NOXOPHARM

# FOCUS

## The Noxopharm Newsletter
## June 2021

**Delivering Science.**
**Transforming Lives.**

Discover

Develop

Deliver

# CEO Update
# Noxopharm 2021


During a pandemic that has disrupted, damaged and taken so many lives, I am hesitant to say that it has benefited the Company, but it has.

The pandemic has reinforced exactly what a versatile and valuable technology platform we have. It has produced a drug capable of restoring cancer-fighting immune function in a cancer patient, while, at the same time, potentially blocking an inappropriately excessive immune system in a patient infected with SARS-C0V-2 virus. There is a great deal of repurpose being looked at in this pandemic, but mostly the repurposing has some link, obvious or tenuous, to the original purpose.

In the case of **Veyonda®** the repurposing is an apparent contradiction, but one that we are well on the way to understanding thanks to the efforts of some very clever scientists we collaborate with around the world. The more we have come to understand that contradiction, the more insight we have gleaned into the true potential of the platform, and the more opportunity we see.

That opportunity takes us into some of the latest and most active areas of interest by the pharmaceutical industry. Areas spanning cancer, chronic inflammatory diseases and autoimmune disorders. The result is an exciting pipeline of drugs now under development within Noxopharm that you will be hearing more about over coming months.

For the moment, however, we focus in this newsletter edition on our signature program – the **Veyonda®** 4-pillars oncology program – and our ambition of seeing **Veyonda®** become a standard go-to drug to boost the effectiveness of a range of anti-cancer therapies.

Our business is more than one drug. Our business is a drug pipeline based on a novel technology platform that we see meeting a range of major unmet needs of key current interest to the global pharmaceutical industry. Our goal now is to continue to provide hard clinical evidence and solid intellectual protection to build on industry attention.

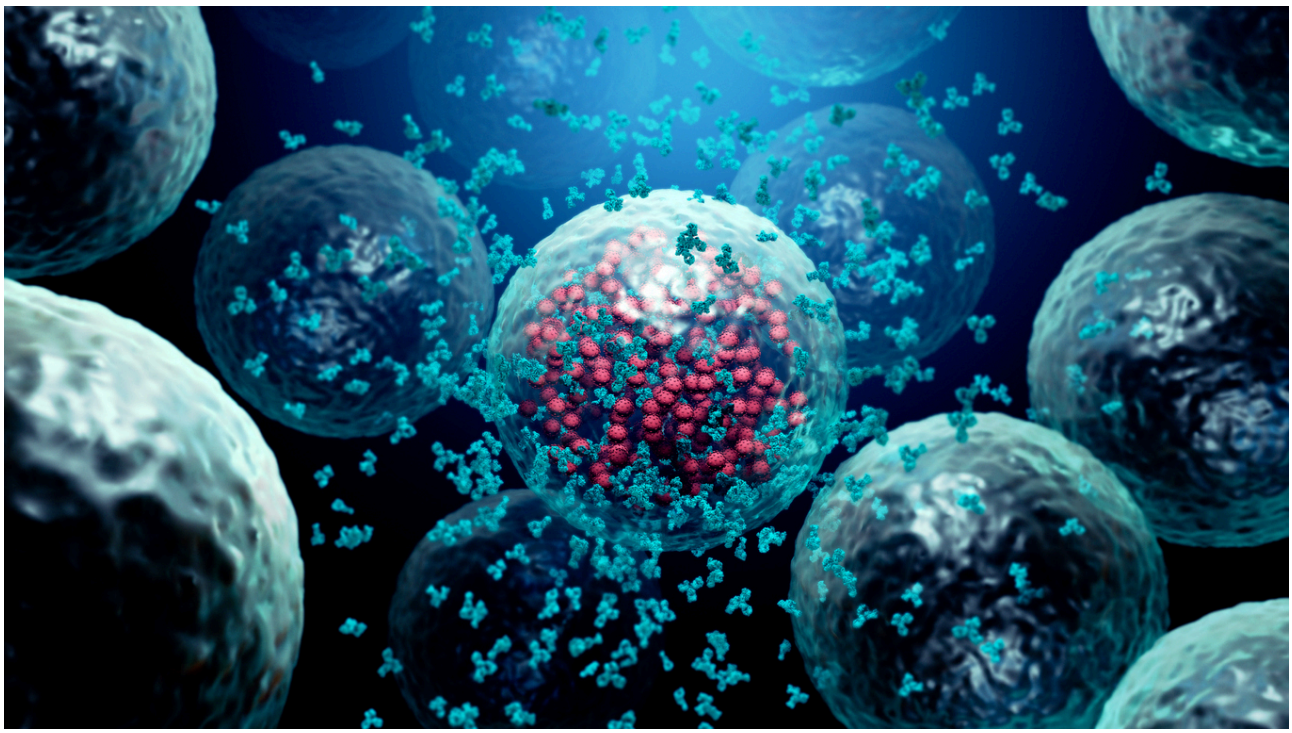
I have gone on record in the past in claiming that our technology platform is potentially one of the most exciting and valuable platforms in the pharmaceutical industry. I still stand by that view.

I hope you enjoy our June 2021 Newsletter.

Graham Kelly

# Clinical Trial program

| | | | |
|---|---|---|---|
| **Checkpoint Inhibitors (IONIC)** | Multiple cancers | Veyonda® + Opdivo® (BMS) | Phase 1 - due to commence |
| **Chemotherapy (CEP-2)** | Soft tissue sarcoma | Veyonda® + doxorubicin | Phase 1 - in planning |
| **Radiotherapy (DARRT-2)** | Prostate, lung, breast | Veyonda® + EBRT | Phase 2 - in planning multinational |
| **Radioligand therapy (LuPIN)** | Late-stage prostate cancer | Veyonda® + $^{177}$Lu-PSMA-617 (Novartis) | Phases 1/2 - finalising |
| **NOXCOVID** | COVID-19 | Veyonda® monotherapy | Phase 1 - finalising |



# Veyonda®
# 4-pillars oncology program

This is the Company' signature clinical program. It has a simple aim … to prove that **Veyonda®** can make other common forms of anti-cancer therapy work better.

> We are not competing with those other therapies. In fact, we welcome new drugs or even improved older ones. We see the role of **Veyonda®** as making those other therapies work even better.
>
> Until medicine is able to convert every case of metastatic cancer into a non-lethal condition, we see **Veyonda®** having a role to play.

The 4-pillars oncology program is testing Veyonda in the following 4 combinations:

| Treatment | Program | Combination |
|---|---|---|
| Chemotherapy | CEP | Standard cytotoxic drugs |
| Radiotherapy | DARRT | Standard radiotherapy |
| Checkpoint inhibitor therapy | IONIC | Nivolumab |
| Radioligand therapy | LuPIN | $^{177}$Lu-PSMA-617 |

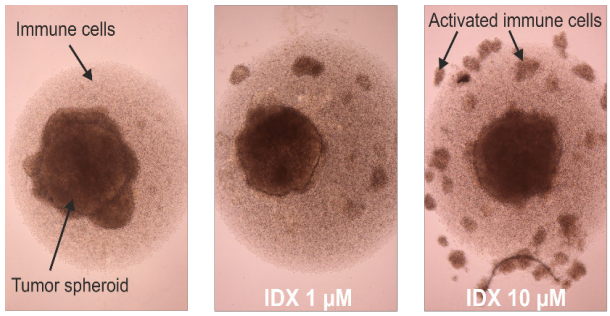
This is a completely new concept in cancer therapy, made possible only because of a unique collection of anti-cancer functions possessed by idronoxil, the active ingredient in Veyonda®. Where almost all other anti-cancer drugs operate via a single or very limited specific mechanisms, idronoxil targets a range of tricks employed by cancer cells to resist treatments ranging from the old standards, chemotherapy to radiotherapy, to the new checkpoint inhibitor drug therapies.

From stopping cancer cells dividing, to blocking cellular repair mechanisms, to increasing immune cell trafficking, to killing cancer cells outright … idronoxil is a unique multi-purpose, cancer-fighting molecule.

However, of these various functions, the one that really stands out as crossing different treatment boundaries is its ability to increase the trafficking of immune cells, by which we mean that idronoxil activates immune cells and then promotes their movement from being on the outer edge of the tumour, to migrating inside the tumour.

Why that is important is because blasting cancer cells with toxic chemicals and radiation has only taken us so far. Going the rest of the way means getting the immune system involved, and that means getting immune cells inside tumours where they can attack cancer cells once they are damaged or disabled by other treatments.

This restoration of immune function is known as converting tumours from COLD to HOT, and with most human tumours believed to be COLD (lacking immune function), this one ability of Veyonda® is what we believe makes it so well placed to become a standard companion drug for anti-cancer treatments.




**COLD to HOT phenomenon.** In this experiment, human lung cancer cells have been grown to form a spheroid representing a micro-tumour. Human immune cell are added. In the absence of IDX (Fig. 1), the immune cells remain inactive. In the presence of IDX (Figs. 2 and 3), the immune cells become activated and proliferate in a dose-dependent way (1 um vs 10 uM). Flow cytometric analysis of the spheroid showed that the micro-tumour contained high levels of the activated immune cells.

*Photographs by Dr Andreas Weigert, Goethe University Frankfurt*

# LuPIN program

The LuPIN program is an important program for us because it is the first of the 4-pillars program to reach Phase 2 level, a level known as intent to treat where you get to see how well your new drug is performing. Phase 2 is where you hope to find proof-of-concept, which in our case is whether adding Veyonda® to another form of anti-cancer therapy makes that other therapy work better.

The question being asked in the LuPIN-1 study was whether Veyonda® was able to boost the effectiveness of the experimental radioligand, $^{177}$Lutetium-PSMA-617, an emerging and promising new treatment for late-stage prostate cancer, and to do so in a well-tolerated way. $^{177}$Lutetium-PSMA-617 is owned by the large Swiss pharmaceutical company, Novartis.

**The Company is confident that the LuPIN trial has delivered proof-of-concept in an unequivocal way.**

$^{177}$Lutetium-PSMA-617 is injected intravenously and seeks out and attaches to prostate cancer cells throughout the body. It is a way of delivering radioactivity with high precision and in a well-tolerated way to all tumours.

For the regulators who grant approval for any new drug to come to market, the key question they ask in the case of new anti-cancer drugs is whether or not they improve patient survival – will a new drug result in a man with late-stage prostate cancer living any longer? A key end-point used by regulators is median Overall Survival (mOS), the time after starting treatment when half the patients have died and half are still alive.

Last Friday, Novartis released data from its VISION study which has now ended. This involved a large (>800) group of men with late-stage prostate cancer receiving $^{177}$Lutetium-PSMA-617 compared to standard of care. They report that the mOS of the two groups of patients was 15.3 vs 11.3 months respectively. That is, the use of $^{177}$Lutetium-PSMA-617 delivered a median 4 month survival advantage, which for any patient with end-stage cancer is a significant outcome.

Both LuPIN and VISION studies involved similar patients in that they were considered end-stage, with progressive disease and having exhausted all standard treatment options. Both studies involved adding the test treatment to standard of care treatment for end-stage patients.

**LuPIN** delivered an mOS of **19.7 months**, an extra 4.4 months beyond the benefit from $^{177}$Lutetium-PSMA-617 on its own.

| | PSA Response* | mOS (months) |
|---|---|---|
| **VISION** | 46% | 15.3 months |
| **LuPIN** | **61%** | **19.7 months** |

**>50% decline in PSA levels*

### How the LuPIN and VISION data compares to current treatments for late-stage prostate cancer.

Currently, there are 2 major forms of treatments approved for prostate cancer once it becomes metastatic and castrate-resistant. The first is androgen signalling inhibitor therapy (two drugs – enzalutamide and abiraterone) and the second is taxane chemotherapy (two drugs – docetaxel and cabazitaxel).

These two forms of treatment are used in various order and in various combinations.

These 4 drug treatments have been approved for clinical use based on the following mOS values obtained in Phase 3 studies:

| **Androgen receptor inhibitors** | **mOS** |
|---|---|
| Enzalutamide | 18.4 months |
| Abiraterone | 14.8 months |
| **Taxane chemotherapy** | **mOS** |
| Docetaxel | 18.9 months |
| Cabazitaxel | 13.6 months |

**An mOS figure of 19.7 months remains the highest for any of the approved treatments for metastatic castrate-resistant prostate cancer, with 46% of men being able to complete their full 6 cycles of treatment.**

# Noxopharm profile: Dr Daniel Wenholz

**Daniel Wenholz *PhD***

Director of Pharmaceutical Chemistry

### 1. Can you tell me a little bit about your background - what drove you to pursue your PhD and a career in pharmaceutical chemistry?

I've pretty much always had a love for science, particularly for chemistry. During my undergraduate Science degree I found that this really translated into a love of research. Although my first industry work as an Environmental Chemist taught me valuable lessons in working as part of scientific team and integrity in science, it involved little to no actual research work. This was one of the main drives for me to return to university to complete a PhD, along with a desire to challenge myself and expand my chemistry knowledge. It was during my PhD that I really found a passion for medicinal chemistry and I took on a keen interest in biotechnology as drug target molecules which formed the basis of my research. Early in my PhD I had the intention of taking on a career in academia, however, as I got used to the academic environment this shifted to a need to pursue a career that would allow my research work to create a more tangible impact and working as a Pharmaceutical Chemist in a biotech gave just the opportunity to do so.

### 2. What was it about Noxopharm and the products it aims to bring to market that led you to want to work with the company?

As I mentioned earlier, I have a deep interest in biotechnology products and their use in the research of therapeutics. This was one of the main factors that attracted me to Noxopharm who have a focus on the development of isoflavonoids, a family of product compounds that I find fascinating. Combined with my other goals state above Noxopharm provided the perfect opportunity.

### 3. What is your primary role at Noxopharm?

As the Director of Pharmaceutical Chemistry I am responsible for directing all of the company's chemistry efforts on the its various projects with the aim of delivering high-quality small molecule as development candidates. This sees me driving every aspect of Noxopharm's Drug Discovery projects alongside my biology orientated team members, from initial target and drug design at a conceptual level to the testing and evaluation of lead candidate molecules. I also oversee and supervise all our internal and external medicinal and synthetic chemists, who work both in CROs and academic institutes in Australia and around the world.

### 4. What does a typical day look like?

A typical day at Noxopharm sees me doing a wide range of activities. I will typically review the latest reports from our chemists at CROs and universities before meeting them to discuss new synthetic strategies, drug targets and problem shooting. I will also spend a decent amount of time meeting with other Noxopharm team members, from discussing drug pipeline strategies with the Drug Discovery team to giving progress updates to preclinical, clinical and management teams. Perhaps the largest part of my day goes towards the organisation of our ever-growing chemical libraries and the biological testing required for newly developed molecules as well as the large amount of data we continually receive from these studies. Then in the little time left of my day I will delve into the latest research publications for new ideas and synthetic chemistry techniques we can apply in our projects.

### 5. What are you hoping to achieve with the company in the long term? Where do you see yourself in 5 years' time?

I have so far really enjoyed my time at Noxopharm and I would certainly be happy to know I was still a member of the team 5 years from now. What I am really striving to achieve in that time is to develop one or possibly more of our lead molecules for use in human beings.

# Working in a pandemic environment

*By Jeanette Bell, COO*

Like most companies during the pandemic, Noxopharm has embraced a semi-remote working model - resulting in a happier and more productive workforce. Interestingly, while many other companies took this approach in response to the pandemic, our Founder and CEO Graham Kelly made the decision in 2016 to build a virtual business model to ensure NOX minimised costs while maximising flexibility and creativity. This business framework has served us well – especially when the pandemic hit.

Pre-pandemic, Noxopharm was an outsourcing project management business, making it a relatively minor adjustment when we needed to work remotely more frequently - all made possible of course by the internet. Although we have enjoyed the benefits (higher productivity and increased employee engagement) we have also had to prepare for unexpected new (cybersecurity) risks. To this end, we respond continuously with the highest level of rigor around cyber security systems and processes.

We are pleased to say that we have embraced, adapted, and flourished in this 'pandemic environment'. Still, Zooming only goes so far. With the well-being of our staff front of mind we often organise Covid-safe office meetings when required. This is where the pre-clinical and clinical teams meet face-to-face to brainstorm and review the progress of our drug development pipeline. Additionally, we have built a strong scientific network where we engage with the best scientists around the world through institutional collaborations or contract frameworks. In other words, we operate like a large-scale company with an innovative, agile, bio-tech mindset. This is a flexible work practice that we see continuing, even with the anticipated growth that the Company expects to experience in the next 18 months.

Finally, despite the forced change, our focus on delivering to plan remains resolute. During this time, the workload has doubled and yet we have delivered our key milestones with a strategic resource model, a mark of a highly efficient, committed and engaged workforce.

**** Coming soon. Watch out for the new Noxopharm website**

***Dr. Graham Kelly, CEO and Managing Director of Noxopharm, has approved the release of this document to the market on behalf of the Board of Directors***

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