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

Katherine Excoffon, PhD

ECFS Conference 2023

Presenter Disclosure

Katherine Excoffon, PhD, VP of Research, Spirovant Sciences, Inc.

Disclaimer

THIS PRESENTATION IS PROVIDED “AS IS”, WITHOUT WARRANTIES OR REPRESENTATIONS OF ANY KIND, EITHER EXPRESSED, IMPLIED OR STATUTORY, INCLUDING, BUT NOT LIMITED TO, THE IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR NON-INFRINGEMENT. YOUR USE OF THIS PRESENTATION IS AT YOUR SOLE RISK.

FURTHER, CERTAIN INFORMATION SET FORTH IN THIS PRESENTATION MAY CONTAIN FORWARD-LOOKING STATEMENTS, INCLUDING BUT NOT LIMITED TO, STATEMENTS REGARDING THE DEVELOPMENT OF THE COMPANY’S LEAD ASSET, SP-101. THESE STATEMENTS ARE NOT GUARANTEES OF FUTURE PERFORMANCE AND UNDUE RELIANCE SHOULD NOT BE PLACED ON THEM. SUCH FORWARD-LOOKING STATEMENTS NECESSARILY INVOLVE KNOWN AND UNKNOWN RISKS AND UNCERTAINTIES, WHICH MAY CAUSE ACTUAL PERFORMANCE IN FUTURE PERIODS TO DIFFER MATERIALLY FROM ANY PROJECTIONS OF FUTURE PERFORMANCE EXPRESSED OR IMPLIED BY SUCH FORWARD-LOOKING STATEMENTS. ALTHOUGH FORWARD-LOOKING STATEMENTS CONTAINED IN THIS PRESENTATION ARE BASED UPON WHAT MANAGEMENT OF SPIROVANT SCIENCES, INC. BELIEVES ARE REASONABLE ASSUMPTIONS, THERE CAN BE NO ASSURANCE THAT FORWARD-LOOKING STATEMENTS WILL PROVE TO BE ACCURATE, AS ACTUAL RESULTS AND FUTURE EVENTS COULD DIFFER MATERIALLY FROM THOSE ANTICIPATED IN SUCH STATEMENTS. SPIROVANT SCIENCES, INC. UNDERTAKES NO OBLIGATION TO UPDATE FORWARD-LOOKING STATEMENTS IF CIRCUMSTANCES OR MANAGEMENT’S ESTIMATES OR OPINIONS SHOULD CHANGE. THE READER IS CAUTIONED NOT TO PLACE UNDUE RELIANCE ON FORWARD-LOOKING STATEMENTS

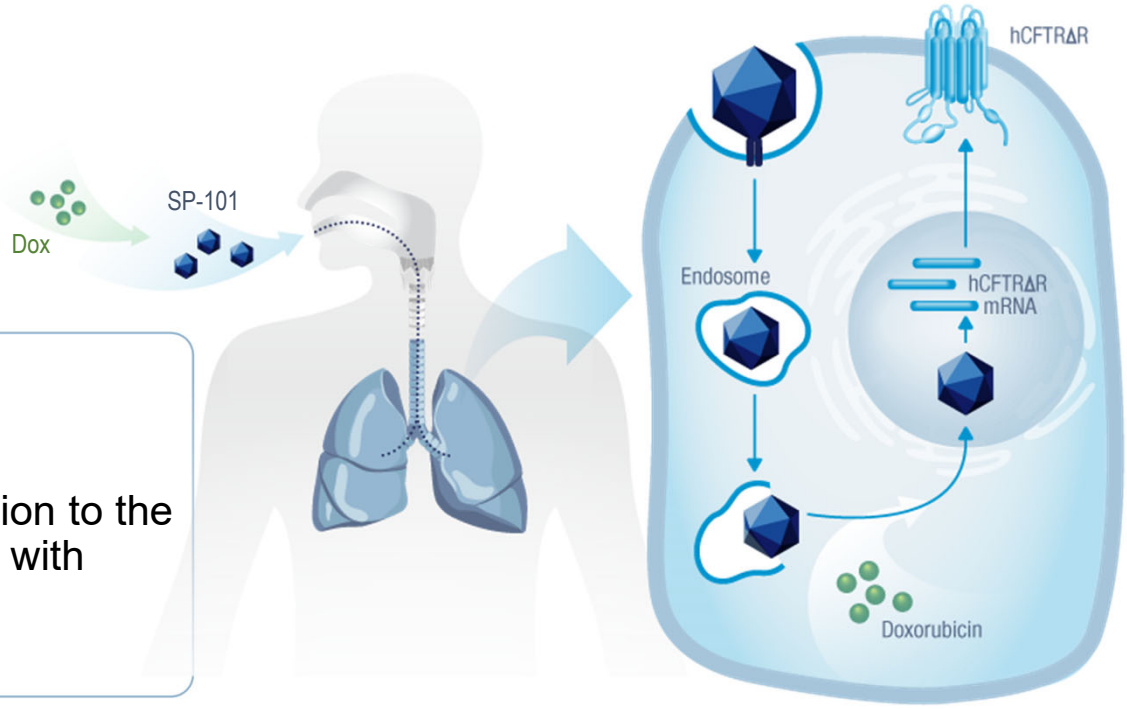
SP-101 – a novel, inhaled gene therapy to treat CF

DESIGN FEATURES

- AAV capsid selected for tropism to the apical surface of human airway epithelia (HAE)[1]
- *hCFTRΔR* minigene with regulatory elements[2,3]

MECHANISM OF ACTION

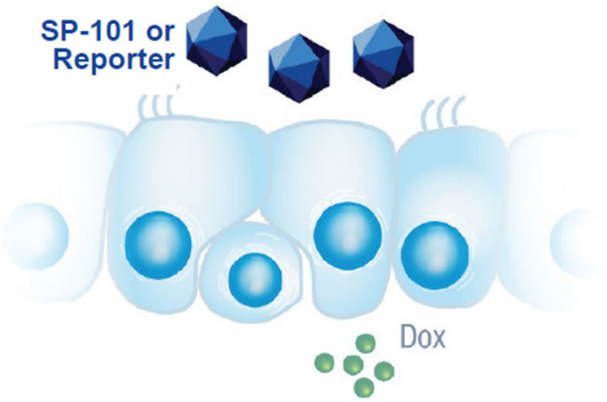
- Efficient apical entry
- Enhanced SP-101 translocation to the nucleus by co-administration with doxorubicin (Dox)[4,5]
- Increased CFTR expression



[1]Excoffon et al., PNAS 2009; [2]Ostedgaard et al., PNAS 2002; [3]Yan et al., Hum Gene Ther. 2015; [4]Yan et al. J Virol. 2004; [5]Zhang et al., Mol Ther. 2004

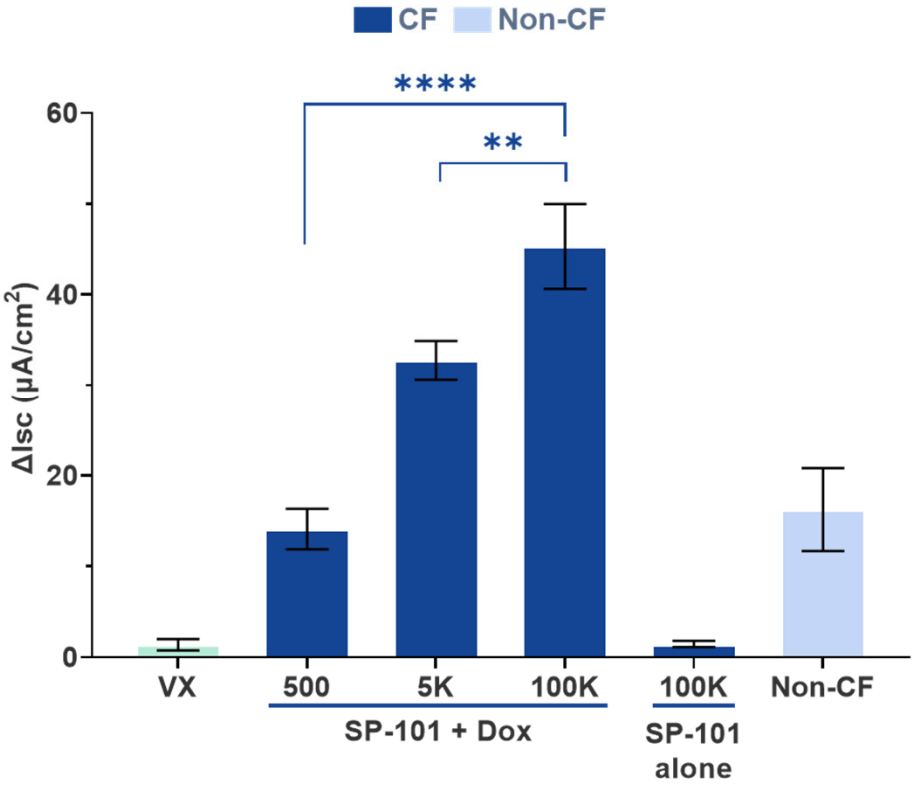
SP-101 demonstrates dose-dependent functional correction

Polarized primary human CF airway epithelia with class I mutations (W1282X/R1162X, N=3)



CFTR Function (Ussing)

SP-101/Dox 16 h incubation, analysis at D7



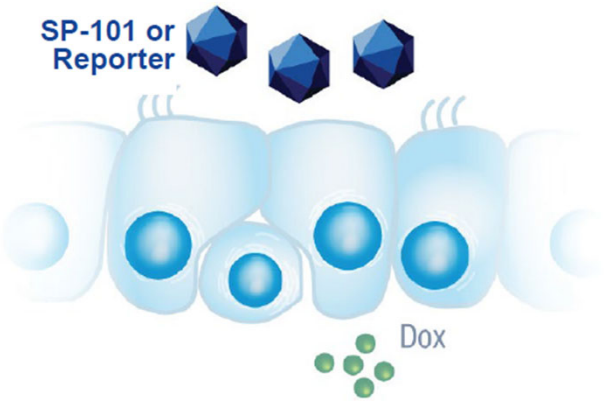
**p < 0.01; ****p < 0.0001

VX - CFTR triple modulators VX-770/661/445

spirovant

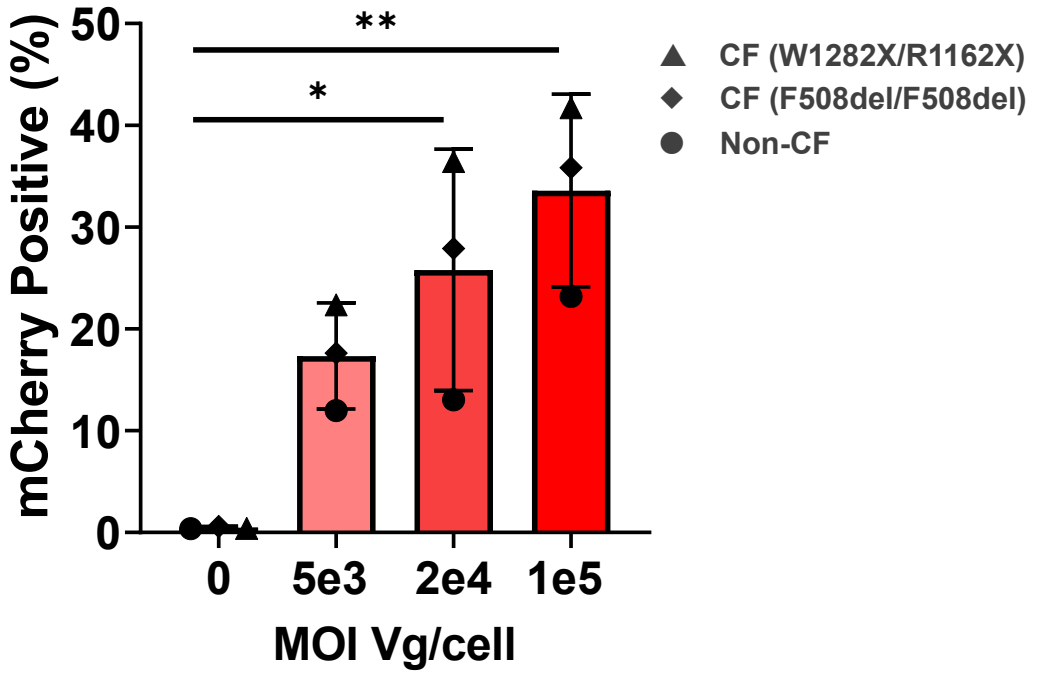
The degree of HAE transduction is SP-101 MOI and donor dependent

Polarized primary human CF or non-CF airway epithelia



Quantitative flow cytometry

SP-101 Capsid mCherry Reporter/Dox 16 h incubation, analysis at D7

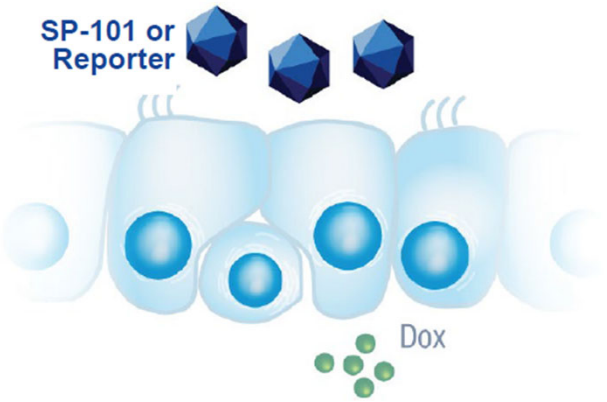


*p < 0.05; **p < 0.01

spirovant

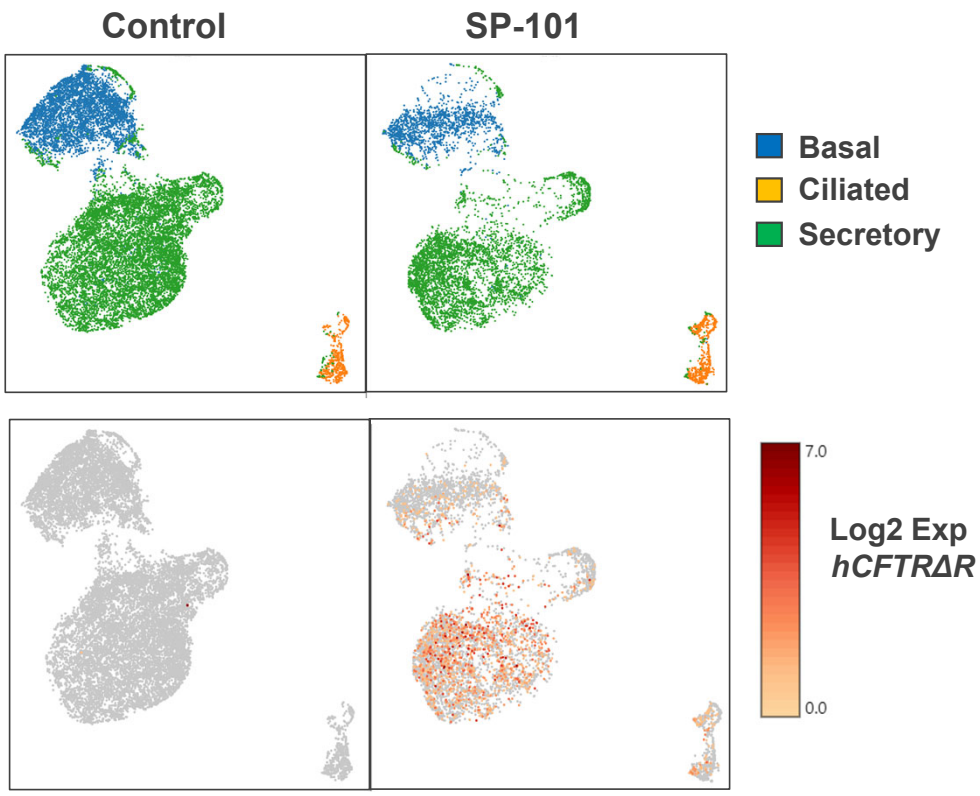
The major cell types in CF HAE are transduced by SP-101

Polarized primary human CF airway epithelia
(W1282X/R1162X)



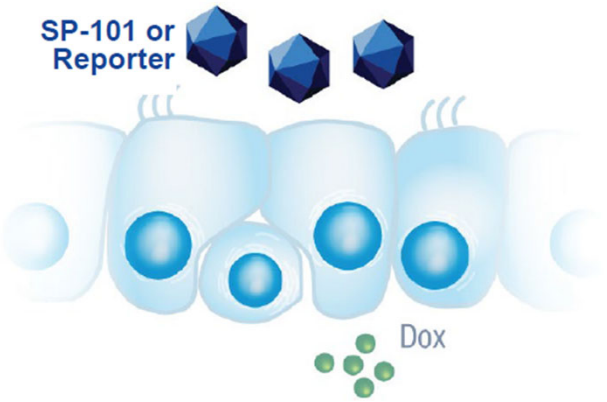
Single-cell RNA sequencing

SP-101/Dox 16 h incubation, analysis at D7



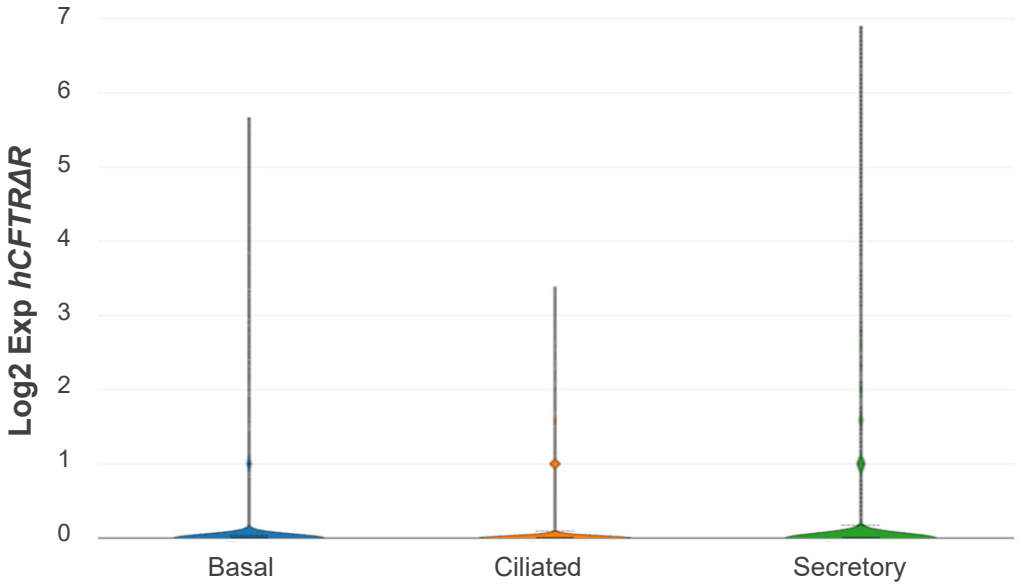
The major cell types in CF HAE are transduced by SP-101

Polarized primary human CF airway epithelia
(W1282X/R1162X)

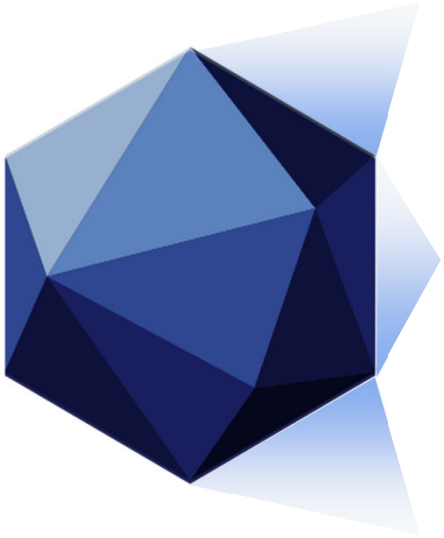


Single-cell RNA sequencing

SP-101/Dox 16 h incubation, analysis at D7



Ferret as a model to evaluate inhaled SP-101

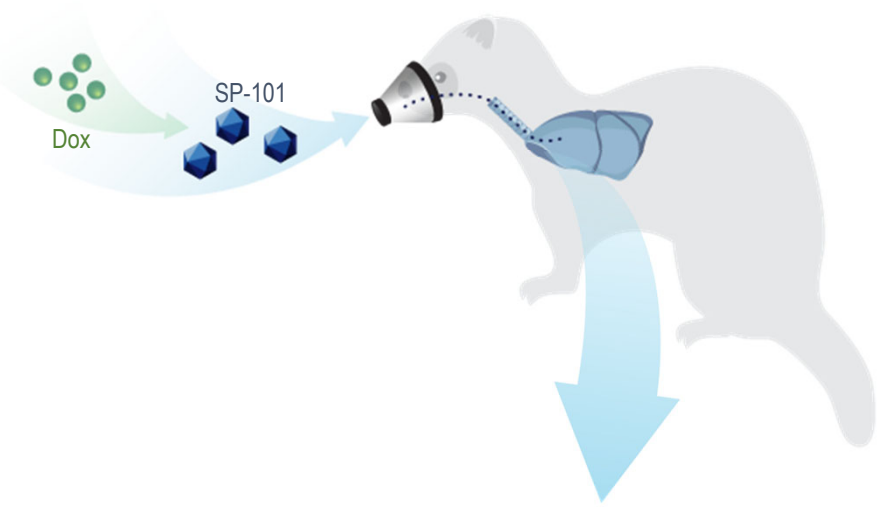


SP-101 capsid is tropic to ferret airway cells[1]

CF ferret model recapitulates human CF lung pathology[2]

Ability to administer via inhalation

METHODS

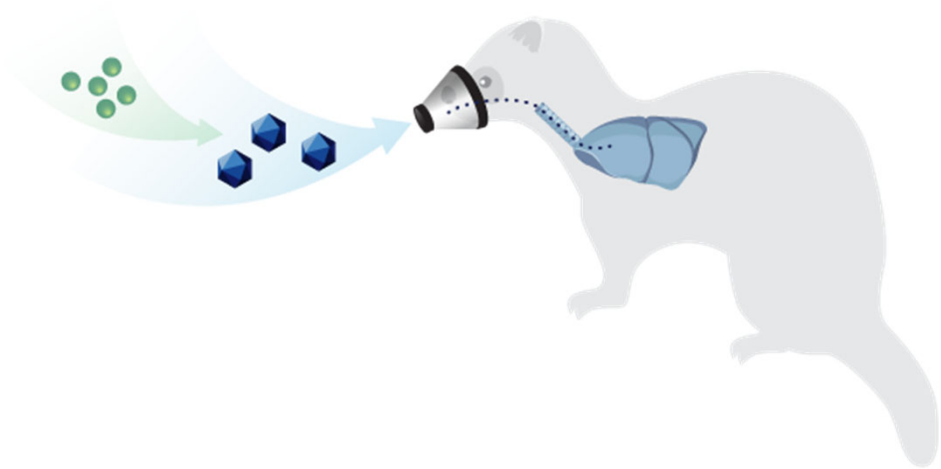


In situ hybridization
SP-101 vector genomes
hCFTRΔR mRNA expression

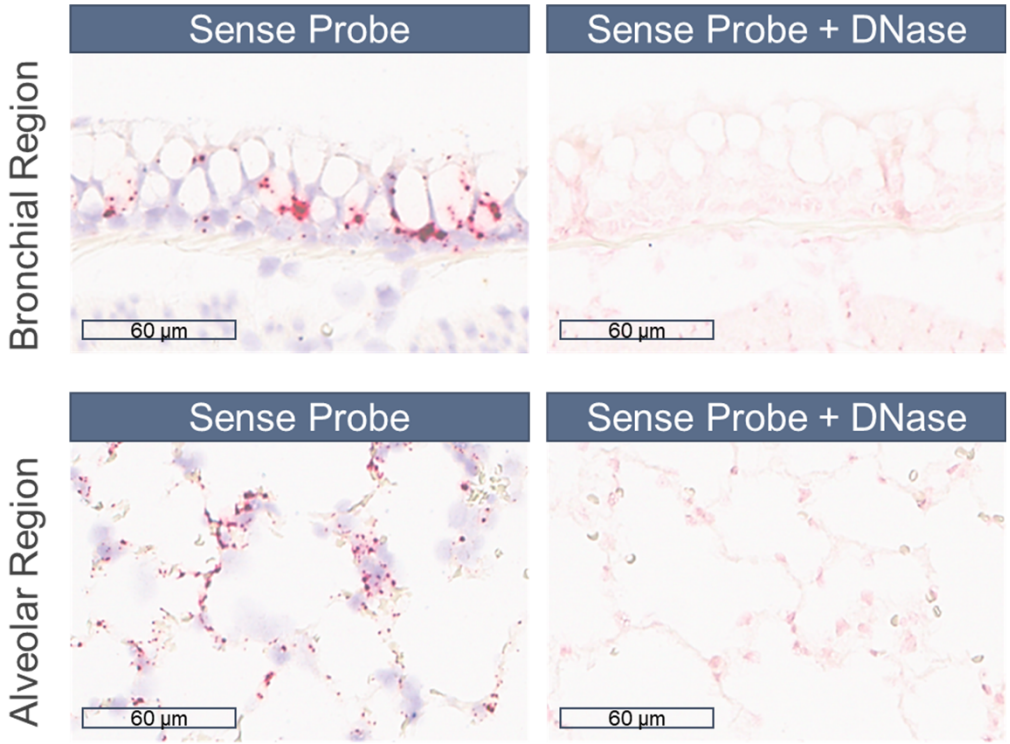
[1] Tang et al, Mol Ther Methods Clin Dev. 2020 [2] Sun et al, Sci Transl Med. 2019

SP-101 vector genomes are abundant in many regions of ferret lungs

Non-CF Ferrets

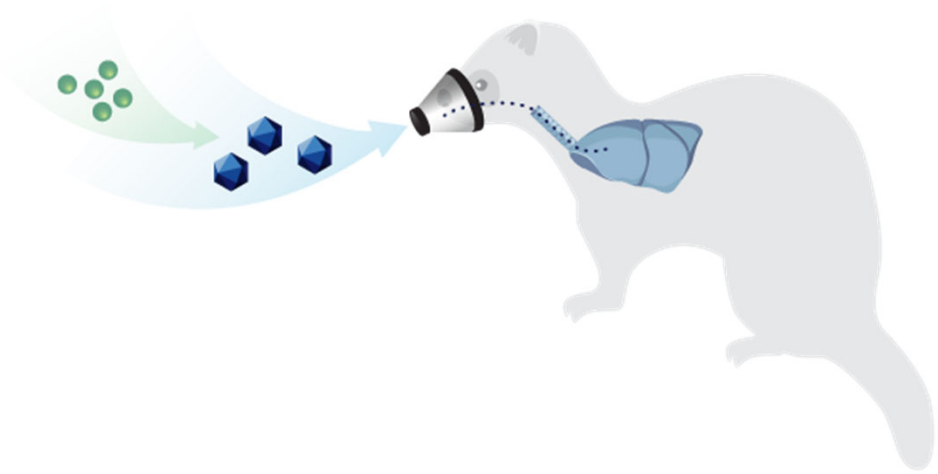


In situ hybridization
2 weeks

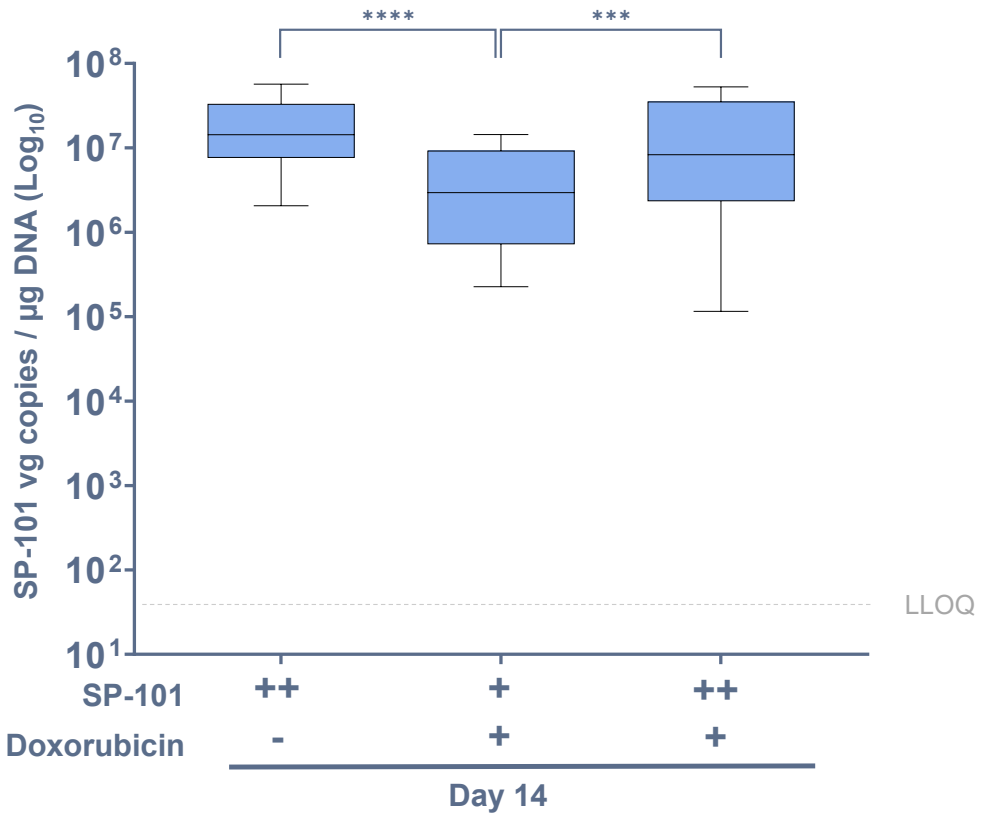


SP-101 biodistribution is dose dependent and is not impacted by doxorubicin

Non-CF Ferrets



SP-101 vector genomes (vg, qPCR)
2 weeks



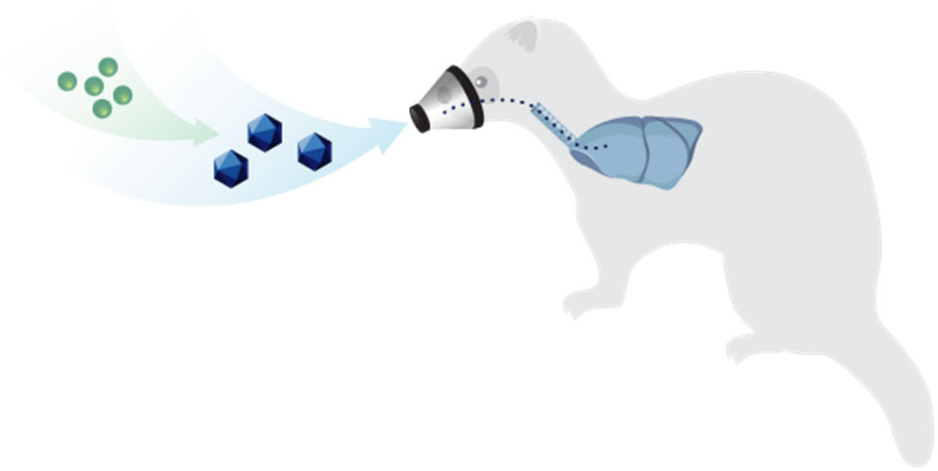
****p < 0.0001
***p<0.001

spirovant

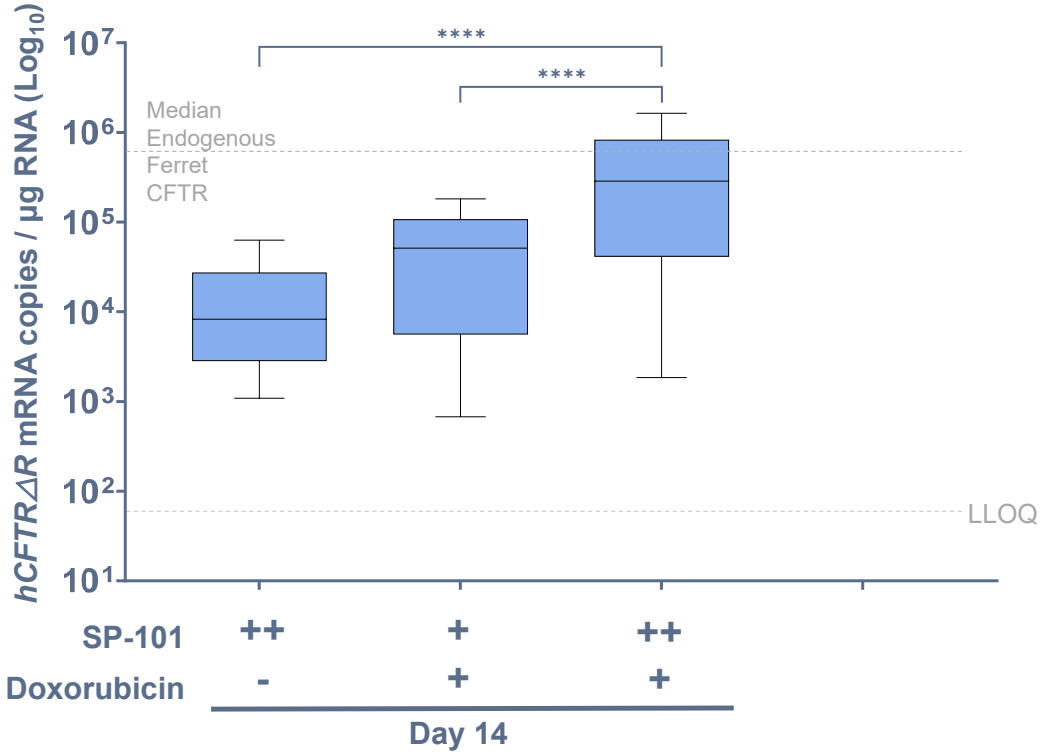
LLOQ – lower limit of quantitation

Doxorubicin increases *hCFTRΔR* mRNA expression >10 fold, reaching levels of endogenous ferret CFTR

Non-CF Ferrets



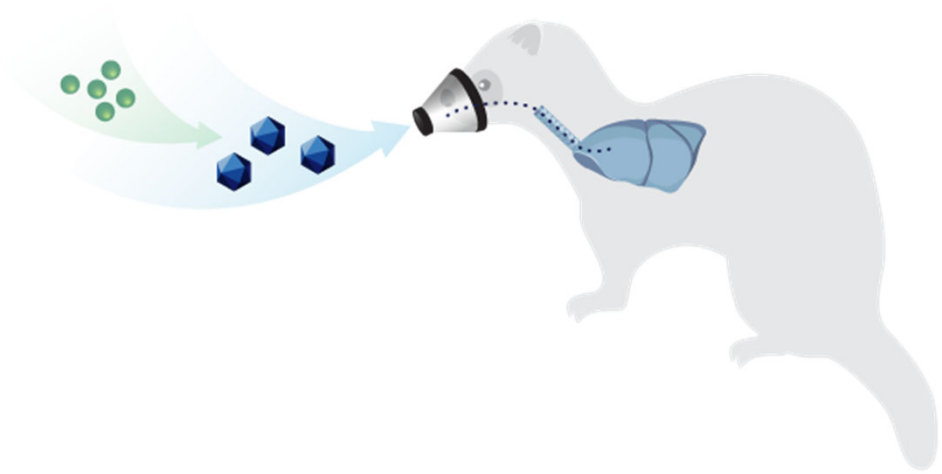
hCFTRΔR mRNA expression (RT-qPCR)
2 weeks



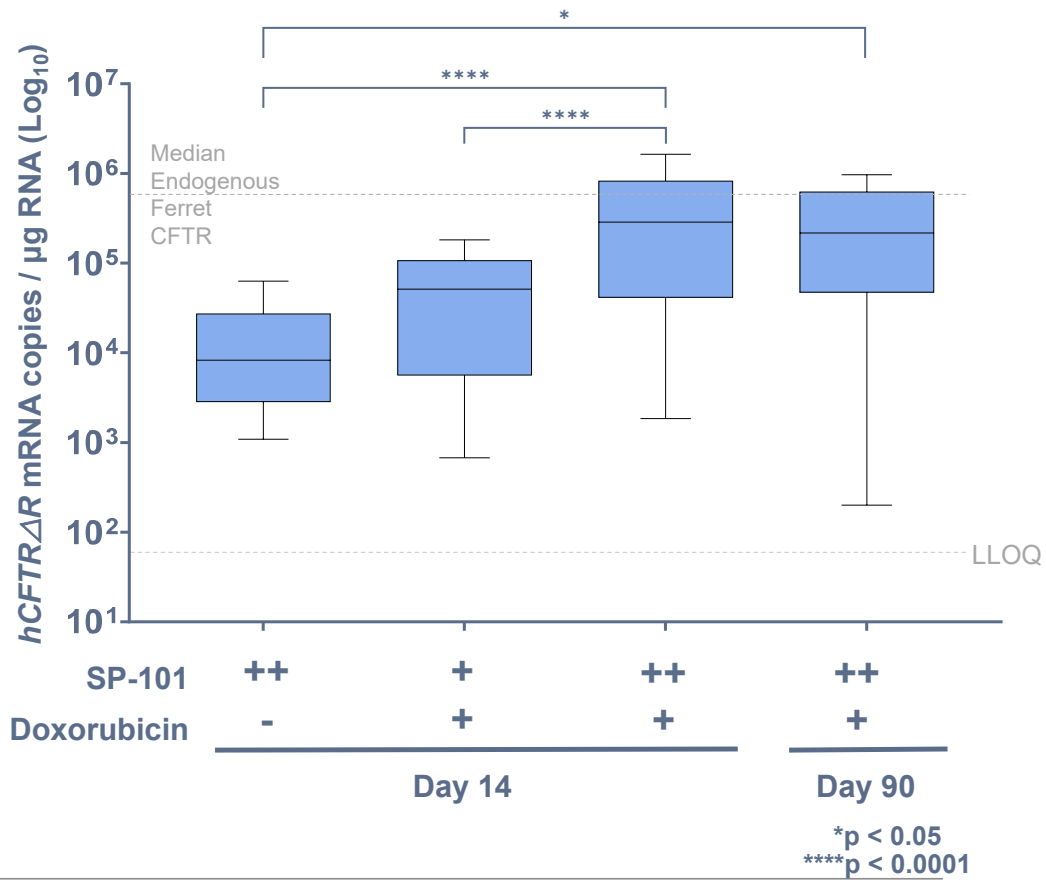
****p < 0.0001

hCFTRΔR mRNA expression is durable

Non-CF Ferrets



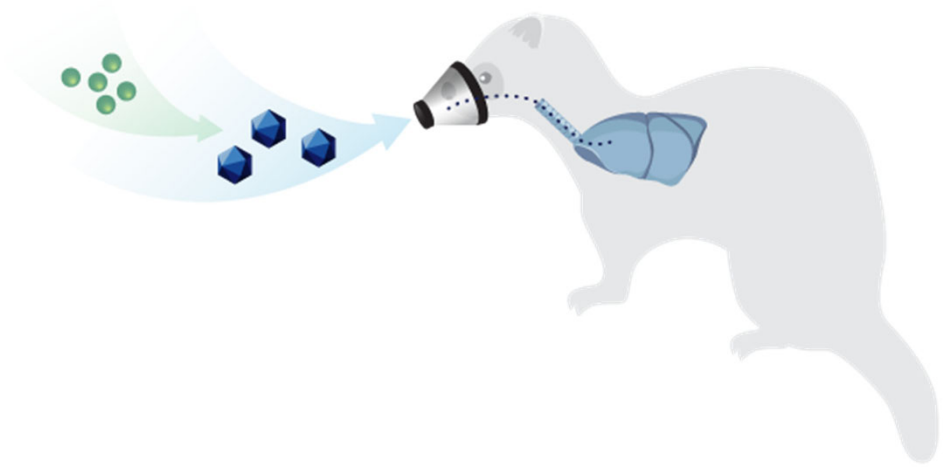
hCFTRΔR mRNA expression
2 weeks and 12 weeks (end of study)



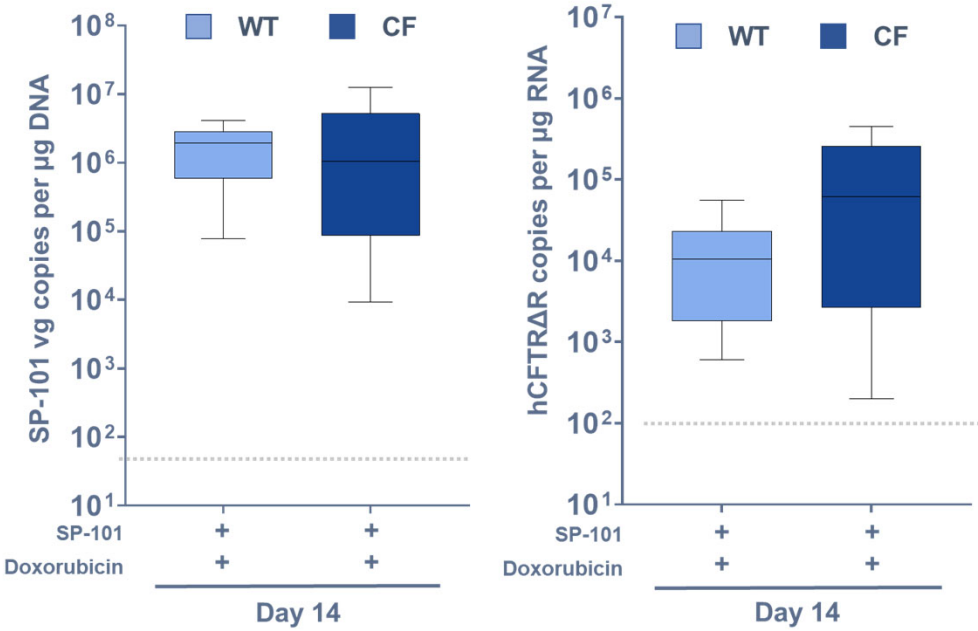
LLOQ – lower limit of quantitation

SP-101 biodistribution and *hCFTRΔR* mRNA expression is similar in CF and non-CF ferrets

CF and Non-CF Ferrets

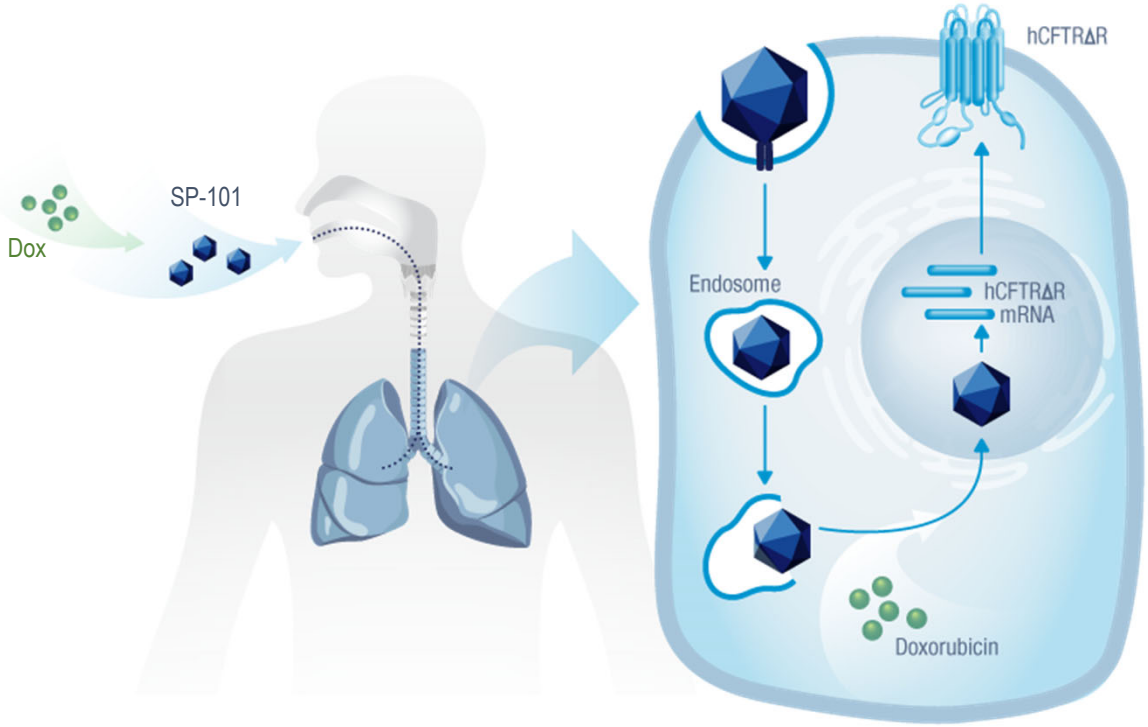


SP-101 vector genomes (vg) and
hCFTRΔR mRNA expression
2 weeks



SP-101 holds great promise for people living with CF

- SP-101 functionally corrects CF HAE
- Doxorubicin is required for efficient CF correction by SP-101
- SP-101 is tropic to many human airway epithelial cell types
- hCFTRΔR expression and CF correction are dose responsive, durable, and reach levels similar to endogenous ferret CFTR
- hCFTRΔR mRNA expression is similar in CF and wild-type ferrets, suggesting that the CF airway is not an additional barrier to SP-101



Acknowledgements

Sumitomo Pharma
Innovation today, healthier tomorrows

Guia Guffanti

LOVELACE BIOMEDICAL

Philip Kuehl
Bryan Gullick
Adam Werts

The University of Iowa

John Engelhardt
Yinghua Tang
Ziying Yan

UNC SCHOOL OF MEDICINE

Scott Randell
Leslie Fulcher

spirovant

Lillian Falese
Matthew Glatfelter
Donna Henry
Melane James
Awal Jimah
Roland Kolbeck
Poornima Kotha
Shen Lin
Madhu Mahankali
Eric Pastor
Robert Schulingkamp
Mark Smith
Matthew Weaver
Eric Yuen