Delivery of SP-101 restores CFTR function in human CF airway epithelial cultures and drives hCFTRΔR transgene expression in the airways of ferrets

**SP-101 – A novel, inhaled gene therapy to treat CF**

**Design Features**
- AAV capsid selected for tropism to the apical surface of human airway epithelia (HAE)
- hCFTRΔR minigene with regulatory elements

**Mechanism of Action**
- Efficient apical entry
- Enhanced SP-101 translocation to the nucleus by co-administration with doxorubicin (Dox)
- Increased CFTR expression

**SP-101 is tropic to and corrects human CF airway epithelia**

**Ferrets as a model to evaluate inhaled SP-101**

- CF ferret model recapitulates human CF lung pathology
- Ability to administer via inhalation

**Methods**
Ferrets were exposed to SP-101 or diluent followed by doxorubicin or diluent on a platform system connected to a mesh respirator. Animals were sacrificed 2 or 12 weeks post-exposure and tissues harvested for in situ hybridization (ISH) or copies of hCFTRΔR mRNA. ISH: Sections from formalin-fixed paraffin-embedded lung were evaluated by RNAscope hybridization (ISH) or copies of hCFTRΔR mRNA. ISH: Sections from formalin-fixed paraffin-embedded lung were evaluated by RNAscope (data not shown). Data are shown as box and whisker plots around the median value.

**Non-CF ferrets**

- No signal was observed in the absence of reverse transcriptase indicating the complete removal of vector genomes (data not shown).

**CF and non-CF ferrets**

- Doxorubicin increases hCFTRΔR mRNA expression >10 fold and is durable in ferret lungs.

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**REFERENCES**