



## PEER-REVIEWED PUBLICATION CONFIRMS PARADIGMS GROUND-BREAKING DISCOVERY REGARDING NEW MOA FOR PPS

### KEY HIGHLIGHTS

- Paradigm reports ground-breaking discovery, which was peer reviewed and published in the international scientific journal PLoS One, identifying the source of the pain mediator, Nerve Growth Factor (NGF) in bone cells (osteocytes) in Knee Osteoarthritis (OA) patients and that PPS (Zilosul®) inhibits NGF production in these cells and thereby reduces pain in patients with OA.
- The inhibition of NGF production by PPS in osteocytes from knee OA patients provides a strong scientific basis for the Mechanism of Action (MOA) of PPS in knee pain reduction reported in Paradigm's Phase 2b clinical trial of 112 subjects and in more than 500 OA patients treated under the TGA Special Access Scheme.
- The newly identified MOA for PPS in pain reduction together with its anti-inflammatory and disease modifying actions that protect cartilage degeneration provide strong support to Paradigm's regulatory submissions to the US-FDA.
- With the ongoing opiate crisis "Big Pharma" have spent billions of dollars attempting to develop non-opioid agents specifically targeting NGF making this new discovery by Paradigm potentially a very attractive commercial partnership opportunity<sup>1</sup>.
- Paradigm have filed patents over the discovery under the Australian Provisional Patent Application 2018903820 and Australian Provisional Patent Application 2019900326 which are both entitled "Treatment of pain with polysulfated polysaccharides" further strengthening Paradigm's intellectual property protections over the repurposing of PPS to treat pain associated with numerous diseases such as OA.

**Paradigm Biopharmaceuticals Ltd (ASX: PAR)** Paradigm is pleased to announce the publication of its data on the Mechanism of Action (MOA) of PPS in pain reduction in the international peer-reviewed scientific journal, PLoS One (<http://dx.plos.org/10.1371/journal.pone.0222602>) entitled "Human osteocyte expression of Nerve Growth Factor: the effect of Pentosan Polysulphate Sodium (PPS) and implications for pain associated with knee osteoarthritis".

Since the discovery in the 1950's Nerve Growth Factor (NGF) (a mediator of pain) has been reported as an exciting target for new drugs to alleviate pain<sup>2</sup>. In the past 20 years a number of big pharma companies, at a cost of many billions of dollars<sup>3</sup>, have developed monoclonal antibodies to block NGF from reaching its pain receptor (known as NGF inhibitors)<sup>4</sup>. Over the

<sup>1</sup> <https://www.statnews.com/2018/01/31/pain-medicine-ngf/>

<sup>2</sup> <https://pdfs.semanticscholar.org/a878/84e139d024a77ee80719ffc6c914dd8f9f82.pdf>

<sup>3</sup> <https://endpts.com/teva-pays-250m-splits-1b-rd-tab-to-buy-into-regenerons-phiii-ngf-pain-drug/>

<sup>4</sup> <https://www.ncbi.nlm.nih.gov/pubmed/24691709>

past 10 years these potential new drugs reducing pain have been placed on clinical hold by the US FDA because of a number of safety issues<sup>5</sup>. As recently as 2018 one of the most advanced anti-NGF products (Pfizer's tanezumab) failed a Phase 3 clinical trial because of safety issues<sup>6</sup>.

Paradigm's Chief Scientific Officer in collaboration with the University of Adelaide undertook a research plan to answer two key questions:

1. Do the bone cells (osteocytes) under the cartilage produce the pain mediator NGF?
2. Can the drug pentosan polysulfate sodium (PPS) reduce the production of NGF by those bone cells?

The data to that research was subject to peer-review and it has now been published. The answers to the scientific questions are Yes, the bone cells do produce high levels of the pain mediator NGF and Yes, the drug pentosan polysulfate can reduce the production of NGF by those bone cells. The mechanism of action of reducing the production of NGF by PPS is novel. The reduction of the production of NGF by PPS is not by blocking the NGF (like NGF antibodies) by rather at the mRNA level to reduce the production of NGF by the bone cells thereby reducing the joint pain. This research now clearly elucidates the mechanism by which PPS reduces pain from osteoarthritis.

This research investigation was a collaborative study between Paradigm and the Centre for Orthopaedic & Trauma Research, University of Adelaide which demonstrated data supporting the MOA of PPS as an inhibitor of NGF gene expression and production in bone cells called osteocytes in knee OA (KOA) patients.

In association with Professor Gerald Atkins (Head of Orthopaedic & Trauma Research) Dr Krishnan (Paradigm's Chief Scientific Officer) tested the hypothesis whether the osteocytes, being the principal cell type in the sub-chondral bone, were capable of expressing the pain mediator Nerve Growth Factor (NGF), and whether this expression of NGF may be altered in the presence of PPS. Professor Atkin's team tested the expression of NGF and the response to PPS in the presence or absence of the proinflammatory cytokine tumour necrosis factor-alpha (TNF $\alpha$ ), in human osteocytes obtained from KOA patients who underwent Total Knee Replacement.

This seminal finding revealed that human osteocytes are capable of producing NGF, suggesting that they potentially contribute to localised pain responses in KOA. Bone is a well innervated tissue, with bone sensory neurons. The secreted neurotropic protein beta-Nerve Growth Factor (NGF) is a major contributor to pain in a number of chronic conditions, including KOA. Furthermore, NGF expression is known to be induced by both inflammatory cytokines TNF $\alpha$  and IL-1beta in a preclinical osteoarthritis model. Moreover, Paradigm's data demonstrated that PPS inhibited TNF $\alpha$ -induced levels of proNGF, secretion (see Figure 1) and TNF $\alpha$  induced NGF mRNA expression (see Figure 2). Together, the data provided evidence that PPS may act at multiple levels to suppress the release of NGF and potentially other pain mediators in the subchondral bone, to ameliorate pain associated with knee osteoarthritis.

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<sup>5</sup> <https://www.reuters.com/article/us-johnsonandjohnson/fda-places-ij-anti-ngf-pain-drug-on-clinical-hold-idUSTR66BR29V20101228>

<sup>6</sup> <https://www.statnews.com/2018/01/31/pain-medicine-ngf/>

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The implications of the finding of pain reduction via inhibition of NGF secretion in osteocytes are far-reaching for the multiple actions of PPS relevant for the treatment of OA complementing its actions in the reduction of inflammation and cartilage protection. The effect of PPS on NGF provides a strong scientific basis to explain the MOA with regard to the clinically meaningful reduction in pain observed in subjects treated with PPS in Paradigm's Phase 2b clinical trial and patients treated through the TGA Special Access Scheme.

OA is a complex, heterogenous disease involving the whole joint which includes different types of cells within different tissues such as cartilage, bone, synovial layer, menisci and ligaments. The multiple actions of PPS imply that it would be an effective agent that manages both clinical symptoms and disease progression that to our knowledge has not been demonstrated in clinical trials of other drugs under development to treat osteoarthritis.

Simply put, when PPS, the active ingredient of Zilosul® is added to TNF stimulated bone cells it showed a statistically significant reduction in the secretion of NGF, being the potential source of pain within patients with OA. This ground breaking discovery when taken in context with the results published from Paradigms phase 2b clinical trial shows that Zilosul® is able to achieve without serious adverse events a reduction in the secretions of NGF. Which further leads to a reduction in pain, improvement of joint function and clinically significant improvements for patients suffering from OA previously reported by Paradigm.

Figure 1: Human osteocyte-like cells secrete proNGF. Secretion of proNGF was tested from cultures of KOA osteocyte-like cells treated with combinations of rhTNF and PPS. Data are means + SD of supernatants harvested from triplicate wells. Significant difference to untreated control (UT) is indicated by \* ( $p < 0.05$ ); significant difference to rhTNF treated cultures is indicated by # ( $p < 0.05$ ).

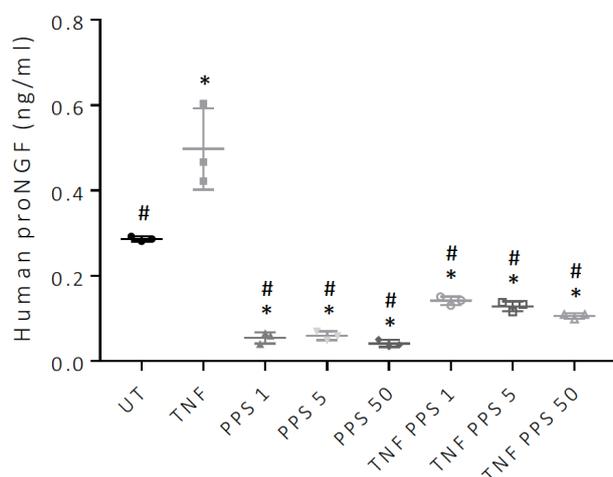
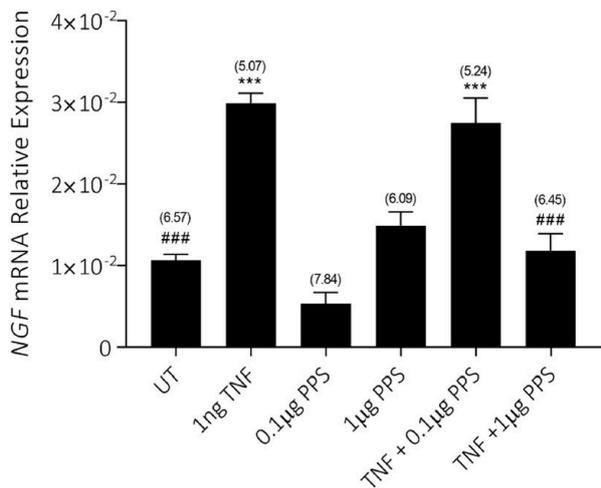


Figure 2: Effects of combinations of rhTNF and PPS on NGF gene expression in osteocyte-like cultures. Human differentiated osteocyte-like cultures were either untreated or pre-treated with PPS (0.1 or 1.0  $\mu\text{g}/\text{ml}$ ) for 24h, then with or without rhTNF $\alpha$  (1 ng/ml) for a further 48h, and then real-time RT-PCR was performed for NGF mRNA. Data are mean + SD of triplicate real-time RT-PCR reactions normalised to the mRNA expression of the housekeeping gene ACTB.



**Mr. Paul Rennie, Paradigm’s Chief Executive Officer said:**

*“We consider peer review as the gold standard for scientific communication. We are impressed that our study was the first to identify osteocytes as the key cells within the subchondral bone that are responsible for the production of the insidious pain in knee OA patients. Most importantly, the scientific validation that PPS inhibits NGF as a mediator of bone pain in OA is a ground-breaking discovery for Paradigm.*

*I believe that this publication should alert the interest of ‘big pharma’ who are actively trying to deal with the opiate crisis by developing pharmaceutical agents that are non-opioid, non-addictive, safe and efficacious. Paradigm continues to demonstrate that PPS meets many of the needs being sought after in treating this disease. We are showing that PPS as the active agent within our product Zilosul® is a pharmaceutical agent that curbs the disease process involved in OA at every level. That being; inflammation, cartilage protection and pain.*

*Having a Mechanism of Action (MoA) which has passed the rigor of peer review is important for Paradigm’s future submissions to the Regulatory Authorities. The MoA and the patent applications also further protect Paradigms intellectual property for use of PPS in treating OA. We continue on the pathway to commercialise Zilosul® and believe this ground-breaking discovery will further attract commercial interest in Paradigm’s clinical development”.*

**About injectable PPS (iPPS)**

Injectable PPS (iPPS) is not currently registered in Australia, but it is was previously registered in four of the seven major global pharmaceutical markets. In those European markets, iPPS is registered as an antithrombotic agent. In Australia, iPPS for human use is not currently available for sale.

Zilosul® is a registered Trademark of Paradigm Biopharmaceuticals Ltd (ASX: PAR).

To learn more please visit: [www.paradigmbiopharma.com](http://www.paradigmbiopharma.com)

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