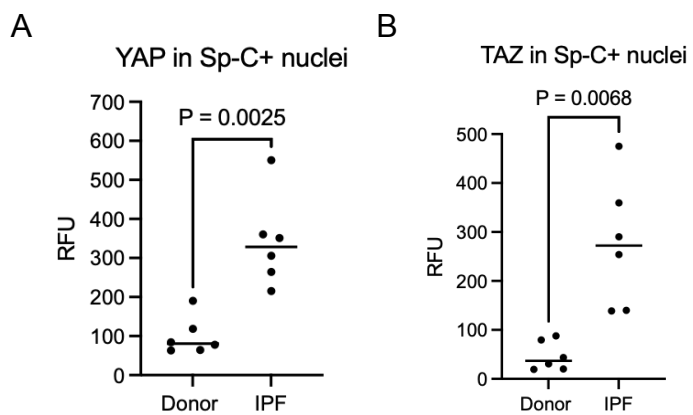
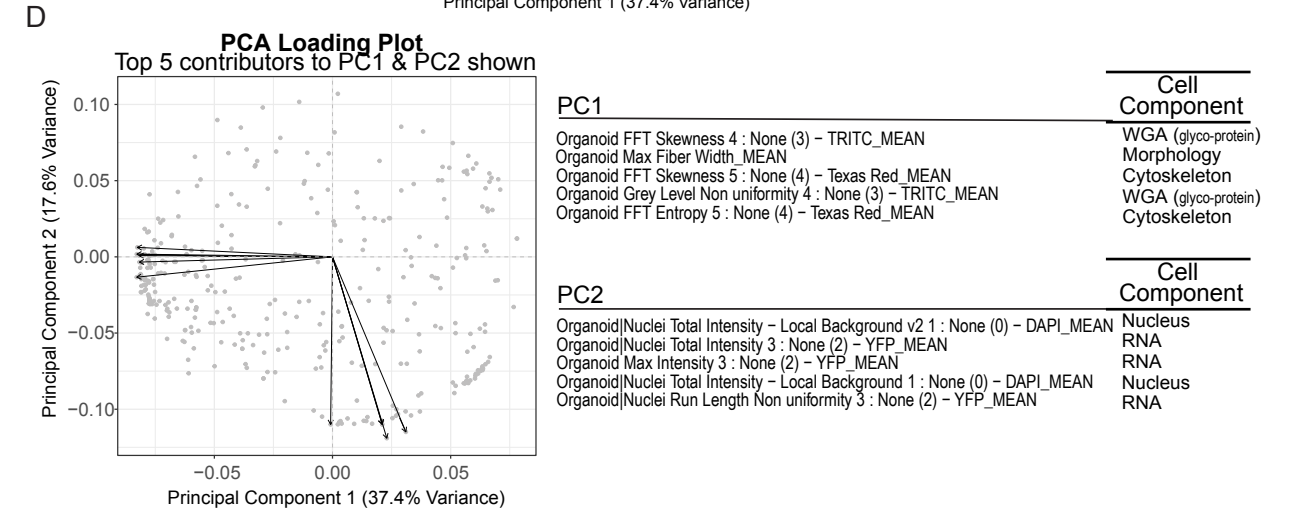
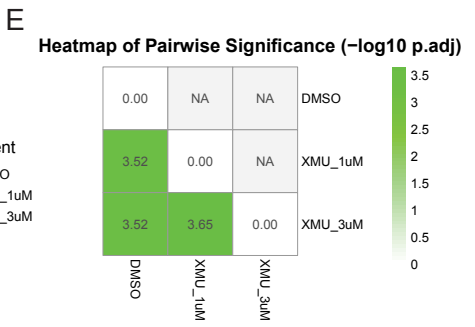
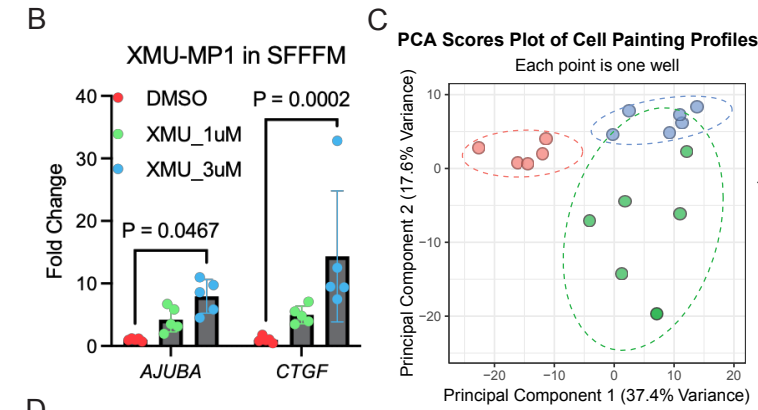
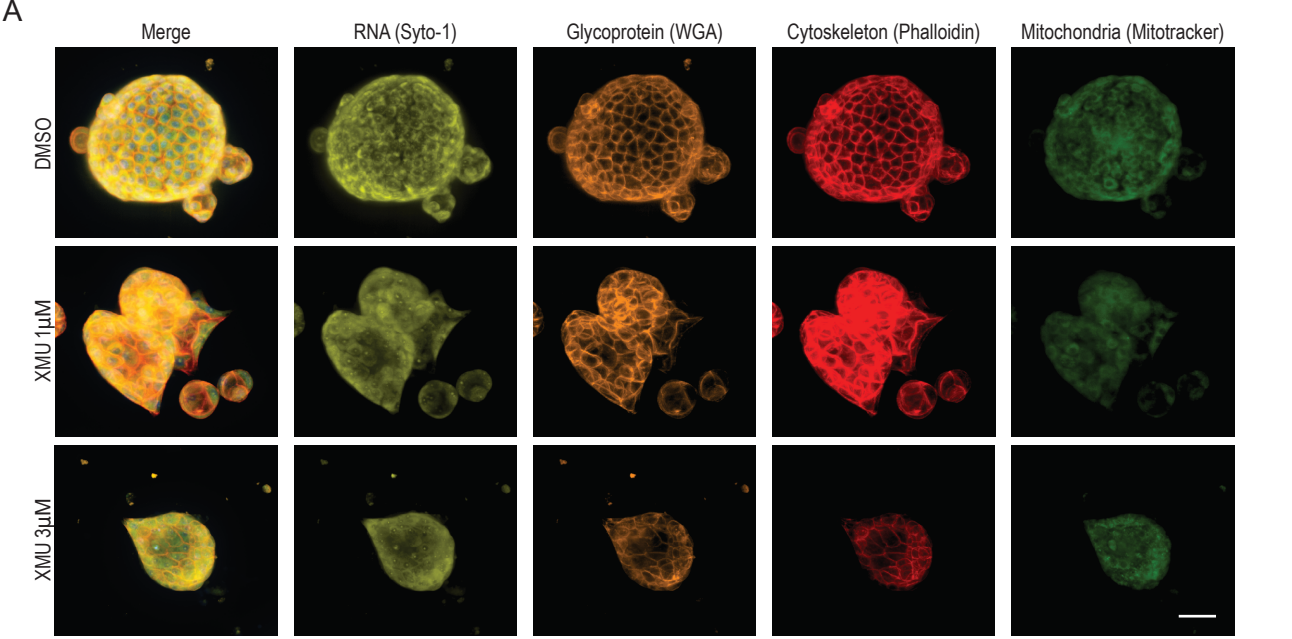


**Supplemental Table 1:** Patient data including age and sex of donor lungs rejected for transplant and IPF lungs used for analysis of YAP/TAZ expression and organoids associated with Figures 1-3.

**Supplemental Table 2:** Antibodies and RNAscope probes used, along with catalog number, supplier, and concentrations used.



**Supplemental Figure S1:** Quantification of relative fluorescence intensity of YAP (**A**) and TAZ (**B**) in Sp-C+ DAPI+ nuclei in IPF and healthy donors. Statistics determined using Welch's t test. Supplemental figure associated with main Figure 1.



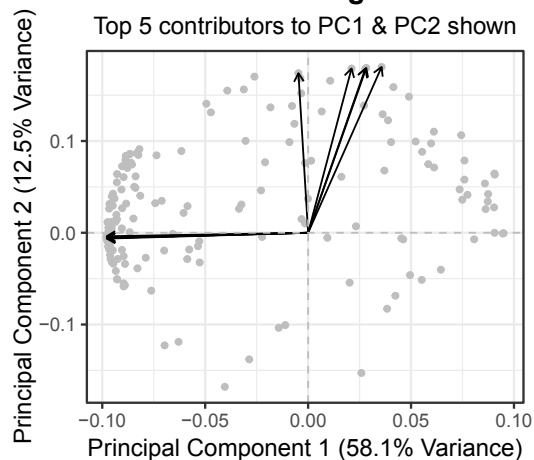


**Supplemental Figure S2:** **A)** Representative images of Cell painting single channel images of organoids with an escalating dose of XMU-MP-1. Scale bars are 50µm. **B)** Gene expression analysis (quantitative qPCR) of *AJUBA* and *CTGF* in XMU-MP1 treated organoids cultured in SFFFM demonstrating increased YAP/TAZ activity in epithelial cells isolated from 5 donor lungs. Statistics determined using 2-way ANOVA with Sidak's multiple comparison test. **C.)** PCA plot of cell painting profiles from Vehicle (DMSO), 1µM XMU-MP-1, or 3 µM XMU-MP-1. **D.)** PCA loadings plot highlighting the top five contributors for PC 1 and 2 as well as their respective general category of cell component based on cell compartment stained. **E.)** Statistical analysis of phenotypic distance between groups. P-values obtained from Hotelling's T-test in PCA space from all replicates. Supplemental figure associated with main Figure 2.

A

## PCA Loading Plot

Top 5 contributors to PC1 & PC2 shown



### PC1

Organoid Gyration Radius\_MEAN  
Organoid Diameter\_MEAN  
Organoid First Principal Axis Length\_MEAN  
Organoid Major Axis\_MEAN  
Organoid Major Axis v2\_MEAN

### Cell Component

Morphology  
Morphology  
Morphology  
Morphology  
Morphology

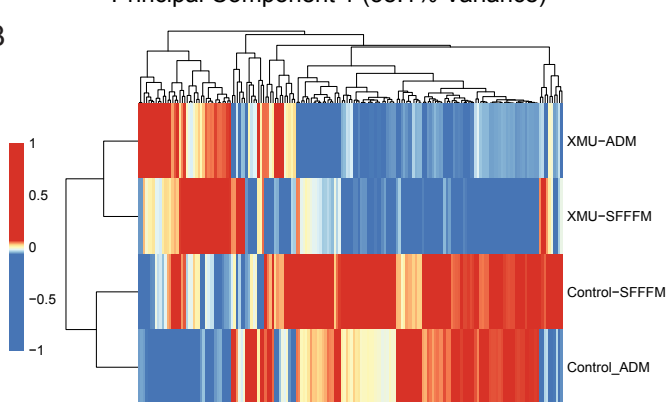
### PC2

Organoid High Grey Level Run Emphasis 4 : None (3) – TRITC\_MEAN  
Organoid Mean Intensity 3 : None (2) – YFP\_MEAN  
Organoid High Grey Level Run Emphasis 3 : None (2) – YFP\_MEAN  
Organoid Median Intensity 3 : None (2) – YFP\_MEAN  
Organoid Max Intensity 3 : None (2) – YFP\_MEAN

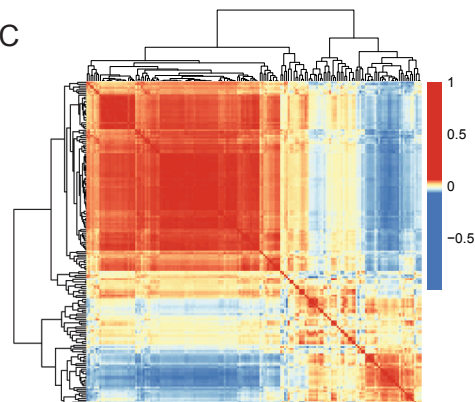
### Cell Component

WGA  
RNA  
RNA  
RNA  
RNA

B

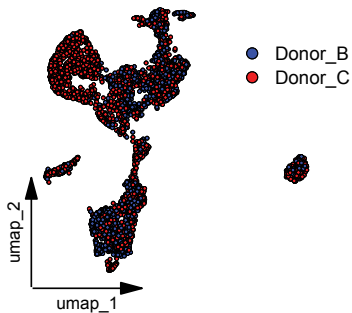


C

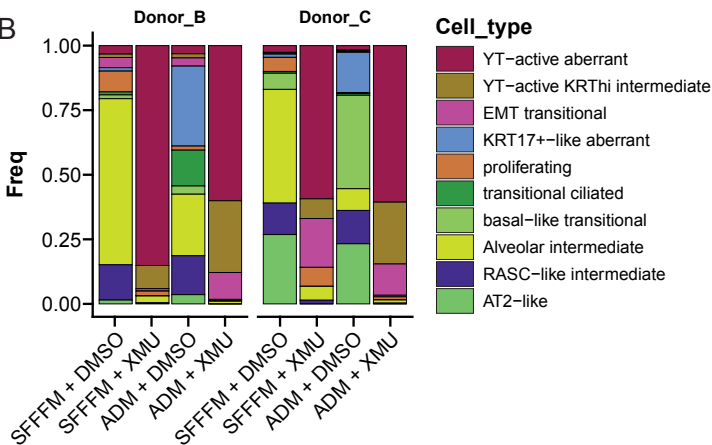


**Supplemental Figure S3:** **A)** PCA loadings plot highlighting the top five contributors for PCA 1 and 2 as well as their respective general category of cell component based on cell compartment stained from PCA analysis presented in main Figure 2. **B)** Hierarchically clustered and scaled heatmap of all extracted features by media condition **C)** Correlation diagram of extracted features, scaled by Pearson correlation value to demonstrate underlying data structure.

A

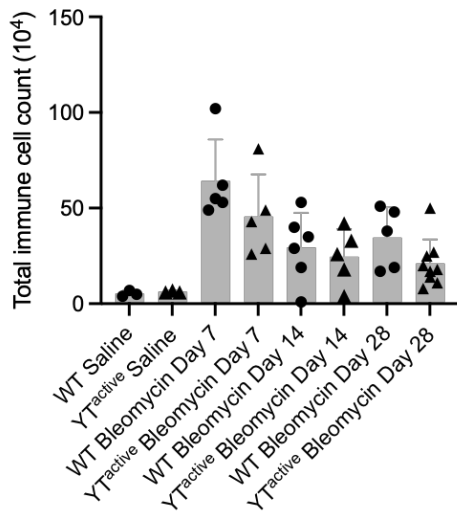


B

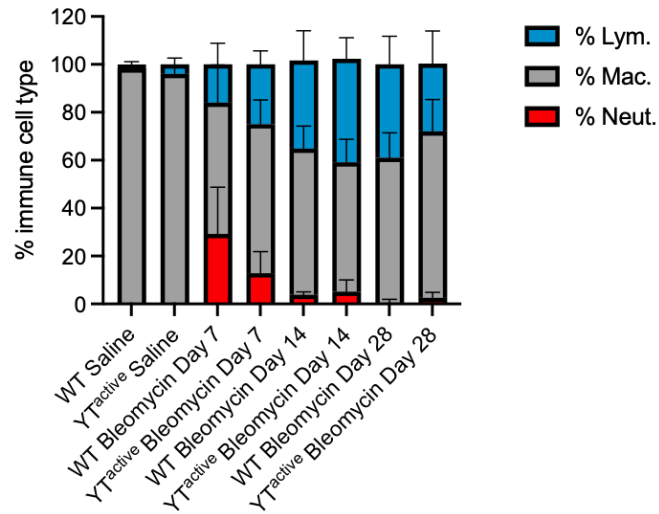


**Supplemental Figure S4:** **A)** UMAP embedding of human organoid scRNA data in main Figure 3 separated by Donor **B)** Stacked bar chart of annotated cell types separated by Donor and media by drug permutations demonstrating conserved response to XMU agonism across biologic donors.

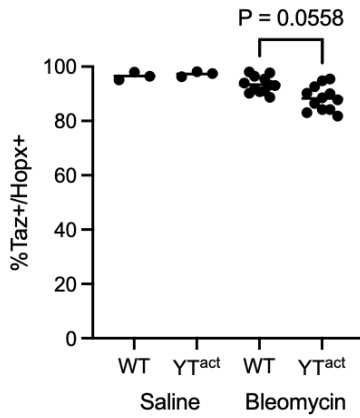
**A** Total BAL Immune Cell Counts



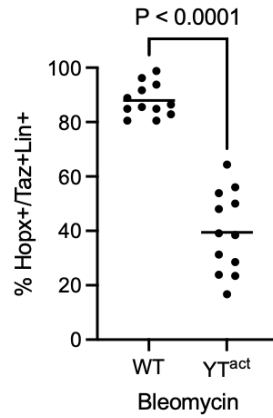
**B** BAL Immune Cells



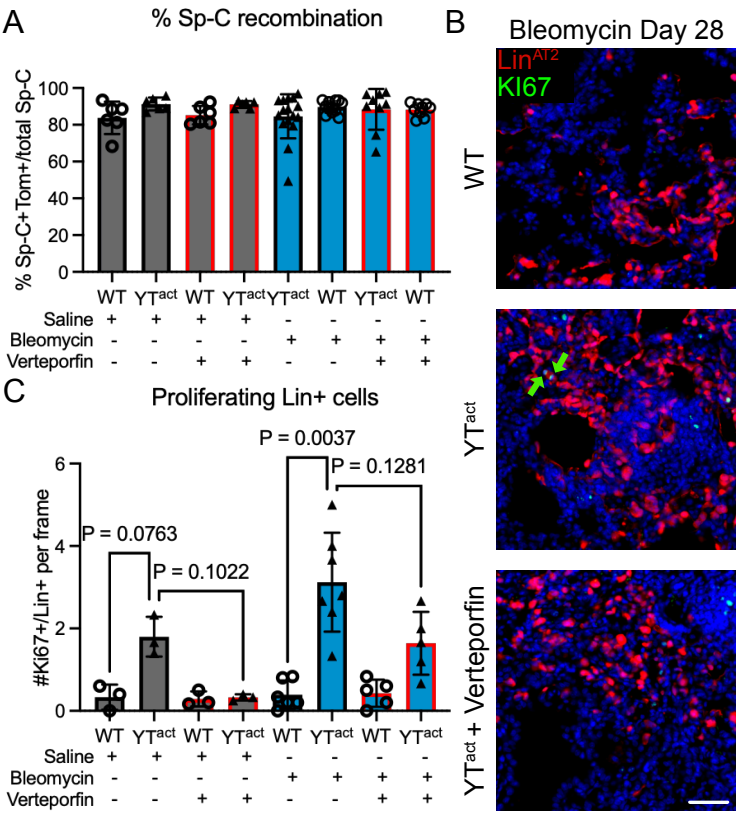
**C** Taz+/Hopx+



**D** Hopx+/Taz+Lin+

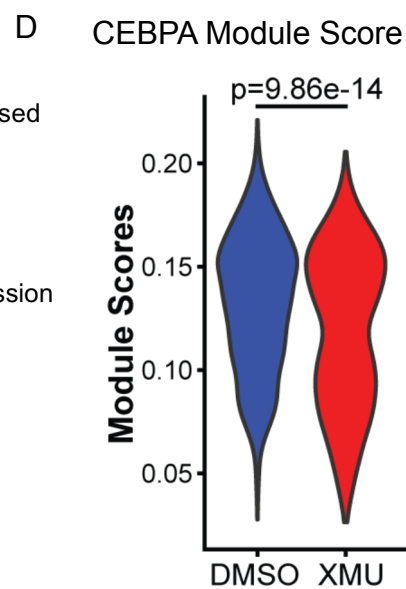
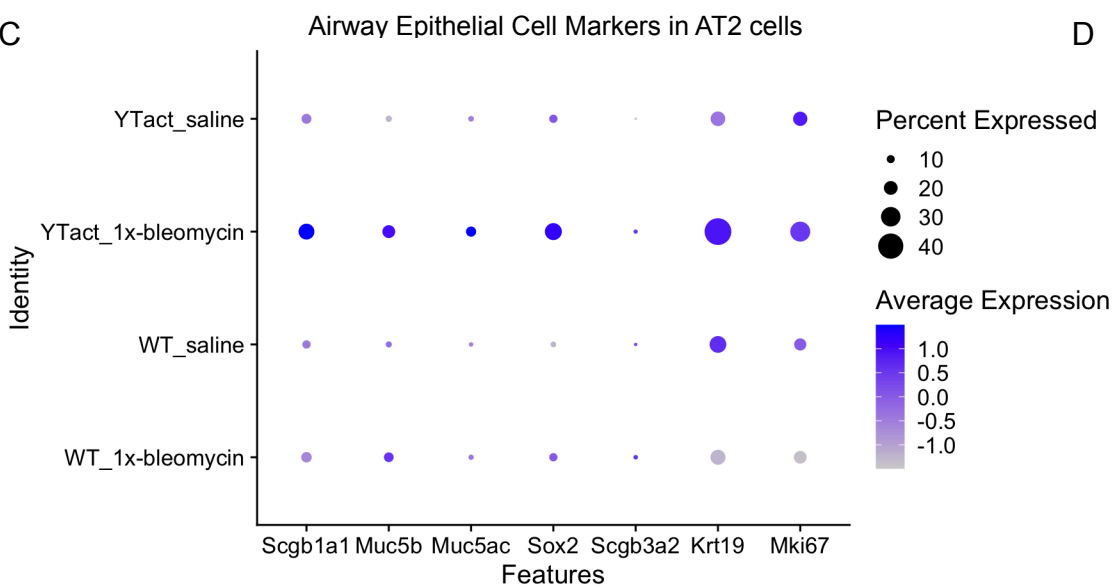
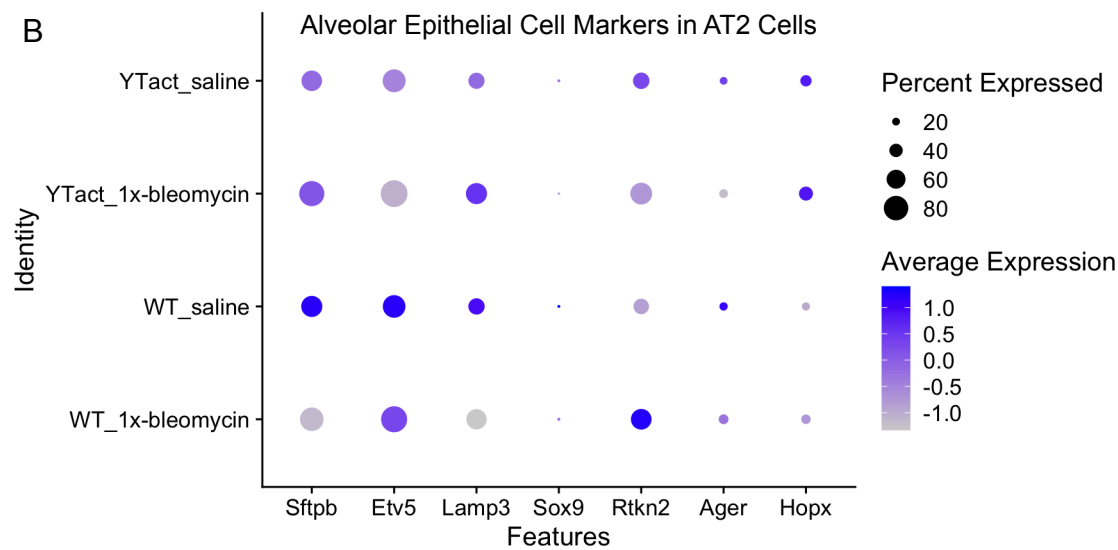
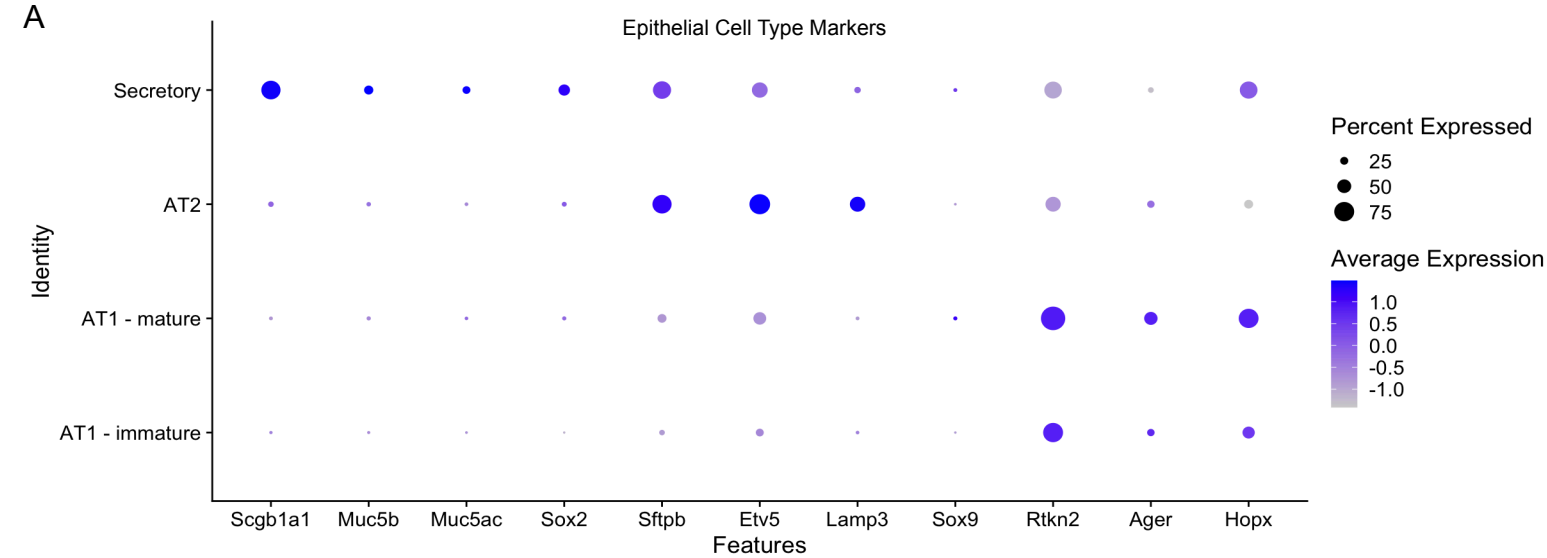


**Supplemental Figure S5:** Total quantification (**A**) and DiffQuick differential immune cell type quantification (**B**) of broncho-alveolar lavage fluid from WT and YT<sup>active</sup> mice subjected to either saline or bleomycin injury collected at 7, 14, and 28-days post bleomycin injury. **C**) Quantification of the percentage of Hopx<sup>+</sup> cells that expressed nuclear Taz<sup>+</sup>. **D**) Quantification of Taz<sup>+</sup> lineage traced cells expressing nuclear Hopx. Statistics determined using non-parametric Two-tailed Mann-Whitney test. Supplemental figure is associated with main Figure 4.

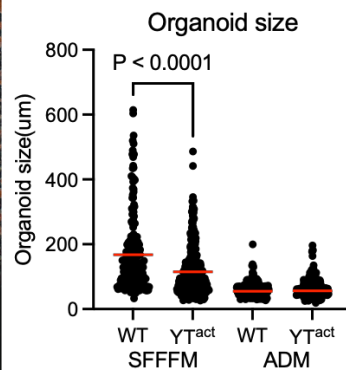
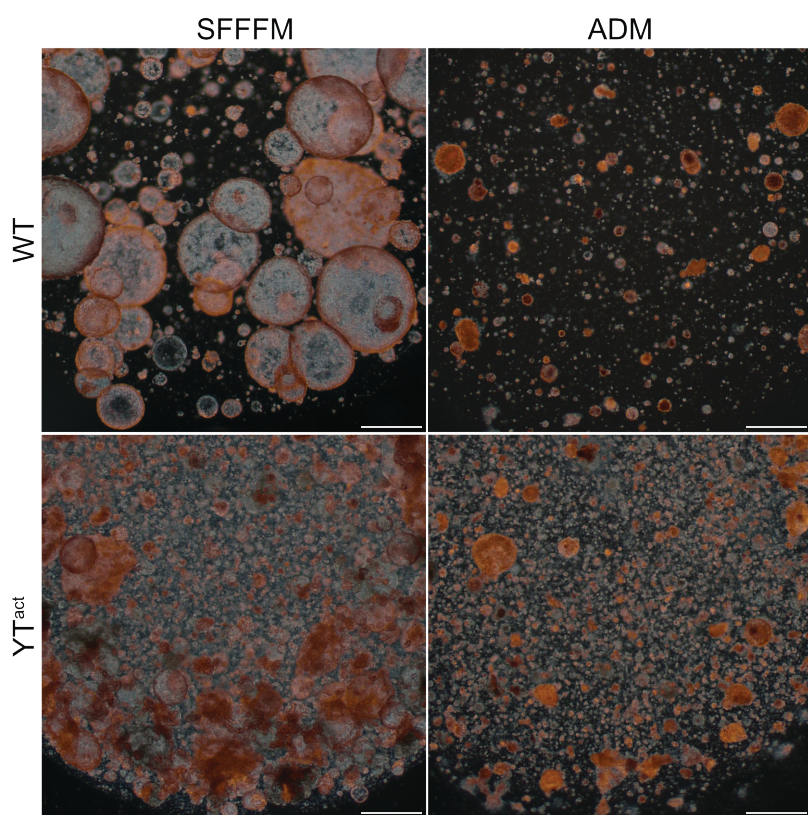




**Supplemental Figure S6:** **A)** Quantification of Sp-C<sup>+</sup>/Lineage traced cells to determine recombination efficiency of the mouse model. **B)** Immunofluorescence analysis of Ki67<sup>+</sup> (green) proliferating lineage traced AT2 cells (red) at 28-days post-bleomycin injury. Green arrows point to proliferating lineage traced cells. **C)** Quantification of the percentage of proliferating cells per frame. Each dot indicates an average per mouse. Scale bar is 50μm. Supplemental figure is associated with main Figure 5.



**Supplemental Figure S7:** **A)** Dotplot of cell type markers of the 4 epithelial cell types identified by our single nucleus multiome (RNA<sup>+</sup> ATACseq) analysis associated with Figure 5. **B)** Dotplot showing AT2 cell associated gene activity scores and **C)** Dotplot showing airway, transitional, and proliferation marker gene activity scores determined from single-cell ATAC sequencing associated with Figure 6. **D)** Gene module score showing decreased signaling associated with CEBPA activity from scRNAseq of human organoids from Figure 3.



**Supplemental Figure S8:** Overlaid light and fluorescent (TdTomato) imaging of mouse AT2 organoids cultured in SFFM and ADM. Quantification of organoid size represented as individual organoids. Red line represents mean value. Organoid analysis was limited to organoids >25 $\mu$ m in size. Supplemental figure is associated with main Figure 8.

| Sample  | Lung state    | Age       | Smoking Status          | COD            | Notes                                                                                                     |
|---------|---------------|-----------|-------------------------|----------------|-----------------------------------------------------------------------------------------------------------|
| VUHD84  | Healthy Donor | 34/Female | 1p/d/7 years            | CPA            |                                                                                                           |
| VUHD85  | Healthy Donor | 53/Male   | unknown                 | CVA/Stoke      | Hypertension, Family History of CAD                                                                       |
| VUHD87  | Healthy Donor | 53/Male   | 1p/d/7 years            | Cardiac Arrest | Etoh Abuse, Hypertension, Family history of CAD                                                           |
| VUHD92  | Healthy Donor | 55/Male   | unknown                 | CVA/Stroke     | Hypertension, Family history of CAD                                                                       |
| VUHD94  | Healthy Donor | 62/Male   | unknown                 | Stroke         | No medical history                                                                                        |
| VUHD140 | Healthy Donor | 61/Male   | unknown                 | CVA            | No medical history                                                                                        |
| VUILD72 | IPF           | 62/Female | unknown                 |                | HTN,DM2, Dyslipidemia, GERD, Osteoarthritis, Rheumatoid Arthritis, Restless Leg Syndrome, Moderate Asthma |
| VUILD74 | IPF           | 62/Male   | 10 PY quit 40 years ago |                |                                                                                                           |
| VUILD76 | IPF           | 53/Male   | unknown                 |                | Obesity, Hyperlipidema                                                                                    |
| VUILD77 | IPF           | 62/Male   | 30 PY quit 18 years ago |                | DM2, HTN, Hypothyroidism                                                                                  |
| VUILD79 | IPF           | 59/Female | Quit 25 years ago       |                | GERD, HLN                                                                                                 |
| VUILD80 | IPF           | 69/Female | unknown                 |                | No medical history                                                                                        |