**Supplementary Methods and Results**

Quantification of recovered viable phage was undertaken using 100 µL of undiluted and diluted serum (1:10 in SM buffer) co-incubated with 300 µL of log-phase bacteria embedded in soft-agar as previously described1. Plates with 30-300 visible plaques were used to obtain the plaque-forming units (PFU)/mL by multiplying the number of plaques by the dilution factor.

DNA from whole blood (in PAXgene® blood RNA tubes; BD Diagnostics, Franklin Lakes, New Jersey, USA) was extracted using a commercial kit (QIAamp DNA Blood Mini Kit®; Qiagen, Hilden, Germany) with previously described modifications1, and quantified using 16-well multiplexed-tandem real time PCR targeting *Pseudomonas* 16S rDNA (custom-designed, AusDiagnostics, Mascot, Australia) according to manufacturer instructions (reaction efficiency 93.1%, R2 0.9983). DNA extracted from serum was used for quantitative (q)PCR targeting a conserved hypothetical gene in PASA16 (F: 5’-GCG AGT CCA GGT CCA ACT AC-3’; R: 5’-GTT GCA TAT CGC CCA GCT TG-3’). Reaction volumes were 6.25 µL QuantiNova SYBR® Green PCR Kit (Qiagen), 1.25 µL of each primer (1mM), 0.75 µL water and 3 µL of DNA template. PCR conditions were two-minute initial denaturation at 95oC, then 45 cycles of 95°C for 5 seconds, 60°C for 10 seconds and 72°C for 10 seconds. Reaction efficiency was 89.8% with R2 of 0.9985.

RNA was extracted from whole blood (PAXgene® tubes) using a commercial kit (PAXgene Blood RNA Kit®, Qiagen) to study human gene expression using the Nanostring nCounter® system with the PanCancer immune panel (NanoString Technologies, Seattle, Washington, USA), as previously described1. Differentially expressed genes were identified after background threshold normalisation carried out to a panel of housekeeping genes and positive and negative probes (n=40), with genes that were below the threshold filtered out. RCC files were imported using nSolver 4.0 (Versions 4.0.66, 4.0.70). Data was log2 transformed using Partek Genomics Suite (v7.19.1125) and one-way ANOVA was used to compare differential gene expression before (day 0), during (days 2-11; period 1 = D2, D4; period 2 = D5, D7; period 3 = D9, D11) and after phage therapy (period 4 = D15, D29).

Differentially expressed (DE) genes were observed for the following via one-way ANOVA and unadjusted *p* < 0.05:

1. D2-4 vs. D0, n=58: *SMPD3, CD244, PTGDR2, BMI1, GPI, IL5RA, FEZ1, CD180, ATF1, TNFSF8, ATG5, CHUK, UBC, IL2RG, CD37, CLEC4A, MICA, FOS, TNF, IL18R1, TNFSF13, TLR8, LY86, MR1, C2, BST1, TLR7, IL15, TBK1, LILRB1, STAT1, PSMB9, CMKLR1, MARCO, TAP1, CTSL, FPR2, MICB, ASP1, FCGR3A, CCR1, STAT2, IFI16, BST2, SOCS1, FCGR1A, IFITM1, CD274, FCGR2B, IFI35, TNFSF10, IRF7, OAS3, DDX58, IFIT2, IFIT1, SERPING1, ISG15.*
* n=18 DE genes were enriched for innate immune response (GO:0045087): *CHUK, DDX58, CD180, LY86, MR1, C2, CLEC4A, BST2, MARCO, TBK1, IFI16, UBC, IRF7, SERPING1, TLR8, TLR7, CD244, ATG5*
1. D5-7 vs. D0, n=13: *PTGDR2, SMPD3, CD244, IL5RA, FEZ1, ATG5, IL2RG, TNFSF8, ATF1, CD180, CD1C, IL8, TNFRSF17.*
	* n=3 DE genes were enriched for adaptive immune response (GO:002250): *TNFRSF17, CD1C, CD244* but this did not reach statistical significance after adjustment, *p* = 0.004 unadjusted
2. D9-11 vs. D0, n=20: *PTGDR2, CCR3, KLRG1, SMPD3, CD244, IL16, CLEC4C, IL5RA, FEZ1, CHUK, ATG5, CD180, IRF4, HMGB1, MR1, CDK1, IL15, TBK1, CD38, TNFRSF17.*
3. D15-29 vs. D0, n=16: *PTGDR2, CCR3, LRP1, IL3RA. SMPD3, CD244, IL5RA, FEZ1, ATF1, ATG5, MAP2K4, HLA-DMB, CD1C, HLA-DPA1, HLA-DPB1, CD180.*

Gene Set Enrichment Analysis and Pathway enrichment analysis (KEGG, <https://www.genome.jp/kegg/>) were calculated based on EASE Score with a modified Fisher exact *p*-value (The Database for Annotation, Visualization and Integrated Discovery2 v6.8, <https://david.ncifcrf.gov/home.jsp>). Visualisation of enriched and biologically significant pathways, i.e., Toll-like receptor signalling pathway (**Supplementary Figure 3a**), Autophagy (**Supplementary Figure 3b**) and JAK-STAT signalling pathway (**Supplementary Figure 3c**) was carried out using PathView3 where genes with fold change greater than 2 and less than 2 were integrated into KEGG pathways. Gene enrichment analyses were based on Gene Ontology (GO) terms for innate and adaptive immune responses with *post-hoc* Benjamini-Hochberg adjustment of *p*-values4. To visualise gene expression changes from D0 to D29, hierarchical clustering analysis was carried out where expression normalisation was undertaken by shifting genes to mean of zero and scaled to standard deviation of one. Of note, the most significant gene profile changes at systems level occurred during days 2-4 in comparison to D0, and then post-D9 these gene expression changes tapered off and by D29 the gene profile was similar to D0. While this was a compassionate-use case and therefore systematic data collection could not be carried out, the gene profiles clearly reflected the patient’s response to a chronic bacterial infection as well as the presence of phage. Gene Set Variation Analysis (GSVA) was carried out to further dissect genes enriched for Innate Immune Response and Adaptive Immune Response from D0 to D295. This was based on REACTOME pathways accessed using MSigDBR6. Overlapping genes from both lists were extracted as a separate gene set prior to GSVA analysis.

Significant differentially expressed genes from each of these periods were visualised as a gene network7-9 and it revealed that 7 genes were expressed in the same directionality D2 to D29. Specifically, *CD180, CD244* and *ATG5* (**Supplementary Table 1**), GO:0045087 – innate immune response, *p* = 0.006, are key gene expression drivers in the pathway enrichment analyses. CD244 is part of the signalling lymphocytic activation molecule (SLAM) family, which are triggered by homo- or heterotypic cell-cell interactions, modulate the activation and differentiation of a wide variety of immune cells and are the interconnection of both innate and adaptive immune response. *CD244* was observed to be downregulated throughout phage therapy.

In comparison, CD180 is part of the natural killer cell mediated cytotoxicity family of pathogen receptors (KEGG: hsa04650). By working in concert with TLR4, Toll-like receptors control B-cell recognition and signalling of lipopolysaccharide, a membrane constituent of Gram-negative bacteria. While we could not find significant correlation between bacterial load and specific gene signatures, upregulation of *CD180* likely reflected the presence of *Pseudomonas* in the system as shown in **Figure 2a** and in the GSVA analysis (**Figure 2c**). Endotoxin level of administered phage preparation was 170 EU/mL with 0.9 mL administered per dose equating to 5 EU/Kg (pyrogenic threshold established by the Food and Drug Administration) whereas the surge of *Pseudomonas* DNA (102-103/mL) during treatment corresponds to 0.05-0.5 ng/mL10,11 or 40-400 EU/Kg (0.05-0.5 ng x 10 EU/Kg x 80 mL/Kg blood volume) of endotoxin release.

ATG5 is involved in several cellular processes, including autophagic vesicle formation, mitochondrial quality control after oxidative damage, lymphocyte development and proliferation, MHC II antigen presentation, adipocyte differentiation, negative regulation of the innate antiviral immune response and apoptosis. In association with ATG12, ATG5 negatively regulates the innate antiviral immune response by impairing the type I IFN production pathway upon vesicular stomatitis virus infection12. Here, during phage therapy, *ATG5* was consistently and significantly upregulated hinting an immunomodulatory function within the human host by the presence of phage.

**References**

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**Supplementary Table 1. Significant genes within enriched innate immune response pathway.**

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| **Probe set ID** | **Accession** | **Official Full Name** | ***p*-value (Period 1 vs. D0)** | **Fold-change (Period 1 vs. D0)** | ***p*-value (Period 2 vs. D0)** | **Fold-change (Period 2 vs. D0)** | ***p*-value (Period 3 vs. D0)** | **Fold-change (Period 3 vs. D0)** | ***p*-value (Period 4 vs. D0)** | **Fold-change (Period 4 vs. D0)** |
| CD244 | NM\_016382.2 | CD244 molecule, natural killer cell receptor 2B4 | 0.0050835 | -1.8474 | 0.0172098 | -1.54048 | 0.016914 | -1.54398 | 0.0344261 | -1.41521 |
| ATG5 | NM\_004849.2 | autophagy related 5 | 0.00220889 | 1.36845 | 0.00772567 | 1.24926 | 0.00342763 | 1.32142 | 0.00396262 | 1.30724 |
| CD180 | NM\_005582.2 | CD180 molecule | 0.0119963 | 1.19037 | 0.0009871 | 1.41165 | 0.0006696 | 1.46428 | 0.00016726 | 1.72345 |