Figure S1: Sampling procedure. Schematic illustration of lung explant inflation, High Resolution Computed Tomography (HRCT) and fixation by immersion (A). Localization of the sampling slice (thickness 1.5cm) in the HRCT-dataset (selected slice are labelled in red) (B). Grading of remodelling intensity in the slice visualised by a soft tissue analysis mode using a maximal intensity projection (C) and the corresponding lung slice (sampled areas are marked by black circles) (D). Extracted human lung biopsy after fixation (E) and clearing in the resin mixture (F). Through sectioning, three complementary analytic procedures (Scanning Laser Optical Tomography (SLOT), histology and mRNA expression) were combined for a comprehensive assessment of the development and progression of diffuse parenchymal lung disease (DPLD) (G).

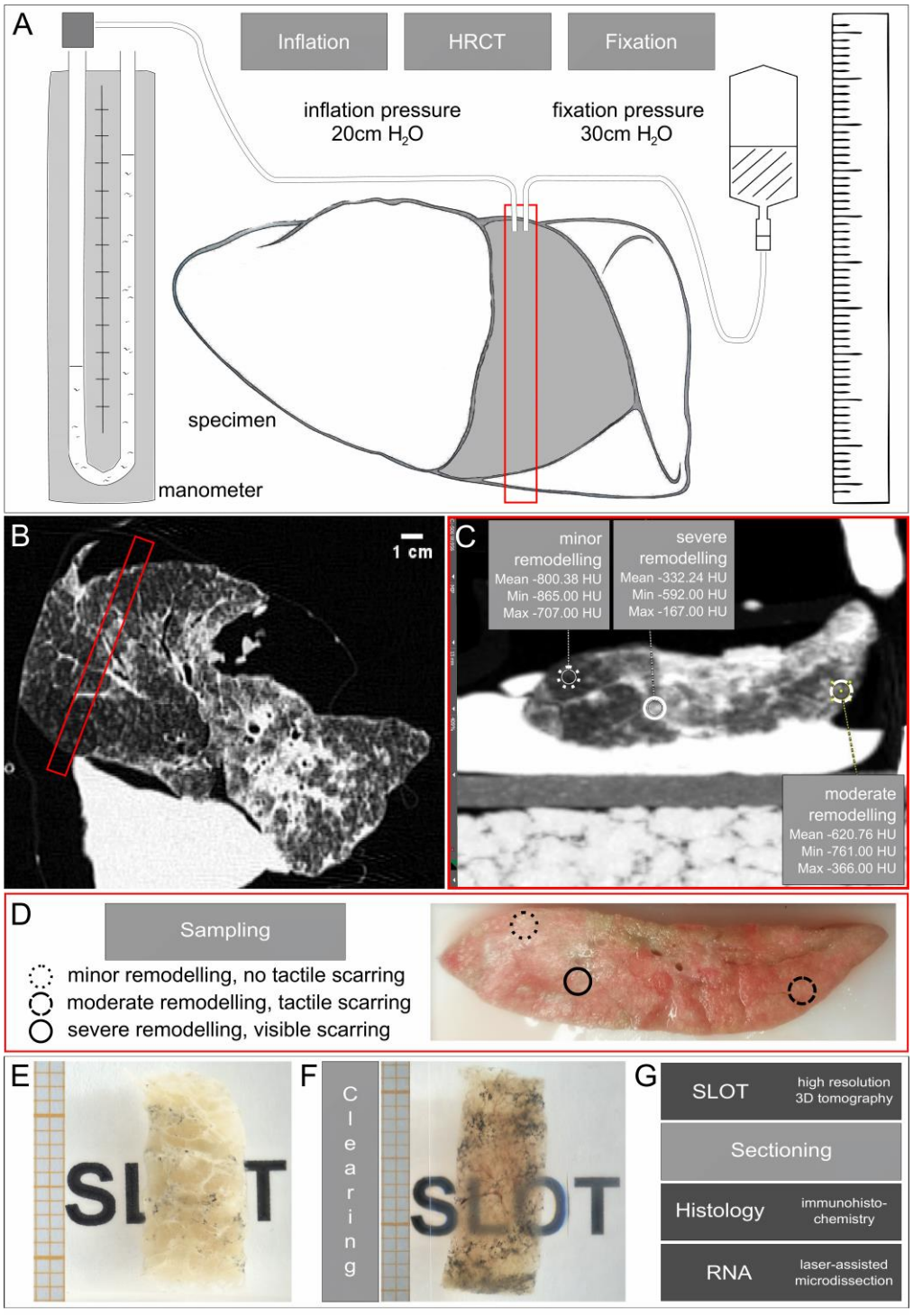


Figure S2: **Projection datasets.** Transmission image (A) and fluorescence image (B). Overlay of the transmission mode in red and the fluorescence mode in green (C). Segmentation of conducting airways with the related acini (white), artery (red) and fibrotic changes (yellow) (D). Pulmonary blood vessel (*), conducting airways (●) and parenchyma (#). For more detail see Movie S1.

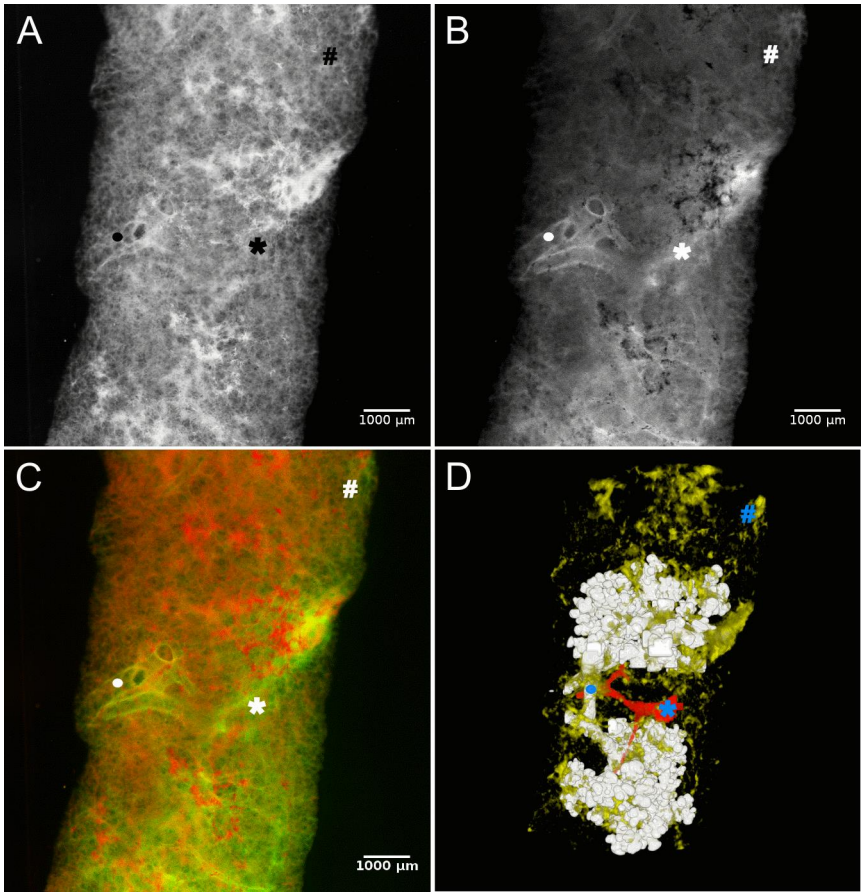


Figure S3: **Resin staining.** Histological sections of the “minor” biopsy with a staining of toluidine blue (A), Hematoxylin and Eosin (HE) (B), van Gieson's Stain (EvG) (C), as well as immunohistochemistry staining for α-1-antitrypsin (D), CD34 (E) and smooth muscle actin (F).

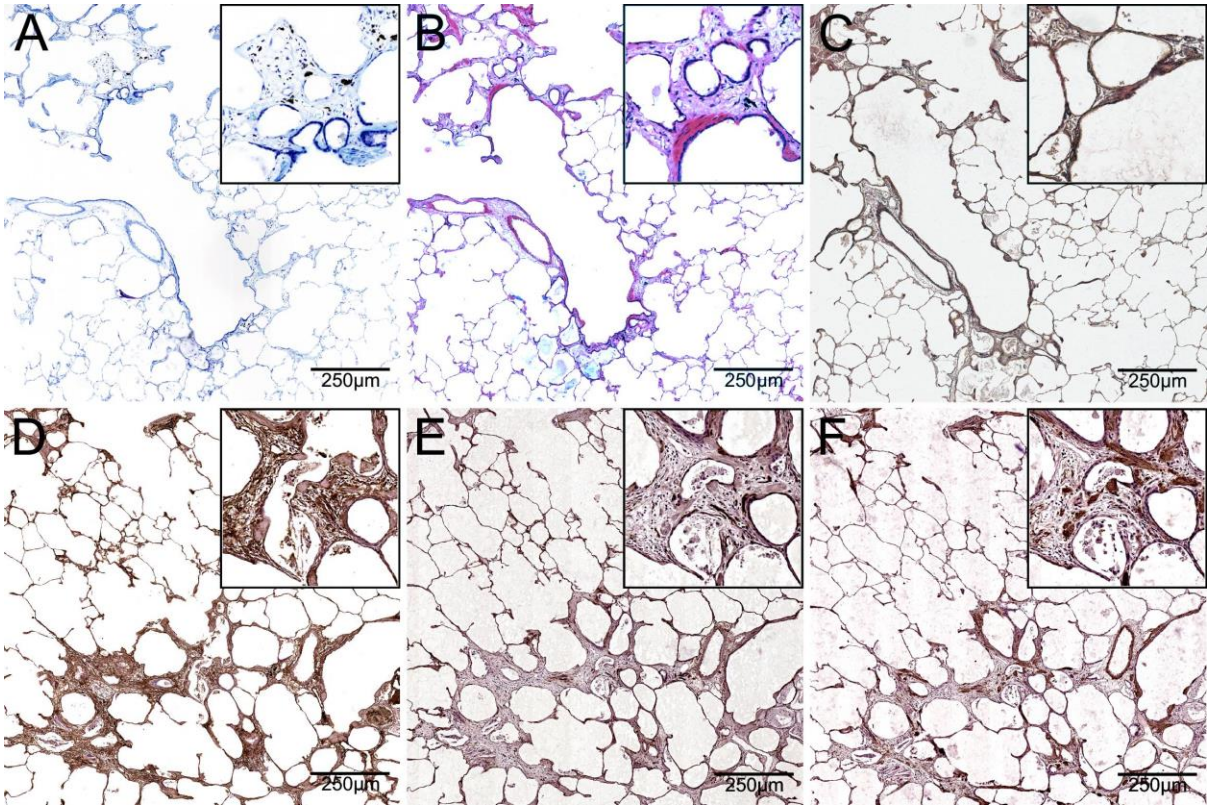


Figure S4: **Correlation of different analysis methods.** Histological section imaged by light microscopy with outlines of the pathological fibrotic findings (black lines) combined with an overlay of the distance cut off model (red lines) (A). Grey value intensity analysis (6 shades lookup-table (LUT) shows relative fluorescence intensity) (B) and distance analysis (16 colour LUT shows distance of tissue in µm at any point in the sample to the surface) (C) combined with the outlines of the distance cut off model marked in white. Otsu threshold of the reconstructed Scanning Laser Optical Tomography (SLOT) data stack combined with the distance cut off model (diameter 300µm) in white with red outlines (D).

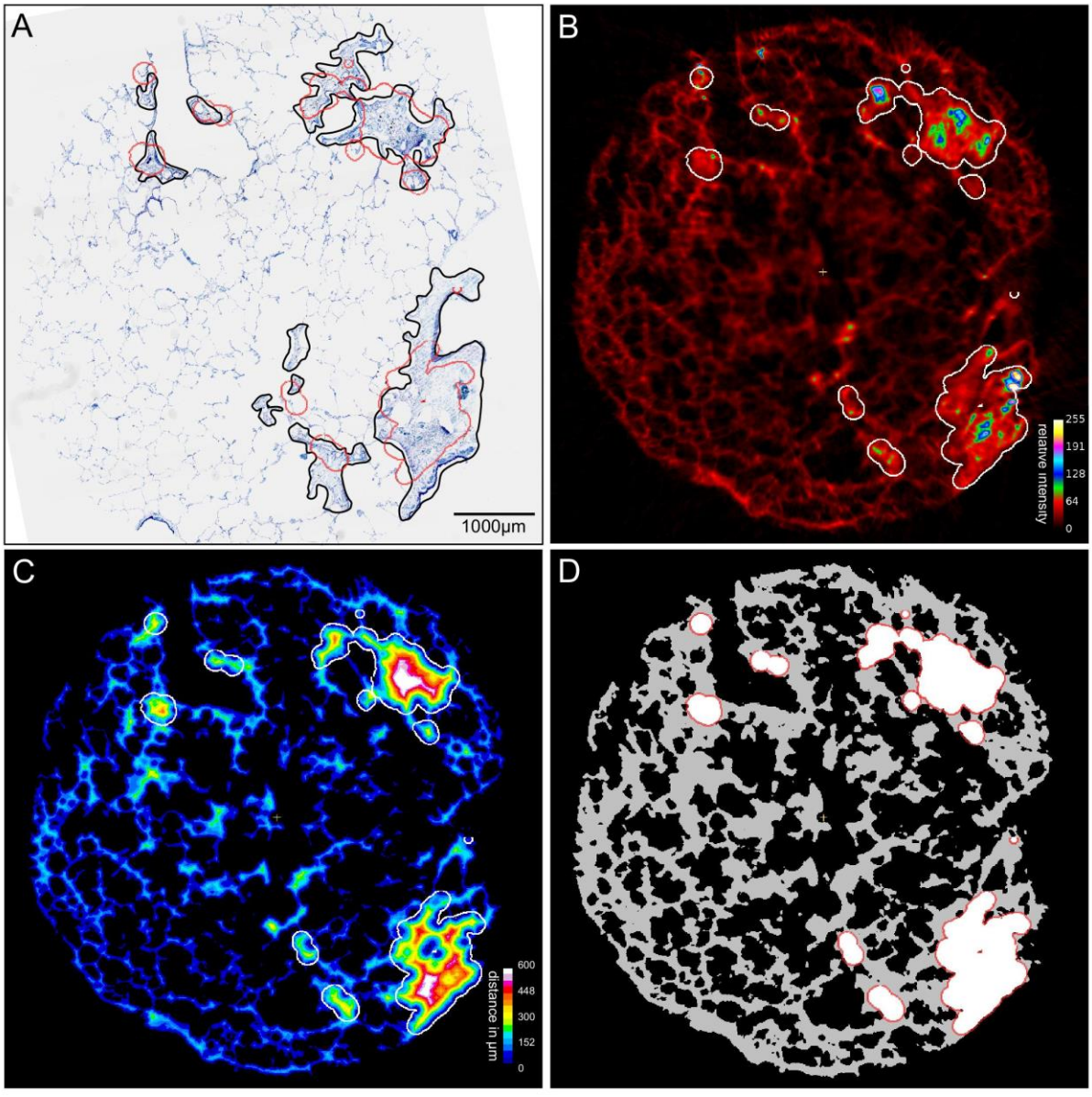


Figure S5: **Visualisation of fibrotic remodelling by distance cut off models.** Rendered absorption tomograms with combined distance cut off models (red). Human biopsy from a healthy lung (A) and an extrinsic allergic alveolitis (EAA) explant showing minor (B), moderate (C) and severe fibrotic changes (D). Analysis results of number of fibroblastic foci per biopsy (E) and volume of fibrotic remodelled tissue in percent (F) of different stages of remodelling. Quantification of branching as a measure for complexity (G) of the skeletons 1 models (H-J).

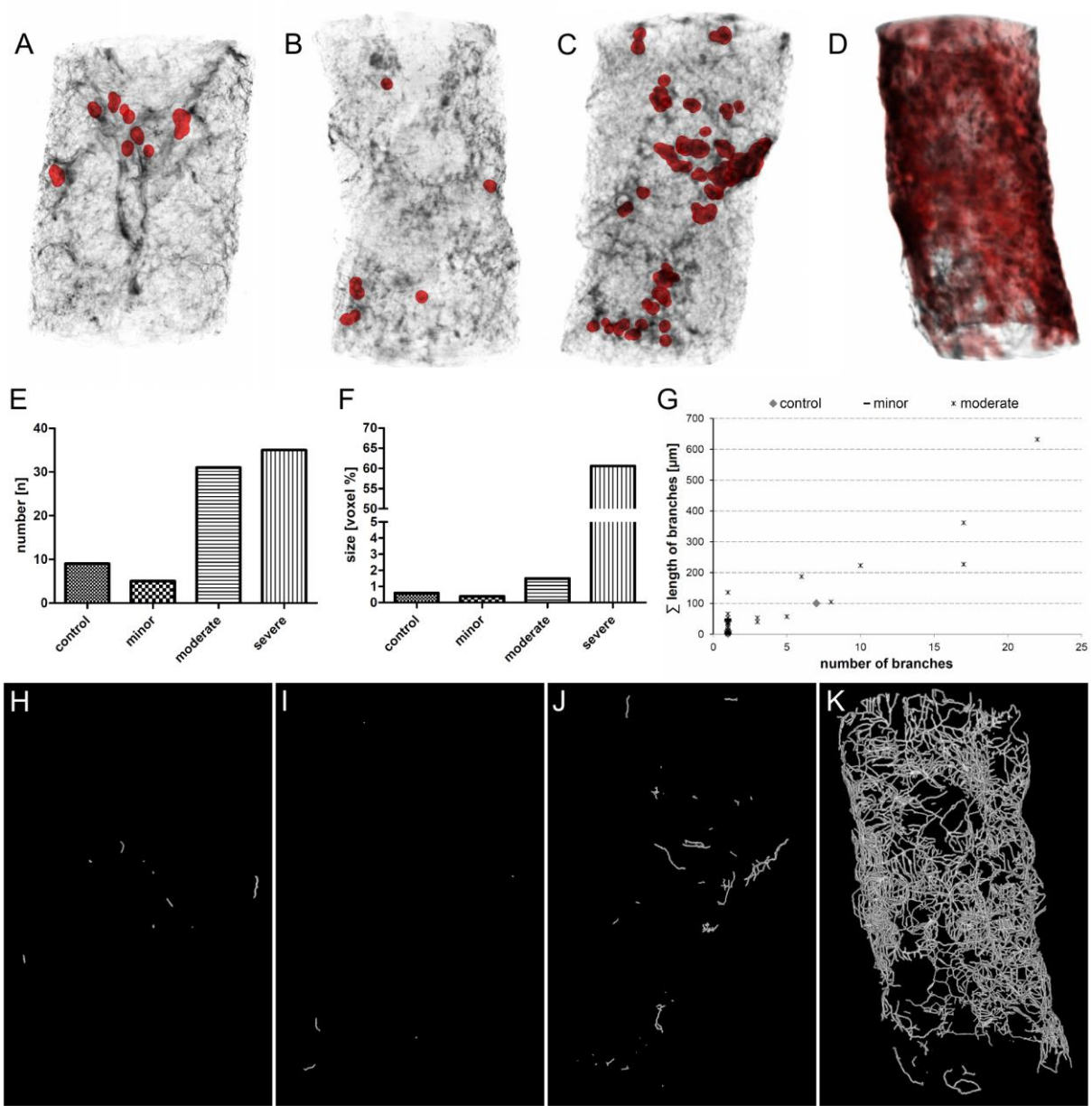
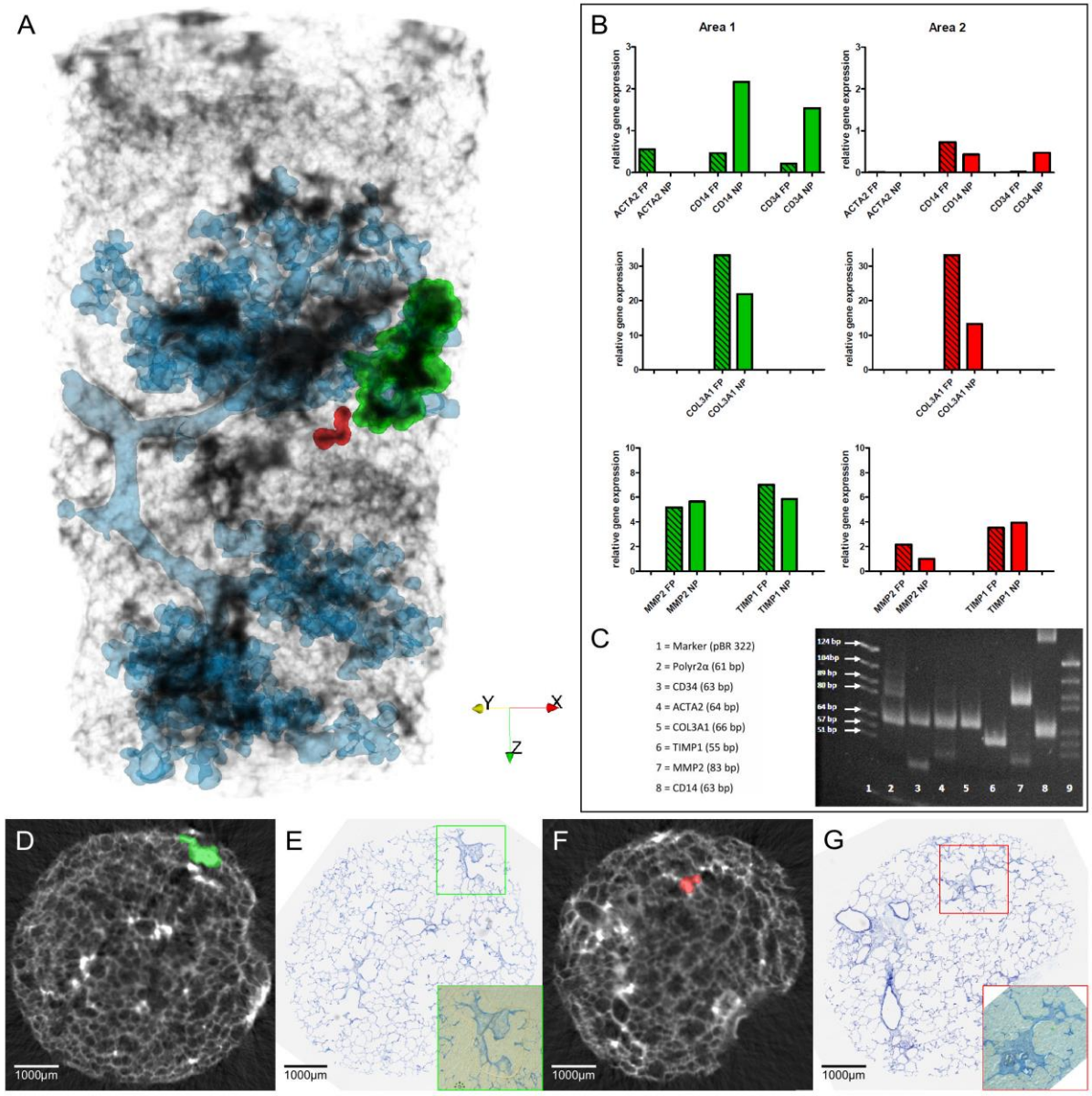


Figure S6: **RNA analysis.** Rendered SLOT-dataset of a biopsy with “moderate” fibrotic remodelling. Two fibrotic foci are highlighted in green and red correspondingly (A) and the complementary gene expression profiles of the fibrotic parenchyma (FP) and the surrounding normal parenchyma (NP): selected target genes include ACTA2, CD14, CD34, COL3A1, MMP2 and TIMP1 (B). Gelelectrophoresis of qPCR products (C). Isolated areas (green (D) and red (F)) marked in SLOT slices and the corresponding histological sections (E and G). Insets show laser-assisted microdissection of selected areas.



MOVIE LEGENDS

Movie S1: SLOT projection datasets of the “moderate” biopsy: Photodiode (PD) (A), photomultiplier tube (PMT) (B) and overlay of PD (in red) and PMT (in green) (C). Corresponding to Figure S2.

Movie S2: Virtual endoscopy of the “moderate” biopsy through a bronchus into the parenchyma. Inset shows an overview of the specimen topology together with the actual position.

Movie S3: Distance analysis of the healthy control biopsy (A), biopsy from an extrinsic allergic alveolitis (EAA) explant identified as minor (B), moderate (C) and severe fibrotic remodelling (D).

Movie S4: Segmentation of airways (grey) and blood vessels (red) in the “moderate” biopsycombined with distance analysis (blue) of the fibrotic areas (green) following by 300µm distance cut off model. Compare Figure S2D, and S5C.