ARO-ENaC KOL Webinar

July 28, 2020

arrowhead pharmaceuticals

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This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

ARO-ENaC KOL Webinar July 2020

Welcome and Introductions

Vince Anzalone, CFA

Panelists

The Charité University Medical Center Berlin

Marcus Mall, M.D.
Professor and Director of the Department of Pediatric Pulmonology and Immunology

Arrowhead Pharmaceuticals

Vince Anzalone, CFA
Vice President, Investor Relations

Erik Bush, Ph.D.
Vice President, Biology

Javier San Martin, M.D.
Chief Medical Officer

Agenda

- Welcome and Introductions – Vince Anzalone
- ENaC as a Therapeutic Target in Cystic Fibrosis: Potential Role in the Era of CFTR Modulators – Dr. Marcus Mall
- ARO-ENaC Preclinical Pharmacology & the TRiM™ Pulmonary Delivery Platform – Dr. Erik Bush
- ARO-ENaC clinical development – Dr. Javier San Martin
- Q & A – Panel

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ENaC as a Therapeutic Target in Cystic Fibrosis: Potential Role in the Era of CFTR Modulators

Marcus Mall, M.D.

ENaC as a Therapeutic Target in Cystic Fibrosis: Potential Role in the Era of CFTR Modulators

Marcus A. Mall, MD, FERS

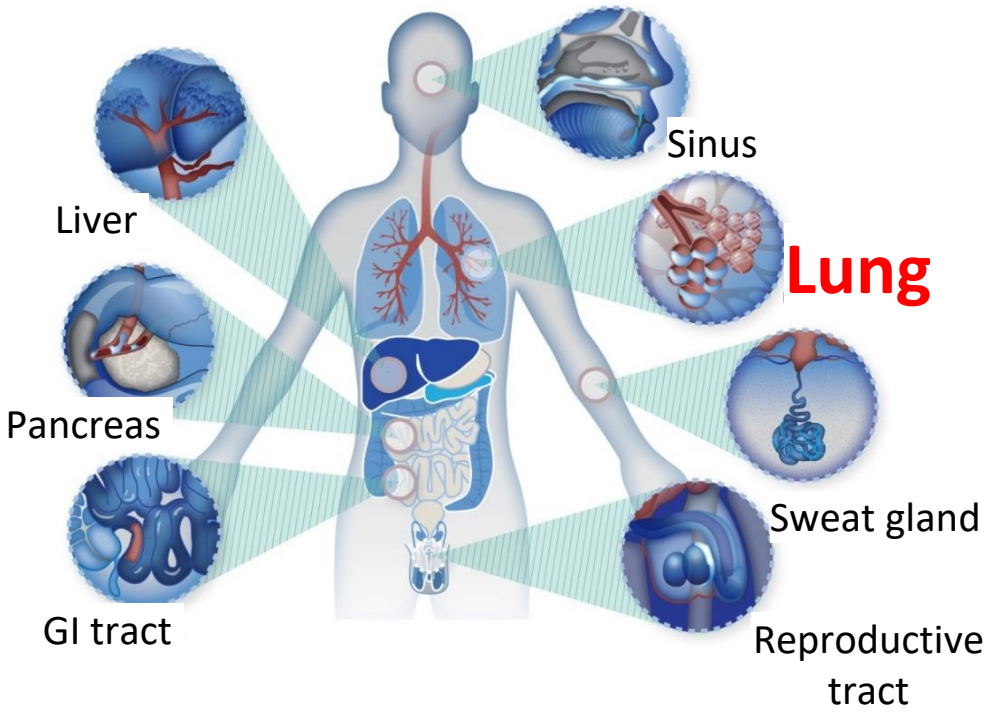
Department of Pediatric Pulmonology, Immunology and Critical Care Medicine

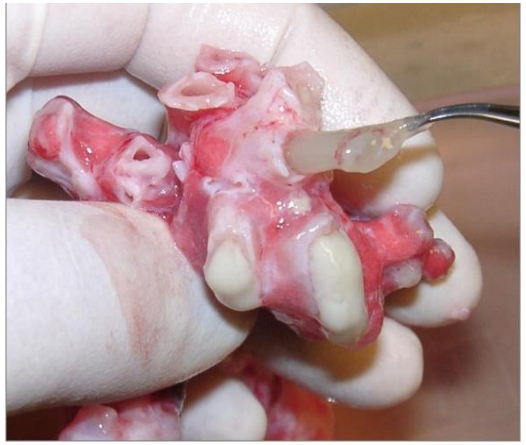
Christiane Herzog Cystic Fibrosis Center

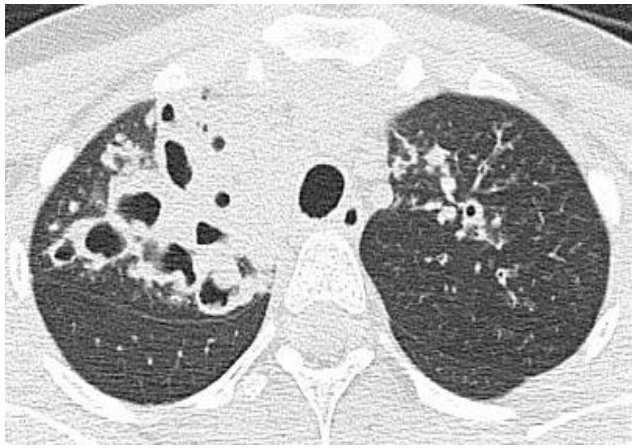
Charité - Universitätsmedizin Berlin

and Berlin Institute of Health

Cystic Fibrosis: Clinical Presentation



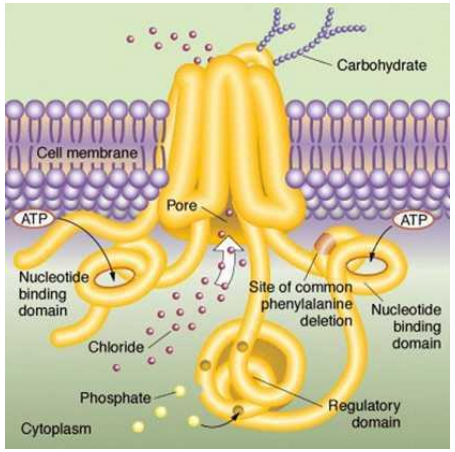




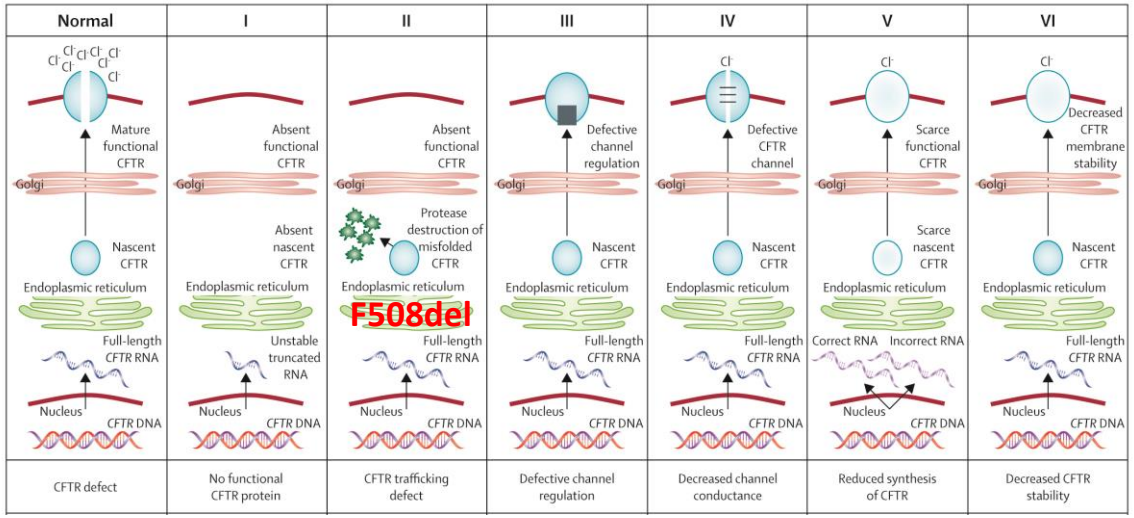
- Multiorgan disease caused by mutations in *CFTR* gene
- Most common fatal genetic disease in Caucasians (~1:3000)
- Lung disease determines >90% of morbidity and mortality
- Chronic airway mucus obstruction
- Chronic airway infection and inflammation
- Progressive irreversible lung damage
- Global patient population: ~90.000 patients (North America, Europe, Australia)
- Current life expectancy ~40 years

O'Sullivan BP, Freedman SD. *Lancet*. 2009
Bell SC & Mall MA et al. *Lancet Respiratory Medicine* 2020

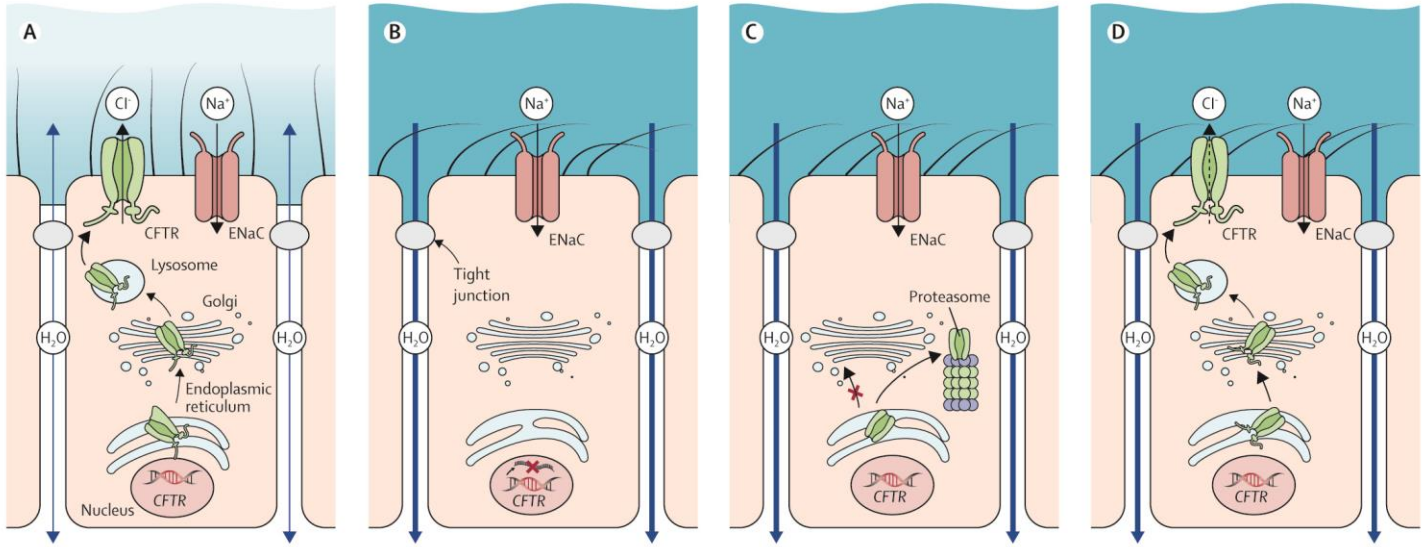
Pathophysiology of Cystic Fibrosis Lung Disease



CFTR anion channel



Molecular mechanisms of CFTR dysfunction

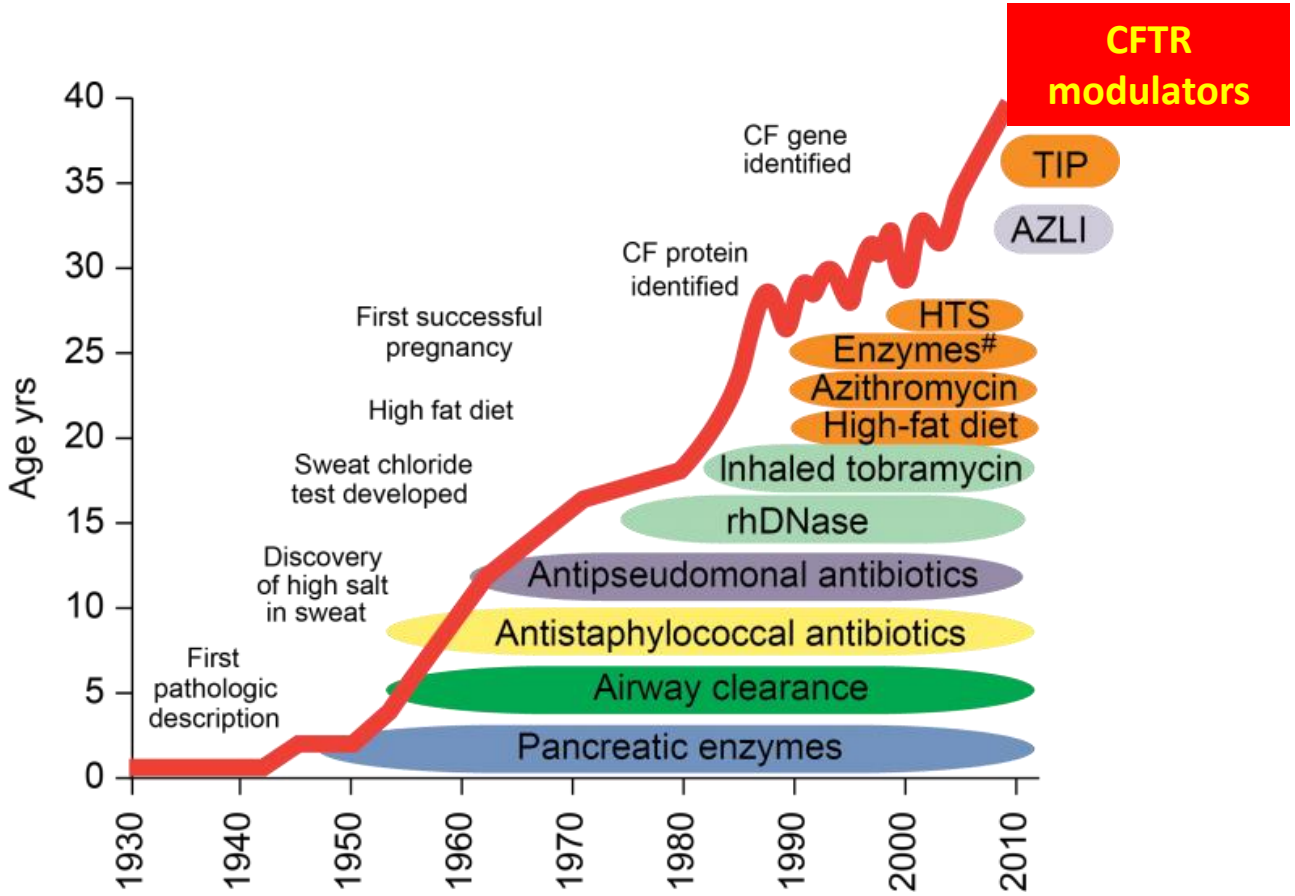


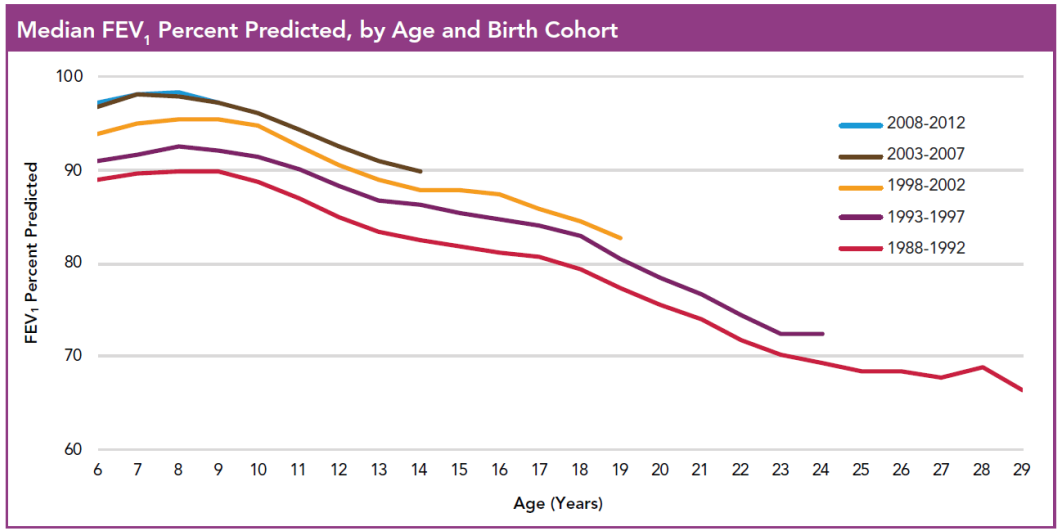
Consequences of CFTR Dysfunction

- Imbalance between CFTR-mediated secretion and ENaC-mediated absorption of salt and water
- Mucus dehydration on airway surfaces
- Impaired mucociliary clearance (key defense mechanism of the lung)
- Mucus plugging, infection, inflammation

Riordan JR et al. *Science* 1989
Bell SC & Mall MA et al. *Lancet Respiratory Medicine* 2020

Evolution of Specialized CF Care, Impact on Clinical Outcomes and Unmet Medical Need



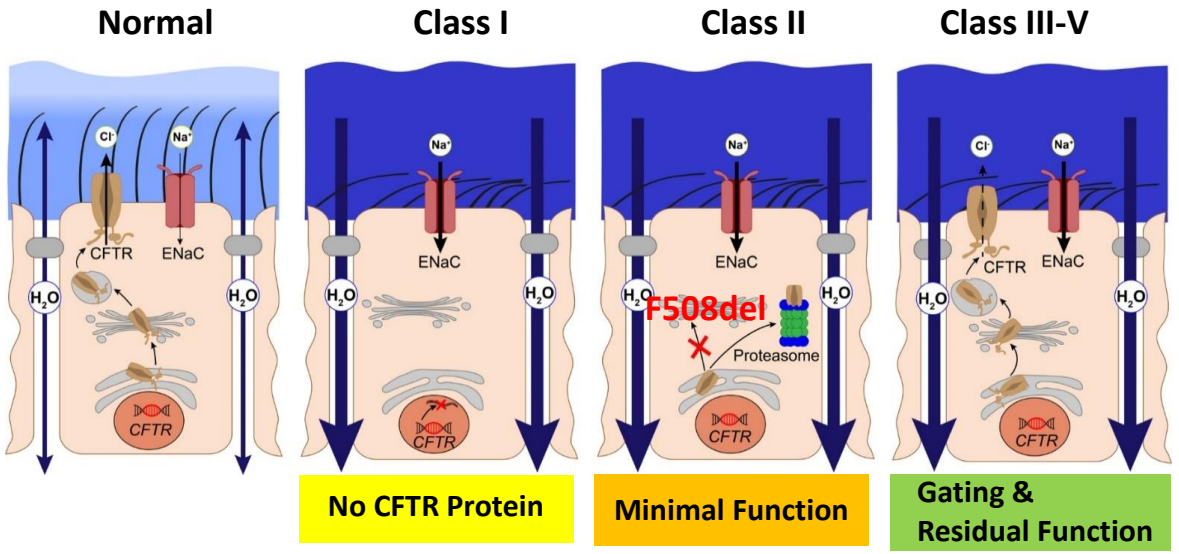


Progression of CF lung disease continues despite improvements in therapy

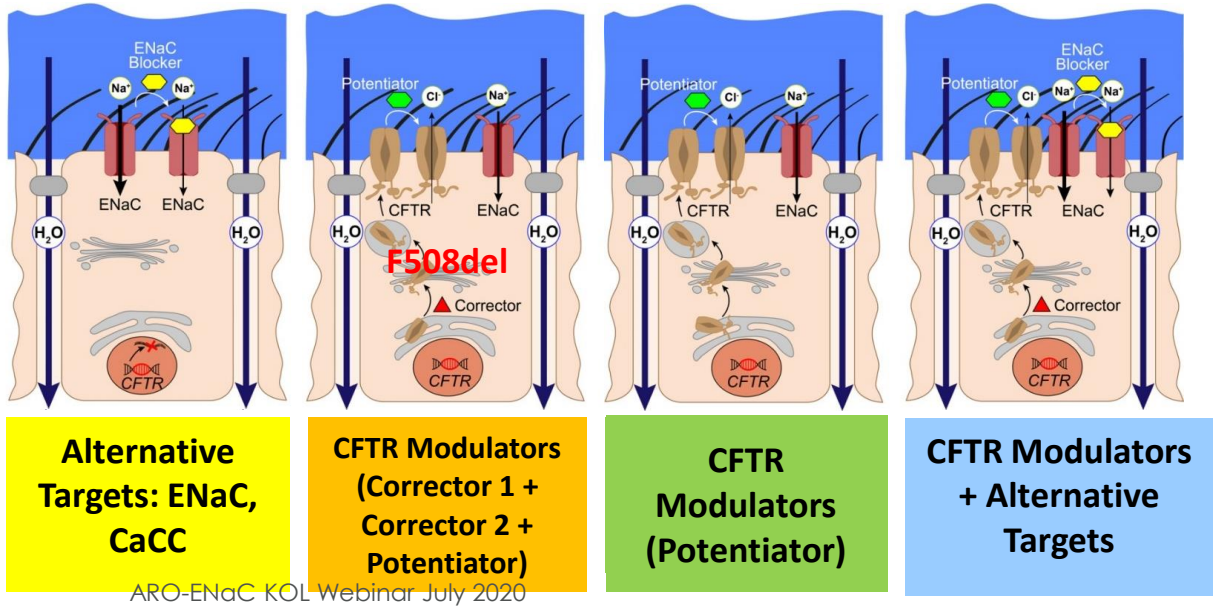
Elborn JS, The European Lung White Book, *ERS*, 2013
CFF Patient Registry, 2017 Annual Data Report

Key to Further Improvement: Targeted Therapy of the CF Ion Transport Defect

CFTR mutation classes & genotype groups

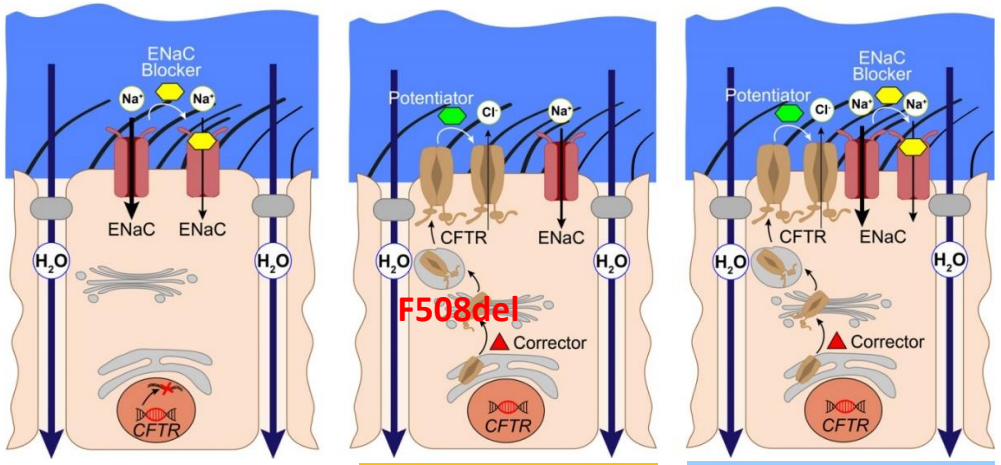


Therapeutic strategies



Gentzsch M & Mall MA, *Chest* 2018

The Role of ENaC Inhibition in Cystic Fibrosis in the Era of CFTR Modulators



Alternative Target: ENaC

CFTR Modulators

CFTR Modulators + ENaC Inhibition

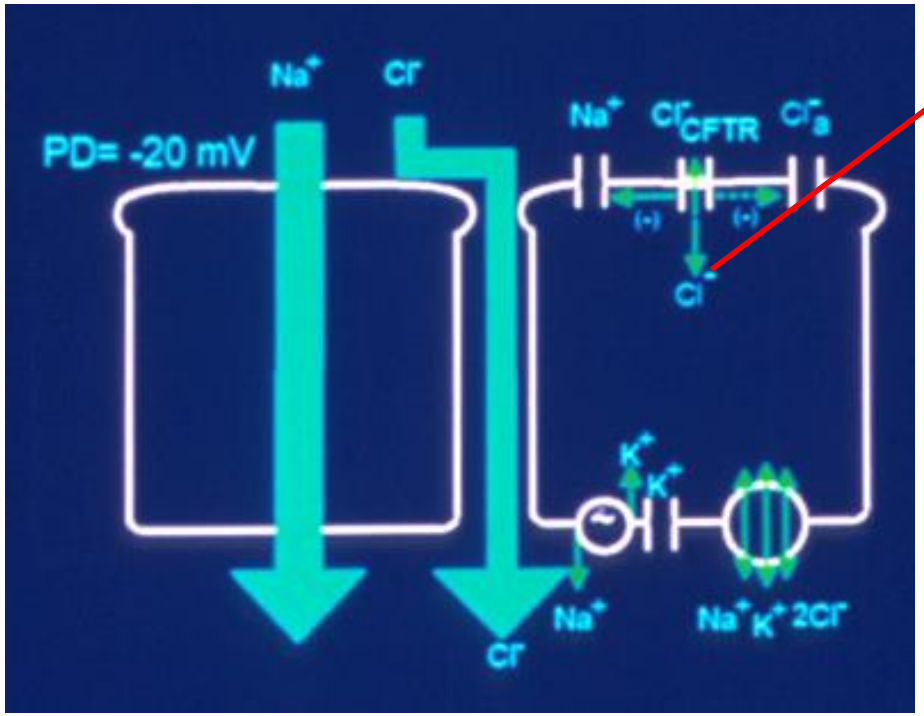
No CFTR modulator therapy in ~15% of patients without F508del mutation

Triple combination therapy effective in ~85% of patients with single F508del mutation

Potential synergy between CFTR modulation and ENaC inhibition

Gentzsch M & Mall MA, *Chest* 2018

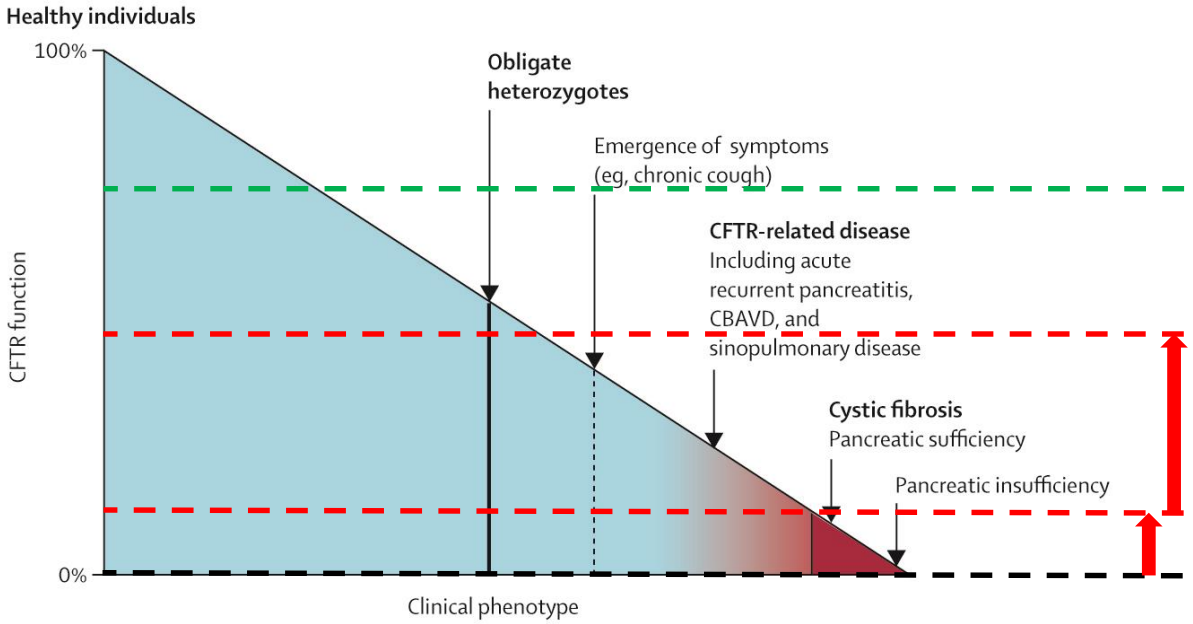
Potential Synergy Between ENaC Inhibition and CFTR Modulation



- Reversal potential for Cl^- in CF airway epithelial cells is = -30 mV
- Membrane potential more negative than -30 mV improves driving force for CFTR-mediated Cl^- secretion
- Apical membrane potential in CF airway epithelial cells is determined by ENaC conductance (V_a = -10 mV)
- ENaC inhibition changes V_a from -10 mV to -60 mV and therefore improves electro-chemical driving force for Cl^- secretion mediated by mutant CFTR rescued by CFTR modulators

Willumsen NJ and Boucher RC. *Am J Physiol* 1991

Relationship Between CFTR Function and Clinical CF Phenotype, and Level of Correction of F508del by Highly Effective CFTR Modulators Therapy Support Clinical Relevance of Synergistic Approach in CF



Goal to achieve optimal benefit

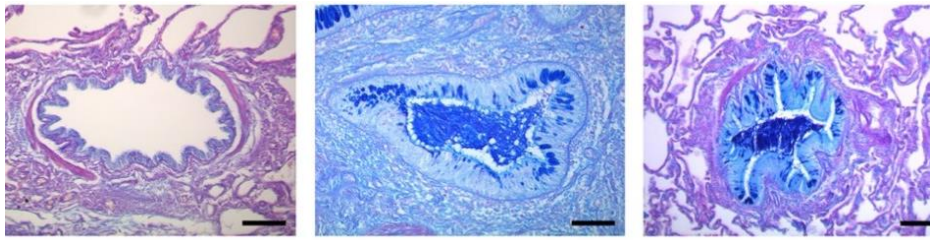
Ivacaftor (G551D/other) and Elexacaftor/Tezacaftor/Ivacaftor (F508del/MF)

Lumacaftor/Ivacaftor (F508del/F508del)

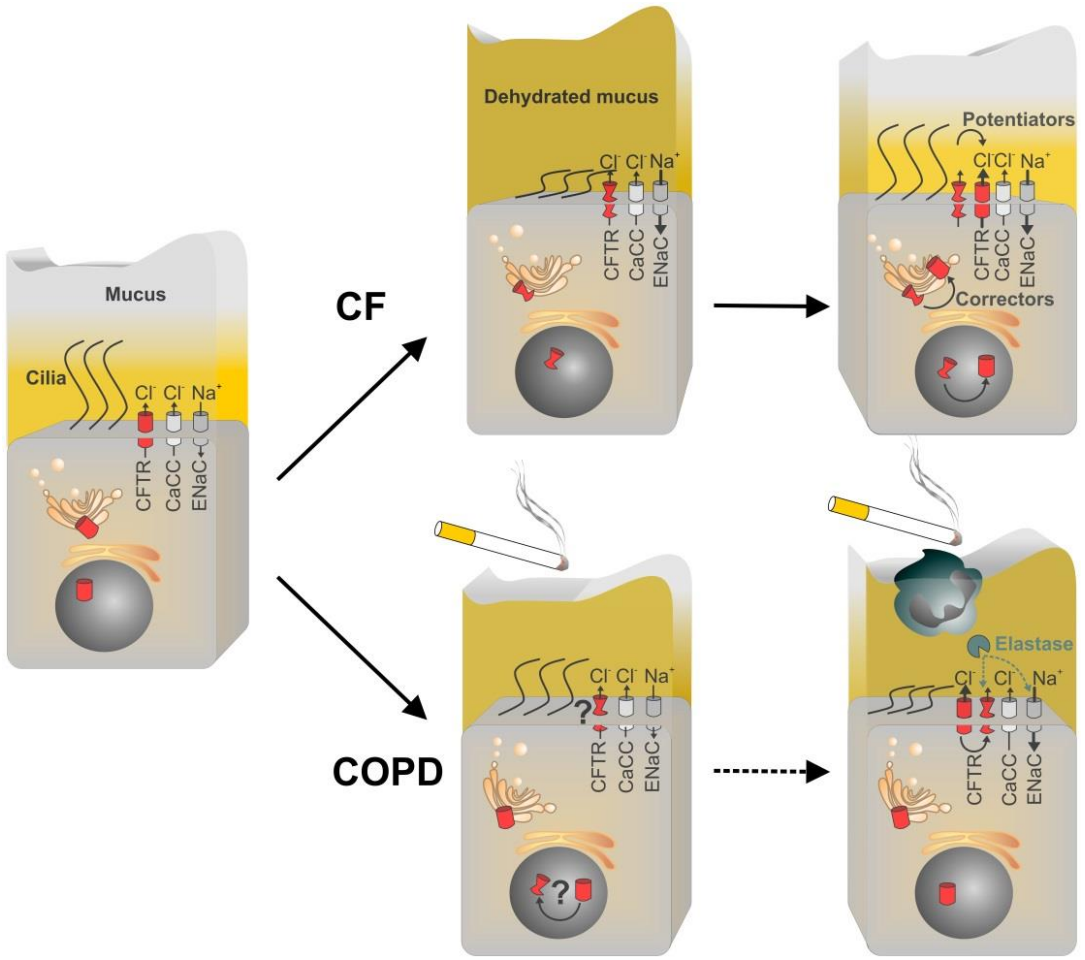
Wilschanski M et al. *AJRCCM* 2006, Ramsey B et al. *NEJM* 2011, Graeber SY et al. *AJRCCM* 2018, Masson A et al. *J Cyst Fibros* 2019, Keating D et al. *NEJM* 2018, Bell SC et al. *LRM* 2020

ENaC as a Target in Other Muco-obstructive Lung Diseases

Healthy Cystic fibrosis COPD



- Mucus plugging
- Chronic inflammation and recurrent infection
- Remodeling and tissue damage



Mall MA & Hartl D. *ERJ* 2014
Boucher RC *NEJM* 2019

Summary and Opportunities

- ENaC plays an important role in the pathophysiology of CF lung disease and constitutes a promising alternative target to improve airway surface hydration and mucus clearance in patients, independent of their *CFTR* genotype
- A substantial number of CF patients (without F508del allele) cannot be treated with current CFTR modulators and could benefit from ENaC inhibition
- Partial rescue of CFTR with current CFTR modulators does not prevent progression of CF lung disease demonstrating an unmet medical need for further improvement of targeted CF therapy
- ENaC inhibition has potential to act synergistically with CFTR modulators by improving the driving force for chloride/fluid secretion mediated by mutant CFTR rescued by CFTR modulators
- ENaC inhibition has potential as novel therapeutic approach to improve mucus clearance and provide clinical benefits to patients with other muco-obstructive lung diseases, including COPD

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ARO-ENaC Preclinical Pharmacology & the Pulmonary TRiM™ Delivery Platform

Erik Bush, Ph.D.

Human genetics validate ENaC as CF target

Excess ENaC activity worsens CF phenotype

J Physiol 2010; 588.8: 1211-1225

***CFTR* (- / -) = cystic fibrosis**

***CFTR* (- / +) = normal**

↓

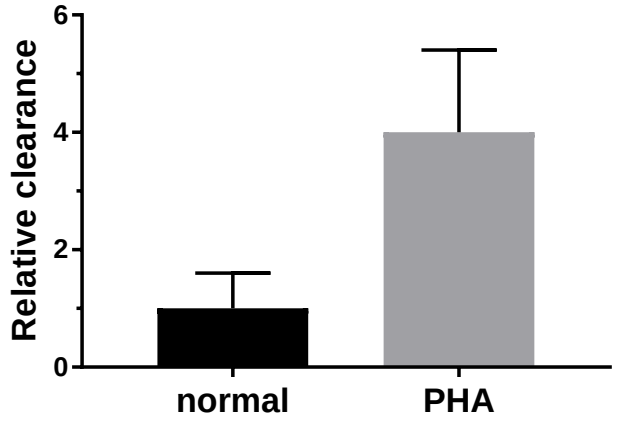
***ENaC* activating mutation** **= 'atypical' CF**

Loss of ENaC activity increases lung hydration and clearance

N Engl J Med 1999;341: 156-62

***ENaC* (- / -) = PHA**

Mucociliary clearance



Partial ENaC activity improves CF phenotype

Am J Respir Cell Mol Biol 2017; 57: 711-720

***CFTR* (- / -) = cystic fibrosis**

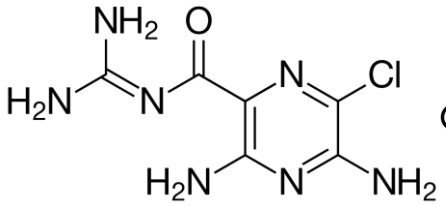
↓

***ENaC* (- /+) = 'nonprogressive' CF**

50% reduction in expression may be disease-modifying?

ARO-ENaC overcomes limitations of small molecule inhibitors

- Inhaled small molecule ENaC inhibitor programs
  - Parion, Gilead, Vertex
  - Astra-Zeneca, Novartis, Amgen, BI



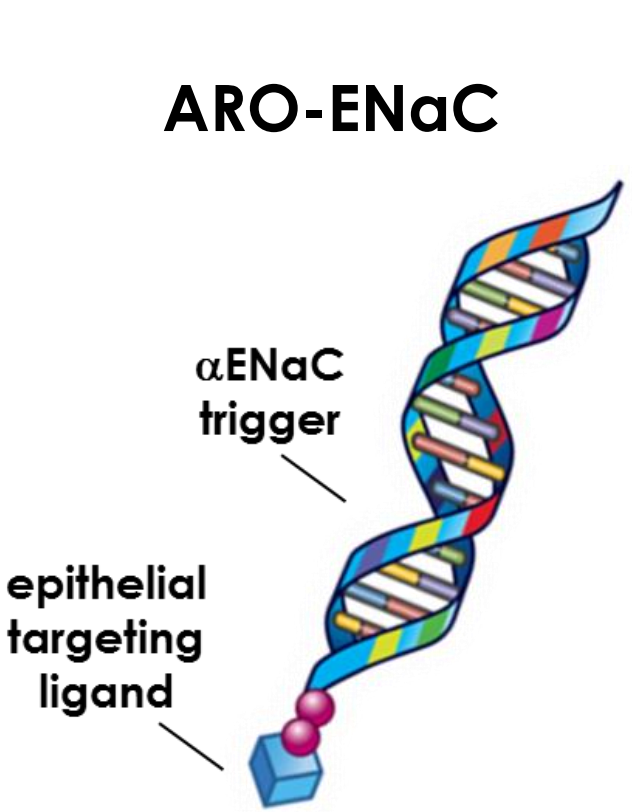
amiloride

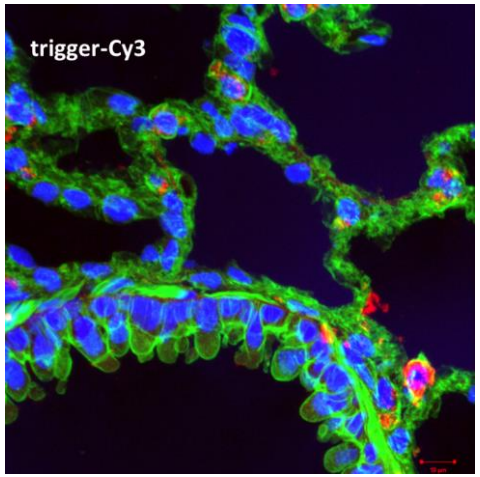
- Challenge #1: Short duration of action
  - Inhaled small molecule inhibitors transiently improve lung clearance, but are rapidly absorbed into circulation
- Challenge #2: On-target renal toxicity
  - ENaC mediates sodium reabsorption in distal nephron
  - Systemic exposure results in renal ENaC inhibition and hyperkalemia

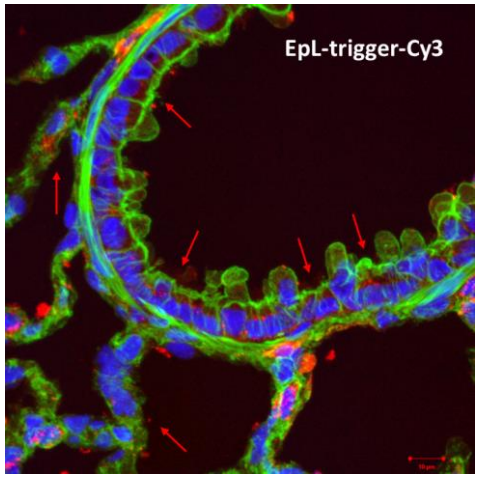
Targeted RNAi delivery to lung overcomes efficacy and safety challenges

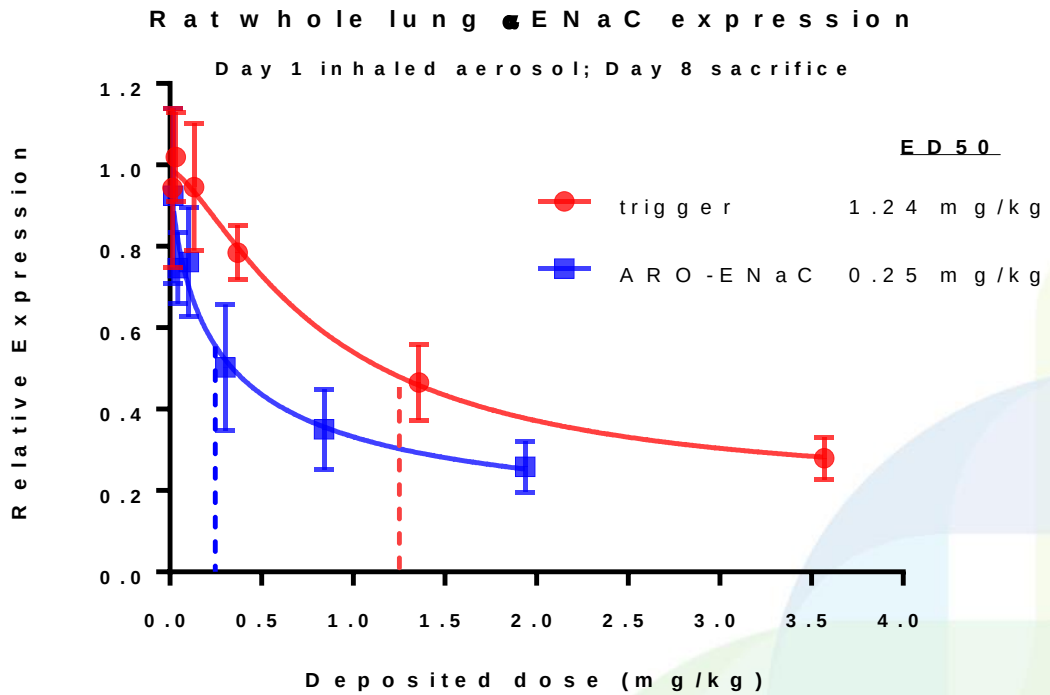
ARO-ENaC utilizes the TRiM™ platform for pulmonary delivery

Epithelial targeting improves trigger uptake and activity

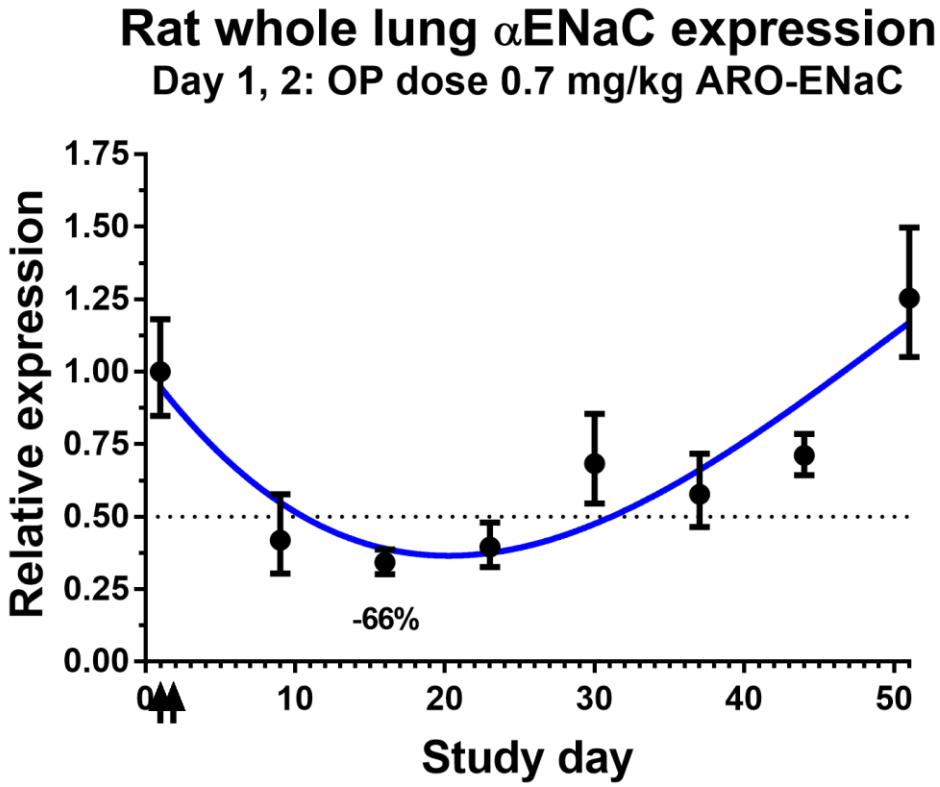






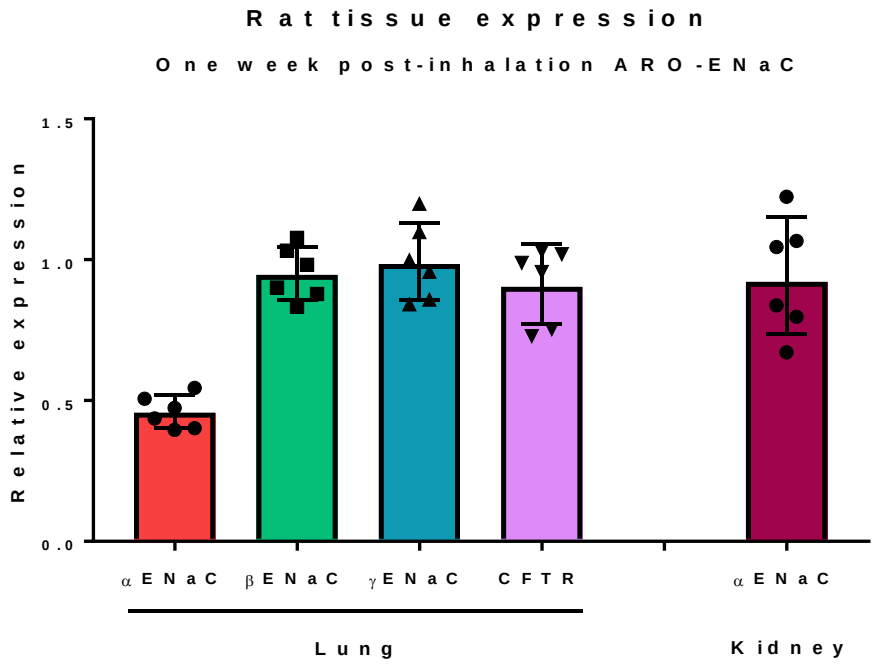


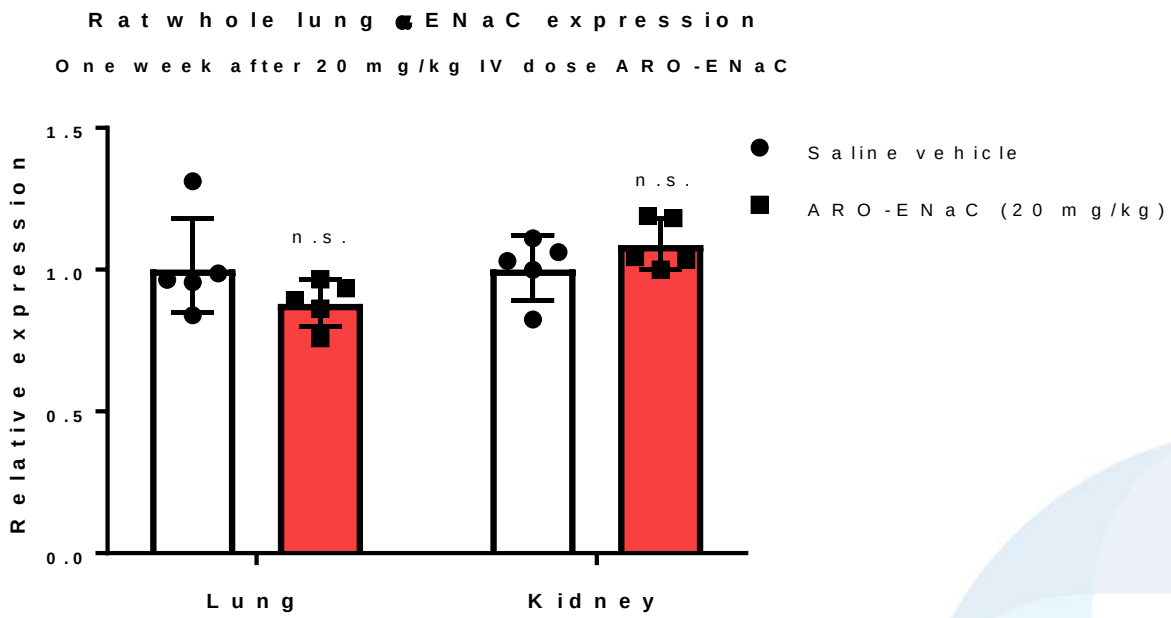
ARO-ENaC durably silences pulmonary αENaC expression



Durable mRNA silencing supports every other week (or less frequent) dose regimens

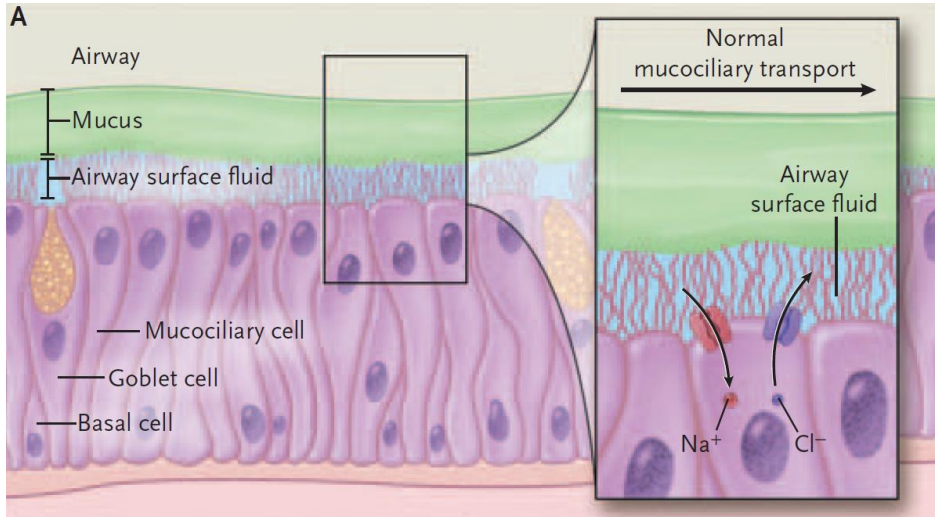
ARO-ENaC spares renal αENaC expression and function





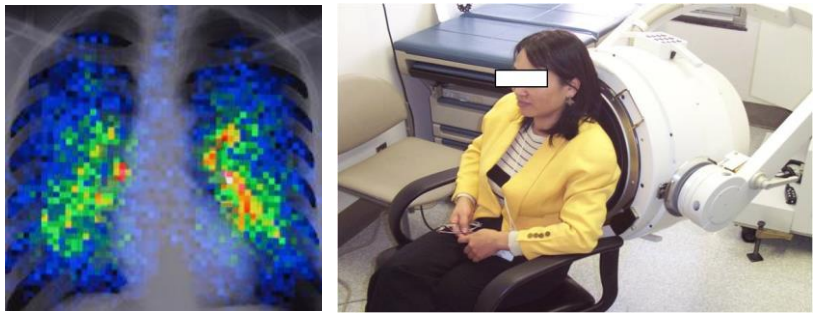
Serum electrolytes in normal range
No evidence of hyperkalemia or other imbalances

Airway hydration, mucociliary clearance and clinical measures of mucoobstruction



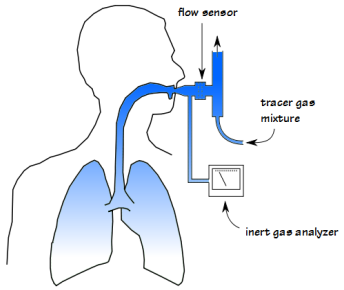
NEJM 2006, 354 (3) 291-293

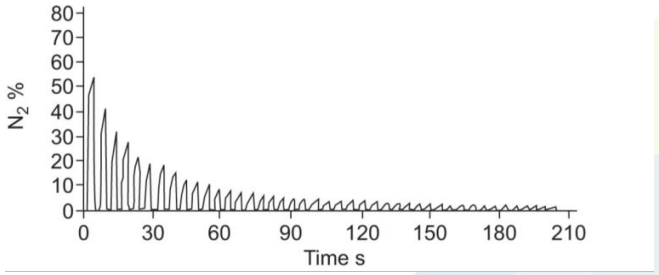
Mucociliary Clearance (MCC)



Inhaled tracer particles deposit in airway surface mucus

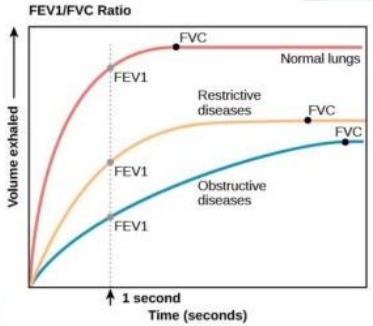
Lung clearance index (LCI)



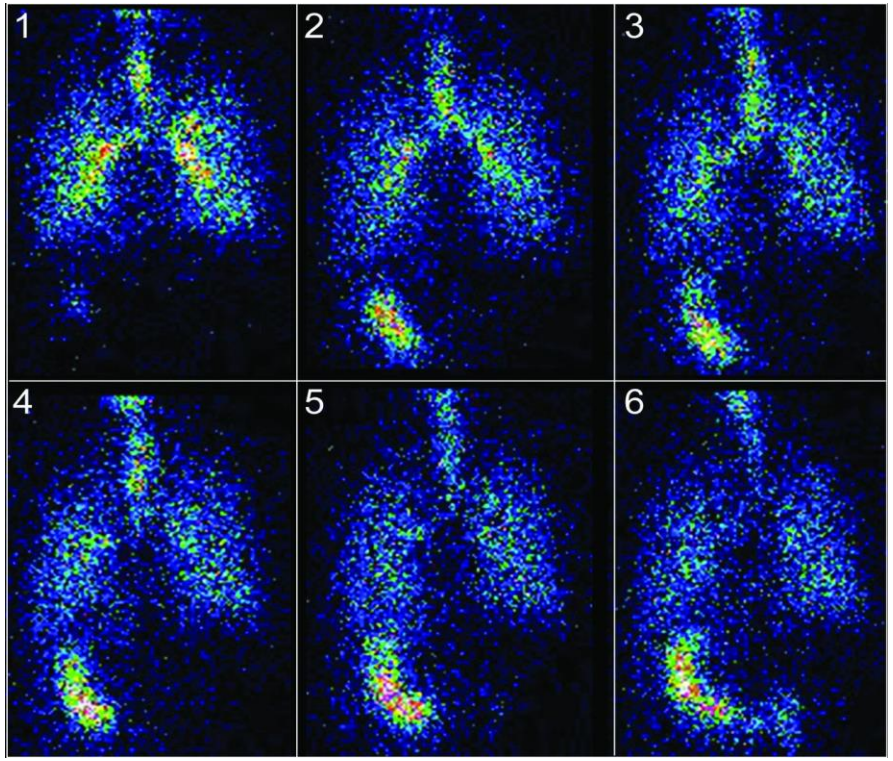


Multiple breath washout of inert gas: index of lung ventilation inhomogeneity

Spirometry

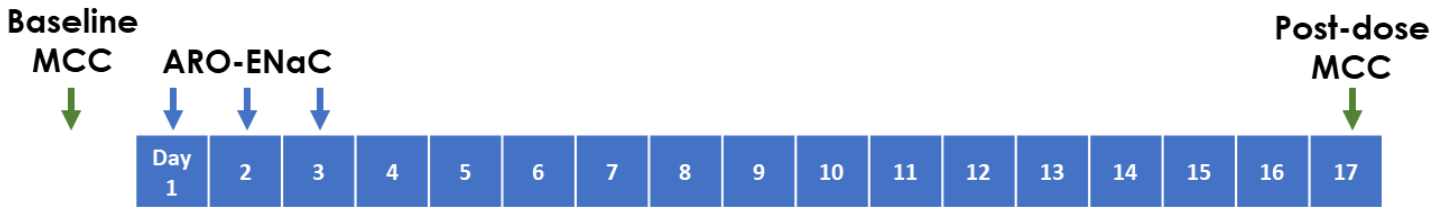


Mucociliary clearance (MCC) in normal sheep
A large animal model of airway physiology



Respiratory Care 2015, 60 (6) 850-857

- Inhaled aerosolized ^{99m}Tc-radiolabeled sulfur colloid
- Gamma imaging over 1-2 hours

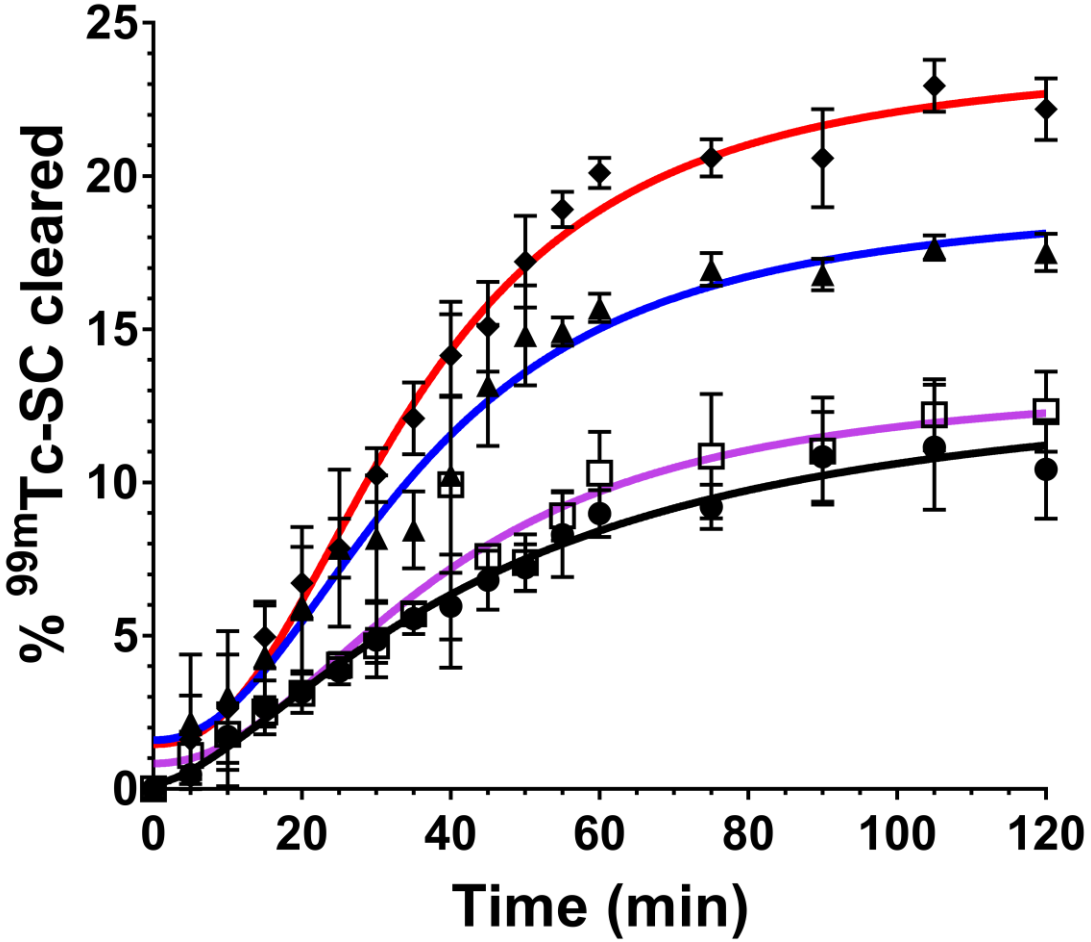


Day -3: Pre-dose baseline MCC scan

Days 1-3: Aerosolized ARO-ENaC inhalation

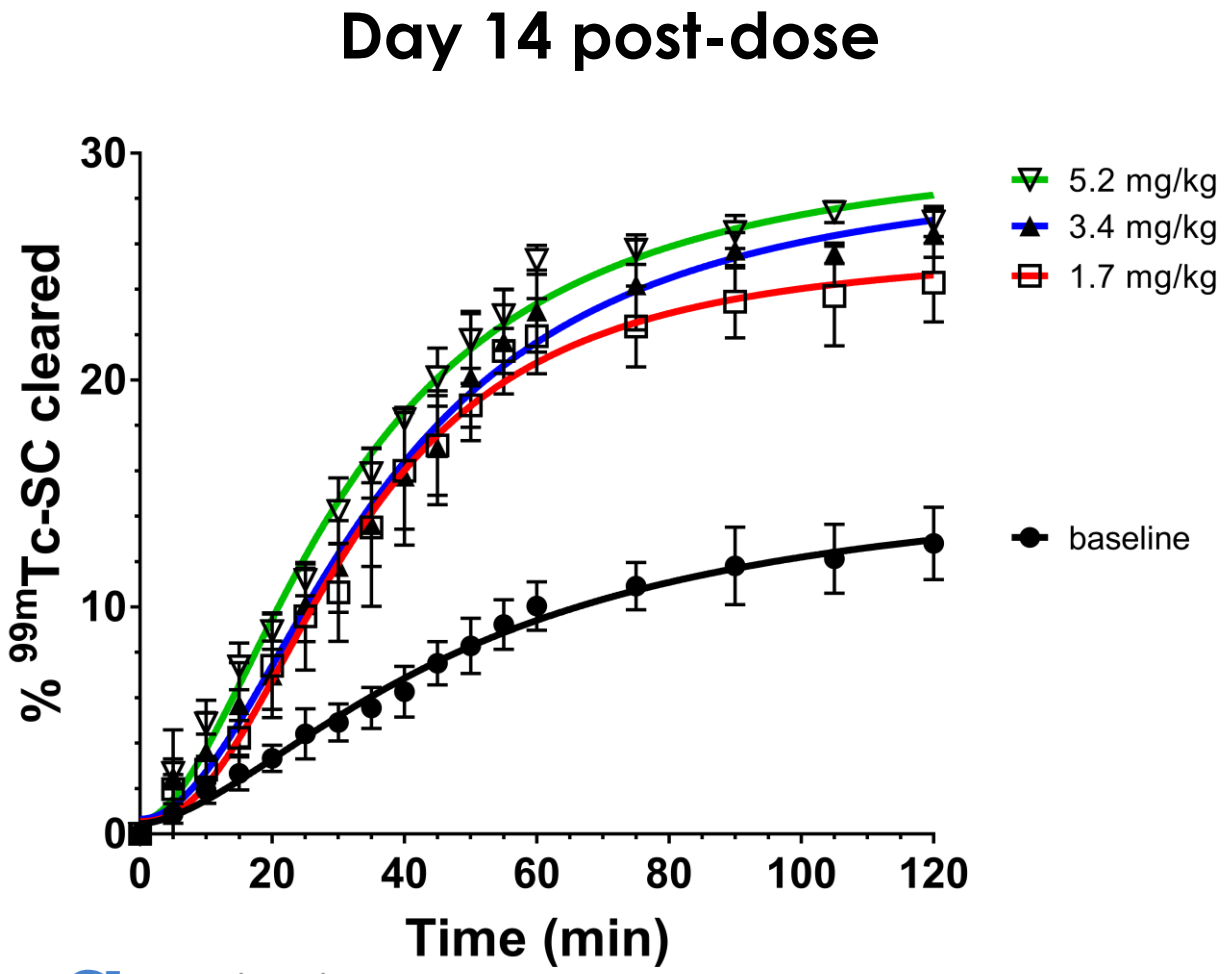
Day 17: Post-dose MCC scan

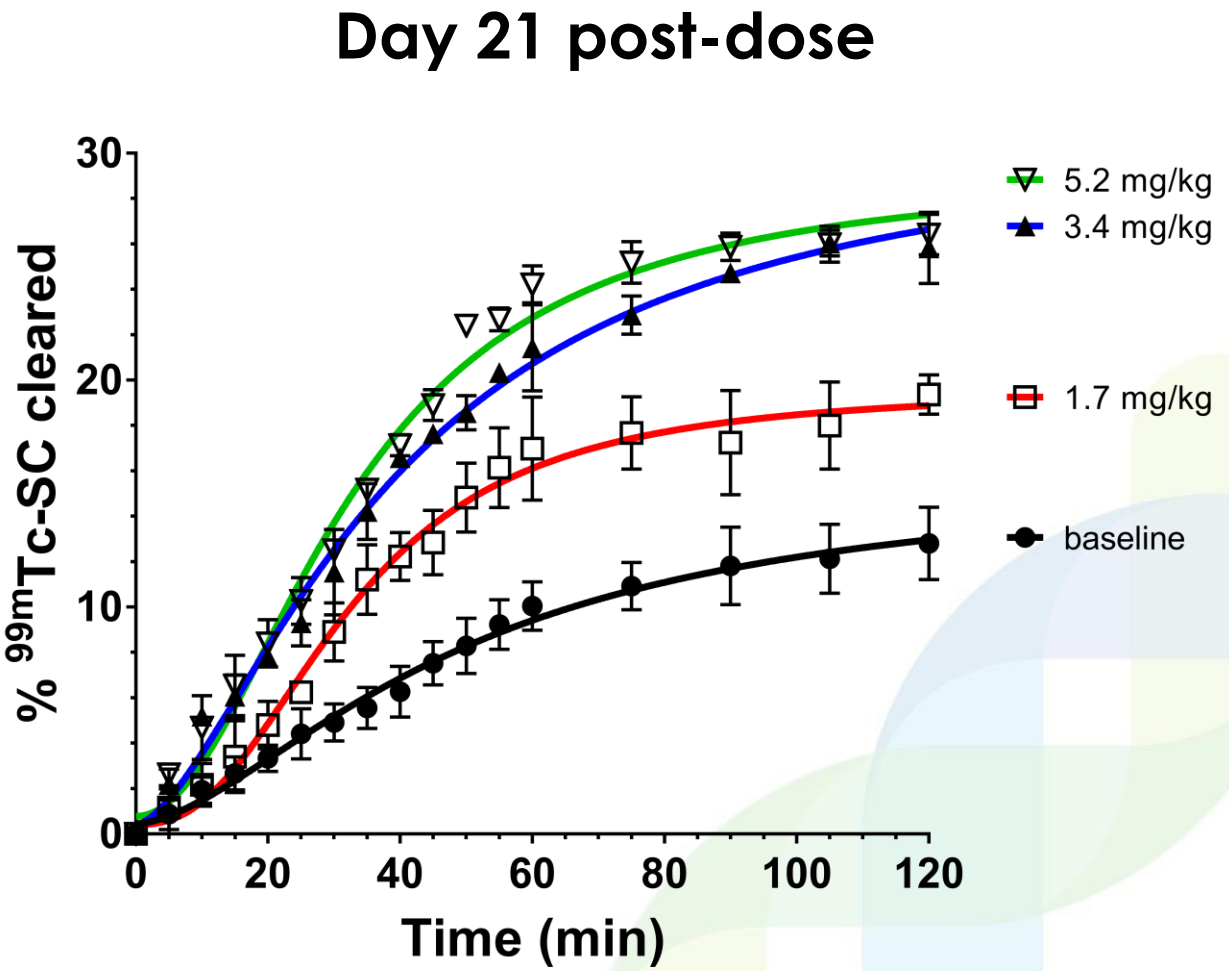
ARO-ENaC accelerates mucociliary clearance in sheep two weeks after inhaled dosing



2x (100%) increase over baseline rate

A single inhaled dose of ARO-ENaC accelerates MCC in normal sheep up to three weeks





ARO-ENaC preserves function in a sheep disease model of impaired mucocilary clearance

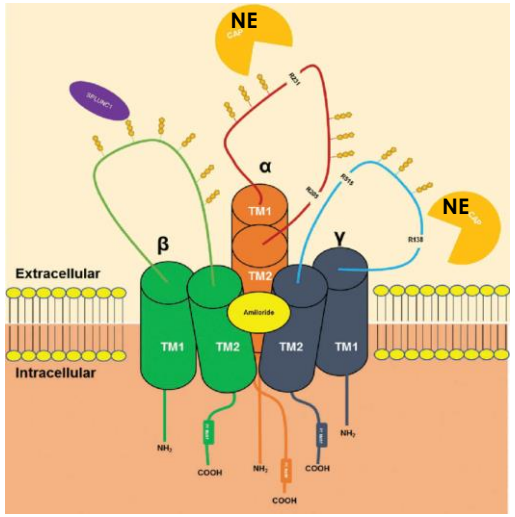
Am J Physiol Lung Cell Mol Physiol 288: L813–L819, 2005.
First published January 7, 2005; doi:10.1152/ajplung.00435.2004.

TRANSLATIONAL PHYSIOLOGY

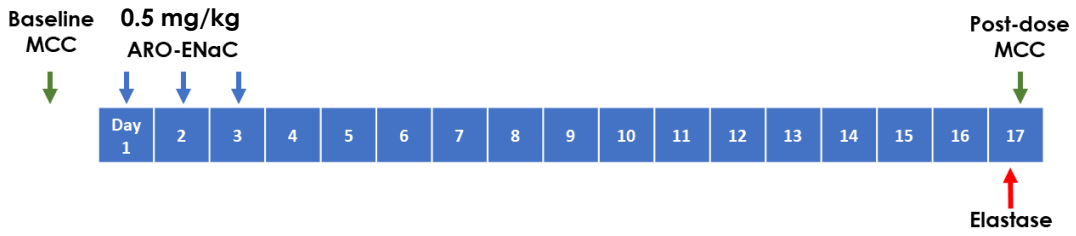
Neutrophil elastase activates near-silent epithelial Na^+ channels and increases airway epithelial Na^+ transport

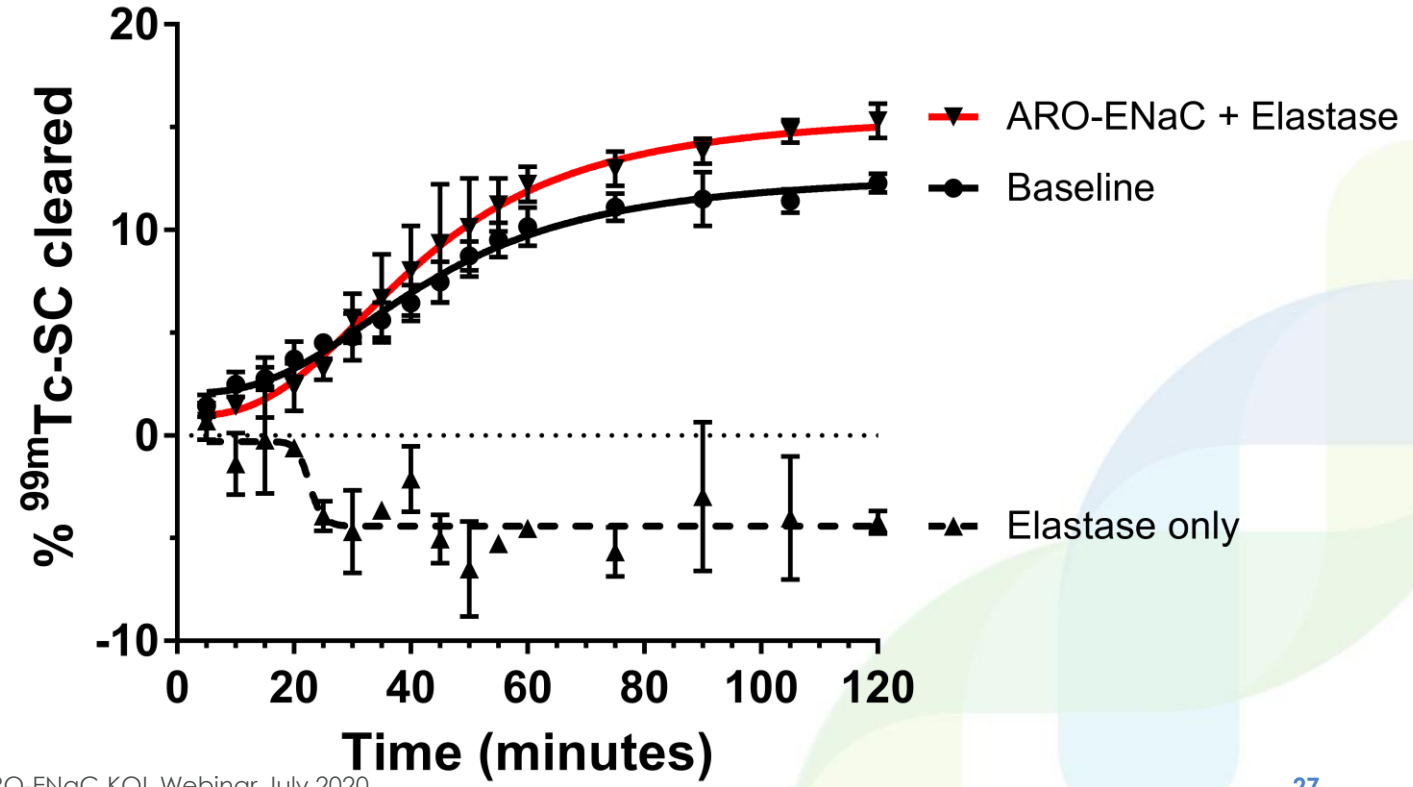
Ray A. Caldwell, Richard C. Boucher, and M. Jackson Stutts
The Cystic Fibrosis/Pulmonary Research and Treatment Center, University of North Carolina, Chapel Hill, North Carolina

Submitted 19 November 2004; accepted in final form 5 January 2005



Expert Opin Ther Tar 2018; 22: 687-701





Doubling of MCC in ivacaftor-treated G551D CF patients correlates with improved clinical outcomes

JCI insight

Effect of ivacaftor on mucociliary clearance and clinical outcomes in cystic fibrosis patients with G551D-CFTR

Scott H. Donaldson, … , Steven M. Rowe, William D. Bennett

JCI Insight. 2018;3(24):e122695. https://doi.org/10.1172/jci.insight.122695.

Clinical Medicine | Pulmonology

BACKGROUND. The ability to restore cystic fibrosis transmembrane regulator (CFTR) function with effective small molecule modulators in patients with cystic fibrosis provides an opportunity to study relationships between CFTR ion channel function, organ level physiology, and clinical outcomes.

METHODS. We performed a multisite, prospective, observational study of ivacaftor, prescribed in patients with the G551D-CFTR mutation. Measurements of lung mucociliary clearance (MCC) were performed before and after treatment initiation (1 and 3 months), in parallel with clinical outcome measures.

RESULTS. Marked acceleration in whole lung, central lung, and peripheral lung MCC was observed 1 month after beginning ivacaftor and was sustained at 3 months. Improvements in MCC correlated with improvements in forced expiratory volume in the first second (FEV_1) but not sweat chloride or symptom scores.

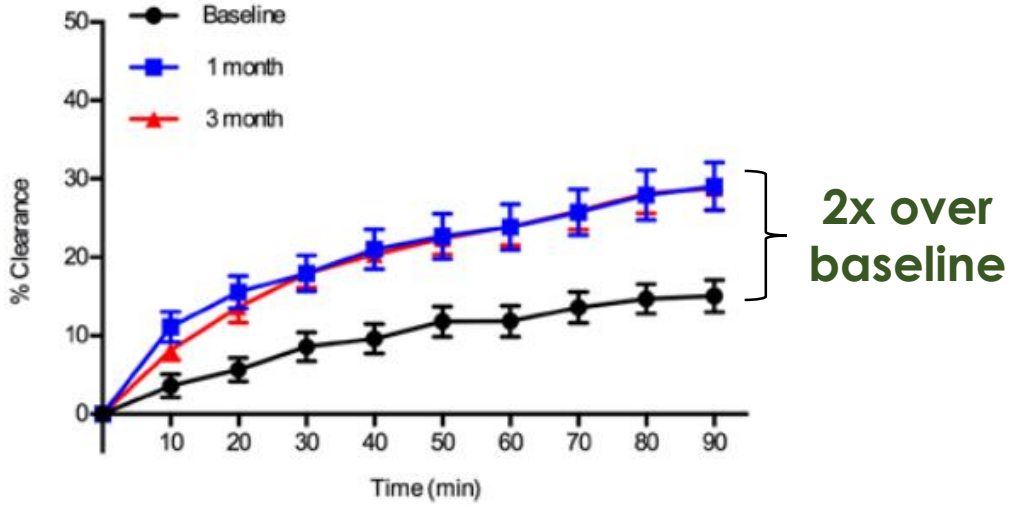
CONCLUSIONS. Restoration of CFTR activity with ivacaftor led to significant improvements in MCC. This physiologic assessment provides a means to characterize future CFTR modulator therapies and may help to predict improvements in lung function.

TRIAL REGISTRATION. ClinicialTrials.gov, NCT01521338.

ivacaftor
150 mg BID

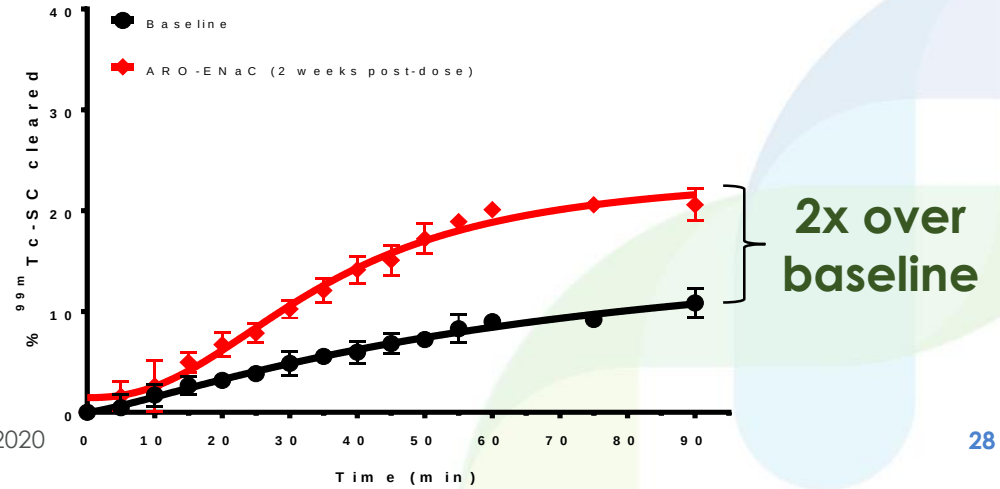
Accelerated MCC correlated with improved FEV_1

CF patient MCC



ARO-ENaC
3 x 0.5 mg/kg

Sheep MCC



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ARO-ENaC preclinical pharmacology
Summary

- ENaC is a well-validated therapeutic target for cystic fibrosis and muco-obstructive lung disease
- ARO-ENaC overcomes critical limitations of small molecule inhibitors
- ARO-ENaC inhalation silences ENaC expression selectively in the lung, doubling mucociliary clearance for weeks post-dose and preserving clearance in a sheep disease model of mucostasis with no evidence of systemic activity (e.g. electrolyte imbalance)
- Promising results observed in various preclinical toxicology studies

ARO-ENaC Clinical Development

Javier San Martin, M.D.

Phase 1/2 Protocol, AROENaC1001

Title

A Phase 1/2a Dose-Escalating Study to Evaluate the Safety, Tolerability and Pharmacokinetic Effects of ARO-ENaC in Normal Healthy Volunteers and Safety, Tolerability and Efficacy in Patients with Cystic Fibrosis

Phase

Phase 1 First-in-human, Phase 2 in CF Patients, Randomized, Double Blinded

Study Objectives

Assess the safety, tolerability, pharmacokinetics of ARO-ENaC in normal healthy volunteers (NHVs) and patients with Cystic Fibrosis (CF)

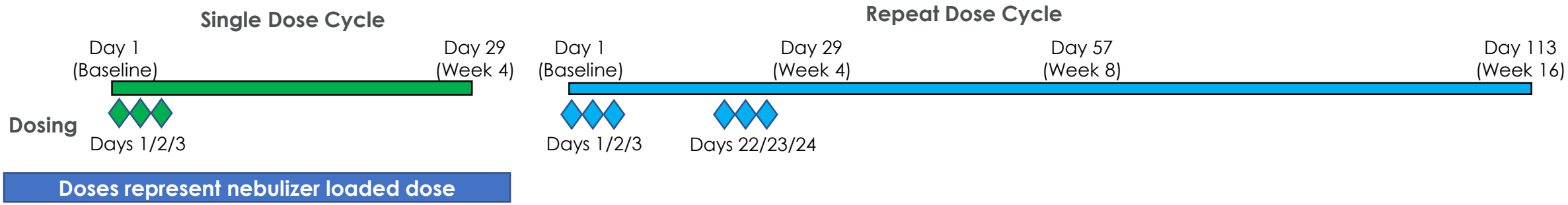
Number of Sites (6) /Subjects (54)

- Normal Healthy Volunteers (NHVs): Single site in New Zealand / up to 24 subjects
- Cystic Fibrosis patients (CF): Multiple sites in New Zealand and Australia / up to 30 subjects

Study Investigational Product

- ARO-ENaC: is a synthetic, double stranded, siRNA duplex conjugated to an integrin $\alpha v\beta 6$ epithelial targeting ligand
- Single or multiple doses of ARO-ENaC by inhalation of nebulized solution
- Placebo (PBO): Sterile normal saline (0.9% NaCl) calculated volume to match active treatment by inhalation of nebulized solution

AROENaC1001 Study Design



Population

Healthy Volunteers

CF Patients

Double-blind, Randomized per Cohort

Cohorts

20 mg Cohort 1: 4 active, 2 PBO

Day 21 Safety Eval

40 mg Cohort 2: 4 active, 2 PBO → **≤ 40 mg Cohort 2b**: 4 active, 2 PBO

Day 21 Safety Eval

65 mg Cohort 3: 4 active, 2 PBO → **≤ 65 mg Cohort 3b**: 4 active, 2 PBO

Day 21 Safety Eval

≤ 180 mg Cohort 4: 4 active, 2 PBO → **≤ 180 mg Cohort 4b**: 9 active, 3 PBO

Day 21 Safety Eval

Primary, Secondary and Exploratory Endpoints

Primary Endpoint

- The incidence and frequency of adverse events

Secondary Endpoints

- **Changes from baseline in serum electrolytes in NHVs and CF patients as a safety measure**
- Changes from baseline in Forced Expiratory Volume (FEV1) in NHVs as a measure of safety
- Pharmacokinetics of ARO-ENaC in NHVs and in CF patients

Key Exploratory Endpoints

- **Changes from pre-dose baseline in lung clearance index (LCI) in CF patients**
- **Changes from pre-dose baseline in FEV1 in CF patients**
- Changes from pre-dose baseline in the revised cystic fibrosis questionnaire (CFQ-R) in CF patients
- Rate of pulmonary exacerbations in CF patients receiving ARO-ENaC versus PBO

Spirometry (FEV1) as an assessment of Efficacy

- Gold standard for measuring lung function and measuring treatment effects in CF
- The forced expiratory volume in one second (FEV1) is the maximal volume of air exhaled in the first second of a forced exhalation that follows a full inspiration, expressed in liters
- Widely used as a primary end point in most CF registration studies
- Approximately 15-20 patients may be sufficient to demonstrate treatment effect.

Potential for early efficacy signal

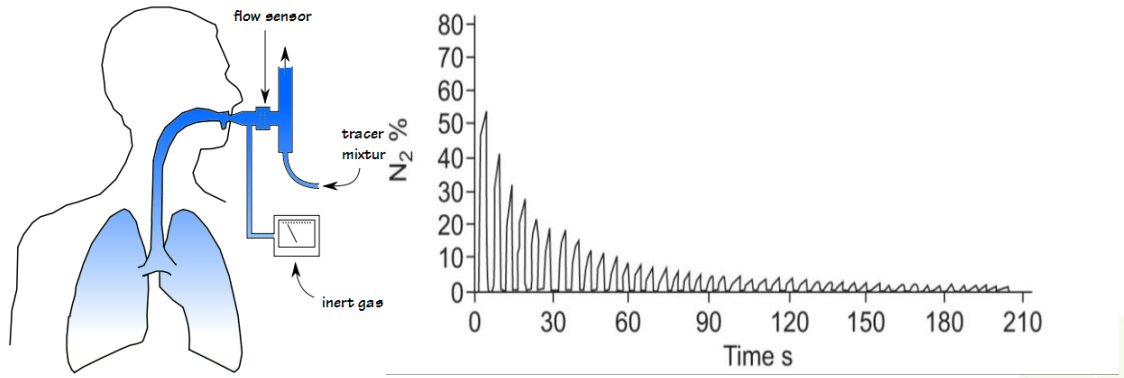
Lung Clearance Index (LCI)

Background

The Multiple Breath Washout (MBW) test has been identified as promising outcome for evaluating the efficacy of new treatments. The MBW testing consists of two phases - a *wash in* and a *washout* phase.

- During the *wash-in* phase of testing, subjects breathe a gas mixture containing a tracer gas until inhaled and exhaled gas concentrations are equal.
- During the *washout* phase, the tracer gas is allowed to disperse out of the lungs; respiratory flow and inert gas concentration are measured breath by breath over a period of time.

By recording the integral of gas concentration with respect to respiratory flow and examining the drop in inert gas concentration over consecutive breaths of the washout phase, it is possible to calculate functional residual capacity (FRC) and a number of parameters, which reflect ventilation inhomogeneity in the lung

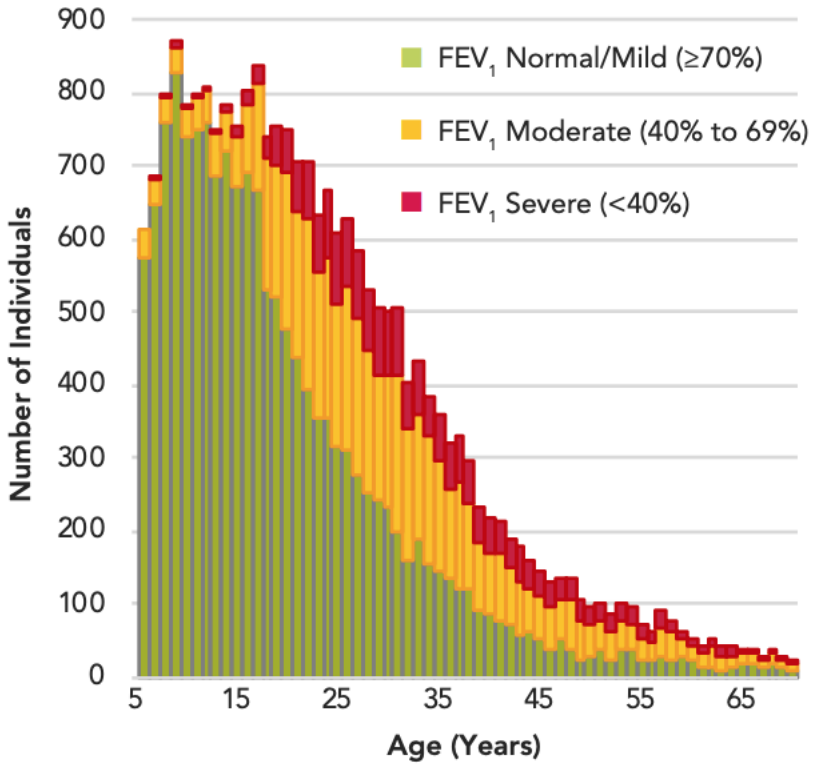


Multiple breath washout of inert gas: index of lung ventilation inhomogeneity

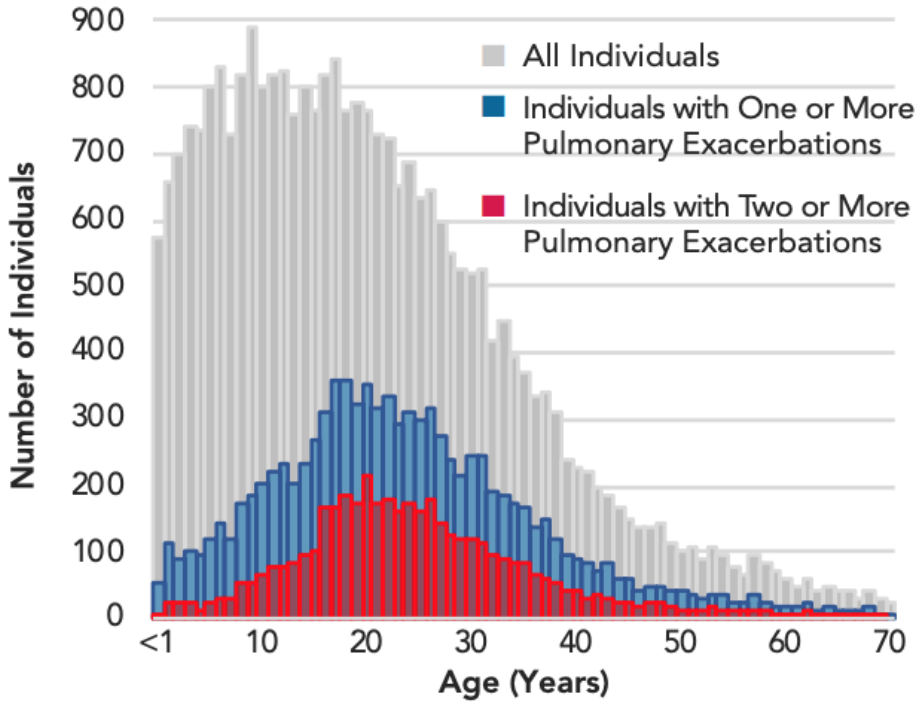
Indirect PD effect to confirm proof of concept

CF Associated Mortality and Morbidity

Patients by ppFEV$_1$



Patients by Number of Exacerbations per Year



Source: 2018 Cystic Fibrosis Patient Registry Data Report (link).

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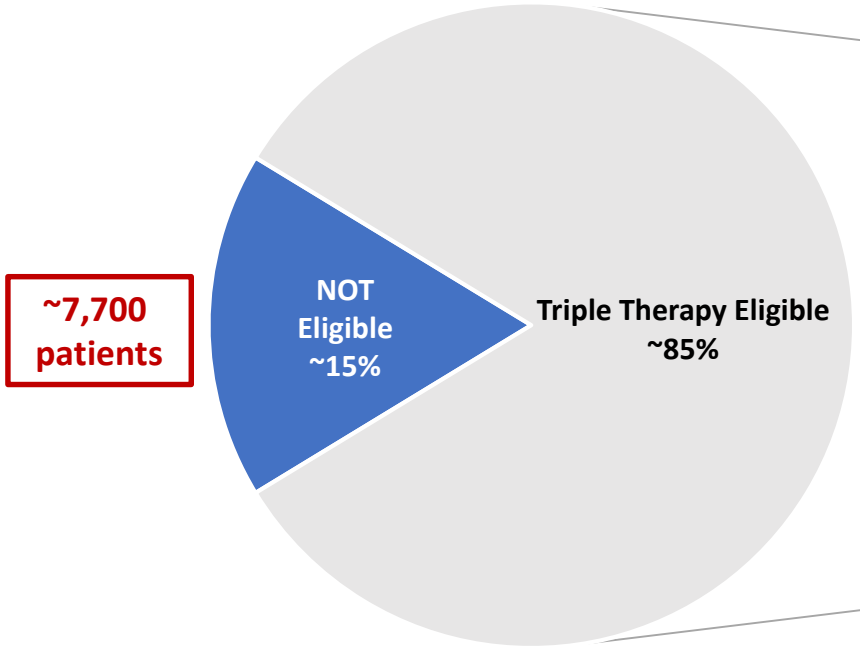
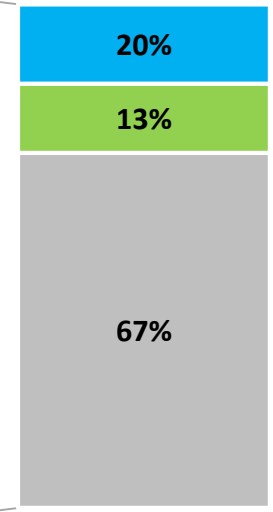
Who Are We Trying to Help?

Triple Therapy Eligibility (Genotype)[1]



Triple Therapy Clinical Response[2]



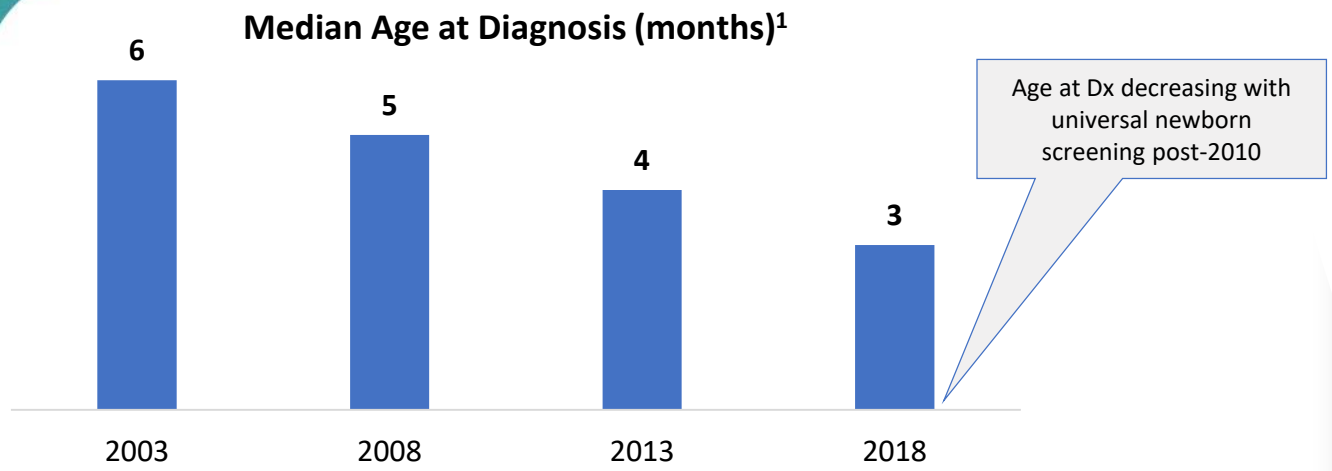
- 20% — FEV_1 improvement <5%
- 13% — Final FEV_1 below <70%
- 67% — FEV_1 improvement >5%, Final FEV_1 > 70%

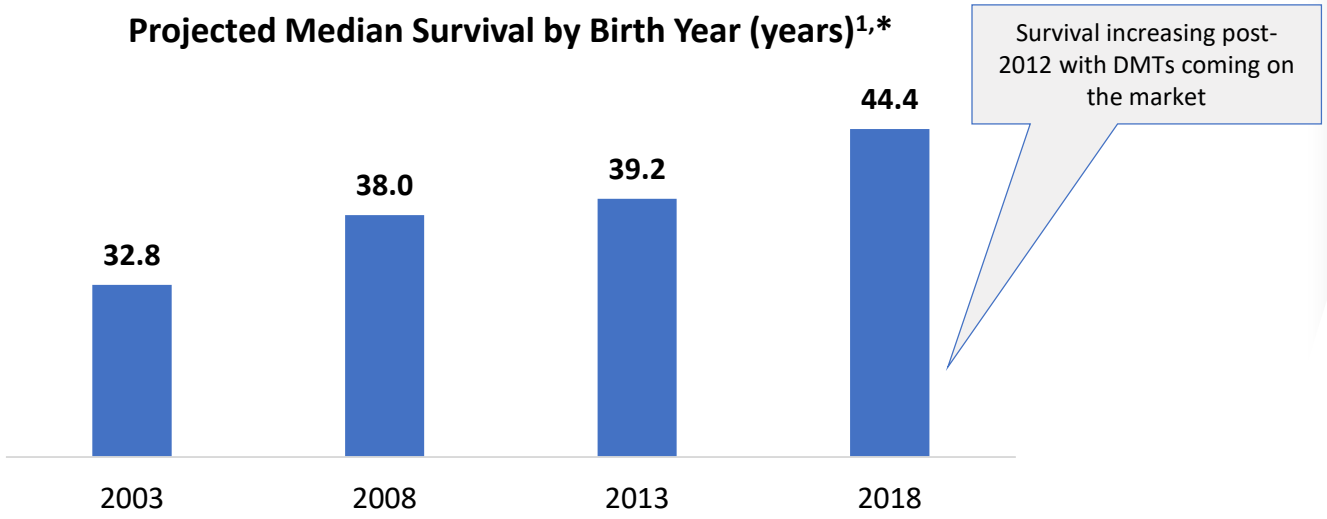
Insufficient Response to Triple Therapy
~6,000 patients over 12 yo

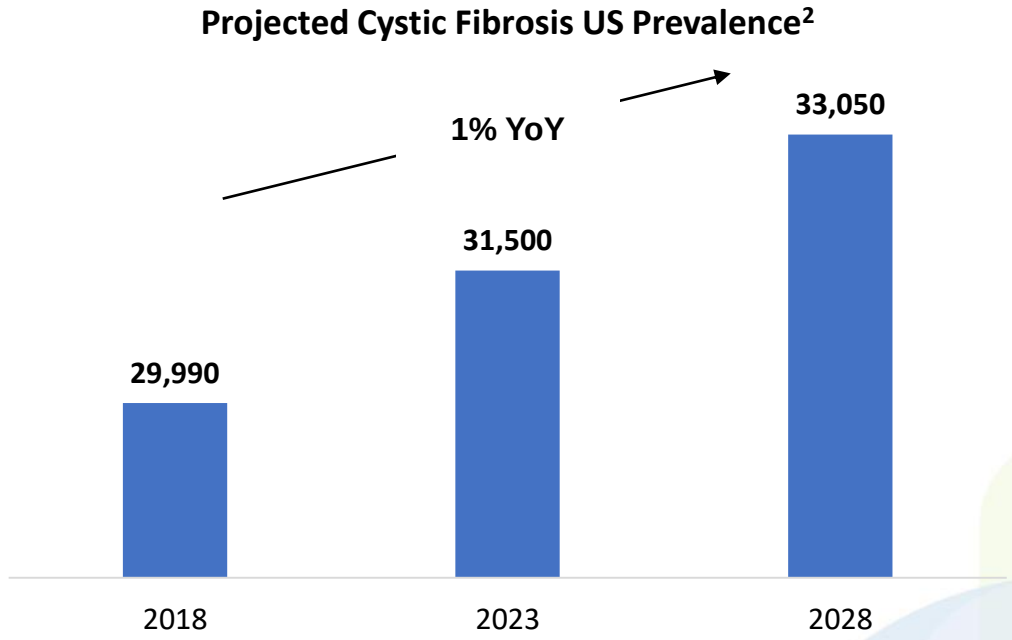
ARO-ENaC may help in a sizeable population

Sources: 1. 2018 Cystic Fibrosis Patient Registry Data Report (link). 2. Middleton et al. N Engl J Med 2019; 381:1809-1819 (link)
3. ICER Report: Modulator Treatments for Cystic Fibrosis: Effectiveness and Value. April 27, 2020 (link)

Increased Prevalence due to Earlier Diagnosis and Prolonged Survival







- Disease incidence expected to remain constant at ~900-1000 new patients per year[1]
- Improvements in age at diagnosis reflect universal newborn screening (NBS) in CF in place since 2010 (and earlier in some states)[1]
  - In 2018, 61.5% of new diagnoses were made by NBS[1]
- Median survival continues to increase due to new therapies providing survival benefits for a substantial percent of patients[1]

Sources: 1. 2018 Cystic Fibrosis Patient Registry Data Report (link); 2. DRG Cystic Fibrosis Landscape and Forecast - November 2019

*Note: Projections assume no further improvement in mortality rate and thus do not take into account new therapies approved post-2018 (i.e. Trikafta)

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Early Development Plan and Timelines

- Expect Phase 1 dosing to start in August
- Engage with US FDA late 2020
- Potential Phase 1/2 readout first half 2021
  - Safety in NHVs and patients
  - Lung function in patients
- We will explore accelerated regulatory pathway for patients with highest unmet need:
  - Class I patients
  - Other patient subsets with insufficient response

Wrap Up

Vince Anzalone, CFA

Why We Are Confident in ARO-ENaC

- Genetic and experimental validation for ENaC as a target for CF
- Promising preclinical data
- ARO-ENaC potentially solves clinical challenges of prior ENaC inhibitors
- Large and growing population of patients without adequate treatment
- Potential for accelerated development program
- Could provide validation for Pulmonary TRiM™ platform broadly

Goal for ARO-ENaC is to improve quality of life and survival in patients with CF

Q&A Session
Panel