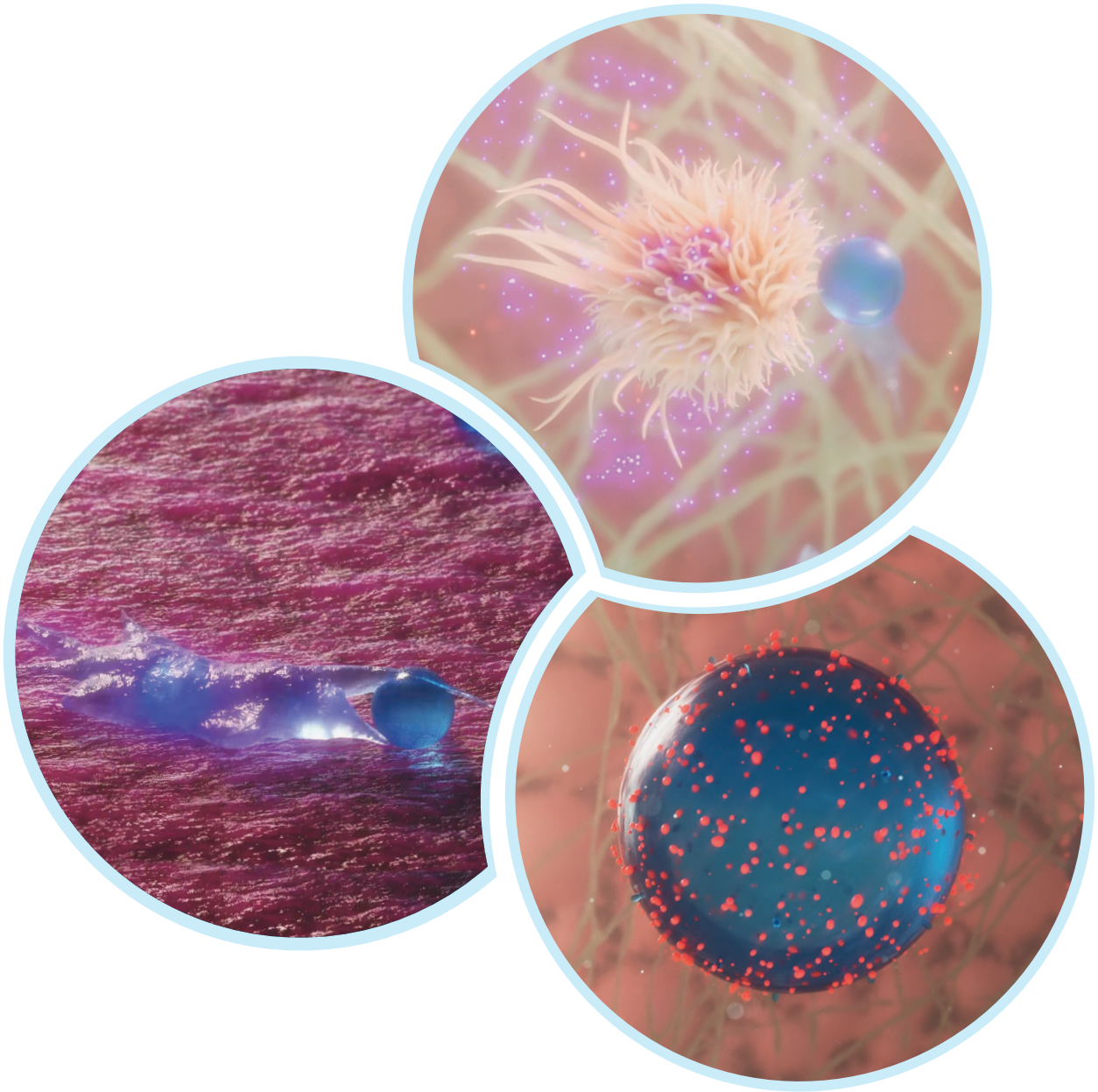
MODE OF ACTION



Praxis Pharmaceutical

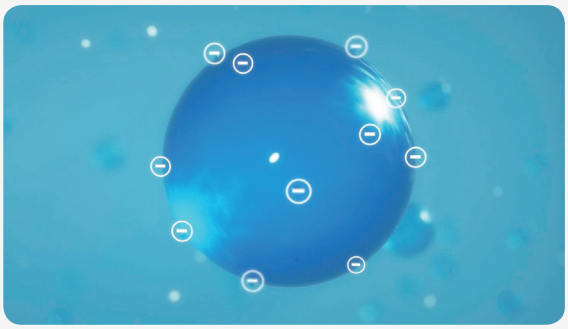
POLYHEAL MICRO

UNIQUE MICROSPHERE TECHNOLOGY
THAT REACTIVATES WOUND HEALING

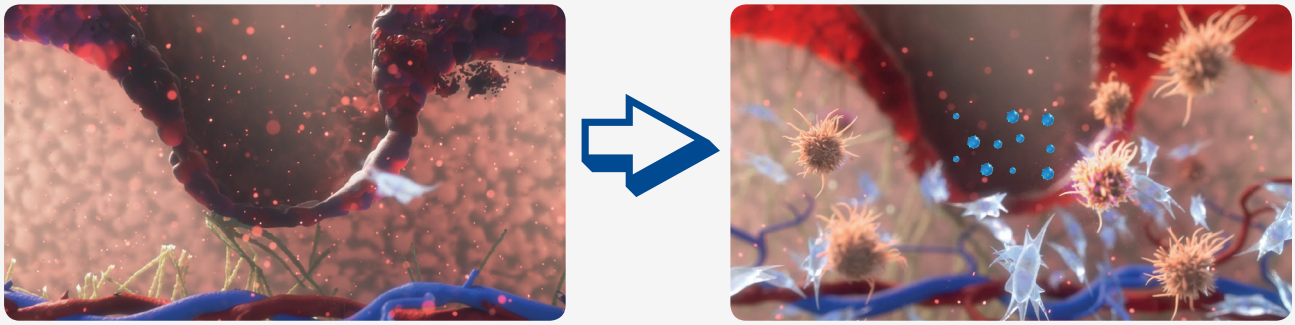
POLYHEAL® MICRO, A SUSPENSION OF POLYSTYRENE NEGATIVELY CHARGED MICROSPHERES (NCM) IN A CONCENTRATION OF 4.5X10⁶ MICROSPHERES/ml, IN 22% GLYCEROL AND WATER FOR INJECTION.

NEGATIVELY CHARGED MICROSPHERES (NCM)[1]

NCM are polystyrene microspheres that carry terminal sulfonate groups that concentrate on their surface, providing a net negative charge. Such charge increases the readiness by which macromolecules may anchor onto their surface.



TREATMENT WITH POLYHEAL® MICRO



1. Before application of PolyHeal® Micro

In a chronic wound situation there is an overall decrease in all components of the Extracellular Matrix. Cells lose their ability to proliferate and, as a consequence, end up in apoptosis.

2. After application of PolyHeal® Micro

NCM provide a passive temporary surface for cell attachment and proliferation. This increases the number of cells in the wound bed, reestablishing the Extracellular Matrix.

NCM REACTIVATE THE HEALING PROCESS AND ACCELERATE THE FORMATION OF GRANULATION TISSUE FAVORING CLOSURE.[2]

INDICATIONS

For the treatment of ulcers of different etiologies and stagnant hard to heal wounds, **including exposed bones and tendons without infection.**

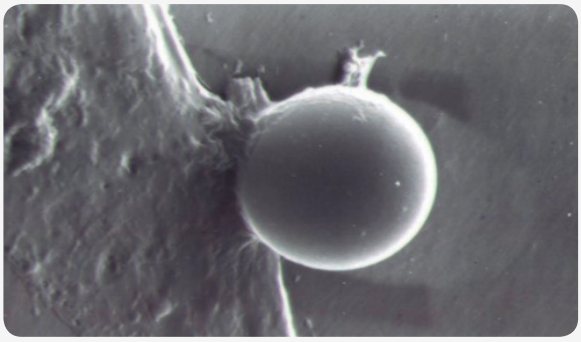
- **Diabetic foot ulcers, venous and arterial leg ulcers, pressure ulcers;**
- Post-traumatic, post-surgical wounds;
- Other ulcers in co-morbid patients.

NCM MIMIC THE FUNCTIONS OF NATIVE EXTRACELLULAR MATRIX (ECM)

NCM provide an additional surface, to which a variety of cells and biological macromolecules involved in the wound healing process can attach and interact, promoting the reactivation of the stagnant situation.[3,4]

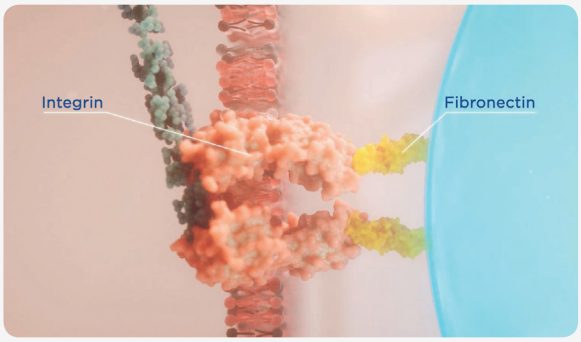
Cell attachment to NCM in the wound bed results in morphological and functional cell changes that reactivate healing.[5,6]

Myofibroblast attachment to NCM results in the formation and extension of pseudopodia. This is a clear evidence of the activation of the cell.[5,6]



CELL ATTACHMENT PROCESS

1. When adhesion proteins, like fibronectin, anchor to structural proteins (collagen fibers), their binding domains are exposed to subsequent cellular attachment.
2. Cell attachment to collagen fibers causes cells to activate, proliferate and migrate.
3. Upon activation, cells initiate processes aimed at wound healing.



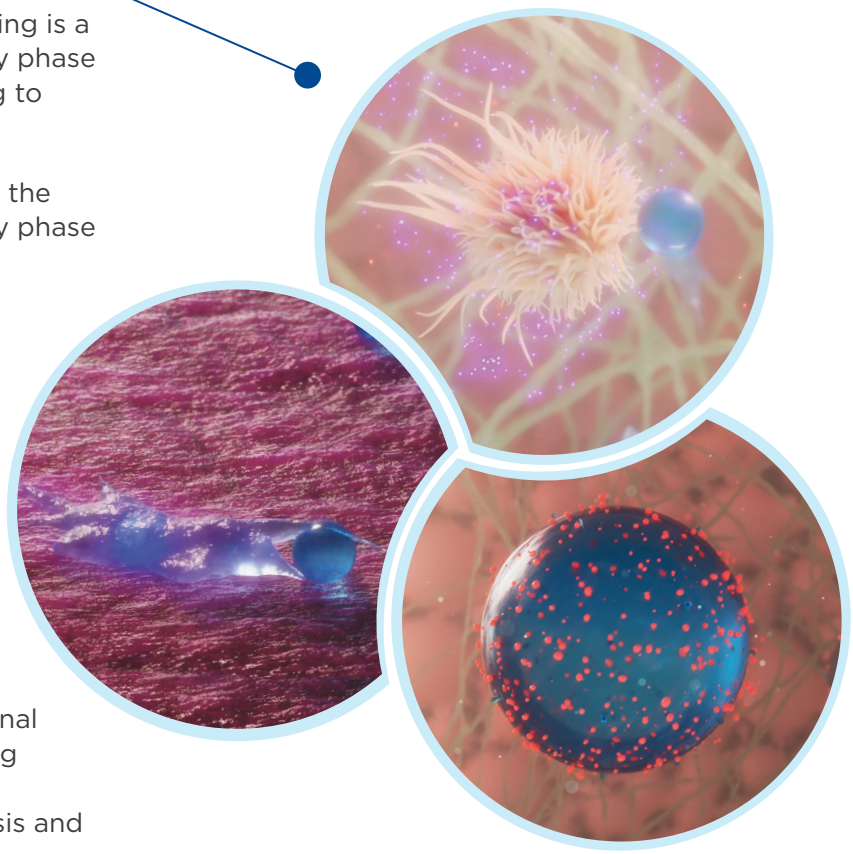
NCM ACT LIKE COLLAGEN FIBERS, FACILITATING THE HEALING PROCESS, WHICH OTHERWISE WOULD BE VERY DIFFICULT IN A CHRONIC WOUND ENVIRONMENT.[2]

AFTER THE APPLICATION OF POLYHEAL® MICRO A SYNCHRONIZED SERIES OF EVENTS ARE TRIGGERED SWITCHING THE WOUND FROM THE INFLAMMATORY TO THE PROLIFERATIVE PHASE.[2,7]

MAIN EFFECTS OF POLYHEAL® MICRO

1. CYTOKINE MODULATION

- One mechanism that fails in wound healing is a persistent activation of the inflammatory phase which doesn't progress properly, leading to stagnation.
- After the application of PolyHeal® Micro, the persistent activation of the inflammatory phase is not further maintained due to local cytokine balance reestablishment.[8,9]



2. ADDITIONAL SURFACE AREA FOR CELL ATTACHMENT

- In a chronic wound there is an overall decrease in all components of the Extracellular Matrix.
- NCM mimic the functions of native Extracellular Matrix providing an additional surface area for cell attachment, enabling cells to activate the processes aimed at wound healing, such as collagen synthesis and angiogenesis, among others.[2,5]

3. METALLOPROTEINASES SEQUESTRATION (MMPs)

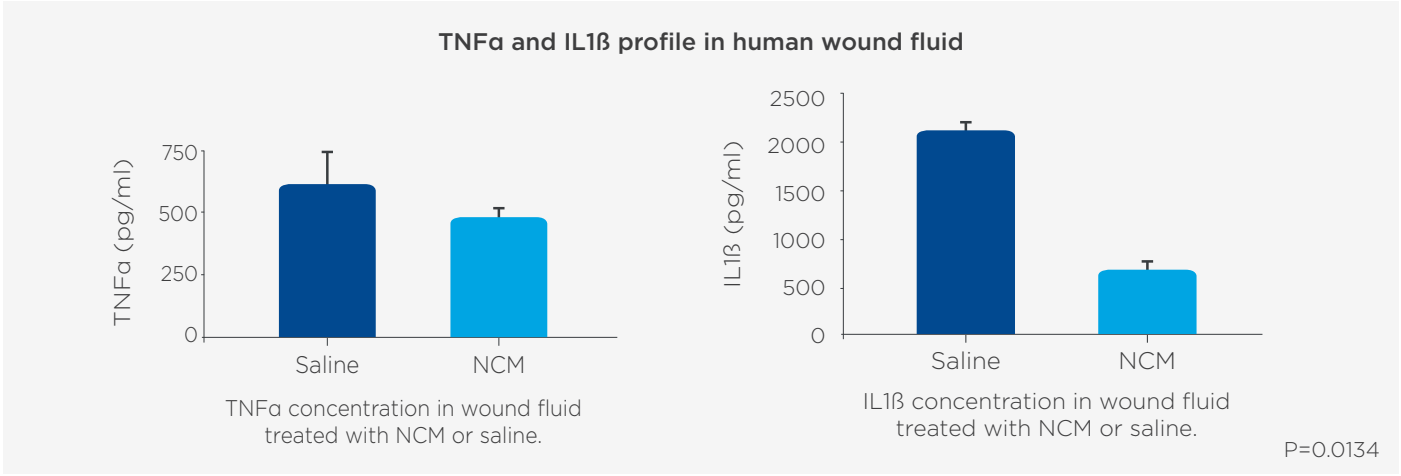
- The excess of protease activity can lead to a chronic non-healing situation.
- When metalloproteinases come into contact with NCM, they can be adsorbed onto their surface favoring tissue regeneration.[7,10]

POLYHEAL® MICRO REACTIVATES THE HEALING PROCESS AND ACCELERATES THE FORMATION OF GRANULATION TISSUE FAVORING CLOSURE.[2]

1. CYTOKINE MODULATION

Cytokines participate in both the inflammatory and the proliferative phase of the wound healing cascade. Controlling the local cytokine milieu is essential for promoting either inflammation or wound healing; in this regard, hydrophilic and anionic surfaces (such as PolyHeal® Micro NCM) promote an anti-inflammatory response by influencing selective cytokine production by adherent monocytes and macrophages.[8,9]

Characterization of cytokine gene expression profile in human monocytes / lymphocytes treated with NCM.[9]



RESULTS

TNFα and IL1ß concentrations were lower in wound fluid treated with NCM than the one treated with saline.

2. ADDITIONAL SURFACE AREA FOR CELL ATTACHMENT

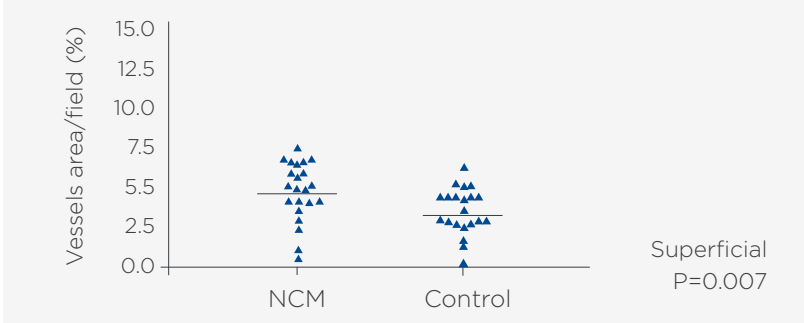
The binding of the cells involved in the healing cascade to NCM results in cell activation, proliferation and migration. These cells are mainly macrophages, fibroblasts, endothelial cells and keratinocytes. Many tests, *in vitro* and *in vivo,* were performed to these cells, proving the effects of NCM.[3,4]

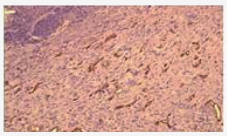
The main results of the activation, proliferation and migration of these cells are:

ENDOTHELIAL CELLS

Their main function is to favor angiogenesis - the formation of new blood vessels in the wound.

Formation of blood vessels in wounds treated with NCM: comparative rat study on granulation tissue appeareance.[6]





Vessels in a treated case, superficial zone.

Vessels in a control case, superficial zone.

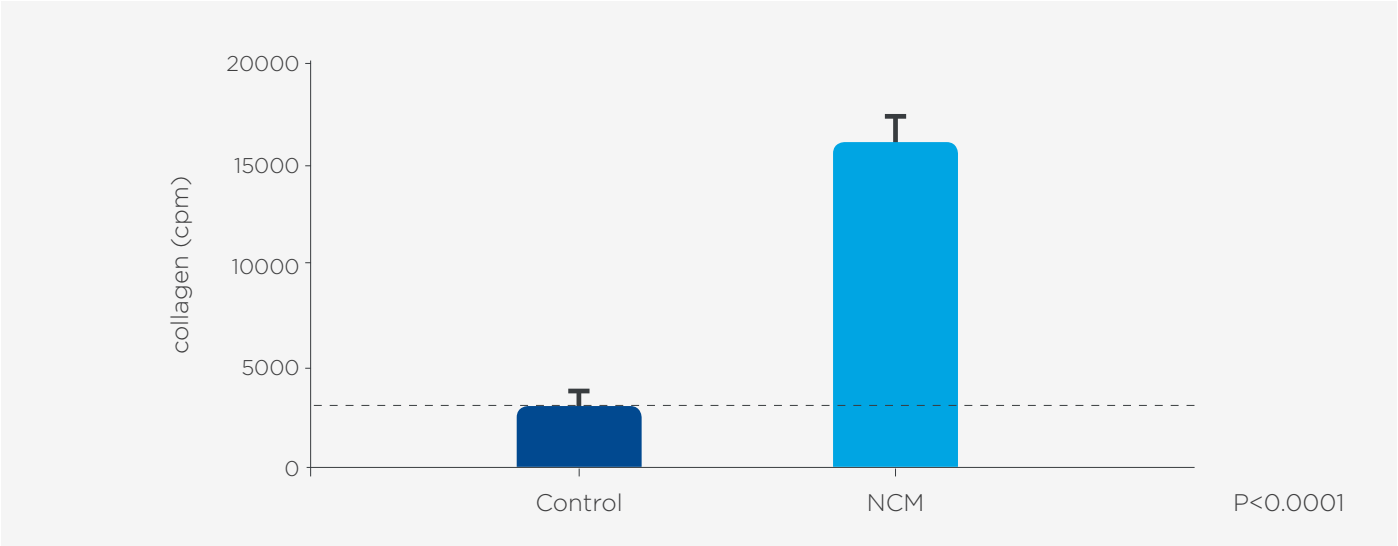
RESULTS

The treatment with NCM of chronic wounds has shown positive results in the formation of new blood vessels.

FIBROBLASTS

Their main function is the synthesis of collagen. An increase in collagen synthesis has been observed both *in vitro* and *in vivo*.[6]

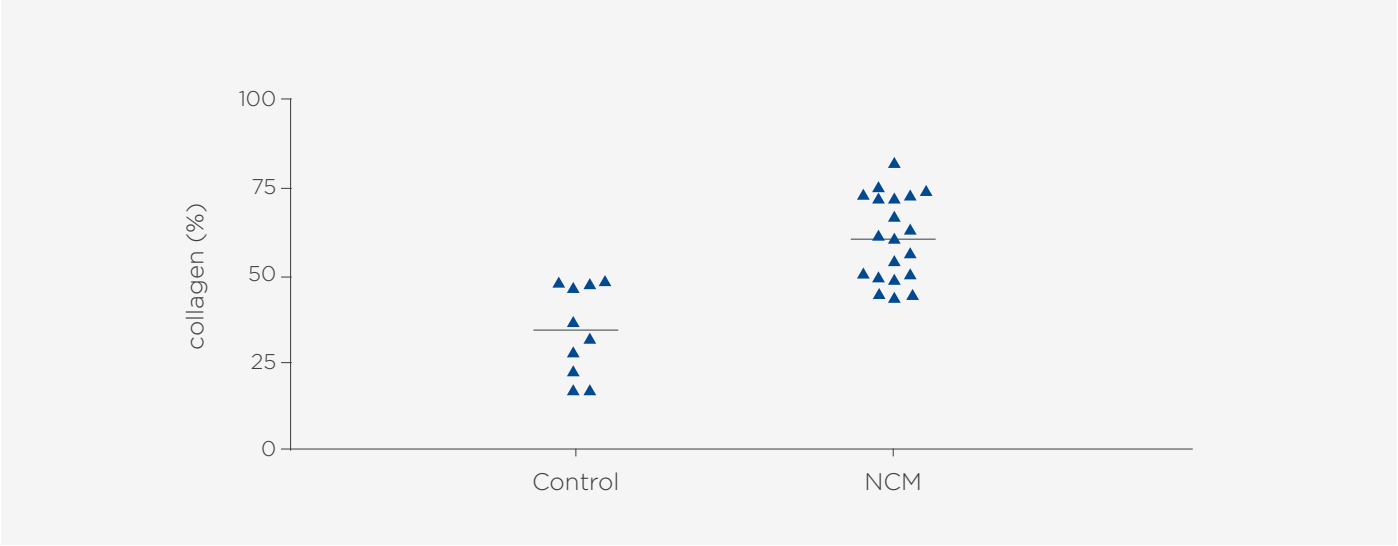
Effect of NCM on collagen synthesis in human dermal fibroblast.[5,6]



RESULTS

The treatment with NCM significantly (P<0.0001) promotes collagen synthesis by cultured fibroblasts, resulting in 5.3 times more collagen in treatment than control.

Effect of NCM on collagen synthesis after 96 hours treatment in excision wound in rats.[6]



RESULTS

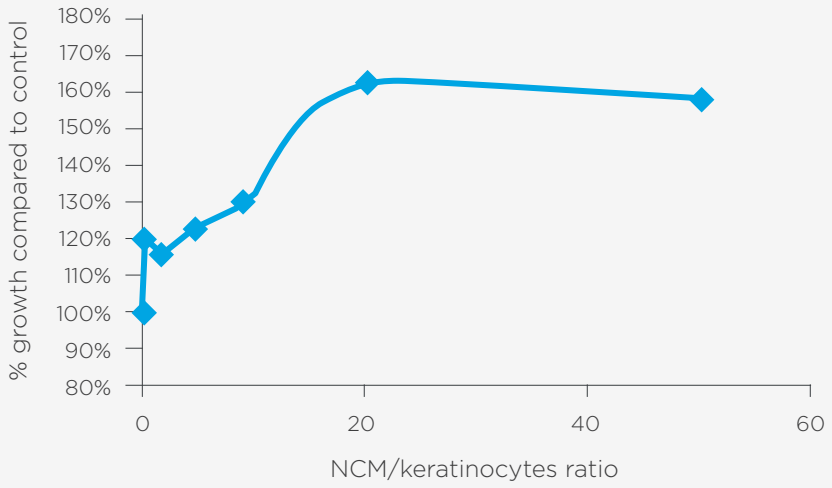
The treatment with NCM increases collagen synthesis in wounds in rats.

KERATINOCYTES

Their main function is wound epithelization.

Effect of NCM on keratinocytes mass.[9]

- Human keratinocytes Proliferation and Migration *in vitro* (HaCaT), 72 hrs.
- Rate of filling of exposed surface by seeded cells with NCM application.



RESULTS

The treatment with NCM increases keratinocytes mass.

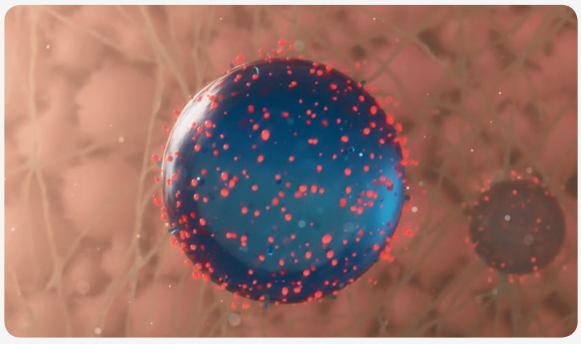
3. METALLOPROTEINASES SEQUESTRATION

PolyHeal® Micro decreases the concentration of Matrix Metalloproteinases (MMPs) in the wound bed. MMPs are enzymes involved in the remodeling of connective tissues during wound healing. Increased concentration of MMPs destroy components of the Extracellular Matrix, impairing tissue regeneration.[7,10]

MMPs adsorbed by NCM

MMPs in contact with NCM, can be adsorbed onto their surface.

This neutralizes their action because of a decrease in their concentration, reducing degradation of Extracellular Matrix and favouring tissue regeneration.[7,10]



POLYHEAL MICRO

- Unique Microsphere Technology that reactivates healing, including wounds with exposed bones and tendons.[7]
- Easy and rapid topical application in difficult access areas like interdigital or cavitated.[11]
- Can be applied by the own patient or a trained caregiver.[11]
- Demonstrated efficacy leading to patient´s own cells to reactivate the healing process.[2,7]
- Rapidly produces healthy red granulation tissue, regardless of wound etiology.[2,7]
- Offers the choice of wound closure by secondary intention or grafting.[2]
- Proven long-term efficacy and safety. Reduction in wound care expenditure and hospitalization burdens.[6]

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This document is addressed to HCPs only.

For further information about PolyHeal® Micro, please refer to the electronic Instructions for Use at the following website: www.polyhealmicro.com/docs/instructions_for_use.pdf

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