Supplemental Figure Legends

Supplemental Figure 1: Gross and microscopic pathological examination of the explanted lungs. The left and right lungs showed similar changes and are described together. **Panel A**: Lateral lung surface, and **Panel B**: Medial lung surface. The pleural surface was tan-purple, wrinkled and dull displaying moderate cobblestoning and induration. There were no grossly discernable masses or lesions. The mainstem bronchus displayed a moderate amount of tan mucinous contents protruding from the margin.

H&E-stained sections of the left and right lungs showed extensive bronchiectasis with dilation of both bronchi and bronchioles frequently associated with acute bronchopneumonia consisting of neutrophils, mucin and cellular debris within the airway lumens. Bronchioles showed severe chronic cellular bronchiolitis with cuffing of the bronchioles by small lymphocytes. Bronchial associated lymphoid aggregates were present, however lymphoid follicles were not identified. Both bronchi and bronchioles show scarring with dense concentric fibrosis around the airways and focally extending into the adjacent alveolated lung parenchyma. Additionally, there were small regions of patchy mild to moderate interstitial scarring likely secondary to previous resolved infectious processes. No granulomas or multinucleated giant cells were identified. Airspaces were free of organizing pneumonia. Histochemical staining for AFB and GMS were negative for mycobacterial and fungal forms.

Panel C: Whole slide image showing dilation of airways with peribronchial and peribronchiolar scarring (H&E-stained section, scale bar 5mm). **Panel D**: Dilated bronchiole with chronic bronchiolitis, peribronchiolar scarring with neutrophils within the lumen (H&E-stained section, 5x objective magnification, scale bar 500 um). **Panel E**: Bronchiole with ciliated columnar epithelium and luminal neutrophils and debris consistent with acute bronchopneumonia (H&E-stained section, 10x objective magnification, scale bar 200 um). **Panel F**: Severe chronic cellular bronchiolitis with concentric lymphocytic inflammation within the bronchiolar walls (H&E-stained section, 4x objective magnification, scale bar 600 um. **Panel G**: Region of mild interstitial scarring likely secondary to remote/resolved infectious process (H&E-stained section, 5x objective magnification, scale bar 500

um). **Panel H**: Region of moderate interstitial scarring likely secondary to remote/resolved infectious process (H&E-stained section, 4x objective magnification, scale bar 600 um). **Panel I**: Chronic cellular bronchiolitis with lymphocytes encircling and infiltrating the ciliated columnar epithelium of a dilated bronchiole (H&E-stained section, 10x objective magnification, scale bar 300 um).

Supplemental Figure 2. Quantitative PCR (qPCR) assay for detection of *M. abscessus* DNA in sputum samples. A standard curve of *M. abscessus* DNA in a background of 5ng/µL of human gDNA was used for quantification including seven 10-fold dilutions ranging from 1ng/µL to 0.001pg/µL (blue diamonds). Cycle thresholds (Ct) of known dilutions are shown on the scatter plot. qPCR analyses of total DNA from sputum samples (gray squares) were compared to standard curve samples, and estimated dilutions were extrapolated from the standard curve.

Supplemental Figure 3. GC/MS chromatogram of Tuberculostearic acid (TBSA; m/z 297.3, CI; Negative), surrogate of mycobacterial lipoarabinomannan, analysis of urine samples. Column A. Panel 1(Pink): TBSA standard showing retention time. **Panel 2 (Grey):** Urine TBSA-LAM on Day 47 post-phage initiation. **Panel 3 (Blue):** Urine TBSA-LAM on Day 4 post-phage initiation. **Panel 4 (Brown):** Urine TBSA-LAM on Day 3 post-phage initiation. **Panel 5 (Green):** Urine TBSA-LAM on Day -1 pre-phage initiation. **Column B. Panel 1 (Grey):** TBSA standard showing retention time. **Panel 2 (Blue):** Urine TBSA-LAM on Day 82 post-phage initiation. **Panel 3 (Pink):** Urine TBSA-LAM on Day 126 post-phage initiation. **Panel 4 (Brown):** Urine TBSA-LAM on Day 152 post-phage initiation. Amount of TBSA-LAM were calculated using Palmitic-2,2-d2 acid (5 ng per sample; m/z 257.3; CI; Negative) as internal standard (IS); The internal standard (IS) has retention time around 18 minutes (not shown).

Supplemental Figure 4. GC/MS chromatogram of D-Arabinose (D-Ara), surrogate of mycobacterial LAM, analysis of urine samples. Column A. Panel 1(Black): D-Ara on Day 47 post-phage initiation. Panel 2 (Blue): Representative Internal standard (UL-13C5-D-Ara) (used in sample

day 47). IS and sample have same retention time but IS mass selection is different. Panel 3 (Pink): Urine D-Ara on Day 4. Panel 4 (Brown): Urine D-Ara on Day 3. Panel 5 (Green): Urine D-Ara on Day -1 pre-phage initiation. **Column B.** Panel 1 (Black): D-Ara on Day 82 of post-phage initiation. Panel 2 (Blue): Representative IS (UL-13C5-D-Ara) (used sample day 82). Panel 3 (Pink): Urine D-Ara on Day 126. Panel 4 (Brown): Urine D-Ara on Day 152. Amount of TBSA-LAM were calculated using intensity of IS (10 ng per sample); Chiral glycosylation is responsible for stereoselective detection of D-Ara as a set of 4-peaks. Natural D-Ara was monitored as m/z 420-m/z 192 transition and IS was monitored as m/z 425-m/z 197 transition during ms-ms analysis on GC/MS (EI; Positive). **Column C.** Panel 1(Black): TBSA standard showing retention time. Panel 2 (Blue): Urine TBSA-LAM on Day 334 post-phage initiation. Panel 3 (Pink): Urine TBSA-LAM on Day 362 post-phage initiation. Panel 4 (Brown): Urine TBSA-LAM on Day 418 post-phage initiation. **Column D:** Panel 1 (Pink) TBSA standard showing retention time. Panel 2 (Black) Urine TBSA-LAM on Day 440 post-phage initiation. Panel 3 (Brown): Urine TBSA-LAM on Day 500 post-phage initiation. Amount of TBSA-LAM were calculated using Palmitic-2,2-d2 acid (5 ng per sample; m/z 257.3; CI; Negative) as IS, with a retention time around 18 minutes (not shown).

Supplemental Figure 5. Divergence dating of *M. abscessus* subspecies *abscessus* study isolates. A. Statistics for the rate of evolution (clock rate) are shown in the table. *Divergence dating analysis was conducted using the 50 genome-wide SNPs found among the 40 isolates. The clock rate for the whole genome was calculated as follows: 7.248×10^{-5} / site / day x 50 (number of SNPs) / 4,916,349bp (core genome) x 365 days / year = 2.69×10^{-7} / site / year. ** HPD = highest posterior density **B.** The marginal posterior histogram is shown, and the blue region indicates the 95% HPD interval. The analysis was conducted using Bayesian Evolutionary Analysis by Sampling Trees (BEAST), and the results were visualized with Tracer.

Supplemental Figure 6. Clustering of accessory genes in *M. abscessus subspecies abscessus* study isolates

Accessory genes (n=153) identified among study isolates (n=57) were analyzed by hierarchical cluster analysis using a Euclidean distance metric. The dendrogram on the left shows the clustering pattern of genes (rows), and the heat map illustrates the presence (blue) or absence (light yellow) of accessory genes (columns). Isolates are ordered by collection date (left to right) from -1555 pre-phage treatment to 245 days post-phage treatment.

Supplemental Table 1. Antibiotic Sensitivities (Minimum Inhibitory Concentrations, MIC)

A 20-drug drug panel for rapid growing NTM was performed for all isolates (n=71), divided between pre-antibiotic isolates, isolates collected during antibiotic treatment, and isolates from phage plus antibiotic treatment.

Supplemental Table 1

SUPPLEMENTAL TABLE 1: ANTIBIOTIC SENSITIVITY (MINIMAL INHIBITORY CONCENTRATIONS) FOR RECOVERED ISOLATES

Treatment phase	Pre-antibiotics											*M. abscessus* antibiotic treatment																							
Date (Day)	-1582	-1556	-1507	-1459	-1437	-1351	-1318	-1310	-1278	-1276	-1241	-1219	-1212	-1205	-1198	-1185	-1170	-1163	-1149	-1138	-1137	-1058	-1056	-1047	-1033	-997	-970	-956	-948	-946	-925	-911	-904	-897	-886
[1]Amikacin	16	16	<=8	16	16	16	16	16	16	16	16	16	16	<=8	16	16	16	16	<=8	<=8	16	16	16	32	32	32	16	32	32	16	32	32	32	16	16
Augmentin	>32/16	>32/16	>32/16	>32/16	>32/16	32/16	>32/16	>32/16	>32/16	>32/16	>32/16	32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	16/8	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16
Azithromycin	<=16	<=16	<=16	<=16	<16	<=16	<=16	32	64	32	64	32	64	64	64	64	64	64	32	<16	<=16	<16	32	32	64	128	64	64	32	64	64	32	64	64	64
Cefepime	>32	32	32	32	>32	32	>32	>32	32	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	32	>32	>32	>32	>32	>32	32	>32	>32	32	32	>32	>32	>32	>32
Cefotaxime	>64	>64	64	64	64	64	64	>64	32	32	32	>64	>64	>64	>64	>64	>64	>64	>64	>64	64	>64	>64	>64	>64	64	32	>64	>64	64	64	>64	>64	>64	>64
[1]Clarithromycine	1	1	1	0.5	1	1	0.5	4	4	2	8	2	4	4	2	8	2	1	2	1	0.5	0.5	0.5	4	4	4	8	4	4	4	8	4	4	4	8
Ceftriaxone	>64	64	>64	64	64	>64	>64	>64	32	64	64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	64	>64	>64	32	>64	>64	>64	>64	>64	>64
Ciprofloxacin	>8	8	8	4	>8	>8	>8	>8	>8	>8	8	>8	>8	>8	>8	>8	>8	>8	>8	>8	8	8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
[1]Cefoxitin	32	<=16	64	<=16	32	<=16	<=16	64	32	<=16	<=16	32	<=16	32	32	32	32	32	32	32	32	32	32	32	32	32	<=16	32	<=16	<=16	32	32	<=16	64	32
Clofazimine	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	0.5
[1]Doxycycline	16	>16	16	16	>16	16	>16	16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	<16	<16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
Gentamicin	8	4	8	16	8	16	16	16	16	8	8	8	16	4	8	16	8	8	8	16	8	8	8	16	16	>16	16	16	16	8	16	16	16	8	8
[1]Imipenem	16	16	>16	8	16	16	8	16	8	16	8	16	16	16	16	16	>16	16	>16	>16	16	>16	>16	>16	>16	>16	16	>16	>16	16	16	>16	>16	>16	>16
Kanamycin	<=8	<=8	<=8	16	16	<=8	<=8	16	16	<=8	16	<=8	<=8	<=8	<=8	<=8	<=8	<=8	<=8	<=8	<=8	<=8	<=8	16	16	16	<=8	32	16	16	16	16	32	16	<=8
[1]Linezolid	16	8	16	4	4	8	16	16	>16	16	>16	16	>16	16	>16	>16	>16	>16	>16	>16	16	16	16	16	>16	>16	>16	16	>16	>16	16	>16	>16	>16	>16
Minocycline	>8	>8	8	8	>8	8	>8	8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
[1]Moxifloxacin	>4	>4	4	2	>4	>4	>4	>4	>4	>4	4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4
Tigecycline	1	2	0.5	<=0.25	1	2	2	1	4	2	2	2	2	2	1	2	0.5	0.5	2	1	1	1	2	2	2	2	2	4	4	2	2	4	4	2	4
Tobramycin	8	8	4	16	8	16	16	16	16	16	16	16	16	4	8	8	8	16	16	16	16	8	8	16	>16	>16	16	16	16	16	16	16	16	8	16
[1,2]TMP/SMX	>4/76	>4/76	>4/76	4/76	>4/76	>4/76	4/76	>4/76	>4/76	4/76	>4/76	>4/76	4/76	4/76	4/76	>4/76	4/76	4/76	>4/76	>4/76	>4/76	4/76	4/76	4/76	>4/76	>4/76	>4/76	4/76	4/76	>4/76	>4/76	4/76	>4/76	>4/76	>4/76

Treatment phase	M. abscessus antibiotic treatment																													Phage and Antibiotics						
Date (Day)	-856	-849	-847	-816	-795	-772	-758	-737	-732	-702	-662	-648	-623	-612	-560	-482	-448	-412	-323	-259	-216	-180	-113	-109	-90	-65	-60	-12	-2	5	12	35	44	86	96	245
[1]Amikacin	16	16	16	16	32	<=8	16	16	16	<=8	32	<=8	16	<=8	<=8	16	16	<=8	32	16	<=8	64	<=8	16	32	32	32	16	32	32	16	<=8	16	16	16	16
Augmentin	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	>32/16	32/16
Azithromycin	256	32	64	64	64	32	32	64	<=16	<=16	>256	<=16	64	64	<=16	32	64	<=16	256	<=16	256	>256	64	32	64	64	128	64	32	64	128	>256	64	128	64	32
Cefepime	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	32	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	32
Cefotaxime	32	32	32	64	>64	64	>64	32	64	<=8	>64	64	16	>64	>64	>64	>64	>64	>64	64	>64	>64	>64	64	64	>64	>64	64	64	>64	>64	>64	>64	64	64	64
[1]Clarithromycine	2	2	8	8	4	<=0.25	2	8	0.5	4	8	1	1	4	1	2	8	1	32	1	8	>32	4	2	2	8	16	2	4	8	2	64	16	16	8	4
Ceftriaxone	32	64	64	>64	>64	64	>64	>64	64	64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Ciprofloxacin	8	>8	>8	>8	>8	>8	>8	>8	8	>8	>8	>8	8	>8	>8	8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	8	>8	>8
[1]Cefoxitin	<=16	32	<=16	<=16	32	<=16	32	32	32	<=16	32	<=16	<=16	<=16	64	32	32	64	32	<=16	<=16	<=16	<=16	32	32	32	32	32	<=16	<=16	<=16	64	<=16	32	32	<=16
Clofazimine	<=0.5	<=0.5	<=0.5	<=0.5	0.5	<=0.5	0.5	0.5	0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5	<=0.5
[1]Doxycycline	>16	16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	16	16	16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
Gentamicin	>16	>16	>16	8	8	8	8	16	8	>16	16	8	8	8	8	>16	16	8	16	8	8	8	8	16	16	16	16	16	16	16	16	16	16	16	16	16
[1]Imipenem	8	8	16	>16	>16	8	>16	16	16	>16	>16	>16	>16	16	16	>16	>16	>16	16	8	>16	>16	>16	>16	16	>16	>16	>16	>16	>16	>16	>16	16	16	16	16
Kanamycin	<=8	16	16	<=8	<=8	<=8	<=8	<=8	16	<=8	16	<=8	16	<=8	<=8	<=8	16	<=8	16	<=8	<=8	16	<=8	16	16	32	32	16	16	16	<=8	<=8	16	16	16	32
[1]Linezolid	16	16	>16	>16	>16	>16	>16	>16	16	>16	>16	>16	>16	16	16	16	>16	16	>16	16	>16	>16	>16	>16	>16	8	16	>16	>16	>16	>16	>16	>16	>16	16	16
Minocycline	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
[1]Moxifloxacin	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4
Tigecycline	2	2	4	1	1	1	1	4	1	8	1	1	2	1	0.5	1	<=0.25	0.5	8	1	4	2	1	2	2	3	4	4	8	4	4	2	4	4	4	2
Tobramycin	16	16	>16	8	8	8	8	16	16	>16	>16	8	16	8	8	16	16	4	16	16	8	16	4	16	16	16	16	16	16	16	16	16	16	16	16	16
[1,2]TMP/SMX	>4/76	4/76	4/76	2/38	>4/76	>4/76	>4/76	>4/76	4/76	>4/76	>4/76	4/76	4/76	>4/76	4/76	>4/76	2/38	>4/76	>4/76	>4/76	>4/76	>4/76	2/38	>2/38	>4/76	>4/76	>4/76	>4/76	4/76	4/76	4/76	4/76	4/76	4/76	4/76	>4/76

[1]Antibiotics represenative of class with available CLSI interpretive guidelines for this antibiotic/organism combination

[2]Trimethoprim/ Sulfamethoxazole

Supplemental Figure 1

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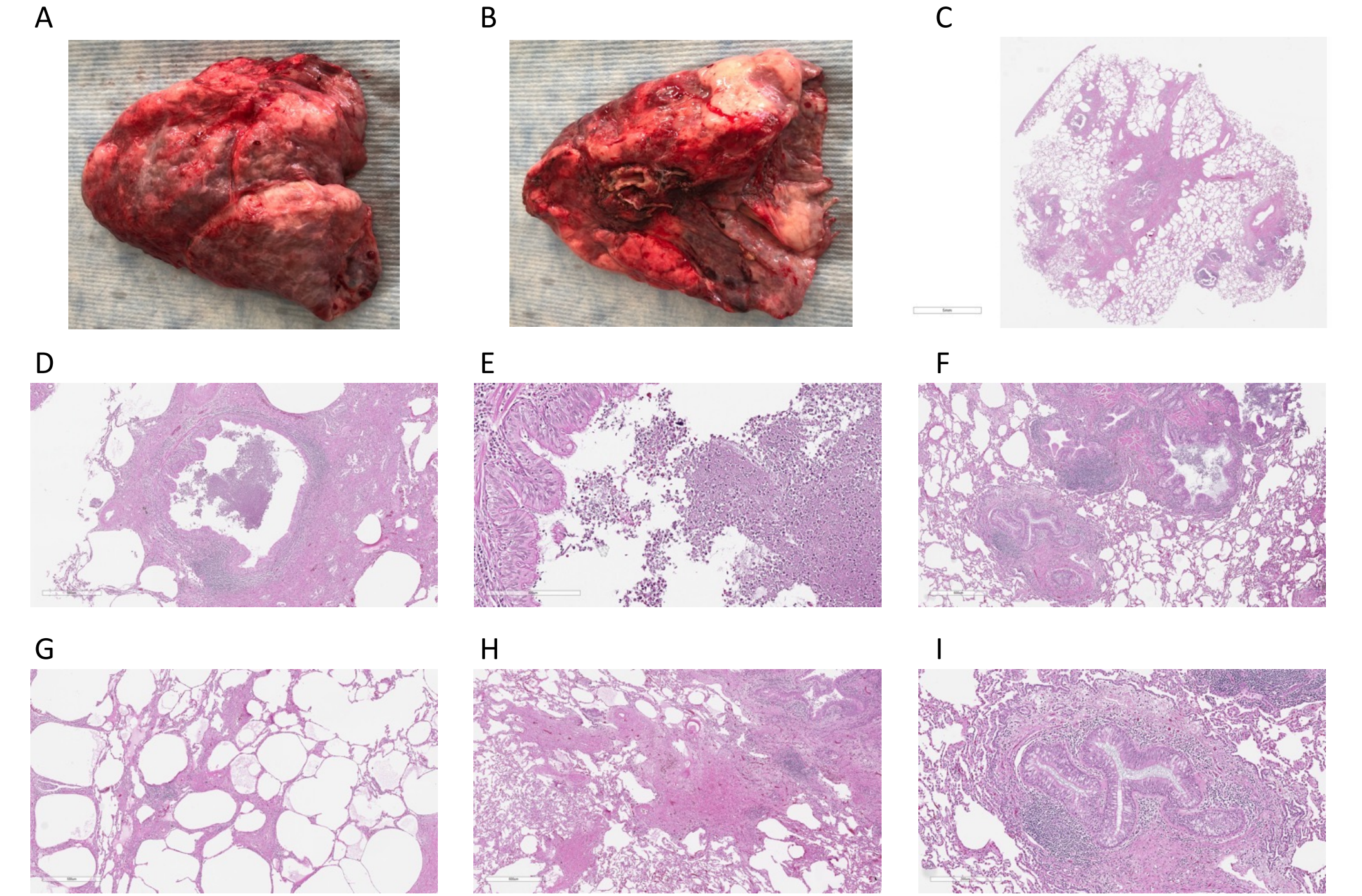

Supplemental Figure 2

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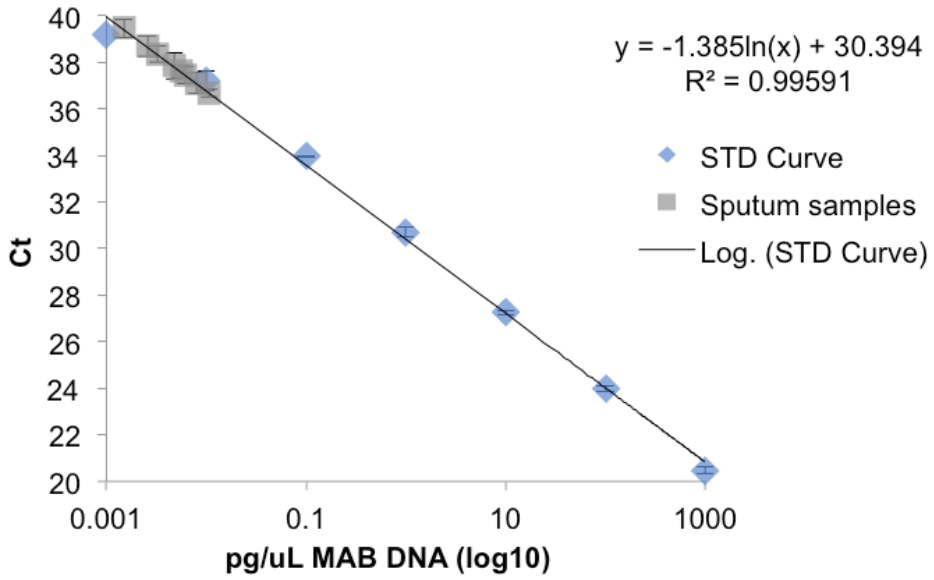

Supplemental Figure 3

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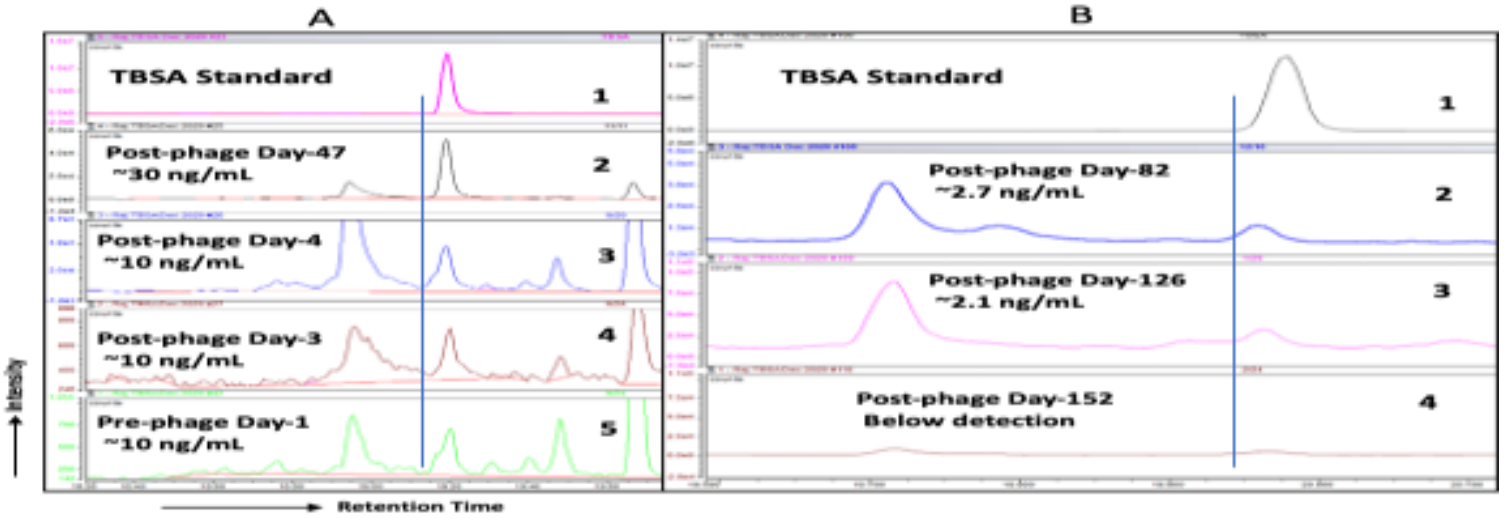

Supplemental Figure 4

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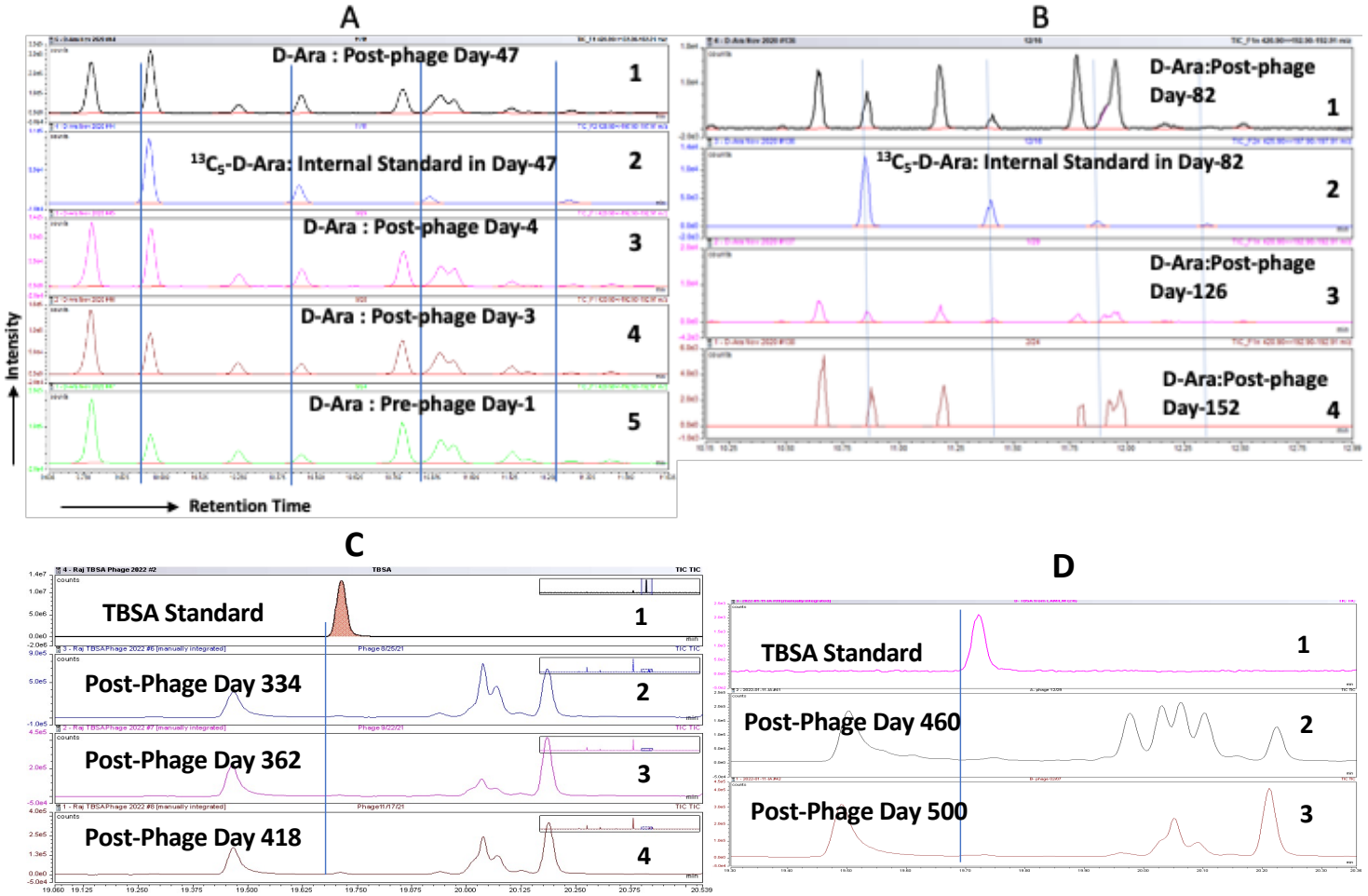
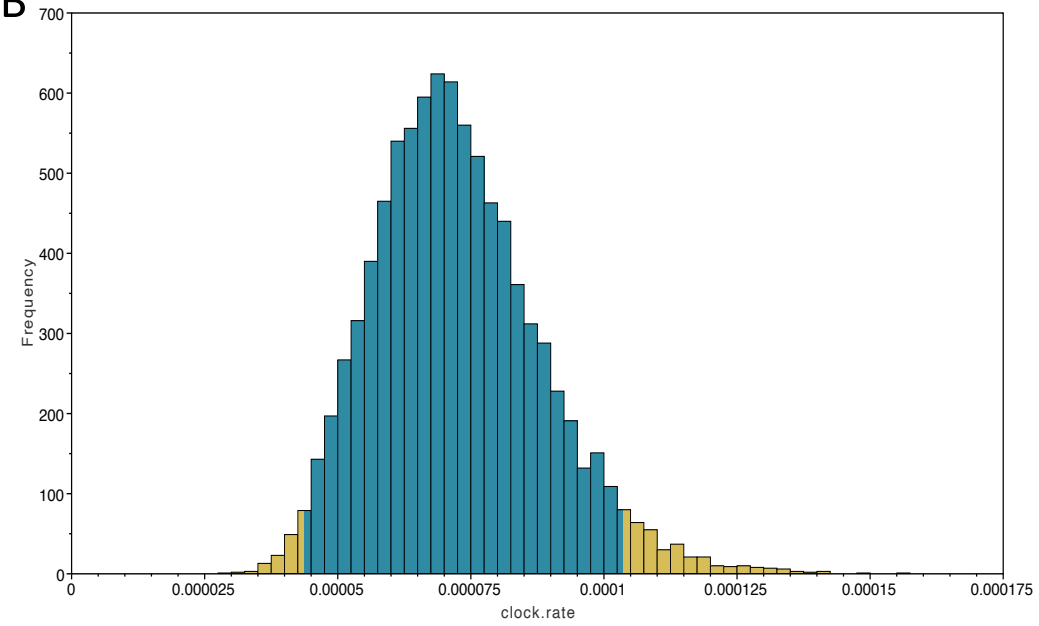


A

Summary Statistic	clock rate
mean	7.2475E-5*
stderr of mean	3.6231E-7
stdev	1.5717E-5
variance	2.4704E-10
median	7.0991E-5
value range	[2.9652E-5, 1.5659E-4]
geometric mean	7.0817E-5
95% HPD** interval	[4.3723E-5, 1.0353E-4]
effective sample size (ESS)	1881.7
number of samples	9001

B



Supplemental Figure 6

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