SpliSense

Making Sense of Splicing

Oligonucleotide Based Therapeutics

Corp. Update
June 2021

NON-CONFIDENTIAL

SpliSense Value Proposition

The Compnay

- An Israeli based company
- Founded based on the research of Prof. Batsheva Kerem (Hebrew University)
- Leadership team and advisors with strong track record in development of ASO therapies and inhaled drugs

R&D Status

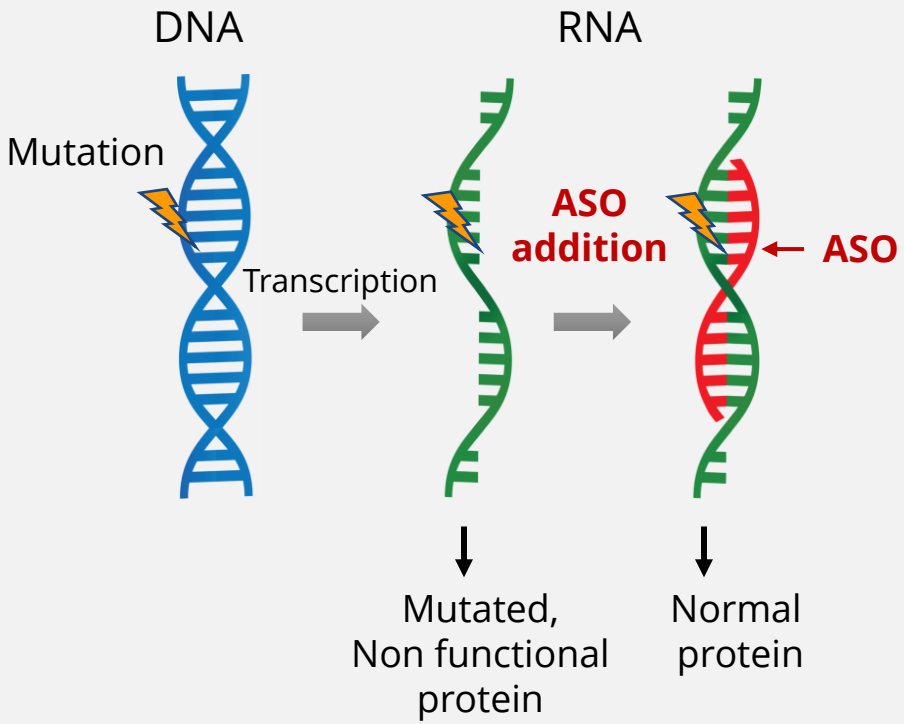
- 3849 ASO program in IND enabling studies phase
  - Phase 1-2a targeted for H2 2022
- Exon 23 program entered IND enabling studies
- 3 Additional indications in discovery stage utilizing the same technology and screening methodology

Financial

- Completed a $28.5M Series B funding from a strong syndicate
  - Orbimed, IBF, CF foundation and Integra

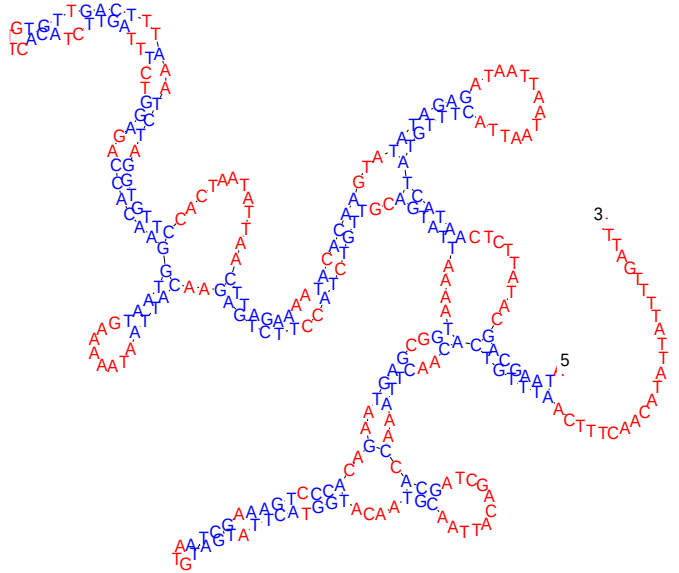
Technology Platform

- SpliSense is developing antisense oligonucleotide (ASO) based therapies to target genetic diseases
- ASO:
  - RNA-like antisense oligonucleotides (ASOs) are short sequences that can bind and modulate RNA
  - The ASO sequences are specific to the target mutation region in RNA and thus avoid potential off-target effects
  - ASOs are chemically modified for stability and increased cell uptake. No vectors or delivery vehicles are needed
  - ASOs were shown to penetrate the cells vis endocytosis
  - Clinically validated (SPINRZA®, Exondys 51®, Sepofarsen)



ASO Design Strategy

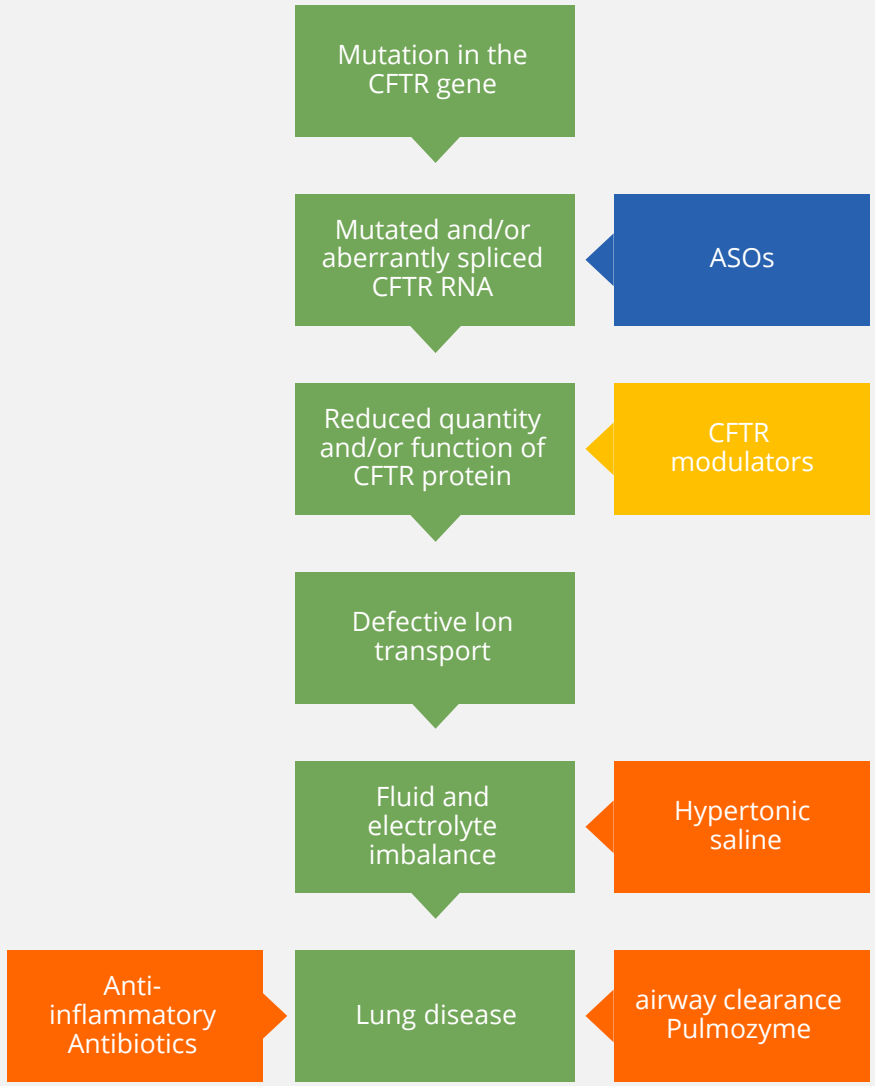
- ASOs are designed and optimized using an in-house computational tool that supports the design of a large number of ASO sequences at a chosen target region
- The algorithm evaluates a set of parameters important for:
  - Optimization of ASO binding to the target
  - Avoiding immunity (sequence)
  - Avoiding off target effects
  - Optimize analytical conditions
    - Solubility
    - Stability



Cystic Fibrosis – Unmet Need

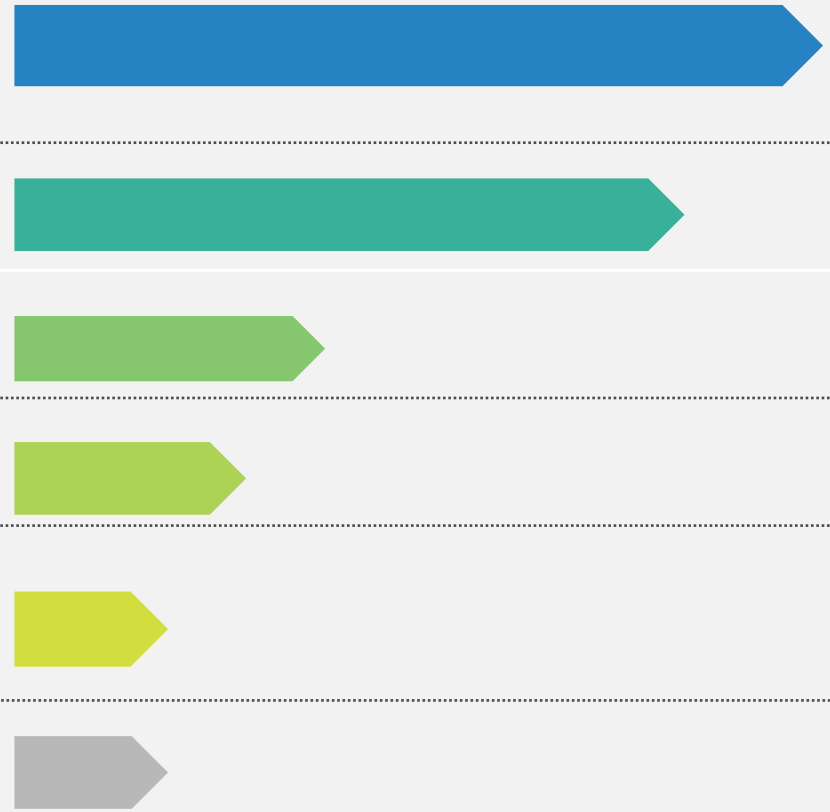
- A progressive, life shortening autosomal recessive genetic disease due to dysfunction of the CFTR transmembrane protein
  - CFTR is a transmembrane chloride channel that is highly expressed in the airways of the lungs as well as extra pulmonary organs
- Affects ~90,000 people worldwide (80% with F508del mutation)
- The median predicted survival of people with CF is about 39 years, but average age of death is < 30 years in US from respiratory failure
- Existing drugs alleviate symptoms but do not cure the disease
  - Small molecule correctors and potentiators target mutations other than SpliSense targets
- Lung transplantation is the only definitive treatment option for CF patients with end stage lung disease

Treatments Strategy



SpliSense's Pipeline

Indication	Approach	Program	Discovery	Lead Selection & Optimization	IND Enabling Studies	Clinical Studies
Cystic Fibrosis	Correction of splicing mutations	SPL84-23-1 (3849)				
	Exon skipping	EXON 23				
		EXON 24				
	Splicing variants	Undisclosed				
	Correction of splicing mutations	Undisclosed				
Pulmonary-Undisclosed	Frame shift	Undisclosed				



Advantages of Inhaled Delivery

- Enables direct non-invasive delivery even of high doses with minimal systemic absorption
- Ideal to treat lung diseases
- Infrastructure for inhalation is established and commercially available
- SpliSense end products is an inhaled drugs, given to patients once a week, thus reducing patients' treatment burden
- ASOs for inhalation:
  - Stable post nebulization
  - Highly soluble

SPL84-23-1
3849 mutation

3849 Mutation - Unmet Need

- >1300 patients globally
  - Tier 1 : Treatment target population (Non-F508del) – 515 patients
  - Tier 2 : Expand to additional F508del hetr. ~820 patients (Combo/Mono)
- In 3849/Non F508del patients the effect of ivacaftor (Kalydeco®) on pulmonary function (FEV1) is only 2.7%
- In 3849/F508del patients the effect of tezacaftor/ivacaftor (Symdeko®) on pulmonary function (FEV1) is only 5.8% (Kalydeco effect is 5.1%)
- Although there is a slight beneficial effect of the Symdeko® to these patients, the effect is limited and there is a need for other more effective drugs
- Annual treatment cost per patient >$0.5M

Rowe et al., NEJM 2017
FDA site, Symdeko printed labeling

3849 Mutation - Market Potential

Patient population
(2020)- 1300

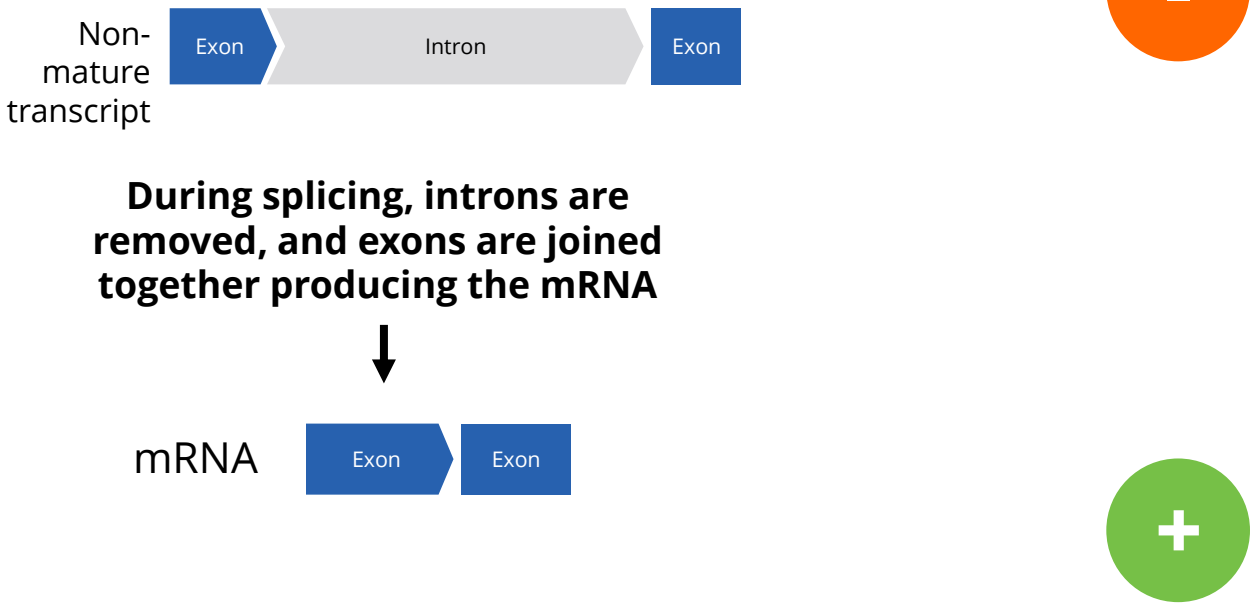
Annual Growth
3%

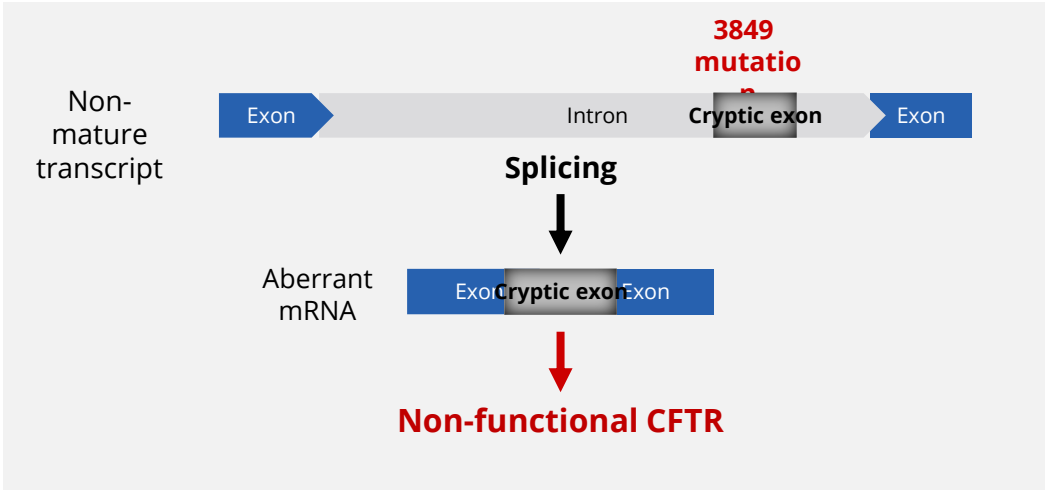
Time to launch –
3.5 yrs
(conditional approval)

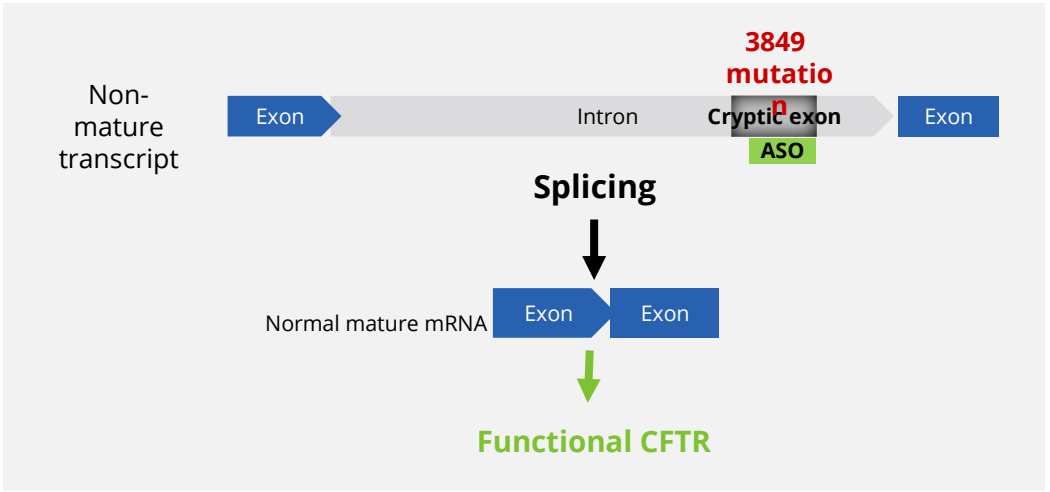
Dev. Cost (phase 2)
– $15M

Drug Annual
cost – $300k

Splicing ASO Technology Produce Mature and Functioning CFTR

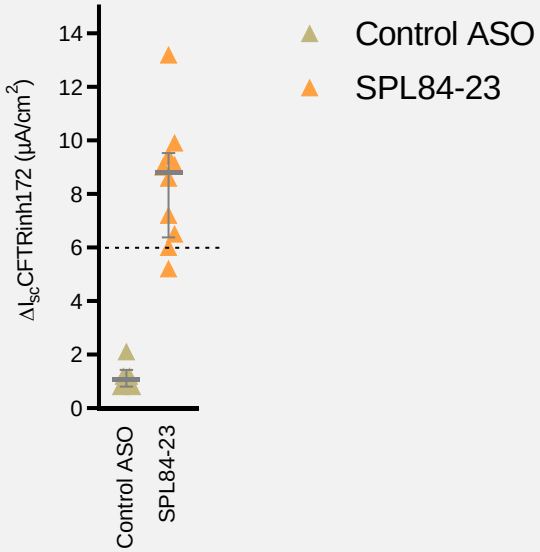






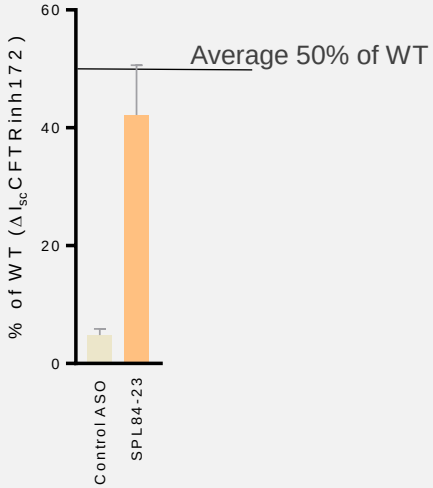
SPL84-23 Completely Restores CFTR Function – Patient's Derived Cells

HNEs from a patient (3849/F508del)*



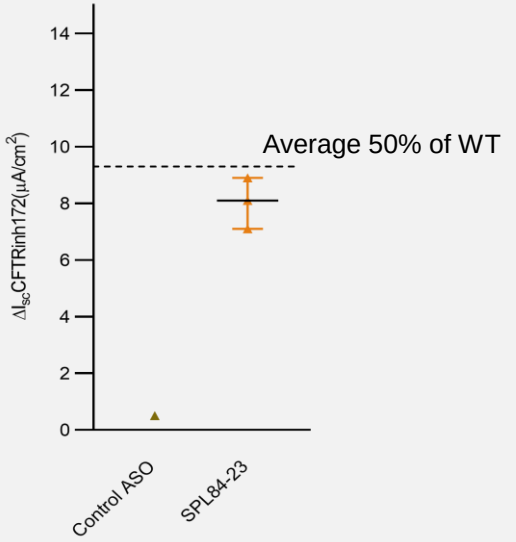
SPL84-23 completely restores the CFTR function in HNEs from a 3849/F508del patient

Average of HNEs from 5 patients carrying the 3849 mutation*



SPL84-23 restores 43% of WT function, across cells from patients with different genotypes (X3 F508del, W1282X, 405+1 G-to-A), reproducible effect among patients on splicing modulation and CFTR function

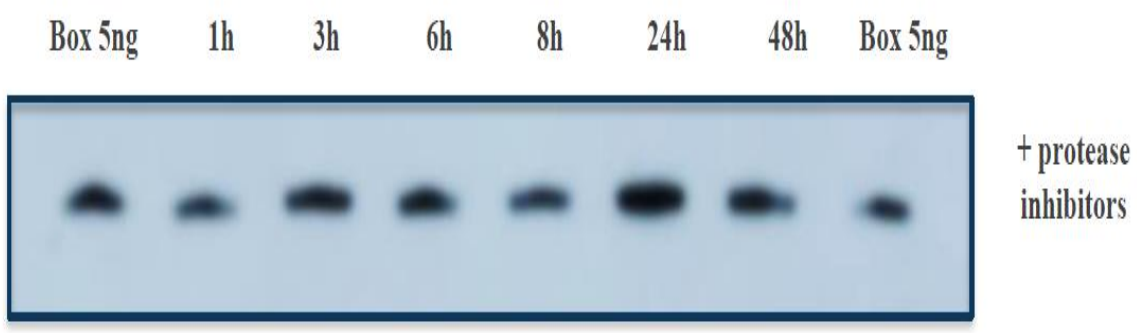
HBEs from a patient (3849/F508del)*

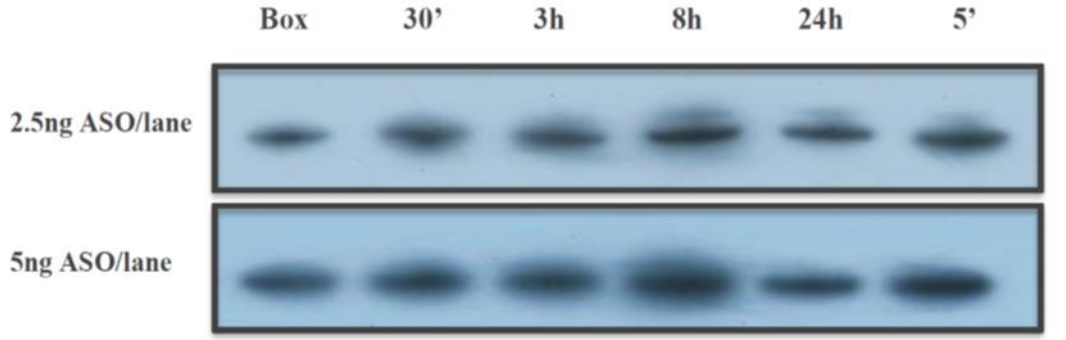


SPL84-23 restores almost 50% of WT CFTR function in HBEs from a 3849/F508del patient

*In collaboration with the lab of Prof Isabelle Sermet-Gaudelus
** Average activation in WT from Pranke, I. M. et al. Sci. Rep. 7, 7375 (2017)

SPL84-23 Stability Studies - Summary

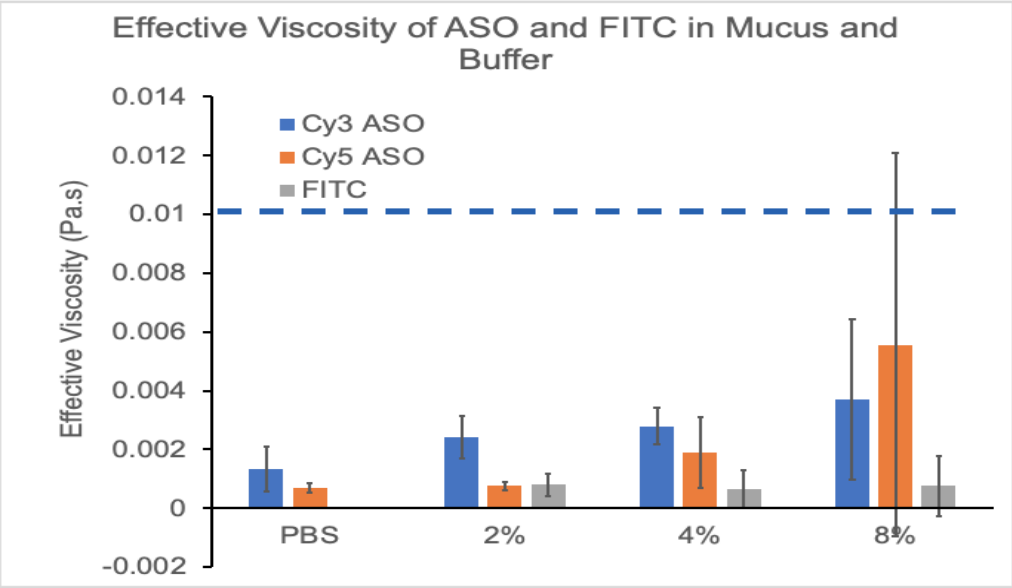


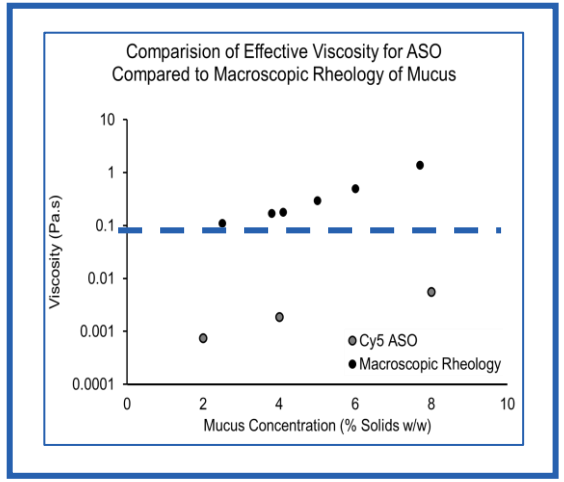


SPL84-23 is stable in mucus from CF patients (N=10).

SPL84-23 is stable in lung lysosomes extraction.

Human Mucous Migration - Study Summary



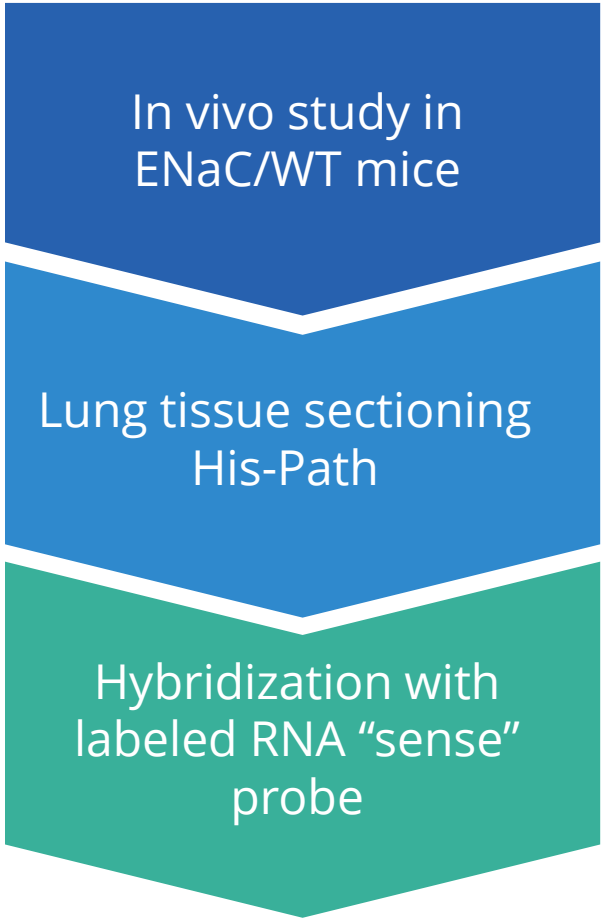


- SPL84-23 experience a viscosity ~ 100-fold lower than macroscopic particles
- SPL84-23 will be able to permeate hyper-concentration mucus associated with CF airway disease.
  - Based on the measured diffusion coefficients, SPL84-23 will, on average, penetrate an 100mm 8% solids mucus layer in ~ 2 minutes.

Biodistribution Study in β-ENaC Mice

- WT and β-ENaC mice were treated Intra-Trachea (IT)
- Regimen: every other day for 6 days
- Lungs were fixed
- In situ hybridization with labeled “sense“ probe (RNA)
- Toxicity assessment

Unlabeled SPL84-23

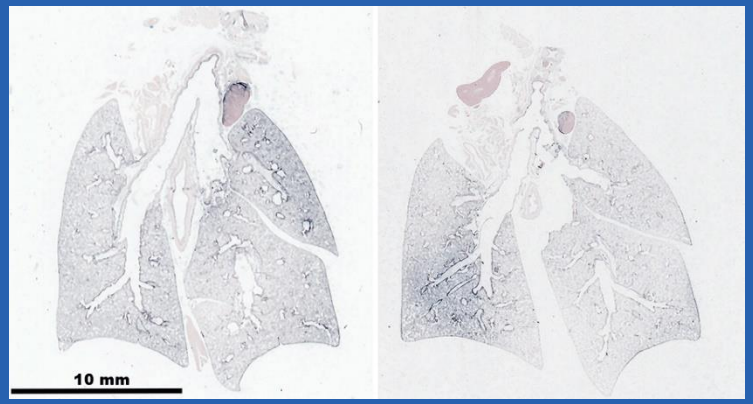


SP8L4-23-1 is Properly Distributed in beta ENaC Mice Lungs

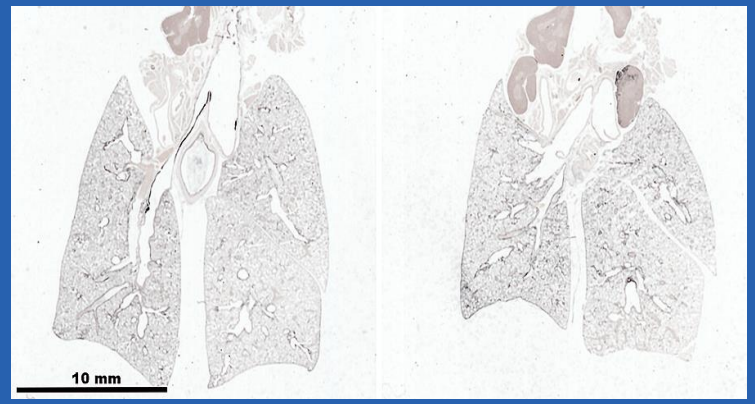
Staining for SPL84-23 following IT administration

3 treatments every 48 hr with SPL84-23; lung collection **12hr following** last treatment

WT

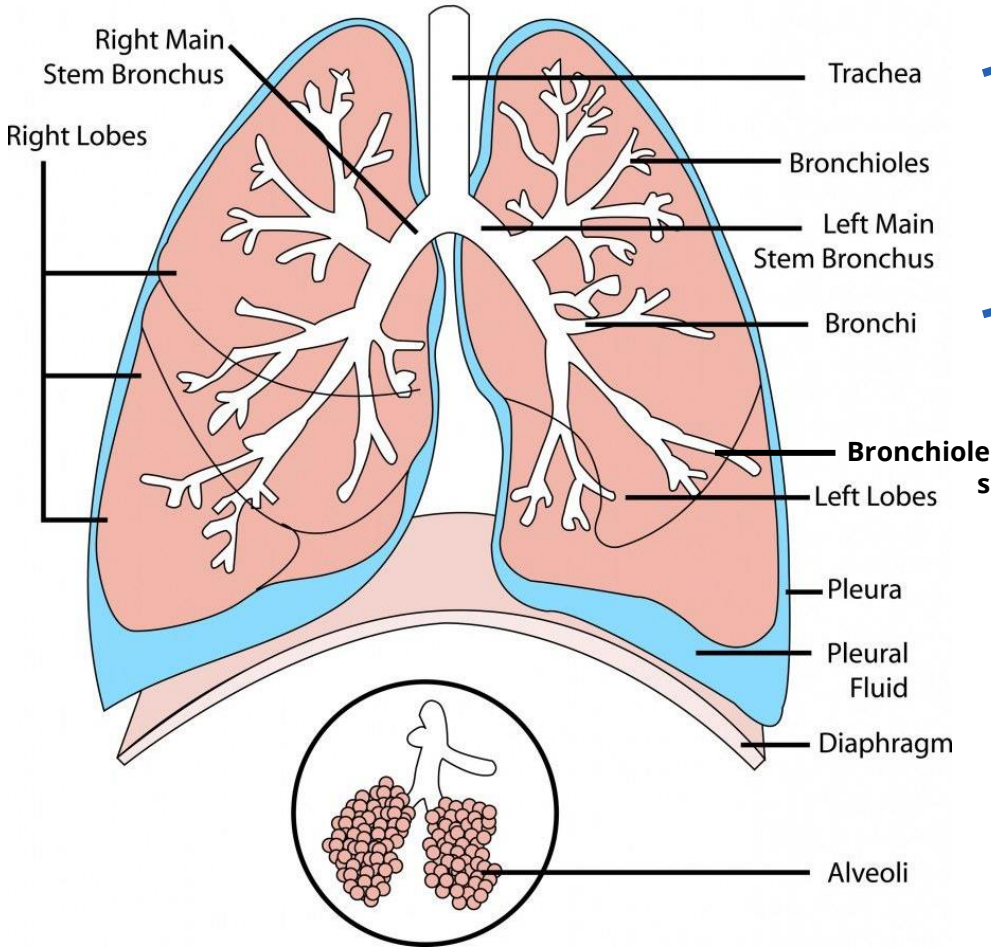


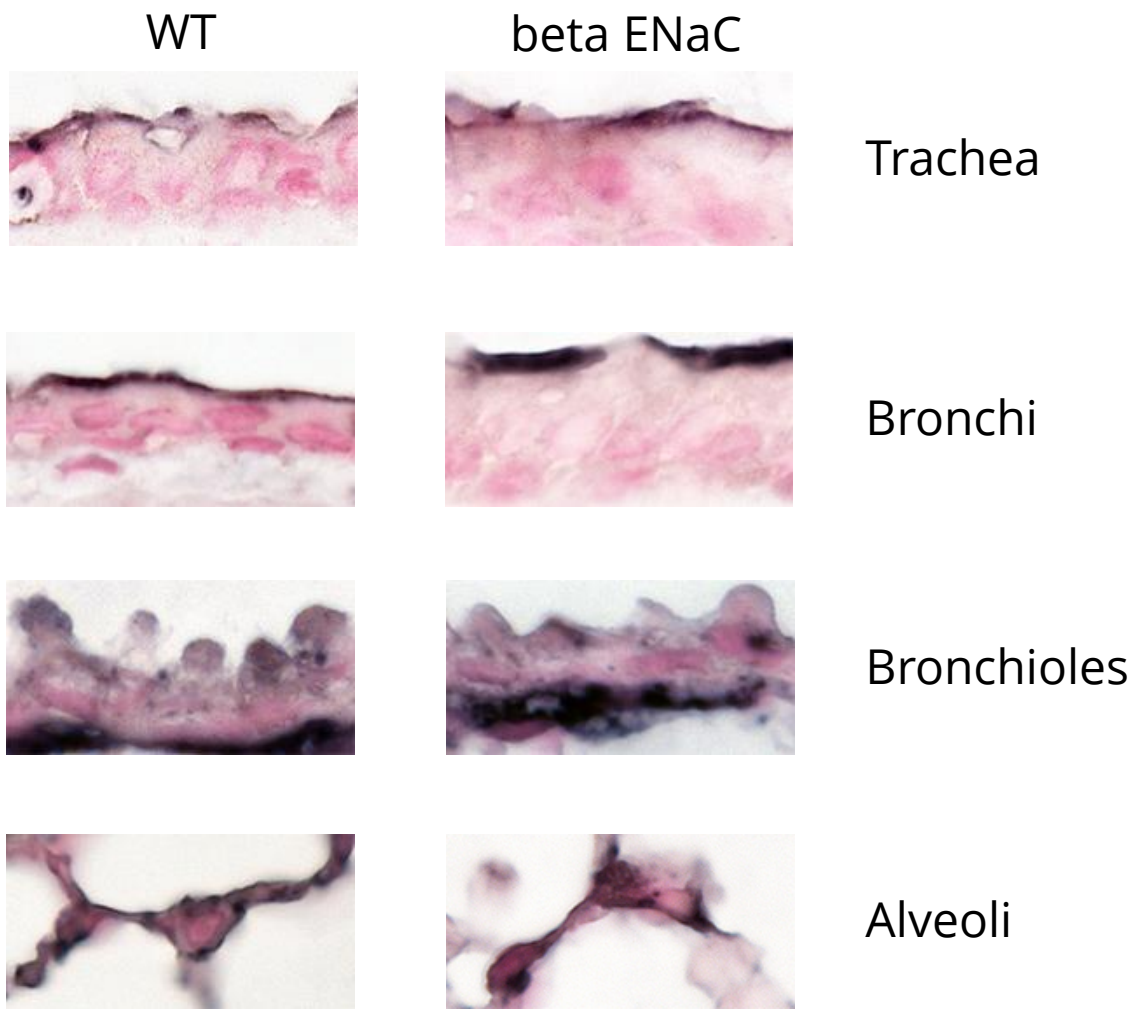
Beta ENaC



SPL-84-23 is distributed in beta-ENaC and WT mice lungs

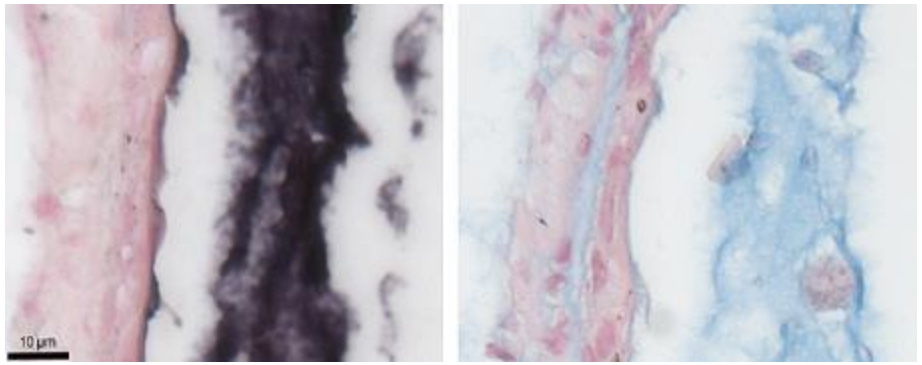
Similar Distribution of SPL84-23 in WT and beta ENaC

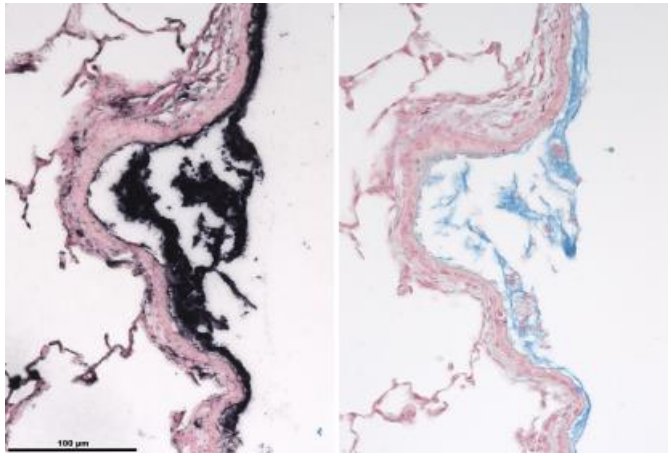




SP8L4-23 Penetrates Through Mucus the Epithelial Cells

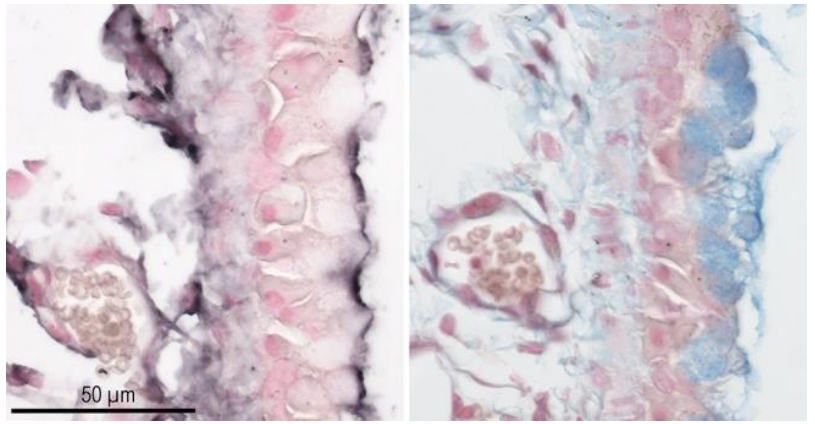
Examples of images from the Bronchus of beta ENaC mice





Black- Probe hybridization to SPL84-23

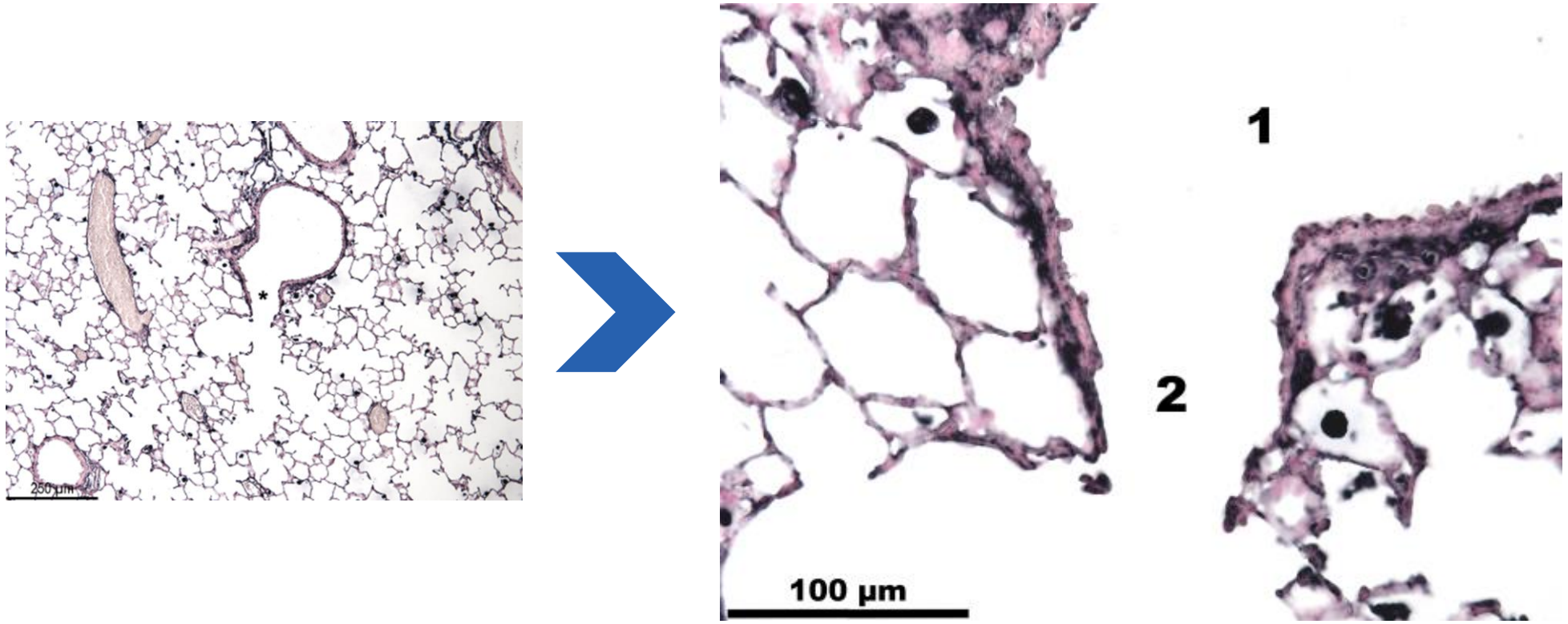
Alcian blue stains mucus and cartilage



Hybridization signal at the apical part of goblet cells

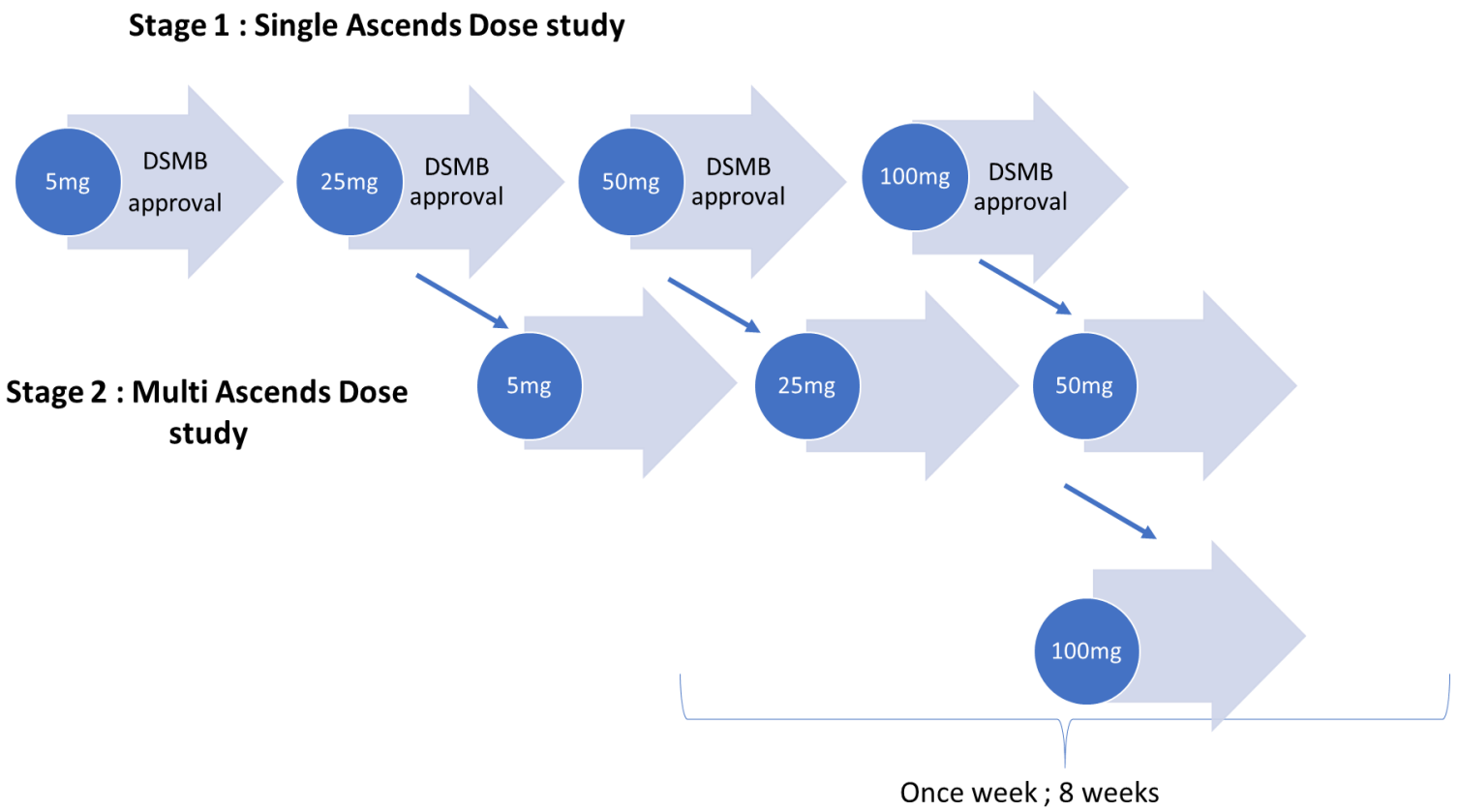
SPL84-23 penetrates through mucus to the epithelial layer of the airways

SPL84-23 Can Penetrate Epithelial Cells (beta ENac)



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

Phase 1-2 Proposed Clinical Study Design



Primary Objectives

- To assess the safety, tolerability of SPL84-23-1 administered by inhalation, in patients CF, homozygous or heterozygous for the 3849+10kb C->T CFTR mutation

Secondary Objectives

- Laboratory parameters and vital signs
- Pharmacokinetics (PK) of SPL84-23-1 administered via inhalation
- Effect of ascending doses of SPL84-23-1 administered via inhalation on disease-related efficacy outcome
  - ppFEV1
  - CFQ-R RSS

SPL84-23 Summary & Perspectives

Research

- Complete rescue of CFTR function in a 3849 homozygote
- High CFTR function (~50% of WT) in 3849 heterozygous patients' HNE/HBE
- Stable in patient's mucus and lung cells lysosome
- Stable and properly distributed in animals' lungs
- Penetrates to lung epithelial cells

Clinical Dev.

- Valid and predictable HNE/HBE data supporting clinical studies (FDA white paper)
- Stable and properly distributed in animals' lungs
- Phase 1-2 initiation H2 2022
  - Safety
  - Preliminary efficacy

Value Proposition

- Poor treatment solutions to patient population (i.e., not approved in EU)
- Can expend to additional patient population (Tier 2)
- Potential accelerated approval targeted for 2024
- Anticipated peak sales in 2029 (75% of the market)

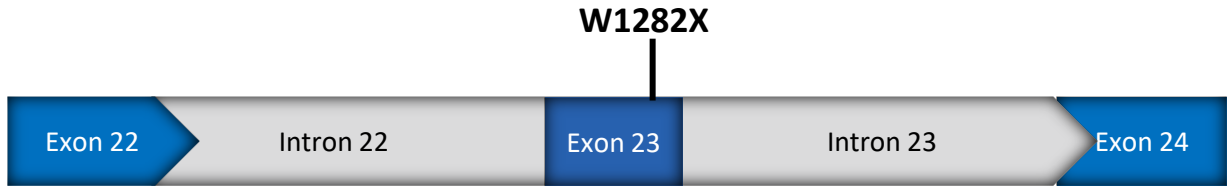
Exon 23 (W1282X mutation)

Unmet Need for W1282X / non-F508del Patients

- There is no available therapy for CF patients carrying various mutations including nonsense, frameshifts, deletions and missense mutations along the CFTR gene
- These mutations lead to CFTR proteins with almost no activity (minimal function)
- We focus on a minimal function mutation in exon 23 (W1282X) –(~1700 patients in US and Europe)
  - ~50% of W1282X patients are non-F508del
  - Treatment target population (Non-F508del) - 800

W1282X/non-F508del patients have no approved drug

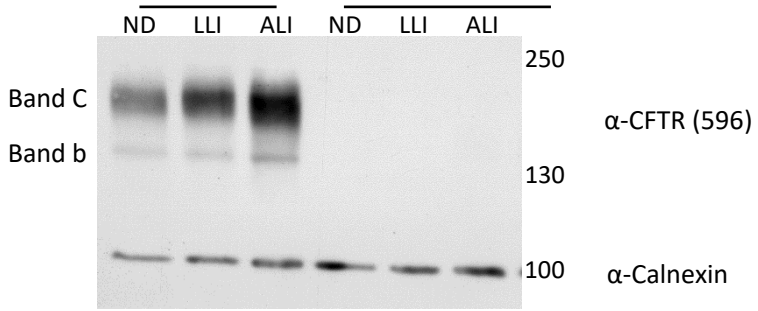
No CFTR Protein & Activity in Cells Carrying the W1282X Mutation



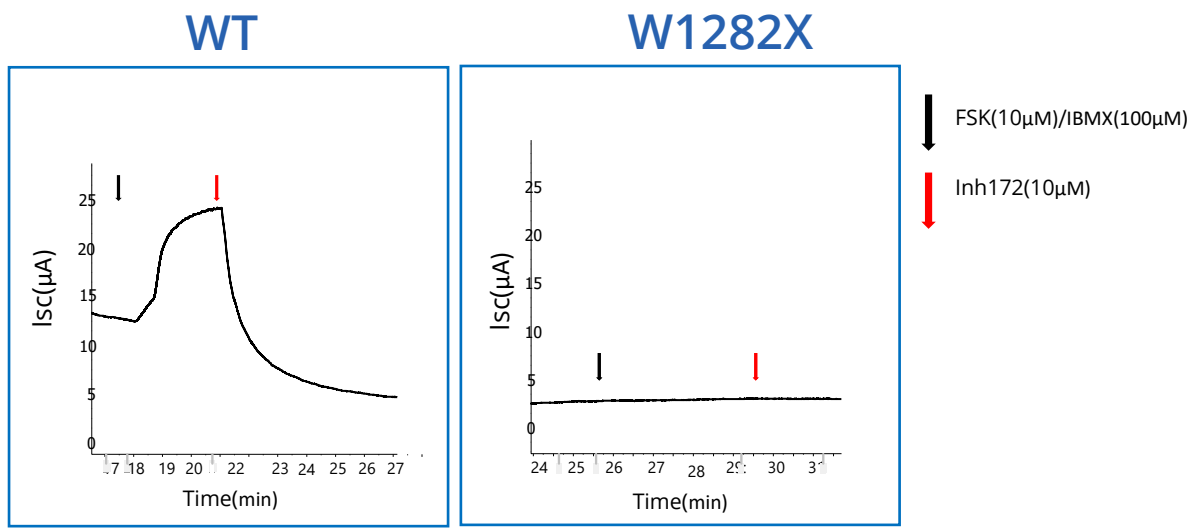
mRNA degradation by NMD

Translation of truncated protein

16HBE14o-



WT ~ 163kDa; W1282X ~ 140kDa;



Exon 23 Mutation - Market Potential

Patient population (2020)- 800

Annual Growth 3.5%

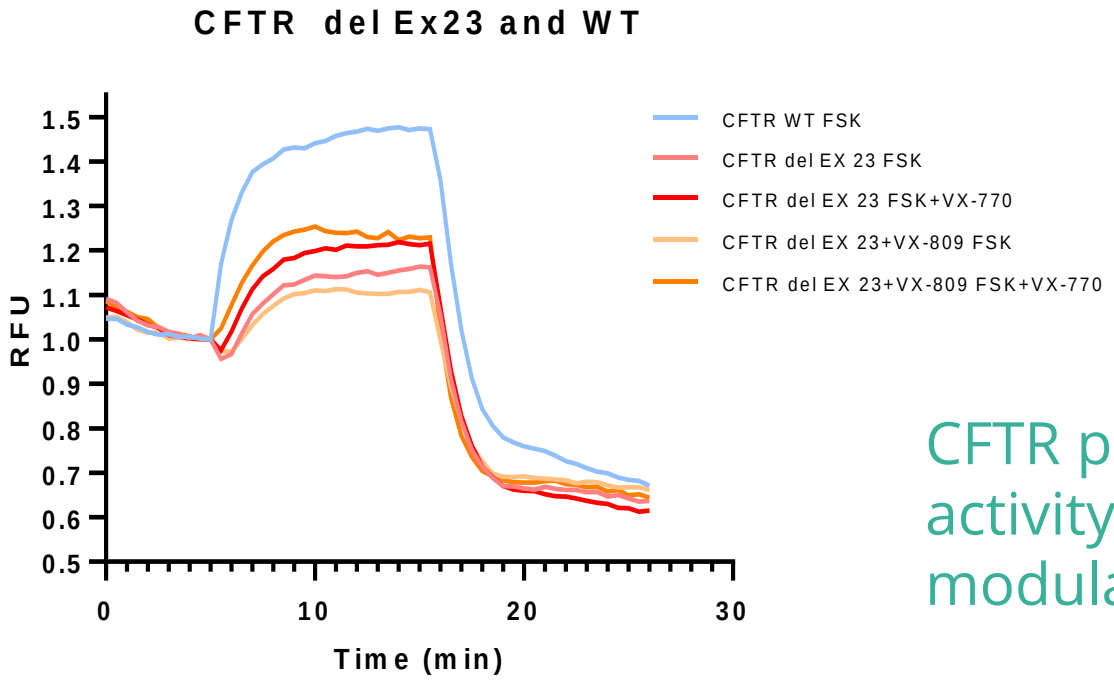
Time to launch – 4.5 yrs (conditional approval)

Dev. Cost (phase 2) – $20M

Drug Annual cost – $300k

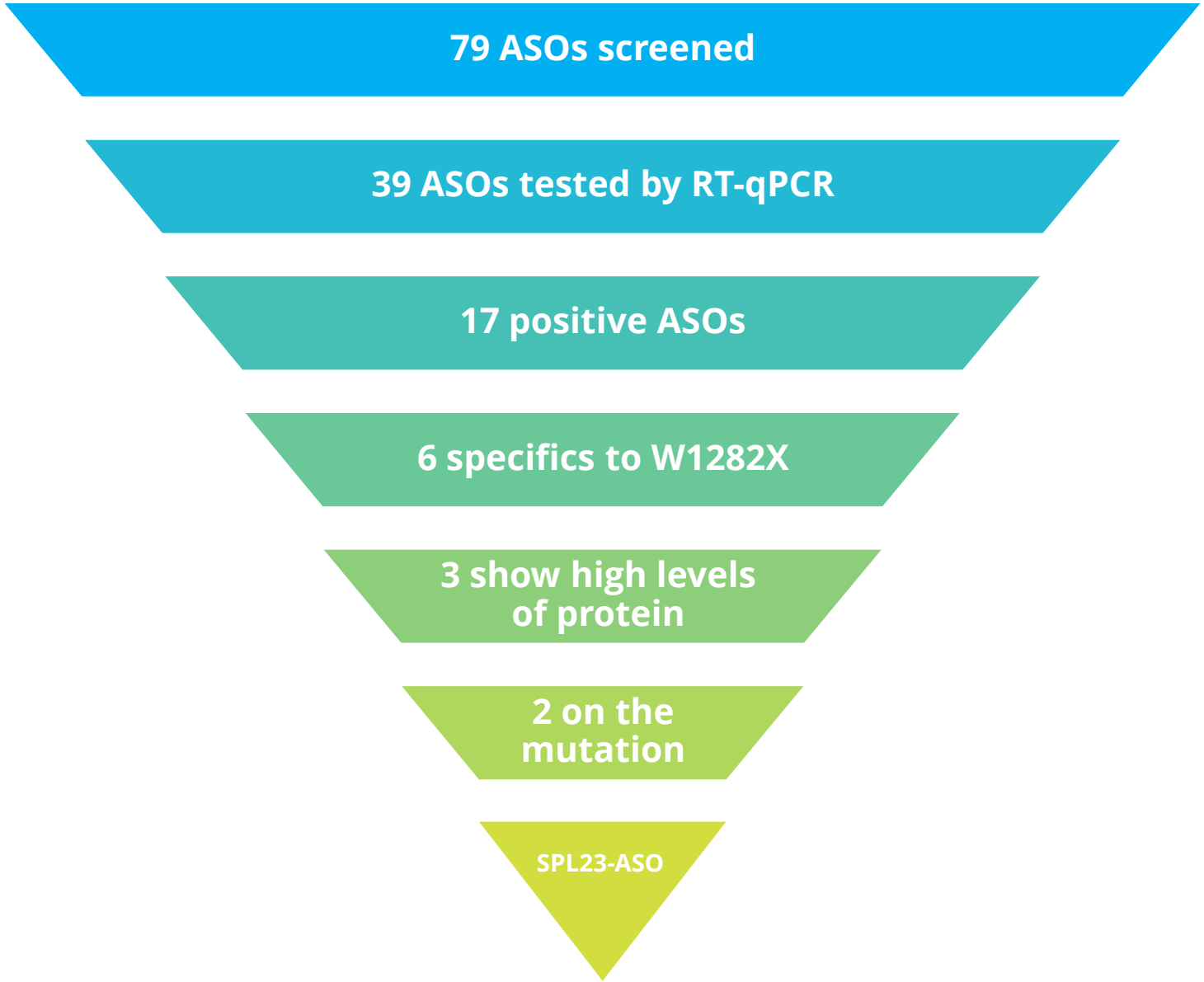
CFTR Lacking Exon 23 is Functional

Channel activity measured in HEK 293 cells transiently transfected with CFTR construct lacking the target exon



CFTR proteins lacking the target exon have residual activity, that is augmented by approved CF modulators

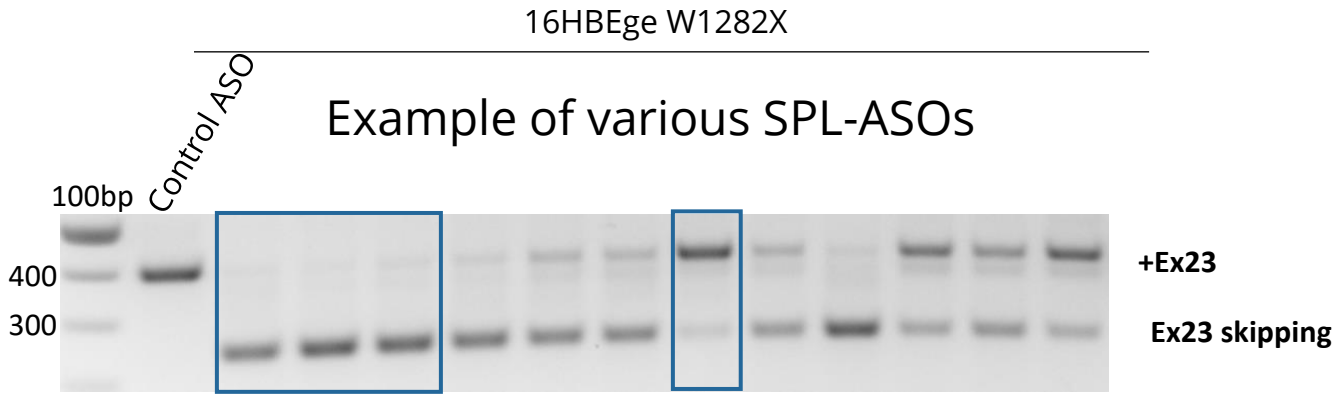
SPL23-ASO is a Lead Candidate for Exon 23 Skipping Program

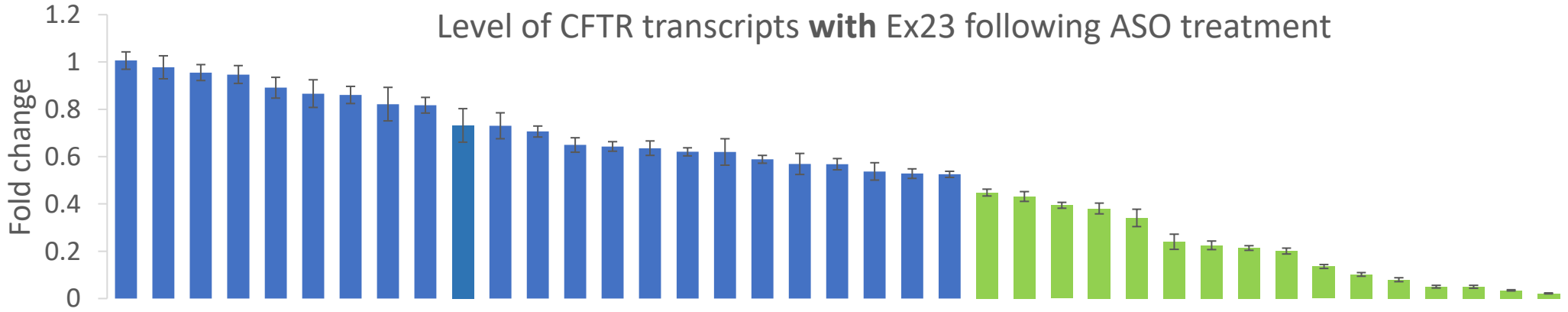


Screen for ASOs Inducing Skipping Over Exon 23

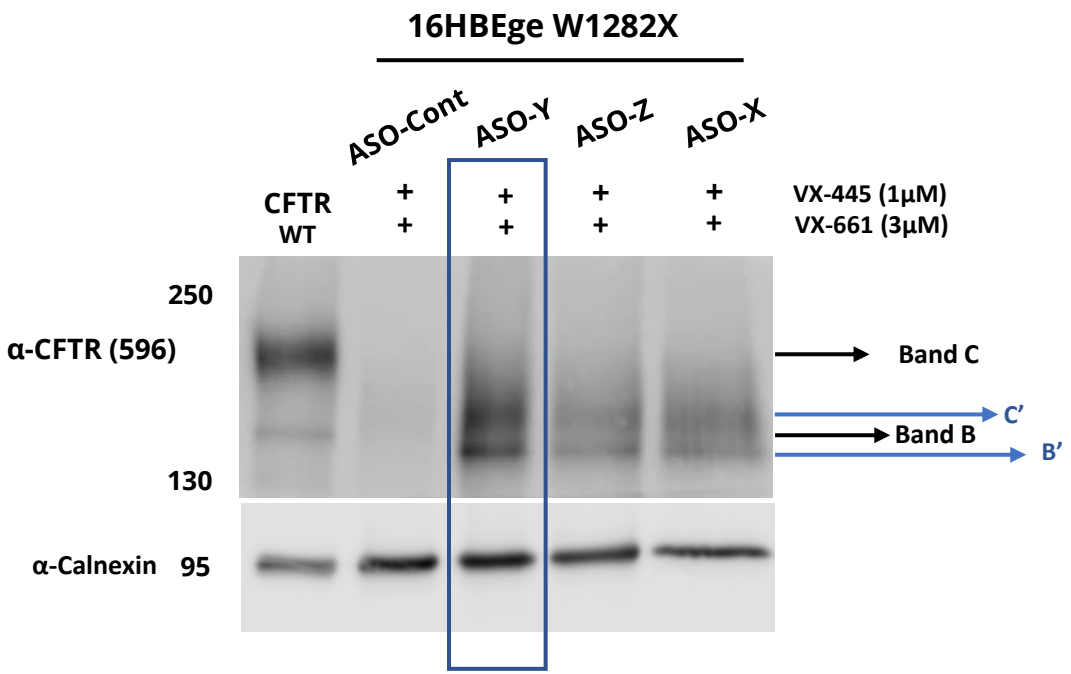
(RT-PCR and RT-qPCR)

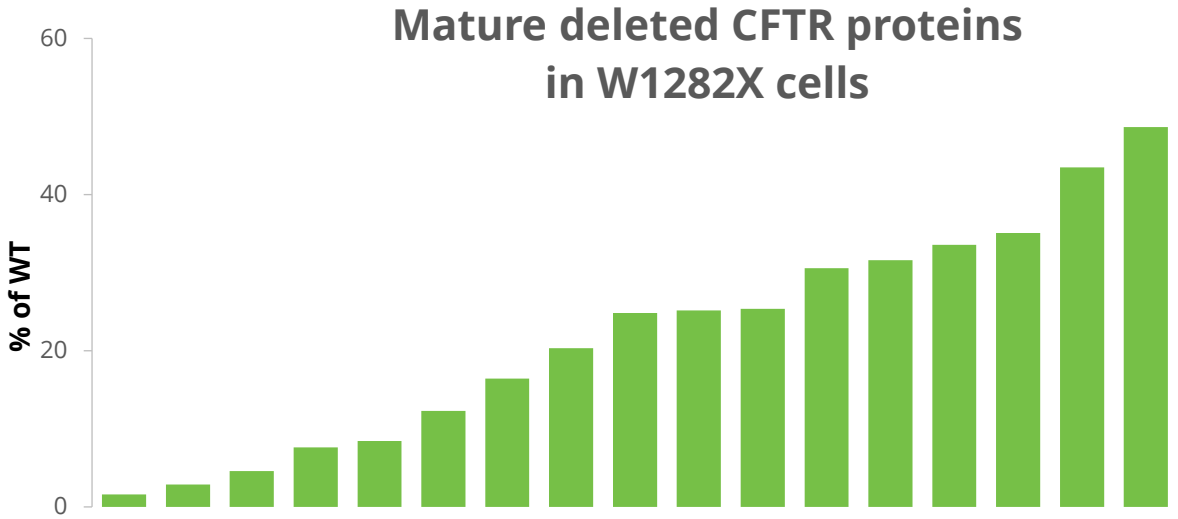
- 79 ASOs tested by RT-PCR
- 39 were further analyzed by RT-qPCR
- **16 positive** ASOs (>50% exon skipping)





Production of Mature C’ (exon 23 deleted) CFTR Proteins

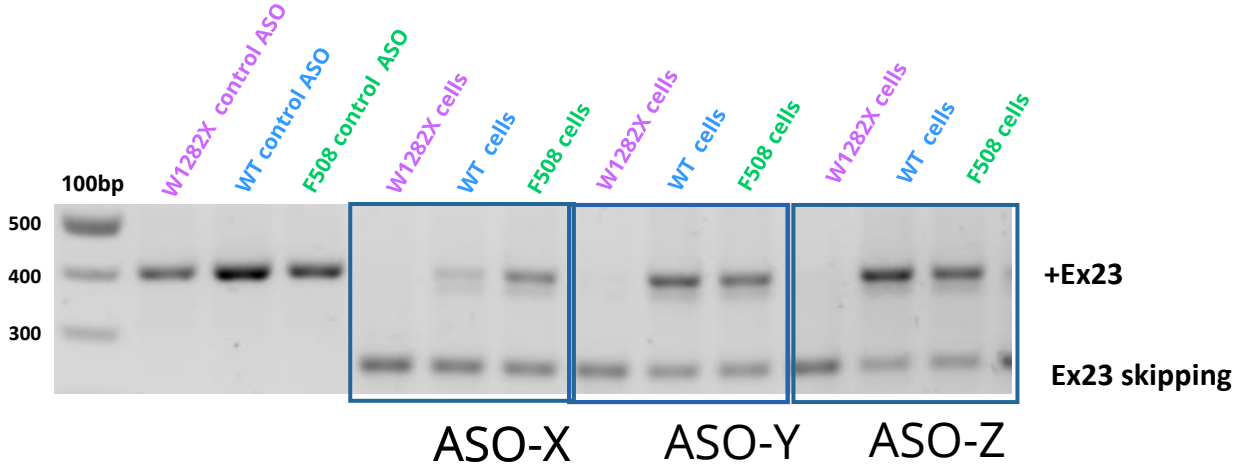


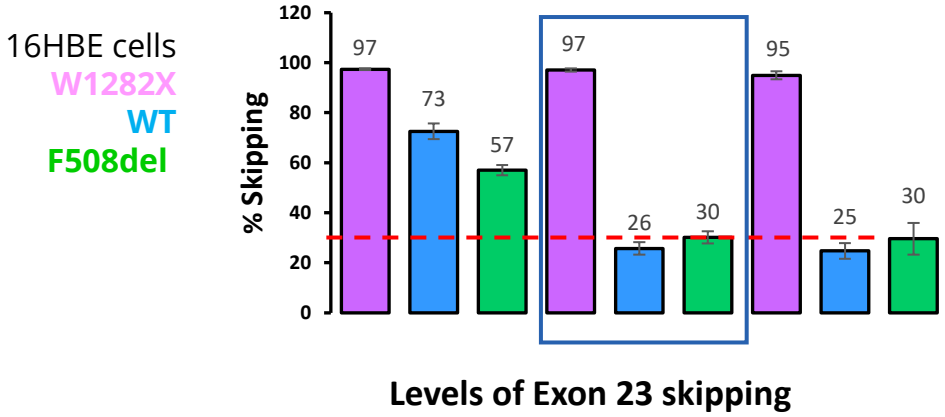


Significant levels of exon 23 deleted CFTR proteins following treatment with various ASOs

Specificity Analysis – RNA level

RT-PCR on 16HBE WT and F508del Cells

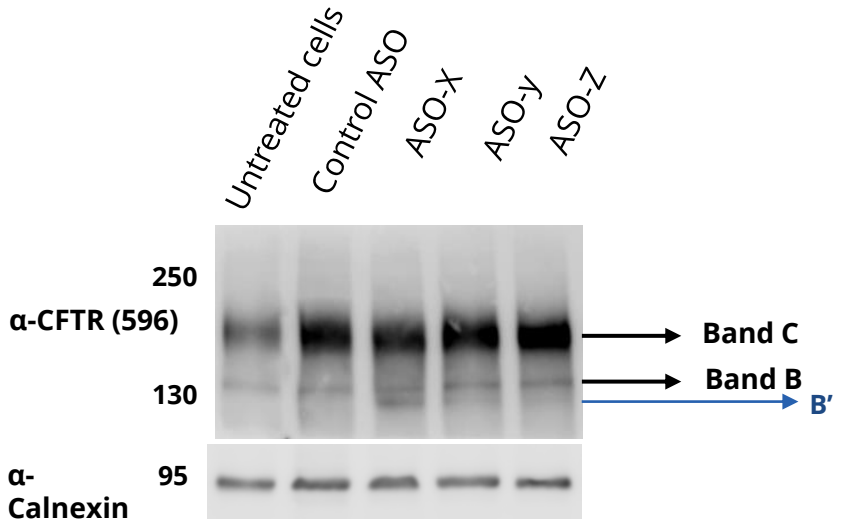




- Several ASOs show a low level of ASO skipping in WT and F508del cells (<30% exon skipping)

Specificity Analysis – CFTR Protein Level

Western Blot on 16HBE WT and F508del Cells



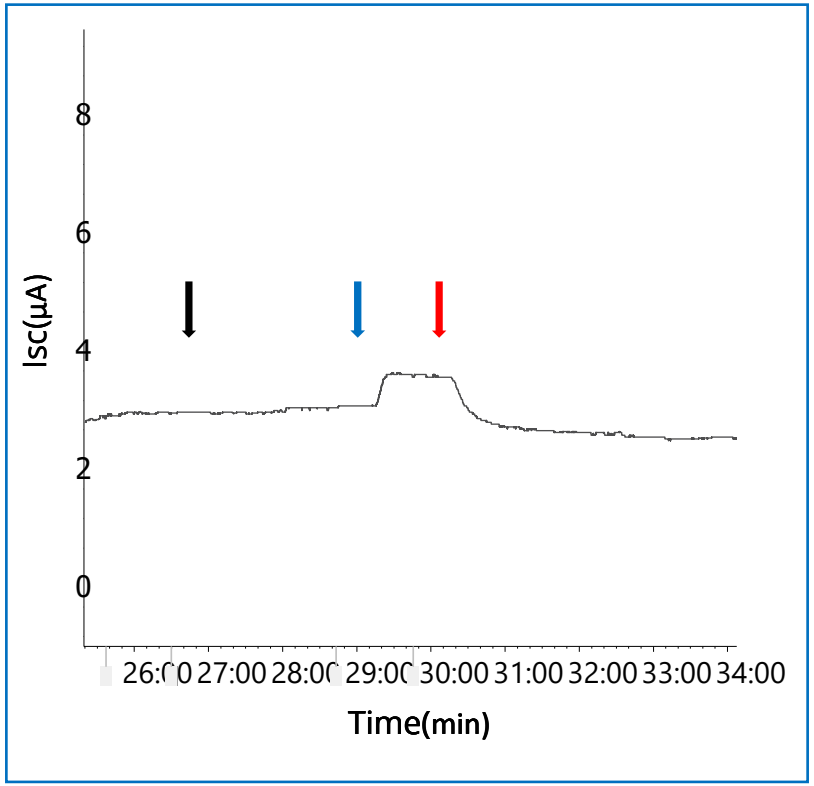
16HBE14o- WT

- The same ASOs that show a low level of ASO skipping in WT and F5508del cells, show specificity at the protein level

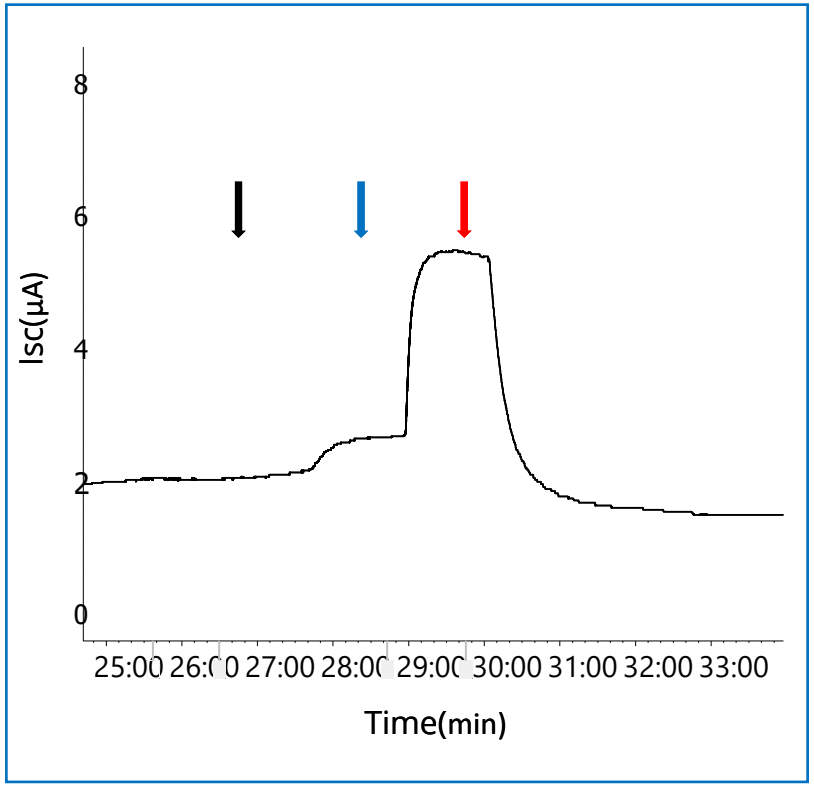
- These specific ASOs were further analyzed for their effect on the CFTR function (Ussing chamber measurements)

The Effect of SpliSense ASOs on the CFTR Function

Control ASO+Trikafta



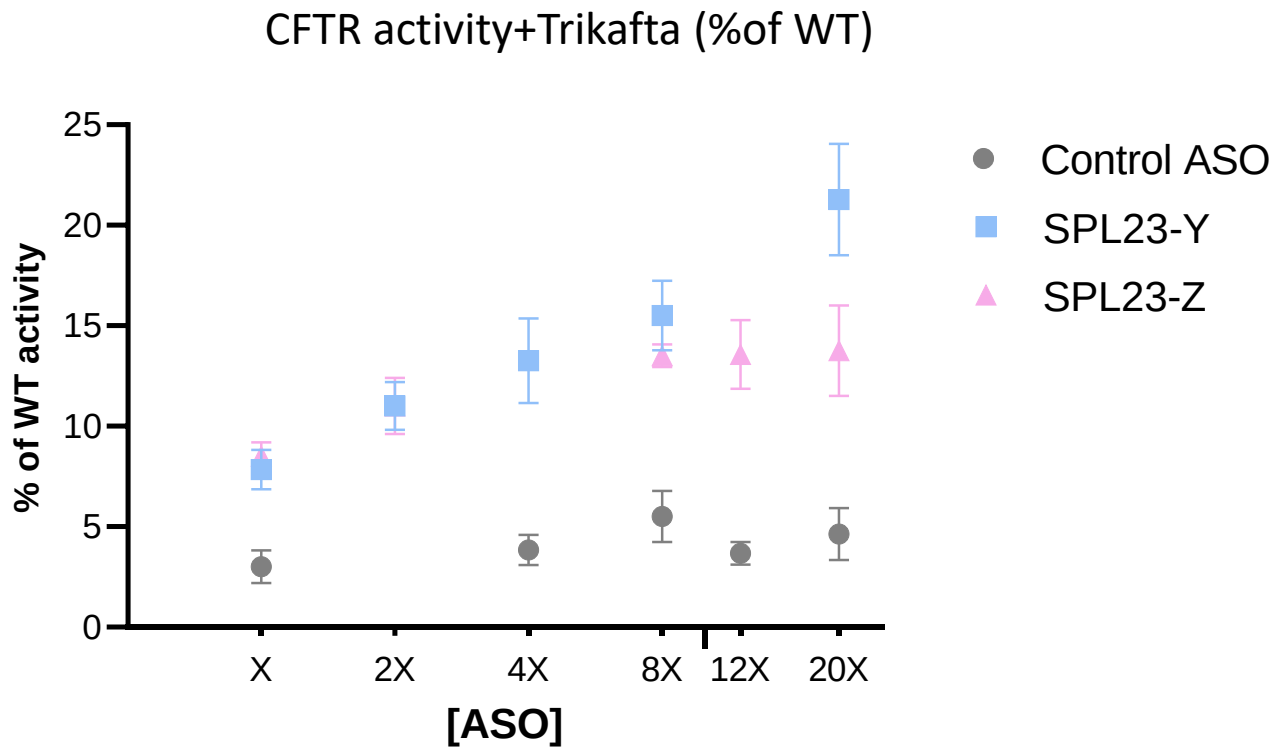
SPL23-Y+Trikafta



FSK(10μM)/IBMX(100μM)
VX770(10μM)
Inh172(10μM)

16HBEge W1282X

SpliSense ASOs for Exon 23 Skipping Restore CFTR Function in a Dose Dependent Manner



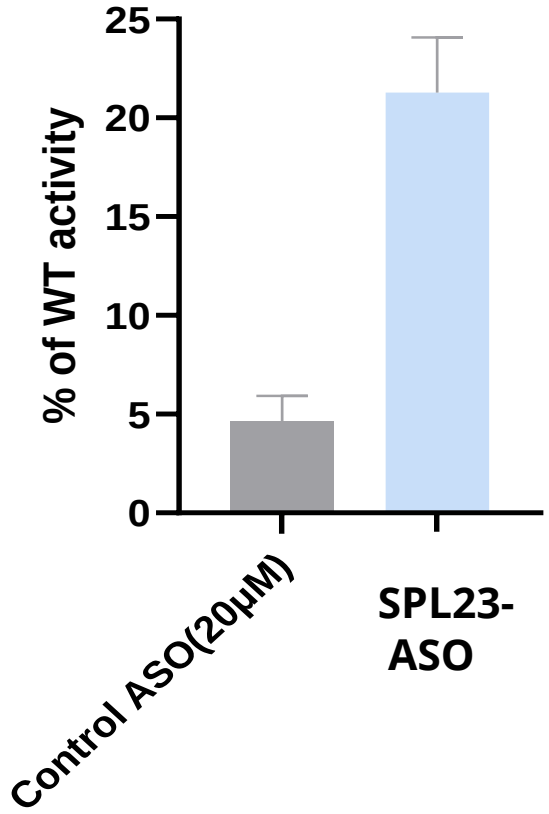
- CFTR activation following ASO treatment is dose dependent
- **The maximal activation reaches 21% of WT levels with ASO-Y**

CFTR Activation Following Treatment with SPL23-2 is Expected to be Greater on Primary Cells

Treatment of F508del cells with Orkambi® (VX-809+VX-770) leads to CFTR activation levels of:

- 2-3% of WT in 16HBEge
- Mean of 15% -25% of WT in primary cells (HNE/HBE) with high variability,

The effect of the ASOs on CFTR function in primary cells is expected to be significantly greater than the effect found in 16HBEge W1282X



Exon 23 Summary & Perspectives

Research

- Leads to high levels of exon 23 skipped CFTR transcripts and Proteins
- CFTR function (~21% of WT) in 16HBEge W1282X cells
- Equate to greater function in primary polarized epithelial cells.
- Valid backbone ASO structure
  - Lungs distribution and epithelial cells penetration

Clinical Dev.

- Phase 1-2 initiation H1 2023
- 3849 program paves the way for Exon 23 clinical program
  - 3849 ASO Toxicological data
  - 3849 “off the shelf” Nebulizer

Value Proposition

- Estimated program cost ~20M
- Unmet need
- Potential accelerated approval in 2024
- Aggressive market penetration with peak sales by 2029

SpliSense Team

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 General Manager of 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 and its role in the disease.

Efrat Ozeri-Galai PhD., MBA.
VP R&D
PHD Hebrew University of Jerusalem in CF genetics. Extensive experience in CF pre-clinical development.

Prof. Eitan Kerem MD
Executive Medical consultant
Head of the CF Center and Chief of the Pediatric Wing, Hadassah Medical Center.

Thank You!