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The Noxopharm Newsletter
Summer 2021-22

NOXOPHARM

Delivering Science.
Transforming Lives.

Discover **Develop** **Deliver**

An Introduction to Pharmorage

Pharmorage was created to treat those suffering from inflammatory diseases. More people suffer from and die from diseases stemming from abnormal inflammation than from any other cause.

Inflammatory diseases range from the hyper-inflammation responsible for putting people with the SARS-CoV-2 virus into ICU beds, to people living years with the pain of rheumatoid arthritis or the debilitation of heart disease or the effects of Alzheimer's, to those suffering auto-immune diseases ranging from Type 1 diabetes to motor neurone disease.

US$95B
Current sales of anti-inflammatory drugs

↓

3 of the 5 biggest selling drugs globally in 2020 were anti-inflammatory drugs

Humira - US$20B

Stelara - US$7.8B

Enbrel - US$6.4B

↓

US$150B
Projected sales in 2025

Treatment options for acute and chronic inflammation and auto-immune disease remain limited, at best, and non-existent for many conditions, something driving a surge in M&A activity.

For more related information:

Johnson & Johnson to buy Momenta for about $6.5 billion (cnbc.com)

Novartis Bolsters Inflammation Pipeline with Up-to-$1.6B Acquisition of IFM Subsidiary (genengnews.com)

Sanofi to acquire Synthorx to bolster its immuno-oncology pipeline for $2.5 Billion - Sanofi

Takeda Acquires License for First-In-Class Celiac Disease Therapy from COUR Pharmaceuticals Following Positive Phase 2a Proof-of-Concept Study

Bayer bolsters R&D platform with $2bn Vividion takeover - (pharmaphorum.com)

AbbVie puts $60M into ex-Dendreon CEO's company in autoimmune drug pact | BioPharma Dive

Pharmorage is taking two fresh approaches to meeting the large unmet need with two technologies that Pharmorage is confident will revolutionise the treatment of inflammation in its various forms.

Pharmorage began with a collaboration in 2019 with Melbourne's Hudson Institute of Medical Research ('HIMR'). Associate Professor Michael Gantier at HIMR identified a novel anti-inflammatory action of the Noxopharm drug, idronoxil (Veyonda®), that suggested a possible therapeutic role in the COVID pandemic. Further research then identified that mechanism of action as blocking a protein known as TBK1, leading to the discovery of an entirely new family of drugs with the potential to treat a broad range of inflammatory diseases. That is the Company's **Pharm-ISO technology platform**.

The strong research relationship with HIMR then led to the opportunity to in-licence from HIMR an anti-inflammatory technology based on RNA technology that they had been working on for 15 years, finally resulting in the discovery of new families of drugs that led to patent lodgements. Pharmorage quickly recognised the very significant commercial potential of this technology platform, perfectly complementing its existing opportunities. This in-licenced technology is known as the **Pharm-RNA technology platform**.

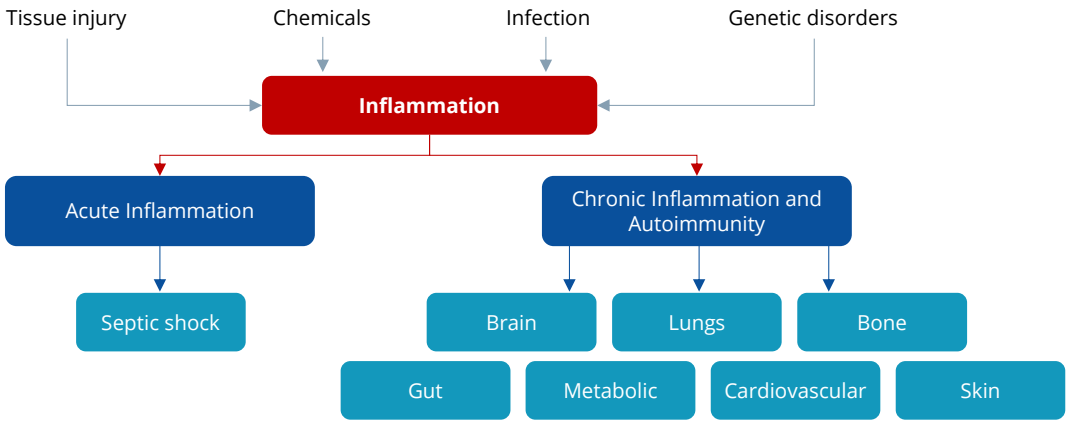
Based on the two technologies, and with a strong research collaboration with HIMR, Pharmorage believes it has a strong chance of achieving success where so many others have been challenged.

> *"This licence is a major coup for the Company and is validation of our ability to translate research from the laboratory to the clinic. Pharmorage already had a strong business relationship with Hudson with a major initiative in anti-inflammatory drug development. The RNA technology and its anti-inflammatory functions is an obvious fit and an opportunity with which we are delighted to be entrusted".*
>
> *Graham Kelly, Noxopharm CEO & Managing Director, ASX Announcement 17 November 2021*

Inflammation Explained – Acute, Chronic & Autoimmunity

Inflammation is part of the body's natural defence system – we need it to fight infections and repair tissue damage from all manner of things. Inflammation is a highly complex and finely balanced process requiring a lot of fine-tuning and integration of many different parts, including needing to switch off the various parts once they have achieved their purposes. Problems come when something causes an imbalance in the fine-tuning or when the 'off switch' doesn't kick in, leading to the inflammatory process becoming chronic.

Those problems can range from acute inflammation such as we are seeing now in the COVID pandemic, through to chronic inflammatory diseases and autoimmune diseases affecting any part of the body.



Acute inflammation

An example of acute inflammation is the hyper-inflammatory response putting so many COVID-19 sufferers into hospital and needing help with respiration. The outcome is a self-destructing process called septic shock, which, apart from this pandemic, accounts for an estimated 10 million deaths globally each year, mostly the result of a massive over-reaction of the immune system to viral and bacterial infections.

Chronic inflammation

Chronic inflammation can affect any part of the body. Common examples are spondylosing arthritis of the spine, chronic lung diseases such as asthma and COPD, neuroinflammatory disorders such as Alzheimer's Disease, and cardiovascular diseases such as atherosclerosis associated with chronic inflammation of the walls of the arteries.

Auto-immunity

Auto-immunity is a form of chronic inflammation where the immune system turns on and attacks its own body. There are more than 100 different forms of auto-immune disease, thought to affect between about 1 in 15-20 people. A common feature of auto-immune diseases is that, once developed, they tend to become life-long. Some, like motor neurone disease, tend to be fatal, while most tend to wax and wane with periods of remission and periods of increased disease activity known as flare-ups. Some examples of auto-immune diseases involve the following organs:

Bone/joints: Rheumatoid arthritis

Pancreas: Type 1 diabetes

Skin: Psoriasis, vitiligo

Liver: NASH

Brain: Motor neurone disease, multiple sclerosis

Gut: Inflammatory bowel disease, ulcerative colitis, Crohn's Disease

Thyroid: Hashimoto's thyroiditis

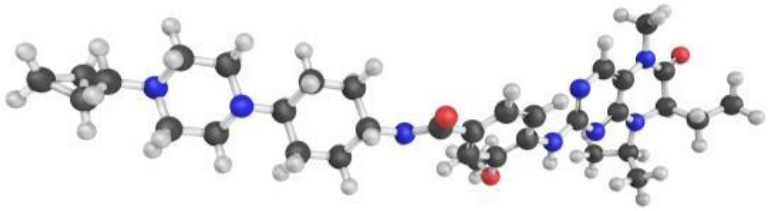
Lung: Lupus, scleroderma

Treatment options for acute and chronic inflammation and auto-immune disease remain limited, at best, and non-existent for many conditions. This unmet need is the opportunity being addressed by Pharmorage.

Pharm-ISO Platform

Building a new generation of anti-inflammatory drugs from the Noxopharm proprietary isoflavonoid platform

The Pharm-ISO platform is a direct offshoot of the Noxopharm isoflavonoid chemistry platform.



The key features of the Pharm-ISO drugs are:

Small molecules

New chemical entities (eligible for composition of matter patent claims)

Intended to be dosed orally

Inhibiting key parts of the inflammatory process that are known to be highly sought after as anti-inflammatory drug targets, but to date have proven to be elusive drug targets.

The Pharm-ISO program initially is focused on inhibition of the enzyme TANK-binding kinase 1 (TBK1). (ASX announcement 23 August 2021).

- **TBK1 is thought to be a key player in acute inflammation.** TBK1 is critical in the body's normal immune response to viral infections including influenza and coronaviruses, with abnormal activation of TBK1 thought to be associated with the excessive and the harmful 'hyper-inflammatory' condition known as a cytokine storm leading to sepsis and possible death
- **TBK1 also is implicated in many chronic inflammatory and auto-immune diseases** including systemic lupus erythematosus (SLE), neurological disorders such as Parkinson's Disease, various liver diseases such as NASH and cardiovascular disease (hypertension, heart attacks, stroke).

These, and other recent discoveries, have led to the cGAS-STING-TBK1 pathway emerging as a major target of interest in the field of inflammation with enormous therapeutic potential.* However, TBK1, like all parts of the inflammation process, has a level of functional complexity that has proven challenging in terms of drug development, with a dedicated TBK1 inhibitor yet to enter the clinic. Pharmorage believes that its family of TBK1 inhibitors has the ability to overcome these challenges and is confident of having one of the first TBK1 inhibitors in the clinic, and thereby likely to attract considerable industry interest.

Pharmorage, in collaboration with HIMR, is at the stage of pre-clinical testing the role of its TBK1 inhibitors across several auto-immune diseases with the aim of identifying a shortlist of potential therapeutic targets.

** Stimulator of Interferon Genes. The cGAS-STING pathway (often referred as STING pathway) is a component of the innate immune system that functions to detect the presence of cytosolic DNA and, in response, trigger expression of inflammatory genes.*

Pharm-RNA Platform

An exciting new approach to the treatment of inflammatory diseases and avoidance of side-effects of mRNA vaccines

The Pharm-RNA platform relates to the use of RNA segments (known as oligonucleotides) as drugs to disable unwanted inflammatory functions.

The Pharm-RNA platform is the result of 15 years of work by a team led by Associate Professor Michael Gantier at Melbourne's Hudson Institute of Medical Research (HIMR), with Noxopharm recently announcing its in-licencing through an exclusive global agreement (*ASX Announcement 17 November 2021*).

The licensed technology comes with two separate general pathways of use as described in the following pyramid.

The pathway on the left-hand side of the pyramid parallels that of the Pharm-ISO program. The aim of both technology platforms is to develop drugs to treat chronic inflammatory and auto-immune diseases. Pharm-ISO drugs and Pharm-RNA drugs are targeting different parts of the inflammatory process so they are not competing. The aim is to double our chances of success. Pharmorage anticipates that different diseases will involve abnormalities in different parts of the inflammatory process. Having two technologies acting on different targets maximises the chances of hitting the most relevant target.

The pathway on the right-hand side of the pyramid relates to some problems associated with mRNA vaccine technology, namely inflammatory side-effects and reduced manufacturing yields.

Associate Professor Michael Gantier leads a group of scientists that have been conducting work into a cell immune sensor called TLR7. This sensor protects the body by recognising and acting against foreign RNA such as from invading viruses. However, an unwanted consequence of this protective effect is an inflammatory response to mRNA of COVID vaccines resulting in common side-effects such as chills, headaches and fatigue.

Professor Gantier and his team have identified a novel way to 'switch off' TLR7 and thereby potentially reduce mRNA vaccine side-effects.

Current mRNA vaccines use a chemical modification step that reduces TLR7 activation, but that step also reduces the manufacturing yield of the vaccine. The Pharm-RNA technology potentially replaces the current chemical modification step, with the aim of providing greater mRNA vaccine yields and better reduction of inflammatory side-effects. Pharmorage and HIMR believe this will allow the use of higher doses of mRNA as a way of boosting vaccine effectiveness without increasing risk to the individual.

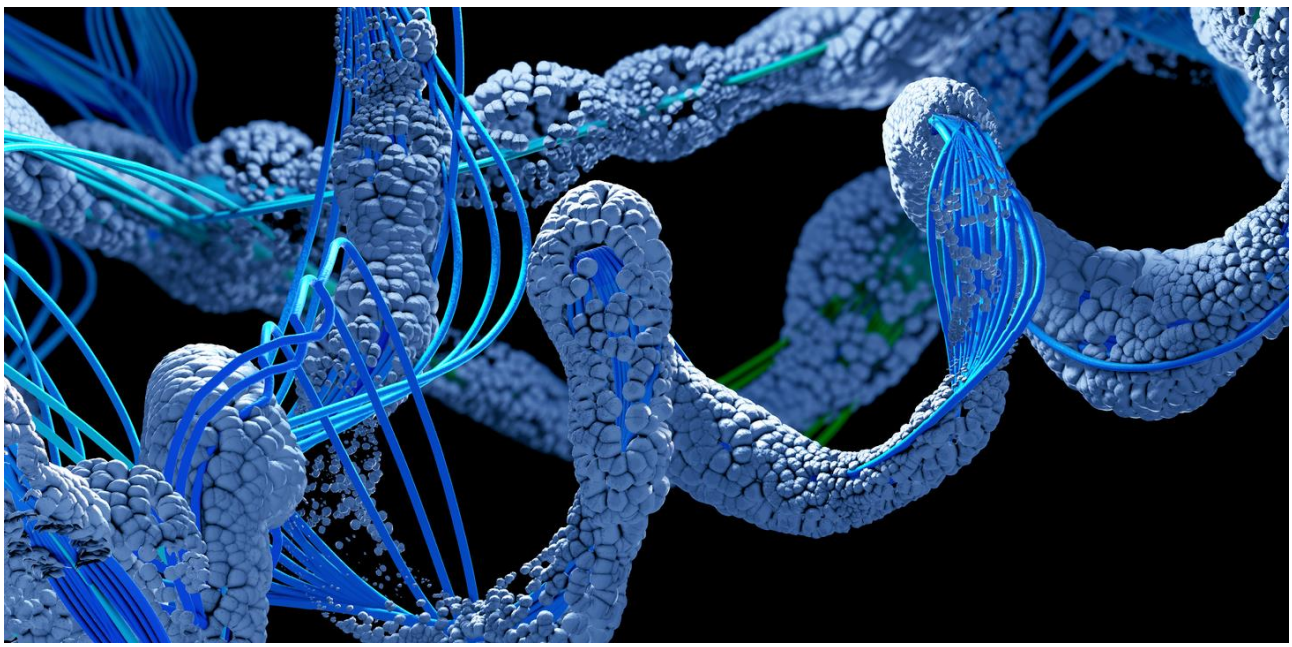
Pharmorage plans on putting this opportunity to the test in mRNA vaccines in animal studies using several TLR7-inhibiting oligonucleotides already identified. Armed with that data, Pharmorage then will reach out to all companies involved in mRNA vaccine manufacture.

While mRNA vaccine technology is being focused on the pandemic in the short term, it is anticipated that mRNA vaccine technology will become more widely adopted from 2025 onwards.

The mRNA vaccine market is forecast to reach up to $30 billion by 2035 with prophylactic vaccines valued at $15B and therapeutic vaccines at $10B[1].

Reference:

1. *W Xie, B Chen, J Wong. Evolution of the market for mRNA technology. Nature Reviews Drug Discovery 20, 735-736 (2021). doi: https://doi.org/10.1038/d41573-021-00147-y*



Profile: Assoc. Professor Michael Gantier

In this newsletter we are getting to know Associate Professor Michael Gantier, Research Group Head from Hudson Institute of Medical Research ("Hudson Institute") and Pharmorage Scientific Advisor. Michael collaborates closely with Noxopharm on its sepsis research and with Pharmorage's RNA technology, recently in-licenced from Hudson Institute.

Michael, to start with, tell us about your career to date, and what brought you to this field of study?

I was born and raised in France and did my undergraduate studies at the University of Technology of Compiegne, one of the most prestigious Engineering schools in France. I always loved science and was not sure what type of science I really wanted to do until I started learning about biotechnology in early 2000. This was a very exciting time as a student with the first compilation of the Human Genome just being completed, and the potential this opened was enormous.

I then enrolled in a PhD program at the University College Dublin and investigated RNA interference (RNAi), which had just been discovered. Specifically, I worked to define how RNAi interacted with innate immune responses. I always hoped that RNAi would make it into the clinics, and I was proven correct in 2018 with the first FDA approved RNAi drug, patisiran. This technology, along with other RNA therapeutics are set to become the third pillar of medicine, along with small molecules and protein-based therapeutics.

After obtaining my PhD in 2006, I moved to Hudson Institute of Medical Research in Melbourne and my research focus has been on innate immunity – which is how our bodies first detect infections.

I started working on how cellular damage could lead to engagement of inflammation back in 2014 after identifying that gene recombination could lead to inflammation. It turned out STING was activated by the gene recombination system we were using.[1] We also started looking at how DNA damage was modulating STING and discovered that low-dose chemotherapy and DNA intercalation could also lead to STING activation.[2]

In 2015, following the award of an ARC Future Fellowship and several NHMRC project grants, I was promoted to lead my own research group in the Hudson Institute of Medical Research and in 2020 was promoted to Associate Professor.

I first began working with Noxopharm in 2018.

Noxopharm credits you with discovering much about the potential of Veyonda®, its lead drug candidate.

In 2018 my lab was working on STING. Noxopharm contacted me to see if I would be interested in conducting research on idronoxil, the active ingredient of Veyonda®. The rationale at the time was that idronoxil would activate the STING pathway, which is involved in anti-tumour immunity.

We discovered that idronoxil was a strong inhibitor of STING signalling in late October 2019. This was a key breakthrough. I knew this was the exact opposite of what we had set out to demonstrate for Noxopharm, but I saw the potential of this discovery since it made idronoxil the first human-ready inhibitor of STING signalling.

Why is the field of inflammation so increasingly important, and why has it interested you for a long time?

Whether we know it or not, we see inflammation in our daily lives. It protects us from all the constant damages the environment we live in throws at our bodies. This ranges from particles we breathe in, solar radiation, things we eat and, of course, pathogens. One of the main reasons that inflammation is increasingly important in our societies is because humans are living much longer. Ageing is tightly interconnected with inflammation, and as our bodies age we get more inflammatory diseases. With this in mind, it is not surprising that the biggest selling drugs over the past decade have been targeting inflammation (e.g. Humira, used to treat many inflammatory diseases such as Crohn's disease or Rheumatoid Arthritis).

My interest in inflammation started during my PhD – I started wondering how RNA interference was impacting the immune system, which led me to come to Australia and start my career in this field.

How do you see the future of RNA therapeutics and their place within the healthcare sector?

RNA therapeutics present many key advantages over other categories of therapeutics such as small molecules or protein based. They can be targeted to any gene of the genome and their action is not limited to extracellular receptors. Another key aspect is that they can remain active for long durations (up to 6 months for some of the current ones), making them attractive for treating chronic inflammatory diseases, which can be lifelong. Beyond mRNA vaccines, there are many kinds of RNA therapeutics, including what we are developing with Pharmorage, and the field has exploded since 2018, when the first siRNA was approved in humans. There is no doubt to me that this will be the decade of RNA therapeutics, with many more treatments currently in advanced clinical trials.[3]

I understand you also are working in the field of mRNA drugs. That's also very relevant to the current situation given the emergence of mRNA vaccines. How is your work relevant to mRNA vaccines?

One of my long-lasting interests in the field of innate immunity has revolved around RNA sensing by the immune system – this is actually what brought me to Australia in 2006 to work with Prof Bryan Williams, one of the pioneers in this field.

RNA technologies such as mRNA vaccines can set off the RNA sensors of our immune system, which was a key problem in the early days of mRNA vaccine development 20 years ago. However, by understanding how the sensors of our immune system actually work, scientists have been able to devise strategies to dampen these immune responses to RNA therapeutics.

One of the approaches used, which is linked to the success of the BioNTech and Moderna vaccines and the failure of the CureVac vaccine, is the use of modifications of the RNA, preventing sensing by selective innate immune receptors.

Over the past 5 years my team discovered that while preventing aberrant immune responses, some of these modifications were broadly immunosuppressive for many innate immune sensors, which is something that has been underappreciated in the field to date.[4,5,6]

My lab is currently leading the research in this field.

Can you tell us a little about the scientist outside of the laboratory?

Life is busy between the lab and my two kids (9 and 5 years), so there is not so much to tell, I am afraid! We somehow survived the past couple of years – with far too much home-schooling here in Melbourne - and accumulated a new family member (our little poodle, Maxi), a trampoline and monkey bar play equipment (which take a lot of space but were invaluable for the kids!), and managed to move homes between lockdowns…

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3 *Wang F, Zuroske T, Watts JK. RNA therapeutics on the rise. Nat Rev Drug Discov. 2020 Jul;19(7):441-442. doi: 10.1038/d41573-020-00078-0.*

4 *Soroush T. Sarvestani, H. James Stunden, Mark A. Behlke, Samuel C. Forster, Claire E. McCoy, Michelle D. Tate, Jonathan Ferrand, Kim A. Lennox, Eicke Latz, Bryan R.G. Williams, Michael P. Gantier, Sequence-dependent off-target inhibition of TLR7/8 sensing by synthetic microRNA inhibitors, Nucleic Acids Research, Volume 43, Issue 2, 30 January 2015, Pages 1177–1188, https://doi.org/10.1093/nar/gku1343*

5 *Arwaf S Alharbi, Aurélie J Garcin, Kim A Lennox, Solène Pradeloux, Christophe Wong, Sarah Straub, Roxane Valentin, Geneviève Pépin, Hong-Mei Li, Marcel F Nold, Claudia A Nold-Petry, Mark A Behlke, Michael P Gantier, Rational design of antisense oligonucleotides modulating the activity of TLR7/8 agonists, Nucleic Acids Research, Volume 48, Issue 13, 27 July 2020, Pages 7052–7065, https://doi.org/10.1093/nar/gkaa523*

6 *Daniel J Rigden, Xosé M Fernández, The 2021 Nucleic Acids Research database issue and the online molecular biology database collection, Nucleic Acids Research, Volume 49, Issue D1, 8 January 2021, Pages D1–D9, https://doi.org/10.1093/nar/gkaa1216*

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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