SpliSense

Making Sense of Splicing

Transformative RNA Based Treatments for CF & Pulmonary Diseases

Corp. Update
2021

NON-CONFIDENTIAL

SpliSense – CF & Pulmonary Diseases Focused Company

The Company

- Founded in 2017 by Prof. Batsheva Kerem (Hebrew University)
  - Part of the global team that cloned the CFTR gene
- Leadership team and advisors with strong track record in pulmonary development of inhaled therapies and ASOs
- Based in Jerusalem, Israel

R&D Status

- Inhaled Antisense Oligonucleotides (ASOs)
  - Initial focus on high unmet need, orphan indications (CF)
  - Subsequent expansion to larger, non orphan pulmonary indications (muco- obstructive diseases)
  - ASOs - clinically validated approach
  - Two clinical programs to be initiated in late 2022

Financial

- Backed by a strong syndicate including: OrbiMed, CF Foundation, IBF and Integra (VC arm of Hebrew University)

OrbiMed Healthcare Fund Management

ISRAEL BIOTECH FUND

CYSTIC FIBROSIS FOUNDATION

INTEGRA HOLDINGS

Management & Leadership Team

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.

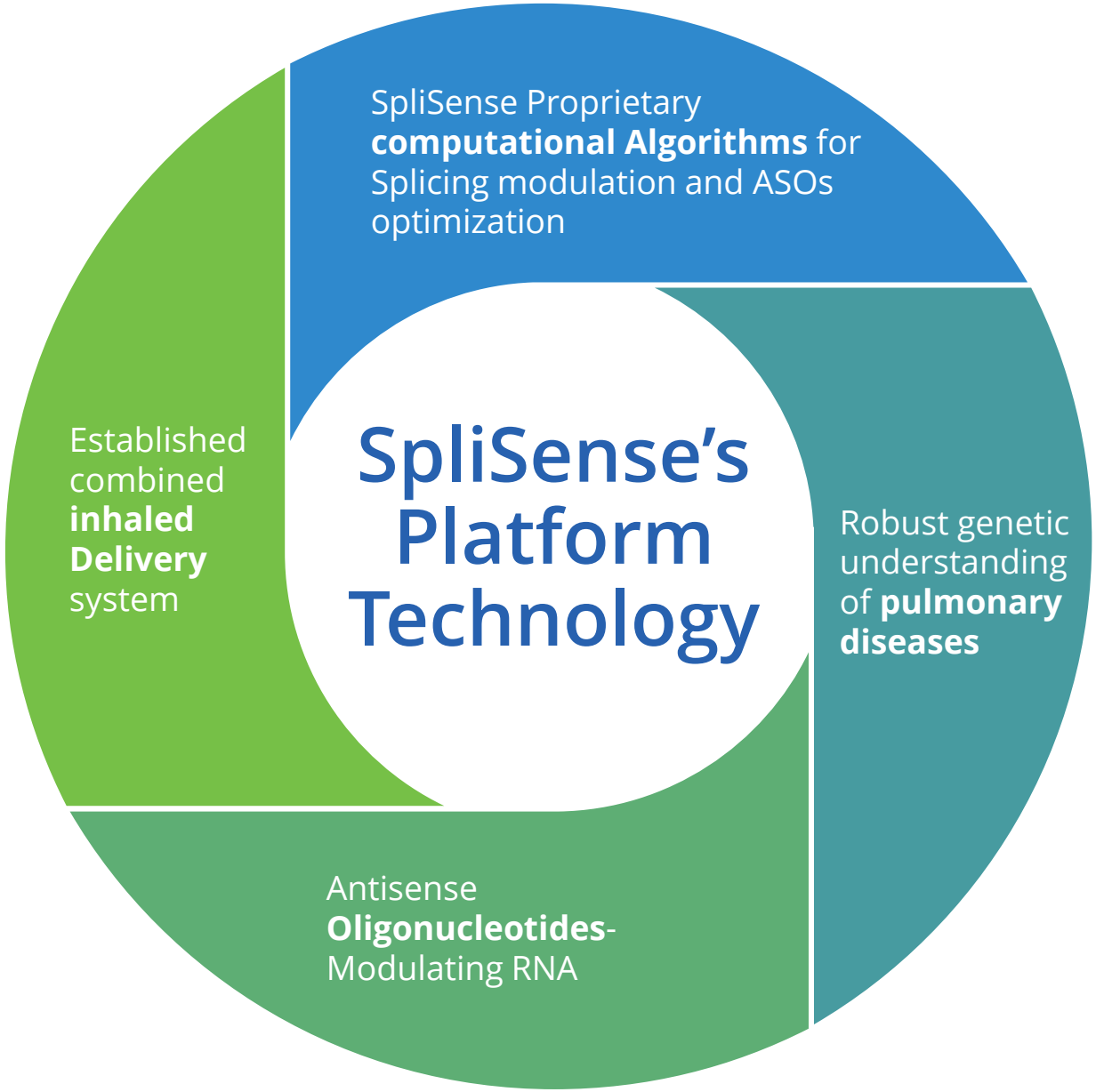
Batsheva Kerem PhD -Co-founder & CSO
Prof. Hebrew University of Jerusalem. 30 years of leading research in CF genetics starting with the discovery of the CFTR gene..

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.

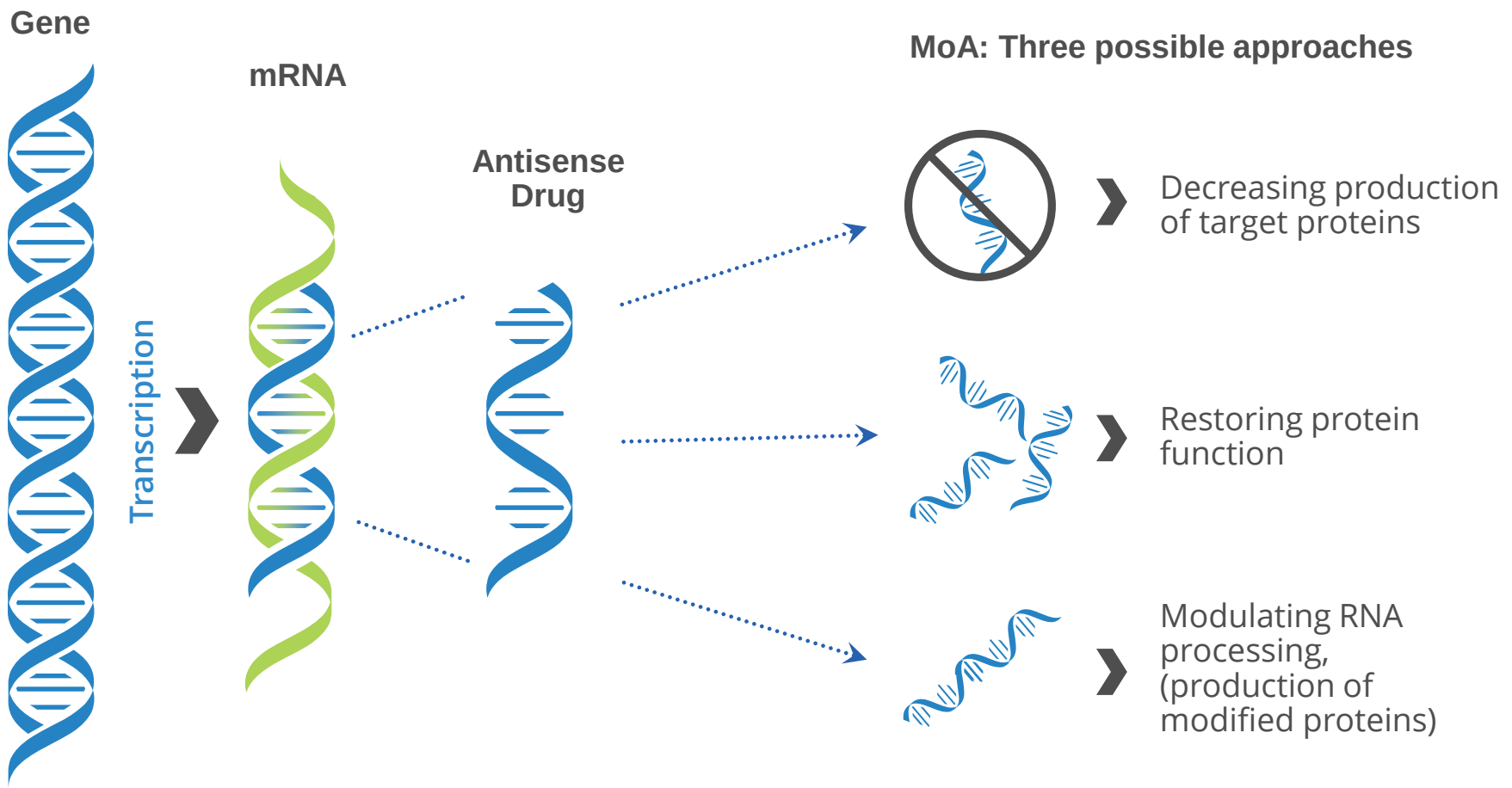
Nissim Darvish, M.D., Ph.D. – Chairman
Managing General Partner at MeOhr Ventures
Former Director at Orbimed Advisors LLC and Orbimed Israel Partners. Spent 8 years prior with Pitango Venture Capital

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

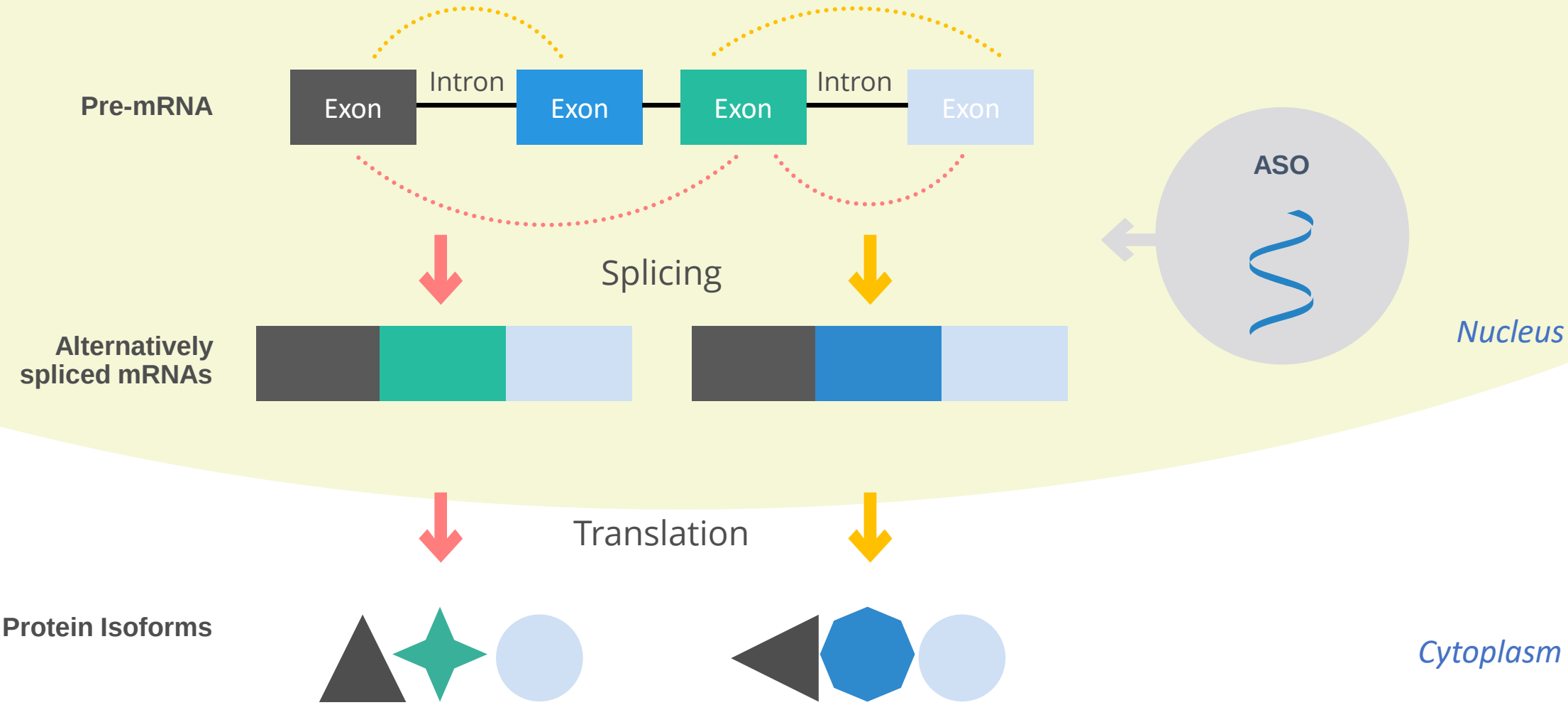
Efrat Ozeri-Galai PhD - VP Research
Extensive experience in CF and pulmonary diseases genetics, discovery and pre-clinical development.


SpliSense Proprietary **computational Algorithms** for Splicing modulation and ASOs optimization
Established combined **inhaled Delivery** system
SpliSense's Platform Technology
Robust genetic understanding of **pulmonary diseases**
Antisense **Oligonucleotides**-Modulating RNA

Antisense Oligonucleotides – Modulating RNA (MoA)



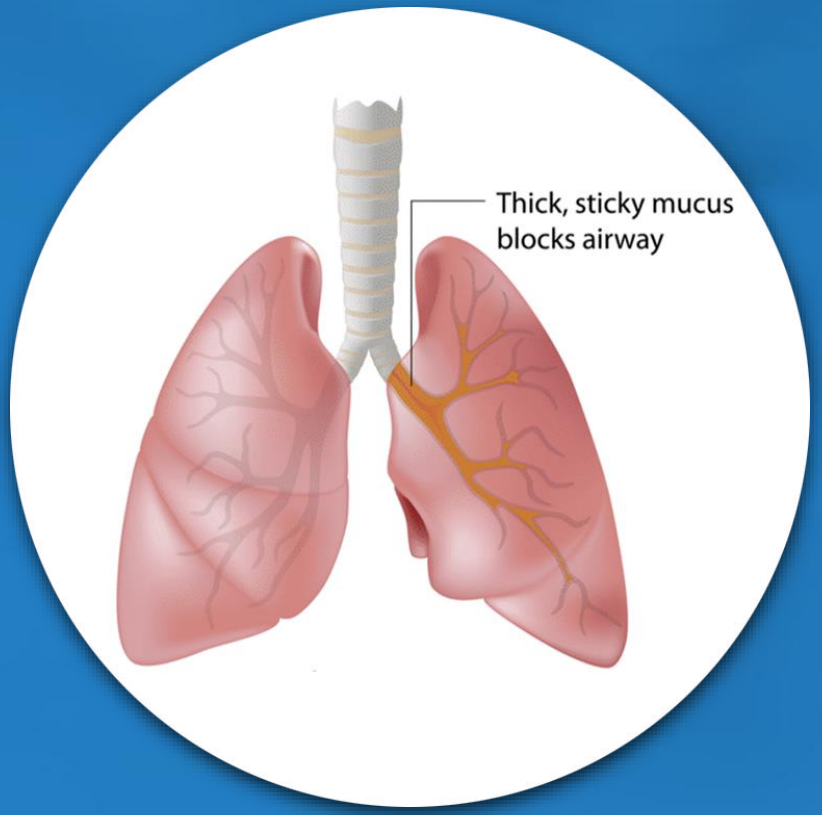
SpliSense Approach – Splicing Modulation of mRNA



SpliSense's CF & Pulmonary Diverse Pipeline

Indication	Approach	Program	Discovery	IND Enabling Studies	Clinical Studies
Cystic Fibrosis	Restoration of Protein Function	**SPL84-23** (3849 Mut.)			H2 2022
		SPL16 (2789 Mut.)			
	Production of Modified Protein	**SPL23-2** (Exon 23 Mut.)			H1 2023
Muco-Obstructive Diseases (COPD, PCD, CF, Asthma, Pulmonary Fibrosis etc.)	Decrease Production of Over-expressed Proteins	**SPL5A/B**			

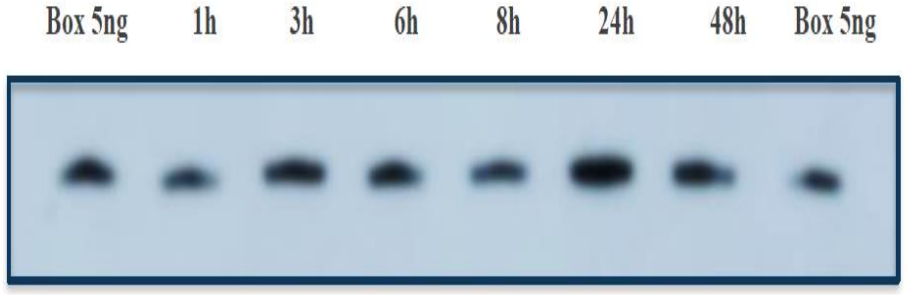
SpliSense ASOs Designed for Proper Delivery to Lungs



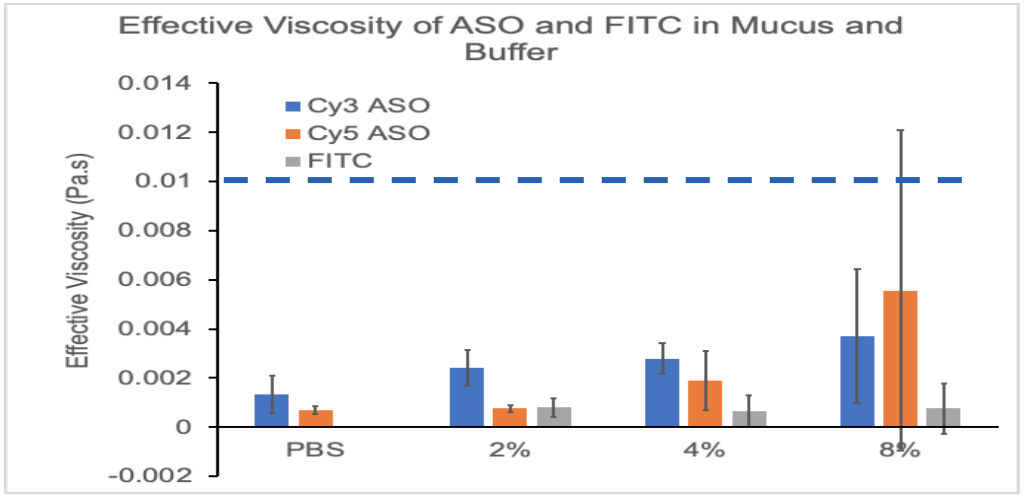
Use of Inhaled Delivery of ASOs for Lung Diseases

- ASOs are chemically modified for stability and increased lung cells uptake
  - No vectors or delivery vehicles are needed
  - shown to penetrate the cells via endocytosis efficiently
- Enables direct non-invasive delivery even of high doses (highly soluble) with minimal systemic exposure
- ASOs for inhalation:
  - Infrastructure for inhalation is established and commercially available
  - Stable post nebulization
- SpliSense end products are expected to be given to patients once a week or less , thus reducing patients' treatment burden

SpliSense ASOs are Stable in Hyper-Concentrated Mucus, and Properly Migrate Through it



SPL ASO is stable in patients' mucus

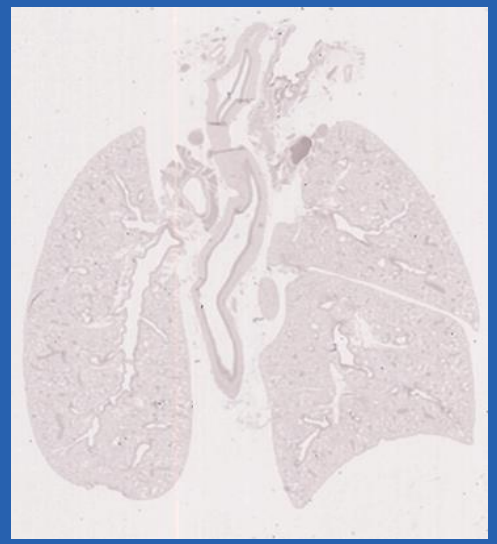


SPL ASO properly migrates through viscous mucus

SpliSense's ASOs Properly Distribute & Are Retained in WT and "Mucus Obstructive" Mice Lungs (β-ENaC Mice Model)

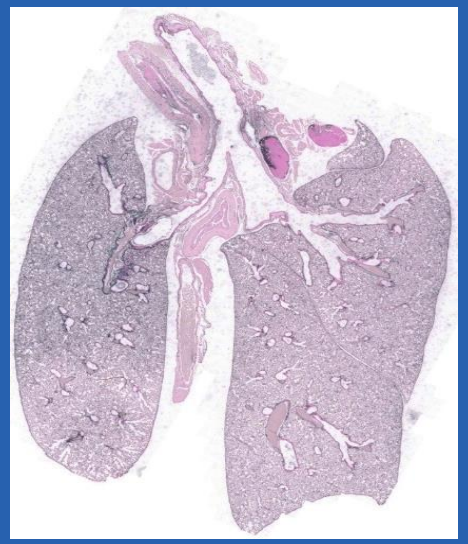
Staining for SPL84-23-1 following IT administration - dark staining

Negative Control

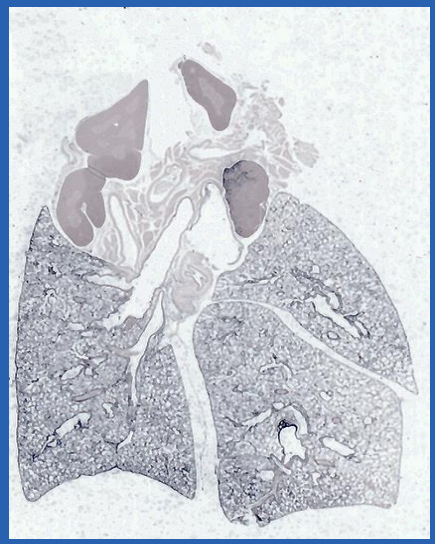


WT
24hr post dose

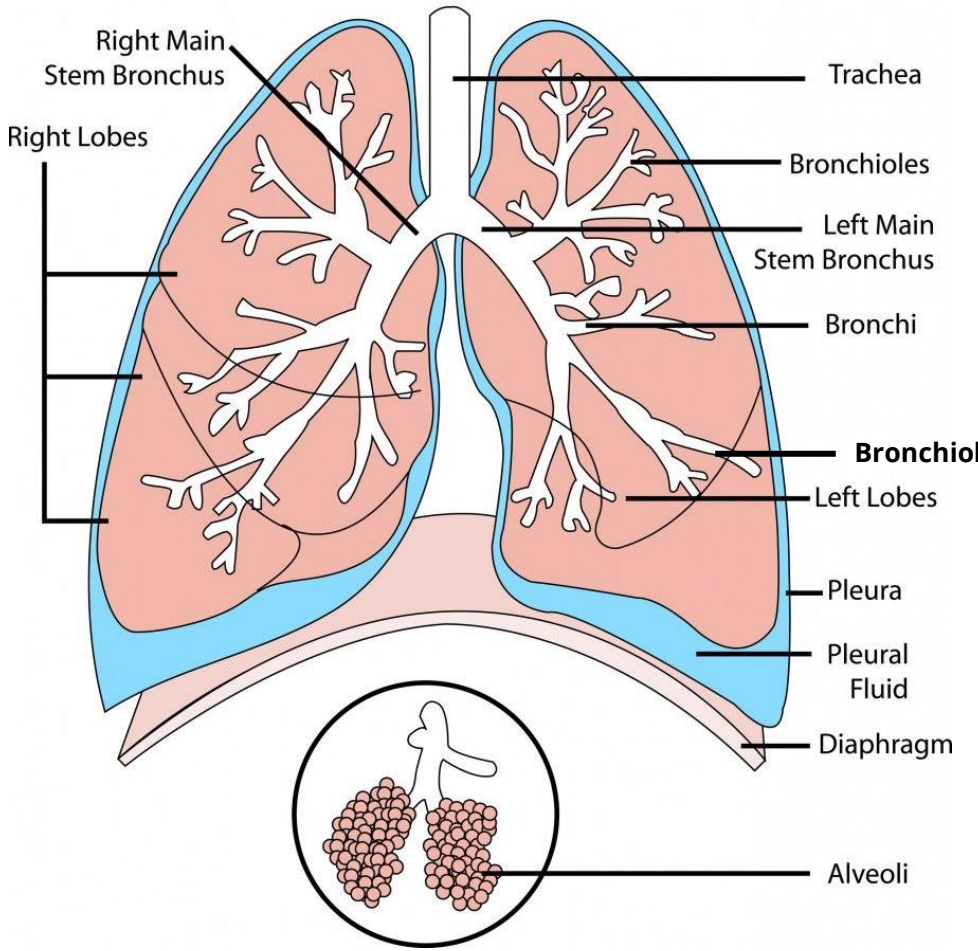
WT
1wk post dose

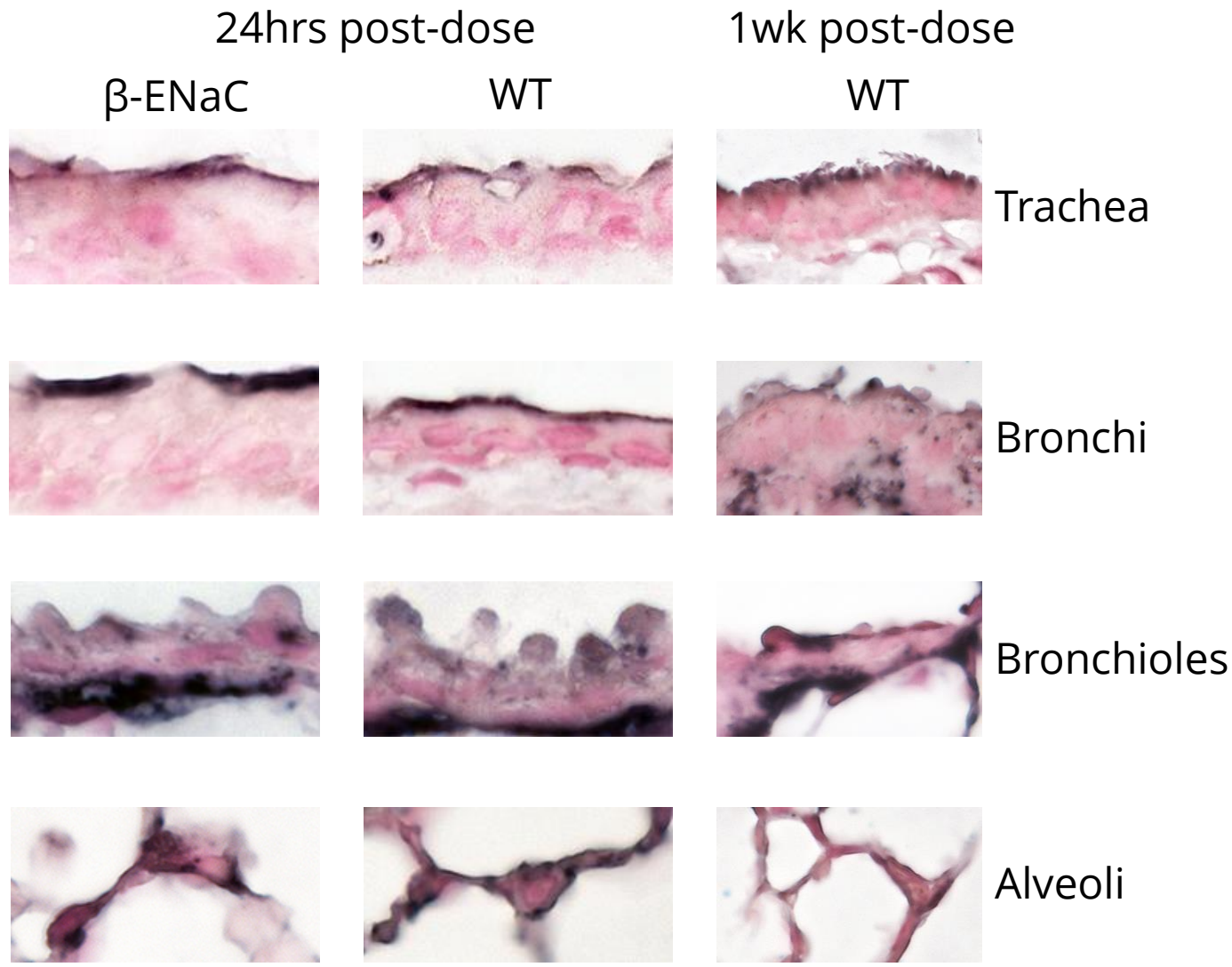


β-ENaC
24hr post dose

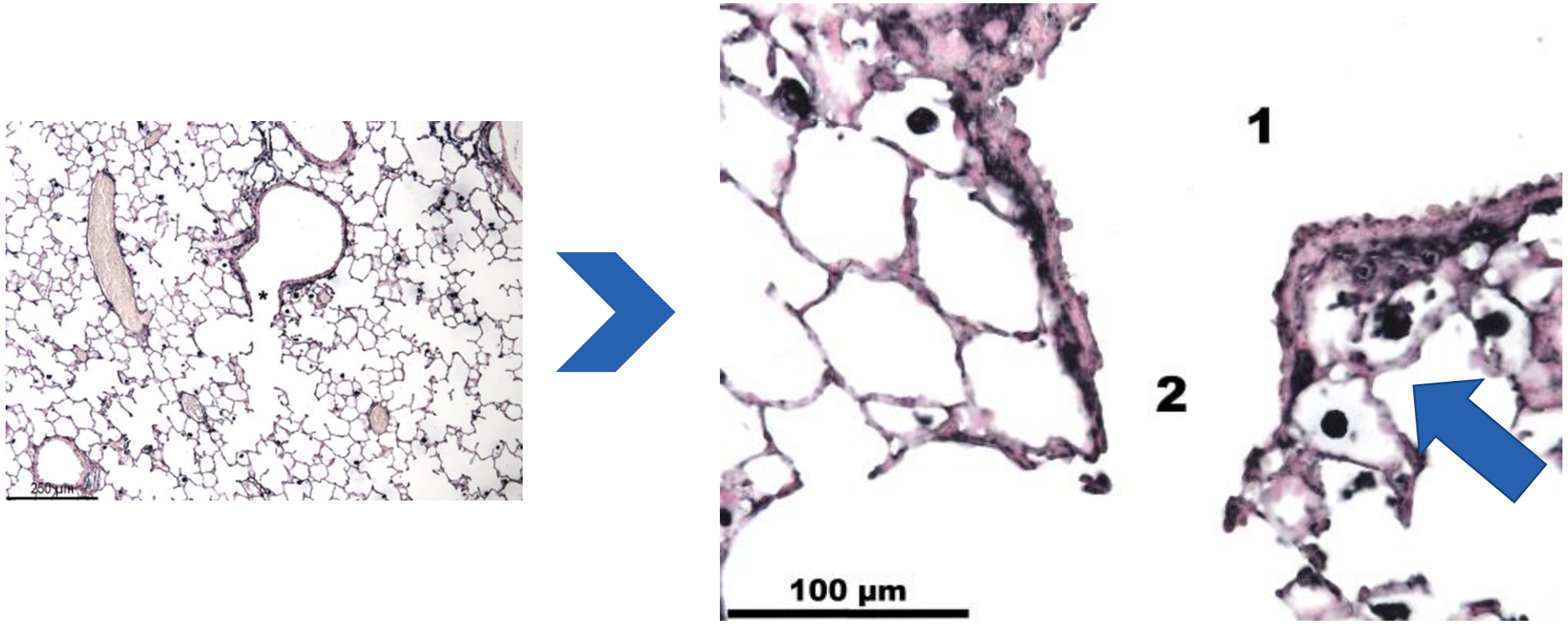


Comparable Distribution of SpliSense' ASOs in WT and "Mucus Obstructive" (β-ENaC) Mice Lungs





SpliSense's ASOs Can Be Detected in the Nucleus of Lung Epithelial Cells

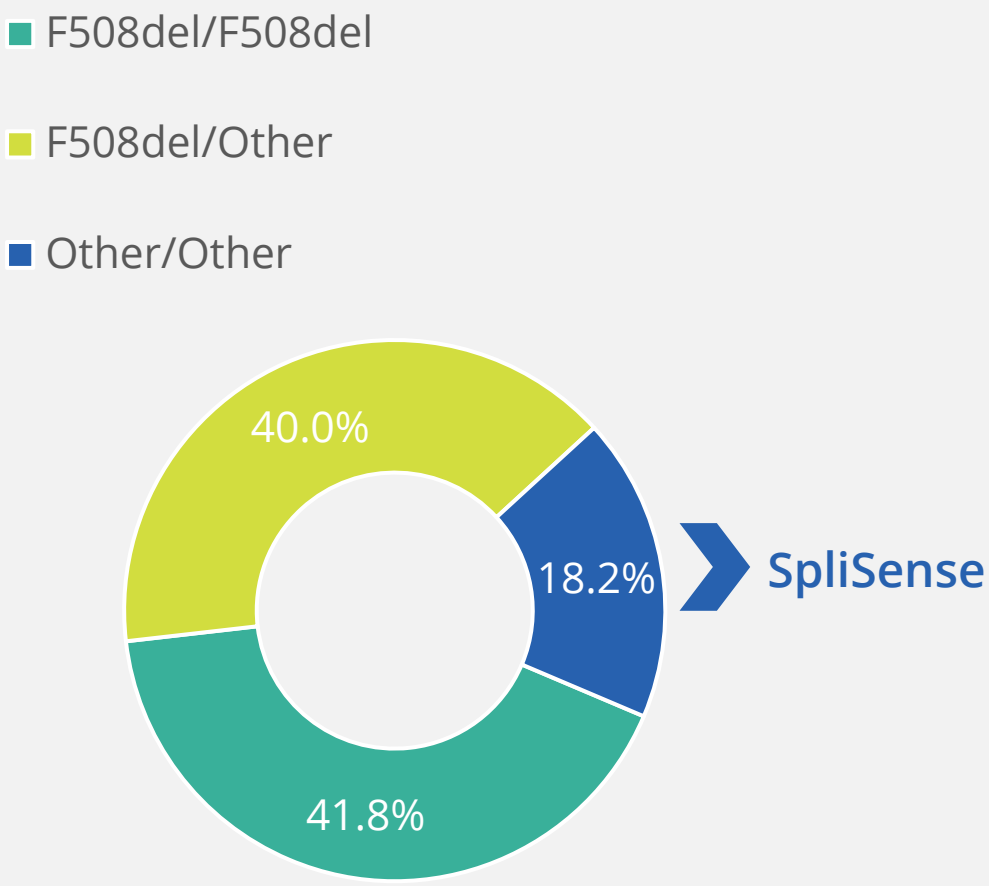


Low and power (objective x10 and x100) microphotograph of lower-level bronchus and bronchiole section of beta ENaC mice lungs suggesting that SPL84-23 penetrates the target cells.

Cystic Fibrosis
Programs

Cystic Fibrosis – Unmet Need

- A progressive, life shortening autosomal recessive genetic disease due to **dysfunction of the CFTR** transmembrane protein – chloride channel
- Affects ~90,000 people worldwide (80% with F508del mutation)
- The median predicted survival of people with CF is about 39 years
  - Unless carrying the F508del mutation (Trikafta®)
- Existing drugs alleviate symptoms but do not cure the disease
  - Lung transplantation is the only definitive treatment option for CF patients with end stage lung disease



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

SPL84-23
(Anti 3849 Mutation ASO)

Retains protein structure and activity

3849 Mutation – Unmet Need

Patient population
~1300
(Annual Growth 3%)

Kalydeco® FEV1
Effect < 2.7%.

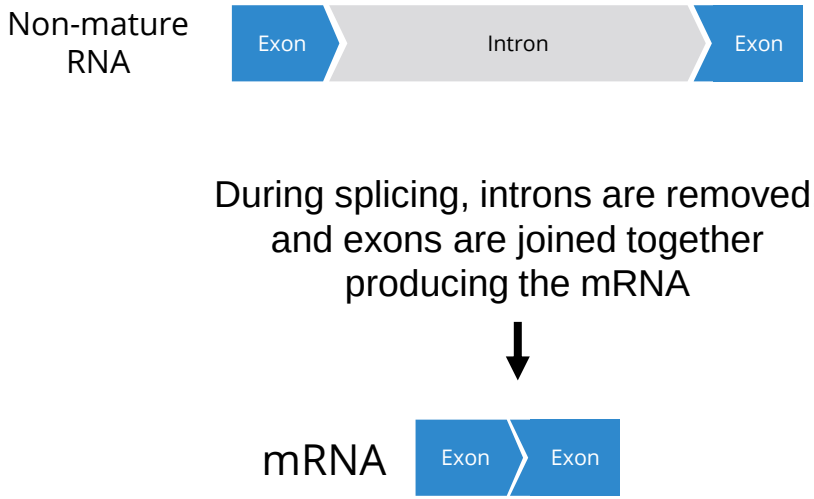
Symdeko® FEV1
Effect <6%.

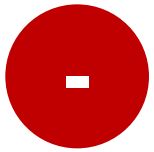
Annual Treatment
Cost – $300k

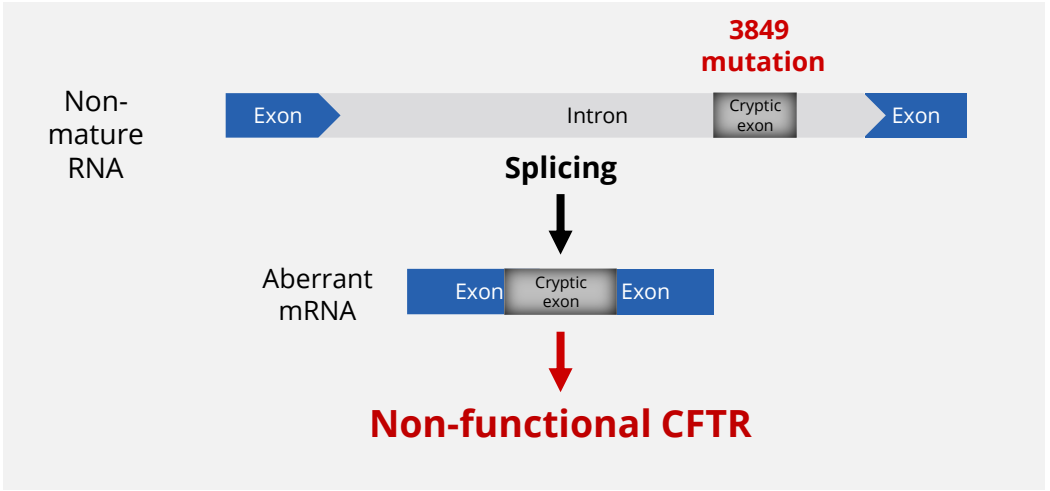
No approved drug
in EU

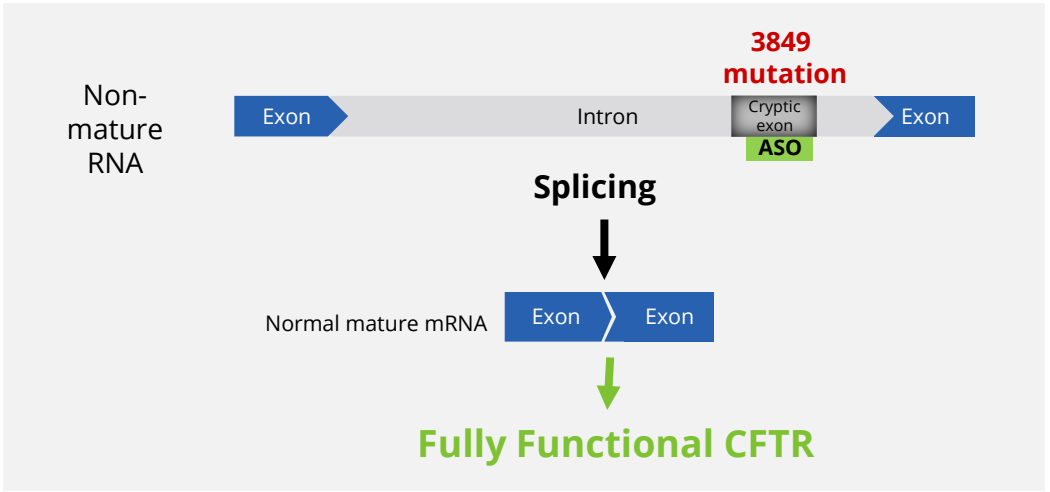
US CF Foundation
Mission and Funding

ASO Technology Produce Mature and Functioning WT CFTR







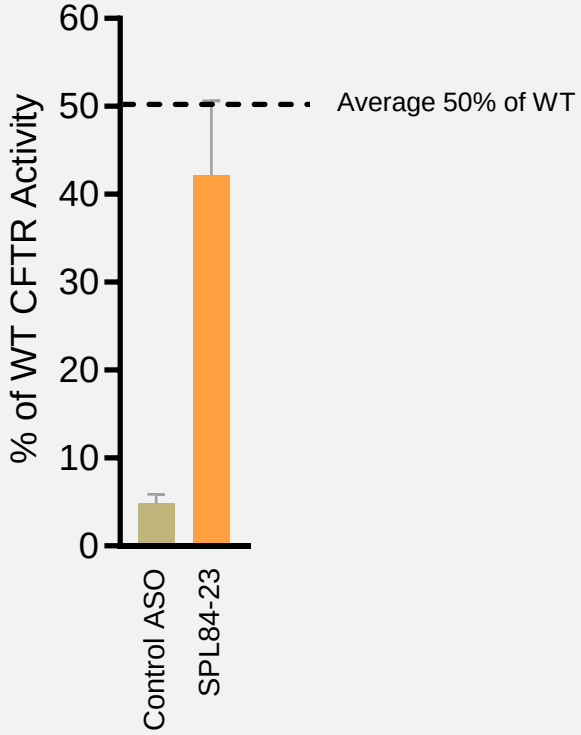


Oren *et al.* 2021

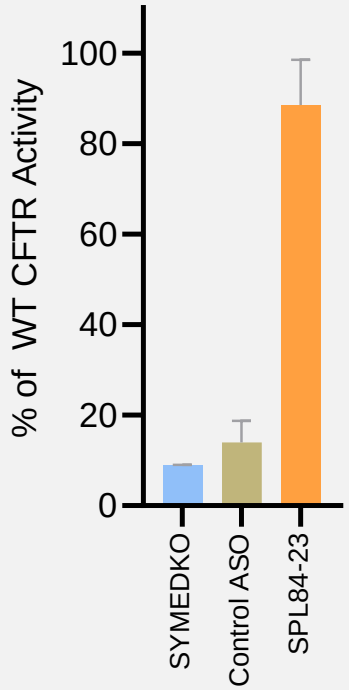
SPL84-23 Completely Restores CFTR Function in Patients Derived Cells (90% of WT- Ussing Assay)

- **Ussing Assay is a Gold Standard for CF drugs efficacy assessment (FDA)**
- SPL84-23 completely restore CFTR function in 3849 patients derived Human Nasal Epithelial Cells (HNEs)
- SPL84-23 completely restore CFTR function in 3849 patients derived Bronchi Epithelial Cells (HBEs)

Average of HNEs from 5 patients carrying the 3849 mutation*



HBEs from a patient (3849/3849)*

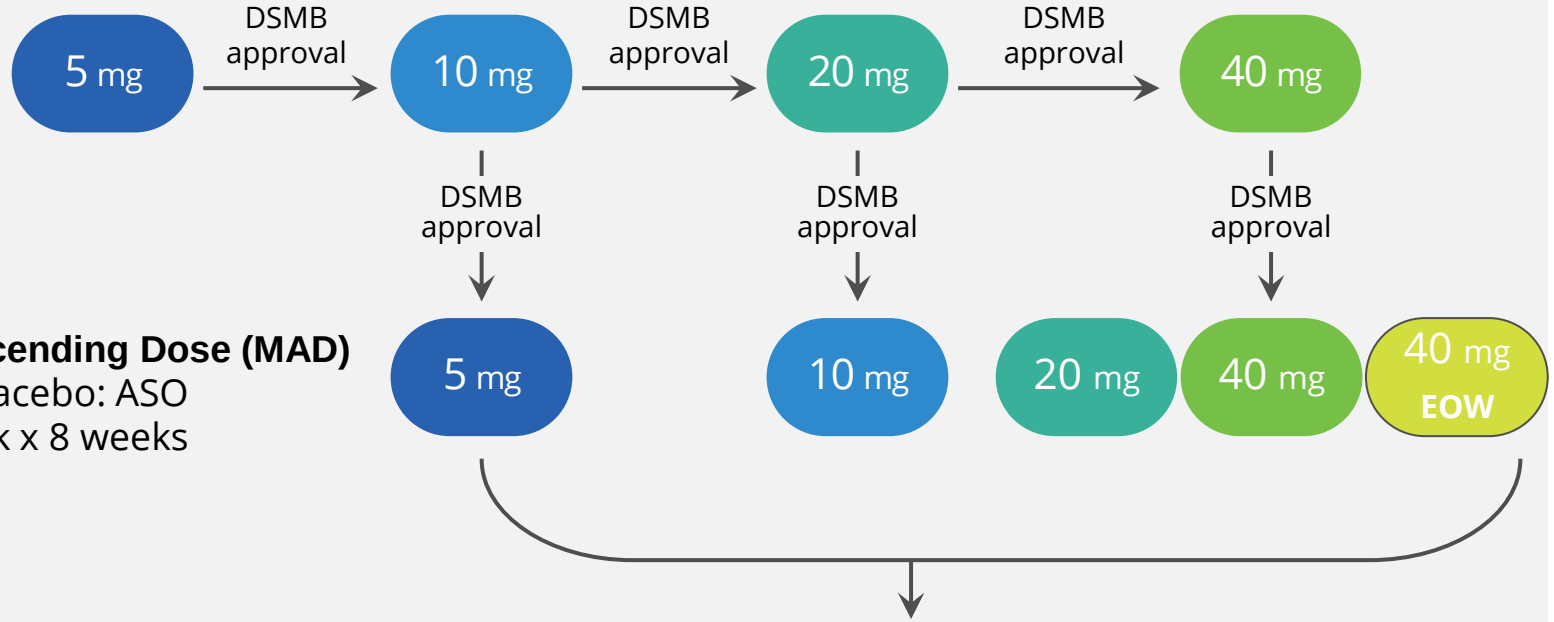


Durmowicz *et al.* 2018, Pranke *et al.* 2017, Oren *et al.* 2021

Phase 1/2a Proposed Clinical Study Design To Be Initiated in H2 2022

Part 1:
Single Ascending Dose (SAD)
n=32, 1:3 Placebo : ASO

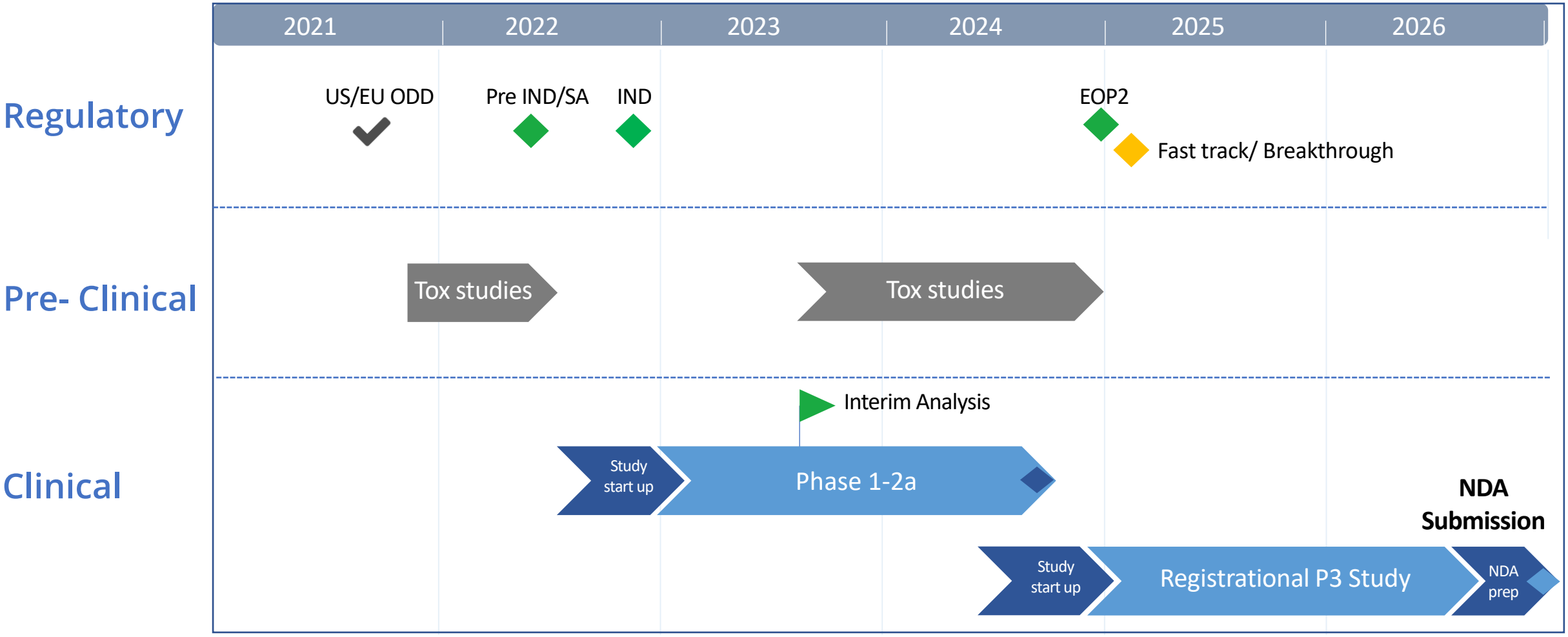
Part 2:
Multiple Ascending Dose (MAD)
n=36 1:3 Placebo: ASO
1 dose/week x 8 weeks



Primary Objective	Assessment of safety and tolerability of inhaled SPL84-23-1
Secondary Objectives	› To evaluate the change from baseline in laboratory parameters and vital signs › To measure the pharmacokinetics (PK) of SPL84-23-1 administered via inhalation
Exploratory Objectives	To explore the efficacy of ascending doses of SPL84-23-1 administered via inhalation (% change in FEV1 at 8 weeks)

*Final doses will be selected based on tox. results

SPL84-23 Program (3849) Expedite Path To Approval



SPL23-2
(Anti W1282X Mutation ASO)

Modulates RNA processing and production of modified proteins

W1282X (Exon 23) Mutation – Unmet Need

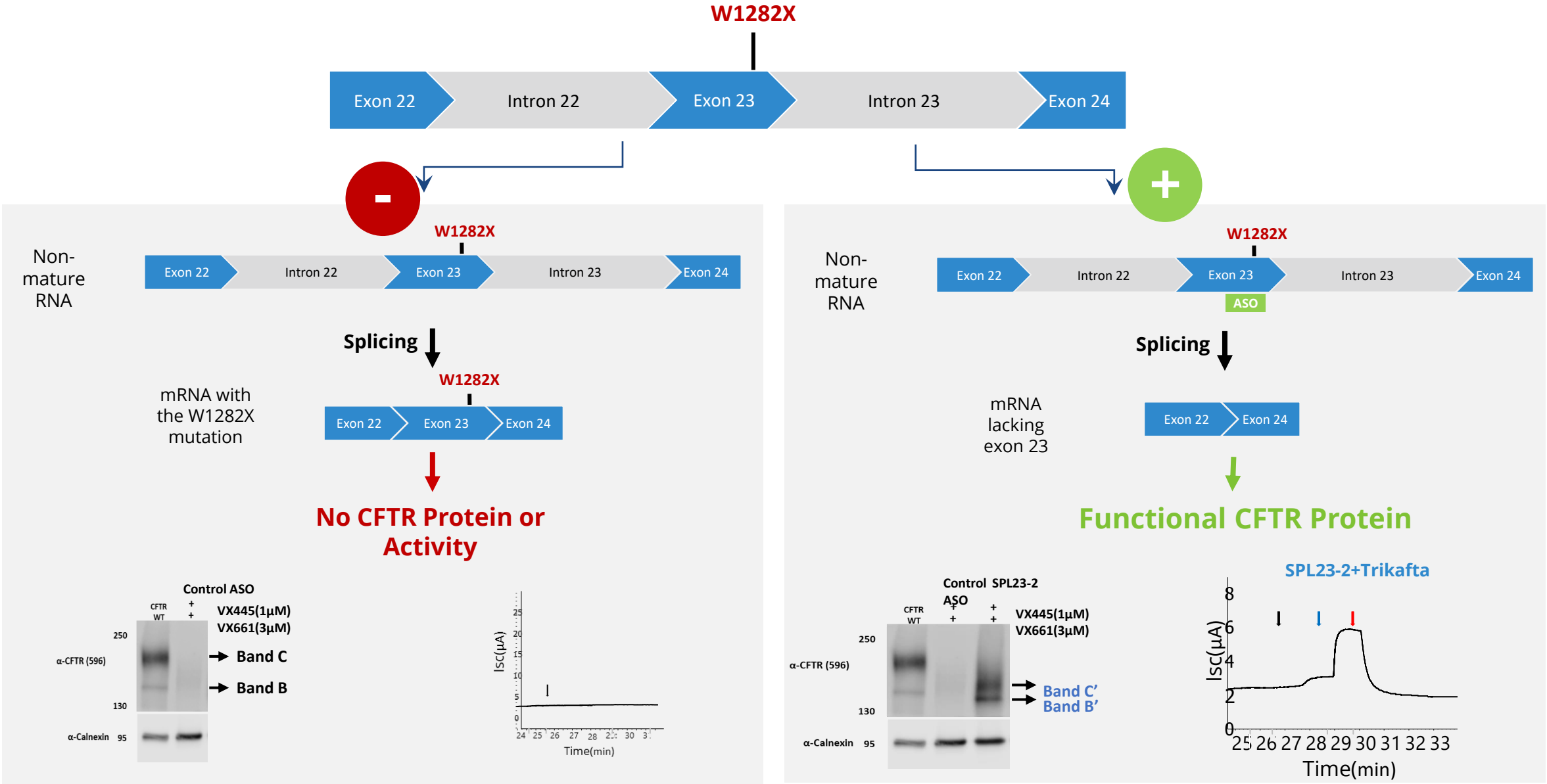
Patient population
~1000

W1282X/non-F508del patients -
no approved drug

Patient # Annual Growth 3.5%

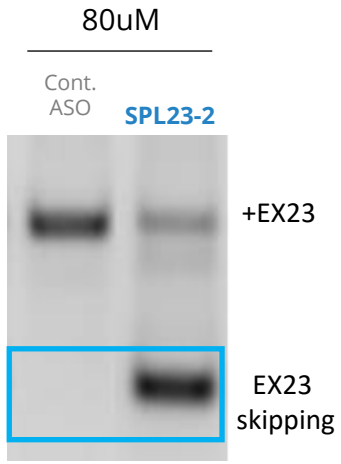
Potential Expedite Regulatory path

W1282X Mutation: No CFTR Protein & No Activity

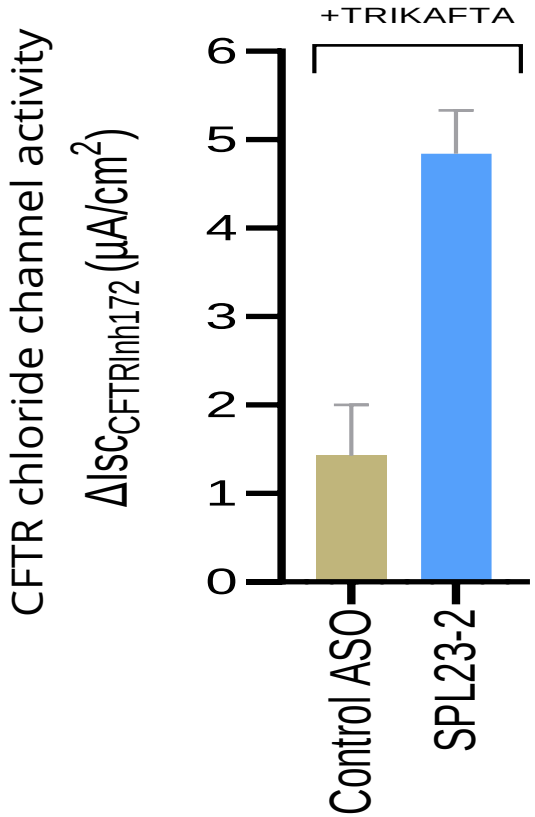


SPL232 Properly Restores CFTR Function in W1282X Patient Derived Cells (36% of WT- Ussing Assay)

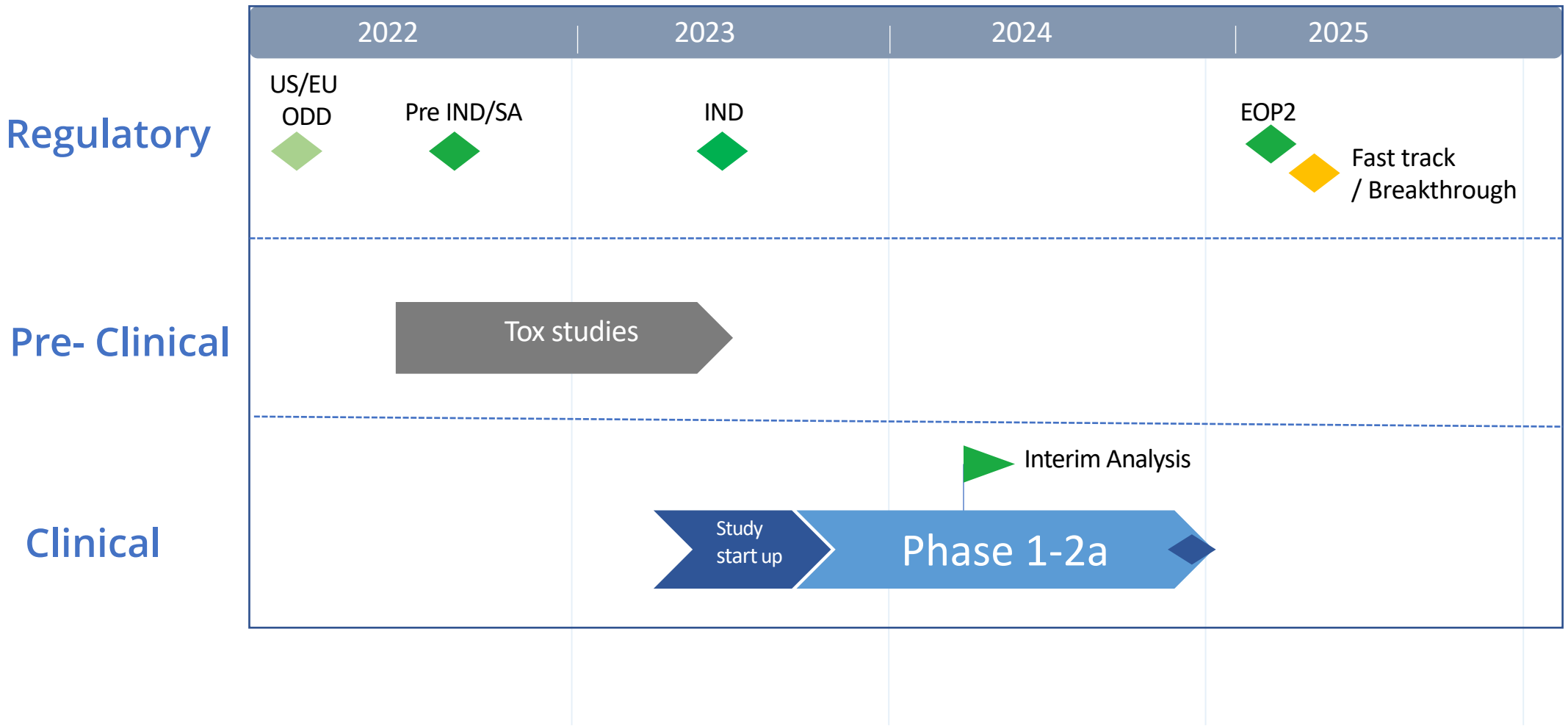
Dose Dependent Exon 23 Skipping (RNA level)



Restoration of CFTR Function by Ussing



SPL23-2 Program (W1282x) Clinical & Regulatory Road Map



Expanding SpliSense Platform Technology from Orphan to Large Pulmonary Indications

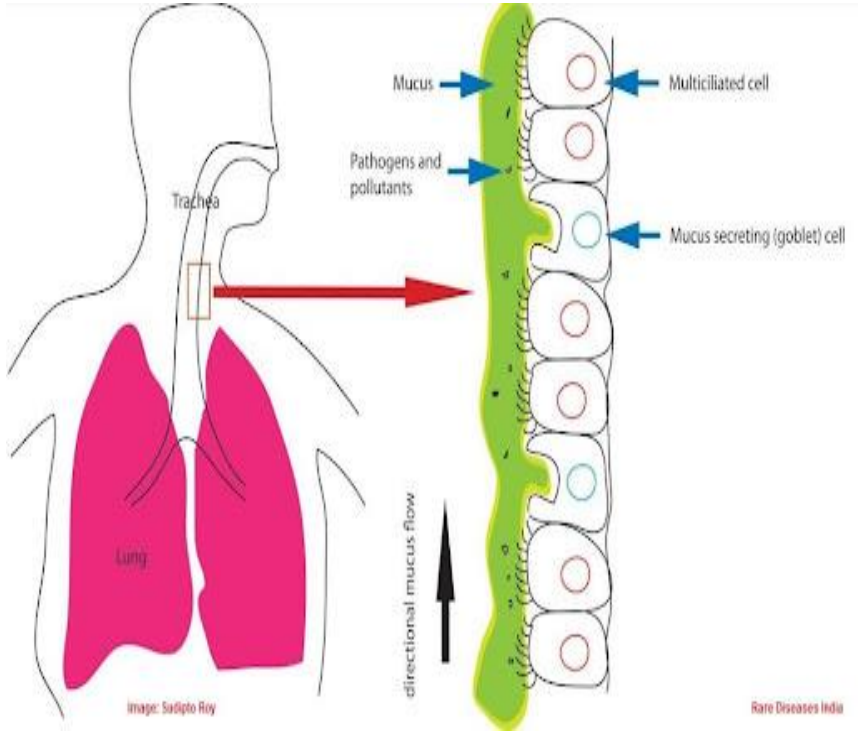
Muco-Obstructive Diseases

Mucin Lowering ASO SPL5

Decrease production of over –expressed proteins

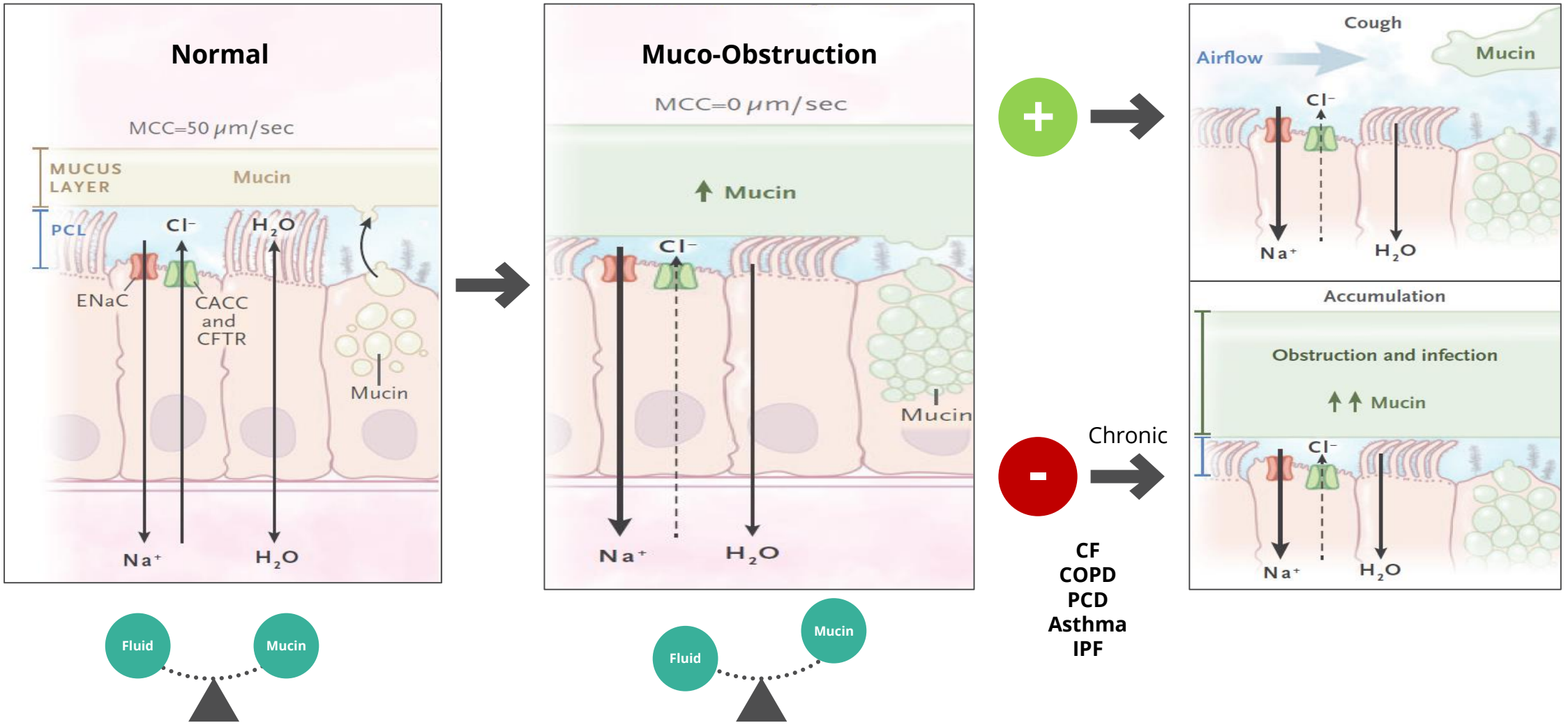
Mucus Hypersecretion is a Clinical Feature of Severe Respiratory Diseases.

- **Mucus-** The first line of innate defense against inhaled pathogens and particles in the respiratory tract is airway mucus
  - Mucus layer comprised of approximately 98% water, 2% solids (mostly mucins)
- MUC5AC, MUC5B are predominate mucins secreted in the lungs and polymerize to form gels
  - In muco-obstructive diseases **mucins content increases to 5-9%**
- Mucus and mucins are generated by goblet cells
- Excessive mucus drives:
  - Respiratory infections
  - Pathogenesis of numerous respiratory diseases
  - Respiratory air blockage



Roy *et al.* 2014, Roy *et al.* 2019, Ridley *et al.* 2018

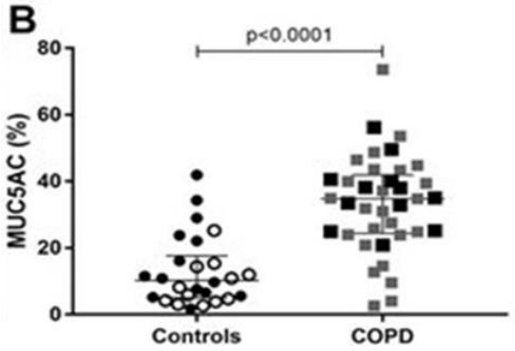
Muco-Obstructive Lung Disease Progression



Bucher *et al.* 2019

MUC5AB and MUC5C are Dominate Players in Pulmonary Diseases Progression and Severity

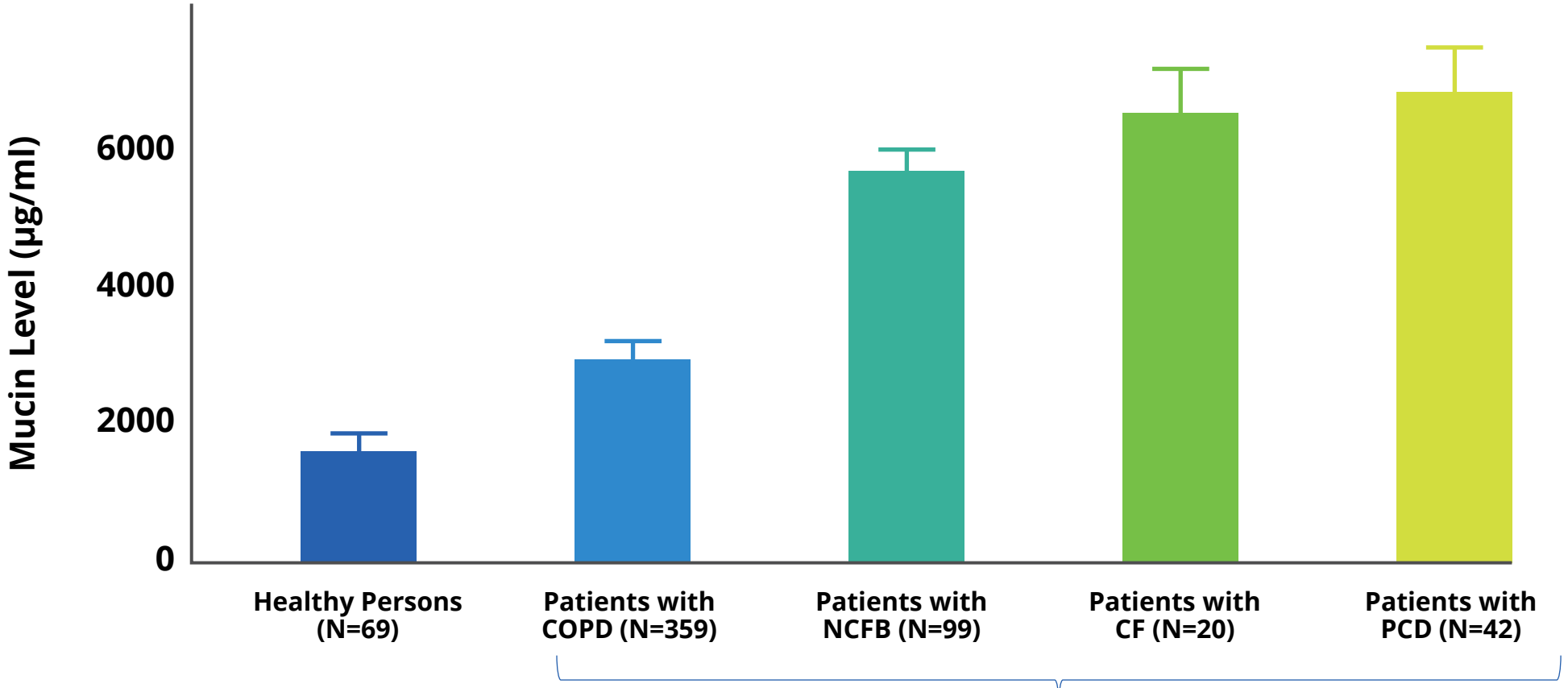
- MUC5AC and MUC5B levels are higher in **COPD patients (3rd leading cause of death by disease in US)**
  - In COPD sputum, both MUC5AC and MUC5B protein levels are significantly increased
  - Levels of MUC5B and MUC5AC in current/ former smokers with severe COPD were approx. 3X and 10X higher, respectively, than non-smokers
  - MUC5B overproduction correlates with an increase in disease severity and decreased lung function



- **In Asthma**, MUC5AC levels are significantly increased
- Total mucin concentrations in **CF sputum** are elevated as compared to healthy control subjects
- Chronic overexpression of MUC5B, driven by single base mutation, is the single greatest risk factor for the development of **Idiopathic Pulmonary Fibrosis (IPF)**

Ridley *et al.* 2018, Roy *et al.* 2019, Symmes *et al.* 2018, Ma *et al.* 2017

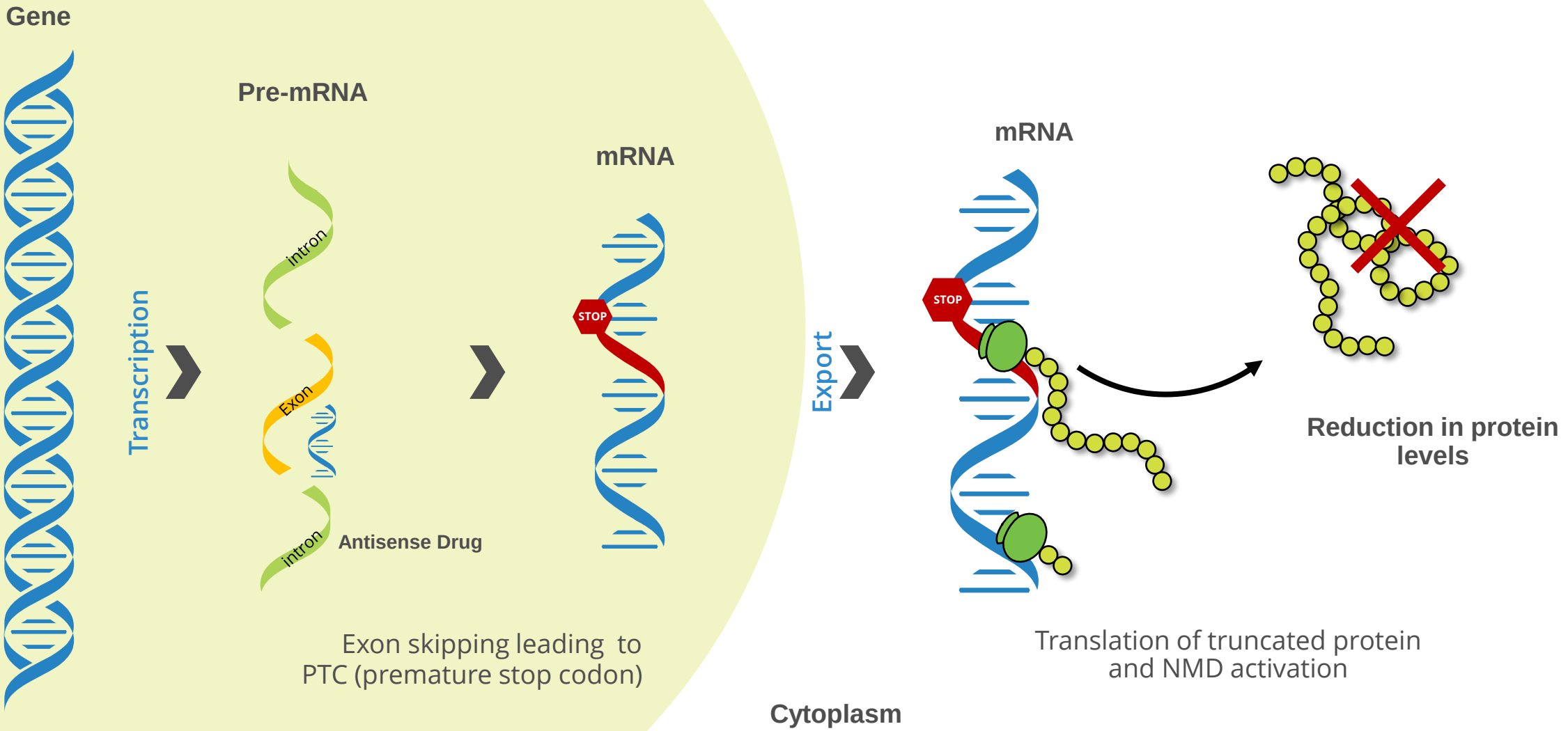
Mucins Excessive Production in Patients with Pulmonary Diseases



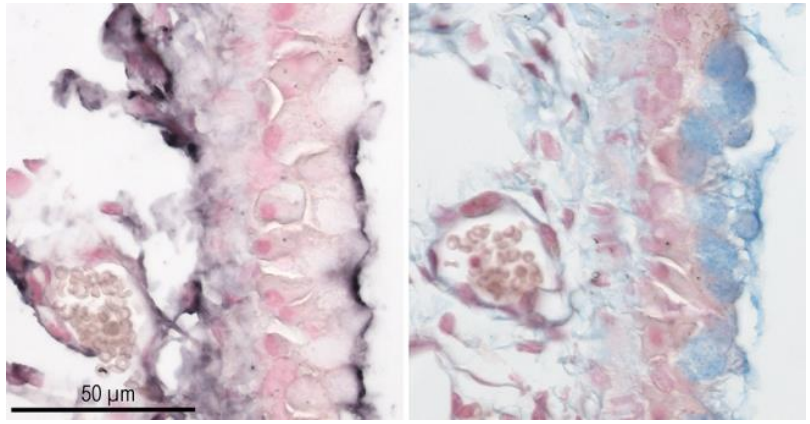
Large Market Potential

Boucher RC *et al.* 2019

SPL5 Lowers RNA and Protein Expression (MoA)



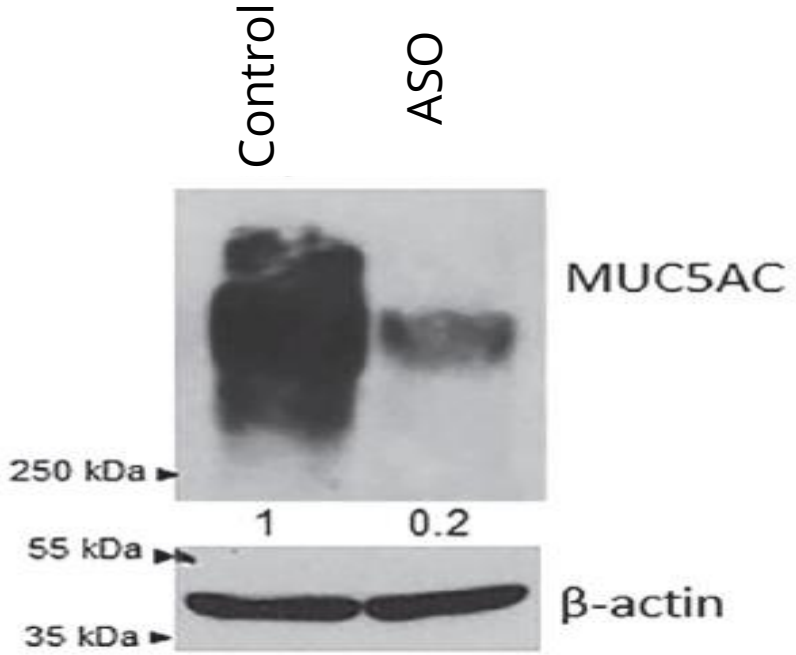
PoC Mucin Lowering ASO: Lungs Goblets Cells Distribution and In Vitro Activity



Hybridization signal at the apical part of goblet cells (Beta ENaC mice)

Black staining - SPL ASO

Blue staining – Mucus in goblet cells



A549 Cells

Lung Cancer Cells

Investment Opportunity (I)

- Splisense is a **pulmonary focused company** using ASO technology to modulate RNA, and thus mastering protein production and expression in a specific and targeted manner.
  - clinically validated technology
- Proper **penetration, migration and stability in Mucus**
- Established and robust inhalation approach (lung distribution, cellular penetration, inhalation device, safety assessment)
- Diverse pipeline
  - Large market potential
    - Initial focus on high unmet need, orphan indications (CF) Subsequent expansion to larger, non orphan pulmonary indications (muco- obstructive diseases)
  - 2 programs in IND enabling phase**; 2 clinical studies to commence in 2022**
- **1st program, SPL84-23, fully funded up to phase 1-2 study completion (CF Foundation)**

Investment Opportunity (II)

2022 Financial round:

- Splisense is seeking to raise $40M to support 2022-24 expenses including:
  - 2 phase 1-2 clinical studies completion:
    - SPL23-2 (Anti W1282X Mutation ASO)
    - SPL16 (Anti 2789 Mutation ASO)
    - Phase 3 setup activities SPL84-23 (Anti 3849 mutation)
  - Advancing 2 pre- clinical programs into the clinic
    - Mucus lowering ASOs
      - MUC5AC
      - MU5B

Thank You!