REGEDENT
smart regeneration

hyaDENT

The natural promoter of regeneration

CONTENT

HYALURONIC ACID

The natural promoter of regeneration

Hyaluronic acid or hyaluronan (HA) is a substance naturally present in the human body. It is one of the main components of the extracellular matrix of connective tissue, synovial fluid, and many other tissues.[1-3]

From a biochemical point of view, hyaluronic acid is a natural polysaccharide macromolecule (straight-chain glycosaminoglycan).

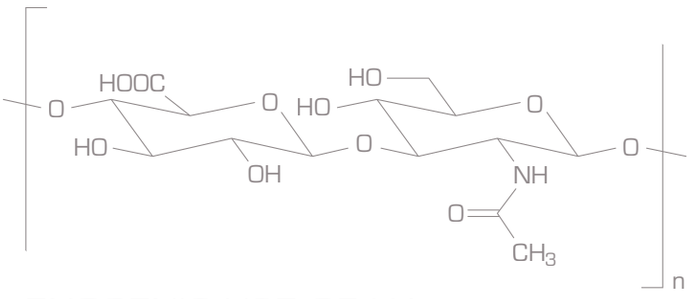
PHYSIOLOGIC FUNCTIONS

HA has important hygroscopic, rheological and viscoelastic properties and thus features numerous physiological and structural functions. Beyond the most prominent task as a tissue lubricator in joints, HA plays a major role in basic regenerative processes like wound healing and embryogenesis. HA is particularly prominent whenever rapid tissue turnover and repair occurs.[4]

The individual functions of HA are dependent on the respective molecular size (chain length).

Long hyaluronic acid chains are generally involved in the modulation of the immune response pathway by means of immunosuppressive, antiangiogenic and anti-inflammatory characteristics.*

Shorter hyaloronic acid chains are relevant for wound and tissue healing by exhibiting angiogenic, immunostimulatory and inflammatory properties.[4,5]



EXOGENIC USE OF HA

Extensive studies on chemical and physicochemical properties of HA and its physiological role in humans have proven that HA is an ideal biomaterial for cosmetic, medical, and pharmaceutical applications.

Depending on indications and functions, either natural or additionally cross-linked HA are used. Natural HA possesses the highest regenerative potential. It is degraded in vivo within a few hours to a few days.

Cross-linked HA is made from natural HA employing well-established technologies. With an increasing cross-linking rate, the degradation pattern can be prolonged to several months. On the other hand, HA becomes more and more inert by losing its physiological properties.

*In detail, long HA chains protect against lymphocyte-mediated cytolysis, suppress septic responses to lipopolysaccharides, support maintaining immune tolerance and induce production of immunosuppressive macrophages. Long HA chains support cellular integrity and protect against apoptosis.

hyaDENT SOLUTIONS

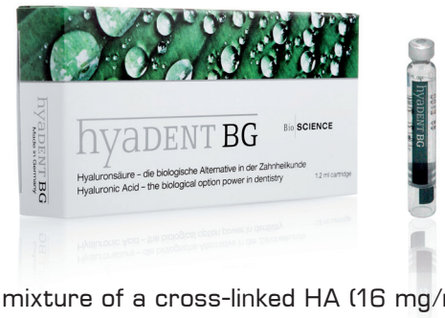
Optimized for dental applications

hyaDENT and hyaDENT BG present hyaluronic acid-based treatment solutions with a non-animal origin optimized for regenerative dental and periodontal applications.

hyaDENT

is a highly concentrated natural hyaluronic acid-gel (14 mg/ml) and is characterized by a fast degradation pattern (a few hours). It is delivered "ready-to-use" in a TopPac® syringe. hyaDENT has the following effects:

- Speeding up of wound healing after surgical procedures
- Supplementing and improvement of periodontal treatments
- Reduction of scar tissue formation



hyaDENT BG

is a highly concentrated hyaluronic acid gel based on a mixture of a cross-linked HA (16 mg/ml) and a natural HA (2 mg/ml). It is characterized by a slow degradation pattern (several weeks). hyaDENT BG is delivered in a cylindric ampula.

hyaDENT BG has the following effects:

- Shielding of the wound area from penetration of bacteria and connective tissue
- Supplementing and improvement of periodontal treatments
- Acceleration of tissue healing

INDICATIONS

hyaDENT and hyaDENT BG can be used in the following indications:

	hyaDENT	hyaDENT BG
Non-surgical Therapy:		
Successive treatment after Scaling and Root Planing (SRP)	×	
Surgical Therapy:		
Recession coverage with Coronally Advanced Flap (CAF) technique		×
Recession coverage with Connective Tissue Graft (CTG) or Free Gingival Graft (FGG)	×	
Topical application to oral wounds (e.g. CTG harvesting sites)	×	
Guided Tissue Regeneration (GTR) procedures	×	×

CONTROLLED WOUND HEALING

HA coordinates the post-operative inflammation process and accelerates neoangiogenesis for improved wound healing

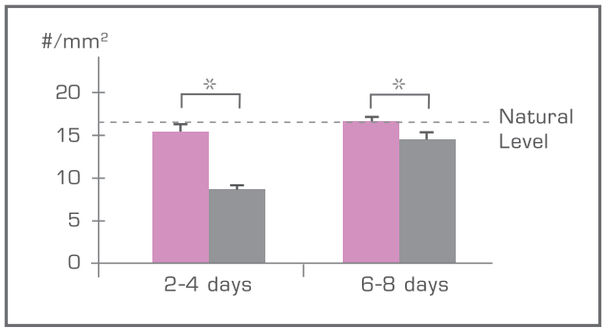
HA is present and plays a large number of widely differing roles throughout the entire process of wound healing. It is a promotor of inflammation and of the whole process of wound repair as well as a sentinel of tissue healing through change in molecular size.[4,7,8]

Application of HA to surgical or chronical wounds stimulates post-operative neoangiogenesis.[9] Thus, HA significantly accelerates the healing process.[9,10] This becomes clinically manifest in a shortened time to reepithelialization, e.g., in burn patients or when treating venous ulcers.[11]

In addition, HA seems to support scarless healing. This is indicated by persistingly high HA levels in granulation tissue as found in fetal wounds known to heal without scar formation.[7,8,12]

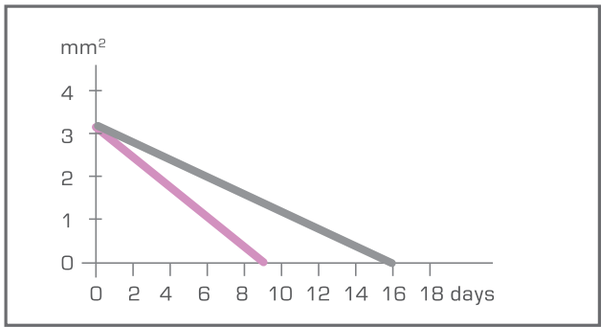
In an animal trial, the effect of exogenous hyaluronic acid (HA) on the healing of experimental wounds created in hamsters was determined. Additional presence of HA accelerated early neoangiogenesis. Additional application of HA significantly reduced healing time from 16 days to 8.6 ± 0.4 days.[9]

Microvessel Density



HA Placebo

Closure of Wound Area



HA Placebo

Additional application of HA leads to increased early angiogenesis and significantly accelerated wound healing.
*statistically significant difference

ROLE OF HYALURONIC ACID IN WOUND HEALING

Wound healing is a series of complex reactions initiated by the disruption of tissue architecture. The goal of this process is to restore the integrity of the injured tissue, either by regeneration of original tissue or by deposition of a fibrotic scar.[4,7]

During wound healing, HA is constantly produced in a long molecular chain form promoting endothelial integrity and inhibiting vascular leakiness.[4] HA is degraded in a series of sequential enzymatic steps. As HA is being fragmented, it organizes specific size-dependent functions.

ROLE OF HYALURONIC ACID IN WOUND HEALING/MODE OF ACTION

HEMOSTASIS

1

The process of wound healing is initiated by the disruption of tissue architecture and the transition from liquid blood to a solid clot.
Hyaluronic acid binds to fibrinogen, thus stabilizing and loosening the blood clot.[4]

HA is a major component of the edema fluid. By its enormous capability of absorbing water, HA fills and expands the tissue surrounding the fresh wound and keeps the space open for infiltration of neutrophils.

INFLAMMATORY PHASE

2

Hyaluronic acid promotes and simultaneously regulates the inflammatory process. It has an anti-oxidative effect by acting as a scavenger for free radicals and Reactive Oxygen Species (ROS) non-healing wounds often suffer from.[13] Thus, the cells of the granulation tissue are protected from damage.[4] HA reduces the activity of pro-inflammatory proteases and mediates the cross-talk between the wound ECM and the incoming inflammatory cells like leucocytes thus allowing formation of a stable granulation tissue matrix.

PROLIFERATIVE PHASE

3

Hyaluronic acid supports granulation tissue organization by promoting cell migration and proliferation.
Furthermore, HA promotes the formation of blood vessels (angiogenesis) within wound sites[11] ensuring blood supply for the healing area. HA stimulates fibroblast proliferation and the production of type III collagen, the soft malleable variant as opposed to more rigid type I collagen.

REMODELING PHASE

4

Hyaluronic acid plays an important role in regulating scar formation, the final phase of wound healing. HA is responsible for ensuring that suppression of collagen production occurs at the right time and for soft scar formation.

IMPROVED PREDICTABILITY OF REGENERATION

HA acts bacteriostatic and slows down pathogen penetration for more predictable periodontal regeneration

ACTS BACTERIOSTATIC AND ANTIFLAMMATORY

Hyaluronic acid has a bacteriostatic effect[14,15] on pathogens commonly found in gingival lesions and periodontal wounds.* Application of HA during the surgical therapy may reduce bacterial contamination of surgical wound sites hence decreasing the risk of postsurgical infection and promoting more predictable regeneration.[14]

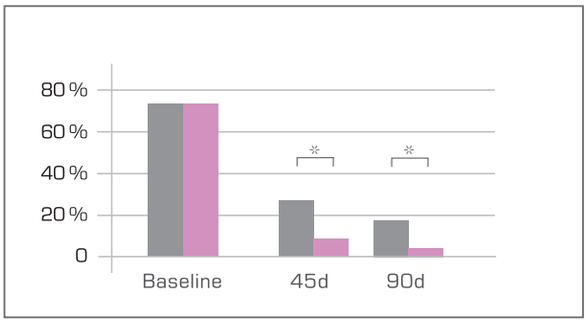
SLOWING DOWN THE PENETRATION OF VIRUSES AND BACTERIA

Hyaluronic acid can influence the cell functions by modifying the surrounding cellular and extracellular environments.[16] HA as a visco-elastic substance assists periodontal regenerative procedures by maintaining spaces and protecting surfaces. Therefore, bacterial penetration into the wound site is impeded.

MORE PREDICTABILITY IN PERIODONTAL TREATMENTS

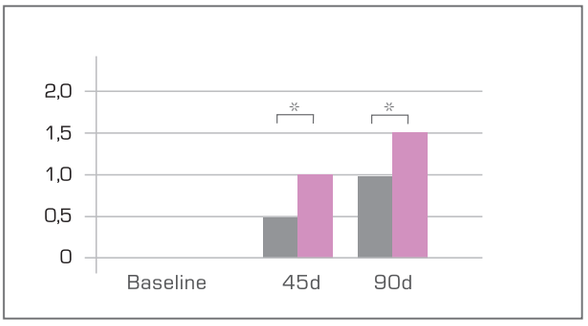
Due to its bacteriostatic properties, HA stimulates tissue regeneration.[14] Adjunct HA application to non-surgical and surgical periodontal treatments may improve periodontal parameters.[17,18] Thus, periodontal therapy supported by HA has been shown to achieve an increase in bone level.[19] HA has a beneficial effect on the outcome of non-surgical periodontal treatments when used in combination with ultrasonic Scaling and Root Planing (SRP).

Reduction of Bleeding on Probing (BOP)[19]



BOP could be reduced statistically significantly from 72.7% to 4.5% at 90 days after treatment[17] when hyaluronic acid was applied after ultrasonic treatment.

Reduction of Probing Pocket Depth (PPD)[19]



In addition, statistically significantly higher reduction of the probing pocket depth has been observed. The mean PPD was reduced by 1.5 mm after 90 days.[17]

(*aggregatibacter actinomycetemcomitans, prevotella oris and staphylococcus aureus)

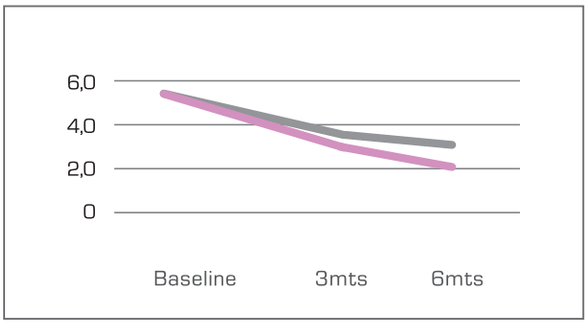
BENEFICIAL TREATMENT OUTCOME

HA supports tissue regeneration for improved treatment outcome

In addition to its elementary function during early wound healing processes, hyaluronic acid plays an important regulatory role in the development and regeneration of skin and bone tissues.[12] It exerts complex effects on skin and bone cells at all stages of healing in its different forms. Therefore, addition of HA to established surgical or non-surgical treatment protocols results in improved clinical treatment outcomes, especially in critical interventions. This was shown in various studies indicating the positive effect of HA towards supporting bone formation[20-22] and periodontal regeneration.[17,18,23-26]

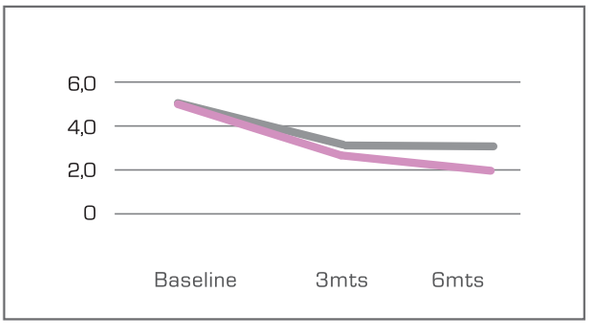
POSITIVE IMPACT ON SURGICAL TREATMENT

Clinical Attachement Level (Median)



The CAL gain was statistically significantly higher after additional HA treatment.[26]

Pocket Depth (Median)



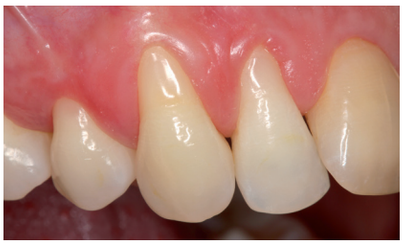
The PD levels were lower after additional HA treatment.[26]

The treatment of infrabony defects with hyaluronic acid offers additional benefits in terms of Clinical Attachment Level (CAL) gain, Pocket Depth (PD) reduction, and predictability compared to treatment with open flap debridement.[25,26]

These beneficial effects of HA were shown in a split mouth design study including 14 patients.[26] One site was treated with a placebo gel and the other site with HA. After 6 months, 86% of the sites treated with HA showed an CAL gain of 3 mm or more for the HA group compared to 50% of the placebo group. As for the pocket depth, only 7% of the HA group still presented a residual pocket of 4 mm (vs. 22% in the placebo group).

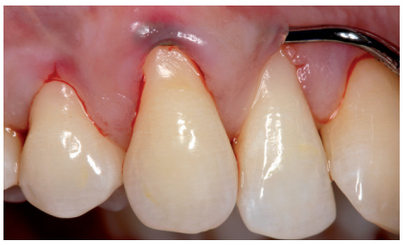
CLINICAL EXPERIENCE – CASE 1

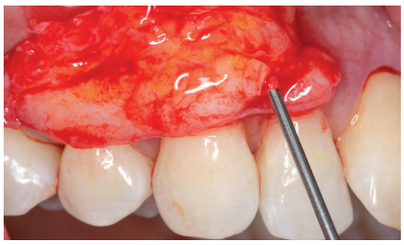
Surgical treatment of multiple gingival recessions in the esthetic zone with CTG and hyaDENT using the tunnel technique.



PRE-OPERATIVE

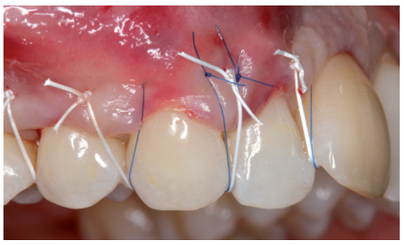
Patient presented with two severe gingival recessions Miller class II in the esthetic zone (regio 1-2 and 1-3).



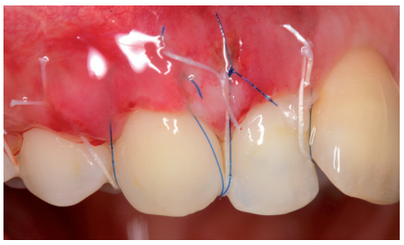


SURGERY

Incision-free mobilization of the gingiva in the recipient site (left). CTG was harvested in the appropriate size and the graft surface was conditioned with hyaDENT.

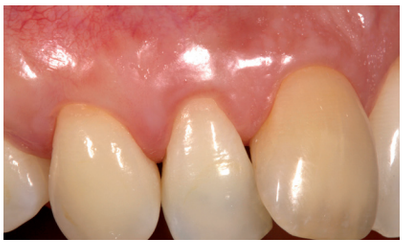


Submucoseous positioning of the CTG using the tunnel technique. Graft stabilization with sutures. hyaDENT was applied underneath the flap before suturing to achieve accelerated post-operative wound healing.



7 DAYS POST-OPERATIVE

Situation before removal of sutures: accelerated wound healing without signs of infections or irritations.



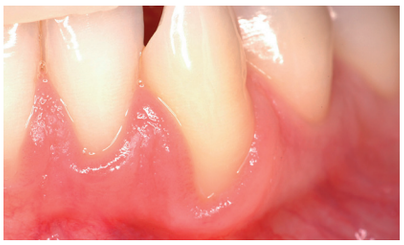
3 MONTHS POST-OPERATIVE

Excellent reconsolidation of the soft tissue indicated by complete recession coverage and sufficient presence of keratinized gingiva, both in height and in width, thus providing an esthetically highly pleasing result for the patient.

This case by courtesy of PD Dr Stefan Fickl, University of Würzburg, Germany.

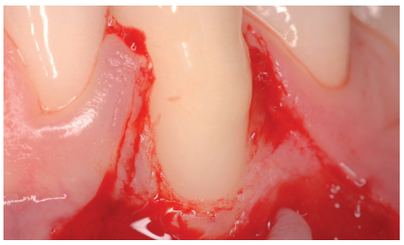
CLINICAL EXPERIENCE – CASE 2

Coronally Advanced Flap (CAF) surgery supported by hyaDENT BG for treatment of a gingival recession.



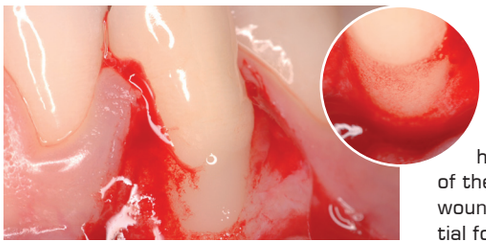
Pre-OPERATIVE

A recession defect of Miller Class II was observed in the lower right canine despite the patient's good dental hygiene and regular dental treatments.

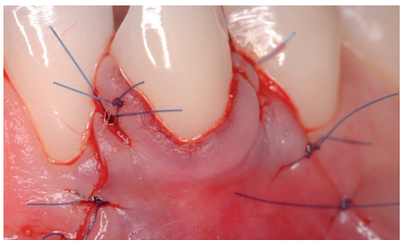


SURGERY

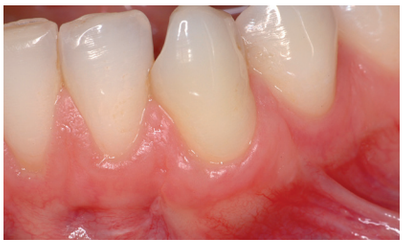
It was decided to treat the recession surgically. After flap preparation, the root surface was carefully cleaned.



hyaDENT BG was applied on the root surface and on the incision areas of the soft tissue. This supports periodontal regeneration and assures fast wound healing (left). hyaDENT BG mixes well with the blood, which is essential for the clinical efficacy of hyaluronic acid (right).



The wound was closed with a Coronally Advanced Flap (CAF).



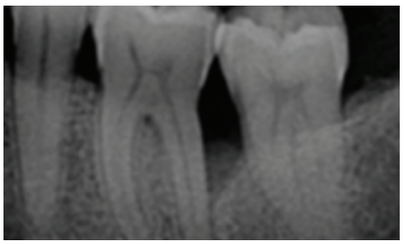
1 YEAR POST-OPERATIVE

The recession is still well covered with a healthy soft tissue.

This case by courtesy of Prof Andrea Pilloni, University Sapienza, Roma, Italy.

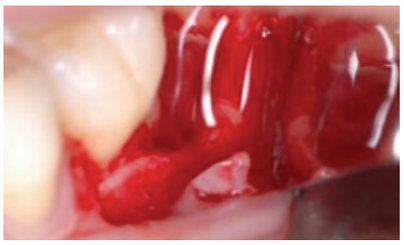
CLINICAL EXPERIENCE – CASE 3

Surgical treatment of an infrabony defect with hyaDENT and hyaDENT BG showing rapid wound healing



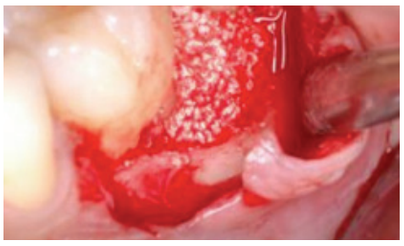
PRE-OPERATIVE

A deep infrabony defect could be detected on the x-ray and by probing.

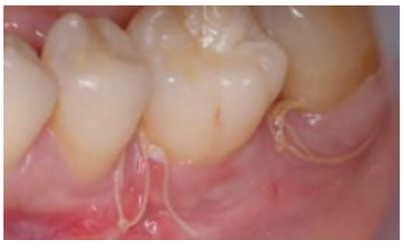


SURGERY

The defect site was opened and cleaned. hyaDENT BG was applied directly on the root surface allowing the stabilization of the clot. .

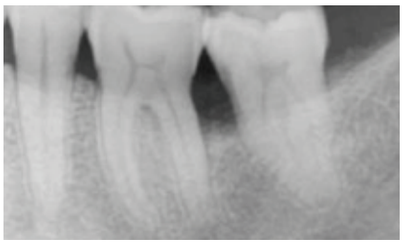


The defect was filled with bone graft material and covered with hyaDENT BG.



72 HOURS POST-OPERATIVE

Thanks to the hyaDENT application between graft material and covering soft tissue, wound healing was accelerated. The wound was closed at this early stage.



12 MONTHS POST-OPERATIVE

Radiographical analysis of the site 12 months after treatment shows solid bone structures and a closure of the infrabony defect.

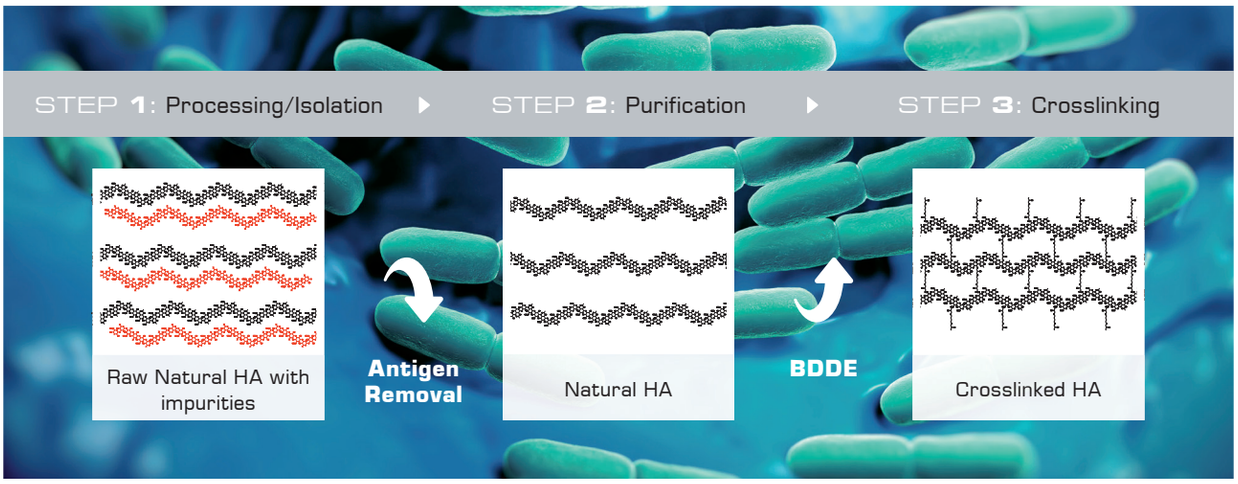
This case by courtesy of Prof Andrea Pilloni, University Sapienza, Roma, Italy.

HYALORONIC ACID
Manufacturing Technologies

SOURCING

Pure hyaluronic acid is identical with all species (incl. even phyla)[4] facilitating the sourcing for exogenous application. Traditionally, HA has been extracted from rooster combs and bovine vitreous humor. However, it is difficult to isolate a defined HA quality from these sources because HA forms a complex with other macromolecules. As a result, animal-derived HA features an inherent composition.[27]
In addition, the use of animal-derived substances for human therapeutics is being met with growing resistance due to ethic arguments and the potential risk of viral infections.

Therefore, modern ways of harvesting HA are based on using a bacterial fermentation process.[6]
In bacterial fermentation, HA is released into the growth medium. As control of polymer characteristics is feasible, a homogenous HA composition can be achieved in a safe and environmentally acceptable manner.
Nevertheless, HA purification plays a crucial role in avoiding host reactions induced by residual bacterial or avian proteins potentially comprising antigenic properties.[28]



CROSSLINKING

While natural HA components generally undergo fast degradation, many successful therapy options afford a longer lifespan in the body. In order to increase degradation time of HA derivatives, natural HA is cross-linked according to well-established (bio)chemical technologies.
The degree of cross-linking affects both degradation time and physiological performance. The best established method is using BDDE (Butanediol-diglycidylether) as a cross-linking agent. The drawback of using BDDE in the HA-implant may consist of adverse reactions, therefore thorough purification of cross-linked HA is mandatory.[29]

hyaDENT AND hyaDENT BG

Highly biocompatible regenerative products

The HA used for hyaDENT and hyaDENT BG is manufactured biotechnologically by bacterial fermentation. This process is considered as state of the art safeguarding a consistently high product quality both in terms of a well-defined molecular weight and a high purification rate.

The manufacturing process for the cross-linked component in hyaDENT BG is performed using the well-established BDDE methodology. The cross-linking conditions are specifically defined to assure a controlled reaction resulting in a homogenously cross-linked product. In addition, the cross-linked HA is purified to such a high extent that sufficient removal of residual BDDE can be assured.

- 100% free from animal-derived raw materials providing maximum safety
- Highest possible purification rate to ensure optimal biocompatibility
- Well defined molecular size providing optimal prerequisites for individual application

hyaDENT SOLUTIONS

hyaDENT

Natural Hyaluronic Acid Gel (1,4% HA)
1 ml syringe

hyaDENT BG

HA Gel as mixture of cross-linked (1,6%) and natural (0,2%) Hyaluronic Acid
1,2 ml cylindric ampula

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