NOXOPHARM

VERSATILITY

THE NOXOPHARM NEWSLETTER

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Exciting data released to conference

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Aiming to improve the outcome for sarcoma patients

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The next big wave in oncology that NOX aims to ride

Discover

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Deliver

From the CEO

Welcome to the July 2019 edition of "Versatility", the new name of our Noxopharm Newsletter. We chose Versatility because we believe it best represents the nature of Veyonda® and what makes it such a unique and valuable anti-cancer drug-candidate. No two patients are the same and no two cancers are the same. In fact, no two tumours within any one patient are likely to be the same. This means that there is never going to be a one-size-fits-all treatment for cancer. The versatility of Veyonda® uniquely places it to meet the distinctive needs of different cancers. Chemotherapy, radiotherapy and immunological interventions are going to continue to be the 3 pillars of cancer therapy for the foreseeable future, and Veyonda® has the versatility to be used across all 3 treatments.

This versatility is brought into focus in our two strategic priorities for Veyonda®:

1. Establish Veyonda® as an essential adjunct to radiotherapy in the treatment of prostate cancer
2. Broaden the clinical value of Veyonda® by improving outcomes in sarcoma and increasing response-rates with immuno-oncology agents

Currently we have three clinical trial programs that leverage this versatility in driving towards achievement of our two strategic priorities:

1. To make Veyonda® an essential adjunct to radiotherapy in the treatment of prostate cancer we are running two programs:
    a. Using Veyonda® to enhance the effectiveness of intravenous radiotherapies (e.g. LuPIN)
    b. Using Veyonda® to enhance the effect of external beam radiotherapies (our DARRT program)
2. To broaden the clinical value of Veyonda by improving outcomes in sarcoma we are using Veyonda® to enhance the effectiveness of chemotherapies in this group of cancers (our CEP program)

In this edition, we highlight three leading articles pertinent to our ongoing strategic work:

An update on the LuPIN trial and the promise coming from combining Veyonda® with radiopharmaceutical treatment in late-stage prostate cancer

A discussion of our plans to use Veyonda® in a trial in the US involving sarcoma, a rare but aggressive form of cancer crying out for better treatment options

An introduction to an exciting new concept in cancer therapy called STING in which we believe we are close to being the world leader.

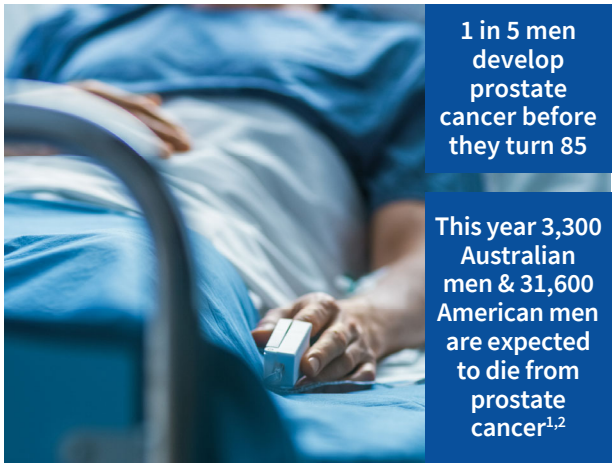
I hope you enjoy reading this newsletter and we look forward to bringing you another edition of Versatility in October.

Dr Greg Van Wyk, C.E.O

Snapshot of progress over last 6 months

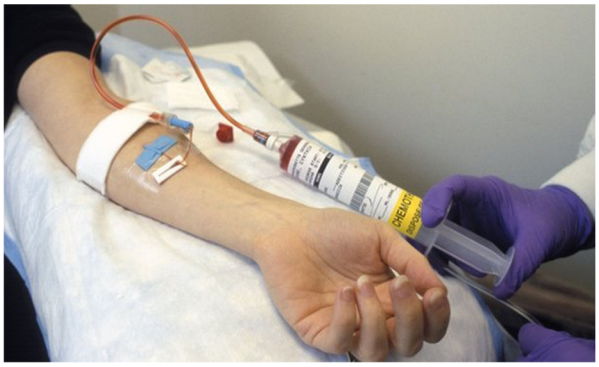
^{177}Lu-PSMA-617: A promising new treatment for late-stage prostate cancer

VEYONDA® LOOKING TO IMPROVE ON THAT PROMISE



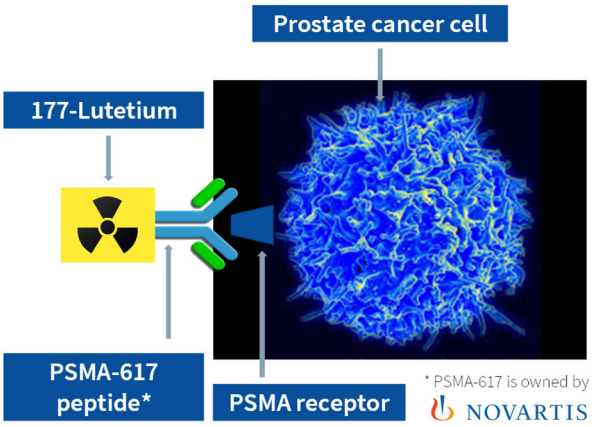
Once prostate cancer has stopped responding to standard radiotherapy and hormone therapy and is growing and spreading to different parts of the body, the disease is known as **metastatic castrate-resistant prostate cancer (mCRPC)**. Treatment now becomes a matter of extending life, rather than curing the disease. Treatment options for mCRPC include strong chemotherapy drugs (e.g., docetaxel, cabazitaxel) and so-called androgen ablation drugs (e.g., abiraterone and enzalutamide). But once those treatments fail, as they inevitably finally do, men generally are left with palliative care as their remaining treatment option because the challenge now facing the patient and the oncologist is that the cancer typically has spread throughout the body, mostly in the skeleton, involving anything from dozens to hundreds of small tumours.

One hopeful approach that is receiving a lot of attention at the moment involves injecting a radioactive drug intravenously so that the radioactivity searches out and seeks to destroy all prostate cancer cells throughout the body. The radioactive drug (or radiopharmaceutical) is known as ^{177}Lu-PSMA-617.



The radioactive particle ^{177}lutetium is attached to a peptide (PSMA-617) that selectively binds to a protein on the surface of the prostate cancer cell known as PSMA (prostate surface membrane antigen).

Figure 1. How ^{177}Lu-PSMA-617 works on prostate cancer



After injection, this radioactive payload seeks out the prostate cancer cells scattered around the body, delivering radiation in a highly targeted way to as many cancer cells as possible.

The ^{177}Lu-PSMA-617 technology is licensed by its German inventors to Endocyte Inc, a wholly-owned subsidiary of Novartis since being acquired late-2018 for US$2.1 billion.

^{177}Lu-PSMA-617 is not intended to be curative, but in studies involving more than 3,000 men over recent years, this experimental drug has shown itself capable of providing significant pain relief and up to 1-2 years additional survival. However, those studies also have shown that most men relapse and therefore come off treatment before completing their full course of treatment.[3]

St Vincent's Hospital in Sydney is at the forefront of looking at ways to get more men to complete their full course of treatment of ^{177}Lu-PSMA-617, thereby hopefully giving them a better quality of life for longer, including longer pain relief. Associate Professor Louise Emmett is leading the academic team involved in that effort.

One of the strategies being looked at by the St Vincent's team is to see if the anti-cancer effect of ^{177}Lu-PSMA-617 can be improved by the addition of Veyonda® by exploiting its ability to boost the cancer-killing effect of radiation.

The interim LuPIN-1 trial data released recently suggests that the answer is that Veyonda® does increase the effectiveness of ^{177}Lu-PSMA-617.4

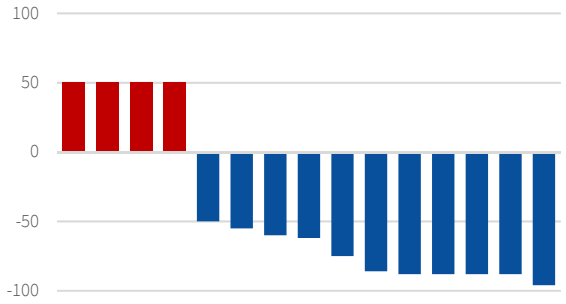
If that outcome is confirmed at the end of the trial, the Company believes that it will have a significant bearing on the likely uptake of the ^{177}Lu-PSMA-617 technology in the marketplace.

The first read-out of the LuPIN-1 data based on 16 men treated with ^{177}Lu-PSMA-617 and either 400 mg (8 subjects) or 800 mg Veyonda® (8 subjects) was presented recently by Associate Professor Emmett at the 2019 Annual Meeting of the Society of Nuclear Medicine and Molecular Imaging (SNMMI).[4]

This was interim data reporting only on PSA response (≥50% fall in PSA compared to baseline), safety and overall survival.

PSA RESPONSE:	PSA response: 11 of the 16 men (69%) treated with either 400 mg or 800 mg Veyonda® showed a PSA response, a well-recognised way of measuring response to treatment in men with prostate cancer (Figure 2); 62.5% of the men treated with 400 mg and 75% of the men treated with 800mg had a PSA response.
SAFETY/ TOLERABILITY:	The combination of Veyonda® and ^{177}Lu-PSMA-617 generally was well-tolerated.
OVERALL SURVIVAL:	93% (15/16) were alive after 6 months and **81% (14/16) were alive after an average of 12 months.**

Figure 2. PSA response in men treated with 400 mg or 800 mg Veyonda® in combination with 177Lu-PSMA-617.



The red bars show men who did not have a decrease in PSA while the blue bars show the men who did. This 'waterfall' graph represents the change in PSA level relative to starting levels.

An overall 69% PSA response rate and an 81% overall 12-month survival rate is a highly encouraging outcome that needs to be seen in the context of the very advanced stage of disease in the men involved in this study.

Based on the favourable safety data, 16 more patients joined the study in September 2018 and are currently being treated with the 800 mg dose.

Then in order to fully test for any dose-response effect, a further study expansion was approved recently which will recruit a further 24 patients who will be treated with a 1200 mg dose of Veyonda®. This will bring the total number of men in the study to 56.

The Company anticipates that the St Vincent's clinicians will release interim clinical data on the three dosages as they progressively reach their 12-month end-of-study read-outs.

Further results are eagerly awaited, and we look forward to them continuing to lay the foundations for Veyonda® eventually becoming a standard of care in combination with ^{177}Lu-PSMA-617.

In addition, it is worth remembering that we see any combination effect with ^{177}Lu-PSMA-617 as validating our strategy of using Veyonda® to boost the effect of intravenous radiopharmaceuticals generally, an important point given the growing application of this technology across a growing number of cancer types.

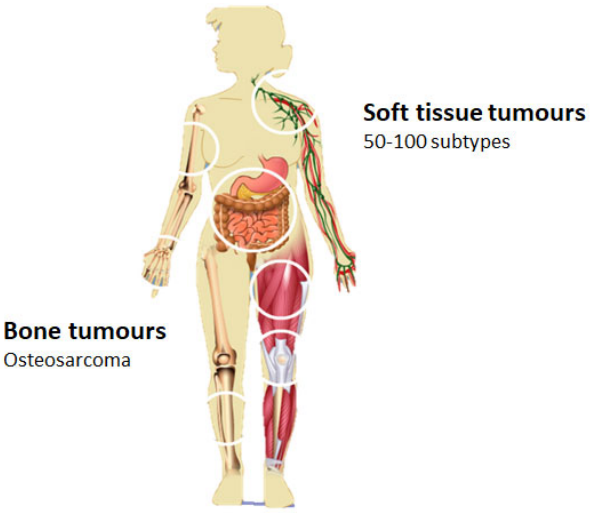
Dr Gisela Mautner

New treatments urgently needed for sarcoma

THE PROMISE OF VEYONDA®

Sarcomas are malignant cancers of the body's connective tissue. Sarcoma is classified according to whether it arises in soft tissues or bone. Soft tissue sarcoma occurs in tissues such as fibrous tissue, fat, muscle, blood vessels, nerves, tendons and cartilage and more than 50 different types have been identified. Bone sarcoma (osteosarcoma) starts in the bone and accounts for 10% of all sarcomas.

Figure 3. Types of sarcoma



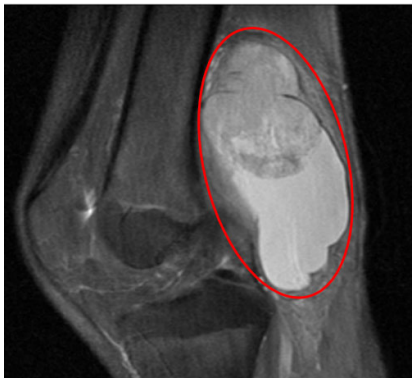
Sarcomas are relatively rare, accounting for about 5% of all cancers diagnosed; 1 in every 350 people in the U.S. will be diagnosed with a sarcoma at some time during their lifetime. Approximately 20% of people with soft tissue sarcoma will be under the age of 35. The main sarcomas in children are Ewing's sarcoma and rhabdomyosarcoma.[5]

The outcomes for patients with sarcoma usually are not good. One out of three people, including children, diagnosed with sarcoma will not survive the cancer. It is estimated that around 5,270 Americans will die from soft tissue sarcomas this year. [5]

There are a number of reasons for such poor patient outcomes. The first is that the soft tissue sarcomas do not have distinct symptoms and people often are diagnosed after the disease has already spread to other parts of the body.

The second reason is that while the treatment options have markedly improved for some other types of cancer, there have been few new treatments for soft tissue sarcoma. In fact, in the last 40 years there has only been one new drug approved as the initial treatment for advanced soft tissue sarcoma.

Figure 4. MRI of a sarcoma in a tendon behind the knee



The current treatment options for soft tissue sarcoma include surgery, radiation and chemotherapy.[6] In patients with metastatic disease, the main treatment is chemotherapy with doxorubicin or other chemotherapy agents combined with doxorubicin. However, the survival of patients treated with doxorubicin is low, with an average survival of only 12–15 months.[7] And the toxicity of doxorubicin means that patients often cannot receive the optimal amount of the drug.

This means that new treatment options, including agents that improve the current therapies are desperately needed for all forms of sarcoma in both adult and children.

The active component of Veyonda®, idronoxil, is proving to be active against a range of sarcoma types in the laboratory, including making doxorubicin far more effective at killing sarcoma cells. We believe that this puts Veyonda® well placed to bring some meaningful benefit to sarcoma patients.

Our confidence in Veyonda® providing a benefit is boosted by the results of the CEP-1 study where Veyonda® combined with carboplatin provided meaningful anti-cancer effects in patients with late-stage breast, lung, ovarian or prostate cancer.

The Noxopharm team currently is in the process of filing an IND with the FDA to run a Phase I/II trial in the U.S. that we anticipate starting early-2020.

This study in about 32 people is designed to confirm that a combination of Veyonda® and doxorubicin is well tolerated, and to confirm evidence of benefit that would justify taking this approach through to a registration study in people with advanced sarcoma.

Dr Gisela Mautner

STING: The next 'big thing' in oncology.

Can NOX be a world leader?

WHAT IS STING?

Never heard the term 'STING' in reference to cancer?…not surprising, because very few people in medical science would have been aware of the term until quite recently. But we all need to start getting our heads around it, because it is the coming wave in the oncology field, and it is a wave that NOX is set to ride.

In a nutshell:

- **STING HAS BEEN HERALDED AS THE TURNING POINT IN TURNING THE TIDE AGAINST CANCER**
- **STING** stands for **St**imulating **In**terferon **G**enes
- **STING** is the mechanism the body uses to fight cancer
- Cancer can only survive if it switches **OFF** the **STING** mechanism
- Switching **STING** back **ON** has been shown to be an essential step in the successful treatment of a wide range of cancers
- There currently is a race to develop a drug that re-activates the **STING** process in tumours throughout the body in a well-tolerated way
- **NOX believes that idronoxil meets these aims and may be the only drug candidate that does so**

THE COMING STING 'TIDE'

STING is creating a lot of excitement in the global pharma world because it is believed it may be the answer to making the much-hyped immuno-oncology (IO) drugs finally work in the way that everyone thought and hoped they would.

IO drugs (or checkpoint inhibitors to give them their functional name) came to market 8 years ago with enormous fanfare and expectation. Ipilimumab (Yervoy®) was the first in 2011, followed by pembrolizumab (Keytruda®) and nivolumab (Opdivo®) in 2014 and atezolizumab (Tecentriq®) in 2016. Cases of long-lasting, dramatic responses in melanoma and lung cancer patients are what caused all the excitement.[8] But then came the reality check – such dramatic responses turned out to be the exception rather than the rule, with only about 1 in 3 patients responding in a meaningful way, and then with extended survival, not a cure.[9]

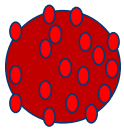
Selecting sub-types of certain cancers can deliver high response rates with IO drugs, but as a general treatment in all-comers across the full spectrum of cancers, including the common cancers such as prostate, breast, ovarian, colorectal cancers, the response rates are less than 10%, and in some cancers close to 0%.[10]

We now understand that for these IO drugs to work, there needs to be functional immune cells within the tumour, available to attack the cancer cells once the IO drug has removed the shield protecting the cancer cell from the immune cells. Unfortunately, it turns out that most tumours have expelled all immune cells, accounting for why only a small number of patients respond to IO drugs, while the majority of patients don't.[11]

This has led to the concept of tumours being described as HOT tumours (lots of immune cells) or COLD tumours (few or no immune cells) or WARM tumours (something in-between).[11]

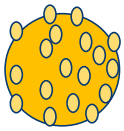
Despite these limitations, sales of IO drugs are expected in 2019 to be about US$15 billion, rising to US$34 billion in 2024.[12]

Figure 5. Tumour classification based on immune function



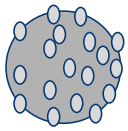
Hot tumors (inflamed)
- +++++ immune cells present

Examples: **lung, melanoma, bladder, head and neck**



Warm tumors (partly inflamed)
- +++ immune cells restricted to periphery of tumor

Examples: **lung, breast, ovarian, kidney**



Cold tumors (non-inflamed)
- +/- immune cells

Examples: **breast, prostate**

Since the IO drugs can only work when there are immune cells present, not surprisingly the hunt is now on to find ways of converting WARM and COLD tumours to HOT.

Which is where STING comes in.

STING

STING is a vigilance mechanism present in every human cell that Nature has designed to protect us from cancer.[13] STING is based on a series of compounds whose role is to look for evidence of DNA leaking out of the nucleus, an early sign of cancerous change. Once a cell detects its own DNA where it shouldn't be, it sends a message to its neighbouring healthy cells to produce a substance called interferon. That interferon floods the local tissue, alerting the local immune cells to come and destroy the cancerous cell. Without STING, humans would be overwhelmed by cancer from an early age.

A cancer gets established either by switching off or somehow subverting STING. Scientists have yet to figure out how cancer does this, but in the meantime **the hunt is on to find a way of turning it back ON.**

ACTIVATING STING

A drug that activates STING in order to convert tumours into a HOT state and hopefully become responsive to an IO drug, is known as a 'STING agonist'.

A number of pharma and biotech companies are working actively in the space. The principal approach has been the use of drugs known as cyclic nucleotides drugs that when injected directly into a tumour are effective at activating the STING mechanism, flooding the tumour with interferon and causing it to turn HOT.[14]

The problem is that these compounds don't distinguish between cancer cells and healthy cells – they activate STING in all cells, which means that these compounds almost certainly would be far too toxic if they were used in a way that exposed the whole body to the STING effect. Having cells all over the body undergoing STING and churning out interferon would likely produce something known as a *cytokine storm* with lethal consequences.

Hence these compounds need to be injected directly into a single tumour that is accessible through the skin. The hope is that activating STING in one tumour, somehow will cause a knock-on effect that will spread to other tumours. A US$700 million collaboration between Novartis and Aduro Biotech is the first to report clinical data using this approach, with an uncertain beneficial outcome.[15]

Noxopharm is of the view that full potential of IO drugs is going to require direct and potent activation of the immune system within each tumour throughout the body, and that the only effective way of doing this is via a drug that reaches all cancer cells throughout the body, and this means a drug that can be safely administered without inducing a *cytokine storm*.

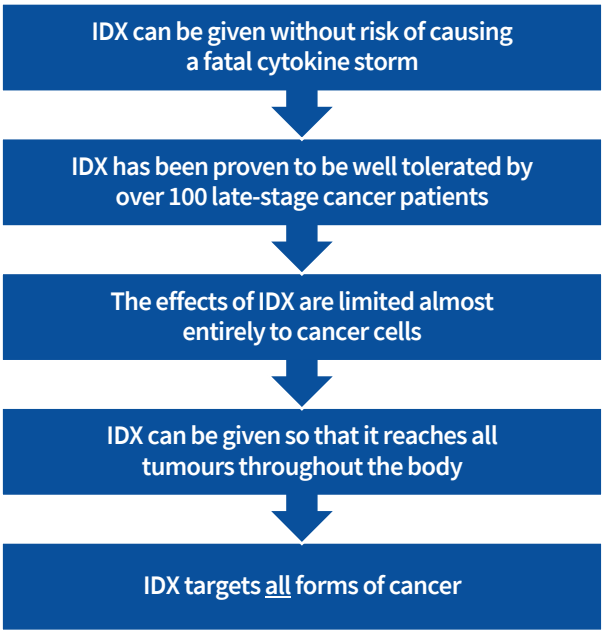
Noxopharm is aware of only two non-nucleotide STING agonists under development, intended to deliver a STING effect on a general basis but limited to cancer cells. One is the compound, MAVU-104, a pre-clinical drug candidate under development by Seattle-based Mavupharma.[16]

Mavupharma was acquired this week by Abbvie.[17]

The second drug candidate is Veyonda®.

IDRONOXIL: A UNIQUE IMMUNO-ACTIVATOR

Working with a number of Australian and overseas researchers at the frontier of this emerging field, the Company has confirmed that idronoxil (IDX) is a potent activator of the innate immune system involving natural killer (NK) cells and monocytes and certain lymphocytes.



Nobody knows to what extent converting all tumours into HOT tumours will change the response rate to IO drugs, and therefore to what extent it will increase their sales. But it would be reasonable to assume by a factor likely to make them the most widely used drugs and most valuable drugs in oncology.

And in the process, making the drug providing the STING (COLD → HOT) effectively one of the most valuable drugs in oncology as well.

Graham Kelly

Meet some new team members

JEANETTE BELL, CHIEF OPERATING OFFICER

Jeanette Bell has over 30 years' experience in healthcare spanning Clinical and Medical Operations, Medical Affairs, Six Sigma, Sales and Marketing. Jeanette has worked in the private, public and commercial healthcare sectors with 15 years' experience in 'big pharma'. During her diverse career, Jeanette held leadership roles in Europe, Asia Pacific and Japan. The scope of work in Asia Pacific involved co-developing the strategy and operations plan for clinical development initiatives, to support the delivery of registration studies in China. Having worked across many therapeutic areas and clinical development phases, Jeanette appreciates the importance of a robust operations platform to accelerate innovative medicines to market. In the role as COO, Jeanette will drive the delivery of the Noxopharm Clinical Development Plan.

DR GISELA MAUTNER, GLOBAL MEDICAL DIRECTOR

MD-PhD (TU-LMU Munich), MPH (Harvard), MBA (Kellogg), FACPE (Australia)

Dr Mautner brings a wealth of experience to her role as Global Medical Director, having held medical leadership roles in the pharma and biotech industry in the USA, Europe and Australia. As a medical doctor, she is dedicated to making the lives of patients better, and as an industry advocate, she is excited by new developments in treatments that provide new hope to many people.

In her early career she was a research scientist at the National Institutes of Health (NIH) in Bethesda, MD, USA and at the Kyoto Prefectural University in Kyoto, Japan. She patients. She transitioned to the pharma industry to focus on taking new drugs out of the lab and making them widely available to patients. Gisela had many successes launching new products for Merck (MSD), Bayer and Amgen. She is proud of her leadership role in one of the most successful drug launches in Australia.

For the last decade her passion has been new therapies in oncology. Her interests encompass small molecules, biologics, gene-modified viruses and radiopharmaceuticals for many different cancer types and from early to late stage disease. She fuels her passion with the knowledge that her efforts improve the life of patients on a daily basis. Balancing patient care and commercial interests has been part of her responsibilities as the medical lead throughout most of her career as well as directing the medical strategies and operations, budget management, compliance and staff performance in Medical Affairs Departments of multinational companies.

Dr Mautner has built and nurtured a broad network of medical doctors, especially oncologists in Australia and in the USA. In addition, she is extensively connected to pharmaceutical professionals in Australia as well as in the USA through her work as the VP of the Australian Association for medical and scientific Professionals in the Pharmaceutical industry (APPA).

We will have more information to share with you on our website that we will add to as we progress. Please visit the website to find more about our story, our science, and our plans for the future.

www.noxopharm.com

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Email: info@noxopharm.com

Phone:(+61) 2 9144 2223

Address: PO Box 824, Turramurra 2074 NSW AUSTRALIA

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