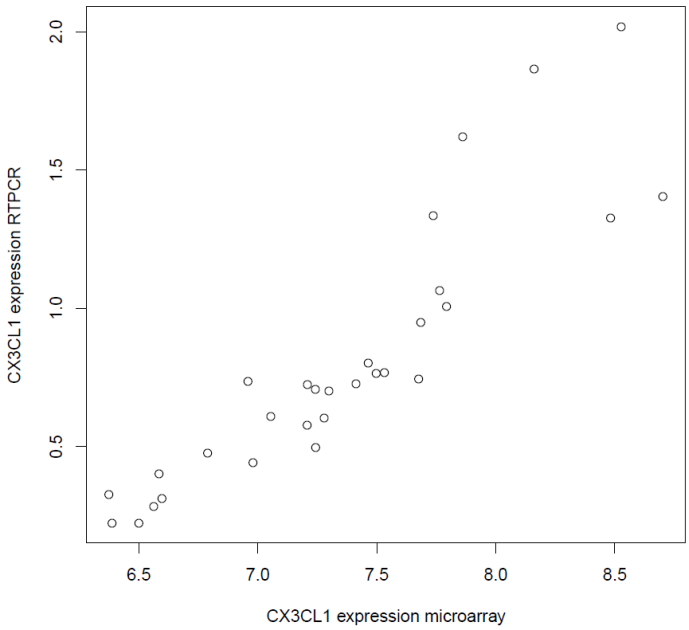
List of genes that are significant after Bonferroni correction and with an (absolute) >1.5 fold-change (FC) between responders and non-responders to anti-TNF therapy at week 0 and week of response. In bold, the genes at week 20 that preserve the differential expression between the two groups at the nominal level ($P < 0.05$). Conversely, none of the differentially expressed genes at week 20 had a nominally significant difference at baseline.



Supplementary Figure 1. Preservation of differential expression changes associated to anti-TNF response in the synovium from baseline. The t-values of the genes that are differential at week 0 between responders and non-responders (n=16) are plotted against the t-values of the same genes at week 0. While not all differences are significant at week 20, it the direction of the change is clearly preserved in all overexpressed (red, n=11) and underexpressed (blue, n=5) genes.

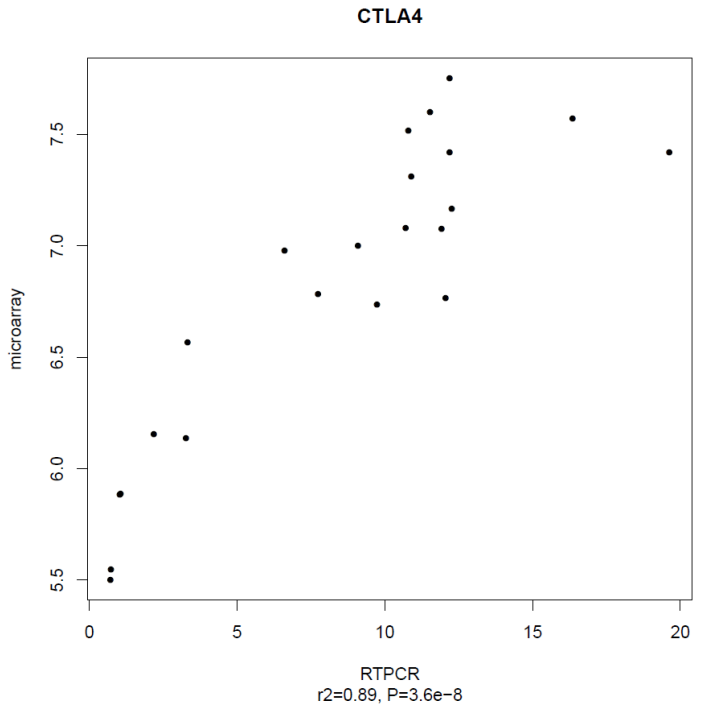
Supplementary Figure 2. RTPCR replication of *CX3CL1* and *PIK3CD* genes.

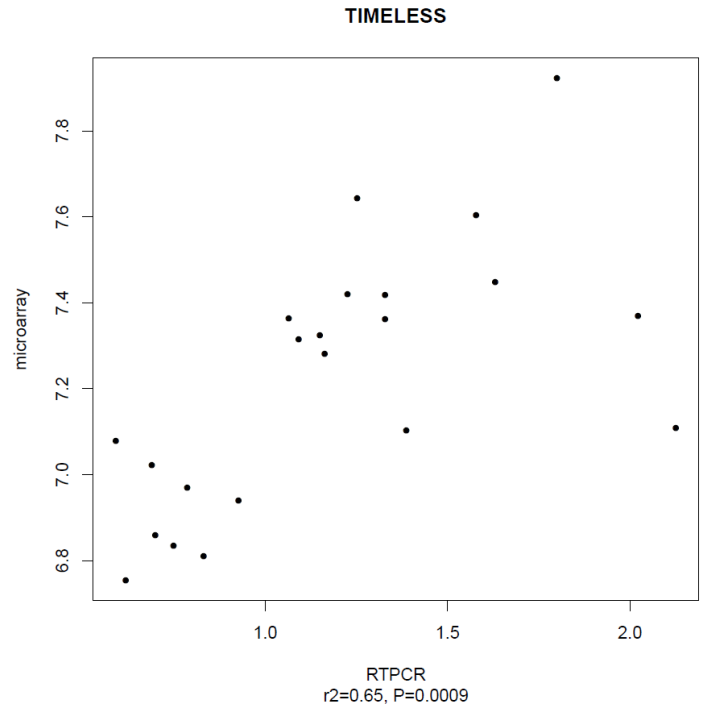




The gene expression of the two genes more differentially expressed at baseline between responders and non-responders was validated using Taqman QRTPCR assays. The correlation between both platform was highly significant (r=0.86 P=2.42e-10 and r=0.90 P=2-11e-11 for PIK3CD and CX3CL1, respectively).

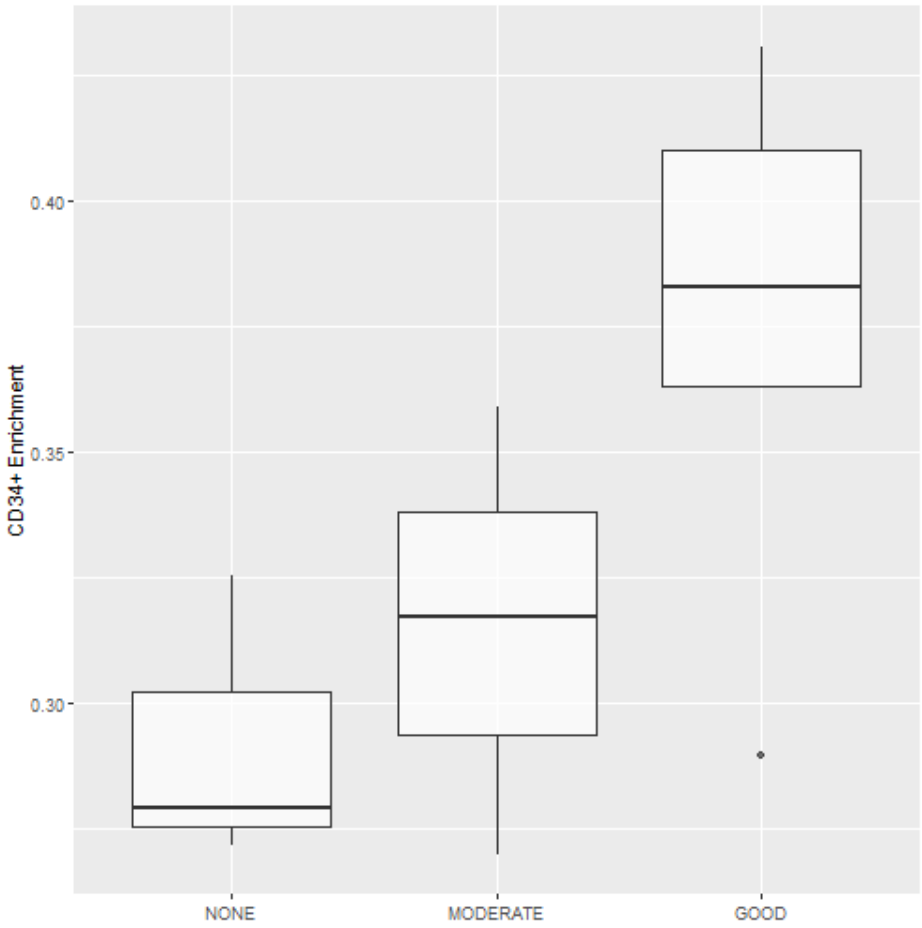
Supplementary Figure 3. QRTPCR replication of T_{PH} biomarker genes *CTLA4* and *TIMELESS*.



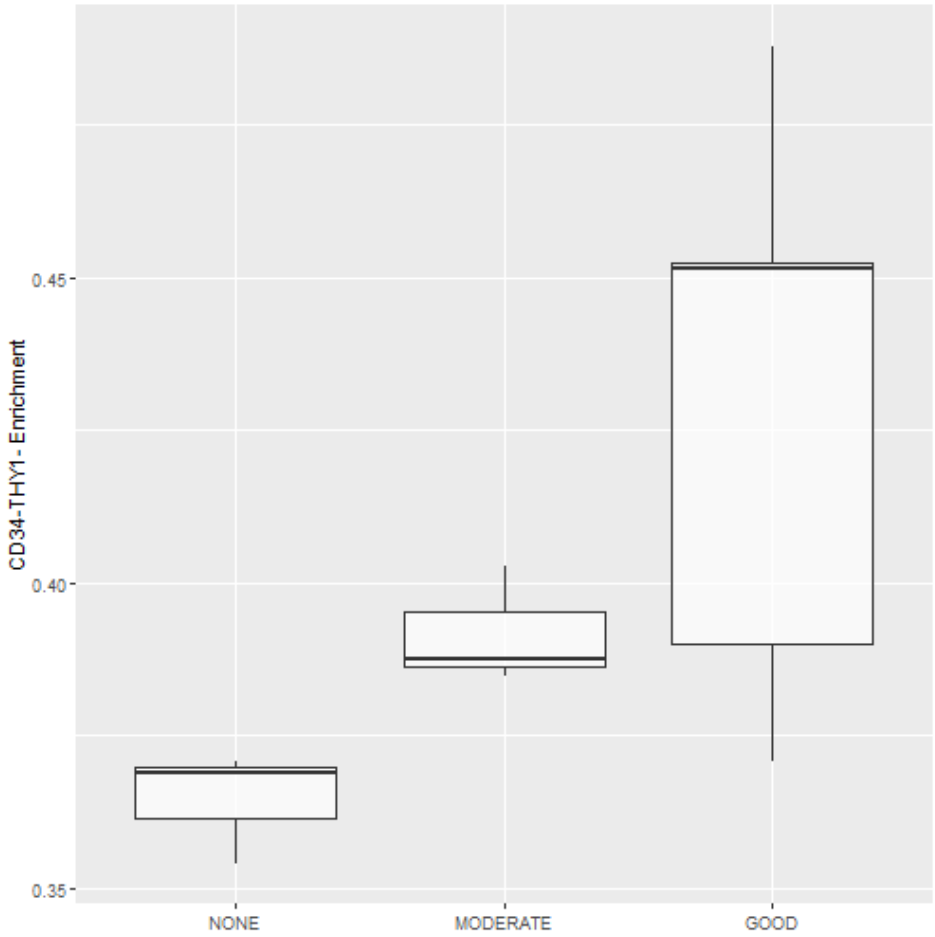


Plot of gene expression measures for *CTLA4* and *TIMELESS* as quantified using Illumina Beadchip microarrays and using Taqman quantitative RTPCR. The high concordance between both platforms confirms the validity of the microarray gene expression quantification for accurate cell type deconvolution estimation.

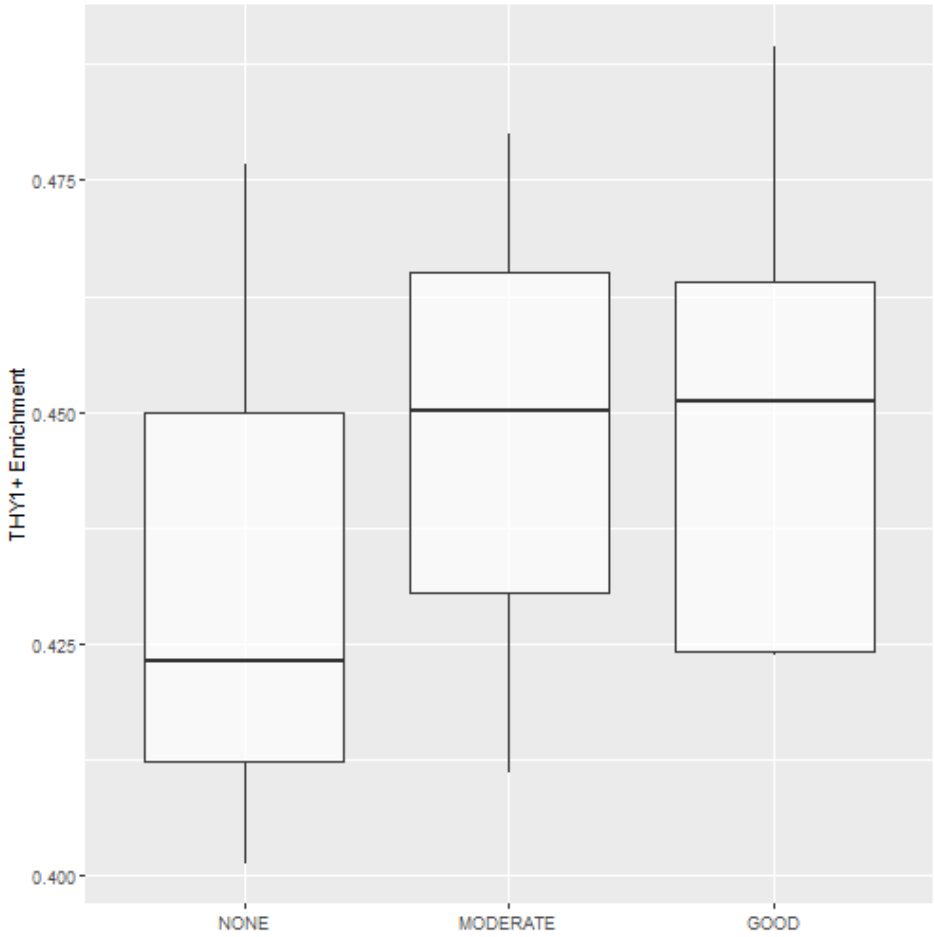
Supplementary Figure 4. Association of the three fibroblast subsets with anti-TNF response.



A. ***Boxplot of CD34+ fibroblast enrichment in the synovial membrane according to the response to anti-TNF therapy at week 20.*** Improvement in response increases linearly with the proportion of CD34+ fibroblast in the synovial membrane (P=0.027).

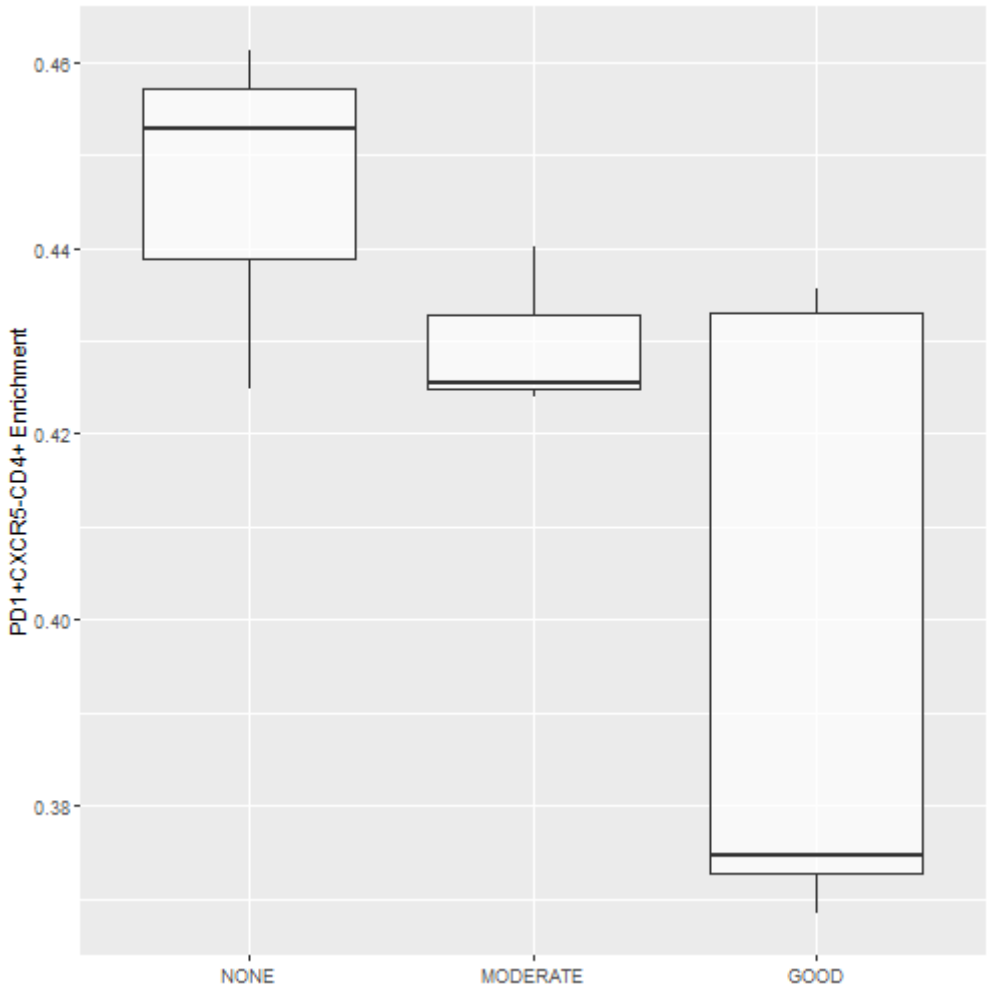


B. ***Boxplot of CD34-THY1- fibroblast enrichment in the synovial membrane according to the response to anti-TNF therapy at week 20.*** Improvement in response increases linearly with the proportion of CD34-THY1- fibroblasts in the synovial membrane (P=0.021).



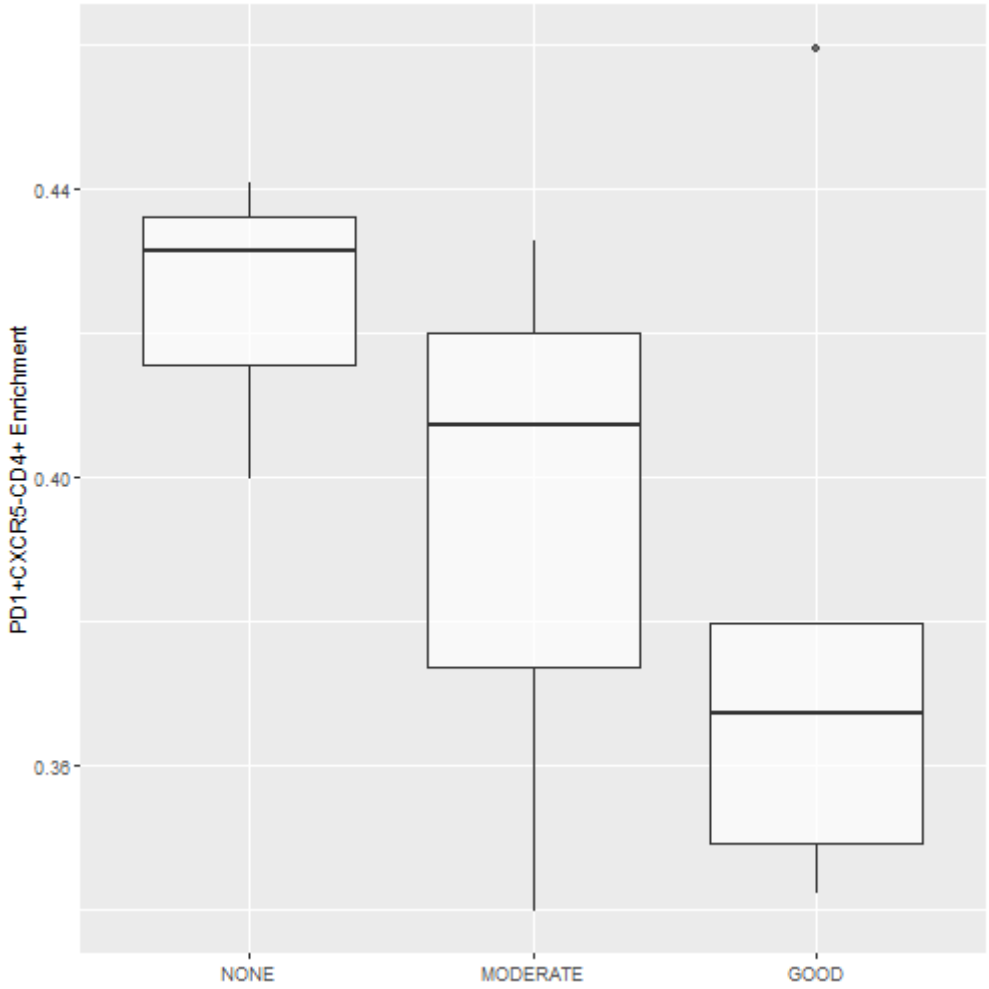
C. ***Boxplot of THY1+ fibroblast enrichment in the synovial membrane according to the response to anti-TNF therapy at week 20.*** The estimated proportion of THY1+ fibroblasts is not significantly associated with the response to anti-TNF therapy (P=0.49).

Supplementary Figure 5. Association of baseline PD1^{hi}CXCR5-CD4+ T cells with the response to anti-TNF therapy.



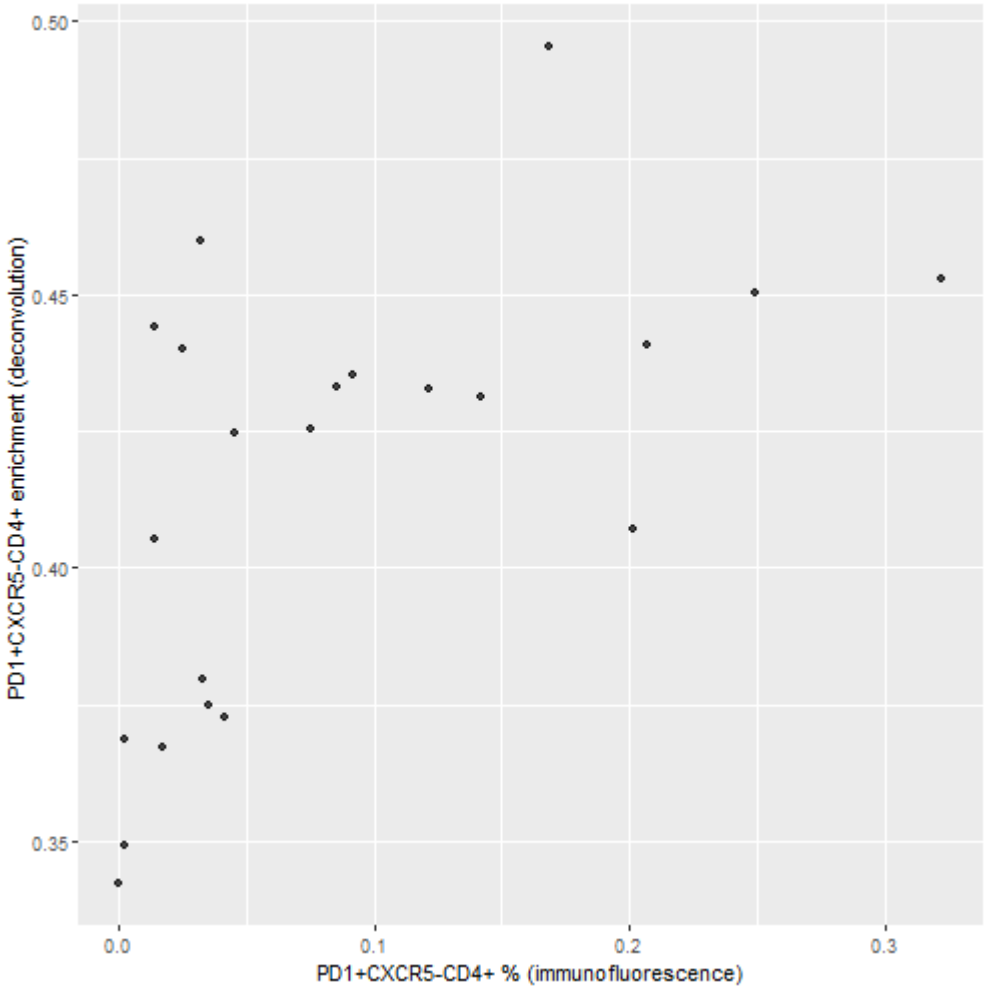
Boxplot of PD1^{hi}CXCR5-CD4+ T cell enrichment in the synovial membrane according to the response to anti-TNF therapy: week 0. A better response is associated with a lower proportion of peripheral helper T cells in the synovial membrane at baseline (P=0.022).

Supplementary Figure 6. Association of fibroblast types and T_{PH} cells with the response to anti-TNF therapy: week 20.



A. ***Boxplot of $PD1^{hi}$CXCR5-CD4+ T cell enrichment in the synovial membrane according to the response to anti-TNF therapy: week 20.*** The trend between lower T_{PH} cells and a better response to anti-TNF therapy identified at baseline is maintained up to week 20 of therapy. Despite this, the association is no longer significant (P=0.29).

Supplementary Figure 6. Correlation between PD1^{hi}CXCR5-CD4+ T cell abundance estimation using the cell deconvolution approach with the percentage quantified using immunofluorescence.



The estimated proportion of T_{PH} cells in the synovial membrane using the cell-type deconvolution approach shows a high correlation with the percentage of cells directly quantified using immunofluorescence on the synovial membrane samples (r2=0.58, P=0.0051). T_{PH} values for all n=11 for the two time points (baseline and wk20) are plotted. This result confirms the suitability of cell type deconvolution approach to estimate even low frequency cell types like T_{PH}.

Supplementary Table 4. Marker genes of the three synovial membrane fibroblast types.

CD34+ markers

ADAM22	*CACHD1*	*FZD4*	*PCDH18*
ADAMTSL3	*CAMK2D*	*G0S2*	*PKNOX2*
AHR	*CD34*	*GDA*	*RHOU*
ANGPT1	*CEP126*	*IQCC*	*SETBP1*
ASPA	*CLIP3*	*LPCAT2*	*SSPN*
BICC1	*CLLU1OS*	*MAB21L2*	*TBX5*
C3	*CP*	*MECOM*	*TMEM108*
C6	*CXCL12*	*NOVA1*	*TMEM133*
C7	*EGR1*	*OSR2*	*TRDMT1*

THY1+ markers

ADCY7	*CCNG1*	*FLRT2*	*PLXDC1*	*THY1*
ADGRA2	*COMP*	*FNDC1*	*PRKD1*	*TTC39C*
ANKRD29	*CRABP2*	*IGF1*	*PTGIS*	*VSTM4*
ARL4C	*CRISPLD2*	*LTBP2*	*SFRP4*	*WISP1*
ARSB	*CUTC*	*MBNL2*	*SMOC2*	
ASPN	*DPP4*	*MCUB*	*SRGAP1*	
AXIN2	*EDIL3*	*MYOF*	*STXBP5*	
C12orf75	*ELN*	*NLGN2*	*THBS1*	
CADM1	*FHL2*	*OAF*	*THBS2*	

CD34-THY1- markers

ADAM10	*ERRFI1*	*MET*	*PPIL6*	*TIMP3*
ADGRA3	*EZR*	*MFSD6*	*RBPMS2*	*TMCO3*
ADGRG2	*FNIP2*	*MSN*	*RELL1*	*TMEM196*
AGFG1	*FOXO1*	*MT1G*	*RGS16*	*TSPAN15*
BTC	*GALNT12*	*MTHFD1L*	*RIOK3*	*TWISTNB*
C10orf105	*GFPT2*	*MTUS2*	*SEC11C*	*UBAP1*
CLIP1	*GPR18*	*NDP*	*SHTN1*	*UGP2*
CNTNAP3	*GPR183*	*NTN4*	*SIX3*	*USP24*
CSN1S1	*GPX3*	*OSTF1*	*SORBS2*	*UST*
CUX1	*GRAMD1B*	*PACSIN2*	*SOX5*	*VPS13A*
CXCL8	*HBEGF*	*PCSK6*	*STK38L*	*WARS*
DAPK1	*HMGA2*	*PDE8A*	*SUSD4*	*ZNF385B*
DNASE1L3	*HTRA4*	*PDLIM5*	*SV2B*	
ENPP1	*KIF1B*	*PGM3*	*SYT17*	
EREG	*LRRFIP2*	*PNP*	*TIAM2*	

Genes differentially overexpressed from each fibroblast subset compared to the other two were selected as markers for cell type deconvolution analysis.

Supplementary Table 5. Significantly overexpressed genes in PD-1^{hi} T cells according to Rao et al.

PD-1	*GZMK*	*F5*
SCO2	*DHFR*	*DUSP2*
CDCA7	*TIMELESS*	*MAF*
TOX	*DUSP4*	*PSMA4*
TOX2	*FABP5*	*SYT11*
ENC1	*FBXO41*	*UBE2A*
HVCN1	*MAP3K9*	*TBC1D4*
CHN1	*PMAIP1*	*UQCRC1*
CCDC86	*PRR5L*	*ANXA2*
CCL5	*MIS18BP1*	*SLAMF6*
AKR1C3	*EPSTI1*	*TUBB4B*
CST7	*BZRAP1*	*UBE2L6*
CEP128	*DPP3*	*ITM2A*
MYL6B	*TIGIT*	*RGS1*
EZH2	*FCRL3*	
CXCR3	*CTLA4*	
ICA1	*DDX54*	
FANCI	*RAB37*	
FAM210A	*SHMT2*	
DIRC2	*PFN1*	