

## Revealing Norwalk Virus' Achilles Heel

Outbreaks of Norwalk virus—a.k.a. Norovirus—are notorious for the havoc they can cause to people living in close quarters, from cruise ships to hospital wards. People afflicted with Norwalk suffer from an acute case of “stomach flu” or “food-poisoning” that is typically accompanied by severe vomiting and diarrhea that lead to dehydration. The U.S. Centers for Disease Control and Prevention estimates 23 million cases occur annually, accounting for at least half of all food borne outbreaks of gastroenteritis. The Public Health Agency of Canada reports between 300 and 400 Norovirus outbreaks every year.

While mostly an unpleasant inconvenience in healthy adults, Norwalk virus can be fatal in the elderly and those with compromised immune systems. It is also highly contagious--during the winter of 2007, over 500 000 people were afflicted with this ‘vomiting bug’ in the United Kingdom.

Using the Canadian Light Source, an international team of researchers from the University of Calgary, University of Oviedo in Spain, Penn State and the CLS determined the detailed structure of the enzyme used by the virus to replicate its genetic code. The information provided by the structure is a crucial first step in the development of drugs to treat outbreaks of the bug.

“These are the first structures showing the enzyme doing its job interacting with RNA,” said Ken Ng, a professor in the Department of Biological Sciences at the University of Calgary and leader of the research team. “These structures provide ideas we can use to try to develop new antiviral drugs that block the enzyme’s activity.”

The Norwalk virus stores its genetic information as RNA. It uses the enzyme, called RNA polymerase, to make new strands of RNA using an existing RNA strand as a template. The copying, which occurs within an area of the enzyme called an active site, can be blocked—or inhibited--with a drug molecule shaped to fit the site, like a key in a key hole.

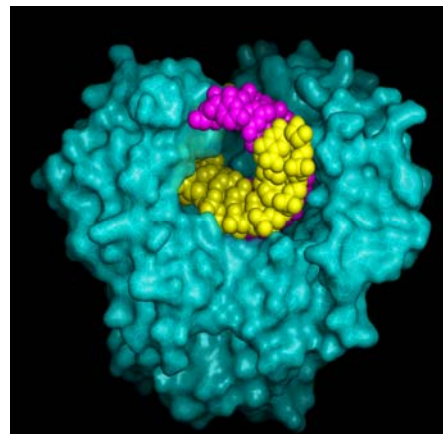
Other members of the same viral ‘superfamily’ as the Norwalk virus, including the viruses that cause polio, hepatitis C, foot-and-mouth disease and SARS, all possess a similar RNA polymerase enzyme that can be targeted for developing new therapies.

“The best doctors can do with Norwalk patients is treat the symptoms. We have the polio vaccine, but many other related diseases, like hepatitis C, lack effective treatments,” explained Professor Ng. “This polymerase is closely related in all of these viruses, so an inhibitor drug that works against Norwalk virus could also work against hepatitis C.”

Additional information on the Norwalk virus can be found on the websites for the Public Health Agency of Canada and the U.S. Centre for Disease Control:

[www.phac-aspc.gc.ca/id-mi/norovirus-eng.php](http://www.phac-aspc.gc.ca/id-mi/norovirus-eng.php)

[www.cdc.gov/ncidod/dvrd/revb/gastro/norovirus-factsheet.htm](http://www.cdc.gov/ncidod/dvrd/revb/gastro/norovirus-factsheet.htm)



Molecular model of Norwalk RNA polymerase, based on data collected by CMCF. Courtesy of Ken Ng, University of Calgary.

### Fast facts:

- Using the CLS, scientists solved the structure of the Norwalk virus’ RNA polymerase enzyme.
- The Norwalk virus and related viruses that cause polio, hepatitis C and SARS use similar RNA polymerases to replicate their genetic code.
- The discovery is a key step to developing drugs that can halt the spread of Norwalk and possibly other related viruses.

Reference: Zamyatkin et al. 2008. Structural insights into mechanisms of catalysis inhibition in Norwalk Virus polymerase. *Journal of Biological Chemistry* 283, Number 12, pp. 7705-12. DOI: 10.1074/jbc.M709563200

