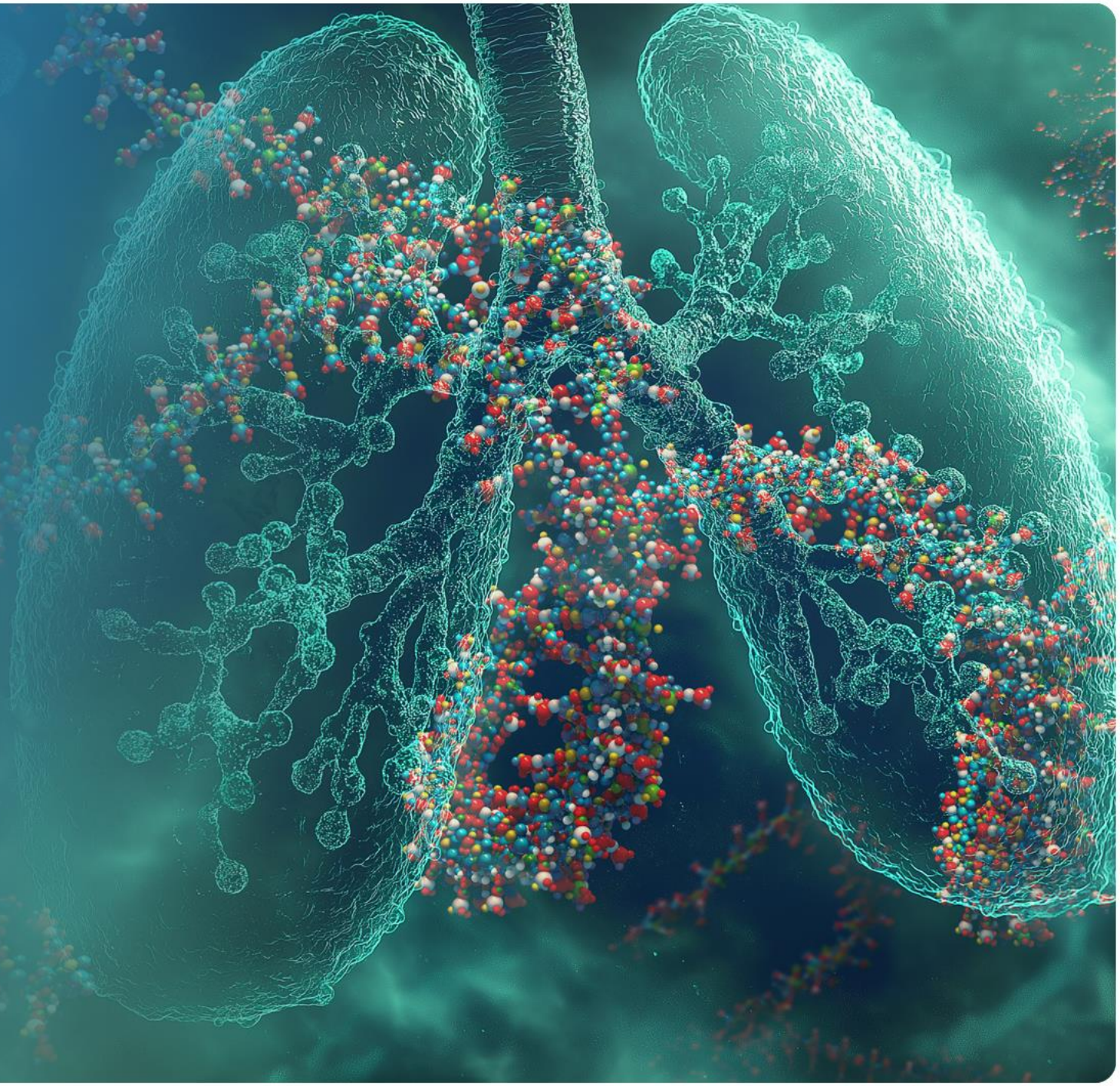
SpliSense

Making Sense of Splicing

RNA Based Platform for Pulmonary Diseases



Corporate Presentation // 2025

NON-CONFIDENTIAL

Introducing SpliSense

Company Foundation

Strong expertise in pulmonary diseases & **ASOs** dev.

2017

R&D

4 advanced pulmonary programs

2018-2022

Technology Validation

Successful First-in-human trial

2023

Platform Expansion & Pipeline Advancement

Ph. 2 ongoing

2024

Main Investors:

orbimed

ISRAEL BIOTECH FUND

CYSTIC FIBROSIS FOUNDATION

Total raised

$40M

IP

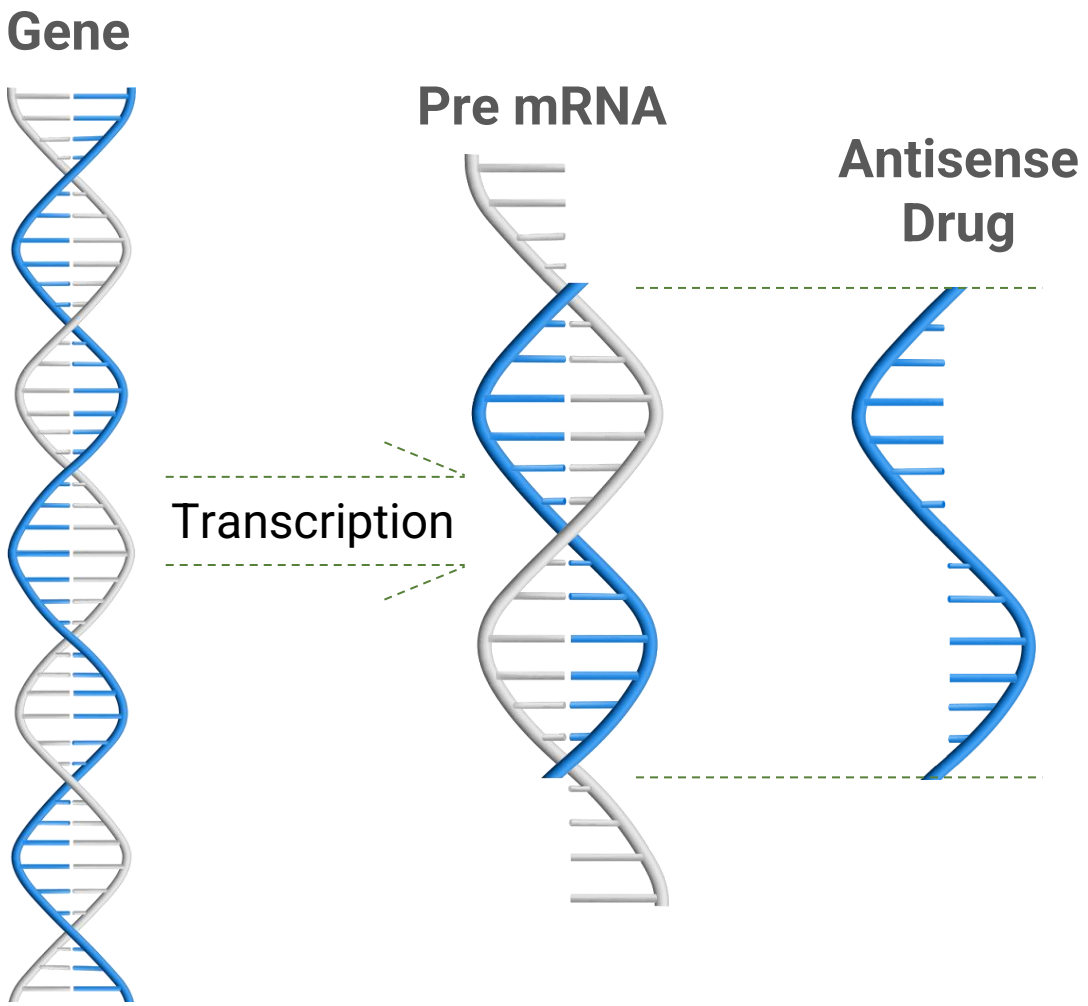
4 patent families

FTOs confirmed

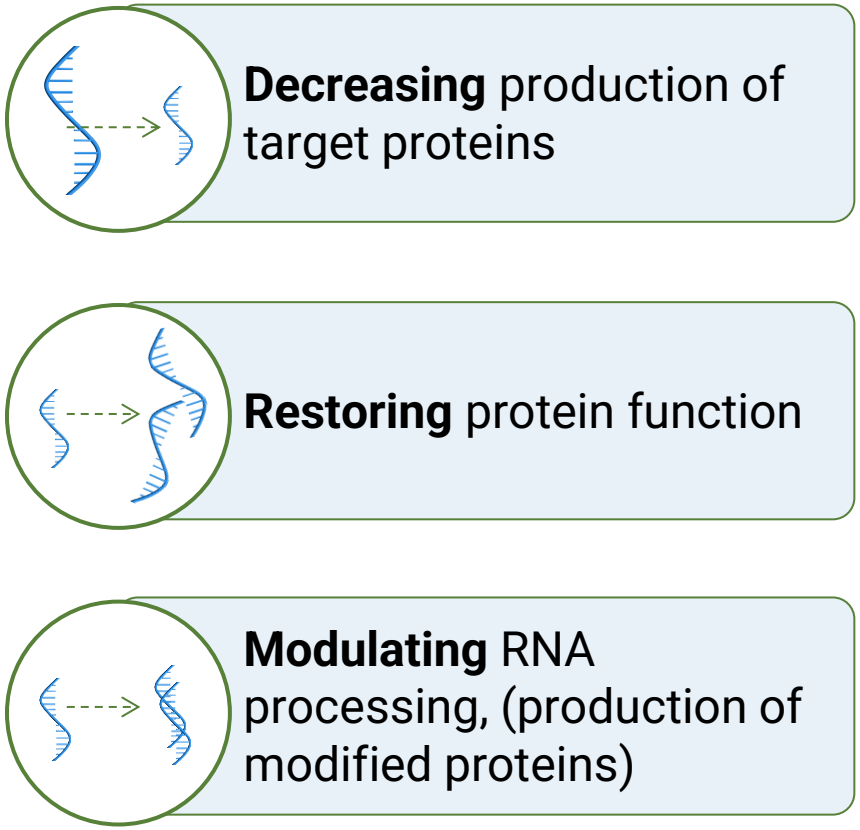
SpliSense
Making Sense of Splicing

Antisense Oligonucleotides – Modulating RNA (MoA)

14 Approved ASOs (2024)



SpliSense: Three MoA strategies



SpliSense's Platform Technology for Precise Pulmonary Therapies

Robust genetic understanding of **pulmonary diseases** & targets

ASO Combined **inhaled delivery** system

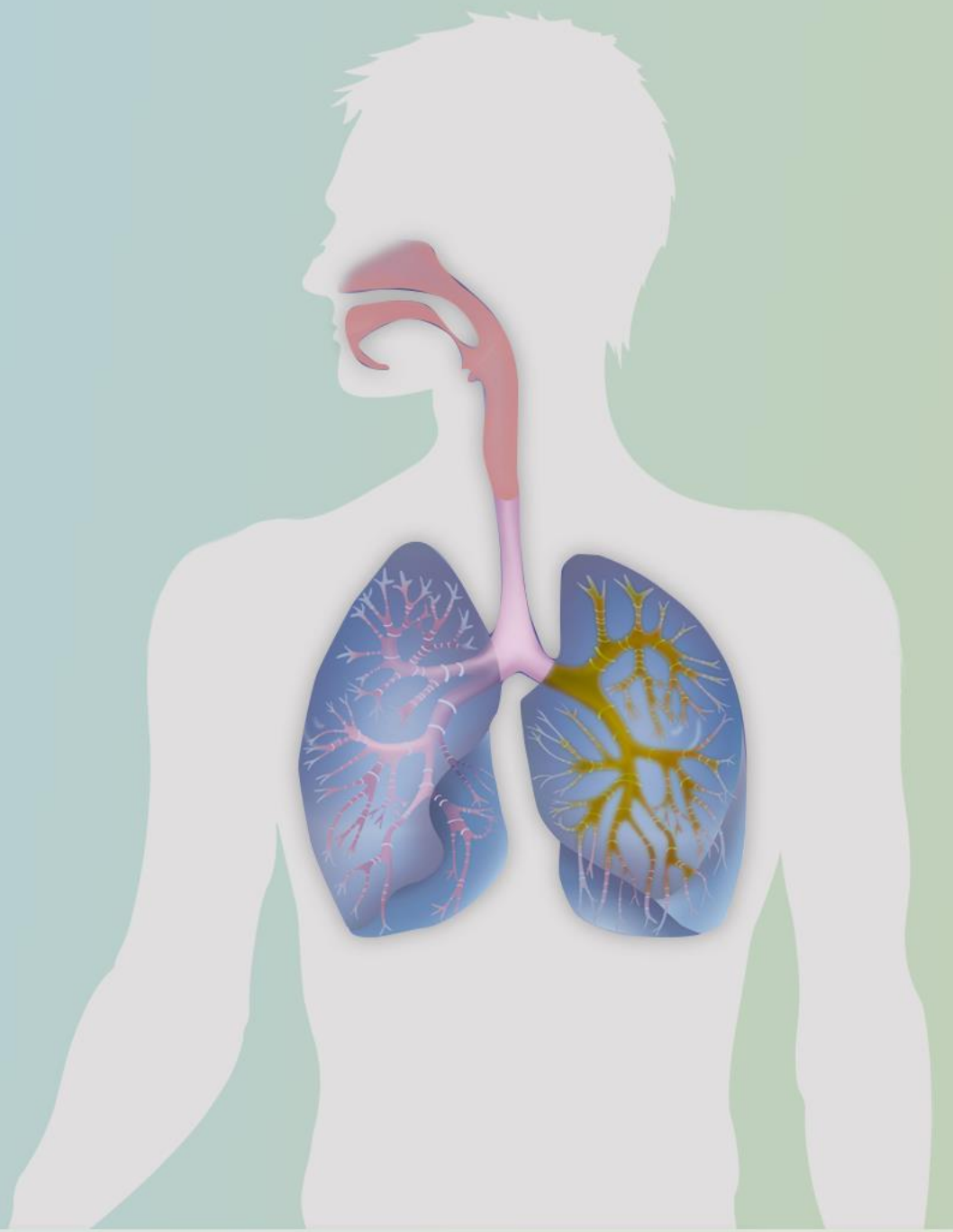
Proprietary **algorithms** for splicing modulation, **ASOs** optimization

Lung focused ASOs screening & validation systems

SpliSense's Diverse Pulmonary ASO Pipeline

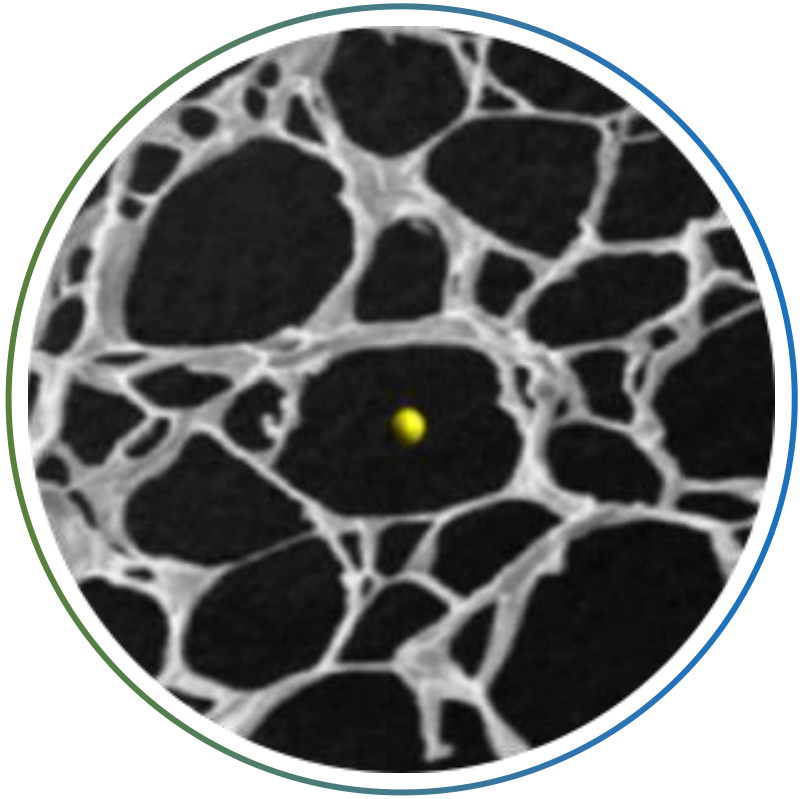
INDICATION	APPROACH	PROGRAM	PRECLINICAL	IND ENABLING STUDIES	Phase 1	Phase 2
Cystic Fibrosis	Restoration of Protein Function	**SPL84** (3849)				**Ongoing**
	RNA Modulation	**SPL23** (W1282X)				
Muco-Obstructive Diseases COPD/Asthma/NCFB	Decrease Production of Over-expressed Protein	**SPL5AC**			**H2 2025**	
IPF		**SPL5B**			**H1 2026**	

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



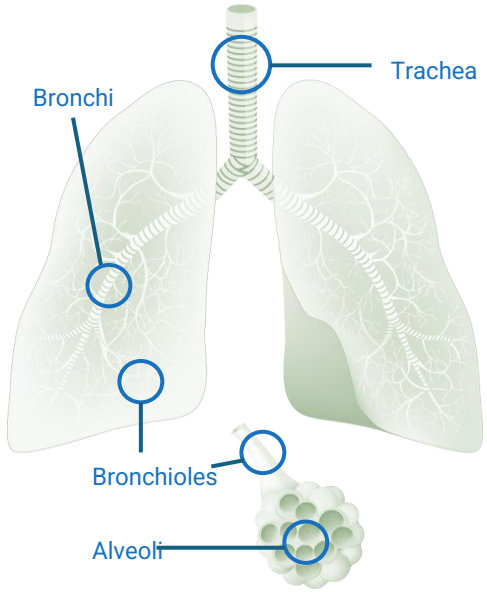
SPL ASOs are Designed for Optimal Pulmonary Delivery and Target Modulation

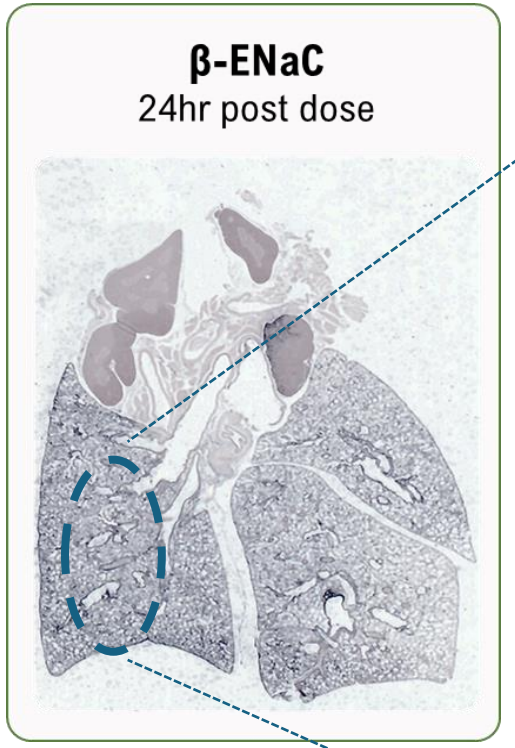
- **SPL ASOs are designed and optimized using SpliSense proprietary algorithms**
  - Identification of splicing motifs within the target sequence
  - Efficient and specific binding to the target sequence
  - Safety and Immunogenicity optimization
- **Optimized chemical modifications that drive stabilization 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)

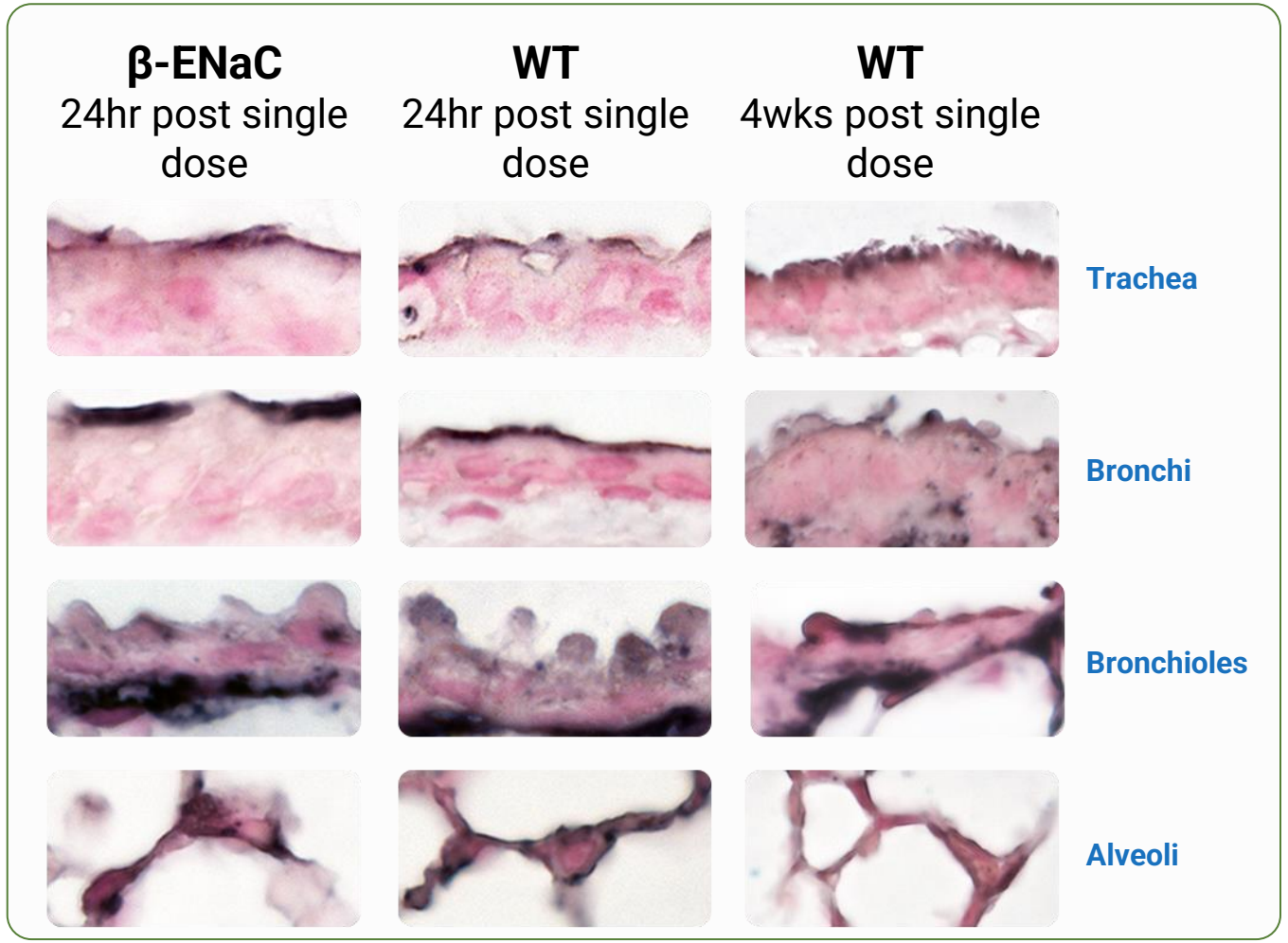


SPL ASOs

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

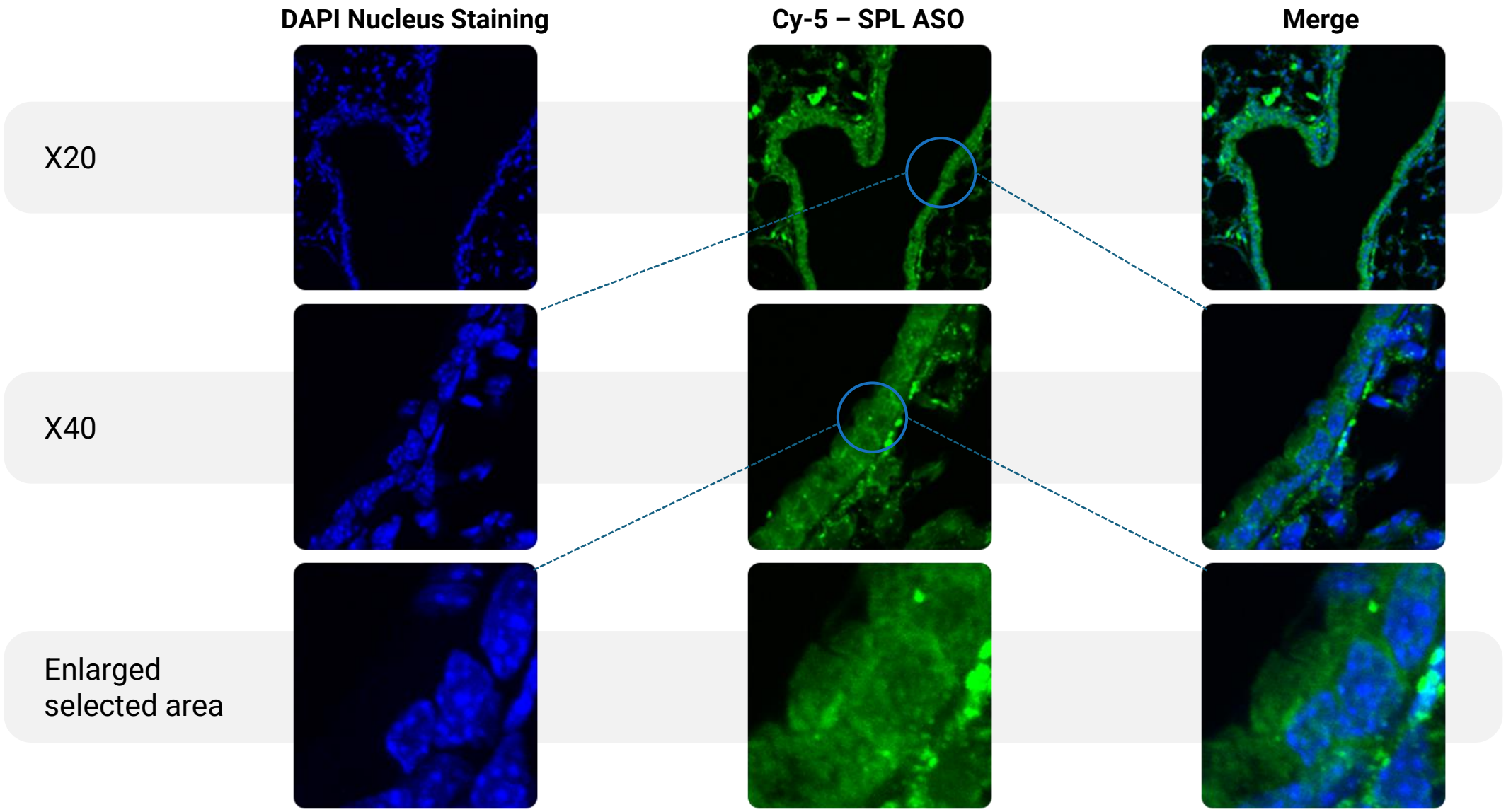






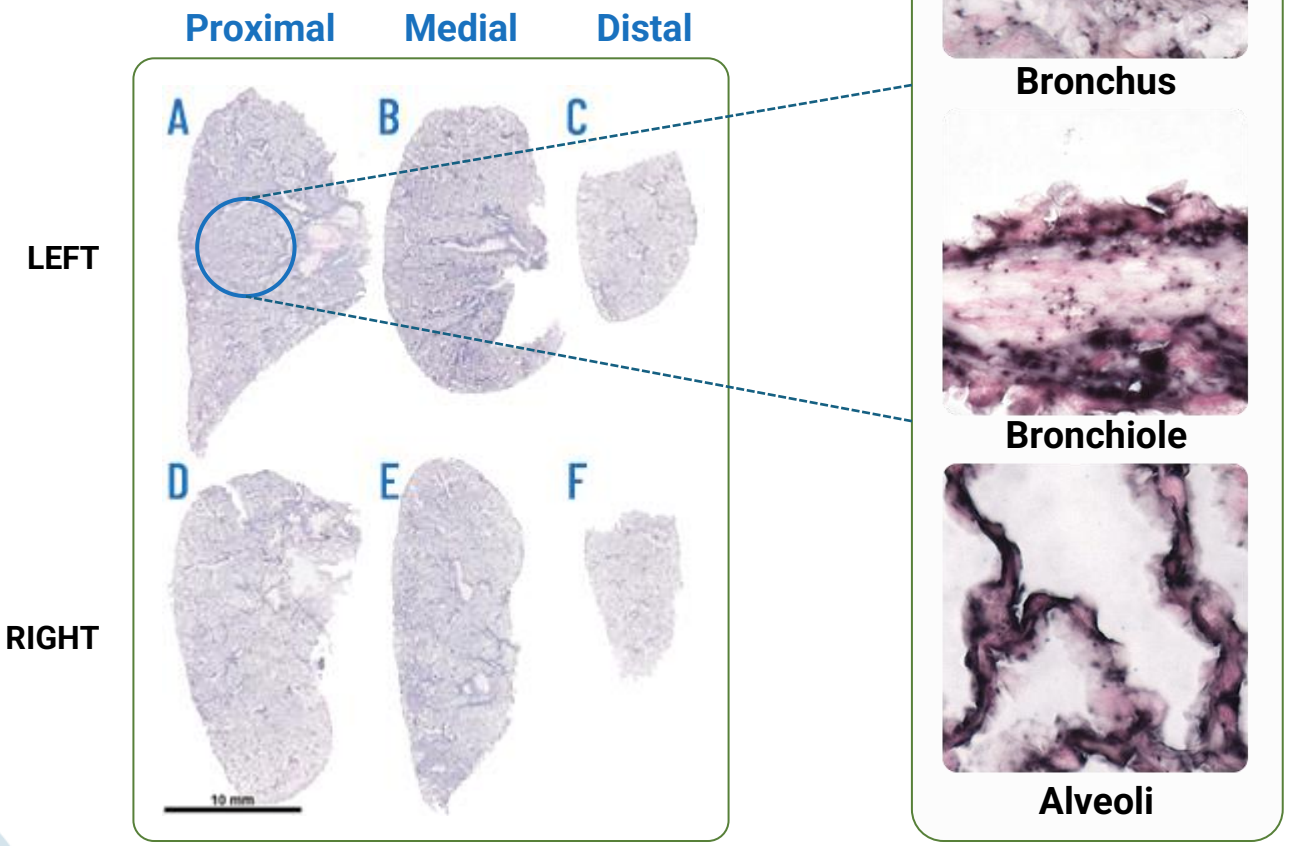
ISH STAINING FOR SPL ASO FOLLOWING IT ADMINISTRATION
DARK STAINING

SPL ASO Enters the Nucleus in Mice Lung Epithelial Cells

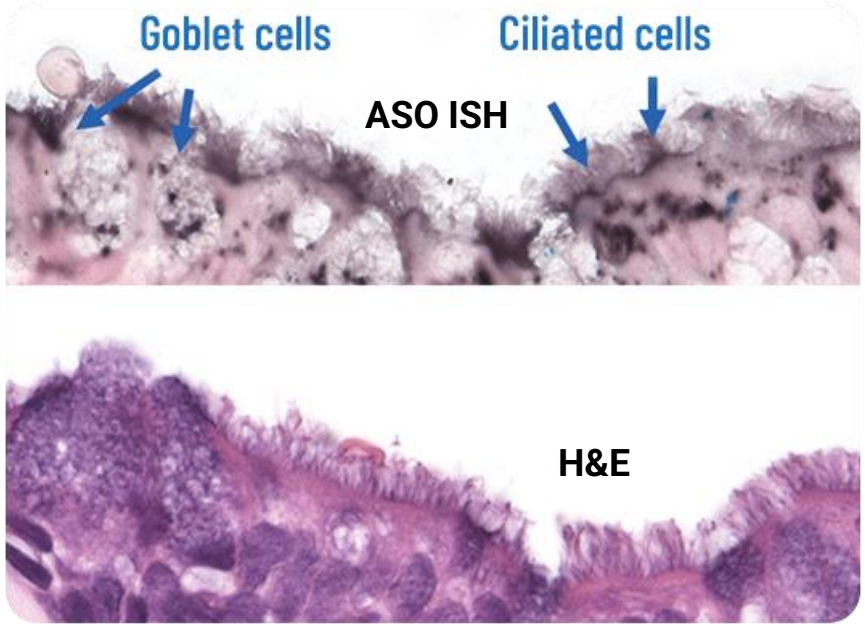


SPL ASO Uniformly Distributes in NHPs Lungs Following Inhalation

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

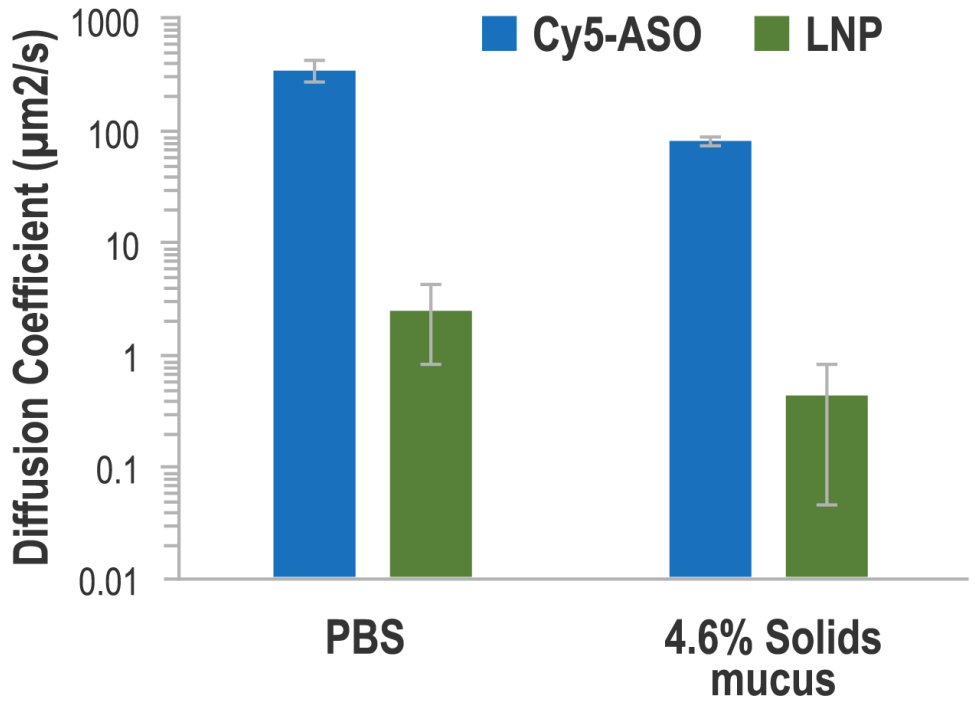


- Uniform labeling in all sampled sections
- Respiratory epithelium and alveolar cells are well labeled

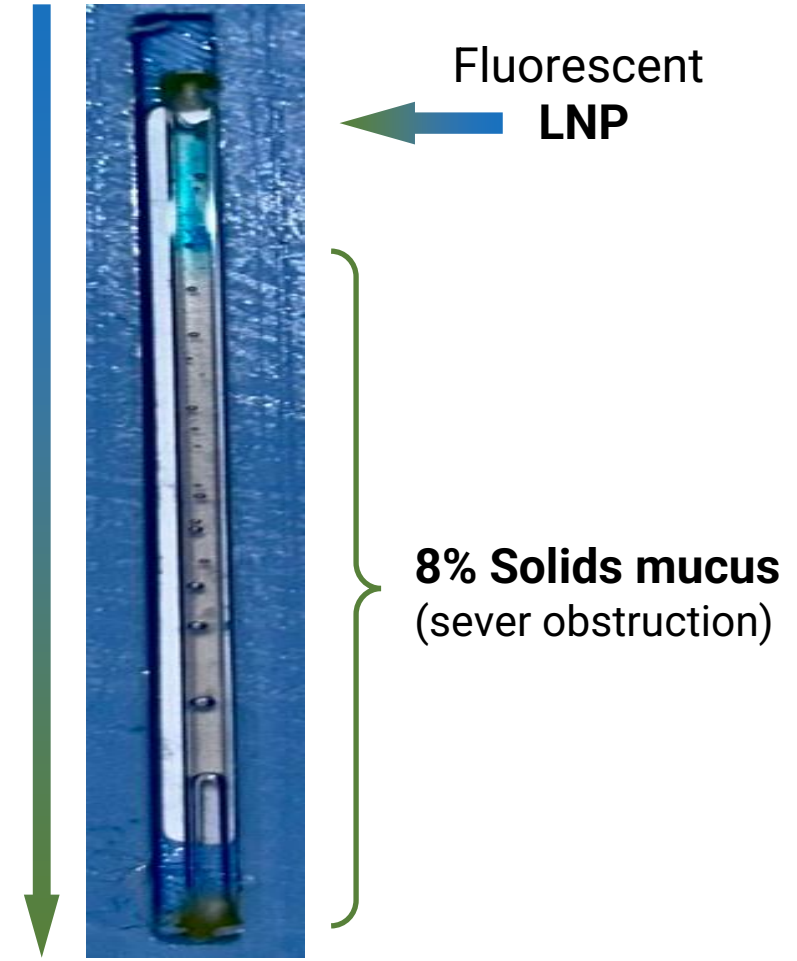


SPL ASO Crosses a Viscous Human Mucus Layer Significantly Faster Than LNPs (>x100)

Marsico Lung Institute; UNC



72 hours post initiation

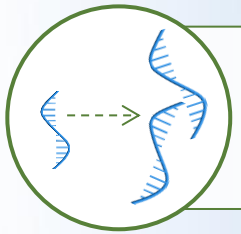


- A larger diffusion coefficient corresponds to the molecule moving “faster”
- **In 8% solids mucus (sever obstruction) significant superiority of SPL ASO was observed over standard LNPs** (a representative image of the LNP concentrating on top of the mucus at 72hr is presented above)

SpliSense
Making Sense of Splicing

SPL84 – Phase 2 on Track

(Unmet 3849 CF Mutation)

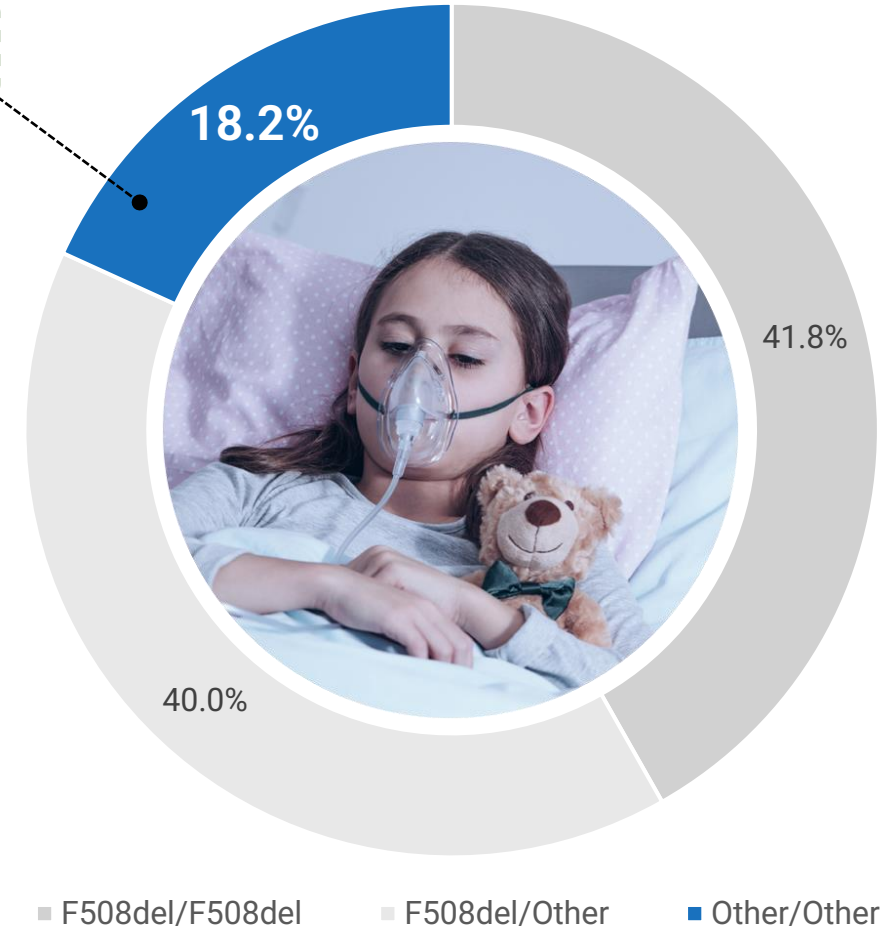


Restoring
protein function

Cystic Fibrosis – Need for Novel Drugs for Unmet Mutations

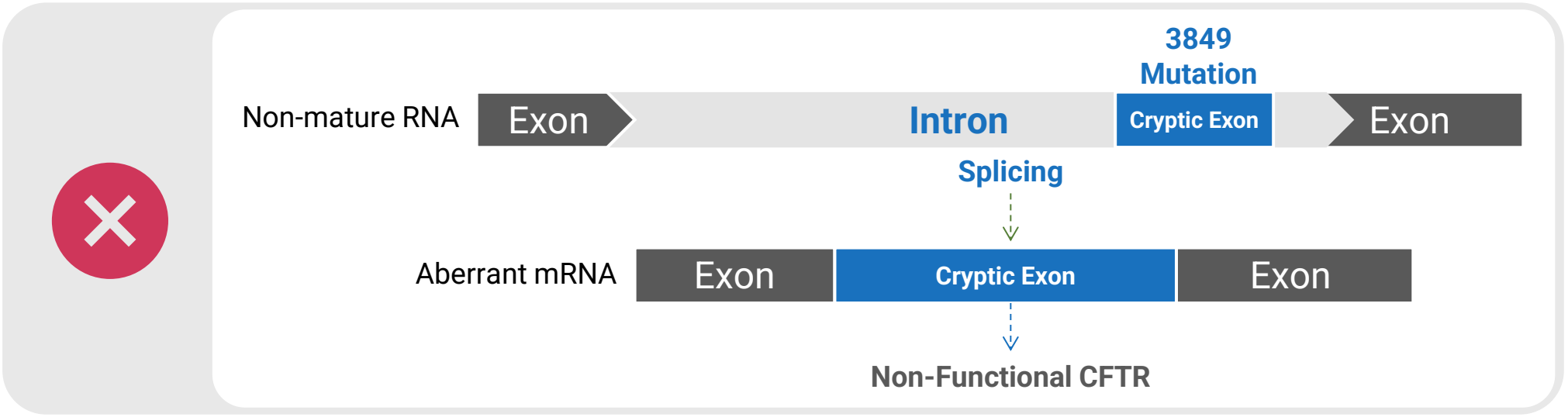
SpliSense (~$3B TAM)

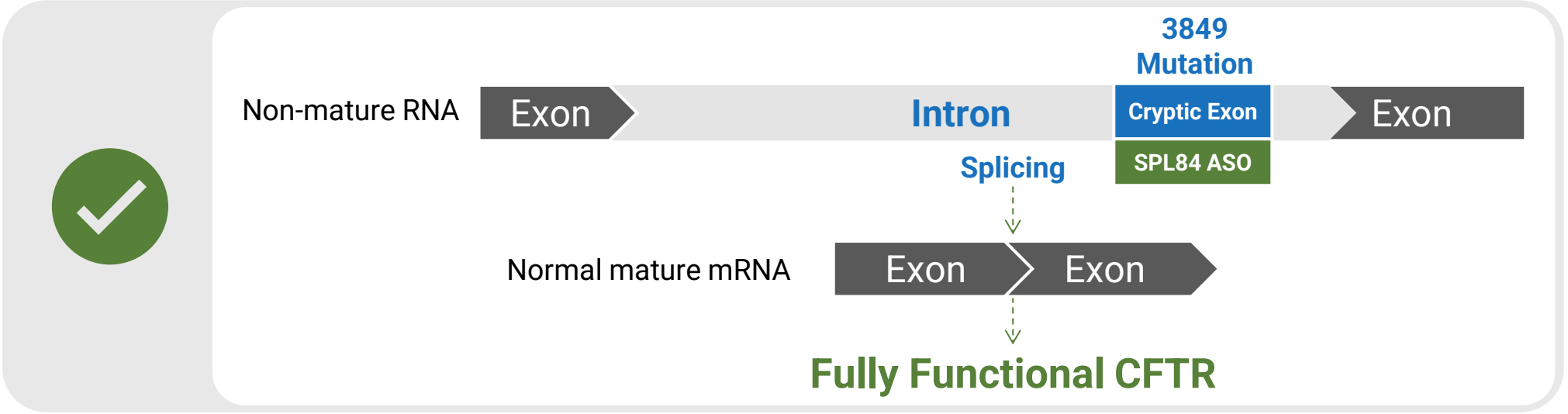
- **A progressive, autosomal recessive genetic disease, affecting >120,000 people worldwide**
- **Existing drugs alleviate symptoms but do not cure the disease**
  - Trikafta® is suitable for ~80% of CF patients (mutations specific- F508del)
  - ~33% of F508del have moderate to no response to Trikafta®
- **3849 is an orphan, severe CF mutation**
  - ~1600 patients
  - No approved mutation specific drug



Castellani & Assael, 2017, Hudock & Clancy, 2017, Cystic Fibrosis Foundation Patient Registry Annual Data Report, 2019, KOLs / Investors day

SPL84 Produces Mature and Functioning WT CFTR

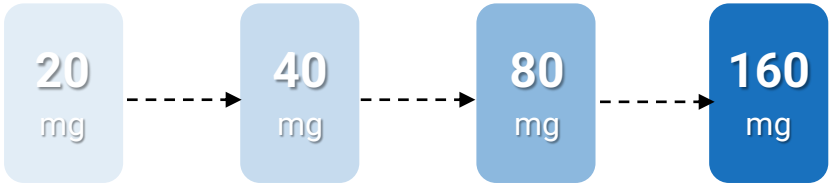




Ongoing SPL84 Phase 2 Study Informed by Phase 1 Results

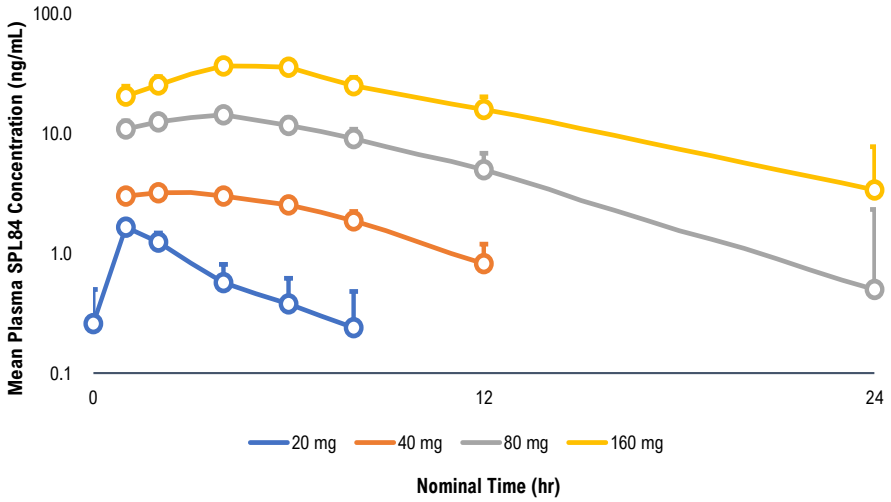
Phase 1 Study Design

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



Study Results

Systemic exposure to SPL84 was low and dose dependent



Study Results

- **SPL84 was safe and well tolerated**
- **No SAEs or significant related AEs**
- **No significant changes from baseline in vital signs, clinical laboratory values, ECG, physical examination, or pulmonary function**
- **Systemic exposure to SPL84 was low and dose dependent.**
  - Exposure margins of ~20 when comparing the AUC at the160 mg clinical dose to the AUC at the NOAEL dose in GLP tox. studies.

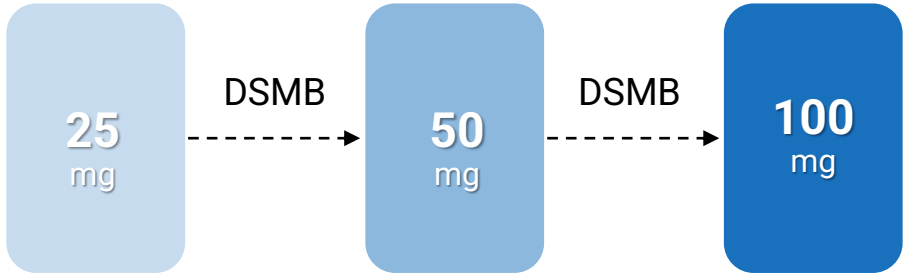
SpliSense
Making Sense of Splicing

Ongoing SPL84 Global Phase 2 Study

Phase 2 Study Design

Placebo Controlled Multiple Ascending Dose (MAD) in subjects with CF 3849+10kb C->T mutation (n=24)

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



n=8	n=8	n=8
6 active; 2 placebo	6 active; 2 placebo	6 active; 2 placebo

Expansion of either cohort to support potential Acc./Con. Approval

Primary Objective:

To evaluate the safety & tolerability of multiple ascending doses of SPL84

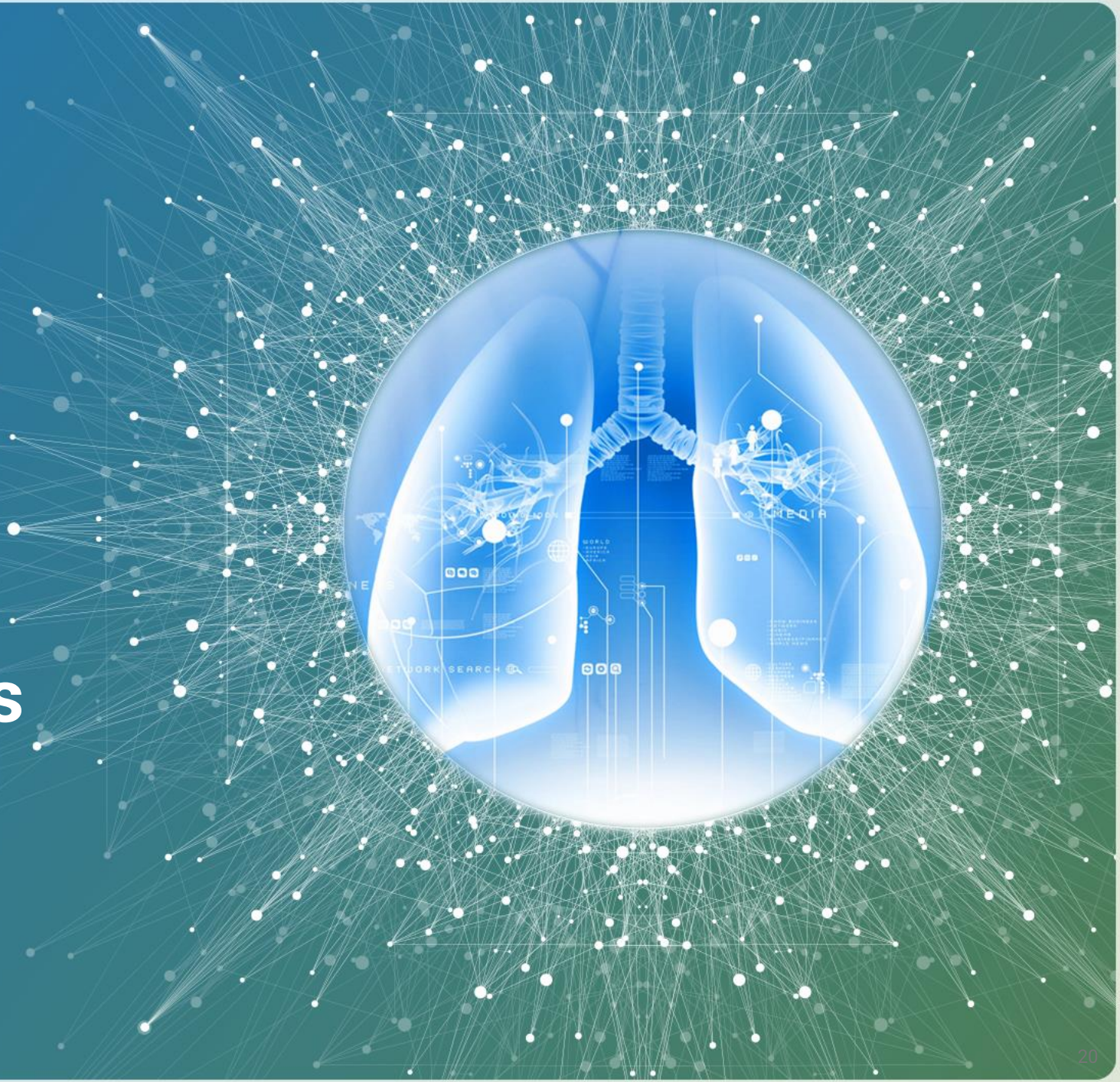
Secondary Objective:

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

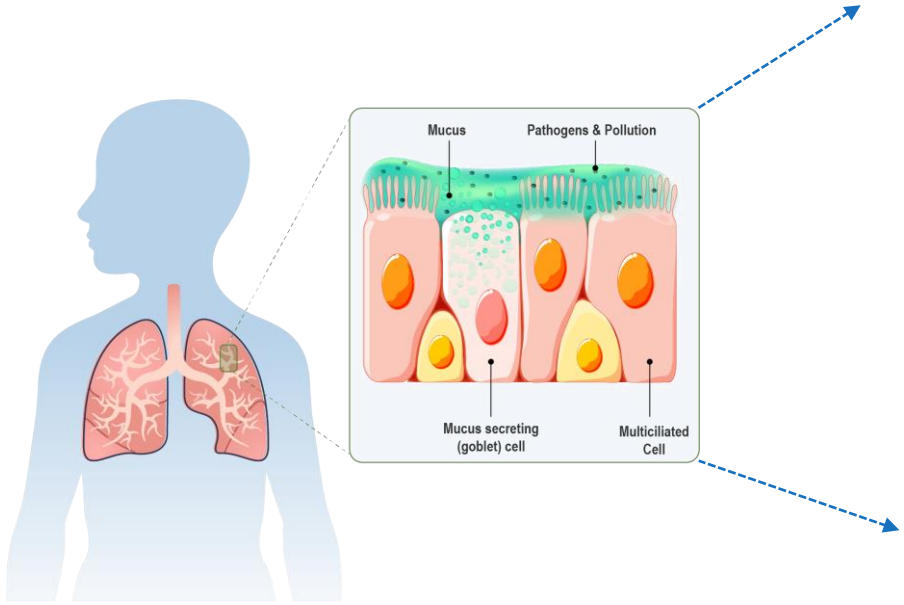
- **Fast Track Designation**
- **IND, CTR approvals**

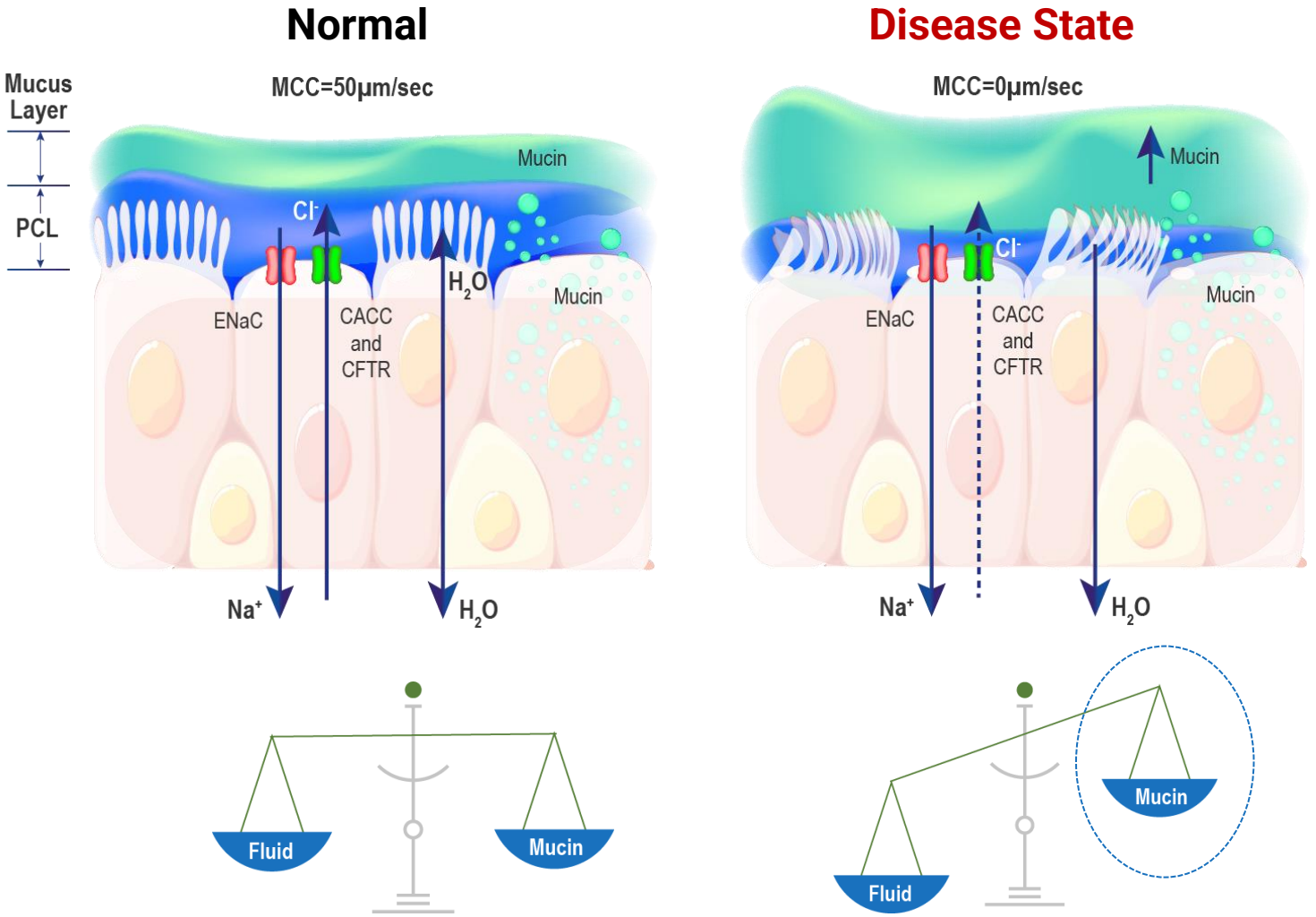
SpliSense
Making Sense of Splicing

Expanding Our ASO Technology From Orphan to Large Pulmonary Indications



Hyper Secreted Mucins (MUC5AC & MUC5B) are Heavily Involved in Pulmonary Diseases Progression and Severity



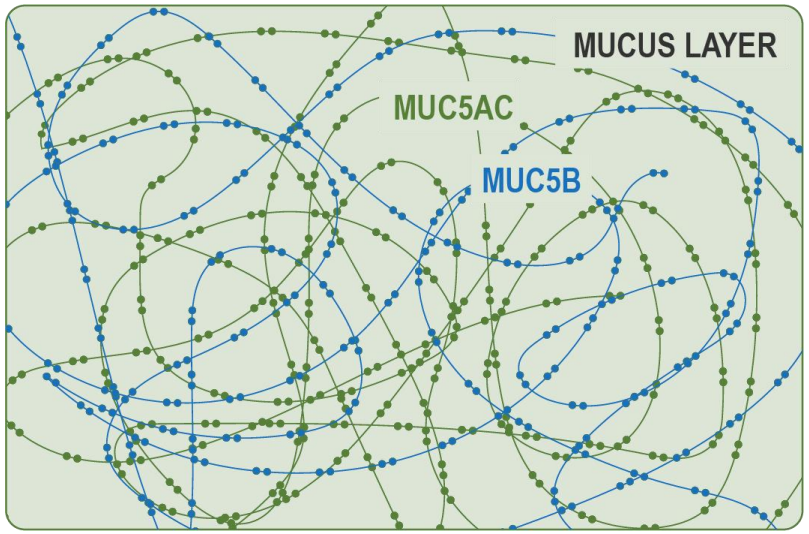


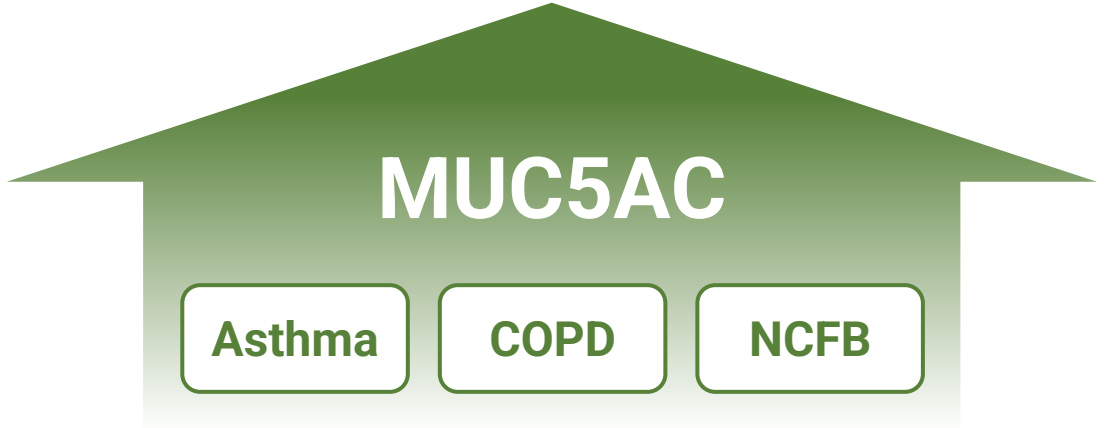
Bucher et al. 2019

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.

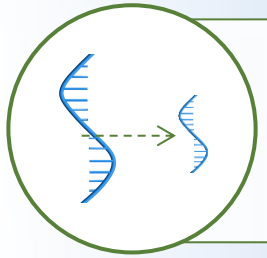




SpliSense
Making Sense of Splicing

Muco-Obstructive Diseases

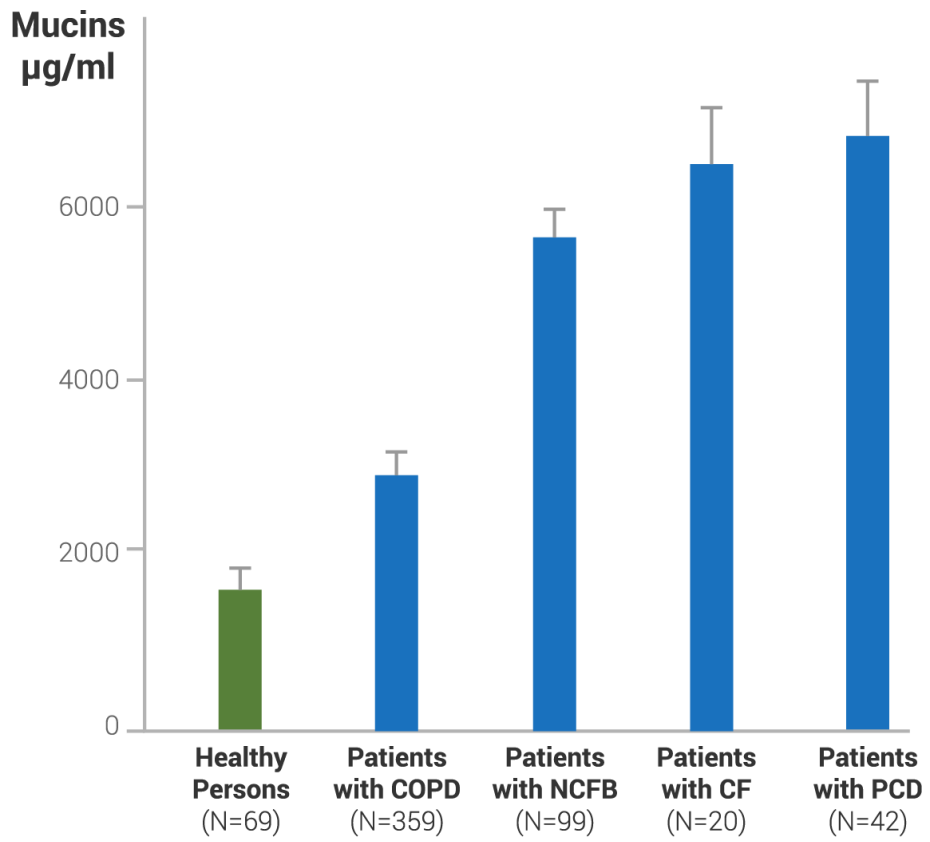
MUC5AC Lowering ASO (SPL5AC)



Decrease production of over –expressed proteins

MUC5AC Concentrations Increase Disproportionately in Muco-Obstructive Diseases

Induced Sputum MS Assay



US Diagnosed Patients

Severe Asthma >25M Pts

MUC5AC levels are significantly increased
- Persistent airway mucus plugs
- Airflow obstruction
- Augmentation of viral induced inflammation

COPD >16M Pts

MUC5AC increases >10x, this correlates to:
- Increase in disease severity
- Decrease lung function
- Increased mortality

NCFB >350K Pts

MUC5AC increases >17x
- Severely obstructive
- Unmet, Orphan indication
- No approved therapies

CF >120K Pts

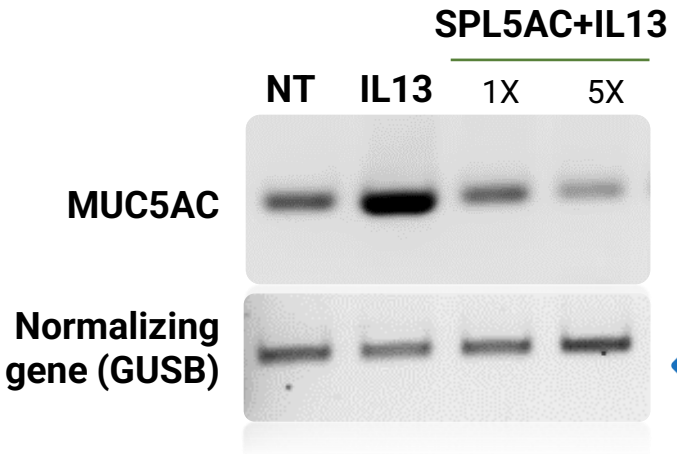
MUC5AC increases >30x

SpliSense Making Sense of Splicing

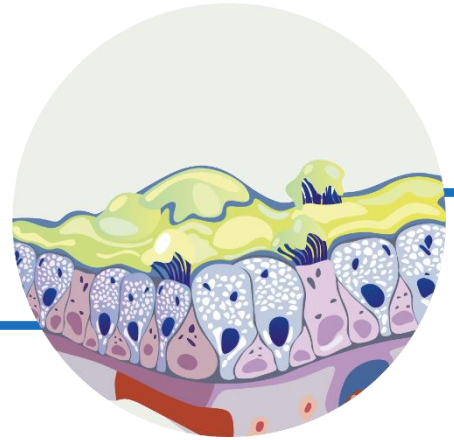
Source: Ridley et al. 2018, Roy et al. 2019, Symmes et al. 2018, Ma et al. 2017; CDC National Center for Health Statistics, National Health Interview Survey (NHIS). National Surveillance of Asthma: United States, 2001-2017. Wheaton AG, Cunningham TJ, Ford ES, Croft JB. Employment and activity limitations among adults with chronic obstructive pulmonary disease — United States, 2013. MMWR Morb Mortal Wkly Rep. 2015:64 (11):290–295; Weycker et al. Chron Respir Dis. 2017;14(4):377-384; McShane et al. Am J Respir Crit Care Med. 2013;188(6):647-656; Maselli et al. Int J Clin Practe. 2017 Feb;71(2); Chalmers. Chest 2017; 151(6): 1204–1206; Cystic Fibrosis Foundation Patient Registry Annual Data Report 2020

SPL5AC ASO Provides Consistent Reduction in MUC5AC Levels in HVs IL13 Hyper - Stimulated Bronchial Epithelial Cells (n=7)

MUC5AC RNA

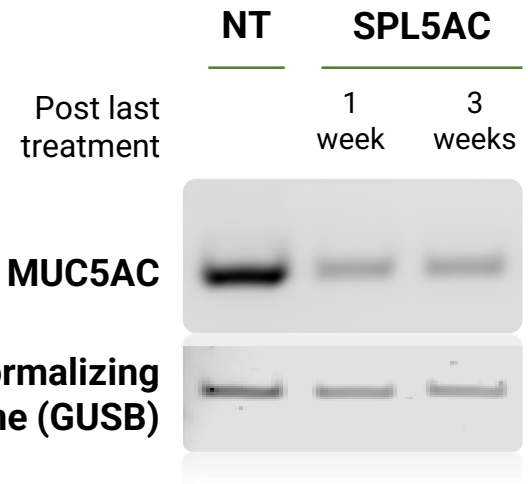


RNA from the cells



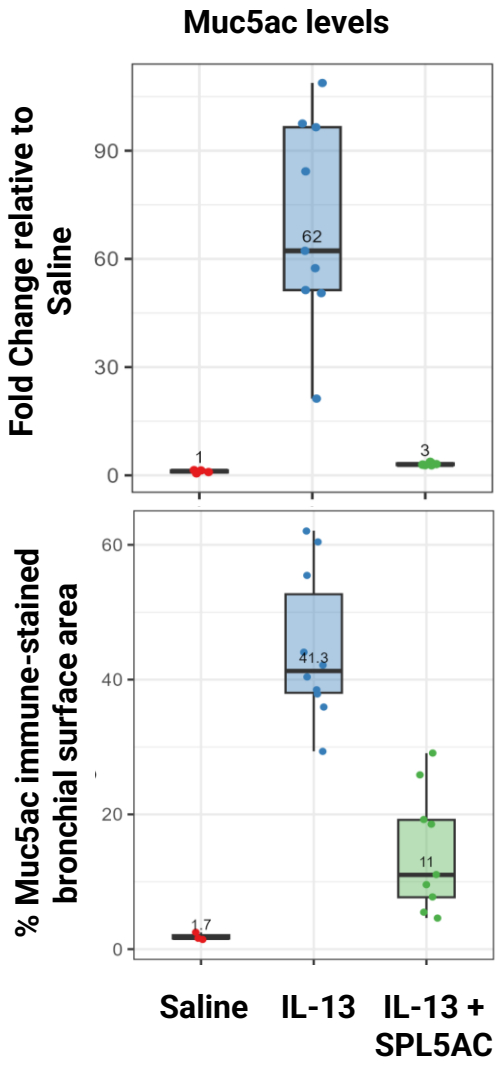
Protein from the mucus

MUC5AC Protein



SPL5AC has a durable and dose dependent effect on MUC5AC levels

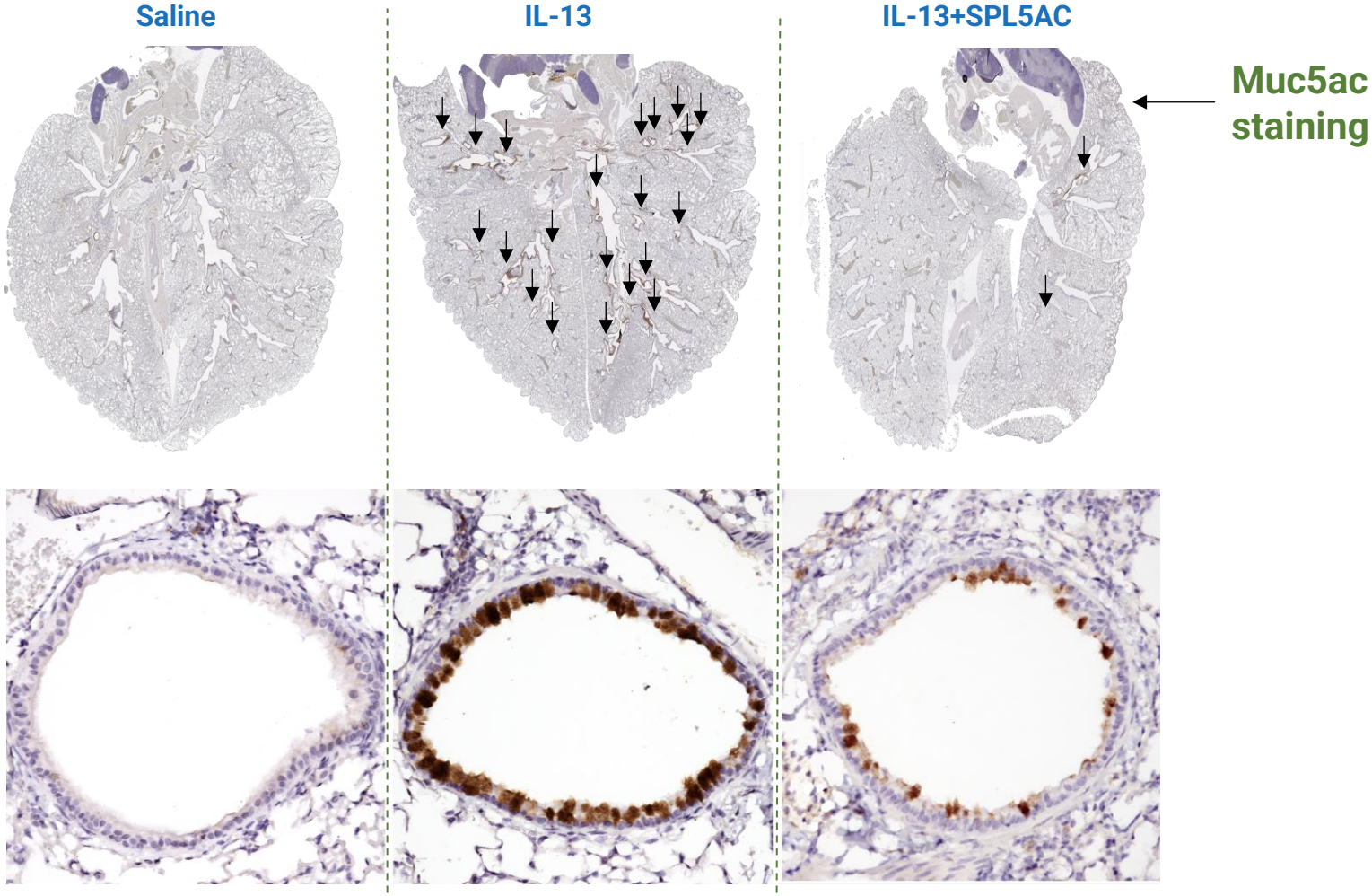
SPL5AC ASO Reduces Muc5ac Protein Levels in Lungs of IL13 Hyper-Stimulated WT Mice



RNA
(96% reduction)

Protein
(73% reduction)

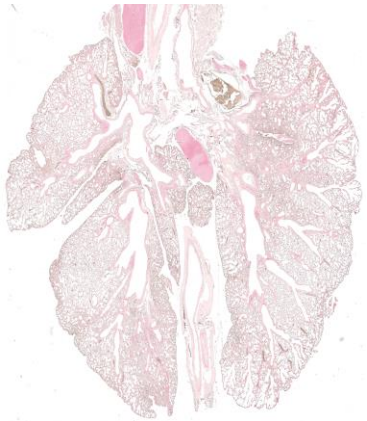
Muc5ac Protein (IHC)



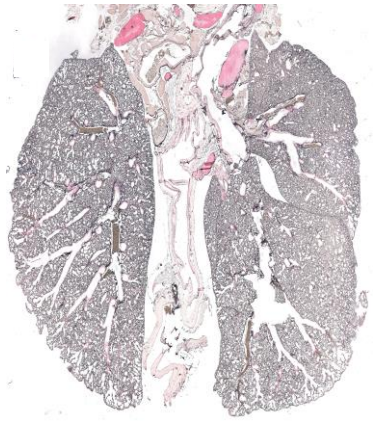
Once a week SPL5AC treatments in mice support EOW treatment regimen in humans

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

SPL5AC distribution (ISH staining)

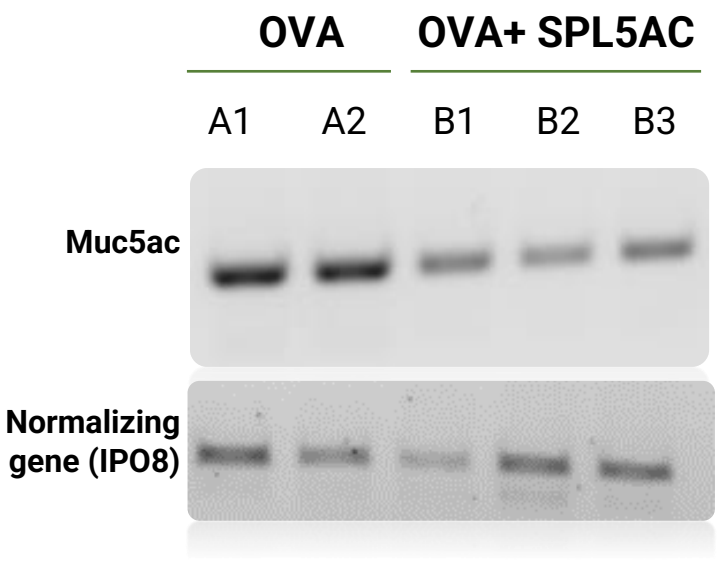


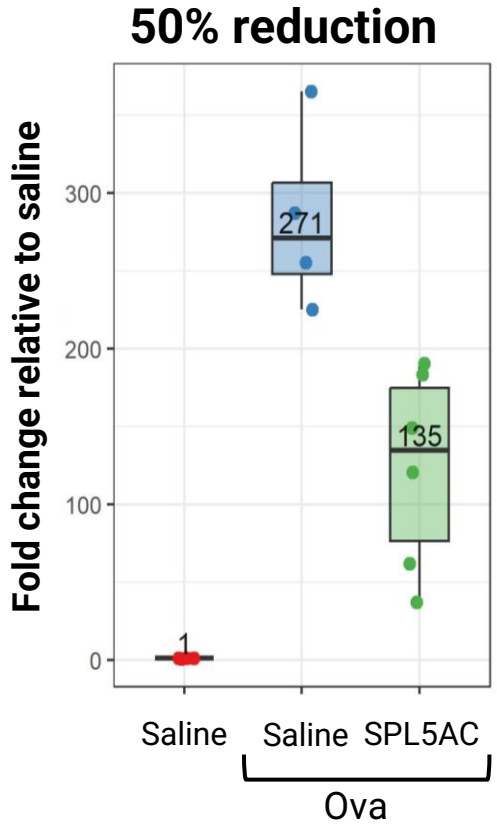
OVA+ Saline



OVA+SPL5AC

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

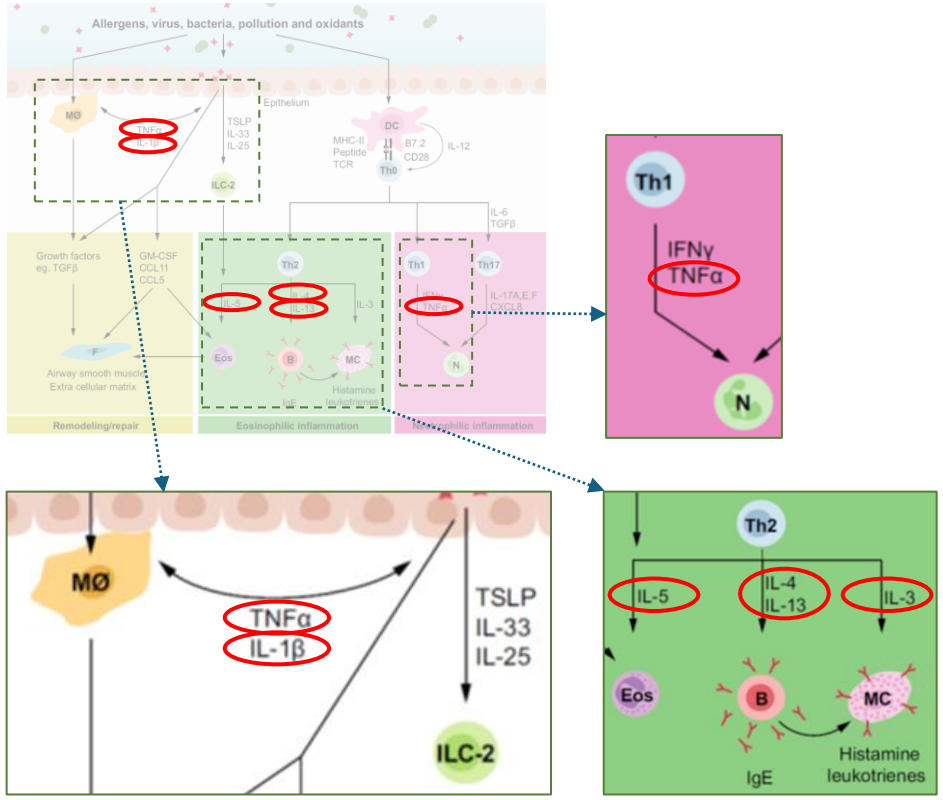




Calculated by median

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

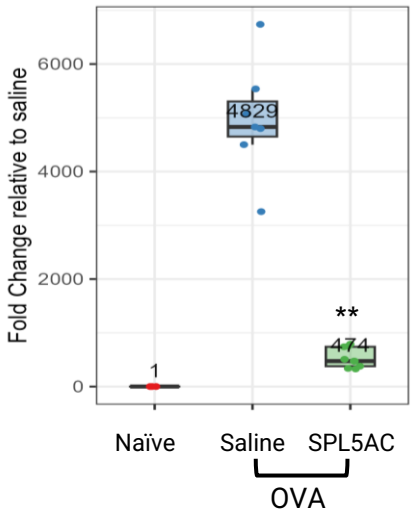
SPL5AC Attenuates Th-2 Inflammatory Response in an Asthma Disease Mouse Model (Ovalbumin)



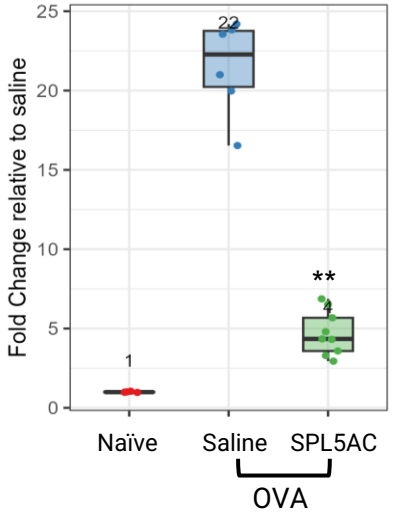
Adopted from Chung et al. 2015

Pro-inflammatory cytokines induced in Asthma

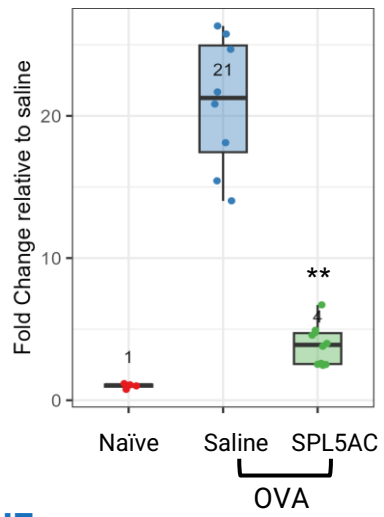
IL-13
90% Reduction



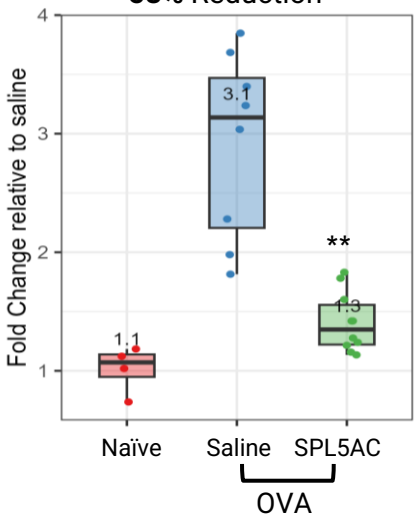
IL-5
83% Reduction



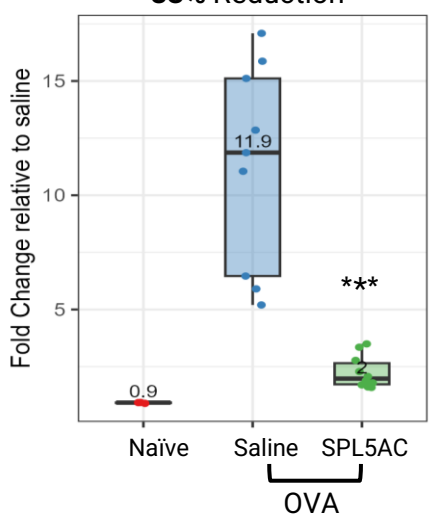
IL-4
81% Reduction



IL1-β
58% Reduction



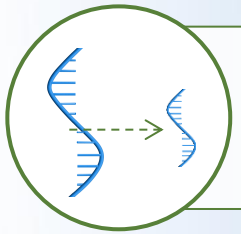
TNFα
83% Reduction



SpliSense
Making Sense of Splicing

Idiopathic Pulmonary Fibrosis (IPF)

MUC5B Lowering ASO (SPL5B)

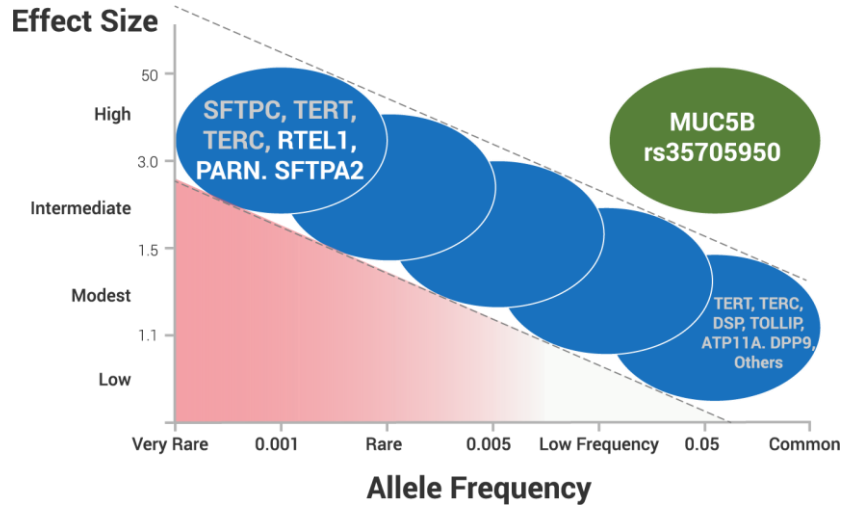


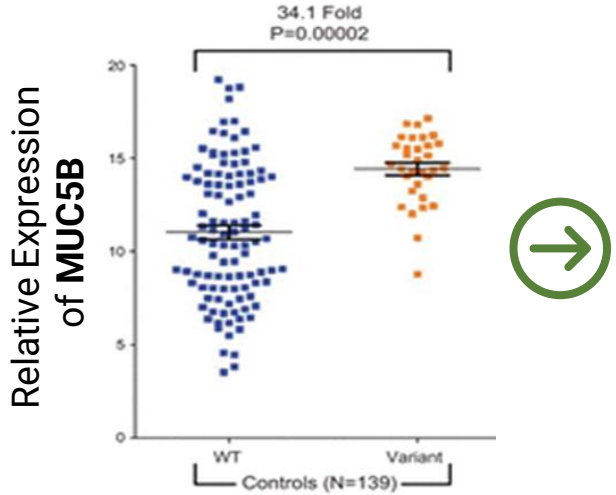
Decrease production of over–expressed proteins

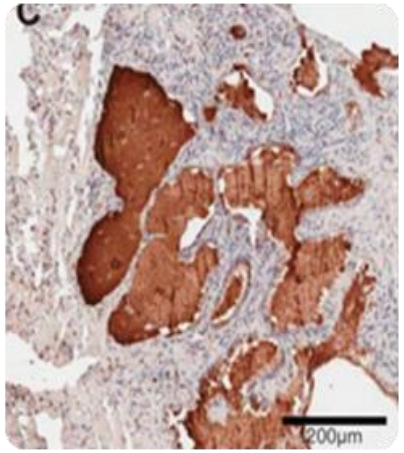
Elevated Levels of MUC5B Potentially Drives IPF

- **A single nucleotide polymorphism (SNP) in MUC5B gene (rs35705950)**
  - Leads to increased expression of MUC5B
  - Accounts for 30–35% 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



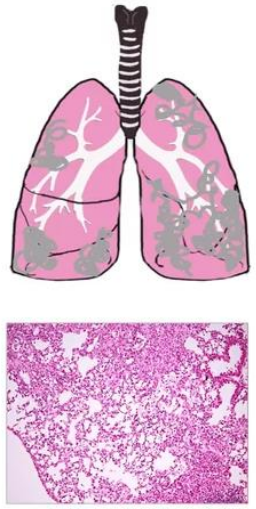




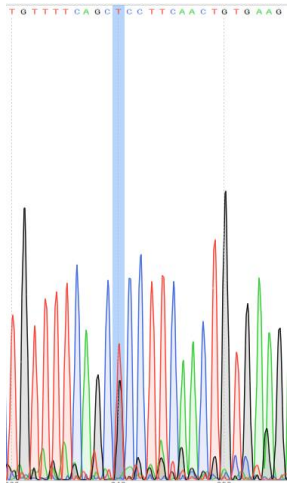
Evans et al 2014, Zhang et. al. 2019

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

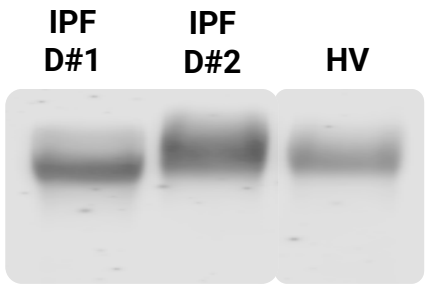
SPL5B Reduces MUC5B Levels in IPF^{SNP+} Patients Bronchial Cells



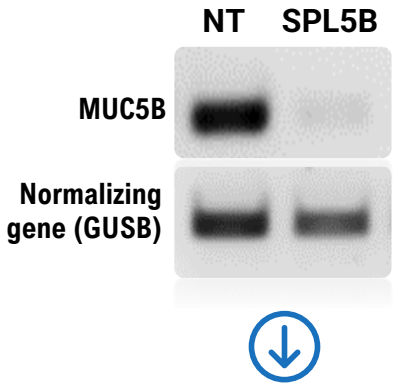
SNP^{+} sequencing

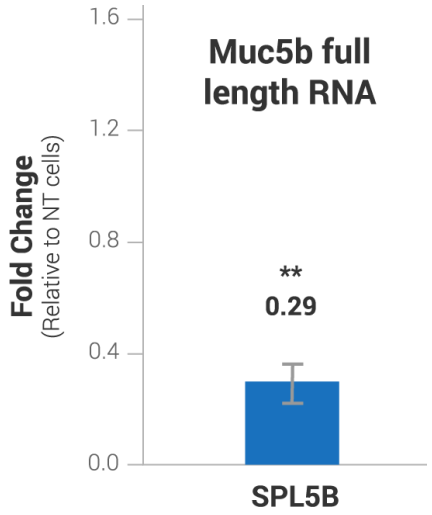


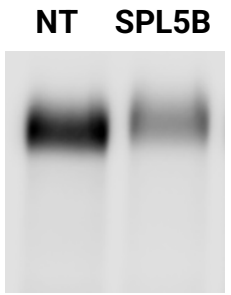
MUC5B elevated protein level in IPF $^{SNP+}$



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





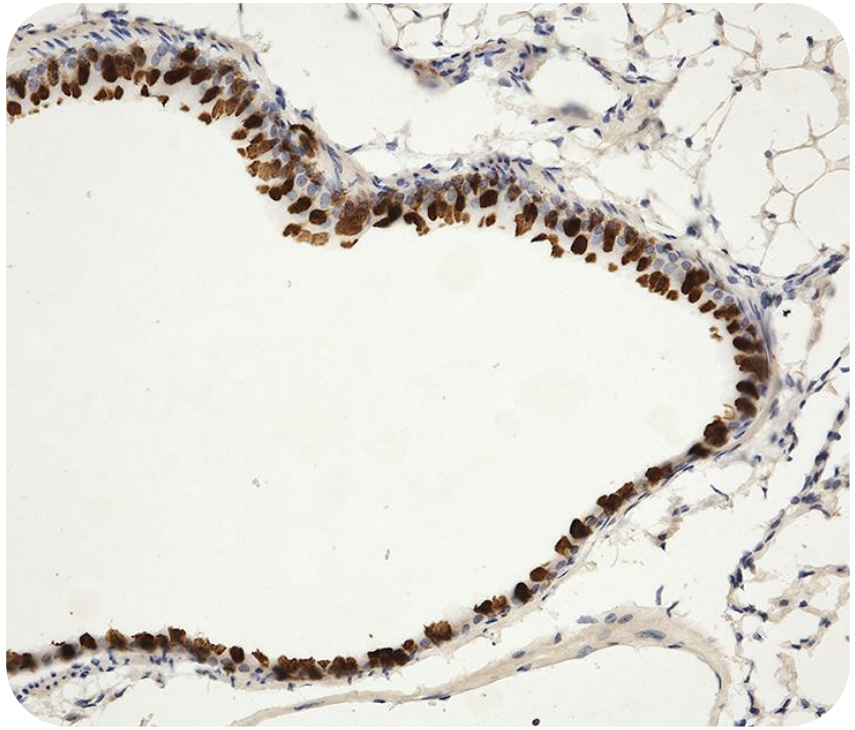


MUC5B Protein

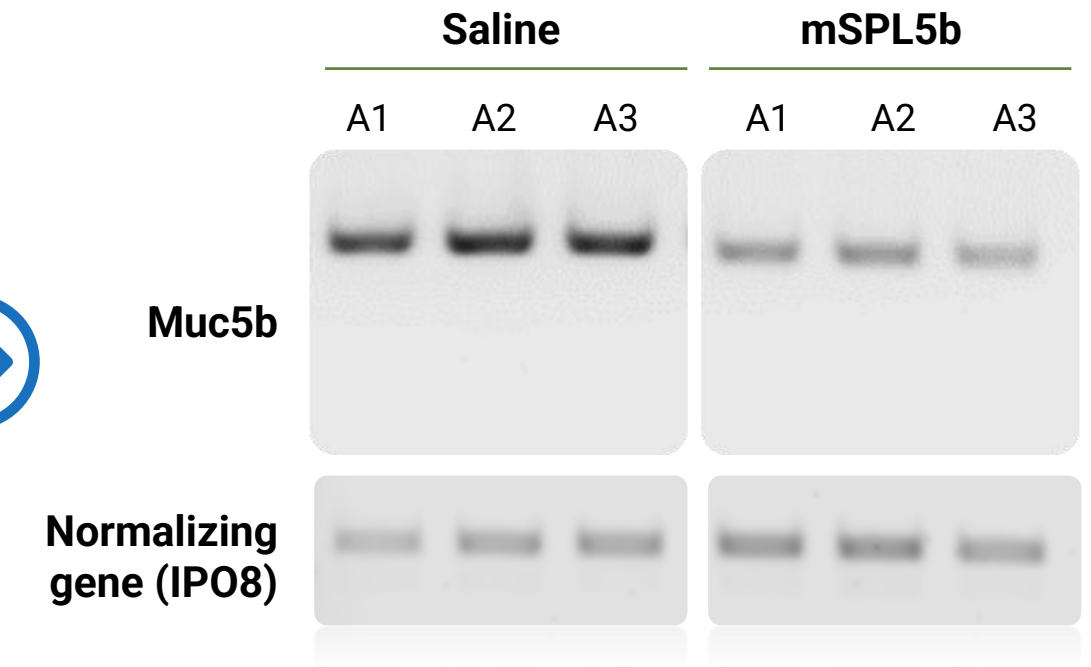
- Both donors carry the MUC5B SNP(G->T)
- In both patients' cells higher levels of MUC5B were found compared to HV cells
- Treatment of differentiated cells with SPL5B ASO reduced the levels of MUC5B

Mouse SPL5B ASO Lowers Muc5b Levels

Muc5b IHC in WT mice



Levels of Muc5b RNA



PoC for Muc5b in-vivo lung reduction was preformed in WT mice

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, Ph.D.

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, Ph.D.

Co-founder & CSO

Prof. Hebrew University of Jerusalem. 30 years of leading research in CF genetics starting with the discovery of the CFTR gene

Prof. Eitan Kerem, M.D

CMO

Pediatric pulmonologist; Head of the Pediatric Pulmonology Unit of HMC Jerusalem, Chairman of the Israeli CF Foundation CAB

Efrat Ozeri-Galai, Ph.D.

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

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

SpliSense
Making Sense of Splicing

Thank You!