Principal investigator: Hadar Lev-Tov

Protocol Title: Autologous Regeneration of Tissue (ART) for Wound Healing

IRB Study Number: 20180154

Version 3, Date: 02 Sep 2021

NCT: NCT03796988

Document Date/Effective Date: 10/11/2021

IRB Study Number: 20180154
Version 3, Date: 02Sep2021

1) Protocol Title

Autologous Regeneration of Tissue (ART) for Wound Healing

2) IRB Review History*

N/A

3) Objectives*

The study objectives include

1) Assessment of pain on harvesting of skin donor sites (using a Visual Analog Scale)
2) Assessment of patient and physician tolerability (using a global assessment tool)
3) Time to healing of donor sites
4) Assessment of short term (2 months) quality of healing of donor site (using a scar assessment tool)

Secondary endpoints will be evaluation of wound healing of the recipient sites and histologic evaluation of the donor site.

4) Background*

Skin wounds sometimes are difficult to heal by primary closure and often require tissue substitution by autologous grafting requiring harvesting of donor skin [1, 2]. The latter may cause morbidities such as risk of infection, discoloration, pain, and scarring of both donor and recipient areas [3].

Full-thickness skin grafts (FTSG) are created when the entire dermis and epidermis are harvested. These grafts are typically used for acute full-thickness wounds where the wound can sustain and nourish the graft and improved cosmesis is important [4]. Split-thickness skin grafting (STSG) has been used to close large skin wounds, [5] and it involves the harvesting of the epidermis and upper dermis from a donor site. It is generally the preferred grafting method for restoring the structural integrity of chronic wounds, as the wound bed may not have the ability to support a FTSG [4]. Nevertheless, because deep dermal structures such sweat glands and hair follicles are not harvested, the STSG is functionally abnormal. Before the grafting process takes place, STSGs are commonly meshed and enlarged, increasing the coverage area and allowing fluid drainage. However, the meshing process produces a “fish-net” appearance of the grafted skin [1]. Other limitations include healing of the donor site, which often is delayed and leaves unappealing pigmentary changes and, at times, scar formation [4].

Currently, engineered “off the shelf” grafts such as cadaveric skin, xenografts, and artificial skin substitutes are being used in the management of chronic, difficult to heal wounds. Skin substitutes work by providing cells, growth factors, and other key elements that promote healing while preventing extracellular matrix degradation [6]. However, these only offer transient wound coverage, and require secondary healing of the wound itself. Thus, autologous skin grafting continues to

be necessary. Scar formation at the donor and grafted site remain most troublesome morbidities in autologous skin grafting. Scar tissue is stiff, dysfunctional, often painful, and tends to contract over time, producing skin irregularities [7].

In contrast, skin remodeling is a process that substitutes missing tissue while preserving tissue architecture. While scarring is triggered by large-scale tissue damage, remodeling is stimulated by microscopic tissue damage [8]. This principle became clear when fractional photothermolysis (FP) was developed that is currently used for photoaged skin treatment and wound scars [8, 9]. In FP, laser microbeams are used to produce microscopic thermal injury per cm2 of skin surface, which causes very thin columns of tissue damage or ablation. It has been found that columns less than 500 μm in diameter heal promptly without scarring [1, 10]. FP involves full-thickness (i.e. complete epidermis and dermis) tissue injury in which the epidermis closes within 1 day, and the dermal damage is fixed in around 2 weeks, followed by tissue remodeling without scarring [9].

Because the experience with FP showed that millions of small, full-thickness columns of skin tissue can be removed without scarring, it was hypothesized that full-thickness microscopic skin tissue columns (MSTCs) could be harvested from healthy skin with insignificant donor site-morbidity and that these MSTCs could function as a graft to accelerate wound healing.

To explore this, a prototype device was developed that can harvest hundreds of full-thickness columns of skin tissue (500 micrometer diameter) using single-needle, fluid-assisted harvesting technology. The harvested MSTCs can subsequently be placed directly onto a wound to aid in healing.

With conventional full thickness grafts and split thickness grafts, the donor area requires sometimes a period of immobility, requiring attentive wound care and pain management [11]. The ART may provide a more effective method of harvesting skin with minimal or no pain, healing rapidly with little scarring [1]. This can take place in an outpatient setting, with the use of only local anesthesia.

5) Inclusion and Exclusion Criteria*

Inclusion criteria:

- Adults from 18 to 90 years of age.
- Patients that have a chronic wound in any area of the body defined as having been present for at least 30 days of duration.
- Able and willing to give consent for the study.

Exclusion criteria:

- Pregnant women (Urine hCG test will be performed at baseline on women of child bearing potential).
- Adults unable to consent.
- Prisoners.
- Subjects requiring concurrent systemic antimicrobials during the study period for any infection.
- Subjects with leg lesions and clinically significant and unreconstructed peripheral arterial disease.
- Subjects who are receiving immunosuppressive agents, radiation therapy, or cytotoxic agents.
- Subjects who require treatment for a primary or metastatic malignancy (other than squamous or basal cell carcinoma of the skin).
- Subjects with other conditions considered by the investigator to be reasons for disqualification that may jeopardize subject safety or interfere with the objectives of the trial (e.g., acute illness or exacerbation of chronic illness, lack of motivation, history of poor compliance).

6) Number of Subjects*

The University of Miami Wound Care Center (1295 NW 14th St, Miami, FL 33136) will enroll 30 subjects locally.

7) Study-Wide Recruitment Methods*

Subject recruitment will be from physician referrals from the University of Miami Wound Care Center and Stanford University Advanced Wound Care Center.

8) Study Timelines*

This study will take 1 year to complete. The first 9 months will be dedicated to subject enrollment and follow up. The last 3 months will be dedicated for data analysis and dissemination.

9) Study Endpoints*

The study objectives include:

1) Assessment of pain on harvesting of skin donor sites (using a Visual Analog Scale)
2) Assessment of patient and physician tolerability (using a global assessment tool)
3) Time to healing of donor sites.
4) Assessment of short term (2 months) quality of healing of donor site (using a scar assessment tool)

Secondary endpoints will be evaluation of wound healing of the recipient sites and histologic evaluation of the donor site.

IRB Study Number: 20180154
Version 3, Date: 02Sep2021

10) Procedures Involved*

Eligible wounds are to be present for at least 4 weeks to be considered chronic. The patient will also have to have an area of intact skin that can serve as the skin donor area for the wound.

Once patients are determined to be eligible to participate, they will sign consent, and then the wound and the donor area will be photographed. The patients will have their wound assessed clinically and through photography.

The donor area will be anesthetized with injected local anesthesia, harvested with the ART device, and bandaged with an occlusive dressing. The skin harvested will be placed on the recipient wound area. The area will be bandaged will a non-stick silicone dressing (covered by appropriate primary and secondary dressings) and left intact for 1-7 days.

The patient will leave the bandage at the recipient site and donor area untouched until they are seen again at the follow up visits.

At each weekly visit, the donor site will be assessed for pain and itch with a Visual analogue scale (VAS), for scar formation, and for cosmetic appearance. The recipient area will be assessed for healing percentage, pain and itch VAS.

At visit 6, day 56 and approximately 2 months after the baseline, an optional 3mm punch biopsy will be collected at the donor site. The biopsy will be formalin fixed and paraffin embedded in order to undergo histologic evaluation by H&E and elastic tissue stains. Patient satisfaction will be determined at the end of the study.

Follow up visits will take place in:
Visit #2 Day 7: 7 ± 1 days later
Visit #3 Day 14: 7 ± 1 days later
Visit #4 Day 21: 7 ± 1 days later
Visit #5 Day 28: 7 ± 1 days later
Visit #6 Day 56: 30 ± 4 days later

11) Data Management*

All of the data, including records of subjects, source documents, and inform consent will be kept in the study centers under lock for 6 years after the study finished. After 1 year of study closure, documents will be sent to off-site storage (Iron Mountain).

12) Provisions to Monitor the Data to Ensure the Safety of Subjects*

The study team will be responsible for protecting the safety, rights, and well-being of study participants.

Recording and reporting of adverse events that occur during the course of the study will help to ensure the continuing safety of participants. Local and systemic adverse

events will be monitored during the study. In case an adverse event does take place, a documentation system will be used to record the following information: description of event, time/date of onset, duration of reaction, does/frequency/route of drug administration, reversibility or sequelae, therapy (if any), and seriousness/severity (based on Common Terminology Criteria for Adverse Events v4). If a subject experiences an adverse event assessed at a Grade 3 according to CTCAE v4, the subject will not receive additional testing and will be followed until the adverse event resolves or stabilizes.

Study stoppage will occur if 15 subjects complete the study (at each site) or if a severe adverse event occurs.

The PI will be responsible for monitoring ongoing activates to ensure compliance with regulatory and protocol requirements, data quality, and participant safety.

13) Withdrawal of Subjects*

All subjects are free to withdraw from participation in this study at any time, for any reason, and without prejudice.

Subjects must be withdrawn from the study if:

1) A subject withdraws consent.
2) The Investigator believes it is in the best interest of the subject to be removed from the study.

The data collected before the withdrawal will still be used in data analysis.

14) Risks to Subjects*

1. Protected Health Information (PHI) will be collected during the study. Every attempt will be made to ensure that this PHI is kept secure. All study data will be kept in a locked office and kept under password protection on a computer that is only accessible by study personnel.

2. There are mild or moderate risks associated with performing a skin biopsy: a risk for a local infection and/or a small scar, and the possibility that at the biopsy site a raised scar could form, e.g. keloid (this depends on individual propensity for scar formation).
3. There are mild or moderate risks associated with ART system: a risk for a local infection and/or a small scar, and the possibility that a raised scar could form, e.g. keloid (this depends on individual propensity for scar formation).

15) Potential Benefits to Subjects*

There may be the benefit of the target wound to be treated and healed with the use of this new technology as well as with use of standard of care therapy in the case of venous leg ulcers.

IRB Study Number: 20180154
Version 3, Date: 02Sep2021

16) Vulnerable Populations*

No pregnant women, children, prisoners, or cognitively impaired adults will be enrolled in this study.

17) Multi-Site Research*

The second site for this study is Stanford University Advanced Wound Care Center (AWCC; 450 Broadway, Redwood City, CA 94063). The PI of that site will conduct this study under their institution's IRB oversight.

Dr. Lev-Tov, the PI of the UM site will not be overseeing the Stanford site.

De-identified data will be shared between sites for data analysis.

18) Sharing of Results with Subjects*

Results of this study will not be shared with the subjects, unless through scientific publication.

19) Setting

Potential subjects will be identified and recruited from department physicians and study team members from the UMH Dermatology outpatient clinic (1295 NW 14th St, South building suites K-M, Miami FL 33136) and the UMH Wound Care Center (1295 NW 14th St, south building, Miami FL 33136).

Research procedures will be performed in the Dermatology Research Clinic (1321 NW 14th St, west building room 504-508, Miami FL 33125).

20) Resources Available

Dr. Hadar Lev-Tov, MD, the Principal Investigator is an Assistant Professor in the Department of Dermatology. He has extensive training performing clinical trials focusing on wounds. He will oversee the clinical portion of this project, including enrollment of and care of patients.

All study personnel will complete their CITI training and be adequately informed about the protocol and study procedures. All duties and functions are appointed and overseen by the PI.

21) Prior Approvals

N/A

22) Recruitment Methods

Potential subjects will be identified and recruited from department physicians and study team members from the UMH Dermatology outpatient clinic (1295 NW 14th St, South building suites K-M, Miami FL 33136) and the UMH Wound Care Center (1295 NW 14th St, south building, Miami FL 33136).

Subjects will be compensated $25 per study visit.

23) Local Number of Subjects

Thirty total subjects will be enrolled in this study.

24) Confidentiality

Every attempt will be made to ensure any information gathered is kept secure. All study data will be kept in a locked office within the Dermatology Research Clinic (1321 NW 14th St, west building room 504-508, Miami FL 33125) and kept under password protection on a computer that is only accessible by study personnel.

Data that is de-identified will be shared between sites for data analysis.

25) Provisions to Protect the Privacy Interests of Subjects

Study subjects will only be asked to provide personal information to approved study personnel, who will ensure the subject is at ease with the situation. Study personnel will clearly explain that the subject does not have to answer any questions or provide any sample they are uncomfortable about.

Medical records will be accessed to review wound history after the subject gives written study ICF and HIPAA consent.

26) Compensation for Research-Related Injury

Treatment will be available if enrolled subjects get sick or injured. However, the subject or the subject's insurance will be responsible for these costs. Funds to compensate for pain, expenses, lost wages, and other damages caused by injury are not available.

27) Economic Burden to Subjects

There will be no charges to the subjects that agree in participating in this study.

28) Consent Process

The research team will follow the "HRP-090 SOP: Informed Consent Process for Research" to obtain informed consent and the "HRP-091 SOP: Written Documentation of Informed Consent" to document informed consent in writing.

Study personnel will meet with each potential subject to discuss the study in detail, answer questions, and allow the subject to read the entire consent form. The informed consent form explicitly states the rationale for the study and requirements for participation, both before and during the session. The informed consent form states that subjects may discontinue participation or be terminated from the study at any time.

All pertinent aspects of the study will be explained to the subject before he or she signs the informed consent form. A signed informed consent form will be obtained from the subject before any activity or treatment is undertaken as part of the study.

Non-English Speaking Subjects

ICFs and subject surveys will be translated into Spanish.

29) Process to Document Consent in Writing

The research team will follow the "HRP--091 SOP: Written Documentation of Informed Consent" to document informed consent in writing.

30) Drugs or Devices

The ART system device and cartridges will be securely stored in the UMH Dermatology Research Clinic. Only approved and designated study personnel will have access to the system. Only approved, designated, and trained study personnel will administer the device.

The ART system from Medline Industries, Inc. is a medical device already on the market within the US.

31) Study Milestones

Study milestones are the completion of visits by enrolled subjects.