Endogenous Regenerative Technology

ORAL SURGERY





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Investigación y Formación

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 53,820 SQUARE FEET DEVOTED TO TRAINING, CLINICAL PRACTICE AND RESEARCH

TRAINING

WE TRAIN IN ORDER TO OPTIMIZE THE CLINICAL RESULTS

Specific training aimed at different medical specializations.

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

More than 1200 international students per year.

CLINICAL PRACTICE

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



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

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

20% of the workforce dedicated to research.

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

Prince Felipe Award for Technological Innovation.



RESEARCH

ENDORET® TECHNOLOGY

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

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 means necessary 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, Andía 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 SUBSTANCES

A. GROWTH FACTORS

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



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 ⁽⁶⁾
- 2. Stimulating cell migration ⁽⁷⁾
- 3. Increasing the proliferation ^{(8) (9) (10)}
- 4. Decreasing inflammation and pain⁽¹¹⁾
- 5. Stimulating autocrine and paracrine secretion of growth factors (8) (9) (10)

ENDORET® ACCELERATES CELL MIGRATION FOR REGENERATIVE PURPOSES ⁽⁶⁾



INITIAL STATUS (OH.)

CONTROL (24H.)

ENDORET TECHNOLOGY® REDUCES THE TISSUE REPAIR TIME^{(12) (13)}



SCAN THE CODE WITH YOUR SMARTPHONE TO WATCH THIS VIDEO



⁽⁶⁾ Anitua E, Alkhraisat MH, Orive G. Perspectives and challenges in regenerative medicine using plasma rich in growth factors. J. Control Release 2012;157(1): 29-38.

⁽⁷⁾ 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-B1-induced myodifferentiation. J Periodontol. 2012 Aug;83(8):1028-37. doi: 10.1902/jop.2011.110505. Epub 2011 Dec 6.

⁽⁸⁾ 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-B1-induced myodifferentiation. J. Periodontol. 2012;83(8):1028-37.

4 THERAPEUTIC FORMULATIONS

With ENDORET[®] technology we can make **4 different therapeutic formulations** and adapt them to the different clinical goals. ⁽¹⁴⁾





100% Autologous product, there are no incompatibilities nor risk of rejection.

All the formulations of ENDORET[®] have a **bacteriostatic effect**, especially during the 4 hours after application.⁽¹⁵⁾

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

⁽⁹⁾ Anitua E, Tejero R, Zalduendo MM, Orive G. Plasma Rich in Growth Factors (PRGF-Endoret) Promotes Bone Tissue Regeneration by Stimulating Proliferation, Migration and Autocrine Secretion on Primary Human Osteoblasts. J. Periodontol. 2012 Oct 22. doi:10.1902/jop.2012.120292

⁽¹⁰⁾ Anitua E, Troya M, Orive G. An Autologous Platelet Rich Plasma Stimulates Periodontal Ligament Regeneration. J. Periodontol. 2013 Jan 5. doi:10.1902/jop.2013.120556

⁽¹¹⁾ 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-kB inhibition via HGF. J Cell Physiol. 2012;225:757-766.

⁽¹²⁾ 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.

⁽¹³⁾ 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.

⁽¹⁴⁾ 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.

⁽¹⁵⁾ Anitua E, Alonso R, Girbau 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[®] IN IMPLANTOLOGY



THE USE OF ENDORET® SIGNIFICANTLY INCREASES THE SUCCESS RATE IN TREATMENTS WITH DENTAL IMPLANTS. (16)(17)(18)

When the surface of the implants is wet with ENDORET[®] liquid a fibrin membrane is formed that adheres to the surface of the implant and releases growth factors and improves the osseointegration.

The nano-rough surface of BTI implants is specially designed to boost the biological effects of ENDORET[®].



(16) Anitua E, Orive G, Aguirre JJ, Ardanza B, Andía I. 5-year clinical experience with BTI dental implants: risk factors for implant failure. J Clin Periodontol. 2008 Aug;35(8):724-32.

(19) Anitua E, Piñas L, Begoña L, Orive G. Long-term retrospective evaluation of short implants in the posterior areas: Clinical results after 10-12 years.. J Clin Perio 2013 (In progress).

⁽¹⁷⁾ Anitua E, Orive G, Aguirre JJ, Andía I. Clinical outcome of immediately loaded dental implants bioactivated with plasma rich in growth factors: a 5-year retrospective study. J Periodontol. 2008 Jul;79(7):1168-76.

⁽¹⁸⁾ Anitua E, Orive G. Short implants in maxillae and mandibles: a retrospective study with 1 to 8 years of follow-up. J Periodontol. 2010;81:819-826.

2 TREATMENT OF POST-EXTRACTION SOCKETS

The application of ENDORET[®] in the treatment of post-extraction sockets reduces inflammation and pain, accelerates the epithelization of soft tissues and promotes bone regeneration. ⁽²⁰⁾ (21) (22)

The survival rate of an implant placed in an alveolus post-extraction immediately is 98%, and is a safe, effective and predictable treatment. ⁽²³⁾



ENDORET®-PRGF®

EXTRACTION AND PLACEMENT OF ENDORET® (PRGF®).

CONTROL



PRIMARY CLOSURE OF THE ALVEOLUS AFTER 15 DAYS.



TREATMENT SCHEDULES OF AN ALVEOLUS POST-EXTRACTION



DEFECT AFTER THE DENTAL EXTRACTION .



EPITHELIALIZATION AFTER 15 DAYS PRIMARY CLOSING HAS NOT BEEN ACHIEVED AND THE THICKNESS OF THE KERATINIZED GUM IS LOWER.

FRACTION 1 Fibrin membrane

(20) 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 Jul-Aug;14(4):529-35.

(23) Del Fabbro M, Boggian C, Taschieri S. Immediate implant placement into fresh extraction sites with chronic periapical pathologic features combined with plasma rich in growth factors: preliminary results of single-cohort study. J Oral Maxillofac Surg. 2009 Nov;67(11):2476-84.

⁽²¹⁾ Anitua E. The use of plasma-rich growth factors (PRGF) in oral surgery. Pract Proced Aesthet Dent. 2001 Aug;13(6):487-93; quiz 487-93.

⁽²²⁾ Anitua E, Alkhraisat M, Orive G, Murias A. A randomized clinical trial evaluating plasma rich in growth factors (Endoret) in the treatment of post-extraction mandibular molars. Clin Oral Impl Res 2013;24 (Suppl. 9): 192.

3 REDUCED RISK OF OSTEONECROSIS

Treatment with ENDORET[®] after resecting the necrotic bone increases the activity of the osteoclasts and causes angiogenesis, which can be used as an **adjuvant for patients with BRONJ.**⁽²⁴⁾

The results of various studies suggest that treatment with ENDORET[®] can lessen the risk of developing BRONJ after a dental extraction in high-risk patients in treatment with bisphosphonates.^{(25) (26)}

Treatment	Number of extractions	Osteonecrosis of the maxilla
Control	267	5
Endoret [®] (PRGF [®])	542	0

CLINICAL TRIAL OF THE PREVENTION OF BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAW (BRONJ)

ENDORET® (PRGF®)







CONTROL



4 ENDORET[®] IN THE TREATMENT OF BRONJ

ENDORET was effective in the surgical treatment of bisphosphonate-associated osteonecrosis of the jaw, achieving closure of the defect in 32 patients in a prospective study.⁽²⁷⁾

Endoret restored the function of the inferior dental nerve affected by the BRONJ lesion. ⁽²⁷⁾



ENDORET[®] can be used to agglutinate biomaterial, making it easier to handle and improving its osteoconductive and biological properties, in both heterologous and autologous grafts. ^{(28) (29) (30)}



(24) Mozzati M, Gallesio G, Arata V, Pol R, Scoletta M. Platelet-rich therapies in the treatment of intravenous bisphosphonaterelated osteonecrosis of the jaw: a report of 32 cases. Oral Oncol. 2012 May;48(5):469-74.

(25) Mozzati M, Arata V, Gallesio G. Tooth extraction in patients on zoledronic acid therapy. Oral Oncol. 2012 Sep;48(9):817-21 (26) Scoletta M, Arata V, Arduino PG, Lerda E, Chiecchio A, Gallesio G, Scully C, Mozzati M. Tooth extractions in intravenous bisphosphonate-treated patients: a refined protocol. J Oral Maxillofac Surg. 2013 Jun;71(6):994-9.

(27) Anitua E, Begoña L, Orive G. Treatment of hemimandibular paresthesia in a patient with bisphosphonate-related osteonecrosis of the jaw (BRONJ) by combining surgical resection and PRGF-Endoret. Br J Oral Maxillofac Surg. 2012 Nov 30.doi:pii: S0266-4356(12)00585-2.

(28) Anitua E, Carda C, Andia I. A novel drilling procedure and subsequent bone autograft preparation: a technical note. Int J Oral Maxillofac Implants. 2007 Jan-Feb;22(1):138-45.

(29) 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 Mar;14(1):51-60.

(30) Taschieri S, Corbella S, Del Fabbro M. Use of plasma rich in growth factor for schneiderian membrane management during maxillary sinus augmentation procedure. J Oral Implantol. 2012 Oct;38(5):621-7.

6 TREATMENT OF MAXILLAR ATROPHY

ENDORET[®] improves tissue regeneration, and because of its versatility, it can be used in varius surgical techniques.



The use of ENDORET[®], in combination with the block graft, improves the healing of the flap, avoids exposure of the graft, and improves the post-operative outlook of the patient.

TWO-STAGE CRESTAL SPLIT TREATMENT



A) LONGITUDINAL CORTICOTOMY WITH ULTRASOUND B) USE OF BONE GRAFTS AND FIBRIN MEMBRANES C) EPITHELIZATION AFTER 3 MONTHS D) REOPENING AFTER 3 MONTHS

B. SINUS ELEVATION

ENDORET[®] reduces inflammation and pain. It increases the bone formed and maintains the survival of the bone cells.⁽²⁹⁾

ENDORET[®] is effective in the treatment of perforations in the Schneider membrane ⁽³³⁾



SPLIT-MOUTH STUDY OF ENDORET® VS. CONTROL IN A SINUS ELEVATION PROCEDURE WITH A LATERAL APPROACH. ⁽³²⁾



CONTROL TREATMENT



TREATMENT WITH ENDORET®

ENDORET[®] INCREASES THE REVASCULARIZATION OF THE BONE GRAFT AND THE FORMATION OF MATURE BONE

(31) Anitua E. begoña L. Orive G. Controlled ridge expansion using a two – stage split – crest technique with ultrasonic bone surgery. Implant Dent. 2012 Jun: 21(3): 163 – 170

(32) 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 Mar;14(1):51-60.

(33) Taschieri S, Corbella S, Del Fabbro M. Use of plasma rich in growth factor for schneiderian membrane management during maxillary sinus augmentation procedure. J Oral Implantol. 2012 Oct;38(5):621-7.

(34) Anitua E, Murias-Freijo A, Alkhraisat MH, Orive G. Implant-guided vertical bone augmentation around extra-short implants for the management of severe bone atrophy. J Oral Impl. 2013 (in progress).

C. VERTICAL BONE REGENERATION

The combination of ENDORET® treatment with short and extra-short implants makes restorations in atrophic crests possible without needing to resort to more aggressive techniques. (34)(35)(36)(37)



PERIODONTAL REGENERATION 7)

ENDORET® may be an alternative to the use of dermal material used in the field of mucogingival surgery.



TREATMENT OF GINGIVAL DEFECTS

ENDORET® achieves favourable results in terms of radicular cover and gain in clinical insertion. In addition, it increases the width of keratinized tissue and corrects recession. (38)(39)

⁽³⁴⁾ Anitua E, Murias-Freijo A, Alkhraisat MH, Orive G. Implant-guided vertical bone augmentation around extra-short implants for the management of severe bone atrophy. J Oral Impl. 2013 (in progress). (35) Torres J, Tamimi F, Alkhraisat MH, et al. Platelet-rich plasma may prevent titanium-mesh exposure in alveolar ridge

augmentation with anorganic bovine bone. J Clin Periodontol. 2010 Oct;37(10):943-51.

⁽³⁶⁾ Anitua E, Alkhraisat MH, Orive G. Novel technique for the treatment of the severely atrophied posterior mandible. Int J Oral Maxillofac Implants. 2013 Sep-Oct;28(5):1338-46.

⁽³⁷⁾ Anitua E, Murias-Freijo A, Alkhraisat MH, Orive G. Implant-guided vertical bone augmentation around extra-short implants for the management of severe bone atrophy. J Oral Impl. 2013 (in press).

⁽³⁸⁾ Anitua E, Murias-Freijo A, Alkhraisat MH, Begoña L, Orive G. Plasma rich in growth factors (PRGF-Endoret) associated with connective tissue grafts in the treatment of gingival recessions. Europerio 7, June 6-12, 2012, Vienna, AustriaLafzi et al. J (39) Lafzi A, Faramarzi M, Shirmohammadi A, Behrozian A, Kashefimehr A, Khashabi E. Subepithelial connective tissue graft with and without the use of plasma rich in growth factors for treating root exposure. J Periodontal Implant Sci. 2012 Dec;42(6):196-203.

COMPONENTS of endoret technology®



START EQUIPMENT

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- · BTI ENDORET[®] Centrifuge
- · Plasmaterm H Warming Oven
- · Work rack
- · Activation glass bowls





THE APPLICATION OF ENDORET TECHNOLOGY COMPLIES WITH ALL THE REGULATIONS REQUIRED BY THE SPANISH AGENCY OF MEDICINES AND MEDICAL DEVICES, FOOD AND DRUG ADMINISTRATION AGENCY (FDA) AND EUROPEAN UNION. FOR EUROPEAN UNION OUR MEDICAL DEVICES ARE IDENTIFIED WITH CE MARK.

2 ENDORET® DISPOSABLE KIT SINGLE-USE KIT*



THE APPLICATION OF ENDORET TECHNOLOGY COMPLIES WITH ALL THE REGULATIONS REQUIRED BY THE SPANISH AGENCY OF MEDICINES AND MEDICAL DEVICES, FOOD AND DRUG ADMINISTRATION AGENCY (FDA) AND EUROPEAN UNION. FOR EUROPEAN UNION OUR MEDICAL DEVICES ARE IDENTIFIED WITH CE MARK.

KMU15 - US KIT

- · 6 extraction tubes (TE9)
- · 4 fractioning tubes (TF9)
- · 1 activation syringe
- 1 PTD 2
- · 1 winged blood collection set
- · 5 identification labels
- · 1 tourniquet
- · 1 single use Activator



KMU15 KIT

3 ENDORET® TRAINING

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





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



ANTAGES

ENDORET[®] technology is the market leader 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. (41)

FORMULATION FREE OF LEUKOCYTES

The inclusion of leukocytes increases pain and inflammation (42) and accelerates the deterioration of the fibrin.

CONTROLLED ACTIVATION

Enables the formation of the fibrin matrix in situ and the gradual release of growth factors, maintaining its efficacy over time. ⁽⁴³⁾

AUTOLOGOUS

It is made from the patient's own blood, so there are no known adverse effects. (44)

REPRODUCIBI E

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

VFRSATILE

4 therapeutic formulations obtained in the same process means we can adapt the product to the patient's clinical needs. (45) (46)

(41) 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.

(42) 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.

(43) Anitua E, Sanchez 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. (44) Anitua E, Sánchez M, Nurden AT, Nurden P, Orive G, Andía I. New insights into and novel applications for platelet-rich fibrin therapies. Trends Biotechnol. 2006;24:227-234.

(45) 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. (46) 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 complies with all the regulations required by the Spanish Agency of Medicines and Medical Devices, Food and Drug Administration Agency (FDA) and European Union.

QUALITY ASSURANCE

- The ENDORET[®] closed-technique system complies with the highest standards of quality.
- Both the system and the materials have the CE health certificate awarded by TÜV for specific application to oral surgery.

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.





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