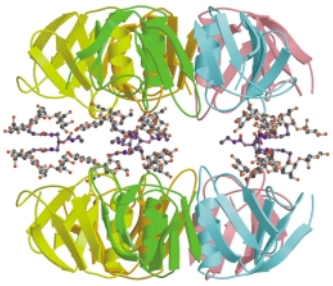
Research Update

A Starfish that stops deadly toxins

A simple injection to treat often-deadly cholera and hamburger disease may be developed in the future, thanks to a research team at the University of Alberta that has designed a molecule to treat enterotoxins (*Nature* 2000;403:669–72).

Shiga and cholera toxins, caused by gastrointestinal pathogens, are responsible for millions of deaths annually. Once the toxins enter the circulatory system, they cause cramps, bloody diarrhea, vomiting and fever. Many patients eventually suffer severe kidney damage because there is no effective cure.

But the newly developed "Starfish" molecule holds tremendous promise, standing out during in vitro tests as 1 million to 10 million times more effective than any other inhibitor of these toxins. That is no small feat. Shiga and shiga-like toxins are armed with 15 binding sites in 3 groups of 5 that lock onto cell surfaces. The Starfish molecule designed by Dr. David Bundle's team mimics receptors on healthy cells that the toxins seek out, acting as a decoy to lure the toxins away from the body. And, because of its shape, the Starfish molecule can lock onto 2 toxin molecules simultaneously.



"We have embraced the whole surface so, if you like, we have taken 2 donuts and stuck them together," says Bundle. "These 2 surfaces are now facing each other with the inhibitor [Starfish molecule] in the middle. The toxins are facing each other so they are totally prohibited from binding to another cell."

The molecule's ability to take on 2 toxin molecules at once was a pleasant surprise. "It was better than we envisaged. It was an accident, but it worked in our favour."

Currently, clinical trials are under way to test an insoluble absorbent called Synsorb Pk that could attack the toxins in the gut. But because the Starfish molecule is soluble, it could be used as an injectable treatment to clean up toxins in the bloodstream, where they cause the most damage.

"The real problem is for patients who have toxins that have exited the gut and entered the circulation. Our molecule could be used as an injectable that could neutralize the toxin in the circulation system," says Bundle. — *Richard Cairney*, Edmonton

Suicide linked to serotonin gene

Canadian researchers have discovered a genetic mutation that appears to double carriers' risk of suicide (*Am J Med Genet* 2000;96:56-60). The finding could be a significant first step toward developing a test to identify at-risk people and improving prevention and treatment.

In a study involving 251 patients, Dr. Pavel Hrdina and colleagues from the University of Ottawa's Institute of Mental Health Research (IMHR), found that a mutation in the gene encoding the serotonin 5-HT_{2A} receptor was much more common in patients with major depression and suicidal tendencies. Serotonin has long been recognized by scientists as playing a major role in mood regulation, depression and suicide.

"Ours is one of the first demonstrations that a variant of a gene encoding a neurotransmitter receptor is associated with clinical signs of suicidal behaviour," says Hrdina, director of the neuropharmacology lab at IMHR. "This is a small step toward understanding the genetic basis of suicidal behaviour and identifying the contribution that various genes may make to a complex behavioural syndrome such as suicide." The Canadian researchers believe the genetic variation also may help explain the higher incidence of suicide among people with schizophrenia.

Hrdina, along with Drs. Lisheng Du and David Bakish, analysed DNA in blood samples drawn from 131 people with no mental illness and 120 patients with major depression, 78 of whom were suicidal. They found the genetic mutation in 41% of suicidal patients and 24% of non-suicidal patients with depression, but in just 18% of the healthy control group.

The team has shown only that a variant of a gene encoding for a seratonin receptor is significantly associated with increased risk of suicidal behaviour in patients with depression, cautions Hrdina. "We did not show the existence of a 'suicide gene.' It is unlikely that any single gene will be a causative factor." Because the study focused on people with major depression, its findings cannot be generalized to otherwise healthy individuals who attempt to take their life as an isolated call for help or attention, say the researchers.

Replicating and confirming the team's results, and identifying other genes linked to increased risk of suicide, would pave the way for a genetic marker test. Treating those individuals who test positive for the genetic variation, says Hrdina, could prevent unnecessary loss of life. — *Greg Basky*, Saskatoon