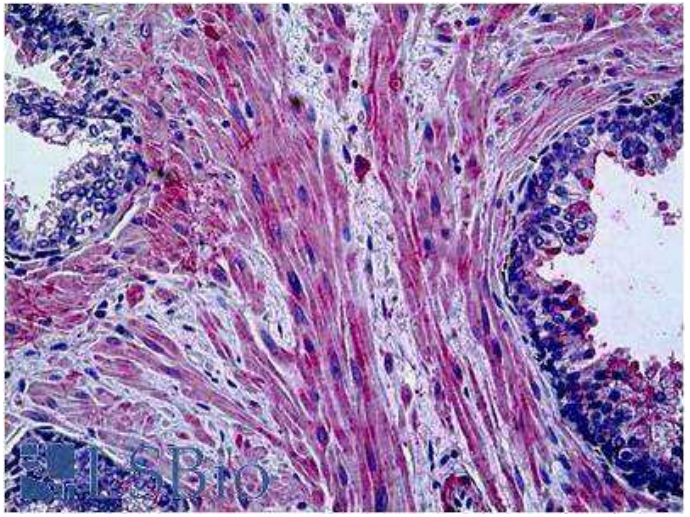
A new class of pro-motility agents for the treatment of IBD

Myosin activators in Gaseous neurotransmission

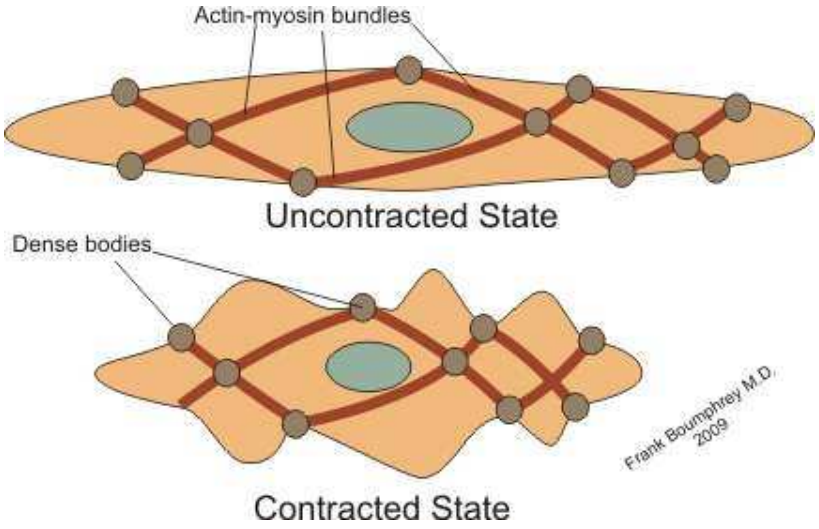
Harvard office of
Technology development

1. Smooth muscles compose most of the intestinal wall and is responsible for peristalsis- involuntary bowel movements that help transfer the food through the gut, allowing for food absorption.

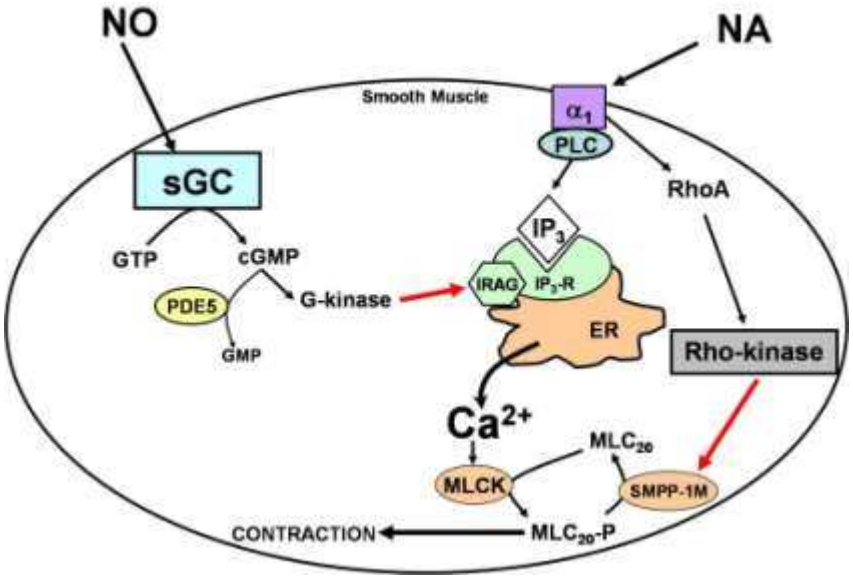


Human Myosin smooth muscle HE staining

2. The smooth muscle contains numerous actin-myosin bundles which upon activation, slide and contract it.



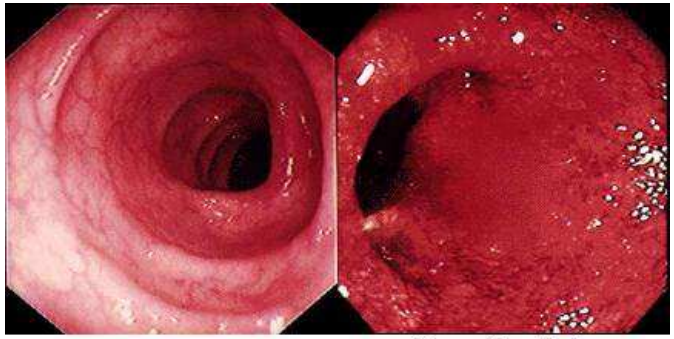
- Recent findings from Dr. Arun Chaudhury in Dr. Raj Goyal's lab at Harvard Medical school showed for the first time the role of Myosin in the nerve terminals of enteric neuromuscular smooth muscle neurotransmission, including nitric oxide (NO) base signaling.



- Impaired nitric oxide neurotransmission is the root cause of numerous gastrointestinal disorders, most classified under the umbrella term "functional bowel disorders“,

Irritable bowel syndrome

- All pathologies diagnosed under the IBS category relate to impaired nitrergic neuromuscular neurotransmission as the underlying pathophysiological cause.
- Characterized by altered bowel dysfunction, lower abdominal pain and bloating
- Affects approximately 20% of the US population; Is the most common GI diagnosis among gastroenterology practices in the US.
- Can significantly disrupt daily life
- To date, success of current treatment options in addressing multiple symptoms of IBS has been limited.



Healthy Colon Ulcerative Colon

Novel Approach

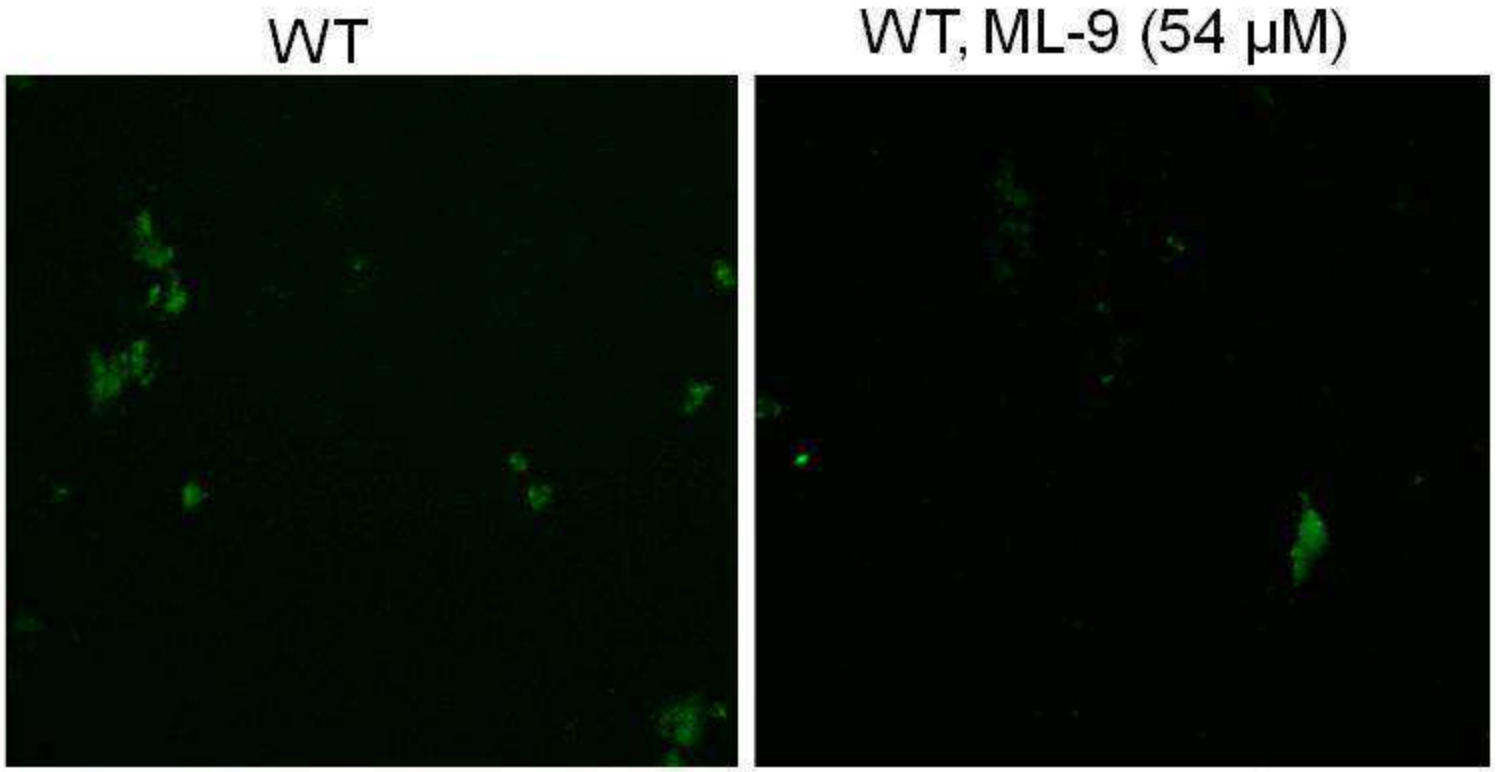
- Use of compounds designed to improve the function of cellular Myosin in the muscle and in the nerve terminal as next generation pro-motility agents, targeting a large market of gastrointestinal motility disorders, where few pharmaco-therapies that improve quality of life exist to date.

Myosin II activators

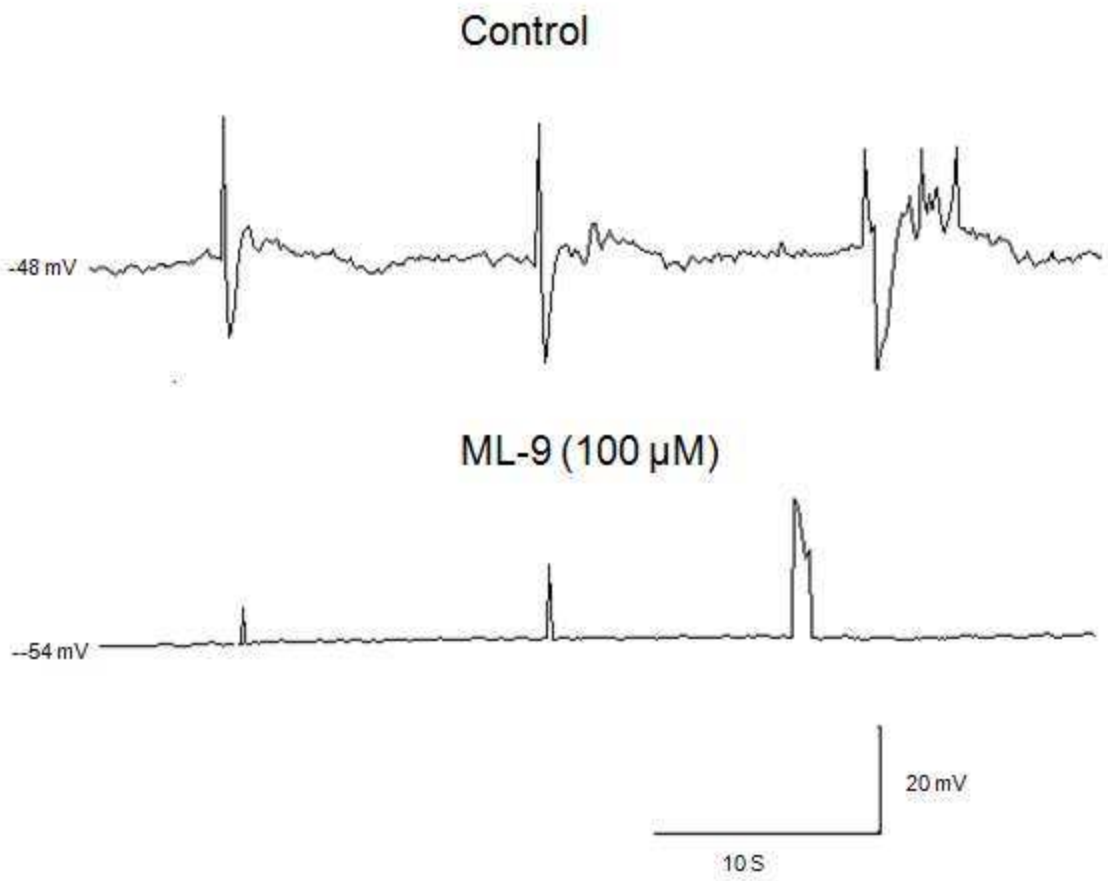
- ML-9, myosin light chain kinase (MLCK) inhibitor, inhibits prejunctional nitric oxide production and nitric oxide mediated hyperpolarization in gastrointestinal smooth muscles. MLCK is a major regulator of myosin II.

- By inference, myosin II agonist is a potential candidate for enhancing nitrergic neurotransmission. Thus, myosin II activator has the potential to become an effective therapeutic agent for IBS.

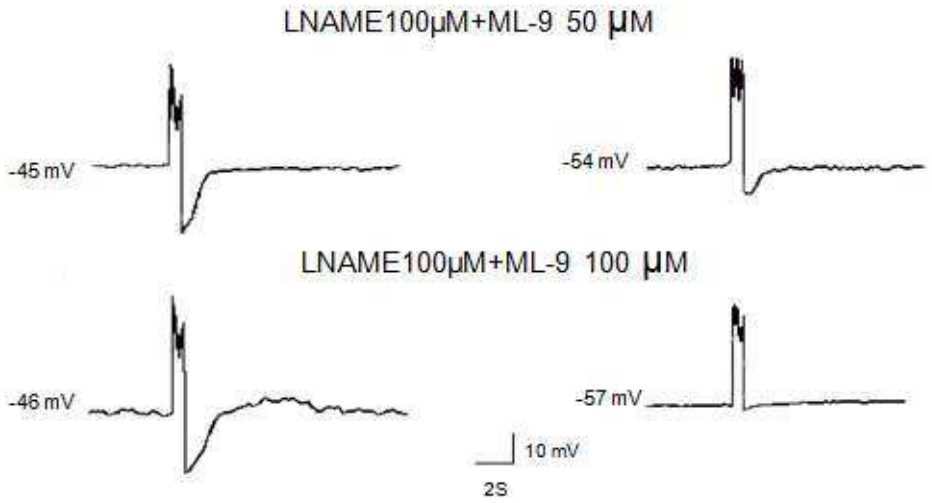
In vitro nitric oxide production (as visualized by DAF-NO imaging) in isolated wild type (WT, C57BL/6J) mice enteric varicosities is inhibited by ML-9



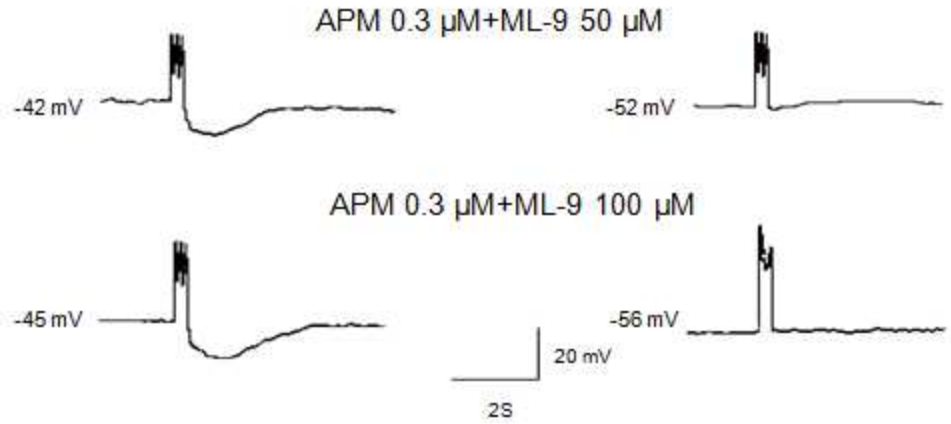
Compound inhibitory junction potential (IJP) recorded from mice antral smooth muscles



Purinergic fast IJP (fIJP) is inhibited by the MLCK inhibitor ML-9



Nitric oxide mediated slow IJP (sIJP) is completely inhibited by MLCK inhibitor ML-9



L-NAME, nNOS inhibitor; APM, apamin, inhibitor of slow conductance SK channel

In summary

- Myosin activators may be the first compounds that improve the function of cellular Myosin in both nerve and muscle terminals in the gut.
- These compounds are aimed at a 2.9 Billion$ market which is projected to grow to 4.5$B by 2018.
- Targeting multiple indications such as functional dyspepsia, early satiety, diabetic gastroparesis, intestinal pseudo-obstruction and constipation-predominant irritable bowel syndrome.
- To this day, very few treatment options exist for pharmacotherapy of these highly prevalent gastrointestinal motility disorders, which are known to severely affect the physical quality of life.