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## RATIONALE: Cav-1 regulates homeostasis; down in IPF

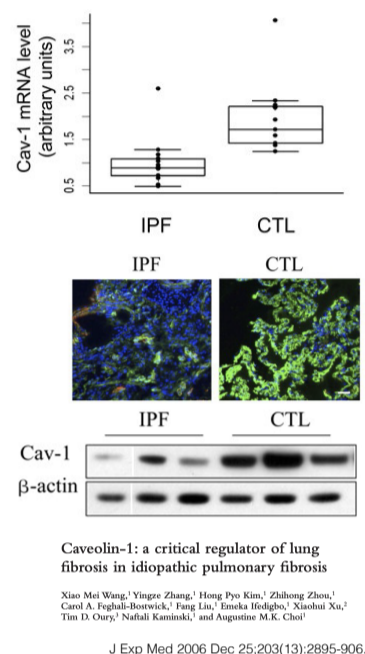
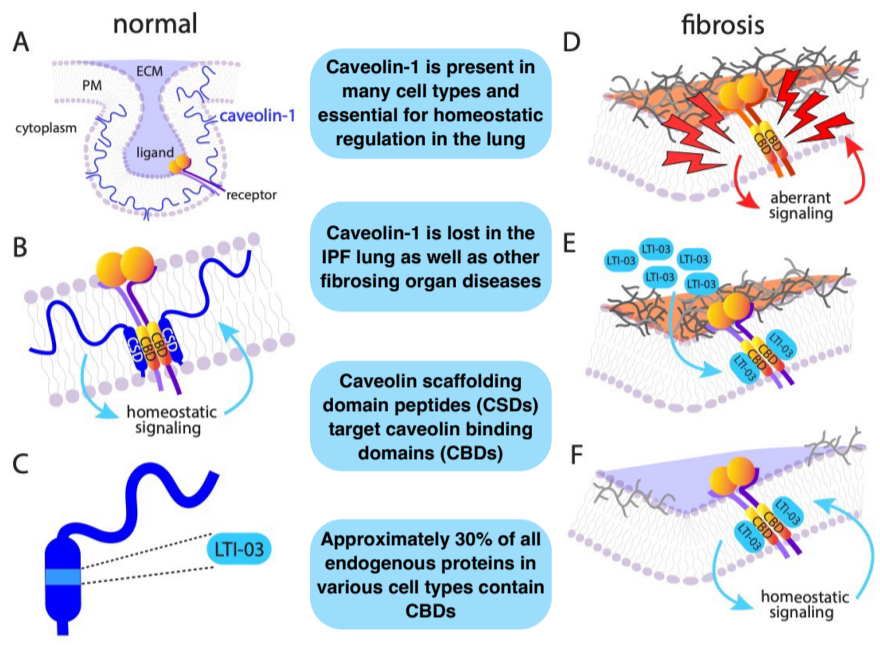
## METHODS: IPF PCLS

**1** Caveolin-1 protein is lost in the fibrotic lung; LTI-03 replaces the homeostatic regulator domain (CSD) of Cav-1

**2** Cav-1 mRNA and protein is down in IPF

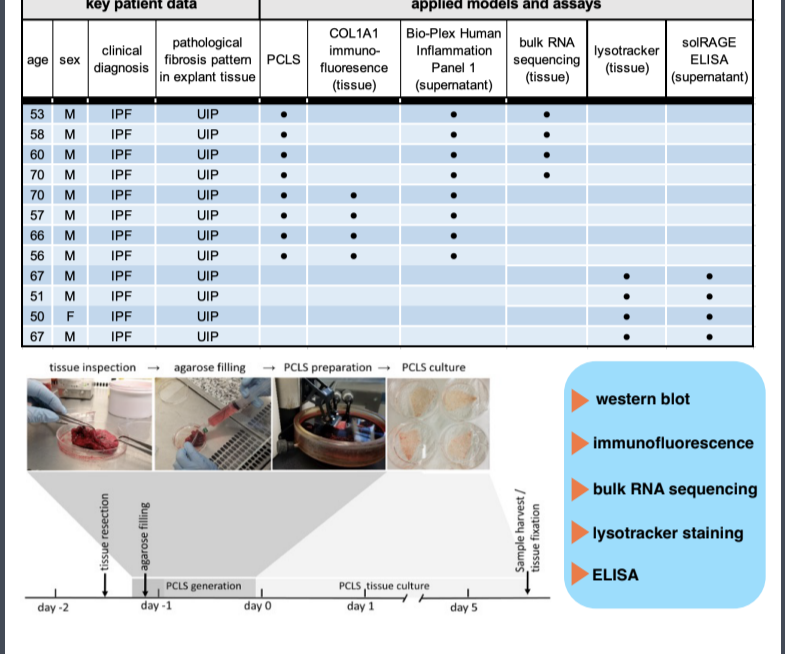
**3** Proteins containing CBD domains are targets of LTI-03 and Nintedanib

**4** PCLS were generated from end-stage IPF patients, cultured ex vivo, treated with LTI-03 every 12 hours up to 7 days



GENE	UNIPROT	CBD motif 1 (φXφXXXφXXφ)	CBD motif 2 (φXXXXφXXφ)	mixed domain (φXφXXXφXXφ)	Nintedanib targets
FGF2	P09038	0	1	0	
FGF5	P12034	0	1	0	
FGF8	P55075	0	1	0	
FGF9	P31371	0	1	0	
FGF11	Q92914	0	1	0	
FGF12	P61328	1	1	0	
FGF13	Q92913	1	1	0	
FGF14	Q92915	1	1	0	
FGF16	O43320	0	1	0	
FGF20	Q9NP95	0	4	0	
FGFR1	P11362	2	1	1	
FGFR2	P21802	1	1	1	
FGFR3	P22607	1	1	1	
FGFR4	P22455	1	1	1	
FZD1	Q9UP38	1	0	0	
FZD2	Q14332	1	0	0	
FZD4	Q9ULV1	1	2	1	
FZD5	O75084	1	0	0	
FZD6	Q9H461	3	0	0	
FZD7	O01144	1	2	1	
FZD10	Q9ULW2	0	1	0	
PCPFA	P16234	1	3	1	
PGFRB	P09619	1	2	1	
VGFR1	P17948	3	1	1	
VGFR3	P35916	2	2	1	

In silico identification of caveolin-1 binding domains in human proteome. CBD motif 1 (φXφXXXφXXφ), CBD motif 2 (φXXXXφXXφ), and the CBD composite motif (φXφXXXφXXφ) were identified using the MOTIF Search tool (setting: nr-aa) available on GenomeNet (genome.jp). The symbol 'φ' represents either Tryptophan (Trp - W), Phenylalanine (Phe - F), or Tyrosine (Tyr - Y), while X is any other amino acid. These sequences were used as queries to identify protein sequences containing CBDs.

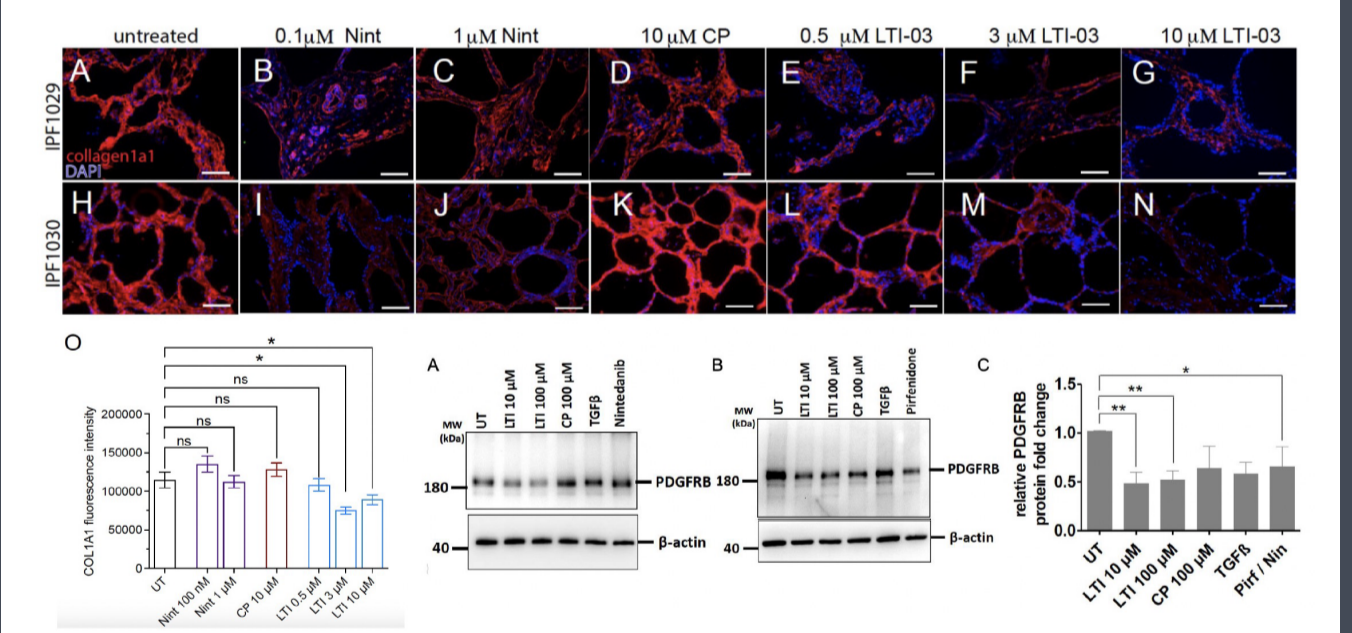
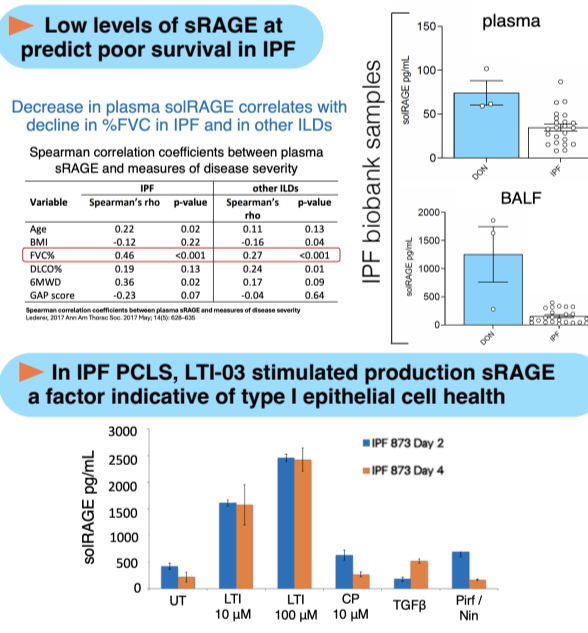
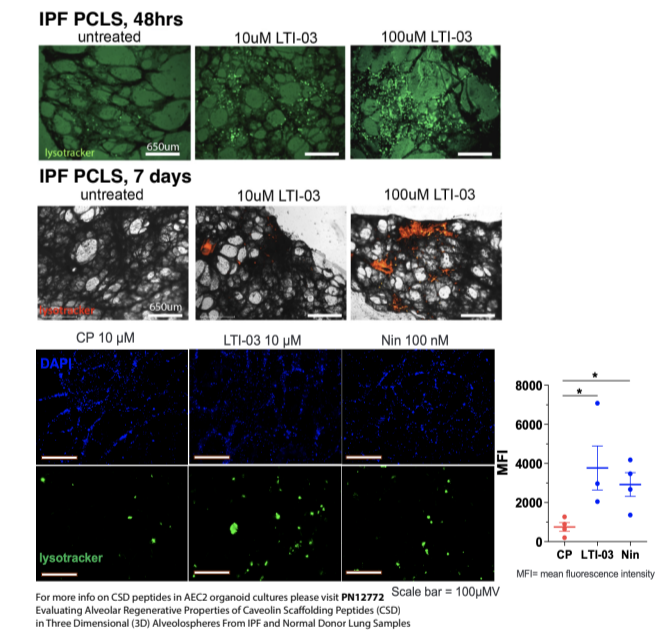


## DATA: LTI-03 is anti-fibrotic and supports epithelium in end-stage IPF PCLS

**5** LTI-03 increased lysotracker staining as well as pro-SPC, ABCA3 and KI-67 positive cells

**6** Decreased solRAGE in IPF plasma and BAL; increased post LTI-03 in IPF PCLS

**7** LTI-03 decreased COL1A1 and PDGFRB expression in end-stage IPF PCLS

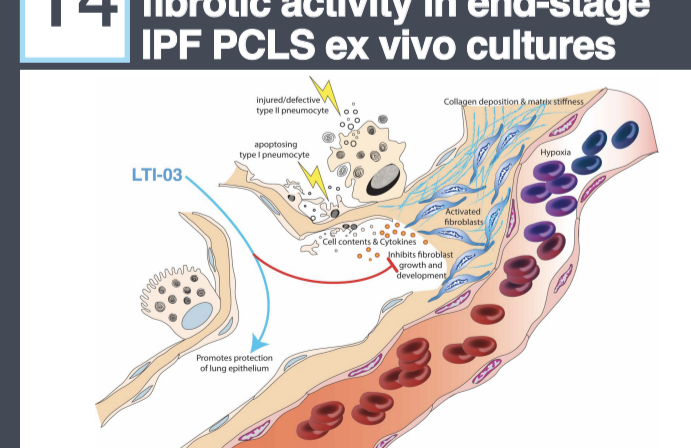
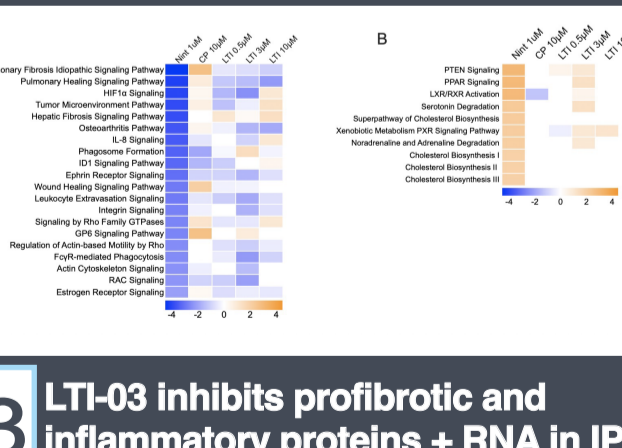
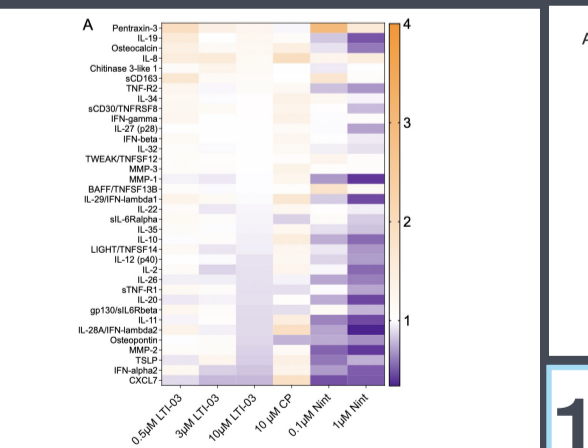
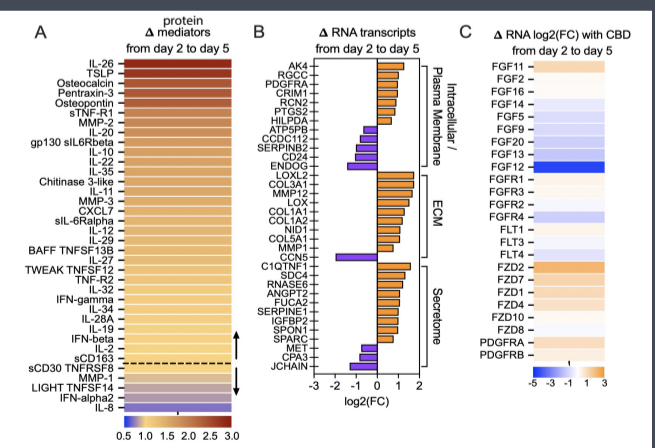


**8** Progressive fibrotic activity was observed in IPF PCLS cultures over 5 days

**9** LTI-03 inhibits profibrotic and inflammatory proteins +5 days of treatment

**10** Canonical pathways modulated by Nintedanib or LTI-03 treatment of cultured IPF PCLS

## SUMMARY



**11** Expression of upstream regulators of fibrotic signaling in IPF PCLS treated with CP, Nintedanib or LTI-03

**12** Disease pathways related to fibrotic signaling in IPF PCLS treated with CP, Nintedanib or LTI-03

**13** LTI-03 inhibits profibrotic and inflammatory proteins + RNA in IPF PCLS following 2 days of treatment

**14** LTI-03 demonstrates anti-fibrotic activity in end-stage IPF PCLS ex vivo cultures

