ASX Announcement | 23 August 2021
Noxopharm Limited (ASX:NOX)

Pre-clinical Data Supports a Role for Veyonda® in the Treatment of COVID-19

Highlights

- **Noxopharm is positioning Veyonda® (idronoxil) as a COVID-19 treatment based on a well-tolerated and selective anti-inflammatory action**
- **The basis of this selective action now identified as inhibition of the enzyme, TANK-binding kinase 1 (TBK1)**
- **TBK1 has been proposed as a potential drug target in blocking COVID-19 disease progression, including the development of long-lasting COVID-19 symptoms**
- **Beyond COVID-19, TBK1 also is the subject of considerable big pharma attention because of its potential involvement in autoimmune diseases**
- **Discovery provides Noxopharm subsidiary, Pharmorage, with a major opportunity in the race to develop TBK1 inhibitors for the treatment of autoimmune diseases.**

Sydney 23 August 2021: Australian clinical-stage drug development company Noxopharm Limited (ASX:NOX) is pleased to announce that its partnership with Hudson Institute of Medical Research ('Hudson Institute') (*ASX: 1 April 2020*), a major Australian medical research body housing more than 120 inflammation scientists, has led to an important discovery about the anti-inflammatory mechanism of action of idronoxil, the active ingredient in Veyonda.

That discovery is the identification of the enzyme, TANK-binding kinase 1 (TBK1), as the molecular target of idronoxil in terms of its anti-inflammatory properties.

The discovery is not yet peer reviewed in a scientific publication, with submission anticipated in 2 months.

This announcement accompanies the release of preliminary topline data from the NOXCOVID phase 1 clinical trial (*ASX: 23 August 2021*) and is intended to provide a scientific rationale for how Veyonda may help prevent worsening of COVID-19 disease.

However, it also flags two other opportunities:

1) A potential use in blocking inappropriate inflammation to respiratory RNA viruses other than coronaviruses, including influenza viruses and respiratory syncytial virus
2) The creation of potential new therapeutic opportunities in the areas of chronic inflammatory and autoimmune diseases for Noxopharm subsidiary, Pharmorage, in partnership with Hudson.

Associate Professor Michael Gantier, Head of the Nucleic Acids and Innate Immunity Laboratory at Hudson Institute said: "TBK1 is a point of convergence of many inflammatory pathways, and a target under significant investigation by several big pharmaceutical companies. Our latest findings, which are being prepared for publication, demonstrate that idronoxil may have applications in a range of diseases

where TBK1 facilitates aberrant inflammation. Critically, TBK1 also directly controls production of interferon-beta, a cytokine associated with long-COVID symptoms.[1] This suggests that idronoxil may not only be useful to prevent progression of COVID-19 patients from mild to severe disease, but also may decrease the risk of long-lasting post-infectious symptoms, seen in up to half of COVID-19 patients."[2]

TBK1 is a key protein in cells through which immune and inflammation signals pass in response to the detection of viruses and cancer. TBK1 has become the subject of considerable industry attention because it could control a form of immune dysregulation that has been incriminated in the development of autoimmune diseases such as rheumatoid arthritis, lupus and motor neuron disease.[3,4]

Details

STING inhibition

Earlier pre-clinical studies had identified idronoxil as a potent inhibitor of STING (STimulator of INterferon Genes) signaling (*ASX: 21 April 2020*). STING plays a key role in orchestrating the body's immune response to the presence of foreign (viral, bacterial) or self (cancer) DNA in a cell's cytoplasm.[5,6]

With coronaviruses and influenza viruses being RNA viruses (not DNA viruses), STING signaling in COVID-19 patients is likely more important in triggering an inflammatory response to repair the tissue damage caused by virus, than it is to triggering an immune response to the virus itself.

This was the basis of testing Veyonda in COVID-19 patients with moderate to severe disease considered at risk of a hyper-inflammatory response to pneumonia and the resulting lung damage.

The Company previously (*ASX: 6 April 2021*) announced preliminary evidence of this anti-inflammatory effect was based on blocking STING signaling, with idronoxil inhibiting the release of inflammatory cytokines (such as IL-6 and TNF-α) and dampening interferon expression in response to stress *in vitro* (human monocytes). Idronoxil also was reported by the Company (*ASX: 6 April 2021*) to lower the levels of cytokines and viral particles in the lung fluid of mice infected with Type A influenza virus.

In addition to that, further *in vitro* studies conducted by Hudson Institute now show that idronoxil blocks expression of the most common Interferon Stimulated Genes (ISGs) in primary macrophages from mice with constitutive STING activation (Figure 1).

TBK1 inhibition

Detailed molecular studies, conducted by Hudson Institute, now have isolated the effect of idronoxil on STING signaling to the IKK-related kinases TBK1 and IKKε, which have redundant activities in the pathway .[7]

The particular relevance of this finding to COVID-19 is that, in addition to its role downstream of STING, TBK1 is an essential component in the transduction of the inflammatory response initiated by several other signaling pathways. This includes pathways controlled by mitochondrial antiviral signaling (MAVS)[8] that has recently been identified as a key driver of the inflammatory response of lung epithelial cells infected by SARS-CoV-2. [9,10]

It is proposed that therapeutic inhibition of the MAVS pathway induced by the detection of the SARS-CoV-2 RNA in lung epithelium, as seen with idronoxil at the level of TBK1, may beneficially mitigate inflammation-associated COVID-19.[10]

The role of TBK1 in MAVS and STING signaling pathways is shown in Figure 2.

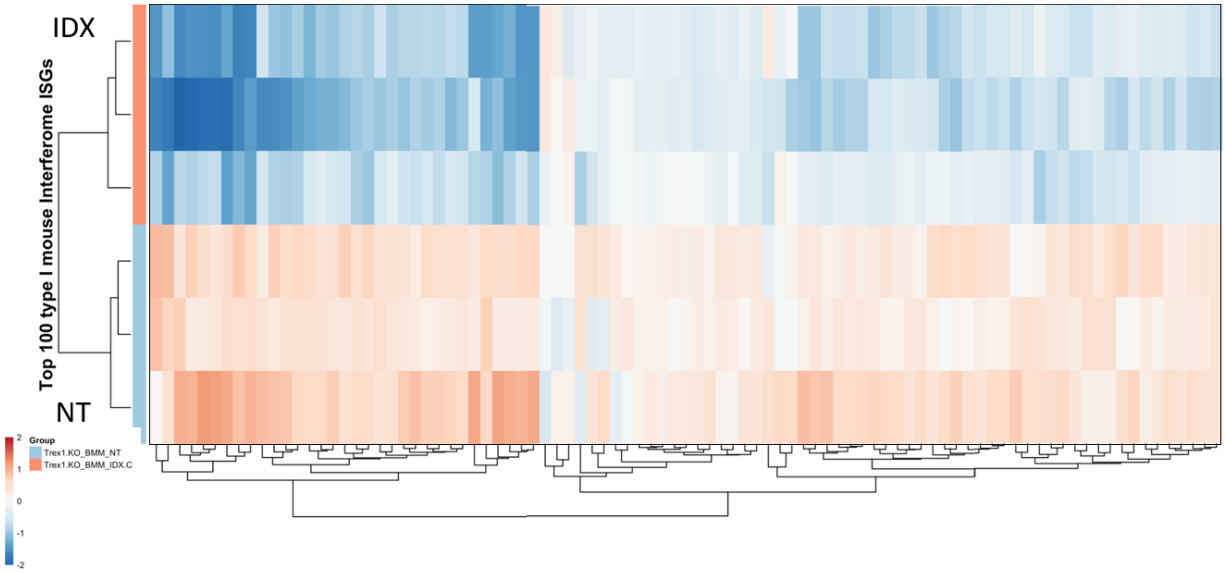

Figure 1: Idronoxil inhibits type-I interferon signature in TREX1-deficient cells.[11] TREX1-mutant bone marrow derived macrophages were stimulated overnight with 1.25 µM idronoxil, prior to RNA purification and RNA sequencing (with paired treated and non-treated samples from 3 independent mice). Gene expression of the 100 most commonly induced interferon stimulated genes (ISGs) (based on the Interferome database) was overlayed with the genes significantly expressed in TREX1-mutant cells and is presented here as a heatmap – where lower expression is depicted in blue, and increased expression in orange. These analyses revealed that the most common ISGs basally engaged in TREX1-mutant cells are decreased with idronoxil treatment, aligning with a strong inhibitory effect upstream of IFN-β production.

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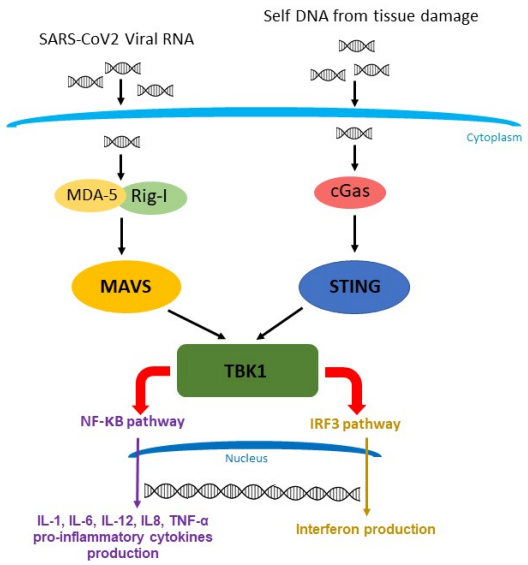

Figure 2: Schematic showing how the MAVS pathway (triggered by sensing of viral RNA by RIG-I and MDA5) and the STING pathway (triggered by self-DNA sensing by cGAS) both converge towards TBK1 to generate an inflammatory response

(composed of interferon-beta and pro-inflammatory cytokines). Inhibition of TBK1 by IDX therefore has the potential to block inflammatory mechanisms driven by both viral infection and tissue damage.

Noxopharm and Hudson Institute propose that the discovery that idronoxil acts on TBK1 further reinforces the potential of Veyonda to provide beneficial impact on moderately ill COVID-19 patients by:

- targeting MAVS-driven inflammation upon detection of viral RNA in infected cells
- dampening STING-driven inflammation upon the onset of tissue damage.

Overall, these two outcomes may cooperatively decrease the infection-driven inflammation that promotes progression of COVID-19 patients from mild to severe disease requiring assisted respiratory support.

Dr Olivier Laczka, Noxopharm Group Chief Scientific Officer, said: "This discovery, which is the result of a great collaborative effort between Noxopharm and experts in the field, further reinforces the relevance of Veyonda as a preventive treatment for cytokine storms driven by RNA virus infections, as is the case with COVID-19, and this to our knowledge makes Veyonda the first TBK1 inhibitor to be tested in the clinic. Pharmorage also is set to benefit considerably from this discovery. With a focus on new generation treatments for inflammatory conditions and autoimmune diseases, TBK1 adds a high-profile and potentially high-value drug target for Pharmorage's emerging pipeline."

References:

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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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About Hudson Institute of Medical Research

A global bioscience medical research leader, Hudson Institute's sole focus is on powering breakthrough scientific discoveries into improved health care that will transform lives. We strive to improve human health through groundbreaking, collaborative, medical research discoveries and the translation of these to real world impact.

Our scientists research five areas of medical need:

- Inflammation
- Reproductive health and pregnancy
- Infant and child health
- Cancer
- Hormones and health

About Noxopharm

Noxopharm Limited (ASX:NOX) is an Australian clinical-stage drug development company focused on the treatment of cancer and cytokine release syndrome (septic shock).

Veyonda® is the Company's first pipe-line drug candidate currently in Phase 2 clinical trialling. Veyonda® has two main drug actions – a moderating effect on the ceramide/sphingosine-1-phosphate balance and inhibition of STING signalling. Activity against the former target contributes to its dual-acting oncotoxic and immunomodulatory functions designed to enhance the effectiveness and safety of standard oncology treatments, i.e., chemotherapies, radiation therapies and immune checkpoint inhibitors. Activity against the latter target provides an anti-inflammatory effect, as well as contributing to an anti-cancer action, but also potentially blocking septic shock.

Noxopharm is running comprehensive drug discovery programs in both oncology and inflammation, and is the major shareholder of US biotechnology company, Nyrada Inc (ASX:NYR), active in the areas of drug development for cardiovascular and neurological diseases.

To learn more, please visit: noxopharm.com

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