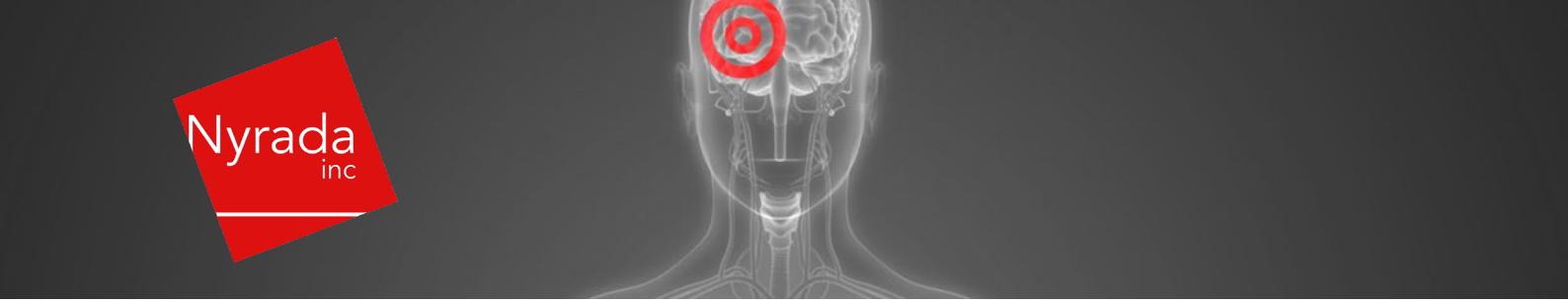

09 July 2020 Sydney, Australia

Nyrada Brain Injury Data Published by Premier US Military Health Conference

Sydney, 09 July 2020: Nyrada Inc (ASX: NYR) is pleased to advise an abstract relating to data from Nyrada's Brain Injury program was published today by the United States' (US) Military Health System Research Symposium (MHSRS).

The MHSRS is the US Department of Defense's foremost scientific meeting for presenting new scientific knowledge resulting from military research and development. It normally draws approximately 3,500 attendees including military providers, research and academic scientists, international partners and industry experts. However, this year the Symposium was cancelled due to COVID-19 safety concerns, with all abstracts and submissions being published online instead.

The abstract relates to preclinical work conducted by Nyrada that showed its small molecule compound, NYX-104, blocks sustained Ca^{2+} build up in cells, which is a key driver of secondary brain injury. Since this work was conducted, Nyrada has designed and synthesised further compounds with greatly improved potency compared to NYX-104. A preliminary pharmacokinetic study recently showed the second-generation compounds NYX-242 and NYX-1010 can readily cross the blood-brain-barrier of healthy animals with intravenous delivery.

Nyrada's Brain Injury program is also focused on formulating its compounds to enable treatment of soldiers on the battlefield following Traumatic Brain Injury (TBI) to improve their survivability. TBI is a major health focus for the US Department of Defense, with no current treatment available that limits the ongoing brain damage from secondary injury.

Abstract Details

Title: *Secondary Brain Injury Following Focal Ischemia in Mice is Reduced by a Synthetic Isoflavone Treatment that Inhibits Gαq – Mediated Ca^{2+} Flux*

Authors: J Parmar, N Gorlamandala, G von Jonquieres, C.J. Perera, G.E. Kelly, A.K. Suchowerska, B.J. Evison, J.A. Bonnar, G.D. Housley

The abstract can be viewed on the MHSRS website at https://mhsrs.amedd.army.mil (requires registration) or via the Nyrada website at nyrada/announcements

About Nyrada Inc

Nyrada is a preclinical stage, drug discovery and development company, specialising in novel small molecule drugs to treat cardiovascular, neurological, and inflammatory diseases. The Company has two main programs, each targeting market sectors of significant size and considerable unmet clinical need. These are a cholesterol lowering drug and a drug to treat brain injury, specifically traumatic brain injury and stroke. Nyrada Inc. ARBN 625 401 818 is a company incorporated in the state of Delaware, USA, and the liability of its stockholders is limited.

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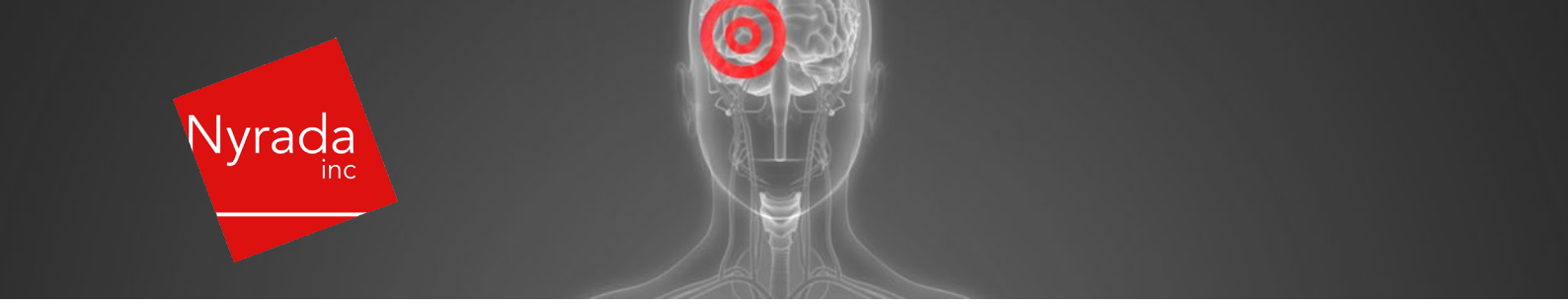

Authorised by Mr John Moore, Non-Executive Chairman, on behalf of the Board

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Forward Looking Statements

This announcement may contain forward-looking statements. You can identify these statements by the fact they use words such as “aim”, “anticipate”, “assume”, “believe”, “continue”, “could”, “estimate”, “expect”, “intend”, “may”, “plan”, “predict”, “project”, “plan”, “should”, “target”, “will” or “would” or the negative of such terms or other similar expressions. Forward-looking statements are based on estimates, projections and assumptions made by Nyrada about circumstances and events that have not yet taken place. Although Nyrada believes the forward-looking statements to be reasonable, they are not certain. Forward-looking statements involve known and unknown risks, uncertainties and other factors that are in some cases beyond the Company’s control that could cause the actual results, performance or achievements to differ materially from those expressed or implied by the forward-looking statement.

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Abstract Details:

Breakout Session: Acute Interventions for Battlefield TBI

Category: Oral Presentation

Title: Secondary Brain Injury Following Focal Ischemia in Mice is Reduced by a Synthetic Isoflavone Treatment that Inhibits Gαq – Mediated Ca2+ Flux

Abstract:

Background: Traumatic brain injury (TBI) is a severe, debilitating health issue faced by soldiers on and off the battlefield. Greater than 300,000 US service members have sustained a TBI in training or combat, with 8% being moderate to severe types of TBI and the remainder are mild TBI. A key factor in the morbidity and mortality arising from TBI is the prodigious expansion of the injury volume in the hours and days after the primary head injury. This stems from a decline in local blood flow and edema leading to metabolic failure in neurons and glia triggering ionic pump failure, alongside excessive unregulated discharge of excitatory neurotransmitters, especially glutamate. Together this causes sustained buildup of the second messenger Ca2+ in the cytosol, activating caspase-coupled, pro-apoptotic signaling. Currently, treatment for TBI is limited to decompressive surgery or physical therapy, but pharmacological treatments that blocks the progressive expansion of the injury size in the days following the trauma do not exist.

Nyrada Inc. is developing a small molecule compound that blocks sustained Ca2+ build up in cells, tied to activation of Gαq-type G protein-coupled receptors. Expressed across a wide range of cell types including neurons, astrocytes, microglia, platelets and endothelial cells, the activation of Gαq receptors switches on the enzyme phospholipase Cβ leading to production of secondary messengers - inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 activates the IP3 receptor on the endoplasmic reticulum, releasing Ca2+ internal stores while DAG activates Ca2+ re-entry via canonical transient receptor potential ion channels. This sustained activation of Gαq-coupled receptors, especially the glutamate dependent class I metabotropic glutamate receptors (mGluR1 and mGluR5), on neurons and astrocytes, is central to the pathophysiology of secondary brain injury expansion.
Methods and Results: Nyrada's synthetic isoflavone compounds were initially screened for their activity in CHO cells stably expressing the Gαq-type human M3 muscarinic receptor (hM3R), with activation via the M3R agonist carbachol. The Ca2+ flux was measured with a FLIPR® Calcium 5 Assay Kit and the IC50 of the lead compound (NYX-104) was determined as 9.8 µM.
NYX-104 was evaluated for its potential to block Ca2+ entry into the cytosol of Purkinje neurons following activation of mGluR1 in mouse brain slices. To assess this, the cerebellae of postnatal day 3 mice (C57BL/6J) were injected with 3 x 109 vg of a recombinant adeno-associated virus vector (AAV1) encoding the genetically encoded Ca2+ indicator, GCaMP5g. Ca2+ imaging was performed on parasagittal acute brain slices (400 µm) 8 – 12 weeks later using the Zeiss confocal system (710NLO LSM; excitation 488 nm). Slices were continuously superfused with artificial cerebrospinal fluid and the activation of mGluR1 was acheived by adding the agonist (s)-3,5-Dihydroxyphenylglycine (DHPG, 100 µM) to the bath for 10 min. During washout, NYX-104 (40 µM), or DMSO vehicle (0.1 %), was delivered to the brain slices for 30 mins and then DHPG was re-applied in the presence of NYX-104, or DMSO vehicle. Ca2+ dynamics in the Purkinje neuron soma were analysed for 40 seconds from DHPG-response onset. In relation to the initial baseline stimulation, DHPG - induced Ca2+ entry in Purkinje neuron soma incubated with NYX-104 was significantly reduced compared to the vehicle control ($p = 0.0175$, paired t-test, two-tailed).
NYX-104 was assessed for in vivo neuroprotection in a photothrombotic model of focal ischemia in mice (C57BL/6J strain; aged 8 - 12 weeks, males and females). Focal ischemia was achieved via tail vein injection of the photosensitive dye rose bengal (50 mg/kg), followed by irradiation of the somatosensory cortex via transcranial illumination with green light (532 nm, 1mW), which triggered localised thrombus formation, blood vessel occlusion and oxygen-glucose deprivation. Mice were rectally administered with NYX-104 (100 mg/kg/d), or a carrier control, commencing 45-minutes after injury induction, and then once daily for four days. In a reference group of mice, the primary injury volume, determined at 2-hours post injury, was 7.87 mm3. The secondary expansion of the brain injury doubled the infarct volume in the control mice by five days (15.21 mm3; $p < 0.001$, one-way ANOVA). In comparison, NYX-104 demonstrated a 38% decrease in the penumbra expansion during this time (12.42 mm3 infarct volume; $p = 0.025$; t-test comparing control and NYX-104 infarct volumes at 5 days post injury).
Conclusion: NYX-104 shows block of Gαq-mediated Ca2+ flux in vitro, including reduction in mGluR-mediated Ca2+ loading in cerebellar Purkinje neuron soma. In an in vivo focal ischemia brain injury model, NYX-104 conferred significant protection from secondary brain injury expansion. Nyrada aims to further optimise this promising lead candidate to enhance potency against the block of Ca2+ and formulation to enable treatment of soldiers on the battlefield following TBI to improve their survivability.

Disclaimer: All animal experiments were undertaken in accordance with the UNSW Animal Care and Ethics Committee Code. The information presented in this abstract is the proprietary information of Nyrada Inc.

Learning Objectives

1. Identify that TBI is a major health problem in the DoD, with no current treatment that limits the ongoing brain damage from secondary injury mechanisms.
2. Recognize the significance of excessive loading of Ca2+ in brain cells as a key driver of secondary brain injury.
3. Evaluate the significance of NYX-104 in reducing pathophysiological Ca2+ loading in brain cells for a neuro-rescue therapy for TBI.

Submit for Young Investigators Competition? No

May We Publish Abstract on the MHSRS website? No

Curriculum Vitae: View CV File *(uploaded: 4/8/2020 1:49 AM)*

Conflict of Interest (COI) Disclosure: View COI Disclosure File *(uploaded: 4/8/2020 2:15 AM)*