nSTRIDE® Autologous Protein Solution (APS) Kit

Once OA Pain Starts, It's Hard to Stop.

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The Knee OA Treatment Gap

It is well recognized that a treatment gap exists when considering solutions for osteoarthritic pain.[12]
Between conservative care and the more invasive implant solutions there are few well researched and clinically proven products that can relieve the patient's pain and potentially delay the need for an implant.

Autologous anti-inflammatory Injection for the Treatment of Knee Osteoarthritis

Once OA pain starts it is hard to stop. The nSTRIDE APS Kit is designed to produce a novel therapy to treat pain and slow the progression of cartilage degradation and destruction in the knee. The nSTRIDE APS Kit is a point of care cell-concentration system which concentrates anti-inflammatory cytokines and anabolic growth factors to significantly decrease pain and promote cartilage health.

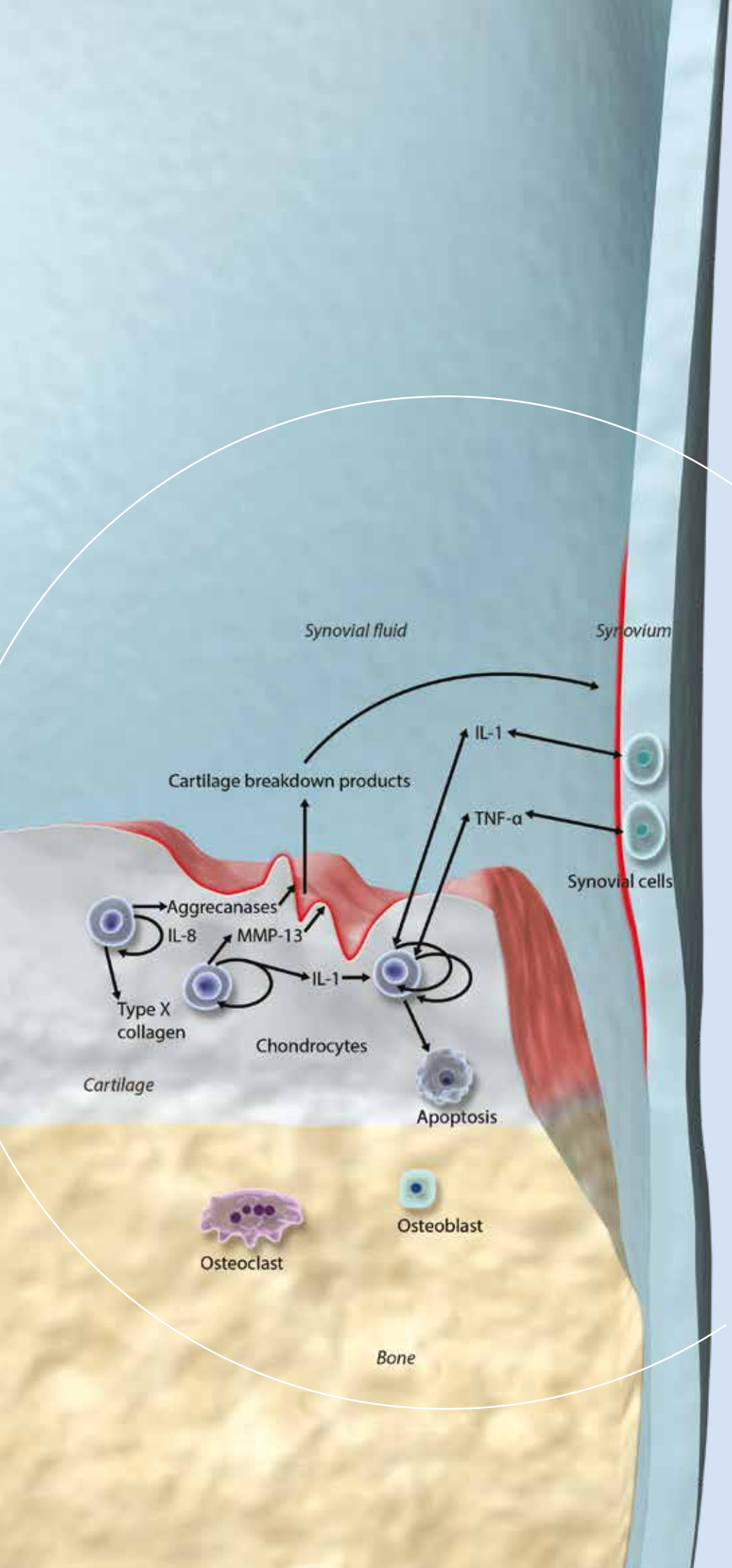
Extensive Research Program and clinical results

nSTRIDE Autologous Protein Solution (APS) was developed after a multi-year research program which focused on understanding the osteoarthritic disease process in the knee and understanding the Mode of Action that an autologous blood based product could have. With the nSTRIDE Kit an Autologous Anti-Inflammatory (AAI) solution is produced from the patient's own blood and this is injected intra articularly into the knee.

nSTRIDE APS has been shown to

- Significantly Reduces Pain Associated with Knee OA up to 2 years[1-3,13]
- Significantly Improves function in the Knee Joint associated with OA[1-3]
- To be effective for patients with Kellgren and Lawrence stage 2 and 3 following a single injection [1-3, 13]
- 70% Improvement in Knee Pain at 2 years following a Single Injection[13]

"There is great need for a safe, effective, and cost effective treatment option for patients with moderate to severe osteoarthritis that enjoys high patient acceptance".[12]



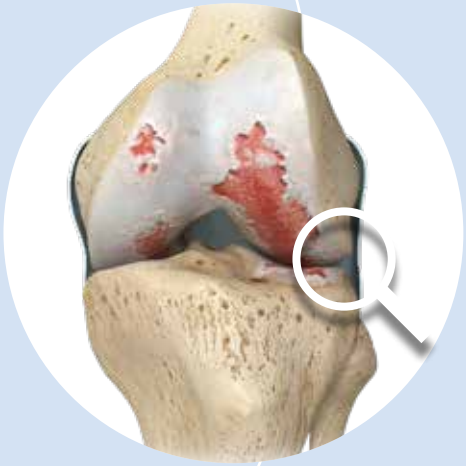


Figure 1:
In an osteoarthritic knee, an increase in inflammatory cytokines results in cartilage degeneration and knee pain. The inflammatory proteins IL-1 and TNFα attack the cartilage. These inflammatory proteins must be stopped simultaneously to decrease pain and slow cartilage degeneration.[5]

Understanding the Mode of Action of Knee Osteoarthritis

In an osteoarthritic knee, an increase in inflammatory cytokines results in cartilage degeneration and knee pain. The inflammatory proteins IL-1 and TNFα attack the cartilage. These inflammatory proteins must be stopped simultaneously to decrease pain and slow cartilage degeneration[5].

Understanding the Mode of Action

In pre-clinical studies, nSTRIDE APS has been shown to:

- Inhibit catabolic enzyme production from chondrocytes stimulated with IL-1ß and TNFα[8]^
- Inhibit inflammatory cytokine production from IL-1ß-stimulated macrophages[9]^
- Inhibit catabolic destruction of cartilage tissue[4^*]
- Protect cartilage in a meniscal-tear model[10*]
- Reduce pain in large animals with naturally occurring OA[11*]
- Stimulates Cartilage Cell Proliferation[4^*]

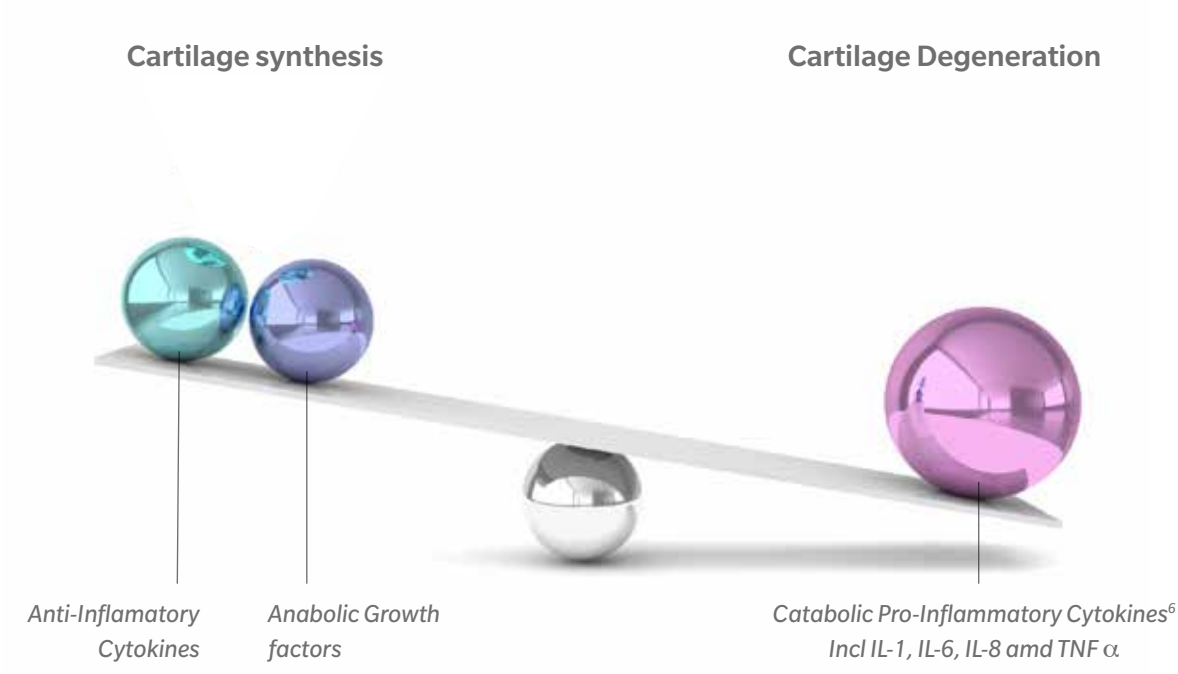


Figure 2: *Cytokine Imbalance in OA[14]*

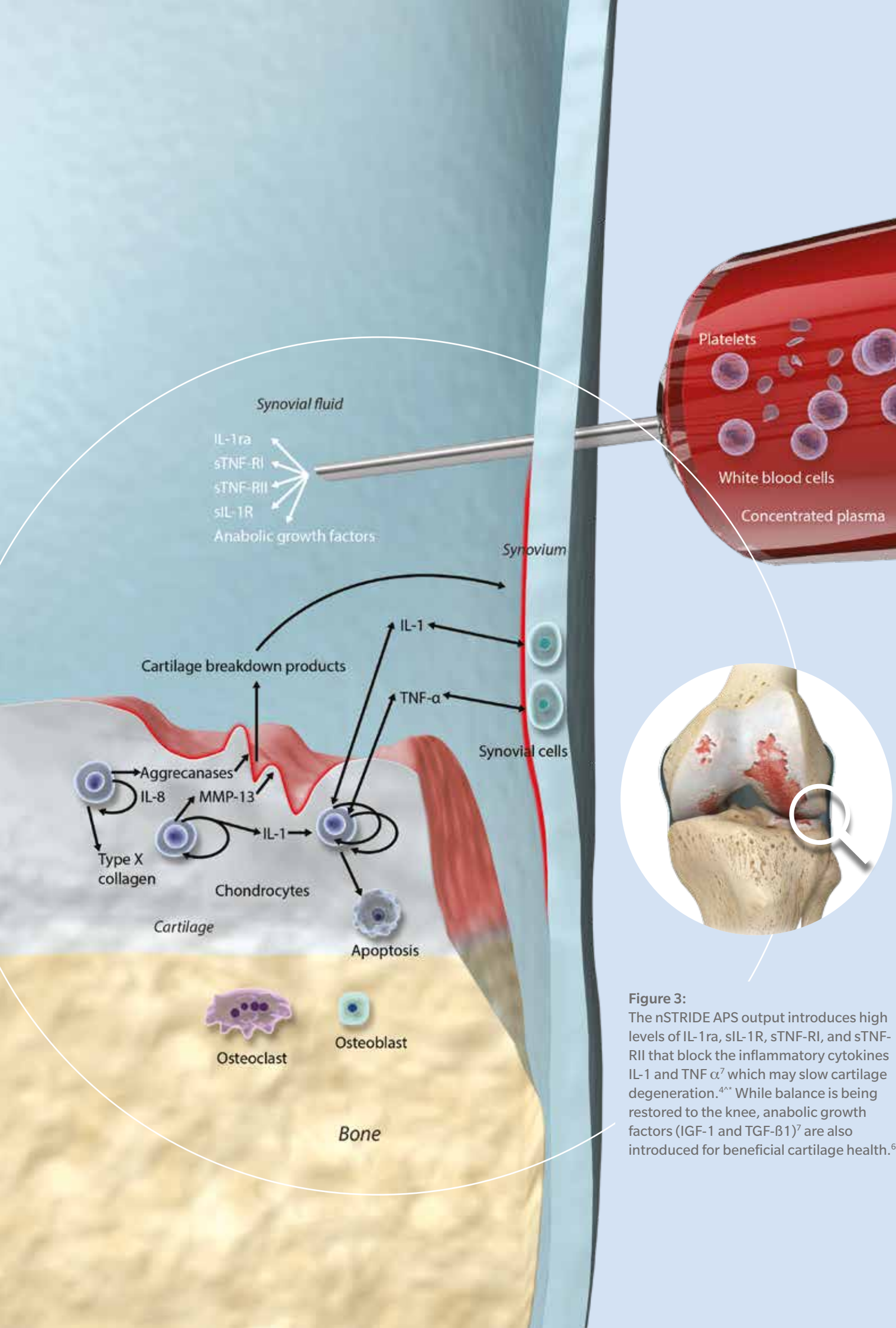


Figure 3:
The nSTRIDE APS output introduces high levels of IL-1ra, sIL-1R, sTNF-RI, and sTNF-RII that block the inflammatory cytokines IL-1 and TNF α[7] which may slow cartilage degeneration.[4^,*] While balance is being restored to the knee, anabolic growth factors (IGF-1 and TGF-ß1)[7] are also introduced for beneficial cartilage health.[6]

How does nSTRIDE APS work?

Autologous Anti-Inflammatory Therapy

The nSTRIDE APS Kit processes a patient's own blood at the point-of-care to concentrate white blood cells, platelets, and plasma proteins into a small volume of plasma. The output contains the anti-inflammatory cytokines IL-1ra, sIL-1R, sTNF-RI, and sTNF-RII in concentrations well above what is found in native whole blood.[6] In addition to the anti-inflammatory cytokines, anabolic cytokines for cartilage including IGF-1 and TGF-α are also concentrated to levels well in excess of that found in whole blood[7].

The APS produced by the nSTRIDE APS Kit reduces prevalent inflammatory cytokine activity which is upregulated in osteoarthritis. These cytokines can cause both pain and cartilage degeneration.[6] Inflammation is implicated in both the pain and the cartilage matrix breakdown in osteoarthritic joints. The cytokines IL-1 and TNFα are the key pro-inflammatory and catabolic targets; however, they need to be inhibited simultaneously.[5] There are several naturally occurring inhibitors of IL-1 and TNFα, including IL-1ra, sIL-1R, sTNF-RI, and sTNF-RII. Additionally, while decreased activity of IL-1 and TNFα will decrease inflammation and slow the progression of cartilage degradation, anabolic cytokines could also assist to stimulate cartilage matrix synthesis. [4^*]

Therefore, the ideal therapy to target pain and cartilage matrix degradation caused by inflammation will include several different anti-inflammatory cytokines and anabolic cytokines together. Autologous Protein Solution, produced using the nSTRIDE Autologous Protein Solution Kit, contains all the anti-inflammatory proteins mentioned above, with an added benefit of anabolic cytokines as well.[7]

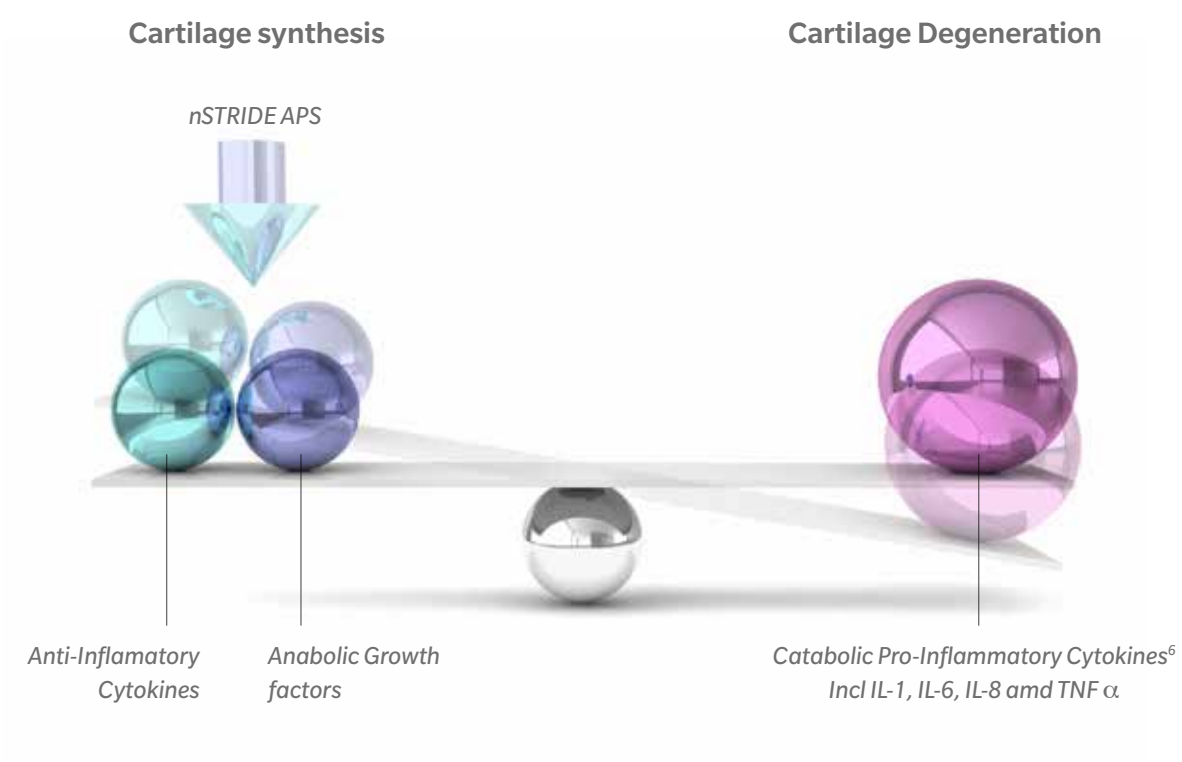


Figure 4: *nSTRIDE APS Addresses Cytokine Imbalance in OA*[14]

Long lasting results

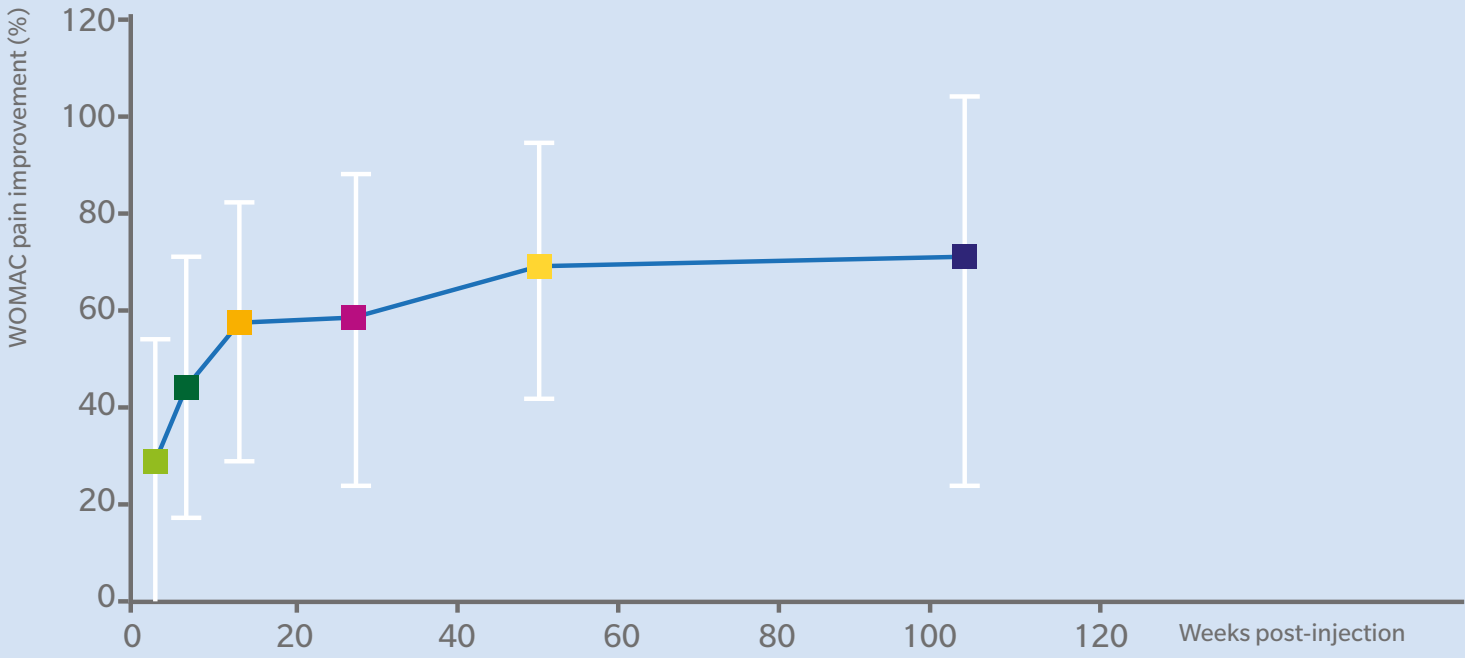


Figure 5: WOMAC percent improvement with nSTRIDE APS. 69.7% improvement, ($p < 0.0001$) 24 months post-injection[#]

70% Improvement in Knee Pain at 2 years following a Single Injection[13 #]

Clinical Results

In a series of clinical studies the autologous anti-inflammatory solution produced by the nSTRIDE APS kit has been shown to have positive effects on knee pain and function in patients with Kellgren-Lawrence stage 2 and 3. Further key findings were:

- Significantly Reduces Pain Associated with Knee OA up to 2 years following a single injection[1-3,13] (Figure 1)
- Significant pain reduction using leukocyte–containing APS compared to baseline [1,2]
- IL-1ra concentration correlated to white blood cell content in APS [1]
- L-1ß concentration did not increase with white blood cell content [1]
- The ratio of IL-1ra to IL-1ß in APS was significantly correlated with improved WOMAC pain scores at six months post-injection[1]
- 72.7% of subjects were OMERACT-OARSI high responders six months post-injection [2]
- Significant percent improvement in pain over saline injection in double blinded pilot study [3,13]

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^ **Cell culture assays are not necessarily indicative of clinical outcomes.**

* **Animal studies are not necessarily indicative of clinical outcomes**

\# **As measured by WOMAC pain scores reported by patients continuing follow-up through 2 years (n = 22)**

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