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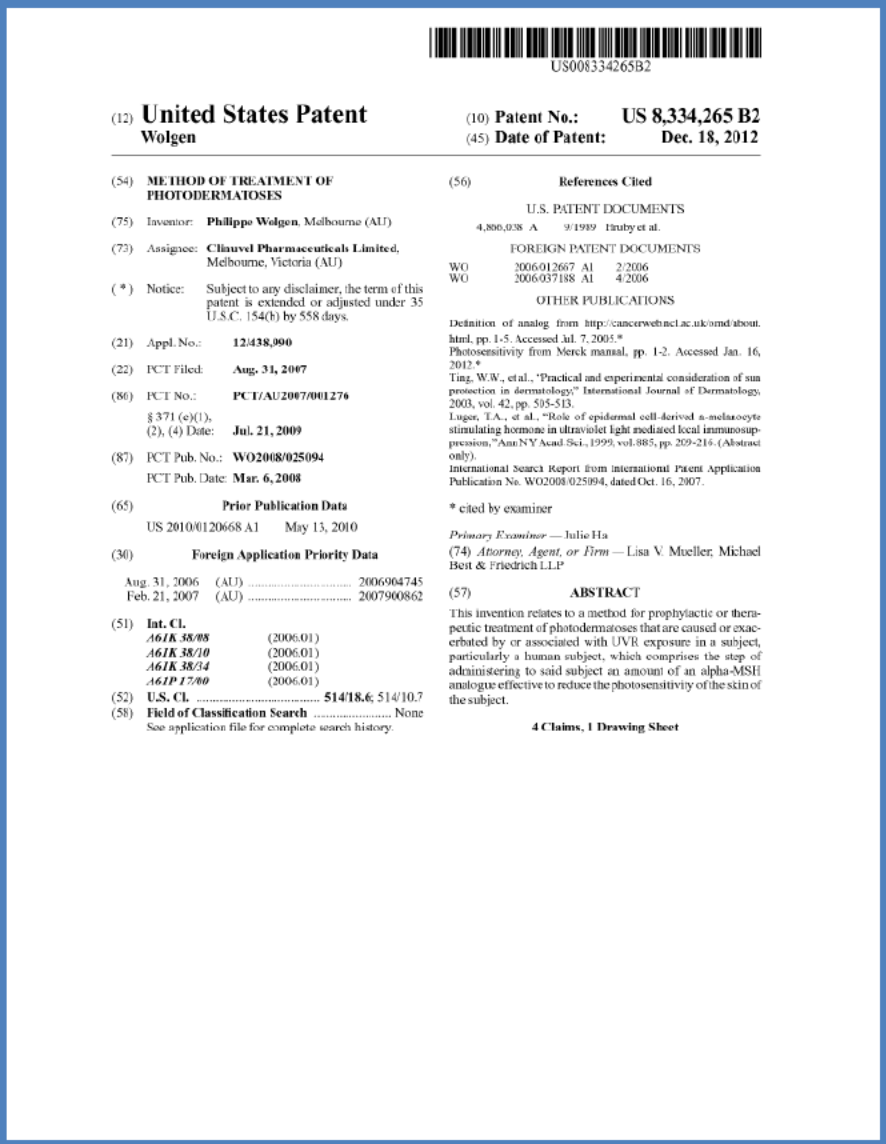

US008334265B2

(12) **United States Patent**
Wolgen

(10) **Patent No.: US 8,334,265 B2**
(45) **Date of Patent: Dec. 18, 2012**

(54) **METHOD OF TREATMENT OF PHOTODERMATOSES**

(75) Inventor: **Philippe Wolgen**, Melbourne (AU)

(73) Assignee: **Clinuvel Pharmaceuticals Limited**, Melbourne, Victoria (AU)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 558 days.

(21) Appl. No.: **12/438,990**

(22) PCT Filed: **Aug. 31, 2007**

(86) PCT No.: **PCT/AU2007/001276**

§ 371 (e)(1),
(2), (4) Date: **Jul. 21, 2009**

(87) PCT Pub. No.: **WO2008/025094**

PCT Pub. Date: **Mar. 6, 2008**

(65) **Prior Publication Data**

US 2010/0120668 A1 May 13, 2010

(30) **Foreign Application Priority Data**

Aug. 31, 2006 (AU) 2006904745
Feb. 21, 2007 (AU) 2007900862

(51) **Int. Cl.**
A61K 38/08 (2006.01)
A61K 38/10 (2006.01)
A61K 38/34 (2006.01)
A61P 17/00 (2006.01)

(52) **U.S. Cl.** **514/18.6**; 514/10.7
(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,866,038 A 9/1989 Hruby et al.

FOREIGN PATENT DOCUMENTS

WO 2006/012667 A1 2/2006
WO 2006/037188 A1 4/2006

OTHER PUBLICATIONS

Definition of analog from http://cancerweb.ncl.ac.uk/omd/about.html, pp. 1-5. Accessed Jul. 7, 2005.*
Photosensitivity from Merck manual, pp. 1-2. Accessed Jan. 16, 2012.*
Ting, W.W., et al., "Practical and experimental consideration of sun protection in dermatology," International Journal of Dermatology, 2003, vol. 42, pp. 505-513.
Luger, T.A., et al., "Role of epidermal cell-derived α-melanocyte stimulating hormone in ultraviolet light mediated local immunosuppression," Ann NY Acad Sci., 1999, vol.885, pp. 209-216. (Abstract only).
International Search Report from International Patent Application Publication No. WO2008/025094, dated Oct. 16, 2007.

* cited by examiner

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(57) **ABSTRACT**

This invention relates to a method for prophylactic or therapeutic treatment of photodermatoses that are caused or exacerbated by or associated with UVR exposure in a subject, particularly a human subject, which comprises the step of administering to said subject an amount of an alpha-MSH analogue effective to reduce the photosensitivity of the skin of the subject.

4 Claims, 1 Drawing Sheet

Method of Treatment of Photodermatoses
US Patent 8334265
Methods of Inducing Melanogenesis in a Subject
US Patent 10076555

Initial Patent Review
US 8334265
US10076555

IPR Initial Review

Patent Information

URL	Priority	Expiration	RC*	FC**
https://patents.google.com/patent/US8334265B2	Aug 31 2006	Mar 11 2029	18	14
https://patents.google.com/patent/US10076555B2	Aug 4 2004	Feb 11 2025	58	20

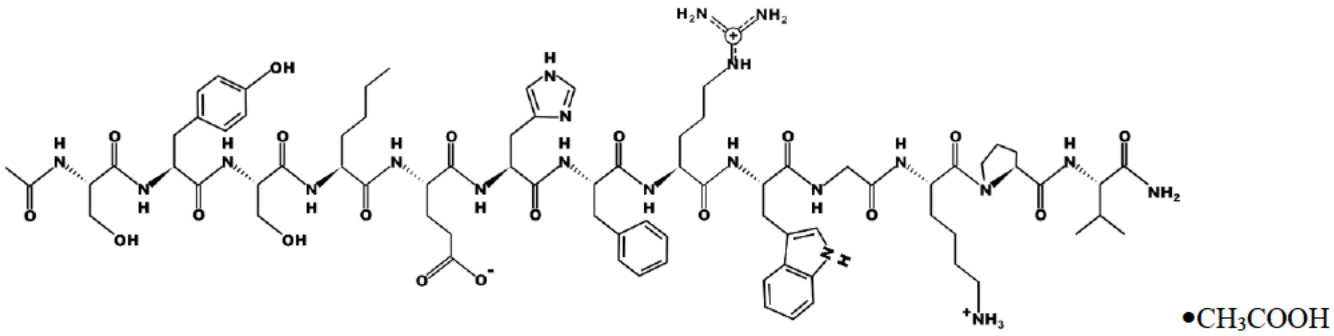
*patent and non-patent literature citations ** citing patents

Technology Description & Application Area

Patent Numbers	Title	Description/Application Area
8334265	Method of treatment of photodermatoses	The present invention relates broadly to a method for prophylactically or therapeutically treating photodermatoses that are associated with photosensitivity of the skin to ultraviolet radiation (UVR).
10076555	Methods of inducing melanogenesis in a subject	Methods for inducing melanogenesis in a subject.

Afamelanotide is a melanocortin 1 receptor (MC1-R) agonist. The active ingredient afamelanotide acetate is a synthetic peptide containing 13 amino acids with molecular formula $C_{78}H_{111}N_{21}O_{19} \cdot xC_2H_4O_2$ ($3 \leq x \leq 4$). The molecular weight of afamelanotide is 1646.85 (anhydrous free base). Afamelanotide acetate has the following structure:

Ac-Ser-Tyr-Ser-Nle-Glu-His-(D)Phe-Arg-Trp-Gly-Lys-Pro-Val-NH2• xCH_3COOH



Prosecution History

U.S. 8334265	Date	Action/Outcome
Claims	Feb 26 2009	Originally filed with Claims 1-16
Notice of Publication	May 13 2010	Published as US 2010/0120668-A1
OA Request for Restriction/Election	Sep 7 2011	104 Groups delineated by Examiner At least 7 separate species identified
Response to OA	Nov 7 2011	Patent owner selected Group 7 in reference to original claim 11 drawn to a method for prophylactic or therapeutic treatment of photodermatoses comprising administering an alpha-MSH analogue effective to reduce the photosensitivity of the skin of the subject, comprising an alphaMSH analogue [Nle4, D-Phe7]-alpha-MSH. Applicant further elected the species [Nle4, D-Phe7]alpha-MSH. This species reads upon at least claim 11.
Non-final Rejection	Jan 20 2012	Claims 6-10, 12, and 14-16 were withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Claims 1-5, 11, and 13 were rejected. Claims 1-5 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recited, "an amount of an alpha-MSH analogue ... " It was unclear what modifications were encompassed within the alpha-MSH analogues. Claims 1-5, 11 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic treatment of photodermatoses that are caused or exacerbated by or associated with UVR exposure, does not reasonably provide enablement for prevention of photodermatoses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Claims 1-2, 11 and 13 were rejected under 35 U.S.C. 102(b) as being anticipated by Kleinig *et al* (WO 2006/012667 A1, filed with IDS).
Response to NFR	Jul 13 2012	Claim 1 was amended and claims 2 and 6-16 were canceled. Claims 1 and 3-5 were pending. As to patenability under 35 U.S.C. § 112, applicant amended claim 1 relating to the administration of a specific hormone: [Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (alpha-MSH). Further, the term "particularly" was deleted from claim 1.

		As to novelty under 35 U.S.C. § 102(b), applicant argued that "Kleinig describes the administration of [Nle4, D-Phe7] to a subject to induce melanogenesis, while referring to nonmelanoma skin tumors and cutaneous melanoma as indications. See page 2, line 1, of Kleinig, for example. In contrast, the presently amended claims are directed to treating humans suffering from photodermatoses that are caused or exacerbated by or associated with ultraviolet radiation (UVR) exposure to reduce photosensitivity of the skin of the subject. Applicant submits that such a treatment cannot be deduced from Kleinig, rendering the presently amended claims novel over Kleinig."
Notice of Allowability	Aug 15 2012	Claims 1, and 3-5 allowed. Specifically with regard to novelty, the examiner stated that "Rejection of claims 1-2, 11 and 13 under 35 U.S.C. 102(b) as being anticipated by Kleinig *et al* (WO 2006/012667, filed with IDS) is hereby withdrawn in view of Applicant's amendment to the claims.
Issue Notification and Patent Term Adjustment	Nov 28 2012	Issue date of Dec 18 2012 US Pat 8334265 Patent term adjusted by 558 days.

U.S. 10076555	Date	Action/Outcome
Original Filing	Apr 21 2016	Originally filed with Claims 1-20
Office Action Requirement for Restriction/Election	Apr 18 2017	Restriction to one of two groups requested.
Applicant Argument/Remarks Made in Amendment	Jun 16 2017	Applicant elected with traverse, Group I, claims 1 and 3-13. The requirement was traversed for the following reasons: Applicant submits that there is no undue burden on the Examiner to examine Groups I and II. Between Group I and Group II, there is substantial overlap in the patient population and the administration steps are analogous.
Non-final Rejection	Aug 8 2017	Claims 1-20 rejected. Claims 1-20 rejected under 35 U.S.C. l 12(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for a method for inducing melanogenesis or reducing the occurrence of UV radiation-induced skin damage in a human subject comprising administering to the subject melanotan I (i.e., [Nle4, D-Phe7]-alpha-MSH) in a controlled release formulation to induce melanogenesis by the melanocytes in the epidermal tissue of the subject without inducing homologous desensitization of the melanocortin-1 receptors of the subject, wherein the melanotan I is contained within an implant or rod containing a biodegradable polymer and administered subcutaneously, does not reasonably provide enablement for a method as recited in independent claims 1-2 wherein the alpha-MSH analogue is administered by all delivery systems. Claims 1-20 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly

		point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Claims 1-20 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Ugwu *et al*. (Biopharmaceutics & Drug Disposition, 1997; 18: 259-269) in view of Bhardwaj and Blanchard (International Journal of Pharmaceutics, 1998; 170: 109-117-reference #2 on PTO-1449 form submitted 12 November 2009). Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-31 of U.S. Patent 9,345,911 ('911). Although the claims at issue are not identical, they are not patentably distinct from each other because both claim sets are drawn to a method for inducing melanogenesis in a human subject comprising administering to the subject an alpha-MSH analogue.
Applicant Argument/Remarks Made in Amendment	Dec 8 2017	Applicant stated Examiner had agreed to examine both Groups I and II, claims 1-20. Applicant argued extensively against the lack of enablement rejections. As to rejection under 35 U.S.C. § 103, applicant argued that "Bardwaj & Blanchard relates to guinea pig studies with extended release afamelanotide. Guinea pigs are distinct from humans, have different melanocortin receptors with different interaction -pharmacodynamic-characteristics with afamelanotide. It can further be assumed that afamelanotide has different pharmacokinetic characteristics in the guinea pig vs the human." Further: "wishing to apply the extended release technology from Bardwaj and Blanchard in the experiment of Ugwu, the skilled person would apply high human plasma levels (Ugwu does not motivate the use of the presently claimed low and extended human plasma levels) and that would result in low melanogenesis results, contrary to the surprising results of the present invention. Claims 21 and 22 were added for the Examiner's consideration.
Non-final Rejection	Feb 9 2018	Claims 1-22 rejected. The following previous rejections and objections are withdrawn in light of applicants amendments filed on 12/8/2017: (i) the rejection of claims 1-20 under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, scope of enablement; (ii) the rejection of claims 1-20 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph; and (iii) the rejection of claims 1-20 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Ugwu *et al*. (Biopharmaceutics & Drug Disposition, 1997; 18: 259-269) in view of Bhardwaj and Blanchard (International Journal of Pharmaceutics, 1998; 170: 109-117). Reiterated non-statutory double patenting over US 9345911. Earlier petition for terminal disclaimer had been denied due to signature irregularities.

Terminal Disclaimer Approved	May 8 2018	Approval of Terminal Disclaimer
Notice of Allowance	May 22 2018	Claims 1-22 allowed.

Current Orange Book Patent Data

SCENESSE
Active Ingredient: AFAMELANOTIDE
Proprietary Name: SCENESSE
Dosage Form; Route of Administration: IMPLANT; SUBCUTANEOUS
Strength: 16MG
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N210797
Product Number: 001
Approval Date: Oct 8, 2019
Applicant Holder Full Name: CLINUVEL INC
Marketing Status: Prescription

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	8334265	03/11/2029			U-2638		11/06/2019
001	10076555	02/11/2025			U-2638		11/06/2019

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
001	NCE	10/08/2024
001	ODE-270	10/08/2026

Litigation Synopsis

Patent	Cases Filed	Cases Terminated	Active Cases
8334265	0	0	0
10076555	0	0	0

No IPRs filed to date

Background and Prior Art

I. LACK OF CANDOR DURING PROSECUTION.

The lack of candor in disclosing the known prior art of [Nle[4] - D-Phe[7]]alpha-melanocyte-stimulating hormone (NDP-MSH or MTI or MT-I or Melanotan) during prosecution is astounding.

A simple search of the term "afamelanotide" on PubChem[1] (PubChem CID 16197727) shows at least 1,760 documents dating back to no sooner than October 23, 1981**. At least 792 of these documents pre-date the priority date of the '265 which is Aug 31, 2006.**

Only ONE U.S. patent document, TWO foreign patent documents, and TWO scientific journal articles were cited on the face of the '265 patent with 14 "references" included at the end in the body of the patent. Such lack of candor is appalling and borders on negligence from the standpoint of the prosecution history of this patent.

Philippe Wolgren, the named "inventor" on the '265 **never published an article, study, or paper related to the NDP-MSH.** Searches of "Wolgen+MSH"[2] "Wolgen+Melanocortin"[3] and "Wolgen+melanocyte"[4] retuned **no results** for non-patent publications and only four US patents (US Pats 8334265, 9801924, [both assigned to Clinuvel Pharmaceuticals Ltd] and US Pats 10508142, 11286288 [both assigned to [Vallaurix Pte Ltd]).

In their review entitled "*Melanocortin peptide therapeutics: Historical milestones, clinical studies and commercialization*" by Hadley and Dorr[5] (hereinafter, HADLEY 2006), the authors state:

> The development of MTI and MTII was only possible because of the concerted and positive interactions of a number of University of Arizona professors, "The Arizona Team" comprising a chemist (Victor J. Hruby), a biologist (Mac E. Hadley), a pharmacologist (Robert T. Dorr), and a clinician (Norman Levine) (Fig. 7). Other important contributors to the team effort included a pathologist (Brenda V. Dawson), a pharmaceutical scientist (James Blanchard), and a physician (Hunter Wessels), as well as other professors and students (Thomi K. Sawyer, Fahad Al-Obeidi). It is not often that the development of a drug results from the efforts of a group of university professors at a single institution.(pg. 929 sec 4)

In contrast to the database searches above concerning "Wolgren," a search of the some of the major developers and researchers involved with the development of NDP-MSH as described by HADLEY 2006 showed *numerous* publications and patents:

Mac Hadley - A search of "Hadley+MSH"[6] showed 42 documents on PubMed and 11 U.S. patents on USPTO[7]:

6,051,555	Stimulating sexual response in females
5,731,408	Peptides having potent antagonist and agonist bioactivities at melanocortin receptors
5,714,576	Linear analogs of alpha-msh fragments
5,683,981	Cyclic bridged analogs of .alpha.-MSH and methods thereof
5,674,839	Cyclic analogs of alpha-MSH fragments

[1] https://pubmed.ncbi nlm nih.gov/advanced/ (general search page)
[2] https://pubmed.ncbi nlm nih.gov/?term=%28wolgen%5BAuthor+-+Last%5D%29+AND+%28MSH%5BText+Word%5D%29&sort=
[3] https://pubmed.ncbi nlm nih.gov/?term=%28wolgen%5BAuthor+-+Last%5D%29+AND+%28Melanocortin%5BText+Word%5D%29
[4] https://pubmed.ncbi nlm nih.gov/?term=%28wolgen%5BAuthor+-+Last%5D%29+AND+%28melanocyte%5BText+Word%5D%29
[5] Hadley, Mac E., and Robert T. Dorr. "Melanocortin peptide therapeutics: historical milestones, clinical studies and commercialization." Peptides 27.4 (2006): 921-930.
[6] https://pubmed.ncbi nlm nih.gov/?term=%28hadley%5BAuthor+-+Last%5D%29+AND+%28msh%5BText+Word%5D%29&sort=
[7] https://patft.uspto.gov/netahtml/PTO/search-adv.htm (general search page)

5,576,290 Compositions and methods for the diagnosis and treatment of psychogenic erectile dysfunction
5,049,547 Composition for stimulating integumental melanocytes
4,918,055 Method of stimulating melanocytes by topical application of analogs of alpha-MSH, and compositions for use in same
4,866,038 Method of stimulating integumental melanocytes by topical application of analogs of alpha-msh
4,485,039 Synthetic analogues of .alpha.-melanotropin
4,457,864 Synthetic analogues of .alpha.-melanotropin

Norm Levine - A search of "Levine+MSH"[8] showed 10 documents on PubMed and a search of "Levine+melanocyte" on USPTO showed three pertinent US patents:

5,049,547 Composition for stimulating integumental melanocytes
4,918,055 Method of stimulating melanocytes by topical application of analogs of alpha-MSH, and compositions for use in same
4,866,038 Method of stimulating integumental melanocytes by topical application of analogs of alpha-msh

Robert Dorr – A search of "Dorr+MSH"[9] showed 3 documents on PubMed and three US patents on USPTO:

5,049,547 Composition for stimulating integumental melanocytes
4,918,055 Method of stimulating melanocytes by topical application of analogs of alpha-MSH, and compositions for use in same
4,866,038 Method of stimulating integumental melanocytes by topical application of analogs of alpha-msh

Victor Hruby – A search of "Hruby+MSH"[10] showed 71 documents on PubMed and 22 US patents on USPTO:

11,230,568 Melanocortin 1 receptor ligands and methods of use
11,124,542 Modulators of melanocortin receptors
10,653,743 Methods for the treatment of depression and anxiety by a melanocortin 5 receptor antagonist, PG-20N
10,550,157 Compositions and methods for treating central nervous system (CNS) disorders and mood disorders
10,329,326 Melanocortin 1 receptor ligands and methods of use
10,188,704 Enhanced melanoma cancer prevention by novel melanotropins
9,821,023 Methods for the treatment of central nervous system (CNS) disorders and mood disorders
9,814,755 Methods for the treatment of depression and anxiety
9,539,301 Melanotropin ligands for skin care
9,441,013 Melanocortin 1 receptor ligands and methods of use
9,290,539 Melanotropin ligands for skin care
7,816,082 Methods of identifying pancreatic cancer cells
5,731,408 Peptides having potent antagonist and agonist bioactivities at melanocortin receptors
5,714,576 Linear analogs of alpha-msh fragments
5,683,981 Cyclic bridged analogs of .alpha.-MSH and methods thereof
5,674,839 Cyclic analogs of alpha-MSH fragments
5,049,547 Composition for stimulating integumental melanocytes
4,918,055 Method of stimulating melanocytes by topical application of analogs of alpha-MSH, and compositions for use in same
4,866,038 Method of stimulating integumental melanocytes by topical application of analogs of alpha-msh
4,649,191 Conformationally constrained alpha-melanotropin analogs with specific central nervous system activity
4,485,039 Synthetic analogues of .alpha.-melanotropin
4,457,864 Synthetic analogues of .alpha.-melanotropin

[8] https://pubmed.ncbi nlm nih.gov/?term=%28levine%5BAuthor+-+Last%5D%29+AND+%28MSH%5BText+Word%5D%29&sort=
[9] https://pubmed.ncbi nlm nih.gov/?term=%28Dorr%5BAuthor+-+Last%5D%29+AND+%28MSH%5BText+Word%5D%29
[10] https://pubmed.ncbi nlm nih.gov/?term=(hruby%5BAuthor%20-%20Last%5D)%20AND%20(msh%5BText%20Word%5D)&sort=

These academic investigators had previously sought "to seek a commercial licensee for the MTI based tanning technology. A new entity, EpiTan Ltd., Melbourne, Australia, was the ultimate recipient of this tanning technology." (HADLEY 2006 pg. 926 first line) EpiTan changed its name to Clinuvel Pharmaceuticals after Philippe Wolgren (the named inventor on the '265 mentioned above) took over in 2006 as the company's CEO[11].

None of Hruby, Dorr, Sawyer, Levine, or Hadley are mentioned anywhere in the '265 issued to Wolgen. This is ludicrous to a fault and points to a lack of candor on the part of the patentee during the prosecution of this patent application. At least the '555 issued to Kleinig *et al.* attempts to cite a bare minimum of some of the early developers of the technology.

II. BRIEF BACKGROUND OF DISCOVERY AND DEVELOPMENT OF NDP-MSH.

The first known description of [Nle^4 - D-Phe^7]alpha-melanocyte-stimulating hormone (NDP-MSH) was in 1980 by Sawyer *et al.* in an article entitled *4-Norleucine, 7-D-phenylalanine-a-melanocyte-stimulating hormone: A highly potent a-melanotropin with ultralong biological activity.*[12] Not only does Sawyer 1980 teach the precise peptide structure claimed by the '265 and the '555 patents, they present data relevant to its synthesis, production, and "its unique biological properties. These include prolonged biological activity, enhanced potency relative to α-MSH in a number of biological systems, and resistance to degradation by serum enzymes." (Sawyer 1980 pg. 5754) Sawyer 1980 concludes this paper by saying

> The hormone stimulates adenylate cyclase activity and, over longer periods of time, tyrosinase activity and melanin production. The high potency of [Nle4, D-Phe7]- α-MSH and its apparent resistance to enzymatic activity make it an especially attractive compound for studying these and other biological effects of melanotropins in both normal and abnormal (melanoma) melanocytes. (Sawyer 1980 pg. 5758)

Expanding on these original studies in an article published in 1982[13] Sawyer 1982 showed that the synthetic NDP-MSH peptide was exceedingly active in a mammalian (mouse) melanoma adenylate cyclase assay (Sawyer 1982 Table 2, below):

Table II. Relative in Vitro Potencies of α-MSH$_{4-10}$ Analogues on Frog (*Rana pipiens*) Skin, Lizard (*Anolis carolinensis*) Skin, and Mouse Melanoma Adenylate Cyclase Assays

peptide	Potency relative to α-MSH[a]		
	frog skin assay	lizard skin assay	mouse melanoma adenylate cyclase assay
α-MSH	1.0	1.0	1.0
α-MSH$_{4-10}$[b]	0.00001	0.00004	ND[c]
Ac-α-MSH$_{4-10}$-NH$_2$	0.0003	0.004	ND
Ac[Tyr^4]-α-MSH$_{4-10}$-NH$_2$	0.0002	0.0006	0.001[d]
Ac-[Nle^4]-α-MSH$_{4-10}$-NH$_2$	0.002	0.06	0.09
Ac-[Nle^4,D-Phe^7]-α-MSH$_{4-10}$-NH$_2$	0.02	10.0	7.7
[Nle^4,D-Phe^7]-α-MSH	60	5.0	26.6

[a] Relative potency = concentration of α-MSH at 50% response/concentration of peptide at 50% response. [b] H-α-MSH$_{4-10}$-OH was obtained from Peninsula Laboratories (San Carlos, CA). [c] Not determined. [d] Ac-[Tyr^4]-α-MSH$_{4-10}$-NH$_2$ was found to be a partial agonist on the melanoma adenylate cyclase assay and possessed about 34% the maximal activity of α-MSH (refer to Figure 3).

[11] Article entitled "Epitan opts for name change." by Ruth Beran, January 25, 2006, Labonline.com.au https://www.labonline.com.au/content/life-scientist/news/epitan-opts-for-name-change-854737925

[12] Sawyer, Tomi K., et al. "4-Norleucine, 7-D-phenylalanine-alpha-melanocyte-stimulating hormone: a highly potent alpha-melanotropin with ultralong biological activity." Proceedings of the National Academy of Sciences 77.10 (1980): 5754-5758.

[13] Sawyer, Tomi K., et al. "Comparative biological activities of highly potent active-site analogs of. alpha.-melanotropin." Journal of Medicinal Chemistry 25.9 (1982): 1022-1027.

By 1985[14], NDP-MSH was being shown to stimulate tyrosinase activity in melanoma cells (Maewan 1985 pg. 172) leading to the conclusion that "amplification of the acute actions (e.g. cyclic AMP formation) of the melanotropins may result in enhanced intracellular processes (cellular hypertrophy) related to melanin synthesis" (Marwan 1985 pg. 176) and that it was "possible that these melanotropin analogues have a greater affinity for the melanotropin receptor than α-MSH" (Marwan 1985 pg. 177). Marwan 1985 conclude by saying that "[Nle4,D-Phe']-substituted α-MSH peptides as well as other potent melanotropin analogues that have been synthesized … should prove important as probes for clarifying basic questions concerning the cellular processes related to melanocyte function, both normal and abnormal." (Marwan 1985 pg. 177)

It was in 1991[15] that Levine *et al.* demonstrated NDP-MSH "can induce increased skin pigmentation in human volunteers" (Levine 1991 pg. 2734 and HADLEY 2006 pg. 924 Section 2.2) Levine 1991 specifically proposed that, given the results of their study, with regards to NDP-MSH "the greatest potential use would be [for use in] in patients who tan poorly and sunburn easily, the group at greatest risk for skin cancer. Increased melanin in the skin might afford these people protection against the effects of ultraviolet light." (Levine 1991 pg. 2730). "Perhaps NDP could stimulate tyrosinase, resulting in an increase in pigmentation. This may afford these individuals protection from ultraviolet light." (Levine 1991 pg. 2736).

By this time, BHARDWAJ had been studying implants to deliver pharmaceutically active amounts of NDP-MSH over extended periods of time for several years[16]. BHARDWAJ 1996[17] described poloxamer gels for the controlled release system and concluded that they "have the potential to increase the therapeutic efficacy of peptides and other drugs by prolonging the ip rate of input into the systemic circulation." (pg. 918 end of second column). By 1997 studies from BHARDWAJ's studies on various poly(D,L lactide-co-glycolide) (PLGA) implants began to be published. These studies published in 1998[18] and 2000[19] included pharmacological profiles on the release of NDP-MSH from biodegradable PLAG copolymers *in vitro* as well as *in vivo* characterization of the implants. They concluded that "the increase in melanin pigment, especially eumelanin, could provide protection against the photodamaging effects of UV radiation… ." (BHARDWAJ 2000 pg. 598)

Those laboratory studies were then followed by the initiation of clinical trials on human subjects. (Sydney Morning Herald[20], Trials 379, 930 and 382). By 2004, "a depot formulation that would be injected under the skin and release the peptide slowly" had been developed and tested in several clinical trials. (New Drug Approvals[21]) HADLEY 2006 describes these clinical studies. HADLEY 2006 states that a "Phase I dose response trial was performed … [that] showed that the maximally effective doses of SC MTI was 0.16 mg/kg/day, delivered over a 2-week period daily… [and] at doses above 0.16/g/kg/day, pigmentation was not enhanced further…" (HADLEY 2006 pg. 924 Section 2.2) HADLEY 2006 then specifically states that "[m]ultiple daily SC injections of MTI were used in the US and Australian studies purely as a means to establish proof of principle that the molecule had biologic activity. Obviously, this route of administration would not be widely embraced by most individuals" leading to the development of subcutaneous (SC) depot (or implant) formulations including a PLAG polymer depot containing 4 mg NDP-MSH (HADLEY 2006 pg. 927 Section 2.7, first sentences and discussed above as in BHARDWAJ 2000 and BHARDWAJ 1996) These studies lead directly to testing of a human depot formulation containing 20 mg NDP-NSH in a PLAG formulation with a release profile of 2-3 weeks. The study produced "profound and long-lasting pigmentation" to such an extent that some volunteers requested removal of the

[14] Marwan, Mohamed M., et al. "Stimulation of S91 melanoma tyrosinase activity by superpotent α-melanotropins." Molecular and cellular endocrinology 41.2-3 (1985): 171-177.
[15] Levine, Norman, et al. "Induction of skin tanning by subcutaneous administration of a potent synthetic melanotropin." JAMA 266.19 (1991): 2730-2736.
[16] Bhardwaj, Renu. Formulation of controlled-release delivery systems for the alpha-melanocyte stimulating hormone analog, Melanotan-I. Dissertation. The University of Arizona, 1997
[17] Bhardwaj, Renu, and James Blanchard. "Controlled-release delivery system for the α-MSH analog Melanotan-I using poloxamer 407." Journal of pharmaceutical sciences 85.9 (1996): 915-919
[18] Bhardwaj, R., and J. Blanchard. "In vitro characterization and in vivo release profile of a poly (d, l-lactide-co-glycolide)-based implant delivery system for the α-MSH analog, melanotan-I." International journal of pharmaceutics 170.1 (1998): 109-117
[19] Bhardwaj, Renu, et al. "Pharmacologic response of a controlled-release PLGA formulation for the alpha-melanocyte stimulating hormone analog, Melanotan-I." Pharmaceutical research 17.5 (2000): 593-599
[20] "Drug trial may reduce sunburn," The Sydney Morning Herald, September 2, 2005, https://www.smh.com.au/national/drug-trial-may-reduce-sunburn-20050902-gdlzm3 html
[21] "New Drug Approvals: Tag Archives: erythropoietic protoporphyria," https://newdrugapprovals.org/tag/erythropoietic-protoporphyria/

implants. This, in turn, lead to studies designed with lowered levels of NDP-MSH in the depot formulation. (HADLEY 2006 pg. 924 Section 2.7 , second paragraph). HADLEY 2006 also describes teaches the utility of NDP-MSH in attempting to use the compound for "subjects who experience polymorphous light eruption (PMLE) reactions" (HADLEY 2006 pg. 926 Section 2.6). HADLEY 2006 further states that the "acute [PMLE] reactions can be both painful and cosmetically unacceptable, and therefore, a means of preventing PMLE could be very beneficial." (HADLEY 2006 pg. 926, Section 2.6)

Both HADLEY 2002[22] and HADLEY 2006 provides detailed reviews of the scientific and commercial development of NDP-MSH.

III. COMMENT ON ARGUMENTS DURING PROSECUTION OF THE '555

During prosecution of the '555, Patentee had two arguments regarding the use of Bardwaj & Blanchard and Ugwu as defeating prior art: 1) "Guinea pigs are distinct from humans, have different melanocortin receptors with different interaction -pharmacodynamic- characteristics with afamelanotide." and 2) "wishing to apply the extended release technology from Bardwaj and Blanchard in the experiment of Ugwu, the skilled person would apply high human plasma levels (Ugwu does not motivate the use of the presently claimed low and extended human plasma levels) and that would result in low melanogenesis results, contrary to the surprising results of the present invention."

Taking each of these arguments separately, as far back as the 1980s, guinea pig models were being designed and recognized as a suitable proxy for human experimentation for the development of MSH-based treatments. Bolognia 1989[23] states that that "the effects of UVB on skin pigmentation are at least in part mediated through the MSH receptor system." (Bolognia 1989 pg. 654 second column). They further "observed potentiation between UVB and MSH in two different mammalian species, mice and guinea pigs. The finding that these animals responded similarly to UV and MSH suggests that this is likely to be a generalized response in mammals" (Bolognia 1989, pg. 654 bottom second column) thereby linking guineas pigs to a generalized MSH receptor mediated system. In fact, one of their suggestions is that this "might also explain why individuals with skin extremely low in melanin content (type I) do not tan after exposure to solar radiation." (Bolognia 1989 pg. 655 first column) This, of course is precisely one of the deficiencies that therapeutic NDP-MSH was developed to alleviate. Later Bolognia 1990[24] was even more direct, saying ""Guinea pigs serve as an excellent animal model because their skin contains active interfollicular epidermal melanocytes as well as active follicular melanocytes. The former are located in the basal layer in a pattern similar to that observed in human skin. An increase in epidermal pigment production and melanocyte number has been observed in guinea pig skin after the following treatments: UVA, UVB, and UVC irradiation (reference omitted); PUVA (reference omitted); topical MSH plus UVB (reference omitted); and injections of MSH or estrogen (reference omitted). The resultant hypermelanosis was diffuse in nature and resembled that in UV-irradiated human skin." (BOLOGNIA 1990 pg. 150). Finally, HADLEY 2002 says

> Our most recent efforts have focused on the use of a very unique animal model to further study the ability of our PLGA implant formulations to stimulate melanogenesis while concurrently determining the pharmacokinetic profile of the delivery system in order to evaluate the controlled release of MT-I by the implants. The melanotropic effects of MT-I were studied using a special breed of pigmented hairless and haired guinea pigs developed by Dr. John Pawelek. The pigmented guinea pigs combine the convenience of a hairless model with a pigmentary system that is similar to human skin in structure and in its response to various stimuli … .

[22] Hadley, Mac E., et al. "Discovery and development of novel melanogenic drugs." Integration of Pharmaceutical Discovery and Development (2002): 575-595.

[23] Bolognia et al., "UVB-induced melanogenesis may be mediated through the MSH-receptor system." Journal of Investigative Dermatology 92.5 (1989): 651-656

[24] Bolognia et al., "Hairless Pigmented Guinea Pigs: A New Model for the Study of Mammalian Pigmentation," Pigment Cell Research 3:150-156 (1990))

> The guinea pig skin contains active interfollicular epidermal melanocytes as well as active follicular melanocytes. The former are located in the basal layer of the epidermis in a pattern similar to that observed in human skin. **The hairless guinea pigs are very useful models as their hairless surface is convenient for testing the effect of UV irradiation as well as for assessing the changes in cutaneous pigmentation in response to external agents such as MTI or MT-II**." (pg. 587-588; emphasis added).

With regard to the statement that guinea pigs have "have different melanocortin receptors," nothing in the claims discusses nor references melanocortin receptors as argued by the Patenee during examination in response to the examiner's denial of the original claims. In fact, different affinities for ATCH and MSH between species does not negate the effects and similarities of MSH binding between species (see, for example, Haskell-Luevano[25]). Therefore, the first argument that the guinea pig model was not appropriate is soundly defeated by the references cited.

As to the second argument - that the person of ordinary skill would be steered toward the use of "high human plasma levels" of NDP-MSH - it is likewise nonsense. If both human and guinea pig receptors show enhanced ("irreversible") binding of NDP-MSH (see, for example, Haskell-Luevano), then it would follow that lowered levels of NDP-MSH would be reasonable to pursue. Regardless of the mechanistic functionality of NDP-MSH however, BHARDWAJ 1998 specifically teaches away from high plasma levels of the peptide saying that part of the reason the study was performed was because "very low concentrations of α-MSH, ranging from 24–72 pg./ml, have been detected in human cerebrospinal fluid … and because MT-I is highly potent (i.e. 'superpotent') and has a *prolonged biological activity* despite its short plasma half life, *the low peptide release (below the 39 pg./ml detection limit of the RIA assay) during the slow release (secondary) phase was adequate to provide a continuous pharmacological effect* as observed in recently completed studies with pigmented guinea pigs" (pg. 115 bottom of first column; emphasis added). Further, HADLEY 2006 specifically notes that implants with 20 mg NDP-MSH "was so great that several subjects requested removal of the partially dissolved implants…since they felt they had become too darkly pigmented. … Based on these findings, the next depot studies will compare tanning efficacy for a [NDP-MSH] depot formulation containing much lower [NDP-MSH] (doses staring with a 5 mg depot)" (pg. 927 Section 2.7 second paragraph).

[25] Haskell-Luevano et al. "Characterizations of the unusual dissociation properties of melanotropin peptides from the melanocortin receptor, hMC1R." Journal of Medicinal Chemistry 39.2 (1996): 432-435 [published online 19 January 1996]

Prior Art Analysis

Prior Art Patent/ Publication	Title	Inventor/Author	Priority Date/Publication Date
HADLEY 2006: Peptides 27.4 (2006): 921-930.	*Melanocortin peptide therapeutics: Historical milestones, clinical studies and commercialization*	Hadley, ME and Dorr, RT	18 January 2006
YASHAR: Dermatologic Therapy, Vol. 16, (2003), 1–7	*Classification and evaluation of photodermatoses*	Yashar, SS and Lim, HW	2 May 2003
BHARDWAJ 2000: Pharmaceutical Research 17.5 (2000): 593-599.	*Pharmacologic response of a controlled-release PLGA formulation for the alpha-melanocyte stimulating hormone analog, Melanotan-I.*	Bhardwaj, R, Hadley, ME, Dorr, RT, Dvorakova, K, Brooks, C, and Blanchard, J	31 May 2000
BHARDWAJ 1998: *International Journal of Pharmaceutics* 170.1 (1998): 109-117.	*In vitro characterization and in vivo release profile of a poly (d, l-lactide-co-glycolide)-based implant delivery system for the α-MSH analog, melanotan-I.*	Bhardwaj, R. and Blanchard, J	31 August 1998
HADLEY 2002: *Integration of Pharmaceutical Discovery and Development* (2002): 575-595.	*Discovery and development of novel melanogenic drugs.*	Hadley, ME, Hruby, VJ, Blanchard, J, Dorr, RT, Levine, N, Dawson, BV, Al-Obeidi, F, and Sawyer, TK	31 December 2002

Ground I - US Patent 8334265

Claims 1 and 4 are unpatentable under 35 USC §102 as being anticipated by HADLEY 2006.

US 8334265	HADLEY 2006
1. A method for treating a human subject suffering from photodermatoses that are caused or exacerbated by or associated with ultraviolet radiation (UVR) exposure which comprises the step of administering to said subject an amount of [Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (alpha-MSH) effective to reduce the photosensitivity of the skin of the subject.	HADLEY 2006 teaches a method for treating a human subject suffering from photodermatoses that are caused or exacerbated by or associated with ultraviolet radiation (UVR) exposure administering to said subject an amount of [Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (alpha-MSH) effective to reduce the photosensitivity of the skin of the subject ("Subjects were randomized 3:1 (MTI:placebo), to receive either MTI (0.16 mg/ kg/day X 10) or saline, with the active group further stratified such that at least 30 subjects each, were skin types I/II or skin types III/IV. The four primary endpoints were: (1) tanning, measured by skin reflectance; (2) a change in

	melanin density measured by UV-spectroscopy; (3) a change in the number of apoptotic (sunburn) cells produced in response to UV-light; (4) a change in minimal crythematous dose (MED) of UV light from baseline to 30 and 60 days after dosing. … MTI reduced the number of apoptotic keratinocytes (sunburn cells), in the skin of subjects with poorly tanning easily burning skin types (I/II).” Pg 526 Section 2.5 Double-blind phase II trial of MTI in Caucasian subjects with skin types I-IV and Figure 2 showing the sequence of MTI)
4. The method of claim 1, wherein the photodermatosis is polymorphous light eruption (PLE).	Claim 1 is anticipated as above. Further, HADLEY 2006 teaches the photodermatosis is polymorphous light eruption (PLE). (“a study of European subjects who experience polymorphous light eruption (PMLE) reactions to the first sun exposure of a season” pg. 926 sec. 2.6; “treat PMLE patients with MTI prior to their first sun exposure, to allow for melanization to occur” pg. 926 sec 2.6)

Ground II - US Patent 8334265

Claims 2 and 3 are unpatentable under 35 USC §103 as obvious over HADLEY 2006.

US 8334265	HADLEY 2006
2. The method of claim 1, wherein the photodermatosis is erythropoietic photoporphyria (EPP).	Claim 1 is obvious over HADLEY 2006 as above. As the photodermatosis erythropoietic photoporphyria (EPP) was well known in the art at the time of the invention to be caused or exacerbated by or associated with ultraviolet radiation (UVR) exposure and because HADLEY 2006 specifically teaches the step of administering to a subject an amount of [Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (alpha-MSH) effective to reduce the photosensitivity of the skin of the subject exposed to ultraviolet radiation exposure and exhibiting a photodermatosis generally, the use of [Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (alpha-MSH) would have been readily obvious to one of ordinary skill in the art.
3. The method of claim 1, wherein the photodermatosis is solar urticaria (SU).	Claim 1 is obvious over HADLEY 2006 as above. As the photodermatosis solar urticaria (SU) was well known in the art at the time of the invention to be caused or exacerbated by or associated with ultraviolet radiation (UVR) exposure and because HADLEY 2006 specifically teaches the step of administering to said subject an amount of [Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (alpha-MSH) effective to reduce the photosensitivity of the skin of the subject exposed

	to ultraviolet radiation exposure and exhibiting a photodermatosis generally, the use of [Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (alpha-MSH) would have been readily obvious to one of ordinary skill in the art.

Ground III - US Patent 8334265
Claims 2 and 3 are unpatentable under 35 USC §103 as obvious over HADLEY 2006 in view of YASHAR.

US 8334265	HADLEY 2006 and YASHAR
2. The method of claim 1, wherein the photodermatosis is erythropoietic photoporphyria (EPP).	Claim 1 is obvious over HADLEY 2006 as above for treating photodermatoses, generally. The photodermatosis erythropoietic photoporphyria (EPP) has long been known to be caused by ultraviolet radiation exposure (UVR) exposure as taught by YASHAR ("Photodermatoses are a broad group of skin disorders primarily caused or exacerbated by exposure to UV or visible light. Photodermatoses can be classified into five general categories: idiopathic, most likely immune mediated; secondary to exogenous agents; secondary to endogenous agents; photoexacerbated dermatoses; and genodermatoses (1–5) (Table 2). (pg1 bottom of first column and Table 6, below)) **Table 6.** Photodermatoses associated with different age groups[a] Childhood Juvenile spring eruption PMLE Childhood porphyrias (EPP, CEP, PCT, HEP) Actinic prurigo Hydroa vacciniforme Genodermatoses Adulthood PMLE Drug-induced photosensitivity Solar urticaria Lupus erythematosus Porphyria cutanea tarda Elderly Chronic actinic dermatitis Drug-induced photosensitivity [a]Modified from reference 3. EPP, erythropoietic protoporphyria; CEP, congenital erythropoietic porphyria; PCT, porphyria cutanea tarda; HEP, hepatoerythropoietic porphyria. Because YASHAR identifies erythropoietic photoporphyria (EPP) as being caused or exacerbated by or associated with ultraviolet radiation (UVR)

	exposure and HADLEY 2006 teaches phototdermatoses that are caused or exacerbated by or associated with ultraviolet radiation (UVR) exposure can be treated by administering to a human subject an amount of [Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (alpha-MSH) effective to reduce the photosensitivity of the skin, the treatment of EPP by administering an amount of [Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (alpha-MSH) effective to reduce the photosensitivity of the skin would have been readily obvious to one of ordinary skill in the art at the time of the invention.
3. The method of claim 1, wherein the photodermatosis is solar urticaria (SU).	Claim 1 is obvious over HADLEY 2006 as above for treating photodermatoses, generally. The photodermatosis solar urticaria (SU) has long been known to be caused by ultraviolet radiation exposure (UVR) exposure as taught by YASHAR ("Photodermatoses are a broad group of skin disorders primarily caused or exacerbated by exposure to UV or visible light. Photodermatoses can be classified into five general categories: idiopathic, most likely immune mediated; secondary to exogenous agents; secondary to endogenous agents; photoexacerbated dermatoses; and genodermatoses (1–5) (Table 2). (pg1 bottom of first column and Table 2, below)) **Table 2.** Classification of photodermatoses (1–5) Idiopathic photodermatoses PMLE Juvenile spring eruption Actinic prurigo Hydroa vacciniforme Solar urticaria Chronic actinic dermatitis Secondary to exogenous agents Phototoxicity Photoallergy Secondary to endogenous agents Cutaneous porphyrias Pellagra Photoexacerbated dermatoses Lupus Dermatomyositis Darier's disease Pemphigus Bullous pemphigoid Genodermatoses Xeroderma pigmentosum Bloom's syndrome Cokayne's syndrome Rothmund–Thomson syndrome Trichothiodystrophy Kindler syndrome Hartnup disease Ataxia telangiectasia Because YASHAR identifies solar urticaria (SU) as being caused or exacerbated by or associated with ultraviolet radiation (UVR) exposure and HADLEY 2006 teaches phototdermatoses that are caused or exacerbated by or associated with ultraviolet radiation

	(UVR) exposure can be treated by administering to a human subject an amount of [Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (alpha-MSH) effective to reduce the photosensitivity of the skin, the treatment of SU by administering an amount of [Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (alpha-MSH) effective to reduce the photosensitivity of the skin would have been readily obvious to one of ordinary skill in the art at the time of the invention.

Ground I - US Patent 10076555

Claims 1-22 are unpatentable under 35 USC §103 as obvious over BHARDWAJ 2000 in view of BARDWAJ 1998.

US 10076555	BHARDWAJ 2000 and BHARDWAJ 1998
1. A method for inducing melanogenesis in a human subject comprising administering to the subject an alpha-MSH analogue in an effective amount and time to induce melanogenesis by melanocytes in epidermal tissue of the subject, wherein the alpha-MSH analogue is [Nle4, D-Phe7]-alpha-MSH, wherein the alpha-MSH analogue is administered in a delivery system that releases the alpha-MSH analogue in the subject for at least 2 days, and wherein the alpha-MSH analogue is administered at a level not exceeding 10 ng/ml in plasma of the subject for a period of at least 24 hours.	To the extent that the preamble provides patenable weight to the terms contained therein[26], BHARDWAJ 2000 teaches a method for inducing melanogenesis in a human subject comprising administering to the subject an alpha-MSH analogue in an effective amount and time to induce melanogenesis by melanocytes in epidermal tissue of the subject, ("MT-I is currently in Phase I trials at the Arizona Cancer Center (University of Arizona, Tucson) to evaluate its potential as a chemopreventive agent for sunlight-induced skin cancers. MT-I has a very short half-life of 1.07 (60.88) hr in humans after intravenous administration … and, as a consequence, multiple injections are required to achieve and maintain the desired therapeutic activity. **Hence, it seemed appropriate to develop a prolonged-action formulation for MT-I in order to provide extended skin protection. The biodegradable polymer, poly (D,L-Lactide-co-glycolide) (PLGA) with 50% lactide and 50% glycolide, was selected to develop an implant delivery system for this peptide**." (pg. 593, second column emphasis added); and "This is the first attempt to formulate a **prolonged-acting delivery system** for this unique melanogenic peptide using a comprehensive approach to evaluate the suitability of an **implant preparation**" (pg. 598 second column Conclusions; emphasis added). "**The increased pigmentation after implantation of the MT-I depot resulted in an increased number of melanin positive cells in the basal layers of the epidermis**." (pg. 595 end of second column) "**Melanogenesis** within the skin and hair follicles results from the synthesis of melanin within the melanosomes, which are the cytoplasmic

[26] Rowe v. Dror, 112 F.3d 473, 478 (Fed. Cir. 1997) stating "a preamble is not limiting 'where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention.' "

	organelles administration of the implant is a measure of the protective within the **melanocytes** … MT-I might produce effects similar to α-MSH, which causes a cascade of biochemical events culminating in enhanced **melanogenesis**." (pg. 598 first column) BHARDWAJ 2000 specifically teaches the α-MSH analogue is [Nle4, D-Phe7]-alpha-MSH ("Melanotan-I an α-Melanocyte Stimulating Hormone (α-MSH) analog, was studies as a potential skin protective agent. … The MT-I molecule differs from α-MSH in the substitution of norleucine (Nle) for methionine at position 4 and D-phenylalanine for L-phenylalanine at position 7" pg. 593 bottom of first column continued to second column; "**a prolonged-action formulation for MT-I**" pg. 593, second column; emphasis added). BHARDWAJ 2000 further teaches the α-MSH analogue is administered in a delivery system that releases the α-MSH analogue for at least 2 days ("The purpose of the controlled-release MT-I implant formulation based on PLGA polymer was to prolong the release of the peptide and thereby maintain enhanced skin pigmentation for at least one month." (pg. 597, first column); and "Due to the prolonged biological activity of MT-I, the melanotropic action lasted for three months, thus reducing the need for implant administration from once-a month to once every three months." (pg. 598 second column; emphasis added). BHARDWAJ 1998 also teaches the α-MSH analogue is administered in a delivery system that releases the α-MSH analogue for at least 2 days ("the release of MT-I from the implant delivery system appeared to be triphasic and lasted **for more than a month**" pg. 114 middle of second column; and "The plasma concentrations of MT-I after subcutaneous administration of implants containing 10% w:w MT-I to guinea pigs are shown in Fig. 6. The release profile showed an initial peak at day 2 as water diffused into the matrix and released MT-I from the surface regions of the device. The initial level of peptide release is controlled by factors such as peptide:polymer ratio, particle size of the dispersed peptide and the size of the delivery device. Pg 114-115; and "**The in vivo studies with guinea pigs demonstrated a prolonged peptide release into the systemic circulation for at least 36 days, which illustrated the potential of the implanted delivery system to increase the therapeutic efficacy of Melanotan-I.** pg. 116 Conclusions) BHARDWAJ 2000 does not specifically teach the α-MSH analogue is administered at a level not exceeding 10 ng/ml in plasma of the subject for a period of at

least 24 hours but does teach "[t]he MT-I released from the implants was bioactive and capable of producing melanotropic activity." (pg. 597 first column).

BHARDWAJ 1998 specifically teaches the alpha-MSH analogue is administered at a level not exceeding 10 ng/ml in plasma for a period of at least 24 hours. (Fig 6 pg. 115) and explaining that "These results indicate that the C_{max} observed in the pharmacokinetic profile of the implant represents a controlled-release of MT-I by the PLGA polymer as opposed to an 'uncontrolled' burst release." Pg 115 first column as well as explanatory material preceding).

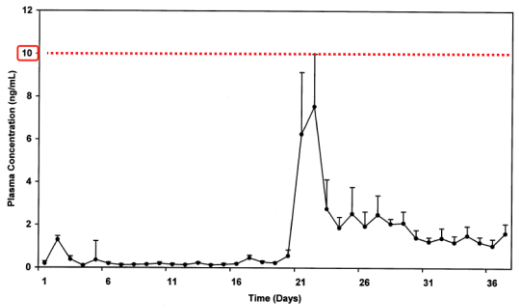


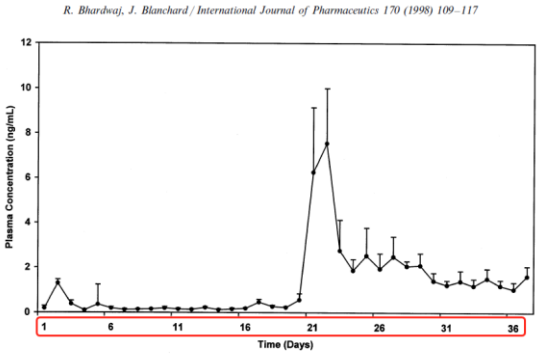
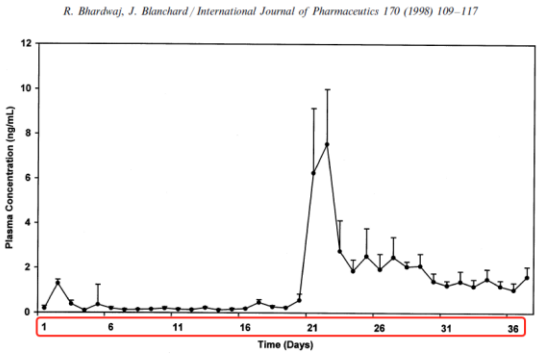
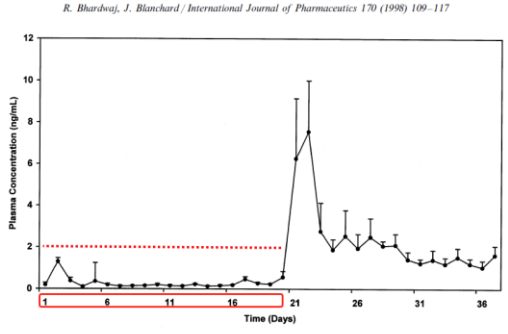
Fig. 6. In vivo profile of MT-I released from PLGA implants containing 10% w/w peptide in guinea pigs. Each point represents the mean ± S.E.M. ($n = 6$).

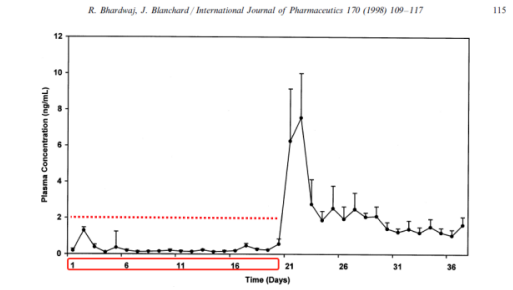
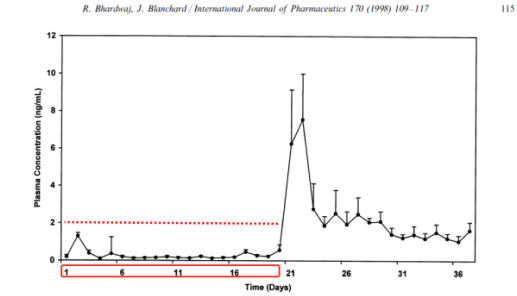
The guinea pig model used for release studies by BHARDWAJ 1998 was a well-known and acceptable model for various pharmaceutical studies directed toward the alpha-MSH analogue. (see discussion herein above in the section entitled "Argument during prosecution of the '555")

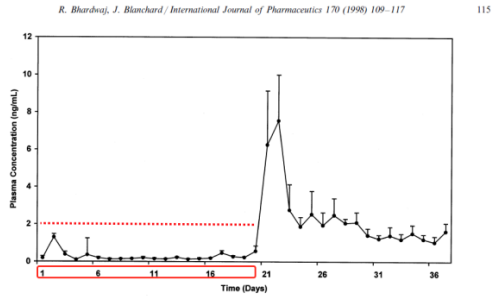
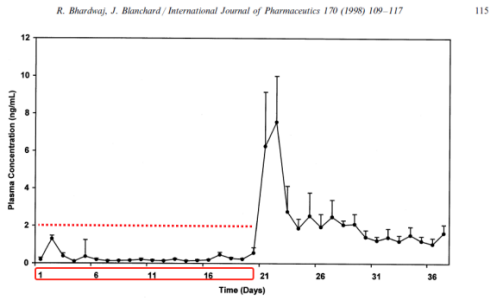
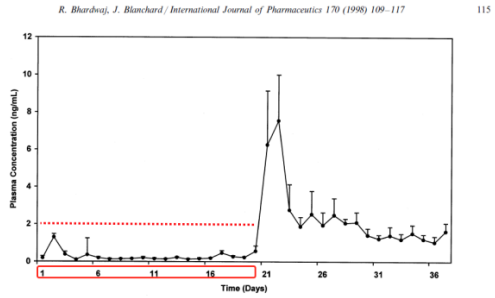
Further BHARDWAJ 1998 states "To compare the concentration of MT-I at the onset of polymer degradation and the C_{max} achieved by the administration of an MT-I solution, a pilot study was performed in which one half and one-tenth of the implant dose of MT-I (*i.e.*, 4 mg) were injected subcutaneously, into two guinea pigs. The C_{max} values observed at 60 min were about 90 and 20 ng/ml, respectively. These results indicate that the C_{max} observed in the pharmacokinetic profile of the implant represents a **controlled-release** of MT-I by the PLGA polymer **as opposed to an 'uncontrolled' burst release**." (pg. 115 first column).

Therefore, the motivation to develop a method for inducing melanogenesis in a human subject as described by BHARDWAJ 2000 was shown in the release profiles of the implant as described in BHARDWAJ 1998. It would have been obvious to one of ordinary skill in the art that the implants described by BHARDWAJ 1998 could have been modified to

	treat a subject as described by BHARDWAJ 2000 without undue experimentation and with routine application of standard pharmacological dosing procedures.
2. A method for reducing occurrence of UV radiation-induced skin damage in a human subject comprising administering to the subject an alpha-MSH analogue in an effective amount and time to induce melanogenesis by melanocytes in epidermal tissue of the subject, wherein the alpha-MSH analogue is [Nle4, D-Phe7]-alpha-MSH, wherein the alpha-MSH analogue is administered in a delivery system that releases the alpha-MSH analogue in the subject for at least 2 days, and wherein the alpha-MSH analogue is administered at a level not exceeding 10 ng/ml in plasma of the subject for a period of at least 24 hours.	See discussion of Claim 1 above. Claim 2 is rendered obvious for essentially the same reasons because melanogenesis results from UV radiation induced skin damage.
3. The method of claim 1, wherein the delivery system comprises up to 20 mg of alpha-MSH analogue.	BHARDWAJ 2000 teaches the delivery system comprises up to 20 mg of α-MSH analogue ("subcutaneous administration of implants containing **4 mg** MT-I " abstract; "The MT-I implants containing 1 and 4 mg peptide (1 mg for in vitro studies) were prepared" pg. 593 second column; emphasis added)
4. The method of claim 1, wherein the delivery system comprises from 5 mg of alpha-MSH analogue.	BHADWAJ 1998 teaches the delivery system comprises from 5 mg of alpha-MSH analogue. (see calculation of implants derived from Sanders' method of preparation immediately below this chart)
5. The method of claim 1, wherein the delivery system comprises from 10 mg to 20 mg of alpha-MSH analogue.	Neither BHADWAJ 2000 nor BHADWAJ 1998 specifically teach the delivery system comprises from 10 mg to 20 mg of alpha-MSH analogue. However, the development of PLGA implants containing incrementally more active ingredient such as alpha-MSH analog was very well understood and would have been readily available to one of ordinary skill in the art at the time of the invention through routine experimentation. Further, the motivation to make implants with concentrations of from 10 mg to 20 mg of alpha-MSH analogue would have been obvious from the teachings of BHADWAJ 2000 and BHADWAJ 1998 that used implants containing 4 mg of alpha-MSH on guinea pigs weighing ~500 gm in order to increase initial dosing to human weighing much more than ~500 gm. Because it was shown that a 4 mg/implant in a guinea pig was deemed to safe and efficacious, and because the general goal for any active ingredient in a pharmaceutic compound is to use the lowest possible effective amount, then the use of incrementally increased implant additions of 10-20 mg would have been obvious for one of ordinary skill in the art to develop in order to treat humans (i.e. subjects larger than guinea pigs) with dosages on average much lower

	than that used for the guinea pig studies in order to begin to determine efficacy for the human subject.
6. The method of claim 1, wherein the alpha-MSH analogue is released for at least 4 days.	BHARDWAJ 1998 teaches the alpha-MSH analogue is released for at least 4 days. ("The MT-I released from the depot implanted subcutaneously in guinea pigs exhibited a release profile extending over **one month**" abstract and Fig 6)  Fig. 6. In vivo profile of MT-I released from PLGA implants containing 10% w/w peptide in guinea pigs. Each point represents the mean ± S.E.M. ($n = 6$).
7. The method of claim 1, wherein the alpha-MSH analogue is released for at least 6 days.	BHARDWAJ 1998 teaches the alpha-MSH analogue is released for at least 6 days. ("The MT-I released from the depot implanted subcutaneously in guinea pigs exhibited a release profile extending over **one month**" abstract and Fig 6)  Fig. 6. In vivo profile of MT-I released from PLGA implants containing 10% w/w peptide in guinea pigs. Each point represents the mean ± S.E.M. ($n = 6$).
8. The method of claim 1, wherein the level is not exceeding 2 ng/ml in the plasma of the subject.	BHARDWAJ 1998 teaches wherein the level is not exceeding 2 ng/ml in the plasma of the subject. (Fig. 6)  Fig. 6. In vivo profile of MT-I released from PLGA implants containing 10% w/w peptide in guinea pigs. Each point represents the mean ± S.E.M. ($n = 6$).

9. The method of claim 1, wherein the period is at least 2 days.	BHARDWAJ 1998 teaches wherein the period is at least 2 days. (Fig. 6)  Fig. 6. In vivo profile of MT-I released from PLGA implants containing 10% w/w peptide in guinea pigs. Each point represents the mean ± S.E.M. ($n = 6$).
10. The method of claim 1, wherein the period is at least 4 days.	BHARDWAJ 1998 teaches wherein the period is at least 4 days. (Fig. 6)  Fig. 6. In vivo profile of MT-I released from PLGA implants containing 10% w/w peptide in guinea pigs. Each point represents the mean ± S.E.M. ($n = 6$).
11. The method of claim 1, wherein the delivery system comprises from 5 to 60% of alpha-MSH analogue.	BHARDWAJ 1998 teaches the delivery system comprises from 5 to 60% of alpha-MSH analogue ("The implants containing **10% w/w peptide** were injected subcutaneously in the abdominal area." Pg 112, first column Section 2.9)
12. The method of claim 1, wherein the delivery system is administered subcutaneously.	BHARDWAJ 1998 teaches the delivery system is administered subcutaneously ("The implants containing 10% w/w peptide were injected **subcutaneously** in the abdominal area. Pg 112, first column Section 2.9)
13. The method of claim 1, wherein the delivery system is a rod or implant.	BHARDWAJ 1998 teaches the delivery system is the delivery system is an implant. ("The **implants** containing 10% w/w peptide were injected subcutaneously in the abdominal area. Pg 112, first column Section 2.9)
14. The method of claim 2, wherein the delivery system comprises up to 20 mg of alpha-MSH analogue.	BHARDWAJ 2000 teaches the delivery system comprises up to 20 mg of alpha-MSH analogue ("subcutaneous administration of implants containing **4 mg** MT-I " abstract; "The MT-I implants containing 1 and 4 mg peptide (1 mg for in vitro studies) were prepared" pg. 593 second column; emphasis added)
15. The method of claim 2, wherein the delivery system comprises from 5 mg of alpha-MSH analogue.	BHADWAJ 1998 teaches the delivery system comprises from 5 mg of alpha-MSH analogue. (see calculation from Sanders' method of preparation immediately below this chart.)

16. The method of claim 2, wherein the delivery system comprises from 10 mg to 20 mg of alpha-MSH analogue.	Claim 16 is obvious for essentially the same reason as given above for claim 5.
17. The method of claim 2, wherein the alpha-MSH analogue is released for at least 4 days.	BHARDWAJ 1998 teaches the alpha-MSH analogue is released for at least 4 days. (Fig. 6)  R. Bhardwaj, J. Blanchard / International Journal of Pharmaceutics 170 (1998) 109–117 115 Plasma Concentration (ng/mL) Time (Days) Fig. 6. In vivo profile of MT-I released from PLGA implants containing 10% w/w peptide in guinea pigs. Each point represents the mean ± S.E.M. ($n = 6$).
18. The method of claim 2, wherein the level is not exceeding 2 ng/ml in the plasma of the subject.	BHARDWAJ 1998 teaches wherein the level is not exceeding 2 ng/ml in the plasma of the subject. (Fig. 6)  R. Bhardwaj, J. Blanchard / International Journal of Pharmaceutics 170 (1998) 109–117 115 Plasma Concentration (ng/mL) Time (Days) Fig. 6. In vivo profile of MT-I released from PLGA implants containing 10% w/w peptide in guinea pigs. Each point represents the mean ± S.E.M. ($n = 6$).
19. The method of claim 2, wherein the period is at least 4 days.	BHARDWAJ 1998 teaches the period is at least 4 days. (Fig. 6)  R. Bhardwaj, J. Blanchard / International Journal of Pharmaceutics 170 (1998) 109–117 115 Plasma Concentration (ng/mL) Time (Days) Fig. 6. In vivo profile of MT-I released from PLGA implants containing 10% w/w peptide in guinea pigs. Each point represents the mean ± S.E.M. ($n = 6$).
20. The method of claim 2, wherein the delivery system is administered subcutaneously.	BHARDWAJ 1998 teaches the delivery system is administered subcutaneously ("The implants containing 10% w/w peptide were injected **subcutaneously** in the abdominal area." pg. 112, first column Section 2.9)
21. The method of claim 1, wherein the delivery system comprises an extended release formulation.	BHARDWAJ 1998 teaches the delivery system comprises an extended release formulation ("The in vivo studies with guinea pigs demonstrated a **prolonged peptide release** into the systemic circulation for at least 36 days, which illustrated the potential of the implanted delivery system to increase the therapeutic efficacy of Melanotan-I. This, in turn,

	provides a prolonged pharmacological activity of MT-I (Bhardwaj *et al*., unpublished results) and should overcome the need for daily administration of MT-I. **PLGA implants are a promising delivery device for providing a prolonged and controlled release of MT-I over a 1-month period." pg. 116 first column Section 4)**
22. The method of claim 2, wherein the delivery system comprises an extended release formulation.	BHARDWAJ 1998 teaches the delivery system comprises an extended release formulation ("The in vivo studies with guinea pigs demonstrated a **prolonged peptide release** into the systemic circulation for at least 36 days, which illustrated the potential of the implanted delivery system to increase the therapeutic efficacy of Melanotan-I. This, in turn, **provides a prolonged pharmacological activity of MT-I** (Bhardwaj *et al*., unpublished results) and should overcome the need for daily administration of MT-I. **PLGA implants are a promising delivery device for providing a prolonged and controlled release of MT-I over a 1-month period." Pg 116 first column Section 4)**

Calculation of alpha-MSH analogue present in the delivery system of BHARDWAJ 1998 implants according to the method of Sanders.

BHARDWAJ 1998 states that the implants were made by the melt extrusion technique of Sanders *et al*. 1986[27] (pg. 110, Section 2.2 - Preparation of depot formulations).

The extruded rods of Sanders containing 5% peptide were:

$\pi r^2 h = \pi (1.5mm)^2$ X 5mm L= ~0.0353 mL
This size rod contains 5% peptide w/w or 3mg peptide
(Sanders pg. 356 Experimental Section)

The extruded rods of BHARDWAJ 1998 containing 10% peptide were:

$\pi r^2 h = \pi (1mm)^2$ X 1cm L = ~0.0314 mL

Ratio of BHADWAJ 1997 rods to Sanders' rods: 0.0314 mL/0.0353 mL= ~0.89

Therefore, a rod from BHADWAJ 1997 with 10% w/v peptide would contain:

3 mg peptide X 2 = 6 mg peptide (from Sanders @10% w/w)

6 mg peptide X 0.89 = ~5.34 mg peptide

[27] Sanders, L. M., et al. "Prolonged controlled-release of nafarelin, a luteinizing hormone-releasing hormone analogue, from biodegradable polymeric implants: influence of composition and molecular weight of polymer." Journal of pharmaceutical sciences 75.4 (1986): 356-360.

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Claims 5 and 16 are unpatentable under 35 USC §103 as obvious over BHARDWAJ 2000 and BARDWAJ 1998 in further view of HADLEY 2002.

5. The method of claim 1, wherein the delivery system comprises from 10 mg to 20 mg of alpha-MSH analogue.	Neither Bhardwaj 2000 nor Bardwaj 1998 specifically teach the delivery system comprises from 10 mg to 20 mg of alpha-MSH analogue. HADLEY 2002 teaches "MT-I is very slowly metabolized in vivo and is active at concentrations 1000-fold lower than alpha-MSH. Mice were administered up to 2 mg/kg of MT-I daily and weekly over 4–12 weeks by topical application (in 90% DMSO) or by intraperitoneal injections (in physiological saline). At the end of this period, no toxic effects\ were observed in various organs, hematological indices, or on weight gain. In a follow-up trial in rats, a slight (30%) increase in alkaline phosphatase levels was observed. There was no evidence in either species of a behavioral effect or any ACTH-like endocrine actions such as elevated serum cortisol levels. Similar results were observed in pigs. These studies demonstrated the nontoxicity of MTI in both chronic and acute high dosage in rodent and larger species, and such results formed the basis of subsequent clinical trials on male volunteers. (pg. 584 section 4.1.1. MT-I Studies, second paragraph). HADLEY 2002 specifically states that further studies based on the PLAG implant showed similar plasma concentration profiles to those of BHARDWAJ 1998: "The plasma concentration versus time profile following the s.c. administration of 4 mg MT-I was similar to the triphasic profile for the in vitro release kinetics observed in earlier studies (Bhardwaj and Blanchard, 1998). The maximum MT-I concentration was observed in about 3 weeks after a slow release phase and the release of peptide continued for about 5 weeks. This peak observed at 3 weeks reflected the onset of erosion of the PLGA polymer. The melanotropic effect of MT-I continued during the slow release phase before the erosion of the polymer and persisted long after the MT-I levels were below the RIA detection limit." (pg. 588) HADLEY 2002 specifically motivated further research into the use of the implants: "The results indicate that the PLGA implant delivery system could provide a therapeutic tanning of the skin to lower the risk of UV-induced melanomas. **Based on the prolonged release, *enhanced biological activity of low, constant levels of MT-I* were noted and the melanotropic action thus lasted for months**. This reduces the frequency of administration from a once-a-month implant to once

	every 3 months. In addition, the increase in melanin pigment, especially eumelanin, could provide protection against the photodamaging effects of UV radiation, thereby aiding in the prevention of skin cancers." (pgs. 589-590) The effective dosing of anywhere from 10mg-20mg would have been obvious to one of ordinary skill in the art through routine experimentation given that these targets had already "formed the basis of subsequent clinical trials on male volunteers." as early as 2002 as described by HADLEY 2002. Knowing the degradative profiles of the PLGA implants as taught by BHARDWAJ 1998 and the relative safety of efficacy of lowered doses of MT-I due to enhanced stability of the analog as taught by HADLEY 2002 (***enhanced biological activity of low, constant levels of MT-I")***, it would have been obvious to develop the delivery system comprising from 10 mg to 20 mg of alpha-MSH analogue in light of the studies of BHARDWAJ 2000.
16. The method of claim 2, wherein the delivery system comprises from 10 mg to 20 mg of alpha-MSH analogue.	Claim 16 is obvious for essentially the same reasons given above for Claim 5.

Non-Patent Prior Art Considered For This Report

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