SpliSense

Making Sense of Splicing

Transformative RNA Based Treatments for Pulmonary Diseases

Corp. Update
2022

NON-CONFIDENTIAL

SpliSense – 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

R&D Status

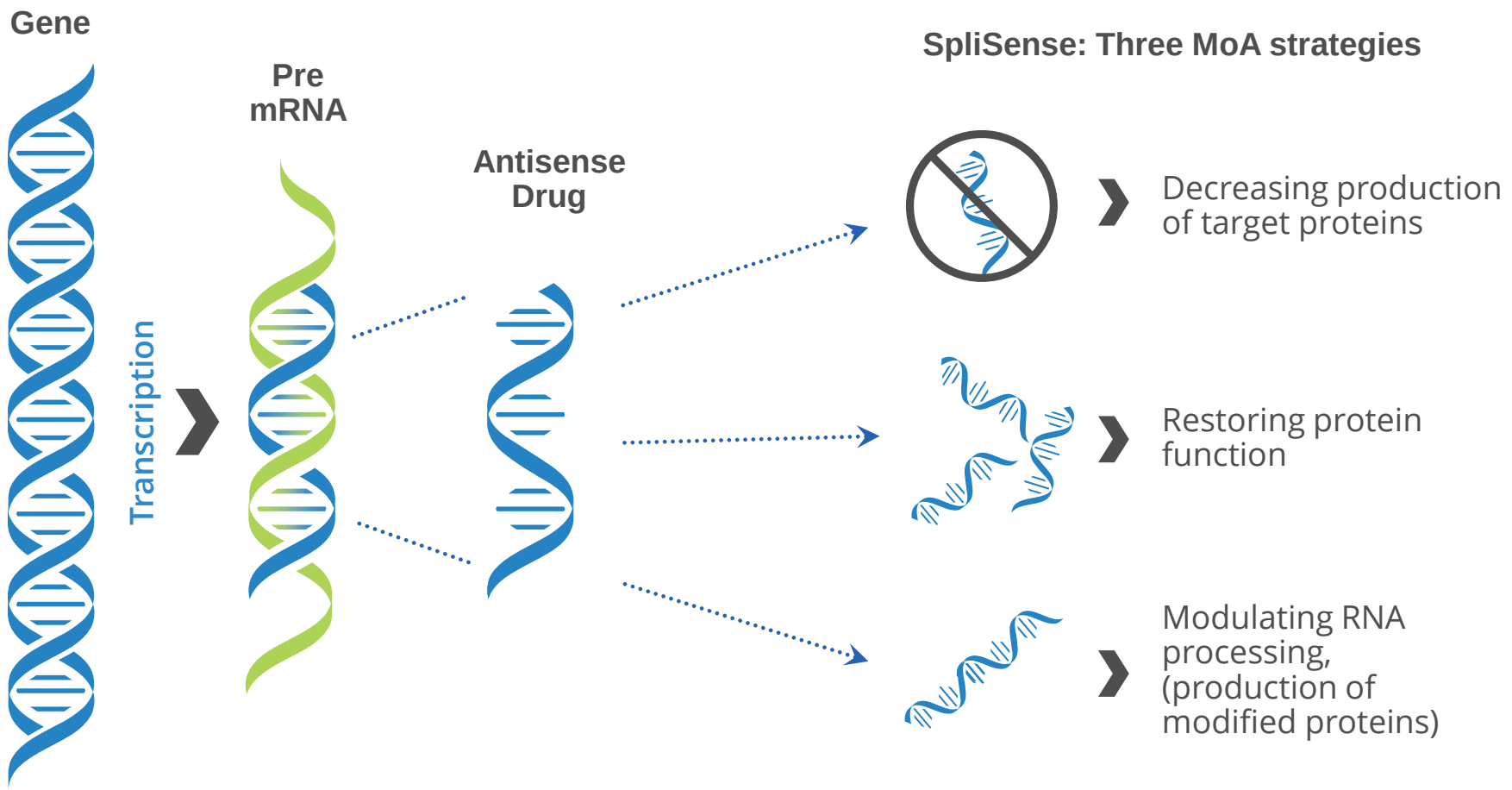
- Inhaled Antisense Oligonucleotides (ASOs)
  - High unmet need, orphan indications –Cystic Fibrosis
  - Larger, non orphan pulmonary indications - Muco- obstructive diseases
  - ASOs - clinically validated approach

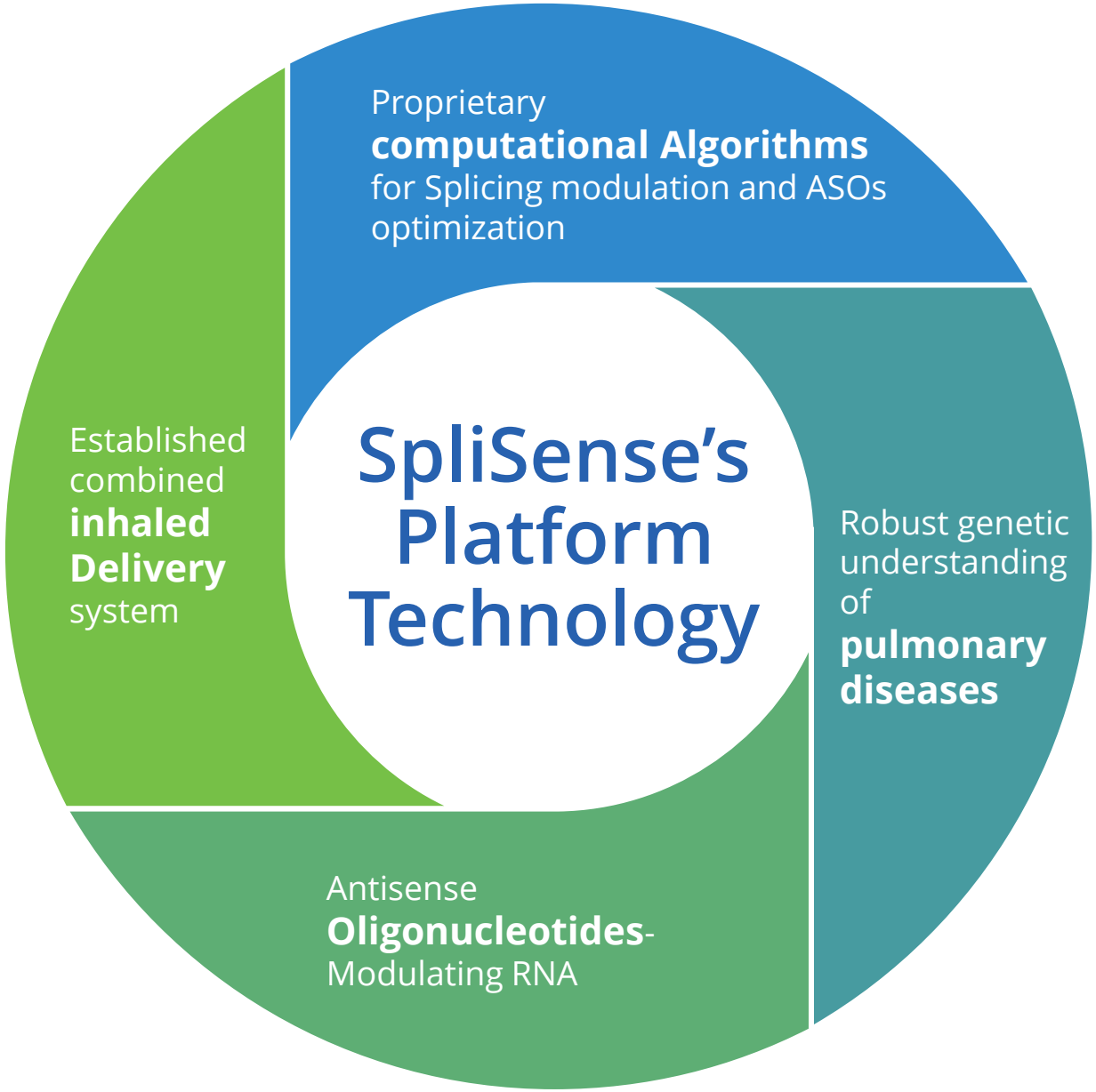
Financial

- Backed by a strong syndicate including IBF, OrbiMed, Integra and CF Foundation

OrbiMed Healthcare Fund Management · ISRAEL BIOTECH FUND · CYSTIC FIBROSIS FOUNDATION · INTEGRA HOLDINGS

Antisense Oligonucleotides – Modulating RNA (MoA)



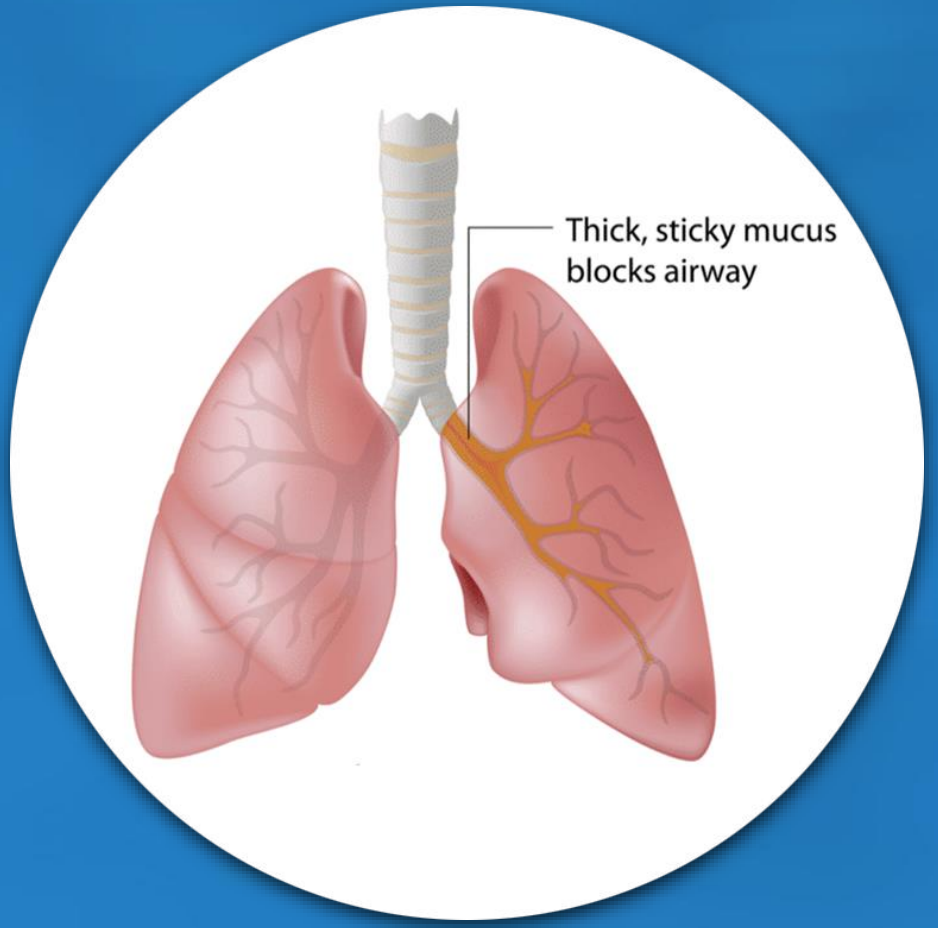

Proprietary
computational Algorithms
for Splicing modulation and ASOs optimization
Established combined **inhaled Delivery** system
SpliSense's Platform Technology
Robust genetic understanding of **pulmonary diseases**
Antisense **Oligonucleotides**-Modulating RNA

SpliSense's Strategy from Orphan to Large Pulmonary Indications

SpliSense's Pulmonary Diverse Pipeline

Indication	Approach	Program	Discovery	IND Enabling Studies	Clinical Studies
Cystic Fibrosis	Restoration of Protein Function	**SPL84** (3849 Mut.)			**H2 2022**
		SPL16 (2789 Mut.)			
	Production of Modified Protein	**SPL23** (W1282X Mut.)			**H2 2023**
		SPL24 (N1303K Mut.)			
Muco-Obstructive Diseases COPD, Asthma, Pulmonary Fibrosis	Decrease Production of Over-expressed Proteins	**SPL5A**			**2024**
		SPL5B			

SpliSense Tackle Key Challenges of ASOs' Delivery to Lungs



SpliSense's ASOs Have Unique Properties for Lung Delivery

Natural

- No vectors or delivery vehicles are needed
- Enable direct, non-invasive delivery
- Lung cells uptake through endocytosis to:
  - Epithelia cells
  - Nucleus

Durable

- Lungs $T_{1/2} \approx 2$ weeks
- Proven stability and Mucus penetration
- Proven stability in lysosomes extract and under acidic conditions
- End products are expected to be given to patients **once a week or less**

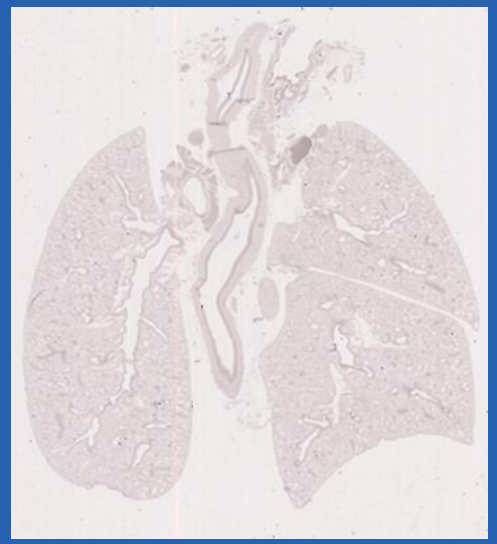
Precise

- Highly specific to target sequence
- Minimal systemic exposure
  - Lung specific
- Proper Distribution in conducting airways
- Clinically validated chemical modification patterns

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

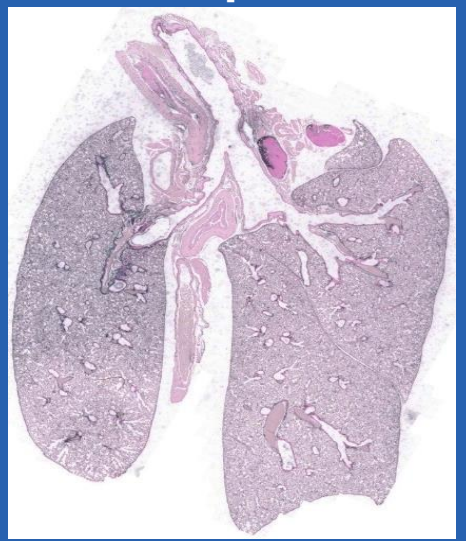
Staining for SPL ASO following IT administration - dark staining

Negative Control

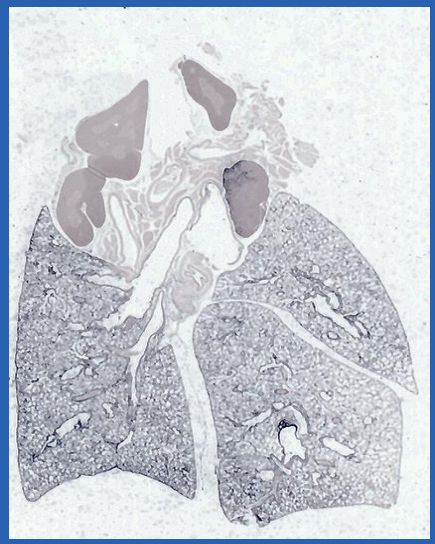


WT
24hr post dose

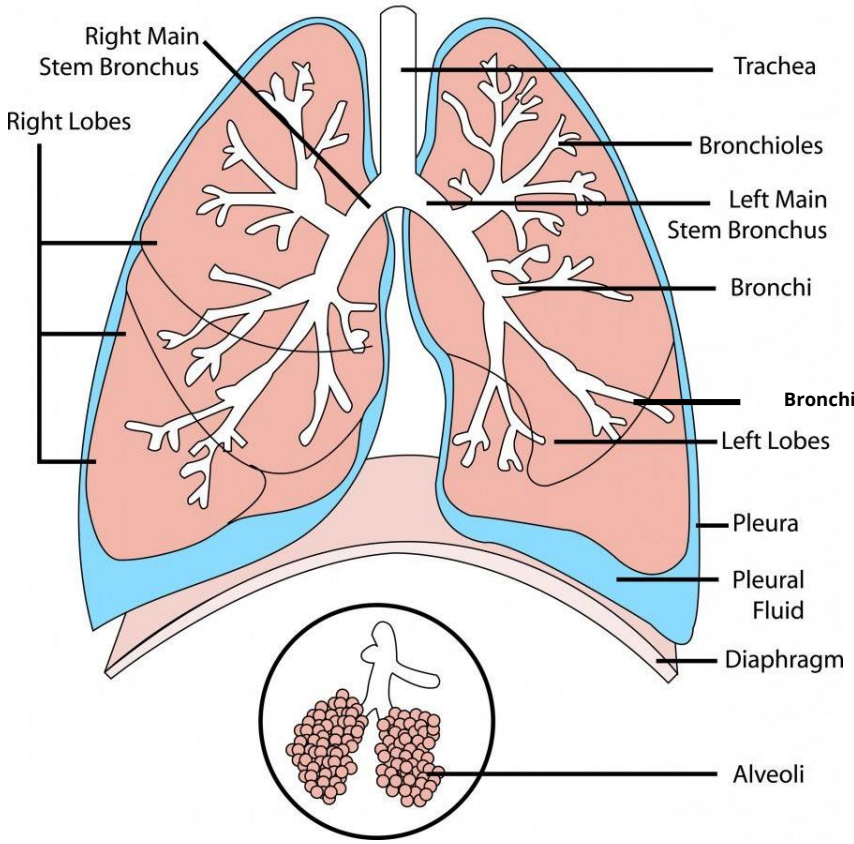
WT
4th wk post dose

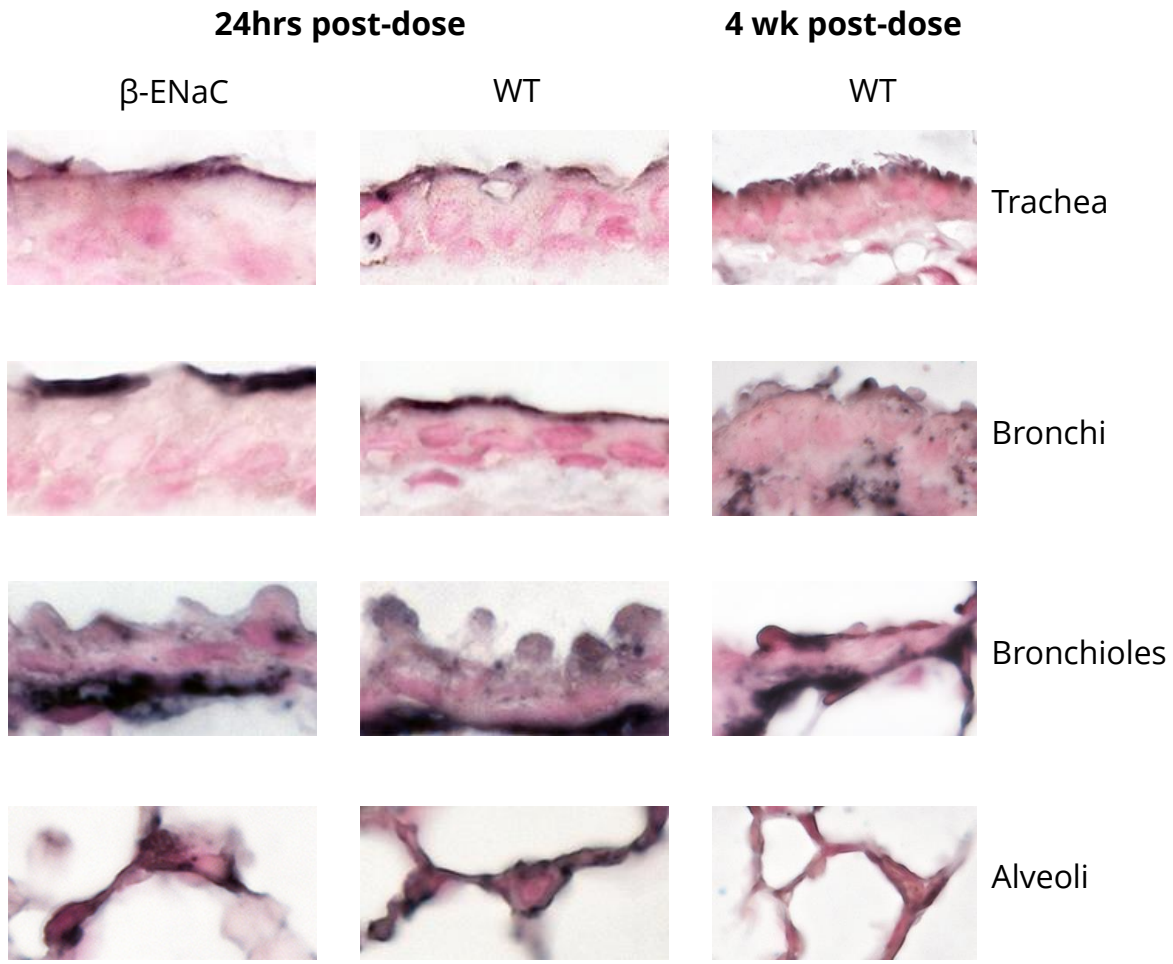


β-ENaC
24hr post dose

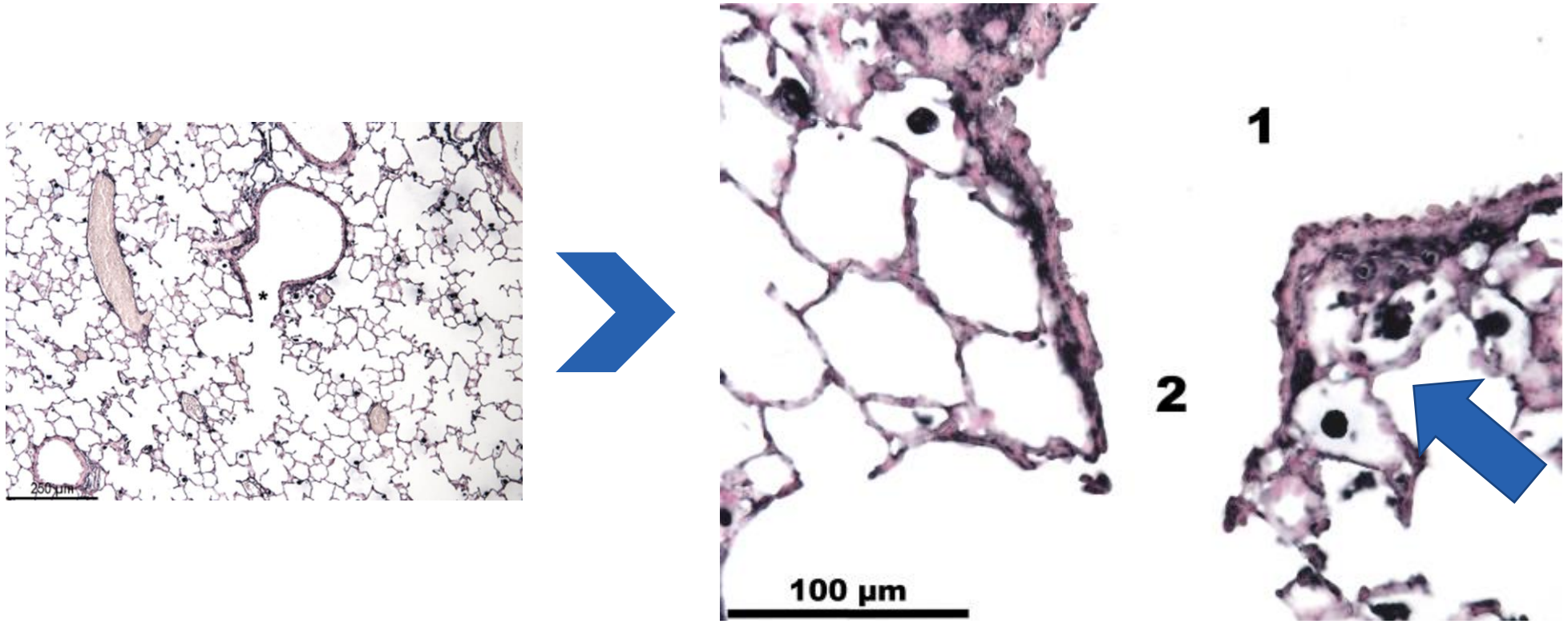


Comparable Distribution of SpliSense' ASOs in WT and "Mucus Obstructive" (β-ENaC) Mice Lungs





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

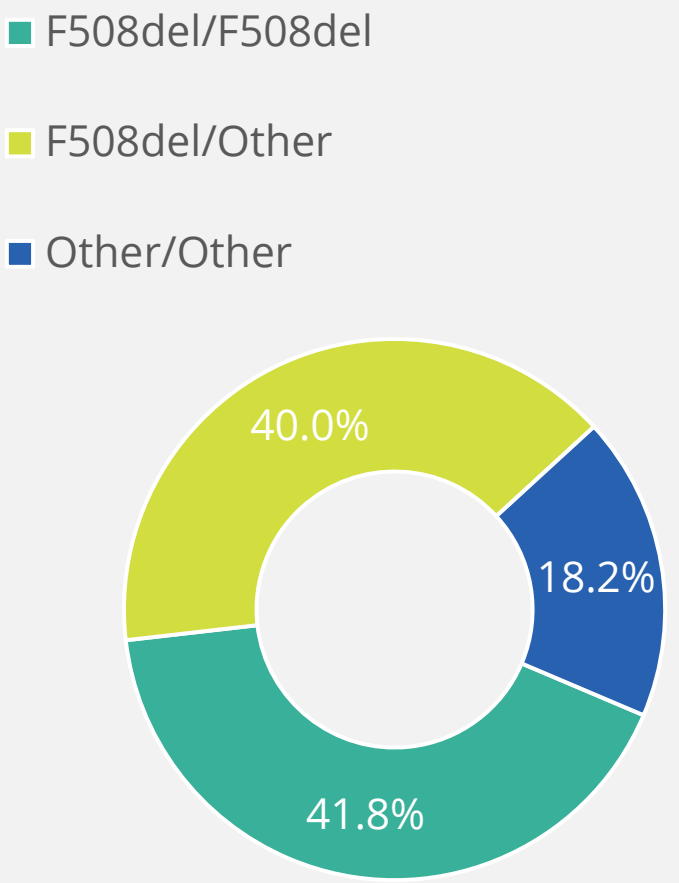


Low and power (objective x10 and x100) microphotograph of lower-level bronchus and bronchiole section of beta ENaC mice lungs suggesting that SPL84-23 penetrates the target cells.

Cystic Fibrosis
Programs

Cystic Fibrosis – Need for Novel Drugs

- A progressive, autosomal recessive genetic disease
- Caused by dysfunction of the **CFTR** transmembrane protein (chloride channel)
- Affects ~100,000 people worldwide
- The median predicted survival of people with CF is about 48 years
- Existing drugs alleviate symptoms but do not cure the disease
  - Suggesting that:
    - 33% of Trikafta® treated patients are not responding
    - 33% of Trikafta® treated patients have moderate response
- Lung transplantation is the only definitive treatment option for CF patients with end stage lung disease



SpliSense ($4B TAM)

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

Future of CF Treatments Modalities

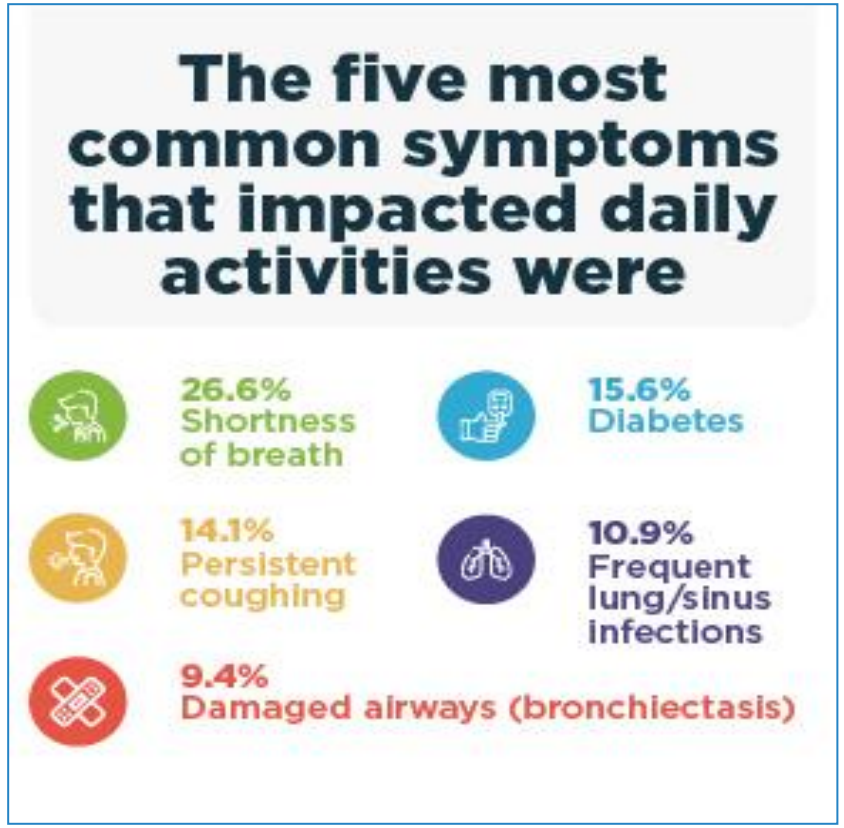
"A third of the people clearly have a big response… Another third have **an obvious response, but it may not be quite as dramatic**… **Another third, there isn't as big a response…"**

Peter Mogayz MD. ; Johns Hopkins School of Medicine

BofA Research, Feb 2022

"Trikafta is an excellent drug – indeed ….However, **it's a band-aid, not a cure**……. worries physicians, who predict that patients will be burdened by **declining lung function** …. eventually leading to substandard quality of life"

Josh Reshnik MD. RA Capital



CF Foundation US survey – Feb 2022

SPL84
(Anti 3849 Mutation ASO)

Retains protein structure and activity

3849 Mutation – Unmet Need

TAM ~$450M

Kalydeco® FEV1
Effect < 2.7%.

Symdeko® FEV1
Effect <6%.

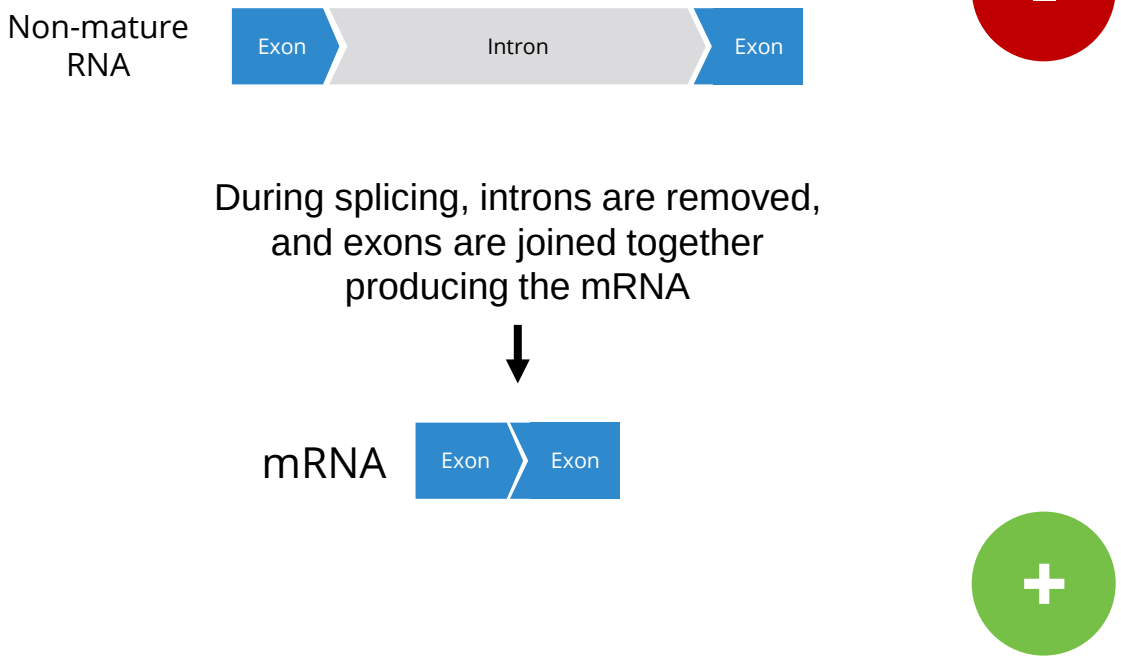
Annual Treatment
Cost – $300k

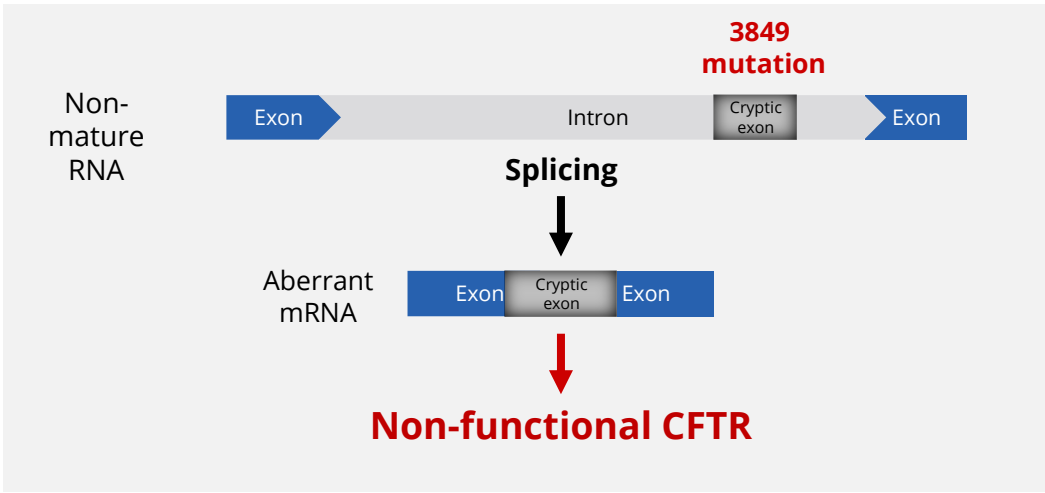
No approved drug
in EU

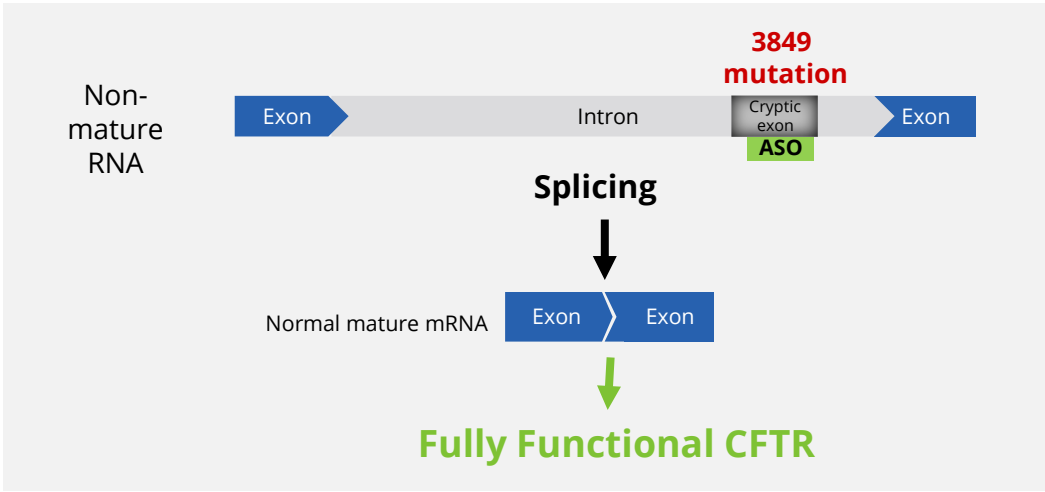
CYSTIC FIBROSIS FOUNDATION®

US CF Foundation
Mission and Funding

ASO Technology Produce Mature and Functioning WT CFTR



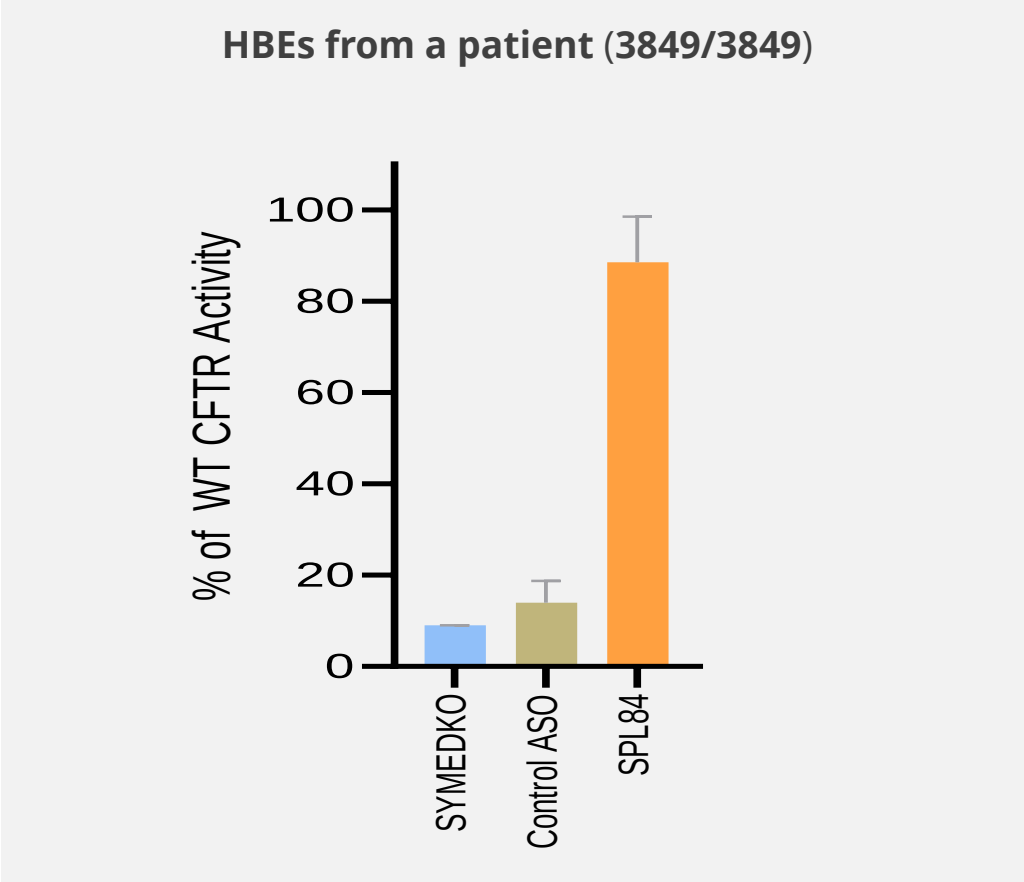




Oren *et al.* 2021

SPL84 Completely Restores CFTR Function in CF Patient Homozygote Derived Lung Cells (HBEs)

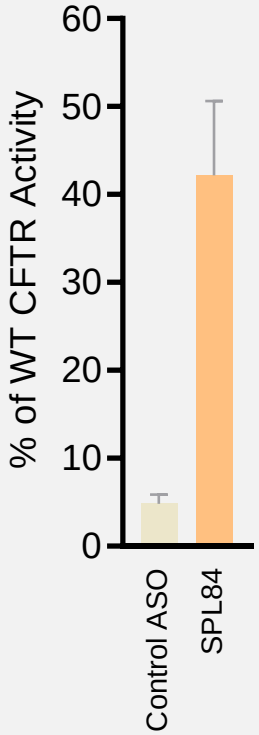
- **Ussing Assay is a Gold Standard for CF drugs efficacy assessment (FDA)**
- SPL84 **completely restores** CFTR function in 3849 patients derived Human Bronchial Epithelial Cells (HBEs)
- Symdeko® (tezacaftor/ivacaftor) has no effect on 3849 CF patient.
  - Strong correlation of Ussing analysis to clinical outcome



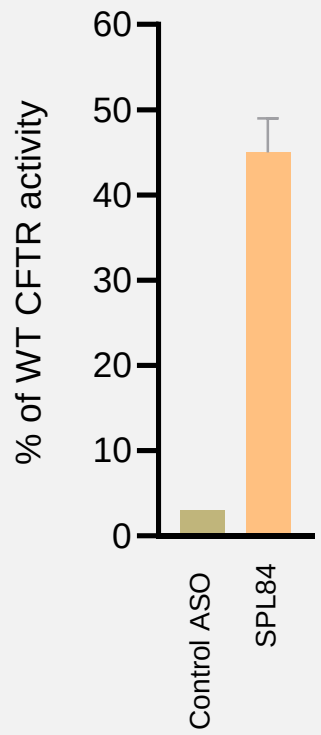
SPL84 Completely Restores CFTR Function in Heterozygous Patients' Derived Cells

- **Ussing Assay is a Gold Standard for CF drug efficacy assessment (FDA)**
- SPL84 **completely restores** CFTR function in 3849 patient derived Human Nasal Epithelial Cells (HNEs) and Bronchial Epithelial Cells (HBEs)

Average of HNEs from 5 patients carrying the 3849 mutation*



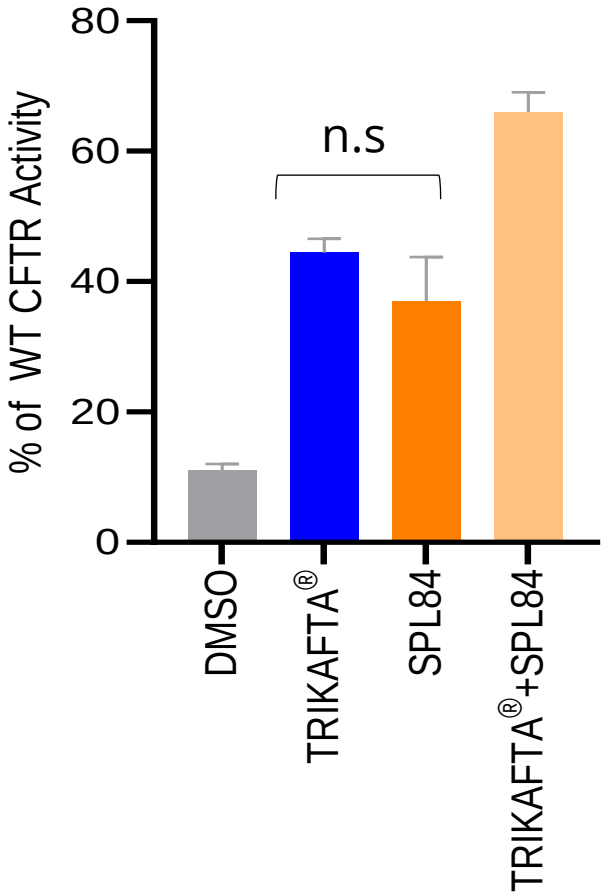
HBEs from a patient (3849/F508del)



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

SPL84 & Trikafta® have comparable & Synergic Effect in Heterozygous CF Patient Derived Lung Cells (HBEs)

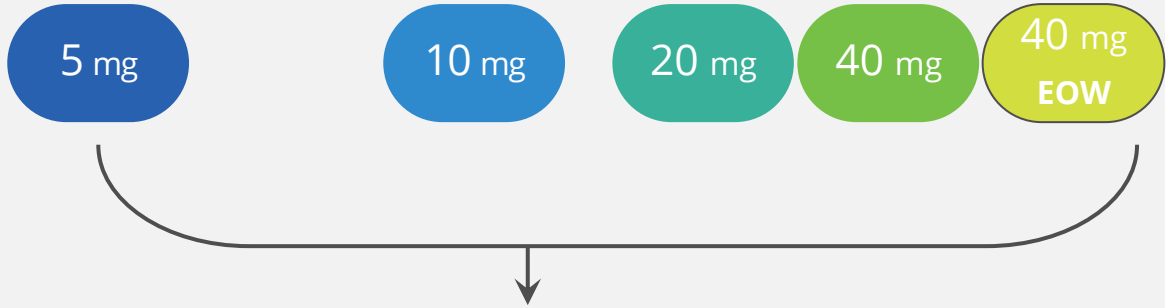
- 50% of WT activity is the maximal effect in heterozygous patients. Synergic effect of combo. is observed
- SPL84/ Trikafta® completely restores CFTR function in F508del/ 3849 patient derived Human Bronchial Epithelial Cells (HBEs)



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

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

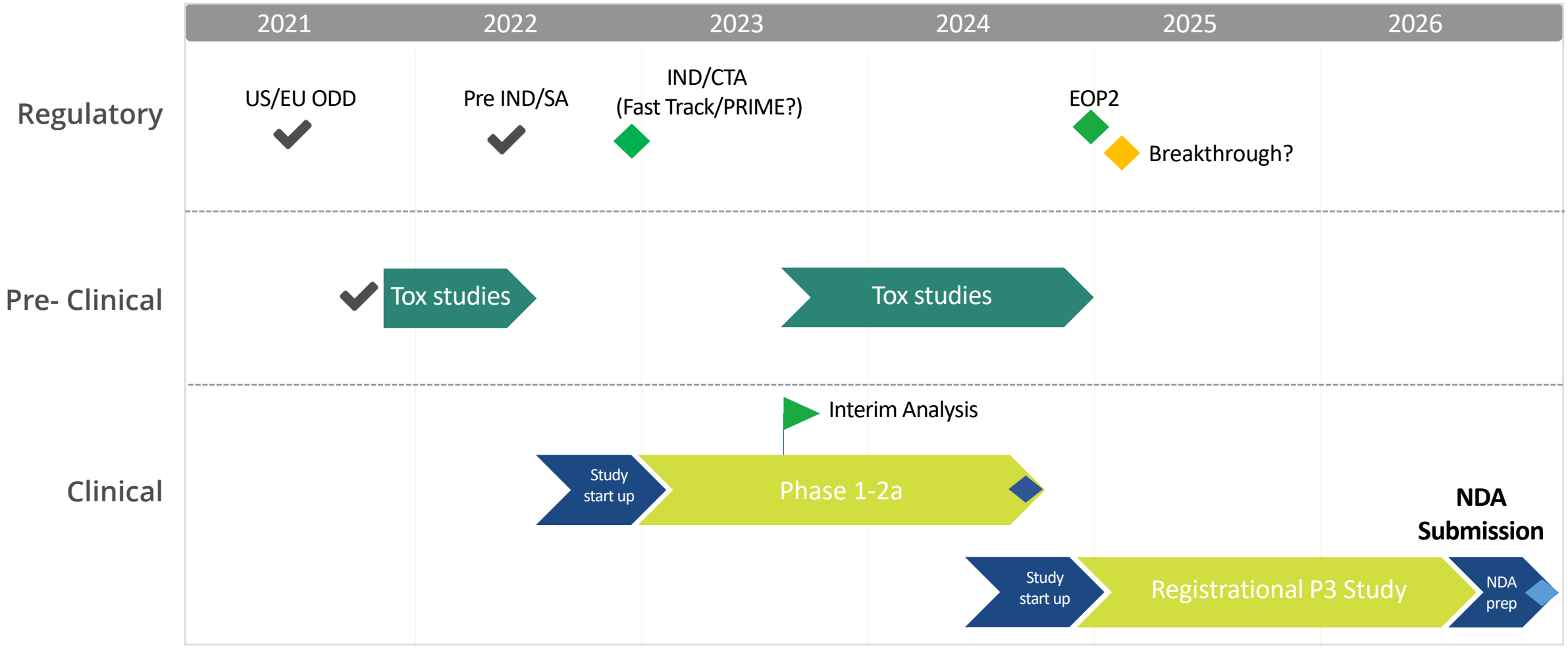
Part 2:
Multiple Ascending Dose (MAD)
3849 subjects
n=38 1:3 Placebo: ASO
1 dose/week x 8 weeks



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
(Anti W1282X Mutation ASO)

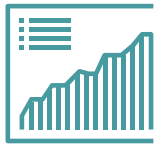
Modulates RNA processing and production of modified proteins

W1282X (Exon 23) Mutation – Unmet Need

TAM ~$550M

W1282X/non-F508del
~30yrs.

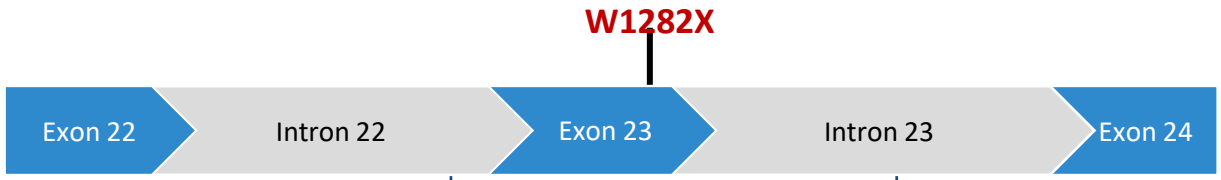
W1282X/non-F508del
No approved drug

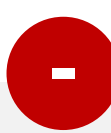


Patient # Annual
Growth 3.5%

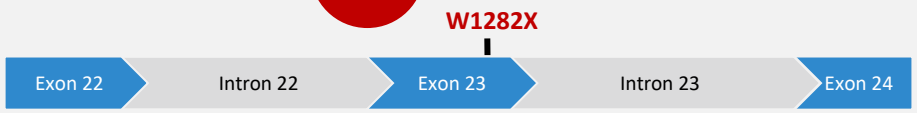
Potential Expedite
Regulatory path

W1282X Mutation - No CFTR Protein & No Activity

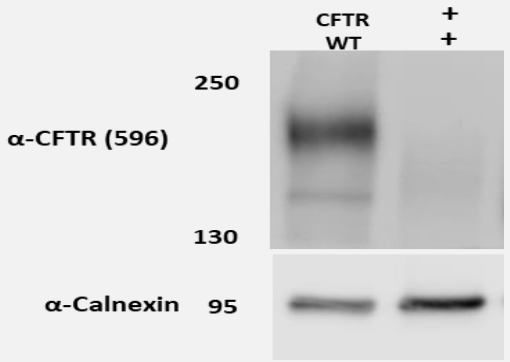




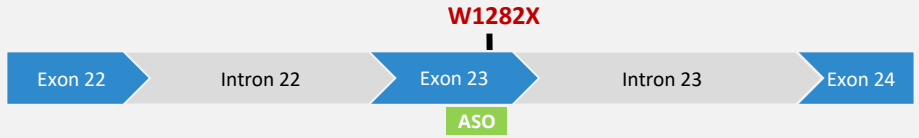
Non-mature RNA



No CFTR Protein or Activity



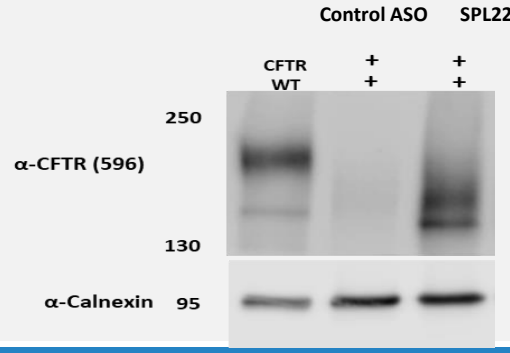
Non-mature RNA



Splicing

mRNA Lacking exon 23

Functional CFTR Protein



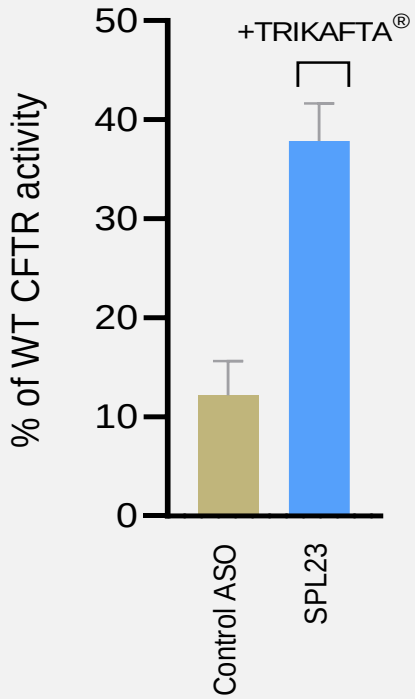
SPL23 Properly Restores CFTR Function in W1282X Patient Derived Nasal Cells

RNA- CFTR Exon 23 Skipping

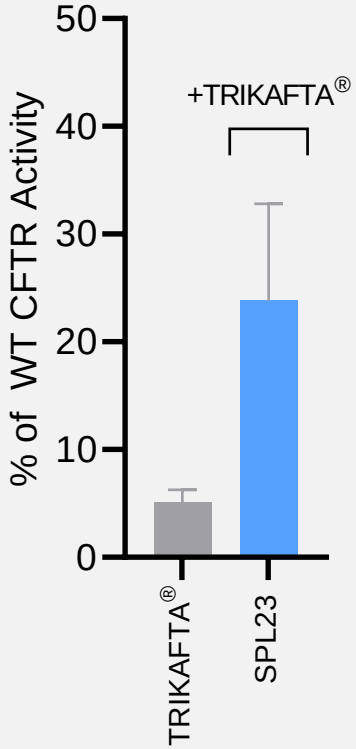
Restoration of CFTR Function by Ussing

CFTR chloride channel activity

Homozygote W1282X

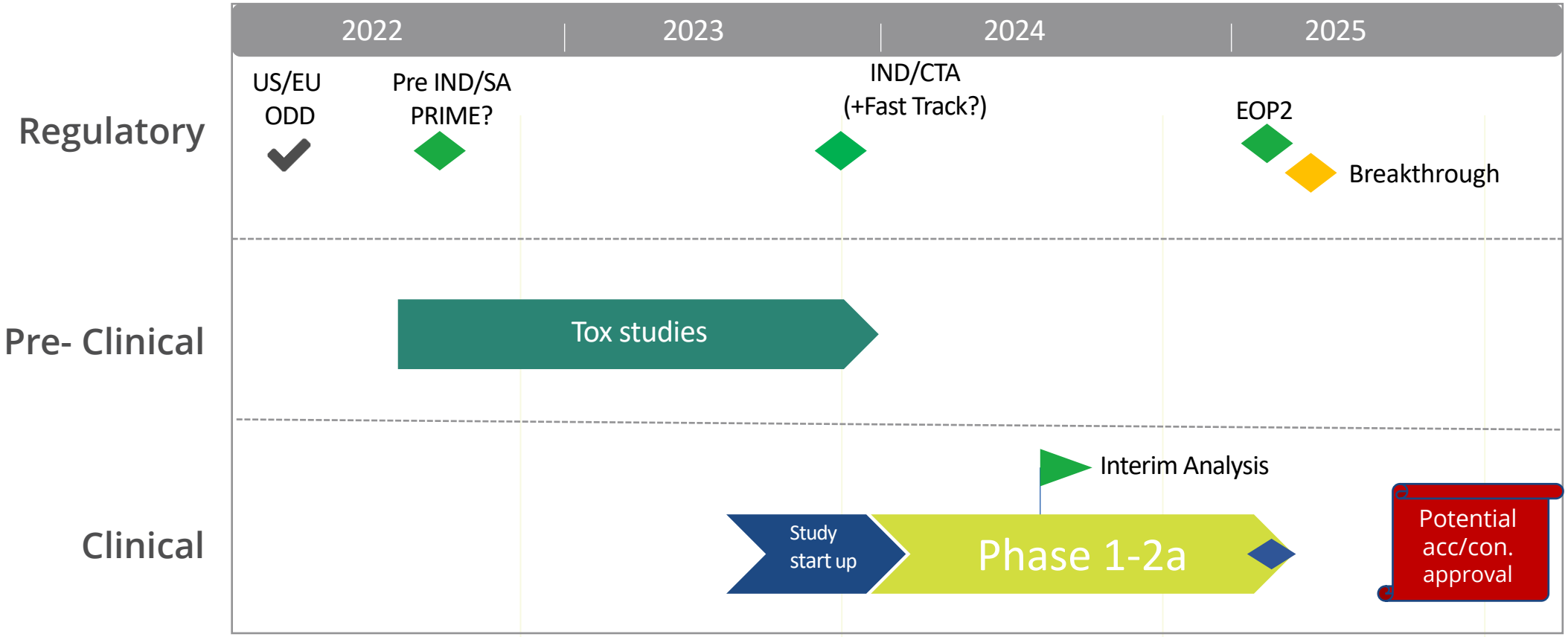


Heterozygote W1282X/ non-F508del

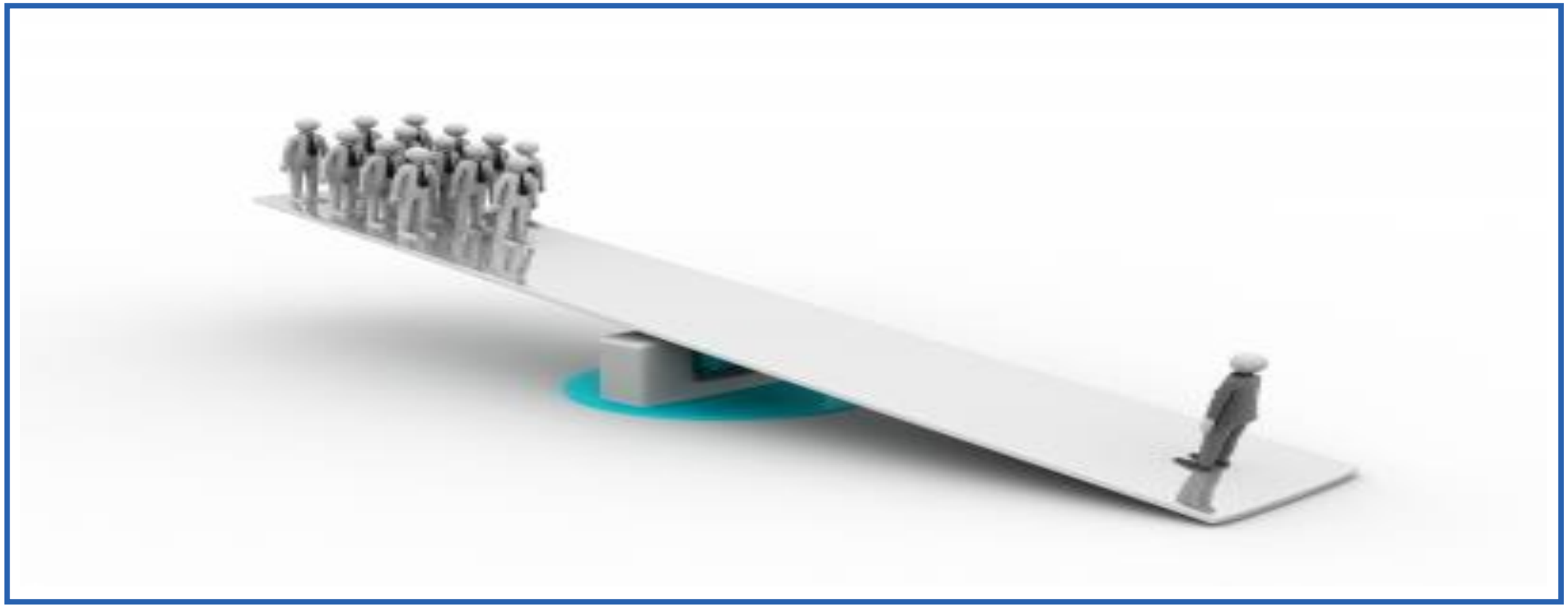


Potentially Translated to Significant Lung Function Improvement (~40% of HVs)

SPL23-2 Program (W1282X) Clinical & Regulatory Road Map



Expanding SpliSense Platform Technology from Orphan to Large Pulmonary Indications



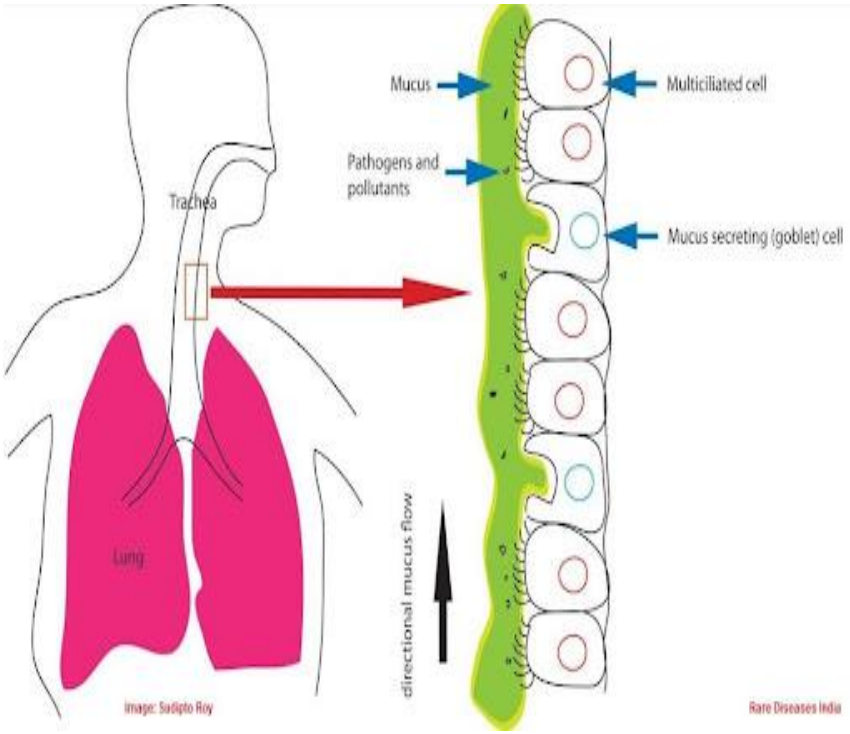
Muco-Obstructive Diseases

Mucin Lowering ASO (SPL5)

› **Decrease production of over – expressed proteins**

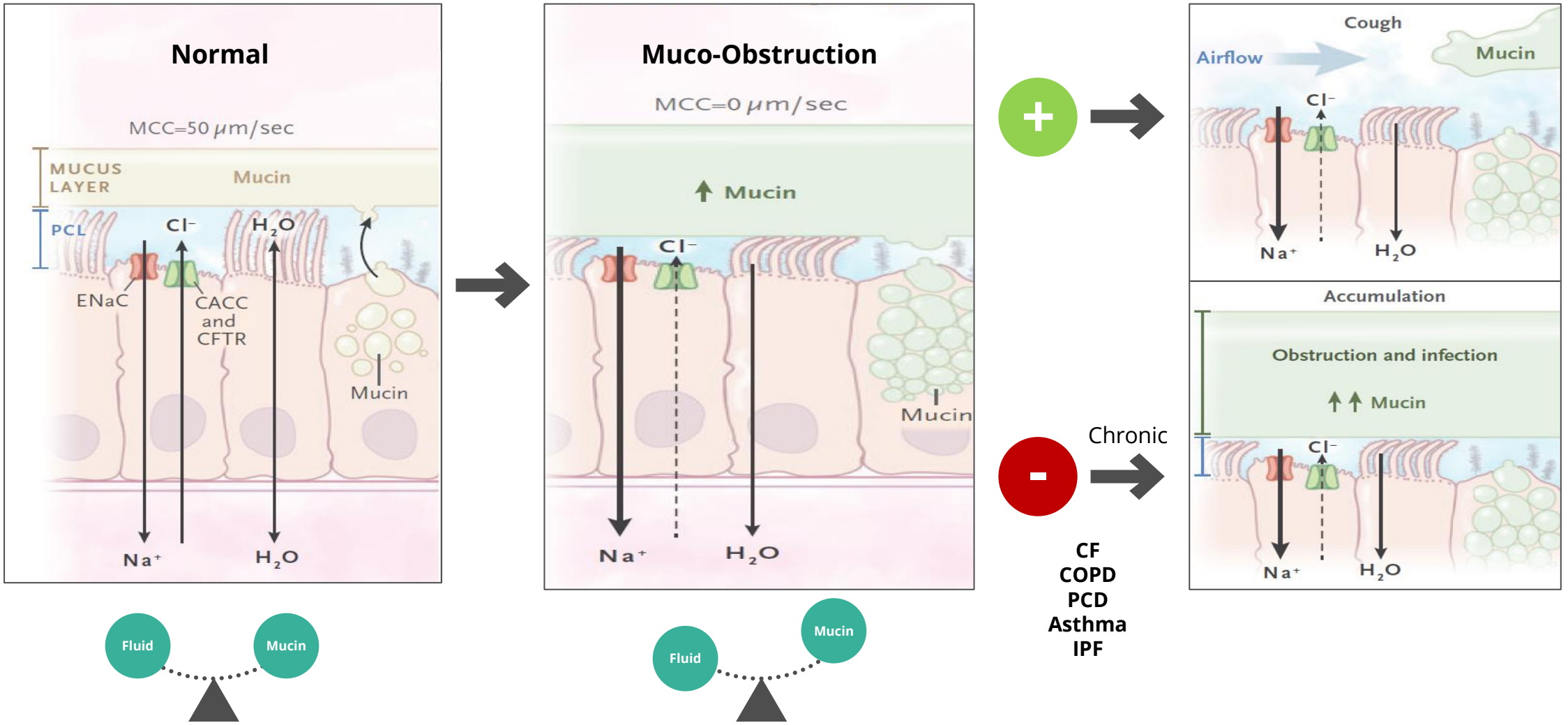
Mucus Hypersecretion is a Clinical Feature of Severe Respiratory Diseases

- 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
  - Respiratory air blockage
  - Respiratory disease worsening



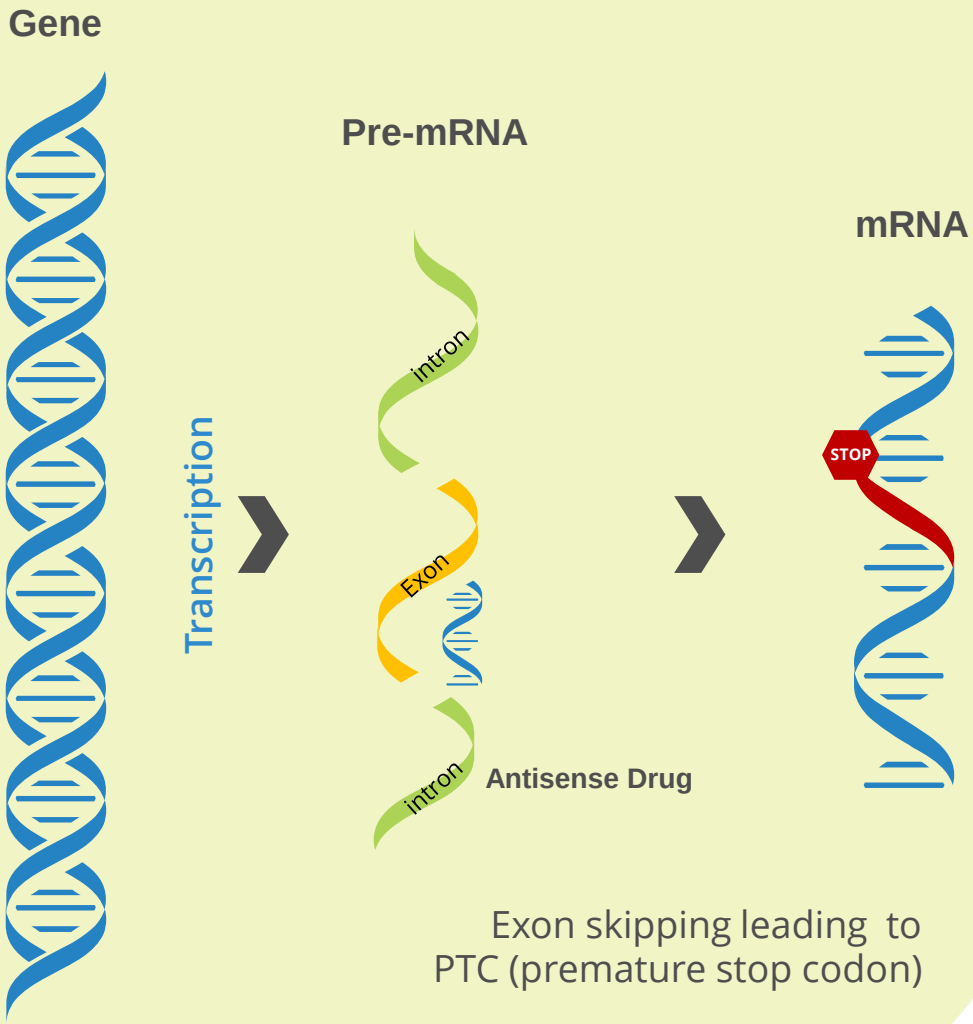
Roy et al. 2014, Roy et al. 2019, Ridley et al. 2018

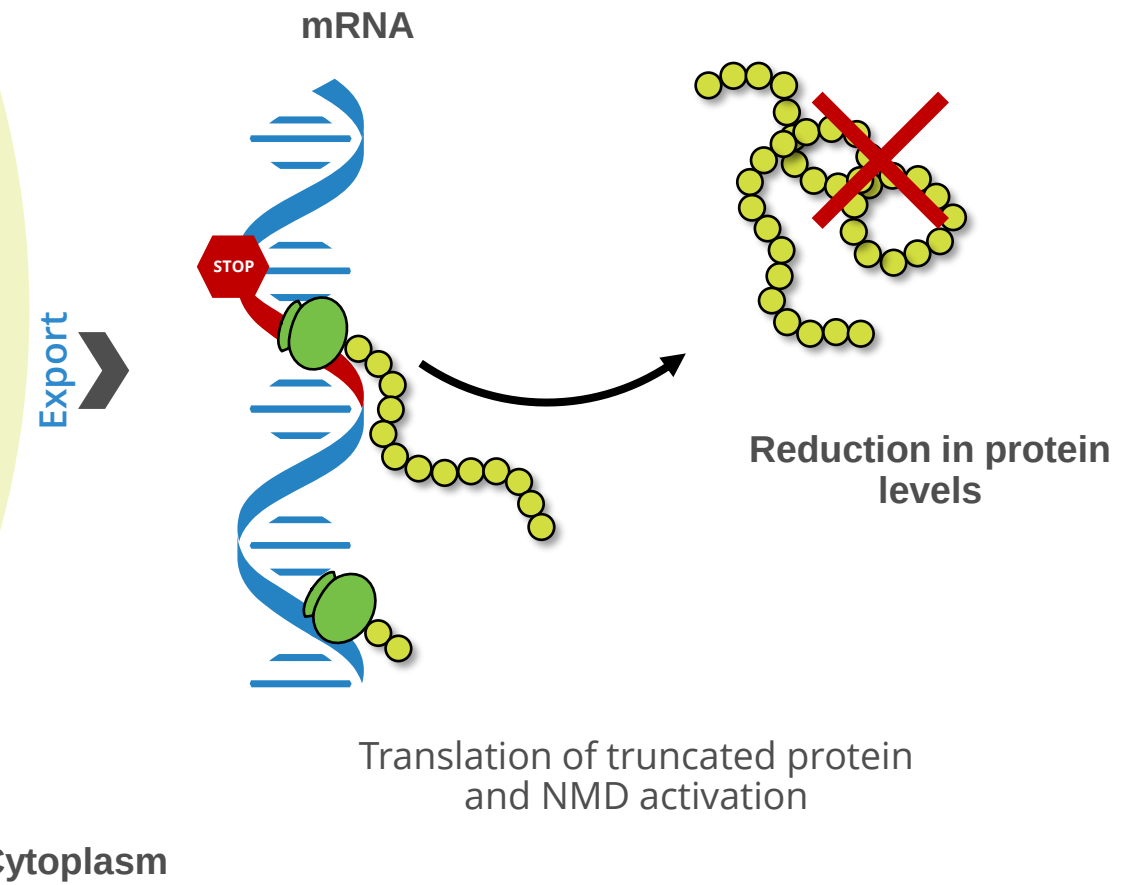
Muco-Obstructive Lung Disease Progression



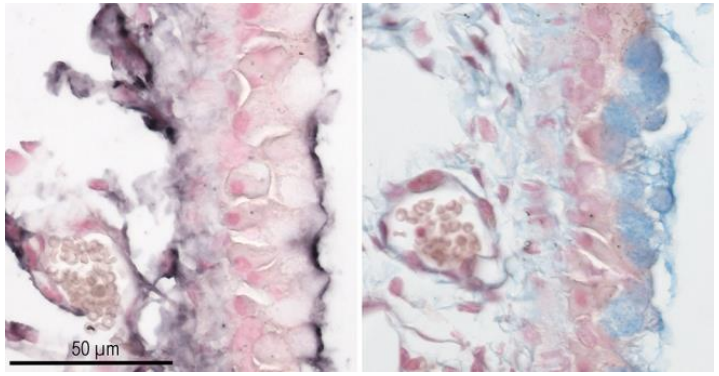
Bucher et al. 2019

SPL5 Lowers RNA and Protein Expression (MoA)

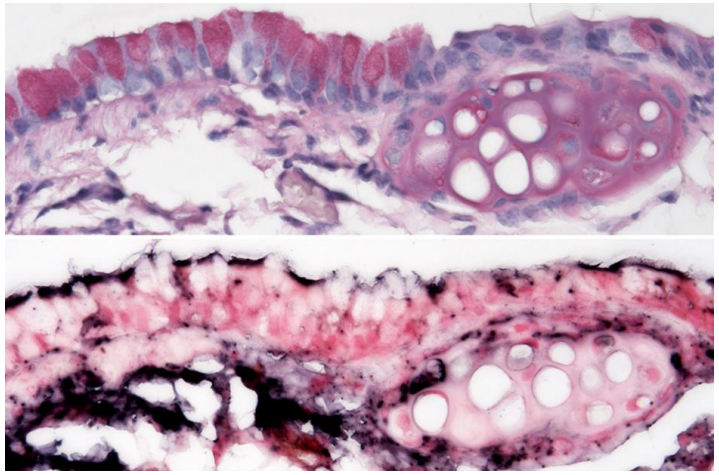




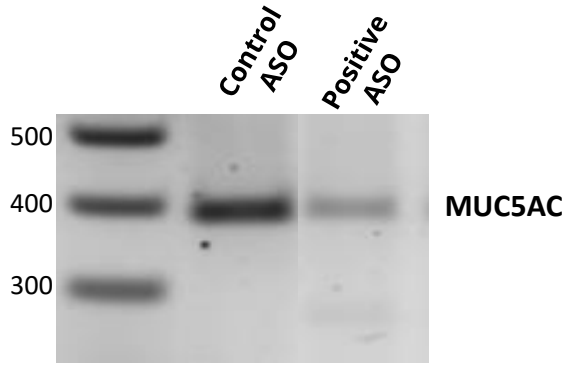
PoC Mucin Lowering ASO: Lungs Goblets Cells Distribution & Mucin Lowering Activity

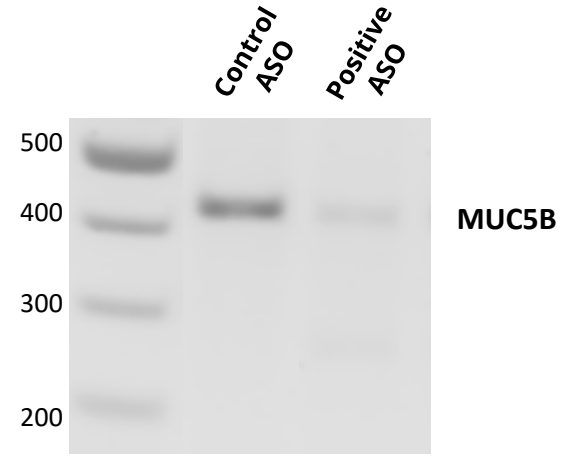


Hybridization signal at the of goblet cells (Beta ENaC/WT mice)



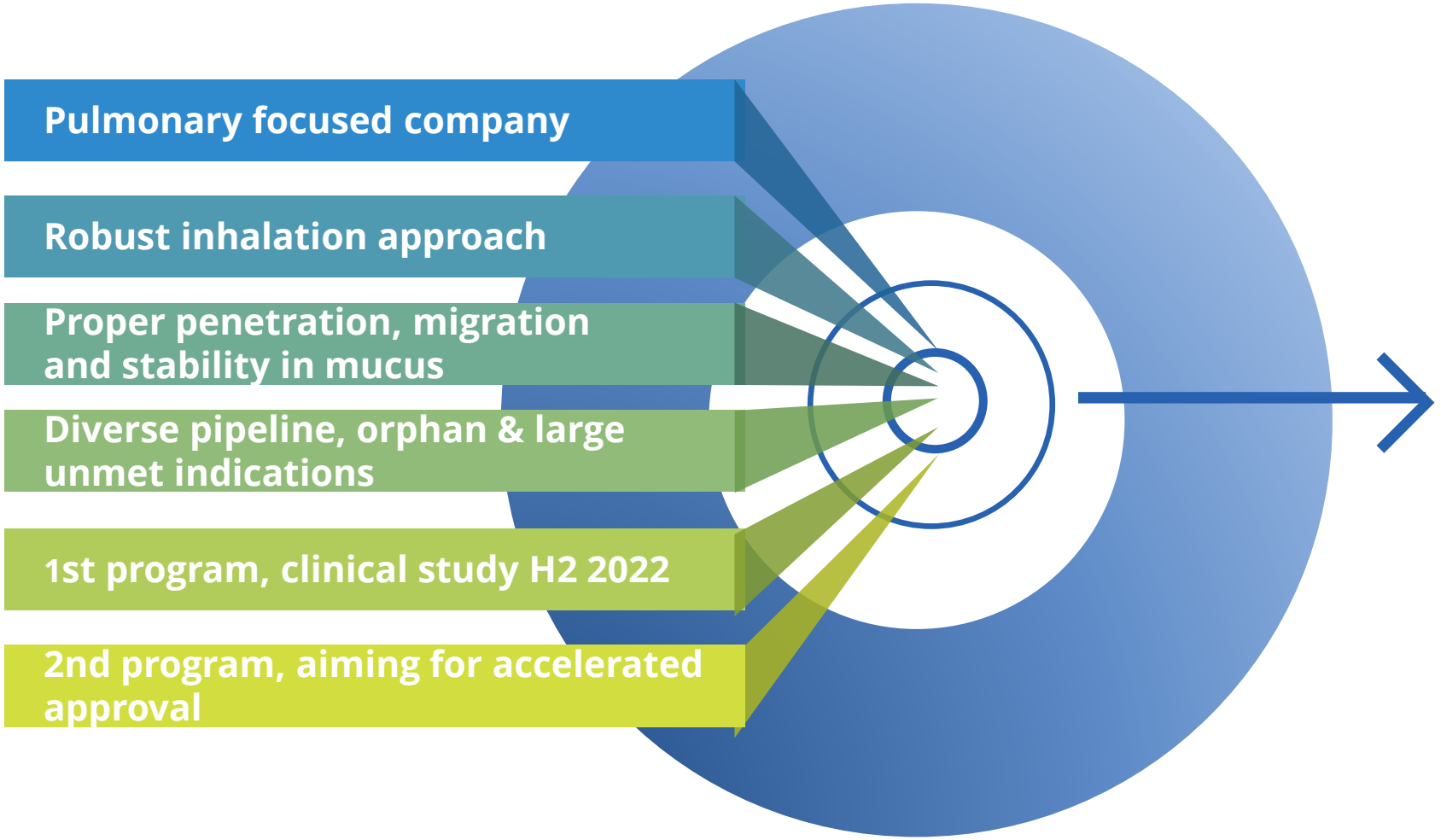
Black staining - SPL ASO
Blue\Purple staining- Mucus in goblet cells





A549 Human Lung Cancer Cells

SpliSense ASOs Approach: Platform Technology for Precises Pulmonary Therapies



Mastering protein production & expression in a targeted manner.

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.

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

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

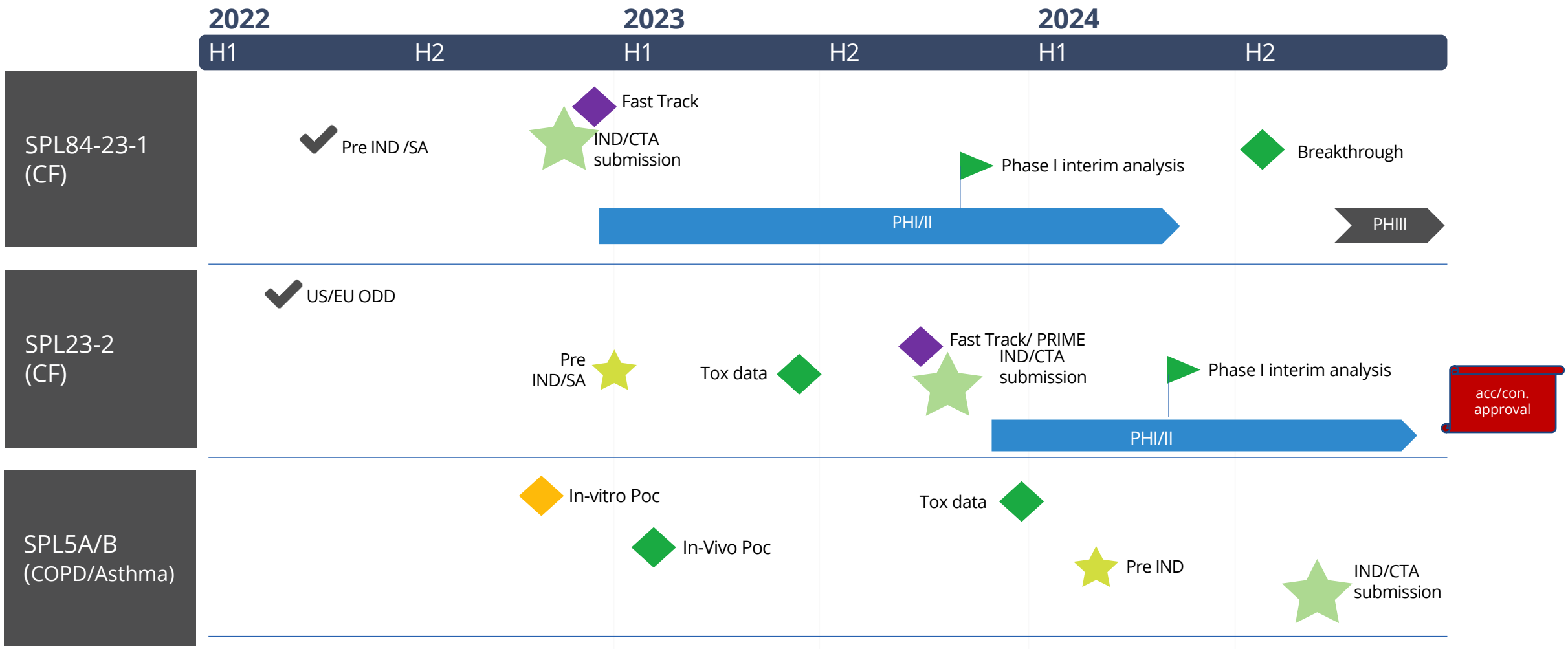
Prof. Eitan Kerem MD -CMO
Pediatric pulmonologist; Head of the Pediatric Pulmonology Unit of HMC Jerusalem, Chairman of the Israeli CF Foundation CAB.

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

Investment Opportunity - 2022 Financial Round

- Splisense is seeking to raise $40M to support 2023-24 expenses including:
  - Advancing additional pre- clinical programs into the clinic (IND)
    - SPL23 (Anti W1282X Mutation ASO)
    - SPL16/SPL24
    - Advancing Mucins lowering ASOs to IND
      - MUC5AC
      - MUC5B

SpliSense Value Inflection Points 2022-2024



Thank You!