

1 SUPPLEMENTARY INFORMATION

2 Supplementary Table 1.

3 Demographic characteristics of IPF and control subjects analyzed by microarray.

	Control (n=64)	IPF, FVC ≥80% (n=17)	IPF, FVC 50-80% (n=60)	IPF, FVC <50% (n=16)	
Characteristic	Mean (±SD) or Number (%)				p-value
Age	65.3 (10.2)	65.2 (10.5)	64.8 (7.96)	59.2 (8.11)	0.121 ¹
Sex					0.018 ²
Male	34 (53.1%)	11 (64.7%)	48 (80%)	11 (68.8%)	
Female	30 (46.9%)	6 (35.3%)	12 (20%)	5 (31.2%)	
Height (inches)	66.4 (3.85)	67.4 (3.28)	68.5 (3.86)	66.6 (3.78)	0.021 ¹
Weight (pounds)	184 (44.6)	193 (31.4)	203 (37.6)	198 (29.6)	0.054 ¹
Pack-years	35.2 (33.1)	33.6 (30.9)	25.7 (20)	25.9 (12.4)	0.209 ¹
FVC Pre-Bronchodilator % predicted	93.6 (11.7)	86.8 (5.71)	65.8 (8.97)	41.4 (6.9)	<0.001 ¹
Severity classification of DLCO	81.2 (17)	58.2 (23)	48.6 (12.9)	26.6 (15.5)	<0.001 ¹
SF12 Physical Component Score	48.1 (11.5)	35 (9.58)	37.3 (10.9)	28.6 (8.46)	<0.001 ¹
Meters walked in 6 minutes	419 (129)	412 (64.1)	385 (109)	279 (128)	0.002 ¹

4 ¹ANOVA F-test ²Chi-Square

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6 **Supplementary Table 2.**

7 Demographic characteristics of IPF and control subjects analyzed by RNA sequencing.

	Control (n=19)	IPF (n=20)	
Characteristic	Mean ($\pm$SD) or Number (%)		p-value
Age	63.1 (14)	57.2 (5.96)	0.095 ¹
Sex			0.267 ²
Male	9 (47.4%)	14 (70%)	
Female	10 (52.6%)	6 (30%)	
Height (inches)	65.6 (2.63)	67.7 (3.1)	0.031 ¹
Weight (pounds)	175 (30.4)	178 (30.2)	0.819 ¹
Pack-years	38.3 (37.8)	27.2 (21.9)	0.438 ¹
FVC Pre-Bronchodilator % predicted	96.2 (15.4)	43 (12.3)	<0.001 ¹
Severity classification of DLCO	88.7 (16.7)	25.3 (11.8)	<0.001 ¹
SF12 Physical Component Score	44 (9.04)	26.1 (6.73)	<0.001 ¹
Meters walked in 6 minutes	373 (73.1)	283 (79.9)	0.006 ¹

8 ¹ANOVA F-test ²Chi-Square

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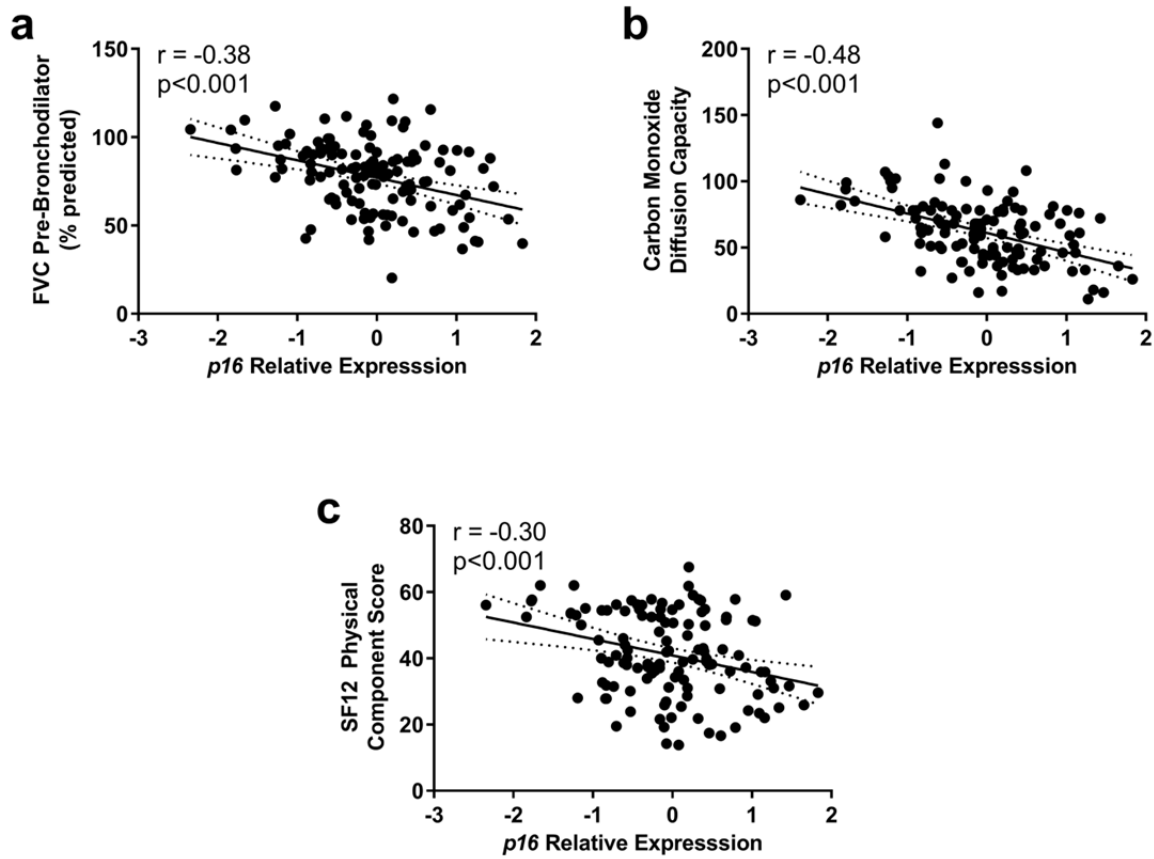
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11 **Supplementary Table 3.**12 Primer sequences used for real-time PCR.

Gene	Species	Primer 1	Primer 2	Probe
Col1a1	Mouse	CATTGTGTATGCAGCTGAC TTC	CGCAAAGAGTCTACATGT CTAGG	CCGGAGGTCCACAAAGCT GAACA
Hprt	Mouse	AGCAGGTCAGCAAAGAAC T	CCTCATGGACTGATTATG GACA	ATTGTGGCCCTCTGTGTGC TCA
Il6	Mouse	TCCTTAGCCACTCCTTCTG T	AGCCAGAGTCCTTCAGAG A	CCTACCCCAATTTCCAATG CTCTCCT
Ccl2 (Mcp1)	Mouse	AACTACAGCTTCTTTGGGA CA	CATCCACGTGTTGGCTCA	ACTCACCTGCTGCTACTCA TTCACC
Mmp10	Mouse	TGTTGCTCTTCAGTATGTG TGT	CCAGGAATTGAGCCACAA GT	CGTCCTGGCATTGGGGTC AAACTC
Mmp12	Mouse	GCTCCTGCCTCACATCATA C	GGCTTCTCTGCATCTGTG AA	AGCTGTCTTTGACCCACTT CGCC
Mmp3	Mouse	TGTGGAGGACTTGTAGACT GG	GATGAACGATGGACAGA GGATG	TGGTTGCTGCTCATGAAC TGGC
Cdkn2a (p16)	Mouse	CTCTGCTCTTGGGATTGGC	GTGCGATATTTGCGTTCC G	TCCGCTGGGTGGTCTTTGT GTAC
Serpine1 (Pai1)	Mouse	CGTGTCAGCTCGTCTACA G	CTATGGTGAAACAGGTGG ACT	ACCTTTGGTATGCCTTTCC ACCCA
Tbp	Mouse	CCAGAACTGAAATCAACG CAG	TGTATCTACCGTGAATCT TGGC	ACTTGACCTAAAGACCATT GCACTTCGT
Tgfβ	Mouse	CCGAATGTCTGACGTATTG AAGA	GCGGACTACTATGCTAAA GAGG	ATAGATGGCGTTGTTGCGG TCCA
Tnf	Mouse	TCTTTGAGATCCATGCCGT TG	AGACCCTCACACTCAGAT CA	CCACGTCGTAGCAAACCAC CAAGT
Vcam1	Mouse	TGTGCAGTTGACAGTGACA	GCAAAGGACACTGGAAAA GAG	TTCAGGGAATGAGTAGACC TCCACCT
CCL2 (MCP1)	Human	GCCTCTGCACTGAGATCTT C	AGCAGCCACCTTCATTCC	TCAATGCCCCAGTCACCTG CT
CDKN1A (p21)	Human	GAGACTAAGGCAGAAGAT GTAGAG	GCAGACCAGCATGACAG AT	TTCTCTTGGAGAAGATCA GCCGG
CDKN2A (p16)	Human	TGAGCTTTGGTTCTGCCAT T	AGTGTCGACTTCATGAC AAG	TAGCAGTGTGACTCAAGAG AAGCCAGT
IL6	Human	CGGCTACATCTTTGGAATC TTC	GCCGAGCTATGAACTCCT TC	ACAAGCGCCTTCGGTCCA GTT
TBP	Human	TCGTGGCTCTCTTATCCTC AT	CAGTGAATCTTGTTGTA AACTTGA	CGCAGCAAACCGCTTGGG ATTAT
ACTA2	Human	GTGAAGAAGAGGACAGCA CTG	CCCATTCCCACCATCACC	n/a
COL1A1	Human	AAGGGACACAGAGGTTTC AGTGG	CAGCACCAGTAGCACCAT CATTTT	n/a
COL1A2	Human	CTTGACGTAACCTTATGCC TAGCA	CCCATCTAACCTCTCTAC CCAGTCT	n/a
FN1	Human	TGTCAGTCAAAGCAAGCC CG	TTAGGACGCTCATAAGTG TCACCC	n/a
GAPDH	Human	GGAAGGGCTCATGACCAC AG	ACAGTCTTCTGGGTGGCA GTG	n/a
STAT3	Human	GAGATTGACCAGCAGTATA GCC	CAATCTCCATTGGCTTCT CAAG	n/a

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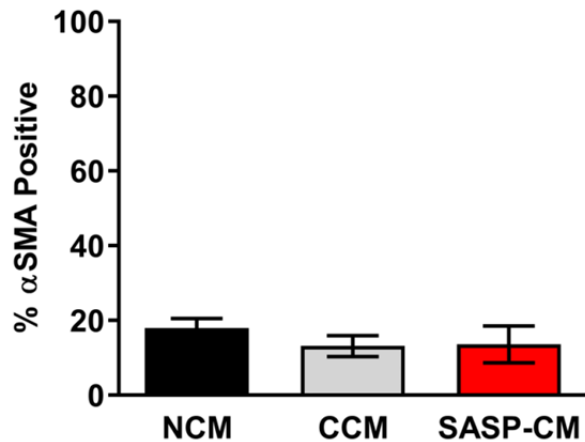
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Supplementary Figure 1.

Increased p16 expression correlates with reduced pulmonary and physical function.

p16 levels in lung specimens from control and IPF subjects were measured by microarray. Age-adjusted expression was compared to (a) forced vital capacity (FVC), (b) carbon monoxide diffusion capacity, and (c) SF12 PCS (control $n=54$, IPF $n=72$; Pearson correlation statistics are indicated).

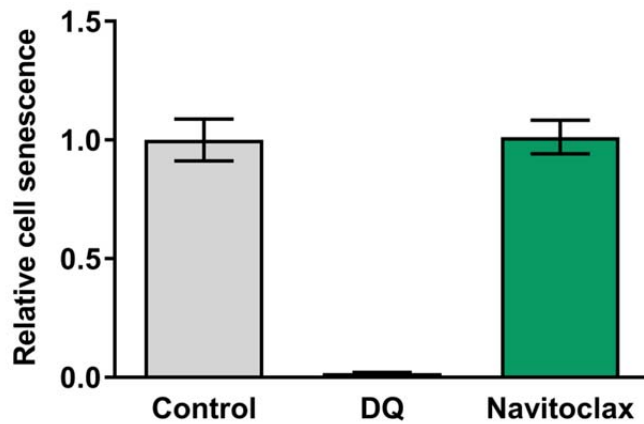


Supplementary Figure 2.

Senescent epithelial cell SASP does not induce αSMA in fibroblasts.

Normal bronchial epithelial cells were exposed to 5 Gy or sham conditions. Naïve IMR90 cells were treated with non-conditioned (NCM, black) or epithelial media collected 21-days post-irradiation (SASP-CM, red) or -sham exposure (gray). Following a 72 hour media treatment, the IMR90 cells were immunostained for αSMA and DAPI. Percentage αSMA positive cells were determined blindly, using a visual threshold (mean ± SEM; n=2 independent experiments).

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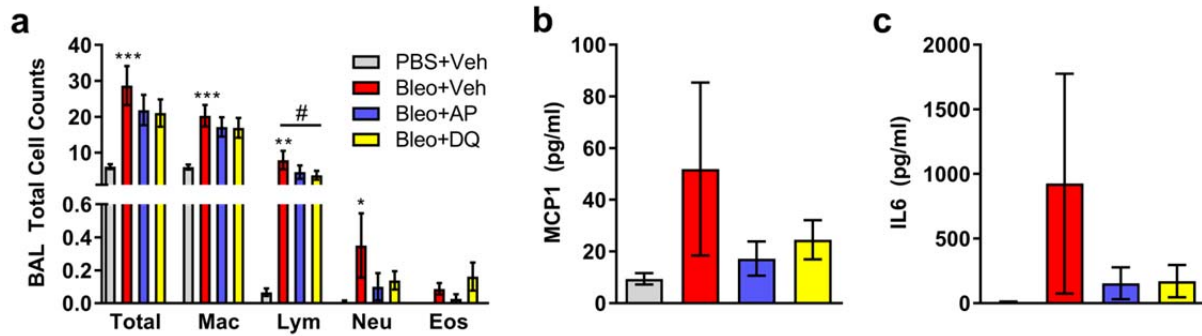
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34 **Supplementary Figure 3.**

35 DQ reduces cellular senescence in etoposide-treated IMR90 fibroblasts.

36 Senescent IMR90 fibroblasts were treated for 48 hours with 20 μ M D + 15 μ M Q (yellow) or 10
37 μ M navitoclax (green). Senescent cells were identified by staining for SA- β -gal activity, using
38 the fluorogenic C₁₂FDG substrate with an IN Cell 6000 microscope. Data are represented as the
39 percentage of SA- β -gal positive cells normalized to control (untreated) cells (gray) (mean $\pm$
40 SEM; n=2).

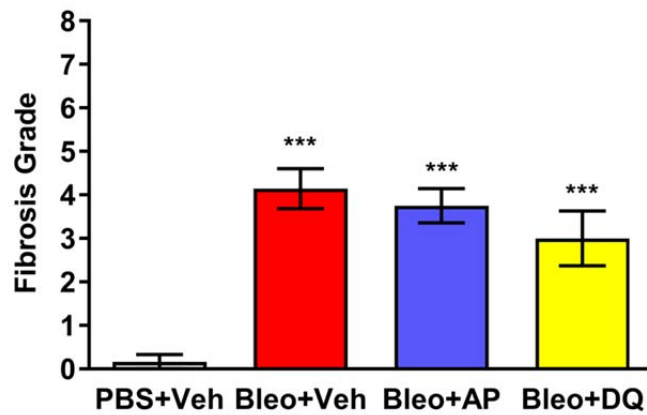
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Supplementary Figure 4.

Bleomycin-induced inflammation is attenuated by senescent cell clearance.

(a) Total and differential inflammatory cells were counted, and immunoassays were used to profile (b) MCP1 and (c) IL6 within BAL fluid. (Mac=macrophages, Lym=lymphocytes, Neu=neutrophils, Eos=eosinophils; mean $\pm$ SEM; PBS+Veh n=13 (gray), Bleo+Veh n=8 (red), Bleo+AP n=12 (blue), Bleo+DQ n=13 (yellow); linear regression model; ***p<0.0005, **p<0.005, *p $\leq$ 0.05, $\nless$ p=0.08, #p=0.1).



Supplementary Figure 5.

Fibrosis attenuation following senescent cell clearance is not significant.

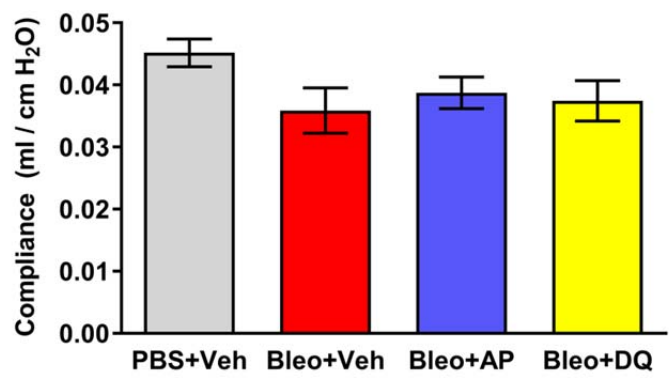
H&E- and MT-stained FFPE lung sections corresponding to the indicated groups were scored

by a blinded pathologist using a standardized, eight-tier Ashcroft scale.

(mean ± SEM; PBS+Veh n=12 (gray), Bleo+Veh n=7 (red), Bleo+AP n=12 (blue), Bleo+DQ=13

(yellow); ANOVA, ***p<0.0005).

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63 **Supplementary Figure 6.**

64 Lung compliance following senescent cell clearance initiated in late-stage pathology.

65 FlexiVent forced oscillation technique was used to assay lung compliance in Ink-Attac mice four

66 weeks post- bleomycin or PBS exposure following two weeks of Veh, AP, or DQ treatment.

67 (mean $\pm$ SEM; PBS+Veh n=6 (gray), Bleo+Veh n=13 (red), Bleo+AP n=15 (blue), Bleo+DQ=13

68 (yellow)).

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