Supplemental Figure Legends

Supplemental Figure 1. Peripheral expression of KLB in female KLB-tdTomato mice. (A-H) Representative tissue sections depicting tdTomato distribution in the (A) liver, (B) thymus, (C) pancreas, (D) skeletal muscle (quadricep), (E) spinal cord, (F) heart, (G) BAT, (H) subcutaneous WAT of 11-14 week old female Cre(-) wild-type (WT) and Cre(+) KLB-tdTomato reporter mice. Blue, DAPI; red, tdTomato.

Supplemental Figure 2. Overview of KLB positive cells in the heart of male KLB-tdTomato reporter mice (*Klb*-CRE;Ai14-tdTomato). Representative overview sections of the heart from KLB-tdTomato reporter mice. Blue, DAPI; red, tdTomato.

Supplemental Figure 3. Overview of KLB positive cells in the heart of Cre negative (Ai14-tdTomato) male littermate mice of KLB-tdTomato reporter mice. Representative overview sections of the heart from Cre(-) WT mice. Blue, DAPI; red, tdTomato.

Supplemental Figure 4. Overview of KLB positive cells in the quadricep of male KLB-tdTomato reporter mice (*Klb*-CRE;Ai14-tdTomato). Representative overview sections of the quadricep from Cre(+) KLB-tdTomato reporter mice. Blue, DAPI; red, tdtomato.

Supplemental Figure 5. Overview of KLB positive cells in the quadricep of Cre negative (Ai14-tdTomato) male littermate mice of KLB-tdTomato reporter mice. Representative overview sections of the quadricep from Cre(-) WT mice. Blue, DAPI; red, tdTomato.

Supplemental Figure 6. (A-M) Representative brain sections depicting tdTomato distribution in the female KLB-tdTomato mouse brain. CTX, Cortex; OLF, Olfactory nucleus; PL, Prelimbic area/Cortex; CP. Caudate putamen; LSr, Lateral septal nucleus; Nac, Nucleus accumbens, CA, Cingulate area; PIR, Piriform nucleus; BST, Bed nuclei of the stria terminalis; HY, Hypothalamus; SFO, Subfornical organ; AMY,

Amygdala; PVN, Paraventricular hypothalamic nucleus; SCN, Suprachiasmatic nucleus; ACA, Anterior cingulate area; AHN, Anterior hypothalamic nucleus; LH, Lateral hypothalamic nucleus; HP, Hippocampus; RSP; Retrosplenial cortex, DMH, Dorsomedial hypothalamic nucleus; VMH, Ventromedial hypothalamic nucleus; ARC; Arcuate hypothalamic nucleus; APN, Anterior pretectal nucleus; PAG, Periaqueductal gray; MM, Mammillary nucleus; CA3, Hippocampus Field CA3; VTA/SNc, Ventral tegmental area/Substantia nigra; AP, Area postrema; NTS, Nucleus of the solitary tract; CB, Cerebellum. Blue, DAPI; red, Tdtomato.

Supplemental Figure 7. Representative video depicting three dimensional distribution of tdTomato in the brain of 11-14 week old male Cre(+) KLB-tdTomato reporter mice.

Supplemental Figure 8. Overview of KLB positive cells in spine of male *Klb*-CRE;PHP.eB;tdTomato mice. Representative sections depicting tdTomato distribution in the Klb-CRE;PHP.eB-tdTomato mouse spinal cord. Blue, DAPI; red, tdTomato.

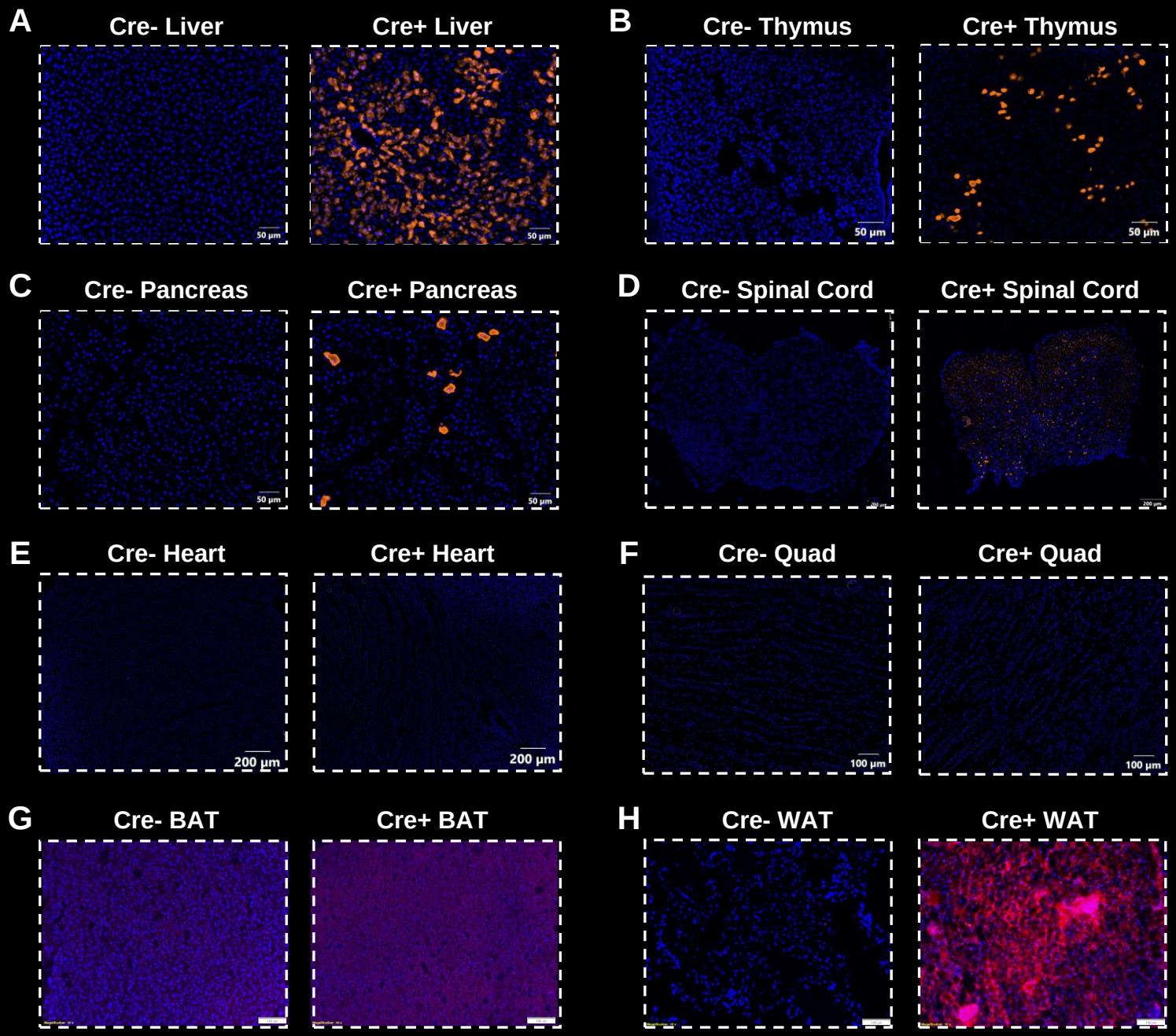
Supplemental Figure 9. Overview of FGF21 expression in the heart of FGF21-tdTomato reporter (*Fgf21*-P2A-CRE;Ai14-tdTomato) male mice. Representative overview sections of the heart from FGF21-tdTomato reporter mice. Blue, DAPI; red, tdtomato.

Supplemental Figure 10. Overview of FGF21 expression in the heart of Cre negative (Ai14-tdTomato) male littermate mice of FGF21-tdTomato reporter mice. Representative overview sections of the heart from Cre(-) mice. Blue, DAPI; red, tdTomato.

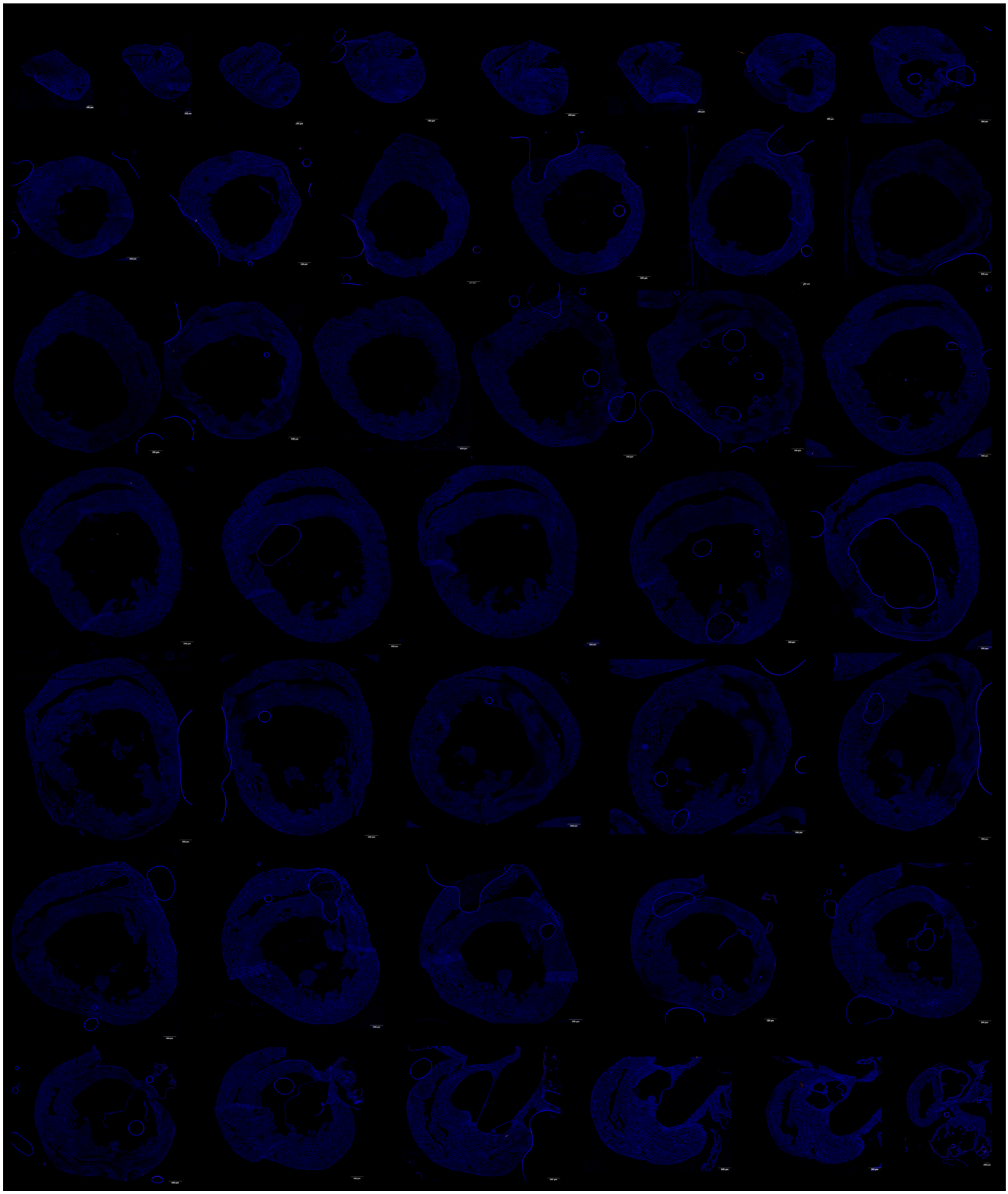
Supplemental Figure 11. Overview of FGF21 expression in the quadricep of male FGF21-tdTomato reporter (*Fgf21*-P2A-CRE;Ai14-tdTomato) mice. Representative overview sections of the quadricep from FGF21-tdTomato reporter mice. Blue, DAPI; red, tdTomato.

Supplemental Figure 12. Overview of FGF21 expression in the quadricep of Cre negative (Ai14-tdTomato) male littermate mice of FGF21-tdTomato reporter mice. Representative overview sections of the quadricep from Cre(-) mice. Blue, DAPI; red, tdTomato.

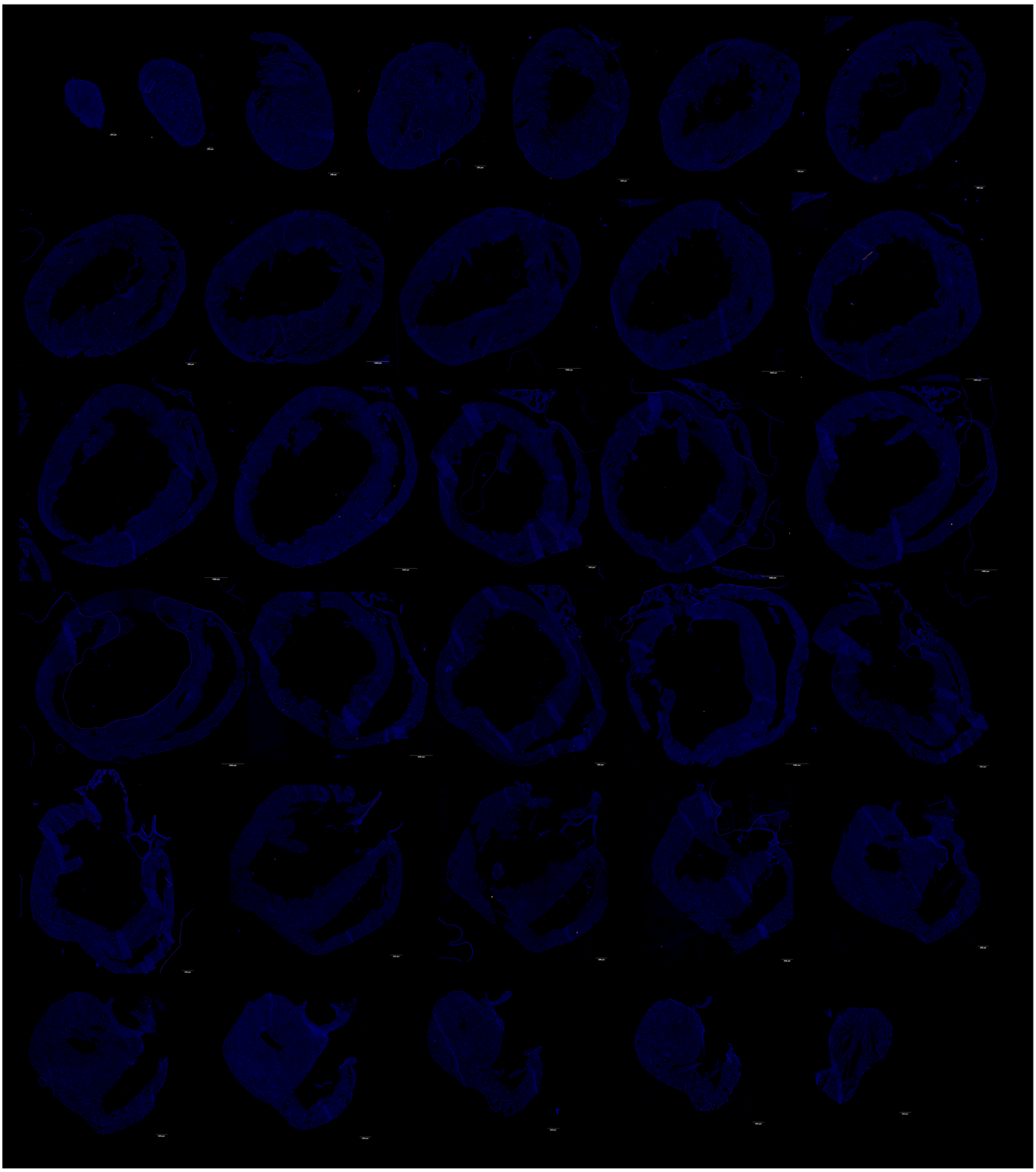
Supplemental Table 1. Analysis of cell type specific expression of KLB and FGF21 in publicly available single cell and single nuclei RNA sequencing of mouse heart samples.



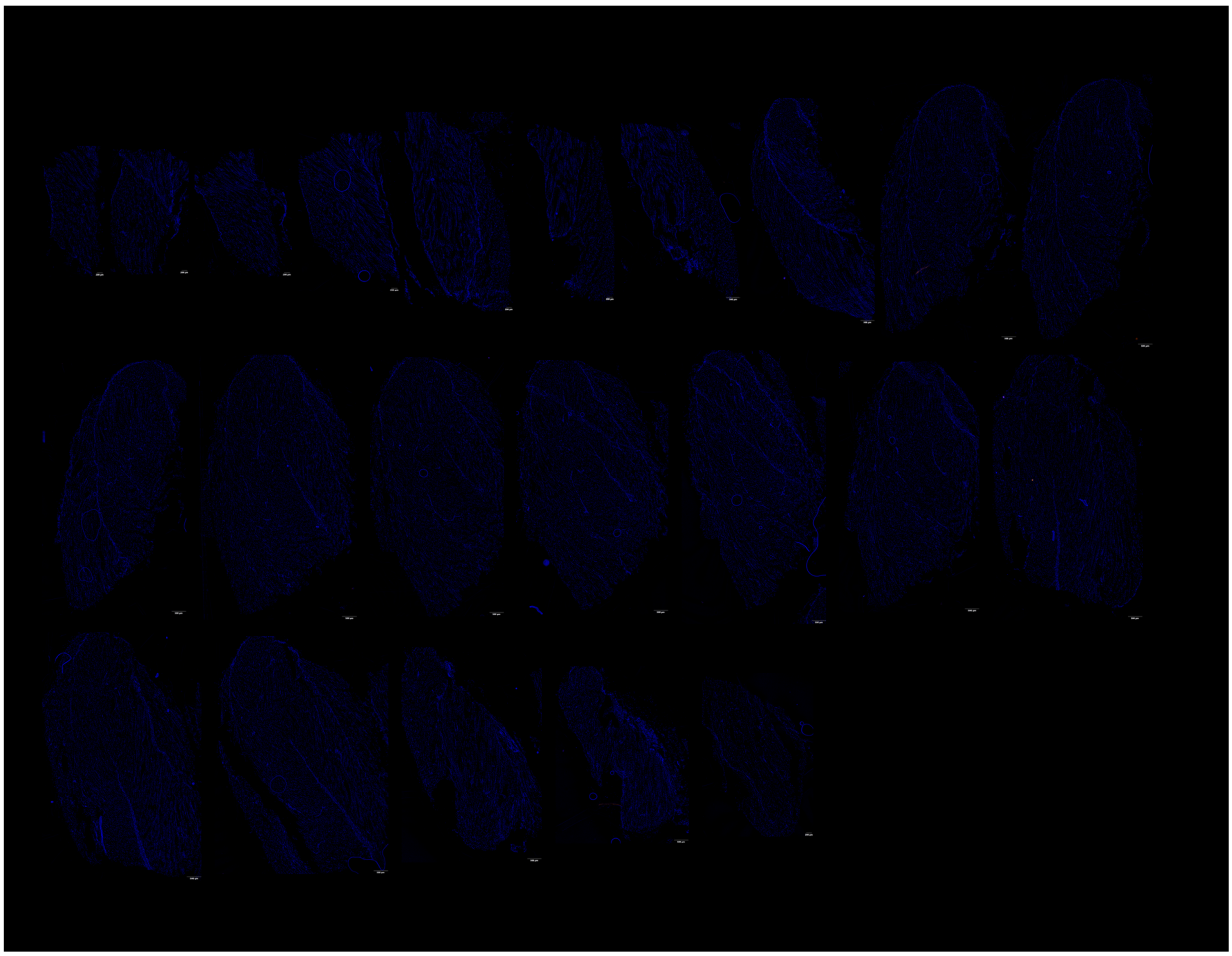
Supplemental Figure 1



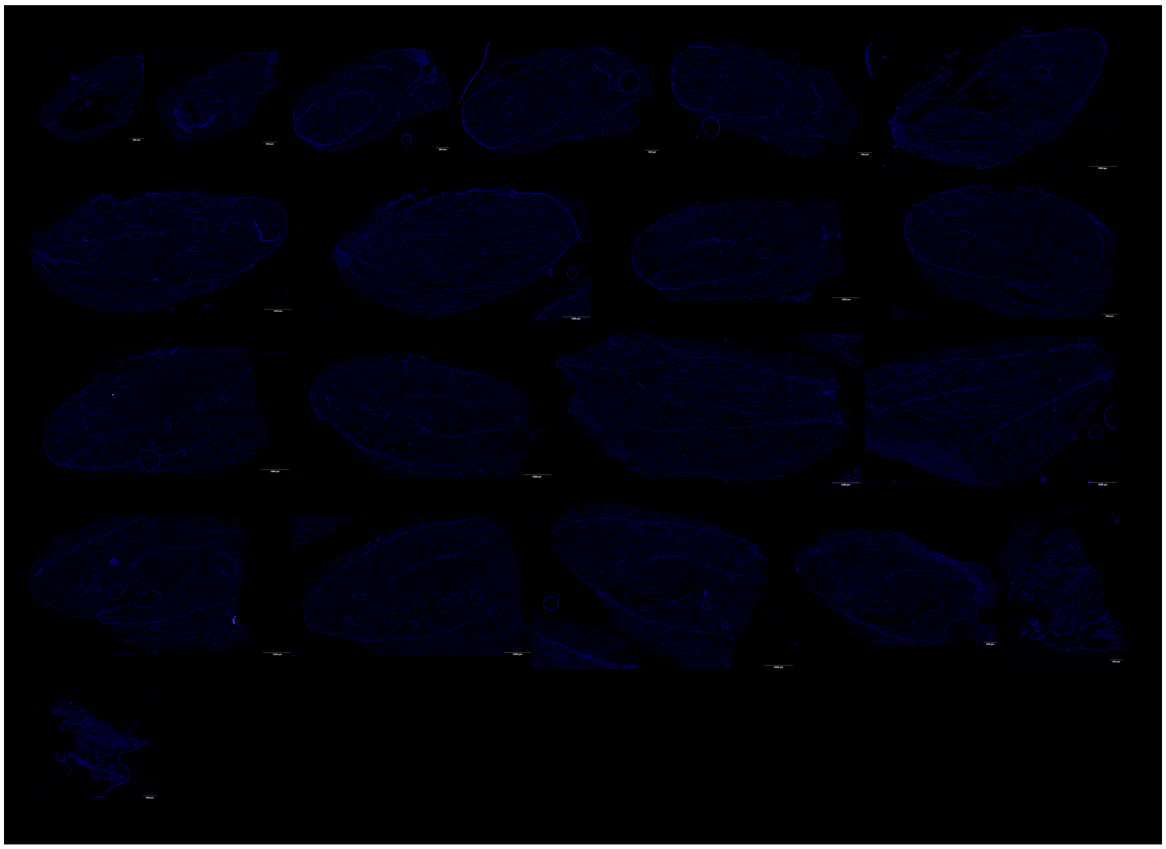
Supplemental Figure 2



Supplemental Figure 3



Supplemental Figure 4



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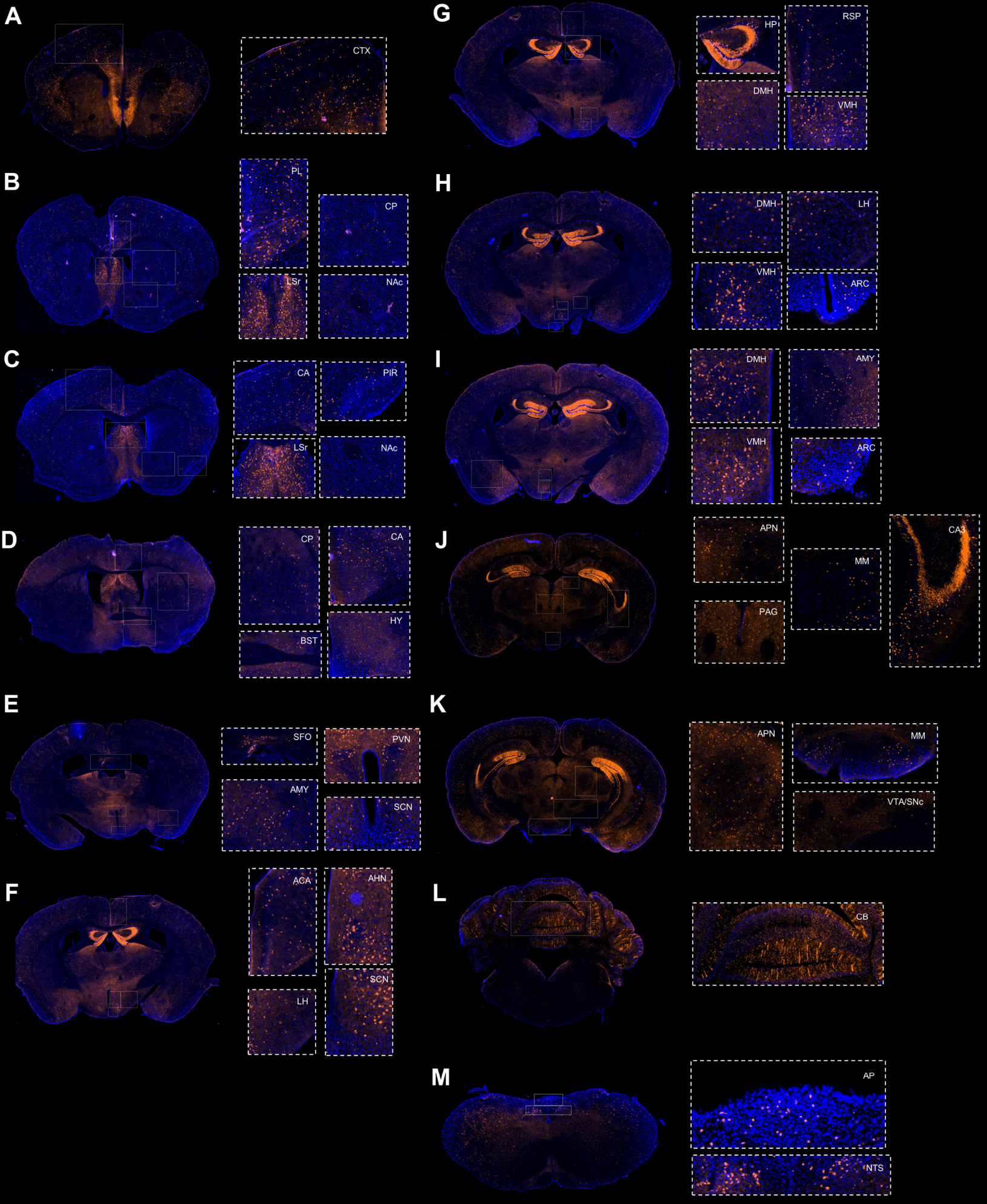

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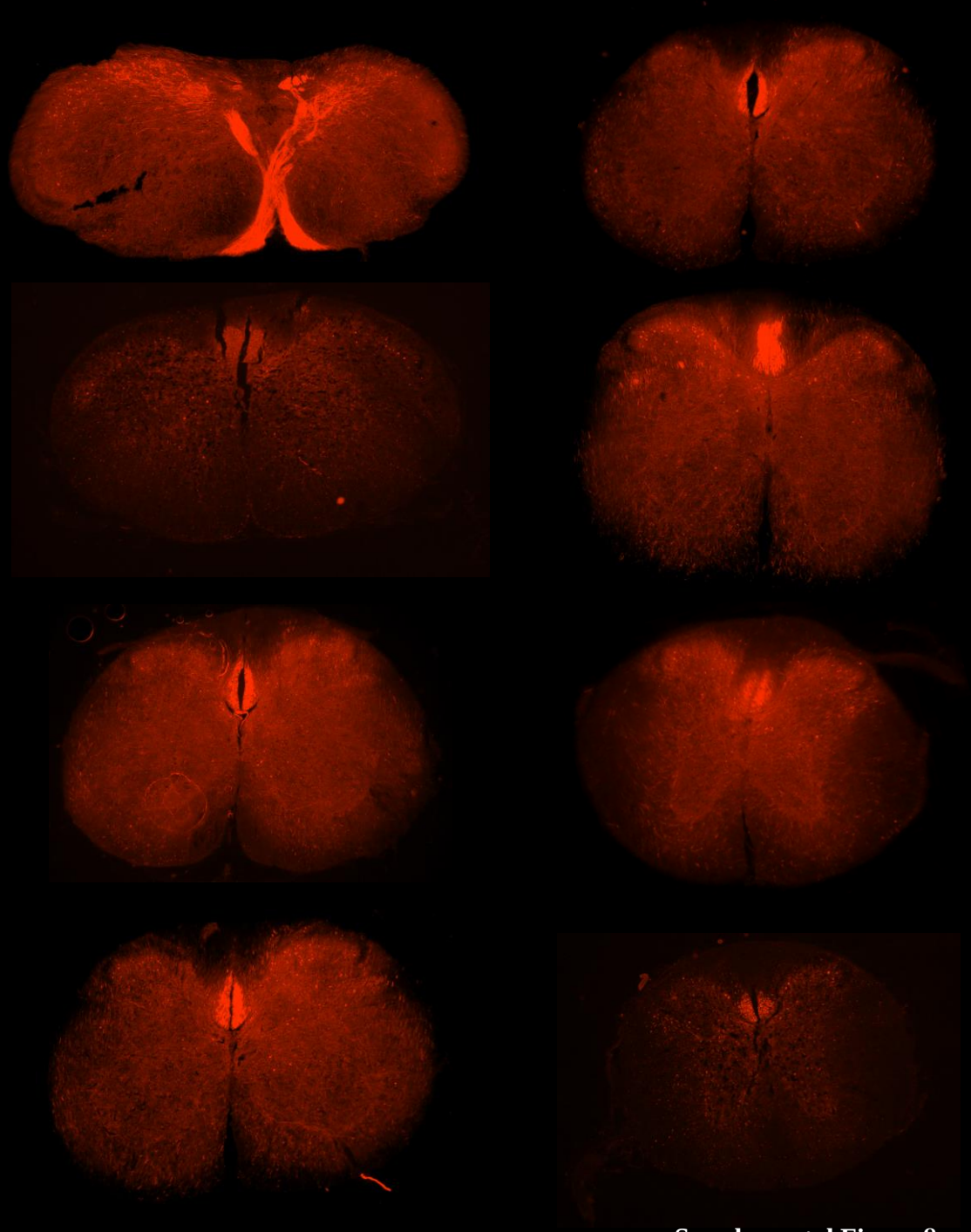
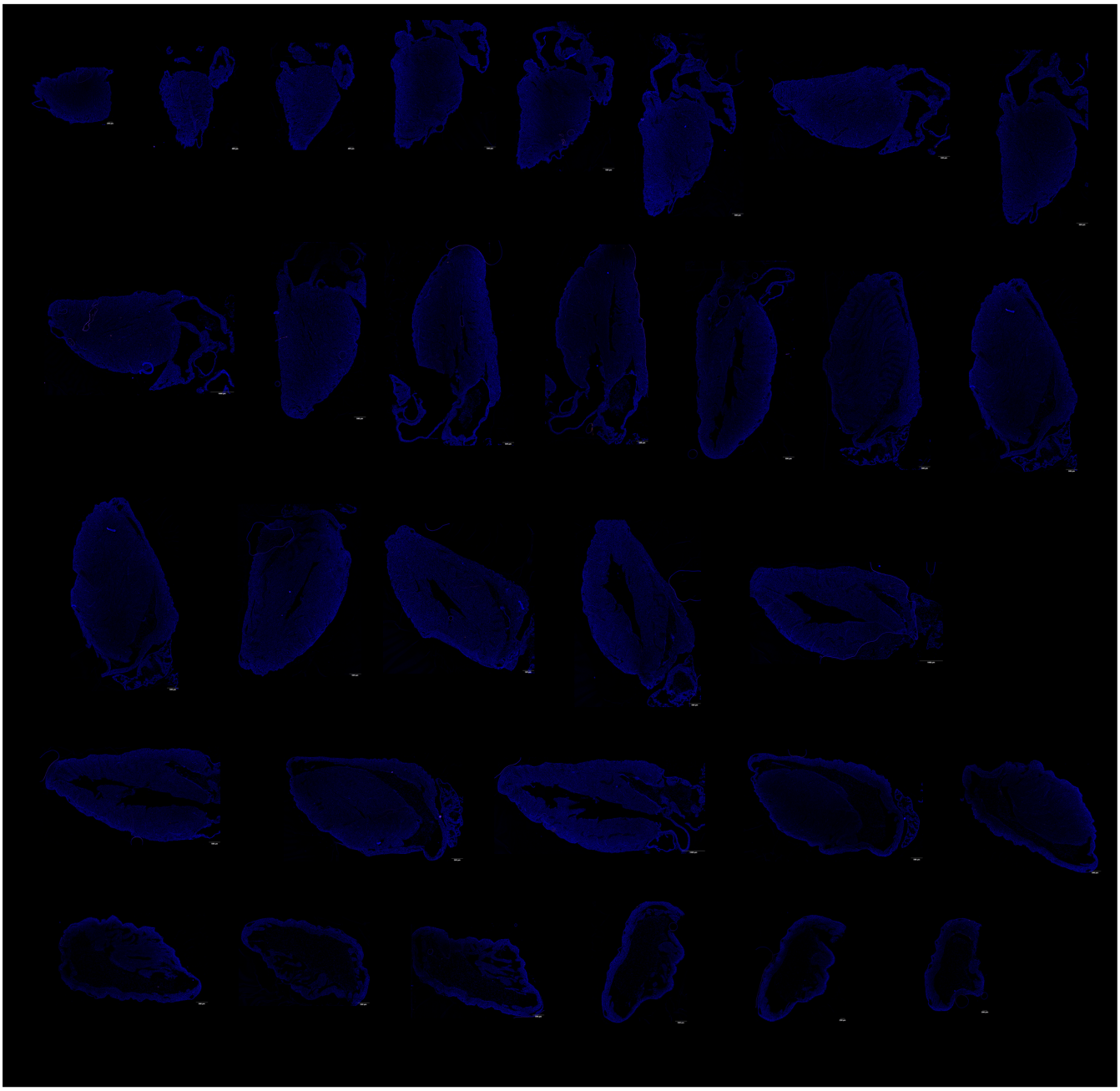
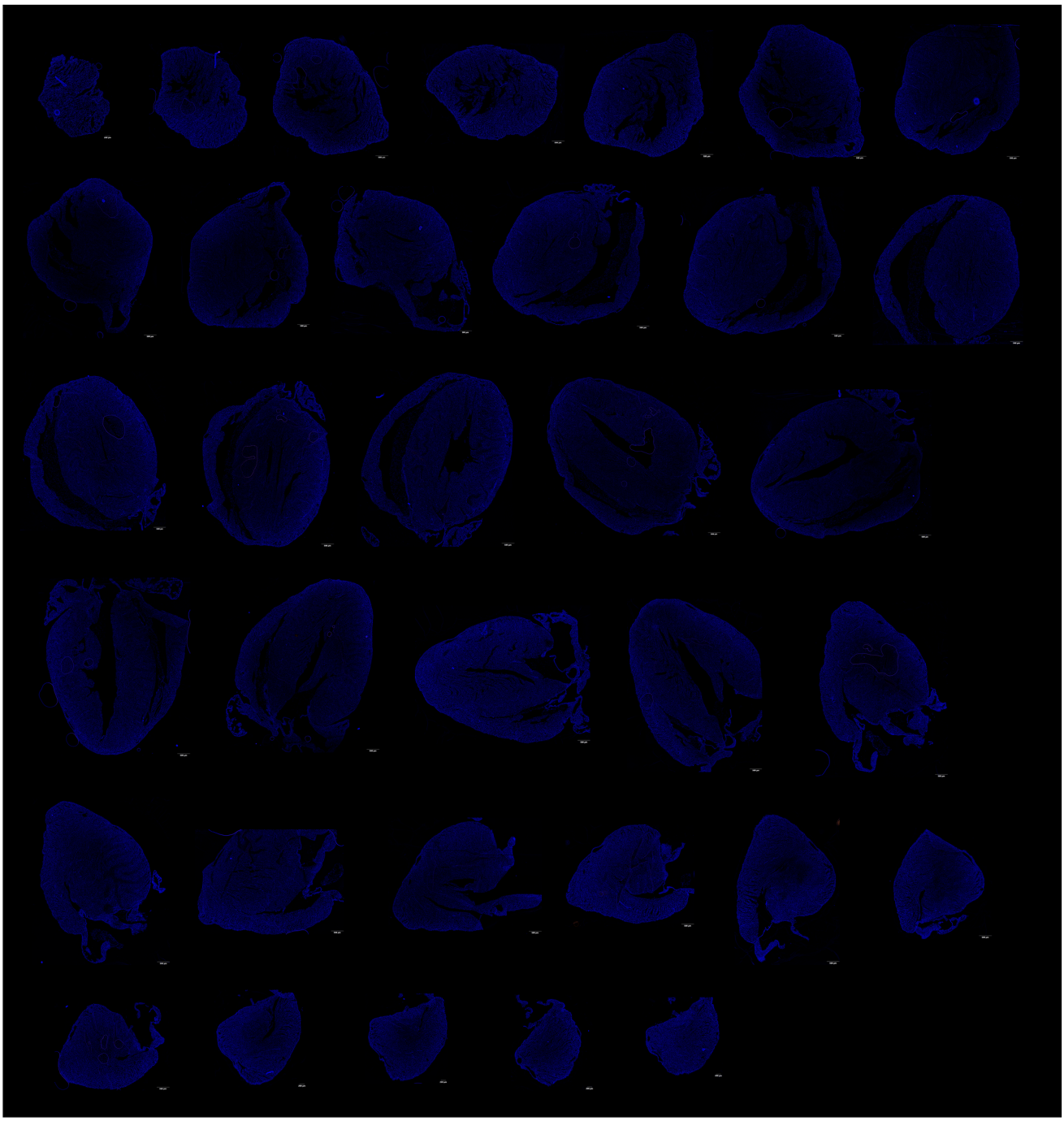


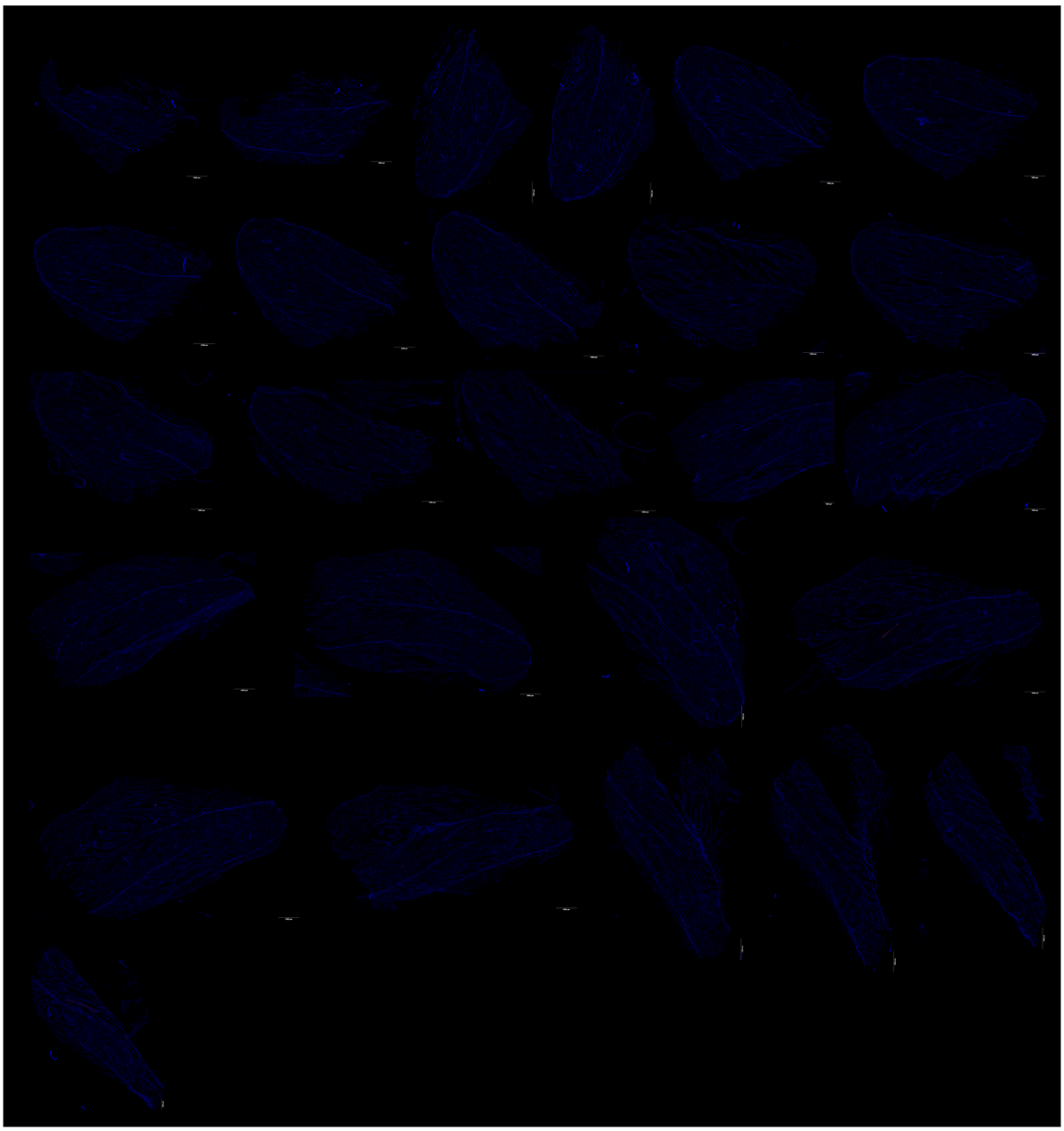
Supplemental Figure 8



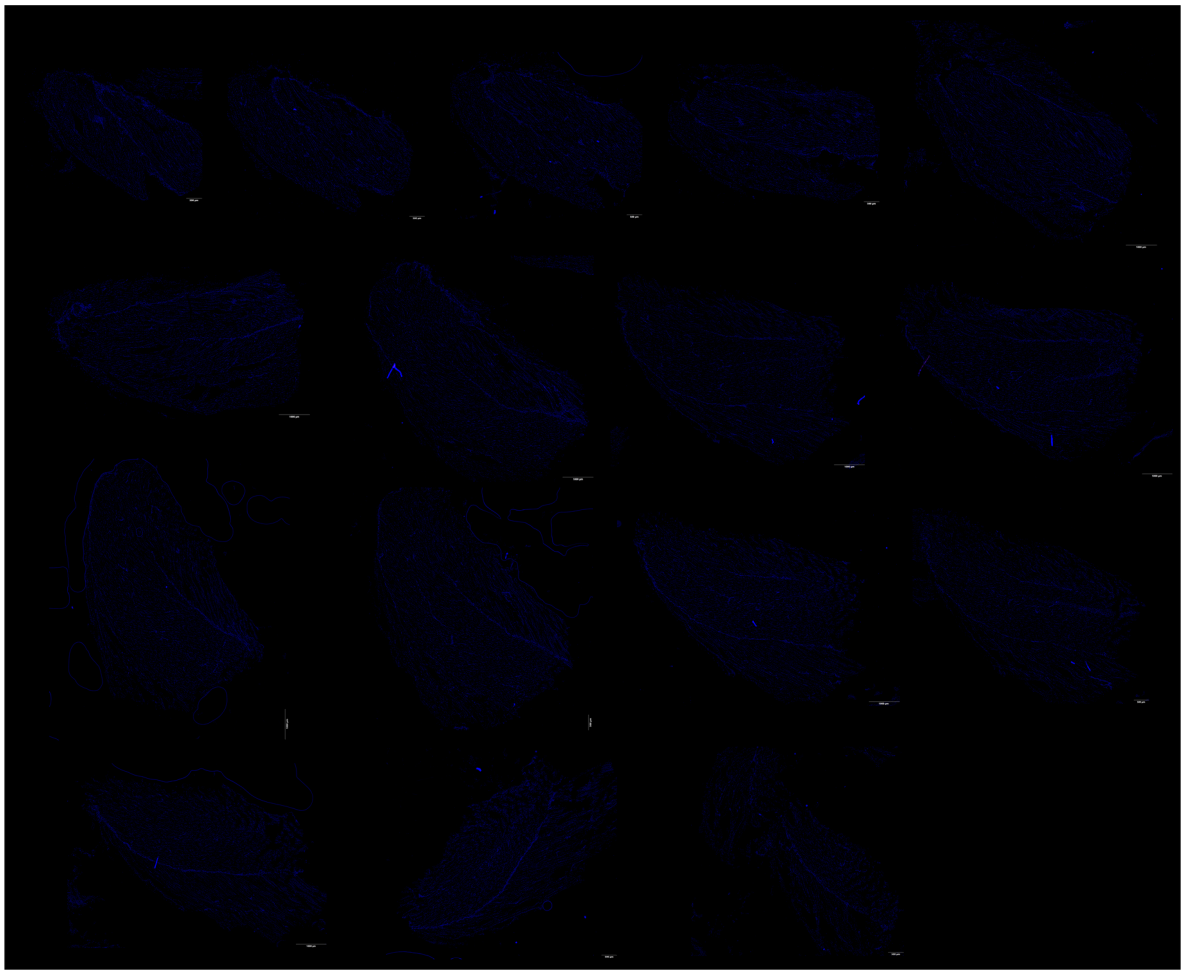
Supplemental Figure 9



Supplemental Figure 10



Supplemental Figure 11



Supplemental Figure 12