

endoret[®] (prgf[®])

Endogenous Regenerative Technology

MUSCULOSKELETAL SYSTEM



www.endoret.com



bti[®]

Regenerative
Medicine
Human Technology

LEADER IN REGENERATIVE MEDICINE

BTI Biotechnology Institute is a Spanish biomedicine company focused on the development of translational research projects (R&D+i).

BTI is a world-level scientific leader in regenerative medicine using ENDORET in different fields of medicine.

**MORE THAN 5000 M² DEVOTED TO TRAINING,
CLINICAL PRACTICE AND RESEARCH**

TRAINING

**WE TRAIN IN ORDER TO OPTIMISE
THE CLINICAL RESULTS**

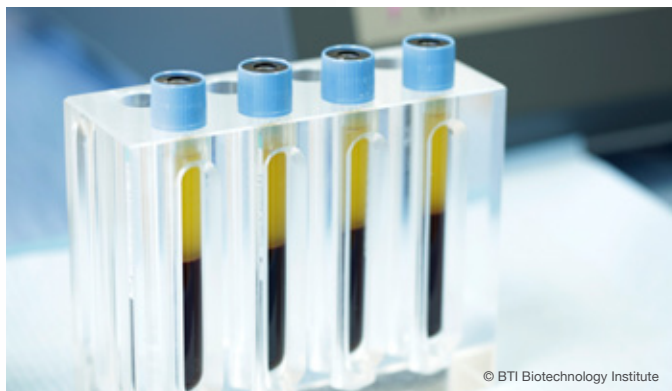
Specific training aimed at different medical specialisations.

More than 40 scientific collaboration agreements with universities and research institutes all over the world.

More than **1200 students** per year of all nationalities.

CLINICAL
PRACTICE

TRANSLATIONAL RESEARCH:
KNOWLEDGE ACQUIRED IN THE
LABORATORY APPLIED TO CLINICAL
PRACTICE



Collaboration with experts from different countries
in different fields of medicine for the development of
clinically effective protocols.

RESEARCH

MORE THAN 100 INDEXED
SCIENTIFIC PUBLICATIONS BACK THE
EFFECTIVENESS AND BIOSAFETY OF
ENDORET®

20% of the workforce dedicated to research.

More than **15 years of research** in tissue regeneration.

"Principe Felipe" prize for technological innovation.



ENDORET® TECHNOLOGY

1 WHAT IS IT?

ENDORET® IS A BIOMEDICAL TECHNOLOGY AIMED AT STIMULATING TISSUE REGENERATION BY APPLYING AUTOLOGOUS PROTEINS.

© BTI Biotechnology Institute

Hundreds of endogenous proteins affect the tissue repair processes, including angiogenesis, chemotaxis and cell proliferation. No exogenic agent can effectively govern all these processes. ⁽¹⁾

Endoret technology provides the necessary means for the isolation and concentration of the blood proteins involved in tissue regeneration, as well as its suitable application at the injury site. ⁽²⁾

(1) Anitua E, Sánchez M, Orive G, Andia I. Delivering growth factors for therapeutics. *Trends Pharmacol Sci.* 2008;29:37-41.

(2) Anitua E. Plasma rich in growth factors: preliminary results of use in the preparation of future sites for implants. *Int J Oral Maxillofac Implants.* 1999;14:529-535.

(3) Anitua E, Sánchez M, Zalduendo MM, de la Fuente M, Prado R, Orive G, Andia I. Fibroblastic response to treatment with different preparations rich in growth factors. *Cell Prolif.* 2009;42:162-170.

(4) Anitua E, Sánchez M, Nurden AT, Zalduendo M, de la Fuente M, Orive G, Azofra J, Andia I. Autologous fibrin matrices: a potential source of biological mediators that modulate tendon cell activities. *J Biomed Mater Res A.* 2006;77:285-293.

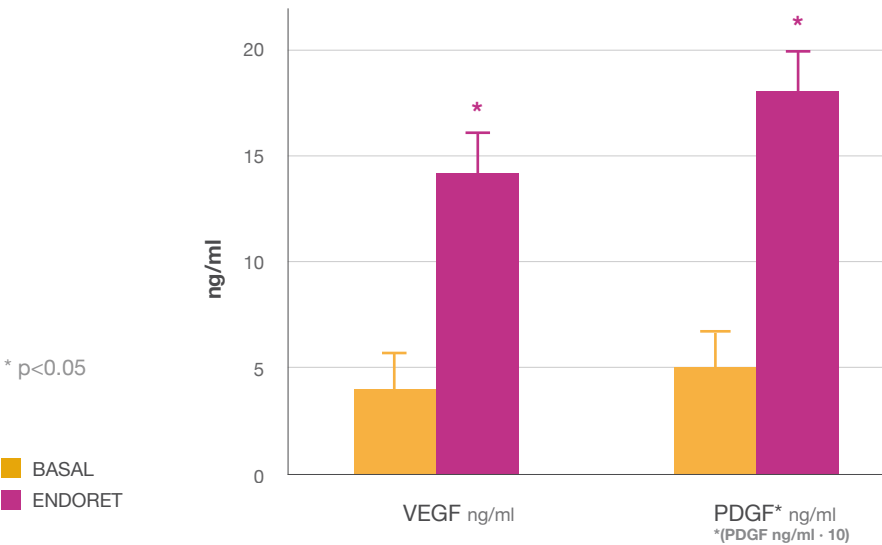
(5) Anitua E, Zalduendo MM, Alkhraisat MH, Orive G. Release kinetics of platelet-derived and plasma-derived growth factors from autologous plasma rich in growth factors. *Ann Anat.* 2013.

2 ACTIVE PRINCIPLE

A. GROWTH FACTORS

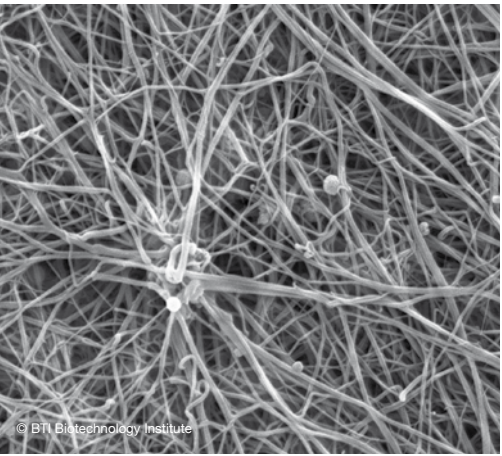
ENDORET stimulates tissue regeneration due to its content in growth factors, in greater concentrations than those of blood. ⁽³⁾

QUANTIFICATION OF THE INCREASE IN VEGF (VASCULAR ENDOTHELIAL GROWTH FACTOR) **AND PDGF** (PLATELET DERIVED GROWTH FACTOR)



B. FIBRIN MEMBRANE

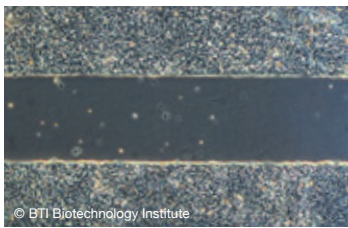
Enables the balanced and gradual release of a large number of molecules, including growth factors and other proteins. ^{(4) (5)}



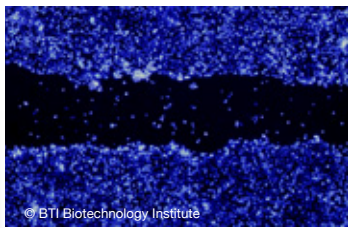
3 MECHANISMS OF ACTION

1. Promoting **angiogenesis**
2. Stimulating **cell migration** ⁽⁶⁾
3. Increasing **cell proliferation** ⁽⁷⁾
4. Decreasing **inflammation** ⁽⁸⁾
5. Stimulating **autocrine and paracrine secretion**

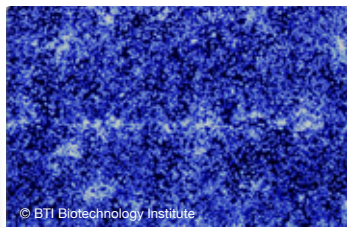
ENDORET ACCELERATES CELL MIGRATION FOR REGENERATIVE PURPOSES ⁽⁶⁾



CONTROL (0H.)



CONTROL (24H.)



ENDORET® (24H.)



SCAN THE CODE WITH
YOUR SMARTPHONE
TO WATCH THIS
VIDEO

ENDORET® TECHNOLOGY REDUCES THE TISSUE REPAIR TIME ^{(9) (10)}

RESPONSE OF THE TISSUE

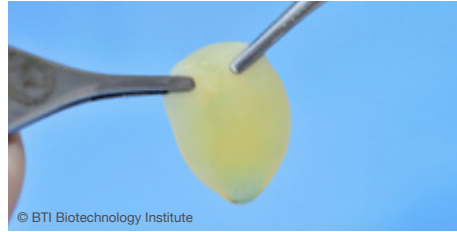


4 THERAPEUTIC FORMULATIONS

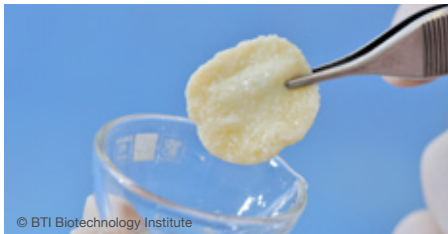
With Endoret technology we can make **4 different therapeutic formulations** and adapt them to the different clinical goals.⁽¹¹⁾



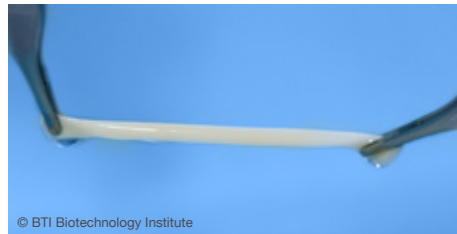
1. LIQUID



2. CLOT



3. AGGLUTINATING A GRAFT
WITH BIOMATERIAL



4. MEMBRANE

5 SAFETY

Autologous product, there are no incompatibilities **nor risk of rejection.**

All the formulations of ENDORET have a **bacteriostatic and bactericidal effect**, especially during the 4 hours after application.⁽¹²⁾

More than 700,000 patients have been treated in more than 20 countries, **without any adverse effects being reported.**

(6) Anitua E, Troya M, Orive G. Plasma rich in growth factors promote gingival tissue regeneration by stimulating fibroblast proliferation and migration and by blocking transforming growth factor- β 1-induced myodifferentiation. *J Periodontol.* 2012 Aug;83(8):1028-37. doi: 10.1902/jop.2011.110505. Epub 2011 Dec 6.

(7) Anitua E, Prado R, Orive G. Bilateral sinus elevation evaluating plasma rich in growth factors technology: a report of five cases. *Clin Implant Dent Relat Res.* 2012;14:51-60.

(8) Bendinelli P, Matteucci E, Dogliotti G, Corsi MM, Banfi G, Maroni P, Desiderio MA. Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: mechanisms of NF- κ B inhibition via HGF. *J Cell Physiol.* 2012;225:757-766.

(9) Sánchez M, Anitua E, Azofra J, Andía I, Padilla S, Mujika I. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. *Am J Sports Med.* 2007;35:245-251.

(10) Anitua E. Plasma rich in growth factors: preliminary results of use in the preparation of future sites for implants. *Int J Oral Maxillofac Implants.* 1999;14:529-535.

(11) Anitua E, Sánchez M, Orive G, Andía I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. *Biomaterials.* 2007;28:4551-4560.

(12) Anitua E, Alonso R, Gírbau C, Aguirre JJ, Muruzabal F, Orive G. Antibacterial effect of plasma rich in growth factors (PRGF) against *Staphylococcus aureus* and *epidermidis* strains. *Clin Exp Dermatol.* 2012.

APPLICATIONS

OF ENDORET® TECHNOLOGY

1 ARTHRITIS

ENDORET® IS THE ONLY PLASMA RICH IN GROWTH FACTORS WHICH HAS BEEN PROVEN TO BE EFFECTIVE IN TWO CLINICAL TRIALS AT EVIDENCE LEVEL I

1.1 EVIDENCE LEVEL I CLINICAL TRIAL

ENTROA⁽¹³⁾: ENDORET® TREATMENT FOR OSTEOARTHRITIS

Randomised clinical trial for the evaluation of ENDORET compared to hyaluronic acid (3 infiltrations) in the treatment of symptomatic osteoarthritis of the knee.

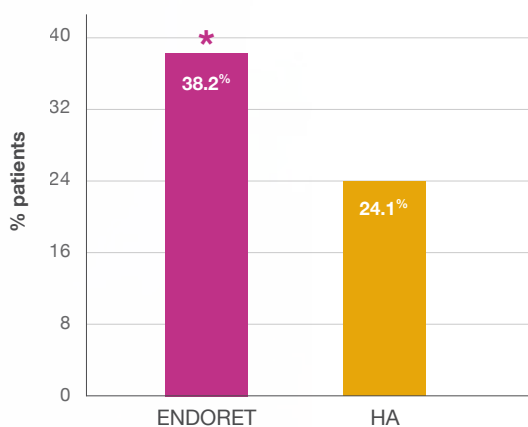
ENDORET® LESSEN SIGNIFICANTLY THE PAIN AND THE RIGIDITY OF THE OSTEOARTHRITIS OF THE KNEE^{(14) (15) (16) (17)}

70% OF PATIENTS IMPROVED WITH ENDORET®⁽¹³⁾

% OF PATIENTS WITH A **SIGNIFICANT** REDUCTION IN PAIN* 6 MONTHS AFTER TREATMENT

* $p < 0.05\%$

& Defined as a reduction of 50% on the WOMAC pain subscale.



During the study period, ENDORET **reduced pain more and more effectively** while the efficiency of hyaluronic acid was gradually reduced.

None of the patients treated with ENDORET presented **adverse reactions to the treatment.**

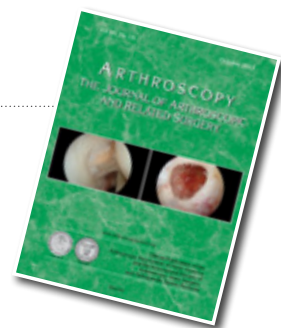
★ ★ ★
PRIZE FOR THE
BEST STUDY
AT EVIDENCE
LEVEL I
2012
★ ★ ★

ARTHROSCOPY
THE JOURNAL OF ARTHROSCOPIC
AND RELATED SURGERY

1.2 EVIDENCE LEVEL I CLINICAL TRIAL

ENLOA⁽¹⁸⁾: ENDORET® LONG TERM TREATMENT FOR OSTEOARTHRITIS

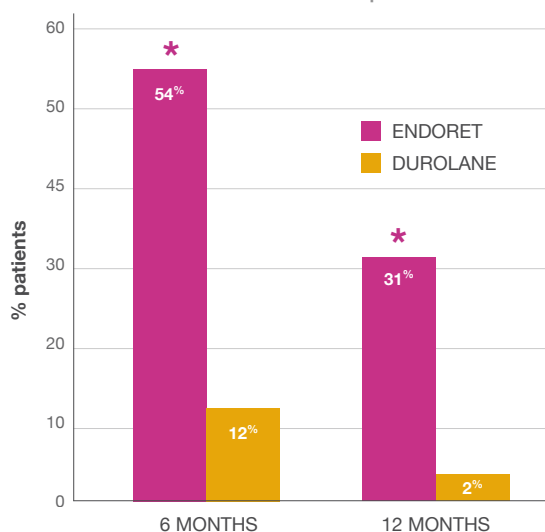
Randomised clinical trial for the evaluation of ENDORET compared to hyaluronic acid in the treatment of symptomatic osteoarthritis of the knee.



% OF PATIENTS WITH A SIGNIFICANT REDUCTION IN PAIN* AFTER TREATMENT

* $p < 0.05\%$

‡ Defined as a reduction of 50% on the WOMAC pain subscale.



UP TO 83% OF PATIENTS TREATED WITH ENDORET® EXPERIENCED LESS PAIN

60% of patients continued to report less pain* a year after treatment with ENDORET.

ENDORET is safe and significantly superior in terms of pain reduction than Durolane (hyaluronic acid) after 24 and 48 weeks of treatment.

*At least a 30% reduction in pain.

- (13) Sánchez M, Fiz N, Azofra J, Usabiaga J, Aduriz Recalde E, García Gutiérrez A, Albillos J, Gárate R, Aguirre JJ, Padilla S, Orive G, and Anitua E. A Randomized Clinical Trial Evaluating Plasma Rich in Growth Factors (PRGF-Endoret) Versus Hyaluronic Acid in the Short-Term Treatment of Symptomatic Knee Osteoarthritis. *Arthroscopy*. 2012. Vol 28, No 8 (August): pp 1070-1078.
- (14) Andia I, Sánchez M, Maffulli N. Joint pathology and platelet-rich plasma therapies. *Expert Opin Biol Ther*. 2012;12:7-22.
- (15) Anitua E, Sánchez M, Nurden AT, Zaldueño MM, de la Fuente M, Prado R, Orive G, Andia I. Relationship between Investigative Biomarkers and Radiographic Grading in Patients with Knee Osteoarthritis. *Int J Rheumatol*. 2009;2009:747432.
- (16) Anitua E, Sánchez M, Nurden AT, Zaldueño MM, de la Fuente M, Azofra J, Andia I. Fibroblastic response to treatment with different preparations rich in growth factors. *Cell Prolif*. 2009;42:162-170.
- (17) Anitua E, Sánchez M, Nurden AT, Zaldueño MM, de la Fuente M, Azofra J, Andia I. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. *Rheumatology (Oxford)*. 2007;46:1769-1772.
- (18) Vaquerizo V, Plasencia MÁ, Arribas I, Seijas R, Padilla S, Orive G, Anitua E. Comparison of Intra-Articular Injections of Plasma Rich in Growth Factors (PRGF-Endoret) Versus Durolane Hyaluronic Acid in the Treatment of Patients With Symptomatic Osteoarthritis: A Randomized Controlled Trial. *Arthroscopy*. 2013 Oct;29(10):1635-43.

2 TENDINOPATHY AND LIGAMENT INJURIES

ENDORET stimulates the proliferation of the tendon cells and increases the synthesis of key molecules such as VEGF and HGF. ⁽¹⁹⁾ ⁽²⁰⁾

OUTPATIENT INFILTRATION WITH ENDORET® MAY BE AN ALTERNATIVE TO RECONSTRUCTIVE SURGERY ⁽²¹⁾ ⁽²²⁾

In cases of:

- Chronic tendinopathy
- Acute tendon rupture
- Chronic tendon rupture in patients with a low functional demand.
- Torn ligaments



© BTI Biotechnology Institute

ULTRASOUND-GUIDED INFILTRATION OF ENDORET FOR TENDINOPATHY

(19) Anitua E, Andía I, Sanchez M, Azofra J, del Mar Zalduendo M, de la Fuente M, Nurden P, Nurden AT. Autologous preparations rich in growth factors promote proliferation and induce VEGF and HGF production by human tendon cells in culture. *J Orthop Res.* 2005;23:281-286.

(20) Anitua E, Sanchez M, Nurden AT, Zalduendo M, de la Fuente M, Azofra J, Andía I. Reciprocal actions of platelet-secreted TGFβ1 on the production of VEGF and HGF by human tendon cells. *Plast Reconstr Surg.* 2007;119:950-959.

(21) Seijas R, Ares O, Alvarez P, Cusco X, García-Balletbo M, Cugat R. Platelet-rich plasma for calcific tendinitis of the shoulder: a case report. *J Orthop Surg.* 2012;20:126-130.

(22) Mei-Dan O, Carmont M, Kots E, Barchilon V, Nyska M, Mann G. Early return to play following complete rupture of the medial collateral ligament of the elbow using preparation rich in growth factors: a case report. *J Shoulder Elbow Surg.* 2010;19:e1-e5.

(23) Sánchez M, Azofra J, Aizpurúa B, Elorriaga R, Anitua E, Andía I. Aplicación de plasma autólogo rico en factores de crecimiento en cirugía artroscópica - Use of autologous plasma rich in growth factors in Arthroscopic surgery. *Cuadernos de Artroscopia* 2003;10:12-19.

(24) Sánchez M, Anitua E, Azofra J, Prado R, Muruzabal F, Andía I. Ligamentization of tendon grafts treated with an endogenous preparation rich in growth factors: gross morphology and histology. *Arthroscopy.* 2010;26:470-480.

(25) Sánchez M, Anitua E, Lopez-Vidriero E, Andía I. The future: optimizing the healing environment in anterior cruciate ligament reconstruction. *Sports Med Arthrosc.* 2010;18:48-53.

(26) Sánchez M, Anitua E, Azofra J, Andía I, Padilla S, Mujika I. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. *Am J Sports Med.* 2007;35:245-251.

(27) Andía I, Sánchez M, Maffulli N. Platelet rich plasma therapies for sports muscle injuries: any evidence behind clinical practice? *Expert Opin Biol Ther.* 2011;11:509-518.

(28) Loo WL, Lee DY, Soon MY. Plasma rich in growth factors to treat adductor longus tear. *Ann Acad Med Singapore.* 2009;38:733-734.

(29) Hammond JW, Hinton RY, Curl LA, et al. Use of autologous platelet-rich plasma to treat muscle strain injuries. *Am J Sports Med.* 2009;37(6):1135-42.

(30) Sánchez M, Anitua E, Andía I. Application of autologous growth factors on skeletal muscle healing. *2nd World Congress on Regenerative Medicine.* Leipzig, Germany; 2005.



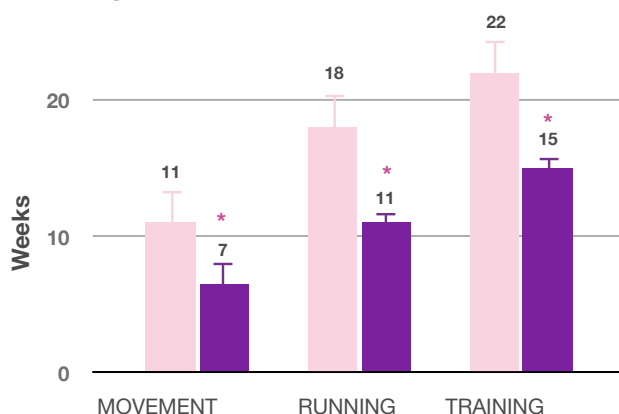
INTRATENDINOUS INFILTRATION DURING SURGERY

ENDORET®
TECHNOLOGY
REDUCES THE
RECOVERY TIME
AFTER SURGERY
BY HALF.⁽²⁶⁾

* $p < 0.05$

■ CONTROL
■ ENDORET

RECOVERY TIME AFTER A SURGICAL RECONSTRUCTION OF A RUPTURED ACHILLES TENDON



Treatment with ENDORET in ACL reconstruction **increases the maturity and ligamentisation of the autologous grafts.** ^{(23) (24) (25)}

3 OTHER APPLICATIONS

ENDORET can help athletes **recover from muscular injuries more quickly.**
^{(27) (28) (29) (30) (31)}

In treatments of pseudoarthritis ENDORET **encourages bone regeneration.** ^{(32) (33)}

(31) Sofian J. Apport des plasmes enrichis en plaquettes dans le traitement des lésions musculaires traumatiques - à propos de 50 cas. Thèse pour l'obtention du diplôme d'Etat de Docteur en Médecine.

(32) Sanchez M, Anitua E, Cugat R, Azofra J, Guadilla J, Seijas R, Andia I. Nonunions treated with autologous preparation rich in growth factors. J Orthop Trauma. 2009;23:52-59.

(33) Seijas R, Santana-Suarez RY, Garcia-Balletbo M, Cuscó X, Ares O, Cugat R. Delayed union of the clavicle treated with plasma rich in growth factors. Acta Orthop Belg. 2010;76:689-693.

COMPONENTS OF ENDORET® TECHNOLOGY

1 ENDORET® DISPOSABLE KIT SINGLE-USE KIT*



* MEDICAL DEVICES CERTIFIED FOR USE WITH MUSCULOSKELETAL INJURIES BY
THE GERMAN NOTIFIED BODY TÜV

EXTRACTION SYSTEM

- Extraction tubes (4)
- Winged blood collection set (1)
- Identification labels (5)

FRACTIONING SYSTEM

- Fractioning tubes (2)
- Plasma Transfer Device® (1)
- Activator (1)
- Activation syringe (1)



KIT EDK1
(AVAILABLE IN OTHER FORMATS)

2 ENDORET® EQUIPMENT*

- Centrifuge System IV
- Plasmaterm H
- Transport rack
- Work rack
- Activation containers



* MEDICAL DEVICES CERTIFIED FOR USE WITH MUSCULOSKELETAL INJURIES BY THE GERMAN NOTIFIED BODY TÜV

3 ENDORET® TRAINING

Exclusive training adapted to medical needs. We share our new clinical research and provide training for innovative, top-quality healthcare.



© BTI Biotechnology Institute

4 ENDORET® CERTIFICATION

We certify the clinical qualification and experience of our customers with our training certificates and BTI certification seals.



ADVANTAGES

OF ENDORET® TECHNOLOGY

Endoret is the technology with the most experience on the market in the development of specific protocols for tissue regeneration, a pioneering technology manufactured exclusively by BTI Biotechnology Institute.

OPTIMUM CONCENTRATION OF PLATELETS

The **right concentration of platelets** affects the final efficacy. ⁽³⁴⁾

FORMULATION FREE OF LEUKOCITES

The inclusion of **leukocytes** increases the pain and inflammation. ⁽³⁵⁾

CONTROLLED ACTIVATION

Enables the formation of the fibrin matrix in situ **and the gradual release of growth factors**, maintaining its efficacy over time. ⁽³⁶⁾

AUTOLOGOUS

It is made from the patient's own blood, so **there are no known adverse effects**. ⁽³⁷⁾

REPRODUCIBLE

The protocol for the preparation process and its clinical application is strictly defined and tested.

VERSATILE

4 therapeutic formulations obtained in the same process means we can adapt the product to the patient's clinical needs. ^{(38) (39)}

(34) Anitua E, Sanchez M, Prado R, Orive G. The type of platelet-rich plasma may influence the safety of the approach. *Knee Surg Sports Traumatol Arthrosc.* 2012.

(35) Filardo G, Kon E, Pereira Ruiz MT, Vaccaro F, Guitaldi R, Di Martino A, Cenacchi A, Fornasari PM, Marcacci M. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. *Knee Surg Sports Traumatol Arthrosc.* 2012.

(36) Anitua E, Sanchez M, Nurdén AT, Zalduendo M, de la Fuente M, Orive G, Azofra J, Andía I. Autologous fibrin matrices: a potential source of biological mediators that modulate tendon cell activities. *J Biomed Mater Res A.* 2006;77:285-293.

(37) Anitua E, Sánchez M, Nurdén AT, Nurdén P, Orive G, Andía I. New insights into and novel applications for platelet-rich fibrin therapies. *Trends Biotechnol.* 2006;24:227-234.

(38) Anitua E, Sánchez M, Orive G. Potential of endogenous regenerative technology for in situ regenerative medicine. *Adv Drug Deliv Rev.* 2010 Jun 15;62(7-8):741-52.

(39) Anitua E, Sánchez M, Orive G, Andía I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. *Biomaterials.* 2007 Nov;28(31):4551-60.

SAFETY AND REGULATORY ASSURANCE

The application of Endoret technology is a **Health Product for Human Use** that **complies with all the regulations** required by the Spanish Agency of Medications and Medical Devices.

QUALITY ASSURANCE

- The ENDORET closed-technique system complies with the **highest standards of quality**.
- Both the system and the materials have the **EC health certificate** awarded by TÜV for specific application to musculoskeletal injuries.

GUARANTEES OF EFFICACY

- BTI has the greatest clinical support in the world published in this field; its effectiveness is proven in **more than 100 international scientific publications**.

ADDITIONAL GUARANTEES

- BTI **certifies its customers' specific training** in the use of this technology.
- In addition, BTI guarantees the **traceability of its materials**, and helps transfer all necessary information to its patients.





bti®

Regenerative
Medicine

Human Technology

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