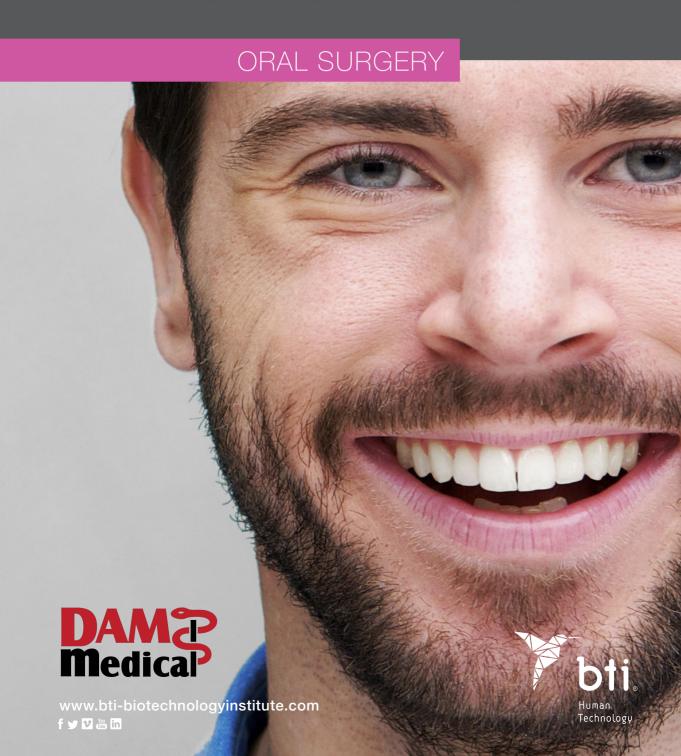


# endoret (prof.)

Endogenous Regenerative 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 M<sup>2</sup> DEVOTED TO TRAINING, CLINICAL PRACTICE AND RESEARCH



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

- · Specific training aimed at different medical specialities.
- More than 40 scientific collaboration agreements with universities and research institutes all over the world.
- · More than 1200 students per year of all nationalities.

# 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.

# MORE THAN 200 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.

## **ENDORET® TECHNOLOGY**

## 1. WHAT IS IT?

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

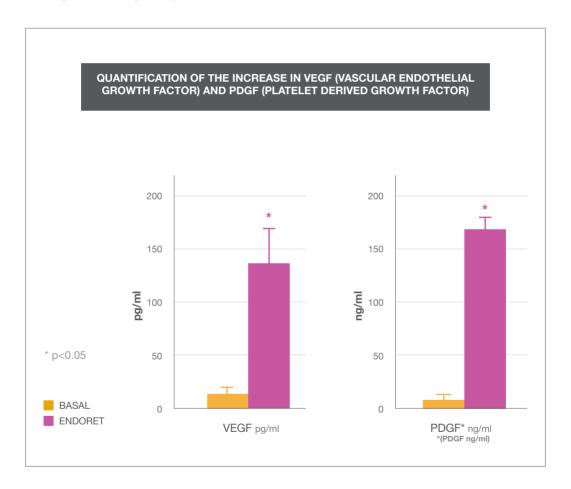
Hundreds of endogenous proteins affect the tissue repair processes, including angiogenesis, chemotaxis and cell proliferation. No exogenic agent can effectively govern all these processes.<sup>(1)</sup>

Endoret technology provides the necessary means for obtaining plasma rich in growth factors from whole blood.

# 2. PROTEINS AND AUTOLOGOUS MATRIX

#### A. GROWTH FACTORS

**ENDORET stimulates tissue regeneration** due to enrichment with growth factors, acting as a biological system. (2)



#### **B. FIBRIN MEMBRANE**

Enables the balanced and gradual release of a large number of molecules, including growth factors and other proteins. (3) (4) (5)

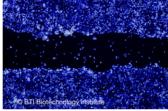
## 3. REGENERATIVE POTENTIAL

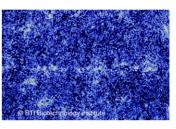
- · Promoting angiogenesis (A).<sup>(6)</sup>
- · Stimulating cell migration (B).(7)
- · Increasing the proliferation (B).(7)(8)(9)
- · Decreasing inflammation and pain(C).(10)(11)(12)
- · Stimulating autocrine and paracrine secretion of growth factors (B). (7)(8)(9)

(A) Pre-clinical study (B) In vitro study (C) Clinical study

#### ENDORET ACCELERATES CELL MIGRATION FOR REGENERATIVE PURPOSES (7)(8)







INITIAL STATUS (OH.)

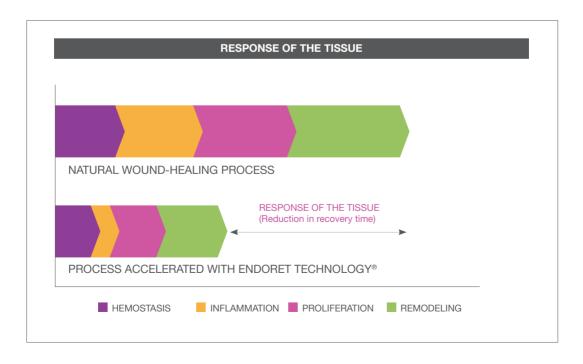
CONTROL (24H.)

ENDORET® (24H.)

# ENDORET® TECHNOLOGY REDUCES THE TISSUE REPAIR TIME IN CLINICAL TRIALS. (13) (14)

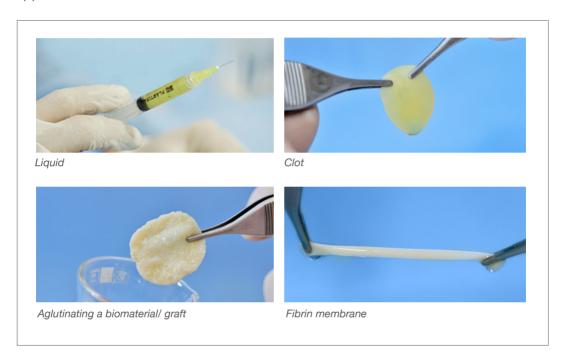


SCAN THE CODE WITH YOUR SMARTPHONE TO WATCH THIS VIDEO



# 4. VERSATILITY

The versatility of the Endoret technology allows for its use in different clinical applications. (15)



# 5. SAFETY

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 (in vitro studies). (16) (17)(18)

More than 1,000,000 patients have been treated in more than 20 countries, without any adverse effects being reported.

### CLINICAL EFFICACY

BTI has the greatest clinical support in the world published in this field; its effectiveness is proven in more than 200 international scientific publications.

# 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. (2) (16)

#### FORMULATION FREE OF LEUKOCYTES

The inclusion of leukocytes increases the pain and inflammation (17) and accelerates the deterioration of the fibrin. (18)

#### CONTROLLED ACTIVATION

Enables the formation of the fibrin matrix in situ and the gradual release of growth factors, maintaining its efficacy over time. (4) (19)

### AUTOLOGOUS

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

#### REPRODUCIBLE

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

#### VERSATILE

4 preparations that can adapt the product to the clinical needs. (15)(21)

# BENEFITS AND APLICATIONS OF ENDORET TECHNOLOGY® IN IMPLANTOLOGY

### 1. INCREASED PREDICTABILITY

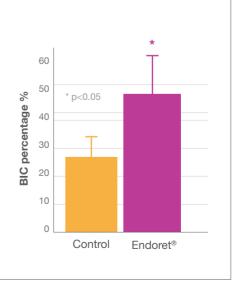
# BTI IMPLANTS COMBINED WITH ENDORET ACHIEVE A HIGH SURVIVAL RATE. (19)(20)(21)(22)

The irrigation of the implant site with ENDORET liquid, contributes to the formation of a fibrin membrane rich in growth factors on the surface of the implant, obtaining with this combination a greater apposition and bone quality. The nano-rough surface of BTI implants is specially designed to boost the biological effects of ENDORET.

HISTOMORPHOMETRIC EVALUATION OF THE BONE-IMPLANT CONTACT SURFACE (BIC) AFTER TWO MONTHS IN GOATS (23)

### SURVIVAL RATES REPORTED IN CLINICAL STUDIES:

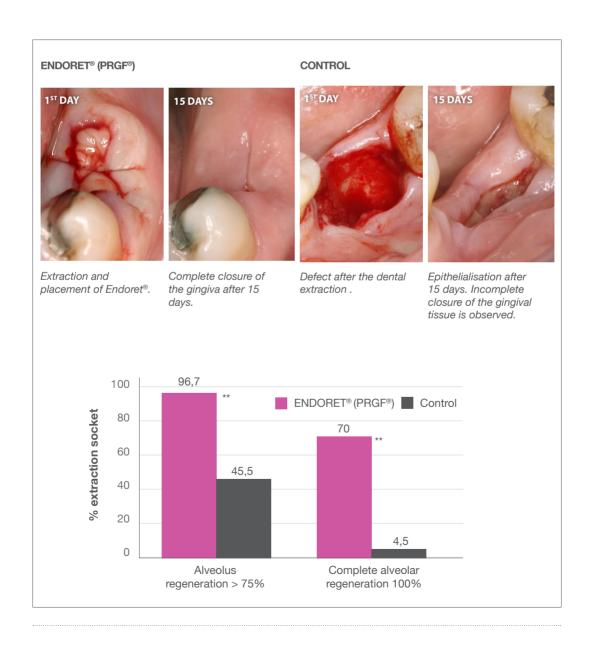
- · Up to 5 years follow-up study 5787 implants. **99.2%** (19)
- Up to 5 years follow-up study
   1139 immediate load implants. 99.3% (17)
- · Up to 8 years follow-up study 1287 short implants. 99.3% (18)
- · 10-12 years follow-up study 111 short implants. **98.9%** (22)



# 2.TREATMENT OF POST-EXTRACTION SOCKET

The application of Endoret® in the treatment of post-extraction socket reduces inflammation and pain, accelerates soft tissues healing and promotes bone regeneration as it has been demostrated in several clinical trials. (11) (14) (24) (25)

The survival rate of inmediately placed dental implant, after tooth extraction, has been 98% in a clinical study. It is a safe, effective and predictable treatment. (26)



PAG. | 9 |

# 3. REDUCED RISK OF OSTEONECROSIS

The results of various clinical studies suggest that treatment with ENDORET can reduce the risk of BRONJ after a dental extraction in high-risk patients under treatment with bisphosphonates. (28)(29)

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) (28)

CONTROL

#### ENDORET® (PRGF®)









# 4. ENDORET® IN THE TREATMENT OF BRONJ

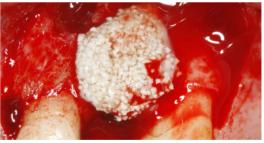
Treatment with ENDORET, after resecting the necrotic bone of BRONJ, may enhance vascularization and regeneration of bone and epithelial tissue as shown in a clinical trial. (27)

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

### 5. PREPARATION OF GRAFTS

ENDORET can be used to agglutinate a biomaterial, making it easier to handle and improving its osteoconductive and biological properties. (10)(30)(31)(32)(33)



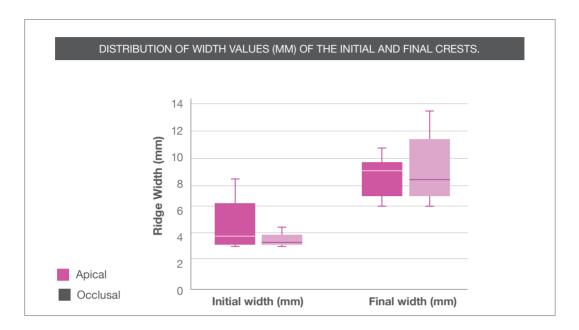


# 6. TREATMENT OF ATROPHIC MAXILLAE

ENDORET improves the tissue regeneration and due to its versatility can be used in various surgical techniques.

#### A. LATERAL BONE AUGMENTATION

The alveolar ridge expansion and the alveolar ridge split techniques in combination with ENDORET can achieve an average bone expansion of 3.35 mm. (34)(35)



The use of ENDORET in combination with the block graft improves the tissue healing, avoiding the exposure of the graft and improves the post-operative recovery of the patient. (36)



### **B.** SINUS ELEVATION

ENDORET reduces inflammation and pain. It increases the new bone formation. (10)(32)(37) ENDORET is effective in the treatment of performations in the Schneider membrane. (31)

### SPLIT-MOUTH STUDY OF ENDORET VS. CONTROL IN A SINUS ELEVATION PROCEDURE WITH A LATERAL APPROACH. (83)



# ENDORET® INCREASES THE FORMATION OF MATURE BONE







treatment with ENDORET®

# **C.** VERTICAL BONE REGENERATION

The combination of Endoret graft with short and extra-short implants makes possible the rehabilitation of atrophic mandible without the need of more aggressive techniques. (38)(39)



# 7. PERIODONTAL REGENERATION

ENDORET may be beneficial in the field of the mucogingival surgery. (40)





Treatment of gingival defects

BIBLIOGRAFY ENDORET® TECHNOLOG

(1) Anitua E, Sánchez M, Orive G, Andia I. Delivering growth factors for therapeutics. Trends Pharmacol Sci. 2008;29:37-41. (2) 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. (3) 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. [4] 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 Oct;195(5):461-6. (5) Anitua E, Prado R, Azkargorta M, Rodriguez-Suárez E, Iloro I, Casado-Vela J, Elortza F, Orive G. High-throughput proteomic characterization of plasma rich in growth factors (PRGF-Endoret)-derived fibrin clot interactome. J Tissue Eng Regen Med. 2015 Nov;9(11):E1-12. (6) Anitua E, Pelacho B, Prado R, Aguirre JJ, Sánchez M, Padilla S, Aranguren XL, Abizanda G, Collantes M, Hernandez M, Perez-Ruiz A, Peñuelas I, Orive G, Prosper F. Infiltration of plasma rich in growth factors enhances in vivo angiogenesis and improves reperfusion and tissue remodeling after severe hind limb ischemia. J Control Release. 2015;202:31-9. (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. (8) 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. 2013 Aug;84(8):1180-90. (9) Anitua E, Troya M, Orive G. An Autologous Platelet Rich Plasma Stimulates Periodontal Ligament Regeneration. J Periodontol. 2013 Nov;84(11):1556-66. (10) 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. (11) Anitua E, Murias-Freijo A, Alkhraisat MH, Orive G. Clinical, radiographical, and histological outcomes of plasma rich in growth factors in extraction socket: a randomized controlled clinical trial. Clin Oral Investig. 2015 Apr; 19(3):589-600. (12) Del Fabbro M, Corbella S, Ceresoli V, Ceci C, Taschieri S. Plasma Rich in Growth Factors Improves Patients' Postoperative Quality of Life in Maxillary Sinus Floor Augmentation: Preliminary Results of a Randomized Clinical Study. Clin Implant Dent Relat Res. 2015 Aug;17(4):708-16. (13) 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. (14) 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. (15) 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. (16) 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 Aug;37(6):652-7. (17) Drago L, Bortolin M, Vassena C, Taschieri S, Del Fabbro M. Antimicrobial activity of pure platelet-rich plasma against microorganisms isolated from oral cavity. BMC Microbiol. 2013 Feb;25(13):47. (18) Drago L, Bortolin M, Vassena C, Romanò CL, Taschieri S, Del Fabbro M. Plasma components and platelet activation are essential for the antimicrobial properties of autologous platelet-rich plasma: an in vitro study. PLoS One. 2014 Sep 18;9(9):e107813. (19) 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. (20) 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. (21) 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. (22) 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 Periodontol. 2014 Apr;41(4):404-11. (23) Anitua E, Orive G, Pla R, Roman P, Serrano V, Andía I. The effects of PRGF on bone regeneration and on titanium implant osseointegration in goats: a histologic and histomorphometric study. J Biomed Mater Res A. 2009 Oct;91(1):158-65. (24) 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. (25) Stumbras A, Januzis G, Gervickas A, Kubilius R, Juodzbalys G. Randomized clinical trial of bone healing after alveolar ridge preservation using xenografts and allografts vs. plasma rich in growth factors. J Oral Implantol. 2020 46(5):515–525. (26) 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. (27) Mozzati M, Gallesio G, Arata V, Pol R, Scoletta M. Platelet-rich therapies in the treatment of intravenous bisphosphonate-related osteonecrosis of the jaw: a report of 32 cases. Oral Oncol. 2012 May;48(5):469-74. (28) Mozzati M, Arata V, Gallesio G. Tooth extraction in patients on zoledronic acid therapy. Oral Oncol. 2012 Sep;48(9):817-21. (29) Scoletta M, Arata V, Arduino PG, Lerda E, Chiecchio A, Gallesio G, Scully C, Mozzati M. Tooth extractions in intravenous bisphosphonatetreated patients: a refined protocol. J Oral Maxillofac Surg. 2013 Jun;71(6):994-9. (30) 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. (31) 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. (32) Torres J, Tamimi F, Martinez PP, Alkhraisat MH, Linares R, Hernández G, Torres-Macho J, López-Cabarcos E. Effect of platelet-rich plasma on sinus lifting: a randomized-controlled clinical trial. J Clin Periodontol. 2009 Aug;36(8):677-87. (33) 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. (34) 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):163-70. (35) Anitua E, Begoña L, Orive G. Clinical evaluation of split-crest technique with ultrasonic bone surgery for narrow ridge expansion: status of soft and hard tissues and implant success. Clin Implant Dent Relat Res. 2013 Apr;15(2):176-87. (36) Anitua E, Alkhraisat MH, Miguel-Sánchez A, Orive G. Surgical correction of horizontal bone defect using the lateral maxillary wall: outcomes of a retrospective study. J Oral Maxillofac Surg. 2014 Apr;72(4):683-93. (37) Del Fabbro M, Corbella S, Ceresoli V, Ceci C, Taschieri S. Plasma Rich in Growth Factors Improves Patients' Postoperative Quality of Life in Maxillary Sinus Floor Augmentation: Preliminary Results of a Randomized Clinical Study. Clin Implant Dent Relat Res. 2015 Aug;17(4):708-16. (38) 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 Implantol. 2015 Oct;41(5):563-9. (39) 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. (40) 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, Austria.

Further readings (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. 2014 Jul;22(7):1708-9. (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 Oct;20(10):2082-91. (43) Anitua E, Zalduendo M, Troya M, Padilla S, Orive G. Leukocyte inclusion within a platelet rich plasma-derived fibrin scaffold stimulates a more pro-inflammatory environment and alters fibrin properties. PLoS One. 2015 Mar 30;10(3):e0121713 (44) 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. (45) Anitua E, Sánchez M, Nurden P, Orive G, Andía I. New insights into and novel applications for platelet-rich fibrin therapies. Trends Biotechnol. 2006;24:227-234. (46) 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.



#### **GERMANY**

Mannheimer Str. 17 75179 Pforzheim · **Alemania** Tel. +49 (0) 7231 428060 Fax +49 (0) 7231 4280615 info@hti-implant de

#### FRANCE

6 Avenue Neil Armstrong Immeuble Le Lindbergh 33692 Merignac CEDEX · Francia Tel: (33) 556 18 11 18 info@bti-implant.fr

#### **ITALY**

Via Conservatorio 22 20122 Milano · Italia Tel: (39) 02 7060 5067 Fax: (39) 02 7063 9876 bti.italia@bti-implant.it

#### MEXICO

B.T.I. Biotechnology Institute S.L. Parque Tecnológico de Álava Leonardo da Vinci ,14 01510 Miñano (Álava) España Ejercito Nacional Mexicano 351, 3A
Col. Granada Delegación Miguel Hidalgo
Messico DF · CP 11520 · Mexico
Tel: (52) 55 52502964
Fax: (52) 55 55319327
bti.mexico@bti-implant.com

#### PORTUGAL

Praça Mouzinho de Albuquerque 113, 54 4100-359 Porto - Portugal Tel: (351) 22 120 1373 Fax: (351) 22 120 1311 bti.portuga|@bticomercial.com

#### UK

3 Churchill Court
Manor Royal
West Sussex, RH10 9LU
Tel: +44 (0) 2039 661873
customerservice@bti-implant.co.ul

#### USA

1730 Walton Road Suite 110 Blue Bell. PA 19422-1802 · USA Tel: (1) 215 646 4067 Fax: (1) 215 646 4066

www.bti-biotechnology institute.com

f 🔰 V 🚻 in



