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Xolatryp™ Protects Cells through Mitochondrial Stabilisation

Highlights:

- Further analysis of earlier WRAIR and UNSW Sydney collaborative traumatic brain injury study has confirmed Xolatryp reduced mitochondrial calcium ion loading in the brain.
- Results provide further preclinical evidence of Xolatryp's mechanism of action in mitigating secondary brain injury and offers Nyrada increased confidence of Xolatryp's benefits in treating myocardial ischemia reperfusion injury.
- Nyrada remains on track to commence its Phase IIa clinical trial of Xolatryp in the first quarter of calendar 2026 targeting patients with acute myocardial infarction.

Nyrada Inc (ASX:NYR), a clinical-stage biotechnology company focused on developing Transient Receptor Potential Canonical (TRPC) ion channel inhibitors to treat a range of medical conditions provides further information from its collaborative study with the Walter Reed Army Institute of Research (WRAIR) and UNSW Sydney.

Background and Further Analysis

In April 2025, Nyrada announced the results of its collaborative traumatic brain injury (TBI) study with WRAIR and UNSW Sydney. This study sought to evaluate the efficacy of Xolatryp in a penetrating TBI rodent model and concluded that Xolatryp significantly preserved brain tissue integrity (p = 0.043; ANOVA).

As a further analysis, an additional cohort of animals underwent TBI followed by a 72-hour continuous intravenous infusion administration of either Xolatryp (5 mg/kg/hour) or vehicle.

The results confirmed that Xolatryp helps preserve mitochondrial health by improving calcium handling, thus protecting the brain's energy centres from reactive oxygen species (ROS) related damage.

Increased Confidence in Xolatryp's Benefits in Cardiac Injury

This further analysis increases Nyrada's confidence that Xolatryp's protective effects on mitochondria will also reduce heart damage. This is because ROS and calcium-driven mitochondrial damage occur in both brain injury and myocardial ischemia reperfusion injury MIRI.

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Reperfusion following percutaneous coronary intervention (PCI) triggers a surge in cytosolic calcium ions (Ca^{2+}) that drives mitochondrial Ca^{2+} overload, ROS generation, permeability transition (mPTP) opening, and cardiomyocyte death. By inhibiting TRPC3/6/7 channels, Xolatryp limits pathological Ca^{2+} entry, a mechanism that aligns with the infarct-sparing and functional benefits previously observed *in vivo*[1], and the reduction in mitochondrial Ca^{2+} observed *ex vivo*.

Study Results

At the 72-hour timepoint, mitochondria were isolated from both the injury core and the surrounding peri-injured area (area around the injury core) and assessed for their Ca^{2+} buffering capacity using a fluorescence-based assay.

Mitochondria from Xolatryp-treated animals demonstrated a significant improvement in Ca^{2+} buffering ability compared to vehicle-treated controls, with an overall 11 percent enhancement in mitochondrial function.

Time (Seconds)	***Vehicle Mean (n = 10)***	***Vehicle SEM***	***Drug Mean (n = 9)***	***Drug SEM***	***p-value (t-test)***
450-550	1.032	0.027	0.917	0.048	**0.035**
550-650	1.082	0.029	0.964	0.053	**0.046**

This degree of reduction in secondary cellular injury following trauma is anticipated to translate into meaningful clinical benefit.

Importantly, these results directly support Nyrada's previous stroke and TBI study findings, where Xolatryp treatment significantly preserved brain tissue integrity compared to vehicle control, and provides evidence of Xolatryp's protective effect at the cellular level. This is also the first instance where mitochondrial function has been evaluated following drug intervention in WRAIR's penetrating TBI model, representing a rigorous demonstration of Xolatryp's ability to protect mitochondrial health.

Most mitochondrial protection studies evaluate compounds by directly adding them to isolated mitochondria *in vitro*, showing whether the compound can acutely protect under controlled lab conditions. In contrast, this study demonstrated that systemic administration

[1] Nyrada's Lead Drug Candidate Demonstrates Significant Cardioprotection, Supplementary NYR-BI03 Studies Confirm Strong Cardioprotection, and NYR-BI03 Extends Cardioprotection to Arrhythmia Control.

of Xolatryp after penetrating TBI *in vivo* resulted in mitochondria that, once isolated, had significantly enhanced Ca^{2+} buffering capacity. This highlights that Xolatryp crosses the blood-brain barrier, engages its molecular target (TRPC3/6/7 ion channels), and confers neuroprotection in terms of mitochondrial protection within a living system.

In the mitochondrial assay, Xolatryp produced a large effect size (Cohen's d = 1.0), indicating a robust and consistent reduction in Ca^{2+} loading. In these conditions, even a 10 percent reduction in mitochondrial calcium load can mean the difference between cells recovering versus undergoing apoptosis/necrosis. Xolatryp's effect (~11 percent reduction in the 450–650 seconds window) aligns with that threshold, and its large effect size (d = 1.0) means this reduction is robust across replicates.

Therapeutic Relevance in Calcium-Driven Injury

Mitochondrial Ca^{2+} overload is central to pathologies in stroke ischemia-reperfusion injury, TBI, and MIRI. There is currently no approved therapy that directly protects cardiomyocytes from reperfusion injury. If clinically validated, Xolatryp's first-in-class mechanism and procedure adjacent dosing have the potential to reduce infarct size, shorten hospital stay, and mitigate downstream heart-failure risk for patients undergoing PCI.

Nyrada CEO James Bonnar commented: "With a successful Phase I completed, and strong cardioprotection efficacy previously shown in a rodent MIRI model, our focus is on translating this mechanism into patient benefit.

"This mitochondrial data demonstrates a significant reduction in Ca^{2+} loading, providing a coherent rationale for Xolatryp as a first-in-class adjunct at the point of reperfusion."

About Xolatryp™

Xolatryp (formerly known as NYR-BI03) is a small-molecule inhibitor of TRPC3/6/7 channels designed to limit pathological Ca^{2+} entry, stabilise mitochondrial function, and mitigate reperfusion injury in acute MI and related settings.

A Phase I clinical trial to assess the safety, tolerability, and pharmacokinetics has been successfully completed and a Phase IIa clinical trial to assess safety and efficacy is scheduled to commence in the first quarter of calendar 2026 targeting patients with acute myocardial infarction. This trial will seek to assess safety and explore efficacy in patients with ST-Elevation Myocardial Infarction (STEMI) undergoing PCI.

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About Nyrada Inc.

Nyrada Inc. is a clinical-stage biotechnology company focused on the discovery and development of innovative small-molecule therapies, specifically targeting Transient Receptor Potential Canonical (TRPC) ion channels. The company's lead candidate, Xolatryp™, has shown efficacy in both cardioprotection and neuroprotection, and has just completed a first-in-human Phase I clinical trial. Nyrada Inc. (ARBN 625 401 818) is incorporated in Delaware, US, with limited liability for its stockholders.

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