

AHEAD OF THE CURVE

EMERGING CF THERAPIES 2009

Ahead of the Curve – Emerging CF Therapies 2009: Who needs CFTR?: Alternatives to Activation of the CFTR for Therapeutic Intervention in CF

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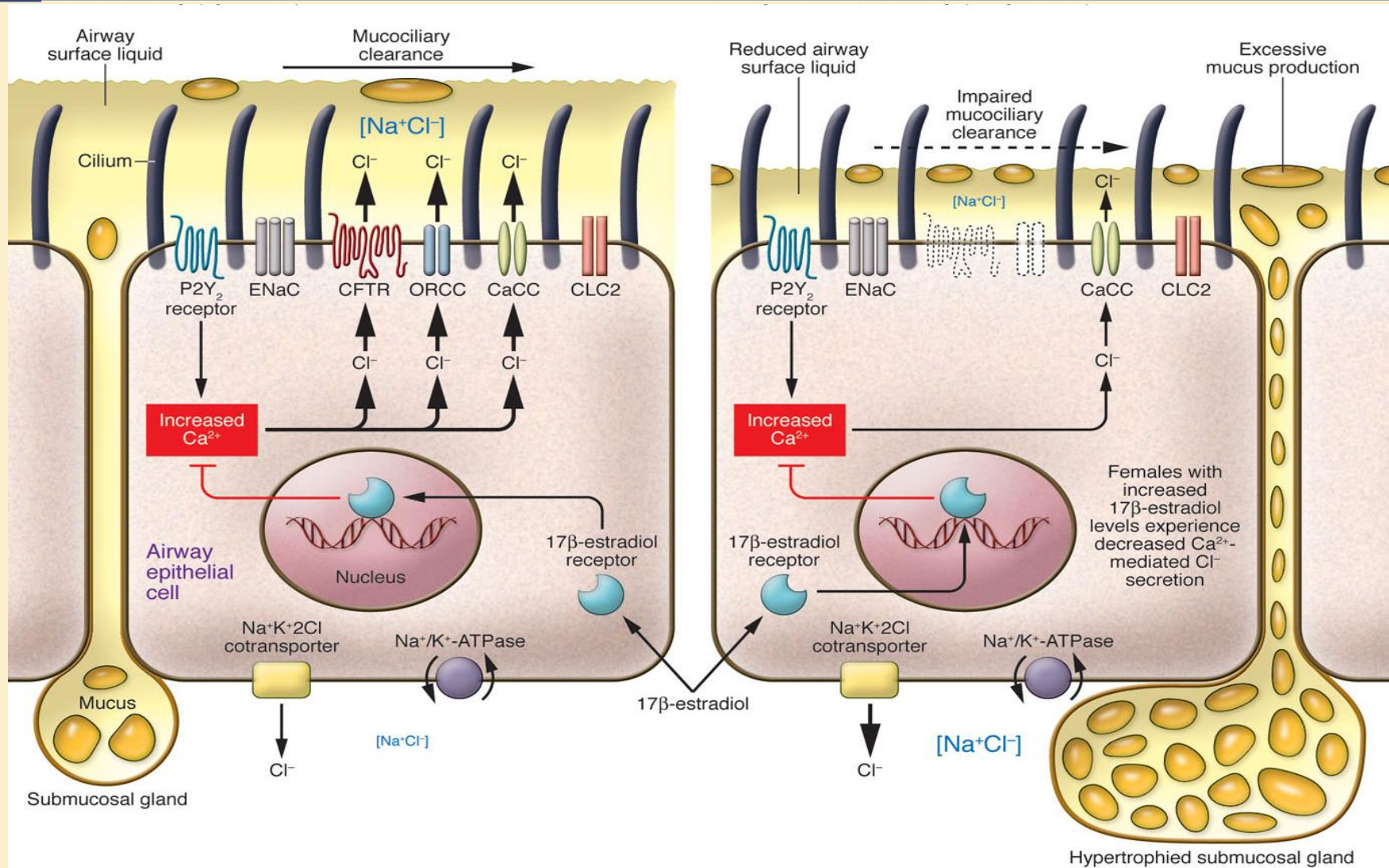


Disclosures

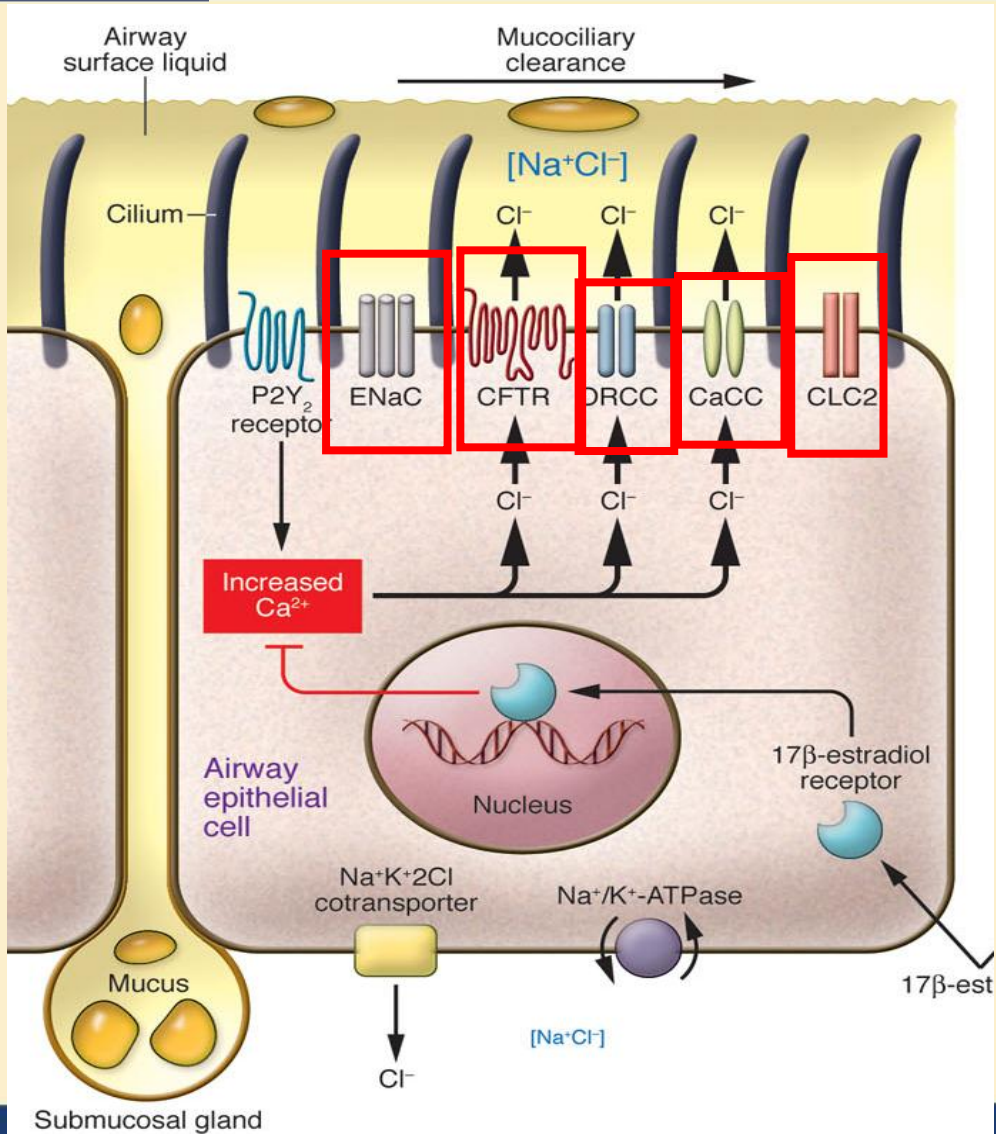
- Patents for cAMP mediated sweat rate test, nanoparticle delivery systems to airways, and butyrate correctors for CF
- Licensing agreements for IB3-1, S9, C38 cell lines
- Medical Advisory Board for Cobiprostone, Sucampo Pharmaceuticals
- Lectures for France Foundation
- Clinical Trials with Inspire Pharmaceuticals, Pharmaxis, PTC Corporation, Vertex Pharmaceuticals, CFTDN
- Grants from NHLBI, CFF, FDA

Normal Airway (hydration)

Cystic Fibrosis Airway (dehydration)

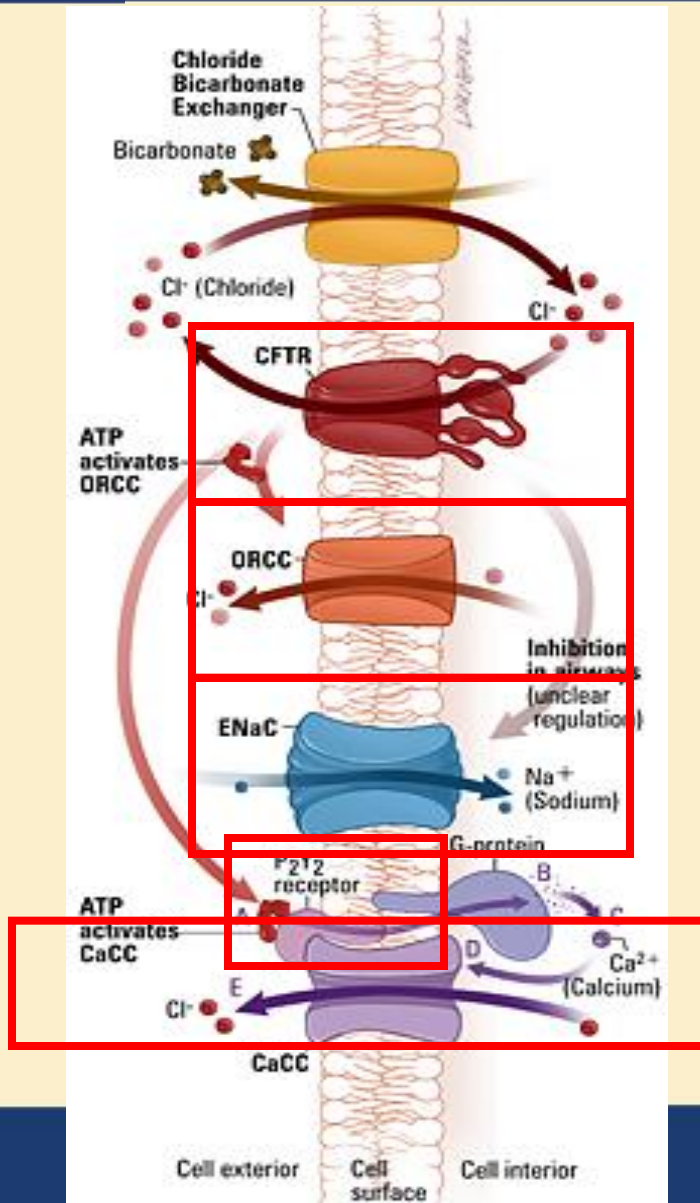


Hydration



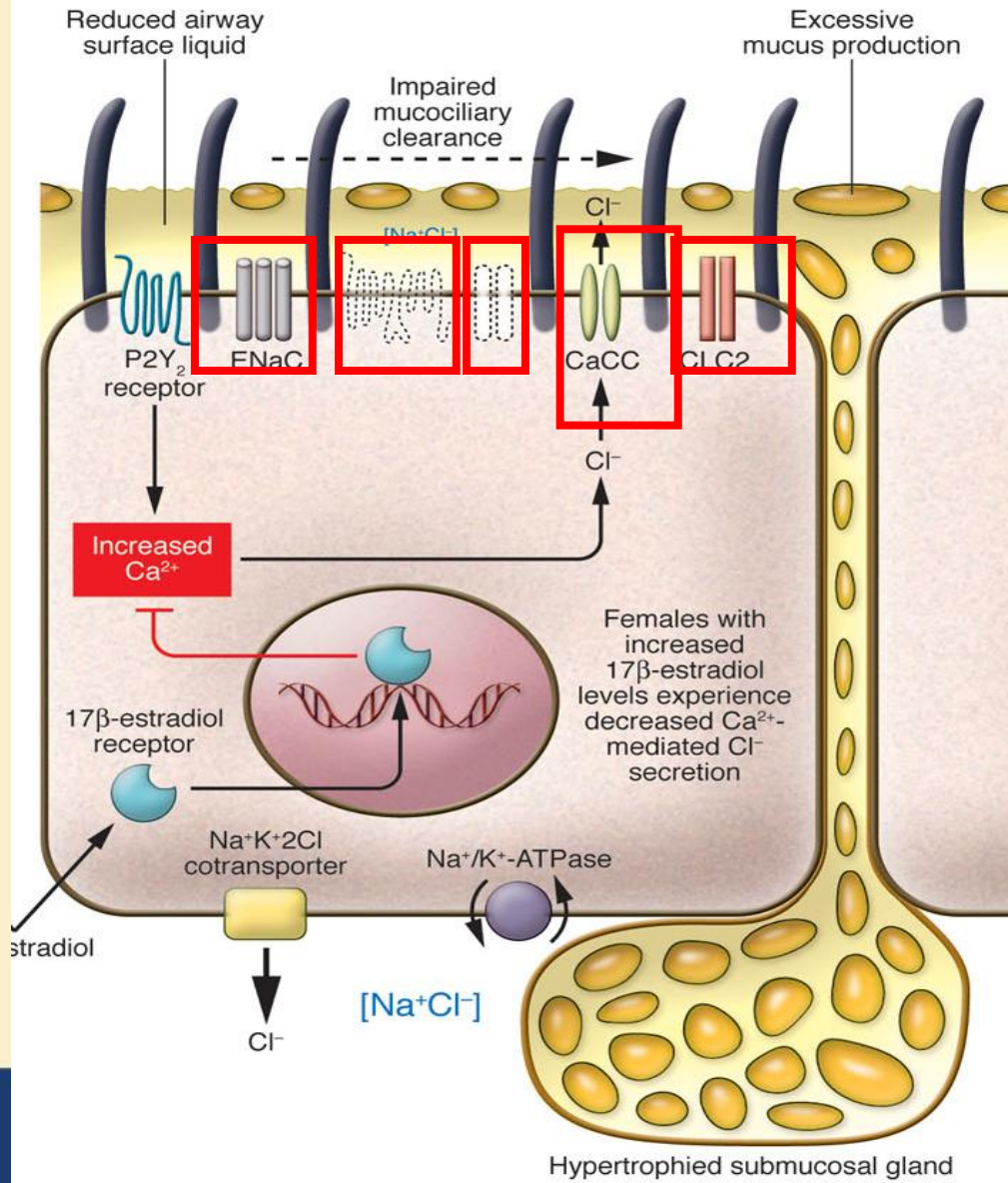
- Master Controller CFTR
 - ORCC
 - CIC-2??
 - ENaC
- CFTR Independent
 - CaCC
 - CIC-2 ??

Functional Interactions



- CFTR—cAMP-regulated chloride
- ORCC—activated by CFTR-transported ATP
- ENaC—inhibited by CFTR
- P2Y2 receptor responds to ATP, increases intracellular calcium and activates CaCC

CF Dehydration



- Absence of master channel CFTR
- Absence of ORCC
- Diminution of ClC-2
- Excessive ENaC
- Increased CaCC except when 17beta estradiol levels high
- Impaired mucociliary clearance (MCC)

Alternative Chloride Channel Agonists

- Denufosal (USA)
 - Ongoing Phase III trial
 - Future trial multinational
- Moli1901 (Canada/Germany/USA) Improves FEV₁ in two European trials
- Prostones (Japan/USA)
 - Oral formulation for CF liver disease
 - Aerosol in development for CF and COPD

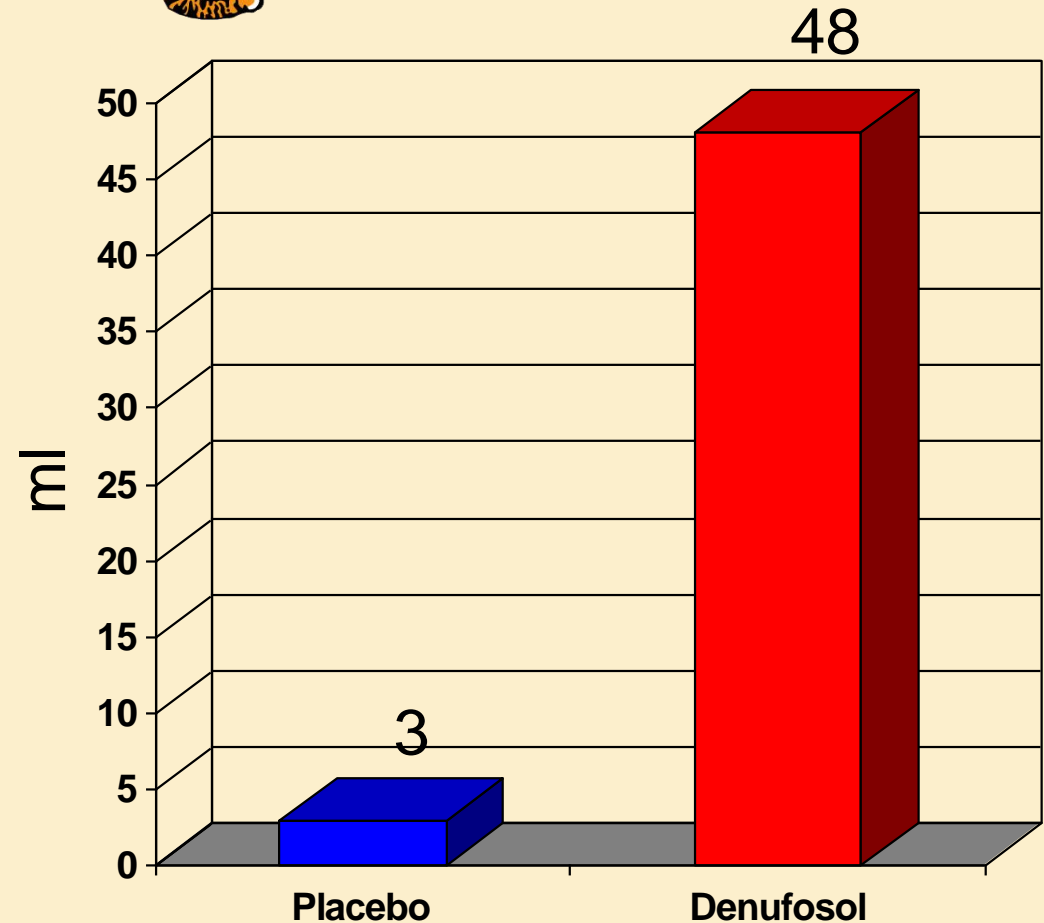
Denufosal tetrasodium (INS37217)

- Second generation, chemically stable, selective P2Y2 receptor agonist
- Increases chloride and mucin secretion, tracheal mucus velocity and cilia beat frequency
- Metabolized more slowly than ATP and UTP
- Cumulative published data in 120 healthy volunteers and 222 patients with CF
- Doses 20-60 mg are well tolerated in CF patients with FEV1 > 75% for 28 days, given t.i.d.
- Over 650 patients/volunteers in 8 completed trials

Tiger 1—08-108



- Met primary efficacy endpoint at trial endpoint (24 weeks) of change from baseline in FEV1 (in liters) vs. placebo
- 45 ml treatment effect ($p < 0.047$)
- “Real world” design (broader population; patients on multiple therapies that improve FEV1)



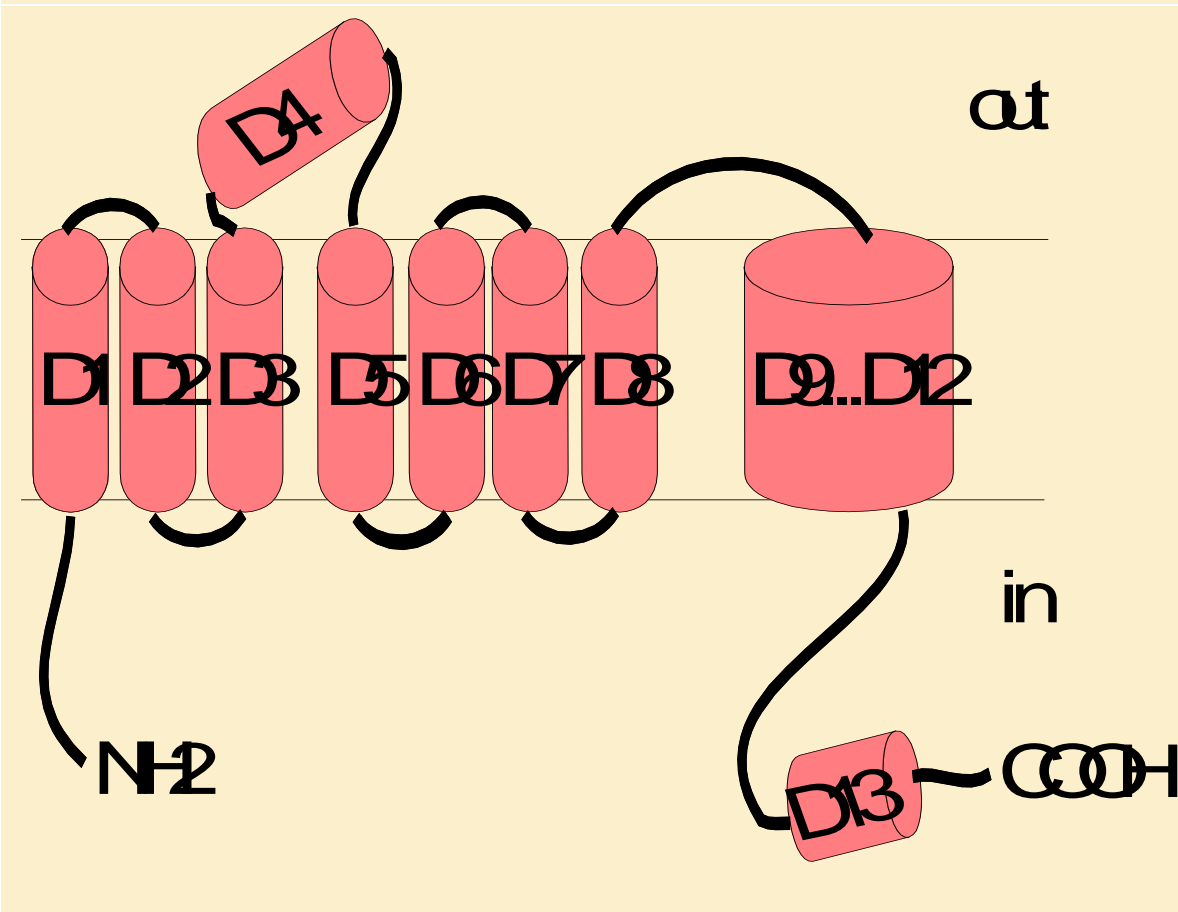
Tiger 2—08-110

- Currently enrolling
- Multiple sites (~100 sites) in US/Canada/Australia/New Zealand
- As of September 29, 2009, 413/450 patients enrolled (92%)
- 48-week placebo-controlled study
- Option for additional open-label 48 week treatment study upon completion of Tiger 2
- Usual standard of care medications allowed
 - Exception: no hypertonic saline

Lancovutide (Moli1901)

- 19 amino acid polycyclic peptide that increases intracellular calcium and chloride secretion
- Binds to polar heads of phosphatidyl ethanolamine and induces change in intracellular calcium levels and activation of calcium-activated chloride channels
- Direct application to nasal epithelium in normal and CF volunteers led to sustained increases in chloride secretion at higher doses
- Prolonged half-life in non-human airways
- Aerosol formulation well-tolerated for 28 days at 2.5 mg daily with increase in FEV1 +2% vs -3% for placebo (Lantibio Inc.)

CIC-2



- Voltage regulated
- pH activated (acidic)
- Volume activated (hypotonic)

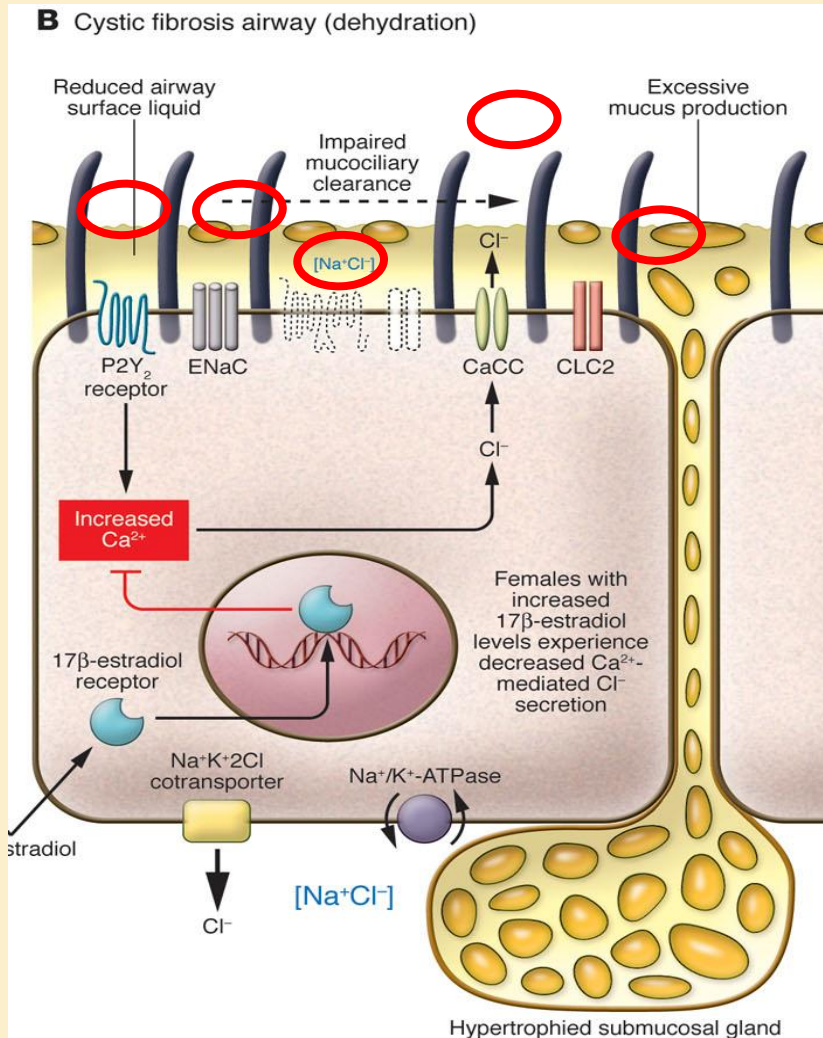
Prostones as CIC-2 agonists

- CIC-2 is present and possibly partially dependent on CFTR in intestine
- CIC-2 is present in airway epithelium of mouse and human. In absence of CFTR in mice, CIC-2 responds to both lubiprostone and cobiprostone (MacDonald and Zeitlin)
- Lubiprostone is non-adsorbable and remains in intestinal lumen where it increases chloride and water secretion in humans
- Lubiprostone is FDA approved for idiopathic constipation
 - In clinical trial in pediatric patients with CF
- Cobiprostone
 - Oral, soluble, absorbable, rapidly metabolized
 - Phase I/II clinical trial in CF demonstrated safety but no significant absorption or change in NPD
 - Re-formulation in progress (Sucampo Pharmaceuticals)

Sodium Channel Inhibitors

- Under preclinical development
 - Novartis (UK)—QAU145
 - Parion (USA)—P552 and P680
- Goal is to improve mucociliary and cough clearance
- Short acting sodium channel blockers (e.g. amiloride by inhalation) are not effective or cause decline in lung function when administered before hypertonic saline
- Long acting sodium channel blockers are still under evaluation

Hypertonic Saline



- Effective in CF
- NaCl is deposited into periciliary fluid layer and water is drawn into it
- Restores MCC in CF
- Currently under study in CF infants (ISIS)
- Rapidly embraced in USA by CF Care Centers

Inhaled mannitol

- Simple sugar, dry powder formulation, hydrates lung and improves MCC
- More slowly permeating, longer lasting than NaCl, but higher MW requires larger doses
- Unique dry powder device requires multiple capsules to be inhaled in each dose, given twice daily
- Second Phase III multi-national trial in CF achieved its recruitment goal September 09.
- Second Phase III clinical trial for use in bronchiectasis underway (Pharmaxis).

rhDNase plus ???

- rhDNase, TOBI, and hypertonic saline are currently used in USA for CF lung disease
- A typical sequence is bronchodilator, then rhDNase, then TOBI
- The effect of rhDNase in combination with other novel therapies is under study

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