

## Noxopharm Limited

### Pharmaceuticals

#### SPECULATIVE BUY

**NOX A\$0.66 TARGET PRICE A\$1.50**

Noxopharm (NOX) is an Australian drug development company with offices in Sydney and Hong Kong.

The Company's overriding objective is to use its lead pipeline drug, NOX66, to make standard radiotherapy and cytotoxic chemotherapy more effective for patients with most forms of cancer. The Company's goal is to see NOX66 become a standard of care treatment in the management of cancer. The development of a drug that enhances radiotherapy in particular has long been a goal of medical research, but that goal remains unrealised with no universally effective and safe drug being brought to market to date.

#### Company Data

Number of shares	121.9M
Market Capitalisation	\$79.8M
Free float (%)	50.5962
12-month high/low	\$1.58/\$0.31
Average Daily Turnover (\$m)	0.0670
% S&P/ASX200	N/A
DDM Ranking	N/A
% All Ordinaries	0.004%
GICS Industry Group	Health Technology

Source: FactSet, EverBlu Capital

#### Share price performance



Source: FactSet, EverBlu Capital

## A closer look at Nyrada – a NOX subsidiary

On 27 August NOX announced key progress with its subsidiary, Nyrada Inc's, cholesterol-lowering drug, NYX-330, as follows:

- NYX-330 designed as small molecule, oral PCSK9 inhibitor;
- Passes initial critical pre-clinical tests of effectiveness;
- Intended for use in combination with statin drugs to achieve substantial falls in blood LDL cholesterol levels; and
- Potential to have a significant impact on the incidence of cardiovascular disease.

Nyrada Inc is a US biotechnology company based in New York City. Nyrada was established in August 2017 with three pre-clinical drug development programs:

- a PCSK9 inhibitor;
- a neuroprotectant drug to block secondary brain damage following stroke and concussion; and
- an anti-inflammatory drug.

The current shareholding of Nyrada is 67% NOX and 33% Altnia Pty Ltd (a company associated with NOX non-exec director, Dr Ian Dixon).

NYX-330 is a cholesterol-lowering drug – NYX-330 is a first-in-class small molecule inhibitor of PCSK9 for the treatment of individuals with blood LDL (low density lipoprotein) cholesterol levels considered 'at risk' of cardiovascular disease (hypertension, heart attack, stroke). NYX-330 is based on a novel family of chemicals and is a small molecule drug candidate that binds to PCSK9 and blocks its ability to bind to the LDL-receptor.

An estimated 71mn US adults have 'at risk' LDL levels. The Company's aim is to develop an oral drug to meet the blood lipid lowering needs of the approximately 50% of patients who either cannot be given the standard statin drugs because of unwanted side-effects or in whom the statin drugs fail to deliver the target clinical outcome.

Early attempts to discover a small molecule drug proved unfruitful, with the only two PCSK9 inhibitors that have come to market being evolocumab and alirocumab, both large molecule drugs (monoclonal antibodies) that need to be injected (every 2 or 4 weeks) on an ongoing basis, plus carrying a cost of about USD\$14,000 p.a. In Australia, subsidisation of both drugs by the Pharmaceutical Benefits Scheme is limited to a relatively small population of patients with familial hypercholesterolaemia.

**NYX-330 now has passed a series of critical tests conducted by the Company and involving both laboratory and animal studies designed to confirm its potential ability to meet those marketing objectives.**

With that proof-of-principle established, ongoing studies are focusing on optimising the drug-like nature of NYX-330. A key test will be its long-term safety, which laboratory and animal studies to date have failed to raise any concerns, but nevertheless now needs to be confirmed in longer-term animal studies ahead of a first-in-human study expected to take place in 2020.

Nyrada is only one of a handful of companies known to be developing a drug against PCSK9, with the Nyrada small molecule approach thought to be unique.

Nyrada is seeking to develop NYX-330 with marketing objectives of being a convenient, oral, once-daily tablet whose cost and level of effectiveness would be more likely to attract subsidisation for a much wider proportion of the community.

#### Valuation

Successful trials of NYX-330 will substantiate a value for NOX well in excess of \$1.50/sh based on the size of the potential market. We are retaining our 12-month price target of \$1.50/sh and our SPECULATIVE BUY recommendation.

## Contents

COMPANY OVERVIEW.....	3
COMPANY STRATEGY.....	4
CURRENT ACTIVITIES.....	4
PRODUCTS.....	5
NYX-330.....	5
Background on PCSK9 .....	6
NYX-205 .....	9
NYX-104 .....	9
INDUSTRY OVERVIEW .....	11
NYX-330.....	11
MARKET OVERVIEW.....	12
NYX-330.....	12
COMPETITORS WITHIN THE PCSK9 MARKET .....	13
NYX-330.....	13
Amgen (NASDAQ: AMGN).....	13
Regeneron Pharmaceuticals Inc. (NASDAQ: REGN) .....	14
Sanofi S.A. (EPA: SAN) .....	14
Alirocumab (Praluent) and Evolocumab (Repatha) .....	14
COMPETITIVE ADVANTAGE.....	15
BOARD AND MANAGEMENT .....	16
Board of Directors and Management .....	16
Scientific Advisory Board .....	18
APPENDIX.....	20
About LDL cholesterol and cardiovascular disease.....	20
About controlling LDL cholesterol levels.....	20
About PCSK9.....	20
About statin drugs.....	20
About the PCSK9i program .....	20



## COMPANY OVERVIEW

Nyrada Inc. is a new US biotechnology company. Their business is drug discovery and drug development in areas of significant community need in the cardiovascular, inflammation and neurodegeneration fields. Their clinical targets are diseases and conditions affecting large numbers of individuals, where current treatment options are viewed as being poor, and in some cases, non-existent. The company was founded in 2017 and is based in New York City. The company operates as a subsidiary of Noxopharm Limited. Noxopharm currently owns 66.7% of Nyrada as a result of the sale of NYX-104 and NYX-205. Altnia Pty Ltd currently owns 33.3% of Nyrada as a result of the sale of NYX-330. Following conversion of the notes to Nyrada securities, Noxopharm and Altnia will own approximately 60% and 27% respectively of Nyrada.

### The guiding principles driving Nyrada's commercial strategies are:

- Sound scientific rationale;
- Significant unmet clinical need;
- Large market opportunity;
- Lack of competition;
- Strong IP protection; and
- Favourable regulatory pathway to approval.

### Nyrada has 3 pipeline drugs under development. Each is first-in-class and pre-clinical.

**NYX-330:** A cholesterol-lowering drug. A small molecule inhibitor of PCSK9 for the treatment of individuals with blood LDL (low density lipoprotein) cholesterol levels considered 'at risk' of cardiovascular disease (hypertension, heart attack, stroke). NYX-330 is being developed as an oral drug to be used in combination with the standard statin cholesterol-lowering drugs to achieve target cholesterol levels or to allow a lower and safer dosage of statin to be used in patients who experience statin side-effects.

**NYX-104:** A neuro-protectant drug intended to protect the brain from glutamate-initiated excitotoxicity following ischaemic stroke. Excitotoxicity is a well-recognized, key mechanism for damage to the brain, which occurs in the hours and days following a stroke or traumatic brain injury such as concussion or accident. Currently there are no drugs approved that block excitotoxicity and offer the ability to limit the extent of damage to the brain following injury.

**NYX-205:** An anti-inflammatory drug designed to target components of the inflammatory process distinct from the standard anti-inflammatory drugs and which are implicated in a range of high-profile diseases where standard drugs provide little or no therapeutic benefit.

## COMPANY STRATEGY

Nyrada is a new and dynamic biopharmaceutical company developing human therapies for cardiovascular, inflammatory and neurodegenerative disorders. Nyrada's strategy is to demonstrate the therapeutic utility of its patented drug candidates towards commercialization in global markets. Applications are selected based on sound scientific rationale, significant unmet clinical need, compelling market opportunity, and the potential for favourable regulatory treatment with a clear path to approval.

The 3 drug candidates that Nyrada has selected and is currently developing have broad applications across a range of target indications, all of considerable interest to large pharmaceutical companies. These target indications are not niche markets. They are large markets of considerable unmet need involving patients with poorly controlled blood cholesterol levels, the rehabilitation of stroke victims, and the treatment of a range of inflammatory diseases including arthritis and asthma, and auto-immune diseases such as lupus.

Nyrada's aim with each drug is to take it through early-stage clinical trials to establish safety and evidence of proof-of-concept. That allows a value of the asset to be determined, with the asset then being passed onto a larger pharma company via a straight sale, licensing, or a partnering arrangement, for them to complete the final steps of the regulatory process and commercialization.

Nyrada is a US-registered company, but in the near-term they will be conducting their business largely in Australia. They are sharing offices and human resources with Noxopharm, and that means that they can save money in their formative stages while having access to all the services (drug manufacture, chemistry, regulatory affairs) they need. They anticipate relocating to the US in 2019 ahead of a proposed listing on Nasdaq. This will enable access to the US capital markets where they expect to get greater attention and better value for the story. It is the home of wealthy foundations and significant government funding, with the Company's therapeutic targets the subject of substantial acquisition activity.

## CURRENT ACTIVITIES

In the short time since Nyrada was established, the focus has been on setting up the infrastructure required to move forward with the 3 drug programs. This involves careful planning in terms of identifying and laying out the tasks that need to be completed in the coming 12-18 months, preparing detailed budgets, and searching out and appointing the core management and science team.

Nyrada has a vision of being able to block the progressive nature of many common degenerative diseases and disorders, rather than just their symptoms. It is aiming to do this with 3 first-in-class drugs that have novel mechanisms of action with each case provided critical proof-of-concept evidence in pre-clinical studies.

**NYX-330** is under development as a treatment for hypercholesterolemia, or elevated blood levels of LDL (low density lipoprotein) cholesterol, which is a recognised risk factor for cardiovascular disease. The objective is to develop an oral drug that can be used in combination with the standard statin cholesterol-lowering drugs, or for use in individuals unable to use a full dosage of statins for safety reasons.

**NYX-104** is being developed as a neuroprotectant, a drug designed to protect the brain from the problem of excitotoxicity that follows any damage to the brain and which considerably worsens the original brain damage. Despite being a very substantial community problem causing considerable costs through lengthy rehabilitation, no drug has yet been successfully developed. NYX-104 has potential use across a broad range of brain injuries but Nyrada's initial focus is on stroke damage. They envisage this drug being used to reduce the severity of paralysis following stroke and to reduce rehabilitation times.

**NYX-205** is being developed as an anti-inflammatory drug, with a particular emphasis on the treatment of those inflammatory and autoimmune diseases where a particular enzyme known as spleen tyrosine kinase (SYK) is now identified as a key drug target.

## PRODUCTS

We prioritise the Company's 3-drug pipeline in the following order in terms of value-drivers and news flow.

**NYX-330** is the Company's lead pipeline drug candidate. It was acquired by Nyrada from a private Australian biotech company, Altnia Holdings. NYX-330 is a small molecule inhibitor of the plasma protein, PCSK9, a key player in cholesterol metabolism. Drugs that inhibit PCSK9 have become hot property in the pharmaceutical world. Nyrada has joined a small number of companies seeking to develop a PCSK9 inhibitor. The Company's aim is to develop an oral drug to meet the blood lipid-lowering needs of the approximately 50% of patients who either cannot be given the standard statin drugs because of unwanted side-effects or in whom the statin drugs fail to deliver the target clinical outcome. High blood LDL levels are associated with increased risk of cardiovascular disease including stroke and transient ischaemic attacks. The catastrophic effect of reduced blood flow on brain function marks NYX-330 as a potentially important preventative medicine in neurotherapeutics.

**NYX-205** looks to be the next in line drug candidate. It is one of a new generation anti-inflammatory drugs targeting a newly identified drug target known as spleen tyrosine kinase (SYK). Drugs against this target are under development for a range of poorly treated disease including rheumatoid arthritis, immune thrombocytopenia, asthma and systemic lupus erythematosus.

**NYX-104** targets an important disease process known as excitotoxicity, not a well-known term, but a condition very well known to most people. This is the disease behind problems associated with repeat concussion ('punch drunk' boxers, early-onset dementia in NFL players) or stroke (permanent paralysis) or loud and concussive noise (rock musicians, service men and women) to name just a few conditions. It is a form of self-destruction in the brain that follows a primary injury. There is no known treatment. Nyrada is developing NYX-104 to treat this debilitating condition, with stroke patients being the first target.

### NYX-330

NYX-330 is under development as a treatment for hypercholesterolemia, or elevated blood levels of LDL (low density lipoprotein) cholesterol where it presents a risk factor for cardiovascular disease.

LDL cholesterol isn't all bad news. Our bodies need cholesterol because it is an essential building block in the body. For example, our nerves wouldn't function without cholesterol providing the insulation around nerves. LDL cholesterol only becomes bad news when there is too much of it in the blood. LDL cholesterol is attracted to the wall of arteries and moves in and out of artery walls as a normal part of its life-cycle. But when LDL cholesterol levels get too high, the fat stays in the artery wall, forming a fatty layer that continues to grow over time eventually leading to the artery becoming blocked. When the blockage is in the arteries supplying blood to the heart muscle, the outcome is a heart attack. When the blockage is in the arteries supplying blood to the brain, the outcome is stroke.

Something like one-third of middle-aged men and women in the US and Australia have LDL cholesterol levels in their blood considered to put them at moderate to high risk of cardiovascular disease. Where changes on lifestyle risk factors don't work, doctors for the past 3 decades have relied on the so-called statin drugs to lower LDL levels. And while that works in some patients, LDL levels don't drop sufficiently in many people to the extent that their risk of getting cardiovascular disease comes back to normal levels. In some patients, the problem is their susceptibility to side-effects of the statins. In other patients, it is just a matter of not responding sufficiently to statins.

Some extra help was needed, and that has come in the form of PCSK9, a plasma protein discovered about 13 years ago that plays an important role in helping to maintain LDL cholesterol levels in blood.

NYX-330 is being developed as an oral, well-tolerated medication that either will augment the efficacy of statins in those individuals unsatisfied with the statin benefit, or to replace statins in patients unable to tolerate statins.

**Nyrada aims to develop NYX330 as:**

- Once a day oral treatment;
- Use in combination with Statins; and
- Particular use in the 40% of ‘at risk’ patients where statins alone fail to achieve target LDL levels.

**Where the Company is now with NYX-330:**

NYX-330 is confirmed in the laboratory as blocking binding between PCSK9 and LDLR, and in mice as having an appropriate pharmacokinetic profile in terms of blood levels and drug half-life (once daily dosing) and being well tolerated after short-term dosing.

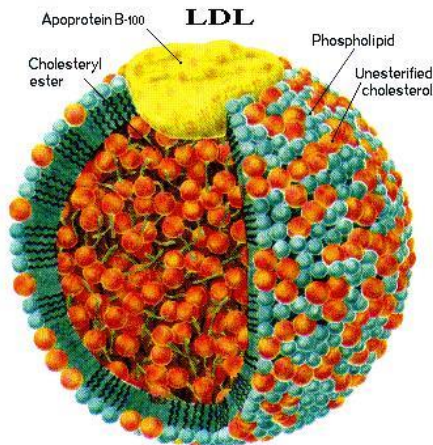
Current studies are aimed at optimising the potency of the drug and determining the long-term safety of the drug in animals.

Background on PCSK9

**We Need Cholesterol**

- Cholesterol is an essential building block in the body (e.g. nerves need an outer sheath of cholesterol as insulation);
- We absorb some cholesterol from our food, but most is made in-house by our livers;
- Cholesterol is transported in the bloodstream to our tissues in a form known as low density lipoprotein (LDL). LDL has a bad rap. It gets called ‘bad’ cholesterol, but it is a vital part of our health. It is only ‘bad’ when its levels get too high; and
- Below is what an LDL cholesterol particle looks like. It is made up of hundreds of individual LDL molecules. This is what circulates in our blood.

Figure 1: The LDL Cholesterol Particle

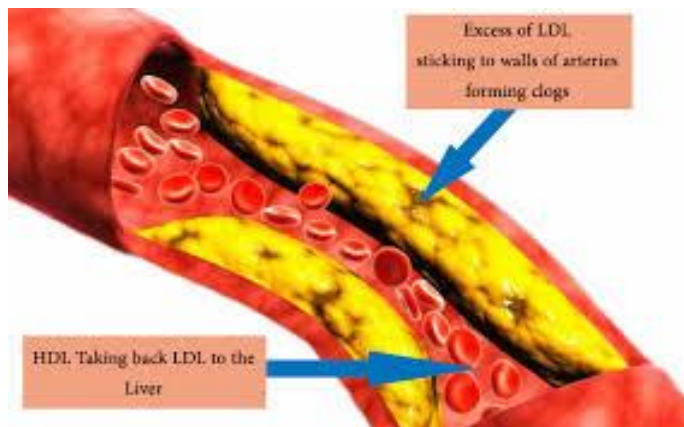


Source: The Company

**Bad' LDL**

- LDL is 'sticky' and tends to accumulate in the lining of our arteries. That is a normal part of its life-cycle;
- When LDL levels are within normal range, the LDL doesn't stay within the artery wall very long and does not cause any problems;
- It is when LDL levels rise to risky levels, that the LDL particles accumulate within the artery wall, forming a fatty layer (called atheromatous plaque) that gradually narrows the internal diameter of the artery; and
- That narrowing causes hypertension in the first instance, and heart failure when the arteries supplying the heart become blocked. Pieces of the fatty layer also can break off and find their way into the arteries supplying the brain where they result in stroke.

Figure 2: 'Bad' LDL

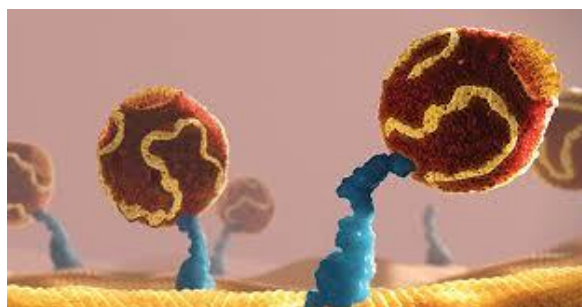


Source: The Company

**Maintaining Normal LDL Levels**

- The liver seeks to maintain blood LDL levels in a narrow range by matching the rate at which it makes LDL and puts it into the bloodstream, with the rate at which it removes the same LDL from the bloodstream; and
- It removes the LDL through receptors that poke out from the surface of the liver cell into the bloodstream. These receptors grab the LDL particles and pull them into the liver cell where the LDL is then broken down.

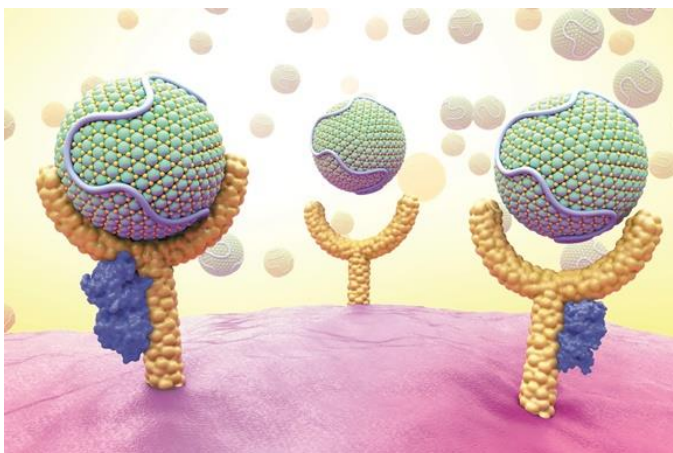
Figure 3: LDL Receptors



Source: The Company

**PCSK9 Function**

- PCSK9 is a protein found in our blood. Its job is to stop the LDL receptors from removing the LDL from the bloodstream. There wouldn't be any point in removing LDL as quickly as it was made, and PCSK9 is serving as a brake to ensure that at least some of the LDL stays in the blood long enough to supply our tissues; and
- The image below shows the LDL receptors (gold) combining with the LDL particles (green). Where PCSK9 (blue) binds to the LDL receptor, the LDL receptor is blocked from carrying its load of LDL into the liver cell. Net result = LDL remains within the bloodstream.

**Figure 4: LDL Receptors Combining with LDL Particles**

Source: The Company

So, that is the 3-part mechanism that the body relies on to maintain a healthy level of LDL in the bloodstream: (1) It makes LDL and puts into the bloodstream, (2) it removes it from the bloodstream, and (3) uses PCSK9 to stop the LDL from being removed as quickly as it is made.

The problem comes when one of two things go wrong: (i) we make more LDL (too much fatty food, obesity, not enough exercise etc) than can be removed, and/or (ii) we make too much PCSK9 that leads to too much LDL staying in our bloodstream.

#### Statin Drugs

- Statins work by inhibiting the ability of the liver to make LDL; and
- Have been the biggest selling class of drugs in the world. In 2012, Lipitor (Pfizer) had sales of US\$12 billion, making it the biggest selling drug in the world in any class. Lipitor is one of about 15 different statin drugs. Annual sales of all statin drugs were about \$45 billion up to a few years ago when they started coming off patent. Last year, statin sales were US\$19 billion.

#### Statin Drugs – Not Good Enough

- Statins should result in blood LDL levels plummeting, but they don't. LDL levels fall, but not enough to result in a meaningful benefit in terms of heart health;
- Reason for this now understood. At the same time as blocking LDL production, statins cause an increase in PCSK9 levels in the blood = more LDL being held in the blood; and
- Thus, statins are applying two brakes – the first is the rate of production of LDL, but this is counteracted by applying the brakes to the removal of LDL from the bloodstream.

#### Statins + Blocking PCSK9 = Best Outcome

- It is now confirmed in 2 large clinical studies that doing both things at once (block LDL production/block PCSK9 function) leads to very substantial falls in LDL levels, and that translates into considerable health benefits (fewer heart attacks and strokes).

#### PCSK9 Inhibiting Drugs Now Major Opportunity

- Objective is to have a PCSK9 inhibitor that would be used in combination with a statin drug. Ideally, both would be taken orally once per day. If that was achieved, then the commercial opportunity is a drug with the same sales as the statins which is US\$19 billion;
- Most big pharma tried making an oral drug, but failed. Instead, they opted for the monoclonal antibody approach which requires an injection every 2 weeks (for life) and costs US\$14,000 p.a. Two drugs on the market (Repatha and Praluent). Combined sales last year of about US\$1 billion. Considerable patient and doctor resistance (cost, inconvenience) limiting uptake; and
- Nyrada has succeeded where the big pharma failed and produced a small molecule drug with the ability to be taken orally and to be affordable.



## NYX-205

Inflammation is a complex biological process involving dozens, if not hundreds, of different chemical players. Some of those are bit players, and some play starring roles. The protein, spleen tyrosine kinase (Syk), appears to be a star player in why certain inflammatory diseases are able to start and how the body's immune system responds to those diseases, which is how it appears to be involved in various auto-immune diseases.

The first Syk inhibitor, a monoclonal antibody (fostamatinib), was approved this year by the FDA for the treatment of chronic immune thrombocytopenia, and is in ongoing studies of autoimmune haemolytic anemia, IgA nephropathy, as well as a range of blood cancers such as lymphoma.

Nyrada is looking at developing NYX-205 as a small molecule inhibitor of Syk, in addition to certain other anti-inflammatory functions such as thromboxane synthase inhibition, particularly for the treatment of certain inflammatory diseases such as rheumatoid arthritis.

### **Where the Company is now with NYX-205:**

NYX-205 is shortly to undergo a range of studies in animal models of certain human inflammatory diseases. From that, the Company will make a decision on which indication(s) to pursue.

## NYX-104

NYX-104 is a small molecule drug selected initially for its ability in the laboratory to block the excitotoxicity pathway described by Professor Housley's team. When given to mice bearing a brain injury mimicking human stroke, NYX-104 blocked the extent of post-injury brain death (excitotoxicity) by 60%. This is key proof-of-principle data that gives the Company confidence that it has a potential major new therapeutic on its hands.

Excitotoxicity is an extraordinary self-destruct phenomenon, seemingly peculiar to the nervous system, that continues to damage and kill nerve cells, for days and weeks following an acute injury. This is a phenomenon that means greater damage, and therefore delayed recovery, after physical injury to the central nervous system (brain and spinal cord) from events such as stroke, concussion, severe epileptic seizure, physical trauma and loud noise. A phenomenon that manifests in permanent disability after stroke, or early onset dementia in professional sports people, or hearing impairment in musicians and service men and women. A common phenomenon in our community in urgent need of an effective therapy. Nyrada's aim is to develop NYX-104 as a first-in-class neuroprotectant to meet this need.

Using the Noxopharm LIPROSE drug delivery system, NYX-104 was delivered rectally to the mice, leading to the formation of a pro-drug form of NYX-104 that crosses the blood-brain barrier of the mice, reaching brain tissue in relatively high, therapeutic levels.

For the scientifically-minded, NYX-104 is a kinase inhibitor, which is a drug that inhibits the ability of kinases, enzymes that activate (phosphorylate) proteins. In the case of NYX-104, they believe it is inhibiting the proteins identified by Professor Housley that are involved in the mobilisation of calcium in neurons. It is this mobilisation of calcium in response to injury that is a major factor in the cascade of neuronal cell death that occurs with strokes and brain injuries.

**Where the Company is now with NYX-104:**

The Company has achieved the first key step in any drug development program in having identified a potential drug candidate.

Nyrada needs to do the following basic studies in order to progress towards starting human studies:

- a) Test the final drug in a large animal model of brain injury
- b) Determine the extent of off-target activity of the drug and its safety in animals.

This is not going to be a quick route into the clinic. The Company is facing several years of study to prove that the drug is sufficiently likely to provide a therapeutic benefit in humans and likely to be without significant safety issues. But each step they take brings them closer to the clinic and increases the value of this asset.

And they won't be on this journey alone. They are going to seek collaborations with high-profile clinical research groups around the world in order to expedite entry into the clinic across a number of different clinical indications.

**NYX-104 development Program 2018-2019**

1H18: proof of concept

- Provided proof-of-concept (mouse ischemia model);
- Confirm target and signalling pathway (well advanced).

2H18: Pre-clinical

- Study in the second animal model to observe symptomatic outcome (motor function, cognitive function, behaviour).

1H19: Pre-clinical

- Standard pre-clinical studies.

2H19: Clinical logistics

- Manufacturing scale-up for first-in-human study;
- Clinical protocol design;
- Regulatory approval.

## INDUSTRY OVERVIEW

### NYX-330

The London-based research firm Visiongain has recently published a new report detailing market analysis for cholesterol-lowering drugs for the next ten years. In 2017 the global cholesterol-lowering industry is worth \$19.2 Billion and is forecast to grow 4.9% each year during the next five years. Which means that the industry will be worth \$24.4 Billion in 2022. The new market analysis includes a range of drugs in addition to statins including cholesterol absorption inhibitors, ion exchange resins, vibrates, PCSK9 Inhibitors, and others. In the statins category, Crestor was leading in 2016, being associated with a market share of 26.7%.

#### The present treatments to reduce LDL-cholesterol:

- Diet, smoking & lifestyle (exercise);
  - Some people have a genetic predisposition that diet etc. cannot resolve, others are unable to achieve control.
- Statins – Atorvastatin (Lipitor™), Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin.
- Biologic PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitor drugs approved by FDA (USA) and EMA (Europe).
  - Evolocumab (Repatha) (Amgen);
  - Alirocumab (Praluent) (Sanofi/Regeneron).

#### Statin Drugs:

- Statin drugs are standard care for patients with ‘at risk’ LDL levels;
- Statins are now off patent (generics) and cheap;
- Global sales in 2017 estimated at US\$19 billion;
- Have safety and toxicity problems “a sizable proportion of statin-treated patients does not achieve recommended target LDL cholesterol levels, and some discontinue treatment owing to drug-related side effects”;
  - Target LDL levels are achieved in 60% patients, leaving 40% of patients still exposed to risk.
- Statins deliver limited cardiovascular benefits;
  - For every 138 ‘at risk’ people treated for 5 years, just 1 fewer dies from heart disease.
- About 600 thousand Americans have a genetic disorder called familial hypercholesterolemia. It affects how your body processes cholesterol. For most people with this condition, even the highest dose of statins won’t bring their LDL cholesterol down to a healthy level;
- Statins have been the first-line drugs for lowering cholesterol since the late 1980s. They’ve been shown to prevent repeat heart attacks in people who have already had one and first heart attacks in a wide range of at-risk individuals. In about one in five people, though, a statin doesn’t lower cholesterol enough. Adding a second drug that lowers cholesterol by a different mechanism doesn’t always help. And some people can’t take a statin because of side effects like muscle pain, liver damage, or the development of diabetes; and
- The trials show that PCSK9 inhibitors are extremely powerful cholesterol-lowering agents. In all three trials, all of the participants took a statin. Half got a PCSK9 inhibitor (either evolocumab or alirocumab) every two to four weeks; the other half got a placebo. After a year, LDL levels were 60% lower in the PCSK9 groups.

#### Side effects:

Around 3%–4% of people don't do well with a statin drug. In a few cases, the drugs simply don't work, but more often the reason is a side effect. The most common statin toxicity is liver inflammation. Most patients with the problem don't even know they have it, but some develop abdominal distress, loss of appetite, or other symptoms. Even without these complaints, liver enzyme abnormalities, such as high aminotransferase levels, show up in the blood tests of 1%–2% of people taking a statin drug. The other major side effect is muscle inflammation, which can be silent or cause cramps, fatigue, or heavy, aching muscles. Like liver inflammation, muscle damage can often be detected with a simple blood test; in this case, it's an abnormally high level of creatine phosphokinase (CPK). It's the reason the statin drug cerivastatin (Baycol) was withdrawn from the market on August 8, 2001, because of 31 cases of fatal rhabdomyolysis (muscle damage). Fortunately, the other statins have proved much safer. Other possible side effects include loss of concentration, sleep disturbance, nerve inflammation, nausea, diarrhea, and rash. A few men may also develop breast enlargement or impotence.

**Biologic PCSK9 Drugs:**

- Work by inhibiting PCSK9 binding to LDL Receptor.
- New (approved in 2015 & 2016) but expensive (~ US\$14,000 p.a.);
- Require injection every 2-4 weeks;
- Currently no reimbursement for most patients;
- Have demonstrated excellent safety and efficacy data since approvals in USA and EU:
  - In combination with statins, they boost LDL reduction by up to an additional 60%.

**Small Molecule PCSK9 Drug:**

Currently, there are currently no known small molecule drug inhibiting PCSK9 is in clinical trials.

- So, there is room for The Company's PCSK9 program – tablet form of PCSK9 inhibitor;
- Genomics and the success of the existing biologic PCSK9 inhibitors tells us that PCSK9 is a good “target” i.e. something to inhibit to treat atherosclerosis and vascular disease;
- Oral drugs are much more acceptable to patients and cost-effective for patients and payers;
- Some experts think that small molecules (i.e. those that are orally available as a tablet taken daily) cannot effectively inhibit the PCSK9-LDL-Receptor interaction. However, Cardio Therapeutics has shown that a small molecule from structure-based design (e.g. ALT-30) can indeed effectively inhibit the PCSK9 - LDL-Receptor interaction in in vitro assays and in-silico screening.

**MARKET OVERVIEW****NYX-330****Hypercholesterolemia (high cholesterol):**

- Cholesterol (a sterol) is essential for our body;
- Cholesterol is carried in our blood in lipoproteins (fat protein);
- Lipoproteins are named after their density - very low density lipoprotein (VLDL), low density lipoprotein (LDL), intermediate density lipoprotein (IDL) and high density lipoprotein (HDL);
- HDL is “good” lipoprotein – the rest are “bad”;
- High levels of LDL-cholesterol are linked to an increased risk of;
- Atherosclerosis and coronary heart disease;
- The National Institutes of Health says that 34 million Americans have elevated “bad” blood cholesterol levels;
- In 2014-15, 7.1% of all Australians (1.6 million people) reported having high cholesterol. This was similar to 2011-12 when 6.8% of the population had high cholesterol (ABS).

**Atherosclerosis (arteriosclerotic vascular disease):**

- Atherosclerosis is a disease in which plaque builds up inside your arteries;
- Arteries are blood vessels that carry oxygen-rich blood to your heart and other parts of your body;
- Cells in your body (brain, muscles etc.) rely upon oxygen to function;
- Atherosclerosis limits the flow of oxygen-rich blood to cells that make your body work well;
- Atherosclerosis starts off as debilitating and restricting activity;
- More severe blockage can lead to serious problems, including heart attack (ischemic heart disease (IHD)), ischemic stroke, and death;
- Ischemic heart disease remains the leading cause of premature adult mortality worldwide.

**Coronary Heart Disease – the most common cause of heart attacks:**

- Stable plaques cause angina and pain, anxiety and discomfort – and in more severe cases a loss of mobility and independence;
- Unstable plaques can lead to a blood clot and heart attack or stroke;
- Causes about one-third of all deaths in people older than 35 years;
- The 2016 Heart Disease and Stroke Statistics from the American Heart Association (AHA) has recently reported that 15.5 million persons ≥20 years of age in the USA have CHD;
- CHD affects around 1.2 million Australians, is the single leading cause of death in Australia, claimed the lives of 19,777 Australians (12% of all deaths) in 2015 and kills one Australian every 27 minutes

**Cardiovascular Disease**

- Kills one Australian every 12 minutes;
- Affects one in six Australians or 4.2 million people;
- Was the main cause for 490,000 hospitalisations in 2014/15;
- Claimed the lives of 45,392 Australians (nearly 30% of all deaths) in 2015 - deaths that are largely preventable.

**Stroke**

- 795,000 people each year in the US have a stroke;
- 140,000 people each year die from stroke in the US;
- Strokes account for 1 in 19 deaths in the US; and
- Strokes indirect and direct medical costs \$34bn per year in the US.

**COMPETITORS WITHIN THE PCSK9 MARKET**

## NYX-330

The top manufacturers and players in the PCSK9 global market are Amgen, Eli Lilly, Sanofi, Pfizer, Novartis, Roche, Merck, Alnylam, AstraZeneca, Affiris, BMS, Ionis Pharmaceuticals, Cyon Therapeutics, Daiichi Sankyo.



## Amgen (NASDAQ: AMGN)

- Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology;
- Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential;
- Amgen established an affiliate in China in 2012, and has since opened its China Headquarters and Asia Research & Development Center in Shanghai. Amgen also has an office in Beijing, which is responsible for drug registration and clinical trials, with the aim to deliver its medicines to patients in China.

**Repatha® (evolocumab)**

- Repatha® (evolocumab) is a human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9). Repatha binds to PCSK9 and inhibits circulating PCSK9 from binding to the low-density lipoprotein (LDL) receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the binding of PCSK9 to LDLR, Repatha increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels;
- Repatha is approved in more than 60 countries, including the U.S., Japan, Canada, and in all 28 countries that are members of the European Union. Applications in other countries are pending.
- On August 8<sup>th</sup>, 2018 Amgen China announced that the Repatha® (evolocumab) Injection was approved by the National Drug Administration of China (CNDA, former CFDA). Repatha is the first PCSK9 inhibitor in China for the treatment of adults and adolescents over 12 years old with homozygous familial hypercholesterolemia (HoFH).
  - "The approval of Repatha in China has the potential to truly improve the lives of patients living with this rare disease," said Penny Wan, Head and General Manager of Amgen's Japan and Asia Pacific Region. "With Amgen's full commitment to serving patients and combating severe and chronic diseases, we look forward to bringing more innovative therapies to Chinese patients and contributing to the Healthy China Initiative."



## Regeneron Pharmaceuticals Inc. (NASDAQ: REGN)

- Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents life-transforming medicines for people with serious diseases. Founded and led by physician-scientists for 30 years, REGN's unique ability to repeatedly and consistently translate science into medicine has led to six FDA-approved treatments and over a dozen product candidates, all of which were homegrown in their laboratories. REGN's medicines and pipeline are designed to help patients with eye disease, heart disease, allergic and inflammatory diseases, pain, cancer, infectious diseases and rare diseases;
- Regeneron is accelerating and improving the traditional drug development process through its proprietary VelociSuite® technologies, including VelocImmune® to yield optimized fully-human antibodies, and ambitious initiatives such as the Regeneron Genetics Center, one of the largest genetics sequencing efforts in the world.



## Sanofi S.A. (EPA: SAN)

- Sanofi operates as a pharmaceutical company. The Company manufactures prescription pharmaceuticals and vaccines. Sanofi also develops cardiovascular, thrombosis, metabolic disorder, central nervous system, and oncology medicines and drugs. Sanofi serves customers worldwide



### **Praluent (alirocumab): Sanofi and Regeneron alliance:**

- Praluent inhibits the binding of PCSK9 to the LDL receptor and thereby increases the number of available LDL receptors on the surface of liver cells, which lowers LDL-C levels in the blood. The use of Praluent to reduce the risk of MACE is investigational and has not been evaluated by any regulatory agency;
- Praluent is approved in more than 60 countries worldwide, including the U.S., Japan, Canada, Switzerland, Mexico and Brazil, as well as the European Union (EU);
- In the U.S., Praluent is approved for use as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C;
- In the EU, Praluent is approved for the treatment of adult patients with primary hypercholesterolemia (HeFH and non-familial) or mixed dyslipidemia as an adjunct to diet: a) in combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach their LDL-C goals with the maximally-tolerated statin or b) alone or in combination with other lipid-lowering therapies for patients who are statin intolerant, or for whom a statin is contraindicated;
- This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions;
- The effect of Praluent on cardiovascular morbidity and mortality has not been determined.

## Alirocumab (Praluent) and Evolocumab (Repatha)

Alirocumab (Praluent) and evolocumab (Repatha) are intended for people whose cholesterol levels remain stubbornly high, despite making lifestyle changes (such as diet and exercise) and taking the maximum dose of a high-potency statin and other cholesterol-lowering drugs. In the past two years, results from two large studies found that both PCSK9 inhibitors lowered the risk of serious heart-related events such as heart attack and stroke by 15%.

### **Fewer Deaths**

Researchers followed nearly 19,000 people with a recent heart attack or unstable angina (worsening chest pain, often at rest, that required hospitalization) who were already taking maximal doses of statins. They took alirocumab or a placebo for an average of nearly three years. Among those whose LDL cholesterol levels started out at 100 milligrams per deciliter (mg/dL) or higher, alirocumab cut deaths by 29% compared with the placebo. Doctors encourage heart attack survivors to strive for an LDL of 70 mg/dL or lower; in this study, the average LDL values for those taking alirocumab were 40 to 50 mg/dL.

### **Prohibitive Pricing**

But to date, the high price of these potent drugs has limited their use. The wholesale cost of a year's supply of one of these drugs is about US\$14,000, although pharmacy benefit managers (middlemen companies that negotiate prices with drug companies on behalf of employers and insurers) pay about 30% less. To help contain costs, these companies require doctors to document that each patient is an appropriate candidate for a PCSK9 inhibitor. That designation includes people with an inherited form of very high cholesterol (familial

hypercholesterolemia) and those with atherosclerotic heart disease and an LDL level of 70 mg/dL or higher, despite taking different high-dose statins.

"If someone has had trouble with statins in the past, we have to provide the dose, the dates, and the person's response to at least two and sometimes three different statins," Dr. Cannon explains. The person also must have tried adding the cholesterol-lowering drug ezetimibe (Zetia).

Even with that evidence, about two-thirds of the requests for PCSK9 inhibitors are denied. For the remaining third that are approved, the out-of-pocket copay is often at least \$300 per month, says Dr. Cannon. Sanofi-Regeneron (which makes alirocumab) and Amgen (which makes evolucumab) also offer payment-assistance programs. But many people with Medicare and other health insurance plans often can't take advantage of such programs.

"Recently, I filled out a six-page form to get one of the companies to help pay for the drug for one of my patients because she couldn't afford the \$700 monthly copay," says Dr. Cannon. "We are waiting to see if they can help."

#### **Possible Increased Access**

Sanofi-Regeneron recently announced that it would lower the wholesale price of alirocumab to less than \$8,000 a year, a figure an outside group deemed to be cost-effective. But there was a condition: pharmacy benefit managers would be required to grant appropriate access to alirocumab to eligible patients. This potential pricing structure change could mean more people will be able to afford these drugs in the future, says Dr. Cannon.

The ODYSSEY Outcomes results also reaffirmed the importance of lowering LDL for preventing repeat heart attacks. In addition, it's a good reminder to people with worryingly high LDL values who have not had a heart attack to pay close attention to their cholesterol, Dr. Cannon says.

And if you're in that smaller, high-risk group of people who are good candidates for a PCSK9 inhibitor, being proactive can make a difference. "We found that if a patient gets directly involved in arguing with the pharmacy benefit manager and challenging the denial, that's often more successful than the doctor alone," says Dr. Cannon.

## **COMPETITIVE ADVANTAGE**

#### **Key Value Drivers:**

##### **Large market size**

- Large community problems;
- Substantial unmet needs.

##### **Lack of competition**

- No known current neuro-protectant;
- No known small molecule inhibitor of PCSK9.

##### **Experience:**

- Board and CEO highly experienced in drug development and running public companies in Australia and the US.

##### **High Profile**

- Three first-in-class drugs capable of achieving high profiles while still in pre-clinical development.

##### **Potential inflection points**

- Anticipated stream of key milestones over next 2 years.

## BOARD AND MANAGEMENT

### Board of Directors and Management



#### **Graham Kelly - Executive Chairman and CEO**

BSc (Vet) (Hons, BVSc (Hons), PhD

Graham currently is part-time CEO while the Company is conducting the search for a full-time US-based CEO. Graham graduated with degrees in Science (1968) and Veterinary Science (1969) from The University of Sydney. After graduation he joined the newly-formed Department of Transplant Surgery in the Faculty of Medicine at The University of Sydney, gaining a Doctor of Philosophy (Medicine) in 1972. The subject of his PhD thesis was the manufacture and use of a novel drug for the treatment of tissue rejection in kidney transplant recipients, with that drug subsequently being commercialised and used globally in kidney transplantation. Graham was appointed Senior Research Fellow in Experimental Surgery at The University of Sydney, conducting active research in the areas of patient monitoring for tissue rejection and organ retrieval for transplantation. By the mid-1980s, the increased susceptibility of organ transplant recipients to malignant cancer eventually led Graham to focus on the cancer-causing mechanisms operating in organ transplant recipients.

In the early-1990s, Graham identified the compound idronoxil as a promising anti-cancer drug.

Graham left academia and founded the company, Norvet Ltd, which listed on the ASX in 1994. That company subsequently changed its name to Novogen Ltd and listed on NASDAQ (1998). Graham was variously CEO, Executive Chairman and an Executive Director of Novogen, 1994-2006. He also was Executive Chairman of Marshall Edwards Inc (MEI) which listed on London's AIM exchange (2001) and NASDAQ (2003). MEI subsequently became MEI Pharma Inc. Graham resigned from his executive and Board positions at Novogen and MEI in 2006.

In 2012, Graham established a private biotechnology company, Macmaster Healthcare, which focused on developing a delivery technology to preserve the activity of idronoxil in the body. That technology eventually became known as the LIPROSE drug delivery technology.

Graham rejoined Novogen in late-2012, remaining as CEO and Executive Chairman until June 2015. In that time, he was responsible for the concepts and development of the drug candidates, Cantrixil and Trilexium, and the creation of a joint venture company with Yale University. After leaving Novogen in 2015, Graham transformed Macmaster Healthcare and the LIPROSE technology platform into Noxopharm Limited, which listed on the Australian Securities Exchange in August 2016.

Graham currently is Group CEO of Noxopharm Ltd, Asian subsidiary, Noxopharm Asia Pty Ltd, and US subsidiary, Nyrada Inc.



#### **Mark Waring - Vice President US Operations**

BSc (Hons), PMP, ASQ C.PGMP

Mark is an executive level project manager/researcher/consultant with a proven track record of designing and effecting positive change in international life science companies. Mark graduated from the University of Sydney in Science (Hons) majoring in Pharmacology and Biochemistry in 1986. He also holds certifications as a Project Management Professional (PMP) from PMI and from the American Society of Quality in Pharmaceutical GMP. He has over 30 year's experience in Research and Development of Pharmaceutical products and Medical Devices. His early career was spent at the University of Sydney and Royal Prince Alfred Hospital (RPAH) Liver Transplant Unit where he lead a team that developed the first Australian Bio-artificial Liver, trialed in humans with liver failure. As part of his work there he also worked with Dr Kelly to describe many new biologically active isoflavones derived from dietary sources.

He joined Novogen Ltd in 1995 and became an early employee of their US subsidiary in 1998, when he moved there with his wife and family to head Clinical Research and Technical affairs in North America. Mark has held roles of increasing responsibility since, including as a project leader for Deloitte Consulting and Quintiles IMS, advising both large and small clients in medical and clinical research, product approval and launch, professional relationship management, safety surveillance, selection and management of strategic partners and GxP compliant systems.





**James Bonnar - Vice President Research and Development**

BSc (Chemistry), MRQA

James joined Nyrada, Inc. in February 2018 and brings over 20 years of global experience in the Life Sciences industry, including pre-clinical research, operations management, CMC (Chemistry, Manufacturing and Controls), Regulatory Affairs, and Quality Assurance. Before joining Nyrada, James was at Neuren for eleven years. During this period, he was the Director, CMC and Regulatory Affairs and then Director, Clinical Operations where he oversaw clinical development for drugs in the areas of traumatic brain injury and neurodevelopmental disorders. Prior to that he worked in diabetes research, GMP manufacturing, and drug formulation development.

James brings a global focus to Nyrada, having led teams from early stage development through to end of Phase II.

**John Moore - Non-Executive Director**

John Moore is a US citizen. John is an investor in emerging technology businesses. He currently serves as Chairman of Trialogics, a clinical trial informatics business and USEED, an education finance technology provider. He was CEO of Acorn Energy from 2006 to 2015 during which time the CoaLogix business was acquired for \$11 million and sold for \$101 million and the Converge business was one of the most successful IPO's of 2007 through Citigroup and a secondary through Goldman Sachs before its sale to Constellation Energy. In 2002 he was a partner and CEO of Edson Moore Healthcare Ventures and acquired for \$148 million a portfolio of sixteen drug delivery investments from Elan Pharmaceuticals. He is a graduate of Rutgers University.

**Owen Andre Dempsey - Non-Executive Director**

Owen Dempsey is a US citizen. Owen is a serial entrepreneur and biotech executive with over 25 years of deep expertise in strategy, biomedical products, drug development and venture finance. His experience is in executive or advisory roles for company formation and growth, as well as efficient allocation of resources - scientific, intellectual property, human, and capital.

Founder or CEO of four successful start-ups including Endogen, Perbio Science AB, SRU Biosystems, and American Aerogel. Track record in finance and value creation: VC funding, strategic partnering, two NASDAQ IPOs/listings, overseas listings (Toronto, Eurozone), private equity and M&A transactions, with multiple successful exits.

**Josiah T. Austin - Non-Executive Director**

Josiah is a US citizen. He is a private investor with an active interest in the banking, oil and biotech industries, serving on the Boards of a number of those companies including New York Bancorp, Inc., North Fork Bancorporation, Monterey Bay Bancorp of Watsonville, California, and Novogen Ltd. Josiah graduated from the University of Denver with a B.S. in Finance in 1971. He owns and operates agricultural properties in the states of Arizona and Montana.

**Peter Marks - Non-Executive Director**

Peter is an Australian citizen. He brings over 30 years' experience in corporate advisory, investment banking and director/advisory roles to the Board. With several leading firms, Peter's corporate skills lie in capital raising for pre-IPO and listed companies, cross border M&A transactions, corporate underwriting, and venture capital transactions for companies in Australia, US & Israel.

Over this period Peter has been involved in a very broad range of transactions, with a special focus in the life sciences, biotechnology, medical technology and high tech segments. He has been a Director and/or Chairman of several public companies. He currently is a Director of Prana Biotechnology Ltd (ASX & Nasdaq listed) since 2005, Chairman of Armadale Capital Plc (AIM listed) since 2009, and Non-Executive Director of Emefcy Group Limited (ASX listed) since 2015.

Peter provides strategic and corporate advice at various stages of technology commercialisation for companies to transition to an operating entity, and helps facilitate significant commercial transactions to create shareholder value.

Peter holds a Bachelor of Economics, Bachelor of Laws and a Graduate Diploma in Commercial Law from Monash University, Australia. He also holds an MBA from the University of Edinburgh, Scotland.

## Scientific Advisory Board

### Gary Housley – Chair (M.Sc. Ph.D)



Prof. Gary Housley holds the Chair in Physiology at the University of New South Wales, where he is the founding Director of the Translational Neuroscience Facility. He brings thirty years of leadership experience prosecuting research programs in the Brain Sciences, spanning from neuroscience discovery to clinical trials.

He completed M.Sc. and Ph.D. studies at the University of Auckland (New Zealand), and post-doctoral research in the U.S.A. and U.K. in cellular and molecular neuroscience in sensori-motor circuits. In 2005 he was awarded the prestigious Royal Society of New Zealand James Cook Fellowship in Health Sciences to undertake international collaborative studies on the molecular physiology of auditory neuropathy. He was recruited to UNSW Sydney in 2006 to establish the translational neuroscience initiative in the School of Medical Sciences.

He has published over 160 primary publications in the areas of molecular and systems neuroscience, receiving broad scientific and lay commentary, and his success in research translation is reflected by 7 patent filings and a National Health and Research Council – funded multi-centre clinical trial of DNA therapeutics for auditory nerve regeneration. The impact of his research has been recognised by medals from both the New Zealand and Australian Physiological Societies. He has served on executive bodies of those Societies, is a board member of a several prominent neuroscience journals and is member of the operations groups for the Australian National Imaging Facility and the Sydney Brain Bank.

The innovative brain injury model his research team has developed, recently published in the journal *Translational Stroke Research*, has been central to the identification of Nyrada Inc. lead compounds. He is a co-inventor of the Nyrada Inc. neuroprotection technology.



### Gilles Lambert (Ph.D)

Prof. Gilles Lambert, Ph.D - a leading researcher and thought leader in the field of blood lipid metabolism.

Dr. Gilles Lambert was awarded a PhD in Pathophysiology from the University of Paris in 1998. Gilles further specialized in lipidology, first as a post-doctoral fellow at the Molecular Disease Branch of the National Institutes of Health (Bethesda MD, USA) and then as a senior research fellow at the Heart Research Institute (Sydney, NSW, Australia).

Dr. Lambert is currently Associate Professor in Cell Biology at University of Nantes Medical School (France) and a group leader within the laboratory of Nutrition and Metabolism of the University Hospital of Nantes.

Since 2004, Dr Lambert has conducted seminal research projects on PCSK9, a major inhibitor of the LDL receptor. He received several competitive research grants in Australia and in France to study the cardiovascular benefits and potential side effects of PCSK9 inhibition.

30 August 2018

Russell Wright | T:+61 2 8249 0008 | E:russell.wright@everblucapital.com

**Junichi Nabekura (Ph.D)**

Prof. Junichi Nabekura - A leading researcher in the field of neuroscience and in particular neural circuit plasticity in the injured brain.

Junichi Nabekura is a Professor of Physiology and Neuroscience and a Vice-Director of the National Institute of Physiological Sciences (NIPS) in Okazaki, one of the top Neuroscience research institutions in Japan.

Prof. Nabekura graduated from Kyushu University in 1987, undertook a postdoctoral fellowship at Washington University, and held academic posts at various Universities across Japan (Tohoku, Akita, Kyushu) before being appointed Professor at NIPS in 2003. His research is focused on neuronal circuit wiring and plasticity during development and following injury measured using electrophysiology and in vivo imaging approaches, and he has published over 130 journal articles (with ≈5,000 citations) in this area. This has included discoveries of transmitter switching at single inhibitory synapses and impact of changes in Cl homeostasis on inhibitory transmission in development and injury.

Over the past decade Prof. Nabekura has been amongst the pioneers in applying two-photon imaging to investigate neural circuit plasticity in the living brain. In particular, the work of his group focuses on how glia contribute to cortical circuit plasticity during development and learning, and during the rewiring that occurs after injury. They have recently reported on microglia as surveyors of cortical synapse integrity in health and ischemic brain, and how astrocytes contribute to synapse and circuit rewiring in chronic pain conditions.

Prof. Nabekura also plays a prominent role in Science leadership in Japan, having served as a Senior Program Officer for both the Ministry of Education, Sports, Science and Technology and the Japan Society for Promotion of Science.

## APPENDIX

### About LDL cholesterol and cardiovascular disease

Low-density lipoprotein cholesterol (LDL) is the form in which cholesterol, an important structural component in the human body, is transported in the blood to the tissues. When LDL cholesterol levels exceed normal levels, the excess LDL particles enter the walls of arteries, creating a fatty deposit disease known as atherosclerosis that leads to hypertension, heart attack and stroke. Cardiovascular disease remains the main cause of death in most communities, and worldwide, an increasingly high proportion of individuals (both adults and children) have blood LDL cholesterol levels considered to be putting them at risk of cardiovascular disease with the medical profession in many countries continuing to advocate for lower blood LDL cholesterol levels.

### About controlling LDL cholesterol levels

LDL cholesterol levels in blood are the result of a balance between the rate at which it is made and placed into the blood, and the rate at which it is removed from the blood, with both functions mainly conducted by the liver. The removal of LDL cholesterol from blood takes place via proteins (known as LDL-receptors) on the outer surface of liver cells. These receptors bind to LDL particles in the passing bloodstream. The receptor and its attached LDL particle then are internalised in the liver cell where the LDL particle is released and degraded and the LDL-receptor recycled back to the surface of the liver cell to repeat the process. The number of LDL-receptors performing this task plays an important role in determining LDL cholesterol levels in blood.

### About PCSK9

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is made by different tissues and plays an important supporting role to the LDL-receptors in the body's ability to maintain LDL cholesterol levels in blood. The role of PCSK9 is to help keep LDL cholesterol within the blood by tempering the rate at which the liver removes LDL cholesterol from the blood. PCSK9 binds to the LDL receptors; when the receptor subsequently binds to an LDL particle and moves inside the liver cell, all 3 components (LDL particle, LDL-receptor, PCSK9) degrade, resulting in the LDL-receptor not being recycled. The result is a net loss of LDL-receptors and a consequent lowered ability to remove LDL particles from the blood.

### About statin drugs

The so-called 'statin' drugs have been standard of care for the treatment of high blood LDL cholesterol levels for 20 years. Approximately 1 in 3 US citizens over the age of 45 and about 200 million people worldwide use statins. Global sales of statins in 2017 totalled US\$19 billion and statins remain the most prescribed drugs in the world, Statins block the production of LDL cholesterol by inhibiting the liver enzyme, HMG-CoA reductase, with LDL cholesterol levels being lowered in the order of about 20-55% depending on dose and the particular statin.

A 2013 review found that for every 138 patients treated for 5 years, one fewer dies and for every 49 treated, one fewer has an episode of heart disease. This relatively modest benefit in terms of lowered risk of cardiovascular disease is now thought to be a consequence of statin therapy producing a compensatory increase in PCSK9 levels, with the resulting higher rate of retention of LDL cholesterol in the blood counter-balancing to some extent the LDL cholesterol-lowering effect of the statins.

Side-effects of statin therapy include liver damage, increased risk of diabetes, muscle pain, and possibly cognitive decline, suggesting that there could be benefit in using a PCSK9i drug to allow statin dosages to be lowered.

### About the PCSK9i program

The PCSK9i drug program was initiated by private Australian drug discovery company, Cardio Therapeutics Pty Ltd ('Cardio'), a subsidiary of Altnia Holdings Pty Ltd ('Altnia'), a family company of Dr Ian Dixon, a non-executive director of Noxopharm. Nyrada acquired Cardio in 2017.

*This Research Report has been prepared by Russell Wright ("Mr Wright") in his capacity as an Authorised Representative (AR: 422117) and issued (in Australia) by EverBlu Capital Pty Ltd (ABN 23 612 793 683) (AFS Licence No. 499 601) ("EverBlu Capital") and remains the property of EverBlu Capital Pty Ltd. No material contained in this Research may be reproduced or distributed, except as allowed by the Copyright Act, without the prior written approval of EverBlu Capital. This Research Report is subject to the disclosures and restrictions set out below.*

### Analyst Certification

The research analyst(s) identified on the cover of this report individually certify that in respect of each security or issuer that the research analyst covers that: this report accurately reflects his or her personal views about any and all of the subject issuer(s) or securities; and no part of the research analyst's compensation was, is, or will be directly or indirectly related to the specific recommendation(s) or views expressed by the research analyst(s) in this report.

EverBlu Capital provides research services to its client. Mr Wright is General Manager of Research and has over twenty (26) years' experience in the financial services industry, particularly in financial analysis and research report writing. Mr Wright joined the EverBlu team in 2017 where he has been involved in the research and publication of reports. Prior to this Mr Wright worked at a number of entities where he held Director/Head of Research and General Manager of Research positions. Mr Wright holds a Bachelor of Mathematics (Honours) from Edinburgh University and has completed the SDIA Accreditation Program (RG146) through DeakinPrime.

### General Disclosure

EverBlu Capital and its associates (as defined in Chapter 1 of the Corporations Act 2001), officers, directors, employees and agents, from time to time, may own or have positions in securities of the company(ies) covered in this report and may trade in the securities mentioned either as principal or agent or may be materially interested in such securities.

EverBlu Capital does and seeks to do business with companies covered in its research reports. As a result, investors should be aware that the firm may have a conflict of interest that could affect the objectivity of this report. Investors should consider this report as only a single factor in making their investment decision.

EverBlu Capital provides research on all ASX200 stocks as well as on other sectors (i.e. artificial intelligence, crypto currencies, food, healthcare, marijuana, mining, payment platforms and technologies) and/or entities which EverBlu Capital considers to be of interest to both EverBlu Capital's clients and the broader financial markets.

### Disclaimer & Warning

This report may contain general advice or recommendations which, while believed to be accurate at the time of publication, are not appropriate for all persons or accounts. This report does not purport to contain all the information that a prospective investor may require. Before making an investment or trading decision, the recipient must consider market developments subsequent to the date of this document, and whether the advice is appropriate in light of his or her financial circumstances or seek further advice on its appropriateness or should form his/her own independent view given the person's investment objectives, financial situation and particular needs regarding any securities or Financial Products mentioned herein. Information in this document has been obtained from sources believed to be true but neither EverBlu Capital nor its associates make any recommendation or warranty concerning the Financial Products or the accuracy, or reliability or completeness of the information or the performance of the companies referred to in this document. Past performance is not indicative of future performance. This document is not an offer, invitation, solicitation or recommendation with respect to the subscription for, purchase or sale of any Financial Product, and neither this document or anything in it shall form the basis of any contract or commitment. Although every attempt has been made to verify the accuracy of the information contained in the document, liability for any errors or omissions (except any statutory liability which cannot be excluded) is specifically excluded by EverBlu Capital, its associates, officers, directors, employees and agents. The securities of such company(ies) may not be eligible for sale in all jurisdictions or to all categories of investors.

**Analysts' Compensation:** The research analysts responsible for the preparation of this report receive compensation based upon various factors, including the quality and accuracy of the analyst(s) research, client evaluation feedback, independent survey rankings and overall firm revenues, which include revenues from, among other business units and corporate finance.

**Other International Investors:** International investors outside the US, UK, UAE or Canada are encouraged to contact their local regulatory authorities to determine whether any restrictions apply to their ability to purchase this investment and should seek their own advice

**Recipient Representations/Warranties:** By accepting this report, the recipient represents and warrants that he or she is entitled to receive such report in accordance with the restrictions set out in this document and agrees to be bound by the limitations contained herein. Any failure to comply with these limitations may constitute a violation of law.

### Meanings of EverBlu Capital Stock Ratings

**Buy** – Describes stocks that we expect to provide a total return (price appreciation plus net yield) of 15% or more within a 12-month period.

**Hold** – Describes stocks that are neither a buy nor underperform.

**Underperform** – Describes stocks that we expect to provide a total return (price appreciation plus net yield) of less than minus 10% within a 12-month period.

**NR** – The investment rating and price target have been temporarily suspended. Such suspensions are in compliance with applicable regulations and/or EverBlu Capital policies.

**Speculative Buy** – Describes stocks we research with a positive bias, whose company fundamentals and/or financials are being covered, but for which there is insufficient information for EverBlu Capital to assign a Buy or Underperform rating.

**Free Float (float / current shares outstanding) \*100** – This float figure is the number of shares that are available to the public and is calculated by subtracting the shares held by insiders and those deemed to be stagnant shareholders. Stagnant holders include ESOP's, ESOT's, QUEST's, employee benefit trusts, founding shareholder equity stake plus senior management equity stake, corporations not actively managing money, venture capital companies and shares held by Governments.

#### Valuation Methodology

EverBlu Capital's methodology for assigning stock and credit ratings may include the following: market capitalisation, maturity, growth/value, volatility and expected total return over the next 12 months. The price targets are based on several methodologies, which may include, but are not restricted to, analyses of peer comparisons, market risk, growth rate, revenue stream, discounted cash flow (DCF), EBITDA, EPS, cash flow (CF), free cash flow (FCF), EV/EBITDA, P/E, PE/growth, P/CF, P/FCF, premium (discount)/average group EV/EBITDA, premium (discount)/average group P/E, sum of parts, net asset value, discounted dividend model (DDM), franking credits and return on equity (ROE) over the next 12 months.

#### Conflicts of Interest

EverBlu Capital declares that it received financial compensation from Noxopharm Limited for the preparation of this report. Investors should consider this report as a single factor in making their investment decision and should consider the information provided in light of their own personal circumstances and needs.

The author Russell Wright made contact with Noxopharm Limited for the preparation of this report for the verification of facts.

EverBlu Capital and its associates also declare that they deal in securities as part of their financial services business and consequently may have a relevant interest in the securities recommended herein (if any). This may include providing equity capital market services to the issuing company, holding a position in the securities or acting as principal or agent and as such may effect transactions not consistent with the recommendation (if any) in this report. EverBlu Capital and its associates therefore may benefit from any increase in the price of those securities. EverBlu and its associates may earn brokerage fees, commissions, other benefits as well as fees or advantages as a result of a transaction arising from any advice mentioned in publications to clients.

EverBlu Capital declares that EverBlu Capital Directors and the author of the report, Russell Wright, own shares in Noxopharm Limited.

#### EverBlu Capital Recommendation Proportions

Buy	44.9%	( 3.8% of stocks with recommendations are EverBlu clients)
Speculative Buy	1.1%	( 100.0% of stocks with recommendations are EverBlu clients)
Hold	23.9%	( 0.0% of stocks with recommendations are EverBlu clients)
Underperform	30.1%	( 0.0% of stocks with recommendations are EverBlu clients)