A discovery by a Yale Cancer Center researcher promises to bring a vaccine against one of the world’s most deadly diseases, typhoid fever. This breakthrough is also likely to cause two important side effects: a decline in the incidence of gallbladder cancer, and more research on the links between bacterial pathogens and cancer.

Typhoid fever is one of the scourges of public health, sickness more than 20 million people every year and killing 200,000, almost all of them in underdeveloped countries, where it is spread by contaminated food or water, usually via the feces of infected people. The incidence of typhoid has been known for more than a century, a bacteria named Salmonella Typhi. But the bacteria’s mechanism to cause disease has been a mystery, preventing the development of a licensed vaccine, one of the holy grails of public health.

That may soon change. A team led by Jorge Galan, PhD, DVM, Lucille P. Markey Professor of Microbial Pathogenesis and Cell Biology, and Chief of Microbial Pathogenesis, has identified the basis for Salmonella Typhi’s unique virulence properties. Dr. Galan’s team identified “typhoid toxins,” which is produced by Salmonella Typhi and its experimental animals, can reproduce most of the symptoms of typhoid fever.

Dr. Galan’s team has also solved the atomic structure of “typhoid toxins,” which should make possible the development of small molecular inhibitors to block the infection, as well as a vaccine that could potentially evaluate typhoid fever.

“This discovery turned the disease upside-down,” said Dr. Galan. “Now we know why S. Typhi causes typhoid fever, and we can create a vaccine against it. That’s the main impact.”

The Bill & Melinda Gates Foundation has put Dr. Galan’s breakthrough onto a fast track towards a vaccine. The discovery also provides a molecular explanation for the epidemiological link between typhoid and gallbladder cancer. Many survivors of typhoid become asymptomatic carriers of S. Typhi, and hold the bacteria in the gallbladder.

“We discovered that S. Typhi encodes what is essentially a genotoxin—a toxin that damages the genome’s DNA,” said Dr. Galan. “So the tumorigenesis is likely to be related to the toxin’s ability to damage the DNA. When the DNA is mis-repaired, mutations are created, providing the basis for the development of cancer. So a vaccine against typhoid fever should also prevent gallbladder cancer.”

That would be significant in the developed world as well. About 10,000 new cases of gallbladder cancer are diagnosed in the United States each year, and 4,000 people die from it.

Dr. Galan believes that the connections between cancer and infections, especially bacterial infections, deserve more attention. “This story of ours is one example. Cancer researchers sometimes forget that 20 percent of known cancers are caused by an infectious organism,” he said, “and that’s probably a gross underestimate, because it only captures instances where the microorganism is the direct cause—for example, in the case of human papillomavirus (HPV) and cervical cancer, or the bacterium Helicobacter pylori and stomach cancer.”

In far more instances, he added, bacteria and viruses are most likely predisposing factors that essentially tilt the scale leading to cancer. “There are many cases of bacteria that produce genotoxic agents, particularly bacteria that hang around in the gut, and the thought is that some of those bacteria could be predisposing factors, for example, for colon cancer. It is also widely believed that the resident microflora in our body most likely plays an important role in predisposing us to certain types of cancer. This is a frontier that we’re just beginning to explore.”

It is also the impetus behind the name change of the Research Program from Molecular Virology to Virus and Other Infection-associated Cancers. “The idea is to broaden the focus, to think about other microorganisms as cancer-causing agents and not just viruses,” said Dr. Galan.

The Links Between Typhoid, Bacteria, and Cancer