CHONDROTRIO

Long acting hyaluronic acid + L - Proline + Glycine +N-Acetylglucosamine microwave stabilized single injection

The Innovative Technology of Single Injection

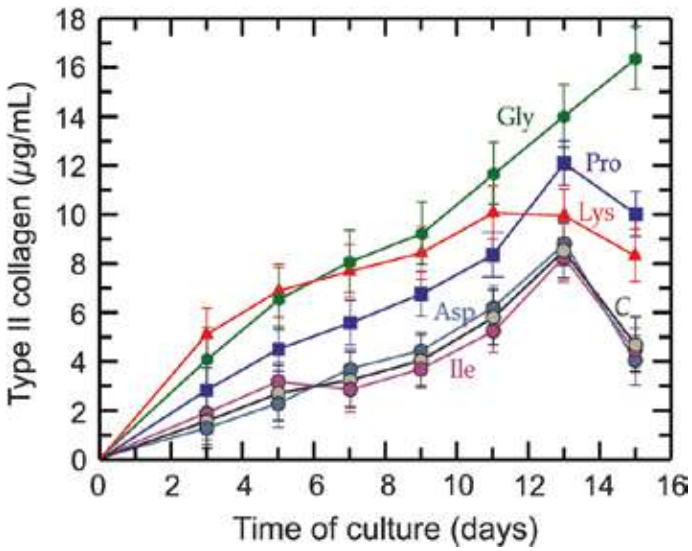
What is Chondrotrio ?

Chondrotrio is Second generation intra articular gel which will change the expectations of patients and health care professionals from viscosupplement.

It contains L - Proline + Glycine + N-A-cetylglucosamine and non animal high moleculer weight long acted hyaluronic acid.

Why Glisin ?

Results presented in Figs. 1 and 2 show that increased concentrations of glycine, proline and lysine in the basal medium enhance type II collagen synthesis. The effects of these amino acids are independent as they are independent variables because the degradation of any one of them does not give rise to a specific metabolite for the synthesis of any other. **These results show that an increase in the concentration of these amino acids could improve the regeneration of the articular cartilage matrix.**[1]



1- High glycine concentration increases collagen synthesis by articular chondrocytes in vitro: acute glycine deficiency could be an important cause of osteoarthritis
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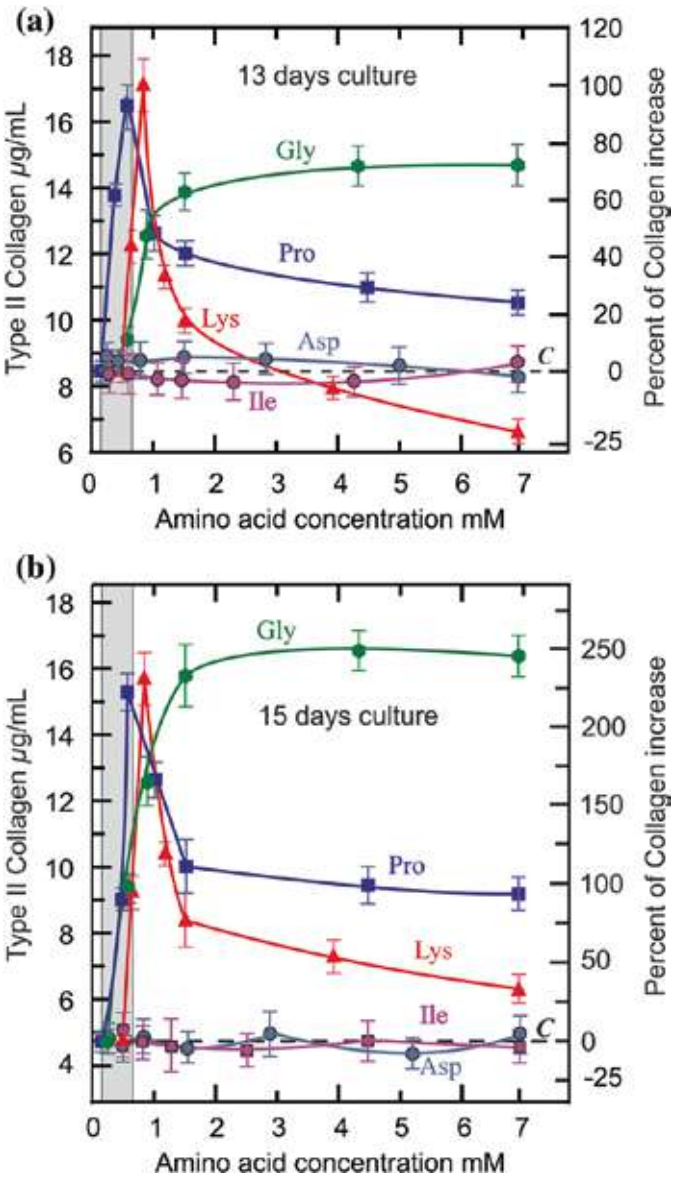

Fig. 2 Effect of each amino acid concentrations on type II collagen synthesis. Type II collagen production by chondrocytes in the monolayer at 13 days (a) and 15 days (b) of culture development under each amino acid concentration: green hexagon: glycine (green line); blue square: l-proline (blue line); red rectangle: l-lysine (red line); dark blue circle: l-aspartic acid (dark blue line); purple circle: l-isoleucine (purple line). The dotted line (C) means the collagen production under control conditions in the regular medium (gly 0.25 mM, pro 0.15 mM, lys 0.5 mM). The area marked in gray to the left of the graph shows the normal range of concentrations of these amino acids in the plasma (Felig and Wahrent 1971; Goodwin 1968; Javitt et al. 2001; Nakazawa et al. 1982; Summer and Roszel 1965)

Results in Fig. 2b, at 15 days culture, show that the need of glycine is the highest, having to be 1.5 mM to reach about 225% collagen increase over the control. The same effects were achieved with proline and lysine, but their need was lower, up to 0.6 and 0.8 mM, respectively. However, the most important feature of these results is that glycine maintains its stimulating effect at higher concentrations (up to 7 mM), while the increased concentrations of proline and lysine declined their effects, their being at 1.5 mM one half and one-third, respectively, of the effect achieved by glycine. Increased concentrations of l-aspartic acid or l-isoleucine in the medium up to 7.0 mM did not produce any effect, which demonstrates the specific need for glycine, proline and lysine.

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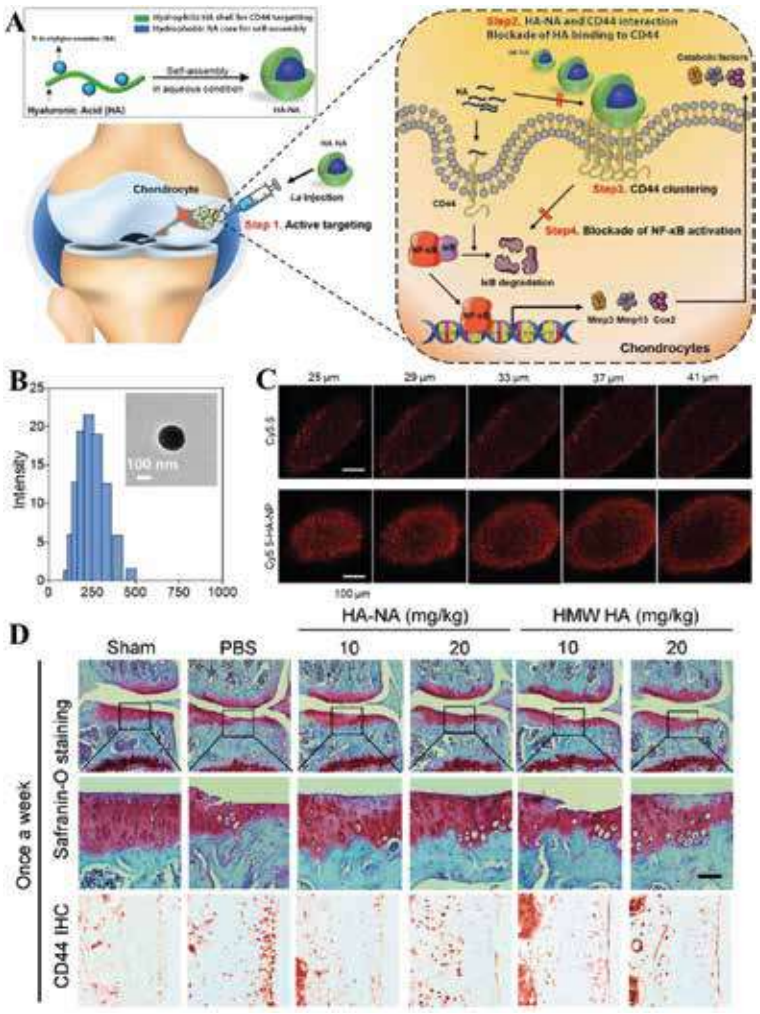

N-Acetylglucosamine act of mechanism

As a cell surface molecule mediating cell interaction and migration, CD44 escalated in chondrocytes, synovial macrophages, lymphocytes and fibroblasts of arthritic joints.

HA, the ligand to CD44, can be decorated onto particles for actively targeting. For instance, HA-NA particles bovine are promising intra-articular therapeutic for OA. Via binding to CD44 on the cell surface, HA potentiates the particles' joint residence and enhances their interaction with chondrocytes.

Fig. 3. HA-NA particles were constructed to target the CD44 receptor and ameliorate OA. A) Scheme of the HA-NA particles induced OA therapy; B) TEM images and size distribution of HA-NA particles. Scale bar, 100 nm; C) Sequential images of the femoral cartilages after normal mice were intra-articularly injected Cy5.5 and Cy5.5-labeled HA-NA particles. Scale bars, 100 μm; D-E) OA mouse cartilage injected intra-articularly once a week with PBS, HA-NA particles, or free highmolecular- weight HA 4 weeks post destabilization of the medial meniscus surgery. Relevant Safranin O, CD44 staining, Osteoarthritis Research Society International (OARSI) grade, and subchondral bone plate thickness were displayed. (F–I) IκB levels in IL-1β-treated (F,G) and Ad-Cd44-infected (H,I) chondrocytes with or without HA-NA particles.

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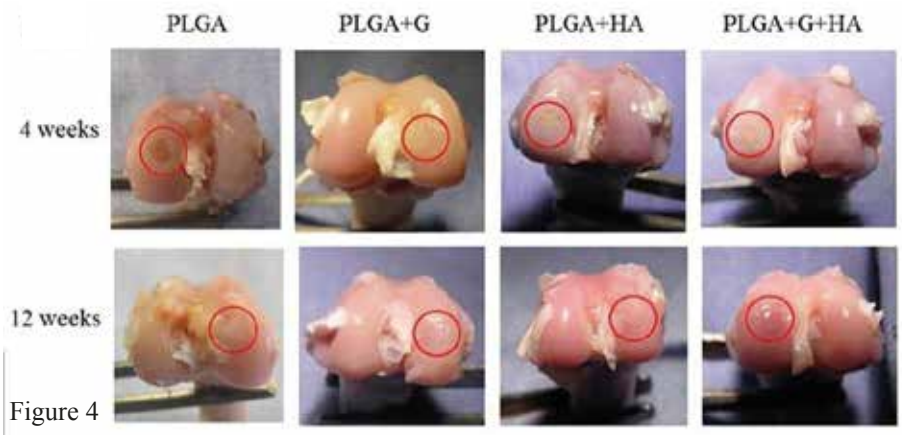


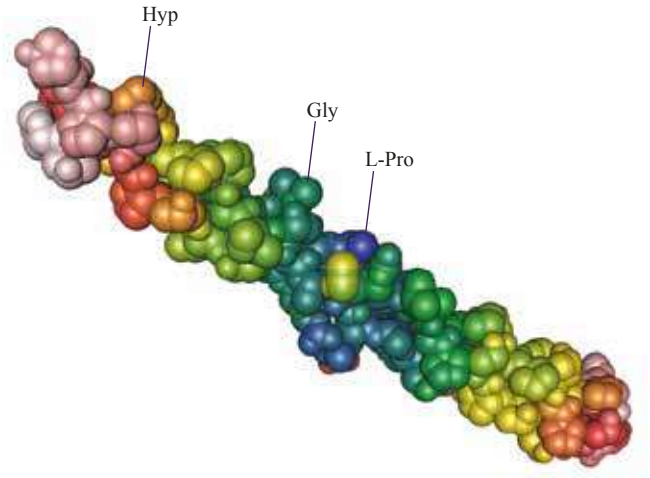
Figure 4

Cartilage Regeneration

Repairing damaged articular cartilage is particularly challenging because of the limited ability of cartilage to perform self-repair. Intra-articular injections of N-acetylglucosamine (GlcNAc) comprise a method of repairing full-thickness articular cartilage defects in the animal knee joint model.(2)

At 4 weeks postoperatively, all defect areas were completely filled with repaired tissue except for those in the PLGA-only group (Fig 4). In the PLGA group, the area showed mild depressions in the defect site and the rim was surrounded with white regenerative tissue for ongoing repair. Regarding the PLGA+G, PLGA+HA, and PLGA+G+HA treatment groups, the partially degraded PLGA scaffold remained visible in thecenter of the defect. However, the surrounding cartilage was the same color as the normal cartilage, thus representing ongoing repair of the hyaline-like cartilage.

Macroscopic evaluations at 12 weeks. At 12 weeks postoperatively, the defect areas in all groups were completely filled with repaired tissue (Fig 4). In the PLGA group, the defects were apparently covered with opaque tissue. In contrast, in the PLGA+G, PLGA+HA, and PLGA+G+HA groups, the repair cartilage became more mature, had the appearance of a smooth joint surface, and the color closely resembled that of the adjacent normal hyaline cartilage.



L-Proline provides site-specific flexibility for in vivo collagen

Fibrillar collagens have mechanical and biological roles, providing tissues with both tensile strength and cell binding sites which allow molecular interactions with cell-surface receptors such as integrins. A key question is: how do collagens allow tissue flexibility whilst maintaining well-defined ligand binding sites? Here we show that proline residues in collagen glycine-proline-hydroxyproline (Gly-Pro-Hyp) triplets provide local conformational flexibility, which in turn confers well-defined, low energy molecular compression-extension and bending, by employing two-dimensional 13C-13C correlation NMR spectroscopy on 13C-labelled intact ex vivo bone and in vitro osteoblast extracellular matrix. We also find that the positions of Gly-Pro-Hyp triplets are highly conserved between animal species, and are spatially clustered in the currently-accepted model of molecular ordering in collagen type I fibrils. We propose that the Gly-Pro-Hyp triplets in fibrillar collagens provide fibril “expansion joints” to maintain molecular ordering within the fibril, thereby preserving the structural integrity of ligand binding sites.(3)

2-Intra-articular injection of Nacetylglucosamine and hyaluronic acid combined with PLGA scaffolds for osteochondral repair in rabbits
Hsueh-Chun Wang1, Yi-Ting Lin1, Tzu-Hsiang Lin1, Nai-Jen Chang2, Chih-Chan Lin3, Horng-Chaung Hsu4, Ming-Long YehID 1,5*

3- Proline provides site-specific flexibility for in vivo collagen
Wing Ying Chow 1,4, Chris J. Forman1,5, Dominique Bihan2,6, Anna M. Puszkarska1, Rakesh Rajan1, David G. Reid1, David A. Slatter3, Lucy J. Colwell1, David J. Wales1, Richard W. Farndale 2 & Melinda J. Duer1

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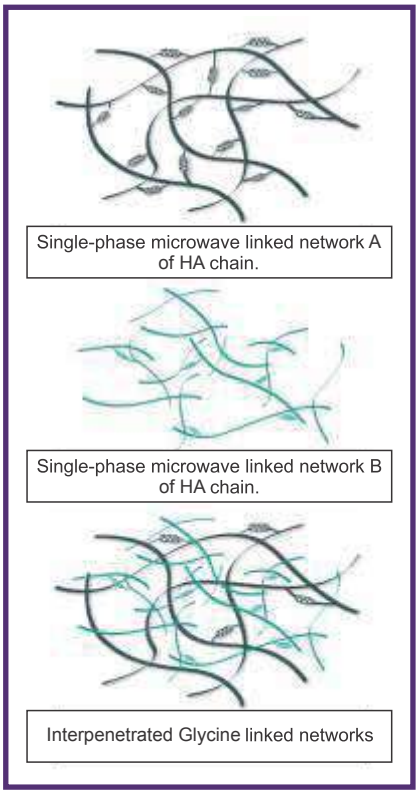

Resistance to degradation

Chondroplus has a greater ability to retain its viscoelastic properties when exposed to free radicals.

The enhanced viscoelastic properties of Chondroplus during degradation due to the network of sustained collagen tripeptide obtained by the high technology.

The data support the use of Chondroplus obtain a satisfactory intra-articular effect and residence time.[4]

This is a new patented technology , we are using Microwaves for linking carboxil group and this process you need more NH group in the gel (Glycine provides this).This is a physical modification not a chemical one.

4-Sinan K et al. The ability of collagen based Hyauronic acid to withstand degradation by free radicals and proteinase enzymes. Poster presented at the OSTEO2013 Annual Meeting of the Osteoporosis ,Ostoartritis and joint surgery , 2013 Antalya Türkiye

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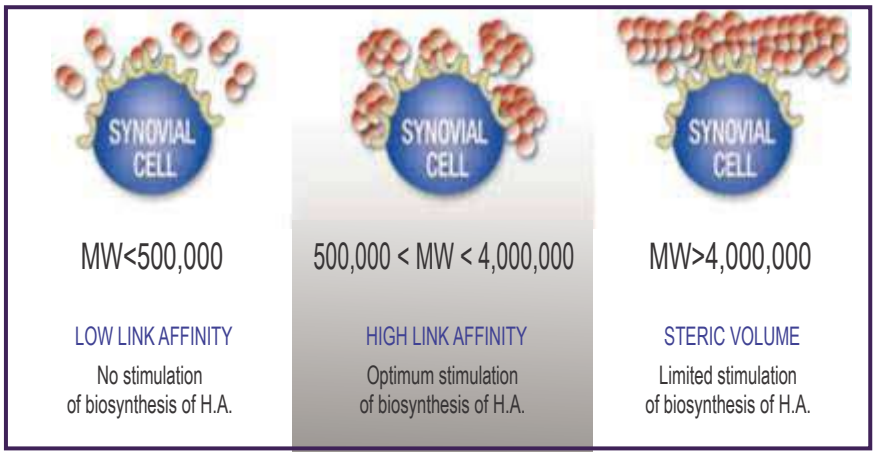
Why Chondrotrio HA Moleculer Weight 2.8-3.6 M Dalton ?

The concept of viscosupplementation, first proposed by Balazs and Denlinger , is based upon the hypothesis that IA injection of HA into OA joints could restore the rheological properties of the SF, promote the endogenous synthesis of a higher MW and more functional HA, thereby improving mobility, and articular function, and decreasing pain.[5]



The larger the molecule of HA, had the higher the affinity of HA receptors for binding. Since HA did not directly bind to BK receptors, then analgesic effects of HA appears to be brought on by the interaction of HA and HA receptors on or surrounding the free nerve endings that detect pain in the joint tissue. Higher- MW HA with high concentration reduced pain by modifying the activity of mechano sensory channels.[6]

5-Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. J Rheumatol. (1993) 39:3–9. [PubMed][Google Scholar][Ref list]
6-Gomis A, Pawlak M, Balazs EA, Schmidt RF, Belmonte C. Effects of different molecular weight elastoviscous hyaluronan solutions on articular nociceptive afferents. Arthr Rheum. (2004) 50:314–26. 10.1002/art.11421

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Why 20 mg HA / ml ?

Low doses, hyaluronic acid has a significant stimulatory effect on the metabolic activity of chondrocytes that may provide an explanation for the longer term clinical benefits. Studies on osteoarthritic cartilage have shown that hyaluronic acid depletion in the extracellular matrix occurs before structural changes in proteoglycans are detectable. It is likely that physiochemical interactions occur between hyaluronic acid and chondrocytes which regulate their activity and ability to produce proteoglycans and type II collagen.(7)

HA is present in articular fluid in a concentration of about 20 mg/mL.(8)

20 mg/mL Injection of knees with HA inhibited apoptosis in chondrocytes.(9)

How we made long acted HA ?

Our major aim is to provide enhanced stability
HA hydrogels are commonly prepared via chemical modification in solution using organic solvents and/or toxic reagents
Alternative methods for the preparation of hydrogels, which importantly avoid the use of organic solvents and reagents that can present toxicity problems for biological applications, have been described during recent years.
This is a new patented technology , we are using Microwaves for linking carboxil group and this process you need more NH group in the gel (Glycine provides this). This is a physical modification not a chemical one.(10)

7-The effects of hyaluronic acid on articular chondrocytes M. Akmal, A. Singh, A. Anand, A. Kesani, N. Aslam, A. Goodship, G. Bentley.
8-Geiss C, Band P. Musculoskeletal applications of hyaluronan and hylan. Potential uses in the foot and ankle. Clin Podiatr Med Surg (1995) 12:497–517.
9-EFFECT OF HYALURONIC ACID ON CHONDROCYTE APOPTOSIS Ronald Bispo Barreto1, David Sadigursky1, Marcia Uchoa de Rezende1, Arnaldo José Hernandez1
10-Synthesis and characterization of hyaluronic acid hydrogels crosslinked using a solvent-free process for potential biomedical applications Eneko Larrañeta , Megan Henry, Nicola J. Irwin, Johann Trotter, Anastasia A. Perminova, Ryan F. Donnelly School of Pharmacy, Queens University Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland, UK

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+N-Acetylglucosamine
microwave stabilized single injection

One Shot
One Year

How does Chondrotrio accomplish its intended objective?

When Chondrotrio is injected directly into the joint, it helps to improve viscoelastic properties of the synovial fluid, thus decreasing pain and improving joint function.

Rheological

- Quickly restore viscosity and elasticity of synovial fluid.

Biological

- Anti-inflammatory effect
- Restores hyaluronate production.
- Promotes the body's production of hyaluronate (positive feedback)
- Effects on cartilage: increase biosynthesis, decrease degradation
- Effects on chondrocytes: decrease programmed cell death and increase proliferation

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One Shot One Year

Why Chondrotrio is Different ?

- Unique formulation in a single injection treatment
- Uses LAH technology to increase residence time in the joint
- Has the longest half-life of any HA,
- The only gel that contains L - Proline + Glycine+N-Acetylglucosamine
- L - Proline + Glycine+N-Acetylglucosamine effects on cartilage can be explained by two different mechanisms: enhancement of cartilage matrix synthesis, and inhibition of cartilage degeneration.
- Chondrotrio is providing ideal viscosupplementation, it also provides soft tissue healing and cartilage regeneration and can be used safely in the treatment of osteoarthritis.

Dosage and Recommendations

Chondrotrio is intended for intra-articular injection only. The product administration should be performed exclusively by physicians.

- Depending upon joint size, up to 2 ml may be administered intra-articularly

ONE SHOT
ONE DOSE
ONE YEAR

- The recommended treatment protocol is 1 injection for 12 to 16 months.

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