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HelicoTAC©, a PROTAC-based small molecule targeting the virulence factor Cag A of *H. pylori* as a potential therapeutic for gastritis and gastric cancers.

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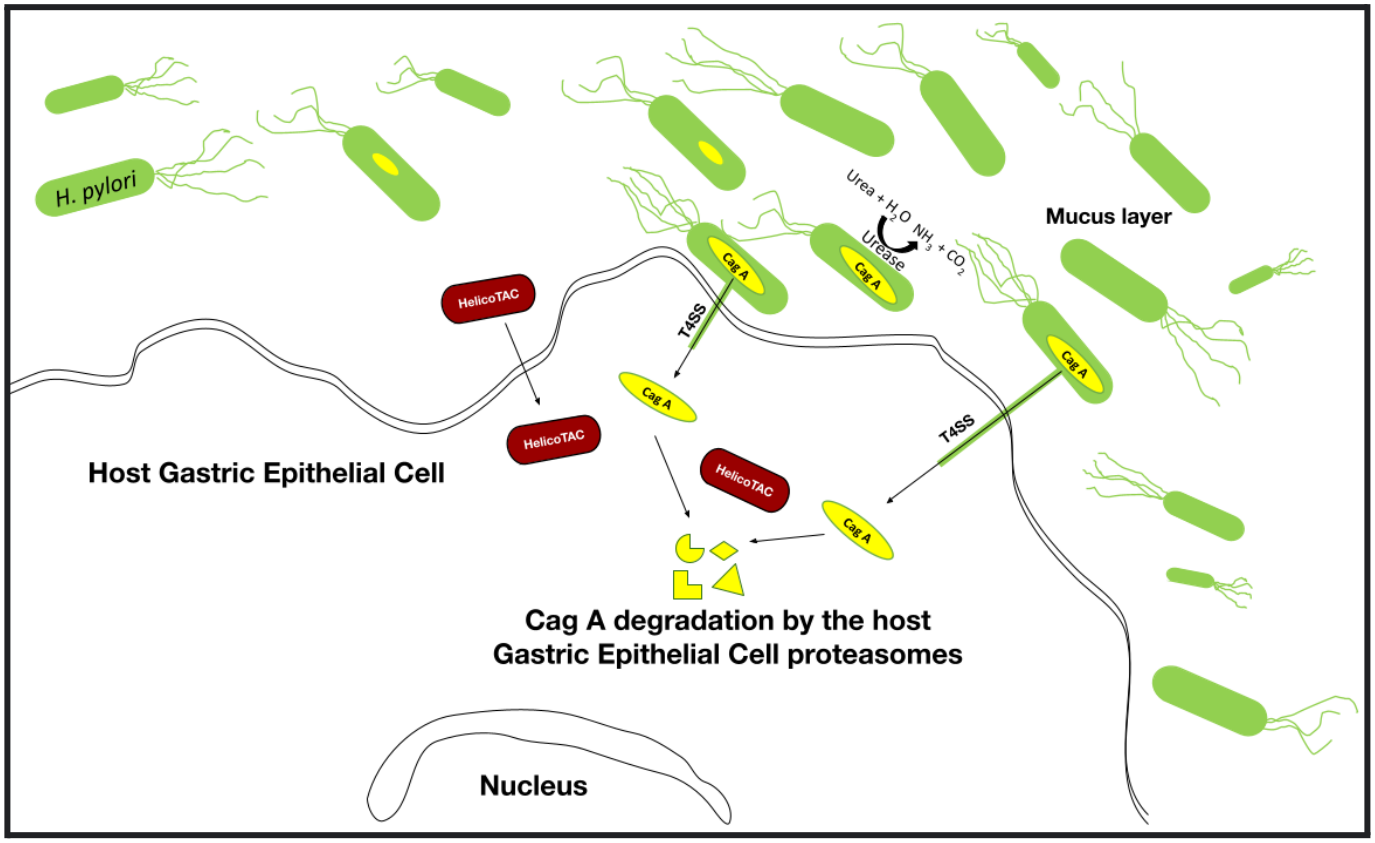

Figure 1. Overview of the proposed strategy for CagA degradation by HelicoTAC©.

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Stressful lifestyle and unusual food habits often lead to acidity problems causing acid reflux issues. However, gastric ulcers, gastritis and gastric cancers can be caused by other reasons such as bacterial infections by *Helicobacter pylori*. During the infection, *H. pylori* protects itself by neutralizing the local acidic environment through urease and hacks the host cell by injecting its virulence factor, cytotoxin associated gene A (Cag A), through its type-4 secretion system (T4SS). Cag A controls cellular proliferation and apoptotic pathways in a variety of different ways ultimately resulting in severe pathologies. In this strategic communication, we designed a proteolysis targeting chimera (PROTAC)-based small molecule, HelicoTAC©, that specifically targets the *H. pylori* Cag A to the host cell ubiquitin-proteasome-mediated degradation. By permanently removing the Cag A one can hypothesize that the bacterium will automatically be removed by the host immune system thus reducing further potential pathological effects that might be caused by the bacterium.

Keywords: Helicobacter pylori, Cag-A, PROTAC, T4SS, HelicoTAC©, gastric ulcers, gastric cancers.

Gastric ulcers are a major medical issue in India as well as globally. *Helicobacter pylori* is a spiral shaped bacteria and stains gram-negative. *H. pylori* is capable of causing gastritis, gastric ulcers which will eventually cause different types of cancer like adenocarcinoma of stomach, gastric cancer, mucosa-associated lymphoid tissue (MALT) lymphoma, etc [1,2,3]. *H. pylori* related infections are observed in almost all the age groups which most of the times don't show any symptoms most of the times. Understanding and investigating *H. pylori* infections is challenging because of its morphological changes that it often undergoes. Though *H. pylori* is spiral-shaped it eventually changes to rod-shape and then reaches a coccid shape after prolonged cultures under *in-vitro* conditions in laboratories. When *H. pylori* changes its shape to coccid shape it can not be cultured any further and is unfit to test for antibiotic responses. Isolation of *H. pylori* from the patients through biopsy is found to be difficult and have a very low success rate as it forms a very thin and translucent layer of smooth colonies after culturing it for 3 to 14 days [2]. But on successful subculturing of the colonies of proper incubation for 1 to 3 days of incubation they tend to adapt to the laboratory conditions for further studies. *H. pylori* bacterium has 2 to 6 unipolar flagella which help it to move faster in the mucus lining present over the gastric epithelial cells of the stomach [2]. *H. pylori* usually secretes urease enzyme that convert urea into ammonia which helps in neutralizing the acidic pH of the stomach that helps in its survival. As the inner lining is less acidic it is easy for them to survive thus escaping from getting detected by the immune cells [3].

H. pylori is known to cause gastric carcinogenesis. Cytotoxin associated antigen-A (Cag-A) is the gene whose locus changes for different strains of *H. pylori*. Cag-A gene encodes to the Type-IV secretion system and is also known as the Bacterial Virulence factor. Cytotoxin associated antigen-A (Cag-A) is injected into the host cells using Cag Type IV secretion system (Cag T4SS). Cag-A is characterized into Oncogenic protein as it is associated in carcinogenesis. After Cag-A gets incorporated into the host cells, it regulates different types of cellular responses like Actin-Cytoskeletal rearrangements, immune responses like inflammation and cell scattering which will eventually cause carcinogenesis [4].

The diagnosis of the infection caused by *H. pylori* is not always possible due to lack of symptoms [1,2]. The *H. pylori* infection is treated with antibiotics or by using proton pump inhibitors. These treatments may or may not really

help in curing the infection. Based on the information treatments available for *H. pylori* infections we designed a Proteolysis Targeting Chimera (PROTAC)-based small molecule, HelicoTAC©, that targets Cag-A (virulence factor of *H. pylori*). HelicoTAC© molecule has two binding sites where one binds to the E3 Ubiquitin Ligase and the other site binds to the target protein of interest that is aimed to be degraded [5]. So that the higher risk and spread of *H. pylori* infection can be controlled.

Currently, we are in the process of synthesis and evaluation of HelicoTAC©. The data obtained from the *in vitro* and *in vivo* studies will be published in the future issues of TCABSE-J.

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Conflict of interest: The applications report presented here is a currently ongoing project at TCABS-E, Rajahmundry, India. The authors invite collaborations without any conflict of interest.