

The path to the clinical development of nerinetide (NA-1)

Today's research results published in the journal *The Lancet* and presented at the International Stroke Conference is a culmination of over two decades of scientific research by Dr. Michael Tymianski and his research and development team, which first began at the University Health Network (UHN) in Toronto.

Below is a timeline of milestones in the development of nerinetide (NA-1), the first neuroprotective agent in the world to have demonstrated the ability to improve the outcomes of patients with acute ischemic stroke – which occurs when an artery that supplies blood to the brain is blocked. Nerinetide acts by enhancing the resilience of brain neurons to withstand the lack of blood flow in ischemic stroke.

- **1990s** – As a Senior Scientist with the Toronto Western Research Institute (now the Krembil Brain Institute), Dr. Michael Tymianski's research focuses on why brain cells die when they are deprived of oxygen and glucose.
- **1999** – Dr. Tymianski's lab discovers that a protein in brain neurons called PSD95 is important in mediating stroke damage. The team turns its attention to determining how to block this protein to reduce the brain's vulnerability to stroke damage from an ischemic stroke. Results are published in [Science](#).
- **2002** – The research team reports that a molecule developed in their lab, the first iteration of the eventual drug nerinetide, blocks PSD95 protein and reduces stroke damage in preclinical models. Results are published in [Science](#).
- **2003** – Dr. Tymianski founds NoNO Inc., a biotechnology startup company aimed at further developing this class of therapeutic molecules called "PSD95 inhibitors."
- **2005–2012** – The team continues its research on PSD95 inhibitors, publishes several papers on their properties and mechanisms of action. Multiple labs around the world independently confirm the results published by Dr. Tymianski's team and extend their findings to other diseases including epilepsy, traumatic brain injury, Huntington's disease and Alzheimer's disease.
- **2012** – The team publishes a paper showing that nerinetide can reduce the damaging effects of strokes in primates, using experimental approaches that simulate the strokes incurred by patients who undergo endovascular surgery for aneurysm repair. The study is published in [Science Translational Medicine](#).
- **2012** – The team publishes a multi-centre, randomized, placebo-controlled trial in 185 patients showing that nerinetide reduces stroke burden in patients who undergo endovascular surgery for brain aneurysm repair. This world-first – showing that neuroprotectants can reduce stroke damage in humans – is published in [The Lancet Neurology](#).
- **2012** – The team publishes further research in old-world primates which bear genetic, anatomic and behavioural similarities to humans. This time, the research shows how a "PSD95 inhibitor" prevents brain cell death and preserves brain function when administered after a major stroke has occurred. The study's experimental approaches simulate protocols that are planned for clinical trials in acute ischemic stroke. These protocols include giving nerinetide within the first hour after stroke, and another where nerinetide is given in scenarios that approximate those

observed in stroke patients who undergo endovascular thrombectomy. Results are published in [Nature](#).

- **2015** – Launch of a Phase III, multi-centre, randomized, placebo-controlled clinical trial in 558 patients in eastern Ontario and western British Columbia, called FRONTIER. Paramedics in the field administer nerinetide or placebo to eligible stroke victims. The drug is being given approximately one hour after stroke onset, simulating one of the experimental approaches previously tested in primates. The trial is ongoing.
- **2017** – Launch of a Phase III, multi-centre, randomized, placebo-controlled clinical trial in 1,105 patients in Canada, the United States, Europe, South Korea and Australia, called ESCAPE-NA-1. Nerinetide is administered to patients selected for endovascular thrombectomy, simulating one of the experimental approaches previously tested by the team in primates. The trial is 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. It is the largest trial involving endovascular thrombectomy in history and the largest ongoing acute stroke trial globally.
- **2020** – Results of the Phase III ESCAPE-NA-1 are published in *The Lancet* and presented at the 2020 International Stroke Conference on February 20, 2020.

Media contacts:

Alexa Giorgi

Senior Public Affairs Advisor
Toronto Western Hospital
416.603.5800 x 6776
Alexa.giorgi@uhn.ca

Heather Sherman

Senior Public Affairs Advisor
Krembil Brain Institute
416.603.5294
Heather.sherman@uhn.ca