Organ, Tissue, Regeneration, Repair, Replacement
OTR3® COMPANY OVERVIEW

A REGENERATIVE MEDICINE BIOTECH

OTR3® is a biotechnology company spun off from the University of Paris in 2000 by Professors Denis BARRITAULT and Jean-Pierre CARUELLE.

Denis BARRITAULT is known for his pioneering work on growth factors (discovery of FGF, HARP/PTN).

OTR3® has developed therapeutic agents based on proprietary RGTA® technology which heals lesions by restoring the extracellular matrix and cellular micro-environment.

RGTA® technology has opened a new branch of regenerative medicine and a new therapeutic class of products.

The company has two medical devices (CACIPLIQ20® and CACICOL20®) sold in Europe and other countries worldwide. OTR3® is ISO 13485 certified and has a QSM.

RGTA® based Matrix therapy has now reached the stage where POC has been provided with robust clinical and preclinical data for several major indications, including RCT for corneal lesions.
OUR PRODUCT: CACIPLIQ20®

MORE THAN 20,000 PATIENTS TREATED

More than five years of commercialization of CACIPLIQ20®
VERY STRONG PROOF OF PRODUCT EFFICACY
NO SIDE EFFECTS

INDICATIONS: Any wound that destroys the skin extracellular matrix

✓ Chronic wounds (skin ulcers, post amputation)
✓ General surgical wounds
✓ Aesthetic and plastic surgery (flaps, grafts, lifting, …)
✓ Burns (severe, benign)
✓ Post cancer surgery, irradiation
OUR PRODUCT: CACIPLIQ20®

SPRAY AND KIT PRESENTATIONS

OTR3® markets CACIPLIQ20®, a Class III CE marked medical device for skin healing available in 2 different forms / presentations

1. Single use kit

Complete kit with a sterile gauze.
Two presentations:
✓ 3x 1.5ml
✓ 2x 5ml - for large wounds

2. Multiple use spray - NEW

CACIPLIQ20® in a spray form, designed for healthcare professionals
✓ Up to 50 sprays
✓ One press is enough for wounds up to 8 cm²
✓ Treatment of multiple wounds
  > Preservative - free
  > Safe up to 1 month after first use
OUR TECHNOLOGY

MODE OF ACTION: GENERAL LESIONAL MODEL

Extracellular matrix degraded

Lesion

Degradation of Heparan sulfates

Structural and cellular communication proteins left unprotected

Degradation of matrix proteins

Consequences of the lesion:

INFLAMMATION
OUR TECHNOLOGY

MODE OF ACTION: CHRONIC AND ACUTE LESION

Enzyme

Cell

Collagen

Hyaluronic acid

Fibronectin

Laminin

Elastin

Glycosaminoglycan

Cytokine

Growth factor

Lesion

Destruction, Repair,

Endless Cycle

Destruction...
OUR TECHNOLOGY

MODE OF ACTION: RGTA® EFFECTS IN A GENERAL LESIONAL MODEL

Action of RGTA®

- Replaces degraded Heparan sulfate
- Reconstructs the spatial organization of the scaffold around the cells
- Interacts and protects Structural Proteins and Growth Factors
- Allows regeneration process to resume, creating a niche that favors cell homing

Blocks enzymatic degradation

Reconstruction of the scaffold around the cells

Lesion

Regeneration

RGTA®
EFFECTS OF RGTA

ACTION OF RGTA® IN A STRONG YES/NO MODEL

Regeneration of the sagittal suture and skull vault shape

Adult rat skull critical size defect never makes bone again

Histological section

Lamellar organisation

Osteoblastic cells

X-Ray

saline

35 days later

Lafont T et al. Growth Factors, 1998
RGTA®: substitutions established through screening for CP protection, binding, receptor presentation and transduction.

- REPLACES degraded HS and participates in ECM scaffold;
- PROTECTS ECM and communication proteins from degradation by steric hindrance;
- RESISTS degradation by mammal glycanases and is not metabolized.
1. **P. Desgranges, Vascular surgery - France**
Ischemic stagnant chronic ulcers (7 month no healing), ABPI<0.5, TcPO2<30 mmHg, (mean age 71)
Endpoint: closure at 2 months
Results: 2 months: 38% ulcers closed, surface reduction of 53% (p*** <0.001), 50% closed 3 months.
2 years follow up: no amputation due to unhealed ulcers

2. **S. Groah, Georgetown University Washington - USA**
Venous, pressure ulcers. Average wound duration: 2.5 years (mean age 42)
Endpoint: reduction size and pain 1 month
Results: All responded, ulcers healed (22%) surface reduction: (15-18%) pain reduction by 70%
(p***<0.001)

3. **L. Chaeib, P.I. Slim, endocrinology - Tunisia**
Stagnant diabetic foot ulcers (duration: 38 weeks)
Endpoint: 10 weeks closure /reduction
Results: all patients responded ulcer surface reduction by 80% (p***<0.001) 60% closed 38 Days
4. N. Papanas endocrinology - Greece

Foot and calf ulcers resistant to other therapies (duration: 16 weeks)

End point: Closure of wound

Results: all patients responded, and wound closure in all patients. 67% patients had a complete healing in 4 month or less.

5. C. Lelouarn and G. Zakine aesthetic surgery - France

Two clinical trials with same surgeon using the same procedure:

a) 15 patients for a mammary reduction surgery (one breast treated with CACIPLIQ20®, the other as control)

Results: reduction of pruritus (5 patients), reduction of inflammation (6 patients), and less hypertrophic scarring (3 patients) in patients on the treated side.

b) 100 patients for concentric malar lift (50 treated with CACIPLIQ20®, 50 untreated)

Results: Faster healing with back to normal life in 1 month on average against 2 with CACIPLIQ20® (stat. signif). Edema disappearance in less than one month for 70% of treated versus 0% non treated. Less red eyelid scar.
77 year old diabetic patient with an ischemic ulcer (7 months with no improvement) treated with CACIPLIQ20®

Before treatment

CACIPLIQ20® after 21 days

Painkillers stopped after 2 weeks of treatment

Desgranges P et al., unpublished
CLINICAL CASE: ISCHEMIC FOOT ULCER

65 years old diabetic patient with an ischemic ulcer lasting for 6 months treated with CACIPLIQ20®

**Before**: necrotic tissue  **CACIPLIQ20® after 15 days**

Necrotic lesion

Ulcer Stagnant for 6 months

Complete healing in 72 days with CACIPLIQ20®

With emphasis on healed tissue quality

Case from KSA
Patient treated with CACIPLIQ20® after VAC therapy failure (> 6 month)

Average reported closing time with VAC or standard techniques is 145-160 days (Armstrong et al. Lancet, 2005)
63 years old patient with 3rd degree burn, stagnant for 2 months then treated for 4 months with CACIPLIQ20®

Before treatment

CACIPLIQ20® after 4 months

CACIPLIQ20® CLINICAL EVIDENCE

CLINICAL CASES : PRESSURE ULCER

13 months non healing pressure ulcer treated with CACIPLIQ20®

CACIPLIQ20® after 1 Day

3 weeks

7 weeks

9 weeks

12 weeks

Case from KFSH by Dr. Ali Al Malaq
Post-radiation and removal of scalp basal cell carcinoma, stagnant for more than 4 months then treated with CACIPLIQ20®

Before treatment  CACIPLIQ20® for 3 months  After 24 months

Right-side treated with a single application of CACIPLIQ20®
Left-side untreated in a mammary reduction operation

After a concentric malar lift protocol

Patient 1 untreated

Patient 2 treated with a single application at the time of surgery CACIPLIQ20®
ADDITIONAL SLIDES

Preclinical studies
RGTA® improves healing speed and quality

- Collagen content
  - Collagen biosynthesis type I reversal to normal expression
  - Collagen type III reversal to normal expression
- Improves collagen organization
- Improves mechanical strength
- Histology is returned to pre-injury status
By magnet compression in normal and diabetic rats:

- Magnet disk diameter = 15 mm
- Clamping time = 16 h

→ Ischemia-reperfusion injury (60% perfusion reduction / 45% reperfusion)

Tong M et al. Diabetes, 2012
ACCELERATED DIABETIC ULCER HEALING

Tong M et al. Diabetes, 2012

EFFECT OF RGTA® ON HEALING TIME
RGTA® accelerates Re-epithelialization

Tong M et al. Diabetes, 2012
**EFFECT OF RGTA® ON SCAR QUALITY – RESISTANCE TO BREAKAGE**

**WOUND BREAKING STRENGTH**

RGTA® increases breaking strength

*Tong M et al. Diabetes, 2012*
**EFFECT OF RGTA® ON SCAR QUALITY – COLLAGEN**

**COLLAGEN BIO SYNTHESIS**

**RGTA® co-regulates collagen I et III biosynthesis in ulcerated skin**

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**Type I collagen biosynthesis**

- **Control skin**
- **Ulcerated skin**
- **Ulcerated treated skin**

**Type III collagen biosynthesis**

- **Control skin**
- **Ulcerated skin**
- **Ulcerated treated skin**

*Test: **t**-test, ***p < 0.001, *p < 0.05*
**EFFECT OF RGTA® ON SCAR QUALITY – COLLAGEN**

**HISTOLOGY - SYRUS RED STAINING OF RGTA® TREATED SKIN**

**RGTA® treated tissue structure is similar to healthy controls**

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**Barbier-Chassefière V et al.**

*JBMR, 2008*
RGTA® induces blood vessel formation in ulcers

Tong M et al. Diabetes, 2012
PRE-CLINICAL PUBLICATIONS ON THE EFFECTS OF RGTA® ON SKIN

WOUND HEALING - SCAR QUALITY - BURNED SKIN - SCAR RESISTANCE

- **Tong M et al. Diabetes 2012**
  Diabetes-Impaired Wound Healing Is Improved by Matrix Therapy with Heparan Sulfate Glycosaminoglycan Mimetic OTR4120 in Rats

- **Tong M et al. Wound Repair Regen. 2011**
  Heparan sulfate glycosaminoglycan mimetic improves pressure ulcer healing in a rat model of cutaneous ischemia-reperfusion injury

  Matrix Therapy with RGTA OTR4120 Improves Healing Time and Quality in Hairless Rats with Deep Second-Degree Burns

  Stimulated neovascularization, inflammation resolution and collagen maturation in healing rat cutaneous wounds by a heparan sulfate glycosaminoglycan mimetic, OTR4120

  Matrix Therapy and regenerative medicine, a new approach for chronic wound healing.

- **Tong M, et Al. Wound Repair and Regeneration , 2008, 16, 294-299**
  RGTA OTR 4120, a heparan sulfate proteoglycan mimetic, increases wound breaking strength and vasodilatory capability in healing rat full-thickness excisional wounds

  OTR4120, a heparan sulfate mimic is a possible long-term active agent to heal burned skin.