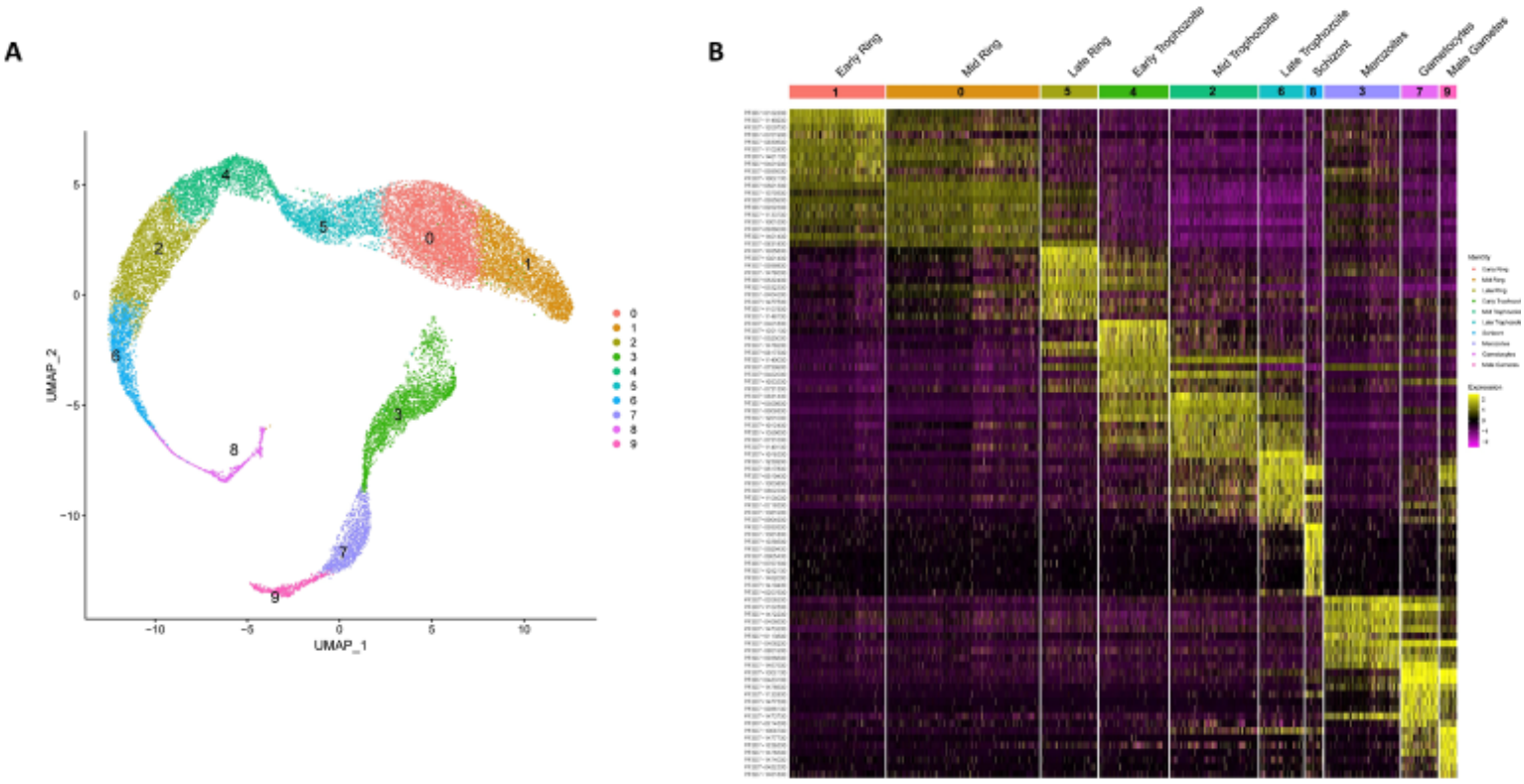
Supplemental Figures and Tables.



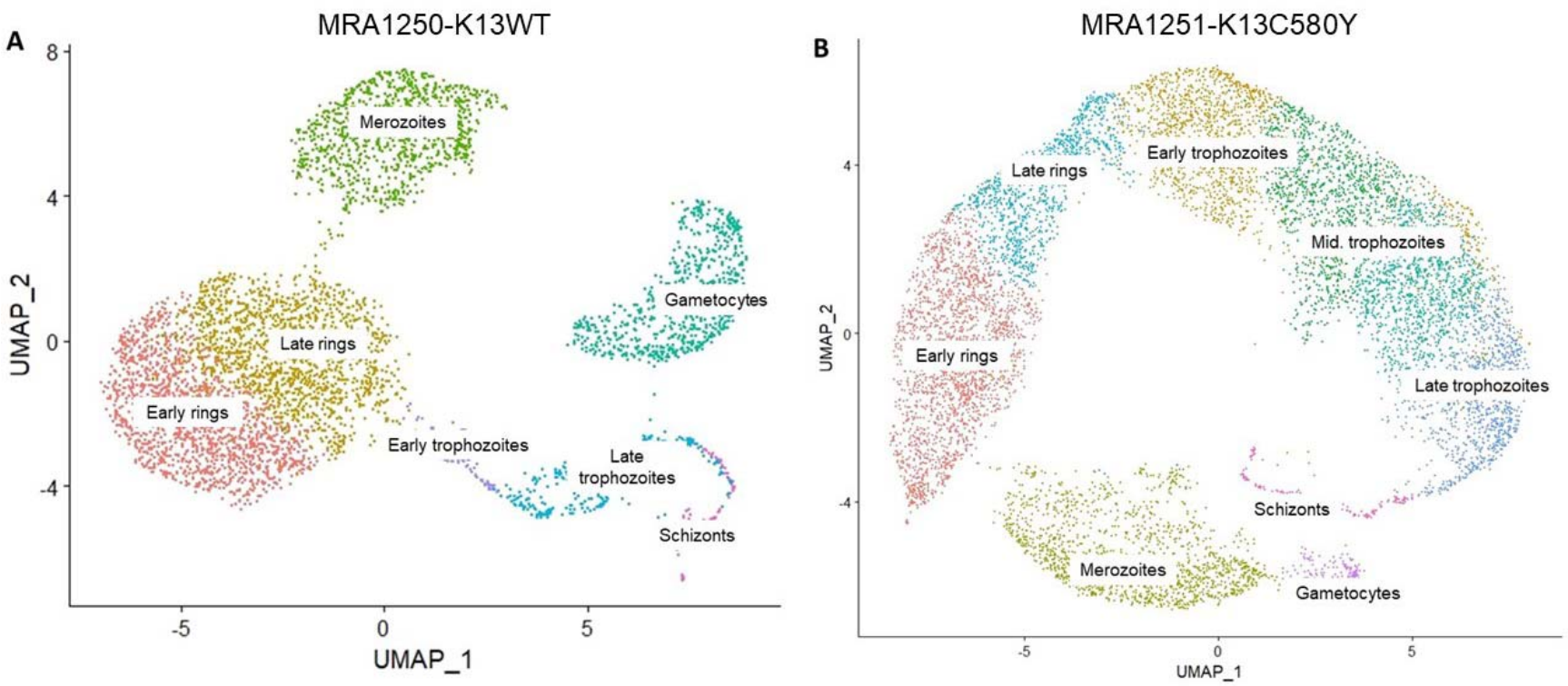
Supplementary Figure S1- A.) UMAP plot of cell clusters generated before annotating clusters. B.) Heatmap showing top 50 genes enriched in each cell cluster which identifies stage specific gene expression profile. The cells in the heatmap are ordered by their developmental progression.

Supplementary Table S1- Top 50 genes enriched in each *P. falciparum* single cell cluster. Gene expression profile associated with parasite stages.

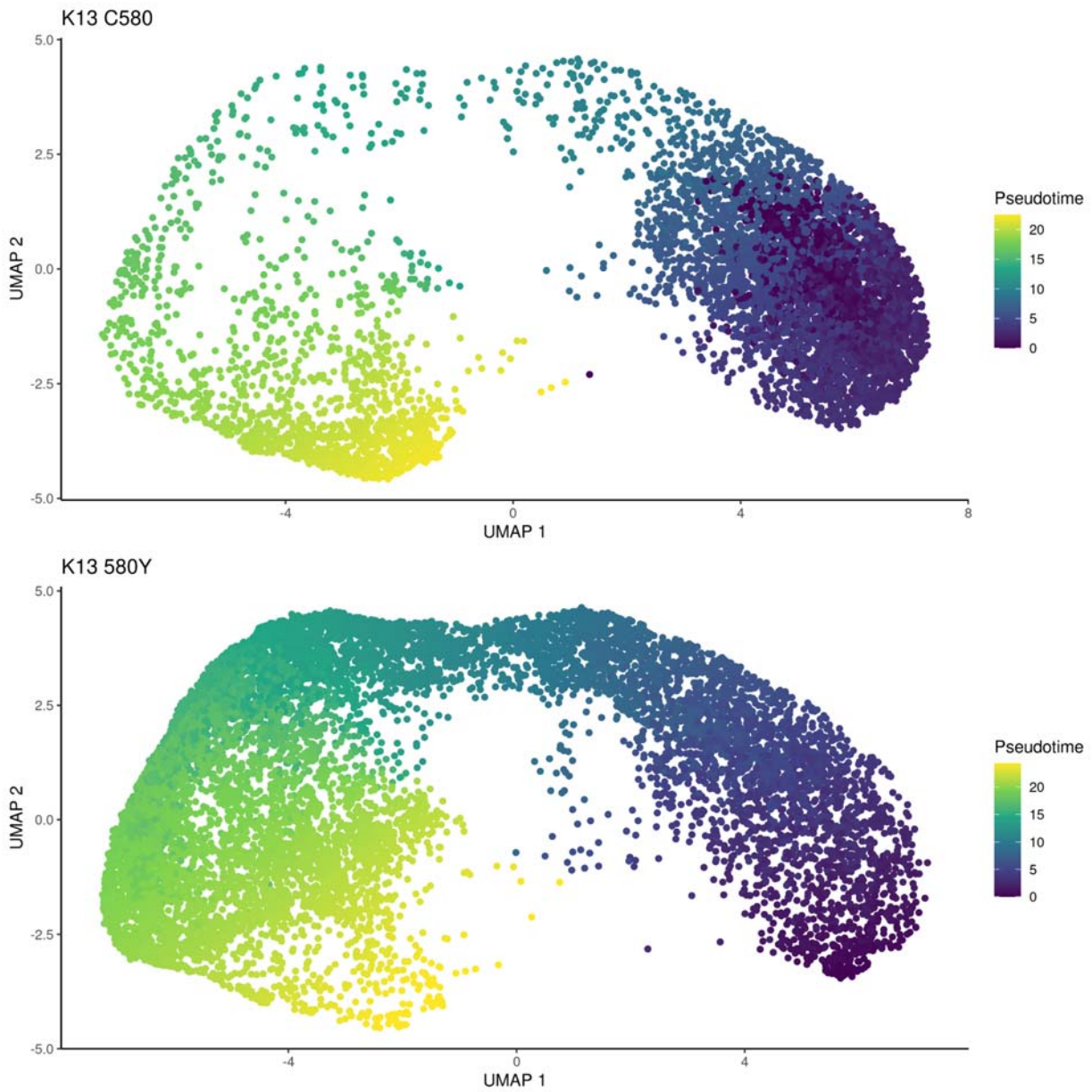
Supplementary Table S2- Genes differentially expressed between the DHA treated K13^{C580} and the DMSO treated K13^{C580} parasite over the course of 6hr DHA treatment.

Supplementary Table S3-Genes differentially expressed between the DHA treated K13^{580Y} and the DMSO treated K13^{580Y} parasite over the course of 6hr DHA treatment.

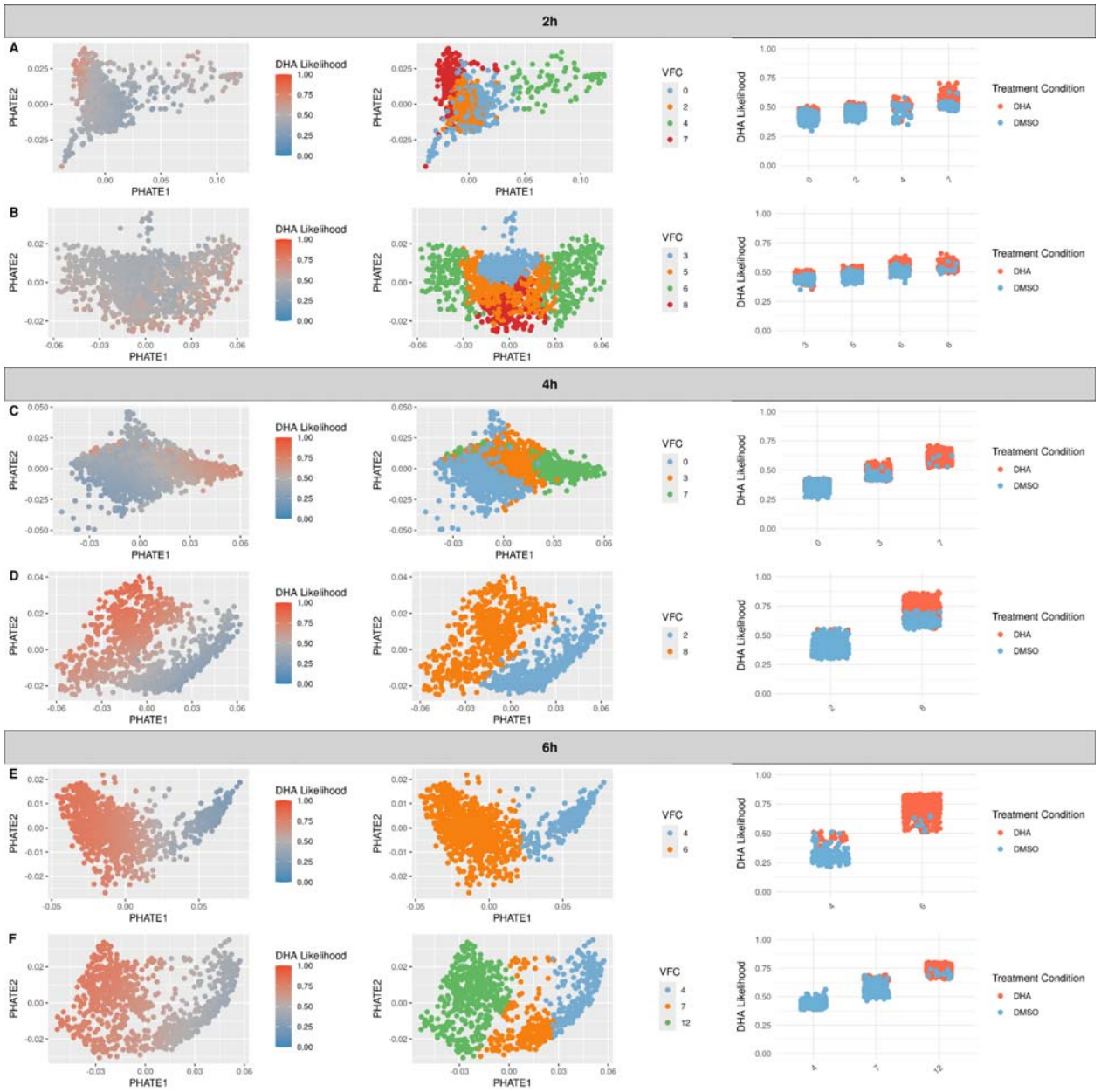
Supplementary Table S4- Genes differentially expressed between the DHA treated K13^{580Y} and the DHA treated K13^{C580} parasite over the course of 6hr DHA treatment.



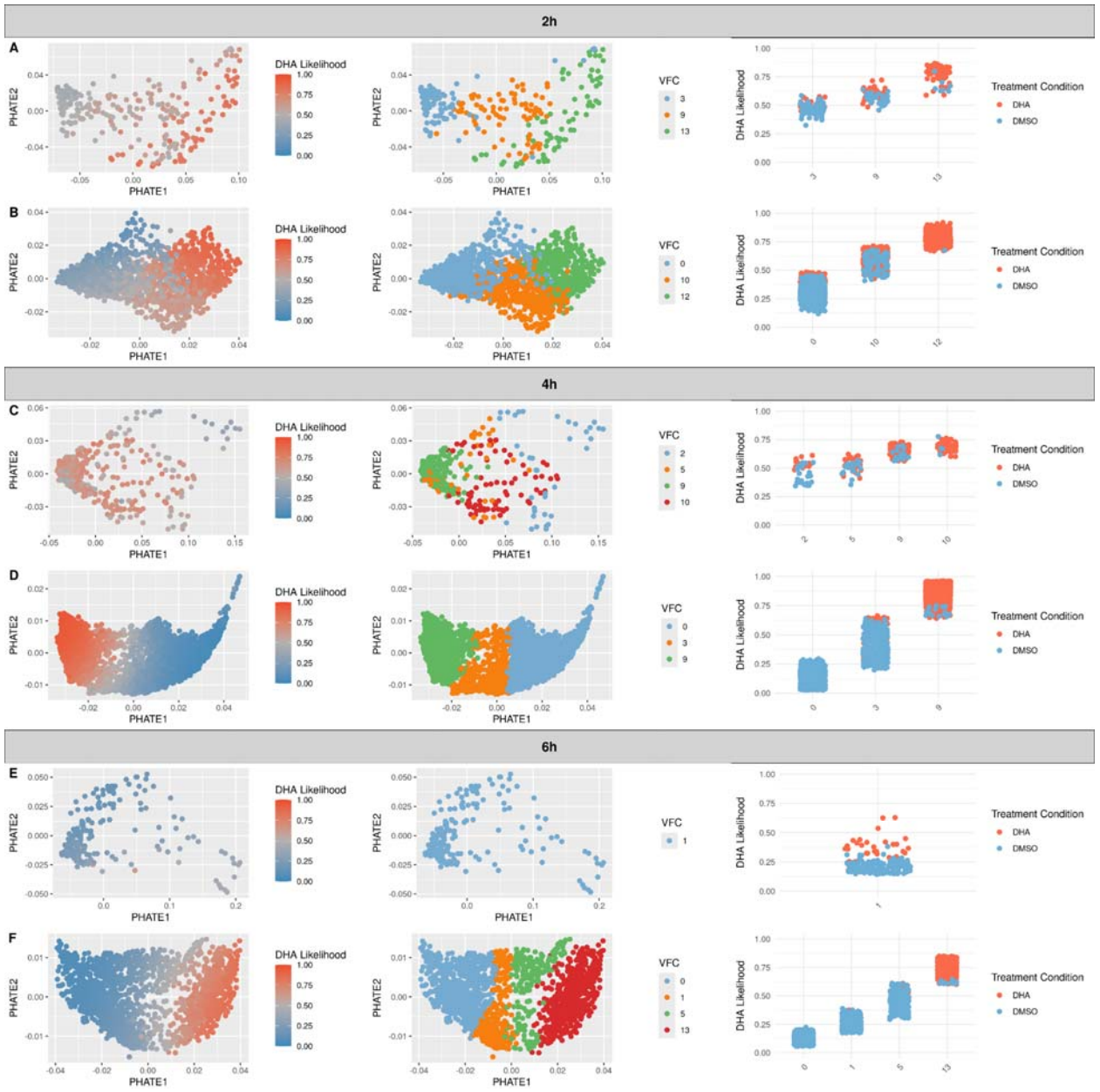
Supplementary Figure S2. UMAP projection plots of K13^{C580} and K13^{580Y} untreated *Pf* parasites.



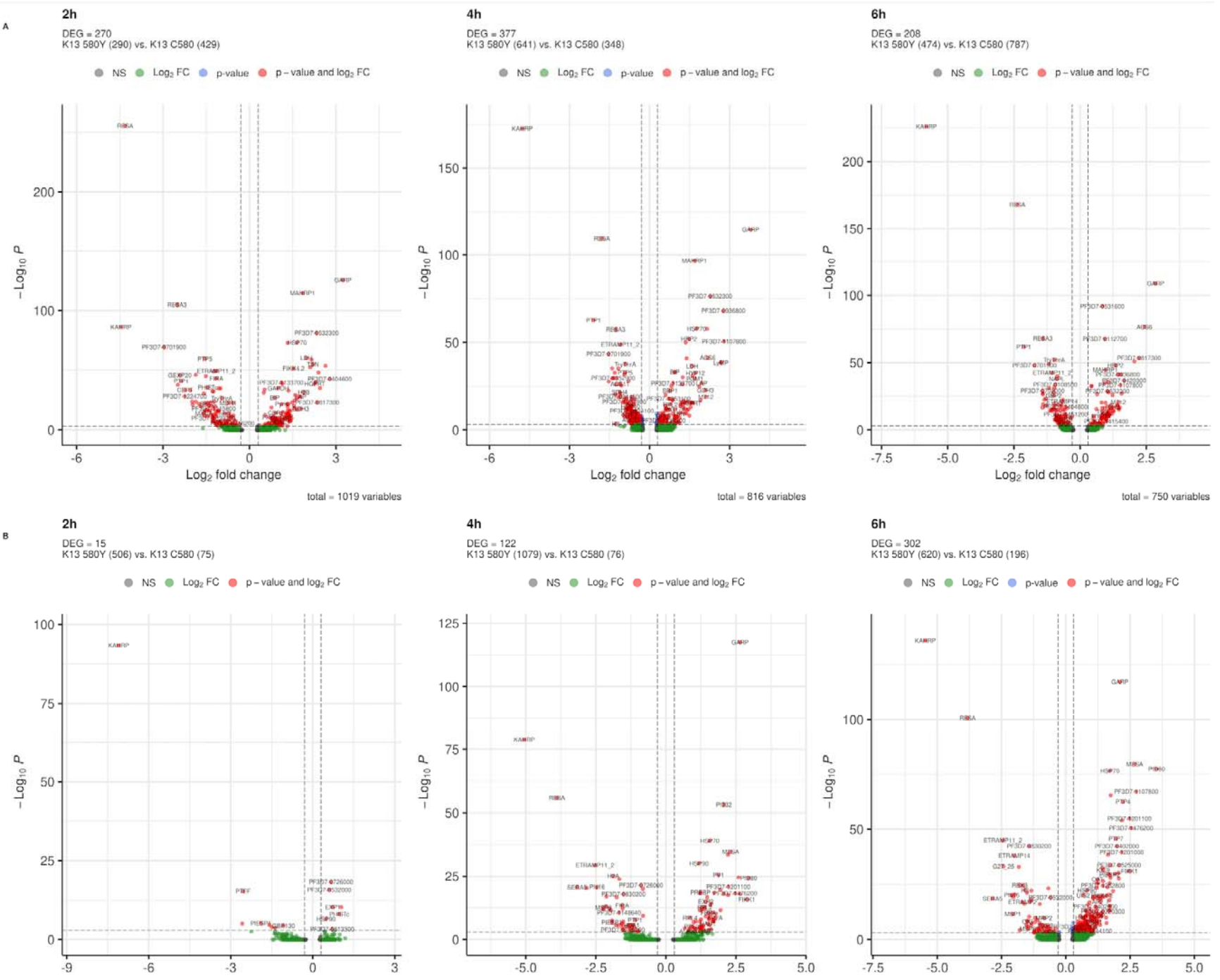
Supplemental Figure S3. Pseudotime over the asexual cycle, separated by strain. Pseudotime was calculated using slingshot for each strain (top: $K13^{C580}$, bottom: $K13^{580Y}$) over the ring, trophozoite and schizont stages. Each cell is assigned a pseudotime value. Lower values correspond to earlier developmental pseudotime (ring stage) and are colored purple. Pseudotime values then increase through the trophozoite stage (green) and the schizont stage (yellow).



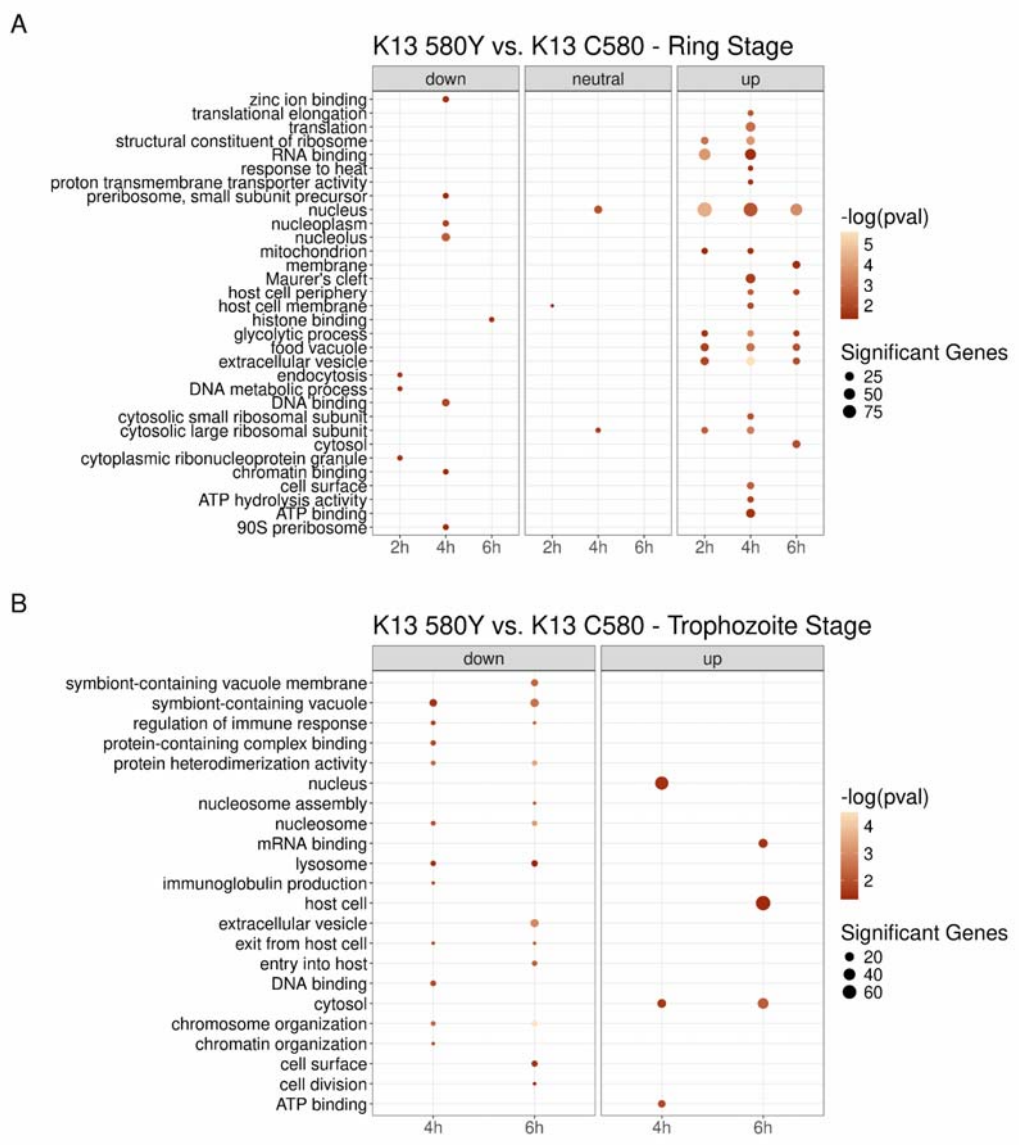
Supplemental Figure S4. Vertex frequency clustering (VFC) results for rings. For each timepoint, the ring stage was sub clustered using Vertex Frequency Clustering. The first row (A,C,E) of each timepoint is $K13^{C580}$ while the second row (B,D,F) is $K13^{580Y}$. For each timepoint, the clusters with the highest DHA likelihood were selected for differential expression. For example, the 2hr timepoint compared VFC cluster 8 in $K13^{580Y}$ vs. VFC cluster 7 in $K13^{C580}$.



Supplemental Figure S5. Vertex frequency clustering (VFC) results for trophozoites. For each timepoint, the trophozoite stage was sub clustered using Vertex Frequency Clustering. The first row (A, C, E) of each timepoint is $K13^{C580}$ while the second row (B,D,F) is $K13^{580Y}$. For each timepoint, the clusters with the highest DHA likelihood were selected for differential expression. For example, the 2hr timepoint compared VFC cluster 12 in $K13^{580Y}$ vs. VFC cluster 13 in $K13^{C580}$.

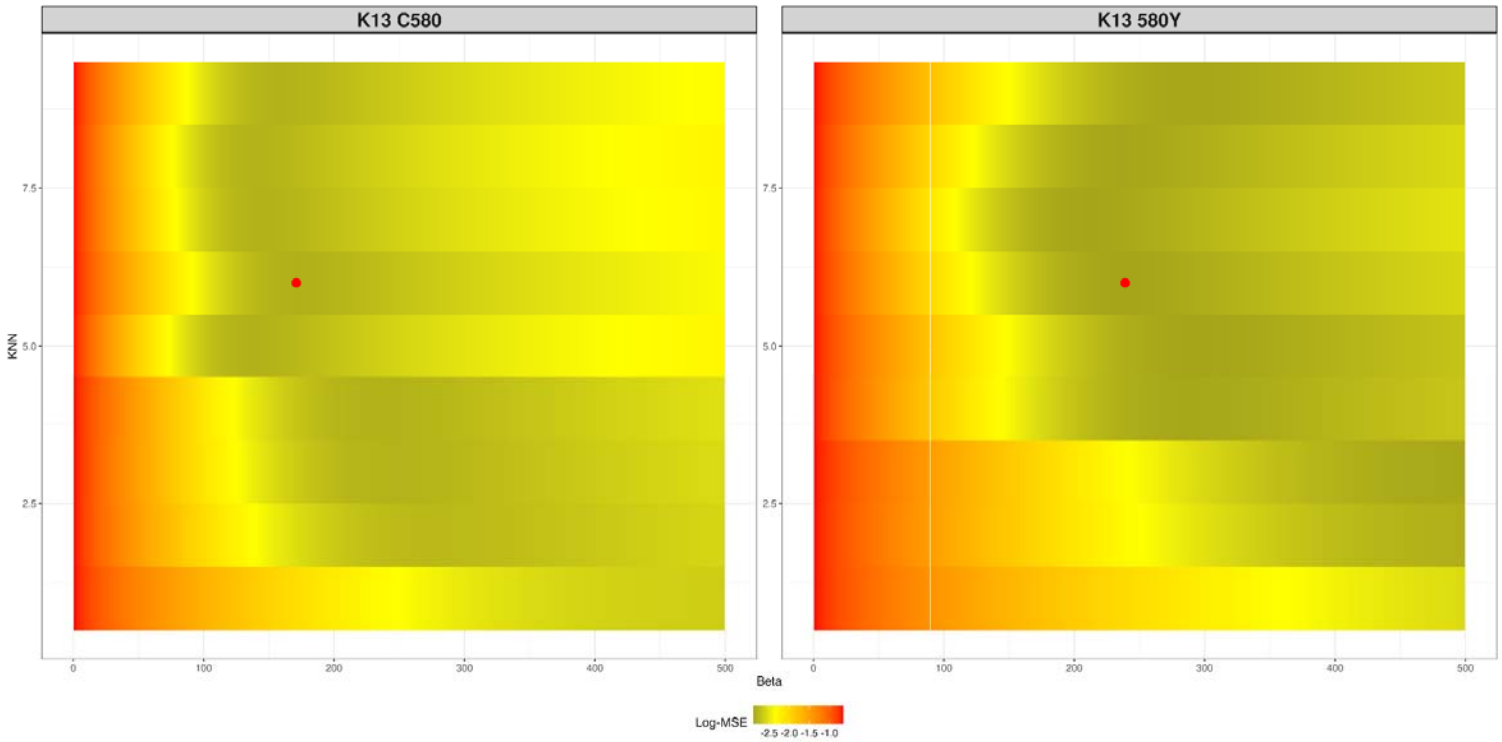


Supplemental Figure S6. Differential expression utilizing MELD and high DHA likelihood subclusters show similar results to traditional differential expression analysis in Figure 6. Ring stage (A) and trophozoite stage (B) comparisons are plotted for each timepoint (2hr (left), 4hr (middle) and 6hr (right)). Below each title, the plots are annotated by the number of differentially expressed genes (DEG) and the cell number of each strain in the differential expression analysis. The x axis plots the average log2FC and the y axis plots the -log10 BH-adjusted p value of each gene. Each dot is a gene, where grey colors indicate non-significant genes at an absolute log2FC > 0.3 and a BH-adjusted p value of < 0.001. Green indicates genes significant with the log2FC threshold and blue indicates genes only significant by the BH-adjusted p value threshold. Red indicates genes significant at both thresholds.

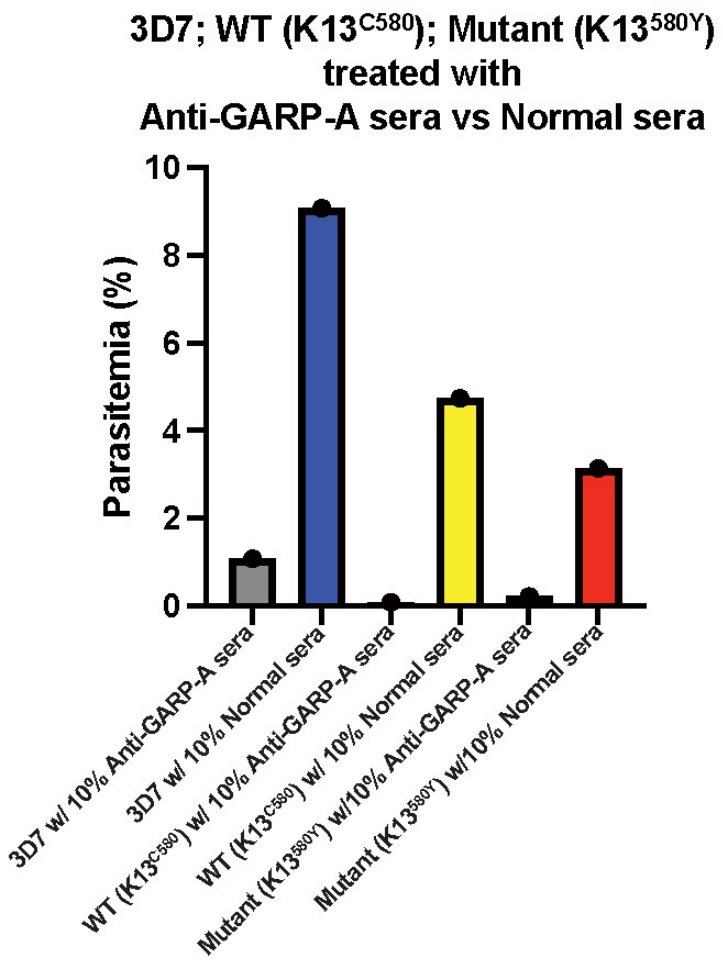


Supplemental Figure S7. GO term enrichment analysis of K13^{580Y} vs. K13^{C580} shows terms enriched related to metabolism and translation in upregulated ring stage genes (A) while terms related to nuclear regulation were

downregulated in trophozoite stages (B). Utilizing differentially expressed genes that were significant at a BH-adjusted p value < 0.001, genes were categorized as downregulated (average log2FC < -0.3), neutral (-0.3 < average log2FC < 0.3) or upregulated (average log2FC > 0.3) after comparing $K13^{580Y}$ vs. $K13^{C580}$. GO term enrichment was performed (see Methods) at each timepoint, except for the 2hr trophozoite timepoint, as there were too few differentially expressed genes.



Supplemental Figure S8. Optimization of MELD algorithm over different KNN (y axis) and beta (x axis) parameters. As described in the Supplemental Methods, MELD was fit to each strain's normalized *cell x gene* matrix separately and over a range of KNN and beta values. The red dot on each plot is the optimal parameters used to run MELD for each line.



Supplementary Figure S9. Anti-PfGARP mAb kills both K13^{580Y} and K13^{C580} parasites *in vitro*.