Clinical Perspectives on Treating Idiopathic Pulmonary Fibrosis

February 15th 2024

Forward-Looking Statements

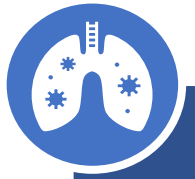
This presentation and various remarks we make during this presentation may contain forward-looking statements of Aileron Therapeutics, Inc. (“Aileron”, the “Company”, “we”, “our” or “us”) within the meaning of the Private Securities Litigation Reform Act of 1995, including statements with respect to: the timing and expectation of the results of the Phase 1b study of LTI-03; future expectations, plans and prospects for the Company following the merger transaction between the Company and Lung Therapeutics, Inc. that closed in the fourth quarter of 2023 (the “Merger”); the use of proceeds from the private placement conducted concurrently with the Merger; the sufficiency of the Company’s cash resources; stockholder approval of the conversion of the non-voting preferred stock; the benefits of the Merger; certain milestones of the Company; the projected cash runway of the Company; the status and plans for clinical trials, including the timing of data; future product development; and the potential commercial opportunity of LTI-03 and LTI-01. We use words such as “anticipate,” ”believe,” “estimate,” “expect,” “hope,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “would,” “can,” “could,” “should,” “continue,” and other words and terms of similar meaning to help identify forward-looking statements, although not all forward-looking statements contain these identifying words. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including risks and uncertainties related to the ability to recognize the anticipated benefits of the Merger, the ability to maintain the listing of the common stock of the Company on The Nasdaq Stock Market, changes in applicable laws or regulations, the possibility that the Company may be adversely affected by other economic, business, and/or competitive factors, including risks inherent in pharmaceutical research and development, such as: adverse results in the Company’s drug discovery, preclinical and clinical development activities, the risk that the results of preclinical studies and early clinical trials may not be replicated in later clinical trials, the Company’s ability to enroll patients in its clinical trials, and the risk that any of its clinical trials may not commence, continue or be completed on time, or at all; decisions made by the U.S. FDA and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies with respect to our development candidates; our ability to obtain, maintain and enforce intellectual property rights for our platform and development candidates; our potential dependence on collaboration partners; competition; uncertainties as to the sufficiency of the Company’s cash resources to fund its planned activities for the periods anticipated and the Company’s ability to manage unplanned cash requirements; and general economic and market conditions; as well as the risks and uncertainties discussed in the “Risk Factors” section of the Company’s Annual Report on Form 10-K for the year ended December 31, 2022, which is on file with the United States Securities and Exchange Commission (the “SEC”), the risks and uncertainties discussed under the heading "Risk Factors" of Company's Current Report on Form 8-K filed with the SEC on January 25, 2024, and in subsequent filings that the Company files with the SEC. These forward-looking statements should not be relied upon as representing the Company's view as of any date subsequent to the date of this presentation, and we expressly disclaim any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

This presentation contains estimates and other statistical data made by independent parties and by us relating to our clinical data, market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Event Agenda:

1. Introduction to Aileron Therapeutics (Brian Windsor, Ph.D.; President and COO)
2. MOA, Clinical Overview & Pre-Clinical Data for LTI-03 (Cory Hogaboam, Ph.D.; Chief Scientist)
3. KOL Panel with:
   - Fernando J. Martinez, M.D., M.S. (Weill Cornell Medicine)
   - Tejaswini Kulkarni, M.D., M. P. H. (Alabama Birmingham Medicine)
   - Andreas Günther, M.D. (Agaplesion Evang. Central Hesse Hospital & Justus Liebig University)
4. Q&A

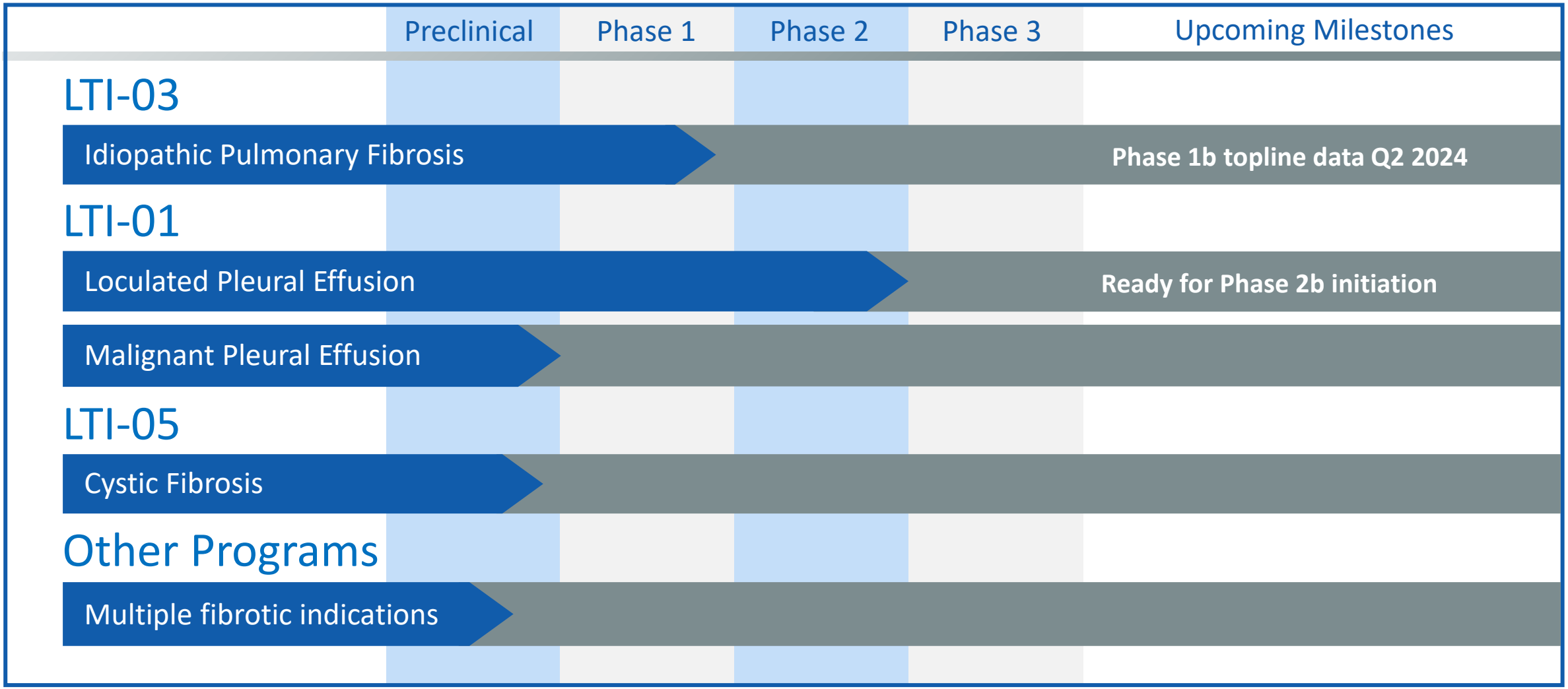
Clinical-stage Biotech with Pulmonary Pipeline



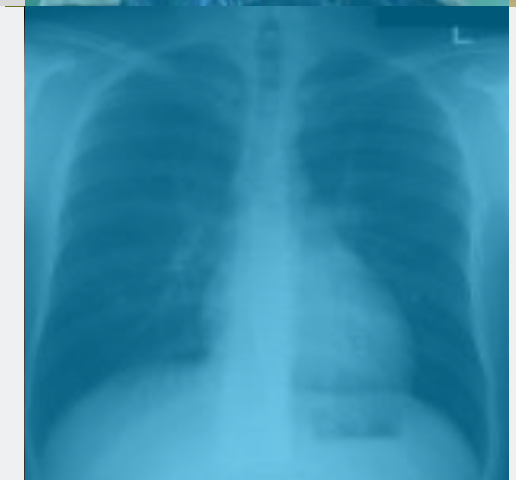
Therapies for Underserved Fibrosis and Pulmonary Conditions

LTI-03 ***Idiopathic Pulmonary Fibrosis***	***Phase 1b***	• Preclinical evidence supporting the ability to **protect healthy lung epithelial cells** and to **reduce pro-fibrotic signaling** • Demonstrated ability to increase sRAGE, a **prognostic biomarker** of IPF
LTI-01 ***Loculated Pleural Effusions***	***Phase 2b ready***	• **Potentially fatal disease** with no approved drugs • Completed Phase 1b and Phase 2 trials; similar mechanism as existing, off label therapeutic use
LTI-05 ***Cystic Fibrosis***	***PC***	• ENaC inhibitor intended for the **15-20% of CF pts.** who **do not respond to CFTR modulators** • **100% inhibition** and **localized** activity (safety profile) in preclinical studies

Multiple Orphan Disease Programs with Upcoming Milestones



LTI-03: A Novel Treatment for Idiopathic Pulmonary Fibrosis



LTI-03 is a Peptide Region of Caveolin-1 Protein Indicated for Idiopathic Pulmonary Fibrosis

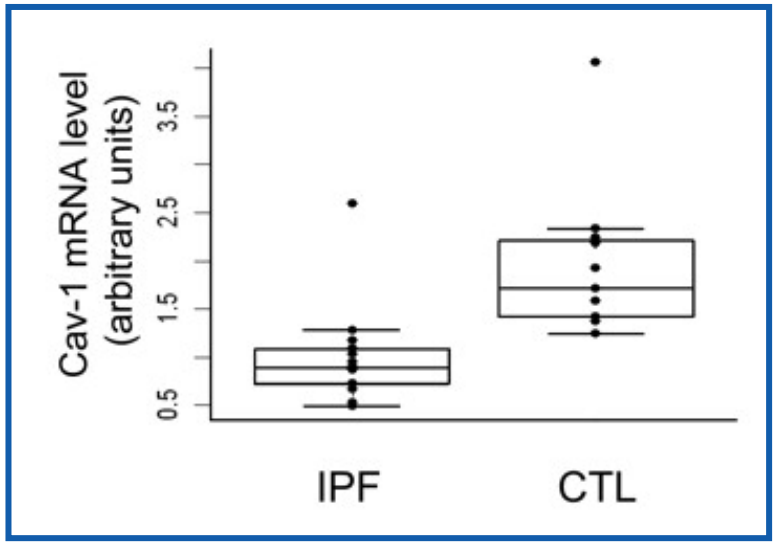
- We believe current SOC treatment options offer modest clinical benefit, have significant side effects and intolerance, and are not curative
  - ~100,000[1] IPF patients in the U.S. with expected median survival 2-5 years[2] from diagnosis
- Multiple preclinical studies support dual mechanism of Cav1 – ability to inhibit multiple pro-fibrotic pathways and protect lung epithelial cells
- Successfully completed Phase 1a randomized, double-blind placebo-controlled study in healthy normal volunteers
  - Currently in a Phase 1b randomized, double-blind placebo-controlled study
- sRAGE - prognostic biomarker of IPF disease preferentially increased in ex-vivo IPF tissue samples and Phase 1a treated patients
  - RAGE is primarily expressed by type 1 epithelial cells in lung tissue

1 Pergolizzi, Jr., J., LeQuang, J., Varrassi, M., Breve, F., Magnusson, P., Varrassi, G., (2023). What Do We Need to Know About Rising Rates of Idiopathic Pulmonary Fibrosis? A Narrative Review and Update. Springer Nature, Published online 2023 Jan 24. doi: 10.1007/s12325-022-02395-9.
2 Nathan et al. Long-term Course and Prognosis of Idiopathic Pulmonary Fibrosis in the New Millennium. *Chest Journa*l Volume 140, ISSUE 1, P221-229, July 2011

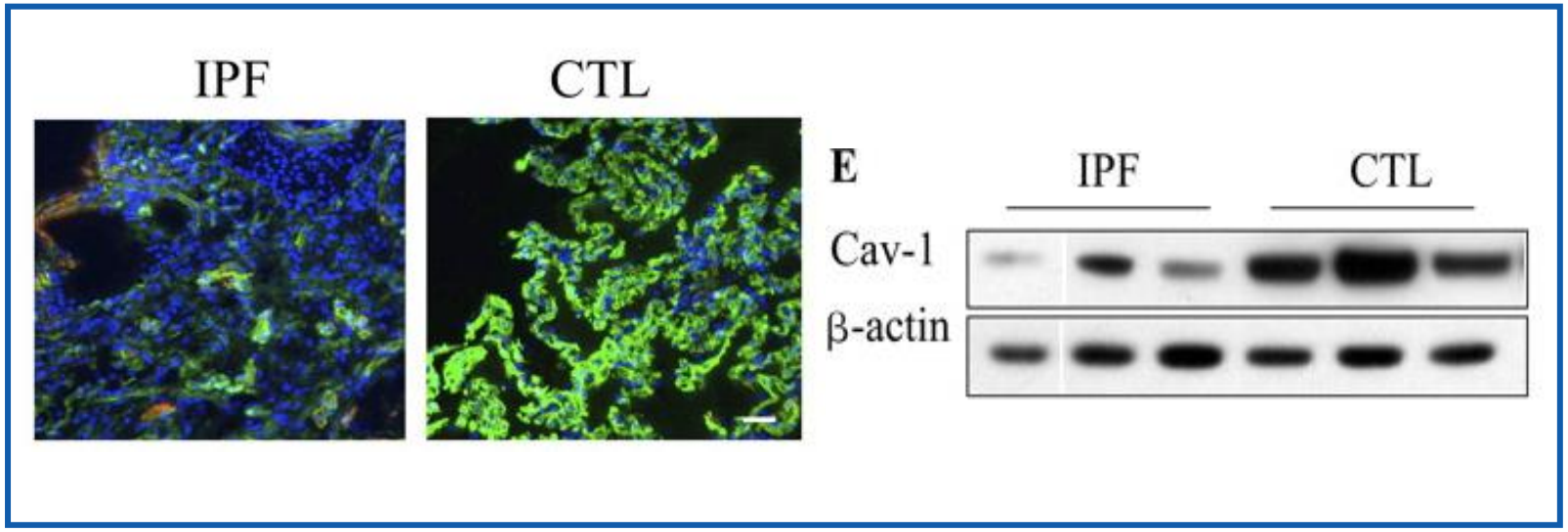
Caveolin-1 is Downregulated in IPF

Caveolin-1: a critical regulator of lung fibrosis in idiopathic pulmonary fibrosis

Xiao Mei Wang,[1] Yingze Zhang,[1] Hong Pyo Kim,[1] Zhihong Zhou,[1]
Carol A. Feghali-Bostwick,[1] Fang Liu,[1] Emeka Ifedigbo,[1] Xiaohui Xu,[2]
Tim D. Oury,[3] Naftali Kaminski,[1] and Augustine M.K. Choi[1]

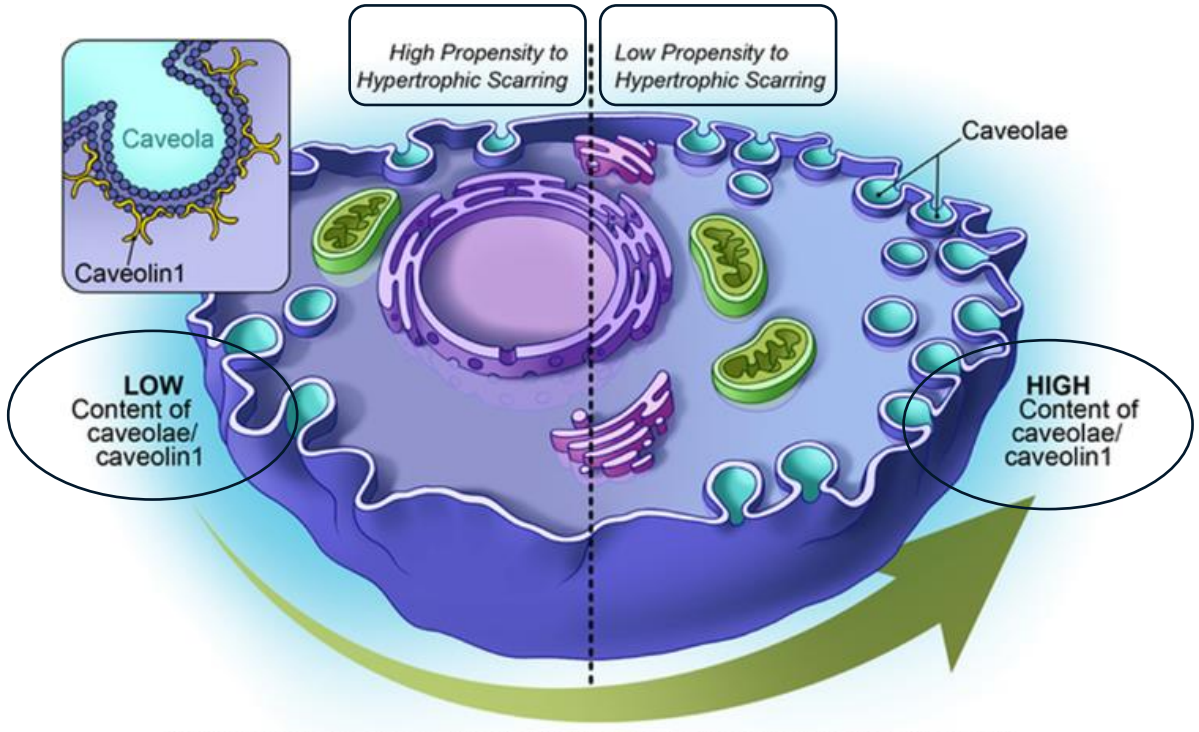


mRNA levels

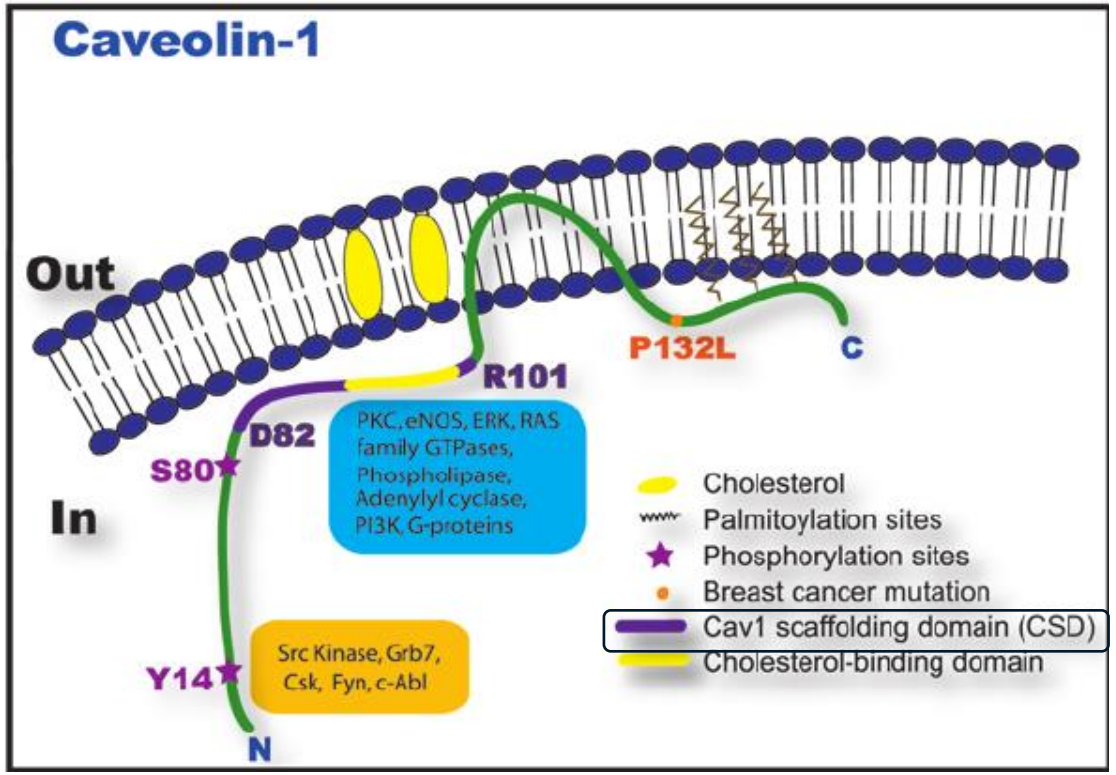


Protein expression

Caveolin-1: a Key Regulator in Fibrosis

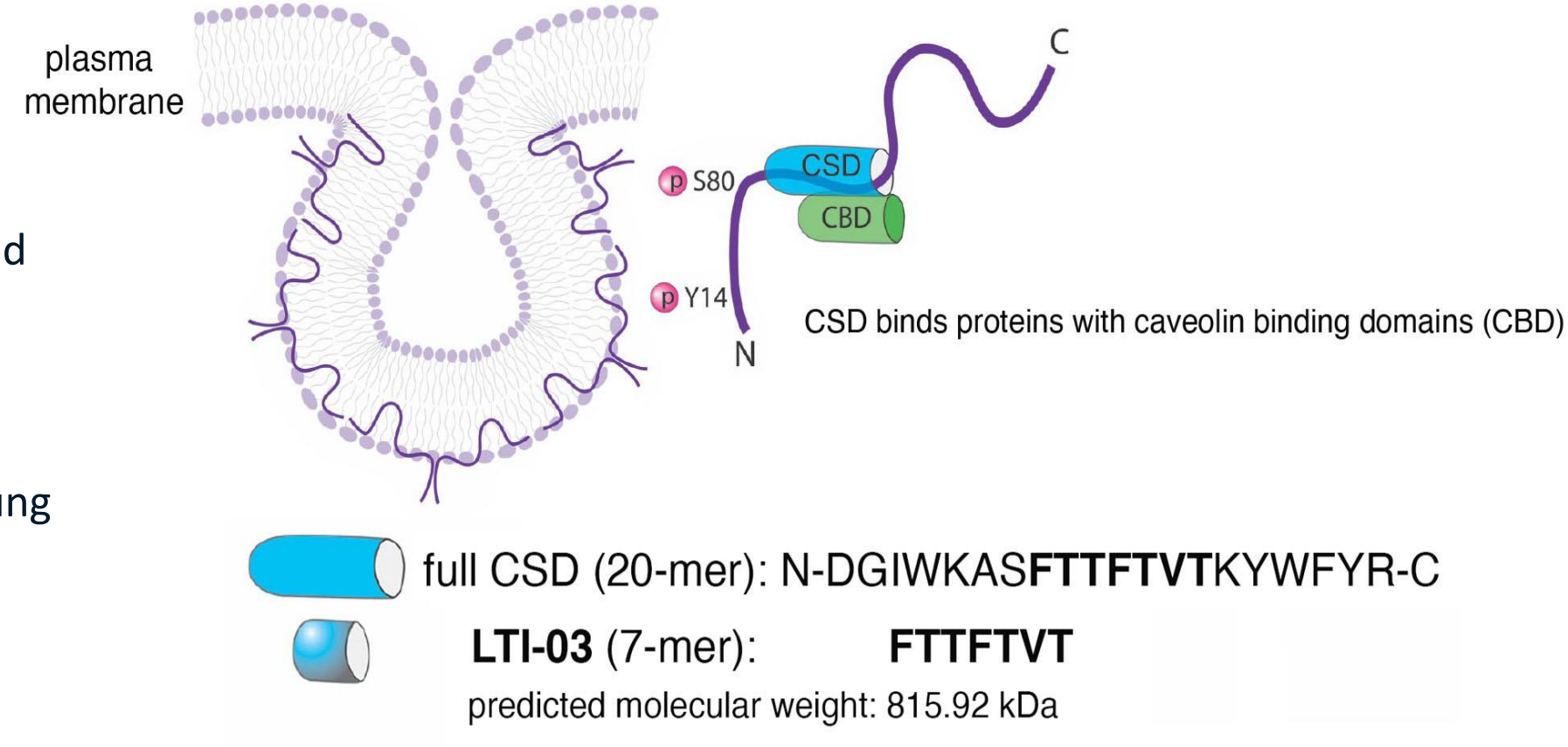


Fibroblasts, epithelial cells, endothelial cells, myocytes, adipocytes, & immune cells.



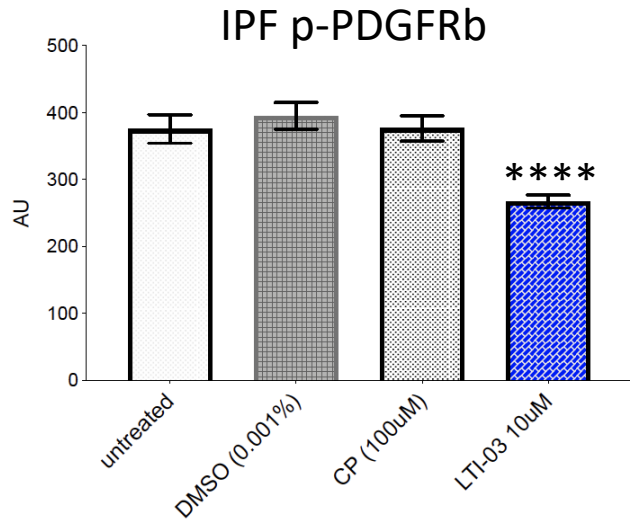
Simulation of Caveolin-1 Activity via CSD Peptide

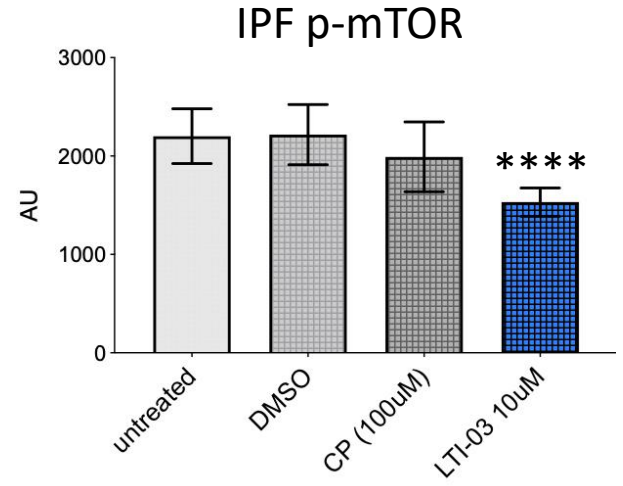
- LTI-03 is a seven amino acid peptide encompassing a portion of the Cav1 CSD
- LTI-03 is dosed direct-to-lung by dry powder inhaler



For a review on CSD/CBD binding domain list, see: Byrne et. al. PLOS One 2012

Attenuates multiple RTK and Metabolic Signaling in IPF Fibroblasts





RTK and associated signaling

ALK(D5F3)	*
p-ALK(3B4)(Y1586)	***
c-Jun	*
p-c-Myc(T58)	**
Herb2/ErbB3	***
p-EGFR(Y1173)(53A5)	***
p-MEK (1/2)	****
p44/42 MAPK (ERK1/2)	*
p-PDK1(S241)	****
p-PDGFRb(Y761)	****
p-RafB(S445)	****
p-Ret(Y905)	**
Stat5a	*
p-Stat5(Y694)	***
PI3Kp110a	**
PTEN	*
p-SRC	****
SRC-1	***
YAP	**

Metabolic signaling

AMPKa	****
p-AMPKb1(S108)	****
Deptor	**
LDHA	**
p-mTOR	****
p-Raptor	****
Raptor	**
p-Tuberin	****

Invasion associated markers

TWIST2	*
Wnt5ab	**

HDACs

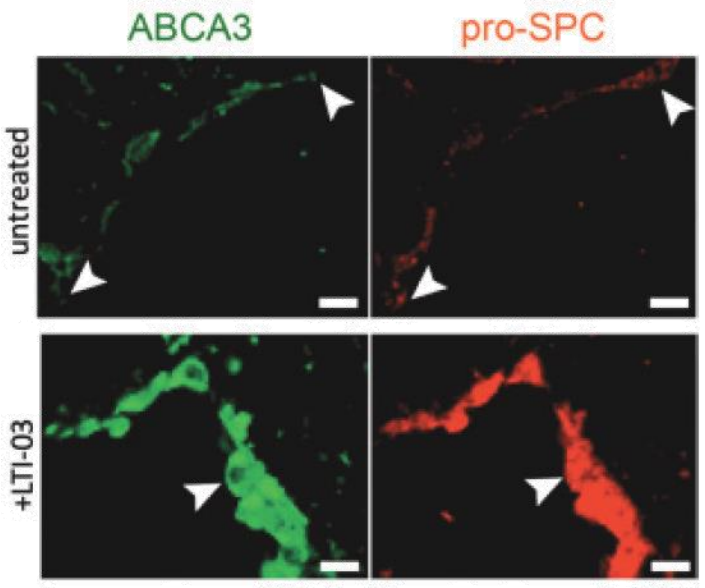
HDAC4	*
HDAC6	***

*RPPA assay, Shixia Huang; Baylor College of Medicine; Note(s) Data expressed as mean values and SDs. *p < .05; ** p < .01; ***p<.001; ****p < .0001*

LTI-03 Supports IPF Tissue Epithelium (Fibrotic PCLS Model)

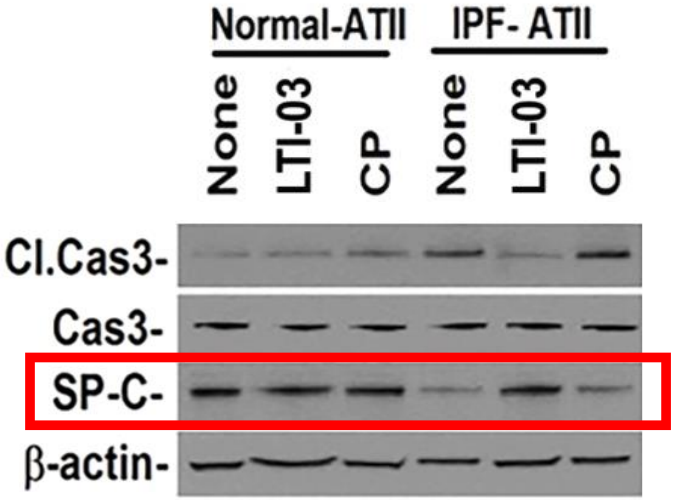
Immunofluorescent Staining for AEC2 Markers

Increases in lysotracker staining also correlated with increases in pro-SPC and ABCA3 gene (the pro-SPC transporter)



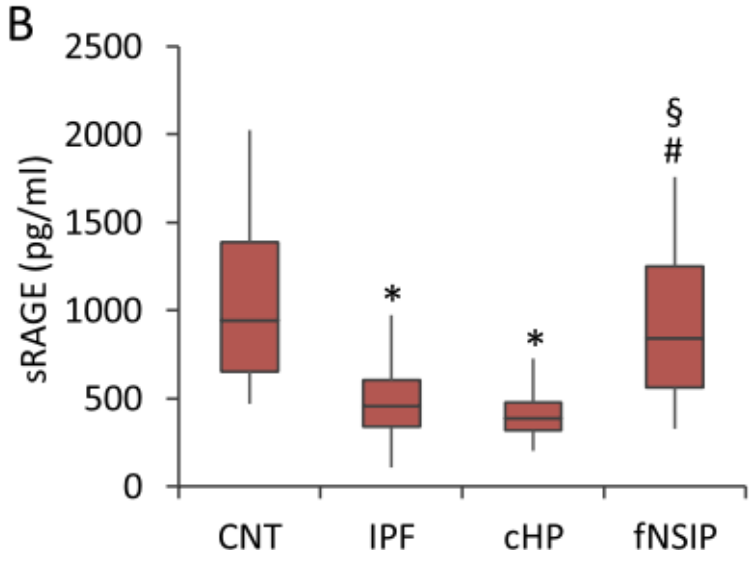
SPC is essential for lung function

LTI-03 also increases levels of SP-C in PCLS IPF Tissue



- In addition to producing AEC1s that make up the majority of the alveolar surface and are **important for proper gas exchange** and ion/water flux, AEC2s **also produce surfactant** that provides for **adequate lung expansion**

Soluble RAGE (sRAGE) is Decreased in Fibrotic Lungs[1]



Machahua *et al. Respiratory Research* (2016) 17:144
DOI 10.1186/s12931-016-0460-2

Respiratory Research

RESEARCH Open Access

Increased AGE-RAGE ratio in idiopathic pulmonary fibrosis

Carlos Machahua[1,2], Ana Montes-Worboys[1,2,3], Roger Llatjos[4], Ignacio Escobar[5], Jordi Dorca[1,2,3], Maria Molina-Molina[1,2,3*†] and Vanesa Vicens-Zygmunt[1,2†]

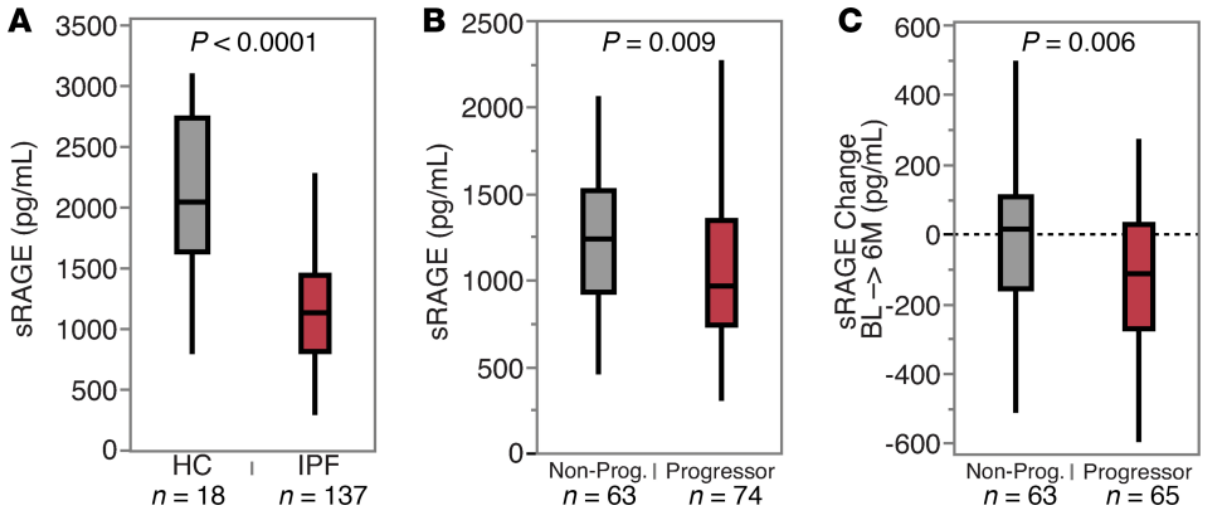


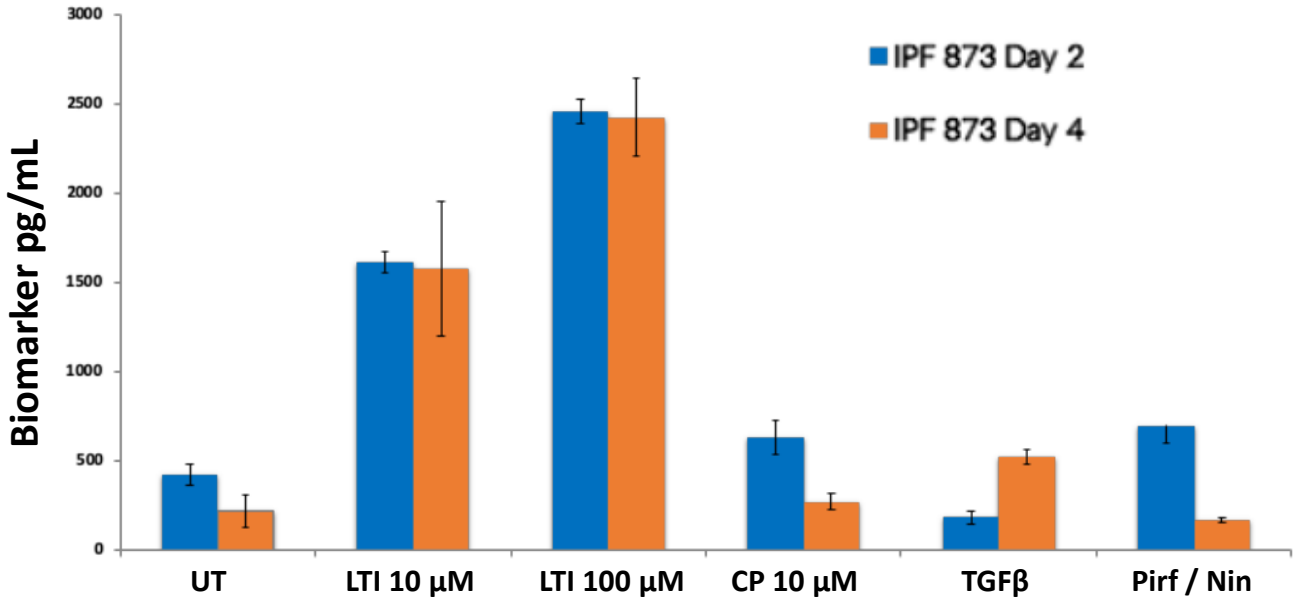
Figure 7. Decreased blood levels of RAGE were associated with more rapid disease progression in IPF patients. (**A**) Soluble RAGE levels in plasma from IPF patients and healthy controls. (**B**) Plasma sRAGE at baseline in IPF patients, dichotomized by disease progression (defined as loss of ≥10% predicted forced vital capacity [FVC] or death) from baseline to 1 year of follow-up. (**C**) Change in plasma sRAGE levels from baseline to 6 months in IPF progressors and nonprogressors. Statistical significance between the groups was determined by Wilcoxon rank sum test. BL, baseline.

[1]Machahua, C., Montes-Worboys, A., Llatjos, R. et al. Increased AGE-RAGE ratio in idiopathic pulmonary fibrosis. Respir Res 17, 144 (2016).

Novel Prognostic Biomarker Data Supports LTI-03 Protection of Epithelial Cells

Biomarker Correlates with LTI-03 Impact in PCLS

Administration of LTI-03 in the PCLS system increased the soluble protein biomarker, sRAGE, while currently approved therapies had negligible effects on sRAGE levels



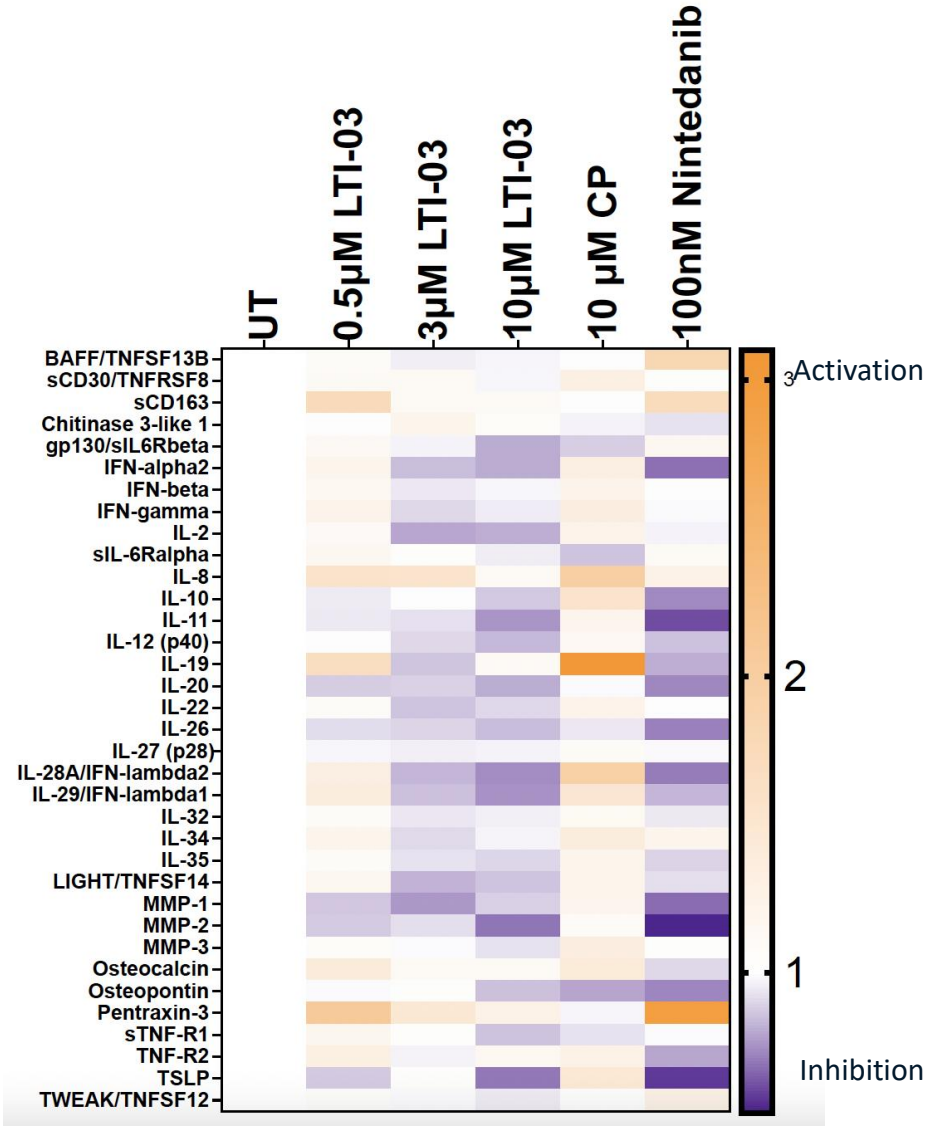
***Low levels** of sRAGE at diagnosis predict poor survival in IPF*[1]

The increase in sRAGE** provides further evidence of increased AEC2 survival, leading to **greater AEC1 production** and thus **overall epithelial cell survival

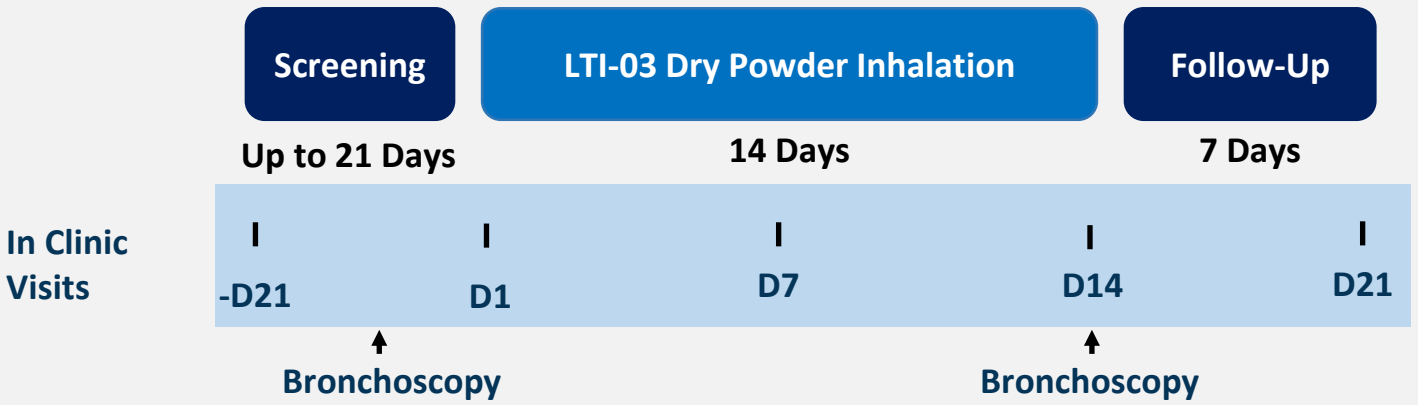
*Ability to **measure sRAGE in broncho-alveolar lavage fluid and blood** makes it a potentially **useful biomarker***

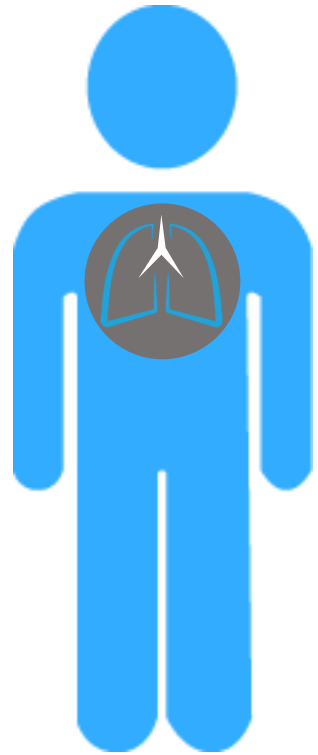
[1]Machahua, C., Montes-Worboys, A., Planas-Cerezales, L. et al. Serum AGE/RAGEs as potential biomarker in idiopathic pulmonary fibrosis. Respir Res 19, 215 (2018).

Anti-Fibrotic Activity at Physiologically Relevant Dose (Every 12hrs in PCLS — Composite of Six Patient Samples)



Phase 1b Clinical Trial Design (Status: In Process)





Study Design

- IPF diagnosis ≤ 3 years; no previous antifibrotic therapy w/in 2 months of baseline
- 24 patients total (18 active, 6 placebo)
  - Low (2.5mg BID) and high (5mg BID) dose cohorts, sequential daily dosing for 14 days
- Bronchoscopy at screening and Day 14
- Primary endpoint: Safety/tolerability
- Key exploratory endpoint: Biomarkers (blood, BAL, brushings)

Phase 1b Clinical Trial Biomarkers

Sample source/Indicator of	epithelial damage/repair	fibrosis	inflammation	thrombosis
Peripheral blood cells		p-AKT		
Platelet rich plasma (PRP)	CYFRA 21-1, SP-D, CA-19-9, KL-6, sRAGE, Galectin 7	MMP-7, Tenascin C (TNC), Periostin, IL-11, MYDGF, MMP-2	CCL18, CXCL13, sICAM1, IL-11, sCD163, CXCL7	PAI-1
Bronchoalveolar lavage	Galectin 7, surfactant protein C, sRAGE	MYDGF, MMP-2, TNC, MMP-7, periostin, IL-11	CCL18, CXCL13, sICAM1, IL-11, sCD163, CXCL7	PAI-1
Deep bronchial brushings		p-SMAD2/3		

Joining Us Today for KOL Panel

Fernando J. Martinez, M.D., M.S.

Chief of Pulmonary and Critical Care Medicine Division at Weill Cornell Medicine

Tejaswini Kulkarni, M.D., M. P. H.

Associate Professor of Pulmonology, Allergy and Critical Care Medicine and Director of the Interstitial Lung Disease Program at University of Alabama at Birmingham Medicine

Andreas Günther, M.D.

Senior Physician of Pulmonology and Intensive Care Medicine and Chief Physician of Pulmonology and Internal Care Medicine at Agaplesion Evang. Central Hesse Hospital; Professor of Interstitial and Rare Lung Diseases at Justus Liebig University

Thank you!

NASDAQ: ALRN

WWW.AILERONRX.COM