



Improving Lives Through Innovation

Corporate Presentation

James Bonnar - CEO

June 2022

ASX: NYR

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

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Portfolio of Novel High Value Small Molecule Drugs

	Indication	Aim	Target Market (US)	Status
Cardiovascular NYX-PCSK9i Oral PCSK9 inhibitor	Cholesterol lowering	Best-in-class small molecule drug to disrupt and broaden the class in CV management	>18m Patients ¹	Phase I Study: late CY2022
Neurology NYR-BI02 TRPC 3/6/7 blocker	Brain Injury	First-in-class treatment to prevent secondary brain injury following moderate-severe TBI, concussion, or stroke	>3m Patients / year ²	Phase I Study: 2H CY2022

Commercially Focused Business Model

Focus Area

- **Novel small molecule treatments** for **serious and life-threatening diseases** where there is **unmet clinical need** and **large market share potential**

Development Objective

- Advance optimized drug candidates towards a **key value inflection point** of **confirming clinical safety and efficacy**

Growth Strategy

- **Build value** in lead drug assets by generating **clinical data** that **differentiates Nyrada's molecules as best-in-class**



Nyrada
inc

Cholesterol-Lowering Drug Program

Novel small molecule PCSK9 Inhibitor



Cholesterol-Lowering Market

Population, Problem, Opportunity



62.6 million

Americans have high cholesterol¹

56 million

between ages 40 and 75
treatment eligible

27.4 million

taking a statin¹

18.4 million

Unable to achieve
LDL-C target despite taking a statin¹

1 in 5 patients
statin intolerant³

Global Cholesterol Drugs Market

- USD 18.8 billion in 2021 (USD 14.7 billion statin drugs)⁴
- Est. sales revenue USD 30 billion by 2027 (**CAGR 8%**)⁵

Drivers of Market Growth

- Increasing rate of high cholesterol in patients
- Awareness of the benefits of cholesterol lowering drugs
- New treatment options entering the market

Current PCSK9 Injectable Drugs

Expensive and Inconvenient



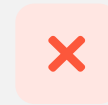
Competitive advantages
of a small molecule PCSK9 inhibitor



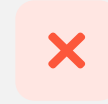
- **Patient convenience:** once per day oral treatment
- **Lower manufacturing cost**
- Dose form **can be combined with a statin** (single pill)



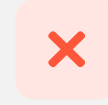
Effective when combined with statin treatment



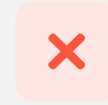
Expensive US\$5,800 to US\$6,500 per year



Inconvenient for patient / poor compliance



Expensive to manufacture



Insurer / patient co-pay reluctance

Development of Drug Candidate NYX-PCSK9i

Discovery to Clinical Lead

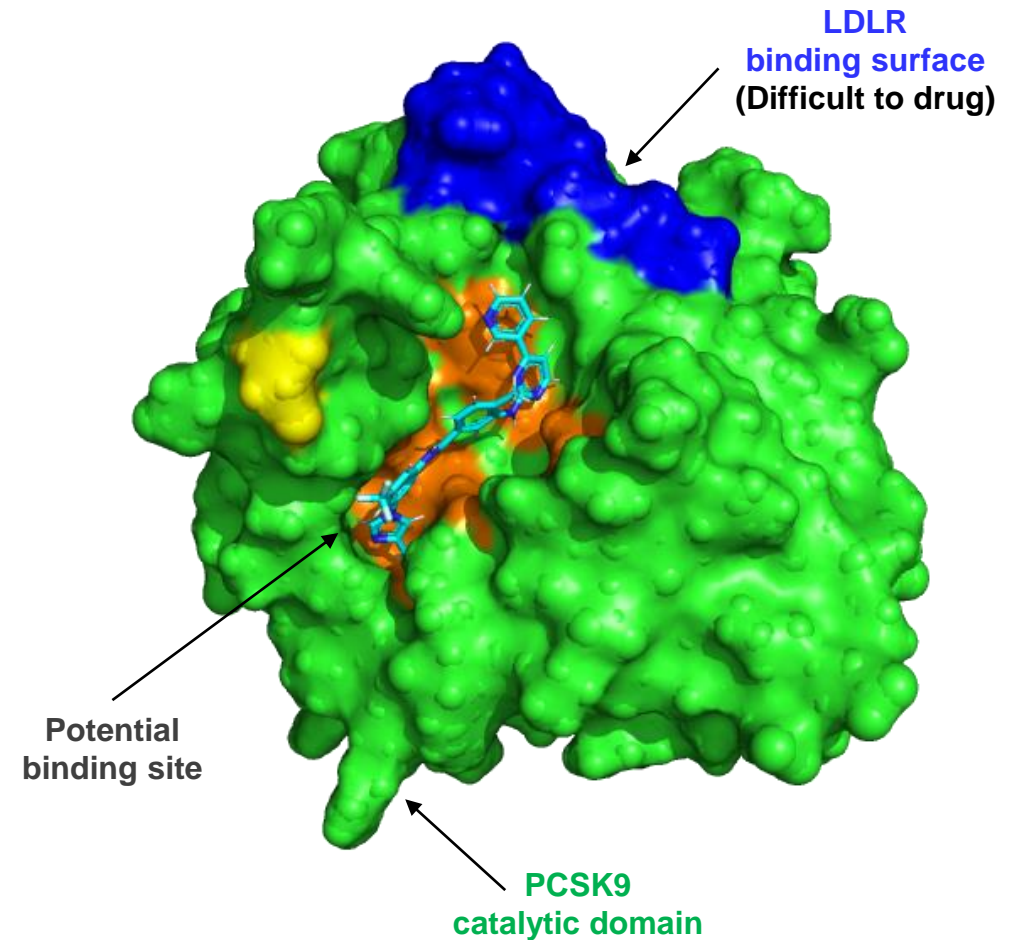


Target Product Profile

- Small molecule suitable for once per day oral dosing
- Sufficiently potent in lowering LDL-C
- Safety / toxicology profile consistent with chronic dosing
- PCSK9 validated CVD target

Development Overview

- Novel accessible binding site was identified
- *In silico* screen of 1,100 FDA-approved drugs and nilotinib (TASIGNA® Bcr-Abl inhibitor) emerged as a hit
- Over 400 analogs modeled, synthesized and tested for PCSK9 binding affinity (ELISA)
- NYX-PCSK9i emerged as lead candidate with nanomolar PCSK9 binding affinity, oral bioavailability, and drug-like ADME-PK and physiochemical properties



Evison *et al.* Bioorg. Med. Chem. (2020) **28**: 115344

Benchmarking Efficacy

NYX-PCSK9i in Human Lymphocyte Cells



- NYX-PCSK9i shows **equivalency to Repatha® and Praluent®** in human lymphocytes
- LDLR retention **confirmed with/without a statin**, supporting NYX-PCSK9i use alone or in combination with statin

	- Mevastatin		+ Mevastatin	
	% LDLR retention (with PCSK9 present)	p-value	% LDLR retention (with PCSK9 present)	p-value
No Drug	51%	n/a	64%	n/a
NYX-PCSK9i (1 µM)	53%	0.74	78%	0.13
NYX-PCSK9i (2 µM)	64%	0.01	77%	0.06
NYX-PCSK9i (4 µM)	89%	0.001	90%	0.003
alirocumab (Praluent®)	78%	0.002	88%	0.04
evolocumab (Repatha®)	84%	0.0009	89%	0.0001

bold = statistically significant

Benchmarking Efficacy

NYX-PCSK9i +/- Lipitor® in Transgenic Mouse Hyperlipidemia Model



Study Objective:

Determine if additive reduction in total cholesterol can be achieved with combination statin therapy

- APOE*3Leiden.CETP mouse hyperlipidemia model
- Mouse treated for 35 days (50 mg/kg BID NYX-PCSK9i)



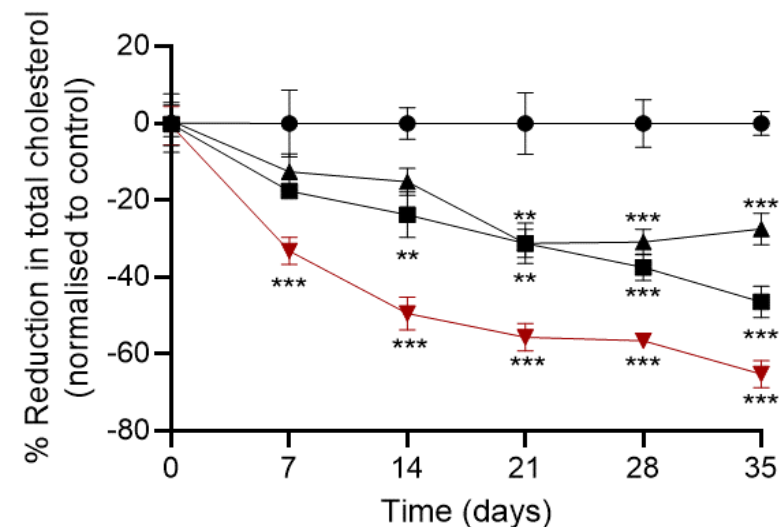
Results:

- NYX-PCSK9i + Lipitor® achieves 65% total cholesterol reduction
- No effect on body weight, food intake, liver enzymes

% Difference in plasma cholesterol versus vehicle control (p-value)

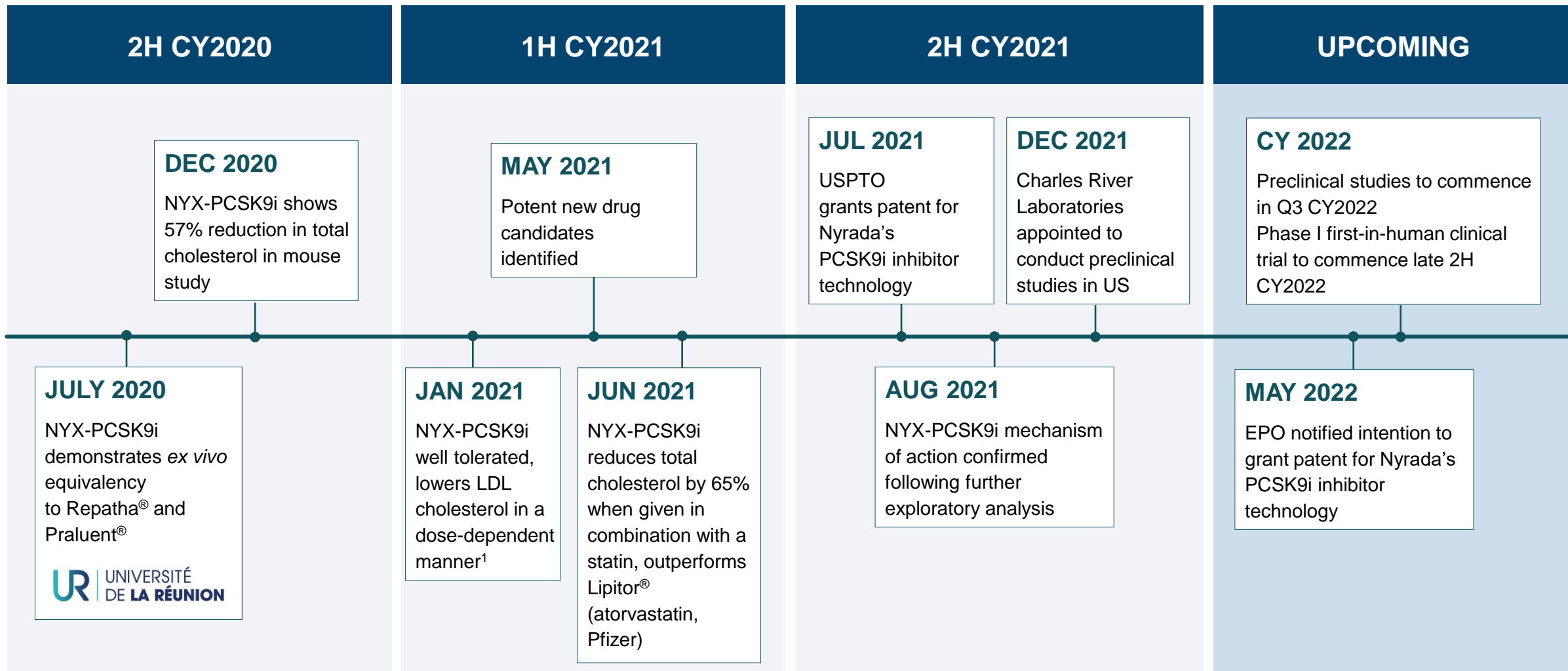
Time (days)	7	14	35
NYX-PCSK9i	-18% (0.066)	-24% (0.002)	-46% (<0.001)
Lipitor®	-13% (0.275)	-15% (0.077)	-27% (<0.001)
NYX-PCSK9i + Lipitor®	-33% (<0.001)	-49% (<0.001)	-65% (<0.001)

bold = statistically significant



- Vehicle control
- ▲ Lipitor
- 50 mg/kg NYX-PCSK9i
- ▼ 50 mg/kg NYX-PCSK9i and Lipitor

Program Milestones and Path to the Clinic



Phase I Study Design

OBJECTIVES

- Evaluate safety, tolerability, and pharmacokinetics of NYX-PCSK9i
- Measure changes in LDL cholesterol

DESIGN

- Double-blind, randomized, placebo-controlled, dose escalation study
- Single ascending oral dose (Cohorts 1-5)
- Once daily oral dose over 14-day treatment period (Cohorts 6, 7)
- Pharmacokinetic and pathology samples will be collected at selected time points over the trial period for all subjects.

PARTICIPANTS

- 56 healthy volunteers (18 to 50 years)
- 7 cohorts (6 active: 2 placebo per cohort)



LOCATION & DURATION

- Study will be conducted at a clinical trial center in Australia
- The dosing period will vary between 1 – 14 days



*trial design subject to ethics approval



Brain Injury Drug Program

Novel small molecule TRPC 3/6/7 blocker



Brain Injury Market

Population, Problem, Opportunity



Each year

2.8 million

Americans suffer a TBI⁶

5.3 million

Americans live with a post-TBI disability⁷

Each year

800 thousand

Americans suffer a stroke⁸

One drug class for stroke (tPA)
suitable for >15% of patients

TBI Treatment Market

- USD 6.7 billion sales revenue in 2020 (US, UK, Europe, Japan)⁹
- Sales revenue **CAGR 5%** to 2030⁹

Stroke Drug Market (tPA)

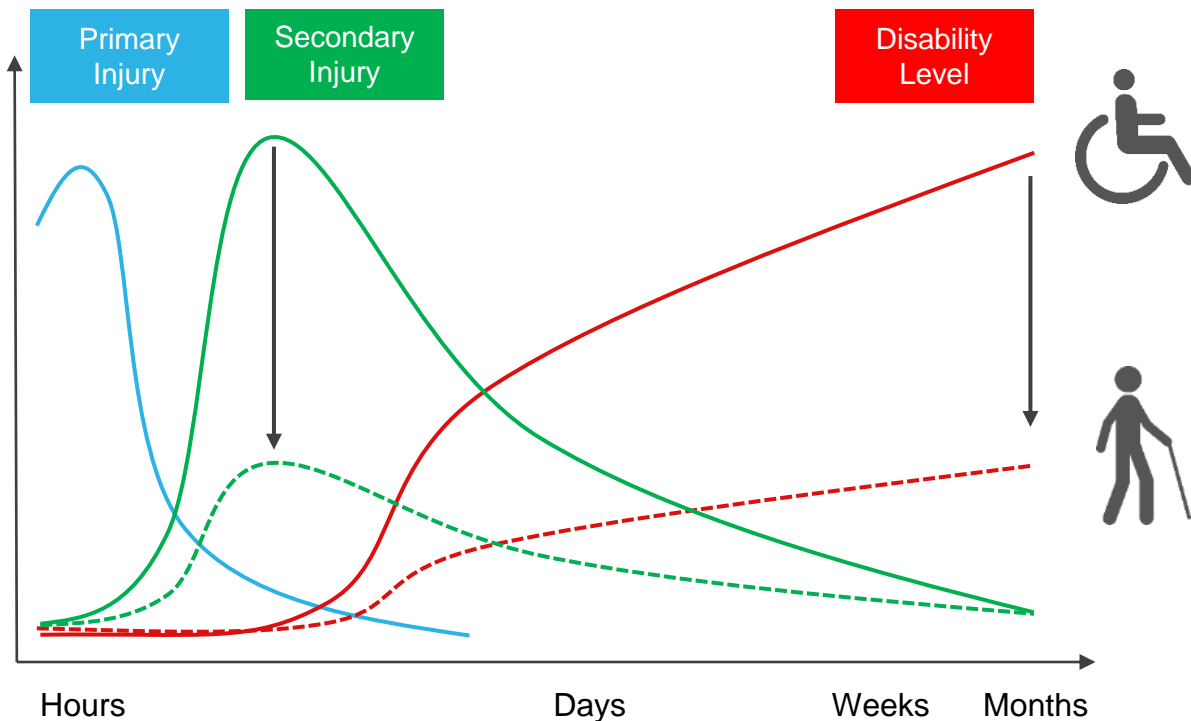
- USD 3.4 billion global revenue in 2018¹⁰
- Sales revenue **CAGR 7%** to 2027¹⁰

Problem and Opportunity

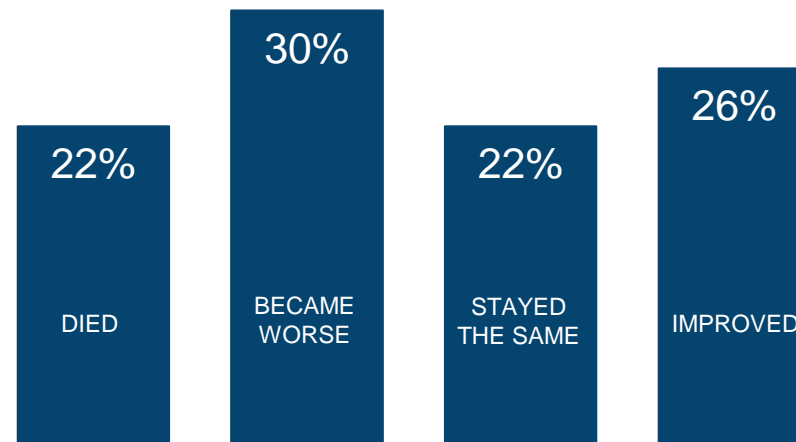
- **Unmet clinical need** with no approved drugs for TBI and limited treatment options for stroke
- **Effective treatment will improve patient outcomes and reduce high costs** associated with long-term care of brain injury survivors
- Moderate to severe TBI is an **orphan indication**

Nyrada is developing a first-in-class **neuroprotectant drug to prevent secondary injury**

Brain Injury Trajectory, Patient Outcomes, Treatment Aims



5-Year Patient Outcomes following TBI¹¹



Data are US population estimates based on the TBIMS National Database. Data refer to people 16 years of age and older who received inpatient rehabilitation services for a primary diagnosis of TBI.

Nyrada drug NYR-BI02
An acute 3-day intravenous treatment

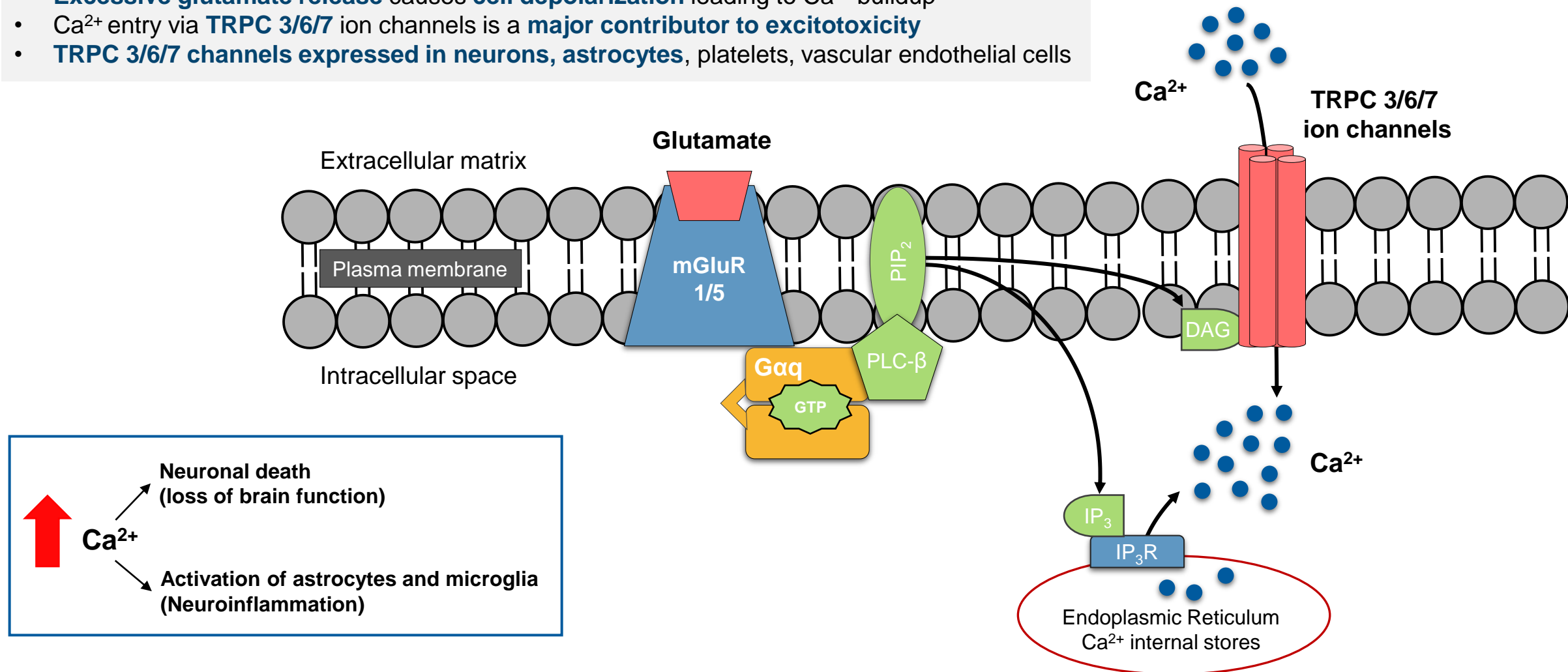


Reduce secondary injury resulting from TBI or stroke

- Improve survivability, limit disability
- Improve quality of life

TRPC 3/6/7 Ion Channels as a Therapeutic Target¹²

- **Excessive glutamate release** causes **cell depolarization** leading to Ca^{2+} buildup
- Ca^{2+} entry via **TRPC 3/6/7** ion channels is a **major contributor to excitotoxicity**
- **TRPC 3/6/7** channels expressed in **neurons, astrocytes, platelets, vascular endothelial cells**

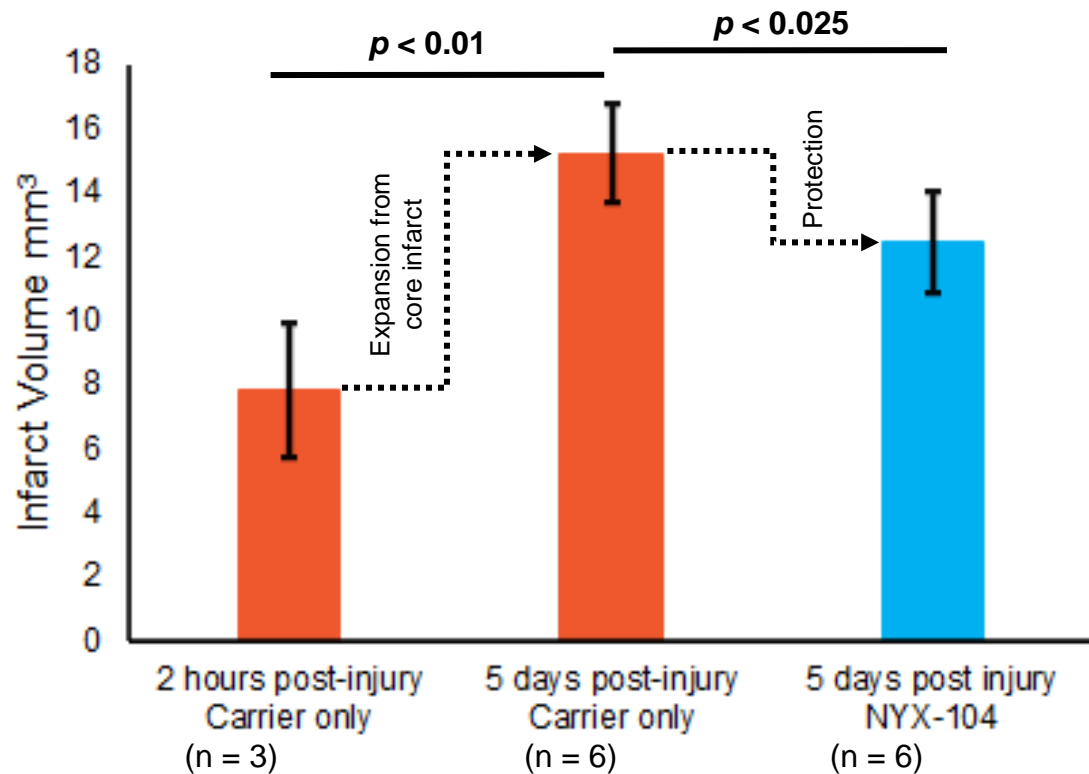


Proof of Concept

Early Discovery Molecule shows Neuroprotection



NYX-104 shows Neuroprotection in a Photothrombotic Mouse Model



- First generation molecule **NYX-104** reduced Ca^{2+} entry via the TRPC ion channel (target upstream of TRPC channel but unknown)
- The 1st dose of NYX-104 (100 mg/kg via suppository) was given 45-mins post stroke, then once daily for 4 days
- Mice given NYX-104 had **38% protection** in the expansion of injury
- Molecule abandoned due to **poor ADME**
- New molecules designed to specifically block the TRPC 3/6/7 ion channels



Proof of Concept

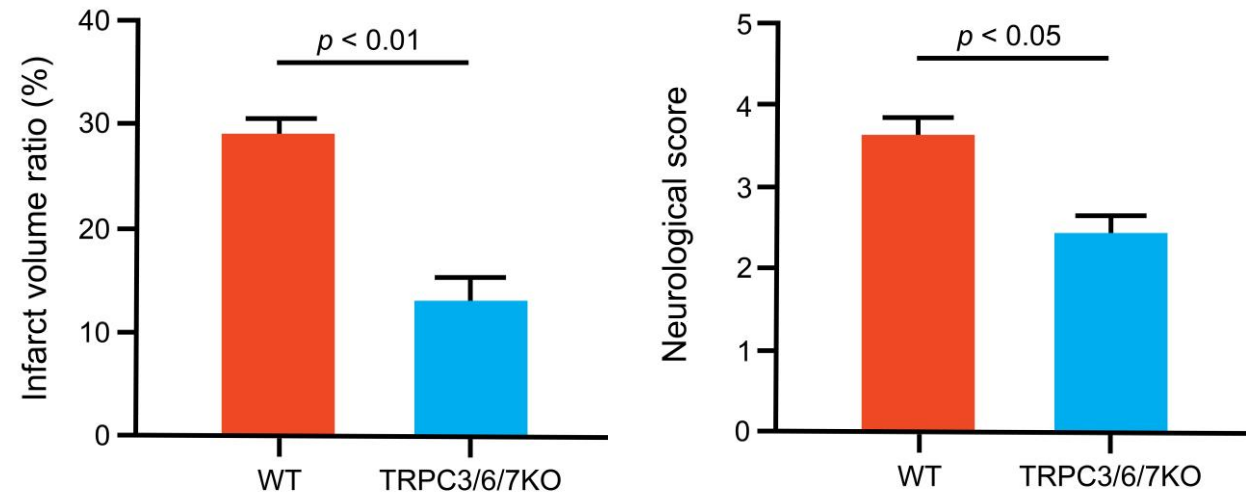
Knockout Model shows Neuroprotection



TTC Staining



Functional Improvement following Brain Injury in TRPC 3/6/7 KO Mice¹³



Adapted from Chen et al. Mol. Neurobiol. 2017

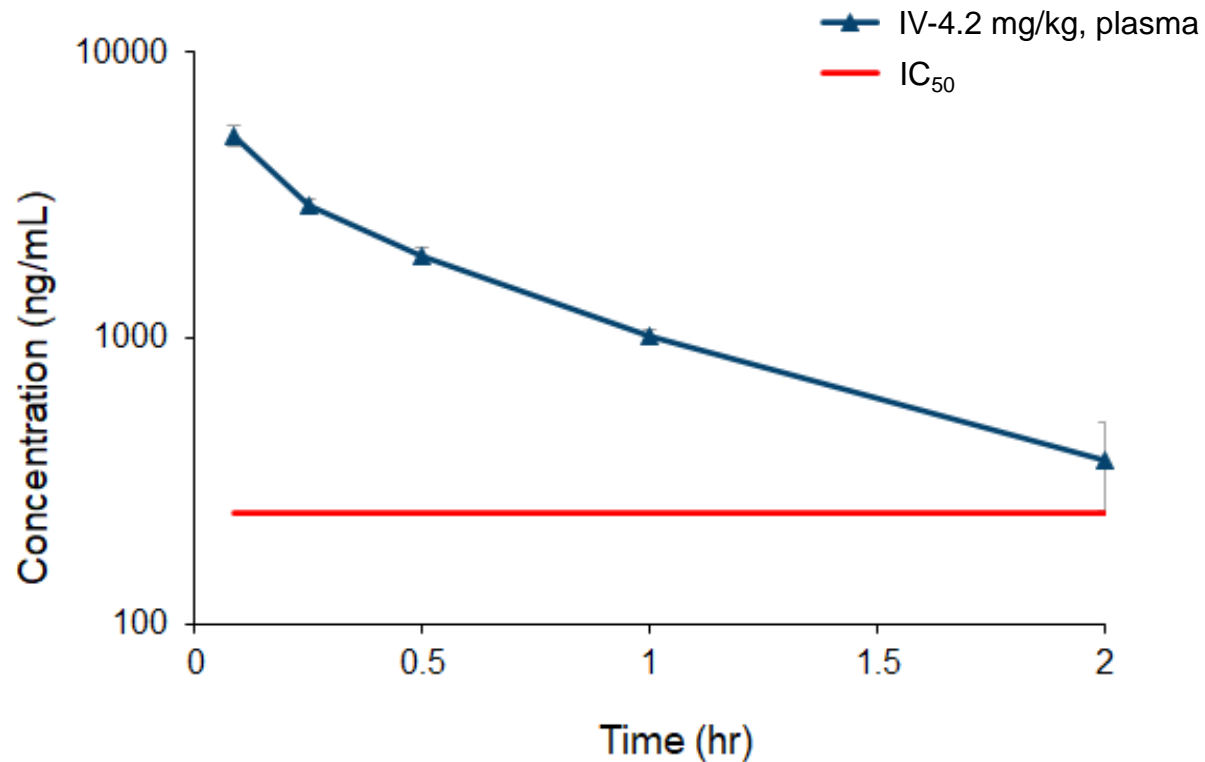
- TRPC 3/6/7 KO mice have significantly **smaller lesion sizes** compared to WT
- TRPC 3/6/7 KO mice have significantly **better neurological score** compared to WT
- Nyrada molecule **NYR-BI02 blocks TRPC3/6/7 channels** ($IC_{50} = 0.6 \mu M$)
- **NYR-BI02 will be tested in models of TBI (WRAIR) and stroke Q3 2022**

Nyrada's Brain Injury Drug NYR-BI02

ADME-PK Profile



Mean Plasma Concentration-Time Profile of NYR-BI02 in Mice

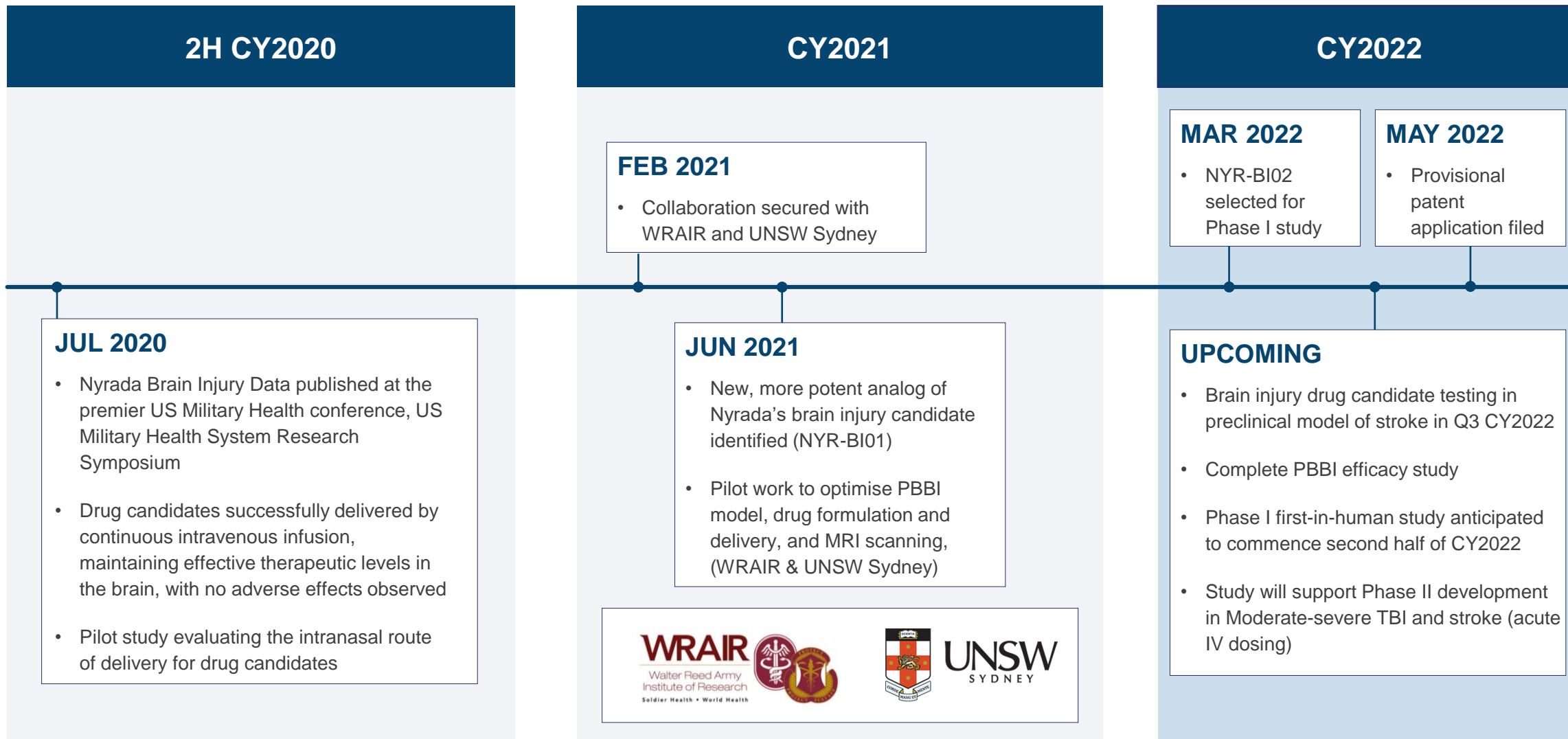


NYR-BI02 **advanced to efficacy studies** in collaboration with WRAIR.

- **Nanomolar potent** TRPC 3/6/7 blocker
- Intact **blood-brain barrier penetration** (>50%)
- ADME-PK **compatible with continuous infusion dosing** (preferred dosing method for moderate to severe TBI and stroke)

Exploratory study shows NYR-BI02 **could be taken orally** (preferred dosing method for concussion)

Program Milestones and Path to the Clinic



Phase I Study Design

OBJECTIVES To assess the safety, tolerability, and pharmacokinetics of NYR-BI02

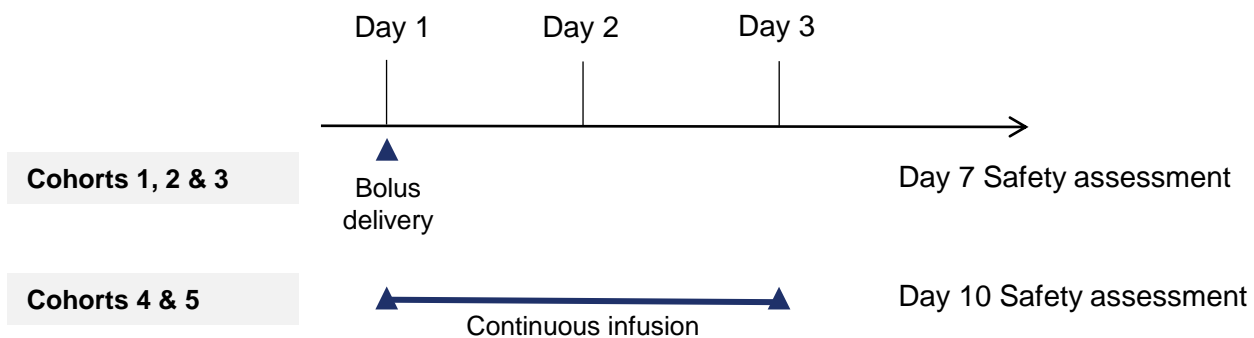
- DESIGN**
- Randomized, double-blind placebo – controlled, dose escalation design
 - 5 cohorts; 8 participants each cohort; 6:2 active and placebo treatments
 - 3 cohorts will be single ascending doses
 - 2 cohorts will be given continuous infusion doses

- PARTICIPANTS**
- Male and female healthy volunteers
 - 18 – 50 years age



Cohort number	Dose administered
1	Low dose single bolus
2	Medium dose single bolus
3	High dose
4	Low dose continuous infusion (72 hrs)
5	High dose continuous infusion (72 hrs)

- LOCATION & DURATION**
- Study will be conducted at a clinical trial center in Australia
 - The study duration will vary between 1 – 4 days



*trial design subject to ethics approval



Corporate Snapshot

ASX:NYR

Key Metrics

Market capitalisation
(as at 06 June 2022) **A\$23.4M (US\$16.9M)**

Share price
(as at 06 June 2022) **A\$0.15 (US\$0.11)**

CDIs free float **156,008,700**

Cash at bank 31 March 2022:
• Adequate funding for Phase I studies **A\$11.3M (US\$8.1M)**

ASX listing **January 16, 2020**

Management Team with Proven Industry Experience



James Bonnar - CEO

- Business executive with 25 years experience in healthcare companies in the UK, China, New Zealand, and Australia
- Experience in drug manufacture, preclinical development, clinical operations, regulatory affairs, and quality assurance
- Biotech experience spanning various therapeutic areas including cardiometabolic disease, neurodevelopment disorders, and brain injury



Cameron Jones - CFO

- Finance executive with experience as CFO and Company Secretary of ASX Listed and VC investee healthcare companies
- Supported several healthcare companies through IPOs, capital raisings and M&A transactions
- Managing Director of Bio101, financial services firm
- Chartered Accountant, Member of the Governance Institute of Australia and Registered Tax Agent



Dr Benny Evison - CSO

- More than 20 years experience in the discovery and development of small molecule inhibitors as therapies for various cancers, cardiovascular diseases and neurodegenerative diseases
- Obtained a PhD at La Trobe University (Melbourne, Australia) in biochemistry and molecular biology, and a postdoctoral fellowship in chemical biology at St Jude Children's Research Hospital, (Memphis TN)

Supported by specialist advisers:

- **Prof Gilles Lambert**
Cholesterol-lowering program
- **Prof Gary Housley**
Brain injury program
- **Dr Jim Palmer**
Medicinal Chemist
- **Dr Phillip Coghlan**
Medicinal Chemist
- **Dr Zoran Rankovic**
Medicinal Chemist
- **Dr John Mao**
Toxicologist

International High Caliber Board

- Nyrada operates under the direction of a board of international caliber
- Strong track record in finding and realizing the value of biotech companies
- Experience in dealmaking, US/AU capital markets, and relevant therapeutic area experience



John Moore
Non-Executive Chairman



Dr Ian Dixon
Non-Executive Director



Peter Marks
Non-Executive Director



Marcus Frampton
Non-Executive Director



Dr Rüdiger Weseloh
Non-Executive Director



Christopher Cox
Non-Executive Director

Best-in-class small molecule PCSK9 inhibitor

- Oral, once per day dosing, patient convenience
- Manufacturing and cost advantages over biologics and peptides
- Can be administered with a statin to achieve additive therapeutic effect (monotherapy or combination)

First-in-class treatment to prevent secondary brain injury

- TBI and stroke
- Novel biological target – TRPC 3/6/7 ion channels
- Collaboration with WRAIR and UNSW - opportunity to pursue non-dilutive funding

Strong cash position

- A\$11.3M as at 31 March 2022
- Adequate funding for Phase I studies

References

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- 4 Cholesterol Lowering Drug Market Research Report by Disease Type, Class of Drug, Distribution Channels, Region - Global Forecast to 2027 - Cumulative Impact of COVID-19, April 2022 and Global Statin Market – Industry Trends and Forecast to 2029, Data Bridge Market Research
- 5 Cholesterol Lowering Drug Market Research Report by Disease Type, Class of Drug, Distribution Channels, Region - Global Forecast to 2027 - Cumulative Impact of COVID-19, April 2022
- 6 Brain Injury Alliance (Connecticut): <http://www.biact.org/understanding-brain-injury/brain-injury-facts-statistics>
- 7 Report to Congress: Traumatic Brain Injury in the United States | Concussion | Traumatic Brain Injury | CDC Injury Center
- 8 US Centers for Disease Control and Prevention: <https://www.cdc.gov/stroke/facts.htm>
- 9 Global Traumatic Brain Injury Market to 2030 - Insight, Epidemiology and Forecast by ResearchAndMarkets.com
- 10 Stroke Treatment Market Insight and Trends 2027 - TMR (transparencymarketresearch.com)
- 11 ‘Moderate to Severe Traumatic is a Lifelong Condition’, CDC publication available at: https://www.cdc.gov/traumaticbraininjury/pdf/moderate_to_severe_tbi_lifelong_a.pdf
- 12 Jeon J, Bu F, Sun G, Tian J, Ting S, Li J, Aronowski J, Birnbaumer L, Freichel M, and Zhu MX (2020). Contribution of TRPC Channels in Neuronal Excitotoxicity Associated With Neurodegenerative Disease and Ischemic Stroke. Front Cell Dev Biol. doi: [10.3389/fcell.2020.618663](https://doi.org/10.3389/fcell.2020.618663)
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Brain Injury Solution
Animation



Cholesterol-Lowering
Animation



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