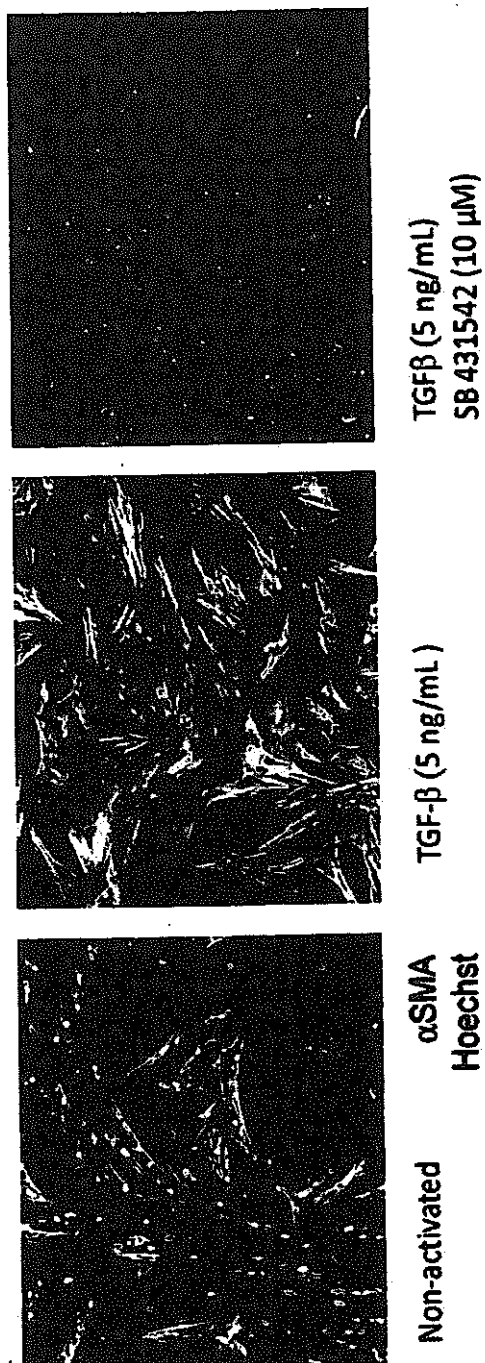


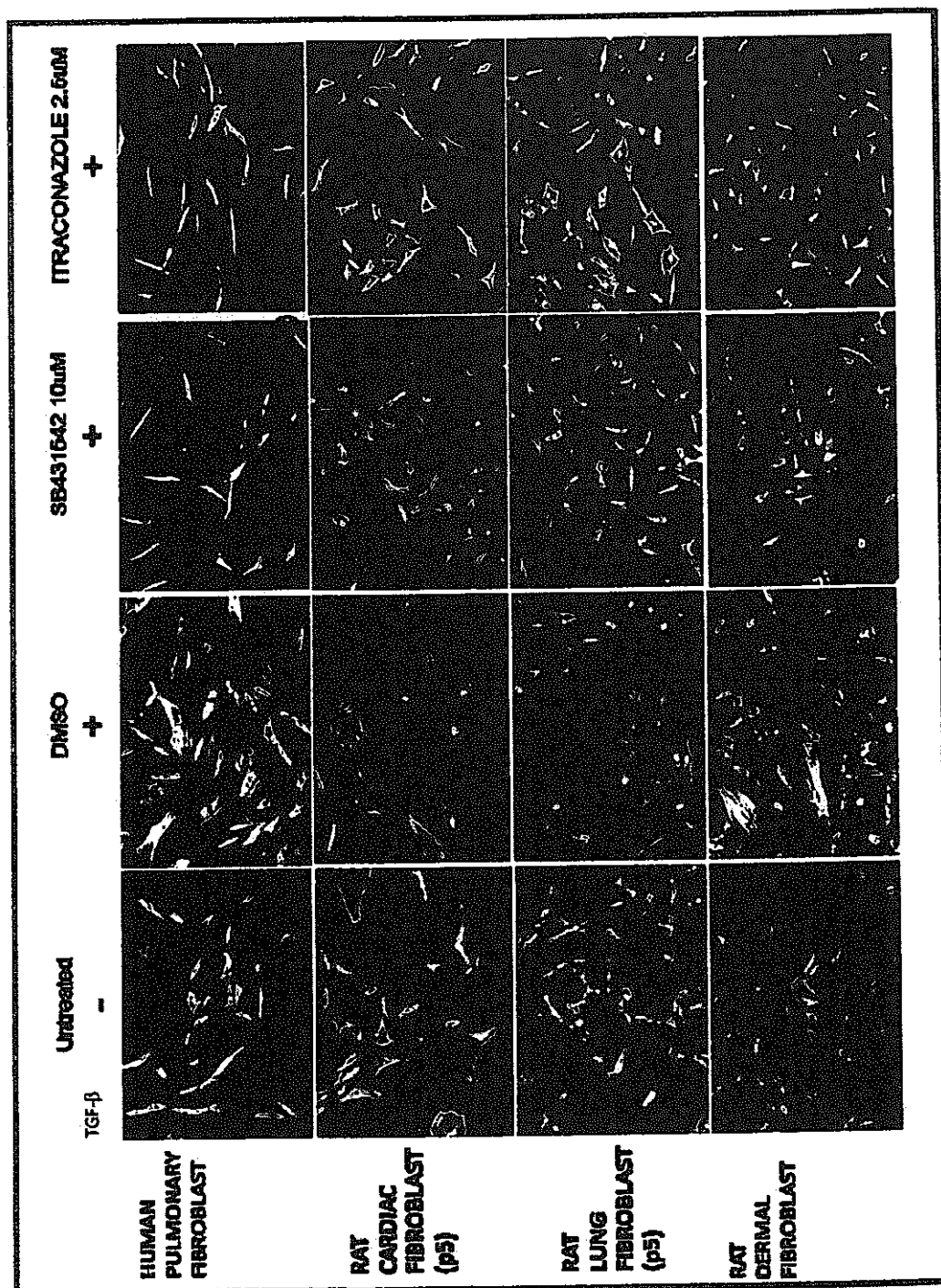
1/20

Figure 1



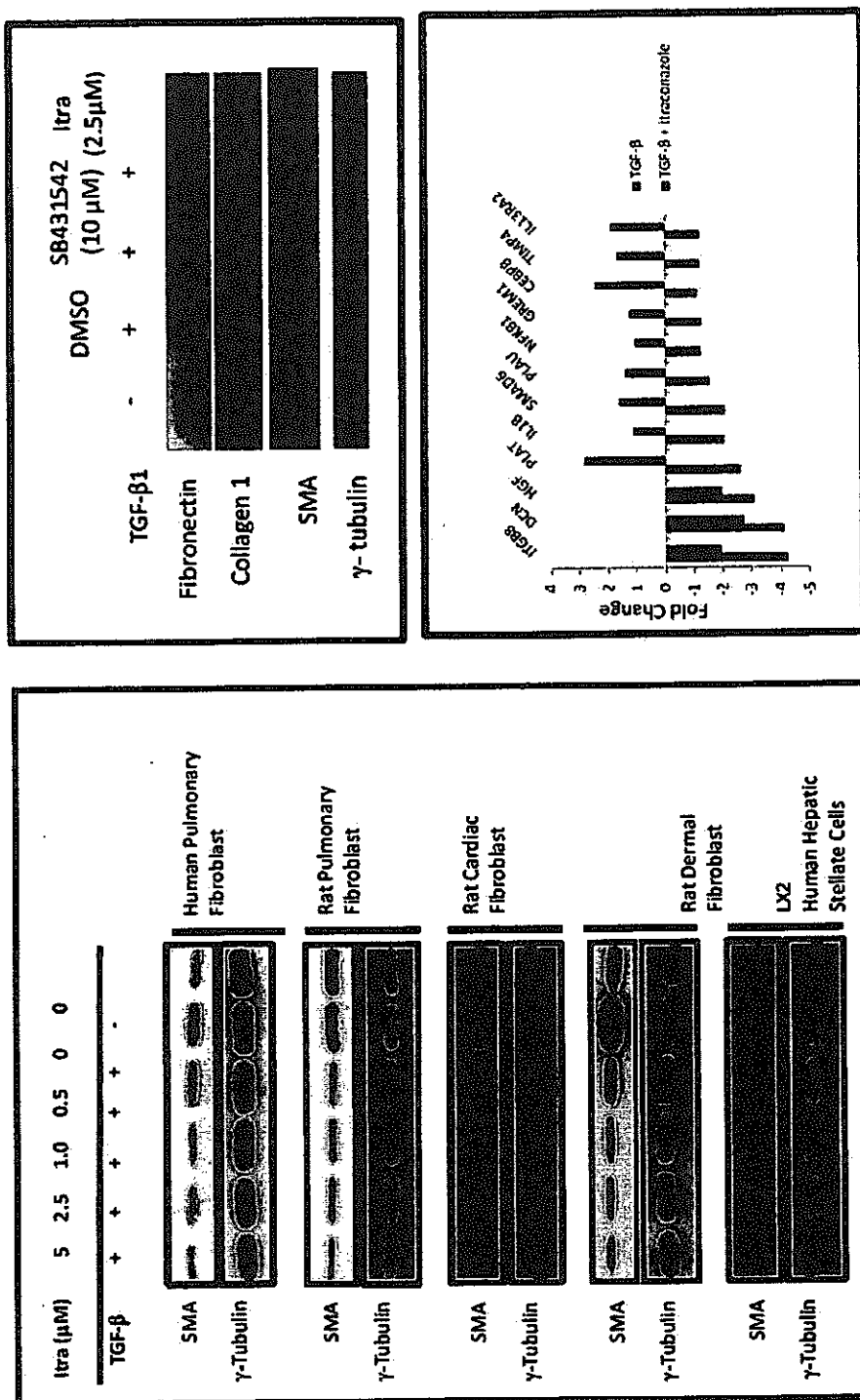
2/20

Figure 2



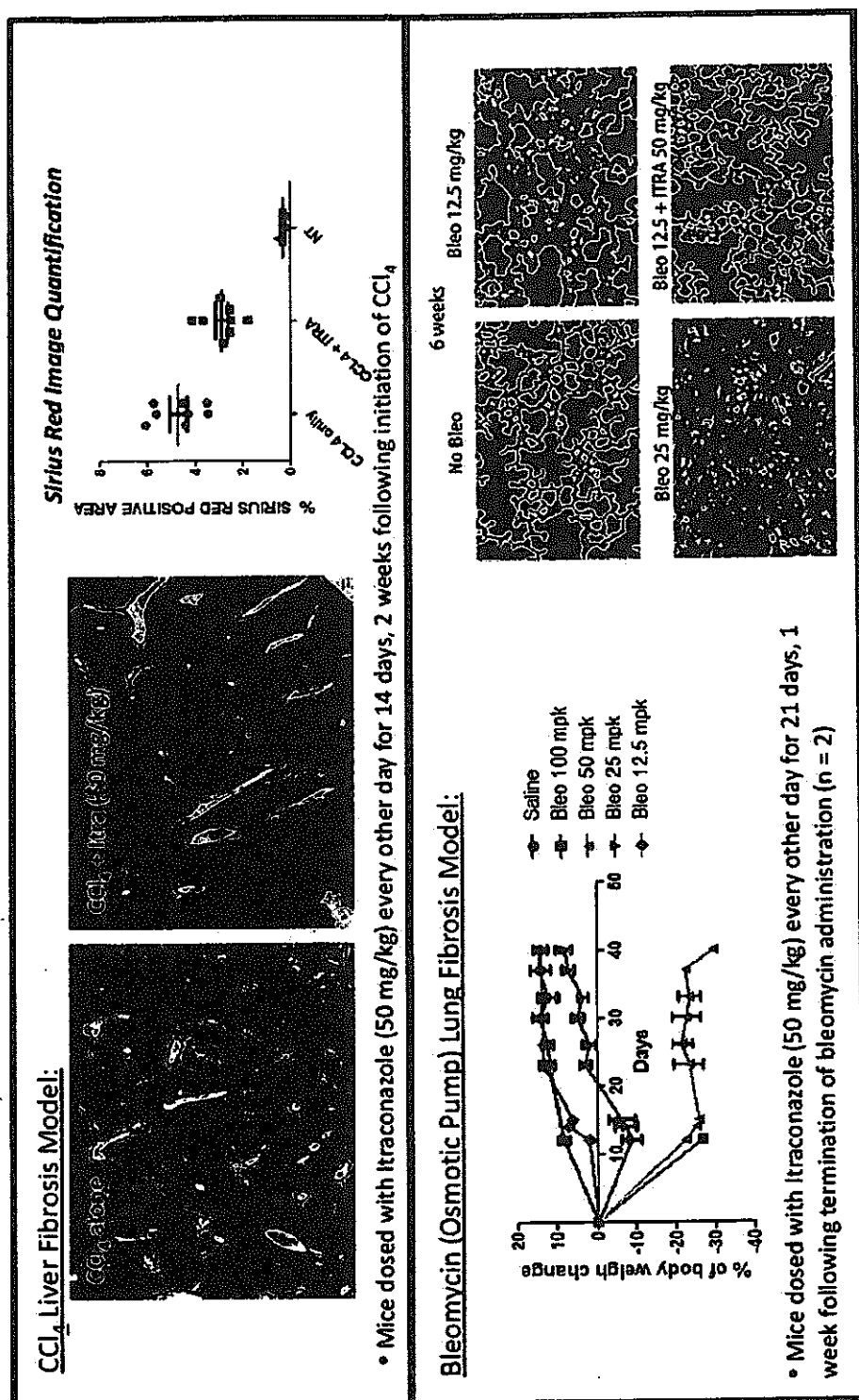
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Figure 3



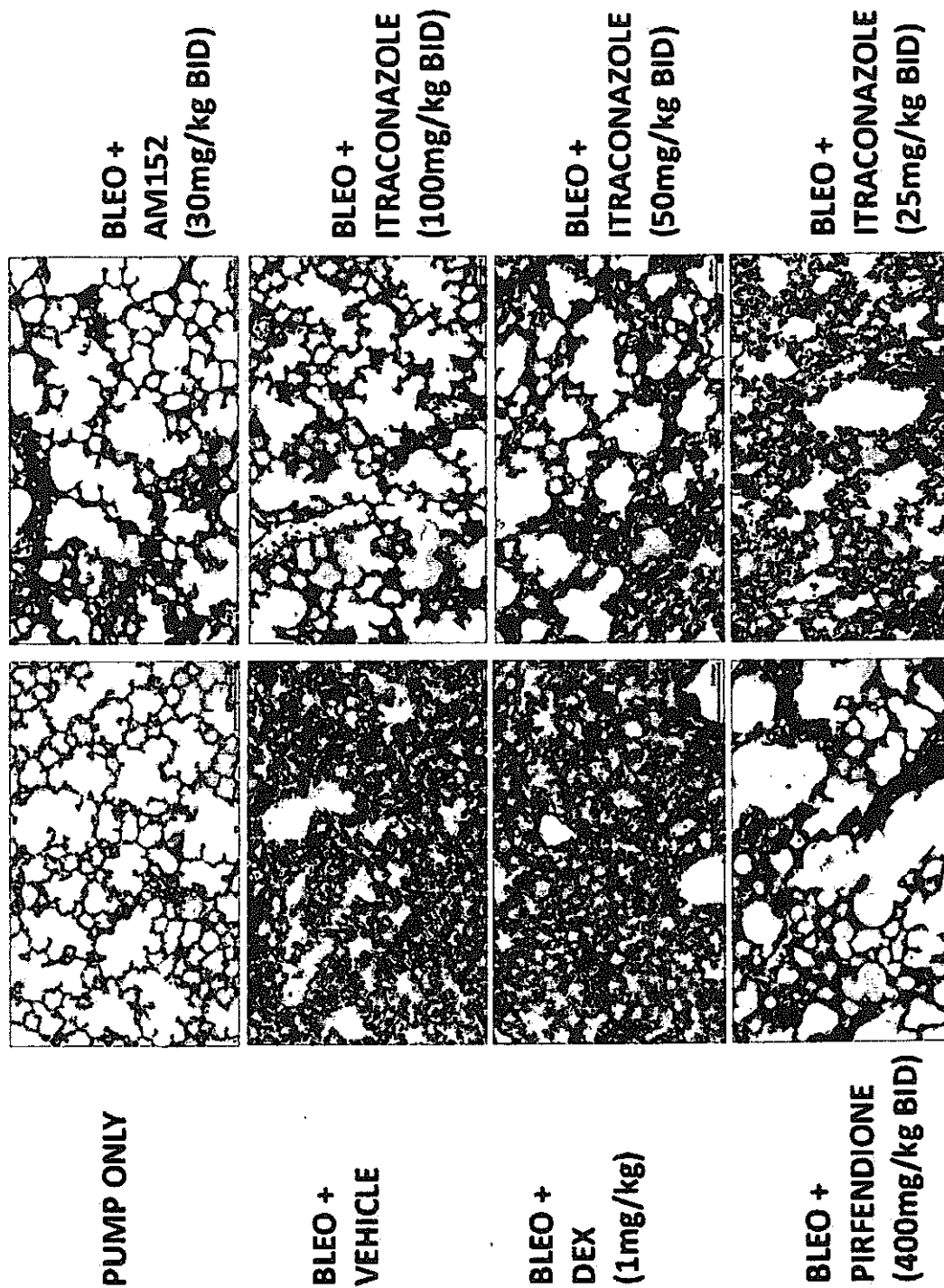
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Figure 4a



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Figure 4b



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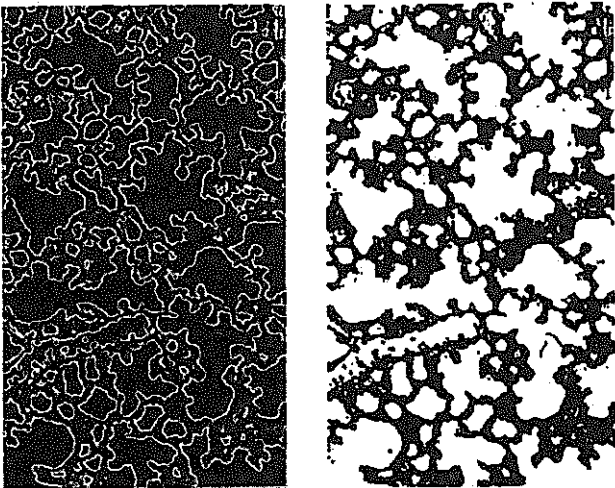
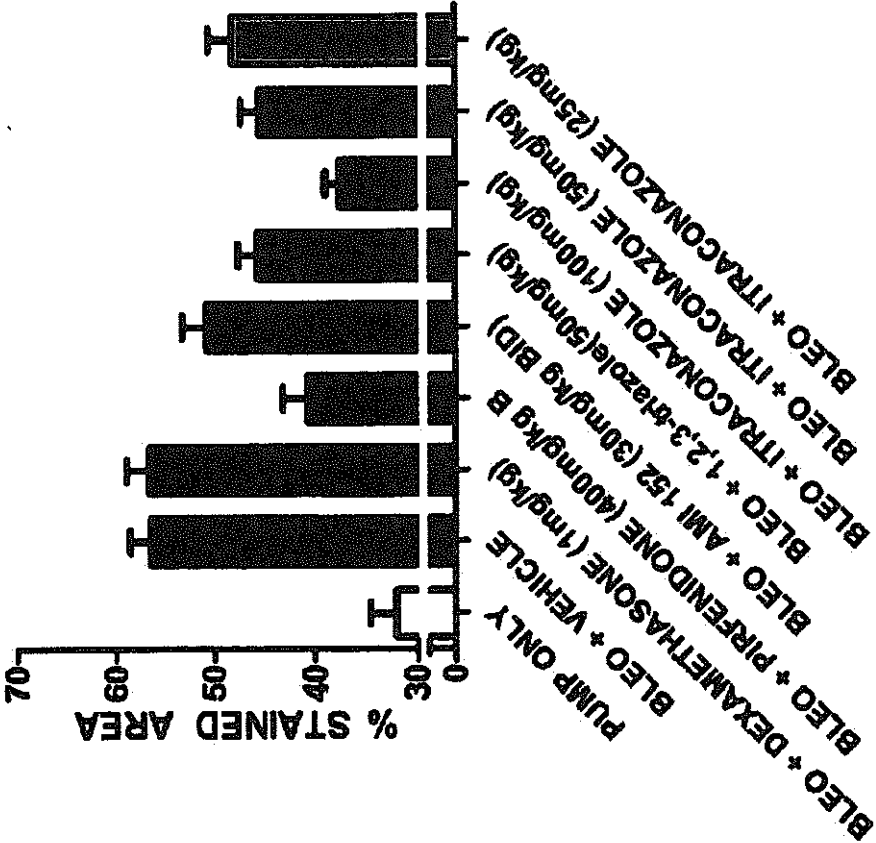


Figure 4c



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Figure 5

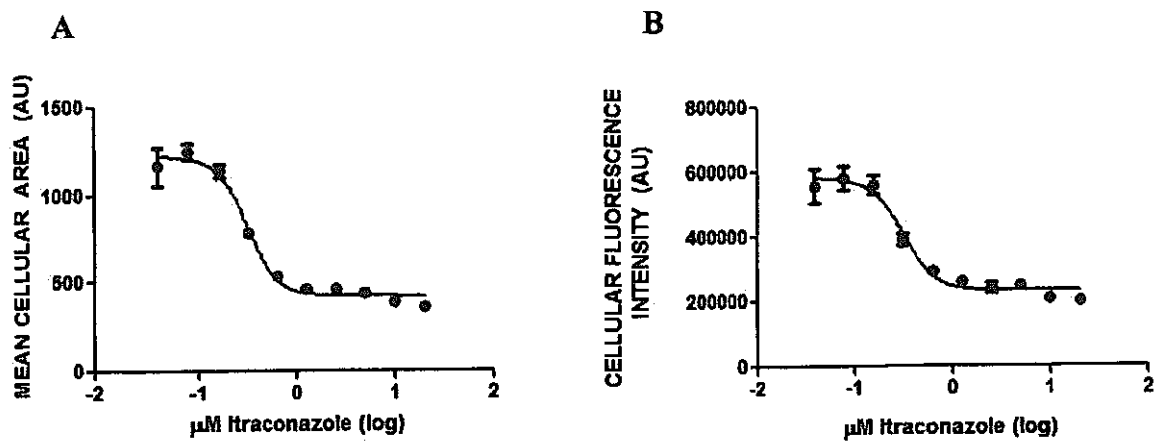
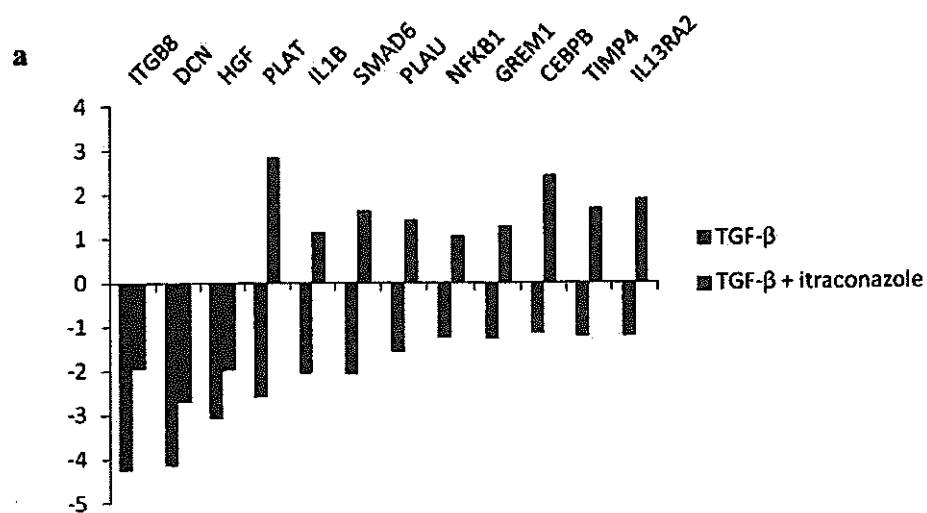


Figure 6

		DMSO	SB431542 (10 μM)	Itraconazole (2.5 μM)
TGF- β 1	-	+	+	+
Fibronectin				
Collagen 1				
Alpha smooth muscle actin				
γ - tubulin				

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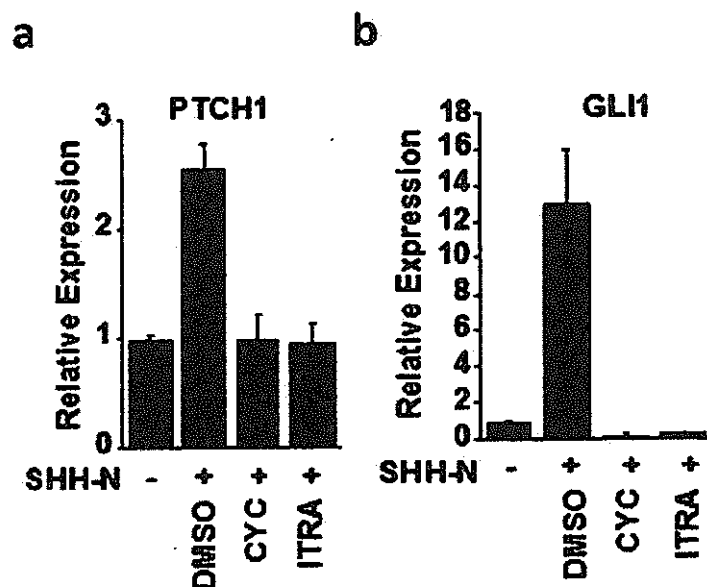
Figure 7

**b**

	TGF- β	TGF- β + CBR-034-1
ITGB8	-4.26	-1.96
DCN	-4.14	-2.72
HGF	-3.09	-2.00
PLAT	-2.61	2.84
IL1B	-2.06	1.15
SMAD6	-2.11	1.61
PLAU	-1.58	1.41
NFKB1	-1.26	1.05
GREM1	-1.28	1.28
CEBPB	-1.16	2.44
TIMP4	-1.25	1.67
IL13RA2	-1.25	1.90

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Figure 8



c

PTCH1 gene expression				
Hh Induction Stimulus	Inhibitor	Average RLQ	Standard Deviation	N
Untreated	Untreated	1.00	0.03	3
Shh-N (1mg/mL)	DMSO	2.55	0.24	3
Shh-N (1mg/mL)	5μM Cyclopamine	1.00	0.22	3
Shh-N (1mg/mL)	1μM Itraconazole	0.96	0.18	3

GLI1 gene expression				
Hh Induction Stimulus	Inhibitor	Average RLQ	Standard Deviation	N
Untreated	Untreated	1.00	0.04	3
Shh-N (1mg/mL)	DMSO	13.00	2.92	3
Shh-N (1mg/mL)	5μM Cyclopamine	0.21	0.15	3
Shh-N (1mg/mL)	1μM Itraconazole	0.32	0.02	3

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Figure 9

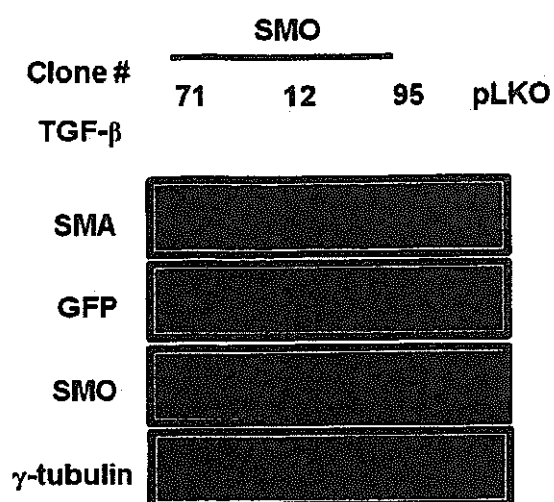


Figure 10

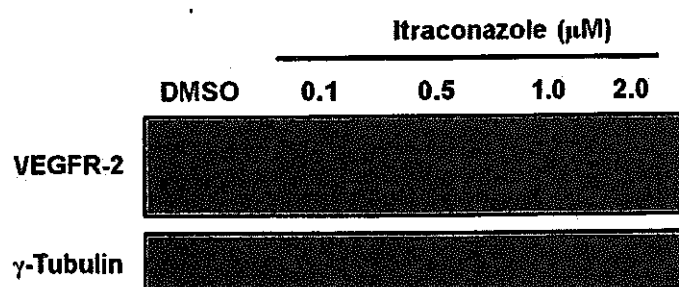
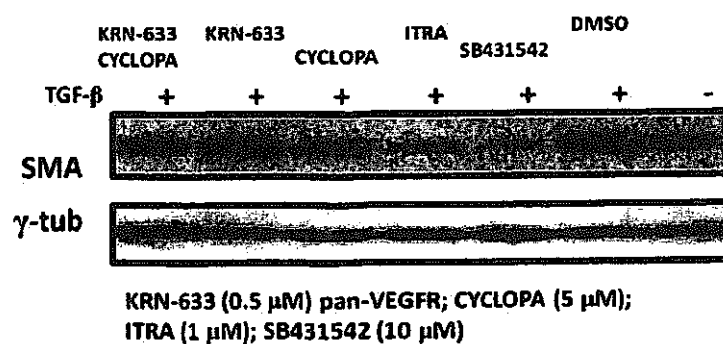


Figure 11



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Figure 12

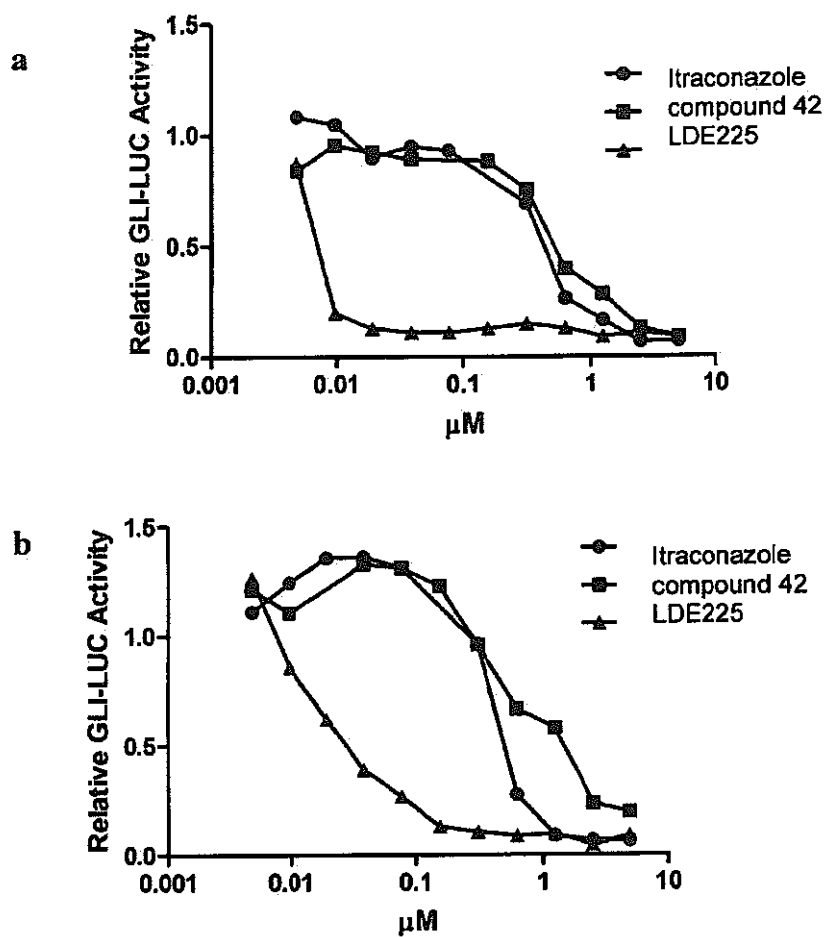


Figure 13

	SMO	FLT1 (VEGFR1)	KDR (VEGFR2)	
Clone #	65	31 32	86	87 pLKO
SMA				
γ-tubulin				

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Figure 14

Experimental groups:

- A- Vehicle implantation
- B-25 mg/kg Bleo + Vehicle 1 (45% beta-cyclodextrin) SID
- C-25 mg/kg Bleo + Vehicle 2 (0.5% MC/0.5% Tween-80) BID
- D-25 mg/kg Bleo + ltra 5 mg/kg SID
- E-25 mg/kg Bleo + ltra 10 mg/kg SID
- F-25 mg/kg Bleo + ltra 25 mg/kg SID
- G-25 mg/kg Bleo + ltra 50 mg/kg SID
- H-25 mg/kg Bleo + Cmpd #42 @ 5 mg/kg SID
- I-25 mg/kg Bleo + Cmpd #42 @ 10 mg/kg SID
- J-25 mg/kg Bleo + Cmpd #42 @ 25 mg/kg SID
- K-25 mg/kg Bleo + Cmpd #42 @ 50 mg/kg SID
- L-25 mg/kg Bleo + Pifenidone 400 mg/kg BID
- M-25 mg/kg Bleo + AMI 152 30 mg/kg BID

Experimental design:

- 104 - 9wk old B6 male mice (Taconic Farms); n=8/ group
- 2 days prior: weigh & single house male B6 mice, 104 total, 8 per group.
- Day 1- Weigh, fill 25 mg/kg bleo into 200ul 7 days Alzet Osmotic pump, prime the filled pumps
- Day 1-2: Surgically implant pumps, 8 mice with saline, 96 mice with bleo.
- Day 1-10: Post surgery monitoring/weigh mice 3 times per week
- Day 17-31: Drug treatment
- Day 30: Bleed at 1, 4, 8, 24 hours after the second last dosing.
- Day 31: Euthanize animals and collect multiple organs. Half of the lungs will be fixed for histology study, half of the lungs will be collected on liquid N2 and stored in -80 for biochemical study. One piece of skin will be fixed for histological study and another piece of skin will be collected on liquid N2 and stored in -80 for biochemical study.

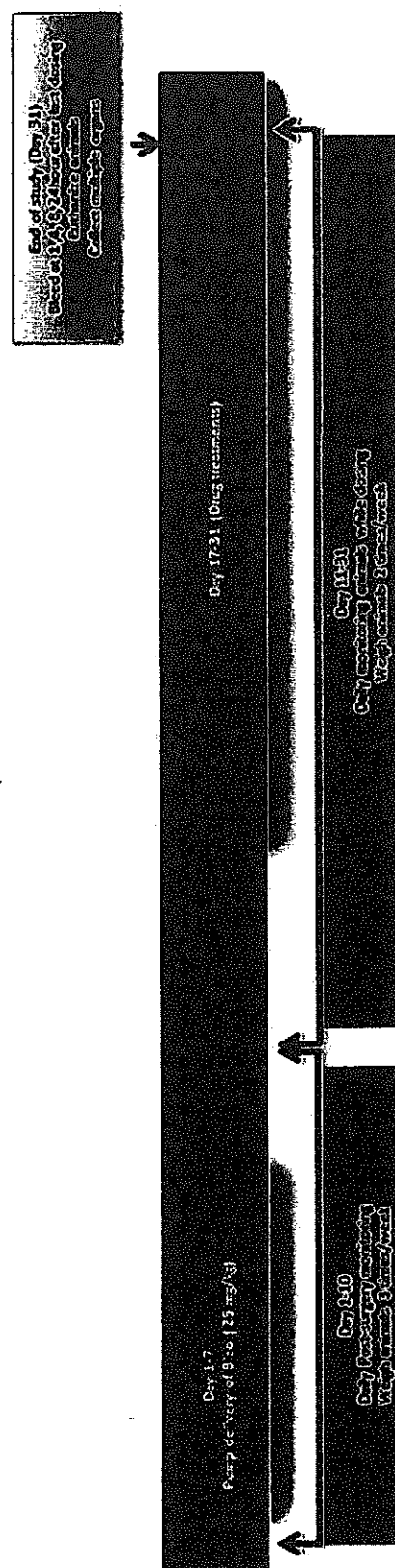
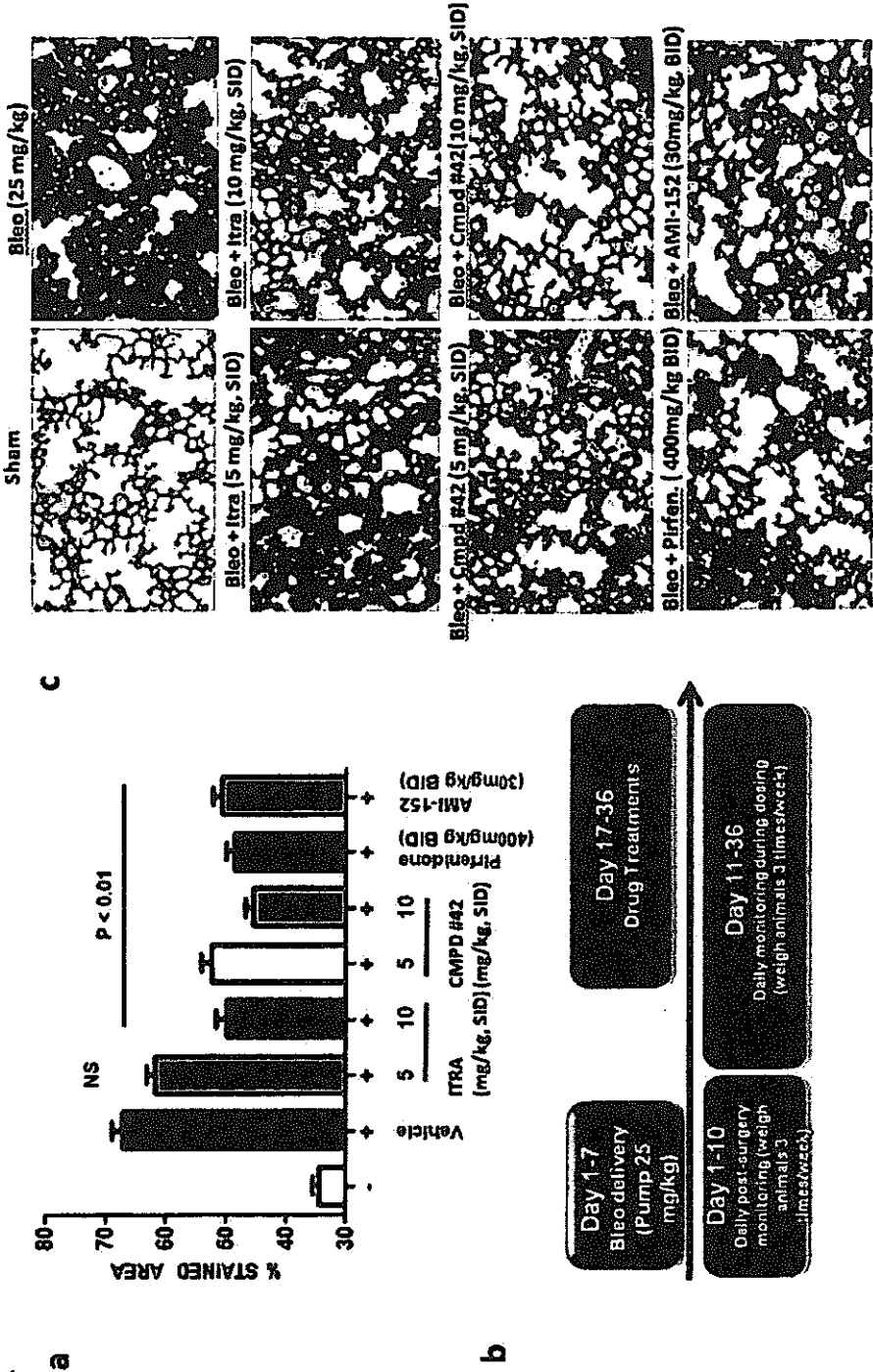


Figure 15



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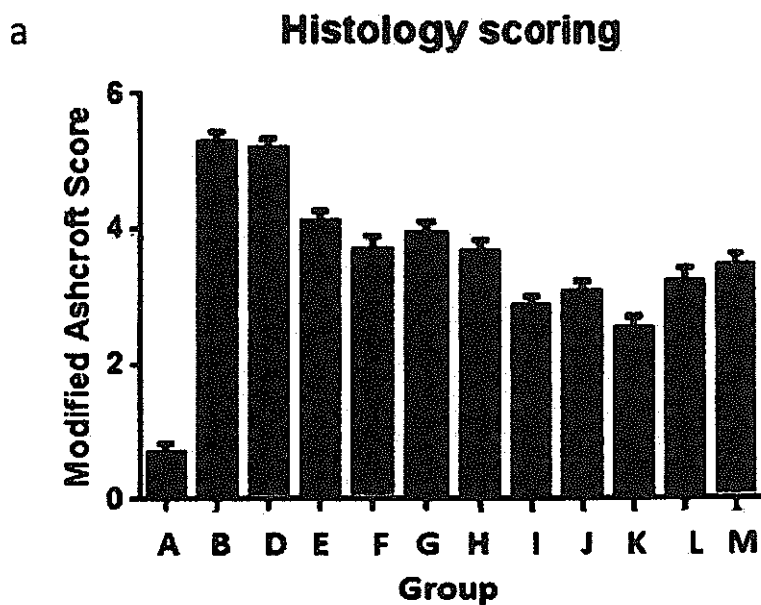
Figure 16

Characterization of the Modified Ashcroft Scale

Grade of fibrosis	Modified Ashcroft Scale
0	Alveolar septa: No fibrotic burden at the most flimsy small fibers in some alveolar walls Lung structure: Normal lung
1	Alveolar septa: Isolated gentle fibrotic changes (septum $\leq 3\times$ thicker than normal) Lung structure: Alveoli partly enlarged and rarefied, but no fibrotic masses present
2	Alveolar septa: Clearly fibrotic changes (septum $> 3\times$ thicker than normal) with knot-like formation but not connected to each other Lung structure: Alveoli partly enlarged and rarefied, but no fibrotic masses
3	Alveolar septa: Contiguous fibrotic walls (septum $> 3\times$ thicker than normal) predominantly in whole microscopic field Lung structure: Alveoli partly enlarged and rarefied, but no fibrotic masses
4	Alveolar septa: Variable Lung structure: Single fibrotic masses ($\leq 10\%$ of microscopic field)
5	Alveolar septa: Variable Lung structure: Confluent fibrotic masses ($> 10\%$ and $\leq 50\%$ of microscopic field). Lung structure severely damaged but still preserved
6	Alveolar septa: Variable, mostly not existent Lung structure: Large contiguous fibrotic masses ($> 50\%$ of microscopic field). Lung architecture mostly not preserved
7	Alveolar septa: Non-existent Lung structure: Alveoli nearly obliterated with fibrous masses but still up to five air bubbles
8	Alveolar septa: Non-existent Lung structure: Microscopic field with complete obliteration with fibrotic masses

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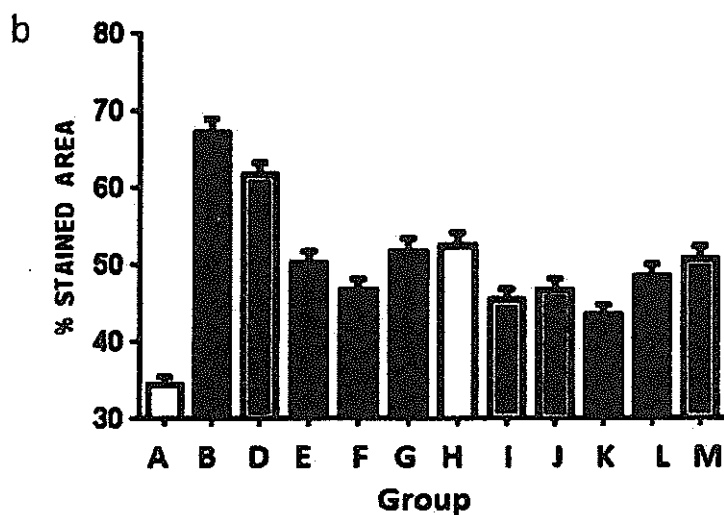
Figure 17a



A- Vehicle Implantation
 B-25 mg/kg Bleo + Vehicle 1 (45% beta-cyclodextrin) SID
 D-25 mg/kg Bleo + Itraconazole 5 mg/kg SID
 E-25 mg/kg Bleo + Itraconazole 10 mg/kg SID
 F-25 mg/kg Bleo + Itraconazole 25 mg/kg SID
 G-25 mg/kg Bleo + Itraconazole 50 mg/kg SID
 H-25 mg/kg Bleo + Cmpd #42 @ 5 mg/kg SID
 I-25 mg/kg Bleo + Cmpd #42 @ 10 mg/kg SID
 J-25 mg/kg Bleo + Cmpd #42 @ 25 mg/kg SID
 K-25 mg/kg Bleo + Cmpd #42 @ 50 mg/kg SID
 L-25 mg/kg Bleo + Pifenidone 400 mg/kg BID
 M-25 mg/kg Bleo + AMI 152 30 mg/kg BID

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Figure 17b



A- Vehicle implantation

B-25 mg/kg Bleo + Vehicle 1 (45% beta-cyclodextrin) SIDD-25 mg/kg Bleo + Itraconazole 5 mg/kg SIDE-25 mg/kg Bleo + Itraconazole 10 mg/kg SIDF-25 mg/kg Bleo + Itraconazole 25 mg/kg SIDG-25 mg/kg Bleo + Itraconazole 50 mg/kg SIDH-25 mg/kg Bleo + #42 @ 5 mg/kg SIDI-25 mg/kg Bleo + Cmpd #42 @ 10 mg/kg SIDJ-25 mg/kg Bleo + Cmpd #42 @ 25 mg/kg SIDK-25 mg/kg Bleo + Cmpd #42 @ 50 mg/kg SIDL-25 mg/kg Bleo + Pifenidone 400 mg/kg BIDM-25 mg/kg Bleo + AMI 152 30 mg/kg BID

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Figure 18

Experimental groups:

- A-0.4 ml/kg CCl₄ + non treatment, n=8
- B-0.4 ml/kg CCl₄ + itraconazole, 10 mg/kg, SID, n=8
- C-0.4 ml/kg CCl₄ + itraconazole, 20 mg/kg, SID, n=8
- D-0.4 ml/kg CCl₄ + itraconazole, 50 mg/kg, SID, n=8

Experimental design:

- 32 - 9wk old B6 male mice (Taconic Farms); n=8/group
- 2 days prior: weigh & sort male B6 mice, 320 total, 8 per group
- Day 1- 35: 0.4 ml/kg CCl₄ diluted in olive oil or olive oil alone will be given i.p. at 5ml/kg twice a week for 5 weeks.
- Day 15-35: Drug treatment
- Day 36: Euthanize animals and collect livers. Half of the livers will be fixed for histology study, another half will be collected on liquid N₂ and stored in -80 for biochemical study.

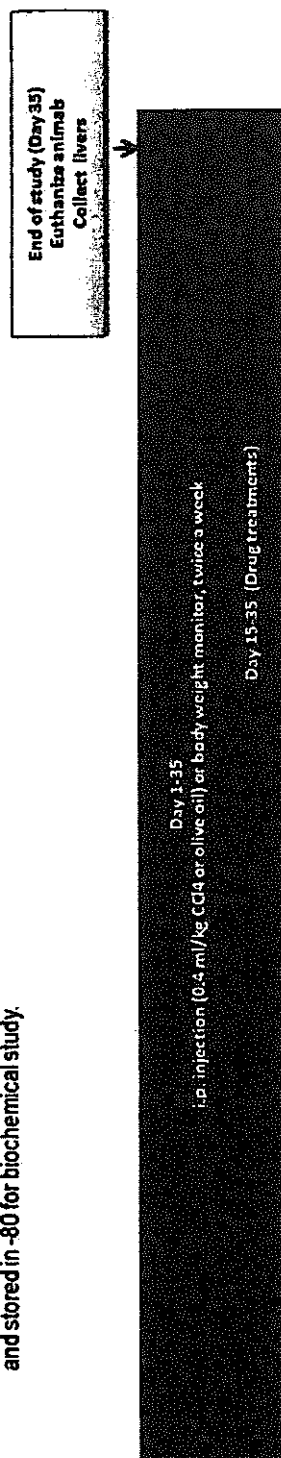
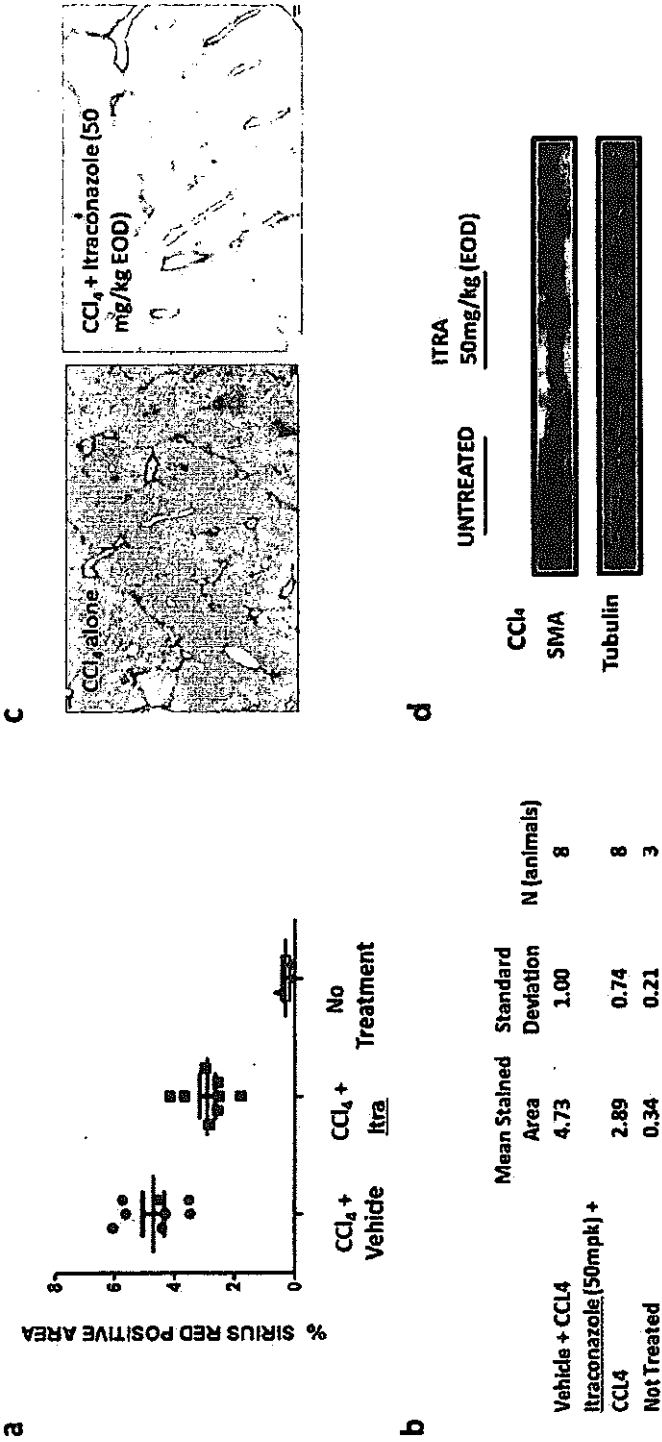
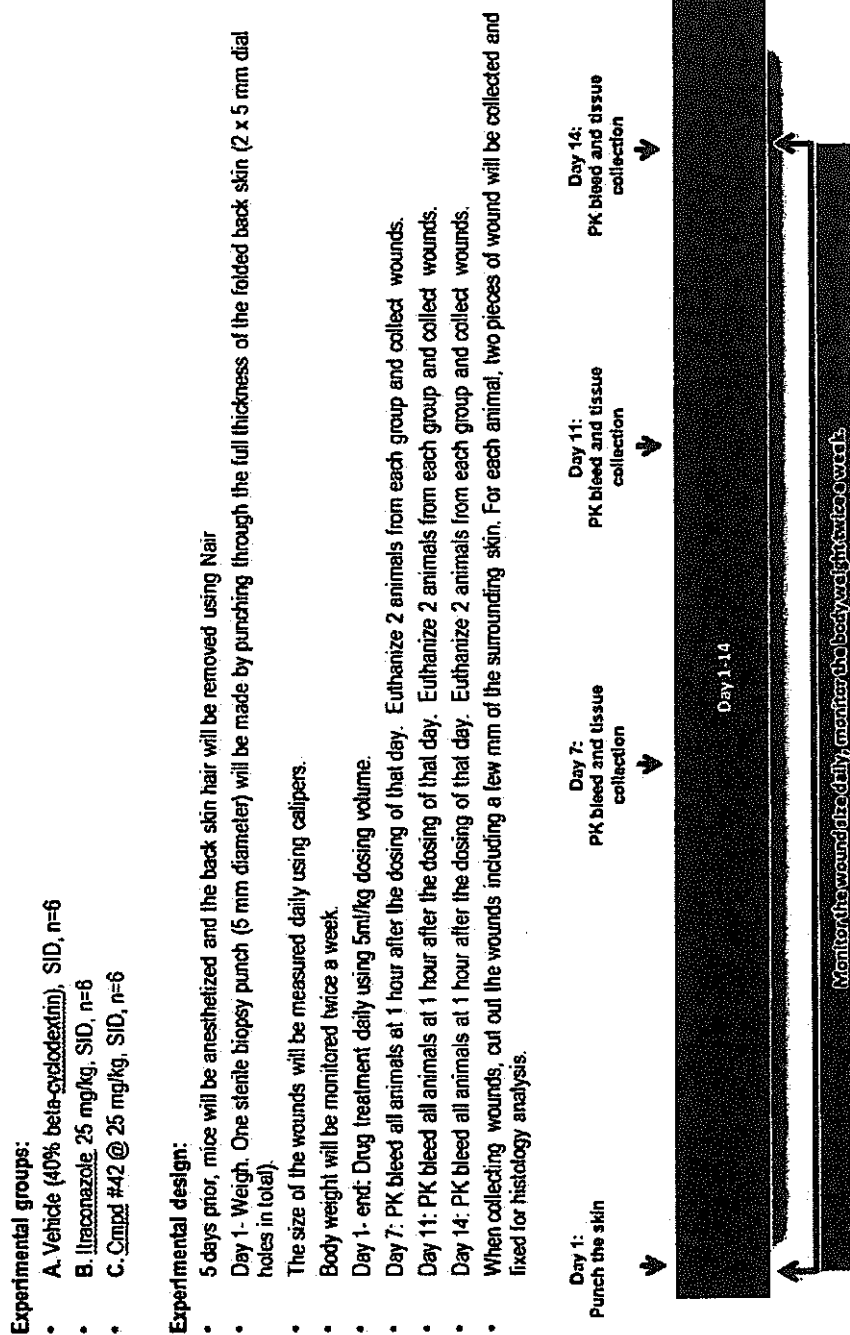


Figure 19



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Figure 20



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Figure 21

