

## Supplementary Figure Legends

Figure S1. Comparison of wild-type and *CFTR*<sup>-/-</sup> sheep fetal pancreas at 80, 100, and 120 of gestation, and term (147 days). WT sheep fetal pancreas (A, C, E, G) and *CFTR*<sup>-/-</sup> sheep pancreas (B, D, F, H) at 80 days (A, B), 100 days (C, D), 120 days (E, F) and term (G, H). In WT tissue, normal pancreatic acini have a central lumen that is either small or not visible (A, C, E, G). In *CFTR*<sup>-/-</sup> tissue, luminal dilation is evident in multiple acini (arrowheads) (B, D, F, H) and ducts (arrows) (B, F), accumulation of mucus (arrowheads) (B, D, H, F), and accumulation of cell debris and neutrophils in dilated acini (long arrowheads) (F) is seen. Excessive loose stroma separating acini and ducts and interstitial neutrophilic inflammation are also present (asterisk) (F, H). Hematoxylin and eosin stain. 400X; bar = 50  $\mu$ m.

Figure S2. Comparison of wild-type and *CFTR*<sup>-/-</sup> sheep fetal colon at 80, 100, and 120 of gestation, and term (147 days). WT sheep fetal colon (A, C, E, G) and *CFTR*<sup>-/-</sup> sheep colon (B, D, F, H) at 80 days (A, B), 100 days (C, D), 120 days (E, F) and term (G, H). Note the number of goblet cells in the colonic mucosa and amount of meconium in the lumen. *CFTR*<sup>-/-</sup> tissues show distention of goblet cells in the colonic mucosa and accumulation of mucus in the lumen, with a progressive divergence from normal tissue with time. Hematoxylin and eosin stain. 100X; bar = 200  $\mu$ m.

Figure S3. Comparison of wild-type and *CFTR*<sup>-/-</sup> sheep fetal liver at 80, 100, and 120 of gestation, and term (147 days). WT sheep fetal liver (A, C, E, G) and *CFTR*<sup>-/-</sup> sheep liver (B, D, F, H) at 80 days (A, B), 100 days (C, D), 120 days (E, F) and term (G, H). C) A normal portal tract is shown with one portal vein, one arteriole, and one bile duct (arrowhead). In the *CFTR*<sup>-/-</sup> liver the portal tract is expanded by bile duct proliferation and collagenous stroma indicative of early biliary fibrosis (B, D, F, H, arrowhead). Bile ducts lack a distinct lumen. Intrahepatic cholestasis is present (B, F, H, arrow). Hematoxylin and eosin stain. 400X; bar = 50  $\mu$ m.

Figure S4. Fetal trachea tissue samples from WT and *CFTR*<sup>-/-</sup> sheep at 80 days gestation.

No histologic difference is seen between the wild-type (A) and *CFTR*<sup>-/-</sup> (B) sheep trachea. Hematoxylin and eosin stain. 400X; bar = 50 μm.

Figure S5. Differential expression of key marker genes in WT and *CFTR*<sup>-/-</sup> fetal trachea through gestation. Data from RNA seq analysis of tracheal tissue samples at 65, 80, 100, 120 days gestation and term (147 days). (n=2 at each time point). Individual graphs show normalized read counts of A) *KRT5* B) *TP63*, C) *FOXA1*, D) *EHF*.

Figure S6. Differential expression of collagen genes in WT and *CFTR*<sup>-/-</sup> fetal trachea through gestation. Data from RNA seq analysis of tracheal tissue samples at 65, 80, 100, 120 days gestation and term (147 days). (n=2 at each time point). Individual graphs show normalized read counts of A) *COL1A1* B) *COL6A1* C) *COL14A1*.