

Mortality is associated with dysregulated host inflammation in the CSF compartment of Malawian adults with pneumococcal meningitis

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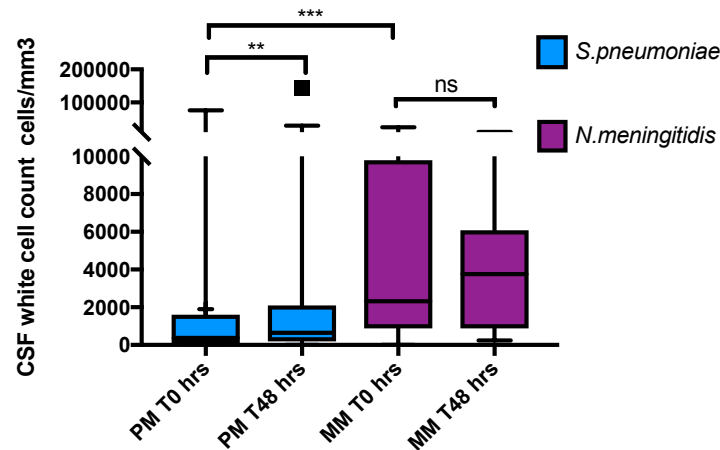
University College London

Mortality from Bacterial meningitis in adults in sub-Saharan Africa is dominated by *Streptococcus pneumoniae*

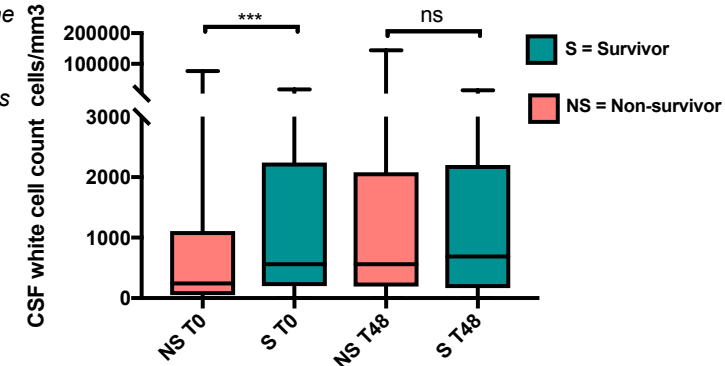
Demographic and clinical parameters of included participants

	PM n=440	NM n=27	Multivariate OR (95% CI)
Age (years) (median, IQR)	31 (25-39)	23 (20-32)	0.93 (0.85-1.0) p=0.09
Gender (n, %)	202 (46%)	21 (77%)	47 (4.6-481) p=0.001
HIV infection (n, %)	351/416 (84%)	16/24 (66%)	0.36 (0.15-0.89) p=0.02
GCS (median, IQR)	11 (8-13)	13 (7.7-15)	2.2 (1.3-3.1) p=0.001
Case fatality rate (n,%)	223/415 (53.7%)	3/27 (11%)	0 5 0 0.005-0.55

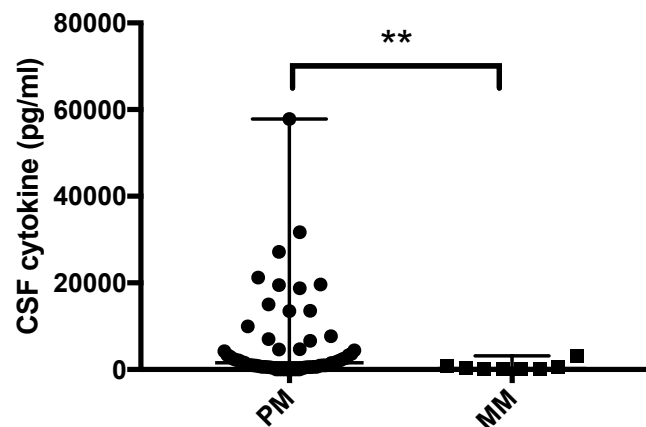
Changes in CSF white cell counts in proven bacterial meningitis over 48 hours



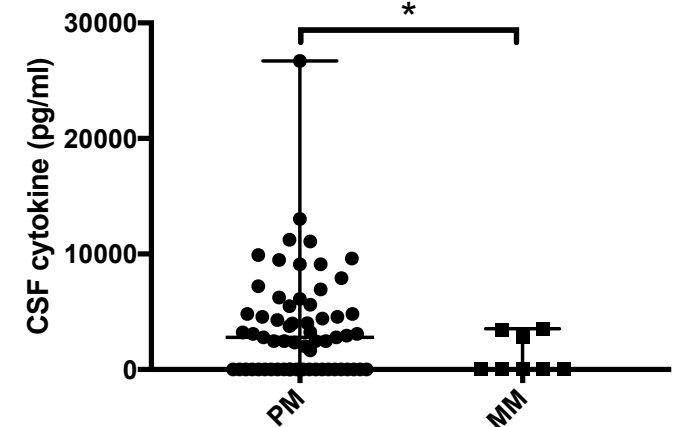
CSF WCC in *Streptococcus pneumoniae* meningitis over 48 hours by outcome group



CSF TNF



IL-1



Patients who underwent CSF transcriptional profiling are young and predominately HIV co-infected

- BAM Trial¹
- CSF culture or PCR positive for *S.pneumoniae*
- CSF & blood collected pre-antibiotics on admission in PAXgene
- All patients received routine or enhanced acute care, follow up to day 40 post admission
- Mortality unaffected by GDT

Variable	Survivors n=5	N-Survivors n=8
Age in years	30 (27-38)	34 (25-47)
Male Gender (n, %)	3 (60%)	3 (37%)
HIV co-infection	5 (100%)	6 (75%)
CD4 count (cells/mm ³)	20, 315 (n=2)	225 (n=1)
GCS	14 (13-14)	11 (7-12)
CSF WCC (cells/mm ³)	19, 119 clumps n=3	365 (75-1320) clumps n=4
CSF Bacterial load (DNA copies/ml)	4309 (1458 – 1.7E+6)	4.5E+7 (1.7E+7-1.4E+ 8)

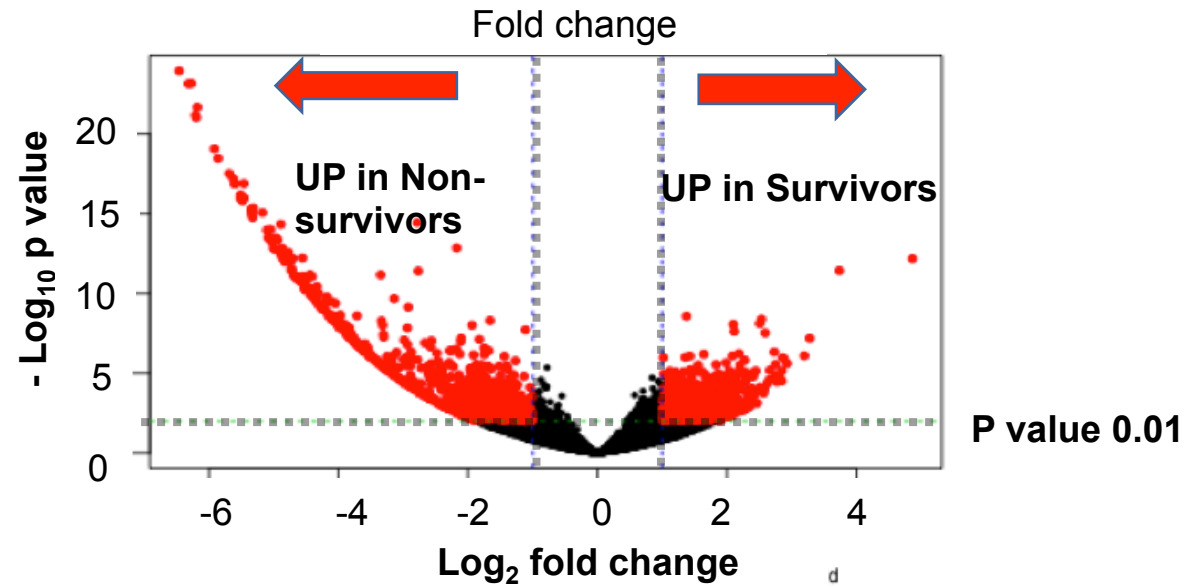
Differential gene expression is marked in the CSF compartment compared to blood

CSF

patients n=13
genes mapped n= 16606

DGE

n=659 in non-survivors
n=753 in survivors

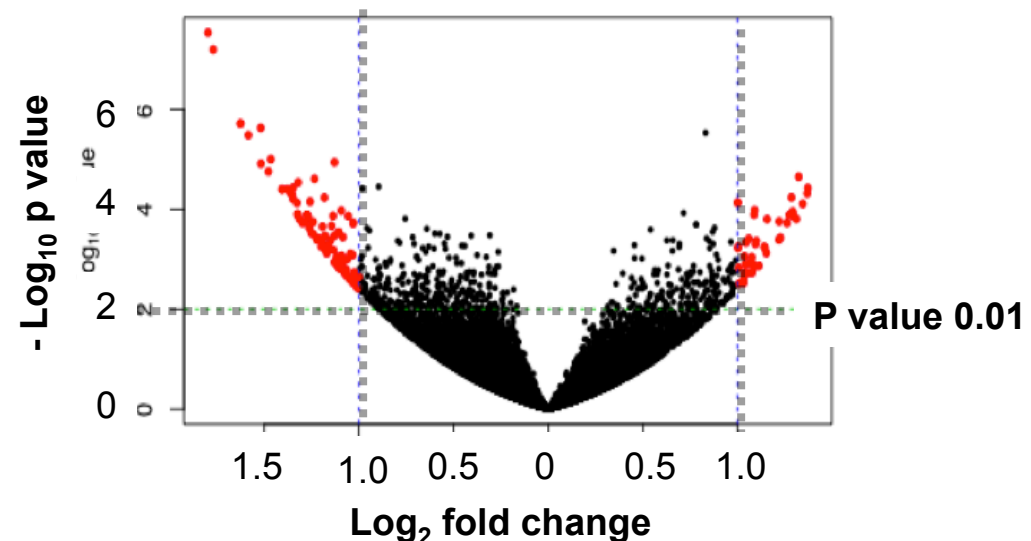


Blood

patients n=28
genes mapped n= 18982

DGE

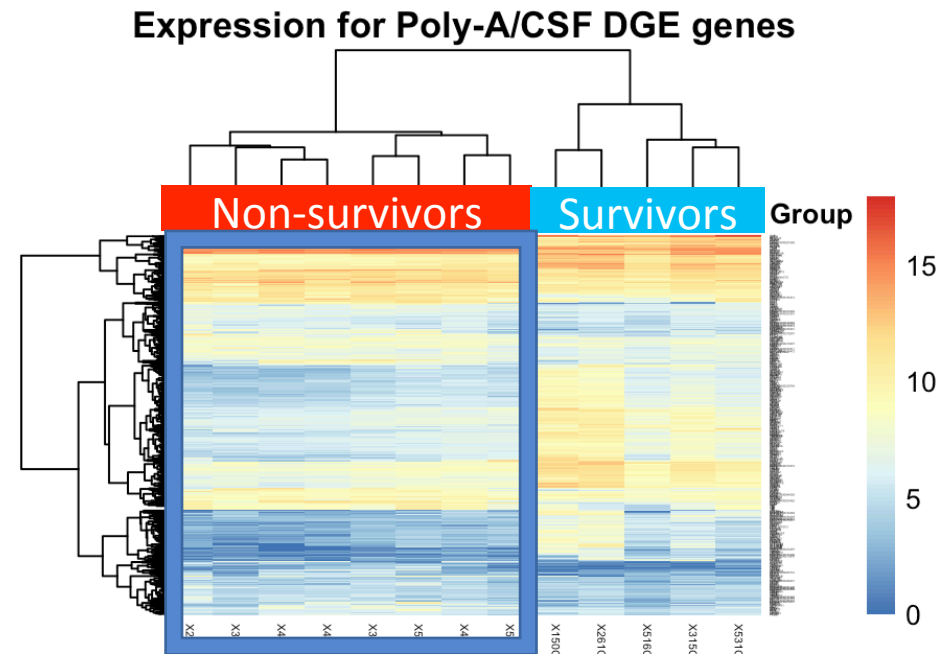
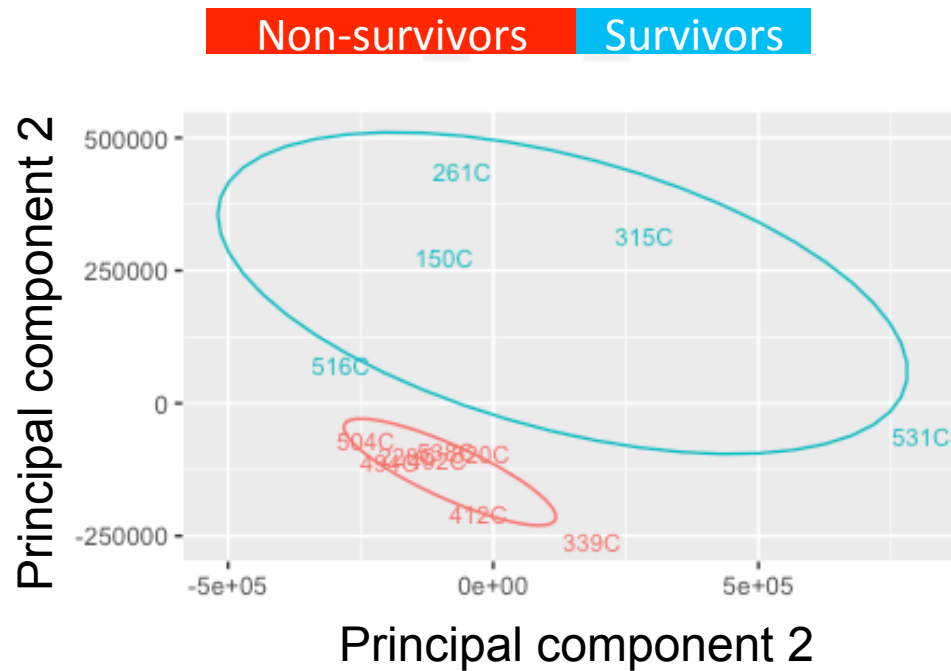
n=25 in non-survivors
8 in survivors



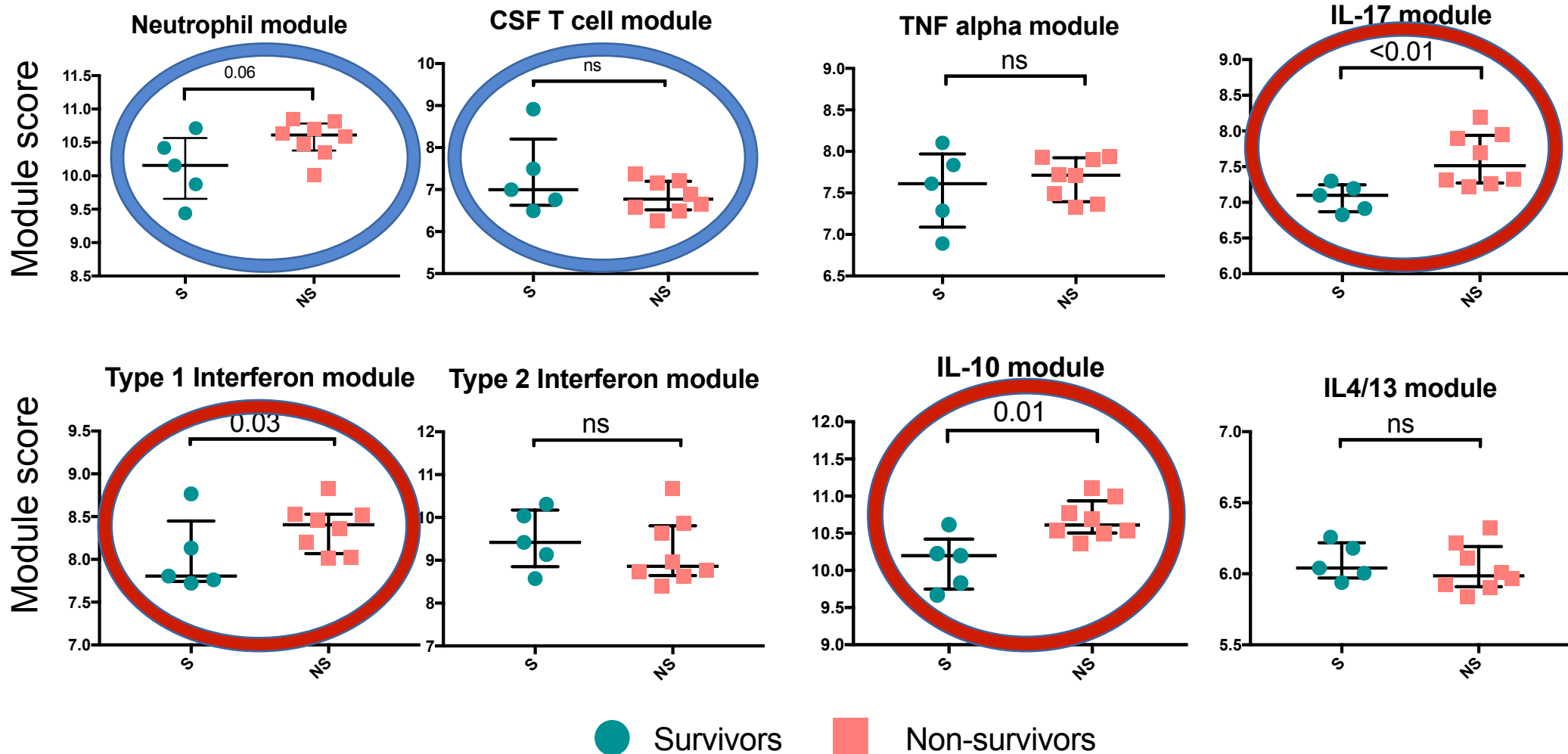
CSF transcriptome describes intense host inflammation and blood-brain barrier breakdown

Cluster number	No. pathways	Annotation of relevant common pathways identified per cluster
1	123	Translation and transcription, HIV and viral RNA processing
2	449	Neuronal signaling , transmembrane transport, GABA receptor receptor interactions , transmission across synapses, cell-cell interactions, CO2 hydration
3	582	Cell cycle, TCR signaling , DNA replication, Mitosis, adaptive immune system, NK cell mediated cytotoxicity , antigen presentation, FCER1 mediated signaling , VEGF mediated signaling
4	251	Damage checkpoints, ubiquitin, regulation of apoptosis, NFkB activation , HIV infection
5	52	RNA surveillance, N-glycan biosynthesis, HIV life cycle , adaptive immune system
6	106	T and B cell receptor & signaling , TGF beta receptor, TLR 2/3/4 signaling, phagosome, chemokine signaling, platelet activation & aggregation
7	24	IL-4 mediated signaling , classical antibody-mediated complement activation and cascade, FCGR immunoglobulin phagocytosis, NFkB activation
8	45	DNA sensing pathway, pathogen sensing , RNA degradation, insulin secretion, TLR3&4 signaling cascade , MyD88 cascade , energy metabolism, interleukin signaling , cellular responses to stress
9	31	Fatty acid receptors, G-protein coupled receptors, Immune-reg interactions , integrin cell surface interactions, apoptosis, TLR signaling , NK cell mediated cytotoxicity , IL-7
10	15	Interferon signaling , antiviral mechanism, pyrimidine metabolism, innate immune system

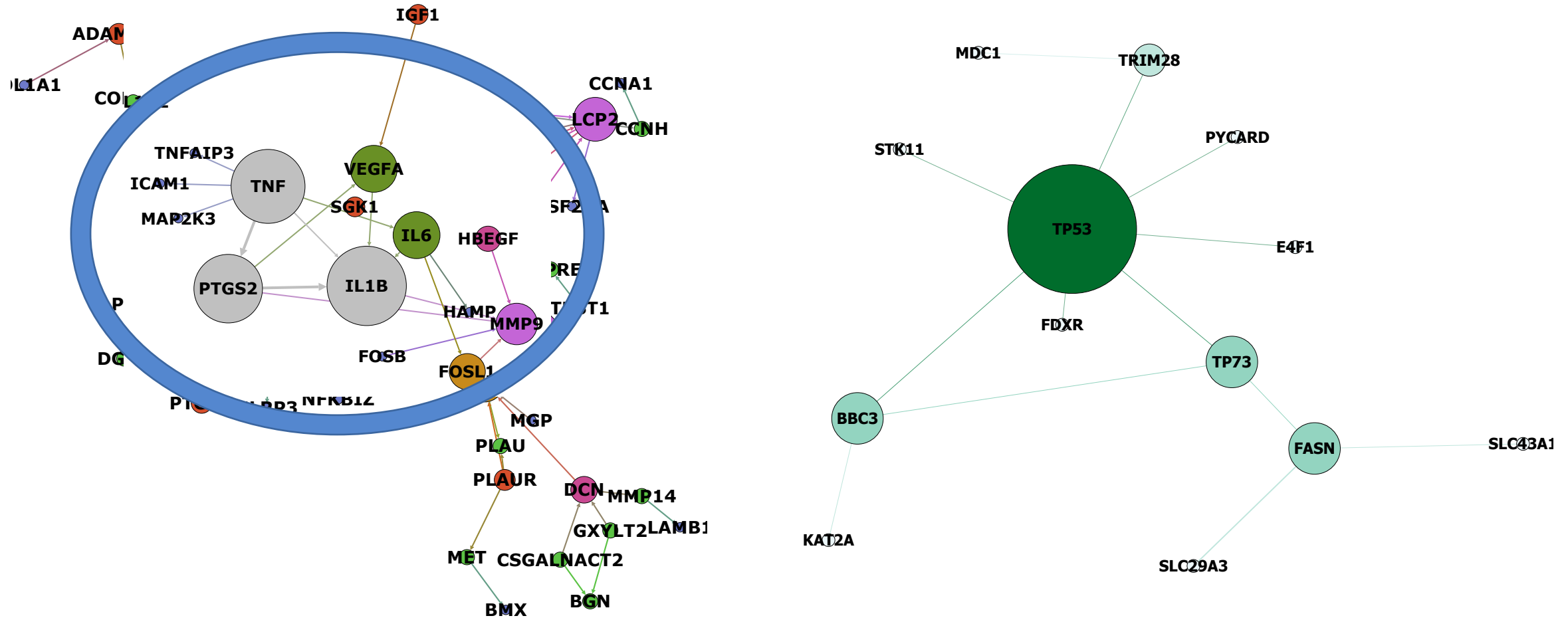
Differential gene expression in non-survivors is tightly clustered



Pro-inflammatory, but not CSF cell-specific, module expression is increased in non-survivors



Network analysis of CSF genes in non-survivors



Analysis done with XGR and InnateDB pathways over-representation analysis

Summary & Discussion

1. Poor outcome in pneumococcal meningitis is strongly associated with attenuated CSF WCC and elevated pro-inflammatory cytokines
2. Homogeneity in CSF responses in non-survivors suggest delay and HIV are less important factors
3. Differences in inflammation are compartmentalised in the CNS, are driven by Th-17 and Type 1 Interferons but not cell-specific responses in this study
4. Is dysregulated inflammation driven by the host or the bug?

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Malawi & LSTM

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