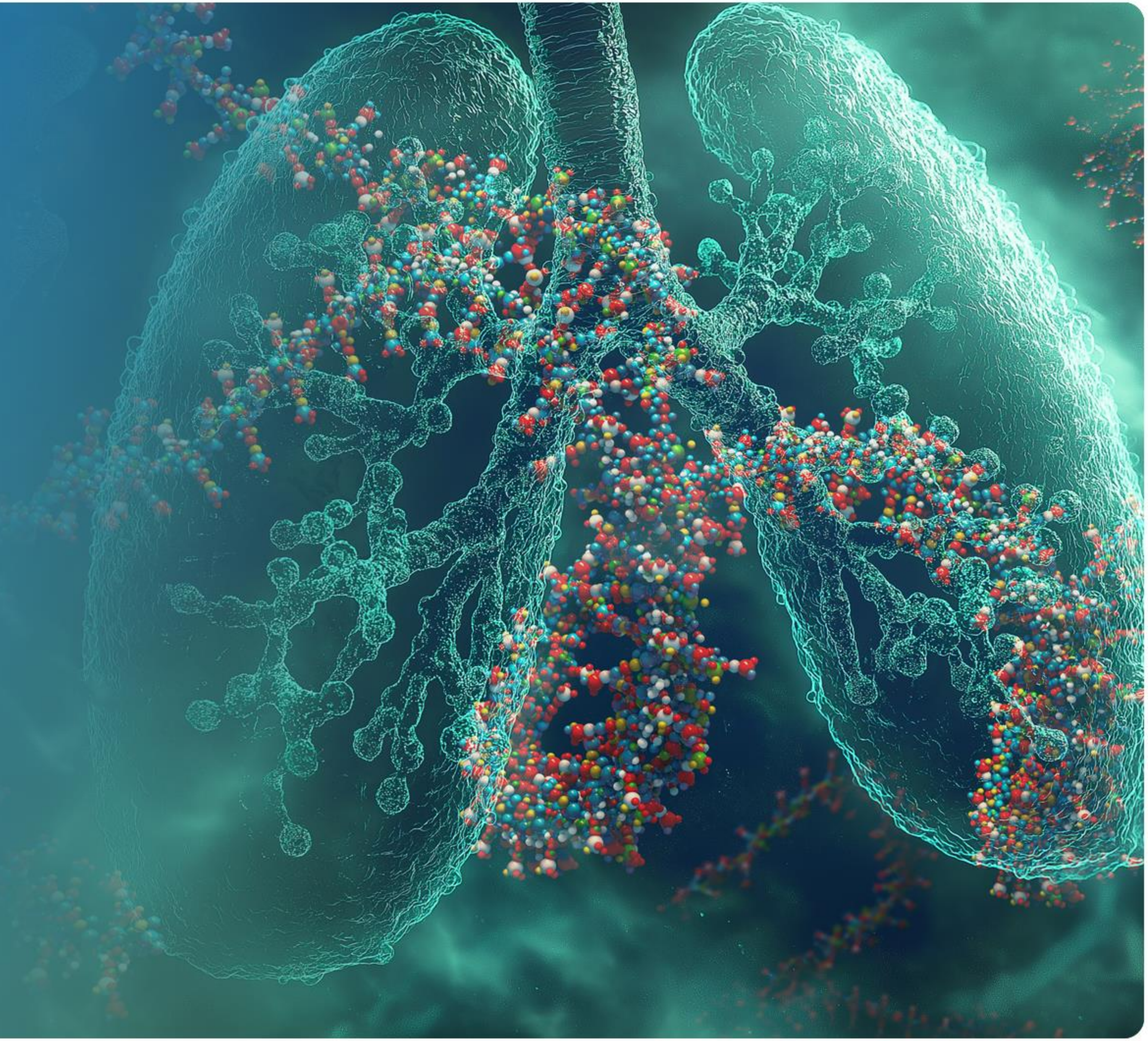
SpliSense
Making Sense of Splicing

RNA Based Platform for Pulmonary Diseases

Corporate Presentation // 2025

NON CONFIDENTIAL



SpliSense's Platform Technology for Precise Pulmonary Therapies

Leadership with deep genetic RNA and **pulmonary expertise**

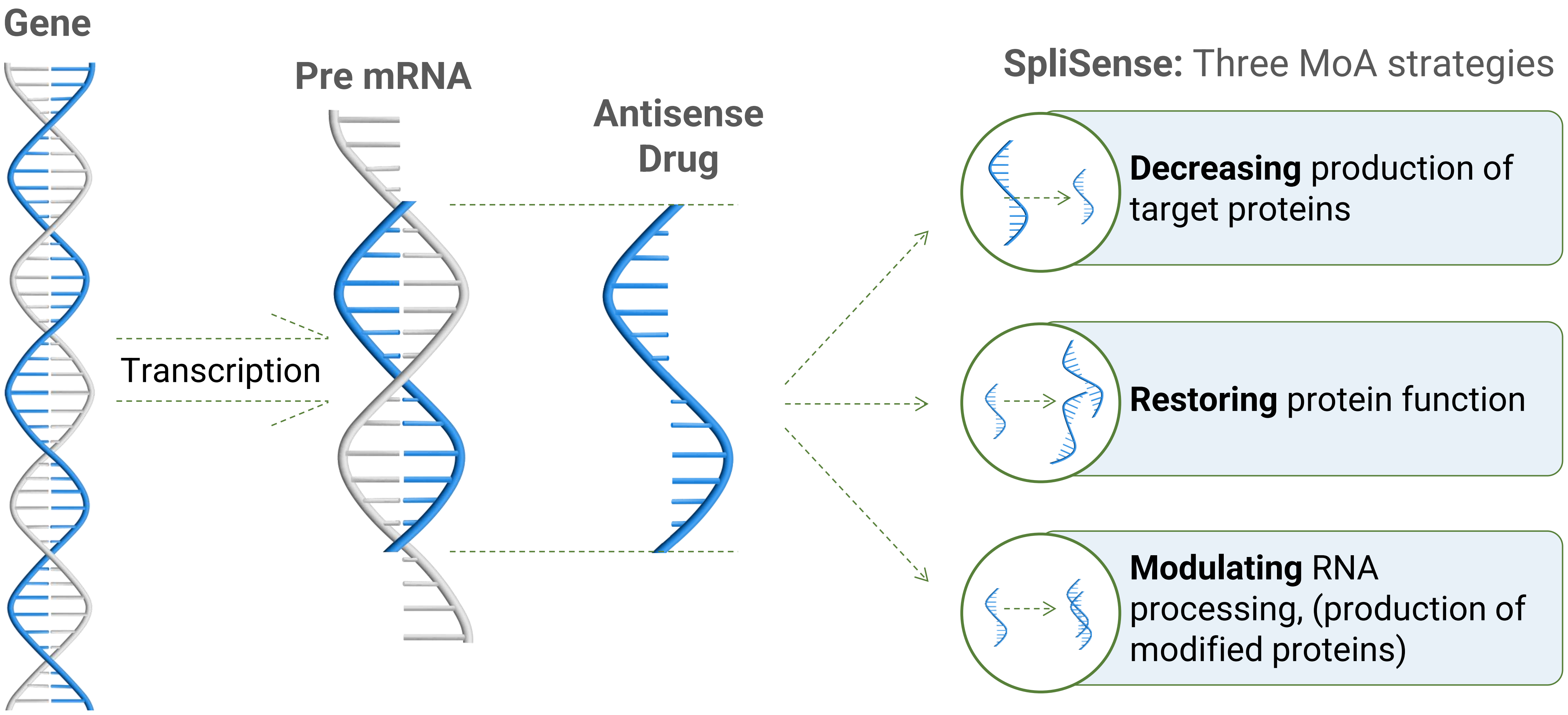
Three clinical programs by 2026; ASO Combined inhaled delivery system

Proprietary **algorithms** for splicing modulation, **ASOs** optimization

First efficacy **evidence for ASO therapy** in a pulmonary disease

Antisense Oligonucleotides – Modulating RNA (MoA)

14 Approved ASOs (2024)



SpliSense - First Evidence of Clinical Benefit of ASO Therapy in a Pulmonary Disease

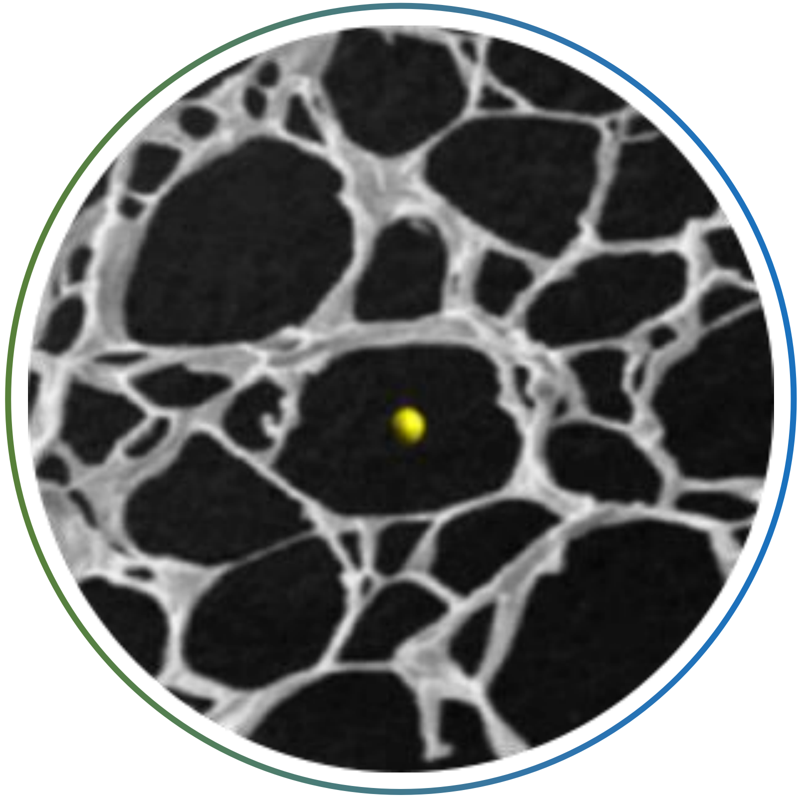
INDICATION	APPROACH	PROGRAM	PRECLINICAL	IND ENABLING STUDIES	Phase 1	Phase 2
Cystic Fibrosis CYSTIC FIBROSIS FOUNDATION	Restoration of Protein Function	**SPL84** (3849)				✓
	Protein Modulation	**SPL23** (W1282X)				
Muco-Obstructive Diseases COPD/Asthma/NCFB	Decrease Production of Over-expressed Protein	**SPL5AC**			**H1 2026**	
IPF		**SPL5B**			**H2 2026**	

SpliSense Tackles the Key Challenges of **Lung Delivery**

SpliSense
Making Sense of Splicing

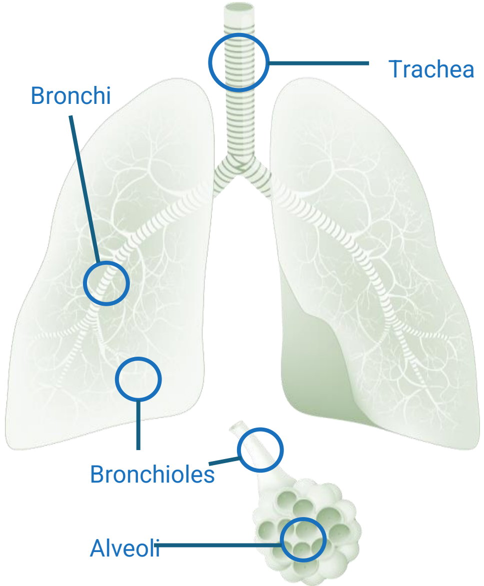
SPL ASOs are Designed for Optimal Pulmonary Delivery and Target Modulation

- **SPL ASOs are designed and optimized using SpliSense proprietary algorithms**
  - Identification of splicing motifs within the target sequence
  - Efficient and specific binding to the target sequence
  - Safety and Immunogenicity optimization
- **Optimized chemical modifications that drive stabilization and longevity**
  - Negatively charged
- **Proper airway mucus penetration and lung distribution:**
  - Single strand of 18-22 nt (~ 1-3 nm) smaller than the mucus pore size (healthy ~100 nm; COPD ~50nm)

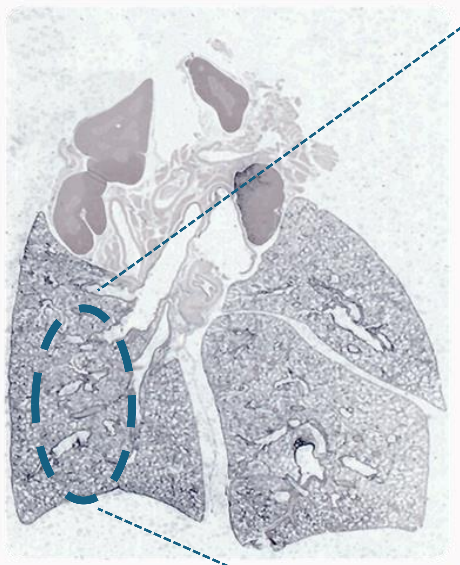


SPL ASOs

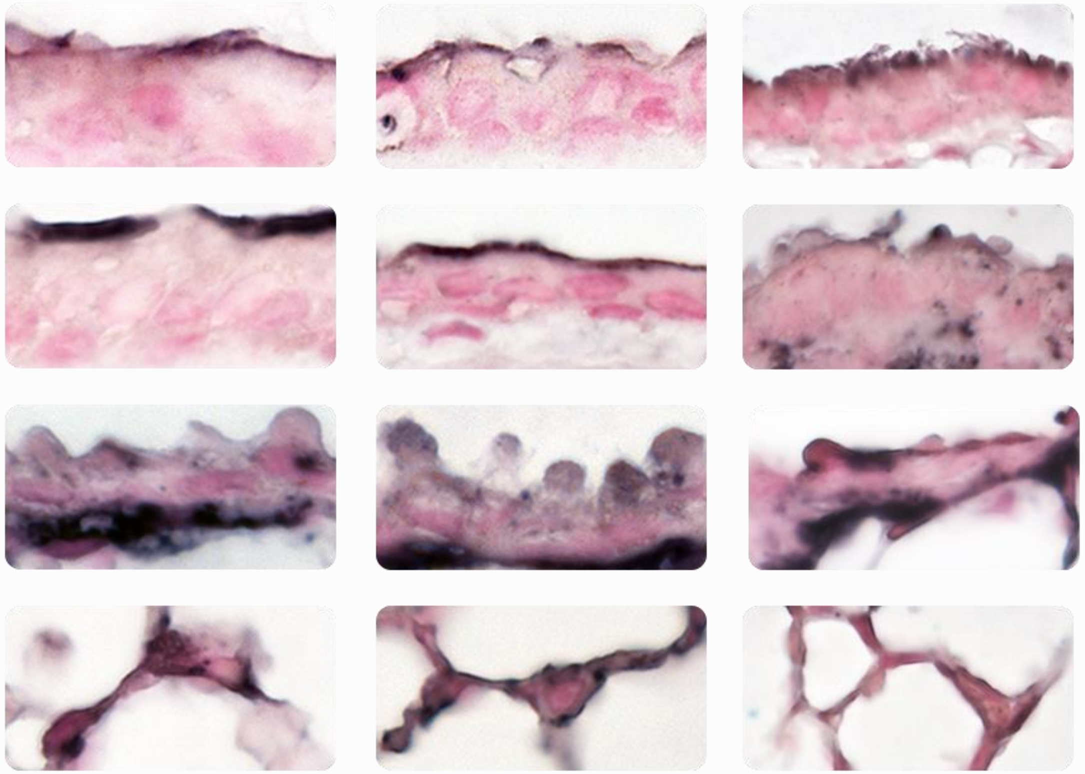
Wide & Efficient Distribution of SPL ASO in WT and "Muco-Obstructive" (β-ENaC) Mice Lungs



β-ENaC
24hr post dose



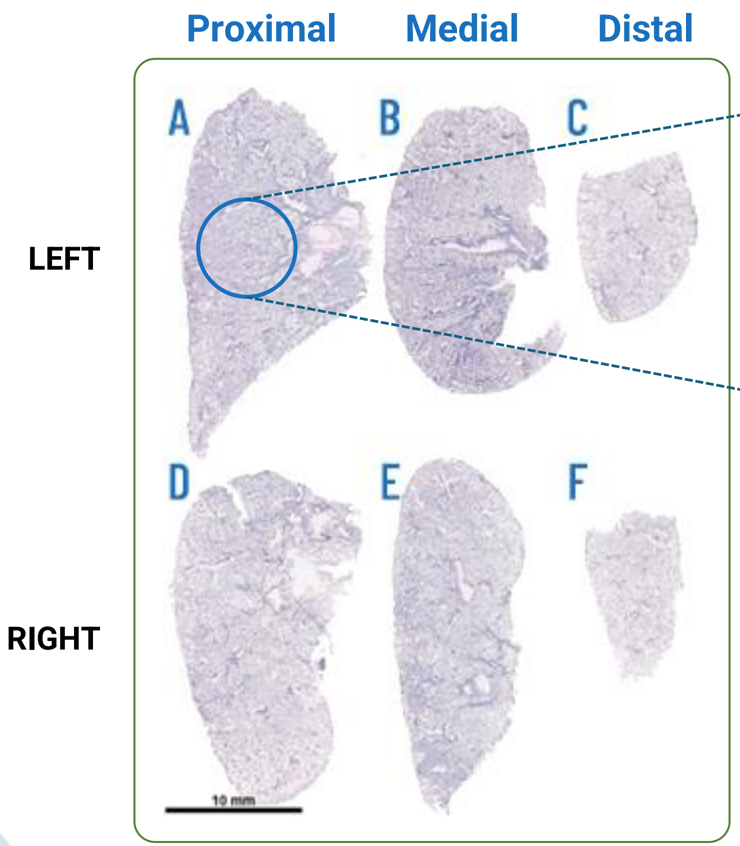
β-ENaC 24hr post single dose	WT 24hr post single dose	WT 4wks post single dose	
			Trachea
			Bronchi
			Bronchioles
			Alveoli

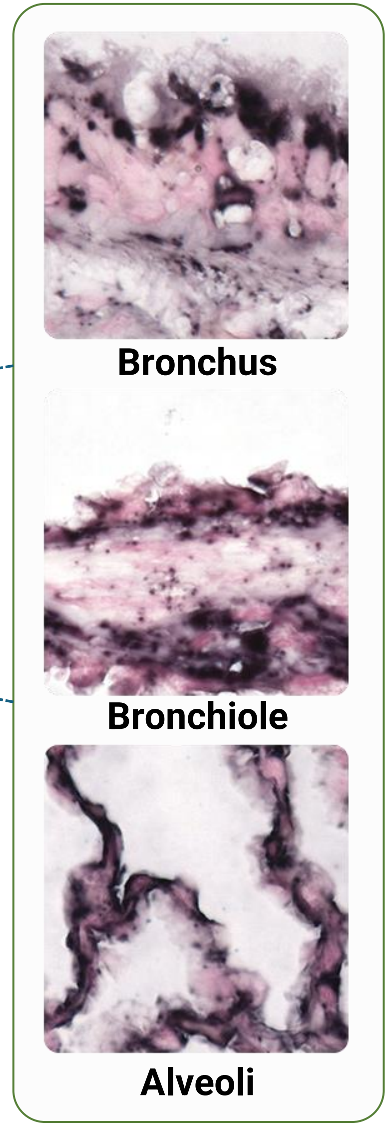


ISH STAINING FOR SPL ASO FOLLOWING IT ADMINISTRATION
DARK STAINING

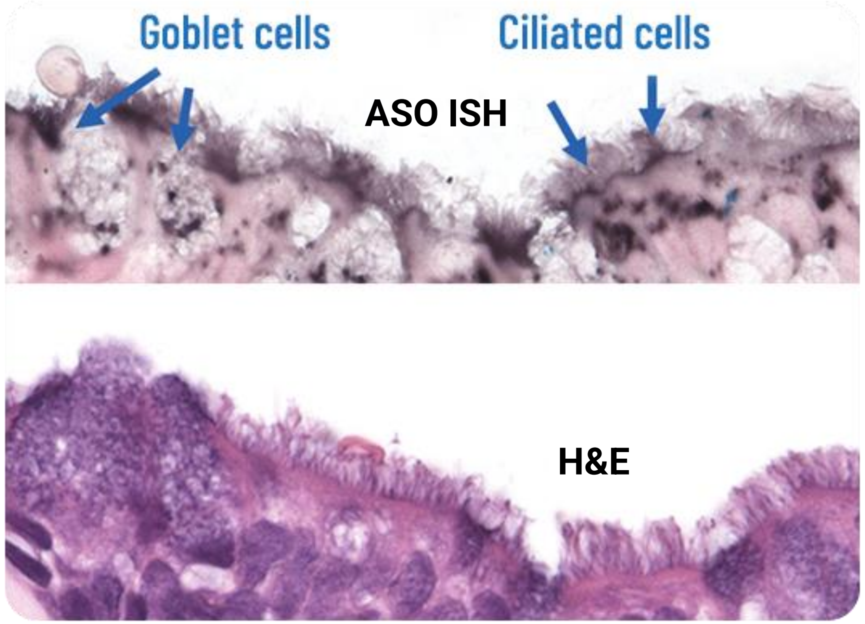
SPL ASO Uniformly Distributes in NHPs Lungs Following Inhalation

Post 4 weekly doses
ISH STAINING FOR SPL ASO - DARK STAINING





- Uniform labeling in all sampled sections
- Respiratory epithelium and alveolar cells are well labeled



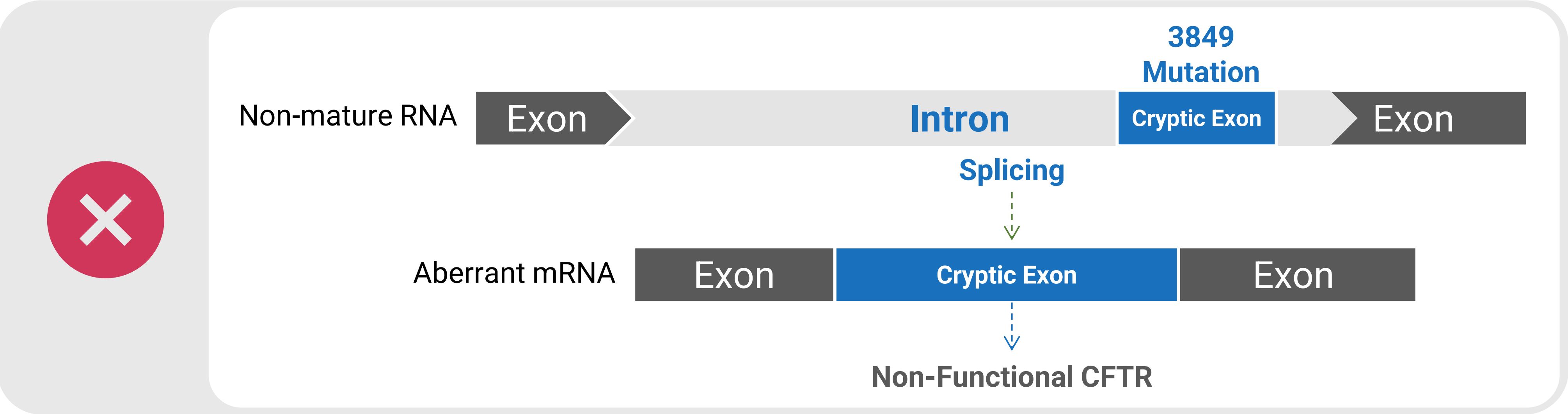
Making Sense of Splicing

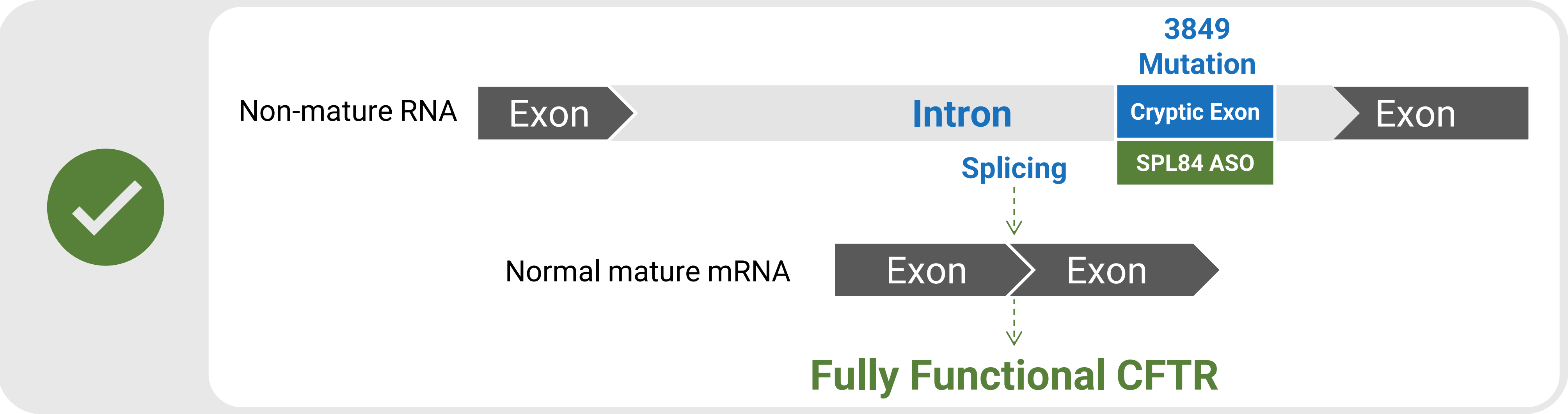
SPL84 – Phase 2

Clinical PoC of SPL ASO Platform in a Pulmonary Disease

Restoring
protein function

SPL84 Produces Mature and Functioning WT CFTR





SPL84 Global Phase 2 Study Design

Placebo Controlled Multiple Ascending Dose (MAD) in subjects with CF 3849+10kb C->T mutation

1 dose/week x 9 weeks; 3:1 active : placebo

25 mg --DSMB--> 50 mg DSMB*

n=8
6 active; 2 placebo

n=8
6 active; 2 placebo

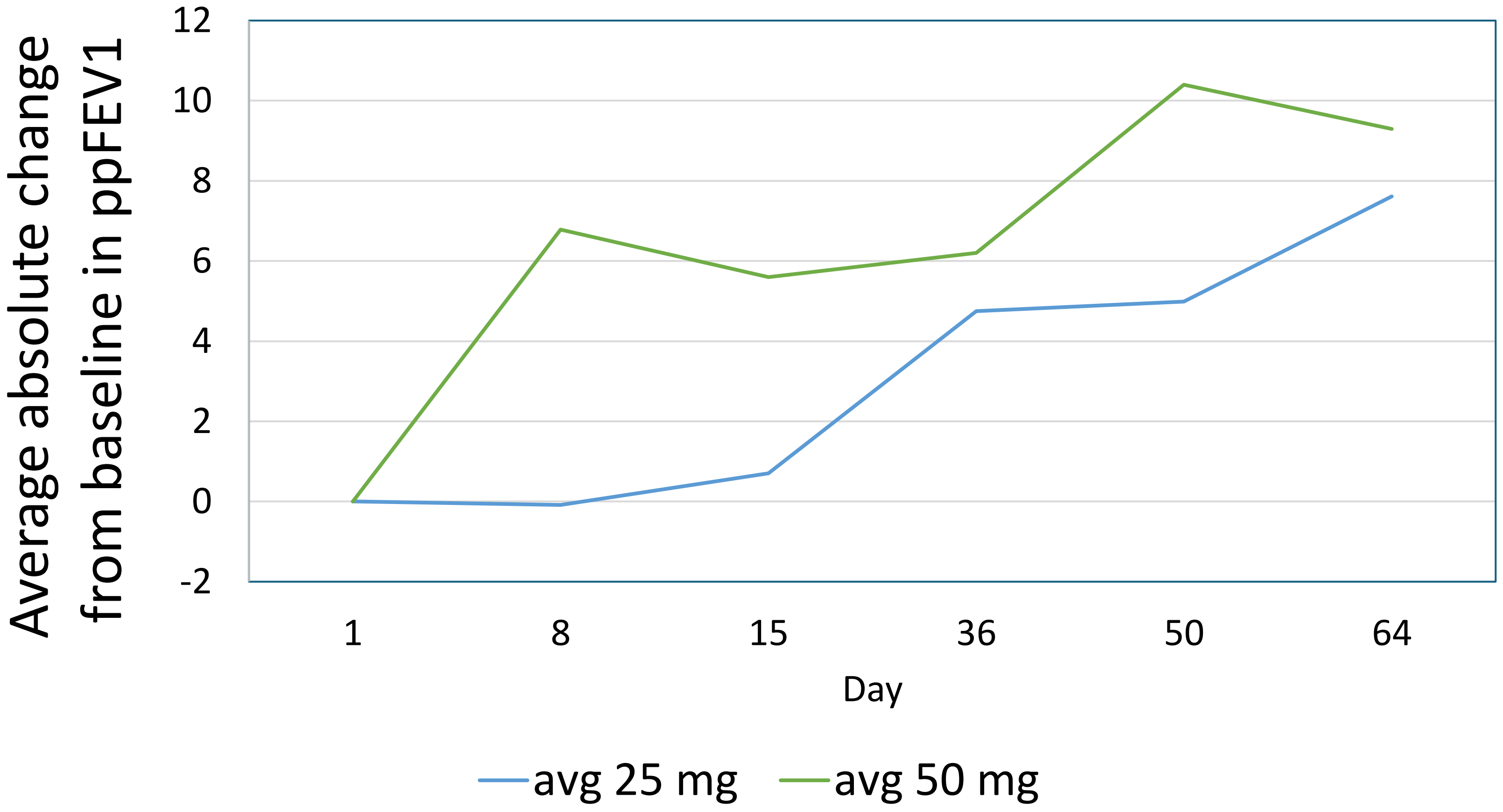
Data Analysis

Primary Objective:
To evaluate the safety & tolerability of multiple ascending doses of SPL84

Secondary Objective:
To assess preliminary efficacy (ppFEV1) of multiple ascending doses of SPL84

- **Fast Track Designation**
- **IND, CTR approvals**

SPL84 Treatment Leads to ppFEV1 Increase Along 9 Weeks of Treatment
(Absolute Change from Baseline)



SpliSense
Making Sense of Splicing

SPL84 – Clinical Validation of SpliSense ASO Platform

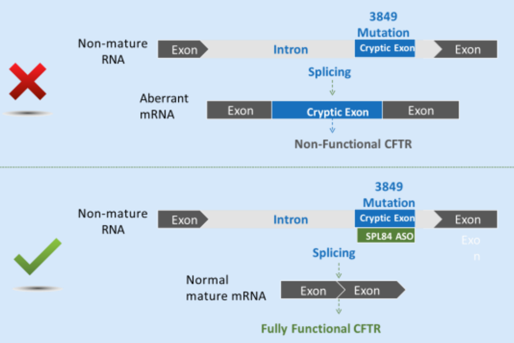
- **Clinical meaningful Improvement in lung function (ppFEV1)**
  - High clinical meaningful response rate
  - Mean absolute change in ppFEV1 for SPL84 compared with placebo was **10 (**sub-analysis).
  - $ppFEF_{25\text{-}75}$ increases and correlates to ΔppFEV1 following SPL84 treatment
  - 4/7 patients demonstrated reduction in microbial burden at study end
  - Longer period of SPL84 might be needed to reach steady state and maximal response
- No safety signals or trends of concern were identified among participants

First Evidence of Potential Clinical Benefit of ASO Therapy in a Pulmonary Disease

SPL84+Trikafta® has the Potential to Break the Ceiling Effect of FEV1

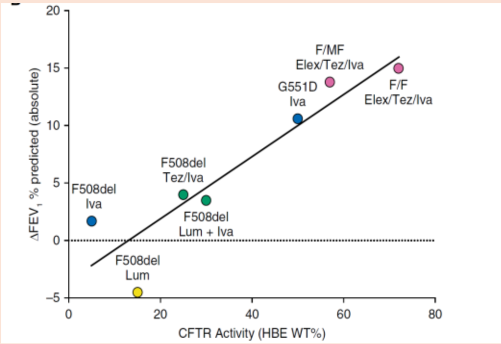
Unmet need

Despite current treatments, ~2/3rd of Patients do not have normal CFTR Function (ppFEV1, SC)



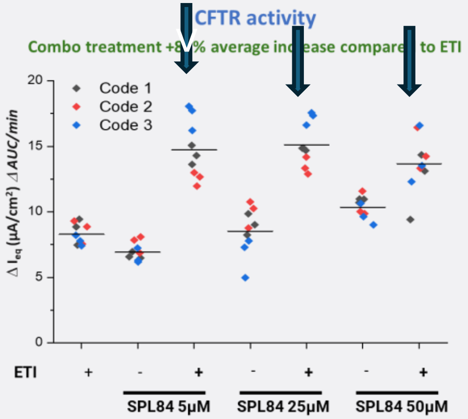
SPL84 Clinically Validated with Unique MoA

SPL84 delivered locally with distinct MoA than Modulators



Predictive Assay

Industry standard HBE assay highly predictive of FEV1 for approved CFTR modulators



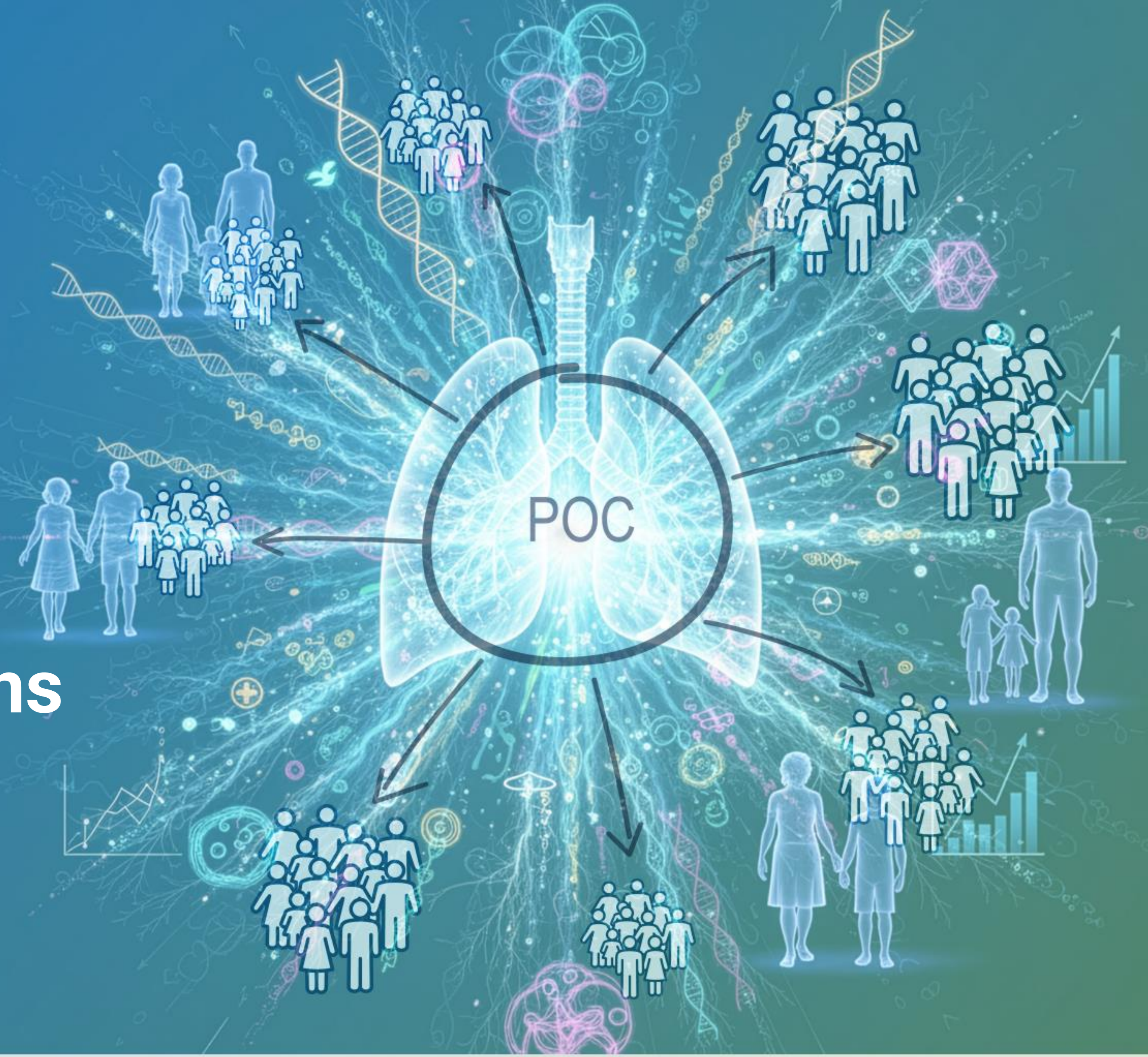
Additive Combo Effect

Combo Effect in vitro predicts significant increase in FEV1 comp. to Trikafta, potential to break the ceiling effect

Moving from Partial to Complete Correction of Lung Function

Taylor-Cousar 2019; 3. Konstan, NACFC poster 2022
Vertex 2Q23 Earnings Call Transcript; . Vertex 2Q24 Earnings Presentation; Sploletini 2022 JCF; Ibrahim 2023 Front Pharmacol, VRTX 4Q24 earnings call; 8. 2024 Wall Street research estimates; 9. Kaftrio EMA

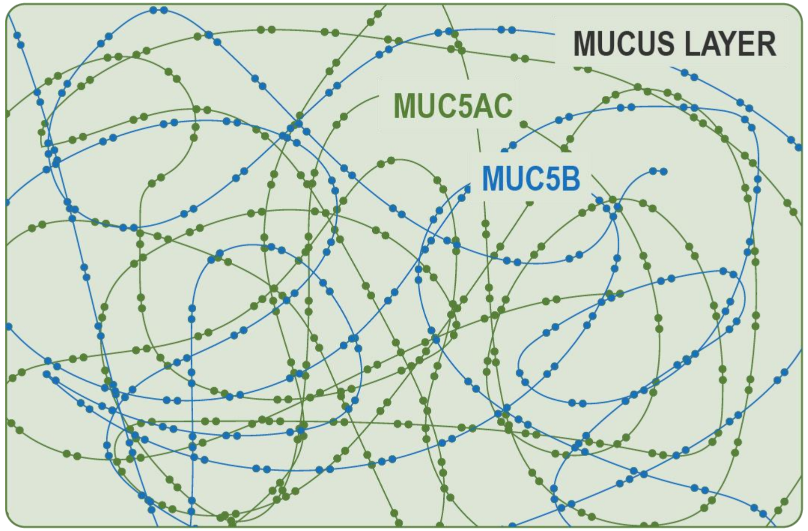
Expanding Our ASO Technology From Orphan to Large Pulmonary Indications

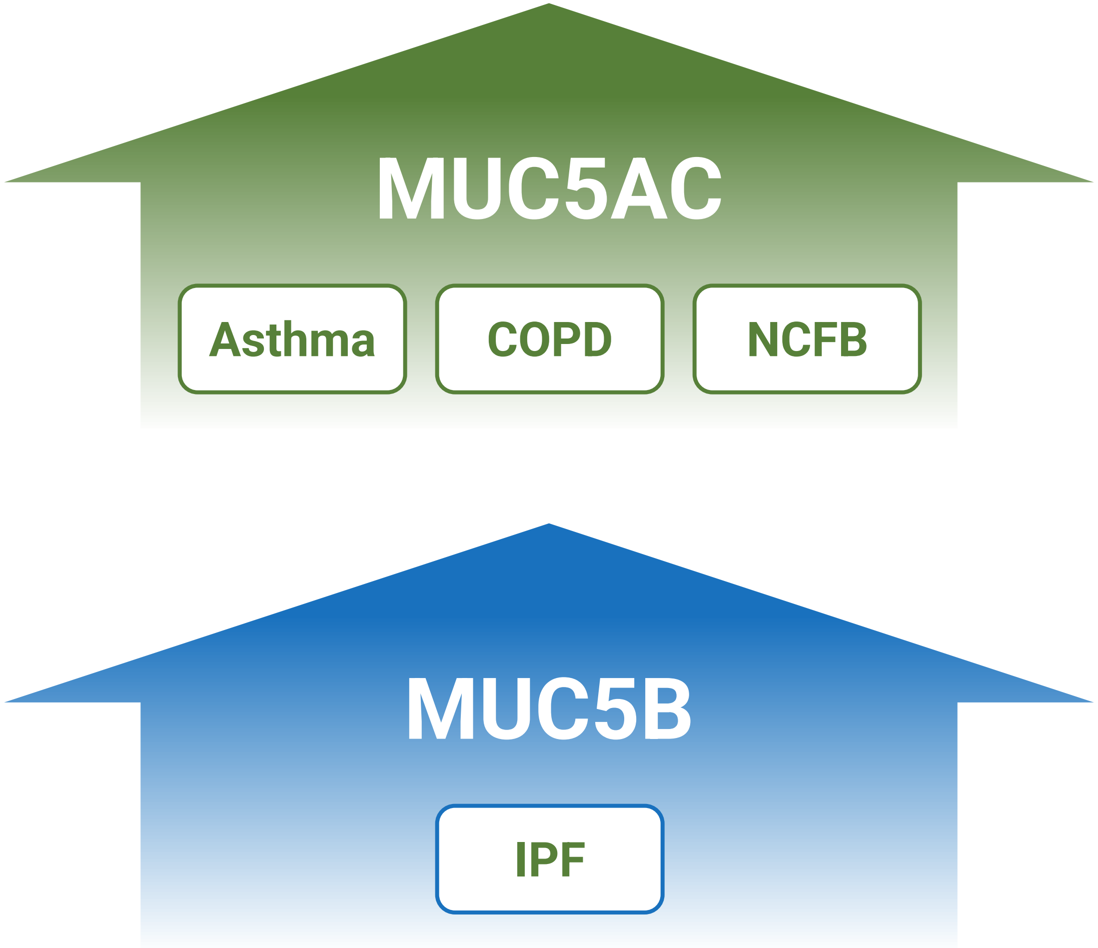


Novel Approach to Treat Pulmonary Indications – Lowering Mucins in the Airways

In the airways, MUC5AC and MUC5B are the secreted polymeric mucins.

- Mucins support the structure and organization of the airway's mucus gel
- Mucin concentrations/secretions dictate its viscoelastic properties.





SpliSense
Making Sense of Splicing

SpliSense
Making Sense of Splicing

Muco-Obstructive Diseases

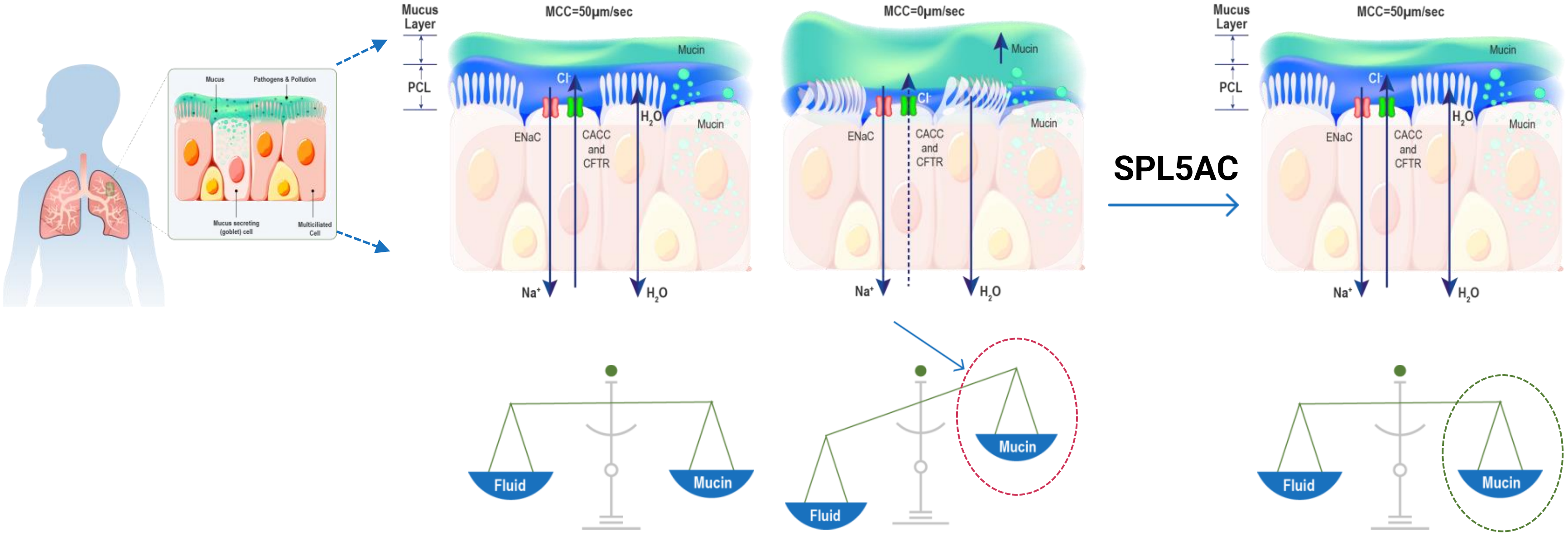
MUC5AC Lowering ASO (SPL5AC)

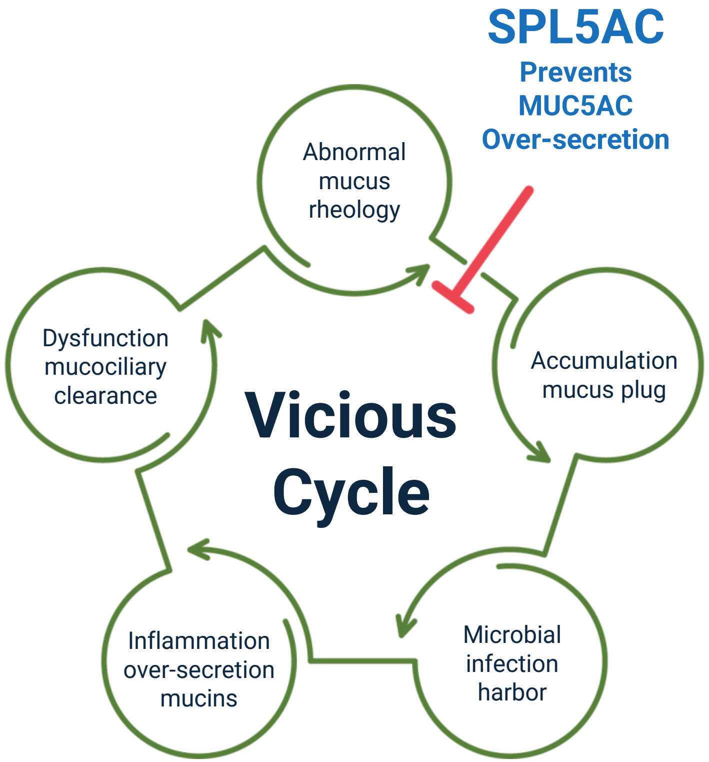
Decrease production of over –expressed proteins

SPL5AC Inhibits the Vicious Cycle in CF and Other Muco-Obstructive Diseases

SPL5AC Reduces MUC5AC Levels to Restore the Balance Between Mucins and Fluids in the Mucus

Normal | **Disease State** | **Balanced Mucus-Restored MCC**

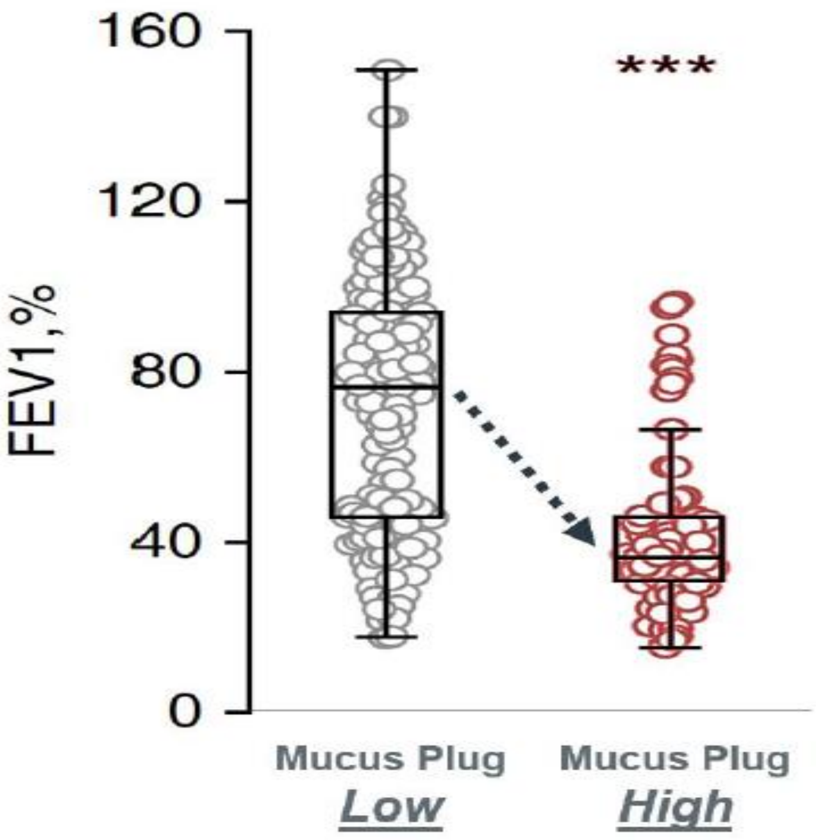


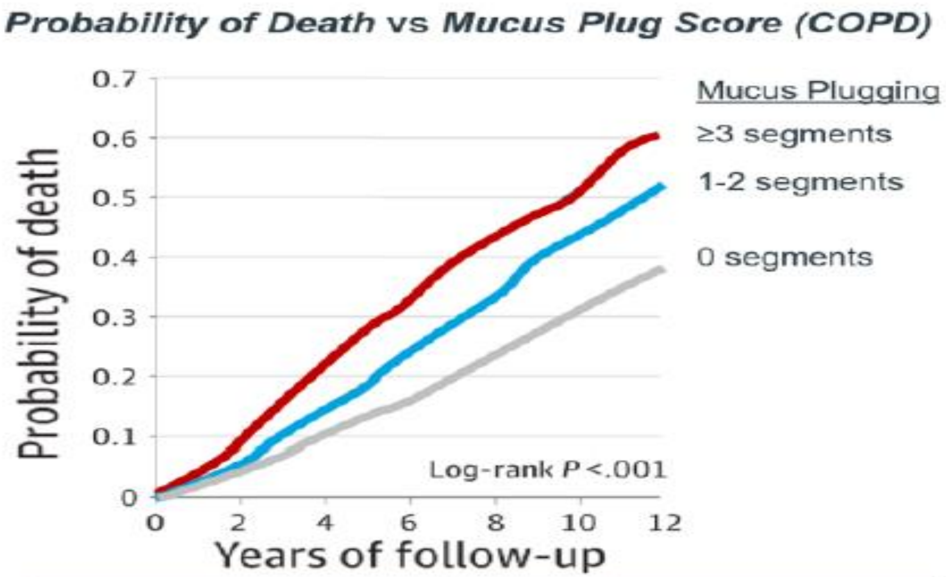


Adopted from Liu et al. 2024

SpliSense
Making Sense of Splicing

Mucus Plugs are Associated with Decreased Lung Function and Higher Mortality





Mucus Plugs per Lung Segment	Mortality Rate (9-year, avg)
0	34.0% (±1.8%)
1-2	46.7% (±3.2%)
≥3	54.1% (±3.3%)

RESPIRATORY AND CRITICAL CARE MEDICINE®

JAMA The Journal of the American Medical Association

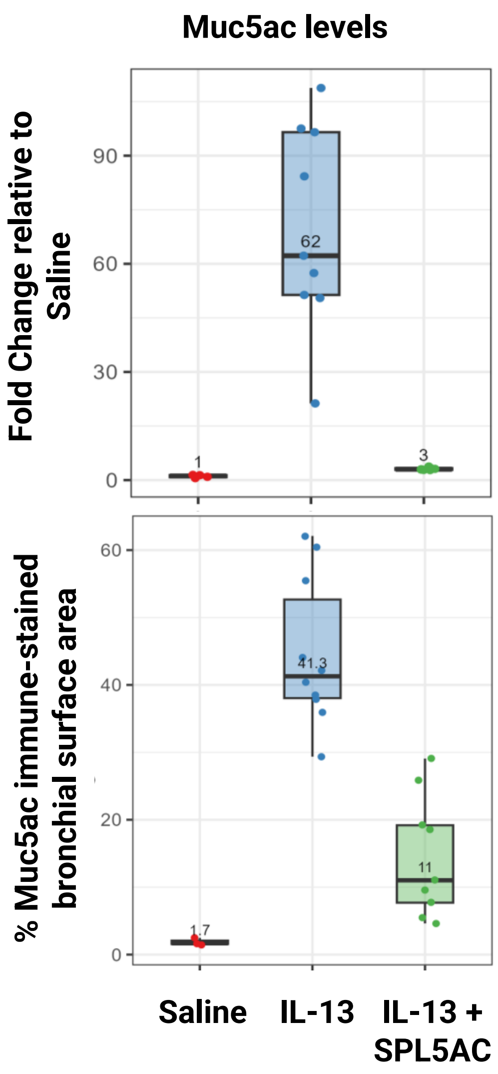
SpliSense Making Sense of Splicing

SPL5AC ASO for Muco–Obstructive Diseases IND Enabling Phase - Program Overview

- **SPL5AC significantly lowers MUC5AC levels (RNA & Protein) in HVs derived bronchial cells (HBEs) w/wo IL13 stimulation**
- **SPL5AC was shown to be effective in relevant disease models**
  - IL13 hyper stimulated mice
  - Ovalbumin stimulated mice model (lung obstruction and Asthma)
  - Aspergillus allergen stimulated Mice model (Asthma)
- **Promising, preliminary lung toxicological profile at high doses**
  - No off-target effect
  - No ex-vivo immunogenic response

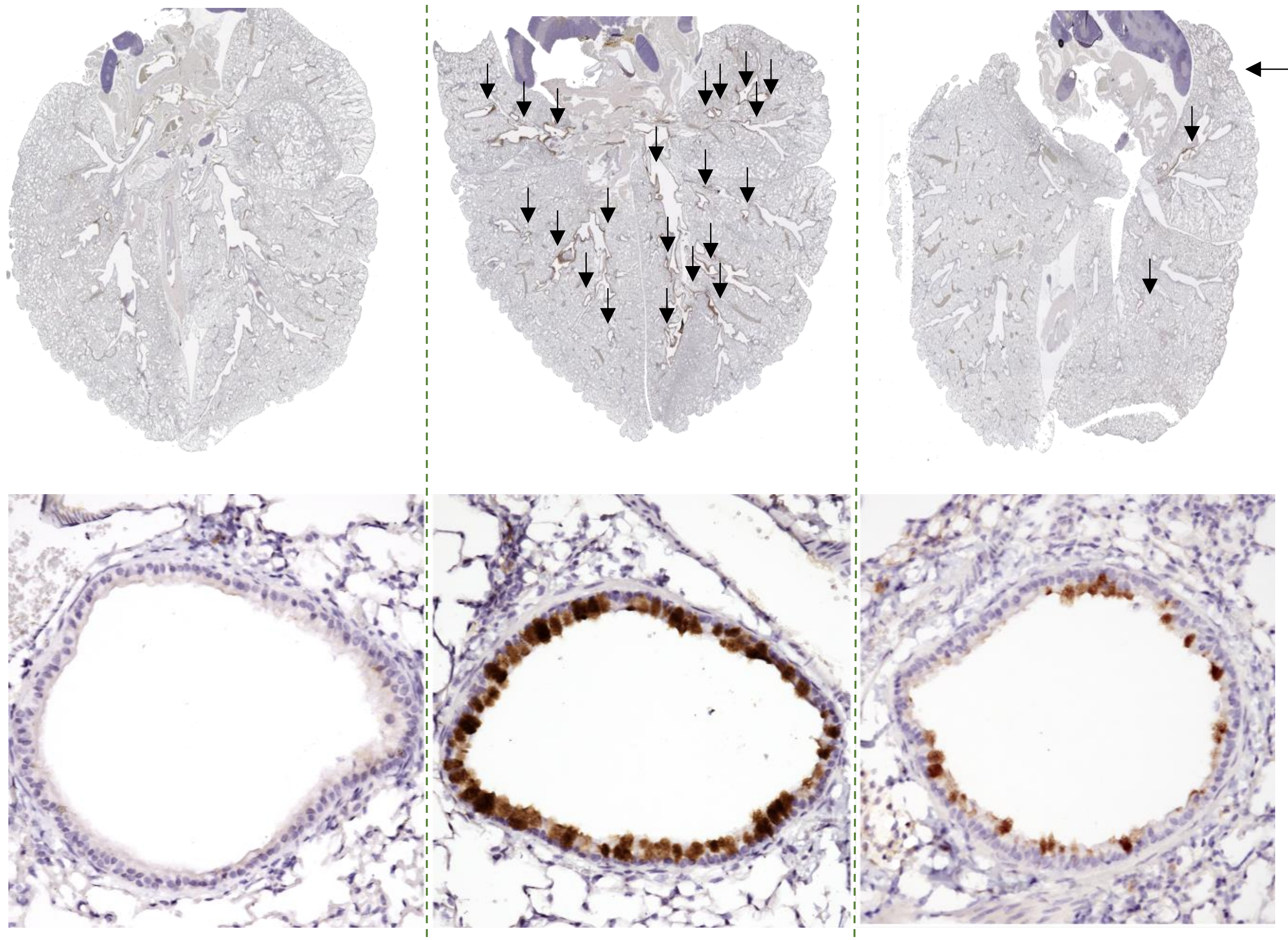
Phase 1-2a targeted for 2026

SPL5AC ASO Reduces Muc5ac Protein Levels in Lungs of IL13 Hyper-Stimulated WT Mice



RNA
(96% reduction)

Protein
(73% reduction)

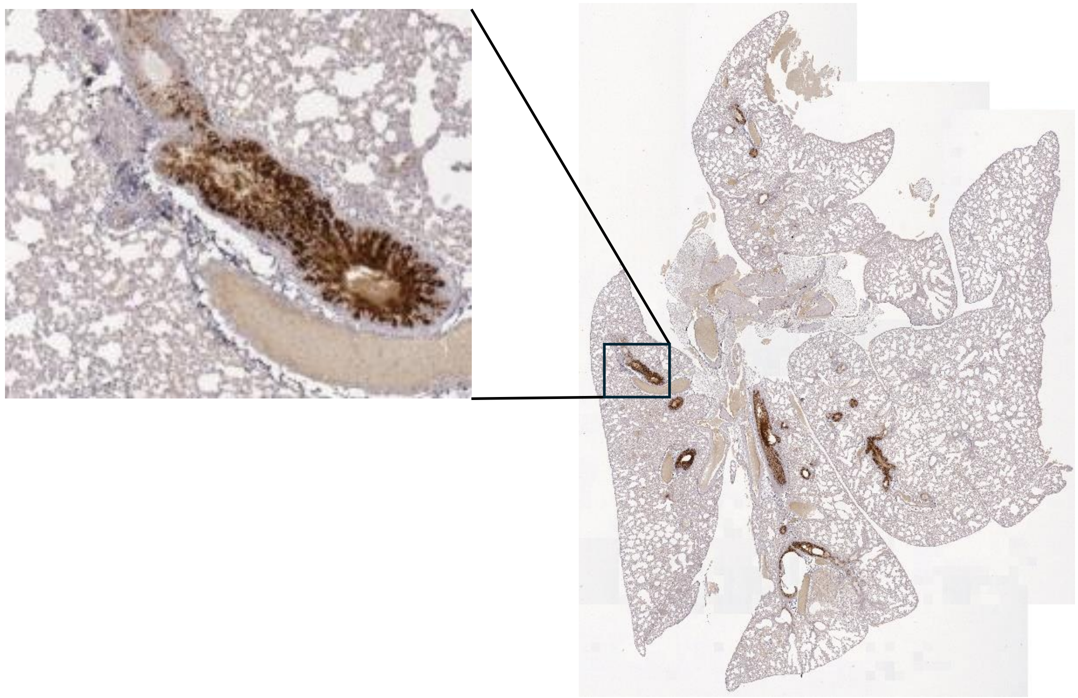


Once a week SPL5AC treatments in mice support EOW treatment regimen in humans

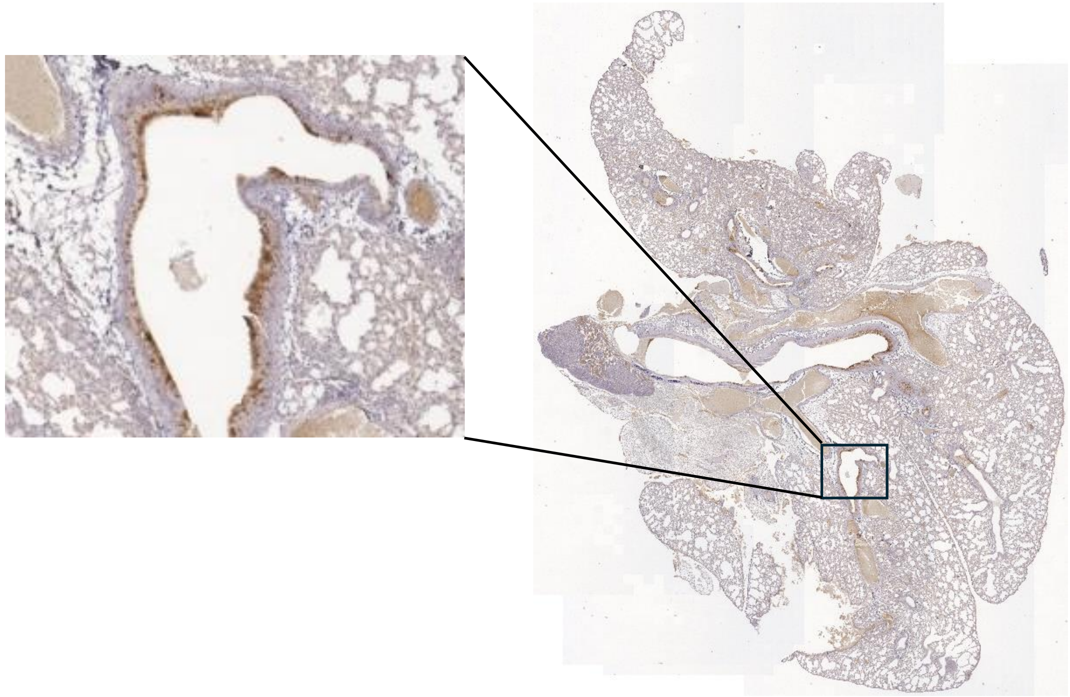
SpliSense
Making Sense of Splicing

SPL5AC Inhibits Mucous Plugs Formation in IL-13 Hyper-Stimulated WT Mice

IL-13

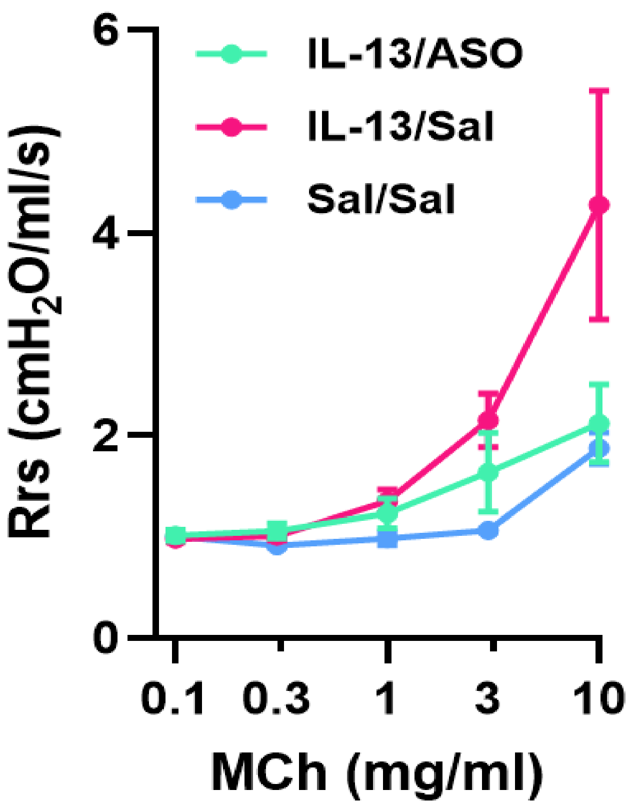


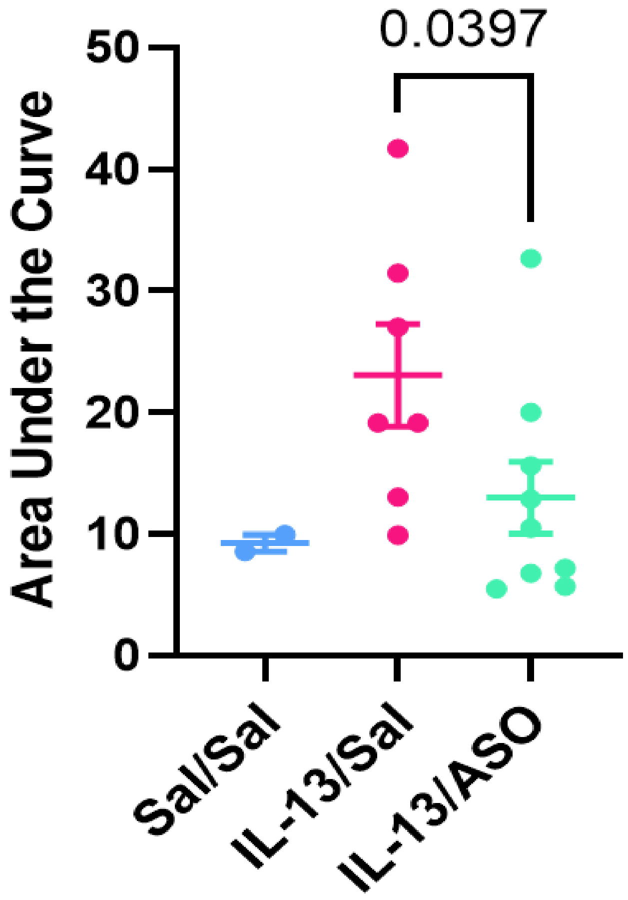
IL-13+SPL5AC



SPL5AC Prevents Airway Disfunction (AHR*) in IL-13 Hyper-Stimulated WT Mice

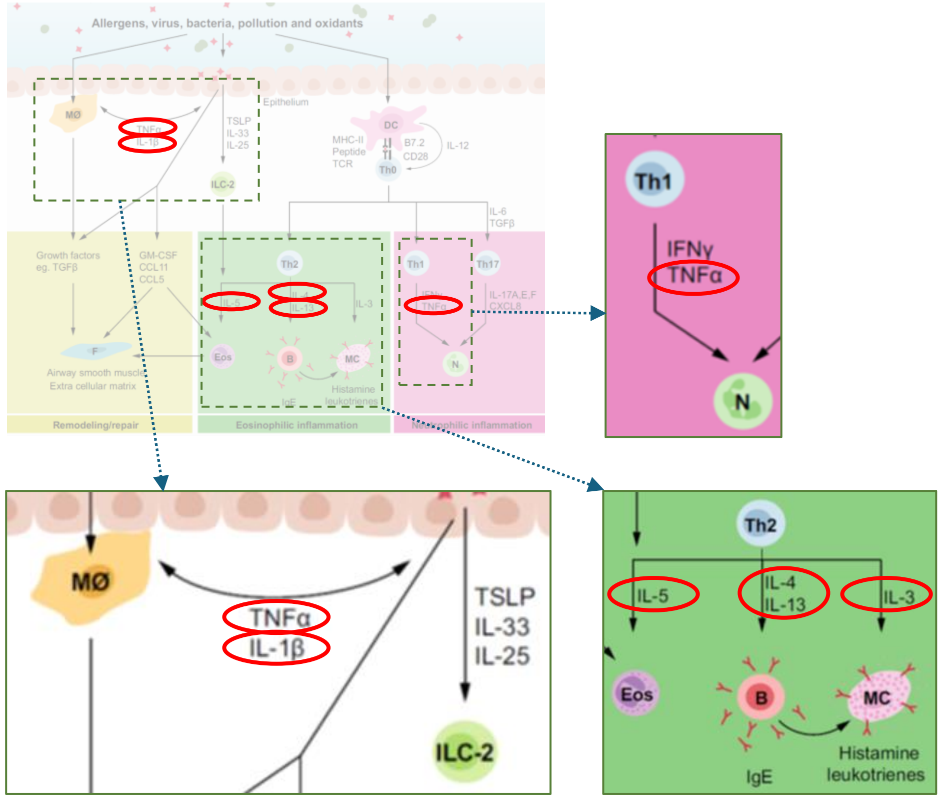
Division of Pulmonary, Allergy School of Medicine, University of Colorado – R. Evans Lab





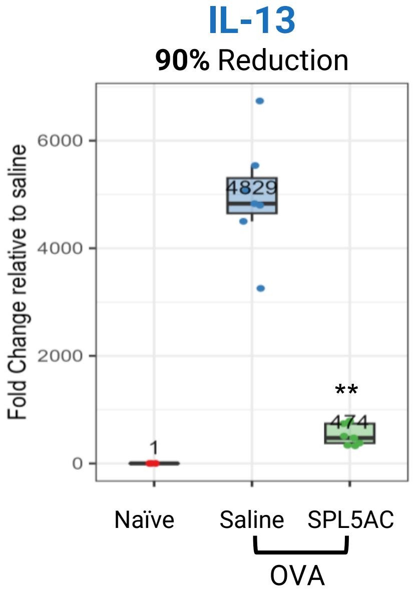
Airway hyperresponsiveness (AHR) is an exaggerated reaction of the airways to stimuli, a key feature of asthma, measured by bronchial provocation tests (MCh).

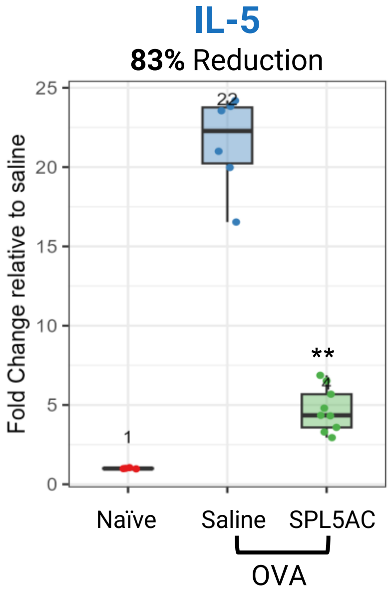
SPL5AC Attenuates Th-2 Inflammatory Response in an Asthma Disease Mouse Model (Ovalbumin)

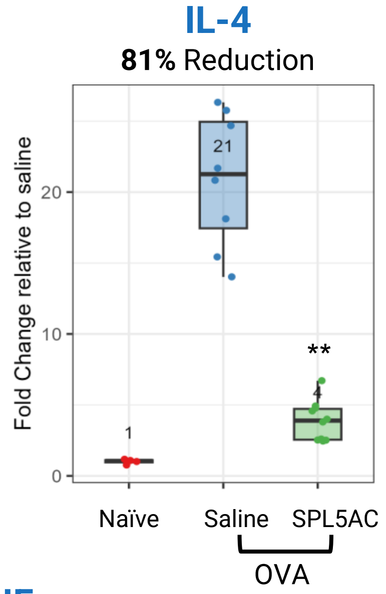


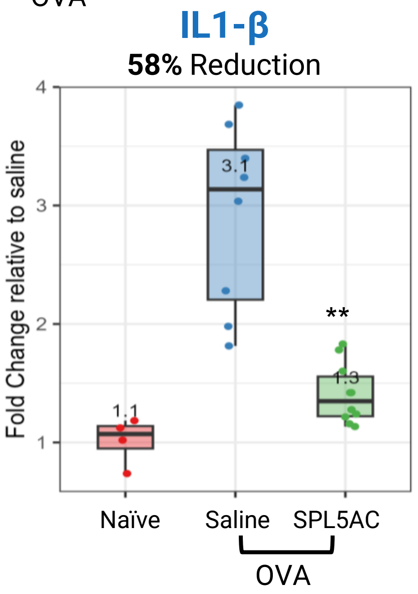
Adopted from Chung et al. 2015

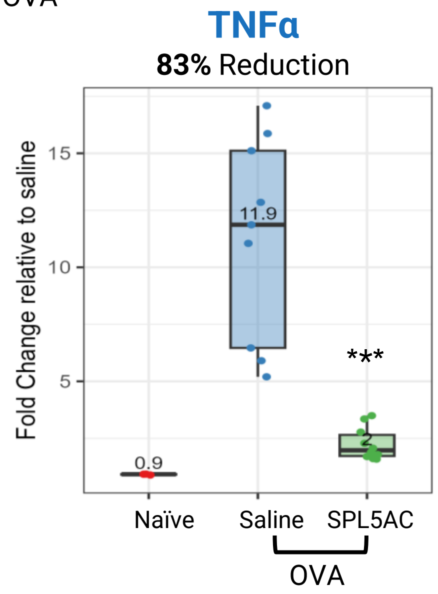
Pro-inflammatory cytokines induced in Asthma







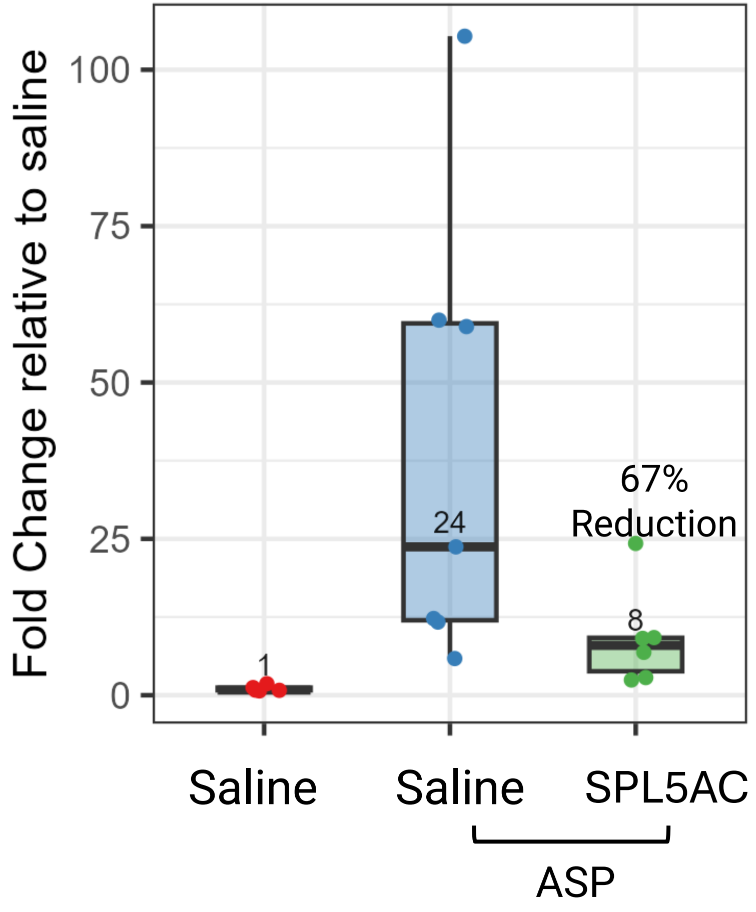




SPL5AC Reduces Muc5ac and Goblet Cells Hyperplasia in Aspergillus Induced Asthma Disease Mouse Model

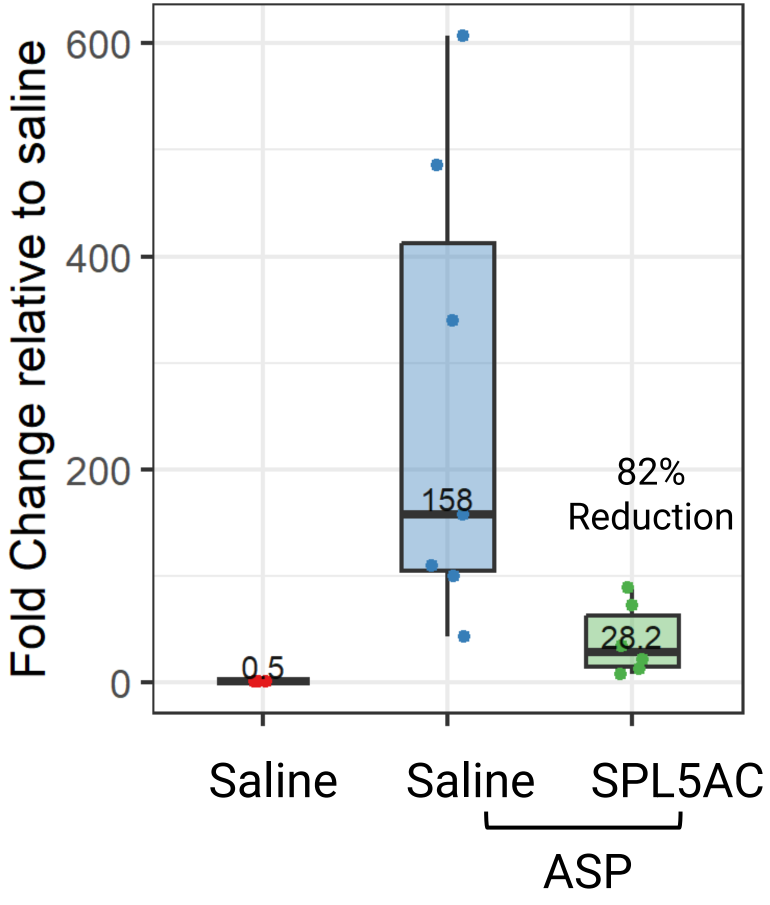
Muc5ac RNA

Full length Muc5ac RNA levels



Goblet Cells Hyperplasia

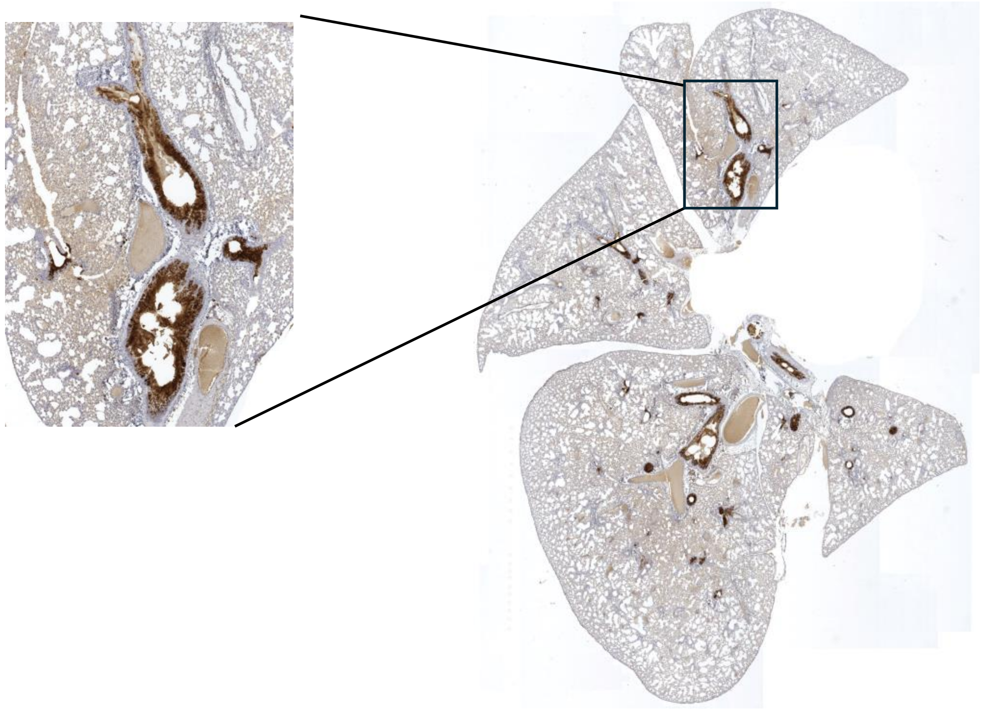
Gob5/Clca1 RNA levels



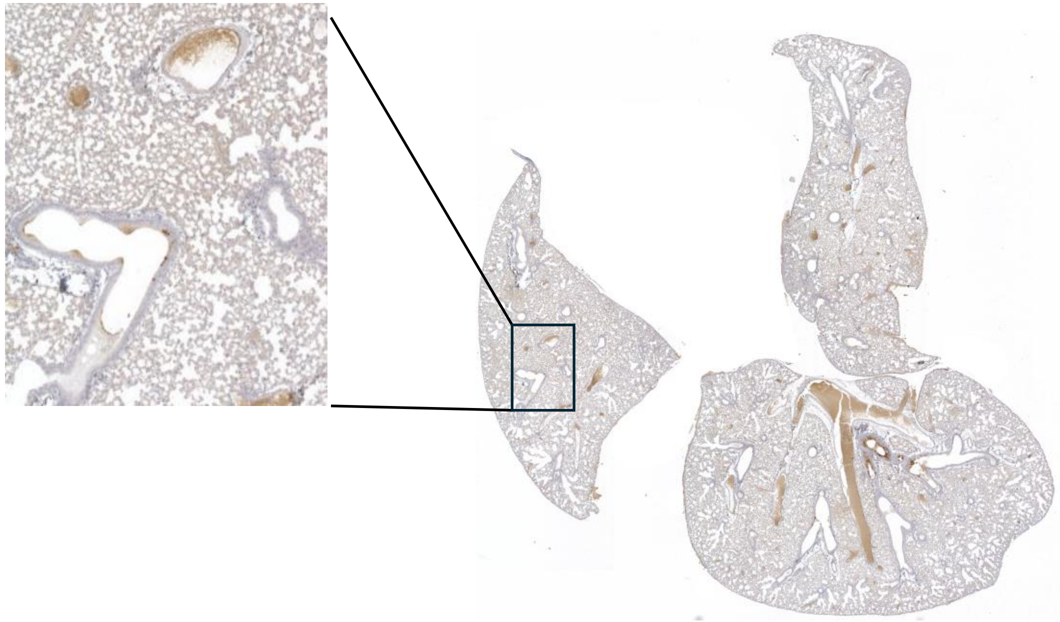
SpliSense
Making Sense of Splicing

SPL5AC Inhibits Mucous Plugs Formation in Aspergillus Induced Asthma Disease Mouse Model

Aspergillus



Aspergillus+SPL5AC



SpliSense
Making Sense of Splicing

Idiopathic Pulmonary Fibrosis (IPF)

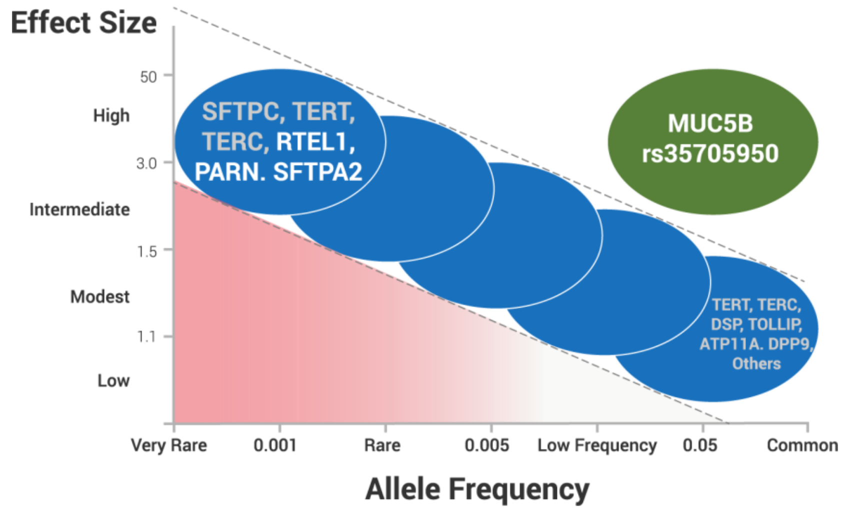
MUC5B Lowering ASO (SPL5B)

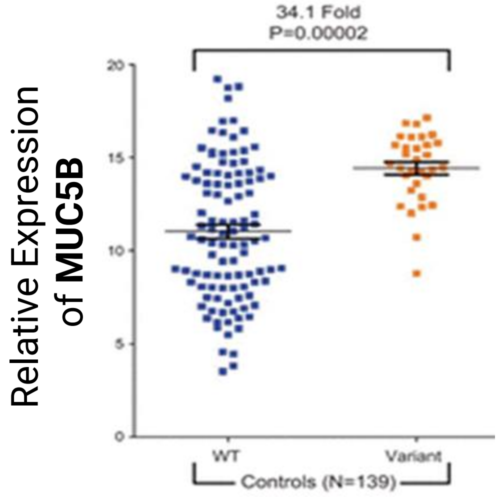
Decrease production of over–expressed proteins

Elevated Levels of MUC5B Potentially Drives IPF

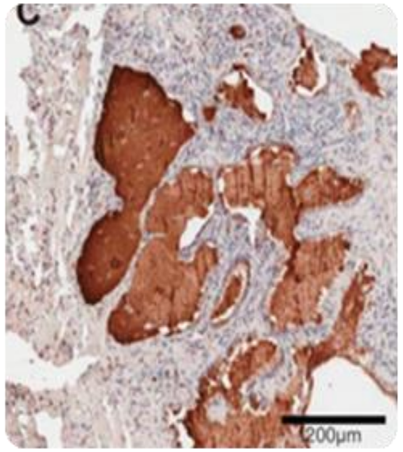
- **A single nucleotide polymorphism (SNP) in MUC5B gene (rs35705950)**
  - Leads to increased expression of MUC5B
  - Accounts for 60% of IPF cases
- **Elevated levels of MUC5B drives IPF Pathogenesis:**
  - Hypoxia at the area of MUC5B plugs
  - Impaired mucus clearance, inducing chronic inflammation and injury
  - Disturb the repair process after injury to the bronchoalveolar regions of the lung

SPL5B ASO aims to treat mild-moderate IPF patients preventing disease progression





IPF Diagnosed Patients

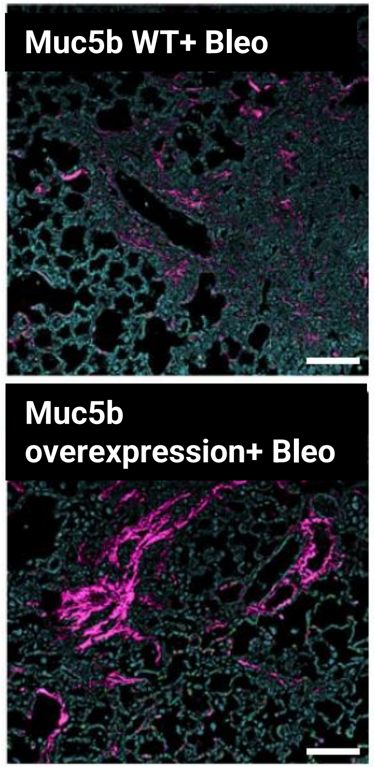


MUC5B plugs

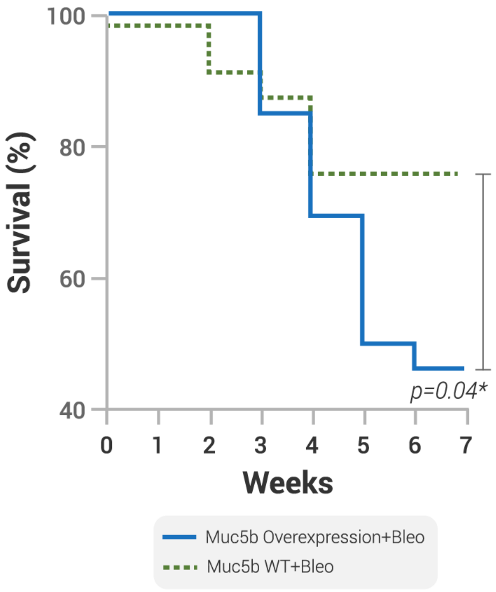
Evans et al 2014, Zhang et. al. 2019

Muc5b is Well Characterized to be Associated with Lung Fibrosis Pathogenesis in Disease Mice Models

Muc5b overexpression predisposes mice to pulmonary fibrosis (bleomycin mouse model)



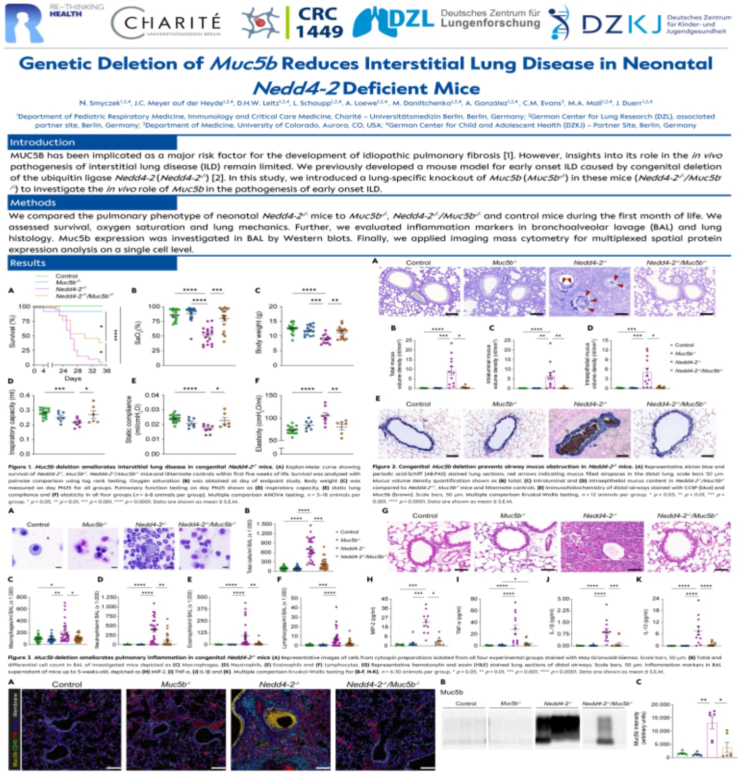
Increased lung fibrosis
(accumulation of collagen- Pink)



Reduced mice survival

Hancock et al. 2018

Knockout of Muc5b Ameliorates Disease Severity in ILD (Nedd4-2 mouse model)


RE-THINKING HEALTH
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN
CRC 1449
DZL Deutsches Zentrum für Lungenforschung
DZKJ Deutsches Zentrum für Kinder- und Jugendgesundheit

Genetic Deletion of *Muc5b* Reduces Interstitial Lung Disease in Neonatal *Nedd4-2* Deficient Mice

N. Smyczek[1,2,4], J.C. Meyer auf der Heyde[1,2,4], D.H.W. Leitz[1,2,4], L. Schaupp[1,2,4], A. Loewe[1,2,4], M. Daniltchenko[1,2,4], A. González[1,2,4], C.M. Evans[3], M.A. Mall[1,2,4], J. Duerr[1,2,4]

[1]Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]German Center for Lung Research (DZL), associated partner site, Berlin, Germany; [3]Department of Medicine, University of Colorado, Aurora, CO, USA; [4]German Center for Child and Adolescent Health (DZKJ) – Partner Site, Berlin, Germany

Introduction

MUC5B has been implicated as a major risk factor for the development of idiopathic pulmonary fibrosis [1]. However, insights into its role in the *in vivo* pathogenesis of interstitial lung disease (ILD) remain limited. We previously developed a mouse model for early onset ILD caused by congenital deletion of the ubiquitin ligase *Nedd4-2* (*Nedd4-2*$^{-/-}$) [2]. In this study, we introduced a lung-specific knockout of *Muc5b* (*Muc5b*$^{-/-}$) in these mice (*Nedd4-2*$^{-/-}$/*Muc5b*$^{-/-}$) to investigate the *in vivo* role of *Muc5b* in the pathogenesis of early onset ILD.

Methods

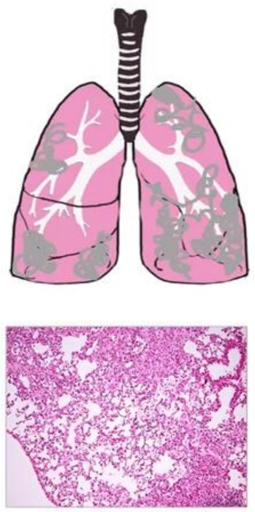
We compared the pulmonary phenotype of neonatal *Nedd4-2*$^{-/-}$ mice to *Muc5b*$^{-/-}$, *Nedd4-2*$^{-/-}$/*Muc5b*$^{-/-}$ and control mice during the first month of life. We assessed survival, oxygen saturation and lung mechanics. Further, we evaluated inflammation markers in bronchoalveolar lavage (BAL) and lung histology. Muc5b expression was investigated in BAL by Western blots. Finally, we applied imaging mass cytometry for multiplexed spatial protein expression analysis on a single cell level.

Results

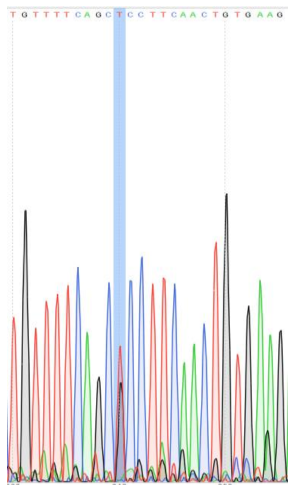
- ✓ Improved mice survival
- ✓ Reduced Inflammation
- ✓ Reduced lung fibrosis

SPL5B Demonstrated Preclinical Efficacy in IPF^{SNP+} Patients Derived Cells

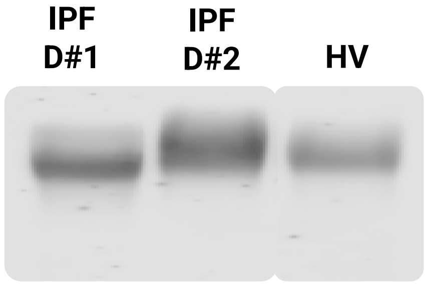
SPL5B Reduces MUC5B Levels in IPF^{SNP+} Patients Bronchial Cells



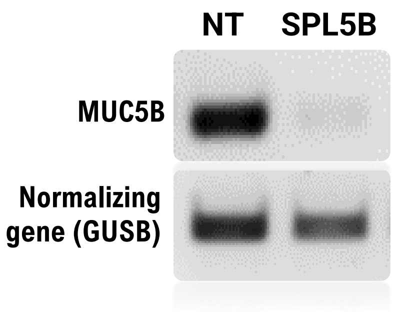
SNP^{+} sequencing

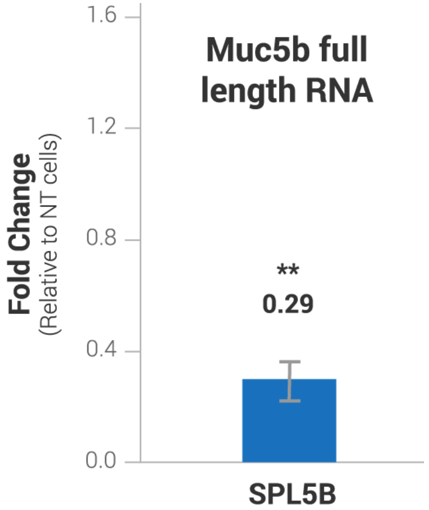


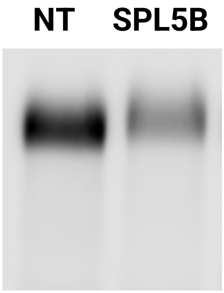
MUC5B elevated protein level in IPF $^{SNP+}$



MUC5B RNA (RT-PCR and RT-qPCR) (70% reduction)







MUC5B Protein

- Both donors carry the MUC5B SNP(G->T)
- In both patients’ cells higher levels of MUC5B were found compared to HV cells
- Treatment of differentiated cells with SPL5B ASO reduced the levels of MUC5B

SpliSense's ASOs Have Unique and Superior Properties for Lung Delivery

NATURAL

- No carriers or LNPs are needed
- Uniform and sufficient distribution in mouse & monkey conducting airways
- In-vitro and in-vivo uptake **through mucus layer**
- Nucleus penetration

DURABLE

- Lung $T_{1/2}$ >2 weeks
- Proven stability in patient-derived mucus
- Proven stability in lung lysosomes
- **Weekly / every other week inhalation regimen**

SAFE

- **Promising phase 1&2 safety data**
- Low administered doses combined with low frequency of administration
  - Highly specific to target sequence
  - Minimal systemic exposure
- Clinically validated chemical modification patterns

EFFICACY

- First evidence of potential clinical benefit of ASO therapy in a pulmonary disease
- Additional pulmonary programs to advance into the clinic in 2026

Management & Leadership Team

Nissim Darvish, M.D., Ph.D.
Chairman
Managing General Partner at MeOhr Ventures. Former Director at Orbimed Advisors LLC and Orbimed Israel Partners. Spent 8 years prior with Pitango Venture Capital

Gili Hart, PhD
CEO
Biotech executive with extensive experience in global drug development from pre-clinical through successful Phase 3 trials. Former CEO of Mitoconix Bio and OPKO Biologics

Batsheva Kerem, PhD
Co-founder & CSO
Prof. Hebrew University of Jerusalem.
30 years of leading research in CF genetics starting with the discovery of the CFTR gene

Oren Gez, MBA
CBO
An experienced and appreciated financer with over 18 years of experience in the global capital market working at local and international investment banking

Prof. Eitan Kerem, MD
CMO
Pediatric pulmonologist; Head of the Pediatric Pulmonology Unit of HMC Jerusalem, Chairman of the Israeli CF Foundation CAB

Efrat Ozeri-Galai, PhD
VP Research
Extensive experience in CF and pulmonary diseases genetics, discovery and pre-clinical development

Asaf Cohen, B.Sc, MBA
VP CMC
Vast experience in CMC worlds, focusing on production, analytical and device development under GMP regulatory environments

SpliSense
Making Sense of Splicing

Thank You!