



HAIR TRANSPLANT forum INTERNATIONAL

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Reflections on the role of hair grafting in wound healing

Francisco Jimenez, MD Las Palmas, Spain fjimenez@clinicadelpelo.com

Introduction

Given the abundant body of evidence indicating that the main cellular machinery that fuels the wound healing process resides in hair follicles, why not use such machinery in clinical practice as a therapeutic weapon to stimulate the healing of chronic ulcers? This is the fundamental question that we tried to address in a paper recently published in the journal *Wound Repair and Regeneration*.¹

The Hair Follicle and the Healing Process

The hair follicle appears to be the main anatomical structure that contributes to the healing process of cutaneous wounds. There is abundant clinical information to support the fact that wound healing starts around the hair follicles. Both the epithelial portion and the mesenchymal portion of the hair follicle contribute to the healing of skin wounds.

I would highly recommend a paper published in 1945 by G.H. Bishop, a neuroanatomist from Washington University in St. Louis.² This paper, published in the *American Journal of Anatomy*, is the most relevant paper I have read about the wound healing process in humans. Bishop studied how the connective tissue and epithelium regenerate after removal of superficial layers of the skin. What is more, he did it in the hardest, but at the same time, the most objective way he could by self-inflicting cutaneous wounds on his forearm at different tissue depths and observing the healing process that took place clinically and histologically. He noted that not only did reepithelialization start around the remaining hair follicles, but also that when the skin was destroyed down to the deep dermis, the granulation tissue that regenerated came from the connective tissue surrounding the hair follicles.

Wounds in hairy areas heal faster than in non-hairy areas. One fact that supports the notion that hair follicles contribute to the healing process is the clinical evidence showing that wounds heal faster in hairy than in non-hairy zones. This property has been clinically demonstrated when scalp is the donor source for harvesting split-thickness grafts (0.2-0.3mm in depth): the healing time to complete reepithelialization of the donor wound averages 5 days in comparison with 10 days in areas such as the thighs, buttocks, or abdomen.³

The hair follicle is the main repository of cutaneous stem cells with multipotent capacity. At cellular level, the follicular stem cells are key players in the proliferation and differentiation of follicular cells in the wound bed. Keratinocytes that reepithelialize the wound are thought to derive from hair follicle epithelial stem cells that reside within the bulge. Hair follicle dermal papilla and dermal sheath harbor mesenchymal stem cells for which a role in wound healing has been proposed. Accordingly, transplantation of hair follicles with vital dye-labeled dermal sheath cells into a murine wound bed resulted in dermal sheath fibroblasts from the lower hair follicle being incorporated into the wounded dermis.⁴

Why Transplant Hair Grafts in Chronic Leg Ulcers?

Chronic leg ulcers are one of the most costly and prevalent diseases for health services worldwide. Have you ever considered how much money is spent on the treatment of a patient with a chronic leg ulcer? Accurate estimations recently published give a figure of 9,569 euros per ulcer per year. We are facing a major health care problem that consumes an enormous amount of highly costly resources.⁵ Most cutaneous chronic ulcers are located in the lower extremity and are caused by venous insufficiency, followed by arterial insufficiency and neuropathy (especially of diabetic etiology). It is estimated that 1 out of 100 adults will suffer from chronic leg venous ulcers at some point in their lifetime.

Chronic leg ulcers need better therapies. Compression therapy and wound dressings continue to be the mainstay treatment for venous ulceration in clinical practice. However, some 20% of ulcers remain unhealed after more than 50 weeks of appropriate compression therapy. Skin grafts have been used, but there is still insufficient evidence for the effectiveness of autologous skin grafting.⁶ Those grafts were taken from non-hair-bearing areas such as the buttocks that are preferentially composed of dermal tissue with no terminal hair follicles. By contrast, the original approach of our research work is that the punches are removed from the patient's scalp using a small punch, as is usually performed in hair transplantation (punch grafting technique).



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President: Carlos J. Puig, DO
cpuig@hairrestorationhouston.com

Executive Director: Victoria Ceh, MPA
vceh@ishrs.org

Editors: Nilofer P. Farjo, MBChB
William H. Reed, II, MD
editors@ishrs.org

Managing Editor, Graphic Design, & Advertising Sales: Cheryl Duckler, 262-643-4212
cduckler@ishrs.org

Cyberspace Chat: Sharon A. Keene, MD

Controversies: Russell Knudsen, MBBS

How I Do It: Bertram Ng, MBBS

Hair's the Question: Sara M. Wasserbauer, MD

Surgical Assistants Corner Editor: Ailene Russell, NCMA
arussell@haircenter.com

Basic Science: Francisco Jimenez, MD
Ralf Paus, MD
Mike Philpott, PhD
Valerie A. Randall, PhD
Rodney Sinclair, MBBS
Ken Washenik, MD, PhD

Review of Literature: Marco Barusco, MD
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President's Message

Carlos J. Puig, DO Houston, Texas, USA
cpuig@hairrestorationhouston.com



Two of Gandhi's "4 Dangers to Humanity" are *Knowledge without Character* and *Business without Ethics*. After years of a cooperative effort by the ISHRS membership to disseminate knowledge and improve the overall quality of outcomes in hair restoration surgery, our profession stands at a crossroads of evolutionary development that threatens the long-term survival of those improvements and possibly the profession itself. There are a few physicians, both ISHRS members and non, who have elected to put patients at risk by delegating critical-to-quality surgical tasks to unlicensed technicians.

A trusted senior colleague recently saw a patient who had three hair restoration procedures in the last few years, whose results were far less than desirable. The hair growth was less than expected after 3,200 grafts, and the donor area had wide, stacked scars. The patient related a historical account of the three procedures that left no doubt that all the critical decision making was made not by the physician, but rather the hair technician, including design of the hairline, distribution of grafts, selection of donor area, and creation of the recipient sites. The surgeon did remove the donor, but according to the patient, he was instructed about where to take the strips and how to close by the technician. Unfortunately, these kinds of occurrences are becoming even more frequent with the advent of novice physicians allowing technicians to harvest FUE grafts.

The entire profession benefits from any single surgeon's high-quality outcomes and is harmed by any surgeon's poor-quality outcomes. Many of us have worked for years to find ways to improve the aesthetic results achieved from prior technologies. The market or demand for our services shrinks a little every time a patient's results demonstrate that the quality of our service is unreliable. High-quality HRS results demand attention to many physiological and aesthetic variables, most of which are beyond the scope of a technician's understanding and certainly beyond their training. Yet we continue to see physicians delegate these responsibilities for the sake of convenience or because they do not want to take the time to develop their own skills.

Worse yet, many physicians are naively being enticed into HRS purely by the profit motive, unconscious of the complexity of the specialty. I was recently contacted by an "FUE-only" physician in my community seeking additional training, explaining to me that after performing 17 or 18 procedures he realizes that there is more to the procedure than just moving a few hairs.

So what must we do to protect our potential patients? Just ignoring these untrained newcomers will result in many more patients with suboptimal outcomes. And those suboptimal outcomes will discourage other potential patients from availing themselves of our services. I truly believe that no physician wants to intentionally harm a patient. I believe we must encourage all physicians, members and non-members alike, to practice with both *Knowledge with Character*, and run their *Business with Ethics*.

The ISHRS has surveyed its membership and published strong positions against technicians harvesting tissue and performing other critical-to-quality parts of the hair restoration procedure. The ISHRS and its members must stand ready to train those responsible physicians who realize they are "in over their heads" to minimize the harm to both the patient and the growth of the industry. I urge those ISHRS members, physicians and technicians alike, who are encouraging these behaviors to abandon those activities, and bring both *Character* and *Ethics* back into your practices.

I realize that this position may not be the easiest to accept, that of essentially asking you to help train your competition, but as physicians we serve a higher calling than the routine businessman. With our Hippocratic Oath, we promise to serve patients before we serve ourselves. Just as we came together to solve the problems created by the HRS techniques of the 60s, 70s, and 80s, we must come together to solve the problem of unlicensed technicians performing surgery, and marginally trained physicians encouraging that behavior.

When you are presented with a patient who may have been better served, please take a moment to call the responsible physician, inform him of what you have observed, and offer suggestions to prevent a recurrence. Encourage communication. The ISHRS encourages its members to be strong patient advocates. As ISHRS members, we should be the textbook example of professional ethics to our patients and within our communities. ♦

Co-editors' Messages

Nilofer P. Farjo, MBChB Manchester, United Kingdom editors@ISHRS.org



Each issue of the *Forum* requires the co-editors to write on a topic of our choice, and I must say that for this issue I struggled to come up with something. For the first time, I experienced writer's block! The deadline came and I was asked to submit my editorial, so I finally sat down to write this and it turns out that when the pressure was on, I had too many topics. But then the decision had to be made: Should I write about the latest regulations that are about to

be forced on those in private cosmetic practices? Or should I write about a recent complication that we had in an FUE procedure? How about recent cases of scalp necrosis that have been referred to us? But as spring is on the horizon in the Northern Hemisphere (I hope), I decided to leave these topics until another issue and discuss something more positive: educational opportunities in the upcoming months. This year seems to be particularly full of ISHRS sponsored workshops each with different themes. So if you want to learn more about female hair restoration, FUE

techniques, strip surgery, hairline design, and eyebrows and eyelashes, then there is a workshop for you. In addition, there are the annual ISHRS meeting and hair research meetings.

The meeting that I'm particularly excited about is the World Congress for Hair Research (see Upcoming Events for the web link). In particular, I am looking forward to attending the pre-congress clinical day. This year there is a different format to the first day with the focus on basics in areas of hair biology. If you want to listen to the world's experts discussing some of the basic concepts in hair sciences, then this is the opportunity to listen to them all in one venue. My dilemma is that I want to listen to all the talks but they have been split into concurrent sessions. Session 1, *Genetics and Epigenetics: All You Wanted to Know but Were Afraid to Ask*, includes such talks as "Reprogramming hair follicle cells to a pluripotent state: an exciting new tool for medicine" by Dr. Michael Rendl. Session 2, *What's New in Hair Follicle Model Systems?*, details mouse model systems, updates on dermal papillae cultures, culture media, reprogramming hair follicle cells to a pluripotent state, and delivering molecules via

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William H. Reed, MD La Jolla, California, USA editors@ISHRS.org

Among the issues that continue to intrigue me from our meeting in the Bahamas is the role of inflammation in producing alopecia of one type or another. The proinflammatory and inflammatory cascade of events are becoming ever more clearly understood. When such questions come to mind, it is satisfying as editor to recall articles in the *Forum* for reference: Marty Sawaya's excellent review of her work on inflammasones,¹ an earlier article on strontium,² as well as other investigations such as that by Dr. Sadick and his study investigating an aspect of the "acquired immune response": basement membranes of follicles being laden with antibodies.³



There seems to be a growing consensus that the "incidental" perifollicular inflammatory infiltrate may not be as incidental and insignificant as was thought for decades. Add to that intriguing questions regarding strontium's anti-inflammatory properties and you're in for a good ride of reflection and speculation.

Dr. Sawaya discusses the "innate immune reaction" (IIR) and especially the "inflammasome." The inflammasome is formed from "pattern recognition receptors" that are on the membranes and in the cytoplasm of many cells including epidermal and dermal cell lines in the skin and its appendages. When activated by a specific "molecular pattern" from an invading pathogen, for instance, these recognition receptors oligomerize with other proteins to form the inflammasome, which in turn can activate both proinflammatory cytokines such as IL-1A, IL-1B, IL-6, and TNF-A as well as the part of the immune system that most of us are more familiar with that involves T and B lymphocytes further downstream and are part of what is called the "Adaptive Immune Response" (AIR).

Dr. Sawaya refers to an article by herself and Drs. Vaccari, Nusbaum, Bauman, and others wherein a protein that interacts with the inflammasome cascade, Caspase-1, is studied in balding scalp.⁴ Caspase-1 is recognized as an inducer of apoptosis and inflammation and they studied its levels as well as quantified androgen receptors in various *in vivo* and *in vitro* conditions involving the presence or absence of testosterone and finasteride. That androgen levels increase Caspase-1 levels and finasteride

decreases them suggest the IIR (i.e., the inflammatory response) is perhaps the final common pathway for AGA.

Dr. Sadick's article summarized a study he performed predominantly on women with AGA. He found IgM deposits continuously along the basement membrane of the dermal-epidermal junction in 64% of afflicted women with associated evidence of complement activation and found that those with this deposition responded better to a combination therapy that included beclomethasone and spironolactone. A non-specific perifollicular lymphocytic infiltrate was present and was perhaps more predominant in the positive group. One can speculate that his findings are compatible with and are a further downstream manifestation of the inflammatory reaction from the AIR and whose "upstream" progenitor, the IIR, is discussed by Dr. Sawaya.

A few years ago I wrote a summary of strontium² that is now marketed as an anti-itch formulation named TriCalm by a San Diego company, Cosmederm Bioscience. Strontium is a divalent cation just beneath Ca++ in the periodic table. It may replace Ca++ and hence affect the Ca++ cellular functions as the mechanism of action. As you can see by reading the review, strontium has strong anti-inflammatory properties via inhibiting the release of Substance P from the "nociceptor" Type C nerves, a non-myelinated nerve type that extends to the outermost layer of the epidermis. This has been termed "neurogenic inflammation" and their stimulation can release Substance P by depolarization exclusively within the terminal arborization of the nerve and needn't go all the way to the dorsal root, much less upstream via the spino-thalamic tract, before returning with its message to release Substance P and its "neurogenic inflammation." There is some evidence that strontium additionally acts even more directly on the pro-inflammatory proteins in addition to this function at the terminal synapse of the Type C nerve.⁵

Another pearl I took away from the Bahamas meeting was from Dr. Jeff Donovan when he said that he finds an itching or tender scalp to be a very useful complaint for detecting cicatricial alopecia. This is not surprising when you think of the inflammation driving the cicatricial alopecia and it begs the question of whether strontium and suppression of the IIR would help these conditions.

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Vision: To establish the ISHRS as the leading unbiased authority in hair restoration surgery.

Mission: To achieve excellence in patient outcomes by promoting member education, international collegiality, research, ethics, and public awareness.

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- Articles should be written with the intent of sharing scientific information with the purpose of progressing the art and science of hair restoration and benefiting patient outcomes.
- If results are presented, the medical regimen or surgical techniques that were used to obtain the results should be disclosed in detail.
- Articles submitted with the sole purpose of promotion or marketing will not be accepted.
- Authors should acknowledge all funding sources that supported their work as well as any relevant corporate affiliation.
- Trademarked names should not be used to refer to devices or techniques, when possible.
- Although we encourage submission of articles that may only contain the author's opinion for the purpose of stimulating thought, the editors may present such articles to colleagues who are experts in the particular area in question, for the purpose of obtaining rebuttal opinions to be published alongside the original article. Occasionally, a manuscript might be sent to an external reviewer, who will judge the manuscript in a blinded fashion to make recommendations about its acceptance, further revision, or rejection.
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- A completed Author Authorization and Release form—sent as a Word document (not a fax)—must accompany your submission. The form can be obtained in the Members Only section of the Society website at www.ishrs.org.
- All photos and figures referred to in your article should be sent as separate attachments in JPEG or TIFF format. Be sure to attach your files to the email. Do NOT embed your files in the email or in the document itself (other than to show placement within the article).
- We CANNOT accept photos taken on cell phones.
- Please include a contact email address to be published with your article.

Submission deadlines:

April 5 for May/June 2013 issue

June 5 for July/August 2013 issue

Farjo Message

from page 43

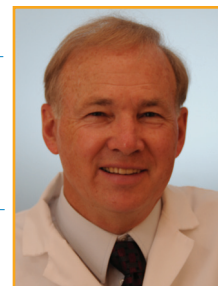
the hair follicle. Session 3, *Hair Fibre Science with a Focus on Curly Hair*, covers the genetics of curly hair, physics of the hair fiber, and protein loss during hair straightening.

The subsequent two days of the meeting will be in the usual format of mainly researchers presenting their new work that to some of us is too complicated to understand. There will be some

clinical sessions, though, on topics such as androgenetic alopecia and alopecia areata, which will be more useful to clinicians. I am very much looking forward to attending this meeting and hope that some others who normally would not attend a research meeting will take the opportunity to join me, especially as it is in such an interesting venue: Edinburgh, Scotland. ♦

Notes from the Editor Emeritus

Michael Beehner, MD Saratoga Springs, New York, USA mlbeehner@saratogahair.com



What we are really selling

I read an article in a local newspaper recently that impressed upon me once again what it is that we are really selling to the public, and that is *trust*. This article emphasized that, no matter what business someone is in, people want more than anything to trust the person with whom they are dealing, no matter what the product or service is. Poll after poll show that the public has lost trust in most companies and professions. There is a pervading feeling of being “marketed” with superficial, glitzy come-on’s and of being disappointed after receiving the service or product. Everything is impersonal. When is the last time you called a car dealer, a bank, or even a doctor’s office and heard a real human’s voice on the other end? The customer wants to trust the integrity of the person and institution he or she is dealing with. It’s not even about expecting a totally perfect product or perfectly performed service, but just knowing that the person you are dealing with has your best interest at heart, cares that you are satisfied and happy with what you are purchasing, and will stand behind it if something isn’t quite right down the road.

This is true in spades in hair transplant surgery, a profession in which we expect patients to take this enormous leap of faith and entrust to us, whom they have never met in their life, the life-changing task of filling the top of their head with hair. To successfully bring about this partnership with the prospective patient, you must first succeed in gaining the trust of the patient. Most patients visit at least two or three clinics before choosing where to go. Eventually they will get a “gut feeling” as to which physician or clinic they trust most, feel they will be most comfortable with, and believe they will receive a professional and competent surgical result. How do you maximize your chances for convincing them of this? I would propose that there are four major components. First is your website. Because the majority of

people today do their window-shopping on the Internet, your website is the first place people will learn about you. What does yours tell people? Do they sense that you are a caring and competent physician? Second is having a very personable person at your front desk to greet the patients and make them feel at home. It is equally important that your greeter’s voice be friendly and upbeat when dealing with patients over the phone. The third component is your clinical staff. Do they create an atmosphere that makes patients feel they are professional, caring, and competent? A great team of assistants who take pride in their work and enjoy working together is an enormous plus—and, believe me, patients can sense whether this is present or not. And fourth—actually, it probably should have been listed first—is the physician himself (herself). He or she should have a significant role during each consultation, to the point of performing the entire interview whenever possible. Patients should see a physician who conveys a warm, caring manner and is truly trying to figure out what is best for them, even if it means sometimes telling them that surgery at this time is not their best option. All questions should be answered by the physician in an honest, thorough way and never in an adversarial type of atmosphere.

A book that does a wonderful job of summarizing much of what I discussed above is Steven Covey’s *Seven Habits of Highly Effective People*. The principle point of his book is that there has to be an inner character to a person or a business, a commitment to certain principles of acting in a fair and honest way in all dealings, and it has to be present all the way from the boss on down to the least important person in the business; and it has to be real. It’s not something you can fake or “cover over” your practice with like icing on a cake. Most people are pretty good at detecting when this commitment isn’t really present. ♦

Reed Message

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With strontium becoming ever better understood and the great work of Dr. Sawaya and her colleagues working to better understand the IIR, I can see intriguing ideas to pursue: Can we be comfortable (as we were with the perifollicular inflammatory infiltrate in AGA for decades) that seborrheic dermatitis and psoriasis, symptomatic chronic inflammatory states, are not contributing to hair loss? Perhaps even their inflammatory states that are below the threshold of producing symptoms are eroding our hair counts. Should scalp biopsies be done more often for routine male pattern balding to consider this, especially if the inflammatory pathogenesis of alopecia becomes more certain? And other questions arise: Will antagonists of the IIR, perhaps strontium or something similar, prove to be useful in reducing the induction of apoptosis in the post-transplant state?

Will antagonists of the IIR prove to be useful in treating any or even all forms of alopecia? One nice feature of writing an editorial instead of a quality investigation of science is that it only has to express an opinion and can be primarily based upon speculation! Whatever the truth, I’m becoming a believer that the

answer is “yes” that many alopecias, and perhaps even the “Big One”—AGA—are related to this immune response... and just in time to save my teenage son’s hair from balding to the Stage VII of his two grandfathers! Many of these questions can be investigated fairly cheaply with the use of Hair Check, for example. I would appreciate a letter to the editor from anybody who can add to this line of thought. Let’s get started and enjoy the speculation that can abound in the emerging sophistication of our field!

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Hair grafting in wound healing

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Pilot Study Results

Ten patients with ulcers (60% venous and 40% mixed) of an average 36.8cm² and a 10.5-year duration were included in this pilot study. Within each ulcer we randomly assigned a 2x2cm “experimental square” to receive 20 hair grafts and a non-grafted “control” square of equal size. A transplant density of 5 follicular grafts/cm² was chosen as we considered this to be the minimum density required to guarantee tissue regeneration of the treated square of the ulcer.

Hair grafts were harvested from the occipital scalp using small-diameter (1-2mm) circular punches. After anesthetizing the “experimental square” of the wound bed, each punch hair graft was introduced one at a time using the “stick-and-place” method. The donor area was left to heal by secondary intention. Once the 20 hair grafts had been inserted in the experimental square, the whole ulcer was covered with Vaseline gauze and closed with an elastic bandage for 24 hours.

At the 18-week end point, we observed a 27% ulcer area reduction in the experimental square as compared with 6.5% in the control square ($p = 0.048$) with a maximum 33.5% vs. 9.7% reduction at week 4 ($p = 0.007$). Improvement of clinical symptoms (appearance of granulation tissue, wound border reactivation, and a lesser amount of exudation) was noted in 7 of the 10 patients.

Conclusions and Research Implications

This pilot study appears to indicate that hair grafting into chronic leg ulcers is not only practical but also successful in improving clinical evolution of ulcers of long duration.

This study was originally conceived as a feasibility trial. We did not address the various questions related to the hair grafting technique that are listed below:

- What is the ideal thickness of the punch (1mm vs. 2mm, or even bigger)? We chose a size of punch that would not require suturing the donor wound but it didn't need to be a 1mm punch since we were not concerned with the naturalness of the transplant. Our main aim was to develop a method without excessive technical difficulties regarding the extraction of entire hair follicles as would occur with a 2mm punch.
- What would be the ideal recipient density in order to ensure inter-mesenchymal connections and to promote granulation tissue?
- Would it be better to insert the hair grafts closest to the border of the ulcer to take advantage of the “edge effect” from the reepithelialization border, or should we transplant the hair grafts randomly?

We do not know why 3 out of the 10 patients did not improve. We wondered if there are other factors that play a role in the success or failure of this technique such as infection of the wound bed, post-op care, etc.

We need to investigate the application of this technique in other non-venous leg ulcers such as diabetic, ischemic, etc. Would there be any influence of the etiology of the ulcers on the outcome of this therapy?

More studies are needed to compare hair grafting with simple dressings or to compare hair grafting obtained from the

scalp versus skin grafts obtained from non-hairy areas. As hair transplant surgeons, we are in the perfect position to undertake this kind of investigation. Our field can expand enormously if we use our skills in other pathologies besides baldness.

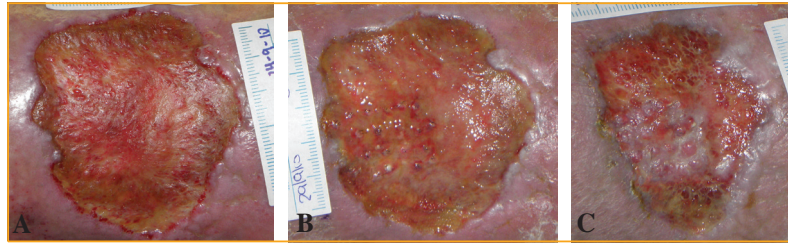


Figure 1. Macroscopic evolution of a chronic venous ulcer treated with hair grafting. A: The ulcer on the day of the surgery just before grafting. B: The ulcer 1 week after grafting. Twenty 2mm punch grafts were inserted into the 2x2cm experimental zone. C: The ulcer 8 weeks post-intervention. Note the remarkable healing and healthy granulation tissue formed only in the grafted area.

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