Advancing a therapeutic platform based on tRNA synthetases for treatment of fibrotic lung diseases

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AARS 2025, Dubrovnik, Croatia

October 1, 2025

Forward Looking Statements

The following slides and any accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. The use of words such as "may," "might," "will," "should," "expect," "plan," "anticipate," "believe," "estimate," "project," "intend," "future," "potential," "opportunity," or "continue," and other similar expressions are intended to identify forward-looking statements. For example, all statements regarding: the potential therapeutic benefits of proteins derived from tRNA synthetase genes and our product candidates and development programs; the ability to successfully advance our product candidates and undertake certain development activities (such as the initiation of clinical trials, clinical trial enrollment, the conduct of clinical trials and announcement of clinical results) and accomplish certain development goals, and the timing of such events; the potential market opportunity for our product candidates; our ability to receive regulatory approvals for, and commercialize, our product candidates; our ability to identify and discover additional product candidates; potential activities and payments under collaboration agreements; and the ability of our intellectual property portfolio to provide protection are forward-looking statements. All forward-looking statements are based on estimates and assumptions by our management that, although we believe to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that we expected. These risks, uncertainties and other factors are more fully described in our filings with the U.S. Securities and Exchange Commission, including our Annual Report on Form 10-K, our subsequently filed Quarterly Reports on Form 10-Q, and in our other filings. The forward-looking statements in this presentation speak only as of the date of this presentation and neither we nor any other person assume responsibility for the accuracy and completeness of any forward-looking statement. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

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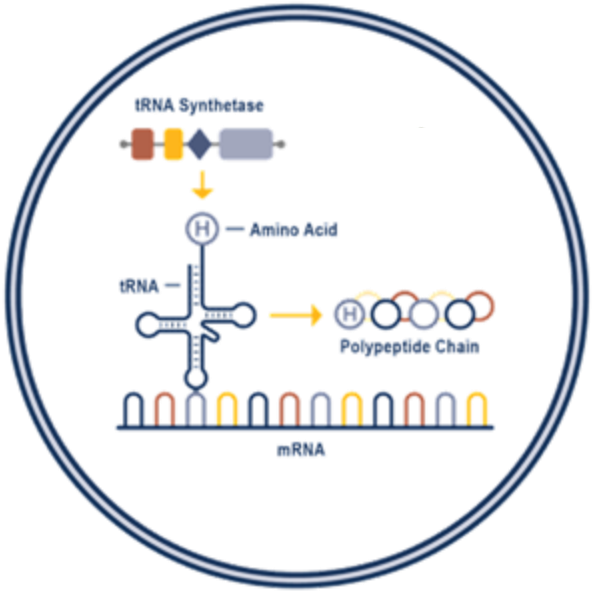
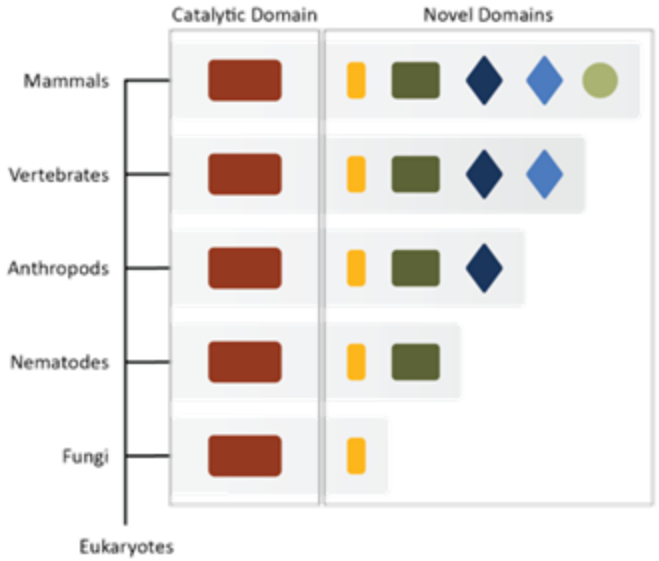
Extracellular tRNA Synthetases Regulate Homeostasis Through Novel Pathways

INTRACELLULAR



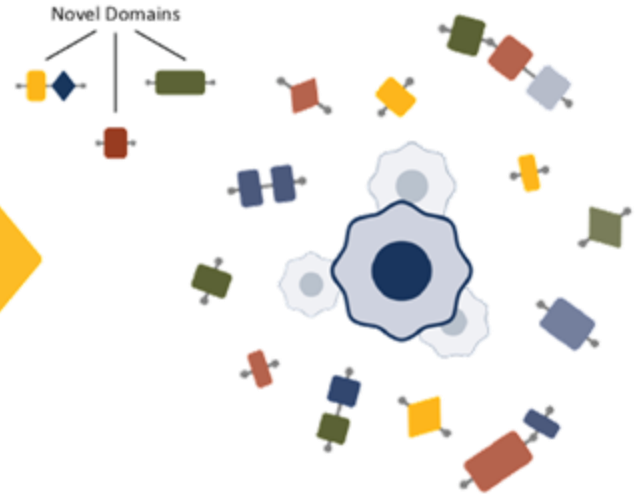
- **Ancient, essential enzymes** that catalyze protein synthesis by conjugating amino acid to tRNA

EVOLUTION



- Evolved to acquire **novel domains**
- Novel domains **persisted through evolutionary pressure**

EXTRACELLULAR



- **Released locally,** enabling function as **parallel signaling molecules**
- Liberated by **alternative splicing** or **proteolysis**

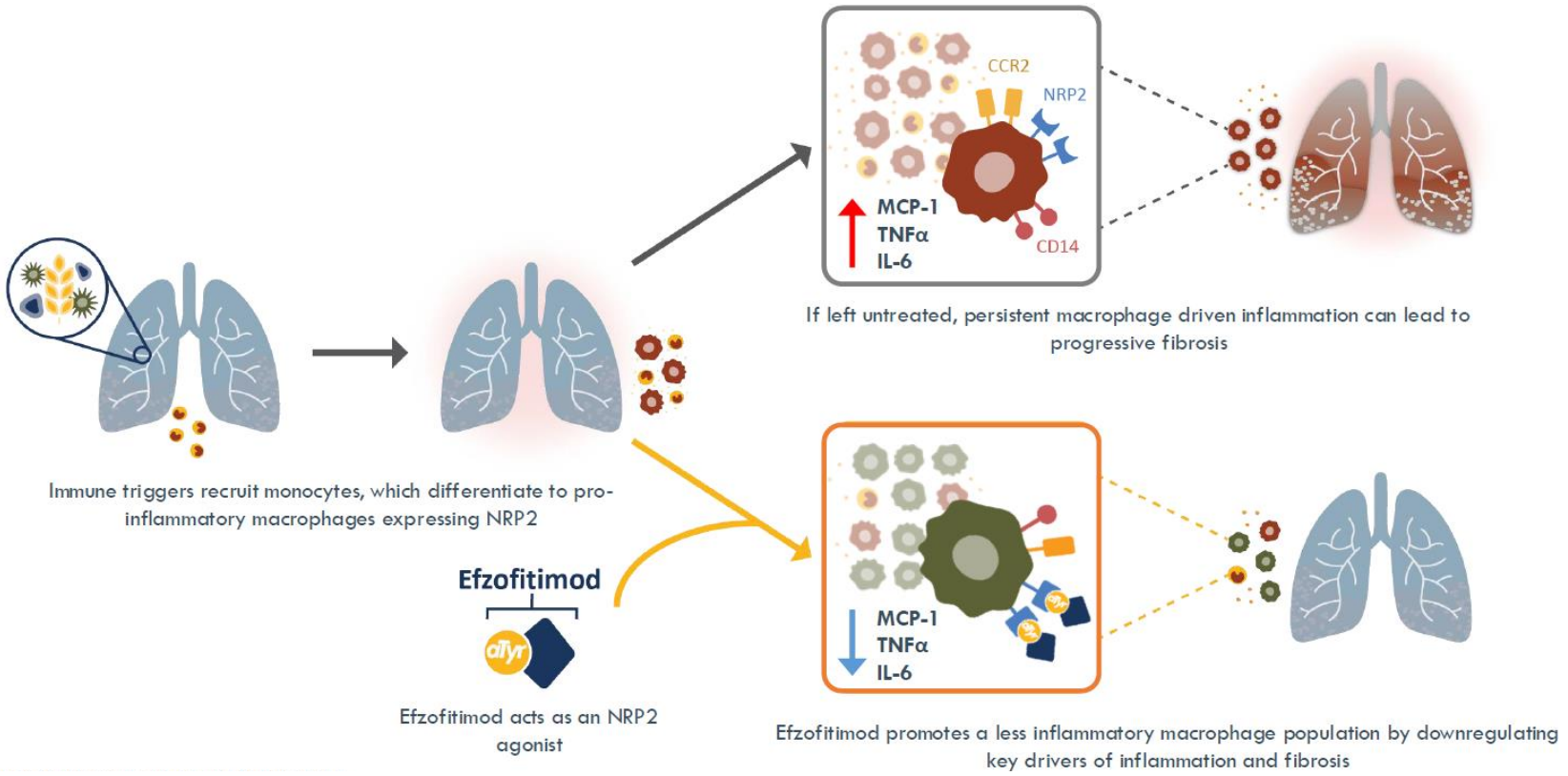
Lo et al Science 2014, Guo et al Nature 2010

Translating tRNA Synthetase Biology for Inflammation and Fibrosis

PROGRAM	tRNA SYNTHETASE	TARGET/MOA	INDICATION	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
Efzofitimod	HARS	NRP2 modulator	Pulmonary Sarcoidosis(1)				efzo-fit
			SSc-ILD			efzo-connect	
			Other ILD (CTD-ILD; CHP)				
ATYR0101	DARS	LTBP1 modulator	Fibrotic diseases				
ATYR0750	AARS	FGFR4 modulator	Fibrotic diseases				
Other tRNA Synthetase Candidates(2)							

(1) In partnership with Kyorin Pharmaceutical Co., Ltd. for the development and commercialization of efzofitimod for ILD in Japan
(2) Pipeline candidates in development based on additional tRNA synthetases from IP portfolio

Efzofitimod Modulates Macrophage Differentiation Via Neuropillin-2



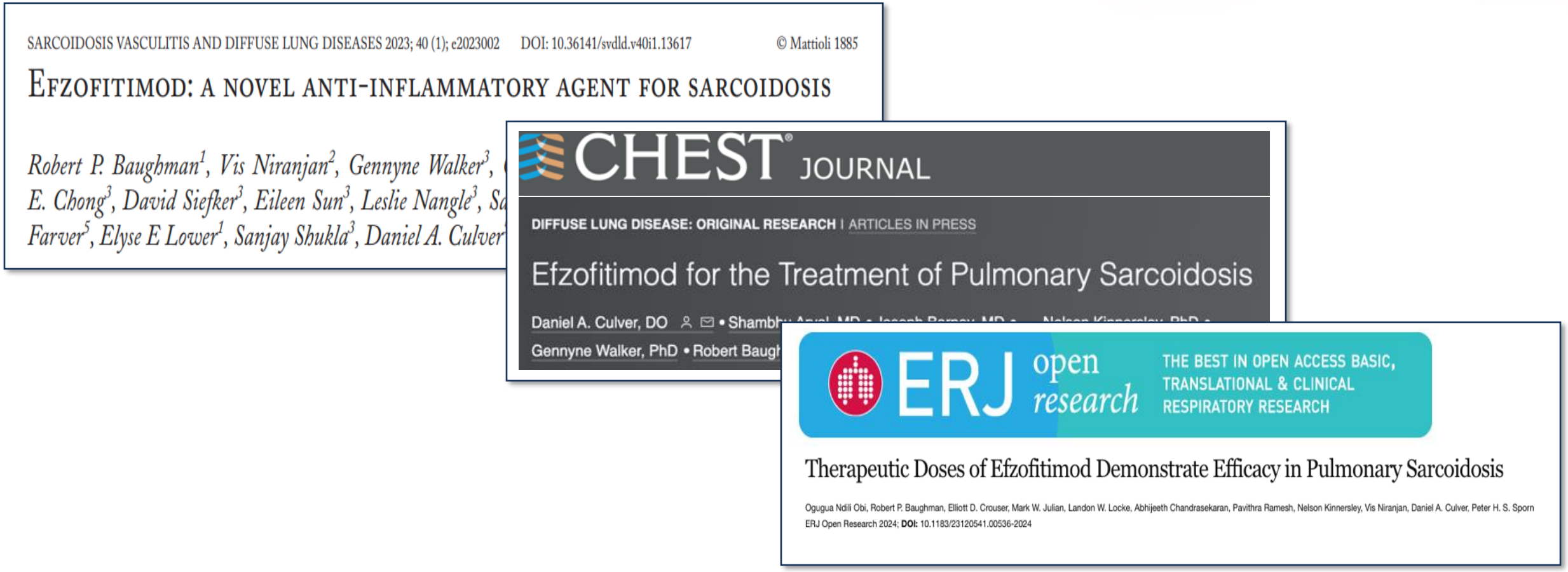
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

INTERSTITIAL LUNG DISEASE

A human histidyl-tRNA synthetase splice variant therapeutic targets NRP2 to resolve lung inflammation and fibrosis

Leslie A. Nangle[1]*, Zhiwen Xu[1], David Siefker[1], Christoph Burkart[1], Yeeting E. Chong[1], Liting Zhai[2,3]†, Yanyan Geng[2,3]‡, Clara Polizzi[1], Lauren Guy[1], Lisa Eide[1]§, Yao Tong[2,3]¶, Sofia Klopp-Savino[1], Michaela Ferrer[1]#, Kaitlyn Rauch[1], Annie Wang[1], Kristina Hamel[1], Steve Crampton[1]**, Suzanne Paz[1]††, Kyle P. Chiang[1]‡‡, Minh-Ha Do[1]§§, Luke Burman[1], Darin Lee[1], Mingjie Zhang[2], Kathleen Ogilvie[1]¶¶, David King[1]##, Ryan A. Adams[1], Paul Schimmel[4]*

Clinical Data Publications Highlight Potential for Efzofitimod in Pulmonary Sarcoidosis



SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2023; 40 (1); e2023002 DOI: 10.36141/svdld.v40i1.13617 © Mattioli 1885

EFZOFITIMOD: A NOVEL ANTI-INFLAMMATORY AGENT FOR SARCOIDOSIS

Robert P. Baughman[1], Vis Niranjan[2], Gennyne Walker[3], E. Chong[3], David Siefker[3], Eileen Sun[3], Leslie Nangle[3], Farver[5], Elyse E Lower[1], Sanjay Shukla[3], Daniel A. Culver

CHEST JOURNAL

DIFFUSE LUNG DISEASE: ORIGINAL RESEARCH | ARTICLES IN PRESS

Efzofitimod for the Treatment of Pulmonary Sarcoidosis

Daniel A. Culver, DO • Shambhu • Gennyne Walker, PhD • Robert Baugh

ERJ open research

THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Therapeutic Doses of Efzofitimod Demonstrate Efficacy in Pulmonary Sarcoidosis

Ogugua Ndili Obi, Robert P. Baughman, Elliott D. Crouser, Mark W. Julian, Landon W. Locke, Abhijeeth Chandrasekaran, Pavithra Ramesh, Nelson Kinnersley, Vis Niranjan, Daniel A. Culver, Peter H. S. Sporn

ERJ Open Research 2024; **DOI:** 10.1183/23120541.00536-2024

Summary of Key Findings from Efzofitimod Phase 3 Trial in Pulmonary Sarcoidosis

- Study did not meet primary endpoint in change from baseline in mean daily OCS dose at week 48
  - 52.6% of patients treated with 5.0 mg/kg efzofitimod achieved complete steroid withdrawal at week 48 vs 40.2% on placebo (p=0.0919)
- Clinical improvement in quality-of-life secondary endpoints
  - KSQ-Lung score (p=0.0479), FAS Total Score (p=0.0226) and KSQ-GH score (p=0.0197) in the 5.0 mg/kg group vs placebo.
- Greater proportion of patients achieved complete steroid withdrawal at week 48
  - KSQ-Lung score improvement in the 5.0 mg/kg group (29.5%) vs placebo (14.4%) (p=0.0196)
- Efzofitimod was generally well-tolerated at both the 3.0 mg/kg and 5.0 mg/kg doses

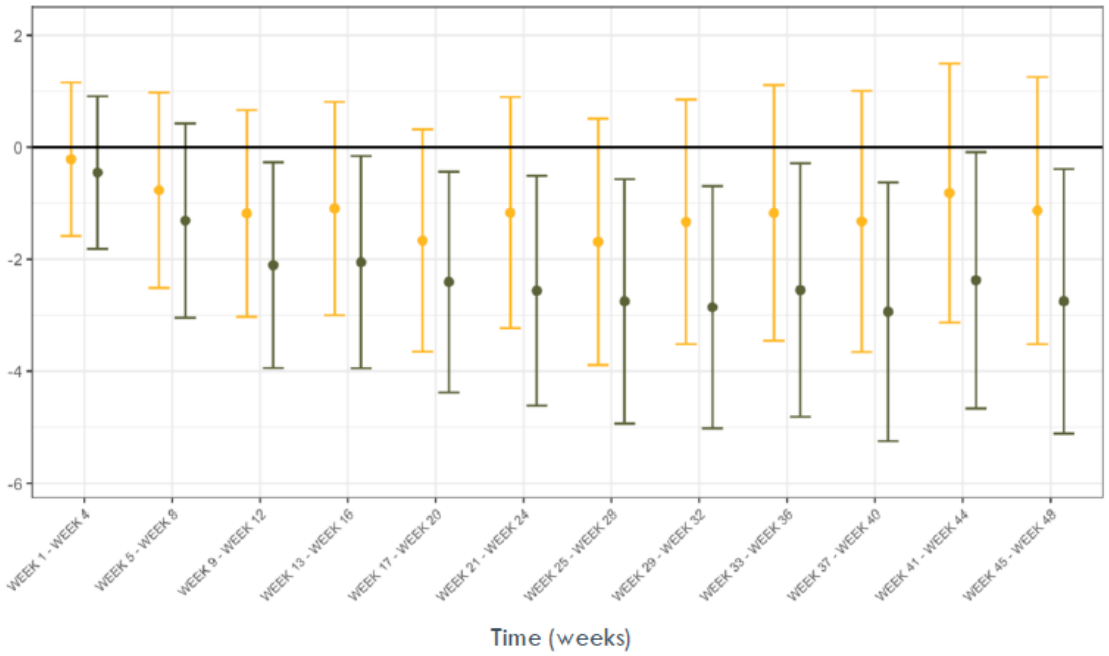
- Findings demonstrate drug activity for efzofitimod across multiple clinically relevant efficacy endpoints
- Company plans to engage with the U.S. FDA to determine the path forward for efzofitimod in pulmonary sarcoidosis

OCS = oral corticosteroids; KSQ = King's Sarcoidosis Questionnaire; FAS = Fatigue Assessment Scale; FDA = Food and Drug Administration

As the primary endpoint did not achieve statistical significance, p-values for other endpoints should be interpreted as nominal p-values.

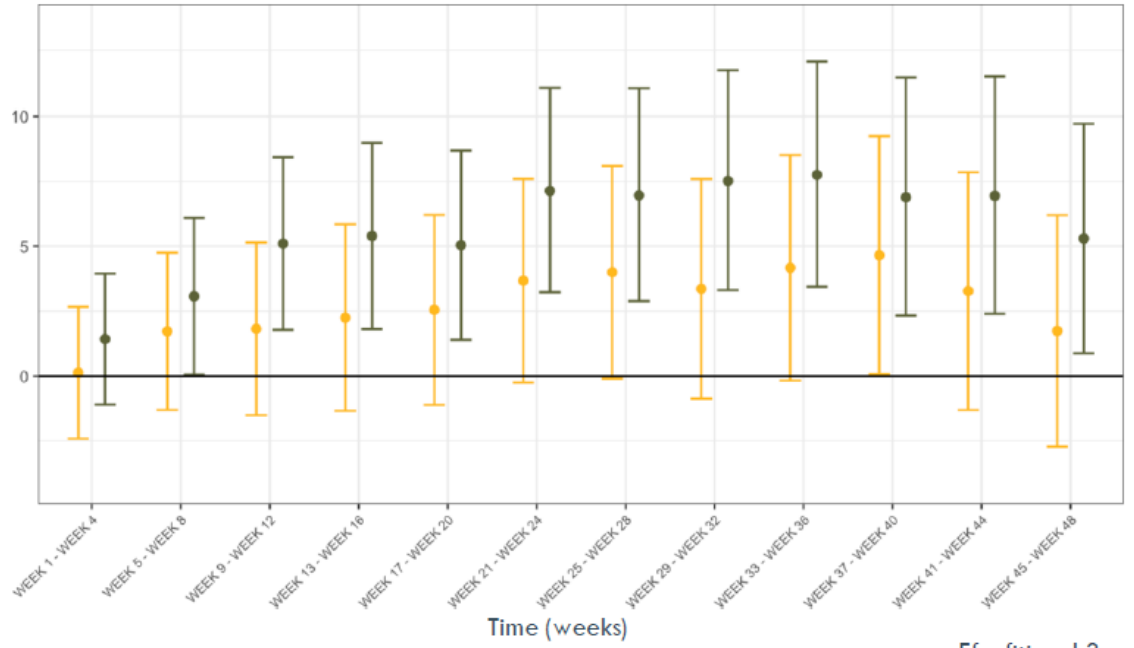
Consistent Benefit Observed on Quality-of-Life Measures

Differences in FAS Total Score Change from Baseline vs Placebo*



*Week 48 difference in LS mean change from baseline nominal p-value = **0.0226***

Differences in KSQ-GH Change from Baseline vs Placebo*



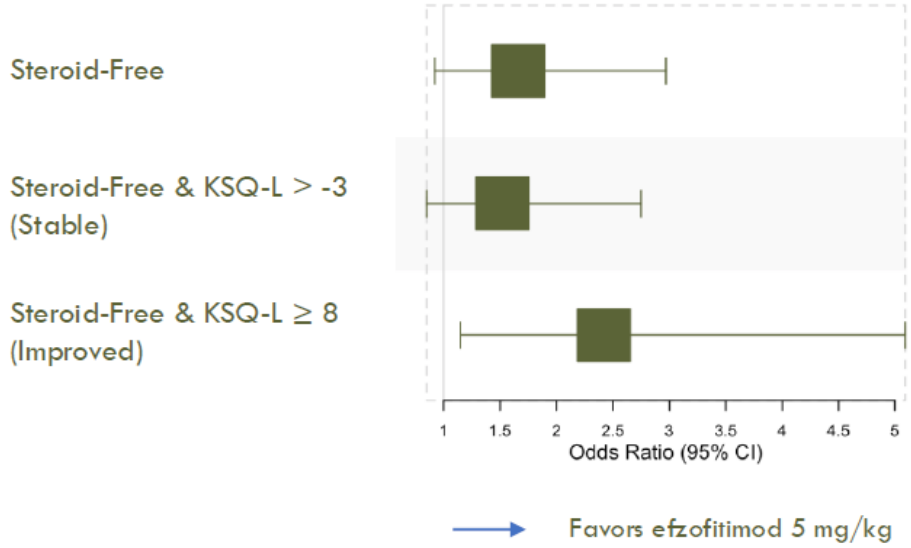
*Week 48 difference in LS mean change from baseline nominal p-value = **0.0197***

King's Sarcoidosis Questionarre-Lung / Steroid Free Composites

Steroid Free and KSQ-L Composite Endpoints

	Placebo N=90	Efzofitimod 3 mg/kg N=86	Efzofitimod 5 mg/kg N=88
Steroid free and stable KSQ-L; n (%) [1]	33 (36.7)	41 (47.7)	41 (46.6)
Odds ratio (95% CI)	-	1.6 (0.8, 2.9)	1.6 (0.8, 2.9)
Nominal p-value	-	*0.1592*	*0.1607*
Steroid free and improved KSQ-L; n (%) [1]	13 (14.4)	24 (27.9)	26 (29.5)
Odds ratio (95% CI)	-	2.2 (1.1, 4.8)	2.4 (1.2, 5.2)
Nominal p-value	-	***0.0381***	***0.0196***

Efzofitimod 5 mg/kg vs Placebo from Logistic Regression



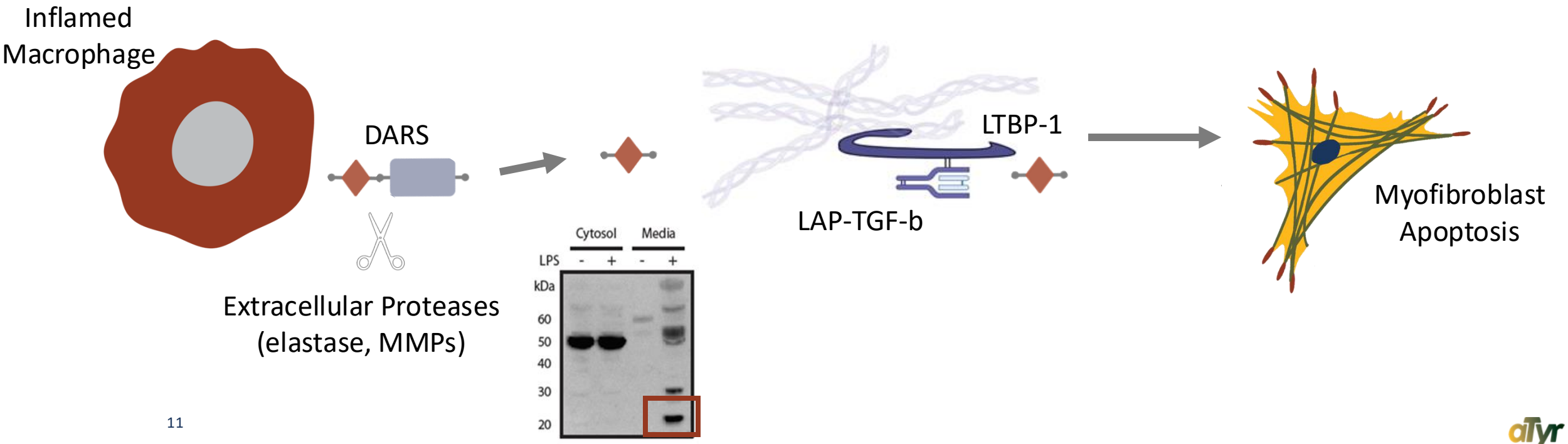
[1]Missing patients treated as non-responders

ATYR0101

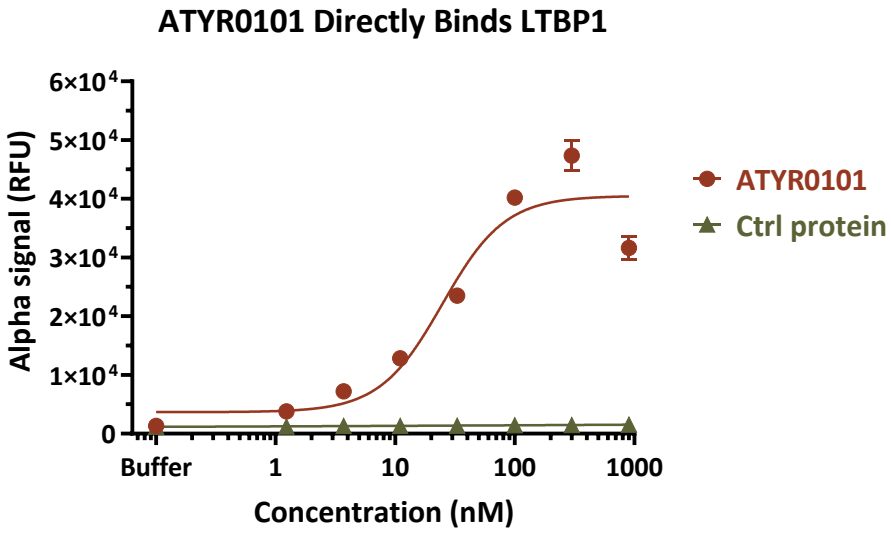
Targeting myofibroblasts to resolve fibrosis

ATYR0101: LTBP1 Modulator Derived from DARS Synthetase

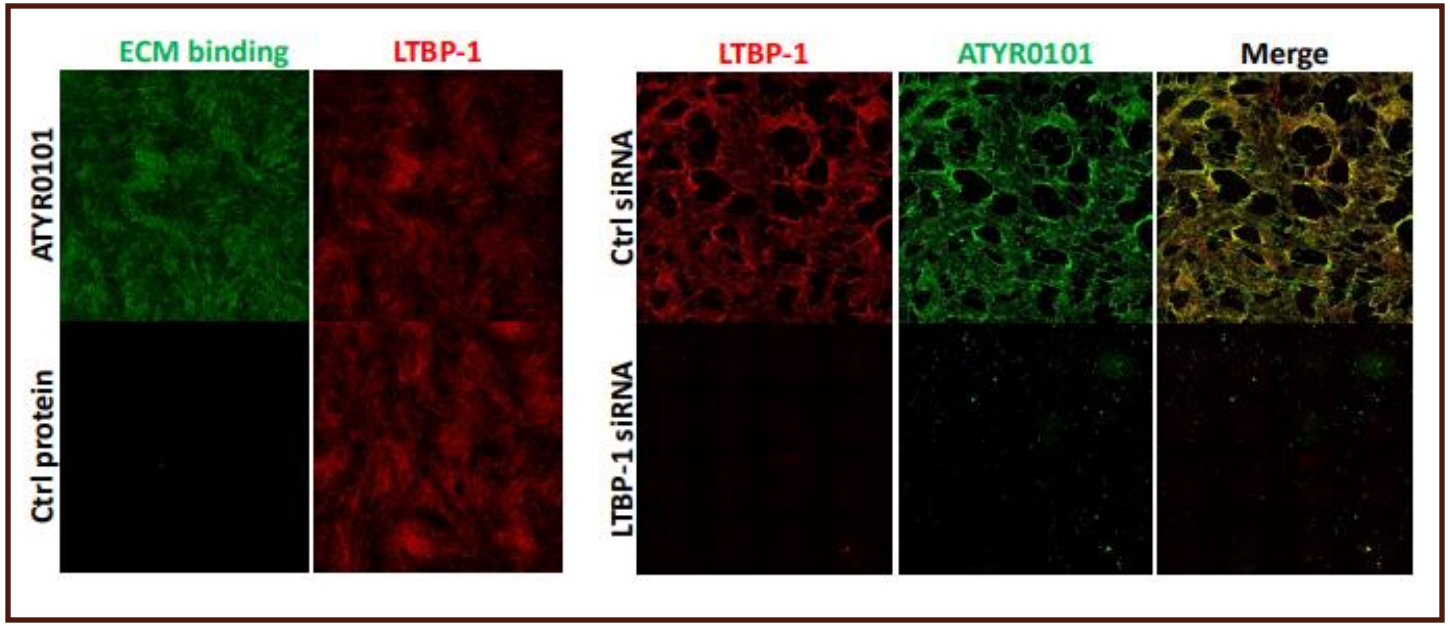
- ATYR0101 is a fusion protein derived from a proprietary extracellular domain of DARS (aspartyl-tRNA synthetase)
- The domain is a naturally occurring fragment released from macrophages in inflammatory conditions
- LTBP1 has been identified as the binding partner for ATYR0101
- Unique anti-fibrotic mechanism of action

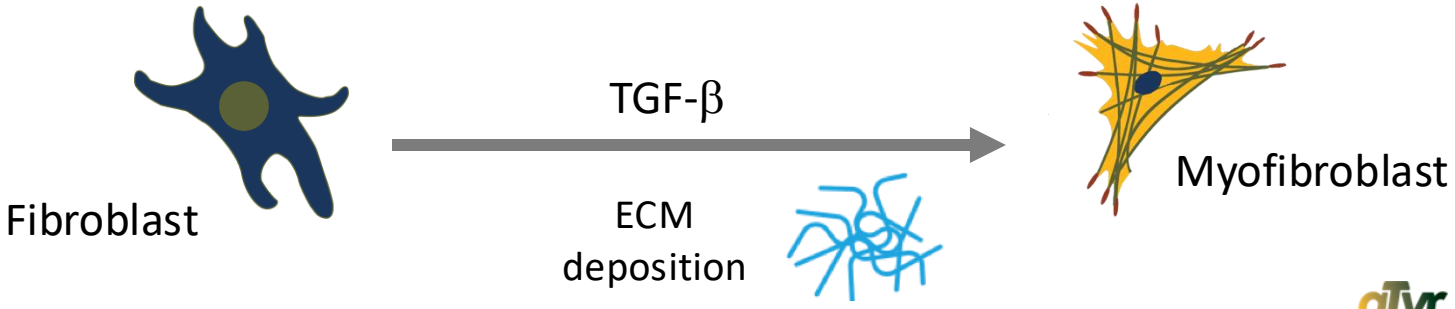


LTBP1 Identified as a Binding Partner of ATYR0101



ATYR0101 binds to ECM deposited by fibroblasts undergoing TGF-β induced differentiation (confirmed with Knock-down)

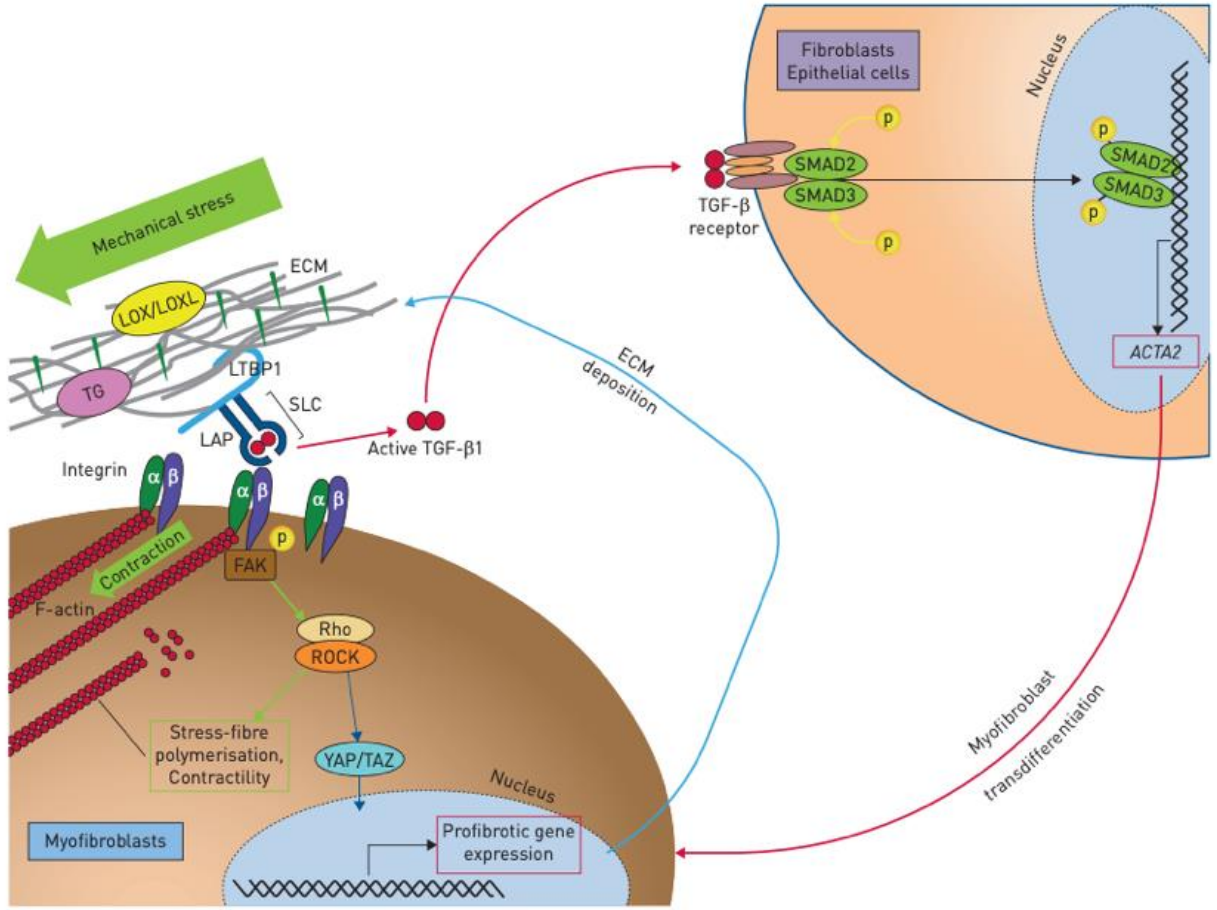




LTBP1: latent TGF-β binding protein 1

LTBP-1 is a Key Regulator of TGF-β Release and Fibrosis

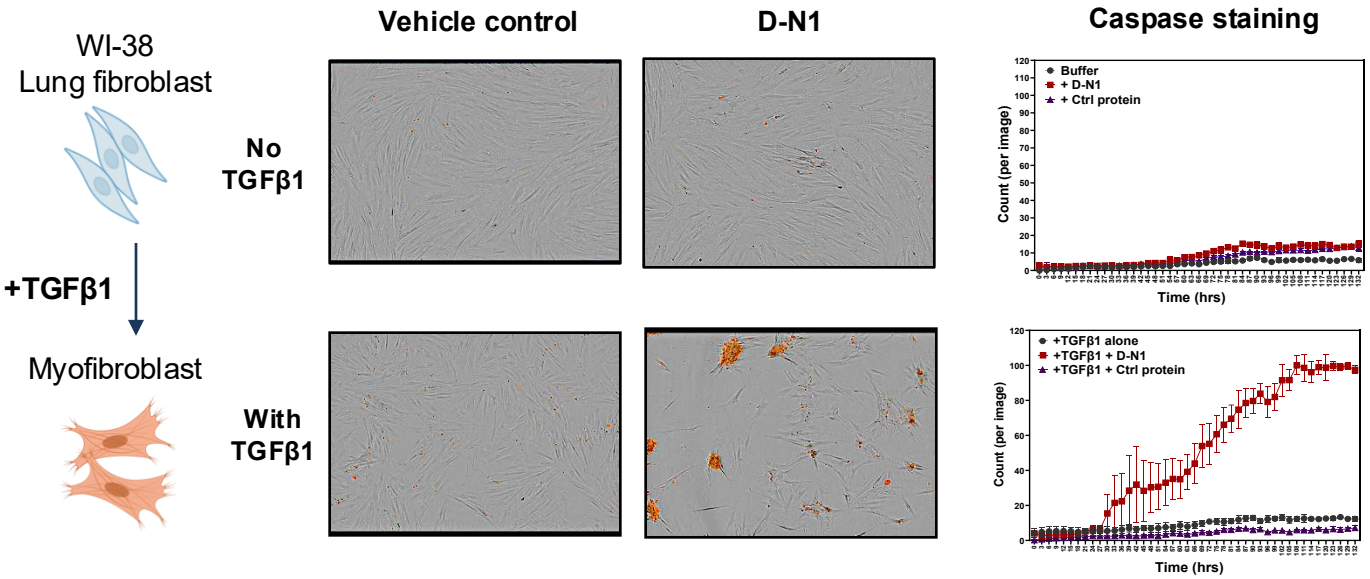
- LTBP1 is expressed in most tissues and in specific cell types such as fibroblasts and smooth muscle cells
- Key regulator of TGF-β by binding latent TGF-β to the extracellular matrix
- Active TGF-β is released from LTBP1 through cleavage by proteases or integrins
- TGF-β drives fibroblast-to-myofibroblast differentiation which is a key driver of fibrosis
- Modulation of LTBP-1 by ATYR0101 indicates the discovery of a previously unknown layer of TGB-β signaling



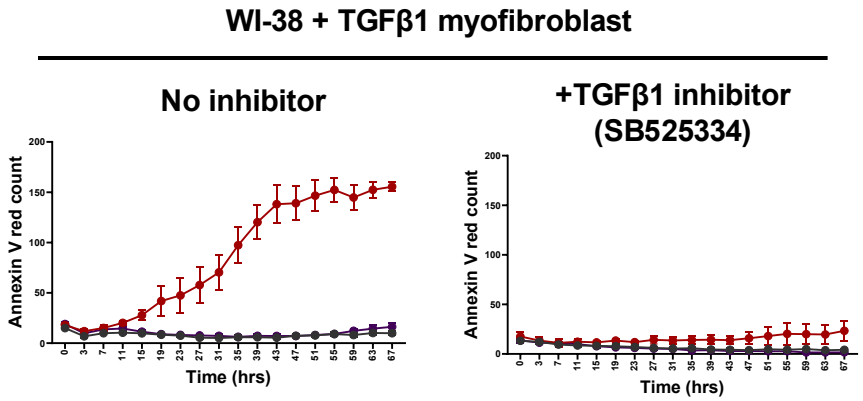
TGFβ1 = transforming growth factor β1; LAP = Latency Associated Peptide; Image from Upagupta et al ERJ 2018

ATYR0101 Induces Myofibroblast Apoptosis in a TGFβ Dependent

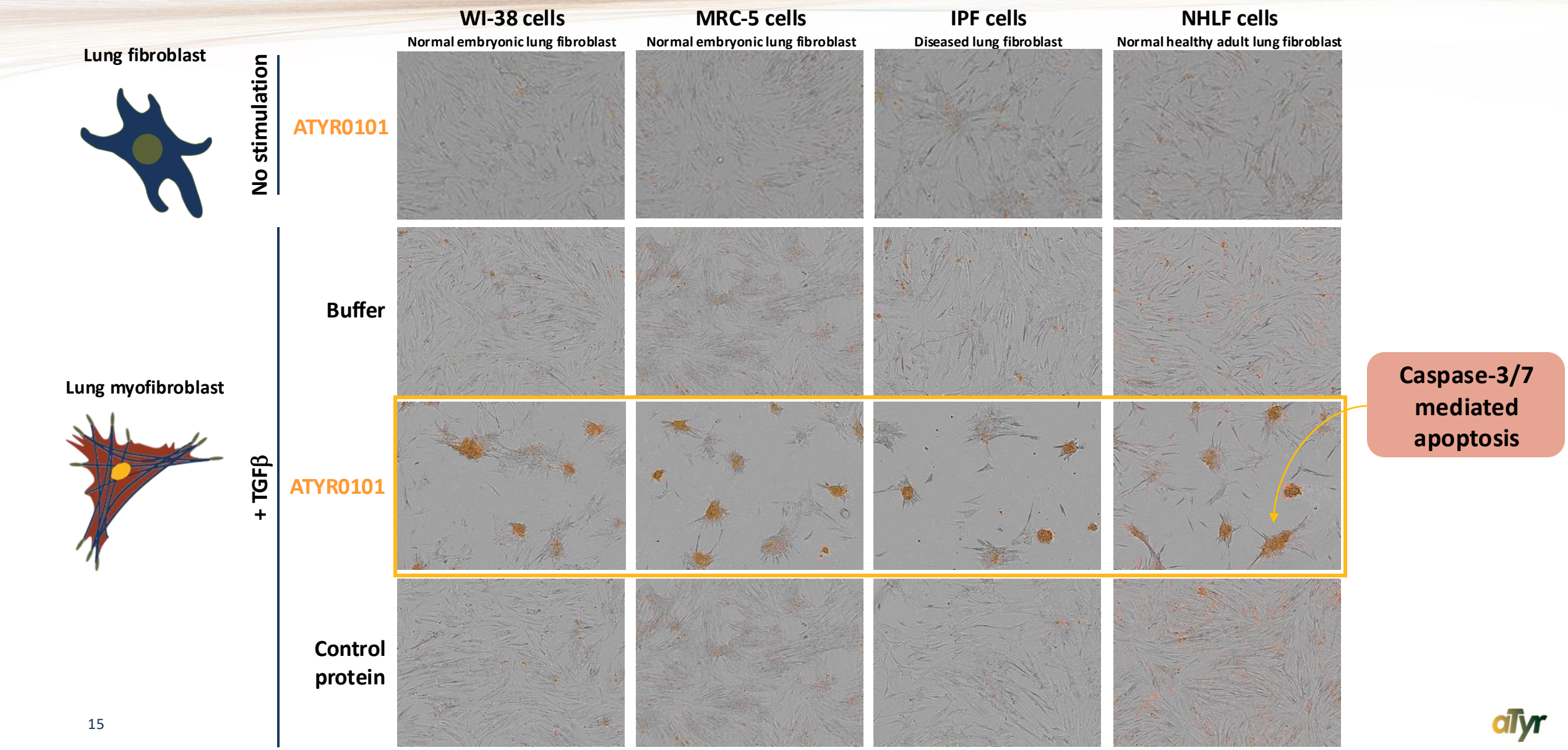
D-N1 induces apoptosis in TGFβ1-activated myofibroblasts



D-N1 induced myofibroblast apoptosis is TGFβ1-dependent

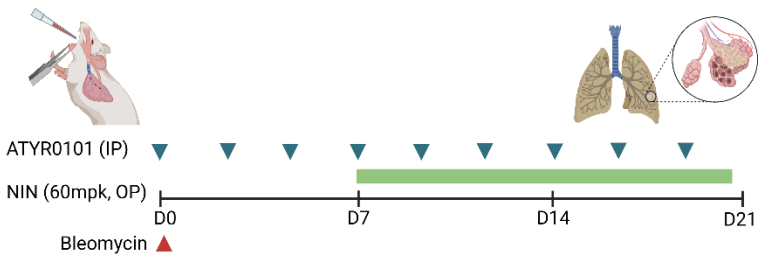


ATYR0101 Induces Apoptosis in Lung Myofibroblasts

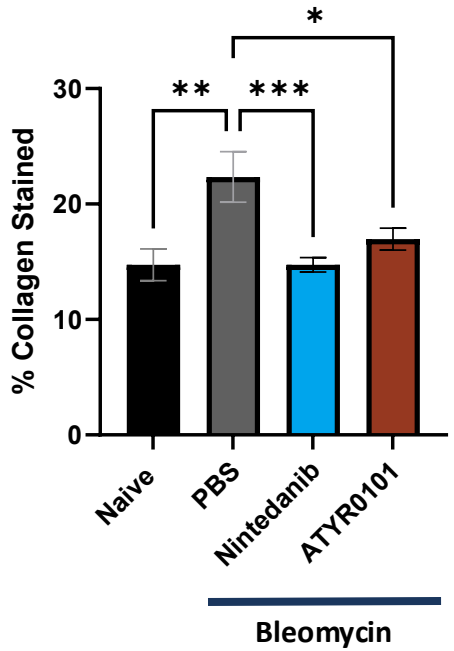


ATYR0101 Reduces Histologic Fibrosis Measures in Bleomycin-induced Lung Fibrosis

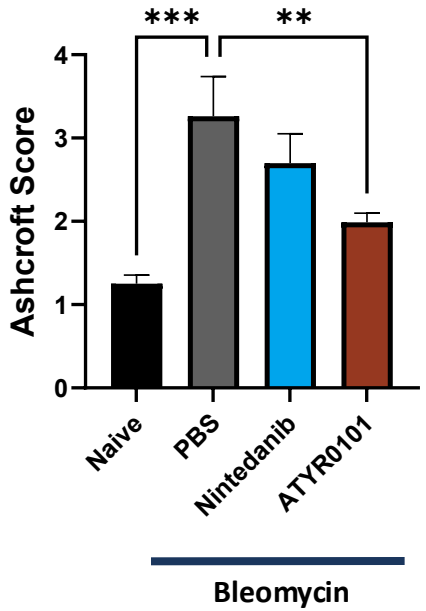
Mouse Bleomycin Model



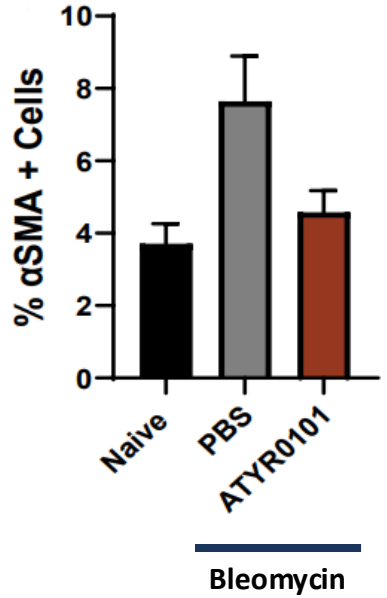
% Collagen in Total Lung Area



Ashcroft Score (Lung Fibrosis)



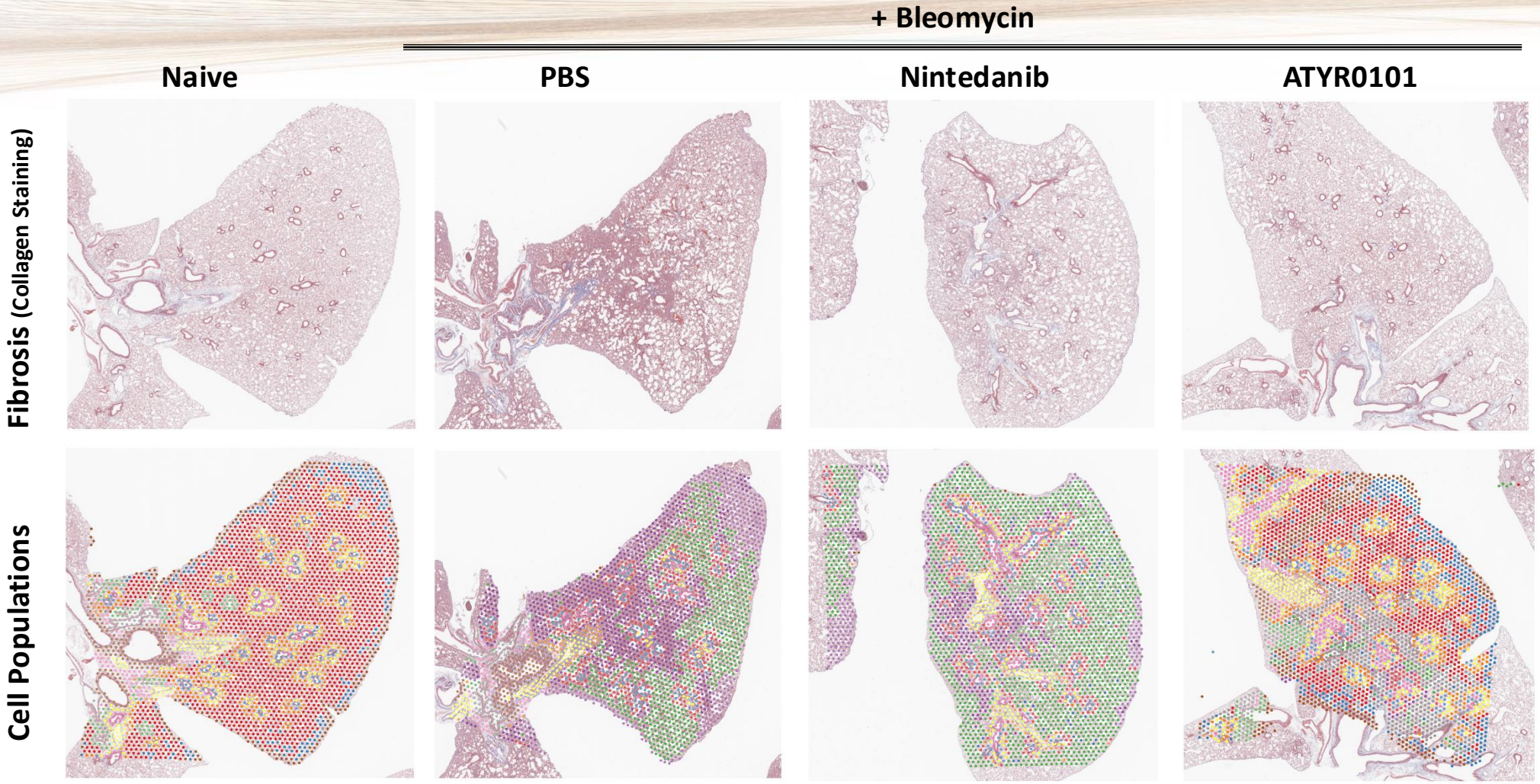
αSMA Immunofluorescence



- The degree of collagen & fibrosis was significantly lower in ATYR0101 treatment groups as compared to the PBS control group
- Immunofluorescence analysis shows that ATYR0101 treatment leads to a reduction of αSMA+ cells

ATYR0101 – 10mg/kg TIW; Nintedanib – 60mg/kg QD; presented at Keystone 2024 https://atyrpharma.com/wp-content/uploads/2024/12/20241208_Keystone-poster-In-Vivo_Final.pdf

ATYR0101 Treatment In Lung Fibrosis Model Results in Unique Anti-Fibrotic Effects



ATYR0101-treated lungs are enriched with cell types present in normal healthy lungs, and the spatial distribution of these cell types is also similar to that of normal lung

Thank You

ATYR0101 MoA Working Model