(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 January 2002 (24.01.2002)

PCT

(10) International Publication Number
WO 02/05834 A2

(51) International Patent Classification[7]: A61K 38/00

(21) International Application Number: PCT/GB01/03182

(22) International Filing Date: 16 July 2001 (16.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/617,052 14 July 2000 (14.07.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/05834 A2

(54) **Title:** NOVEL USES FOR THYROID HORMONES OR THYROID HORMONE-LIKE AGONIST COMPOUNDS

(57) **Abstract:** The present invention is directed to the sue of at least one thyroid hormone compound or thyroid hormone-like agonist compound in the preparation of a topical medicament for the treatment of a dermatological condition affecting the dermis. The thyroid hormone compound or the thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M. The invention is also directed to a composition for treating a dermatological conditions affecting the dermis and to an article of manufacture comprising packaging material and a pharmaceutical agent contained within the packaging material, wherein the pharmaceutical agent is therapeutically effective for treating such a condition. Use of at least one thyroid hormone or thyroid hormone-like agonist compound in the preparation of a topical medicament for the pre-treatment of skin in dermatological surgery is also provided.

Novel Uses for Thyroid Hormones or Thyroid hormone-like Agonist Compounds

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to thyroid-hormone receptor binding compounds, and more particularly to thyroid-hormone receptor binding compounds useful as dermatological treatments of the dermis.

2. Brief Description of the Related Art

Human skin is composed of two distinct anatomical layers, the epidermis and the dermis (Gray's Anatomy, p1105, 1966, 28th edition.) There are a considerable number of medically important conditions which significantly affect the dermis of the skin. Examples of these include wounding of the dermis for example by an abrasion, chemical or other burn or a skin biopsy, diabetic dermopathy, intrinsically aged skin especially crinkles or wrinkles, and atrophy of the dermis which may result from a variety of etiologies such as prolonged glucocorticoid use, rheumatoid disease, poikloderma, atrophic scars, anetoderma, chronic atrophic acrodermatitis, follicular atrophoderma, vermiculate atrophoderma, atrophoderma of Pasini and Pierini, and panatrophy (page 1764ff Textbook of Dermatology, Rook, Wilkinson, Ebling, 5th edition 1992). These conditions could be ameliorated, treated and improved by medicaments which help to regrow, thicken and replenish the dermis.

Currently there are no medically useful remedies for treatment of the dermis in these conditions. Treatments which are commercially available for some form of wound healing such as becaplermin gel (Regranex) demonstrate improved healing in diabetic foot ulcers over usual care, but no especial effect on the dermis or the ability to promote regrowth of the cells, capillaries, ground substance or collagen of the dermis or to increase the depth of the dermis has been explicitly demonstrated.

Dermal atrophy results from reduced collagen in the dermis, decreased cellularity in the dermis, a decrease in activated fibroblasts, a reduction in ground substance such as

glycosaminoglycans and mucopolysaccharides and reduces the depth of the dermis, resulting in increased fragility of the skin, transparency of the skin, and easy bruising (Talwar et al., J. Inv. Derm. **105**:285 (1995); (Uitto, H. Geriatric Dermatology **5**:127 (1989)), Textbook of Dermatology, Rook, Wilkinson, Ebling, 5th edition 1992). Skin atrophy may be either atrophy of the dermis or epidermis or both and is sometimes used in the dermatology literature to refer to either variety of atrophy or both together (see Electronic Textbook of Dermatology, www.tlemedicine.org). The dermis is approximately 70-80% collagen, with predominantly type 1 collagen and lesser amounts of type 3 collagen (Uitto, H. Geriatric Dermatology **5**:127 (1989). The most studied collagens in the dermis have been of type 1 and type 3 although other collagens exist in skin such as the type XIII collagen making up epidermal cell-cell contacts and the type XVII collagen which is an epidermal adhesion molecule important in the pathophysiology of blistering diseases and type 4 collagen in the basement membrane.

Glucocorticoid induced atrophy of the skin has been shown to initially affect primarily the epidermis (Dermatologica 152 (suppl 1)p107-115 1976). Epidermal changes are considered by most to be reversible and transitory with cessation of glucocorticoid therapy. More prolonged therapy with more potent topical corticosteroids produces effects in both dermis and epidermis (Jablonska *et al*, Br. J Dermatology 1979 100, p193). The effects of dermal atrophy induced by glucocorticoids appear to involve both an inhibition of the synthesis of both collagen, primarily types 1 and types 3, and glycosoaminoglycans (ground substance) (Lehman et al J. Invest. Derm, 1983 vol81 p169 and V. Koivukangas *et al*, BR. J Derm 1995 v132 p66; Oikarinen, A. J Invst Derm 1992 v98 p 220)) and a reduction in the size of collagen fibrils and in fibroblasts, although there are many additional effects.

Photodamaged and photoaged adult skin also has reduced collagen of the type I and type III variety (Talwar et al p285 J invst Derm 1995), but authors such as Green *et al* (p97 Dermatologic Clinics vol 11 no 1 1993) distinguish intrinsically aged skin and photodamaged skin by ascribing dermal atrophy only to intrinsically aged skin, not to photodamaged skin, unless of course the affected individual is elderly. Intrinsically aged skin is defective in more than simply dermal atrophy and is well known to have other epidermal defects (Clinical Dermatology, 1991 unit 32-2 vol 4 , D.Joseph Demis ed.)

Retinoic acid has been shown to partially ameliorate the condition of photoaging (Drugs and Aging **1**:12-16 (1996)), but has not been fully successful in reversing steroid induced dermal skin atrophy in humans (Griffiths, Br. J. Dermatology **135**:60-64 (1996)). Other medically useful treatments involve the use of alpha hydroxy acids as disclosed in U.S. Patent No. 5,254,343; . Currently, there are no treatments available which help to regrow or replenish the dermis of the skin that are widely accepted by the medical community or can reverse glucocorticoid-induced dermal atrophy.

For example, topical retinoids do not successfully treat glucocorticoid induced atrophy of the human dermis and have an effect primarily on the epidermis. Topical retinoids do not reverse the type 1 or type 3 collagen reduction seen after topical betamethasone treatment, nor when applied alone. (K-M Haapasari et al, Br. J. Dermatology, 136, 1997 p891). Oral retinoids do not seem to affect type I or 3 collagen either, (Br J Dermatol 1994 Nov;131(5):660-3). Lac-hydrin cream increases epidermal thickness but is not claimed to affect dermal thickness and does not promote collagen regrowth, but does promote amelioration of cutaneous atrophy in topical glucocorticoid associated cutaneous atrophy by increasing epidermal thickness and in part by increasing production of glycosoaminoglycans by stimulation of fibroblasts in the dermis. (US patentS 5,807,600 5,254,343)

The structurally similar thyroid hormone compounds 3,3',5-triiodo-L-thyronine (T3) and L-thyroxine (T_4) have a very wide range of effects. In adult mammals they influence nearly all organs, the metabolism of nutrients, basal metabolic rate, and oxygen consumption. In humans, the deficiency or excess of circulating thyroid hormone compounds results in the well characterized syndromes, hypo- and hyperthyroidism. Small concentrations of thyroid hormone metabolites which are also endocrinologically active exist. Among these compounds are tri-iodothyroacetic acid ("Triac" [4-(4-hydroxy-3-iodophenoxy)-3,5-diodophenyl]acetic acid) and tri-iodopropionic acid ("Tri-prop" [4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl)] propionic acid).

Thyroid hormone compounds exert many of their actions by binding to a family of receptor proteins termed the *C-erb-A* family. In humans, their receptor protein family is now known to comprise several members and it is possible other members exist, notably the human

thyroid receptor a-1 (NRA1A), the human thyroid receptor a-2 which binds the hormone poorly or not at all, the human thyroid receptor b-1 (NR1A2), and the human thyroid receptor b-2. These proteins are part of a larger superfamily of steroid hormone receptors which comprises the glucocorticoid receptors, the retinoic acid receptors, the vitamin D receptors, and the insect molting receptors (e.g., the receptors for ecdysone and the insect juvenile hormones). Receptors for hormone compounds are found in human skin, human fibroblasts and keratinocytes and they are also found in many other tissues within the human body.

In addition to the naturally occurring thyroid hormone compounds (e.g., triiodothyronine and tetraiodothyronine), a large number of chemical compounds which bind to the thyroid hormone receptor and which produce thyroid hormone-like effects have been synthesized (see, for example, U.S. Patent Nos. 5,401,772; 6,236,946; 5,883,294; 5,585,404; and 5,567,728). Other suitable thyroid hormone-like compounds, are disclosed for example in U.S. Pat. Nos. 5,284,971; 3,649,679; 3,357,887; 412,579; 4,168,385; 5,179,097; EP0580550; EP018351 and H. A. Selenkow and S. P. Asper. Jr., Physiol. Rev. 35 426 (1955); C. S. Pitman and J. A. Pitman In Handbook of Physiology, Section 7: Endocrinology, Vol. 3, R. O. Greep and E. B. Astwood. Eds., Thyroid American Physiological Society, Washington D.C., 1974, p. 233; E. C. Jorgensen, Pharm. Ther. B, 2, 661 (1976); and E. C. Jorgensen, "Thyroid Hormones and Analogs. II. Structure-Activity Relationships," in Hormonal Proteins and Peptides, Vol. 6. Thyroid Hormones, C. H. Li, Ed., Academic, New York, 1978, p. 108 all of which are incorporated by reference herein. The choice of other suitable thyroid hormone-like compounds for use in the compositions and methods of the present invention is within the scope of the skilled worker.

Binding constants ,Kd, for various ligands to the thyroid receptor vary over a very broad range from approximately 5×10^{-6} to 50×10^{-12}, with TriAc being among the most potent compounds.

Commercially available topical glucocorticoid compounds have at least an 1800 fold range of activity (Dermatologic therapy 1988 vol 6 no4 page 643, Harris *et al.*) . Commercially available dermatological preparations vary in concentration of the active glucocorticoid in a range from .0025% to 2.5%, a one thousand fold range . (Textbook of Dermatology,

Rook, Wilkinson, Ebling, fifth edition 1992, page 3075).

This wide range of concentrations in commercially available preparations results from variations in the formulation used, and the pharmaceutical properties of the formulation interacting with the active compound, together with receptor binding activity of the individual glucocorticoid. For example cortisol binds to its receptor with an affinity of approximately 3 nMolar and hydrocortisone creams are available at concentrations of 2.5% , a concentration of approximately 0.07 Molar. This is a concentration of greater than 2 x 10^7 times its binding constant (K_d) of 3 nMolar. Topical thyroid hormone or thyroid hormone like topical drugs can be expected to have similar concentration ranges of activity and therefore weight percent concentrations in topical formulations.

For example, it is well known in the art that alterations in formulation can produce a poorly therapeutic cream and produce many fold changes in effective concentration of an active ingredient. The general objective in the state of the art is to produce topical therapeutics with a low concentration of active ingredient using a highly favorable formulation. But the effects of a highly favorable formulation can be achieved by utilizing a higher concentration of an active ingredient. In this way a concentration of active ingredient is not the limiting factor in a topical therapeutic; but rather the limiting factor is the combination of the formulation and the concentration of the active ingredient. (P.Clarys *et al* 1999 Skin Pharmacol Appl Skin Physiol 12:85 and Weigmann HJ et al, Skin Pharmacol Appl Skin Physiol 1999 1246-53).

Thyroid hormone compounds, in many cases, act indirectly by influencing the effects of other hormones and tissues. For example in the rat, thyroid administration increases pituitary growth hormone production which in turn affects hepatic protein production including that of alpha-2 euglobulin. Functionally, in the rat, growth hormone may act as a second message for thyroid hormone. The biology of thyroid hormone compounds has been extensively studied only after oral administration, which makes the relationship between a direct effect of thyroid hormone compounds and an indirect effect mediated by thyroid hormone modulation of other autocrine, paracrine or endocrine factors difficult to ascertain.

Orally administered thyroid hormones influence the connective tissue biology of the skin.

When given orally, thyroid hormones induce an increase in neutral salt and acid soluble collagen, but decrease insoluble collagen in the skin of guinea pigs (Drozdzm, M. et al., Endokrinologie **73**:105-111, 1979). In cell culture, fibronectin production is decreased in human fibroblasts and fibroblast glycosaminoglycans are either decreased or unchanged depending on the experimental conditions used (Murata, Y. et al., J. Clin. Endocrinol. Metab. **64**:334-339, 1987; Watxke, H. et al., Thrombosis Res. **46**:347-353, 1987; Murata, Y. et al., JCEM **57**:1233-1239, 1983; Ceccarelli, Pl, et al., JCEM **65**:242-246, 1987). Keratin gene expression for both the basal cell keratin K5 and K14 genes and the differentiation-specific K10 gene is negatively regulated by thyroid hormones in certain cell culture conditions(Tomic-Canic, M. et al., J. Invest. Dermatol. 99:842-847, 1992; Blumenberg, M. et al., J. Invest. Dermatol. **98**:42S-49S, 1992) Thyroid hormone added to fibroblasts in culture decreases collagen production (De Ryker, FEBS Lett. **174**:34-37 (1984)). Thyroid hormones inhibit cardiac collagen 1 gene activity (Lee at al, J Mol Cell Cardio p2495, 1998. Histological studies of skin from individuals who have the medical condition hyperthyroidism show an increased number of cells in the epidermis of the skin, reflected by mean epidermal cell number, increased protein turnover with increased proline incorporation and generalized increases in epidermal proliferation compared to normal skin (Holt, P.J.A. et al., Br. J. Dermatol. **95**:513-518, 1976). In human clinical biology, thyroid hormone excess leads to a general smoothing of the skin and the loss of wrinkles especially over the olecranon (elbow) surface.

Orally given thyroid hormone compounds in excess of normal bodily requirements or medical conditions which are associated with excess thyroid hormone compounds such as Grave's disease or toxic nodular goiter produce an acceleration of heart beat with associated heart failure, cardiac arrhythmias, osteoporosis, increased intestinal motility leading to diarrhoea, psychiatric abnormalities, and an increase in the basal metabolic rate. Attempts to use oral thyroid hormone compounds for diminishing lipid levels in man resulted in increased cardiac deaths.

In WO96/40048, the use of topical thyroid hormone and thyroid hormone-like compound formulations for the treatment of skin abnormalities and for controlling subcutaneous fat deposition is shown. No especial effects on the dermis are shown.

What is needed in the art is a method of treating dermal skin conditions that require regrowth of the dermis that does not suffer the drawbacks of current treatment used in the art. The present invention is believed to be an answer to that need.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides the use of at least one thyroid hormone or thyroid hormone-like agonist compound selected from those which bind to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, in the preparation of a topical medicament for the treatment of a dermatological condition affecting the dermis.

Preferably, the medicament has its predominant effect on the dermis. It may have no substantial effect, possibly no effect, on the epidermis.

The at least one one thyroid hormone compound or thyroid hormone-like agonist compound is preferably selected from the group consisting of Tri-iodothyronine (3,5,3'-triiodothyronine, T3); D and L thyroxine (T4); 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol, 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol, 3,3'5'tri-iodothyronine (reverse T3); 3,3'-diiodothyronine; T3 and T4 analogues such as 3,5,3',-Triiodo-L-thyronine methyl ester; 3,5,3'-Triiodo-L-thyronine hydrochloride; L-thyroxine hydrochloride; Tetrac (3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid); Triac ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid); Tetraprop; Triprop ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionic acid); T4Bu; T3Bu; Thyroxamine; Triiodothyronamine; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyrimidin-5-yl)-methanol; Benzyloxy-2-methoxyphenyl)-(6-methylpyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(5-bromo-2-methoxypyridin-4-yl)methanol; (5-benzyloxy-2-methoxyphenyl)-(2,6-difluoropyridin-3-yl)methanol;

(5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyridin-4-yl)methanol;
4-Methoxy-3-[(2-methoxypyrimidin-5-yl)methyl]phenol;
4-Methoxy-3-[(6-methylpyrid-3-yl)methyl]phenol; 5-Benzyloxy-2-methoxybenzyl Bromide; (5-Benzyloxy-2-methoxyphenyl-(6-chloropyridazin-3-yl)-acetonitrile;
4-Benzyloxy-2-[2-methoxythiazol-5-yl)methyl]anisole;
6-[(5-Hydroxy-2-methoxyphenyl)methyl]thiazol-2-(3H);
3'-Heteroarylmethyl-4'-)-methyl-3,5-dinitro-N-trifluoro-acetyl-L-thyronine Ethyl Esters;
3'-heteroarylmethyl-3,5-di-iodo-4')-methyl-N-trifluoro-acetyl-L-thyronine Ethyl Esters;
3'-heteroarylmethyl analogues of 3,3',5-tri-iodo-L-thyronine (T3); 3'-substituted derivatives of the thyroid hormone 3,3'5-triiodo-L-thyronine (T3); L-3,3'-T2; DL-Br2I; L-Br2iPr; L-Me2I; L-Me3; L-Me4; L-Me2IPr; DL-IMeI;
L-3,5-Dimethyl-3'-isopropylthyronine (DIMIT); DL-BPT4; B-triac; BP-tetrac; DL-SBT3; DL-SBT4; DL-MBT3; MB-tetrac; T2F; T2Cl; T2Br; T2Me; T2Et; T2iPr; T2nPr; T2sBu; T2tBu; T2iBu; T2Phe; T2F2; T2Cl2; T2Me2; 3,5,3'-Triiodo-D-thyronine;
3,5-Diiodo-4-hydroxyphenylpropionic acid (DIHPA); Aryloxamic acids; (arylamino)acetic acids; arylpropionic acids; arylthioacetic acids; (aryloxy)acetic acid; 3,3'-T2; 3,5-T2; 3',5'-T2; α-methyl-3,5,3'-triiodothyroacetic acid, α-methyl-3,5,3'-triiodothyropropionic acid, and α-methyl-3,5,3',5'-tetraiodothyropropionic acid; methylene- and carbonyl-bridged analogs of iodinated thyronines or thyroacetic acids or iodinated benzofurans;
3,5-diiodo-4-(2-N,N-diethylaminoethoxy)phenyl-(2-butylbenzofur-3-yl)methanol hydrochloride; 2-n-butyl-3-(3,5-diiodo-4-carboxymethoxy-benzoyl)benzofuran;
2-methyl-3-(3,5-diiodo-4-hydroxy-benzoyl)benzofuran;
2-methyl-3-(3,5-diiodo-4-carboxymethoxy-benzyl)benzofuran;] 4'-hydroxy-3'-iodo-3,5 diiodo-4-(2-N,N-dimethylamino-(ethoxy)benzophenone hydrochloride;
2-butyl-3-(3-iodo-4-hydroxybenzoyl)benzfuran; 4',4-dihydroxy
3'3,5-triiodo-diphenylmethane; 3,5-diethyl,3'-isopropyl thyronine (DIET); and IpTA2 (3,5 diiodo-3'isopropyl thyroacetic acid) and pharmacologically acceptable salts and derivatives thereof.

The medicament preferably comprises a concentration of 5 x 10^8 times K_d or less of the at least one thyroid hormone compound or thyroid hormone-like agonist compound. More preferably, the at least one thyroid hormone or thyroid hormone-like agonist compound

comprises less than 500 mg/100 ml, more preferably less than 200 mg/100 ml and, most preferably, less than 50 mg/100 ml, of the medicament.

The condition affecting the dermis is preferably selected from the group consisting of wounding of the dermis for example as by abrasion or a skin biopsy or chemical or other burn, photodamaged and/or photoaged skin, diabetic dermopathy and atrophy of the dermis which may result from a variety of etiologies such as intrinsically aged skin especially crinkles or wrinkles, prolonged glucocorticoid use, rheumatoid disease, poikloderma, atrophic scars, anetoderma, chronic atrophic acrodermatitis, follicular atrophoderma, vermiculate atrophoderma, atrophoderma of Pasini and Pierini, and panatrophy.

In another aspect, the invention provides the use of at least one thyroid hormone or thyroid hormone-like agonist compound selected from those which bind to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R) \bullet (L) / (RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, in the preparation of a topical medicament for the pre-treatment of skin in dermatological surgery.

In a further aspect, the present invention is directed to a method for treating a dermatological condition affecting the dermis, the method comprising the step of applying a composition to the skin of a mammal suffering from the condition, the composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound together with a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or the thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein $K_d = (R)\bullet(L)/(RL)$, where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex.

In yet another aspect, the present invention is directed to an article of manufacture comprising packaging material and a pharmaceutical agent contained within the packaging

material, wherein the pharmaceutical agent is therapeutically effective for treating a dermatological condition affecting the dermis, and wherein the packaging material comprises a label which indicates that the pharmaceutical agent can be used for treating a dermatological condition affecting the dermis, and wherein the pharmaceutical agent comprises at least one thyroid hormone compound or thyroid hormone-like agonist compound in a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or the thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein $K_d = (R)\bullet(L)/(RL)$, where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex.

In a further aspect, the present invention is directed to a composition for treating a dermatological condition affecting the dermis, the composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound selected from the group listed above and a pharmacologically acceptable base comprising oil in water emulsions, water in oil emulsions, sprays, liposomes, creams, lotions, solutions, and combinations thereof.

In yet another aspect, the present invention is directed to a method of improving healing of dermally wounded skin of a patient, comprising the step of applying a composition to the dermal wound, which may be the result of an abrasion or chemical or other burn or other dermal wound, or applying it to the skin in a preventative manner before wounding takes place, the composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound together with a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or the thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein $K_d = (R)\bullet(L)/(RL)$, where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, and wherein the healing of the wounded skin is improved.

Preferably, the dermal wound does not penetrate substantially further into the body than the dermis. For these purposes, the penetration depth may be less than 5 mm. More preferably, the dermal wound does not penetrate the dermis. In another aspect, the present invention is

directed to a method of dermatological surgical pretreatment of a patient, comprising the step of applying a composition to the skin of the patient prior to dermatological surgery, the composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound together with a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or the thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} wherein $K_d = (R)\bullet(L)/(RL)$, where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex.

The invention also provides, in yet another aspect, the use of at least one thyroid hormone or thyroid hormone-like agonist agonist compound selected from those which bind to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, in the preparation of a topical medicament for improving the healing of wounds which have not penetrated the dermis.

In still a further aspect, the invention provides the use of at least one thyroid hormone or thyroid hormone-like agonist compound selected from those which bind to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, in the preparation of a medicament for increasing the number and activity of fibroblasts in the dermis.

Another aspect of the invention provides a method of increasing the number and activity of fibroblasts in the dermis the method comprising the step of applying a composition to the skin of the patient, the composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound together with a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or thyroid hormone-like agonist agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex.

Furthermore, a further aspect of the invention provides The use of at least one thyroid hormone or thyroid hormone-like agonist compound selected from those which bind to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, in the preparation of a topical medicament for increasing the thickness of the dermis of a mammal.

One further aspect of the invention provides a method of increasing the thickness of the dermis of a mammal, the method comprising the step of applying a composition to the skin of the patient, the composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound together with a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex.

These and other aspects will become apparent from the following drawings and detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be more fully understood from the following detailed description taken in conjunction with the accompanying drawings in which:

Figure 1 is a biopsy micrograph analysis (200x magnification) of mouse skin treated with betamethasone and visualized with van Gieson, and/or hematoxylin/eosin stains;

Figure 2 is a biopsy micrograph analysis (200x magnification) of mouse skin treated with

betamethasone plus 0.8 mM Triac and visualized with van Gieson, and/or hematoxylin/eosin stains;

Figure 3 is biopsy micrograph analysis (100x magnification) of treatment of mouse skin with Triac and visualized with van Gieson, and/or hematoxylin/eosin stains;

Figure 4 is a photograph showing a volunteer's forearm extensor skin surface after 5 months of control cream-placebo formulation;

Figure 5 is a photograph showing a volunteer's forearm extensor skin surface after 5 months of treatment with the composition of the invention;

Figure 6 is a photograph showing a volunteer's forearm volar forearm skin surface after five months of treatment with the composition of the invention;

Figure 7 is a photograph showing a volunteer's forearm volar forearm skin surface after 5 months of treatment with a control composition;

Figure 8 is a photograph showing a volunteer's control extensor forearm and biopsy site;

Figure 9 is a photograph showing a volunteer's experimental extensor forearm and biopsy site; and

Figure 10 is a graph showing the results of a human *in vivo* trial on the effects of a formulation of TriAc on skin pro-collagen production.

DETAILED DESCRIPTION OF THE INVENTION

Agents which improve the structure and integrity of the dermis and increase the thickness of the dermis are not well known. It has now been found that topical application of a composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound in a pharmacologically acceptable base is effective in treating the dermis of the skin. Thyroid hormone compounds or thyroid hormone-like agonist compounds have also been found to diminish easy bruising of the skin. They also provide an improved cosmetic appearance to aging, atrophied, steroid-affected, or sun damaged skin which exhibits fragility, transparency, mottling, and appearance of capillaries. They also reverse

and prevent the dermal atrophy induced by glucocorticoids . These conditions are improved or reversed, according to the method of the invention, by application of the above topical composition. Other dermal conditions which may be improved by regrowth and replenishment of the dermis include, but are not limited to, wounding of the dermis, for example by abrasion, a chemical or other burn, or by a skin biopsy, photodamaged and/or photoaged skin, diabetic dermopathy, , , and atrophy of the dermis which may result from a variety of etiologies such as intrinsically aged skin especially crinkles or wrinkles, prolonged glucocorticoid use, rheumatoid disease, poikloderma, atrophic scars, anetoderma, chronic atrophic acrodermatitis, follicular atrophoderma, vermiculate atrophoderma, atrophoderma of Pasini and Pierini, and panatrophy (page 1764ff Textbook of Dermatology, Rook, Wilkinson, Ebling, fifth edition 1992).

Medical textbooks define thyroids as those hormones that circulate in the human body, namely T-3 (Tri-iodothyronine, 3,5,3'-triiodothyronine and T-4 (D and L thyroxine) and their metabolites. However, it s now clear that many compounds which possess thyroid hormone activity may have considerably different chemical structure, including for example the loss of an amino acid group or the elimination of iodine from the molecule. Accordingly, for the purposes of this invention a "thyroid hormone compound" or "thyroid hormone-like compound", which terms are used interchangeably herein, is any chemical entity, including peptides, which binds to thyroid hormone receptor TR-α or β with a dissociation constant, K_d, of less than 5×10^{-6} molar (Goodman and Gilman, The Pharmacologic Basis of Therapeutics, p. 30, 1975) when measured by any of the methods known in the art. Furthermore, the thyroid hormone receptor binding drug should be active when applied topically at a concentration no higher than 0.1 Molar. Such ligands may be considered agonists when they have similar agonistic effects as the natural hormone or may be considered antagonists when the compounds antagonize the effects of the natural hormone compounds. Partial agonist/antagonists also may exist. Suitable ligands may be agonists or antagonists. The thyroids may be any natural or synthetic analog of triiodothyroacetic acid ("Triac") which binds to the thyroid hormone receptor within the above range of K_d and possesses the biological activity of triiodothyroacetic acid.

For the purposes of this invention, the term thyroid hormone receptor will include all of the

gene products of C-erb-A and its variants which bind thyroid hormone compounds or thyroid hormone-like compounds.

Additionally, the terms steroids, glucocorticoids, and corticosteroids are used interchangeably for the dermatological purposes described herein.
As indicated above, the present invention is directed to a method for treating the dermis, reversing, or preventing dermal skin atrophy, and helping to regrow and replenish the dermis. The method of the present invention comprises the step of apply a composition to the skin of a mammal suffering from the dermis of the skin, the composition comprising at least one thyroid hormone compound or thyroid hormone-like compound together with a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or the thyroid hormone-like compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein $K_d = (R)\bullet(L)/(RL)$, where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, and wherein the the dermis of the skin is reduced. The present invention is also directed to an article of manufacture comprising packaging material and a pharmaceutical agent contained within said packaging material. The pharmaceutical agent is therapeutically effective for treating the dermis of the skin, and comprises at least one thyroid hormone compound or thyroid hormone-like compound in a pharmacologically acceptable base suitable for topical application, wherein said thyroid hormone compound or said thyroid hormone-like compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M. The packaging material comprises a label which indicates that the pharmaceutical agent can be used for treating the dermisof the skin.

The thyroid hormone compound or thyroid hormone-like agonist compound may be any compound that meets the above definition. Suitable thyroid hormone or thyroid hormone-like agonist compounds include Tri-iodothyronine (3,5,3'-triiodothyronine, T3); D and L thyroxine (T4); 3,3'5'tri-iodothyronine (reverse T3); 3,3'-diiodothyronine; T3 and T4 analogues such as 3,5,3',-Triiodo-L-thyronine methyl ester; 3,5,3'-Triiodo-L-thyronine hydrochloride; L-thyroxine hydrochloride; Tetrac (3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid); Triac

([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid); Tetraprop; Triprop ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionic acid); T4Bu; T3Bu; Thyroxamine; Triiodothyronamine; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyrimidin-5-yl)-methanol; Benzyloxy-2-methoxyphenyl)-(6-methylpyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(5-bromo-2-methoxypyridin-4-yl)methanol; (5-benzyloxy-2-methoxyphenyl)-(2,6-difluoropyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyridin-4-yl)methanol; 4-Methoxy-3-[(2-methoxypyrimidin-5-yl)methyl]phenol; 4-Methoxy-3-[6-methylpyrid-3-yl)methyl]phenol; 5-Benzyloxy-2-methoxybenzyl Bromide; (5-Benzyloxy-2-methoxyphenyl-(6-chloropyridazin-3-yl)-acetonitrile; 4-Benzyloxy-2-[2-methoxythiazol-5-yl)methyl]anisole; 6-[(5-Hydroxy-2-methoxyphenyl)methyl]thiazol-2-(3H); 3'-Heteroarylmethyl-4'-)-methyl-3,5-dinitro-N-trifluoro-acetyl-L-thyronine ethyl esters; 3'-heteroarylmethyl-3,5-di-iodo-4')-methyl-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl analogues of 3,3',5-tri-iodo-L-thyronine (T3); 3'-substituted derivatives of the thyroid hormone 3,3'5-triiodo-L-thyronine (T3); L-3,3'-T2; DL-Br2I; L-Br2IPr; L-Me2I; L-Me3; L-Me4; L-Me2IPr; DL-IMeI; L-3,5-Dimethyl-3'-isopropylthyronine (DIMIT); DL-BPT4; B-triac; BP-tetrac; DL-SBT3; DL-SBT4; DL-MBT3; MB-tetrac; T2F; T2Cl; T2Br; T2Me; T2Et; T2iPr; T2nPr; T2sBu; T2tBu; T2iBu; T2Phe; T2F2; T2Cl2; T2Me2; 3,5,3'-Triiodo-D-thyronine; 3,5-Diiodo-4-hydroxyphenylpropionic acid (DIHPA); Aryloxamic acids; (arylamino)acetic acids; arylpropionic acids; arylthioacetic acids; (aryloxy)acetic acid; 3,3'-T2; 3,5-T2; 3',5'-T2; a-methyl-3,5,3'-triiodothyroacetic acid, a-methyl-3,5,3'-triiodothyropropionic acid, and a-methyl-3,5,3',5'-tetraiodothyropropionic acid; methylene- and carbonyl-bridged analogs of iodinated thyronines or thyroacetic acids or iodinated benzofurans; 3,5-diiodo-4-(2-N,N-diethylaminoethoxy)phenyl-(2-butylbenzofur-3-yl)methanol hydrochloride; 2-methyl-3-(3,5-diiodo-4-(2-N,N-diethylamino-ethoxy)-benzoyl)benzofuran hydrochloride; 2-n-butyl-3-(3,5-diiodo-4-carboxymethoxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-hydroxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-carboymethoxy-benzyl)benzofuran; [4'-hydroxy-3'-iodo-3,5 diiodo-4-(2-N,N-dimethylamino-ethoxy)benzophenone hydrochloride;

2-butyl-3-(3-iodo-4-hydroxybenzoyl)benzofuran; 4',4-dihydroxy 3'3,5-triiodo-diphenylmethane; 3,5-diiodo-4-(2-N,N-diethylaminoethoxy)phenyl-(2-butylbenzofur-3-yl)methanol hydrochloride; 2-methyl-3-(3,5-diiodo-4-(2-N,N-diethylamino-ethoxy)-benzoyl)benzofuran hydrochloride; 2-n-butyl-3-(3,5-diiodo-4-carboxymethoxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-hydroxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-carboxymethoxy-benzyl)benzofuran; 4'-hydroxy-3'-iodo-3,5-diiodo-4-(2-N,N-dimethylamino-ethoxy)benzophenone hydrochloride; 2-butyl-3-(3-iodo-4-hydroxybenzoyl)benzofuran; 4',4-dihydroxy-3'3,5-triiodo-diphenylmethane; 3,5-diethyl,3'-isopropyl thyronine (DIET); and IpTA2 (3,5 diiodo-3'isopropyl thyroacetic acid) and pharmacologically acceptable salts and derivatives thereof.

The thyroid hormone compound or thyroid hormone-like agonist compound is preferably in pure form, i.e., not contaminated with other compounds greater than about 0.1%.

The thyroid hormone compound or thyroid hormone-like agonist compound is preferably at least partially dissolved in a solvent. The solvent is preferably an organic solvent selected from alcohol and alcohol and water solutions. More preferably, the organic solvent is selected from isopropanol, isopropanol and water, ethanol, and ethanol and water solutions containing at least 20% alcohol.

As described above, the thyroid hormone compound or thyroid hormone-like agonist compound is mixed with a pharmacologically acceptable base that is suitable for topical application. Examples of suitable pharmacologically acceptable bases include oil in water (or water in oil) emulsions, sprays, liposomes, creams, lotions, solutions, and combinations thereof. The composition may also include suitable epidermal penetration-enhancing agents. The pharmacologically acceptable base is preferably an oil in water emulsion, a cream, or an alcoholic solution with glycerol. One particularly preferred pharmacologically acceptable base composition is a cream that includes linoleic, oleic, palmitic, and linolenic fatty acids or esters thereof and/or combined with triglycerides. This composition is preferably combined with one or more additional substituents including glyceryl stearate, safflower oil, sorbitol, cetyl alcohol, stearic acid, triethanolamine, and the like.

Preferably, the composition comprises less than about 500 mg/100 ml, more preferably less than about 100 mg/100 ml of the thyroid hormone compound or thyroid hormone-like agonist compound. Preferably the composition comprises a concentration 5×10^8 times or less than the receptor dissociation constant, K_d, of the said at least one thyroid hormone compound or thyroid hormone-like agonist compound. Preferably the composition is used to supply an effective amount of the thyroid hormone compound or thyroid hormone-like agonist compound which generally ranges from 500 mg/m^2 to 0.1 mg/m^2 in one or more applications, preferably 250 mg/m^2 to 1 mg/m^2 per day in one or more applications. A useful amount to apply is 100 ml – 1000 ml at the above concentrations. As will be appreciated by those skilled in the art, the effective concentration of the thyroid hormone compound or thyroid hormone-like agonist compound will depend on factors such as metabolism of the compound, the pharmaceutical or cosmetic base employed, and the like.

The composition of the invention may also include other additional ingredients such as Vitamin D, estrogens, glucocorticoids and retinoids or analogues thereof to potentiate and modify the effects of the thyroid hormone compound or thyroid hormone-like agonist compound for increased benefit. The composition may also include BHT (butylated hydroxy toluene) or BHA (butylated hydroxy anisole) as a hindered phenol to decrease iodine decomposition or oxidation. Furthermore, the composition may include compounds which facilitate passage of the thyroid hormone through the skin and compounds which act as sunscreens such as PABA. Preferably, the composition also includes a suitable antioxidant such as Tinuvin P or vitamin E. The choice of such compounds is within the scope of the skilled addressee. See for example Hermens W.A.J. J Pharmaceutisch Weekblad Scientific Edition 14(4A) 1992. Preferably, the thyroid hormone compound or thyroid hormone-like agonist compound is not halogenated as such compounds are less prone to photodecomposition.

The composition used in the method of the invention is preferably applied to the skin of a mammal suffering from a dermatologic condition which affects the dermis of the skin, and more preferably to the skin of a human suffering from the dermis of the skin. Preferably, the composition is applied from twice a day to every three days.

Topical administration of thyroid hormone to the skin allows direct thyroid hormone to

modulation of the skin without influence by modulating factors produced in the pituitary, liver, or other organs. Further, the extensive metabolism by the liver and kidney of thyroid hormones into inactive metabolites is avoided by topical application. However, the dermatological effect of topically applied thyroid hormones in humans and animals is for the most part entirely unknown, and no medical publications appear which relate to this topic.

The topically-applied thyroid hormone compounds, or thyroid hormone-like agonist compounds, used in the compositions and methods of the present invention are advantageous in that they enable the use of these chemical compounds to treat dermal skin atrophy, and helping to regrow and replenish the dermis, or normalize the physiology of the skin under pathophysiologic conditions without causing the undue adverse effects of orally administered thyroid hormone compounds, and avoids renal and hepatic metabolism of the thyroid hormone receptor binding chemical entity. In particular, the method of delivery of the thyroid hormone compounds and thyroid hormone-like agonist compounds avoids liver and kidney metabolism of the hormones, blood circulation of the hormones to other tissue and binding to blood carrier proteins which can alter efficacy. Moreover, topical administration of the composition of the invention should not cause a hyperthyroid state.

The compositions and methods of the present invention are also useful for improving healing of wounded skin of a patient, as shown in detail in Example 3 below.

The compositions and methods of the present invention are also useful for pretreatment of a patient's skin prior to dermatologic surgery. It has been found that application of the composition of the present invention to the skin prior to dermatologic surgery results in faster healing of the skin in the weeks following the surgery. While not wishing to be bound by any particular theory, it is thought that the topically-applied thyroid hormone compounds or thyroid hormone-like agonist compounds treat the dermis by increasing the cellularity and thickness of the dermis and by an associated increase in collagen fibers, among other biological substances.

EXAMPLES

The invention is further described by the following Examples, but is not intended to be

limited by the Examples. All parts and percentages are by weight and all temperatures are in degrees Celsius unless explicitly stated otherwise.

Example 1

Prevention of Glucocorticoid-Induced Atrophy in Normal Mice by Thyroid Hormones or Thyroid Hormone-like Agonists

Normal Balb/c mice were used for the experiments. 100 ml solution of either betamethasone (0.2 mM in 50% isopropanol/water), topical thyroid agonist (Triac, Triprop, 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol (KB-067), 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol (KB-026) in 50% isopropanol/water at various concentrations, or both were applied daily to the shaved back of the animals for one week. Biopsies were taken and the thickness of the dermal layer was measured microscopically after staining of collagen with Van Gieson stain. Five mice were used for each measurement at each concentration of test material and 5 sections were averaged from each mouse. Therefore each averaged measurement represents 25 determinations. Figures 1-3 and Tables 1 and 2 show the effects of a range of doses of Triac or Triac cream in preventing betamethasone-induced atrophy after one week.In Figures 1-3, the arrows show the dermal layer which is predominantly collagen fibers. In some of the Experiments, Triac was used in an isopropanol waer vehicle or formulated as a 0.2%, 0.1% or 0.03% cream and 100 ml was applied to the mice.

Figure 1 shows a biopsy micrograph analysis (200x magnification) of mouse skin treated with betamethasone alone for one week, which is known to cause dermal skin atrophy. As shown in Figure 1, the dermis appears to be very thinned, and some of the deep dermis has pulled away from the fat and muscle layer of the subcutaneous tissues (a biopsy fixation artifact).

Figure 2 shows a biopsy micrograph analysis (200x magnification) of mouse skin treated with 0.2 mM betamethasone plus 0.8 mM Triac, both in 50% isopropanol/water for one week. As shown in Figure 2, the dermis is almost double the thickness of the skin treated with betamethasone alone shown in Figure 1. Although mucopolysacharides or hyaluronic acid were not specifically stained, it is likely that the increased dermal thickness was due to an increase both in the collagen fibrils and also likely the ground substance. Thus, the

Triac appears to be preventing betamethasone-induced dermal skin atrophy.

Example 2

Increase in dermal thickness in Normal mice

Figure 3 shows a biopsy micrograph analysis (100x magnification) of treatment of mouse skin with Triac alone for one week. As shown in Figure 3, the dermis is very dense and thicker than that shown in Figure 2. Compared to normal mouse skin, the collagen layers are very thick and dense. Additionally, as shown in Table 2 below, Triac treated skin increased to 0.79 mm as compared to 0.54 mm in a mouse treated with isopropanol/water alone, almost a 50% increase in the dermis. Therefore, Triac by itself can improve skin thickness in the absence of betamethasone-induced atrophy. Thyroid hormone or thyroid hormone-like agonists therefore help to regrow, replenish and thicken the dermis and may be useful for in-vitro use in the production, development and use of artificial skin (skin equivalents) or natural skin grafts.

Table 1 – Effect of Various Concentrations of TriAc on Corticosteroid-Induced Skin Atrophy in a Mouse Model									
Group	Thickness of dermis (mm) in 5 low power fields (x10)					mean (mm)	SD	no of mice	*p
Betamethasone 0.2 mM	0.38	0.37	0.36	0.40	0.35	0.37	0.01	5	
Bet. + 0.0008 mM TriAc	0.40	0.40	0.36	0.38	0.36	0.38	0.02	4	
Bet. + 0.008 mM TriAc	0.40	0.47	0.48	0.44	0.46	0.45	0.02	5	
Bet. + 0.08 mM TriAc	0.50	0.48	0.53	0.49	0.50	0.50	0.02	5	<0.05
Bet. + 0.8 mM TriAc	0.49	0.54	0.51	0.48	0.48	0.50	0.02	5	<0.05
Bet. + 8 mM TriAc	0.52	0.50	0.47	0.52	0.49	0.50	0.02	5	<0.05
Vehicle (50% isopropanol/water)	0.53	0.45	0.52	0.51	0.49	0.50	0.01	5	<0.05

Table 2 -- Effect of Various Concentrations of TriAc and TriAc Cream on Betamethasone-induced Skin Atrophy in a Mouse Model									
Group	Thickness of dermis (mm) in 5 low power fields (x10)					mean (mm)	SD	no of mice	*p
Betamethasone 0.2 mM	0.39	0.41	0.37	0.37	0.4	0.39	0.02	5	
Bet. + TriAc 0.0008 mM	0.4	0.37	0.4	0.43	0.4	0.40	0.02	4	
Bet. + TriAc 0.008 mM	0.41	0.37	0.4	0.43	0.4	0.40	0.02	5	
Bet. + TriAc 0.08 mM	0.52	0.53	0.45	0.5	0.52	0.50	0.03	5	<0.05
Bet. + TriAc 0.8 mM	0.54	0.6	0.6	0.56	0.62	0.58	0.03	5	<0.05
TriAc 0.8 mM	0.72	0.82	0.84	0.76	0.82	0.79	0.05	5	<0.05
Bet. + placebo cr.	0.35	0.4	0.37	0.39	0.4	0.38	0.02	5	
Bet. + TriAc cr. (0.01 % TriAc)	0.46	0.48	0.5	0.49	0.5	0.49	0.02	5	<0.05
Bet. + TriAc cr. (0.03 % TriAc)	0.5	0.58	0.56	0.55	0.58	0.55	0.03	5	<0.05
Vehicle (50 % propanol/water)	0.6	0.58	0.57	0.59	0.58	0.58	0.01	4	<0.05

*p is defined as the probability that the result is due to chance alone.

"cr." = hydrophilic cream

As can be seen in Tables 1 and 2, a gradual increase in effectiveness occurs as the concentration of Triac increases from 0.0008 to 8 mM, with the effect saturating at approximately 0.8 mM.

Table 3 shows the effects of Triac alone, Triac cream, TriProp, 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol, 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol on betamethasone-induced skin atrophy in a mouse model.

Table 3 -- Effect of Various Concentrations of Triac cream, TriProp, 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol (KB-067), 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol (KB-026) on Betamethasone-Induced Skin Atrophy in a Mouse Model

Group	Thickness (mm) of dermis in 5 low power fields (mm)					mean (mm)	SD	no of mice	*p
Triac 0.8 mM	0.72	0.82	0.84	0.76	0.82	0.079			
Betamethasone 0.2 mM	0.50	0.38	0.41	0.42	0.39	0.42	0.05	4	
Bet. 0.2 mM + placebo cr.	0.40	0.42	0.38	0.40	0.39	0.40	0.01	5	
Bet. + TriAc cr. (0.01 % TriAc)	0.50	0.52	0.45	0.53	0.50	0.50	0.03	5	<0.05
Bet. + TriAc cr. (0.03 %)	0.50	0.55	0.60	0.56	0.57	0.56	0.04	5	<0.05
Bet + TriAc cr. (0.2%)	0.50	0.56	0.58	0.50	0.58	0.55	0.04	5	
Bet. + 0.0008 mM KB-026	0.40	0.41	0.40	0.42	0.41	0.41	0.01	4	
Bet. + 0.008 mM KB-026	0.45	0.42	0.46	0.44	0.45	0.44	0.01	4	
Bet. + 0.08 mM KB-026	0.44	0.50	0.49	0.46	0.50	0.48	0.03	4	
Bet. + 0.8 mM KB-026	0.50	0.52	0.48	0.51	0.50	0.50	0.01	4	<0.05
Bet. + 0.0008 mM TriProp	0.41	0.40	0.46	0.40	0.41	0.42	0.03	4	
Bet. + 0.008 mM TriProp	0.45	0.50	0.40	0.42	0.48	0.45	0.04	4	
Bet. + 0.08 mM TriProp	0.50	0.48	0.47	0.50	0.44	0.48	0.02	4	
Bet. + 0.8 mM TriProp	0.50	0.45	0.47	0.48	0.52	0.48	0.03	4	
Bet. + 0.0008 mM KB-067	0.42	0.39	0.40	0.39	0.40	0.40	0.01	4	
Bet. + 0.008 mM KB-067	0.40	0.39	0.41	0.40	0.39	0.40	0.01	4	
Bet. + 0.08 mM KB-067	0.40	0.40	0.41	0.39	0.41	0.40	0.01	4	
Bet. + 0.8 mM KB-067	0.45	0.46	0.47	0.45	0.48	0.46	0.01	4	
Vehicle (50 % propanol/water)	0.52	0.55	0.53	0.56	0.55	0.54	0.02	4	<0.05

*p is defined as the probability that the result is due to chance alone.
"cr." = hydrophilic cream

As shown in Table 3, all compounds were capable of preventing betamethasone-induced atrophy and thinning of the dermis. Each was effective at a slightly different concentration range. A 200 mg/ml TriAc containing cream however was equally effective or somewhat worse than a 7 fold lower concentration of triac in vehicle, exemplifying the differences in therapeutic effectiveness is not only determined by the amount of active material in the formulation, but by the formulation itself. From the above tables, one can therefore conclude that topical thyroids including tri-iodothryoacetic acid (triac) and others are effective at preventing glucocorticoid-induced dermal skin atrophy in mice.

Example 3

Treatment of Atrophy in a Human with multifactorial dermal atrophy

A 78-year old volunteer with rheumatoid arthritis displayed tissue paper thin transparent skin on the forearm, with atrophy of the dermis, epidermis and subcutaneous fat, and easy bruisability. The forearm skin showed the effects of aging, photodamage, rheumatoid disease and also, potentially, orally glucocorticoids, although the dosage was physiologic. The patient had a history of rheumatoid arthritis treated with oral prednisone, but had been currently receiving only an oral maintenance dose (5 mg) of prednisone for a period of many years. Multiple bruises covered each forearm extensor surface. Surface capillaries were visible through the skin and the forearms had a brown cast (Figure 4).

A hydrophilic vanishing cream containing 30 mg of Triac per 100 ml vehicle alone was prepared as follows. Triac was added in 10 ml of 70% isopropanol per 120 ml vehicle and mixed to produce a 29 mg Triac per 100 ml cream. After 8 weeks of application, the cream was further diluted with vehicle (a mixture of glyceryl stearate, safflower oil containing linoleic, oleic, palmitic, linolenic, and other fatty acid substituents, sorbitol, cetyl alcohol, stearic acid, triethanolamine) to produce the 10 mg/ml cream one part plus two parts vehicle, and subsequently diluted again in the same manner to produce a 3.3 mg/100 ml cream after another 8 weeks.

The above preparations were applied to the other forearm of the patient in a blinded fashion for a period of approximately six months. Due to the effects of the cream, patient blinding became

impossible after approximately eight weeks. The following dose schedule was used in a consecutive manner: (1) Eight weeks of 30 mg Triac per 100 ml vehicle, followed by (2) 4 weeks of 10 mg Triac per 100 ml vehicle, followed by (3) 12 weeks of 3.3 mg Triac per 100 ml vehicle.

At the 30 mg/ml, 5.6% isopropanol dose some pruritus occurred which was infrequent and did not prevent cream application. No pruritus occurred at the lowered dosages. During the treatment period, the patient had intermittent courses of prednisone ranging from 10 to 30 mg per day for periods up to two weeks.

Clinically, a change in the skin could be seen in eight weeks, and was remarked upon by untrained observers. Purpura (bruising) was markedly decreased in the treated arm (Figure 5). After a total of six months of treatment, the patient was examined by a dermatologist. On blinded clinical examination, the treated arm (Figures 5, 6, and 9) appeared healthier with more even pigmentation, less brown cast, less wrinkling and slightly higher turgor and elasticity than the control arm (Figures 4, 7, and 8). Superficial veins were also more difficult to detect.

After six months of treatment, 3 mm punch biopsies were taken to identical depths. Biopsy of the extensor surface of the control forearm revealed solar elastosis, orthokeratosis, with epidermal and prominent dermal atrophy and reduced collagen with a flattened dermal -epidermal border. Biopsy of the extensor surface of the treated arm revealed no dermal atrophy and increased cellularity of the dermis, and continued solar elastosis, orthokeratosis, and evidence for hyperkeratosis and lessened epidermal atrophy. The rete pegs had become elongated and the dermal -epidermal border was no longer flattened. The major effect was on the dermis; effects on the epidermis were significantly less. Physically the treated specimen was thicker than the untreated one. Trichrome staining revealed an increase in collagen fibers in the reticular dermis in the treated specimen. No other specific stains were used to identify other substances in the dermis other that collagen, but it would be likely that the increase in thickness of the sample and the restoration of a normal dermis was not due only to collagen. Eccrine glands were situated far more superficially in the untreated side and there was an increased cellularity in the treated sample.After the biopsy, bruising around the biopsy occurred in the control forearm associated with the biopsy site and also with the bandage (Figure 8). It did not develop in the

treated arm (Figure 9). The treated arm also has a greatly reduced purpuric response to day to day injury and the wound at the biopsy site healed more readily (Figure 9).

Skin thickness measurements were performed with a spring-loaded micrometer during skin tenting. The results are show in Table 4.

Table 4 – Skin Thickness Measurements

Site	Double Skin Measurement	Calculated Thickness
Treated Extensor Forearm	2.16 mm	1.08 mm
Untreated Extensor Forearm	1.65 mm	0.83 mm

As shown in Table 4, double thickness skin measurements were taken from the extensor surface of each forearm, revealing a 0.25 mm single skin thickness difference in apparent skin thickness, or a 30% increase in the thickness of the skin.

Example 4

Effect of TriAc on dermal thickness, collagen production and number of activated fibroblasts in humans

Further testing of a 0.1% TriAc cream was perfomed in humans. Normal volunteers first applied betamethasone valerate cream, a potent topical glucocorticoid to an area of one side of the abdomen for three days. A full thickness skin biopsy was taken after application for three days within the treated area (visit 3). Triac cream at 0.1% concentration was then applied for 14 days and another biopsy was taken in taken within the treated area (visit 5 treated). A third biopsy was taken in opposite side of the abdomen in a non treated area which received neither active formulation or placebo formulation (Visit 5 no treatment). Five patients receiving an identical vehicle without the TriAc were evaluated in the same manner, but biopsies were not performed at Visit 3 for some patients. Measurement of both the dermis and epidermis thickness at all three visits were performed on three patients receiving 0.1% TriAc cream. The histological samples were sectioned into at least 5 slices and 5 measurements were made of each dermis and epidermis (see Table 5). Additional measurements were made of the numbers of activated fibroblasts in the samples for many of the patients as shown in Table 6.

Epidermal and dermal thickness measurements and percent change in dermis from Visit 5 treated

and not treated areas. In this short study with only a three day steroid application and a two week treatment period, most patients recovered their glucocorticoid induced histological changes in the epidermal and dermal thickness whether in the placebo or treated groups. However the study design allowed comparison between areas treated with either placebo or active drug with matching skin areas which received no drug or vehicle (not treated).

Table 5

Dermal and Epidermal Measurements:

Treatment with TriAc cream or placebo -vehicle	Patient	Visit/ area of biopsy	Epidermis	Dermis	Range of dermal measure in the five measurements taken	% change in Dermis visit 5 treated versus visit 5 not treated area
0.1%	103	3	.13	2.31		
		5 treated	.13	3.44	3.44-3.44	
		5 not treated	.13	2.37	2.37-2.37	45%
	105	3	.23	4.94		
		5 treated	.23	8.48	8.44-8.53	
		5 not treated	.23	6.61	6.57-6.44	28%
	116	3	.10	1.21		
		5 treated	.10	1.59	1.57-1.63	
		5 not treated	.10	1.51	1.4-1.57	5%
placebo	102	3	Poorly determined	2.3		
		5 treated	.17	2.86	2.86-2.86	
		5 not treated	.17	2.45	2.43-2.46	17%
placebo	118	3	.10			
		5 treated	.15	2.02	2.0-2.04	none
		5 not treated	.14	1.98	1.93-2.04	
	106	5 treated		5.92	5.87-5.94	none
		5 not treated		5.88	5.83-5.9	

Treatment with TriAc cream or placebo -vehicle	Patient	Visit/ area of biopsy	Epidermis	Dermis	Range of dermal measure in the five measurements taken	% change in Dermis visit 5 treated versus visit 5 not treated area
	108	5 treated		2.71	2.66-2.74	none
		5 not treated		2.70	2.63-2.77	
	110	5 treated		2.09	2.03-2.01	-15%
		5 not treated		2.37	2.37-2.37	

Table 6

Immunohistochemistry change in the number of activated fibroblasts from visit 3 to end of treatment (No. of positive cells in five high power fields)

	n	Mean	Std	Min	Median	Max
Placebo	4	10.50	6.61	3.00	10.00	19.00
TRIAC 0.1%	5	21.80	14.82	1.00	22.00	39.00

The above data, albeit obtained in only a few patients clearly show the ability of TriAC creams applied topically to increase the thickness of the dermis, in one case up to 45% above the thickness of a paired sample in an untreated area. The three samples that were available for analysis showed 5% ,28% ,and 45% increases in dermal thickness as compared to untreated normal skin. Patients receiving only vehicle had responses relative to a untreated site of 17%, -15%, 0,0 and 0%. Furthermore there was a doubling of the number of activated fibroblasts measured from just after steroid treatment to the end of 14 days of treatment in the group treated with 0.1% TriAc compared to the placebo group (Table 6). The increase in the dermal size was

likely due to collagen production and to an increase in ground substance since activated fibroblasts are known to produce both substances. The collagen structure as observed in the skin had a trend toward thickened collagen fibers. The result is surprising since in cell culture skin fibroblasts and rat cardiac fibroblasts have been shown to decrease their collagen production in response to thyroid hormone.(De Ryker, FEBS Lett. **174**:34-37 (1984), Lee at al, J Mol Cell Cardio p2495, 1998.)The ability of thyroid hormone like compounds to increase the thickness of the dermis, to increase the cellularity of the dermis, to increase the collagen production in the dermis suggeest that thyroid creams will act whenever a condition presents that requires restoration of the dermis from an atrophied or injured state.

Example 5
The effect of formulation on drug release
Release tests in formulation development

The Institute for Applied Dermato-Pharmacie at Martin-Luther Universität in Halle (Saale), Germany (IAPD) was contacted and it was decided to test their *in vitro* release model as a tool for formulation development. The release model was developed by Professor Reinhardt Neubert (Neubert, R., Bendas, C., Wohlrab, W., Gienau, B., Furst, W. A multilayer membrane system for modelling drug penetration into skin *Int J. Pharm.* **75** (1991) 89-94;
Knorst, M., Neubert, R., Wohlrab, W. Release of urea from semisolid formulations using a multilayer membrane system. *Drug Dev. Ind. Pharm.* **23** (1997) 253-257) and has been used to evaluate the release of urea and dithranol and other dermatological drugs from different topical formulations. The model is based on the release of the active ingredient from the vehicle into a layer of gel-membranes of dolichol/ propylene glycol manufactured to mimic human stratum corneum. The composition of the membranes was developed to give the same release profile of reference compounds as in explanted human skin. The in-vitro release method has been validated versus release methods in explanted human skin. (Neubert *et al.* and Knorst *et al.* above).

The release method is standardized and data obtained on a particular formulation can be used to predict if the formulation will have clinical efficacy (that is, if the release rate of the drug will be fast or slow). A fast release rate of a drug-substance from the formulation to the membranes

predicts for fast release into stratum corneum and thus clinical efficacy of the drug formulation. The method has significant advantages over traditional release systems (such as Franz-cells) and was developed to compare generic formulations of drugs. The method has not yet obtained a regulatory status (i.e. a release profile of a drug from a generic formulation is not accepted in a registration file).

An oil-in-water cream formulation (F1) was developed containing (% w/w) deionized water (77-79), octyl palmitate (5.0), cetostearyl alcohol (1.0), glyceryl monostearate (6.0), cetyl alcohol (2.0), stearic acid (3.0), sorbitol (2.8), triethanolamine (0.4 - 0.8), methylparaben (0.2), propylparaben (0.1), Dowicil 200 (0.1), imidurea (0.3), disodium EDTA (0.2), isopropanol (0.7), carbopol 980 (0.2) and TriAc (0.03 or 0.1). (Dowicil is 94%, 1-(3-chloroallyl)-3,5,7-triaZa-1-azoniaadomaniane chloride). Manufacture of the formulation started with heating the water to 75-85° C under stirring then adding methylparaben, propylparaben, EDTA, thickening agent (Carbopol) and sorbitol. The emollients and emulsifiers were then blended at 75-85° C and this oil-phase was added to the water-phase. Then triethanolamine was added to adjust pH to around 6.1-7.1. The vessel temperature was then reduced to 60° C and imidurea or Promulgen was added. TriAc was dissolved in isopropanol (70%) and incorporated in the cream.

The multilayer membrane system (MMS)-method was used for evaluation of release of TriAc from the formulation into the membranes (see Neubert *et al.* and Knorst *et al.* above). In each of the experiments reported herein, around 10 mg of the formulation was placed on top of a pack of membranes. Samples were then incubated at 32° C for 30, 100 and 300 minutes (n=5). TriAc was then extracted from the membranes by shaking each membrane in absolute ethanol. The membrane was then removed and the ethanol-fraction was injected into an HPLC-system. The total amount of TriAc (as % fraction of total TriAc added in the cream) in the membranes was plotted as "TriAc-released" versus incubation time. AUC (Area Under Curve) in the interval 0-100 minutes was calculated.

Table 7 shows the release data for a set of batches of the inventive formulation (F1) and two other TriAc formulations. TriAc was incorporated in Essex-cream dissolved in propylene glycol.

TriAcana™ is a commercial formulation of TriAc (registered in France for obesity treatment). F1 was first produced as a pilot-batch in the formulation development program. Later, large scale batches of F1 containing 0.1% TriAc (F1A, F1B, F1C) or 0.03% TriAc (F1D, F1E, F1F) were manufactured on three occasions in accordance with GMP. F1TestA is a test batch where TriAc was added to the oil phase instead (oil phase addition of TriAc) and therefore this variant did not include isopropanol. In the test batch F1TestB TriAc was added to the oil-phase as well but the same amount of isopropanol as used in all other batches was also added to the cream.

Table 7 - Comparison between different formulations and batches for TriAc release in the MMS-model.

Product	Strength (% TriAc)	TriAc added	Released 30 min	Released 100 min	Released 300 min	AUC 0→100 min mg*min	AUC 0→100 min % *min
Essex-cream	0.1%	10 mg	1.1+/-0.2 mg (11+/-2 %)	2.5+/-0.2 mg (25+/-2%)	3.2+/-0.3 mg (32.+/-3%)	144+/-11	1436+/-108
TriAcana™	0.2%	20 mg	1.4+/-0.4 mg (8.1+/-2.5 %)	5.5+/-0.6 mg (31+/-3.2%)	11+/-0.6 mg (63+/-3.4%)	265+/-37	1480+/-209
F1 pilot batch	0.1%	10 mg	3.5+/-0.5 mg (35.4+/-5%)	5.5+/-0.4 mg (55.2+/-4%)	5.5+/-0.2 mg (54.9+/-2%)	371+/-43	3706+/-427
F1A	0.1%	10 mg	3.9+/-0.4 mg (39.3+/-4 %)	6.5+/-0.4 mg (65.3+/-5 %)	6.9+/-0.3 mg (69.5+/-3 %)	425+/-19	4255+/-187
F1D	0.03%	3.3 mg	1.3+/-0.1 mg (43.1+/-4 %)	1.9+/-0.1 mg (63.2+/-4 %)	2.2+/-0.1 mg (72.8+/-2 %)	131+/-8	4365+/-264

Product	Strength (% TriAc)	TriAc added	Released 30 min	Released 100 min	Released 300 min	AUC 0→100 min mg*min	AUC 0→100 min % *min
F1B		10 mg	4.6+/-0.3 mg	6.7+/-0.4 mg	6.6+/-0.3 mg	463+/-30	
	0.1%		(45.8+/-3 %)	(66.9+/-4 %)	(65.5+/-3 %)		4633+/-295
F1E		3.3 mg	1.3+/-0.2 mg	2.1+/-0.2 mg	2.0+/-0.1 mg	138+/-15	
	0.03%		(44.0+/-6 %)	(69.0+/-6 %)	(66.2+/-4 %)		4616+/-510
F1C		10 mg	5.1+/-0.2 mg	7.1+/-0.4 mg	7.2+/-0.2 mg	503+/-24	
	0.1%		(50.9+/-2 %)	(71.0+/-4 %)	(72.3+/-2 %)		5028+/-268
F1F		3.3 mg	1.4+/-0.1 mg	2.1+/-0.1 mg	2.0+/-0.1 mg	143+/-11	
	0.03%		(46.1+/-5 %)	(70.4+/-4 %)	(66.9+/-3 %)		4772+/-370
F1TestA		10 mg	4.1+/-0.4 mg	7.3+/-0.5 mg	7.3+/-0.1 mg	461+/-10	
	0.1%		(41.4+/-4 %)	(72.7+/-5 %)	(73.2+/-1 %)		4614+/-101

Product	Strength (% TriAc)	TriAc added	Released 30 min	Released 100 min	Released 300 min	AUC 0→100 min mg*min	AUC 0→100 min % *min
F1TestB	0.1%	10 mg	4.9+/-0.6 mg (48.9+/-6 %)	7.2+/-0.2 mg (71.9+/-2 %)	7.1+/-0.2 mg (71.0+/-2 %)	496+/-31	4962+/-309

Results and Conclusions

Based upon empirical observations by experts on the method (Professor R. Neubert, IAPD), a fast release predicts greater clinical efficacy. The fastest theoretical release that could be obtained in the MMS-model would be if 100% of the test compound were retrieved in the membranes after 30 minutes. However, such a fast release rate has never been seen in any studies with the MMS-model and a release of 40-50% of the active compound after 30 minutes (as with F1) is considered as superior to the values seen for the Essex-cream and for TriAcana™. An alternative way to compare release-rate from different products is to calculate the AUC (Area Under Curve) as % released x minute for the first 100 minutes. The AUC 0→100 min is around three times larger for F1 than for the other products Essex-cream and TriAcana™.

If the fastest theoretical release was obtained (100% in 30 minutes), the value of AUC after 100 min. would be 8500 (% x min.). Final batches of TriAc (0.03-0.1%) in F1 (i.e. F1A to F1F) all show a release rate larger than 50% of 8500. This is in contrast to less than 20% of 8500 for Essex-cream and TriAcana formulations.

The results obtained are very similar for different batches of F1 and this demonstrates the usefulness of the MMS-method as a tool for quality control to compare batch-to batch variations or to evaluate whether generic formulations of TriAc can be predicted to have the same clinical efficacy as F1.

The results obtained also indicate that the same percentage of TriAc is released from the low dosage form (0.03%) as from the high dosage form (0.1%). In addition, the results indicate that the release rate of TriAc from F1 is not dependent on how TriAc is added to the cream-base. The manufacturing process for F1TestB and F1TestA differed from the process for the other batches in that TriAc was added to the oil-phase during manufacture (see example 1) rather than being added as the last ingredient to the cooled cream-base. Moreover, the similarity in release rates between F1TestA and all other batches of F1 indicates that isopropanol may be omitted from the cream-base. Importantly, release rate and therefore vehicle suitability were superior with the F1 type formulation over the Triacana formulation despite a 7 fold difference in concentration of TriAc in the material. In fact the release rate of a .03% ceram was more than double the 0.2% Triacana cream. It is well known in the art that

formulations can make a topical drug more or less potent simply by manipulating the formulation. The release studies closely parallel the clinical results in the mouse study described in Example 2 above.

Example 6

Formulation F1 efficacy studies in clinical trials

A human clinical trial with TriAc in F1 has been completed. The trial was a single centre, phase I study of two doses of TriAc (0.03% or 0.1% w/w) in comparison with placebo (F1 cream base) on the effect on skin pro-collagen production. The trial was performed at the Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden. The trial was a double blind, parallel group, comparative, randomized, single centre study. The volunteers were randomized to receive either 0.03 % TriAc, 0.1 % TriAc or placebo cream. There were six volunteers per treatment group. The abdominal area of the body was treated. The primary objective was to compare the change in skin pro-collagen types I and III.

It is known that topical betamethasone (a potent corticosteroid frequently used to treat various inflammatory dermatological conditions) leads to reduced synthesis of collagen in dermal fibroblasts. It has been demonstrated that three days of topical treatment with betamethasone (and with other potent corticosteroids) leads to a significant reduction (around 70% decrease from base-line) in expression of pro-collagen I (pro-collagens are precursors to collagen) and that the recovery is slow. Even after a 14 day corticosteroid-free period, pro-collagen production was decreased by 50% (Haapasaari K-M, Risteli J, Koivukangas V, Oikarinen A., Comparison of the effect of hydrocortisone, hydrocortisone-17-butyrate and betamethasone on collagen synthesis in human skin in vivo. *Acta Derm Venerol* (Stockholm) **75** (1995) 269-271). The precursor to another collagen (collagen III) is also known to be regulated by topical treatment with bethamethasone in a similar manner to pro-collagen I.

The amounts of pro-collagens (the aminoterminal propeptides of type I and type III collagens, PINP and PIIINP) in the dermis can be measured by radioimmunoassays on suction blister fluids (Kiistla U. Suction blister device for separation of viable epidermis from dermis. *J. Invest Dermatol* **50** (1968) 220-5). The suction blisters were induced and the fluid in the blisters was collected for analysis.

Figure 10 shows a representative response to treatment with F1-placebo or F1-TriAc (0.03%). The subjects' abdominal skin was treated with topical betamethasone (twice/day) for three days (day 0-3). The areas of skin were then treated with F1-placebo or with F1-TriAc (0.03%) respectively for 14 days.

Suction blister fluids were obtained on days 3, 10 and 17 and the content of PINP was determined and compared with baseline value. PINP content is shown in Figure 2 as % of baseline value.

The results demonstrate that treatment with F1-TriAc (0.03%) restores PINP-expression in betamethasone treated skin faster than treatment with F1-placebo. Since PINP is a precursor to collagen this implies that treatment with F1-TriAc (0.03%) will increase the thickness and elasticity of the dermis and thus restore dermal atrophy.

While the invention has been described in combination with embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, it is intended to embrace all such alternatives, modifications and variations as fall within the spirit and broad scope of the appended claims. All patent applications, patents, and other publications cited herein are incorporated by reference in their entireties.

Claims

1. The use of at least one thyroid hormone or thyroid hormone-like agonist compound selected from those which bind to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, in the preparation of a topical medicament for the treatment of a dermatological condition affecting the dermis.

2. Use according to claim 1, wherein the medicament has its predominant effect on the dermis.

3. Use according to claim 1, wherein the medicament has no substantial effect on the epidermis.

4. Use according to any preceding claim, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound is selected from the group consisting of Tri-iodothyronine (3,5,3'-triiodothyronine, T3); D and L thyroxine (T4); 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol, 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol, 3,3'5'tri-iodothyronine (reverse T3); 3,3'-diiodothyronine; T3 and T4 analogues such as 3,5,3',-Triiodo-L-thyronine methyl ester; 3,5,3'-Triiodo-L-thyronine hydrochloride; L-thyroxine hydrochloride; Tetrac (3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid); Triac ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid); Tetraprop; Triprop ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionic acid); T4Bu; T3Bu; Thyroxamine; Triiodothyronamine; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyrimidin-5-yl)-methanol; Benzyloxy-2-methoxyphenyl)-(6-methylpyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(5-bromo-2-methoxypyridin-4-yl)methanol; (5-benzyloxy-2-methoxyphenyl)-(2,6-difluoropyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyridin-4-yl)methanol;

4-Methoxy-3-[(2-methoxypyrimidin-5-yl)methyl]phenol;
4-Methoxy-3-[(6-methylpyrid-3-yl)methyl]phenol; 5-Benzyloxy-2-methoxybenzyl Bromide; (5-Benzyloxy-2-methoxyphenyl-(6-chloropyridazin-3-yl)-acetonitrile;
4-Benzyloxy-2-[2-methoxythiazol-5-yl)methyl]anisole;
6-[(5-Hydroxy-2-methoxyphenyl)methyl]thiazol-2-(3H);
3'-Heteroarylmethyl-4'-)-methyl-3,5-dinitro-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl-3,5-di-iodo-4')-methyl-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl analogues of 3,3',5-tri-iodo-L-thyronine (T3);
3'-substituted derivatives of the thyroid hormone 3,3'5-triiodo-L-thyronine (T3);
L-3,3'-T2; DL-Br2I; L-Br2iPr; L-Me2I; L-Me3; L-Me4; L-Me2IPr; DL-IMeI;
L-3,5-Dimethyl-3'-isopropylthyronine (DIMIT); DL-BPT4; B-triac; BP-tetrac;
DL-SBT3; DL-SBT4; DL-MBT3; MB-tetrac; T2F; T2Cl; T2Br; T2Me; T2Et; T2iPr;
T2nPr; T2sBu; T2tBu; T2iBu; T2Phe; T2F2; T2Cl2; T2Me2;
3,5,3'-Triiodo-D-thyronine; 3,5-Diiodo-4-hydroxyphenylpropionic acid (DIHPA);
Aryloxamic acids; (arylamino)acetic acids; arylpropionic acids; arylthioacetic acids;
(aryloxy)acetic acid; 3,3'-T2; 3,5-T2; 3',5'-T2; α-methyl-3,5,3'-triiodothyroacetic acid,
α-methyl-3,5,3'-triiodothyropropionic acid, and
α-methyl-3,5,3',5'-tetraiodothyropropionic acid; methylene- and carbonyl-bridged analogs of iodinated thyronines or thyroacetic acids or iodinated benzofurans;
3,5-diiodo-4-(2-N,N-diethylaminoethoxy)phenyl-(2-butylbenzofur-3-yl)methanol hydrochloride; 2-n-butyl-3-(3,5-diiodo-4-carboxymethoxy-benzoyl)benzofuran;
2-methyl-3-(3,5-diiodo-4-hydroxy-benzoyl)benzofuran;
2-methyl-3-(3,5-diiodo-4-carboxymethoxy-benzyl)benzofuran;] 4'-hydroxy-3'-iodo-3,5 diiodo-4-(2-N,N-dimethylamino-(ethoxy)benzophenone hydrochloride;
2-butyl-3-(3-iodo-4-hydroxybenzoyl)benzfuran; 4',4-dihydroxy
3'3,5-triiodo-diphenylmethane; 3,5-diethyl,3'-isopropyl thyronine (DIET); and IpTA2 (3,5 diiodo-3'isopropyl thyroacetic acid) and pharmacologically acceptable salts and derivatives thereof.

5. Use according to any preceding claim, wherein the medicament comprises a concentration of 5 x 10^8 times K_d or less of the at least one thyroid hormone compound or thyroid hormone-like agonist compound.

6. Use according to any preceding claim, wherein said at least one thyroid hormone compound or said thyroid hormone-like agonist compound is in chemically pure form.

7. Use according to any preceding claim, wherein the medicament comprises a pharmacologically acceptable base selected from the group consisting of oil in water emulsions, water in oil emulsions, sprays, liposomes, creams, lotions, solutions, and combinations thereof.

8. Use according to claim 7, wherein the pharmacologically acceptable base comprises one or more fatty acids, esters, or triglycerides selected from the group consisting of linoleic, oleic, palmitic, and linolenic fatty acids, esters, or triglycerides.

9. Use according to any preceding claim, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound is at least partially dissolved in a solvent.

10. Use according to claim 9, wherein the solvent is an organic solvent.

11. Use according to claim 10, wherein the solvent comprises water and an alcohol.

12. Use according to claim 11, wherein the alcohol is selected from the group consisting of isopropanol, ethanol, and combinations thereof.

13. Use according to any of claims 1 to 4 and 6 to 12, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 500 mg/100 ml of said medicament.

14. Use according to claim 13, wherein the at at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 200 mg/100 ml of said medicament.

15. Use according to claim 14, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 50 mg/100 ml of said medicament.

16. Use according to any preceding claim, wherein the condition affecting the dermis is selected from the group consisting of wounding of the dermis for example as by abrasion or a skin biopsy or chemical or other burn, photodamaged and/or photoaged skin, diabetic dermopathy, and atrophy of the dermis which may result from a variety of etiologies such as intrinsically aged skin especially crinkles or wrinkles, prolonged glucocorticoid use, rheumatoid disease, poikloderma, atrophic scars, anetoderma, chronic atrophic acrodermatitis, follicular atrophoderma, vermiculate atrophoderma, atrophoderma of Pasini and Pierini, and panatrophy.

17. Use according to any preceding claim, wherein the at least one thyroid hormone or thyroid hormone-like agonist compound is selected from the group consisting of tri-iodothyroacetic acid, tri-iodopropionic acid, 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol and 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol.

18. Use according to claim 1, wherein the condition affecting the dermis is characterised by a deficiency of collagen in the skin and wherein the at least one thyroid hormone or thyroid hormone-like agonist compound comprises less than 500 mg/100 ml, but more than 50 mg/100 ml of the medicament.

19. A composition for treating a dermatological condition affecting the dermis, the composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound selected from the group consisting of Tri-iodothyronine (3,5,3'-triiodothyronine, T3); D and L thyroxine (T4); 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol, 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol, 3,3'5'tri-iodothyronine (reverse T3); 3,3'-diiodothyronine; T3 and T4 analogues such as 3,5,3',-Triiodo-L-thyronine methyl ester; 3,5,3'-Triiodo-L-thyronine hydrochloride;

L-thyroxine hydrochloride; Tetrac (3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid); Triac ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid); Tetraprop; Triprop ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionic acid); T4Bu; T3Bu; Thyroxamine; Triiodothyronamine; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyrimidin-5-yl)-methanol; Benzyloxy-2-methoxyphenyl)-(6-methylpyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(5-bromo-2-methoxypyridin-4-yl)methanol; (5-benzyloxy-2-methoxyphenyl)-(2,6-difluoropyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyridin-4-yl)methanol; 4-Methoxy-3-[(2-methoxypyrimidin-5-yl)methyl]phenol; 4-Methoxy-3-[(6-methylpyrid-3-yl)methyl]phenol; 5-Benzyloxy-2-methoxybenzyl Bromide; (5-Benzyloxy-2-methoxyphenyl-(6-chloropyridazin-3-yl)-acetonitrile; 4-Benzyloxy-2-[2-methoxythiazol-5-yl)methyl]anisole; 6-[(5-Hydroxy-2-methoxyphenyl)methyl]thiazol-2-(3H); 3'-Heteroarylmethyl-4'-)-methyl-3,5-dinitro-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl-3,5-di-iodo-4')-methyl-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl analogues of 3,3',5-tri-iodo-L-thyronine (T3); 3'-substituted derivatives of the thyroid hormone 3,3'5-triiodo-L-thyronine (T3); L-3,3'-T2; DL-Br2I; L-Br2iPr; L-Me2I; L-Me3; L-Me4; L-Me2IPr; DL-IMeI; L-3,5-Dimethyl-3'-isopropylthyronine (DIMIT); DL-BPT4; B-triac; BP-tetrac; DL-SBT3; DL-SBT4; DL-MBT3; MB-tetrac; T2F; T2Cl; T2Br; T2Me; T2Et; T2iPr; T2nPr; T2sBu; T2tBu; T2iBu; T2Phe; T2F2; T2Cl2; T2Me2; 3,5,3'-Triiodo-D-thyronine; 3,5-Diiodo-4-hydroxyphenylpropionic acid (DIHPA); Aryloxamic acids; (arylamino)acetic acids; arylpropionic acids; arylthioacetic acids; (aryloxy)acetic acid; 3,3'-T2; 3,5-T2; 3',5'-T2; α-methyl-3,5,3'-triiodothyroacetic acid, α-methyl-3,5,3'-triiodothyropropionic acid, and α-methyl-3,5,3',5'-tetraiodothyropropionic acid; methylene- and carbonyl-bridged analogs of iodinated thyronines or thyroacetic acids or iodinated benzofurans; 3,5-diiodo-4-(2-N,N-diethylaminoethoxy)phenyl-(2-butylbenzofur-3-yl)methanol hydrochloride; 2-n-butyl-3-(3,5-diiodo-4-carboxymethoxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-hydroxy-benzoyl)benzofuran;

2-methyl-3-(3,5-diiodo-4-carboxymethoxy-benzyl)benzofuran;] 4'-hydroxy-3'-iodo-3,5 diiodo-4-(2-N,N-dimethylamino-(ethoxy)benzophenone hydrochloride; 2-butyl-3-(3-iodo-4-hydroxybenzoyl)benzfuran; 4',4-dihydroxy 3'3,5-triiodo-diphenylmethane; 3,5-diethyl,3'-isopropyl thyronine (DIET); and IpTA2 (3,5 diiodo-3'isopropyl thyroacetic acid) and pharmacologically acceptable salts and derivatives thereof, together with a pharmacologically acceptable base comprising oil in water emulsions, water in oil emulsions, sprays, liposomes, creams, lotions, solutions, and combinations thereof.

20. A composition according to claim 19, wherein the at least one thyroid hormone or thyroid hormone-like agonist compound is selected from the group consisting of tri-iodothyroacetic acid, tri-iodopropionic acid, 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol, 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol.

21. A composition according to claim 19 or claim 20,wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 500 mg/100 ml of said composition.

22. A composition according to claim 21, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 200 mg/100 ml of said composition.

23. A composition according to claim 22, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 50 mg/100 ml of said composition.

24. A composition according to any of claims 19 to 23, wherein the pharmacologically acceptable base further comprises one or more fatty acids, esters, or triglycerides selected from the group consisting of linoleic, oleic, palmitic, and linolenic fatty acids, esters, or triglycerides.

25. A composition according to any of claims 19 to 24, wherein the condition affecting the dermis is selected from the group consisting of wounding of the dermis for example as by abrasion or a skin biopsy or chemical of other burn, diabetic dermopathy, and atrophy of the dermis which may result from a variety of etiologies such as intrinsically aged skin especially crinkles or wrinkles, prolonged glucocorticoid use, rheumatoid disease, poikloderma, atrophic scars, anetoderma, chronic atrophic acrodermatitis, follicular atrophoderma, vermiculate atrophoderma, atrophoderma of Pasini and Pierini, and panatrophy.

26. The use of at least one thyroid hormone or thyroid hormone-like agonist compound selected from those which bind to TR-β or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R) \bullet (L) / (RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, in the preparation of a topical medicament for the pre-treatment of skin in dermatological surgery.

27. Use according to claim 26, wherein the compound is selected from the group consisting of Tri-iodothyronine (3,5,3'-triiodothyronine, T3); D and L thyroxine (T4); 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol, 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol, 3,3'5'tri-iodothyronine (reverse T3); 3,3'-diiodothyronine; T3 and T4 analogues such as 3,5,3',-Triiodo-L-thyronine methyl ester; 3,5,3'-Triiodo-L-thyronine hydrochloride; L-thyroxine hydrochloride; Tetrac (3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid); Triac ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid); Tetraprop; Triprop ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionic acid); T4Bu; T3Bu; Thyroxamine; Triiodothyronamine; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyrimidin-5-yl)-methanol; Benzyloxy-2-methoxyphenyl)-(6-methylpyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(5-bromo-2-methoxypyridin-4-yl)methanol; (5-benzyloxy-2-methoxyphenyl)-(2,6-difluoropyridin-3-yl)methanol;

(5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyridin-4-yl)methanol;
4-Methoxy-3-[(2-methoxypyrimidin-5-yl)methyl]phenol;
4-Methoxy-3-[(6-methylpyrid-3-yl)methyl]phenol; 5-Benzyloxy-2-methoxybenzyl Bromide; (5-Benzyloxy-2-methoxyphenyl-(6-chloropyridazin-3-yl)-acetonitrile;
4-Benzyloxy-2-[2-methoxythiazol-5-yl)methyl]anisole;
6-[(5-Hydroxy-2-methoxyphenyl)methyl]thiazol-2-(3H);
3'-Heteroarylmethyl-4'-)-methyl-3,5-dinitro-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl-3,5-di-iodo-4')-methyl-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl analogues of 3,3',5-tri-iodo-L-thyronine (T3);
3'-substituted derivatives of the thyroid hormone 3,3'5-triiodo-L-thyronine (T3);
L-3,3'-T2; DL-Br2I; L-Br2iPr; L-Me2I; L-Me3; L-Me4; L-Me2IPr; DL-IMeI;
L-3,5-Dimethyl-3'-isopropylthyronine (DIMIT); DL-BPT4; B-triac; BP-tetrac;
DL-SBT3; DL-SBT4; DL-MBT3; MB-tetrac; T2F; T2Cl; T2Br; T2Me; T2Et; T2iPr;
T2nPr; T2sBu; T2tBu; T2iBu; T2Phe; T2F2; T2Cl2; T2Me2;
3,5,3'-Triiodo-D-thyronine; 3,5-Diiodo-4-hydroxyphenylpropionic acid (DIHPA);
Aryloxamic acids; (arylamino)acetic acids; arylpropionic acids; arylthioacetic acids;
(aryloxy)acetic acid; 3,3'-T2; 3,5-T2; 3',5'-T2; α-methyl-3,5,3'-triiodothyroacetic acid, α-methyl-3,5,3'-triiodothyropropionic acid, and
α-methyl-3,5,3',5'-tetraiodothyropropionic acid; methylene- and carbonyl-bridged analogs of iodinated thyronines or thyroacetic acids or iodinated benzofurans;
3,5-diiodo-4-(2-N,N-diethylaminoethoxy)phenyl-(2-butylbenzofur-3-yl)methanol hydrochloride; 2-n-butyl-3-(3,5-diiodo-4-carboxymethoxy-benzoyl)benzofuran;
2-methyl-3-(3,5-diiodo-4-hydroxy-benzoyl)benzofuran;
2-methyl-3-(3,5-diiodo-4-carboxymethoxy-benzyl)benzofuran;] 4'-hydroxy-3'-iodo-3,5 diiodo-4-(2-N,N-dimethylamino-(ethoxy)benzophenone hydrochloride;
2-butyl-3-(3-iodo-4-hydroxybenzoyl)benzfuran; 4',4-dihydroxy
3'3,5-triiodo-diphenylmethane; 3,5-diethyl,3'-isopropyl thyronine (DIET); and IpTA2 (3,5 diiodo-3'isopropyl thyroacetic acid) and pharmacologically acceptable salts and derivatives thereof.

28. Use according to claim 27, wherein the compound is selected from the group consisting of tri-iodothyroacetic acid, tri-iodopropionic acid,

4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol and 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol.

29. Use according to any of claims 26 to 28, wherein the medicament comprises a pharmacologically acceptable base comprising oil in water emulsions, water in oil emulsions, sprays, liposomes, creams, lotions, solutions, and combinations thereof.

30. Use according to any of claims 26 to 29, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 500 mg/100 ml of said composition.

31. Use according to claim 30, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 200 mg/100 ml of said composition.

32. Use according to claim 31, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 50 mg/100 ml of said composition.

33. Use according to any one of claims 29 to 32, wherein the pharmacologically acceptable base further comprises one or more fatty acids, esters, or triglycerides selected from the group consisting of linoleic, oleic, palmitic, and linolenic fatty acids, esters, or triglycerides.

34. A method for treating a dermatological condition affecting the dermis, comprising the step of applying a composition to the skin of a patient suffering from the condition, said composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound together with a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, and wherein the dermal effects of the condition are reduced.

35. The method of claim 34, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound is selected from the group consisting of Tri-iodothyronine (3,5,3'-triiodothyronine, T3); D and L thyroxine (T4); 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol, 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol, 3,3'5'tri-iodothyronine (reverse T3); 3,3'-diiodothyronine; T3 and T4 analogues such as 3,5,3',-Triiodo-L-thyronine methyl ester; 3,5,3'-Triiodo-L-thyronine hydrochloride; L-thyroxine hydrochloride; Tetrac (3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid); Triac ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid); Tetraprop; Triprop ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionic acid); T4Bu; T3Bu; Thyroxamine; Triiodothyronamine; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyrimidin-5-yl)-methanol; Benzyloxy-2-methoxyphenyl)-(6-methylpyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(5-bromo-2-methoxypyridin-4-yl)methanol; (5-benzyloxy-2-methoxyphenyl)-(2,6-difluoropyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyridin-4-yl)methanol; 4-Methoxy-3-[(2-methoxypyrimidin-5-yl)methyl]phenol; 4-Methoxy-3-[(6-methylpyrid-3-yl)methyl]phenol; 5-Benzyloxy-2-methoxybenzyl Bromide; (5-Benzyloxy-2-methoxyphenyl-(6-chloropyridazin-3-yl)-acetonitrile; 4-Benzyloxy-2-[2-methoxythiazol-5-yl)methyl]anisole; 6-[(5-Hydroxy-2-methoxyphenyl)methyl]thiazol-2-(3H); 3'-Heteroarylmethyl-4'-)-methyl-3,5-dinitro-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl-3,5-di-iodo-4')-methyl-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl analogues of 3,3',5-tri-iodo-L-thyronine (T3); 3'-substituted derivatives of the thyroid hormone 3,3'5-triiodo-L-thyronine (T3); L-3,3'-T2; DL-Br2I; L-Br2iPr; L-Me2I; L-Me3; L-Me4; L-Me2IPr; DL-IMeI; L-3,5-Dimethyl-3'-isopropylthyronine (DIMIT); DL-BPT4; B-triac; BP-tetrac;

DL-SBT3; DL-SBT4; DL-MBT3; MB-tetrac; T2F; T2Cl; T2Br; T2Me; T2Et; T2iPr; T2nPr; T2sBu; T2tBu; T2iBu; T2Phe; T2F2; T2Cl2; T2Me2; 3,5,3'-Triiodo-D-thyronine; 3,5-Diiodo-4-hydroxyphenylpropionic acid (DIHPA); Aryloxamic acids; (arylamino)acetic acids; arylpropionic acids; arylthioacetic acids; (aryloxy)acetic acid; 3,3'-T2; 3,5-T2; 3',5'-T2; α-methyl-3,5,3'-triiodothyroacetic acid, α-methyl-3,5,3'-triiodothyropropionic acid, and α-methyl-3,5,3',5'-tetraiodothyropropionic acid; methylene- and carbonyl-bridged analogs of iodinated thyronines or thyroacetic acids or iodinated benzofurans; 3,5-diiodo-4-(2-N,N-diethylaminoethoxy)phenyl-(2-butylbenzofur-3-yl)methanol hydrochloride; 2-n-butyl-3-(3,5-diiodo-4-carboxymethoxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-hydroxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-carboxymethoxy-benzyl)benzofuran;] 4'-hydroxy-3'-iodo-3,5 diiodo-4-(2-N,N-dimethylamino-(ethoxy)benzophenone hydrochloride; 2-butyl-3-(3-iodo-4-hydroxybenzoyl)benzfuran; 4',4-dihydroxy 3'3,5-triiodo-diphenylmethane; 3,5-diethyl,3'-isopropyl thyronine (DIET); and IpTA2 (3,5 diiodo-3'isopropyl thyroacetic acid) and pharmacologically acceptable salts and derivatives thereof.

36. The method of claim 35, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound is selected from the group consisting of tri-iodothyroacetic acid, tri-iodopropionic acid, 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol and 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol.

37. The method of any of claims 34 to 36, wherein the composition comprises a concentration of 5×10^8 times K_d or less of the at least one thyroid hormone compound or thyroid hormone-like agonist compound.

38. The method of any of claims 34 to 37, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound is in chemically pure form.

39. The method of any of claims 34 to 38, wherein the pharmacologically acceptable base

is selected from the group consisting of oil in water emulsions, water in oil emulsions, sprays, liposomes, creams, lotions, solutions, and combinations thereof.

40. The method of any of claims 34 to 39, wherein the pharmacologically acceptable base comprises one or more fatty acids, esters, or triglycerides selected from the group consisting of linoleic, oleic, palmitic, and linolenic fatty acids, esters, or triglycerides.

41. The method of any of claims 34 to 40, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound is at least partially dissolved in a solvent.

42. The method of claim 41, wherein the solvent is an organic solvent.

43. The method of claim 42, wherein the organic solvent comprises water and an alcohol.

44. The method of claim 43, wherein the alcohol is selected from the group consisting of isopropanol, ethanol, and combinations thereof.

45. The method of any of claims 34 to 44, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 500 mg/100 ml of said composition.

46. The method of claim 45, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 200 mg/100 ml of said composition.

47. The method of claim 46, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 50 mg/100 ml of said composition.

48. The method of any of claims 34 to 47, wherein the condition is selected from the group consisting of wounding of the dermis for example as by abrasion or a skin biopsy or

chemical or other burn, photodamaged and/or photoaged skin, diabetic dermopathy, and atrophy of the dermis which may result from a variety of etiologies such as intrinsically aged skin especially crinkles or wrinkles, prolonged glucocorticoid use, rheumatoid disease, poikloderma, atrophic scars, anetoderma, chronic atrophic acrodermatitis, follicular atrophoderma, vermiculate atrophoderma, atrophoderma of Pasini and Pierini, and panatrophy.

49. The method of any of claims 34 to 48, wherein the composition has its predominant effect on the dermis.

50. The method of any of claims 34 to 49, wherein the composition has no substantial effect on the epidermis.

51. An article of manufacture comprising packaging material and a pharmaceutical agent contained within the packaging material, wherein the pharmaceutical agent is therapeutically effective for treating a dermatological condition affecting the dermis, and wherein the packaging material comprises a label which indicates that the pharmaceutical agent can be used for treating a dermatological condition affecting the dermis, and wherein the pharmaceutical agent comprises at least one thyroid hormone compound or thyroid hormone-like agonist compound in a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or said thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex.

52. The article of manufacture of claim 51, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound is selected from the group consisting of Tri-iodothyronine (3,5,3'-triiodothyronine, T3); D and L thyroxine (T4); 3,3'5'tri-iodothyronine (reverse T3); 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol,

4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol, 3,3'-diiodothyronine; T3 and T4 analogues such as 3,5,3',-Triiodo-L-thyronine methyl ester; 3,5,3'-Triiodo-L-thyronine hydrochloride; L-thyroxine hydrochloride; Tetrac (3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid); Triac ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid); Tetraprop; Triprop ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionic acid); T4Bu; T3Bu; Thyroxamine; Triiodothyronamine; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyrimidin-5-yl)-methanol; Benzyloxy-2-methoxyphenyl)-(6-methylpyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(5-bromo-2-methoxypyridin-4-yl)methanol; (5-benzyloxy-2-methoxyphenyl)-(2,6-difluoropyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyridin-4-yl)methanol; 4-Methoxy-3-[(2-methoxypyrimidin-5-yl)methyl]phenol; 4-Methoxy-3-[(6-methylpyrid-3-yl)methyl]phenol; 5-Benzyloxy-2-methoxybenzyl Bromide; (5-Benzyloxy-2-methoxyphenyl-(6-chloropyridazin-3-yl)-acetonitrile; 4-Benzyloxy-2-[2-methoxythiazol-5-yl)methyl]anisole; 6-[(5-Hydroxy-2-methoxyphenyl)methyl]thiazol-2-(3H); 3'-Heteroarylmethyl-4'-)-methyl-3,5-dinitro-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl-3,5-di-iodo-4')-methyl-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl analogues of 3,3',5-tri-iodo-L-thyronine (T3); 3'-substituted derivatives of the thyroid hormone 3,3'5-triiodo-L-thyronine (T3); L-3,3'-T2; DL-Br2I; L-Br2iPr; L-Me2I; L-Me3; L-Me4; L-Me2IPr; DL-IMeI; L-3,5-Dimethyl-3'-isopropylthyronine (DIMIT); DL-BPT4; B-triac; BP-tetrac; DL-SBT3; DL-SBT4; DL-MBT3; MB-tetrac; T2F; T2Cl; T2Br; T2Me; T2Et; T2iPr; T2nPr; T2sBu; T2tBu; T2iBu; T2Phe; T2F2; T2Cl2; T2Me2; 3,5,3'-Triiodo-D-thyronine; 3,5-Diiodo-4-hydroxyphenylpropionic acid (DIHPA); Aryloxamic acids; (arylamino)acetic acids; arylpropionic acids; arylthioacetic acids; (aryloxy)acetic acid; 3,3'-T2; 3,5-T2; 3',5'-T2; α-methyl-3,5,3'-triiodothyroacetic acid, α-methyl-3,5,3'-triiodothyropropionic acid, and α-methyl-3,5,3',5'-tetraiodothyropropionic acid; methylene- and carbonyl-bridged analogs of iodinated thyronines or thyroacetic acids or iodinated benzofurans; 3,5-diiodo-4-(2-N,N-diethylaminoethoxy)phenyl-(2-butylbenzofur-3-yl)methanol

hydrochloride; 2-n-butyl-3-(3,5-diiodo-4-carboxymethoxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-hydroxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-carboxymethoxy-benzyl)benzofuran;] 4'-hydroxy-3'-iodo-3,5 diiodo-4-(2-N,N-dimethylamino-(ethoxy)benzophenone hydrochloride; 2-butyl-3-(3-iodo-4-hydroxybenzoyl)benzfuran; 4',4-dihydroxy 3'3,5-triiodo-diphenylmethane; 3,5-diethyl,3'-isopropyl thyronine (DIET); and IpTA2 (3,5 diiodo-3'isopropyl thyroacetic acid) and pharmacologically acceptable salts and derivatives thereof.

53. The article of manufacture of claim 51 or claim 52, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound is selected from the group consisting of
tri-iodothyroacetic acid, tri-iodopropionic acid,
4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol and
4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol, and combinations thereof.

54. The article of manufacture of claim 52 or claim 53, wherein the composition comprises a concentration of 5×10^8 times K_d or less of the at least one thyroid hormone compound or thyroid hormone-like agonist compound.

55. The article of manufacture of any of claims 52 to 54, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound is in chemically pure form.

56. The article of manufacture of any of claims 51 to 55, wherein the pharmacologically acceptable base is selected from the group consisting of oil in water emulsions, water in oil emulsions, sprays, liposomes, creams, lotions, solutions, and combinations thereof.

57. The article of manufacture of any of claims 52 to 56, wherein the pharmacologically acceptable base comprises one or more fatty acids, esters, or triglycerides selected from the group consisting of linoleic, oleic, palmitic, and linolenic fatty acids, esters, or triglycerides.

58. The article of manufacture of any of claims 52 to 57, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound is at least partially dissolved in a solvent.

59. The article of manufacture of claim 58, wherein the solvent is an organic solvent.

60. The article of manufacture of claim 59, wherein the organic solvent comprises water and an alcohol.

61. The article of manufacture of claim 60, wherein the alcohol is selected from the group consisting of isopropanol, ethanol, and combinations thereof.

62. The article of manufacture of any of claims 52 to 61, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 500 mg/100 ml of said composition.

63. The article of manufacture of claim 62, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 200 mg/100 ml of said composition.

64. The article of manufacture of claim 62, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 50 mg/100 ml of said composition.

65. The article of manufacture of any of claims 51 to 64, wherein the condition affecting the dermis is selected from the group consisting of wounding of the dermis for example as by abrasion or a skin biopsy, photodamaged and/or photoaged skin or chemical or other burn, diabetic dermopathy, and atrophy of the dermis which may result from a variety of etiologies such as intrinsically aged skin especially crinkles or wrinkles, prolonged glucocorticoid use, rheumatoid disease, poikloderma, atrophic scars, anetoderma, chronic atrophic acrodermatitis, follicular atrophoderma, vermiculate

atrophoderma, atrophoderma of Pasini and Pierini, and panatrophy.

66. A method of improving healing of dermally wounded skin of a patient, comprising the step of applying a composition to the dermal wound, the composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound together with a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5 x 10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, and wherein the healing of the wounded skin is improved.

67. The method of claim 66, wherein the composition comprises at least one thyroid hormone compound or thyroid hormone-like agonist compound selected from the group consisting of Tri-iodothyronine (3,5,3'-triiodothyronine, T3); D and L thyroxine (T4); 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol, 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol, 3,3'5'tri-iodothyronine (reverse T3); 3,3'-diiodothyronine; T3 and T4 analogues such as 3,5,3',-Triiodo-L-thyronine methyl ester; 3,5,3'-Triiodo-L-thyronine hydrochloride; L-thyroxine hydrochloride; Tetrac (3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid); Triac ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid); Tetraprop; Triprop ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionic acid); T4Bu; T3Bu; Thyroxamine; Triiodothyronamine; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyrimidin-5-yl)-methanol; Benzyloxy-2-methoxyphenyl)-(6-methylpyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(5-bromo-2-methoxypyridin-4-yl)methanol; (5-benzyloxy-2-methoxyphenyl)-(2,6-difluoropyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyridin-4-yl)methanol; 4-Methoxy-3-[(2-methoxypyrimidin-5-yl)methyl]phenol;

4-Methoxy-3-[(6-methylpyrid-3-yl)methyl]phenol; 5-Benzyloxy-2-methoxybenzyl Bromide; (5-Benzyloxy-2-methoxyphenyl-(6-chloropyridazin-3-yl)-acetonitrile; 4-Benzyloxy-2-[2-methoxythiazol-5-yl)methyl]anisole; 6-[(5-Hydroxy-2-methoxyphenyl)methyl]thiazol-2-(3H); 3'-Heteroarylmethyl-4'-)-methyl-3,5-dinitro-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl-3,5-di-iodo-4')-methyl-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl analogues of 3,3',5-tri-iodo-L-thyronine (T3); 3'-substituted derivatives of the thyroid hormone 3,3'5-triiodo-L-thyronine (T3); L-3,3'-T2; DL-Br2I; L-Br2iPr; L-Me2I; L-Me3; L-Me4; L-Me2IPr; DL-IMeI; L-3,5-Dimethyl-3'-isopropylthyronine (DIMIT); DL-BPT4; B-triac; BP-tetrac; DL-SBT3; DL-SBT4; DL-MBT3; MB-tetrac; T2F; T2Cl; T2Br; T2Me; T2Et; T2iPr; T2nPr; T2sBu; T2tBu; T2iBu; T2Phe; T2F2; T2Cl2; T2Me2; 3,5,3'-Triiodo-D-thyronine; 3,5-Diiodo-4-hydroxyphenylpropionic acid (DIHPA); Aryloxamic acids; (arylamino)acetic acids; arylpropionic acids; arylthioacetic acids; (aryloxy)acetic acid; 3,3'-T2; 3,5-T2; 3',5'-T2; α-methyl-3,5,3'-triiodothyroacetic acid, α-methyl-3,5,3'-triiodothyropropionic acid, and α-methyl-3,5,3',5'-tetraiodothyropropionic acid; methylene- and carbonyl-bridged analogs of iodinated thyronines or thyroacetic acids or iodinated benzofurans; 3,5-diiodo-4-(2-N,N-diethylaminoethoxy)phenyl-(2-butylbenzofur-3-yl)methanol hydrochloride; 2-n-butyl-3-(3,5-diiodo-4-carboxymethoxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-hydroxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-carboxymethoxy-benzyl)benzofuran;] 4'-hydroxy-3'-iodo-3,5 diiodo-4-(2-N,N-dimethylamino-(ethoxy)benzophenone hydrochloride; 2-butyl-3-(3-iodo-4-hydroxybenzoyl)benzfuran; 4',4-dihydroxy 3'3,5-triiodo-diphenylmethane; 3,5-diethyl,3'-isopropyl thyronine (DIET); and IpTA2 (3,5 diiodo-3'isopropyl thyroacetic acid) and pharmacologically acceptable salts and derivatives thereof.

68. The method of claim 66 or claim 67, wherein the thyroid hormone compound or thyroid hormone-like agonist compound is selected from the group consisting of tri-iodothyroacetic acid, tri-iodopropionic acid, 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol and

4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol.

69. The method of any of claims 66 to 68, wherein the pharmacologically acceptable base comprises oil in water emulsions, water in oil emulsions, sprays, liposomes, creams, lotions, solutions, and combinations thereof.

70. The method of any of claims 66 to 69, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 500 mg/100 ml of the composition.

71. The method of claim 70 wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 200 mg/100 ml of the composition.

72. The method of claim 71, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 50 mg/100 ml of the composition.

73. The method of any of claims 66 to 72, wherein the pharmacologically acceptable base further comprises one or more fatty acids, esters, or triglycerides selected from the group consisting of linoleic, oleic, palmitic, and linolenic fatty acids, esters, or triglycerides.

74. The method of any of claims 66 to 73, wherein the dermal wound to be treated is the result of an abrasion or chemical or other burn.

75. The method of any of claims 65 to 74, wherein the dermal wound does not penetrate substantially further into the body than the dermis.

76. A method of dermatological surgical pretreatment of a patient, comprising the step of applying a composition to the skin of the patient prior to dermatological surgery, the composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound together with a pharmacologically acceptable base

suitable for topical application, wherein the thyroid hormone compound or thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex.

77. The method of claim 76, wherein the composition comprises at least one thyroid hormone compound or thyroid hormone-like agonist compound selected from the group consisting of Tri-iodothyronine (3,5,3'-triiodothyronine, T3); D and L thyroxine (T4); 4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol, 4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol, 3,3'5'tri-iodothyronine (reverse T3); 3,3'-diiodothyronine; T3 and T4 analogues such as 3,5,3',-Triiodo-L-thyronine methyl ester; 3,5,3'-Triiodo-L-thyronine hydrochloride; L-thyroxine hydrochloride; Tetrac (3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid); Triac ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid); Tetraprop; Triprop ([4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propionic acid); T4Bu; T3Bu; Thyroxamine; Triiodothyronamine; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyrimidin-5-yl)-methanol; Benzyloxy-2-methoxyphenyl)-(6-methylpyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(5-bromo-2-methoxypyridin-4-yl)methanol; (5-benzyloxy-2-methoxyphenyl)-(2,6-difluoropyridin-3-yl)methanol; (5-Benzyloxy-2-methoxyphenyl)-(2-methoxypyridin-4-yl)methanol; 4-Methoxy-3-[(2-methoxypyrimidin-5-yl)methyl]phenol; 4-Methoxy-3-[(6-methylpyrid-3-yl)methyl]phenol; 5-Benzyloxy-2-methoxybenzyl Bromide; (5-Benzyloxy-2-methoxyphenyl-(6-chloropyridazin-3-yl)-acetonitrile; 4-Benzyloxy-2-[2-methoxythiazol-5-yl)methyl]anisole; 6-[(5-Hydroxy-2-methoxyphenyl)methyl]thiazol-2-(3H); 3'-Heteroarylmethyl-4'-)-methyl-3,5-dinitro-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl-3,5-di-iodo-4')-methyl-N-trifluoro-acetyl-L-thyronine Ethyl Esters; 3'-heteroarylmethyl analogues of 3,3',5-tri-iodo-L-thyronine (T3);

3'-substituted derivatives of the thyroid hormone 3,3'5-triiodo-L-thyronine (T3); L-3,3'-T2; DL-Br2I; L-Br2iPr; L-Me2I; L-Me3; L-Me4; L-Me2IPr; DL-IMeI; L-3,5-Dimethyl-3'-isopropylthyronine (DIMIT); DL-BPT4; B-triac; BP-tetrac; DL-SBT3; DL-SBT4; DL-MBT3; MB-tetrac; T2F; T2Cl; T2Br; T2Me; T2Et; T2iPr; T2nPr; T2sBu; T2tBu; T2iBu; T2Phe; T2F2; T2Cl2; T2Me2; 3,5,3'-Triiodo-D-thyronine; 3,5-Diiodo-4-hydroxyphenylpropionic acid (DIHPA); Aryloxamic acids; (arylamino)acetic acids; arylpropionic acids; arylthioacetic acids; (aryloxy)acetic acid; 3,3'-T2; 3,5-T2; 3',5'-T2; α-methyl-3,5,3'-triiodothyroacetic acid, α-methyl-3,5,3'-triiodothyropropionic acid, and α-methyl-3,5,3',5'-tetraiodothyropropionic acid; methylene- and carbonyl-bridged analogs of iodinated thyronines or thyroacetic acids or iodinated benzofurans; 3,5-diiodo-4-(2-N,N-diethylaminoethoxy)phenyl-(2-butylbenzofur-3-yl)methanol hydrochloride; 2-n-butyl-3-(3,5-diiodo-4-carboxymethoxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-hydroxy-benzoyl)benzofuran; 2-methyl-3-(3,5-diiodo-4-carboxymethoxy-benzyl)benzofuran;] 4'-hydroxy-3'-iodo-3,5 diiodo-4-(2-N,N-dimethylamino-(ethoxy)benzophenone hydrochloride; 2-butyl-3-(3-iodo-4-hydroxybenzoyl)benzfuran; 4',4-dihydroxy 3'3,5-triiodo-diphenylmethane; 3,5-diethyl,3'-isopropyl thyronine (DIET); and IpTA2 (3,5 diiodo-3'isopropyl thyroacetic acid) and pharmacologically acceptable salts and derivatives thereof.

78. The method of claim 76 or claim 77, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound is selected from the group consisting of
tri-iodothyroacetic acid, tri-iodopropionic acid,
4-[2,6-dibromo-4-(1H-tetrazol-5-ylmethyl)-phenoxy]-2-isopropyl-phenol and
4-(4-hydroxymethyl-2,6-diiodophenoxy)-2-iodo-phenol.

79. The method of any of claims 76 to 78, wherein the pharmacologically acceptable base comprises oil in water emulsions, water in oil emulsions, sprays, liposomes, creams, lotions, solutions, and combinations thereof.

80. The method of any of claims 76 to 79, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 500 mg/100 ml of the composition.

81. The method of claim 80, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 200 mg/100 ml of the composition.

82. The method of claim 81, wherein the at least one thyroid hormone compound or thyroid hormone-like agonist compound comprises less than 50 mg/100 ml of the composition.

83. The method of any of claims 76 to 82, wherein the pharmacologically acceptable base further comprises one or more fatty acids, esters, or triglycerides selected from the group consisting of linoleic, oleic, palmitic, and linolenic fatty acids, esters, or triglycerides.

84. The method of any of claims 76 to 82, wherein the dermatological surgery comprises laser ablation dermotherapy.

85. The use of at least one thyroid hormone or thyroid hormone-like agonist compound selected from those which bind to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, in the preparation of a topical medicament for improving the healing of wounds which have not penetrated substantially further into the body than the dermis.

86. The use of at least one thyroid hormone or thyroid hormone-like agonist compound selected from those which bind to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, in the preparation of a topical medicament for increasing the number and activity of fibroblasts in the dermis.

87. Use according to claim 86, wherein the dermis has been subjected to photodamaged and/or photoaging.

88. A method of increasing the number and activity of fibroblasts in the dermis the method comprising the step of applying a composition to the skin of a patient, the composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist compound together with a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex.

89. A method according to claim 88, wherein the dermis has been subjected to photodamaged and/or photoaging.

90. The use of at least one thyroid hormone or thyroid hormone-like agonist compound selected from those which bind to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex, in the preparation of a topical medicament for increasing the thickness of the dermis of a patient.

91. A method of increasing the thickness of the dermis of a patient, the method comprising the step of applying a composition to the skin of the patient, the composition comprising at least one thyroid hormone compound or thyroid hormone-like agonist

compound together with a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or thyroid hormone-like agonist compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex.

92. A method of increasing the number and activity of fibroblasts in the dermis of an *in vitro* skin section, the method comprising the step of applying a composition to the skin section, the composition comprising at least one thyroid hormone compound or thyroid hormone-like compound together with a pharmacologically acceptable base suitable for topical application, wherein the thyroid hormone compound or thyroid hormone-like compound binds to TR-α or TR-β with an equilibrium dissociation constant, K_d, of less than 5×10^{-6} M, wherein

$$K_d = (R)\bullet(L)/(RL),$$

where (R) is the concentration of receptor, (L) is the concentration of ligand, and (RL) is the concentration of the receptor-ligand complex.

93. A method according to claim 92, wherein the skin section comprises excised human skin.

94. A method according to claim 92, wherein the skin section comprises artificial skin.

Fig. 1

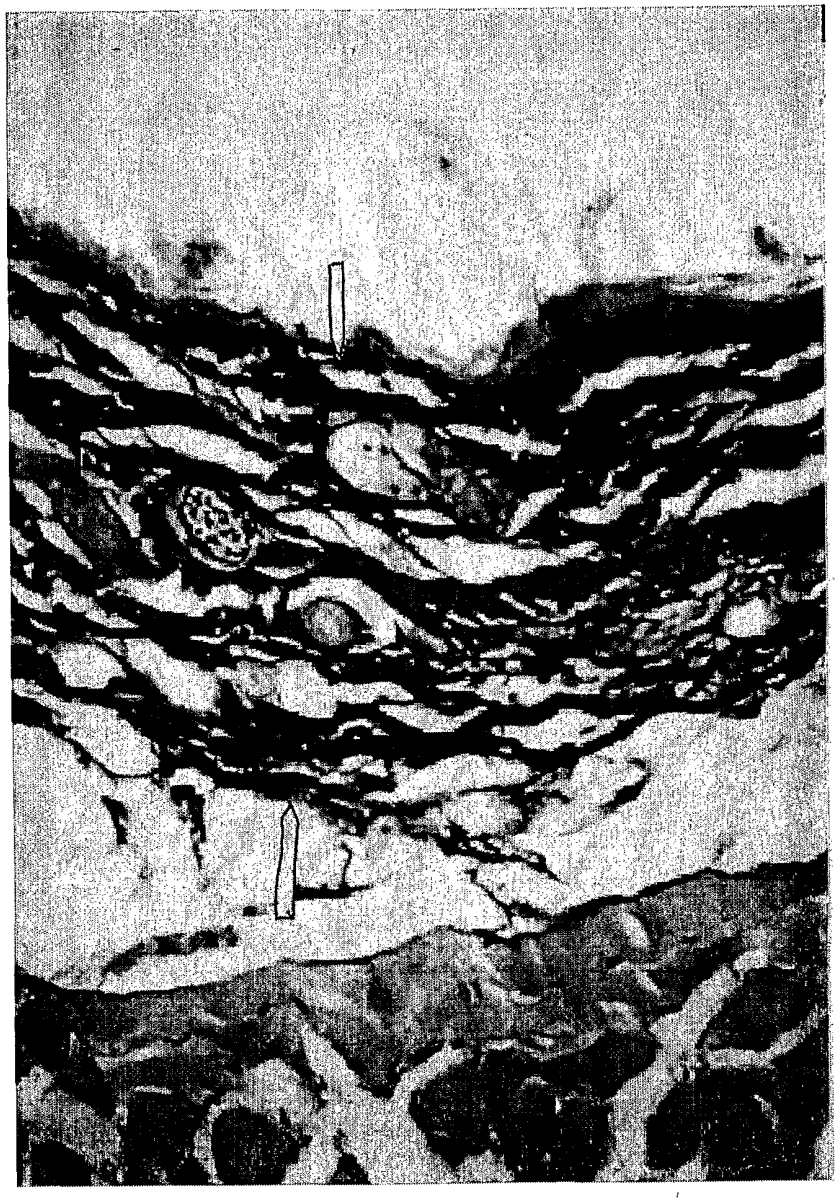


Fig. 2

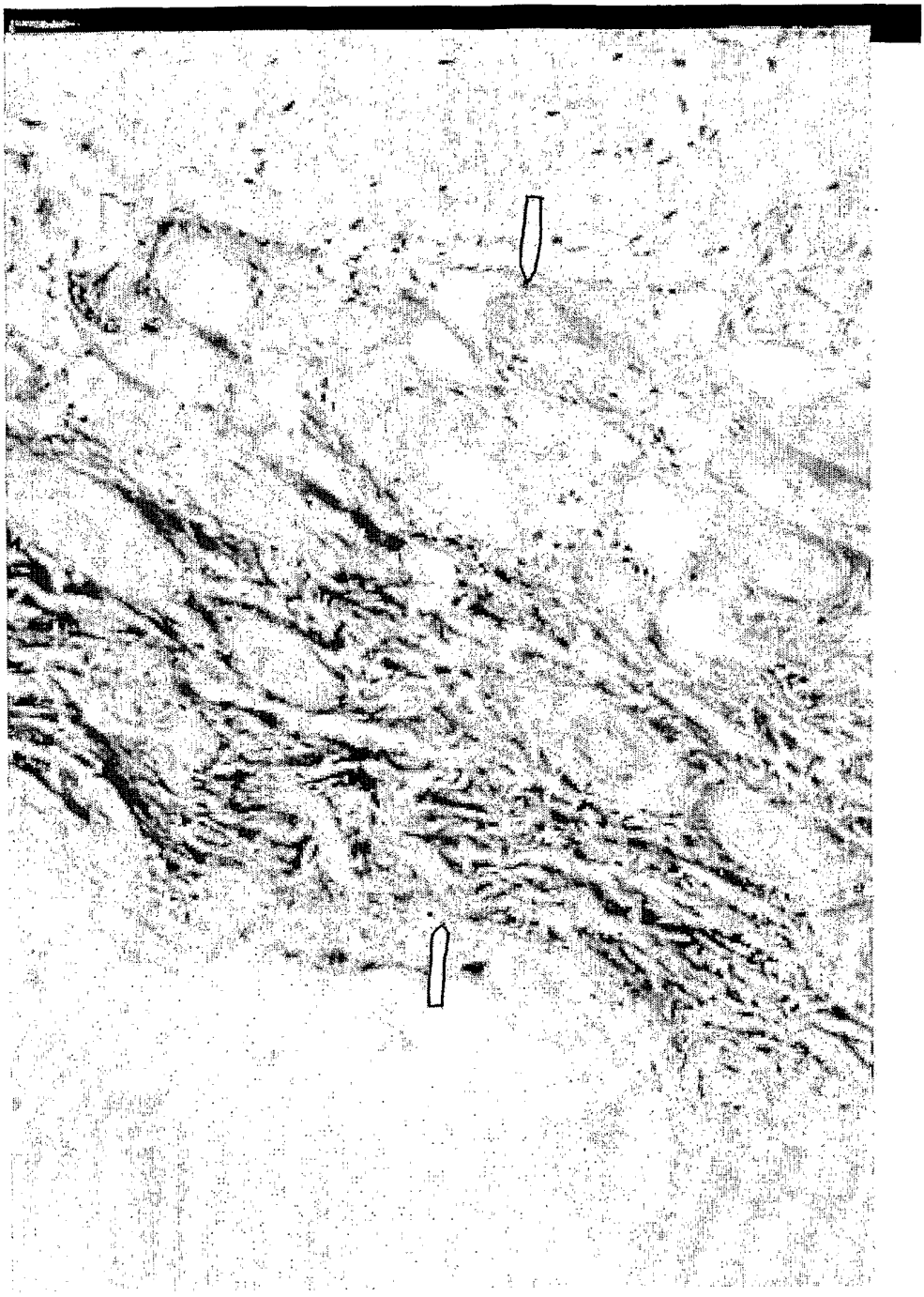


Fig. 3

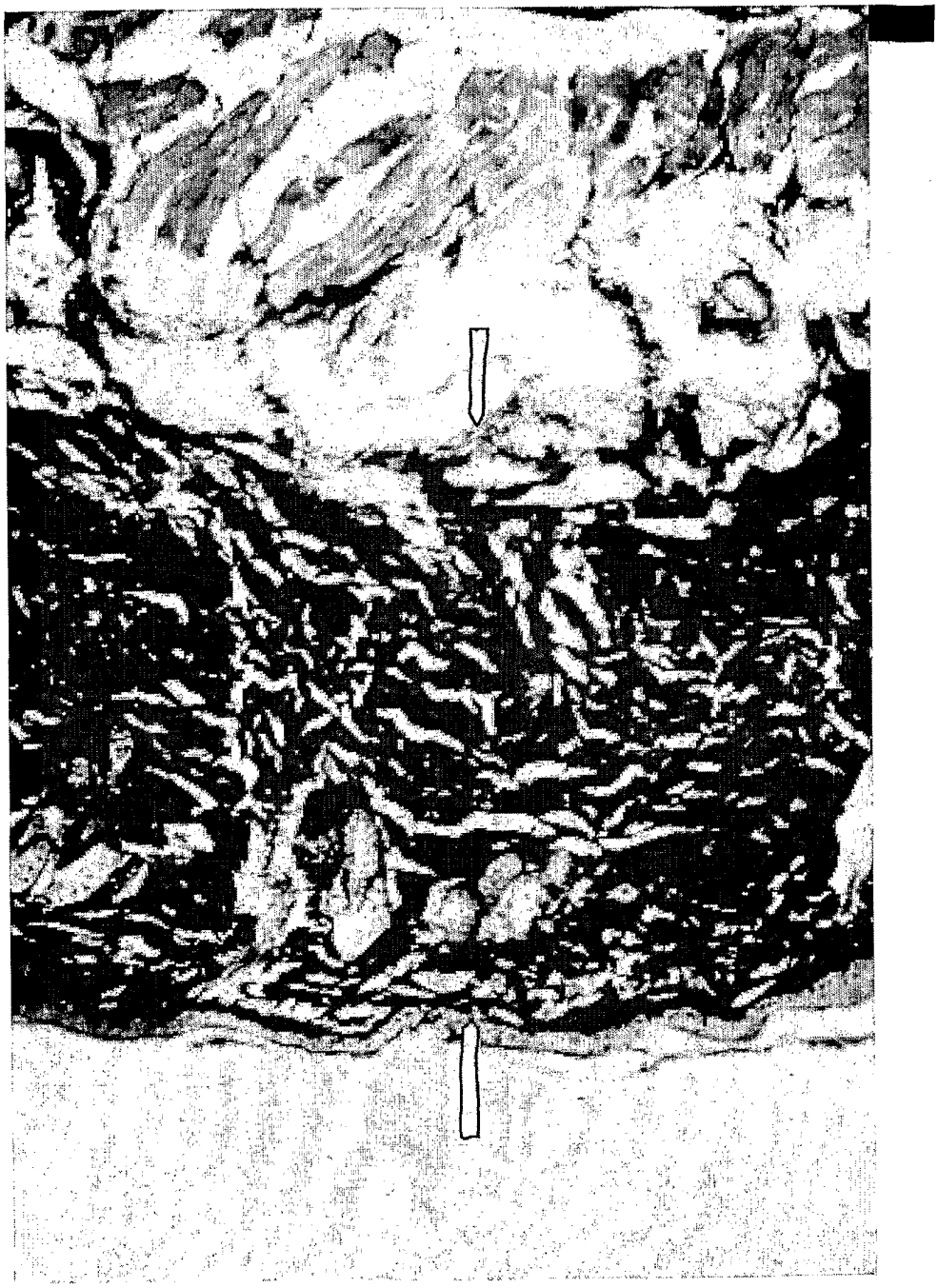


Fig. 4

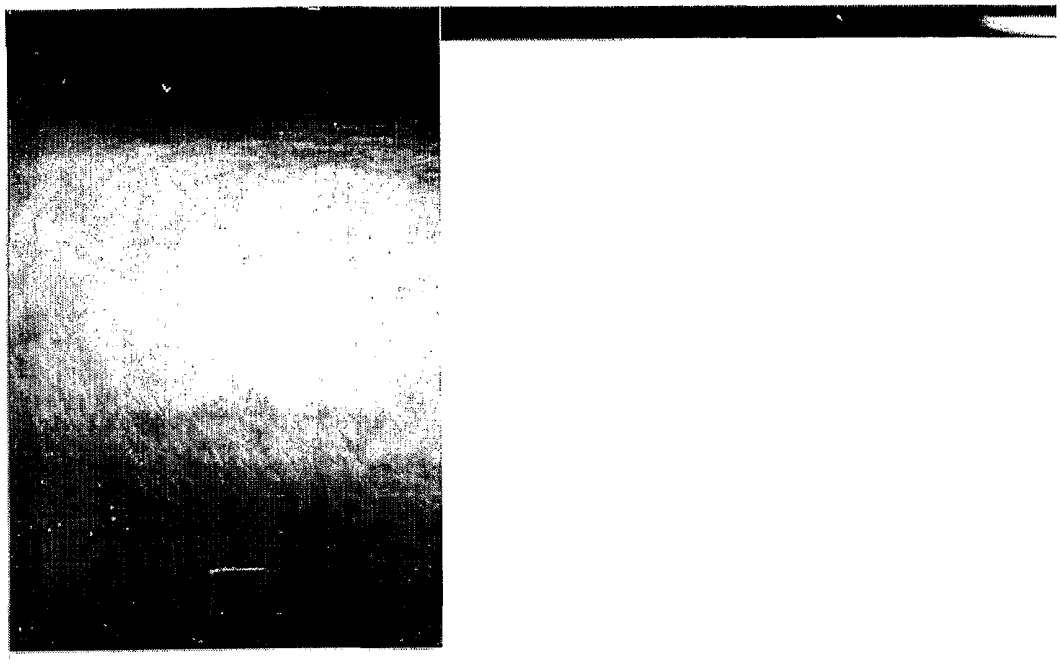


Fig. 5

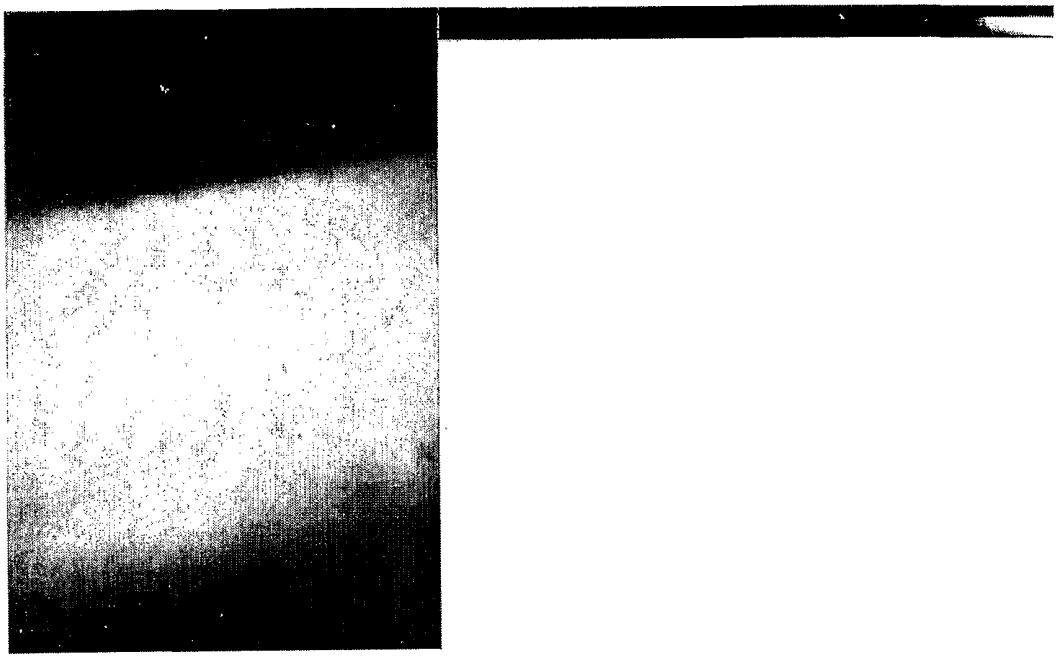


Fig. 6

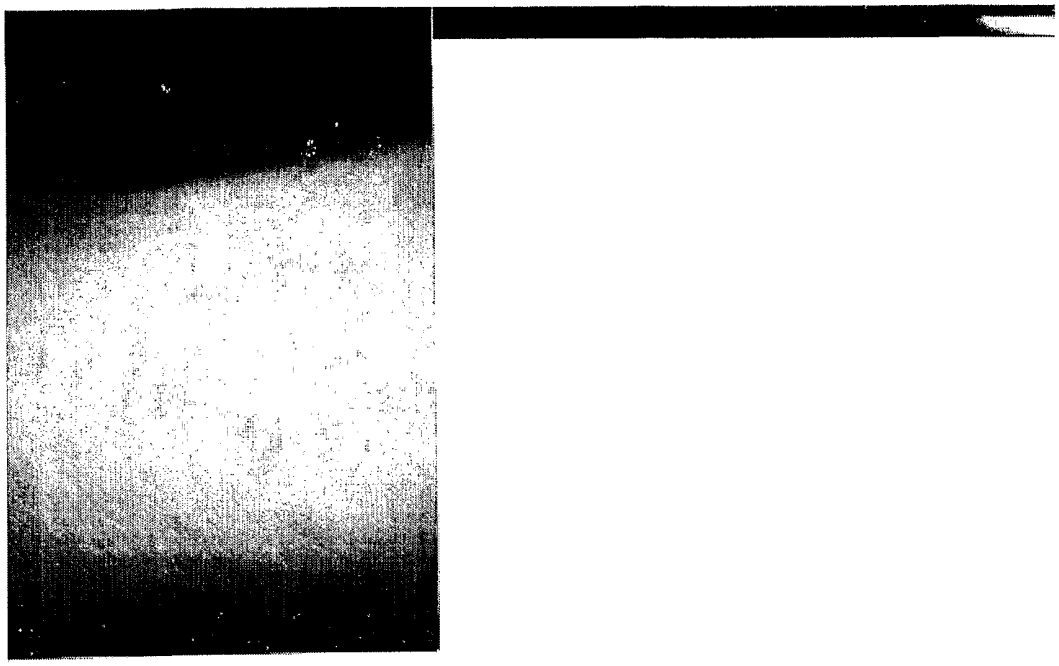


Fig. 7

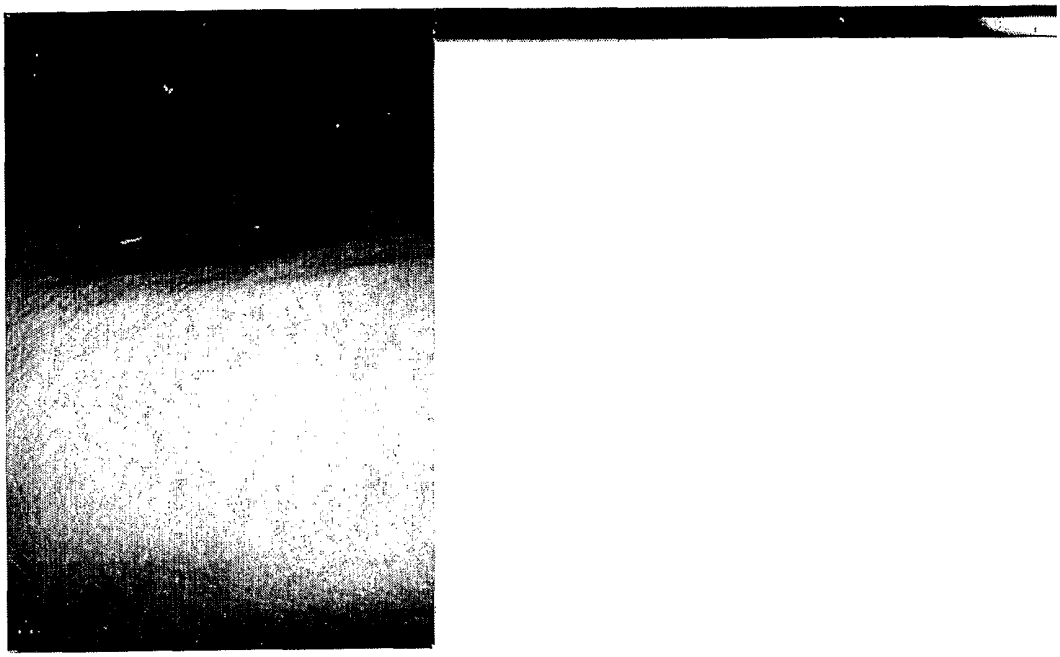


Fig. 8

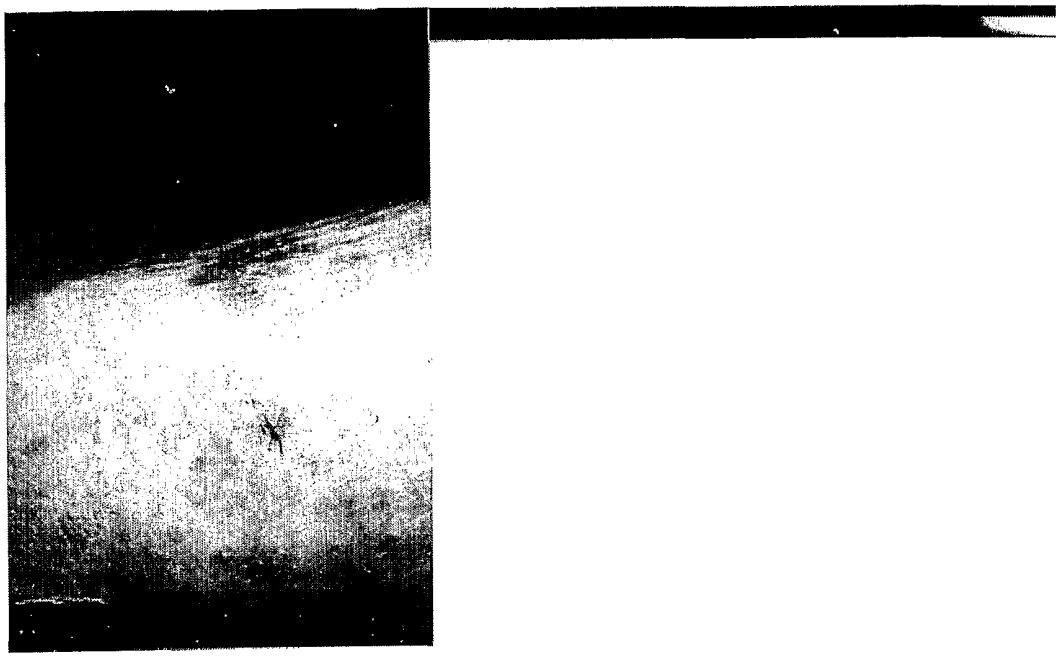


Fig. 9

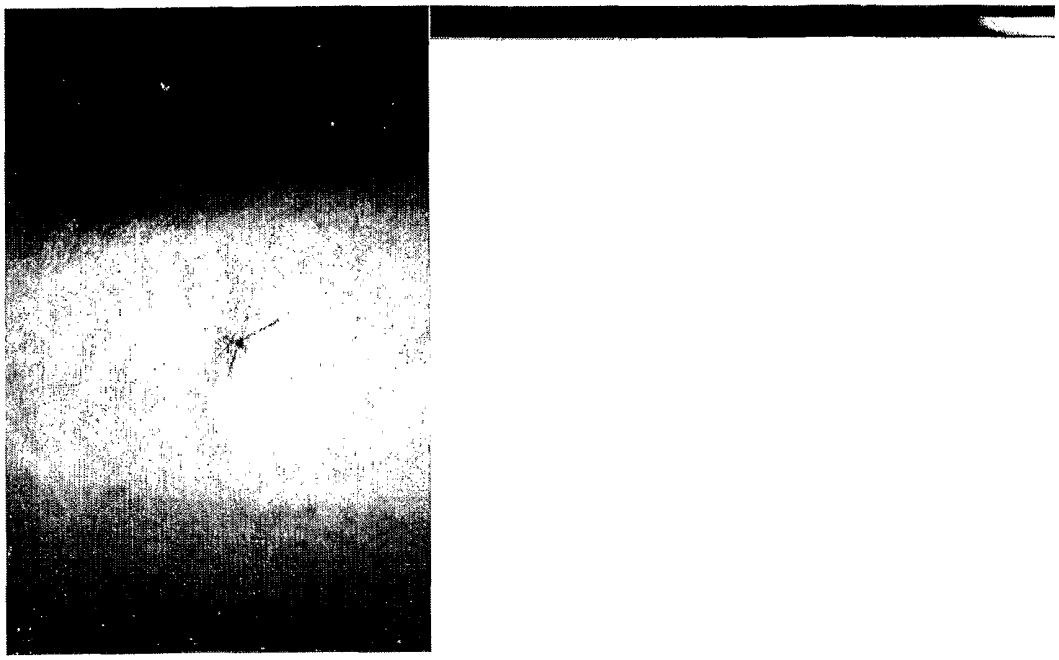
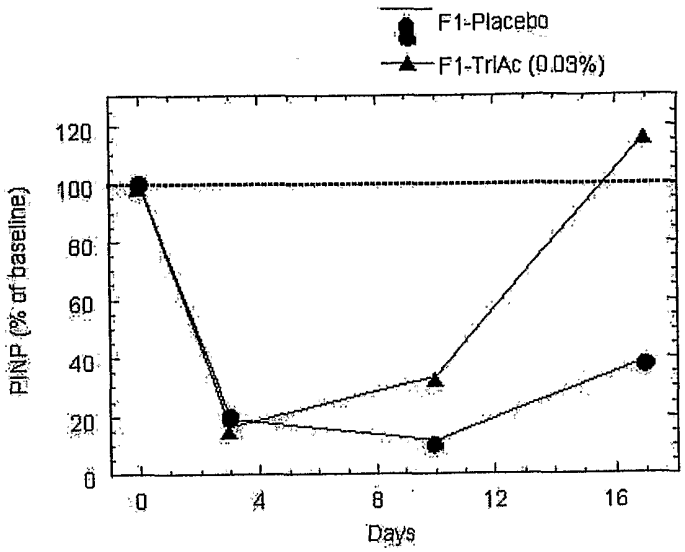


Fig. 10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F1-TrlAc (0.09%)
PINP (% of baseline)
120
100
80
60
40
20
0
0
4
8
12
16
Days