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Supplementary information

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A longitudinal single-cell atlas of anti-tumour necrosis factor treatment in inflammatory bowel disease

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Supplementary Figures for:

A longitudinal single-cell atlas of anti-tumour necrosis factor treatment in inflammatory bowel disease

Tom Thomas[1,2,3], Matthias Friedrich[1,3*], Charlotte Rich-Griffin[2*], Mathilde Pohin[1*], Devika Agarwal[1*], Julia Pakpoor[1,2,3], Carl Lee[1], Ruchi Tandon[4], Aniko Rendek[5], Dominik Aschenbrenner[3], Ashwin Jainarayanan[1], Alexandru Voda[1], Jacqueline HY Siu[1], Raphael Sanches-Peres[1], Eloise Nee[1], Dharshan Sathananthan[6,7], Dylan Kotliar[8,9], Peter Todd[2], Maria Kiourlappou[2], Lisa Gartner[3], Nicholas Ilott[1], Fadi Issa[10], Joanna Hester[10], Jason Turner[11], Saba Nayar[11,12,13], Jonas Mackerodt[1], IBD Cohort Investigators, AMP RA investigators, Fan Zhang[8,9,14], Anna Jonsson[8,9], Michael Brenner[8,9], Soumya Raychaudhuri[8,9], Ruth Kulicke[15], Danielle Ramsdell[15], Nicolas Stransky[15], Ray Pagliarini[15], Piotr Bielecki[15], Noah Spies[15], Brian Marsden[2], Stephen Taylor[2], Allon Wagner[16,17], Paul Klenerman[3], Alissa Walsh[3], Mark Coles[1], Luke Jostins-Dean[1], Fiona M Powrie[1], Andrew Filer[11,12,13], Simon Travis[1,3,18#], Holm H Uhlig[3,18, 19#], Calliope A Dendrou[1,2,18#], Christopher D Buckley[1,3,11,18#]

[*] These authors contributed equally [#] These authors jointly supervised this work

[1]Kennedy Institute of Rheumatology, Old Road Campus, University of Oxford, Oxford, UK

[2]Centre for Human Genetics, Old Road Campus, University of Oxford, Oxford, UK

[3]Translational Gastroenterology & Liver Unit, John Radcliffe Hospital, Headington, Oxford, UK

[4]University College London Hospitals NHS Foundation Trust, London, UK

[5]Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[6]University of Adelaide, Adelaide, Australia

[7]Lyell McEwin Hospital, Haydown Road, Elizabeth Vale, Australia

[8]Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

[9]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

[10] Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom

[11]Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, UK

[12]National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre and NIHR Clinical Research Facility, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

[13]Birmingham Tissue Analytics, Institute of Translational Medicine, University of Birmingham, UK

[14]Center for Health AI, University of Colorado Anschutz, Colorado, USA

[15]Celsius Therapeutics, 399 Binney St, Cambridge, Massachusetts, USA

[16]Department of Electrical Engineering and Computer Science, University of California, Berkeley, California, USA

[17]The Center for Computational Biology, University of California, Berkeley, California, USA

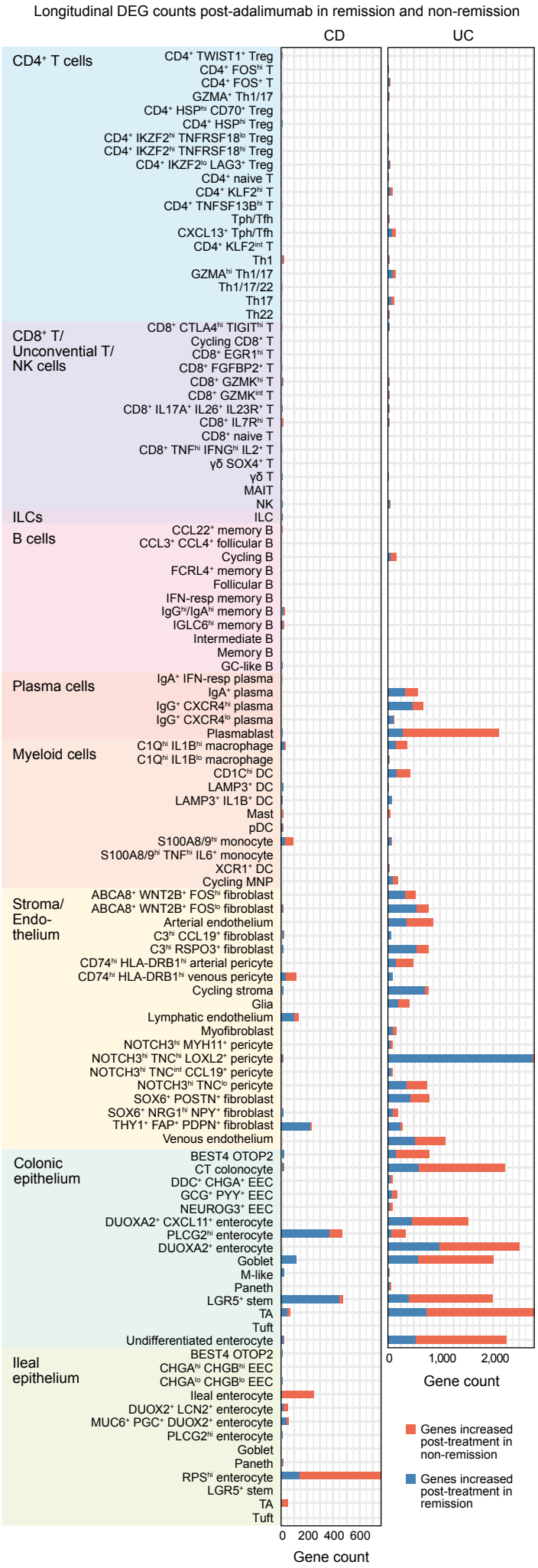
[18]NIHR Oxford Biomedical Research Centre, Oxford, UK

[19] Department of Paediatrics, University of Oxford, Oxford, UK

Supplementary Figure List:

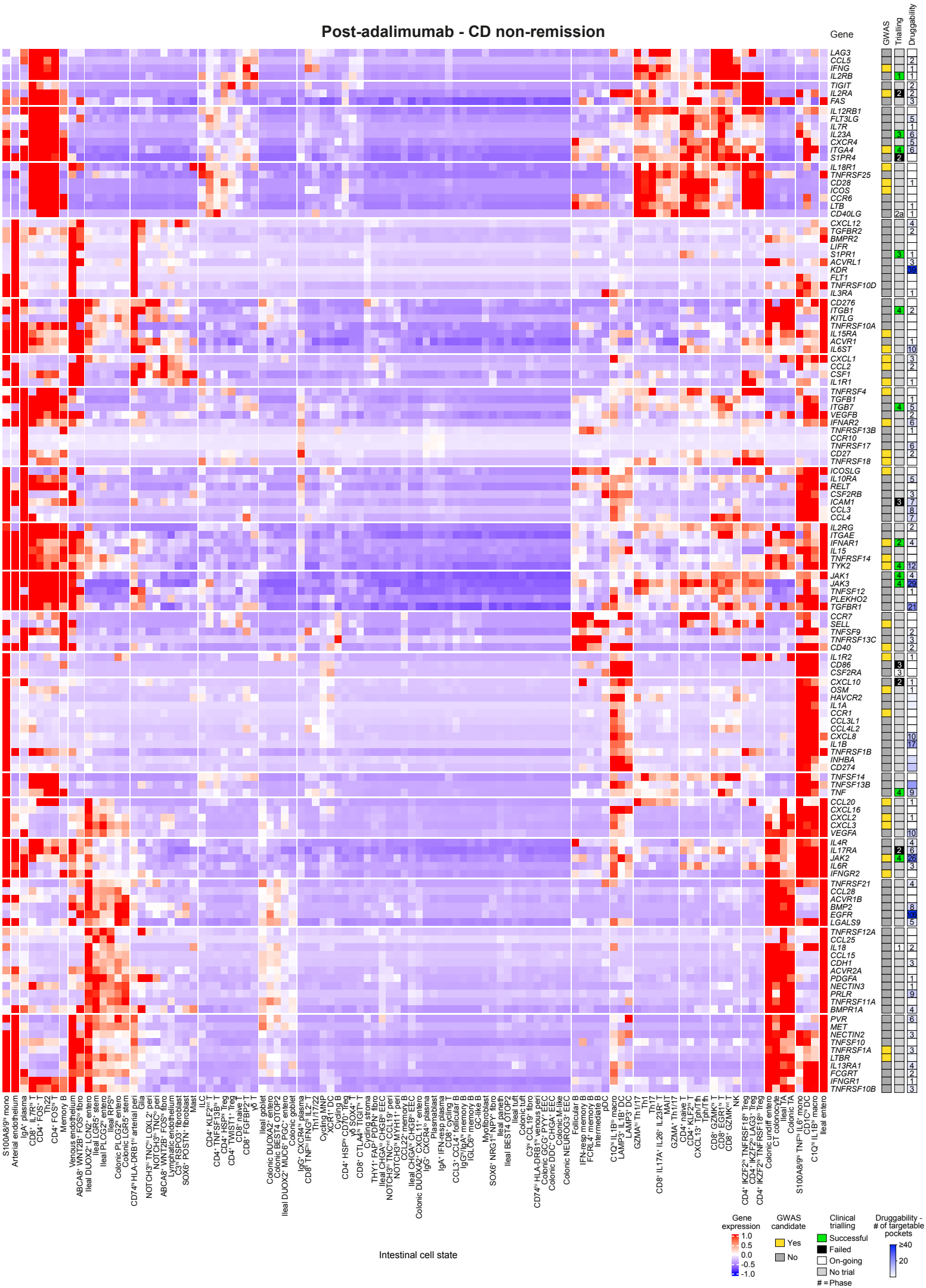

pCD4T01
NEAT1
MALAT1
SYNE2
AHNAK
GOLGB1
VMP1
AC016831.5
RNF213
DDX3X
XIST
0.000 0.005 0.010
Score
pCD4T02
ZNF331
NR4A2
YPEL5
SELENOK
CREM
BCAS2
CXCR4
ATP1B3
SLC2A3
AREG
0.005 0.015
Score
pCD4T04
Z85994.1
CCL3
CSF2
IFNG
CCL4
CCL4L2
CCL1
CCL3L1
GZMB
GNLY
0.00 0.02 0.04
Score
pCD4T05
MT-ND4
MT-CO2
MT-CO3
MT-CYB
MT-ATP6
MT-ND2
MT-ND1
MT-ND3
MT-CO1
MT-ND5
0.01 0.03
Score
pCD4T06
S100A4
ACTB
SH3BGRL3
TMSB4X
S100A6
CD52
ACTG1
PFN1
GAPDH
TMSB10
0.000 0.010 0.020
Score
pCD4T07
FOXP3
IL32
CARD16
TIGIT
CTSC
BATF
IKZF2
CD27
TNFRSF9
TNFRSF18
0.003 0.009
Score
pCD4T08
DRAIC
RNF19A
AC004585.1
ICA1
GNG4
TOX2
PGM2L1
KSR2
CD200
MAGEH1
0.003 0.009
Score
pCD4T09
BTG2
IER2
DUSP2
NFKBIA
PPP1R15A
EGR1
ZFP36
CD83
FOS
CD69
0.005 0.015
Score
pCD4T10
HSP90AA1
HSPA1B
HSPA1A
HSP90AB1
HSPH1
HSPE1
HSPD1
DNAJB1
MRPL18
UBB
0.01 0.03
Score
pCD4T11
ANXA1
KLF6
IL7R
TSC22D3
TNFAIP3
MYADM
LMNA
VIM
CD69
ANKRD28
0.004 0.012
Score
pCD4T12
TUBB4B
GADD45B
UBE2S
SERTAD1
SNHG12
ID2
H2AFZ
MARCKSL1
RSRP1
H2AFX
0.005 0.015
Score
pCD4T13
LAG3
PTMS
LINC01871
CD3D
HAVCR2
IL26
ENTPD1
GZMA
ZEB2
CD2
0.005 0.015
Score
pCD4T14
MIR155HG
TNFRSF4
TNFRSF18
PIM3
LTA
REL
BATF3
PKM
NME1
BCL2A1
0.005 0.015 0.025
Score
pCD4T15
HLA-DRB1
HLA-DRA
HLA-DPB1
HLA-DQA1
CD74
HLA-DPA1
HLA-DQB1
CHN1
ALOX5AP
PKIG
0.01 0.03
Score
pCD4T16
KLF2
GIMAP7
CCR7
SELL
RPL13
RPS3A
RPL11
RPS14
RPS12
RPS23
0.005 0.015
Score
pCD8T01
FCER1G
TYROBP
IL2RB
KLRF1
TRDC
GNLY
TNFRSF18
NCAM1
ITGAX
ADGRG3
0.005 0.015
Score
pCD8T02
RPS8
RPS12
RPS3A
RPL32
RPL3
RPS14
RPS6
RPS23
RPL11
RPL34
0.005 0.015
Score
pCD8T04
TUBB4B
UBE2S
GADD45B
ID2
SERTAD1
SNHG12
H2AFZ
MARCKSL1
RSRP1
CITED2
0.005 0.015
Score
pCD8T05
GZMK
HLA-DRB1
CST7
HLA-DPB1
CD74
HLA-DPA1
HLA-DRA
NKG7
CMC1
SH2D1A
0.005 0.010
Score
pCD8T06
MT-ND4
MT-ATP6
MT-CO2
MT-CYB
MT-CO3
MT-ND1
MT-ND2
MT-ND3
MT-CO1
MT-ND5
0.00 0.02 0.04
Score
pCD8T07
CCL4L2
CCL4
CCL3L1
XCL2
CCL3
XCL1
TNF
NFKBID
IFNG
CSF2
0.01 0.03
Score
pCD8T08
HSPA1B
HSPA1A
HSP90AA1
HSPH1
HSP90AB1
DNAJB1
HSPE1
HSPD1
MRPL18
UBB
0.01 0.03
Score
pCD8T09
CTLA4
IL4I1
MAF
LTB
CXCR6
KLRB1
LINC01871
NCR3
0.003 0.009
Score
pCD8T10
REL
CREM
ATP1B3
NR4A2
ZNF331
KDM6B
NR4A3
EZR
FOSL2
SELENOK
0.0025 0.0075
Score
pCD8T11
FGFBP2
FCGR3A
PRF1
SPON2
CX3CR1
NKG7
GZMB
ADGRG1
AKR1C3
S1PR5
0.005 0.015
Score
pCD8T12
KLF6
IL7R
ANXA1
TSC22D3
TNFAIP3
MYADM
ANKRD28
ATF3
SPRY1
GPR183
0.005 0.010
Score
pCD8T14
BTG2
NFKBIA
IER2
PPP1R15A
EGR1
CD69
DUSP2
ZFP36
FOS
CD83
0.010 0.020
Score
pCD8T15
TMSB4X
ACTB
SH3BGRL3
CD52
PFN1
GAPDH
CD3D
IL32
CCL5
TRAC
0.005 0.015
Score
pCD8T16
CAV1
PGM2L1
CD27
FABP5
CXCL13
TIMD4
GK
PCAT4
GNG4
AC004585.1
0.005 0.015
Score
pB01
AC068535.1
LDHA
NPM1
LINC00111
ENO1
GAPDH
TUBA1B
RANBP1
UBE2C
0.001 0.003
Score
pB02
CXCR4
EZR
YPEL5
GPR183
NR4A2
CREM
RGS2
REL
ZNF331
NR4A3
0.002 0.006
Score
pB03
MT-ND4
MT-CO3
MT-CO2
MT-CYB
MT-ATP6
MT-ND2
MT-ND1
MT-CO1
MT-ND3
MT-ND5
0.000 0.010 0.020
Score
pB05
IGHD
FCER2
RPL18A
TCL1A
CD72
TMSB10
YBX3
HLA-DPA1
HLA-DRB1
RPS19
0.0025 0.0075
Score
pB07
TMSB4X
ACTG1
FCRL4
ACTB
DUSP4
ITGAX
ARPC2
COTL1
PLEK
PFN1
0.002 0.006
Score
pB08
MYBL1
MKI67
HIST1H4C
RGS13
HMGN2
HMCES
LRMP
CCDC144A
HMGB2
SYNE2
0.002 0.006
Score
pB09
DUSP2
IER2
EGR1
NFKBIA
BTG2
FOS
ZFP36
PPP1R15A
NR4A1
FOSB
0.005 0.015
Score
pB10
HSPA1B
HSPA1A
HSP90AA1
DNAJB1
UBB
HSPH1
HSP90AB1
DNAJA1
UBC
JUN
0.005 0.010
Score
pB11
IFIT3
IFIT1
ISG15
IFIT2
OASL
IFI6
CXCL10
RSAD2
MX1
IFI44L
0.01 0.03
Score
pP01
IGHG1
IGHG3
IGHG4
IGHGP
PRDX4
HLA-C
CD79A
PTP4A3
MZB1
TMBIM6
0.000 0.005 0.010
Score
pP02
UBE2C
GAPDH
CDC20
TUBA1B
TOP2A
BIRC5
HMGB1
PTTG1
HMGB2
TUBB
0.000 0.004 0.008
Score
pP03
MT-CO3
MT-ND4
MT-CO2
MT-ND1
MT-ATP6
MT-CO1
MT-CYB
MT-ND2
MT-ND3
MT-ND4L
0.00 0.01 0.02
Score
pP04
DUSP5
ANKRD28
PDE4B
EZR
MCL1
TRIB1
TNFAIP3
NUP53
RGS1
MIR155HG
0.000 0.004 0.008
Score
pP06
AL138733.1
AC127496.4
HIST1H1B
HIST1H3B
HIST1H3G
HIST1H2AL
HIST2H2AC
HIST1H2AI
HIST1H4C
RRM2
0.005 0.015
Score
pP07
AC007952.4
HIST1H2BG
AC245014.3
Z93241.1
MALAT1
HNRNPUL1
AL360012.1
AL031777.3
PTCH2
PPP1R10
0.000 0.004 0.008
Score
pP08
DNAJB1
HSPA1A
ZFAND2A
HSPA1B
HSP90AA1
UBB
HSP90AB1
DNAJA1
EGR1
0.000 0.004 0.008
Score
pP09
JCHAIN
RPL10
RPL5
RPS5
RPL3
EEF1A1
RPS4X
RPL8
RPS3
RPL19
0.0025 0.0075
Score
pM01
CCL4
CCL3
IL1A
CCL3L1
IL1RN
CCL4L2
CXCL8
IL1B
TNIP3
0.000 0.005 0.010
Score
pM02
S100A9
S100A4
S100A8
S100A6
VCAN
FCN1
CD300E
S100A12
SLC11A1
TSPO
0.003 0.009
Score
pM03
GZMB
CLIC3
TCF4
SMPD3
LILRA4
C12orf75
TSPAN13
PPP1R14B
SCT
MZB1
0.000 0.005 0.010
Score
pM04
CHI3L1
APOC1
CYP27A1
APOE
GPNMB
NUPR1
CAPG
CHIT1
RARRES1
CTSD
0.002 0.006
Score
pM05
CLEC9A
CADM1
CPNE3
SNX3
CPVL
XCR1
CLNK
C1orf54
ENPP1
CCND1
0.000 0.005 0.010
Score
pM06
MT-ND4
MT-ATP6
MT-CO3
MT-CYB
MT-CO2
MT-ND5
MT-CO1
MT-ND3
MT-ND1
MT-ND2
0.00 0.01 0.02
Score
pM08
CCR7
BIRC3
LAMP3
FSCN1
MARCKSL1
LIMCH1
CCL19
SLCO5A1
NUB1
TBC1D4
0.000 0.005 0.010
Score
pM09
C1QB
SELENOP
C1QA
C1QC
FSAP
SLC40A1
CTSB
LIPA
SLCO2B1
CTSD
0.000 0.004
Score
pM10
FOS
JUN
DUSP1
IER2
ZFP36
HSPA1A
HSP90AA1
JUNB
HSPA1B
BTG2
0.0025 0.0075
Score
pM11
CLEC10A
HLA-DPB1
HLA-DRA
RPS18
CD1C
HLA-DPA1
RPS2
HLA-DQB1
RPS14
RPL26
0.000 0.002 0.004
Score
pM12
HIST1H4C
HMGB2
MKI67
TUBB
TUBA1B
STMN1
PCLAF
TOP2A
TYMS
TPX2
0.002 0.006
Score
pM13
FOLR1
FBP1
NCBP2L
AC007610.2
IL1
AC015660.2
MT1H
CYP27B1
MT1G
LINC02384
0.00 0.01
Score
pM14
CXCL10
TNFSF10
GBP1
CXCL11
ISG15
CXCL9
MX1
WARS
IFIT1
GBP4
0.010 0.015
Score
pFP01
CXCL5
MMP3
MMP1
MT2A
PI15
SBSN
FTH1
MT1X
IL7R
GAS1
0.005 0.015
Score
pFP02
COL4A1
COL4A2
SPARC
THY1
ANGPT2
IGFBP7
CALD1
RGS5
EGFL6
ITGA1
0.002 0.004
Score
pFP03
SFRP2
CCDC80
MGP
C1QTNF3
DPT
DCN
FBLN1
MFAP5
OGN
C3
0.005 0.010
Score
pFP04
MT-ND4
MT-CO2
MT-CYB
MT-CO1
MT-CO3
MT-ATP6
MT-ND5
MT-ND1
MT-ND2
MT-ND3
0.005 0.015
Score
pFP05
PDGFRA
CXCL14
F3
POSTN
EDNRB
ENHO
HSD17B2
NSG1
PLAT
ALKAL2
0.002 0.006
Score
pFP06
PLAU
COL3A1
COL1A1
PDPN
TNFRSF11B
TMEM158
COL1A2
RARRES2
COL6A3
CTSK
0.000 0.004
Score
pFP07
HSP90AA1
FOSB
JUN
FOS
JUNB
HSPA1A
HSPA1B
ZFP36
HSPA8
SOCS3
0.000 0.005 0.010
Score
pFP08
ADAMDEC1
APOE
CFD
EDIL3
MFAP4
HAPLN1
TCF21
LUM
ABCA8
CTSC
0.0025 0.0075
Score
pFP11
MYH6
CXCL11
MADCAM1
CXCL10
ACKR1
IDO1
CXCL9
SELE
IL32
PLA1A
0.01 0.03
Score
pV01
COL1A2
COL3A1
COL1A1
ACTA2
SOD3
COL6A3
RGS5
ADAMDEC1
SYNPO2
COL14A1
0.000 0.005 0.010
Score
pV02
JUNB
FOS
HSPA1A
FOSB
ZFP36
JUN
HSPA1B
HSP90AA1
DNAJA1
SOCS3
0.000 0.004 0.008
Score
pV03
ACKR1
PRCP
SELP
MADCAM1
COTL1
NPC2
PDLIM1
CDKN3
TPT1
THY1
0.002 0.006
Score
pV04
EFEMP1
PROX1
PDPN
TFPI
RBP1
LYVE1
RELN
SEMA3A
MMRN1
EFNA5
0.005 0.015
Score
pV05
MT-ND4
MT-CYB
MT-CO1
MT-CO2
MT-CO3
MT-ND1
MT-ATP6
MT-ND5
MT-ND2
MT-ND3
0.00 0.01
Score
pV06
SRP14
PCSK5
FBLN5
TSPAN2
JAG1
KCTD12
SEMA3G
TM4SF1
SULF1
S100A6
0.0025 0.0075
Score
pV07
PLVAP
SPARC
COL15A1
COL4A1
FLT1
KDR
VWA1
PLPP3
COL4A2
PRSS23
0.002 0.006
Score
CD4⁺ T cells
CD8⁺ T/IL cells
B cells
Plasma cells
Myeloid cells
Fibroblasts/ pericytes
Vascular cells

Supplementary Figure 1| Top weighted genes of GEPs in the gut.
Weighted genes for each gene expression programme (GEP) derived from the gut. cNMF was run separately in: $CD4^+$ T, $CD8^+$ T, B, plasma cells, myeloid cells (monocytes, macrophages and DC), vascular cells, and fibroblasts and pericytes. See **Supplementary Table 5** for full list of weighted genes, results of overrepresentation analysis, and results of enrichment testing of GEPs in inflammation. pB: B cell GEP; pCD4T: $CD4^+$ T cell GEP; pCD8T: $CD8^+$ T cell/NK GEP; pFP: fibroblast and pericyte GEP; pM: myeloid cell GEP; pP: plasma cell GEP; pV: vascular cell GEP.


Longitudinal DEG counts post-adalimumab in remission and non-remission
CD
UC
CD4+ T cells
CD4+ TWIST1+ Treg
CD4+ FOShi T
CD4+ FOS+ T
GZMA+ Th1/17
CD4+ HSPhi CD70+ Treg
CD4+ HSPhi Treg
CD4+ IKZF2hi TNFRSF18lo Treg
CD4+ IKZF2hi TNFRSF18hi Treg
CD4+ IKZF2lo LAG3+ Treg
CD4+ naive T
CD4+ KLF2hi T
CD4+ TNFSF13Bhi T
Tph/Tfh
CXCL13+ Tph/Tfh
CD4+ KLF2int T
Th1
GZMAhi Th1/17
Th1/17/22
Th17
Th22
CD8+ T/ Unconventional T/ NK cells
CD8+ CTLA4hi TIGIThi T
Cycling CD8+ T
CD8+ EGR1hi T
CD8+ FGFBP2+ T
CD8+ GZMKhi T
CD8+ GZMKint T
CD8+ IL17A+ IL26+ IL23R+ T
CD8+ IL7Rhi T
CD8+ naive T
CD8+ TNFhi IFNGhi IL2+ T
γδ SOX4+ T
γδ T
MAIT
NK
ILCs
ILC
B cells
CCL22+ memory B
CCL3+ CCL4+ follicular B
Cycling B
FCRL4+ memory B
Follicular B
IFN-resp memory B
IgGhi/IgAhi memory B
IGLC6hi memory B
Intermediate B
Memory B
GC-like B
Plasma cells
IgA+ IFN-resp plasma
IgA+ plasma
IgG+ CXCR4hi plasma
IgG+ CXCR4lo plasma
Plasmablast
Myeloid cells
C1Qhi IL1Bhi macrophage
C1Qhi IL1Blo macrophage
CD1Chi DC
LAMP3+ DC
LAMP3+ IL1B+ DC
Mast
pDC
S100A8/9hi monocyte
S100A8/9hi TNFhi IL6+ monocyte
XCR1+ DC
Cycling MNP
Stroma/ Endo- thelium
ABCA8+ WNT2B+ FOShi fibroblast
ABCA8+ WNT2B+ FOSlo fibroblast
Arterial endothelium
C3hi CCL19+ fibroblast
C3hi RSPO3+ fibroblast
CD74hi HLA-DRB1hi arterial pericyte
CD74hi HLA-DRB1hi venous pericyte
Cycling stroma
Glia
Lymphatic endothelium
Myofibroblast
NOTCH3hi MYH11+ pericyte
NOTCH3hi TNChi LOXL2+ pericyte
NOTCH3hi TNCint CCL19+ pericyte
NOTCH3hi TNClo pericyte
SOX6+ POSTN+ fibroblast
SOX6+ NRG1hi NPY+ fibroblast
THY1+ FAP+ PDPN+ fibroblast
Venous endothelium
Colonic epithelium
BEST4 OTOP2
CT colonocyte
DDC+ CHGA+ EEC
GCG+ PYY+ EEC
NEUROG3+ EEC
DUOXA2+ CXCL11+ enterocyte
PLCG2hi enterocyte
DUOXA2+ enterocyte
Goblet
M-like
Paneth
LGR5+ stem
TA
Tuft
Undifferentiated enterocyte
Ileal epithelium
BEST4 OTOP2
CHGAhi CHGBhi EEC
CHGAlo CHGBlo EEC
Ileal enterocyte
DUOX2+ LCN2+ enterocyte
MUC6+ PGC+ DUOX2+ enterocyte
PLCG2hi enterocyte
Goblet
Paneth
RPShi enterocyte
LGR5+ stem
TA
Tuft
0
200
400
600
Gene count
0
1,000
2,000
Gene count
Genes increased post-treatment in non-remission
Genes increased post-treatment in remission

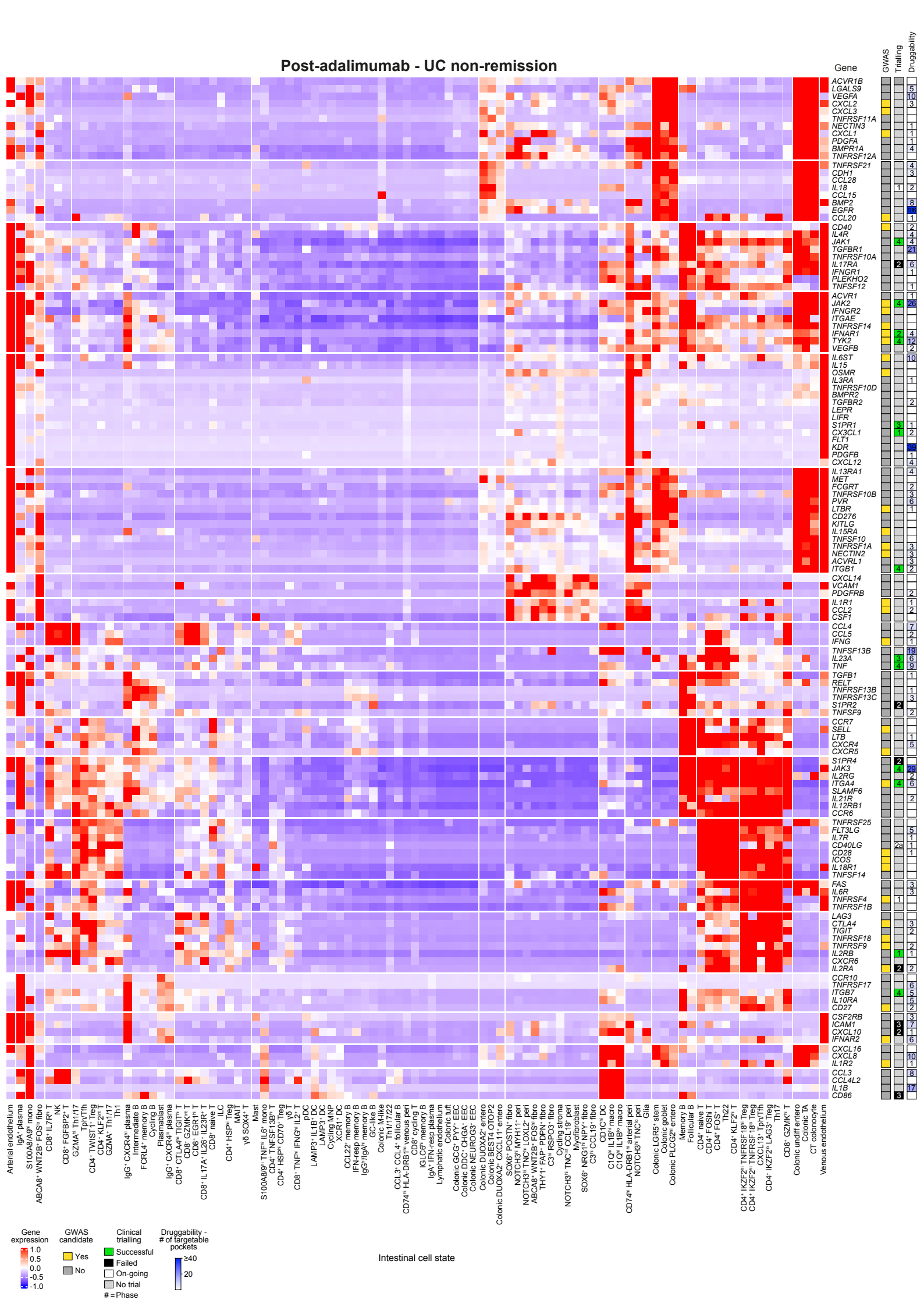
Supplementary Figure 2| Longitudinal gene expression following adalimumab in CD and UC.

Longitudinal gene expression analysis was conducted separately for CD and UC using MAST on paired samples i.e. (samples from the same region in the same patient before pre- and after post-treatment). Sample pairs were required to have at least one sample inflamed sample for inclusion in this analysis. Sample numbers are presented in main Fig. 4 legend. Only genes expressed in 10% of a cell state were tested for differential expression. Covariates included, age, sex, site, disease duration, number of genes detected, and a nested random effects design, (1| donor/sample) to account for multiple samples per patient. For longitudinal analyses, an interaction term of treatment (pre/post) by remission (remission/non- remission) was used. Stacked barplots show genes increasing in non-remission (post-pre, red), and remission (post-pre, blue) in CD (left) and UC (right). DC, dendritic cell; DEG, differentially expressed gene; EEC, enteroendocrine cell; FC, fold change; fibro, fibroblast; GC, germinal centre; hi, high; IFN-resp, interferon-responsive; ILC, innate lymphoid cell; int, intermediate; lo, low; MAIT, mucosal-associated invariant T; MNP, mononuclear phagocyte; mono, monocyte; NK, natural killer cells; pDC, plasmacytoid dendritic cell; $RPS^{hi,}$ ribosomal protein S-high; TA, transit-amplifying; Tfh, $CD4^+$ follicular helper T cell; Tph, $CD4^+$ peripheral helper T cell; Th, $CD4^+$ T helper cell; Treg, $CD4^+$ regulatory T cell.

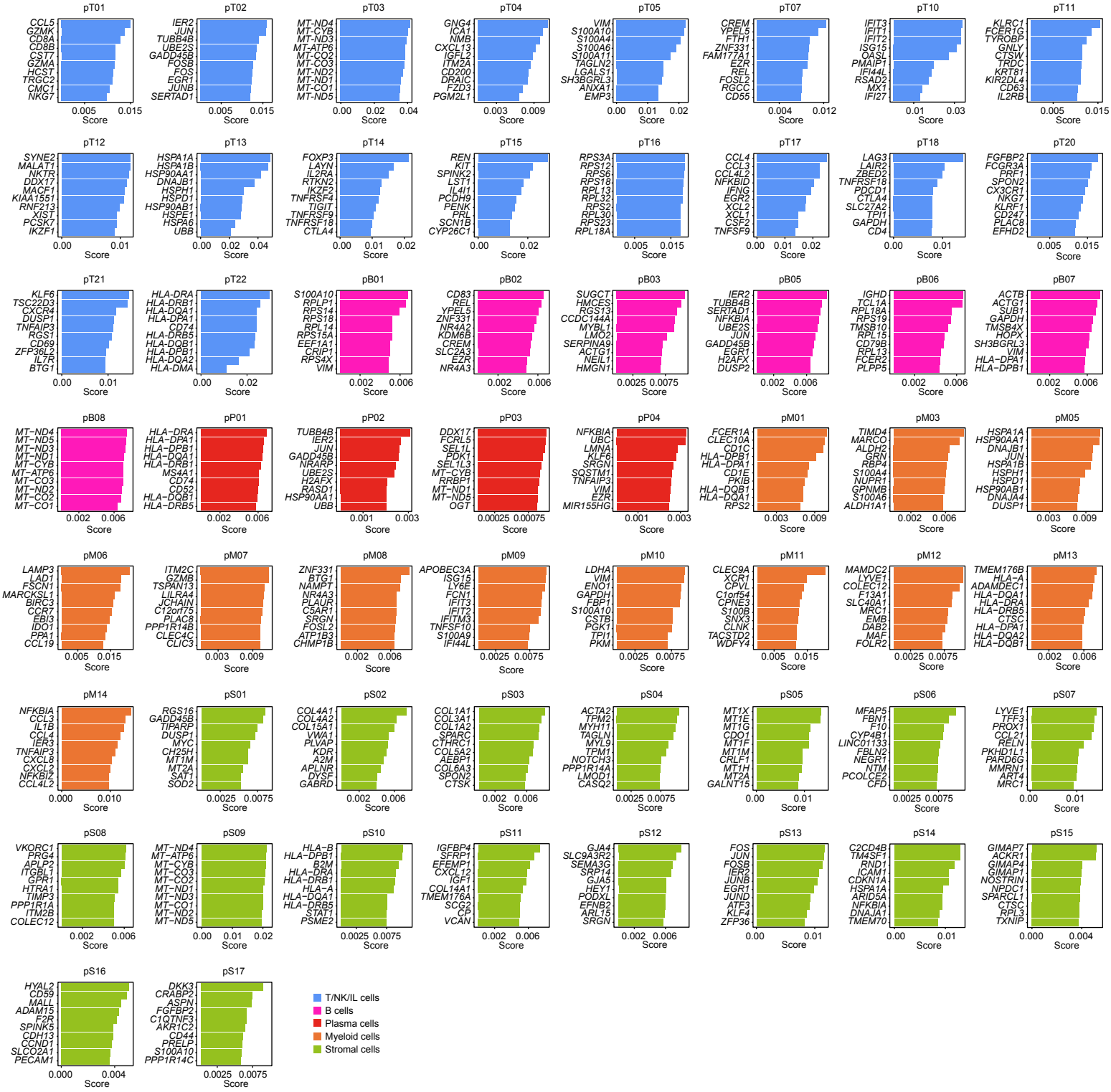

Post-adalimumab - CD non-remission
Gene
GWAS
Trialling
Druggability
LAG3
CCL5
IFNG
IL2RB
TIGIT
IL2RA
FAS
IL12RB1
FLT3LG
IL7R
IL23A
CXCR4
ITGA4
S1PR4
IL18R1
TNFRSF25
CD28
ICOS
CCR6
LTB
CD40LG
CXCL12
TGFBR2
BMPR2
LIFR
S1PR1
ACVRL1
KDR
FLT1
TNFRSF10D
IL3RA
CD276
ITGB1
KITLG
TNFRSF10A
IL15RA
ACVR1
IL6ST
CXCL1
CCL2
CSF1
IL1R1
TNFRSF4
TGFB1
ITGB7
VEGFB
IFNAR2
TNFRSF13B
CCR10
TNFRSF17
CD27
TNFRSF18
ICOSLG
IL10RA
RELT
CSF2RB
ICAM1
CCL3
CCL4
IL2RG
ITGAE
IFNAR1
IL15
TNFRSF14
TYK2
JAK1
JAK3
TNFSF12
PLEKHO2
TGFBR1
CCR7
SELL
TNFSF9
TNFRSF13C
CD40
IL1R2
CD86
CSF2RA
CXCL10
OSM
HAVCR2
IL1A
CCR1
CCL3L1
CCL4L2
CXCL8
IL1B
TNFRSF1B
INHBA
CD274
TNFSF14
TNFSF13B
TNF
CCL20
CXCL16
CXCL2
CXCL3
VEGFA
IL4R
IL17RA
JAK2
IL6R
IFNGR2
TNFRSF21
CCL28
ACVR1B
BMP2
EGFR
LGALS9
TNFRSF12A
CCL25
IL18
CCL15
CDH1
ACVR2A
PDGFA
NECTIN3
PRLR
TNFRSF11A
BMPR1A
PVR
MET
NECTIN2
TNFSF10
TNFRSF1A
LTBR
IL13RA1
FCGRT
IFNGR1
TNFRSF10B
S100A8/9hi mono
Arterial endothelium
IgA+ plasma
CD8+ IL7Rhi T
CD4+ FOS- T
Th22
CD4+ FOS+ T
Memory B
Venous endothelium
ABCA8+ WNT2B+ FOS+ fibro
Ileal DUOX2+ LCN2+ entero
Ileal LGR5+ stem
Ileal PLCG2+ entero
Ileal RPS+
Colonic PLCG2+ entero
Colonic LGR5+ stem
CD74hi HLA-DRB1hi arterial peri
Glia
NOTCH3hi TNChi LOXL2+ peri
NOTCH3hi TNChi peri
ABCA8+ WNT2B+ FOS+ fibro
Lymphatic endothelium
CXCL2+ fibroblast
SOX6+ POSTN+ fibroblast
Mast
ILC
CD4+ KLF2hi T
CD4+ TNFSF13Bhi T
CD4+ HSPhi Treg
CD4+ TWIST1+ Treg
CD8+ naive T
CD8+ FGFBP2+ T
γδ
Ileal goblet
Colonic DUOX2+ entero
Colonic BEST4 OTOP2
Ileal DUOX2+ MUC6+ PGC+ entero
Colonic goblet
IgG+ CXCR4+ plasma
CD8+ TNFhi IFNGhi IL2+ T
Th1/17/22
Cycling MNP
XCR1+ DC
Cycling B
CD4+ HSPhi CD74hi Treg
γδ SOX4+ T
CD8+ CTLA4hi TIGIThi T
Cycling stroma
THY1+ FAP+ PDPNhi fibro
Ileal CHGAlo CHGBhi EEC
NOTCH3hi TNChi CCL19+ peri
NOTCH3hi MYH11+ peri
CD27+ IGHG+ B
Ileal CHGA+ CHGBhi EEC
Colonic DUOX2+ CXCL11+ entero
IgG+ CXCR4hi plasma
Plasmablast
IgA+ IFN-resp plasma
CD8+ cycling T
CCL3+ CCL4+ follicular B
IgGhi IgA+ memory B
IGLC6hi memory B
GC-like B
Myofibroblast
SOX6+ NRG1hi NPY+ fibro
Ileal paneth
Ileal BEST4 OTOP2
Ileal tuft
Colonic tuft
C3hi CCL19+ fibro
CD74hi HLA-DRB1hi venous peri
Colonic GCG+ PYY+ EEC
Colonic DDC+ CHGA+ EEC
Colonic M-like
Colonic NEUROG3+ EEC
Follicular B
IFN-resp memory B
FCRL4+ memory B
Intermediate B
pDC
C1Qhi IL1Bhi macro
LAMP3+ IL1B+ DC
GZMAhi Th1/17
Th1
Th17
CD8+ IL17A+ IL26+ IL23R+ T
MAIT
GZMA+ Th1/17
CD4+ naive T
CD4+ KLF2hi T
CXCL13+ Tph1/Tfh
Tph1/Tfh
CD8+ GZMKhi T
CD8+ EOMEShi T
CD8+ GZMKhi T
NK
CD4+ IKZF2hi TNFRSF18hi Treg
CD4+ IKZF2hi LAG3hi Treg
CD4+ IKZF2hi TNFRSF18hi Treg
Colonic undiff entero
CT colonocyte
Ileal TA
Colonic TA
S100A8/9hi TNFhi IL6+ mono
CD1Chi DC
C1Qhi IL1Bhi macro
Ileal entero
Intestinal cell state
Gene expression
1.0
0.5
0.0
-0.5
-1.0
GWAS candidate
Yes
No
Clinical trialling
Successful
Failed
On-going
No trial
= Phase
Druggability - # of targetable pockets
≥40
20

Supplementary Figure 3| Therapeutic atlas for CD.

Samples from the CD non-remission group following treatment with adalimumab were pseudobulked at the cell-state resolution. A list of therapeutically relevant genes including curated cytokine and receptors from KEGG (M9809)[1], members of the JAK family, checkpoint co-inhibitory and co-stimulatory molecules, and cell trafficking molecules was compiled. Genes with expression in over 97% of cells were kept. Column-wise, and row-wise k-means clustering was applied. The first column to the right of the genes indicates whether the gene has been implicated in genome-wide association studies (GWAS; yellow). The second column indicates stage of development of therapeutic agent associated with the gene (Phase 1/2/3/4), green colour indicative of trial success. The third column is indicative of the number of druggable pockets as outlined on Pi[2]. DC, dendritic cell; EEC, enteroendocrine cell; GC, germinal centre; hi, high; IFN-resp, interferon-responsive; ILC, innate lymphoid cell; lo, low; macro, macrophage; MAIT, mucosal-associated invariant T; MNP, mononuclear phagocyte; mono, monocyte; NK, natural killer cells; pDC, plasmacytoid dendritic cell; peri, pericyte; TA, transit-amplifying; Tfh, $CD4^+$ follicular helper T cell; Tph, $CD4^+$ peripheral helper T cell; Th, $CD4^+$ T helper cell; Treg, $CD4^+$ regulatory T cell.


Post-adalimumab - UC non-remission
Gene
GWAS
Trialling
Druggability
ACVR1B
LGALS9
VEGFA
CXCL2
CXCL3
TNFRSF11A
NECTIN3
CXCL1
PDGFA
BMPR1A
TNFRSF12A
TNFRSF21
CDH1
CCL28
IL18
CCL15
BMP2
EGFR
CCL20
CD40
IL4R
JAK1
TGFBR1
TNFRSF10A
IL17RA
IFNGR1
PLEKHO2
TNFSF12
ACVR1
JAK2
IFNGR2
ITGAE
TNFRSF14
IFNAR1
TYK2
VEGFB
IL6ST
IL15
OSMR
IL3RA
TNFRSF10D
BMPR2
TGFBR2
LEPR
LIFR
S1PR1
CX3CL1
FLT1
KDR
PDGFB
CXCL12
IL13RA1
MET
FCGRT
TNFRSF10B
PVR
LTBR
CD276
KITLG
IL15RA
TNFSF10
TNFRSF1A
NECTIN2
ACVRL1
ITGB1
CXCL14
VCAM1
PDGFRB
IL1R1
CCL2
CSF1
CCL4
CCL5
IFNG
TNFSF13B
IL23A
TNF
TGFB1
RELT
TNFRSF13B
TNFRSF13C
S1PR2
TNFSF9
CCR7
SELL
LTB
CXCR4
CXCR5
S1PR4
JAK3
IL2RG
ITGA4
SLAMF6
IL21R
IL12RB1
CCR6
TNFRSF25
FLT3LG
IL7R
CD40LG
CD28
ICOS
IL18R1
TNFSF14
FAS
IL6R
TNFRSF4
TNFRSF1B
LAG3
CTLA4
TIGIT
TNFRSF18
TNFRSF9
IL2RB
CXCR6
IL2RA
CCR10
TNFRSF17
ITGB7
IL10RA
CD27
CSF2RB
ICAM1
CXCL10
IFNAR2
CXCL16
CXCL8
IL1R2
CCL3
CCL4L2
IL1B
CD86
Arterial endothelium
IgA+ plasma
S100A8/A9hi mono
ABCA8+ WNT2B+ FOSlo fibro
CD8+ IL7Rhi T
NK
CD8+ FGFBP2+ T
GZMAhi Th1/17
Tph/Tfh
CD4+ TWIST1+ Treg
CD4+ KLF2int T
GZMA+ Th1/17
Th1
IgG+ CXCR4hi plasma
Intermediate B
FCRL4+ memory B
Cycling B
Plasmablast
IgG+ CXCR4lo plasma
CD8+ CTLA4hi TIGIThi T
CD8+ GZMKint T
CD8+ EGR1hi T
CD8+ IL17A+ IL26+ IL23R+ T
CD8+ naïve T
ILC
CD4+ HSPhi Treg
MAIT
γδ SOX4+ T
Mast
S100A8/9hi TNFhi IL6+ mono
CD4+ TNFSF13Bhi T
CD4+ HSPhi CD70+ Treg
γδ T
CD8+ TNFhi IFNGhi IL2+ T
pDC
LAMP3+ IL1B+ DC
LAMP3+ DC
Cycling MNP
XCR1+ DC
CCL22+ memory B
IFN-resp memory B
IgG/IgA+ memory B
GC-like B
Colonic M-like
Th1/17/22
CCL3+ CCL4+ follicular B
CD74hi HLA-DRB1hi venous peri
CD8+ cycling T
IGLC6+ memory B
IgA+ IFN-resp plasma
Lymphatic endothelium
Colonic tuft
Colonic GCG+ PYY+ EEC
Colonic DDC+ CHGA+ EEC
Colonic NEUROG3+ EEC
Colonic DUOXA2+ entero
Colonic BEST4 OTOP2
Colonic DUOXA2+ CXCL11+ entero
SOX6+ POSTN+ fibro
NOTCH3hi MYH11+ peri
NOTCH3hi TNChi LOXL2+ peri
ABCA8+ WNT2B+ FOSlo fibro
THY1+ FAP+ PDPN+ fibro
C3hi RSPO3+ fibro
Cycling stroma
NOTCH3int TNCint CCL19+ peri
Myofibroblast
SOX6+ NRG1hi NPYhi fibro
C3hi CCL19+ fibro
CD1Chi DC
C1Qhi IL1Bhi macro
C1Qlo IL1Blo macro
CD74hi HLA-DRB1hi arterial peri
NOTCH3hi TNClo peri
Glia
Colonic LGR5+ stem
Colonic goblet
Colonic PLCG2hi entero
Memory B
Follicular B
CD4+ naïve T
CD4+ FOShi T
CD4+ FOSlo T
Th22
CD4+ KLF2hi T
CD4+ IKZF2hi TNFRSF18hi Treg
CD4+ IKZF2hi TNFRSF18lo Treg
CXCL13+ Tph/Tfh
CD4+ IKZF2lo LAG3+ Treg
Th17
CD8+ GZMKhi T
Colonic undiff entero
Colonic TA
CT colonocyte
Venous endothelium
Gene expression
1.0
0.5
0.0
-0.5
-1.0
GWAS candidate
Yes
No
Clinical trialling
Successful
Failed
On-going
No trial
= Phase
Druggability - # of targetable pockets
≥40
20
Intestinal cell state

Supplementary Figure 4| Therapeutic atlas for UC.
Samples from the UC non-remission group following treatment with adalimumab were pseudobulked at the cell-state resolution. A list of therapeutically relevant genes: curated cytokine and receptors from KEGG (M9809)[1], members of the JAK family, checkpoint co-inhibitory and co-stimulatory molecules, cell trafficking molecules was compiled. Genes with expression in over 97% of cells were kept. Column-wise, and row-wise K-means clustering applied. The first column to the right of the genes indicates whether the gene has been implicated in in genome-wide association studies (GWAS; yellow). The second column indicates stage of development of therapeutic agent associated with the gene (Phase 1/2/3/4), green colour indicative of trial success. The third column is indicative of the number of druggable pockets as outlined on Pi[2]. DC, dendritic cell; EEC, enteroendocrine cell; GC, germinal centre; hi, high; IFN-resp, interferon-responsive; ILC, innate lymphoid cell; lo, low; macro, macrophage; MAIT, mucosal-associated invariant T; MNP, mononuclear phagocyte; mono, monocyte; NK, natural killer cells; pDC, plasmacytoid dendritic cell; peri, pericyte; TA, transit-amplifying; Tfh, $CD4^+$ follicular helper T cell; Tph, $CD4^+$ peripheral helper T cell; Th, $CD4^+$ T helper cell; Treg, $CD4^+$ regulatory T cell.


pT01
CCL5
GZMK
CD8A
CD8B
CST7
GZMA
HCST
TRGC2
CMC1
NKG7
0.005
0.015
Score
pT02
IER2
JUN
TUBB4B
UBE2S
GADD45B
FOSB
FOS
EGR1
JUNB
SERTAD1
0.005
0.015
Score
pT03
MT-ND4
MT-CYB
MT-ND3
MT-ATP6
MT-CO2
MT-CO3
MT-ND2
MT-ND1
MT-CO1
MT-ND5
0.00
0.02
0.04
Score
pT04
GNG4
ICA1
NMB
CXCL13
IGFL2
ITM2A
CD200
DRAIC
FZD3
PGM2L1
0.003
0.009
Score
pT05
VIM
S100A10
S100A4
S100A6
S100A11
TAGLN2
LGALS1
SH3BGRL3
ANXA1
EMP3
0.00
0.01
0.02
Score
pT07
CREM
YPEL5
FTH1
ZNF331
FAM177A1
EZR
REL
FOSL2
RGCC
CD55
0.004
0.012
Score
pT10
IFIT3
IFIT1
IFIT2
ISG15
OASL
PMAIP1
IFI44L
RSAD2
MX1
IFI27
0.01
0.03
Score
pT11
KLRC1
FCER1G
TYROBP
GNLY
CTSW
TRDC
KRT81
KIR2DL4
CD63
IL2RB
0.005
0.015
Score
pT12
SYNE2
MALAT1
NKTR
DDX17
MACF1
KIAA1551
RNF213
XIST
PCSK7
IKZF1
0.00
0.01
Score
pT13
HSPA1A
HSPA1B
HSP90AA1
DNAJB1
HSPH1
HSPD1
HSP90AB1
HSPE1
HSPA6
UBB
0.00
0.02
0.04
Score
pT14
FOXP3
LAYN
IL2RA
RTKN2
IKZF2
TNFRSF4
TIGIT
TNFRSF9
TNFRSF18
CTLA4
0.00
0.01
0.02
Score
pT15
REN
KIT
SPINK2
LST1
IL4I1
PCDH9
PENK
PRL
SCN1B
CYP26C1
0.00
0.02
Score
pT16
RPS3A
RPS12
RPS6
RPS18
RPL13
RPL32
RPS2
RPL30
RP523
RPL18A
0.005
0.015
Score
pT17
CCL4
CCL3
CCL4L2
NFKBID
IFNG
EGR2
XCL2
XCL1
CSF2
TNFSF9
0.00
0.01
0.02
Score
pT18
LAG3
LAIR2
ZBED2
TNFRSF18
PDCD1
CTLA4
SLC27A2
TPI1
GAPDH
CD4
0.00
0.01
Score
pT20
FGFBP2
FCGR3A
PRF1
SPON2
CX3CR1
NKG7
KLRF1
CD247
PLAC8
EFHD2
0.005
0.015
Score
pT21
KLF6
TSC22D3
CXCR4
DUSP1
TNFAIP3
RGS1
CD69
ZFP36L2
IL7R
BTG1
0.00
0.01
Score
pT22
HLA-DRA
HLA-DRB1
HLA-DQA1
HLA-DPA1
CD74
HLA-DRB5
HLA-DQB1
HLA-DPB1
HLA-DQA2
HLA-DMA
0.00
0.02
Score
pB01
S100A10
RPLP1
RPS14
RPS18
RPL14
RPS15A
EEF1A1
CRIP1
RPS4X
VIM
0.002
0.006
Score
pB02
CD83
REL
YPEL5
ZNF331
NR4A2
KDM6B
CREM
SLC2A3
EZR
NR4A3
0.002
0.006
Score
pB03
SUGCT
HMCES
RGS13
CCDC144A
MYBL1
LMO2
SERPINA9
ACTG1
NEIL1
HMGN1
0.0025
0.0075
Score
pB05
IER2
TUBB4B
SERTAD1
NFKBIA
UBE2S
JUN
GADD45B
EGR1
H2AFX
DUSP2
0.002
0.006
Score
pB06
IGHD
TCL1A
RPL18A
RPS19
TMSB10
RPL15
CD79B
RPL13
FCER2
PLPP5
0.002
0.006
Score
pB07
ACTB
ACTG1
SUB1
GAPDH
TMSB4X
HOPX
SH3BGRL3
VIM
HLA-DPA1
HLA-DPB1
0.002
0.006
Score
pB08
MT-ND4
MT-ND5
MT-ND3
MT-ND1
MT-CYB
MT-ATP6
MT-CO3
MT-ND2
MT-CO2
MT-CO1
0.002
0.006
Score
pP01
HLA-DRA
HLA-DPA1
HLA-DPB1
HLA-DQA1
HLA-DRB1
MS4A1
CD74
CD52
HLA-DQB1
HLA-DRB5
0.002
0.006
Score
pP02
TUBB4B
IER2
JUN
GADD45B
NRARP
UBE2S
H2AFX
RASD1
HSP90AA1
UBB
0.001
0.003
Score
pP03
DDX17
FCRL5
SELL
PDK1
SEL1L3
MT-CYB
RRBP1
MT-ND1
MT-ND5
OGT
0.00025
0.00075
Score
pP04
NFKBIA
UBC
LMNA
KLF6
SRGN
SQSTM1
TNFAIP3
VIM
EZR
MIR155HG
0.001
0.003
Score
pM01
FCER1A
CLEC10A
CD1C
HLA-DPB1
HLA-DPA1
CD1E
PKIB
HLA-DQB1
HLA-DQA1
RPS2
0.003
0.009
Score
pM03
TIMD4
MARCO
ALDH2
GRN
RBP4
S100A4
NUPR1
GPNMB
S100A6
ALDH1A1
0.002
0.006
Score
pM05
HSPA1A
HSP90AA1
DNAJB1
JUN
HSPA1B
HSPH1
HSPD1
HSP90AB1
DNAJA4
DUSP1
0.003
0.009
Score
pM06
LAMP3
LAD1
FSCN1
MARCKSL1
BIRC3
CCR7
EBI3
IDO1
PPA1
CCL19
0.005
0.015
Score
pM07
ITM2C
GZMB
TSPAN13
LILRA4
JCHAIN
C12orf75
PLAC8
PPP1R14B
CLEC4C
CLIC3
0.003
0.009
Score
pM08
ZNF331
BTG1
NAMPT
NR4A3
PLAUR
C5AR1
SRGN
FOSL2
ATP1B3
CHMP1B
0.002
0.006
Score
pM09
APOBEC3A
ISG15
LY6E
FCN1
IFIT3
IFIT2
IFITM3
TNFSF10
S100A9
IFI44L
0.0025
0.0075
Score
pM10
LDHA
VIM
ENO1
GAPDH
FBP1
S100A10
CSTB
PGK1
TPI1
PKM
0.0025
0.0075
Score
pM11
CLEC9A
XCR1
CPVL
C1orf54
CPNE3
S100B
SNX3
CLNK
TACSTD2
WDFY4
0.005
0.015
Score
pM12
MAMDC2
LYVE1
COLEC12
F13A1
SLC40A1
MRC1
EMB
DAB2
MAF
FOLR2
0.0025
0.0075
Score
pM13
TMEM176B
HLA-A
ADAMDEC1
HLA-DQA1
HLA-DRA
HLA-DRB5
CTSC
HLA-DPA1
HLA-DQA2
HLA-DQB1
0.002
0.006
Score
pM14
NFKBIA
CCL3
IL1B
CCL4
IER3
TNFAIP3
CXCL8
CXCL2
NFKBIZ
CCL4L2
0.000
0.010
Score
pS01
RGS16
GADD45B
TIPARP
DUSP1
MYC
CH25H
MT1M
MT2A
SAT1
SOD2
0.0025
0.0075
Score
pS02
COL4A1
COL4A2
COL15A1
VWA1
PLVAP
KDR
A2M
APLNR
DYSF
GABRD
0.002
0.006
Score
pS03
COL1A1
COL3A1
COL1A2
SPARC
CTHRC1
COL5A2
AEBP1
COL8A3
SPON2
CTSK
0.002
0.006
Score
pS04
ACTA2
TPM2
MYH11
TAGLN
MYL9
TPM1
NOTCH3
PPP1R14A
LMOD1
CASQ2
0.0025
0.0075
Score
pS05
MT1X
MT1E
MT1G
CDO1
MT1F
MT1M
CRLF1
MT2A
GALNT15
0.00
0.01
Score
pS06
MFAP5
FBN1
F10
CYP4B1
LINC01133
FBLN2
NEGR1
NYM1
PCOLCE2
CFD
0.0025
0.0075
Score
pS07
LYVE1
TFF3
PROX1
CCL21
RELN
PKHD1L1
PARD6G
MMRN1
ART4
MRC1
0.00
0.01
Score
pS08
VKORC1
PRG4
APLP2
ITGBL1
GPR1
HTRA1
TIMP3
PPP1R1A
ITM2B
COLEC12
0.002
0.006
Score
pS09
MT-ND4
MT-ATP6
MT-CYB
MT-CO3
MT-CO2
MT-ND1
MT-ND3
MT-CO1
MT-ND2
MT-ND5
0.00
0.01
0.02
Score
pS10
HLA-B
HLA-DPB1
B2M
HLA-DRA
HLA-DRB1
HLA-A
HLA-DQA1
HLA-DRB5
STAT1
PSME2
0.0025
0.0075
Score
pS11
IGFBP4
SFRP1
EFEMP1
CXCL12
IGF1
COL14A1
TMEM176A
SCG2
CP
VCAN
0.002
0.006
Score
pS12
GJA4
SLC9A3R2
SEMA3G
SRP14
GJA5
HEY1
PODXL
EFNB2
ARL15
SRGN
0.002
0.006
Score
pS13
FOS
JUN
FOSB
IER2
JUNB
EGR1
JUND
ATF3
KLF4
ZFP36
0.00
0.01
Score
pS14
C2CD4B
TM4SF1
RND1
ICAM1
CDKN1A
HSPA1A
ARID5A
NFKBIA
DNAJA1
TMEM70
0.00
0.01
Score
pS15
GIMAP7
ACKR1
GIMAP4
GIMAP1
NOSTRIN
NPDC1
SPARCL1
CTSC
RPL3
TXNIP
0.000
0.004
Score
pS16
HYAL2
CD59
MALL
ADAM15
F2R
SPINK5
CDH13
CCND1
SLCO2A1
PECAM1
0.000
0.004
Score
pS17
DKK3
CRABP2
ASPN
FGFBP2
C1QTNF3
AKR1C2
CD44
PRELP
S100A10
PPP1R14C
0.0025
0.0075
Score
T/NK/IL cells
B cells
Plasma cells
Myeloid cells
Stromal cells

Supplementary Figure 5| Top weighted genes of GEPs in the synovium.
Weighted genes for each gene expression programme (GEP) derived from the synovium. cNMF was run separately in: T cells, B cells, plasma cells, myeloid cells and stromal cells. See **Supplementary Table 9** for full list of weighted genes, as well as results of overrepresentation analysis. See **Supplementary Table 9** for results of enrichment testing of GEPs in inflammation. pB, B cell GEP; pM, myeloid cell GEP; pP, plasma cell GEP; pS, stromal cell GEP; pT, T/NK cell GEP.

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