ASX Announcement

Melbourne, Australia, 28 April 2023

Exopharm achieves early-stage success with in-house Elastin (ELN) program

- **Exopharm has produced prototype exosome (extracellular vesicle [EV]) products containing Elastin Messenger Ribonucleic Acid (ELN-mRNA-EV) using a number of its proprietary manufacturing technologies**
- **Exopharm has demonstrated *in vitro* exosome-mediated delivery of functional elastin mRNA with its prototype**
- **Elevated gene expression translated to more than two-fold increase in ELN protein content compared to controls as determined by FASTIN assay**
- **Further future testing could be conducted in *ex vivo* skin models and *in vivo* as steps towards potential clinical trials of ELN-mRNA-EV**

Exopharm's *in vitro* delivering of mRNA encoding tropoelastin to increase elastin in the extracellular matrix

As announced on 12 October 2022, Exopharm has been working on an in-house exosome prototype product to increase elastin - as a potential additive gene-therapy product to treat elastin deficiency in skin, arteries, lungs and other tissue.

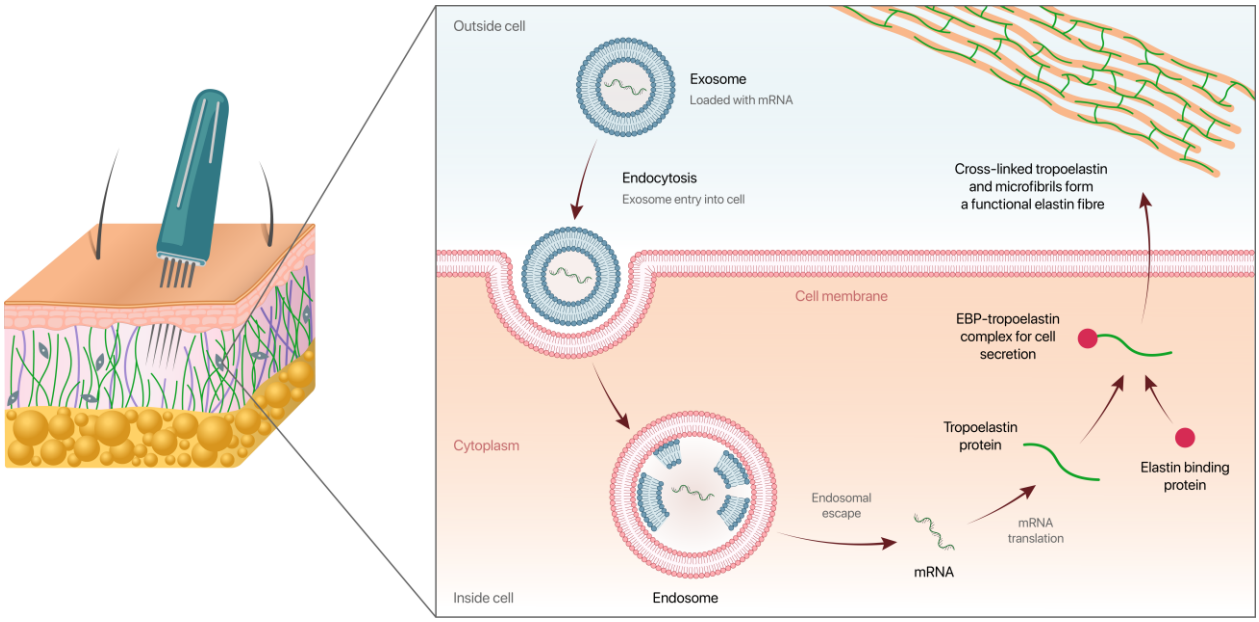
Elastin (ELN) is a large natural molecule found in the extracellular matrix surrounding cells – elastin imparts elasticity to the tissue. ELN normally has a long half-life of approximately 70 years and its natural replacement is limited in adults. Elastin constitutes about 28%–32% of major blood vessels, 30%–57% of the aorta, 50% of elastic ligaments, 3%–7% of lung, and 2%–3% of the dry weight of skin [1].

With aging, injuries, exposure to UV light (from sun exposure) and many other environmental factors, such as smoke, the normal levels of elastin decrease and medical and aesthetic issues arise from that elastic deficiency.

Exopharm selected an additive gene-therapy for elastin deficiency as a development target as elastin deficiency is not readily treated by dietary or other means and Exopharm's exosomes could be a useful drug-delivery chassis for ELN mRNA.

Medical problems that could potentially be treated with an additive gene-therapy for elastin include photoaging, striae distensae alba (stretch marks), aging skin, photoaged skin, arterial stiffness, chronic obstructive pulmonary disease (COPD) and Williams-Beuren syndrome amongst others.

[1] De Novo Synthesis of Elastin by Exogenous Delivery of Synthetic Modified mRNA into Skin and Elastin-Deficient Cells by Lescan et al 2018 https://doi.org/10.1016/j.omtn.2018.03.013



Market metrics by potential application field			
Chronic Obstructive Pulmonary Disease (COPD)	Cardiovascular (CV) incl. arterial stiffness	Scar prevention & treatment	Aging / photoaging / stretch marks
COPD market to reach US$19.3B in 2028 in top 7 world markets	CV market to reach US$231.7B by 2030; Hypertension market to reach US$31.5B by 2028	Scar treatment market to reach US$16.7B by 2031	Anti-aging market worth US$88B by 2028; Stretch marks treatment to reach US$4.17B by 2028

For more details see presentation released by Exopharm on 12 October 2022.

Prototype exosome product to increase elastin production by human cells

The work was designed to compare 'naked' (i.e. no drug-delivery technology used) ELN mRNA with exosome-delivered ELN mRNA as a way of increasing human cell production of elastin.

Making the prototype ELN-mRNA-EV product involved a number of steps:

1. Culture human HEK293 cells in Exopharm's proprietary collection media Hexocollect
2. Purify exosomes from cells using Exopharm's patented LEAP technology
3. Use Exopharm's LOAD technology to add mRNA into exosomes
4. Conduct analytics to determine copy-number of mRNA LOADing

Exopharm's suite of proprietary manufacturing technologies has enabled this work.

ELN-mRNA-EVs and other test materials were delivered to human fibroblasts *in vitro* to form 4 test materials.

Two days following treatment with various test materials, cells were collected and assessed for ELN content.

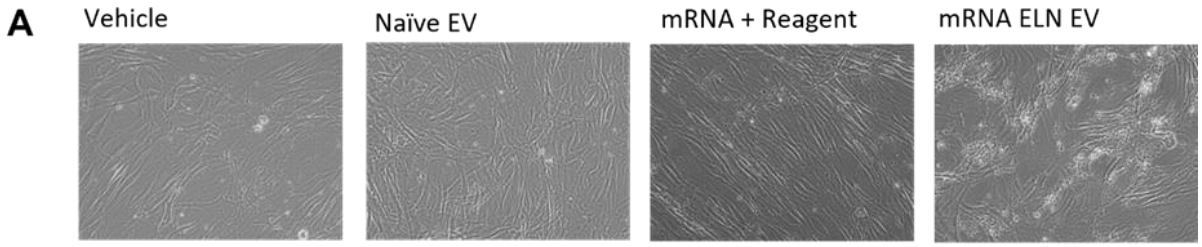
ELN-mRNA-EVs were compared to a PBS (Phosphate Buffered Saline) vehicle control, an unloaded HEK293 (naïve) EV control and an equivalent amount of loading reagent and ELN mRNA (equivalent to LOADed test material) control.

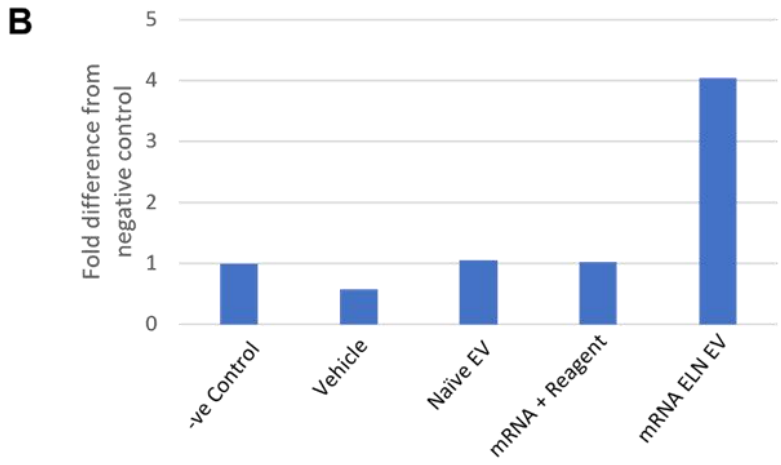
Findings and results

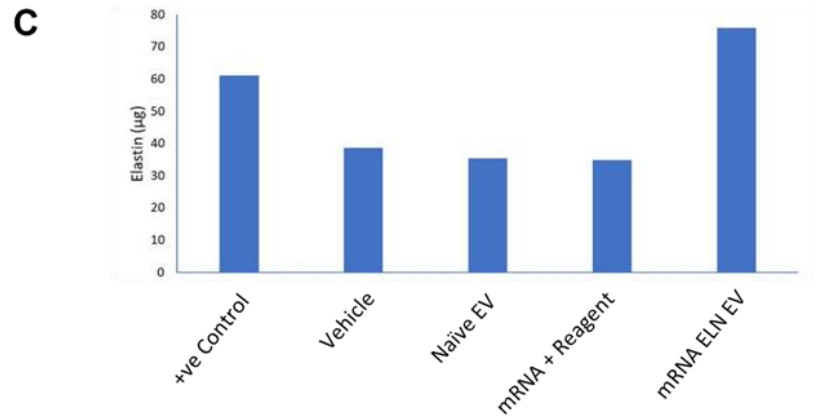
Figure 1A. At the end of treatment, cells administered ELN-mRNA-EVs showed a clear difference in cell morphology (i.e. how the cells appear) compared to control and other test panels.

Figure 1B. Following cell harvest, analysis showed ELN gene expression was elevated 4-fold in ELN-mRNA-EVs treated cells compared to controls (normalised to native ELN), and around 4-fold increase over 'naked' ELN mRNA materials.

Figure 1C. Elevated gene expression translated to more than two-fold increase in ELN protein content compared to controls as determined by FASTIN assay.







This data shows ability to load mRNA into EVs and that the ELN mRNA is subsequently processed within the cells into ELN protein.

ELN is not typically produced by mature cells, so using ELN-mRNA-EVs to induce ELN protein expression is a step towards potential clinical utility of exosomes as a drug-delivery chassis for additive gene therapy for elastin-deficiency.

Limitations and next steps

This study is an *in vitro* study with limited replicates. The next step would be to test the ELN-mRNA-EVs in *ex vivo* human skin experiments. Previous testing has demonstrated HEK293 naïve exosomes to be nontoxic and non-immunogenic in animal studies. A further potential step could be to conduct an animal study or a small human study.

Glossary

CV	cardiovascular
extracellular matrix	A large network of proteins and other molecules that surround, support, and give structure to cells and tissues in the body
FASTIN™ assay	The Fastin™ Elastin kit is a quantitative, colorimetric assay for measurement of elastin extracted from in-vivo and in-vitro sources
mRNA	Messenger RNA
PBS	Phosphate Buffered Saline, a research solution
RNA	Ribonucleic acid
UV	Ultraviolet (radiation)

This announcement has been authorised for release by the Board of Directors of EX1.

About Exopharm

Exopharm (ASX:EX1) is a leader in advancing Genetic Medicines and other exosome-based medicines using exosomes or extracellular vesicles (EVs) as a chassis for improved and non-viral drug-delivery.

Exosomes can be loaded with a variety of active pharmaceutical ingredients (APIs) and can be targeted to selected cell-types and tissue types, improving the safety-profile of the APIs and providing better treatments. Exosomes can be used to deliver small molecule drugs, mRNA, DNA and other types of APIs.

Exosomes are an alternative means of drug-delivery inside the body, alongside technologies such as lipid nanoparticles (LNP), cell-penetrating peptides, viral vectors and liposomes.

Exopharm's exosome technologies solve important needs for the success of exosome medicines – **LEAP** manufacturing technology, **LOAD** API loading technologies and **EVPS** tropism technologies.

Exosome-based medicines could improve the treatment of many chronic or inherited medical conditions.

Exopharm is making its proprietary technologies available to pharmaceutical and biotechnology companies that want to harness exosome-delivery for their own products.

Exopharm is also seeking to develop important exosome medicines itself.