Supplementary figure 1. CCSP- driven transgenic EMAP II overexpression is lung-specific and causes apoptosis of lung endothelial cells, monocyte accumulation, and airspace enlargement. A. EMAP II localization in the lung epithelium of EMAP II-overexpressing double transgenic (DT; EMAP II/CCSP-rtTA) mice detected by co-immunofluorescence with EMAP II antiserum (red), pro-SP-C epithelial marker antibody (green), and DAPI (blue) compared to control single transgenic (ST) mice; size bar=10μm. **B.** EMAP II expression in DT animals after 4 weeks of induction, analyzed by immunostaining with specific EMAP II polyclonal anti-serum (brown) and hematoxylin counterstaining (blue) in paraffin-embedded lung (**i, iv, and vii**), heart (**ii and v**), and kidney (**iii and vi**). Note the exclusive EMAP II expression in the lung (arrows). **C.** Representative immunofluorescent images of lung sections immunostained with active caspase-3 antibody (red, arrows) from control ST (**i**) versus DT (**ii**) animals after 4 weeks of induction. Panel **iii** depicts a confocal micrograph of lung from DT mice induced for 4 weeks followed by triple immunostaining for active caspase-3 (red), endothelial cell marker VE-cadherin (green), and nuclei (blue). Note apoptosis of endothelial cells (yellow, arrowheads). **D.** Lungs from control ST (**i**) or DT (**ii**) mice induced for 3 weeks were immunostained for the lung macrophage marker Mac-3 (green, arrows) with DAPI-stained nuclei (blue). Note a marked increase in the number of macrophages (green, arrows) in DT mice. **E.** Acinar airspace size was expressed volume-weighted mean airspace volume**,** measured by interactive computer-assisted stereology (boxplot with median; *p =0.02; ANOVA; n=8-10) on

Richardson-stained glycol methacrylate lung sections after 28 weeks of induction with doxycycline of ST (control) or DT mice.

Supplementary figure 2. Pro-apoptotic effects of EMAP II in human lung endothelial cells. Apoptosis measured by TUNEL immunofluorescence staining and expressed as a TUNEL index (ratio of positive cells normalized to total DAPI nuclear positive cells, %) in primary human lung microvascular endothelial cells treated with the indicated concentrations of pro- or mature EMAP II (24h) with or without neutralizing EMAP II- or control antibodies (M7/1 or IgG, respectively); mean +SEM; * $p < 0.05$ vs. untreated control; # $p < 0.05$ vs. 50 μg/ml EMAP II; n=3.

Supplementary figure 3. Efficacy of EMAP II neutralizing antibodies in cigarette smoke-induced inflammation, apoptosis and airspace enlargement. A. Effectiveness of lung deposition of antibodies administered by aerosolized inhalation. Cryosections were obtained from lungs and visualized using fluorescent microscopy with nuclear counterstaining (DAPI). Unlabeled IgG (i) or Cy5-labeled IgG (ii) were administered via aerosolized inhalation once (50 μg; 100 μl). Note the intense red punctuate fluorescence of the Cy5 label in both large airways (triple arrows) and lung parenchyma (arrows); lung auto-fluorescence captured with the FITC filter, green; size bar is 50 μm. **B**. Boxplot with recovery of biotinylated antibody in the plasma 4 hours after nebulization (IgG-neb;70 μg) or intra-peritoneal delivery (IgG-ip;70 μg), compared to saline nebulization. Antibody detected via immune-adsorption assay on streptavidin-coated plates (n=6; * $p<0.05$ vs. control; ** $p<0.05$ vs. IgG-neb). **C-G.** DBA/2 mice exposed to ambient air control (AC), cigarette smoke (Cig Smoke or CS) for 4 months, or CS for 4 months plus

EMAP II neutralizing antibody (Ab; 50 μg;100 μl; tiw) via inhalation during the third month of exposure. **C.** Apoptosis detected by active caspase-3 immunostaining. Note increased active caspase-3-expressing cells (both alveolar structural cells and macrophages) in the acinar lung of CS-exposed mice (arrows), but not in mice treated with EMAP II Ab. **D.** Levels of lung ceramide 16:0, a prevalent pro-apoptotic ceramide, measured by mass spectrometry and normalized by lipid phosphorus (Pi) in lung homogenates, is increased by CS (4 months), but not in mice treated with EMAP II Ab (mean + SEM; *p<0.05 vs. AC control). **E**. Pie charts indicate abundance of macrophages, lymphocytes, and PMN in the BALF of mice (mean percentage, *p<0.05 vs. control, #p<0.05 vs. CS; ANOVA). **F.** PMN expression detected by immunohistochemistry in the lung sections quantified by image analysis (*p<0.05 vs. control, ** p<0.05 vs. CS). **G**. Bronchial epithelial wall thickness (mean + SEM; (*p<0.05 vs. control, ** p<0.05 vs. CS) in large, medium and small diameter airways measured via image analysis software on blinded slides from mice exposed to ambient air (AC) or CS, in the presence of EMAP II Ab or control IgG.

Supplementary figure 4. Dose-dependent effects of EMAP II augmentation in the lung. Boxplot of caspase-3 activity in lung lysates (**A**) and surface to volume ratio of the lungs (**B**) in mice untreated (0) or treated with recombinant mature EMAP II by aerosol nebulization (EMAP II i-t; 10 or 90 μg/100 μl/dose; three times a week; 4 weeks); *p<0.05 vs. control; n= 5.

Supplementary Table 1. Demographic characteristics of individuals whose BAL fluid was analyzed for EMAP II expression in Figure 4A. Abbreviations: A: Asian; C: Caucasian; AA:

African American; F: female; M: male; NS: non-smoker; S: smoker. Of note, these asymptomatic healthy volunteers did not have pulmonary function tests measured.

Supplementary Table 2. Demographic and clinical characteristics of individuals whose BAL fluid was analyzed for EMAP II expression in Figure 4B-C. Abbreviations: C: Caucasian; AA: African American; F: female; M: male; NS: non-smoker; S: smoker. *$p<0.05$ vs. non-smokers and #$p<0.05$ vs. ex-smokers without COPD. Patients with COPD were further characterized for GOLD classification, inhaled corticosteroid use (ICS), beta agonist, anticholinergic, or aminophylline treatment.

Table S1

ID	AGE (years)	RACE	SEX	SMOKING
1	24	A	F	**NS**
2	50	C	F	**NS**
3	25	C	F	**NS**
4	49	C	F	**NS**
5	54	C	M	**NS**
6	26	C	F	**NS**
7	25	C	F	**NS**
8	53	C	F	**NS**
9	26	C	F	**NS**
10	33	AA	M	**NS**
1	27	C	M	S
2	27	C	M	S
3	28	C	M	S
4	23	C	M	S
5	37	C	M	S
6	27	C	M	S

7	28	C	M	S
8	31	C	M	S
9	55	C	F	S

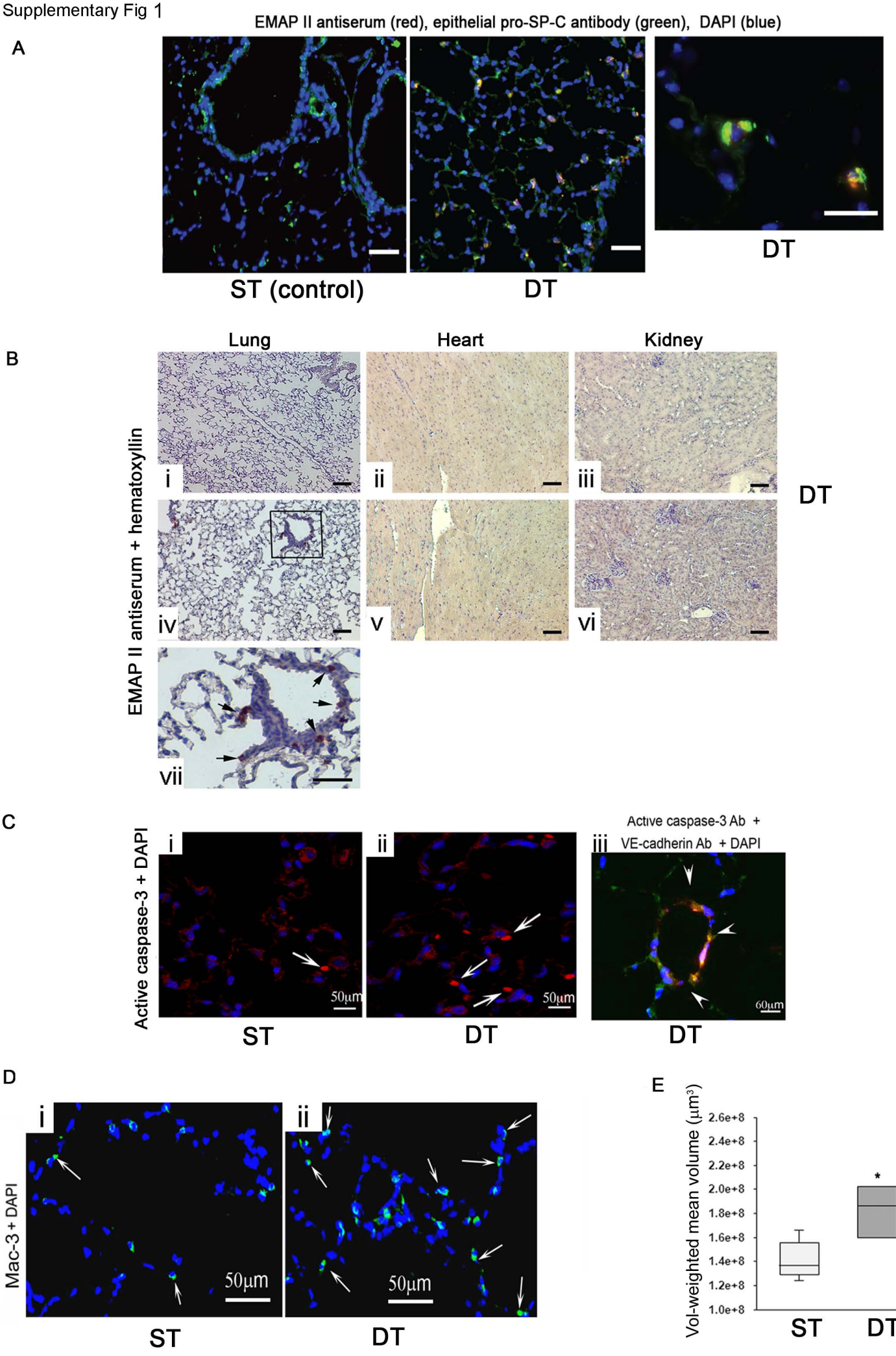
Table S2

Group	ID	Age	Sex	Race	pack yrs	FEV1	FEV1 %	FVC	FVC %	FEV1/FVC
Non-smokers	1	34	m	c		3.62	91	4.31	90	83.99
	2	42	m	c		3.55	91	4.44	93	79.95
	3	56	m	c		1.93	82	2.61	92	73.94
	4	47	f	aa	2.5	2.23	130	2.9	146	76.89
	5	35	f	aa		2.3	90	2.61	87	88.12
	6	70	m	c		3.22	104	4.11	105	78.34
	7	40	f	c		3.17	103	4.23	115	74.94
	8	47	f	c		2.69	97	3.5	105	76.85
	9	73	m	c		3.52	105	4.47	105	78.74
	10	73	f	c		2.03	94	2.93	100	69
	11	53	m	c	2	3.54	102	4.84	114	73.14
	12	49	m	c		4.22	112	4.94	106	85.55
	13	73	m	c		4.09	107	3.14	104	77
	14	61	f	c		2.38	106	3.14	114	75.79
	15	34	f	c		3.76	109	4.66	112	81
	MEAN	**52.5**	**53.3%**	**86.7%**	**2.3**	**3.1**	**101.5**	**3.8**	**105.9**	**78.2**
	SEM	**3.8**	**M**	**C**	**0.1**	**0.2**	**3.0**	**0.2**	**3.7**	**1.3**
ex-smokers	16	58	f	c	30	2.09	82	2.86	91	73.07
no COPD	17	74	m	c	25	2.87	91	3.85	96	74.54
	18	46	m	aa	29	2.48	77	3.66	93	67.75
	19	50	m	aa	49.5	2.67	82	3.5	87	76.28
	20	48	f	aa	34	1.93	88	2.63	100	73.38
	21	53	f	c	30	2.36	98	3	103	78.66
	22	57	f	c	34	2.83	106	3.96	121	71.46
	23	52	f	c	35	2.9	109	3.48	107	83.33
	24	52	f	c	34	2.37	95	2.86	94	82.86
	25	58	m	c	25	3.24	94	4.44	90	73
	26	79	f	c	31	1.47	78	1.73	66	84.97
	27	52	f	c	23	2.36	101	2.97	106	79.46
	28	79	f	c	22	1.81	93	2.77	89	66
	29	57	f	c	46	2.2	95	2.56	91	86
	30	43	m	c	23	3.1	80	3.78	80	82
	MEAN	**57.2**	**33.3%**	**80.0%**	**31.4**	**2.4**	**91.3**	**3.2**	**94.3**	**76.9**
	SEM	**2.9**	**M**	**C**	**2.1**	**0.1**	**2.6**	**0.2**	**3.3**	**1.6**
	p value				*	*	*	*	*	

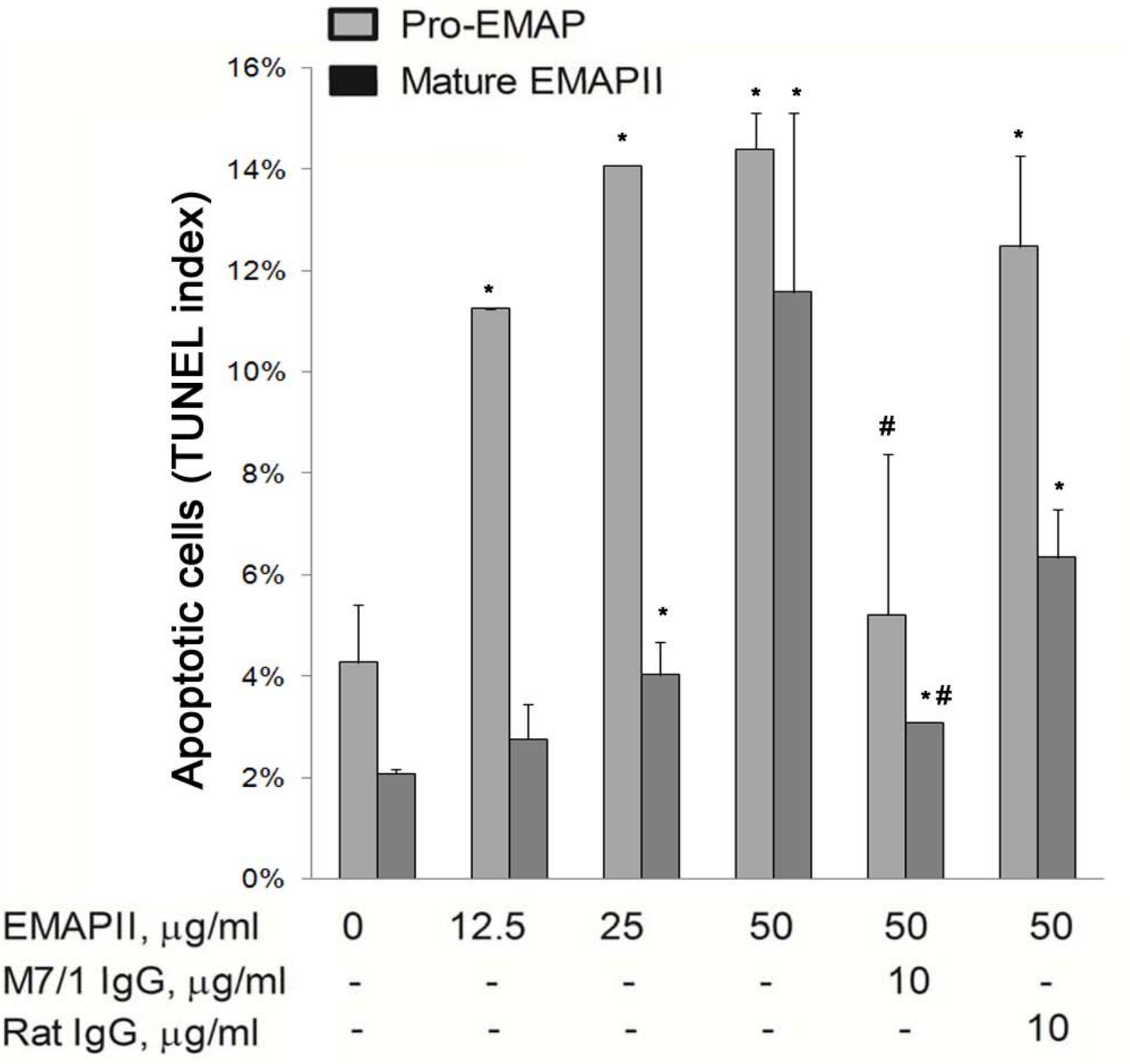
Table S2

	ID	Age	Sex	Race	pack yrs	FEV1	FEV1 %	FVC	FVC %	FEV1/FVC	GOLD	ICS	b agonists	antichol	aminophy
COPD (ex-smokers)	31	62	m	c	102	1.99	52	3.12	65	63.78	2	y	y	n	n
	32	65	f	c	30	1.02	47	1.02	47	58.95	3	n	y	y	n
	33	71	m	c	75	1.02	29	2.04	45	50	4	n	y	y	y
	34	57	m	c	140	2.39	66	3.62	80	66.02	2	n	n	n	n
	35	61	m	c	100	1.84	61	3.57	95	51.54	2	y	y	y	n
	36	73	m	c	50	0.91	29	1.93	48	47.15	4	y	y	y	y
	37	78	m	c	75	1.58	59	3.95	114	40	2	n	y	y	n
	38	59	m	c	52.5	1.62	41	4.55	93	35.6	3	n	y	y	y
	39	59	m	c	88	1.97	68	2.99	83	65.88	2	n	n	n	n
	40	65	m	c	45	2.81	78	4	89	70.25	2	n	y	n	n
	41	65	f	c	40.5	2.41	103	3.51	120	68.66	1	n	n	n	n
	42	53	f	c	30	2.85	98	4.01	112	71.07	1	n	n	n	n
	43	52	f	c	40	2.67	94	3.56	102	75	1	n	n	n	n
	44	49	f	c	30	2.38	89	3.25	101	73	1	n	n	n	n
	45	66	f	c	44	2.21	74	3.22	84	69	2	n	n	n	n
	MEAN	**62.3**	**60.0%**	**100.0%**	**62.8**	**2.0**	**65.9**	**3.2**	**85.2**	**60.4**	**2.1**	**20.0%**	**53.3%**	**33.3%**	**20.0%**
	SEM	**2.1**	**M**	**C**	**8.5**	**0.2**	**6.1**	**0.2**	**6.3**	**3.2**	**0.3**				
	p value	*			*; #	*; #	*; #		*	*; #					

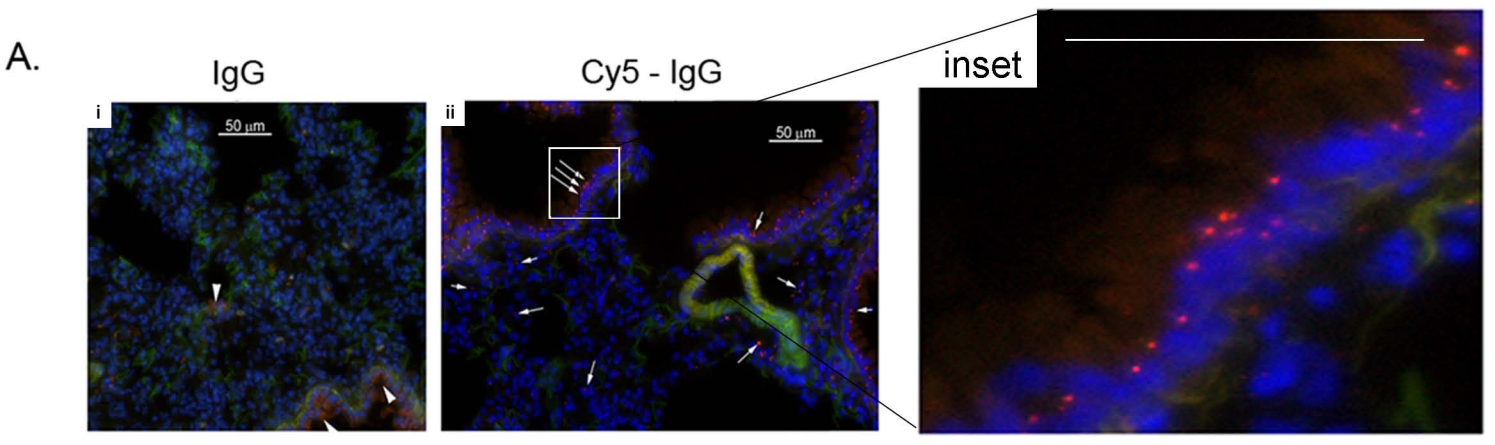
Supplementary Fig 1

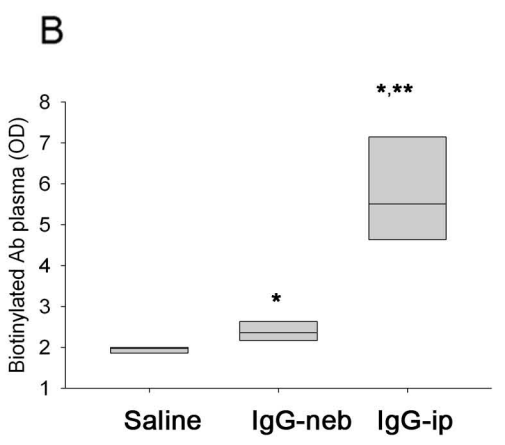


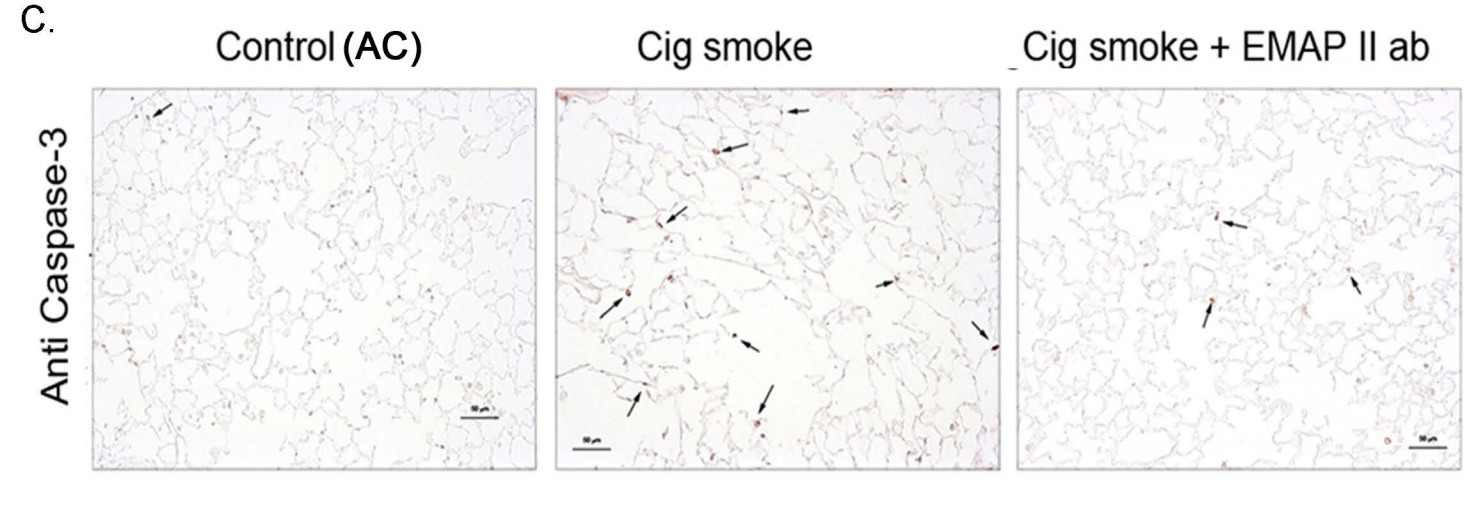
Supplementary Figure 2

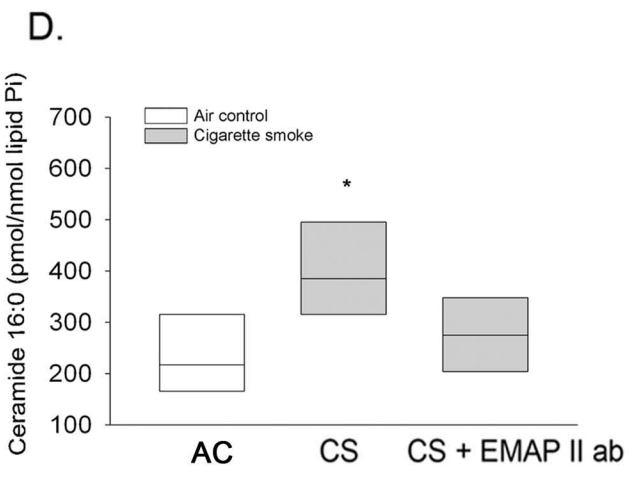


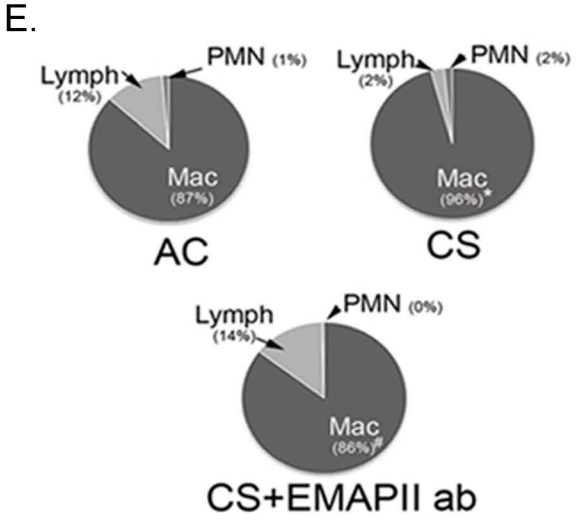
Supplementary Figure 3

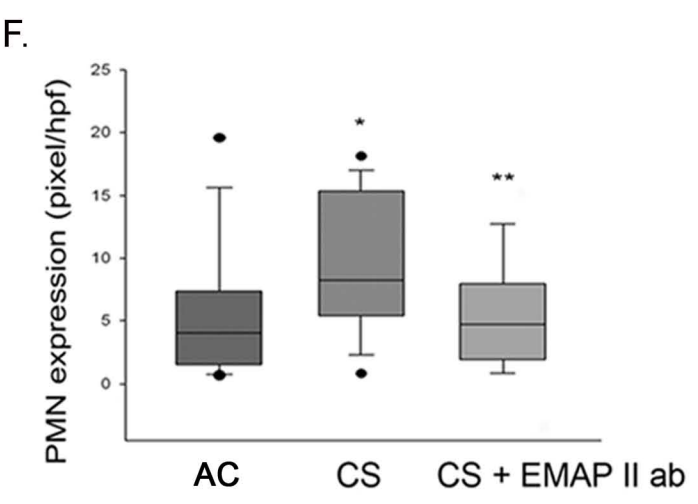


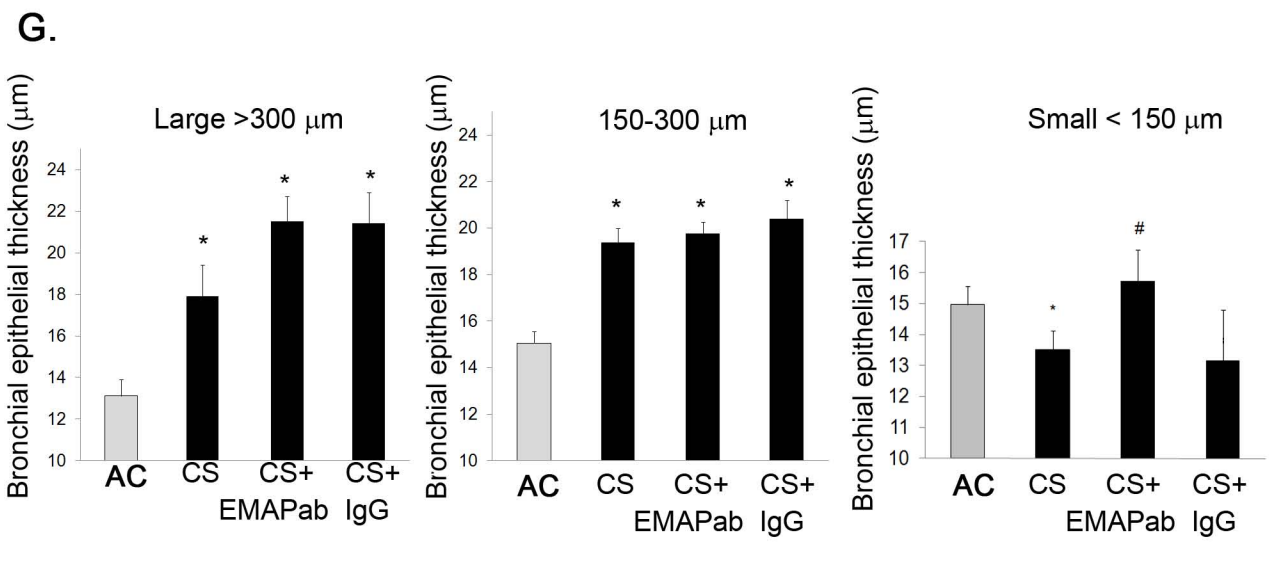












Supplementary Figure 4