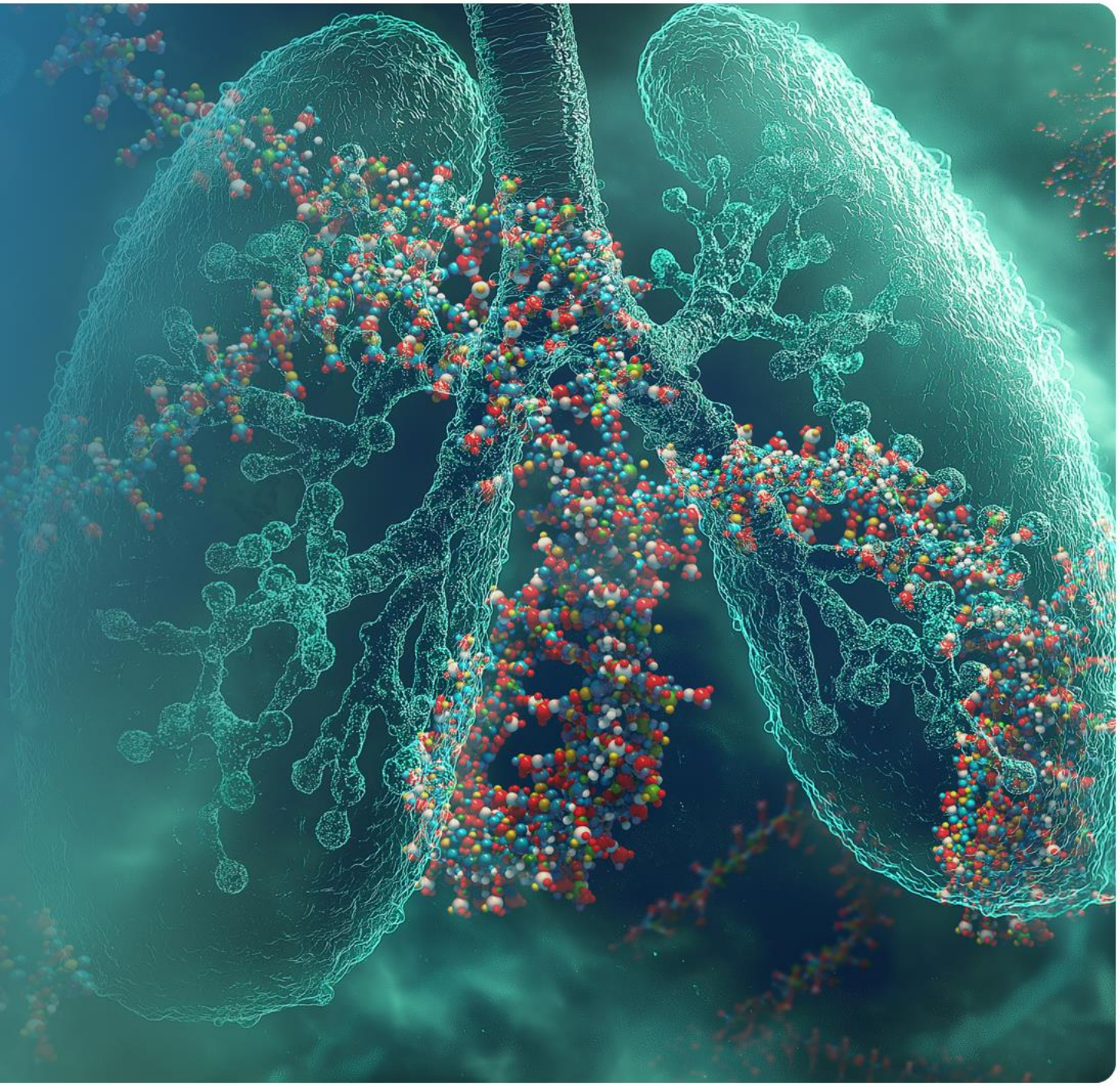
SpliSense

Making Sense of Splicing

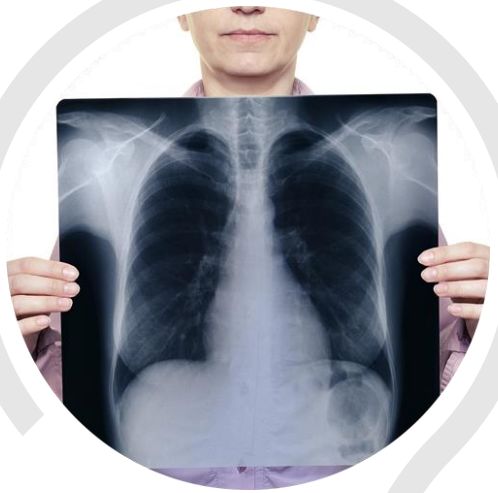
RNA Based Platform for Pulmonary Diseases



Corporate Presentation // 2025

NON-CONFIDENTIAL

SpliSense ASO; First Clinical Proof of Benefit in Pulmonary Disease – Platform Technology Validation



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

ASO Combined inhaled delivery system **weekly /monthly inhalations** (~5min)

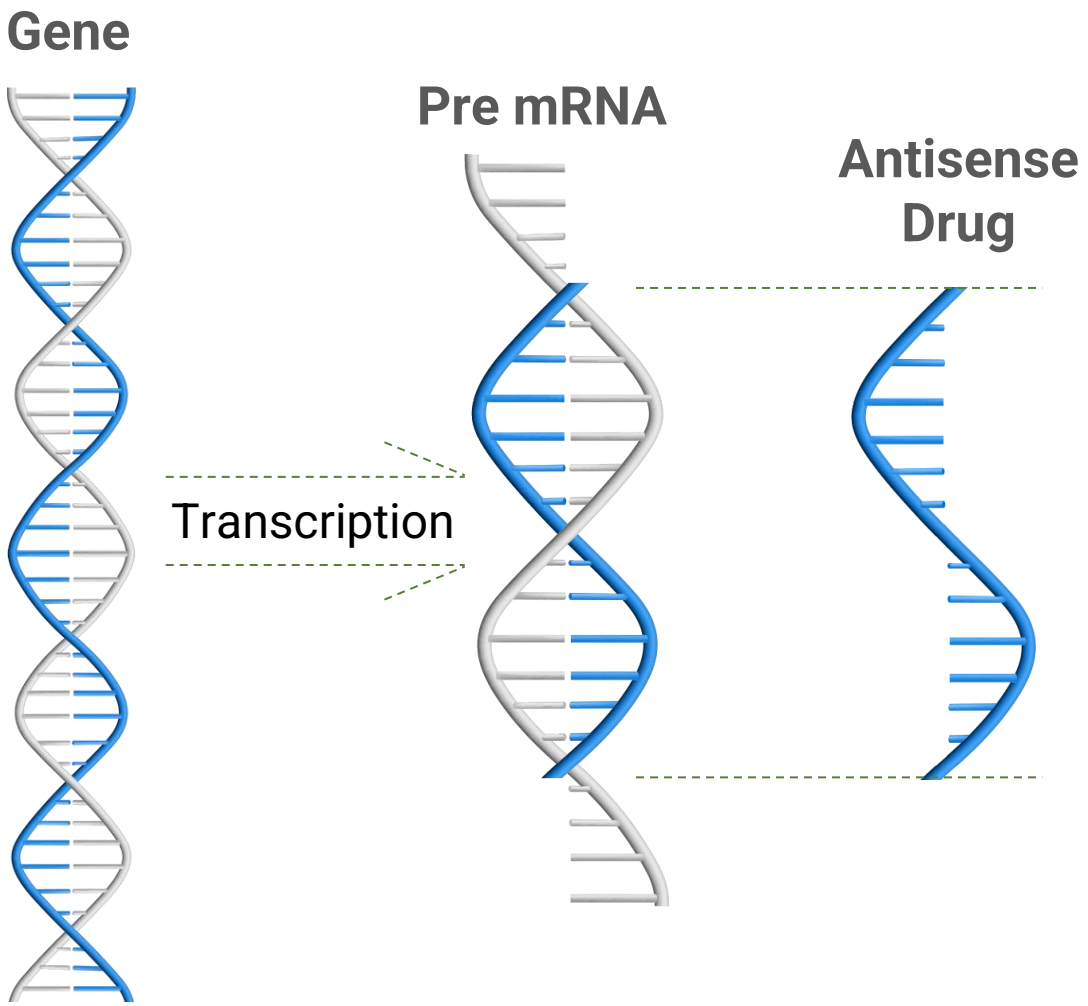
Proprietary **algorithms** for RNA modulation, **ASOs** optimization

Three clinical programs in 2026; Platform expandable across diseases

SpliSense
Making Sense of Splicing

Antisense Oligonucleotides – Modulating RNA (MoA)

20 Approved ASOs (2025)



SpliSense: Three MoA strategies

Decreasing production of target proteins

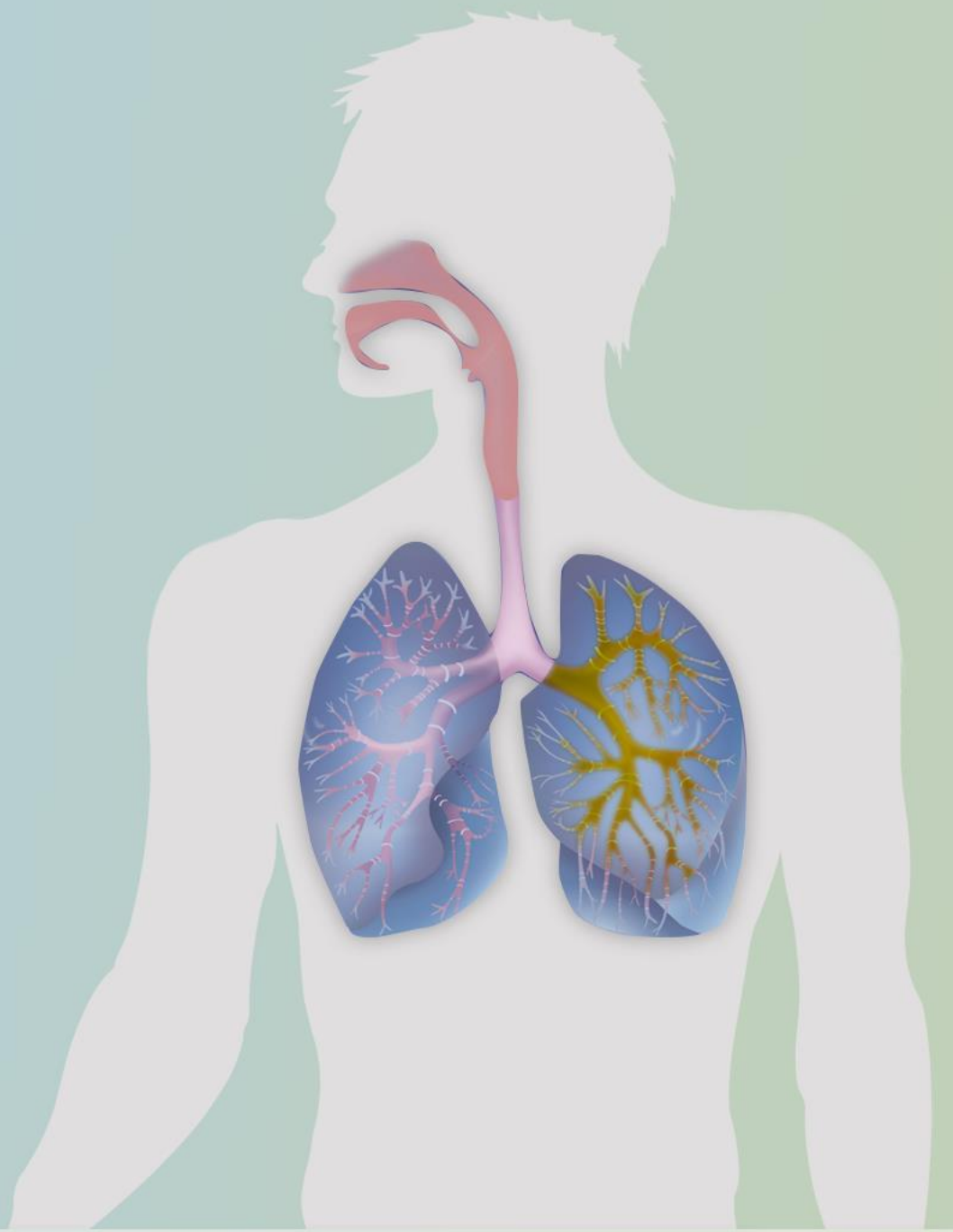
Restoring protein function

Modulating RNA processing, (production of modified proteins)

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

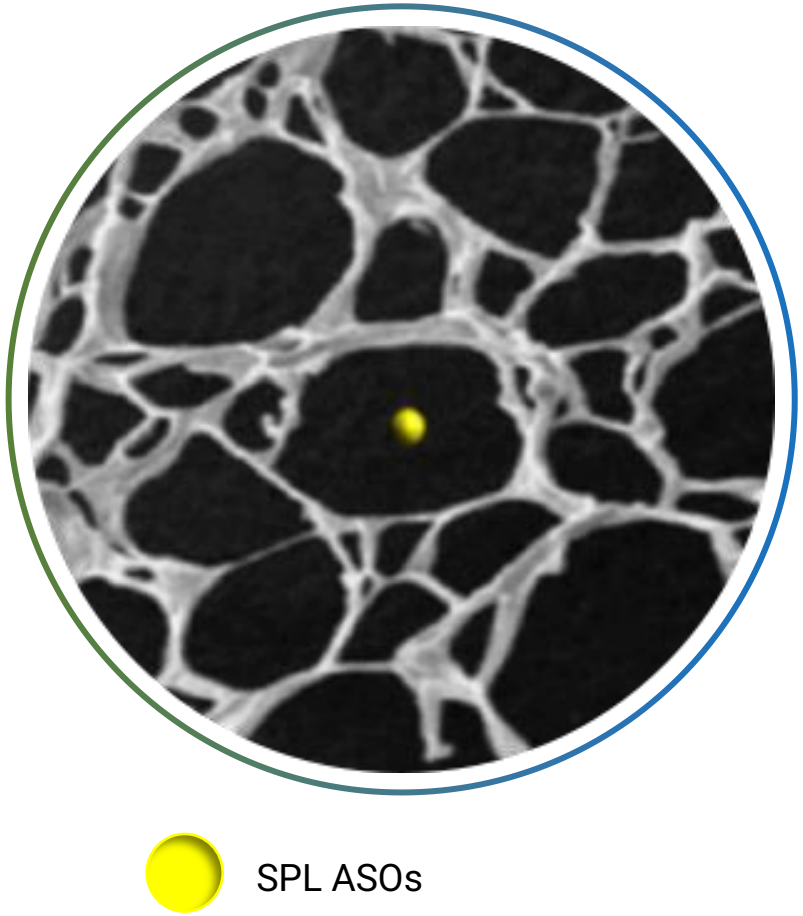
INDICATION	PROGRAM	PRECLINICAL	IND ENABLING STUDIES	Phase 1	Phase 2
Cystic Fibrosis (CYSTIC FIBROSIS FOUNDATION)	**SPL84** (3849 mutation)				✓
	SPL23 (W1282X mutation)				
Muco-Obstructive Diseases COPD/Asthma/NCFB	**SPL5AC**			**H2 2026**	
IPF	**SPL5B**			**H1 2027**	

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



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)

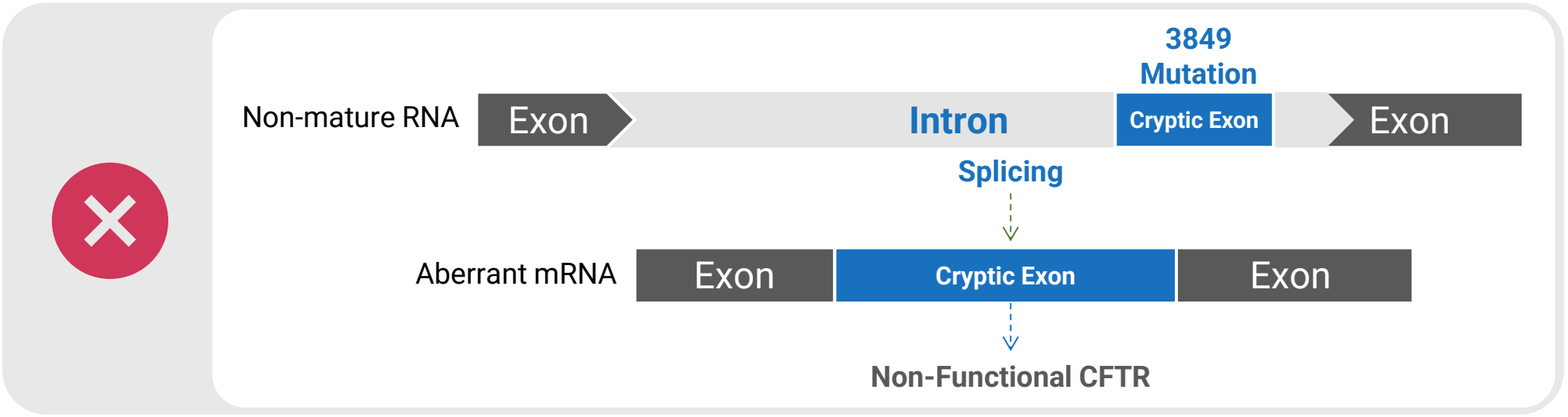


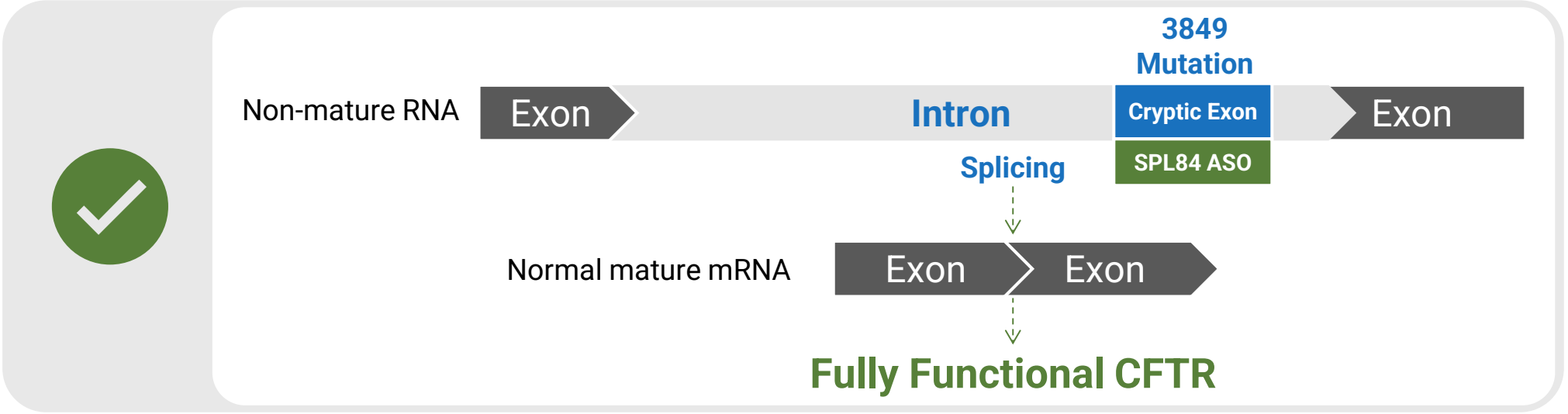
SpliSense
Making Sense of Splicing

SPL84 – Phase 2

Clinical PoC of SPL ASO Platform in a Pulmonary Disease

SPL84 Produces Mature and Functioning WT CFTR



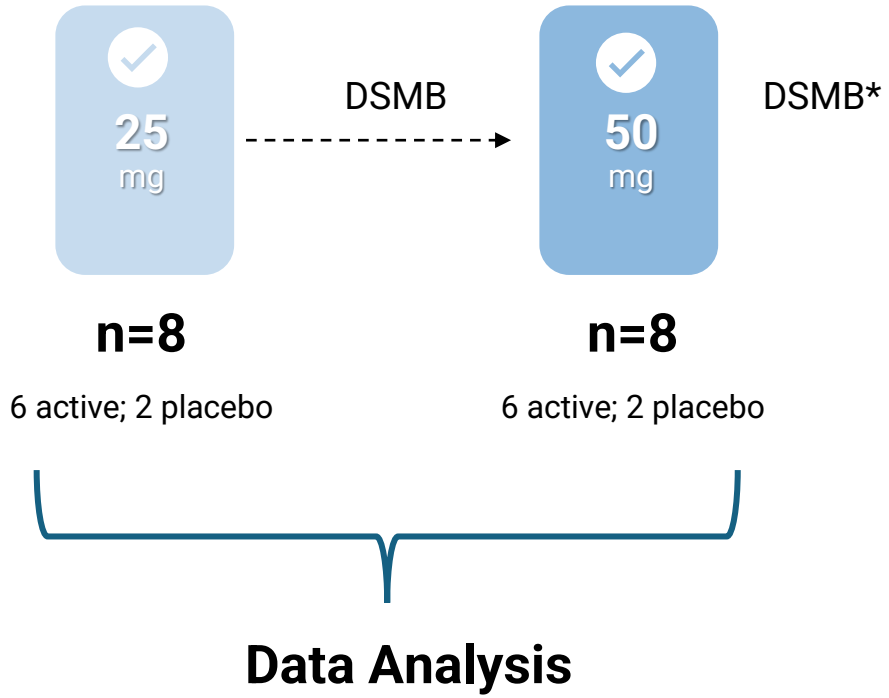


SpliSense
Making Sense of Splicing

SPL84 Global Phase 2a 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



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**
- **EMA PRIME Designation**

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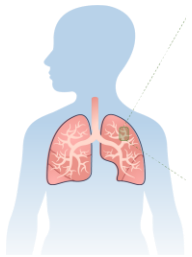
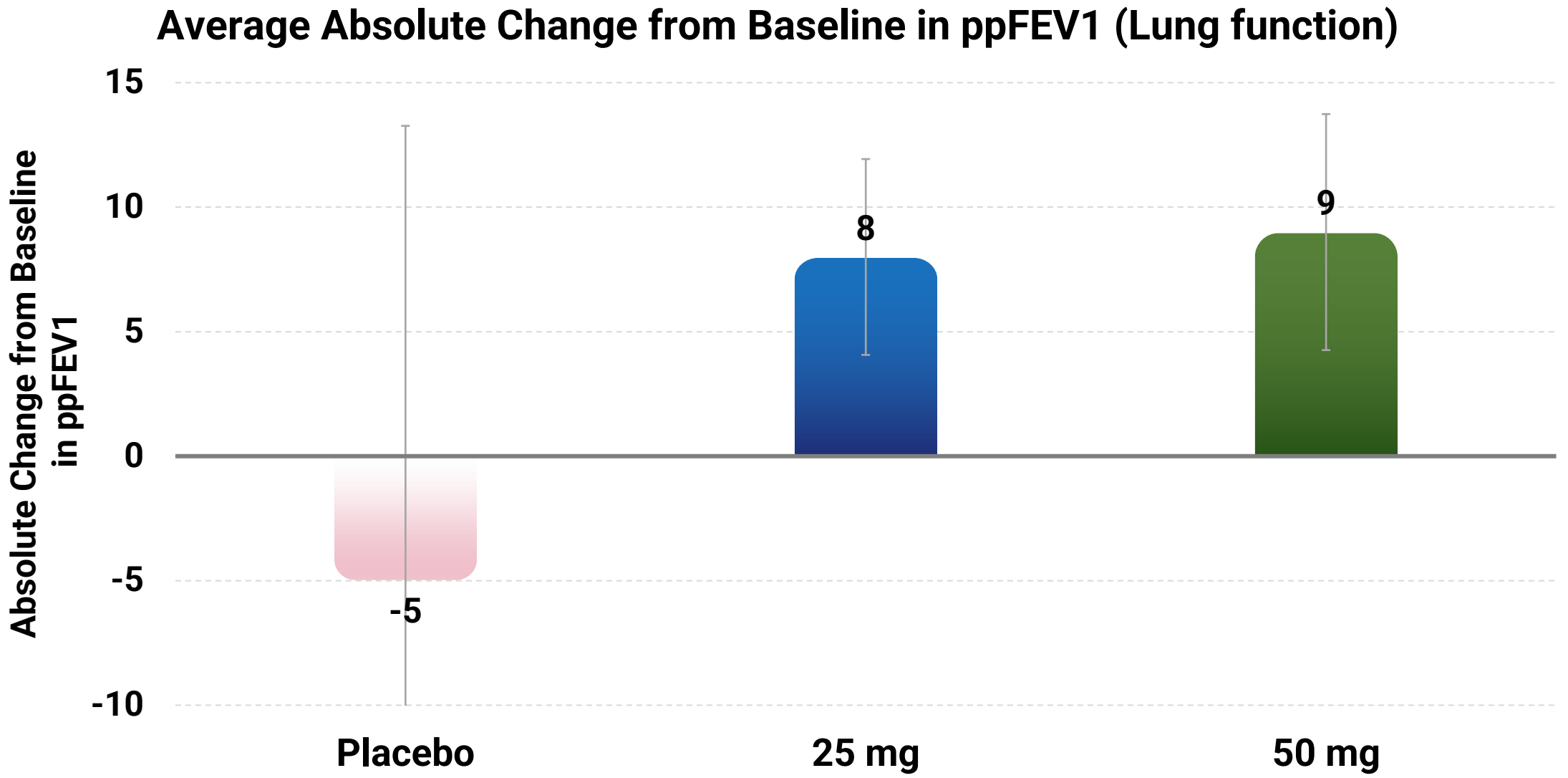
Making Sense of Splicing

SPL84 Treatment Leads to a Significant Absolute Change in ppFEV1 vs. Placebo (up to 70% Responders Rate)



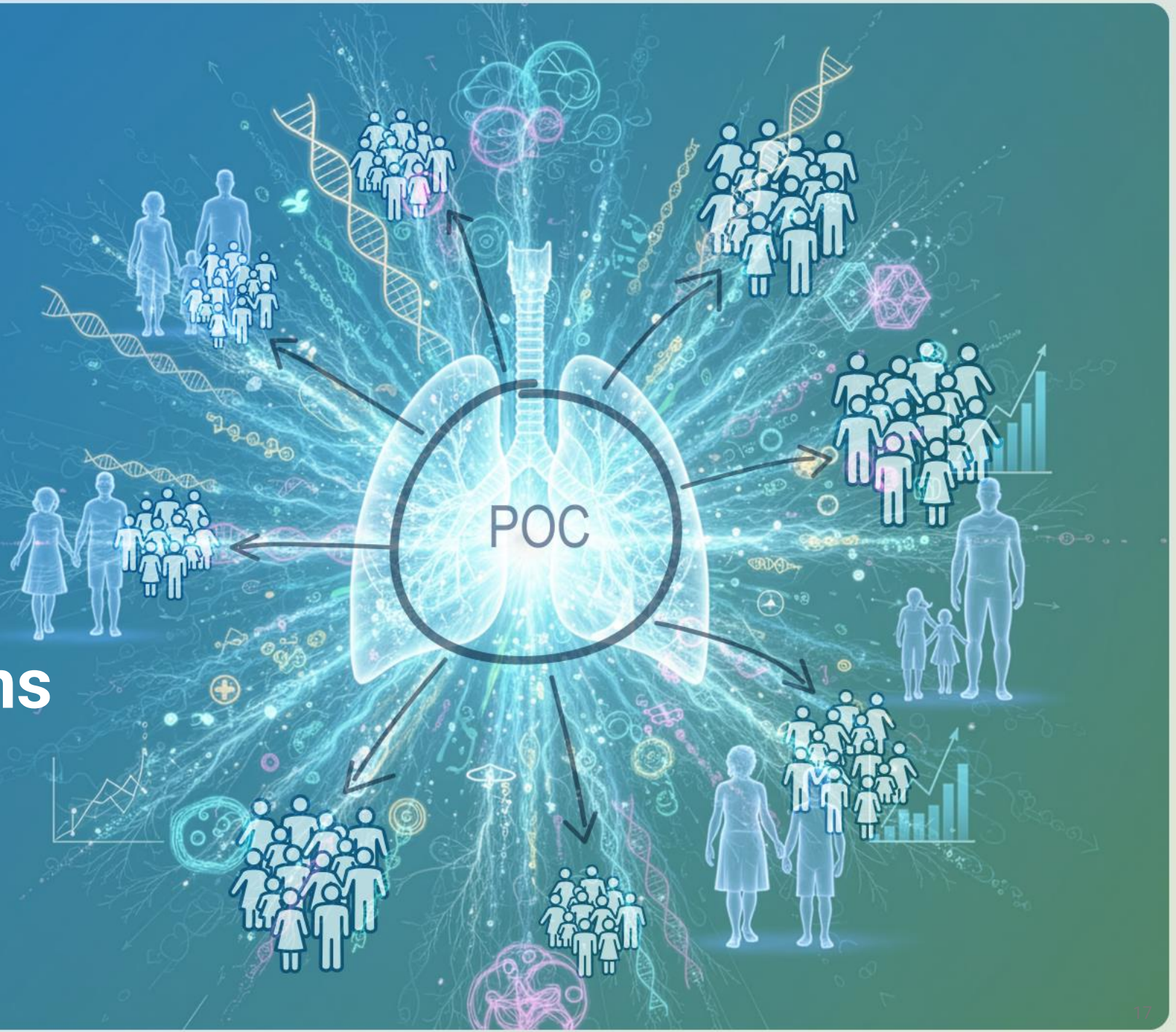


SPL84 – Clinical Validation of SpliSense ASO Platform

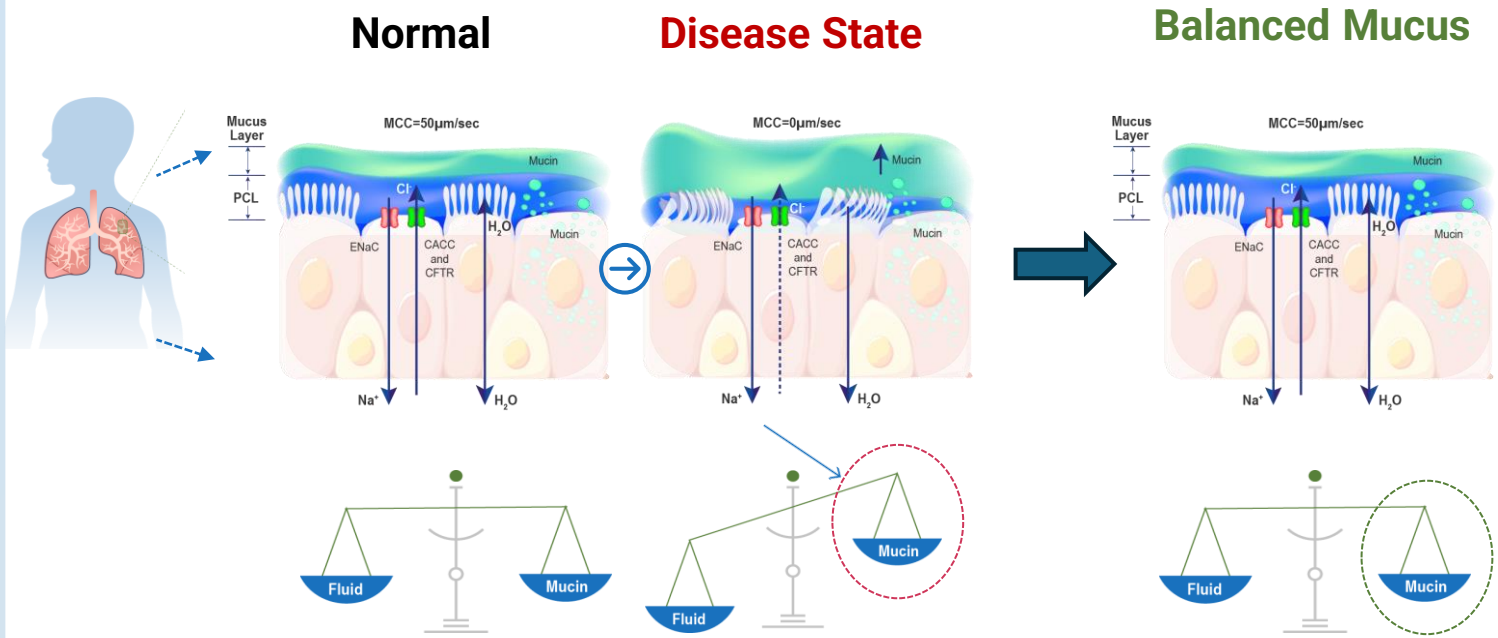
- **Clinically significant and meaningful improvement in lung function (ppFEV1)**
  - $ppFEF_{25-75}$ increases and correlates to ppFEV1 following SPL84 treatment
  - Increase in the Cystic Fibrosis (CFQ-R RSS) quality of life measurement.
  - 4/7 patients demonstrated elimination of microbial load at study end
- No safety signals or trends of concern were identified among participants
- **Weekly inhalation <8min, easy to handle and use**
- **SPL84 Phase 2b study initiation Q1 2026**

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

Expanding Our ASO Technology From Orphan to Large Pulmonary Indications



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



MUC5AC

- Asthma
- COPD
- NCFB

MUC5B

- IPF

SpliSense
Making Sense of Splicing

Muco-Obstructive Diseases

MUC5AC Lowering ASO

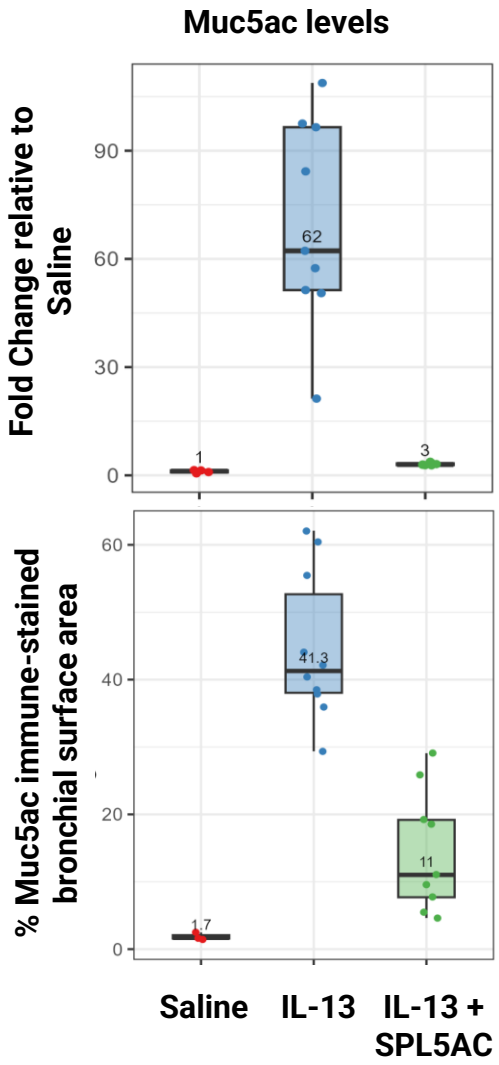
SPL5AC

SPL5AC ASO for Muco–Obstructive Diseases

- **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

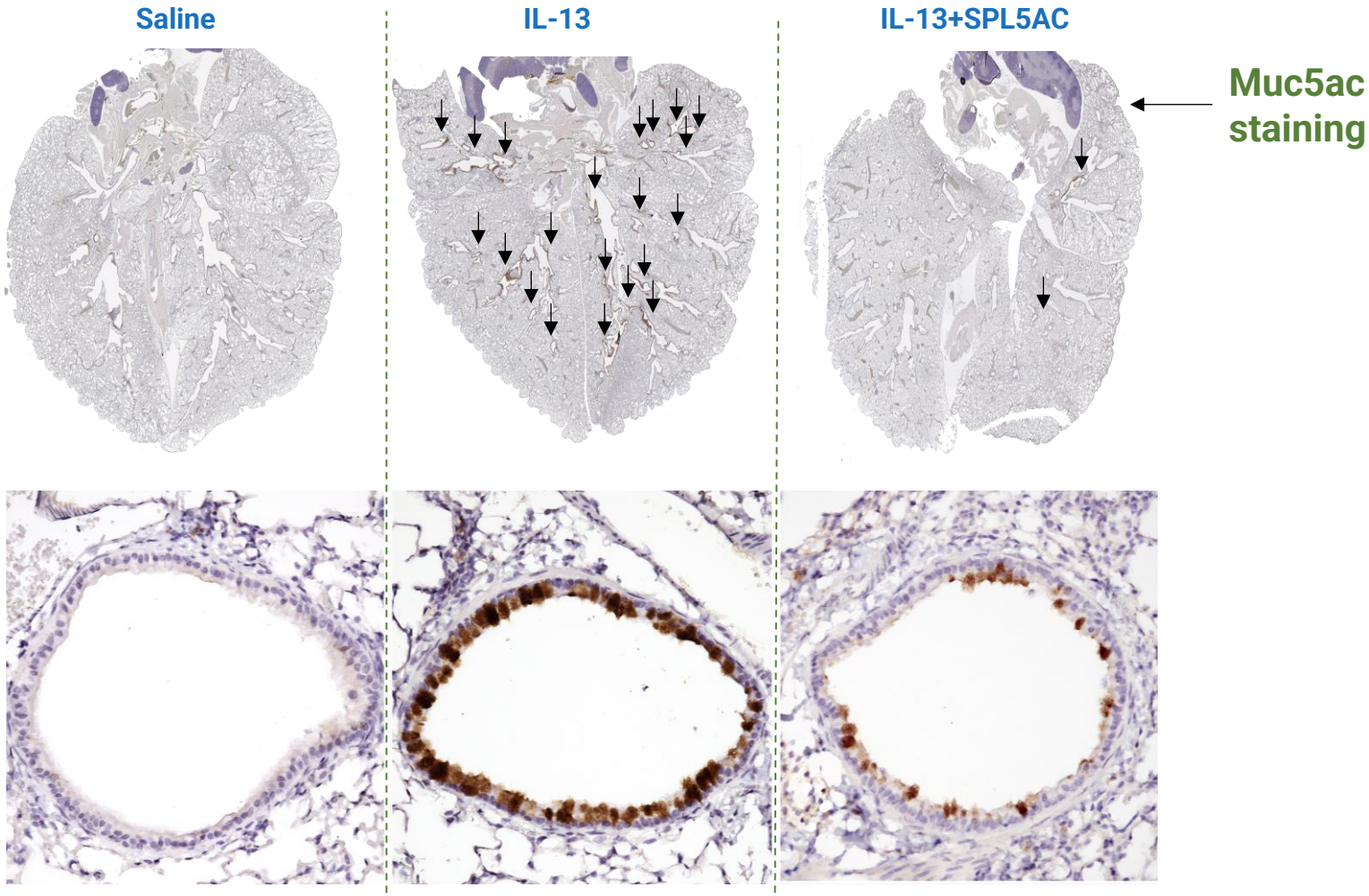
SPL5AC ASO Reduces Muc5ac Protein Levels in Lungs of IL13 Hyper-Stimulated WT Mice



RNA
(96% reduction)

Protein
(73% reduction)

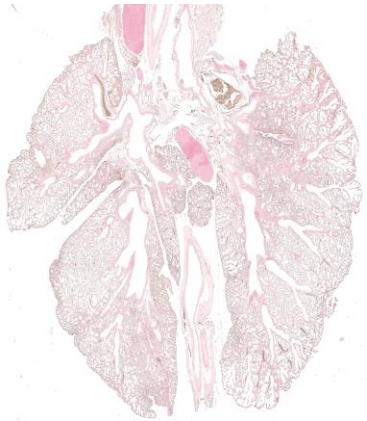
Muc5ac Protein (IHC)



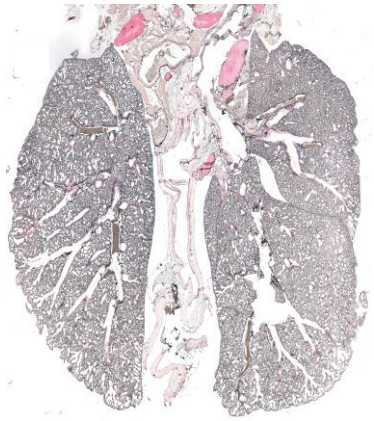
Effect persist for at least 28 days, supporting monthly treatment regimen

SPL5AC ASO Reduces Muc5ac Levels in Lungs of Asthma Disease Mouse Model (Ovalbumin)

SPL5AC distribution (ISH staining)

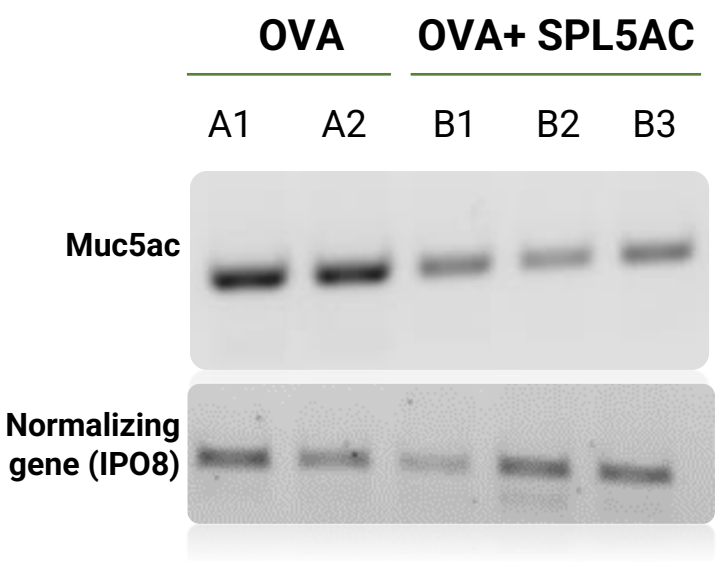


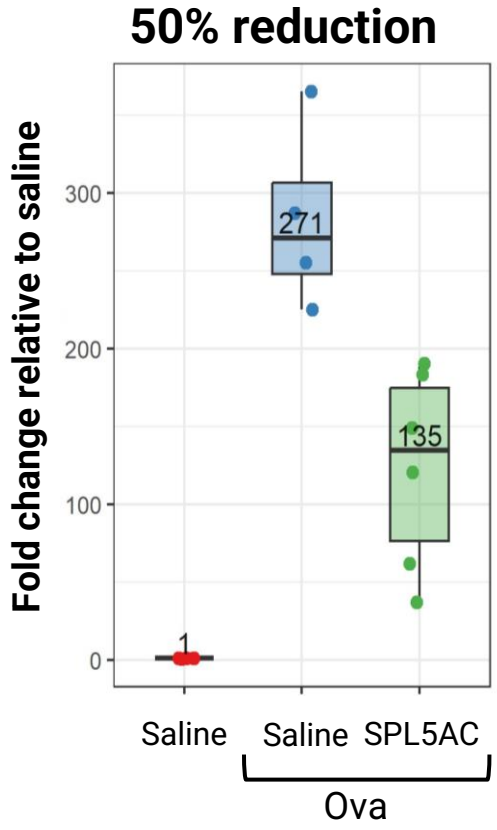
OVA+ Saline



OVA+SPL5AC

Levels of Muc5ac RNA (RT-PCR and RT-qPCR)

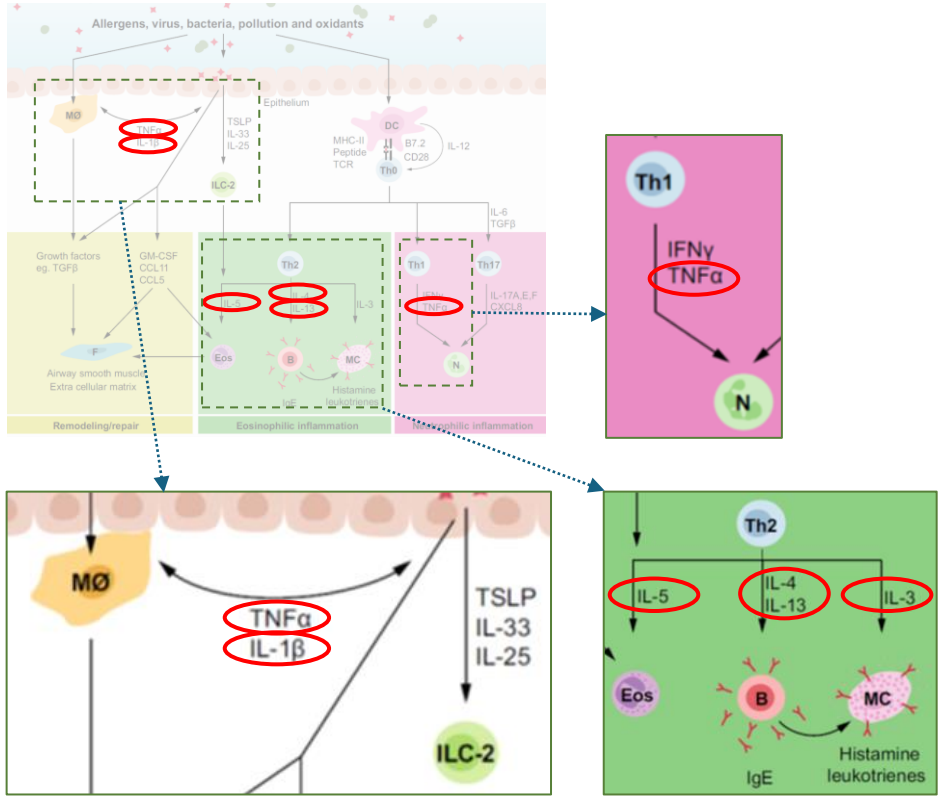




Calculated by median

OVA leads to very high levels of Muc5ac (x~250)

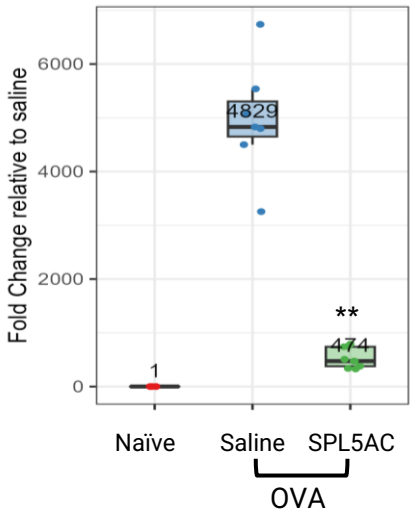
SPL5AC Attenuates Th-2 Inflammatory Response in an Asthma Disease Mouse Model (Ovalbumin)



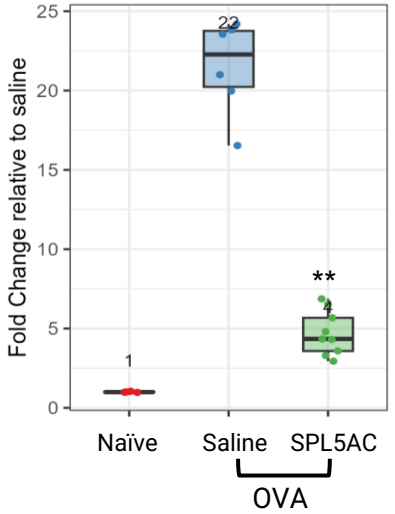
Adopted from Chung et al. 2015

Pro-inflammatory cytokines reduction by SPL5AC

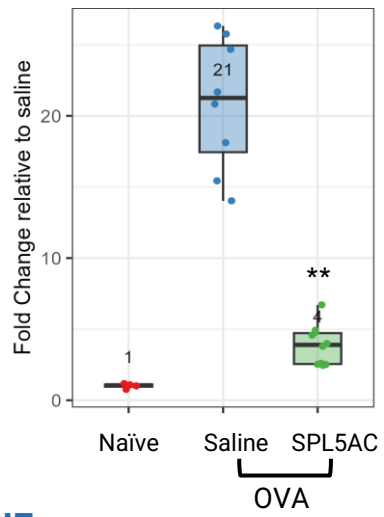
IL-13
90% Reduction



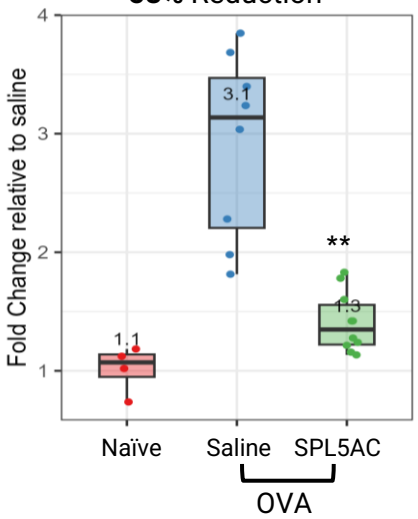
IL-5
83% Reduction



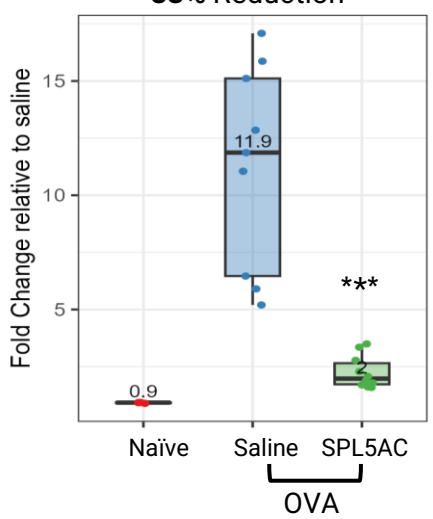
IL-4
81% Reduction



IL1-β
58% Reduction

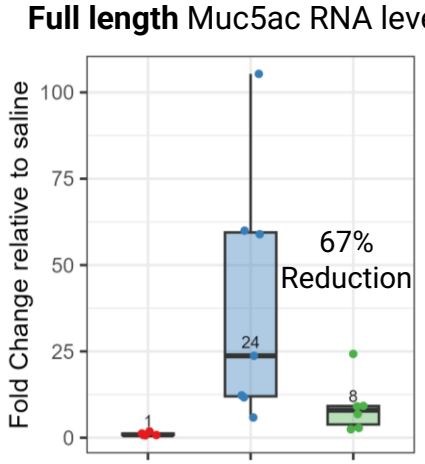


TNFα
83% Reduction

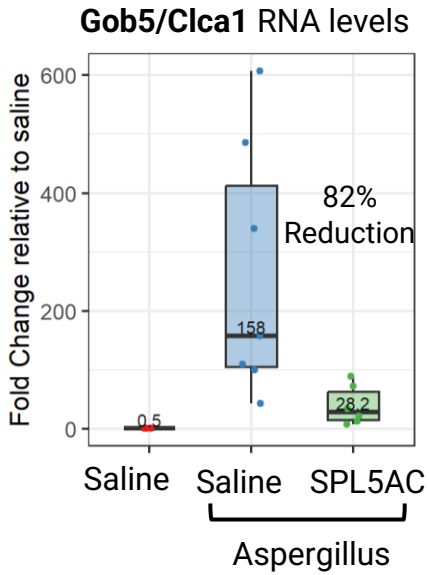


SPL5AC Reduces Muc5ac, Goblet Cells Hyperplasia and Mucus plugs in Aspergillus Induced Asthma Disease Mouse Model

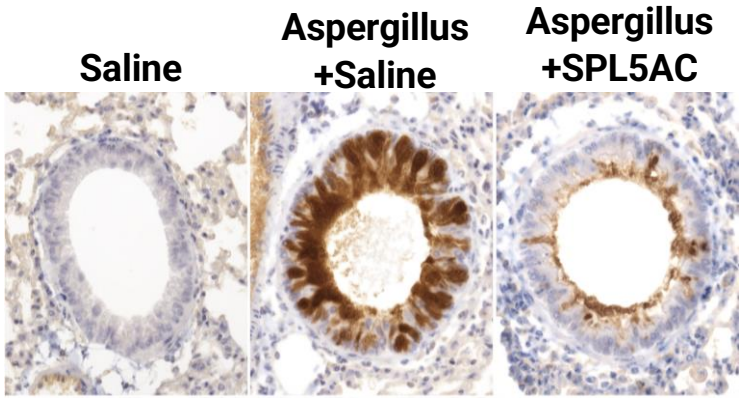
Muc5ac RNA



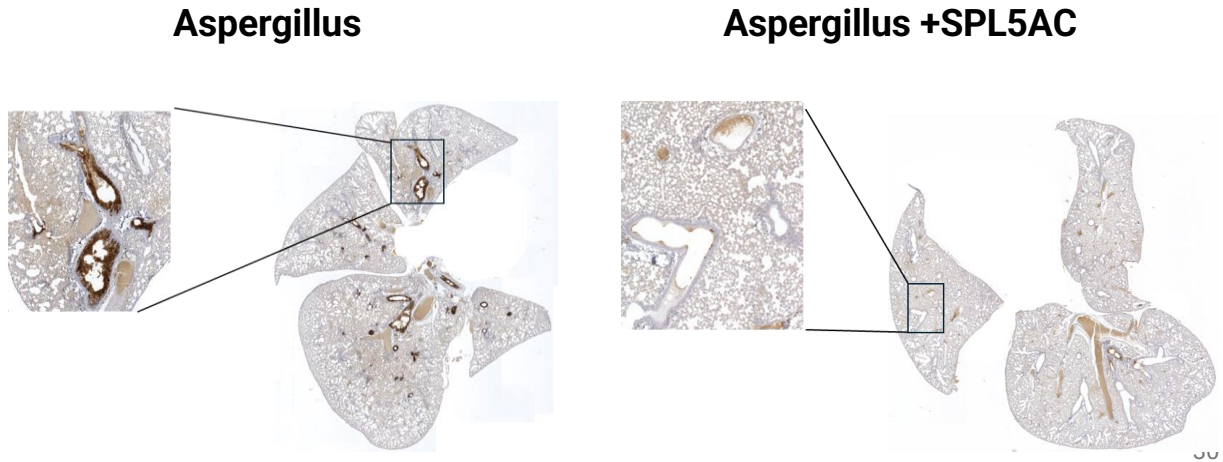
Goblet Cells Hyperplasia



Muc5ac Protein

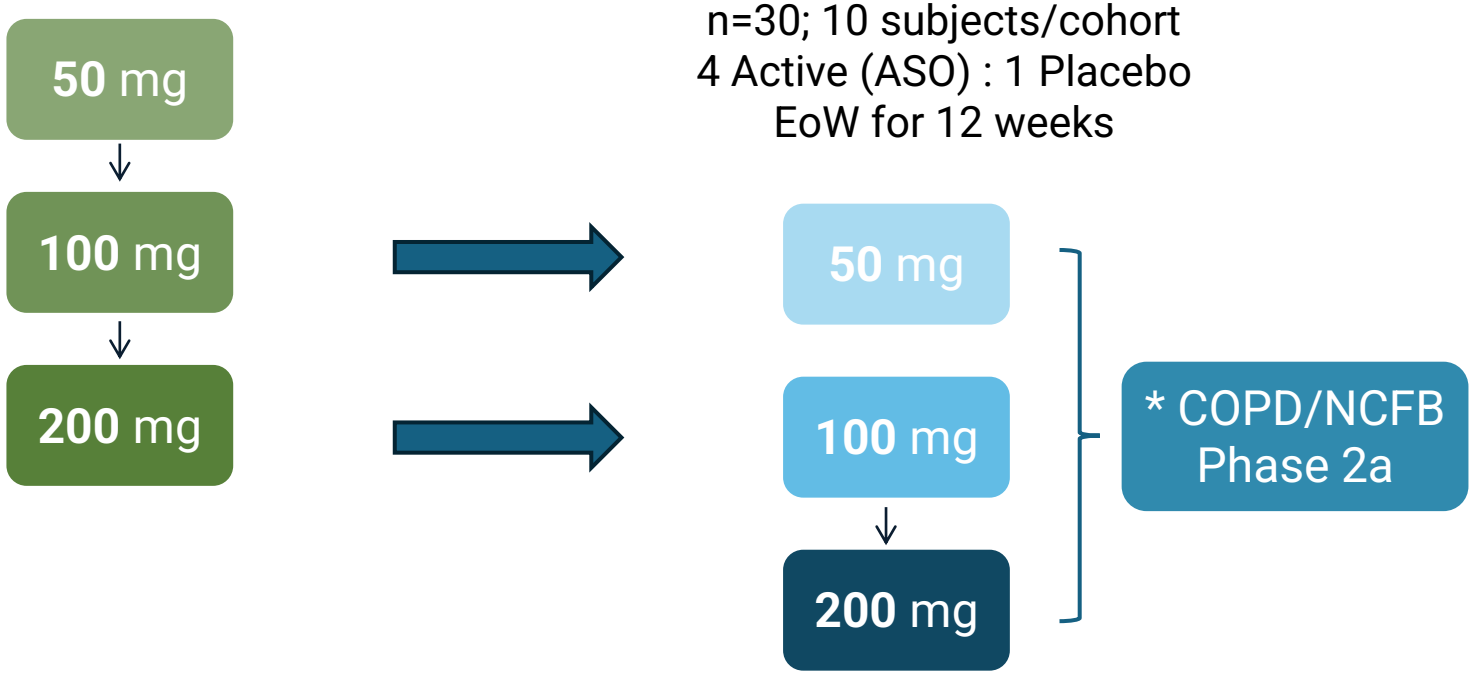


Mucus Plugs



Proposed Phase 1/2 Clinical Trial Design – Late 2026

Single Ascending Dose (SAD) in Healthy Volunteers
n=32; 8 subjects/cohort
3 Active (ASO) : 1 Placebo



*Target Engagement &PD Assessment

- MUC5AC measurement by induced sputum:
- Bronchoscopy (HBEs for MUC5AC mRNA expression)
- Plugs grading by CT scans
- Spirometry

- Single center study enrolling both SAD HVs and MAD

SpliSense
Making Sense of Splicing

IPF

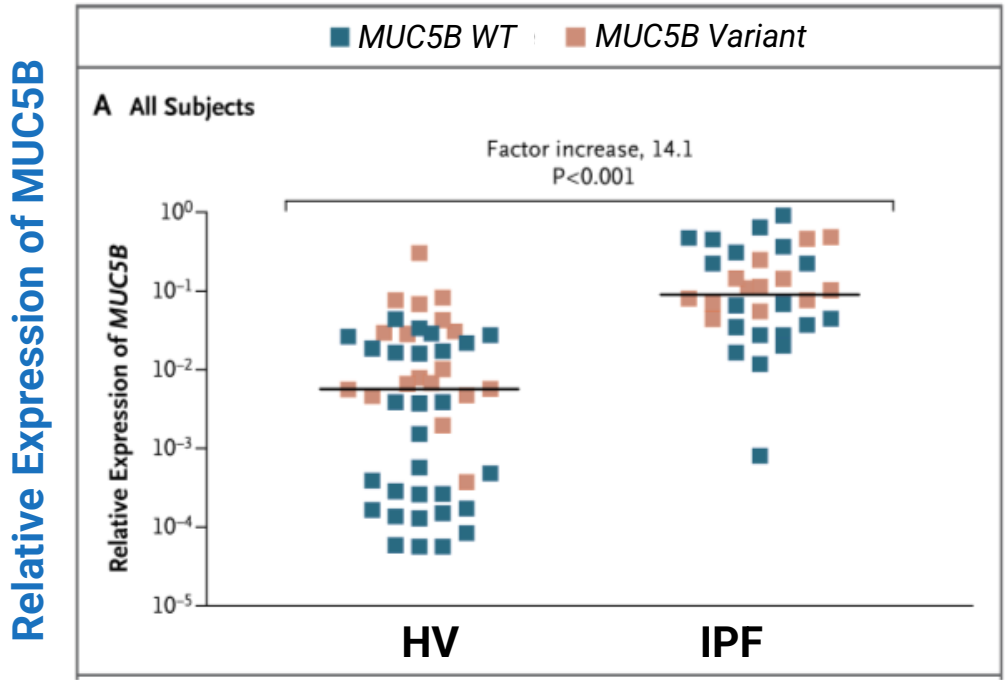
MUC5B Lowering ASO

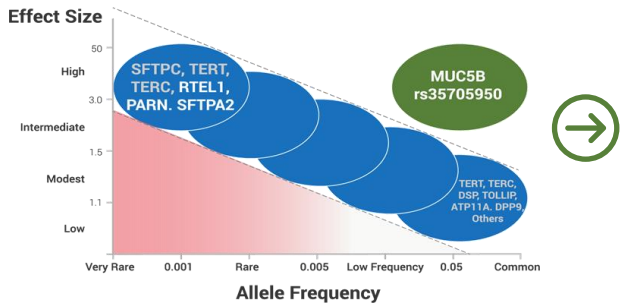
SPL5B

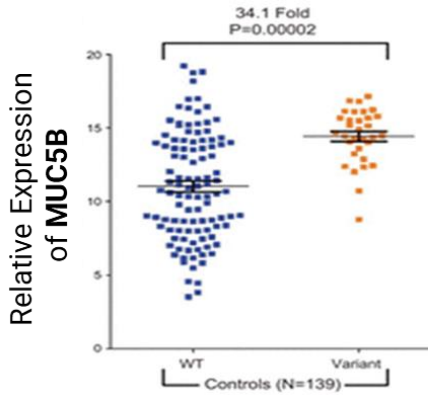
MUC5B is Overexpressed in IPF Patients

- **Idiopathic pulmonary fibrosis is a severe progressive fibrotic lung disease**
  - Primarily affecting older adults
  - Characterized by progressive lung fibrosis (scarring) and respiratory failure
  - The median survival after diagnosis is ~3–5 years

- **MUC5B is over–expressed in IPF patients (X14.1)**
  - A single nucleotide polymorphism (SNP) in the MUC5B gene (rs35705950) is major risk factor
    - Accounts for **60%** of IPF cases
    - **X34.1** higher level of MUC5B in rs35705950 SNP compared to WT SNP
  - MUC5B hypersecretion is a common pathological feature in all IPF patients





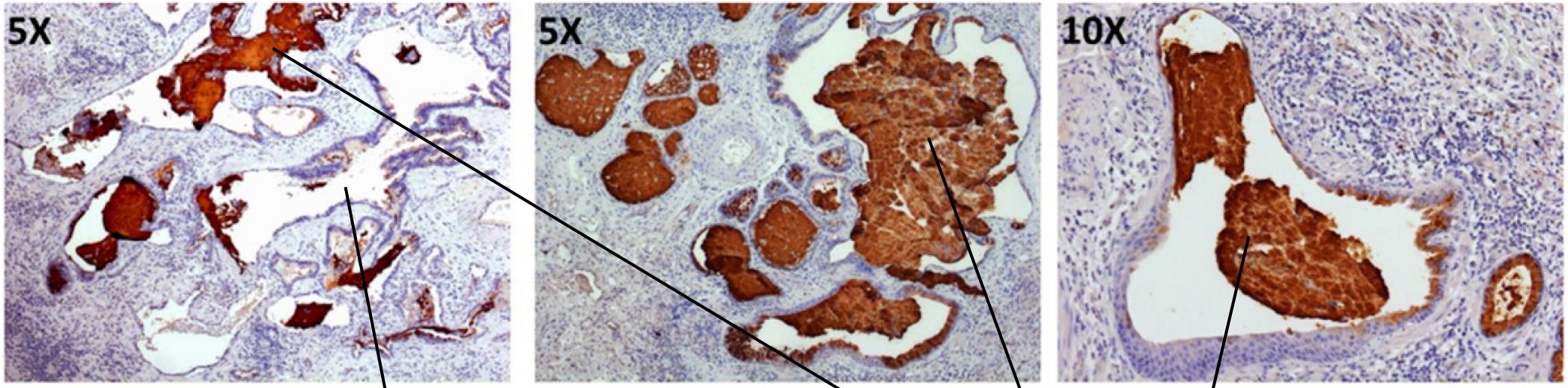


Seibiold et al. 2011 ;Evans et al. 2016

MUC5B is Overexpressed and Accumulates in IPF lungs

MUC5B accumulates in terminal bronchioles as well as the pseudostratified bronchial epithelium and fibrotic areas (lumen of honeycomb cysts) in IPF lung

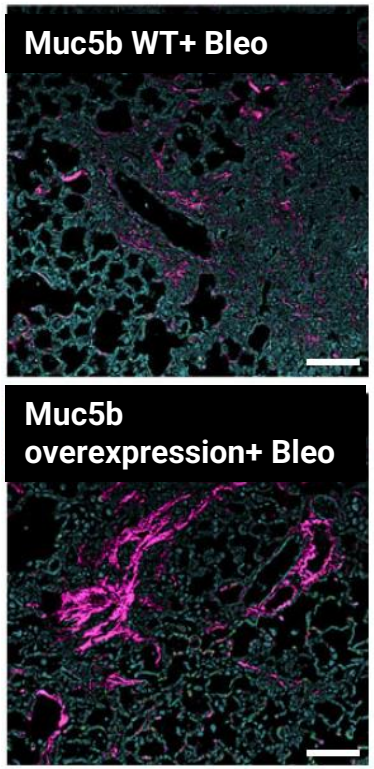
IHC of MUC5B (brown) in IPF lung



Yang et al. 2015

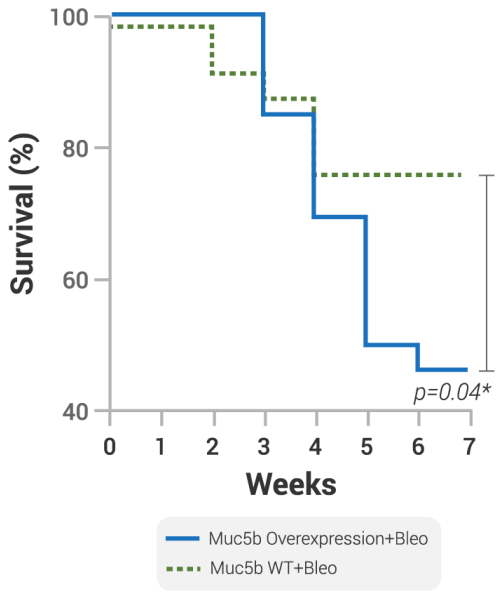
Muc5b is Well Characterized to be Associated with Lung Fibrosis Pathogenesis in Disease Mice Models

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



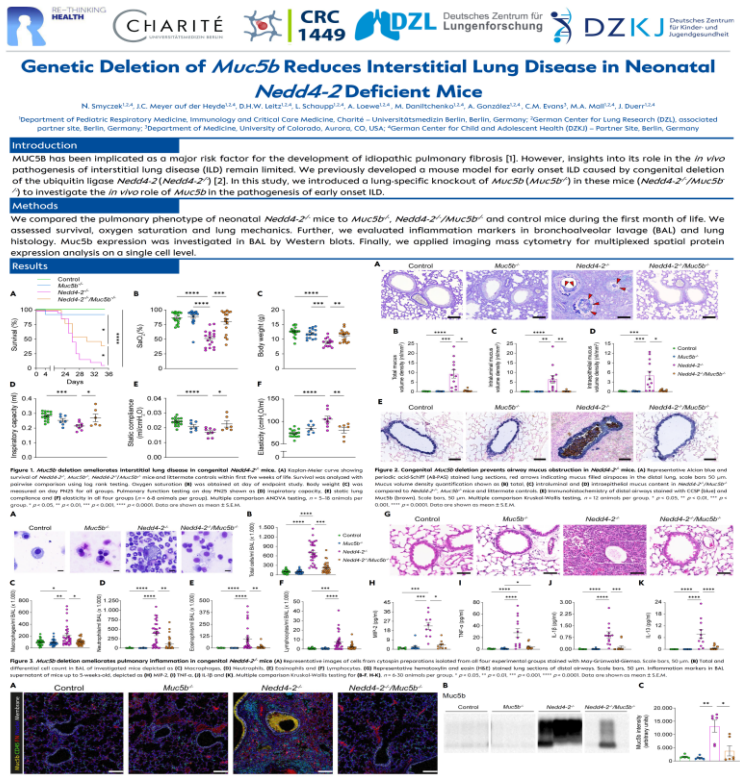
Increased lung fibrosis
(accumulation of collagen- Pink)

Hancock et al. 2018



Reduced mice survival

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

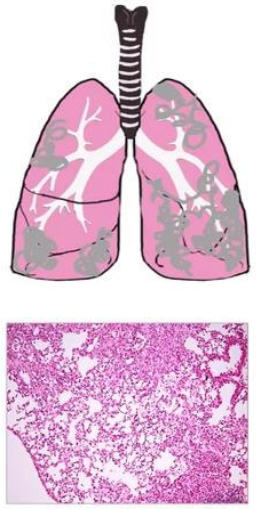


Genetic Deletion of *Muc5b* Reduces Interstitial Lung Disease in Neonatal *Nedd4-2* Deficient Mice

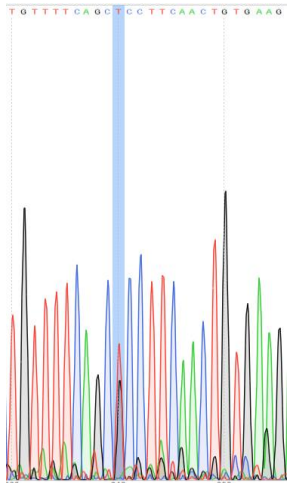
- ✓ Improved mice survival
- ✓ Reduced Inflammation
- ✓ Reduced lung fibrosis

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

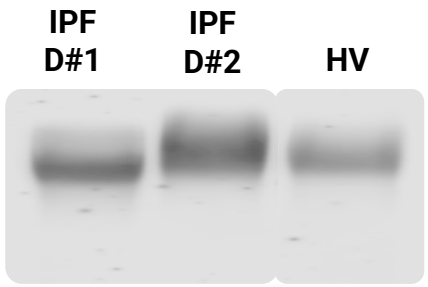
SPL5B Reduces MUC5B Levels in IPF^{SNP+} Patients Bronchial Cells



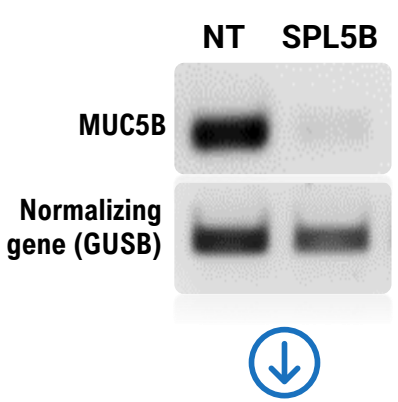
SNP^{+} sequencing

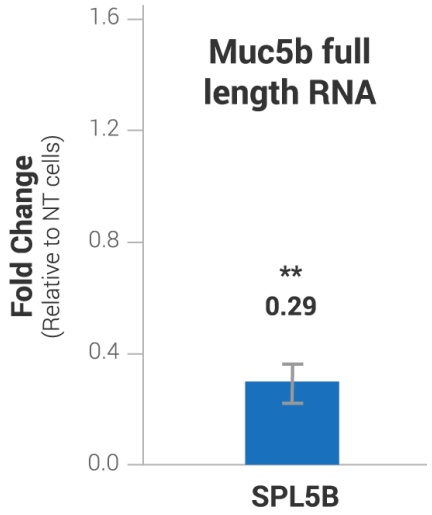


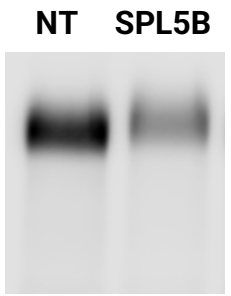
MUC5B elevated protein level in IPF $^{SNP+}$



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 Platform Clinically Validated for Pulmonary Diseases

NATURAL

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

DURABLE

- Lung $T_{1/2}$ >2 weeks
- Proven stability in patients' mucus
- **Weekly / every other week inhalation regimen**

SAFE

- **Promising phase 1 & 2 safety data**
- Low administered doses combined with low frequency of administration
- Clinically validated modification patterns

EFFICACY

- **First evidence of potential clinical benefit o**f ASO therapy in a pulmonary disease
- **3 pulmonary programs targeted to the clinic in 2026**

SpliSense
Making Sense of Splicing

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
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Thank You!