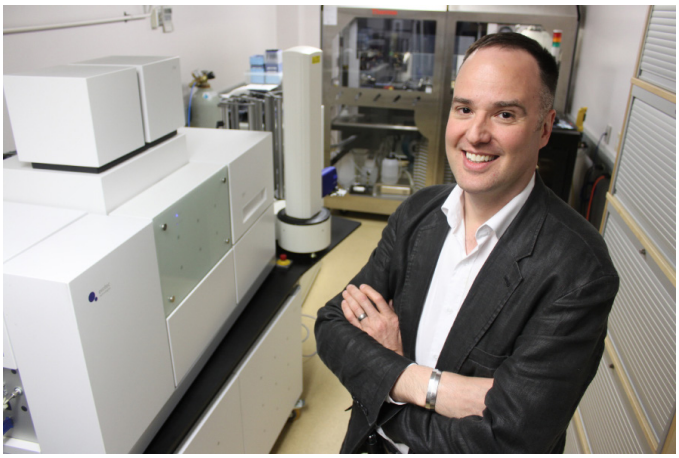
Huntington Society of Canada
HUNTINGTON
Société Huntington du Canada

Research Update

Major Breakthrough "Reshapes" the Search for Treatments

By Julie Stauffer

What is so special about the number 37? For years, Huntington disease (HD) researchers have known that if you have 37 or more CAG repeats, you will develop HD. Thanks to McMaster researcher Dr. Ray Truant, who also heads up HSC's Research Council, we now know why. Not only does his breakthrough solve a longstanding mystery, it will also dramatically speed up the hunt for treatments.



Using highly sophisticated FLIM-FRET microscopy, Dr. Truant has been able to see that the huntingtin protein produced by the disease-causing HD gene folds into a different shape than the protein produced by the normal gene.

Genes serve as a step-by-step instruction manual for cells, telling them which amino acids to string together to create the right protein. As Dr. Truant's experiments reveal, the CAG repeats in the normal gene create a stretch of amino acids that is very flexible, allowing the protein to fold into the right shape to do its job.

However, too many CAG repeats in the Huntington's gene produces a longer stretch of amino acids that is too stiff to bend correctly. "The right parts of the protein can't line up to work properly," Dr. Truant explains. "It is like trying to use a paperclip after someone has bent it out of shape."

His research, published in the Proceedings of the National Academy of Sciences in July, leads to some intriguing questions. Are there drugs that could reshape the disease-causing protein? And if so, would they halt HD? To explore those ideas, Dr. Truant turned to GM1, a drug that reverses HD symptoms in mice. Sure enough, he found that GM1 restores the huntingtin protein to its normal shape.

The problem with GM1 is that it can't cross the protective barrier that stops many drugs from reaching the brain. In mice, the solution is to inject GM1 directly into the brain. However, that is not a practical treatment option in humans. Dr. Truant's discovery means that we can now screen other potential drugs quickly and efficiently, looking for compounds that can refold the protein and cross the blood-brain barrier.

Dr. Truant has already developed an automatic, large-scale screening system. Working with a pharmaceutical company, he is searching libraries of potential drugs for the magic combination. "That is where things get exciting," he says. "We can look at thousands of compounds."

His approach will also prove invaluable when treatments currently being developed move to clinical trials. While it may take years to determine whether a drug is slowing or stopping the progress of HD, scrutinizing the shape of the huntingtin protein in patients' cells will immediately reveal if the treatment is on the right track.

Dr. Truant says his discovery would not have happened without a NAVIGATOR grant from the Huntington Society of Canada, which allowed him to run preliminary experiments. The results from those experiments were promising enough to attract funding for a full-scale study from the Canadian Institutes for Health Research, the Kembril Foundation and CHDI.

The other key to success was HD families. Dr. Truant's experiments relied on skin cells from people with HD, which he compared to samples from their HD-free spouses. He credits the HD Buzz website (www.hdbuzz.net) with helping families understand the impact they can have by getting involved in HD research and clinical studies.

"We are tremendously excited by Dr. Truant's discovery and proud to have helped make it possible," says Bev Heim- Myers, CEO and Executive Director of HSC. "This new tool puts scientists on the fast track to identifying promising treatments."

Huntington Society of Canada
151 Frederick St.,
Suite 400,
Kitchener ON
N2H 2M2
1-800-998-7398
info@huntingtonsociety.ca
www.huntingtonsociety.ca
Charitable Registration
Number
1 1896 5516 RR0001

August 2013