

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 April 2011 (28.04.2011)

PCT

(10) International Publication Number
WO 2011/048601 A1

(51) International Patent Classification:

A01N 33/08 (2006.01) *A61K 31/045* (2006.01)
A01N 33/18 (2006.01)

(21) International Application Number:

PCT/IL2010/000875

(22) International Filing Date:

21 October 2010 (21.10.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/254,268 23 October 2009 (23.10.2009) US

(71) Applicants (for all designated States except US): **TEL HASHOMER MEDICAL RESEARCH INFRASTRUCTURE AND SERVICES LTD.** [IL/IL]; The Chaim Sheba Medical Center, Tel HaShomer, 52621 Ramat-Gan (IL). **RAMOT AT TEL-AVIV UNIVERSITY LTD.** [IL/IL]; P.O. Box 39296, 61392 Tel-Aviv (IL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LEOR, Jonathan** [IL/IL]; 10 HaTzukim Street, 38329 Hadera (IL). **LAN-DAU, Marina** [IL/IL]; 56 Yehoshua Ben Nun Street, 46763 Herzlia (IL).

(74) Agents: **G.E. EHRLICH (1995) LTD.** et al.; 11 Menachem Begin Street, 52521 Ramat Gan (IL).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))

(54) Title: TREATMENT OF SCARRED HEART TISSUE BY A CHEMICAL PEELING COMPOSITION

(57) Abstract: Chemical peeling compositions and methods utilizing same for treating scarred heart tissue are disclosed. The chemical peeling compositions may include phenol as a peeling agent and may optionally further include additional peeling agents and/or agents for enhancing the penetration of phenol into the scarred heart tissues. Devices containing the disclosed chemical peeling compositions, configured for applying the chemical peeling composition onto heart tissue are also disclosed.



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TREATMENT OF SCARRED HEART TISSUE BY A CHEMICAL PEELING COMPOSITION

FIELD AND BACKGROUND OF THE INVENTION

5 The present invention, in some embodiments thereof, relates to medical treatment and, more particularly, but not exclusively, to treatment of scarred heart tissue.

 Ischemic heart disease (IHD) is a disease characterized by reduced blood supply to the heart muscle, due to occlusion of cardiac vessels, leading to loss of cardiomyocytes. IHD is one of the leading causes of mortality worldwide, resulting in
10 millions of deaths each year.

 Myocardial infarction is a common presentation of IHD, occurring when a coronary artery has become blocked, thus preventing the supply of blood to an area of the myocardium. The myocardium becomes rapidly ischaemic and then necrotic. The necrotic area is unable to contract or to conduct electrical impulses and therefore will
15 reduce the efficiency of the chamber affected.

 Following acute myocardial infarction, necrotic tissue is replaced by scar tissue within a few weeks. Scar thinning, enlargement, and spherical deformation of the left ventricle with a concomitant increase in wall stress are key elements in the pathogenesis of adverse remodeling and heart failure after myocardial infarction.

20 Congestive heart failure (CHF) is a condition that can result from any structural or functional cardiac disorder that impairs the ability of the heart to fill with blood or pump a sufficient amount of blood through the body.

 Approximately 23 million people worldwide are afflicted with CHF, and 2 million new cases of CHF are diagnosed each year. In contrast to other cardiovascular
25 disorders that have actually declined during the past few decades, the incidence of heart failure is on the rise. In fact, it is the most rapidly growing cardiovascular disease in the United States.

 In the United States alone, heart failure accounts for 400,000-700,000 deaths per year, \$20-40 billion in yearly healthcare costs, and is the leading hospital discharge
30 diagnosis. These considerations provide the impetus for an ongoing search for novel approaches to therapy.

It has been suggested that left ventricular (LV) remodeling may contribute independently to the progression of heart failure and death. Thus, any intervention that will increase scar thickness and strength will reduce LV remodeling [Wall et al. *Circulation* 2006, 114:2627-2635].

5 Cardiac transplantation is a potential treatment for many patients. However, lack of donors, combined with an increasing number of patients has led to the search for other surgical strategies.

10 Patients with symptomatic left ventricular aneurysms have been treated with resection of the aneurysm and closure of the left ventricle, either directly or by implantation of a patch. Scar areas of the left ventricle have also been successfully treated by the latter method.

15 According to the law of Laplace, large dilated ventricles have increased wall tension and thus increased oxygen consumption. Based on this fact, Batista and coworkers [see, for example, Batista RJ. Reduction ventriculoplasty. *Z Kardiol.* 2001;90 Suppl 1:35-37] have reduced the volume of enlarged left ventricles in patients in terminal heart failure by removing a wedge of myocardium from the apex of the heart towards the base of the left ventricular free wall. However, this method is currently not recommended for treatment of heart failure because of high surgical failure rates.

20 After MI, failure of extra cellular matrix (ECM) support has been associated with LV wall thinning and slippage of myocyte fascicles. This adverse remodeling process has been termed "infarct expansion", and occurs in the absence of additional myocyte injury or alterations in LV loading conditions. This post-MI remodeling process is a significant problem that can lead to LV dilation and dysfunction, the progression to heart failure. Indeed, post-MI remodeling process, which includes changes in ECM structure and composition, is an independent predictor of morbidity and mortality. It has been postulated that an acceleration of ECM degradation occurs within the scar and the myocardium surrounding the MI (border zone) and facilitates the infarct expansion process in this later phase of post-MI remodeling.

25 These remodeling processes involve synthesis and degradation of collagens as major components of the ECM. Collagen degradation and production postinfarction constitute the most dominant protein change in the myocardial matrix.

Although advances in pharmacology have led to better treatment, 50 % of patients with the most advanced stage of heart failure die within a year. Typically, heart failure patients receive several chronic oral therapies, including diuretics, ACE inhibitors, beta-blockers and inotropic agents. However, despite optimal therapy, many patients continue to suffer from progressive cardiac remodeling and heart failure.

In order to sufficiently repair cardiac injury, it is necessary to provide new methods for infarct repair and scar rejuvenation.

The human heart has little capacity to regenerate. This is a major medical problem, because inadequate regeneration contributes to myocardial scarring, heart failure, arrhythmias and death. Reversing the process of heart disease progression is a major aim of cardiovascular regenerative medicine.

More recently, resident cardiac stem cells have been shown to differentiate into multiple cell types present in the heart, including cardiac muscle cells, indicating that the heart is not terminally differentiated [Beltrami et al. *Cell*. 2003;114:763-776]. These new findings have stimulated optimism that the progression of heart failure can be prevented or even reversed.

Recent studies have observed the preservation of myogenic and vasculogenic potential of adult epicardial cells *in vivo*. A subpopulation of these epicardial cells undergoes epithelial-to-mesenchymal transition (EMT), invades the wound, and provides new vasculature to regenerating muscle. See, for example, Castaldo et al. *Stem Cells*. 2008, 26:1723-1731; Lepilina et al. *Cell*. 2006;127:607-619; Limana et al. *Circ Res*. 2007;101:1255-1265; Smart et al. *Nature*. 2007;445:177-182; van Tuyn et al. *Stem Cells*. 2007;25:271-278; and Winter et al. *Circulation*. 2007;116:917-927. These CD-117 positive cells contribute to cardiac cell turnover in the normal and pathological conditions.

U.S. Patent Applications having Publication Nos. 2010/0143317, 2010/0190731, 2007/0065866, 2007/0031389, 2006/0264367 and teach methods for treating or preventing infarct injury after MI, which are effected by administering anti-fibrotic agents.

Chemical peeling of skin is reviewed by Fischer et al. [*J Eur Acad Dermatol Venereol* 2010, 24:281-292] and Monheit [*Skin Therapy Lett* 2004, 9:6-11]. As discussed therein, the peeling action of phenol on skin was described in 1882. Modified

phenol solutions which contain croton oil (a caustic substance which contributes to the peeling effect of the solution), Septisol® soap (a surface tension modifier) and water, have been used since the 1960s. Phenol-based peeling solutions typically comprise at least 50 % phenol, as well as croton oil.

5 Piamphongsant [*Dermatol Surg* 2006, 32:611-617] describes the use of phenol with castor oil for chemical peeling of skin.

Phenol, as well as other chemicals for skin peeling, and various formulations thereof, are also described in, for example, U.S. Patent Nos. 6,787,148 and 5,948,416, US 20100239645 and US 20070010580.

10

SUMMARY OF THE INVENTION

According to an aspect of some embodiments of the present invention there is provided a method of treating scarred heart tissue in a subject in need thereof, the method comprising applying a chemical peeling composition to scar tissue in the heart of
15 the subject, thereby treating the scarred heart tissue.

According to an aspect of some embodiments of the present invention there is provided a use of a chemical peeling composition in the manufacture of a medicament for treating scarred heart tissue.

According to an aspect of some embodiments of the present invention there is
20 provided a use of a chemical peeling composition in the manufacture of an article-of-manufacturing configured for delivering the chemical peeling composition to the scarred heart tissue.

According to an aspect of some embodiments of the present invention there is provided a chemical peeling composition for use in the treatment of scarred heart tissue.

25 According to an aspect of some embodiments of the present invention there is provided an article-of-manufacturing for treating scarred heart tissue in a subject in need thereof, the article-of-manufacturing being loaded with a chemical peeling composition, and being configured for delivering the chemical peeling composition to the scarred heart tissue.

30 According to an aspect of some embodiments of the present invention there is provided an implantable medical device comprising a chemical peeling composition

being deposited on at least a portion of a surface of the medical device, the medical device being biodegradable.

According to an aspect of some embodiments of the present invention there is provided a pharmaceutical composition comprising phenol and a pharmaceutically acceptable carrier, wherein a concentration of phenol ranges from 5 % to 50 %, the composition being identified for use in the treatment of scarred heart tissue in a subject in need thereof.

According to some embodiments of the invention, applying the chemical peeling composition is performed during an open-heart surgery.

According to some embodiments of the invention, applying the chemical peeling composition comprises applying a medical device which comprises the chemical peeling composition.

According to some embodiments of the invention, applying the chemical peeling composition is performed via a minimally-invasive procedure.

According to some embodiments of the invention, the article-of-manufacturing is configured so as to be capable of delivering the chemical peeling composition to the heart tissue without open-heart surgery.

According to some embodiments of the invention, the article-of-manufacturing comprises a catheter configured for delivering the chemical peeling composition to the heart tissue.

According to some embodiments of the invention, the article-of-manufacturing is configured such that the chemical peeling composition flows through the catheter to the heart tissue.

According to some embodiments of the invention, the article-of-manufacturing comprises an insertable medical device, wherein the chemical peeling composition is being deposited on at least a portion of a surface of the medical device, the medical device being configured for contacting the heart tissue with the chemical peeling composition.

According to some embodiments of the invention, the article-of-manufacturing comprises an implantable medical device, the chemical peeling composition being deposited on at least a portion of a surface of the medical device, the medical device being adapted for implantation on heart tissue.

According to some embodiments of the invention, the implantable medical device is biodegradable.

According to some embodiments of the invention, the chemical peeling composition comprises at least one peeling agent and a pharmaceutically acceptable carrier.

According to some embodiments of the invention, a concentration of the at least one peeling agent in the composition ranges from 5 % to 50 % by weight.

According to some embodiments of the invention, the at least one peeling agent is selected from the group consisting of phenol, an alpha-hydroxy acid, a beta-hydroxy acid, retinoic acid, trichloroacetic acid, benzoic acid, anthranilic acid, dihydroxyphenyl acetic acid, pyruvic acid, and resorcinol.

According to some embodiments of the invention, the at least one peeling agent comprises phenol.

According to some embodiments of the invention, a composition comprising phenol as described herein further comprising at least one additional peeling agent.

According to some embodiments of the invention, the additional peeling agent is a salicylate.

According to some embodiments of the invention, the at least one peeling agent further comprises a beta-hydroxy acid.

According to some embodiments of the invention, the alpha-hydroxy acid is selected from the group consisting of glycolic acid, lactic acid, citric acid, tartaric acid and malic acid.

According to some embodiments of the invention, the beta-hydroxy acid is selected from the group consisting of salicylic acid and lipohydroxy acid.

According to some embodiments of the invention, the composition comprises Jessner's solution.

According to some embodiments of the invention, the carrier comprises an aqueous solution.

According to some embodiments of the invention, the carrier comprises an oil.

According to some embodiments of the invention, the carrier comprising an aqueous solution further comprises an oil.

According to some embodiments of the invention, the oil is selected from the group consisting of sesame oil, olive oil, glycerin and a mixture thereof.

According to some embodiments of the invention, the composition is being devoid of croton oil.

5 According to some embodiments of the invention, the composition further comprises croton oil.

According to some embodiments of the invention, a concentration of the croton oil ranges from 0.001 % to 2 % by weight.

10 According to some embodiments of the invention, a concentration of croton oil is lower than 0.5 % by weight.

According to some embodiments of the invention, a concentration of croton oil is lower than 0.1 % by weight.

According to some embodiments of the invention, the composition further comprises an adjuvant.

15 According to some embodiments of the invention, the adjuvant is selected from the group consisting of an alcohol, a polyethylene glycol, a film-forming agent and a buffer.

According to some embodiments of the invention, the buffer comprises tris(hydroxymethyl)aminomethane.

20 According to some embodiments of the invention, the scarred heart tissue is caused by a condition selected from the group consisting of myocardial infarction, heart failure, cardiomyopathy, heart surgery and inflammation.

According to some embodiments of the invention, the cardiomyopathy is selected from the group consisting of dilated cardiomyopathy and hypertensive cardiomyopathy.

25 According to some embodiments of the invention, the composition is packaged in a packaging material and identified in print, in or on the packaging material, for use in the treatment of scarred heart tissue in a subject in need thereof.

According to some embodiments of the invention, the carrier further comprises a surface active agent.

30 Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those

described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

5

BRIEF DESCRIPTION OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for
10 purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the Drawings:

FIG. 1 is a photograph showing rat heart stained with hematoxylin and eosin
15 (HE) one week after chemical peeling with 50 % phenol;

FIG. 2 is a photograph showing the sample presented in FIG. 1 at a higher magnification;

FIG. 3 is a photograph showing mouse heart immunostained (red) for CD117 one week after chemical peeling with 50 % phenol (cell nuclei are stained blue by 4'-6-diamidino-2-phenylindole (DAPI));
20

FIG. 4 is a photograph showing mouse heart immunostained (red) for CD117 one week after chemical peeling with 50 % phenol (cell nuclei are stained blue by DAPI);

FIG. 5 is a photograph showing mouse heart immunostained (red) for CD117 without being subjected to chemical peeling (cell nuclei are stained blue by DAPI);
25

FIGs. 6A-6D are photographs showing rat hearts treated with saline 2 months after myocardial infarction and stained with Masson trichrome 2 months after saline treatment, with (FIGs. 6C and 6D) and without (FIGs. 6A and 6B) magnification;

FIGs. 7A-7D are photographs showing rat hearts treated with 50 % phenol 2 months after myocardial infarction and stained with Masson trichrome 2 months after phenol treatment, with (FIGs. 7C and 7D) and without (FIGs. 7A and 7B) magnification;
30

FIG. 8 is a graph showing the relative scar area in rat hearts treated with 50 % phenol or saline 1 month (1m) or 2 months (2m) after myocardial infarction;

FIG. 9 is a graph showing the expansion index in rat hearts treated with 50 % phenol or saline 1 month (1m) or 2 months (2m) after myocardial infarction;

FIG. 10 is a graph showing the muscle area in rat hearts treated with 50 % phenol or saline 1 month (1m) or 2 months (2m) after myocardial infarction;

5 FIGs. 11A and 11B are graphs showing the change in the left ventricular diastolic dimension in rat hearts during the course of 1 (FIG. 11A) or 2 (FIG. 11B) months after being treated with 50 % phenol or saline, 1 month (1m) or 2 months (2m) after myocardial infarction; and

10 FIGs. 12A-12O are representative photographs of rat hearts following application of exemplary chemical peeling compositions (FIGs. 12A-12G and 12I-12M) or control formulations (FIGs. 12H and 12O).

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

15 The present invention, in some embodiments thereof, relates to medical treatment and, more particularly, but not exclusively, to treatment of scarred heart tissue.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

20 Scar tissue in the heart presents an obstacle to normal cardiac function and poses a significant health threat. While searching for an effective method to treat scarred heart tissue, the present inventors have uncovered that chemical peeling may be used to rejuvenate scar tissue in the heart, by destroying scar tissue and allowing for the growth of normal tissue.

25 While reducing the present invention to practice, the inventors have found that application of chemical peeling solutions to heart tissue during surgery is a safe and feasible method for rejuvenating scar tissue.

30 The present inventors have further devised chemical peeling compositions, which are formulated so as to be suitable for treating scarred heart tissue. These chemical peeling compositions can be utilized within devices configured for delivering the compositions to the scarred heart tissue.

Referring now to the drawings, Figures 1 and 2 show that chemical peeling of heart tissue stimulates neovascularization at the epicardium. These results indicate that the peeling stimulates healing, regeneration and repair of tissue, and allows for the viability of new tissue.

5 Figures 3-5 show that chemical peeling results in accumulation of CD117-positive cells at the epicardium. These results indicate that chemical peeling stimulates cardiac cell turnover and mobilizes progenitor cells capable of generating healthy tissue to replace scar tissue.

10 Figures 6A-8 and 10 show that chemical peeling enhances healing of scar tissue following myocardial infarction. Figures 8, 9, 11A and 11B show that chemical peeling improves cardiac remodeling after myocardial infarction. These results indicate that chemical peeling can attenuate or arrest the deterioration of heart tissue which results from myocardial infarction.

15 Figures 12A-12O show the effect of various chemical peeling solutions on heart, and that compositions comprising phenol are more effective than other chemical peeling compositions.

20 Hence, according to one aspect of embodiments of the present invention, there is provided a method of treating scarred heart tissue in a subject in need thereof, which is effected by applying a chemical peeling composition to scar tissue in the heart of the subject.

As used herein, the phrase "scarred heart tissue" refers to heart tissue comprising one or more abnormal fibrous regions of tissue (scar tissue). Typically, the scar tissue exhibits inferior contractility relative to normal heart tissue.

25 As used herein the term "peeling" refers to controlled formation of a wound (e.g., killing cells), at a desired depth and area, which is followed by tissue regeneration. The phrase "chemical peeling" refers to peeling induced by one or more chemical compounds (as opposed to, for example, mechanical peeling).

30 A chemical peeling composition can be readily applied to a relatively broad area, as is commonly necessary for treating scarred heart tissue, in contrast to laser techniques for treating scar tissue, which are difficult to apply to broad areas.

It is to be understood that the phrases "chemical peeling solution", "chemical peeling composition", "peeling composition" and "peeling solution" are used herein

interchangeably and are intended to encompass all liquid and semisolid substances capable of inducing peeling, including suspensions, emulsions, creams, foams, pastes, patches and gels.

Without being bound by any particular theory, it is believed that the use of a chemical peeling composition, as described herein, activates cardiac stem cells, leading to generation of healthy tissue and extracellular matrix.

The chemical peeling solution optionally comprises at least one peeling agent.

As used herein, the phrase "peeling agent" refers to a compound which causes peeling, as defined herein. This phrase also encompasses keratolytic agents (typically used to remove skin warts).

Peeling agents are typically caustic agents that cause cell death.

It is expected that during the life of a patent maturing from this application additional relevant peeling agents will be developed and the scope of the term "peeling agent" is intended to include all such new technologies *a priori*.

Any chemical peeling agent and/or keratolytic agent known to effect skin peeling is contemplated.

Chemical peeling agents which are currently known for skin peeling are typically divided into agents for superficial peeling, agents for medium peeling and agents for deep peeling.

Agents for superficial peeling include, but are not limited to, alpha-hydroxy acids and beta-hydroxy acids (as described herein below), retinoic acid, benzoic acid, anthranilic acid, dihydroxyphenyl acetic acid and resorcinol.

Agents for medium peeling include, but are not limited to, phenol, when used in the absence of a penetration enhancer and/or at low concentrations (e.g., less than 10 %), and trichloroacetic acid.

Agents for deep peeling include, but are not limited to, phenol, when used in combination with a penetration enhancer.

It is to be noted that phenol-containing compositions for skin peeling typically further include croton oil for effecting penetration of phenol into deep skin tissues.

In the absence of croton oil, or any other suitable penetration enhancer, the penetration of phenol is limited and its effect is considered as medium peeling.

It is to be further noted that the degree of peeling (e.g., superficial, medium or deep) is often determined not only by the peeling agent but also by other factors such as, for example, the concentration of the peeling agent, the presence of penetration enhancers and/or surface active agents, and/or the pH of the peeling composition.

5 Thus, some agents which are classified as agents for superficial or medium peeling when used *per se*, can be formulated into deep peeling compositions. An exemplary such agent is TCA, which at high concentrations (e.g., higher than 50 % by weight) may exhibit deep peeling effect.

According to some embodiments, the peeling agent is selected so as to effect
10 peeling of a suitable depth, which depends, for example, on the dimensions (e.g., depth) of the scarred heart tissue to be treated. Thus, for example, relatively strong peeling agents such as phenol and, to a lesser extent, trichloroacetic acid (when used at concentrations of at least 20 %, and particularly at concentrations of at least 35 %), are selected for removing scarred tissue to a substantial depth (e.g., as much as 2 or 3 mm),
15 whereas other peeling agents (as well as lower concentrations of trichloroacetic acid), which are typically milder, are selected for removing shallower layers of tissue (e.g., superficial scar tissue).

Optionally, a relatively strong peeling agent (e.g., phenol, trichloroacetic acid), capable of deep peeling, is used in combination with a milder peeling agent, such that
20 the mild peeling agent enhances the activity of the strong peeling agent, for example, by enhancing penetration of the strong peeling agent.

As demonstrated in the Examples section that follows, the present inventors have demonstrated that for the purpose of treating a scarred heart tissue, agents known for medium or deep peeling exhibit a desired activity.

25 Thus, in some embodiments, the peeling agent is an agent that exhibits medium or deep peeling of the skin.

The present inventors have further uncovered that when applied to heart tissue, some peeling agents exhibit a modified penetration profile, and thus, exhibit a modified degree of peeling effect, as compared to skin peeling, due to the different features of
30 heart and skin tissues.

Examples of peeling agents suitable for use in the context of embodiments of the present invention include, without limitation, phenol, alpha-hydroxy acids (e.g., glycolic

acid, lactic acid, citric acid, tartaric acid, and malic acid), beta-hydroxy acids (e.g., salicylic acid, lipohydroxy acid), pyruvic acid, retinoic acid, trichloroacetic acid, benzoic acid, anthranilic acid, dihydroxyphenyl acetic acid and resorcinol.

As used herein and in the art, the term "lipohydroxy acid" refers to lipophilic derivatives of salicylic acid, such as salicylic acid substituted by an acyl group (e.g., 2-hydroxy-5-octanoyl benzoic acid).

According to an optional embodiment, the peeling solution comprises phenol. As shown herein in the Examples section, phenol is more effective than other peeling agents at treating heart tissue. Phenol may be included as a sole peeling agent, or as one of a plurality of peeling agents.

Phenol may be present at a concentration of up to 100 %. Optionally, a concentration of phenol ranges from 5 % to 50 % by weight. Optionally, the concentration of phenol is lower than 50 % by weight. Thus, in some embodiments, the concentration of phenol ranges from 5 to 40 %, from 5 to 30 %, from 5 to 35 %, from 5 to 20 % or from 5 to 10 %, by weight. Optionally, the concentration of phenol is no more than 30 %, and optionally no more than 20 % by weight.

Without being bound by any particular theory, it is believed that penetration of phenol into tissue is self-limiting (i.e., the effect of phenol on tissue limits further penetration of phenol into the tissue), such that it penetrates tissue to a substantial depth (and is therefore effective at removing scar tissue), but does not penetrate very deeply into tissue, which could harm the function of the heart.

Optionally, the peeling composition comprises croton oil and/or phorbol (an active ingredient of croton oil). Croton oil is a caustic agent which enhances peeling, and is used for this purpose in many skin peeling compositions. Croton oil is optionally present at a concentration in a range of up to 2 % (e.g., from 0.0001 % to 2 % by weight), optionally lower than 1 %.

Optionally, the concentration of croton oil is in a range of 0.5 % to 2 % by weight, as is commonly used in skin peeling compositions.

Alternatively, the concentration of croton oil is lower than 0.5 % by weight, optionally lower than 0.1 %, and optionally lower than 0.01 % by weight, so as to avoid the potential adverse effects of applying too many caustic substances to the heart.

Optionally, the peeling composition is devoid of croton oil (and phorbol), so as to avoid the potential adverse effects (e.g., excessively deep penetration of the peeling agent) of croton oil.

In some embodiments, the peeling agent(s) are selected so as to provide a therapeutic effect, for example, a therapeutic effect against a heart disease or disorder and/or against an adverse effect of surgery. Optionally, the peeling composition comprises salicylic acid and/or a derivative thereof (e.g., lipohydroxy acid).

Without being bound by any particular theory, it is believed that salicylic acid and related compounds provide a therapeutic effect due to the anti-inflammatory properties of salicylic acid, which may be useful, for example, for treating heart disease. Salicylic acid also exhibits antibiotic activity, which may be useful, for example, in preventing infection associated with surgery.

According to some embodiments, the peeling composition comprises Jessner's solution.

As used herein, the phrase "Jessner's solution" refers to a solution comprising salicylic acid, lactic acid and resorcinol, as well as a solvent. The concentration of salicylic acid is optionally in a range of from 10 to 20 %, optionally about 14 %. Optionally, the concentrations of lactic acid and resorcinol are each independently similar to the concentration of salicylic acid (e.g., from 50 to 150 %, optionally from 80 to 120 %, and optionally about 100 % of the salicylic acid concentration). The solvent optionally comprises an alcohol (e.g., ethanol).

Jessner's solution may optionally be included in the peeling solution as a sole source of peeling agents (e.g., salicylic acid, lactic acid and resorcinol), or in combination with additional peeling agents (e.g., phenol).

A chemical peeling composition as described herein optionally further comprises a pharmaceutically acceptable carrier in combination with the peeling agent(s) such as are described herein.

A "pharmaceutically acceptable carrier" refers to a carrier which does not cause significant irritation to a subject when the chemical peeling solution is applied to heart tissue of the subject, and does not to abrogate the physiological activity and properties of the administered chemical peeling composition.

Examples of carriers include, without limitations, aqueous solutions, glycerin, polyethylene glycol, and fats and oils (e.g., mineral oils, glycerin, silicone oils, and/or vegetable fats and oils, such as almond oil, avocado oil, cocoa butter, emu oil, evening primrose oil, fractionated coconut oil, grapeseed oil, jojoba oil, macadamia oil, peanut oil, pecan oil, rapeseed oil, safflower oil, shea butter, soybean oil, sunflower oil, walnut oil, sesame oil and olive oil).

According to exemplary embodiments, the carrier comprises an aqueous solution.

In some embodiments, the carrier comprises an oil.

In some embodiments, the peeling solution comprises a mixture of a plurality of types of carriers. Optionally, the mixture is an emulsion, for example, an emulsion comprising an aqueous solution and at least one oil.

In some embodiments, a carrier comprising an oil in combination with an aqueous solution is used in a composition in combination with croton oil.

Without being bound by any particular theory, it is believed that the presence of oil in the carrier results in controlled release of the lipophilic croton oil.

The chemical peeling solution optionally further comprises additional ingredients, for example, adjuvants.

As used herein, the term "adjuvant" describes compounds which modulates the peeling activity of the chemical peeling solution, but which does not induce peeling by itself. An adjuvant may modulate peeling, for example, by enhancing peeling activity (e.g., peeling induced by a peeling agent), by providing a more homogeneous peeling, and/or by localizing peeling to a particular region of the body, such as a particular type of tissue and/or cell.

Examples of adjuvants include, without limitation, an alcohol (e.g., ethanol), a surfactant (e.g., Tween surfactants such as Tween 80, Septisol® soap, and/or carboxymethyl cellulose), a buffer, polyethylene glycol, and a film-forming agent.

Optionally, the buffer is selected so as to maintain a pH of the solution in a range of from about 5 to about 7, and optionally from about 5.5 to about 6.5. Optionally, the buffer is tris(hydroxymethyl)aminomethane (also known in the art as "Tris").

Without being bound to any particular theory, it is believed that the use of a buffer provides the composition with a relatively constant pH, which limits penetration

of the composition into tissue. Consequently, a controlled penetration depth may be obtained, which is relatively unaffected by the amount of peeling agent being applied.

Optionally, the peeling solution further comprises a viscosity modifier, for example, to thicken the peeling solution such that the solution can be applied to a particular region of the heart without running off and/or so as to stabilize the peeling solution (e.g., when the peeling solution comprises an emulsion). Examples of suitable viscosity modifiers include sugars, starches, cellulose derivatives, gelatin and polymers such as polyethylene glycols and carboxymethyl cellulose. Carboxymethyl cellulose (e.g., sodium carboxymethyl cellulose) is an exemplary viscosity modifier.

As heart tissue has different properties than skin, for which chemical peeling solutions have been previously used, the present inventors have devised pharmaceutical compositions which are suitable for peeling of scarred heart tissue. Thus, according to another aspect of embodiments of the present invention, there is provided a pharmaceutical composition comprising phenol and a pharmaceutically acceptable carrier (e.g., as described herein), wherein a concentration of phenol is in a range of from 5 % to 50 % (e.g., a phenol concentration described herein), the composition being identified for use in the treatment of scarred heart tissue in a subject in need thereof.

The pharmaceutical composition is optionally packaged in a packaging material and identified in print, in or on the packaging material, for use in the treatment of scarred heart tissue in a subject in need thereof.

Optionally, the composition further comprises a surface active agent (e.g., as described herein).

In some embodiments, the composition is devoid of croton oil, or comprises a low concentration of croton oil (e.g., less than 0.5 %, less than 0.1 %, less than 0.01 %, by weight), so as to minimize or altogether avoid potential adverse effects of croton oil, as described herein.

In some embodiments, the composition comprises, in addition to phenol, an additional peeling agent, such as a peeling agent described herein (e.g., salicylate and derivatives thereof).

Compositions of embodiments of the present invention may, if desired, be presented in a pack or dispenser device, such as an FDA (the U.S. Food and Drug Administration) approved kit, which may contain one or more unit dosage forms of a

chemical peeling solution described herein. The pack may, for example, comprise metal or plastic foil, such as, but not limited to a blister pack or a pressurized container (for inhalation). The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated
5 with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions for human or veterinary administration. Such notice, for example, may be of labeling or product insert approved by the U.S. Food and Drug Administration. Chemical peeling solutions of embodiments of the
10 invention formulated as described herein may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition, as is detailed herein.

Any of the compositions described herein may be formulated in the form of a solution, a gel, a cream, an ointment, a paste, a suspension, an aerosol, a spray, a foam, a serum, a swab, a pledget, a pad or a patch. According to another aspect of embodiments
15 of the invention, there is provided a use of a chemical peeling solution (e.g., a chemical peeling solution described herein) in the manufacture of a medicament for treating scarred heart tissue.

According to another aspect of embodiments of the invention, there is provided a chemical peeling composition (e.g., as described herein) for use in the treatment of
20 scarred heart tissue.

The methods and compositions described herein according to all aspects of the invention are suitable for treating scarred heart tissue caused by a variety of conditions, including, without limitation, myocardial infarction (acute and/or chronic), heart failure, cardiomyopathy (e.g., dilated cardiomyopathy, hypertensive cardiomyopathy), heart
25 surgery (e.g., ischemia caused by the surgery, as well as any complications resulting from the surgery), and inflammation (e.g., cardiac inflammation).

In some embodiments, heart surgery is performed in order to facilitate application of the peeling composition to the heart tissue. Heart surgery may optionally be performed primarily for the purpose of applying the peeling composition.
30 Alternatively, the method may optionally be effected when heart surgery is performed for any other reason.

In some embodiments, the pericardium is opened, thereby facilitating application of the peeling solution onto the heart tissue.

In some embodiments, a peeling composition as described herein is applied onto the scarred heart tissue *per se*. In some embodiments, a peeling composition embedded
5 or absorbed in or on a biodegradable carrier is utilized.

In some embodiments, a patch or a pad comprising the peeling composition, such as described herein below, is applied onto the scarred heart tissue.

In some embodiments, the chemical peeling composition is applied onto the scarred heart tissue by means of a catheter and/or other medical instrument, as is further
10 detailed herein below for various articles-of-manufacturing, while circumventing the need for open-heart surgery and applying the composition via minimally-invasive procedures.

Hence, according to another aspect of embodiments of the invention, there is provided an article-of-manufacturing for treating scarred heart tissue (e.g., according to a
15 method described herein). The article-of-manufacturing is loaded with a chemical peeling composition (e.g., a composition described herein) and is configured for delivering the chemical peeling composition to heart tissue in a subject.

By "loaded" it is meant that the chemical peeling composition is integrated or is capable of being integrated with the article-of-manufacturing. It encompasses cases
20 where the chemical peeling composition is packaged independently and is loaded to the article-of-manufacturing when utilized.

The article-of-manufacturing is preferably constructed so as to be compatible with the chemical peeling composition, for example, being constructed from materials which are not corroded (e.g., via chemical reaction, hydrolysis, dissolution, and/or
25 absorption) by any of the components of the chemical peeling composition (e.g., phenol, acids).

One of skill in the art will be capable of selecting compatible materials for any particular chemical peeling composition.

Optionally, the article-of-manufacturing is configured for delivering the
30 composition to heart tissue during open-heart surgery (e.g., surgery as described herein).

Alternatively or additionally, the article-of-manufacturing is configured so as to be capable of delivering the composition to the heart without performing open-heart

surgery. The technical difficulty, cost and/or risks of open-heart surgery can thereby be avoided.

The article-of-manufacturing is optionally designed suitable for minimally invasive surgery or procedure (e.g., laparoscopic procedures).

5 In some embodiments, the article-of-manufacturing comprises an imaging device adapted for imaging the inside of the body, to thereby facilitate application of the composition with minimally invasive surgery. The imaging is optionally used for identifying scarred heart tissue for treatment and/or for guiding other devices in the article-of-manufacturing to scarred heart tissue.

10 In some embodiments, the article-of-manufacturing comprises a catheter configured for delivering the chemical peeling composition to the desired region of heart tissue. The catheter is optionally configured so as to deliver the composition without open-heart surgery or other highly invasive surgery (e.g., configured for being inserted through, for example, the femoral artery and/or a thoracoscopic surgical incision, and/or
15 by a percutaneous pericardial access device approach).

In some embodiments, the composition (e.g., the chemical peeling composition *per se*) flows through the catheter (e.g. as a fluid composition). The opening of the catheter is placed in proximity to the tissue to be treated.

In some embodiments, the article-of-manufacturing comprises both a catheter
20 and an imaging device, being in communication with one another.

In some embodiments, the article-of-manufacturing comprises a medical device adapted for applying the chemical peeling composition, with the chemical peeling composition being deposited on at least a portion of a surface of the device. The medical device may be implanted in a bodily site permanently (i.e. permanent medical device) or
25 transiently (i.e. transient insertable medical device).

Optionally, the medical device comprises chemical peeling composition absorbed within the device (e.g., within an absorbent material), as well chemical peeling composition on a surface thereof.

In some embodiments the medical device is a transiently insertable medical
30 device.

A transient insertable medical device is a device which is inserted into a bodily site as part of a medical procedure for treating a disease, and upon the completion of the procedure is withdrawn from the body.

In some embodiments the transiently insertable medical device is a balloon catheter.

The term "balloon catheter" describes a thin catheter tube that can be guided through a body conduit of a patient such as a blood vessel, and a distensible balloon located at the distal end of the catheter tube or inserted through the catheter to its distal end. Actuation of the balloon is accomplished through use of a fluid filled syringe or similar device that can inflate the balloon by filling it with fluid (e.g., water or saline solution) to a desired degree of expansion and then deflate the balloon by withdrawing the fluid back into the syringe. By depositing the chemical peeling composition (e.g., as described herein) on the balloon surface (or a portion thereof), in a suitable formulation, upon inflating the balloon in a proximity of heart tissue, the composition is applied to a surface of the heart tissue. Such a transiently insertable medical device can be used, for example, for applying a chemical peeling composition to a particular region of heart tissue with minimally invasive heart surgery (e.g., without open-heart surgery).

Optionally the balloon catheter is designed for being suitable for use in transluminal coronary balloon angioplasty (PTCA) for treatment of myocardial infarction, thrombosis and/or coronary atherosclerosis and/or in other cardiovascular interventions, such that the chemical peeling composition may optionally be applied by the balloon catheter during any of the aforementioned treatments.

Other examples of transient insertable medical devices are described in U.S. Patents Nos. 5,611,775, 5,573,515, 5,857,464, 6,964,649 and 6,280,414 and in U.S. Patent Applications having Publication Nos. 2005/0226855, 2004/0048375, 2004/0097905, 2002/0107504 and 2009/0246252, wherein are all incorporated by reference as if all fully set forth herein. These, as well as other transient insertable devices known to be used for implanting a medical device and/or for administering a therapeutically active therethrough, are contemplated herein.

In some embodiments, the article-of-manufacturing comprises an implantable medical device adapted for implantation on heart tissue, i.e., being adapted for being

placed on heart tissue without being removed therefrom. The chemical peeling composition is deposited on a surface of the device, as described hereinabove.

Optionally, the implantable medical device is biodegradable, such that the device is substantially degraded after at least 5 months, optionally after at least 2 months, optionally after at least 1 month, optionally after at least two weeks, optionally after at least one week, and optionally after 1-3 days.

The implantable medical device is optionally in the form of a patch (e.g., an absorbent and/or biodegradable patch). Exemplary biodegradable patches include SURGICEL® Absorbable Hemostats, as exemplified in the Examples section.

10 The implantable device optionally includes an adhesive material for adhering to the heart tissue at a desired location.

Patches are useful for reducing or preventing undesired contact of the peeling agents with tissues other than the scarred tissue to be treated.

15 An implantable medical device may optionally be delivered to the heart tissue via a catheter of the article-of-manufacturing, such as a catheter described herein. The implantable device is optionally deployed by a balloon of a balloon catheter (e.g., a balloon catheter described herein).

20 According to another aspect of embodiments of the invention, there is provided a biodegradable implantable medical device comprising a chemical peeling composition deposited on at least of a surface of the device, as described hereinabove.

The articles of manufacturing and medical devices according to the present embodiments may, if desired, be presented in a pack, such as an FDA (the U.S. Food and Drug Administration) approved kit. The pack device may be accompanied by instructions for administration. The pack may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions for human or veterinary administration. Such notice, for example, may be of labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. The pack may be further labeled for treatment of an indicated condition, as is detailed herein.

Thus, according to embodiments of the invention, an article of manufacturing and/or medical device described herein is packaged in a packaging material and

identified in print, in or on the packaging material, for use in a method of treating scarred heart tissue, as described herein.

In some embodiments of the present invention, there is provided a kit comprising an article-of-manufacturing configured for delivering the chemical peeling composition to a scarred heart tissue and a chemical peeling composition as described
5 herein independently packaged within the kit. In some embodiments, the kit further comprises instructions for loading the chemical peeling composition onto the article-of-manufacturing, and may optionally further comprise instructions how to perform such loading.

10 As used herein the term "about" refers to $\pm 10\%$.

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to".

The term "consisting of" means "including and limited to".

The term "consisting essentially of" means that the composition, method or
15 structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

The word "exemplary" is used herein to mean "serving as an example, instance or illustration". Any embodiment described as "exemplary" is not necessarily to be
20 construed as preferred or advantageous over other embodiments and/or to exclude the incorporation of features from other embodiments.

The word "optionally" is used herein to mean "is provided in some embodiments and not provided in other embodiments". Any particular embodiment of the invention may include a plurality of "optional" features unless such features conflict.

25 As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

Throughout this application, various embodiments of this invention may be
30 presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should

be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions illustrate some embodiments of the invention in a non-limiting fashion.

EXAMPLE 1***Phenol-based chemical peeling solutions formulated for use on heart tissue***

Phenol solutions used for chemical peeling of skin typically comprise from 45 to 80 % phenol, mostly from 45 % to 55 %, as a peeling agent. Phenol-containing peeling solutions typically further include croton oil, at a concentration range of from 0.5 to 2 %.

10 % The croton oil is aimed at enhancing the penetration of phenol into deep skin tissues in order to effect deep peeling. In the absence of croton oil, the penetration of phenol is limited and only moderate peeling is effected.

When used for chemical peeling of the skin, phenol and croton oil are typically formulated into solutions that contain water, oils and optionally surface active agents.

15 The addition of oils to the formulation is assumed to provide for a controlled-release effect of the croton oil.

According to some embodiments of the present invention, a chemical peeling solution is formulated for use on heart tissue by using phenol at a concentration of 50 % or lower (e.g., 30 %, 25 %, 10 %, and even lower).

20 Since penetration into deep heart tissues is often undesired, in some embodiments, phenol is utilized in such solutions also without croton oil. Thus, the self-limited penetration of phenol assures that penetration into deep tissues is reduced or avoided.

In some embodiments, in formulations that contain relatively low phenol concentration (e.g., lower than 30 %, lower than 20 %, or lower than 10 %), croton oil is added.

25

A concentration of croton oil in the formulation can range from 0.0001 % to 2 %. In some embodiments, the concentration of croton oil is lower than 2 %, lower than 1 %, lower than 0.5 %, lower than 0.1 % and even lower than 0.01 %.

30 In some embodiments, phenol, and optionally croton oil, are formulated into an aqueous solution. In some embodiments, the solution further comprises oils (e.g., olive

oil, sesame oil and/or glycerin). In some embodiments, the solution further comprises surface active agents (e.g., Septisol®, TWEENS and/or Na-CMC).

Other features of solutions suitable for use in the context of the present embodiments are described hereinabove.

5 Exemplary solutions are demonstrated in the following Examples.

The solution is formulated by procedures well known in the art for preparing chemical peeling formulations.

EXAMPLE 2

10 *Chemical peeling of rat heart*

The effect of a phenol-based peeling composition on heart tissue was examined in healthy rats (i.e., rats without scar tissue in the heart).

Male Sprague-Dawley rats (250 grams) were anesthetized with a combination of 40 mg/kg ketamine and 10 mg/kg xylazine, and then intubated and mechanically
15 ventilated. The chest was opened by left thoracotomy and the pericardium was removed. A sterile cotton applicator was soaked in a solution of phenol (50 %) in saline and placed in the middle of the scar for 4 seconds. The chest was closed by suturing with 4-0 vicryl suture, and the animal was left on the ventilator for an additional 20 minutes.

One week after treatment, the hearts were arrested with 15 % KCl and sectioned
20 into 3 to 4 transverse slices, parallel to the atrioventricular ring. Each slice was fixed with 10 % buffered formalin, embedded in paraffin, and sectioned into 5 mm slices. Serial sections were cryosectioned and stained with hematoxylin and eosin.

As shown in Figure 1, hematoxylin and eosin (HE) staining of rat heart one week
25 after chemical peeling showed granulation tissue formation (indicated by arrows) and a thin layer of inflammation with intensive neovascularization.

As further shown in Figure 2, intensive neovascularization (indicated by arrows) was observed in granulation tissue at the epicardium subjected to chemical peeling.

These results indicate that chemical peeling in heart tissue stimulates neovascularization, which is essential for healing, repair, and regeneration of tissue, and
30 viability of new tissue.

EXAMPLE 3***Chemical peeling of mouse heart***

The effect of phenol-based peeling composition on heart tissue was examined further in healthy mice.

5 BalbC mice were anesthetized using isoflurane, and then intubated and mechanically ventilated. The chest was opened by left thoracotomy and the pericardium was removed. A sterile cotton applicator was soaked in a solution of phenol (50 %) in saline and placed in the middle of the scar for 4 seconds. The chest was closed by suturing with 4-0 vicryl suture, and the animal was left on the ventilator for additional 20
10 minutes. Histological analysis of the heart tissue was then performed as described above.

One week after treatment, the hearts were arrested with 15 % KCl and sectioned into 3 to 4 transverse slices, parallel to the atrioventricular ring. Each slice was fixed with 10 % buffered formalin, embedded in paraffin, and sectioned into 5 mm slices.
15 Serial sections were cryosectioned and immunolabeled with antibodies against CD117, a marker of hematopoietic and cardiac stem cells. Tissue samples were embedded for frozen sections and sectioned into 5 µm slices. The slices were fixed with methanol-acetone for 15 minutes. After several washing in phosphate buffered saline (PBS) for 15 minutes incubation with blocking solution containing 0.1 % BSA for 20 minutes.
20 After washing the samples several times in PBS for 15 minutes, blocking was performed using 0.1 % bovine serum albumin (BSA) and PBS. The samples were then incubated with primary antibody against c-kit (Dako) for 30-45 minutes, washed twice in PBS for 15 minutes, and incubated with Cy5 goat anti-mouse antibody (R&D) for 1 hour in the dark. The samples were then washed twice with PBS for 15 minutes,
25 incubated with 4'-6-diamidino-2-phenylindole (DAPI) (Vectrashild) nuclear staining for 15 minutes.

As shown in Figures 3-5, chemical peeling resulted in an accumulation of CD117 positive cells at the epicardium one week after peeling (Figures 3 and 4), whereas no accumulation of CD117 positive cells occurred in the control (Figure 5).

30 In addition, among 6 mice treated with phenol, no mortality occurred.

These results indicate that chemical peeling of heart tissue is safe, feasible and can stimulate CD117-positive epicardial cells.

EXAMPLE 4***Chemical peeling of rat heart following myocardial infarction***

The effect of a phenol-based peeling composition on scar tissue was examined in rats subjected to myocardial infarction.

5 In order to generate a myocardial infarction, rats were anesthetized, intubated and mechanically ventilated. The chest was opened by left thoracotomy, the pericardium was removed, and the proximal left coronary artery was permanently occluded with an intramural 6-0 Prolene stitch. After occlusion, the chest is closed with a 4-0 Vicryl suture.

10 After 1 or 2 months, a phenol-based composition was applied to the scarred heart tissue, using the procedures described in Example 2. Control rats were treated with saline.

The rat hearts were examined by echocardiography 1 or 2 months after treatment with the peeling composition (or saline), and by postmortem morphometry of Masson trichrome-stained heart slices 2 months after treatment.

15 Eight weeks after treatment, hearts were arrested with 15 % KCl, perfused with formaldehyde 4 % (15 mmHg) for 20 minutes, embedded in paraffin and sectioned into 5 μ m slices from the heart's apex. Serial sections were stained with hematoxylin and eosin, and Masson trichrome, and immunolabeled with antibodies against α -smooth muscle actin (Sigma). The slides were digitally photographed and analyzed using manual planimetry with Sigma Scan Pro version 5 (SPSS Inc, Chicago).

20 Postmortem morphometric analysis was performed on slides stained for Masson trichrome. The following left ventricle (LV) variables were measured and calculated:

average scar thickness (mm) - averaged from three measurements of scar thickness;

relative scar thickness - average scar thickness/average septum thickness;

scar area (mm^2);

relative scar area - scar area/ LV muscle area;

expansion index - (LV cavity area/whole LV area)/relative scar thickness;

30 collagen area (mm^2); and

percentage of collagen in the scar - collagen area/ scar area.

Slides were also examined for the number of myocardial islands in the scar by one researcher blinded to treatment.

As shown in Figures 6A and 6B, heart tissue exhibited extensive infarct expansion, scar thinning and remodeling in saline treated animals.

5 In contrast, as shown in Figures 7A and 7B, the heart tissue of phenol-treated animals showed thicker and smaller scars, and less remodeling, as compared to saline treated animals.

In addition, as shown in Figures 6C and 6D, scar tissue in saline treated animals was thin and fibrotic.

10 In contrast, as shown in Figures 7C and 7D, scar tissue of phenol-treated was thicker and smaller, and with small islands of viable myocardium.

As shown in Figure 8, phenol treatment one or two months after myocardial infarction considerably reduced the scar area in hearts, in comparison with the control (saline treatment).

15 As shown in Figure 9, phenol treatment two months after myocardial infarction reduced the expansion index observed in rat hearts.

As shown in Figure 10, phenol treatment one or two months after myocardial infarction considerably increased muscle area in rat hearts.

20 As shown in Figures 11A and 11B, phenol treatment one or two months after myocardial infarction considerably reduced the degree to which the left ventricular end diastolic dimension changed following myocardial infarction, as determined by echocardiography.

These results indicate that chemical peeling is effective at treating the scarring of heart tissue, such as occurs following myocardial infarction.

25 In addition, among rats subjected to myocardial infarction, 18 of 24 mice treated with phenol survived at least 2 months after phenol treatment, whereas 30 of 38 mice treated with saline survived at least 2 months after saline treatment.

These results further indicate that phenol may be safely applied to a heart, with no more mortality than is observed for saline treatment.

EXAMPLE 5***Effects of different chemical peeling solutions on rat heart***

Chemical peeling solutions (designated solutions 1-15) were prepared from various peeling agents (phenol, salicylic acid, benzoic acid, trichloroacetic acid, anthranilic acid, dihydroxyphenyl acetic acid) and various combinations thereof with sodium carboxymethyl cellulose (Na-CMC), olive oil, glycerin, sesame oil, citric acid and/or Tween 80, in water. Solutions 8 and 15 comprised no peeling agent, and served as controls. The compositions of the various solutions are shown in Table 1.

Table 1: Compositions of tested peeling solutions (water added to 100 %)

Solution	Peeling agent(s)	% Peeling agent	Na-CMC (%)	Olive oil (%)	Glycerin (%)	Sesame oil (%)	Citric acid (%)	Tween 80 (%)
1	phenol	25	0	15	15	10	6	0.5
2	phenol	10	0	15	15	10	6	0.5
3	salicylic acid	30	0	15	15	10	6	0.5
4	salicylic acid benzoic acid	20 10	0	15	15	10	6	0.5
5	trichloroacetic acid	30	0	15	15	10	6	0.5
6	anthranilic acid	30	0	0	0	10	6	0.5
7	dihydroxyphenyl acetic acid	30	0	15	15	10	6	0.5
8	(none)	0	0	15	15	10	6	0.5
9	phenol	25	1	0	0	0	0	0
10	salicylic acid	30	1	0	0	0	0	0
11	salicylic acid benzoic acid	20 10	1	0	0	0	0	0
12	trichloroacetic acid	30	1	0	0	0	0	0
13	anthranilic acid	30	1	0	0	0	0	0
14	dihydroxyphenyl acetic acid	30	1	0	0	0	0	0
15	(none)	0	1	0	0	0	0	0

The solutions were applied to rat hearts using the procedures described in Example 2. The effect of the solutions on the heart tissue was observed 48 hours after treatment based on histological examination of hematoxylin and eosin stained sections.

Inflammation was graded based on thickness and extension of the inflammatory infiltrate as follows:

0 – no inflammation or minimal inflammation;

1 – thin (<10 μm), patchy, sparse, and narrow infiltrate;

5 2 – thick (>10 μm), patchy, sparse, and extensive infiltrate;

3 – very thick (>20 μm), dense, and extensive infiltrate.

Survival at 48 hours after peeling was also recorded.

The results are summarized in Table 2. In addition, representative photographs of hearts treated with each of solutions 1-15 are presented Figures 12A-12O,
10 respectively.

Table 2: Effects of chemical peeling solutions on rat heart

Solution	Peeling agent(s) (%)	Inflammation (scale of 0-3)	Survival	Observations
1	phenol (25 %)	3	3/4	Large white area which disappeared after ~1 minute
2	phenol (10 %)	3	3/4	Light white spot which disappeared after ~1-2 minutes
3	salicylic acid (30 %)	1-2	3/5	White flakes adhered to the heart
4	salicylic acid (20 %) benzoic acid (10 %)	1-2	3/4	Bright white flakes which stayed on the heart
5	trichloroacetic acid (30 %)	0-1	3/3	No visible effect
6	anthranilic acid (30 %)	1	3/4	Adhered yellow material
7	dihydroxyphenyl acetic acid (30 %)	0-1	3/3	Slight pinkish abrasion
8	(none)	2	3/3	No visible effect, but heart rate increased
9	phenol (25 %)	2	3/3	Large white spot visible for ~3 minutes
10	salicylic acid (30 %)	1	3/3	White flakes adhered to heart, which remained without disappearing

11	salicylic acid (20 %) benzoic acid (10 %)	0-1	3/3	White flakes adhered to heart, which remained without disappearing
12	trichloroacetic acid (30 %)	2-3	4/4	Slight discoloration or no visible effect
13	anthranilic acid (30 %)	1	3/3	Pinkish flakes adhered to heart, with small abrasion underneath
14	dihydroxyphenyl acetic acid (30 %)	0-1	4/4	Small, pink, well defined abrasion
15	(none)	0	3/3	No visible effect

As shown in Table 2, phenol was the most effective agent for peeling heart tissue. As further shown therein, the compositions which included oil, glycerin and citric acid in addition to the tested peeling agent (solution nos. 1-7) were more effective than compositions comprising a simple aqueous solution of the peeling agent (solution nos. 9-14).

EXAMPLE 6

Repair of scarred heart tissue with phenol solution and salicylic acid solution in a biodegradable implant

Phenol-based solution and salicylic acid-based solution are used in a rat model (e.g., rat) to treat scars formed by chronic myocardial infarction.

On day 0, rats are anesthetized, intubated and mechanically ventilated. The chest is opened by left thoracotomy, the pericardium is removed, and the proximal left coronary artery is permanently occluded with an intramural 6-0 Prolene stitch, in order to generate a myocardial infarction. After occlusion, the chest is closed with a 4-0 Vicryl suture.

Sixty days after infarction, the rats are anesthetized and the chest is opened under sterile conditions. The scarred tissue is identified, and phenol-based or salicylate-based chemical peeling solutions (or saline as a control) in a biodegradable patch (SURGICEL® Absorbable Hemostat, ETHICON 360) are placed onto the left ventricular myocardium. The tested solutions comprise 5 % or 15 % phenol, or 30 % salicylic acid. The chest is then closed with a 4-0 Vicryl suture.

The effect of the peeling solutions on the heart is monitored by echocardiography on day 60 (prior to treatment with chemical peeling), and on days 90 and 120 (subsequent to chemical peeling), using a commercially available echocardiography system. Posterior wall thickness and left ventricle (LV) internal dimensions are measured (by an experienced blinded technician) according to the leading edge method of the American Society of Echocardiography. Measured dimensions include maximal LV end-diastolic dimension, minimal LV end-systolic dimension, and fractional shortening (FS), which is calculated as:

$$FS = [(LVIDd - LVIDs) / LVIDd] * 100$$

where LVID is LV internal dimension, s is systole, and d is diastole.

A portion of the rats are sacrificed one month after treatment and a portion are sacrificed 2 months after treatment. Hearts are then fixed with 4 % formaldehyde solution, sectioned into 5 µm slices, stained (e.g., hematoxylin, eosin, Masson-trichrome stains), and subjected to histological examination. The following parameters are determined by morphometric analysis:

LV maximal diameter (mm) - the longest diameter perpendicular to a line connecting the insertions of the septum to the ventricular wall;

Average septum thickness (mm);

Average scar thickness (mm);

Relative scar thickness - average scar thickness/average septum thickness;

Muscle area (mm²) - including the septum;

Scar area (mm²);

Relative scar /muscle area;

LV cavity area (mm²);

Whole LV area (mm²) - including intra-ventricular space;

Expansion index - (LV cavity area/whole LV area)/relative scar thickness;

Epicardial scar length (mm);

Endocardial scar length (mm);

Epicardial LV free wall length (mm) - including the septum;

Endocardial LV free wall length (mm) - including the septum;

Percentage of scar tissue out of the surface - $\{\text{epicardial scar length} + \text{endocardial scar length}\} \times 100 / \{\text{epicardial LV free wall length} + \text{endocardial LV free wall length}\}$.

Statistical analysis is performed by standard methods (e.g., 2-tail paired t-tests in the case of normal distribution, Kruskal-Wallis test in the absence of normal distribution). The effects of the tested chemical peeling solutions are observed as differences between the hearts of rats treated with chemical peeling and those of control rats (treated with saline).

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A method of treating scarred heart tissue in a subject in need thereof, the method comprising applying a chemical peeling composition to scar tissue in the heart of said subject, thereby treating said scarred heart tissue.
2. The method of claim 1, wherein applying said chemical peeling composition is performed during an open-heart surgery.
3. The method of claim 1, wherein applying said chemical peeling composition comprises applying a medical device which comprises said chemical peeling composition.
4. The method of claim 1, wherein applying said chemical peeling composition is performed via a minimally-invasive procedure.
5. Use of a chemical peeling composition in the manufacture of a medicament for treating scarred heart tissue.
6. Use of a chemical peeling composition in the manufacture of an article-of-manufacturing configured for delivering said chemical peeling composition to the scarred heart tissue.
7. A chemical peeling composition for use in the treatment of scarred heart tissue.
8. An article-of-manufacturing for treating scarred heart tissue in a subject in need thereof, the article-of-manufacturing being loaded with a chemical peeling composition, and being configured for delivering said chemical peeling composition to the scarred heart tissue.

9. The article-of-manufacturing of claim 8, being configured so as to be capable of delivering said chemical peeling composition to said heart tissue without open-heart surgery.

10. The article-of-manufacturing of any of claims 8 to 9, comprising a catheter configured for delivering said chemical peeling composition to said heart tissue.

11. The article-of-manufacturing of claim 10, being configured such that said chemical peeling composition flows through said catheter to said heart tissue.

12. The article-of-manufacturing of any of claims 8 to 10, comprising an insertable medical device, wherein said chemical peeling composition is being deposited on at least a portion of a surface of said medical device, the medical device being configured for contacting said heart tissue with said chemical peeling composition.

13. The article-of-manufacturing of any of claims 8 to 10, comprising an implantable medical device, said chemical peeling composition being deposited on at least a portion of a surface of said medical device, the medical device being adapted for implantation on heart tissue.

14. The article-of-manufacturing of claim 13, wherein said implantable medical device is biodegradable.

15. An implantable medical device comprising a chemical peeling composition being deposited on at least a portion of a surface of said medical device, said medical device being biodegradable.

16. The method, use, article-of-manufacturing, medical device or chemical peeling composition of any of claims 1 to 15, wherein said chemical peeling

composition comprises at least one peeling agent and a pharmaceutically acceptable carrier.

17. The method, use, chemical peeling composition, article-of-manufacturing, medical device or use of claim 16, wherein a concentration of said at least one peeling agent ranges from 5 % to 50 % by weight.

18. The method, use, article-of-manufacturing, medical device or chemical peeling composition of claim 16, wherein said at least one peeling agent is selected from the group consisting of phenol, an alpha-hydroxy acid, a beta-hydroxy acid, retinoic acid, trichloroacetic acid, benzoic acid, anthranilic acid, dihydroxyphenyl acetic acid, pyruvic acid, and resorcinol.

19. The method, use, chemical peeling composition, article-of-manufacturing, medical device or use of claim 18, wherein said at least one peeling agent comprises phenol.

20. The method, chemical peeling composition, article-of-manufacturing, medical device or use of claim 19, wherein said at least one peeling agent further comprises a beta-hydroxy acid.

21. The method, chemical peeling composition, article-of-manufacturing, medical device or use of claim 18, wherein said alpha-hydroxy acid is selected from the group consisting of glycolic acid, lactic acid, citric acid, tartaric acid and malic acid.

22. The method, chemical peeling composition, article-of-manufacturing, medical device or use of any of claims 18-20, wherein said beta-hydroxy acid is selected from the group consisting of salicylic acid and lipohydroxy acid.

23. The method, chemical peeling composition, article-of-manufacturing, medical device or use of claim 18, wherein said chemical peeling composition comprises Jessner's solution.

24. The method, chemical peeling composition, article-of-manufacturing, medical device or use of any of claims 16 to 23, wherein said carrier comprises an aqueous solution.

25. The method, chemical peeling composition, article-of-manufacturing, medical device or use of any of claims 16 to 24, wherein said carrier comprises an oil.

26. The method, chemical peeling composition, article-of-manufacturing, medical device or use of claim 25, wherein said oil is selected from the group consisting of sesame oil, olive oil, glycerin and a mixture thereof.

27. The method, chemical peeling composition, article-of-manufacturing, medical device or use of any of claims 16 to 26, wherein the chemical peeling composition is being devoid of croton oil.

28. The method, chemical peeling composition, article-of-manufacturing, medical device or use of any of claims 16 to 26, wherein the chemical peeling composition further comprises croton oil.

29. The method, chemical peeling composition, article-of-manufacturing, medical device or use of claim 28, wherein a concentration of said croton oil ranges from 0.001 % to 2 % by weight.

30. The method, chemical peeling composition, article-of-manufacturing, medical device or use of any of claims 16 to 27, wherein said chemical peeling composition further comprises an adjuvant.

31. The method, chemical peeling composition, article-of-manufacturing, medical device or use of claim 30, wherein said adjuvant is selected from the group consisting of an alcohol, a polyethylene glycol, a film-forming agent and a buffer.

32. The method, chemical peeling composition, article-of-manufacturing, medical device or use of claim 31, wherein said buffer comprises tris(hydroxymethyl)aminomethane.

33. The method, chemical peeling composition, article-of-manufacturing, medical device or use of any of claims 1 to 32, wherein said scarred heart tissue is caused by a condition selected from the group consisting of myocardial infarction, heart failure, cardiomyopathy, heart surgery and inflammation.

34. The method, chemical peeling composition, article-of-manufacturing, medical device or use of claim 33, wherein said cardiomyopathy is selected from the group consisting of dilated cardiomyopathy and hypertensive cardidomyopathy.

35. A pharmaceutical composition comprising phenol and a pharmaceutically acceptable carrier, wherein a concentration of phenol ranges from 5 % to 50 %, the composition being identified for use in the treatment of scarred heart tissue in a subject in need thereof.

36. The composition of claim 35, being packaged in a packaging material and identified in print, in or on said packaging material, for use in the treatment of scarred heart tissue in a subject in need thereof.

37. The composition of any of claims 35 and 36, being devoid of croton oil.

38. The composition of any of claims 35 and 36, further comprising croton oil at a concentration lower than 0.5 % by weight.

39. The composition of any of claims 35 and 36, wherein a concentration of said croton oil is lower than 0.1 % by weight.

40. The composition of any of claims 35-39, further comprising at least one additional peeling agent.

41. The composition of claim 40, wherein said additional peeling agent is a salicylate.

42. The composition of any of claims 35-41, wherein said carrier comprises an aqueous solution.

43. The composition of claim 42, wherein said carrier further comprises an oil.

44. The composition of any of claims 42 and 43, wherein said carrier further comprises a surface active agent.

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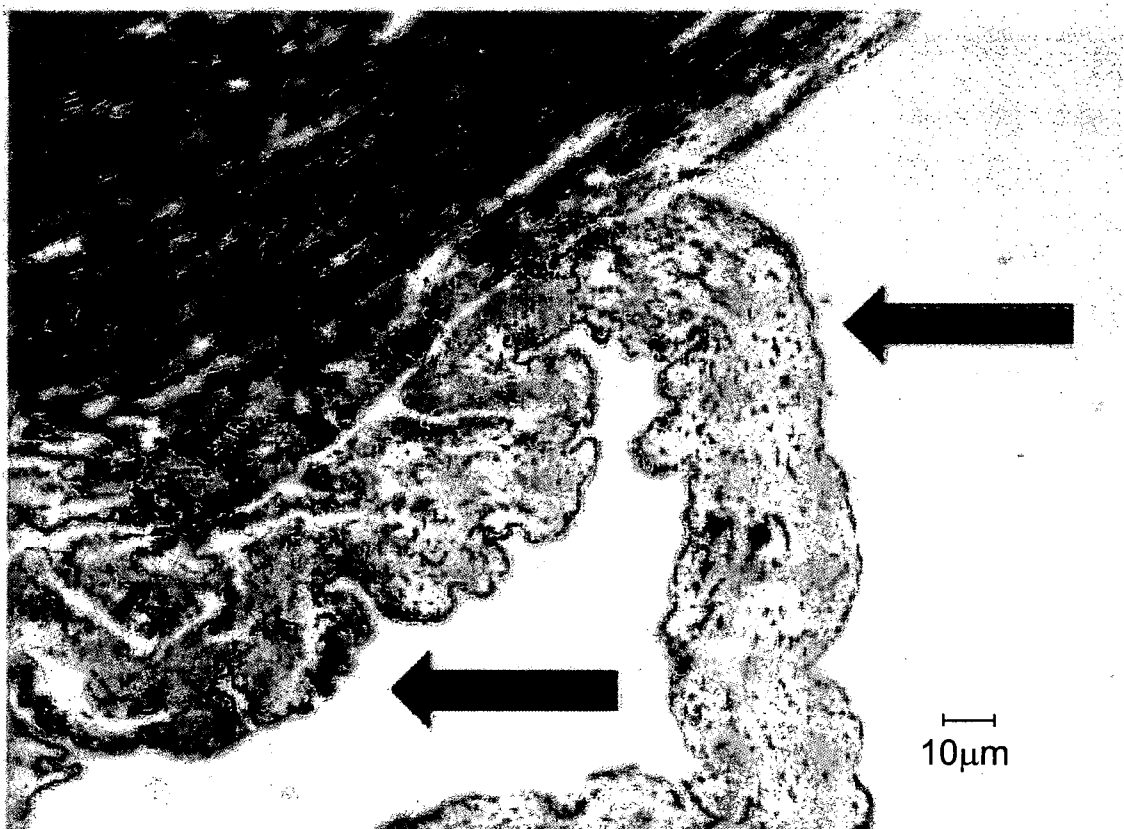


FIG. 1

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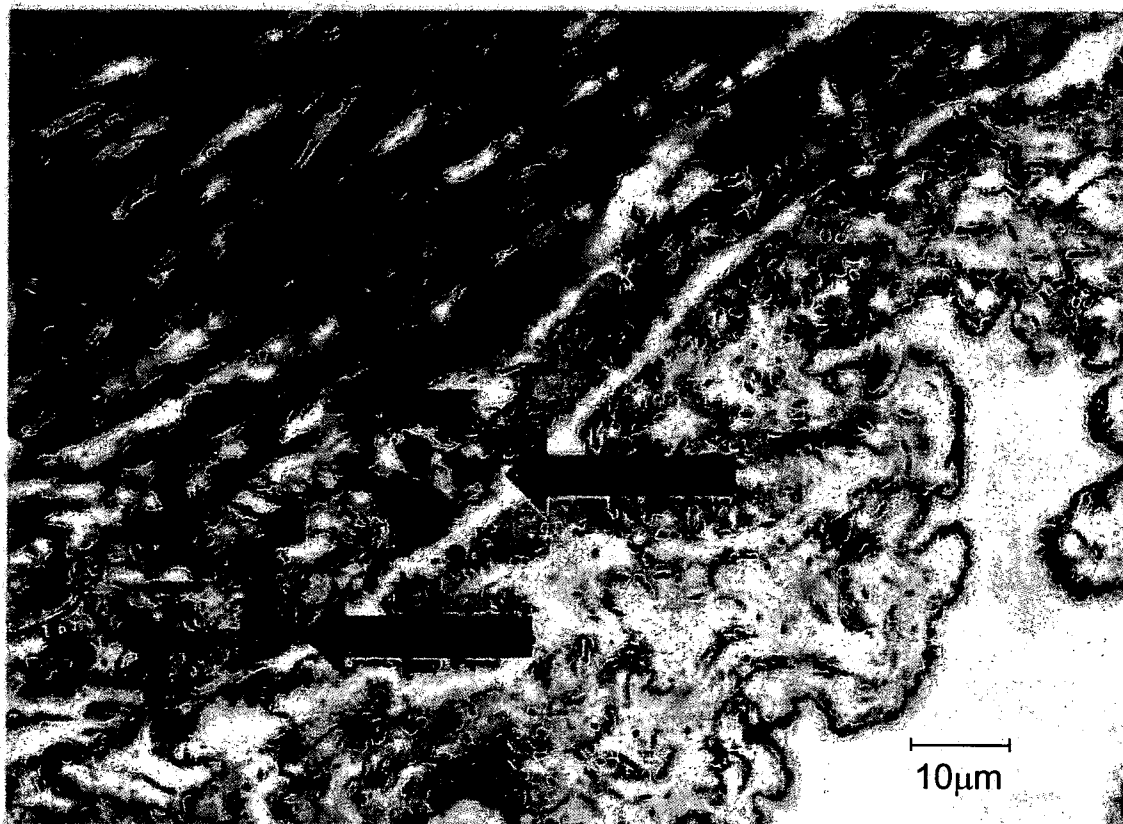


FIG. 2

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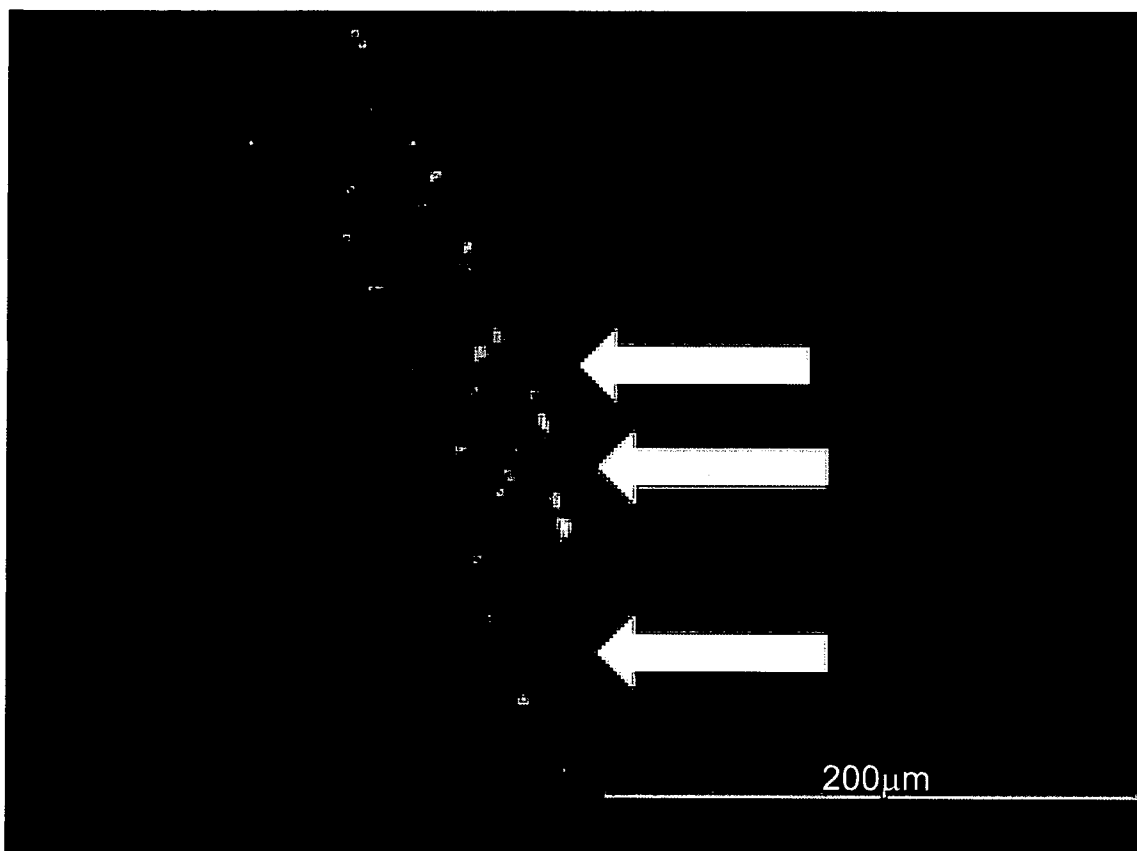


FIG. 3

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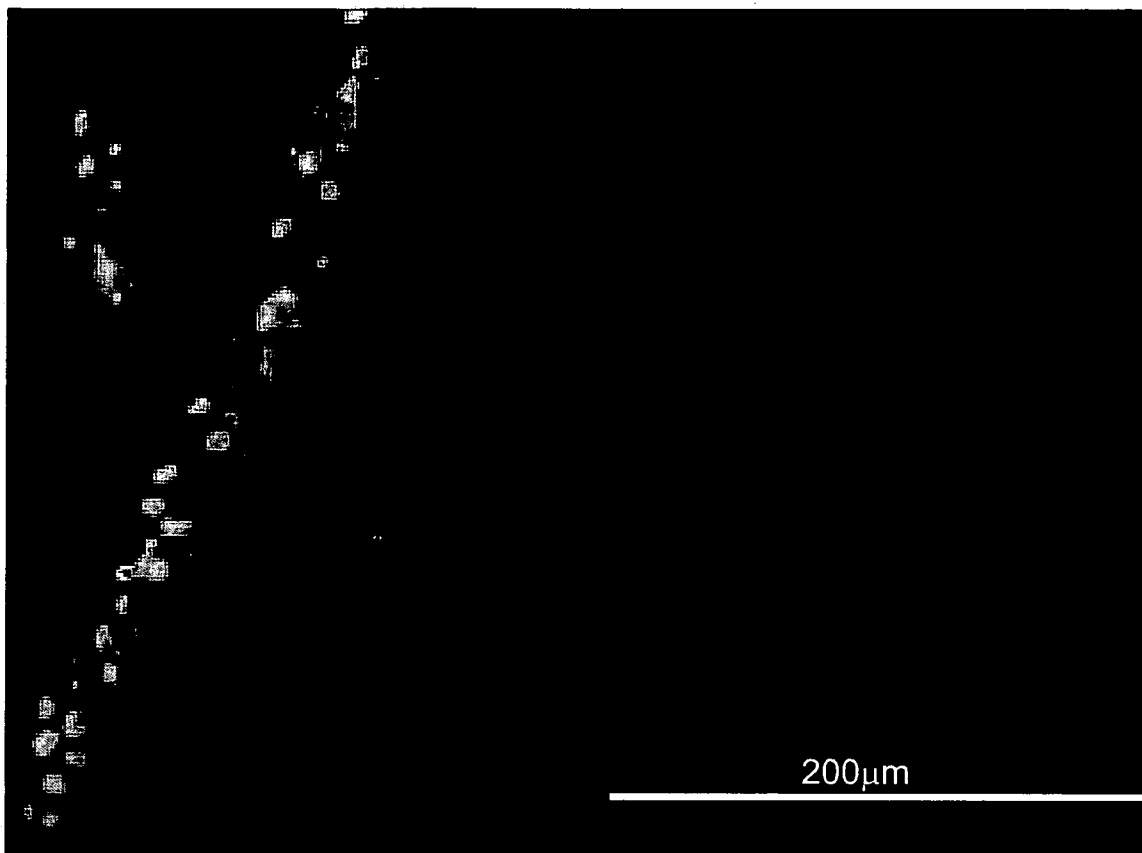


FIG. 4

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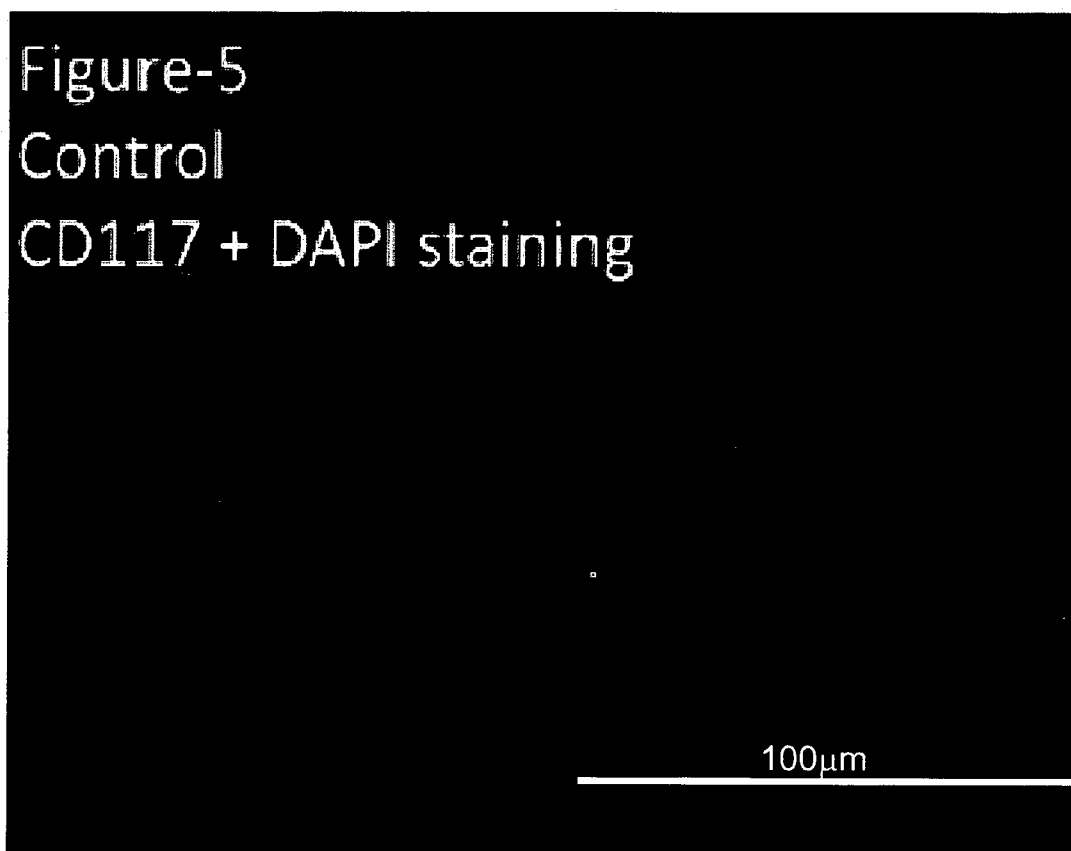


FIG. 5

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FIG. 6A

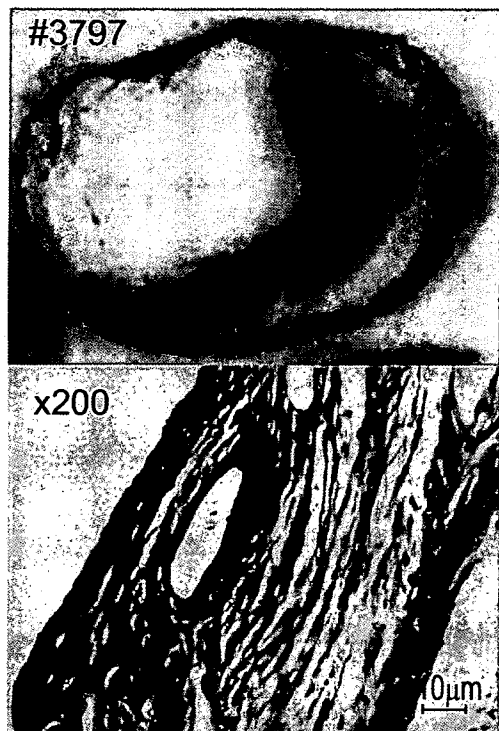


FIG. 6B



FIG. 6C

FIG. 6D

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FIG. 7A

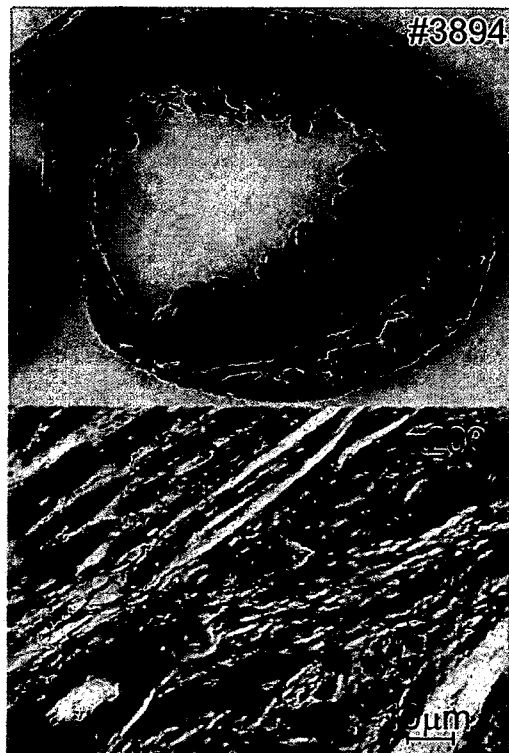


FIG. 7B

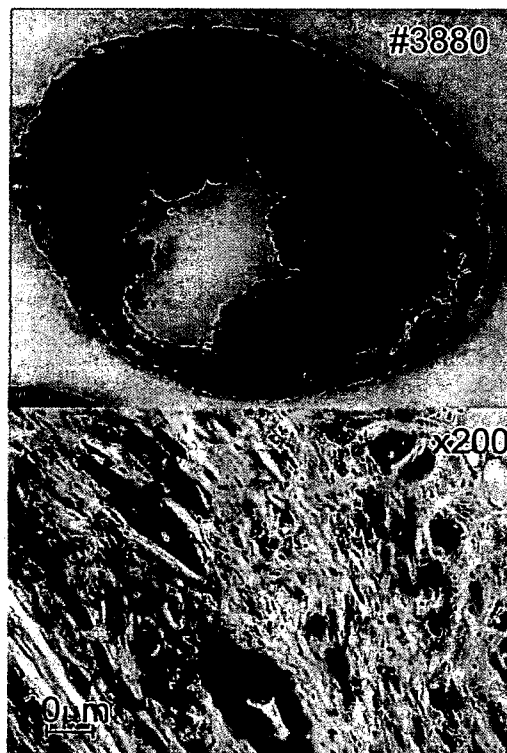


FIG. 7C

FIG. 7D

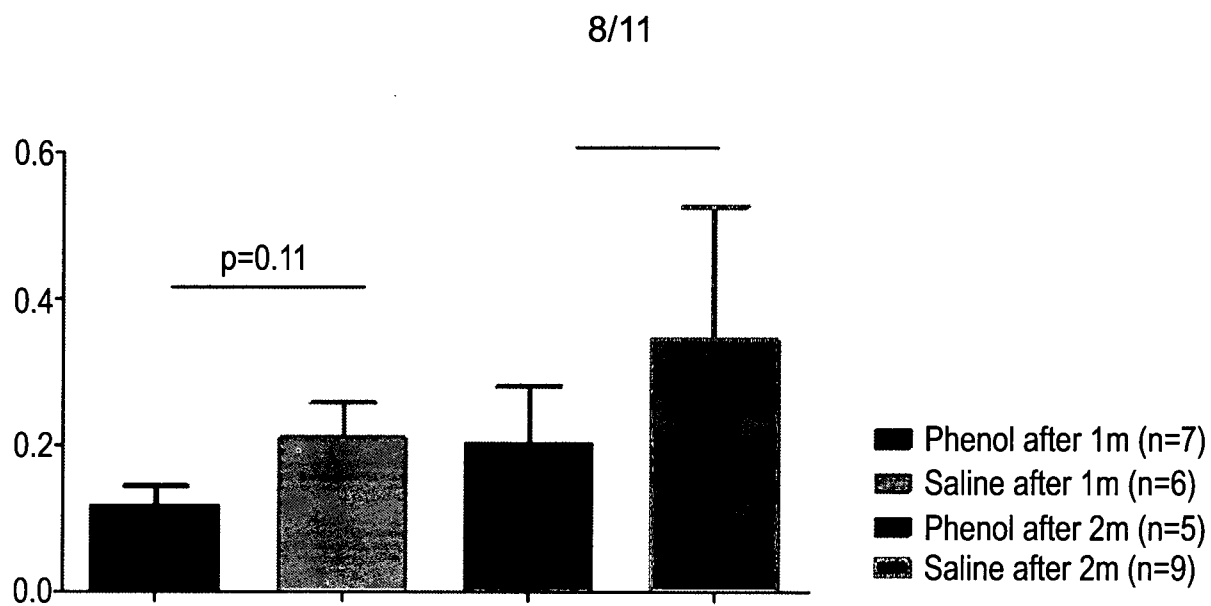


FIG. 8

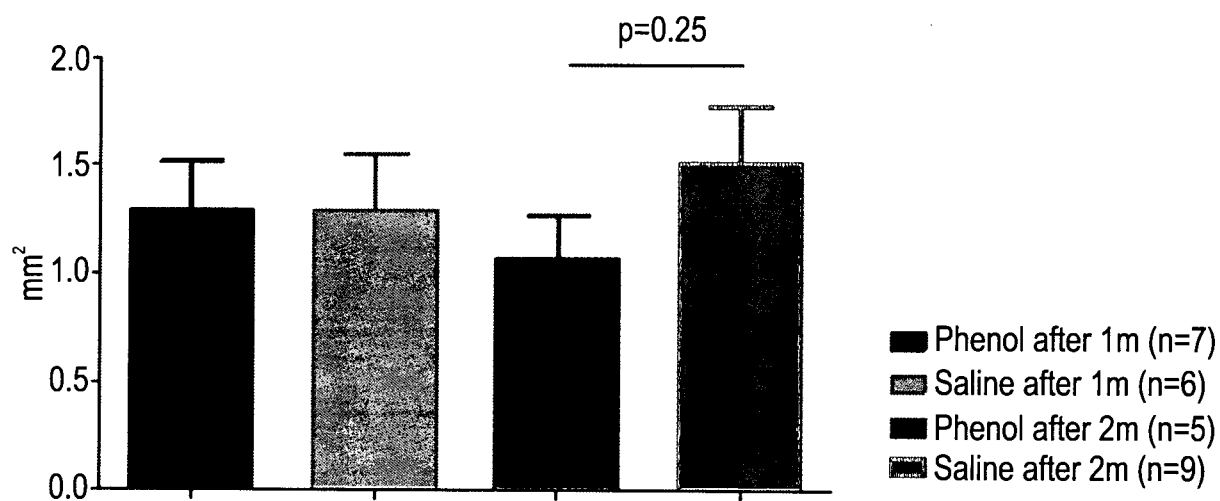


FIG. 9

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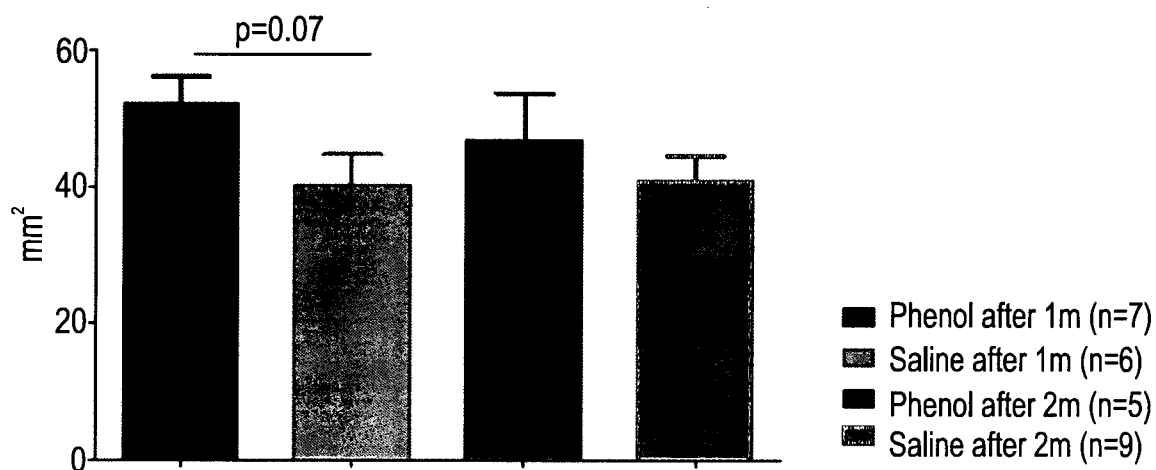


FIG. 10

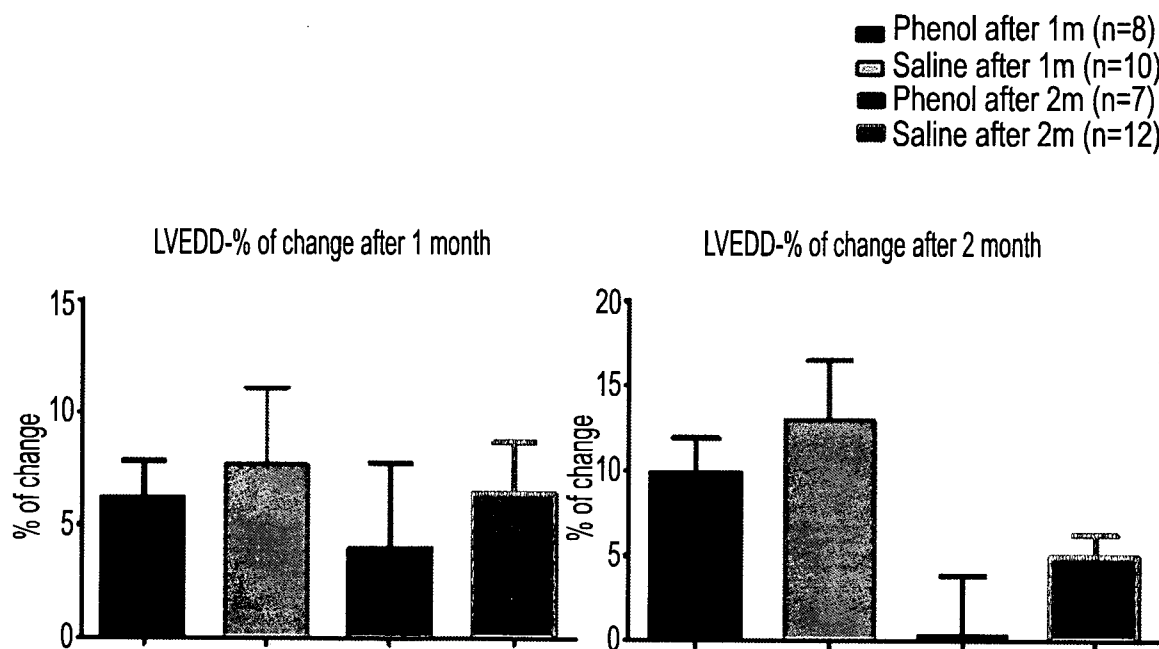


FIG. 11A

FIG. 11B

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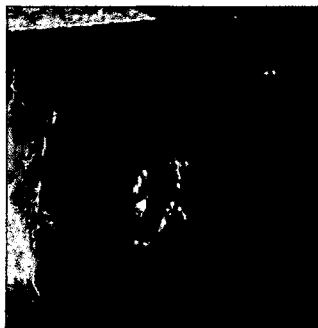


FIG. 12A



FIG. 12B

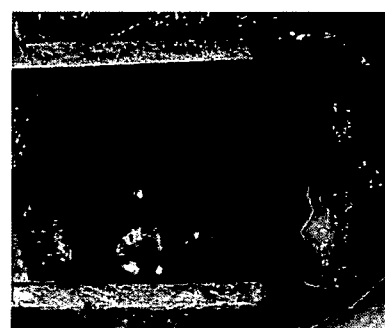


FIG. 12C



FIG. 12D



FIG. 12E



FIG. 12F



FIG. 12G



FIG. 12H



FIG. 12I

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FIG. 12J



FIG. 12K

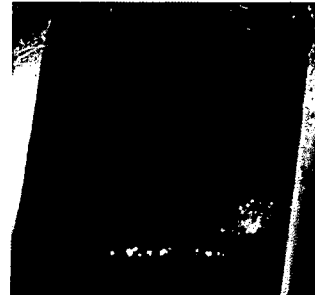


FIG. 12L



FIG. 12M

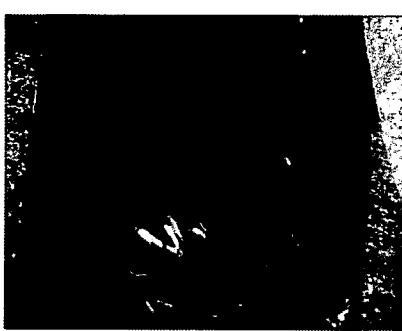


FIG. 12N

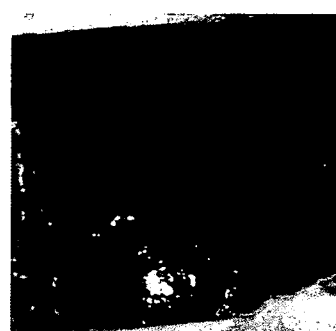


FIG. 12O

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL 10/00875

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 33/08, 33/18; A61K 31/045 (2011.01)

USPC - 514/728, 731

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/728, 731

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC: 514/728, 731; 514/182, 232.5, 502, 737 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPTO PubWEST (USPT, PGPUB, EPAB, JPAB); scarred, tissue, heart, 'chemical peel\$', 'chemical peeling', scar\$, chemical, peel\$, 'croton oil'

Google Scholar; 'chemical peeling scarred heart tissue'

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2008/0038352 A1 (SIMPSON, et al.) 14 February 2008 (14.02.2008) para [0077]-[0078], [0080], [0127], [0163], [0225]-[0226], [0228], [0233], [0269]	1-11, 15, 35-37 ----- 38-39
Y	US 2009/0137534 A1 (CHAUDHURI) 28 May 2009 (28.05.2009) para [0009]	38-39

☐ Further documents are listed in the continuation of Box C.


* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

30 January 2011 (30.01.2011)

Date of mailing of the international search report

11 FEB 2011

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL 10/00875

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 12-14, 16-34, 40-44
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.