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CFTR mRNA delivery with a revolutionary non-LNP nanoemulsion formulation to differentiated primary human airway epithelium and airway organoid

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COI

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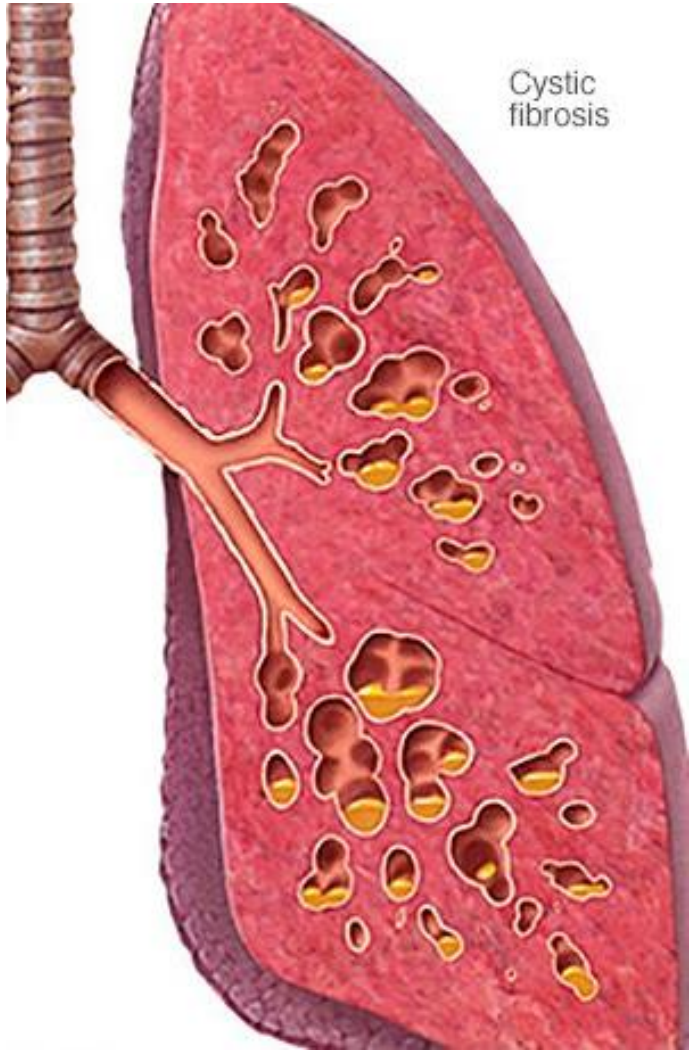
K.I., J.S. and G.R serve as consultants to RIGImmune
S.S. is an employee of RIGImmune
Y.Y. is an employee of HiLung Inc.

Challenges of Gene Delivery to Airways



Mayo Foundation For Medical and Research

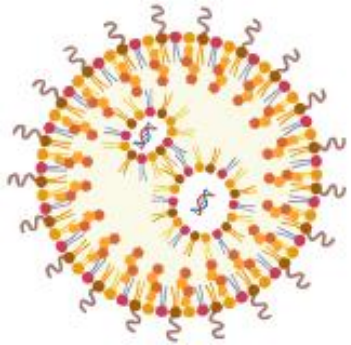
- **Limited permeability to polar molecules**
- **Thick tenacious secretion**
- **Biofilm or mucus based on DNA from inflammatory cells**
- **Impaired mucociliary clearance or quick clearance**
- **Protective enzymes**
- **Impaired lung function**

Drug side

- Adequate drug loading
- Biodegradability and biocompatibility
- Preservation from nucleic acid/drug deterioration
- Aerosol stability

Innovative non-LNP Gene Delivery system to Airway Mucosa

Lipid-based Nanoparticles

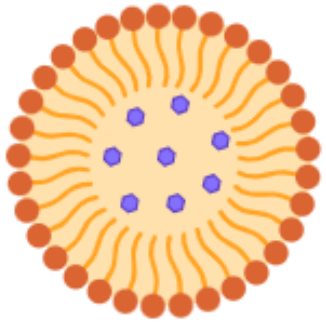


Not ideal for airway delivery

- **Highly pro-inflammatory**
- **Antigenicity**
- **Not Aerosol viable**

NEED™ (Nano Emulsion Effective Delivery: RIGImmune Inc.) is a proprietary non-LNP complex of surfactants & fatty acids to encapsulate RNA payloads (patent pending) , which offers

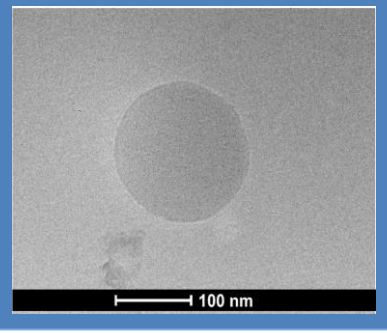
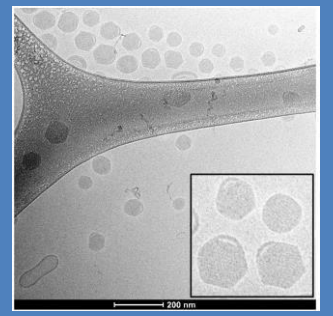
- Aerosolization
- Enhanced RNA Transfection to human primary epithelium
- Particle integrity is maintained ex device
- Versatile Formulation
- GRAS excipients
- Safety advantages



Created by BioRender

NEED ™ Technology Compares Favorably with LNPs

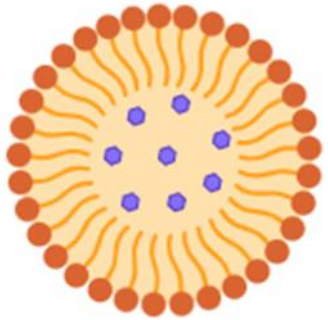
RIGImmune

Feature	NEED™ 	LNP 
Structure	Amorphous structure supported by an internal mesh structure.	Well-defined hexagonal internal structure.
Number of Components (excluding Buffers)	2	4+
Tolerability	GRAS excipients and know-use in respiratory medicines.	Pro-inflammatory.
Tensile Strength	Highly compressible.	Cubsomic rigid structure.
Size	80 - 200 nm.	40-200 nm in diameter with internal striations with spacing of 5-10 nm.
Aerosolization Viability	Diffuse structure enables viable aerosolization from respiratory inhaler devices.	High surface free energy and prone to disruption upon aerosolization, leading to lower aerosol viability.

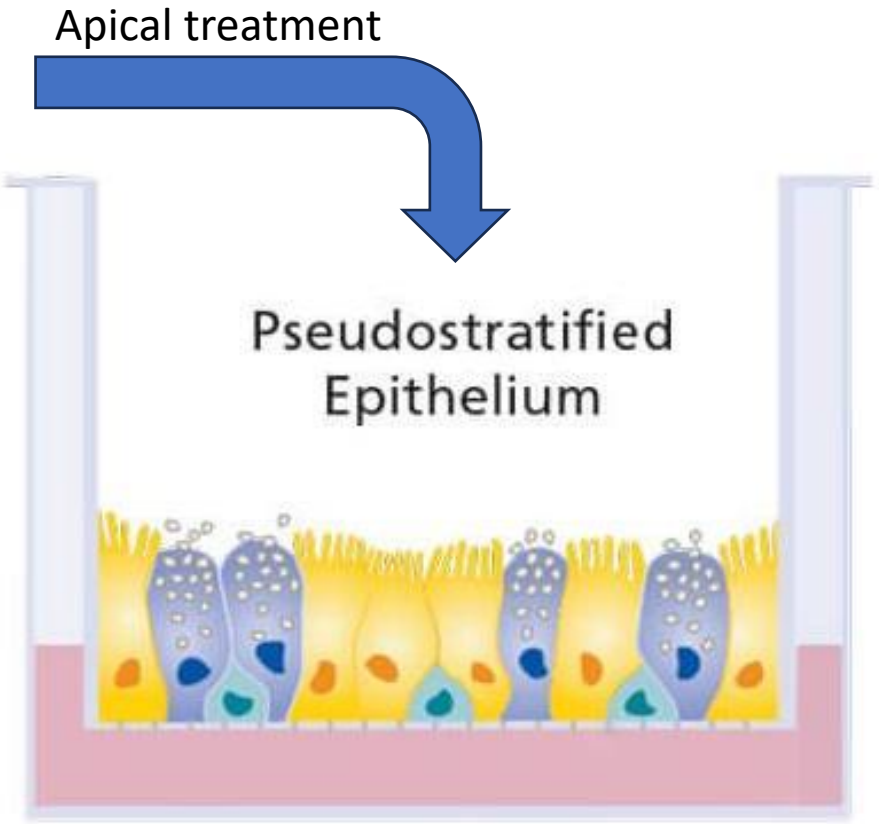
CFTR mRNA NEED™ delivery to air-liquid interface (ALI) cultured alveolar/bronchial epithelium

RIG-301

Optimised *CFTR* mRNAs (Northern RNA, Canada) formulated with NEED™



z-average particle size 176.9 nm



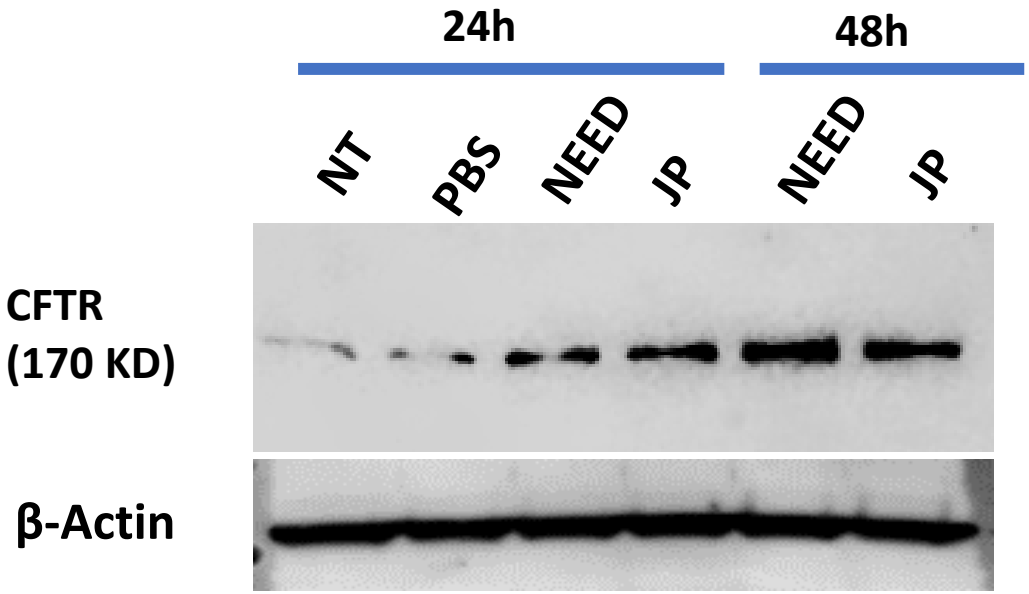
4h, then remove

24h- 72h incubation

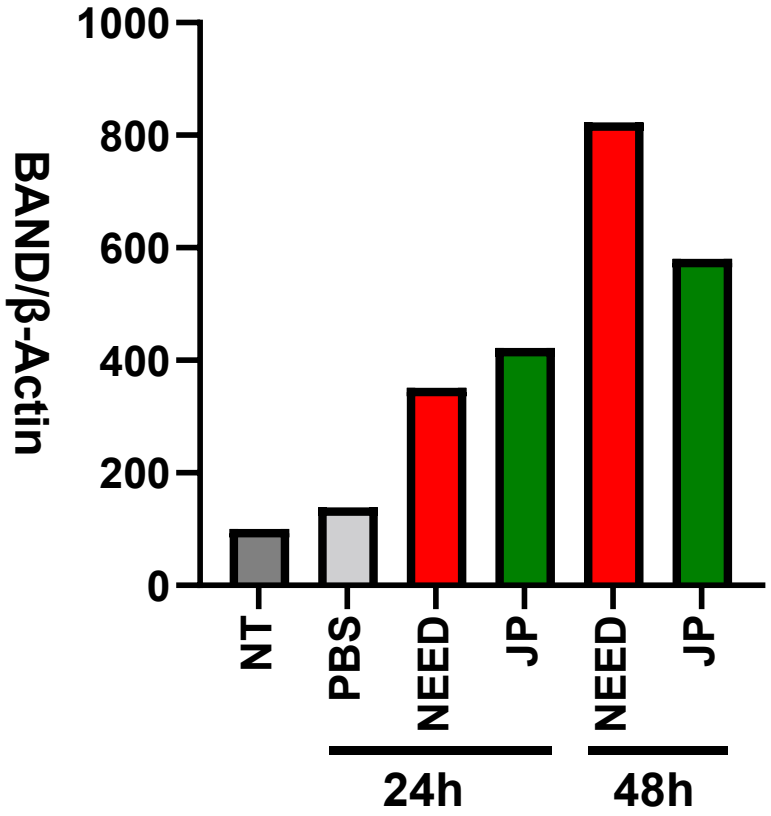
AlveolAir™ or MucilAir™ [Epithelix]

RIG-301 delivery to ALI-Healthy Alveolar epithelium

Incubation time post delivery

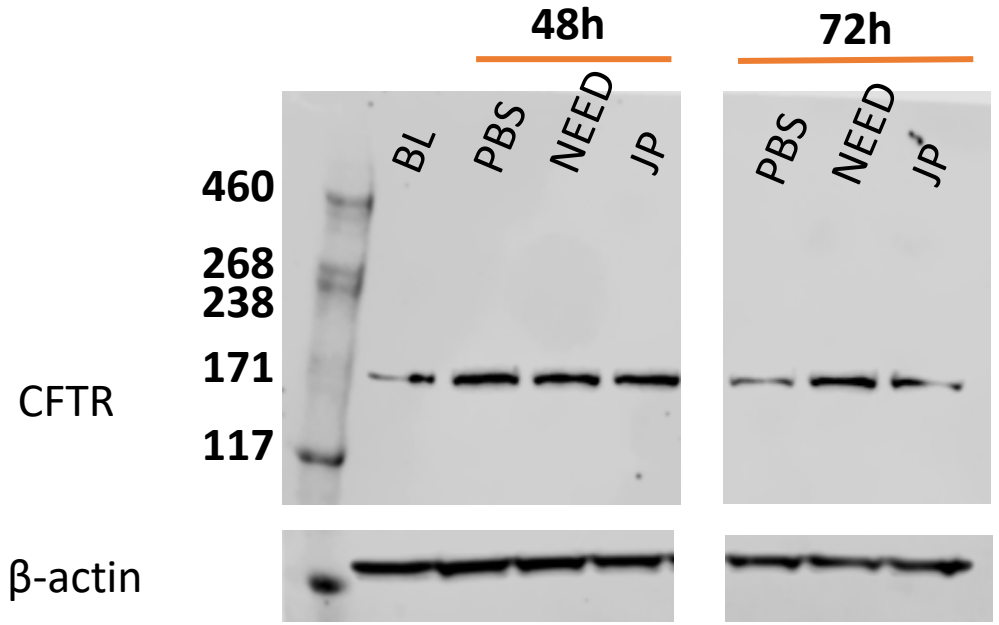


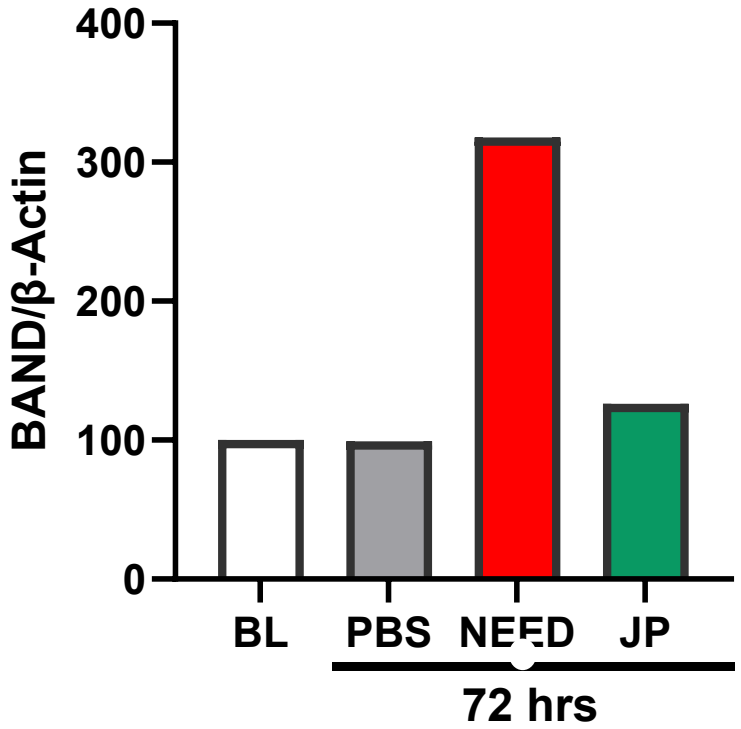
NT:	non-treatment
PBS:	CFTR mRNA in PBS
NEED:	CFTR mRNA in NEED™
JP:	CFTR mRNA in JetPrime



RIG-301 delivery to ALI Healthy bronchial epithelium

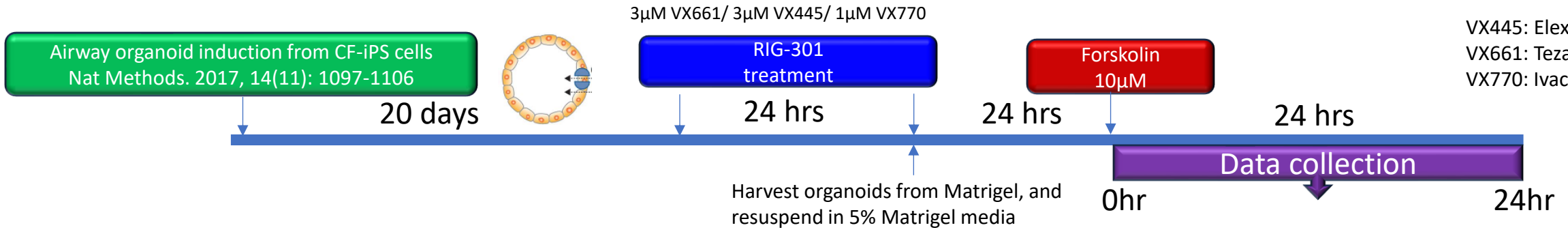
Incubation time post delivery

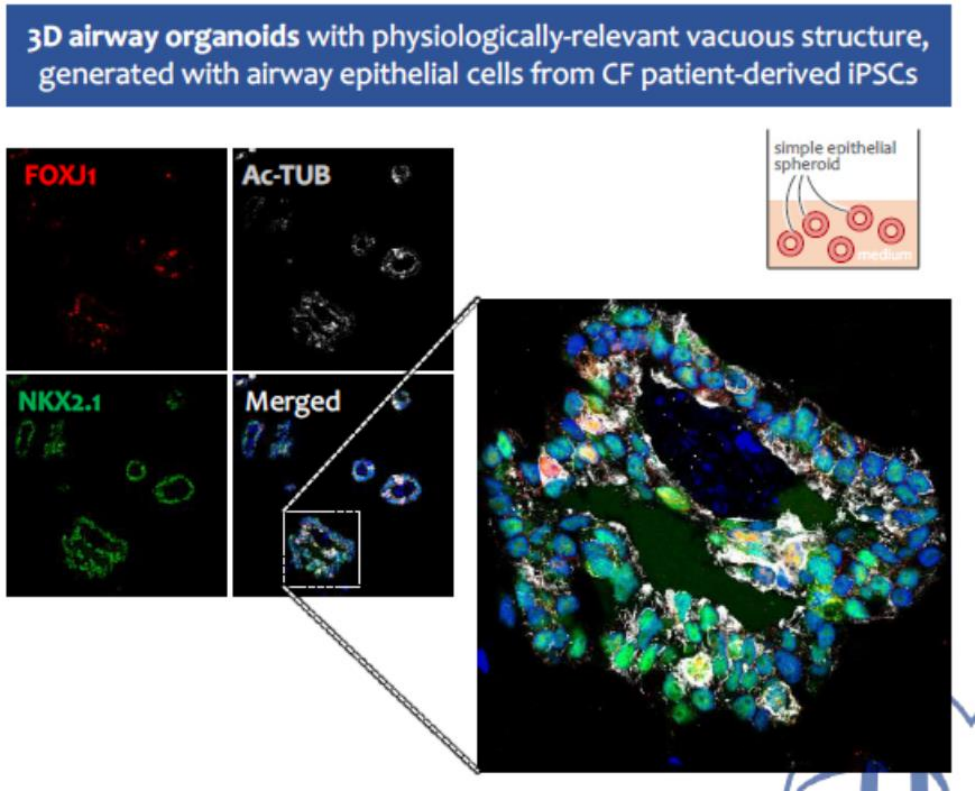


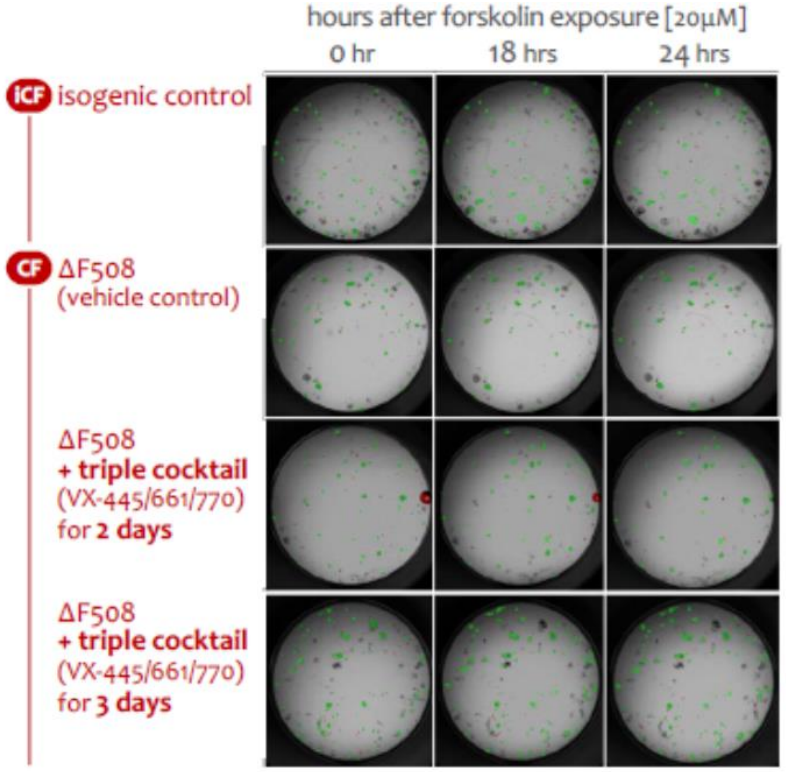


BL:	Baseline
PBS:	CFTR mRNA in PBS
NEED:	CFTR mRNA in NEED™
JP:	CFTR mRNA in JetPrime

Cystic fibrosis (ΔF508) airway Organoid assay [HiLung Inc.]

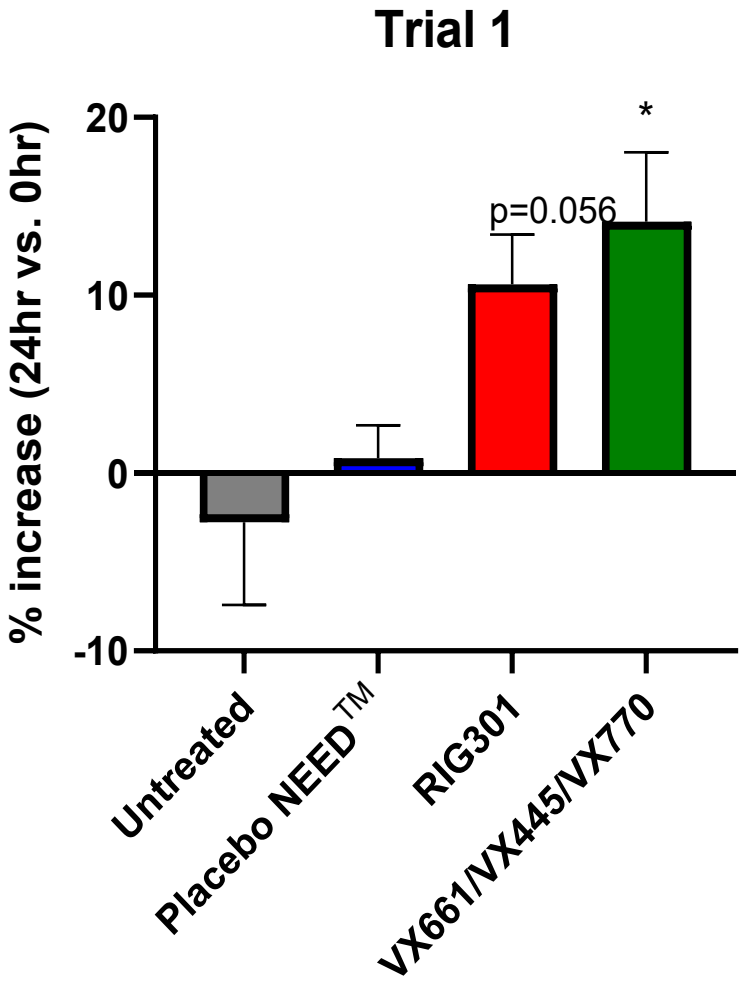


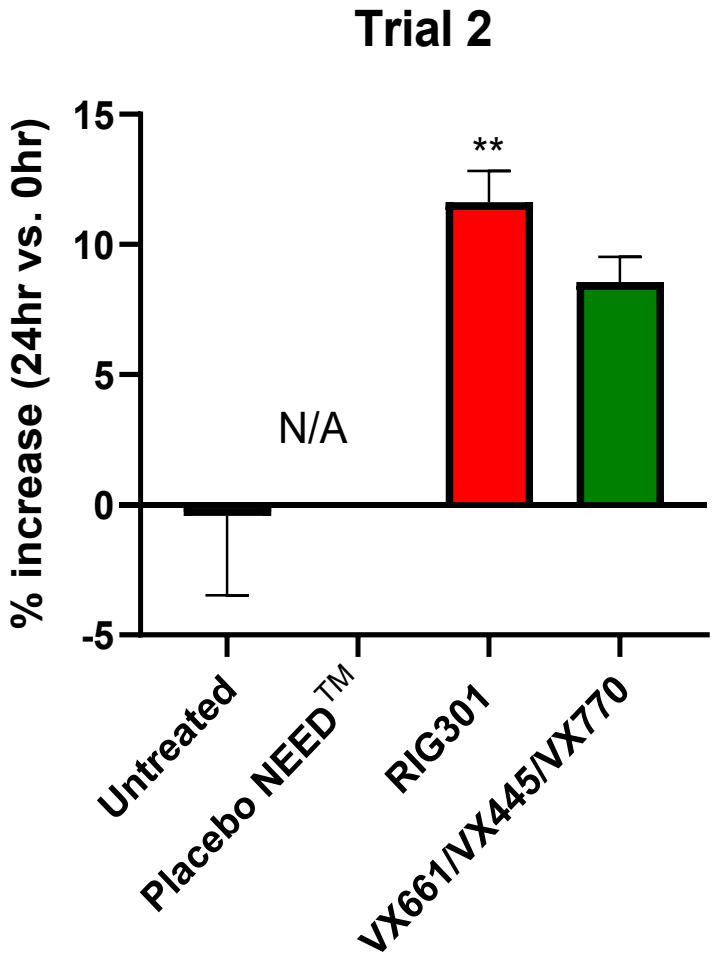




AI-base FIS assay

Cystic fibrosis airway Organoid assay [HiLung Inc.]





VX445: Elexacaftor
VX661: Tezacaftor
VX770: Ivacaftor

CONCLUSION

Our results demonstrate the capability of the NEED™ platform to deliver optimised CFTR mRNA in ALI hAE and hBE cultures, as well as CF organoid. These preclinical data warrant further investigation of CFTR delivery and functional rescue in cells derived from CF patients.