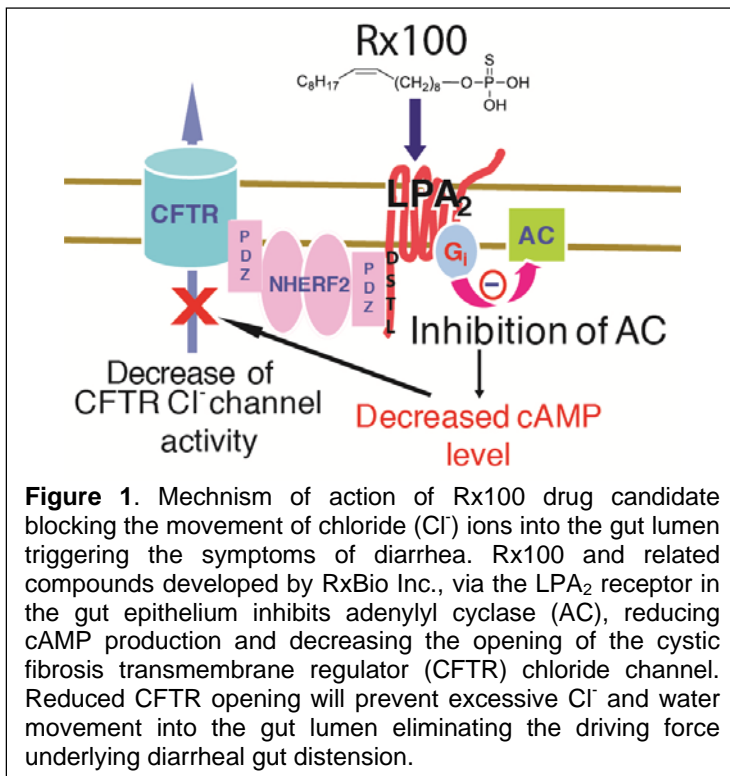


Targeted Cure for Secretory Diarrheas Affecting Millions World-wide Summary of RxBio Inc.'s Platform Technologies

Diarrheal disease is a severe health problem with an estimated 1.5 million deaths per year and is the second leading cause of death in children under the age of 5. In the Western World, toxin-induced diarrheas often plague the recovery of patients following gastrointestinal surgical procedures in hospitals. A critical barrier in treating diarrheal disease is the lack of easy-to-use effective treatments that target the core mechanism responsible for fluid secretion into the gut lumen. Existing symptomatic treatments often depend on fluid reconstituting medicines with contaminated water which is the source of the problem. Many types of bacterial toxins, cholera toxin (CTX) and clostridium toxins (CLT), target the primary chloride ion channel that is responsible for chloride (Cl⁻) ion movement into the gut lumen followed by water leading to the distension of the bowel that manifests with symptoms of diarrhea. **Our goal is to develop a safe, effective, and easy-to-use treatment for secretory diarrhea that targets the cause of the disease rather than treats its symptoms.**

Secretory diarrhea, best exemplified by the disease caused by the cholera toxin (CTX) produced by *Vibrio cholerae* bacterium, is due to CTX binding to the adenylyl cyclase (AC) enzyme, which in turn generates cyclic-adenosine monophosphate (cAMP) a very potent



second messenger. cAMP is the activates the opening of the cystic fibrosis transmembrane regulator (CFTR), which is the main chloride ion channel in the gut epithelium. Opening of the CFTR channel floods the gut with chloride ions that creates an osmotic gradient the movement of water into the gut lumen leading to its distension and propagates the symptoms of diarrhea (Figure 1).

RxBio scientists discovered that the bioactive lipid mediator lysophosphatidic acid (LPA) via the LPA₂ receptor subtype, that is abundantly expressed in the gut epithelium cells, blocks the activity of AC caused by diarrhea-causing bacterial toxins. A drug discovery

program aimed at developing drug-like LPA₂ receptor activators conducted by RxBio-affiliated scientists identified several drug-like small molecules selectively activating the LPA₂ receptor. RxBio's lead molecule, Rx100 is a metabolically stable analog of LPA. Our data showed that Rx100 significantly inhibited CFTR-mediated secretory diarrhea in mouse models of enterotoxin poisoning. In these studies, we have determined the efficacy and bioavailability of Rx100. Using both the open- and closed-loop mouse diarrhea models, we

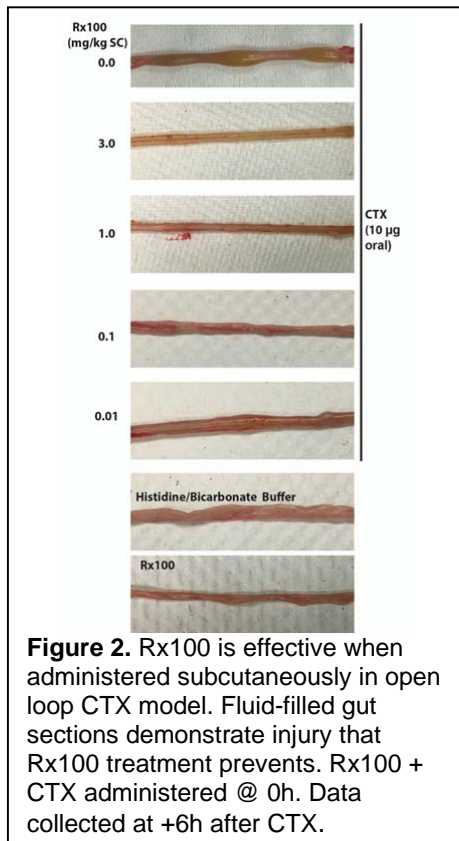


Figure 2. Rx100 is effective when administered subcutaneously in open loop CTX model. Fluid-filled gut sections demonstrate injury that Rx100 treatment prevents. Rx100 + CTX administered @ 0h. Data collected at +6h after CTX.

have optimized the dosing regimen and timeline of delivery for Rx100 via oral and parenteral delivery (**Figure 2**).

Finally, we have demonstrated the therapeutic efficacy of Rx100 in a mouse model using *Clostridium rodentium* infection to induce diarrhea [4-6]. These findings were published in the **Journal of Experimental Medicine** (Li et al, 2005. 202: 975-986, PMID:16203867), in **Experimental Biology and Medicine** (Thompson, et al, 2018 243:1056-1065. PMID: 30253666) and reviewed in Tigyí et al. Journal of Lipid Research 2019 (**J Lipid Res.** 60:464-474. PMID:30692142).

RxBio Inc. obtained exclusive world-wide license for a family of LPA₂ activator drug candidates developed by Dr. Gabor Tigyí's research group at the University of Tennessee Health Science Center Memphis (UTHSC) that are superior in many ways to Rx100.

RxBio and UTHSC with funding from NIH has conducted several studies establishing the drug like properties of these compounds, shown the lack of toxicity, established their molecular mechanism of action and demonstrated their antidiarrheal activity in murine models of toxin-induced diarrheas. These

drug candidates represent a portion of the RxBio platform technologies.

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