Optimising RNA Vaccines and Therapeutics

Novel Approach to Modulating Inflammation

Noxopharm Ltd (ASX:NOX) is an innovative Australian biotech company discovering and developing novel drugs based on proprietary inflammation-related technologies. Led by a highly experienced management team, its Sofra™ platform represents a pioneering approach to optimizing RNA vaccines and therapeutics via its SOF-VAC™ program, and treating autoimmune and inflammatory diseases via its SOF-SKN™ program.

The platform, which also has potential for future cancer treatments, is based on oligonucleotides (oligos) that bind to immune sensors in order to either inhibit or potentiate their activity.

SOF-VAC for Targeted Inhibition

Noxopharm and its subsidiary Pharmorage, in strategic collaboration with Hudson Institute of Medical Research, have developed an extensive portfolio of assets under the SOF-VAC™ program as part of the Sofra technology platform.

These include an array of oligos targeting various nucleic acid (RNA / DNA) inflammation sensors such as TLR7, TLR8, RIG-I and cGAS. The program is also being extended to modulate other critical sensors, with promising leads for targets such as MDA5, TLR3 and TLR9.

The significance of these novel oligos lies in their highly targeted anti-inflammatory action, which is based on a breakthrough discovery of how the human immune system works to keep inflammation in check – namely the discovery of the natural ligands for specific inhibitory binding sites located on critical immune receptors. This has enabled Noxopharm to mimic and optimise these ligands in order to develop new drugs.

Using ultra-short oligos from the SOF-VAC portfolio, strong anti-inflammatory efficacy has now been demonstrated both *in vitro* and *in vivo*.

Use Case Example: Enhancing Vaccines

Vaccine enhancement is just one example of SOF-VAC's broader promise. Upon administration of an mRNA vaccine, the mRNA gets broken down within the cells into fragments, some of which can activate inflammation receptors, leading to reactogenicity that results in potentially severe side effects.

To mitigate this, SOF-VAC technology blocks these specific inflammation receptors, thereby reducing the reactogenicity caused by mRNA vaccines at its source.

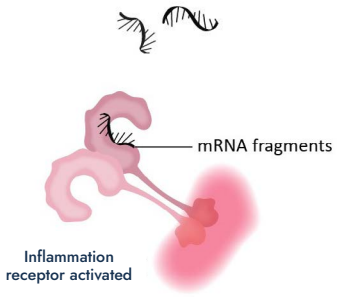
With a well-defined selective mechanism of action, the oligos in the SOF-VAC program can improve vaccine safety while preserving and potentially increasing vaccine efficacy.

Industry Opportunity

SOF-VAC offers industry the opportunity to enhance many types of existing mRNA vaccines, including self-amplifying mRNAs and RNA therapeutics in a rapidly expanding and competitive field that involves substantial private and public investment worldwide.

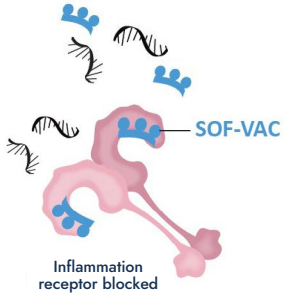
In terms of financial opportunity, the global mRNA market alone in 2021 was US$42 billion and is expected to grow to US$128 billion by 2030 at a compound annual growth rate of 13%.

Current mRNA vaccines



Fragments of mRNA vaccine bind to inflammation receptors in the body causing overstimulation, which results in inflammation and potentially severe vaccine side effects.

mRNA vaccine with SOF-VAC™



SOF-VAC™ blocks the inflammation receptors which reduces vaccine side-effects.

Figure 1. Working hypothesis of the action of SOF-VAC co-administered with mRNA vaccines.

In vivo Study Results

SOF-VAC reduces mRNA-induced inflammation

To determine if SOF-VAC was effective at reducing mRNA-induced inflammation (reactogenicity) in a mouse model, inflammatory cytokine levels were measured in the blood six hours post-injection. Averaged across nine cytokines (inflammatory markers), an approximate 50% reduction (48.2%) in cytokine levels was detected (Fig. 2), including highly significant decreases ($p<0.001$) in several critical cytokines driving post-vaccine inflammation and side effects.

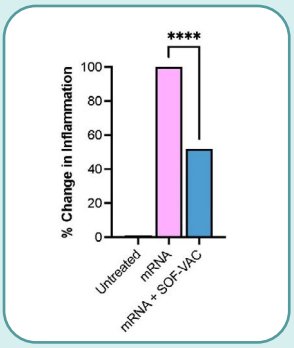


Figure 2. Compounded average percentage showing highly significant decrease in levels of nine inflammatory cytokines ($p<0.001$) detected in the blood of mice six hours post-injection with mRNA alone or mRNA co-packaged with SOF-VAC.

Full RNA effectiveness maintained in combination with SOF-VAC

To measure whether the mRNA activity was preserved in the presence of SOF-VAC, the mRNA used was translated by cells in the body to make a protein (luciferase), allowing for in-life bioluminescent detection and quantification of mRNA expression using a specialised imaging machine.

Luciferase activity in the mice at six hours post-injection showed no significant difference in protein expression between the mice that received the luciferase mRNA alone and those that received luciferase mRNA co-packaged with SOF-VAC (Fig. 3). The function, or the biological activity of the mRNA, was fully preserved, demonstrating that SOF-VAC did not reduce mRNA translation.

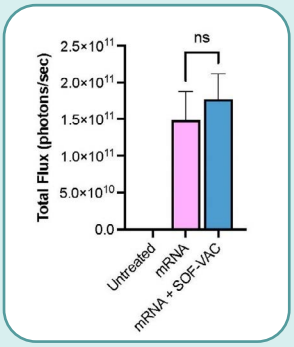


Figure 3. Measurement of mRNA expression (bioluminescence) in mice six hours post-injection with luciferase mRNA alone or mRNA co-packaged with SOF-VAC showed no significant difference.

SOF-VAC is not approved for use in Australia or any other country.

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