Gastric Cancer Vaccine

A Novel Approach for Protecting Against Gastric Cancer and *Helicobacter pylori*-associated Disease

The opportunity

Helicobacter pylori infect the stomachs of half the world's population. The worldwide prevalence of this infection means that large numbers of people suffer from *H. pylori*-associated diseases, including peptic ulcers and gastric adenocarcinoma (hereafter gastric cancer).

Gastric cancer is the 3rd leading cause of death due to cancer globally, with approximately 734,000 gastric cancers annually attributable to *H. pylori*. It is well established that gastric cancers develop as a direct result of severe chronic inflammation (gastritis) in response to infection with *H. pylori*. Indeed, along with the human papillomavirus and the hepatitis B and C viruses, *H. pylori* is a leading cause of cancer due to infection (see Figure 1).

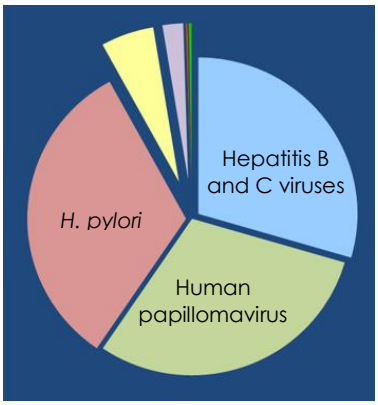


Figure 1 World cancer incidence attributable to infections in 2008 (data from *Lancet Oncology*, Vol. 13, Issue 5, 2012).

Sales of the human papillomavirus vaccine Gardasil (Merck) totalled US$2.03 billion in 2014 and are forecast to reach US$2.52 billion by 2020. In 2013, sales of GSK's Hepatitis vaccine franchise totalled US$984 million.

In the US, the direct costs associated with peptic ulcer disease (a high proportion of which would be associated with *H. pylori* infection) are approximately $2.6 billion annually. Further, health economics studies have shown a vaccine against *H. pylori* in the US would be cost effective.

H. pylori infections are currently treated with combination of antibiotics; however, there are several reasons why antibiotics can not be used in the prevention of gastric cancer, including:

- Rising *H. pylori* antibiotic resistance.
- The majority of people are asymptomatic for *H. pylori* infection before being diagnosed with gastric cancer, i.e. no point for intervention unless screening is undertaken.
- Screening and population level antibiotic use is likely to increase the prevalence of antibiotic-resistant pathogens within the community.

Accordingly, there is a clinical need and commercial and economic rationale for a vaccine against *H. pylori*, especially to protect against gastric cancers.

To date, efforts to make a vaccine against *H. pylori* have largely failed because of the ability of *H. pylori* to evade host protective immunity. Researchers at MCRI, led by Associate Professor Phil Sutton, have developed a novel vaccine strategy that, rather than eradicating infection, prevents the *H. pylori*-induced inflammation that is responsible for disease.

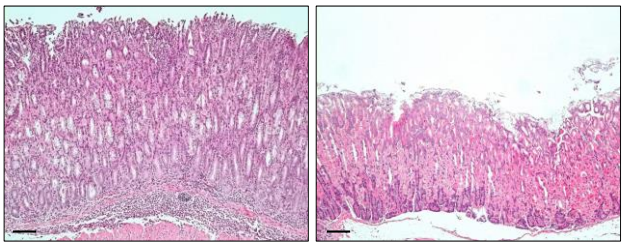
The technology

The vaccine candidate is recombinant HtrA, a ~55 kDa protein and the only serine protease produced by *H. pylori*. HtrA is both expressed on the bacterial surface and secreted, and is essential for *H. pylori* survival.

Researchers at MCRI have shown that mice vaccinated with HtrA are protected against *H. pylori*-induced inflammation compared to controls (Figure 2).

Average *H. pylori* infected control mouse

Average therapeutically vaccinated mouse



Median (IQR):
Alum alone control
Metaplasia = 2.1 (1.0-2.5)
Atrophy = 2.0 (1.0-2.0)

HtrA+alum vaccine –
Metaplasia = 0.0 (0.0-2.0)
Atrophy = 0.0 (0.0-2.0)

Figure 2 Therapeutic vaccination protects against *H. pylori*-induced gastritis.

Proposed mechanism of action: *H. pylori* HtrA has been shown to disrupt the epithelial barrier by cleaving E-cadherin and thereby opening the junctions between gastric epithelial cells. It is proposed that a leaky epithelium would allow shed bacterial components, and possibly a limited number of whole bacteria, to cross the epithelial barrier into underlying tissues, interacting with cells of the immune system and driving gastritis (Figure 3).

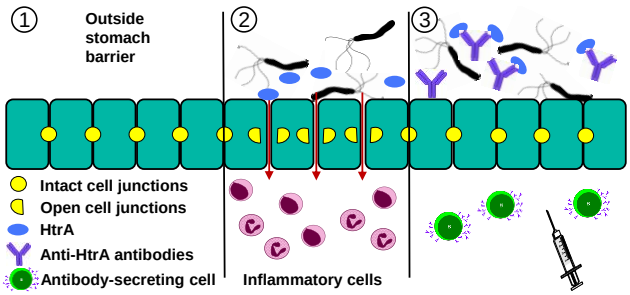


Figure 3 Proposed mechanism of how an HtrA vaccine protects against *H. pylori*-induced gastritis. (1) No infection; (2) *H. pylori* infection; (3) HtrA vaccination.

In support of the proposed mechanism of action, MCRI researchers have shown that sera from HtrA-vaccinated mice neutralises HtrA protease activity *in vitro* (Figure 4).

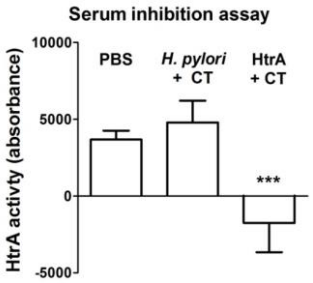


Figure 4 Vaccination against HtrA induces a serum response that neutralises protease activity

Applications

In addition to a therapeutic or prophylactic vaccine against *H. pylori*-induced disease, a further application of this technology includes a monoclonal antibody therapy for the treatment of acute disease.

Opportunity for partnership

The Murdoch Childrens Research Institute is seeking a partner to develop the gastric cancer vaccine technology through either a research development and option agreement or license agreement.

Intellectual Property

This technology is the subject of an International (PCT) application (PCT/AU2015/000380) in the name of the Murdoch Childrens Research Institute. The application relates to methods of treating or preventing bacteria induced inflammation and immunogenic compositions comprising a HtrA polypeptide or a fragment.

Key publications

International (PCT) Patent Application No. PCT/AU2015/000380, in the name of Murdoch Childrens Research Institute and entitled HELICOBACTER THERAPEUTIC, was published by the International Bureau on 7 January 2016 under Publication No. WO 2016/000022.

Contact: Dr Joanne Boag
Senior Manager, IP & Commercialisation
Murdoch Childrens Research Institute
P +613 8341 6445
joanne.boag@mcri.edu.au