AlveoGene

# Transforming Rare Respiratory Disease Outcomes Using Inhaled Gene Therapy

**May 2025**

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*AlveoGene is developing unique inhaled gene therapies for rare respiratory disease*

*These include:*

- *Surfactant protein deficiencies, SPB and ABCA3*
  *- $250m+ near term opportunity*
- *Alpha-1 Antitrypsin Deficiency Lung Disease*
  *- $2.5B+ mid term opportunity*
- *Idiopathic Pulmonary Fibrosis*
  *- $10B market in 2033*

# Introduction

- **InGenuiTy® platform combines efficacy, safety and long-term durability with the convenience of inhaled delivery**
- **The only vector platform capable of repeat re-dosing with no loss of efficacy, if required**
- **CMC and clinically de-risked, leveraging prior inhaled gene therapy deal for Cystic Fibrosis with Boehringer Ingelheim, now in clinical trials**
- **Compelling pre-clinical data supports clinical development of own product pipeline of first and best in class therapies**
- **Raising new £20m+ Series A financing to advance 4 programs, with $Bn commercial potential**

# AlveoGene Team

Internationally recognised and experienced expert founder team, combined with proven biotech success

## Management Team

### David Hipkiss[1]
**Executive Chair**

- Serial Life Science Entrepreneur
- >30 yrs experience
- >18 yrs as Chair/CEO/CBO
- Respiratory, Biologics, Vaccines, Devices, Combination Products
- Fund raising, scaling, strategy development and execution, VC Management, licencing, Exits

### Julien Cotta
**Acting CFO**

- Chartered Accountant
- >30 yrs experience as CFO of Private & Public Life Science Companies
- Fund Raising, IPO, M&A, Licensing corporate governance

## Founder Team

### Prof Eric Alton[1]
**Imperial College**

- Respiratory Physician with 30+ years experience in translational gene therapy
- Coordinator of UK Respiratory Gene Therapy Consortium
- Chair, UK Advanced Therapies Coordinating Group

### Prof Deborah Gill
**University of Oxford**

- 30+ years experience in respiratory gene therapy
- GMP manufacturing of clinical grade vector
- Project lead on gene therapy for surfactant deficiencies

### Dr Gerry McLachlan
**University of Edinburgh**

- 25 years experience in pre-clinical evaluation of safety and efficacy of lung-directed gene therapy protocols in sheep and pig models

### Prof Uta Griesenbach
**Imperial College**

- 25 yrs experience in ATMP translation research
- Toxicology and clinical assay development
- Non-Exec Director, Cell and Gene Therapy Catapult
- AVG-001 Project Lead

### Prof Stephen Hyde
**University of Oxford**

- 30 years experience in respiratory gene therapy
- PI/Co-PI on four respiratory gene therapy clinical trials
- Designed current rSIV.F/HN vector system & manufacturing process

### Dr Christopher Boyd
**University of Edinburgh**

- Molecular biologist with experience in vector gene expression & genotoxicity.
- IPF project lead.

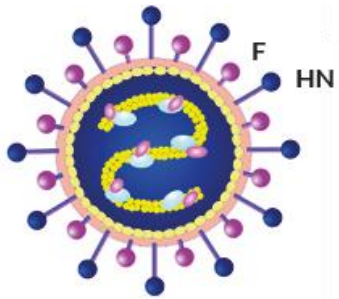
[1] AlveoGene Board Director

- **AlveoGene Team has proven experience in toxicology, CMC, device, regulatory, GMP manufacture and the undertaking of several Phase1/2A/2B clinical trials, coupled with strong financial discipline and proven commercial success**

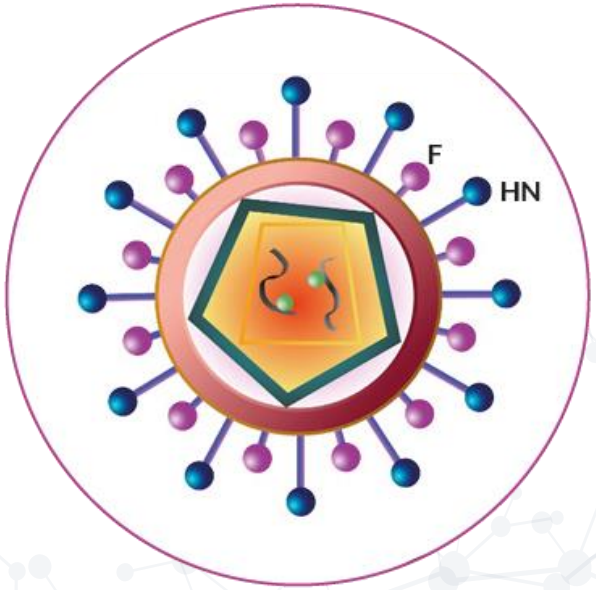
# InGenuiTy® Combines Efficiency, Durability & Localised Delivery

Efficiently delivering therapeutic proteins directly to the lung for maximum impact and patient benefit

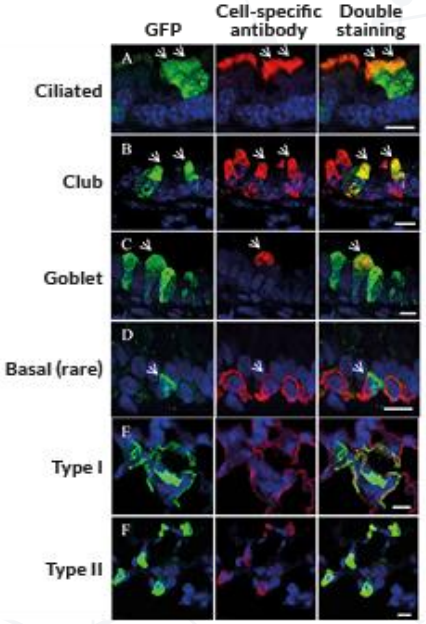
Sendai virus




**3rd Generation Lentivirus**




**InGenuiTy® Vector rSIV.F/HN Lentivirus**




**Highly Efficient & Agnostic Lung Cell Transduction**

**Neonate Instillation Delivery**

**Child / Teen / Adult Nebulisation Delivery**

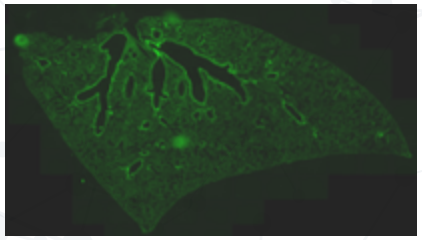
| Proven Safety Data | Long Term Durability | Unique Re-dosability | Large Payload Capacity | Scalable GMP Manufacture | Cost Effective | High Impact |
|---|---|---|---|---|---|---|
| ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

# InGenuiTy® Platform - Key Advantages

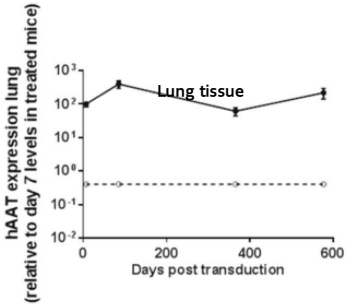
## Enabling first and best-in-class products for rare respiratory diseases

- **Efficient transduction of lung epithelial cells**[a]
  - Takes advantage of Sendai virus surface proteins which are tropic for lung cell entry
- **Long duration of expression using AlveoGene's proprietary promoter**[b]
  - Stable integration of transgene into target cell genome
  - Current trajectory consistent with single dose offering potential life-long protection
- **Benign safety profile**
  - Proven long-term safety data in rodent and higher mammal lungs
  - Risk of oncogenesis mitigated by design and deletion of 3'-LTR U3 element from vector
- **Large transgene packaging capacity**
  - Pragmatic InGenuiTy® packaging capacity of ~10kb to enable CMC (PMID: 11589831, 34095341)
  - More than double that of AAV facilitates multiple respiratory indications (strict physical AAV packaging constraint 4.7kb)
- **Efficacy maintained after repeated administration, if required**[c]
  - Ad and AAV vector efficacy lost after ≥2 repeated doses in lung (PMID: 10545523, 17855531)
  - Uniquely, InGenuiTy® vector efficacy maintained after ≥3 repeated doses to lung (PMID:20332767, 22955314)
- **GMP production already demonstrated at leading CDMO**
  - Provides core risk mitigation for future supply for first-in-human trials and beyond
  - 4 of 5 plasmids used in vector production common to all indications mitigating CMC risk and cost

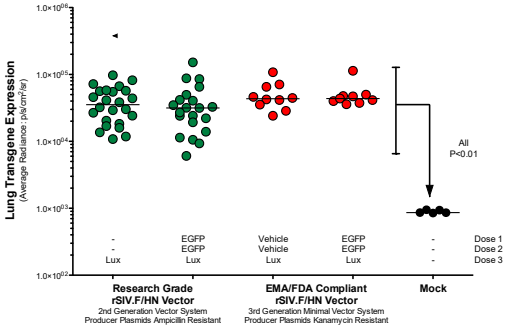
*(a) Transduction shown in Mice, Rats, Ferrets, Sheep, Piglets, NHP & ex-vivo Human Lungs*



*(b) rSIV.F/HN duration of hAAT gene expression for life of mouse*




*(c) rSIV.F/HN Efficacy maintained after > 3 doses*



# InGenuiTy® enabled Cystic Fibrosis indication is now in clinic with BI

## Provides significant forward mitigation for AlveoGene future product developments

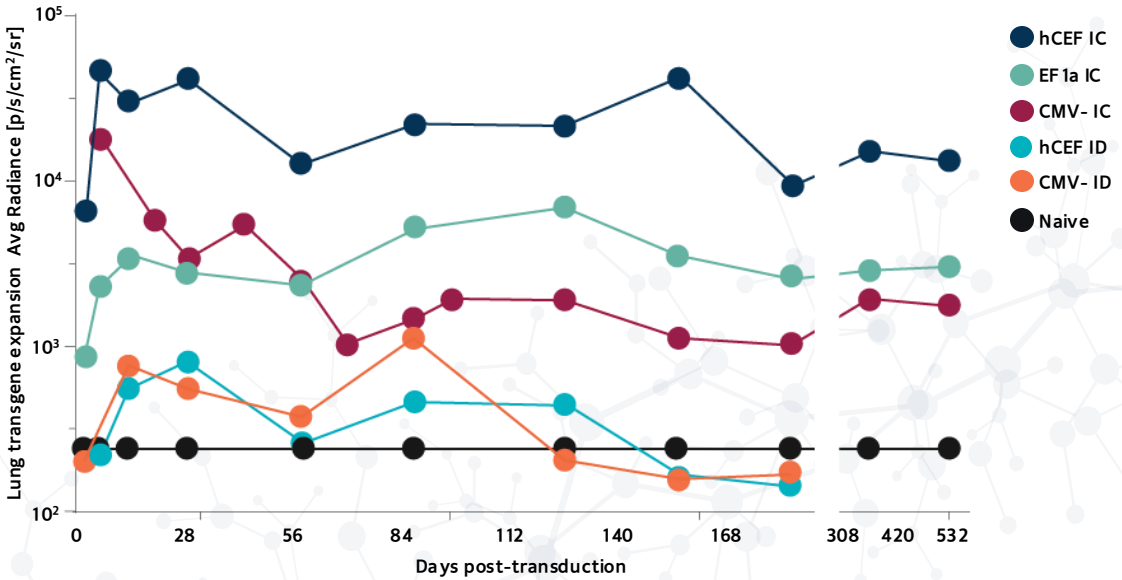
~£50m historic funding secured to develop the platform

UK Respiratory Gene Therapy Consortium

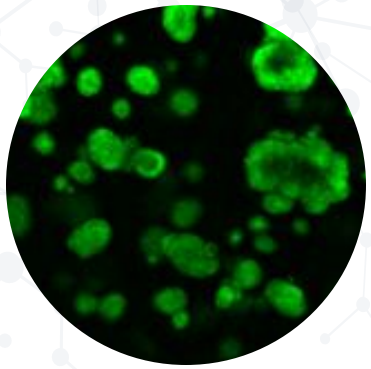
Major tripartite deal[1] signed to take CFTR product to clinic

*Note*
*[1] BI have IP rights to use of CFTR transgene only*

- Optimal hCEF-IC promoter/enhancer identified




- CFTR function demonstrated



CF

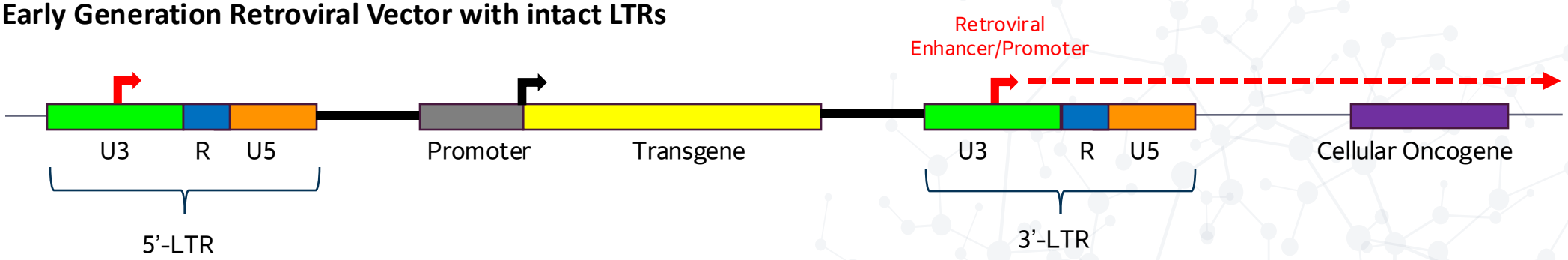
CF + CFTR Vector

- InGenuiTy® enables the ability to tune and control the magnitude and durability of effect
- hCEF-IC promoter/enhancer has already been proven in clinical trials; also currently being used in BI Lenticlair™ trial

# Lentiviral vectors & potential oncogenesis; solved with InGenuiTy®

## InGenuiTy® self-inactivating (SIN) vectors are safer as genotoxic LTR promoter/enhancers have been deleted

**A: Early Generation Retroviral Vector with intact LTRs**




**B: InGenuiTy® 3rd Generation Self-Inactivating (SIN) Vector**

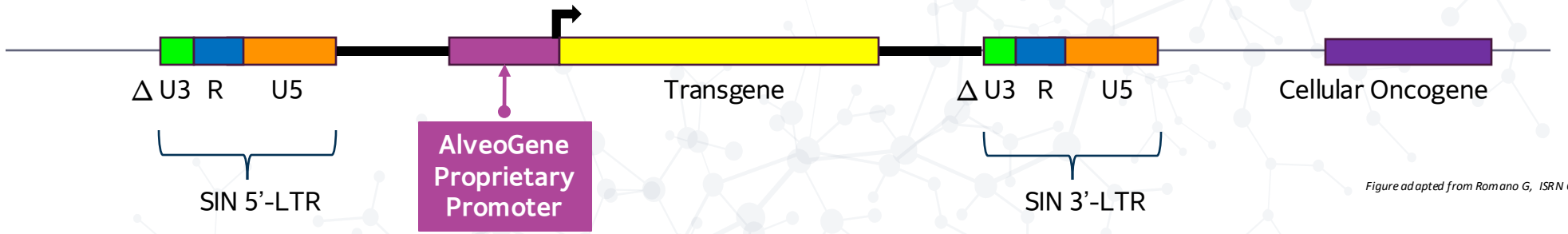


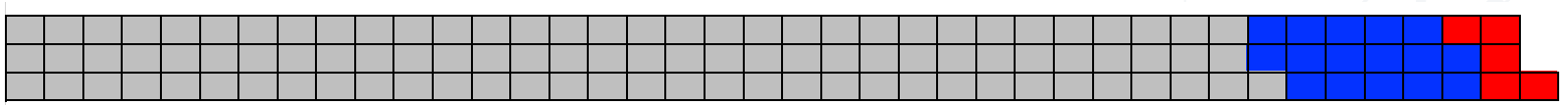

*Figure adapted from Romano G, ISRN Oncol 2012:616310*

- Long terminal repeats (LTRs) are identical sequences at each end of an integrated retrovirus genome
- Promoter/enhancer activity in early retroviral vectors from intact 3'-LTR U3 element may activate a cellular oncogene
- Deletion of a significant portion of the U3 element ablates the LTR-initiated genotoxic effect
- Key and innate in-built safety feature of InGenuiTy® vector and AlveoGene product design
- Positive support from regulators for new lentiviral therapies e.g. FDA approval of Orchard Therapeutics Lenmeldy™

# Lentiviral vectors & potential oncogenesis; the actual data

## InGenuiTy® self-inactivating (SIN) vectors are safer as genotoxic LTR promoter/enhancers have been deleted

- Legacy Gamma-retrovirus (Non-SIN)

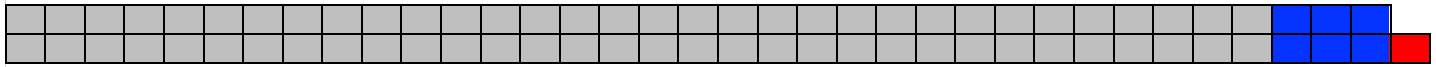


97 Negative
16 Cases
5 Deaths

118 patients

- **Strong LTR-derived promoter/enhancer *included***

- Bluebird Bio (CALD Trial Only)

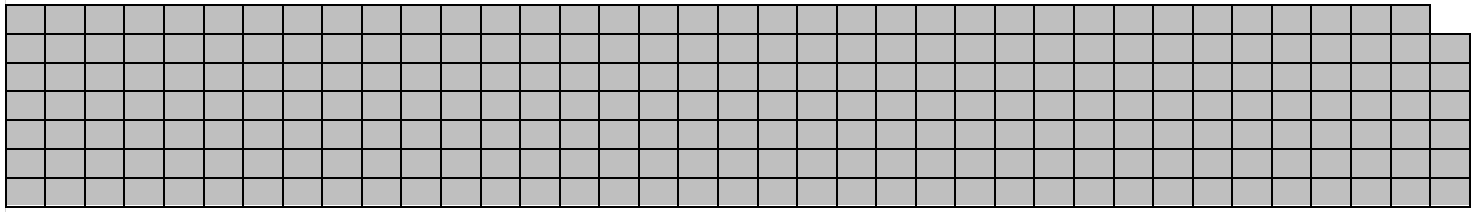


60 Negative
6 Cases
1 Deaths

67 patients

- **Strong LTR-derived promoter/enhancer *included***

- 3rd Generation SIN Lentiviral Vectors such as InGenuiTy®



258 Negative
Cases
Deaths

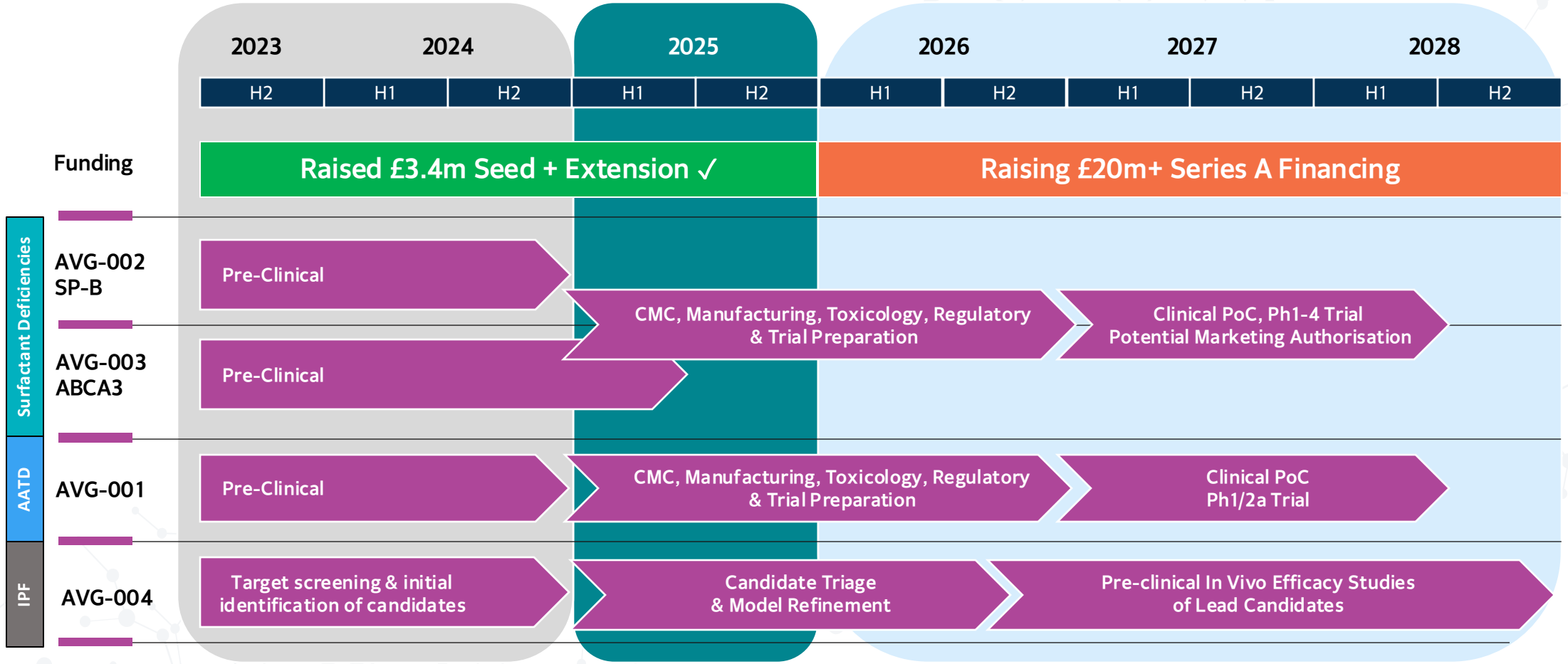
258 patients

- **Strong LTR-derived promoter/enhancers *deleted***

**Zero incidence of oncogenesis with 3rd Generation SIN lentiviral vectors like InGenuiTy®**

# AlveoGene - Near Term Plan

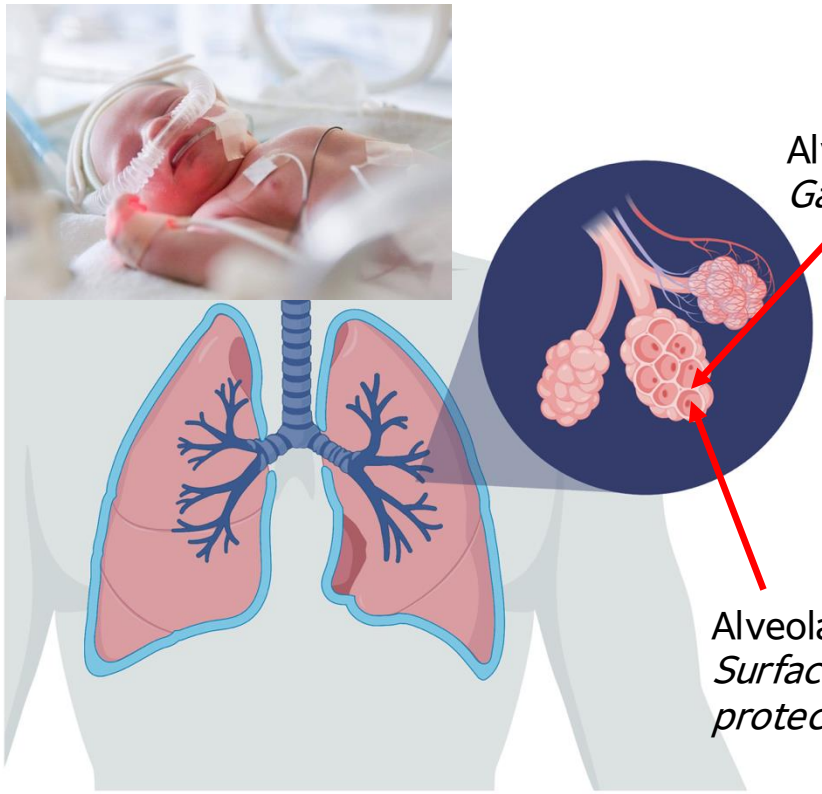
## Relentless focus on achieving accelerated clinical success to maximise value inflection in <3 yrs




- **>£50m in non-dilutive funding secured to date to develop platform prior to AlveoGene formation in July 2023**

# AVG-002 & AVG-003 - Surfactant Protein Deficiencies SP-B & ABCA3

A critical unmet need exists for these full-term neonatal patients with ultra rare disease




- SP-B & ABCA3 proteins are fundamental to the ATII cell surfactant metabolic pathway and secretion
- SP-B and ABCA3 genetic deficiencies present clinically at birth as respiratory distress syndrome (RDS)
- These full-term neonates cannot breathe spontaneously
- Initially supported by mechanical ventilation for short period, genetic screening then undertaken
- But once genetic diagnosis confirmed, ventilation is usually withdrawn as no treatment options exist
- Children die within first few weeks of life

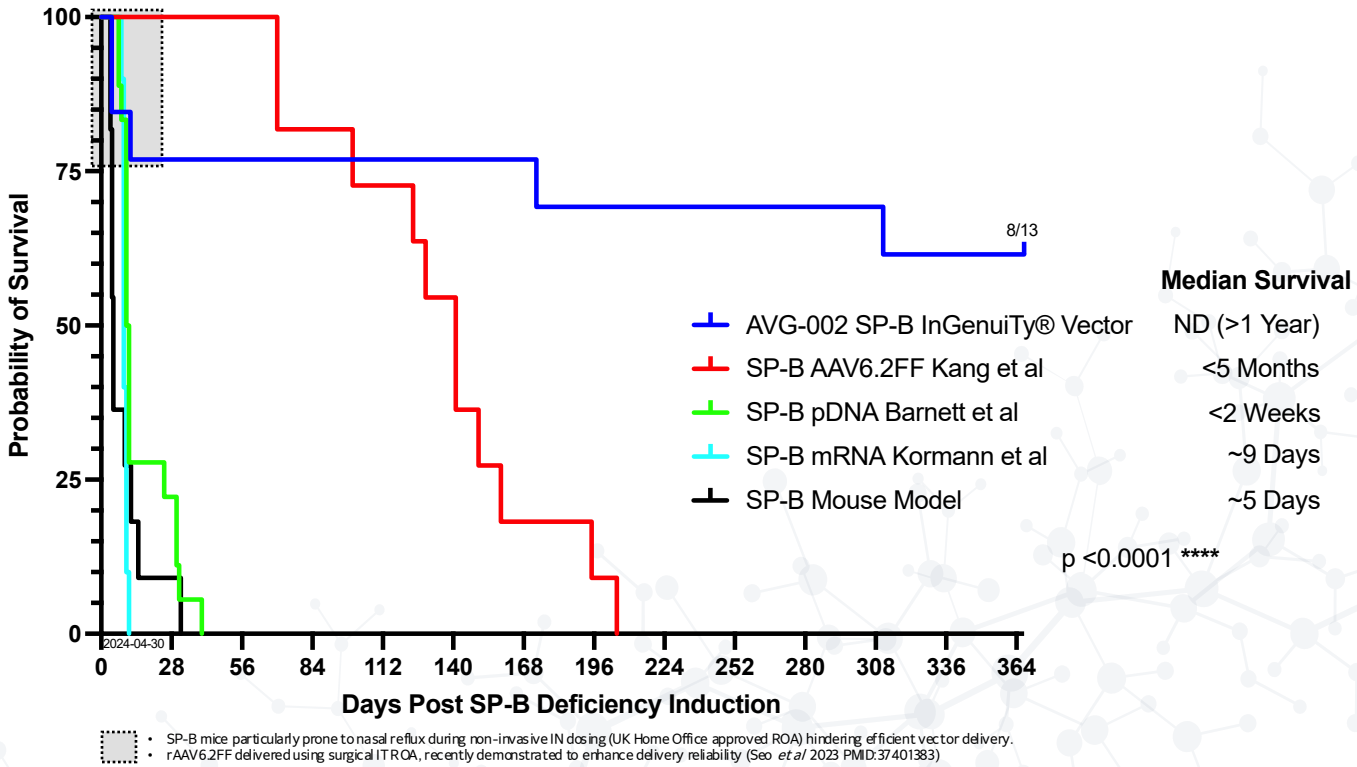
**One year survival for the severe population is ZERO**

**AlveoGene's '*Vial-to-Child*' approach will enable diagnosis to gene therapy treatment within 4 weeks of birth**

# AVG-002 - Model Confirms Life Saving Potential in Lethal SP-B

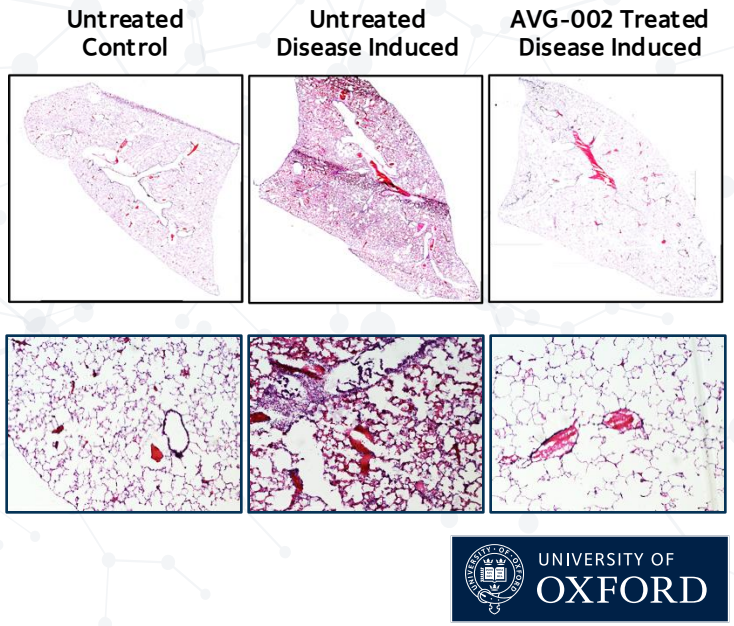
## Clear superiority demonstrated offering potential for lifelong treatment from a single dose

**World Leading Data**




- SP-B mice particularly prone to nasal reflux during non-invasive IN dosing (UK Home Office approved ROA) hindering efficient vector delivery.
- rAAV6.2FF delivered using surgical IT ROA, recently demonstrated to enhance delivery reliability (Seo *et al* 2023 PMID:37401383)

**SP-B Knock-out Mice Histology**




UNIVERSITY OF OXFORD

- Paediatric Rare Disease Designation granted from FDA enabling subsequent award of Priority Review Voucher (PRV)
- Orphan Drug Designation also granted
- AVG-003 for ABCA3 deficiency being developed at pace; only possible with InGenuiTy® vector
- Data evidences core platform translatability and key advantages over other delivery methods independent of indication

# AVG-002 & AVG-003 - Surfactant Protein Deficiencies SP-B & ABCA3

A compelling business case supports rapid clinical development and marketing authorisation in <3 yrs

## Current SoC

No therapeutic options exist

## Future SoC

Potential single dose administration of AVG-002 or AVG-003

## Prevalence EU & US

SP-B Lethal: 10 pa
ABCA3 Lethal: 30-50 pa

Upside from awareness and increased genetic testing & non-lethal ABCA3 label

**AVG-002 & AVG-003 have the potential to be the only disease modifying options for neonates with lethal SP-B or ABCA3 deficiency**

**Estimated base annual revenues > $250m**

**2 x Potential Priority Review Vouchers (PRV)**
**~$150m tradable value potential per product**

**Orphan Drug Disease Designation Assured**

**~ $27m to Market Authorisations with potential approval in < 3 years**

1. Subject to US PRDD / PRV legislation being renewed
2. Conservative basis used to calculate annual revenues:
   Lower base prevalence, lower WTP QALY pricing, higher QALY discount rates, and additional macro NICE discount as exemplar
3. Revenues represent combination sales of AVG-002 and AVG-003

## Outline Clinical Design

Dosing Method informed from in vivo Piglet Studies
(Roslin Institute, UK)

*'Basket Trial' for SP-B and ABCA3*
n = 1-10

*'Instantaneous read out'*

## CMC

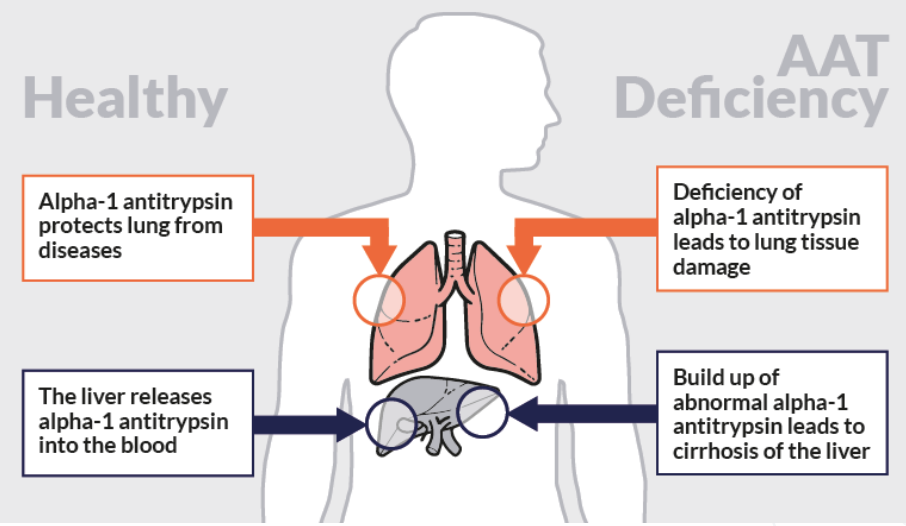
Leverages existing knowledge

1x 200L batch per year per product for global supply needs

Simple
Product to Patient Pathway
*'Vial-to-Child'*

# AVG-001 - Alpha-1 Antitrypsin Deficiency (AATD) Lung Disease

## AATD lung disease combines an important unmet clinical need with large & growing patient numbers




| Lung Index Cases | Liver Index Cases |
|---|---|
| 80% | 20% |

- Most prevalent in Europe and North America with Z and S mutations in 95% of affected individuals
- Global number of ZZ, SZ or SS genotype est. at 3.4 million
- AlveoGene's initial target are severe genotypes null/null, Z/null & Z/Z where AATD lung disease in dominant
- Only 10% of with severe AAT disease patients have been diagnosed to date
- Significant upside in COPD where 10% of GOLD II patients have AATD Lung Disease

- AATD caused by mutations in the SERPINA1 gene leads to deficiency or dysfunction of the AAT protein.
- AAT produced in the liver has a crucial role protecting lungs from damage from enzymes like neutrophil elastase.

**Therapies targeting the liver likely do not impact lung function**

**KOLs agree; liver transplant has little or no effect**

**AVG-001 treats the lung directly and topically**

**Triggers potential long term local production of hAAT**

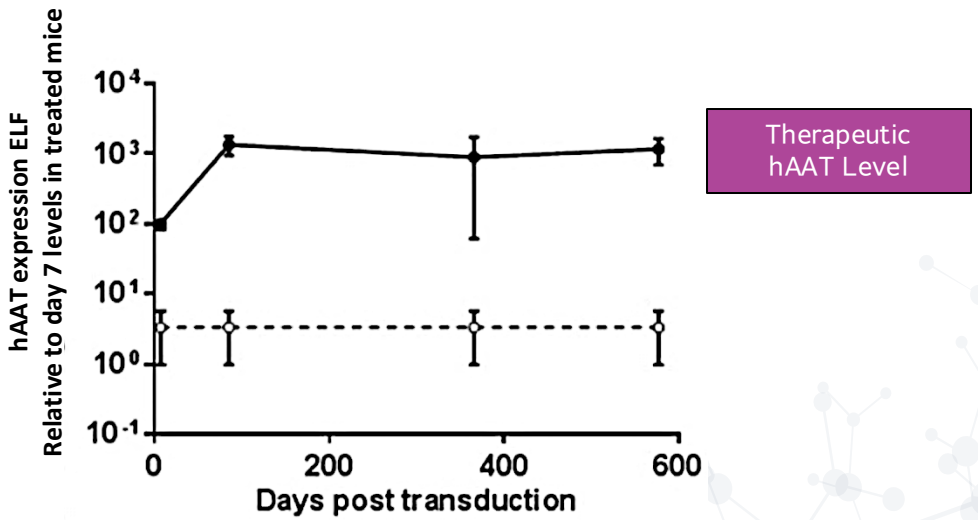
**High impact on lung function**

**Benefits majority of AATD patients**

# AVG-001 –Therapeutic hAAT Expression & Market Leading Durability

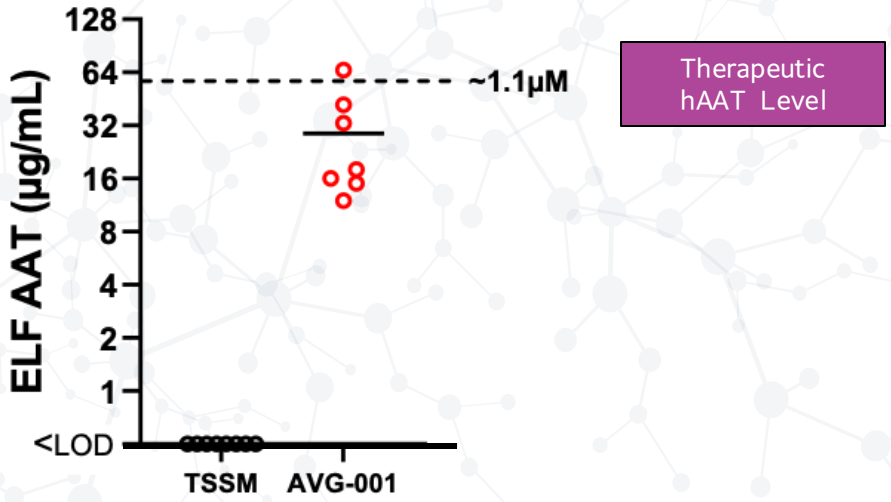
Market leading data in murine & NHP models with hAAT measured directly in epithelial lung fluid (ELF)

**2 Year Durability in murine ELF**




Therapeutic hAAT Level

**NHP 28 Day Expression in NHP ELF**

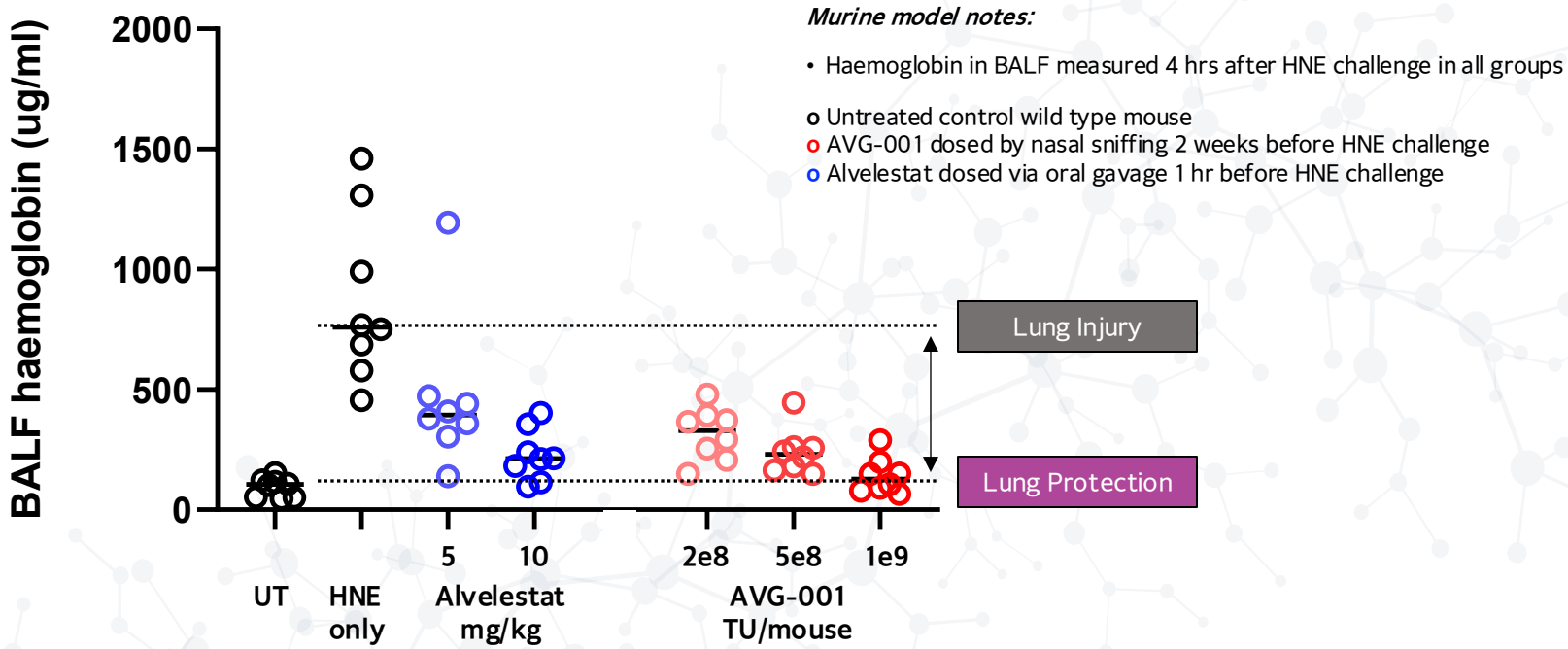



Therapeutic hAAT Level

- Recirculating levels of hAAT measured in serum may not be indicative of improvements in lung health and function
- Therapeutic hAAT expression levels in murine ELF evidences unprecedented durability of AVG-001 for 2 years
- Therapeutic hAAT expression levels in NHP ELF at 7 days & remarkably maintained at 28 days, despite no immunosuppression
- No safety or tox issues seen in NHP studies, reflecting prior product development experience in Cystic Fibrosis

# AVG-001 – HNE Challenge Model Evidences Long Term Protection

## Protective response to exogenous HNE challenge as good as oral daily dosed HNEI[1] Phase 2 candidate Alvelestat[2]

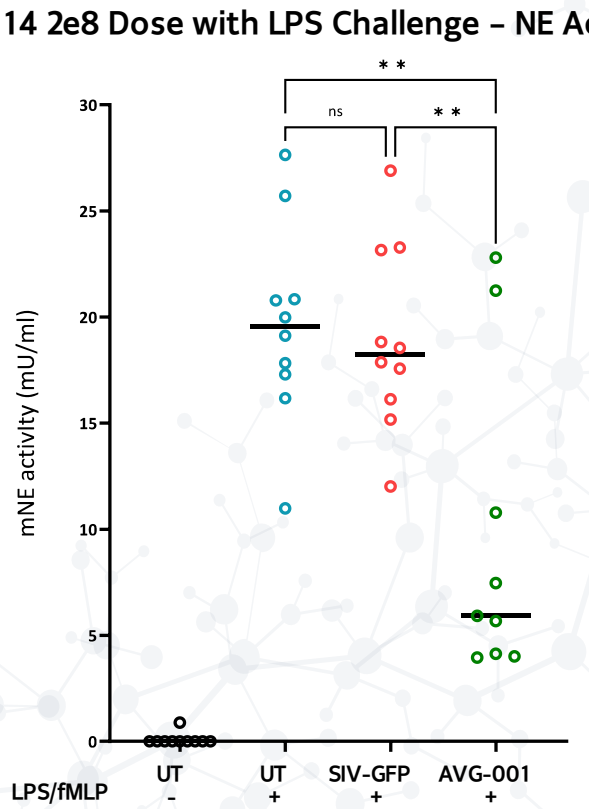



- Only AlveoGene reports in-vivo lung challenge data to evidence function in a commercially relevant model
- Protective response of single low dose AVG-001 to HNE challenge is as good as oral daily dosed HNEI P2 candidate Alvelestat
- AVG-001 will not suffer from program limiting dose related side effects associated with Alvelestat
- FDA Phase 2 guidance given to Mereo provides clear pathway to marketing authorisation for AlveoGene

*Notes:*
1. HNEI = Human Neutrophil Elastase Inhibitor
2. Alvelestat owned by Mereo Plc, UK

# AVG-001 – LPS/fMLP Challenge Shows Neutrophil Elastase Inhibition

## In-vivo functional inhibition of endogenous murine neutrophil elastase supports efficacy in a 2nd lung injury model




- Data confirms ability of AVG-001 to inhibit function of endogenous neutrophil elastase in-vivo

**Market leading durability, in-vivo HNE & LPS/fMLP challenge data support forward clinical development of AVG-001 as the preferred product for AATD Lung Disease**

# AVG-001 - Alpha-1 Antitrypsin Deficiency (AATD) Lung Disease

A compelling business case for development of a novel lung targeted product with maximal impact on disease

## Prevalence

Global number of ZZ, SZ or SS genotype est. at 3.4 million

200,000+
have severe disease

## Current SoC

Weekly IV
protein replacement

## Future SoC

Single administration of AVG-001 via nebulisation
Occasional top up dosing, if required

AVG-001 has a compelling development case to replace weekly IV protein infusion with inhaled gene therapy

AVG-001 to be developed as a potential single inhaled dose affecting direct production of AAT in the lungs combining efficacy, safety, convenience and durability

Orphan Drug Disease Designation Assured

Estimated base annual revenues of $500m rising to $2.5Bn over time with increased diagnosis and awareness of new treatment option

Additional upside in COPD
(estimated 10% of COPD GOLD II patients have AATD lung disease)

## Outline Clinical Design

Phase 1/2 Trial
n=3+3+3, then 9 v 9

Primary Outcome: Safety

Secondary Outcomes:
Changes in AAT in epithelial lining fluid, FDA suggested surrogate biomarkers, SGRQ, $FEV_1$, CT Lung Density

## CMC

Leverages existing knowledge

3x 200L batch sufficient to meet clinical trial supply

# AVG-001 – Ideal Targeted Product for AATD Pathology in the Lung

## Deliver InGenuiTy® enabled products directly to lung where its impact on disease & for patients is the greatest

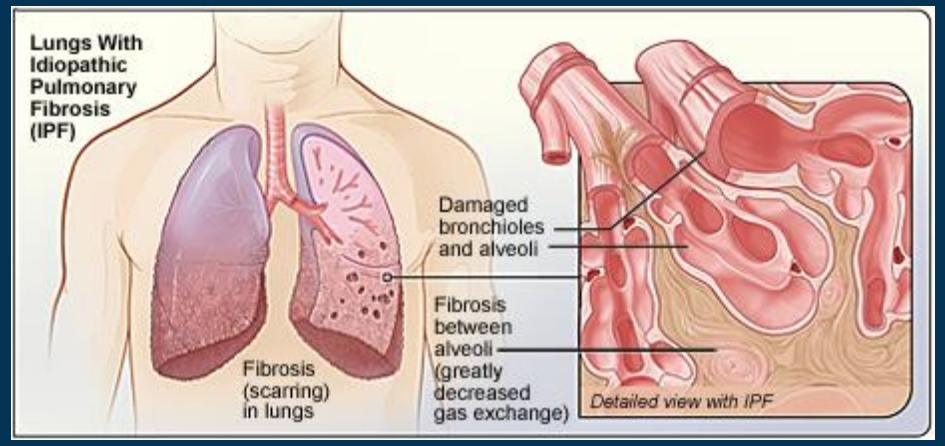
| Company | Clinical Target Organ | Site of hAAT Production | Platform and Administration Method | Frequency of Administration | Lung Efficacy | Safety Considerations | Summary |
|---|---|---|---|---|---|---|---|
| Grifols, Kamada, Inhibrx (SoC) | Lung | N/A | Protein Replacement, IV or Inhaled | Frequent (Weekly, tri-weekly) | Some | Good | + - - |
| Wave, Korro, AIRNA | Lung, Liver | Liver | RNAi, Sub-Q | Very frequent | Unknown | Off target issues? | - - - |
| Intellia, Beam (Withdrawn) | Lung, Liver | Liver | CRISPR / Base editing, IV | Infrequent ? (Unknown) | Unknown | Off target Issues? | - - - |
| Mereo, Vertex (On-Hold) (Withdrawn) | Lung, Liver | N/A, Liver | Small Molecule, Oral | Very frequent | Some, Unknown | Dose-related toxicity | - - - |
| Krystal, 4DMT | Lung | Lung | HSV / AAV, Inhaled | Frequent (Bi-weekly if possible) | Some | Inflammation? Tox? | + - - |
| **AlveoGene** | **Lung** | **Lung** | **InGenuiTy® 3G Lentivirus, Inhaled** | **Infrequent & Re-dosable** | **High (murine)** | **Good** | **+ + +** |

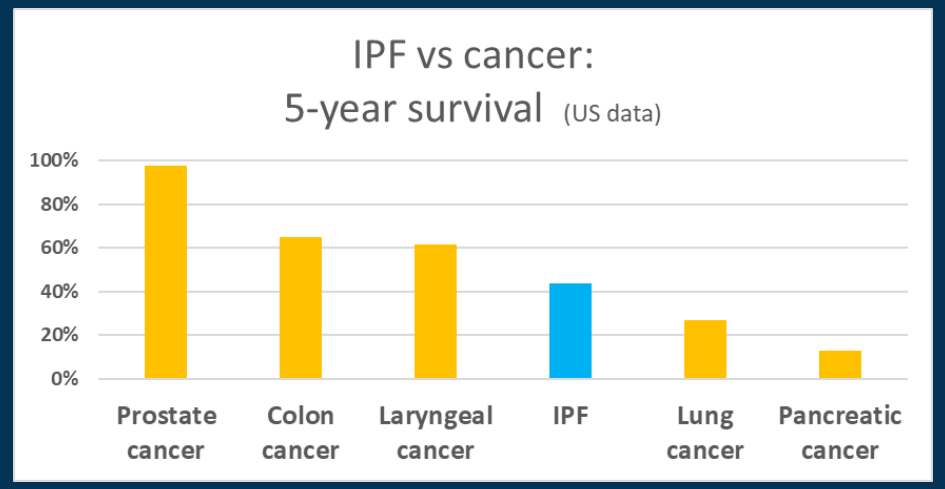
- Recombinant protein IV candidate therapies may only marginally improve standard of care over plasma derived weekly IV infusions
- Oral and RNA products require frequent dosing and have associated dose and AE based limitations
- Base & Gene Editing approaches very early; likely frequent dosing, off target issues, and unknown lung efficacy and durability
- All other viral vector approaches with regards to efficacy and durability are inferior to InGenuiTy®
- InGenuiTy® remains the only vector system that can be safely and reliably re-dosed to the lung with no loss of efficacy

**AlveoGene's InGenuiTy® approach is the ideal solution to treat AATD pathogenesis in the lung**

# AVG-004 - Idiopathic Pulmonary Fibrosis (IPF)

## IPF gene therapy opportunity addresses unmet clinical need in increasingly prevalent life-threatening disease

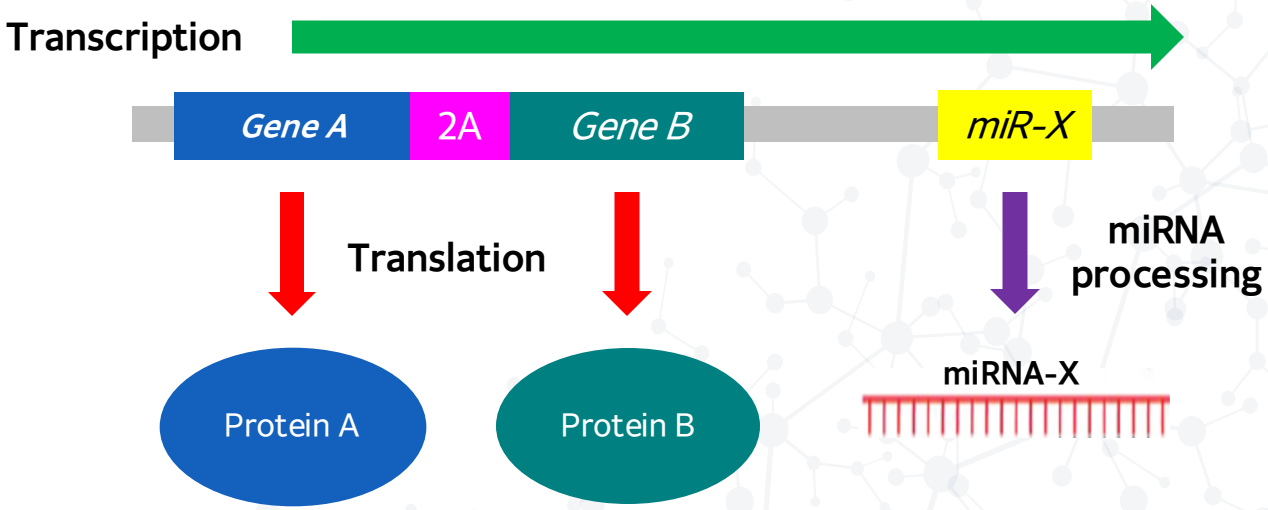



- The global IPF market in 2024 is estimated at $4.60B, and is expected to grow by ~7% pa
- IPF is a fatal, nongenetic, progressive lung condition resulting in cumulative lung scarring & affecting ~3 million people worldwide
- The US and EU have more than 300,000 IPF cases, and incidence is rising significantly as the population ages coupled with post COVID effects
- Post-diagnosis life expectancy is only 3-5 years
- Standard-of-care conventional drugs slow, but do not arrest, disease progression, with lung transplantation is presently the only effective treatment for end stage IPF, but organ supply is extremely limited
- AVG-004's goal is to deliver transformative outcomes through inhibiting profibrotic pathways and enhancing antifibrotic targets by leveraging the high cloning capacity and long-lasting expression properties of InGenuiTy®

# AVG-004 - Multiplexing genes for combination therapy in IPF

## Gene-based combination therapy for complex diseases will provide better outcomes with fewer adverse effects




- Combination therapies provide more effective treatment in several complex diseases including respiratory[1]
- However, combining conventional drugs often causes adverse drug interactions and combined side effects
- Gene-based combination therapies using a single vector can minimize such adverse effects
- AlveoGene is developing InGenuiTy®-enabled own products capable of expressing multiple therapeutic genes and RNAs for treating conditions such as IPF directly in the lung
- Additional potential in oncology

[1] "Combination drug therapy is widely used across a range of diseases, including **cancer**, **pulmonary hypertension**, **asthma**, and **diabetes**, to enhance efficacy and improve outcomes."
Toby Maher (2018) Am J Respir Crit Care Med, 197, 283-284

*AlveoGene is developing unique inhaled gene therapies for rare respiratory disease*

*These include:*

- *Surfactant protein deficiencies, SPB and ABCA3*
  *- $250m+ near term opportunity*
- *Alpha-1 Antitrypsin Deficiency Lung Disease*
  *- $2.5B+ mid term opportunity*
- *Idiopathic Pulmonary Fibrosis*
  *- $10B market in 2033*

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AlveoGene

# Summary

- **InGenuiTy® platform combines efficacy, safety and long-term durability with the convenience of inhaled delivery**
- **The only vector platform capable of repeat re-dosing with no loss of efficacy, if required**
- **CMC and clinically de-risked, leveraging prior inhaled gene therapy deal for Cystic Fibrosis with Boehringer Ingelheim, now in clinical trials**
- **Compelling pre-clinical data supports clinical development of own product pipeline of first and best in class therapies**
- **Raising new £20m+ Series A financing to advance 4 programs, with $Bn commercial potential**