Turning the page on toxins

A *Research* magazine story helped turn this writer into a toxin hunter

BY ROBERT FIELDHOUSE

Newly identified cholera- and anthrax-like toxins threaten human health, but they could also hold the key to new vaccines, drugs and cancer treatments. I became interested in protein toxins as a SPARK student, reading in the pages of *Research* about Prof. Rod Merrill, Department of Molecular and Cellular Biology.

Merrill's work on a protein toxin that punches holes through target cells to kill them caught my attention. Now, as a PhD candidate in the Merrill lab, I've worked on a new computational approach to identify and characterize novel toxins. Our team has uncovered several new toxins including Chelt, a cholera-like toxin from *Vibrio cholerae*, and Certhrax, an anthrax-like toxin from *Bacillus cereus*.

Chelt is cholera toxin with a twist – the usual cell-entry portion is swapped with a different structure.

And Certhrax is anthrax lethal factor with a twist – it has similar cell-entry machinery but kills target cells a different way.

Genome sequencing projects have ushered in a data-rich era, but making sense of the available information remains challenging. A new protein toxin is a needle in the haystack because such toxins often have little similarity to known examples.

We've developed a tactic called fold recognition to detect new toxins based on protein structure similarity. Combined with rules for filtering possible toxins, including, for example, conservation of key amino acids needed for enzyme function and a yeast-based screening step in the lab, we identified the new toxins.

Now, we're pinpointing details of each toxin such as 3-D structure, the strategy the toxin uses to leave one cell and enter another, and how the toxin interacts with molecules in the target cell. Eventually, I'd like to use supercomputers to simulate toxin function and find new inhibitor drugs that could prevent them from causing harm.

Protein toxins aren't all bad, however. For example, modified toxins that activate the immune response without causing harm are the basis for many vaccines. Also, toxins are used to kill cancer cells in some therapies.

M.Sc. graduate Zachari Turgeon and technician Dawn White made key contributions to this work, published in *PLoS Computational Biology*. Our team also includes PhD candidate Danielle Visschedyk and post-doctoral fellows Amanda Rochon and Ravi Ravulapalli, among others. This research was sponsored by the Natural Sciences and Engineering Research Council, and by the Canadian Institutes of Health Research.