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HOST-TARGETED THERAPIES FOR ACUTE SECRETORY DIARRHEA: A SURVEY OF CLINICAL-STAGE DRUG CANDIDATES ACROSS MULTIPLE PATHOGENIC MECHANISMS

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BACKGROUND

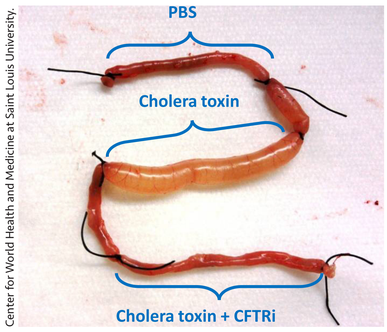
Diarrheal disease is preventable and treatable, yet it remains the second-leading cause of child death worldwide.[1] Existing treatments are hindered by design and function. Because oral rehydration therapy does not reduce symptoms, caregivers cannot immediately see its value and uptake remains low. There is rampant inappropriate use of antibiotics. In this context there is urgent need for alternatives that ease symptoms. Host antisecretory targets are a promising option.

OBJECTIVES

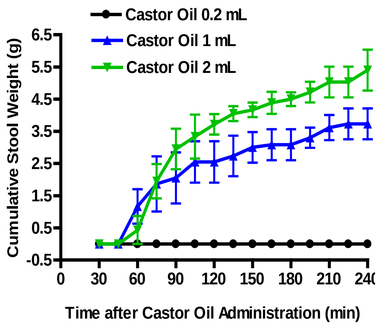
To accelerate progress toward new treatments, we established rodent models of secretory diarrhea and tested a series of diverse clinical-stage candidates in these models.

METHODS

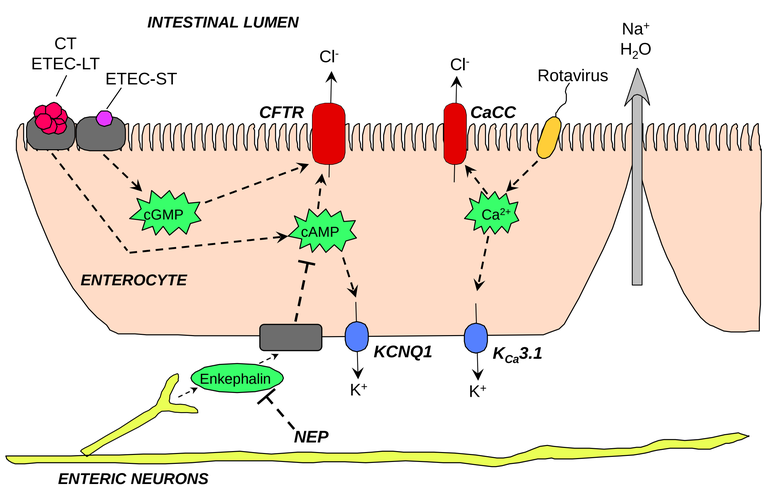
Mouse and rat closed loop, rat castor oil, and neonatal rat rotavirus models were performed according to published protocols.[2-4]



Center for World Health and Medicine at Saint Louis University.



DRUG TARGETS INTERROGATED



CT = cholera toxin

ETEC-LT = enterotoxigenic *E. coli* heat-labile toxin

ETEC-ST = enterotoxigenic *E. coli* heat-stable toxin

CFTR = cystic fibrosis transmembrane conductance regulator chloride channel

CaCC = calcium-activated chloride channel

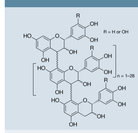
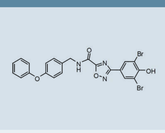
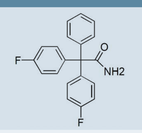
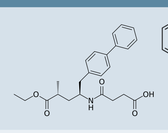
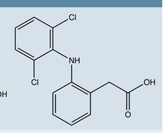
NEP = neprilysin (neutral endopeptidase, enkephalinase)

$K_{Ca}3.1$ = calcium-activated potassium channel

KCNQ1 = cAMP-gated potassium channel

Adapted from: Thiagarajah J et al. Clin Pharmacol Ther. 2012; 92(3):287-90.

COMPOUNDS TESTED

Crofelemer (Fulyzaq, Mytesi)	iOWH032	Senicapoc (ICA-17403)	Sacubitril (AHU-377)	Diclofenac
				
Natural product extract Cl^- channel blocker, avg MW ~2,100 g/mol	CFTR Cl^- channel blocker	$K_{Ca}3.1$/KCNQ1 K^+ channel blocker	Neprilysin inhibitor	COX-2 inhibitor/ NSAID, ion channel blocker[9]
FDA-approved for antiretroviral therapy-associated diarrhea[5]	Completed Phase 1 clinical trials in cholera patients[6]	Reached Phase 3 clinical trial for sickle cell disease[7]	FDA-approved for heart failure[8] (as Entresto combination with valsartan)	FDA-approved analgesic/anti-inflammatory

RESULTS

- All compounds were active in at least one rodent model. No compound was active in all models.
- Crofelemer had the broadest activity and was the only compound efficacious against rotavirus.
- Diclofenac was the only compound efficacious against ETEC-ST.

Summary of rodent model efficacy tests

Putative Target(s)	CFTR	CFTR/CaCC	$K_{Ca}3.1$/KCNQ1	COX-2/CFTR/ CaCC/$K_{Ca}3.1$/ KCNQ1	Neprilysin
Compound	iOWH032	Crofelemer	Senicapoc	Diclofenac	Sacubitril
CT closed loop	Active @100 µg†	Active @10 µg†	Active @100 µg†	Active @80 mpk‡	Not active @200 mpk
ETEC-LT closed loop	Active @300 µg†	n/d	Active @160 mpk	n/d	n/d
ETEC-ST closed loop	Not active @300 µg†	Not active @100 µg†	Not active @160 mpk	Active @80 mpk‡	n/d
Rat castor oil	Not active @150 mpk	Active @50-150 mpk	Active @160 mpk	n/d	Active @30-100 mpk
Neonatal rat rotavirus	Not active @150 mpk	Active @50-150 mpk	Not active @160 mpk	Not active @80 mpk	Not active @100 mpk

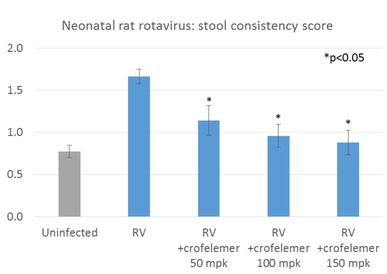
All doses delivered orally except, as noted: †intraluminal, ‡intraperitoneal.

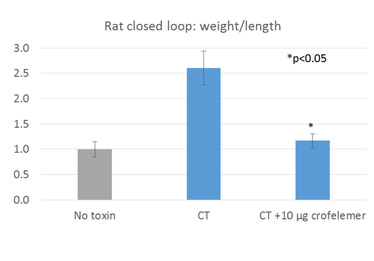
"Active" indicates intestinal secretion was suppressed by the test article in the model ($p<0.05$).

mpk = mg/kg body weight

n/d = not determined

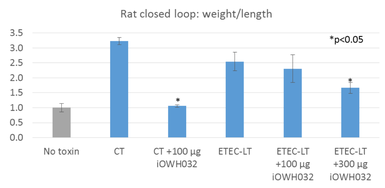
Crofelemer reduces secretion in rodent diarrhea models

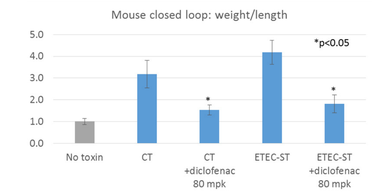




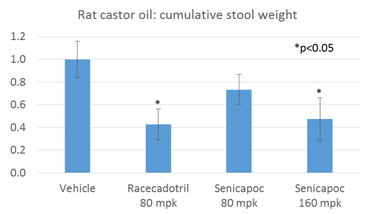
RESULTS CONTINUED

CFTR Cl^- channel blocker iOWH032 and NSAID/ion channel blocker diclofenac reduce secretion in rodent diarrhea models

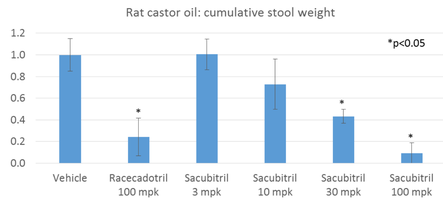




K^+ channel blocker senicapoc reduces secretion in rodent diarrhea models



Neprilysin inhibitor sacubitril reduces secretion in a rodent diarrhea model[10]



CONCLUSION

The study identified several clinical-stage drug candidates with potential for treating acute secretory diarrhea.

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