RNA Based Platform for Pulmonary Diseases

Corporate Presentation // Sept 2023
NON-CONFIDENTIAL
Introducing SpliSense

Idea
>30 years of research (Prof. Kerem - Hebrew University)

2017
Company Foundation

2018-2022
R&D

2023
Technology Validation

Main Investors:

Total raised $24M
5 patent families FTO confirmed
Antisense Oligonucleotides – Modulating RNA (MoA)

11 Approved ASOs (2023)

Gene

Pre mRNA

Antisense Drug

**SpliSense: Three MoA strategies**

- **Decreasing** production of target proteins
- **Restoring** protein function
- **Modulating** RNA processing, (production of modified proteins)
Platform Technology for Precise Pulmonary Therapies

- Proprietary algorithms for splicing modulation, **ASOs** optimization
- Robust genetic understanding of **pulmonary diseases** & targets
- Lung focused **ASOs** screening & validation systems
- **ASO Combined inhaled delivery** system
## SpliSense’s Diverse Pulmonary ASOs Pipeline

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<th>INDICATION</th>
<th>APPROACH</th>
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<th>PRECLINICAL</th>
<th>IND ENABLING STUDIES</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<td><strong>Cystic Fibrosis</strong> (CF Foundation Support)</td>
<td>Restoration of Protein Function</td>
<td>SPL84 (3849 Mut.)</td>
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<td>H1 2024</td>
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<td>Production of Modified Protein</td>
<td>SPL23 (W1282X Mut.)</td>
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<td><strong>Muco-Obstructive Diseases</strong></td>
<td>Decrease Production of Over-expressed Protein</td>
<td>SPL5AC</td>
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<td>H1 2024</td>
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<td>COPD/Asthma/NCFB</td>
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<td><strong>IPF</strong></td>
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<td>SPL5B</td>
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SpliSense Tackles the Key Challenges of Lung Delivery

Galai and Friedman et al. 2023
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
- 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)
  - Negatively charged
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 Uniformly Distributes in NHPs Lungs Following Inhalation

- 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)

- 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’s ASOs Have Unique and Superior Properties for Lung Delivery

- **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
SPL84 - Phase 2 on Track
(Unmet 3849 CF Mutation)

Restores protein function
Cystic Fibrosis – Need for Novel Drugs for Unmet Mutations

- 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 unmet CF mutation**

**SpliSense (~$3B TAM)**

- F508del/F508del
- F508del/Other
- Other/Other

SPL84 ASO Phase 2 Study for 3849 CF Patients – On Track

✓ SPL84 proved to completely restore CFTR activity, potential cure
✓ SPL84 demonstrated promising safety profile following inhalation
  ✓ High safety margins above the nominal clinical doses ~40X
  ✓ In 9-week tox. studies in mice and monkeys the NOAEL was the highest administrated dose

✓ Phase 1 successfully completed
  ✓ SPL84 was safe and well tolerated, highest dose -160mg
  ✓ Very low systemic exposure; dose dependent

• Phase 2 semi-global study – Early 2024
  • High priority study as graded by TDN/ECFS Clinical Trial Network (CTN)
  • Weekly treatment
    • Nebulization time ~8 min
Expanding Our ASOs Technology From Orphan to Large Pulmonary Indications
Hyper Secreted Mucins (MUC5AC & MUC5B) are Heavily Involved in Pulmonary Diseases Progression and Severity
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.
Muco-Obstructive Diseases

MUC5AC Lowering ASO (SPL5AC)

Decrease production of over-expressed proteins
SPL5AC ASO for Muco – Obstructive Diseases
IND Enabling Phase - Program Overview

✓ 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)
  ✓ House Dust 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 early 2024
  • On top of SoC (optional)
SPL5AC ASO Reduces MUC5AC Levels in HVs
IL13 Hyper - Stimulated Bronchial Epithelial Cells (N=7)

**MUC5AC RNA levels**

- **NT**
- **IL13**
- **Dose Dep. SPL5AC +IL13**

**MUC5AC Protein levels**

- **NT**
- **IL13**
- **Dose Dep. SPL5AC +IL13**

**SPL5AC Dose dependent effect**
SPL5AC ASO Reduces Muc5ac Protein Levels in Lungs of IL13 Hyper-stimulated Mice Model

Levels of Muc5ac Protein plugs

Levels of Muc5ac Protein (IHC)

Saline | IL-13 | IL-13+SPL5AC
---|---|---
Saline | IL-13 | IL-13+SPL5AC

Levels of Muc5ac RNA (RT-PCR)
SPL5AC ASO Reduces Muc5ac Levels in Lungs of Asthma Disease Mouse Model (Ovalbumin)

OVA leads to very high levels of Muc5ac (x~300)

Levels of Muc5ac RNA (RT-PCR)

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<tr>
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<th>Naive</th>
<th>OVA</th>
<th>OVA+ SPL5AC</th>
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<tr>
<td></td>
<td>1</td>
<td>A1</td>
<td>A2</td>
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<td>2</td>
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50% reduction calculated by median
Idiopathic Pulmonary Fibrosis (IPF)
MUC5B Lowering ASO (SPL5B)

Decrease production of over-expressed proteins
Idiopathic Pulmonary Fibrosis (IPF)

- IPF is a progressive and fatal lung disease affecting older adults.
- Characterized by progressive lung fibrosis (scarring) and respiratory failure.
- The median survival after diagnosis is ~3–5 years.
- No effective treatment options.
- Pirfenidone® and Nintedanib® modestly slow IPF progression and have not been shown to alter the 3-5 year median survival after diagnosis.
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
  - On top of SoC (optional)
Muc5b Overexpression Enhances Lung Fibrosis in Mice

Overexpression of MUC5B in IPF leads to:
• Lung fibrosis (accumulation of collagen - Pink)
• Reduced mice survival

Muc5b was overexpressed in the distal airways

Schwartz et al. 2018

Hancock et al. 2018
SPL5B ASO Reduces MUC5B Levels in IL1β Hyper - Stimulated Human Bronchial Cells (HBEs)

SPL5B ASO Reduces MUC5B RNA & Protein in a dose dependent manner
SPL5B ASO Reduces MUC5B Levels in IPF^{SNP+} Patients Bronchial Cells

- 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 ASOs Approach: Platform Technology for Precise Pulmonary Therapies

- Robust inhalation approach
- Proper lung penetration & distribution
- Diverse pipeline, orphan & large unmet indications
- SPL84 clinical program ongoing, SPL5AC CTA/IND H1 2024 (estimated)
SpliSense is Seeking to Raise $50M

**Round C: $50M**

- CFF supports the development of SPL84 Phase 2 study + internals (~10M)
- SPL5AC – MUCAC lowering program; completion of Phase 2a (HVs and COPD/Asthma patients target engagement and PoC)- **19M**
- SPL5B- MUC5B lowering program; completion PoC IPF mice study, Phase 1b (HVs- target engagement and modulation)- **21M**

- SpliSense most recent round raised $22.5M at a post-money valuation of $28.5mm
- Funding will support the company until the end of 2025
  - Completion of 3 clinical studies; PoC
  - Potential acc./cond. approval for SPL84 CF program
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
Thank You!