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Sydney, Australia

Noxopharm Investigating Potential COVID-19 Treatment

Highlights:

- Hudson Institute identifies anti-inflammatory properties of idronoxil as consistent with blocking 'cytokine storm' believed responsible for many COVID-19 deaths
- Pre-clinical models suggest ability to treat patients with early-stage organ failure and prevent need for intensive care treatment
- NOX will require non-dilutive funding for a proposed clinical trial
- Australian provisional patent application filed
- Idronoxil clinic-ready and with high safety profile
- Special oral formulation (NOX-19) to be used
- Veyonda® clinical program to continue while meeting social obligation to investigate potential ability to help reduce the mortality rate of COVID-19

Sydney, 1 April 2020: Noxopharm (NOX:ASX) announces that the Hudson Institute of Medical Research (Hudson Institute) in Melbourne has identified that idronoxil inhibits a key inflammatory pathway involved in a process known as a *cytokine storm*. Cytokine storm is associated with an abnormally excessive inflammatory response and is believed to be responsible for most deaths in patients with COVID-19 infection.¹

In light of this important finding, Noxopharm now proposes to evaluate idronoxil use in patients at risk of developing acute respiratory distress syndrome (ARDS) and multi-organ failure associated with COVID-19 infection. Noxopharm will be seeking non-dilutive support both in Australia and overseas for the clinical study.

Background

Noxopharm and the Hudson Institute have been collaborating for the past 12 months in looking to gain a better understanding of the actions of idronoxil on the innate immune system. For Noxopharm, this is important in helping to explain clinical benefits observed in patients with late-stage prostate cancer that are believed to have an immuno-oncology basis.

Using pre-clinical models, the Hudson Institute discovered that idronoxil suppresses the production of molecules known as cytokines that are responsible for triggering inflammation,



with the inhibitory action of idronoxil on some of these cytokines reaching potent levels. The mechanism of action and the suite of cytokines inhibited has certain novel aspects and immediately was recognised by both parties as potentially important in the treatment of cytokine storm as it applies to septic shock. Septic shock is the overwhelming inflammatory process associated with viral and bacterial infections in some patients, a condition which remains essentially untreatable and accounts for a significant number of deaths across the world.

These findings are the subject of a provisional patent application lodged by Noxopharm this week with the Australian Patent Office and directed to the use of idronoxil for early-stage organ damage associated with inflammation caused by viral or bacterial infection in order to limit organ damage and prevent sepsis and ARDS. The Inventors are named as Graham Kelly, Olivier Laczka and Michael Gantier. It also is proposed to publish the data in the scientific literature as soon as possible.

Noxopharm and the Hudson Institute now propose to build on this discovery with the aim of developing an idronoxil derivative as an effective therapy for the treatment of septic shock generally.

In the meantime, and given the emerging global emergency with the COVID-19 pandemic, Noxopharm has decided to make idronoxil available for immediate clinical use as a potential cytokine storm inhibitor.

Comments

Dr Michael Gantier, Head of the Nucleic Acids and Innate Immunity Laboratory at Hudson Institute, said, "Our research indicates that in cell models of tissue damage seen in ARDS, idronoxil inhibits a broad range of cytokines including IL-6 and TNF α . However, unlike treatment strategies selectively targeting IL-6 and TNF α actions, our findings suggest that idronoxil blocks the process of inflammatory cytokine production along with that of other key mediators of organ failure."

Dr Graham Kelly, Noxopharm CEO, said, "Noxopharm is focused on developing Veyonda[®] as a treatment for late-stage prostate cancer, and this opportunity will in no way disrupt the Company's Veyonda[®] clinical development program. However, when you are told by respected scientists that your lead drug candidate might prevent deaths in a global pandemic, then you don't walk away from that possibility. Having idronoxil already in the clinic means that we are in a good position to commence clinical testing as soon as we receive the necessary funding and regulatory approvals."



“We propose using a special oral formulation of idronoxil called NOX-19. The current proposal is to give NOX-19 to patients with early-stage organ damage and with early signs of cytokine storm with the aim of blocking the rapid progression of the cytokine storm and thereby preventing sepsis and ARDS. This is all with the aim of having fewer patients needing to be admitted to the ICU and a reduction in the number of patients needing ventilators. This would greatly reduce the pressure on hospitals and healthcare systems,” Kelly added.

COVID-19 deaths

The danger with COVID-19 infection lies in its progression from a mild disease into an overwhelming and fulminant condition characterised by respiratory failure, ARDS, multi-organ failure (heart and kidney failure), clotting problems and septic shock. Treatment at that end stage is limited to supportive treatment including antibiotics and the use of ventilators. The concern is that hospital facilities are at risk of being overwhelmed in the short-term by large numbers of patients requiring admission to intensive care units (ICUs).

Cytokines are proteins secreted by immune cells and which trigger inflammation and tissue repair. These include interleukins (IL-6, IL-8, IL-1 β , tumour necrosis factor (TNF) and interferon beta (IFN β). Cytokine levels in blood rise in response to COVID-19 infection, but undergo extreme rise in a small proportion of patients in what is known as cytokine storm, with this extreme rise being highly predictive of death.²

Pharmaceutical industry response

The bulk of industry response lies in two approaches. The first is the development of a vaccine to prevent viral infection taking hold in the first place. The second approach is drugs such as hydroxychloroquine to block viral replication once infection has occurred.

A third but far more limited approach is to try and block the cytokine storm, with just five studies planned of which the Company is aware.

- 3 of these studies are seeking to inhibit IL-6 action with three IL-6 inhibiting drugs. All three are injectable monoclonal antibodies – tocilizumab (Roche), sarilumab (Sanofi and Regeneron) and siltuximab (EUSA Pharma) – developed originally to treat chronic inflammatory conditions such as rheumatoid arthritis and psoriasis and other viral conditions like herpes and HIV.³⁻⁶
- A fourth trial is using adalimumab, a monoclonal antibody against TNF α ⁷
- A fifth trial involves the drug, colchicine, an older anti-inflammatory drug used in the treatment of gout.⁸

Rationale for clinical use

Idronoxil is a potent IL-6 inhibitor, an action now thought to contribute to this compound's immuno-oncology functions along with its cancer-specific inhibitory action on sphingosine-1-phosphate production. It is the cytokine-inhibitory function of this molecule that is being exploited in this case.

The Hudson Institute has found in their pre-clinical models that idronoxil has two distinctive features:



- First, that it appears to inhibit the production of cytokines such as IL-6, potentially shutting down their downstream signalling pathways, rather than simply blocking their function as the monoclonal antibodies do
- Second, and likely associated with the first feature, that a broader suite of cytokines beyond IL-6 and TNF α are inhibited, all incriminated in the cytokine storm.

It is this broader cytokine coverage that Noxopharm and the Hudson Institute believe has the potential to offer a more effective treatment in the face of a cytokine cascade in COVID-19 patients.

The proposal is to use NOX-19 in patients who are at the beginning of a cytokine storm response and who are showing early evidence of organ damage with elevated blood levels of a number of cytokines. Noxopharm envisages patients being selected on the basis of symptoms of early multi-organ failure and/or rising blood levels of particular cytokines such as interleukin-6 (IL-6).

The hope is that by blocking the progression of the cytokine storm and the worsening of ARDS and multi-organ failure, both the pressure on limited ICU facilities and mortality rates will be reduced.

Next steps

1. Following the lodgement of the provisional patent, Noxopharm has begun discussions with various governmental agencies with a view to gaining the necessary funding
2. The Company also has begun essential studies on the NOX-19 oral dosage formulation. This will distinguish it from the suppository form of Veyonda[®] which delivers a particular pharmacokinetic profile necessary for cancer patients. Noxopharm remains confident in light of the emergency situation that these studies will be appropriately short, but that remains to be confirmed
3. Noxopharm also has started the process of reaching out to clinicians in various countries with a view to recruiting potential clinical sites
4. Noxopharm also will work with its regulatory affairs advisors on the steps required to gain regulatory approval to conduct a clinical trial.

About Noxopharm

Noxopharm is a clinical-stage Australian oncology drug development company with offices in Sydney and New York. The Company has a primary focus on the development of Veyonda[®] and is the major shareholder in the non-oncology drug development company, Nyrada Inc. (ASX:NYR).

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Graham Kelly, CEO and Chairman of Noxopharm, has approved the release of this document to the market.

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