NEWSLETTER

December 2018

It's been not quite a full year of operation, but I didn't want our first calendar year of operation to pass without a progress report.

To recap our objectives. We have set our sights on developing three drugs:

- a drug that would be administered within 24 hours of suffering a stroke or serious concussion to assist in rehabilitation of brain function
- a drug that would be used to boost the cholesterol-lowering effect of statin drugs in people at high risk of heart attack and stroke
- an anti-inflammatory drug to treat painful inflammation associated with peripheral nerve damage.

I will start with a review of each of these three drugs – how far we have come over the course of the last nine months and what you might expect the next twelve months to hold for each program.

As a general comment, these past nine months have been a highly productive time for the Company. We have made significant progress across all three of these programs, and we believe we have three major opportunities on our hands.

It is rare to get the opportunity to be involved in the development of a drug with the potential to meet a significant unmet community health need. In our case we have identified at least three such programs and you only need to look at one of these, the stroke/concussion program, to appreciate what opportunity lies ahead.

Here is a snapshot of stroke and the potential market opportunity for our NYX-104 program.

Next year, about 800,000 people are expected to suffer a stroke in the U.S., of whom about 140,000 will die as a result. Of the surviving patients, 60% will experience a long-term disability requiring assisted care – that's about 350,000 people who will never fully recover their lost brain function. The cost of caring for these survivors in the U.S. is estimated to be US $34 billion annually.

There are three time points of potential therapeutic intervention for stroke:

- the first is the lead-up to the stroke
- the second is the 12-hours immediately post-stroke
- the third is the 1-2 week period post-stroke.

Most research efforts to date have gone into the first time point – **prevention** – including lowering blood pressure, lowering blood cholesterol levels, using anti-coagulants etc. But even with these efforts, stroke remains a major community problem.

The second time point revolves around trying to re-establish a blood supply to the damaged part of the brain. To have any real effect, this needs to happen within a matter of hours following the stroke. It involves trying either to dissolve the clot by injecting enzymes, or physically pulling the clot out. Either way, time is critical, requiring the patient to have quick access to high level hospital care. For most patients, that doesn't happen, which is why we have such a high rate of long-term disability. Biotech and big pharma have tried many times to make progress here, but almost all have failed, in large part because of the time factor. The harsh reality is that brain cells can only live without oxygen for a matter of minutes, meaning that even the best therapies need to be administered within a matter of hours.

It's the third time period, the 1-2 weeks post-stroke, that we are addressing. This is where the most long-term damage arguably occurs. It is during this period that the original area of brain damage can multiply up to six times. This is due to a self-destructive process unique to nerve tissue and for which there is currently no effective treatment. We believe we are well on-track to developing the first drug capable of blocking this process. We have developed a drug candidate that appears to work in the laboratory, including blocking the self-destructive process in animals. We have some tweaking to do, but we are making the progress necessary to test it in humans. The eminent advisors we have, the neurobiologists who are well known in this field, indicate that they are unaware of any other drug with the potential of this compound. What is its value? Anyone's guess at this stage because no treatment exists against which to measure it. But we envision a drug that could be administered to a stroke victim, beginning the day after the stroke and continuing for a week or two, all with the aim of limiting the area of brain damage to the original injury. We believe this would translate into far fewer long-term disabilities.

That is just one of the assets that Nyrada shareholders own.

The other general comment I want to make is that it is important to set appropriate expectations for the lengthy timelines that drug development requires. As drug developers, we live with the fact that it is a long, hard haul before a new drug will reach the market – usually between 10 to 15 years by some estimates. This stands in stark contrast to a considerably shorter investor horizon.

Nyrada has no intention at the moment of taking any of its drug asset all the way to market. That would not be playing to our strengths. Our horizon is far more aligned to the investor horizon. We are aiming to bring our assets through to a point where we have maximised their risk/reward value to a larger partner. That could be at any stage, but following a successful Phase 1b study is a likely end-point. That means a horizon of two to three years, with key milestones needing to be achieved along the way, all capable of serving as valuation inflection points for the Company.

There are no short-cuts in drug development, but our strategy is to maximize the returns on our investment dollar.

Graham Kelly
Group CEO

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Neuroprotection

Background:

The concept of neuroprotection is fairly recent and refers to a means of protecting the structure and the function of the brain and spinal cord following injury. Drugs that confer this protection are referred to as *neuroprotectants*.

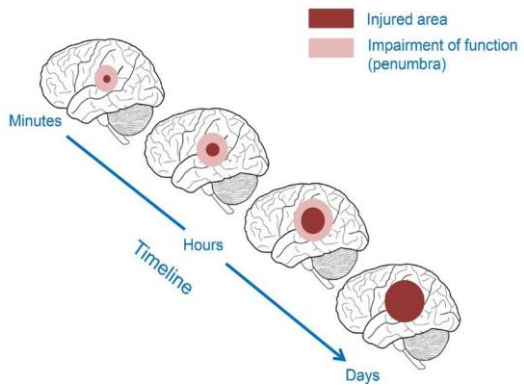
While the term *neuroprotectant* might not be well-known, the need for a neuroprotectant would be well known to most people. The most obvious being the need to limit permanent disability (paralysis, loss of speech, loss of memory and cognitive function etc.) that follows a stroke and traumatic brain or spinal cord injury, including severe concussion.

A neuroprotectant drug isn't going to resolve the initial brain injury because, unlike the rest of the body, the brain and spinal cord have almost no ability to repair or replace damaged nerve cells. That damage is permanent. The brain does have a degree of plasticity, meaning that it is possible to train unaffected parts of the brain to compensate for some of the lost function, but the physical damage to neurons following injury is permanent and irreversible.

The reason we see such poor outcomes for patients suffering from brain injury is largely due to a secondary wave of damage that is unique to the brain and spinal cord, where dead and dying nerve cells trigger a process of self-destruction. This wave of cell death spreads out from the original injury, continuing for up to a week following the original injury, and resulting in as much as six times the amount of cell death compared to that from the original injury. This wave of secondary brain damage is known as *glutamate-initiated excitotoxicity* (GIE). Currently, there is no effective way of stopping or slowing down this harmful process.

Glutamate is the main chemical responsible for transmitting impulses between nerve cells. In healthy nerve cells, glutamate *excites* the receiving nerve cell, triggering an electrical impulse. When a nerve cell is damaged, it offloads all of its glutamate stores, which instead of triggering an impulse, overexcites the receiving nerve cell and kills it (= *excitotoxicity*).

If GIE could be stopped and the degree of brain damage restricted to the original injury, then many neuroscientists believe that the long-term effects resulting from stroke and traumatic brain injury would be considerably lessened. A neuroprotectant isn't going to prevent death in the most severe cases of brain injury, however, where the area of initial damage is non-fatal, a neuroprotectant offers the hope of helping those 60% of surviving stroke patients who end up requiring ongoing assisted care. A neuroprotectant offers the prospect of limiting damage from the primary injury, by reducing GIE.



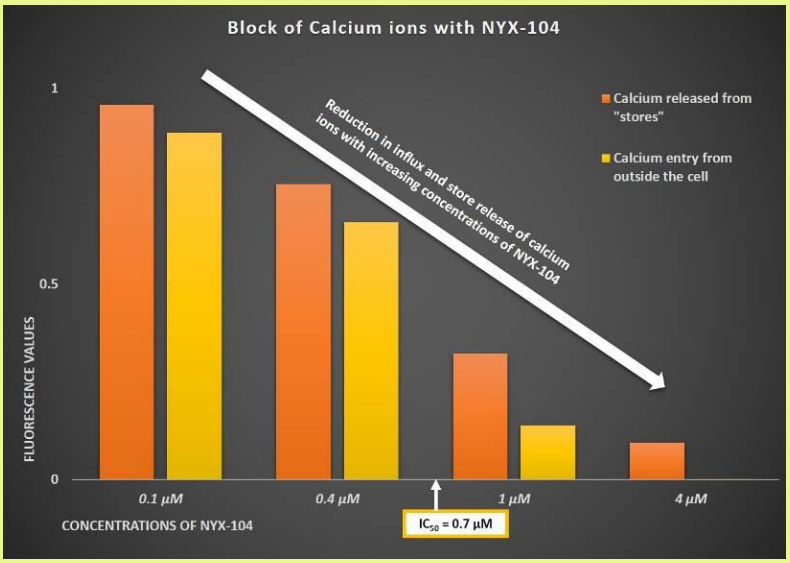
Following an ischemic (blocked artery) stroke, the area of brain deprived of oxygen dies. This dead area is surrounded by an area where oxygen is present but lower than normal and where the brain cells are injured but not dead (*penumbra*). Current approaches to the treatment of stroke focus on getting oxygen to this penumbra within a matter of hours. For most patients, the primary area of brain death = the original injury + penumbra. This eventual area of primary damage then triggers GIE, resulting in an area of brain much larger than the original injury. This is what a neuroprotectant drug is intended to prevent.

Neuroprotection

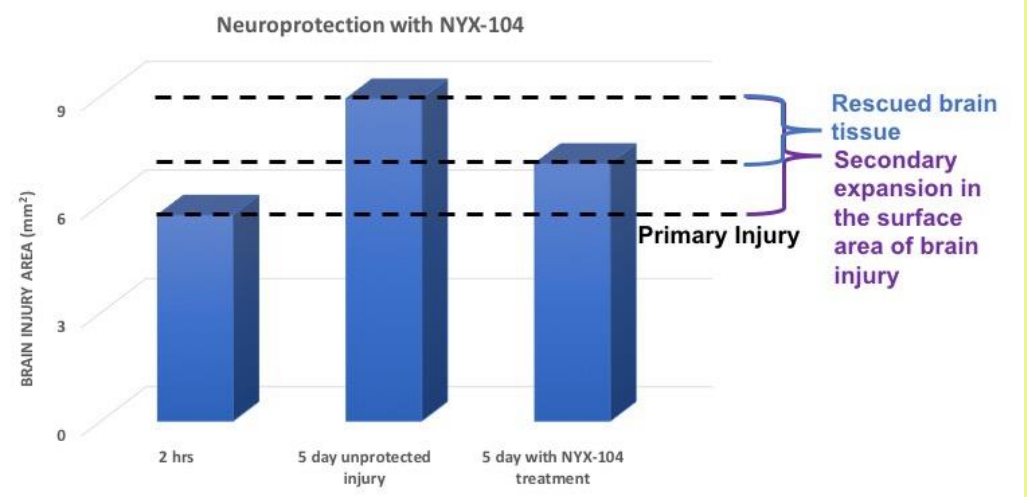
Last report:

At the time of our mid-year (June 2018) briefing, we reported on the following:

- ➔ GIE was known to result from an overload of glutamate, resulting in excessive levels of calcium ions (Ca^{2+}) entering the nerve cell, resulting in cell death. It also was known that this Ca^{2+} came from two sources - both from outside the cell and from Ca^{2+} stores inside the nerve cell – and that any neuroprotectant drug that was aiming to block GIE would need to block both sources of Ca^{2+}.
- ➔ Our collaborators at UNSW (Sydney) had shown that **NYX-104** inhibited **both sources of Ca^{2+}**. Previous attempts by others to block GIE only blocked the external source of Ca^{2+} and thereby were ineffective. On that basis, we understood NYX-104 to be the first drug capable of effectively blocking the underlying pathology of GIE.



- ➔ When NYX-104 was administered to mice for five days following induction of a stroke injury, the drug was successful in reducing the extent of GIE lesion area by 58%.



Neuroprotection

Since then:

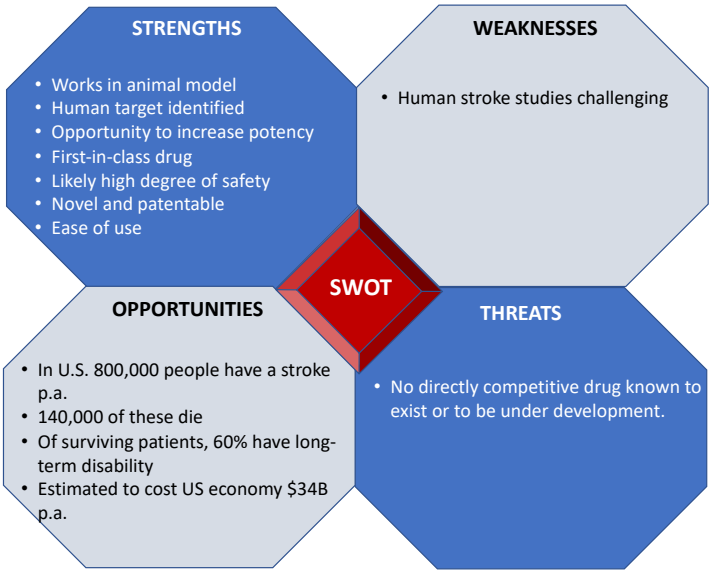
➔ The Nyrada team has achieved an important breakthrough in identifying exactly how NYX-104 is working. We knew it was blocking the build-up of Ca^{2+} in the damaged nerve cell, but we didn't understand how. The team now has identified the pathway that NYX-104 is acting through, including the actual protein target that it binds to and the way in which that action leads to the wave of GIE being blocked. This is vitally important new intellectual property that is testament to the capabilities of our team of scientists. **The result is that we have the first known inhibitor of this key protein.** The name of this protein will remain confidential while the patent process is underway.

➔ One of the big advantages of knowing the drug's target is that it now provides the opportunity to design molecules with even greater potency than NYX-104. Once a drug's binding location on the target protein is known, small changes to the drug's structure often can make the drug bind more firmly to the target, resulting in improved potency.

58% inhibition is not a trivial outcome because if we were able to reproduce that level of activity in a human, that should translate into significantly less disability and shorter rehabilitation times following a stroke. But we believe that it is possible to do better. Using state-of-the-art computer design software, our chemists have designed analogues (variations) of NYX-104 that we are hopeful will be more potent inhibitors of GIE than NYX-104. These new compounds currently are being manufactured for us and we expect to take delivery of them in early January.

From here:

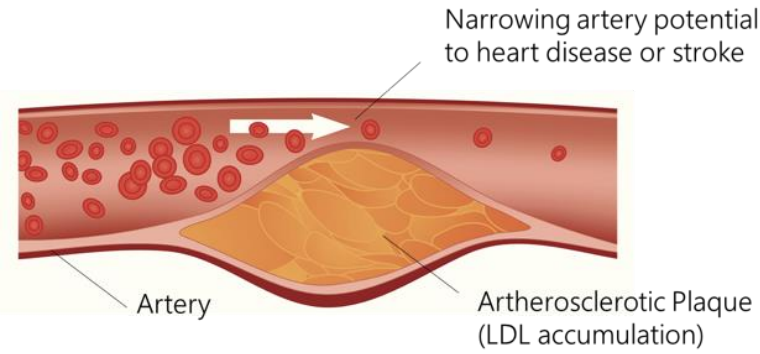
➔ The new compounds will be put through preclinical testing in 2019 in the hope of identifying a compound that will go beyond the current gold-standard mark of 58%. Those tests are expected to take until April 2019 to complete.



Cholesterol-lowering drug

Background:

The drug being developed in this program is known as a **PCSK9 inhibitor**. PCSK9 is a blood protein that plays an important role in how the body regulates cholesterol levels. Its main function is to act as a brake on the removal of LDL-cholesterol (the main form of cholesterol in the body) from blood by the liver. This is a normal part of the body's mechanism in maintaining healthy blood cholesterol levels. LDL-cholesterol is an essential component of the body, but can become a problem when the level in the blood becomes high. This leads to an excess accumulation of LDL-cholesterol in the walls of the arteries, leading in turn to atherosclerosis.



Aside from the well-known lifestyle factors that lead to high LDL-cholesterol levels (poor diet, obesity, lack of exercise, smoking etc.), abnormally high levels of PCSK9 also contribute to high LDL-cholesterol levels by reducing the rate at which LDL-cholesterol is removed from the blood. This can occur in two ways:

1) The first is a genetic cause where the body manufactures excessively high levels of PCSK9. This results in the condition known as *familial hypercholesterolemia*, a rare condition resulting in pathologically high levels of LDL-cholesterol. These individuals are at very high risk of heart attack and stroke.
2) The second is as a consequence of treatment with the so-called 'statin' drugs, the standard means of treating people with high blood levels of LDL-cholesterol. Statins block the ability of the body to make LDL-cholesterol, but an unintended consequence of this is that the body makes more PCSK9 as an off-set move to hold in the blood the little cholesterol that now is being made. The effect of this is to reduce the ability of statin drugs to lower LDL-cholesterol levels.

Where it has been possible to inhibit PCSK9 concurrent with statin therapy, the combined treatment led to LDL-cholesterol levels falling about 50 - 60% greater than with statin treatment alone. That level allows most people to achieve LDL-cholesterol levels deemed by the medical profession to be 'low risk' for cardiovascular disease.

In addition to a combination treatment (statin + PCSK9 inhibitor) increasing the likelihood of achieving much lower "safe" LDL-cholesterol levels, a combination also offers the opportunity of lowering the daily dose of the statin. This opportunity has arisen with growing awareness of the undesirable side-effects of long-term statin therapy including liver damage, muscle pain, predisposition to diabetes, and possible brain dysfunction such as memory loss and dementia.

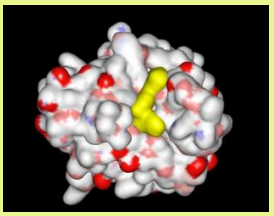
The Nyrada program is working to develop an oral, once-a-day medication that will be used in combination with statin drugs.

Cholesterol-lowering drug

Last report:

At the time of our mid-year (June 2018) briefing, we reported on the following:

➔ That we had identified a small molecule, NYX-330, that bound to the PCSK9 protein and successfully blocked its ability to bind to the LDL-cholesterol receptor.



This shows NYX-330 (yellow) binding to the part of the PCSK9 molecule that needs to be blocked to prevent binding to the LDL-cholesterol receptor

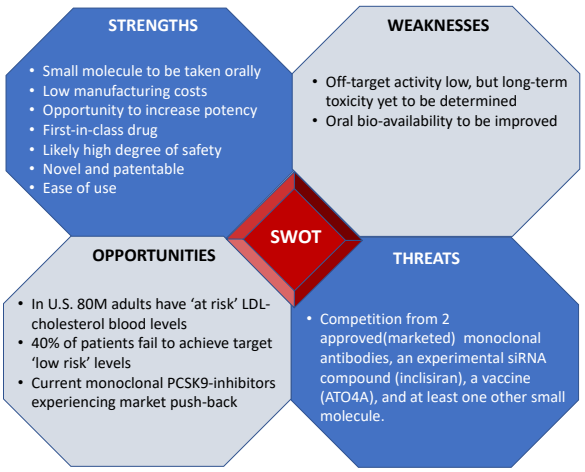
Since then:

➔ We successfully completed an animal (mouse) study which provided proof-of-concept evidence of NYX-330's ability to block the ability of PCSK9 to interfere with LDL-cholesterol uptake by the liver. This study was a crucial STOP: GO point, as failure to achieve any evidence of any anti-PCSK9 activity would have been a major setback to the program. Fortunately, that wasn't the case. These animal studies are being conducted in the French laboratories of Professor Gilles Lambert, one of the pioneers of the role of PCSK9 in cholesterol metabolism.

➔ As with NYX-104, our chemists also identified a possible way to increase the potency of NYX-330 by modifying its structure. This has led to the design of the next generation of compounds which have been synthesized and are currently undergoing laboratory testing for their anti-PCSK9 activity.

From here:

➔ Our immediate goal is to identify a form of NYX-330 that will provide at least the equivalent ability to lower LDL-cholesterol in the accepted animal model to that obtained with the marketed monoclonal drug, evolocumab. The projected timetable for this is year-end 2019.



Anti-neural inflammation

Background:

Nerve tissue (brain, spine, peripheral nerves) is as prone to chronic Inflammatory disorders just as much as the rest of the body. But where nerve tissue differs is the existence of a barrier that protects the brain, spine and peripheral nerves from the entry of foreign compounds. The *blood-brain* and *blood-nerve* barriers act to limit the entry of all major anti-inflammatory drugs to nothing more than trivial levels.

Damage to peripheral nerves (the nerves running from the brain and spinal cord to the rest of the body) is a major global health issue, particularly because of the debilitating pain that can be associated with it and because it is poorly managed with anti-inflammatory and pain-killing drugs.

The symptoms associated with damage to peripheral nerves vary depending on whether motor, sensory, or autonomic nerves are damaged:

- Motor nerves control voluntary movement of muscles, such as those used for walking, grasping things, or talking.
- Sensory nerves transmit information such as the feeling of a light touch or the pain from a cut.
- Autonomic nerves control organ activities that are regulated automatically, such as breathing, digestion, and heart and gland functions.

Peripheral nerve damage can be caused by degenerative disease processes, infections, and trauma. Degenerative disease processes (known as peripheral neuropathy) account for most peripheral nerve damage, with 20 million people in the U.S. estimated to have some form of peripheral neuropathy. Over 100 different causes have been identified, with diabetes accounting for about 60% of these cases.

Nerve damage caused by trauma is another major global health issue and can be caused by crush injuries, lacerations or over-stretching.

Regardless of the cause, many cases of peripheral nerve damage are associated with long-term pain (neuropathic pain), which in many cases remains poorly managed.

The purpose of the Nyrada anti-inflammatory drug program is the development of a drug that will cross the blood-nerve barrier and reach damaged nerve tissue to provide effective control of inflammation and the causes of neuropathic pain.

Anti-neural inflammation

Last report:

At the time of our mid-year (June 2018) briefing, we reported on the following:

➔ NYX-205 was confirmed as a selective anti-inflammatory drug that crossed the blood-nerve barrier in rats and reached peripheral nerve tissue in substantial amounts. This was the key STOP: GO point in this program, confirming that we possess the ability to deliver the drug into the peripheral nerves at potentially therapeutic levels.

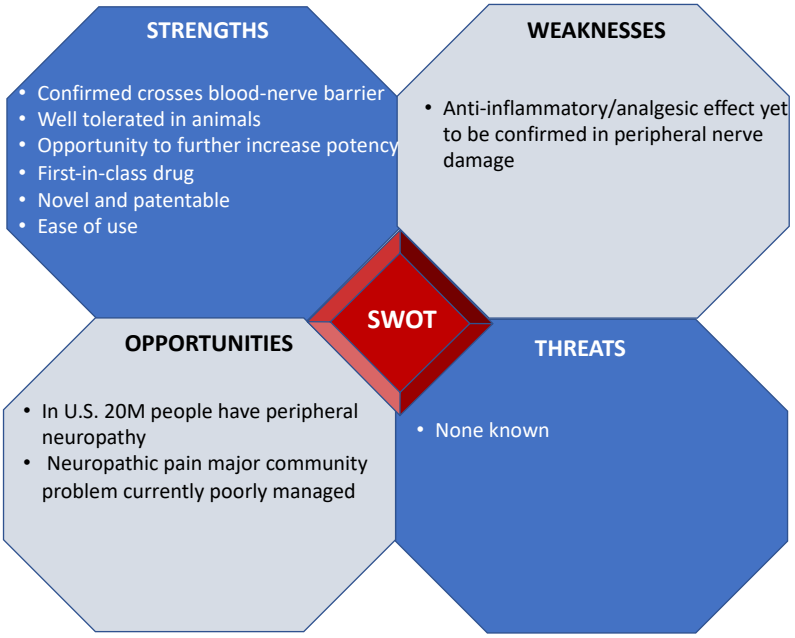
Since then:

➔ We have focused on identifying the mechanism of action of NYX-205.

➔ The inflammatory cascade is a complex and intricate sequence of events involving dozens, if not hundreds, of different end-products that collectively contribute to inflammation and pain. As a general principle, the more upstream the drug works, the more likely it is to maximise the number of end-products that will be blocked, thereby providing better pain control; conversely, the more downstream the drug works, the fewer end-products are likely to be blocked. Most commonly-used anti-inflammatory drugs work well downstream. Our studies suggest that NYX-205 works highly upstream. A small number of likely targets have been identified, and studies are currently underway to confirm the actual target.

From here:

➔ NYX-205 will be tested in an animal model of a nerve crush injury to provide proof-of-principle evidence of efficacy. These studies are scheduled to commence in Q1 2019 and be completed by Q3 2019.



General comments

Use of funds. The first comment to make is in regard to the use of funds. We raised $4M earlier this year, of which approximately $1.3M remains. This expenditure reflects an active R&D program with high front-end expenditure embracing a major collaboration with UNSW (Sydney), animal testing, laboratory tests, chemical synthesis and patenting costs.

The team. Under the direction of our Chief Executive Officer, James Bonnar, we have assembled a team of three highly-qualified scientists (Drs. Benny Evison, Alexandra Suchowerska, Jasneet Parmar). James reports directly to myself as Group CEO. Congratulations to Jasneet who recently was awarded her PhD by UNSW in the field of neurobiology.

Drug development strategy. The current strategy is to run all three drug programs on an equal basis with a review point in Q2 2019. At that time a decision will be made as to which program will receive priority funding to be advanced through to the clinic, with the other two programs to continue, but at a lesser priority. Priority will be based on several factors, including stage of development, likely time/cost of reaching the clinic, potential industry interest in the particular drug sector, and various factors affecting licensing opportunities and potential market size.

Anticipated timelines. The current R&D effort across all three programs is focused on identifying the lead candidate compound. In each case, we have identified an active drug candidate, each of which is capable of being identified as the lead candidate. However, in each case, we believe that we can improve on what we have. This is an iterative process of repeat design/testing/re-design/further testing until we reach a point of diminishing returns where we accept that we are unlikely to achieve significant further improvements. We anticipate that the process will take an additional 6-8 months for each program. After that, we intend to advance the lead candidate through standard preclinical testing, a process that typically takes 12-18 months before the drug can be considered suitable for human testing.

Final word. Finally, on behalf of the Nyrada team and the NOX Board, I want to thank you, the Note Holders, who have supplied the capital to make this significant progress possible. Whether you see this investment purely in dollar terms or tinged with altruism, it is important to remember that you have a team dedicated to making your investment make a considerable difference to the lives of a lot of people, in addition to the retirement funds of Note Holders.

Yours sincerely
Graham Kelly