



The stakes are high for an acclaimed cerebrovascular surgeon searching for a stroke drug

Surgeon and entrepreneur Dr. Michael Tymiński is developing a drug that reduces brain damage associated with stroke

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In Canada, stroke is the third-leading cause of death, after cancer and heart disease, striking down more than 13,000 people each year and leaving thousands with life-changing disabilities. In 2012, the World Health Organization reported that strokes killed 6.7 million people worldwide.

And yet, with more than 1,000 drugs tested in preclinical models, with more than 200 drugs tested in human trials and with billions spent by multinational pharmaceutical companies, a drug to mitigate the effects of stroke remains elusive. Only the clot-busting medication, tPA, is currently approved – but under highly restricted conditions. But that could be old news soon.

Since 2002, Dr. Michael Tymiński, head

of the Division of Neurosurgery at University Health Network and a senior scientist at the Krembil Research Institute, who also holds the Harold & Esther Halpern Chair in Neurosurgical Stroke Research and the Chair in Innovations for the Head of Division of Neurosurgery, has been testing the drug he has named NA-1. In ongoing human trials, the drug has reduced the amount of brain damage incurred during a stroke by about half, without serious side effects.

“We already have data to show that the drug is effective,” Dr. Tymiński says. “I’ve seen it work in lab models and in people.”

NA-1 is what’s known as a neuroprotectant, a substance that can preserve brain neuron function and structure under condi-

tions of stress, such as in a stroke.

When a stroke occurs, brain cells die at a rate of 1.9 million per minute. NA-1 can prevent that, but the drug must be administered before the stroke damage is completed.

A physician since 1987, Dr. Tymiński entered the neurosurgery training program at the University of Toronto in 1988 and completed clinical fellowship training in cerebrovascular surgery at Toronto Western Hospital in 1995 and then for a further year in Phoenix, under renowned neurosurgeon, Robert Spetzler. As a specialist in cerebrovascular surgery, Dr. Tymiński went on to conduct the world’s first outpatient surgery for aneurysms, and he is one of the few surgeons, anywhere, who uses laser surgery to control the brain’s blood flow to prevent stroke. In December, Dr. Tymiński was made a Member of the Order of Canada by Governor General David Johnston. Dr. Tymiński was cited, “For his contributions to neuroscience, particularly through his leadership in investigating new mechanisms to protect the brain following a stroke.”

“As a cerebrovascular surgeon, I treat conditions that lead to stroke. We all know someone who’s been touched by stroke. It’s a devastating disease,” he says.

Stroke targets a Canadian every nine minutes; 405,000 Canadians are living with the effects of stroke, be it loss of memory, speech or mobility. The costs of treating stroke and poststroke care are approximately \$3.7 billion each year in Canada. As well, a recent Canadian report on strokes revealed that having a stroke more than doubles the risk of developing dementia. One in three Canadians will develop stroke, dementia, or both, the study says.

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Dr. Tymiński’s challenge has been that although stroke drugs appear to work in lab models, decades of research by major pharmaceutical companies have not yielded a drug that helps people. Therefore, in 2003, he started his company NoNO Inc., operating within Krembil, to develop NA-1 so that patients may benefit. He continues his unflagging mission to secure funding that would enable the conduct of new and original clinical trials that will succeed, where the major pharmaceutical companies haven’t. He does this while still saving lives as a surgeon.

“Developing a drug for stroke is an enormous challenge. Everyone else has failed, and therefore the roadmap to success has not yet been travelled,” he says.

If someone is developing a new blood pressure medicine, or even new software, they can get advice from someone who’s done it successfully, Dr. Tymiński notes. When it comes to the challenge of stroke, there is no playbook.

But for this surgeon-scientist-entrepreneur, known for his deft skills with a scalpel or a laser, the importance of creating a stroke drug cannot be overstated. “It [NA-1] would help a lot more people than I ever could as a surgeon,” he says.

Around 300 people have been given NA-1 in various clinical trials in Canada and the United States since 2007. Results have been encouraging, and since last year the Tymiński team has stepped up to final clinical trials to enable them to apply to Health Canada and the U.S.’s Food and Drug Administration (FDA) for approval to get NA-1 on the market as a stroke treatment.

NA-1 is particularly important in a country like Canada, where the time it takes to transport patients from small or isolated communities to larger hospitals with stroke centres can be longer than a 20-minute ambulance ride in the city. “NA-1 will give more time,” Dr. Tymiński says.

In 2015, one of Dr. Tymiński’s trials began. It will run until sometime in 2019, with the aim of treating more than 500 patients.

Those experiencing stroke will receive NA-1 from paramedics via intravenous bags in an ambulance or on-site in the double-blind experiment. Double-blind means that the paramedics, hospital staff and patients don’t know who is receiving the drug or a placebo. The gold standard when it comes to trials, the double-blind method prevents the placebo effect or observer bias from influencing outcomes. After the stroke patient is brought to the hospital, the hope is that NA-1 has preserved their brain cells. “The trials are proceeding smoothly. So far there have been no serious safety concerns,” Dr. Tymiński says.

Dr. Tymiński’s team is embarking on a second even more ambitious trial, which has just started, and is taking place in 35 hospitals across Canada, the U.S., Europe, South Korea and Australia. It also has a 2019 finish date and is being led by Dr. Michael Hill, a neurology professor and director of the Calgary Stroke Program, and Dr. Mayank Goyal, a professor of radiology at the University of Calgary.

Drs. Hill and Goyal were part of the Alberta team that led a recent and very promising trial, where endovascular therapy was used on more than 300 patients in 22 sites worldwide to remove blood clots in the brain, thus restoring blood flow to the vital organ.

The three doctors have known each another since the mid-1990s, and all have dedicated their professional lives to the treatment of stroke.

In this second trial, NA-1 will be used in patients undergoing endovascular thrombectomy, once again in a double-blind trial. The first patient to be enrolled was planned in Calgary.

The stakes are high. “If we win this, it’s a big win, not just for stroke but for neuroscience,” Dr. Hill says.

“One thing that some scientists do, they’re overly exuberant about their pet projects. But some conditions are so challenging to deal with. They’re humbling. My cautious tone doesn’t mean I’m lacking conviction. It’s an appreciation that the road is still fraught with challenges,” Dr. Tymiński says.

If the destination is reached, Dr. Tymiński notes that NA-1 has a very fundamental method of action and because of that may also be effective with traumatic brain injuries, epilepsy and, as related to stroke, Alzheimer’s disease.

“We have something that we truly believe in,” Dr. Tymiński says. “We have a social responsibility not to let go.”

Based on the already very promising results, combined with his great desire to tame the damage strokes have wrought, Dr. Tymiński expects that results from the two trials will be life-changing and life-saving. ■

Understanding how the breakthrough drug NA-1 works

Strokes come in two types:

- In North America, 85 per cent are ischemic and occur when a blood vessel supplying blood to a region of the brain suddenly becomes obstructed.
- The other 15 per cent are hemorrhagic and happen when a weakened vessel ruptures and bleeds into surrounding brain.
- NA-1 is being tested for efficacy on ischemic strokes. The average adult brain has about 86 billion neurons (the “grey matter”), with more than 60 trillion connections (synapses) joining them together. After a stroke, brain cells die at a rate of 1.9 million per minute. Every 30 minutes, a favourable outcome diminishes by 10 to 20 per cent, which is why stroke victims can be left blind or paralyzed. What NA-1 does is keep brain cells alive for a number of hours, until hospital treatment is available.

Dr. Michael Tymiński began his NA-1 odyssey in the early 1990s. By 1999, he and his team identified a protein found in neurons called PSD-95. When a stroke happens:

- Neurons release a lethal amount of neurotransmitters, one of them being glutamic acid.
- A blocked brain artery prevents necessary nutrients (like glucose and oxygen) from reaching the brain cell, nutrients which are critical for preventing damage induced by a massive dose of glutamate.
- The glutamate binds to the neurons’ receptors, opening the door to cell-killing reactions. One such chemical is nitric oxide (NO), which kills neurons.

Dr. Tymiński’s team determined that PSD-95 was the mediator between glutamate receptors and the manufacturer of nitric oxide, known as nNOS (neuronal nitric oxide synthase). If PSD-95 was stifled, glutamate receptors couldn’t then activate nNOS. So, if the nNOS isn’t activated, the brain cell destroyer NO cannot be produced. NA-1 removes PSD-95.