Cellular Therapies and Regenerative Medicine Strategies in Diabetes and Chronic Degenerative Disease Conditions

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September 2015

MILLER
SCHOOL OF MEDICINE
UNIVERSITY OF MIAMI

DIABETES RESEARCH INSTITUTE
UNIVERSITY OF MIAMI

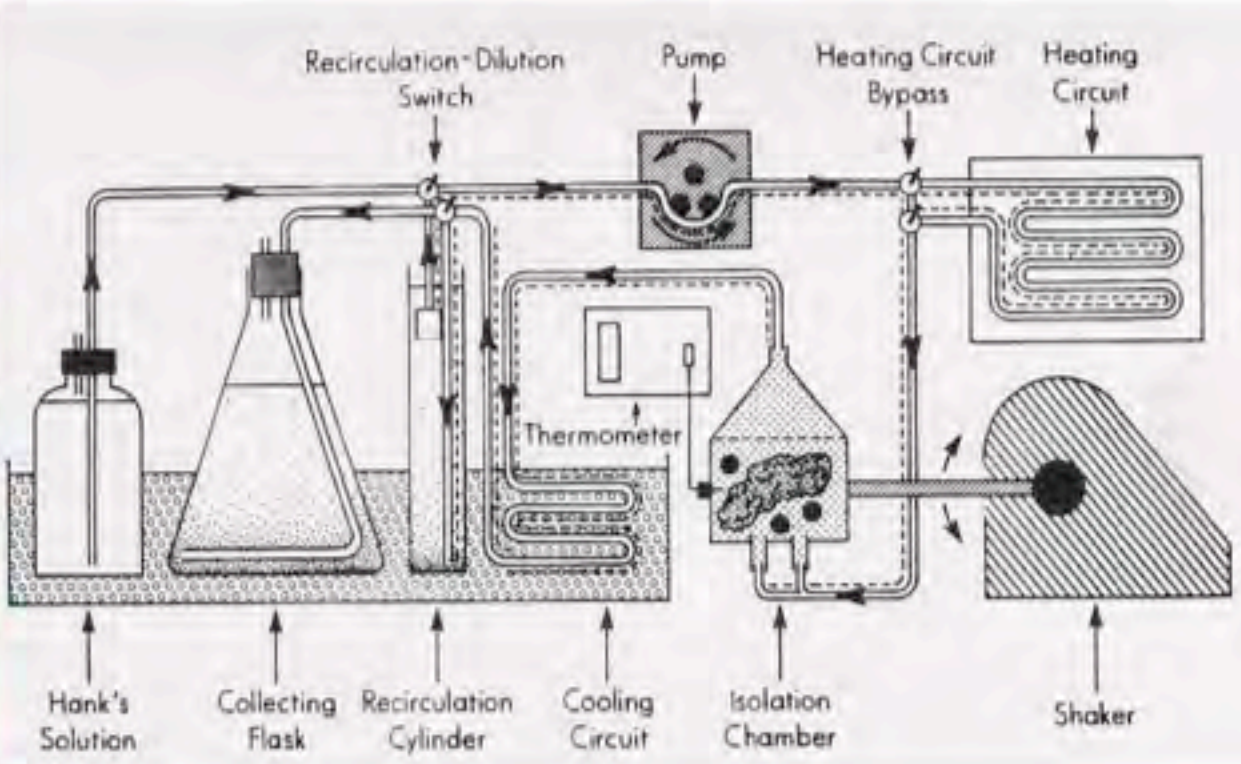
- Center of Excellence of the University of Miami
- MISSION: To Cure Diabetes in the Fastest, Most Efficient and Safest Way Possible
- Home of the UM Cell Transplant Program and the Division of Cellular Transplantation, Dept . Of Surgery
- First cGMP Human Cell Processing Facility in the USA FDA approved to deliver therapeutic cell products across state barriers
- NIH Cell Distribution Center
- FDA approved, FACT and AABB Certified
- Over 160 Physicians, Scientists and Staff
- Coordinating Center of the DRI Federation

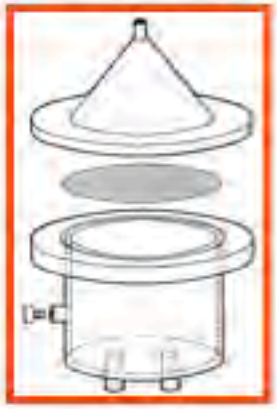
- 387 million people have diabetes
- by 2035 this will rise to 592 million
- Diabetes caused 4.9 million deaths in 2014
- Every seven seconds a person dies from diabetes
- Diabetes caused at least USD 612 billion dollars in health expenditure in 2014 – 11% of total spending on adults
- More than 79,000 children developed type 1 diabetes in 2013
- More than 21 million live births were affected by diabetes during pregnancy in 2013

Reprinted from DIABETES, VOL. 37, NO. 4, APRIL 1988

Automated Method for Isolation of Human Pancreatic Islets

CAMILLO RICORDI, PAUL E. LACY, EDWARD H. FINKE, BARBARA J. OLACK, AND DAVID W. SCHARP





Pancreatic islet transplantation after upper abdominal exenteration and liver replacement

ANDREAS G. TZAKIS CAMILLO RICORDI RODOLFO ALEJANDRO
YIJUN ZENG JOHN J. FUNG SATORU TODO
ANTHONY J. DEMETRIS DANIEL H. MINTZ THOMAS E. STARZL

Lancet 336:402-405, 1990

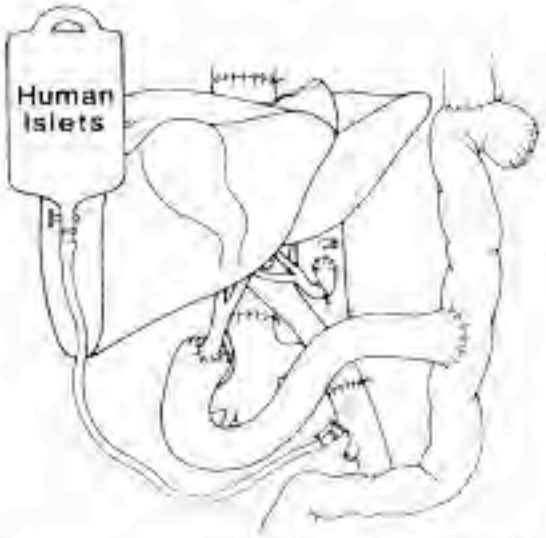


Fig 1—Liver and pancreatic islet transplantation after upper abdominal exenteration.

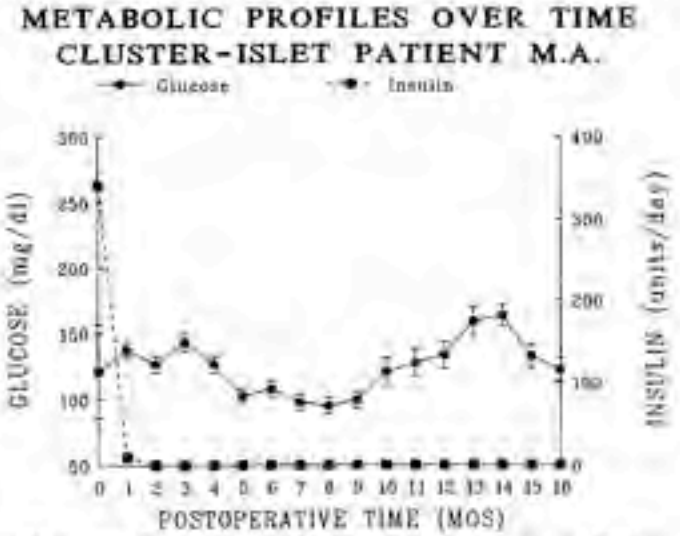
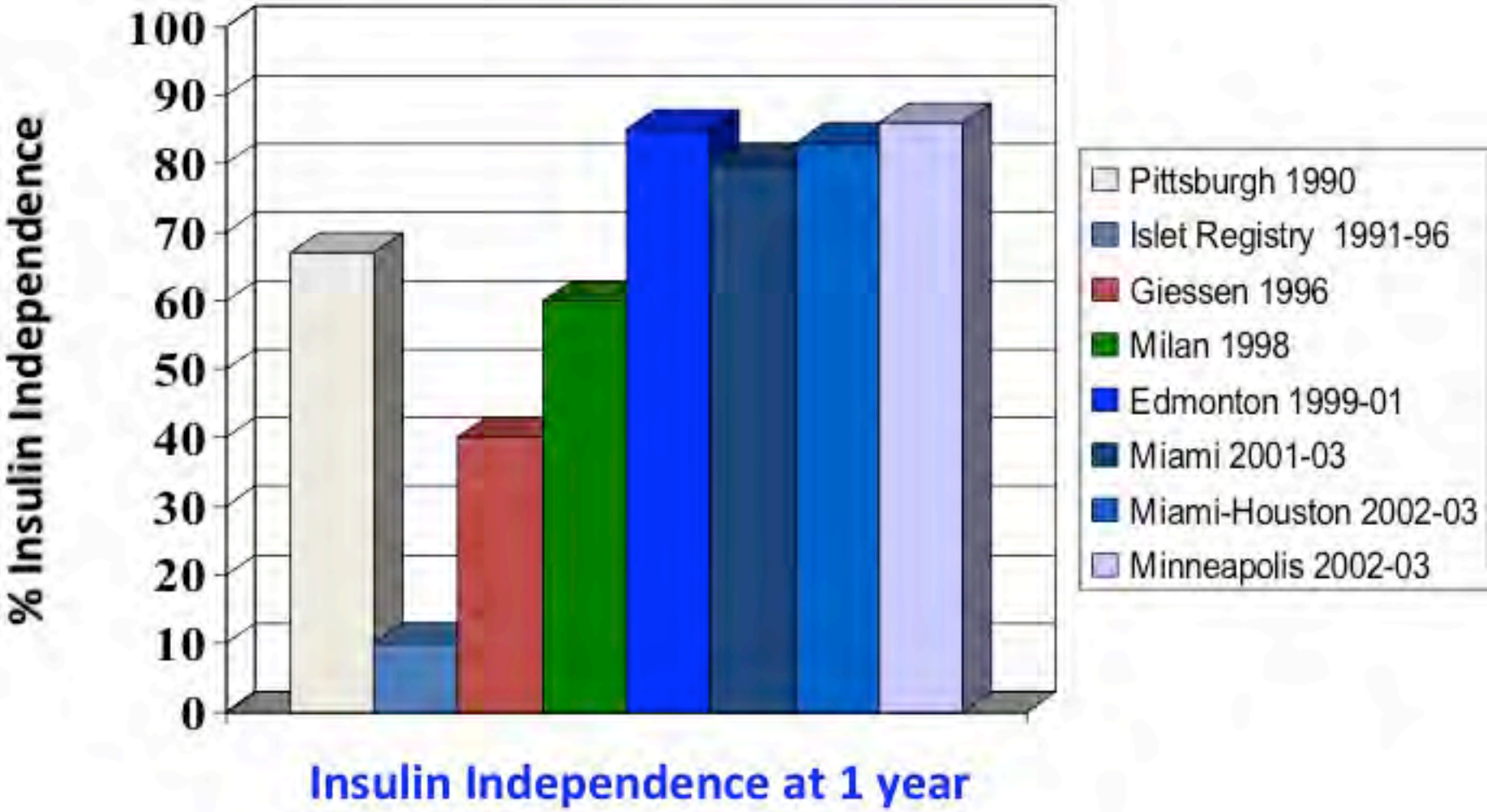


FIGURE 2. Plasma glucose and daily insulin requirements of a cluster-islet patient (group 1, No. 1, Tables 1 and 2), who is still insulin-independent over 16 months following liver-islet allotransplantation.

Islet Transplantation Trials



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The Official Journal of The Cure Alliance

25 Years of the Ricordi Automated Method for Islet Isolation

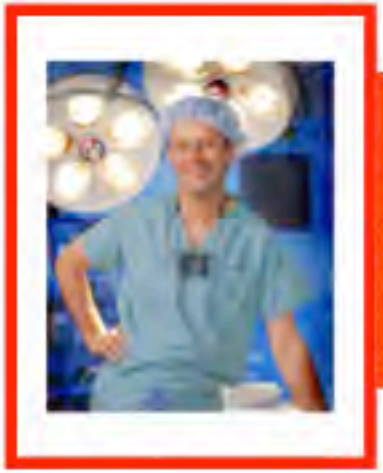
Lorenzo Piemonti , ✉ Antonello Pileggi

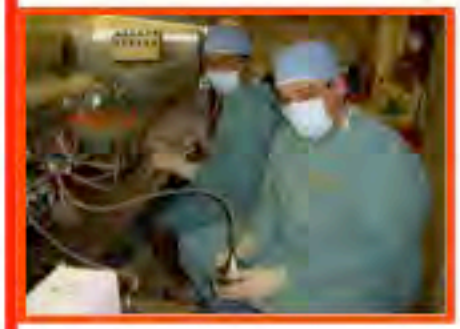
http://www.cellr4.org/article/128

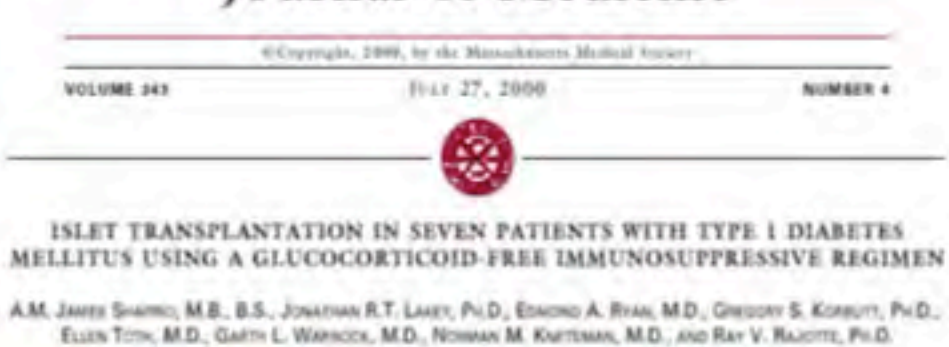
EDOMONTON PROTOCOL

1985-1998 10% Insulin Independence

37% Partial allograft function






The New England
Journal of Medicine

VOLUME 343 JULY 27, 2000 NUMBER 4

ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

A.M. JAMES SHAPIRO, M.B., B.S., JONATHAN R.T. LAKEY, PH.D., EDMOND A. RYAN, M.D., GREGORY S. KOROTT, PH.D., ELLEN TOTH, M.D., GARTH L. WARNOCK, M.D., NORMAN M. KNETEMAN, M.D., AND RAY V. RAJOTTE, PH.D.

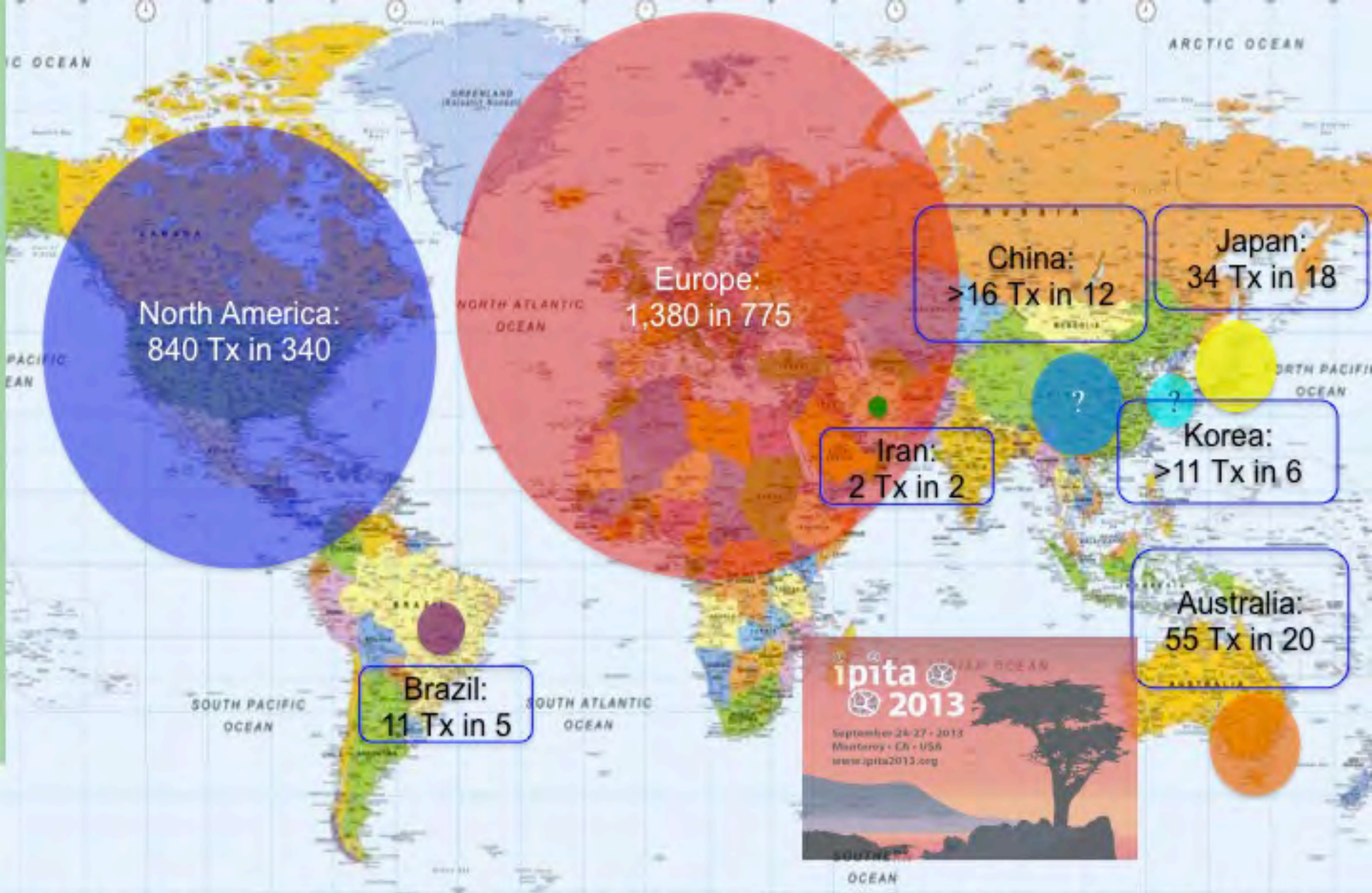
Immunosuppression

- Sirolimus
- Tacrolimus
- Daclizumab
- No steroids

Islet Transplant

- No culture
- 2-4 pancreata (sequential infusions)

2000 100% Insulin Independence rate



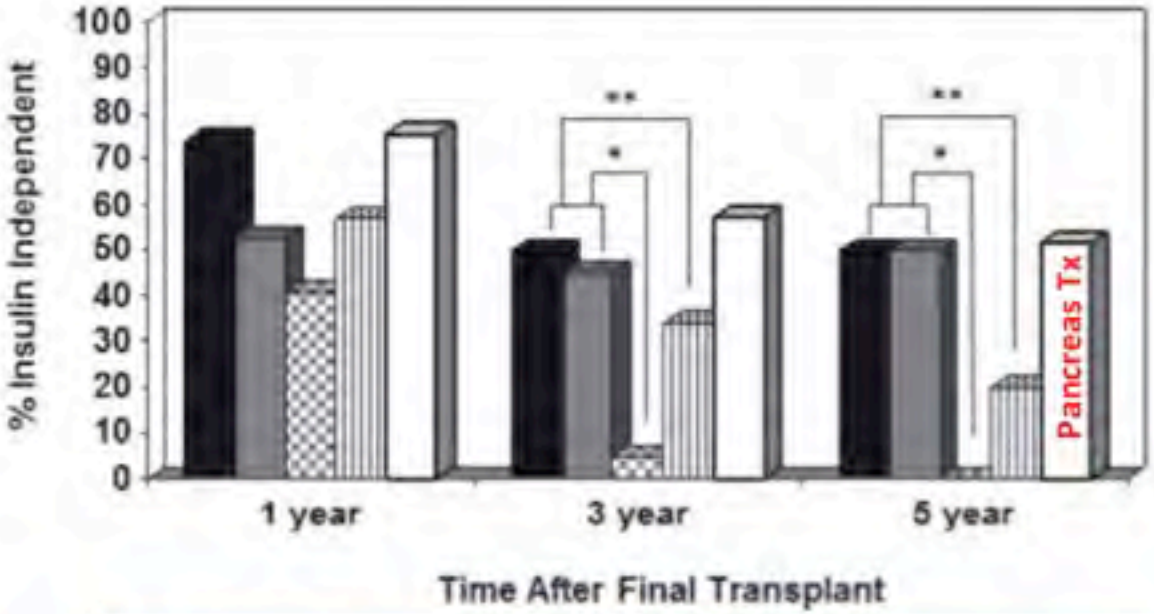
Worldwide clinical islet transplant activity since 1999

T Cell Depleting Antibodies and TNF-α Blockade

Potent Induction Immunotherapy Promotes Long-Term Insulin Independence After Islet Transplantation in Type 1 Diabetes

M. D. Bellin[a,*], F. B. Barton[b], A. Heitman[b], J. Harmon,[c] A. N. Balamurugan,[a] R. Kandaswamy,[c] D.E. Sutherland,[a] R. Alejandro[d] and B. J. Hering[a]

American Journal of Transplantation
2012; 12: 1576–1583

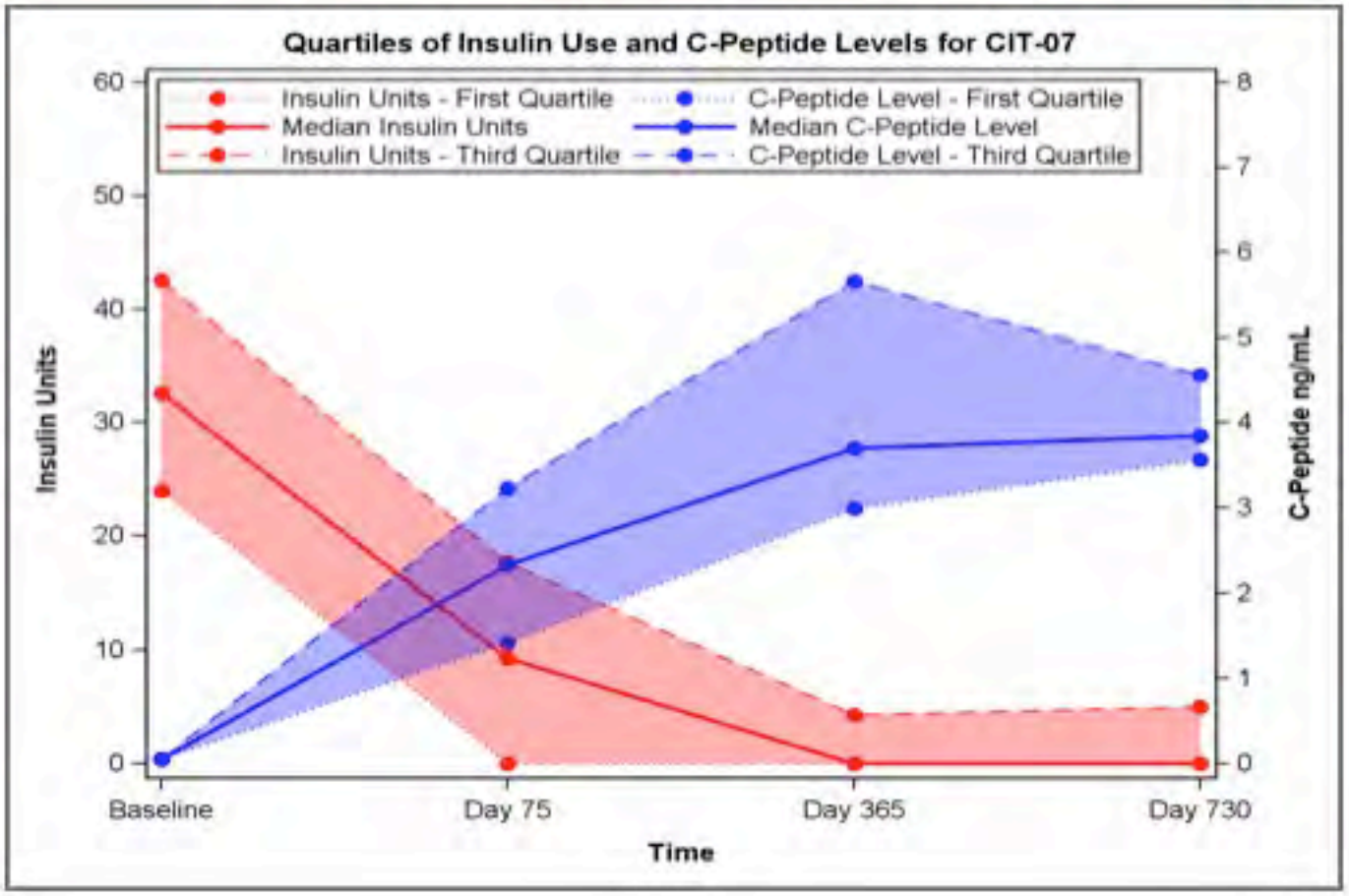


Comparable 5-yr insulin independence rates after solitary pancreas (white bars, 52%) and islet transplantation (grey and black bars, 50%) in non-uremic patients w/ type 1 diabetes

Clinical Islet Transplantation Consortium

Chairperson Steering Committee:
Dr. Camillo Ricordi
University of Miami

Insulin Use and C-Peptide Levels (CIT-07)



Preliminary Conclusions: CIT-07

- Islet products meeting all release criteria can be prepared at multiple manufacturing centers using a standardized protocol
- Subjects enrolled in CIT-07 experienced substantially reduced insulin use and glycemic lability post-transplant
- To date, the CIT-07 protocol shows a favorable safety profile

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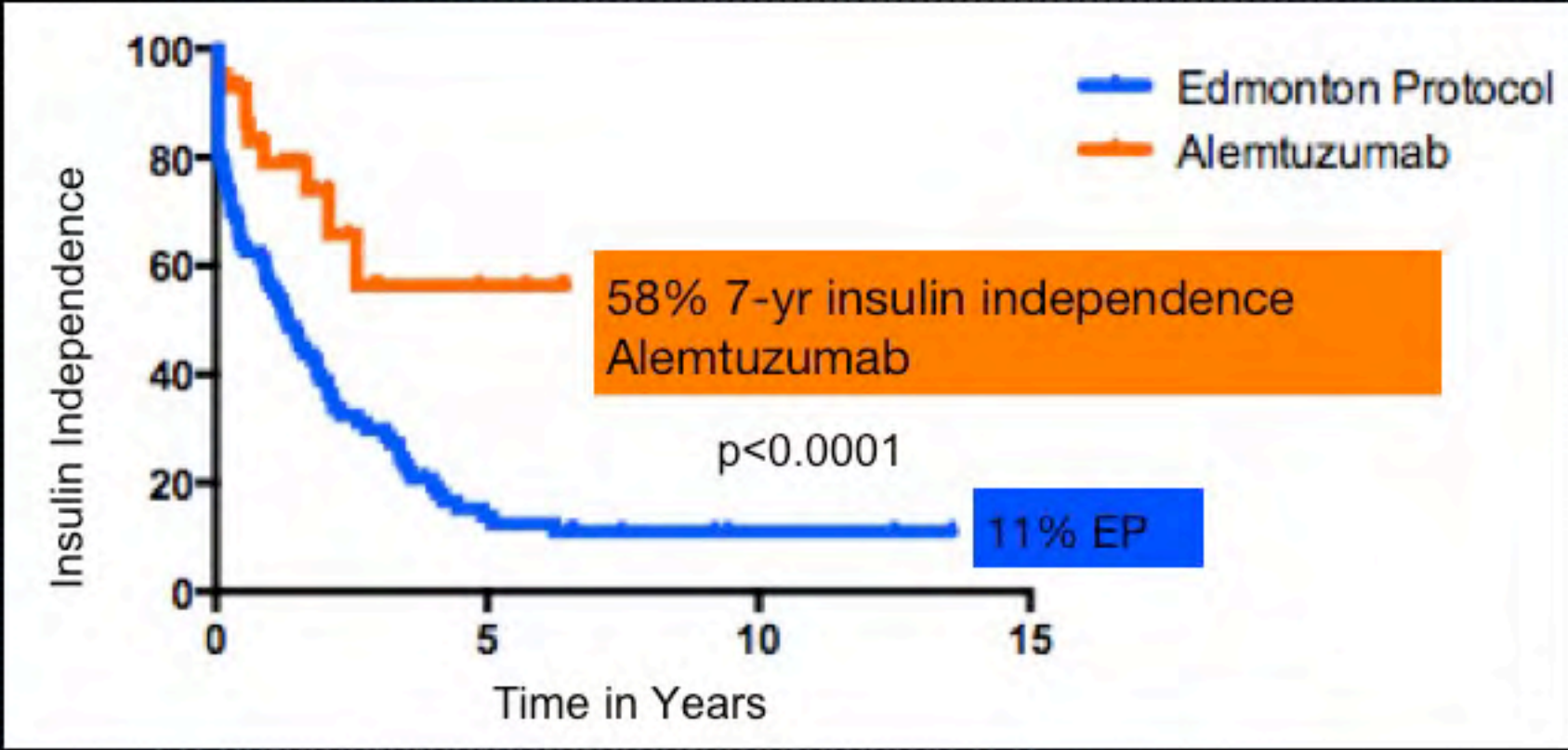
Purified Human Pancreatic Islets (PHPI) Master Production Batch Record – A Standard Operating Procedure of the NIH Clinical Islet Transplantation Consortium

Centers with 5-Yr Insulin Independence ≥ 50%

Author	Center	Approach	Ref	Year	5-Yr
Hering, B	Minnesota	CD3, Thymo, Etanercept	JAMA and IPITA	2011	70% (at 7 years)
Bellin M	Minnesota and CITR	CD3, Thymo, Etanercept	ATJ	2012	50%
Shapiro AMJ	Edmonton	Alemtuzumab, Tac + MMF + Etanercept (+ Anakinra)	-	-	58% (at 7 years)
Szot, G	USCF	Thymo + Efalizumab or Bela + SRL or MMF	ATC [32]	2012	80% (at 4 years)
Qi, M	UIC	EP Tac/SRL or MMF (4) + Exenatide + Etanercept (6)	ATC [1275]	2012	60%
Pattou, F	Lille	EP	IPITA	2011	50%
Berney, T	Geneva GRAGIL		IPITA	2011	50%

Alemtuzumab
7-Yr Insulin Independence



Clinical Islet Transplantation 2015

- Requires immunosuppression
- Insulin independence in ~50% at 5 years (Similar to Pancreas Transplant Alone)
- Approximately ~ 70-80 % have significant graft function 5 years after transplantation
- **Near normalization of A1c ~ 6.5% (with or without insulin)**
- **Resolution of impaired hypoglycemia awareness**
- **No Severe Hypoglycemia**

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Remaining Challenges

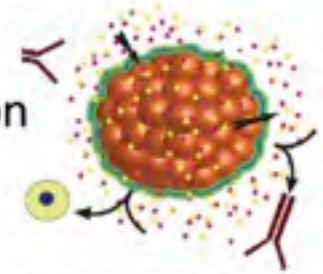
- Transplant Site
- Immune tolerance
- Adequate Supply to Transplant >100 Million
- Cost Efficiency

Engineering the Implantation Site for Insulin Producing Cell Products

Modulating the Local Environment

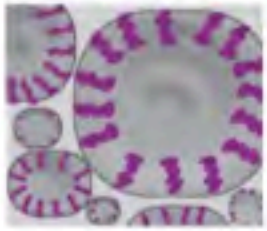
Co-delivery of "helper" cells

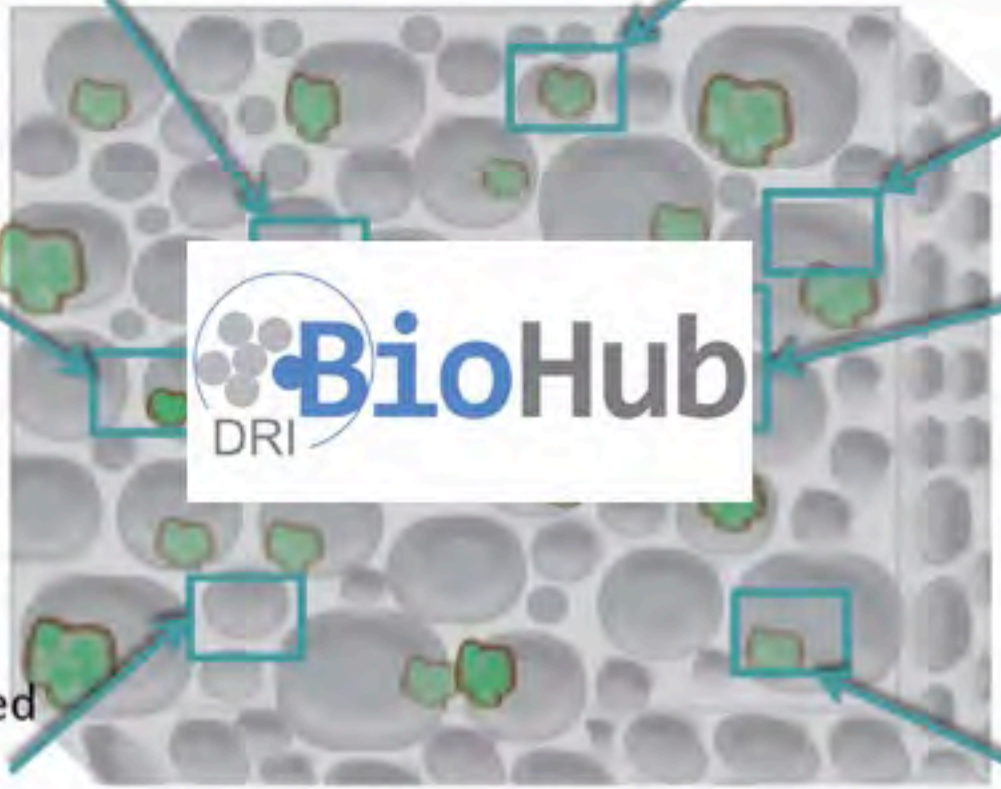
Encapsulation



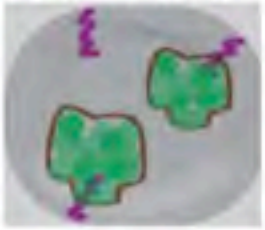
Vascular Infiltration

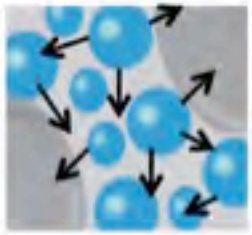
Bioactive Surfaces



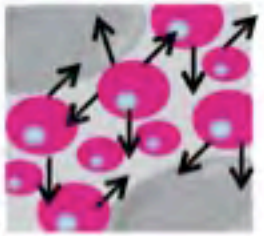


Mechanical Protection



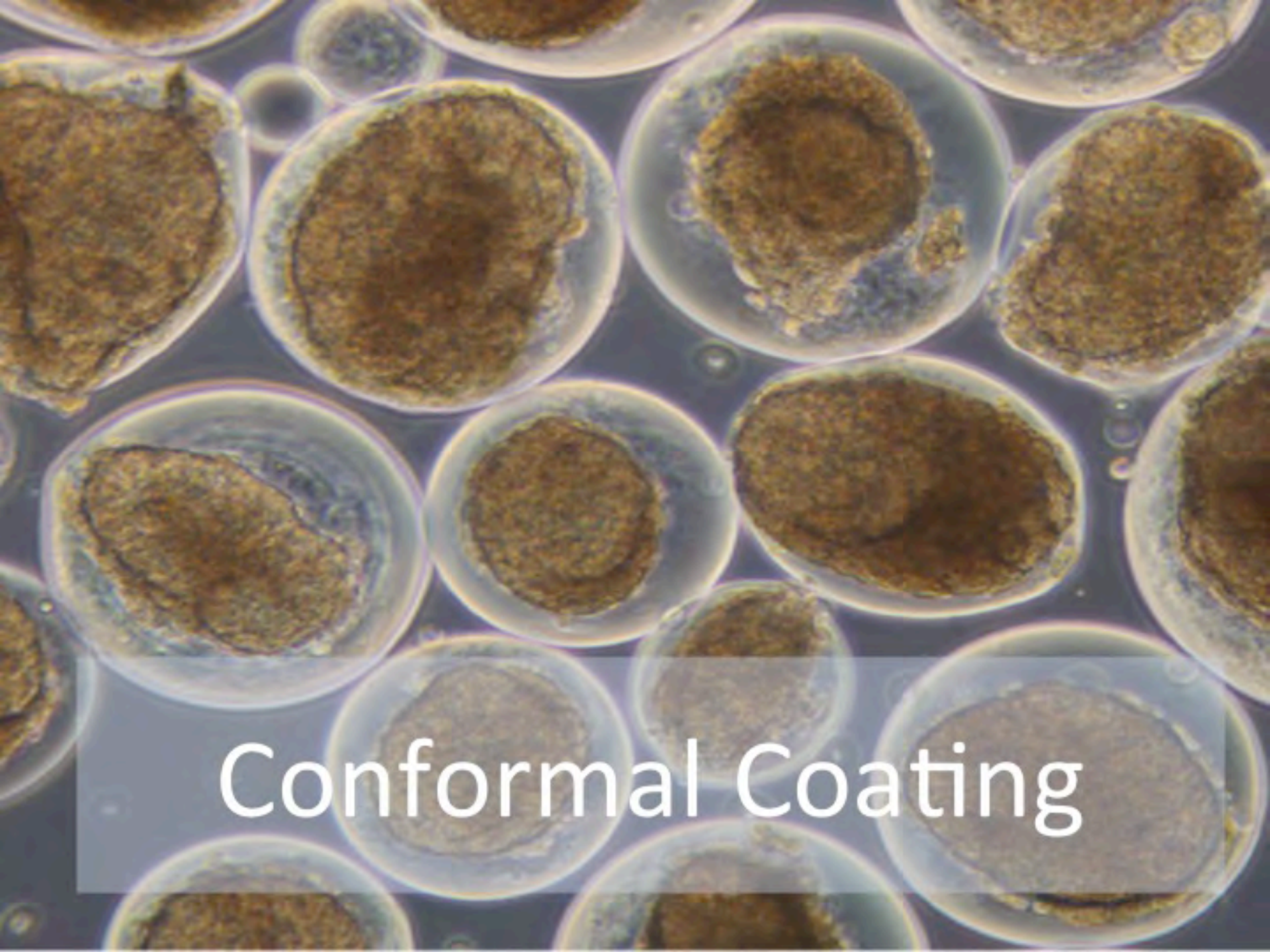


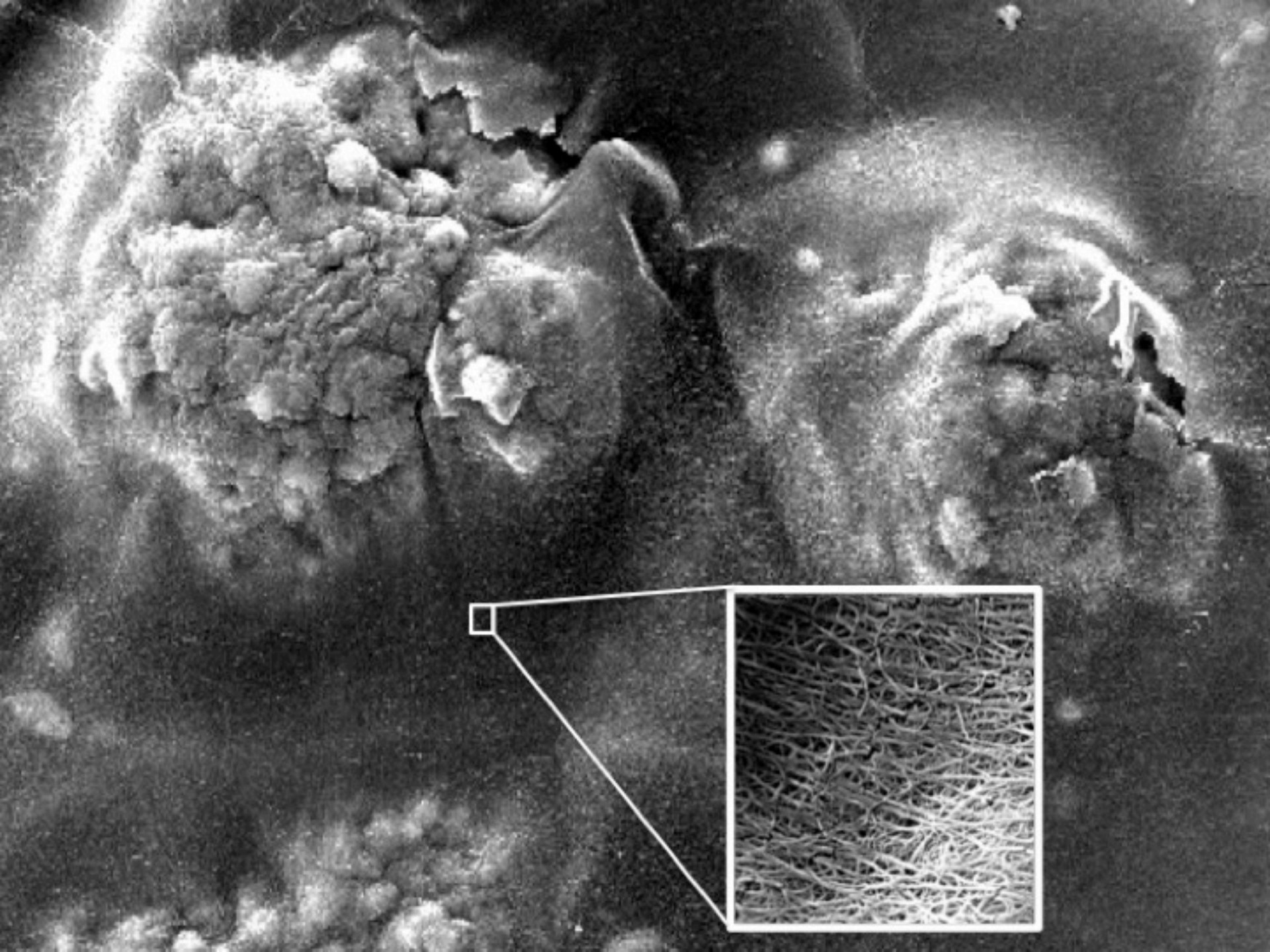
Localized Drug Delivery



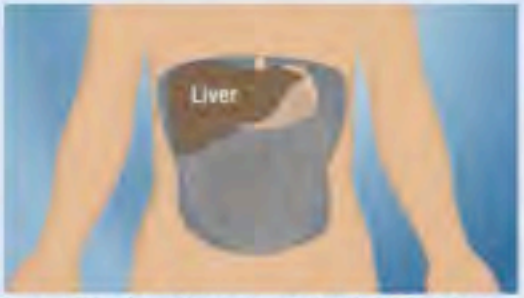
In situ oxygen generation

Multi-functional Platform

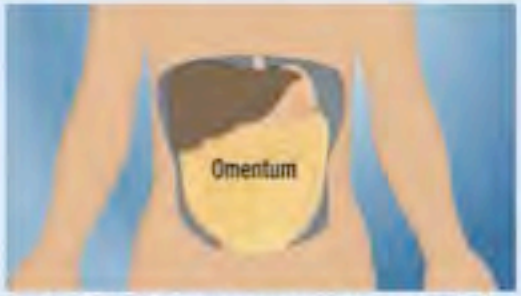

Conformal Coating



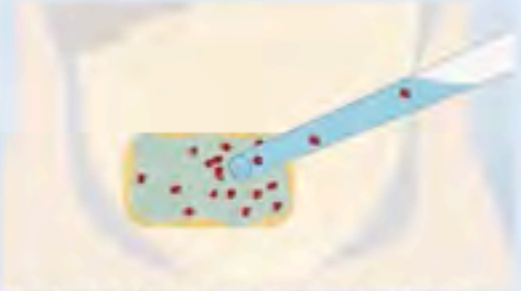
Engineering a Biological Scaffold for a DRI BioHub Platform



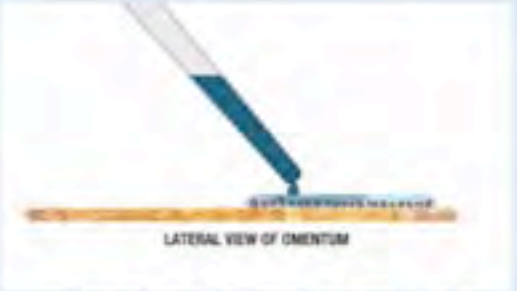
Researchers have been transplanting islets into the liver to restore natural insulin production in those with type 1 diabetes. But the liver is not an ideal location.



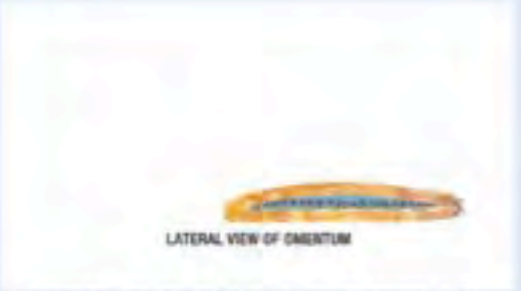
The DRI is testing the omentum, the inside lining of the abdomen, as a new transplant site. The omentum, rich with blood vessels, can be easily accessed with minimally invasive surgery.



The donor islet cells are combined with the patient's own plasma, the liquid part of the blood, and placed onto the surface of the omentum.



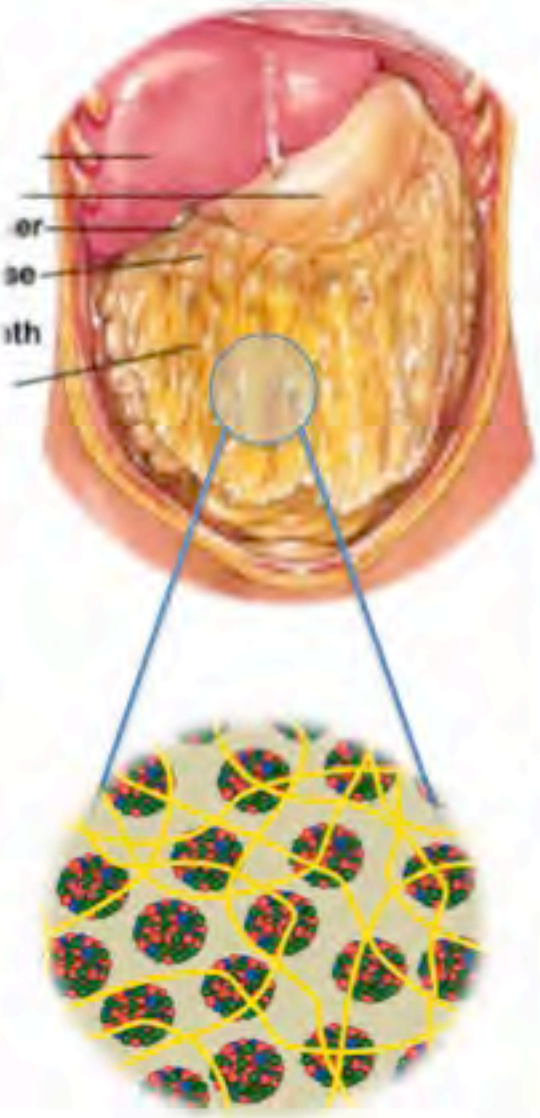
Researchers then add thrombin, a commonly used, clinical-grade enzyme. When combined, the mixture creates a gel-like material that sticks to the omentum and holds the islets in place.

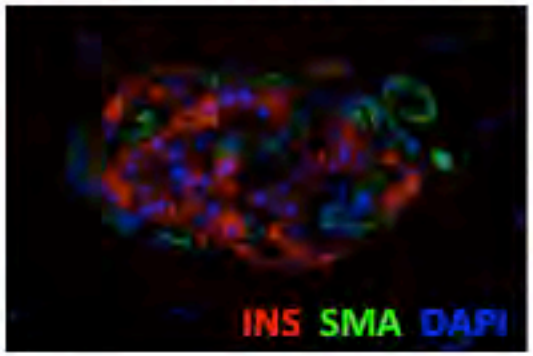


The omentum is then folded over around the biodegradable scaffold mixture.

Over time, the body will absorb the gel, leaving the islets intact, while new blood vessels are formed to provide critical oxygen and other nutrients that support the cells' survival.

Intra-Omental Islet Transplantation with Biologic Scaffold



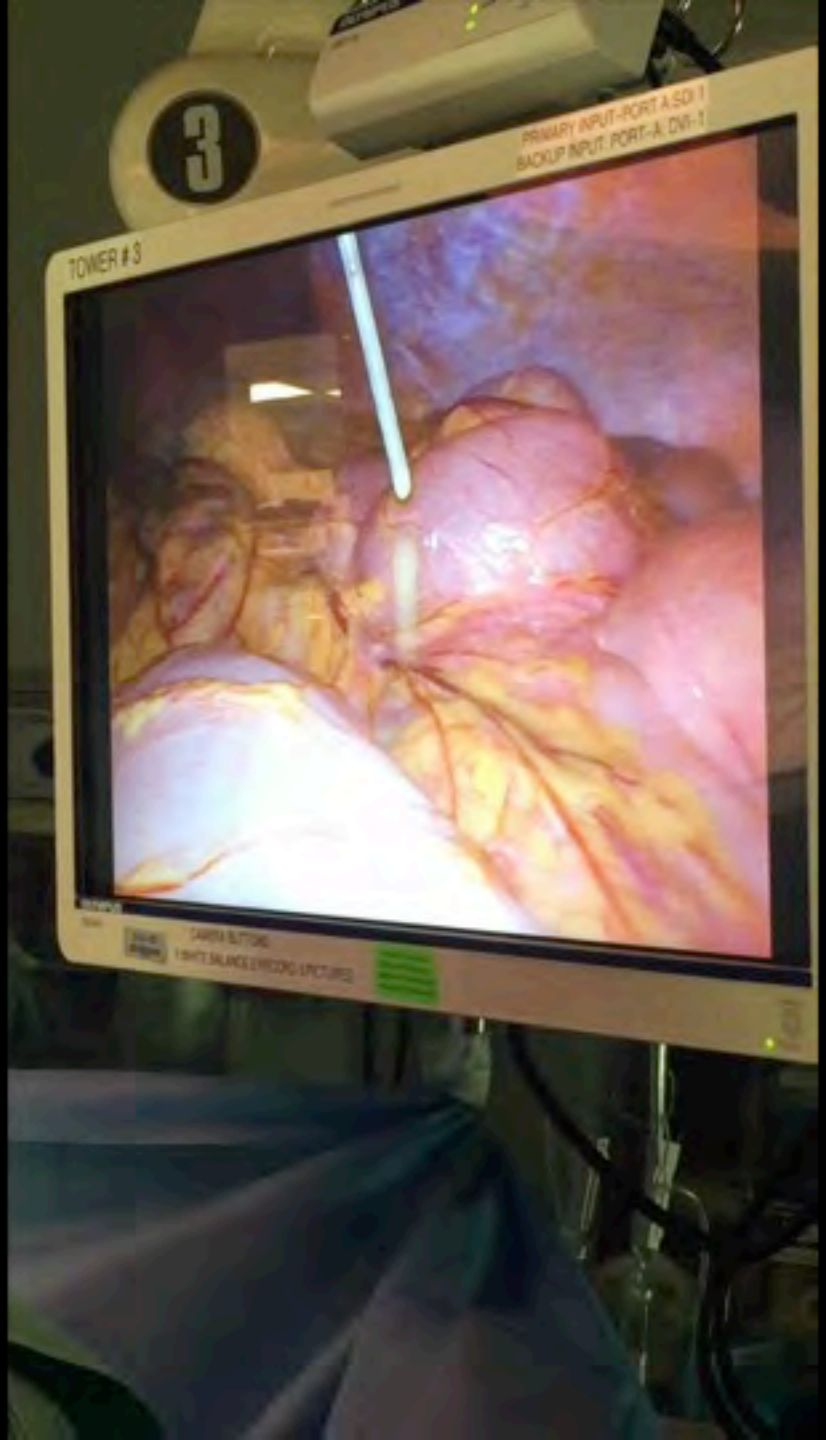


PILOT CLINICAL TRIAL TIMELINE

IND Submission: 01/30/2014
IND Approval: 02/27/2014

IRB Submission: 04/15/2014
IRB approval: July 2014
PAPERWORK Aug-Jan 6th

1st Patient: Apr-May 2015
2nd Patient: Jun-Jul 2015
3rd Patient: Aug-Sep 2015
(as per IND)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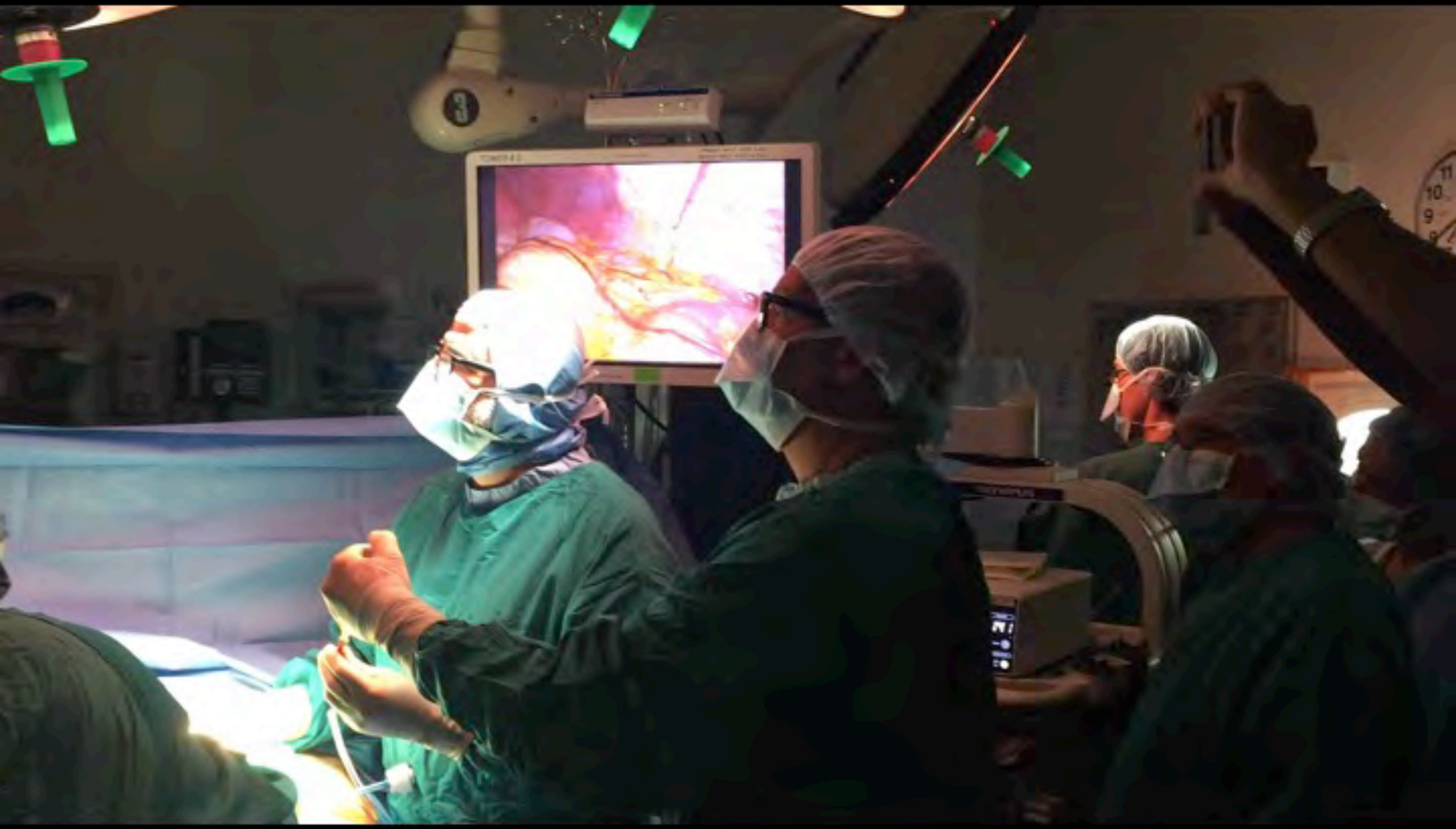
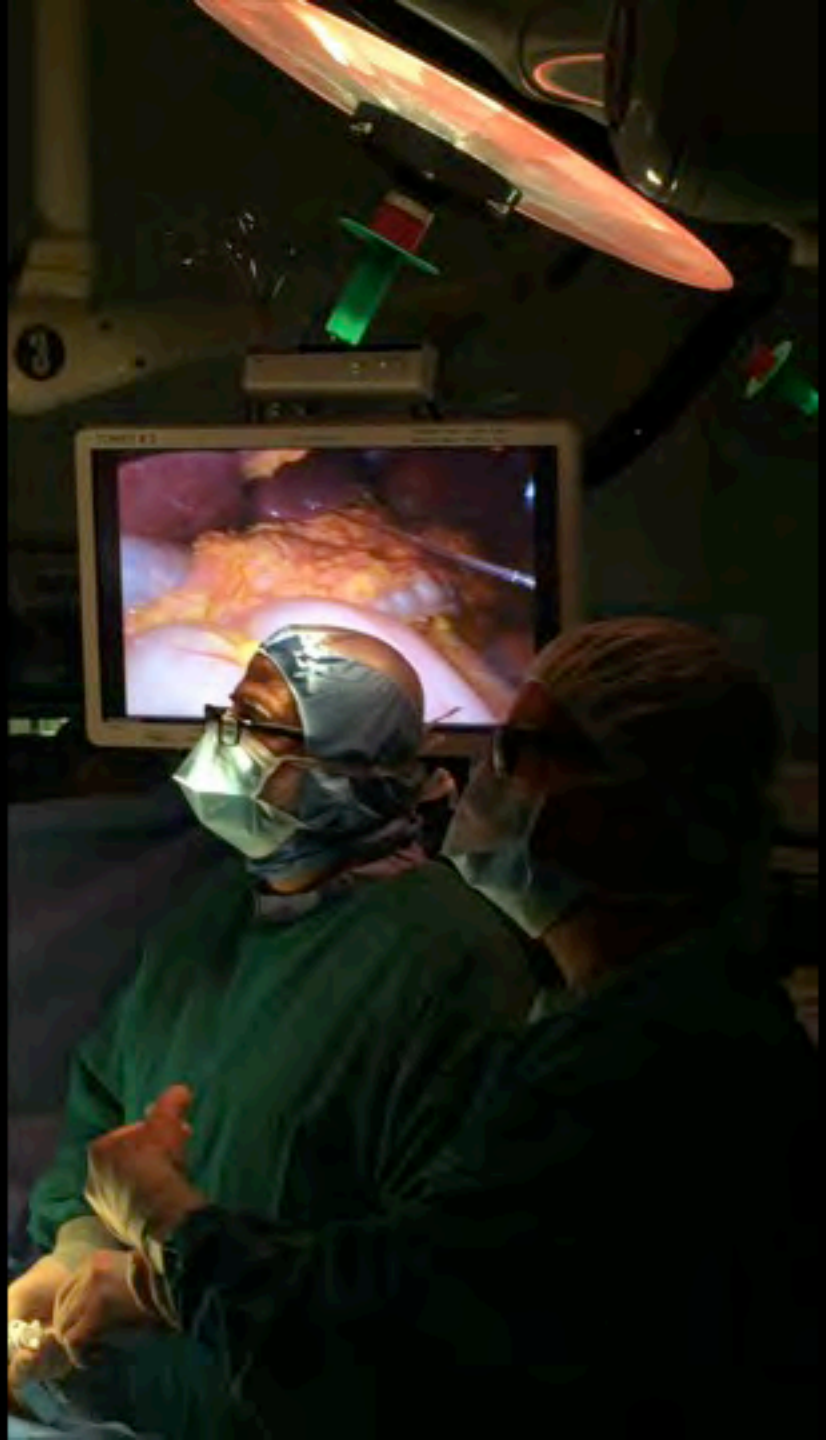
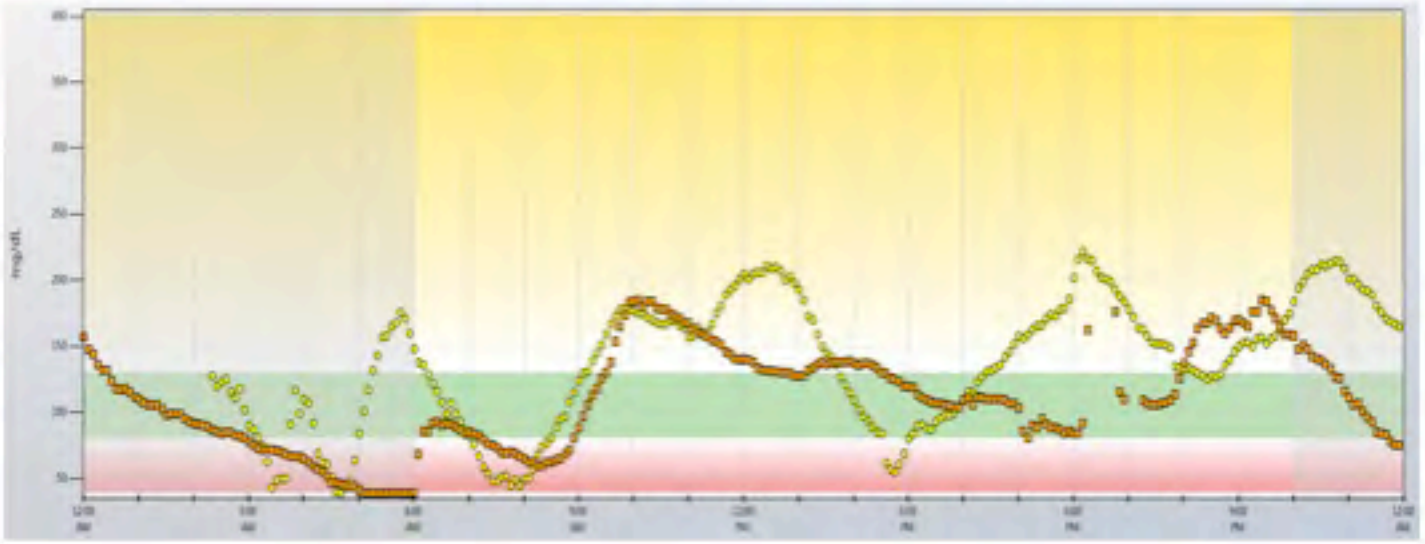
TOWER # 3

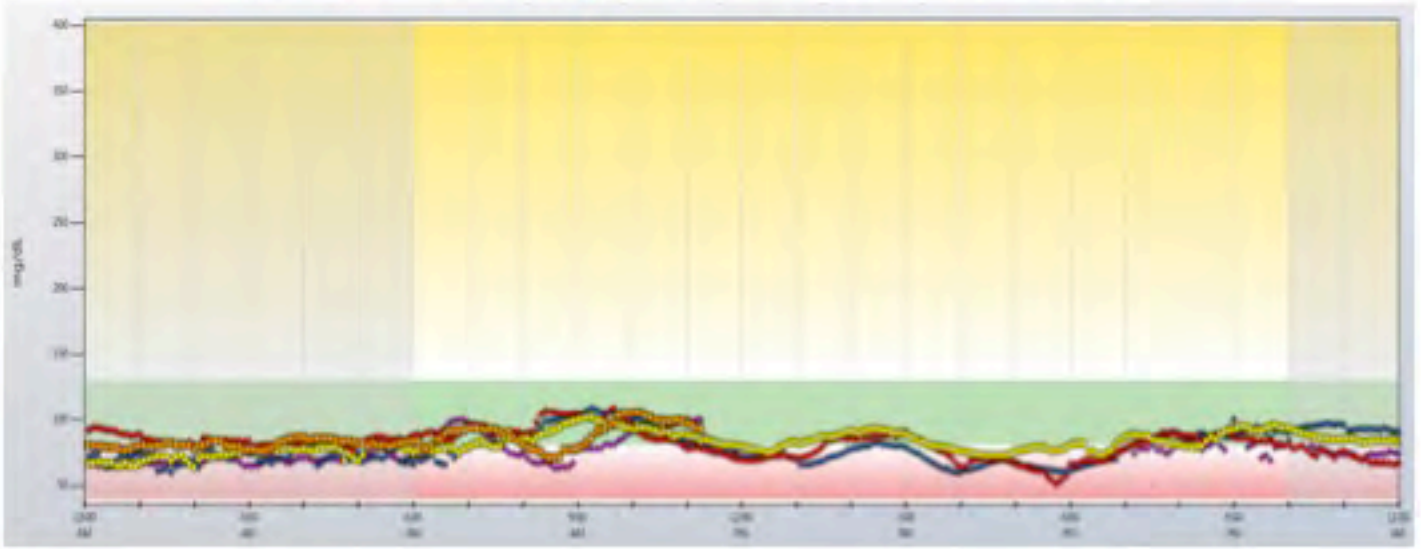




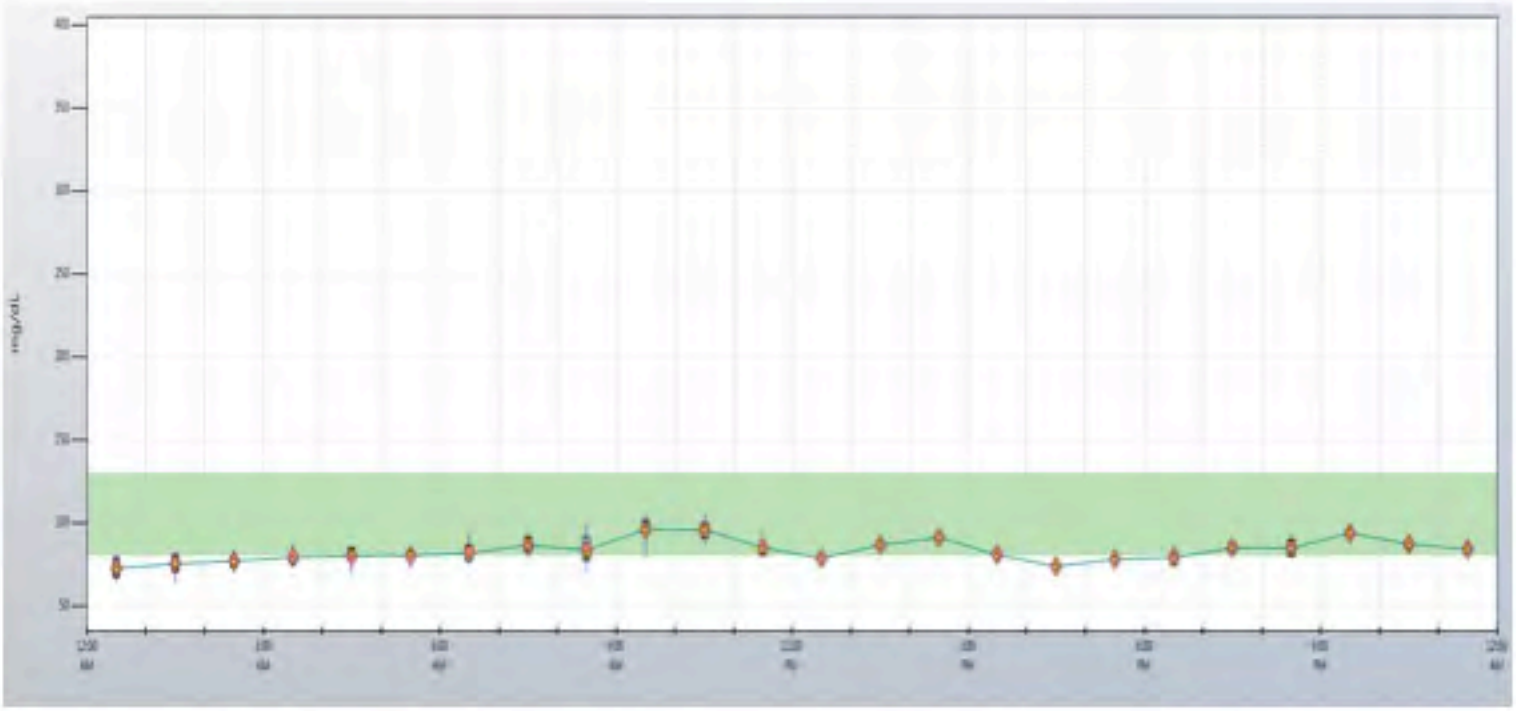
Before Islet Transplantation and on 31U/day Insulin



After transplant and off insulin



Insulin Independence following Intra-Omental Islet Transplantation in a Biologic Resorbable Scaffold



Intra-Omental Islet Transplantation in a Biologic Resorbable Scaffold: Possible Explanations for Early Success

- Elimination of IBMIR and minimiziation of early inflammatory reaction
- Early phases like intraperitoneal insulin delivery system
- Re-vascularization provides blood supply and drainage similar to the pancreas
- Exposure to lower diabetogenic IS drug levels
- Better counter-regulatory systems
- Resorbable scaffold disappears within 2 weeks

The Path for Tolerance Permissive Immunomodulation in Islet Transplantation

Camillo Ricordi[1,2]

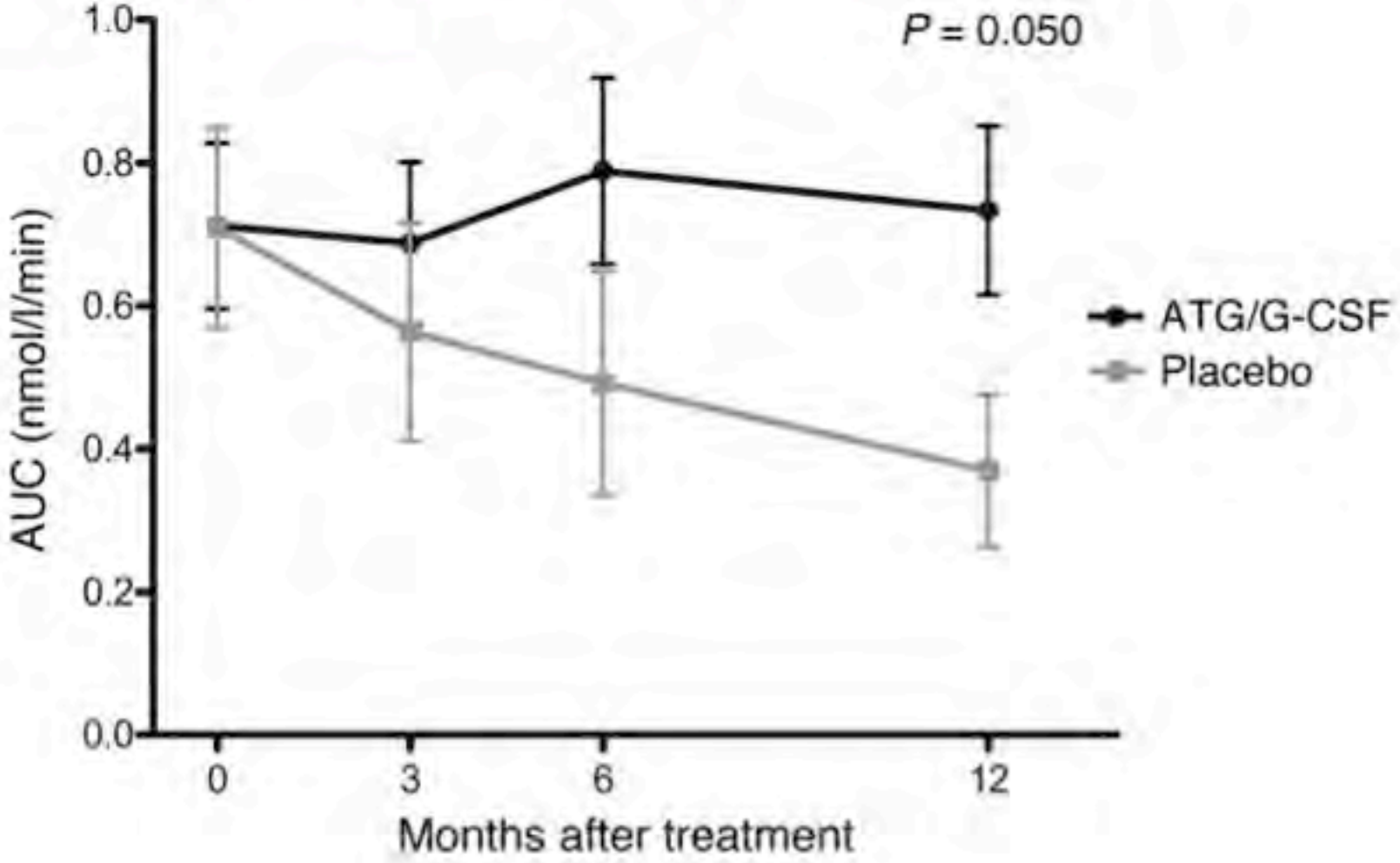
Clinical islet transplantation has progressed significantly over the past three decades (*1, 2*). Major collaborative efforts have contributed to a progressive improvement of both immunosuppressive strategies and the complex sequential procedural steps required for the manufacturing of human islet cell products (*2, 3*, Fig. 1). Islet allotransplantation has been approved in selected countries for treatment of the most severe forms of type 1 diabetes mellitus (T1DM), such as those associated with hypoglycemia unawareness and an increased risk for severe hypoglycemic episodes. A multicenter Food and Drug Administration Phase III trial, which included centers in North America and Europe, has been completed and may lead to approval and eventual reimbursement of the procedure also in the United States. However, for islet transplantation to become applicable to most patients with T1DM and possibly also to other forms of insulin-requiring diabetes, it is now critically important to refocus collective efforts on the development of successful strategies for transplantation of insulin-producing cells in the absence of continuous recipient immunosuppression toward what has been for decades the Holy Grail of transplantation: immune tolerance. Unfortunately, traditional immunosuppressive protocols, although successful at controlling the effector phase of the immune response and early autoimmune recurrence, may not be highly conducive to tolerance induction. To achieve this goal, it is important to develop novel approaches of immunosuppression or immunomodulation that are compatible with the survival, function, and posttransplant expansion of regulatory cell subsets. The recent article by Maffi and collaborators (*4*) represents an excellent step in this direction. The protocol was in fact designed to avoid immunosuppressive agents with a mechanism of action that can affect T cell receptor signaling and calcineurin pathways, which could be detrimental to the survival, expansion, and function of regulatory cells (*4*). In contrast, rapamycin has been associated with both expansion of human regulatory cells in vitro and promotion of their immunomodulatory function in vivo, without affecting interleukin-10–mediated regulatory pathways (*4*). However, some of the challenges associated with the requirement of balancing an adequate T-cell–directed induction immunosuppression with a regulatory permissive overall immunomodulatory strategy have also been highlighted. In fact, it was of interest that all early graft losses (median graft survival of 37 days) were observed in recipients treated with lower doses of antithymocyte globulin (ATG) in the induction phase of immunosuppression. In these subjects, a less efficient depletion of CD3-CD8 T lymphocytes (in particular memory subset) was also observed (*4*), and none of them reached the primary endpoint of insulin independence at 3 years. In addition, a de novo, post-islet infusion expression of autoantibodies and alloantibodies was more often observed in these patients. In striking contrast, the total median islet graft survival in islet transplant recipients treated with higher-dose ATG induction was longer than 1,616 days and four of five of them reached the 3-year primary endpoint of insulin independence. Other variables that may have contributed to the success of this protocol in subjects receiving higher-dose ATG induction treatment could include the selected peritransplant anti-inflammatory strategy and recipient treatment with granulocyte colony stimulating factor (GCSF), whose administration has been associated with tolerance-permissive, regulatory cell-promoting effects. Interestingly, the association of low-dose ATG (2.5 mg/kg, intravenous) followed by pegylated GCSF (Neulasta; 6 mg SQ q2 weeks × 6 doses) was recently reported to have a significant effect on the preservation of area under the curve C-peptide in the subject with T1DM compared to placebo-treated subjects (Haller et al. ADA 2014, 173-OR), and this effect was associated with preservation of regulatory T cells and increased T regulatory-to-T memory ratios. However, GCSF variable has not been discussed in the context of the observed outcomes of the reported pilot clinical trial (*4*).

This work was supported by NIH grant 5U01DK070430; JDRF grant 17-2012-361; and the Diabetes Research Institute Foundation.

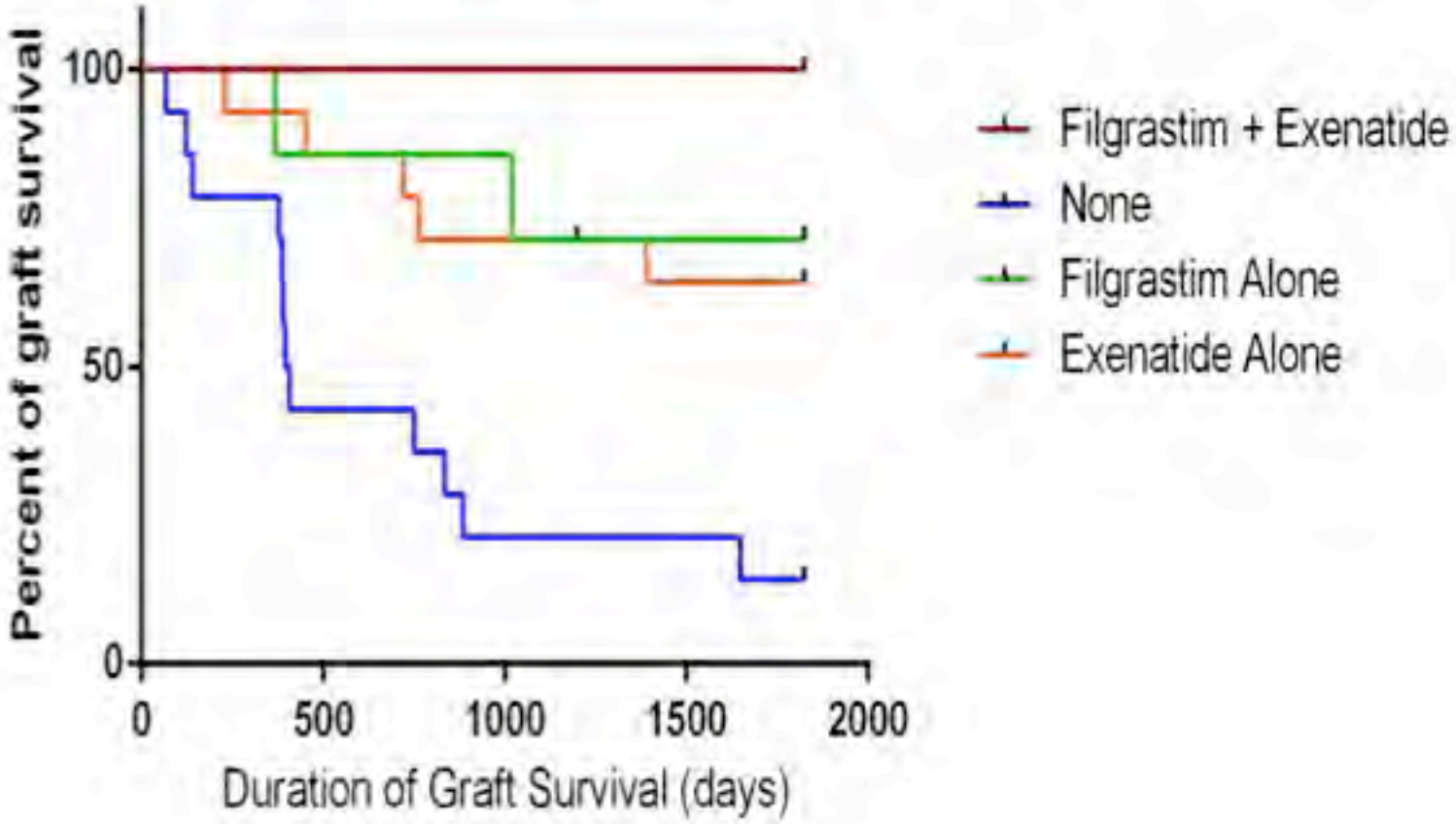
The Journal of Clinical Investigation; January 2015

Anti-thymocyte globulin/G-CSF treatment preserves β cell function in patients with established type 1 diabetes

Michael J. Haller, Stephen E. Gitelman, Peter A. Gottlieb, et al.



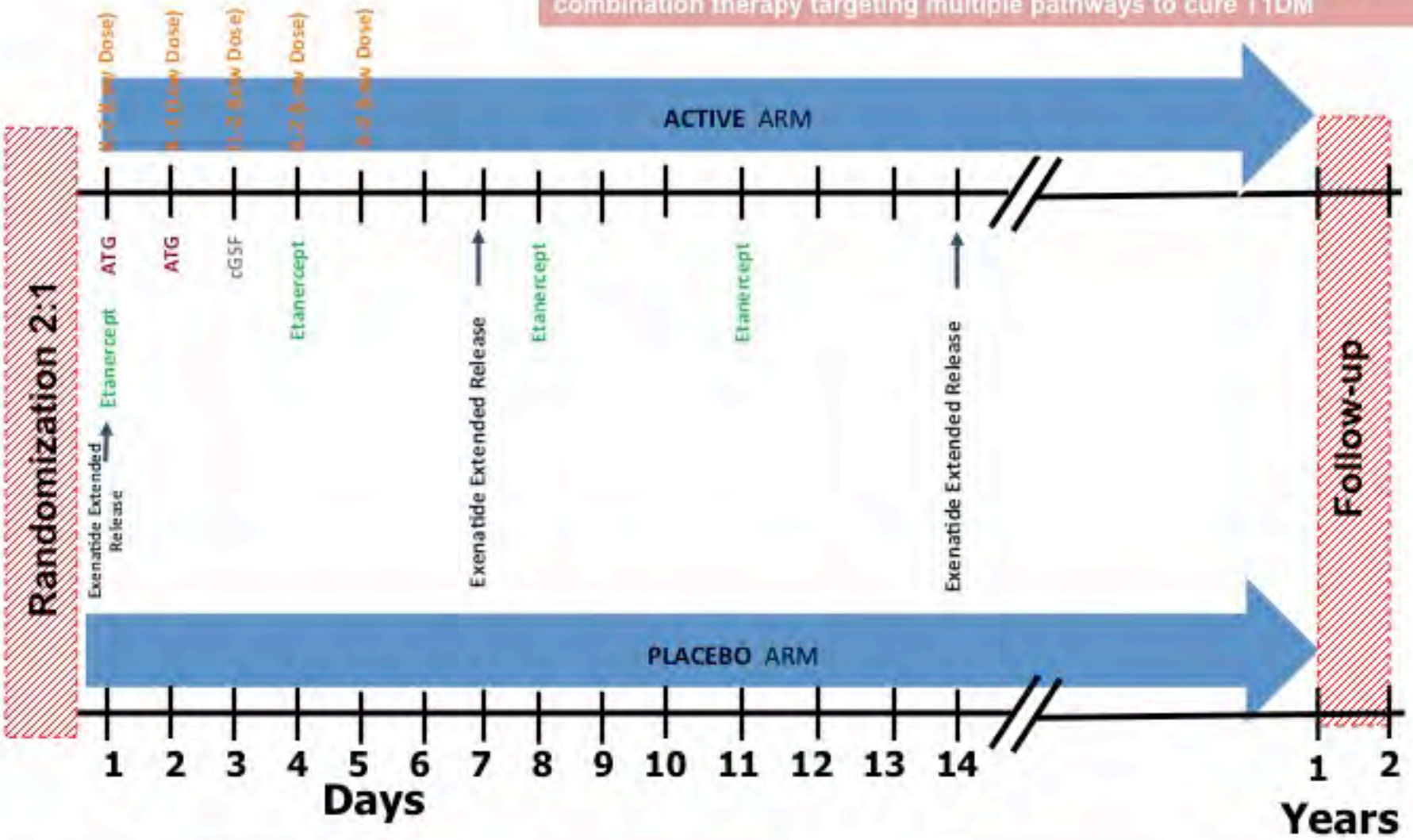
Effect of Filgrastim and Exenatide on Graft Function at 5 years



NEW FDA APPROVED TRIAL TO REVERSE TYPE 1 DM BY TRANSIENT IMMUNOMODULATION

NEW FDA APPROVED TRIAL TO REVERSE TYPE 1 DM BY TRANSIENT IMMUNOMODULATION

FDA Approved randomized, placebo-controlled, immunomodulatory combination therapy targeting multiple pathways to cure T1DM



Drug	Exenatide Extended Release	ATG	Etanercept (Enbrel®)	G-CSF (Pegfilgrastim)	Low-Dose IL-2
Dose	2 mg/week, SC	[illegible]	25 mg SC	6 mg SC	1 million IU
Duration	Weekly up to 52 weeks	[illegible]	Day 1, 4, 8, 11	Day 3, 17, 31, 45, 59, 73 (Every 2 weeks, 6 doses)	Day 1-5, 15, then every 15 days

DIABETES RESEARCH INSTITUTE
UNIVERSITY OF MIAMI

Diabetes September 9, 2014 - EPub September 9, 2014, doi: 10.2337/db14-0656, PMID: 25204974

Preserved Beta-Cell Function in Type 1 Diabetes by Mesenchymal Stromal Cells

Per-Ola Carlsson[1,2], Erik Schwarcz[3], Olle Korsgren[4*] and Katarina Le Blanc[5*]

[1]Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden; [2] Department of Medical Sciences, Uppsala University, Sweden; [3]Department of Internal Medicine, Örebro University Hospital, Sweden; [4]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden; [5]Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

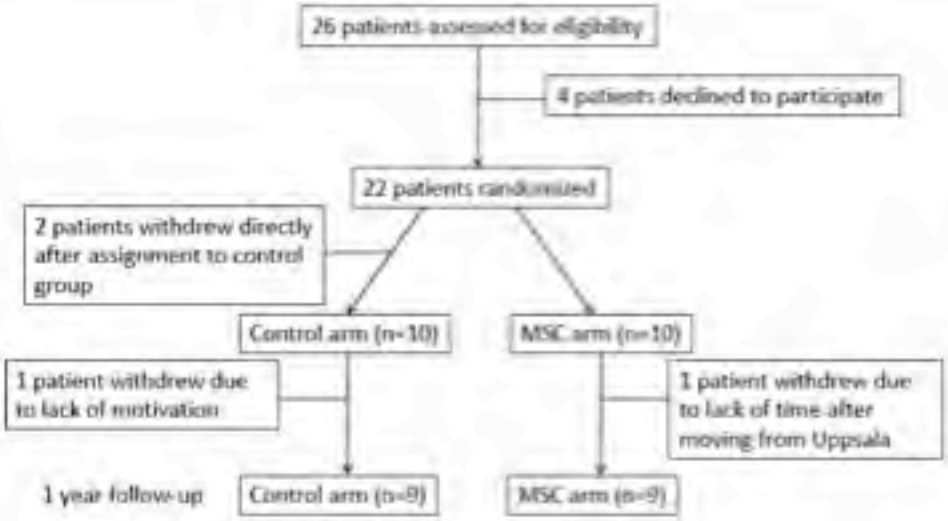
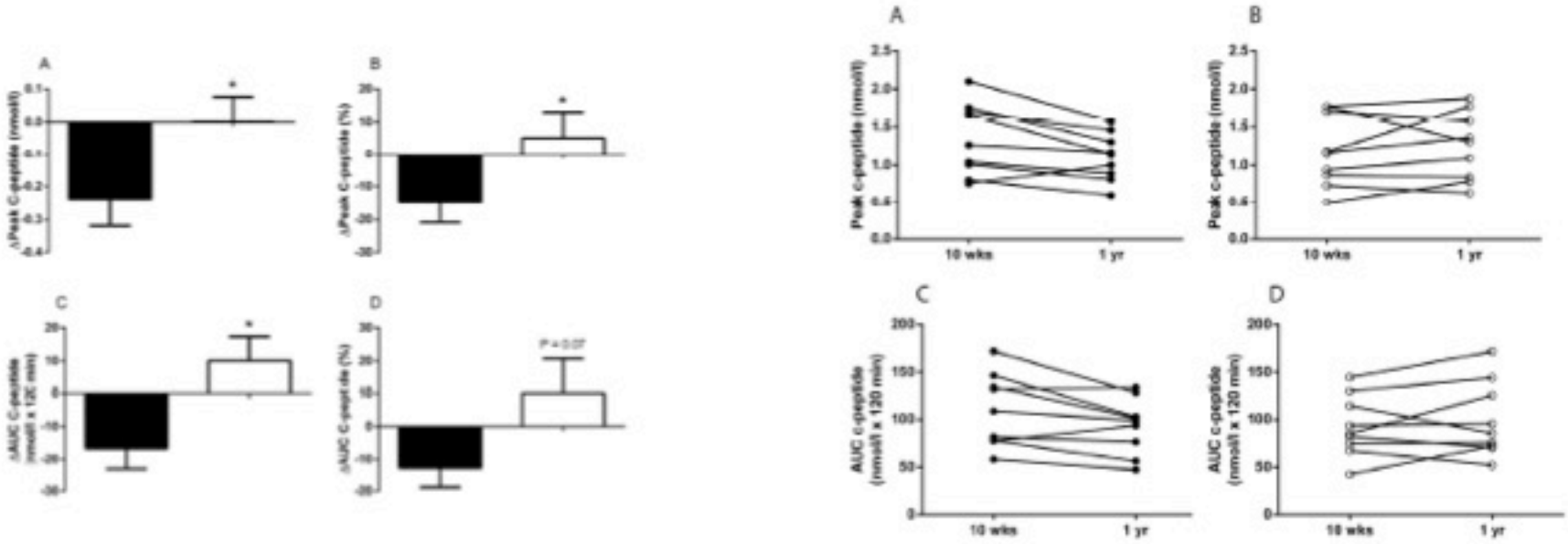


Table 1. Characteristics of the patients at diagnosis.

Characteristic	Control (n=9)	MSC-treated (n=9)
Sex (male/female)	5/4	8/1
Age (yr)	27±2	24±2
Body weight (kg)	68±4	78±3
BMI (kg/m2)	22.5±0.9	23.3±1.1
GAD65 antibodies (no. of all)	8/9	6/9
IA2 antibodies (no. of all)	4/9	6/9
Both GAD65 and IA2 antibodies (no. of all)	4/9	3/9
Diabetes-associated HLA alleles		
DR4 (no. of all)	8/9	7/9
DR3 (no. of all)	0/9	0/9
Neither DR3 nor DR4 (no. of all)	1/9	2/9
DQ8 (no. of all)	9/9	7/8
DQ2 (no. of all)	4/9	4/9
DQ2/8 (no. of all)	3/9	2/9
Neither DQ2 nor DQ8 (no. of all)	0/9	0/9
DR4-DQ8 (no. of all)	8/9	7/9
Diabetic ketoacidosis (no. of all)	1/9	1/9
Polyuria and weight loss (no. of all)	8/9	9/9

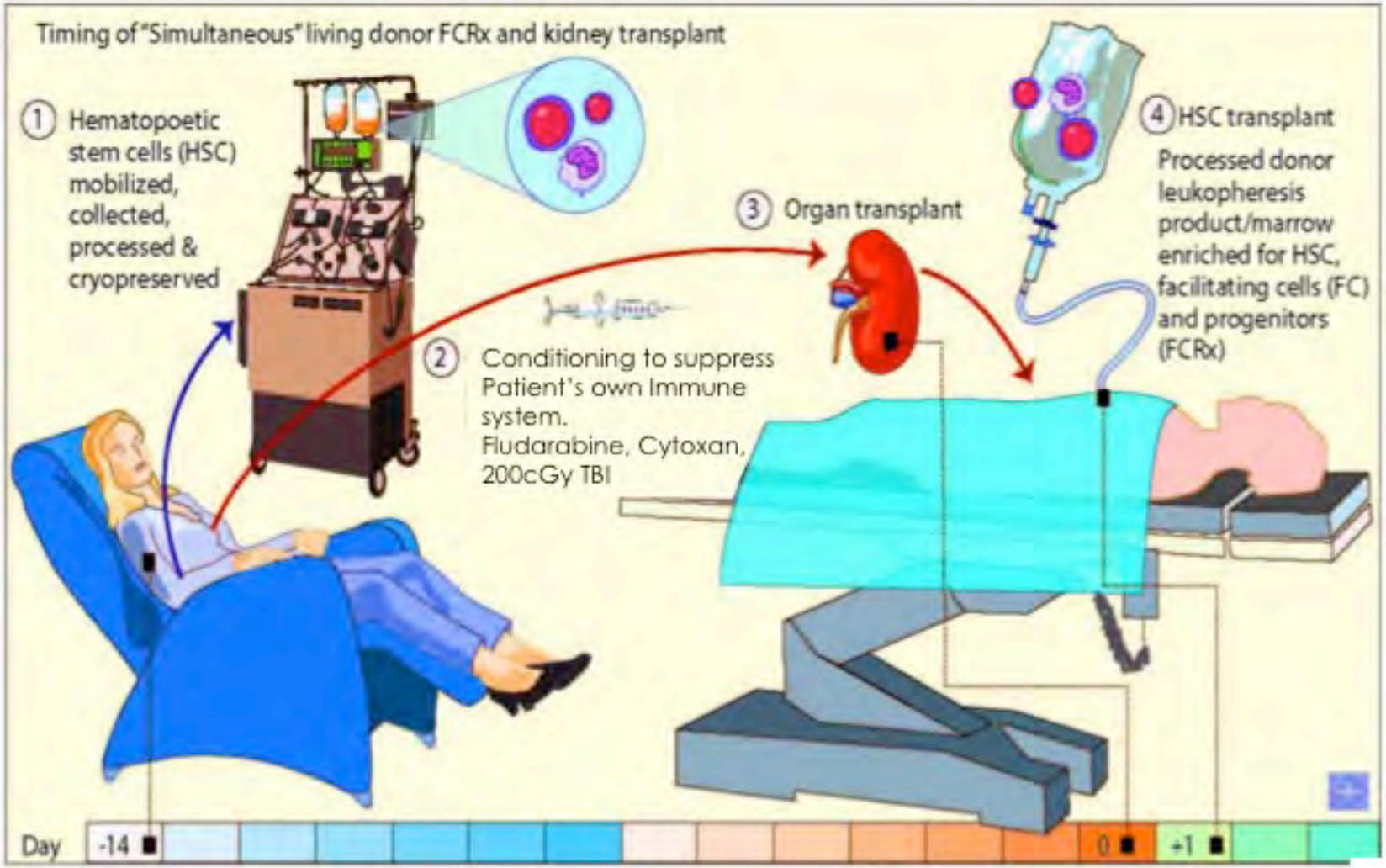
Plus-minus values are mean±SEM. There were no statistically significant differences between the two groups. Concentrations of GAD65 and IA2 antibodies were determined by ELISA technique, where values of GAD IgG ≥5U/ml and IA2 IgG ≥8kU/l indicated their presence. HLA class II alleles were measured with PCR amplification and sequence-specific hybridization.



This prospective clinical study describes the translation of this cellular intervention strategy to patients with recent onset type 1 diabetes. Twenty adult patients with newly diagnosed type 1 diabetes were enrolled and randomized to MSC treatment or to the control group. Residual beta-cell function was analyzed as C-peptide concentrations in blood in response to a mixed meal tolerance test (MMTT) at one-year follow-up. In contrast to the patients in the control arm, who showed loss in both C-peptide peak values and C-peptide when calculated as area under the curve during the first year, these responses were preserved or even increased in the MSC-treated patients. Importantly, no side effects of MSC treatment were observed. We conclude that autologous MSC treatment in new onset type 1 diabetes constitute a safe and promising strategy to intervene in disease progression and preserve beta-cell function.

Carlsson P-O , Schwarcz E, Korsgren O and Le Blanc K. **Diabetes** 2014 doi: 10.2337/db14-0656, PMID: 25204974

Simultaneous FCRx + Kidney Transplant



Leventhal J et al, *J Clin Pharmacol Thera*, September 2012

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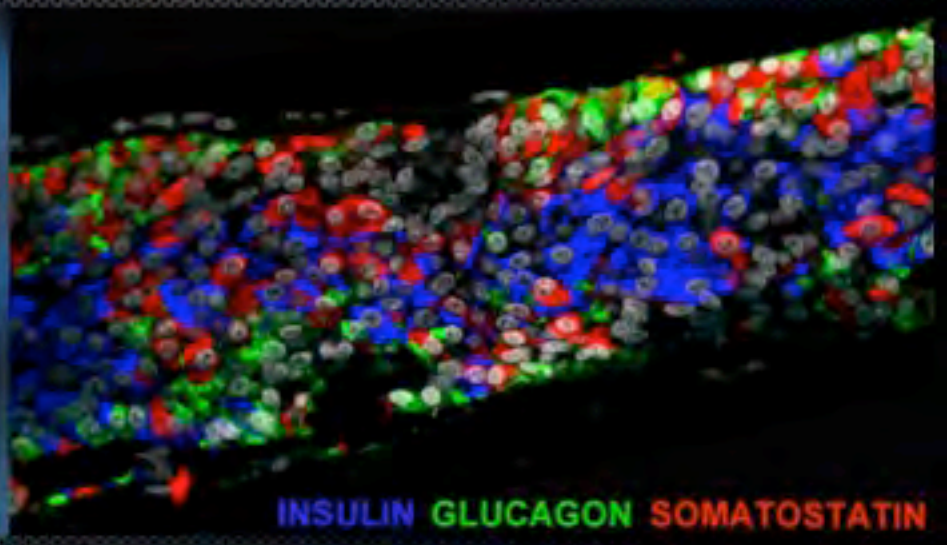
Alternative Sources of Insulin Producing Cells:

- animal cells (xenotransplantation)
- cord blood stem cells
- amniotic progenitor cells
- amniotic fluid stem cells
- adipose derived stem cells
- endometrial and menstrual blood
- embryonic pancreatic precursors
- fetal and neonatal progenitor cells
- transdifferentiated & tissue reprogramming
- epigenetic conversion

U-T San Diego

ViaCyte starts diabetes trial

ViaCyte's VC-01™ Investigational Stem Cell-Derived Islet Replacement Therapy Successfully Implanted into First Patient

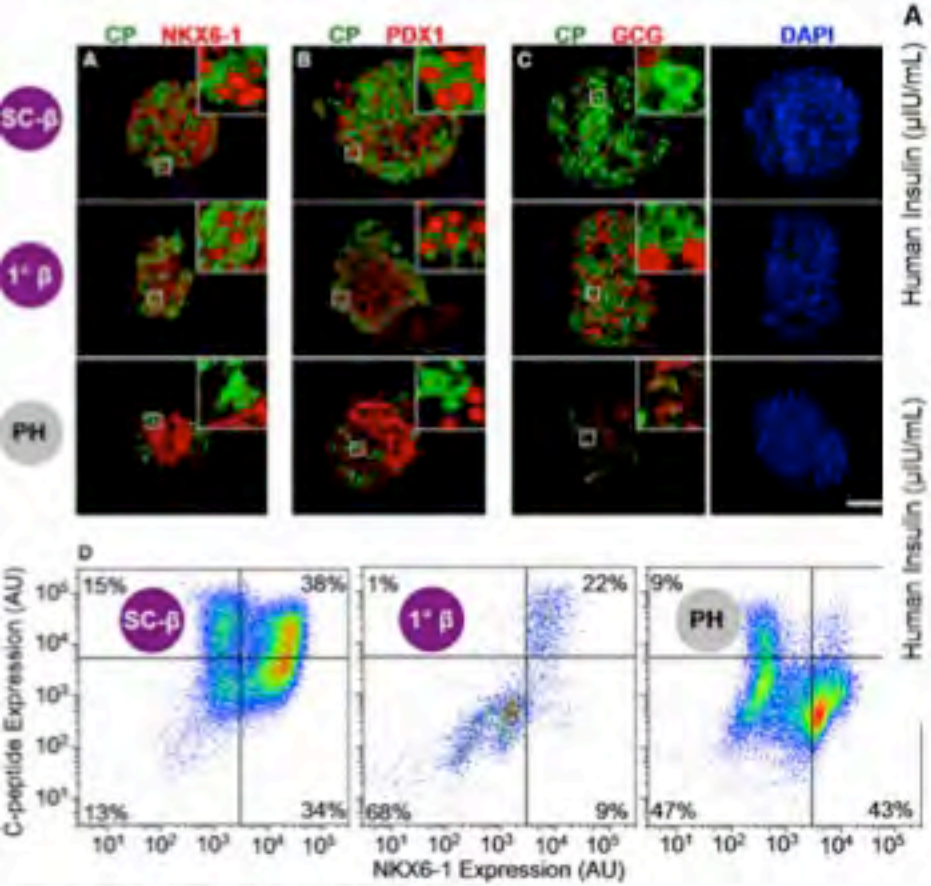


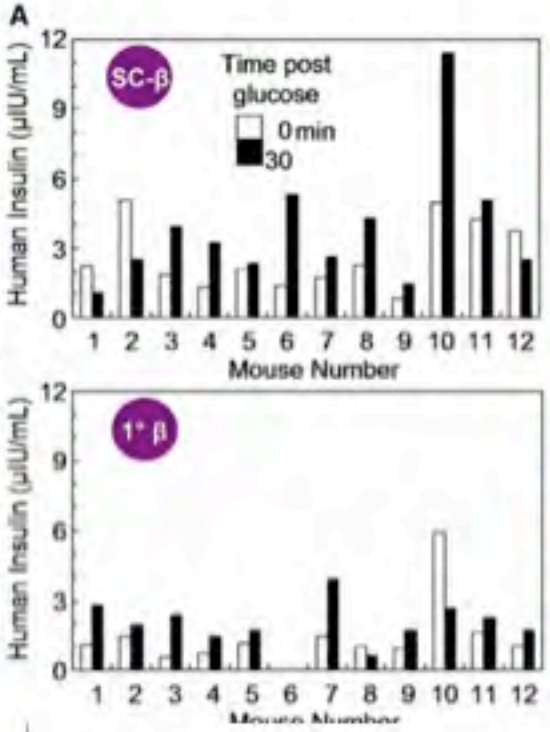
SAN DIEGO, CA, USA I October 29, 2014 I ViaCyte, Inc., a privately-held regenerative medicine company, announced today that the first patient in its Phase 1/2 study was successfully implanted with VC-01™, its embryonic stem cell-derived islet replacement product candidate being developed as a treatment for type 1 diabetes. This Phase 1/2 clinical trial, designed to evaluate the VC-01 product candidate directly in patients with type 1 diabetes, is initially being conducted at UC San Diego Health System, with the support of the UC San Diego Sanford Stem Cell Clinical Center, under the direction of Principal Investigator Robert Henry, MD.

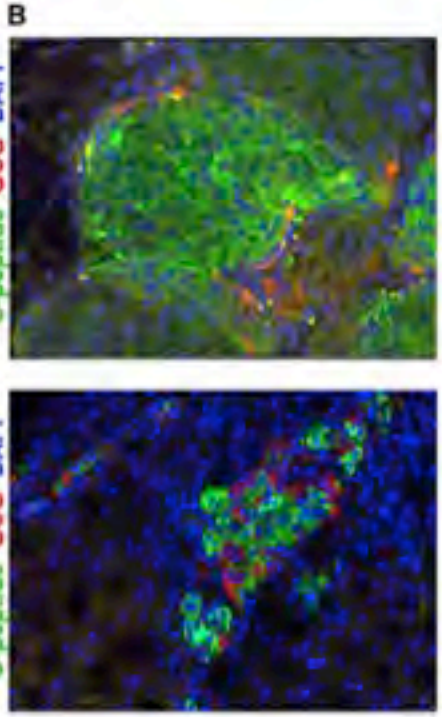
Cell

Generation of Functional Human Pancreatic β Cells In Vitro

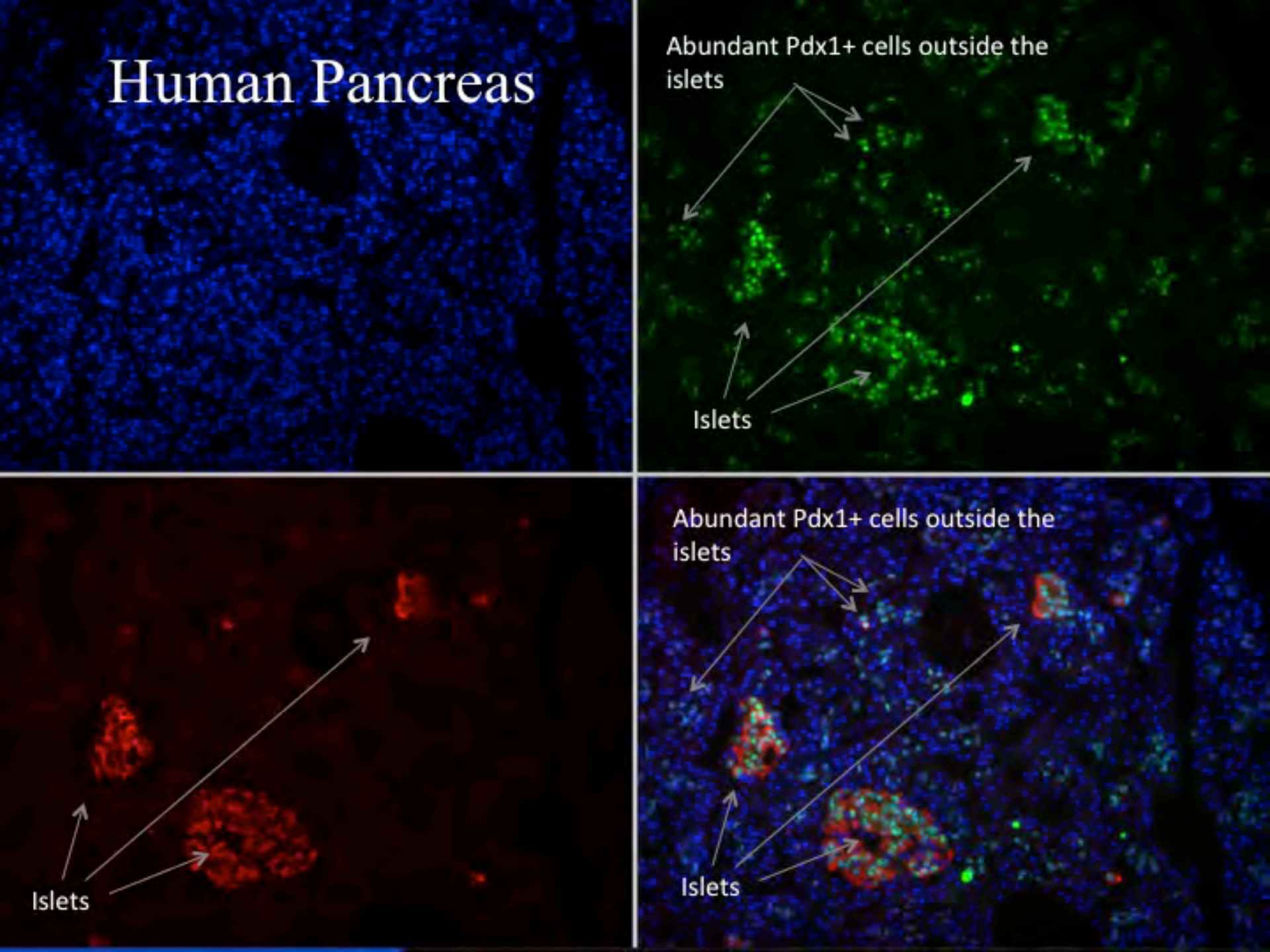
Felicia W. Pagliuca,[1,3] Jeffrey R. Millman,[1,3] Mads Gürtler,[1,3] Michael Segel,[1] Alana Van Dervort,[1] Jennifer Hyoje Ryu,[1] Quinn P. Peterson,[1] Dale Greiner,[2] and Douglas A. Melton[1,*]







Cell *159*, 428–439, October 9, 2014


Human Pancreas
Abundant Pdx1+ cells outside the islets
Islets
Islets
Abundant Pdx1+ cells outside the islets
Islets

MSC which are derived from pericytes and indirecty selected in colture FROM ALMOST ALL TISSUES are key to natural healing and anti-inflammatory response

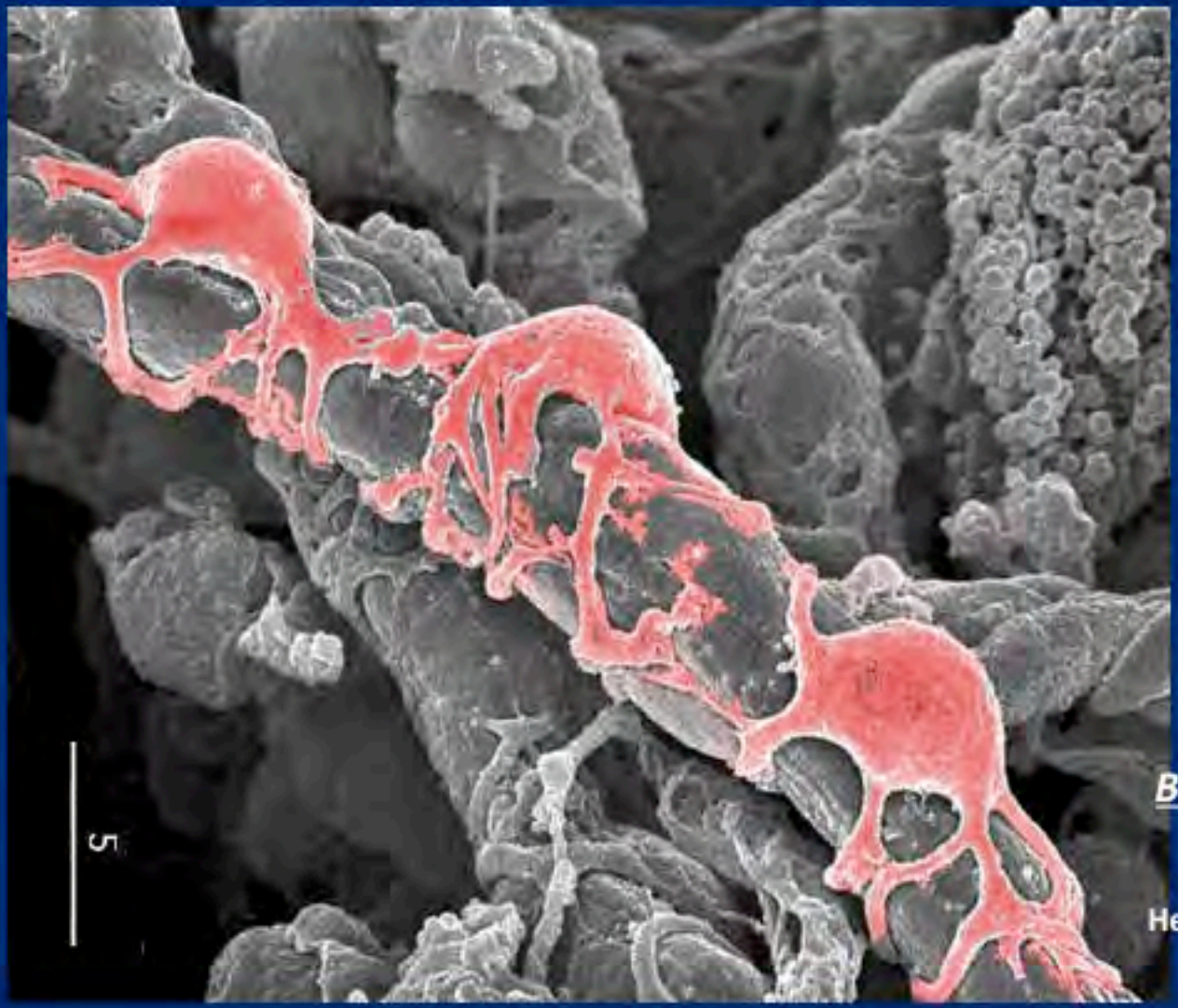
Arnold Caplan, Case Western, Cleveland
Bruno Peoult, UCLA, Los Angeles

Adipose Tissue and MSC

Prof. Sbarbati- University of Verona

Pericytes: cells on capillaries and microvessels.

ALL MSCs are PERICYTES!



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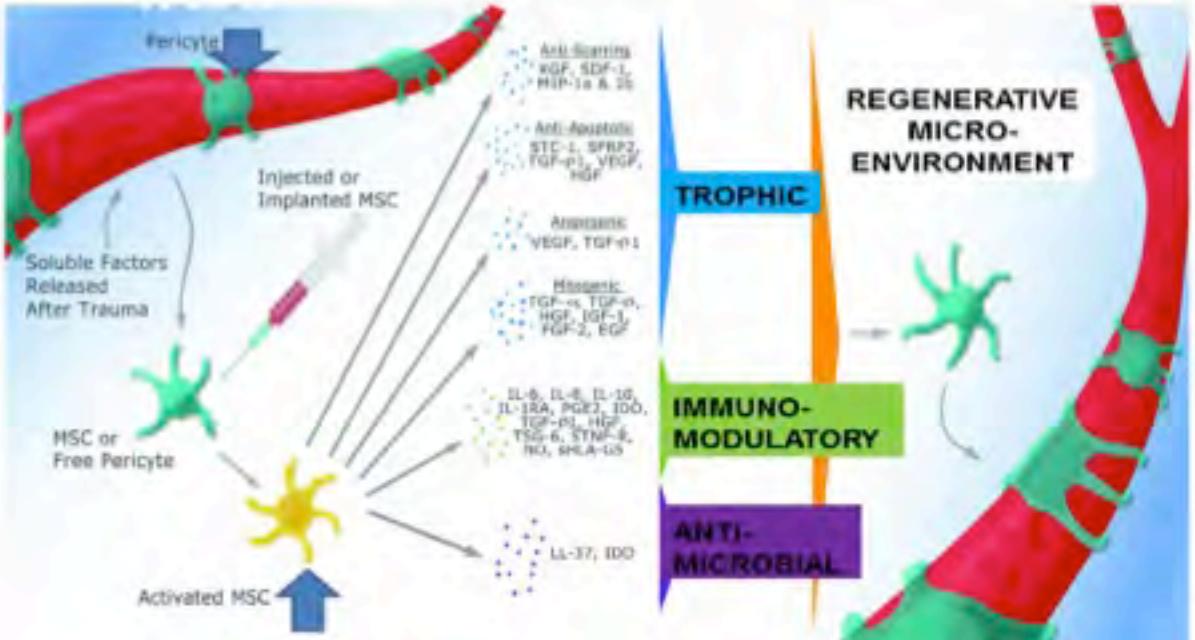
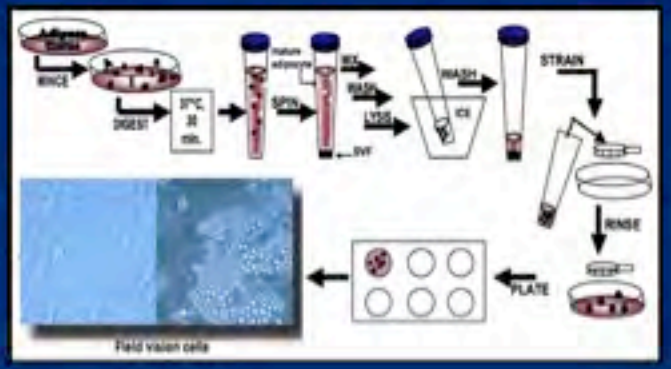

Pericyte
Injected or
Implanted MSC
Soluble Factors
Released
After Trauma
MSC or
Free Pericyte
Activated MSC
Anti-Scarring
KGF, SDF-1,
MIP-1α & 1β
Anti-Apoptotic
STC-1, SFRP2,
TGF-β1, VEGF,
HGF
Angiogenic
VEGF, TGF-β1
Mitogenic
TGF-α, TGF-β,
HGF, IGF-1,
FGF-2, EGF
IL-6, IL-8, IL-10,
IL-1RA, PGE2, IDO,
TGF-β1, HGF,
TSG-6, STNF-6,
NO, sHLA-G5
LL-37; IDO
TROPHIC
IMMUNO-
MODULATORY
ANTI-
MICROBIAL
REGENERATIVE
MICRO-
ENVIRONMENT

Methods to obtain MSC cultures (Prof Camillo Ricordi)

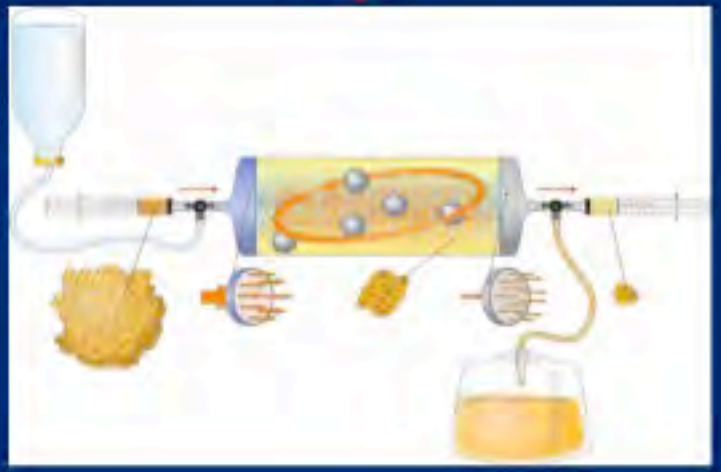
Enzymatic Digestion

(Collagenase)

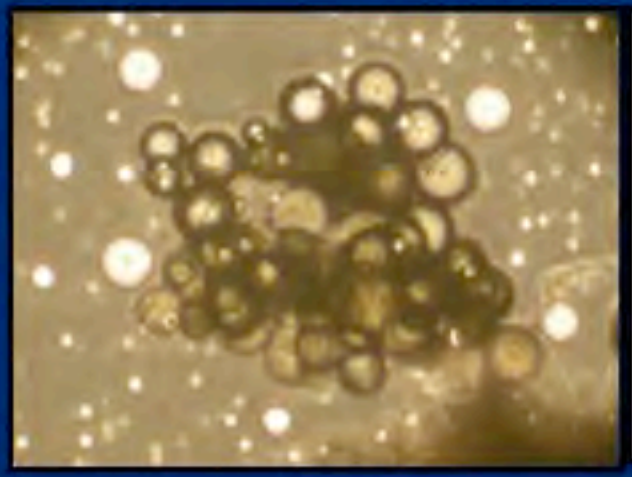


Mechanical Method

(Lipogems device)



1 ml cryopreserved Lipogems cellular growth after thawing (prof C Ventura and prof M Maioli)

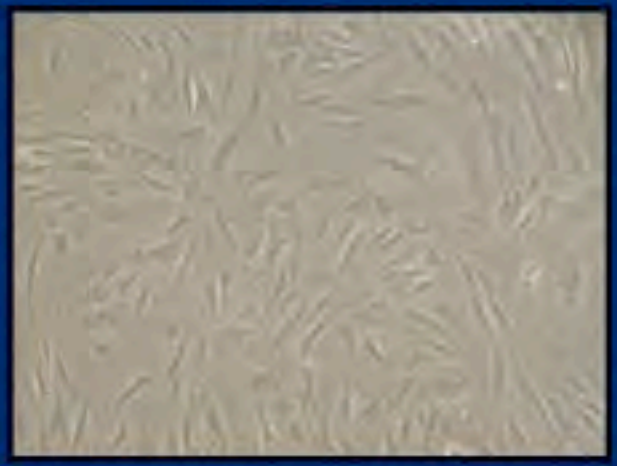


Day 4

Adipose/stem cells floating

Day 6

Cells become adherent



Day 17

After transfer the cells in a new 75 cm^2 cell culture flask at day 14 Percentage of adherent cells 90%.

Comparison of Cell Surface Markers by FACS Analysis in Adipose Derived Stem Cells in Fresh and Cryopreserved Cultures after Non-Enzymatic ADSC Processing (Lipogems™ Method) (prof C.Ricordi)

	% of Gated Cells	
Markers	Fresh/Cultured	Cryopreserved/Cultured
CD105	99.90	99.40
CD90	99.90	100.00
CD44	74.20	97.00
CD3	0.60	2.00
CD11c	6.40	2.20
CD14	5.30	1.90
CD20	2.40	0.20
CD31	5.20	2.70
CD34	1.50	2.10
CD45	0.10	0.40
HLA-DR	1.30	0.60

Cells were cultured for 16 days prior to FACS analysis

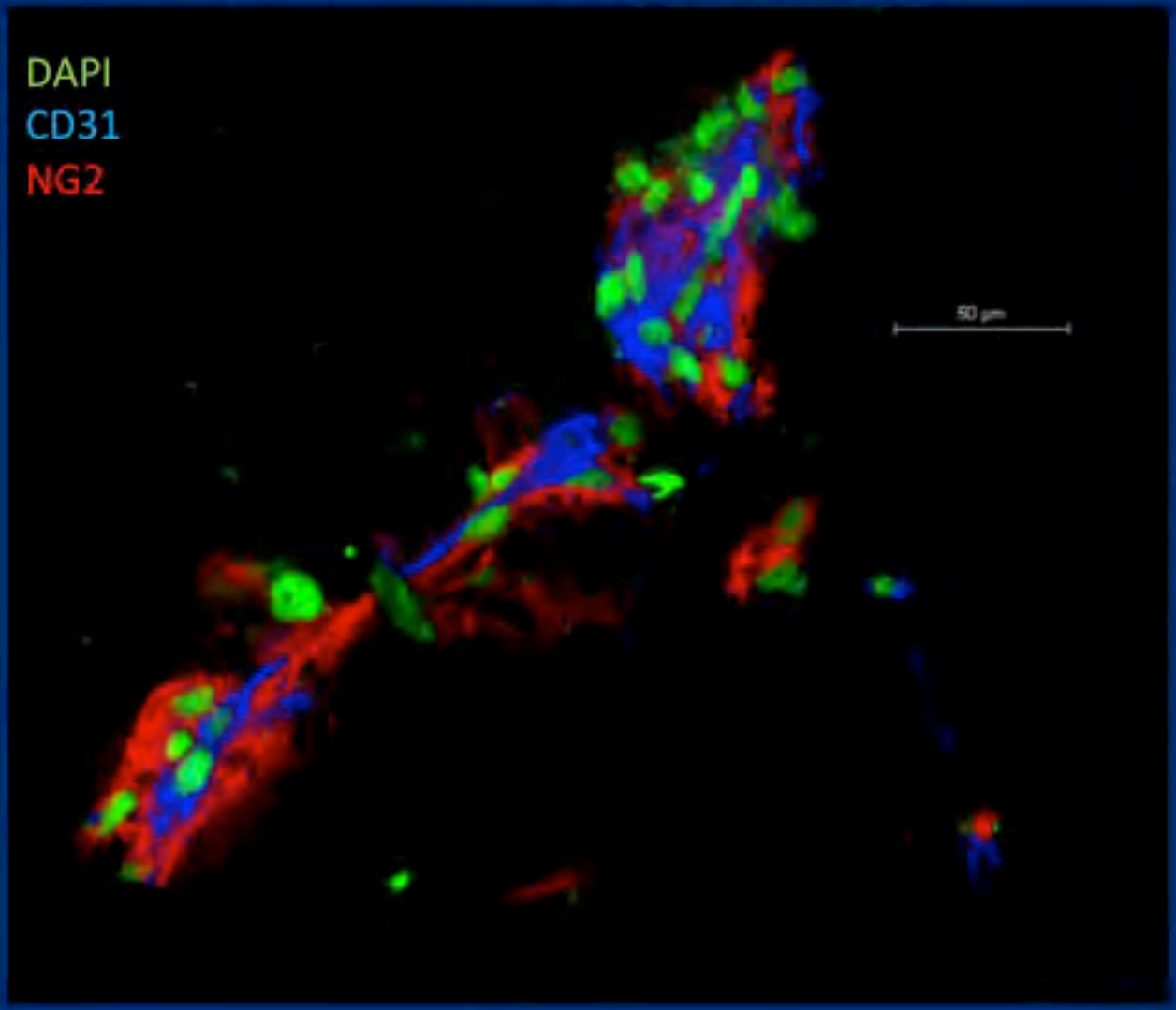
Lipogems®: Characterising a New Therapeutic Product

detailed data on proteomic characterization will be presented at ifat 2015 in new Orleans (usa)

By Isaac Shaw,

Supervisor: Bruno Péault

Proliferative Vascular Bodies in Cultured Lipogems®



Summary of Results

Quality	Lipogems
Overall structure	Clusters of adipocytes, stromal and vascular cells.
Microscopic Structure	Less vessels, no large vessels. Altered endothelial morphology. Enriched in pericytes after culture.
SVF Composition	Enriched in pericytes and endothelial cells. Depleted in haematopoietic cells.
Culture Properties	Cells spontaneously migrate out. Mainly adventitial, lacks leptin receptor (CD295)
Secretome	Altered by digestion. Leptin, MMP-9, TIMP-4 → wound healing association. Less IL-8 (pro-inflammatory cytokine)

Total cases treated with final version of lipogems device: 4208 patients (December 2014) in different centers

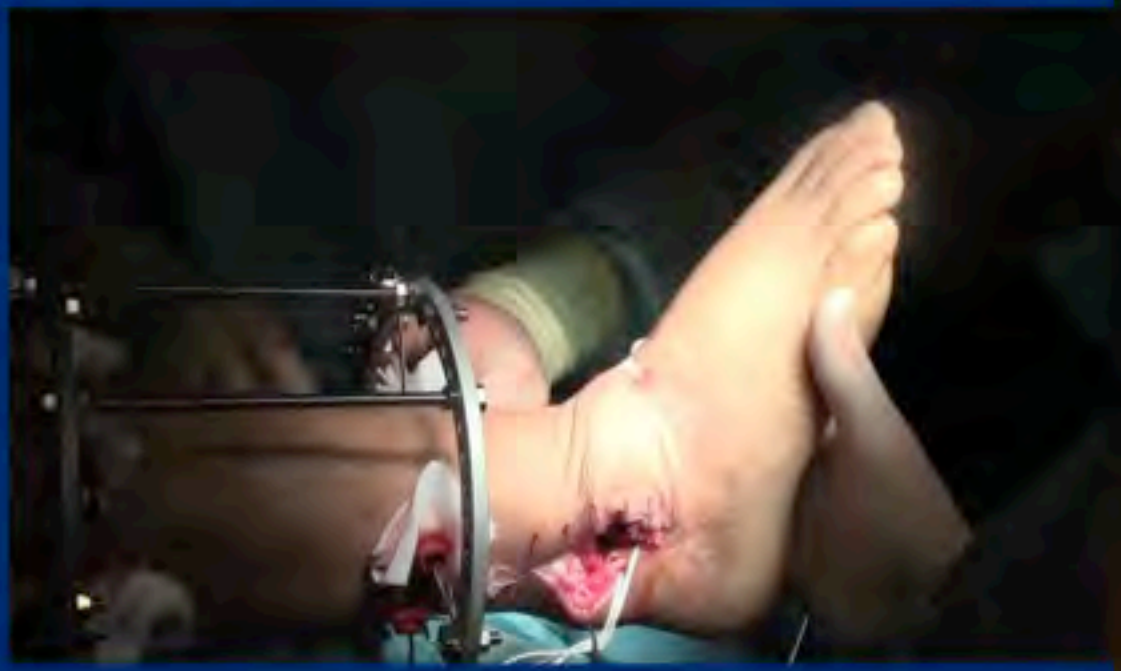
3180 aesthetic surgery
1038 miscellaneous REGENERATIVE SURGERY applications

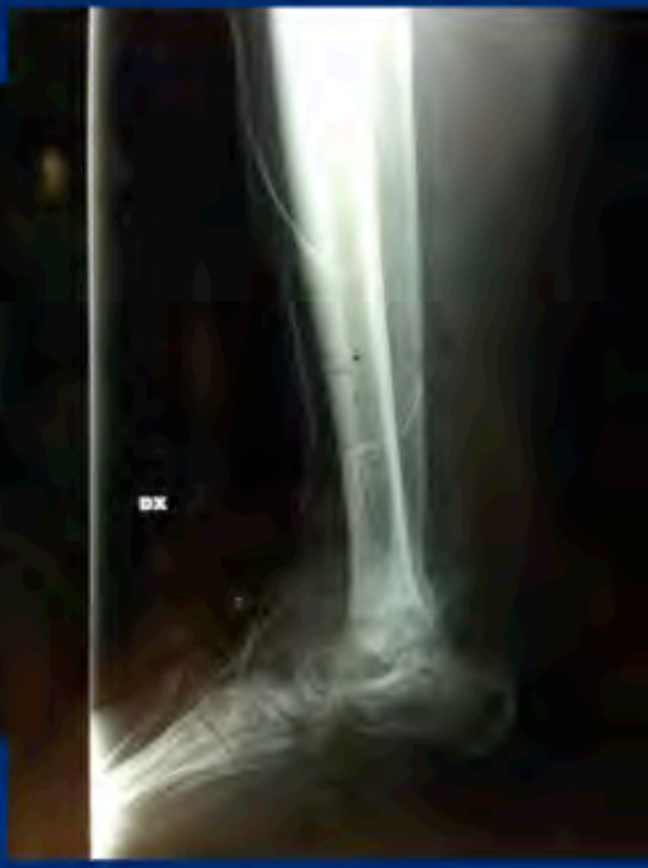
May 2015: over 5000 clinical cases

Regulatory Pathway (TISSUE TRANSPLANT NO CELLULAR THERAPY)

- EUROPE: CE mark obtained in march 2014 (IRB studies on diabetic foot, chronic ulcers, fecal incontinence, vocal cord reconstr, alopecia areata , sclerodermia, aesthetic applications, intraarticolar injections)
- USA : FDA 510k (VERY LARGE CLINICAL APPLICATIONS): cleared (dec 2014)
- CINA: cFDA applications (same as above + gmp cutivated cells for immunsuppression in kidney transplant) filed by chinese army in 2015
- AUSTRALIA: cleared by Afda (oct 2014)
- ISRAEL AND MIDDLE EAST: cleared by iFDA (nov 2014)

Charcot-Marie-Tooth: arabian 76 year old patient scheduled in Linz for amputation: anckle reduction and fixation after pre and intraoperative lipogems treatment
NO SWELLING , NO INFECTIONS, NO PAIN

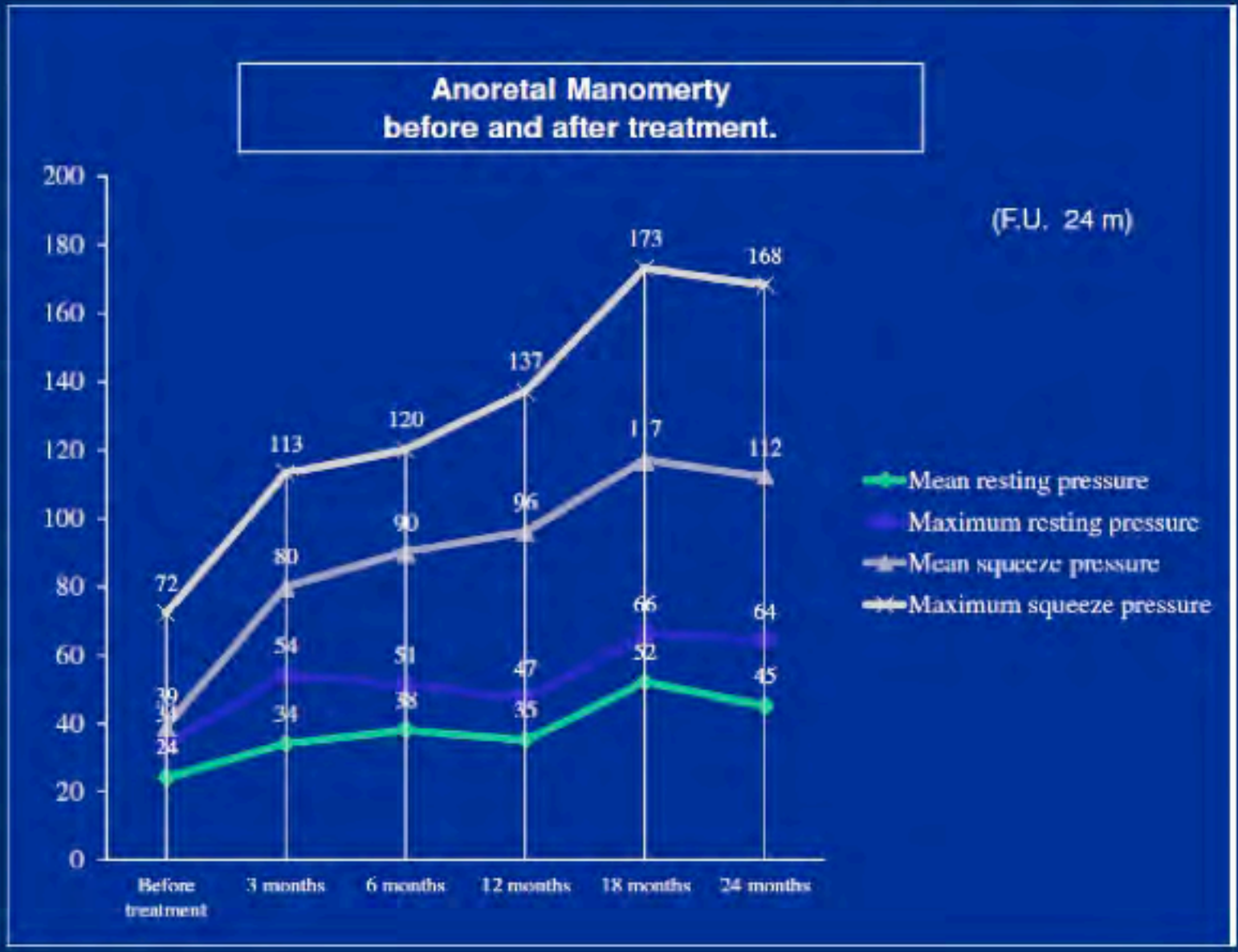




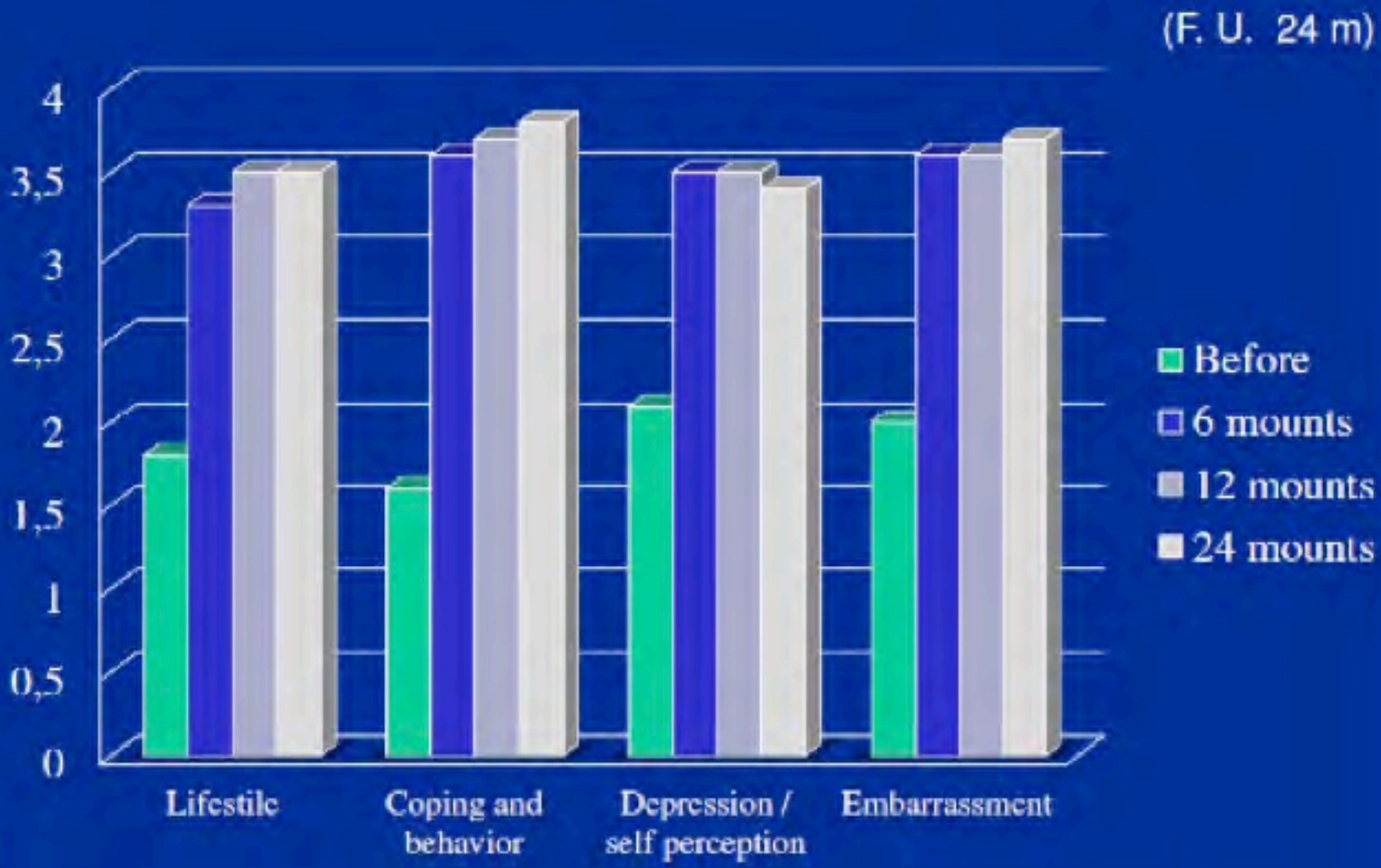
NOW THE PATIENT CAN WALK AGAIN AND DID ALSO THE OTHER FOOT

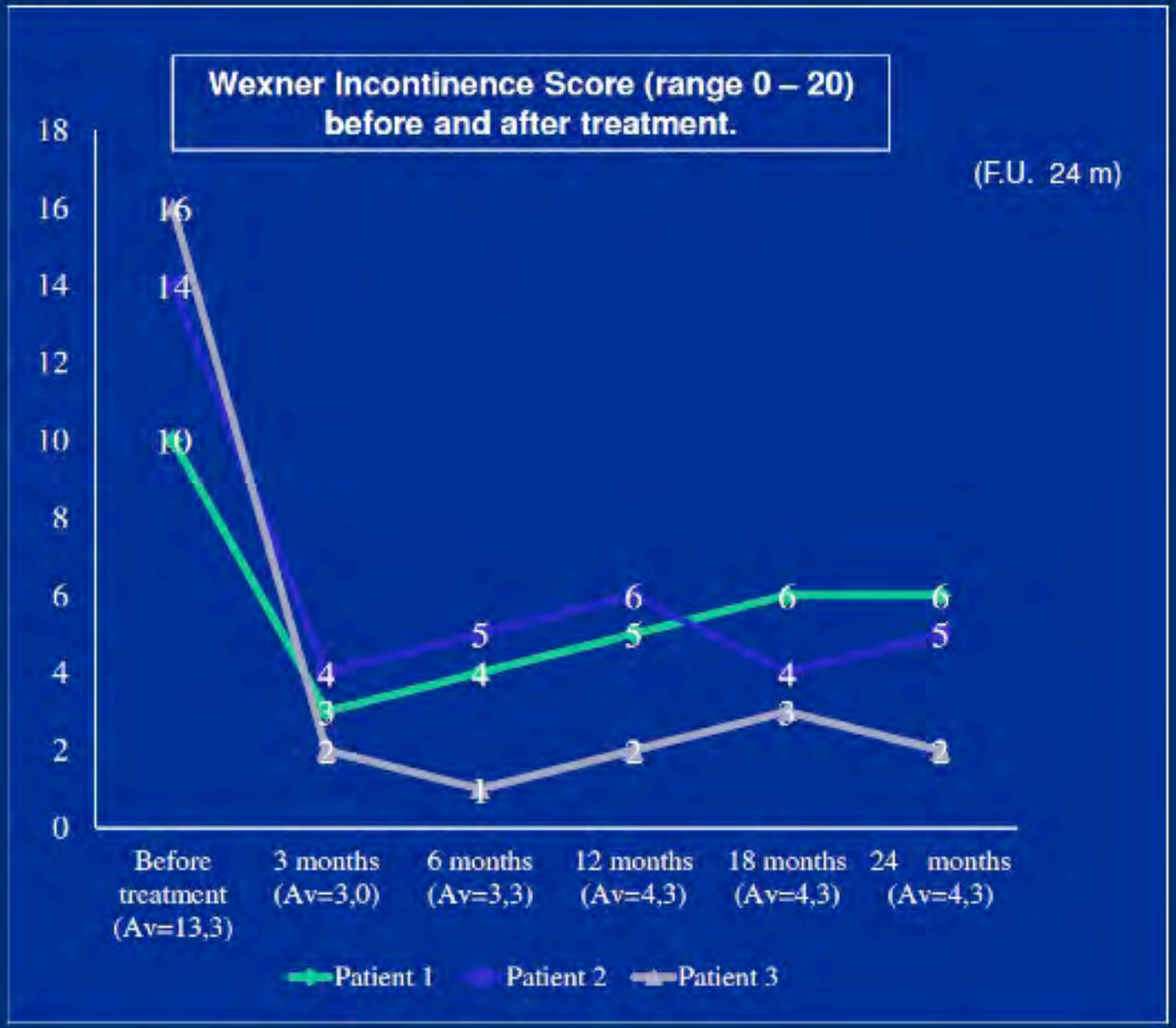
Facial Atrophy for irradiation for palatal tumor in infancy: Lipogems direct treatment (VOLUMETRIC lipofilling)
7 re-treatments (1 year after last treatment and bimaxillary surgery)

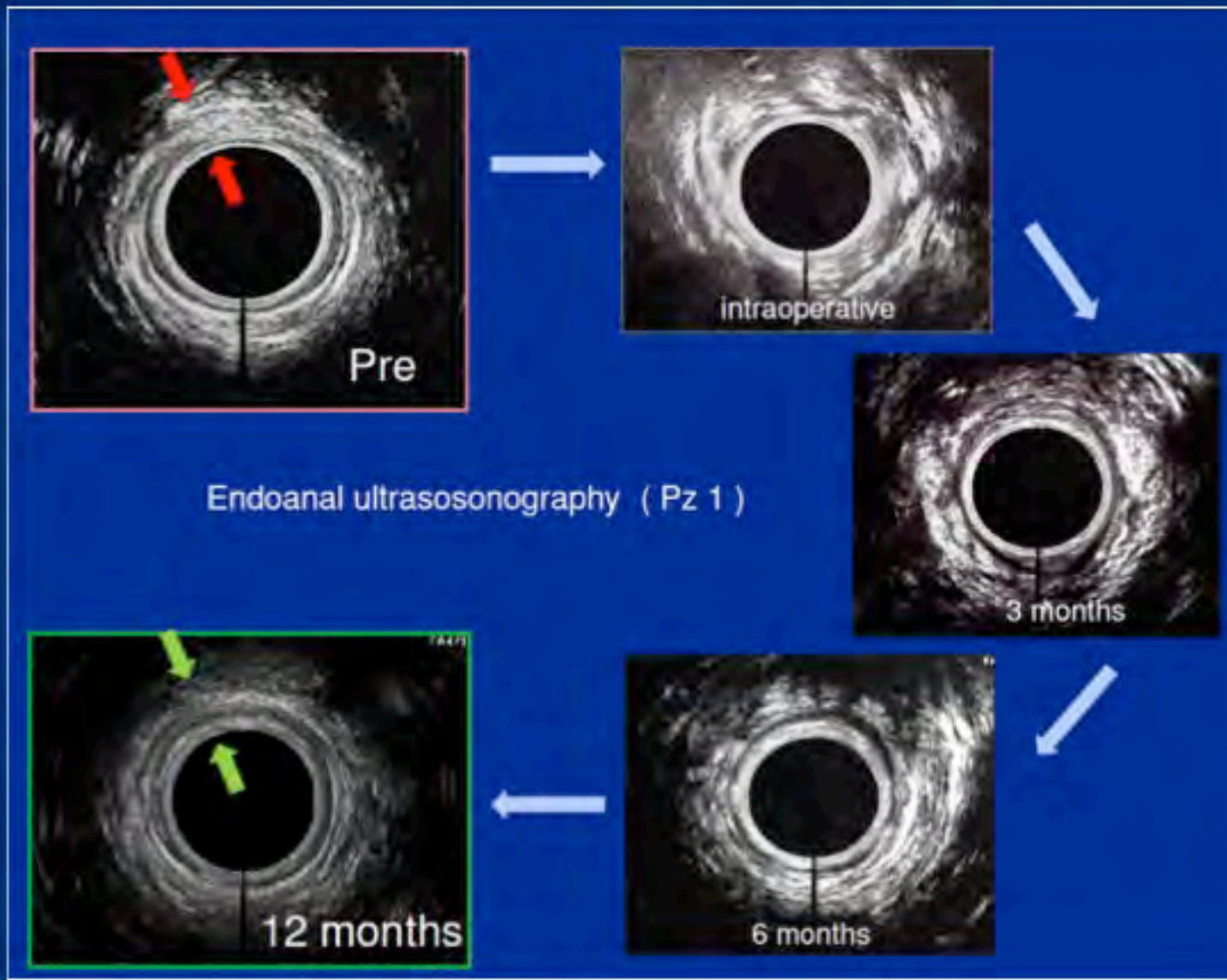
Treatment of Fecal Incontinency



Fecal Incontinence Quality of Life Scale
FIQoL




Wexner Incontinence Score (range 0 – 20) before and after treatment.
(F.U. 24 m)
18
16
14
12
10
8
6
4
2
0
16
14
10
4
3
2
5
4
1
6
5
2
6
4
3
6
5
2
Before treatment (Av=13,3)
3 months (Av=3,0)
6 months (Av=3,3)
12 months (Av=4,3)
18 months (Av=4,3)
24 months (Av=4,3)
Patient 1
Patient 2
Patient 3


Pre
intraoperative
3 months
6 months
12 months
Endoanal ultrasosonography (Pz 1)

RESULTS

All of the patients show a remarkable improvement of the clinical picture.

a) Significant increase in Fecal Incontinence Quality of Life Scale – FIQoL SCORE starting from 6 months post-operation.

b) Significant decrease in Wexner Incontinence Score starting from 3 months post-operation.

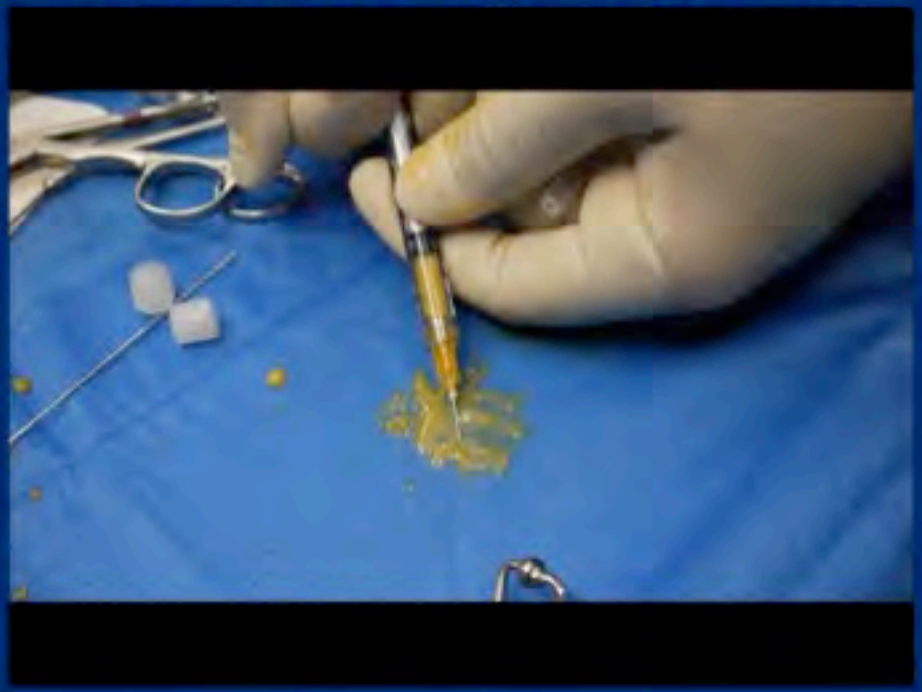
c) Significant increase of pressure values (mmHg) at rest and in squeeze after treatment.

d) Endoanal ultrasonography confirms the improvements.

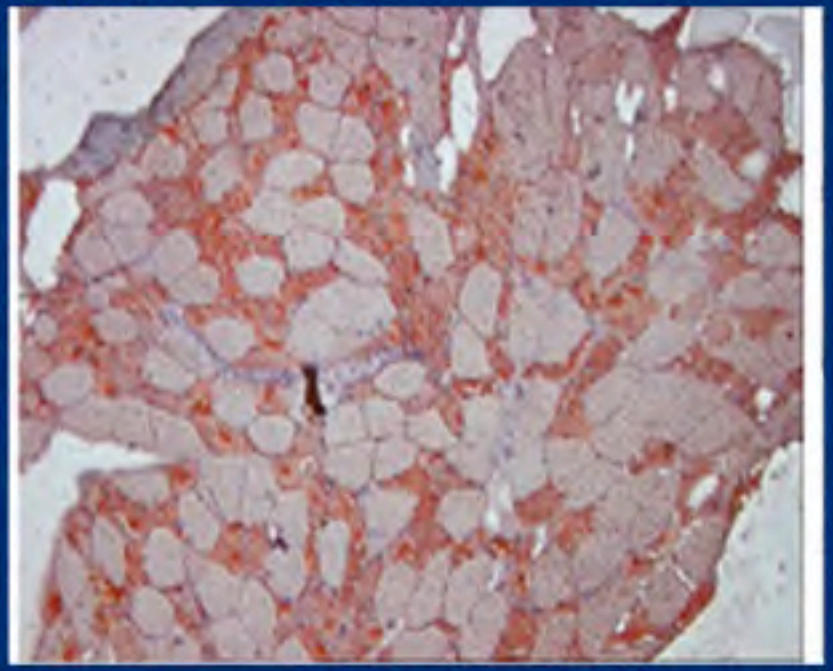
The study has been performed by *Alberto Giori 1°Surgical Division San Paolo Hospital - Milan*

Main difference in Lipofilling technique

Cellular product is much more fluid and the needle much finer



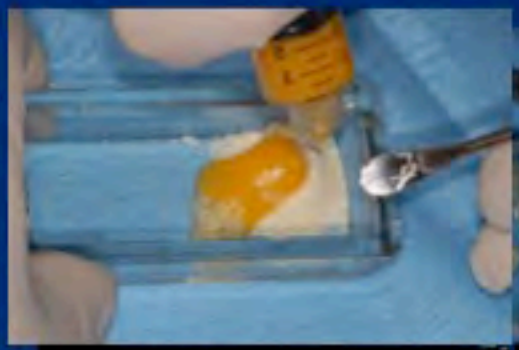
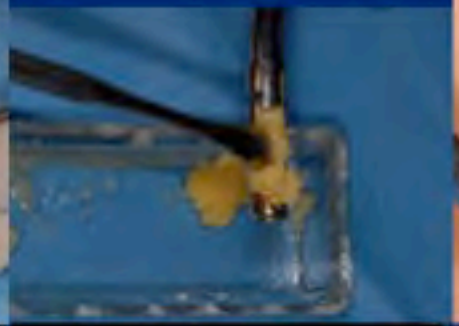
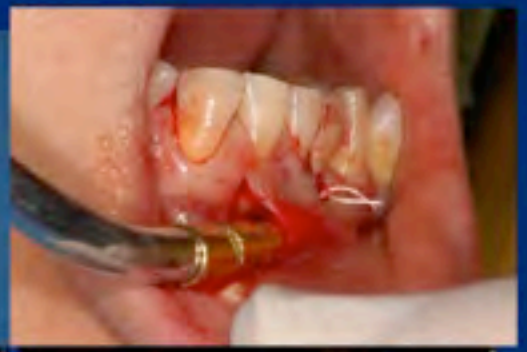
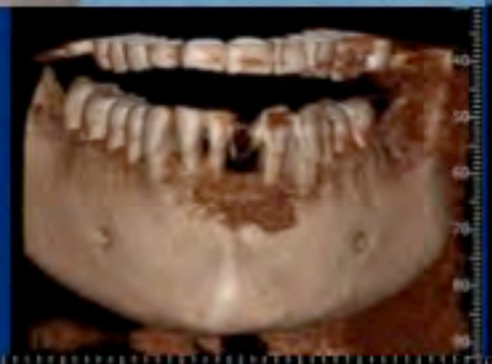
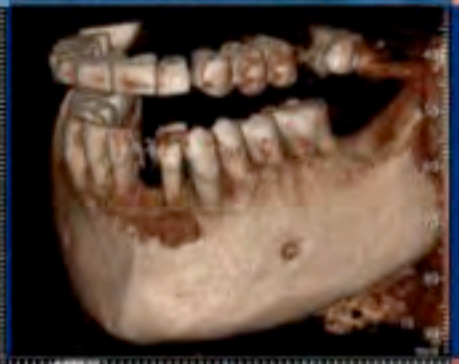
Adipose cell clusters can penetrate through the muscular fibers maximizing tissue contact

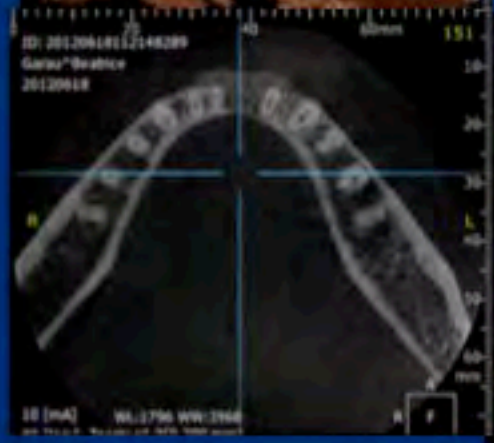
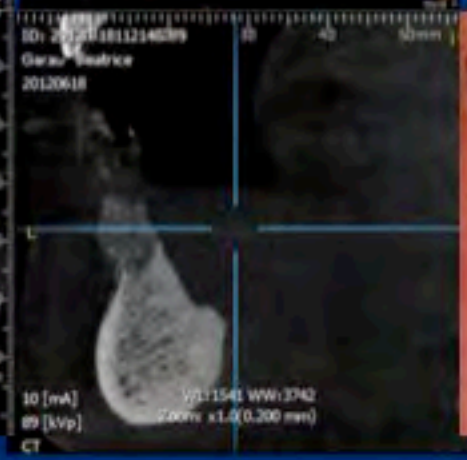


Coleman®

Bone regeneration in oral surgery applications

Published in CellR4, May 2015
« microfractured lpoaspiratemay help oral bone and soft tissue regeneration: a case report»


Garau^Beatrice
20120618
10 [mA]

Garau^Beatrice
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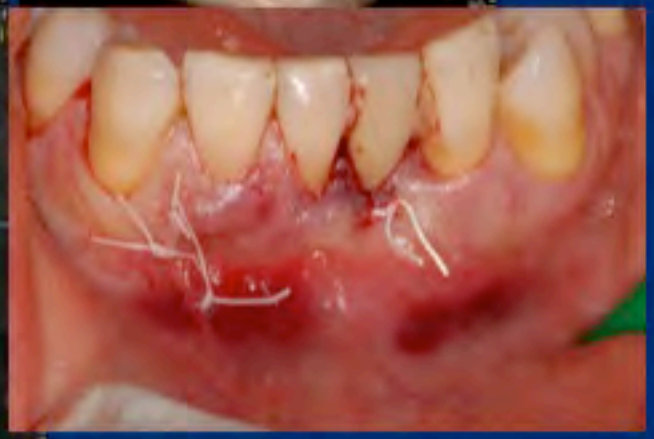
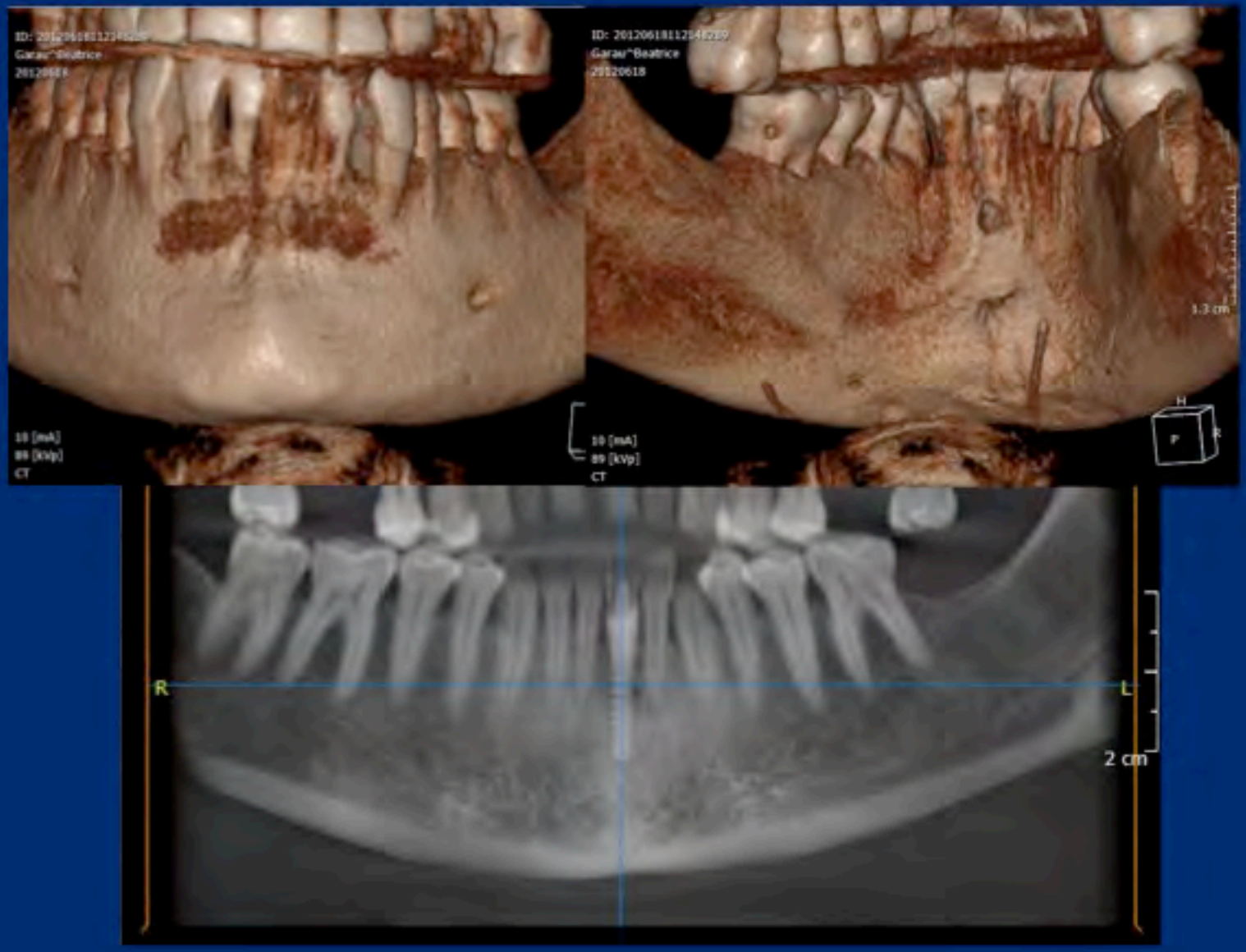
10 [mA]
89 [kVp]
CT



10 [mA]
89 [kVp]
CT
10 [mA]
89 [kVp]
CT
R
L
2 cm

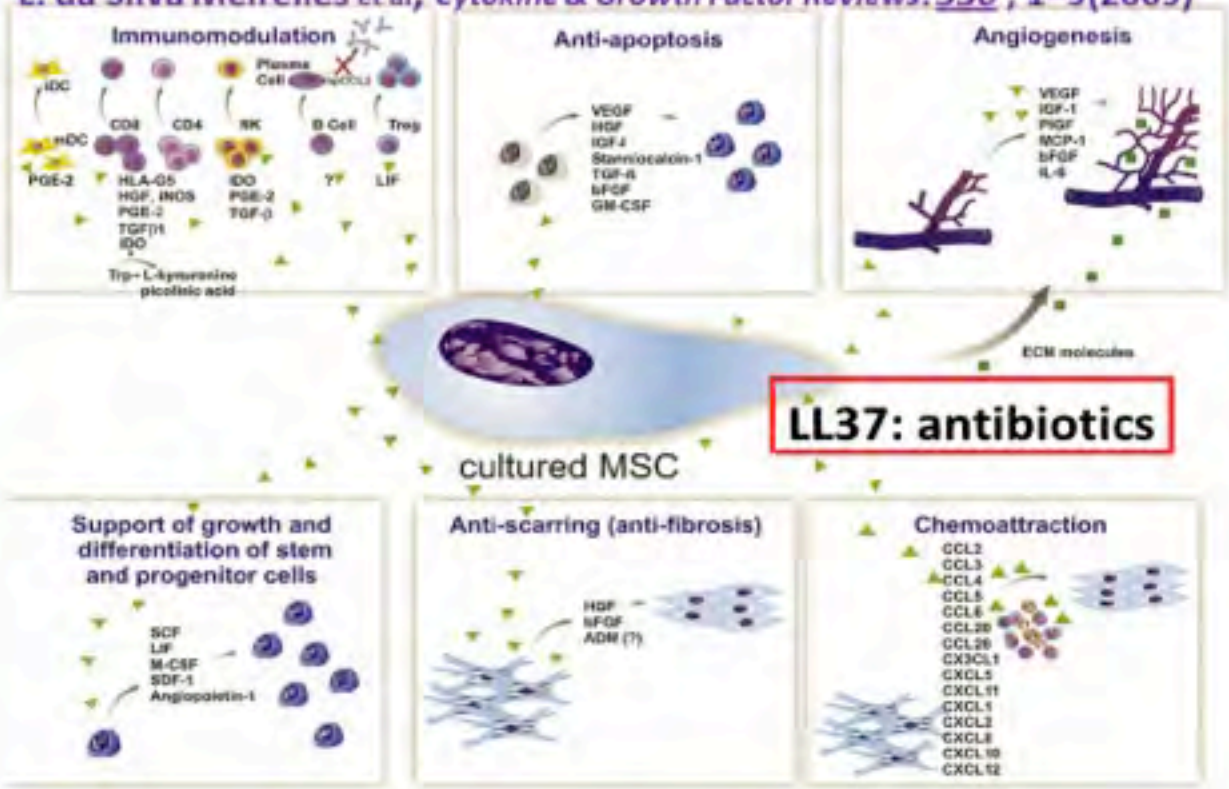
Possible reasons for absence of any significant infection in over 5000 cases

*Antibacterial Effects of hMSCs

A. Krasnodembskaya, et al. ***Stem Cells***, 2010

LL37 IS A VERY EFFECTIVE ANTIBACTERIAL PEPTIDE ALSO PRESENT IN SALIVA. ACTIVELY SECRETED BY LIPOGEMS MSC

L. da Silva Meirelles et al, *Cytokine & Growth Factor Reviews*: 550 , 1–9(2009)



VASCULOGENIC PROPERTIES

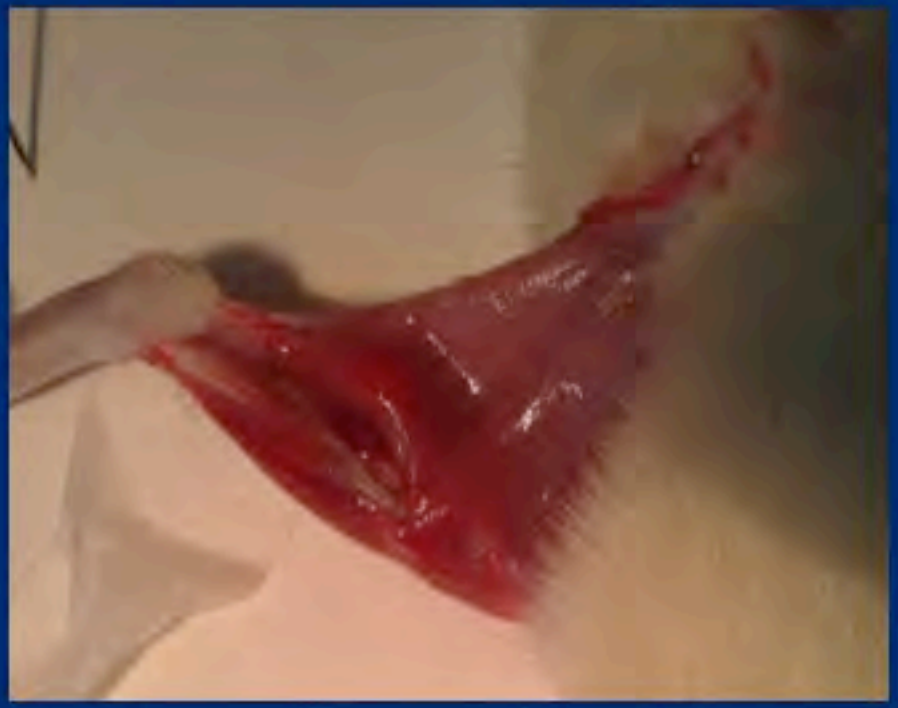
93 Non-healing leg ulcers (defined as non healing in more than 6months with appropiate specialistic care).
Treated with wound debridment and injections around and into the wound bed.

All treated ulcers continued their traditional wound care and 89/93 began to showed clear signs of improvement after about 3 to 6 weeks from lipogems treatment.

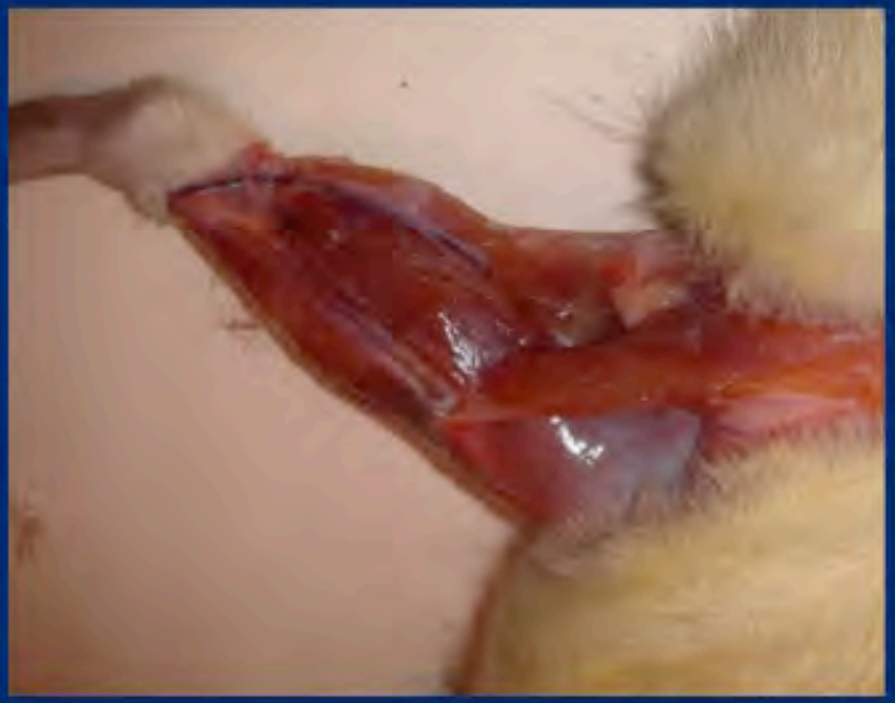
76% completed healing in less than 6 months with no recurrences.

VASCULOGENIC PROPERTIES

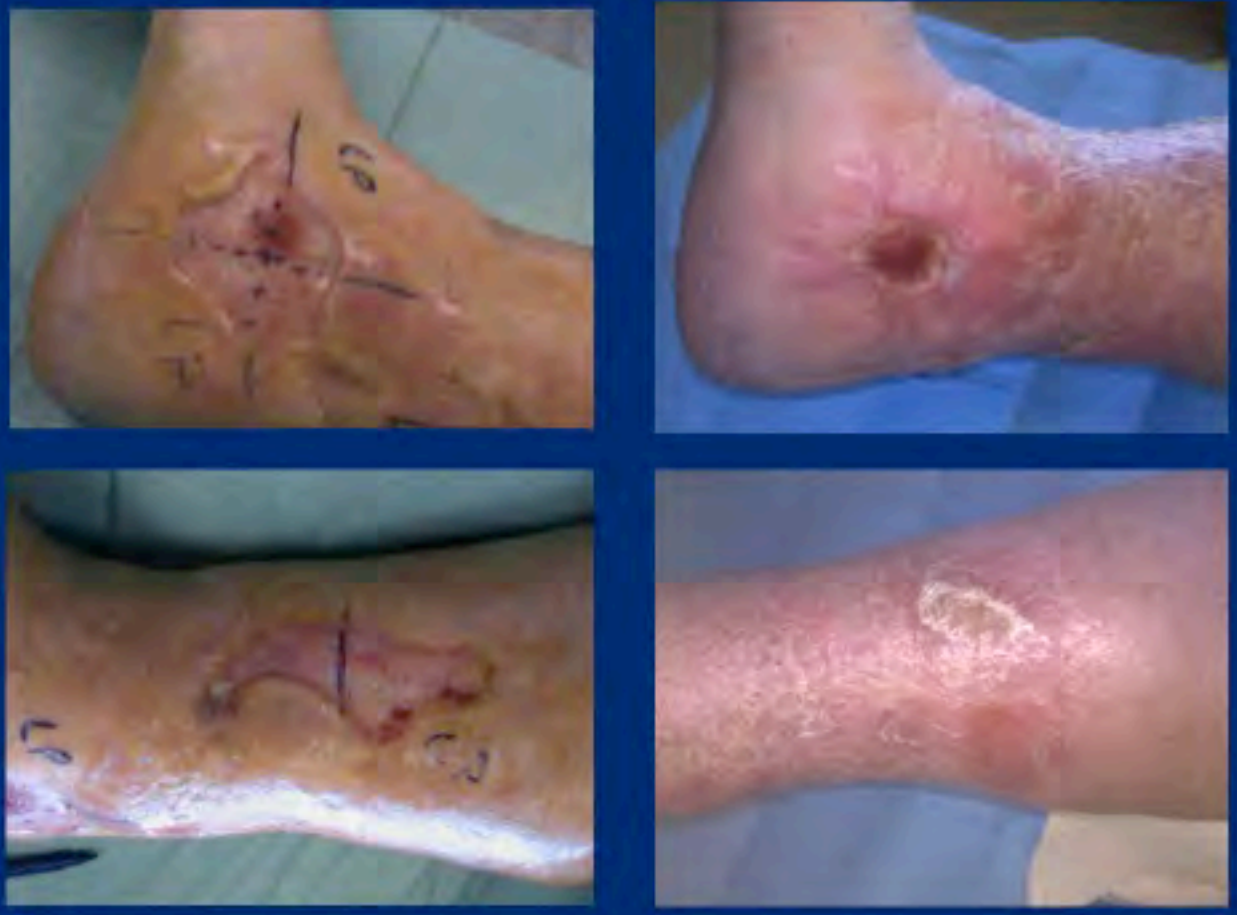
Human Lipogems affords effective tissue repair in model of acute hindlimb ischemia in rats (C. Ventura)
CELLr4 2014



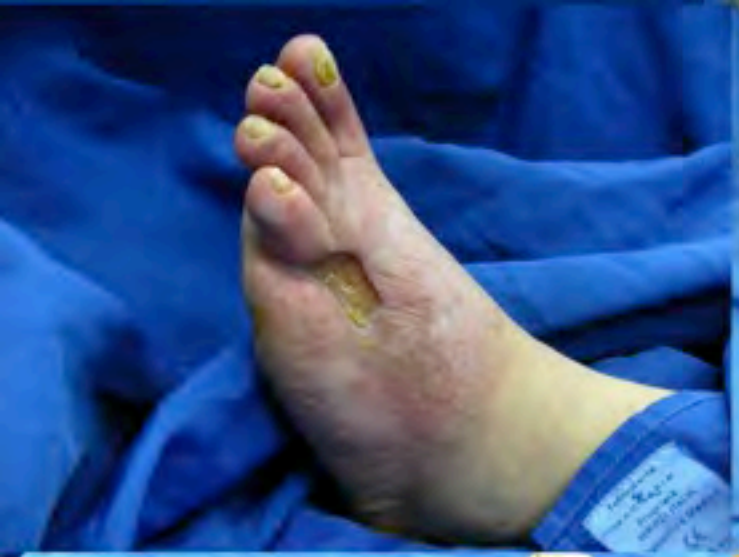
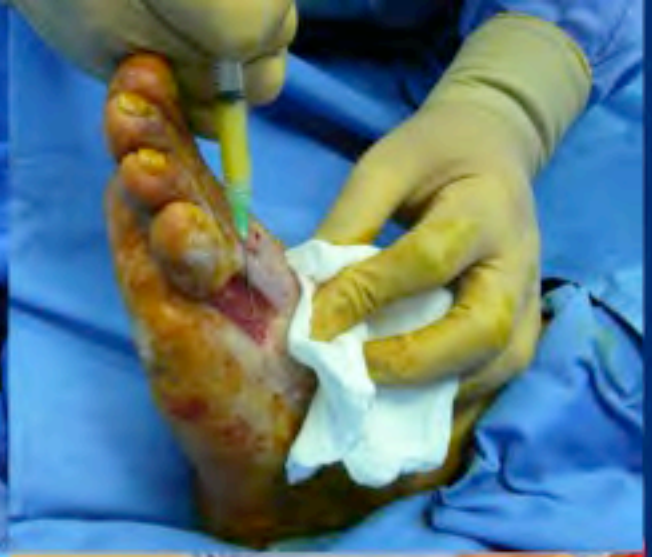
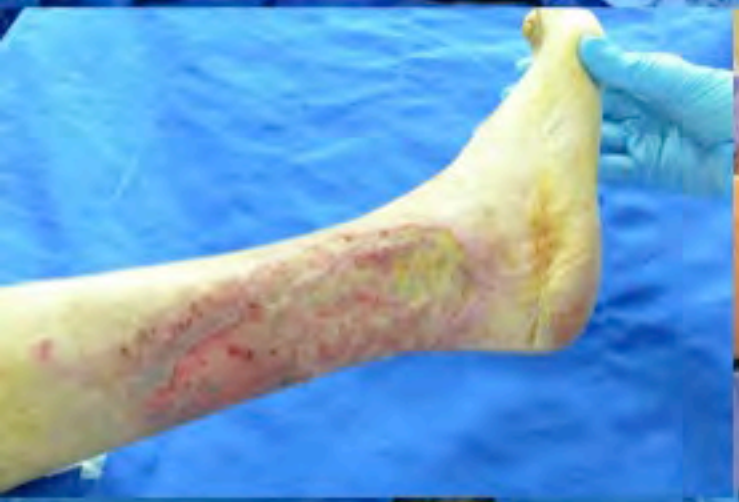
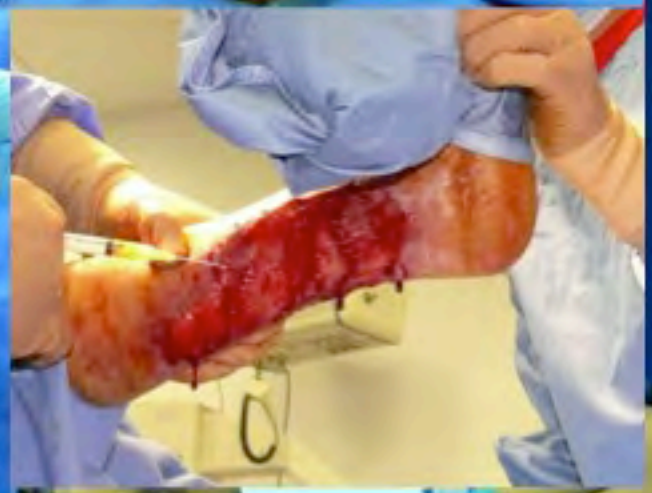
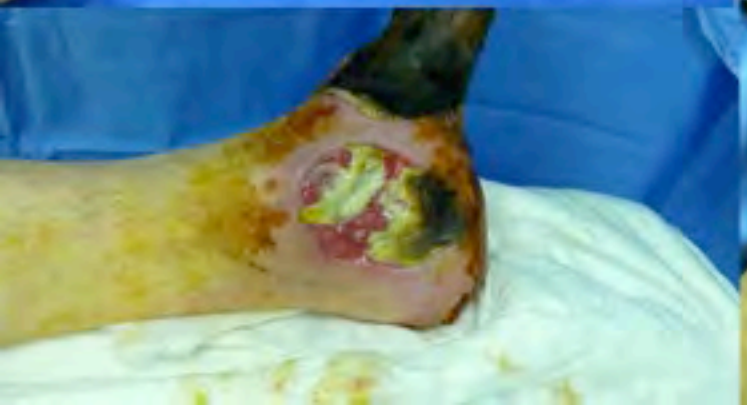
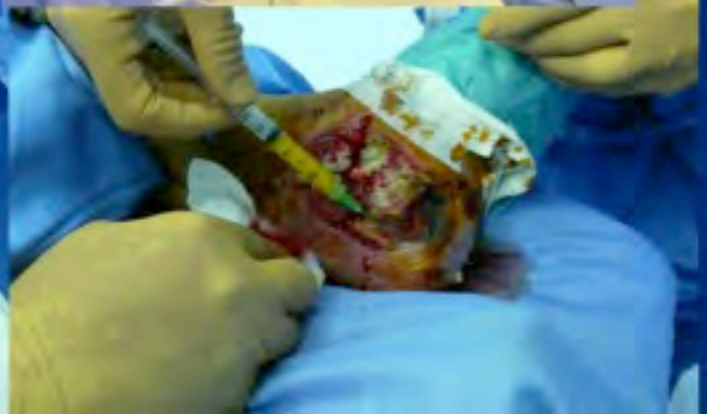
PBS
14 days



Lipogems
14 days



86 years old patient with chronic ulceration during more then three years. 5 weeks after lipogems treatment with clear improvement

Lipogems® and diabetic foot (3)

Prof Brocco
Abano Terme –regional center for diabetic foot

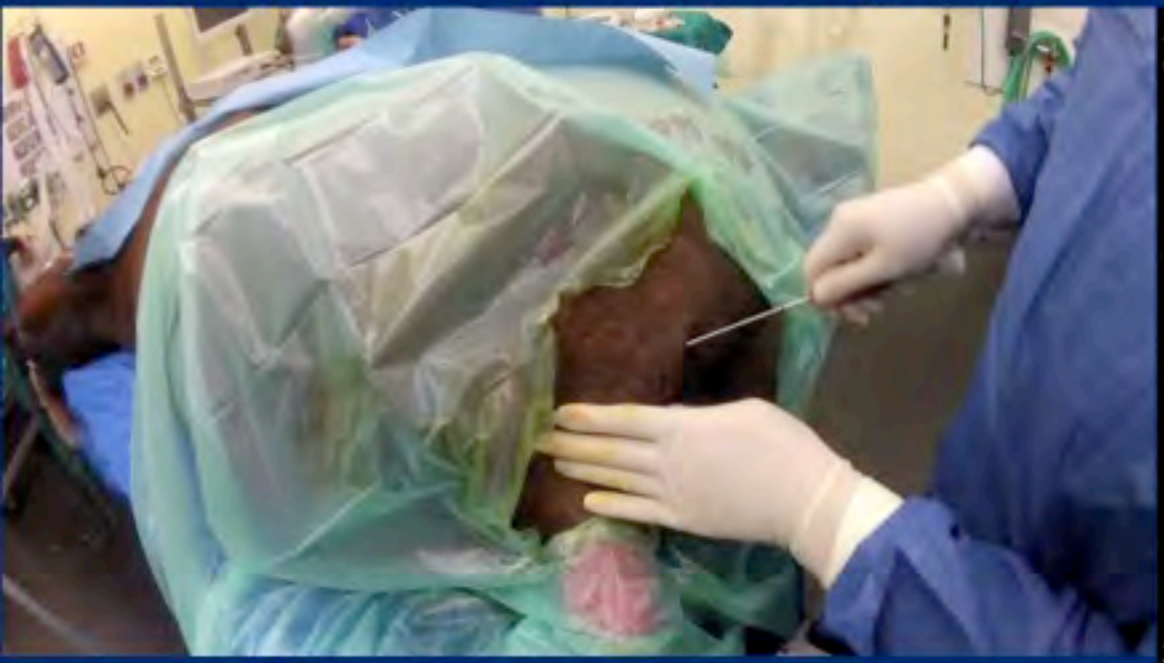
Prof Coppi
Modena – regional center

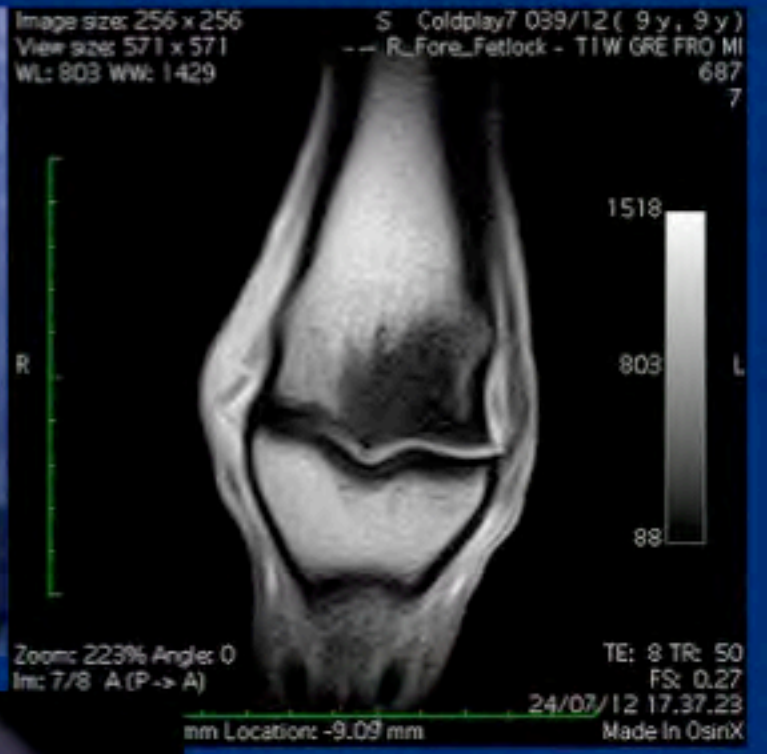
Dr. Brambilla Monza – regional center

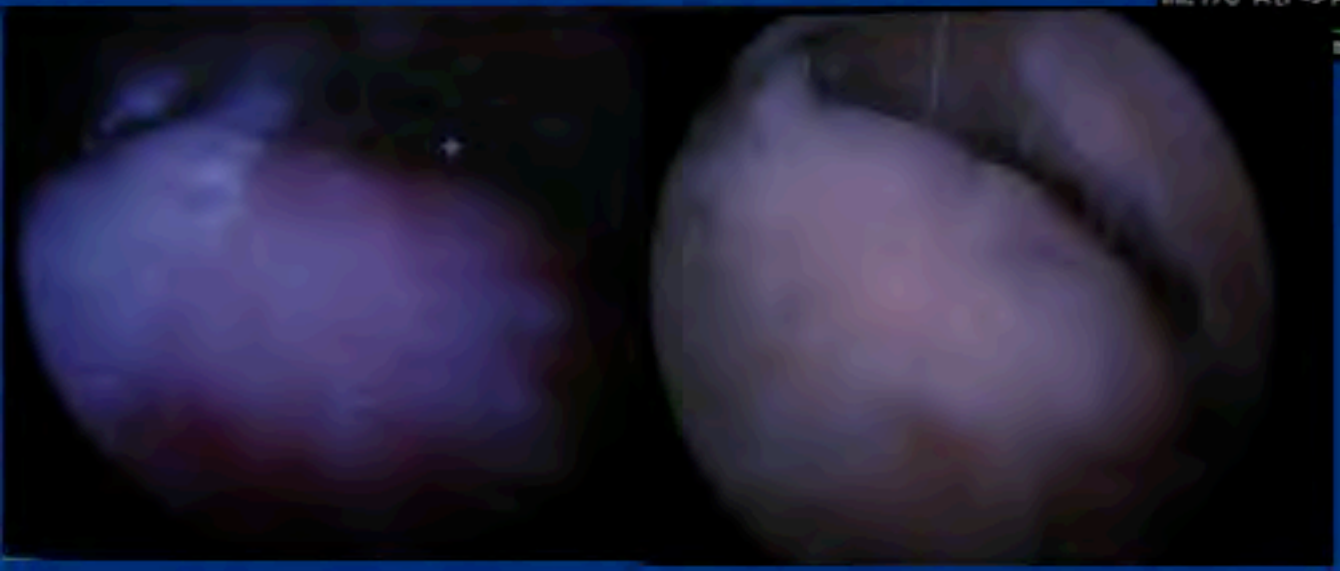
ORTHOPEDICS

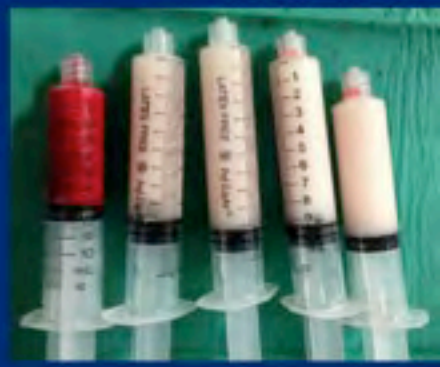
VETERINARY CLINICAL EXPERIENCE

Lipogems® in chondropathy horse (COLDPLAY)

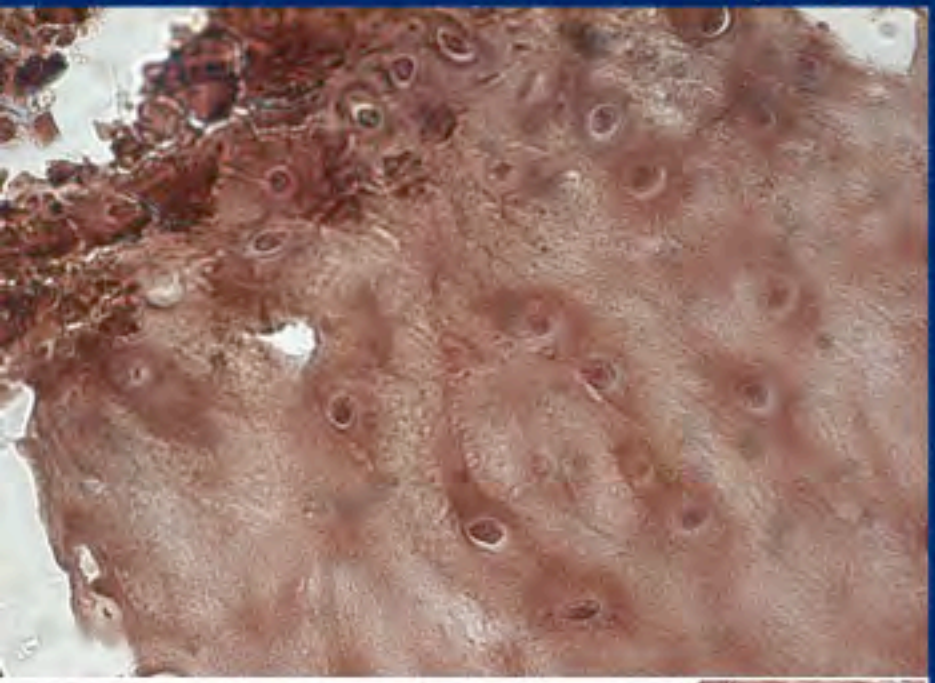


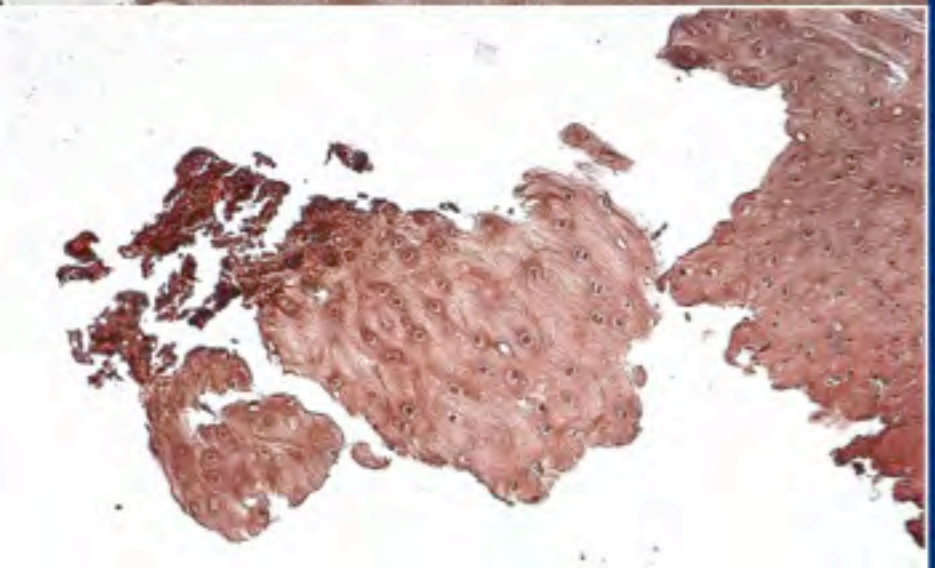


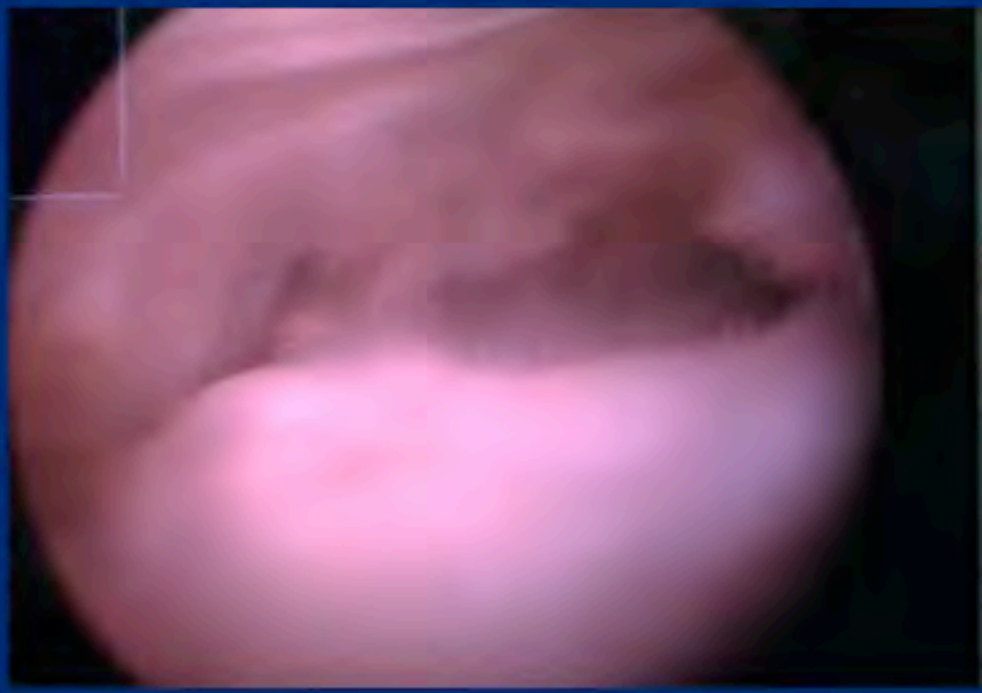




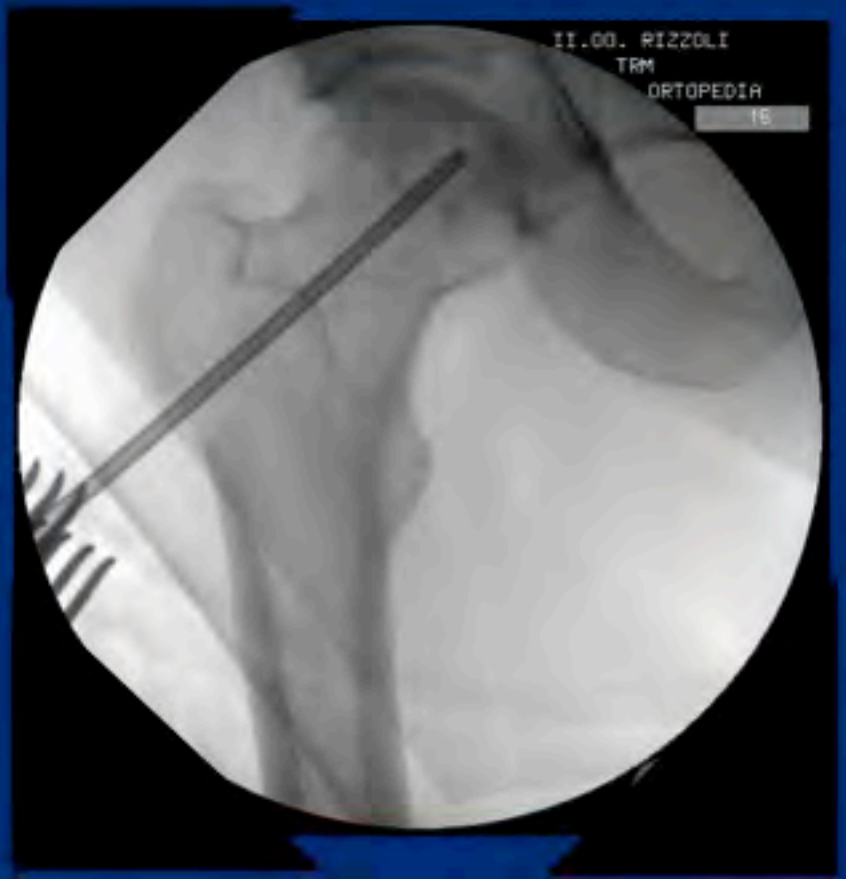
Lipogems® in chondropathy horse (COLDPLAY)



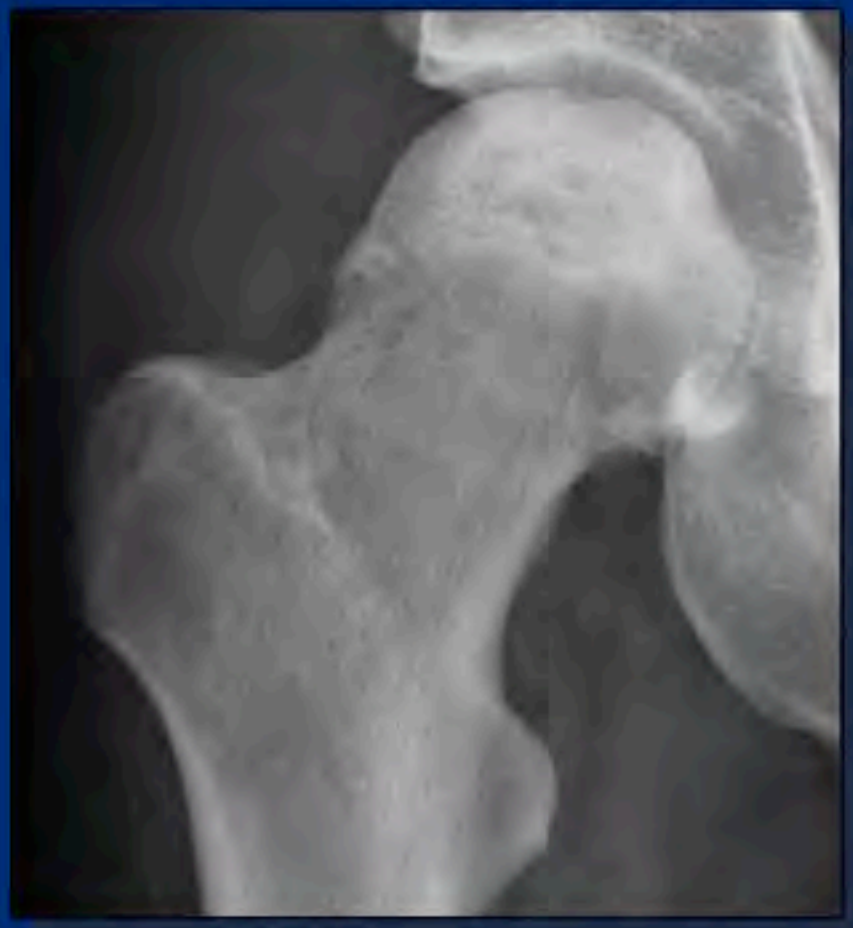


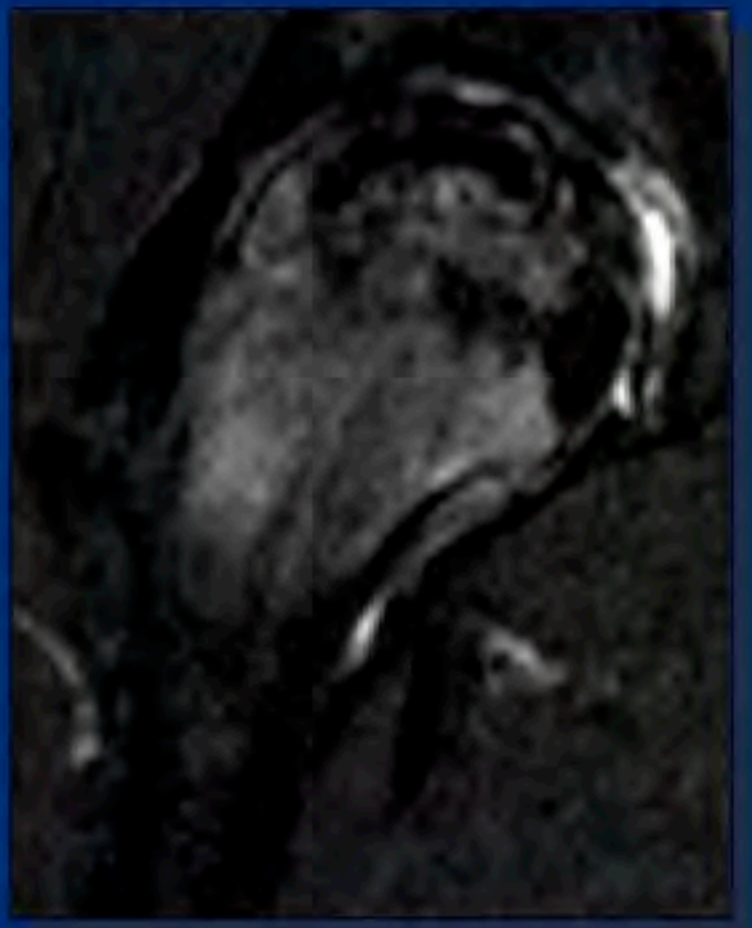


ONFH Surgical treatment LIPOGEMS INJECTION AFTER DRILLING THE CAVITY (prof. Donati – Rizzoli hosp)



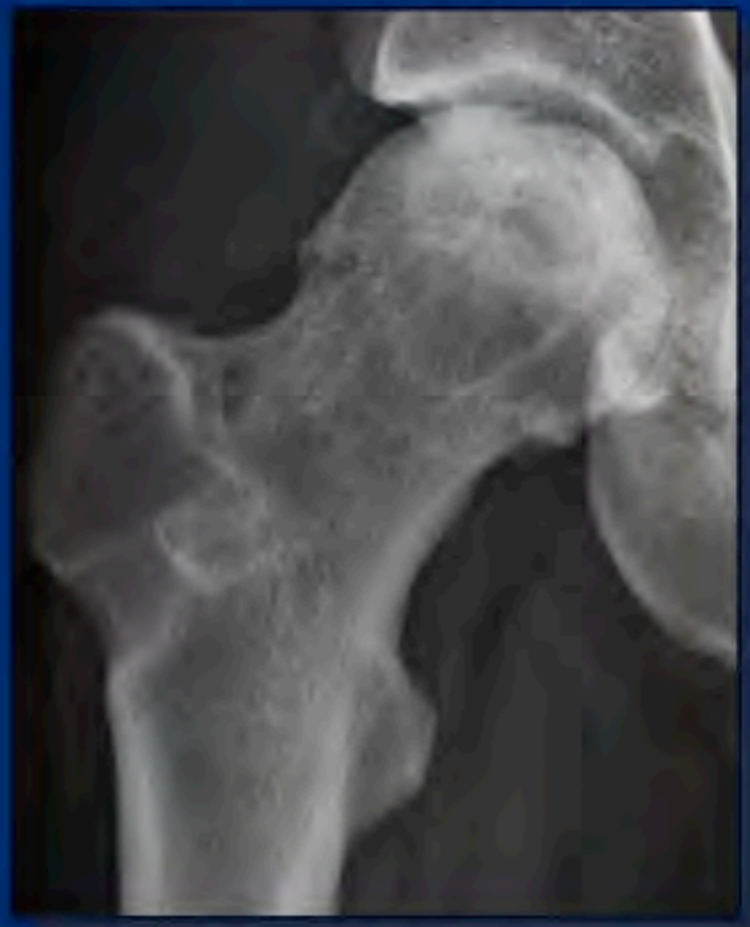
B.M., male, 33 y.o., prednisolone, Ficat IIB, HHS 80

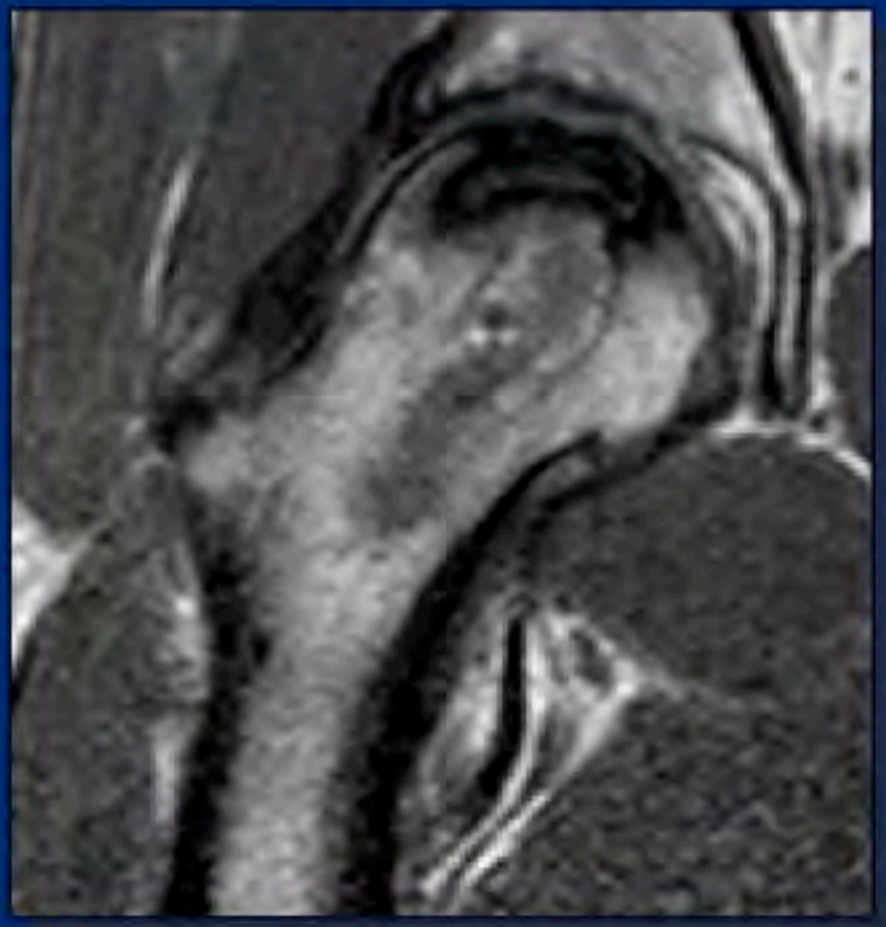




- Pain since 4 years, previously treated with shock wave course
- Very few joint effusion associated to marked sclerotic bone

12 months post-op, HHS 95 no more pain during walking, or joint movements

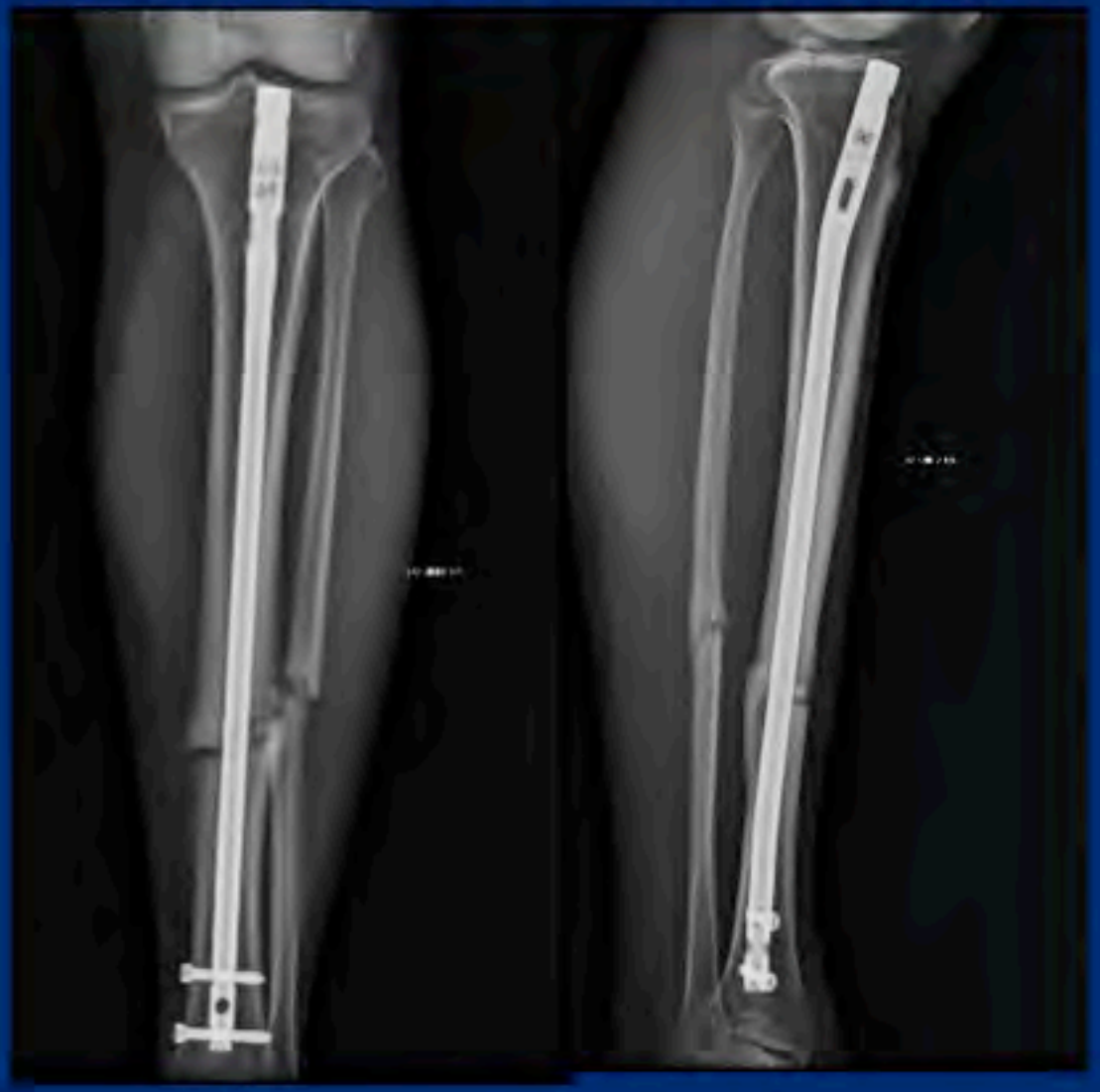




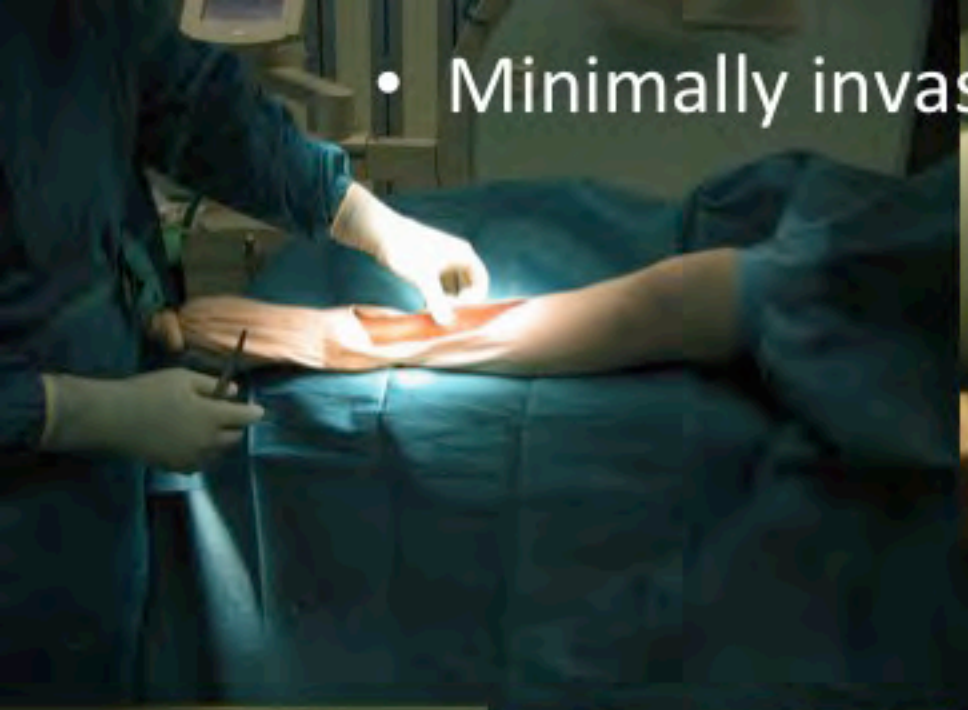
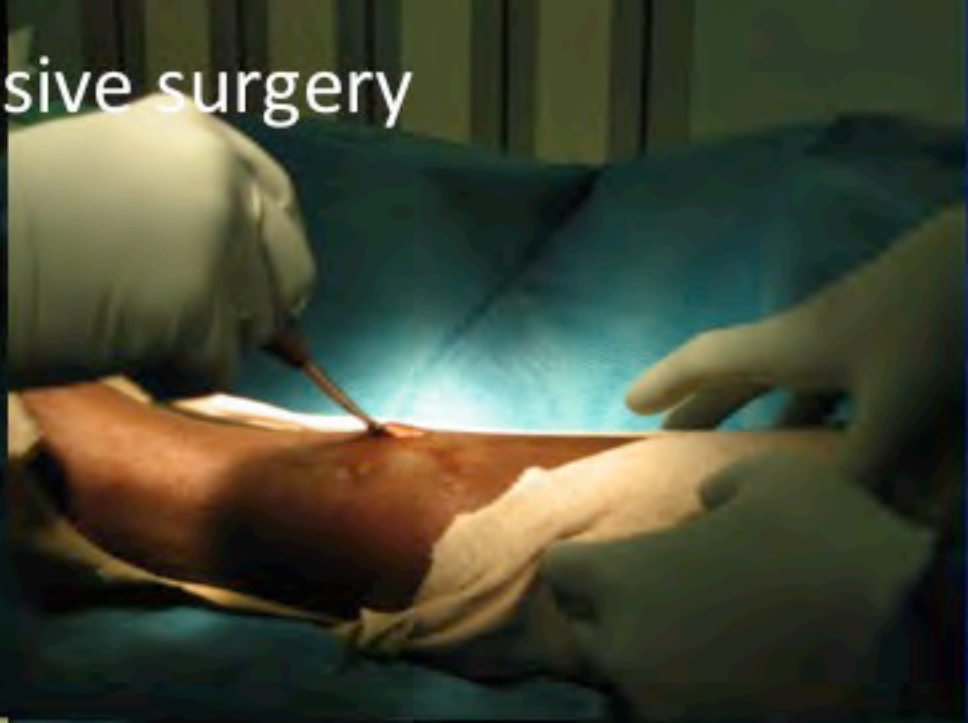
- femoral head shape unchanged
- Part of the necrosis still present with no sign of progression, while the femoral canal resulting more dense

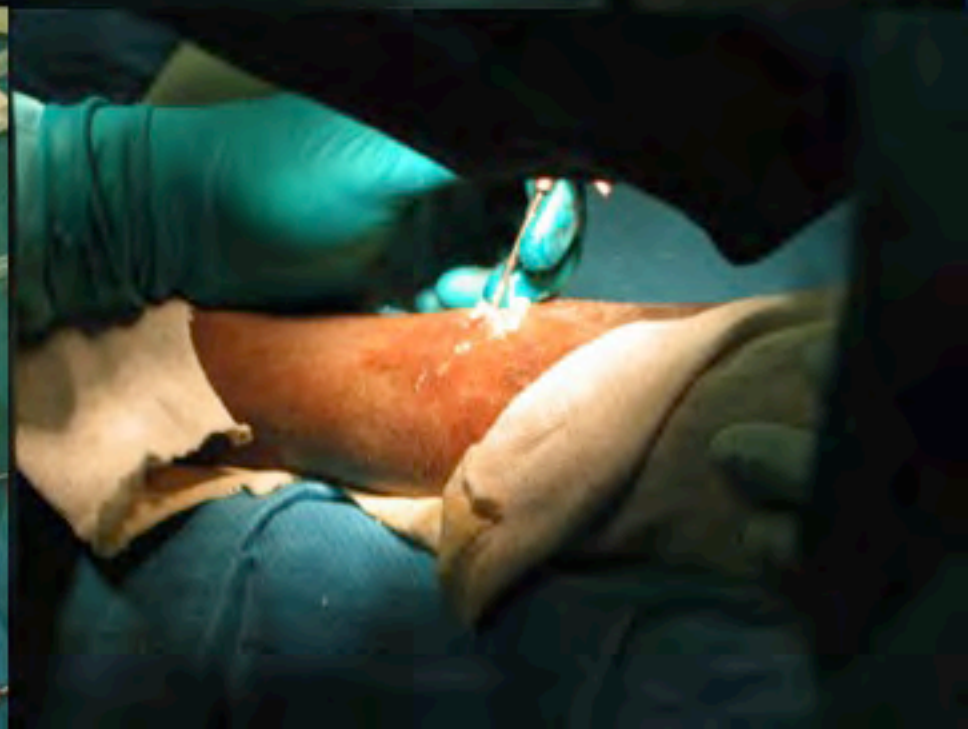
B.R., male, 37 y.o., delayed union fracture treated 9 months earlier

- Walking with one cane, pain at the fracture site

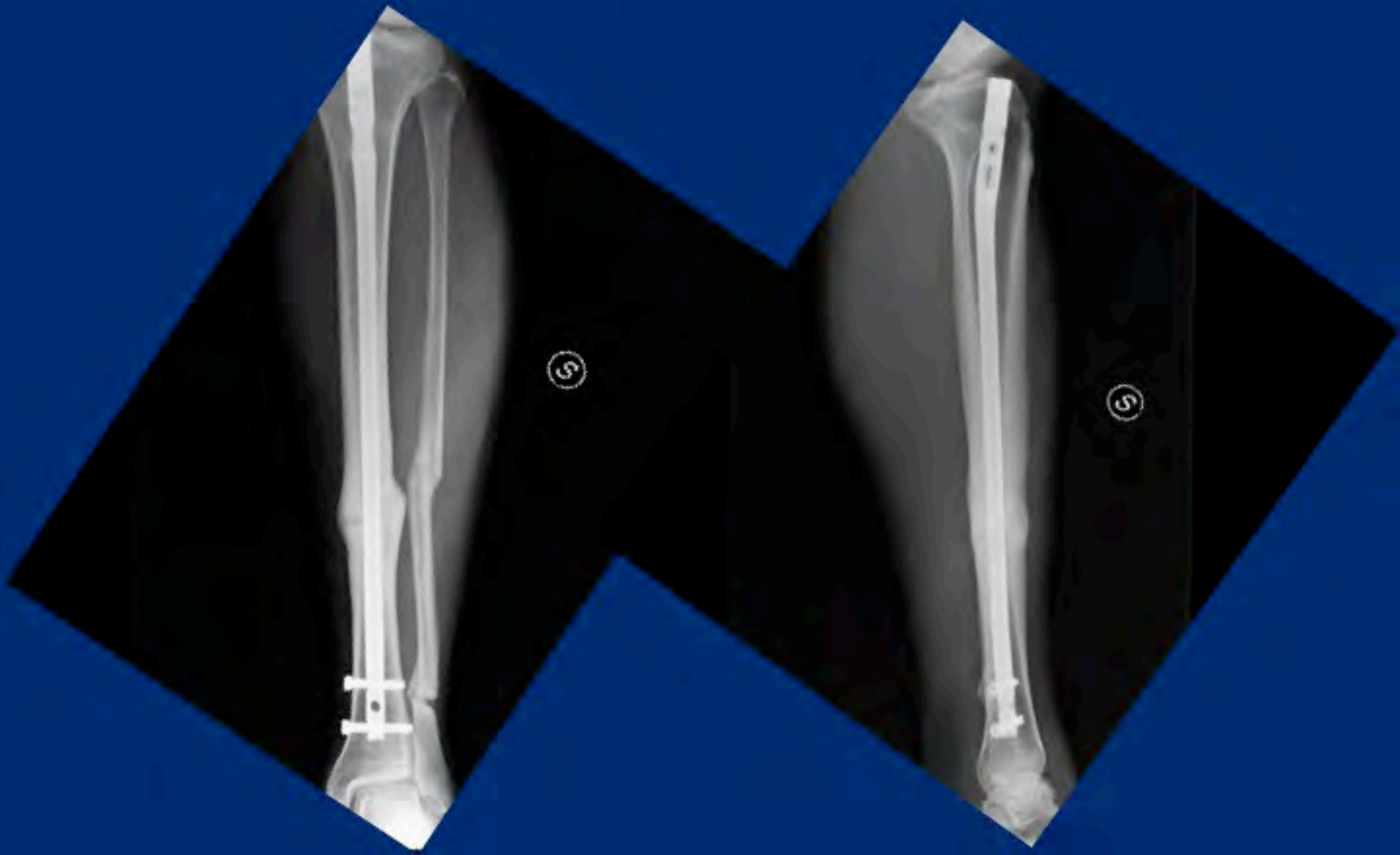


- Minimally invasive surgery

10 months post- op, complete recovery including running and jumping



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www.diabetesresearch.org

JDRF Juvenile Diabetes Research Foundation International

dedicated to finding a cure

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NM Kenyon

J Gimeno
E Zahr-Akrawi
U Ulissi


R Alejandro

Miami Transplant Institute


G Ciancio

Pathology


DM Andrews

NHP Team
W Diaz
J Geary
R Rodriguez
M Willman
E Poumian-Ruiz
A Hernandez
DM Han
A Rabassa

DRI Small Animal Core


Y Gadea
A Tamayo-Garcia
A Lopez

DRI Cell Tx Program
E Linetsky
E Peixoto
A Alvarez Gil

UM SEM (Pat Blackwelder)
UM DVR
UM IACUC

DRI Histology Lab (K Johnson)
DRI Imaging Core
DRI Flow Cytometry Core
DRI Human cGMP Core
DRI Administrative Core

Converge
P Latta
P Buchwald
L Inverardi

Biorep Technologies

Multi-Disciplinary Challenge


Alice Tomei


J. Hubbell


Rodolfo Alejandro

Clinicians


Jay Skyler


A. Pugliese


L. Inverardi

Bioengineers

Immunologists


C. Fraker


C. Stabler


Norma Kenyon

Stem cell biologists

Animal Model Experts


J. Domínguez-Bendala

Pharmacologists


Peter Buchwald


A. Pileggi

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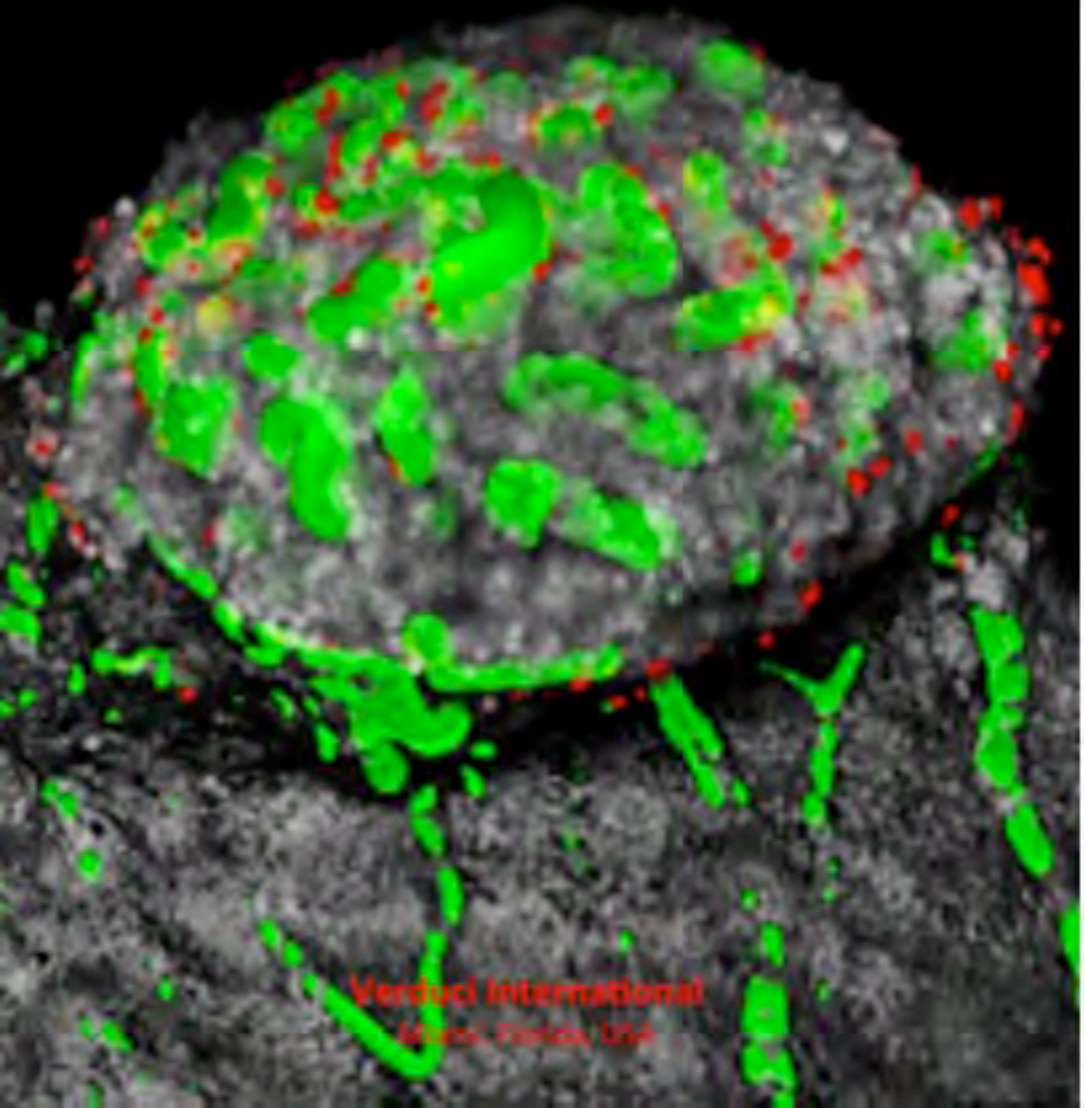

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