NeuroScientific
BIOPHARMACEUTICALS
ASX:NSB

ASX ANNOUNCEMENT
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NEUROSCIENTIFIC CHARACTERISES BIOMARKERS FOR EMTIN PEPTIDES COMPLEMENTARY TO LEAD DRUG EMTINB

HIGHLIGHTS

- **NeuroScientific's pipeline of candidate peptides modulated key inflammatory and immune biomarkers relevant for important drug targets**
- **Candidate peptide EmtinAC regulated TNFα, a major driver of inflammatory conditions and the same drug target as highly successful drug Humira®**
- **Candidate peptide EmtinAN significantly decreased biomarkers strongly associated with lung inflammation**
- **Candidate peptide EmtinBN modulated key biomarkers of tissue repair and wound healing**

NeuroScientific Biopharmaceuticals Ltd (ASX: **NSB**) (**"NeuroScientific"** or **"the company"**) is pleased to announce results from recently completed biomarker studies of the company's other peptide candidates (in addition to lead drug candidate EmtinB™) EmtinAC, EmtinAN and EmtinBN. The activity of EmtinAC, EmtinAN, and EmtinBN was characterised using BioMAP profiling in validated human primary cell-based assays modelling complex tissue and disease biology (multiple cell types and pathways stimulated) which are predictive for disease outcomes, specific drug effects, and toxicity. The preclinical biomarker studies were conducted by leading independent contract research organisation Eurofins, US in human primary cell-based models of complex tissue and disease biology.

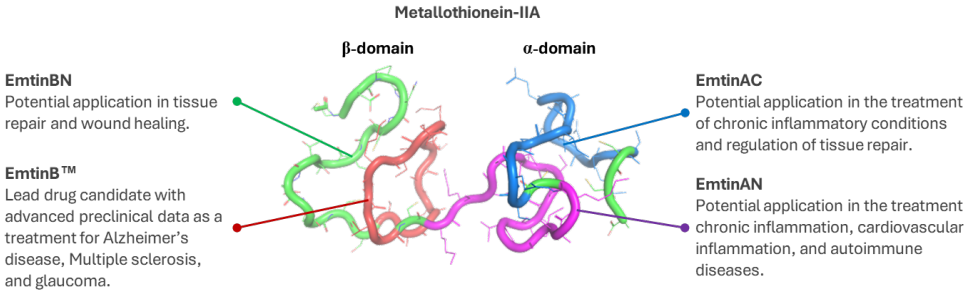
In addition to advanced lead drug candidate EmtinB™, NeuroScientific's product pipeline consists of three closely related peptide-based compounds generated from the active domains of the protective human protein metallothionein-IIA (MTIIA) (**Figure 1**). Both EmtinAC and EmtinAN are derived from the α-domain, and EmtinBN from the β-domain of MTIIA. MTIIA plays an important role in regulating processes of the innate immune system that stabilise tissue damage and aid in tissue repair.

Candidate peptides EmtinAC and EmtinAN both modulated key immune and inflammatory biomarkers relevant for important drug targets. EmtinAC regulated a major driver of inflammatory and autoimmune conditions called TNFα, which is also the drug target for highly successful drug Humira®, a disease modifying treatment for autoimmune conditions that generated global sales revenue of US$20 billion in 2020.[1] EmtinAN significantly decreased biomarkers strongly associated with lung inflammation (CXCL9, CXCL10, and CXCL11), and candidate peptide EmtinBN modulated biomarkers relevant for tissue healing and wound repair (tPA and TF). Importantly, these studies generated data that furthers our understanding of off-target safety, mechanism of action, and potential treatment indications for each peptide candidate.

NeuroScientific's Managing Director and Chief Executive Officer Matt Liddelow commented: *"These results are highly encouraging and allow us to confidently prioritise development of the most promising peptide candidates from our current drug pipeline. Biomarker data has become an essential element of de-risking our R&D programs and has helped to accelerate decision-making processes. With the transition of our lead drug candidate EmtinB™ into clinical development in 2022, the selective and strategic advancement of our other peptide candidates adds future security and increases the value of our developing pipeline."*

[1] Urquhart, L. 2021. Top companies and drugs by sales in 2020. Nature Reviews Drug Discovery. 20(4):253

FIGURE 1: Emtin peptides are modelled on specific domains of human metallothionein-IIA



EmtinAC modulates a key driver of inflammation
EmtinAC was active in 6 systems modelling human disease biology, was not toxic across the dose range used, and was anti-proliferative in coronary artery cells, endothelial cells, and fibroblast cells.

EmtinAC modulated the important inflammatory biomarker tumour necrosis factor alpha (TNFα), a major driver of inflammatory disease and a key drug target for autoimmune diseases. Humira, one of the most successful drugs ever developed, works by inactivating TNFα.[2]

TNFα is a cytokine that attracts other immune cells to sites of inflammation as part of the body's immune response to infections. Dysregulation of TNFα causes chronic inflammation and autoimmune diseases, such as psoriasis, rheumatoid arthritis, Crohn's disease, and Ulcerative colitis.[3] EmtinAC significantly decreased TNFα in a system modelling chronic inflammation and cardiovascular disease, indicating potential application in the treatment of chronic inflammatory conditions. EmtinAC may also positively regulate tissue repair processes by preventing proliferation of coronary artery cells, endothelial cells, and fibroblast cells as demonstrated in systems modelling chronic inflammation and cardiovascular disease.

EmtinAN significantly decreased proinflammatory biomarkers for lung inflammation
EmtinAN was active in 9 systems modelling human disease biology, was not toxic across the dose range used, and was antiproliferative in coronary artery cells and endothelial cells.

EmtinAN significantly decreased proinflammatory biomarkers CXCL9 (also known as Monokine Induced by Gamma Interferon) CXCL10 (also known as Interferon gamma-induced protein 10, or IP-10) and CXCL11 (also known as Interferon-inducible T cell Alpha Chemoattractant, or ITAC). CXCL9, CXCL10 and CXCL11 are chemokines that control the influx of immune cells to sites of inflammation. The persistent presence of these chemokines can result in hyperinflammatory responses and chronic tissue damage. CXCL9, CXCL10 and CXCL11 contribute to disease pathology in many chronic inflammatory disorders including rheumatoid arthritis, psoriasis, multiple sclerosis, diabetes, and cardiovascular disease.[4] Additionally, CXCL9, CXCL10 and CXCL11 chemokines have been shown to be strongly induced in severe COVID-19 patients, suggesting reduced induction of these chemokines as a potential treatment pathway.[5]

EmtinAN decreased both CXCL10 and CXCL11 biomarkers in the system modelling lung inflammation, and decreased CXCL10 in systems modelling cardiovascular inflammation, chronic inflammation, dermatitis, and psoriasis. EmtinAN decreased CXCL9 biomarker in systems modelling chronic inflammation, autoimmune diseases, and cardiovascular inflammation. EmtinAN may also positively regulate tissue repair processes by preventing proliferation of coronary artery cells and endothelial cells as demonstrated in systems modelling chronic inflammation and cardiovascular disease.

[2] Urquhart, L. 2021. Top companies and drugs by sales in 2020. Nature Reviews Drug Discovery. 20(4):253

[3] Domling, A. & Li, X. 2021. TNFα – the shape of small molecules to come. Drug Discovery Today.

[4] Metzemaekers, M. et al. 2018. Overview of mechanisms that may contribute to the non-redundant activities of interferon inducible CXC chemokine receptor 3 ligands. Front. Immunol. 8:1970

[5] Callahan, V. et al. 2021. The Pro-Inflammatory chemokines CXCL9, CXCL10 and CXCL11 are upregulated following SARS-CoV-2 infection in an AKT-dependent manner. Viruses. 13:1062

EmtinBN regulates tissue repair and wound healing
EmtinBN was active in 6 systems modelling human disease biology, was not toxic across the dose range used, and was antiproliferative in fibroblasts cells.

EmtinBN decreased biomarker Tissue Plasminogen Activator (tPA) and modulated biomarkers Tissue Factor (TF) and CCL3 (also known as Macrophage Inflammatory Protein 1 alpha - MIP-1). In systems modelling chronic inflammation and fibrosis, tPA and TF are associated with tissue repair. CCL3 is a chemokine that controls the influx of immune cells at the site of inflammation and is specifically released by important immune cells called Macrophages.[6]

The effect of EmtinBN on tPA and TF biomarkers in conjunction with preventing fibroblast cells from proliferating indicates that EmtinBN regulates tissue repair and wound healing processes. Modulation of the CCL3 biomarker indicates that EmtinBN can influence the inflammatory state of Macrophages, which help to remove cellular debris after tissue injury.

BIOMAP Diversity PLUS
Biomarker activities were annotated when 2 or more consecutive concentrations changed in the same direction relative to vehicle controls, were outside of the significance envelope and had at least one concentration with an effect size > 20% ($|\log_{10}$ ratio$|$ >0.1). The significance envelopes were calculated using historical controls (95% confidence interval). Log_{10}ratio values have been collected by Eurofins over time (>3 years, >100 experiments) to generate a historical envelope of negative control values. The 95% significance envelope was the symmetrical upper and lower bound values of 95% of historical vehicle controls.

This announcement is authorised by the Board of NeuroScientific Biopharmaceuticals Ltd.

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About NeuroScientific Biopharmaceuticals Ltd
NeuroScientific Biopharmaceuticals Limited (ASX: NSB) is a company developing peptide-based pharmaceutical drugs that target a number of neurodegenerative conditions with high unmet medical demand. The company's product portfolio includes EmtinB™, a therapeutic peptide initially targeting Alzheimer's disease and glaucoma, as well as other Emtin peptides (EmtinAc, EmtinAn, and EmtinBn) which have demonstrated similar therapeutic potential as EmtinB™. For more information, please visit www.neuroscientific.com

About EmtinB™
EmtinB™ is a peptide-based compound that binds to surface-based cell receptors from the LDLR family, activating intracellular signalling pathways that stimulate neuroprotection, neuroregeneration and modulate neuroinflammation. EmtinB™ is modelled on a specific active domain of the complex human protein called Metallothionein-IIA, which is produced as part of the human body's innate immune response to cell injury.

[6] Trifilo, M. et al. 2020. CCL3 regulates CD8+ T cell effector function and migration following viral infection. J. Virology. 77(7):4004-4014

Our preclinical research has established that EmtinB™ is highly specific and selective for its target receptor, safe and well tolerated at high concentrations, and is able to penetrate the blood brain barrier. A series of Phase I clinical studies will be conducted to establish the safety profile of EmtinB™ in humans.

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