

ARCT-032 (LUNAR[®]-CFTR) Improves Mucociliary Clearance in CF Ferrets

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Arcturus Therapeutics and University of Iowa



mRNA Replacement Therapy

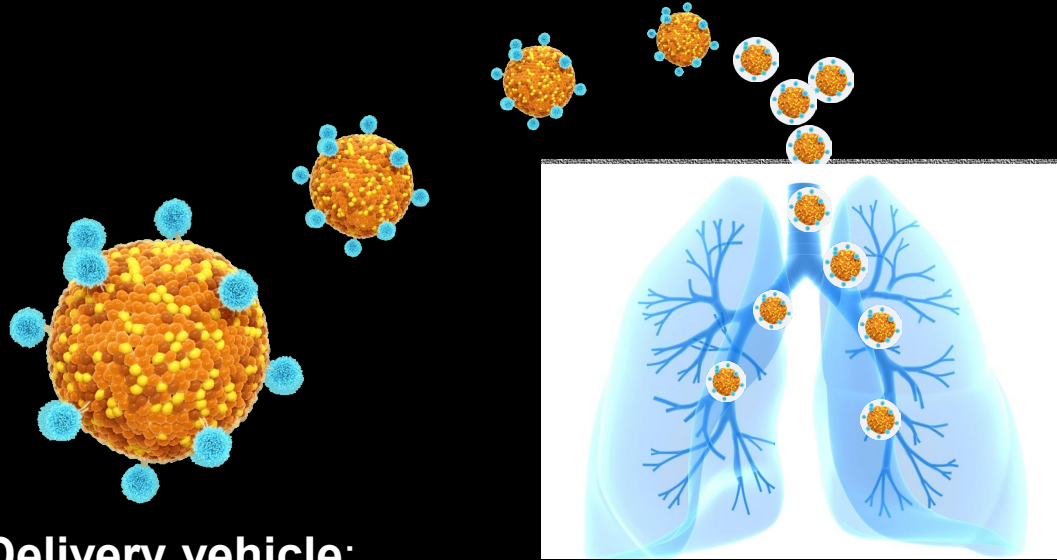
LUNAR[®]-CFTR (ARCT-032)



**Cargo: Optimized
hCFTR mRNA**

**Delivery vehicle:
LUNAR[®] Lipid
Nanoparticles**

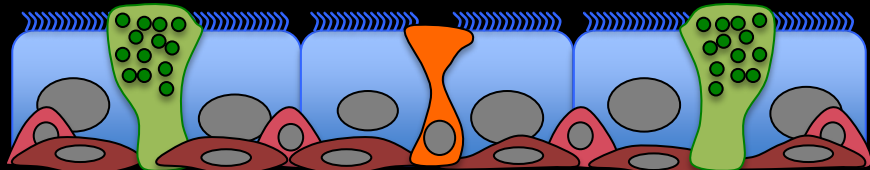
Delivery format: Aerosol



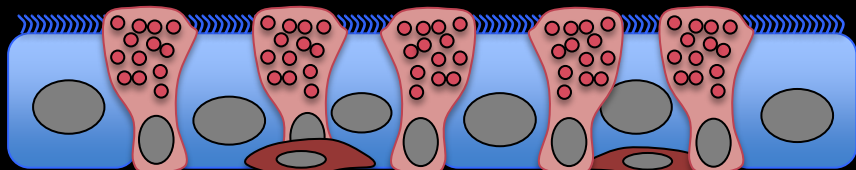
- Arcturus Therapeutics has developed mutation-agnostic mRNA treatment for CF lung disease
- ARCT-032 is currently being evaluated in a Phase 1 clinical trial

Epithelial Cell Types in Airways

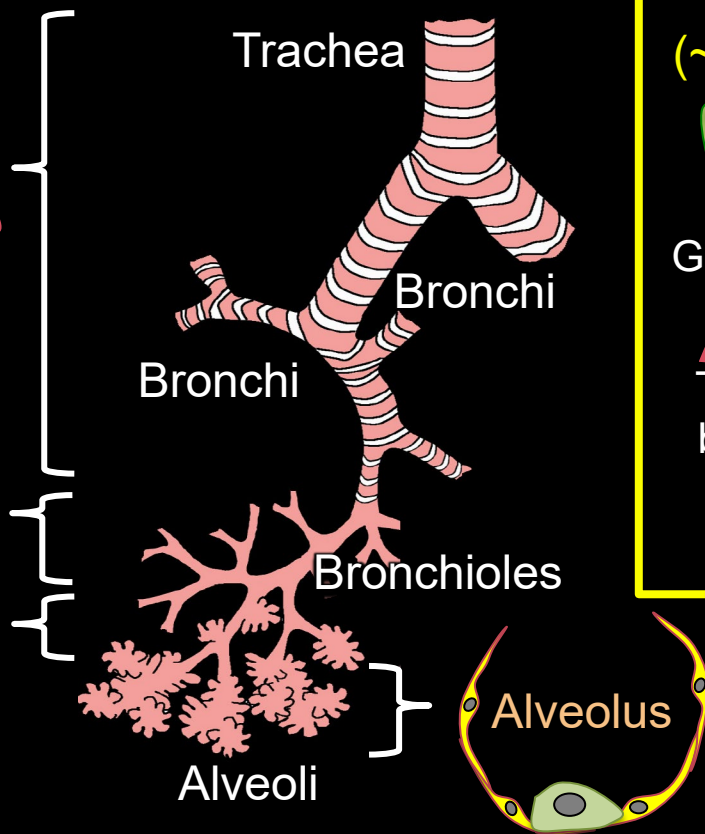
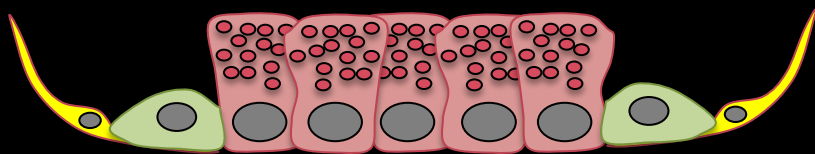
Major Proximal Airway Cell Types (Cartilaginous Airways)



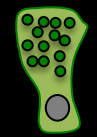
Terminal Bronchiole Cell Types



Respiratory Bronchiole Cell Types



**CFTR
Expression
(~15 to >90%)**



Goblet



Ionocyte



Trans
basal



Club



AT2

CF Ferret Models at University of Iowa



CFTR^{WT}

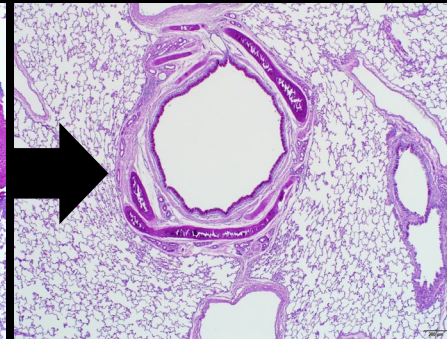
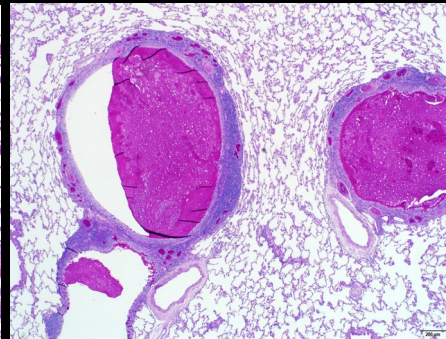
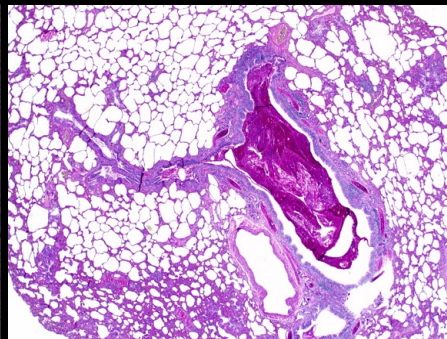
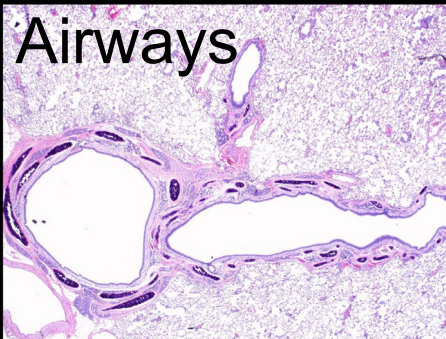
CFTR^{KO}

CFTR^{G551D}

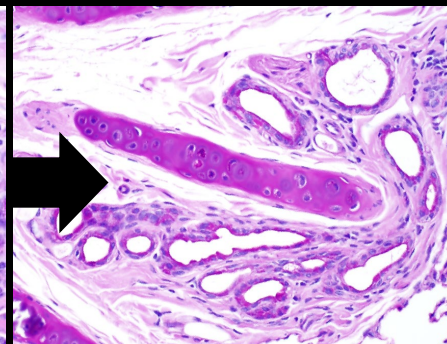
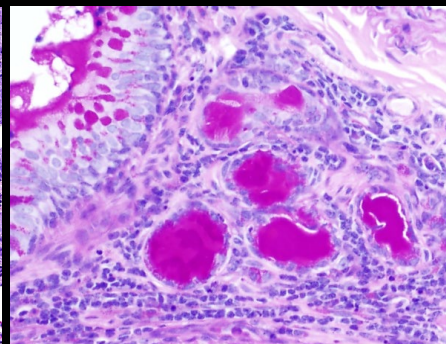
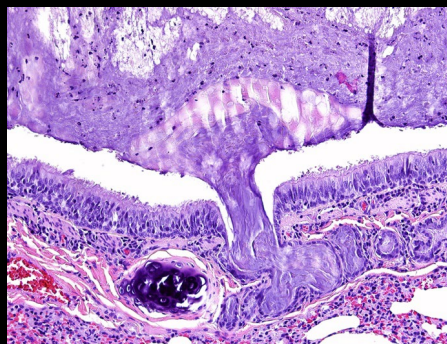
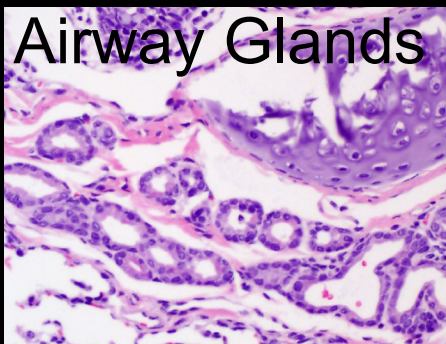
+VX-770

CFTR^{G551D}

Airways

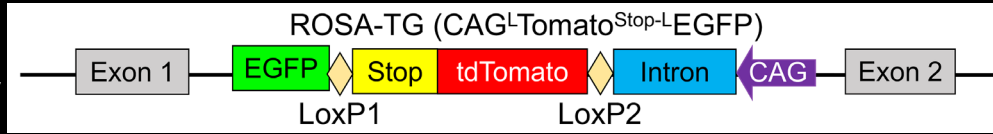


Airway Glands

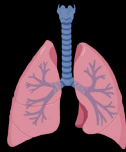


LUNAR[®] Mediated Delivery of mRNA Payloads to Ferret ALI Cultures

ROSA-TG
Cre Reporter



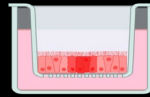
ROSA-TG
Wild type



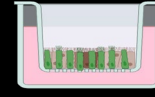
Airway
basal cells

CF

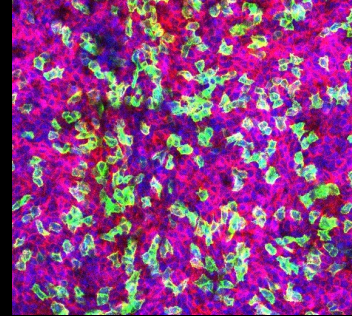
ALI



LUNAR[®]-
hCFTR
2-days



Tomato GFP



Vehicle (V)	KO		ΔF		WT	
CFTR (C)	V	C	V	C	V	C

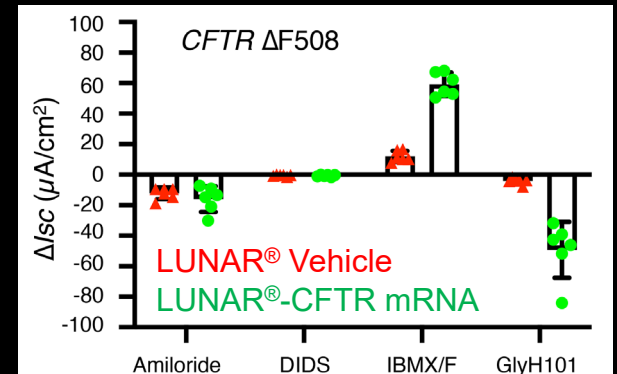
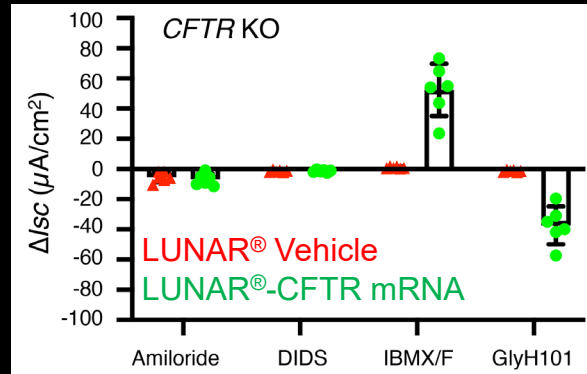
Anti-
CFTR



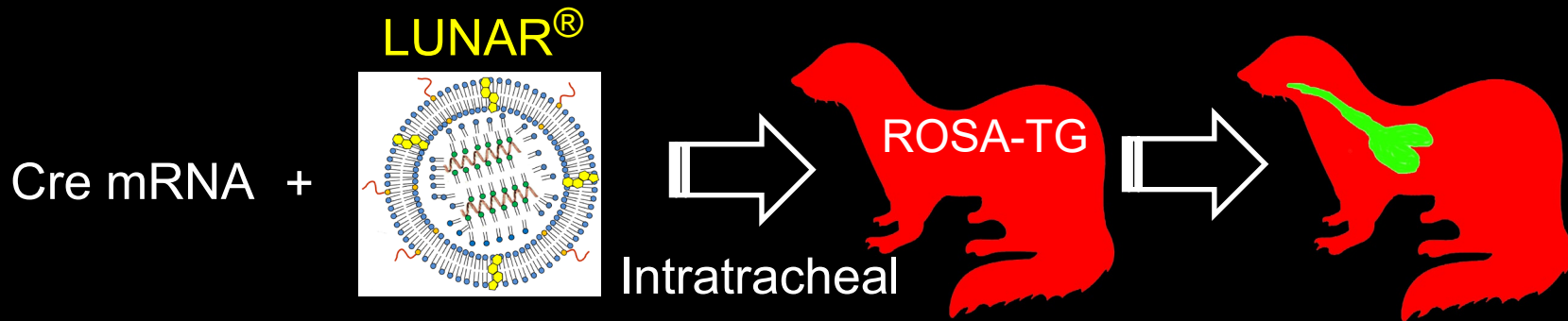
Anti-
HSP90



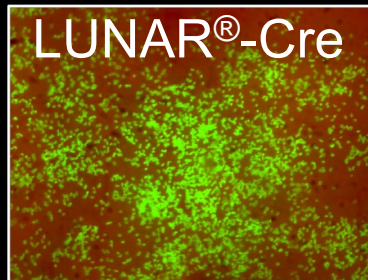
Short Circuit Current



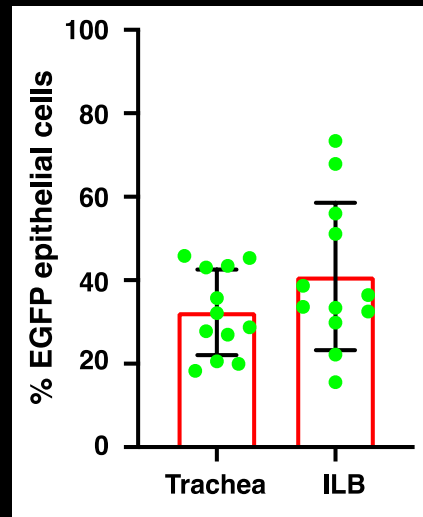
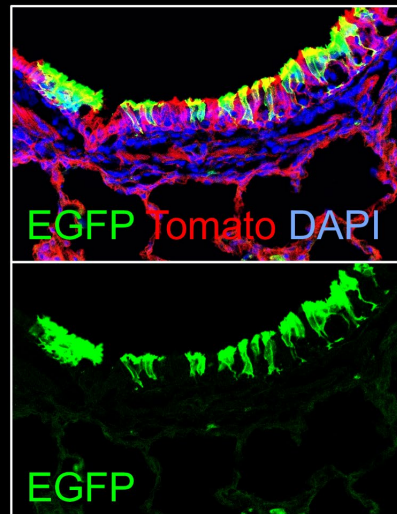
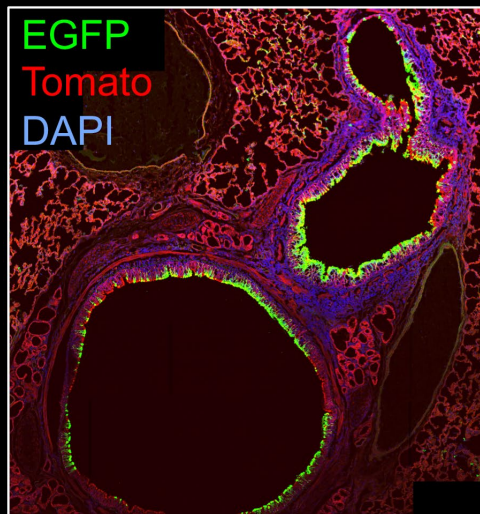
LUNAR[®] Mediated Delivery of mRNA Payloads to Ferret Airways



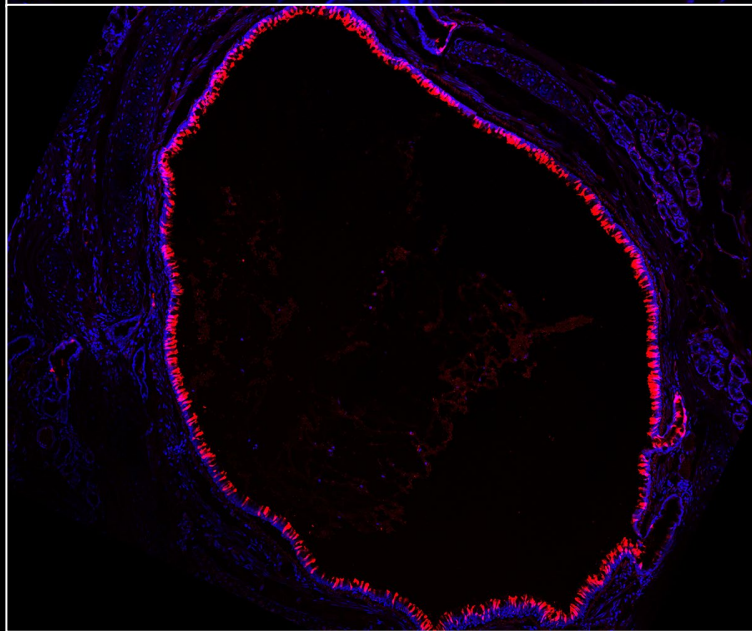
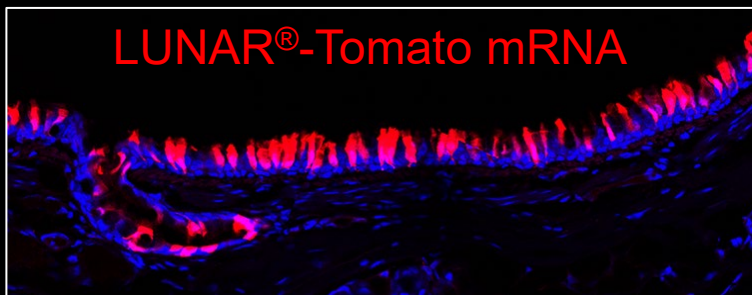
En Face Trachea



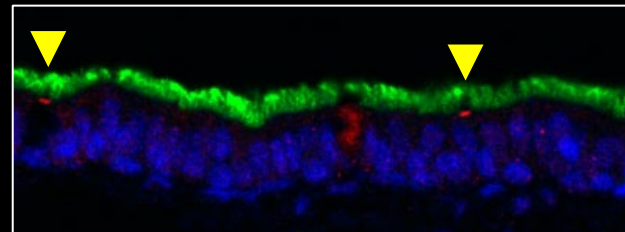
Intralobar Airways



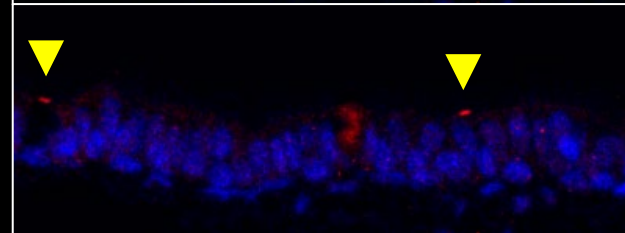
LUNAR[®]-CFTR and LUNAR[®]-tdTomato Delivery to Ferret Airways



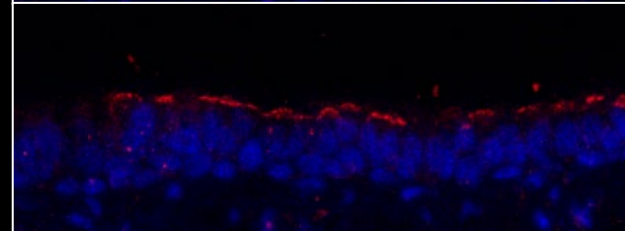
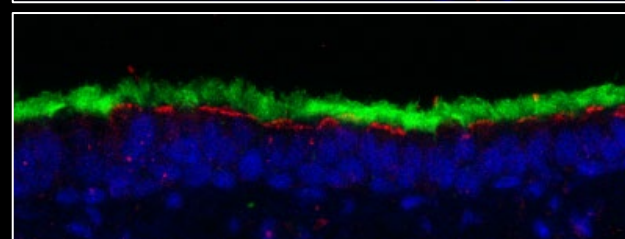
LUNAR[®]
Vehicle



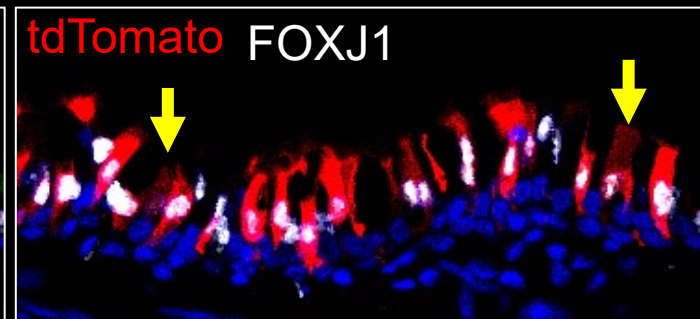
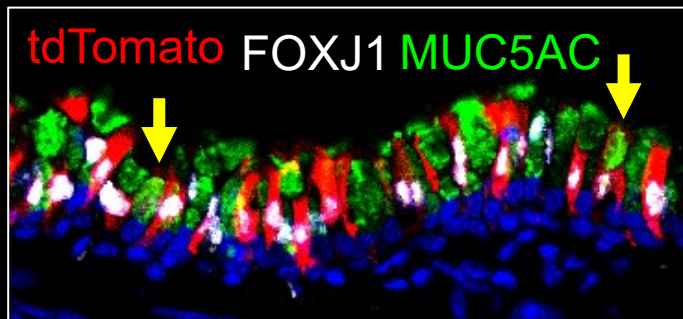
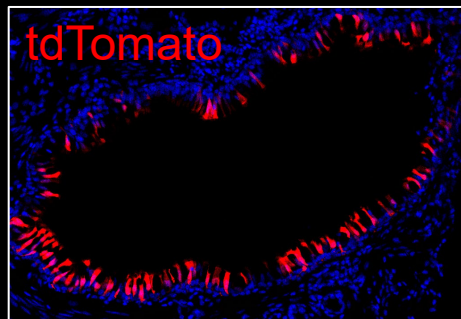
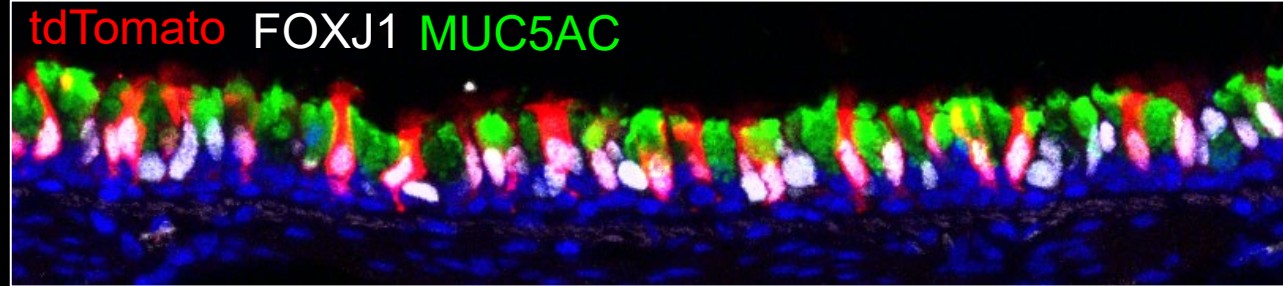
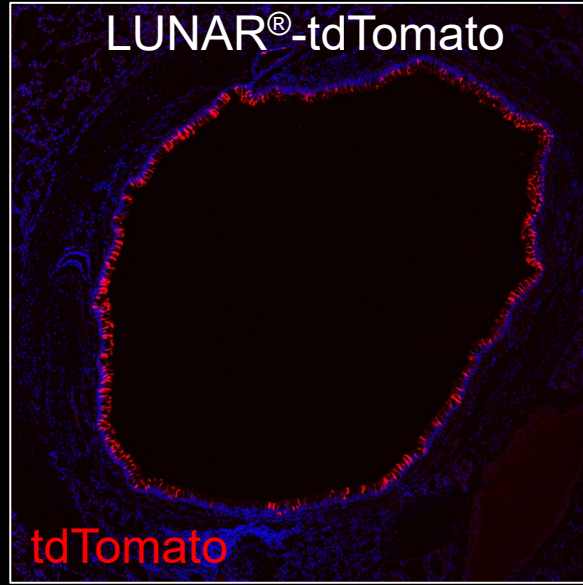
Act-Tubulin
CFTR



LUNAR[®]
hCFTR

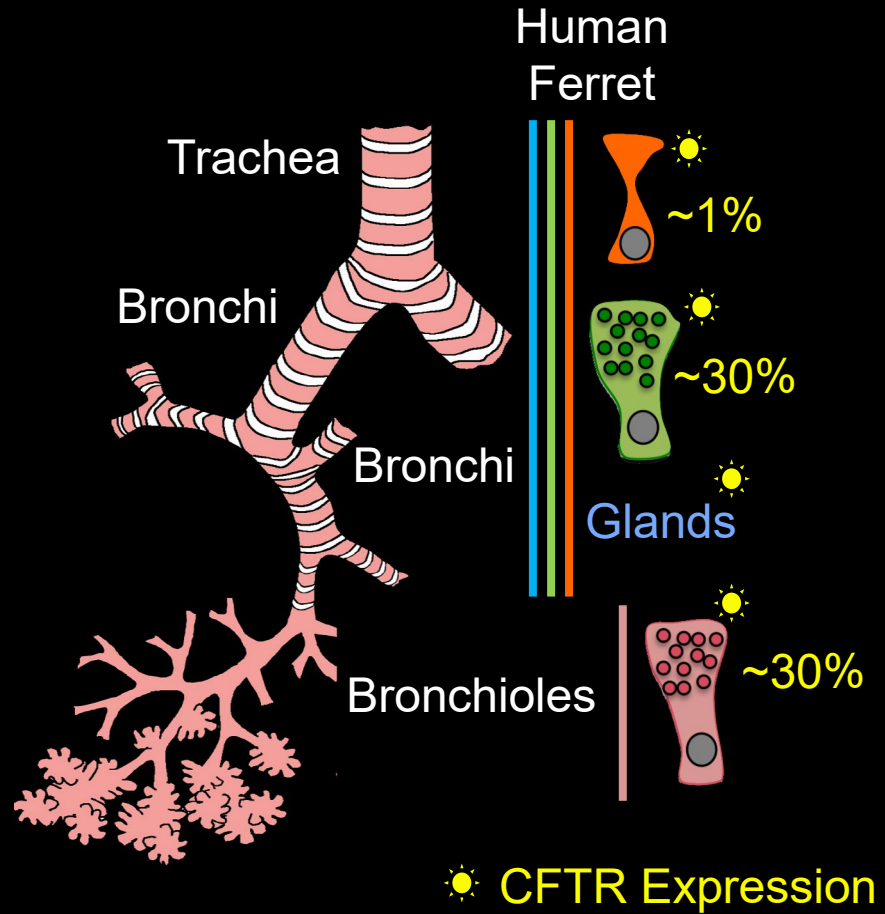
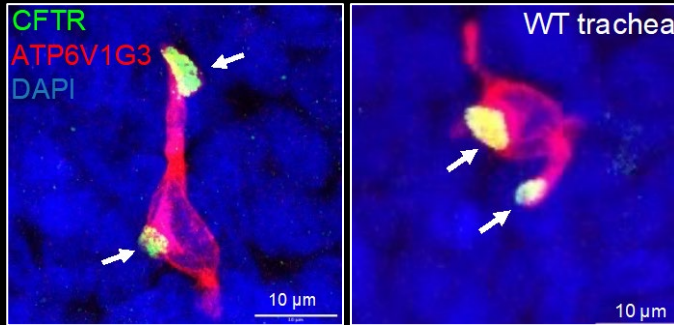


LUNAR[®] Platform Targets Ciliated Cells

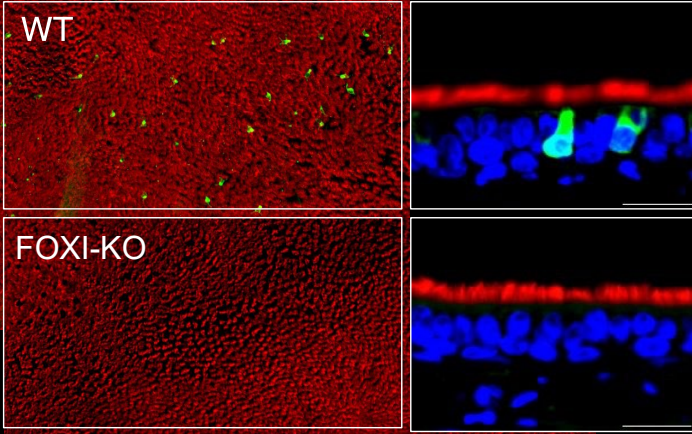


Pulmonary Ionocytes in the Proximal Airway

Ferret Trachea
Whole Mount
Yuan et al.
Nature 2023



ATP6V1G3 (Ionocyte) Act-Tubulin (Ciliated)



CFTR-KO
FOXI1-KO

pH ↓

ASL Volume ↓

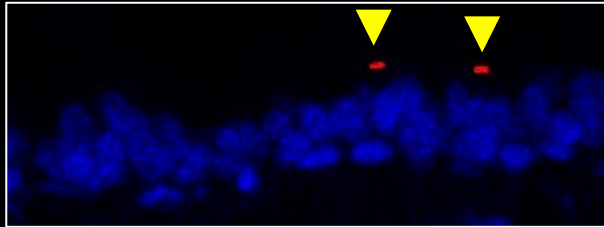
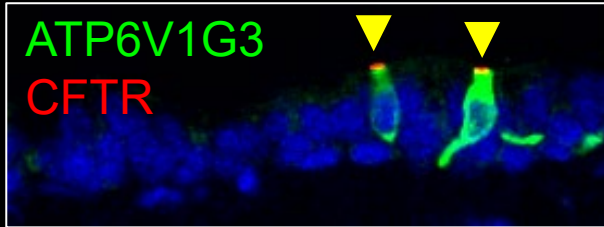
ASL Viscosity ↑

Clearance ↓

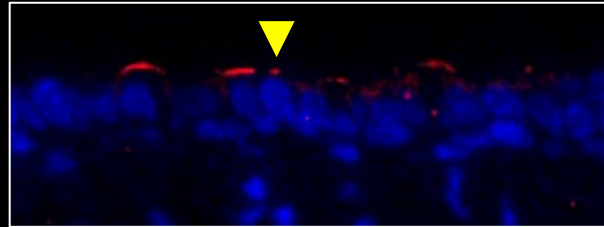
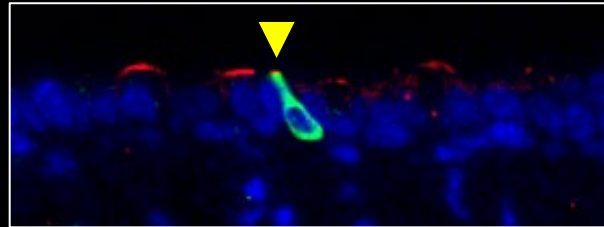
Trachea (Whole Mount) Trachea (Section)

LUNAR[®] Platform Predominantly Targets Non-Ionocytes in the Ferret Proximal Airways

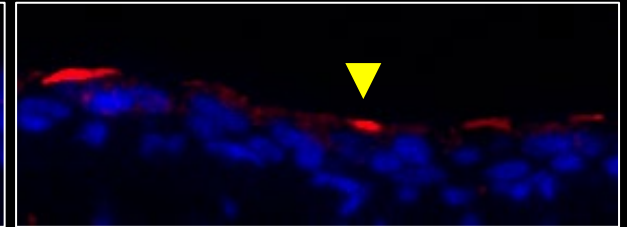
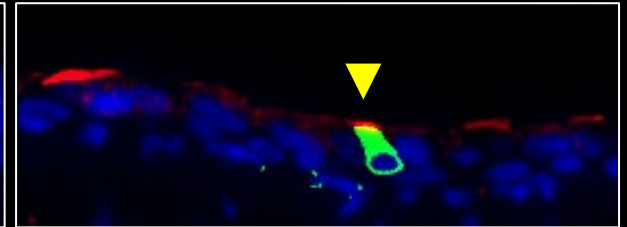
LUNAR[®] Vehicle



LUNAR[®]-CFTR

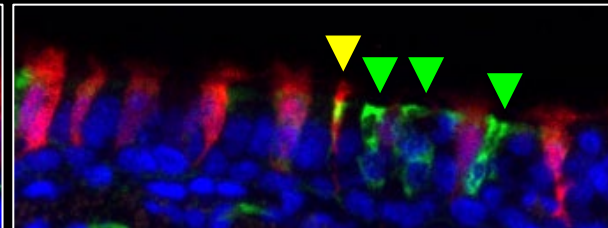
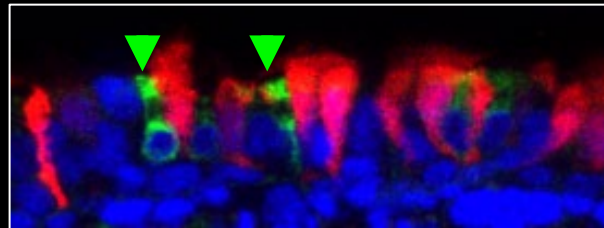


LUNAR[®]-CFTR



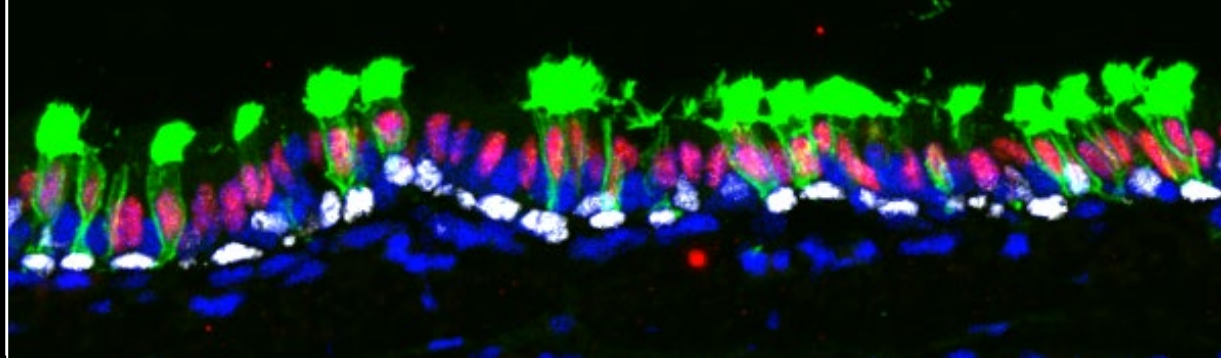
LUNAR[®] -tdTomato

ATP6V1G3
Tomato

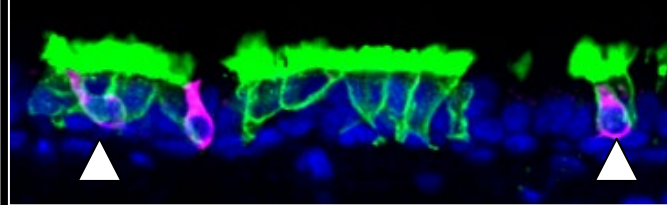


LUNAR[®]-Cre Transfection in ROSA-TG Ferrets

EGFP FOXJ1 P63



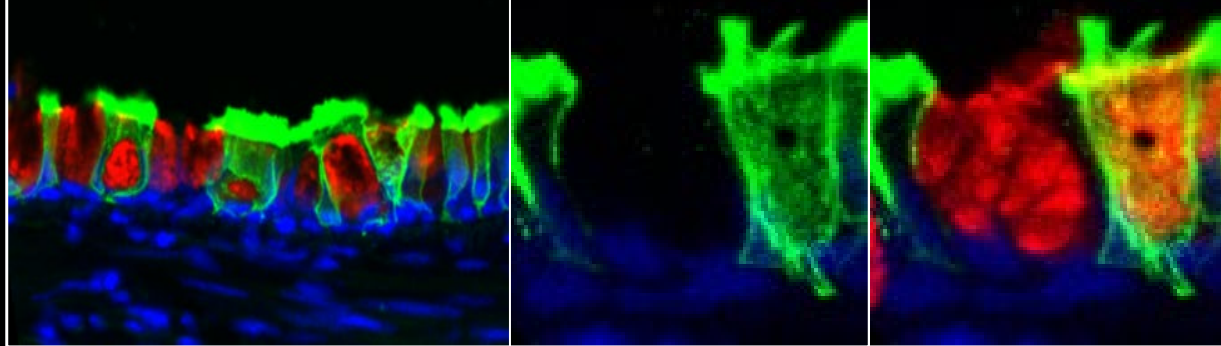
EGFP BSND



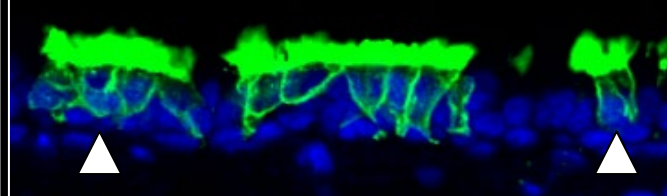
BSND



EGFP MUC5AC

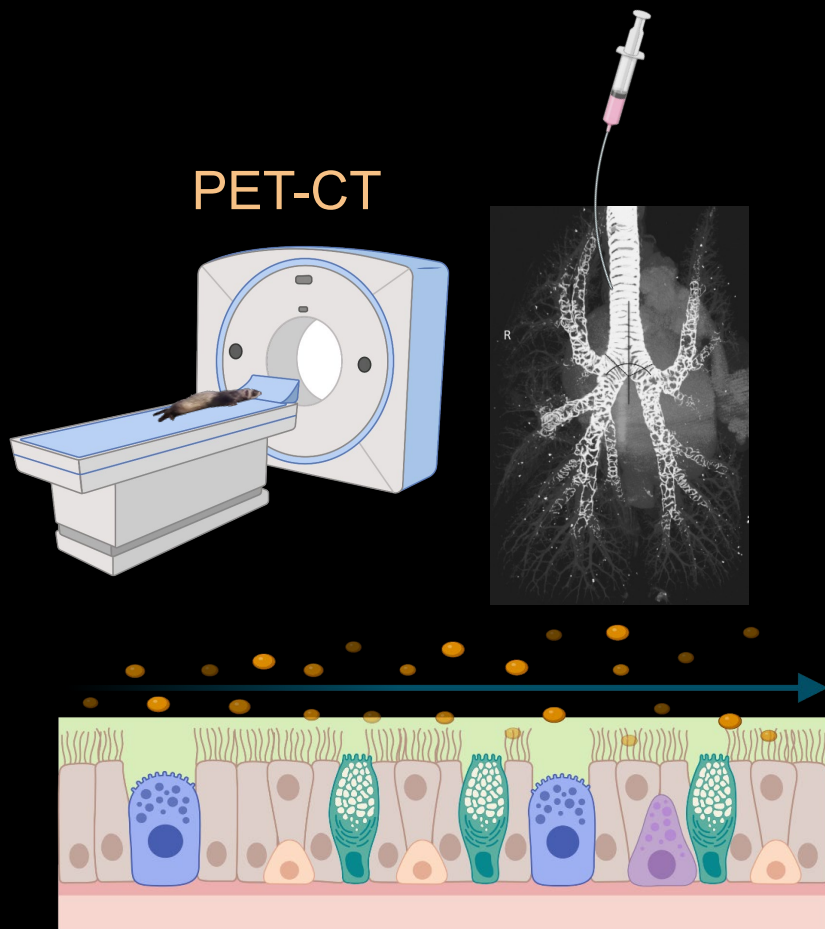


EGFP

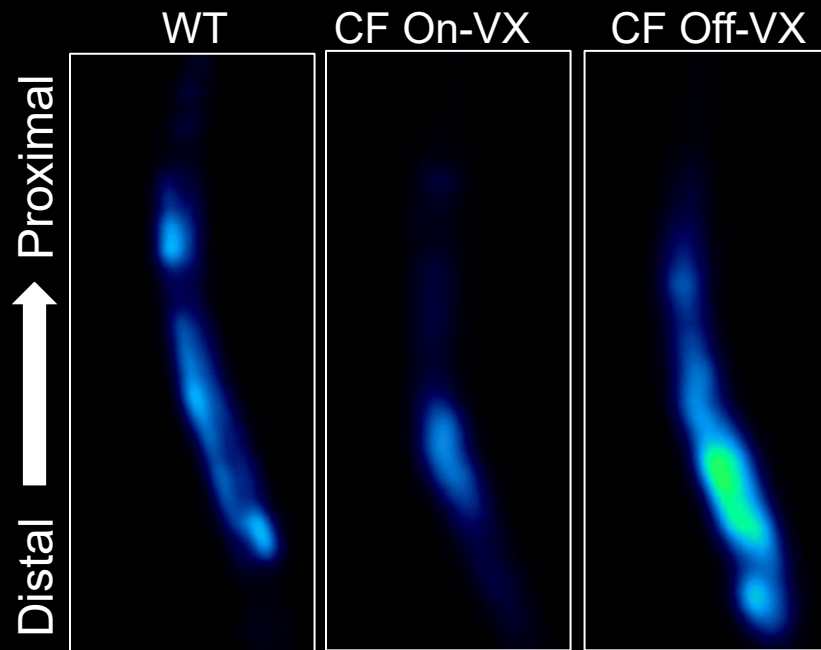


LUNAR[®] platform efficiently delivered mRNA payloads to multiple epithelial cell types including ciliated cells and some ionocytes in ferret airways.

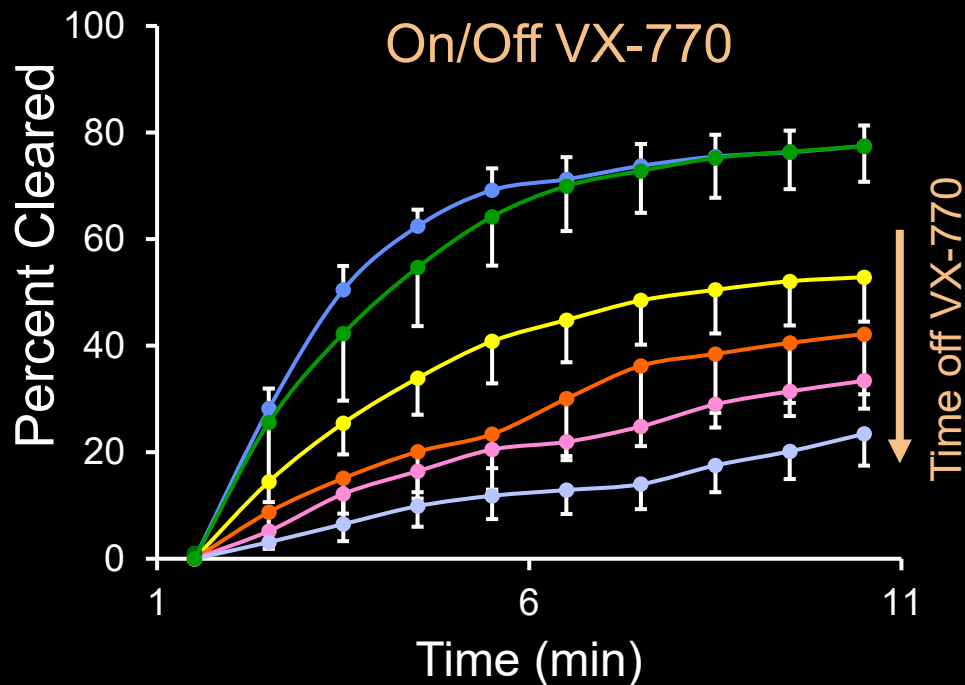
Mucociliary Clearance (MCC) Endpoints in CF Ferrets



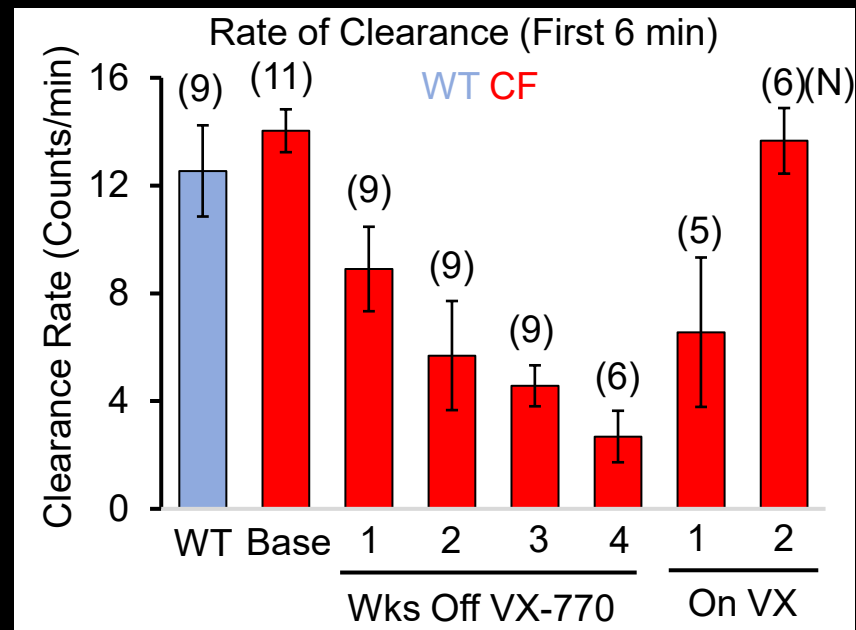
Gallium-68-albumin
SPECT/CT (Trachea)



G551D/G551D Ferrets On/Off VX-770



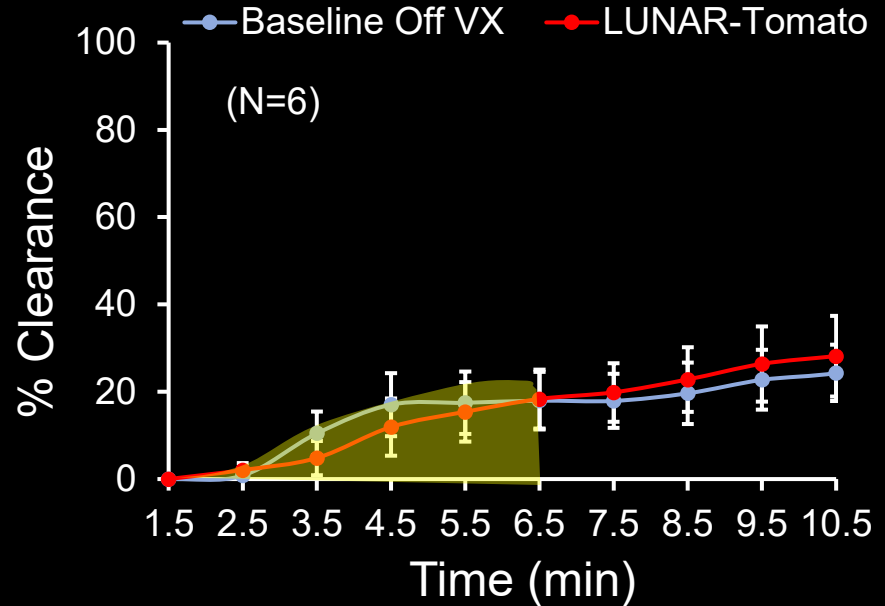
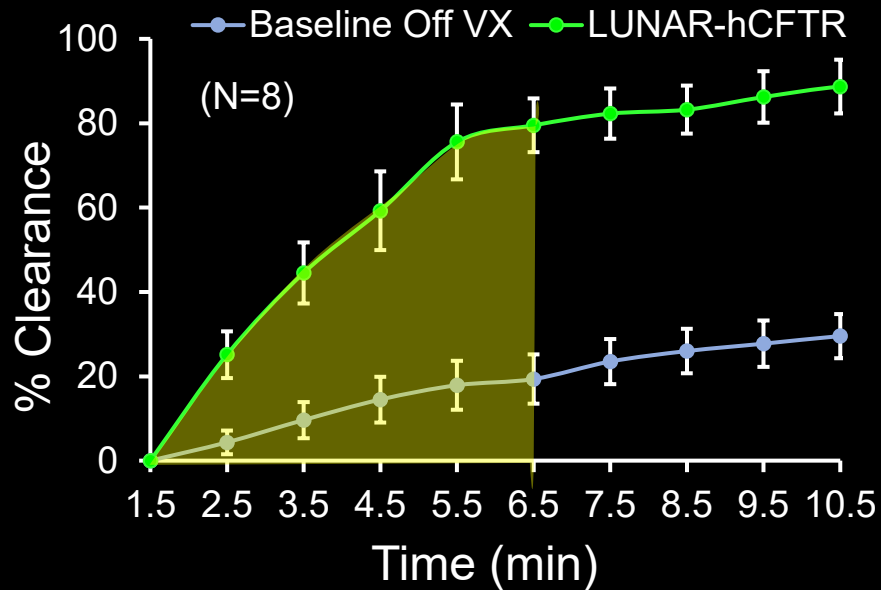
- Baseline
- Off 1 Wk
- Off 2 Wk
- Off 3 Wk
- Off 4 Wk
- On 2 Wk



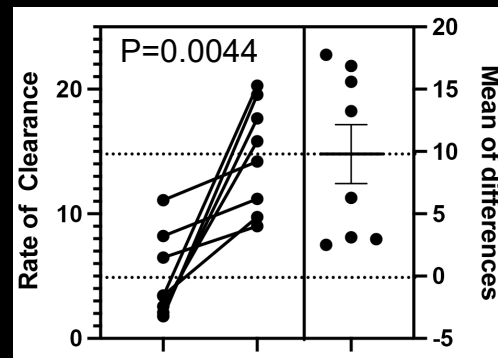
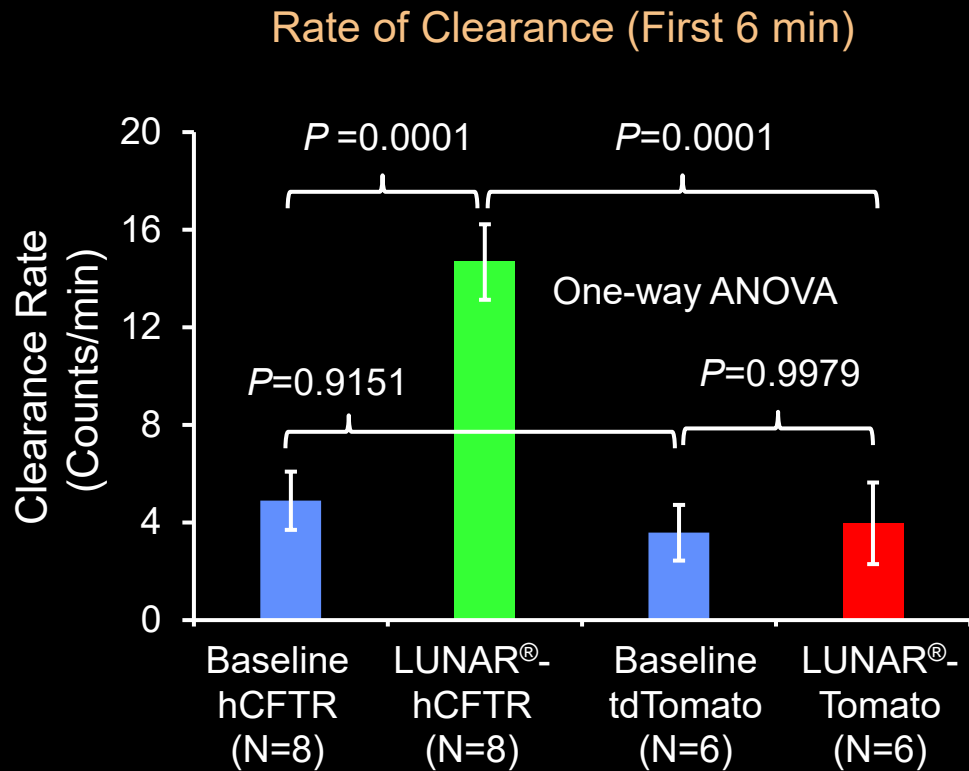
Airway clearance in the CF ferret model is CFTR-dependent.

ARCT-032 (LUNAR[®]-hCFTR) Improved MCC in CF Ferrets

- G551D ferrets were removed from VX-770 to achieve a MCC defect (20-40% of WT)
- MCC evaluated 24 hr post-dosing with LUNAR[®]-hCFTR or LUNAR[®]-TdTomato

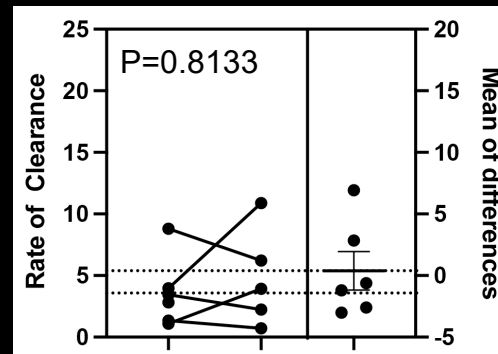


ARCT-032 (LUNAR[®]-hCFTR) Improved MCC in CF Ferrets



LUNAR[®]-hCFTR (N=8)

Paired Analysis



LUNAR[®]-tdTomato (N=6)

Pre Post Diff

Conclusions

- LUNAR[®] platform demonstrates efficient delivery of mRNA payloads and transfection in various cell types in ferret airways.
- ARCT-032 (LUNAR[®]-CFTR) improved CFTR activity in CF ferret model as demonstrated by significantly improved MCC.
- These in vivo results complement findings from in vitro studies in human bronchial epithelial cells (HBEs) derived from CF patients where ARCT-032 restored CFTR-mediated chloride conductance.
- ARCT-032 is currently being studied in a Phase 1 trial in healthy volunteers and adults with CF.